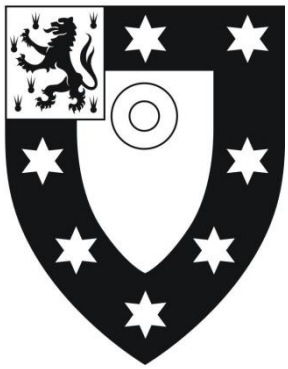
Studies Towards the Nucleophilic Dearomatisation of Electron-Deficient Heteroaromatics and Hydrogen Borrowing Reactions of Methanol





A thesis submitted to the Board of the Faculty of the Mathematical, Physical and Life Sciences Division for the degree of

Doctor of Philosophy

in the

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by

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St John's College

and

The Chemistry Research Laboratory

Trinity Term 2014

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Abstract

Studies Towards the Nucleophilic Dearomatisation of Electron-Deficient Heteroaromatics and Hydrogen Borrowing Reactions of Methanol

A thesis submitted for the degree of **Doctor of Philosophy**
Darren L. Poole, St John's College and the Chemistry Research Laboratory, Trinity 2014

Introduction – Dearomatisation of Heteroaromatic Compounds

The introduction provides a survey of dearomatisation reaction of heteroaromatics, with a particular focus on pyridines/pyridinium salts and furans. The mechanism, scope, and limitations of various approaches are covered, along with the goals of this project.

Results and Discussion – Dearomatisation of Electron-Deficient Heteroaromatics

This chapter initially explores the asymmetric addition of organometallic nucleophiles to pyridinium salts bearing a chiral counterion. Unfortunately, this approach ultimately proved unsuccessful, due to low observed enantioselectivities, and the low solubility of such salts.

The second part of this chapter concerns the attempted asymmetric addition of dicarbonyl nucleophiles to electron-deficient furans, under conditions of chiral phase-transfer catalysts, affording bicyclic products in moderate enantioselectivity. Various alternative routes were also explored for the dearomatisation of furans and benzenoid systems.

Introduction – Hydrogen Borrowing Alkylation Reactions with Alcohols

The introduction surveys the range of methods available for the alkylation of various nucleophiles with alcohols under transition metal-catalysed conditions. Related methodologies are also explored, along with methods for the dehydrogenation of methanol.

Results and Discussion - Rhodium-catalysed Methylation of Ketones Using Methanol

This chapter describes the development of a novel ketone α-methylation using methanol. The development of reaction conditions is explored, followed by expansion of the substrate scope, including limitations of the methylation reaction. Mechanistic investigations support a methanol oxidation, aldol reaction/elimination, conjugate reduction pathway. Investigations into the role of O_2 in the methylation reaction proved inconclusive. The utility of the reaction was also expanded *via* one-pot dialkylation reactions (work by Di Shen), Baeyer-Villiger oxidation of the products, and an attempted asymmetric transfer-hydrogenation.

Results and Discussion - Interrupted Hydrogen Borrowing Reactions of Methanol

This chapter looks to intercept intermediates from the α-methylation reaction. The selective methylenation of ketones is described, and a range of nucleophiles are screened for further functionalisation of ketones. Finally, a number of nucleophiles, including nitroalkanes, amines, peroxides and boronic acids are applied to one pot methylenation/conjugate addition protocols, affording complex products after two steps in one reaction vessel.

Experimental

Full experimental procedures and spectroscopic characterisation of compounds are provided.

Acknowledgements

Firstly, my thanks must go to my supervisor, Professor Tim Donohoe, for allowing me to work in his group for the past five years. His guidance and advice have been invaluable in helping me out of the various problems that have arisen during the course of my DPhil, and his boundless enthusiasm has driven me to achieve as much as I possibly could during my time in Oxford. Thanks are also owed to my industrial supervisor Dr Mark Healey, at Novartis, for his help during the course of this project, and of course for the provision of lunch after CASE meetings!

I am forever indebted to my army of proofreaders, Alice Gatland, Di Shen, Jacqueline Habegger and Harish Kumar Potukuchi. Without their help, this thesis would surely contain many more errors, and I am incredibly grateful for the time and care they took in checking through it.

During my time in the Donohoe group, I have had the privilege to work with, and learn from, a number of outstanding people. My thanks must of course go to the entire Donohoe group, past and present. In particular, I am grateful to all members of lab F8 who have made my time in the Donohoe group as fun as it is. Thanks to Alice Gatland for helping me DJ so effectively, and providing some genuine moments of hilarity, Michael Tucker for schooling me in the art of music in my Part II year, and everyone else who has been in F8, including (but not limited to) Rob, Raddy, Kirsty, Emma, Grainne, Jackie, Kate, Xuezheng, Anatol and Henrique.

I am incredibly lucky to have worked on such a fast-moving and rapidly-expanding project as the 'methanol project'. My thanks therefore must go to Dr Louis Chan, Di Shen, Anne Kornahrens, and Camilla Shotton. Working together on the varying aspects of this project has been incredibly fulfilling, and I am proud of what we have achieved in such a short time.

My thanks again to Jackie for running crystal structures for me, and also to Dr Barbara Odell for NOE and deuterium NMR experiments, and to the Mass Spec service for their help with my mechanistic experiments.

My family must be thanked for all their help and encouragement over the years. The support of my mum, dad, and brother Aaron, were essential in helping me through the dark patches, including (but not limited to), snapping my knee and nearly dying of pneumonia!

Last, but very far from least, my thanks to my wonderful partner Beth. Your love, kindness, patience, and general brilliantness have kept me going over the final three years of my DPhil, and I am sure that it would not have been the same wonderful experience without you. This thesis is dedicated to you, as I am not sure how I would ever have come near finishing it without your support. I am an incredibly, incredibly lucky man, and I look forward to having you by my side for many years to come. Champion.

Declaration

This thesis, and the work it describes, is entirely my own, except where I have *either* acknowledged help from a named person, *or* given a reference to a published source or thesis. Text taken directly from another source has been enclosed in quotation marks and a reference given.

Darren Lee Poole

Oxford, Trinity Term 2014

Glossary of Abbreviations and Acronyms

° C	Degrees Celsius
Ac	Acetyl
Acac	Acetylacetonate
Ad	Adamantyl
Anth	9-Anthracenyl
Ar	Argon/Aryl
ATP	Adenosine triphosphate
aq.	Aqueous
BARF	Tetrakris(3,5-bis(trifluoromethyl)phenyl)borate
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-Bi-2-naphthol
BMEA	Bis(methoxyethyl)amine
BMIM	1-Butyl-3-methylimidazolium
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bs	Benzenesulfonyl
Bz	Benzoyl
cat.	Catalyst/catalytic
CataCXium A	Di-(1-adamantyl)-*n*-butylphosphine
cm^{-1}	Wavenumbers
cod	1,5-Cyclooctadiene
cot	1,3,5,7-Cyclooctatetraene
COSY	Correlated spectroscopy
Cp	Cyclopentadienyl
Cpr	Cyclopropyl
Cp*	Pentamethylcyclopentadienyl
CTH-P-Phos	2,2',6,6'-tetramethoxy-4,4'-(diphenylphosphino)-3,3'-bipyridine
Cy	Cyclohexyl
CyJohnPhos	2-(Dicyclohexylphosphino)biphenyl
DBB	4,4'-di-*tert*-butylbiphenyl
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	Dichloroethane
DCM	Dichloromethane
DCPE	1,2-Bis(dicyclohexyphosphino)ethane
Dec	Decyl
DEPT	Distortionless enhancement by polarisation transfer
DFT	Density functional theory
DMAP	4-Dimethylaminopyridine
DMB	3,4-Dimethoxybenzyl
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide

DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidone
DMSO	Dimethylsulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dr	Diasteriomeric ratio
e.g.	*exempli gratia* (Latin: for example)
EDC·HCl	*N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride
eq.	Equivalent(s)
ESI^+	Electrospray ionisation (positive ion detection)
Et	Ethyl
et al.	*et alii* (Latin: and others)
EWG	Electron-withdrawing group
FCC	Flash column chromatography
Fur	Furyl
g	Gram(s)
h	Hour(s)
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMPA	Hexamethylphosphoramide
HOMO	Highest-occupied molecular orbital
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
HT	Hydrotalcite ($Mg_6Al_2CO_3(OH)_{16}\cdot 4H_2O$)
Hz	Hertz
ICy·HCl	*N*,*N'*-dicyclohexylimidazolium chloride
ip-foxap	2-(4-Isopropyl-Δ^2-oxazolin-2-yl)-ferrocenyl(diphenyl)phosphine
*i*Pr	Isopropyl
IPr·HCl	*N*,*N'*-Diisopropylimidazolium chloride
J	Coupling constant
KIE	Kinetic isotope effect
L	Ligand
LDA	Lithium diisopropylamide
Lit.	Literature value
m	*meta*
M	Molar
*m*CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MeO-BIPHEP	2,2'-Bis(diphenylphosphino)-6,6'-dimethoxy-1,1'-biphenyl
Mes	Mesityl/2,4,6-trimethylphenyl
mg	Milligram(s)
MIDA	*N*-Methyliminodiacetic acid
min	Minute(s)
mL	Millilitre(s)
mmol	Millimole(s)

mol%	Molar percent
m.p.	Melting point
MS	Molecular sieves
MTBE	Methyl *tert*-butyl ether
MW	Microwave
n-	*primary*-
nbd	2,5-Norbornadiene
NHC	*N*-Heterocyclic carbene
NK_1	Neurokinin 1
NMO	*N*-Methylmorpholine-*N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
n/o	Not observed
o	*ortho*
p	*para*
Ph	Phenyl
Phth	Phthalimido
pKa	Logarithmic acid dissociation constant
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
Pr	Propyl
PTC	Phase-transfer catalyst
Py	Pyridyl
rbf	Round-bottomed flask
RDS	Rate-determining step
RSM	Recovered starting material
rt	Room temperature
sat.	Saturated
SSRI	Selective serotonin reuptake inhibitor
T	Temperature
t/*tert*-	*tertiary*-
TBAI	Tetrabutylammonium iodide
TBHP	*tert*-Butylhydroperoxide
TBS	*tert*-Butyldimethylsilyl
*t*BuXPhos	2-Di-*tert*-butylphosphino-2',4',6'-triisopropylbiphenyl
Tf	Triflyl/Trifluoromethansulfonyl
TFA	Trifluoroacetic acid
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TM	Transition metal
TMO	Trimethylamine-*N*-oxide
TMS	Trimethylsilyl
TMEDA	Tetramethylethylenediamine

Tol	Tolyl
TRIP	3,3′-Bis(2,4,6-triisopropylphenyl)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate
Triton B	Benzyltrimethylammonium hydroxide
Triton X-100	Poly(ethylene glycol) *p*-(1,1,3,3-tetramethylbutyl)-phenyl ether
Troc	2,2,2-Trichloroethoxycarbonyl
$trop_2dad$	*N*,*N*-Bis(5H-dibenzo[a,d]cycloheptene-5-yl)-1,4-diazabuta-1,3-diene
Ts	Tosyl
vide infra	Latin: See below
vide supra	Latin: See above
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene
xs	Excess
[α]	Specific rotation
δ	Chemical shift
Δ	Heated at reflux
μ	Micro (prefix: 10^{-6})
ν_{max}	Infra-red absorption maximum

1: Introduction – Dearomatisation of Heteroaromatic Compounds

1.1 Introduction

Aromatic compounds provide an abundant pool of materials for the synthesis of target molecules, providing cheap, readily-available, pre-functionalised scaffolds for further derivatisation. Unsurprisingly, reactions which take advantage of these benefits such as the Birch reduction,[1] are particularly popular methods for the synthesis of complex alicyclic compounds. One difficulty encountered relates to the high degree of stabilisation in aromatic systems which results in a preference for substitution reactions, whereby addition is followed by elimination, resulting in rearomatisation. Fortunately, the aromatic stabilisation energy of heteroaromatic compounds are lower than for benzene, facilitating dearomatisation (**Figure 1.1**).[2] However, numerous methods now exist for the successful dearomatisation of both carbo- and heterocyclic aromatic compounds (*vide infra*).

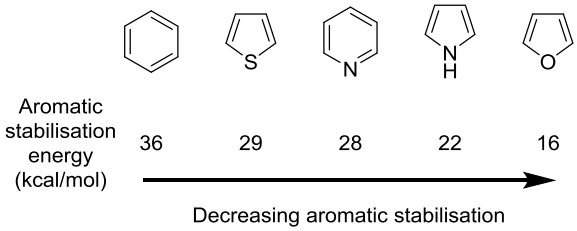


Figure 1.1 *Aromatic stabilisation energy of simple heterocycles*

1.2 Dearomatisation of Pyridines

1.2.1 The piperidine motif in natural products and biologically active molecules

In natural product chemistry (**Figure 1.2a**), as well as the chemistry of biologically active molecules (**Figure 1.2b**), the piperidine core occupies a privileged position, as is clear from the plethora of examples in the chemical literature.[3-7] Indeed, in the 10 years from 1988 to 1998, 12,000 entries for piperidine-containing compounds were reported as being utilised in clinical trials, further emphasising their utility.[8] The complexity of the various piperidine-based natural products varies hugely, from the simple alkylpiperidine, (−)-coniine **1**, isolated from poison hemlock, to the more complex histronicotoxin **2**, found in the skin of poison frogs, or the complex polycylic systems strychnine **3**, and the marine toxin azaspiracid 1 **4**. All these compounds vary in their degree of substitution, and unsaturation, as is also clear from the structures of paroxetine **5**, an SSRI antidepressant, droperidol **6**, a

tetrahydropyridine with use as both an antiemetic and an antipsychotic, and piperophos **7**, a simple alkylpiperidine with utility as a herbicide.

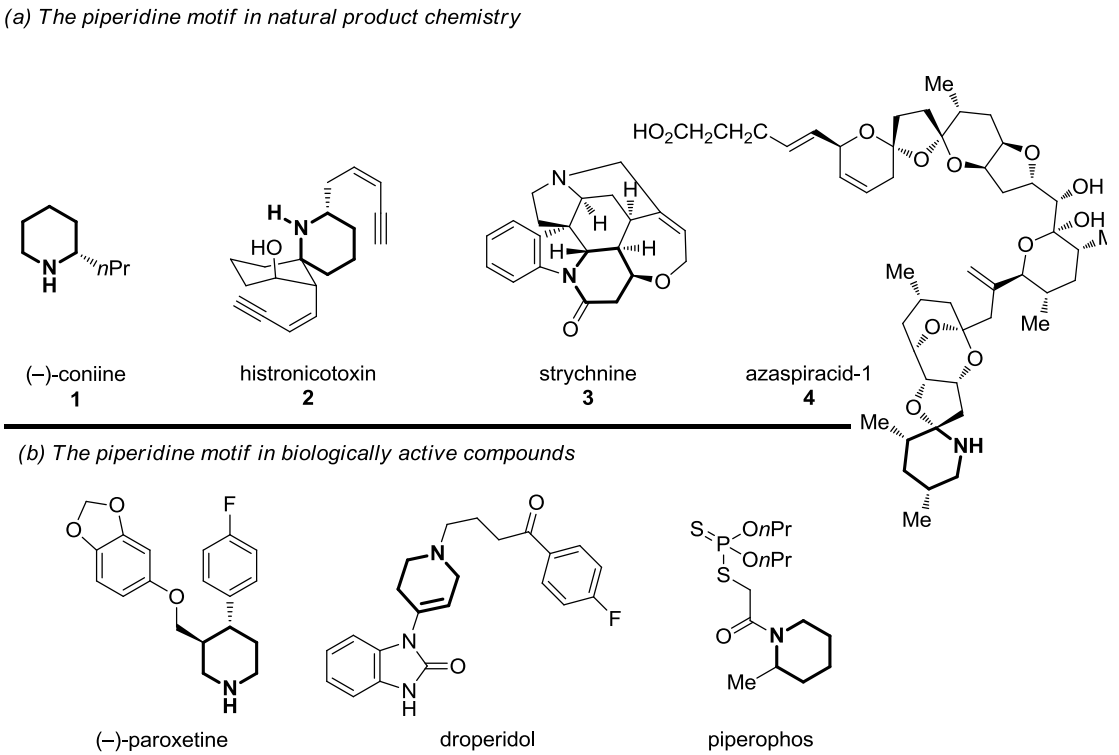


Figure 1.2 *Piperidine-containing natural products and pharmaceutical compounds*

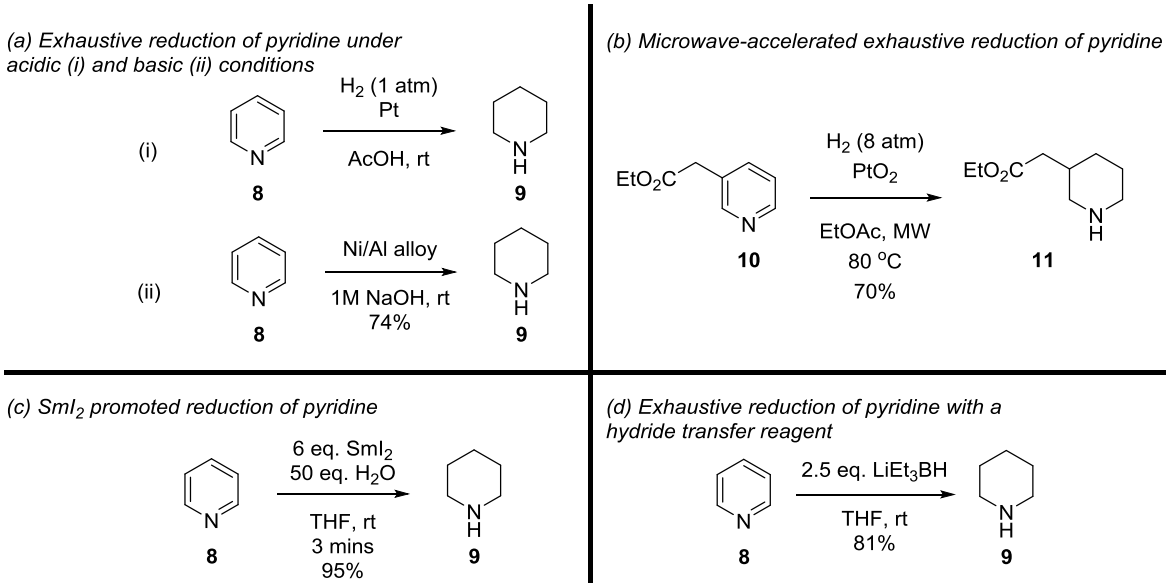
It is clear therefore that a multitude of methods are required to enable the synthesis of piperidine moieties with varied substitution patterns and oxidation levels, and the reductive/nucleophilic dearomatisation is central to the synthesis of complex piperidines (*vide supra*).

1.2.2 Reductive dearomatisation of pyridines and pyridinium salts

The reduction of pyridines to their non-aromatic analogues (piperidines, and isomeric dihydro- and tetrahydropyridines) is a synthetically valuable technique, and can be achieved in a number of ways (**Scheme 1.1**).

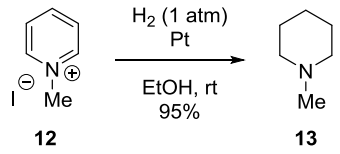
Classically, total reduction of pyridine **8** to piperidine **9** may be achieved by hydrogenation under heterogeneous conditions, typically using Pt metal in acidic solution (**Scheme 1.1a(i)**),[9] although this transformation is also readily achieved in dilute alkali solution with Ni-Al alloy (**Scheme 1.1a(ii)**),[10] or in neutral solution, where microwave heating provides rate acceleration for the conversion of pyridine **10** to piperidine **11** (**Scheme 1.1b**).[11] Exhaustive

reduction may also be achieved by employing radical reducing agents such as samarium(II) iodide (**Scheme 1.1c**),[12] or with strongly-reducing hydride transfer reagents, for example lithium triethylborohydride (**Scheme 1.1d**).[13]



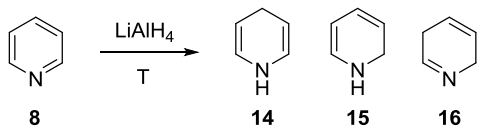
Scheme 1.1 *Exhaustive reduction of pyridines*

Pyridinium salts may also be reduced to the piperidine oxidation level under mild conditions. For example, the hydrogenation of *N*-methylpyridinium iodide **12** over Pt in ethanol proceeds at room temperature to afford *N*-methylpiperidine **13** in 95% yield (**Scheme 1.2**).[2]



Scheme 1.2 *Exhaustive reduction of pyridinium salt* **12**

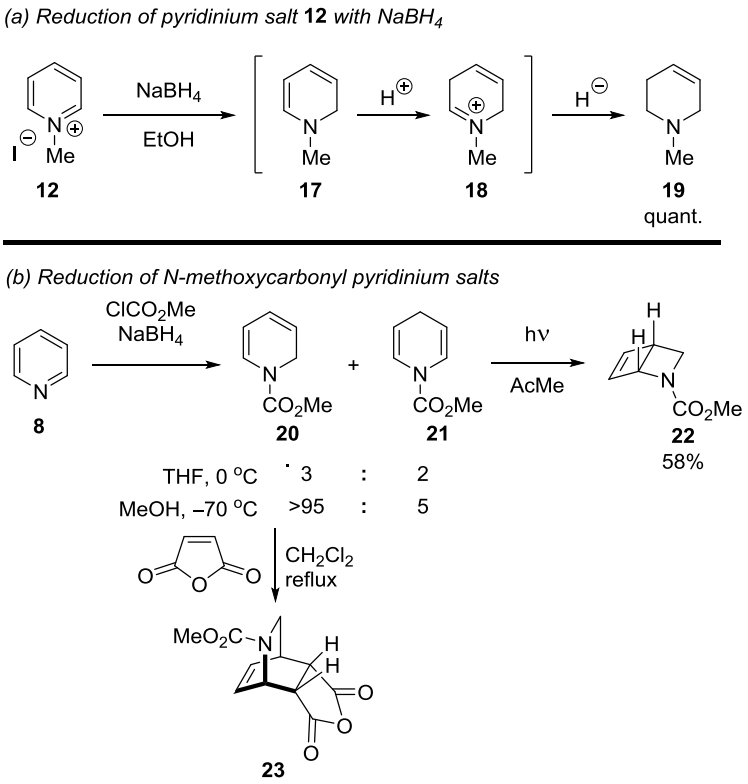
Although $LiBEt_3H$ proves effective for the complete reduction of pyridine **8** to piperidine **9**, other hydride transfer reagents are not so effective. Sodium borohydride is found not to react with pyridine at all,[2] whereas lithium aluminium hydride undergoes addition only once, producing a mixture of isomeric dihydropyridines **14-16** (**Scheme 1.3**), whose ratio varies depending on the temperature at which the reaction is conducted.[14]



	14	:	15+16
T = –30 °C	1	:	5
0 °C	1	:	2
90 °C	2.5	:	1

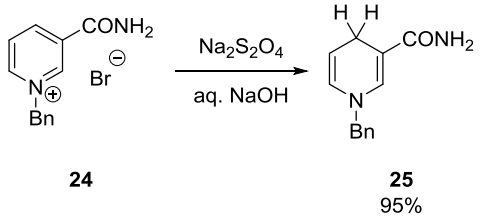
Scheme 1.3 *Reduction of pyridine by $LiAlH_4$*

Pyridinium salts, on the other hand, are considerably more reactive to sources of nucleophilic hydride than the neutral pyridine, and *N*-methylpyridinium iodide **12** can be reduced very efficiently with sodium borohydride to the 1,2,3,6-tetrahydropyridine **19**, *via* protonation and reduction of the enamine **17,** and iminium species **18**, respectively (**Scheme 1.4a**).[15] Similarly, pyridinium ions formed *in situ* from the reaction of pyridine **8** with chloroformate esters may also be reduced by sodium borohydride, to afford a mixture of the 1,2- and 1,4-dihydropyridines **20** and **21**, dependent on reaction conditions, which do not undergo further reduction due to the mesomerically electron-withdrawing effect of the carboxymethyl group (**Scheme 1.4b**).[16] These 1,2- and 1,4-dihydropyridines are versatile intermediates which may be utilised in a variety of synthetic protocols, for example they may be trapped in a Diels-Alder reaction,[16] or undergo photochemical cyclisations to provide azabicyclohe[2.2.0]hex-5-enes such as **22**, valuable as a synthetic equivalent to reactive 1,2-dihydropyridines, and obtainable by thermal ring opening.[17]



Scheme 1.4 *Hydride reduction of pyridinium salts*

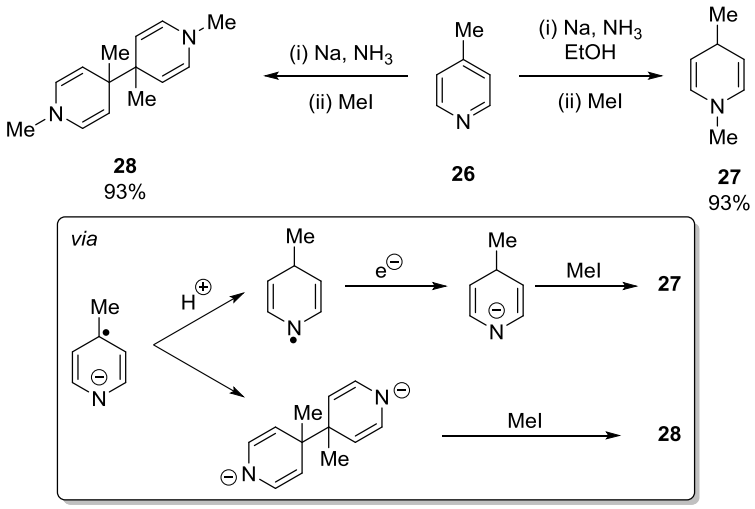
Pyridinium salts, such as *N*-benzyl-3-carbamoylpyridinium bromide **24** are also known to be reduced by sodium dithionite ($Na_2S_2O_4$) to form the 1,4-dihydropyridine **25** (Scheme **1.5**).



24 **25** 95%

Scheme 1.5 *Reduction of pyridinium salt* **24** *with sodium dithionite*

Electron transfer from dissolved metal species has also proved a popular method for the synthesis of dihydropyridines. In 1975, Birch reported the first isolation of a dihydropyridine from the dissolving metal reduction of 4-methylpyridine **26**. In alcoholic solvent, such as ethanol, the 1,4-dihydropyridine **27** was isolated in 93% yield, as its *N*-methylated derivative, whereas in the absence of alcohol, only the dimeric species **28** was isolated (**Scheme 1.6**).[18]



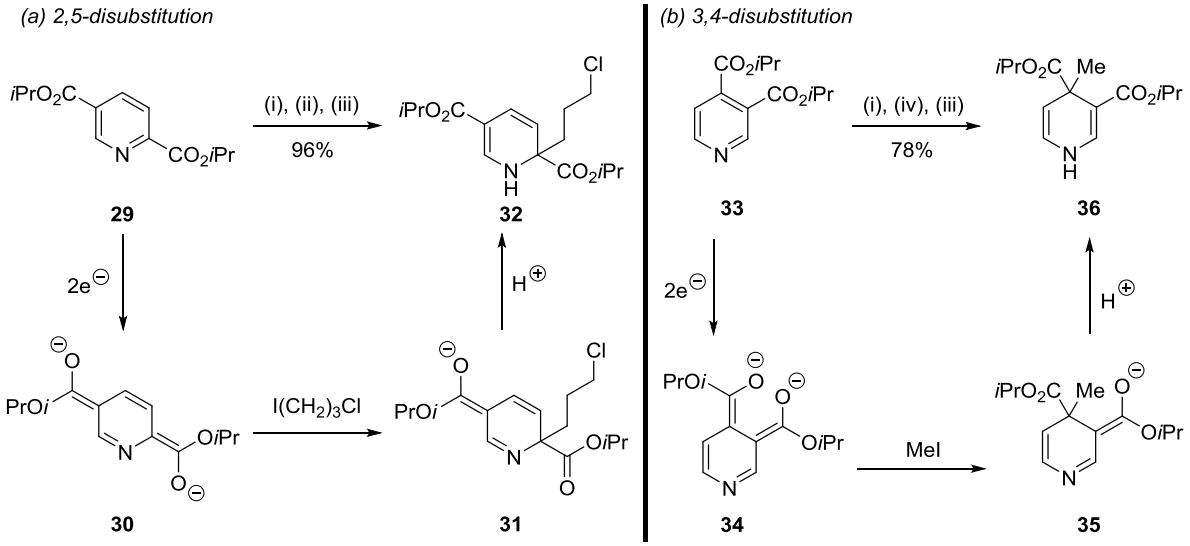
28 93% **26** **27** 93%

Scheme 1.6 *Birch reduction of pyridine* **26**

These observations can be explained through a mechanism in which the addition of an electron to **26** forms a radical anion, which may then either be protonated in the presence of a protic co-solvent, or which may also undergo dimerisation. The anions were then quenched with iodomethane to yield the respective products **27** and **28**. However, it should be noted that Birch reported this reaction to be particularly capricious, resulting in a mixture of 1,2- and 1,4-dihydropyridines being isolated, along with the corresponding tetrahydropyridines and piperidine resulting from over-reduction.

In an attempt to stabilise the products formed from the Birch reduction of pyridines, Donohoe and coworkers hypothesised that this could be overcome by decreasing the electron-density of the dihydropyridine ring, by appending suitable electron-withdrawing groups. Indeed,

pyridines possessing 2,5- and 3,4-disposed electron-withdrawing groups both proved to be excellent substrates for Birch reduction, presumed to be due to the formation of a stable dianion in both cases (**Scheme 1.7**).[19-21]

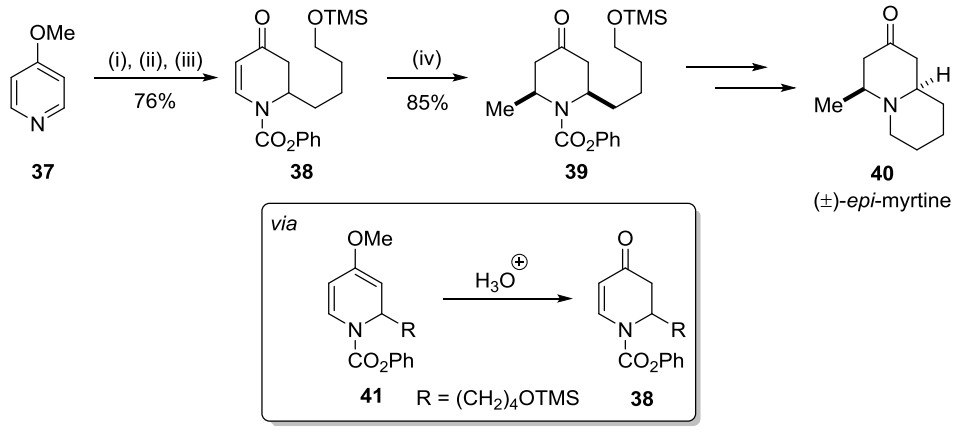


Scheme 1.7 *Ammonia-free Birch reduction of electron-deficient pyridines* **29** *and* **33**
Conditions: (i) LiDBB, THF, −78 °C (ii) $I(CH_2)_3Cl$ (iii) NH_4Cl (aq.) (iv) MeI

Indeed, the use of ammonia-free Birch conditions, using dissolving lithium and 4,4'-di-*tert*-butylbiphenyl (DBB) as an electron carrier, developed within the Donohoe group, allowed the generated *bis*-enolates to be quenched with nucleophiles that were not compatible with classical ammonia Birch conditions. This is due to the fact that reactive electrophiles (for example benzyl iodide, chloroformates, or enolizable carbonyl compounds), would be consumed by reaction with ammonia solvent before reacting with the desired enolate nucleophiles.

Despite the increased stability of the electron-deficient dihydropyridines formed in the Birch reduction of pyridines **29** and **33**, it was still found that the products were prone to decompose over a period of time. In an effort to circumvent this, Donohoe and coworkers looked to findings by Comins, which suggested that nucleophilic addition to 4-methoxypyridines such as **37** allowed formation of the 4-methoxydihydropyridine, which could then be hydrolysed to the corresponding dihydropyridone **38** *in situ*. These dihydropyridones were found to be more stable to air oxidation than dihydropyridines, and

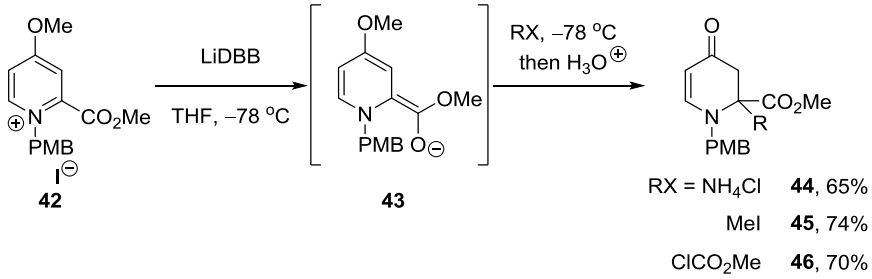
also imparted new synthetic utility, as shown in Comins' synthesis of (±)-*epi*-myrtine **40** (**Scheme 1.8**).[22]



Scheme 1.8 *Comin's synthesis of (±)-epi-myrtine* **40**

Conditions: (i) $BrMg(CH_2)_4OCHMeOEt$, PhOCOCl, THF (ii) H_3O^+ (iii) TMSCl, Et_3N, THF (iv) MeMgBr, CuI, THF, −25 °C, then $(CO_2H)_2$

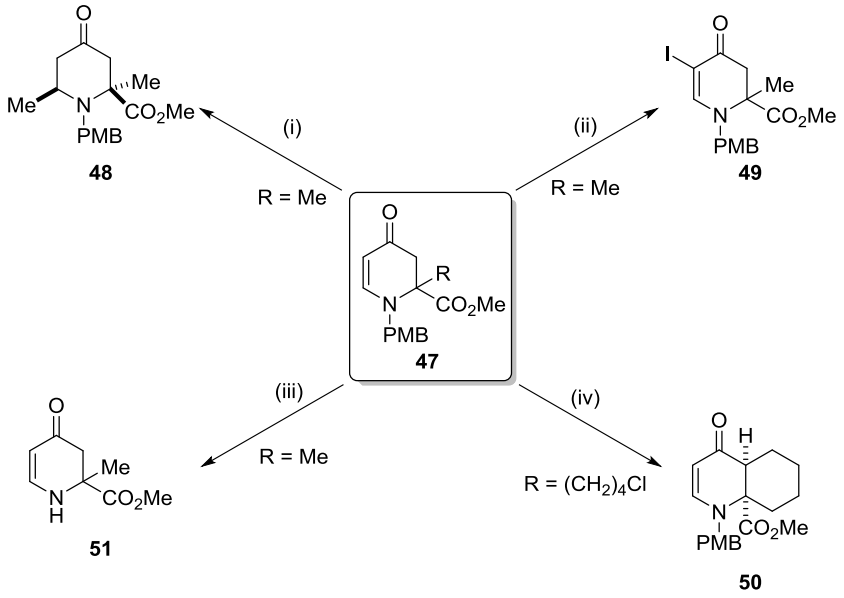
Application of Comins' route to the ammonia-free Birch reduction of 4-methoxypyridinium salt **42**, followed by quenching of the enolate thus formed with an electrophile, and subsequent hydrolysis of the enol ether moiety, allowed for the formation of a range of dihydropyridones (**Scheme 1.9**). It is noteworthy that this method afforded dihydropyridones, which although racemic, possessed a quaternary centre adjacent to the ring nitrogen at *C*-2, the first example of such a methodology in the literature.[23,24]



Scheme 1.9 *Ammonia-free Birch reduction of pyridinium salts*

Donohoe and coworkers also conducted a comprehensive study into the synthetic utility of the dihydropyridones formed *via* this methodology, showing that it was possible to further functionalise the dihydropyridone at each position of the ring (**Scheme 1.10**). For example, treatment with an organocuprate derived from methylmagnesium bromide and $CuBr.SMe_2$ afforded the conjugate addition product **48**, treatment with elemental iodine and base allowed formation of the vinyl iodide **49**, and by judicious choice of side-chain, enolate alkylation

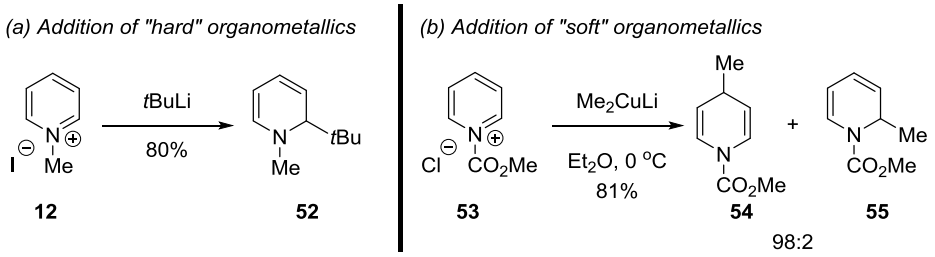
could be performed to form bicyclic dihydropyridones such as **50**. It was also possible to remove the PMB protecting group by refluxing **47** in TFA, affording the free dihydropyridone **51**.



Scheme 1.10 *Functionalisation of dihydropyridones*
Conditions: (i) $CuBr.SMe_2$, $BF_3.OEt_2$, MeMgBr, THF, −10 °C (ii) I_2, K_2CO_3, CH_2Cl_2, (iii) TFA, reflux (iv) $NaNH_2$, DMF

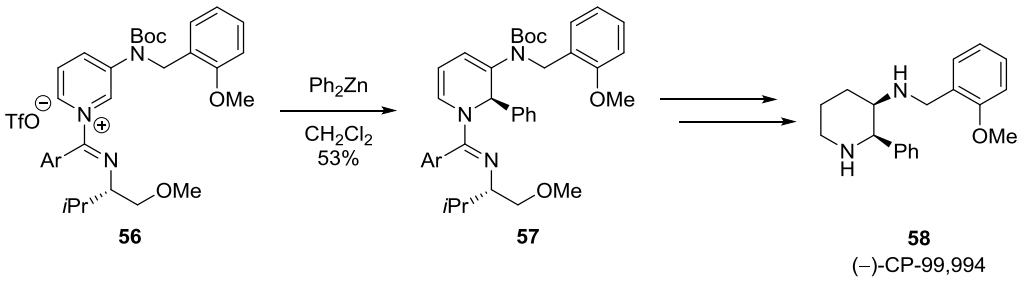
1.2.3 Nucleophilic dearomatisation of pyridinium salts

The addition of organometallic reagents to pyridinium salts has been thoroughly explored in the chemical literature, and there is a plethora of examples. In unsubstituted pyridinium salts, the regiochemistry of addition can cause further complications, since addition may occur at either the 2- or the 4- position. In general, it is found that "hard" nucleophiles, such as organolithium reagents, tend to attack pyridinium salts at the 2-position, for example the addition of *tert*-butyllithium to *N*-methylpyridinium iodide **12** by Francis and coworkers, where complete selectivity for 1,2-addition was observed (**Scheme 1.11a**).[25] On the other hand, organometallics considered to be "soft", such as organocuprates, tend to show a preference for attack at the 4-position, such as with the addition of lithium dialkylcuprates developed by Piers, which showed 98:2 selectivity for 1,4-addition in the case of dimethylcopper lithium, and similarly high regioselectivities and good yields for a range of other cuprates (**Scheme 1.11b**).[26]



Scheme 1.11 *Regioselectivity of organometallic addition to pyridinium salts*

It is, however, important to note that the regioselectivity of nucleophilic dearomatisation is highly dependent on a number of factors, including the counterion and solvent employed. These factors may result in decreased regioselectivity, leading to a mixture of 1,2- and 1,4-dihydropyridines, or even a complete reversal in regioselectivity. For example, the "soft" nucleophile Ph_2Zn was found to undergo 1,2-addition in Charette's synthesis of the NK_1 receptor agonist (−)-CP-99,994 **58**, despite the inherent preference for 1,4 addition, due to coordination of zinc to the free lone pair on the imidate chiral auxiliary (**Scheme 1.12**).[27]

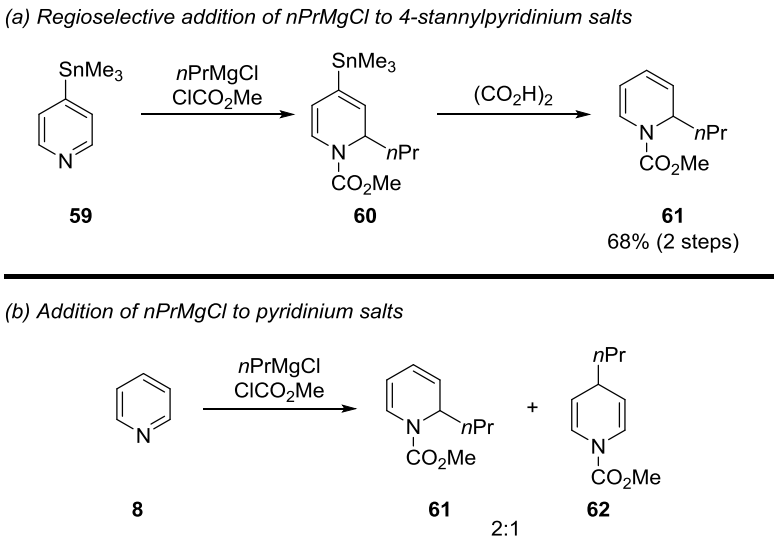


Scheme 1.12 *1,2-addition of Ph_2Zn in Charette's synthesis of (−)-CP-99,994* **58**

However, despite this difficulty in predicting regioselectivity in the addition of organometallic reagents, a number of different techniques have been developed to control the regioselectivity of addition.

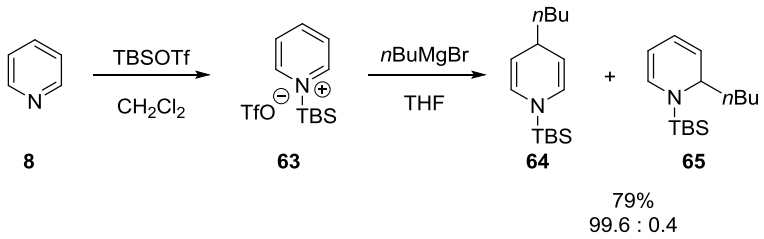
One early attempt at controlling the regioselectivity of nucleophilic addition to pyridinium salts, developed by Comins and coworkers, was to employ a trimethyltin blocking group at the 4-position of the pyridine **59** in the presence of methylchloroformate (**Scheme 1.13**). Addition of *n*-propylmagnesium chloride, followed by destannylation with oxalic acid afforded the desired alkylated 1,2-dihydropyridine **60** in 68% yield over the two step sequence (**Scheme 1.13a**). This result compared very favourably with the result achieved in

the non-stannylated example **61**, where a 2:1 mixture of 1,2- and 1,4-dihydropyridines was isolated (**Scheme 1.13b**).



Scheme 1.13 *$SnMe_3$ blocking group to control regioselectivity in addition to pyridinium salts*

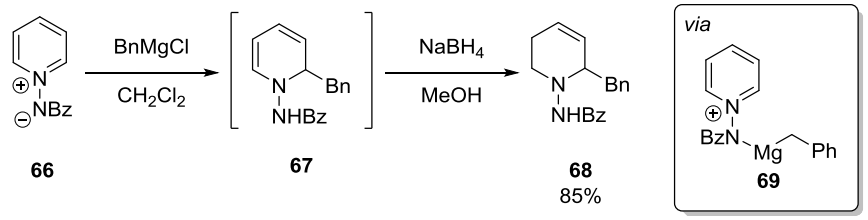
Akiba and coworkers developed an alternative strategy for the control of regioselectivity in the addition of Grignard reagents to pyridinium salts, without the requirement of blocking either of the two potential positions of nucleophilic attack. It was found that *N*-(*tert*-butyldimethylsilyl)pyridinium salt **63** showed a strong preference for attack at the 4-position, since the bulky TBS group blocked approach of the nucleophile for attack at the 2-position, affording 4-alkyldihydropyridine **64** in good yield, with regioselectivity of greater than 99% (**Scheme 1.14**).[28]



Scheme 1.14 *N-TBS-pyridinium salts for regioselective addition of Grignard reagents*

Further work by the group of Charette showed that *N*-iminobenzoylpyridinium ylids were also effective at directing addition to the 2-position of pyridinium salts, such as **66**, even for organometallic reagents that strongly favoured attack at the 4-position,[29] such as benzylmagnesium chloride, with a regioselectivity ratio of greater than 95:5 (**Scheme 1.15**).[30]

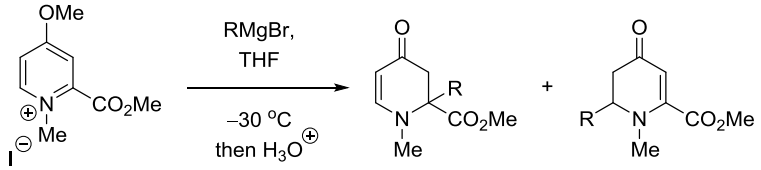
This was postulated to be due to coordination of the Grignard reagent to the exocyclic nitrogen of the *N*-iminopyridinium ylid **69**. The 1,2-dihydropyridine **67** thus formed were unstable with respect to aerobic oxidation, which necessitated their reduction with sodium borohydride to the corresponding tetrahydropyridine **68** to increase their stability.



66 **67** **68** 85% **69**

Scheme 1.15 *N-iminopyridinium ylid directed attack of Grignard reagents*

As an extension of their previous work on the ammonia-free Birch reduction of 4-methoxypyridinium salts (*vide supra*), in 2009 the Donohoe group reported a regioselective addition of organometallic nucleophiles to pyridinium salts (**Scheme 1.17**).[31] It was observed that in the case of *N*-methylpyridinium salt **70**, "harder" sp^3 Grignard reagents added selectivity to the more electron-deficient *C*-2 of the pyridinium salt **A**, whereas "softer" sp^2 and sp Grignard reagents, and organozinc reagents, gave exclusively the product of addition to *C*-6 **B**.

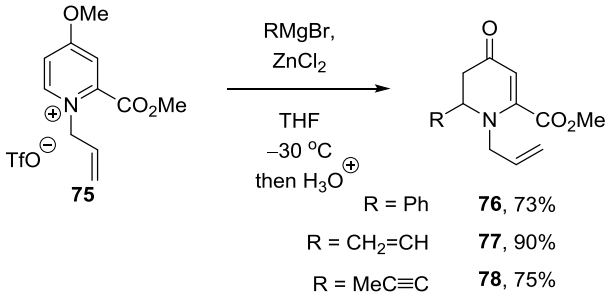


70

	A	**B**
R = Me	**71**, 89%	n/o
R = Et	**72**, 97%	n/o
R = CH_2=CH	n/o	**73**, 69%
R = MeC≡C	n/o	**74**, 60%

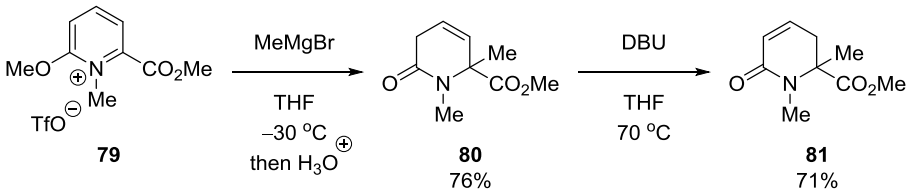
Scheme 1.17 *Regioselective addition of Grignard reagents to 4-methoxypyridinium salt* **70**

It was found that for a bulkier *N*-allyl group **75**, the regioselectivity of addition for sp^2 and sp Grignard reagents was significantly diminished, producing both regioisomers in low yield. However, by replacing the Grignard reagent with a softer organozinc reagent this problem could be overcome, yielding the 6-alkyl dihydropyridones in excellent yields as a single regioisomer (**Scheme 1.18**).



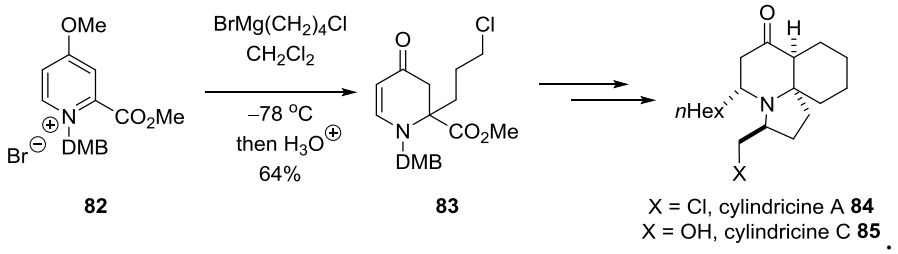
Scheme 1.18 *Regioselective addition of organozinc nucleophiles to pyridinium salt* **75**

This work was also extended to the regioisomeric 6-methoxypyridinium salt **79**, which could undergo addition at *C*-2 with alkylgrignard reagents to yield the dihydropyridone **80**, where the endocyclic double bond was found to lie exclusively out of conjugation with the carbonyl. Treatment of **80** with DBU in THF at 70 °C allowed isomerisation of the double bond to afford conjugated dihydropyridone **81** in good yield (**Scheme 1.19**).



Scheme 1.19 *Regioselective addition of MeMgBr to pyridinium salt* **79**

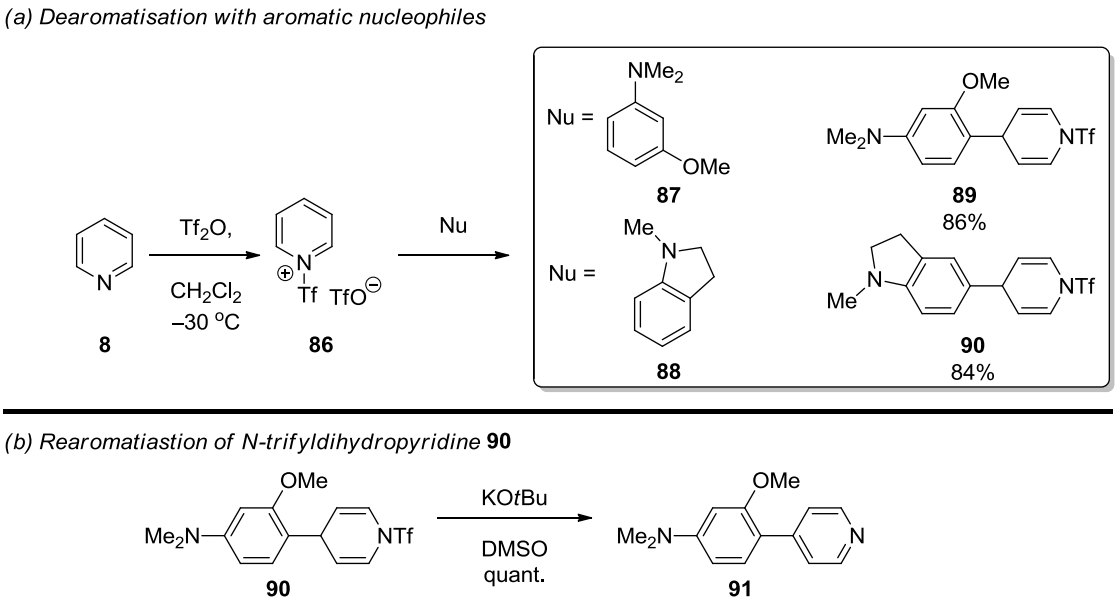
This work was also applied to the total synthesis of (±)-cylindricine C **85**, and a formal synthesis of (±)-cylindricine A **84**, both members of a large family of natural products that show a variety of biological activity, including against murine leukaemia and human solid tumour cell lines.[32] Thus, treatment of pyridinium salt **82** provided a convenient and regioselective synthesis of dihydropyridone **83**, setting up the required *C*-2 stereocentre for further elaboration into the natural products **84** and **85** (**Scheme 1.20**).[33]



Scheme 1.20 *Donohoe's synthesis of cylindricines A and B,* **84** *and* **85**

Although the majority of the work in the field of nucleophilic dearomatisation of pyridinium salts has revolved around the use of organometallic reagents as the nucleophile, seminal work

by Corey demonstrated that the activation of pyridines as the *N*-triflylpyridinium salt **86** enabled the addition of weaker, non-organometallic nucleophiles to afford a variety of dihydropyridines (**Scheme 1.21a**).[34]

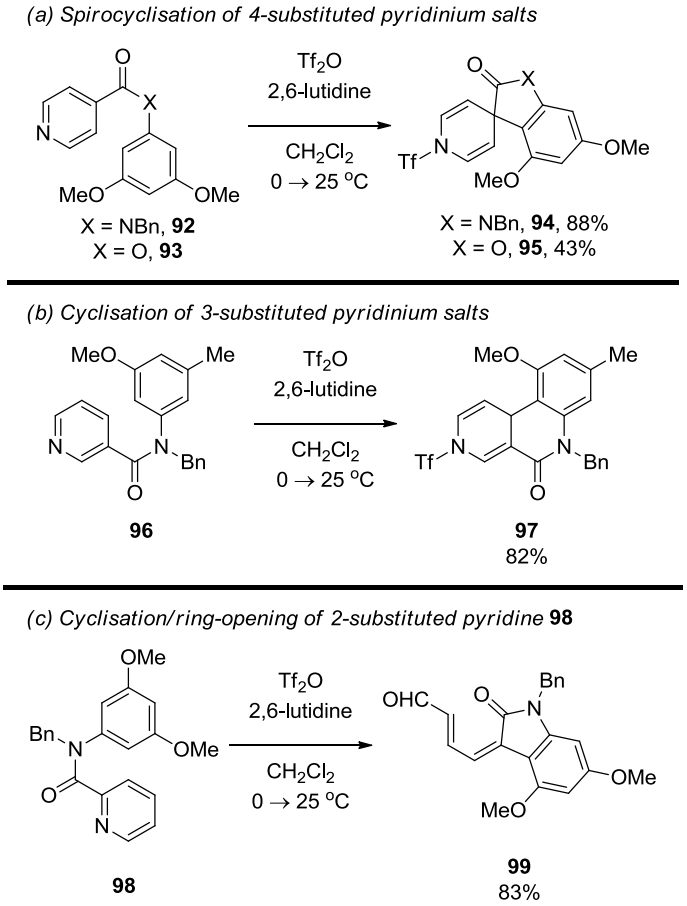


Scheme 1.21 *Corey's dearomatisation of N-triflylpyridines with aromatic nucleophiles*

The highly reactive nature of the *N*-triflylpyridinium electrophile **86** could be explained as a result of the strongly electron-withdrawing nature of the trifluoromethanesulfonyl group. This reaction also proved to be highly regioselective, with a strong preference for attack at the 4-position of the pyridine, presumably as a result of steric-crowding of the 2-position of the pyridinium salt by the *N*-SO_2CF_3 group. It is also noteworthy that these *N*-triflyldihydropyridines could be rearomatised to the corresponding pyridine by treatment with potassium *tert*-butoxide in DMSO at room temperature. Thus this methodology allows expedient access to 4-aryl substituted pyridines from the corresponding unsubstituted pyridine (**Scheme 1.21b**)

This work was expanded upon greatly by Clayden and coworkers, whereby spirocyclic dihydropyridines were prepared by the intramolecular trapping of *N*-triflylpyridinium salts bearing a pendant aromatic nucleophile (**Scheme 1.22**).[35] This methodology has proved to be particularly versatile, with the ability to incorporate amide, and ester linkers for the preparation of spirocyclic dihydropyridines (**Scheme 1.22a**). Clayden suggested that the high reactivity of tertiary amide linkers in this methodology was a result of their preference to

adopt the s-*cis* conformation, whereas those compounds with ester linkages reacted more slowly, presumably due to the less favourable nature of the required s-*cis* conformation in these substrates. The methodology could also be extended to compounds with tethered nucleophiles in other positions, with a nucleophile in the 3-position affording fused tricyclic product **97** (**Scheme 1.22b**), although positioning the pendant nucleophile in the 2-position of the pyridine resulted in a post-cyclisation ring-opening to yield the dienal **99** (**Scheme 1.22c**).

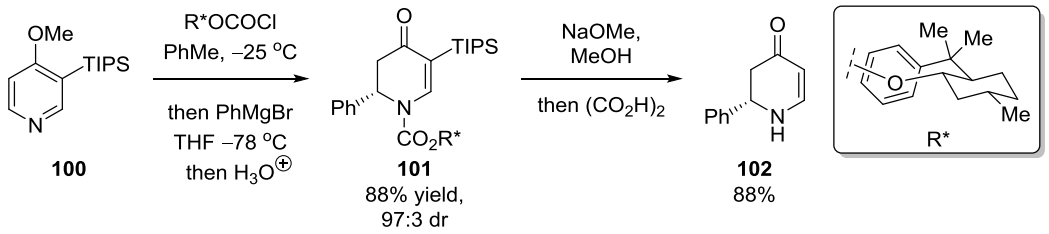


Scheme 1.22 *Clayden's dearomisation of pyridinium salts to spircoyclic dihydropyridines*

1.2.4 Stereoselective nucleophilic dearomatisation of pyridinium salts

Whilst many methods are known for the addition of nucleophiles to pyridinium salts, producing racemic dihydropyridines (*vide supra*), the synthesis of dihydropyridines (and their derivatives) as single enantiomers would clearly constitute a valuable tool for their application in synthesis. There exist a variety of methods to achieve this goal,[36] too numerous to mention in their entirety, although a number of important methods are discussed below.

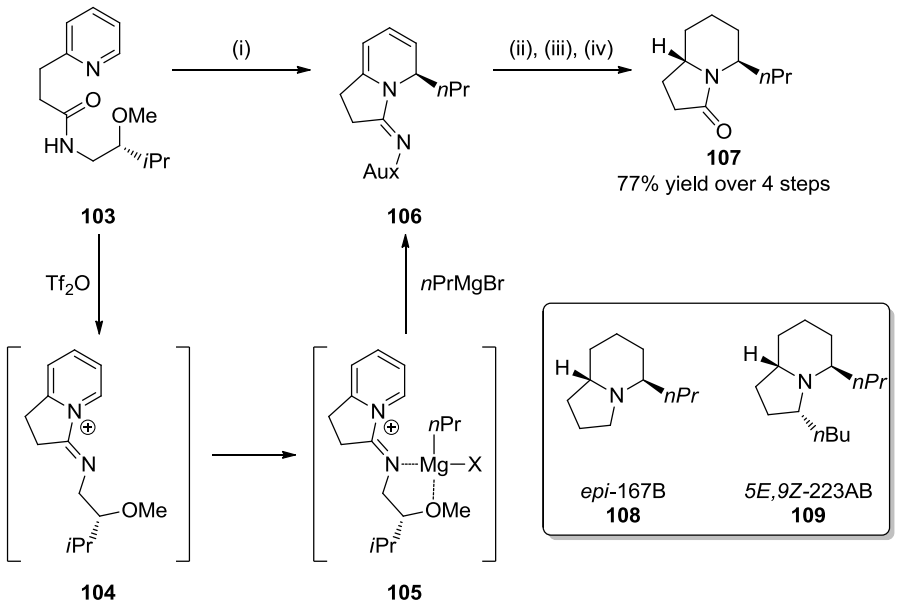
Comins first reported a chiral auxiliary based route for the asymmetric addition of Grignard reagents for the formation of enantioenriched dihydropyridones.[37] Use of an (−)-8-phenylmenthol moiety as part of the *N*-alkoxycarbonyl activating group for pyridine **100**, allowed for the formation of dihydropyridones with high diastereoselectivity. Treatment of 3-TIPS substituted pyridine **100** with PhMgCl after addition of the chiral alkoxycarbonyl chloride, afforded dihydropyridone **101** in an excellent 88% yield and 97:3 dr (**Scheme 1.23**). It is important to note that the presence of the TIPS group was necessary for maintaining high diastereoselectivity in this reaction, presumably due to its role in restricting rotation of the chiral auxiliary around the C-N bond. Indeed, X-ray crystallographic analysis revealed that π-stacking between the pyridinium salt and the phenyl group of the chiral auxiliary shielded one face of the pyridinium cation, favouring addition to the less hindered face, with the conformational preference reinforced by the presence of the TIPS group. Both the TIPS group and the chiral auxiliary could be removed in a subsequent one-pot process, and in high yield, by treatment of the dihydropyridone **101** with sodium methoxide to remove the chiral auxiliary, and then subsequently with oxalic acid to remove the silyl group (**Scheme 1.23**).



Scheme 1.23 *Comins' chiral auxiliary approach to chiral dihydropyridone* **102**

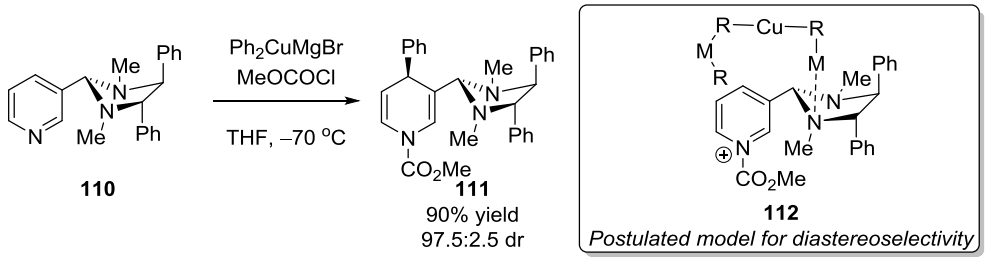
A multitude of other chiral auxiliaries have been developed for the synthesis of enantioenriched dihydropyridines and dihydropyridones. For example, Wanner and coworkers employed a chiral *N*-acylisoquinolinium species for the asymmetric addition of Grignard and organozinc reagents, forming enantioenriched dihydroisoquinolines, in moderate to good yield, and good to excellent diastereoselectivity.[38] Charette and coworkers have also developed a valine derived chiral auxiliary which can then participate in the reaction with a variety of Grignard reagents, and subsequently be used in the synthesis of a variety of indolizidinone products (**Scheme 1.24**).[39] This methodology provided the first method to synthesise dihydropyridines with a *C*-2 quaternary stereocentre, as a single

diastereomers and in high yields. The stereoselectivity observed was believed to arise as a result of coordination of the exocyclic nitrogen of pyridine-amidinium salt **104** with the incoming Grignard reagent **105**. Intermediate **107** was a known compound in routes to the *Dendrobatidae* alkaloids, isolated from the skin secretions of poison frogs, *epi*-167B **108** and 5*E*,9*Z*-223AB **109**.[40,41]



Scheme 1.24 *Charette's chiral auxiliary approach to indolizidine alkaloids*
Conditions: (i) Tf_2O, 2-ClPy, −20 °C (ii) *n*PrMgBr, CH_2Cl_2, −78 °C (iii) Pd/C, H_2, AcMe (iv) MeI, K_2CO_3, CH_2Cl_2, 40 °C then 2.5 M NaOH, Et_2O

Research has also been conducted on the use of chiral auxiliaries in the 3-position of pyridinium salts for the asymmetric addition of organometallic nucleophiles. In 1994, Alexakis and coworkers reported the use of chiral C_2-symmetric aminal chiral auxiliaries as a directing group for the addition of organocuprate reagents to *N*-acyloxy pyridinium salts.[42] Whilst Grignard reagents showed poor selectivity for 1,4-addition, giving a mixture of the the 4- and 6-substituted products, organocuprates were found to add with excellent regioselectivity, and high diastereoselectivity (**Scheme 1.25**).

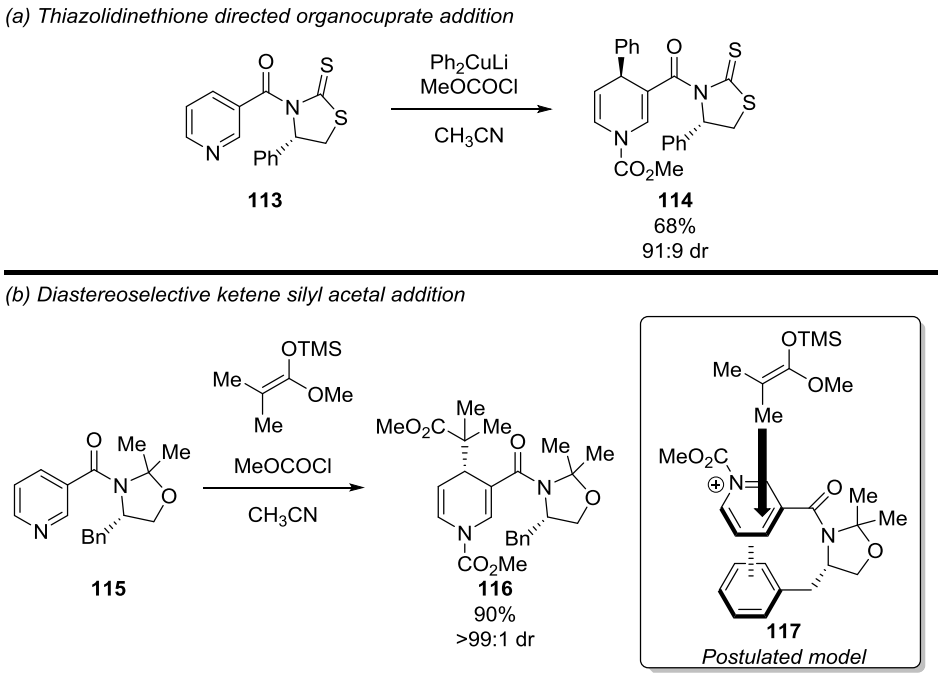


Scheme 1.25 *Aminal-directed diastereoselective addition of organocuprates to pyridine* **110**

It was postulated that the high diastereoselectivity was a direct result of coordination of one of the aminal nitrogens to the organometallic species, thus directing the attacking nucleophile to the same face of the pyridinium cation as depicted in model **112**.

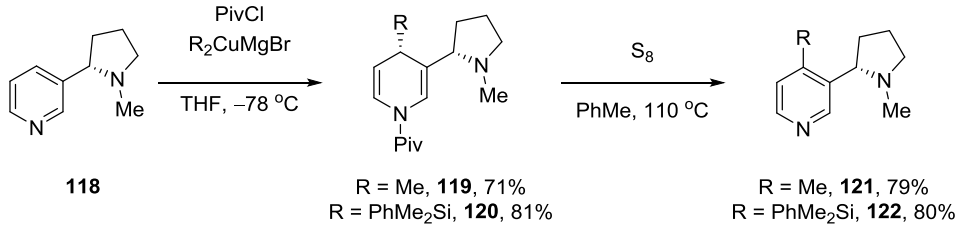
Another methodology that employed a chiral auxiliary in the 3-position of the pyridinium cation was developed by Yamada and coworkers.[43] In this case, the use of a thiazolidinethione auxiliary led to the formation of the 4-substituted dihydropyridine in moderate to high selectivity for addition at 4-position, and in diastereomeric ratios of up to 91:9, for the example of pyridine **113** with Ph_2CuLi (**Scheme 1.26a**).

A later study by Yamada found that the use of a *gem*-dimethyl oxazolidine chiral auxiliary led to greatly increased diastereoselectivity in the reaction of pyridine **115** with silylketene acetals (**Scheme 1.26b**).[44] This high selectivity was suggested to be as a result of a π-stacking interaction between the pyridinium cation, and the benzyl moiety of the chiral auxiliary **117**, thus greatly favouring attack on the *Si* face of the pyridinium cation. It should be noted however, that regioselectivity was still an issue in this methodology, with 1,6-addition contributing significantly to the product yield in solvents other than acetonitrile.



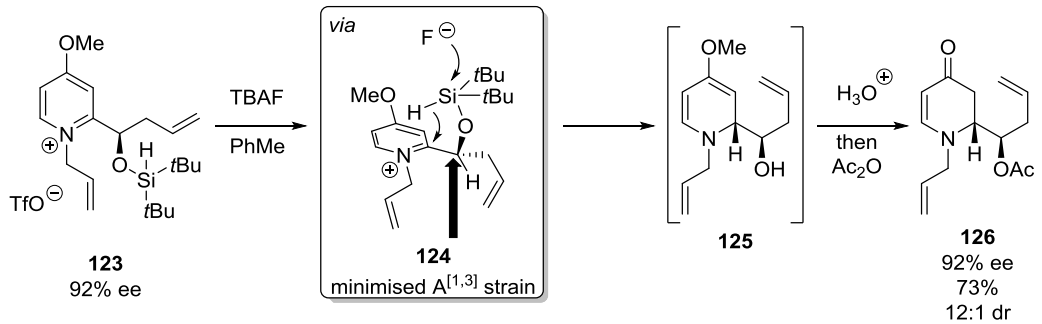
Scheme 1.26 *Yamada's chiral auxiliary approaches to dihydropyridines*

Whilst not strictly an approach to enantioenriched dihydropyridines, in an attempt to synthesise a variety of non-addictive nicotine derivatives, Comins and coworkers developed a regio- and diastereoselective addition of organocuprates to pyridinium salts derived from (*S*)-nicotine **118** (**Scheme 1.27**).[45] It was found that organocuprates added to **118** to yield single regio- and diastereoisomers, with the stereoselectivity observed to be directed by the chelation of the organocuprate to the lone pair of the pyrrolidine nitrogen. Both carbon and silicon-based cuprates were found to be amenable to this reaction, and could subsequently be reoxidised to the pyridine with the use of elemental sulfur.



Scheme 1.27 *Comin's diastereoselective addition of organocuprates to (S)-nicotine* **118**

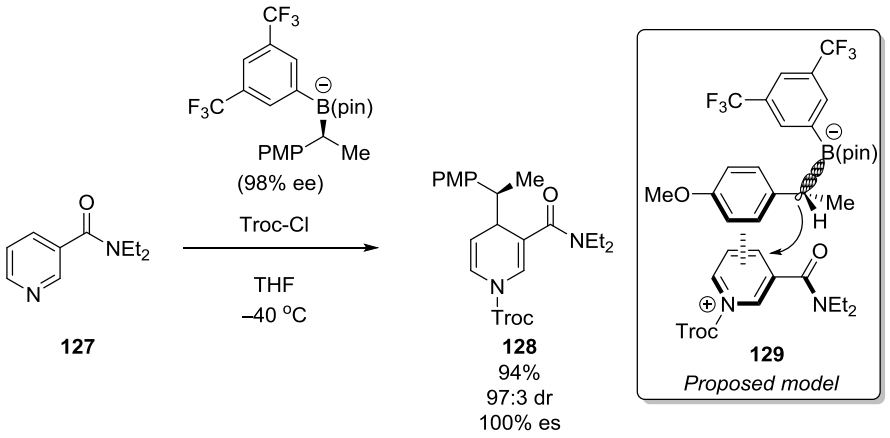
An innovative approach to dihydropyridones taken in the Donohoe group, which also relied on substrate control to impart diastereoselectivity, saw the use of a pendant alcohol to deliver one equivalent of hydride, thus reducing the pyridinium salt to the dihydropyridone upon hydrolysis (**Scheme 1.28**).[46] Thus, enantioenriched di-*tert*-butylsilane **123**, when treated with tetrabutylammonium fluoride, delivered hydride with excellent facial selectivity, affording, upon hydrolysis and subsequent acetylation of the free alcohol, the corresponding dihydropyridone **126** in good yield, with complete retention of ee, and in high dr.



Scheme 1.28 *Donohoe's diastereoselective intramolecular hydride delivery*

Aggarwal and coworkers have recently taken a different approach to the synthesis of enantioenriched dihydropyridines.[47] Instead of utilising pre-existing chiral functionality in a

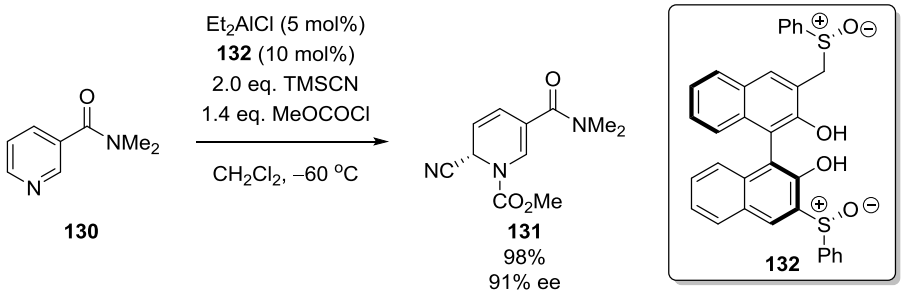
pyridinium salt, they developed an asymmetric addition of chiral boron-ate complexes to pyridinium salts formed *in situ* with 2,2,2-trichloroethyl chloroformate (Troc-Cl) (**Scheme 1.29**). These enantioenriched boron-ate complexes, were capable of adding to a variety of nicotine derivatives including **127**, producing dihydropyridine **128** in high yield, and excellent diastereo- and enantioselectivity.



Scheme 1.29 *Aggarwal's use of chiral boron-ate complexes for dihydropyridine synthesis*

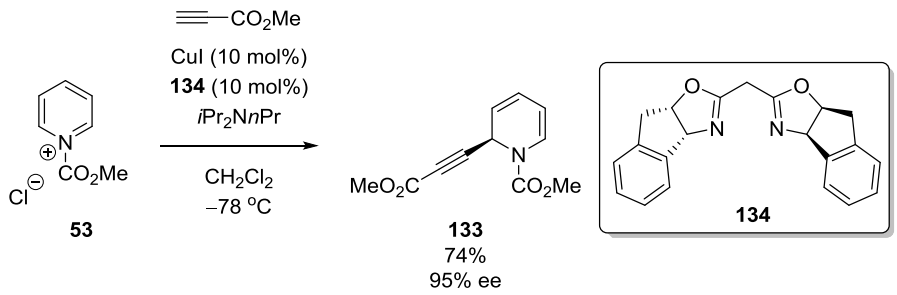
Aggarwal proposed a model for the enantioselectivity of addition whereby steric interactions between the boron-ate complex methyl group and the pyridinium side chain are avoided, whilst the approach is directed by a strong cation-π interaction between the incoming nucleophile and the pyridinium salt, through a transition state such as **129**.

Whilst there are numerous methods for the stereoselective formation of dihydropyridines and dihydropyridines which rely on substrate control, the number of catalytic asymmetric methods for their synthesis is relatively few. In work reported by Shibasaki, nicotinamides such as **130** undergo an efficient Reissert reaction with TMSCN, with high enantioselectivity imparted by a complex of diethylaluminium chloride with *bis*-sulfoxide **132** (**Scheme 1.30**).[48]



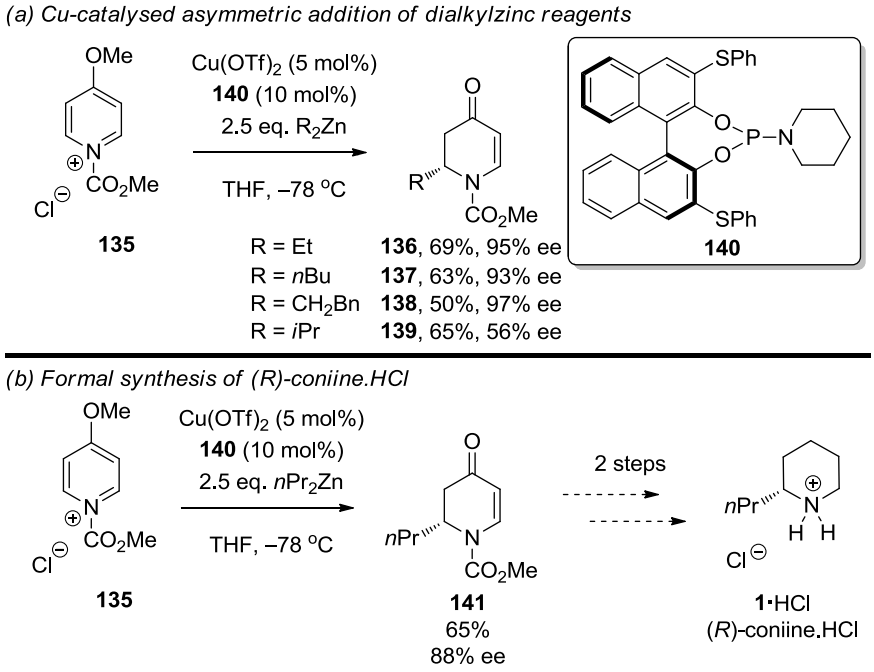
Scheme 1.30 *Shibasaki's enantioselective Reissert reaction*

A further example of catalytic asymmetric addition to pyridinium salts was published by Ma and coworkers in 2007.[49] An *N*-acylpyridinium salt **53**, generated *in situ* from pyridine **8** and methylchloroformate was dearomatised by the addition of alkynes, with stereocontrol provided by copper(I) iodide and chiral oxazoline ligand **134**. Addition at *C*-4 would be the expected outcome for addition by a "soft" organocuprate nucleophile, whereas *C*-2 addition was observed in this case, further highlighting the fact that it can be difficult to predict the exact regioselectivity of addition to pyridinium salts (*vide supra*). This method afforded dihydropyridines such as **133** in high yields and excellent enantioselectivities (**Scheme 1.31**).



Scheme 1.31 *Ma's asymmetric addition of alkynes to pyridinium salts*

A significant development in this area was the discovery of a catalytic asymmetric addition of organozinc reagents to *N*-acylpyridinium salts by Feringa and coworkers (**Scheme 1.32**).[50]

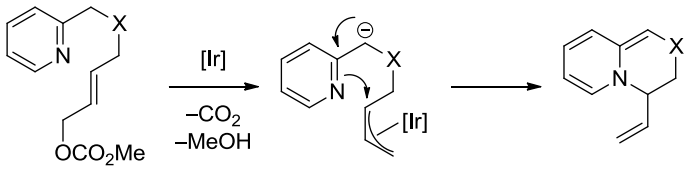


Scheme 1.32 *Feringa's Cu-catalysed asymmetric addition of organozinc reagents*

In this work, dialkylzinc reagents add in good yields and excellent enantioselectivities to 4-methoxypyridinium salts such as **135**, in the presence of $Cu(OTf)_2$ and a chiral phosphoramidite ligand **140** (**Scheme 1.32a**), affording enantioenriched dihydropyridones **136-139**. To demonstrate the synthetic utility of this protocol, Feringa applied this methodology to the formal synthesis of (*R*)-coniine·HCl **1**·HCl (**Scheme 1.32b**), in 3 steps, compared to the previous 8 step synthesis reported by Comins and coworkers.[51]

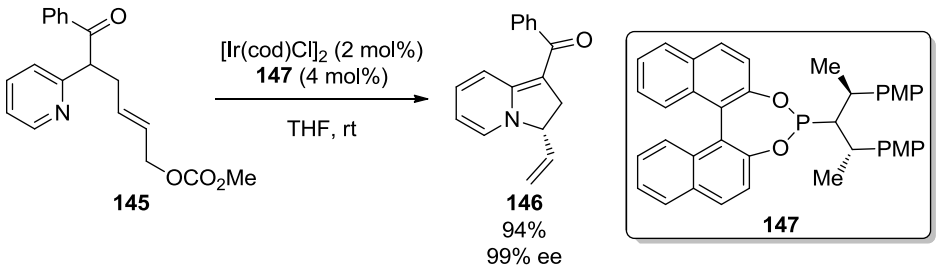
Although not strictly a nucleophilic dearomatisation process, You and coworkers have also developed a catalytic asymmetric dearomatisation of pyridines, utilising an Ir-catalysed allylic amination reaction (**Scheme 1.33a**).[52] In this process, activation of an allylic carbonate **142** by oxidative addition of Ir^I affords the η^3-allyl complex, which upon deprotonation by methoxide base yields α-deprotonated pyridine **143**, which may then cyclise onto the metal-allyl species, thus forming dearomatised pyridine **144**. For example, treatment of pyridine **145** with $[Ir(cod)Cl]_2$ and chiral phosphoramidite ligand **147** in THF at room temperature afforded dearomatised compound **146** in an outstanding 94% yield and 99% ee (**Scheme 1.33b**). This methodology could tolerate a wide variety of functionality on both the pyridine ring, and in the α-position, including esters, ketones, ethers, and halides, in both the 4- and 5-position of the pyridine ring.

(a) Proposed mechanism for dearomatising allylic amination of pyridines **142**



142 **143** **144**

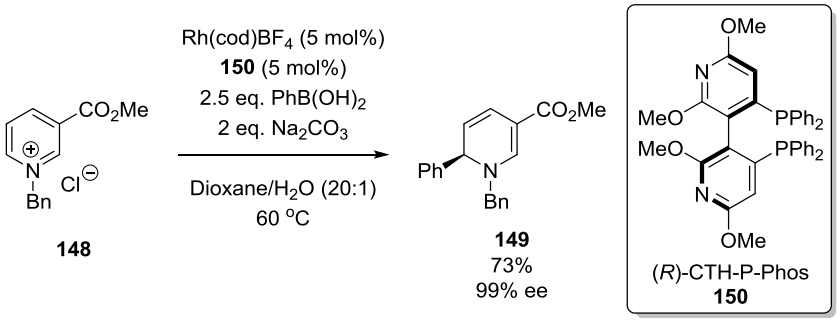
(b) Asymmetric dearomatising allylic amination of pyridine **145**



145 **146** 94% 99% ee **147**

Scheme 1.33 *You's dearomatising allylic amination of pyridines*

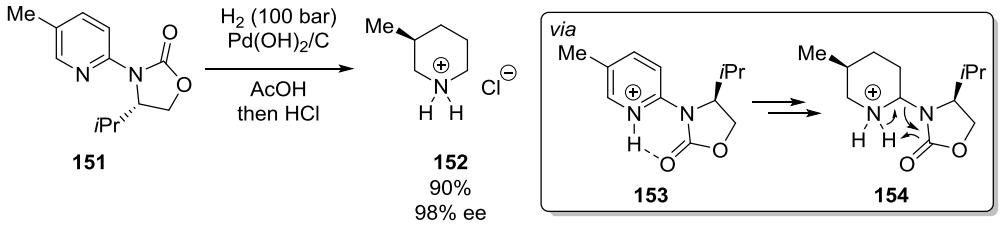
In 2011, the group of Nadeau reported the asymmetric addition of arylboronic acids to pyridinium salts, catalysed by a chiral [Rh^I] complex (**Scheme 1.34**).[53] A range of boronic acids could be added to pyridinium salt **148** in moderate to high yield, with excellent enantioselectivity. For example, in the presence of the chiral ligand (*R*)-CTH-P-Phos **150**, phenylboronic acid added to *N*-benzylpyridinium salt **148** in 73% yield and 99% ee.



Scheme 1.34 *Nadeau's asymmetric addition of arylboronic acids to pyridinium salt* **148**

1.2.5 Stereoselective reduction of pyridines

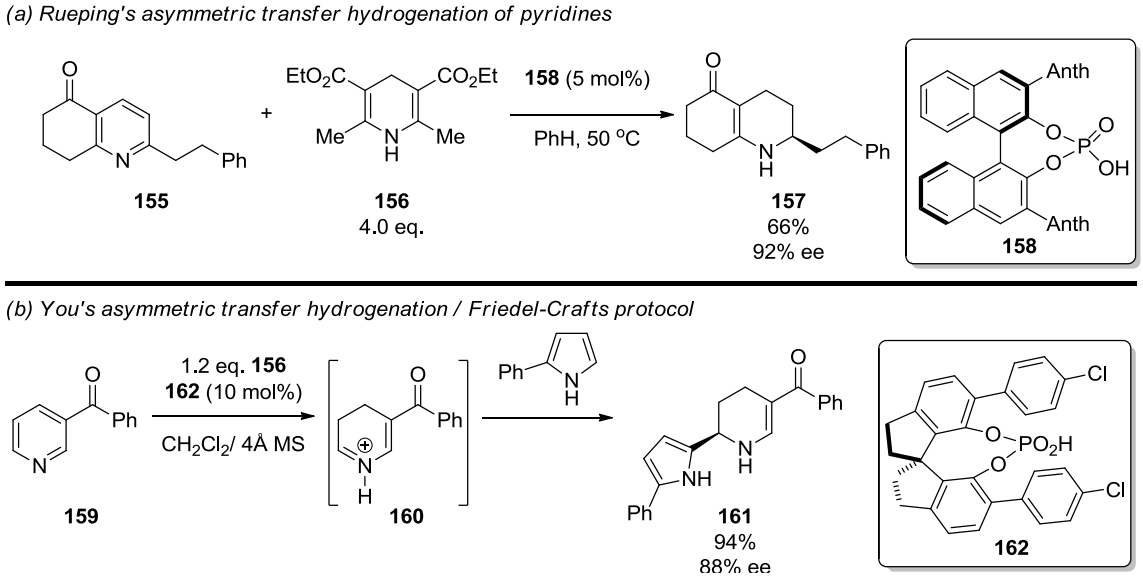
A related area for the synthesis of chiral pyridine derivatives is the asymmetric reduction of pyridines and pyridinium salts. An early report by Glorius showed that the use of an oxazolidinone chiral auxiliary in the pyridine 2-position, in compounds such as **151** afforded the corresponding piperidinium salt **152** in high yield and enantioselectivity (**Scheme 1.35**). The observed enantioselectivity was proposed to be a result of efficient hydrogen-bonding in the protonated intermediate **153**, shielding one face of the pyridinium, with the chiral auxiliary subsequently lost, affording the piperidinium salt **152** upon reduction of the iminium salt thus formed.



Scheme 1.35 *Chiral auxiliary-directed asymmetric hydrogenation of pyridines*

Whilst there are numerous other methods for the asymmetric dearomatisation of pyridines using hydrogen,[54-59] more recently examples of nucleophilic reduction affording tetrahydropyridines have also been reported. Rueping and coworkers reported the use of

Hantzsch ester **156** in the presence of a catalytic amount of chiral phosphoric acid **158** for the dearomatisation of pyridine **155**, affording tetrahydropyridines such as **157** in moderate to high yield, and high enantioselectivity (**Scheme 1.36a**).[60]



Scheme 1.36 *Chiral phosphoric acid-directed transfer hydrogenation of pyridines*

This work has also been expanded on by You and coworkers, who have developed a strategy to trap the iminium intermediate **160** with heterocyclic nucleophiles such as 2-phenylpyrrole in high yields and good enantioselectivity (**Scheme 1.36b**).

1.3 Dearomatisation of Furans

In comparison to the dearomatisation of pyridines and pyridinium salts, less attention has been paid to the dearomatisation of furans, whilst keeping the furan ring intact, especially in the field of nucleophilic addition to furans. However, it is clear that dihydro- and tetrahydrofurans are key moieties in the realm of organic synthesis, and as such novel methodologies for their synthesis are of great value.

1.3.1 The THF and dihydrofuran motifs in natural products and biologically active compounds

The tetra- and dihydrofuran motifs are found in a wide range of natural products and other biologically active compounds (**Figure 1.3**). There are numerous examples of natural products containing these important functionalities, including the halogenated secondary

metabolite *trans*-kumausyne **163**, isolated from red algae of the genus *Laurencia*;[61] autocystin A **164**, a dihydrofuro[3',2':4,5]furo[3,2-b]xanthenone isolated from the microfungus *Aspergillus ustus* related to the aflatoxin family of natural products;[62] and mitochondrial ATP synthetase inhibitor citreoviridin **165**, isolated from a number of *Penicillium* species, and responsible for epidemics of cardiac beriberi in East Asia.

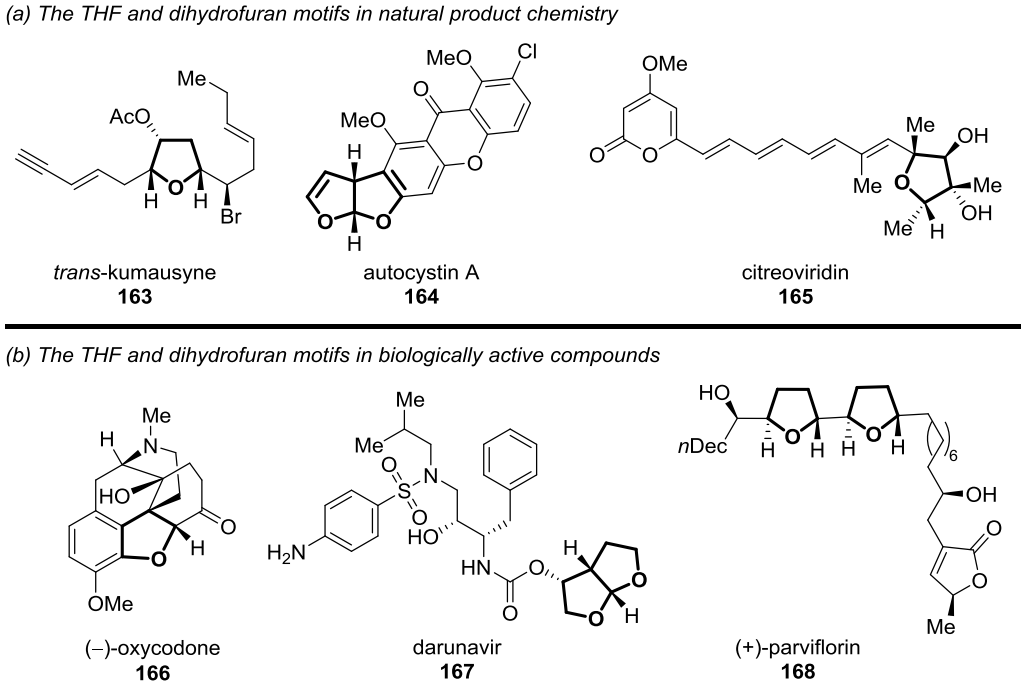


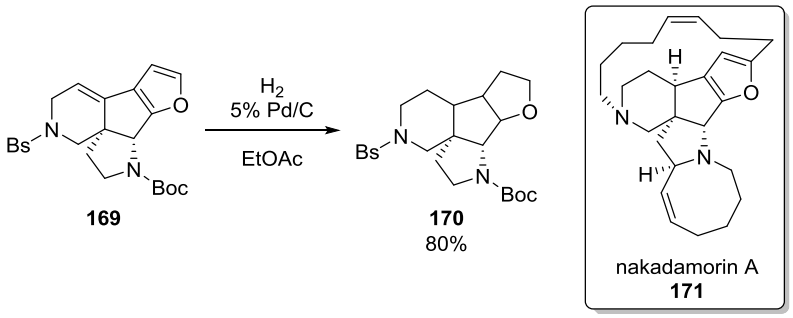
Figure 1.3 *Tetra- and dihydrofuran natural products and biologically active molecules*

These structures are also prevalent in a number of "blockbuster" drugs, and agrichemical products. For example, the semi-natural product (−)-oxycodone **166** is used for the relief of moderate to severe acute and chronic pains;[63] darunavir **167** is a protease inhibitor indicated in the treatment of infection with Human Immunodeficiency Virus;[64] and (+)-parviflorin **168**, isolated from *Asimina parviflora*, which shows remarkably selective cytotoxicity against certain human solid tumours, as well as pesticidal activity.[65]

1.3.2 Reductive dearomatisation of furans

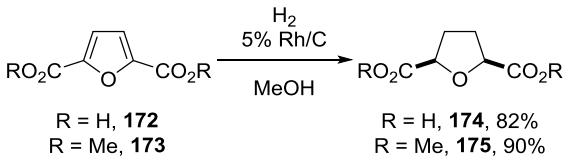
Complete reduction of furans to the corresponding tetrahydrofuran can be accomplished by hydrogenation over a variety of catalysts. In 1907 Padoa and coworkers reported the hydrogenation of furfural over nickel at 190 °C, affording a mixture of 2-methylfuran, 2-methyltetrahydrofuran and pentan-2-ol.[66] Other catalysts that have been used for the

hydrogenation of furan derivatives, include Raney nickel,[67] Pd,[68] PdO,[69] PtO_2,[70] Os,[71] and Rh.[72] Despite the harsh conditions initially developed for the hydrogenation of furans, they can also be reduced under remarkably mild conditions. In their studies towards the synthesis of nakadamorin A **171**, Nakagawa and coworkers observed the reduction of tetracyclic furan **169** to the corresponding THF **170** in 80% yield, whilst attempting the reduction of the tetrahydropyridine moiety (**Scheme 1.37**).



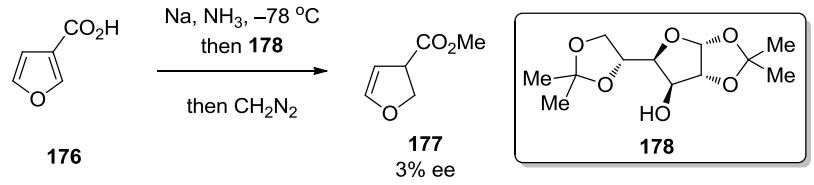
Scheme 1.37 *Unexpected furan hydrogenation in studies towards nakadamorin A* **171**

The use of catalytic rhodium for the hydrogenation of furans appears to avoid the problem of hydrogenative ring-opening of furans, and also affords tetrahydrofurans in a highly *cis*-selective fashion.[73] For example, the hydrogenation of furan-2,5-dicarboxylic acid **172** and its ester derivative **173** both proceed in excellent yield with sole formation of the *cis* isomer during hydrogenation with Rh/C (**Scheme 1.38**).[74] It is noteworthy that using Raney nickel, the maximum yield reported for this process is only 48%.[75]



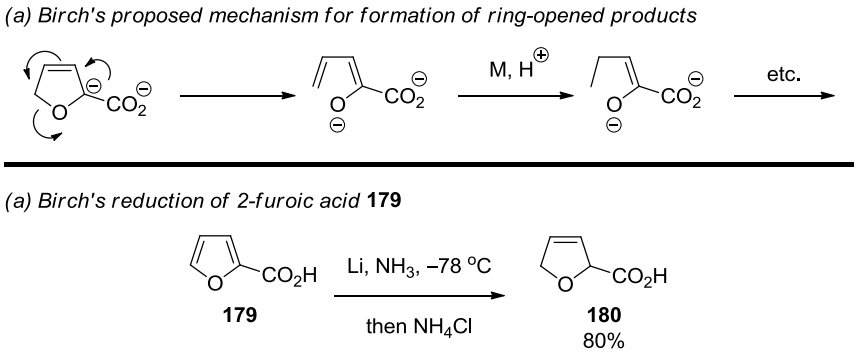
Scheme 1.38 *Rh-cataylsed reduction of furan-2,5-dicarboxylic acid derivatives*

Although more electron-rich furans are resistant to dissolving metal reduction,[2] Birch reduction of 3-furoic acid **176** was first reported by Kinoshita and coworkers in 1975. Treatment of **176** with sodium in liquid ammonia, followed by quenching with glucofuranose **178**, afforded 2,3-dihydrofuran **177** (after esterification), in 3% ee (**Scheme 1.39**).[76]



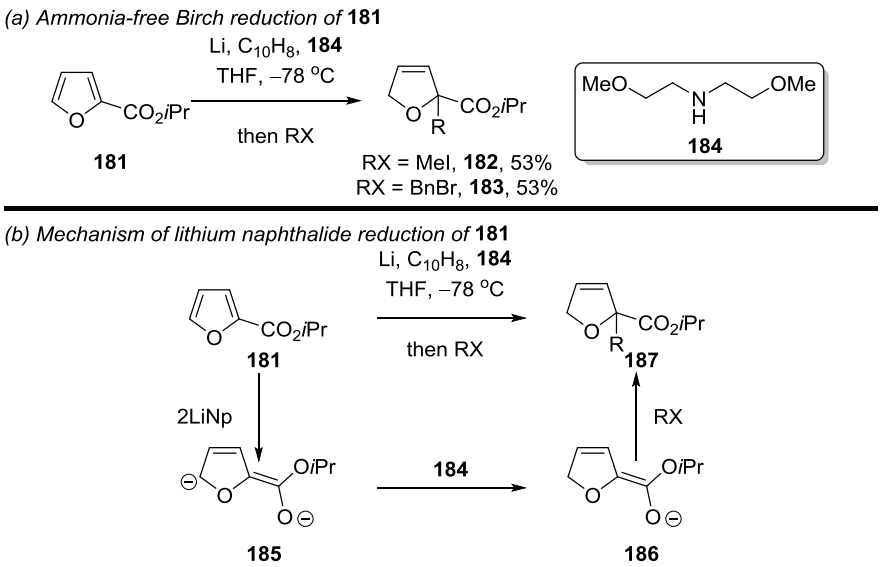
Scheme 1.39 *Kinoshita's attempt at asymmetric reduction of furan* **176**

Birch reported that the yield of this process was low due to the formation side products formed by electrocyclic ring-opening (**Scheme 1.40a**).[77,78] Quenching the reduction of 2-furoic acid **179** by lithium with methanol or water, afforded mixtures including ring-opened products, whereas rapid addition of **179** to a solution of Li in NH_3, followed by quenching with NH_4Cl, afforded 3,4-dihydrofuran **180** in high yield (**Scheme 1.40b**).



Scheme 1.40 *Birch's reduction of 2-furoic acid* **179**

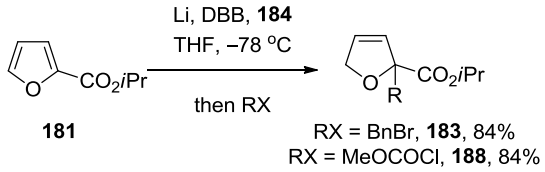
In 2000, Donohoe and coworkers reported the use of lithium metal with naphthalene as an electron carrier in THF as a method for the dissolving metal reduction of heteroaromatic compounds (**Scheme 1.41**).[79]



Scheme 1.41 *Donohoe's ammonia-free Birch reduction of furan* **181**

For example, furoic ester **181** could be reduced with lithium naphthalide, in the presence of $NH(CH_2CH_2OMe)_2$ (BMEA) **184**, then quenched with different electrophiles to afford alkylated dihydrofurans in moderate yields (**Scheme 1.41a**). The presence of BMEA **184** was desirable due to its decreased nucleophilicity relative to $LiNH_2$ in a typical Birch reduction, and its ability to protonate the dianion **184** formed during the reduction, but not the resultant enolate **186** (**Scheme 1.41b**), allowing it to be trapped with a range of nucleophiles.

A further improvement to this protocol was developed by Donohoe and coworkers, whereby naphthalene was replaced by di-*tert*-butylbiphenyl (DBB).[80] Treatment of heteroaromatic compounds with lithium metal, DBB, and BMEA **184** led to significant increases in yield relative to the use of naphthalene. For example, treatment of furan **181** under the reaction conditions, followed by quenching with benzyl bromide afforded alkylated dihydrofuran **183** in 84% yield, a yield also achieved in the acylation of furan **181** with methyl chloroformate (**Scheme 1.42**).



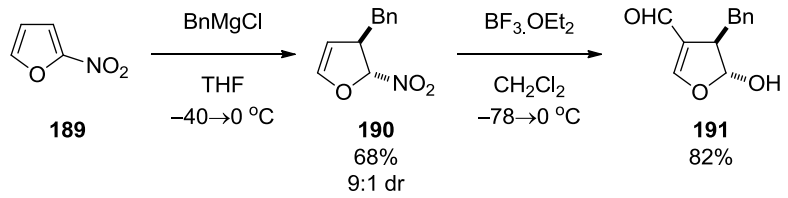
Scheme 1.42 *The use of DBB as an electron-carrier in the reduction of furan* **181**

1.3.3 Nucleophilic dearomatisation of furans

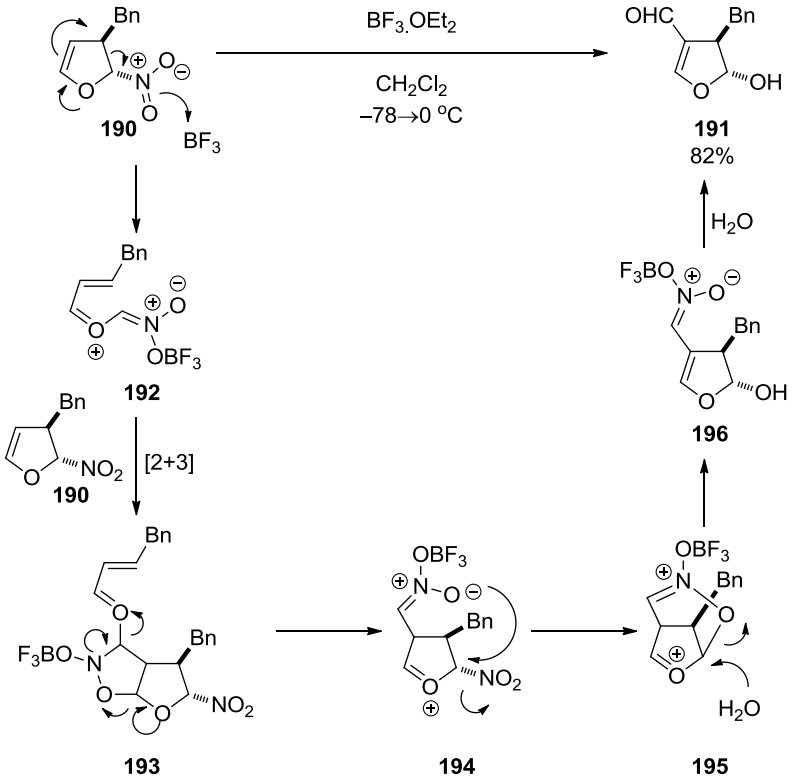
In comparison to pyridines the number of examples of addition of nucleophiles to furans is somewhat limited, presumably as a result of the electron-rich nature of the furan moiety. There are a number of examples instead of nucleophilic substitution reactions of furans, whereby the presence of a leaving group on the furan itself (often also the activating group), or on the incoming nucleophile (a vicarious nucleophilic substitution) allows for the formation of substituted furans.[81-84] However, limited examples do exist of the nucleophilic dearomatisation of furans containing electron-withdrawing groups to promote the addition of nucleophilic species (*vide infra*).

In further comparison to pyridine, where there are extensive examples of the addition of Grignard reagents to pyridinium salts, there are only a few examples of addition of Grignard reagents to furans. Hwu and coworkers reported the addition of Grignard reagents to 2-nitrofuran **189** during their synthesis of multi-functionalised dihydrofurans.[85,86] Treatment of 2-nitrofuran **189** with an appropriate Grignard reagent, followed by addition of boron trifluoride diethyl ether complex, afforded the 3-formyl-5-hydroxy-2,3-dihydrofurans **191** in moderate yields over two steps (**Scheme 1.43a**). The mechanism for the second step of this process involves ring opening of the dihydrofuran **190**, [2+3]-cycloaddition with another equivalent of **190**, loss of aldehyde, elimination of nitrite to form **195**, hydrolytic ring opening of the bicycle **195**, and hydrolysis of the formed nitronate **196** (**Scheme 1.43b**).

(a) Hwu's Grignard addition route to polysubstituted 2,3-dihydrofurans



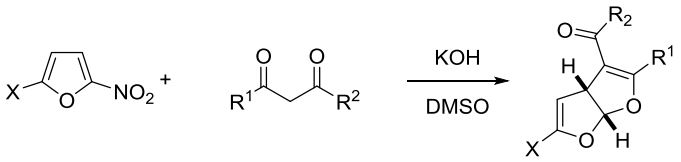
(b) Proposed mechanism for the formation of **191**



Scheme 1.43 *Addition of Grignard reagents to 2-nitrofuran* **189** *and subsequent modification*

Makosza and coworkers reported an interesting route to the synthesis of dihydrofuro[2,3-b]furans **202-207** that employed a novel dearomatisation, rearomatisation and cyclisation process (**Scheme 1.44a**).[87] Addition of a 1,3-dicarbonyl to nitrofuran **197**, followed by elimination of nitrite, afforded 3-substituted furan enolate **209**, which then underwent further cyclisation (either *via* a 6π-electrocyclisation process, or a disfavoured 5-endo-trig cyclisation) to afford the [5,5]-fused ring system **202** (**Scheme 1.44b**). This methodology could be applied to a small range of 1,3-diketone nucleophiles, although in the case of unsymmetrical dicarbonyls the regioselectivity was low.

(a) Makosza's dearomatiastion of furans with 1,3-diketones

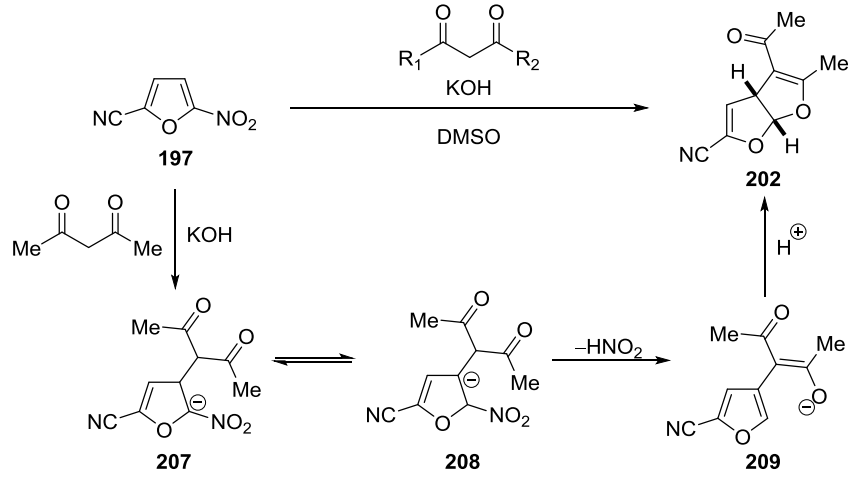


X = CN, **197**
X = CO_2Me, **198**

R^1,R^2 = Me, **199**
R^1,R^2 = $(CH_2)_3$, **200**
R^1 = Me, R^2 = Ph, **201**

X	R^1, R^2	Yield	
CN	Me, Me	75%	**202**
CN	$(CH_2)_3$	72%	**203**
CN	Me, Ph	52%	**204**
	Ph, Me	34%	**205**
CO_2Me	Me, Me	58%	**206**

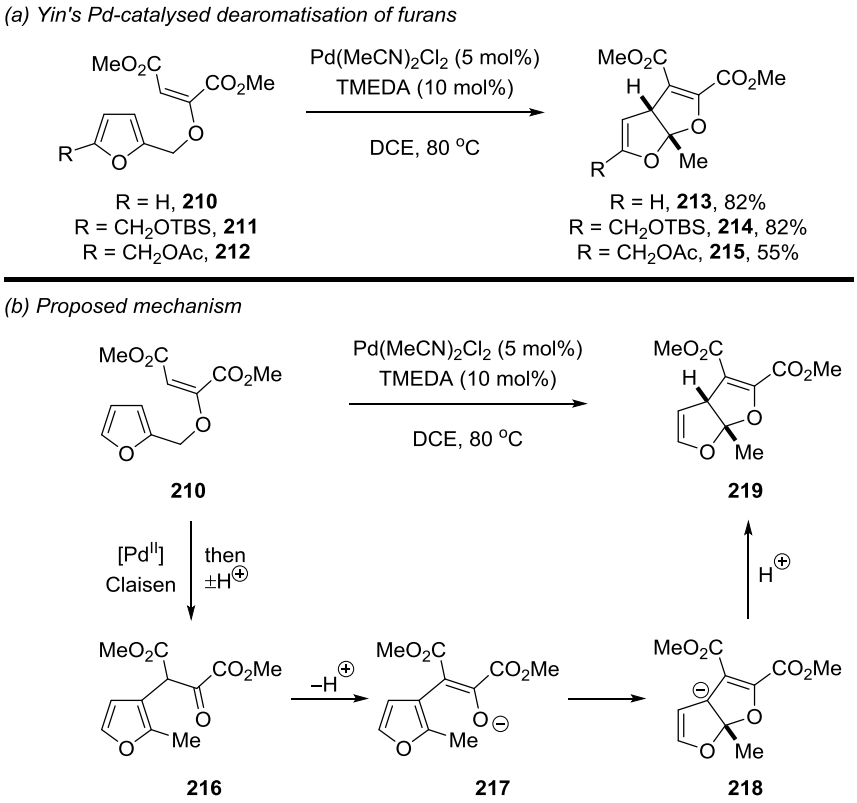
(b) Proposed mechanism



Scheme 1.44 *Makosza's dearomatisation of electron-deficient furans with 1,3-diketones*

In 2012, Yin and coworkers developed a similar methodology to that reported by Makosza for the formation of dihydrofurofurans, whereby electron-deficient vinyl ethers such as **210-212** could undergo a Pd-catalysed Claisen rearrangement to form the required enolate for a dearomatising cyclisation, either *via* conjugate addition or a 6π-electrocyclic ring closure (**Scheme 1.45**).[88] This reaction showed a much broader substrate scope, and did not require the presence of an electron-withdrawing group in the 2-position of the furan (as exemplified

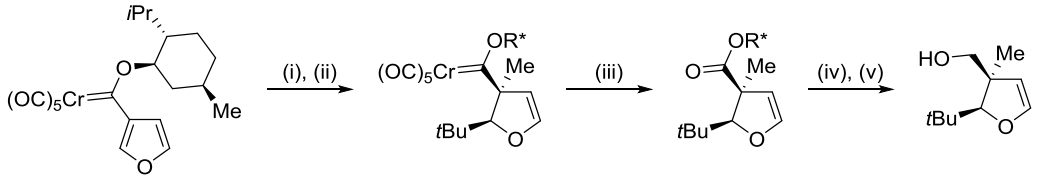
by the cyano and carboxymethyl functionality in **Scheme 1.44a**) to facilitate cyclisation, presumably due to the requirement for vicinal ester groups on the vinyl ether, and allowed formation of a wide range of dihydrofurofurans in moderate to high yield.



Scheme 1.45 *Yin's Pd-catalysed Claisen rearrangement/dearomatisation of furans*

1.3.4 Stereoselective nucleophilic dearomatisation of furans

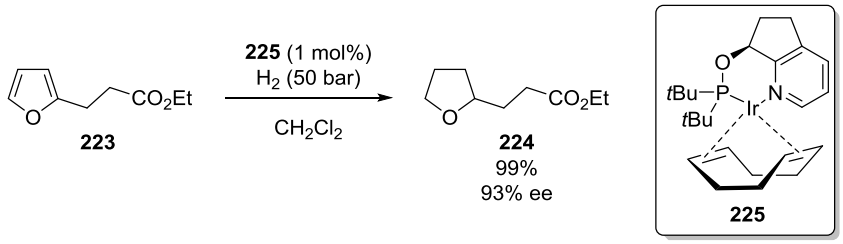
To the best of our knowledge, only one example existed of a stereoselective addition of a nucleophilic species to a neutral furan resulting in dearomatisation. In 2003, Barluenga and coworkers reported the dearomatisating addition of organolithium reagents to (menthyloxy)(3-furyl)chromium carbene complexes as a method for diastereoselective formation of 2,3-dihydrofurans.[89] Addition of *t*BuLi to furan **219** in Et_2O at −80 °C, followed by trapping of the lithiated species with MeOTf afforded the corresponding dearomatised product **220** in 66% yield and 84:16 dr (**Scheme 1.46**). The chromium carbene **220** could be cleaved by stirring in hexane under air, furnishing the ester **221** in 78% yield. Subsequent reduction of the ester gave the alcohol **222** in 90% yield, with an enantiomeric excess of 78% as measured by chiral Mosher's ester analysis.



Scheme 1.46 *Barluenga's asymmetric addition of organolithium reagents*
Conditions: (i) *t*BuLi, Et_2O, −80 °C (ii) MeOTf, −80 °C→rt (iii) air, hν, hexane (iv) $LiAlH_4$, THF, 0 °C→rt (v) $MeOH/H_2O$, NaCl

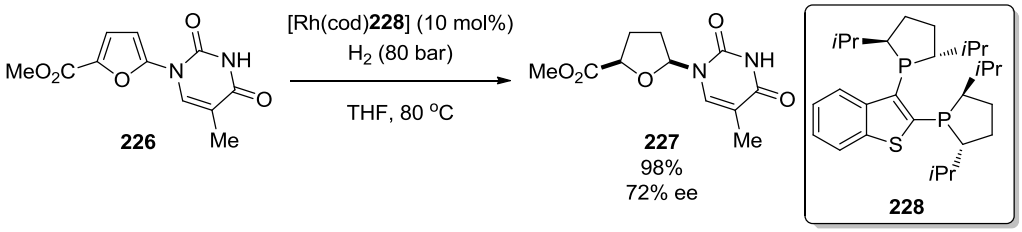
1.3.5 Stereoselective reduction of furans

A number of methods are available for the stereoselective reduction of furans. Pfaltz and coworkers reported an Ir-catalysed hydrogenation of furans utilising an Ir^I catalyst with bulky phosphinite ligand **225** (**Scheme 1.47**).[90] A number of furans were hydrogenated under these conditions, including **223**, affording the THF **224** in near-quantitative yield and 93% ee.



Scheme 1.47 *Pfaltz's asymmetric hydrogenation of furans*

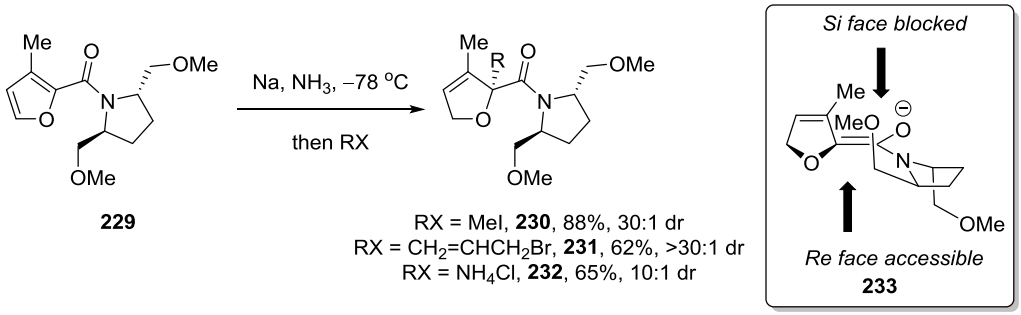
One other method for the asymmetric hydrogenation of 2,5-substituted furans was reported by Albert and coworkers in 2006.[91] By employing [Rh(cod)**228**]BF_4 catalyst, under a 90 bar atmosphere of hydrogen, it was possible to selectivity hydrogenate the furan moiety of the thymine-substituted furan without reduction of the thymine motif, in an excellent 98% yield, and moderate ee of 72%, as a single diastereomer (**Scheme 1.48**).



Scheme 1.48 *Albert's asymmetric hydrogenation of furan* **226**

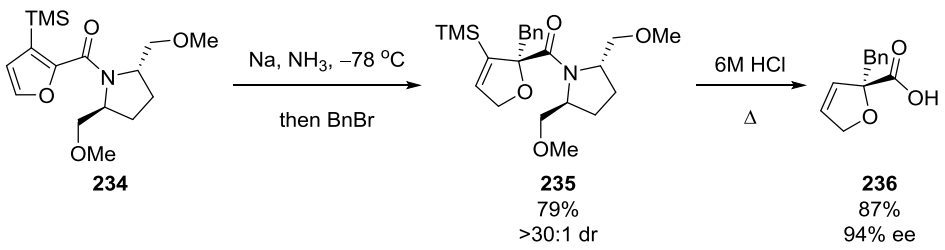
Donohoe and coworkers employed a chiral auxiliary approach to the stereoselective partial reduction of furans.[92] Use of the C_2-symmetric bis(methoxyphenyl)pyrrolidine chiral

auxiliary in furan **229**, allowed Birch reduction using sodium in liquid ammonia. The enolate thus formed could then be quenched with a variety of electrophiles, affording the products **230-232** in high diastereoselectivity (10:1→>30:1) (**Scheme 1.49**). A stereochemical model **233** was proposed whereby the *E*-enolate was formed preferentially (due to unfavourable [$A^{1,3}$]-strain in the *Z*-enolate), and subsequently the electrophile adds to the least hindered face. It is important to note that the methyl group in the 3-position was necessary for efficient asymmetric induction, with a dr of only 61:39 when this was replaced with a proton.



Scheme 1.49 *Donohoe's chiral auxiliary-based stereoselective Birch reduction of furan* **229**

Although this method provided access to chiral furoic acid derivatives in good yield and excellent diastereoselectivity, it did suffer from the drawback of the requirement for a methyl group in the 3-position of the furan. Subsequent replacement of the methyl group with a trimethylsilyl group allowed formation of chiral furoic acid derivatives unsubstituted in the 3-position, once the trimethylsilyl group had been cleaved (**Scheme 1.50**).[93] For example, reduction of 3-silylfuran **234** with sodium in liquid ammonia, followed by addition of benzyl bromide afforded the benzylated 3,4-dihydrofuran **235** in 79% yield, and greater than 30:1 diastereoselectivity. Treatment of **235** with 6 M HCl allowed for both deprotection of the vinyl silane functionality, and hydrolysis of the chiral auxiliary to yield dihydrofuroic acid **236** in 87% yield, with excellent enantioselectivity of 94%.

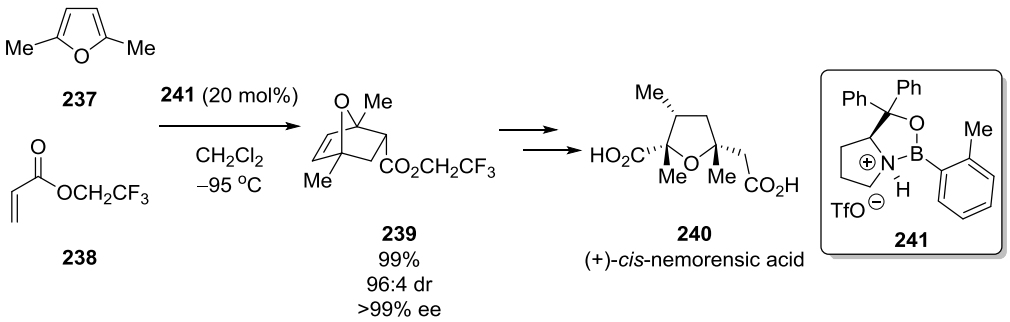


Scheme 1.50 *Donohoe's synthesis of 3-unsubstituted chiral furoic acid* **234**

1.3.6 Other methods of dearomatisation

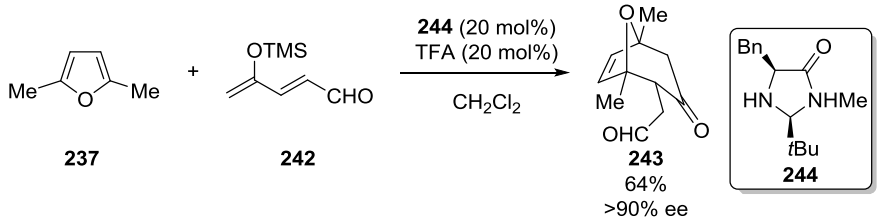
Aside from reduction and nucleophilic dearomatisation processes, a number of other methods are also available for the dearomatisation of furans. Many of these methods however do not leave the five-membered ring intact.

One particularly popular method for the dearomatisation of furan is its use in cycloaddition reactions.[94-98] Indeed, Diels-Alder reactions utilising furan as a 4π component constitute some of the earliest known examples of this type of reaction.[99] Diels-Alder reactions with furans give access to 7-oxanorbornenes as an initial product, and these provide valuable synthetic intermediates that can be further manipulated to form the desired product. An impressive example of the Diels-Alder reaction of a furan with an alkene can be observed in Ryu's synthesis of (+)-*cis*-nemorensic acid **240**.[100] Reaction of 2,5-dimethylfuran **237** with 2,2,2-trifluoroacrylate **238** in the presence of chiral oxaborolidium catalyst **241** afforded the corresponding Diels-Alder adduct **239** in an outstanding 99% yield, 96:4 endo:exo ratio and >99% ee (**Scheme 1.51**). Adduct **239** was subsequently elaborated in ten steps to (+)-*cis*-nemorensic acid **240**.



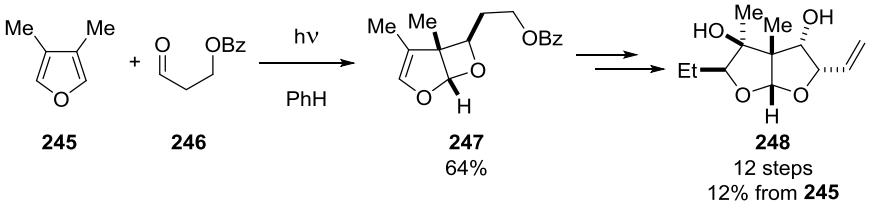
Scheme 1.51 *Asymmetric furan [4+2]-cycloaddition in the synthesis of* **240**

The use of furans in cycloaddition chemistry is not just limited to [4+2]-cycloaddition. Furans may also partake in [4+3]-cycloadditions with stabilised oxyallyl cations, as in the iminium catalysed reaction of 2,5-dimethylfuran **237** with dienal **242**. Harmata and coworkers have reported the use of MacMillan imidazolidinone **244** as a catalyst for the synthesis of bicycle **243** in a moderate 64% yield, with 90% ee (**Scheme 1.52**).[101]



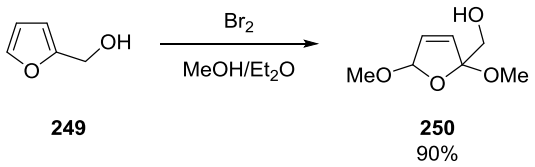
Scheme 1.52 *Asymmetric organocatalytic [4+3]-cycloaddition of furan* **237**

Furans can also be dearomatised to the 2,3-dihydrofuran in [2+2] photocycloadditions. For example, in Schreiber's studies towards the bis-THF moiety of asteltoxin, irradiation of 3,4-dimethylfuran **245** with aldehyde **246** in benzene afforded the *exo*-photoadduct **247** in 64% yield (**Scheme 1.53**).[102] This intermediate was subsequently elaborated into bis-THF **248**, an advanced intermediate in the synthesis of asteltoxin.



Scheme 1.53 *[2+2] photocycloaddition of furan* **245**

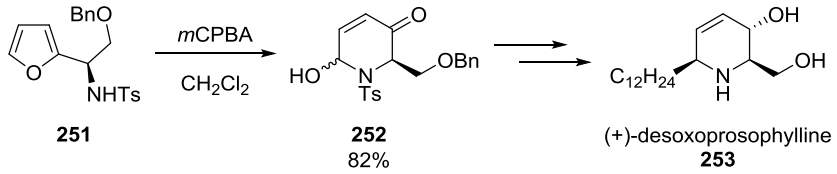
The oxidative dearomatisation of furans has been known for a considerable amount of time. In 1934, Meinel reported the reaction of 2-furylmethanol **249** with elemental bromine in methanol, affording the cyclic diacetal **250** (**Scheme 1.54**).[103] This reaction may be accomplished with a number of different oxidising agents including bromine,[103] *m*CPBA,[104] PCl_5,[105] O_2/hν,[106], $^1O_2/V_2O_5$,[107] $Pb(OAc)_4$,[108] and magnesium monoperoxyphthalate hydrate.[109] The diverse range of methods developed for the synthesis of 2,5-dialkoxy-THFs demonstrates their importance in the synthesis of a number of compounds, particularly due to their use as masked 1,4-dicarbonyl compounds.[110-114]



Scheme 1.54 *Oxidative dearomatisation of furfuryl alcohol* **249**

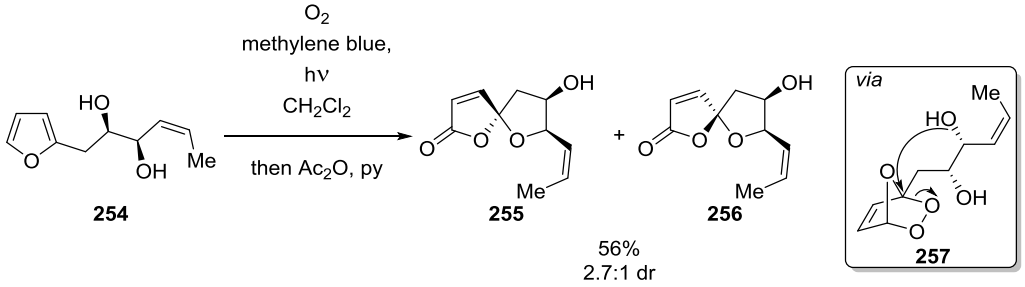
The 2,5-dialkoxy-THFs formed *via* the oxidative dearomatiastion of furans are of particular use in the Achmatowicz reaction, whereby furans bearing a pendant alcohol or amine may be cyclised under acidic conditions to form dihydropyridones or dihydrofuranones.[115] In Zhou's

total synthesis of (+)-desoxoprosophyllin **253**, Achmatowicz reaction of the α-aminofuran **251** using *m*CPBA in dichloromethane afforded the corresponding dihydropyridone **252** in 82% yield (**Scheme 1.55**). Dihydropyridone **252** was subsequently derivatised in nine further steps to afford (+)-desoxoprosophylline **253** in an overall yield of 4% over 10 steps.



Scheme 1.55 *Achmatowicz reaction of α-aminofuran* **251**

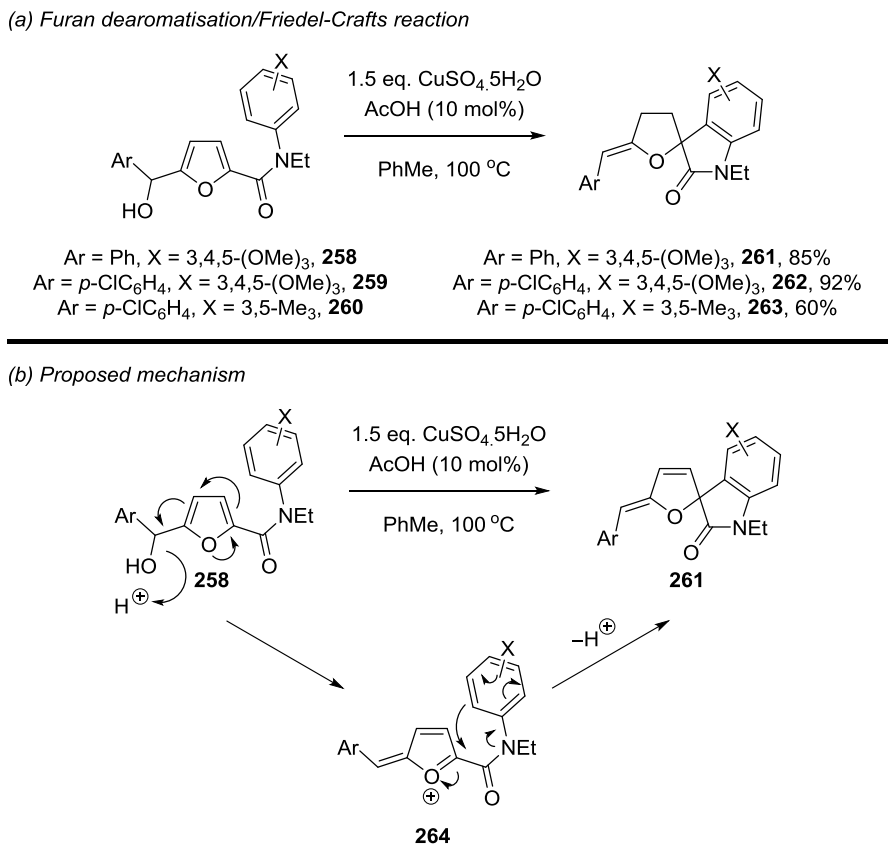
One particularly interesting example of oxidative dearomatisation of furans is the formation of γ-spiroketal-γ-lactones by the reaction of furans bearing a γ-hydroxy group such as **254**, with $^1O_2$, *via* the formation of the bicyclic peroxide **257**, as reported by Vassilikogiannakis and coworkers (**Scheme 1.56**).[116] This intermediate is then trapped with the pendant alcohol, and subsequent dehydration of the peroxy-acetal affords the spirocyclic γ-lactones **255** and **256**. The oxidation-spirocyclisation protocol proceeded in moderate yield and diastereoselectivity (2.7:1) over two steps, and the spirocycle **255** could then be converted in two steps to the natural product 9-*epi*-pyrenolide D.



Scheme 1.56 *Oxidative dearomatisation of* **254** *with* $^1O_2$

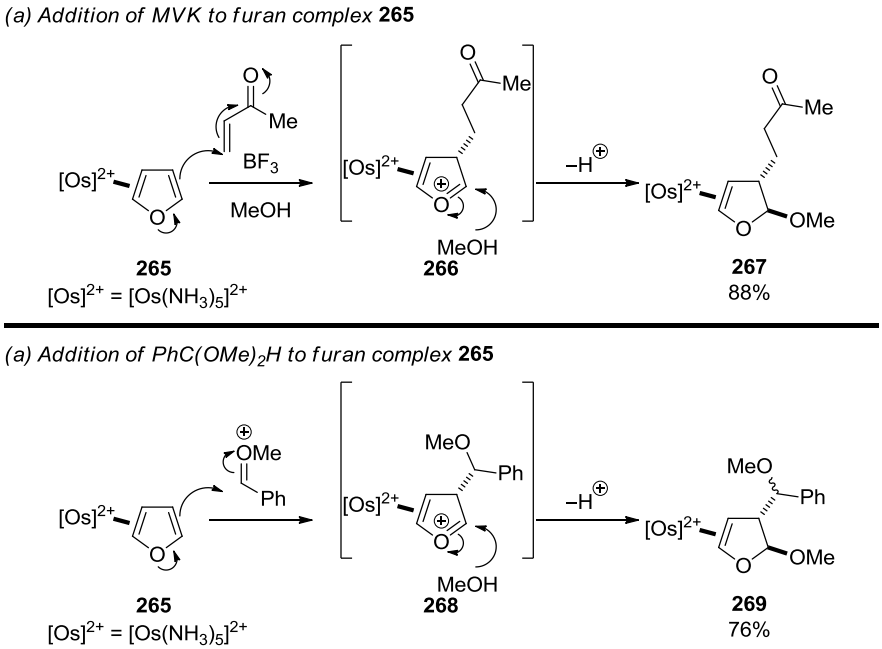
Furans may also be activated by electrophiles, creating an oxonium ion that may then be trapped by a nucleophile, in either an intra- or intermolecular fashion. An interesting example of intramolecular trapping of furans is provided by the work of Yin and coworkers, who utilised the dearomatisation of furans in the synthesis of spirooxindoles.[117] Treatment of furan **258**, bearing a benzylic alcohol in the α-position, and a pendant electron-rich acetanilide moiety, with $CuSO_4 \cdot 5H_2O$ and acetic acid in toluene promoted dehydration, followed by

Friedel-Crafts dearomatiastion of the furan (**Scheme 1.57b**). A number of different aryl groups were tolerated in both the benzylic alcohol (both electron rich, and electron-poor), and the acetanilide portions of the molecule, affording spirofuroxindoles **261**-**263** in moderate to excellent yields (**Scheme 1.57a**).



Scheme 1.57 *Dearomatisation/spircocyclisation of furans* **258-260**

Dearomatisation of furans with electrophilic activation can also be accomplished whilst coordinated to a metal centre.[118,119] For example, treatment of the η^2-pentammineosmium(II) furan complex **265** with methylvinylketone (MVK) and BF_3 in methanol affords the η^2-2,3-dihydrofuran complex **267**, with addition of MVK at the 3-position of the furan, and subsequent trapping of the oxonium ion with methanol, in 88% yield (**Scheme 1.58a**). Addition of benzaldehyde dimethyl acetal and $BF_3{\cdot}OEt_2$ afforded the corresponding product of oxonium addition, followed by trapping with methanol to yield the *trans*-product **269** in 76% yield (**Scheme 1.58b**).



Scheme 1.58 *Electrophilic activation/dearomatisation of η^2-furan complex* **265**

1.4 Project Aims

It is clear from the above review of the literature that there are numerous methods available for the dearomatisation of pyridines and pyridinium salts, and a number of different techniques available to conduct these processes in an asymmetric fashion. However, there is no general procedure for the asymmetric dearomatisation process, and both regio- and stereoselectivity are highly dependent on a number of factors. It is also clear that the use of chiral phosphoric acids has been particularly useful in the reduction of pyridines, and the use of a chiral counterion might also prove feasible for the transition-metal free addition of organometallics to pyridinium salts. The aims of this project therefore were to:

1) Extend the previous methodology developed in the Donohoe group to the asymmetric addition of Grignard reagents to pyridinium salts, *via* a novel chiral counterion methodology.
2) To render this process catalytic in chiral counterion.
3) To expand the scope of this methodology to allow the synthesis of a range of dihydropyridines and dihydropyridones, with a range of different nucleophiles.

Furthermore, there is an even greater dearth of methodology for the asymmetric nucleophilic dearomatisation of furans. Therefore, it was also postulated that it might be possible to

develop this area, as an expansion of the previous work in the Donohoe group on the stereoselective reduction of furan derivatives.[92,93] It was clear that the methodology developed by Makosza and coworkers for the formation of dihydrofuro[2,3-*b*]furans would provide access to important natural products and their derivatives, such as the autocystin family of aromatic dihydrofurofurans,[62] and as such, a further aim of this project was to:

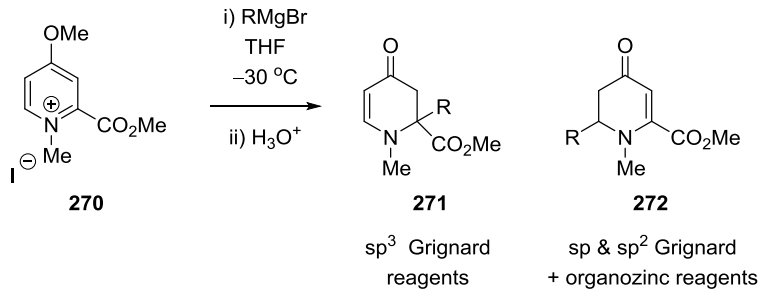
1) Investigate further the scope of the dearomatisation of electron-deficient furans with carbon nucleophiles.
2) Develop an asymmetric methodology for the synthesis of chiral dihydrofuro[2,3-*b*]furans.

2: Results and Discussion – Studies Towards Asymmetric Nucleophilic Dearomatisation

2.1 Studies Towards Asymmetric Nucleophilic Dearomatisation of Pyridinium Salts

2.1.1 Introduction

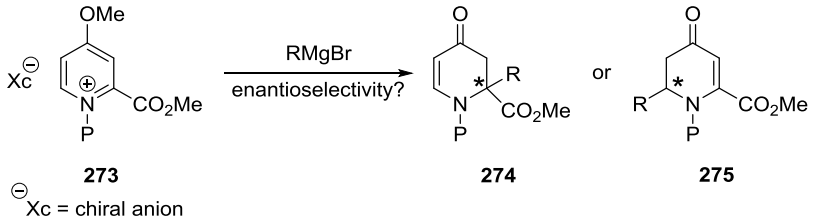
Previous work in the Donohoe group had investigated the addition of organometallic reagents to 2-carboxymethyl-4-methoxypyridinium salts **270** (*vide supra*),[31] providing access to 2- or 6-substituted dihydropyridones **271** or **272** depending on the choice of reagent (**Scheme 2.1**). One drawback of this methodology was that, despite complete regioselectivity depending on the choice of reagent, it only provided the dihydropyridones **271** and **272** as a racemic mixture, and thus it was desirable to develop a novel enantioselective method for the addition of organometallic reagents to this class of pyridinium salts.



Scheme 2.1 *Addition of organometallic reagents to pyridinium salt* **270**

A variety of methods already exist for the asymmetric addition of nucleophiles to pyridinium salts (See **Chapter 1.2.4**). Our attention turned to the use of chiral counterions as an alternative to the traditional use of chiral auxiliaries or ligands, since this was a rapidly expanding area in organic chemistry (**See section 2.1.2 below**). It was envisaged that in the first instance, synthesis of the pyridinium salts bearing a chiral anion would enable initial investigation into the feasibility of this method. It was postulated that the presence of a chiral counterion should direct the addition of the reagent to one of the two enantiotopic faces of the pyridinium salt **273**, *via* the diasterotopic transition state formed by the presence of the chiral counterion, providing enantioenriched dihydropyridone **274** or **275** upon hydrolysis (**Scheme 2.2**). If successful, this would provide an alternative and general method for the synthesis of chiral dihydropyridones, in comparison to the chiral auxiliary and ligand-based methodologies in the literature, since this might be amenable to a number of different

nucleophiles rather than just a single class, and would also benefit from a greater atom economy if the process could be made catalytic in chiral counterion.



Scheme 2.2 *Proposed asymmetric addition to chiral pyridinium salts*

The aims of this project were therefore to:

1) Extend the previous methodology developed in the Donohoe group to the asymmetric addition of Grignard reagents to pyridinium salts, *via* a novel chiral counterion methodology.
2) To render this process catalytic in the chiral counterion.
3) To expand the scope of this methodology to allow the synthesis of a range of dihydropyridines and dihydropyridones, with a range of different nucleophiles.

2.1.2 Chiral counterions in organic synthesis

The use of chiral anions as a remote auxiliary is a rapidly expanding area in organic chemistry.[120,121] In this area there are two main modes of catalysis, that which is strictly the result of ion-pairing between a cationic substrate and chiral counterion **276**, relying solely on an electrostatic interaction, and that which is a hydrogen-bonded supramolecular complex **277** between a protonated species and the chiral counterion, as demonstrated here for iminium ions (**Figure 2.1**). Since we were to attempt the addition of organometallics to *N*-alkylpyridinium salts, the discussion below will predominantly focus on interactions of the type **276**.

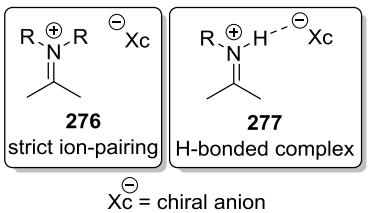
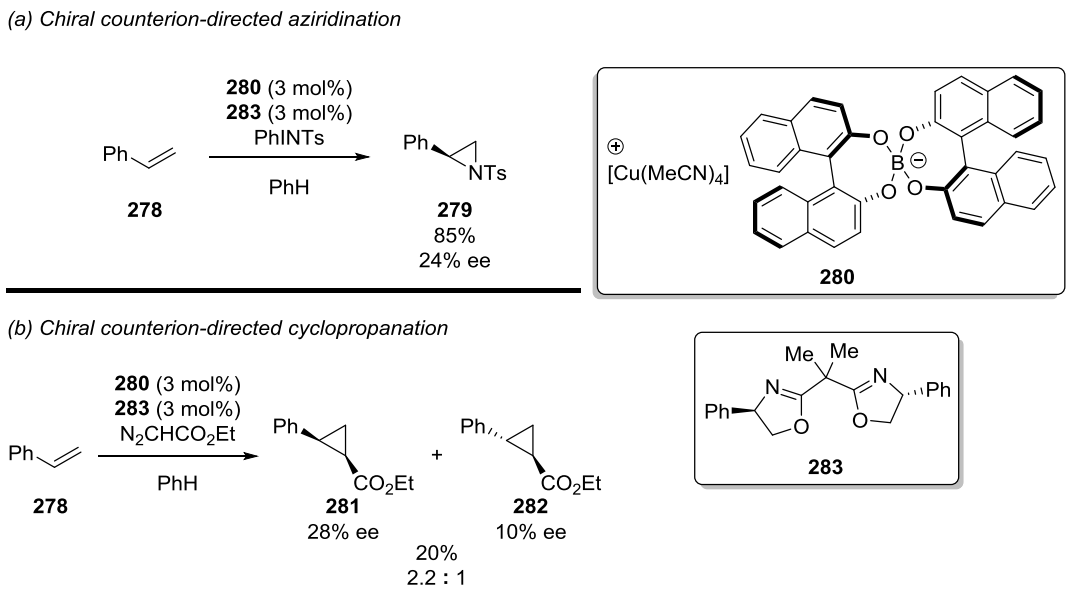


Figure 2.1 *Possible modes of chiral-counterion catalysis*

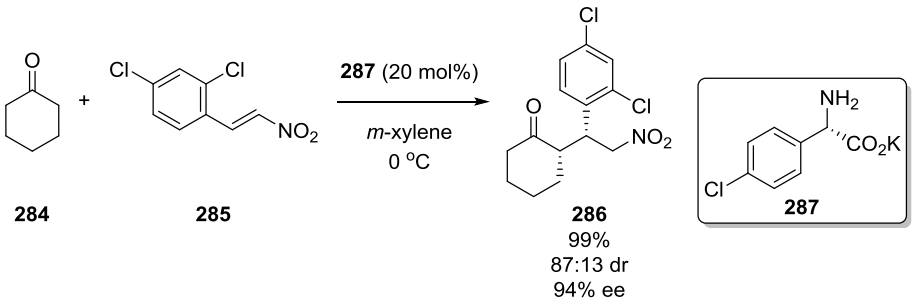
An early attempt at influencing the enantioselectivity of a chemical reaction under the influence of a chiral counterion was developed by Arndtsen and coworkers, utilising the chiral binaphthylborate salt **280** in the aziridination and cyclopropanation of styrene **278**.[122] By employing **280** along with a chiral bis(oxazoline) ligand **283**, enantioselectivities of up to 24% for aziridination (**Scheme 2.3a**) and 28% for cyclopropanation (**Scheme 2.3b**) could be achieved in good yield for aziridination, but poor yield for cyclopropanation. Use of the chiral counterion enabled the use of lower equivalents of catalyst compared to a standard aziridination protocol only employing ligand **283**, and switching to the opposite enantiomer of the chiral counterion showed a strong effect on enantioselectivity, further confirming the role of the counterion in directing the facial selectivity of the reaction.



Scheme 2.3 *Chiral counterion directed aziridination and cyclopropanation*

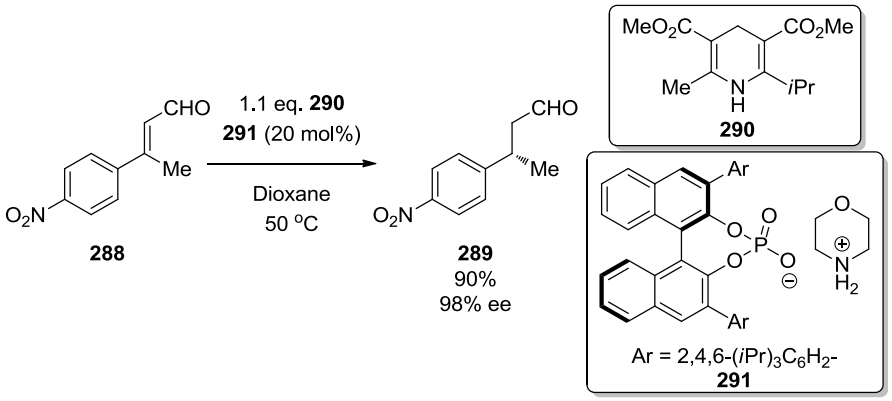
Numerous other early examples exist of chiral counterions delivering only low enantioselectivity in the synthesis of a variety of compounds. Nelson and coworkers attempted the asymmetric addition of chiral metal borates to iminium and aziridinium ions, resulting in observed enantioselectivities of <15%.[123] Milstein and coworkers attempted the hydrogenation of dehydroalanines in the presence of the rhodium(I) camphorsulfonate and *N*-acetylphenyalanine salts, but no enantioselectivity was observed, and these catalysts were found to be less active relative to a BF_4 salt used as a reference.[124]

However, some promising results were observed. Feng and coworkers developed an asymmetric addition of ketones to nitroolefins catalysed by chiral amino acid-derived salts.[125] For example, addition of catalyst **287** to cyclohexanone **284** and nitroolefin **285** in *m*-xylene at 0 °C afforded product **286** in 99% yield, 87:13 *syn*:*anti*, and 94% ee (**Scheme 2.4**). A number of different β-nitrostyrene derivatives were tolerated, giving the corresponding adduct in moderate to high yields and diastereoselectivity, with enantioselectivies of greater than 78% in all cases.



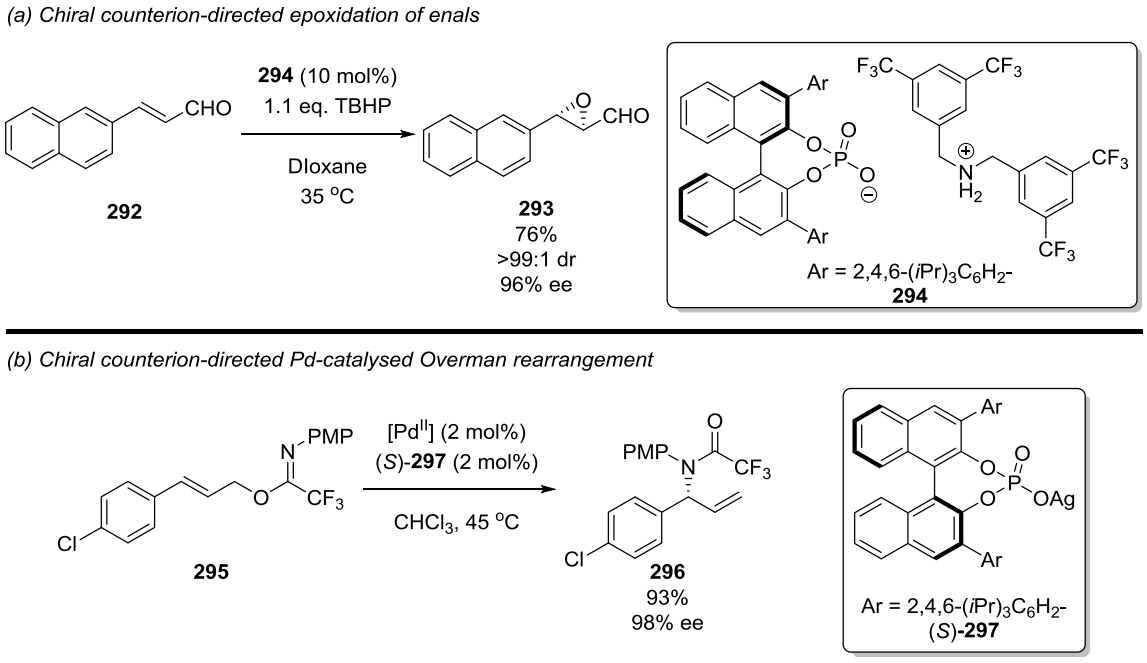
Scheme 2.4 *Chiral counterion-promoted asymmetric addition of ketones to nitroolefins*

In 2006, List and coworkers reported a major breakthrough in the field of chiral counterion catalysis. Addition of the morpholinium salt of (*R*)-TRIP **291** in the presence of Hantzsch dihydropyridine **290** allowed for the transfer hydrogenation of enals in good to excellent yield and outstanding enantioselectivities of up to 98%.[126] The *p*-nitrophenyl enal **288** was reduced under these conditions in an impressive 90% yield and 98% ee (**Scheme 2.5**).



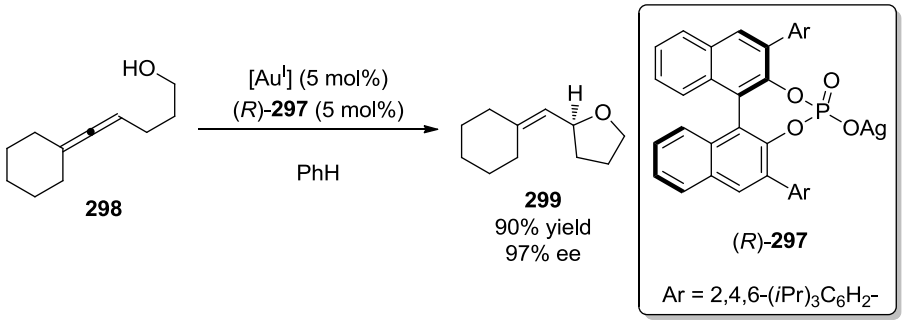
Scheme 2.5 *List's asymmetric chiral anion-directed transfer hydrogenation of enals*

Salts of the type **291** have found use in a variety of transformations. List also demonstrated their use in the epoxidation of enals with TBHP (**Scheme 2.6a**),[127] and a chiral counterion-mediated Overman rearrangement of trifluoromethyl imidates such as **295** (**Scheme 2.6b**).[128]



Scheme 2.6 *TRIP anion directed epoxidation and Overman rearrangement*

The use of the TRIP chiral anion has also been used in transition-metal catalysed chemistry. In 2007, Toste and coworkers reported a powerful strategy for the cyclisation of alcohols, amines and carboxylic acids onto allenes in an intramolecular fashion, using the silver salt (*R*)-**297** with a gold(I) catalyst. Use of a phosphine ligand on gold, along with (*R*)-**297** afforded the hydroalkoxylated products in up to 99% ee and in good to excellent yield (**Scheme 2.7**).

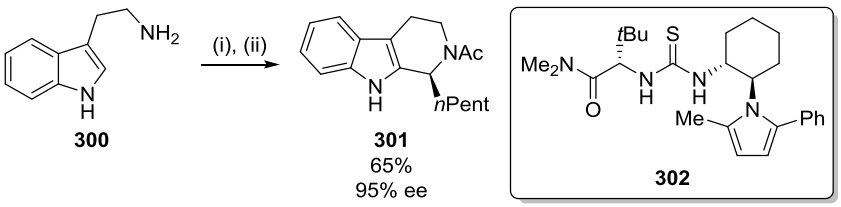


Scheme 2.7 *Toste's chiral counterion-directed asymmetric hydroalkoxylation of allenes*

In the intervening period since Toste's publication of the hydroalkoxylation of allenes, the use of chiral phosphate anions has become a fruitful area in the field of asymmetric catalysis. For example, chiral phosphate anions have been utilised in a number of other processes including the semi-Pinacol rearrangement of benzylic cyclobutanols,[129] copper-catalysed diamination of dienes,[130] a copper-catalysed cycloisomerisation/nucleophilic addition

cascade,[131] allylic alkylation of α-nitro esters,[132] asymmetric Tsuji-Trost reaction,[133] fluorocyclisation of alkenes bearing pendant amides,[134] and many other processes.[135-137]

Jacobsen and coworkers adopted an alternative approach to the use of chiral anions for asymmetric synthesis. Use of the chiral thiourea **302** promoted binding of chloride, liberated from the acetylation of the imine formed from tryptamine **300** and hexanal with acetyl chloride, which then promoted an asymmetric Pictet-Spengler reaction (**Scheme 2.8**). A range of different substrates could be cyclised in good to excellent yield, with enantioselectivity of up to 95%. For example, tryptamine **300** cyclised with *n*-hexanal to form tricyclic indole **301** in 65% yield and 95% ee.



Scheme 2.8 *Jacobsen's chiral thiourea-anion binding asymmetric Pictet-Spengler reaction*
Conditions: (i) *n*PentCHO, 3Å MS (ii) 1.0 eq. AcCl, 1.0 eq. 2,6-lutidine, **302** (10 mol%), Et_2O, −78→−60 °C

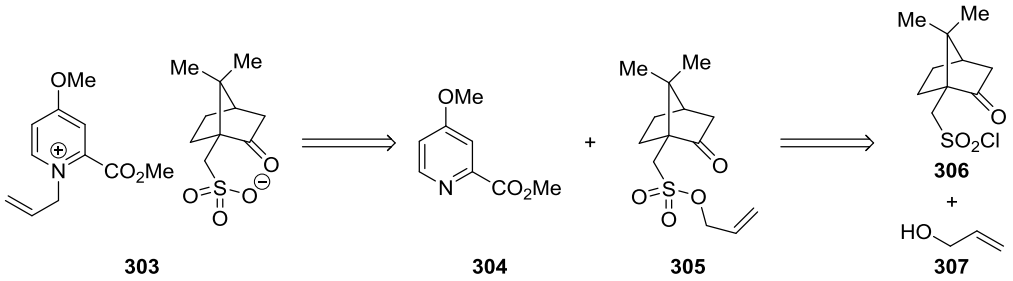
This approach has been extended to a range of different reactions, including the Mannich reaction of *N*-acyloxyisoquinolines,[138] the Pictet-Spenger reaction of tethered hydroxylactams,[139] the cyclisation of pyrroles onto *N*-acyliminium ions,[140] addition to oxocarbenium ions,[141] α-alkylation of aldehydes with carbocations,[142] and acylation of silyl ketene acetals.[143]

It is clear, therefore, that there is an impressive range of options for the area of asymmetric synthesis using chiral counterion catalysis, although perhaps not all are applicable to the addition of organometallic agents to pyridinium salts. For example, it is unlikely that the acidic thiourea catalysts employed by Jacobsen (pKa = 21) would be compatible with our reaction conditions due to their relatively high acidity, and thus will be deprotonated by the organometallic reagent, preventing anion binding and thus asymmetric induction. [144]

Results and Discussion

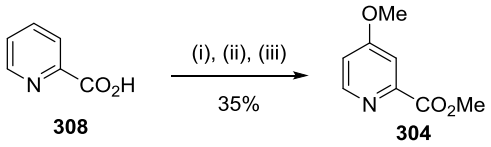
2.1.2 Preparation of chiral pyridinium salts by nucleophilic displacement

The proposed route to the synthesis of the chiral pyridinium salts would follow the standard route for preparation of *N*-allyl pyridinium salts previously reported, by displacement of an allylic leaving group to yield the salt directly. Thus it was envisaged that the reaction of pyridine **304** with allyl camphorsulfonate **305** (formed by addition of allyl alcohol **307** to the sulfonyl chloride **306**) would provide access to the chiral salt directly **303** (**Scheme 2.9**).



Scheme 2.9 *Proposed retrosynthesis of pyridinium salt* **303**

Thus, treatment of picolinic acid **308** with 0.1 equivalents NaBr in refluxing thionyl chloride, followed by refluxing in basic methanol afforded methyl 4-methoxypicolinate **304** in 35% yield (**Scheme 2.10**). Spectroscopic data were consistent with those reported in the literature,[31] with the presence of both the ester and the 4-methoxy group confirmed by the presence of two 3H singlets at 4.01 and 3.92 ppm in the ^{1}H NMR spectrum, and peaks at 166.5 and 165.8 ppm in the ^{13}C NMR spectrum, corresponding to the ester and the pyridine 4-position respectively.

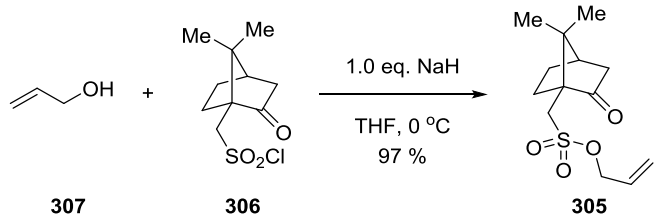


Scheme 2.10 *Synthesis of pyridine* **304**

Conditions: (i) 0.1 eq. NaBr, $SOCl_2$, 90 °C, 30 h (ii) MeOH, 70 °C, 36 h (iii) 1.5 eq. Na_2CO_3, MeOH, 70 °C, 3 h

Preparation of allyl sulfonate **305** was achieved by the reaction of allyl alcohol **307** with (1*R*)-10-camphorsulfonyl chloride **306** in THF at 0 ^{o}C, after deprotonation with sodium hydride, affording the desired product in 97% yield (**Scheme 2.11**). The structure was confirmed by the presence of the three vinylic protons at 5.96 (1H, m), 5.46 (1H, dd, *J* 17.8, 1.1 Hz), and 5.36 (1H, dd, *J* 10.4, 1.1 Hz), and the allyl ester methylene protons at 4.82-4.71

ppm (2H, m). Further confirmation was provided *via* HRMS with the product observed at 295.0972 $[M+Na]^+$ (calculated 295.0975).

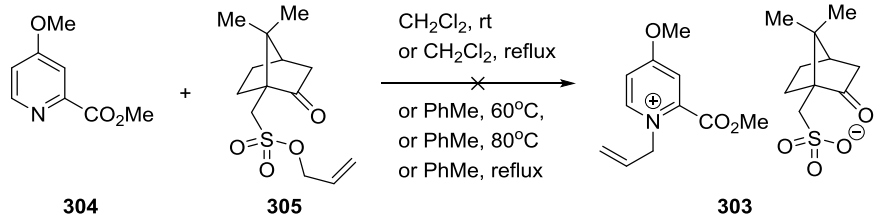


307 **306** **305**

Scheme 2.11 *Synthesis allyl camphorsulfonate* **305**

With chiral counterion precursor **305** in hand, our attention now turned to the synthesis of a chiral pyridinium salt by displacement of the camphorsulfonate leaving group.

It was expected that simple stirring of the pyridine **304** with allyl sulfonate **305** would afford the pyridinium salt **303**, following the standard procedure for the formation of *N*-allyl pyridinium salts from allyl triflate.[31] Unfortunately, at room temperature in CH_2Cl_2 no reaction was observed (**Scheme 2.12**). Increasing the reaction temperature to 40 °C still resulted in no observable reaction, as did conducting the reaction in toluene at elevated temperature. This is presumably due to the considerably higher pKa of camphorsulfonic (pKa = 1.2) acid relative to trifluoromethanesulfonic acid (pKa = −12),[145] and thus the camphorsulfonate salt is a poorer leaving group in the displacement reaction.



304 **305** **303**

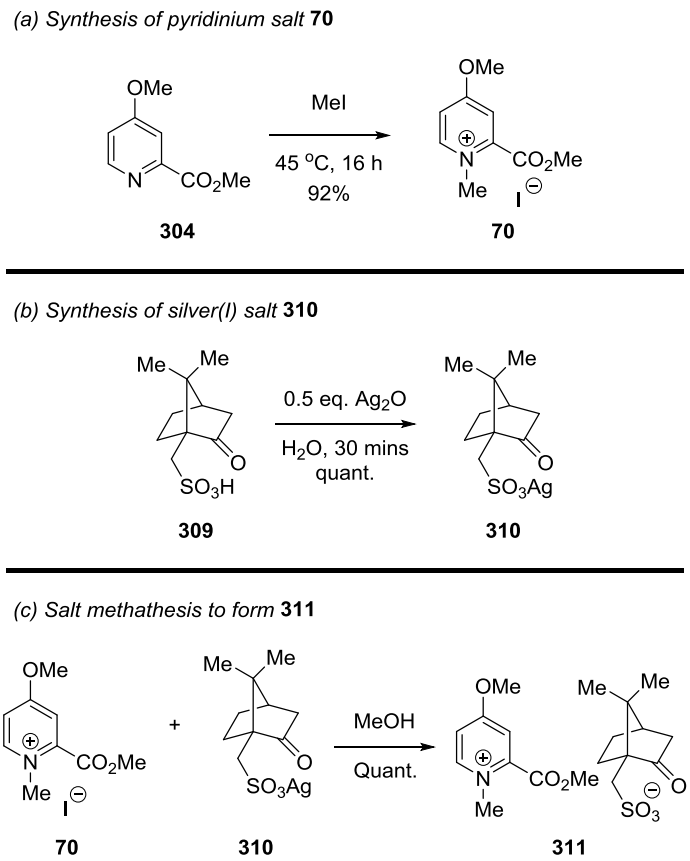
Scheme 2.12 *Attempted synthesis of pyridinium salt* **303**

2.1.3 Salt metathesis route to pyridinium salts

Due to the failure of this method to afford chiral pyridinium salt **303**, an alternative approach was devised whereby the salt would be formed from the corresponding pyridinium iodide **70**, and the silver(I) salt **310** of camphorsulfonic acid **309** *via* a salt metathesis reaction, precipitating silver(I) iodide. As such *N*-methylpyridinium salt **70** was prepared in 92% yield by stirring pyridine ester **304** in refluxing iodomethane for 16 hours (**Scheme 2.13a**).

Silver(I) camphorsulfonate **310** was prepared in quantitative yield from (1*R*)-10-camphorsulfonic acid **309** by treatment with silver(I) oxide in water (**Scheme 2.13b**),[146] and used without further purification.

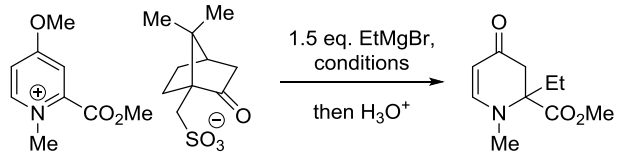
Stirring a 1:1 mixture of pyridinium iodide **70** and silver salt **310** in methanol at room temperature resulted in the formation of a cream precipitate (presumed to be AgI) (**Scheme 2.13c**). Filtration afforded chiral pyridinium salt **311** in quantitative yield. The formation of **311** was evidenced by the 1:1 ratio of peaks corresponding to the pyridinium and anionic components in the ^{1}H NMR spectrum, and the presence of each species in the ESI+ and ESI− mass spectra, respectively.



Scheme 2.13 *Synthesis of chiral pyridinium salt* **311**

With chiral salt **311** in hand, this substrate was treated with ethylmagnesium bromide (1.5 equivalents) in CH_2Cl_2 at −65 °C, affording dihydropyridone **72** in 85% yield as a single regioisomer (**Table 2.1, Entry 1**). HPLC analysis revealed that product **72** was formed as a racemic mixture. It was therefore decided to use a less polar solvent, such that tighter ion-pairing might be encouraged during the reaction. Performing the reaction at −30 °C in toluene

afforded dihydropyridone **72** in a diminished yield of 42% (**Entry 2**), however HPLC analysis revealed a small ee of 6%. Lowering the temperature to −40 °C resulted in further erosion of the yield to 10%, with no change in the ee (**Entry 3**). Reaction in THF at −30 °C saw an increase in yield to 69% (**Entry 4**), but afforded **72** as a racemic mixture, presumably as a result of the increased polarity of the solvent, and better solvation of the cation and anion. The reaction did not proceed at all in diethyl ether, even at room temperature, due to the insolubility of the chiral pyridinium salt **311** (**Entries 5-7**).



311 **72**

Entry	Solvent	Temperature	Yield (%)[a]	ee (%)[b]
1	CH_2Cl_2	−65 °C	85	0
2	PhMe	−30 °C	42	6
3	PhMe	−40 °C	10	6
4	THF	−30 °C	69	0
5	Et_2O	−30 °C	n/o	-
6	Et_2O	0 °C	n/o	-
7	Et_2O	rt	n/o	-

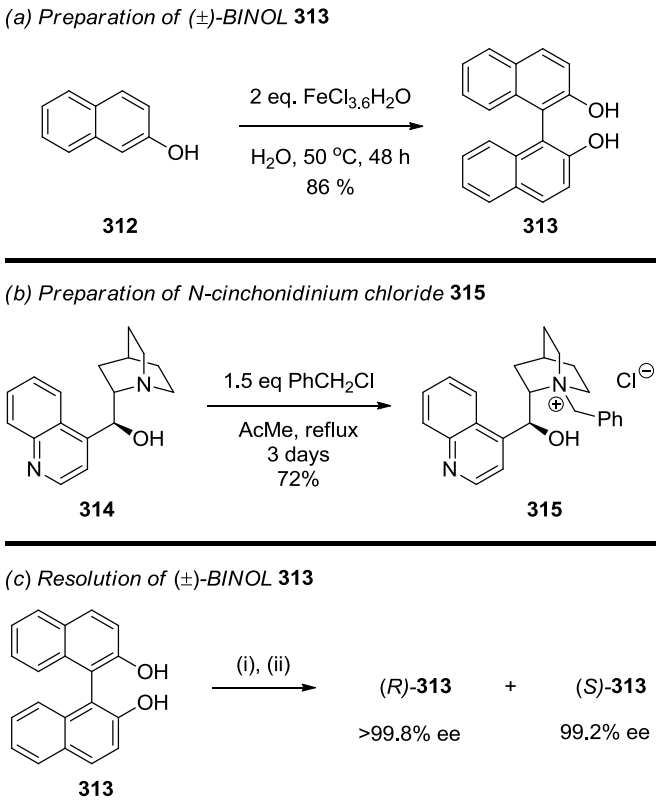
Table 2.1 *Addition of EtMgBr to chiral pyridinium salt* **311**
[a]Isolated yield [b] Enantiomeric excess was determined by chiral HPLC.

2.1.4 Synthesis of chiral phosphoric acid salts

Due to the lack of decent enantioselectivity observed in the reaction of camphorsulfonate salt **311**, it was decided to attempt a different motif for the asymmetric addition of Grignard reagents to pyridinium salts. Due to their prevalence in the literature (*vide supra*), our attention turned to the use of chiral phosphonates to direct addition of the Grignard reagent in a facial-selective manner.

The synthesis of binapthyl phosphoric acid **316** began with the synthesis of (*R*)-BINOL (*R*)-**313**. Oxidative coupling of 2-napthol **312** with 2 equivalents of $FeCl_3 \cdot 6H_2O$ in water at 50 °C afforded racemic BINOL **313** in 86% yield, the structure of which was confirmed by comparison to the literature data (**Scheme 2.14a**).[147] Subsequent resolution with *N*-benzylcinchonidinium chloride **315** (prepared from cinchonidine **314** and benzyl chloride in

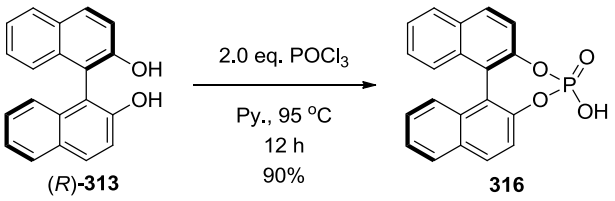
72% yield (**Scheme 2.14b**)[148]) afforded both enantiomers of BINOL in >99% ee, as confirmed by HPLC analysis (**Scheme 2.14c**).[149]



Scheme 2.14 *Synthesis and resolution of* BINOL **313**
Conditions: (i) 0.5 eq. **315**, MeCN, reflux, 4 h. (ii) MeOH, reflux, 24 h
[a] Enantiomeric excess was determined by chiral HPLC.

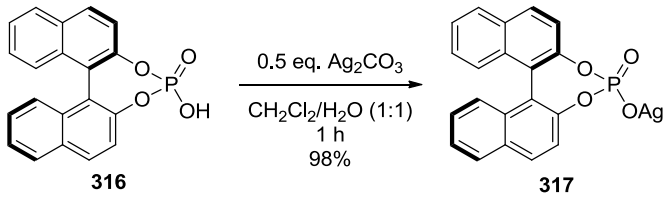
(*R*)-BINOL **313** was then converted into the corresponding phosphoric acid **316** by treatment with phosphorus oxychloride in pyridine, followed by hydrolysis, affording phosphoric acid **316** in 90% yield (**Scheme 2.15a**), with the characteristic phosphoric acid $O_2P(O)OH$ peak observed as a broad singlet at 14.65 ppm in the ^1H NMR spectrum.[150] Subsequent treatment of acid **316** with silver carbonate in dichloromethane/water afforded silver salt **317**, used crude in the next step (**Scheme 2.15b**).[151] Subsequent salt metathesis with pyridinium iodide **70** afforded chiral pyridinium salt **318** in 96% yield (**Scheme 2.15c**). The formation of pyridinium salt **318** was confirmed by the presence of a 1:1 ratio of peaks corresponding to the pyridinium and phosphate moieties in the ^1H NMR spectrum, along with the presence of peaks at 182.1 and 347.1 in the ESI+ and ESI− mass spectra, for the pyridinium and phosphate respectively.

(a) Preparation of phosphoric acid **316**



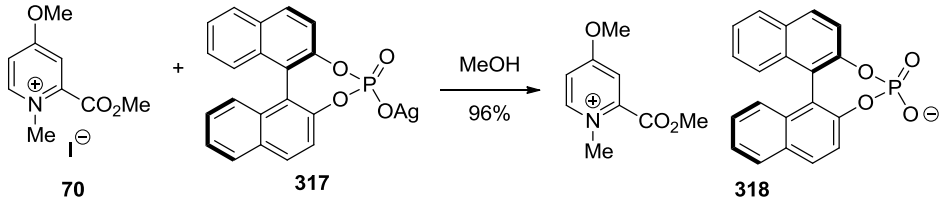
(*R*)-**313** **316**

(b) Preparation of silver(I) salt **317**



316 **317**

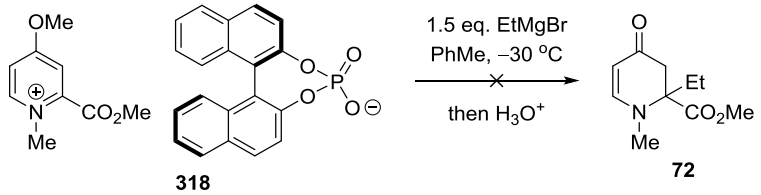
(c) Salt methathesis to form **318**



70 **317** **318**

Scheme 2.15 *Synthesis of chiral pyridinium salt* **318**

Chiral salt **318** was then subjected to the reaction conditions for the dearomatisation reaction. Unfortunately, the salt proved to be completely insoluble in toluene, and thus only recovered starting material was observed (**Scheme 2.6**).

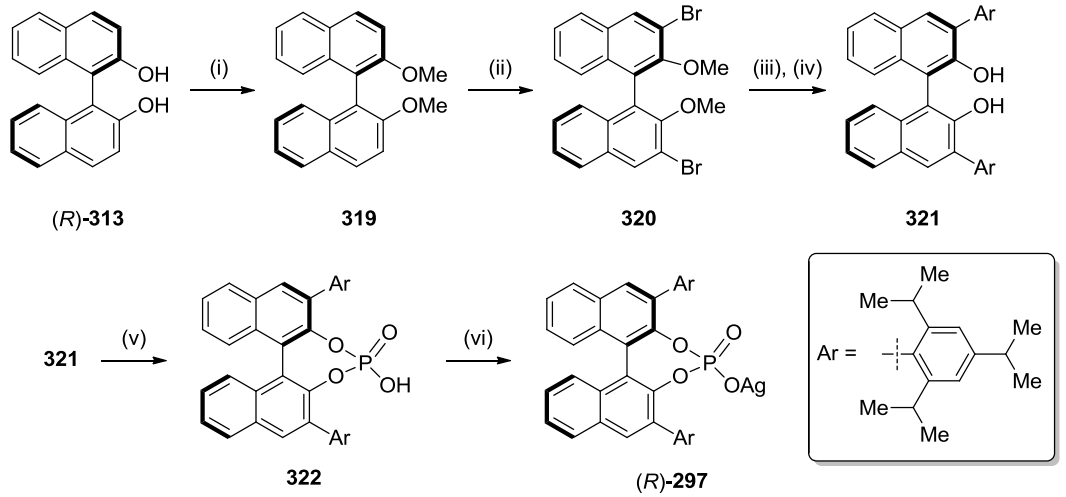


318 **72**

Scheme 2.16 *Attempted dearomatisation of chiral pyridinium salt* **318**

Since solubility appeared to be the limiting factor in the reaction of the previously synthesised chiral pyridinium salts **311** and **318**, it was postulated that appending hydrophobic substituents at the 3- and 3'- positions of the biaryl scaffold might aid in solubilising the salt in apolar solvents such as toluene. The most popular group used in the literature is the 2,4,6-tri(isopropyl)phenyl- moiety, in what has become known as the TRIP phosphoric acid **322**, developed by List and co-workers.[150] This acid has been used for asymmetric induction in a variety of different reactions from Mannich-type reactions,[152] to the Au(I)-catalysed functionalization of allenes.[151]

The synthesis of TRIP **322** began with the methylation of (*R*)-BINOL (*R*)-**313** with iodomethane in basic acetone, affording dimethyl ether **319** in 98% yield (**Scheme 2.7**). The structure was confirmed by the disappearance of the two phenolic protons at 5.06 ppm (2H, s), and the appearance of a singlet (6H) at 3.79 ppm in the ^{1}H NMR, corresponding to the two chemically and magnetically equivalent methyl groups. Bromination of ether **319** with *n*BuLi/TMEDA and elemental bromine in diethyl ether afforded dibromo biaryl **320** in 54% yield. Subsequent Kumada coupling with freshly prepared 2,4,6-triisopropylphenylmagnesium bromide and demethylation of the crude reaction mixture with BBr_3 yielded 3,3'-diaryl BINOL **321** in 45% yield over two steps, identified by the presence of peaks corresponding to the two phenolic protons at 5.06 ppm (2H, s), and also by the presence of peaks corresponding to the 2,4,6-triisopropylphenyl moiety, including a 12H doublet at 1.40 ppm corresponding to the *p*-isopropyl groups, and four 6H doublets corresponding to the *o*-isopropyl groups, which are non-equivalent due to restricted rotation, consistent with the literature data.[150] BINOL **321** was then converted to the silver(I) phosphate by the same procedure as for compound **317** affording silver salt (*R*)-**297** in 80% yield over two steps.

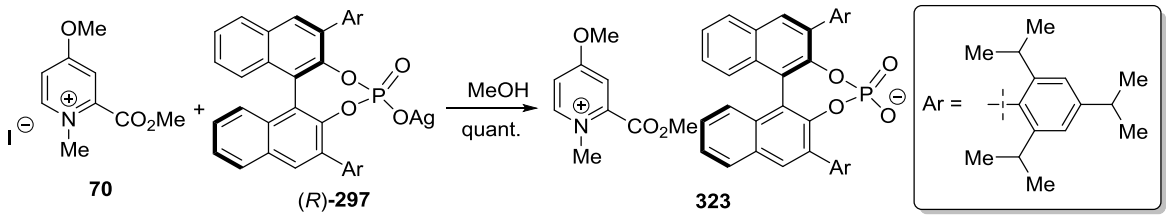


Scheme 2.17 *Synthesis of TRIP silver(I) salt* (*R*)-**297**

Conditions: (i) 3.40 eq. K_2CO_3, 4.0 eq. MeI, AcMe, reflux, 98% (ii) 3.5 eq. *n*BuLi, 2.2 eq. TMEDA, Et_2O, rt; 5.0 eq. Br_2, −78 °C, 54% (iii) 10 mol% $NiCl_2(PPh_3)_2$, 6.1 eq. ArMgBr, Et_2O, reflux (iv) 7.0 eq. BBr_3, CH_2Cl_2, 0 °C→ rt, 45% over 2 steps (v) 3.0 eq. $POCl_3$, Py., 90 °C, 80% (vi) 0.5 eq. Ag_2CO_3, CH_2Cl_2/H_2O (1:1), quant.

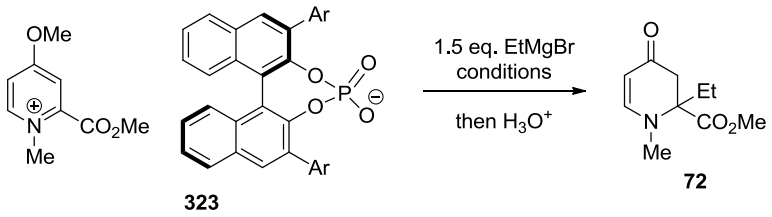
Salt metathesis of silver(I) salt (*R*)-**297** with pyridinium iodide **70** afforded pyridinium TRIP salt **323** in quantitative yield (**Scheme 2.18**). Again, the formation of salt **323** was confirmed

by the formation of a cream precipitate (presumably AgI), and the presence of 1:1 peaks in the ^{1}H NMR spectrum corresponding to the pyridinium and phosphate ions respectively.



Scheme 2.18 *Synthesis of TRIP silver(I) salt* **323**

Salt **323** was then subjected to the dearomatisation conditions with EtMgBr (**Table 2.2**). However, the salt was still insoluble in all non-polar solvents, and no reaction was found to occur in pentane (**Entry 1)**, diethyl ether (**Entry 2**) or toluene (**Entry 3**). The reaction did proceed in a 1:1 mixture of toluene and dichloromethane (**Entry 4**), affording dihydropyridone **72** in 54% yield, albeit as a racemic mixture.



Entry	Solvent	Temperature	Yield (%)[a]	ee (%)[b]
1	Pentane	−30 °C	n/o	-
2	Et_2O	−30 °C	n/o	-
3	PhMe	−30 °C	n/o	-
4	PhMe/CH_2Cl_2 (1:1)	−30 °C	54	0

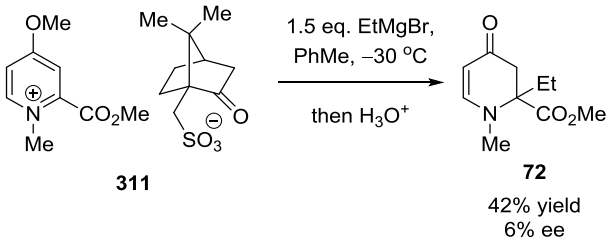
Table 2.2 *Addition of EtMgBr to chiral pyridinium salt* **323**
[a] Isolated yield [b] Enantiomeric excess was determined by chiral HPLC.

2.1.5 Conclusions

During the course of this work, a number of chiral pyridinium salts (**311**, **318** and **323**) were prepared *via* a salt metathesis reaction, since the previously utilised method of nucleophilic displacement of the corresponding alkyl sulfonate had proved ineffective in this case.

The chiral salts were subjected to the previously developed reaction conditions,[31] but their solubility in non-polar organic solvents was found to be too low for the efficient induction of enantioselectivity in the formation of dihydropyridone **72**, with a best result of 6% ee

achieved for the reaction of camphorsulfonate salt **311** with EtMgBr in toluene at −30 °C (**Scheme 2.19**).



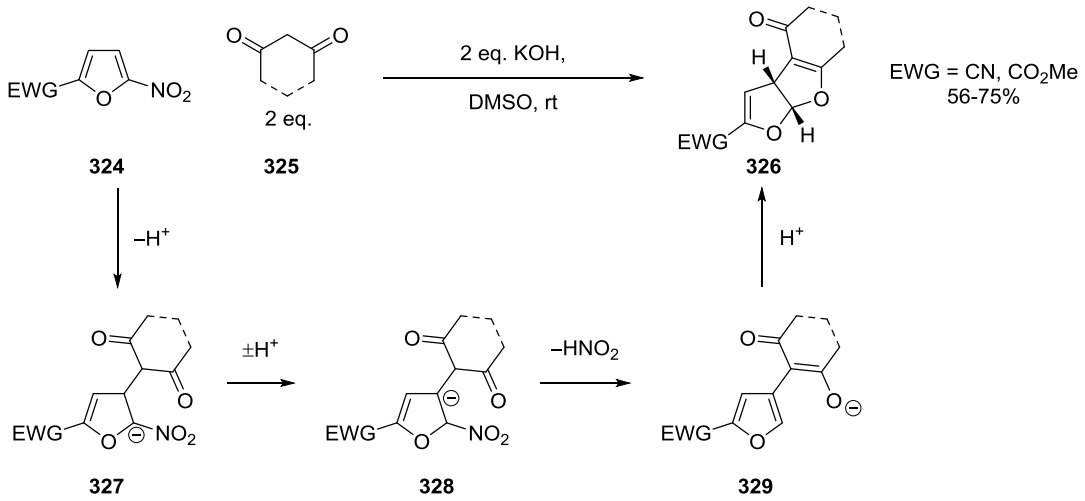
Scheme 2.19 *Optimal result for the dearomatisation of pyridinium salt* **311**

The clear difficulty in developing conditions under which these chiral salts would be soluble, and possess the tight ion-pairing necessary for efficient enantioinduction precluded further investigation into this methodology as a route to the synthesis of chiral dihydropyridones. Furthermore, there are no clear anchor points in the substrate to enable the tight binding required for efficient asymmetric induction, in stark constrast to other methods of asymmetric synthesis, where for example, hydrogen-bonding control aids in the orientation of substrates for the formation of enantioenriched product.

2.2 Studies Towards Asymmetric Nucleophilic Dearomatisation of Electron-Deficient Furans

2.2.1 Introduction

In our effort to further investigate the potential for asymmetric nucleophilic dearomatisation of electron-deficient heteroaromatics, our focus turned to the reaction of 2-nitrofurans **324** with 1,3-diketones **325** to furnish dihydrofuro[2,3-*b*]furans **326** in the presence of base, as developed by Makosza and co-workers (**Scheme 2.20**).[87] The reaction appears to proceed *via* initial addition of the enolate of the diketone **325** to the position β to the nitro group of furan **324**, followed by lose of nitrite, formation of the intermediate enolate **329**, and subsequent cyclisation, either *via* a conjugate addition or 6π-electrocyclisation, to afford the dihydrofurofurans **326**.



Scheme 2.20 *Nucleophilic dearomatisation of furans with 1,3-diketones*

Our aims for this project were to:

1) Investigate further the scope of the dearomatisation of electron-deficient furans with carbon nucleophiles.
2) Develop an asymmetric methodology for the synthesis of chiral dihydrofuro[2,3-*b*]furans.

It was hoped that by judicious choice of reaction conditions, an increase in substrate scope (both in the heteroaromatic and dicarbonyl moieties) might be accessible, along with the

potential to develop an asymmetric variant of this reaction. This would then provide access to chiral dihydrofurofurans, which are present in a range of natural products and biologically active compounds, such as the aflatoxins **330**,[153] sterigmatocystine **331**,[62] vericolorins **332**, [154] and rhodomyrtosones **333** (**Figure 2.2**).

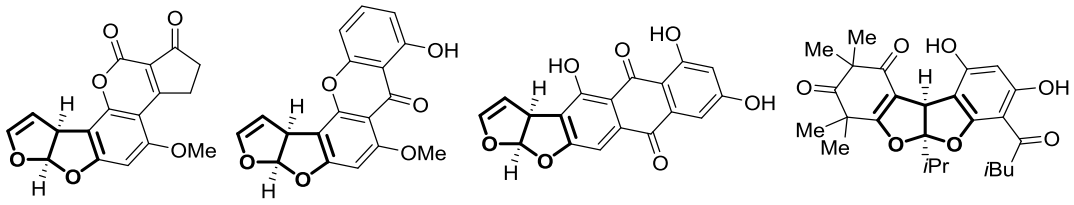


Figure 2.2 *Dihydrofuro[2,3-b]furan containing natural products*

Results and Discussion

2.2.2 Initial screen of conditions

In order to find a more convenient solvent that would also be capable of enhancing asymmetric induction in the reaction, a number of different solvents were screened for their effect on the yield of the reaction between 5-nitro-2-furonitrile **197** and acetylacetone **199** in the presence of KOH (**Table 2.3**). Confirmation of the structure of **202** was evident from its ^{1}H NMR spectrum, with a doublet at 6.45 ppm, corresponding to the acetal C*H* proton coupled to a multiplet at 4.56-4.50 ppm, corresponding to the doubly allylic C*H* proton. This proton was also coupled to a vinylic proton at 6.18 ppm (d, *J* 3.0 Hz), consistent with the previously reported literature data.[87] Confirmation of the *cis*-stereochemistry was obtained *via* an NOE experiment. Irradiation of the acetal C*H* proton of dihyrofurofuran **202** resulted in an NOE enhancement of the doubly allylic proton, clearly demonstrating their proximity in space, and thus supporting the assignment of *cis*-stereochemistry. Further confirmation of the structure of **202** was provided by single crystal X-ray diffraction (**Figure 2.3**).

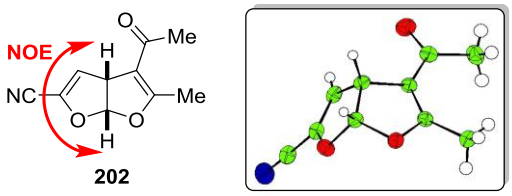
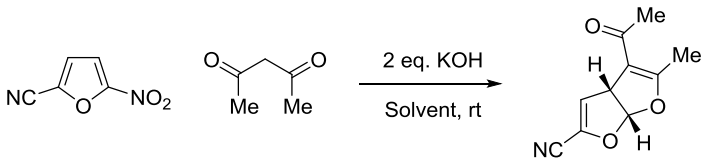


Figure 2.3 *NOE correlation and X-ray structure to confirm cis-stereochemistry of* **202**

Reaction in DMF (**Entry 2**) afforded dihydrofurofuran **202** in a marginally diminished yield of 67% compared to 75% for DMSO (**Entry 1**), as might be expected for solvents of similar polarity (ε_{DMF} = 36.7, ε_{DMSO} = 46.7). Surprisingly, HMPA (**Entry 3**) and DMPU (**Entry 4**) were much poorer solvents for this reaction, affording **202** in only 18% and 23% respectively after 24 hours. However, this did not present a significant problem, as these would not be desirable solvents for the reaction, both in terms of the toxicity of HMPA, and also due to the relatively high polarity of these solvents, which might preclude efficient asymmetric induction. Acetonitrile (**Entry 5**) afforded furan **202** in a pleasing 72% yield after a slightly prolonged reaction time, presumably due to the low solubility of KOH in this solvent, whilst also proving much simpler to remove during work up. Less polar solvents such as CH_2Cl_2, Et_2O and PhMe did not show any conversion after 48 hours (**Entries 6-8**).



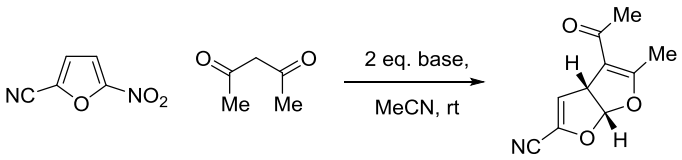
197 **199** (2 eq.) **202**

Entry	Solvent	Time (h)	Yield (%)[a]
1	DMSO	3	75
2	DMF	6	67
3	HMPA	24	18
4	DMPU	24	23
5	MeCN	16	72
6	CH_2Cl_2	24	n/o
7	Et_2O	24	n/o
8	PhMe	24	n/o

Table 2.3 *Solvent screen*
[a]*Isolated yield*

A number of bases were screened in acetonitrile to find optimal conditions for this reaction (**Table 2.4**). Alkali metal hydroxides (**Entries 1-3**) all furnished **202** in good yield, although with marginally higher yield for KOH. Of the alkali metal carbonates (**Entries 4-6**), Cs_2CO_3 appeared to be optimal, yielding **202** in an excellent yield of 87%, in a slightly shorter reaction time. $NaHCO_3$ (**Entry 7**) also appeared to be a good base for this reaction, with **202** formed in 77% yield. $Ca(OH)_2$ (**Entry 8**) did not appear to promote the reaction at all, presumably due to the complete insolubility of the base in acetonitrile. Organic bases

(**Entries 9-11**) also proved to be inefficient at promoting the reaction, with DMAP (**Entry 9**) showing no conversion, and DBU (**Entry 10**) and Et_3N (**Entry 11**) only affording dihydrofurofuran **202** in poor yield after 24 hours.



197 **199** (2 eq.) **202**

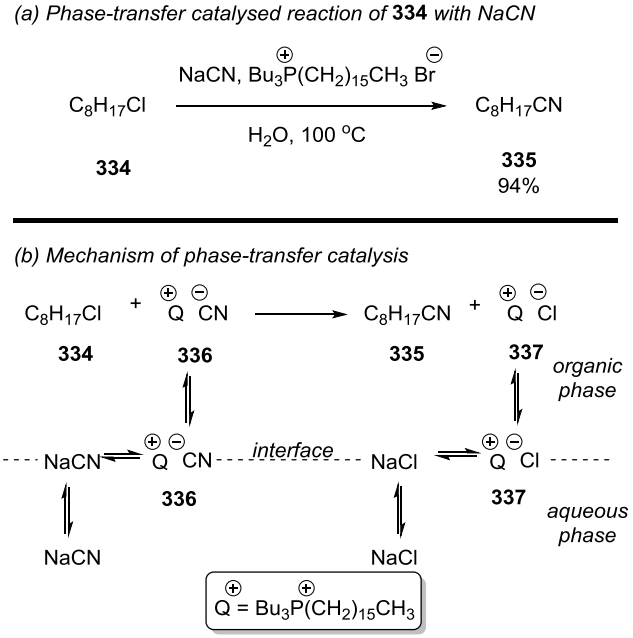
Entry	Base	Time (h)	Yield (%)[a]
1	KOH	16	75
2	NaOH	16	53
3	LiOH	16	57
4	Na_2CO_3	16	62
5	K_2CO_3	16	60
6	Cs_2CO_3	14	87
7	$NaHCO_3$	24	77
8	$Ca(OH)_2$	24	n/o
9	DMAP	24	n/o
10	DBU	24	37
11	Et_3N	24	27

Table 2.4 *Base screen*
[a]*Isolated yield*

2.2.3 Asymmetric phase-transfer catalysis in organic synthesis

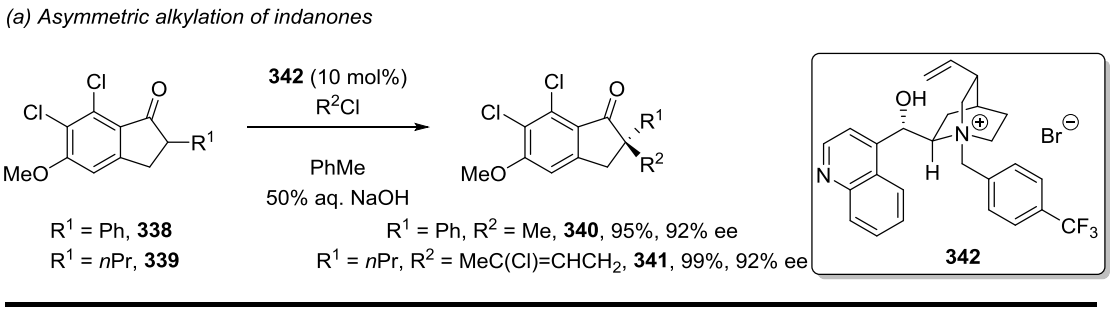
In recent years, the use of asymmetric phase-transfer catalysts (PTCs), particularly those based on quaternary ammonium salts has become an increasingly useful tool for the construction of chiral molecules.[155-157] Phase-transfer catalysts were first recognised as useful reagents for the acceleration of reactions by Starks and Makosza, reporting on the utility of tetrasubstituted ammonium or phosphonium salts in a range of different processes.[158-161]

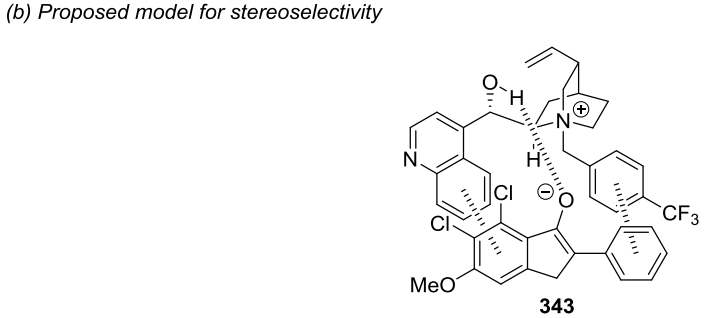
The general process of phase-transfer catalysis is governed by the ability of the counterion to facilitate transfer of the reaction species from one phase, into another phase where reaction occurs (**Scheme 2.21b**). This therefore promotes the reaction of two otherwise mutually insoluble compounds, such as for the example shown here, of the reaction of NaCN with an alkyl halide **334** (**Scheme 2.21a**).[156]



Scheme 2.21 *Phase-transfer catalysis in the reaction of* **334** *with NaCN*

The first example of an asymmetric reaction under phase-transfer conditions was reported by Dolling and coworkers at Merck.[162] By using chiral cinchonium salt **342** they were able to alkylate the substituted indanone **338** with chloromethane in excellent yield and very high enantioselectivity (**Scheme 2.22a**).



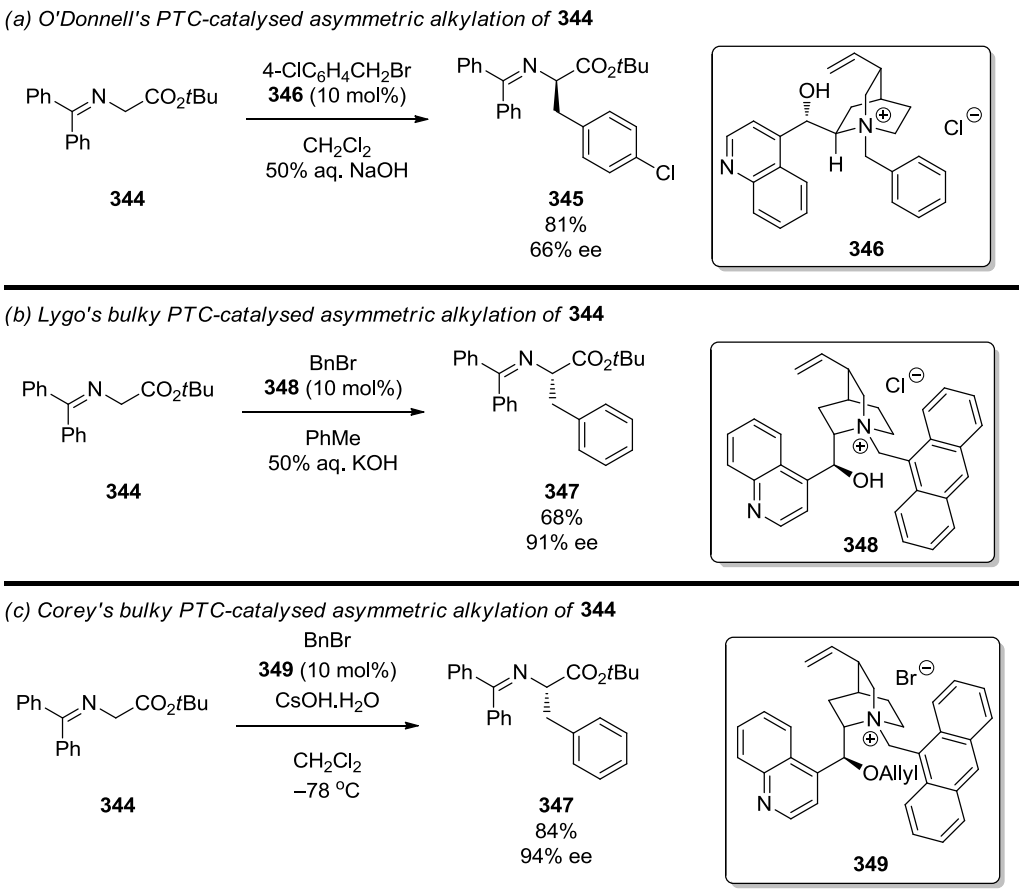


Scheme 2.22 *Dolling's asymmetric PTC-catalysed alkylation of indanones*

The reaction also proceeded smoothly with the use of 1,3-dichloro-2-butene as an electrophile for the α-propyl analogue **339**. The selectivity was proposed to be a result of π-

stacking between the quinoline ring of the catalyst with the indanone, and hydrogen bonding between the enolate of **338** and the free hydroxyl moiety in the catalyst (**Scheme 2.22b**).

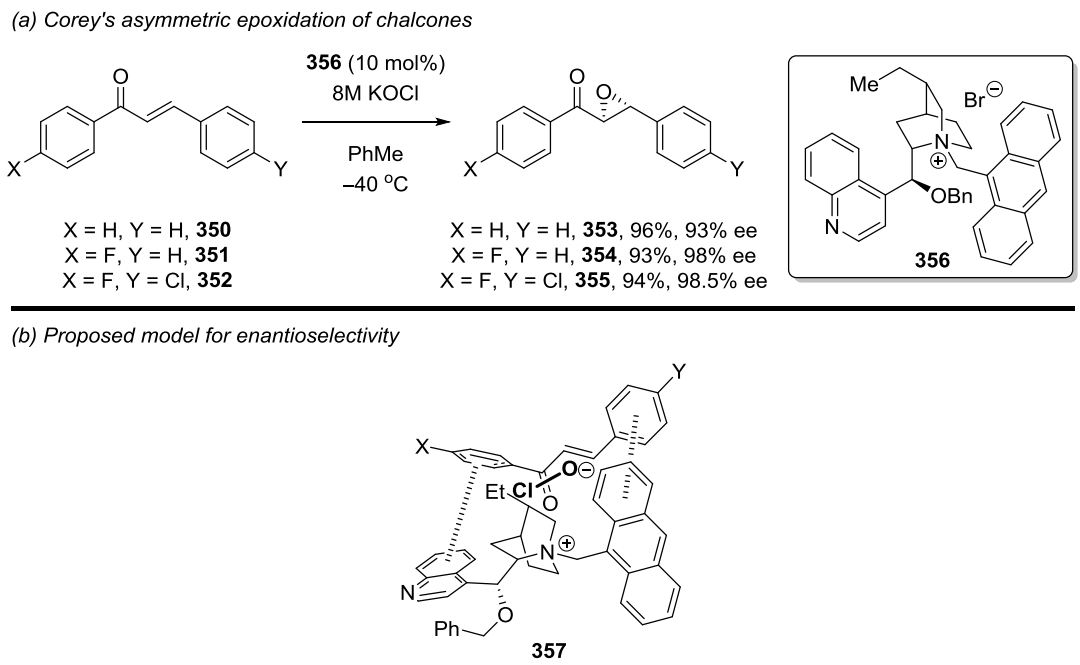
Further development of this process by O'Donnell saw the use of *Cinchona* alkaloid derived ammonium salts as PTCs for the alkylation of glycinate Schiff bases. For example, treatment of Schiff base **344** with 4-chlorobenzyl bromide in the presence of catalytic *N*-benzylcinchoninium chloride **346** afforded the desired alkylated product **345** in excellent yield, but only moderate enantioselectivity (**Scheme 2.23a**).[163] This process was improved by both Lygo (**Scheme 2.23b)**,[164-166] and Corey (**Scheme 2.23c**),[167] by the use of bulkier chiral PTCs based on the *N*-anthracenylmethyl moiety.



Scheme 2.23 *Asymmetric PTC-catalysed alkylation of Shiff base* **344**

PTCs based on *Cinchona* alkaloids have been applied to a diverse range of different reactions.[156,155] Examples include conjugate addition of enolates to Michael acceptors,[168,169] asymmetric nucleophilic aromatic substitution,[170] aldol reactions,[171,172] Darzens reaction,[173,174] Horner-Wadsworth-Emmons reaction,[175] cyclopropanation,[176]

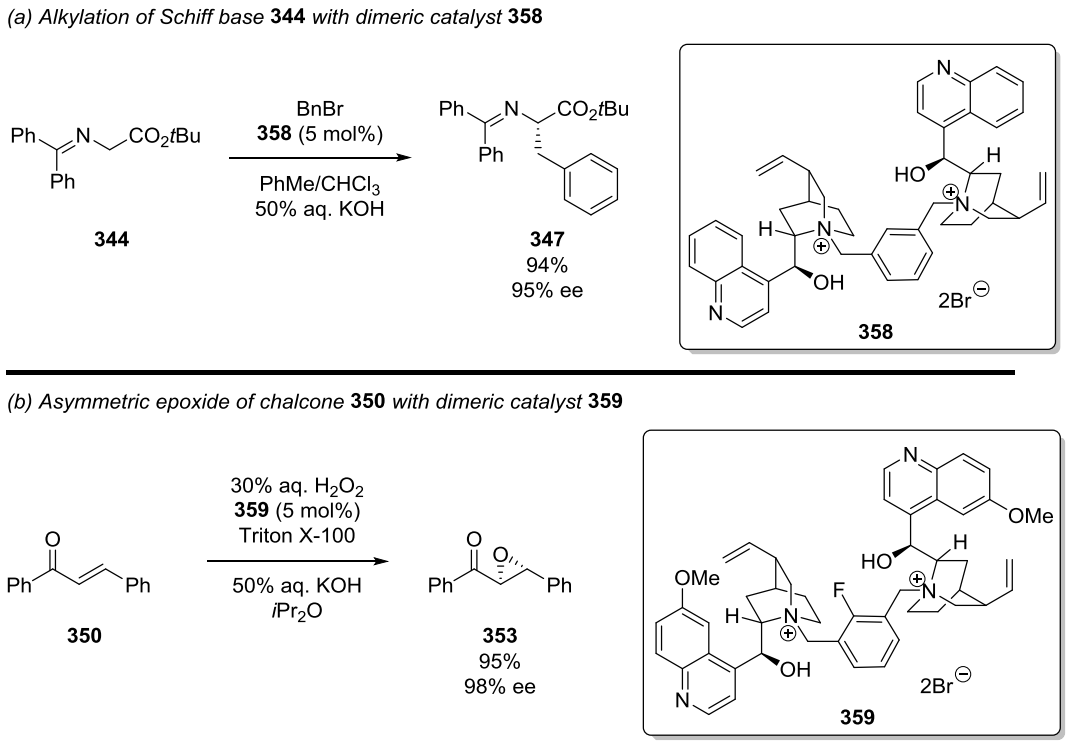
aziridination,[177,178] α-hydroxylation of ketones,[179] reduction of ketones,[180] and the α-fluorination of 1,3-dicarbonyl compounds.[181] One particularly impressive example is the epoxidation of chalcones developed by Lygo (up to 98% ee),[182] Shiori (up to 92% ee),[183] and Corey (up to 98.5% ee).[184] Corey's conditions employed 8M KOCl as the oxidising agent, with **356** as the PTC, which was able to oxidise a range of substituted chalcones in good to excellent yield and with enantioselectivities all over 91% (**Scheme 2.24a**). A plausible transition-state structure **357** was proposed, whereby the ketone aromatic ring and the carbonyl are out of conjugation (postulated since constrained ketones showed low enantioselectivity), allowing π-stacking between the ketone aryl group and the quinoline ring, and also between the chalcone moiety and the anthracenyl group, along with placement of the carbonyl oxygen close to the quaternary ammonium group. Thus, ion-pairing of hypochlorite allows facial selectivity in the addition to the chalcone (**Scheme 2.24b**).



Scheme 2.24 *Corey's asymmetric PTC-catalysed epoxidation of chalcones*

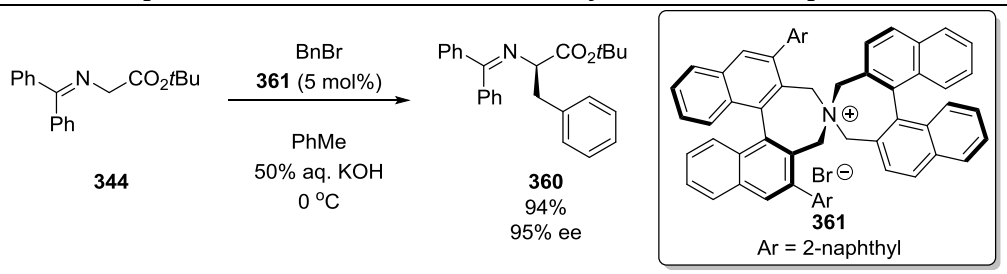
Other variations of *Cinchona* alkaloid PTCs have also appeared in the literature, including the use of dimeric PTCs based on a variety of aromatic linkers, developed by Jew and coworkers.[185-188] These catalysts have been utilised in a variety of processes. For example, *m*-xylyl PTC **358** has been used for the asymmetric alkylation of glycine Schiff base **344**, affording the benzylated product **347** in an impressive 95% ee, and 94% yield (**Scheme**

2.25a). [185,188] The fluorinated quinine analogue **359** has also been utilised in the epoxidation of the epoxidation of chalcones with hydrogen peroxide, allowing for the formation of epoxide **353** in an excellent 95% yield and 98% ee (**Scheme 2.25b**).[187]



Scheme 2.25 *Dimeric PTCs for asymmetric alkylation and epoxide reactions*

Aside from PTCs based on the *Cinchona* alkaloid scaffold, a number of different structures exist for asymmetric phase-transfer catalysis.[156] Perhaps the most well-known of these structures was the introduction of C_2-symmetric quaternary ammonium salts by Maruoka and coworkers in 1999.[189] Chiral ammonium salts based on a binaphthyl motif such as **361** showed excellent activity for the alkylation of Schiff base **344** in good to excellent yields, and with very high enantioselectivity (90-95% ee). For example, alkylation of **344** with benzyl bromide afforded the phenylalanine derivative **360** in an excellent 95% yield and 96% ee (**Scheme 2.26**). The synthetic route to these catalysts provided easy modification of the catalyst substructure, allowing tuning of the catalyst depending on requirements, although one downside was that preparation of the catalysts required a 10 step synthetic route from BINOL **313**, whereas *Cinchona* alkaloid derivatives can be prepared in 1 or 2 steps from the naturally-occurring alkaloid.[164, 167]



Scheme 2.26 *Asymmetric alkylation of Schiff base* **344** *with Maruoka's PTC* **361**

Maruoka and coworkers found that the second binaphthyl unit was not necessary for efficient catalytic activity.[190] Indeed, asymmetric catalysis was still possible with catalysts bearing only a conformationally flexible biphenyl unit, allowing greater opportunities for catalyst design. It was proposed that the activity of these catalysts could be attributed to the fact that the homochiral catalyst **362** had high catalytic activity, resulting in high enantioselectivities, whereas the atropoisomeric heterochiral **363** showed low activity (**Figure 2.4**), with the two species in rapid equilibrium under the reaction conditions.

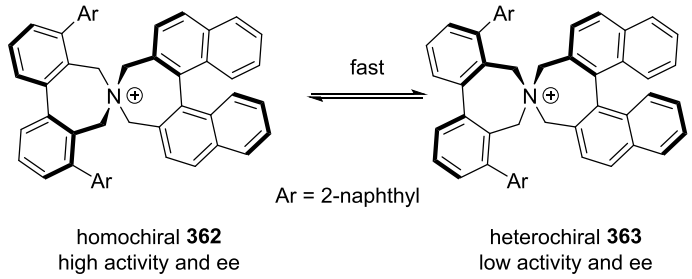


Figure 2.4 *Rapid equilibration of homo- and heterochiral atropisomers*

Various Maruoka-type catalysts, with highly varied substituents and substitution patterns, have been used in a plethora of different transformations, including the double alkylation of Schiff bases,[191] epoxidation,[192] Neber rearrangement,[193] Mannich reaction,[194] aldol reaction,[195,196] and Michael additions,[197] demonstrating their synthetic utility in forming carbon-carbon and heteroatom-carbon bonds in good yields and high enantioselectivities. However, the lengthy synthetic route to these catalysts, and also the high dependence of enantioselectivity on the catalyst substructure, somewhat limit their use in synthesis.

It is clear from the above review of asymmetric phase-transfer catalysis, that this can be a powerful method for the formation of chiral molecules with high enantiomeric excess. Thus,

it was decided to investigate its use in the synthesis of dihydrofuro[2,3-*b*]furans, in order to determine whether it would be possible to synthesise these structures as a single enantiomer.

Results and Discussion

2.2.4 Exploration of potential for phase-transfer catalysis

Due to the higher yields obtained in the above reaction with inorganic bases, it was considered that phase-transfer catalysis would provide a feasible mechanism to induce asymmetry in the formation of dihydrofurofurans such as **202**. Since the reaction is presumed to proceed *via* enolate **209**, ion-pairing of **209** with a chiral counterion, such as in **364** should provide a method for asymmetric induction, since it is the final intramolecular cyclisation that sets up both stereocentres in the product **202** (**Figure 2.5**).

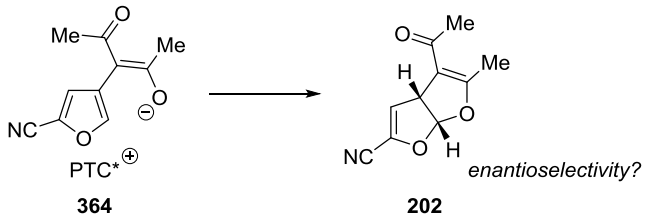
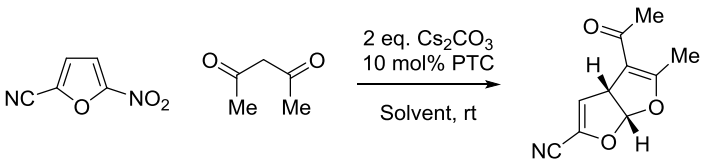


Figure 2.5 *Potential mechanism for asymmetric phase-transfer catalysis*

Conducting the reaction without a phase-transfer catalyst (PTC) in MeCN/H_2O (4:1) (**Table 2.5**, **Entry 1**) resulted in a similar yield for the formation of **202**, with a slight decrease in reaction time, presumably due to the increased solubility of Cs_2CO_3 in the aqueous phase.



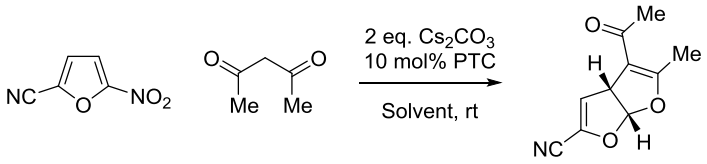
Entry	Solvent	PTC	Time (h)	Yield (%)[a]
1	MeCN/H_2O (4:1)	-	10	71
2	MeCN/H_2O (4:1)	TBAI	2	80
3	PhMe/H_2O (4:1)	TBAI	12	75

Table 2.5 *Effect of phase-transfer catalyst TBAI*

[a] Isolated yield

Use of Cs_2CO_3 as the optimal base, along with TBAI (**Entry 2**) resulted in a dramatically shortened reaction time, with bisdihydrofurofuran **202** being isolated in 80% yield after only 2 hours. It was considered that the use of a less polar organic solvent was necessary in order to facilitate efficient asymmetric induction, due to the requirement for tight ion-pairing between the enolate **209** and the chiral counterion. Pleasingly, conducting the reaction in toluene (**Entry 3**) afforded the desired product **202** in 75% yield after just 12 hours.

At this juncture, it was decided to use investigate the possibility of asymmetric phase-transfer catalysis for the formation of bicycle **202**. As such, *N*-benzylcinchonidinium chloride **315**, and *O*-allyl derivative **365** were investigated under a variety of conditions to see if any enantioselectivity could be observed under the reaction conditions (**Table 2.6**).



197 **199** (2 eq.) **202**

Entry	Solvent	PTC	Time (h)	Yield (%)[a]	ee (%)[b]
1	MeCN	**315**	4	65 (23% RSM)	0
2	PhMe	**315**	24	86	0
3	MeCN	**365**	4	94	0
4	PhMe	**365**	24	81	0
5	MeCN/H_2O (4:1)	**315**	6	67 (20% RSM)	0
6	PhMe/H_2O (4:1)	**315**	24	91	0

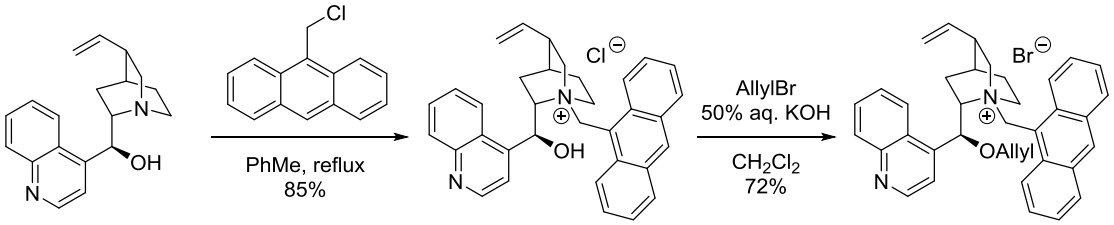
Table 2.6 *Initial attempts at asymmetric phase-transfer catalysis*
[a] Isolated yield [b] Enantiomeric excess was determined by chiral HPLC.

Unfortunately, none of the above conditions attempted proved amenable to the induction of enantioselectivity in the reaction, as confirmed by HPLC. Reaction times appeared to be considerably slower in PhMe (**Entries 2**,**4** and **6**), presumably due to lower solubility of base, even under phase-transfer conditions, resulting in a lower concentration of the enolate of diketone **199**, and thus slower reaction times, but yields were generally high.

2.2.5 Synthesis and testing of bulkier phase-transfer catalysts

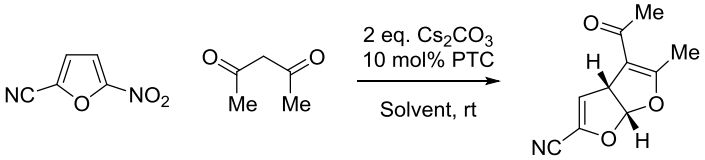
Cinchona alkaloid-derived PTCs with bulkier aromatic substituents, such as the *N*-(9-anthracenylmethyl) derivatives developed by groups of Corey and Lygo, [155,164,166,198,199] are known to be efficient catalysts for a variety of different transformations. As such,

anthracenyl cinchodinium catalyst **348** and its allyl derivative **349** were prepared *via* the method of Corey and co-workers (**Scheme 2.27**).[199] Cinchonidine **314** was stirred with 9-(chloromethylanthracene) in refluxing toluene for 3 hours to furnish *N*-(9-anthracenylmethyl)cinchonidinium chloride **348** in 85% yield. Subsequent treatment of **348** with allyl bromide and 50% aqueous KOH in CH_2Cl_2 afforded *O*-allyl derivative **349** in 72% yield. Spectroscopic data for both compounds were consistent with the literature reported values.[199]



Scheme 2.27 *Preparation of PTCs* **348** *and* **349**

PTCs **348** and **349** were then employed in the reaction of furan **197** with acetylacetone **199** to ascertain the efficiency for these catalysts in imparting enantioselectivity in the nucleophilic dearomatisation/cyclisation reaction (**Table 2.7**).



Entry	Solvent	PTC	Time (h)	Yield (%)[a]	ee (%)[b]
1	MeCN/H_2O (4:1)	**348**	72	52 (18% RSM)	0
2	PhMe/H_2O (4:1)	**348**	72	87	13
3	MeCN/H_2O (4:1)	**349**	72	49 (24% RSM)	0
4	PhMe/H_2O (4:1)	**349**	72	51 (36% RSM)	0

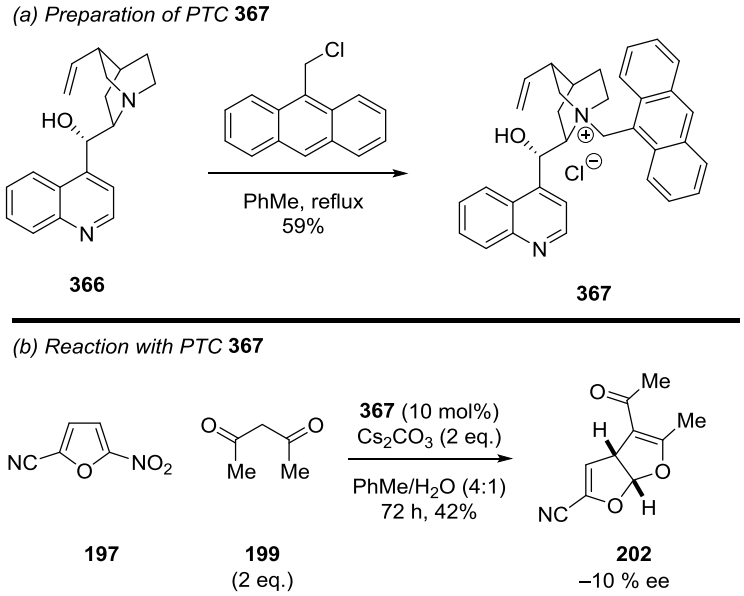
Table 2.7 *Screening of PTCs* **348** *and* **349**

[a] Isolated yield [b] Enantiomeric excess was determined by chiral HPLC.

It is noteworthy that the reaction time when PTCs **348** and **349** were employed were considerably longer than for the *N*-benzyl derivatives **315** and **365**, presumably as a consequence of the larger catalyst bulk leading to less efficient reaction. As such, the reactions were all worked up at 72 hours for consistency. Pleasingly, PTC **348** induced modest enantioselectivity in the reaction when performed in a PhMe/H_2O mixture (**Entry 2**),

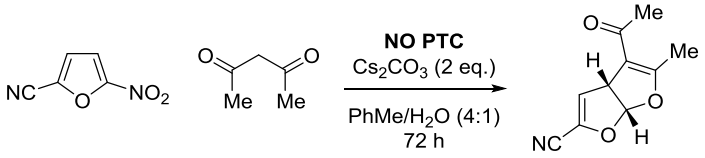
affording **202** in an excellent yield of 87% and 13% ee. However, allyl protected PTC **349** (**Entry 4**) was not found to promote asymmetric addition to furan **197**, and also resulted in a lower yield and lower conversion after 72 hours. This result is suggestive of the hydroxyl group in catalyst **348** being involved in the ordering of the transition state leading to enantioenriched product **202**, presumably *via* formation of a hydrogen-bond, or that the allyl group is too bulky to allow for efficient enantioinduction.

To confirm that the observed enantioselectivity observed was a genuine result, the pseudoenantiomeric PTC **367**, prepared from cinchonine **366** in 59% yield was also utilised as a PTC in the reaction. Pleasingly, PTC **367** afforded compound **202** in 10% ee in favour of the opposite enantiomer, although in a considerably reduced yield of only 42% (**Scheme 2.28**). This result therefore confirmed that the observed enantioselectivity was genuine.



Scheme 2.28 *Preparation of PTC* **367** *and application to dearomatisation of furan* **197**

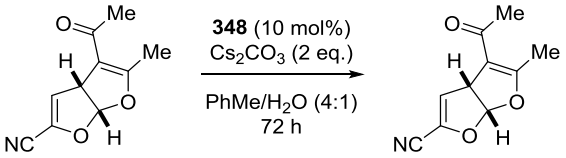
A background reaction in the absence of PTC would potentially be responsible for a low ee in these reactions. Previous results had indicated this not to be the case with toluene as solvent (*vide supra*), but to confirm this the reaction was conducted in the absence of a PTC, perhaps due to the marginal solubility of Cs_2CO_3 in toluene (**Scheme 2.29**). Pleasingly, only trace formation of product was observed after 72 hours, confirming that background reaction was not the cause of low ee in this reaction.



197 **199** (2 eq.) **202** trace

Scheme 2.29 *Control reaction in the absence of PTC*

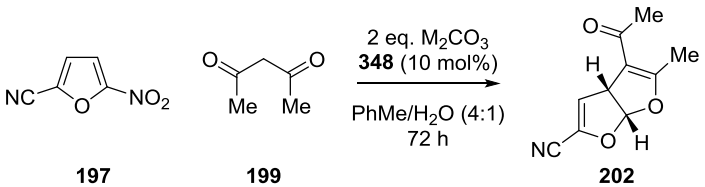
The lack of a background reaction was promising, indicating that the ee observed was likely the upper limit for PTC **348** under the present reaction conditions. However, to further confirm this fact, enantioenriched product **202** (13%) ee was resubjected to the reaction conditions for a further 72 h (**Scheme 2.30**). Pleasingly, product **202** was recovered with the same degree of enantiomeric excess, indicating that long reaction time under basic conditions was not resulting in a loss of enantioselectivity *via* a reversible reaction.



202 13% ee **202** 13% ee

Scheme 2.30 *Control experiment – erosion of ee under reaction conditions*

This result was very promising, as combined with the lack of background reaction, it seemed to suggest that the reaction conditions were not causing the low value observed for the enantiomeric excess. A further test for any solubility of Cs_2CO_3 under the reaction conditions was conducted by utilising other alkali metal carbonates (**Table 2.8**), to see if these had any observable effect on the enantioselectivity of the reaction.



197 **199** (2 eq.) **202**

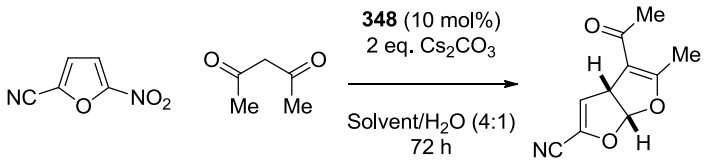
Entry	M	Yield (%)[a]	ee (%)[b]
1	Li	52	13
2	Na	54	10
3	K	46	12
4	Cs	87	13

Table 2.8 *Use of other alkali metal carbonates*

[a] Isolated yield [b] Enantiomeric excess was determined by chiral HPLC.

However, with Li_2CO_3, Na_2CO_3 and K_2CO_3 the yields were all observed to be considerably lower than for Cs_2CO_3, although the enantioselectivity observed was in the region 10-13%, further confirming that the low ee observed was not due to some marginal solubility of Cs_2CO_3 in toluene.

The choice of solvent was then investigated for this reaction, to see if other non-polar solvents were more appropriate for the induction of the enantioselectivity in the formation of **202** (**Table 2.9**).



197 **199** (2 eq.) **202**

Entry	Solvent	Yield (%)[a]	ee (%)[b]
1	Pentane	n/o	-
2	Hexane	n/o	-
3	DCE	39	<5
4	DME	31	0
5	PhCl	43	<5
6	*m*-Xylene	51	10
7	MTBE	n/o	-
8	*i*Pr_2O	n/o	-
9	Diglyme	18	0
10	2-MeTHF	57	<5
11	$PhCF_3$	77	<5

Table 2.9 *Screening of solvents for enantioselectivity*
[a] Isolated yield [b] Enantiomeric excess was determined by chiral HPLC.

It was found that there was no conversion to product **202** at all in hydrocarbon solvents (**Entries 1 and 2**), or in ethereal solvents (**Entries 7 and 8**). Low ee was observed in dichloroethane (**Entry 3**), chlorobenzene (**Entry 5**), *m*-xylene (**Entry 6**), 2-methyltetrahydrofuran (**Entry 10**), and α,α,α-trifluorotoluene (**Entry 11**), all in lower yields and enantioselectivity than the reaction in toluene. Only racemic **202** was afforded in dimethoxyethane (**Entry 4**) and diglyme (**Entry 9**). As such it appeared that toluene was still the optimal choice of solvent, and variation of catalyst structure might be an appropriate area of investigation in terms of improving enantioselectivity.

2.2.6 Synthesis and screening of a library of phase-transfer catalysts

In order to investigate the effect of catalyst structure and electronics on the observed enantioselectivity of the nucleophilic dearomatisation reaction, a range of different *Cinchona* alkaloid-derived PTCs were prepared according to literature procedures (**Figure 2.6**).

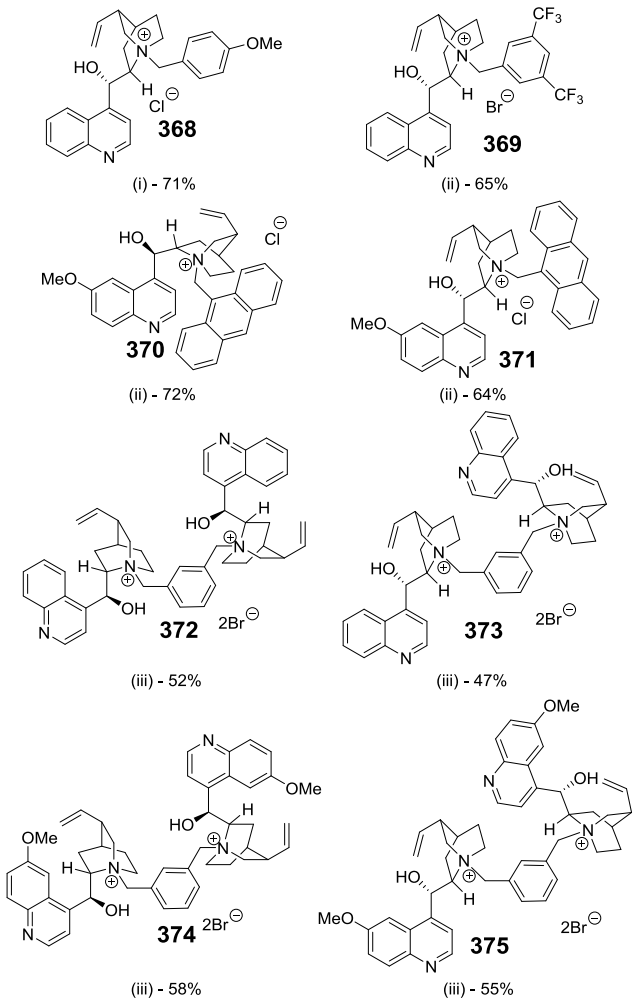


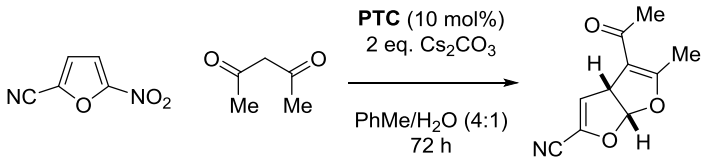
Figure 2.6 *Synthesis of PTCs* **368-375**

Conditions: (i) THF, reflux (ii) PhMe, reflux (iii) EtOH/DMF/$CHCl_3$ (5:2:6, v/v/v), 100 ^oC

To look at the effects of the *N*-benzylic aromatic substituent, electron-rich *p*-methoxybenzyl catalyst **368** was prepared according to the literature procedure in 71% yield,[200] and *m,m'*-bis(trifluoromethyl) catalyst **369** was prepared in 65% yield.[201] To investigate the nature of the electronics of the quinoline functionality of the catalyst, *N*-(9-anthracenylmethyl) derivatives of quinine and quinidine were prepared, affording catalysts **370** and **371** in 72% and 64% yields respectively. There has also been an increased interest in dimeric dicationic PTCs since their introduction by Jew and co-workers in 2001,[185] and as such the *m*-xylyl

derivatives of cinchonidine, cinchonine, quinine and quinidine (PTCs **372-375**) were prepared according to the known literature procedure.[185] In each case, spectroscopic data was consistent with that reported in the literature.

These catalysts were then resubjected to the standard reaction conditions to see their effect on the enantioselectivity of the reaction (**Table 2.10**).



197 **199** (2 eq.) **202**

Entry	PTC	Configuration	Solvent	Yield (%)[a]	ee (%)[b]
1	**368**	(8*R*, 9*S*)	PhMe	51	<−5
2	**369**	(8*R*, 9*S*)	PhMe	39	<−5
3	**370**	*(8S, 9R)*	PhMe	12	<5
4	**371**	(8*R*, 9*S*)	PhMe	52	−26
5	**372**	*(8S, 9R)*	PhMe	46	−26
6	**373**	(8*R*, 9*S*)	PhMe	23	<5
7	**374**	*(8S, 9R)*	PhMe	7	<−5
8	**375**	(8*R*, 9*S*)	PhMe	9	<5
9	**372**	*(8S, 9R)*	PhMe/$CHCl_3$ (7:3)	25	−20
10	**373**	(8*R*, 9*S*)	PhMe/$CHCl_3$ (7:3)	14	<5
11	**374**	*(8S, 9R)*	PhMe/$CHCl_3$ (7:3)	21	<−5
12	**375**	(8*R*, 9*S*)	PhMe/$CHCl_3$ (7:3)	24	<5

Table 2.10 *Screening of PTCs* **368-375**

[a] Isolated yield [b] Enantiomeric excess was determined by chiral HPLC.

Use of the *p*-methoxybenzyl catalyst **368** (**Entry 1**) afforded **202** in only a moderate yield of 51%, and negligible ee, of the same sign as with PTC **367**, as would be expected given that they are both derived from cinchonine **366**. A similar result was observed for the electron-deficient *m*,*m*'-bis(trifluoromethyl) PTC **369** (Entry **2**), albeit with a marginally lower yield. The lower ee for these two substrates suggest that the bulkyl anthracenyl moiety was important in imparting enantioselectivity in the reaction. *N*-(9-Anthracenylmethyl)quininium catalyst **370** (**Entry 3**) also showed a low degree of asymmetric induction in this reaction, whereas its pseudoenantiomer, quinidine-derived **371** showed a considerably improved ee of −26% (**Entry 4**), although in a relatively disappointing yield of 52%. Dimeric cinchonidine catalyst **372** also showed a promising level of enantioselectivity of −26% (**Entry 5**), but again in only 46% yield, a result of the sluggish rate of this reaction with the increasing bulk

of catalyst. Interestingly, the sense of enantioselectivity with this catalyst is opposite to that observed with the monomeric *N*-(9-anthracenylmethyl)cinchonidinium salt **348**, although this is perhaps not entirely surprising, since the different structure of the cation, and therefore presumably altered mode of binding is likely to lead to a significantly different transition state for the cyclisation. This trend to show the opposite sense of enantioselectivity to the monomeric PTC was observed for all PTCs **372-375** (**Entries 5-8**), although only catalyst **372** showed a decent degree of induction. Conducting the reaction of these PTCs in a toluene/chloroform mixture, as in the initial reports utilising these catalysts in high ee,[185] solely resulted in a decrease in yield and enantioselectivity (**Entries 9-12**).

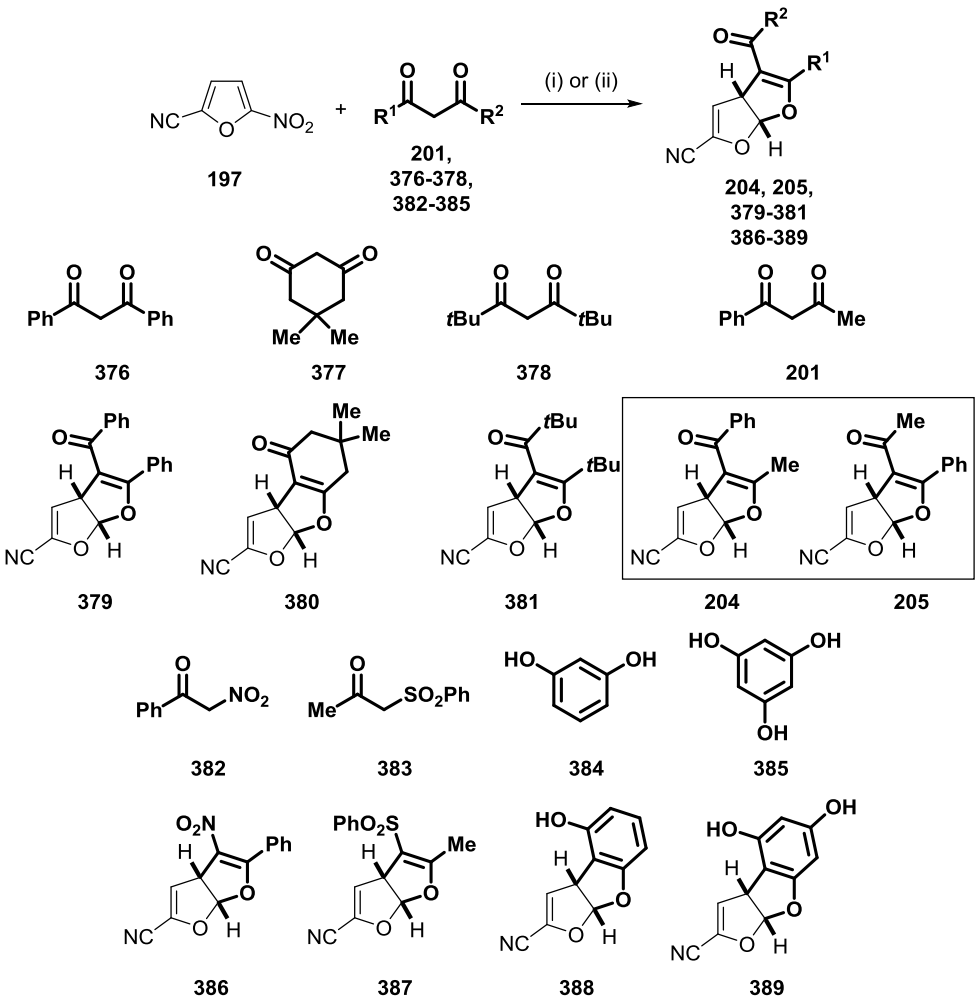
2.2.7 Application to other substrates

Although overall enantioselectivities were observed to be poor for this reaction, it was still deemed worthwhile to investigate the viability of other 1,3-diketone derivatives in this reaction, since by variation of the R groups of the diketone, one might expect this to have some role to play in the enantioselectivity of the reaction. As such, a number of 1,3-diketones were subjected to the reaction conditions (**Table 2.11**).

The use of diphenylketone **376** afforded bisdihydrofurofuran **379** in moderate yield with both TBAI and PTC **348** (**Entries 1** and **2**). It was envisaged that the two phenyl groups of diketone **376** might encourage π-stacking with the catalyst in the transition state, but unfortunately no enantioinduction was observed when PTC **348** was employed. Dimedone **377** was also a good substrate for the reaction, affording tricyclic compound **379** in good to excellent yield, although again with no observed enantioselectivity. Unsymmetrical ketone **201** gave two regioisomeric ketones **204** and **205** under the reaction conditions, and thus was not investigated in the enantioselective reaction.

Disappointingly, bulky *tert*-butyl ketone **378** did not participate in the reaction at all. Ketones with α-electron withdrawing groups such as α-nitroacetophenone **382** and phenylsulfonyl acetone **383** also did not take part in the reaction (**Entries 8** and **9**). It was hoped that phenolic compounds such as resorcinol **384** and phloroglucinol **384** might be amenable to the cyclisation reaction, since they would provide access to benzo-fused compounds such as **388**

and **389**, which are related to the aflatoxin family of biologically active natural products,[153] however, these too proved resistant to the reaction conditions.



Entry	Diketone	Product	Conditions	Yield (%)[a]	ee (%)[b]
1	**376**	**379**	(i)	65	-
2	**376**	**379**	(ii)	56	0
3	**377**	**380**	(i)	78	-
4	**377**	**380**	(ii)	61	0
5	**201**	**204** and **205**	(i)	31 + 26	-
7	**378**	**381**	(i)	n/o	-
8	**382**	**386**	(i)	n/o	-
9	**383**	**387**	(i)	n/o	-
10	**384**	**388**	(i)	n/o	-
11	**385**	**389**	(i)	n/o	-

Table 2.11 *Screening of other 1,3-diketones*

Conditions: (i) TBAI (10 mol%), 2 eq. Cs_2CO_3, PhMe/H_2O (4:1), 72 h (ii) **348** (10 mol%), 2 eq. Cs_2CO_3, PhMe/H_2O (4:1), 72 h

[a] Isolated yield [b] Enantiomeric excess was determined by chiral HPLC.

2.2.8 Attempted alternative route to dihydrofuro[2,3-b]furans

Since it appeared the substrate scope was limited, we were interested in exploring an alternative route to these types of products. The proposed mechanism for the reaction proceeds *via* a 1,3-diketone **390** that then undergoes cyclisation, and so if this 1,3-diketone could be prepared *via* an alternative route this should then provide access to a range of differentially substituted dihydrofurofurans **392** (**Figure 2.7**)

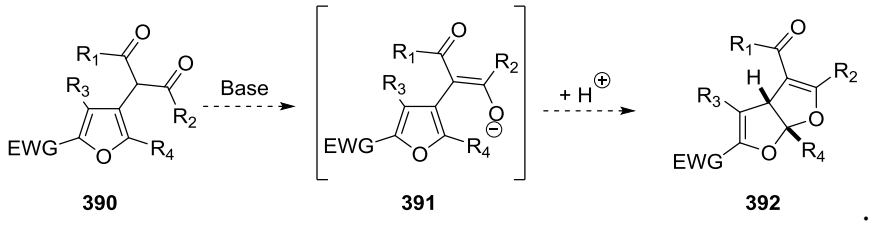
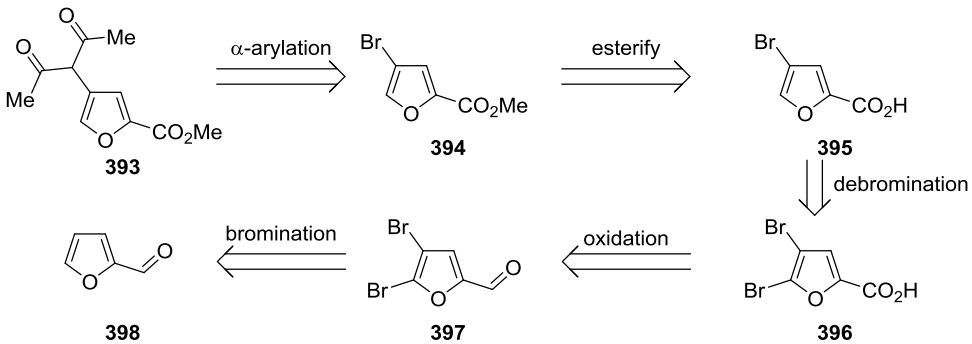


Figure 2.7 *Proposed alternative route to dihydrofurofurans* **392**

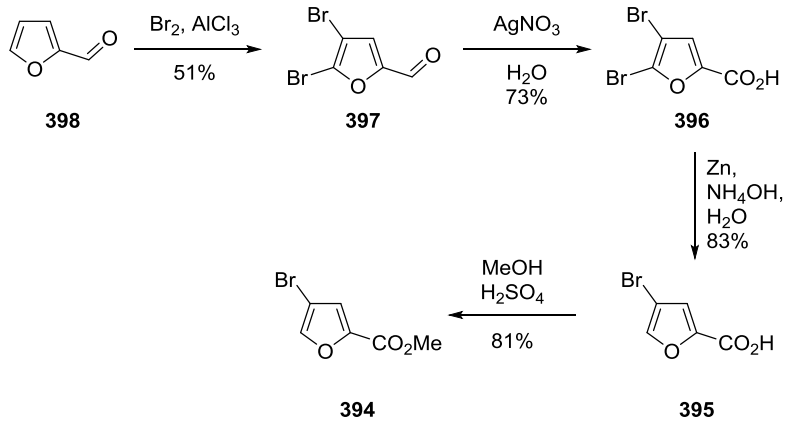
It was proposed that the requisite 2-(3-furyl)-1,3-diketone **390** could be synthesised *via* a transition metal-catalysed α-arylation reaction of a 1,3-diketone. However, there are no examples in the literature of the α-arylation of 1,3-diketones with 3-halofurans, although there is at least one example of the coupling of a 1,3-diester with 3-bromothiophene, providing some promise.[202] 1,3-Diketones have also proven to be less widely applicable to the α-arylation reaction than other ketones, although there are still a number of methods available for the coupling of 1,3-diketones with aryl halides.[203]

A synthetic route was devised for the synthesis of diketone **393**, possessing an electron-withdrawing ester group. Retrosynthetic analysis suggested the synthesis of the 4-bromofuroic acid ester **394** would be desirable for the α-arylation reaction, synthesisable in four steps from commercially available furfural **398** (**Scheme 2.31**).



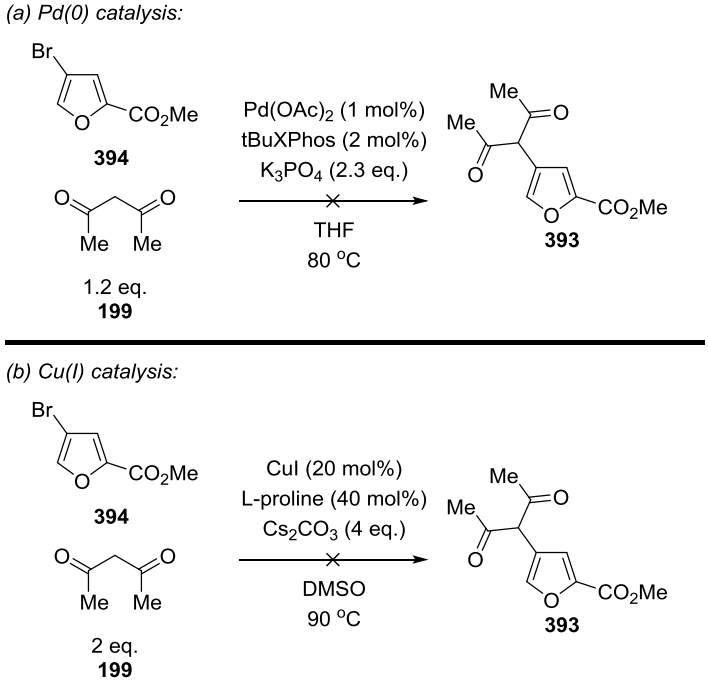
Scheme 2.31 *Retrosynthetic analysis of 1,3-diketone* **393**

As such, 4,5-dibromofurfural **397** was prepared in 51% yield from furfural **398** upon treatment with $AlCl_3$ and neat Br_2, according to the known literature procedure (**Scheme 2.32**).[204] Oxidation with $AgNO_3$ in water furnished the carboxylic acid **396** in 73% yield,[205] which was subsequently debrominated with elemental Zn in aqueous ammonia solution in 87% yield.[206] Finally, formation of the methyl ester **394** was achieved from 4-bromo-2-furoic acid **395** in 81% yield by treatment with H_2SO_4 in methanol at 50 °C,[207] affording the desired compound **395** in 25% yield over 4 steps from cheap, commercial available furfural **398** (£0.03/g, Sigma-Aldrich). Compound **398** exhibited two 1H doublets (*J* 0.7 Hz) in the 1H NMR spectrum at 7.61 and 7.17 ppm respectively, corresponding to a weak ^4J coupling, along with a 3H singlet at 3.90 ppm corresponding to the ester methyl group, consistent with the literature data.[207]



Scheme 2.32 *Synthesis of methyl 4-bromo-2-furoate* **394**

The α-arylation of 1,3-diketones with the bromofuran **394** was then investigated under conditions of both palladium(0) (**Scheme 2.33a**),[208] and copper(I) catalysis (**Scheme 2.33b**).[209] Unfortunately all efforts returned a complex mixture of products, with no evidence suggesting formation of the desired 2-(3-furyl)-1,3-diketone **393**.



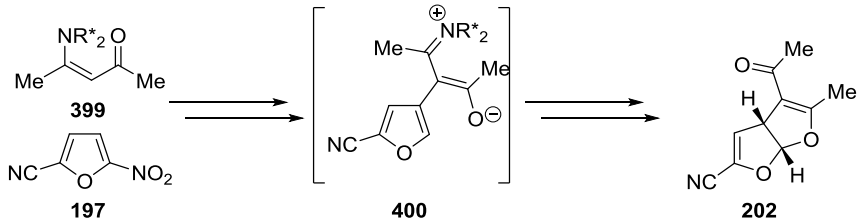
Scheme 2.33 *Attempts at α-arylation of bromofuran* **394**

The inability to synthesise the desired 2-(3-furyl)-1,3-diketones required precluded further investigation of this method in the synthesis of dihydrofurofurans.

2.2.9 Chiral amine catalysis for the nucleophilic dearomatisation of furans

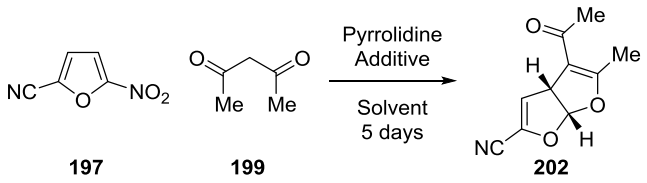
As an alternative method for the synthesis of chiral dihydrofurofurans, it was considered that enamine catalysis might provide a feasible option for promoting enantioselectivity in the reaction. There are a number of examples of enamine catalysis in the reaction of 1,3-diketones,[210] and thus it was envisaged that this might provide a fruitful area of research.

It was proposed that amine-catalysed addition of the 1,3-diketone, *via* enamine **399** to nitrofuran **197**, followed by elimination of HNO_2, would provide the requisite imino-enolate **400**, which might then cyclise on one face of the furan selectivity to provide enantioenriched dihydrofurofuran **202** upon hydrolysis (**Scheme 2.34**).



Scheme 2.34 *Proposed route to chiral dihydrofurofurans* **197** *via enamine catalysis*

To investigate the feasibility of this method for the synthesis of dihydrofurofurans, pyrrolidine was chosen as a model amine for the cyclisation of furan **197** with acetylacetone **199**, and screened to a variety of conditions (**Table 2.12**).



197 **199** **202**

Entry	eq. pyrrolidine	Additive (0.1 eq.)	Solvent	Yield (%)[a] (RSM)
1	0.5	-	DMSO	36 (58)
2	0.5	-	MeCN	22 (74)
3	0.5	-	DMF	29 (65)
4	0.5	-	CH_2Cl_2	Trace
5	0.5	-	THF	Trace
6	0.5	-	Dioxane	Trace
7	0.5	-	Et_2O	n/o
8	0.5	-	PhMe	n/o
9	1.0	-	DMSO	73 (22)
10	1.0	$Sc(OTf)_3$	DMSO	n/o
11	1.0	$Cu(OTf)_2$	DMSO	n/o
12	1.0	$Zn(OTf)_2$	DMSO	n/o
13	1.0	$ZnCl_2$	DMSO	n/o
14	1.0	TFA	DMSO	Trace
15	1.0	TFA	DMF	Trace
16	1.0	TFA	CH_2Cl_2	n/o
17	1.0	$PhCO_2H$	DMSO	Trace
18	1.0	$PhCO_2H$	DMF	Trace
19	1.0	$PhCO_2H$	CH_2Cl_2	n/o
20	1.0	**405**	DMSO	15 (72)

Table 2.12 *Screening of conditions for enamine-promoted formation of* **202**

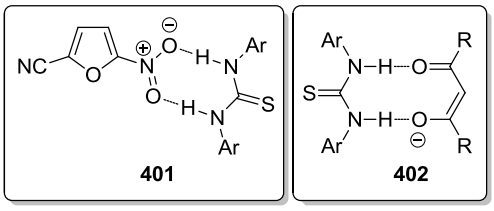
[a] Isolated yield

Conducting the reaction with 0.5 eq. pyrrolidine in the absence of any additives in a variety of solvents resulted only in low conversion to the desired product **202**, with the highest yields obtained in DMSO, MeCN and DMF (**Entries 1-3**), although these were unfortunately no higher than the 36% achieved in DMSO (**Entry 1**). The use of less polar solvents resulted in only trace conversion (**Entries 4-8**). However, increasing the equivalents of pyrrolidine in DMSO resulted in a much higher yield of the desired product, affording dihydrofurofuran **202** in 76% yield (**Entry 9**).

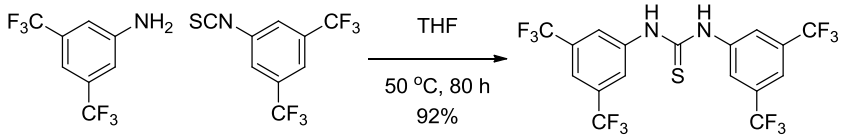
In an attempt to increase both the yield, and the rate of reaction, a number of different Lewis and Brønsted acids were screened, in the hope that they would either coordinate to, or protonate the nitro group of **197**, thus increasing the electrophilicity, and increasing the rate of conjugate addition. Using 0.1 equivalents of $Sc(OTf)_3$, $Cu(OTf)_2$, $Zn(OTf)_2$ and $ZnCl_2$ solely led to complete retardation of the reaction (**Entries 10-13**), and similar results were achieved with the Brønsted acids TFA and benzoic acid in a variety of solvents (**Entries 14-19**).

It was also hypothesised that the nitro group might be activated *via* hydrogen bonding, or that a thiourea might hydrogen bond to the dicarbonyl, increasing its acidity (**Scheme 2.35a**). Thioureas are well known in the literature as activating groups in the conjugate addition to nitroalkenes,[211] and as such, electron-deficient thiourea **405** was prepared *via* the known literature method (**Scheme 2.35b**),[212] combining bis(trifluoromethyl)aniline **403** with the isothiocyanate **404** to afford thiourea **405** in 92% yield. The structure of **405** was confirmed by the broad singlet (2H) at 10.65 ppm in the ^{1}H NMR spectrum, corresponding to the two thiourea N*H* protons, and a peak at 180.6 ppm in the ^{13}C spectrum, consistent with the presence of a thiourea, and consistent with data reported in the literature.[212] Addition of 0.1 equivalents of the thiourea **405** to the cyclisation reaction also appeared to retard the reaction, affording **202** in only 15% after 5 days, with 72% of the starting material **197** recovered (**Entry 20**).

(a) Proposed methods of activation by thiourea **405**



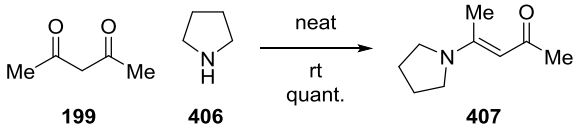
(b) Synthesis of thiourea **405**



403 **404** **405**

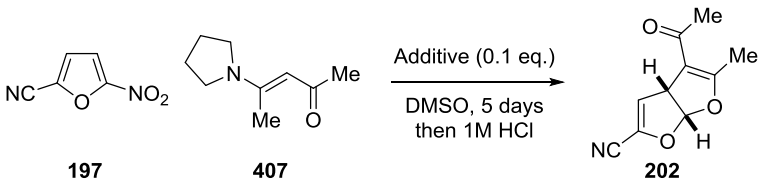
Scheme 2.35 *Proposed activation by, and synthesis of, thiourea* **405**

At this point, it was decided that due to the requirement for stoichiometric amounts of pyrrolidine for the reaction to occur, the reaction may not be proceeding *via* enamine catalysis at all. Rather, pyrrolidine might just be acting as a base for the reaction. To determine whether an enamine was playing a role in the reaction, the enamine **407** formed by the condensation of pyrrolidine **406** with acetylacetone **199** was prepared by mixing the two starting materials neat for one hour at room temperature, to afford ketoenamine **407** in quantitative yield (**Scheme 2.36**).[213] NMR data was consistent with that reported in the literature for the (*E*)-isomer, as confirmed by the original authors *via* a NOESY experiment.[213]



Scheme 2.36 *Synthesis of enaminoketone* **407**

Enamine **407** was then reacted with nitrofuran **197** under a variety of conditions, followed by hydrolysis of the postulated iminium ion product to form **202**, to ascertain whether the reaction was indeed enamine-promoted, or if pyrrolidine was just acting as a base (**Table 2.13**).



Entry	Additive	Yield (%)
1	- (rt→100 °C)	n/o
2	$Sc(OTf)_3$	n/o
3	$Cu(OTf)_2$	n/o
4	$Zn(OTf)_2$	n/o
5	$ZnCl_2$	n/o
6	TFA	n/o
7	$PhCO_2H$	n/o
8	**406**	n/o

Table 2.13 *Attempts at cyclisation of enamine* **407**

Unfortunately, no reaction was observed under any of the attempted conditions, with only enamine **407** and furan **197** observed by TLC, thus providing further evidence that the reaction did indeed not proceed *via* enamine catalysis.

The fact that this reaction was amine promoted, if not *via* an enamine, still led to the possibility of the reaction being promoted by a chiral amine, *via* chiral Brønsted base catalysis, which is well documented in the literature for a number of different amines.[214] Accordingly, a library of chiral amines (**408-416**) was compiled (**Figure 2.8**), and screened as bases in the reaction of acetylacetone **199** with nitrofuran **197** for both yield and enantioselectivity (**Table 2.14**).

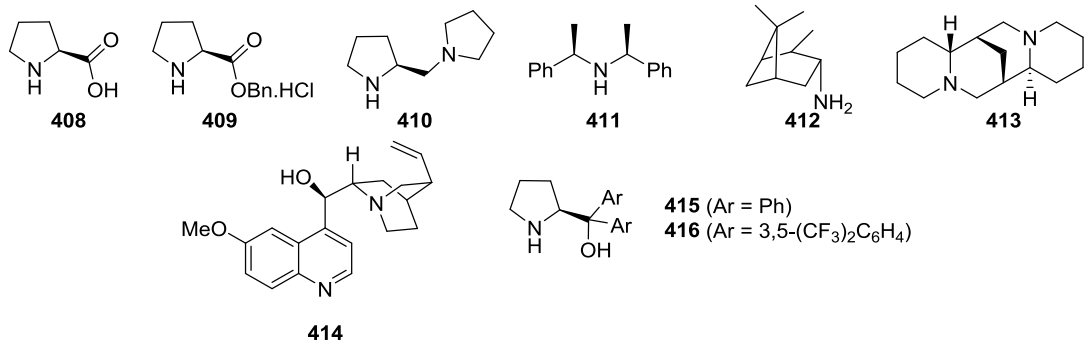
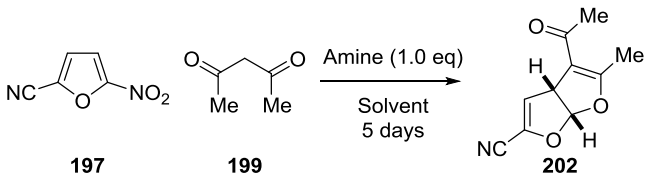


Figure 2.8 *Library of chiral amines* **408-416**



Entry	Amine	Solvent	Yield (%)[a] (RSM)	ee (%)[a]
1	**408**	DMSO (rt → 100°C)	n/o	-
2[c]	**409**	DMSO	36 (51)	0
3	**410**	DMSO	53 (39)	0
4	**411**	DMSO	28 (63)	0
5	**412**	DMSO	50 (42)	0
6	**413**	DMSO	68 (27)	0
7	**414**	DMSO	26 (65)	0
8	**415**	DMSO	43 (46)	0
9	**416**	DMSO	41 (43)	0
10	**413**	MeCN	68 (22)	0
11	**413**	DCM	53 (37)	0
12	**413**	PhMe	7 (88)	<5
13	**413**	PhMe (100°C)	36 (55)	0
14	**410**	PhMe	n/o	-
15	**410**	PhMe (100°C)	Complex mixture	-
16	**415**	PhMe	n/o	-
17	**416**	PhMe	n/o	-

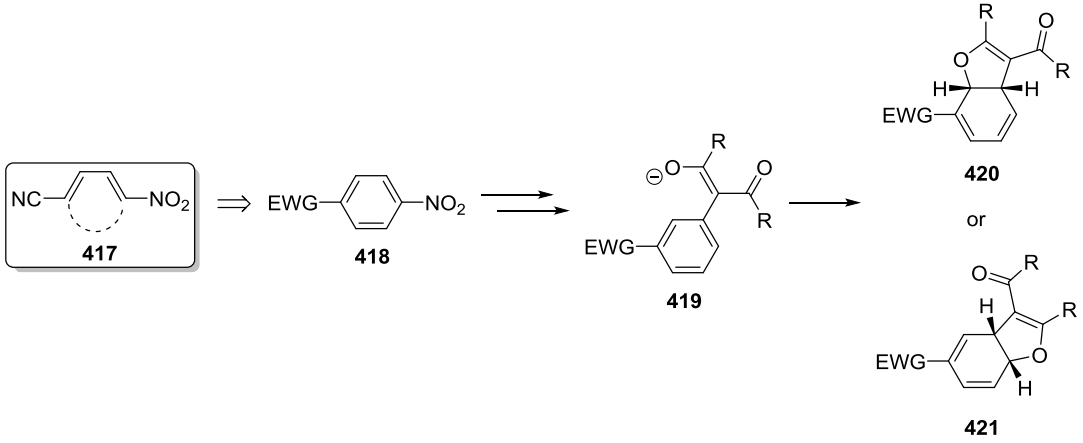
Table 2.14 *Screening of chiral amines* **408-416**

[a] Isolated yield [b] Enantiomeric excess was determined by chiral HPLC [c] 1.0 eq. $NaHCO_3$ added

Use of L-proline **408** showed no reaction at all (**Entry 1**), whereas benzyl ester **409** (along with 1 eq. of $NaHCO_3$ to yield the free base), afforded the desired product in 36% yield (**Entry 2**), although as a racemic mixture, as would be expected in such a polar solvent as DMSO. Bis-pyrrolidine **410** proved more efficient at promoting the reaction (**Entry 3**), yielding dihydrofurofuran **202** in 53% yield after 5 days, although again as a racemic mixture. Sparteine **413**, proved to be particularly efficient at promoting the reaction in comparison to the other amines screened, giving product **202** in 68% yield in both DMSO and MeCN (**Entries 6** and **10**). Attempts at performing the reaction in a less polar solvent such as toluene, resulted in a marked decrease in the yield of dihydrofurofuran **202** of only 7% yield (**Entry 12**), with a small excess of one enantiomer observed by HPLC. Warming the reaction to 100 °C afforded the desired product in an increased yield of 36% (**Entry 13**), but unfortunately as a racemic mixture. Bis-pyrrolidine **410** showed no reactivity at room temperature (**Entry 14**), whilst warming the reaction to 100 °C caused decomposition of the starting material (**Entry 15**) Attempts at using Jorgensen-Hayashi amines **415** and **416** in toluene resulted only in recovery of furan **197** at both room temperature and at 100 °C (**Entries 16** and **17**). These negative results thus obviated further investigation into the use of chiral amines for the asymmetric synthesis of dihydrofurofurans.

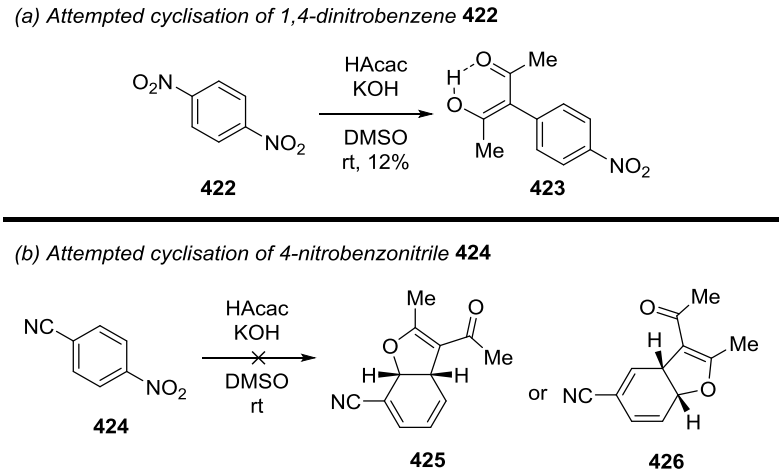
2.2.10 Attempts at dearomatisation of a benzenoid system

Although attempts to develop a methodology for the dearomatisation of furans in high yield and enantioselectivity had proved hitherto unsuccessful, the opportunity to expand the scope of this reaction by varying the structure of the electrophilic partner still presented a challenge that would lead to a variety of interestingly-structured products. As the furan **197** employed previously effectively contained a 1-nitro-4-cyano-1,3-butadiene unit **417**, it was reasoned that other substrates possessing this moiety might also prove responsive to the dearomatisation reaction. Despite a higher aromatic stabilisation energy, it was considered that under appropriate conditions this might be applied to the synthesis of [6,5]-fused heterocycles such as **420** or **421** (**Scheme 2.37**), which might then be oxidised to the corresponding benzofurans.



Scheme 2.37 *Potential nucleophilic dearomatisation of benzenoid systems*

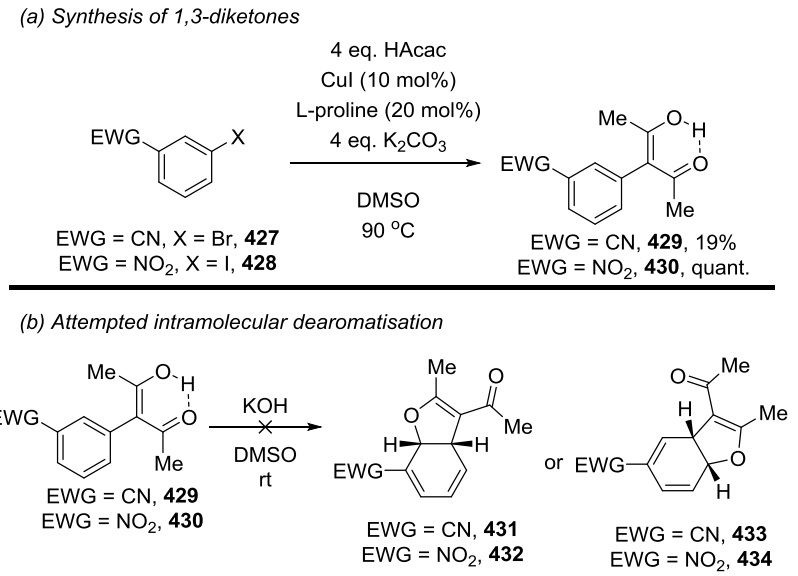
Treatment of 1,4-dinitrobenzene **422** with acetylacetone **199** and KOH in DMSO at room temperature, the standard conditions for dearomatisation of furans reported by Makosza and co-workers,[87] gave S_NAr product **423** as the solely observed product in 12% yield (**Scheme 2.38a**), confirmed by the presence of a broad singlet at 16.78 ppm in the ^1H NMR spectrum, consistent with literature data for this known compound. 4-Nitrobenzonitrile, however, proved resistant to reaction even at elevated temperature, yielding only recovered starting material (**Scheme 2.38b**).



Scheme 2.38 *Attempted dearomatisation of nitrobenzenes* **422** *and* **424**

Since it was considered that it might be difficult to achieve the desired addition *ortho* to the nitro group of the aromatic system, given the 1,4-disposition of the two electron-withdrawing groups in **422** and **424**, an alternative route to construct the desired intermediate was devised. Treatment of the halobenzenes **427** and **428** with excess acetylacetone **199**, catalytic CuI and L-proline in DMSO at 90 ^oC afforded *m*-cyano diketone **429** and *m*-nitro diketone **430** in 19%

and quantitative yield respectively (**Scheme 2.39a**). Unfortunately, no reaction was observed for the cyclisation to form the desired products, whereas at elevated temperatures only complex decomposition of the starting materials was observed (**Scheme 2.39b**).



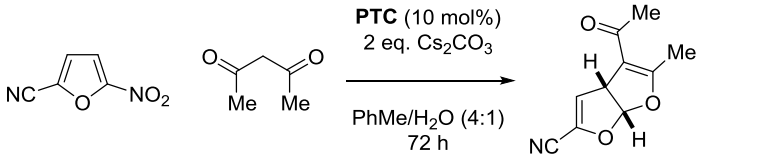
Scheme 2.39 *Synthesis of 2-aryl-1,3-diketones and attempted dearomatisation*

The failure of these substrates to show any tendency towards cyclisation left the project at a convenient position to move on to new areas of investigation, since it appeared that this route was not viable for the synthesis of [6,5]-fused heterocycles.

2.2.11 Conclusions

Initial studies into the variation of conditions for the nucleophilic dearomatisation of nitrofurans by 1,3-diketones showed that it was possible to conduct the reactions under conditions of racemic phase-transfer catalysis, resulting in short reaction times, in more experimentally convenient solvents.

The use of chiral PTCs based on *Cinchona* alkaloids was then attempted. It was found that bulkier *N*-benzylic groups were necessary on the PTC to achieve even modest ee. Optimal results in terms of enantioselectivity were found for the *N*-(9-anthracenylmethyl)quinidinium PTC **371**, and the dicationic quininium PTC **372**, affording dihydrofurofuran **202** in 52 and 46% yields respectively, both with a modest enantioselectivity of 26% ee (**Scheme 2.40**). However, the use of bulkier PTCs solely resulted in longer reaction times, and considerably diminished yields compared to less bulky *Cinchona* alkaloid-based PTCs.



Scheme 2.40 *Optimal results for the asymmetric PTC-catalysed formation of* **202**

Attempts to expand the scope of the reaction by changing the 1,3-diketone partner showed a limited range of compounds that were able to participate in the reaction. The use of ketones bearing an α-electron-withdrawing group such as nitro- **382**, or phenylsulfonyl **383**, resulted solely in the recovery of starting material, as was also the case for phenolic compounds **383** and **384**.

An alternative route was developed for the synthesis of the 2-(3-furyl)-1,3-diketone required for the cyclisation, but synthesis of this compound was hindered by difficulty in the α-arylation of 3-bromofuran **394**, a reaction unknown in the literature.

Attempts at an amine-catalysed/enamine-promoted reaction also proved unsuccessful, and control experiments showed that the reaction did not appear to be proceeding *via* an enamine-type mechanism. The lack of enantioselectivity observed in a screen of chiral amines obviated further investigation into this area.

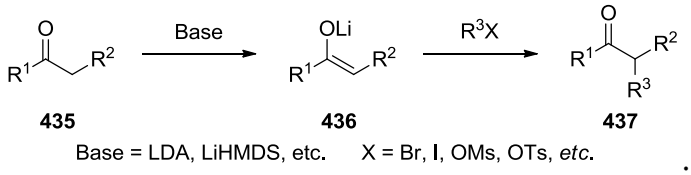
Finally, attempts at cyclisation of benzenoid systems was unsuccessful, presumably as a result of the higher aromatic stabilisation energy of the benzene ring, preventing nucleophilic addition to the ring.[2]

3: Introduction – Hydrogen Borrowing Alkylation Reactions with Alcohols

3.1 General principles of hydrogen borrowing

3.1.1 Alkylation of enolate equivalents

New methods for the formation of C-C bonds are of fundamental interest in the field of organic chemistry, allowing the rapid construction of complex molecular scaffolds.[215] The coupling of an enolate (or equivalent species) with an alkyl halide or sulfonate is one of the most highly utilised methods for such a transformation, although there are significant disadvantages to this process.[216-218] For example, these reactions require the use of (super)stoichiometric high molecular weight strong bases (typically LDA), large leaving groups (typically halides or tosylates, which are often toxic), and the resulting problems of low atom economy, and large amounts of inorganic waste (**Scheme 3.1**).

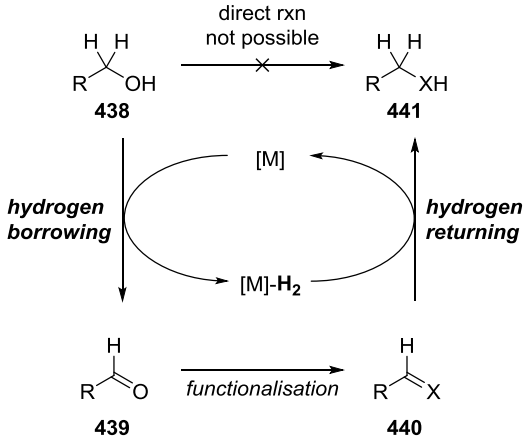


Scheme 3.1 *Typical enolate alkylation reaction*

The use of alcohols as alkylation agents would be desirable due to the low molecular weight waste produced (H_2O), but the direct displacement of hydroxide from an alcohol is inherently difficult due to the strength of the C-O bond (≈90 kcal mol^{-1}),[215] a problem exacerbated further under the strongly basic conditions usually required for such alkylation reactions, since the hydroxyl group becomes deprotonated, and thus an even worse leaving group. Despite these intrinsic difficulties in the alkylation of carbonyl compounds with alcohols, a great deal of research has been conducted in this field, and the transition metal-catalysed hydrogen borrowing reaction has become a powerful method to effect not only this conversion, but also the alkylation of a number of different functional groups.[215,219-223]

The general mechanism for a hydrogen borrowing reaction is a three step process (**Scheme 3.2**): (1) An alcohol **438** has two hydrogen atoms temporarily removed by the metal catalyst, in an oxidation of the substrate, to generate a more reactive intermediate **439**; (2) the reactive intermediate **439** undergoes further functionalisation with an incoming nucleophilic species

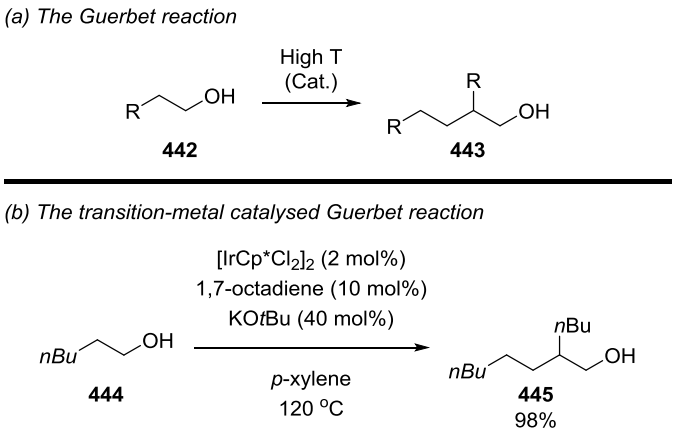
to form a new intermediate **440**; (3) this final intermediate is reduced by the redelivery of two hydrogen atoms previously "borrowed" to form the final product **441**.



Scheme 3.2 *General mechanism for hydrogen borrowing reactions*

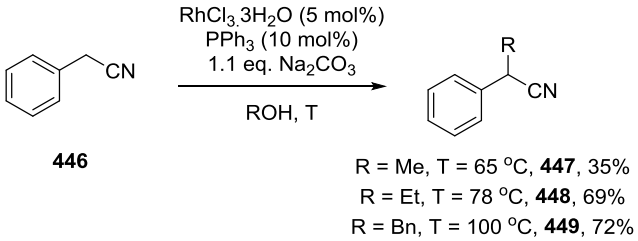
3.1.2 Early examples of hydrogen borrowing chemistry

The earliest examples of hydrogen borrowing-type chemistry are evident in the β-autoalkylative dimerisation of alcohols, a process known as the Guerbet reaction.[224,225] In this reaction, a primary alcohol dimerises to form a β-branched primary alcohol *via* oxidation, aldol reaction, and reduction steps (**Scheme 3.3a**). Although this reaction may occur in the absence of a hydrogen-transfer catalyst at high temperatures, this results in a variety of side products, often from Cannizzaro-type reactions, and thus lower temperature metal-catalysed variants are now well known (**Scheme 3.3b**).[226] Furthermore, the reaction does not have to be limited to the dimerisation of alcohols, and crossed-condensation may also occur, for example by the coupling of methanol and ethanol to form *iso*-butanol.[227]



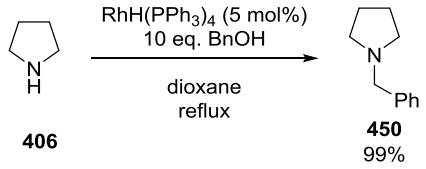
Scheme 3.3 *The Guerbet reaction*

One of the earliest recorded transition metal-catalysed processes for the alkylation of carbon nucleophiles with alcohols was the alkylation of arylacetonitriles reported by Grigg and coworkers in 1981.[228-230] In this work, treatment of phenylacetonitrile **446** with methanol, ethanol, or benzyl alcohol in the presence of $RhCl_3.3H_2O$, PPh_3 and Na_2CO_3 at elevated temperature afforded the desired alkylated phenylacetonitriles **447**-**449** in moderate to good yield (**Scheme 3.4**).



Scheme 3.4 *Grigg's α-alkylation of arylacetonitriles with alcohols*

At a similar time, Grigg and coworkers also reported the alkylation of amines utilising alcohols.[231] Using catalytic $RhH(PPh_3)_4$, a range of different amines were alkylated with a variety of alcohols (including MeOH, EtOH, *i*PrOH and BnOH) in moderate to excellent yield. For example, refluxing pyrrolidine **406** with 10 eq. of benzyl alcohol in dioxane afforded *N*-benzylpyrrolidine **450** in 99% yield (**Scheme 3.5**).



Scheme 3.5 *Grigg's alkylation of amines with alcohols*

Since the publication of these seminal works utilising hydrogen borrowing methodology, their scope has been expanded tremendously, in terms of the alcohols employed, the substrates alkylated, and also the metal complexes that have been utilised. These variations will be explored below, demonstrating the utility of hydrogen borrowing methodology in the alkylation of a variety of different functional groups.

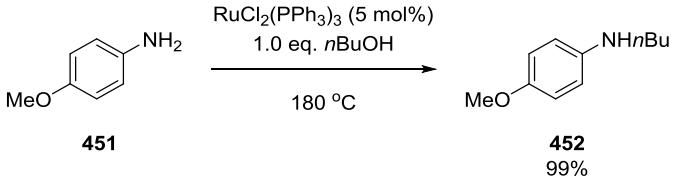
3.2 Hydrogen borrowing alkylation of different functional groups

3.2.1 Alkylation of amines with alcohols

The alkylation of amines is typically undertaken with alkyl halides as the alkylating agent, although this can lead to serious problems of selectivity, due to the propensity for the products to undergo further alkylation.[219] Traditional routes to avoid this overalkylation include the Gabriel synthesis, whereby an alkali metal salt of phthalimide is alkylated with an alkyl halide, followed by deprotection of the *N*-phthaloyl group with hydrazine,[232] although careful control of conditions can also yield the desired monoalkylated product.[233] However, this method clearly requires an extra deprotection step, and the loss of the high molecular weight phthaloyl group severely decreases the atom economy. As such, a hydrogen borrowing alkylation would prove more efficient in these circumstances, requiring only a single step, and with water as a leaving group.

Since Grigg's groundbreaking publication on the alkylation of amines (*vide supra*), numerous different sets of conditions have been developed for the alkylation of primary and secondary amines, as well as ammonia, with alcohols. A wide range of different catalysts have been utilised for this purpose, particularly, but not exclusively, based on ruthenium and iridium.

Watanabe and coworkers reported the use of $RuCl_2(PPh_3)_3$ for the alkylation of anilines with primary alcohols.[234] Although the conditions were relatively harsh (heating at 180 °C in an autoclave), alkylated secondary anilines could be formed in moderate to high yield. One problem observed with this set of conditions was the formation of a considerable amount of dialkylated product in certain cases, although this could be controlled by limiting the amount of alcohol. The reaction of 4-methoxyaniline **451** with 1-butanol afforded the desired *N*-butyl-4-methoxyaniline **452** in an excellent 99% yield (**Scheme 3.6**).

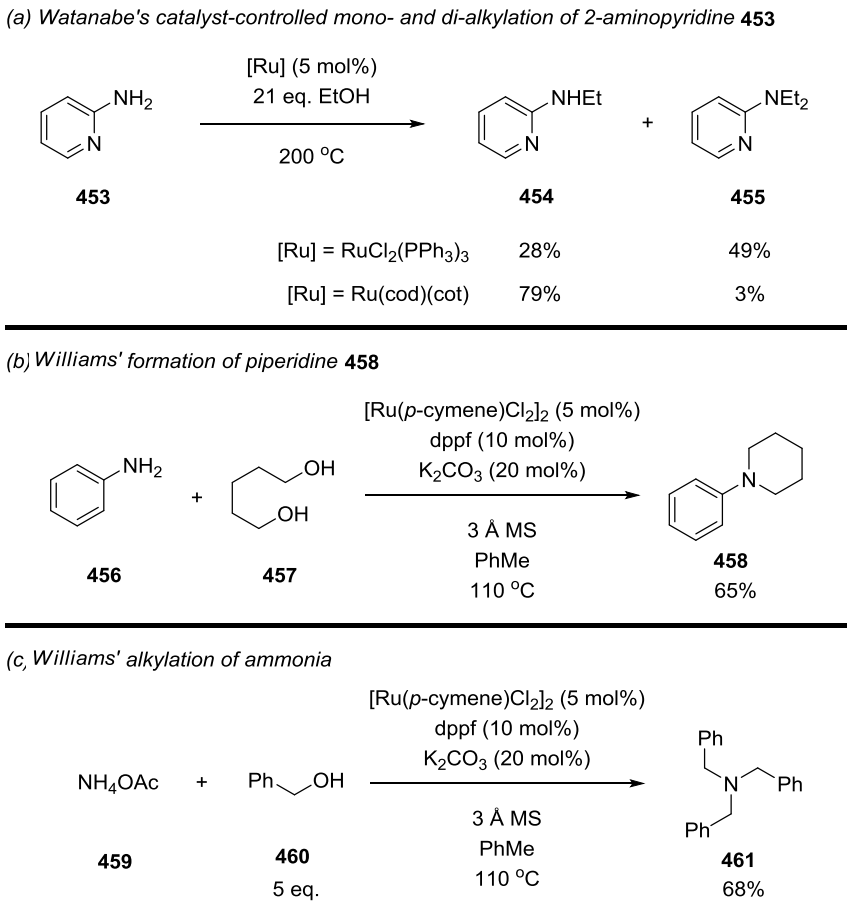


451 **452** 99%

Scheme 3.6 *Watanabe's N-alkylation of anilines*

Numerous other ruthenium-catalysed amine alkylation processes are known, including the use of Ru(cod)(cot) for the alkylation of 2-aminopyridine, which, in contrast to $RuCl_2(PPh_3)_2$, gave the monoalkylated aminopyridine **454** as the major product (**Scheme 3.7a**). Presumably this reactivity is due to increased steric hindrance in the Ru(cod)(cot) catalyst preventing complexation of the monoalkylated pyridine **454** to the ruthenium centre.[235]

Williams and coworkers also demonstrated the use of $[Ru(p\text{-cymene})Cl_2]_2$/dppf as a catalyst for the alkylation of primary, benzylic, and aromatic amines with a range of primary alcohols and diols, providing the alkylated products in good to excellent yield.[236] Using this catalyst/ligand combination, the formation of piperidine **458** from aniline **456** and pentane-1,5-diol **457** proceeded in 65% yield in refluxing toluene (**Scheme 3.7b**).

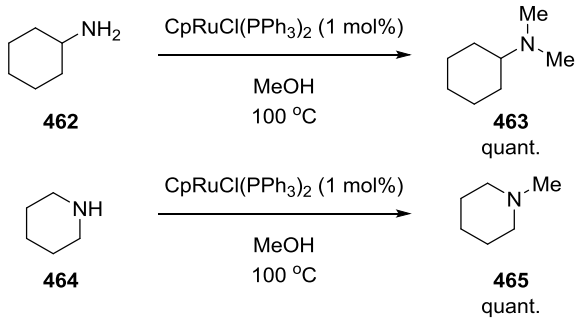


Scheme 3.7 *Other [Ru]-catalysed alkylation of amines*

Williams and coworkers also showed the utility of their $[Ru(p\text{-cymene})Cl_2]_2$/dppf ligand system for the first example of an alkylation of ammonia with alcohols. Treatment of

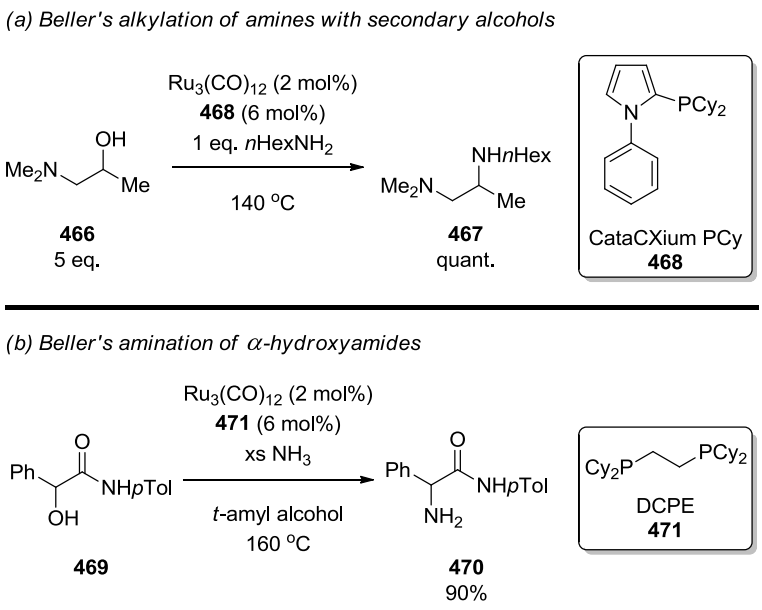
ammonium acetate with five equivalents of benzyl alcohol **460** with [Ru(*p*-cymene)Cl_2]$_2$/ dppf in refluxing toluene furnished tribenzylamine **461** in 68% yield (**Scheme 3.7c**)

Another interesting example employing Ru-catalysis is the methylation of amines reported by Del Zotto and coworkers (**Scheme 3.8**).[237] This procedure was successful for the formation of tertiary amines from primary and secondary amines, although the procedure was not applicable to anilines. For example, treatment of cyclohexylamine **462** with CpRuCl(PPh_3)$_2$ in MeOH at 100 °C afforded the dimethylated tertiary amine **463** in quantitative yield, whereas treatment of piperidine **464** afforded *N*-methylpiperidine **465** in 100% yield.



Scheme 3.8 *Del Zotto's N-methylation of primary and secondary alkylamines*

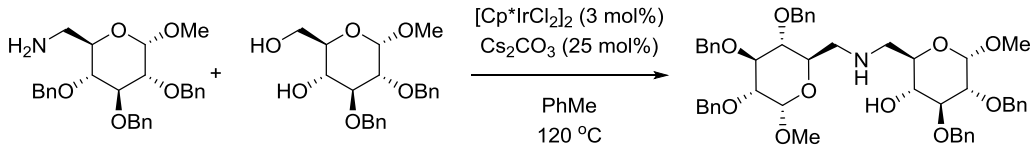
Generally, examples of the alkylation of amines are limited to primary alcohols. However, Beller and coworkers reported the use of $Ru_3(CO)_{12}$ with P(*o*-Tol)$_3$, or CataCXium PCy **468**, for the alkylation of amines with secondary alcohols (**Scheme 3.9a**).[238,239]



Scheme 3.9 *Beller's $Ru_3(CO)_{12}$-catalysed alkylation of amines*

A range of alkylamines were amenable to this process, along with a range of different secondary alcohols, including the reaction of hexylamine with (dimethylamino)alcohol **466**, to yield the corresponding alkylated product **467** in 87% yield. Beller and coworkers also applied this catalyst, along with DCPE **471** as ligand, to the amination of more complex systems. For example, treatment of α-hydroxyamides, such as **469**, with excess ammonia resulted in the formation of amino acid derivatives, such as **470**, in yields of up to 90%. (**Scheme 3.9b**).

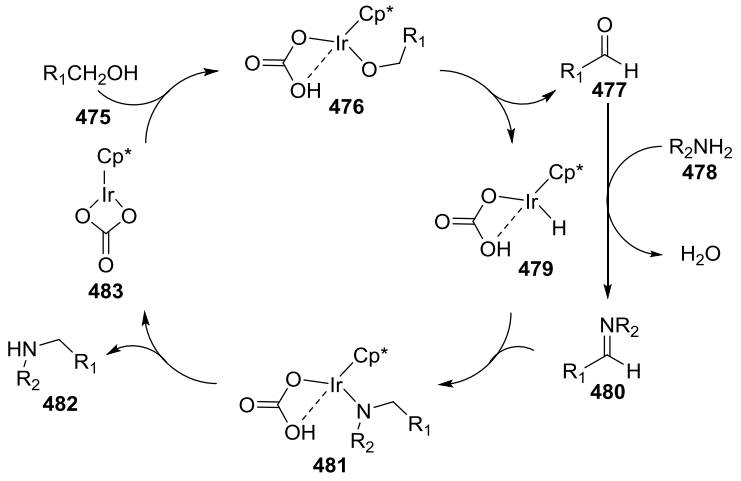
A number of iridium catalysts have also been shown to be effective for the alkylation of amines. $[CpIr^*Cl_2]_2$ and its derivatives have proven particularly popular since they were introduced for the alkylation of amines by Fujita and coworkers.[240-243] Recently, Cumpstey and coworkers reported the amination of sugar alcohols with carbohydrate-based amines, allowing the formation of pseudo-disaccharides.[244] Treatment of glucose derivatives **472** and **473** with $[Cp^*IrCl_2]_2$ and Cs_2CO_3 in toluene led to the formation of disaccharide **474** in 71% yield (**Scheme 3.10**). It is also noteworthy that this reaction tolerated a second free-hydroxyl group, which showed no reactivity in the process, allowing selective alkylation at the *C*-6 position.



472 **473** **474** 78%

Scheme 3.10 *Cumpstey's alkylation of carbohydrate-based amines with sugar alcohols*

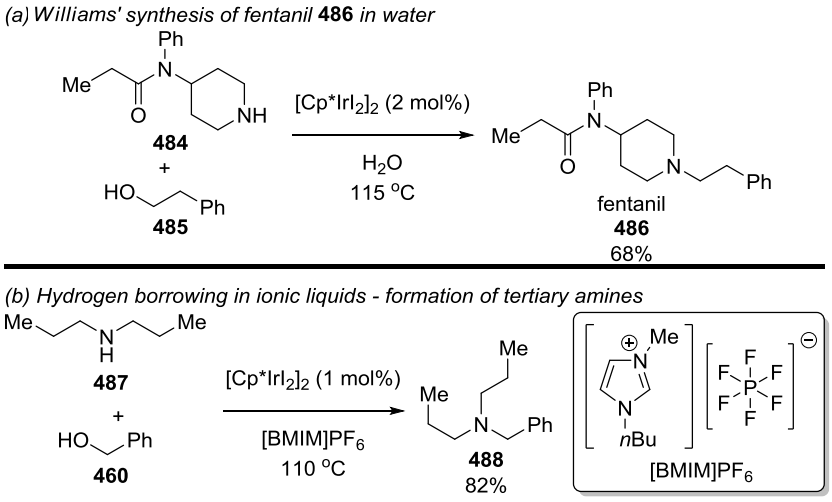
It is important to note that alkylation processes utilising $[Cp^*IrCl_2]_2$ all require base (typically K_2CO_3, $NaHCO_3$ or Cs_2CO_3), as opposed to the majority of examples utilising Ru (*vide supra*). DFT studies by Crabtree and coworkers have suggested a mechanism for the reaction whereby coordinated carbonate ligand is vital to the activity of the catalyst (**Scheme 3.11**).[245]



Scheme 3.11 *Crabtree's proposed catalytic cycle for [Cp*IrCl$_2$]$_2$-catalysed alkylations*

It is proposed that the carbonate acts as a proton acceptor, accepting a proton from the incoming alcohol **475**, to form complex **476**, and then can assist the elimination of the oxidised alcohol (formed *via* β-hydride elimination), helping to turn over the catalytic cycle, and generate hydride species **479**. The proton on the carbonate can then be returned to the amine **482** after reduction of the imine **480**, regenerating the active catalytic species **483**.

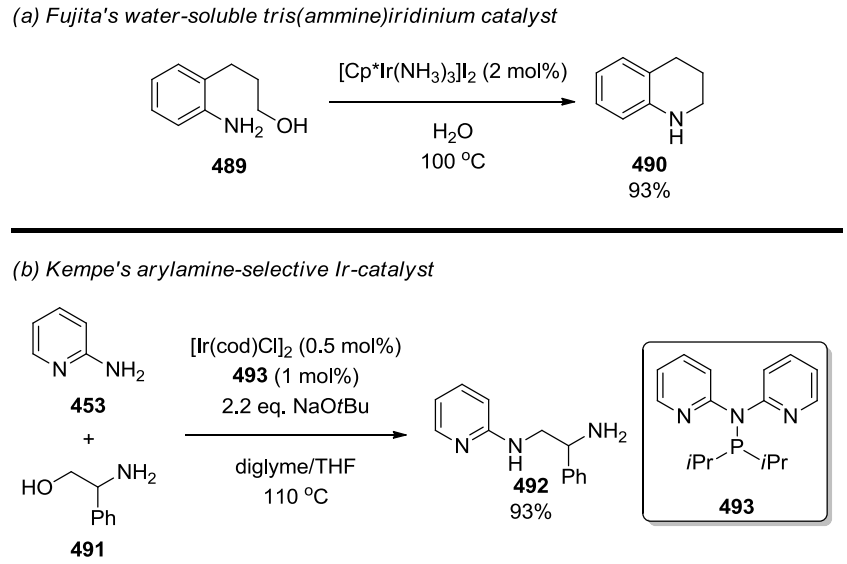
Interestingly, the use of other catalysts containing the Cp*Ir- moiety do not require the usee of base for their catalytic activity. Williams and coworkers have demonstrated the capability of the catalyst [Cp*IrI$_2$]$_2$ to facilitate the alkylation of amines in water,[246] and ionic liquids.[247] The alkylation of amines in water proceeded in good to excellent yield for a range of primary amines, and the authors were able to demonstrate the synthesis of the synthetic opioid fentanil **486** in 68% yield from amine **484** and homobenzyl alcohol **485** (**Scheme 3.12a**).



Scheme 3.12 *Hydrogen borrowing in water and ionic liquids*

However, water was found to be a poor solvent for the formation of tertiary amines from secondary amines. This problem could be circumvented by the use of ionic liquid solvent [BMIM]PF_6, for example yielding tertiary amine **488** in 82% isolated yield with only 1 mol% of $[Cp^*IrI_2]_2$ (**Scheme 3.12b**).

A very large range of other iridium-based catalysts have been used for the synthesis of amines.[248-251] For example, $[Cp^*Ir(NH_3)_3]I_2$ was shown by Fujita and coworkers to be stable to both air and moisture, allowing the alkylation of primary and secondary amines in water under air (**Scheme 3.13a**).[252] Kempe and coworkers have also developed an arylamine selective alcohol protocol by the combination of $[Ir(cod)Cl]_2$ with the bis(2-pyridyl)amino phosphine **493**, allowing selective alkylation of amino alcohols with aryl amines such as **453** in good to excellent yield (**Scheme 3.13b**).[253-256]

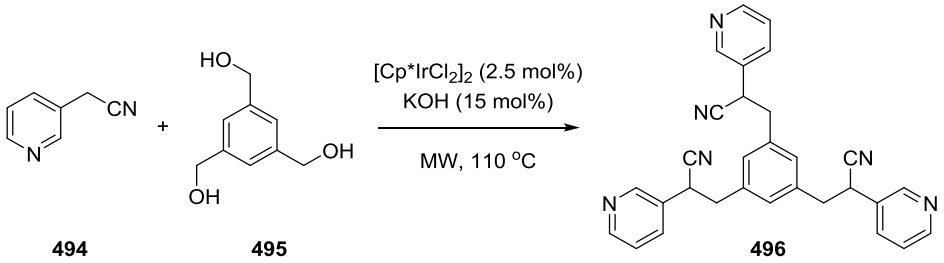


Scheme 3.13 *Other Ir-catalysts for the alkylation of amines with alcohols*

3.2.2 Alkylation of nitriles

Since Grigg's initial report on the alkylation of arylacetonitriles with alcohols,[230] there has been significant further development in catalytic systems for the alkylation of nitrile compounds. In 2006,[257] Grigg and coworkers reported further advances in this area, with the use of catalytic $[IrCp^*Cl_2]_2$ in the presence of catalytic base under microwave irradiation delivering good to excellent yields of alkylated products with a range of (hetero)arylacetonitriles and variably-susbtituted benzylic and aliphatic alcohols. For

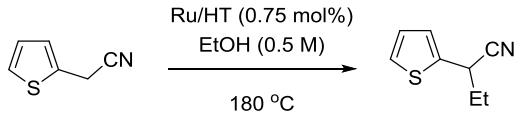
example, the synthesis of trimeric compound **496** proceeded in 72% yield from 2-pyridylacetonitrile **494** and the tris-benzyl alcohol **495**, in only ten minutes, demonstrating the compatibility of heteroaromatic groups in this methodology (**Scheme 3.14**).



494 **495** **496**

Scheme 3.14 *Grigg's alkylation of heteroaromatic nitriles*

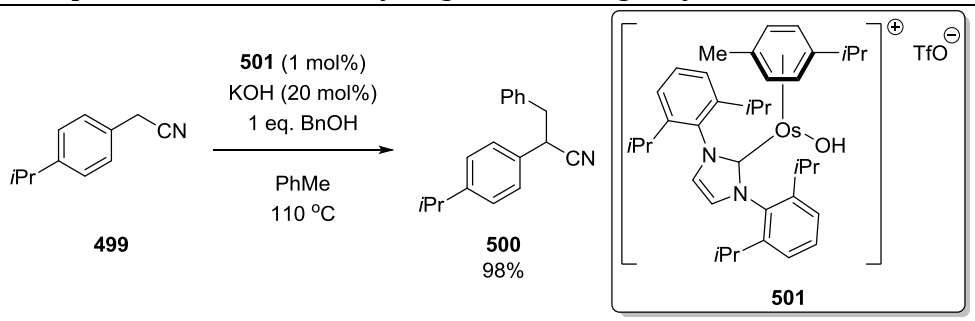
Fujita and coworkers have also investigated conditions for the α-alkylation of nitriles with alcohols, with their system employing ruthenium, and palladium nanoparticles grafted onto a hydrotalcite surface (Ru/HT and Pd^{nano}/HT).[258] This methodology was applicable to a range of different nitriles, both aromatic, and those possessing an α-electron-withdrawing group, such as a second nitrile, or ester. Crucially, the authors were also able to extend this methodology to the use of shorter aliphatic alcohols, and to combine the reaction with a conjugate addition of the nitrile anion to a Michael acceptor, thus allowing formation of diverse products. The alkylation of 2-thiophenylacetonitrile **497** with ethanol yielded 86% of the ethylated compound **498**, demonstrating the compatibility of this methodology with heteroaromatic functionality and also short chain alcohols (**Scheme 3.15**).



497 **498** 86%

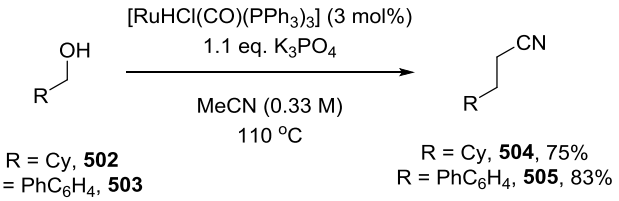
Scheme 3.15 *Fujita's alkylation of heteroarylacetonitriles with short-chain alcohols*

Yus and coworkers have also demonstrated the ability of the novel catalyst [Os(*p*-cymene)(OH)IPr]OTf **501**.[259] This catalyst is notable for the remarkably short reaction times possible for the alkylation of arylacetonitriles with benzylic alcohols, affording the desired alkylated products in less than one hour, in excellent yield. The alkylation of *p*-(isopropyl)phenylacetonitrile **499** with benzyl alcohol was complete in just 45 minutes, and afforded the benzylated product **500** in 98% yield (**Scheme 3.16**).



Scheme 3.16 *Yus's alkylation of arylacetonitriles employing Os-catalyst* **501**

The research group of Fukuyama showed that this reaction was not just limited to the use of stabilised nitrile compounds, by developing a novel alkylation of acetonitrile with benzylic and aliphatic alcohols in moderate to good yields.[260] Reaction of 1-cyclohexylmethanol **502** in acetonitrile in the presence of $[RuHCl(CO)(PPh_3)_3]$ and K_3PO_4 afforded the homologated nitrile **504** in 75% yield, whereas the use of 4'-phenylbenzyl alcohol **503** afforded the corresponding biphenyl nitrile **505** in 83% yield (**Scheme 3.17**). Another process for the alkylation of acetonitrile was also developed by Obora and coworkers, employing catalytic $[Ir(OH)cod]_2$, PPh_3, and KO*t*Bu, and afforded the desired alkylated products with primary and secondary alcohols, and diols, in moderate to excellent yield.[261]

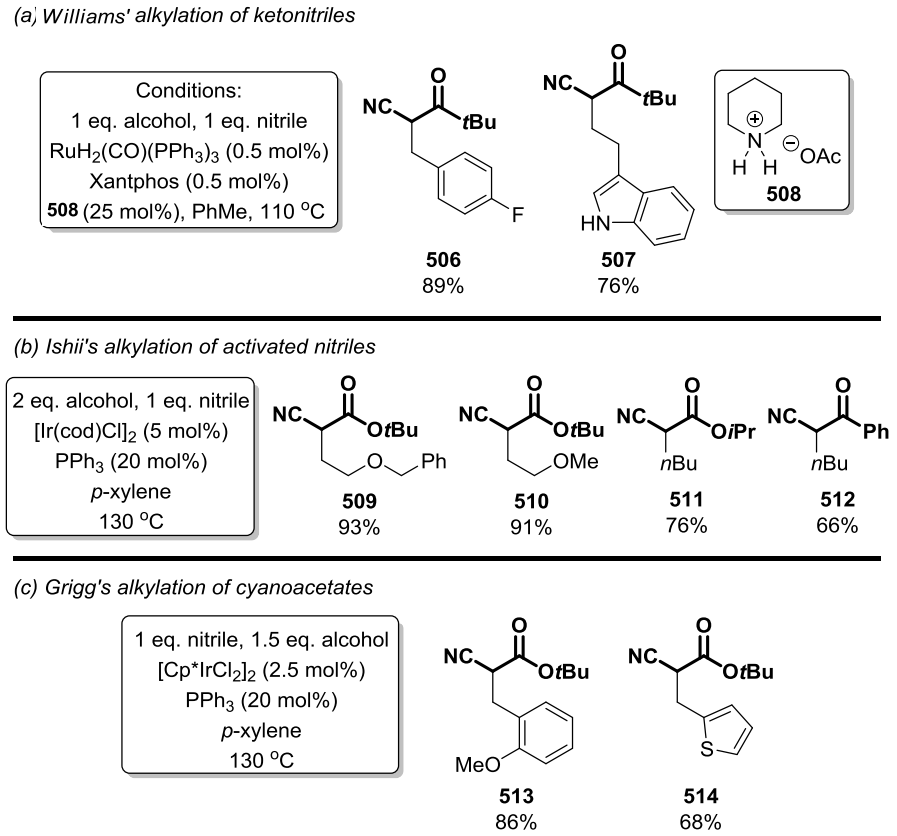


Scheme 3.17 *Fukuyama's alkylation of acetonitrile with aliphatic and benzylic alcohols*

A number of research groups have applied this methodology to the alkylation of activated methylene compounds such as cyanoacetates, including Fujita and coworkers, as previously discussed.[258] Further work by the groups of Williams,[262] Ishii,[263] and Grigg,[264] has demonstrated the compatibility of these substrates in the alkylation of alcohols.

Williams and coworkers utilised $RuH_2(CO)(PPh_3)_3$ with Xantphos ligand, and were able to alkylate ketonitriles with a range of benzylic and aliphatic alcohols in moderate to excellent yield, although this methodology proved unsuccessful when applied to heteroaromatic alcohols such as furfuryl alcohol (**Scheme 3.18a**). Piperidinium acetate **508** was required as

an additive in this reaction to promote the condensation of the ketonitrile with the aldehyde formed by oxidation of the alcohol.



Scheme 3.18 *Alkylation of activated nitrile compounds*

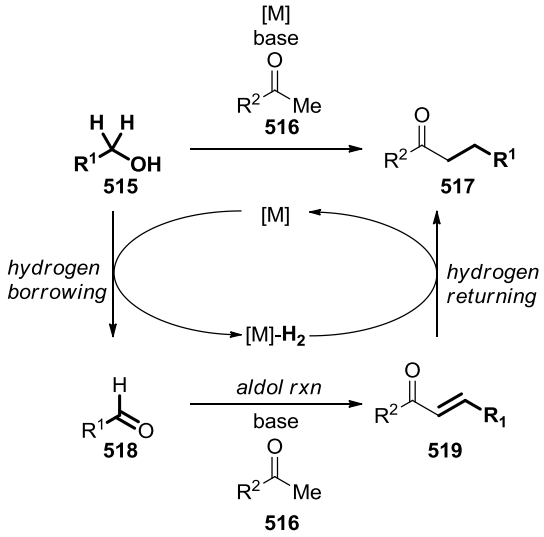
Ishii and coworkers were able to alkylate a number of activated nitrile compounds such as cyanoacetates or ketonitriles, with a range of aliphatic, benzylic, and functionalised alcohols, all in good to excellent yield by employing [Ir(cod)Cl_2] and PPh_3 in refluxing xylene (**Scheme 3.18b**).

Grigg and coworkers meanwhile demonstrated the utility of [IrCp*Cl_2]$_2$ for the alkylation of *t*-butyl cyanoacetate with a range of benzylic and heteroaromatic alcohols, although it is noteworthy that in a number of cases the product of decarboxylation was also observed (**Scheme 3.18c**).

3.2.3 Alkylation of ketones

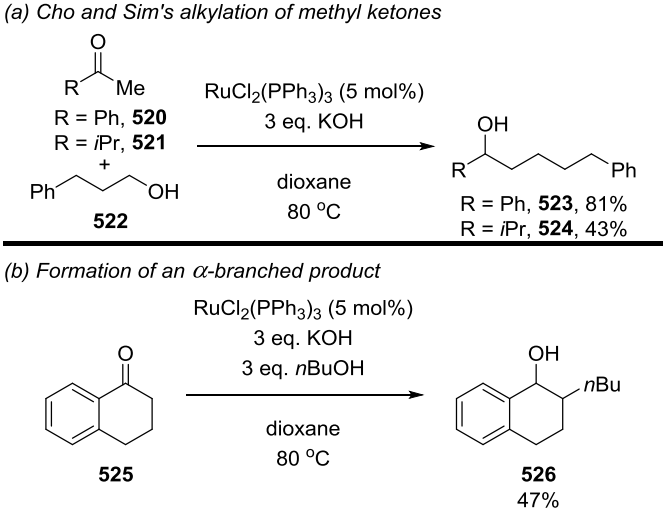
Perhaps the most widely explored area, aside from that of the alkylation of amines, is the alkylation of ketones under hydrogen borrowing conditions. This process clearly provides a green alternative to traditional lithium bases and alkyl halides, generates less waste, and also

does not suffer from the greater toxicity problems of these alkylating agents, since the only byproduct of the reaction is water. These α-alkylations of ketones proceed *via* an oxidation of alcohol **515** to the corresponding aldehyde **518** (or ketone), (with concurrent generation of a metal hydride species), aldol reaction with the ketone **516**, and subsequent reduction of the enone **519** by the metal hydride, as depicted in **Scheme 3.19**.



Scheme 3.19 *Hydrogen borrowing alkylation of ketones*

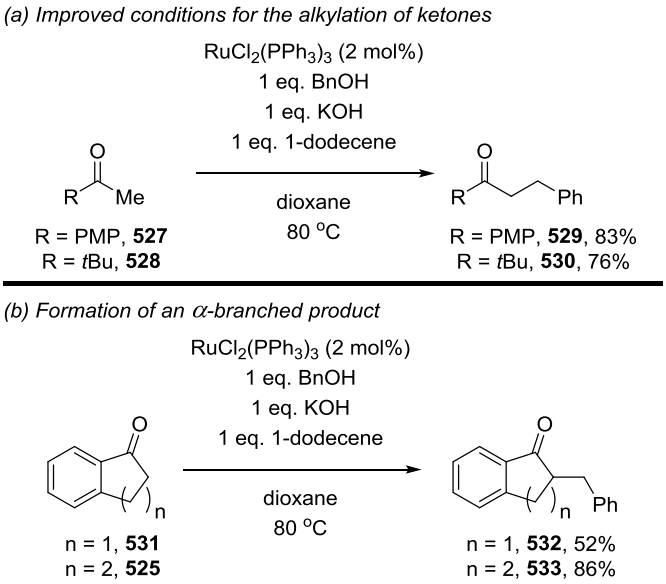
Cho, Shim and coworkers reported an α-alkylation of methyl ketones in 2001, demonstrating the reaction of a variety of methyl ketones with primary aliphatic and benzylic alcohols with concomitant reduction of the ketone moiety, in moderate to excellent yields.[265] Yields were generally very high for the reaction of acetophenone **520**, but lower for the reaction of bis-alkyl ketones such as **521** (**Scheme 3.20a**).



Scheme 3.20 *Cho and Sim's alkylation of methyl ketones with alcohols*

Interestingly, they were also able to report the reaction of the cyclic ketone **525** with *n*-butanol, providing the alkylated product **526** in 47% yield, one of the few examples of the formation of an α-branched product in the alkylation of simple ketones *via* hydrogen borrowing (**Scheme 3.20b**).

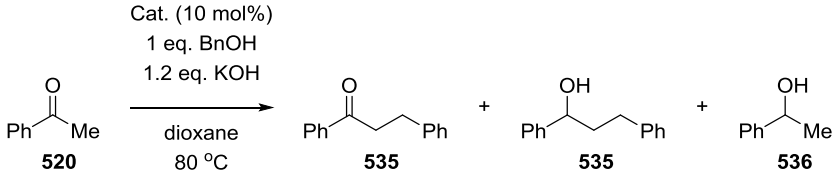
In order to circumvent this problem of overreduction of the ketone moiety, Cho, Sim and coworkers developed a protocol whereby the addition of 1-dodecene acted as a scavenger for the metal hydride.[266] Under these conditions, the α-alkylation of methyl ketones proceeded smoothly, without reduction to the corresponding alcohol, in moderate to high yields, and with considerably lower loadings of $RuCl_2(PPh_3)_3$. Once again, the alkylation of alkyl-alkyl ketones suffered from lower yields than aromatic ketones, except in the case of tertiary alkyl ketones such as **528**, which afforded the benzylated product **529** in 76% yield (**Scheme 3.21a**). Furthermore, the alkylation of cyclic ketones proceeded well under these conditions, providing further examples of the formation of branched products, though still rare in the alkylation of ketones (**Scheme 3.21b**).



Scheme 3.21 *Improved conditions for the α-alkylation of ketones*

$RuCl_2(DMSO)_4$ was introduced as an effective catalyst for the alkylation of methyl ketones by the group of Yus.[267,268] During the course of their studies, the authors showed that a range of metals were capable of performing the reaction of acetophenone **520** with benzyl alcohol **460**, giving a mixture of the expected benzylated ketone **534**, the product arising from

reduction of the ketone **535**, and the product derived from reduction of acetophenone **536** (**Table 3.1**). This showed that both the oxidation and reduction of starting material and product were clearly feasible with a range of catalysts, although the course of the reaction was highly dependent on the choice of metal and counterion, with $FeCl_3$ (**Entry 4**), $RuCl_2(DMSO)_4$ (**Entry 8**), $RuCl_2(PPh_3)_3$ (**Entry 9**), and $[Ir(cod)Cl]_2$ (**Entry 12**) providing the optimal conditions.

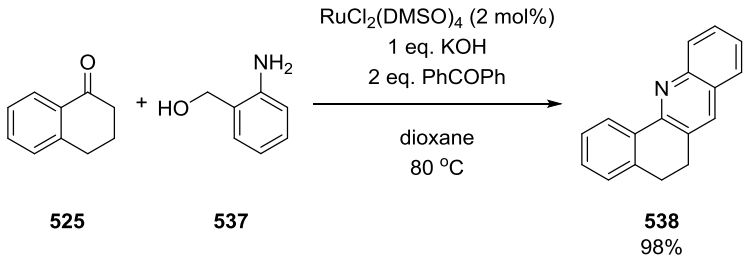


520 **535** **535** **536**

Entry	Cat.	534 (%)	535 (%)	536 (%)
1	$Al(OiPr)_3$	15	25	25
2	VCl_2	21	16	41
3	$CrCl_2$	26	19	32
4	**$FeCl_3$**	**60**	**12**	**15**
5	$CuCl_2$	25	30	11
6	$Cu(OTf)_2$	38	23	16
7	$ZnCl_2$	16	35	10
8	**$RuCl_2(DMSO)_4$**	**80**	**8**	**Trace**
9	**$RuCl_2(PPh_3)_3$**	**61**	**15**	**7**
10	$RhCl(PPh_3)_3$	49	20	10
11	$PdCl_2$	52	11	21
12	**$[Ir(cod)Cl]_2$**	**82**	**5**	**Trace**

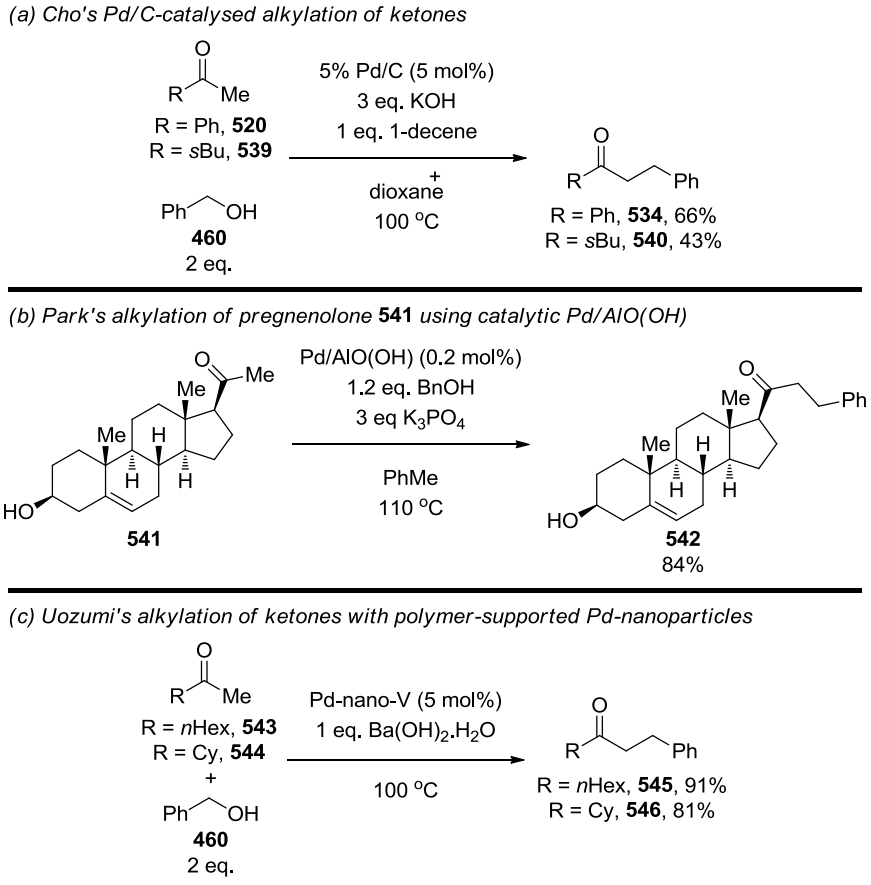
Table 3.1 *Screen of catalysts for the alkylation of acetophenone* **520**

Yus and coworkers took the result for $RuCl_2(DMSO)_4$ and further investigated this catalyst for the alkylation of methyl ketones. This catalyst was capable of facilitating the reaction of a range of electron-rich and electron-poor aromatic ketones with benzylic alcohols in moderate to high yield. This methodology was then also applied to the synthesis of quinolines, whereby alkylation with an *o*-aminobenzyl alcohol, followed by condensation of the aniline moiety with the ketone, would furnish the desired quinoline. It should be noted that the addition of benzophenone was necessary for high yields in this reaction, to act as a hydrogen-scavenger and prevent reduction of the quinoline moiety under the reaction conditions. A range of aryl and heteroaryl-substituted quinolines were formed from the reaction of methyl ketones with *o*-amino benzyl alcohols, in good to excellent yields, including the alkylation/cyclisation of tetralone **525** with *o*-aminobenzyl alcohol **537** in an impressive 98% yield (**Scheme 3.22**).



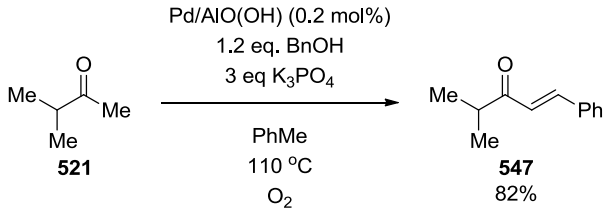
Scheme 3.22 *Yus's α-alkylation/cyclisation for the synthesis of quinolines*

A number of different methods have been developed utilising palladium for the α-alkylation of ketones with alcohols. Cho and coworkers published the use of Pd/C for the alkylation reaction.[269] This catalyst proved suitable for the alkylation of aromatic and aliphatic ketones, providing regioselective alkylation in preference for reaction at the ketone methyl group, for benzylic and long-chain aliphatic alcohols in moderate to high yield (**Scheme 3.23a**). Once again, the only example of the alkylation of a secondary centre occurred in the case of cyclic tetralone **525** with benzyl alcohol, albeit in a low 46% yield (not shown). 1-Decene was required to prevent the over-reduction of the ketone product to the corresponding alcohol.



Scheme 3.23 *Pd-catalysed alkylation of ketones*

Park and coworkers developed a novel catalyst, composed of Pd-nanoparticles entrapped in aluminium hydroxide, termed Pd/AlO(OH).[270] This catalyst had previously shown activity in alkene hydrogenation, and aerobic alcohol oxidation,[271] and thus the authors turned their attention to hydrogen borrowing for the alkylation of ketones. This catalyst proved capable of alkylating alkyl- and aryl-methyl ketones in excellent yields, with both aliphatic, benzylic and heteroaromatic alcohols. Under these conditions, even pregnenolone **541** could be alkylated in 84% yield with benzyl alcohol in the presence of a remarkable 0.2 mol% Pd/AlO(OH), and 3 eq. K_3PO_4 in toluene (**Scheme 3.23b**). The catalyst could also be recycled for six consecutive runs with no decrease in yield. An interesting observation for this process was that by conducting the reaction under an atmosphere of O_2, instead of Ar, only the unreduced enone product was observed, for example in the alkylation of 3-methyl-2-butanone with benzyl alcohol, enone **547** was isolated in 82% yield, suggesting that under an aerobic atmosphere, the metal hydride was being consumed by oxygen present in solution (**Scheme 3.24**).

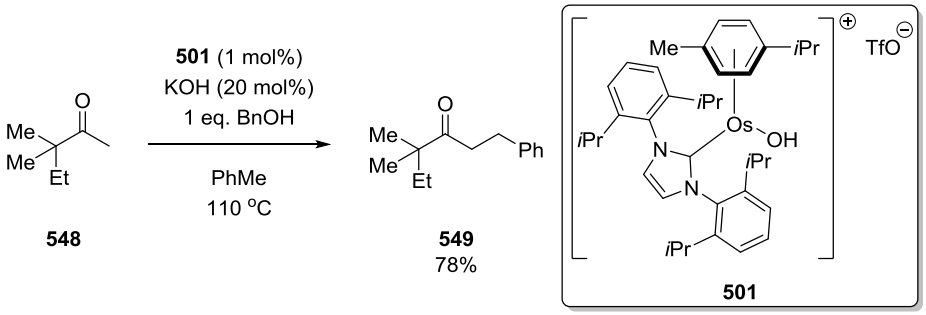


Scheme 3.24 *Selective enone formation under O_2 atmosphere*

Another catalyst bearing entrapped Pd-nanoparticles was developed by Uozumi and coworkers.[272] This catalyst comprised Pd-nanoparticles immobilised on a viologen polymer, and was named Pd-nano-V by the authors. This catalyst proved efficient at promoting the alkylation of aromatic and aliphatic methyl ketones with benzylic and aliphatic primary alcohols in excellent yields (**Scheme 3.23c**). Once again, this catalyst could be recycled a minimum of three times with no detrimental effect on the yield of reaction.

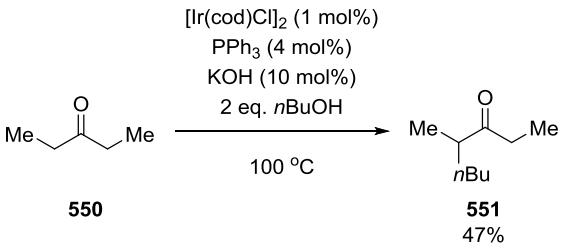
An Os-catalysed alkylation of alcohols was reported by Yus and coworkers, previously described for the alkylation of arylacetonitriles (*vide supra*), allowing the effective alkylation of acetophenone **520** in high yields with benzyl alcohols. This catalyst proved less effective for the alkylation of alkyl ketones, and with aliphatic alcohols, but still afforded the desired

alkylated products in good yields. The alkylation of *tert*-alkyl ketone **548** with benzyl alcohol afforded the alkylated ketone **549** after a short reaction time of only four hours in 78% yield (**Scheme 3.25**).



Scheme 3.25 *Yus's Os-catalysed α-alkylation of tert-alkyl ketone* **548**

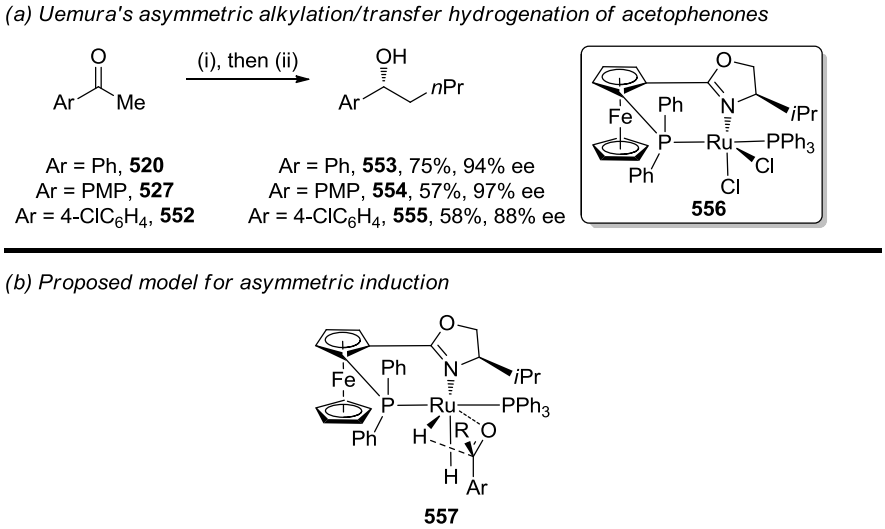
Ishii and coworkers were able to demonstrate the utility of their $[Ir(cod)Cl]_2/PPh_3$ catalytic system, as previously discussed for the alkylation of nitriles (**Scheme 3.18b**), in the hydrogen borrowing alkylation of ketones.[273] Initial studies showed that the use of an arylphoshine was important to prevent reduction either of the desired alkylated product, or the starting material, to the corresponding alcohol, with over-reduction observed with the use of P*n*Bu$_3$ and PCy$_3$, suggestive of a more reactive metal-hydride species. A number of alkyl- and aryl- ketones could be alkylated in moderate to high yield, with one example of particular note being the alkylation of 3-pentanone **550**, with *n*BuOH, which afforded the branched product **551** in a moderate 47% yield (**Scheme 3.26**). However, this does provide the only example of branched product formation for an acyclic ketone using hydrogen borrowing methodology in the alkylation of ketones.



Scheme 3.26 *Ishii's formation of branched ketone* **551** *via hydrogen borrowing*

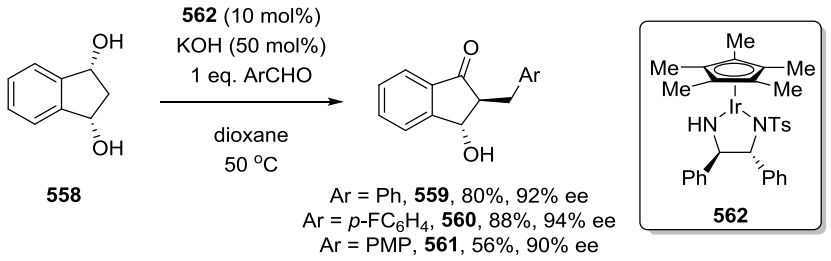
Ishii's method for the alkylation of ketones has also been adopted for the first example of an asymmetric reaction utilising the hydrogen borrowing alkylation of ketones. Uezuma and coworkers utilised a two-step, one-pot procedure for the alkylation of ketones under Ishii's

conditions, followed by transfer hydrogenation in *i*PrOH with chiral ruthenium catalyst $RuCl_2(PPh_3)$(ip-foxap) **556**. A range of aromatic ketones could be alkylated in moderate to high yield, and with excellent enantioselectivities (**Scheme 3.27a**). The authors propose a model **557** for the enantioselectivity of the reaction invoking docking of the ketone, with the bulky aromatic group pointing away from the aryl groups of the two phosphine moieties and the oxazoline substituent (**Scheme 3.27b**).[274]



Scheme 3.27 *Uemura's asymmetric alkylation/transfer hydrogenation of acetophenones*
Conditions: (i) $[Ir(cod)Cl]_2$ (1 mol%), PPh_3 (4 mol%), KOH (10 mol%), 2 eq. *n*PrOH, 100 °C (ii) **556** (1 mol%), NaO*i*Pr (4 mol%), *i*PrOH, rt

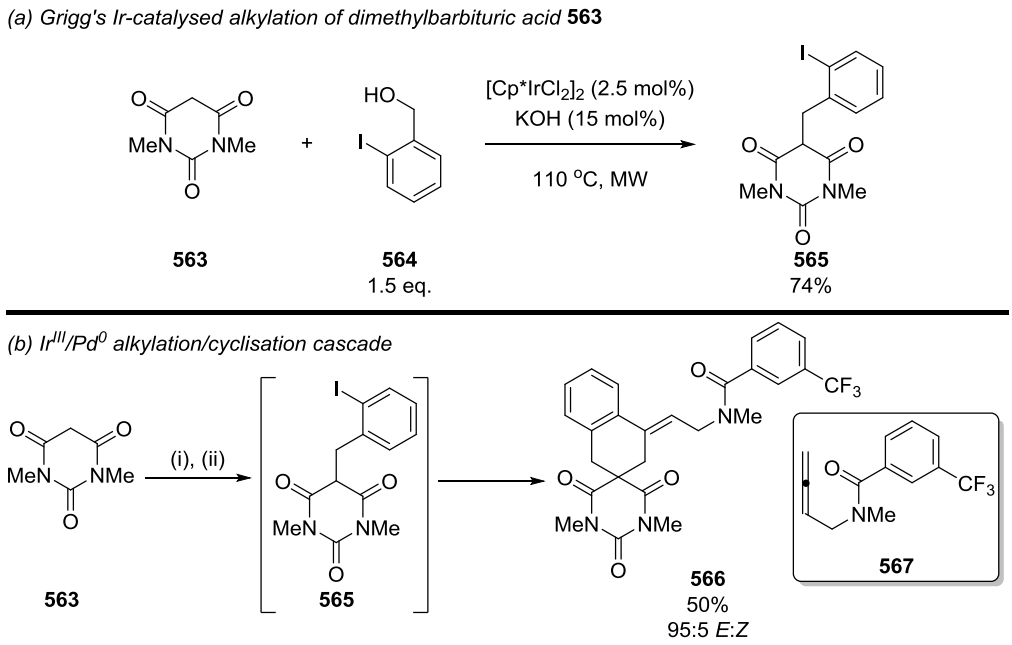
Another asymmetric variant of the hydrogen borrowing alkylation of ketones was developed by Suzuki and coworkers, for the asymmetric desymmetrisation and alkylation of *meso*-diol **558** (**Scheme 3.28**).[275] Selective oxidation of one alcohol by the chiral Cp*Ir complex, followed by reaction with an aldehyde, and subsequent reduction furnished the alkylated ketones **559-561**. This reaction performed well for a range of aromatic aldehydes, although yields were generally higher for electron-neutral and electron-poor species, with high enantioselectivities, although relatively high catalyst loadings were required.



Scheme 3.28 *Suzuki's asymmetric alkylation of meso-diol* **558**

3.2.4 Other substrates

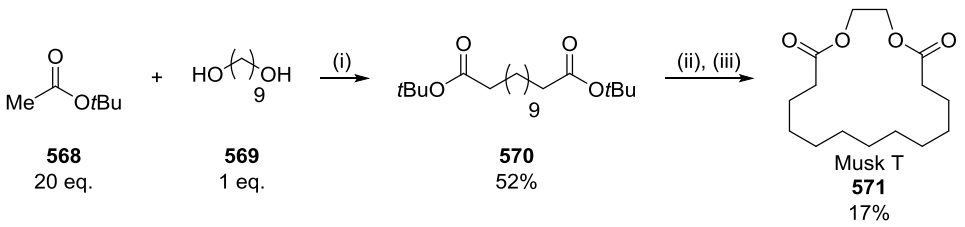
As discussed previously in the alkylation of nitrile derivatives, activated methylene compounds have provided a useful platform for hydrogen borrowing alkylations. An interesting substrate employed by Grigg and coworkers was dimethylbarbituric acid **563**, which was shown to alkylate efficiently with a variety of functionalised benzylic and short chain aliphatic alcohols in high yield when $[Cp^*IrCl_2]_2$ was employed as catalyst under microwave conditions.[276] For example, alkylation of **563** with *o*-iodobenzyl alcohol **564** afforded the desired compound **565** in 74% yield (**Scheme 3.29a**). Alkylations with alcohol **564** were of particular interest since they were then employed in a one-pot Ir^{III}/Pd^0 cyclisation cascade with allenes such as **567**, which allowed the formation of spirocycle **566** in 50% yield, with 95:5 selectivity for the (*E*)-isomer (**Scheme 3.29b**).



Scheme 3.29 *Grigg's alkylation of dimethylbarbituric acid and one-pot cascade cyclisation*
Conditions: (i) $[Cp^*IrCl_2]_2$ (2.5 mol%), KOH (15 mol%), 1.5 eq. **564**, 110 °C, MW (ii) Pd_2dba_3 (5 mol%), P(2-Fur)$_3$ (20 mol%), 1 eq. **567**, 2 eq. K_2CO_3, MeCN, 110 °C, MW

The group of Ishii expanded the use of their versatile $[Ir(cod)Cl]_2/PPh_3$ catalyst system to the alkylation of the ester *tert*-butyl acetate **568**.[277] This procedure could be utilised for alkylation of **568** with a range of primary alcohols (secondary alcohols were observed to afford no alkylated product), both benzylic and aliphatic, in good to excellent yields. However, 10 eq. of the acetate **568** were required for the alkylation to occur, and no higher esters were

alkylated, and thus the yield was based on the 1 eq. of alcohol employed during the reaction. Also, as opposed to previous studies by Ishii and coworkers, *t*BuOH was required as cosolvent to prevent transesterification. This alkylation was applied to the synthesis of Musk T **571**, by alkylation with diol **569** in 52% yield, followed by hydrolysis of **570** to the diacid, and esterification with ethylene glycol (**Scheme 3.30**).

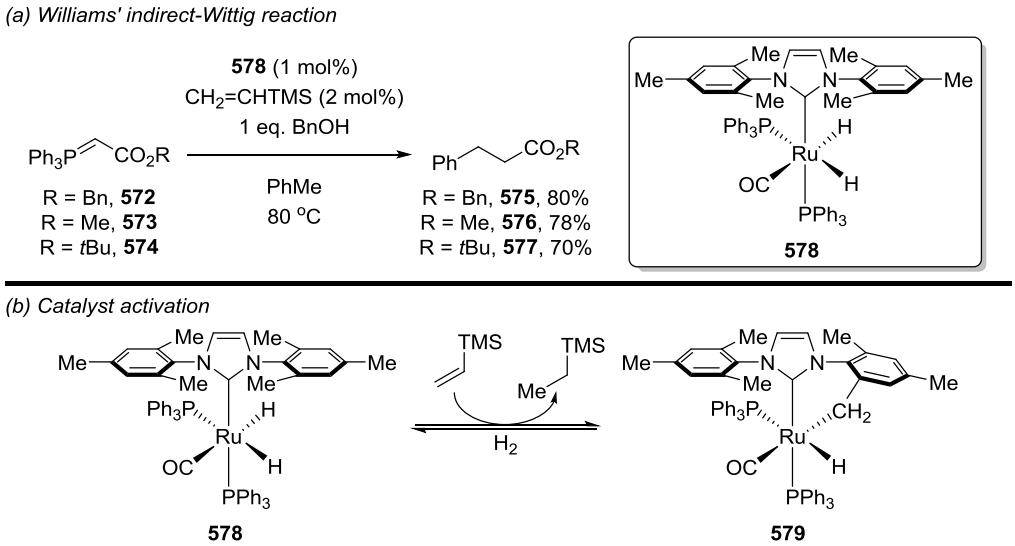


568 20 eq. **569** 1 eq. **570** 52% **571** 17%

Scheme 3.30 *Ishii's alkylation of acetate* **568** *and synthesis of Musk T* **571**

Conditions: (i) $[Ir(cod)Cl]_2$ (10 mol%), PPh_3 (30 mol%), KO*t*Bu (4 eq.), *t*BuOH, 100 °C (ii) TFA, CH_2Cl_2/H_2O (iii) ethylene glycol, *p*TsOH, PhH, Dean-Stark, reflux

An alternative approach to the alkylation of esters was taken by Williams and coworkers. Using the Ru^{II}-NHC complex **578**, the alkylation of ester ylids with benzylic alcohols afforded the desired alkylated esters in high yields (**Scheme 3.31**).

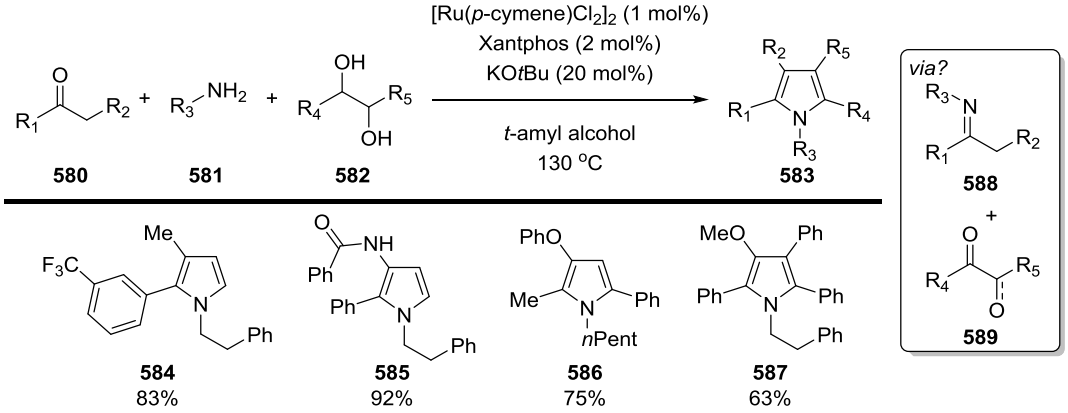


Scheme 3.31 *William's indirect-Wittig reaction*

The reaction is presumed to proceed *via* oxidation of the alcohol to the corresponding aldehyde, stabilised-ylid Wittig reaction, and subsequent reduction of the α,β-unsaturated ester thus formed, to furnish the desired alkylated ester. For example, treatment of ylids **572-574** with benzyl alcohol afforded the alkylated esters **575-577** in 80%, 78% and 80% yield respectively (**Scheme 3.31a**). Vinyltrimethylsilane was required as an additive to the reaction

in order to form the activated complex **579,** via a C-H activation of one of the ligand methyl groups (**Scheme 3.31b**).

Recently, Beller and coworkers utilised hydrogen borrowing for the one-pot, multi-component synthesis of polysubstituted pyrroles.[278] By treatment of a ketone **580**, amine **581**, and vicinal diol **582** with catalytic [Ru(*p*-cymene)Cl_2]$_2$/Xantphos and KO*t*Bu in *t*-amyl alcohol, Beller was able to synthesise a range of pyrroles **583** of varying substitution pattern in moderate to high yield (**Scheme 3.32**). Although the mechanism is not entirely clear, deuteration experiments suggest first the formation of an imine **588** from the ketone **580** and amine **581**, followed by coupling with the product resulting from mono- or di-oxidation **589** of the diol **582**.



Scheme 3.32 *Beller's multi-component hydrogen borrowing approach to pyrroles*

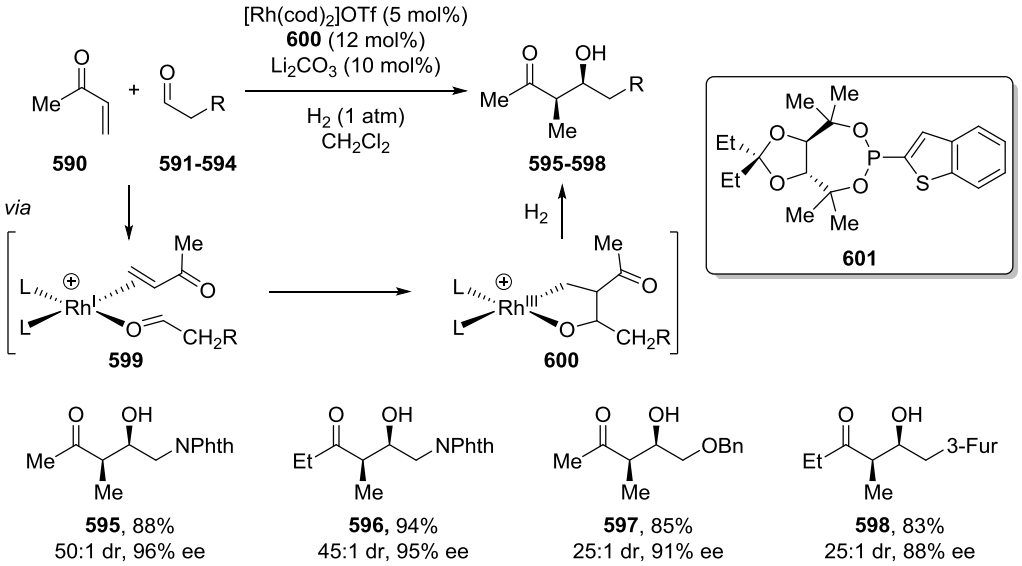
3.3 Related methodologies

As demonstrated above, hydrogen borrowing has become a vibrant and diverse area of chemical research in recent years. There are, however, other related methodologies for the construction of varied molecular scaffolds that do not themselves class as hydrogen borrowing, whilst still involving acceptorless dehydrogenation of alcohols to their corresponding carbonyl derivatives and their subsequent utilisation in synthesis.[223]

3.3.1 Krische's transfer-hydrogenative coupling methodology

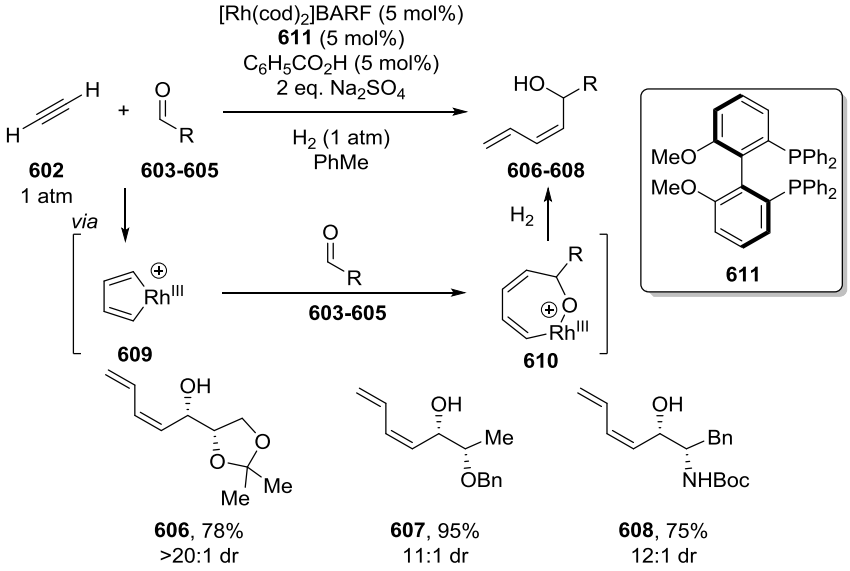
The group of Krische and coworkers has conducted a great deal of work on the reductive activation of π-unsaturated reactants for the addition to carbonyl compounds.[279]

Examples of this type of process include reductive aldol- and Mannich-type reactions, whereby hydrometallation of an α,β-unsaturated carbonyl compound affords the metal enolate, which then undergoes subsequent addition to an aldehyde or imine (**Scheme 3.33**). For example, reaction of vinyl ketone **590** with a range of aldehydes in the presence of cationic Rh^{I} catalyst and chiral phosphite **601** afforded the aldol products **595-598** in excellent yields, diastereoselectivities and enantioselectivities. The reaction is believed to proceed *via* an oxidative coupling of the two reacting partners under the influence of the metal species, followed by hydrogenolysis of the resultant complex **600** to afford the desired product.



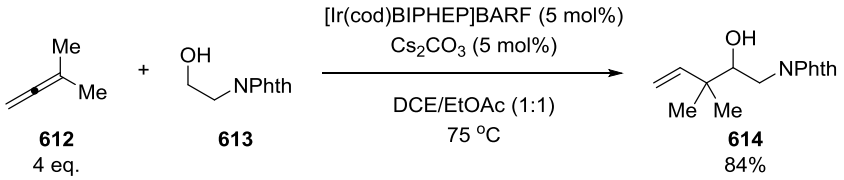
Scheme 3.33 *Krische's asymmetric reductive aldol reaction*

Another hydrogen-mediated process developed by Krische and coworkers was the asymmetric addition of acetylene for the butadienylation of carbonyl compounds, whereby the metal catalyses the formation of a metallacyclopentadiene, which subsequently inserts into a C=O or C=NR bond (**Scheme 3.34**).[280] Treatment of aldehydes **603-605** with the weakly-coordinating $[Rh(cod)_2]$BARF and (*S*)-MeO-BIPHEP **611** under an atmosphere of acetylene **602** and hydrogen afforded the corresponding butadienylated compounds **606-608** in good yields and diastereoselectivities, as >95:5 mixtures of *Z* and *E* isomers.



Scheme 3.34 *Krische's rhodium-catalysed butadienylation of aldehydes*

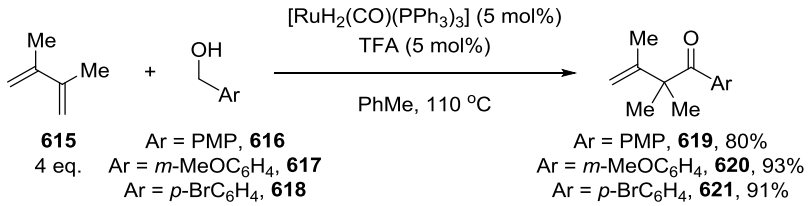
A breakthrough in this area was made when it was realised that the use of hydrogen could be removed altogether, and the carbonyl component replaced with the corresponding alcohol. Thus, dehydrogenation of the alcohol by the metal-catalyst would afford both the desired carbonyl compound, and the metal hydride species required to facilitate the reaction.[281] In 2007, Krische and coworkers reported the reverse prenylation, crotylation and allylation of alcohols with allenes, in the presence of a cationic Ir^{I} catalyst.[282] A range of different alcohols could be prenylated and crotylated in high yield, although allylation proved much less efficient. The reaction tolerated both electron-rich, electron-poor, alkyl and heteroaromatic alcohols. The reverse prenylation of *N*-phthalimido alcohol **613** afforded the desired product **614** in 84% yield (**Scheme 3.35**).



Scheme 3.35 *Krische's Ir-catalysed reverse prenylation of alcohols*

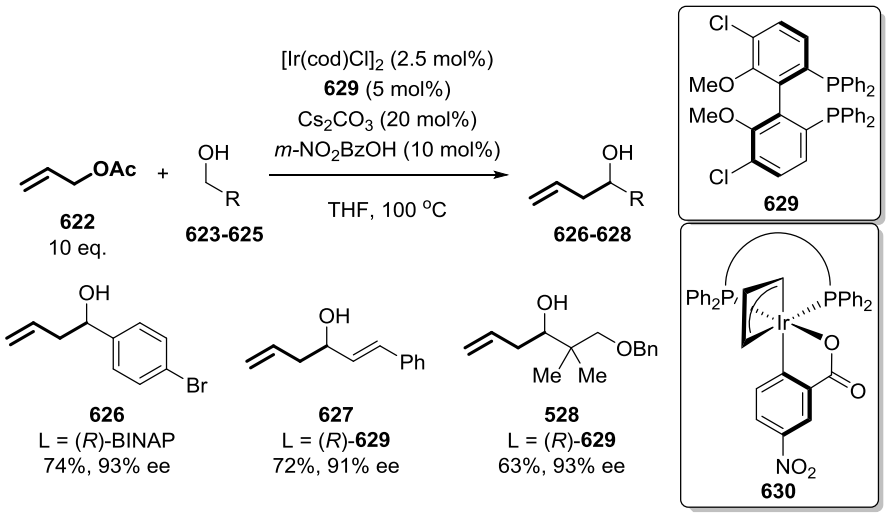
A number of other "pro-nucleophiles" have been explored by Krische and coworkers for employment in these processes. Using the Ru^{II} catalyst $[RuH_2(CO)(PPh_3)_3]$, acyclic diene **615** underwent addition to alcohols **616-618** to afford the allylated ketones **619-621** in good to

excellent yields, and with complete regioselectivity for formation of the more hindered alkyl-metal nucleophile (**Scheme 3.36**).[283]



Scheme 3.36 *Krische's Ru-catalysed allylation of alcohols with acyclic dienes*

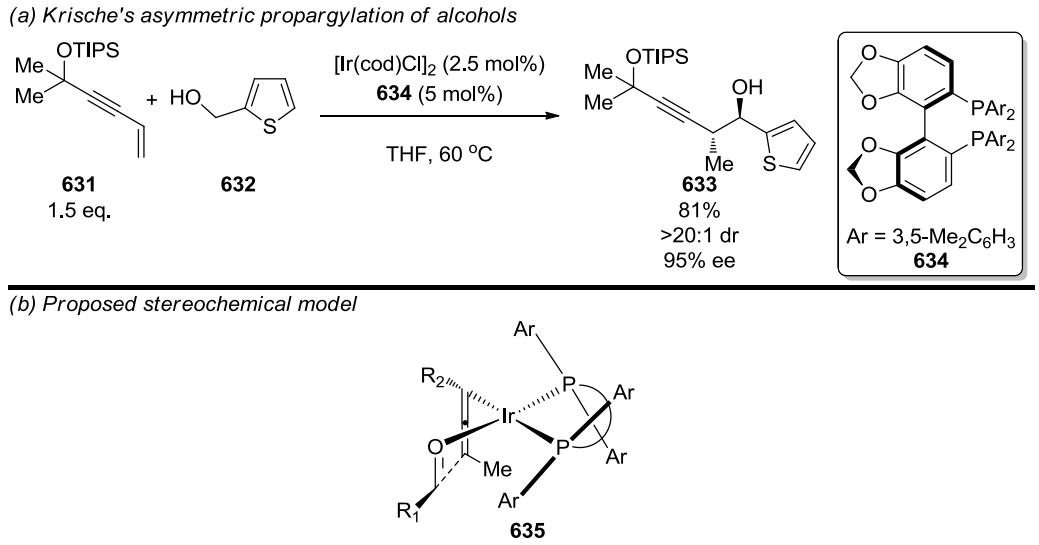
These processes have also proved amenable to use in asymmetric synthesis. Krische and coworkers have developed a number of different methodologies based on similar structures for the formation of chiral alcohols. Under conditions of Ir^{I} catalysis it proved possible to employ allyl acetate **622** as an allyl donor for the formation of chiral homoallylic alcohols (**Scheme 3.37**). (*R*)-BINAP and (*R*)-Cl,MeO-BIPHEP **629** proved to be efficient ligands for this process, dependent on the substrate structure.[284,285] *m*-Nitrobenzoic acid was also required as an additive for the formation of the active catalytic species, which was isolated and characterised as as complex of the type **630**. Both benzylic and aliphatic alcohols could be allylated under these conditions in high yields and enantioselectivities.



Scheme 3.37 *Krische's asymmetric allylation of alcohols*

1,3-Enynes were also shown to be good substrates for asymmetric addition to a number of different alcohols, both benzylic and aliphatic.[286] For example, addition of TIPS-protected enyne **634** to 2-(thiophenyl)methanol **632** with catalytic $[Ir(cod)Cl_2]_2$ and (*R*)-DM-Segphos **634** as chiral liand, yielded the corresponding homopropargylic alcohol **633** in 81% yield,

95% ee, and with >20:1 selectivity for the antidiastereomer (**Scheme 3.38a**). The selectivity in this case was postulated to be a result of minimising steric interaction between the allenyl-metal substituent and the side-chain of the alcohol in a transition state structure such as **635** (**Scheme 3.38b**).



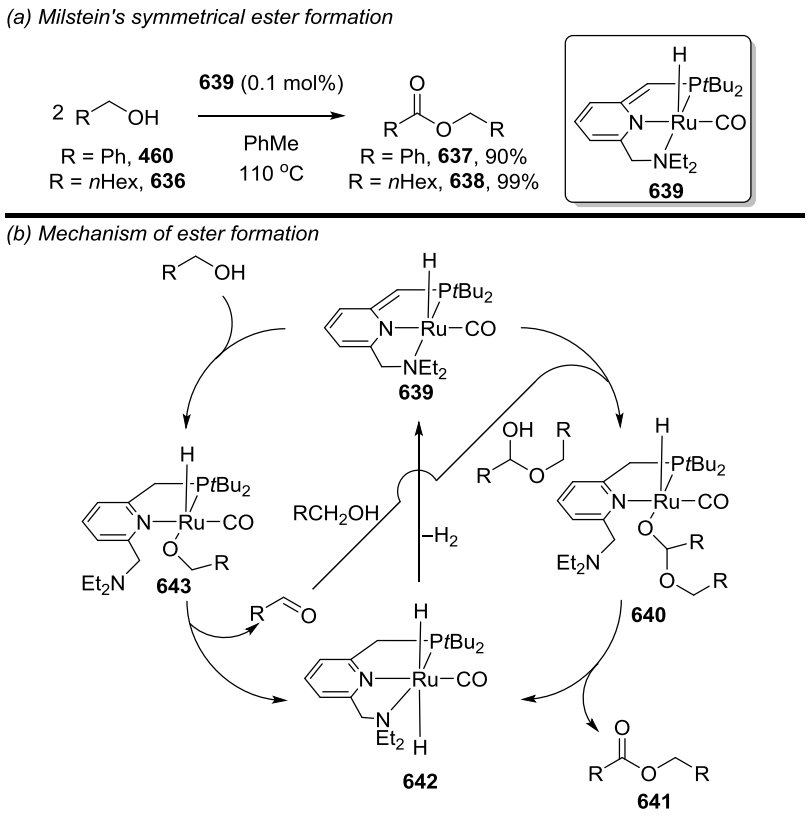
Scheme 3.38 *Krische's asymmetric propargylation of alcohols*

A number of other nucleophiles have been utilised by Krische and coworkers for similar asymmetric transformations, including propargyl chlorides,[287] simple alkenes,[288] alkynes,[289] allyl carbonates,[290] acrylates,[291] and allenamides.[292] The synthetic utility of these processes has also been demonstrated in the total synthesis of (+)-roxaticin, in a total synthesis that employs the Ir-catalysed allylation of alcohols (*vide supra*) on a total of seven alcohols in four discrete steps for the construction of a complex polyol.[293]

3.3.2 Alcohol dehydrogenation for the synthesis of esters and amides

Milstein and coworkers have demonstrated the use of Ru-pincer complex **639** with alcohols for the formation of a range of different carboxylic acid and carbonyl derivatives.[294] For example, by refluxing alkyl or benzylic alcohols with only 0.1 mol% **639** in toluene, they were able to synthesise a range of symmetrical esters in >90% yield (**Scheme 3.39a**). The reaction is believed to proceed *via* oxidation to an aldehyde, followed by hemiacetal formation, and oxidation to the corresponding ester *via* dehydrogenation. These pincer

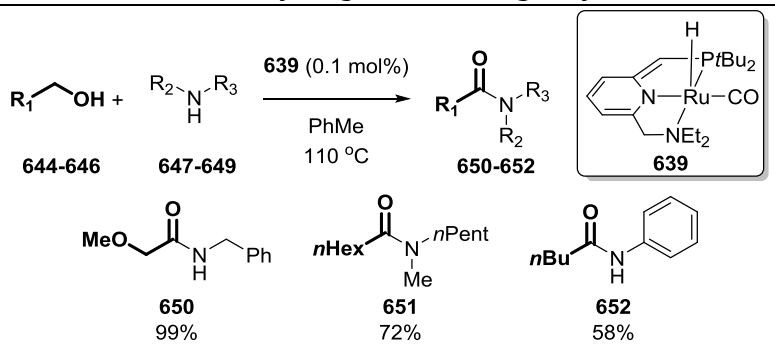
complexes are part of the family of "non-innocent" complexes, where it is believed that the ligand itself plays a role in the mechanism (**Scheme 3.39b**).



Scheme 3.39 *Milstein's Ru-pincer complexes for alcohol-dehydrogenation/ester formation*

A variety of other research groups have conducted research into the area of acceptorless dehydrogenation for the formation of esters including Shvo,[295] Murahashi,[296] Gusev,[297] and Beller.[298] Recently, Milstein and coworkers have also reported the dehydrogenative cross-coupling of primary and secondary alcohols for the formation of unsymmetrical esters.[299] The synthesis of methyl esters by the reaction of primary alcohols with methanol in the presence of $Ru(PPh_3)_3(CO)H_2$/Xantphos was also reported by Williams and coworkers.[300]

Milstein's Ru-pincer complexes have also shown themselves to be efficient for the formation of amides from alcohols and amines.[301]A variety of unhindered primary and secondary amines **647-649** were found to undergo efficient amide formation with primary aliphatic alcohols **644-646** (**Scheme 3.40**). Unfortunately, hindered amines, for example, $NHBn_2$ did not undergo this particular reaction, and anilines were found to afford poorer yields of the desired amide, with the remaining alcohol being converted into the corresponding ester.



Scheme 3.40 *Amide formation via acceptorless-dehydrogenation of alcohols*

Further examples for the formation of amides from alcohols and amines have subsequently been developed by a number of different groups, predominantly using catalysts based on Ru^{II}.[302,303,304]

3.4 Dehydrogenation of methanol and C-C coupling reactions of methanol

3.4.1 Reforming of methanol for hydrogen production

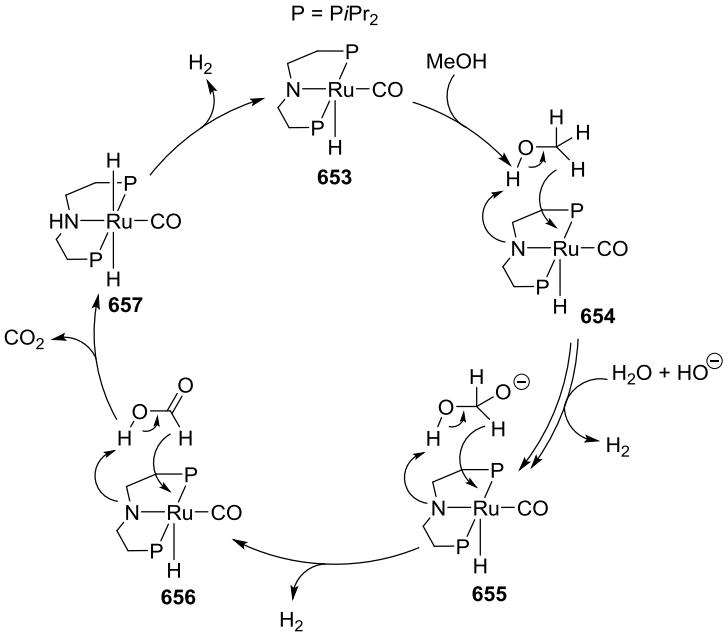
From the above survey of the literature in relation to hydrogen borrowing and related methodologies, it is clear that alkylation reactions of alcohols are predominantly based on benzylic and longer chain aliphatic alcohols. There are notable exceptions to this, for example Grigg's and Fujita's methylation of arylacetonitriles,[230,258] and Del Zotto's methylation of amines.[237] However, to the best of our knowledge, there did not exist prior to the commencement of our work in the area, a single example of the methylation of ketones, for example.

Methanol is a highly abundant chemical feedstock, with in excess of 35 million tons of methanol produced industrially every year.[305,306] Methanol is available from a number of different renewable pathways, including the gasification of industrial or municipal waste, biomass, or by carbon capture technologies.[307] Utilisation of methanol as a renewable C1-building block in catalytic processes would contribute greatly in the drive towards sustainable chemistry, and would avoid the need for the prefunctionalisation of methanol (such as the formation of MeI, MeOTf, or Me_2SO_4) for one carbon C-C bond forming reactions. However, it should be noted that catalytic C-C bond forming reactions are already employed

on an industrial scale, with the Monsanto and Cativa processes for the synthesis of acetic acid being some of the highest volume applications of industrial homogeneous catalysis.[308]

The dehydrogenation of methanol for the production of hydrogen traditionally requires harsh conditions (>200 °C).[309] Examples of catalysts employed for this process are Pt/Al_2O_3 (200-225 °C, 25-50 bar),[310] or $Cu/Zn/Al_2O_3$, although the latter catalyst requires higher temperatures.[306] However, a number of low temperature processes have now been developed for the dehydrogenation of methanol, particularly with the aim of hydrogen production.

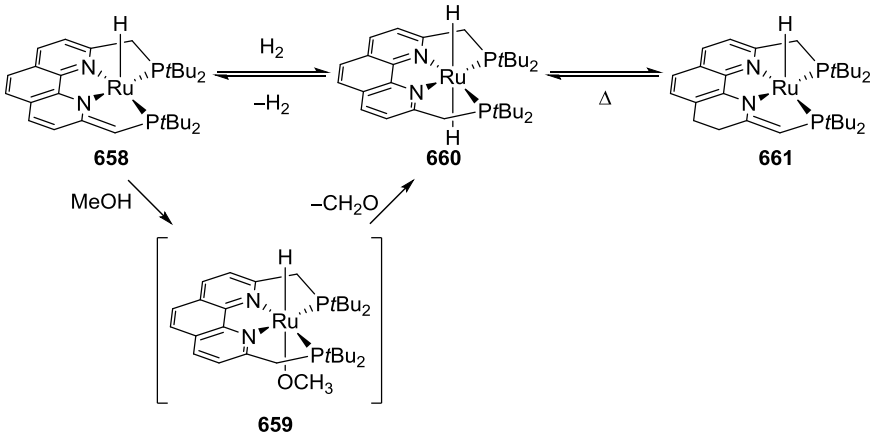
In 2013, Beller and coworkers reported the use of the Ru^{II}-pincer complex **653** for the low temperature dehydrogenation of methanol to carbon dioxide (**Scheme 3.41**).[309] The catalyst was able to achieve remarkable efficiency for this dehydrogenation, requiring only 1.6 ppm in MeOH (8M in KOH) at 95 °C, with a long-term turnover frequency of >4,700 h^{-1}. The catalyst also proved to be stable over a long period of time (>3 weeks). A mechanism was proposed whereby three consecutive ligand-assisted outer-sphere oxidations occur, first of methanol **654**, then of formaldehyde hydrate **655**, and finally of formic acid **656**, generating three molecules of H_2 and one molecule of CO_2 per molecule of methanol.



Scheme 3.41 *Proposed catalytic cycle for Ru-PNP catalysed MeOH dehydrogenation*

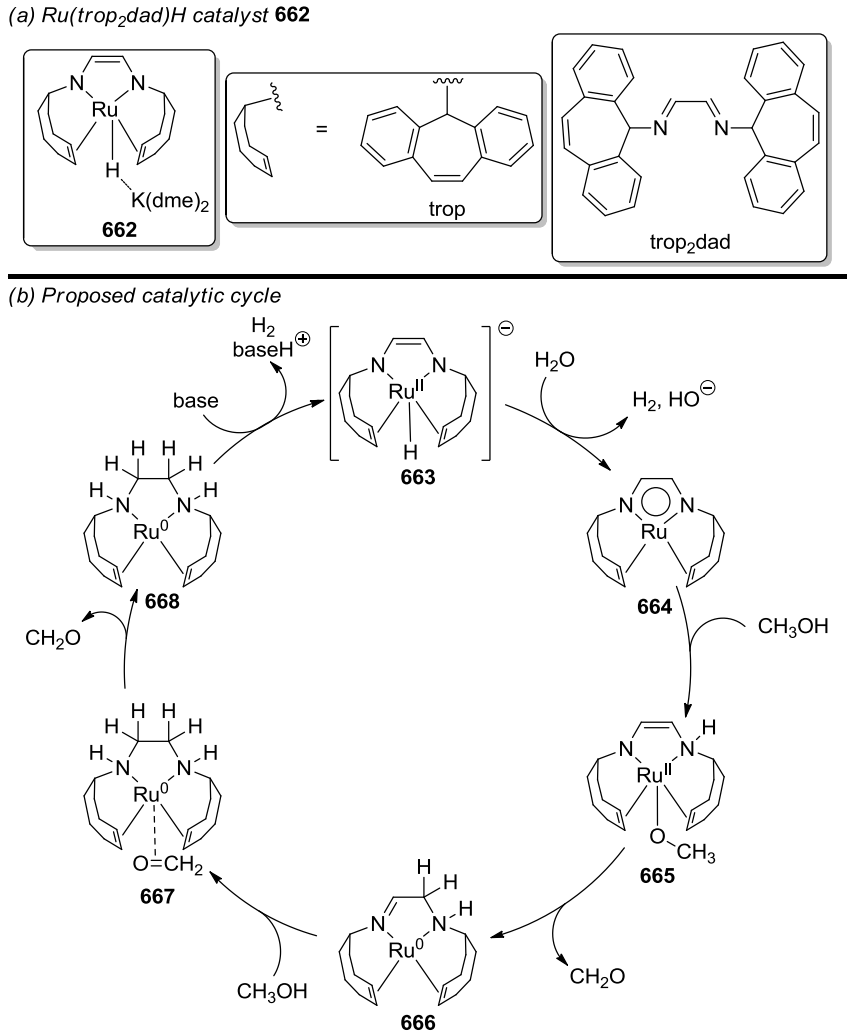
Milstein and coworkers have also demonstrated that complex **658** is capable of activating methanol *via* dehydrogenation at low temperatures (**Scheme 3.42**).[222] Treatment of **658** with

an excess of methanol at −40 °C in d_8-toluene resulted in the formation of complex **660**, presumably *via* the intermediacy of alkoxide complex **659**. This complex rapidly decomposed to starting complex **658** and isomer **661** under the reaction conditions.



Scheme 3.42 *Milstein's phenanthroline pincer complex* **658**

Trincado and Grutzmacher also reported remarkable activity for the dehydrogenation of methanol with Ru-trop$_2$dad complex **662** (**Scheme 3.43a**).[311] Using 0.01 mol% of catalyst **662**, turnover numbers of up to 24,000 h^{-1} were achieved for the dehydrogenation of methanol employing 1 eq. of Et_3N and 1 eq. of $Ba(OH)_2$ relative to methanol in a THF/H_2O mixture at 90 °C. The mechanism for this reaction is proposed to proceed *via* activation of the catalyst with water to produce neutral complex **664**, coordination of substrate **665**, and transfer of hydride to one imine of the ligand to form **666**, dearomatisation of another molecule of substrate to form the fully hydrogenated complex **668**, and subsequent base-assisted dehydrogenation to reform species **663** (**Scheme 3.43b**). The formaldehyde thus formed can re-enter the catalytic cycle as its hydrate, affording formic acid, which can then itself be dehydrogenated to CO_2.



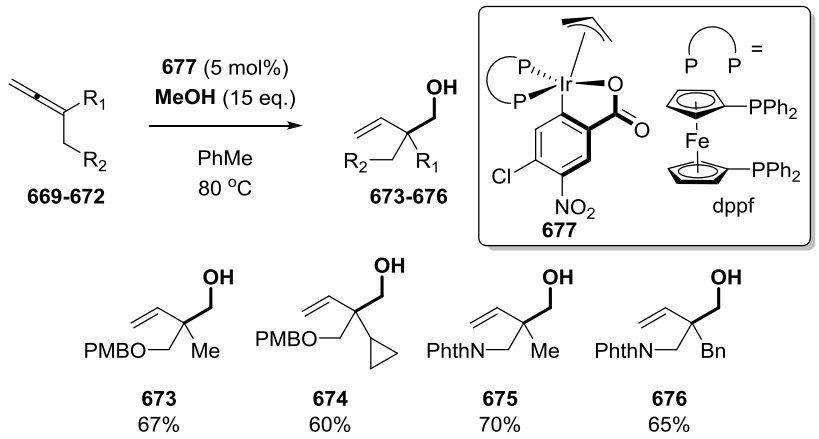
Scheme 3.43 *Trincado and Grutzmacher's low temperature reforming of methanol*

3.4.2 Synthetic applications of methanol dehydrogenation

As previously discussed, there are a few known applications of methanol dehydrogenation in the area of hydrogen borrowing chemistry, notably in the methylation of nitriles and amines (*vide supra*). However, other applications of methanol dehydrogenation have also been utilised in related applications.

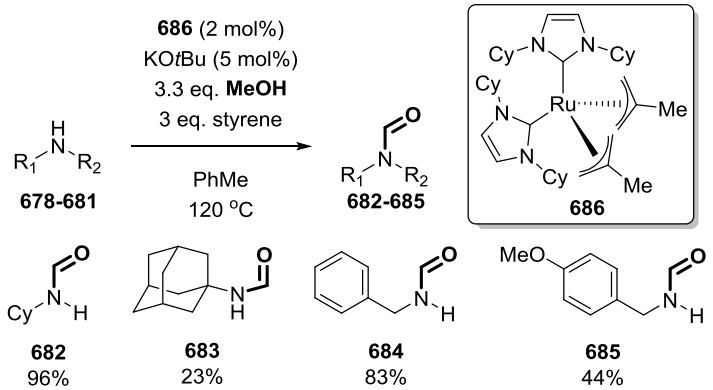
In an extension to their work on carbonyl activation/nucleophilic addition reactions with primary alcohols, Krische and coworkers developed a C-C coupling reaction of functionalised allenes with methanol.[305] Using the *o*-cyclometallated π-allyl iridium complex **677**, Krische and coworkers were able to allylate the formaldehyde generated from methanol dehydrogenation with a range of allenes in good yields, using only 15 eq. of methanol, and at a relatively mild temperature of 80 °C (**Scheme 3.44**). Deuteration experiments showed that

methanol dehydrogenation was the turnover-limiting step, whereas with higher alcohols carbonyl addition was turnover-limiting. This result is consistent with the higher enthalpy of dehydrogenation of methanol *versus* higher alcohols ($\Delta H_{dehydrogenation}$(MeOH) = +84 kJ mol^{-1}, $\Delta H_{dehydrogenation}$(EtOH) = +68 kJ mol^{-1}). [305]



Scheme 3.44 *Krische's hydroxymethylation of allenes*

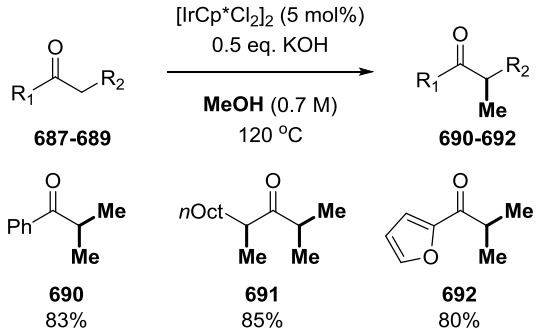
Glorius and coworkers have employed methanol in a similar manner to the groups of Milstein and others, for the synthesis of formamides *via* acceptorless dehydrogenative coupling.[312] By using bis(2-methylallyl)ruthenium NHC complex **686**, they were able to formylate a range of primary and secondary amines **678-681** in good to excellent yield (**Scheme 3.45**). However, the reaction performed less well for the formation of bulky amides such as **679**, or with substituted benzylamines such as **681**.



Scheme 3.45 *Glorius's formylation of alkylamines with methanol*

During the course of the work that contributed to this thesis, and subsequent to the publication of the work presented in **Chapter 4**,[313] Obora and coworkers published an iridium-catalysed methylation of ketones with methanol.[314] Using [Cp*IrCl$_2$]$_2$ and KOH at

elevated temperatures (120 °C), the mono- and dimethylation of a variety of ketones was reported in good to excellent yield (**Scheme 3.46**), importantly showing the possibility for the formation of α-branched products in the hydrogen borrowing mediated alkylation of ketones.



Scheme 3.46 *Obora's methylation of ketones with methanol*

It is clear, therefore, that whilst the use of methanol dehydrogenation in organic synthesis is a developing area, there is still a great deal of room for further exploration of its use.

3.5 Project aims

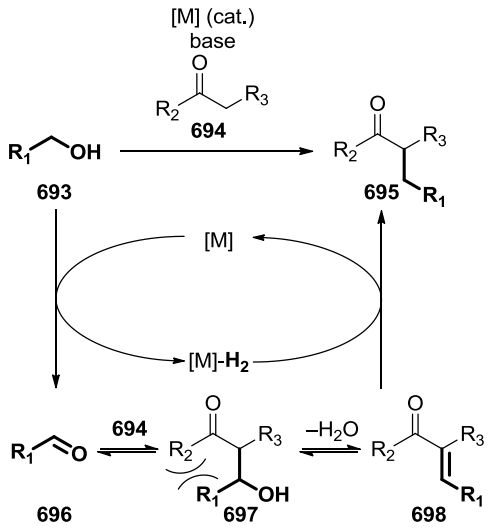
Prior to the commencement of our work in this area, the use of methanol in hydrogen borrowing chemistry had been limited to its use in the methylation of amines and nitriles, along with its use by Krische in the hydroxymethylation of allenes (*vide supra*). We envisaged that the use of methanol for the alkylation of ketones would be a useful addition to organic synthesis, providing mild conditions, and limiting the use of toxic methylation agents. Our aims for this project, therefore, were to:

1) Investigate the possibility of methylation of ketones using methanol, with a particular aim to develop mild, and general, conditions.
2) Explore the range of substrates that this methodology would be applicable to.
3) Expand the scope of this methodology to demonstrate its broad synthetic utility.

4: Results and Discussion – Rhodium-Catalysed Methylation of Ketones Using Methanol

4.1 Introduction

As discussed in **Chapter 3**, although hydrogen borrowing methods for the alkylation of ketones has matured as a methodology, this method currently extends predominantly to the alkylation of methyl ketones, primarily with benzylic and long-chain primary alcohols, with the vast majority of products containing linear alkyl ketones, with no branching at the α-position. We postulated that the inability to form α-branched products was due to the strain involved in the formation of the aldol adduct **697** upon reaction with the aldehyde **696** derived from the starting alcohol **693**, favouring a retro-aldol reaction, and thus preventing branched product formation. It therefore seemed feasible that with a small, highly-reactive aldehyde such as formaldehyde (R^1 = H), the formation of branched, methylated products should be feasible (**Scheme 4.1**).



Scheme 4.1 *Borrowing hydrogen for the alkylation of ketones*

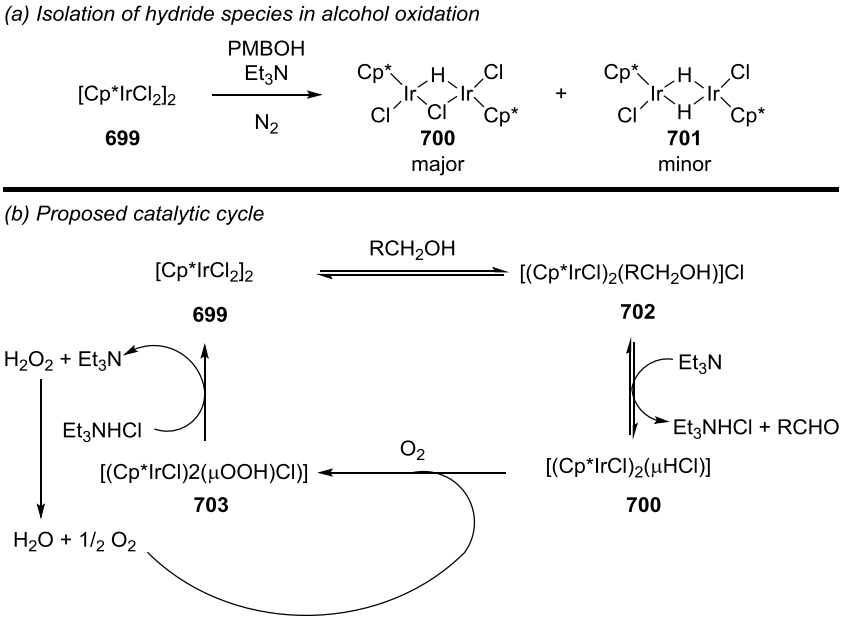
We therefore set out to test this hypothesis, and develop a metal-catalysed methylation of ketones with methanol.

4.2 Initial development of reaction conditions

4.2.1 Key leads in choosing reaction conditions

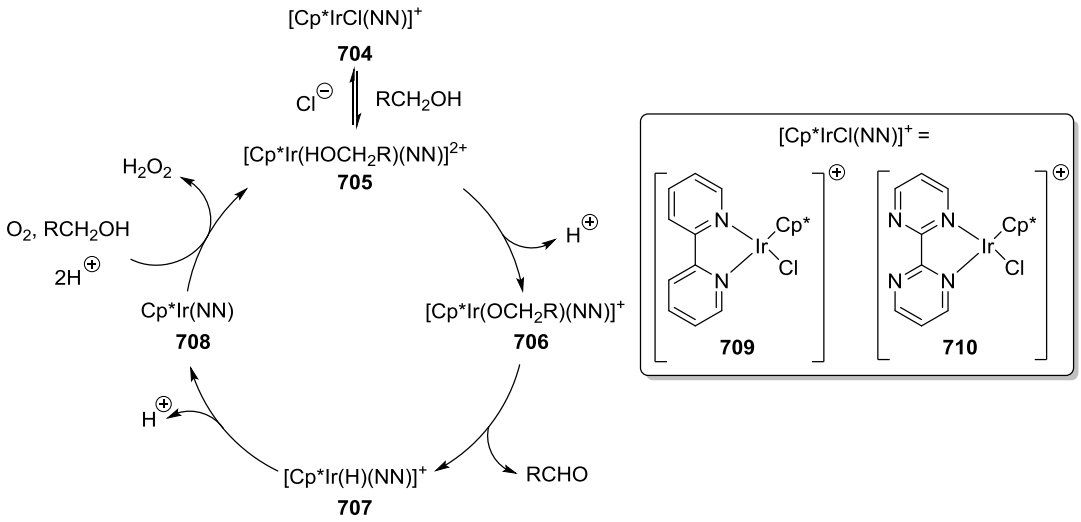
During our investigation into feasible precedent for the methylation of ketones, our attention was caught by investigations into the aerobic oxidation of alcohols by both Ison,[315] and Gabrielsson.[316] Ison and coworkers reported the beneficial effect of oxygen on the oxidation

of benzyl alcohols by $[Cp^*IrCl_2]_2$. Under an atmosphere of N_2, they were able to isolate the Ir-hydride species **700** and **701** (**Scheme 4.2a**). Resubjection experiments showed that monohydride complex **700** was a key intermediate in the aerobic oxidation of alcohols by $[Cp^*IrCl_2]_2$, and allowed the authors to propose a catalytic cycle whereby oxygen allows the regeneration of the active catalyst by formation of hydrogen peroxide (**Scheme 4.2b**).



Scheme 4.2 *Ison's aerobic oxidation of alcohols catalysed by $[Cp^*IrCl_2]_2$*

Gabrielsson and coworkers proposed that the role of oxygen in the aerobic oxidation of alcohols (including methanol) with **709** and **710** was due to the requirement to reoxidise an Ir^I species formed by the deprotonation of an acidic hydride species **707** (**Scheme 4.3**).

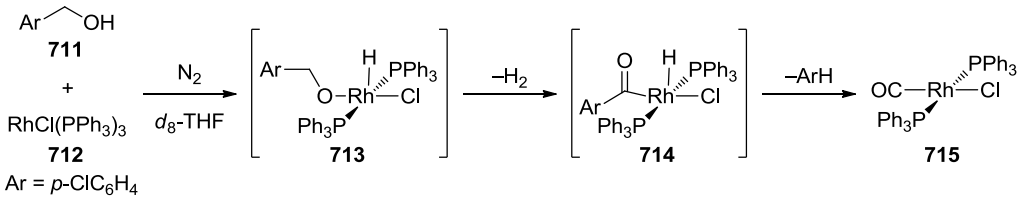


Scheme 4.3 *Gabrielsson's aerobic oxidation of alcohols with Ir-complexes* **709** *and* **710**

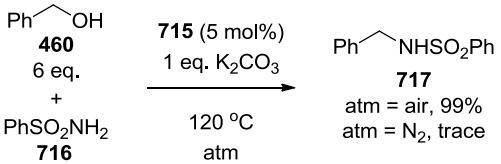
The pKa of the hydride formed from complex **709** was measured to be *ca*. 6 in $MeCN/H_2O$, while complex **710** was found to still exist in hydride form at pH 7.[316] Oxygen was proposed to reoxidise the catalyst and result in the formation of hydrogen peroxide, which subsequently decomposes to molecular oxygen, allowing one mole of oxygen to reoxidise two moles of the catalyst.

Oxygen has also shown to be beneficial in the borrowing hydrogen method for the alkylation of a variety of nucleophiles. Xu and coworkers have reported a variety of transformations which show increased rate and yields in the presence of air, including the alkylation of amines,[317,318,] ketones,[319,320] and secondary alcohols.[320] Interestingly, during the attempted alkylation of sulfonamides such as **716** with Wilkinson's catalyst $RhCl(PPh_3)_3$ conducted under air, Xu and coworkers were able to isolate the Rh-carbonyl complex **715**, presumably formed *via* formation of the Rh-acyl complex **714** and loss of arene (**Scheme 4.4a**).[317] Resubjecting complex **715** to the reaction conditions under nitrogen, no alkylation of sulfonamide **716** with benzyl alcohol was observed, whereas under an atmosphere of air, *N*-benzylsulfonamide **717** could be isolated in essentially quantitative yield (**Scheme 4.4b**). These results seem to suggest, therefore, that oxygen is beneficial in the alkylation of nucleophiles, by maintaining catalytic activity *via* decarbonylation of any inactive metal-carbonyl species formed in the course of the reaction.

(a) Formation of Rh-CO complex **715** *in the hydrogen borrowing alkylation of ketones*



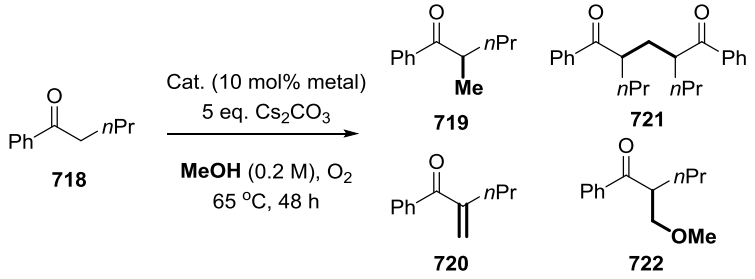
(b) Resubjection of catalyst **715** *in the alkylation of sulfonamides*



Scheme 4.4 *Xu's use of oxygen in the alkylation of sulfonamides*

4.2.2 Catalyst screening

With these conditions in mind, we chose to investigate the use of a range of metal catalysts for the methylation of ketones. Choosing valerophenone **718** as a standard substrate, different metal catalysts were screened, using Cs_2CO_3 as base (initial work by Dr Louis Chan had shown that higher equivalents of base were necessary to increase conversion of starting material)*, under an atmosphere of O_2 in refluxing methanol (**Table 4.1**).



Entry	Catalyst	719 (%)[a]	720 (%)[a]	721 (%)[a]	722 (%)[a]	RSM (%)[a]
1	$[Cp^*IrCl_2]_2$	42	14	12	27	n/o
2	$[Cp^*RuCl_2]_n$	trace	23	19	39	n/o
3	**$[Cp^*RhCl_2]_2$**	**98**	**n/o**	**n/o**	**n/o**	**n/o**
4	$RhCl_3.xH_2O$, Cp*H (10 mol%)	73	n/o	12	n/o	n/o
5	$RhCl_3.xH_2O$, $CpPh_5H$ (10 mol%)	16	15	6	36	n/o
6	$RhCl_3.xH_2O$, fluorene (10 mol%)	13	15	38	22	n/o
7[b]	$[Cp^*RhCl_2]_2$	34	trace	6	24	n/o
8[c]	$[Cp^*RhCl_2]_2$	53	n/o	33	n/o	n/o
9	$RhCl_3.xH_2O$	14	18	10	30	n/o
10	$RhCl_3.xH_2O$, PPh_3 (10 mol%)	15	27	12	44	n/o
11	$RhCl_3.xH_2O$, dppe (10 mol%)	13	18	17	35	n/o
12	$RhCl_3.xH_2O$, dppf (10 mol%)	8	11	20	40	n/o
13	$RhCl_3.xH_2O$, PCy_3 (10 mol%)	7	11	19	27	n/o
14	$RhCl_3.xH_2O$, $P(2\text{-Fur})_3$ (10 mol%)	13	13	17	26	5
15	$RhCl_3.xH_2O$, **725** (10 mol%)	n/o	7	15	16	33
16	$RhCl(PPh_3)_3$	23	n/o	n/o	n/o	n/o
17	$Rh_2(OAc)_4$	10	5	21	23	n/o
18	RuO_2	n/o	n/o	82	n/o	10
19	Pd/C	36	n/o	n/o	n/o	17

Table 4.1 *Catalyst screen*
[a] Isolated yield [b] 2 eq. Cs_2CO_3 [c] 5 eq. KOH

Interestingly, a range of different products were formed; the desired methylated ketone **719**, enone **720**, dimeric compound **721**, and also methanol adduct **722**. Both dimer **721** and methanol adduct **722** were presumed to derive from nucleophilic addition to the enone **720** during the course of the reaction. The structure of methylated ketone **719** was confirmed by

* Example by Dr L. K. M. Chan

^{1}H NMR spectroscopy, with an apparent 1H sextet at 3.49 ppm, corresponding to the ketone α-proton, which was correlated in the COSY spectrum to a diastereotopic methylene group (1.85-1.75 and 1.48-1.27 ppm), and a 3H doublet at 0.91 ppm, consistent with previously reported literature data.[321] The enone **720** exhibited two singlets at 5.83 and 5.59 ppm, correlated to a peak at 125.2 in the HSQC spectrum, corresponding to the two methylene protons. Dimer **721** was formed as an approximately 1:1.2 *anti*:*syn* ratio of diastereomers in all cases, and was initially identified from the high-resolution mass spectrum, where the mass of 359.1971 $[M+Na]^+$ was equal to ($2\times M_{\mathbf{718}}$+C+Na). The diastereomeric ratio, and assignment of diastereomers could be assigned by comparison of the two non-equivalent protons of the methylene bridge in *syn*-**721** (2.34-2.25 and 1.79-1.69 ppm), and the two equivalent protons in *anti*-**721** (2.10-2.04 ppm). Finally, methanol adduct **722** could be assigned by the presence of the $OC\underline{H}_3$ singlet at 3.21 ppm, and the presence of diastereotopic protons, corresponding to the $C\underline{H}_2OCH_3$ group, downfield at 3.75-3.60 and 3.46-3.39 ppm.

Initial treatment of valerophenone **718** with $[Cp^*IrCl_2]_2$, a catalyst known to be effective in a range of hydrogen borrowing processes,[244,245,246,247,264] and also shown to be effective for the aerobic oxidation of alcohols (*vide supra*), showed ability for the oxidation of methanol (**Table 4.1**, **Entry 1**), but was less efficient at reduction of enone **720** to the desired methylated compound **719**, affording a mixture of the desired methylated compound, unreduced enone **720**, dimeric compound **721** and methanol adduct **722**. Ruthenium(II) complex $[Cp^*RuCl_2]_n$ was also capable of efficiently oxidising methanol under the reaction conditions, but only trace reduction to methyated ketone **719** was observed (**Entry 2**).

Rhodium has shown itself to be an effective catalyst for a variety of transfer hydrogenations, including the 1,4-reduction of enones.[322,323] Thus, we theorised that use of the catalyst $[Cp^*RhCl_2]_2$ might facilitate reduction of the enone, and thus improve the yield of methylated product **719**. Pleasingly, using 5 mol% $[Cp^*RhCl_2]_2$, ketone **719** was afforded in an excellent 98% yield after 48 hours (**Entry 3**). By forming the catalyst *in situ*, performing the reaction with 10 mol% $RhCl_3.xH_2O$ and 10 mol% Cp*H, we observed a drop in yield to 73%, also isolating 12% of dimer **721** (**Entry 4**). Presumably this lower yield is a result of incomplete

formation of the catalytic species *in situ*, resulting in a slower oxidation of methanol, and increasing the chance of trapping the enone with a further equivalent of starting material **718**.

To investigate the influence of the pentamethylcyclopentadienyl ligand, the methylation reaction was also performed with other cyclopentadienyl-type ligands, by addition of 10 mol% 1,2,3,4,5-pentaphenylcyclopentadiene **723**, and fluorene **724** to the reaction (**Entries 5** and **6**, **Figure 4.1**). In both cases a mixture of all 4 products was achieved, suggesting both slower oxidation of methanol, and also a lower ability for the reduction of the enone **720**. Interestingly, the ratios achieved were slightly different, with more dimer formed in the case of fluorene **724**, suggestive of a slower rate of oxidation of methanol under these conditions. Use of $RhCl_3.xH_2O$ in the absence of any added ligand also showed little propensity for reduction, with a range of products again observed.

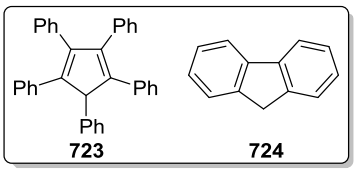


Figure 4.1 *Pentaphenylcyclopentadien*e **723** *and fluorene* **724**

Lowering the number of equivalents of Cs_2CO_3 to 2 eq. resulted in a significant decrease in yield, with only 34% of the methylated ketone **719** being isolated, along with trace enone **720**, 6% of dimer **721**, and 24% of methanol adduct **722** (**Entry 7**). However, replacing Cs_2CO_3 with 5 eq. KOH resulted in a relatively high yield of dimer **721** (33%) along with 53% of the desired methylated compound **719**. This therefore suggests that at higher pH, there is a higher concentration of the enolate of ketone **718**, and thus trapping of the enone to form dimer occurs at a faster rate relative to that of the aldol reaction between ketone **718** and the generated formaldehyde.

A number of phosphine ligands also proved ineffective at catalysing the formation of methylated ketone **719** (**Entries 10-14**). Neither the use of monodentate (PPh_3, PCy_3, P(2-Fur)$_3$) or bidentate phosphines (dppe, dppf) resulted in greater than 15% yield of **719**, with the remainder of the mass being made up by enone **720**, dimer **721**, and methanol adduct **722**. The use of *N*-heterocyclic carbene ligand 1,3-bis(mesityl)imidazolium chloride **725** (**Figure**

4.2) slowed the reaction considerably, with 33% RSM after 48 hours (**Entry 15**), and no methylated product being observed.

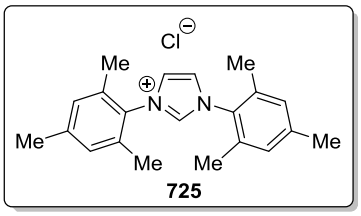


Figure 4.2 *NHC ligand* **725**

Other transition metal catalysts also showed ability to catalyse the oxidation of methanol, with Wilkinson's catalyst $RhCl(PPh_3)_3$ affording 23% of the methylated ketone **719**, but with low mass recovery (**Entry 16**). Dirhodium(II) tetraacetate also proved capable of oxidising methanol, but yielded a mixture of all products, again with low mass recovery (**Entry 17**).

An interesting result was observed when ruthenium(IV) oxide was employed as catalyst, with dimer **721** isolated in an excellent 82% yield (**Entry 18**). This result suggests that with RuO_2 catalyst, the rate of oxidation of methanol, and the rate of aldol reaction are balanced such that there is always a source of the enolate of ketone **718** available to trap any enone **720** formed, and that reduction of the enone is slow, with the methylated ketone **719** not observed.

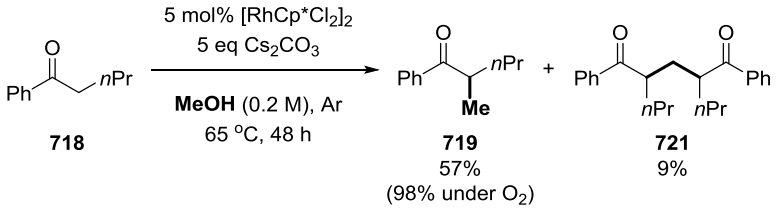
Even Pd/C, utilised by Cho and coworkers for the alkylation of methyl ketones,[269] showed activity for the oxidation of methanol, with 36% of methylated compound **719** isolated (**Entry 19**).

It was clear however, that the use of $[Cp^*RhCl_2]_2$ appeared optimal for the methylation of valerophenone, and thus the use of this catalyst with Cs_2CO_3 was taken as the standard procedure for the methylation of ketones.

4.2.3 Control Experiments

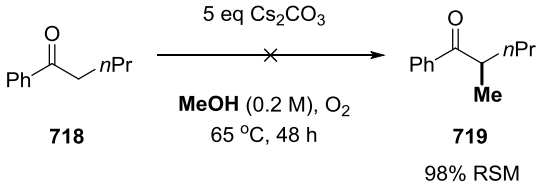
With optimum conditions in hand, it was necessary to conduct some control experiments in order to further understand the reaction. Although very high yields had been obtained by the use of an atmosphere of oxygen with $[Cp^*RhCl_2]_2$ catalyst in the methylation of valerophenone **718**, it was necessary to confirm that this reaction was more efficient than

under an inert atmosphere. Treatment of valerophenone **718** with 5 mol% $[Cp^*RhCl_2]_2$, 5 eq. Cs_2CO_3 in methanol at 65 °C under an atmosphere of argon afforded methylated ketone **719** in 57% yield, isolated along with 9% of dimer **721** (**Scheme 4.5**). This result confirmed that the reaction was more efficient, resulting in higher yield under at atmosphere of oxygen, and thus all further reactions were carried out under O_2.



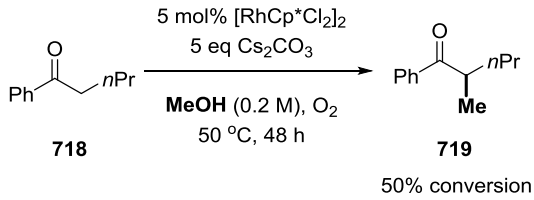
Scheme 4.5 *Control reaction under argon*

Since examples in the literature exist for the autocatalytic alkylation of ketones,[324] it was also desirable to confirm that the reaction did not proceed in the absence of catalyst. Subjecting valerophenone **718** to the reaction conditions in the absence of $[Cp^*RhCl_2]_2$ resulted solely in the recovery of starting material (98%) (**Scheme 4.6**), confirming that the metal catalyst was essential for methanol oxidation, and the subsequent aldol reaction/elimination and reduction to proceed.



Scheme 4.6 *Control reaction in the absence of [Cp*RhCl2]2*

Although the reaction was already conducted at a relatively mild 65 °C, we wondered if it would be possible to achieve the same transformation at even lower temperatures. Performing the methylation of valerophenone **718** at 50 °C resulted in slow conversion to the desired product, with approximately 50% conversion of starting being material observed by analysis of the ^1H NMR of the crude reaction mixture after 48 hours (**Scheme 4.7**).



Scheme 4.7 *Attempted methylation at 50 °C*

4.3 Substrate scope

With optimal conditions in hand for the methylation of valerophenone **718**, our attention then turned to exploring the substrate scope of the methylation reaction. As such, a variety of different ketones were prepared, to explore whether the substitution on aromatic ketones had an impact on the course of the reaction, and also whether other ketones with alkyl groups situated on either side of the ketone could be tolerated in the reaction.

4.3.1 Preparation of substrates

For the exploration of aromatic substrates in the methylation reaction, a range of aryl-ethyl ketones were prepared. The ethyl group was kept constant in these substrates so that the effects of the aromatic group could be more accurately compared for these substrates.

m-Fluorophenyl ketone **728** and *m*-methylphenyl ketone **729** were prepared following the method reported by Carroll and coworkers for the addition of Grignard reagents to nitrile compounds.[206] Thus, treatment of *m*-fluorobenzonitrile **726** and *m*-methylbenzonitrile **727** with EtMgBr in THF at room temperature, followed by hydrolysis of the intermediate imine, resulted in the formation of ethyl ketones **728** and **729** in 88% and 67% respectively (**Scheme 4.8**).



Scheme 4.8 *Synthesis of ketones* **728** *and* **729**

Product formation was confirmed by the observation of peaks corresponding to the formation of an ethyl ketone at 2.99 ppm (2H, q) and 1.23 ppm (3H, t) for **728**, and 3.00 ppm (2H, q)

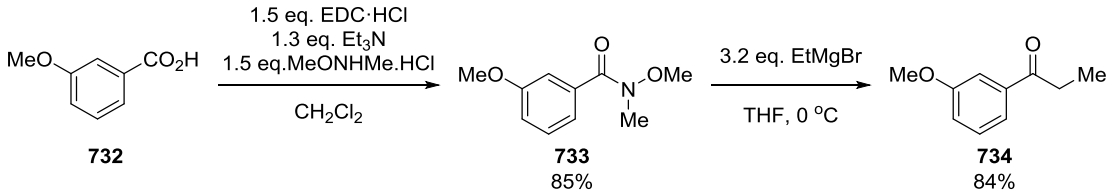
and 1.23 ppm (3H, t) for **729** in the ^{1}H NMR spectra, along with peaks present at 199.4 ppm (d) and 201.6 ppm in the ^{13}C NMR for ketones **728** and **729** respectively.

p-Dimethylaminophenyl ketone **731** was prepared by a similar method, *via* addition of a cuprate to the corresponding nitrile **730**.[325] Addition of EtMgBr and catalytic CuBr to nitrile **730**, followed by hydrolysis with 1 M H_2SO_4 yielded the desired ketone **731** in 82% yield (**Scheme 4.9**). Once again, formation of the ketone was confirmed by the observation of the characteristic peak at 199.1 in the ^{13}C NMR spectrum for the carbonyl group.



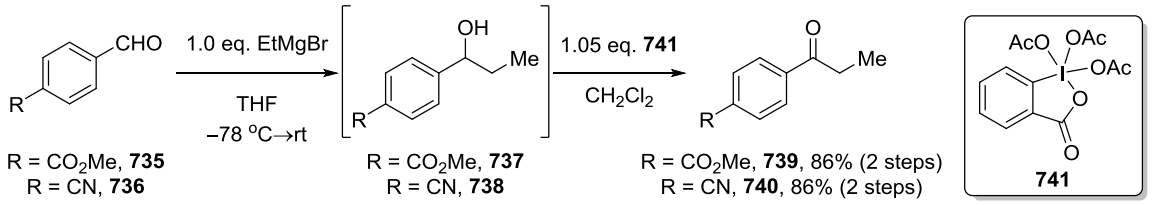
Scheme 4.9 *Synthesis of p-(dimethylamino)ketone* **731**

The *m*-methoxy substituted ketone was prepared *via* the Weinreb amide **733,** formed in 85% yield by the coupling of *m*-methoxybenzoic acid **732** with *N*,*O*,-dimethoxyhydroxylamine hydrochloride using EDC·HCl as the coupling agent.[326] Subsequent treatment of **733** with 3.2 eq. EtMgBr in THF at 0 °C afforded the ethyl ketone **734** in 84% yield (**Scheme 4.10**).



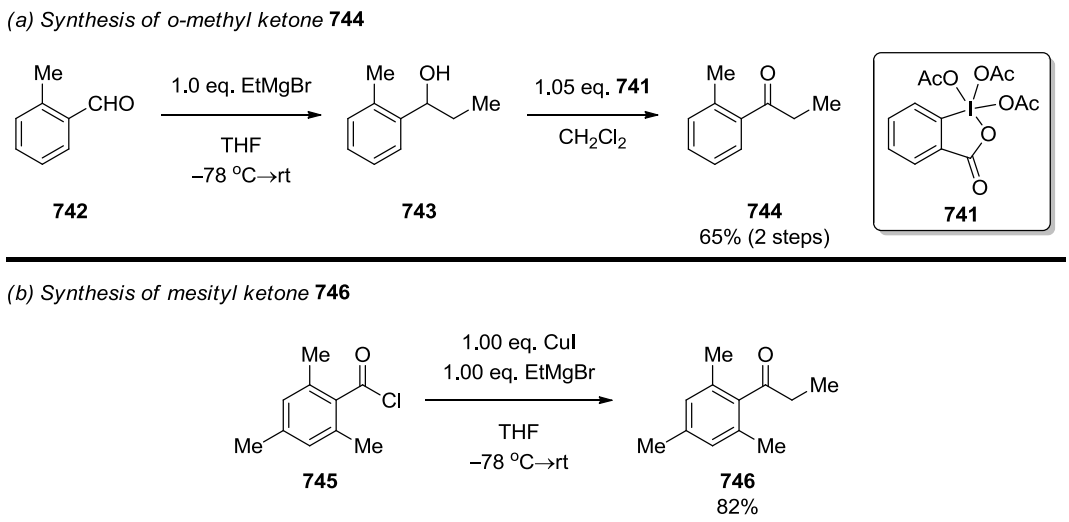
Scheme 4.10 *Synthesis of m-methoxyphenyl ketone* **734**

Ketones substituted with *para* electron-withdrawing groups were prepared by addition of 1.0 eq. EtMgBr to the aldehyde,[327] followed by Dess-Martin oxidation,[328] thus yielding ester **739** and nitrile **740** both in 86% yield over 2 steps (**Scheme 4.11**).



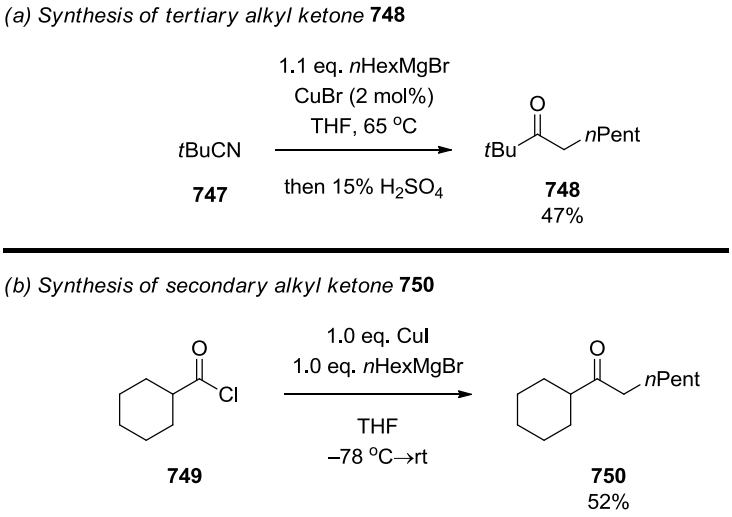
Scheme 4.11 *Synthesis of electron-deficient ketones* **739** *and* **740**

The same method was also used for the preparation of *ortho* substituted ketone **744**, which were prepared in 65% yield over 2 steps (**Scheme 4.12a**). Another *ortho*-substituted ketone, 1-mesitylpropan-1-one **746** was synthesised by the copper-mediated addition of EtMgBr to mesitoyl chloride **745** in 82% yield (**Scheme 4.12b**)



Scheme 4.12 *Preparation of ortho-substituted ketones* **744** *and* **746**

A range of alkyl-alkyl ketones were also prepared as substrates. *tert*-Butyl ketone **748** was prepared by the copper-catalysed addition of *n*HexMgBr to pivalonitrile **747**, followed by hydrolysis, affording the desired ketone in 47% yield (**Scheme 4.13a**).[329]

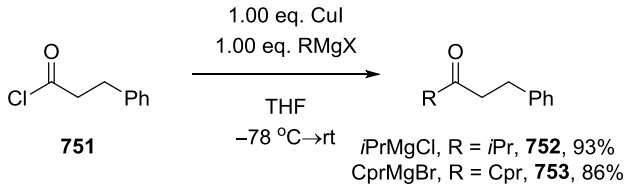


Scheme 4.13 *Synthesis of tertiary and secondary alkyl ketones* **748** *and* **750**

It was also desirable to synthesise a secondary alkyl ketone, to compare its reactivity with that of the tertiary ketone **748**. Treatment of cyclohexanecarbonyl chloride **749** with

stoichiometric copper iodide and *n*HexMgBr afforded the desired 2°-alkyl ketone **750** in 52% yield (**Scheme 4.13b**).[330]

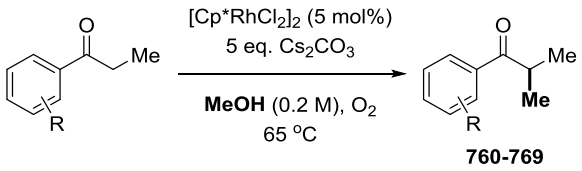
Two further secondary alkyl ketones were prepared by either the addition of *i*PrMgCl, or CprMgBr (Cpr = cyclopropyl) to hydrocinnamoyl chloride **751** to afford the desired ketones **752** and **753** in 93% and 86% respectively (**Scheme 4.14**).[330]



Scheme 4.14 *Synthesis of secondary alkyl ketones* **752** *and* **753**

4.3.2 Substrate screening

With a diverse range of substrates in hand, our attention then turned to screening them to determine the effect of different substituents on the reaction. Substrates were treated with 5 mol% $[Cp^*RhCl_2]_2$, and 5 eq. Cs_2CO_3 at 0.2 M concentration in methanol under O_2 in the first instance. First, a range of differently substituted aromatic substrates were screened, so that the effects of both electronics and sterics in the reaction could be studied.(**Table 4.2**).



Entry	Starting Ketone	Product	R	t (h)	Product (%)[a]
1	**754**	**760**	H	24	73 (58)[e]
2	**728**	**761**	*m*-F	3	77 (77)[e]
3	**734**	**762**	*m*-OMe	12	77 (62)[e]
4	**755**	**763**	*m*-Cl	4	64 (79)[e]
5	**729**	**764**	*m*-Me	48	71 (54)[e]
6	**756**	**765**	*p*-Br	24	76 (53)[e]
7[b]	**731**	**766**	*p*-NMe_2	72	80
8	**757**	**767**	*p*-CF_3	4	41 (73)[e]
9	**758**	**768**	*p*-OMe	24	64 (74)[e]
10[c,d]	**759**	**769**	*p*-F	24	58 (52)[d,e]

Table 4.2 *Screening of aromatic ketones*

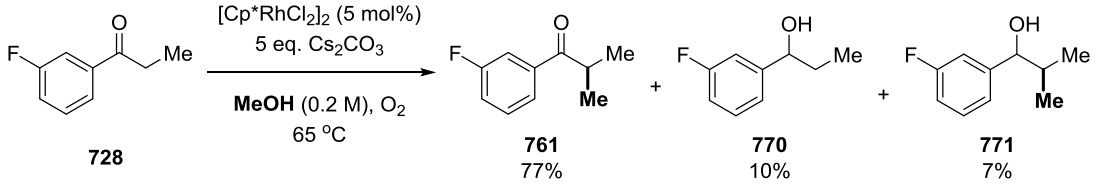
[a] Isolated yield [b] 7.5 mol% $[RhCp^*Cl_2]_2$ added in 3 portions over 72 h [c] 2 eq Cs_2CO_3 [d] **768** isolated in 21% yield [e] 2.5 mol% $[RhCp^*Cl_2]_2$

The isopropyl ketones formed from the methylation of the ethyl ketones could easily be identified in the ^{1}H NMR spectrum by the presence of a 1H septet in the region of 3.5 ppm, coupled to a 6H doublet at approximately 1.2 ppm, corresponding to the two methyl groups. From the results in **Table 4.2**, a number of interesting observations can be made. It is clear that electron-deficient ketones react faster in this reaction, with *m*-fluoro ketone **728** (**Entry 2**), *m*-MeO ketone **734** (**Entry 3**), *m*-chloro ketone **755** (**Entry 4**), and *p*-CF_3 ketone **757** (**Entry 8**) all showing complete conversion in between 4 and 12 hours. In the case of the *m*-chloro ketone **755** and *p*-CF_3 ketone **757**, the yields could be improved substantially by lowering the catalyst loading to 2.5 mol%.

On the other hand, electron-neutral and electron-rich ketones such as propiophenone **754** (**Entry 1**), *m*-methylpropiophenone **729** (**Entry 5**), *p*-(dimethylamino)propiophenone **731** (**Entry 7**) and *p*-methoxypropiophenone **758** (**Entry 9**) reacted at a much slower rate. It is possible that this is a result of formation of low concentration of the enolate due to lower acidity of electron-rich ketones, thus slowing the rate of the initial aldol reaction. Another possibility is that reduction of the enone formed is slower for electron-rich ketones due to the lower electrophilicity of the corresponding enone.

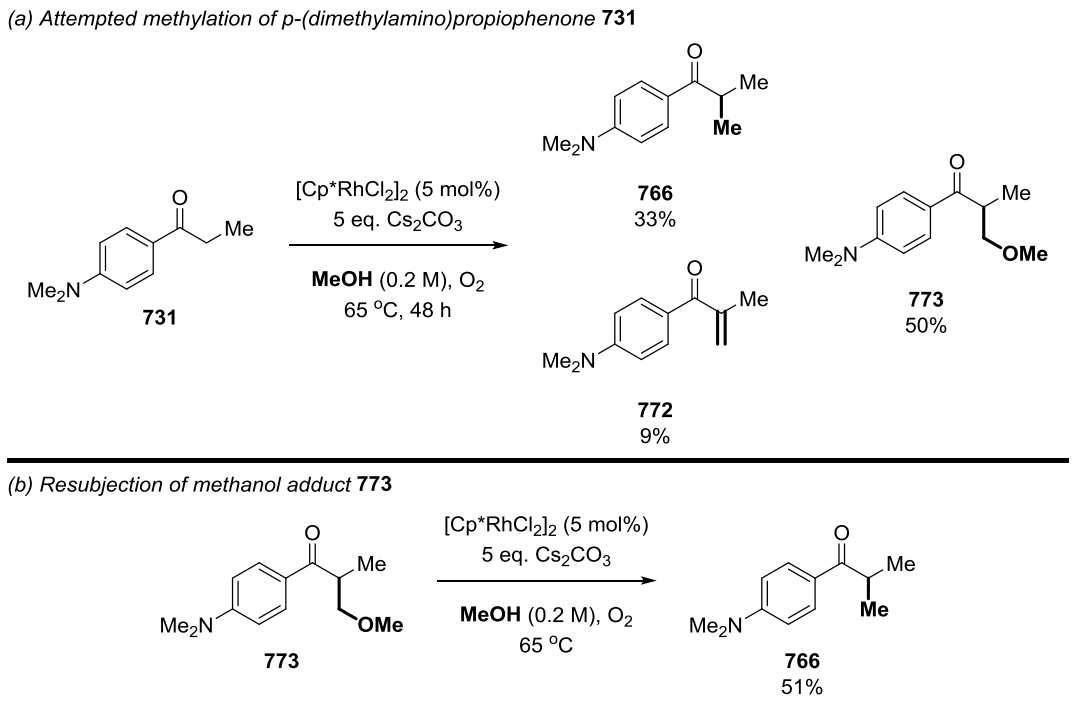
Indeed, some electron-deficient ketones were so reactive that over-reduction of the carbonyl moiety was observed in the course of the reaction. For example, in the methylation of *m*-fluoropropiophenone **728**, 10% of the secondary alcohol **770**, resulting from reduction of starting material, and 7% of the secondary alcohol **771** formed by reduction of methylated product **761** (**Scheme 4.15**). Reduced starting material **770** could be identified by the presence of a 1H triplet at 4.55 ppm in the ^{1}H NM R, indicating the presence of a proton α- to an alcohol, which was coupled to the ethyl CH_2 group. HSQC analysis showed that this proton was coupled to a peak at 75.2 ppm in the ^{13}C spectra, providing further evidence of the formation of secondary alcohol **770**. Similarly, the structure of the reduced product **771** could be confirmed by the presence of a 1H doublet at 4.40 ppm, showing coupling to the C*H* of an *i*Pr group, providing evidence for the formation of the secondary alcohol. *p*-(Trifluoromethyl)propiophenone **757** was methylated in only 41% yield, and it is possible

that its high reactivity under the methylation conditions was responsible for such a diminished yield, although no reduced products were isolated.



Scheme 4.15 *Over-reduction of m-fluoropropiophenone* **728**

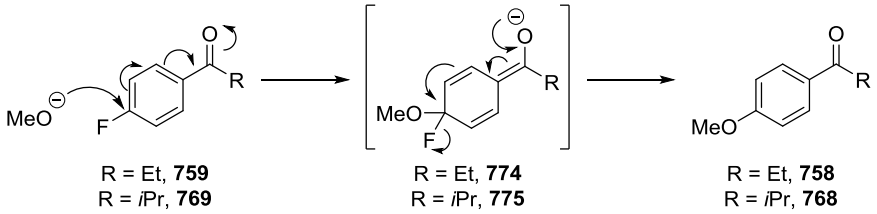
As previously discussed, electron-rich substrates appeared to react more slowly under the methylation conditions. Under the standard reaction conditions of 5 mol% $[Cp^*RhCl_2]_2$, *p*-(dimethylamino)propiophenone **731** did not go to complete conversion after 48 h, instead affording a mixture of methylated ketone **766** (32%) and enone **772** (10%), along with the methanol adduct **773** (51%) (**Scheme 4.16a**).



Scheme 4.16 *Methylation of p-(dimethylamino)propiophenone* **731**

Resubjecting the methanol adduct **773** to the reaction conditions afforded the desired methylated product **766** in 51% yield (**Scheme 4.16b**). It was postulated that the amine functionality might be sequestering the rhodium catalyst, thus addition of 3 batches of $[Cp^*RhCl_2]_2$ over 72 hours afforded the desired methylated ketone **766** in 80% yield (**Table 4.2**, **Entry 7**).

During the methylation of *p*-fluoropropiophenone **759** with 5 mol% $[Cp^*RhCl_2]_2$ and 5 eq. Cs_2CO_3 complete formation of *p*-methoxy product **768** was observed by ^1H NMR analysis of the crude NMR mixture. It was presumed that this product was formed by S_NAr reaction of either starting material **759** or product **769** with methoxide (**Scheme 4.17**). To alleviate this problem, and allow the formation of ketone **769**, the reaction was conducted with only 2 eq. Cs_2CO_3, and afforded the desired product **769** in 58% yield (**Table 4.2**, **Entry 10**), although the S_NAr product **768** was still isolated in 21% yield.



Scheme 4.17 *Nucleophilic aromatic substitution in the methylation of* **759**

Despite these overall positive results for the methylation of aromatic ketones, there were a number of substrates that did not prove to be successful under the reaction conditions (**Figure 4.3**). Ketone **739**, containing an ester in the *para* position, showed complete hydrolysis in the ^1H NMR of the crude reaction mixture. *p*-Cyano ketone **740** did not show any of the desired product, and TLC analysis only indicated the presence of a mixture of polar compounds, suggesting reaction of the nitrile group under the reaction conditions.

It also appeared that the methylation reaction could not tolerate groups in the *ortho* position of aromatic ketones. Both *o*-tolyl ketone **744**, and mesityl ketone **746** failed to show more than trace conversion to product under the reaction conditions. One possible reason for this is that the stability of the aldol adduct **776** is decreased due to steric hindrance caused by the presence of *ortho* groups on the aromatic ring, favouring retro-aldol rather than elimination to form the desired enone.

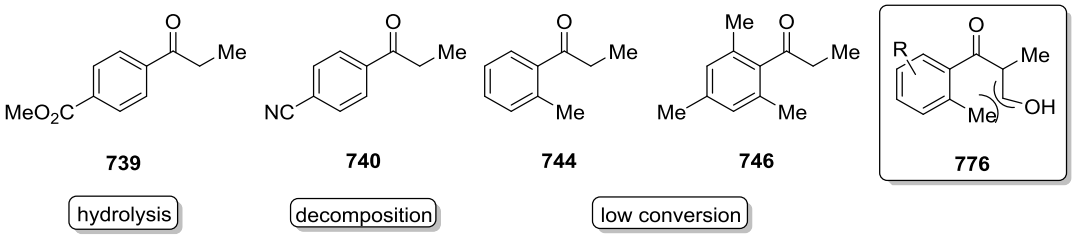
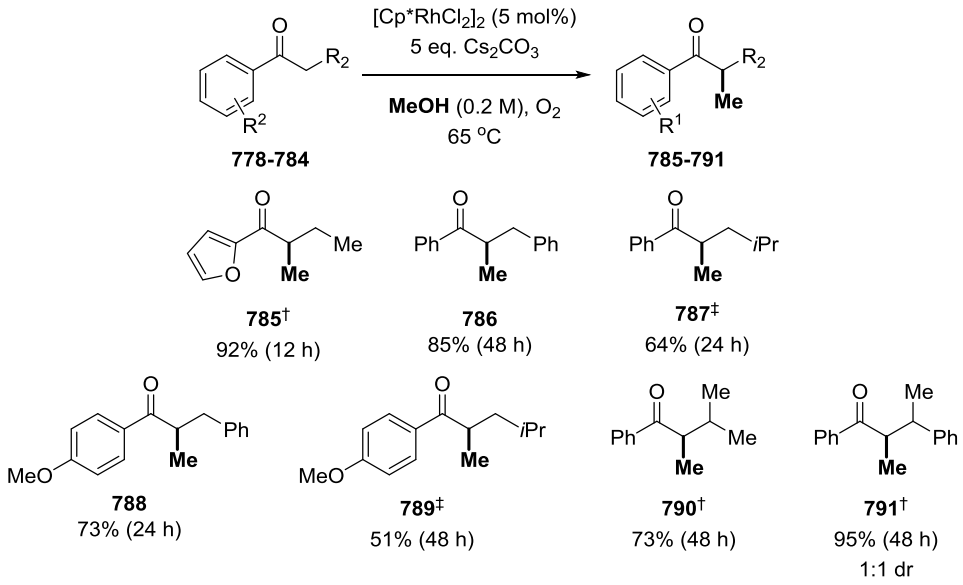


Figure 4.3 *Failed substrates*

Our attention then turned to explore the range of other aromatic substrates that could be methylated under these conditions (**Scheme 4.18**).

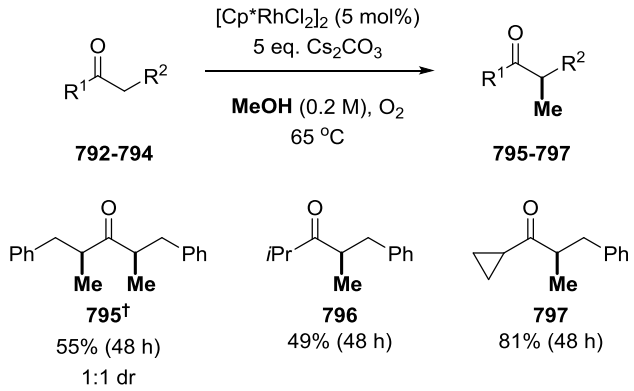


Scheme 4.18 *Further methylation of aromatic ketones*

Pleasingly, heteroaromatic ketones such as 2-furyl ketone **778** could be methylated successfully, with the corresponding product **785** isolated in 92% yield.[†] Longer and more substituted side chains could also be methylated in good to high yields. Homobenzyl ketone **779**, and isopentyl ketone **780**[‡] were methylated in 85% and 64% yield respectively. Similarly, the *p*-methoxyphenyl analogues **781** and **782**[‡] were methylated in 73% and 51% respectively. It is interesting to note that the yields for the isopentyl ketones **780** and **782** were lower in both cases than their equivalent homobenzyl ketones **779** and **781**. β-Substitution could also be tolerated on the alkyl chain, for example, β-methyl ketones **783** and **784** could be alkylated in 73% and 95% respectively, [†] although no diastereoselectivity was observed in the methylation of **784**, presumably due to the basic reaction conditions.

With a range of different aromatic ketones in hand, we were also determined to demonstrate the utility of the rhodium-catalysed methylation reaction for the methylation of alkyl-alkyl ketones (**Scheme 4.19**).

[†] Example by Dr L. K. M. Chan
[‡] Example by D. Shen



Scheme 4.19 *Methylation of alkyl-alkyl ketones*

1,5-Diphenylpentan-3-one **792** could be methylated in 55% yield, although no 1,3-diastereoselectivity was observed, affording methylated ketones *syn*- and *anti*-**795** in 1:1 dr. [†] Although this ketone was methylated in only a moderate 55% yield, this still equates to a yield of approximately 75% per methylation, in the normal range for methylation of other ketones. Isopropyl ketone **793** could also be methylated, although only in a relatively low yield of 49% after 48 h. Resubjection of methylated isopropyl ketone **796** showed complete decomposition after 48 h, suggesting that the product is unstable to the reaction conditions, and that this is responsible for the low yield. However, replacement of the isopropyl group in **793** with a cyclopropyl moiety resulted in a much higher yield of methylation, with methylated ketone **794** isolated in 81% yield. It is possible that cyclopropyl ketone **794** is much closer to aromatic ketones in terms of reactivity, due to hyperconjugation between the two occupied cyclopropyl group HOMOs and carbonyl π* (**Figure 4.4**),[331] resulting in increased stability to oxidation, and also a lower pKa for formation of the enolate.

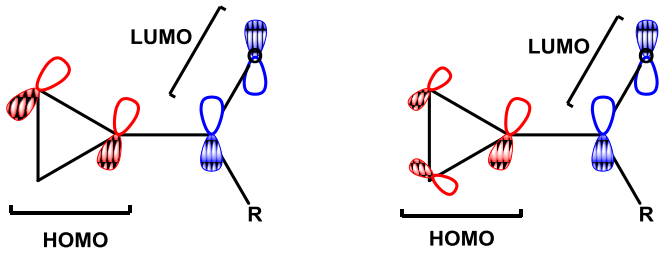
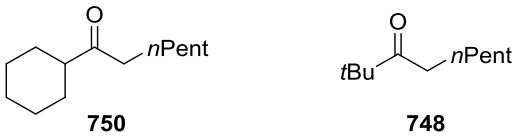


Figure 4.4 *Possible hyperconjugation in ketone* **794**

Further evidence for this hyperconjugation can be obtained from both ^{13}C NMR, and also IR spectroscopy, with the *C*=O peak for *i*Pr ketone **793** occurring at 213.7 ppm, whereas in the case of cyclopropyl ketone **794**, this peak appears at 209.9 ppm, intermediate between an

alkyl and aryl ketone. Furthermore, in IR analysis reveals that, in the case of *i*Pr ketone **793**, the C=O stretch appears at 1709 cm^{-1}, whereas for cyclopropyl ketone **794** this value is lower at 1696 cm^{-1}, again intermediate between alkyl and aryl ketones.[§]

Unfortunately, other alkyl-alkyl ketones exposed to the methylation conditions did not prove to be effective substrates (**Figure 4.5**). Cyclohexyl ketone **750** showed only minimal reactivity, with almost complete starting material observed by ^{1}H NMR analysis of the crude reaction mixture. *tert*-Butyl ketone **748**, however, showed itself to be completely inert to the methylation reaction under all conditions attempted. Exchange of Cs_2CO_3 for 5 eq. KOH, or 5 eq. NaOMe, and heating the reaction to 80 °C still resulted in complete recovery of starting material.



750 **748**

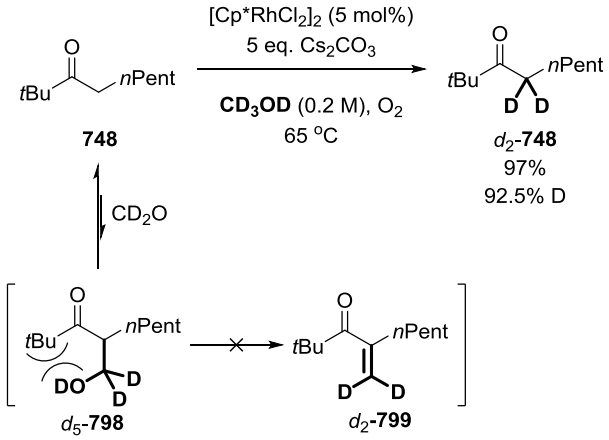
too hindered?
high pKa?

Figure 4.5 *Failed substrates*

We postulated that the unreactivity of *tert*-butyl ketone **748** could be a result of one of two factors. It was possible that the presence of the *t*Bu group rendered the aldol adduct too hindered, and thus favoured a retro-aldol reaction, rather than elimination to form the required enone for methylation to occur. It was also possible that the acidity of this ketone was considerably less than for other ketones that had been screened, and this might be resulting in a low formation of enolate, and thus slow aldol reaction. If one compares the pKa of propiophenone **754** (24.4 in DMSO), with pinacolone (27.7 in DMSO), it is clear that there is a considerable difference in acidity between aromatic and alkyl substituted ketones.[332] To test this hypothesis, ketone **748** was resubjected to the reaction conditions in d_4-methanol for 18 hours (**Scheme 4.20**). Subsequently, d_2-**748** was isolated in 97% yield, with 92.5% deuterium incorporation at the α-position as measured by integration of the ^{1}H NMR spectrum, with near-complete disappearance of the triplet at 2.45 ppm, corresponding to the α-methylene group. This experiment therefore confirmed that the enolate of **748** was

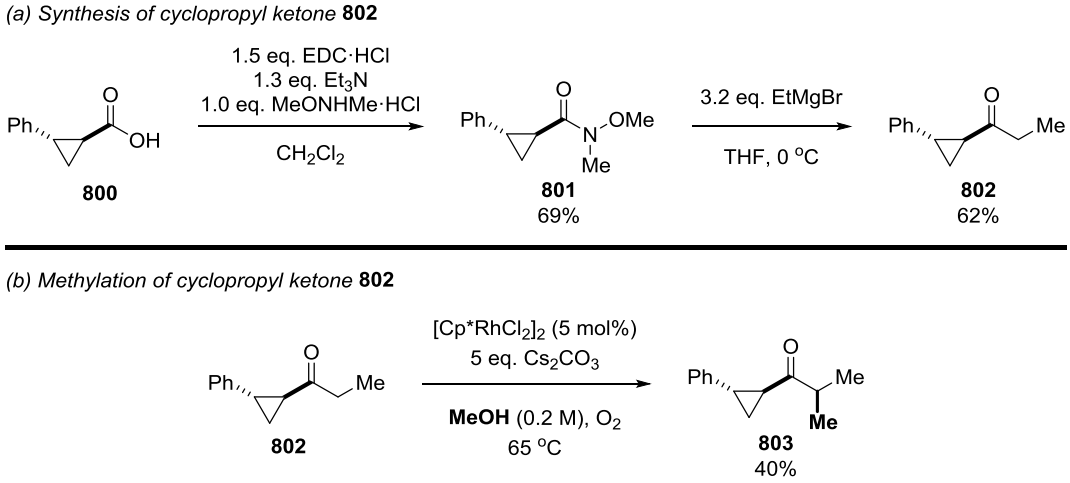
[§] Data provided by Lena Raker.

formed under the reaction conditions, which therefore suggests that it is the formation of the aldol adduct d_5-**798** and subsequent formation of enone d_2-**799** by elimination of water that is preventing the methylation reaction from occurring.



Scheme 4.20 *Deuterium incorporation in tert-butyl ketone* **748**

Since it appeared that of all alkyl-alkyl ketones, cyclopropyl ketones seemed to offer the best reactivity, it was decided to investigate the methylation of a more substituted cyclopropyl ketone. Thus, coupling of *trans*-2-phenyl-1-cyclopropanecarboxylic acid **800** and *N*,*O*-dimethylhydroxylamine, employing EDC·HCl as the coupling agent, afforded Weinreb amide **801** in 69% yield (**Scheme 4.21a**).[326] Subsequent treatment of **801** with EtMgBr in THF afforded the desired ethyl ketone **802** in 62% yield. Unfortunately, attempted methylation of **802** afforded the desired methylated product **803** in only 40% yield, with no other major product isolated (**Scheme 4.21b**).

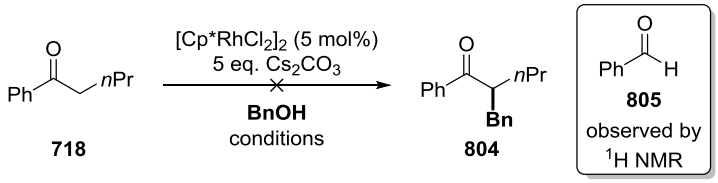


Scheme 4.21 *Synthesis and methylation of cyclopropyl ketone* **802**

4.3.3 Attempted alkylation with other alcohols

Although it was clear that alkylation with methanol allowed for the formation of α-branched ketones *via* this methodology, there exist only a handful examples of the formation of α-branched products using higher alcohols (**See Chapter 3.2.3**). Thus, we were interested to find out if the catalytic system developed using $[Cp^*RhCl_2]_2$ were also capable of enabling the alkylation of ketones with higher alcohols.

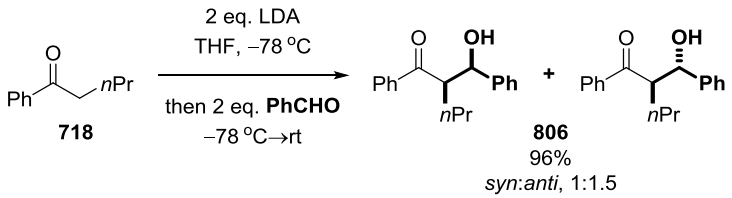
Benzylic alcohols are among the most common alcohols used for the hydrogen borrowing alkylation of ketones. Conducting the reaction under the standard conditions employed for methylation, replacing methanol with benzyl alcohol resulted only in the recovery of starting material, along with the formation of benzaldehyde (**Table 4.3**). Conducting the reaction at higher concentrations, and also at higher temperatures under O_2 and argon also resulted only in the observation of PhCHO, and the recovery of valerophenone **718**.



Entry	Conditions	804 (%)
1	BnOH (0.2 M), O_2, 65 °C	n/o
2	BnOH (0.2 M), Ar, 65 °C	n/o
3	BnOH (0.2 M), O_2, 100 °C	n/o
4	BnOH (0.2 M), Ar, 100 °C	n/o
5	5 eq. BnOH, Ar, 100 °C	n/o

Table 4.3 *Attempted benzylation of valerophenone* **718**

We postulated that the reason for the difficulty of alkylation of ketones with bulkier alcohols lay in the position of equilibrium of the initial aldol reaction. To investigate the stability of the aldol adduct **806** with respect to the retro-aldol process, it was decided to synthesise the aldol adduct independently and resubject it to reaction conditions for benzylation and methylation. Therefore, aldol adduct **806** was prepared by treatment of valerophenone **718** with freshly-prepared LDA, followed by quenching with benzaldehyde, affording a 1:1.5 ratio of *syn* and *anti* diastereomers in 96% yield (**Scheme 4.22**).



Scheme 4.22 *Synthesis of aldol adduct* **806**

Assignment of the *syn* and *anti* diastereomers was made from the coupling constants in the ^{1}H NMR spectrum.[333] Previous work by Stiles and coworkers, and House and coworkers,[334] has shown that for aldol products, assumption of an intramolecular hydrogen bond allows determination of the product stereochemistry by observation of the coupling constant between the ketone α- and β- protons (**Figure 4.6**). The formation of an intramolecular hydrogen bond is postulated to hold the compound in a chair conformation, and thus the vicinal coupling constants between the α- and β- protons are indicative of their relative orientation. In the *anti* diastereomers, these two protons have a 1,2-diaxial relationship, and thus one would expect a higher coupling constant (approximately 7-12 Hz), whereas in the *syn* diastereomers a lower coupling constant would be expected (approximately 0-4 Hz), due to the gauche relationship between the two protons.[335] Indeed, in compounds *anti*-**806** and *syn*-**806**, coupling constants of 4.5 Hz, and 7.0 Hz respectively were observed for the splitting of the C*H*OH proton, supporting this assignment of stereochemistry. Furthermore, Heathcock and coworkers have demonstrated that ^{13}C NMR shifts for the *anti* diastereomers appears further downfield than for *syn* diastereomers in aldol adducts, which is also apparent in the ^{13}C NMR spectrum of *anti*-**806** and *syn*-**806**, with the carbinol *C*HOH appearing at 76.1 ppm for the *anti* diastereomers, and 73.9 ppm for the *syn* diastereomer.[336]

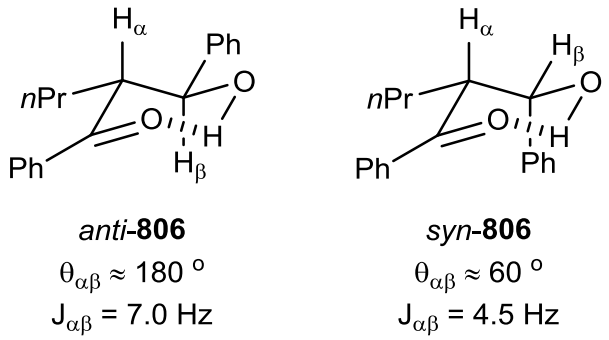
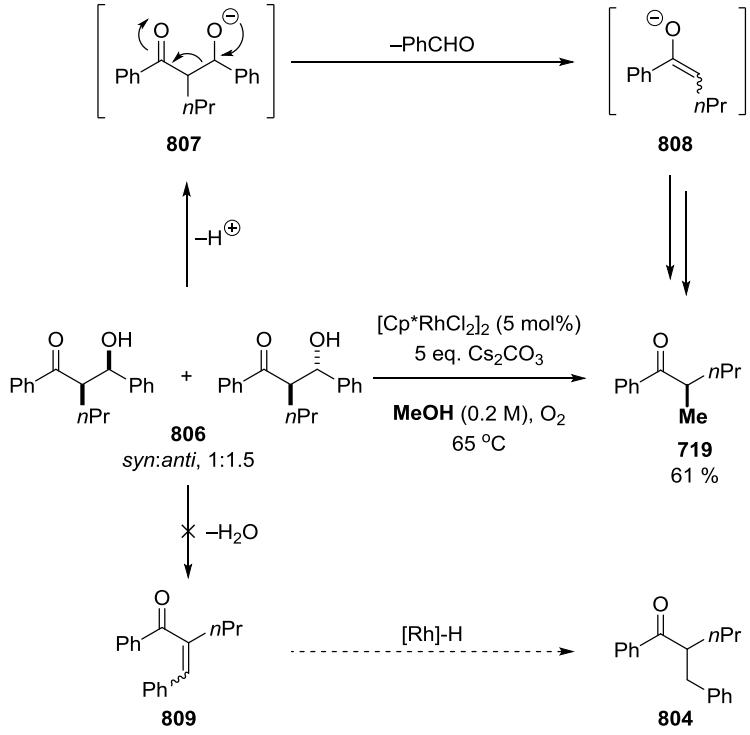


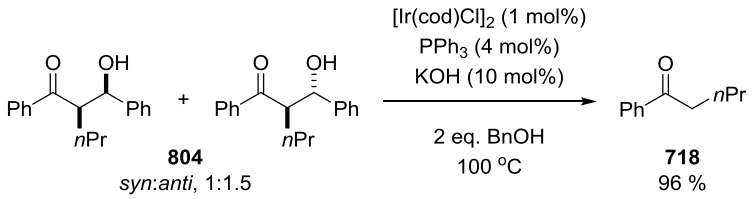
Figure 4.6 *Stereochemcial assignment of aldol adducts anti*-**806** and *syn*-**806**

With aldol adducts **806** in hand, this product was then resubjected to conditions for the rhodium-catalysed methylation reaction. Treatment of **806** with 5 mol% $[Cp^*RhCl_2]_2$ and 5 eq. Cs_2CO_3 in methanol at 65 °C under an atmosphere of O_2 resulted in the formation of methylated ketone **719** in 61% yield, with no observation of the benzylated product **804** (**Scheme 4.23**). This outcome therefore suggested that under the reaction conditions, deprotonation of the alcohol **806** and retro-aldol reaction to form enolate **808** was much faster than elimination of water, and subsequent reduction of the 1,1,2-trisubstituted enone **809** that would be formed by elimination. This is presumably a result of an unfavourable steric interaction between the pendant phenyl group, and the phenyl group of the ketone.



Scheme 4.23 *Resubjection of aldol adduct* **806** *to methylation conditions*

Since previous attempts to perform a benzylation under of valerophenone **718** under rhodium-catalysed conditions had proved unsuccessful, the aldol adducts **806** were also subjected to conditions known to promote benzylation of methyl ketones, developed by Ishii and coworkers.[273] Thus, treatment of aldol adducts **806** with 1 mol% $[Ir(cod)Cl]_2$, 4 mol% PPh_3. 10 mol% KOH and 2 eq. BnOH at 100 °C under at atmosphere of argon afforded only valerophenone **718** in 96% yield, providing further evidence for the favoured retro-aldol reaction of adducts *anti*- and *syn*-**804** (**Scheme 4.24**).



Scheme 4.24 *Attempted benzylation of aldol adducts* **804**

It was clear from these experiments that alkylation of ketones with bulky alcohols to form α-branched products did not appear to be a viable synthetic option, which is perhaps unsurprising given the dearth of high-yielding examples in the literature, and their limited variety in structure, predominantly focused on cyclic ketones. This therefore precluded further studies into the attempted formation of branched products of acyclic ketones using bulkier alcohols.

4.4 Mechanistic experiments

Having explored the range of substrates amenable to the reaction, and conducted some preliminary experiments on the possibility of formation of other branched products with higher alcohols, our attention turned to trying to gain a deeper understanding of the methylation reaction, and in particular its mechanism, as there were a number of areas in which we considered there to be unanswered questions, with two main areas in particular:

1) What is the mechanism of the reaction? What role do the species isolated in initial screening play in the catalytic cycle?
2) What is the role of O_2 in the reaction?

To probe these areas a number of different mechanistic experiments were conducted.

4.4.1 Resubjection experiments

During the course of the initial screening of reaction conditions, a number of different products were observed along with the desired methylated ketone **719** (**Figure 4.7**). These were the enone **720**, the dimeric compound **721**, and the methanol adduct **722**. It was assumed that enone **720** was a species on the reaction pathway, formed *via* aldol reaction/elimination, before it would be subsequently reduced to methyl compound **719**. It appeared that dimer **721** and methanol adduct **722** resulted from a conjugate addition of either

starting material **718** or methanol to the enone **720**, but whether these were intermediates on the reaction pathway, or dead-end byproducts that played no further part in the reaction was as yet uncertain. We also postulated the existence of aldol adduct **811**, formed *via* aldol reaction with formaldehyde, the presumed nucleophile in the reaction, but this compound has not been isolated.

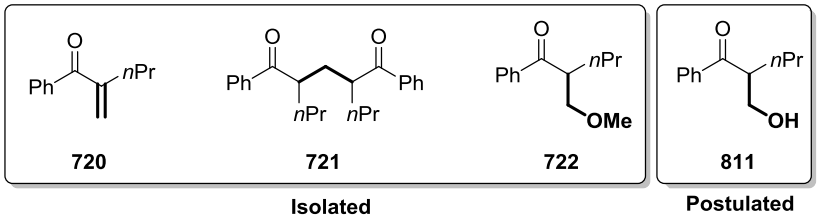
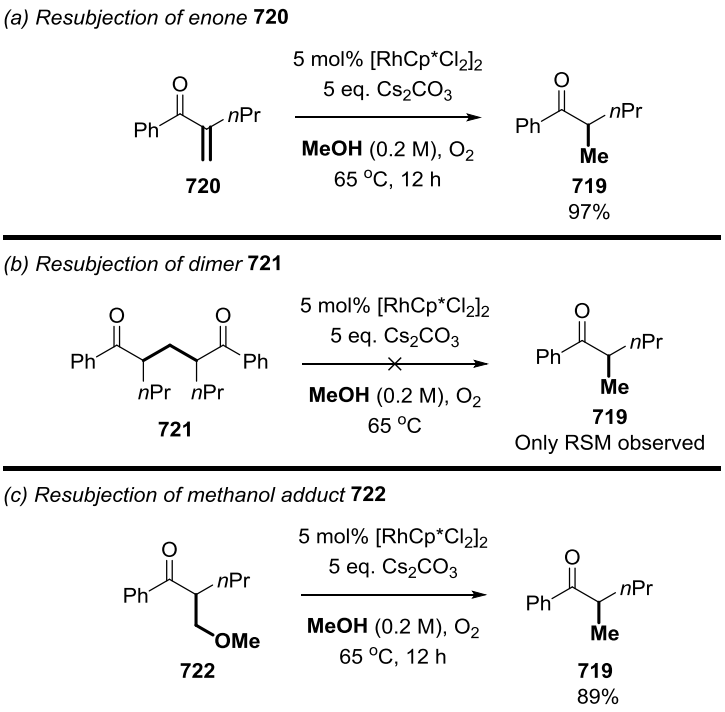


Figure 4.7 *Isolated and postulated intermediates in the Rh-catalysed methylation reaction*

In order to determine the role of each compound in the reaction, each was resubjected to the methylation conditions in turn (**Scheme 4.25**).



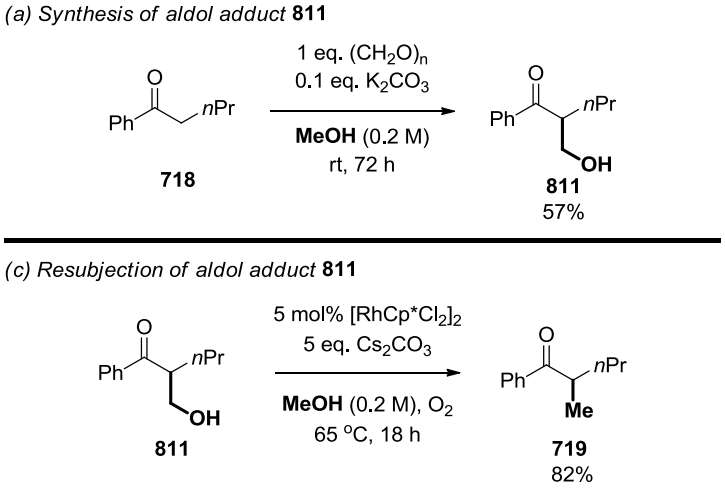
Scheme 4.25 *Resubjection of isolated intermediates* **720**, **721**, *and* **722**

Under the conditions for methylation reaction, enone **720** afforded methylated ketone **719** in 97% yield after only 12 hours (**Scheme 4.25a**). Similarly, methanol adduct **722** afforded methyl ketone **719** in 89% after 12 hours (**Scheme 4.25c**). These results both suggest that these two species are active in the reaction pathway, with methanol adduct **722** presumably

consumed by elimination of methanol to form enone **720** and subsequent reduction with a rhodium-hydride species.

We also considered it feasible that dimer **721** could be formed reversibly under the reaction conditions, and thus a retro-Michael reaction would regenerate enone **720**, and thus this product could also be active in the reaction. However, resubjection of dimer **721** to the rhodium-catalysed methylation conditions solely resulted in the recovery of starting material, suggesting that the formation of this product was a dead-end in the reaction pathway (**Scheme 4.25b**). Presumably this product is formed under conditions where either the oxidation of methanol, or the reduction of enone **720** are slow, and thus there is a higher concentration of starting ketone **718** present to trap enone **720**, thus forming dimer **721**.

In order to test the plausibility of aldol adduct **811** as an intermediate in the reaction pathway, it was first necessary to synthesise it. Since it had not been observed during the course of the reaction, it was hypothesised that milder conditions would be required for its formation, since forcing conditions might result in the elimination of water, and thus formation of enone **720**. Treatment of valerophenone **718** with 1.0 eq. of paraformaldehyde and catalytic K_2CO_3 in methanol at room temperature for 72 h afforded 57% yield of hydroxymethyl ketone **811** (**Scheme 4.26a**).

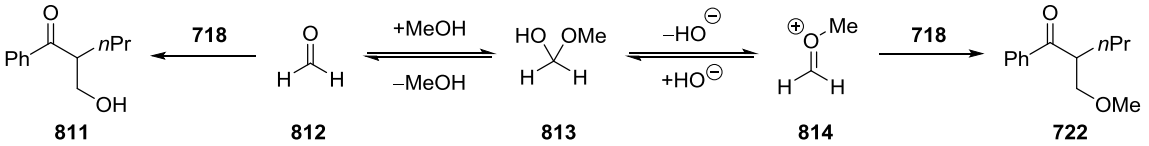


Scheme 4.26 *Synthesis and resubjection of aldol adduct* **811**

The formation of this product was confirmed by the presence of a broad O-H stretching band at 3429 cm^{-1} in the IR spectrum, a peak in the high-resolution mass spectrum at 215.1043

ppm corresponding to the $[M+Na]^+$ species, and the appearance of two double doublets at 3.97 and 3.86 ppm, for the two geminal hydroxymethyl protons, in the ^1H NMR spectrum, coupled in the COSY spectrum to a broad singlet at 2.25 ppm (O*H*). Resubjection of aldol adduct **811** to the reaction conditions afforded methylated ketone **719** in 82% yield after 18 h (**Scheme 4.26b**).

From these resubjection experiments it is clear that enone **720** and methanol adduct **722** are both active intermediates on the reaction pathway. Presumably enone **720** is reduced directly to the methylated product, and methanol adduct **722** is in equilibrium with this enone, *via* addition/elimination of methanol. It is also evident that dimer **721** is the result of a non-productive pathway. In the case of the aldol adduct **811**, the fact that this compound quickly affords product **719** under the methylation conditions certainly supports the possibility of its involvement in the reaction pathway, this does not necessarily have to be the case. It is also possible that under reaction conditions, free formaldehyde **812** reacts with methanol to form the hemiaminal **813**, and this could eliminate either methanol to reform formaldehyde (and hence aldol adduct **811**), or water, to form the methyl(methylene)oxonium ion **814**, which could directly afford methanol adduct **722** (**Scheme 4.27**).

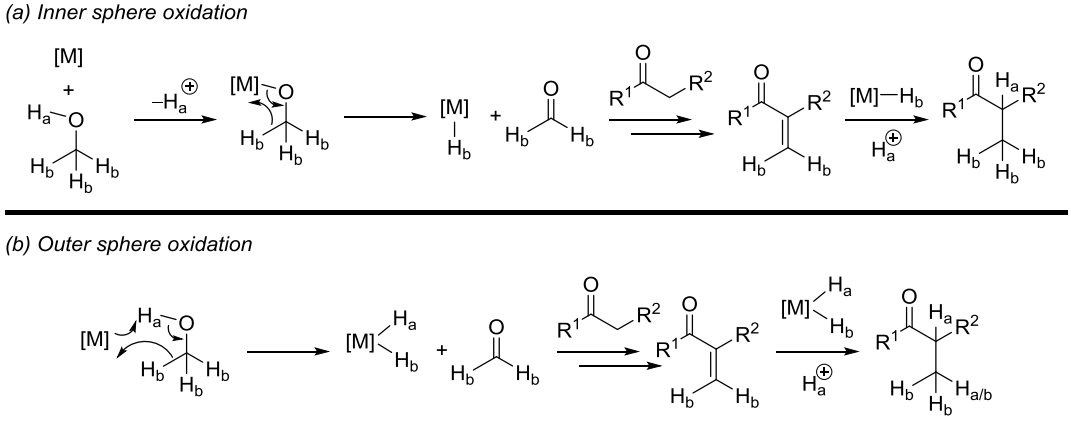


Scheme 4.27 *Possible intermediacy of oxonium ion* **814**

4.4.2 Deuteration experiments

Having determined the potential role of a number of the species isolated (and postulated) in the reaction mechanism, we then deemed it necessary to investigate more about the catalytic mechanism of the reaction, particularly the delivery of hydride. We considered that there were two possible mechanisms *via* which the metal hydride could be formed from methanol.[337] The first of these is an inner sphere mechanism, whereby coordination of methanol (after loss of a proton) to rhodium, is followed by β-hydride elimination to form formaldehyde, and a rhodium monohydride complex (**Scheme 4.28a**). Under these

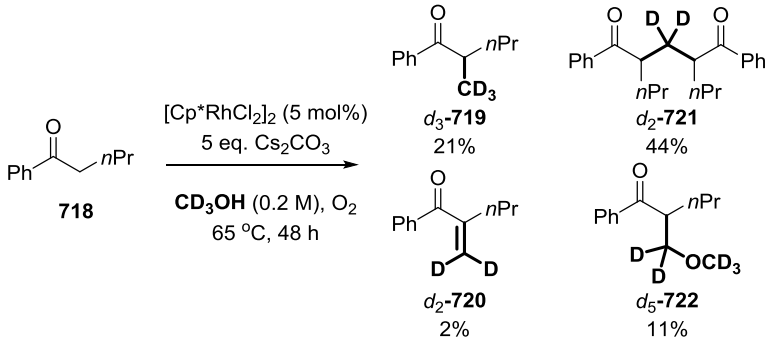
circumstances the hydride delivered would derive from one of the C-H_b bonds of the methanol $C(H_b)_3$ group. The second alternative mechanism is an outer sphere mechanism, whereby methanol oxidation occurs without binding to the metal, forming a metal dihydride, with one hydride deriving from the hydroxyl group, and one from a methyl C-H bond (**Scheme 4.28b**). Under this mechanism, the hydride delivered to the enone in the formation of the new methyl group could be expected to derive from either the OH_a or $C(H_b)_3$ groups of methanol.



Scheme 4.28 *Potential mechanisms for methanol oxidation*

4.4.2.1 Reaction in CD_3OH

To investigate whether this reaction was proceeding *via* a rhodium monohydride or dihydride, an experiment was devised whereby the reaction would be conducted in d_3-methanol, CD_3OH. It was postulated that if the reaction were to proceed *via* a monohydride, then only deuterium would be incororated in the product methyl group, whereas if the reaction were to proceed *via* a dihydride, then one would expect a mixture of both hydrogen and deuterium in the methyl group of the product (See **Scheme 4.28**, H_a = H, H_b = D). The reaction of valerophenone **718** was conducted in CD_3OH for 48 h, the same amount of time as a standard methylation reaction, so that a more direct comparison could be made (**Scheme 4.29**).



Scheme 4.29 *Methylation reaction in CD_3OH*

Surprisingly, the major product in this reaction was not the methylated compound *d*$_3$-**719**, which was isolated in 98% yield for the non-deuterated protocol. Methylated ketone *d*$_3$-**719** was in fact only isolated in 21% yield for this reaction (along with 2% of enone *d*$_2$-**720**), whereas dimer *d*$_2$-**721** was isolated in 44% yield. Methanol adduct *d*$_5$-**722** was also isolated in 11% yield.

By analysis of the ^{1}H NMR spectrum of *d*$_3$-**719** it was clear that complete deuteration of the methyl group had occurred, since there was no evidence of the usual doublet at 1.12 ppm, nor any other peak corresponding to a partially deuterated methyl group. Furthermore, the ketone α-proton, which exhibits a sextet at 3.48 ppm for the non-deuterated ketone **719**, showed a change in multiplicity to a triplet, due to the loss of coupling to the methyl CH_3 protons. Further evidence for the presence of the perdeuterated methyl group can be observed in the ^{2}D NMR spectrum, with a large singlet at 1.18 ppm corresponding to the presence of the CD_3 group. In the ^{13}C NMR spectrum, the peak at 16.4 ppm, corresponding to the α-methyl group, occurred as a septet, indicating coupling to 3 nuclei with a spin of 1, providing further evidence for the presence of a CD_3 group. Similarly, for enone *d*$_2$-**720**, the two peaks present in the non-deuterated enone **720** at 5.83 and 5.59 ppm in the ^{1}H NMR, corresponding to the terminal alkene protons, were absent, showing complete deuteration at this position. Indeed, in the ^{2}D NMR spectrum, two broad singlets at 5.86 and 5.61 ppm confirmed the presence of deuteration at these positions. The NMR spectra for these two compounds are shown in **Figure 4.8**.

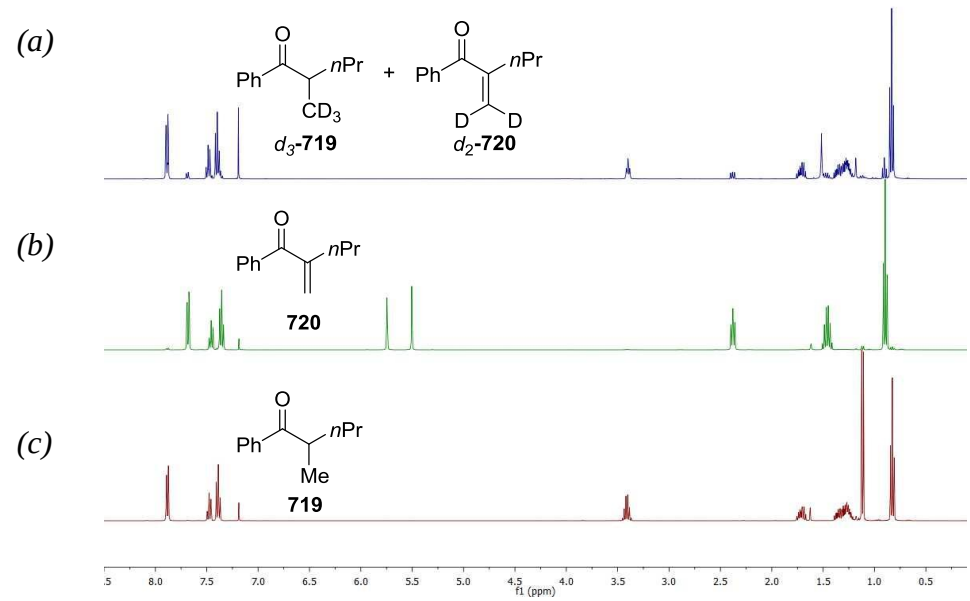


Figure 4.8 *NMR spectra of (a)* d_3-**719** *and* d_2-**720** *(b)* **720** *and (c)* **719**

Deuteration of the bridging methylene group of dimer d_2-**721** was confirmed by the disappearance of these protons in the 1H NMR spectra for both *anti*-d_2-**721** (2.10−2.04 ppm), and *syn*-d_2-**721** (2.34−2.25 and 1.79−1.69 ppm), which were present as broad singlets in the ^{2}D NMR spectrum (*anti*-d_2-**721**, 2.05 ppm; *syn*-d_2-**721**, 2.27 and 1.61 ppm). The multiplicity of the α-protons in both cases was changed due to the loss of coupling to the protons of the methylene bridge, resulting in the observation of a triplet at 3.36 ppm for *anti*-d_2-**721** and 3.52 ppm for *syn*-d_2-**721**, as opposed to the complex multiplet seen in d_0-**721**(**Figure 4.9**).

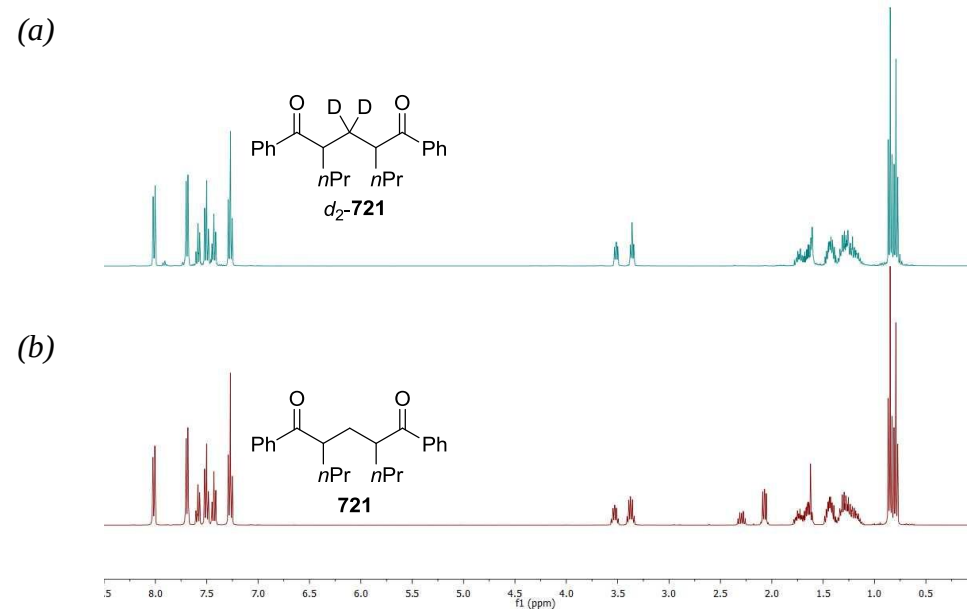


Figure 4.9 *NMR spectra of (a)* d_2-**721** *and (b)* **721**

In the case of the d_5-methanol adduct d_5-**722**, the ^{1}H NMR spectrum showed a loss of peaks corresponding to the -CH_2OCH_3 moiety, with the diastereotopic protons at 3.75−3.60 and 3.46−3.39 ppm absent in the deuterated product, along with the methyl group at 3.21 ppm. ^{2}D NMR analysis revealed the presence of broad singlets at 3.72, 3.50, and 3.27 ppm in a 1:1:3 ratio, corresponding to the presence of a $CD_aD_bOCD_3$ group. The α-proton, previously a complex multiplet in the region 3.75−3.60 ppm, was now present as a triplet, due to the absence of coupling to the diastereotopic C$\underline{H}_2$OCH$_3$ protons (**Figure 4.10**).

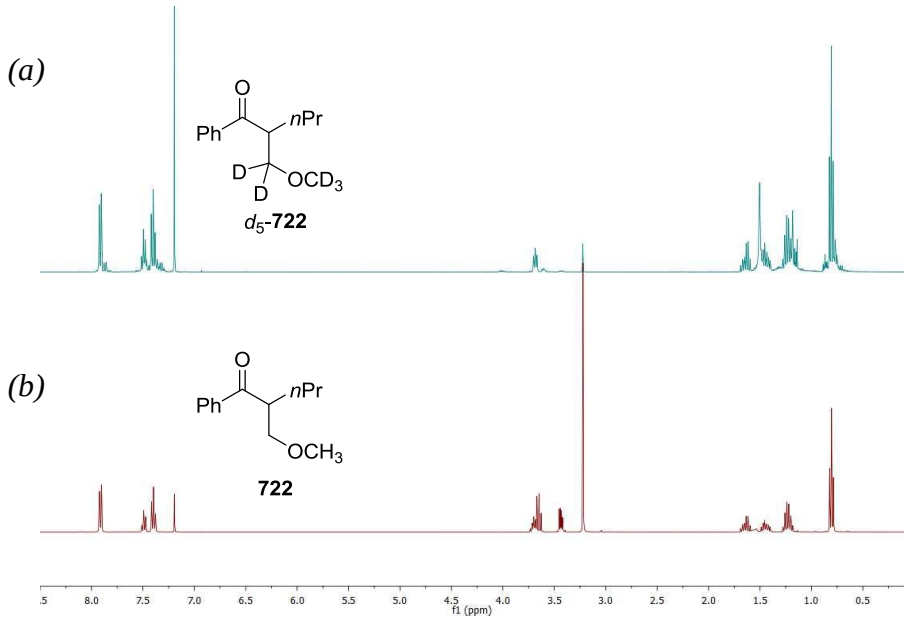


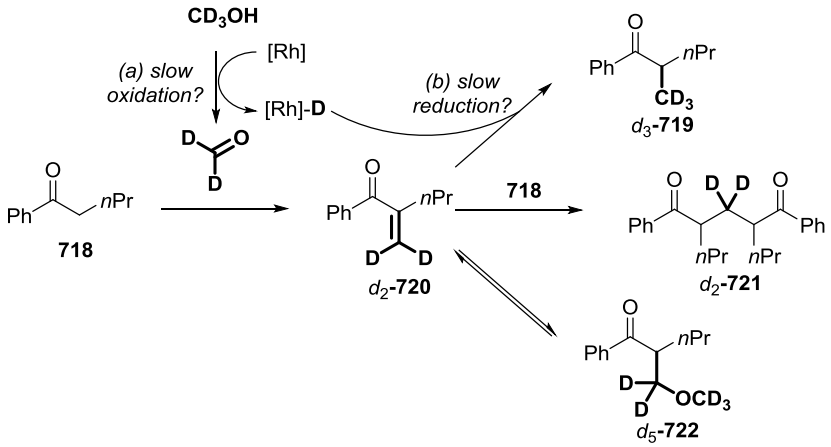
Figure 4.10 *NMR spectra of (a) d_5-***722** *and (b)* **722**

It is important to note, that in the cases of d_3-**719**, d_2-**721**, and d_5-**722**, a small amount of deuteration (<5%) was observed in the α-position of each ketone. There are two potential causes for this deuteration. The first possible cause is simply the incomplete presence of the CD_3OH species in the solvent used, and the presence of trace CD_3OD competing for protonation of the enolate of product d_3-**719** formed in solution. The second possible causes is a result of deprotonation of an acidic [Rh]-D species in solution, thus leading to a source of D^+, and thus incorporation into the ketone α-position.

We were interested in further investigating the unusual product distribution of the reaction conducted in CD_3OH, since the product distribution was markedly different to conducting the reaction under the standard methylation conditions. It was considered that there were two potential reasons for this difference (**Scheme 4.30**):

a) Reduction of enone **720** with [Rh]-D was considerably slower than with [Rh]-H, resulting in an increased chance of trapping the enone with another equivalent of starting material **718**, and hence an increased yield of dimer.

b) Slow oxidation of CD_3OH compared to CH_3OH. This would result in a low concentration of formaldehyde (or equivalent) and metal-deuteride, and thus a lower concentration of enone **720** formed *via* the aldol reaction. The rate of reduction would subsequently be lower, as the likelihood of [Rh]-D encountering d_2-**720** in solution would be decreased, and thus trapping with ketone **718** to form dimer d_2-**721**, more likely.

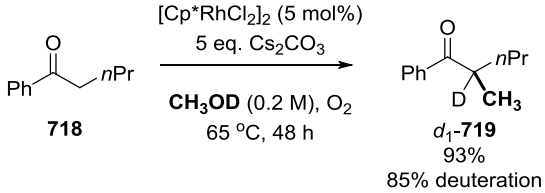


Scheme 4.30 *Potential causes of unusual product distribution in CD_3OH*

4.4.2.2 Reaction in CH_3OD

To further probe the mechanism of the reaction, and to help determine the slow step in the reaction pathway, the methylation reaction was conducted in CH_3OD. It was expected that in this case, regardless of which step was slower, the reaction should proceed in high yield, due to either efficient oxidation of CH_3OD, or faster reduction by [Rh]-H, then subsequent protonation by D^+, thus affording the α-deuterated product. Indeed, subjecting valerophenone **718** to the standard reaction conditions afforded α-deuterated methyl ketone d_1-**719** as the sole product, in 93% yield, with 85% deuteration in the α-position (measured by integration of the small peak at 3.49 ppm corresponding to undeuteration at the α-position) (**Scheme 4.31**). This reaction is therefore consistent with the argument that either oxidation of d_3-

methanol, or reduction with [Rh]-D, is the slow step in the reaction, as this result corresponds closely to the yield observed in undeuterated methanol (98%).



Scheme 4.31 *Methylation of valerophenone* **718** *in* CH_3OD

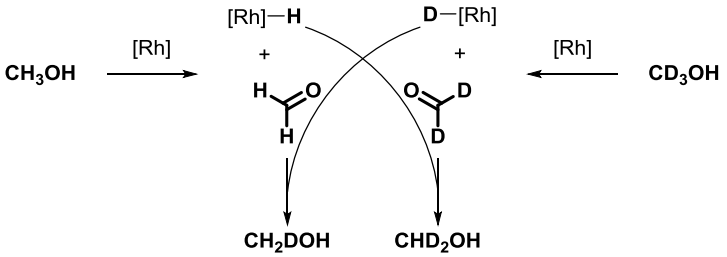
The lower amount of deuteration present in the α-position of the product d_1-**719** could either result from contamination of CH_3OD with CH_3OH, or it is also possible that [Rh]-H is marginally more acidic than [Rh]-D, and thus more [Rh]-H is deprotonated in solution, resulting in a larger $[H^+]$, and thus more incorporation of a proton rather than deuterium in the α-position.[338] Another possible alternative, is the relative rates of oxidation of CH_3OD *versus* CD_3OH. If CH_3OD is oxidised faster than CD_3OH, one would expect faster formation of [Rh]-H in the CH_3OD experiment. Thus, one would expect a higher $[H^+]$ relative to $[D^+]$ than otherwise, and as such the proton incorporation at the ketone α-position would arise as a result of the thermodynamic ratio of $[H^+]$ and $[D^+]$. This could be further probed by investigating the proton/deuterium incorporation ratio at the ketone α-position at varying times during the course of the reaction, since one would expect the [H+] to increase as the reaction proceeds and more [Rh]-H is formed.

4.4.2.3 Competition reaction in CH_3OH/CD_3OH

To get a clearer idea of the turnover-limiting step of the reaction, a competition experiment in a 1:1 CH_3OH/CD_3OH solvent mixture was conducted, as this should allow a more direct comparison of the relative rates of oxidation of each isotopologue, and also the relevant rate of reduction by their corresponding hydrides, [Rh]-H and [Rh]-D.

However, there is one important corollary to this method: that the oxidation of methanol be essentially irreversible on the timescale of the reaction. If the formaldehyde formed by β-hydride elimination is subsequently reduced back to methanol, then scrambling may occur, giving mixtures of all possible d_0-d_3 isotopologues of methanol (**Scheme 4.32**). The result of

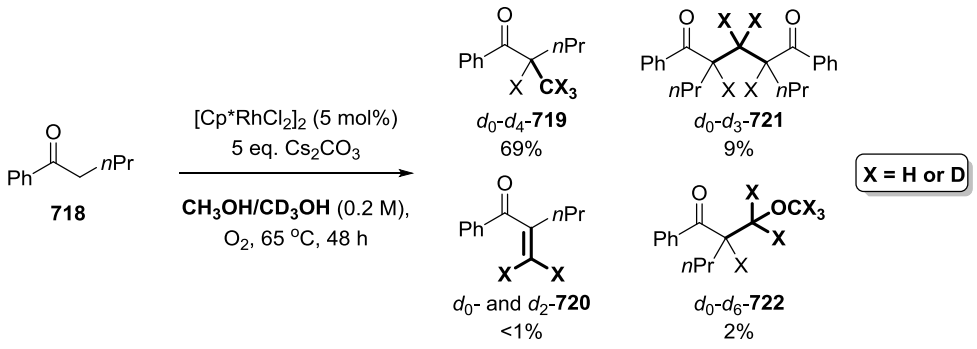
the experiment would then subsequently not reflect the true ratios for oxidation of methanol, or reduction of the enone.



Scheme 4.32 *Potential for deuterium scrambling in competition experiment*

Work conducted by Fristrup and coworkers, on the iridium-catalysed alkylation of amines found that although deuterium scrambling does occur in a competition experiment with d_2-benzyl alcohol and *p*-chlorobenzyl alcohol, this was considerably slower than the consumption of the alcohol, and thus accurate kinetic isotopes could still be obtained.[339] Thus, we sought to investigate the relative rates of both oxidation of methanol, and reduction with [Rh]-H/D, whilst remaining aware that there may be some limitation to the accuracy of the data, due to the potential for a degree of scrambling.

Thus, when the reaction was conducted in 1:1 CH_3OH/CD_3OH, the major product afforded was methylated ketone **719** in 69% yield, as a mixture of all possible isotopologues (d_0-**719**, d_1-**719**, d_2-**719**, d_3-**719** and d_4-**719**, the latter derived from partial deuteration of the ketone α-position), containing <1% of alkene **720** (d_0-**720** and d_2-**720**). Dimer **721** was isolated in 9% yield, as a mixture of d_0-d_3 isotopologues. Finally, methanol adduct **722** was isolated in 2% yield as a mixture of d_0-d_6 isotopologues (**Scheme 4.33**).



Scheme 4.33 *Methylation reaction in CD_3OH/CH_3OH*

In order to determine the relative rate of oxidation of CH_3OH *versus* CD_3OH, we were able to compare data from a number of different sources. ^1H NMR data for all compounds **719**-**722** should allow some calculation of the ratio of isotopologues, but overlap of peaks might limit the accuracy of these measurements, along with their usefulness. Peak intensity from high resolution mass spectrometry should allow also allow the measurement of the ratio of each isotopologue (once the presence of ^{13}C isotopomers have been accounted for), with a greater degree of accuracy than by NMR, allowing at least a qualitative analysis of the data, although there may of course be some error here introduced by any peak broadening due to the overlap of ^{13}C isotopomers with the desired product peaks.

For methylated ketone **719**, integration of the terminal methyl group at 0.91 ppm (3H, t) *versus* the newly installed methyl group at 1.20 ppm (d), along with two smaller multiplets at 1.17 ppm (t, *J* 1.8 Hz) and 1.16 ppm (m, *J* 1.9 Hz) showed an integral of 2.20 rather than the expected 3.00 (**Figure 4.11**). This result therefore suggests that 74% of the possible positions on methyl groups are occupied by a proton rather than deuterium, i.e. CH_3 (d_0-**719**), CH_2D (d_1-**719**), and CHD_2 (d_2-**719**). Whilst this cannot give a clear value for the isotope effect in the oxidation of methanol, due to the presence of CHD_2 compound d_2-**719** in the same region of the spectrum, the large integral of d_0-**719** to d_1-**719** and d_2-**719** indicates a considerable difference in rate between the oxidation of CH_3OH and CD_3OH by $[Cp^*RhCl_2]_2$. It is also notable again, that ^2D NMR analysis indicated a trace amount of deuteration in the ketone α-position of **719**, although only corresponding to around 3% deuteration in this position.

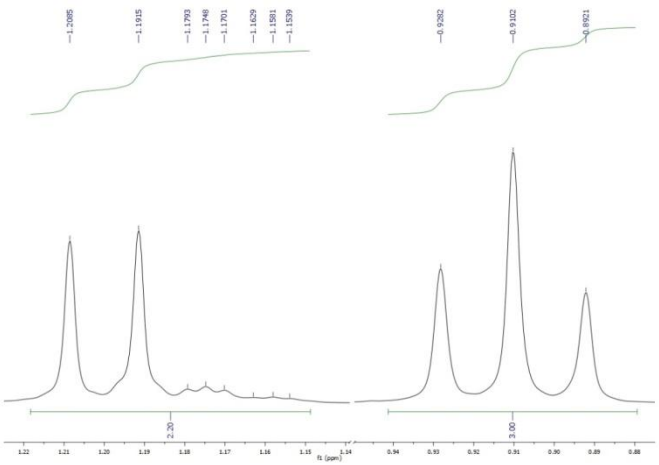
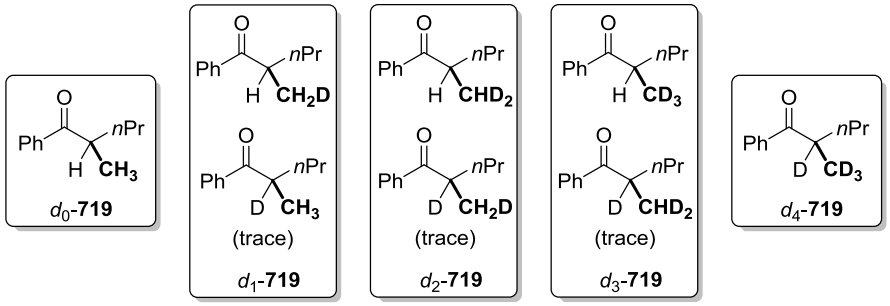


Figure 4.11 *Integration of methyl groups in d_0-d_4-***719**

It was also possible to obtain data for determining the ratio of the isotopologues of **719** through HRMS experiments. In this case it is necessary to account for the presence of naturally-occurring ^{13}C isotopomers, since these may not be fully resolved from the different deuterated species. Calculations for the determination of the ratios of products d_0-d_4-**719** can be found in **Appendix 4.2.2**, and the results are presented in **Table 4.4** below. It is important to note that products with α-deuteration are impossible to distinguish from other products with the same deuterium content, so this may have a small effect on the precise values given, but given the low deuterium incorporation at this position, should not impart a significant distortion to the results.



Product	d_0-719[a]	d_1-719[a]	d_2-719[b]	d_3-719[b]	d_4-719[b]
% of mixture	52.6	14.0	24.5	7.9	1.0

Table 4.4 *Ratio of isotopologues* d_0 *to* d_4-**719**

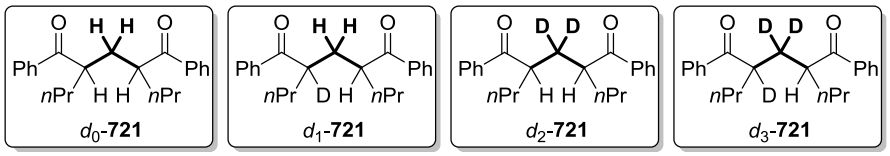
[a] Derived from oxidation of CH_3OH [b] Derived from oxidation of CD_3OH

In comparison to the ^1H NMR data, a weighted average of the ratios of products d_0-**719** to d_4-**719** reveals that 70% of the possible positions on methyl groups are undeuterated. This shows a good correlation with the 74% observed by integration of the methyl peaks in the ^1H NMR spectrum.

From the HRMS data, it is also possible to compare the ratios of which products are derived from CH_3OH and CD_3OH. Ignoring any α-deuteration present, compounds d_0-**719** and d_1-**719** should both be derived from CH_3OH, whereas products d_2- to d_4-**719** should be derived from CD_3OH oxidation. It is clear from the data in **Table 4.4**, therefore, that 66.6% of the methylated compound **719** is derived from CH_3OH, with the remainder derived from CD_3OH. This is therefore suggestive of a $\frac{kH}{kD}$ value of 2 for the oxidation of methanol by $[Cp^*RhCl_2]_2$.

Comparison of this data with the other products isolated in the reaction yields a similar result. Integration of the alkenyl C=C$\underline{H}_2$ peaks for enone **720** *versus* the allylic C$\underline{H}_2$ protons yields a value of 64:36 for the ratio of d_0:d_2-**720** (**Appendix 4, Figure A4.5**), providing further support for a $\frac{kH}{kD}$ value of 2. Further evidence for deuteration of the olefin was observed in the ^{2}D NMR spectrum with broad singlets observed at 5.86 and 5.61 ppm, in a 1:1 ratio, corresponding to the partial deuteration of the enone **720**.

For dimer **721**, analysis of the ^{1}H NMR spectrum appeared to show a somewhat higher isotope effect for the oxidation if methanol, since integration of the bridging methylene protons for the *syn* and *anti* diastereomers at 2.26-2.17 ppm (*syn*-**721**, 1H), and 2.03-1.95 ppm (*anti*-**721**, 2H) shows the peaks are 80% of the height that one would expect for complete presence of hydrogen rather than deuterium (**Appendix 4, Figure A4.6**). This would therefore be suggestive of a $\frac{kH}{kD}$ value of 4. However, analysis of the HRMS data shows the following isotopic composition (**Table 4.5**). Given that there is a significant proportion of d_1- and d_3-isotopologues present according to the HRMS data, it is possible that the integration of the α-proton is relatively unreliable, and thus a higher value for $\frac{kH}{kD}$ is observed. Indeed, the HRMS data provides further support for a value of 2 for $\frac{kH}{kD}$, with 65.8% (d_0- and d_1-**721**) of the observed product being related from CH_3OH, and the remaining 34.2% derived from CD_3OH (d_2- and d_3-**721**).



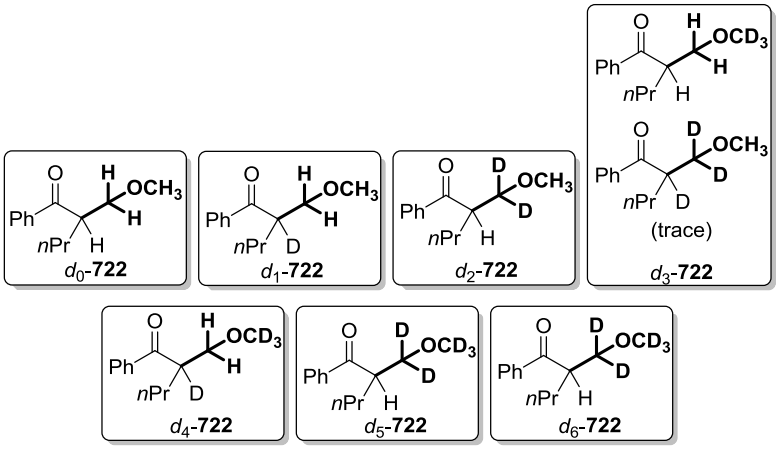
Product	***d*$_0$-721**[a]	***d*$_1$-721**[a]	***d*$_2$-721**[b]	***d*$_3$-721**[b]
% of mixture	63.9	1.9	27.8	6.4

Table 4.5 *Ratio of isotopologues* ***d*$_0$-** *to* ***d*$_3$-721**

[a] Derived from oxidation of CH_3OH [b] Derived from oxidation of CD_3OH

Methanol adduct **722** provided a somewhat complicated picture for the determination of isotopologues due to the variety of possible products that could be formed. Enone d_0-**720** and d_2-**720** could be formed by aldol reaction with CH_2O or CD_2O formed by the oxidation of CH_3OH and CD_3OH respectively. Subsequently, this enone could be trapped by either

CH_3OH, or CD_3OH, thus affording either d_0-, d_2-, d_3- or d_5-**722**, which may then be further deuterated in the α-position, to give all possible d_0-d_6 isotopologues. ^{1}H NMR analysis of this mixture proved difficult due to the overlapping peaks for the α-proton and one of the diastereotopic C$\underline{H_2}$OCH$_3$ protons, but the HRMS data gave a clearer picture (**Table 4.6**).



Product	d_0-722[a]	d_1-722[a]	d_2-722[b]	d_3-722[a]	d_4-722[a]	d_5-722[b]	d_6-722[b]
% of mixture	33.1	1.5	15.7	27.3	5.2	15.2	2.0

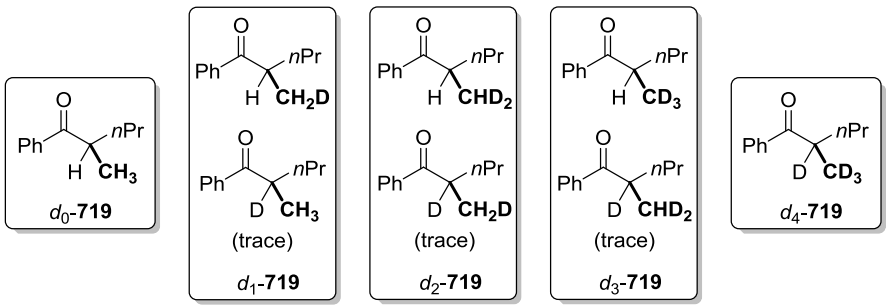
Table 4.6 *Ratio of isotopologues* d_0- *to* d_6-**722**
[a] Derived from oxidation of CH_3OH [b] Derived from oxidation of CD_3OH

From this data, it appears that 67% of the isotopologues present derive from oxidation of CH_3OH (d_0-, d_1-, d_3- and d_4-**722**), with the remaining 33% (d_2-, d_5, and d_6-**722**) being derived from CD_3OH. This therefore further supports a kinetic isotope effect of 2 in methanol oxidation. It is also apparent from the data in **Table 4.6** that 50% of compounds result from trapping by CH_3OH (d_0-, d_1-, and d_2-**722**), and 50% from trapping by CD_3OH (d_3-, d_4-, d_5-, and d_6-**722**), as one would expect for a reaction step that does not involve the breaking of an X-H or X-D bond, such as the addition of methoxide to the enone **720**.

This data all points to a value for $\frac{kH}{kD}$ of 2 in the oxidation of methanol compared to d_3-methanol by $[Cp^*RhCl_2]_2$ (or at least the active species in solution). This value is consistent with a dehydrogenation of methanol occurring by β-hydride elimination, where C-H bond breaking is involved in the transition state. This data is closely in accordance to that reported in the literature by Krische,[305] and Milstein,[340] for the oxidation of methanol with [Ir^{III}] species, where values of 2 and 2.45 are reported respectively.

This slow oxidation would certainly explain the observation of a large degree of dimer formation in the attempted methylation reaction in CD_3OH, since the slow oxidation of methanol would result in a lower concentration of d_2-formaldehyde, and subsequently a lower concentration of enone d_2-**720**. This would then be more likely to be trapped by starting ketone **718**, than reduced by [Rh]-D, which would similarly be lower in concentration, resulting in the formation of larger amounts of dimer d_2-**721**.

Apart from allowing a comparison of the rate of methanol oxidation, we also considered that the data for methylated ketone **719** would allow a comparison of the rates of the reduction of enone **720** by [Rh]-H and [Rh]-D. Given that approximately 67% of the product **719** (d_0- and d_1-**719**) appear to derive from oxidation of CH_3OH, and 33% from the oxidation of CD_3OH (d_2-, d_3- and d_4-**719**), one would therefore expect that 67% of the hydride species in solution would be [Rh]-H, with 33% present as [Rh]-D. As such, if there was no isotope effect in the reduction step, one would expect that 67% of reduction was effected by [Rh]-H, and 33% by [Rh]-D. Inspection of the HRMS data reveals that this is not the case (**Table 4.7**).



Product	d_0-**719**[a]	d_1-**719**[b]	d_2-**719**[a]	d_3-**719**[b]	d_4-**719**[b]
% of mixture	52.6	14.0	24.5	7.9	1.0

Table 4.7 *Ratio of isotopologues* d_0 *to* d_4-**719**

[a] Derived from reduction by [Rh]-H [b] Derived from reduction by [Rh]-D

From the data, it is clear that d_0- and d_2-**719**, which should result from the reduction by a [Rh]-H species, account for 77.1% of the isotopic mixture, whereas d_1-, d_3-, and d_4-**719**, account for 22.9% of the mixture. This therefore suggests a small isotope effect for the reduction, of the order $\frac{kH}{kD}$ = 1.15. This is considerably smaller than for the methanol oxidation, and is similar to the isotope effect observed in the reduction of alkenes by rhodium catalysts. In the reduction of cyclohexene by Wilkinson's catalyst, an isotope effect of 1.15

was observed in the turnover-limiting step.[341] James and coworkers also reported an isotope effect of 1.08 in the reduction of maleic acid with $RhCl_3$.[342]

It is not surprising that the isotope effect for the reduction of the enone is small, since the nature of the transition state of hydride transfer from Rh to the enone is likely to proceed *via* a non-linear transition state, with Rh coordinated to the enone before delivery of hydride. In non-linear transition states, bending modes are more significant than stretching modes, whilst also having lower force constants (**Figure 4.12a**). As such, the zero-point energy difference between reactions and transition states is not as large. Furthermore, the new symmetrical stretch in a non-linear transition state allows a large degree of motion for the hydrogen atom (**Figure 4.12b**), and thus is highly dependent on mass.

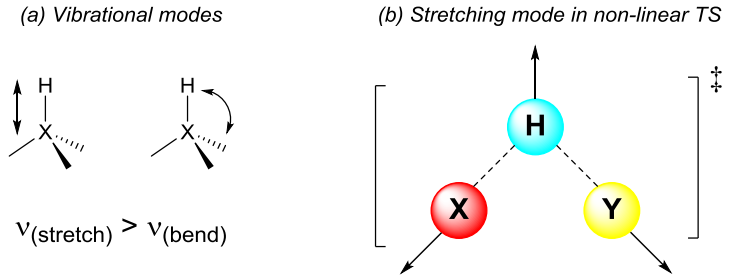


Figure 4.12 *Factors affecting isotope effects in non-linear transition states*

Thus, from these results it seems likely that for the $[Cp^*RhCl_2]_2$-catalysed methylation of ketones, there is a significant isotope effect in the step involving the oxidation of methanol. There is also a small isotope effect apparent in the reduction of enone by [Rh]-H, of the same order as other examples of rhodium-catalysed reduction in the literature. It is therefore possible that methanol oxidation is the turnover-limiting step in the reaction, as was also reported to be the case for Krische's hydroxymethylation of allenes with methanol, employing an $[Ir^{III}]$ complex.[305]

However, it is important to remember that kinetic isotope effects can arise for a wide range of reasons, and are not definitive proof of the presence of a rate- or turnover-limiting step.[343] In his detailed paper on the interpretation of deuterium kinetic isotope effects, Hartwig makes clear that evidence for a KIE does not explicitly mean that C-H bond cleavage occurs in the rate- or turnover-limiting step. Since the competition experiment conducted here is

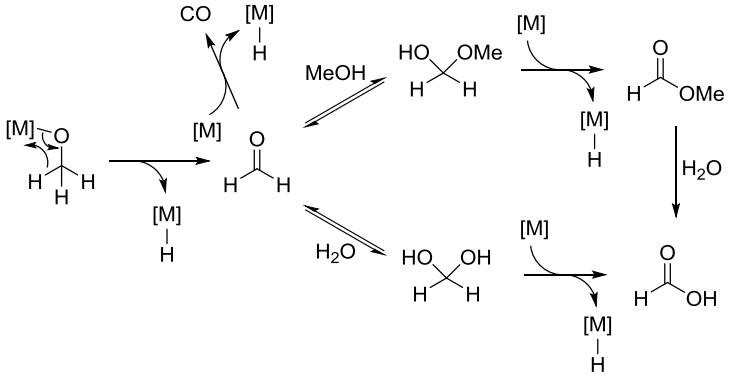
intermolecular, the absence of a KIE would indicate that C-H/D bond-cleavage was not involved in the turnover-limiting step, but the presence of a KIE does not prove that such cleavage does occur in the turnover-limiting step. Therefore, the results provided above, whilst qualitatively showing that oxidation of methanol shows a significant KIE, with only a minor KIE for the reduction step, must be treated cautiously.

4.4.3 Investigation of the role of O_2

We were also interested to know what the role of O_2 was in the course of the ketone methylation reaction. It was clear that O_2 had a particularly beneficial effect on the reaction, as indicated in initial screening experiments (*vide supra*), with a 98% yield for the methylation of valerophenone **718** after 48 h under O_2, but only 57% yield under an atmosphere of argon.

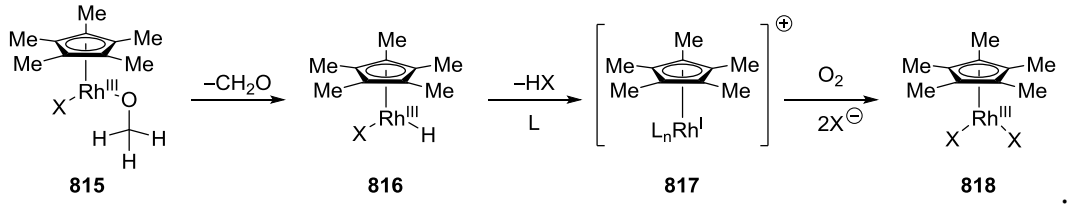
As previously discussed (**Chapter 4.2.1**), oxygen has been shown to provide a beneficial effect in both the oxidation of alcohols,[315,316] and also in the hydrogen-borrowing alkylation of a range of different nucleophiles.[317,318,319,320]

Ison and coworkers had proposed that the beneficial effect of oxygen on the oxidation of alcohols was as a result of the insertion of O_2 into an [Ir^{III}]-H species, resulting in formation of hydrogen peroxide, and liberating the catalytically active species.[315] Clearly, although this effect could be operating in the rhodium-catalysed methylation of ketones, it could not be removing all metal-hydride from solution, or reduction of the enone to the methylated ketone would not occur. It is possible that over-oxidation of methanol may occur (for example to methyl formate, formic acid, or carbon monoxide), resulting in an excess of metal hydride relative to formaldehyde (**Scheme 4.34**). Thus, oxygen may remove this metal hydride *via* insertion into the rhodium-hydride bond, thus allowing further oxidation of methanol to occur, and thus preventing the reaction from being halted.



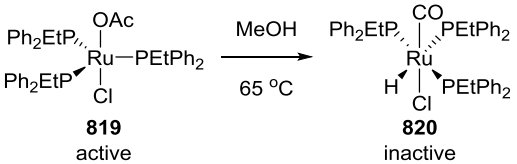
Scheme 4.34 *Potential overoxidation of formaldehyde resulting in excess metal hydride*

Gabrielsson and coworkers, however, proposed the reoxidation of an [Ir^{I}] complex formed by deprotonation of an acidic [Ir^{III}]-H species by oxygen, thus regenerating the active catalyst in their [Ir^{III}]-catalysed oxidation of alcohols.[316] Thus, the role of O_2 in the rhodium-catalysed methylation could be to regenerate an active [Rh^{III}] species if deprotonation of the [Rh^{III}]-H removes the catalyst from the catalytic cycle (**Scheme 4.35**).



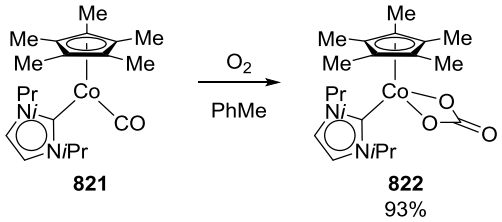
Scheme 4.35 *Possible deprotonation of a [Rh^{III}]-H species and reoxidation by O_2*

As previously discussed in **Chapter 4.2.1**, Xu and coworkers showed that the formation of a [Rh]-CO species, formed by decarbonylation of an aldehyde resulted in an inactive catalyst, which could be reactivated under at atmosphere of O_2, in the alkylation of amines with benzylic alcohols.[317] A further example of a the formation of an inactive metal-carbonyl complex for the oxidation of alcohols was reported by Saito and coworkers.[344] They found that performing methanol dehydrogenation with [Ru(OAc)Cl($PEtPh_2$)$_3$] **819**, the catalytic activity decreased over time, until hydrogen evolution stopped completely (**Scheme 4.36**).



Scheme 4.36 *Deactivation of methanol oxidation catalyst* **819** *by carbonylation*

It has also been demonstrated by Iwashita and coworkers that a [Rh]-CO complex may be oxidised under an atmosphere of oxygen to the corresponding carbon dioxide complex.[345] Thus, by exposing $[Rh_2(CO)_4(PPh_3)_4]$ to an atmosphere of oxygen, $[Rh_2(CO)_2(CO_2)_2(PPh_3)_3(C_6H_6)$ was observed to form as fine yellow needles, which are unstable to prolonged heating under air. A further example of the oxidation of a metal bound carbonyl ligand was observed by Radius and coworkers, whereby, in the presence of air, Cp*Co- carbonyl complex **821** was oxidised to the corresponding carbonate complex **822** (**Scheme 4.37**).[346]



821 **822** 93%

Scheme 4.37 *Oxidation of cobalt carbonyl complex* **821**

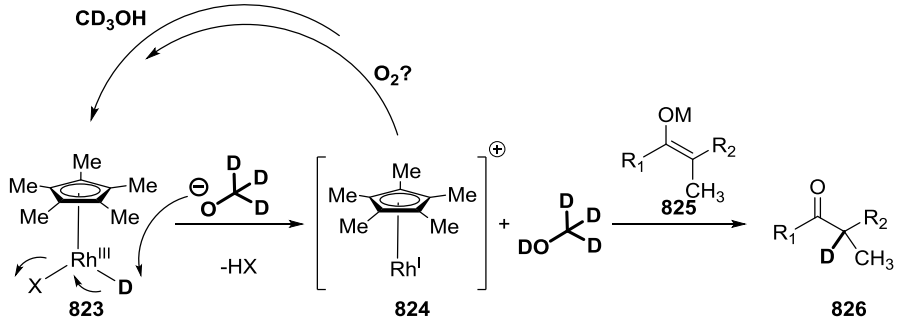
Thus, we considered that there were three major possibilities for the role of oxygen in the rhodium-catalysed methylation of ketones:

a) Reoxidation of a $[Rh^{I}]$ species formed by deprotonation of an acidic $[Rh^{III}]$-H species.
b) Oxidation of an inactive $[Rh^{III}]$-CO complex back to an active $[Rh^{III}]$ species.
c) Removal of "excess" metal hydride formed.

4.4.3.1 Evidence for acidic rhodium hydride

As previously discussed in **Chapter 4.4.2**, in the reaction of valerophenone **718** in CD_3OH, partial deuteration was observed in the α-position of all products observed (<5% by NMR) (**Appendix 4**). Similarly, in the reverse reaction conducted in CH_3OD, the α-methylated ketone **719** was isolated with only 85% deuteration in the α-position (**Scheme 4.31**).

It is possible that the incorporation of the unexpected isotope of hydrogen in these positions is a result of deprotonation of the rhodium hydride **823** formed *via* β-hydride elimination from a methoxyrhodium complex (**Scheme 4.38**).

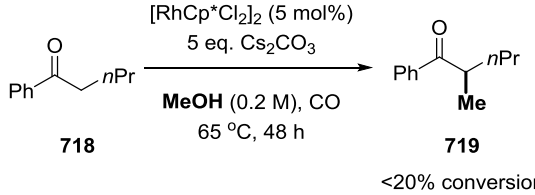


Scheme 4.38 *Potential role of O_2 in reoxidising a [Rh^I]-complex*

If there was no cross-contamination in the sample solution (i.e. CD_3OH contained only trace CD_3OD, or CH_3OD contained only trace CH_3OH), then this would provide the most obvious mechanism by which an acidic source of the unexpected hydrogen isotope could be found. Thus, whilst accepting the limitation that the solvents provided may have not contained perfect isotopic labelling, it is certainly possible that deprotonation of a rhodium-hydride species is responsible for the requirement of oxygen to promote efficient methylation.

4.4.3.2 Evidence for inhibition of the reaction by carbon monoxide

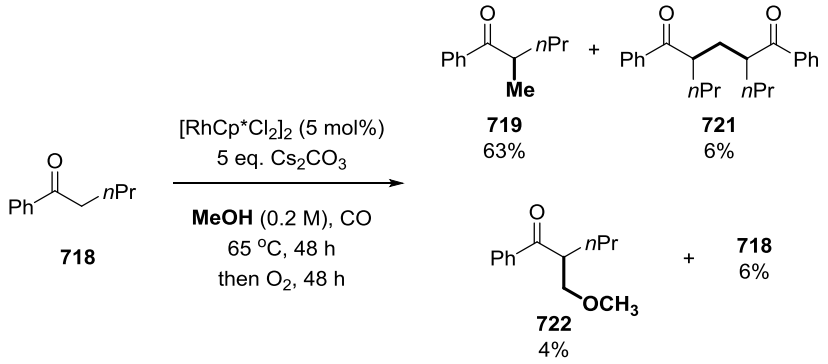
To investigate whether the role of oxygen was to aid in regeneration of an active rhodium species, subsequent to overoxidation of methanol affording a rhodium carbonyl, it was first decided to test whether an atmosphere of carbon monoxide would inhibit the methylation of valerophenone **718** (**Scheme 4.39**). Indeed, by conducting the methylation reaction under an atmosphere of CO, less than 20% conversion was observed by NMR after 48 hours, as opposed to the 98% yield of methyl ketone **719** observed after 48 hours under an atmosphere of O_2.



Scheme 4.39 *Inhibition of ketone methylation under CO atmosphere*

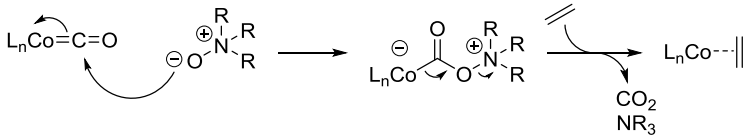
To determine whether oxygen could play a role in the regeneration of an active rhodium catalyst for the methylation reaction after carbonylation of rhodium, a second reaction was conducted, whereby the reaction was initially inhibited with carbon monoxide before being degassed with O_2 and stirred under an atmosphere of O_2 for a further 48 h (**Scheme 4.40**).

This procedure afforded 63% of the desired methylated ketone **719**, along with small amounts of recovered starting material **718** (6%), dimer **721** (6%) and methanol adduct **722** (4%). Although the yield in this reaction was somewhat lower than for the reaction performed purely under an O_2 atmosphere, it was evident that oxygen was capable of regenerating an active catalytic species. The range of products suggested that the reaction was somewhat slower after initial deactivation with CO, perhaps therefore suggesting a slow regeneration of the active catalytic species, and thus a slow initial rate of methanol oxidation, hence the formation of more dimer **721**, and the recovery of 6% starting material **718**.



Scheme 4.40 *Reactivation of CO-deactivated reaction under O_2*

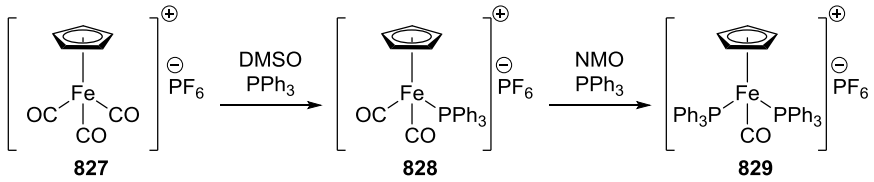
We considered that if decarbonylation was an important step in maintaining activity in the rhodium-catalysed methylation reaction, that this was similar in concept to the decarbonylation required for the activation of cobalt carbonyl complexes in the Pauson-Khand reaction by amine-*N*-oxides. The use of NMO and TMO as a promoter for the Pauson-Khand reaction was developed independently by both Schreiber,[347] and Jeong.[348] In the case of these reactions, it is proposed that oxidation of one carbonyl ligand by the amine-*N*-oxide affords an open coordination site on cobalt, allowing the binding of an alkene ligand, and thus promote reaction at low temperatures (**Scheme 4.41**).



Scheme 4.41 *Proposed decarbonylation of Co-carbonyl complexes by amine-N-oxides*

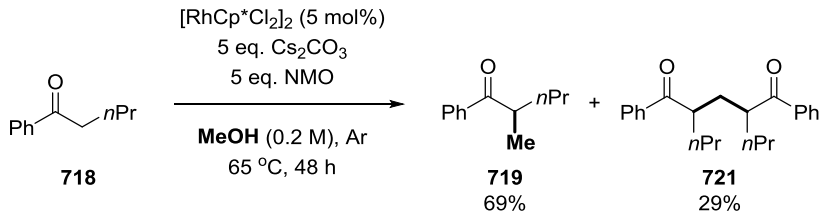
Work by Davies and coworkers also showed that metal carbonyl complexes could be decarbonylated by a range of oxides including TMO, NMO and DMSO.[349] Treatment of iron

carbonyl complex **827** with DMSO and PPh_3 resulted in monodecarbonylation, with a second decarbonylation achieved by the use of NMO (**Scheme 4.42**).



Scheme 4.42 *Davies' sequential decarbonylation of iron tricarbonyl* **827**

With these results in mind, we wanted to investigate whether similar oxides could also promote the ketone methylation reaction. Conducting the reaction under an atmosphere of argon with 5 equivalents of DMSO resulted in only trace conversion of starting material **718**, suggesting that DMSO was in fact inhibiting the reaction, since the conversion was much lower than under an atmosphere of argon without the addition of DMSO. Similarly the reaction using TMO resulted in only a minor conversion of starting material. On the other hand, addition of 5 equivalents of NMO afforded 69% methylated ketone **719**, with 29% dimer **721** (**Scheme 4.43**). Although it is clear that the reaction proceeds moderately well under these conditions, this is not a significant improvement on the yield observed under argon alone (57% yield methylated ketone **719**). Thus, it is difficult to make an assessment from this result whether NMO is making a significant difference in the reaction.



Scheme 4.43 *Methylation reaction with 5 eq. NMO*

Although these results might be consistent with the decarbonylation of a [Rh]-CO species, this is by no means the only possible explanation for the beneficial effect of NMO on the course of the reaction. NMO may also act as a reoxidant for any [Rh^{I}] species formed by deprotonation of the [Rh^{III}]-H species formed in the reaction, regenerating [Rh^{III}] active catalyst, or by direct insertion into the [Rh^{III}]-H to regenerate an active catalyst.

4.4.4 Proposed mechanism

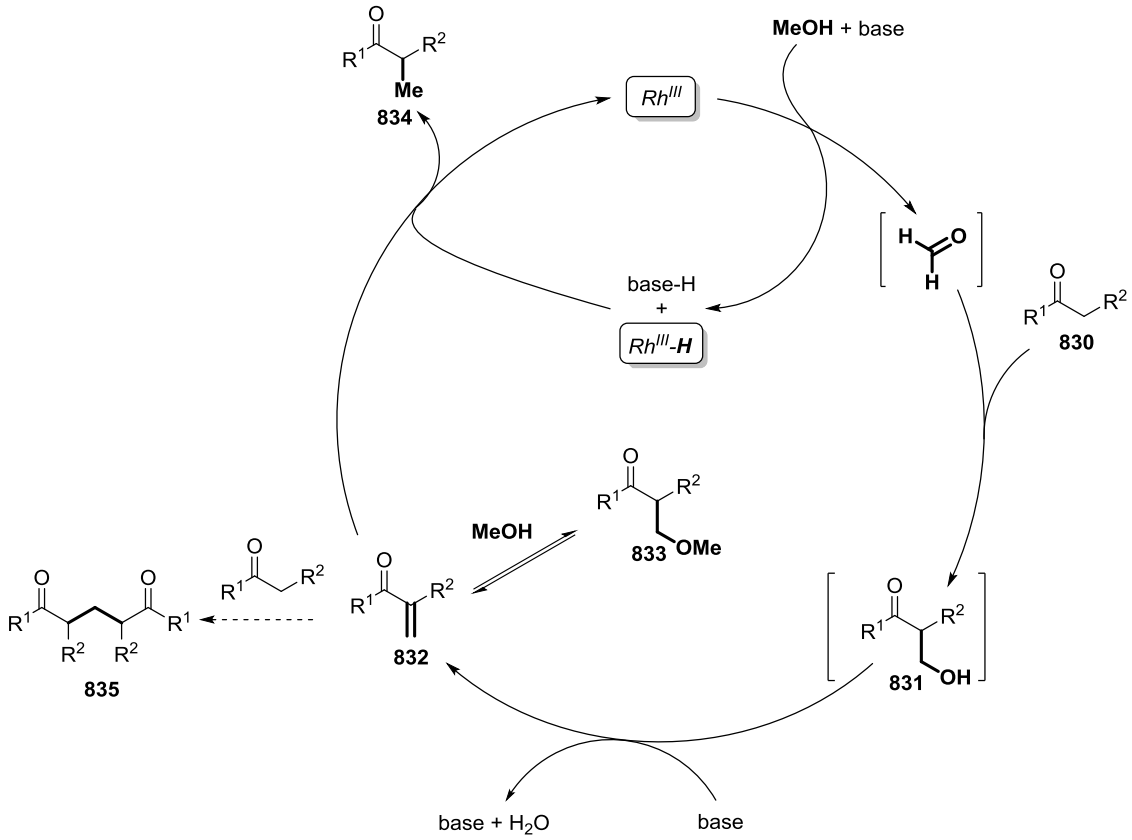
From all the above mechanistic experiments we were able to obtain some clear facts about the mechanism. Firstly, from the resubjection experiments, it was clear that enone **720** and methanol adduct **722** were active on the reaction pathway, and converted to the desired methylated ketone **719**, whereas dimer **721** appeared to be an unreactive side product. It was also clear, that whilst it had not been isolated, aldol adduct **811** was certainly capable of undergoing elimination and reduction under the reaction conditions, suggesting its involvement in the reaction mechanism.

From the deuteration experiments, the sole incorporation of deuterium in the ketone methyl group when the reaction was conducted in CD_3OH was suggestive in the formation of the formation of a rhodium-monohydride species rather than dihydride, *via* an inner-sphere oxidation mechanism. The competition experiment conducted in CD_3OH/CH_3OH was also suggestive that the slow step in the catalytic cycle may be the oxidation of methanol.

Finally, although no clear evidence has been gained to definitively ascertain the role of O_2 in the reaction mechanism, the fact that the reaction is inhibited under an atmosphere of CO, and may be restarted by degassing with O_2, is suggestive that formation of an inactive metal-carbonyl complex may indeed be important in keeping the catalyst on the main catalytic cycle.

Thus, we were able to propose the following mechanism for the ketone methylation reaction (**Scheme 4.44**). Oxidation of methanol by a [Rh^{III}] complex (the precise structure of which is unknown, presumably of the structure Cp^*RhX_2), affords formaldehyde and a [Rh^{III}] monohydride species. The formaldehyde then undergoes an aldol reaction with ketone **830** to afford the aldol adduct **831**, which subsequently loses water to the enone **832**, which is in equilibrium with the methanol adduct **833**. In a productive reaction pathway, the enone **832** is then reduced by the [Rh^{III}]-H, thus affording the desired methylated ketone **834**, and regenerating the required [Rh^{III}] complex to continue the reaction. If the rate of methanol oxidation is too low, or the concentration of enolate too high, then competing Michael

addition of ketone **830** to enone **832** will result in the formation of dimer **835**, rather than reduction to the methyl ketone **834**.



Scheme 4.44 *Proposed mechanism for rhodium-catalysed methylation reaction*

4.5 Synthetic utility of the rhodium-catalysed methylation

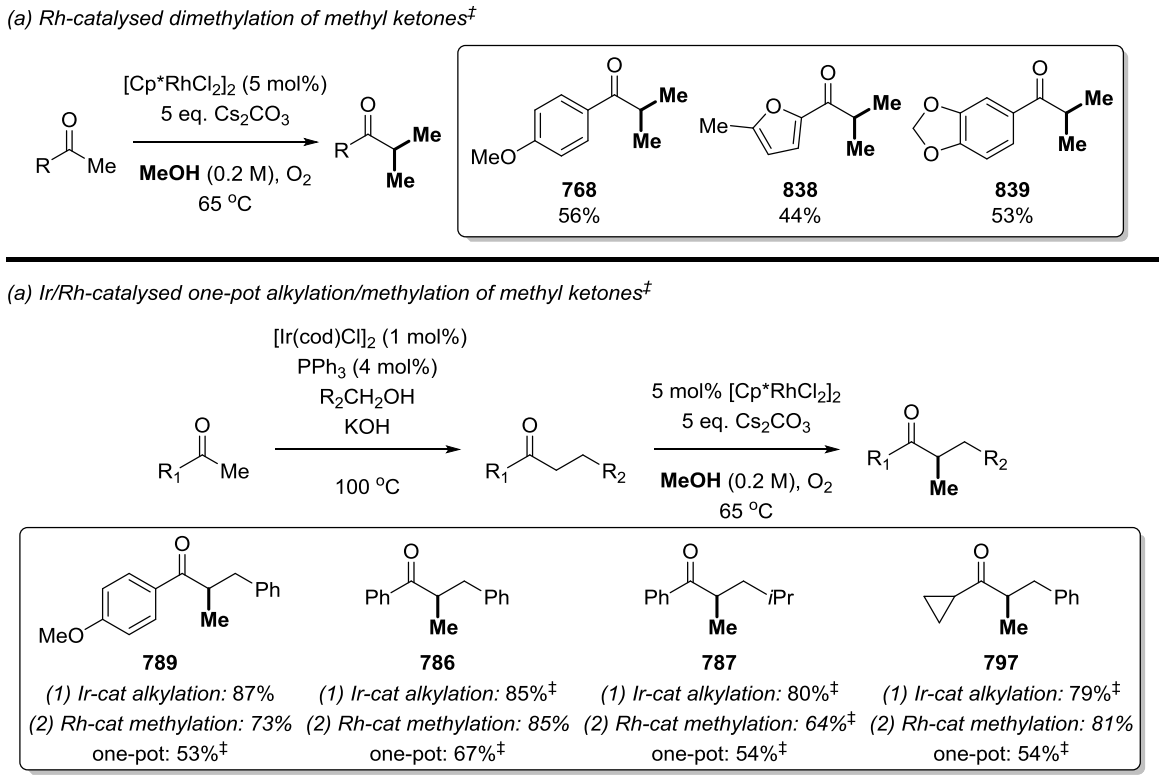
Having developed the rhodium-catalysed methylation reaction, screened its utility for a range of substrates, and made preliminary investigations into the mechanism of the reaction, we then sought to expand the synthetic utility of this protocol. A range of different methods were envisaged to showcase the usefulness of this reaction, and will be discussed below.

4.5.1 One-pot dialkylation[‡]

It was clear from the synthesis of the starting materials for the methylation reaction (**Chapter 4.3.1**), that often this required at least one or two steps for their synthesis, either from the nitrile, the carboxylic acid *via* the Weinreb amide, or a two-step procedure from the aldehyde. Methyl ketones are much more abundant in terms of commercial availability, and thus Di Shen in the Donohoe group developed both a Rh-catalysed dimethylation reaction (**Scheme**

[‡] Example by Di Shen

4.45a), and also a two-step, one-pot protocol for the consecutive Ir-catalysed alkylation reaction (using a procedure developed by Ishii and coworkers),[273] followed by a Rh-catalysed methylation reaction (**Scheme 4.45b**). Both of these protocols afforded dialkylated ketones in moderate to excellent yields, with a range of substitution patterns.

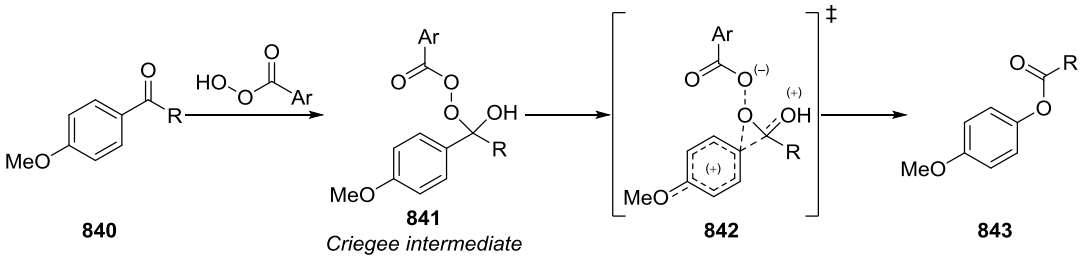


Scheme 4.45 *Rh-catalysed dimethylation and one-pot Ir/Rh-dialkylation of methyl ketones*‡

4.5.2 Baeyer-Villiger Oxidation

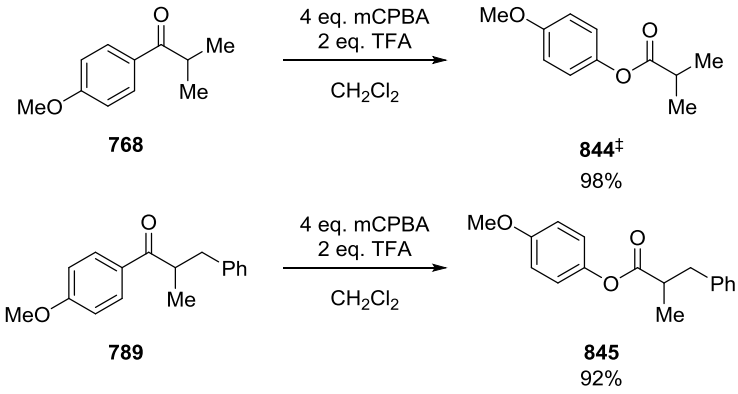
To further expand the synthetic utility of the ketone methylation, we devised a method to allow the formation of other carbonyl derivatives from the methylated ketones. It was evident that *p*-methoxyphenyl ketones such as **789** would be ideal substrates for Baeyer-Villiger oxidation, allowing regioselective formation of *p*-methoxyphenyl esters. This regioselectivity was expected to arise as a result of the Baeyer-Villiger oxidation to proceed with selective migration of the more electron-rich group. The preference for the migration of electron-rich groups has been attributed to the enhanced ability of electron-donating groups to accommodate a positive charge, stabilising the transition state **842** for migration, following the formation of the 'Criegee intermediate' **841** (**Scheme 4.46**).

‡ Example by Di Shen



Scheme 4.46 *Regioselectivity in the Baeyer-Villiger oxidation of electron-rich ketones*

Thus, treatment of *p*-methoxyphenyl ketones **768** and **789** with 4 eq. *m*CPBA and 2 eq. TFA in dichloromethane afforded the desired esters **844**,‡ and **845**, in 98% and 92% respectively, both with near complete regioselectivity for the desired regioisomer (**Scheme 4.47**).



Scheme 4.47 *Regioselective Baeyer-Villiger oxidation of p-methoxyphenyl ketones*

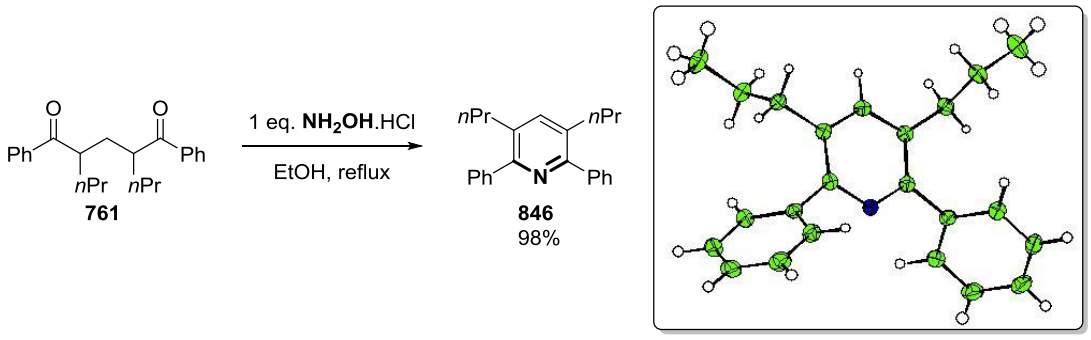
The utility of esters such as **845** was subsequently demonstrated by Camilla Shotton in the Donohoe group, with their derivatisation into a range of carboxylic acid derivatives including carboxylic acids, alkyl esters, primary alcohols, amides (primary, secondary and Weinreb amides).[350]

4.5.3 Pyridine synthesis

During the initial screening of reaction conditions, it was found that the use of RuO_2 as a catalyst afforded solely the dimer **721**, in 82% yield (**Table 4.1**, **Entry 18**). 1,5-Dicarbonyl compounds are well known intermediates for the synthesis of pyridines,[2] and thus we envisaged that treatment of dimer **721** with an appropriate source of ammonia, followed by oxidation would afford the corresponding pyridine.[351] Thus, treatment of 1,5-dicarbonyl **621** with 1 eq. of hydroxylamine hydrochloride in refluxing ethanol afforded the symmetrical

‡ Example by Di Shen

pyridine **846** in 98% yield (**Scheme 4.48**), the structure of which was confirmed by X-ray crystallographic analysis (**Appendix 5**).

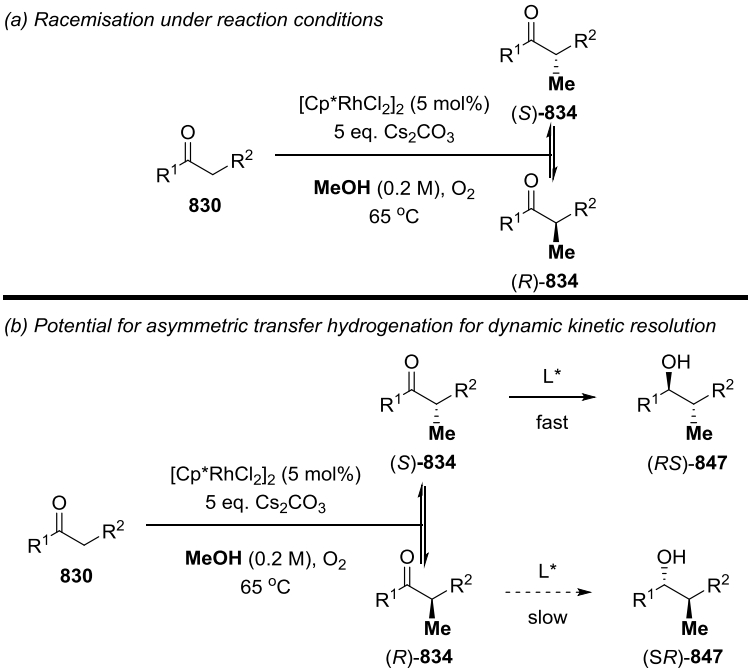


Scheme 4.48 *Synthesis of symmetrical tetrasubstituted pyridine* **846**

Clearly, the ability to synthesise unsymmetrical 1,5-dicarbonyls *via* this methodology would allow for the synthesis of unsymmetrical tetrasubstituted pyridines, and would provide a valuable synthetic tool.[36] Investigations into this methodology for the synthesis of unsymmetrical pyridines are an ongoing area of research in the Donohoe group.

4.5.4 Attempted asymmetric transfer-hydrogenation

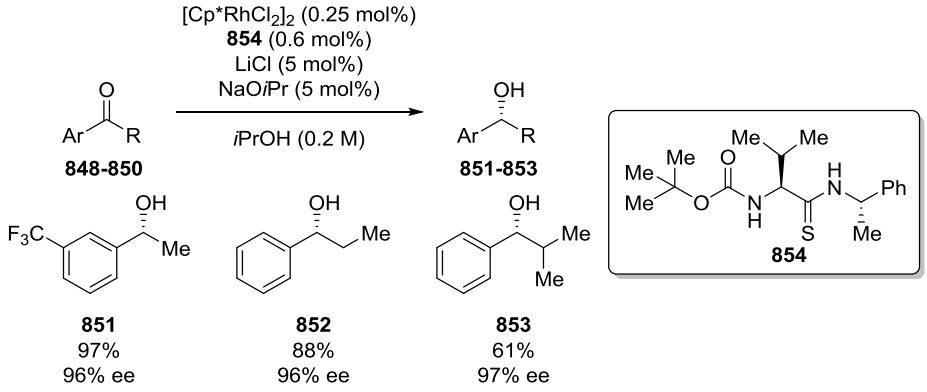
It was envisaged that a direct asymmetric methylation protocol would not be feasible under the current reaction conditions, due to the highly basic conditions, and thus it was considered that racemisation of the newly formed stereocentre would present a problem (**Scheme 4.49a**).



Scheme 4.49 *Potential for asymmetric transfer hydrogenation/dynamic kinetic resolution*

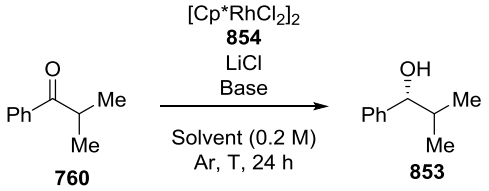
However, methods for the asymmetric transfer hydrogenation of ketones using $[Cp^*RhCl_2]_2$ are known,[352,353] and as such, it might prove feasible to effect an asymmetric reduction of the ketone carbonyl in the methylated product. It was also considered that under the reaction conditions, epimerisation of the methylated ketone **834** might therefore allow an asymmetric dynamic kinetic resolution to enantiopure β-methyl alcohols **847** (**Scheme 4.49b**).

Our attention was caught by work by Adolfsson and coworkers, who utilised $[Cp^*RhCl_2]_2$ as catalyst along with thioamide ligand **854** for the asymmetric transfer hydrogenation of a range of aryl ketones **848**-**850** in high conversion and excellent enantioselectivities (**Scheme 4.50**). We considered that the fact that α-methylated ketones such as **850** could be reduced in excellent enantioselectivities might lend itself to a one-pot methylation/asymmetric transfer hydrogenation protocol.



Scheme 4.50 *Adolfsson's $[Cp^*RhCl_2]_2$-catalysed asymmetric transfer hydrogenation*

To determine whether the catalyst/ligand system could be applied under conditions similar to our methylation conditions, first ligand **854** was prepared according to the literature procedure in two steps from *N*-Boc-valine. Using isobutyrophenone **760** as a model methylated ketone, conditions were then sought whereby the asymmetric transfer hydrogenation reaction could be conducted in methanol (**Table 4.8**).



Entry	$[Cp^*RhCl_2]_2$ (mol%)	854 (mol%)	LiCl (mol%)	Base (eq.)	Solvent	T (°C)	Yield (%)[a]	ee (%)[b]
1	5	12	100	Cs_2CO_3 (5 eq.)	MeOH	65	n/o	-
2	5	12	100	Cs_2CO_3 (5 eq.)	MeOH/*i*PrOH	65	n/o	-
3	5	12	100	Cs_2CO_3 (5 eq.)	*i*PrOH	65	trace	-
4	5	12	100	NaOMe (5 eq.)	MeOH	65	47	-
5	5	12	100	NaOMe (5 eq.)	MeOH/*i*PrOH	65	63	82
6	5	12	100	NaOMe (5 eq.)	*i*PrOH	65	quant.	80
7[b]	5	12	100	NaOMe (5 eq.)	*i*PrOH	65	quant.	88
8	0.25	0.6	5	NaOMe (0.05 eq.)	*i*PrOH	rt	72	96

Table 4.8 *Attempted asymmetric transfer hydrogenation of* **760** *in MeOH*
[a] Isolated yield [b]Enantiomeric excess was determined by chiral HPLC [b] Reaction run under O_2

Unfortunately, running the reaction under similar conditions to the methylation reaction (Cs_2CO_3 base, in methanol) resulted in no observable conversion (**Entry 1**), even with *i*PrOH as a cosolvent or sole solvent (**Entries 2** and **3**). Replacement of Cs_2CO_3 with the stronger base NaOMe showed increased conversion, but this was significantly lower than that observed in *i*PrOH (**Entries 4-7**). Indeed, using *i*PrOH as solvent allowed the use of drastically decreased catalyst loadings even at low temperature, whilst giving a significantly increased ee, yielding the (*R*)-enantiomer of **853** in 72% yield as essentially a single enantiomer (**Entry 8**). Thus, it seemed unlikely that it would be possible to combine the $[Cp^*RhCl_2]_2$-catalysed transfer hydrogenation in a single pot with the rhodium-catalysed methylation reaction, and thus further investigations into this area were ceased.

4.6 Conclusion

During the course of this work, a novel rhodium-catalysed methylation of ketones using methanol has been developed. This is one of only a handful of techniques available for the formation of C-C bonds using methanol.[230, 305,312]

A range of different transition-metal catalysts were screened for optimal activity in the methylation reaction, showing that $[Cp^*RhCl_2]_2$ was the most efficient catalyst for promoting this reaction, in the presence of Cs_2CO_3 base. It was also clear that methylation was most efficient under an atmosphere of O_2, allowing methylation to be achieved at a relatively mild

65 °C, in comparison to the 120-130 °C reported in the literature for a ketone methylation reaction published subsequent to the work presented here.[314]

The ketone methylation reaction was shown to be applicable to a range of aryl and alkyl substituted ketones, whilst proving to be particularly efficient for the methylation of electron-deficient ketones.

Mechanistic studies have allowed us to postulate a catalytic cycle based upon methanol oxidation, aldol reaction, and conjugate reduction. Furthermore, deuteration experiments suggest that the reaction proceeds *via* a rhodium monohydride species, and that methanol dehydrogenation appears to be a slow step in the catalytic cycle.

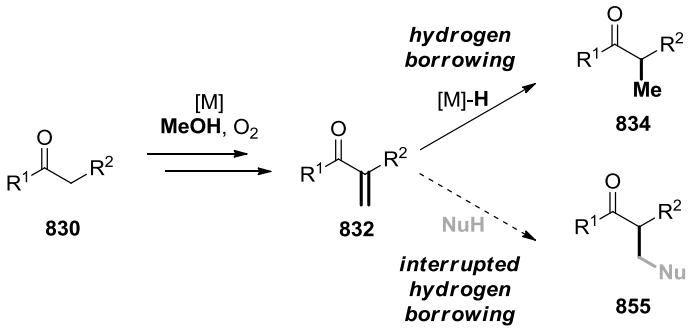
Finally, this methodology has been extended to allow one-pot dialkylation reactions, [‡] Baeyer-Villiger oxidation to afford the methylated ester, pyridine formation (in the case of formation of 1,5-dicarbonyl compounds), and also an attempted asymmetric transfer hydrogenation of the methylated products.

[‡] Example by Di Shen

5: Results and Discussion – Interrupted Hydrogen Borrowing Reactions of Methanol

5.1 Introduction

After the successful development of the rhodium-catalysed methylation of ketones utilising methanol (**Chapter 4**),[313] and subsequent exploration of the synthetic utility of this reaction, we looked to further expand the scope and value of this reaction. Mechanistic studies had revealed that the reaction proceeded *via* formation of a 1,1-disubstituted enone **832**, which was subsequently reduced to the corresponding α-methyl ketone **834**. We theorised that selective formation of this enone without subsequent reduction would allow access to more complex alkylated structures, since this enone would be able to undergo a number of different transformations, including conjugate addition reactions, to form **855** (**Scheme 5.1**).



Scheme 5.1 *Proposed interrupted hydrogen borrowing reaction*

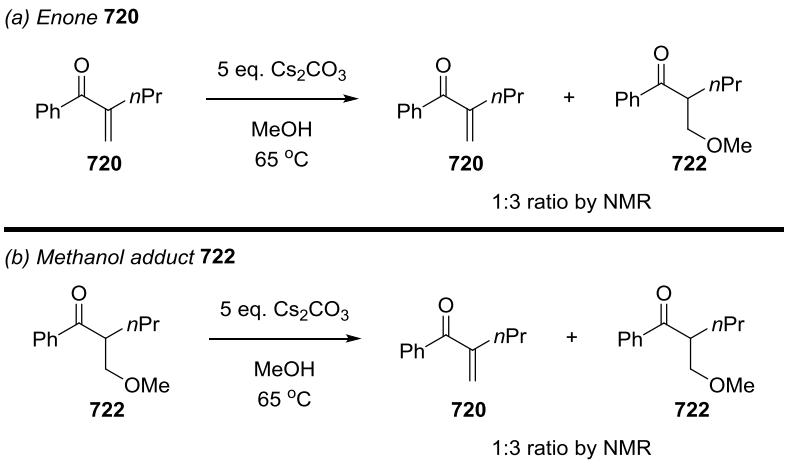
With this goal in mind, we therefore first set out to develop conditions to afford the enone **832** selectively.

5.2 Development of methylenation conditions

Previous catalyst screening for the methylation of ketones (**Table 4.1**) revealed that the reduction of the enone **720** depended markedly on the structure of the metal species, with $[Cp^*RhCl_2]_2$ showing a strong tendency towards reduction, whereas $[Cp^*RuCl_2]_n$ showed almost no reduction at all, affording only trace of the methylated ketone **719**. Other preliminary studies had also shown that the effect of base played a significant role in the ratio of products formed (due to dimer formation being more efficient in the presence of strong base). Therefore, we set out to explore the possibility for selective methylenation, using valerophenone **718** as the model substrate. As previously, methylated ketone **719**, enone **720**, dimer **721** and methanol adduct **722** were all observed.

5.2.1 Equilibrium between enone and methanol adduct

We had previously postulated that enone **720** was in equilibrium with methanol adduct **722** under the reaction conditions, and thus to confirm this subjected clean samples of both compounds to the basic conditions employed for the methylation reaction, in the absence of $[Cp^*RhCl_2]_2$ catalyst. Indeed, both enone **720** (**Scheme 5.2a**), and methanol adduct **722** (**Scheme 5.2b**) afforded the same ratio of 1:3 **720**:**722** after 18 hours, suggesting that they are indeed in equilibrium.

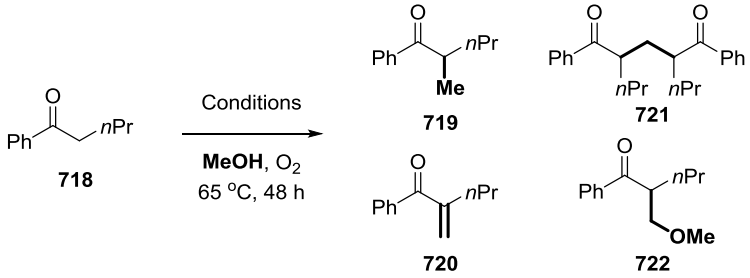


Scheme 5.2 *Evidence for equilibrium between* **720** *and* **722**

Since these two species appeared to be in equilibrium, we envisaged that selective formation of **720** and **722** (a masked enone equivalent) would allow subsequent conversion to the desired conjugate addition products, since base-promoted elimination of methanol would afford enone **720**. As such, we then sought to screen conditions to form **720** and **722** in high yield, with minimal formation of methylated ketone **719** or dimer **722**.

5.2.2 Screening of reaction conditions

During the development of the methylation reaction, it had become clear that $[Cp^*RuCl_2]_n$ had shown itself to be incapable of promoting efficient reduction of enone **720** to the methylated ketone **719**. We therefore initiated our studies using this catalyst, and exploring how altering conditions affected the ratio of products formed (**Table 5.1**).



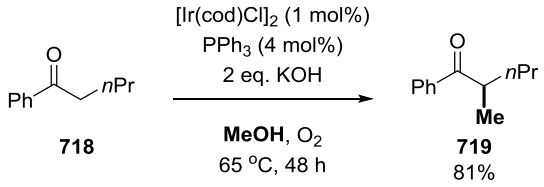
Entry	Conditions	719 (%)[a]	720 (%)[a]	722 (%)[a]	721 (%)[a]	RSM (%)[a]
1	$[Cp^*RuCl_2]_n$ (10 mol%), 5 eq. Cs_2CO_3, 0.2M	trace	23	39	19	n/o
2	$[Cp^*RuCl_2]_n$ (10 mol%), 1 eq. Cs_2CO_3, 0.2M	trace	28	51	6	n/o
3	$[Cp^*RuCl_2]_n$ (10 mol%), 5 eq. NaOMe, 0.2M	trace	41	39	trace	n/o
4	$[Cp^*RuCl_2]_n$ (10 mol%), 5 eq. NaOMe, 0.1M	trace	25	58	trace	n/o
5	$[Cp^*RuCl_2]_n$ (10 mol%), 2 eq. NaOMe, 0.1M	trace	25	53	trace	12

Table 5.1 *Screening of methylenation conditions with $[Cp^*RuCl_2]_n$*
[a] Isolated yield

The original conditions employed for methylation, with 5 eq. Cs_2CO_3 afforded a combined yield of 62% for the desired compounds **720** and **722** (**Entry 1**). However, 19% of dimer was also isolated in this reaction, suggesting that the concentration of enolate was too high, and thus facilitating conjugate addition of starting ketone **718** to enone **720**. Lowering the equivalents of Cs_2CO_3 to 2 eq. resulted in an increased yield of 79% of the methylenated compounds (**Entry 2**). Exchanging the base for sodium methoxide resulted in a similar yield of 80% (**Entry 3**), and lowering the concentration to 0.1 M had little effect on the overall yield of the reaction, affording enone **720** and methanol adduct **722** in a combined yield of 83% (**Entry 4**). Lowering the equivalents of NaOMe to 2 eq. at this concentration resulted in a slight decrease in yield to 78%, but with a considerable amount of recovered starting material (**Entry 5**).

Although these initial reaction conditions appeared promising, we considered that it might be possible to find conditions for the reaction that employed a lower catalyst loading. Studies had been initiated in the Donohoe group (work by Di Shen) to investigate the use of the $[Ir(cod)Cl]_2/PPh_3$ catalyst system for the methylation of ketones, conditions initially employed by Ishii and coworkers for the alkylation of methyl ketones.[273] Studies had shown

that by employing an atmosphere of oxygen it was possible to methylate valerophenone **718** under these conditions in an 81% yield (**Scheme 5.3**). Importantly, this process enabled the methylation of ketones with only 1 mol% $[Ir(cod)Cl]_2$ (2 mol% Ir), a considerable improvement of the minimum 2.5 mol% $[Cp^*RhCl_2]_2$ (5 mol% Rh) required for the original methylation conditions, or the 10 mol% Ir subsequently reported in the literature.[314] Furthermore, the cost of $[Ir(cod)Cl_2]$ (£81/mmol, Sigma-Aldrich) is considerably lower than for $[Cp^*RhCl_2]_2$ (£233/mmol, Sigma-Aldrich), thus making this reaction more economical.



Scheme 5.3 *$[Ir(cod)Cl]_2$/PPh_3-catalysed methylation of valerophenone* **718**‡

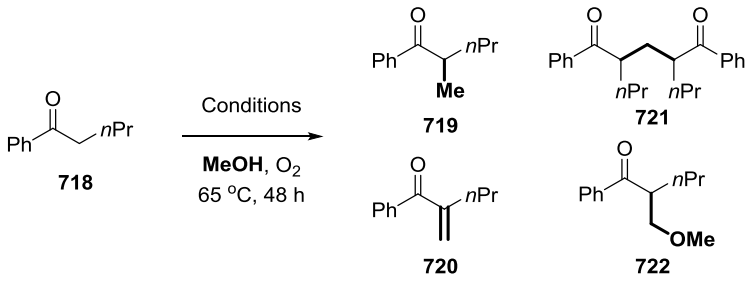
Screening of different ligands had shown that the phosphine employed had a considerable effect on the outcome of the reaction. Thus, it was decided to carry out a screen of phosphine ligands under these conditions to determine whether these would provide a more convenient route to the desired methylenated compounds **720** and **722** (**Table 5.2**).

Initially, conducting the reaction with 1 mol% $[Ir(cod)Cl]_2$ and 4 mol% PCy_3 (2:1 ligand:metal ratio) under the standard conditions of 2 eq. KOH and 0.2 M in MeOH, afforded enone **720** and methanol adduct **722** in a combined yield of 76% (**Entry 1**). However, in this case 16% of the dimer **721** was observed, thus significantly lowering the overall yield. Diluting the reaction to a concentration of 0.1 M in MeOH lowered the amount of observed dimer considerably, whilst still affording the desired products in a combined yield of 69% (**Entry 2**), however, conversion was lower in this case with 12% of starting ketone **718** recovered.

To determine whether oxygen was necessary for this reaction, as it was for the methylation reaction (*vide supra*), the reaction was also conducted under an atmosphere of argon (**Entry 3**). However, in this case conversion was considerably lower, with 32% of **718**

‡ Example by Di Shen

recovered unreacted. Interestingly, in this case, the majority of the product isolated was methylated ketone **719**, with only 19% of the enone **720** and methanol adduct **722** observed. Indeed, this suggests that oxygen plays a role in preventing reduction under these conditions, presumably *via* interception of the hydride species. This would be in accordance with the mechanism for catalyst regeneration proposed by Ison and coworkers, whereby insertion of O_2 into an [Ir]-H species allows for the regeneration of the active catalyst for alcohol oxidation (see **Chapter 4**, **Scheme 4.2**).[315]



Entry	Conditions	719 (%)[a]	720 (%)[a]	722 (%)[a]	721 (%)[a]	RSM (%)[a]
1	$[Ir(cod)Cl]_2$ (1 mol%), PCy_3 (4 mol%), 2 eq. KOH, 0.2 M	trace	17	59	16	trace
2	$[Ir(cod)Cl]_2$ (1 mol%), PCy_3 (4 mol%), 2 eq. KOH, 0.1 M	trace	7	62	trace	12
3[b]	$[Ir(cod)Cl]_2$ (1 mol%), PCy_3 (4 mol%), 2 eq. KOH, 0.1 M	43	3	16	trace	32
4	$[Ir(cod)Cl]_2$ (1 mol%), PCy_3 (4 mol%), 5 eq. KOH, 0.1 M	13	8	69	trace	trace
5	$[Ir(cod)Cl]_2$ (1 mol%), P*n*Bu_3 (4 mol%), 2 eq. KOH, 0.1 M	trace	12	58	trace	24
6	$[Ir(cod)Cl]_2$ (1 mol%), CyJohnPhos **856** (4 mol%), 2 eq. KOH, 0.1 M	9	12	52	trace	22
7	$[Ir(cod)Cl]_2$ (1 mol%), *t*BuXPhos **857** (4 mol%), 2 eq. KOH, 0.1 M	trace	10	45	4	38
8	$[Ir(cod)Cl]_2$ (1 mol%), CataCXium A **858** (4 mol%), 2 eq. KOH, 0.1 M	trace	11	49	trace	32
9	$[Ir(cod)Cl]_2$ (2 mol%), PCy_3 (8 mol%), 2 eq. KOH, 0.1 M	5	23	56	trace	8
10	$[Ir(cod)Cl]_2$ (2 mol%), PCy_3 (8 mol%), 3 eq. KOH, 0.1 M	7	11	65	trace	trace
11	$[Ir(cod)Cl]_2$ (2 mol%), CataCXium A **858** (8 mol%), 3 eq. KOH, 0.1 M	5	**26**	**63**	4	trace

Table 5.2 *Screening of methylenation conditions with $[Ir(cod)Cl]_2$*
[a] Isolated yield [b] Reaction conducted under Ar

Increasing the amount of base from 2 to 5 eq. KOH resulted in a 77% combined yield of enone **720** and methanol adduct **722**, but a slight increase in the amount of methylated

compound **719** to 13% (**Entry 4**). This might arise as a result of an increased rate of methanol oxidation due to a higher concentration of MeO^- ion in solution, thus resulting in an increased concentration of [Ir]-H species.

Our attention then turned to screening a range of other alkyl phosphine ligands (**Figure 5.1**). The use of P*n*Bu_3 as ligand resulted in lower activity, with 24% recovered starting material, but still afforded the methylenated compounds **720** and **722** in a combined yield of 70% (**Entry 5**). The (2-biphenyl)dicyclohexylphoshine, CyJohnPhos **856**, which we considered would have similar steric properties to PCy_3, whilst slightly lowering the electron-donating ability of the phosphine due to the presence of the aromatic ring, showed somewhat slower reactivity, with 22% of starting ketone **718** recovered, but still affording 64% of the methylenated compounds **720** and **722** (**Entry 6**). Interestingly, there was a moderate increase in the observed amount of methylated ketone **719** to 9%, which, whilst still low, may have arisen due to the slightly lower electron-donating ability of the phosphine, modulating the reactivity of the [Ir]-H species.

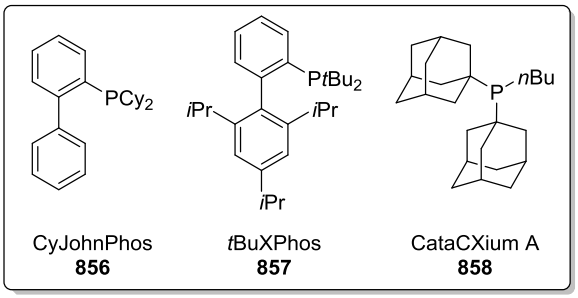


Figure 5.1 *Other phosphine ligands*

The more hindered aryl-dialkyl phosphine *t*BuXPhos **857** showed yet lower reactivity, showing conversion of only slightly over 60% after 48 hours (**Entry 7**). The required products **720** and **722** were afforded in a collective yield of 55%, but with 4% of dimer **721** also observed, a considerable amount considering the low conversion.

The bulky trialkyl phosphine CataCXium A **858** (di-(1-adamantyl)-*n*-butylphosphine), showed approximately 70% conversion after 48 h, but still afforded a combined yield of 60% of the desired compounds **720** and **722** with only traces of the methylated ketone **719** and

dimer **721** observed (**Entry 8**), suggesting that if the conversion could be improved, that this ligand showed similar promise to PCy_3.

In an attempt to increase the rate of reaction, we attempted to increase the catalyst loading for the reaction. Employing 2 mol% $[Ir(cod)Cl]_2$ and 8 mol% PCy_3 with 2 eq. KOH in MeOH (0.1 M) afforded the methylenated compounds **720** and **722** in 79% combined yield, but still with 8% of starting ketone **718** recovered (**Entry 9**). Increasing the loading of KOH to 3 eq. afforded 77% yield of **720** and **722**, with only traces of starting material observed, but resulted in an increased yield of methylated ketone **719** to 7% (**Entry 10**). However, employing the bulky ligand CataCXium A **858** under these conditions afforded the desired methylenated ketones **720** and **722** in a collective yield of 89%, with traces of methylated ketone **719** and dimer **721** observed (**Entry 11**).

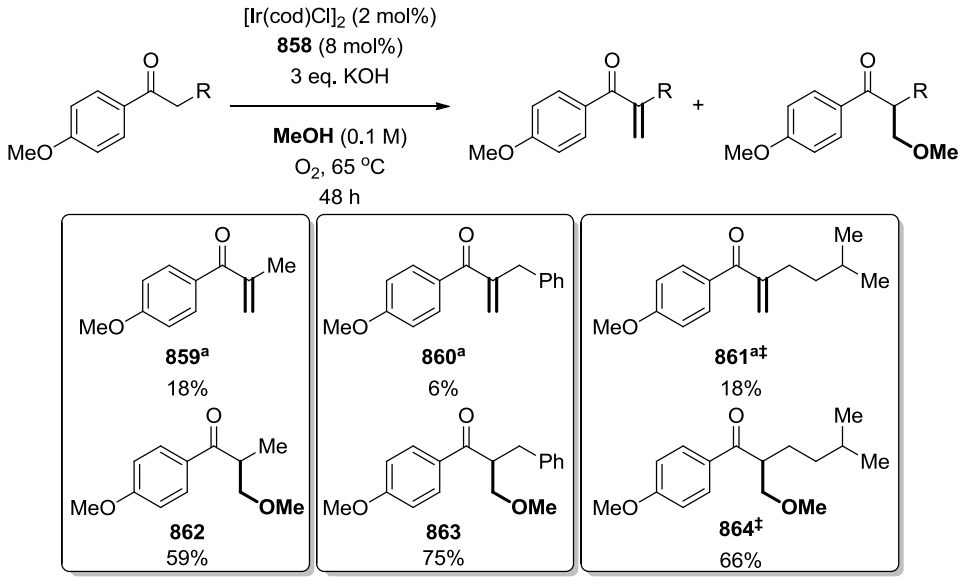
Thus, it appeared that the use of the bulky alkyl phosphine **858** was the optimum choice for conducting methylenation reactions going forwards. It is clear that the electronic nature of the phosphine plays a considerable role in course of the reaction, since alkyl phosphines show a much lower propensity for the reduction of enone **720**. Furthermore, the fact that under Ar reduction of enone **720** is facile, suggests that O_2 plays a role in the decomposition of the iridium hydride species formed from methanol oxidation, and that this process is expedited in the presence of a more strongly electron-donating phosphine ligand. However, it cannot be ruled out that reduction of the enone is simply slower under the reaction conditions employing alkyl phosphines such as CataCXium A **858**, thus resulting in an increased likelihood of trapping of the metal hydride species with O_2, and thus continuing the cycle.

A standard method for the description of the electron-donating ability of phosphine ligands is the Tolman electronic parameter.[354] In this method, the ν_{CO} stretching frequency of a $Ni(CO)_3PR_3$ compound is measured, and this stretching frequency can be directly correlated to the electron-donating ability of the phosphine. For strong σ-donating phosphine ligands, there will be increased π-back donation from the metal to the CO ligands, and thus weakening the C≡O bond, and lowering the ν_{CO} stretching frequency. For example, Tolman reported a value of ν_{CO} = 2056 cm^{-1} for PCy_3, representing a strongly electron-donating

ligand. On the other hand, PPh_3 has a Tolman electron parameter ν_{CO} = 2069 cm^{-1} indicating a lower value for electron donation for this ligand. Although values are not available for CataCXium A **858**, it is likely that the steric and electron properties of **858** are similar to other bulky alkyl phosphines such as P*t*Bu$_3$ (ν_{CO} = 2056 cm^{-1}), indicating perhaps that it is the steric and electronic nature of this ligand that results in its optimal activity for the methylenation reaction.

5.2.3 Methylenation of *p*-methoxyphenyl ketones

In the development of this reaction, we determined that *p*-methoxyphenyl ketones would represent a synthetically important class of substrates, due to their overall synthetic utility, and the ability to convert these ketones into a range of other carboxylic acid derivatives *via* Baeyer-Villiger oxidation (*vide supra*). As such, we subjected a range of different *p*-methoxyphenyl ketones to the methylenation conditions to afford the corresponding enone and methanol adducts selectively (**Scheme 5.4**).



Scheme 5.4 *Methylenation of p*-methoxyphenyl ketones
[a] Product obtained as a mixture with the corresponding methylated ketone

In the case of ethyl ketone **758**, the enone **859** and methanol adduct **862** were obtained in a combined yield of 77%, although the enone **862** was contaminated with 14% of the corresponding methylated ketone 768. The high yield of methylated ketone in this case may have arisen as a result of the relatively unhindered steric environment in enone **859**,

facilitating the addition of [Ir]-H to form **768** before decomposition of the hydride species could occur.

Benzylated ketone **781** was also methylenated successfully, affording the desired compounds **860** and **863** in a combined yield of 81%. In this case, enone **860** was contaminated with 4% of the corresponding methylated ketone **788**. Similarly, the longer chain alkyl ketone **782** could be methylenated in an excellent 84% collective yield,‡ although once again the enone **861** was contaminated with trace amount of the corresponding methylated compound **789**.

5.3 Conjugate addition reactions

With conditions for the successful methylenation of *p*-methoxyphenyl ketones in hand, our focus now turned to the development of conditions for successful conjugate addition reactions to the corresponding enones, and then the application of these conditions to one-pot methylenation/conjugate-addition reactions.

We envisaged that this could be applied to a range of different nucleophiles, for example other ketones (allowing the formation of unsymmetric 1,5-diketones), nitronate anions, peroxides for the formation of epoxides, and a multitude of other nucleophiles for the formation of a diverse range of alkylated products (**Figure 5.2**).

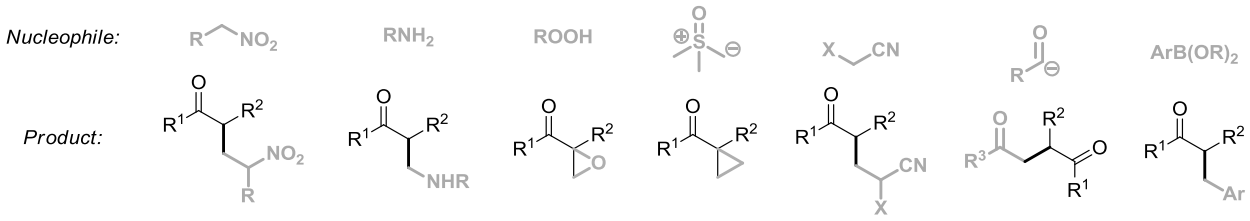


Figure 5.2 *Nucleophiles to be explored in one-pot methylenation/conjugate addition*

It was clear that for these methods to be effective as one-pot methylenation/conjugate addition reactions, the conditions for addition would have to closely reflect those developed for the methylenation reaction, i.e. conducted in methanol, preferably at the same concentration as the methylenation reaction, and also employing KOH as base. For initial screening of conditions for the conjugate addition reaction, we chose to employ the

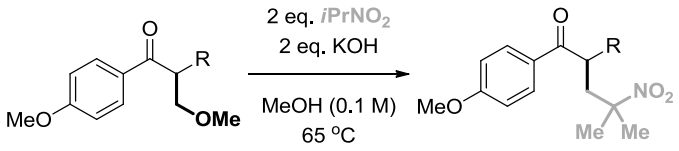
‡ Example by Di Shen

corresponding methanol adduct **862-864**, since these would be required to be in equilibrium under the reaction conditions for an efficient conjugate addition reaction.

5.3.1 Conjugate addition of nitronate anion

The conjugate addition of nitronate anions to enones is a well-known process, first reported by Kohler and coworkers in 1916.[355] The utility of this process is clear, since the products may then be converted *via* a number of methods to the corresponding amine (*via* reduction of the nitro group),[356] or carbonyl (*via* Nef reaction).[357]

To test the conjugate addition of a nitronate anion to our *p*-methoxyphenyl enones, 2 eq. 2-nitropropane and 2 eq. KOH were added to benzylated methanol adduct **863**, and subsequently stirred at 65 °C for 15 hours. Pleasingly, this afforded the corresponding γ-nitro ketone **865** in quantitative yield (**Scheme 5.5**). Confirmation of the structure of the product was provided by the presence of two diastereotopic C$\underline{H_2}$ protons adjacent to the CMe_2NO_2 group, at 2.72-2.59 ppm (m, due to overlap with CH_aH_bPh proton) and 2.18 ppm (dd) in the ^{1}H NMR spectrum. The occurrence of a peak at 88.0 ppm in the ^{13}C NMR spectrum was also suggestive of a nitrated alkyl group. Further validation of successful addition to enone **860** was afforded by a peak at 364.1519 in the HRMS, corresponding to the $[M+Na]^+$ species. We were also delighted to find that the long chain alkyl compound **866** could be formed in 84% yield by the addition of 2-nitropropane to methanol adduct **864**.



R = Bn, **863**
R = CH_2CH_2*i*Pr, **864**

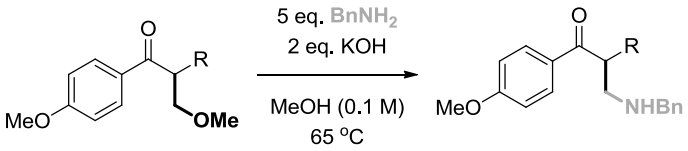
R = Bn, **865**, quant.
R = CH_2CH_2*i*Pr, **866**, 84%

Scheme 5.5 *Conjugate addition of 2-nitropropane to compounds* **863** *and* **864**

5.3.2 Conjugate addition of amines

It was envisaged that the conjugate addition of amines,[358] affording β-amino ketones would also provide useful synthetic intermediates, as β-amino carbonyls and their derivatives are important targets for a range of biologically-active compounds.[359]

Thus, addition of benzylamine to methanol adduct **863** was attempted. Unfortunately, the use of low equivalents of benzylamine afforded only low conversion. It was also found to be necessary to include stoichiometric amounts of KOH to promote an efficient reaction, presumably due to slow equilibration to the enone **860** in only the presence of benzylamine. However, by treatment of **863** with 5 eq. benzylamine and 2 eq. KOH in MeOH at 65 °C, the desired aminated product **867** was furnished in 97% yield (**Scheme 5.6**). Despite being diastereotopic, the benzylamine NHC$\underline{H_2}$Ph protons appeared as a 2H singlet in the ^{1}H NMR, coupled to a $\underline{C}H_2$ peak at 54.0 ppm in the ^{13}C NMR, by HSQC analysis, and also a broad singlet at 1.46 ppm in the ^{1}H NMR by COSY analysis. Benzylamine addition was also successful for the long-chain alkyl compound **864**, affording the aminated ketone **868** in 93% yield, whose spectroscopic data was similarly consistent with the structure shown, with a peak at 340.2271 in the HRMS corresponding to the $[M+H]^+$ species.

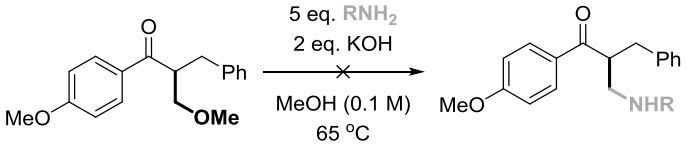


R = Bn, **863**
R = CH_2CH_2iPr, **864**

R = Bn, **867**, 97%
R = CH_2CH_2iPr, **868**, 93%

Scheme 5.6 *Conjugate addition of benzylamine to compounds* **863** *and* **864**

A range of other amines were also examined for activity in conjugate addition to the methanol adduct **863** (**Scheme 5.7**). Unfortunately, *p*-methoxyaniline only yielded recovered starting material, presumably due to the lower nucleophilicity of aromatic amines. A similar result was also observed for 3-amino-1,2,4-triazole, once again as a result of the lower nucleophilicity of the amine relative to benzylamine. We were also disappointed to find that functionalised amines such as glycine ethyl ester were also unreactive under the reaction conditions.

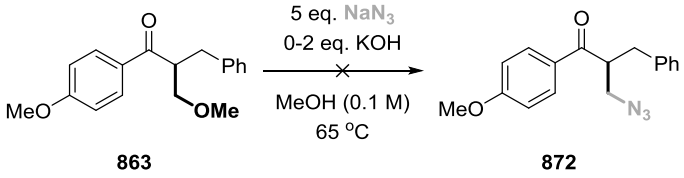


863

R = PMP, **869**
R = 3-(1,2,4-triazolyl), **870**
R = CH_2CO_2Et, **871**

Scheme 5.7 *Attempted addition of other amines to* **863**

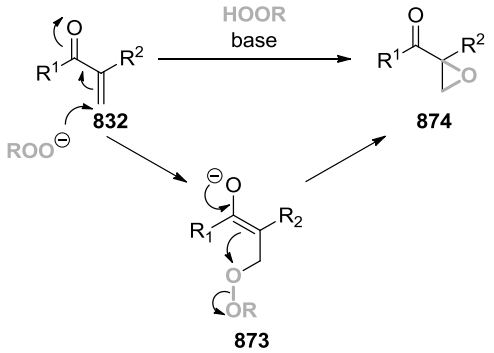
Another alternative to the addition of amines was the addition of azide,[360] which could subsequently be reduced to the primary amine,[361] or functionalised *via* the plethora of known reactions for the further derivatisation of azide, such as the Schmidt,[362] or azido-Mannich reaction.[363] However, addition of sodium azide, both in the presence or absence of additional base, only methanol adduct **863** and enone **860** were observed by TLC of the reaction, or ^{1}H NMR of the crude reaction mixture (**Scheme 5.8**).



Scheme 5.8 *Attempted addition of NaN_3 to* **863**

5.3.3 Epoxidation of methanol adducts

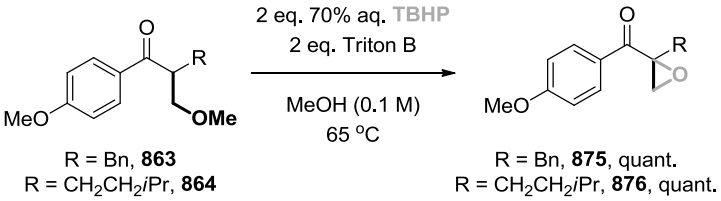
Epoxidation of enones is a reaction of fundamental importance in organic chemistry and has been known since it was first reported by Weitz and coworkers in 1921.[364] This process traditionally requires the use of a nucleophilic epoxidation reagent, such as hydrogen peroxide or *tert*-butylhydroperoxide (TBHP).[365] In these reactions, addition of peroxide anion to a ketone **832** forms the enolate of a β-peroxyl ketone **873**, which subsequently displaces the leaving group from the peroxyl group, thus forming the epoxide **874** (**Scheme 5.9**).



Scheme 5.9 *Nucleophilic epoxidation of enones*

Initial attempts at epoxidation focussed on the use of 2 eq. 30% aqueous H_2O_2 with KOH as base,[366] however, this resulted only in low conversion to the epoxide, with the majority of the recovered material observed being methanol adduct **863**. Similarly, employing 70% aqueous TBHP with KOH as base resulted in low conversion to product. However, upon

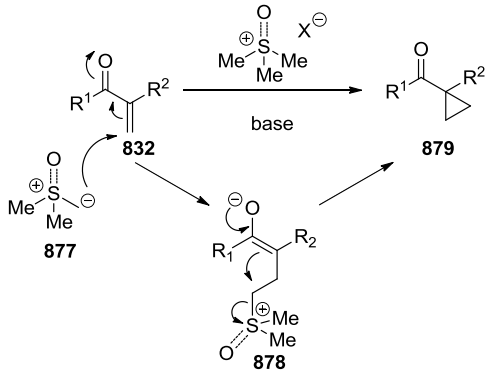
attempting the epoxidation reaction with Triton B (benzyltrimethylammonium hydroxide) as base, modifying conditions reported by Ireland and coworkers,[367] the corresponding epoxide **875** was formed in quantitative yield (**Scheme 5.10**). Formation of the epoxide was readily confirmed in the ^{1}H NMR spectrum of the product, with the presence of two 1H doublets at 2.77 and 2.73 ppm, with coupling constants of 5.0 Hz, characteristic of geminally coupled protons on a three-membered ring. The isopentyl methanol adduct **864** could also be epoxidised in quantitative yield under the same conditions, with the presence of two geminally coupled protons (*J* 5.0 Hz) at 2.93 and 2.88 ppm once again characteristic of the formation of the desired epoxide **876**.



Scheme 5.10 *Epoxidation of compounds* **863** *and* **864**

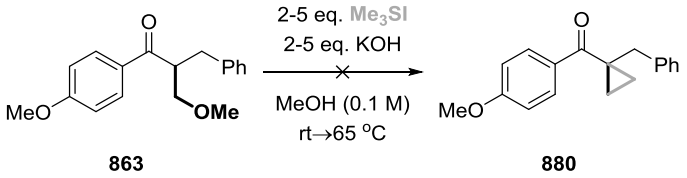
5.3.4 Cyclopropanation of methanol adducts

A logical conceptual extension to the nucleophilic epoxidation of the methanol adducts **863** and **864** would be a cyclopropanation utilising the Corey-Chaykovsky reaction.[368] In this reaction, a sulfonium (or sulfoxonium) ylid **877** undergoes a conjugate addition to an enone **832** to form the enolate **878**, which may then cyclise with elimination of a sulfide (or sulfoxide) (**Scheme 5.11**). Although sulfonium salts are in general said to prefer addition to the carbonyl of an enone, rather than conjugate addition,[368] thus forming epoxides, there are numerous examples where attack at the enone is observed.[369-371]



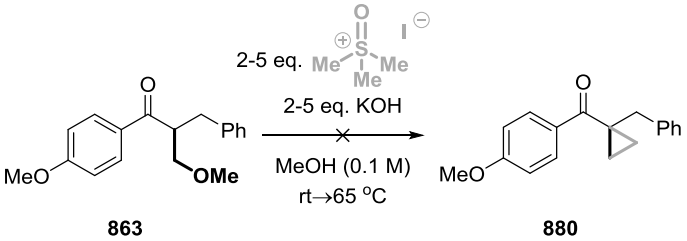
Scheme 5.11 *Corey-Chaykovsky reaction of enones*

In general, sulfonium salts require the use of a strong base such as NaH for efficient Corey-Chaykovsky cyclopropanation (pKa ≈ 24 in DMSO).[372] Reactions are typically conducted in aprotic solvents such as CH_2Cl_2 or THF, although examples in hydroxylic solvents such as MeOH and EtOH are known.[373] Thus, it was considered unlikely that addition of trimethylsulfonium iodide would proceed in methanol with KOH as base. Indeed, treatment of methanol adduct **863** with Me_3SI and KOH afforded no product at room temperature or 65 °C, even with increased loadings of the cyclopropanation reagent and base (**Scheme 5.12**).



Scheme 5.12 *Attempted cyclopropanation of* **863** *with trimethylsulfonium iodide*

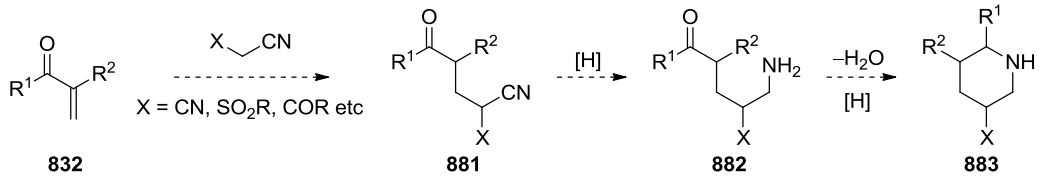
Since we considered that the unreactivity of Me_3SI arose as a result of the high pKa of the sulfonium salt, the reaction was also attempted with the corresponding sulfoxonium salt (pKa = 18.2 in DMSO).[372] Disappointingly, replacing Me_3SI with the corresponding sulfoxonium salt, trimethylsulfoxonium iodide, did not result in the desired cyclopropanated product **880**, instead just affording a mixture of recovered starting material as a mixture of enone **860** and methanol adduct **863** (**Scheme 5.13**).



Scheme 5.13 *Attempted cyclopropanation of* **863** *with trimethylsulfoxonium iodide*

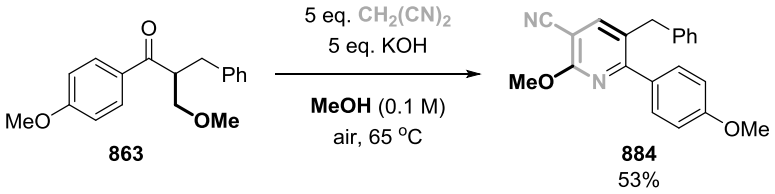
5.3.5 Conjugate addition of activated methylene compounds

The addition of activated methylene compounds such as malononitrile to enones is a well-established process in the chemical literature.[374] We considered that the addition of such compounds, including nitriles bearing an electron-withdrawing group α- to the cyano functionality, would provide access to a range of compounds which could subsequently be derivatised to provide access to more interesting compounds (**Scheme 5.14**).



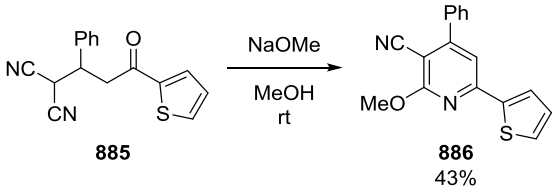
Scheme 5.14 *Proposed addition of activated nitriles for the synthesis of piperidines*

To determine whether the addition of these compounds to enones would prove a suitable route, the addition of malononitrile ($CH_2(CN)_2$) to methanol adduct **863** was tested. With 2 eq. of malononitrile, and 2 eq. KOH the reaction proved to be slow, with <50% conversion achieved after 48 h. However, increasing the equivalents of malonitrile and KOH to 5 eq. resulted in complete conversion after only 6 h. The product did not appear to be the desired product of conjugate addition, with an extra aromatic proton evident at 7.61 ppm in the ^{1}H NMR spectrum and the benzylic protons appearing as a 2H singlet 4.03 ppm, rather than two 1H double doublets in the region 2.50−3.10 ppm as for the other conjugate addition products previously discussed. This latter point suggested that the benzylic protons were doubly benzylic, adjacent to another aromatic ring. Furthermore, the presence of two OC*H*$_3$ groups, as confirmed by the presence of two 3H singlets at 3.87 and 3.75 ppm suggested that one equivalent of MeOH had been incorporated in the product. Careful analysis of the HMBC spectrum, and the presence of a peak at 306.1489 in the HRMS resulted in the assignment of the product as pyridine **884**, formed in 53% yield from methanol adduct **863** (**Scheme 5.15**).



Scheme 5.15 *Formation of pyridine* **884** *by reaction of* **863** *with malonitrile*

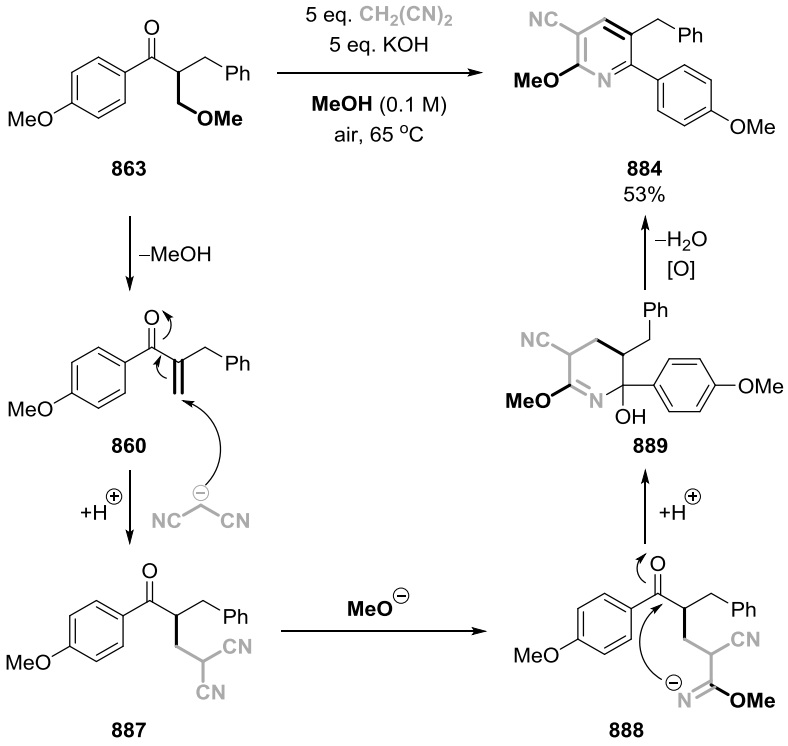
Interestingly, cyclisation reactions to form pyridines of this type are previously known. For example, reaction of nitrile **885** in basic methanol afforded the corresponding pyridine **886** in 43% yield (**Scheme 5.16**).[375]



885 **886** 43%

Scheme 5.16 *Formation of pyridine* **886** *from nitrile* **885**

A proposed mechanism for the formation of pyridine **884** from methanol adduct **863** proceeds *via* elimination of methanol to form enone **860**, followed by conjugate addition of malononitrile to form the expected product **887**. Subsequent addition of methoxide to one of the two nitrile moieties would afford the imidate anion **888**. Cyclisation, followed by loss of water from **889** and aerobic oxidation would thus afford the pyridine **884** (**Scheme 5.17**).

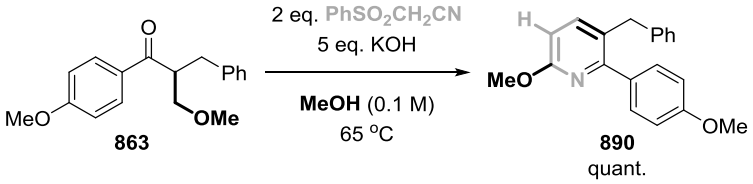


863 **884** 53% **860** **889** **887** **888**

Scheme 5.17 *Proposed mechanism for the formation of pyridine* **884**

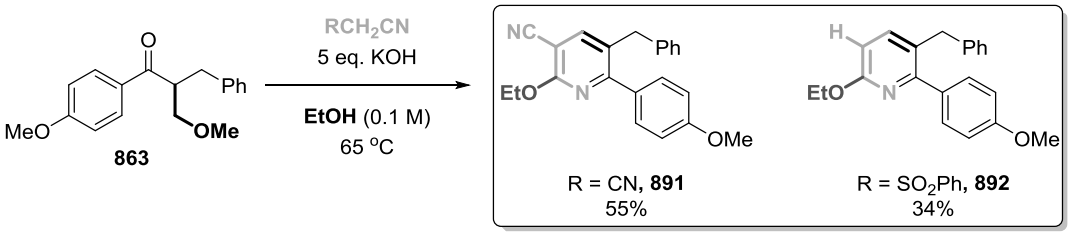
To see if this reaction was applicable to other activated nitrile species, methanol adduct **863** was also reacted with 2 eq. (phenylsulfonyl)acetonitrile and 5 eq. KOH in MeOH at 65 °C. Pleasingly, a single product was formed. However, to our surprise, there were 2 pyridyl protons observable in the ^{1}H NMR spectrum, appearing as doublets at 7.29 and 6.85 ppm, the latter indicating the presence of an aromatic proton adjacent to the pyridyl -OMe group. HRMS analysis showed a peak at 306.1489, indicating that the phenylsulfonyl moiety had been lost during the reaction. The product was thus assigned as the 2,3,6-trisubstituted

pyridine **890**, obtained in quantitative yield (**Scheme 5.18**). Presumably in the case of (phenylsulfonyl)acetonitrile, aerobic oxidation of the dihydropyridine does not occur, rather elimination of phenylsulfinate would lead directly to the fully aromatised product **890**.



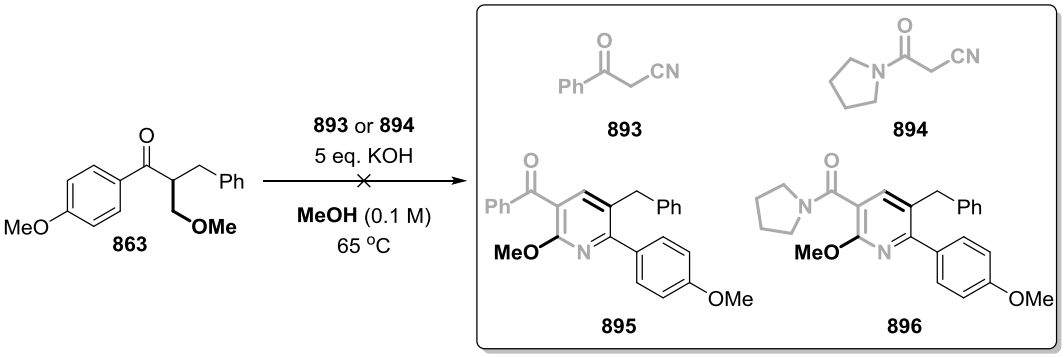
Scheme 5.18 *Formation of pyridine* **890** *with (phenylsulfonyl)acetonitrile*

Although it would not be applicable to a one-pot methylenation/conjugate addition reaction, we were also interested in seeing if the reaction was applicable to other alcohols. Conducting the corresponding reaction in EtOH with malononitrile and (phenylsulfonyl)acetonitrile afforded the corresponding pyridines **891** and **892** in 55% and 34% yield respectively, with the latter reaction giving a complex mixture of products (**Scheme 5.19**). Unfortunately, the reaction appeared to be slow in more hindered alcohols such as *i*PrOH and *t*BuOH, and only enone **860** and methanol adduct **863** were observed as major spots by TLC.



Scheme 5.19 *Pyridine formation in EtOH*

In an attempt to form more diverse pyridines with other groups in the pyridine 5-position, two other commercially available activated nitriles were utilised in the reaction. Benzoylacetonitrile **893**, and pyrrolidinyl amide **894** both proved to be unreactive under the reaction conditions, affording only unreacted starting material (as a mixture of enone **860** and methanol adduct **863**) (**Scheme 5.20**).



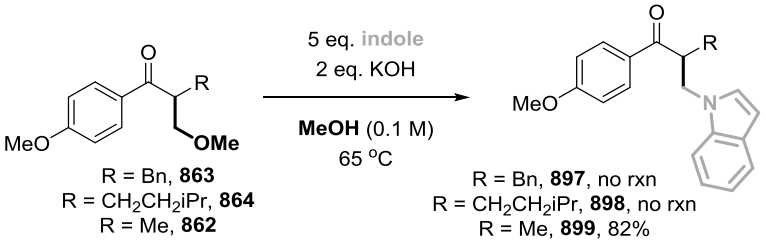
Scheme 5.20 *Attempted pyridine formation using nitriles* **893** *and* **894**

Despite some promising initial results on the formation of pyridines, we considered that the generally lower yields for this process would result in low yields for a one-pot methylenation/conjugate addition, and thus this protocol was not investigated further.

5.3.6 Conjugate addition of heterocycles

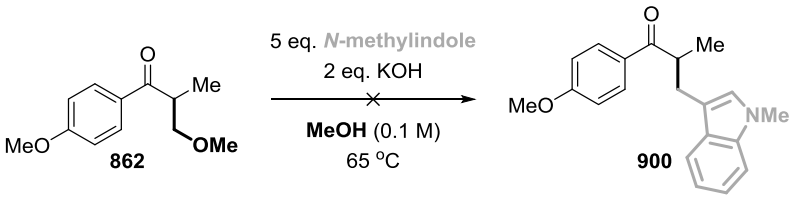
The conjugate addition of heterocycles would provide a useful addition to this reaction, allowing access to a range of β-heteroarylated ketones, which would not be available *via* alkylation with the corresponding alcohol, since this does not proceed for branched ketone formation.

Initial attempts at addition of a heteroaromatic species focussed on the use of indole as a nucleophile. Unfortunately, addition of indole to methanol adduct **863** did not proceed, even with 5 eq. indole and 2 eq. KOH at 65 °C. Similarly, the isopentyl methanol adduct **864** showed no conversion to the desired alkylated product. However, use of the less hindered methanol adduct **862** showed excellent conversion to the product, affording **899** in 82% yield (**Scheme 5.21**). Spectral analysis confirmed the product formed to be the *N*-alkylated product, due to the presence of both the indole C-2 and C-3 protons in the ^{1}H NMR spectrum at 7.14-7.09 ppm (m, due to overlap with other aromatic protons), and 6.49 ppm (dd, *J* 3.1, 0.6 Hz) respectively. Presumably, the lower reactivity of the bulkier methanol adducts **863** and **864** is as a result of steric hindrance, the larger side chains preventing close approach of the indole nucleophile.



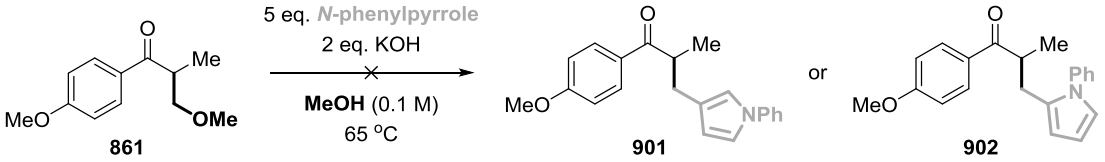
Scheme 5.21 *Conjugate addition of indole to methanol adducts* **862-864**

Although this was clearly a successful strategy for the less hindered methanol adduct **862**, we were keen to attempt the conjugate addition of a range of different heteroaromatic nucleophiles. In an effort to avoid *N*-alkylation, the reaction was now attempted with *N*-methylindole, using the unhindered methanol adduct **862**. Unfortunately, even over prolonged reaction times, no reaction was observed (**Scheme 5.22**).



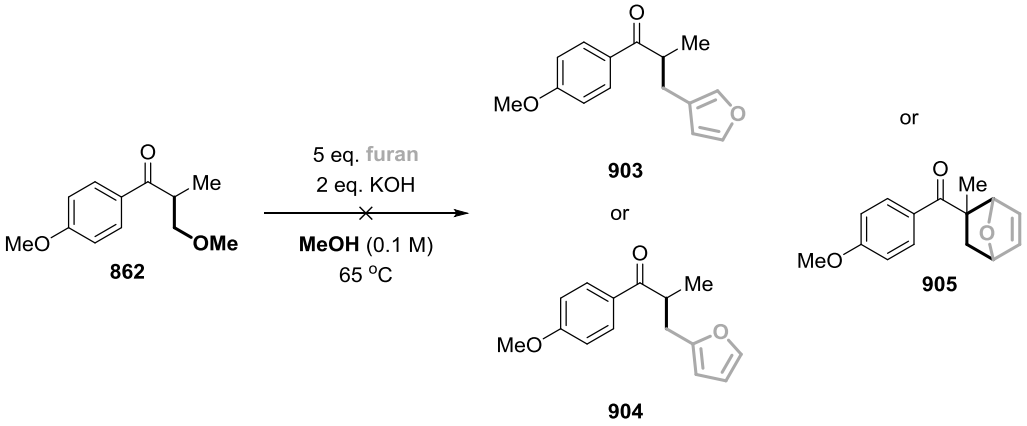
Scheme 5.22 *Attempted conjugate addition of N-methylindole to* **862**

Aside from indoles, the reaction was also attempted with *N*-phenylpyrrole, but again no reactivity was observed for this nucleophile (**Scheme 5.23**).



Scheme 5.23 *Attempted conjugate addition of N-phenylpyrrole to* **862**

Finally, furan was utilised as a nucleophile for the conjugate addition to methanol adduct **862**, in the expectation of forming either a normal conjugate addition product, with substitution at either C-2 or C-3 of furan to afford **903** or **904**, or the product of a formal Diels-Alder cycloaddition **905**. Unfortunately, once again, under the desired reaction conditions, no product formation was observed (**Scheme 5.24**).

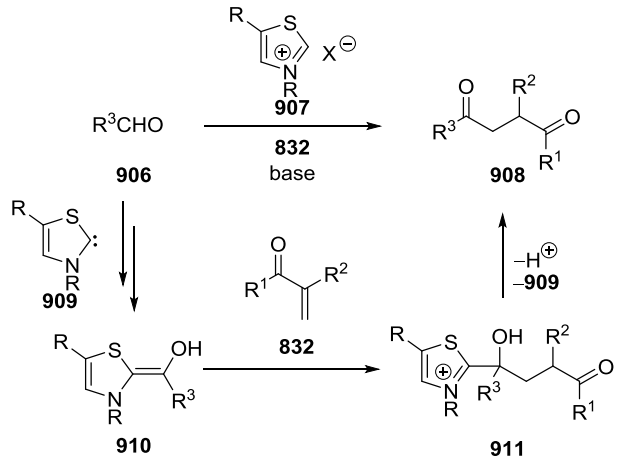


Scheme 5.24 *Attempted conjugate addition of furan to* **862**

The failure of other heteroaromatics to add in a conjugate addition reaction precluded further investigation into this area.

5.3.7 Conjugate addition of aldehydes

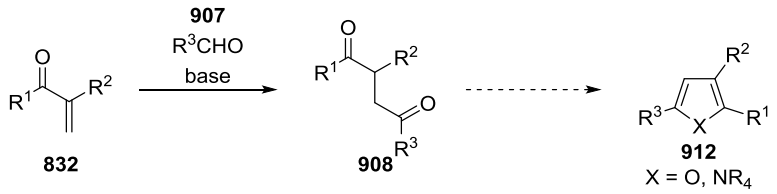
The carbene-catalysed conjugate addition of aldehydes, the Stetter reaction, provides an excellent method for the formation of 1,4-dicarbonyl compounds.[376] Typically, the reaction is promoted by a catalytic amount of a thiazolium salt **907**, which is deprotonated by the added base. Addition of the carbene **909** to the aldehyde **906**, forming the Breslow intermediate **910**, precedes conjugate addition to the enone **832**. Finally, elimination of the carbene **909** affords the 1,4-dicarbonyl product **908** (**Scheme 5.25**)



Scheme 5.25 *Stetter reaction of enones*

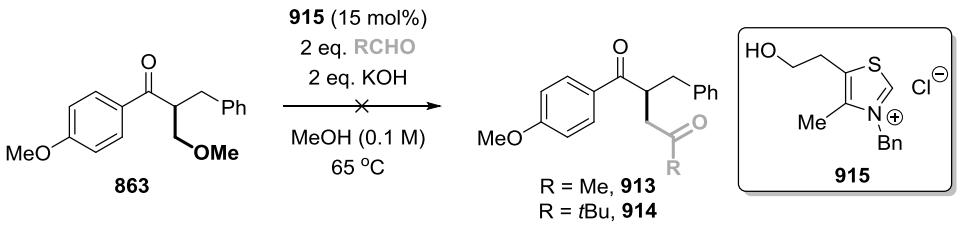
It was considered that a methylenation/Stetter reaction protocol would allow expeditious formation of a variety of substituted 1,4-dicarbonyl compounds, allowing access to furans

and pyrroles (**Scheme 5.26**), a topic which has been explored extensively in the Donohoe group.[377-379]



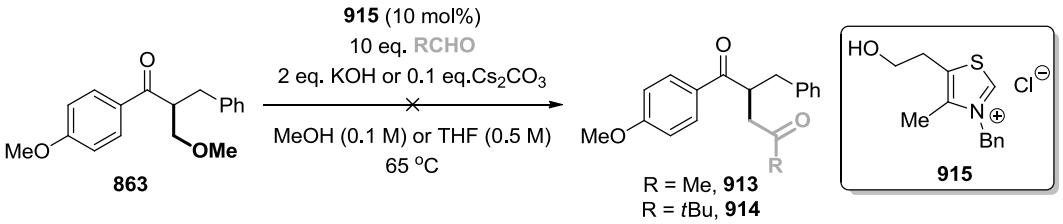
Scheme 5.26 *Potential methylenation/Stetter reaction route to furans and pyrroles*

To test the feasibility of this route for the formation of 1,4-dicarbonyl compounds, the Stetter reaction of methanol adduct **863** was initially tested using conditions modified from those developed by Ullrich and coworkers.[380] Treatment of **863** with 15 mol% thiazolium catalyst **915**, 2 eq. acetaldehyde and 2 eq. KOH in MeOH at 65 °C resulted in no observable formation of the desired product **913**. Similarly, the reaction with pivaldehyde (*t*BuCHO) afforded only returned starting material, as a mixture of enone **860** and methanol adduct **863** (**Scheme 5.27**). The reaction was also attempted at 0.2 M in EtOH to more closely mimic the conditions employed in the original publication, but unfortunately this also resulted in the observation of recovered starting material.



Scheme 5.27 *Attempted Stetter reaction of methanol adduct* **863** *using Ullrich's conditions*

The Stetter reaction of **863** was also attempted by modification of conditions reported by Kim and coworkers for the asymmetric Stetter reaction of acetaldehyde,[381] employing 10 eq. of aldehyde, either at a concentration of 0.1 M in MeOH, or 0.5 M in THF (as reported in the original publication). However, once again, this procedure only afforded recovered starting material (**Scheme 5.28**). Attempts at the use of catalytic Cs_2CO_3 as base instead of stoichiometric KOH also only resulted in the observation of recovered starting material.



Scheme 5.28 *Attempted Stetter reaction of methanol adduct* **863** *using Ryu's conditions*

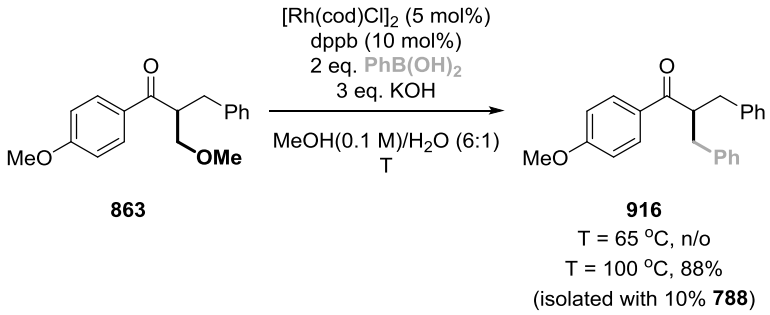
Unfortunately, it appeared in this case that conjugate addition of aldehydes would be challenging under the conditions required for methylenation, and thus we determined to focus our attention on other nucleophiles.

5.3.8 Conjugate addition of boronic acids

As previously discussed (**Chapter 4.3.3**), the alkylation of ketones with benzyl alcohol to form branched ketones is challenging, and is only known for cyclic ketones. We considered that α-benzylated branched ketones could however be formed by the addition of an aryl anion equivalent to an enone formed *via* a methylenation reaction. The rhodium-catalysed conjugate addition of boronic acids is a well-explored area for this process, allowing the addition of a range of boronic acids to enones and other α,β-unsaturated carbonyl derivatives in generally high yields.[382] Enantioselective variants of the reaction are also well-known, employing a wide variety of chiral ligands, including phosphines, phosphites, phosphoramidites, *N*-heterocyclic carbenes, bis-sulfoxides, and dienes.[382] However, under the conditions required for the methylenation reaction, it is unlikely that an asymmetric reaction would prove successful due to the possibility for racemisation *via* enolisation of the product under the basic conditions required.

The conjugate addition of $PhB(OH)_2$ was first attempted using conditions modified from those employed by Miyaura and coworkers,[383] and Balmer and coworkers,[384] employing 5 mol% $[Rh(cod)Cl]_2$ as catalyst, 10 mol% dppb ligand, 2 eq. $PhB(OH)_2$ and 3 eq. KOH, in a 6:1 $MeOH/H_2O$ mixture at 65 °C. Unfortunately, the reaction did not proceed for methanol adduct **863**, instead affording only recovered starting material as a mixture of enone **860** and methanol adduct **863** (**Scheme 5.29**). However, by conducting the reaction at 100 °C, the desired product **916** could be afforded as a mixture with the undesired methylated compound

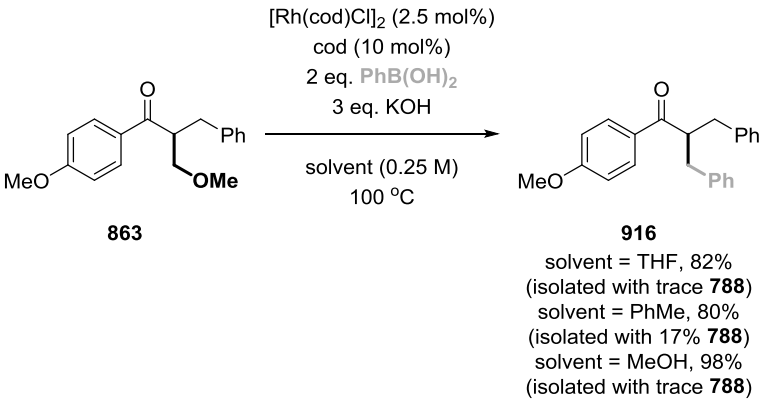
788 (88% and 10% yield respectively, calculated by integration of the ^{1}H NMR spectrum). The product could be identified by the presence of 2×2H double doublets in the ^{1}H NMR spectrum, at 3.14 and 2.81 ppm, corresponding to the diastereotopic benzylic protons of the two benzyl side chains. The presence of any of the methylated compound **788** at all suggests that $[Rh(cod)Cl]_2$/dppb is also capable of oxidising methanol under the reaction conditions, and the [Rh]-H species produced thus subsequently reducing enone **860**, a process which clearly needs to be minimised for high yields of the desired benzylated compound **916**. Limiting the formation of methylated compound **788** is also preferable from a practical perspective, as the similar polarity of **788** and **916** makes separation difficult, requiring lengthy purification by FCC, eluting with toluene.



Scheme 5.29 *Conjugate addition of $PhB(OH)_2$ to* **863**

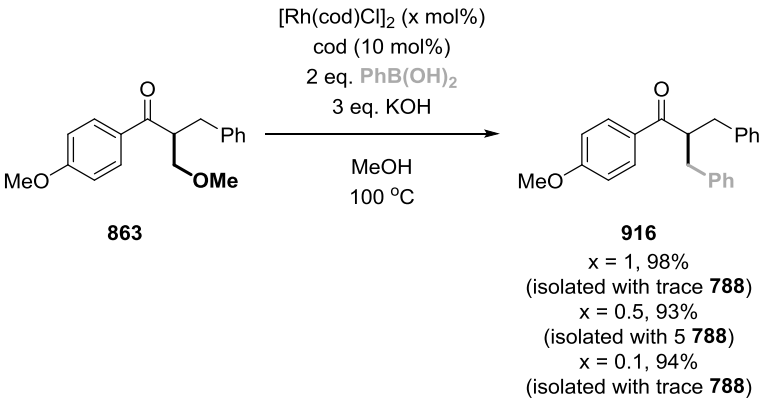
In exploring further conditions for the reaction, conditions utilised by Fioravanti and coworkers were attempted, as these represented one of the few examples of conjugate addition of an arylboronic acid to a 1,1-disubstituted alkene.[385] The reaction employed $[Rh(cod)Cl]_2$ (2.5 mol%) as catalyst, with extra added 1,5-cyclooctadiene (10 mol%), in THF or PhMe at 100 °C. Surprisingly, more of the methylated compound **788** was observed in this case, with 80% benzylated compound **916** and 17% methyl ketone **788** isolated as a mixture (**Scheme 5.30**). Given that the solvent employed in the reaction was toluene, the only source of methanol in the reaction could have resulted from elimination from adduct **863**, this seemed like a remarkably high activity for the oxidation of methanol to allow for nearly 20% of the isolated product to have arisen as a result of reduction of enone **860** rather than conjugate addition of boronic acid. Interestingly, attempting the reaction at 100 °C in MeOH

as solvent afforded the benzylated product **916** in near-quantitative yield, with only a trace of the methylated compound **788** observed by ^{1}H NMR.



Scheme 5.30 *Attempted conjugate addition of PhB(OH)$_2$ using Fioravanti's conditions*

Pleasingly, the loading of the [Rh(cod)Cl]$_2$ catalyst could be lowered for the conjugate addition reaction with no significant loss of activity. Indeed, even with catalyst loadings as low as 0.1 mol%, the bis-benzylated ketone **916** was still afforded in an excellent 94% yield, containing a trace amount of **788** (**Scheme 5.31**). However, conducting the reaction in the absence of [Rh(cod)Cl]$_2$ catalyst resulted in no conversion to the desired product, confirming that the presence of catalyst was required for the conjugate addition.

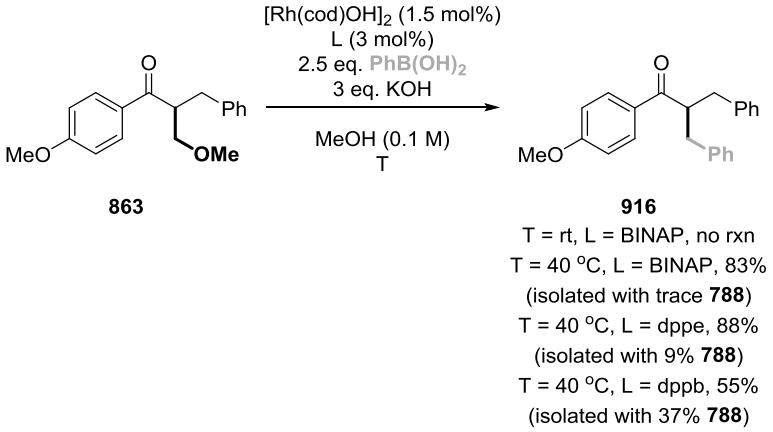


Scheme 5.31 *Lowering the loading of [Rh(cod)Cl]$_2$ for the conjugate addition of PhB(OH)$_2$*

Although this latter reaction clearly provided the desired compound in an excellent yield, the high temperature required for the reaction (significantly higher than the boiling point of MeOH) was undesirable. Therefore, conditions that would enable the addition of PhB(OH)$_2$ to occur at lower temperatures were sought. Hayashi and coworkers reported the use of the

hydroxorhodium(I) catalyst $[Rh(cod)OH]_2$ with diphosphine ligands for the room temperature addition of aryl boronic acids to enones.[386]

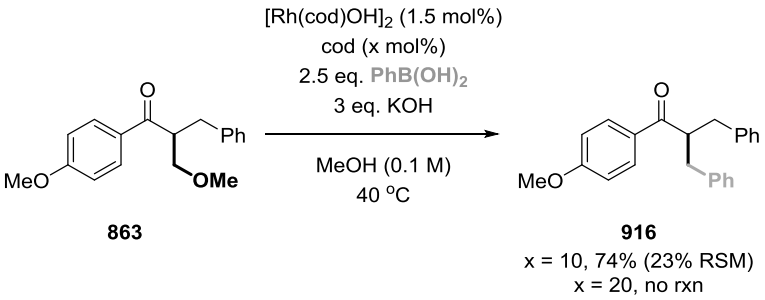
Treatment of methanol adduct **863** with 1.5 mol% $[Rh(cod)OH]_2$, 3 mol% (±)-BINAP**,** 2.5 eq. $PhB(OH)_2$ and 3 eq. KOH at room temperature showed no conversion to product **916** at all (**Scheme 5.32**). At this temperature, no reduction to the methylated ketone **788** was observed either, suggesting that methanol oxidation does not occur at this temperature. Increasing the reaction temperature to 40 °C afforded the desired benzylated ketone **916** in 83% yield after 18 h, with only a trace observed of the methylated ketone by ^{1}H NMR. Exchanging (±)-BINAP for the simple chelating phosphine dppe afforded the benzylated ketone **916** in 88% yield, as a mixture with 9% of the methylated ketone **788**. In the absence of added ligand, the reaction did not proceed at all. Interestingly, the use of dppb as ligand increased the ratio of methylated product substantially, affording benzylated ketone **916** in 55% yield, as a mixture with 37% methylated ketone **788**.



Scheme 5.32 *Lowering the reaction temperature for the conjugate addition of $PhB(OH)_2$*

Hayashi and coworkers had also reported that replacing phosphine ligands with diene ligands led to an increase in catalytic activity for the rhodium-catalysed conjugate addition of boronic acids, due to faster transmetallation with the boronic acid.[387] Modification of the reaction conditions to include 10% 1,5-cyclooctadiene rather than 3% diphosphine ligand afforded 74% of the benzyl ketone **916** after 48 hours, although still containing 23% of recovered starting material **863** (**Scheme 5.33**). Increasing the loading of 1,5-cyclooctadiene to 20 mol% resulted in complete retardation of the reaction, resulting in only recovery of starting

material. Presumably, increasing the concentration of 1,5-cyclooctadiene results in a higher degree of coordination to Rh, and thus prevents efficient transmetallation from boron to Rh.

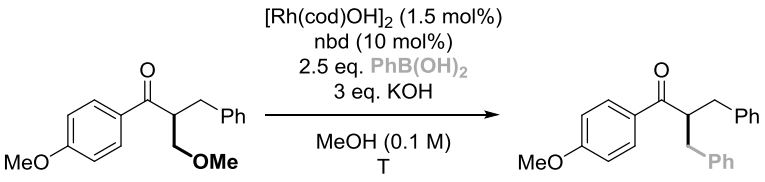


863 **916**

x = 10, 74% (23% RSM)
x = 20, no rxn

Scheme 5.33 *Use of diene ligands for the conjugate addition of PhB(OH)$_2$*

Replacement of 1,5-cyclooctadiene with the bicyclic diene norbornadiene (nbd) afforded the benzylated ketone **916** in quantitative yield after 48 h (**Scheme 5.34**). At higher temperatures, the yield of benzylated ketone **916** was found to decrease, and the yield of methylated ketone **788** increase slightly, suggesting that at lower temperatures, methanol oxidation does not occur with the [Rh(cod)OH]$_2$/nbd complex formed *in situ*.

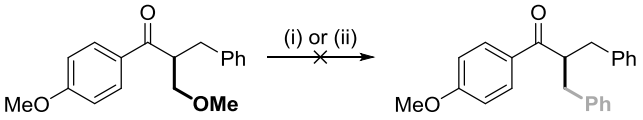


863 **916**

T = 40 °C, quant
T = 65 °C, 88%
(isolated with 9% **788**)
T = 100 °C, 79%
(isolated with 12% **788**)

Scheme 5.34 *Effect of temperature on the addition of PhB(OH)$_2$ with nbd as ligand*

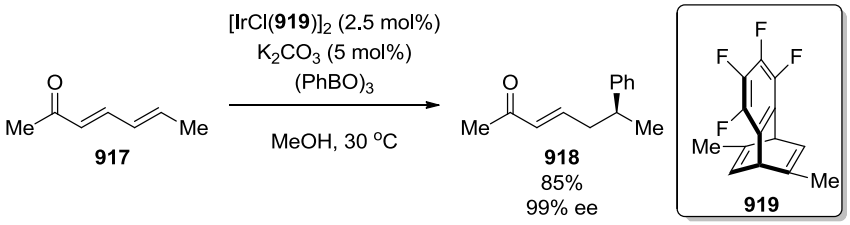
A number of other conditions were also tested for the low temperature addition of PhB(OH)$_2$. Yu and coworkers reported the use of Wilkinson's catalyst (RhCl(PPh$_3$)$_3$) as an efficient catalyst for the room temperature addition of boronic acids to 1,1-disubstituted enones.[388] However, treatment of methanol adduct **863** under these conditions resulted in the observation of recovered starting material (**Scheme 5.35**). Similarly, using Miyaura's original conditions of 3 mol% Rh(acac)(CO)$_2$/dppb to promote the reaction afforded only recovered starting material at 50 °C.



863 **916**

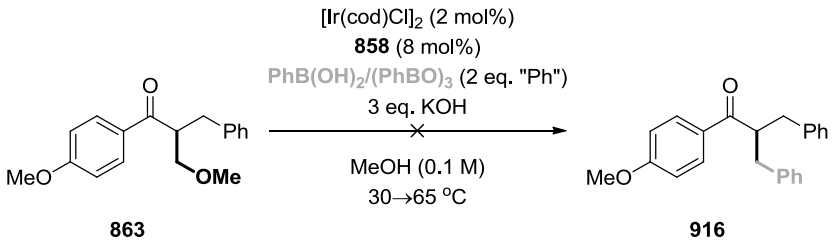
Scheme 5.35 *Attempted low temperature conjugate additions of PhB(OH)$_2$ to* **863**
Conditions: (i) RhCl(PPh$_3$)$_3$ (5 mol%), 2 eq. PhB(OH)$_2$, 3 eq. KOH, MeOH (0.1 M), rt
(ii) Rh(acac)(CO)$_2$ (3 mol%), dppb (3 mol%), 2 eq. PhB(OH)$_2$, 3 eq. KOH, MeOH (0.1 M), rt

We also considered that if the conjugate addition reaction could be conducted using $[Ir(cod)Cl]_2$ instead of a [Rh^I] catalyst, this would simplify the reaction considerably, allowing for the use of only one transition metal catalyst. In 2006, Hayashi and coworkers reported the [Ir^I]-catalysed 1,6-addition of boroxines to dienones in MeOH,[389] later using chiral dienes to promote asymmetric addition, although no 1,4-addition was observed (**Scheme 5.36**).[390]



Scheme 5.36 *Hayashi's asymmetric 1,6-addition of boroxines to dienones*

However, subjecting methanol adduct **863** to similar conditions using $[Ir(cod)Cl]_2$, including CataCXium A **858** (included since it would be present in the methylenation reaction), afforded none of the desired product, either with $PhB(OH)_2$ or the corresponding boroxine, at 30 °C or at elevated temperatures (**Scheme 5.37**).



863 **916**

Scheme 5.37 *Attempted [Ir(cod)Cl]$_2$-catalysed conjugate addition of PhB(OH)$_2$/(PhBO)$_3$*

Nevertheless, despite the failure to promote conjugate addition with an [Ir^I] catalyst, we considered that there were now a number of conditions under which to attempt the one-pot methylenation/conjugate addition of boronic acids for the formation of benzylated ketones directly from the ketone.

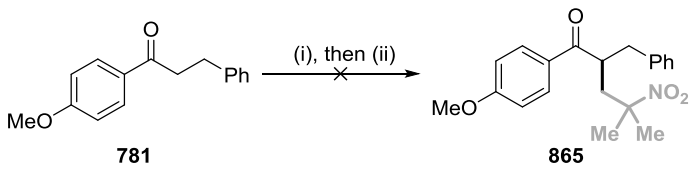
5.4 One-pot methylenation/conjugate addition reactions

With conditions in hand for the conjugate addition of a variety of different nucleophiles to the products of methylenation, it remained to develop one-pot methods for the formation of the conjugate addition products from the starting ketone.

5.4.1 Initial attempts at one-pot methylenation/conjugate addition

5.4.1.1 One-pot methylenation/nitronate anion addition

Initially, in an attempt to conduct a one-pot methylenation/conjugate addition reaction, *p*-methoxyphenyl ketone **781** was methylenated under the conditions previously developed, and upon completion of the first step, 2 eq. 2-nitropropane and a further 2 eq. KOH were added to the reaction vessel, which was resealed, and heated at 65 °C for a further 24 hours. Unfortunately, crude ^{1}H NMR analysis revealed only the presence of intermediates enone **860** and methanol adduct **863**, and only a trace of the desired product (**Scheme 5.38**).

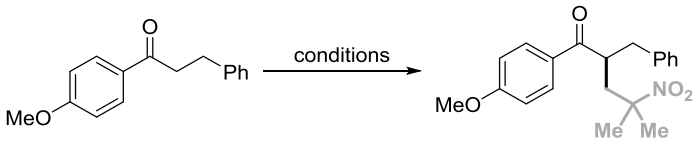


781 865

Scheme 5.38 *Attempted one-pot methylenation/conjugate addition of 2-nitropropane*
Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h*
(ii) 2 eq. iPrNO$_2$, 2 eq. KOH, 65 °C, 24 h

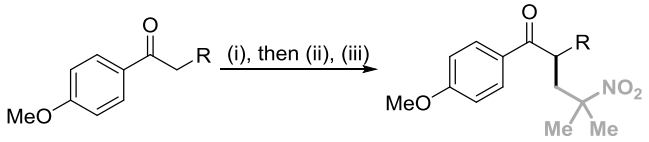
It was proposed that an excess of formaldehyde (or a related species) present in the reaction flask was preventing further reaction by reacting with the nitronate anion before it could add to the enone **860**. An initial attempt to circumvent this was made by diluting the reaction mixture and filtering it through SiO_2 before concentrating the reaction, and redissolving the crude residue in MeOH. Adopting this process afforded the desired product **865** in 72% yield (**Scheme 5.39**). In an attempt to maintain the possibility of a one-pot process, it was also considered that sonication of the crude reaction mixture after the methylenation step might promote the removal of any species preventing reaction. Pleasingly, sonicating the reaction open to the air for 15 minutes prior to addition of 2-nitropropane and KOH resulted in the formation of **865** in 72% yield, matching the yield formed *via* the filtration method.

Therefore, it did seem that conduction of a one-pot methylenation/conjugate addition protocol would indeed be a feasible process.



Scheme 5.39 *Attempted one-pot methylenation/conjugate addition of 2-nitropropane*
Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) dilute with Et_2O, filter (SiO_2) (iii) sonicate for 15 mins(iv) 2 eq. iPrNO$_2$, 2 eq. KOH, 65 °C, 24 h*

Given the success of this protocol in affording the nitroalkylated product **865** in good yield in a two-step, one-pot process, this procedure was then extended to other *p*-methoxyphenyl ketones (**Scheme 5.40**). Exposure of ethyl ketone **758** and long chain ketone **782** to the methylenation/conjugate addition afforded the corresponding products **920** and **866** in 90% and 77% yield respectively.



R = Me, **758**
R = CH_2CH_2*i*Pr, **782**

R = Me, **920**, 90%
R = CH_2CH_2*i*Pr, **866,** 77%

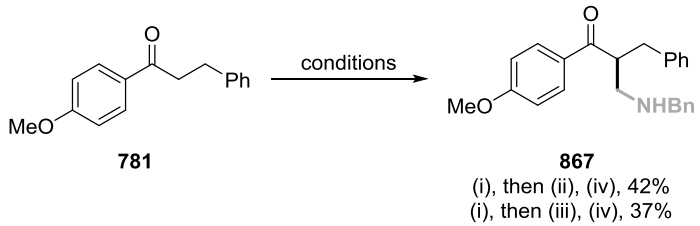
Scheme 5.40 *Attempted one-pot methylenation/conjugate addition of 2-nitropropane*
Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) sonicate for 15 mins (iii) 2 eq. iPrNO$_2$, 2 eq. KOH, 65 °C, 24 h*

With the successful application of a one-pot protocol for conjugate addition of 2-nitropropane subsequent to methylenation now developed, it now became worthwhile to apply the same technique for the conjugate addition of other nucleophiles.

5.4.1.2 One-pot methylenation/amine conjugate addition

The conjugate addition of benzylamine was then attempted as part of a one-pot protocol. As with 2-nitropropane, addition of benzylamine did not proceed to afford the desired product **867** if the amine was added immediately to the crude methylenation reaction mixture (**Scheme 5.41**). Dilution of the reaction mixture with Et_2O and filtration of the reaction mixture through SiO_2 before addition of benzylamine did afford the product, however in only

42% yield. Attempted addition of benzylamine after sonication also only afforded the desired aminated product **867** in 37% after 18 hours.



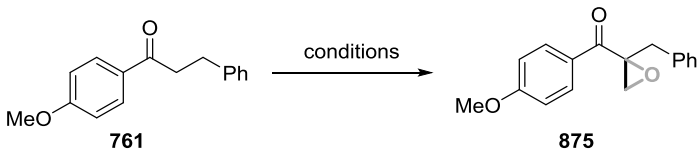
781 **867**
(i), then (ii), (iv), 42%
(i), then (iii), (iv), 37%

Scheme 5.41 *Attempted one-pot methylenation/conjugate addition of benzylamine*
Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h*
(ii) dilute with Et_2O, filter (SiO_2) (iii) sonicate for 15 mins (iv) 5 eq. $BnNH_2$, 2 eq. KOH, 65 °C, 24 h

The poor results under these conditions suggest that there is an additional problem in addition to the proposed removal of volatiles such as formaldehyde in the addition of benzylamine, since 2-nitropropane added in good yield under the same conditions.

5.4.1.3 One-pot methylenation/epoxidation

We then turned to the application of the epoxidation conditions previously developed for methanol adducts **863** and **864** for a one-pot methylenation/epoxidation protocol. Addition of 2 eq. 70% aq. TBHP and 2 eq. Triton B after removal of MeOH, dilution with Et_2O and filtration through a short pad of SiO_2 afforded the corresponding epoxidised product **875** in 75% yield over two steps (**Scheme 5.42**). However, addition of the epoxidation reagents directly after sonication of the crude reaction mixture afforded only trace conversion to the desired product **875**. This is not a surprising result, since transition metals are well-known to catalyse the decomposition of peroxides, and as such it is likely that very little TBHP would be present in the solution, thus we hypothesised that any iridium species present in solution may inhibit the reaction.



761 **875**
(i), then (ii), (iv), 75%
(i), then (iii), (iv), trace

Scheme 5.42 *Attempted one-pot methylenation/conjugate addition of 2-nitropropane*
Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h*
(ii) dilute with Et_2O, filter (SiO_2) (iii) sonicate for 15 mins (iv) 2 eq. TBHP, 2 eq. Triton B, 65 °C, 24 h

It was clear therefore, along with the results obtained for the methylenation/amination of **781** (**Scheme 5.41**), that for a one-pot reaction to be feasible for these processes, that it would be desirable to remove iridium from solution, and thus prevent it from inhibiting the conjugate addition reaction performed subsequent to methylenation.

5.4.2 Functionalised SiO_2 for metal scavenging

At this juncture, we became aware of the possibility of the use of functionalised SiO_2 particles or polymer resins for the scavenging of transition metals in solution. These particles are generally utilised for the removal of metal particles during purification processes where high purity and low concentrations of metal are required in the product, e.g. in the purification of pharmaceutical lead compounds.[391] However, we considered that it might be possible to scavenge iridium from solution after the initial methylenation step, thus allowing for the second conjugate addition step to proceed without the metal interfering significantly in this step.

5.4.2.1 Screening of scavenger particles

After a brief survey of commercially available scavenger particles, we initially decided to test the efficiency of the range of functionalised SiO_2 particles developed by Silicycle (**Figure 5.3**).[392,393]

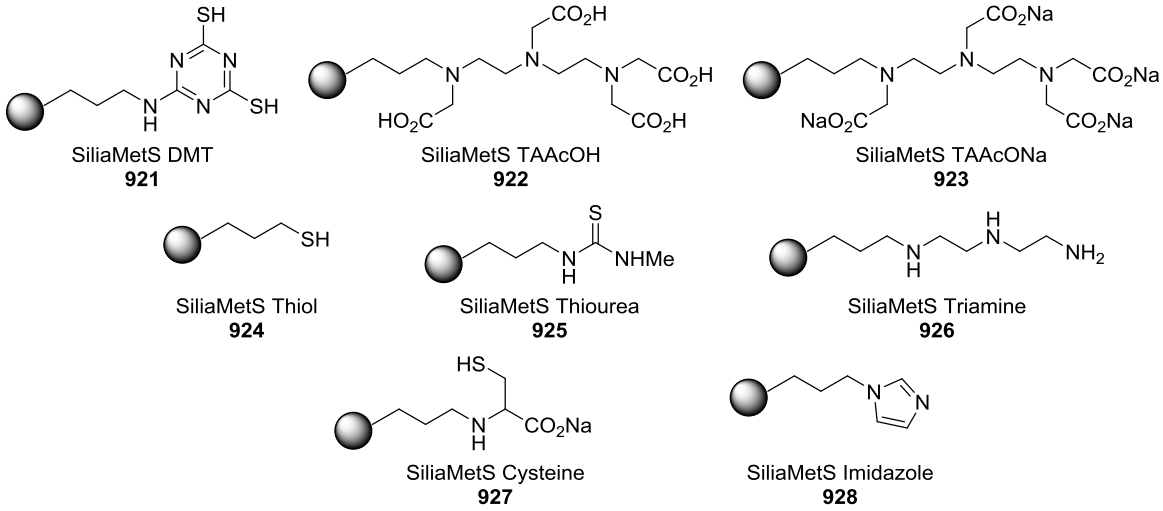
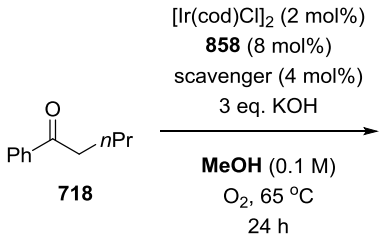


Figure 5.3 *Functionalised SiO_2 particles for metal scavenging*

These scavengers are functionalised with a range of different metal-scavenging groups, and have significant selectivity for a range of metals, as well as reported stability at high pH

values in organic solvents, as would be the case following a methylenation reaction containing 3 eq. KOH.

To determine whether any of these scavengers were indeed capable of removing iridium from solution, we conducted test reactions where $[Ir(cod)Cl]_2$ (2 mol%), CataCXium A **858** (8 mol%), 3 eq. KOH and the starting ketone **718** were stirred at room temperature for 2 hours with 8 mol% of the scavenger, prior to the addition of O_2 and heating at 65 °C for 24 hours. Conversion was then measured by ^{1}H NMR of the crude reaction mixture to determine the effectiveness of each particle (**Table 5.3**).



Entry	Scavenger	Conversion (%)[a]
1	SiliaMetS DMT **921**	<5
2	SiliaMetS TAAcOH **922**	10
3	SiliaMetS TAAcONa **923**	60
4	SiliaMetS Thiol **924**	10
5	SiliaMetS Thiourea **925**	10
6	SiliaMetS Triamine **926**	10
7	SiliaMetS Cysteine **927**	35
8	SiliaMetS Imidazole **928**	15

Table 5.3 *Screening of SiliaMetS functionalised silica particles*
[a] Measured by ^{1}H NMR

The dimercaptotriazole-capped scavenger SiliaMetS DMT (**921**) showed only trace conversion of starting ketone **718** under the standard methylenation conditions after 24 h (**Entry 1**). The triaminetetraacetic acid functionalised particle SiliaMetS TAAcOH **922** showed only minimal conversion (10%) after 24 h (**Entry 2**), whereas the corresponding sodium salt SiliaMetS TAAcONa **923** showed considerable conversion of 60% after 24 h, suggesting that the sodium salt was less well able to bind iridium (**Entry 3**). Low conversion of approximately 10% was also observed for the thiol, thiourea and triamine functionalised SiO_2 particles **924**, **925** and **926** (**Entries 4-6**). The cysteine functionalised scavenger, SiliaMetS Cysteine **927** (containing the sodium salt of cysteine), again showed an increased

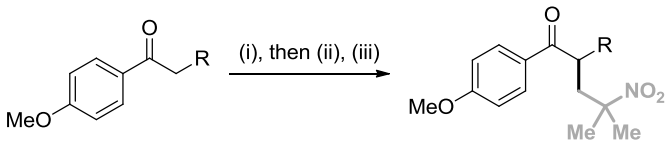
conversion of 35% after 24 h, suggesting that sodium carboxylates are poor binding residues for iridium (**Entry 7**). Finally, the imidazole functionalised scavenger, SiliaMetS Imidazole **928** showed low conversion, with 15% of ketone **718** reacted after 24 h (**Entry 8**).

The results of this screening therefore suggested that the addition of the dimercaptotriazole-capped SiO_2 particle, SiliaMetS DMT **921**, could prove an efficient method for the scavenging of iridium after the initial methylenation step. We therefore turned our attention to developing a one-pot methylenation/scavenging/conjugate addition protocol for the range of nucleophiles previously investigated.

5.4.2.2 One-pot methylenation/scavenging/conjugate addition

With conditions for efficient iridium scavenging in hand, we were hopeful that this procedure would now be applicable to a one-pot methylenation/conjugate addition reaction, since scavenging of iridium should prevent any further reaction that would prove detrimental to the subsequent conjugate addition.

To observe if the addition of **928** would improve the yield of the conjugate addition of 2-nitropropane, *p*-methoxyphenyl ketone **781** was subjected to the standard methylenation conditions, followed by the addition of 16 mol% SiliaMetS DMT **921** (to ensure complete scavenging), and stirring for 1 h at room temperature prior to the addition of 2 eq. *i*PrNO$_2$ and 2 eq. KOH (**Scheme 5.43**).



R = Bn, **781**
R = CH_2CH_2*i*Pr, **782**
R = Me, **758**

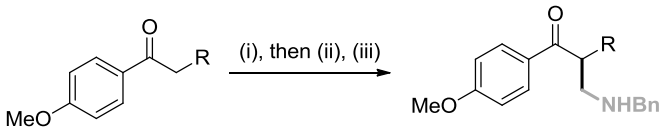
R = Bn, **865**, 94%
R = CH_2CH_2*i*Pr, **866**, 84%
R = Me, **920**, 90%

Scheme 5.43 *One-pot methylenation/conjugate addition of 2-nitropropane*
Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) SiliaMetS DMT* **921** *(16 mol%), rt, 1 h (iii) 2 eq. iPrNO$_2$, 2 eq. KOH, 65 °C, 14-20 h*

Pleasingly, this protocol afforded the corresponding conjugate addition product **865** in an excellent 94% yield, suggesting that the presence of iridium had previously played some role in diminishing the yield of the reaction, perhaps due to the continued oxidation of methanol

under the reaction conditions. This procedure could also be applied to the long chain ketone **782**, and the ethyl ketone **758**, affording the desired nitroalkylated products **866** and **920** in 84% and 90% yield respectively, in a one-pot, two-step process.

With the successful improvement of yield for the conjugate addition of 2-nitropropane, we were also hopeful that this protocol would be applicable to the other conjugate additions investigated. Methylenation/amination of ketone **781** with benzylamine under the newly developed conditions of iridium scavenging afforded the desired aminoalkylated product **867** in a good yield of 60% over the two steps for the reaction (**Scheme 5.44**).



R = Bn, **781**
R = CH_2CH_2*i*Pr, **782**

R = Bn, **867**, 60%
R = CH_2CH_2*i*Pr, **868**, 60%

Scheme 5.44 *One-pot methylenation/conjugate addition of benzylamine*
Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) SiliaMetS DMT* **921** *(16 mol%), rt, 1 h (iii) 5 eq. $BnNH_2$, 2 eq. KOH, 65 °C, 14-18 h*

Although this yield was still considerably lower than for the isolated conjugate addition to methanol adduct **863**, it was at least a considerable improvement on the previously-attempted one-pot reaction, where very little reactivity had been observed at all. The long chain ketone **782** was also subjected to the one-pot protocol, again affording the desired aminated product **868** in 60% yield.

As an extension to the aminoalkylation of the ketones **781** and **782**, the conjugate addition of indole was also attempted subsequent to the methylenation reaction. Unfortunately, as was expected to be the case after the failure of the conjugate addition on methanol adducts **863** and **864**, the desired conjugate addition products **897** and **898** were not observed after the attempted addition of indole in a one-pot methylenation/conjugate addition, with only enones **860** and **861** and methanol adducts **863** and **864** observed by ^{1}H NMR of the crude reaction mixture. However, we were pleased to observe that methylenation/conjugate addition of indole to the ethyl ketone **758** afforded the product **899** in 80% yield in the one-pot protocol (**Scheme 5.45**).

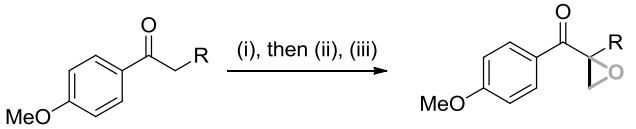


R = Bn, **781**
R = CH_2CH_2*i*Pr, **782**
R = Me, **758**

R = Bn, **897**, n/o
R = CH_2CH_2*i*Pr, **898**, n/o
R = Me, **899**, 80%

Scheme 5.45 *One-pot methylenation/conjugate addition of indole*
Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h*
(ii) SiliaMetS DMT **921** *(16 mol%), rt, 1 h (iii) 5 eq. indole, 2 eq. KOH, 65 °C, 15 h*

For the one-pot methylenation/epoxidation reaction, *p*-methoxyphenyl ketone **781** was exposed to the standard methylenation conditions, stirred for 2 hours at room temperature with 16 mol% SiliaMetS DMT **921**, and then 2 eq. 70% aq. TBHP and 2 eq. Triton B were added, and the reaction subsequently stirred for 24 hours. Disappointingly, conversion was still very low for the desired epoxide **875**, with less than 20% of the mixture observed by ^{1}H NMR of the crude reaction mixture comprising **875**, the remainder of which was the enone **860** and methanol adduct **863**. This result suggested that either the scavenger interfered with the epoxidation process by reaction with TBHP, or that iridium was not completely removed from the solution, and was subsequently still catalysing the decomposition of TBHP under the reaction conditions. Disappointingly, increasing the equivalents of TBHP and Triton B to 5 eq. each still resulted in only low conversion to product **875**. However, increasing the equivalents further to 10 eq. TBHP and Triton B resulted in the formation of the desired epoxide **875** in 81% yield (**Scheme 5.46**). Similarly, the long chain ketone **782** could be methylenated and epoxidised in one-pot under these reaction conditions in 89% yield, thus demonstrating the potential for epoxide formation on a range of substrates under these conditions, although it is clear that the scavenger was not as effective for the epoxidation reaction.



R = Bn, **781**
R = CH_2CH_2*i*Pr, **782**

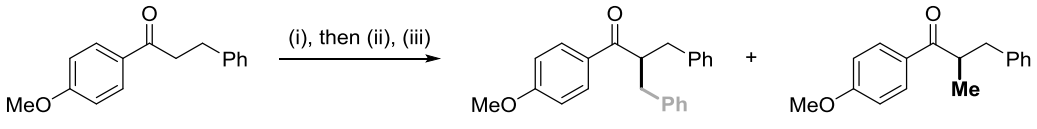
R = Bn, **875**, 81%
R = CH_2CH_2*i*Pr, **876**, 89%

Scheme 5.46 *One-pot methylenation/conjugate addition of indole*
Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h*
(ii) SiliaMetS DMT **921** *(16 mol%), rt, 1 h (iii) 10 eq. TBHP, 10 eq. Triton B, rt, 15 h*

5.4.3 One-pot methylenation/conjugate addition of boronic acids

Following on from the successful one-pot addition of nitronate anions, amines, and epoxidation, we were keen to explore the Rh-catalysed addition of boronic acids in this context, as we considered that this would allow the formation of a wide range of alkylated ketones, depending on the choice of boronic acid, allowing the formation of products that would not be possible *via* hydrogen borrowing alkylation reactions of alcohols.

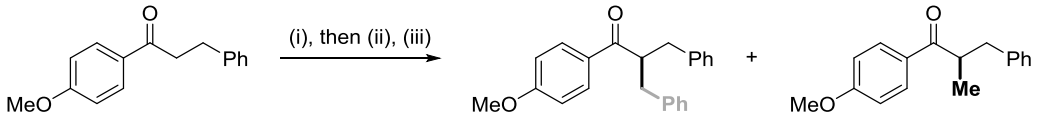
Treatment of ketone **781** under the typical methylenation conditions, followed by addition of 4 mol% SiliaMetS DMT **921** (to avoid scavenging of rhodium), and subsequent addition of $[Rh(cod)OH]_2$ (1.5 mol%), (±)-BINAP (3 mol%), 2.5 eq. $PhB(OH)_2$ and 3 eq. KOH, heated to 40 °C for 18 hours afforded the desired benzylated ketone **916** in 49% yield, as a mixture with 45% yield of methylated ketone **788** (**Scheme 5.47**). This result was somewhat surprising, given that the benzylated ketone **916** was formed in 83% yield when the conjugate addition step was conducted on its own under the same conditions.



781 **916** 49% **788** 45%

Scheme 5.47 *Attempted one-pot methylenation/conjugate addition of $PhB(OH)_2$*
Conditions: (i) $[Ir(cod)Cl]_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) SiliaMetS DMT* **921** *(4 mol%), rt, 1 h (iii) $[Rh(cod)OH]_2$ (1.5 mol%), (±)-BINAP (3 mol%), 2.5 eq. $PhB(OH)_2$, 3 eq. KOH, 40 °C, 24 h*

This result seemed somewhat confusing, but suggested that the SiliaMetS DMT **921** was perhaps having an effect on the reaction, or some other combination of the metal catalysts and ligands (due to incomplete scavenging) was affecting the course of the reaction. To test whether the presence of scavenger was inhibiting the conjugate addition reaction, the reaction was carried out without the presence of SiliaMetS DMT **912**, instead sonicating the reaction for 15 minutes prior to the addition of the reagents for the boronic acid conjugate addition. In this case, the result was broadly similar, with the benzylated ketone **916** afforded in 46% yield, and the corresponding reduced ketone **788** isolated in 54% yield (**Scheme 5.48**).



781 **916** 46% **788** 54%

Scheme 5.48 *Attempted one-pot methylenation/conjugate addition of PhB(OH)$_2$*
Conditions: (i) [Ir(cod)Cl]2 (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O2, 65 °C, 48 h (ii) sonicate for 15 mins (iii) [Rh(cod)OH]2 (1.5 mol%), (±)-BINAP (3 mol%), 2.5 eq. PhB(OH)$_2$, 3 eq. KOH, 40 °C, 24 h*

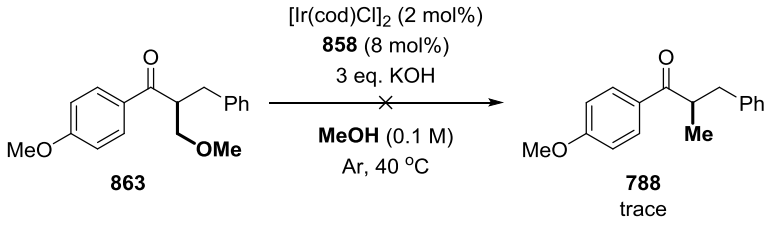
This latter result suggested that the presence of scavenger had little effect on this reaction. One potential issue was that the low loading of scavenger added (1:1 Ir:**921** ratio), in order to avoid scavenging any rhodium, since SiliaMetS DMT **921** is also known to scavenge rhodium efficiently, resulted in inefficient scavenging, and thus a considerable amount of iridium presence in the reaction mixture. However, this process did represent the possibility of performing the reduction of enones at low temperature, and perhaps therefore improving the previously developed conditions for methylation.

5.4.3.1 Potential for low-temperature methylation

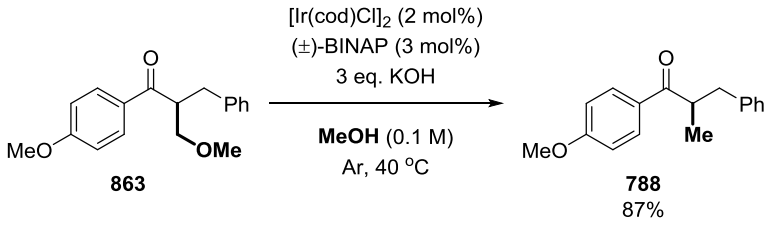
To investigate the cause of low temperature reduction of enone **860** to form methylated ketone **788**, a number of different control experiments were conducted. Treatment of methanol adduct **863** with [Ir(cod)Cl]$_2$ (2 mol%), CataCXium A **858** (8 mol%) and 3 eq. KOH in MeOH (0.1 M) under argon at 40 °C resulted in only trace conversion to the corresponding methylated ketone **788** (**Scheme 5.49a**).

However, use of 3 mol% (±)-BINAP as ligand resulted in near complete reduction to the methylated ketone **788**, affording **788** in 87% yield, along with 12% recovered starting material **863** (**Scheme 5.49b**). Finally, the combination of [Rh(cod)OH]$_2$ and CataCXium A **858** was observed to be ineffective at promoting reduction under the reaction conditions (**Scheme 5.49c**). Thus, it appeared that the combination of [Ir(cod)Cl]$_2$ and (±)-BINAP was at least partially responsible for the observed reduction under the reaction conditions.

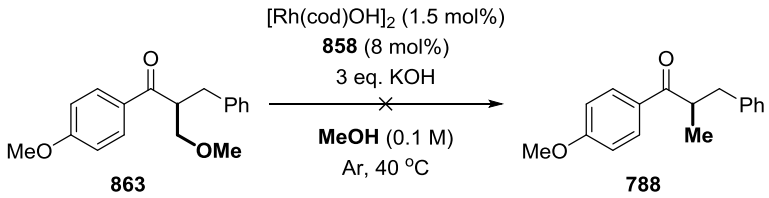
(a) Combination of $[Ir(cod)Cl]_2$ and **858**



(b) Combination of $[Ir(cod)Cl]_2$ and (±)-BINAP

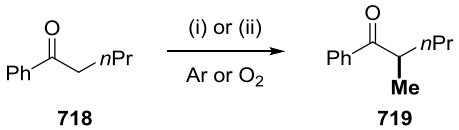


(c) Combination of $[Rh(cod)OH]_2$ and **858**



Scheme 5.49 *Determining the source of reduction in the conjugate addition of $PhB(OH)_2$*

With clear conditions for the reduction of methanol adduct **863** to the methylated ketone **788** (*via* enone **860**), we then considered that it thus might be possible to perform the methylation of ketones at a lower temperature. Since partial reduction had also previously been observed with both $[Rh(cod)OH]_2$/(±)-BINAP and $[Ir(cod)Cl_2]_2$/(±)-BINAP, under Ar or under O_2 (O_2 had shown a beneficial effect previously in the methylation reaction), were employed for the attempted methylation of valerophenone **718** (**Scheme 5.50**).



(i), O_2 - 15% conversion[a]
(i), Ar - 10% conversion[a]
(ii), O_2 - 20% conversion[a]
(ii) Ar - 15% conversion[a]

Scheme 5.50 *Attempted low temperature methylation of valerophenone* **718**
Conditions: (i) $[Ir(cod)Cl]_2$ (2 mol%), (±)-BINAP (4 mol%) 3 eq. KOH, MeOH (0.1 M), 40 °C, 48 h
(ii) $[Rh(cod)OH]_2$ (1.5 mol%), (±)-BINAP (3 mol%) 3 eq. KOH, MeOH (0.1 M), 40 °C, 48 h
[a] Conversion measured by ^{1}H NMR of the crude reaction mixture

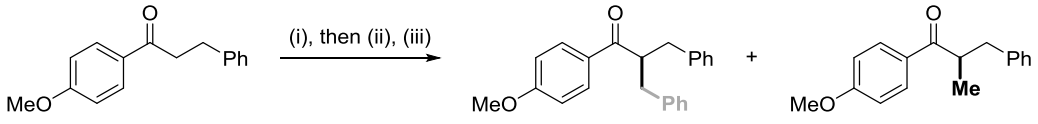
Unfortunately, in both cases, approximately 20% conversion of starting ketone **718** to methylated ketone **719** was observed by ^{1}H NMR of the crude reaction mixture after 48 h.

This suggests that although methanol oxidation occurs under these reaction conditions, and enone reduction, that the limiting step at this temperature is the aldol reaction for the formation of enone, which was unfortunately too slow.

Unfortunately, the attempted low temperature methylation did not proceed efficiently at 40 °C, but this area had at least showed the potential for reduction at relatively low temperatures, opening up the possibility for an asymmetric reduction of enones in future.

5.4.3.2 Further attempts at one-pot methylenation/boronic acid addition

Following on from the failure to perform the boronic acid addition at 40 °C with (±)-BINAP as ligand, the reaction was also attempted with norbornadiene as ligand. Since it appeared that the scavenger resin **921** was having an unusual effect on the course of the reaction, subsequent reactions were carried out in the absence of scavenger. Thus, methylenation of ketone **781**, followed by addition of $[Rh(cod)OH]_2$ (1.5 mol%), nbd (10 mol%), 2.5 eq. $PhB(OH)_2$, and 3 eq. KOH afforded the desired benzylated ketone **916** in a unsatisfactory 37% yield, as a mixture with 57% of methylated ketone **788** (**Scheme 5.51**).



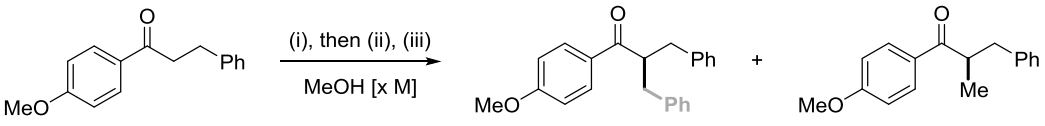
788 | **916** 37% | **788** 57%

Scheme 5.51 *Attempted one-pot methylenation/conjugate addition of $PhB(OH)_2$*
Conditions: (i) $[Ir(cod)Cl]_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) sonicate for 15 mins (iii) $[Rh(cod)OH]_2$ (1.5 mol%), nbd (10 mol%), 2.5 eq. $PhB(OH)_2$, 3 eq. KOH, 40 °C, 24 h*

It was clear therefore that it was not just the addition of (±)-BINAP that resulted in the reduction of enone **860**, formed during the methylenation step, to the methylated ketone **788**. We considered, therefore, that it may not be feasible to conduct the methylenation/boronic acid addition at low temperatures, and determined to investigate the high temperature conditions also developed, in the hope that the rate of boronic acid addition would be sufficiently fast under these conditions to out-compete reduction.

However, the conditions developed for reaction in MeOH at 100 °C showed optimal reactivity at a concentration of 0.25 M, whereas the methylenation reaction was conducted at

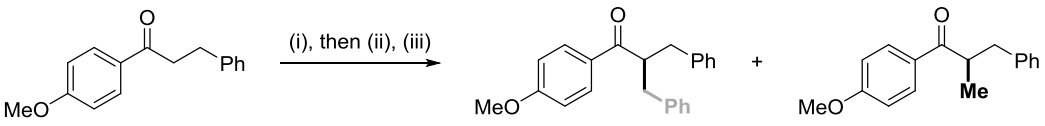
0.1 M. Therefore, it was necessary to concentrate the reaction mixture between the methylenation step and boronic acid addition steps. This was achieved by bubbling argon through the solution until the desired concentration was reached, at which time the subsequent reagents were added. Thus, methylenation of **781**, concentration to 0.25 M, and addition of $[Rh(cod)Cl]_2$ (2.5 mol%), 1,5-cyclooctadiene (10 mol%), 2 eq. $PhB(OH)_2$ and 3 eq. KOH and heating to 100 °C, afforded benzylated ketone **916** in 62% yield, as a mixture with 21% of methylated ketone **788** (**Scheme 5.52**). To discern if there was a significant effect of concentration on the progress of the reaction, the reaction was also concentrated to 0.5 M. However, this resulted in a significantly increased yield of methylated ketone, with 77% of **788** isolated and only 12% of benzylated ketone **916**.



781		916	788
	x = 0.25	62%	21%
	x = 0.50	12%	77%

Scheme 5.52 *Effect of concentration on the conjugate addition of $PhB(OH)_2$*
Conditions: (i) $[Ir(cod)Cl]_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) conc. to x M (Ar) (iii) $[Rh(cod)Cl]_2$ (2.5 mol%), cod (10 mol%), 2 eq. $PhB(OH)_2$, 3 eq. KOH, 100 °C, 6 h*

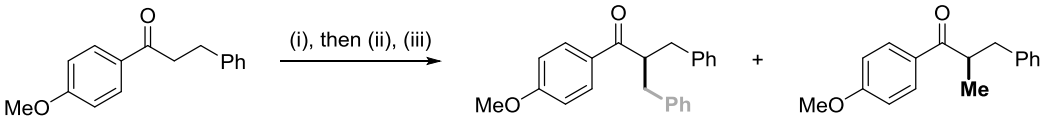
It was also desirable to find out what effect the loading of catalyst $[Rh(cod)Cl]_2$ had on the reaction. At 1.5 mol% loading of $[Rh(cod)Cl]_2$, the yield of benzylated ketone **916** dropped 62% to 37%, while the yield of methylated ketone **788** rose to 57% (**Scheme 5.53**). Strangely, increasing the loading of $[Rh(cod)Cl]_2$ to 5 mol% also lowered the yield of benzylated ketone **916**, with only 10% isolated, as a mixture with an 85% yield of methylated ketone **788**.



781		916	788
	$[Rh(cod)Cl]_2$ (1.5 mol%), cod (6 mol%)	37%	57%
	$[Rh(cod)Cl]_2$ (5 mol%), cod (20 mol%)	10%	85%

Scheme 5.53 *Effect of catalyst loading on the conjugate addition of $PhB(OH)_2$*
Conditions: (i) $[Ir(cod)Cl]_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) conc. to 0.25 M (Ar) (iii) $[Rh(cod)Cl]_2$, cod, 2 eq. $PhB(OH)_2$, 3 eq. KOH, 100 °C, 6 h*

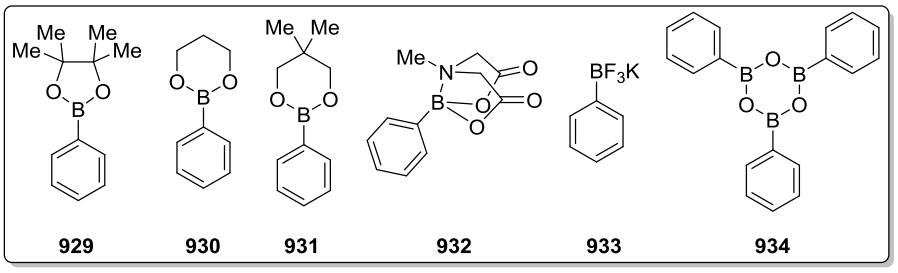
Although a good yield of the desired benzylated ketone **916** had been obtained with 2 eq. $PhB(OH)_2$, lower loadings of the boronic acid would clearly be an improvement to the reaction conditions, improving both atom- and cost-economy for the reaction. Lowering the number of equivalents of $PhB(OH)_2$ to 1.5 eq. resulted in only a minor fall in yield of the benzylated ketone **916** to 60%, isolated with 30% of methylated ketone **788** (**Scheme 5.54**). Further reduction of the number of equivalents to 1.1 eq. $PhB(OH)_2$ still afforded the benzylated product **916** in 53% yield, as a mixture with 40% yield of methylated ketone **788**.



781		**916**	**788**
	1.5 eq. $PhB(OH)_2$	60%	30%
	1.1 eq. $PhB(OH)_2$	53%	40%

Scheme 5.54 *Effect of boronic acid eq. on the conjugate addition of $PhB(OH)_2$*
Conditions: (i) $[Ir(cod)Cl]_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h*
(ii) conc. to 0.25 M (Ar) (iii) $[Rh(cod)Cl]_2$ (2.5 mol%), cod (10 mol%), x eq. $PhB(OH)_2$, 3 eq. KOH, 100 °C, 6 h

Since it appeared that this catalyst loading, equivalents of $PhB(OH)_2$ and concentration were the optimum achievable for the current reaction conditions, the effect of changing the boronic acid derivative was then considered. A number of derivatives of phenylboronic acid are available, for example, the pinacol ester **929**,[394] the propanediol ester **930**,[395] the neopentyl glycol ester **931**,[385] the *N*-methyliminodiacetic acid (MIDA) ester **932,**[396] the trifluoroborate **933**,[397] and the boroxine **934** (**Figure 5.5**).[398]

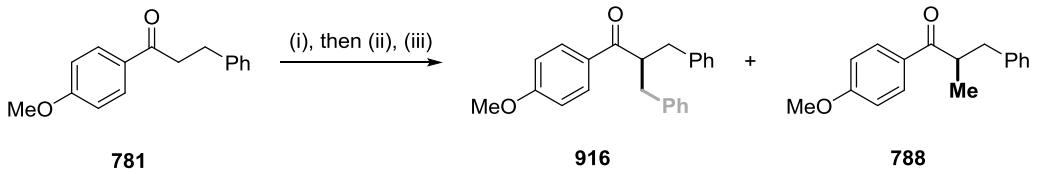


929 **930** **931** **932** **933** **934**

Figure 5.5 *Other boronic acid derivatives*

These different boronic acid derivatives are known to show different reactivity in a range of reactions, normally attributed to their relative rates of hydrolysis to the boronic acid *in situ*.[382] Furthermore, boronic acid derivatives such as boroxines are also considered to be less susceptible to protodeboration than the free boronic acid, and therefore possess a longer

half-life in solution. It was postulated that increasing the stability of the boronic acid under the conjugate addition conditions might result in an increased yield of the desired benzylated ketone **916**, thus a range of different boronic acid derivatives were examined for their activity in the one-pot methylenation/conjugate addition reaction (**Table 5.4**).



781 **916** **788**

Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) conc. to 0.25 M (Ar) (iii) [Rh(cod)Cl]$_2$ (2.5 mol%), cod (10 mol%), 1.5 eq. PhB, 3 eq. KOH, 100 °C, 6 h*

Entry	PhB	Result
1	**PhB(OH)$_2$**	60% **916**,[b] 30% **788**[b]
2	**929**	63% **916**, 33% **788**[a]
3	**930**	60% **916**, 36% **788**[a]
4	**931**	73% **916**[b]
5	**932**	sole product **788**[c]
6	**933**	30% **916**, 62% **788**[a]
7	**934**	73% **916**[b]

Table 5.4 *Methylenation/conjugation addition of substituted boroxines*

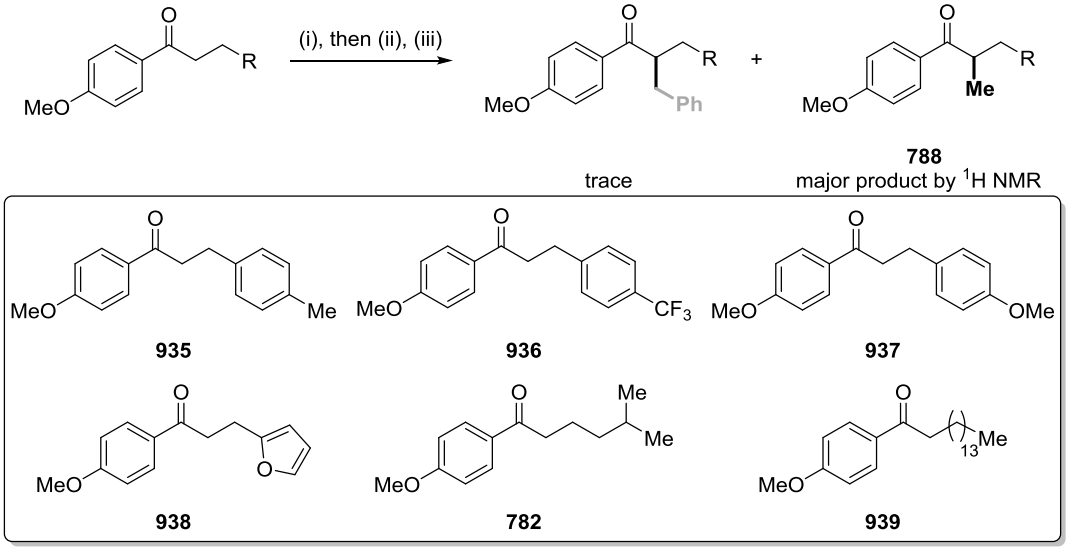
[a] Isolated as a mixture, yield determined by ^{1}H NMR [b] Isolated yield [c] Determined by ^{1}H NMR of the crude reaction mixture

Application of 1.5 eq. of phenylboronic acid pinacol ester **929** in the one-pot methylenation/boronic acid addition protocol afforded benzylated ketone **916** in 63% yield, essentially the same result as for PhB(OH)$_2$ (**Entry 2**). Similarly, the 1,3-propanediol ester **930** gave 60% yield of the desired compound **916**, again isolated as a mixture with methylated ketone **788** (**Entry 3**). We were delighted to find that phenylboronic acid neopentylglycol ester **931** gave a 73% yield of the benzylated ketone **916** (**Entry 4**), which could be separated by challenging and laborious purification by flash column chromatography, eluting with toluene. Surprisingly, the MIDA boronate **932** showed no reactivity at all under the conjugate addition conditions (**Entry 5**), suggesting that hydrolysis to the boronic acid was too slow, and thus reduction by [Rh]-H outcompeted conjugate addition. Potassium phenyltrifluoroborate **933** also showed methylated ketone **788** as the major product (62%), isolated with 30% of the desired product **916** (**Entry 6**), perhaps also suggesting that hydrolysis was too slow under the reaction conditions, thus limiting the rate of transmetallation to rhodium, and allowing reduction to occur preferentially. Finally,

addition of 0.5 eq. of triphenylboroxine **934** afforded benzylated ketone **916** in 73% isolated yield (**Entry 7**). The use of the boroxine has the added benefit of being more atom efficient.

5.4.3.3 Exploration of substrate scope for the boronic acid addition

Although a good yield was obtained for a one-pot methylenation/conjugate addition of triphenylboroxine **934** in the reaction of *p*-methoxyphenyl ketone **781**, we considered that other substrates would also need to be explored in order to show that this was a general and useful reaction. Thus, a number of different substrates, varying in both substitution on the preinstalled aromatic ring (**935-938**), or with alkyl side chains (**782** and **939**) were subjected to the methylenation/conjugate addition protocol (**Scheme 5.55**).[††]



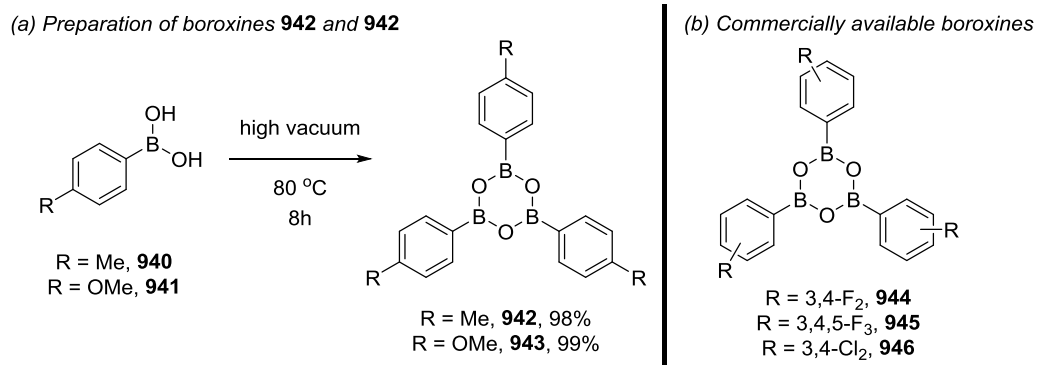
Scheme 5.55 *Attempted methylenation/conjugation of $(PhBO)_3$ to other substrates*
Conditions: (i) $[Ir(cod)Cl]_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h (ii) conc. to 0.25 M (Ar) (iii) $[Rh(cod)Cl]_2$ (2.5 mol%), cod (10 mol%), 0.5 eq. $(PhBO)_3$, 3 eq. KOH, 100 °C, 6 h*

Unfortunately, of the substrates attempted, only the corresponding methylated ketones were observed by ^{1}H NMR analysis of the crude reaction mixtures. It is clear, therefore, that the reaction is highly sensitive to any substructure on the starting material, since methylenation still occurs, but conjugate addition essentially did not occur relative to reduction in the second step.

Aside from the variation of the substrate, it was also desirable to explore variation in the substructure of the boronic acid derivative. Since the triphenylboroxine **934** had afforded the

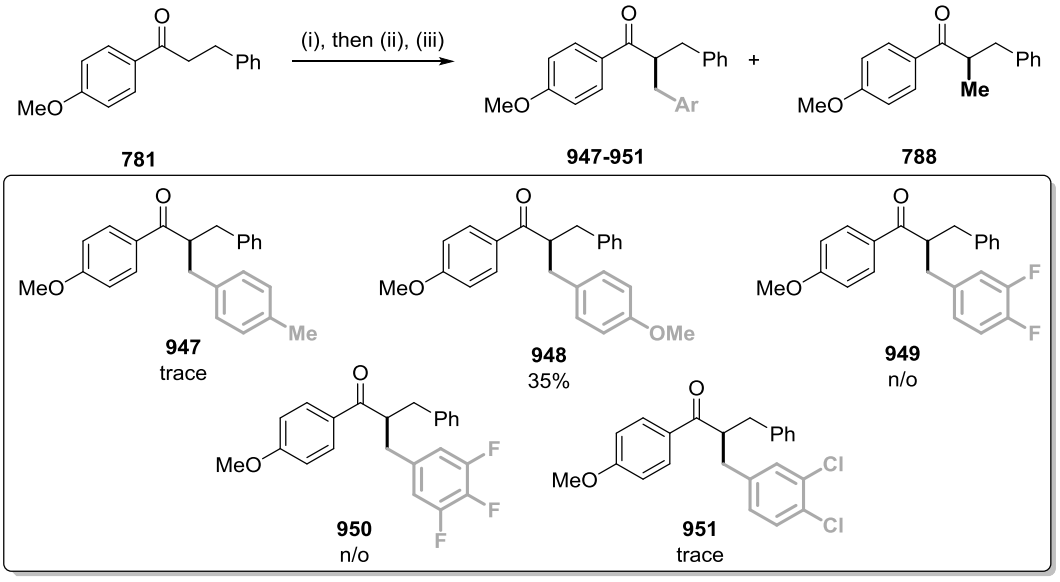
[††] I am grateful to Camilla Shotton and Di Shen for providing these subtrates.

highest yield for the addition of a phenylboronic acid derivative, initially the conjugate addition of a range of boroxines was examined. Due to the lack of commercial availability for many boroxines, it was necessary to prepare some boroxines from the corresponding boronic acid. Heating *p*-tolylboronic acid **940** and *p*-methoxyphenylboronic acid **941** at 80 °C under high vacuum afforded the corresponding boroxines **942** and **943** in 98% and 99% yields respectively (**Scheme 5.56a**). A number of electron-deficient boroxine derivatives were also available commercially (**Scheme 5.56b**).



Scheme 5.56 *Preparation of boroxines* **942** *and* **943**

These boroxines were then subsequently applied in the one-pot methylenation/conjugate addition protocol. Unfortunately, in all cases, except for tri(*p*-methoxyphenyl)boroxine **943**, boroxines **942-946** all afforded methylated ketone **788** as the major product as observed by ^{1}H NMR of the crude reaction mixture, with only traces of the corresponding benzylated ketones **947-951** observed (**Table 5.5**).



Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** *(8 mol%), 3 eq. KOH, MeOH (0.1 M), O_2, 65 °C, 48 h*

(ii) conc. to 0.25 M (Ar) (iii) [Rh(cod)Cl]$_2$ (2.5 mol%), cod (10 mol%), 0.5 eq. (ArBO)$_3$, 3 eq. KOH, 100 °C, 6 h

Entry	Boroxine	Result
1	**942**	trace **947**, major product **788**[a]
2	**943**	35% **948**[b], 63% **788**[b]
3	**944**	**949** n/o, sole product **788**[a]
4	**945**	**950** n/o, sole product **788**[a]
5	**946**	trace **951**, major product **788**[a]

Table 5.5 *Methylenation/conjugation addition of substituted boroxines*
[a] Determined by ^{1}H NMR of the crude reaction mixture [b] Isolated yield

Given that these boroxines had not proved to be successful for the arylation of ketone **781** in a one-pot methylenation/conjugate addition, a range of other substituted boronic acids and their derivatives were also screened (**Figure 5.4**).

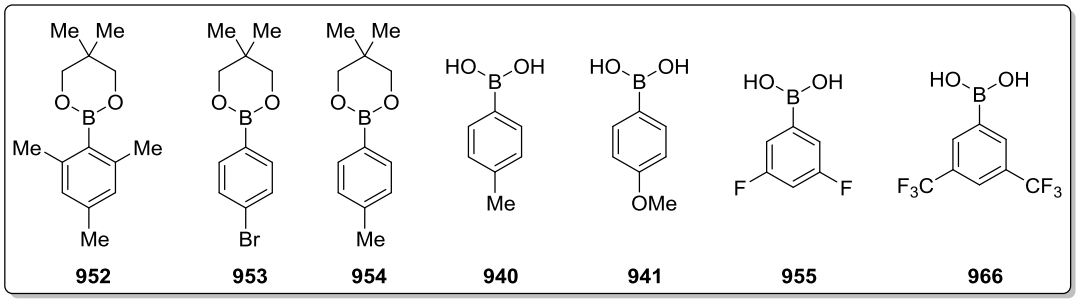
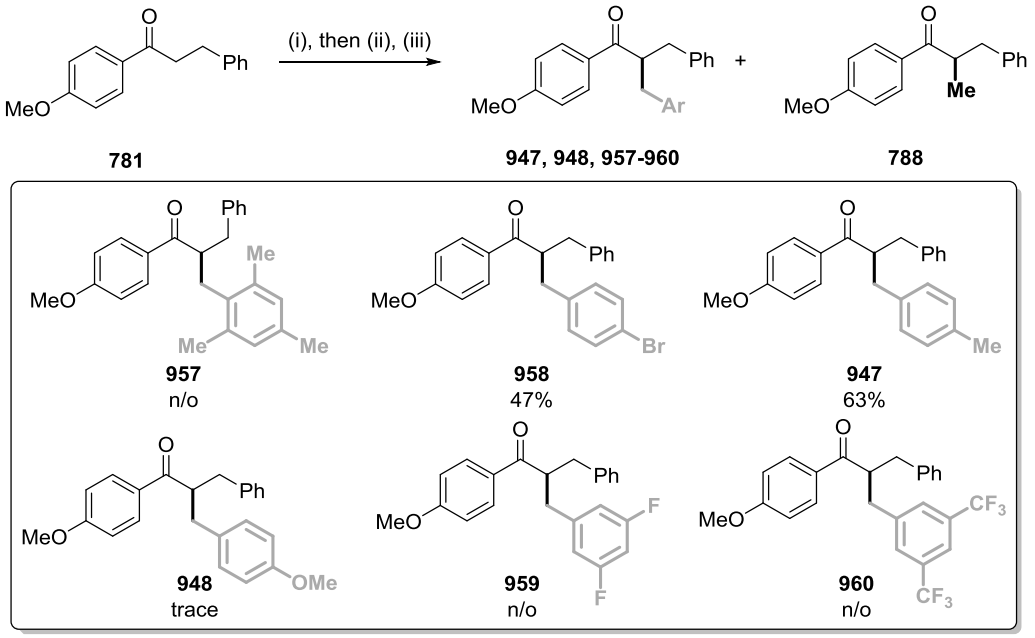


Figure 5.4 *Other boronic acid derivatives screened*

These boronic acid derivatives were subsequently utilised in one-pot methylenation/conjugate addition reactions with *p*-methoxyphenyl ketone **781** as the starting ketone (**Table 5.6**).



*Conditions: (i) [Ir(cod)Cl]$_2$ (2 mol%), **858** (8 mol%), 3 eq. KOH, MeOH (0.1 M), O$_2$, 65 °C, 48 h*
(ii) conc. to 0.25 M (Ar) (iii) [Rh(cod)Cl]$_2$ (2.5 mol%), cod (10 mol%), 1.5 eq. ArB, 3 eq. KOH, 100 °C, 6 h

Entry	*ArB*	Result
1	**952**	**957** n/o, sole product **788**[a]
2	**953**	47% **958**[b], 50% **788**[b]
3	**954**	trace **947**, major product **788**[a]
4	**940**	63% **947**[b], 28% **788**[b]
5	**941**	trace **948**, major product **788**[a]
6	**955**	**959** n/o, sole product **788**[a]
7	**956**	**960** n/o, sole product **788**[a]

Table 5.6 *Methylenation/conjugation addition of substituted boroxines*
[a] Determined by 1H NMR of the crude reaction mixture [b] Isolated yield

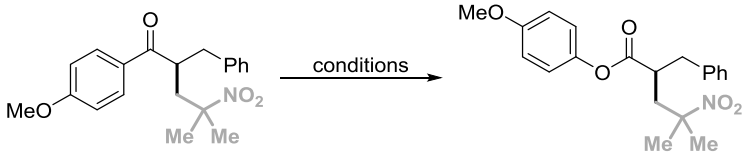
Unfortunately, mesitylboronic acid neopentylglycol ester **952** showed no conversion to the desired benzylated product **957**, with only methylated ketone **788** observed by ^{1}H NMR of the crude reaction mixture (**Entry 1**). *p*-Bromophenylboronic acid neopentylglycol ester **953** showed some reactivity, affording the anticipated *p*-bromobenzylated ketone **958** in 47% isolated yield (**Entry 2**), although 50% of the methylated ketone **788** was also isolated, suggesting that addition of this boronate ester was considerably slower than the unsubstituted neopentylglycol ester **931**, which gave a 73% yield of benzylated ketone **916**. Surprisingly, the *p*-tolylboronic acid neopentylglycol ester **954** showed almost no reactivity at all under the reaction conditions, affording methylated ketone **788** as the major product by ^{1}H NMR of the crude reaction mixture (**Entry 3**). Conversely, the unprotected *p*-tolylboronic acid **940** furnished the arylated ketone **947** in 63% isolated yield (**Entry 4**). *p*-Methoxyphenylboronic acid **941** showed markedly different reactivity to the corresponding boroxine **943** (*vide supra*), affording only traces of PMB ketone **948** (**Entry 5**). Finally, the electron-deficient boronic acids **955** and **966** showed no propensity for conjugate addition at all, with ^{1}H NMR spectra of the crude reaction mixtures containing only methylated ketone **788** as the major product (**Entries 6** and **7**).

It was clear, therefore, that the choice of boronic acid derivative was complicated, with no clear trend appearing for the most appropriate choice for optimal yield of the one-pot methylenation/conjugate addition reaction. Further investigation into the one-pot methylenation/boronic acid conjugate addition protocol was thus discontinued, due to time constraints.

5.4.4 Derivatisation of the conjugate addition products

To emphasise the synthetic utility of the conjugate addition products, we were hopeful that they could then be successfully subjected to Baeyer-Villiger oxidations,[399] thus allowing for the formation of the ester, which could then be further derivatised to a range of alkylated carbonyl derivatives.

Treatment of the product **865**, resulting from the conjugate addition of 2-nitropropane in a one-pot methylenation/conjugate addition reaction, with 4 eq. *m*CPBA and 2 eq. TFA in CH_2Cl_2 at room temperature unfortunately showed no conversion to the desired product **961**, as observed by TLC, ^{1}H NMR analysis and mass spectrometry (**Table 5.7**, **Entry 1**). In an attempt to increase reactivity, the reaction was heated to 40 °C, but still no product formation was observed (**Entry 2**). To enable the reaction to be conducted at higher temperature, CH_2Cl_2 was replaced with DCE as the reaction solvent, and the reaction heated to 80 °C, but still no ester formation was observed (**Entry 3**). Baeyer-Villiger oxidation was also attempted with the more active trifluoroperacetic acid (CF_3CO_3H, formed *in situ* by reaction of urea-hydrogen peroxide complex and trifluoroacetic anhydride),[400] but once again no conversion to the desired ester was observed (**Entry 4**). These results appeared to suggest that the limiting factor in the Baeyer-Villiger oxidation of nitroalkylated ketone **865** was addition of the peracid to the carbonyl, perhaps as a result of steric factors, since one would expect rapid migration to occur with a strongly electron-donating substitutent such as *p*-methoxyphenyl.

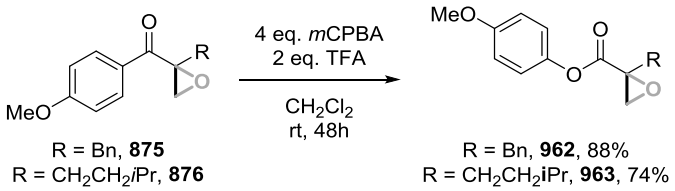


865 **961**

Entry	Conditions	961 (%)
1	4 eq. *m*CPBA, 2 eq. TFA, CH_2Cl_2, rt,48 h	n/o
2	4 eq. *m*CPBA, 2 eq. TFA, CH_2Cl_2, 40 °C, 48 h	n/o
3	4 eq. *m*CPBA, 2 eq. TFA, DCE, 80 °C, 48 h	n/o
4	2 eq. CF_3CO_3H, 5 eq. NaH_2PO_4, CH_2Cl_2, rt, 48 h	n/o

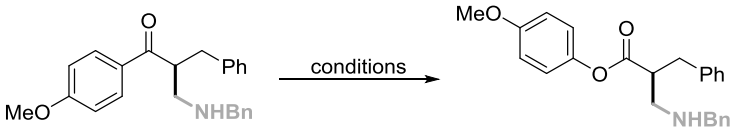
Table 5.7 *Attempted Baeyer-Villiger esterification of nitroalkylated ketone* **865**

The esterification of epoxides **875** and **876** were subsequently attempted under the standard conditions initially used for Baeyer-Villiger oxidation. Pleasingly, epoxides **875** and **876** both underwent oxidation smoothly to afford the corresponding *p*-methoxyphenyl esters **962** and **963** in 88% and 74% yields respectively, both with near-complete regioselectivity (>50:1) for the desired product (**Scheme 5.57**)



Scheme 5.57 *Baeyer-Villiger oxidation of epoxides* **875** *and* **876**

The Baeyer-Villiger oxidation of aminoalkylated ketone **867** was then attempted. Unfortunately, under the standard esterification conditions, a complex mixture of products was observed, with no evidence for the formation of the desired ester **964**, presumably due to reaction of the amine with *m*CPBA (**Table 5.8**, **Entry 1**). Since reactions of *m*CPBA in the presence of protonated ammonium species are known, such as the ammonium directed epoxidation of olefins,[401] we considered that prior protonation of the amine with 4 eq. TFA, followed by addition of *m*CPBA might alleviate this problem and allow esterification to occur. Disappointingly, this proved not to be the case, with complex decomposition of starting ketone **867** again observed (**Entry 2**).

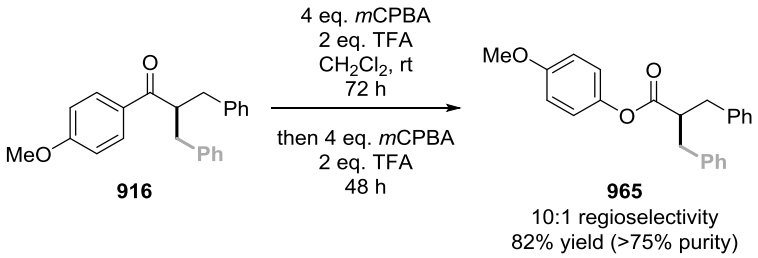


Entry	Conditions	964 (%)
1	4 eq. *m*CPBA, 2 eq. TFA, CH_2Cl_2, rt, 24 h	n/o
2	4 eq. TFA, CH_2Cl_2, rt, 1 h, then 4 eq. *m*CPBA, 24 h	n/o

Table 5.8 *Attempted Baeyer-Villiger oxidation of aminoalkylated ketone* **867**

Finally, our attention turned to the esterification of the product of phenylboronic acid addition **916**. With 4 eq. *m*CPBA and 2 eq. TFA the reaction appeared slow, with a considerable amount of starting ketone **916** observed after 72 h. Addition of a further 4 eq. *m*CPBA and 2 eq. TFA, followed by stirring for an extra 48 h afforded the esterified product **965** as an

acceptable 10:1 mixture of regioisomers. Unfortunately, the product contained an inseparable impurity (purity >75%), thereby giving a maximum yield of 82% (**Scheme 5.58**). The lower regioselectivity for this reaction suggests an increased migratory aptitude for the doubly benzylic secondary centre relative to the *p*-methoxyphenylgroup.



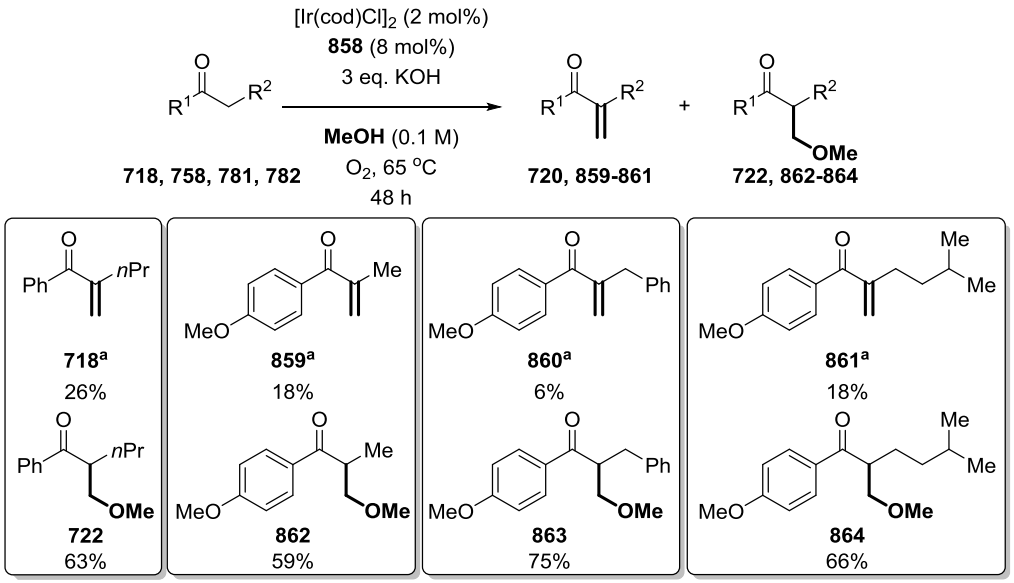
Scheme 5.58 *Esterification of benzylated ketone* **916**

The low reactivity and regioselectivity in this reaction prompted us to cease further investigation into the Baeyer-Villiger oxidation of ketone **916**, thus concluding our studies in this area.

5.5 Conclusions

The work described above provides an extension to the previously-developed rhodium-catalysed methylation of ketones.[313] In this case, an interrupted hydrogen borrowing reaction with methanol to form an enone, followed by nucleophilic trapping, affords a range of more complex alkylated products, providing a novel catalytic method for C-C bond formation with methanol.

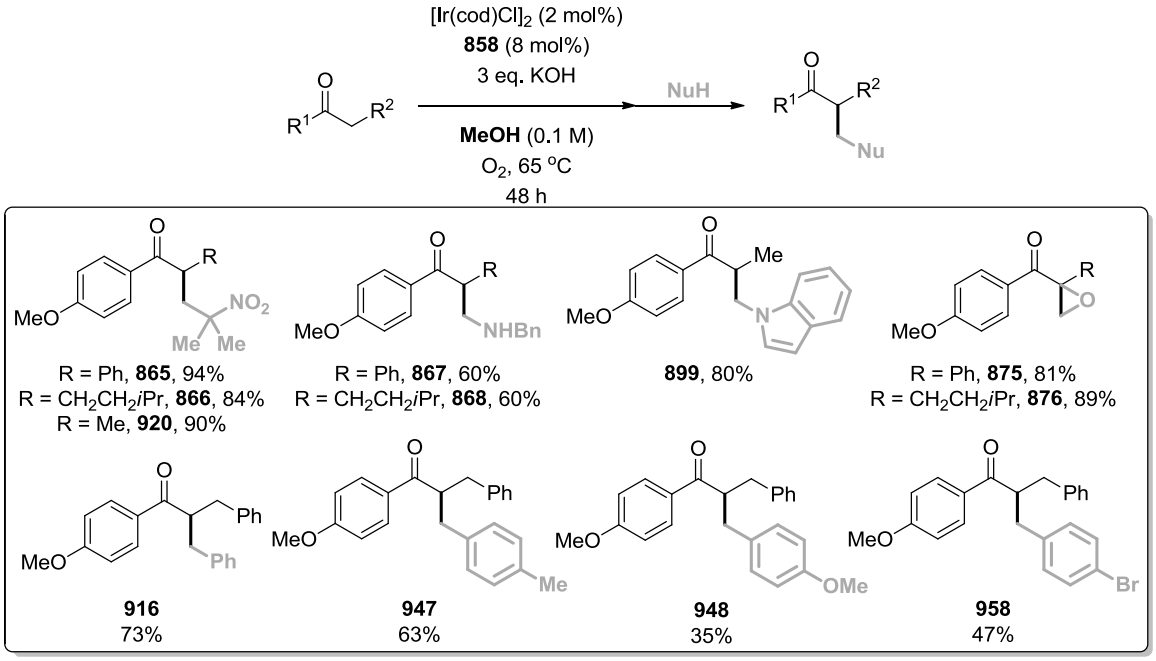
Screening of a range of catalysts and conditions showed that a combination of $[Ir(cod)Cl]_2$, CataCXium A, and KOH in MeOH, under at atmosphere of O_2 were optimum for achieving selectivity methylenation of a range of ketones (**Scheme 5.59**).



Scheme 5.59 *Methylenation of ketones*

[a] Product obtained as a mixture with the corresponding methylated ketone

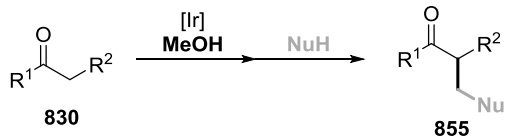
These methylenation conditions were then successfully applied to the one-pot methylenation/conjugate addition of a range of different nucleophiles, thus forming a range of products not previously accessible *via* hydrogen-borrowing alkylation reactions of ketones (**Scheme 5.60**).



Scheme 5.60 *Successful one-pot methylenation/conjugate addition reactions*

5.6 Future work

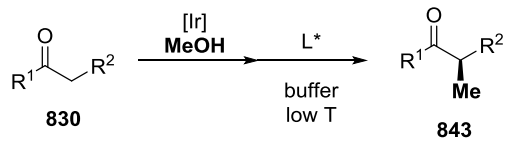
There are numerous areas derived from the hydrogen borrowing reactions of methanol described in **Chapters 4** and **5** which could be further investigated in the future. The one-pot methylenation/conjugate addition shown here has thus far only been investigated for ketones bearing a *p*-methoxyphenyl group, with a few to allowing subsequent regioselective Baeyer-Villiger oxidation to further derivatise the products. Arguably, the relatively electron-rich nature of the enone thus formed has made the conjugate addition process more difficult, and thus many conjugate addition reactions which were challenging with the *p*-methoxyphenyl substrates might be more suitable with other, less electron-rich substrates, allowing the formation of a more diverse range of products (**Scheme 5.61**).



R^1,R^2 = aryl, heteroaryl, 1° alkyl, 2° alkyl...

Scheme 5.61 *Potential methylenation of electronically-diverse ketones*

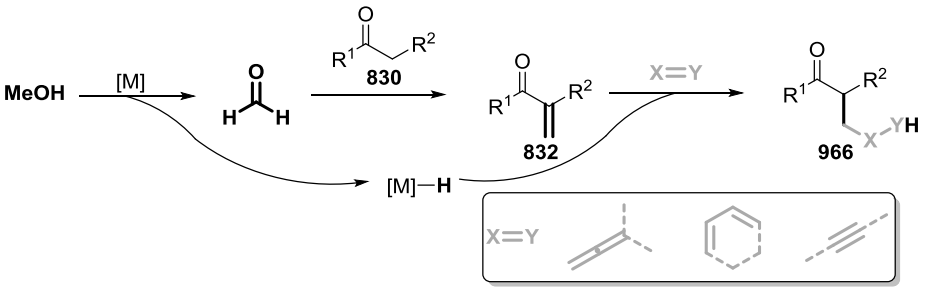
During the development of conditions for the rhodium-catalysed boronic acid addition, it became clear that methanol oxidation, and metal-hydride reduction could be performed at temperatures as low as 40 °C (*vide supra*). Although racemisation is likely to occur under the current basic conditions utilised, methylenation followed by buffering of the solution and addition of a chiral ligand such as BINAP may allow for the formation of enantioenriched methylated ketones (**Scheme 5.62**).



Scheme 5.62 *Potential asymmetric methylation of ketones*

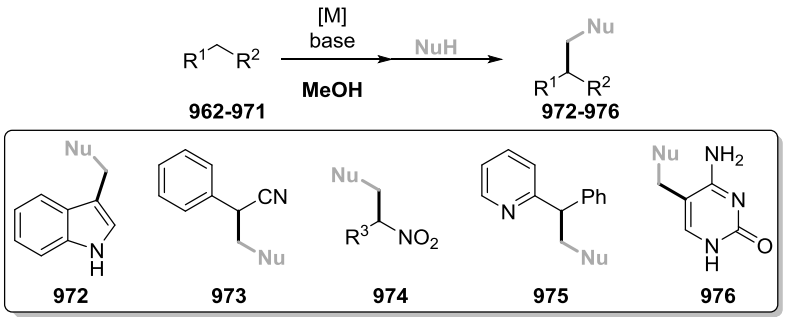
Although the one-pot methylenation/conjugate addition reaction gave access to a diverse range of product, it had proved impossible to completely prevent hydride reduction of the enones thus formed. It may also prove possible to utilise the metal hydride for the activation of a 'pronucleophile', such as an unsaturated system, e.g. allenes, dienes, alkynes, to form a

hydrometallated species which may then add back in to the enone formed *via* methanol oxidation and aldol reaction (**Scheme 5.63**). This process is conceptually similar to the addition of unsaturated compounds to alcohols developed by Krische and coworkers, albeit where addition would not occur directly to the alcohol, but instead to a species derived from reaction with the alcohol formed by metal-catalysed dehydrogenation.



Scheme 5.64 *Potential activation of pronucleophiles followed by addition to enones*

One final and broader extension to the work presented for the hydrogen-borrowing reactions of methanol could be their application to substrates other than ketones. Although investigation in the Donohoe group has shown that the methylation of esters is not viable under the currently developed reaction conditions,[350] there are a range of other compounds with similar or lower pKa values than ketones (pKa ≈ 25 in DMSO)[402] that could be alkylated. For example, the methylation of indoles **967** (pKa ≈ 21 in DMSO),[403] arylacetonitriles **968** (pKa ≈ 20-25 in DMSO),[404] nitroalkanes **969** (pKa ≈ 17 in DMSO),[405] and 2- or 4-benzylpyridines **970** (pKa ≈ 26-28 in DMSO)[406] are all potential substrates. Indeed, even the enamine functionality of nucleobases such as cytosine **971** might prove amenable to such a process. These substrates have the potential to either be methylated or undergo methylenation followed by conjugate addition, including many of the other proposed items of future work described above (**Scheme 5.65**).



Scheme 5.65 *Other potential substrates for hydrogen borrowing reactions of methanol*

6: Experimental Section

6.1 Experimental techniques

Toluene, THF, CH_2Cl_2, Et_2O, MeOH and MeCN were dried by purification through an activated alumina purification column. Petrol refers to the petroleum ether fraction that boils in the range 30–40 °C. Reagents were obtained from Acros, Aldrich, Fluka, Fluorochem, Strem and TCI, and were used as supplied or purified by standard laboratory procedures.[407]

All non-aqueous reactions were carried out in flame-dried glassware under an atmosphere of argon, unless otherwise stated.

Flash column chromatography (FCC) was carried out on silica gel 60 (40–63 μm BDH) using Still's method.[408] TLC analyses were performed on Merck Kieselgel 60 F254 0.25 mm precoated aluminium-backed plates. Product spots were visualised under UV light (λ_{max} = 254 nm) and/or by staining with basic potassium permanganate solution, or acidic vanillin solution as deemed appropriate for the compound.

^{1}H nuclear magnetic resonance (NMR) spectra were recorded using Bruker AVII400, AVIII400, or AVII500 instruments at 400 MHz or 500 MHz. ^{13}C NMR spectra were recorded at 101 MHz. Chemical shifts δ are reported relative to residual solvent peaks and quoted in parts per million (ppm) to the nearest 0.01 ppm for ^{1}H and 0.1 ppm for ^{13}C. Coupling constants *J* are quoted to the nearest 0.1 Hz. Assignments were based upon DEPT, COSY, HMQC, and HMBC experiments.

Mass spectra (MS) were recorded on a Fisons Platform II spectrometer under electrospray ionisation (ESI). High resolution mass spectra (HRMS) are given to four decimal places and were recorded on a Bruker MicroTof (resolution = 10000 FWHM). Mass spectra were calibrated *via* the lock-mass of tetraoctylammonium bromide for positive and sodium dodecyl sulfate for negative ions.

Fourier transform infrared (FTIR) spectra were obtained from evaporated films using a Bruker Tensor 27 spectrometer, equipped with a PIKE Miracle Attenuated Total Reflectance sampling accessory. Absorption maxima are quoted in wavenumbers (cm^{-1}) for the range 3500–1000 cm^{-1}.

Melting points (m.p.) were obtained using a Leica VMTG heated-stage microscope and are uncorrected.

Specific optical rotations ($[\alpha]_D$) were recorded on a Perkin Elmer 241 Polarimeter at the sodium D line (589.3 nm) and are quoted in the units of 10^{-1} deg cm^2 g^{-1}. Solution concentrations are given in units of 10^{-2} g cm^{-3}.

6.2 General procedures

General Procedure A: Grignard addition to pyridinium salts[31]

Grignard reagent (1.5 eq.) was added dropwise to a stirred solution of pyridinium salt (1.0 eq.) in solvent (0.15 M in substrate) at the stated temperature and stirred at this temperature for 16 h. 1 M HCl solution (0.08 M in substrate) was added and the biphasic mixture was allowed to warm to room temperature and stirred for a further 1 h. The mixture was diluted with CH_2Cl_2 (10 mL) and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by FCC (EtOAc) afforded dihydropyridone **72**.

General Procedure B: Salt metathesis to form chiral pyridinium salts

To a solution of pyridinium iodide **270** (1.0 eq.) in MeOH was added silver salt (1.0 eq.), eliciting a cream precipitate. The resultant mixture was filtered and concentrated *in vacuo* to afford the corresponding pyridinium salt.

General Procedure C: Nucleophilic dearomatisation of electron-deficient furans[87]

To a stirred solution of 5-nitro-2-furonitrile **197** (80 mg, 0.58 mmol), additive and base in solvent (5 mL), was added 1,3-dicarbonyl compound. The reaction was stirred at room temperature until TLC analysis indicated the complete consumption of starting material. The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC afforded product.

General Procedure D: Synthesis of dimeric phase-transfer catalysts[185]

A suspension of *Cinchona* alkaloid (1.0 eq.) and *α,α*'-dibromo-*m*-xylene (0.50 eq.) in $CHCl_3$/EtOH/DMF (0.50 M in alkaloid, 5:2:6, v/v) was stirred at 100 °C for 12 h. The mixture was cooled to room temperature, added to Et_2O (30 mL/mmol alkaloid) with stirring, and filtered. The resultant solid was washed with Et_2O (30 mL/mmol alkaloid), then recrystallised from MeOH/Et_2O to afford the desired ammonium salt.

General Procedure E: α-Arylation of 1,3-diketones[203]

Acetylacetone **199** (3.0–4.0 eq.), aryl halide (1.0 eq.), CuI (0.1 eq.), base (4.0 eq.) and L-proline (0.2 eq.) in DMSO (0.25 M) were stirred at 90 °C for 12 h. The reaction was quenched with 1 M HCl (20 mL/mmol halide) and extracted with EtOAc (3 × 20 mL/mmol halide). The combined organic layers were washed with brine (20 mL/mmol halide), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification by FCC afforded product.

General Procedure F: Rh-catalysed methylation of ketones[313]

$[RhCp^*Cl_2]_2$ (5 mol%) and Cs_2CO_3 (2.0–5.0 eq.) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (5 mL/mmol ketone) and ketone (1.0 eq.). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted *via* a needle through the septum. The reaction was heated to 65 °C for the period of time stated. The reaction was quenched by diluting with water (20 mL/mmol substrate), and extracted with CH_2Cl_2 (20 mL/mmol substrate). The combined organic layers were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC afforded product.

General Procedure G: Baeyer–Villiger oxidation of ketones

Ketone (1.0 eq.), *m*CPBA (4.0 eq.), trifluoroacetic acid (2.0 eq.) and CH_2Cl_2 were added to a Biotage® microwave vial equipped with a stir bar. The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and stirred at rt for 48 h. The organic phase was washed with sat. aq. $NaHCO_3$ (3 × 30mL/mmol substrate), dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Purification by FCC afforded product.

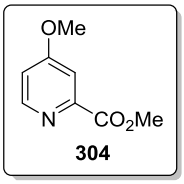
General Procedure H: Ir-catalysed methylenation of ketones

$[Ir(cod)Cl]_2$ (2 mol%), CataCXium A **858** (8 mol%) and KOH (3.0 eq.) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (10 mL/mmol ketone) and ketone (1.0 eq.). The vial was sealed with a microwave vial cap (containing a

Reseal™ septum) and degassed with a ballon of O_2 *via* a needle inserted through the septum. The reaction was heated to 65 °C with the O_2 balloon attached *via* a needle for the period of time stated. The reaction mixture was diluted with Et_2O, filtered through a short plug of silica, and concentrated *in vacuo*. Purification by FCC afforded product.

6.3 Experimental details

Methyl 4-methoxypicolinate 304[31]



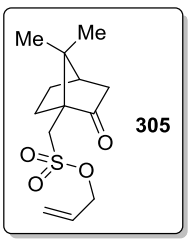
304

Picolinic acid **308** (15.7 g, 128 mmol) and sodium bromide (1.31 g, 12.8 mmol) were dissolved in thionyl chloride (110 mL) and the resultant mixture was heated to 90 °C for 30 h with vigorous stirring. The mixture was then concentrated *in vacuo* and the residue cooled to 0 °C. Methanol (50 mL) was added cautiously and the resultant mixture heated to 70 °C for 36 h. The reaction mixture was concentrated *in vacuo* and the residue dissolved in CH_2Cl_2 (100 mL). Sodium carbonate (20.3 g, 191 mmol) was added and the mixture stirred for 3 h before the addition of water (100 mL). The mixture was extracted with CH_2Cl_2 (5 × 75 mL), and the combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification by FCC (9:1 Et_2O/Petrol → Et_2O) yielded *pyridine* **304** (7.49 g, 44.8 mmol, 35%) as brown needles.

m.p. 47–49 °C [Lit: 47–49 °C][31]; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.55 (1H, d, *J* 5.6 Hz, $NC_{Py}{}^6\underline{H}$), 7.68 (1H, d, *J* 2.6 Hz, $C_{Py}{}^3\underline{H}$), 6.98 (1H, dd, *J* 2.6, 5.6 Hz, $C_{Py}{}^5\underline{H}$), 4.01 (3H, s, $OC\underline{H}_3$), 3.92 (3H, s, $OC\underline{H}_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 166.5 ($\underline{C}O_2Me$), 165.8 ($\underline{C}_{Py}{}^4OMe$), 150.9 ($N\underline{C}_{Py}{}^2(CO_2Me)$), 149.5 ($N\underline{C}_{Py}{}^6H$), 113.2 ($\underline{C}_{Py}{}^5H$), 111.1 ($\underline{C}_{Py}{}^3H$), 55.6 ($O\underline{C}H_3$), 53.0 ($O\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[31]

Allyl ((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate 305



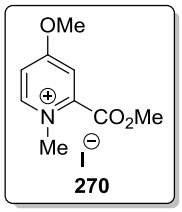
305

To a suspension of sodium hydride (60% dispersion in mineral oil, 96 mg, 4.0 mmol) in THF (50 mL) at 0 °C was added allyl alcohol (0.27 mL, 4.0 mmol) and allowed to stir for 10 minutes. (+)-Camphorsulfonyl chloride **306** (1.0 g, 4.0 mmol) was added and the reaction allowed to warm to room

temperature over 5 h. The reaction was quenched with water (20 mL), and the organic phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by FCC (10:1 Petrol/EtOAc) yielded *allylsulfonate* **305** (1.05 g, 3.9 mmol, 97%) as a colourless oil.

$[\alpha]_D^{20}$ = +54.6 (c = 1.0, CH_2Cl_2); ν_{max} (cm^{-1}) 2962, 1744, 1353, 1167; δ_H (400MHz, $CDCl_3$) 5.96 (1H, m, $CH_2C\underline{H}=CH_2$), 5.46 (1H, dd, *J* 17.8, 1.1 Hz, $CH_2CH=CH_{cis}\underline{H}_{trans}$), 5.36 (1H, dd, *J* 10.4, 1.1 Hz, $CH_2CH=C\underline{H}_{cis}H_{trans}$), 4.82–4.71 (2H, m, $OC\underline{H}_2$), 3.61 (1H, d, *J* = 15.1 Hz, $C\underline{H}_aH_bSO_3$), 3.01 (1H, d, *J* 15.1 Hz, $CH_a\underline{H}_bSO_3$), 2.54-2.34 (2H, m, $C\underline{H}_2CO$), 2.16-2.00 (2H, m, $C\underline{H}_2$), 1.96 (1H, d, *J* 18.4 Hz, $C\underline{H}_aH_b$), 1.67 (1H, m, $CH_a\underline{H}_b$), 1.44 (1H, ddd, *J* 12.7, 9.2, 3.9 Hz, C*H*), 1.11 (3H, s, $C\underline{H}_3$), 0.88 (3H, s, $C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 214.5 (*C*O), 130.6 $\underline{C}H=CH_2$), 120.7 ($CH=\underline{C}H_2$), 70.8 ($O\underline{C}H_2$), 58.0 ($\underline{C}CH_2SO_3$), 48.0 ($\underline{C}(CH_3)_2$), 47.3 ($\underline{C}H_2SO_3$), 42.7 (*C*H), 42.6 ($\underline{C}H_2CO$), 26.9 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 19.8 ($\underline{C}H_3$), 19.7 ($\underline{C}H_3$); **m/z** (ESI+) 295.09 $[M+Na]^+$ **HRMS** (ESI+) $C_{13}H_{20}O_4S$ requires 295.0975 $[M+Na]^+$, found 295.0972 (Δ = 1.0 ppm).

4-Methoxy-3-(methoxycarbonyl)-1-methylpyridinium iodide 270[23]



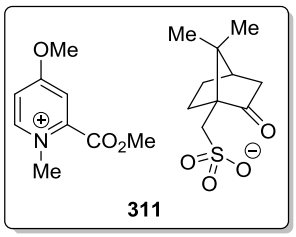
270

Methyl 4-methoxypicolinate **304** (1.00 g, 5.99 mmol) was dissolved in methyl iodide (10 mL) and the resulting solution was heated to 45 °C for 16 h. The reaction mixture was allowed to cool to room temperature, before the addition of Et_2O (20 mL). The resulting precipitate was filtered and washed with Et_2O (3 x 10 mL) before being dried under high vacuum to furnish *pyridinium salt* **270** (1.70 g, 5.51 mmol, 92%) as a pale yellow solid.

m.p. 113–115 °C (dec.) [Lit: 113–115 °C (dec.)][2a]; δ_H (400MHz, $CDCl_3$) 9.41 (1H, d, *J* 7.2 Hz, $NC_{Py}{}^6\underline{H}$), 7.88 (1H, d, *J* 3.1 Hz, $C_{Py}{}^3\underline{H}$), 7.72 (1H, dd, *J* 7.2, 3.1 Hz, $C_{Py}{}^5\underline{H}$), 4.49 (3H, s, $NC\underline{H}_3$), 4.18 (3H, s, $OC\underline{H}_3$), 4.01 (3H, s, $OC\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 171.5 ($\underline{C}_{Py}{}^4OCH_3$), 159.5 ($\underline{C}O_2Me$), 151.5 ($N\underline{C}_{Py}{}^2(CO_2Me)$), 143.3 ($N\underline{C}_{Py}{}^6H$), 117.8 ($\underline{C}_{Py}{}^5H$), 114.8 ($\underline{C}_{Py}{}^3H$), 59.5 ($O\underline{C}H_3$), 55.0 ($O\underline{C}H_3$), 47.9 ($N\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[23]

4-Methoxy-3-(methoxycarbonyl)-1-methylpyridinium((1*R*,4*R*)-7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonate 311

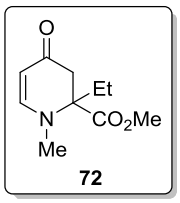


311

Pyridinium iodide **270** (100 mg, 0.330 mmol), silver salt **310** (110 mg, 0.330 mmol) and MeOH (25 mL) were subjected to **general procedure B** to afford *pyridinium salt* **311** (132 mg, 0.330 mmol, quant.) as a yellow oil.

$[\alpha]_D^{20}$ = +31.3 (c = 1.0, CH_2Cl_2); ν_{max} (cm^{-1}) 2959, 1736, 1574, 1527; δ_H (400 MHz, $CDCl_3$) 9.33 (1H, d, *J* 6.8 Hz, $C_{Py}{}^6\underline{H}N^+$), 7.84 (1H, dd, *J* 6.8, 3.0 Hz, $C_{Py5}\underline{H}$), 7.77 (1H, d, *J* 3.0 Hz, $C_{Py}{}^3\underline{H}$), 4.42 (3H, s, $N^+C\underline{H}_3$), 4.14 (3H, s, $OC\underline{H}_3$), 4.00 (3H, s, $OC\underline{H}_3$), 2.67 (1H, d, *J* 14.7 Hz, $C\underline{H}_aH_bCO$), 2.51–2.63 (1H, m, $CH_a\underline{H}_bCO$), 2.21 (1H, d, *J* 18.2 Hz, $C\underline{H}_aH_bSO_3$), 1.98–1.84 (2H, m, $C\underline{H}_2$), 1.77 (1H, d, *J* 18.2 Hz, $CH_a\underline{H}_bSO_3$), 1.58 (1H, ddd, *J* 14.3, 9.5, 4.5 Hz, $C\underline{H}$), 1.41–1.32 (1H, m, $C\underline{H}_aH_b$), 1.31–1.23 (1H, m, $CH_a\underline{H}_b$), 0.99 (3H, s, $C(C\underline{H}_3)_a(CH_3)_b$), 0.73 (3H, s, $C(CH_3)_a(C\underline{H}_3)_b$); δ_C (100 MHz, $CDCl_3$) 217.2 ($\underline{C}$=O), 171.5 ($\underline{C}_{Py}{}^4OCH_3$), 159.8 ($\underline{C}O_2CH_3$), 152.9 ($\underline{C}_{Py}{}^2CO_2CH_3$), 142.8 ($\underline{C}_{Py}{}^6HN^+$), 117.6 ($\underline{C}_{Py}{}^5$), 114.5 ($\underline{C}_{Py}{}^3H$), 58.7 ($O\underline{C}H_3$), 58.4 ($O\underline{C}H_3$), 54.6 ($\underline{C}CH_2SO_3^-$), 47.9 ($\underline{C}(CH_3)_2$), 47.1 ($N^+\underline{C}H_3$), 46.9 ($\underline{C}H_2SO_3^-$), 42.9 ($\underline{C}H$), 42.5 ($\underline{C}H_2CO$), 27.0 ($\underline{C}H_2$), 24.5 ($\underline{C}H_2$), 19.9 ($\underline{C}H_3$), 19.8 ($\underline{C}H_3$); **m/z** (ESI+) 182.08 [M+] (ESI-) 231.04 [CSA-] **HRMS** (ESI+) $C_9H_{12}NO_3$+ requires 182.0812, found 182.0810 (Δ = 1.1 ppm).

Methyl 2-ethyl-1-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate 72[31]



72

Pyridinium salts **311, 318** and **323** were subjected to **general procedure A**, using ethylmagnesium bromide (3.0 M solution in Et_2O) as the Grignard reagent under a variety of conditions. Purification by FCC (EtOAc) gave *dihydropyridone* **72** as a colourless oil (yields in **Table 6.1**).

Entry	Salt	Solvent	Temperature (°C)	Yield (%)	ee (%)
1	**311**	CH_2Cl_2	−65	85	0
2	**311**	PhMe	−30	42	6
3	**311**	PhMe	−40	10	6
4	**311**	THF	−30	69	0
5	**311**	Et_2O	−30	0	-
6	**311**	Et_2O	0	0	-

7	**311**	Et_2O	rt	0	-
8	**318**	PhMe	−30	0	-
9	**323**	PhMe	−30	0	-
10	**323**	CH_2Cl_2	−65	62	0
11	**323**	THF	−30	53	0
12	**323**	CH_2Cl_2/PhMe 1:1	−65	54	0

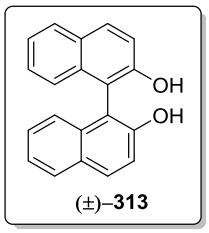
Table 6.1 *Results for addition of EtMgBr to pyridinium salts*

δ_H (400 MHz, $CDCl_3$) 7.01 (1H, d, *J* 7.6 Hz, NC*H*=CH), 4.94 (1H, d, *J* 7.6 Hz, CH=C*H*CO), 3.72 (3H, s, OC*H*$_3$), 3.10 (3H, s, NC*H*$_3$), 2.51–2.83 (2H, m, C*H*$_2$CO), 1.94 (2H, q, *J* 7.6 Hz, C*H*$_2$CH$_3$), 1.01 (3H, t, *J* 7.6 Hz, CH$_2$C*H*$_3$); **δ_C** (100 MHz, $CDCl_3$) 190.6 (CH*C*OCH$_2$), 173.0 (*C*O$_2$Me), 156.3 (N*C*H), 98.9 (NCH*C*H), 68.3 (N*C*(CH$_2$CH$_3$)CO$_2$Me), 52.7 (CO$_2$*C*H$_3$), 42.1 (*C*H$_2$CO), 39.0 (N*C*H$_3$), 27.6 (*C*H$_2$CH$_3$), 8.25 (CH$_2$*C*H$_3$).

Spectroscopic data are consistent with those previously reported.[31]

Enantiomeric excess was determined by chiral HPLC (Chiralcel OD, 254 nm, 1.0 mL/min, heptane/*i*-PrOH 9:1 v/v, tR_1 = 26.2 min, tR_2 = 30.3 min).

[1,1'-Binapthalene]-2,2'-diol 313[147]



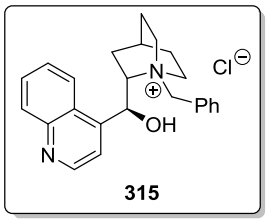
(±)–**313**

A suspension of 2-naphthol **312** (28.8 g, 200 mmol) and iron(III) chloride hexahydrate (108 g, 400 mmol) in distilled water (400 mL) was heated to 50 °C for 48 h. The resultant solid was filtered, washed three times with distilled water and recrystallized from PhMe, to afford *diol* **(±)-313** (24.6 g, 86.0 mmol, 86%) as a white crystalline solid.

m.p. 209–213 °C [Lit: 209–210 °C][18]; **δ_H** (400MHz, $CDCl_3$) 7.99 (2H, d, *J* 8.8 Hz, C$_{Ar}$*H*), 7.91 (2H, d, *J* 7.8 Hz, C$_{Ar}$*H*), 7.44–7.36 (4H, m, C$_{Ar}$*H*), 7.35–7.29 (2H, m, C$_{Ar}$*H*), 7.17 (2H, d, *J* 8.3 Hz, C$_{Ar}$*H*), 5.06 (2H, s, O*H*); **δ_C** (100 MHz, $CDCl_3$) 152.8 (*C*$_{Ar}$OH), 133.4 (*C*$_{Ar}$), 131.4 (*C*$_{Ar}$H), 129.5 (*C*$_{Ar}$), 128.4 (*C*$_{Ar}$H), 127.5 (*C*$_{Ar}$H), 124.2 (*C*$_{Ar}$H), 124.1 (*C*$_{Ar}$H), 117.8 (*C*$_{Ar}$H), 110.8 (*C*$_{Ar}$C$_{Ar}$OH).

Spectroscopic data are consistent with those previously reported.[147]

***N*-Benzylcinchonidinium chloride 315[148]**



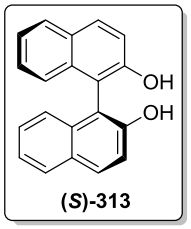
315

A solution of cinchonidine **314** (29.4 g, 100 mmol) and benzyl chloride (15.7 mL, 150 mmol) in acetone (400 mL) was heated under reflux for 3 days. The suspension was filtered and the solid suspended in acetone (150 mL) and stirred for a further 1 h, filtered and washed with acetone (2 × 80 mL). The solid was dried *in vacuo* to afford *ammonium salt* **315** (30.3 g, 72.0 mmol, 72%). as a white solid.

m.p. 212–216 °C (dec.) [Lit: 212–213 °C (dec.)][20]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ −165 (c = 0.5, H_2O) [Lit: −175.4 (c = 0.5, H_2O)][20]; $\boldsymbol{\delta_H}$ (400 MHz, d_4–methanol) 8.96 (1H, d, *J* 4.4 Hz, $C_{Ar}\underline{H}$), 8.30 (1H, m, $C_{Ar}\underline{H}$), 8.13 (1H, dd, *J* 8.2, 1.1 Hz, $C_{Ar}\underline{H}$), 7.98 (1H, d, *J* 4.4 Hz, $C_{Ar}\underline{H}$), 7.89–7.78 (2H, m, $C_{Ar}\underline{H}$), 7.76 (2H, dd, *J* 6.7, 2.9 Hz, $C_{Ar}\underline{H}$), 7.62–7.56 (3H, m, $C_{Ar}\underline{H}$), 6.68 (1H, s, C$\underline{H}$OH), 5.69 (1H, ddd, *J* 17.3, 10.4, 6.8 Hz, CH_2=C$\underline{H}$), 5.23 (1H, d, *J* 12.4 Hz, C$\underline{H}_a$$H_b$Ph), 5.16 (1H, dt, *J* 17.3, 1.3 Hz, CH=C$\underline{H}_2$), 5.05–4.98 (2H, m, CH=C$\underline{H}_2$, $CH_a\underline{H}_b$Ph), 4.54–4.43 (1H, m, C$\underline{H}_a$$H_b$$N^+$), 4.02 (1H, t, *J* 9.1 Hz, C$\underline{H}N^+$), 3.74–3.66 (1H, m, $CH_a\underline{H}_bN^+$), 3.53–3.45 (1H, m, C$\underline{H}_a$$H_b$$N^+$), 3.45–3.37 (1H, m, $CH_a\underline{H}_bN^+$), 3.32 (1H, dt, *J* 3.3 Hz, 1.6 Hz,), 2.77–2.69 (1H, m, C$\underline{H}$CH=CH_2), 2.33–2.20 (2H, m, C$\underline{H}_2$$CH_2$), 2.08 (1H, d, *J* 2.8 Hz, C$\underline{H}_a$$H_b$), 1.95–1.88 (1H, m, C$\underline{H}$), 1.46–1.40 (1H, m, $CH_a\underline{H}_b$); $\boldsymbol{\delta_C}$ (100 MHz, d_4–methanol) 150.1 ($\underline{C}_{Ar}$H), 147.7 ($\underline{C}_{Ar}$), 146.6 ($\underline{C}_{Ar}$), 137.8 ($\underline{C}$H=CH_2), 133.9 ($\underline{C}_{Ar}$H), 130.7 ($\underline{C}_{Ar}$H), 130.2 ($\underline{C}_{Ar}$H), 129.4 ($\underline{C}_{Ar}$H), 129.4 ($\underline{C}_{Ar}$H), 128.1 ($\underline{C}_{Ar}$H), 127.8 ($\underline{C}_{Ar}$H), 125.1 ($\underline{C}_{Ar}$H), 123.1 ($\underline{C}_{Ar}$H), 120.4 ($\underline{C}_{Ar}$H), 116.5 (CH=$\underline{C}H_2$), 68.7 ($\underline{C}$HOH), 65.3 ($\underline{C}HN^+$), 64.2 ($\underline{C}H_2$Ph), 61.0 ($\underline{C}H_2N^+$), 51.7 ($\underline{C}H_2N^+$), 38.1 ($\underline{C}$HCH=CH_2), 27.0 ($\underline{C}H_2$), 24.9 ($\underline{C}$H), 21.5 ($\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[409]

(S)-[1,1'-Binaphthalene]-2,2'-diol (*S*)-313[149]



(*S*)-313

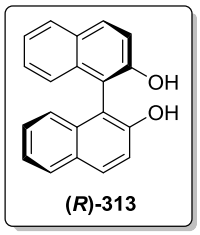
N-Benzylcinchonidium chloride **315** (6.51 g, 14.3 mmol) was added to a stirred solution of (±)-[1,1'-binaphthalene]-2,2'-diol **(±)-313** (8.06 g, 28.5 mmol) in dry MeCN (100 mL) and heated under reflux for 4 h. The resultant suspension was then cooled to room temperature and allowed to stir overnight. The suspension was cooled to 0 °C and stirred for a further 2 h, before being

filtered. The filtrate was concentrated to dryness, dissolved in 80 mL EtOAc, washed with 1 M HCl (2 x 30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to give *(S)-diol* **(*S*)-313** (3.79 g, 94%, 99.2% *ee*) as an off-white solid.

$[\alpha]_D^{20}$ −34.3 (c = 1.0, THF) [Lit: −29.4 (c = 1.0, THF)].[149]

Enantiomeric excess was determined by chiral HPLC. (Chiralcel AD, 254nm, 0.8 mL/min, heptane/*i*-PrOH 9:1 v/v, tR_1 = 37.3 min (*S*), tR_2 = 45.7 min(*R*)).

(R)-[1,1'-Binaphthalene]-2,2'-diol (*R*)-313[149]



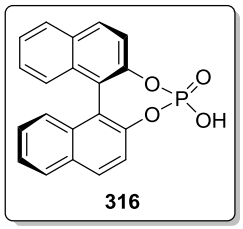
(*R*)-313

The filtered solid complex from the isolation of **(*S*)-313** was washed with MeCN (100 mL) and the MeCN solution discarded. The resulting solid was then refluxed in MeOH (30 mL) for 24 h. The solution was then cooled to room temperature, filtered and the solid washed with MeOH (5 mL). The solid was suspended in ethyl acetate (80 mL) and 1 M HCl (45 mL) and stirred until dissolution occurred. The organic layer was then washed with 1 M HCl (45 mL) and brine (45 mL), dried over Na_2SO_4, filtered and concentrated to give *(R)*-diol **(*R*)-313** (3.75 g, 93%, >99.8% *ee*) as an off-white solid.

$[\alpha]_D^{20}$ +35.0 (c = 1.0, THF) [Lit: + 30.9 (c = 1.0, THF)].[149]

Enantiomeric excess was determined by chiral HPLC. (Chiralcel AD, 254nm, 0.8 mL/min, heptane/*i*-PrOH 9:1 v/v, tR_1 = 37.3 min (*S*), tR_2 = 45.7 min(*R*)).

(R)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate 316[150]



316

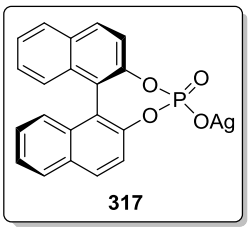
To a suspension of (*R*)-BINOL **(*R*)-313** (573 mg, 2.00 mmol) in pyridine (6 mL) at room temperature, phosphorus oxychloride (0.37 mL, 4.0 mmol) was added dropwise with rapid stirring. The resultant suspension was heated to 95 °C for 12 h. The reaction was cooled to 0 °C and 2 mL of distilled water was added dropwise. The reaction mixture was then heated to 95 °C and stirred for a further 6 h. The mixture was diluted with chloroform (20 mL) and washed with 1 M HCl (20mL). The organic phase was separated and dried over Na_2SO_4,

filtered, and the solvent removed *in vacuo* to yield *phosphoric acid* **316** (596 mg, 1.72 mmol, 86%); as an off-white solid.

m.p >320 °C [Lit: >300 °C][22]; $[\boldsymbol{\alpha}]_{\boldsymbol{20}}^{\boldsymbol{D}}$ −687 (c = 1.0, MeOH) [Lit: −726 (c = 1.0, MeOH)][23]; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 14.26 (1H, br s, $OPO_2\underline{H}$), 8.18 (2H, d, *J* 8.7 Hz, $C_{Ar}\underline{H}$), 8.09 (2H, d, *J* 8.3 Hz, $C_{Ar}\underline{H}$), 7.59 (2H, d, *J* 8.8 Hz, $C_{Ar}\underline{H}$), 7.51 (2H, t, *J* 7.5 Hz, $C_{Ar}\underline{H}$), 7.35 (2H, t, *J* 7.5 Hz, $C_{Ar}\underline{H}$), 7.24 (2H, d, *J* 8.7 Hz, $C_{Ar}\underline{H}$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 148.5 ($\underline{C}_{Ar}O$), 148.4 ($\underline{C}_{Ar}$), 132.5 ($\underline{C}_{Ar}$), 131.9 ($\underline{C}_{Ar}H$), 129.5 ($\underline{C}_{Ar}H$), 127.8 ($\underline{C}_{Ar}H$), 127.0 ($\underline{C}_{Ar}H$), 126.4 ($\underline{C}_{Ar}H$), 122.1 ($\underline{C}_{Ar}H$), 121.9 ($\underline{C}_{Ar}$); $\boldsymbol{\delta_P}$ (101 MHz, $CDCl_3$) 7.42.

Spectroscopic data are consistent with those previously reported.[410, 411]

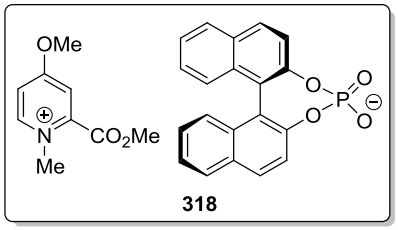
Silver(I) *(R)*-1,1'-binaphthyl-2,2'-diyl phosphate, 317[151]



317

To a solution of *(R)*-1,1'-binaphthyl-2,2'-diyl hydrogenphopshate **316** (220 mg, 0.63 mmol), in CH_2Cl_2 (3 mL) in the dark, was added in one portion Ag_2CO_3 (88 mg, 0.32 mmol), followed by distilled H_2O (3 mL). The resulting mixture was stirred vigorously for 1 h. The mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers of the biphasic suspension were separated and the aqueous layer extracted with CH_2Cl_2 (2x15 mL). The combined organic extracts were filtered through celite and concentrated to afford *silver salt* **317** (281 mg, 0.62 mmol, 98%) as a white solid, used in the next step without further purification.

4-Methoxy-3-(methoxycarbonyl)-1-methylpyridinium *(R)*-1,1'-binaphthyl-2,2'-diyl phosphate 318



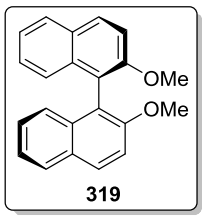
318

Pyridinium iodide **270** (213 mg, 0.730 mmol), silver(I) phosphate **317** (330 mg, 0.730 mmol) and MeOH (10 mL) were subjected to **general procedure B** to afford *pyridinium salt* **318** (371 mg, 0.701 mmol, 96%) as a yellow oil.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −47.9 (c = 1.0, CH_2Cl_2); $\boldsymbol{\nu_{max}}$ (cm^{-1}) 3052, 2936, 1629, 1526, 1319; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.07 (1H, d, *J* 6.6 Hz, $C_{Py}{}^6\underline{H}N^+$) 7.81 (2H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 7.74 (2H, d, *J* 8.1 Hz,

$C_{Ar}\underline{H}$), 7.59 (2H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 7.34 (1H, d, *J* 4.3 Hz, $C_{Py}{}^{5}\underline{H}$), 7.32–7.24 (3H, m, $C_{Ar}\underline{H}$, $C_{Py}{}^{3}\underline{H}$), 7.21 (2H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 7.15–7.07 (2H, m, $C_{Ar}\underline{H}$), 4.01 (3H, s, $N^{+}C\underline{H}_3$), 3.82 (3H, s, $OC\underline{H}_3$), 3.75 (3H, s, $OC\underline{H}_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$); 170.5 ($\underline{C}_{Py}{}^{4}OCH_3$), 159.4 ($\underline{C}O_2CH_3$), 152.5 ($\underline{C}_{Py}{}^{2}(CO_2CH_3)$), 150.1 ($\underline{C}_{Ar}O$), 132.4 ($\underline{C}_{Ar}$), 130.6 ($\underline{C}_{Ar}$), 129.9 ($\underline{C}_{Ar}H$), 128.2 ($\underline{C}_{Ar}H$), 126.7 ($\underline{C}_{Ar}H$), 125.7 ($\underline{C}_{Ar}H$), 124.4 ($\underline{C}_{Ar}H$), 122.6 ($\underline{C}_{Ar}$), 122.2 ($\underline{C}_{Ar}H$), 117.0 ($\underline{C}_{Py}{}^{5}H$), 113.7 ($\underline{C}_{Py}{}^{3}H$), 58.2 ($O\underline{C}H_3$), 54.2 ($O\underline{C}H_3$), 48.6 ($N^{+}\underline{C}H_3$); **m/z** (ESI+) 182.07 [M^{+}] (ESI-) 347.06 [BNP^{-}] **HRMS** $C_9H_{12}NO_3^{+}$ requires 182.0812, found 182.0810 (Δ = 1.1 ppm).

(R)-2,2'-Dimethoxy-1,1'-binaphthalene 319[150]

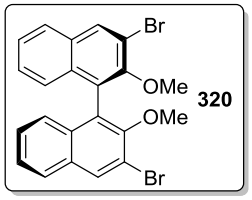


A suspension of *(R)*-[1,1'-binaphthalene]-2,2'-diol **(*R*)-313** (1.17 g, 4.09 mmol) in acetone (100 mL) was heated until complete dissolution occurred. K_2CO_3 (1.91 g, 13.8 mmol) and methyl iodide (1.00 mL, 16.1 mmol) were added and the solution heated to reflux for 24 h. Further methyl iodide (0.50 mL, 8.1 mmol) was added and the solution heated to reflux for a further 12 h. The solvent was removed *in vacuo* and the resultant slurry was suspended in distilled H_2O (100 mL) and stirred for a further 8 h. The resulting solid was filtered, washed with H_2O (3×50 mL) and dried to afford *diether* **319** (1.22 g, 3.90 mmol, 95%) as a white solid.

m.p. 229–231 °C [Lit: 228–232 °C][10]; $\boldsymbol{[\alpha]_D^{20}}$ = +45.6 (c = 1.0, $CHCl_3$) [Lit: +57.5 (c = 1.0, $CHCl_3$)][24]; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.00 (2H, d, *J* 8.8 Hz, $C_{Ar}\underline{H}$), 7.89 (2H, d, *J* 8.1 Hz, $C_{Ar}\underline{H}$), 7.48 (2H, d, *J* 9.1 Hz, $C_{Ar}\underline{H}$), 7.37–7.31 (2H, m, $C_{Ar}\underline{H}$), 7.28–7.19 (2H, m, $C_{Ar}\underline{H}$), 7.13 (2H, d, *J* 8.8 Hz, $C_{Ar}\underline{H}$), 3.79 (6H, s, $OC\underline{H}_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 155.0 ($\underline{C}_{Ar}O$), 134.0 ($\underline{C}_{Ar}$), 129.4 ($\underline{C}_{Ar}$), 129.2 ($\underline{C}_{Ar}H$), 127.9 ($\underline{C}_{Ar}H$), 126.3 ($\underline{C}_{Ar}H$), 125.3 ($\underline{C}_{Ar}H$), 123.5 ($\underline{C}_{Ar}H$), 119.6 ($\underline{C}_{Ar}$), 114.2 ($\underline{C}_{Ar}H$), 56.9 ($O\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[150]

(R)-3,3'-Dibromo-2,2'-dimethoxy-1,1'-binaphthalene 320[150]



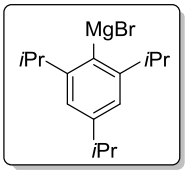
To a solution of *N,N,N',N'*-tetramethylethylenediamine (2.75 mL, 18.4 mmol) in Et_2O (125 mL) *n*-butyllithium (1.6M in hexanes, 18.3

mL, 29.2 mmol) was added dropwise and allowed to stir for 1 h at room temperature. *(R)*-2,2'-dimethoxy-1,1'-binaphthalene **319** (2.62 g, 8.34 mmol) was added in one portion and the resultant suspension stirred for a further 3 h. After this time the reaction was cooled to −78 °C and bromine (3.33 g, 41.7 mmol) was added dropwise. After complete addition, the reaction was allowed to warm to room temperature and stirred for a further 20 h. The reaction was quenched with aqueous saturated Na_2SO_3 (40 mL) and stirred for 1 h. The mixture was extracted with Et_2O (3 x 50 mL), the combined organic layers washed with brine, dried over $MgSO_4$, filtered and dried *in vacuo*. Purification by FCC (Petrol/EtOAc 10:1) and recrystallisation from CH_2Cl_2/hexane afforded *dibromide* **320** (2.12 g, 4.50 mmol, 54%) as a yellow crystalline solid.

m.p. 175–179 °C [Lit: 178–182 °C][10]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +12.1 (c = 1.2, $CHCl_3$) [Lit: +14.1 (c = 1.0, $CHCl_3$)][25]; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.28 (2H, s, $C_{Ar}\underline{H}$), 7.83 (2H, d, *J* 8.2 Hz, $C_{Ar}\underline{H}$), 7.47–7.40 (2H, m, $C_{Ar}\underline{H}$), 7.31–7.24 (2H, m, $C_{Ar}\underline{H}$), 7.09 (2H, d, *J* 8.2 Hz, $C_{Ar}\underline{H}$), 3.52 (6H, s, OCH_3); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 152.5 ($\underline{C}_{Ar}O$), 133.1 ($\underline{C}_{Ar}$), 133.0 ($\underline{C}_{Ar}$), 131.4 ($\underline{C}_{Ar}H$), 127.1 ($\underline{C}_{Ar}H$), 126.9 ($\underline{C}_{Ar}H$), 126.5 ($\underline{C}_{Ar}H$), 125.8 ($\underline{C}_{Ar}H$), 117.5 ($\underline{C}_{Ar}Br$), 61.1 ($O\underline{C}H_3$).

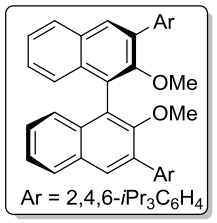
Spectroscopic data are consistent with those previously reported.[150]

2,4,6-Triisopropylphenylmagnesium bromide[150]



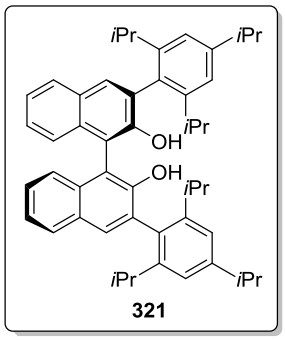
Magnesium turnings (250 mg, 9.30 mmol) were activated with a spatula tip of iodine and covered with Et_2O (3 mL). Subsequently, 2-bromo-1,3,5-triisopropylbenzene (1.23 mL, 4.66 mmol), Et_2O (10 mL) and 1,2-dibromoethane (25 μL, 0.29 mmol) were added slowly, in such a manner as to maintain the reaction at self-reflux. After complete addition the grey solution was refluxed for 24 h. The resultant solution was used crude in the next step without further purification.

(*R*)-3,3'-Bis(2,4,6-triisopropylphenyl)-2,2'-dimethoxy-1,1'-binaphthalene[150]



To a stirred solution of *(R)*-3,3'-dibromo-2,2'-dimethoxy-1,1'-binaphthalene **320** (355 mg, 0.760 mmol) in diethyl ether (12 mL) was added bis(triphenylphosphine)nickel(II) chloride (45 mg, 0.080 mmol). Subsequently, 2,4,6-triisopropylphenylmagnesium bromide (solution in Et_2O, 4.66 mmol) was added dropwise at room temperature. After complete addition the resulting mixture was refluxed for 6 h. The resulting solution was cooled to 0 °C and quenched with 1 M HCl solution (10 mL). The aqueous phase was extracted with diethyl ether (3 x 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to give crude product, used in the next step without further purification.

(*R*)-3,3'-Bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol 321[150]



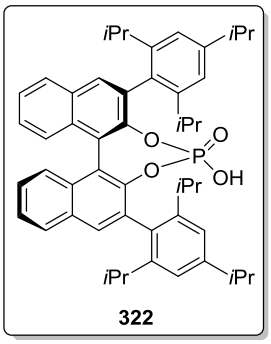
To a stirred solution of crude 3,3'-bis(aryl)-2,2'-dimethoxy-1,1'-binaphthalene (0.76 mmol) in dichloromethane (15 mL) at 0 °C, BBr_3 (1.0M solution in dichloromethane, 5.3 mL, 5.3 mmol) was added dropwise. The resultant solution was allowed to warm to room temperature and stirred for 24 h. The reaction was quenched with water (10 mL) and extracted with dichloromethane (3×25 mL). The combined organic phase was dried over $MgSO_4$, filtered and concentrated. Purification by FCC (Petrol/EtOAc, 100:1) afforded *bisaryl-BINOL* **321** (234 mg, 0.34 mmol, 45% over 2 steps) as a pale cream solid.

m.p. 116–120 °C; $[\alpha]_D^{20}$ = +79.4 (c = 3.0, THF) [Lit: +88.0 (c = 3.0, THF)][26]; δ_H (400MHz, CD_2Cl_2) 7.99 (2H, d, *J* 7.8 Hz, $C_{Ar}\underline{H}$), 7.86 (2H, s, $C_{Ar}\underline{H}$), 7.49–7.37 (4H, m, $C_{Ar}\underline{H}$), 7.34 (2H, d, *J* 8.8 Hz, $C_{Ar}\underline{H}$), 7.27–7.22 (2H, m, $C_{Ar}\underline{H}$), 5.13 (2H, s, O$\underline{H}$), 3.06 (2H, sept, *J* 6.9 Hz, C$\underline{H}$(CH_3)$_2$), 2.93 (2H, sept, *J* 6.9 Hz, C$\underline{H}$(CH_3)$_2$), 2.80 (2H, sept, *J* 6.9 Hz, C$\underline{H}$(CH_3)$_2$), 1.40 (12H, d, *J* 6.9 Hz, CH(C$\underline{H}_3$)$_2$), 1.33 (6H, d, *J* 6.9 Hz, CH(C$\underline{H}_3$)$_2$), 1.28 (6H, d, *J* 6.9 Hz, CH(C$\underline{H}_3$)$_2$), 1.20 (6H, d, *J* 6.9 Hz, CH(C$\underline{H}_3$)$_2$), 1.14 (6H, d, *J* 6.9 Hz, CH(C$\underline{H}_3$)$_2$);

δ_C (100 MHz, CD_2Cl_2) 151.3 (<u>*C*</u>$_{Ar}$O), 149.8 (<u>*C*</u>$_{Ar}$CH(CH$_3$)$_2$), 148.3 (<u>*C*</u>$_{Ar}$CH(CH$_3$)$_2$), 148.3 (<u>*C*</u>$_{Ar}$CH(CH$_3$)$_2$), 133.9 (<u>*C*</u>$_{Ar}$), 131.4 (<u>*C*</u>$_{Ar}$H), 131.2 (<u>*C*</u>$_{Ar}$), 129.7 (<u>*C*</u>$_{Ar}$), 128.8 (<u>*C*</u>$_{Ar}$H), 127.2 (<u>*C*</u>$_{Ar}$H), 124.6 (<u>*C*</u>$_{Ar}$H), 124.3 (<u>*C*</u>$_{Ar}$H), 121.6 (<u>*C*</u>$_{Ar}$H), 113.3 (<u>*C*</u>$_{Ar}$), 34.9 (<u>*C*</u>H(CH$_3$)$_2$), 31.4 (<u>*C*</u>H(CH$_3$)$_2$), 31.3 (<u>*C*</u>H(CH$_3$)$_2$), 24.6 (CH(<u>*C*</u>H$_3$)$_2$), 24.5 (CH(<u>*C*</u>H$_3$)$_2$), 24.4 (CH(<u>*C*</u>H$_3$)$_2$), 24.3 (CH(<u>*C*</u>H$_3$)$_2$), 24.1 (CH(<u>*C*</u>H$_3$)$_2$).

Spectroscopic data are consistent with those previously reported.[150]

***(R)*-3,3'-Bis(2,4,6-triisoppropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate 322[150]**



322

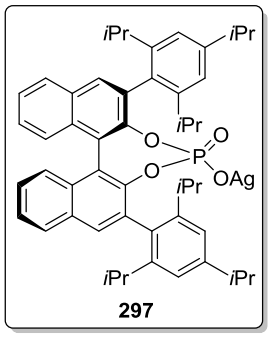
To a suspension of BINOL **321** (130 mg, 0.190 mmol) in pyridine (2 mL) at room temperature, phosphorus oxychloride (53 μL, 0.57 mmol) was added dropwise with rapid stirring. The resultant suspension was heated to 95 °C for 12 h. The reaction was cooled to 0 °C and 2 mL of distilled water was added dropwise. The reaction mixture was then heated to 95 °C and stirred for a further 6 h. The mixture was diluted with chloroform (20 mL) and washed with 1 M HCl (20 mL). The organic phase was separated, dried over Na_2SO_4, and the solvent removed *in vacuo* to yield *phosphoric acid* **322** (115 mg, 0.152 mmol, 80%). as an off-white solid.

m.p. 193-195 °C; $[\alpha]_D^{20}$ = −54.6 (c = 1.0, $CHCl_3$) [Lit: −59.4 (c = 1.0, $CHCl_3$)][27]; **δ_H** (400 MHz, CD_2Cl_2) 7.95 (2H, d, *J* 8.1 Hz, C$_{Ar}$<u>*H*</u>), 7.83 (2H, s, C$_{Ar}$<u>*H*</u>), 7.57–7.51 (2H, m, C$_{Ar}$<u>*H*</u>), 7.37–7.27 (4H, m, C$_{Ar}$<u>*H*</u>), 7.02 (2H, d, *J* 1.8 Hz, C$_{Ar}$<u>*H*</u>), 2.89 (2H, sept, *J* 6.9 Hz, C<u>*H*</u>(CH$_3$)$_2$), 2.61 (4H, sept, *J* 6.9, C<u>*H*</u>(CH$_3$)$_2$), 1.30–1.23 (12H, m, CH(C<u>*H*</u>$_3$)$_2$), 1.11 (6H, d, *J* 6.9 Hz, CH(C<u>*H*</u>$_3$)$_2$), 1.03 (6H, d, *J* 6.9 Hz, CH(C<u>*H*</u>$_3$)$_2$), 0.94 (6H, d, *J* 6.9 Hz, CH(C<u>*H*</u>$_3$)$_2$), 0.86 (6H, d, *J* 6.9 Hz, CH(C<u>*H*</u>$_3$)$_2$); **δ_C** (100 MHz, CD_2Cl_2) 148.6 (<u>*C*</u>$_{Ar}$*i*-Pr), 148.0 (<u>*C*</u>$_{Ar}$*i*-Pr), 147.5 (<u>*C*</u>$_{Ar}$O), 145.8 (<u>*C*</u>$_{Ar}$), 145.8 (<u>*C*</u>$_{Ar}$) 132.8 (<u>*C*</u>$_{Ar}$), 132.4 (<u>*C*</u>$_{Ar}$), 132.0 (<u>*C*</u>$_{Ar}$), 132.0 (<u>*C*</u>$_{Ar}$), 131.4 (<u>*C*</u>$_{Ar}$H), 131.1 (<u>*C*</u>$_{Ar}$H), 128.2 (<u>*C*</u>$_{Ar}$H), 127.2 (<u>*C*</u>$_{Ar}$H), 126.3 (<u>*C*</u>$_{Ar}$H), 125.8 (<u>*C*</u>$_{Ar}$H), 122.0 (<u>*C*</u>$_{Ar}$H) , 121.2 (<u>*C*</u>$_{Ar}$), 120.4 (<u>*C*</u>$_{Ar}$H), 34.3 (<u>*C*</u>H(CH$_3$)$_2$), 31.1 (<u>*C*</u>H(CH$_3$)$_2$), 30.8 (<u>*C*</u>H(CH$_3$)$_2$),

26.2 (CH($\underline{C}$H$_3$)$_2$), 24.7 (CH($\underline{C}$H$_3$)$_2$), 24.0 (CH($\underline{C}$H$_3$)$_2$), 22.9 (CH($\underline{C}$H$_3$)$_2$), 22.8 (CH($\underline{C}$H$_3$)$_2$); **δ_P** (126 MHz, CD_2Cl_2) 3.43.

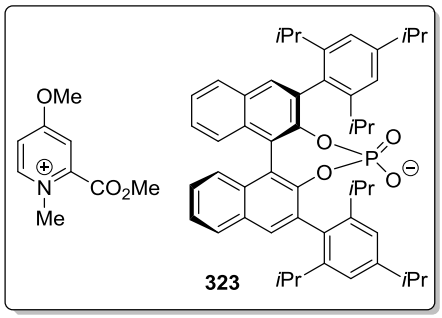
Spectroscopic data are consistent with those previously reported.[150]

Silver *(R)*-3,3'-bis(2,4,6-triisoppropylphenyl)-1,1'-binaphthyl-2,2'-diyl phosphate 297[151]



To a solution of phosphoric acid **322** (56 mg, 0.075 mmol), in CH_2Cl_2 (1 mL) in the dark, was added in one portion Ag_2CO_3 (10 mg, 0.037 mmol), followed by 1 mL distilled H_2O. The resulting mixture was stirred vigorously for 1 h. The mixture was diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The layers of the biphasic suspension were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 15 mL). The combined organic extracts were filtered through celite and concentrated *in vacuo* to afford *silver salt* **297** as a white solid (64 mg, 0.075 mmol, quant.), used in the next step without further purification.

4-Methoxy-3-(methoxycarbonyl)-1-methylpyridinium *(R)*-3,3'-bis(2,4,6-triisoppropylphenyl)-1,1'-binaphthyl-2,2'-diyl phosphate 323

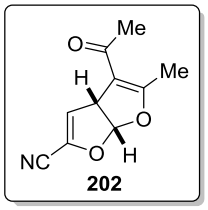


Pyridinium iodide **270** (23 mg, 0.075 mmol), silver salt **297** (64 mg, 0.075 mmol) and MeOH (10 mL) were subjected to **general procedure B** to afford *pyridinium salt* **323** (68 mg, 0.075 mmol, quant.) as a light yellow solid.

m.p. 151–153 °C; $[\alpha]_D^{20}$ = –16.8 (c = 1.0, CH_2Cl_2); **ν_{max}** (cm^{-1}) 2960, 1747, 1633, 1529; **δ_H** (400 MHz, $CDCl_3$) 9.10 (1H, d, *J* 6.6 Hz, $C_{Py}{}^6\underline{H}N^+$), 7.85 (2H, d, *J* 8.1 Hz, $C_{Ar}\underline{H}$), 7.77 (2H, s, $C_{Ar}\underline{H}$), 7.74 (2H, d, *J* 2.8 Hz, $C_{Ar}\underline{H}$), 7.46–7.43 (3H, m, $C_{Ar}\underline{H}$, $C_{Py}{}^5\underline{H}$), 7.36–7.26 (3H, m, $C_{Ar}\underline{H}$, $C_{Py}{}^3\underline{H}$), 7.07 (2H, d, *J* 1.5 Hz, $C_{Ar}\underline{H}$), 6.98 (2H, d, *J* 1.5 Hz, $C_{Ar}\underline{H}$), 4.10 (3H, s, $N^+C\underline{H}_3$), 3.96 (3H, s, $OC\underline{H}_3$), 3.95 (3H, s, $OC\underline{H}_3$), 3.01 (2H, sept, *J* 6.4 Hz, $C\underline{H}(CH_3)_2$), 2.89 (2H, sept, *J* 6.8 Hz, $C\underline{H}(CH_3)_2$), 2.73 (2H, sept, *J* 6.8 Hz, $C\underline{H}(CH_3)_2$), 1.23 (12H, d, *J* 6.7 Hz,

CH(C$\underline{H}_3$)$_2$), 1.20 (6H, m, *J* 6.7 Hz, CH(C$\underline{H}_3$)$_2$), 1.15 (6H, d, *J* 6.6 Hz, CH(C$\underline{H}_3$)$_2$), 1.08 (6H, d, *J* 6.8 Hz, CH(C$\underline{H}_3$)$_2$), 0.91 (6H, d, *J* 6.8 Hz, CH(C$\underline{H}_3$)$_2$); **δ_C** (100 MHz, $CDCl_3$) 171.1 ($\underline{C}_{Py}{}^4OCH_3$), 159.6 ($\underline{C}O_2CH_3$), 152.5 (N$\underline{C}_{Py}{}^2$), 148.2($C_{Ar}\underline{C}i$-Pr), 147.6 ($C_{Ar}\underline{C}i$-Pr), 147.4 ($C_{Ar}\underline{C}O$, 142.8 ($\underline{C}_{Py}{}^6HN^+$), 133.1($\underline{C}_{Ar}$), 132.8 ($\underline{C}_{Ar}$), 131.5 ($\underline{C}_{Ar}$), 130.2 ($\underline{C}_{Ar}H$), 127.9 ($\underline{C}_{Ar}H$), 127.0 ($\underline{C}_{Ar}H$), 125.5 ($\underline{C}_{Ar}H$), 124.4 ($\underline{C}_{Ar}H$), 122.8 ($\underline{C}_{Ar}H$), 120.9 ($\underline{C}_{Ar}$), 119.9 ($\underline{C}_{Ar}H$), 117.2 ($\underline{C}_{Py}{}^5H$), 111.3 ($\underline{C}_{Py}{}^3H$), 58.6 (O$\underline{C}H_3$), 54.6 (O$\underline{C}H_3$), 46.8 ($N^+CH_3$), 34.2 ($\underline{C}H(CH_3)_2$), 30.9 ($\underline{C}H(CH_3)_2$), 30.6 ($\underline{C}H(CH_3)_2$), 26.3 (CH($\underline{C}H_3$)$_2$), 24.8 (CH($\underline{C}H_3$)$_2$), 24.2 (CH($\underline{C}H_3$)$_2$), 24.0 (CH($\underline{C}H_3$)$_2$), 23.5 (CH($\underline{C}H_3$)$_2$), 23.4 (CH($\underline{C}H_3$)$_2$); **$\delta_P$** (162 MHz, $CDCl_3$) 4.79; **m/z** (ESI+) 182.08 [M+] **HRMS** (ESI+) $C_9H_{12}NO_3$+ requires 182.0812, found 182.0810 (Δ = 1.1 ppm).

(3*R,6*R**) 4-Acetyl-5-methyl-3a,6a-dihydrofuro[2,3-*b*]furan-2-carbonitrile 202[87]**



202

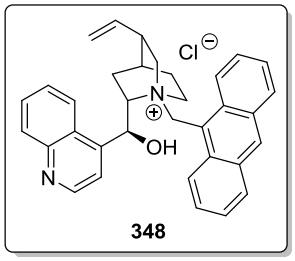
Racemic: 5-Nitro-2-furonitrile **197** (80 mg, 0.58 mmol), TBAI (21 mg, 0.058 mmol), Cs_2CO_3 (378 mg, 1.16 mmol), acetylacetone **199** (150 μL, 1.16 mmol), and PhMe/H_2O (5 mL, 4:1 v/v) were subjected to **general procedure C** for 12 h. Purification by FCC (CH_2Cl_2) afforded *bisdihydrofuran* **202** (83 mg, 0.44 mmol, 75%) as a colourless solid.

Chiral PTC: 5-Nitro-2-furonitrile **197** (80 mg, 0.58 mmol), *N*-(9-anthracenylmethyl)quinidinium chloride **371** (39 mg, 0.058 mmol), Cs_2CO_3 (378 mg, 1.16 mmol), acetylacetone **199** (150 μL, 1.16 mmol), and PhMe/H_2O (5 mL, 4:1 v/v) were subjected to **general procedure C** for 72 h. Purification by FCC (CH_2Cl_2) afforded *bisdihydrofuran* **202** (57 mg, 0.30 mmol, 52%, 26% ee) as a colourless solid.

m.p 83–86 °C; **ν_{max}** (cm^{-1}) 3001, 2928, 2185, 1632; **δ_H** (400 MHz, $CDCl_3$) 6.45 (1H, d, *J* 7.8 Hz, OC$\underline{H}$O), 6.18 (1H, d, *J* 3.0 Hz, OC=C$\underline{H}$), 4.56–4.50 (1H, m, C$\underline{H}$), 2.30 (3H, s, C$\underline{H}_3$), 2.29 (3H, s, C$\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 192.4 ($\underline{C}OCH_3$), 166.4 (O$\underline{C}CH_3$), 129.2 (O$\underline{C}$CN), 118.6 (O$\underline{C}$HO), 115.3 ($\underline{C}$N), 110.8 ($\underline{C}COCH_3$), 108.9 (OC=$\underline{C}$H), 52.9 ($\underline{C}$H), 29.1 (CO$\underline{C}H_3$), 14.9 ($\underline{C}H_3$); **m/z** (ESI+) not observed; **HRMS** (FI+) $C_{10}H_9NO_3{}^+$ requires 191.0582, observed 191.0580 (Δ = 1.0 ppm).

Enantiomeric excess was determined by chiral HPLC. (Chiralcel AD, 254nm, 2.0 mL/min, heptane/*i*-PrOH 95:5 v/v, tR_1 = 8.1 min, tR_2 = 12.0 min).

N-(9-Anthracenylmethyl)cinchonidinium chloride 348[199]



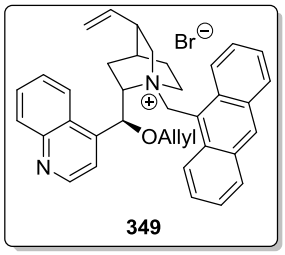
348

To a suspension of cinchonidine **314** (1.96 g, 6.65 mmol) in toluene (20 mL) was added 9-(chloromethyl)anthracene (1.58 g, 6.95 mmol) and the mixture stirred at reflux for 3 h. The mixture was cooled to room temperature, and Et_2O (20 mL) added over 10 minutes. The resultant suspension was stirred for 10 minutes, filtered, and the resultant solid washed with Et_2O (10 mL). The solid was dried *in vacuo* to afford *ammonium salt* **348** (2.53 g, 4.85 mmol, 73 %) as a light yellow solid.

m.p 166–170 °C (dec.) [Lit: 168–171 °C (dec.)][412]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = −381 (c = 0.81, $CHCl_3$) [Lit: −363 (c = 0.81, $CHCl_3$)][412]; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.07 (1H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 8.83 (1H, d, *J* 8.3 Hz, $C_{Ar}\underline{H}$), 8.78 (1H, d, *J* 4.3 Hz, $C_{Ar}\underline{H}$), 8.62 (1H, d, *J* 9.1 Hz, $C_{Ar}\underline{H}$), 8.12 (1H, d, *J* 4.8 Hz, $C_{Ar}\underline{H}$), 8.00 (1H, d, *J* 4.3 Hz, $C_{Ar}\underline{H}$), 7.93 (1H, s, $C_{Ar}\underline{H}$), 7.62–7.57 (2H, m, $C_{Ar}\underline{H}$), 7.53 (1H, d, *J* 8.3 Hz, $C_{Ar}\underline{H}$), 7.37–7.30 (1H, m, $C_{Ar}\underline{H}$), 7.26–7.10 (4H, m, $C_{Ar}\underline{H}$), 7.06–6.95 (1H, m, C$\underline{H}$OH), 6.82 (1H, d, *J* 13.4 Hz, ArC$\underline{H}_a$H$_b$N$^+$), 6.56 (1H, d, *J* 13.4 Hz, ArCH$_a\underline{H}_b$N$^+$), 5.46–5.35 (1H, m, C$\underline{H}$=CH$_2$), 5.23 (1H, d, *J* 17.4 Hz, CH=CH$_{cis}\underline{H}_{trans}$), 4.86 (1H, dd, *J* 10.6, 1.3 Hz, CH=C$\underline{H}_{cis}$H$_{trans}$), 4.79–4.70 (1H, m, C$\underline{H}$N$^+$), 4.68–4.57 (1H, m, C$\underline{H}_a$H$_b$N$^+$), 4.09 (1H, d, *J* 12.6 Hz, CH$_a\underline{H}_b$N$^+$), 2.57 (1H, dd, *J* 12.6, 10.9 Hz, CH$_a\underline{H}_b$N$^+$), 2.34 (1H, app t, *J* 11.2 Hz, CH$_a\underline{H}_b$N$^+$), 2.17–2.06 (1H, m, C$\underline{H}$CH=CH$_2$), 1.81–1.69 (2H, m, C$\underline{H}_a$H$_b$, C$\underline{H}_a$H$_b$), 1.65 (1H, br s, $\underline{C}$H), 1.13–1.01 (1H, m, CH$_a\underline{H}_b$), 1.00–0.91 (1H, m, CH$_a\underline{H}_b$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 149.4 ($\underline{C}_{Ar}$H), 147.0 ($\underline{C}_{Ar}$), 145.7 ($\underline{C}_{Ar}$), 136.4 ($\underline{C}$H=CH$_2$), 133.1 ($\underline{C}_{Ar}$), 132.7 ($\underline{C}_{Ar}$), 131.0 ($\underline{C}_{Ar}$H), 130.3 ($\underline{C}_{Ar}$), 130.1 ($\underline{C}_{Ar}$), 129.1 ($\underline{C}_{Ar}$H), 128.6 ($\underline{C}_{Ar}$H), 128.4 ($\underline{C}_{Ar}$H), 128.2 ($\underline{C}_{Ar}$H), 127.6 ($\underline{C}_{Ar}$H), 127.4 ($\underline{C}_{Ar}$H), 126.8 ($\underline{C}_{Ar}$H), 126.3 ($\underline{C}_{Ar}$H), 125.4 ($\underline{C}_{Ar}$H), 124.8 ($\underline{C}_{Ar}$H), 124.6 ($\underline{C}_{Ar}$H), 124.2 ($\underline{C}_{Ar}$), 124.1 ($\underline{C}_{Ar}$H), 120.0 ($\underline{C}_{Ar}$H), 118.4 ($\underline{C}_{Ar}$), 117.7 (CH=$\underline{C}$H$_2$), 67.2 ($\underline{C}$HN$^+$), 66.8 (CHOH), 61.3 (CH$_2$N$^+$), 54.7 (ArCH$_2$N$^+$), 50.4 (CH$_2$N$^+$), 38.4 ($\underline{C}$HCH=CH$_2$), 25.8 ($\underline{C}$H), 25.7 ($\underline{C}$H$_2$), 23.4 ($\underline{C}$H$_2$).

Spectroscopic data are consistent with those previously reported.[412]

O-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide 349[199]



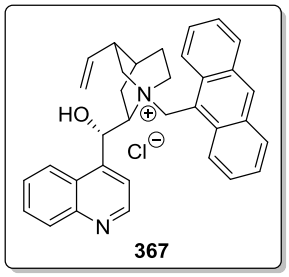
349

To a solution of *N*-(9-anthracenylmethyl)cinchonidinium chloride **348** (2.00 g, 3.26 mmol) in CH_2Cl_2 (20 mL) was added allyl bromide (1.01 mL, 11.7 mmol), and 50% w/v aq. KOH (2 mL). The reaction was stirred at room temperature for 4 h, diluted with H_2O (20 mL) and stirred for a further 5 minutes. The organic phase was separated, washed with 1M aq. NaBr (10 mL), dried over Na_2SO_4, and filtered. Et_2O (40 mL) was added to precipitate the product, and the suspension stirred for a further 1 h. The resultant solid was collected by filtration, washed with 1:4 CH_2Cl_2/Et_2O (50 mL) and dried *in vacuo* to afford *allyl ether* **349** (1.36 g, 2.25 mmol, 69%) as a yellow solid.

m.p 196–200 °C [Lit: 194–197 °C][199]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −331 (c = 0.45, $CHCl_3$) [Lit: = −320 (c = 0.45, $CHCl_3$)][199]; $\boldsymbol{\delta_H}$ (400MHz, d_4-methanol) 9.02 (1H, d, *J* 4.6 Hz, $C_{Ar}\underline{H}$), 8.86 (1H, br s, $C_{Ar}\underline{H}$), 8.79 (1H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 8.63–8.56 (1H, m, $C_{Ar}\underline{H}$), 8.42 (1H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 8.25–8.15 (3H, m, $C_{Ar}\underline{H}$), 7.97–7.88 (3H, m, $C_{Ar}\underline{H}$), 7.82–7.70 (2H, m, $C_{Ar}\underline{H}$), 7.66–7.56 (2H, m, $C_{Ar}\underline{H}$), 6.94 (1H, br s, C*H*OAllyl), 6.45–6.30 (2H, m, C*H*=CH_2, Ar$C\underline{H}_aH_bN^+$), 5.91 (1H, d, *J* 13.9 Hz, Ar$CH_a\underline{H}_bN^+$), 5.73–5.62 (2H, m, C*H*=CH_2, CH=$CH_{cis}\underline{H}_{trans}$), 5.54 (1H, dd, *J* 10.5, 1.3 Hz, CH=C$\underline{H}_{cis}H_{trans}$), 5.02–4.90 (2H, m, CH=C$\underline{H}_2$), 4.58-4.36 (4H, m, C$\underline{H}N^+$, OC$\underline{H}_2$CH=CH_2 C$\underline{H}_aH_bN^+$), 3.85–3.76 (1H, m, C$\underline{H}_aH_bN^+$), 3.21 (1H, t, *J* 12.2 Hz, $CH_a\underline{H}_bN^+$), 2.86 (1H, dt, *J* 11.0, 4.9 Hz, $CH_a\underline{H}_bN^+$), 2.48–2.36 (2H, m, C*H*CH=CH_2, C$\underline{H}_aH_b$), 2.19–2.06 (1H, m, C$\underline{H}_aH_b$), 1.94 (1H, d, *J* 2.9 Hz, C*H*), 1.64–.50 (2H, m, $CH_a\underline{H}_b$, $CH_a\underline{H}_b$); $\boldsymbol{\delta_C}$ (100 MHz, d_4-methanol) 151.2 ($\underline{C}_{Ar}H$), 149.5 ($\underline{C}_{Ar}$), 143.1 ($\underline{C}_{Ar}$), 138.7 (CH$\underline{C}$H=CH_2), 135.0 ($\underline{C}_{Ar}$), 134.9 ($\underline{C}_{Ar}H$), 134.8 ($\underline{C}_{Ar}$), 134.0 ($\underline{C}_{Ar}H$), 133.2 (OC$H_2\underline{C}$H=CH_2), 133.2 ($\underline{C}_{Ar}$), 131.7 ($\underline{C}_{Ar}H$), 131.4 ($\underline{C}_{Ar}H$), 131.3 ($\underline{C}_{Ar}H$), 130.7 ($\underline{C}_{Ar}H$), 129.6 ($\underline{C}_{Ar}H$), 129.6 ($\underline{C}_{Ar}H$), 129.4 ($\underline{C}_{Ar}H$), 127.3 (C_{Ar}), 126.8 ($\underline{C}_{Ar}H$), 126.7 ($\underline{C}_{Ar}H$), 125.7 ($\underline{C}_{Ar}H$), 125.1 ($\underline{C}_{Ar}H$), 121.9 ($\underline{C}_{Ar}$), 119.2 (CH=$\underline{C}H_2$), 118.0 (CH=$\underline{C}H_2$), 71.6 (O$\underline{C}H_2$CH=CH_2), 70.1 (CHN^+), 70.1 ($\underline{C}$HOAllyl), 63.6 (CH_2N^+), 57.5 ($ArCH_2N^+$), 53.8 (CH_2N^+), 39.6 ($\underline{C}$HCH=CH_2), 27.5 (CH), 26.4 (CH_2), 23.5 (CH_2).

Spectroscopic data are consistent with those previously reported.[199]

N-(9-Anthracenylmethyl)cinchoninium chloride 367[198]



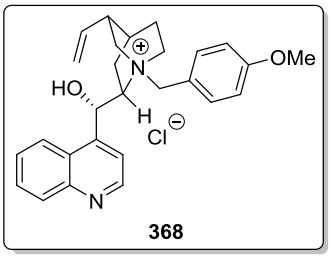
367

To a suspension of cinchonine **366** (3.11 g, 10.6 mmol) in toluene (25 mL) was added 9-(chloromethyl)anthracene (2.50 g, 11.0 mmol) and the mixture stirred at reflux for 3 h. The mixture was cooled to room temperature, and Et_2O (20 mL) added over 10 minutes. The resultant suspension was stirred for 10 minutes, filtered, and the resultant solid washed with 10 mL Et_2O. The solid was dried *in vacuo* to afford *ammonium salt* **367** (3.52 g, 6.75 mmol, 64 %) as a light yellow solid.

m.p 164–166 °C [Lit: 166–167 °C][198]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +245 (c = 1.0, $CHCl_3$) [Lit: +240 (c = 1.0, $CHCl_3$)][198]; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.26 (1H, d, *J* 9.1 Hz, $C_{Ar}\underline{H}$), 8.93 (1H, d, *J* 8.3 Hz, $C_{Ar}\underline{H}$), 8.84 (1H, d, *J* 4.0 Hz, $C_{Ar}\underline{H}$), 8.41 (1H, d, *J* 9.1 Hz, $C_{Ar}\underline{H}$), 8.04 (1H, d, *J* 4.5 Hz, $C_{Ar}\underline{H}$), 7.86 (1H, s, $C_{Ar}\underline{H}$), 7.55 (2H, t, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 7.45 (1H, d, *J* 8.3 Hz, $C_{Ar}\underline{H}$), 6.89–7.31 (8H, m, $C_{Ar}\underline{H}$, C$\underline{H}$OH, ArC$\underline{H}_a$H$_b$N$^+$), 6.47 (1H, d, *J* 13.4 Hz, ArC$\underline{H}_a$H$_b$N$^+$), 5.57 (1H, ddd, *J* 17.2, 10.5, 6.7 Hz, C$\underline{H}$=CH$_2$), 5.02 (1H, d, *J* 10.5 Hz, CH=C$\underline{H}_{cis}$H$_{trans}$), 4.86 (1H, d, *J* 17.2 Hz, CH=CH$_{cis}\underline{H}_{trans}$), 4.77–4.67 (1H, m, C$\underline{H}N^+$), 4.46–4.37 (1H, m, C$\underline{H}_aH_bN^+$), 4.21–4.18 (1H, m, CH$_a\underline{H}_bN^+$), 2.46 (1H, t, *J* 11.6 Hz, C$\underline{H}_a$H$_b$N$^+$), 2.37–2.27 (1H, m, CH$_a\underline{H}_b$N$^+$), 1.99–1.88 (1H, m, C$\underline{H}$CH=CH$_2$), 1.76–1.62 (2H, m, C$\underline{H}_2$), 1.54–1.48 (1H, m, CH), 1.40–1.30 (1H, m, C$\underline{H}_a$H$_b$), 0.69–0.55 (1H, m, CH$_a\underline{H}_b$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 149.3 ($\underline{C}_{Ar}$H), 147.0 ($\underline{C}_{Ar}$), 145.4 ($\underline{C}_{Ar}$H), 135.5 ($\underline{C}$H=CH$_2$), 133.0 ($\underline{C}_{Ar}$), 132.6 ($\underline{C}_{Ar}$), 130.9 ($\underline{C}_{Ar}$H), 130.3 ($\underline{C}_{Ar}$), 129.9 ($\underline{C}_{Ar}$), 129.0 ($\underline{C}_{Ar}$H), 128.3 ($\underline{C}_{Ar}$H), 128.1 ($\underline{C}_{Ar}$H), 127.5 ($\underline{C}_{Ar}$H), 127.2 ($\underline{C}_{Ar}$H), 126.9 ($\underline{C}_{Ar}$H), 124.8 ($\underline{C}_{Ar}$H), 124.4 ($\underline{C}_{Ar}$), 124.0 ($\underline{C}_{Ar}$H), 120.0 ($\underline{C}_{Ar}$H), 118.0 ($\underline{C}_{Ar}$), 117.4 (CH=$\underline{C}$H$_2$), 67.7 ($\underline{C}$HN$^+$), 66.6 ($\underline{C}$HOH), 57.4 ($\underline{C}$H$_2$N$^+$), 54.1(Ar$\underline{C}$H$_2$N$^+$), 53.9 ($\underline{C}$H$_2$N$^+$), 38.0 ($\underline{C}$HCH=CH$_2$), 26.3 ($\underline{C}$H), 24.1 ($\underline{C}$H$_2$), 22.6 ($\underline{C}$H$_2$).

Spectroscopic data are consistent with those previously reported.[198]

N-(4-Methoxybenzyl)cinchoninium chloride 368[200]



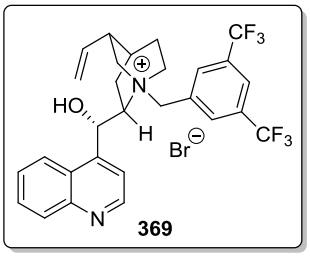
368

A mixture of cinchonine **366** (1.47 g, 5.00 mmol) and *p*-methoxybenzyl chloride (0.68 mL, 5.0 mmol) in THF (20 mL) was stirred at reflux for 88 h. The resultant suspension was cooled to room temperature, the precipitate collected by filtration, and washed with benzene (20 mL). Recrystallisation from MeOH afforded *ammonium salt* **368** (1.20 g, 2.56 mmol, 51 %) as a white solid.

m.p 224–227 °C (dec.) [Lit: 226 °C (dec.)][200]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +150 (c = 1.2, MeOH) [Lit: +130 (c = 1.0, MeOH)][200]; $\boldsymbol{\delta_H}$ (400 MHz, d_4-methanol) 8.95 (1H, d, *J* 4.5 Hz, $C_{Ar}\underline{H}$), 8.33 (1H, d, *J* 7.8 Hz, $C_{Ar}\underline{H}$), 8.11 (1H, d, *J* 8.2 Hz, $C_{Ar}\underline{H}$), 7.98 (1H, d, *J* 4.5 Hz, $C_{Ar}\underline{H}$), 7.89–7.79 (2H, m, $C_{Ar}\underline{H}$), 7.66 (2H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 7.11 (2H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 6.65 (1H, s, C$\underline{H}$OH), 6.09 (1H, ddd, *J* 17.3, 10.4, 7.2 Hz, C$\underline{H}$=CH_2), 5.34–5.25 (2H, m, CH=C$\underline{H_2}$), 5.11–4.95 (1H, m, O$\underline{H}$), 4.94–4.87 (2H, m, ArC$\underline{H_2}N^+$), 4.44–4.36 (1H, m, C$\underline{H_a}H_bN^+$), 4.08–3.98 (1H, m, C$\underline{H}N^+$), 3.88 (4H, s, OC$\underline{H_3}$, C$\underline{H_a}H_bN^+$), 3.66–3.57 (1H, m, $CH_a\underline{H_b}N^+$), 3.14–3.05 (1H, m, $CH_a\underline{H_b}N^+$), 2.69–2.58 (1H, m, C$\underline{H}$CH=CH_2), 2.53–2.42 (1H, m, C$\underline{H_a}H_b$), 2.00–1.77 (3H, m, C$\underline{H}$, C$\underline{H_2}$), 1.11–0.93 (1H, m, $CH_a\underline{H_b}$); $\boldsymbol{\delta_C}$ (100 MHz, d_4-methanol) 161.9 ($\underline{C}_{Ar}$OMe), 150.1 ($\underline{C}_{Ar}$H), 147.7 ($\underline{C}_{Ar}$), 146.5 ($\underline{C}_{Ar}$), 136.7 ($\underline{C}$H=CH_2), 135.3 ($\underline{C}_{Ar}$H), 130.2 ($\underline{C}_{Ar}$H), 129.3 ($\underline{C}_{Ar}$H), 128.1 ($\underline{C}_{Ar}$H), 125.2 ($\underline{C}_{Ar}$), 123.4 ($\underline{C}_{Ar}$H), 120.2 ($\underline{C}_{Ar}$H), 119.3 ($\underline{C}_{Ar}$), 116.9 (CH=$\underline{C}H_2$), 114.7 ($\underline{C}_{Ar}$H), 67.8 ($\underline{C}$HOH), 65.9 ($\underline{C}HN^+$), 63.2 (Ar$\underline{C}H_2N^+$), 56.8 ($\underline{C}H_2N^+$), 55.0 (O$\underline{C}H_3$), 54.5 ($\underline{C}H_2N^+$), 37.9 ($\underline{C}$HCH=CH_2), 27.6 ($\underline{C}$H), 23.7 ($\underline{C}H_2$), 21.3 ($\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[200]

N-(3,5-Bis(trifluoromethyl)benzylcinchoninium chloride 369[201]



369

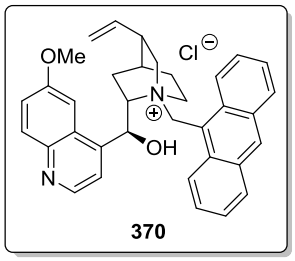
A mixture of cinchonine **366** (800 mg, 2.72 mmol) and 3,5-bis(trifluoromethyl)benzyl bromide (0.60 mL, 4.3 mmol) in THF (80 mL) was stirred at reflux for 12 h. The reaction was

cooled to room temperature and the solvent removed *in vacuo*. Recrystallisation from CH_2Cl_2/Et_2O afforded *ammonium salt* **369** (1.09 g, 1.82 mmol, 67 %) as a colourless solid.

m.p 200–205 °C (dec.) [Lit: 245 °C (dec.)][201]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = +108 (c = 1.0, $CHCl_3$) [Lit: +102.9 (c = 1.0, $CHCl_3$)][201]; $\boldsymbol{\delta_H}$ (400 MHz, d_4-methanol) 8.93 (1H, d, *J* 4.6 Hz, $C_{Ar}\underline{H}$), 8.48 (2H, s, $C_{Ar}\underline{H}$), 8.42–8.36 (1H, m, $C_{Ar}\underline{H}$), 8.21 (1H, s, $C_{Ar}\underline{H}$), 8.11–8.07 (1H, m, $C_{Ar}\underline{H}$), 7.95 (1H, d, *J* 4.6 Hz, $C_{Ar}\underline{H}$), 7.86–7.77 (2H, m, $C_{Ar}\underline{H}$), 6.62 (1H, s, C$\underline{H}$OH), 6.11–5.59 (1H, m, C$\underline{H}$=CH_2), 5.40 (1H, d, *J* 12.6 Hz, CH=C$\underline{H}_{cis}H_{trans}$), 5.32–5.18 (3H, m, ArC$\underline{H}_2N^+$, CH=$CH_{cis}\underline{H}_{trans}$), 4.56-4.48 (1H, m, C$\underline{H}_aH_bN^+$), 4.12-3.99 (2H, m, C$\underline{H}_aH_bN^+$, $\underline{C}HN^+$), 3.55 (1H, t, *J* 11.3 Hz, $CH_a\underline{H}_bN^+$), 3.30–3.26 (1H, m, O$\underline{H}$), 3.21-3.05 (1H, m, $CH_a\underline{H}_bN^+$), 2.65 (1H, q, *J* 8.4 Hz, C$\underline{H}$CH=CH_2), 2.53–2.44 (1H, m, C$\underline{H}_aH_b$), 1.96–1.77 (3H, m, C$\underline{H}_2$, C$\underline{H}$), 1.13–1.03 (1H, m, $CH_a\underline{H}_b$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 149.6 ($\underline{C}_{Ar}H$), 147.3 ($\underline{C}_{Ar}$), 145.8 ($\underline{C}_{Ar}$), 136.1 ($\underline{C}H=CH_2$), 134.1 ($\underline{C}_{Ar}H$), 132.2 (q, *J* 33.5 Hz, $\underline{C}_{Ar}CF_3$), 130.7 ($\underline{C}_{Ar}$), 129.8 ($\underline{C}_{Ar}H$), 128.8 ($\underline{C}_{Ar}H$), 127.8 ($\underline{C}_{Ar}H$), 124.7 ($\underline{C}_{Ar}$), 124.2 (m, $\underline{C}_{Ar}H$), 123.8 (q, *J* 271 Hz, $\underline{C}F_3$) 123.2 ($\underline{C}_{Ar}H$), 119.8 ($\underline{C}_{Ar}H$), 116.7 (CH=$\underline{C}H_2$), 68.3 ($\underline{C}$HOH), 65.5 ($\underline{C}HN^+$), 61.4 (Ar$\underline{C}H_2N^+$), 56.5 ($\underline{C}H_2N^+$), 55.0 ($\underline{C}H_2N^+$), 37.5 ($\underline{C}$HCH=CH_2), 27.0 ($\underline{C}$H), 23.3 ($\underline{C}H_2$), 20.9 ($\underline{C}H_2$); $\boldsymbol{\delta_F}$ (377 MHz, d_4-methanol) −64.1.

Spectroscopic data are consistent with those previously reported.[201]

N-(9-Anthracenylmethyl)quininium chloride 370[169]



370

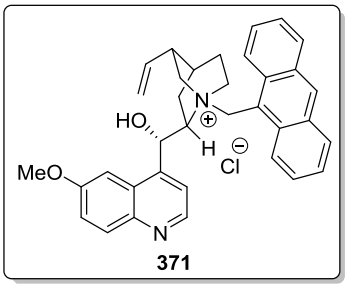
A mixture of quinine (1.43 g, 4.41 mmol) and 9-(chloromethyl)anthracene (1.00 g, 4.41 mmol) in THF (20 mL) was stirred at reflux for 72 h. The suspension was cooled to room temperature, filtered, and the resultant solid washed with toluene (20 mL). Recrystallisation from MeOH afforded *ammonium salt* **370** (1.07 g, 1.94 mmol, 44 %) as a light brown solid.

m.p 185–187 °C (dec.) [Lit: 190 °C (dec.)][169]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −389 (c = 0.8, $CHCl_3$) [Lit: −415 (c = 0.8, $CHCl_3$)][169]; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 9.27 (1H, d, *J* 9.1 Hz, $C_{Ar}\underline{H}$), 8.72 (1H, d, *J* 4.5 Hz, $C_{Ar}\underline{H}$), 8.51 (1H, s, $C_{Ar}\underline{H}$), 8.40 (1H, d, *J* 8.8 Hz, $C_{Ar}\underline{H}$), 8.10–7.93 (5H, m, $C_{Ar}\underline{H}$) 7.71–

7.60 (2H, m, $C_{Ar}\underline{H}$) 7.58–7.52 (1H. m, $C_{Ar}\underline{H}$), 7.50–7.41 (2H, m, $C_{Ar}\underline{H}$), 7.39–7.28 (1H, m, $C_{Ar}\underline{H}$), 7.14 (1H, d, *J* 13.6 Hz, $ArC\underline{H}_aH_bN^+$), 7.12 (1H, d, $C\underline{H}OH$), 6.07 (1H, d, *J* 13.6 Hz, $ArCH_a\underline{H}_bN^+$), 5.53–5.46 (1H, m, $C\underline{H}=CH_2$), 5.33–5.28 (1H, m, $C\underline{H}_aH_bN^+$), 4.98 (1H, d, *J* 10.3 Hz, $CH=C\underline{H}_{cis}H_{trans}$), 4.90 (1H, d, *J* 17.2 Hz, $CH=CH_{cis}\underline{H}_{trans}$), 4.25–4.19 (1H, m, $C\underline{H}N^+$), 3.97 (3H, s, $OC\underline{H}_3$), 3.34–3.28 (1H, m, $C\underline{H}_aH_bN^+$), 3.02–2.94 (1H, m, $CH_a\underline{H}_bN^+$), 2.68–2.60 (1H, m, $CH_a\underline{H}_bN^+$), 2.39–2.34 (1H, m, $C\underline{H}_aH_b$), 2.33–2.27 (1H, m, $C\underline{H}_aH_b$), 2.24–2.18 (1H, m, $C\underline{H}CH=CH_2$), 1.94–1.85 (1H, $C\underline{H}$), 1.55–1.49 (1H, m, $CH_a\underline{H}_b$), 1.48–1.41 (1H, m, $CH_a\underline{H}_b$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 157.9 ($\underline{C}_{Ar}OCH_3$), 147.3 ($\underline{C}_{Ar}H$), 144.2 ($\underline{C}_{Ar}$), 143.5 ($\underline{C}_{Ar}$), 136.5 ($CH=\underline{C}H_2$), 133.1 ($\underline{C}_{Ar}H$), 132.8 ($\underline{C}_{Ar}H$), 131.7 ($\underline{C}_{Ar}$), 131.7 ($\underline{C}_{Ar}$), 130.9 ($\underline{C}_{Ar}$), 130.7 ($\underline{C}_{Ar}$), 129.5 ($\underline{C}_{Ar}$), 128.6 ($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 127.7 ($\underline{C}_{Ar}H$), 126.5 ($\underline{C}_{Ar}H$), 125.4 ($\underline{C}_{Ar}$), 124.9 ($\underline{C}_{Ar}H$), 124.3($\underline{C}_{Ar}H$), 120.9 ($\underline{C}_{Ar}H$), 120.9 ($\underline{C}_{Ar}H$), 118.0 ($\underline{C}_{Ar}H$), 117.6 ($CH=\underline{C}H_2$), 112.3 ($\underline{C}_{Ar}H$), 70.1 ($\underline{C}HOH$), 66.5 ($\underline{C}HN^+$), 60.9 ($Ar\underline{C}H_2N^+$), 56.4 ($O\underline{C}H_3$), 56.3 ($\underline{C}H_2N^+$) 52.1 ($\underline{C}H_2N^+$), 38.3 ($\underline{C}HCH=CH_2$), 25.8 ($\underline{C}H$), 25.4 ($\underline{C}H_2$), 22.5 ($\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[180]

N-(9-Anthracenylmethyl)quinidinium chloride 371[169]



371

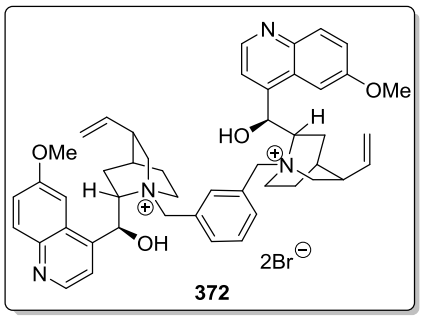
A mixture of quinidine (324 mg, 1.00 mmol), and 9-(chloromethyl)anthracene (272 mg, 1.20 mmol) in toluene (5 mL) was refluxed for 8 h. The resultant solution was cooled to room temperature, poured onto Et_2O (30 mL), and stirred for a further 1 h. Purification by FCC (10:1 EtOAc/MeOH) afforded *ammonium salt* **371** (412 mg, 0.74 mmol, 74%) as a light yellow solid.

m.p 160–162 °C (dec.) [Lit: 161 °C (dec.)][413]; $\boldsymbol{[\alpha]_D^{20}}$ = +402 (c = 0.15, MeOH) [Lit: +390 (c = 0.12, MeOH)][413]; $\boldsymbol{\delta_H}$ (400MHz, DMSO-d_6); 8.98 (1H, s, $C_{Ar}\underline{H}$), 8.86 (1H, d, *J* 4.4 Hz, $C_{Ar}\underline{H}$), 8.79 (1H, d, *J* 9.2 Hz,$C_{Ar}\underline{H}$), 8.70 (1H, d, *J* 9.2 Hz, $C_{Ar}\underline{H}$), 8.28 (2H, dd, *J* 8.2, 3.0 Hz, $C_{Ar}\underline{H}$), 8.05 (1H, d, *J* 9.2 Hz, $C_{Ar}\underline{H}$), 7.90 (1H, d, *J* 4.4 Hz, $C_{Ar}\underline{H}$), 7.82–7.74 (3H, m, $C_{Ar}\underline{H}$), 7.69–7.64 (3H, m, $C_{Ar}\underline{H}$), 7.53 (1H, dd, *J* 7.6, 2.4 Hz, $C_{Ar}\underline{H}$), 6.98 (1H, s, $O\underline{H}$), 6.33 (1H, d, *J* 14.4 Hz, $C\underline{H}OH$), 6.03 (1H, ddd, *J* 17.2, 10.2, 7.2 Hz, $C\underline{H}=CH_2$), 5.88 (1H, d, *J* 14.0 Hz,

ArC$\underline{H}_a$H$_b$N$^+$), 5.18 (1H, d, *J* 10.4 Hz, CH=C$\underline{H}_{cis}$H$_{trans}$), 5.08 (1H, d, *J* 17.2 Hz, CH=C$\underline{H}_{cis}\underline{H}_{trans}$), 4.54–4.42 (2H, ArCH$_a\underline{H}_bN^+$, C$\underline{H}_aH_bN^+$), 4.25–4.09 (4H, m, OC$\underline{H}_3$, C$\underline{H}N^+$), 3.18 (1H, t, *J* 11.2 Hz, 1H, C$\underline{H}_a$H$_b$N$^+$), 2.62–2.54 (m, 1H, CH$_a\underline{H}_b$N$^+$), 2.46–2.35 (2H, m, C$\underline{H}_a$H$_b$N$^+$, C$\underline{H}$), 1.78 (1H, s, C$\underline{H}_a$H$_b$), 1.69 (1H, d, *J* 8.4 Hz, C$\underline{H}_a$H$_b$), 1.56–1.53 (1H, m, CH$_a\underline{H}_b$), 1.10–1.04 (1H, m, CH$_a\underline{H}_b$); **δ$_C$** (100 MHz, DMSO-*d*$_6$) 158.0 ($\underline{C}_{Ar}$OCH$_3$), 147.9 ($\underline{C}_{Ar}$H), 144.2 ($\underline{C}_{Ar}$), 143.9 ($\underline{C}_{Ar}$), 139.2 ($\underline{C}_{Ar}$H), 137.8 ($\underline{C}$H=CH$_2$), 135.7 ($\underline{C}_{Ar}$H), 131.9 ($\underline{C}_{Ar}$H), 130.2 ($\underline{C}_{Ar}$H), 129.0 ($\underline{C}_{Ar}$), 125.9 ($\underline{C}_{Ar}$), 121.8 ($\underline{C}_{Ar}$H), 120.9 ($\underline{C}_{Ar}$H), 117.4 (CH=$\underline{C}$H$_2$), 102.8 ($\underline{C}_{Ar}$H), 68.0 ($\underline{C}$HOH), 65.1 ($\underline{C}$HN$^+$), 63.2 (Ar$\underline{C}$H$_2$N$^+$), 56.2 (O$\underline{C}$H$_3$), 56.2 ($\underline{C}$H$_2$N$^+$), 54.1 ($\underline{C}$H$_2$N$^+$), 37.2 ($\underline{C}$HCH=CH$_2$), 26.9 ($\underline{C}$H), 23.4 ($\underline{C}$H$_2$), 21.1 ($\underline{C}$H$_2$).

Spectroscopic data are consistent with those previously reported.[413]

α,α'-Bisquininium-*m*-xylene dibromide 372[185]



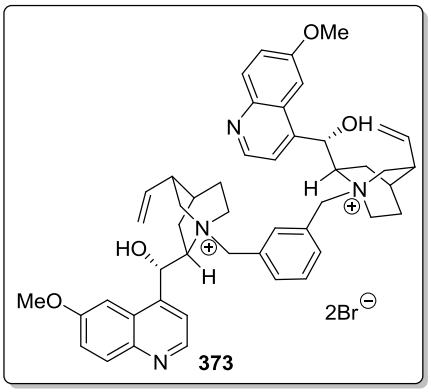
Quinine (2.16 g, 6.66 mmol), *α,α*'-dibromo-*m*-xylene (880 mg, 3.33 mmol) and CHCl$_3$/EtOH/DMF (13 mL, 5:2:6 v/v) were subjected to **general procedure D** to afford *ammonium salt* **372** (1.28 g, 1.40 mmol, 42%) as a pink solid.

m.p 215–217 °C (dec.) [Lit: 213 °C (dec.)][187]; **$[\alpha]_D^{20}$** = −188 (c = 0.12, MeOH) [Lit: −202 (c = 0.1, MeOH)][187]; **δ$_H$** (400 MHz, DMSO-*d*$_6$) 8.82 (2H, d, *J* 4.5 Hz, C$_{Ar}\underline{H}$), 8.08 (1H, s, C$_{Ar}\underline{H}$), 8.03 (2H, d, *J* 9.2 Hz, C$_{Ar}\underline{H}$), 7.88 (2H, d, *J* 7.7 Hz, C$_{Ar}\underline{H}$), 7.79 (2H, d, *J* 4.5 Hz, C$_{Ar}\underline{H}$), 7.73 (1H, t, *J* 7.6 Hz, C$_{Ar}\underline{H}$), 7.51 (2H, dd, *J* 9.2, 2.5 Hz, C$_{Ar}\underline{H}$), 7.42 (2H, d, *J* 2.3 Hz, C$_{Ar}\underline{H}$), 6.71 (2H, d, *J* 3.8 Hz, $\underline{C}$HOH), 6.65 (2H, br s, O$\underline{H}$), 5.83–5.72 (2H, m, C$\underline{H}$=CH$_2$), 5.59 (2H, d, *J* 12.4 Hz, ArC$\underline{H}_a$H$_b$N$^+$), 5.12 (2H, d, *J* 17.2 Hz, CH=C$\underline{H}_{trans}$H$_{cis}$), 5.01 (2H, d, *J* 10.4 Hz, CH=CH$_{trans}\underline{H}_{cis}$), 4.80 (2H, d, *J* 12.3 Hz, ArCH$_a\underline{H}_b$N$^+$), 4.31–3.21 (2H, m, C$\underline{H}_a$H$_b$N$^+$), 4.05 (6H, s, OC$\underline{H}_3$), 3.90–3.84 (2H, m, C$\underline{H}$N$^+$), 3.76–3.67 (2H, m, C$\underline{H}_a$H$_b$N$^+$), 3.59 (2H, t, *J* 11.5 Hz, CH$_a\underline{H}_b$N$^+$), 3.42–3.28 (2H, m, CH$_a\underline{H}_b$N$^+$) 2.82–2.74 (2H, m, C$\underline{H}$CH=CH$_2$), 2.31–2.18 (2H, m, C$\underline{H}_a$H$_b$), 2.17–2.07 (2H, m, C$\underline{H}_a$H$_b$), 1.86–1.75 (2H, m, CH$_a\underline{H}_b$), 1.47 (2H, t, *J* 11.2 Hz, CH$_a\underline{H}_b$); **δ$_C$** (100 MHz, DMSO-*d*$_6$) 157.5 ($\underline{C}_{Ar}$OCH$_3$), 147.5

($\underline{C}_{Ar}H$), 143.8 ($\underline{C}_{Ar}$), 143.7 ($\underline{C}_{Ar}$), 138.7 ($\underline{C}_{Ar}H$), 138.1 ($\underline{C}H=CH_2$), 131.2 ($\underline{C}_{Ar}H$), 131.5 ($\underline{C}_{Ar}H$), 129.7 ($\underline{C}_{Ar}H$), 128.6 ($\underline{C}_{Ar}$), 125.4 ($\underline{C}_{Ar}$), 121.5 ($\underline{C}_{Ar}H$), 120.4 ($\underline{C}_{Ar}H$), 116.5 ($CH=\underline{C}H_2$), 102.0 ($\underline{C}_{Ar}H$), 68.5 ($\underline{C}HOH$), 63.7 ($\underline{C}HN^+$), 62.9 ($Ar\underline{C}H_2N^+$), 59.1 ($\underline{C}H_2N^+$), 55.7 ($O\underline{C}H_3$), 50.7 ($\underline{C}H_2N^+$), 37.0 ($\underline{C}HCH=CH_2$), 26.0 ($\underline{C}H$), 24.1($\underline{C}H_2$), 20.4 ($\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[187]

α,α'-Bisquinidinium-*m*-xylene dibromide 373[185]

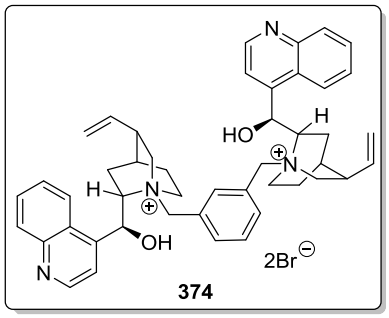


Quinidine (2.16 g, 6.66 mmol), *α,α'*-dibromo-*m*-xylene (880 mg, 3.33 mmol) and $CHCl_3$/EtOH/DMF (13 mL, 5:2:6 v/v) were subjected to **general procedure D** to afford *ammonium salt* **373** (1.70 g, 1.86 mmol, 56%) as a pink solid.

m.p 227–230 °C (dec.) [Lit: 218 °C (dec.)][187]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{20}}$ = +206 (c = 0.14, MeOH) [Lit: +197 (c = 0.14, MeOH)][187]; $\boldsymbol{\delta_H}$ (400 MHz, DMSO-d_6) 8.82 (2H, d, *J* 4.5 Hz, ArC$\underline{H}$), 8.12 (1H, br s, $C_{Ar}\underline{H}$), 8.03 (2H, d, *J* 9.2 Hz, $C_{Ar}\underline{H}$), 7.93 (2H, d, *J* 7.6 Hz, $C_{Ar}\underline{H}$), 7.82–7.73 (3H, m, $C_{Ar}\underline{H}$), 7.52 (2H, dd, *J* 9.2, 2.4 Hz, $C_{Ar}\underline{H}$), 7.46 (2H, d, *J* 2.4 Hz, $C_{Ar}\underline{H}$), 6.87 (2H, d, *J* 3.5 Hz, O$\underline{H}$), 6.58 (2H, br s, C$\underline{H}$OH,), 6.09–5.99 (2H, m, C$\underline{H}$=CH_2), 5.22–5.12 (6H, m, CH=C$\underline{H}_2$, ArC$\underline{H}_aH_bN^+$), 4.85 (2H, d, *J* 12.3 Hz, $ArCH_a\underline{H}_bN^+$), 4.23 (2H, t, *J* 9.2 Hz, C$\underline{H}_aH_b$), 4.11–4.00 (8H m, OC$\underline{H}_3$, C$\underline{H}_aH_b$), 3.85 (2H, t, *J* 9.5 Hz, C$\underline{H}N^+$), 3.54 (2H, t, *J* 11.0 Hz, $CH_a\underline{H}_b$), 3.40–3.27 (2H, m, $CH_a\underline{H}_b$), 2.85–2.74 (2H, m, C$\underline{H}$CH=CH_2), 2.47–2.37 (2H, m, C$\underline{H}_aH_b$), 1.94–1.88 (2H, m, C$\underline{H}$), 1.81–1.79 (4H, m, C$\underline{H}_2$), 1.18–1.12 (2H, m, $CH_a\underline{H}_b$); $\boldsymbol{\delta_C}$ (100 MHz, DMSO-d_6) 158.0 ($\underline{C}_{Ar}OCH_3$), 147.9 ($\underline{C}_{Ar}H$), 144.2 ($\underline{C}_{Ar}$), 143.9 ($\underline{C}_{Ar}$), 139.2 ($\underline{C}_{Ar}H$), 137.8 ($\underline{C}H=CH_2$), 135.7 ($\underline{C}_{Ar}H$), 131.9 ($\underline{C}_{Ar}H$), 130.2 ($\underline{C}_{Ar}H$), 129.0 ($\underline{C}_{Ar}$), 125.9 ($\underline{C}_{Ar}$), 121.8 ($\underline{C}_{Ar}H$), 120.9 ($\underline{C}_{Ar}H$), 117.4 ($CH=\underline{C}H_2$), 102.8 ($\underline{C}_{Ar}H$), 68.0 ($\underline{C}HOH$), 65.1 ($\underline{C}HN^+$), 63.2 ($Ar\underline{C}H_2N^+$), 56.2 ($O\underline{C}H_3$), 56.2 ($\underline{C}H_2N^+$), 54.1 ($\underline{C}H_2N^+$), 37.2 ($\underline{C}HCH=CH_2$), 26.9 ($\underline{C}H$), 23.4 ($\underline{C}H_2$), 21.1 ($\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[413]

α,α'-Biscinchonidinium-*m*-xylene dibromide 374[185]

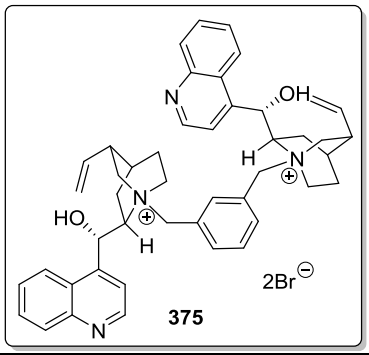


Cinchonidine (4.00 g, 13.6 mmol), *α,α*'-dibromo-*m*-xylene (1.76 g, 6.66 mmol) and $CHCl_3$/EtOH/DMF (26 mL, 5:2:6 v/v) were subjected to general procedure D to afford *ammonium salt* **374** (4.66 g, 5.40 mmol, 81%) as a pink solid.

m.p 212-216 °C (dec.) [Lit: 205 °C (dec.)][185]; $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\boldsymbol{20}}$ = −177 (c = 0.39, MeOH) [Lit: −171 (c = 0.28, MeOH)][185]; $\boldsymbol{\delta_H}$ (400 MHz, DMSO-d_6) 8.99 (2H, d, *J* 4.5 Hz, $C_{Ar}\underline{H}$), 8.37 (2H, d, *J* 8.4 Hz, $C_{Ar}\underline{H}$), 8.15 (1H, s, $C_{Ar}\underline{H}$), 8.12 (2H, d, *J* 1.1 Hz, $C_{Ar}\underline{H}$), 7.98 (2H, d, *J* 7.8 Hz, $C_{Ar}\underline{H}$), 7.88–7.81 (4H, m, $C_{Ar}\underline{H}$), 7.79–7.72 (3H, m, $C_{Ar}\underline{H}$), 6.77 (2H, d, *J* 4.4 Hz, O$\underline{H}$), 6.60 (2H, d, *J* 3.2 Hz, C$\underline{H}$OH), 5.73–5.64 (2H, m, C$\underline{H}$=CH_2), 5.32 (2H, d, *J* 12.4 Hz, ArC$\underline{H}_aH_bN^+$), 5.26–5.13 (4H, m, C=$CH_{cis}\underline{H}_{trans}$, $ArCH_a\underline{H}_bN^+$), 4.94 (2H, d, *J* 10.5 Hz, CH=C$\underline{H}_{cis}H_{trans}$), 4.37–4.25 (2H, m, C$\underline{H}_aH_bN^+$), 3.98 (2H, t, *J* 8.9 Hz, C$\underline{H}N^+$), 3.89–3.81 (2H, m, C$\underline{H}_aH_bN^+$), 3.61 (2H, t, *J* 11.4 Hz, $CH_a\underline{H}_bN^+$), 3.45–3.38 (m, 2 H, $CH_a\underline{H}_bN^+$), 2.76 (2H, br s, C$\underline{H}$CH=CH_2), 2.16–1.97 (6H, m, C$\underline{H}_aH_b$, C$\underline{H}_aH_b$, C$\underline{H}$), 1.90–1.80 (2H, m, $CH_a\underline{H}_b$), 1.34–1.23 (2H, m, $CH_a\underline{H}_b$); $\boldsymbol{\delta_C}$ (100 MHz, DMSO-d_6) 150.6 ($\underline{C}_{Ar}$), 148.0 ($\underline{C}_{Ar}$), 145.6 ($\underline{C}_{Ar}$), 139.3 ($\underline{C}_{Ar}$H), 138.6 ($\underline{C}$=CH_2), 135.7 ($\underline{C}_{Ar}$H), 130.3 ($\underline{C}_{Ar}$H), 129.9 ($\underline{C}_{Ar}$H), 129.9 ($\underline{C}_{Ar}$), 129.1 ($\underline{C}_{Ar}$H), 127.7 ($\underline{C}_{Ar}$H), 124.7 ($\underline{C}_{Ar}$), 124.1 ($\underline{C}_{Ar}$H), 120.6 ($\underline{C}_{Ar}$H), 116.7 (C=$\underline{C}H_2$), 68.0 ($\underline{C}$HOH), 64.6 ($\underline{C}HN^+$), 62.6 ($Ar\underline{C}H_2N^+$), 59.6 ($\underline{C}H_2N^+$), 51.0 ($\underline{C}H_2N^+$), 37.2 ($\underline{C}$HCH=CH_2), 26.2 ($\underline{C}$H), 24.6 ($\underline{C}H_2$), 21.5 ($\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[185]

α,α'-Biscinchoninium-*m*-xylene dibromide 375[185]

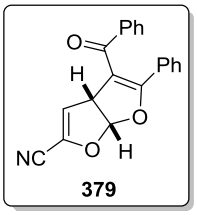


Cinchonine (2.00 g, 6.80 mmol), *α,α*'-dibromo-*m*-xylene (0.88 g, 3.33 mmol) and $CHCl_3$/EtOH/DMF (13 mL, 5:2:6 v/v) were subjected to general procedure D to afford *ammonium salt* **375** (1.78 g, 2.06 mmol, 62%) as a pink solid.

m.p 231–235 °C (dec.) [Lit: 222–225 °C (dec.)][185]; $[\alpha]_D^{20}$ = +149 (c = 0.5 , MeOH) [Lit: +165 (c = 0.53, MeOH)][185]; **δ_H** (400 MHz, d_4-methanol) 8.95 (2H, d, *J* 4.4 Hz, $C_{Ar}\underline{H}$), 8.46–8.39 (2H, m, $C_{Ar}\underline{H}$), 8.35 (1H, s, $C_{Ar}\underline{H}$), 8.15–8.08 (2H, m, $C_{Ar}\underline{H}$), 8.00–7.91 (4H, m, $C_{Ar}\underline{H}$), 7.88–7.80 (4H, m, $C_{Ar}\underline{H}$), 7.75 (1H, t, *J* 7.6 Hz, $C_{Ar}\underline{H}$), 6.66 (2H, s, C$\underline{H}$OH), 6.12–5.99 (2H, m, C$\underline{H}$=CH_2), 5.40–5.07 (8H, m, CH=C$\underline{H_2}$, ArC$\underline{H_2}N^+$), 4.50–4.41 (2H, m, C$\underline{H}_aH_bN^+$), 4.15–4.05 (4H, m, C$\underline{H}_aH_bN^+$, C$\underline{H}N^+$), 3.72 (2H, t, *J* 11.2 Hz, $CH_a\underline{H}_bN^+$), 3.47–3.41 (2H, m, $CH_a\underline{H}_bN^+$), 2.83–2.71 (2H, m, C$\underline{H}$CH=CH_2), 2.48 (2H, t, *J* 12.4 Hz, C$\underline{H}_aH_b$), 2.00–1.76 (6H, m, C$\underline{H}_aH_b$, $CH_a\underline{H}_b$, C$\underline{H}$), 1.15–0.99 (2H, m, $CH_a\underline{H}_b$); **δ_C** (100 MHz, d_4-methanol) 151.2 ($\underline{C}_{Ar}$), 148.8 ($\underline{C}_{Ar}$), 147.5 ($\underline{C}_{Ar}$), 140.6 ($\underline{C}_{Ar}H$), 137.9 ($\underline{C}$=CH_2), 137.1 ($\underline{C}_{Ar}H$), 131.4 ($\underline{C}_{Ar}H$), 131.3 ($\underline{C}_{Ar}H$), 130.3 ($\underline{C}_{Ar}$), 130.1 ($\underline{C}_{Ar}H$), 129.5 ($\underline{C}_{Ar}H$), 126.2 ($\underline{C}_{Ar}$), 124.8 ($\underline{C}_{Ar}H$), 121.4 ($\underline{C}_{Ar}H$), 118.1 (C=$\underline{C}H_2$), 69.4 ($\underline{C}$HOH), 67.1 ($\underline{C}HN^+$), 64.0 (Ar$\underline{C}H_2N^+$), 58.4 ($\underline{C}H_2N^+$), 56.2 ($\underline{C}H_2N^+$), 38.9 ($\underline{C}$HCH=CH_2), 28.6 ($\underline{C}$H), 24.7 ($\underline{C}H_2$), 22.5 ($\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[188]

(3a*R,6a*R**)-4-Benzoyl-5-phenyl-3a,6a-dihydrofuro[2,3-*b*]furan-2-carbonitrile 379**



379

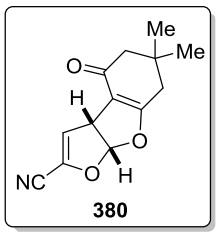
Racemic: 5-Nitro-2-furonitrile **197** (80 mg, 0.58 mmol), TBAI (21 mg, 0.058 mmol), Cs_2CO_3 (378 mg, 1.16 mmol), dibenzoylmethane **376** (260 mg, 1.16 mmol), and PhMe/H_2O (5 mL, 4:1 v/v) were subjected to **general procedure C** for 72 h. Purification by FCC (CH_2Cl_2) afforded *bisdihydrofuran* **379** (120 mg, 0.38 mmol, 65%) as a colourless oil.

Chiral PTC: 5-Nitro-2-furonitrile **197** (80 mg, 0.58 mmol), *N*-(9-anthracenylmethyl)cinchonidinium chloride **348** (30 mg, 0.058 mmol), Cs_2CO_3 (378 mg, 1.16 mmol), dibenzoylmethane **376** (260 mg, 1.16 mmol), and PhMe/H_2O (5 mL, 4:1 v/v) were subjected to **general procedure C** for 72 h. Purification by FCC (CH_2Cl_2) afforded *bisdihydrofuran* **379** (104 mg, 0.33 mmol, 56%) as a colourless oil.

ν_{max} (cm^{-1}) 3060, 2238, 1628, 1610, 1595, 1575, 1492, 1447, 1347, 1229; **δ_H** (400 MHz, $CDCl_3$) 7.44–7.39 (2H, m, $C_{Ar}\underline{H}$), 7.31–7.17 (4H, m, $C_{Ar}\underline{H}$), 7.13–7.06 (4H, m, $C_{Ar}\underline{H}$), 6.74 (1H, d, *J* 7.6 Hz, OC$\underline{H}$O), 6.45 (1H, d, *J* 3.0 Hz, OC=C$\underline{H}$), 4.91 (1H, dd, *J* 7.6, 2.8 Hz, C$\underline{H}$);

δ_C (100 MHz, $CDCl_3$) 192.1 (*C*=O), 164.6 (O*C*Ph), 137.7 (*C*$_{Ar}$), 132.0 (*C*$_{Ar}$), 130.9 (*C*$_{Ar}$), 129.6 (*C*$_{Ar}$H), 129.4 (O*C*CN), 128.9 (*C*$_{Ar}$H), 128.2 (*C*$_{Ar}$H), 127.9 (*C*$_{Ar}$H), 127.8 (*C*$_{Ar}$H), 118.9 (O*C*HO), 112.2 (*C*N), 110.9 (*C*COPh), 109.0 (OC=*C*H), 55.2 (*C*H); **m/z** (ESI+) 338.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{20}H_{13}NO_3$ requires 338.0788 $[M+Na]^+$, found 338.0792 ($\Delta = -1.2$ ppm).

(3aR*, 8aR*)-6,6-Dimethyl-4-oxo-3a,4,5,6,7,8a-hexahydrofuro[2,3-*b*]benzofuran-2-carbonitrile 380



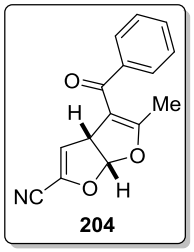
380

Racemic: 5-Nitro-2-furonitrile **197** (80 mg, 0.58 mmol), TBAI (21 mg, 0.058 mmol), Cs_2CO_3 (378 mg, 1.16 mmol), dimedone **377** (162 mg, 1.16 mmol), and PhMe/H_2O (5 mL, 4:1 v/v) were subjected to **general procedure C** for 72 h. Purification by FCC (CH_2Cl_2) afforded *bisdihydrofuran* **380** (105 mg, 0.45 mmol, 78%) as a colourless solid.

Chiral PTC: 5-Nitro-2-furonitrile **197** (80 mg, 0.58 mmol), *N*-(9-anthracenylmethyl)cinchonidinium chloride **348** (30 mg, 0.058 mmol), Cs_2CO_3 (378 mg, 1.16 mmol), dimedone **377** (162 mg, 1.16 mmol), and PhMe/H_2O (5 mL, 4:1 v/v) were subjected to **general procedure C** for 72 h. Purification by FCC (CH_2Cl_2) afforded *bisdihydrofuran* **380** (82 mg, 0.35 mmol, 61%) as a colourless oil.

ν_{max} (cm^{-1}) 2961, 2873, 2239, 1644, 1397, 1321, 1225, 1210, 1163; **δ_H** (400MHz, $CDCl_3$) 6.64 (1H, d, *J* 7.6 Hz, OC*HO*), 6.19 (1H, d, *J* 2.5 Hz, OC=C*H*), 4.47 (1H, dd, *J* 7.6, 2.5 Hz, C*H*), 2.38 (2H, d, *J* 1.0 Hz, CH_2), 2.21 (2H, d, *J* 3.5 Hz, CH_2), 1.09 (3H, s, CH_3), 1.07 (3H, s, CH_3); **δ_C** (100 MHz, $CDCl_3$) 193.5 (*C*OCH_2), 175.5 (O*C*CH_2), 129.4 (O*C*CN), 117.9 (O*C*HO), 112.7 (*C*N), 112.1 (*C*COCH_2), 110.7 (OC=*C*H), 50.8 (*C*H), 49.1 (*C*H_2CO), 37.4 (*C*H_2), 34.2 (*C*$(CH_3)_2$), 28.5 (*C*H_3), 28.5 (*C*H_3); **m/z** (ESI+) 254.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{13}H_{13}NO_3$ requires 254.0788 $[M+Na]^+$, found 254.0797 ($\Delta = -3.6$ ppm).

(3aR*,6aR*)-4-Benzoyl-5-methyl-3a,6a-dihydrofuro[2,3-b]furan-2-carbonitrile 204

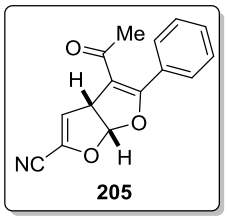


204

Racemic: 5-Nitro-2-furonitrile **197** (80 mg, 0.58 mmol), TBAI (21 mg, 0.058 mmol), Cs_2CO_3 (378 mg, 1.16 mmol), benzoylacetone **201** (188 mg, 1.16 mmol), and PhMe/H_2O (5 mL, 4:1 v/v) were subjected to **general procedure C** for 72 h. Purification by FCC (CH_2Cl_2) afforded *bisdihydrofurans* **204** (46 mg, 0.18 mmol, 31%) and **205** (39 mg, 0.15 mmol, 26%) as colourless oils.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 3121, 2926, 2234, 1625, 1610, 1383, 1352, 1318, 1219, 1195, 1196; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.57–7.50 (3H, m, $C_{Ar}\underline{H}$), 7.48–7.40 (2H, m, $C_{Ar}\underline{H}$), 6.55 (1H, d, *J* 7.6 Hz, OC$\underline{H}$O), 6.19 (1H, d, *J* 2.5 Hz, OC=C$\underline{H}$), 4.76–4.68 (1H, m, C$\underline{H}$), 1.80 (3H, d, *J* 1.3 Hz, C$\underline{H_3}$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 191.9 ($\underline{C}$=O), 166.9 (O$\underline{C}$$CH_3$), 139.5 ($\underline{C}_{Ar}$CO), 132.2 (O$\underline{C}$CN), 131.9 ($\underline{C}_{Ar}$H), 128.6 ($\underline{C}_{Ar}$H), 127.9 ($\underline{C}_{Ar}$H), 127.0 ($\underline{C}_{Ar}$H), 118.9 ($\underline{C}$CO), 114.0 (O$\underline{C}$HO), 110.9 ($\underline{C}$N), 109.1 (OC=$\underline{C}$H), 15.2 ($\underline{C}H_3$); **m/z** (ESI+) 254.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{15}H_{12}NO_3$ requires 254.0812 $[M+H]^+$, found 254.0812 (Δ = 0.0 ppm).

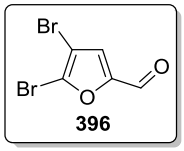
(3aR*,6aR*)-4-Acetyl-5-phenyl-3a,6a-dihydrofuro[2,3-b]furan-2-carbonitrile 205



205

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 3247, 2964, 2242, 1640, 1594, 1383, 1344, 11234, 1212; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.58–7.52 (5H, m, $C_{Ar}\underline{H}$), 6.61 (1H, d, *J* 7.7 Hz, OC$\underline{H}$O), 6.27 (1H, d, *J* 3.1 Hz, OC=C$\underline{H}$), 4.73 (1H, dd, *J* 7.7, 3.1 Hz, C$\underline{H}$), 1.96 (3H, s, C$\underline{H_3}$); $\boldsymbol{\delta_C}$ (100 MHz) 193.5 ($\underline{C}$=O), 165.8 (O$\underline{C}$Ph), 131.4 ($\underline{C}_{Ar}$), 129.5 ($\underline{C}_{Ar}$H), 129.2 (O$\underline{C}$CN), 128.9 ($\underline{C}_{Ar}$H), 128.6 ($\underline{C}_{Ar}$H), 118.7 (O$\underline{C}$HO), 116.1 ($\underline{C}$N), 110.8 ($\underline{C}$COMe), 109.0 (OC=$\underline{C}$H), 53.8 ($\underline{C}$H), 28.6 ($\underline{C}H_3$); **m/z** (ESI+) 254.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{15}H_{12}NO_3$ requires 254.0812 $[M+H]^+$, found 254.0811 (Δ = −0.1 ppm).

4,5-Dibromofurfural 396[204]



396

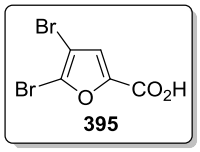
Freshly distilled furfural **397** (10.0 g, 104 mmol) was added over 2 h by addition funnel to $AlCl_3$ (32.0 g, 240 mmol) at 0 ^oC with mechanical stirring. Bromine (37.0 g, 232 mmol) was added dropwise over 2 h by addition

funnel. The reaction was allowed to stand overnight. The reaction was cautiously poured onto ice (500 mL). The organic phase was then extracted with Et_2O (3 x 100 mL). The combined organic layers were washed with $NaHCO_3$ (2 x 50 mL) and brine (100 mL), then dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Purification by FCC (CH_2Cl_2) afforded *dibromofurfural* **396** (8.98 g, 35.4 mmol, 34 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 9.51 (1H, s, C*H*O), 7.24 (1H, s, $C^3{}_{Fur}H$); **δ_C** (100 MHz, $CDCl_3$) 176.0 (*C*HO), 153.7 ($C^2{}_{Fur}CHO$), 131.4 ($C^3{}_{Fur}H$), 123.8 ($C^{5Fur}Br$), 105.1 ($C^4{}_{Fur}Br$).

Spectroscopic data are consistent with those previously reported.[204]

4,5-Dibromo-2-furoic acid 395[205]



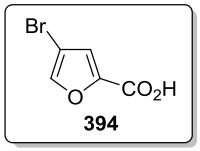
395

A mixture of dibromofurfural **396** (2.50 g, 9.85 mmol) and $AgNO_3$ (1.67 g, 9.85 mmol) in H_2O (7.5 mL) was stirred at room temperature for 6 h. The pH was adjusted to 2–3 with 6 M HCl, and the organic phase extracted with EtOAc (3×30 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by FCC (4:1 Petrol/EtOAc) afforded *furoic acid* **395** (1.94 g, 7.19 mmol, 73%) as a colourless solid.

m.p 166–170 °C [Lit: 167–168 °C][414]; **δ_H** (400 MHz, d_4-methanol) 7.22 (1H, s, $C^3{}_{Fur}H$); **δ_C** (100 MHz, d_3-methanol) 159.8 (*C*O_2H), 148.4 ($C^2{}_{Fur}CO_2H$), 129.4 ($C^5{}_{Fur}Br$), 122.9 ($C^3{}_{Fur}H$), 104.8 ($C^4{}_{Fur}Br$).

Spectroscopic data are consistent with those previously reported.[414]

4-Bromo-2-furoic acid 394[206]



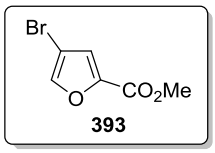
394

To a stirred suspension of 4,5-dibromo-2-furoic acid **395** (1.70 g, 6.30 mmol) in H_2O (140 mL), was added Zn (411 mg, 6.30 mmol), and 25% aq. NH_4OH (40 mL). The reaction was stirred at room temperature for 4 h, acidified to pH = 3 with 3 M HCl, and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered and dried *in vacuo*. Purification by FCC (Et_2O) afforded *furoic acid* **394** (1.05g, 5.50 mmol, 87%) as a colouress solid.

m.p. 125–127 °C [Lit:115–127 °C][415]; **ν_{max}** (cm^{-1}) 1681, 1570, 1488, 1425, 1282, 1196, 1138; **δ_H** (400 MHz, $CDCl_3$) 11.38 (1H, br s, $CO_2\underline{H}$), 7.68–7.62 (1H, m, $C^5{}_{Fur}\underline{H}$), 7.37–7.32 (1H, m, $C^3{}_{Fur}\underline{H}$); **δ_C** (100 MHz, $CDCl_3$) 162.7 ($\underline{C}O_2H$), 145.6 ($\underline{C}^5{}_{Fur}H$), 144.1 ($\underline{C}^2{}_{Fur}CO_2H$), 122.4 ($\underline{C}^3{}_{Fur}H$), 101.6 ($\underline{C}^4{}_{Fur}Br$); **m/z** (ESI-) 188.9 $[M-H]^-$, 190.9 $[(M+2)-H]^-$; **HRMS** (ESI+) $C_5H_3BrO_3$ requires 212.9158 and 214.9138 $[M+Na]^+$, found 212.9158 and 214.9138 (Δ = 0.0 ppm).

Spectroscopic data are consistent with those previously reported.[206]

Methyl 4-bromo-2-furoate 393[207]



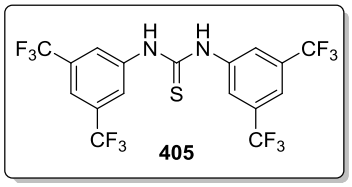
393

To a solution of 4-bromo-2-furoic acid **394** (250 mg, 1.31 mmol) in methanol (15 mL), conc. H_2SO_4 (3 drops) was added. The reaction was stirred at 50 °C for 12 h. Methanol was removed *in vacuo* and the resultant residue redissolved in CH_2Cl_2 (10 mL). The organic phase was washed with $NaHCO_3$ (10 mL), and the aqueous layer extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to afford *methyl ester* **393** (217 mg, 1.06 mmol, 81 %) as a colourless solid.

m.p 37–39 °C [Lit: 42–44 °C][416]; **δ_H** (400 MHz, $CDCl_3$) 7.61 (1H, d, *J* 0.65 Hz, $C^5{}_{Fur}\underline{H}$), 7.17 (1H, d, *J* 0.65 Hz, $C^3{}_{Fur}\underline{H}$), 3.90 (3H, s, $CO_2C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 157.8 ($\underline{C}$=O), 144.7 ($\underline{C}^2{}_{Fur}CO_2Me$), 144.3 ($\underline{C}^5{}_{Fur}H$), 120.0 ($\underline{C}^3{}_{Fur}H$), 100.0 ($\underline{C}^4{}_{Fur}Br$), 51.9 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[416]

1,3-Bis(3,5-bis(trifluoromethyl)phenyl)thiourea 405[212]

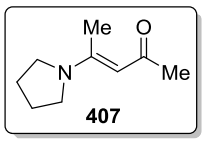


405

To a solution of 3,5-bis(trifluoromethyl)aniline **403** (86 µL, 0.55 mmol) in THF (2 mL) was added 3,5-bis(trifluoromethyl)phenylisothiocyanate **404** (100 µL, 0.55 mmol). The solution was stirred at 50 °C for 80 h and concentrated *in vacuo*. Purification by FCC (7:1→1:1 Petrol/CH_2Cl_2) afforded *thiourea* **405** (253 mg, 0.510 mmol, 92%) as a white solid.

m.p 172–174 °C [Lit: 171–173 °C][417]; **δ_H** (400 MHz, DMSO-d_6) 10.65 (2H, br s, N$\underline{H}$), 8.20 (4H, s, $C_{Ar}\underline{H}$), 7.85 (2H, s, $C_{Ar}\underline{H}$); **δ_C** (100 MHz, DMSO-d_6) 180.6 ($\underline{C}$=S), 141.2 ($\underline{C}_{Ar}$NH), 130.3 (q, *J* 33.6 Hz, $\underline{C}_{Ar}CF_3$), 124.1 ($\underline{C}_{Ar}H$), 123.2 (q, *J* 271 Hz, $\underline{C}F_3$), 117.7 ($\underline{C}_{Ar}H$). **δ_F** (377 MHz, DMSO-d_6) −61.54.

(*E*)-4-(Pyrrolidin-1-yl)pent-3-en-2-one 407[213]



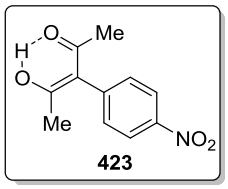
407

Acetylacetone **199** (1.00 mL, 7.80 mmol), and pyrrolidine **406** (0.94 mL, 12 mmol) were stirred at room temperature for 1 h. The crude material was dissolved in CH_2Cl_2 and purified by FCC (Alumina, 3:1 Petrol/EtOAc) to afford *enamine* **407** (1.11g, 7.24 mmol, 93 %) as a yellow solid.

m.p. 115–119 °C; [Lit: 115-116 °C][418]; **δ_H** (400MHz, $CDCl_3$) 4.94 (1H, s, C=C$\underline{H}$), 3.51-3.36 (2H, m, $CH_a\underline{H}_bN$), 3.30-3.13 (2H, m, $C\underline{H}_aH_bN$), 2.51 (3H, s, $C\underline{H}_3$), 2.05 (3H, s, $C\underline{H}_3$), 1.99-1.87 (4H, m, $\underline{C}H_2$); **δ_C** (101 MHz, $CDCl_3$) 194.1 ($\underline{C}$=O), 159.7 ($\underline{C}$=CH), 95.1 (C=$\underline{C}$H), 48.1 ($\underline{C}H_2N$), 31.5 ($\underline{C}H_3$), 25.2 ($\underline{C}H_2$), 17.2 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[213]

(*Z*)-4-Hydroxy-3-(4-nitrophenyl)pent-3-en-2-one 423[87]



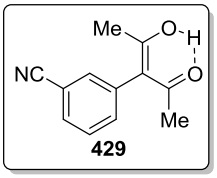
423

To a stirred solution of 1,4-dinitrobenzene **422** (132 mg, 0.780 mmol) and KOH (88 mg, 1.6 mmol) in DMSO (5 mL), acetylacetone **199** (0.20 mL, 1.6 mmol) was added dropwise. The reaction was stirred at room temperature for 24 h. The mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo* to afford *dicarbonyl* **423** (21 mg, 0.094 mmol, 12%) as a light yellow solid.

m.p. 110–112 °C [Lit: 108–110 °C][420]; **δ_H** (400 MHz, $CDCl_3$) 16.78 (1H, s, O$\underline{H}$), 8.23 (2H, d, *J* 8.4 Hz, $C_{Ar}\underline{H}$), 7.38 (2H, d, *J* 8.4 Hz, $C_{Ar}\underline{H}$). 1.87 (6H, s, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 190.6 ($\underline{C}$=O), 147.5 ($\underline{C}_{Ar}$), 144.0 ($\underline{C}_{Ar}$), 132.2 ($\underline{C}_{Ar}H$), 124.1 ($\underline{C}_{Ar}H$), 113.7 (Ar-$\underline{C}$), 24.2 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[420]

3-(3-Cyanophenyl)-pentane-2,4-dione, enol tautomer 429[203]

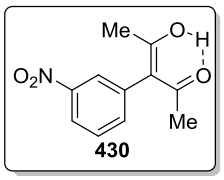


Acetylacetone **199** (1.70 mL, 16.6 mmol), 3-bromobenzonitrile **427** (1.00 g, 5.50 mmol), CuI (105 mg, 0.550 mmol), K_2CO_3 (3.04 g, 22.0 mmol), L-proline (130 mg, 1.13 mmol) and DMSO (20 mL) were subjected to general procedure E. Purification by FCC (15:1→4:1 Petrol/Et_2O) afforded *dicarbonyl* **429** (223 mg, 1.07 mmol, 19%) as a colourless solid.

m.p 103–105 °C [Lit: 108 °C][421]; **δ_H** (400 MHz, $CDCl_3$) 16.73 (1H, br s, O*H*), 7.67–7.63 (1H, m, C_{Ar}*H*), 7.56–7.49 (2H, m, C_{Ar}*H*), 7.47–7.43 (1H, m, C_{Ar}*H*), 1.87 (6H, s, CH_3); **δ_C** (100 MHz, $CDCl_3$) 190.7 (*C*=O), 138.3 (C_{Ar}), 135.7 (C_{Ar}H), 134.5 (C_{Ar}H), 131.3 (C_{Ar}H), 129.8 (C_{Ar}H), 118.3 (*C*N), 113.4 (Ar-*C*), 113.1 (C_{Ar}CN), 24.1 (CH_3).

Spectroscopic data are consistent with those previously reported.[421]

3-(3-Nitrophenyl)-pentane-2,4-dione, enol tautomer 430 [203]

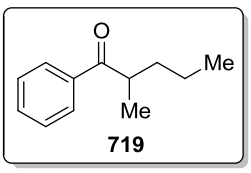


Acetylacetone **199** (164 μL, 1.60 mmol), 3-nitroiodobenzene **428** (100 mg, 0.400 mmol), CuI (8 mg, 0.04 mmol), Cs_2CO_3 (565 mg, 1.60 mmol), L-proline (9 mg, 0.08 mmol) and DMSO (2 mL) were subjected to general procedure E. Purification by FCC (5:1 petrol/Et_2O) afforded *dicarbonyl* **430** (88 mg, 0.40 mmol, quant.) as a colourless solid.

m.p 75–77 °C [Lit: 77.9–78.1 °C][422]; **δ_H** (400 MHz, $CDCl_3$) 16.76 (1H, br s, O*H*), 8.25–8.20 (1H, m, C_{Ar}*H*), 8.12–8.07 (1H, m, C_{Ar}*H*), 7.62–7.53 (2H, m, C_{Ar}*H*), 1.90 (6H, s, CH_3); **δ_C** (100 MHz, $CDCl_3$) 190.8 (*C*=O), 148.5 (C_{Ar}), 138.7 (C_{Ar}), 137.4 (C_{Ar}H), 129.9 (C_{Ar}H), 126.0 (C_{Ar}H), 122.7 (C_{Ar}H), 113.4 (Ar-*C*), 24.2 (CH_3).

Spectroscopic data are consistent with those previously reported.[422]

2-Methyl-1-phenylpentan-1-one 719



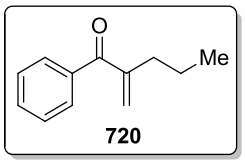
Valerophenone **718** (50 μL, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (195 mg, 0.600 mmol), and methanol (1.5 mL)

were subjected to **general procedure F** for 48 h. Purification by FCC (20:1 Petrol/Et_2O) afforded *methylated ketone* **719** (52 mg, 0.29 mmol, 98%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.99–7.94 (2H, m, $C_{Ar}\underline{H}$), 7.59–7.53 (1H, m, $C_{Ar}\underline{H}$), 7.51–7.44 (2H, m, $C_{Ar}\underline{H}$), 3.49 (1H, app. sext, *J* 6.7 Hz, $C\underline{H}(CH_3)CH_2$), 1.85–1.75 (1H, m, $C\underline{H}_aH_b$), 1.48–1.27 (3H, m, $CH_a\underline{H}_b$, $C\underline{H}_2$), 1.20 (3H, d, *J* 6.8 Hz, $CHC\underline{H}_3$), 0.91 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 203.5 ($\underline{C}$=O), 135.8 ($\underline{C}_{Ar}$), 131.7 ($\underline{C}_{Ar}$H), 127.6 ($\underline{C}_{Ar}$H), 127.2 ($\underline{C}_{Ar}$H), 39.3 ($\underline{C}H(CH_3)CH_2$), 34.9 ($\underline{C}H_2$), 19.5 ($\underline{C}H_2$), 16.1 ($\underline{C}H_3$), 13.1 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[321]

2-Methylene-1-phenylpentan-1-one 720



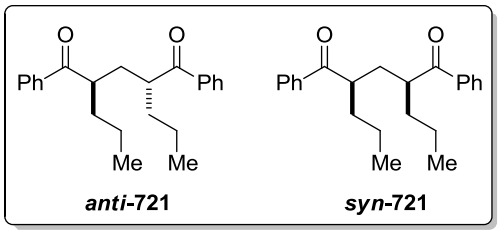
720

Enone **420** was isolated as a colourless oil from the incomplete reaction of valerophenone **718** according to **general procedure F**.

δ_H (400 MHz, $CDCl_3$) 7.80–7.74 (2H, m, $C_{Ar}\underline{H}$), 7.58–7.52 (1H, m, $C_{Ar}\underline{H}$), 7.47–7.41 (2H, m, $C_{Ar}\underline{H}$), 5.83 (1H, s, C=C$\underline{H}_aH_b$), 5.59 (1H, s, C=$CH_a\underline{H}_b$), 2.46 (2H, t, *J* 7.3 Hz, $C\underline{H}_2$), 1.55 (2H, app. sext, *J* 7.3 Hz, $C\underline{H}_2$), 0.98 (3H, t, *J* 7.3 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 198.5 ($\underline{C}$=O), 148.3 ($\underline{C}$=CH_2), 137.9 ($\underline{C}_{Ar}$), 132.1 ($\underline{C}_{Ar}$H), 129.5 ($\underline{C}_{Ar}$H), 128.1 ($\underline{C}_{Ar}$H), 125.2 (C=$\underline{C}H_2$), 34.3 ($\underline{C}H_2$), 21.4 ($\underline{C}H_2$), 13.8 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[423]

(2*R,4*R**)-1,5-Diphenyl-2,4-dipropylpentane-1,5-dione and (2*R**,4*S**)-1,5-Diphenyl-2,4-dipropylpentane-1,5-dione, 721**



***anti*-721** ***syn*-721**

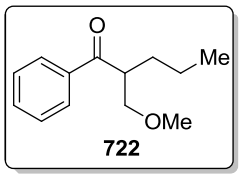
Dimers *anti*-**721** and *syn*-**721** were isolated as a 1:1.2 mixture of inseparable diastereoisomers from the incomplete reaction of valerophenone **418** according to **general procedure F**.

ν_{max} (cm^{-1}) 2959, 2932, 2873, 1682, 1447, 1248, 1212; **m/z** (ESI+) 337.3 $[M+H]^+$; **HRMS** (ESI+) $C_{23}H_{28}O_2$ requires 359.1982 $[M+Na]^+$, found 359.1971 (Δ = 2.7 ppm).

***anti*-721 δ_H** (400 MHz, $CDCl_3$) 7.72–7.68 (4H, m, $C_{Ar}\underline{H}$), 7.46–7.39 (2H, m, $C_{Ar}\underline{H}$), 7.31–7.23 (4H, m, $C_{Ar}\underline{H}$), 3.42–3.33 (2H, m, C$\underline{H}$CO), 2.10–2.04 (2H, m, C$\underline{H}_2$), 1.80–1.58 (4H, m, C$\underline{H}_2$), 1.49–1.37 (2H, m C$\underline{H}_a$H$_b$), 1.36–1.11 (2H, m, CH$_a\underline{H}_b$), 0.85 (6H, t, *J* 7.3 Hz, C$\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 204.9 ($\underline{C}$=O), 137.4 ($\underline{C}_{Ar}$), 132.8 ($\underline{C}_{Ar}$H), 128.5 ($\underline{C}_{Ar}$H), 128.0 ($\underline{C}_{Ar}$H), 43.7 ($\underline{C}$HCO), 36.2 ($\underline{C}H_2$), 34.4 ($\underline{C}H_2$), 20.5 ($\underline{C}H_2$), 14.1 ($\underline{C}H_3$).

***syn*-721 δ_H** (400 MHz, $CDCl_3$) 8.04–7.98 (4H, m, $C_{Ar}\underline{H}$), 7.61–7.55 (2H, m, $C_{Ar}\underline{H}$), 7.53–7.47 (4H, m, $C_{Ar}\underline{H}$), 3.57–3.49 (2H, m, C$\underline{H}$CO), 2.34–2.25 (1H, m, C$\underline{H}_a$H$_b$), 1.79–1.69 (1H, m, CH$_a\underline{H}_b$), 1.49–1.37 (2H, m, C$\underline{H}_a$H$_b$), 1.36–1.11 (6H, m, CH$_a\underline{H}_b$, C$\underline{H}_2$), 0.79 (6H, t, *J* 7.3 Hz, C$\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 203.9 ($\underline{C}$=O), 137.2 ($\underline{C}_{Ar}$), 133.0 ($\underline{C}_{Ar}$H), 128.7 ($\underline{C}_{Ar}$H), 128.3 ($\underline{C}_{Ar}$H), 43.4 ($\underline{C}$HCO), 36.2 ($\underline{C}H_2$), 34.0 ($\underline{C}H_2$), 20.4 ($\underline{C}H_2$), 14.1 ($\underline{C}H_3$).

2-(Methoxymethyl)-1-phenylpentan-1-one 722

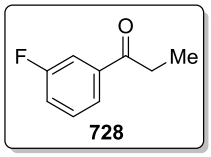


722

β-Methoxyketone **722** was isolated as a colourless oil from the incomplete reaction of valerophenone **718** according to **general procedure F**.

ν_{max} (cm^{-1}) 2959, 2930, 2873, 1688, 1448, 1135, 1026; **δ_H** (400 MHz, $CDCl_3$) 7.94–7.87 (2H, m, $C_{Ar}\underline{H}$), 7.53–7.44 (1H, m, $C_{Ar}\underline{H}$), 7.42–7.34 (2H, m, $C_{Ar}\underline{H}$), 3.75–3.60 (2H, m, C$\underline{H}_a$H$_b$OCH$_3$, C$\underline{H}$CO), 3.46–3.39 (1H, m, CH$_a\underline{H}_b$OCH$_3$), 3.21 (3H, s, OC$\underline{H}_3$), 1.71–1.56 (1H, m, C$\underline{H}_a$H$_b$Et), 1.51–1.37 (1H, m, CH$_a\underline{H}_b$Et), 1.22 (2H, app. sext, *J* 7.8 Hz, C$\underline{H}_2$CH$_3$), 0.80 (3H, t, *J* 7.2 Hz, C$\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 203.1 ($\underline{C}$=O), 137.7 ($\underline{C}_{Ar}$), 132.9 ($\underline{C}_{Ar}$H), 128.6 ($\underline{C}_{Ar}$H), 128.3 ($\underline{C}_{Ar}$H), 74.3 ($\underline{C}H_2$OCH$_3$), 59.1 (O$\underline{C}H_3$), 46.5 ($\underline{C}$H), 32.0 ($\underline{C}H_2$), 20.6 ($\underline{C}H_2$), 14.2 ($\underline{C}H_3$); **m/z** (ESI+) 229.2 $[M+Na]^+$; **HRMS** (ESI+) $C_{13}H_{18}O_2$ requires 229.1199 $[M+Na]^+$, found 229.1198 (Δ = 0.3 ppm).

1-(3-Fluorophenyl)propan-1-one 728[424]



728

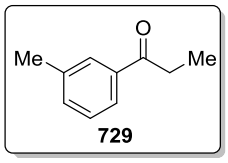
To a solution of 3-fluorobenzonitrile **726** (1.00 mL, 8.64 mmol) in THF (44 mL), EtMgBr (1 M in THF, 13.0 mL, 13.0 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for 18 h. The reaction

mixture was cooled to 0 °C and 1 M H_2SO_4 (50 mL) was added. The organic phase was extracted with EtOAc (50 mL), and washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Purification by FCC (20:1 Petrol/Et_2O) afforded *ketone* **728** (1.15 g, 7.60 mmol, 88%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.77–7.72 (1H, m, $C_{Ar}\underline{H}$), 7.67–7.60 (1H, m, $C_{Ar}\underline{H}$), 7.47–7.41 (1H, m, $C_{Ar}\underline{H}$), 7.28–7.22 (1H, m, $C_{Ar}\underline{H}$), 2.99 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CO$), 1.23 (3H, t, *J* 7.2 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 199.4 (d, *J* 1.9 Hz, $\underline{C}$=O), 162.8 (d, *J* 246.2 Hz, $\underline{C}_{Ar}F$), 139.0 (d, *J* 6.0 Hz, $\underline{C}_{Ar}$), 130.2 (d, *J* 7.7 Hz, $\underline{C}_{Ar}H$), 123.7 (d, *J* 3.0 Hz, $\underline{C}_{Ar}H$), 119.8 (d, *J* 21.3 Hz, $\underline{C}_{Ar}H$), 114.7 (d, *J* 22.0 Hz, $\underline{C}_{Ar}H$), 31.9 ($\underline{C}H_2$), 8.0 ($\underline{C}H_3$); **δ_F** (376 MHz, $CDCl_3$) −115.5 (Ar$C\underline{F}$).

Spectroscopic data are consistent with those previously reported.[425]

1-(*m*-Tolyl)propan-1-one 729[424]

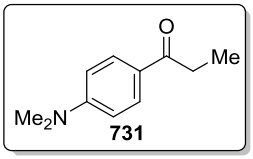


729

To a solution of *m*-tolunitrile **727** (1.00 mL, 8.33 mmol) in THF (40 mL), EtMgBr (1 M in THF, 16.7 mL, 16.7 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for 18 h. The reaction mixture was cooled to 0 °C and 1 M H_2SO_4 (50 mL) was added. The organic phase was extracted with EtOAc (50 mL), and washed with sat. aq. $NaHCO_3$ (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Purification by FCC (25:1 Petrol/Et_2O) afforded *ketone* **729** (821 mg, 5.54 mmol, 67 %) as a colourless oil.

ν_{max} (cm^{-1}) 2978, 2938, 1686, 1605, 1586, 1417, 1347, 1249, 1185, 1166; **δ_H** (400 MHz, $CDCl_3$) 7.80–7.73 (2H, m, $C_{Ar}\underline{H}$), 7.40–7.32 (2H, m, $C_{Ar}\underline{H}$), 3.00 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CO$), 2.42 (3H, s, Ar$C\underline{H}_3$), 1.23 (3H, t, *J* 7.2 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 201.6 ($\underline{C}$=O), 138.3 ($\underline{C}_{Ar}$), 136.9 ($\underline{C}_{Ar}$), 133.6 ($\underline{C}_{Ar}H$), 128.5 ($\underline{C}_{Ar}H$), 128.4 ($\underline{C}_{Ar}H$), 125.2 ($\underline{C}_{Ar}H$), 31.8 ($\underline{C}H_2CO$), 21.3 (Ar$\underline{C}H_3$), 8.3 ($\underline{C}H_3$); **m/z** (ESI+) 171.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{10}H_{12}O$ requires 171.0780 $[M+Na]^+$, found 171.0780 (Δ = 0.5 ppm).

1-(4-(Dimethylamino)phenyl)propan-1-one 731[325]

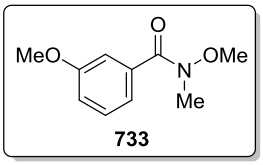


To a solution of 4-(dimethylamino)benzonitrile **730** (500 mg, 4.12 mmol) in THF (10 mL) at 0 °C, EtMgBr (1M in THF, 12.4 mL, 12.4 mmol) was added dropwise, followed by CuBr (10 mg, 0.070 mmol). The reaction was heated to 60 °C and stirred at this temperature for 4 h. The reaction mixture was cooled to 0 °C and quenched cautiously with H_2O (5 mL) and 1 M H_2SO_4 (20 mL) and heated to reflux for 1 h. The reaction was cooled to room temperature and the pH adjusted to 9 with 2 M NaOH. The organic phase was extracted with EtOAc (3 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by FCC ($CHCl_3$) afforded **731** (596 mg, 3.37 mmol, 82 %) as a light yellow solid.

m.p 90–92 °C [Lit: 94–95 °C][426]; **δ_H** (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 6.63 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 3.02 (6H, s, $N(C\underline{H}_3)_2$), 2.89 (2H, q, *J* 7.3 Hz, $C\underline{H}_2CO$), 1.20 (t, 3H, *J* 7.3 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 199.1 ($\underline{C}$=O), 153.3 ($\underline{C}_{Ar}$), 130.1 ($\underline{C}_{Ar}$H), 124.9 ($\underline{C}_{Ar}$H), 110.6 ($\underline{C}_{Ar}$), 40.0 ($N(\underline{C}H_3)_2$), 31.0 ($\underline{C}H_2$), 8.8 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[427]

***N*,3-Dimethoxy-*N*-methylbenzamide 733**[326]



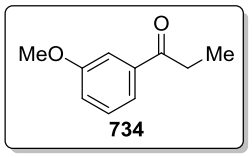
To a solution of 3-methoxybenzoic acid **732** (530 mg, 3.45 mmol) in CH_2Cl_2 (16 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (370 mg, 5.18 mmol), Et_3N (0.63 mL, 4.5 mmol) and EDC·HCl (1.00 g, 5.22 mmol). The resultant mixture was stirred at rt for 18 h. The solvent was removed *in vacuo*, and the resultant residue redissolved in EtOAc (50 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL) and was dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to afford *Weinreb's amide* **733** (575 mg, 2.94 mmol, 85 %) as a light yellow oil.

δ_H (400MHz, $CDCl_3$) 7.32 (1H, t, *J* 7.9 Hz, $C_{Ar}\underline{H}$), 7.28-7.18 (2H, m, $C_{Ar}\underline{H}$), 7.02-6.97 (1H, m, $C_{Ar}\underline{H}$), 3.84 (3H, s, $OC\underline{H}_3$), 3.58 (3H, s, $OC\underline{H}_3$), 3.36 (3H, s, $NC\underline{H}_3$); **δ_C** (101 MHz,

$CDCl_3$) 169.7 (<u>*C*</u>=O), 159.2 (<u>*C*</u>$_{Ar}$), 135.4 (<u>*C*</u>$_{Ar}$H), 129.1 (<u>*C*</u>$_{Ar}$), 120.4 (<u>*C*</u>$_{Ar}$H), 116.6 (<u>*C*</u>$_{Ar}$H), 113.3 (<u>*C*</u>$_{Ar}$H), 61.1 (O<u>*C*</u>H$_3$), 55.4 (O<u>*C*</u>H$_3$), 33.8 (N<u>*C*</u>H$_3$).

Spectroscopic data are consistent with those previously reported.[428]

1-(3-Methoxyphenyl)propan-1-one 734[326]

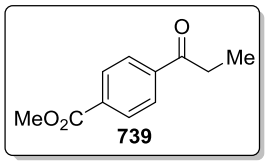


734

To a solution of *N*,3-dimethoxy-*N*-methylbenzamide **733** (575 mg, 2.94 mmol) in THF (15 mL) at 0 °C, EtMgBr (1 M in THF, 9.40 mL, 9.40 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for a further 4 h. The reaction was quenched with 1 M HCl (20 mL), extracted with EtOAc (50 mL), and the organic phase washed with H_2O (20 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Purification by FCC (Petrol/Et_2O 5:1) afforded *ketone* **734** (405 mg, 2.47 mmol, 84 %) as a colourless oil.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 2978, 2939, 2836, 1689, 1598, 1581, 1430, 1257; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.55 (1H, d, *J* 7.7 Hz, C_{Ar}<u>*H*</u>), 7.52–7.48 (1H, m, C_{Ar}<u>*H*</u>), 7.37 (1H, t, *J* 7.7 Hz, C_{Ar}<u>*H*</u>), 7.10 (1H, ddd, *J* 8.2, 2.6, 0.8 Hz, C_{Ar}<u>*H*</u>), 3.86 (3H, s, OC<u>*H*</u>$_3$), 3.00 (2H, q, *J* 7.2 Hz, C<u>*H*</u>$_2$CO), 1.23 (3H, t, *J* 7.2 Hz, C<u>*H*</u>$_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 200.7 (<u>*C*</u>=O), 159.8 (<u>*C*</u>$_{Ar}$), 138.3 (<u>*C*</u>$_{Ar}$), 129.5 (<u>*C*</u>$_{Ar}$H), 120.6 (<u>*C*</u>$_{Ar}$H), 119.3 (<u>*C*</u>$_{Ar}$H), 112.3 (<u>*C*</u>$_{Ar}$H), 55.4 (O<u>*C*</u>H$_3$), 31.9 (<u>*C*</u>H$_2$), 8.3 (<u>*C*</u>H$_3$); **m/z** (ESI+) 187.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{10}H_{12}O_2$ requires 187.0723 $[M+Na]^+$, found 187.0730 (Δ = 3.3 ppm).

Methyl 4-propionyl benzoate 739[327, 328]



739

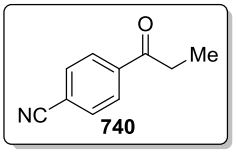
To a stirred solution of **735** (1.00 g, 6.09 mmol) in THF (20 mL) at −78 °C, EtMgBr (1 M in THF, 6.09 mL, 6.09 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for a further 16 h. The reaction was quenched with sat. aq. NH_4Cl (20 mL), and extracted with Et_2O (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and dried *in vacuo*. Crude alcohol **737** (0.50 g, 2.6 mmol) was dissolved in CH_2Cl_2

(10 mL), and Dess-Martin periodinane (1.15 g, 2.70 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The resultant solution was stirred at room temperature for 30 minutes, diluted with Et_2O (50 mL), and 1.3 M NaOH (20 mL) was added. The biphasic solution was stirred for a further 10 minutes, the organic phase was separated, and extracted with 1.3 M NaOH (20 mL). The organic phase was dried over $MgSO_4$, filtered and dried *in vacuo*. Purification by FCC (4:1 Petrol/Et_2O) afforded *ketone* **739** (427 mg, 2.22 mmol, 86% over 2 steps) as a colourless solid.

m.p. 71–73 °C [Lit: 76–78 °C][429]; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.12 (2H, d, *J* 8.5 hz, $C_{Ar}\underline{H}$), 8.01 (2H, d, *J* 8.5 Hz, $C_{Ar}\underline{H}$), 3.95 (3H, s, $OC\underline{H}_3$), 3.04 (2H, q, *J* 7.2Hz, $C\underline{H}_2CO$), 1.24 (3H, t, *J* 7.2 Hz, $C\underline{H}_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 199.6 ($\underline{C}$=O), 165.6 ($\underline{C}O_2Me$), 139.5 ($\underline{C}_{Ar}$), 133.1 ($\underline{C}_{Ar}$), 129.2 ($\underline{C}_{Ar}H$), 127.2 ($\underline{C}_{Ar}H$), 51.8 ($O\underline{C}H_3$), 31.6 ($\underline{C}H_2$), 7.4 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[430]

4-Propionylbenzonitrile 740[327, 328]



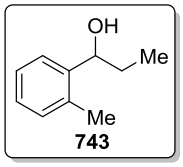
740

To a stirred solution of 4-formylbenzonitrile **736** (500 mg, 3.81 mmol) in THF (10 mL) at −78 °C, EtMgBr (1 M in THF, 3.81 mL, 3.81 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for a further 8 h. The reaction was quenched with 1 M HCl (20 mL), and the organic phase extracted with Et_2O (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and dried *in vacuo*. Crude alcohol **738** (130 mg, 0.810 mmol) was dissolved in CH_2Cl_2 (8 mL) and Dess-Martin periodinane (359 mg, 0.850 mmol) in CH_2Cl_2 (4 mL) was added dropwise. The reaction was stirred for 2 h at rt, diluted with Et_2O (25 mL), and 1.3 M NaOH (10 mL) was added. The biphasic solution was stirred for a further 10 minutes, the organic phase was separated, and extracted with 1.3 M NaOH (10 mL). The organic phase was dried over $MgSO_4$, filtered, and dried *in vacuo*. Purification by FCC (10:1 Petrol/Et_2O) afforded *p-cyano ketone* **740** (112 mg, 0.70 mmol, 86%) as a colourless solid.

m.p 49–51 °C [Lit: 54–55 °C][429]; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 8.02 (2H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 7.74 (2H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 3.00 (2H, q, *J* 7.1 Hz, $C\underline{H}_2CO$), 1.20 (3H, t, *J* 7.1 Hz, $C\underline{H}_3$); $\boldsymbol{\delta_C}$

(100 MHz, $CDCl_3$) 199.3 (*C*=O), 139.8 (*C*$_{Ar}$), 132.5 (*C*$_{Ar}$H), 128.4 (*C*$_{Ar}$H), 118.0 (*C*$_{Ar}$), 116.1 (*C*N), 32.2 (*C*H_2), 7.9 (*C*H_3).

1-(*o*-Tolyl)propan-1-ol 743[327]



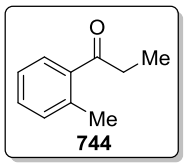
743

To a stirred solution of *o*-tolualdehyde **742** (1.00 mL, 8.65 mmol) in THF (20 mL) at −78 °C, EtMgBr (1 M in THF, 8.65 mL, 8.65 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for a further 16 h. The reaction was quenched with 1 M HCl (10 mL), and extracted with Et_2O (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and dried *in vacuo* to afford *benzylic alcohol* **743** (1.29 g, 8.59 mmol, 99%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.47 (1H, d, *J* 7.6 Hz, $C_{Ar}H$), 7.27–7.13 (3H, m, $C_{Ar}H$), 4.88 (1H, t, *J* 6.4 Hz, C*H*OH), 2.35 (3H, s, CH_3), 1.83–1.69 (3H, m, CH_2, O*H*), 1.00 (3H, t, *J* 7.5 Hz, CH_3); **δ_C** (100 MHz, $CDCl_3$) 142.8 (*C*$_{Ar}$), 134.6 (*C*$_{Ar}$), 130.4 (*C*$_{Ar}$H), 127.1 (*C*$_{Ar}$H), 126.4 (*C*$_{Ar}$H), 125.2 (*C*$_{Ar}$H), 72.1 (*C*HOH), 30.9 (*C*H_3), 19.1 (*C*H_2), 10.4 (*C*H_3).

Spectroscopic data are consistent with those previously reported.[431]

1-(*o*-Tolyl)propan-1-one 744[328]



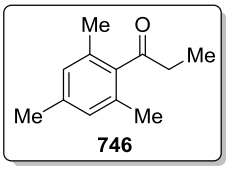
744

Alcohol **743** (500 mg, 3.33 mmol) was dissolved in CH_2Cl_2 (20 mL) and Dess-Martin periodinane (1.48 g, 3.49 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction was stirred for 3 h at rt, diluted with Et_2O (70 mL), and 1.3 M NaOH (30 mL) was added. The biphasic solution was stirred for a further 10 minutes, the organic phase was separated, and extracted with 1.3 M NaOH (30 mL). The organic phase was dried over $MgSO_4$, filtered, and dried *in vacuo*. Purification by FCC (30:1→20:1 Petrol/Et_2O) afforded **744** (327 mg, 2.21 mmol, 66%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.62 (1H, d, *J* 7.8 Hz, $C_{Ar}H$), 7.35 (1H, dt, *J* 8.1, 1.0 Hz, $C_{Ar}H$), 7.27–7.22 (2H, m, $C_{Ar}H$), 2.91 (2H, q, *J* 7.3 Hz, *C*H_2CO), 2.49 (3H, s, *C*H_3), 1.19 (3H, t, *J* 7.3 Hz, CH_3); **δ_C** (100 MHz, $CDCl_3$) 205.1 (*C*=O), 138.2 (*C*$_{Ar}$), 137.8 (*C*$_{Ar}$), 131.9 (*C*$_{Ar}$H), 131.0 (*C*$_{Ar}$H), 128.0 (*C*$_{Ar}$H), 125.6 (*C*$_{Ar}$H), 34.7 (*C*H_3), 21.2 (*C*H_2), 8.4 (*C*H_3).

Spectroscopic data are consistent with those previously reported.[432]

1-Mesitylpropan-1-one 746[330]



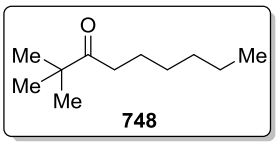
746

To a stirred solution of mesitoyl chloride **745** (1.00 mL, 6.00 mmol) and CuI (1.14 g, 6.00 mmol) at −78 °C, EtMgBr (1M in THF, 6.00 mL, 6.00 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for a further 16 h. The reaction was quenched with 1 M HCl (20 mL), and the organic phase extracted with Et_2O (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and dried *in vacuo*. Purification by FCC (40:1→30:1 Petrol/Et_2O) afforded *mesityl ketone* **746** (871 mg, 4.94 mmol, 82%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 6.84 (2H, s, $C_{Ar}\underline{H}$), 2.71 (2H, q, *J* 7.2 Hz, $C\underline{H}_2CO$), 2.29 (3H, s, *p*-$C\underline{H}_3$), 2.19 (6H, s, *o*-$C\underline{H}_3$), 1.20 (3H, t, *J* 7.2 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 211.5 ($\underline{C}$=O), 139.9 ($\underline{C}_{Ar}$), 138.2 ($\underline{C}_{Ar}$), 132.4 ($\underline{C}_{Ar}$), 128.4 ($\underline{C}_{Ar}H$), 37.9 ($\underline{C}H_2$), 21.0 (*p*-$\underline{C}H_3$), 19.1 (*o*-$\underline{C}H_3$), 7.7 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[433]

2,2-Dimethylnonan-3-one 748[329]



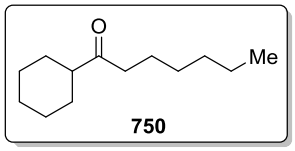
748

To a solution of pivalonitrile **747** (1.00 g, 12.0 mmol) in THF (50 mL) at room temperature was added CuBr (35 mg, 0.24 mmol) and *n*HexMgBr (2M in Et_2O, 6.62 mL, 13.2 mmol). The resultant solution was stirred for 16 h at 65 °C, cooled to room temperature, and quenched with H_2O (50 mL), followed by 15% H_2SO_4 (25 mL). The aqueous phase was extracted with Et_2O (3×50 mL), dried over $MgSO_4$ and the solvent removed *in vacuo*. Purification by FCC (100:1 Petrol/Et_2O) afforded *tert-butyl ketone* **748** (960 mg, 5.64 mmol, 47%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 2.45 (2H, t, *J* 7.1 Hz, $C\underline{H}_2CO$), 1.59–1.49 (2H, m, $C\underline{H}_2$), 1.35–1.22 (6H, m, $C\underline{H}_2$), 1.13 (9H, s, $C(C\underline{H}_3)_3$), 0.88 (3H, t, *J* 6.8 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 216.2 ($\underline{C}$=O), 44.1 ($\underline{C}(CH_3)_3$, 36.4 ($\underline{C}H_2$), 31.7 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 26.4 ($C(\underline{C}H_3)_3$), 23.9 ($\underline{C}H_2$), 22.5 ($\underline{C}H_2$), 14.0 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[434]

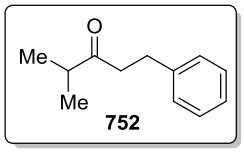
1-Cyclohexylheptan-1-one 750[330]



To a stirred solution of cyclohexanecarbonyl chloride **749** (1.00 g, 6.82 mmol) and CuI (1.30 g, 6.82 mmol) in THF (15 mL) at −78 °C was added *n*HexMgBr (2 M in Et_2O, 3.41 mL, 6.82 mmol) over 15 inutes. The reaction was allowed to warm slowly to room temperature and stirred for a further 18 h. The reaction was quenched with 1M HCl (20 mL) and extracted with Et_2O (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and dried *in vacuo*. Purification by FCC (50:1 Petrol/Et_2O) afforded *cyclohexyl ketone* **750** (703 mg, 3.58 mmol, 52%) as a light yellow oil.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 2927, 2854, 1707, 1450, 1375, 1147; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 2.41 (2H, t, *J* 7.4 Hz, C$\underline{H}_2$CO), 2.37–2.27 (1H, m, C$\underline{H}$CO), 1.86–1.72 (4H, m, C$\underline{H}_2$), 1.69–1.62 (1H, m, C$\underline{H}_a$H$_b$), 1.59–1.47 (2H, m, C$\underline{H}_2$), 1.37–1.12 (11H, m, CH$_a\underline{H}_b$, C$\underline{H}_2$), 0.87 (3H, t, *J* 6.8 Hz); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 214.5 (<u>C</u>=O), 50.8 (<u>C</u>HCO), 40.6 (<u>C</u>H$_2$CO), 31.6 (<u>C</u>H$_2$), 29.0 (<u>C</u>H$_2$), 28.5 (<u>C</u>H$_2$), 25.9 (<u>C</u>H$_2$), 25.7 (<u>C</u>H$_2$), 23.7 (<u>C</u>H$_2$), 22.5 (<u>C</u>H$_2$), 14.0 (<u>C</u>H$_3$); m/z (ESI+) 219.2 $[M+Na]^+$; **HRMS** (ESI+) $C_{13}H_{24}O$ requires 219.1719 $[M+Na]^+$, found 219.1723 (Δ = −1.8 ppm).

4-Methyl-1-phenylpentan-3-one 752[330]

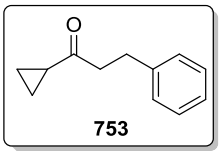


To a suspension of hydrocinnamyl chloride **751** (2.00 mL, 13.5 mmol) and CuI (2.57 g, 13.5 mmol) in THF (20 mL) at −78 °C, isopropylmagnesium chloride (2.0 M in THF, 6.75 mL, 13.5 mmol) was added dropwise. The reaction was allowed to warm to rt and stirred for a further 18 h. The reaction was quenched with 1M HCl (40 mL), extracted with Et_2O (3×40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by FCC (50:1 Petrol/Et_2O) afforded *isopropyl ketone* **752** (2.21 g, 12.6 mmol, 93 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.32–7.26 (2H, m, $C_{Ar}\underline{H}$), 7.23–7.17 (3H, m, $C_{Ar}\underline{H}$), 2.93–2.88 (2H, m, $C\underline{H}_2Ph$), 2.81–2.76 (2H, m, $C\underline{H}_2CO$), 2.58 (1H, sept, *J* 6.9 Hz, $C\underline{H}(CH_3)_2$), 1.08 (6H, d, *J* 6.9 Hz, $C\underline{H}(CH_3)_2$); **δ_C** (100 MHz, $CDCl_3$) δ 213.7 ($\underline{C}$=O), 141.3 ($\underline{C}_{Ar}$), 128.4 ($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 126.0 ($\underline{C}_{Ar}H$), 42.0 ($\underline{C}H(CH_3)_2$), 41.0 ($\underline{C}H_2CO$), 29.8 ($\underline{C}H_2Ph$), 18.1 ($CH(\underline{C}H_3)_2$).

Spectroscopic data are consistent with those previously reported.[435]

1-Cyclopropyl-3-phenylpropan-1-one 753[330]



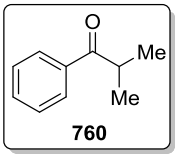
753

To a suspension of hydrocinnamyl chloride **751** (1.00 mL, 6.80 mmol) and CuI (1.28 g, 6.80 mmol) in THF (8 mL) at −78 °C, cyclopropylmagnesium bromide (0.5-0.7 M in THF, 13.5 mL) was added dropwise. The reaction was allowed to warm to rt and stirred for a further 18 h. The reaction was quenched with 1 M HCl (20 mL), extracted with Et_2O (3×20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by FCC (40:1→25:1 Petrol/Et_2O) afforded *cyclopropyl ketone* **753** (1.02 g, 5.83 mmol, 86 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.25–7.06 (5H, m, $C_{Ar}\underline{H}$), 2.89–2.76 (4H, m, $COC\underline{H}_2C\underline{H}_2Ph$), 1.87–1.79 (1H, m, $C\underline{H}CO$), 0.97–0.91 (2H, m, $C\underline{H}_aH_b$), 0.81–0.74 (2H, m, $CH_a\underline{H}_b$); **δ_C** (100 MHz, $CDCl_3$) 209.9 ($\underline{C}$=O), 141.2 ($\underline{C}_{Ar}$), 128.4 ($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 126.0 ($\underline{C}_{Ar}H$), 44.9 ($\underline{C}H_2CO$), 29.9 ($\underline{C}H_2Ph$), 20.5 ($\underline{C}H$), 10.7 ($\underline{C}H_2\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[436]

2-Methyl-phenylpropan-1-one 760

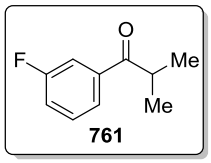


760

Propiophenone **754** (100 μL, 0.750 mmol), $[RhCp^*Cl_2]_2$ (23 mg, 5.0 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (3.8 mL) were subjected to **general procedure F** for 24 h. Purification by FCC (20:1 Petrol/Et_2O) afforded *methylated ketone* **760** (81 mg, 0.55 mmol, 73%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.09–7.89 (2H, m, $C_{Ar}\underline{H}$), 7.66–7.38 (3H, m, $C_{Ar}\underline{H}$), 3.57 (1H, sept, *J* 6.9 Hz, $C\underline{H}(CH_3)_2$), 1.23 (6H, d, *J* 6.8 Hz, $CH(C\underline{H}_3)_2$); **δ_C** (100 MHz, $CDCl_3$) 204.5 ($\underline{C}$=O), 136.2 ($\underline{C}_{Ar}$), 132.8 ($\underline{C}_{Ar}$H), 128.6 ($\underline{C}_{Ar}$H), 128.3 ($\underline{C}_{Ar}$H), 35.4 ($\underline{C}H(CH_3)_2$), 19.2 ($CH(\underline{C}H_3)_2$). Spectroscopic data are consistent with those previously reported.[437]

1-(3-Fluorophenyl)-2-methylpropan-1-one 761

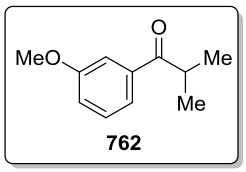


761

1-(3-Fluorophenyl)propan-1-one **728** (46 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (4.7 mg, 2.5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 3 h. Purification by FCC (12:1 Petrol/Et_2O) afforded *methylated ketone* **761** (39 mg, 0.23 mmol, 77%) as a colourless oil.

ν_{max} (cm^{-1}) 3074, 2975, 2935, 2875, 1688, 1588, 1484, 1384, 1190, 1167; **δ_H** (400 MHz, $CDCl_3$) 7.74 (1H, dt, *J* 7.8, 1.2 Hz, $C_{Ar}\underline{H}$), 7.63 (1H, ddd, *J* 9.6, 2.6, 1.7 Hz, $C_{Ar}\underline{H}$), 7.45 (1H, td, *J* 7.8, 5.6 Hz, $C_{Ar}\underline{H}$), 7.27 (1H, tdd, *J* 8.2, 2.6, 0.9 Hz, $C_{Ar}\underline{H}$), 3.50 (1H, sept, *J* 6.8 Hz, $C\underline{H}CO$), 1.22 (6H, d, *J* 6.8 Hz, $CH(C\underline{H}_3)_2$); **δ_C** (100 MHz, $CDCl_3$) 203.2 (d, *J* 1.8 Hz, $\underline{C}$=O), 163.0 (d, *J* 246.0 Hz, $\underline{C}_{Ar}$F), 138.4 (d, *J* 6.0 Hz, $\underline{C}_{Ar}$), 130.2 (d, *J* 7.6 Hz, $\underline{C}_{Ar}$H), 124.0 (d, *J* 3.0 Hz, $\underline{C}_{Ar}$H), 119.8 (d, *J* 21.4 Hz, $\underline{C}_{Ar}$H), 115.1 (d, *J* 22.1 Hz, $\underline{C}_{Ar}$H), 35.6 ($\underline{C}H(CH_3)_2$), 19.0 ($CH(\underline{C}H_3)_2$); **m/z** (ESI+) Not observed; **HRMS** (FI+) $C_{10}H_{11}FO$ requires 167.0794 $[M]^+$, found 166.0792 (Δ = −1.2 ppm).

1-(3-Methoxyphenyl)-2-methylpropan-1-one 762



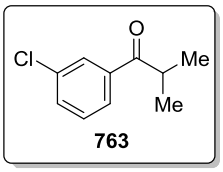
762

1-(3-Methoxyphenyl)propan-1-one **734** (49 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 12 h. Purification by FCC (15:1→10:1 Petrol/Et_2O) afforded *methylated ketone* **762** (41 mg, 0.23 mmol, 77 %) as a colourless oil.

ν_{max} (cm^{-1}) 2971, 2934, 1683, 1597, 1583, 1487, 1466, 1429, 1287; **δ_H** (400 MHz, $CDCl_3$) 7.56–7.52 (1H, m, $C_{Ar}\underline{H}$), 7.51–7.48 (1H, m, $C_{Ar}\underline{H}$), 7.37 (1H, t, *J* 7.8 Hz, $C_{Ar}\underline{H}$), 7.10 (1H, ddd, *J* 8.2, 2.6, 0.6 Hz, $C_{Ar}\underline{H}$), 3.86 (3H, s, $OC\underline{H}_3$), 3.54 (1H, sept, *J* 6.8 Hz, $C\underline{H}(CH_3)_2$), 1.22 (6H, d, *J* 6.8 Hz, $CH(C\underline{H}_3)_2$); **δ_C** (100 MHz, $CDCl_3$) 204.3 ($\underline{C}$=O), 159.8 ($\underline{C}_{Ar}OCH_3$), 137.6

(<u>*C*</u>$_{Ar}$), 129.5 (<u>*C*</u>$_{Ar}$H), 120.8 (<u>*C*</u>$_{Ar}$H), 119.1 (<u>*C*</u>$_{Ar}$H), 112.7 (<u>*C*</u>$_{Ar}$H), 55.4 (O<u>*C*</u>H$_3$), 35.5 (<u>*C*</u>H(CH$_3$)$_2$), 19.2 (CH(<u>*C*</u>H$_3$)$_2$); **m/z** (ESI+) 201.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{11}H_{14}O_2$ requires 201.0886 $[M+Na]^+$, found 201.0878 (Δ = 4.0 ppm).

1-(3-Chlorophenyl)-2-methylpropan-1-one 763

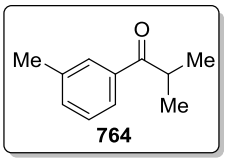


763

1-(3-Chlorophenyl)propan-1-one **755** (51 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (4.7 mg, 2.5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 3 h. Purification by FCC (15:1 Petrol/Et$_2$O) afforded *methylated ketone* **763** (43 mg, 0.24 mmol, 79 %) as a colourless oil.

ν_{max} (cm^{-1}) 3068, 3034, 2973, 2934, 2874, 1686, 1590, 1571, 1218; **δ_H** (400 MHz, $CDCl_3$) 7.92 (1H, t, *J* 1.8 Hz, C$_{Ar}$<u>*H*</u>), 7.83 (1H, dt, *J* 7.8, 1.3 Hz, C$_{Ar}$<u>*H*</u>), 7.53 (1H, ddd, *J* 8.0, 2.1, 1.1 Hz, C$_{Ar}$<u>*H*</u>), 7.41 (1H, t, *J* 8.0 Hz, C$_{Ar}$<u>*H*</u>), 3.50 (1H, sept, *J* 6.8 Hz, C<u>*H*</u>(CH$_3$)$_2$), 1.22 (6H, d, *J* 6.8 Hz, CH(C<u>*H*</u>$_3$)$_2$); **δ_C** (100 MHz, $CDCl_3$) 203.1 (<u>*C*</u>=O), 137.8 (<u>*C*</u>$_{Ar}$), 134.9 (<u>*C*</u>$_{Ar}$), 132.7 (<u>*C*</u>$_{Ar}$H), 129.9 (<u>*C*</u>$_{Ar}$H), 128.4 (<u>*C*</u>$_{Ar}$H), 126.3 (<u>*C*</u>$_{Ar}$H), 35.6 (<u>*C*</u>H(CH$_3$)$_2$), 19.0 (CH(<u>*C*</u>H$_3$)$_2$); **m/z** (ESI+) Not observed; **HRMS** (FI+) $C_{10}H_{11}ClO$ requires 182.0498 $[M]^+$, found 182.0499 (Δ = −2.5 ppm).

2-Methyl-1-(*m*-tolyl)propan-1-one 764



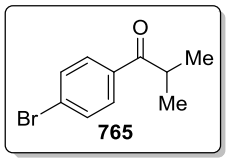
764

1-(*m*-Tolyl)propan-1-one **729** (45 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 48 h. Purification by FCC (30:1 Petrol/Et$_2$O) afforded *methylated ketone* **764** (34 mg, 0.21 mmol, 71%) as a light yellow oil.

ν_{max} (cm^{-1}) 2972, 2931, 2873, 1682, 1603, 1585, 1467, 1383, 1198; **δ_H** (400 MHz, $CDCl_3$) 7.80–7.72 (2H, m, C$_{Ar}$<u>*H*</u>), 7.40–7.33 (2H, m, C$_{Ar}$<u>*H*</u>), 3.56 (1H, sept, *J* 6.8 Hz, C<u>*H*</u>CO), 2.42 (3H, s, ArC<u>*H*</u>$_3$), 1.22 (6H, d, *J* 6.8 Hz, CH(C<u>*H*</u>$_3$)$_2$); **δ_C** (100 MHz, $CDCl_3$) 204.8 (<u>*C*</u>=O), 138.3 (<u>*C*</u>$_{Ar}$), 136.3 (<u>*C*</u>$_{Ar}$), 133.5 (<u>*C*</u>$_{Ar}$H), 128.8 (<u>*C*</u>$_{Ar}$H), 128.4 (<u>*C*</u>$_{Ar}$H), 125.5 (<u>*C*</u>$_{Ar}$H), 35.3 (<u>*C*</u>H$_2$CO),

21.4 (Ar<u>C</u>H$_3$), 19.2 (<u>C</u>H$_3$); **m/z** (ESI+) 185.1 [M+Na]$^+$; **HRMS** (ESI+) $C_{11}H_{14}O$ requires 185.0937 [M+Na]$^+$, found 185.0930 (Δ = 3.7 ppm).

1-(4-Bromophenyl)-2-methyl-propan-1-one 765



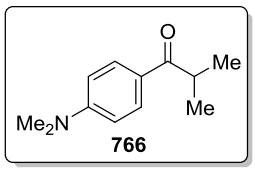
765

4'-Bromopropiophenone **756** (64 mg, 0.30 mmol), [RhCp*Cl$_2$]$_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 48 h. Purification by FCC (20:1 Petrol/Et$_2$O) afforded *methylated ketone* **765** (52 mg, 0.23 mmol, 76 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.82 (2H, d, *J* 8.6 Hz, C$_{Ar}$<u>H</u>), 7.60 (2H, d, *J* 8.6 Hz, C$_{Ar}$<u>H</u>), 3.49 (1H, sept, *J* 6.8Hz, C<u>H</u>(CH$_3$)$_2$), 1.20 (6H, d, *J* 6.8Hz, CH(C<u>H</u>$_3$)$_2$); **δ_C** (100 MHz, $CDCl_3$) 203.4 (<u>C</u>=O), 134.9 (<u>C</u>$_{Ar}$), 131.9 (<u>C</u>$_{Ar}$H), 129.9 (<u>C</u>$_{Ar}$H), 127.9 (<u>C</u>$_{Ar}$Br), 35.4 (<u>C</u>H(CH$_3$)$_2$), 19.0 (CH(<u>C</u>H$_3$)$_2$).

Spectroscopic data are consistent with those previously reported.[438]

1-(4-(Dimethylamino)phenyl)-2-methylpropan-1-one 766



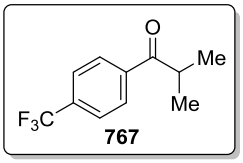
766

1-(4-(Dimethylamino)phenyl)propan-1-one **731** (53 mg, 0.30 mmol), [RhCp*Cl$_2$]$_2$ (4.7 mg, 2.5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 24 h. Another batch of [RhCp*Cl$_2$]$_2$ (4.7 mg 2.5 mol%) was then added and this was repeated at 48 h. The reaction was run at 65 °C for a total of 72 h. Purification by FCC (5:1 Petrol/Et$_2$O) afforded *methylated ketone* **766** (46 mg, 0.24 mmol, 80 %) as a light yellow solid.

m.p. 47–49 °C [Lit: 46–49 °C][439]; **δ_H** (400 MHz, $CDCl_3$) 7.91 (2H, d, *J* 9.1 Hz, C$_{Ar}$<u>H</u>), 6.66 (2H, d, *J* 9.1 Hz C$_{Ar}$<u>H</u>), 3.51 (1H, sept, *J* 6.8 Hz, C<u>H</u>(CH$_3$)$_2$), 3.06 (6H, s, N(C<u>H</u>$_3$)$_2$), 1.20 (6H, d, *J* 6.8 Hz, CH(C<u>H</u>$_3$)$_2$); **δ_C** (100 MHz, $CDCl_3$) 202.7 (<u>C</u>=O), 153.2 (<u>C</u>$_{Ar}$), 130.4 (<u>C</u>$_{Ar}$), 124.0 (<u>C</u>$_{Ar}$H), 110.7 (<u>C</u>$_{Ar}$H), 40.0 (N(<u>C</u>H$_3$)$_2$), 34.3 (<u>C</u>H(CH$_3$)$_2$), 19.5 (CH(<u>C</u>H$_3$)$_2$.

Spectroscopic data are consistent with those previously reported.[440]

2-Methyl-1-(4-(trifluoromethyl)phenyl)propan-1-one 767



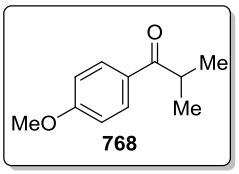
767

4'-(Trifluoromethyl)propiophenone **757** (61 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (4.7 mg, 2.5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 2 h. Purification by FCC (20:1 Petrol/Et_2O) afforded *methylated ketone* **767** (47 mg, 0.22 mmol, 73%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.98 (2H, d, *J* 8.1 Hz, $C_{Ar}\underline{H}$), 7.66 (2H, d, *J* 8.2 Hz, $C_{Ar}\underline{H}$), 3.48 (1H, sept, *J* 6.8 Hz, $C\underline{H}(CH_3)_2$), 1.16 (6H, d, *J* 6.8 Hz ($CH(C\underline{H}_3)_2$); **δ_C** (100 MHz, $CDCl_3$) 203.4 ($\underline{C}$=O), 139.0 ($\underline{C}_{Ar}$), 134.1 (q, *J* 32.6 Hz, $\underline{C}_{Ar}CF_3$), 128.6 ($\underline{C}_{Ar}H$), 125.7 (q, *J* 3.8 Hz, $\underline{C}_{Ar}H$), 123.6 (q, *J* 271 Hz, $\underline{C}F_3$), 35.8 ($\underline{C}H(CH_3)_2$), 18.9 ($CH(\underline{C}H_3)_2$); **δ_F** (377 MHz, $CDCl_3$) −63.10.

Spectroscopic data are consistent with those previously reported.[441]

1-(4-Methoxyphenyl)-2-methylpropan-1-one 768



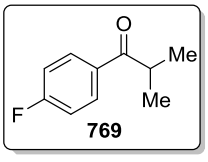
768

4'-Methoxypropiophenone **758** (49 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (4.7 mg, 2.5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) was subjected to **general procedure F** for 24 h. Purification by FCC (20:1 Petrol/Et_2O) afforded *methylated ketone* **768** (40 mg, 0.22 mmol, 74%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.98–7.92 (2H, m, $C_{Ar}\underline{H}$), 6.97–6.92 (2H, m, $C_{Ar}\underline{H}$), 3.86 (3H, s, $OC\underline{H}_3$), 3.50 (1H, sept, *J* 6.8 Hz, $C\underline{H}(CH_3)_2$), 1.20 (6H, d, *J* 6.8 Hz, $CH(C\underline{H}_3)_2$); **δ_C** (100 MHz, $CDCl_3$) 203.1 ($\underline{C}$=O), 163.3 ($\underline{C}_{Ar}OCH_3$), 130.6 ($\underline{C}_{Ar}H$), 129.1 ($\underline{C}_{Ar}$), 131.7 ($\underline{C}_{Ar}H$), 55.4 ($O\underline{C}H_3$), 34.9 ($\underline{C}H(CH_3)_2$), 19.3 ($CH(\underline{C}H_3)_2$).

Spectroscopic data are consistent with those previously reported.[442]

1-(4-Fluorophenyl)-2-methyl-propan-1-one 769



769

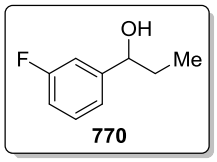
4'-Fluoropropiophenone **759** (42 μL, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (195 mg, 0.600 mmol), and methanol (1.5 mL) were

subjected to **general procedure F** for 48 h. Purification by FCC (30:1 Petrol/Et_2O) afforded *methylated ketone* **769** (29 mg, 0.17 mmol, 58 %) as a colourless oil along with *p-methoxyphenyl ketone* **758** (11 mg, 0.062 mmol, 21%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 8.02–7.96 (2H, m, $C_{Ar}\underline{H}$), 7.17–7.10 (2H, m, $C_{Ar}\underline{H}$), 3.52 (1H, sept, *J* 6.8 Hz, $C\underline{H}(CH_3)_2$), 1.22 (6H, d, *J* 6.8 Hz, $CH(C\underline{H}_3)_2$); **δ_C** (100 MHz, $CDCl_3$) 202.8 ($\underline{C}$=O), 165.5 (d, *J* 252.6 Hz, $\underline{C}_{Ar}F$), 132.5 (d, *J* 2.9 Hz, $\underline{C}_{Ar}$), 130.9 (d, *J* 9.8 Hz, $\underline{C}_{Ar}H$), 115.6 (d, *J* 21.6 Hz, $\underline{C}_{Ar}H$), 35.3 ($\underline{C}H(CH_3)_2$), 19.1 ($CH(\underline{C}H_3)_2$); **δ_F** (377 MHz, $CDCl_3$) −105.9.

Spectroscopic data are consistent with those previously reported.[325]

1-(3-Fluorophenyl)propan-1-ol 770



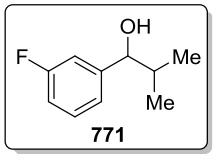
770

Alcohol **770** was observed as a byproduct, isolated as a light-brown oil (4 mg, 0.03 mmol, 10%) in the methylation of 3'-fluoropropiophenone **728** with 5 mol% $[RhCp^*Cl_2]_2$.

δ_H (400 MHz, $CDCl_3$) 7.30–7.23 (1H, m, $C_{Ar}\underline{H}$), 7.09–6.99 (2H, m, $C_{Ar}\underline{H}$), 6.96–6.89 (1H, m, $C_{Ar}\underline{H}$), 4.55 (1H, t, *J* 6.5 Hz, $C\underline{H}OH$), 2.27 (1H, br s, $O\underline{H}$), 1.81–1.62 (2H, m, $C\underline{H}_2$), 0.88 (3H, t, *J* 7.4 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 162.9 (d, *J* 244.1 Hz, $\underline{C}_{Ar}$), 147.2 (d, *J* 6.5 Hz, $\underline{C}_{Ar}$), 129.8 (d, *J* 8.1 Hz, $\underline{C}_{Ar}H$), 121.5 (d, *J* 2.7 Hz, $\underline{C}_{Ar}H$), 114.2 (d, *J* 21.2 Hz, $\underline{C}_{Ar}H$), 112.8 (d, *J* 21.6 Hz, $\underline{C}_{Ar}H$), 75.2 (d, *J* 1.4 Hz, $\underline{C}HOH$), 31.8 ($\underline{C}H_2$), 9.9 ($\underline{C}H_3$); **δ_F** (377 MHz, $CDCl_3$) −113.2 ($C_{Ar}\underline{F}$).

Spectroscopic data are consistent with those previously reported.[443]

1-(3-Fluorophenyl)-2-methylpropan-1-ol 771



771

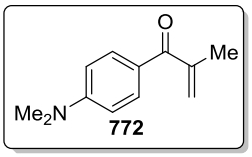
Alcohol **771** was observed as a byproduct, isolated as a colourless oil (3 mg, 0.02 mmol, 7%) in the methylation of 3'-fluoropropiophenone **728** using 5 mol% $[RhCp^*Cl_2]_2$.

ν_{max} (cm^{-1}) 3384 (br), 2961, 2874, 1604, 1510, 1222; **δ_H** (400 MHz, $CDCl_3$) 7.33–7.26 (1H, m, $C_{Ar}\underline{H}$), 7.10–7.02 (2H, m, $C_{Ar}\underline{H}$), 6.99–6.93 (1H, m, $C_{Ar}\underline{H}$), 4.40 (1H, d, *J* 6.6 Hz, $C\underline{H}OH$),

2.01–1.83 (2H, m, C*H*(CH_3)$_2$, O*H*), 0.98 (3H, d, *J* 6.8 Hz), 0.83 (3H, d, *J* 6.8 Hz); **δ_C** (100 MHz, $CDCl_3$) 162.8 (d, *J* 246 Hz, *C*$_{Ar}$F), 146.3 (d, *J* 6.6 Hz, *C*$_{Ar}$), 129.6 (d, *J* 8.3 Hz, *C*$_{Ar}$H), 122.2 (d, *J* 2.6 Hz, *C*$_{Ar}$H), 114.2 (d, *J* 21.3 Hz, *C*$_{Ar}$H), 113.4 (d, *J* 21.7 Hz, *C*$_{Ar}$H), 79.2 (d, *J* 1.3 Hz, *C*HOH), 35.2 (*C*H(CH_3)$_2$), 18.9 (CH(*C*H_3)$_a$(CH_3)$_b$), 17.9 (CH(CH_3)$_a$(*C*H_3)$_b$); **δ_F** (377 MHz, $CDCl_3$) −113.3; **m/z** (ESI+) 191.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{10}H_{13}FO$ requires 191.0843 $[M+Na]^+$, found 191.0835 (Δ = 3.7 ppm).

1-(4-(Dimethylamino)phenyl)-2-methylprop-2-en-1-one 772

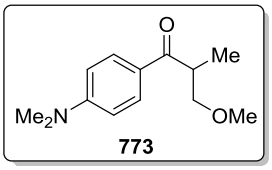
4'-(Dimethylamino)propiophenone **731** (53 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (488 mg, 1.50 mmol) and methanol (1.5 mL) were subjected to **general procedure F** for 48 h. Purification by FCC (5:1 Petrol/Et_2O) afforded *methylated ketone* **766** (19 mg, 0.10 mmol, 33%) as a light yellow solid, and *enone* **772** (5.0 mg, 0.026 mmol, 9%) and *methanol adduct* **773** (34 mg, 0.15 mmol, 50%) as colourless oils.



772

ν_{max} (cm^{-1}) 2920, 2818, 1639, 1591, 1549, 1527, 1368, 1330, 1167; **δ_H** (400 MHz, $CDCl_3$) 7.76–7.82 (2H, m, C$_{Ar}$*H*), 6.62–6.69 (2H, m, C$_{Ar}$*H*), 5.65–5.67 (1H, m, C=C*H*$_a$H$_b$), 5.42–5.45 (1H, m, C=CH$_a$*H*$_b$), 3.06 (6H, s, N(C*H*$_3$)$_2$), 2.06 (3H, m, C*H*$_3$); **δ_C** (100 MHz, $CDCl_3$) 196.8 (*C*=O), 153.2 (*C*$_{Ar}$), 144.1 (*C*=CH$_2$), 132.0 (*C*$_{Ar}$H), 124.3 (*C*$_{Ar}$), 122.0 (C=*C*H$_2$), 110.4 (*C*$_{Ar}$H) , 39.9 (N(*C*H$_3$)$_2$), 19.5 (*C*H$_3$); **m/z** (ESI+) 190.2 $[M+H]^+$; **HRMS** (ESI+) $C_{12}H_{15}NO$ requires 212.1046 $[M+Na]^+$, found 212.1044 (Δ = 1.1 ppm).

1-(4-(Dimethylamino)phenyl)-3-methoxy-2-methylpropan-1-one 773

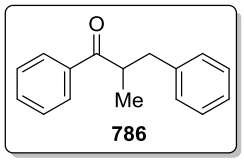


773

ν_{max} (cm^{-1}) 2984, 2906, 2876, 2813, 1658, 1596, 1371, 1188, 1109; **δ_H** (400 MHz, $CDCl_3$) 7.92 (2H, d, *J* 9.1 Hz, C$_{Ar}$*H*), 6.67 (2H, d, *J* 9.1 Hz, C$_{Ar}$*H*), 3.78–3.69 (2H, m, C*H*$_a$H$_b$OCH$_3$, C*H*(CH$_3$)CH$_2$OCH$_3$), 3.46–3.39 (1H, m, CH$_a$*H*$_b$OCH$_3$), 3.33 (3H, s, OC*H*$_3$), 3.06 (6H, s, N(C*H*$_3$)$_2$), 1.19 (3H, d, *J* 6.8 Hz, C*H*$_3$). **δ_C** (101 MHz, $CDCl_3$) 200.5 (*C*=O), 153.4 (*C*$_{Ar}$), 130.6 (*C*$_{Ar}$H), 124.5 (*C*$_{Ar}$), 110.7 (*C*$_{Ar}$H), 75.3 (*C*H$_2$OCH$_3$), 59.1 (O*C*H$_3$), 40.3 (*C*H), 40.0

($N(\underline{C}H_3)_2$), 15.4 ($\underline{C}H_3$); **m/z** (ESI+) 244.2 $[M+Na]^+$; **HRMS** (ESI+) $C_{13}H_{19}NO_2$ requires 244.1308 $[M+Na]^+$, found 244.1315 ($\Delta = -2.7$ ppm).

2-Methyl-1,3-diphenylpropan-1-one 786

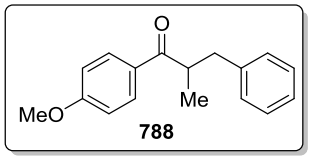


3-Phenylpropiophenone **779** (63 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 48 h. Purification by FCC (30:1 Petrol/Et_2O) afforded *methylated ketone* **786** (53.5 mg, 0.24 mmol, 85%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.99–7.93 (2H, m, $C_{Ar}\underline{H}$), 7.61–7.54 (1H, m, $C_{Ar}\underline{H}$), 7.51–7.45 (2H, m, $C_{Ar}\underline{H}$), 7.34–7.17 (5H, m, $C_{Ar}\underline{H}$), 3.85–3.75 (1H, m, C$\underline{H}$CO), 3.21 (1H, dd, *J* 13.7, 6.3 Hz, C$\underline{H}_a$H$_b$Ph), 2.73 (1H, dd, *J* 13.7, 7.9 Hz, CH$_a\underline{H}_b$Ph), 1.24 (3H, d, *J* 6.9 Hz, C$\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 203.7 ($\underline{C}$=O), 139.9 ($\underline{C}_{Ar}$), 136.4 ($\underline{C}_{Ar}$), 132.9 ($\underline{C}_{Ar}$H), 129.1 ($\underline{C}_{Ar}$H), 128.6 ($\underline{C}_{Ar}$H), 128.3 ($\underline{C}_{Ar}$H), 128.3 ($\underline{C}_{Ar}$H), 126.2 ($\underline{C}_{Ar}$H), 42.7 ($\underline{C}$HCO), 39.3 ($\underline{C}$H$_2$Ph), 17.4 ($\underline{C}$H$_3$).

Spectroscopic data are consistent with those previously reported.[444]

1-(4-Methoxyphenyl)-2-methyl-3-phenylpropan-1-one 788

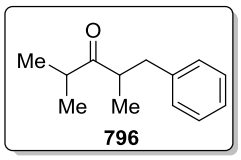


1-(4-Methoxyphenyl)-3-phenylpropan-1-one (72 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 24 h. Purification by FCC (10:1 Petrol/Et_2O) afforded *methylated ketone* **788** (56 mg, 0.22 mmol, 73 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.91 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.28–7.13 (5H, m, $C_{Ar}\underline{H}$), 6.91 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 3.84 (3H, s, OC$\underline{H}_3$), 3.74–3.65 (1H, m, C$\underline{H}$CO), 3.15 (1H, dd, *J* 13.6, 6.7 Hz, C$\underline{H}_a$H$_b$Ph), 2.68 (1H, dd, *J* 13.6, 7.9 Hz, CH$_a\underline{H}_b$Ph), 1.19 (3H, d, *J* 6.9 Hz, C$\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 202.2 ($\underline{C}$=O), 163.3 ($\underline{C}_{Ar}$), 140.0 ($\underline{C}_{Ar}$), 130.5 ($\underline{C}_{Ar}$H), 129.3 ($\underline{C}_{Ar}$), 129.0 ($\underline{C}_{Ar}$H), 128.3 ($\underline{C}_{Ar}$H), 126.1 ($\underline{C}_{Ar}$H), 113.7 ($\underline{C}_{Ar}$H), 55.4 (O$\underline{C}$H$_3$), 42.3 ($\underline{C}$HCO), 39.5 ($\underline{C}$H$_2$Ph), 17.5 ($\underline{C}$H$_3$).

Spectroscopic data are consistent with those previously reported.[445]

2,4-Dimethyl-1-phenylpentan-3-one 796



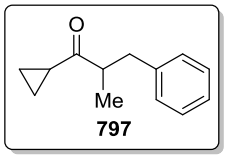
796

1,5-Diphenylpentan-3-one **752** (50 mg, 0.28 mmol), $[RhCp^*Cl_2]_2$ (8.6 mg, 5.0 mol%), Cs_2CO_3 (456 mg, 1.40 mmol), and methanol (1.4 mL) were subjected to general procedure F for 48 h. Purification by FCC (10:1 Petrol/Et_2O) afforded *methylated ketone* **796** (26 mg, 0.14 mmol, 49 %) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.25–7.02 (5H, m, $C_{Ar}\underline{H}$), 2.99–2.82 (2H, m, $C\underline{H}_aH_bPh$, $C\underline{H}CO$), 2.55–2.36 (2H, m, $CH_a\underline{H}_bPh$, $C\underline{H}(CH_3)_2$), 1.01 (3H, d, *J* 6.7, $C\underline{H}_3$), 0.94 (3H, d, *J* 6.9 Hz, $C\underline{H}_3$), 0.80 (3H, d, *J* 6.9 Hz, $C\underline{H}_3$). **δ_C** (100 MHz, $CDCl_3$) 217.9 ($\underline{C}$=O), 140.0 ($\underline{C}_{Ar}$), 129.0 ($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 126.2 ($\underline{C}_{Ar}H$), 46.6 ($\underline{C}HCO$), 40.4 ($\underline{C}H(CH_3)_2$), 39.5 ($\underline{C}H_2Ph$), 18.0 ($CH(\underline{C}H_3)_2$), 17.7 ($CH(\underline{C}H_3)_2$), 17.2 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[446]

1-Cyclopropyl-2-methyl-3-phenylpropan-1-one 797



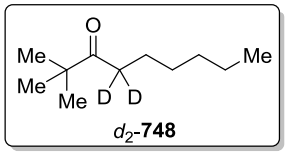
797

1-Cyclopropyl-3-phenylpropan-1-one **753** (52 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 48 h. Purification by FCC (20:1 Petrol/Et_2O) afforded *methylated ketone* **797** (46 mg, 0.24 mmol, 81%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.30–7.13 (5H, m, $C_{Ar}\underline{H}$), 3.05 (1H, dd, *J* 13.4, 6.6 Hz, $C\underline{H}_aH_bPh$), 2.97 (1H, app sext, *J* 7.2 Hz, $\underline{C}HCO$), 2.58 (1H, dd, *J* 13.4, 7.6 Hz, $CH_a\underline{H}_bPh$), 1.94–1.86 (1H, m, $C\underline{H}CO$), 1.12 (3H, d, *J* 6.9 Hz, $C\underline{H}_3$), 1.00–0.90 (2H, m, $C\underline{H}_aH_b$), 0.88–0.74 (2H, m, $C\underline{H}_aH_b$); **δ_C** (100 MHz, $CDCl_3$) 213.8 ($\underline{C}$=O), 139.9 ($\underline{C}_{Ar}$), 129.1 ($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 126.2 ($\underline{C}_{Ar}H$), 48.9 ($\underline{C}HCO$), 39.0 ($\underline{C}H_2Ph$), 19.7 ($\underline{C}HCO$), 16.3 ($\underline{C}H_3$), 10.9 ($\underline{C}H_2$), 10.8 ($\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[446]

2,2-Dimethylnonan-3-one-4,4-d_2 d_2-748

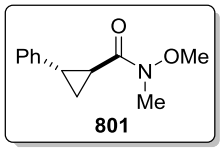


d_2-**748**

2,2-Dimethylnonan-3-one **748** (51 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5 mol%), KOH (84 mg, 1.5 mmol) and d_4-methanol (1.5 mL) were subjected to **general procedure F** for 18 h. The reaction mixture was diluted with Et_2O (10 mL), filtered through SiO_2, and the solvent removed *in vacuo*. Purification by FCC (100:1 Petrol/Et_2O) afforded d_2-**748** (50 mg, 0.29 mmol, 97%, 92.5% deuterium incorporation by ^{1}H NMR) as a colourless oil.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 2920, 2818, 1709, 1639, 1368, 1330; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 1.57–1.47 (2H, m (C$\underline{H}_2$), 1.36–1.19 (6H, m (C$\underline{H}_2$)), 1.12 (9H, s (C(C$\underline{H}_3$)$_3$), 0.90–0.83 (3H, m, C$\underline{H}_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 216.2 ($\underline{C}$=O), 44.1 ($\underline{C}$(CH$_3$)$_3$), 35.9 (quint, *J* 18.9 Hz, $\underline{C}D_2CO$), 31.7 ($\underline{C}H_2$), 28.9 ($\underline{C}H_2$), 26.3 ($\underline{C}H_2$), 23.8 (C($\underline{C}H_3$)$_3$), 22.5 ($\underline{C}H_2$), 14.0 ($\underline{C}H_3$); **m/z** (ESI+) 195.2 $[M+Na]^+$; **HRMS** (ESI+) $C_{11}H_{20}D_2O$ requires 195.1688 $[M+Na]^+$, found 195.1681 (Δ = 4.0 ppm).

(1*S, 2*S**)-*N*-Methoxy-*N*-methyl-2-phenylcyclopropane-1-carboxamide 801[326]**



801

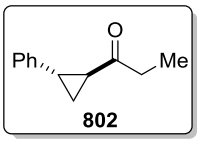
To a stirred solution of of *trans*-2-phenyl-1-cyclopropanecarboxylic acid **800** (1.00 g, 6.17 mmol) in CH_2Cl_2 (30 mL) was added *N*,*O*-dimethylhydroxylamine hydrochloride (603 mg, 6.17 mmol), Et_3N (1.12 mL, 8.02 mmol) and EDC·HCl (1.78 g, 9.26 mmol). The resultant mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo*, and the resultant residue redissolved in EtOAc (50 mL). The organic phase was washed with sat. aq. $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent removed *in vacuo* to afford *Weinreb's amide* **801** (878 mg, 4.28 mmol, 69 %) as a colourless oil.

$\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.32–7.26 (2H, m, $C_{Ar}\underline{H}$), 7.23–7.18 (1H, m, $C_{Ar}\underline{H}$), 7.17–7.12 (2H, m, $C_{Ar}\underline{H}$), 3.70 (3H, s, OC$\underline{H}_3$), 3.25 (3H, s, NC$\underline{H}_3$), 2.54–2.37 (2H, m, C$\underline{H}$Ph, C$\underline{H}$CO), 1.67–1.61 (1H, m, C$\underline{H}_a$H$_b$), 1.35–1.29 (1H, m, CH$_a\underline{H}_b$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.1 ($\underline{C}$=O), 140.8

($\underline{C}_{Ar}$), 128.4 ($\underline{C}_{Ar}H$), 126.2 ($\underline{C}_{Ar}H$), 126.2 ($\underline{C}_{Ar}H$), 61.7 (O$\underline{C}H_3$), 32.6 (N$\underline{C}H_3$), 25.9 ($\underline{C}$HPh), 21.5 ($\underline{C}$HCO), 16.4 ($\underline{C}H_2$).

Spectroscopic data are consistent with those previously reported.[447]

1-((1*S,2*S**)-2-Phenylcyclopropyl)propan-1-one 802[326]**



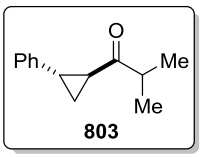
802

To Weinreb amide **801** (500 mg, 2.44 mmol) in THF (15 mL) at 0 °C, EtMgBr (1 M in THF, 7.80 mL, 7.80 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for a further 18 h. The reaction was quenched with 1 M HCl (10 mL), extracted into EtOAc (20 mL), then washed with water (10 mL) and brine (10 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Purification by FCC ($CHCl_3$) afforded *ketone* **802** (263 mg, 1.52 mmol, 62%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.33–7.26 (2H, m, $C_{Ar}\underline{H}$), 7.24–7.19 (1H, m, $C_{Ar}\underline{H}$), 7.13–7.08 (2H, m, $C_{Ar}\underline{H}$), 2.64 (2H, q, *J* 7.3 Hz, C$\underline{H}_2$), 2.54–2.48 (1H, m, C$\underline{H}$Ph), 2.23–2.17 (1H, m, C$\underline{H}$CO), 1.70–1.64 (1H, m, C$\underline{H}_a$H$_b$), 1.40–1.34 (1H, m, CH$_a\underline{H}_b$), 1.11 (3H, t, *J* 7.3 Hz, C$\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 209.5 ($\underline{C}$=O), 140.5 ($\underline{C}_{Ar}$), 128.5 ($\underline{C}_{Ar}H$), 126.4 ($\underline{C}_{Ar}H$), 126.0 ($\underline{C}_{Ar}H$), 37.1($\underline{C}H_2$CO), 31.9 ($\underline{C}$HCO), 28.7 ($\underline{C}$HPh), 18.8 ($\underline{C}H_2$), 7.9 ($\underline{C}H_3$).

Spectroscopic data are consistent with those previously reported.[448]

2-Methyl-1-((*1*S*,2*S)-2-phenylcyclopropyl)propan-1-one 803**



803

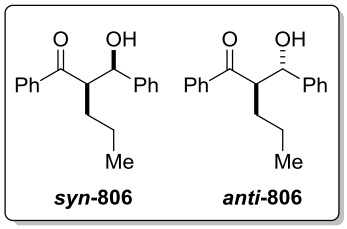
1-((1*S**,2*S**)-2-Phenylcyclopropyl)propan-1-one **802** (52 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and methanol (1.5 mL) were subjected to **general procedure F** for 48 h. Purification by FCC (10:1 Petrol/Et_2O) afforded *methylated ketone* **803** (22 mg, 0.12 mmol, 40%) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.32–7.26 (2H, m, $C_{Ar}\underline{H}$), 7.24–7.19 (1H, m, $C_{Ar}\underline{H}$), 7.14–7.09 (2H, m, $C_{Ar}\underline{H}$), 2.79 (1H, sept, *J* 6.9 Hz, C$\underline{H}$(CH$_3$)$_2$), 2.47 (1H, ddd, *J* 9.1, 6.5, 4.0 Hz, C$\underline{H}$Ph), 2.24 (1H, ddd, *J* 8.1, 5.3, 4.1 Hz, C$\underline{H}$CO), 1.68–1.63 (1H, m, C$\underline{H}_a$H$_b$), 1.37 (1H, ddd, *J* 8.1, 6.5,

4.1 Hz, $CH_a\underline{H}_b$), 1.17 (6H, app t, *J* 6.8 Hz, $CH(C\underline{H}_3)_2$); **δ_C** (100 MHz, $CDCl_3$) 212.5 ($\underline{C}$=O), 140.5 ($\underline{C}_{Ar}$), 128.5 ($\underline{C}_{Ar}H$), 126.4 ($\underline{C}_{Ar}H$), 126.1 ($\underline{C}_{Ar}H$), 41.8 ($\underline{C}H(CH_3)_2$), 30.6 ($\underline{C}$HPh), 28.9 ($\underline{C}$HCO), 18.6 ($\underline{C}H_2$), 18.0 ($CH(\underline{C}H_3)_2$).

All spectroscopic data were consistent with those previously reported.[449]

(*R)-2-((*R**)-hydroxy(phenyl)methyl)-1-phenylpentan-1-one, and (*R**)-2-((*S**)-hydroxy(phenyl)methyl)-1-phenylpentan-1-one *syn*-806 and *anti*-806**



n-Buli (2.5 M in hexane, 2.53 mL, 6.32 mmol) was added dropwise to a solution of DIPA (886 μL, 6.32 mmol) in THF at 0 °C. The solution was stirred at this temperature for 10 minutes, cooled to −78 °C, then valerophenone **718** (500 μL, 3.16 mmol) was added dropwise and stirred for a further 15 minutes. Benzaldehyde (642 μL, 6.32 mmol) was added dropwise, and the solution allowed to warm to rt, and stirred for a further 6 h. The reaction was quenched by by the addition of sat. aq. NH_4Cl (20 mL), and extracted with Et_2O (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and dried *in vacuo*. Purification by FCC (10:1→5:1 petrol/Et_2O) afforded *syn*-**806** and *anti*-**806** as a 1:1.5 mixture of diastereomers (820 mg, 3.06 mmol, 96%).

syn-**806** **δ_H** (400 MHz, $CDCl_3$) 7.95–7.87 (2H, m, $C_{Ar}\underline{H}$), 7.60–7.52 (1H, m, $C_{Ar}\underline{H}$), 7.48–7.19 (7H, m, $C_{Ar}\underline{H}$), 5.07 (1H, d, *J* 4.5 Hz, C$\underline{H}$OH), 3.83–3.77 (1H, m, C$\underline{H}$CO), 3.27 (1H, br s, O$\underline{H}$), 1.95–1.83 (1H, m, $C\underline{H}_aH_b$), 1.76–1.64 (1H, m, $CH_a\underline{H}_b$), 1.27–1.02 (2H, m, $C\underline{H}_2$), 0.78 (3H, t, *J* 7.3 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 205.4 ($\underline{C}$=O), 142.0 ($\underline{C}_{Ar}$), 137.3 ($\underline{C}_{Ar}$), 133.4 ($\underline{C}_{Ar}H$), 128.6 ($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 128.2 ($\underline{C}_{Ar}H$), 127.4 ($\underline{C}_{Ar}H$), 126.1 ($\underline{C}_{Ar}H$), 73.9 ($\underline{C}$HOH), 52.7 ($\underline{C}$HCO), 29.5 ($\underline{C}H_2$), 21.1 ($\underline{C}H_2$), 14.3 ($\underline{C}H_3$).

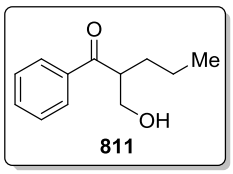
anti-**806** **δ_H** (400 MHz, $CDCl_3$) 7.95–7.87 (2H, m, $C_{Ar}\underline{H}$), 7.60–7.52 (1H, m, $C_{Ar}\underline{H}$), 7.48–7.19 (7H, m, $C_{Ar}\underline{H}$), 5.00 (1H, d, *J* 7.0 Hz, C$\underline{H}$OH), 3.89–3.83 (1H, m, C$\underline{H}$CO), 3.19 (1H, br s, O$\underline{H}$), 1.76–1.64 (1H, m, $C\underline{H}_aH_b$), 1.52–1.40 (1H, m, $CH_a\underline{H}_b$), 1.27–1.14 (2H, m, $C\underline{H}_2$), 0.78 (3H, t, *J* 7.3 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 205.8 ($\underline{C}$=O), 142.8 ($\underline{C}_{Ar}$), 138.2 ($\underline{C}_{Ar}$), 133.2

(<u>*C*</u>$_{Ar}$H), 128.5 (<u>*C*</u>$_{Ar}$H), 128.4 (<u>*C*</u>$_{Ar}$H), 128.2 (<u>*C*</u>$_{Ar}$H), 127.7 (<u>*C*</u>$_{Ar}$H), 126.3 (<u>*C*</u>$_{Ar}$H), 76.1 (<u>*C*</u>HOH), 52.7 (<u>*C*</u>HCO), 32.8 (<u>*C*</u>H$_2$), 20.5 (<u>*C*</u>H$_2$), 14.1 (<u>*C*</u>H$_3$).

Spectroscopic data are consistent with those previously reported.[450]

Resubjection of Suggested Reaction Intermediates

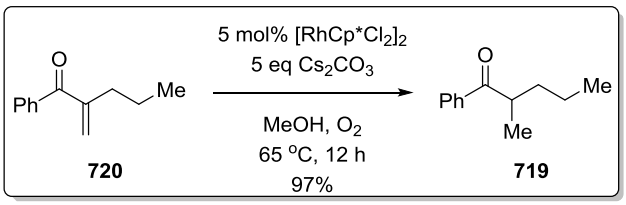
2-Hydroxymethyl-1-phenylpentan-1-one 811



811

To a stirred solution of valerophenone **718** (1.00 mL, 6.05 mmol) in methanol (40 mL) was added paraformaldehyde (185 mg, 6.05 mmol) and K_2CO_3 (84 mg, 0.61 mmol). The resultant mixture was stirred at rt for 72 h. The solvent was removed *in vacuo*, 1 M HCl (10 mL) was added and the mixture extracted with $CHCl_3$ (3×20 mL). The combined organic phase was dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Purification by FCC ($CHCl_3$) afforded *hydroxymethyl ketone* **811** (668 mg, 3.47 mmol, 57 %) as a colourless oil.

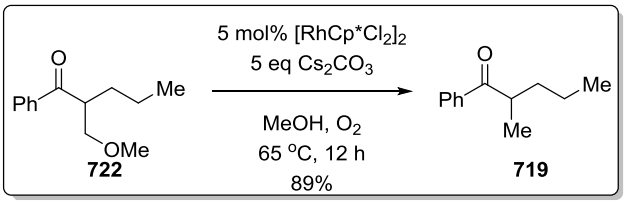
ν_{max} (cm^{-1}) 3429 (br), 2958, 2873, 1675, 1596, 1580, 1448, 1379, 1245, 1213; **δ_H** (400 MHz, $CDCl_3$) 8.00–7.93 (2H, m, C$_{Ar}$<u>*H*</u>), 7.62–7.56 (1H, m, C$_{Ar}$<u>*H*</u>), 7.52–7.46 (2H, m, C$_{Ar}$<u>*H*</u>), 3.97 (1H, dd, *J* 11.1, 6.9 Hz, C<u>*H*</u>$_a$H$_b$OH), 3.86 (1H, dd, *J* 11.1, 3.8 Hz, CH$_a$<u>*H*</u>$_b$OH), 3.67–3.59 (1H, m, C<u>*H*</u>CO), 2.25 (1H, br s, O<u>*H*</u>), 1.74–1.56 (2H, m, C<u>*H*</u>$_2$), 1.47–1.30 (2H, m, C<u>*H*</u>$_2$), 0.92 (3H, t, *J* 7.3 Hz, C<u>*H*</u>$_3$); **δ_C** (100 MHz, $CDCl_3$) 204.7 (<u>*C*</u>=O), 136.8 (<u>*C*</u>$_{Ar}$), 133.3 (<u>*C*</u>$_{Ar}$H), 128.7 (<u>*C*</u>$_{Ar}$H), 128.3 (<u>*C*</u>$_{Ar}$H), 62.9 (<u>*C*</u>H$_2$OH), 47.9 (<u>*C*</u>HCO), 31.3 (<u>*C*</u>H$_2$), 20.6 (<u>*C*</u>H$_2$), 14.1 (<u>*C*</u>H$_3$); **m/z** (ESI+) 215.1 [M+Na]$^+$, **HRMS** (ESI+) $C_{12}H_{16}O_2$ requires 215.1043 [M+Na]$^+$, found 215.1043 (Δ = 0.0 ppm).



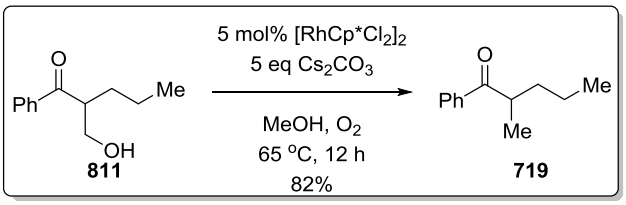
720 **719**

2-Methylene-1-phenylpentan-1-one **720** (52 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol) and MeOH (1.5 mL), were subjected to **general procedure F**

for 12 h. Purification by FCC (30:1 Petrol/Et_2O) afforded *methylated ketone* **719** (51 mg, 0.29 mmol, 97%) as a colourless oil.

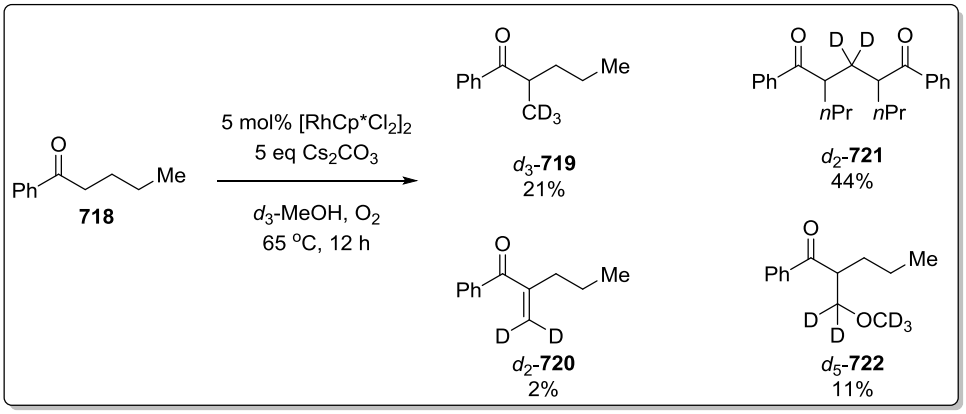


2-(Methoxymethyl)-1-phenylpentan-1-one **722** (40 mg, 0.19 mmol), $[RhCp^*Cl_2]_2$ (6.0 mg, 5 mol%), Cs_2CO_3 (309 mg, 0.950 mmol), and MeOH (0.95 mL) were subjected to **general procedure F** for 12 h. Purification by FCC (30:1 Petrol/Et_2O) afforded *methylated ketone* **719** (30 mg, 0.17 mmol, 89%) as a colourless oil.



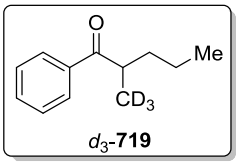
2-Hydroxymethyl-1-phenylpentan-1-one **811** (58 mg, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol), and MeOH (1.5 mL) were subjected to **general procedure F** for 18 h. Purification by FCC (30:1 Petrol/Et_2O) afforded *methylated ketone* **719** (43 mg, 0.25 mmol, 82%) as a colourless oil.

Deuteration Experiment



Valerophenone **718** (33 μL, 0.20 mmol), $[RhCp^*Cl_2]_2$ (6.2 mg, 5 mol%), Cs_2CO_3 (325 mg, 1.00 mmol), and CD_3OH (1.0 mL) were subjected to **general procedure F** for 48 h. Purification by FCC (50:1→20:1 Petrol/Et_2O) afforded *methylated ketone* ***d*$_3$-719** and *enone* ***d*$_2$-720** as a 10:1 mixture (8.2 mg, 21% ***d*$_3$-2a** and 2% ***d*$_2$-4a**), *dimer* ***d*$_2$-721** (14.8 mg, 0.044 mmol, 44%, 1.25:1 dr (*anti*:*syn*)) and *methanol adduct* ***d*$_5$-722** (4.7 mg, 0.023 mmol, 11%).

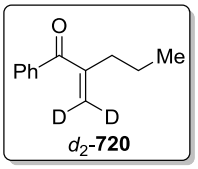
2-(Methyl-*d*$_3$)-1-phenylpentan-1-one, *d*$_3$-719



d$_3$-719

δ$_H$ (400 MHz, $CDCl_3$) 7.99–7.93 (2H, m, $C_{Ar}\underline{H}$), 7.59–7.53 (1H, m, $C_{Ar}\underline{H}$), 7.50–7.44 (2H, m, $C_{Ar}\underline{H}$), 3.48 (1H, t, *J* 6.5 Hz, $C\underline{H}CD_3$), 1.84–1.73 (1H, m, $C\underline{H}_aH_b$), 1.47–1.28 (3H, m, $CH_a\underline{H}_b$, $C\underline{H}_2$), 0.91 (3H, t, *J* 7.2 Hz, $C\underline{H}_3$); **δ$_C$** (100 MHz, $CDCl_3$) 204.6 ($\underline{C}$=O), 136.8 ($\underline{C}_{Ar}$), 132.8 ($\underline{C}_{Ar}$H), 128.6 ($\underline{C}_{Ar}$H), 128.2 ($\underline{C}_{Ar}$H), 40.1 ($\underline{C}$HCO), 35.8 ($\underline{C}H_2$), 20.6 ($\underline{C}H_2$), 16.4 (sept, *J* 20.1 Hz, $\underline{C}D_3$) 14.2 ($\underline{C}H_3$); **δ$_D$** (77 MHz, $CHCl_3$) 1.18 (br s, $C\underline{D}_3$); **m/z** (ESI+) 202.1 $[M+Na]^+$, **HRMS** (ESI+) $C_{12}H_{13}D_3O$ requires 202.1282 $[M+Na]^+$, found 202.1284 (Δ = −1.0 ppm).

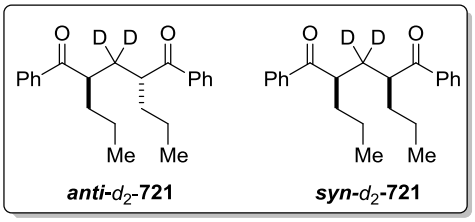
2-(Methylene-*d*$_2$)-1-phenylpentan-1-one, *d*$_2$-720



d$_2$-720

δ$_H$ (400 MHz, $CDCl_3$) 7.79–7.74 (2H, m, $C_{Ar}\underline{H}$), 7.59–7.52 (1H, m, $C_{Ar}\underline{H}$), 7.50–7.41 (2H, m, $C_{Ar}\underline{H}$), 2.46 (2H, t, *J* 7.6 Hz, $C\underline{H}_2$), 1.62–1.49 (2H, m, $C\underline{H}_2$), 0.98 (3H, t, *J* 7.4 Hz, $C\underline{H}_3$); **δ$_C$** (100 MHz, $CDCl_3$) 198.5 ($\underline{C}$=O), 148.1 ($\underline{C}$=CD_2), 137.9 ($\underline{C}_{Ar}$), 132.1 ($\underline{C}_{Ar}$H), 129.5 ($\underline{C}_{Ar}$H), 128.1 ($\underline{C}_{Ar}$H), 34.2 ($\underline{C}H_2$), 21.3 ($\underline{C}H_2$), 13.8 ($\underline{C}H_3$) (one carbon signal missing due to weak intensity after coupling); **δ$_D$** (77MHz, $CHCl_3$) 5.86 (br s, C=C$\underline{D}_aD_b$), 5.61 (br s, C=C$D_a\underline{D}_b$); **HRMS** (FI+) $C_{12}H_{12}D_2O$ requires 176.1170 $[M]^+$, found 176.1176 (Δ = −3.4 ppm).

(2*R,4*R**)-1,5-Diphenyl-2,4-dipropylpentane-1,5-dione-3,3-*d*$_2$ and (2*R**,4*S**)-1,5-Diphenyl-2,4-dipropylpentane-1,5-dione-3,3-*d*$_2$, *syn*-*d*$_2$-721 and *anti*-*d*$_2$-721**



anti-*d*$_2$-721 *syn*-*d*$_2$-721

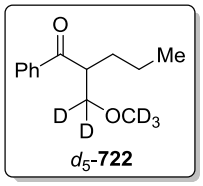
ν$_{max}$ (cm^{-1}) 2958, 2931, 2872, 1677, 1447, 1230, 1210; **m/z** (ESI+) 361.2 $[M+Na]^+$, **HRMS** (ESI+) $C_{23}H_{26}D_2O_2$ requires 361.2107 $[M+Na]^+$, found

361.2103 (Δ = 1.1 ppm).

***Anti-d*$_2$-721 δ_H** (400 MHz, $CDCl_3$) 7.71–7.67 (4H, m $C_{Ar}\underline{H}$), 7.46–7.39 (2H, m $C_{Ar}\underline{H}$), 7.31–7.24 (4H, m $C_{Ar}\underline{H}$), 3.36 (2H, t, *J* 6.5 Hz, $\underline{C}HCO$), 1.80–1.58 (4H, m, $\underline{C}H_2$), 1.49–1.37 (2H, m, $C\underline{H}_aH_b$), 1.36–1.11 (2H, m, $CH_a\underline{H}_b$), 0.85 (6H, t, *J* 7.2 Hz, CH_3); **δ_C** (100 MHz, $CDCl_3$) 204.8 ($\underline{C}$=O), 137.4 ($\underline{C}_{Ar}$), 132.8 ($\underline{C}_{Ar}H$), 128.5 ($\underline{C}_{Ar}H$), 128.0 ($\underline{C}_{Ar}H$), 43.6 ($\underline{C}HCO$), 36.1 ($\underline{C}D_2$), 34.3 ($\underline{C}H_2$), 20.5 ($\underline{C}H_2$), 14.1 ($\underline{C}H_3$); **δ_D** (77 MHz, $CHCl_3$) 2.05 (br s, $C\underline{D}_2$);

***Syn-d*$_2$-721 δ_H** (400 MHz, $CDCl_3$) 8.04–7.98 (4H, m, $\underline{C}_{Ar}H$), 7.61–7.55 (2H, m, $\underline{C}_{Ar}H$), 7.53–7.47 (4H, m, $\underline{C}_{Ar}H$), 3.52 (2H, dd, *J* 7.6, 5.5 Hz, $\underline{C}HCO$), 1.49–1.37 ($C\underline{H}_aH_b$), 1.37–1.11 (m, 6H, $CH_a\underline{H}_b$, $C\underline{H}_2$), 0.79 (t, *J* 7.3 Hz, 6H, $\underline{C}H_3$); **δ_C** (100 MHz, $CDCl_3$) δ 204.0 ($\underline{C}$=O), 137.2 ($\underline{C}_{Ar}$), 133.0 ($\underline{C}_{Ar}H$), 128.7 ($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 43.2 ($\underline{C}HCO$), 36.1 ($\underline{C}D_2$), 34.3 ($\underline{C}H_2$) 20.4 ($\underline{C}H_2$), 14.1 ($\underline{C}H_3$); **δ_D** (77 MHz, $CHCl_3$) 2.27 (br s, $C\underline{D}_aD_b$), 1.61 (br s, $CD_a\underline{D}_b$).

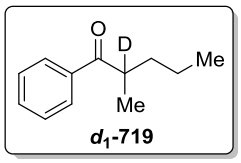
2-((Methoxy-*d*$_3$)methyl-*d*$_2$)-1-phenylpentan-1-one, *d*$_5$-722



d$_5$-**722**

ν_{max} (cm^{-1}) 2959, 2932, 2873, 1681, 1448, 1132; **δ_H** (400 MHz, $CDCl_3$) 8.01–7.97 (2H, m, $C_{Ar}\underline{H}$), 7.60–7.53 (1H, m, $C_{Ar}\underline{H}$), 7.50–7.44 (2H, m, $C_{Ar}\underline{H}$), 3.76 (1H, t, *J* 6.7 Hz, $\underline{C}HCO$), 1.76–1.66 (1H, m, $C\underline{H}_aH_b$), 1.56–1.46 (1H, m, $CH_a\underline{H}_b$), 1.35–1.20 (2H, m, $C\underline{H}_2$), 0.88 (3H, t, *J* 7.3 Hz, $C\underline{H}_3$); **δ_C** (126 MHz, $CDCl_3$) 203.2 ($\underline{C}$=O), 137.7 ($\underline{C}_{Ar}$), 133.0 ($\underline{C}_{Ar}H$), 128.6 ($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 46.4 ($\underline{C}HCO$), 32.0 ($\underline{C}H_2$), 20.6 ($\underline{C}H_2$), 14.2 ($\underline{C}H_3$) (2 carbon signals missing due to weak intensity after coupling); **δ_D** (77 MHz, $CHCl_3$) 3.72 (br s, $C\underline{D}_aD_bOCD_3$), 3.50 (br s, $CD_a\underline{D}_bOCD_3$), 3.27 (br s, $OC\underline{D}_3$); **m/z** (ESI+) 234.2 $[M+Na]^+$; **HRMS** (ESI+) $C_{13}H_{13}D_5O_2$ requires 234.1513 $[M+Na]^+$, found 234.1507 (Δ = 2.6 ppm).

2-Methyl-1-phenylpentan-1-one-2-*d* *d*$_1$-719



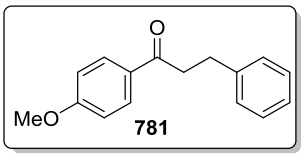
d$_1$-**719**

Valerophenone **718** (50 μL, 0.30 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5.0 mol%), Cs_2CO_3 (195 mg, 0.600 mmol), and CH_3OD (1.5 mL) were subjected to **general procedure F** for 48 h. Purification by FCC (20:1

Petrol/Et_2O) afforded *methylated ketone* ***d*$_1$-719** (49 mg, 0.28 mmol, 93%, 85% deuterium incorporation) as a colourless oil.

δ_H (400 MHz, $CDCl_3$) 7.99–7.94 (2H, m, $C_{Ar}\underline{H}$), 7.59–7.53 (1H, m, $C_{Ar}\underline{H}$), 7.51–7.44 (2H, m, $C_{Ar}\underline{H}$), 1.85–1.75 (1H, m, $C\underline{H}_aH_b$), 1.48–1.27 (3H, m, $CH_a\underline{H}_b$, $C\underline{H}_2$), 1.20 (3H, s, $CDC\underline{H}_3$), 0.91 (3H, t, *J* 7.2 Hz, $CH_2C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 204.6 ($\underline{C}$=O), 136.7 ($\underline{C}_{Ar}$), 132.8 ($\underline{C}_{Ar}H$), 128.6 ($\underline{C}_{Ar}H$), 128.2 ($\underline{C}_{Ar}H$), 39.8 (t, *J* 19.4 Hz, $\underline{C}D(CH_3)$), 35.8 ($\underline{C}H_2$), 20.5 ($\underline{C}H_2$), 17.1 ($\underline{C}H_3$), 14.1 ($\underline{C}H_3$).

1-(4-Methoxyphenyl)-3-phenylpropan-1-one 781[273]



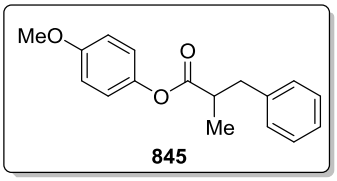
781

4'-Methoxyacetophenone **527** (300 mg, 2.00 mmol), $[Ir(cod)Cl]_2$ (11.2 mg, 1.0 mol%), KOH (13.4 mg, 0.200 mmol), PPh_3 (21 mg, 0.080 mmol) and benzyl alcohol (416 μL, 4.00 mmol) were subjected to general procedure F for 6 h. Purification by FCC (10:1→4:1 Petrol/Et_2O) afforded *benzylated ketone* **781** (418 mg, 1.74 mmol, 87 %) as a colourless solid.

m.p. 95–97 °C [Lit: 96–98 °C][451]; **δ_H** (400 MHz, $CDCl_3$) 7.93 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 7.30–7.20 (5H, m, $C_{Ar}\underline{H}$), 6.90 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 3.85 (3H, s, $OC\underline{H}_3$), 3.24 (2H, t, *J* 7.9 Hz, $C\underline{H}_2Ph$), 3.04 (2H, t, *J* 7.9 Hz, $C\underline{H}_2CO$); **δ_C** (100 MHz, $CDCl_3$) 197.8 ($\underline{C}$=O), 163.4 ($\underline{C}_{Ar}OCH_3$), 141.4 ($\underline{C}_{Ar}$), 130.3 ($\underline{C}_{Ar}H$), 129.9 ($\underline{C}_{Ar}$), 128.5 ($\underline{C}_{Ar}H$), 128.4 ($\underline{C}_{Ar}H$), 126.0 ($\underline{C}_{Ar}H$), 113.7 ($\underline{C}_{Ar}H$) , 55.4 ($O\underline{C}H_3$), 40.1 ($\underline{C}H_2CO$), 30.3 ($\underline{C}H_2Ph$).

Spectroscopic data are consistent with those previously reported.[451]

4-Methoxyphenyl 2-methyl-3-phenylpropanoate 845

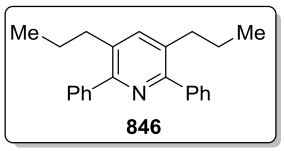


845

(4-Methoxyphenyl)-2-methyl-3-phenylpropan-1-one **788** (30 mg, 0.12 mmol), mCPBA (80 mg, 0.48 mmol), trifluoroacetic acid (19 μL, 0.24 mmol) and CH_2Cl_2 (2.4 mL) were subjected to **general procedure G** for 48 h. Purification by FCC (20:1 Petrol/Et_2O) afforded *ester* **845** (30 mg, 0.11 mmol, 92 %) as a colourless oil.

ν_{max} (cm^{-1}) 3063, 3028, 2973, 2935, 2837, 1751, 1606, 1597, 1505, 1455, 1248, 1192, 1137; **δ_H** (400 MHz, $CDCl_3$) 7.27–7.20 (2H, m, $C_{Ar}\underline{H}$), 7.19–7.14 (3H, m, $C_{Ar}\underline{H}$), 6.79–6.72 (4H, m, $C_{Ar}\underline{H}$), 3.70 (3H, s, $OC\underline{H}_3$), 3.04 (1H, dd, *J* 13.3, 7.6 Hz, $C\underline{H}_aH_bPh$), 2.90 (1H, app sext, *J* 7.0 Hz, $C\underline{H}CO$), 2.75 (1H, dd, *J* 13.3, 7.2 Hz, $CH_a\underline{H}_bPh$), 1.24 (3H, d, *J* 6.9 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 179.9 ($\underline{C}$=O), 157.1 ($\underline{C}_{Ar}$), 144.1 ($\underline{C}_{Ar}$), 139.0 ($\underline{C}_{Ar}$), 129.1 ($\underline{C}_{Ar}H$), 128.4 ($\underline{C}_{Ar}H$), 126.5 ($\underline{C}_{Ar}H$), 122.2 ($\underline{C}_{Ar}H$), 114.3 ($\underline{C}_{Ar}H$), 55.5 ($O\underline{C}H_3$), 41.6 ($\underline{C}HCO$), 39.8 ($\underline{C}H_2Ph$), 16.9 ($\underline{C}H_3$); **m/z** (ESI+) 293.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{17}H_{18}O_3$ requires 293.1148 $[M+Na]^+$, found 293.1149 (Δ = −0.4 ppm).

2,6-Diphenyl-3,5-dipropylpyridine 846[90]

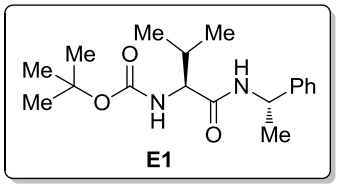


846

A solution of dimer **721** (37 mg, 0.11 mmol) and hydroxylamine hydrochloride (7.6 mg, 0.11 mmol) was refluxed in EtOH (0.5 mL) for 20 h. The reaction was quenched by the addition of sat. aq. $NaHCO_3$ (5 mL), and the aqueous phase extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent removed *in vacuo*. Purification by FCC (5:1 Petrol/Et_2O) afforded *pyridine* **846** (34 mg, 0.11 mmol, quant.) as a colourless solid.

m.p 134–136 °C; **ν_{max}** (cm^{-1}) 2963, 2925, 2866, 1440; **δ_H** (400 MHz, $CDCl_3$) 7.58–7.51 (5H, m, $C_{Ar}\underline{H}$, $C_{Py}{}^4\underline{H}$), 7.47–7.39 (4H, m, $C_{Ar}\underline{H}$), 7.38–7.33 (2H, m, $C_{Ar}\underline{H}$), 2.71–2.64 (4H, m, $C\underline{H}_2$), 1.62 (4H, app sext, *J* 7.3Hz, $C\underline{H}_2$), 0.92 (6H, t, *J* 7.3 Hz, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 155.8 ($\underline{C}_{Py}{}^2$), 140.8 ($\underline{C}_{Py}{}^4H$), 138.6 ($\underline{C}_{Ar}$), 133.8 ($\underline{C}_{Py}{}^3$), 129.1 ($\underline{C}_{Ar}$, 128.0 ($\underline{C}_{Ar}$, 127.5 ($\underline{C}_{Ar}$, 34.2 ($\underline{C}H_2$), 24.2 ($\underline{C}H_2$), 14.0 ($\underline{C}H_3$); **m/z** (ESI+) 316.2 $[M+H]^+$; **HRMS** (ESI+) $C_{23}H_{26}N$ requires 316.2060 $[M+H]^+$, found 316.2066 (Δ = −2.5 ppm).

tert-Butyl ((*S*)-3-methyl-1-oxo-1-(((*S*)-1-phenylethyl)amino)butan-2-yl)carbamate E1[353]



E1

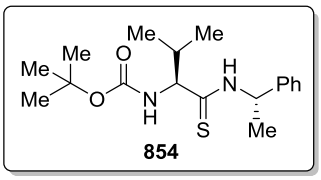
To a stirred solution of Boc-Val-OH (533 mg, 2.46 mmol), EDC·HCl (518 mg, 2.70 mmol), and HOBt (365 mg, 2.70 mmol) in CH_2Cl_2 (12 mL), was added (*S*)-methylbenzylamine (317 μL, 2.46 mmol), and the solution stirred at rt for 24 h. The solution was diluted with

EtOAc (50 mL) and washed with 10% aq. citric acid (50 mL), sat. aq. $NaHCO_3$ (50 mL), and brine (50 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford *amide* **E1** (784 mg, 2.45 mmol, 99%) as a colourless solid.

m.p. 148–150 °C; $[\alpha]_D^{20}$ = −61.5 (c = 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 7.36–7.23 (5H, m, $C_{Ar}\underline{H}$)), 6.35 (1H, d, *J* 7.8 Hz, CON$\underline{H}$), 5.17–5.08 (2H, m, C$\underline{H}$Me, BocN$\underline{H}$), 3.86 (1H, dd, *J* 8.6, 6.4 Hz, C$\underline{H}i$Pr), 2.14-2.02 (1H, m, C$\underline{H}(CH_3)_2$), 1.49 (3H, d, *J* 6.9 Hz, CHC$\underline{H}_3$), 1.43 (9H, s C(C$\underline{H}_3)_3$), 0.93–0.86 (6H, m, CH(C$\underline{H}_3)_2$); δ_C (100 MHz, $CDCl_3$) 170.7 ($\underline{C}$ON), 155.9 (*t*BuO$\underline{C}$ON), 143.0 ($\underline{C}_{Ar}$), 128.6 ($\underline{C}_{Ar}$H), 127.3 ($\underline{C}_{Ar}$H), 126.1 ($\underline{C}_{Ar}$H), 79.8 ($\underline{C}(CH_3)_3$), 60.2 ($\underline{C}$H*i*Pr), 48.7 ($\underline{C}$HMe), 30.8 ($\underline{C}H(CH_3)_2$), 28.3 (C($\underline{C}H_3)_3$), 21.7 (CH$\underline{C}H_3$), 19.3 (CH($\underline{C}H_3)_2$), 17.8 (CH($\underline{C}H_3)_2$).

Spectroscopic data are consistent with those previously reported.[353]

tert-Butyl ((*S*)-3-methyl-1-(((*S*)-1-phenylethyl)amino)-1-thioxobutan-2-yl)carbamate 854[353]



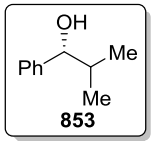
854

To a stirred solution of *tert*-Butyl ((*S*)-3-methyl-1-oxo-1-(((*S*)-1-phenylethyl)amino)butan-2-yl)carbamate **E1** (320 mg, 1.00 mmol) in THF (4 mL) was added Lawesson's Reagent (317 mg, 0.800 mmol). The reaction was stirred at 60 °C for 8 h. The solvent was removed *in vacuo* and the resultant residue purified by FCC (EtOAc) to afford *thioamide* **854** (287 mg, 0.85 mmol, 85%) as a light yellow solid.

m.p. 44–46 °C; $[\alpha]_D^{20}$ = −166.1 (c = 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 8.65 (1H, br s, N$\underline{H}$CS), 7.39–7.22 (5H, m, $C_{Ar}\underline{H}$), 5.79–5.67 (1H, m, C$\underline{H}$Me), 5.43 (1H, d, *J* 8.7 Hz, BocN$\underline{H}$), 4.17–4.06 (1H, m, C$\underline{H}i$Pr), 2.25–2.11 (1H, m, C$\underline{H}(CH_3)_2$), 1.58 (3H, d, *J* 6.9 Hz, CHC$\underline{H}_3$), 1.39 (9H, s, C(C$\underline{H}_3)_3$), 0.93–0.81 (6H, m, CH(C$\underline{H}_3)_2$); δ_C (100 MHz, $CDCl_3$) 202.9 ($\underline{C}$=S), 155.9 (*t*BuO$\underline{C}$ON), 141.2 ($\underline{C}_{Ar}$), 128.7 ($\underline{C}_{Ar}$H), 127.7 ($\underline{C}_{Ar}$H), 126.5 ($\underline{C}_{Ar}$H), 80.1 ($\underline{C}(CH_3)_3$), 67.1 (C$\underline{H}i$Pr), 54.1 ($\underline{C}$HMe), 33.0 ($\underline{C}H(CH_3)_2$), 28.2 (C($\underline{C}H_3)_3$), 20.0 CH$\underline{C}H_3$), 19.7 (CH($\underline{C}H_3)_2$), 18.0 (CH($\underline{C}H_3)_2$).

Spectroscopic data are consistent with those previously reported.[353]

(*R*)-2-Methyl-1-phenylpropan-1-ol 853[353]



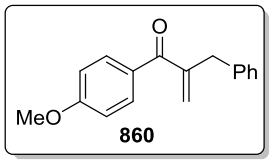
A solution of isobutyrophenone **760** (150 μL, 1.00 mmol), $[Cp^*RhCl_2]_2$ (1.5 mg, 0.25 mol%), thioamide **854** (1.9 mg, 0.55 mol%), NaOMe (2.7 mg, 5 mol%), and LiCl (2.1 mg, 5 mol%) were stirred in *iso*-propanol at room temperature for 24 h. The reaction mixture was diluted with Et_2O and filtered through a short pad of silica, and the solvent removed *in vacuo*. Purification by FCC (2:1 petrol/Et_2O) afforded *benzylic alcohol* **854** (108 mg, 0.720 mmol, 72%, 98% ee) as a colourless oil, along with RSM **760** (34 mg, 0.23 mmol, 23%).

$[\alpha]_D^{20}$ = +36.5 (c = 1.0, Et_2O) [Lit: +34 (c = 1.0, Et_2O)][452]; δ_H (400 MHz, $CDCl_3$) 7.37–7.24 (5H, m, $C_{Ar}\underline{H}$), 4.36 (1H, d, *J* 6.9 Hz, C<u>*H*</u>OH), 2.02–1.90 (1H, m, C<u>*H*</u>$(CH_3)_2$), 1.83 (1H, br s, O<u>*H*</u>), 1.00 (3H, d, *J* 6.8 Hz, CH(C<u>*H*</u>$_3)_2$), 0.80 (3H, d, *J*, 6.8 Hz); δ_C (100 MHz, $CDCl_3$) 143.6 (<u>*C*</u>$_{Ar}$), 128.2 (<u>*C*</u>$_{Ar}$H), 127.4 (<u>*C*</u>$_{Ar}$H), 125.5 (<u>*C*</u>$_{Ar}$H), 80.0 (<u>*C*</u>HOH), 35.2 (<u>*C*</u>H$(CH_3)_2$), 19.0 (CH(<u>*C*</u>$H_3)_2$), 18.2 (CH(<u>*C*</u>$H_3)_2$).

Enantiomeric excess was determined by chiral HPLC. (Chiralcel OD, 254nm, 1.0 mL/min, heptane/*i*-PrOH 98:2 v/v, tR_1 = 12.4 min, tR_2 = 14.9 min).

Spectroscopic data are consistent with those previously reported.[353]

2-Benzyl-1-(4-methoxyphenyl)prop-2-en-1-one 860

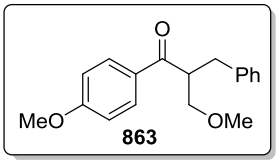


1-(4-Methoxyphenyl)-3-phenylpropan-1-one **781** (73 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol), and MeOH (3.0 mL) were subjected to **general procedure H**. Purification by FCC (10:1→5:1 petrol/Et_2O) afforded RSM **781** (0.006 mmol, 2%), *methylated ketone* **788** (0.012 mmol, 4%) and *enone* **860** (0.018 mmol, 6%) as an inseparable mixture (14 mg), along with *methanol adduct* **863** (64 mg, 0.225 mmol, 75%).

δ_H (400 MHz, $CDCl_3$) 7.69 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.24–7.09 (5H, m, $C_{Ar}\underline{H}$), 6.82 (2H, d, *J* 8.9 Hz), 5.59–5.57 (1H, m, C=C$\underline{H}_a$$H_b$), 5.53–5.51 (1H, m, C=C$H_a\underline{H}_b$), 3.78 (3H, s, OC$\underline{H}_3$), 3.71 (2H, s, C$\underline{H}_2$Ph); **$\delta_C$** (100 MHz, $CDCl_3$) 196.5 ($\underline{C}$=O), 163.1 ($\underline{C}_{Ar}$), 147.7 ($\underline{C}_{Ar}$), 138.7 ($\underline{C}_{Ar}$), 132.0 ($\underline{C}_{Ar}$H), 130.1 ($\underline{C}$=CH_2), 129.2 ($\underline{C}_{Ar}$H), 128.5 ($\underline{C}_{Ar}$H), 126.3 ($\underline{C}_{Ar}$H), 124.7 (C=$\underline{C}H_2$), 113.4 ($\underline{C}_{Ar}$H), 55.4 (O$\underline{C}H_3$), 38.8 ($\underline{C}H_2$Ph).

Spectroscopic data are consistent with those previously reported.[453]

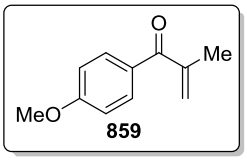
2-Benzyl-3-methoxy-1-(4-methoxyphenyl)propan-1-one 863



863

ν_{max} (cm^{-1}) 2929, 1669, 1598, 1169; **δ_H** (400 MHz, $CDCl_3$) 7.89 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.25–7.15 (5H, m, $C_{Ar}\underline{H}$), 6.89 (2H, d, *J* 8.9 Hz, $\underline{C}_{Ar}$H), 3.98 (1H, td, *J* 7.1, 1.9 Hz, C$\underline{H}$CO), 3.84 (3H, s, OC$\underline{H}_3$), 3.72 (1H, dd, *J* 9.0, 7.4 Hz, C$\underline{H}_a$$H_b$$OCH_3$), 3.51 (1H, dd, *J* 9.0, 5.4 Hz, $CH_a\underline{H}_b$$OCH_3$), 3.28 (3H, s, OC$\underline{H}_3$), 3.06 (1H, dd, *J* 13.8, 7.5 Hz, C$\underline{H}_a$$H_b$Ph), 2.88 (1H, dd, *J* 13.8, 6.7 Hz, $CH_a\underline{H}_b$Ph); **δ_C** (100 MHz, $CDCl_3$) 200.5 ($\underline{C}$=O), 163.5 ($\underline{C}_{Ar}OCH_3$), 139.3 ($\underline{C}_{Ar}$), 130.7 ($\underline{C}_{Ar}$H), 130.4 ($\underline{C}_{Ar}$H), 129.0 ($\underline{C}_{Ar}$H), 128.4 ($\underline{C}_{Ar}$H), 126.3 ($\underline{C}_{Ar}$H), 113.7 ($\underline{C}_{Ar}$H), 73.7 ($\underline{C}H_2OCH_3$), 59.1 (O$\underline{C}H_3$), 55.4 (O$\underline{C}H_3$), 48.3 ($\underline{C}$HCO), 35.5 ($\underline{C}H_2$Ph); **m/z** (ESI+) 307.1 $[M+Na]^+$ **HRMS** (ESI^+) $C_{18}H_{20}O_3$ requires 307.1305 $[M+Na]^+$, found 307.1303 (Δ = −0.3 ppm).

1-(4-Methoxyphenyl)-2-methylprop-2-en-1-one 859



859

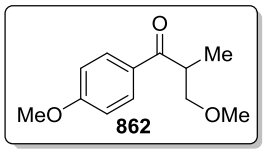
4'-Methoxypropiophenone **758** (53 μL, 0.30 mmol), $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol), and MeOH (3.0 mL) were subjected to **general procedure H**. Purification by FCC (12:1 petrol/Et_2O) afforded *methylated ketone* **768** (0.042 mmol, 14%) and *enone* **859** (0.055 mmol, 18%) as an inseparable mixture (17 mg), along with *methanol adduct* **862** (55 mg, 0.18 mmol, 59%) as colourless oils.

δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 6.93 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 5.82–5.79 (1H, m, C=C$\underline{H}_a$$H_b$), 5.55–5.52 (1H, m, C=C$H_a\underline{H}_b$), 3.87 (3H, s, OC$\underline{H}_3$), 2.07 (3H, app t, *J* 1.1

Hz, C*H*$_3$); **δ$_C$** (100 MHz, $CDCl_3$) 197.1 (*C*=O), 163.0 (*C*$_{Ar}$OCH$_3$), 143.9 (*C*=CH$_2$), 131.9 (*C*$_{Ar}$H), 130.0 (*C*$_{Ar}$), 124.7 (C=*C*H$_2$), 113.4 (*C*$_{Ar}$H), 55.4 (O*C*H$_3$), 19.1 (*C*H$_3$).

Spectroscopic data are consistent with those previously reported.[454]

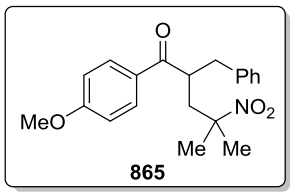
3-Methoxy-1-(4-methoxyphenyl)-2-methylpropan-1-one 862



862

ν$_{max}$ (cm^{-1}) 2930, 1672, 1598, 1574, 1252, 1221, 1172, 1108; **δ$_H$** (400 MHz, $CDCl_3$) 7.97 (2H, d, *J* 9.0 Hz, C$_{Ar}$*H*), 6.94 (2H, d, *J* 9.0 Hz, C$_{Ar}$*H*), 3.87 (3H, s, C$_{Ar}$OC*H*$_3$), 3.78–3.70 (2H, m, C*H*CO, C*H*$_a$-H$_b$OCH$_3$), 3.48–3.39 (1H, m, CH$_a$*H*$_b$OCH$_3$), 3.32 (3H, s, OC*H*$_3$), 1.19 (3H, d, C*H*$_3$); **δ$_C$** (100 MHz, $CDCl_3$) 201.1 (*C*=O), 163.5 (*C*$_{Ar}$OCH$_3$), 130.6 (*C*$_{Ar}$H), 129.6 (*C*$_{Ar}$), 113.7 (*C*$_{Ar}$H), 75.1 (*C*H$_2$OCH$_3$), 59.0 (O*C*H$_3$), 55.4 (O*C*H$_3$), 40.8 (*C*HCO), 14.9 (*C*H$_3$); **m/z** 231.1 [M+Na]$^+$; **HRMS** (ESI+) $C_{12}H_{16}O_3$ requires 209.1172 [M+H]$^+$, found 209.1170 (Δ = −1.3 ppm).

2-Benzyl-1-(4-methoxyphenyl)-4-methyl-4-nitropentan-1-one 865



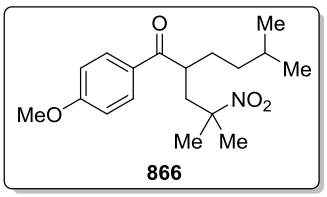
865

Conjugate addition: A solution of 2-benzyl-3-methoxy-1-(4-methoxyphenyl)propan-1-one **863** (43 mg, 0.15 mmol), 2-nitropropane (27 μL, 0.30 mmol) and KOH (17 mg, 0.30 mmol) in MeOH (0.75 mL) was stirred at 65 °C for 15 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (15:1 Petrol/Et_2O) afforded *nitro ketone* **865** (53 mg, 0.15 mmol, quant.) as a colourless oil. **One-pot methylenation/conjugate addition:** 1-(4-Methoxyphenyl)-3-phenylpropan-1-one **781** (73 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol) and MeOH (3 mL) were subjected to **general procedure H**. After 48 h, SiliaMetS DMT (77 mg, 16 mol%) was added, and the resultant solution stirred at room temperature for 1 h. 2-Nitropropane (54 μL, 0.60 mmol), and KOH (34 mg, 0.60 mmol) were added, and the resultant solution stirred at 65 °C for a further 14 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in*

vacuo. Purification by FCC (20:1 Petrol/Et_2O) afforded *nitro ketone* **865** (96 mg, 0.28 mmol, 94%) as a colourless oil.

ν_{max} (cm^{-1}) 2935, 1671, 1598, 1535, 1260, 1235, 1169; **δ_H** (400 MHz, $CDCl_3$) 7.87 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.28–7.21 (2H, m, $C_{Ar}\underline{H}$), 7.20–7.15 (1H, m, $C_{Ar}\underline{H}$), 7.13–7.08 (2H, m, $C_{Ar}\underline{H}$), 6.91 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 3.87 (3H, s, $OC\underline{H}_3$), 3.72-3.64 (1H, m, $C\underline{H}CO$), 2.97 (1H, dd, *J* 13.8, 6.3 Hz, $C\underline{H}_aH_bPh$), 2.72–2.59 (2H, m, $C\underline{H}_aH_b$, $CH_a\underline{H}_bPh$), 2.18 (1H, dd, *J* 14.7, 1.1 Hz, $CH_a\underline{H}_b$), 1.50 (3H, s, $C\underline{H}_3$), 1.34 (3H, s, $C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 200.6 ($\underline{C}$=O), 163.7 ($\underline{C}_{Ar}OCH_3$), 137.9 ($\underline{C}_{Ar}$), 130.6 ($\underline{C}_{Ar}H$), 129.3 ($\underline{C}_{Ar}$), 129.0 ($\underline{C}_{Ar}H$), 128.5 ($\underline{C}_{Ar}H$), 126.7 ($\underline{C}_{Ar}H$), 113.9 ($\underline{C}_{Ar}H$), 88.0 ($\underline{C}Me_2NO_2$), 55.5 ($O\underline{C}H_3$), 43.4 ($\underline{C}HCO$), 40.9 ($\underline{C}H_2Ph$), 40.5 ($\underline{C}H_2CMe_2NO_2$), 27.7 ($\underline{C}H_3$), 24.9 ($\underline{C}H_3$); **m/z** (ESI+) 342.2 $[M+H]^+$; **HRMS** (ESI+) $C_{20}H_{23}NO_4$ requires 364.1519 $[M+Na]^+$, found 364.1519 (Δ = 0.0 ppm).

1-(4-Methoxyphenyl)-5-methyl-2-(2-methyl-2-nitropropyl)hexan-1-one 866

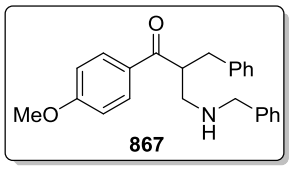


866

Conjugate addition: A solution of 2-(methoxymethyl)-1-(4-methoxyphenyl)-5-methylhexan-1-one **864** (40 mg, 0.15 mmol), 2-nitropropane (27 μL, 0.30 mmol) and KOH (17 mg, 0.30 mmol) in MeOH (0.75 mL) was stirred at 65 °C for 18 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (15:1 Petrol/Et_2O) afforded *nitro ketone* **866** (40 mg, 0.125 mmol, 84%) as a colourless oil. **One-pot methylenation/conjugate addition:** 1-(4-methoxyphenyl)-5-methylhexan-1-one **782** (66 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol), and MeOH (3 mL) were subjected to **general procedure H**. After 48 h, SiliaMetS DMT (77 mg, 16 mol%) was added, and the resultant solution stirred at room temperature for 1 h. 2-Nitropropane (54 μL, 0.60 mmol), and KOH (34 mg, 0.60 mmol) were added, and the resultant solution stirred at 65 °C for a further 14 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (20:1 Petrol/Et_2O) afforded *nitro ketone* **866** (81 mg, 0.25 mmol, 84%) as a colourless oil.

ν_{max} (cm^{-1}) 2955, 1672, 1599, 1574, 1536, 1260, 1171; δ_H (400 MHz, $CDCl_3$) 7.93 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 6.96 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 3.88 (3H, s, $OC\underline{H}_3$), 3.31–3.24 (1H, m, $C\underline{H}CO$), 2.68 (1H, dd, *J* 14.8, 9.6 Hz, $C\underline{H}_aH_bCMe_2NO_2$), 2.20 (1H, dd, *J* 14.8, 0.7 Hz, $CH_a\underline{H}_bCMe_2NO_2$), 1.65–1.54 (4H, m, $C(C\underline{H}_3)_a(CH_3)_bNO_2$, $C\underline{H}_aH_b$*i*Bu), 1.48–1.37 (2H, m, $C\underline{H}(CH_3)_2$, $CH_a\underline{H}_b$*i*Bu), 1.35 (3H, s, $C(CH_3)_a(C\underline{H}_3)_bNO_2$), 1.22-1.05 (2H, m, $C\underline{H}_2$*i*Pr), 0.82 (3H, d, *J* 6.6 Hz, $CH(C\underline{H}_3)_a(CH_3)_b$), 0.80 (3H, d, *J* 6.6 Hz, $CH(CH_3)_a(C\underline{H}_3)_b$); δ_C (101 MHz, $CDCl_3$) 201.0 ($\underline{C}$=O), 163.7 ($\underline{C}_{Ar}OCH_3$), 130.6 ($\underline{C}_{Ar}H$), 129.3 ($\underline{C}_{Ar}$), 114.0 ($\underline{C}_{Ar}H$), 88.4 ($\underline{C}Me_2NO_2$), 55.5 ($O\underline{C}H_3$), 41.6 ($\underline{C}HCO$), 41.3 ($\underline{C}H_2CMe_2NO_2$) 35.8 ($\underline{C}H_2$*i*Bu), 32.5 ($\underline{C}H_2$*i*Pr), 28.2 ($C(\underline{C}H_3)_a(CH_3)_bNO_2$), 28.0 ($\underline{C}H(CH_3)_2$), 24.5 ($C(CH_3)_a(\underline{C}H_3)_bNO_2$), 22.5 ($CH(\underline{C}H_3)_a(CH_3)_b$), 22.2 ($CH(CH_3)_a(\underline{C}H_3)_b$); **m/z** (ESI+) 344.2 $[M+Na]^+$; **HRMS** (ESI+) $C_{18}H_{27}NO_4$ requires 322.2013 $[M+H]^+$, found 322.2001 (Δ = −2.0 ppm).

2-Benzyl-3-(benzylamino)-1-(4-methoxyphenyl)propan-1-one 867

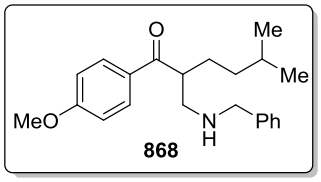


867

Conjugate addition: A solution of 2-benzyl-3-methoxy-1-(4-methoxyphenyl)propan-1-one **863** (43 mg, 0.15 mmol), benzylamine (84 μL, 0.75 mmol) and KOH (17 mg, 0.30 mmol) in THF (0.75 mL) was stirred at 65 °C for 18 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (3:1 Petrol/Et_2O, 1% v/v Et_3N) afforded *amine* **867** (52 mg, 0.145 mmol, 97%) as a light yellow oil. **One-pot methylenation/conjugate addition:** 1-(4-Methoxyphenyl)-3-phenylpropan-1-one **781** (73 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol), and MeOH (3 mL) were subjected to **general procedure H**. After 48 h, SiliaMetS DMT (77 mg, 16 mol%) was added, and the resultant solution stirred at room temperature for 1 h. Benzylamine (164 μL, 1.50 mmol), and KOH (34 mg, 0.60 mmol) were added, and the resultant solution stirred at 65 °C for a further 18 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (10:1 → 1:1 Petrol/Et_2O) afforded *amine* **867** (64 mg, 0.18 mmol, 60%) as a light yellow oil.

ν_{max} (cm^{-1}) 3062, 3027, 2934 (br), 1667, 1599, 1259, 1340, 1170; δ_H (400 MHz, $CDCl_3$) 7.80 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 7.22–7.03 (10H, m, $C_{Ar}\underline{H}$), 6.80 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 3.85–3.78 (1H, m, C$\underline{H}$CO), 3.76 (3H, s, OC$\underline{H}_3$), 3.63 (2H, s, NHC$\underline{H}_2$Ph), 3.02–2.94 (2H, m, C$\underline{H}_a$H$_b$NH, C$\underline{H}_a$H$_b$Ph), 2.75 (1H, dd, *J* 13.7, 7.4 Hz, CH$_a\underline{H}_b$Ph), 2.69 (1H, dd, *J* 11.9, 5.0 Hz, CH$_a\underline{H}_b$NH), 1.46 (1H, br s, N$\underline{H}$); δ_C (100 MHz, $CDCl_3$) 201.5 ($\underline{C}$=O), 163.4 ($\underline{C}_{Ar}OCH_3$), 140.1 ($\underline{C}_{Ar}$), 139.5 ($\underline{C}_{Ar}$), 130.6 ($\underline{C}_{Ar}$H), 130.1 ($\underline{C}_{Ar}$), 128.9 ($\underline{C}_{Ar}$H), 128.4 ($\underline{C}_{Ar}$H), 128.3 ($\underline{C}_{Ar}$H), 128.0 ($\underline{C}_{Ar}$H), 126.8 ($\underline{C}_{Ar}$H), 126.2 ($\underline{C}_{Ar}$H), 113.7 ($\underline{C}_{Ar}$H), 55.4 (O$\underline{C}$H$_3$), 54.0 (NH$\underline{C}$H$_2$Ph), 50.8 ($\underline{C}$H$_2$NH), 48.4 ($\underline{C}$HCO), 36.8 ($\underline{C}$H$_2$Ph); **m/z** (ESI+) 360.2 $[M+H]^+$; **HRMS** (ESI+) $C_{24}H_{26}NO_2$ requires 360.1958 $[M+Na]^+$, found 360.1959 (Δ = −0.2 ppm).

2-((Benzylamino)methyl)-1-(4-methoxyphenyl)-5-methylhexan-1-one 868



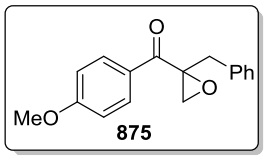
868

Conjugate addition: A solution of 2-(methoxymethyl)-1-(4-methoxyphenyl)-5-methylhexan-1-one **864** (40 mg, 0.15 mmol), benzylamine (84 μL, 0.75 mmol) and KOH (17 mg, 0.30 mmol) in THF (0.75 mL) was stirred at 65 °C for 18 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (3:1 Petrol/Et_2O, 1% v/v Et_3N) afforded *amine* **868** as a light yellow oil (48 mg, 0.14 mmol, 93%). **One-pot methylenation/conjugate addition:** 1-(4-methoxyphenyl)-5-methylhexan-1-one **782** (66 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol), and MeOH (3 mL) were subjected to **general procedure H**. After 48 h, SiliaMetS DMT (77 mg, 16 mol%) was added, and the resultant solution stirred at room temperature for 1 h. Benzylamine (164 μL, 1.50 mmol), and KOH (34 mg, 0.60 mmol) were added, and the resultant solution stirred at 65 °C for a further 14 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (10:1 → 1:1 Petrol/Et_2O) afforded *amine* **868** (62 mg, 0.18 mmol, 60%) as a colourless oil.

ν_{max} (cm^{-1}) 3004, 2954, 2868, 2841, 1668, 1599, 1257, 1239, 1170; δ_H (400 MHz, $CDCl_3$) 7.88 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.24–7.10 (5H, m, $C_{Ar}\underline{H}$), 6.86 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 3.79 (3H, s, OC$\underline{H}_3$), 3.69 (2H, s, NHC$\underline{H}_2$Ph), 3.46–3.48 (1H, m, C$\underline{H}$CO), 2.99 (1H, dd, *J* 11.7, 8.2

Hz, C$\underline{H}_a$H$_b$NBn), 2.67 (1H, dd, *J* 11.7, 4.9 Hz, CH$_a\underline{H}_b$NBn), 1.69–1.58 (1H, m, C$\underline{H}_a$H$_b$*i*Bu), 1.53–1.34 (3H, m, CH$_a\underline{H}_b$*i*Bu, C$\underline{H}$(CH$_3$)$_2$, N$\underline{H}$), 1.12–1.02 (2H, m, C$\underline{H}_2$*i*Pr), 0.75 (3H, d, *J* 6.6 Hz, CH(C$\underline{H}_3$)$_a$(CH$_3$)$_b$), 0.74 (3H, d, *J* 6.6 Hz, CH(CH$_3$)$_a$(C$\underline{H}_3$)$_b$); **δ_C** (100 MHz, $CDCl_3$) 202.4 ($\underline{C}$=O), 163.4 ($\underline{C}_{Ar}$OCH$_3$), 140.3 ($\underline{C}_{Ar}$), 130.6 ($\underline{C}_{Ar}$H), 130.4 ($\underline{C}_{Ar}$), 128.3 ($\underline{C}_{Ar}$H), 128.0 ($\underline{C}_{Ar}$H), 126.8 ($\underline{C}_{Ar}$H), 113.7 ($\underline{C}_{Ar}$H), 55.4 (O$\underline{C}$H$_3$), 54.1 (N$\underline{C}$H$_2$Ph), 51.1 ($\underline{C}$H$_2$NHPh), 46.7 ($\underline{C}$HCO), 36.5 ($\underline{C}$H$_2$*i*Bu), 29.1 ($\underline{C}$H$_2$*i*Pr), 28.2 ($\underline{C}$H(CH$_3$)$_2$) , 22.4 (CH($\underline{C}$H$_3$)$_a$(CH$_3$)$_b$), 22.4 (CH(CH$_3$)$_a$($\underline{C}$H$_3$)$_b$); **m/z** (ESI+) 340.2 $[M+H]^+$; **HRMS** (ESI+) $C_{22}H_{29}NO_2$ requires 340.2271 $[M+H]^+$, found 340.2264 (Δ = −2.1 ppm).

(2-Benzyloxiran-2-yl)(4-methoxyphenyl)methanone 875[455]



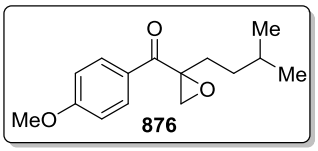
875

Epoxidation: A solution of 2-benzyl-3-methoxy-1-(4-methoxyphenyl)propan-1-one **836** (43 mg, 0.15 mmol), *tert*-butylhydroperoxide (70% w/w aqueous solution, 41 μL, 0.30 mmol) and Triton B (40% w/w solution in MeOH, 154 μL, 0.30 mmol) in THF (0.75 mL) was stirred at rt for 18 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (10:1 Petrol/Et_2O) afforded *epoxide* **875** (40 mg, 0.15 mmol, quant.) as a colourless oil. **One-pot methylenation/epoxidation:** 1-(4-Methoxyphenyl)-3-phenylpropan-1-one **781** (73 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol), and MeOH (3 mL) were subjected to **general procedure H**. After 48 h, SiliaMetS DMT (77 mg, 16 mol%) was added, and the resultant solution stirred at room temperature for 1 h. *tert*-Butylhydroperoxide (70% w/w aqueous solution, 410 μL, 3.00 mmol), and Triton B (40% w/w solution in MeOH, 1.62 mL, 3.00 mmol) were added, and the resultant solution stirred at rt for a further 15 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (20:1 Petrol/Et_2O) afforded *epoxide* **875** (65 mg, 0.24 mmol, 81%) as a colourless oil.

ν_{max} (cm^{-1}) 3031, 2932, 1664, 1598, 1258, 1173; **δ_H** (400 MHz, $CDCl_3$) 7.87 (2H, d, *J* 9.0 Hz, C$_{Ar}\underline{H}$), 7.21–7.10 (5H, m, C$_{Ar}\underline{H}$), 6.79 (2H, d, *J* 9.0 Hz, C$_{Ar}\underline{H}$), 3.76 (3H, s, OC$\underline{H}_3$), 3.52 (1H, d, *J* 14.6 Hz, C$\underline{H}_a$H$_b$Ph), 3.00 (1H, d, *J* 14.6 Hz, CH$_a\underline{H}_b$Ph), 2.77 (1H, d, *J* 5.0 Hz, C$\underline{H}_a$H$_b$O),

2.73 (1H, d, *J* 5.0 Hz, $CH_a\underline{H}_bO$); δ_C (100 MHz`, $CDCl_3$) 196.3 ($\underline{C}$=O), 163.7 ($\underline{C}_{Ar}OCH_3$), 135.3 ($\underline{C}_{Ar}$), 131.8 ($\underline{C}_{Ar}H$), 129.8 ($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 127.5 ($\underline{C}_{Ar}$), 126.9 ($\underline{C}_{Ar}H$), 113.6 ($\underline{C}_{Ar}H$), 63.5 ($O\underline{C}H_3$), 55.4 ($\underline{C}H_2O$), 50.3 ($\underline{C}CO$), 38.7 ($\underline{C}H_2Ph$); **m/z** (ESI+) 291.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{17}H_{16}O_3$ requires 291.0992 $[M+Na]^+$, found 291.0989 (Δ = 1.1 ppm).

(2-Isopentyloxiran-2-yl)(4-methoxyphenyl)methanone 876[455]



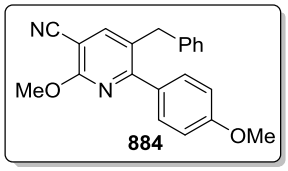
876

Epoxidation: A solution of 2-(methoxymethyl)-1-(4-methoxyphenyl)-5-methylhexan-1-one **864** (40 mg, 0.15 mmol), *tert*-butylhydroperoxide (70% aqueous solution, 41 μL, 0.30 mmol) and Triton B (40% solution in MeOH, 154 μL, 0.30 mmol) in THF (0.75 mL) was stirred at rt for 18 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (10:1 Petrol/Et_2O) afforded *epoxide* **876** (37 mg, 0.15 mmol, quant.) as a colourless oil. **One-pot methylenation/epoxidation:** 1-(4-Methoxyphenyl)-5-methylhexan-1-one **782** (66 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol), and MeOH (3 mL) were subjected to **general procedure H**. After 48 h, SiliaMetS DMT (77 mg, 16 mol%) was added, and the resultant solution stirred at room temperature for 1 h. *tert*-Butylhydroperoxide (70% w/w aqueous solution, 410 μL, 3.0 mmol), and Triton B (40% w/w solution in MeOH, 1.62 mL, 3.0 mmol) were added, and the resultant solution stirred at rt for a further 15 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (20:1 Petrol/Et_2O) afforded *epoxide* **876** (67 mg, 0.27 mmol, 89%) as a colourless oil.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 2956, 1667, 1599, 1257, 1165; δ_H (400 MHz, $CDCl_3$) 8.07 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 6.94 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 3.88 (3H, s, $OC\underline{H}_3$), 2.93 (1H, d, *J* 5.0 Hz, $C\underline{H}_aH_bO$), 2.88 (1H, d, *J* 5.0 Hz, $CH_a\underline{H}_bO$), 2.23 (1H, ddd, *J* 14.1, 11.8, 5.1 Hz, $C\underline{H}_aH_b$*i*Bu), 1.72 (1H, ddd, *J* 14.1, 11.7, 5.1 Hz, $CH_a\underline{H}_b$*i*Bu), 1.61–1.48 (1H, m, $C\underline{H}(CH_3)_2$), 1.44–1.21 (2H, m, $C\underline{H}_2$*i*Pr), 0.86 (6H, d, *J* 6.6 Hz, $CH(C\underline{H}_3)_2$); δ_C (100 MHz, $CDCl_3$) 196.4 ($\underline{C}$=O), 163.8 ($\underline{C}_{Ar}OCH_3$), 131.8 ($\underline{C}_{Ar}H$), 127.6 ($\underline{C}_{Ar}$), 113.7 ($\underline{C}_{Ar}H$), 63.6 ($\underline{C}CO$), 55.5 ($O\underline{C}H_3$), 50.9 ($\underline{C}H_2O$), 33.5 ($\underline{C}H_2$*i*Bu), 31.3 ($\underline{C}H_2$*i*Pr), 28.0 ($\underline{C}H(CH_3)_2$), 22.3 ($CH(\underline{C}H_3)_a(CH_3)_b$), 22.3

($CH(CH_3)_a(\underline{C}H_3)_b$); **m/z** (ESI+) 271.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{15}H_{20}O_3$ requires 249.1485 $[M+H]^+$, found 249.1482 ($\Delta = -1.1$ ppm).

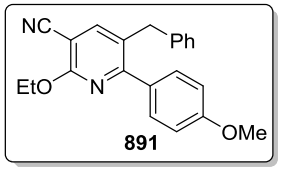
5-Benzyl-2-methoxy-6-(4-methoxyphenyl)nicotinonitrile 884



A solution of 2-benzyl-3-methoxy-1-(4-methoxyphenyl)propan-1-one **863** (43 mg, 0.15 mmol), malononitrile (50 mg, 0.75 mmol) and KOH (42 mg, 0.75 mmol) in MeOH (0.75 mL) was stirred at 65 °C for 6 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (6:1→1:1 Petrol/Et_2O) afforded *methoxypyridine* **884** (28 mg, 0.08 mmol, 53%) as a colourless oil.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 2955, 2838, 2227, 1594, 1514, 1495, 1300, 1251; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.61 (1H, s, $C_{Py}{}^4\underline{H}$), 7.51 (2H, d, *J* 8.8 Hz, $C_{Ar}\underline{H}$), 7.32–7.20 (3H, m, $C_{Ar}\underline{H}$), 7.04–7.00 (2H, m, $C_{Ar}\underline{H}$), 6.96 (2H, d, *J* 8.8 Hz, $C_{Ar}\underline{H}$), 4.06 (3H, s, $C_{Py}{}^2OC\underline{H}_3$), 4.03 (2H, s, $C\underline{H}_2Ph$), 3.85 (3H, s, $OC\underline{H}_3$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 161.7 ($\underline{C}_{Ar}$), 160.4 ($\underline{C}_{Ar}$), 159.7 ($\underline{C}_{Ar}OCH_3$), 145.4 ($C_{Py}{}^4\underline{C}H$), 139.7 ($\underline{C}_{Ar}$), 131.2 ($\underline{C}_{Ar}$), 130.6 ($\underline{C}_{Ar}H$), 128.8 ($\underline{C}_{Ar}H$), 128.7 ($\underline{C}_{Ar}H$), 126.7 ($\underline{C}_{Ar}H$), 126.3 ($\underline{C}_{Ar}$), 115.6 ($C_{Py}{}^3\underline{C}N$), 113.7 ($\underline{C}_{Ar}H$), 94.4 ($\underline{C}_{Py}{}^3CN$), 55.4 ($O\underline{C}H_3$), 54.3 ($C_{Py}{}^2O\underline{C}H_3$), 37.5 ($\underline{C}H_2Ph$); **m/z** (ESI+) 331.1 $[M+H]^+$; **HRMS** (ESI+) $C_{21}H_{18}N_2O_2$ requires 353.1260 $[M+Na]^+$, found 353.1265 ($\Delta = -1.2$ ppm).

5-Benzyl-2-ethoxy-6-(4-methoxyphenyl)nicotinonitrile 891

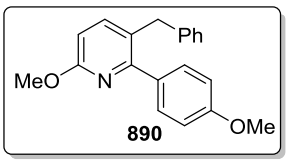


A solution of 2-benzyl-3-methoxy-1-(4-methoxyphenyl)propan-1-one **863** (43 mg, 0.15 mmol), malononitrile (50 mg, 0.75 mmol) and KOH (42 mg, 0.75 mmol) in EtOH (0.75 mL) was stirred at 65 °C for 16 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (10:1→5:1 Petrol/Et_2O) afforded *ethoxypyridine* **891** (20 mg, 0.083 mmol, 55%) as a colourless oil.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 2981, 2933, 2838, 2227, 1593, 1512, 1438, 1323, 1251, 1177, 1031; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.63 (1H, s, $C_{Py}{}^4\underline{H}$), 7.50 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.34–7.21 (3H, m,

$C_{Ar}\underline{H}$), 7.05–7.01 (2H, m, $C_{Ar}\underline{H}$), 6.97 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 4.53 (2H, q, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 4.04 (2H, s, $C\underline{H}_2Ph$), 3.87 (3H, s, $OC\underline{H}_3$), 1.45 (3H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 161.5 ($\underline{C}_{Ar}$), 160.3 ($\underline{C}_{Ar}$), 159.7 ($\underline{C}_{Ar}OCH_3$), 145.4 ($\underline{C}_{Ar}H$), 139.7 ($\underline{C}_{Ar}$), 131.3 ($\underline{C}_{Ar}$), 130.5 ($\underline{C}_{Ar}H$), 128.8 ($\underline{C}_{Ar}H$), 128.6 ($\underline{C}_{Ar}H$), 126.6 ($\underline{C}_{Ar}H$), 126.0 ($\underline{C}_{Ar}$), 115.7 ($C_{Py}{}^3\underline{C}N$), 113.7 ($\underline{C}_{Ar}H$), 94.5 ($\underline{C}_{Py}{}^3CN$), 63.0 ($O\underline{C}H_2CH_3$), 55.3 ($O\underline{C}H_3$), 37.5 ($\underline{C}H_2Ph$), 14.5 ($OCH_2\underline{C}H_3$); **m/z** (ESI+) 345.2 $[M+H]^+$; **HRMS** (ESI+) $C_{22}H_{20}N_2O_2$ requires 367.1417 $[M+Na]^+$, found 367.1427 ($\Delta = -2.6$ ppm).

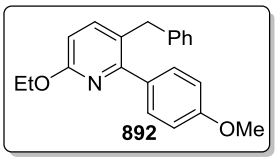
3-Benzyl-6-methoxy-2-(4-methoxyphenyl)pyridine 890



A solution of 2-benzyl-3-methoxy-1-(4-methoxyphenyl)propan-1-one **863** (43 mg, 0.15 mmol), phenylsulfonylacetonitrile (54 mg, 0.30 mmol) and KOH (42 mg, 0.75 mmol) in MeOH (0.75 mL) was stirred at 65 °C for 6 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (15:1 Petrol/Et_2O) afforded *methoxypyridine* **890** (45 mg, 0.15 mmol, quant.) as a colourless oil.

ν_{max} (cm^{-1}) 2951, 2836, 1593, 1514, 1471, 1422, 1321, 1246, 1175, 1032; **δ_H** (400 MHz, $CDCl_3$) 7.40 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.29 (1H, d, *J* 8.5 Hz, $C_{Py}{}^4\underline{H}$), 7.21–7.14 (2H, m, $C_{Ar}\underline{H}$), 7.13–7.07 (1H, m, $C_{Ar}\underline{H}$), 6.99–6.94 (2H, m, $C_{Ar}\underline{H}$), 6.85 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 6.56 (1H, d, *J* 8.5 Hz, $C_{Py}{}^5\underline{H}$), 3.92 (2H, s, $C\underline{H}_2Ph$), 3.87 (3H, s, $C_{Py}{}^6OC\underline{H}_3$), 3.75 (3H, s, $OC\underline{H}_3$); **δ_C** (101 MHz, $CDCl_3$) 161.9 ($\underline{C}_{Py}{}^6OCH_3$), 159.4 ($\underline{C}_{Ar}OCH_3$), 155.1 ($\underline{C}_{Ar}$), 141.6 ($\underline{C}_{Py}{}^4H$), 141.3 ($\underline{C}_{Ar}$), 132.8 ($\underline{C}_{Ar}H$), 130.4 ($\underline{C}_{Ar}H$), 128.7 ($\underline{C}_{Ar}H$), 128.5 ($\underline{C}_{Ar}H$), 126.0 ($\underline{C}_{Ar}H$), 125.5 ($\underline{C}_{Ar}$), 113.4 ($\underline{C}_{Ar}H$), 108.9 ($\underline{C}_{Py}{}^5H$), 55.3 ($C_{Py}{}^6O\underline{C}H_3$), 53.3 ($O\underline{C}H_3$), 37.6 ($\underline{C}H_2Ph$); **m/z** 306.1 $[M+H]^+$; **HRMS** (ESI+) $C_{20}H_{20}NO_2$ requires 306.1489 $[M+H]^+$, found 306.1488 ($\Delta = 0.2$ ppm).

3-Benzyl-6-ethoxy-2-(4-methoxyphenyl)pyridine 892

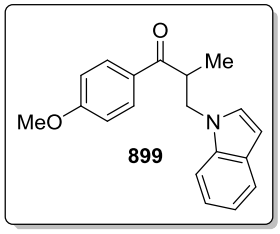


A solution of 2-benzyl-3-methoxy-1-(4-methoxyphenyl)propan-1-one **863** (43 mg, 0.15 mmol), phenylsulfonylacetonitrile (54 mg,

0.30 mmol) and KOH (42 mg, 0.75 mmol) in EtOH (0.75 mL) was stirred at 65 °C for 10 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (20:1 Petrol/Et_2O) afforded *ethoxypyridine* **892** (16 mg, 0.051 mmol, 34%) as a colourless oil.

ν_{max} (cm^{-1}) 2977, 2932, 2837, 1609, 1594, 1575, 1514, 1455, 1319, 1303, 1248, 1175, 1032; **δ_H** (400 MHz, $CDCl_3$) 7.47 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.38 (1H, d, *J* 8.4 Hz, $C_{Py}{}^{4}\underline{H}$), 7.30–7.24 (2H, m, $C_{Ar}\underline{H}$), 7.22–7.16 (1H, m, $C_{Ar}\underline{H}$), 7.08–7.04 (2H, m, $C_{Ar}\underline{H}$), 6.94 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 6.64 (2H, d, *J* 8.4 Hz, $C_{Py}{}^{5}\underline{H}$), 4.30 (2H, q, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 4.01 (2H, s, $C\underline{H}_2Ph$), 3.85 (3H, s, $OC\underline{H}_3$), 1.40 (3H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 161.7 ($\underline{C}_{Py}{}^{6}OCH_3$), 159.4 ($\underline{C}_{Ar}OCH_3$), 155.1 ($\underline{C}_{Ar}$), 141.6 ($\underline{C}_{Py}{}^{4}$), 141.3 ($\underline{C}_{Ar}$), 132.9 ($\underline{C}_{Ar}H$), 130.4 ($\underline{C}_{Ar}H$), 128.7 ($\underline{C}_{Ar}H$), 128.5 ($\underline{C}_{Ar}H$), 126.0 ($\underline{C}_{Ar}H$), 125.4 ($\underline{C}_{Ar}H$), 113.4 ($\underline{C}_{Ar}H$), 109.0 ($\underline{C}_{Py}{}^{5}H$), 61.5 ($O\underline{C}H_2CH_3$), 55.3 ($O\underline{C}H_3$), 37.6 ($\underline{C}H_2Ph$), 14.7 ($OCH_2\underline{C}H_3$); **m/z** 320.2 $[M+H]^+$; **HRMS** (ESI+) $C_{21}H_{21}NO_2$ requires 320.1645 $[M+H]^+$, found 320.1642 (Δ = 0.8 ppm).

3-(1*H*-Indol-1-yl)-1-(4-methoxyphenyl)-2-methylpropan-1-one 899



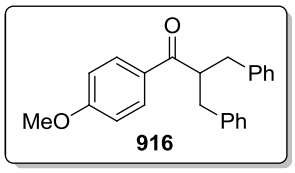
899

Conjugate addition: A solution of 3-methoxy-1-(4-methoxyphenyl)-2-methylpropan-1-one **862** (31 mg, 0.15 mmol), indole (75 μL, 0.75 mmol) and KOH (17 mg, 0.30 mmol) in MeOH (0.75 mL) was stirred at 65 °C for 18 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (20:1 Petrol/Et_2O) afforded *indolyl ketone* **899** (36 mg, 0.12 mmol, 82%) as a light yellow oil. **One-pot methylenation/conjugate addition:** 4-Methoxypropiophenone **758** (53 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol) and MeOH (3 mL) were subjected to **general procedure H**. After 48 h, SiliaMetS DMT (77 mg, 16 mol%) was added, and the resultant solution stirred at room temperature for 1 h. Indole (176 mg, 1.50 mmol), and KOH (34 mg, 0.60 mmol) were added, and the resultant solution stirred at 65 °C for a further 15 h. The reaction was diluted with

Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (20:1 Petrol/Et_2O) afforded *indolyl ketone* **899** (79 mg, 0.24 mmol, 80%) as a light yellow oil.

ν_{max} (cm^{-1}) 2931, 1668, 1598, 1257, 1228, 1171; **δ_H** (400 MHz, $CDCl_3$) 7.83 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.62 (1H, dt, *J* 7.8, 0.8 Hz, $C_{ind}\underline{H}$), 7.41 (1H, dd, *J* 8.2, 0.6 Hz, $C_{ind}{}^{7}\underline{H}$), 7.27–7.22 (1H, m, $C_{ind}\underline{H}$), 7.14–7.09 (2H, m, $C_{ind}\underline{H}$, $C_{ind}{}^{2}\underline{H}$), 6.88 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 6.49 (1H, dd, *J* 3.1, 0.6 Hz, $C_{Ind}{}^{3}\underline{H}$), 4.61 (1H, dd, *J* 14.4, 7.2 Hz, $C\underline{H}_aH_b$(1-ind)), 4.24 (1H, dd, *J* 14.4, 6.8 Hz, $CH_a\underline{H}_b$(1-ind)), 4.02 (1H, app sext, *J* 7.0 Hz, $C\underline{H}CO$), 3.85 (3H, s, $OC\underline{H}_3$), 1.25 (3H, d, *J* 7.0 Hz, $CHC\underline{H}_3$); **δ_C** (100 MHz, $CDCl_3$) 200.7 ($\underline{C}$=O), 163.7 ($\underline{C}_{Ar}OCH_3$), 135.9 ($\underline{C}_{Ar}$), 130.5 ($\underline{C}_{Ar}H$), 130.5 ($\underline{C}_{Ar}$), 128.9 ($\underline{C}_{Ar}$), 128.7 ($\underline{C}_{ind}{}^{2}H$), 121.5 ($\underline{C}_{ind}H$), 121.0 ($\underline{C}_{ind}H$), 119.3 ($\underline{C}_{ind}H$), 113.8 ($\underline{C}_{Ar}H$), 109.2 ($\underline{C}_{ind}{}^{7}H$), 101.2 ($\underline{C}_{ind}{}^{3}H$), 55.5 ($O\underline{C}H_3$), 48.8 ($\underline{C}H_2$(1-ind), 41.1 ($\underline{C}HCO$), 16.7 ($\underline{C}H_3$); **m/z** (ESI+) 316.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{19}H_{19}NO_2$ requires 294.1489 $[M+H]^+$, found 294.1482 (Δ = −2.3 ppm).

2-Benzyl-1-(4-methoxyphenyl)-3-phenylpropan-1-one 916



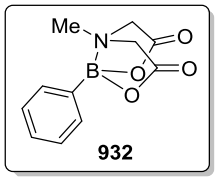
916

1-(4-Methoxyphenyl)-3-phenylpropan-1-one **781** (73 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol), and MeOH (3 mL) were subjected to **general procedure H**. After 48 h, the reaction was concentrated to 0.25 M (1.2 mL) by bubbling argon through the solution. Subsequently, $[Rh(cod)Cl]_2$ (3.7 mg, 2.5 mol%), 1,5-cyclooctadiene (3.7 μL, 10 mol%), KOH (50 mg, 0.90 mmol) and 1,3,5-triphenylboroxine (47 mg, 0.45 mmol) were added. The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and degassed with a ballon of Ar *via* a needle inserted through the septum. The balloon was them removed, and the reaction heated at 100 °C for 6 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (PhMe) afforded *benzylated ketone* **916** (72 mg, 0.22 mmol, 73%) as a colourless oil.

ν_{max} (cm^{-1}) 3027, 2932, 1669, 1599, 1261, 1238, 1170; **δ_H** (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 7.28–7.11 (10H, m, $C_{Ar}\underline{H}$), 6.82 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 3.98 (tt, *J* 7.9 Hz,

6.2 Hz, C*H*CO), 3.79 (3H, s, OC*H*$_3$), 3.14 (2H, dd, *J* 13.8, 8.0 Hz, C*H*$_a$H$_b$Ph), 2.81 (2H, dd, *J* 13.8, 6.3 Hz, CH$_a$*H*$_b$Ph); **δ$_C$** (100 MHz, $CDCl_3$) 201.6 (*C*=O), 163.2 (*C*$_{Ar}$OCH$_3$), 139.7, (*C*$_{Ar}$), 130.4 (*C*$_{Ar}$H), 130.3 (*C*$_{Ar}$) 129.0 (*C*$_{Ar}$H), 128.3 (*C*$_{Ar}$H), 126.2 (*C*$_{Ar}$H), 113.6 (*C*$_{Ar}$H), 55.4 (O*C*H$_3$), 49.9 (*C*HCO), 38.3 (*C*H$_2$Ph); **m/z** 363.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{23}H_{22}O_2$ requires 353.1512 $[M+Na]^+$, found 353.1511 (Δ = 0.3 ppm).

Phenylboronic acid MIDA ester 932[396]



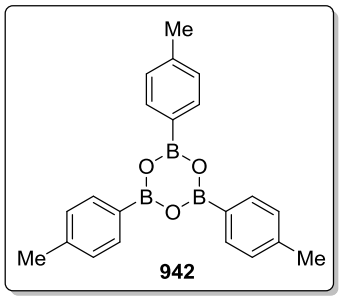
932

A solution of *N*-methyliminodiacetic acid (446 mg, 3.03 mmol) in benzene (100 mL) and DMSO (20 mL) in a 250 mL round-bottom flask was fitted with a Dean-Stark trap. Phenylboronic acid (370 mg, 3.03 mmol) was added and the mixture was stirred at reflux for 8 h. The solvents were removed *in vacuo*, and the resultant residue redissolved in EtOAc (100 mL). The organic phase was washed with brine (5×100 mL), dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. Purification by FCC (Et_2O→4:1 Et_2O/MeCN) afforded *MIDA ester* **932** (522 mg, 2.24 mmol, 74%) as a colourless solid.

m.p. 163–167 °C [Lit: 193 °C][456]; **δ$_H$** (400 MHz, DMSO-d_6) 7.46–7.40 (2H, m, C$_{Ar}$*H*), 7.39–7.32 (3H, m, C$_{Ar}$*H*), 4.33 (2H, d, *J* 17.1 Hz, C*H*$_a$H$_b$CO), 4.11 (2H, d, *J* 17.1 Hz, CH$_a$*H*$_b$CO), 3.48 (3H, s, NC*H*$_3$); **δ$_C$** (100 MHz, DMSO-d_6) 169.4 (*C*=O), 132.3 (*C*$_{Ar}$H), 128.9 (*C*$_{Ar}$H), 127.6 (*C*$_{Ar}$H), 67.8 (N*C*H$_2$CO), 47.6 (N*C*H$_3$), (*C*B not observed).

Spectroscopic data are consistent with those previously reported.[456]

2,4,6-tri-*p*-Tolyl-1,3,5,2,4,6-trioxatriborinane 942[457]



942

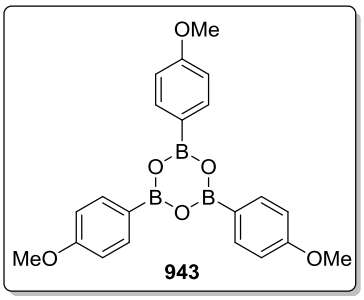
p-Tolylboronic acid **940** (170 mg, 1.25 mmol) was heated at 80 °C under high vacuum for 8 hours to afford *boroxine* **942** (152 mg, 0.41 mmol, 98%) as a colourless solid.

m.p. 155–157 °C [Lit: 165–166 °C][458]; **δ$_H$** (400 MHz, $CDCl_3$) 8.14 (2H, d, *J* 8.0 Hz, C$_{Ar}$*H*), 7.32 (2H, d, *J* 8.0 Hz, C$_{Ar}$*H*), 2.45

(3H, s, C*H*$_3$); **δ$_C$** (100 MHz, $CDCl_3$) 142.9 (*C*$_{Ar}$), 135.7 (*C*$_{Ar}$H), 128.7 (*C*$_{Ar}$H), 21.9 (C$_{Ar}$*C*H$_3$), (*C*B not observed).

Spectroscopic data are consistent with those previously reported.[458]

2,4,6-Tris(4-methoxyphenyl)-1,3,5,2,4,6-trioxatriborinane 943[457]



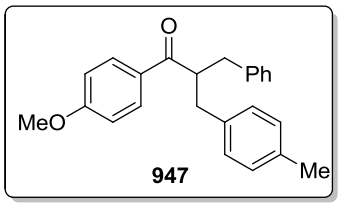
943

4-Methoxybenzeneboronic acid **941** (500 mg, 3.29 mmol) was heated at 80 °C under high vacuum for 8 hours to afford *boroxine* **943** (438 mg, 1.09 mmol, 99%) as a colourless solid.

m.p. 195–197 °C [Lit: 204–207 °C][459]; **δ$_H$** (400 MHz, $CDCl_3$) 8.17 (2H, d, *J* 8.7 Hz, C$_{Ar}$*H*), 7.02 (2H, d, *J* 8.7 Hz, C$_{Ar}$*H*), 3.90 (3H, s, OC*H*$_3$) **δ$_C$** (100 MHz, $CDCl_3$) 163.2 (*C*$_{Ar}$OCH$_3$), 137.5 (*C*$_{Ar}$H), 113.5 (*C*$_{Ar}$H), 55.1 (O*C*H$_3$), (*C*B not observed).

Spectroscopic data are consistent with those previously reported.[460]

2-Benzyl-1-(4-methoxyphenyl)-3-(p-tolyl)propan-1-one 947

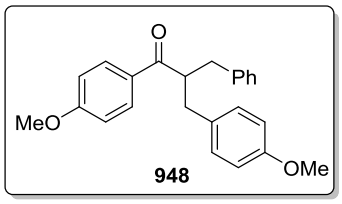


947

1-(4-Methoxyphenyl)-3-phenylpropan-1-one **781** (73 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol) and MeOH (3.0 mL) were subjected to **general procedure H**. After 48 h, the reaction was concentrated to 0.25 M (1.2 mL) by bubbling argon through the solution. Subsequently, $[Rh(cod)Cl]_2$ (3.7 mg, 2.5 mol%), 1,5-cyclooctadiene (3.7 μL, 10 mol%), KOH (50 mg, 0.90 mmol) and *p*-tolylboronic acid **740** (61 mg, 1.50 mmol) were added. The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and degassed with a ballon of Ar *via* a needle inserted through the septum. The balloon was them removed, and the reaction heated at 100 °C for 6 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (PhMe) afforded *benzylated ketone* **947** (65 mg, 0.19 mmol, 63%) as a colourless oil, along with *methylated ketone* **788** (21 mg, 0.083 mmol, 21%) as a colourless oil.

ν_{max} (cm^{-1}) 2906, 1689, 1598, 1510, 1237, 1169; δ_H (400 MHz, $CDCl_3$) 7.78 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.25–7.12 (5H, m, $C_{Ar}\underline{H}$), 7.05 (4H, s, $C_{Ar}\underline{H}$), 6.84 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 4.01–3.91 (1H, m, C$\underline{H}$CO), 3.83 (3H, s, OC$\underline{H}_3$), 3.17–3.07 (2H, m, C$\underline{H}_a$H$_b$Ph, C$\underline{H}_a$H$_b$Ar), 2.85–2.73 (2H, m, CH$_a\underline{H}_b$Ph, CH$_a\underline{H}_b$Ar), 2.29 (3H, s, $C_{Ar}C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 201.6 ($\underline{C}$=O), 163.2 ($\underline{C}_{Ar}OCH_3$), 139.7 ($\underline{C}_{Ar}$), 136.5 ($\underline{C}_{Ar}$), 135.6 ($\underline{C}_{Ar}$), 130.4 ($\underline{C}_{Ar}$H), 130.3 ($\underline{C}_{Ar}$), 129.0 ($\underline{C}_{Ar}$H), 129.0 ($\underline{C}_{Ar}$H), 128.8 ($\underline{C}_{Ar}$H), 128.3 ($\underline{C}_{Ar}$H), 126.1 ($\underline{C}_{Ar}$H), 113.6 ($\underline{C}_{Ar}$H), 55.3 (O$\underline{C}H_3$), 50.0 ($\underline{C}$HCO), 38.1 ($\underline{C}H_2$Ar), 37.8 ($\underline{C}H_2$Ar), 20.9 ($C_{Ar}\underline{C}H_3$); **m/z** (ESI+) 367.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{24}H_{24}O_2$ requires 367.1669 $[M+Na]^+$, found 367.1661 (Δ = −2.1 ppm).

2-Benzyl-1,3-bis(4-methoxyphenyl)propan-1-one 948



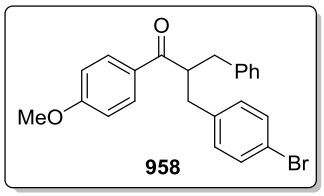
948

1-(4-Methoxyphenyl)-3-phenylpropan-1-one **781** (73 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol) and MeOH (3.0 mL) were subjected to **general procedure H**. After 48 h, the reaction was concentrated to 0.25 M (1.2 mL) by bubbling argon through the solution. Subsequently, $[Rh(cod)Cl]_2$ (3.7 mg, 2.5 mol%), 1,5-cyclooctadiene (3.7 μL, 10 mol%), KOH (50 mg, 0.90 mmol) and 2,4,6-tris(4-methoxyphenyl)-1,3,5,2,4,6-trioxatriborinane **943** (60 mg, 0.50 mmol) were added. The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and degassed with a ballon of Ar *via* a needle inserted through the septum. The balloon was them removed, and the reaction heated at 100 °C for 6 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (PhMe) afforded *benzylated ketone* **948** (38 mg, 0.105 mmol, 35%) as a colourless oil, along with *methylated ketone* **788** (48 mg, 0.19 mmol, 63%) as a colourless oil.

ν_{max} (cm^{-1}) 2933, 1689, 1599, 1510, 1243, 1170, 1032; δ_H (400 MHz, $CDCl_3$) 7.75 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 7.25−7.18 (2H, m, $C_{Ar}\underline{H}$), 7.17−7.11 (3H, m, $C_{Ar}\underline{H}$), 7.06 (2H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 6.82 (2H, d, *J* 8.9 Hz, $C_{Ar}\underline{H}$), 6.77 (2H, d, *J* 8.6 Hz, $C_{Ar}\underline{H}$), 3.99−3.88 (1H, m, C$\underline{H}$CO), 3.82 (3H, s, OC$\underline{H}_3$), 3.75 (3H, s, OC$\underline{H}_3$), 3.15−3.02 (2H, m, C$\underline{H}_a$H$_b$Ph, C$\underline{H}_a$H$_b$Ar), 2.83−2.71 (2H, m, CH$_a\underline{H}_b$Ph CH$_a\underline{H}_b$Ar); δ_C (100 MHz, $CDCl_3$) 201.8 ($\underline{C}$=O), 163.2 ($\underline{C}_{Ar}OCH_3$), 157.9 ($\underline{C}_{Ar}OCH_3$), 139.8 ($\underline{C}_{Ar}$), 131.7 ($\underline{C}_{Ar}$), 130.4 ($\underline{C}_{Ar}$H), 129.9 ($\underline{C}_{Ar}$H), 129.0

($\underline{C}_{Ar}H$), 128.3 ($\underline{C}_{Ar}H$), 126.1 ($\underline{C}_{Ar}H$), 113.7 ($\underline{C}_{Ar}H$), 113.6 ($\underline{C}_{Ar}H$), 55.3 (O$\underline{C}H_3$), 55.2 (O$\underline{C}H_3$), 50.2 ($\underline{C}$HCO), 38.2 ($\underline{C}H_2$Ar), 37.5 ($\underline{C}H_2$Ar); **m/z** (ESI+) 361.2 $[M+H]^+$; **HRMS** (ESI+) $C_{24}H_{24}O_3$ requires 361.1798 $[M+H]^+$, found 361.1793 ($\Delta = -1.5$ ppm).

2-Benzyl-3-(4-bromophenyl)-1-(4-methoxyphenyl)propan-1-one 958

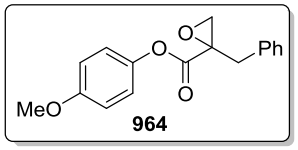


958

1-(4-Methoxyphenyl)-3-phenylpropan-1-one **781** (73 mg, 0.30 mmol). $[Ir(cod)Cl]_2$ (4.0 mg, 2.0 mol%), CataCXium A (8.6 mg, 8.0 mol%), KOH (50 mg, 0.90 mmol), and MeOH (3 mL) were subjected to **general procedure H**. After 48 h, the reaction was concentrated to 0.25 M (1.2 mL) by bubbling argon through the solution. Subsequently, $[Rh(cod)Cl]_2$ (3.7 mg, 2.5 mol%), 1,5-cyclooctadiene (3.7 μL, 10 mol%), KOH (50 mg, 0.90 mmol) and 4-bromobenzene boronic acid neopentyl glycol ester **953** (121 mg, 1.50 mmol) were added. The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and degassed with a ballon of Ar *via* a needle inserted through the septum. The balloon was them removed, and the reaction heated at 100 °C for 6 h. The reaction was diluted with Et_2O, filtered through a short pad of silica, and concentrated *in vacuo*. Purification by FCC (PhMe) afforded *benzylated ketone* **958** (58 mg, 0.14 mmol, 47%) as a colourless oil, along with *methylated ketone* **788** (38 mg, 0.15 mmol, 50%) as a colourless oil.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 2930, 1688, 1609, 1484, 1258, 1227, 1179; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.74 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 7.32 (2H, d, *J* 8.4 Hz, $C_{Ar}\underline{H}$), 7.27–7.21 (2H, m, $C_{Ar}\underline{H}$), 7.19–7.13 (3H, m, $C_{Ar}\underline{H}$), 7.00 (2H, d, *J* 8.4 Hz, $C_{Ar}\underline{H}$), 6.83 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 3.97–3.88 (1H, m, C$\underline{H}$CO), 2.83 (3H, s, OC$\underline{H}_3$), 3.16−3.04 (2H, m, C$\underline{H}_a$H$_b$Ph, C$\underline{H}_a$H$_b$Ar), 2.81–2.71 (2H, m, C$\underline{H}_a$H$_b$Ph, C$\underline{H}_a$H$_b$Ar); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 201.2 ($\underline{C}$=O), 163.4 ($\underline{C}_{Ar}OCH_3$), 139.3 ($\underline{C}_{Ar}$), 138.7 ($\underline{C}_{Ar}$), 131.4 ($\underline{C}_{Ar}H$), 130.7 ($\underline{C}_{Ar}H$), 130.4 ($\underline{C}_{Ar}H$), 130.1 ($\underline{C}_{Ar}$), 129.0 ($\underline{C}_{Ar}H$), 128.4 ($\underline{C}_{Ar}H$), 126.3 ($\underline{C}_{Ar}H$), 120.0 ($\underline{C}_{Ar}Br$), 113.7 ($\underline{C}_{Ar}H$), 55.4 (O$\underline{C}H_3$), 49.8 ($\underline{C}$HCO), 39.0 ($\underline{C}H_2$Ar), 37.4 ($\underline{C}H_2$Ar); **m/z** (ESI+) 431.0 $[M+Na]^+$; **HRMS** (ESI+) $C_{23}H_{21}O_2Br$ requires 431.0617 and 433.0597 $[M+Na]^+$, found 431.0613 and 433.0593 ($\Delta = -0.9$ ppm).

4-Methoxyphenyl 2-benzyloxirane-2-carboxylate 964

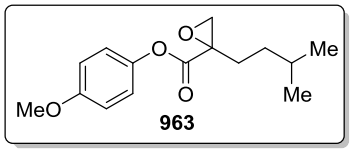


964

(2-Benzyloxiran-2-yl)(4-methoxyphenyl)methanone **875** (26 mg, 0.10 mmol), mCPBA (66 mg, 0.40 mmol), trifluoroacetic acid (14 μL, 0.20 mmol) and CH_2Cl_2 (2.0 mL) were subjected to **general procedure G** for 48 h. Purification by FCC (20:1→10:1 Petrol/Et_2O) afforded *ester* **964** (25 mg, 0.088 mmol, 88 %) as a colourless oil.

ν_{max} (cm^{-1}) 2925, 1753, 1503, 1248, 1190, 1097; **δ_H** (400 MHz, $CDCl_3$) 7.38–7.24 (5H, m, $C_{Ar}\underline{H}$), 6.91–6.84 (4H, m, $C_{Ar}\underline{H}$), 3.79 (3H, s, $OC\underline{H}_3$), 3.51 (1H, d, *J* 14.9 Hz, $C\underline{H}_aH_bPh$), 3.24 (1H, d, *J* 5.8 Hz, $C\underline{H}_aH_bO$), 3.22 (1H, d, *J* 14.9 Hz, $CH_a\underline{H}_bPh$), 2.86 (1H, d, *J* 5.8 Hz, $CH_a\underline{H}_bO$); **δ_C** (100 MHz, $CDCl_3$) 169.1 ($\underline{C}$=O), 157.5 ($\underline{C}_{Ar}OCH_3$), 143.7 ($\underline{C}_{Ar}OCO$), 135.3 ($\underline{C}_{Ar}$), 129.8 ($\underline{C}_{Ar}H$), 128.4 ($\underline{C}_{Ar}H$), 127.0 ($\underline{C}_{Ar}H$), 121.9 ($\underline{C}_{Ar}H$), 114.5 ($\underline{C}_{Ar}H$), 57.2 ($O\underline{C}H_3$), 55.5 ($\underline{C}CO$), 51.2 ($\underline{C}H_2O$), 36.9 ($\underline{C}H_2Ph$); **m/z** (ESI+) 307.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{17}H_{16}O_4$ requires 307.0941 $[M+Na]^+$, found 307.0932 ($\Delta = -2.8$ ppm).

4-Methoxyphenyl 2-isopentyloxirane-2-carboxylate 963



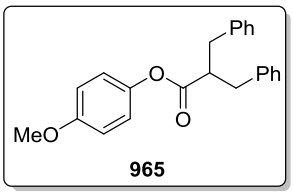
963

(2-Isopentyloxiran-2-yl)(4-methoxyphenyl)methanone **876** (22 mg, 0.090 mmol), mCPBA (61 mg, 0.36 mmol), trifluoroacetic acid (14 μL, 0.20 mmol) and CH_2Cl_2 (1.8 mL) were subjected to **general procedure G** for 48 h. Purification by FCC (10:1 Petrol/Et_2O) afforded *ester* **963** (17.5 mg, 0.066 mmol, 74%, >98:2 regioselectivity) as a colourless oil.

ν_{max} (cm^{-1}) 2956, 1753, 1505, 1248, 1192; **δ_H** (400 MHz, $CDCl_3$) 7.02 (2H, d, *J* 9.1 Hz, $C_{Ar}\underline{H}$), 6.90 (2H, d, *J* 9.1 Hz, $C_{Ar}\underline{H}$), 3.81 (3H, s, $OC\underline{H}_3$), 3.23 (1H, d, *J* 5.8 Hz, $C\underline{H}_aH_bO$), 2.91 (1H, d, *J* 5.8 Hz), 2.19 (1H, ddd, *J* 14.2, 11.6, 5.0 Hz, $C\underline{H}_aH_b$*i*Bu), 1.79 (1H, ddd, *J* 14.2, 11.4, 5.2 Hz, $CH_a\underline{H}_b$*i*Bu), 1.67–1.56 (1H, m, $C\underline{H}(CH_3)_2$), 1.53–1.34 (2H, m, $C\underline{H}_2$), 0.93 (6H, d, *J* 6.7 Hz, $CH(C\underline{H}_3)_2$); **δ_C** (100 MHz, $CDCl_3$) 169.5 ($\underline{C}$=O), 157.4 ($\underline{C}_{Ar}OCH_3$), 143.8 ($\underline{C}_{Ar}OCO$), 122.0 ($\underline{C}_{Ar}H$), 114.5 ($\underline{C}_{Ar}H$), 57.3 ($\underline{C}CO$) 55.6 ($O\underline{C}H_3$), 52.0 ($\underline{C}H_2O$), 33.6 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 28.0 ($\underline{C}H(CH_3)_2$), 22.4 ($CH(CH_3)_a(\underline{C}H_3)_b$)), 22.3 ($CH(CH_3)_a(\underline{C}H_3)_b$)); **m/z** (ESI+)

287.1 $[M+Na]^+$; **HRMS** (ESI+) $C_{15}H_{20}O_4$ requires 287.1254 $[M+Na]^+$, found 287.1255 (Δ = −1.9 ppm).

4-Methoxyphenyl 2-benzyl-3-phenylpropanoate 965



965

2-Benzyl-1-(4-methoxyphenyl)-3-phenylpropan-1-one **916** (36 mg, 0.11 mmol), *m*CPBA (76 mg, 0.44 mmol), trifluoroacetic acid (17 μL, 0.22 mmol) and CH_2Cl_2 (2.2 mL) were subjected to general procedure G for 72 h. After 72 h further *m*CPBA (76 mg, 0.44 mmol) and trifluoracetic acid (17 μL, 0.22 mmol) were added and the reaction stirred for a further 48 h. Purification by FCC (10:1 Petrol/Et_2O) afforded *ester* **965** (31 mg, 0.090 mmol, 82%, 10:1 regioselectivity, >75% purity) as a colourless oil.

$\boldsymbol{\nu_{max}}$ (cm^{-1}) 2930, 1751, 1506, 1455, 1248, 1193, 1133; $\boldsymbol{\delta_H}$ (400 MHz, $CDCl_3$) 7.28–7.14 (10H, m, $C_{Ar}\underline{H}$), 6.68 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 6.51 (2H, d, *J* 9.0 Hz, $C_{Ar}\underline{H}$), 3.67 (3H, s, $OC\underline{H}_3$), 3.20–3.09 (1H, m, $C\underline{H}CO$), 3.00 (2H, dd, *J* 13.4, 9.1 Hz, $C\underline{H}_aH_bPh$), 2.89 (2H, dd, *J* 13.4, 5.9 Hz, $CH_a\underline{H}_bPh$); $\boldsymbol{\delta_C}$ (100 MHz, $CDCl_3$) 173.8 ($\underline{C}$=O), 157.1 ($\underline{C}_{Ar}OCH_3$), 143.8 ($\underline{C}_{Ar}OCO$), 138.7 ($\underline{C}_{Ar}$), 129.0 ($\underline{C}_{Ar}H$), 128.5 ($\underline{C}_{Ar}H$), 126.6 ($\underline{C}_{Ar}H$), 122.1 ($\underline{C}_{Ar}H$), 114.3 ($\underline{C}_{Ar}H$), 55.5 ($O\underline{C}H_3$), 49.8 ($\underline{C}HCO$), 38.6 ($\underline{C}H_2Ph$); **m/z** (ESI+) 369.0 $[M+Na]^+$; **HRMS** (ESI+) $C_{23}H_{22}O_3$ requires 369.1461 $[M+Na]^+$, found 369.1455 (Δ = −1.7 ppm).

Appendix 1: References

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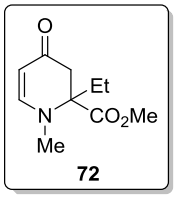
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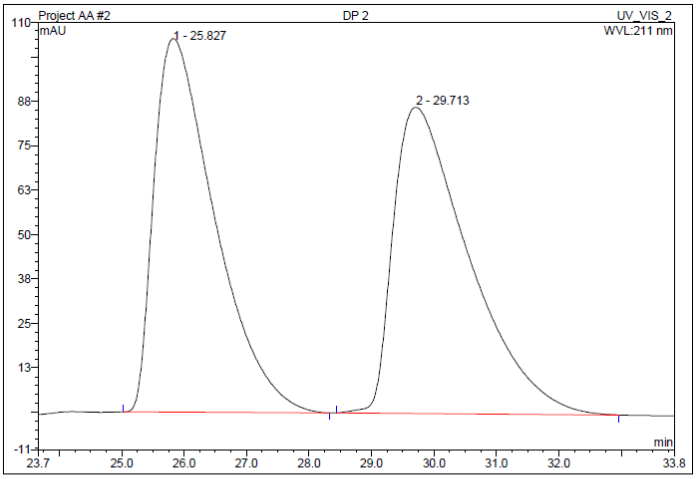
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Appendix 2: Representative HPLC Traces

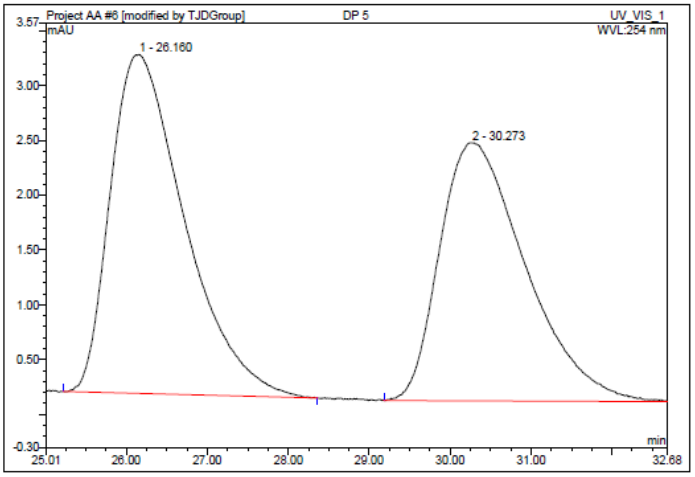
Methyl 2-ethyl-1-methyl-4-oxo-1,2,3,4-tetrahydropyridine-2-carboxylate 72



Chiralcel OD, 254nm, 1.0 mL/min, heptane/*i*-PrOH 9:1 v/v, tR_1 = 26.2 min, tR_2 = 30.3 min

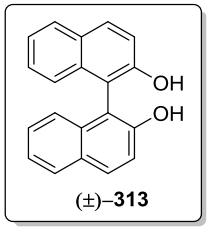


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	25.83	n.a.	105.199	118.811	49.63	n.a.	BMB
2	29.71	n.a.	86.230	120.569	50.37	n.a.	BMB
Total:			191.429	239.380	100.00	0.000	

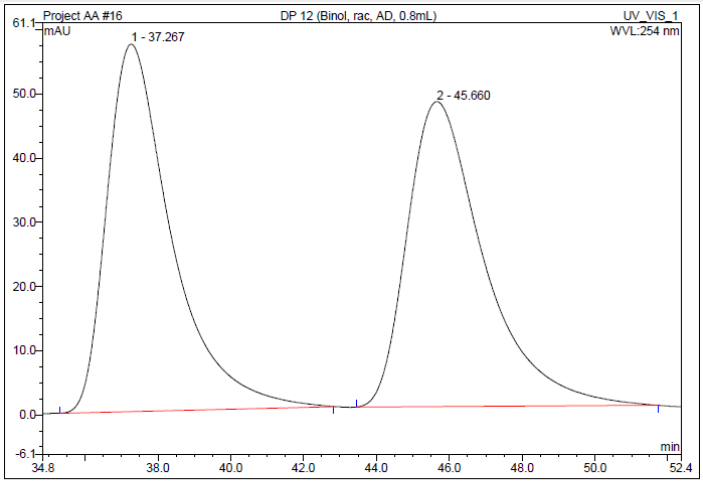


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.16	n.a.	3.088	3.279	53.14	n.a.	BMB*
2	30.27	n.a.	2.354	2.891	46.86	n.a.	BMB*
Total:			5.442	6.170	100.00	0.000	

[1,1'-Binapthalene]-2,2'-diol 313

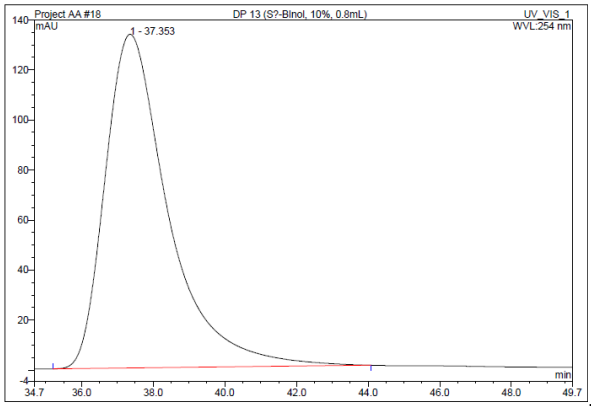


Chiralcel AD, 254nm, 0.8 mL/min, heptane/*i*-PrOH 9:1 v/v, tR_S = 37.3 min, tR_R = 45.7 min

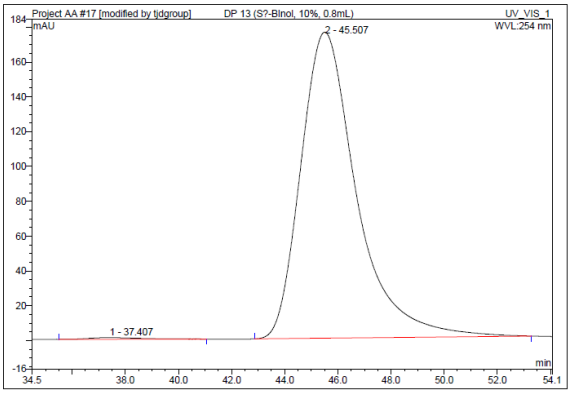


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	37.27	n.a.	57.241	117.771	50.44	n.a.	BMB
2	45.66	n.a.	47.526	115.731	49.56	n.a.	BMB
Total:			104.767	233.502	100.00	0.000	

(*S*)-313 and **(*R*)-313**

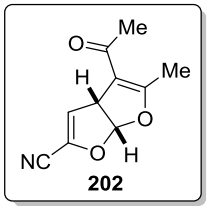


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	37.35	n.a.	133.503	273.464	100.00	n.a.	BMB
Total:			133.503	273.464	100.00	0.000	



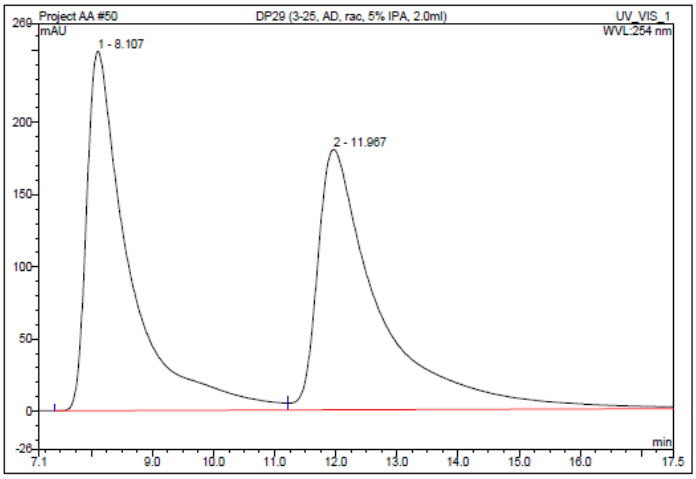
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	37.41	n.a.	0.909	1.933	0.45	n.a.	BMB*
2	45.51	n.a.	175.692	426.599	99.55	n.a.	BMB
Total:			176.600	428.532	100.00	0.000	

(3*R,6*R**) 4-Acetyl-5-methyl-3a,6a-dihydrofuro[2,3-*b*]furan-2-carbonitrile 202**

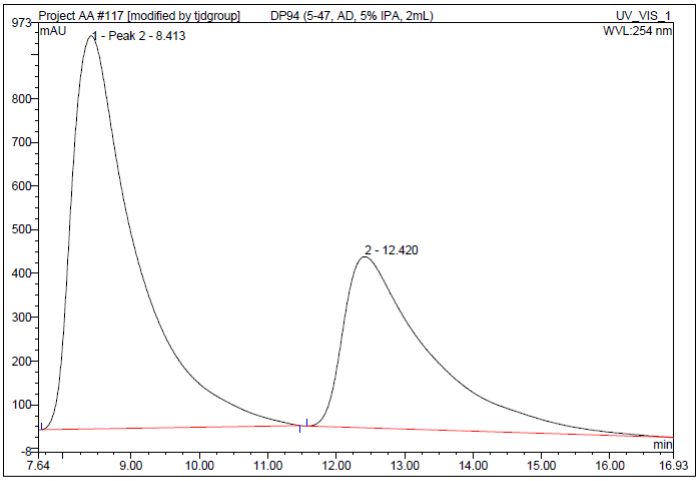


202

Chiralcel AD, 254nm, 2.0 mL/min, heptane/*i*-PrOH 95:5 v/v, tR_1 = 8.1 min, tR_2 = 12.0 min

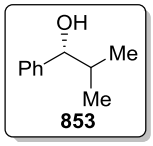


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.11	n.a.	248.992	202.007	48.85	n.a.	BM
2	11.97	n.a.	180.322	211.541	51.15	n.a.	MB
Total:			429.314	413.548	100.00	0.000	

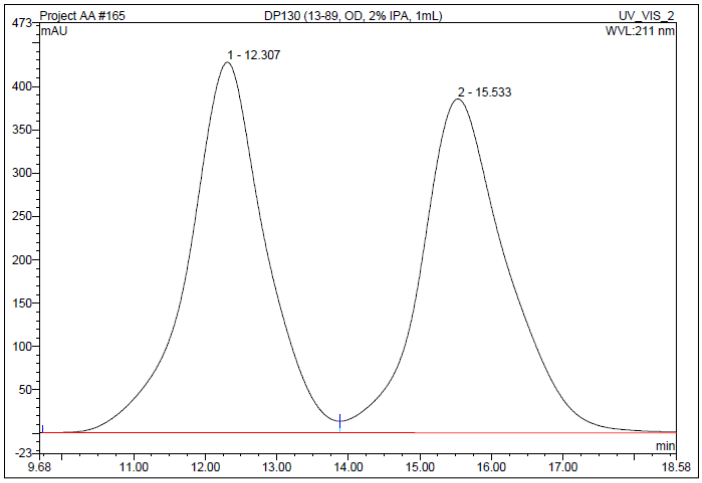


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	8.41	Peak 2	898.528	974.390	63.22	n.a.	BMB*
2	12.42	n.a.	391.507	566.869	36.78	n.a.	BMB*
Total:			1290.035	1541.259	100.00	0.000	

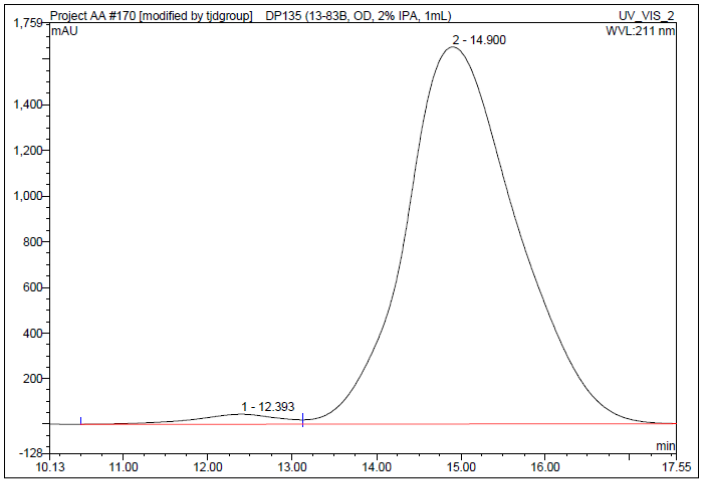
(*R*)-2-Methyl-1-phenylpropan-1-ol 853



Chiralcel OD, 211nm, 1.0 mL/min, heptane/*i*-PrOH 98:2 v/v, tR_S = 12.4 min, tR_R = 14.9 min.

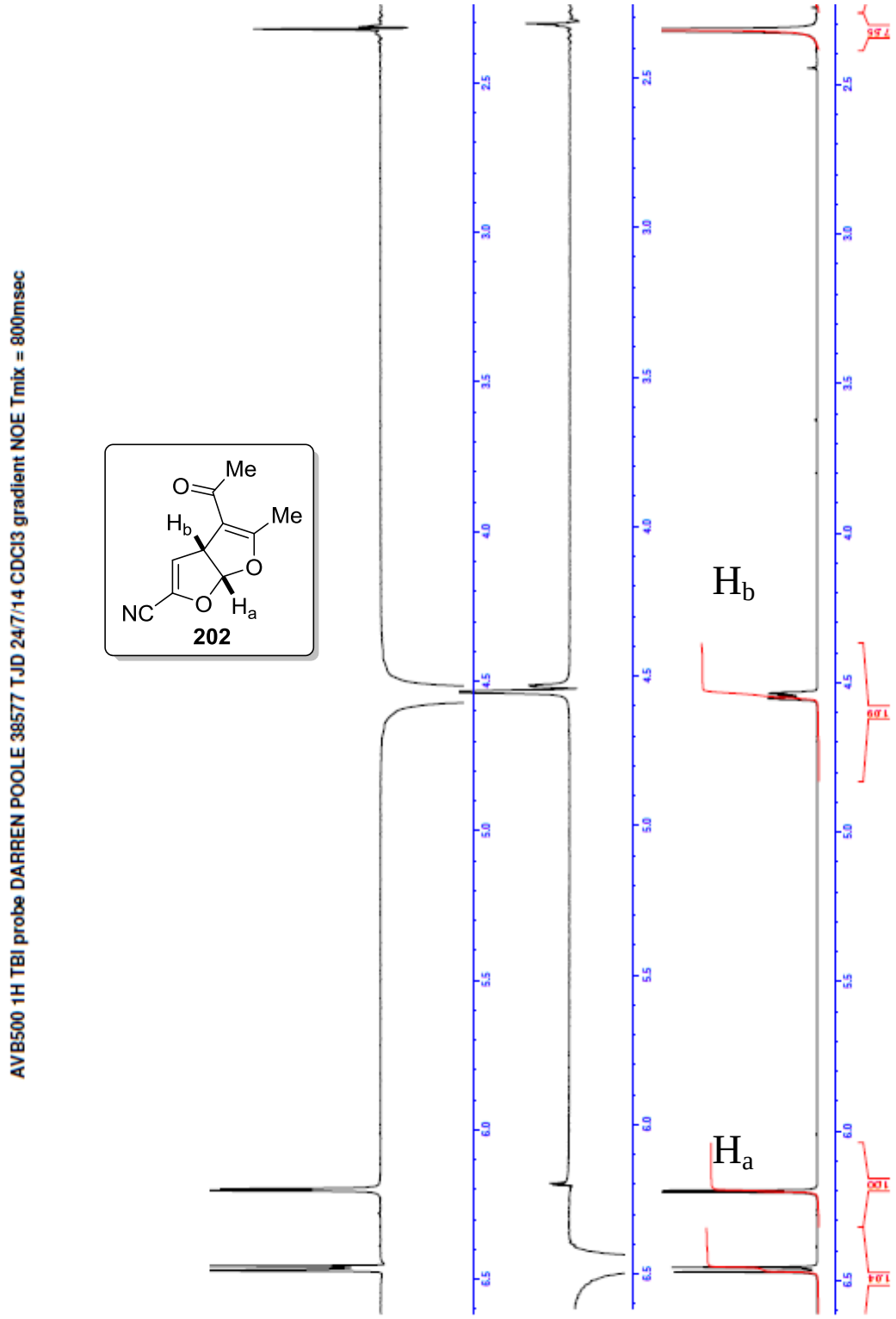


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.31	n.a.	427.151	529.616	49.76	n.a.	BM
2	15.53	n.a.	385.088	534.626	50.24	n.a.	MB
Total:			812.239	1064.242	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	12.39	n.a.	43.304	49.774	1.94	n.a.	BM
2	14.90	n.a.	1652.627	2513.766	98.06	n.a.	MB
Total:			1695.931	2563.540	100.00	0.000	

Appendix 3: NOE Data for Compound 202


AVB500 1H TBI probe DARREN POOLE 38577 TJD 24/7/14 CDCl3 gradient NOE Tmix = 800msec
Me
O
Hb
Me
O
NC
O
Ha
202
Hb
Ha

Appendix 4: Deuteration Experiments

A4.1 CD_3OH Experiment

A4.1.1 ^2D NMR Spectra

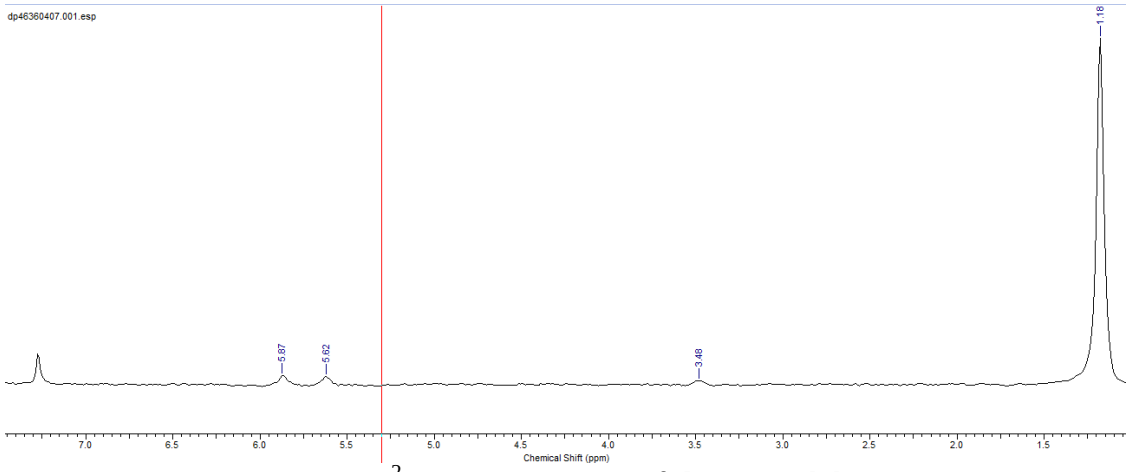


Figure A4.1 ^{2}D NMR spectrum of d_3-**719** *and* d_2-**720**

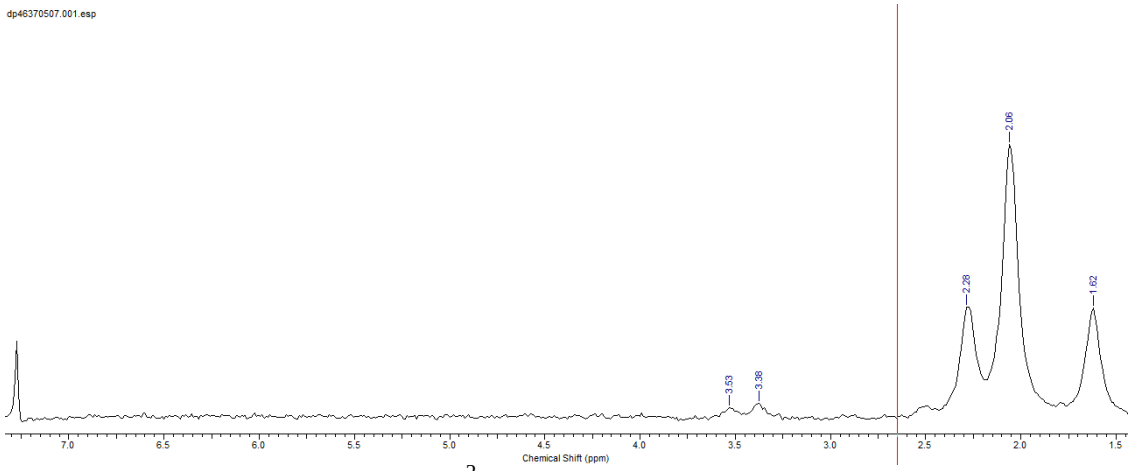


Figure A4.2 ^{2}D NMR spectrum of d_2-**721**

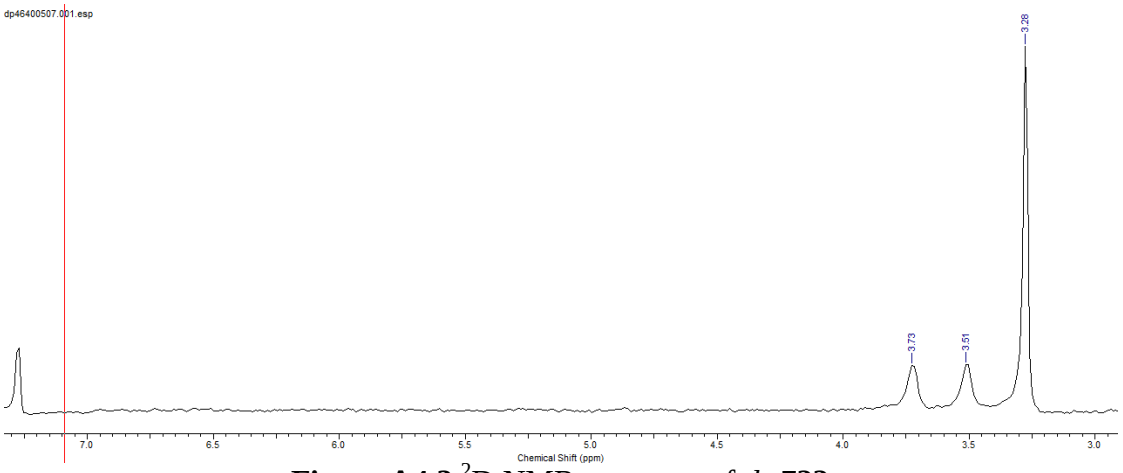


Figure A4.3 ^{2}D NMR spectrum of d_5-**722**

A4.2 CD_3OH/CH_3OH Competition experiment

A4.2.1 Integration of ^1H NMR spectra

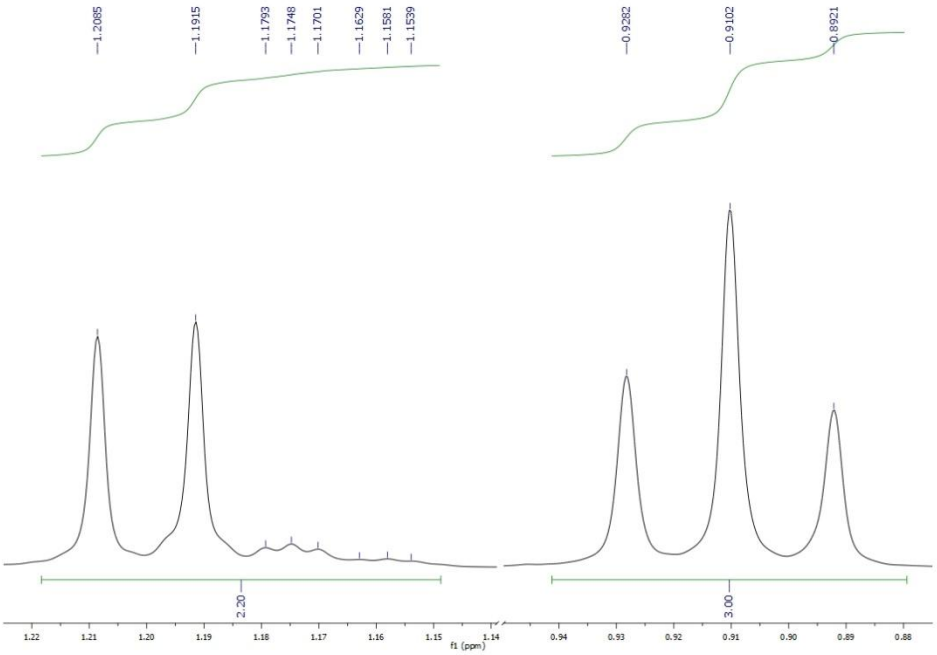


Figure A4.4 *Integration of methyl groups in d_0-d_2-***719**

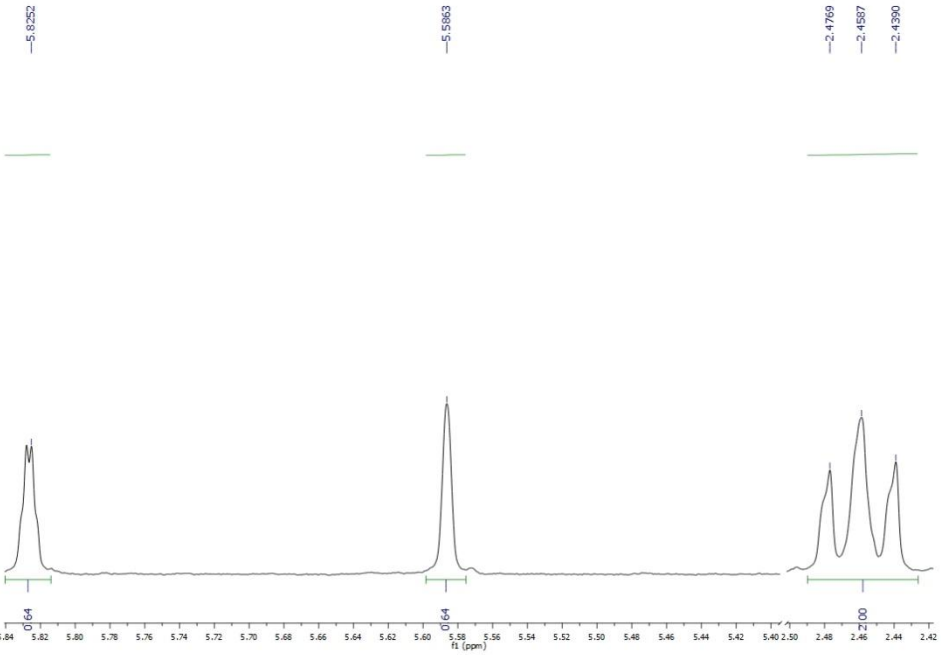


Figure A4.5 *Integration of alkyenyl protons in d_0-***720** *and d_2-***720** *relative to allylic protons*

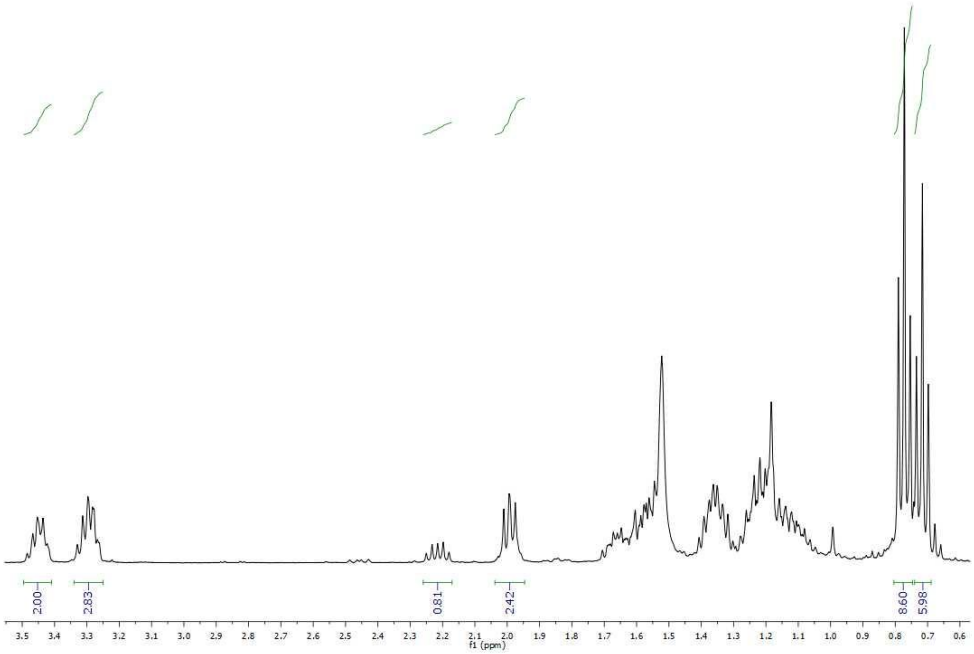
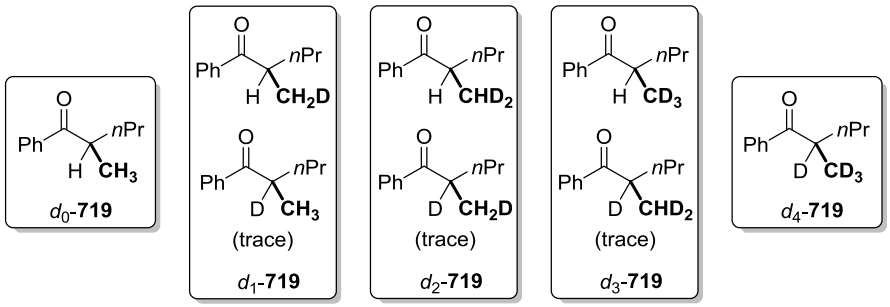


Figure A4.6 *Integration of bridging methylene protons in d_0- to d_3-***721**

A4.2.2 HRMS Data

Methyl ketone 719

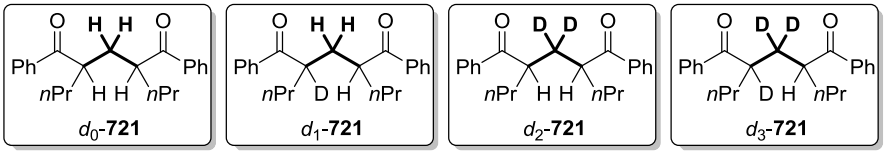


Parent compound: $C_{12}H_{16}O$

Ion: $[M+Na]^+$

	***d*-0**	***d*-1**	***d*-2**	***d*-3**	***d*-4**
Theoretical Mass	199.1093	200.1127	201.1160	202.1262	203.1344
Observed Mass	199.1092	200.1145	201.1215	202.1271	203.1265
Predicted intensity for non-D compound	112556	14816	1127	0	0
Observed Intensity	112556	44842	53576	16929	2000
Account for 13C isotopes	112556	30026	52449	16929	2000
Percentage	52.63%	14.00%	24.53%	7.89%	0.95%

Dimer 721

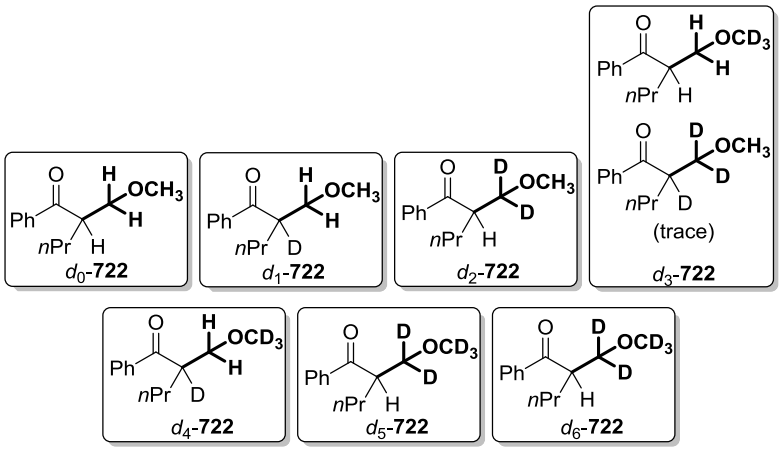


Parent compound: $C_{23}H_{28}O_2$

Ion: $[M+Na]^+$

	***d*-0**	***d*-1**	***d*-2**	***d*-3**
Theoretical Mass	359.1982	360.2015	361.2049	362.2082
Observed Mass	359.1980	360.2017	361.2100	362.2133
Predicted intensity for non-D compound	485074	122230	16739	1636
Observed Intensity	485074	136907	227607	50078
Account for 13C isotopes	485074	14677	210868	48442
Percentage	63.94%	1.92%	27.75%	6.39%

Methanol adduct 722



Parent compound: $C_{13}H_{18}O_2$

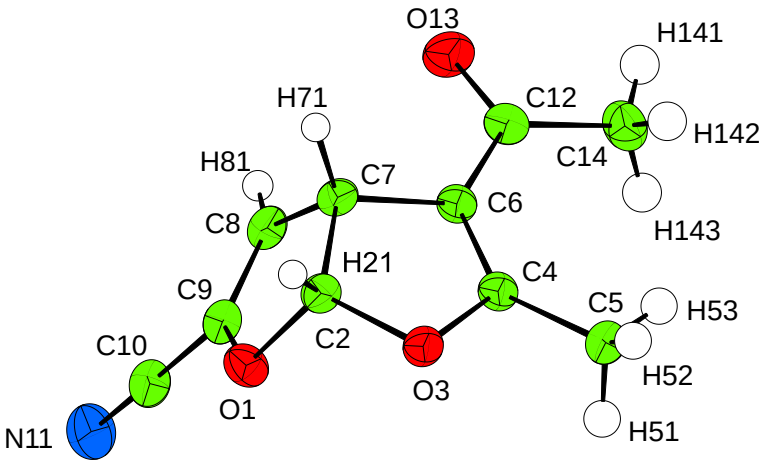
Ion: $[M+Na]^+$

	***d*-0**	***d*-1**	***d*-2**	***d*-3**
Theoretical Mass	229.1199	230.1233	231.1266	232.1393
Observed Mass	229.1208	230.1251	231.1332	232.1387
Predicted intensity for non-D compound	136746	19510	1850	0
Observed Intensity	136746	25876	66628	113012
Account for 13C isotopes	136746	6366	64778	113012
Percentage	33.06%	1.54%	15.66%	27.32%

	d-4	*d*-5	d-6
Theoretical Mass	233.1456	234.1518	235.1581
Observed Mass	233.1442	234.1515	235.1548
Predicted intensity for non-D compound	0	0	0
Observed Intensity	21360	63083	8277
Account for 13C isotopes	21360	63083	8277
Percentage	5.16%	15.25%	2.00%

Appendix 5: X-ray Crystallographic Data for Compound **202**

Single crystal X-ray diffraction report for 4-acetyl-5-methyl-3a,6a-dihydrofuro[2,3-b]furan-2-carbonitrile (202)



Crystals of **202** were grown from $CHCl_3$/petrol. A single crystal representing the bulk of the sample was selected for the X-ray analysis.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al*., 2003); molecular graphics: *CAMERON* (Watkin *et al*., 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al*., 2003).

Crystal data

$C_{10}H_9NO_3$	$F(000)$ = 400
M_r = 191.19	D_x = 1.397 Mg m^{-3}
Monoclinic, $P2_1/n$	Mo $K\alpha$ radiation, λ = 0.71073 Å
Hall symbol: -P 2yn	Cell parameters from 2287 reflections
a = 14.2033 (5) Å	θ = 5–27°
b = 4.3069 (2) Å	μ = 0.11 mm^{-1}
c = 15.0385 (6) Å	T = 150 K
β = 98.7952 (16)°	Plate, clear_colourless
V = 909.12 (6) Å^3	0.2 × 0.1 × 0.1 mm
Z = 4	

Data collection

Nonius KappaCCD diffractometer
Graphite monochromator
ω scans
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)
T_{min} = 0.93, T_{max} = 0.99
12106 measured reflections
2080 independent reflections

1620 reflections with $I > 2.0\sigma(I)$
R_{int} = 0.018
θ_{max} = 27.5°, θ_{min} = 5.5°
h = −18→18
k = −5→5
l = −19→19

Refinement

Refinement on F^2
Least-squares matrix: full
$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.112
S = 0.95
2080 reflections
127 parameters
0 restraints

Primary atom site location: Other
Hydrogen site location: difference Fourier map
H-atom parameters constrained
Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = 1.0/[A_0*T_0(x) + A_1*T_1(x) ⋯ + A_{n-1}]*T_{n-1}(x)] where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 27.6 41.4 20.5 5.49
$(\Delta/\sigma)_{max}$ = 0.0003
$\Delta\rho_{max}$ = 0.26 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
O1	0.63990 (7)	0.1062 (3)	0.25774 (7)	0.0308
C2	0.68914 (10)	−0.0377 (4)	0.33719 (10)	0.0260
O3	0.77980 (7)	0.1108 (3)	0.36096 (7)	0.0284
C4	0.78367 (10)	0.2482 (3)	0.44386 (9)	0.0253
C5	0.87581 (11)	0.4083 (4)	0.47248 (11)	0.0326
C6	0.70336 (10)	0.2068 (4)	0.48030 (9)	0.0250
C7	0.63222 (10)	0.0277 (4)	0.41447 (10)	0.0256
C8	0.55131 (10)	0.2239 (4)	0.36857 (10)	0.0283
C9	0.56265 (10)	0.2595 (4)	0.28357 (10)	0.0277
C10	0.50437 (11)	0.4280 (4)	0.21374 (11)	0.0338
N11	0.45652 (11)	0.5618 (4)	0.15839 (11)	0.0464
C12	0.67707 (11)	0.3112 (4)	0.56557 (10)	0.0286
O13	0.59632 (8)	0.2543 (3)	0.58038 (8)	0.0392
C14	0.74590 (13)	0.4839 (5)	0.63375 (11)	0.0384

H21	0.6985	−0.2667	0.3233	0.0316*
H53	0.8790	0.5124	0.5300	0.0511*
H52	0.9281	0.2567	0.4794	0.0525*
H51	0.8895	0.5567	0.4267	0.0518*
H71	0.6087	−0.1630	0.4407	0.0317*
H81	0.5005	0.3108	0.3970	0.0360*
H141	0.7144	0.5201	0.6849	0.0583*
H142	0.8044	0.3580	0.6516	0.0574*
H143	0.7617	0.6829	0.6078	0.0586*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
O1	0.0299 (5)	0.0363 (6)	0.0265 (5)	0.0052 (5)	0.0053 (4)	0.0005 (5)
C2	0.0262 (7)	0.0243 (7)	0.0276 (7)	−0.0013 (6)	0.0043 (5)	0.0004 (6)
O3	0.0261 (5)	0.0332 (6)	0.0268 (5)	−0.0034 (5)	0.0071 (4)	−0.0039 (4)
C4	0.0266 (7)	0.0241 (7)	0.0248 (6)	0.0007 (6)	0.0025 (5)	0.0023 (6)
C5	0.0272 (7)	0.0384 (9)	0.0318 (7)	−0.0049 (7)	0.0029 (6)	0.0006 (7)
C6	0.0259 (7)	0.0242 (7)	0.0248 (7)	0.0010 (6)	0.0037 (5)	0.0015 (6)
C7	0.0263 (7)	0.0230 (7)	0.0281 (7)	−0.0028 (6)	0.0068 (5)	0.0003 (6)
C8	0.0232 (6)	0.0286 (8)	0.0333 (7)	−0.0027 (6)	0.0050 (5)	−0.0032 (6)
C9	0.0243 (7)	0.0263 (7)	0.0318 (7)	−0.0015 (6)	0.0019 (5)	−0.0021 (6)
C10	0.0283 (7)	0.0357 (8)	0.0362 (8)	−0.0023 (7)	0.0013 (6)	−0.0013 (7)
N11	0.0380 (8)	0.0524 (10)	0.0458 (8)	0.0033 (8)	−0.0035 (6)	0.0066 (8)
C12	0.0309 (7)	0.0272 (7)	0.0283 (7)	0.0039 (6)	0.0063 (6)	0.0016 (6)
O13	0.0355 (6)	0.0460 (7)	0.0392 (6)	−0.0019 (6)	0.0153 (5)	−0.0030 (6)
C14	0.0395 (9)	0.0464 (10)	0.0288 (7)	−0.0002 (8)	0.0038 (6)	−0.0066 (7)

Geometric parameters (Å, º)

O1—C2	1.4300 (17)	C6—C12	1.460 (2)
O1—C9	1.3859 (18)	C7—C8	1.506 (2)
C2—O3	1.4332 (17)	C7—H71	0.991
C2—C7	1.5398 (19)	C8—C9	1.322 (2)
C2—H21	1.021	C8—H81	0.969
O3—C4	1.3735 (17)	C9—C10	1.431 (2)
C4—C5	1.484 (2)	C10—N11	1.146 (2)
C4—C6	1.351 (2)	C12—O13	1.2261 (19)
C5—H53	0.969	C12—C14	1.501 (2)
C5—H52	0.982	C14—H141	0.959
C5—H51	0.980	C14—H142	0.994
C6—C7	1.513 (2)	C14—H143	0.982
C2—O1—C9	106.22 (11)	C2—C7—C8	102.03 (12)
O1—C2—O3	108.73 (11)	C6—C7—C8	113.59 (12)
O1—C2—C7	107.77 (11)	C2—C7—H71	113.4

O3—C2—C7	106.59 (11)	C6—C7—H71	113.2
O1—C2—H21	108.1	C8—C7—H71	111.6
O3—C2—H21	110.0	C7—C8—C9	108.13 (13)
C7—C2—H21	115.5	C7—C8—H81	125.6
C2—O3—C4	109.17 (11)	C9—C8—H81	126.3
O3—C4—C5	112.01 (13)	O1—C9—C8	115.76 (13)
O3—C4—C6	113.09 (13)	O1—C9—C10	115.45 (13)
C5—C4—C6	134.90 (14)	C8—C9—C10	128.76 (15)
C4—C5—H53	113.1	C9—C10—N11	178.98 (18)
C4—C5—H52	109.9	C6—C12—O13	118.02 (14)
H53—C5—H52	106.4	C6—C12—C14	121.68 (14)
C4—C5—H51	111.1	O13—C12—C14	120.30 (14)
H53—C5—H51	109.8	C12—C14—H141	107.0
H52—C5—H51	106.3	C12—C14—H142	110.1
C4—C6—C7	108.83 (12)	H141—C14—H142	110.2
C4—C6—C12	131.36 (14)	C12—C14—H143	109.0
C7—C6—C12	119.78 (13)	H141—C14—H143	109.8
C2—C7—C6	102.23 (11)	H142—C14—H143	110.6

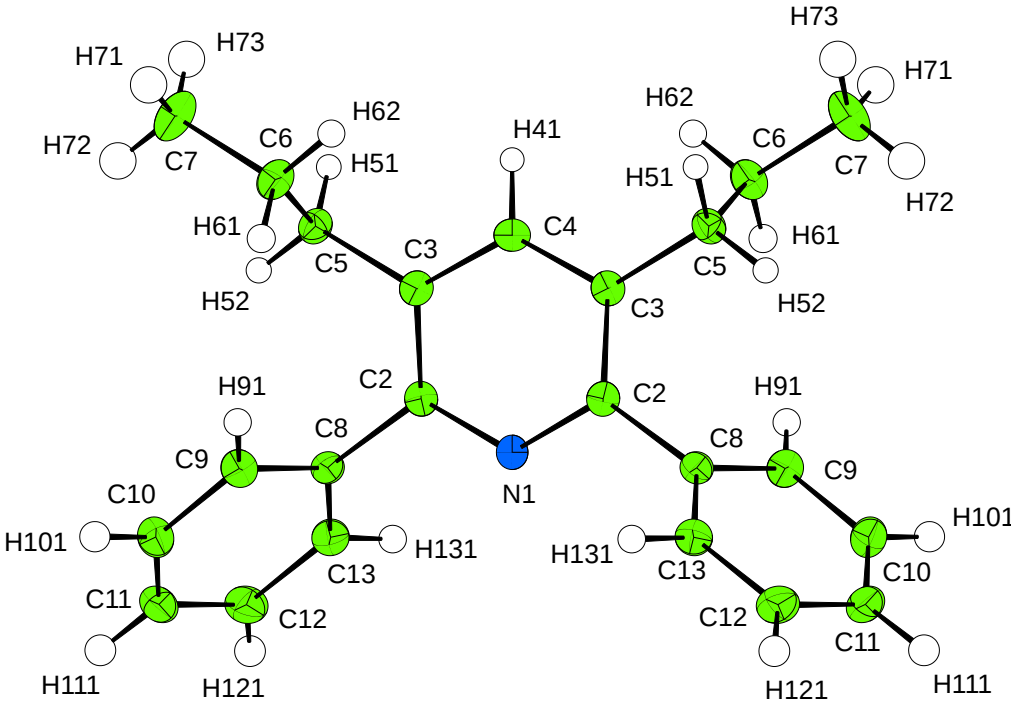
Hydrogen-bond geometry (Å, º)

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
C8—H81···O13^{i}	0.97	2.38	3.245 (2)	149 (1)

Symmetry code: (i) −*x*+1, −*y*+1, −*z*+1.

Appendix 6: X-ray Crystallographic Data for Compound **846**

Single Crystal X-ray diffraction report 2,6-diphenyl-3,5-dipropylpyridine (846)



Crystals of **846** were grown from CH_2Cl_2/Petrol. A single crystal representing the bulk of the sample was selected for the X-ray analysis.

Computing details

Data collection: *COLLECT* (Nonius, 2001).; cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); program(s) used to solve structure: Superflip (Palatinus & Chapuis, 2007); program(s) used to refine structure: *CRYSTALS* (Betteridge *et al*., 2003); molecular graphics: *CAMERON* (Watkin *et al*., 1996); software used to prepare material for publication: *CRYSTALS* (Betteridge *et al*., 2003).

Crystal data

$C_{23}H_{25}N$	$F(000) = 680$
$M_r = 315.46$	$D_x = 1.166$ Mg m^{-3}
Monoclinic, *C*2/*c*	Melting point = 407–409 K
Hall symbol: -C 2yc	Mo *K*α radiation, λ = 0.71073 Å
a = 21.4308 (4) Å	Cell parameters from 2171 reflections
b = 9.6778 (2) Å	θ = 5–27°
c = 8.7060 (2) Å	μ = 0.07 mm^{-1}
β = 95.5141 (8)°	*T* = 150 K
V = 1797.30 (6) Å^3	Plate, clear_pale_colourless
Z = 4	0.4 × 0.2 × 0.15 mm

Data collection

Nonius KappaCCD diffractometer	1774 reflections with $I > 2.0\sigma(I)$
Graphite monochromator	$R_{int} = 0.015$
ω scans	$\theta_{max} = 27.5°$, $\theta_{min} = 5.2°$
Absorption correction: multi-scan *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997)	$h = -27 \rightarrow 27$
$T_{min} = 0.95$, $T_{max} = 0.99$	$k = -12 \rightarrow 10$
19969 measured reflections	$l = -11 \rightarrow 11$
2058 independent reflections	

Refinement

Refinement on F^2	Primary atom site location: Other
Least-squares matrix: full	Hydrogen site location: difference Fourier map
$R[F^2 > 2\sigma(F^2)] = 0.042$	H-atom parameters constrained
	Method, part 1, Chebychev polynomial, (Watkin, 1994, *P*rince, 1982) [*w*eight] = $1.0/[A_0*T_0(x) + A_1*T_1(x) \cdots + A_{n-1}]*T_{n-1}(x)]$
$wR(F^2) = 0.110$	where A_i are the Chebychev coefficients listed below and x = *F* /*F*max Method = Robust Weighting (*P*rince, 1982) W = [*w*eight] * [1-(delta*F*/6*sigma*F*)^2]^2 A_i are: 31.6 51.4 30.4 12.8 3.10
$S = 0.92$	$(\Delta/\sigma)_{max} = 0.001$
2058 reflections	$\Delta\rho_{max} = 0.27$ e Å^{-3}
112 parameters	$\Delta\rho_{min} = -0.21$ e Å^{-3}
4 restraints	

Fractional atomic coordinates and isotropic or equivalent isotropic displacement parameters (Å^2)

	x	*y*	*z*	U_{iso}*/U_{eq}
N1	0.5000	0.74936 (13)	0.7500	0.0196
C2	0.54175 (5)	0.67921 (11)	0.67374 (11)	0.0188
C3	0.54447 (5)	0.53451 (11)	0.67221 (11)	0.0189
C4	0.500000 (7)	0.46480 (15)	0.750000 (7)	0.0194
C5	0.59142 (5)	0.45309 (11)	0.59028 (12)	0.0208
C6	0.64493 (5)	0.39207 (12)	0.69862 (13)	0.0250
C7	0.68969 (6)	0.30881 (15)	0.60981 (16)	0.0362
C8	0.58215 (5)	0.76971 (11)	0.58541 (12)	0.0203
C9	0.64730 (5)	0.77056 (12)	0.61110 (13)	0.0251
C10	0.68268 (6)	0.86049 (13)	0.52948 (15)	0.0298
C11	0.65344 (6)	0.94852 (12)	0.41965 (15)	0.0311
C12	0.58852 (6)	0.94898 (13)	0.39255 (14)	0.0313
C13	0.55313 (5)	0.86066 (12)	0.47601 (13)	0.0256
H41	0.5000	0.3660	0.7500	0.0234*

H52	0.6094	0.5110	0.5104	0.0257*
H51	0.5687	0.3756	0.5342	0.0246*
H61	0.6683	0.4693	0.7552	0.0319*
H62	0.6268	0.3318	0.7762	0.0300*
H71	0.7243	0.2680	0.6791	0.0537*
H72	0.7088	0.3676	0.5331	0.0538*
H73	0.6678	0.2345	0.5524	0.0530*
H91	0.6672	0.7100	0.6875	0.0305*
H101	0.7287	0.8599	0.5518	0.0369*
H111	0.6779	1.0086	0.3614	0.0383*
H121	0.5677	1.0098	0.3179	0.0387*
H131	0.5076	0.8630	0.4590	0.0309*

Atomic displacement parameters (Å^2)

	U^{11}	U^{22}	U^{33}	U^{12}	U^{13}	U^{23}
N1	0.0185 (6)	0.0203 (6)	0.0204 (6)	0.0000	0.0037 (4)	0.0000
C2	0.0181 (5)	0.0208 (5)	0.0174 (5)	0.0000 (4)	0.0009 (4)	0.0009 (4)
C3	0.0189 (5)	0.0209 (5)	0.0167 (4)	0.0007 (4)	0.0004 (4)	−0.0005 (4)
C4	0.0215 (7)	0.0180 (7)	0.0183 (6)	0.0000	−0.0004 (5)	0.0000
C5	0.0222 (5)	0.0216 (5)	0.0190 (5)	0.0018 (4)	0.0040 (4)	−0.0016 (4)
C6	0.0243 (5)	0.0272 (6)	0.0237 (5)	0.0058 (4)	0.0029 (4)	−0.0004 (4)
C7	0.0311 (6)	0.0422 (7)	0.0357 (6)	0.0134 (5)	0.0060 (5)	−0.0055 (6)
C8	0.0233 (5)	0.0178 (5)	0.0206 (5)	−0.0007 (4)	0.0058 (4)	−0.0025 (4)
C9	0.0238 (5)	0.0244 (5)	0.0274 (5)	−0.0011 (4)	0.0041 (4)	0.0007 (4)
C10	0.0261 (5)	0.0280 (6)	0.0365 (6)	−0.0046 (5)	0.0096 (5)	−0.0037 (5)
C11	0.0384 (7)	0.0229 (6)	0.0343 (6)	−0.0055 (5)	0.0161 (5)	−0.0002 (5)
C12	0.0396 (7)	0.0238 (6)	0.0316 (6)	0.0016 (5)	0.0093 (5)	0.0060 (5)
C13	0.0260 (5)	0.0228 (5)	0.0286 (5)	0.0023 (4)	0.0055 (4)	0.0025 (4)

Geometric parameters (Å, º)

N1—C2^{i}	1.3478 (12)	C7—H72	0.994
N1—C2	1.3478 (12)	C7—H73	0.970
C2—C3	1.4016 (15)	C8—C9	1.3927 (15)
C2—C8	1.4953 (14)	C8—C13	1.3981 (15)
C3—C4	1.3951 (12)	C9—C10	1.3931 (16)
C3—C5	1.5100 (14)	C9—H91	0.956
C4—H41	0.956	C10—C11	1.3847 (18)
C5—C6	1.5315 (15)	C10—H101	0.986
C5—H52	0.999	C11—C12	1.3886 (18)
C5—H51	0.996	C11—H111	0.960
C6—C7	1.5198 (15)	C12—C13	1.3928 (16)
C6—H61	1.002	C12—H121	0.955

C6—H62	0.999	C13—H131	0.972
C7—H71	0.993		
$C2^{i}$—N1—C2	119.50 (13)	C6—C7—H72	111.0
N1—C2—C3	122.56 (10)	H71—C7—H72	107.7
N1—C2—C8	113.76 (9)	C6—C7—H73	111.0
C3—C2—C8	123.62 (9)	H71—C7—H73	108.3
C2—C3—C4	116.59 (10)	H72—C7—H73	106.7
C2—C3—C5	123.78 (9)	C2—C8—C9	122.82 (10)
C4—C3—C5	119.62 (10)	C2—C8—C13	118.52 (9)
C3—C4—$C3^{i}$	122.16 (14)	C9—C8—C13	118.63 (10)
C3—C4—H41	118.9	C8—C9—C10	120.54 (11)
$C3^{i}$—C4—H41	118.9	C8—C9—H91	118.8
C3—C5—C6	113.81 (8)	C10—C9—H91	120.7
C3—C5—H52	110.8	C9—C10—C11	120.28 (11)
C6—C5—H52	109.2	C9—C10—H101	118.6
C3—C5—H51	107.9	C11—C10—H101	121.2
C6—C5—H51	108.3	C10—C11—C12	119.92 (11)
H52—C5—H51	106.5	C10—C11—H111	120.2
C5—C6—C7	111.28 (9)	C12—C11—H111	119.9
C5—C6—H61	108.9	C11—C12—C13	119.76 (11)
C7—C6—H61	109.6	C11—C12—H121	120.9
C5—C6—H62	108.9	C13—C12—H121	119.3
C7—C6—H62	109.9	C8—C13—C12	120.86 (11)
H61—C6—H62	108.1	C8—C13—H131	119.5
C6—C7—H71	112.0	C12—C13—H131	119.7

Symmetry code: (i) −*x*+1, *y*, −*z*+3/2.