The Iridium-Catalysed Alkylation of Aromatic Ketones *via* Hydrogen Borrowing

Volume 1

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

University of Oxford

by

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and

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Declaration

I declare that this thesis and the work described herein are entirely my own, except where I have acknowledged help and/or data from a named person, or given reference to a published source.

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Trinity Term, 2018

List of Abbreviations

ATR	Attenuated total reflectance
BBFO	Broadband fluorine observation
BCP	[1.1.1]-Bicyclopentane
BINAP	2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene
BINOL	1,1′-Bi-2-naphthol
BOM	Benzyloxymethyl
COD	1,5-Cyclooctadiene
COSY	Correlated spectroscopy
Cp*	Pentamethylcyclopentadienyl
Cy	Cyclohexyl
Cyp	Cyclopropyl
DEPT	Distortionless enhancement by polarisation transfer
DPEPhos	Bis[(2-diphenylphosphino)phenyl] ether
dppb	1,4-Bis(diphenylphosphino)butane
DPPBz	1,2-Bis(diphenylphosphino)benzene
dppe	1,2-Bis(diphenylphosphino)ethane
dppf	1,1′-Bis(diphenylphosphino)ferrocene
dpph	1,6-Bis(diphenylphosphino)hexane
dppp	1,3-Bis(diphenylphosphino)propane
d.r.	Diastereomeric ratio
e.e.	Enantiomeric excess
e.g.	*exempli gratia* (Latin: for example)
equiv	Equivalent(s)
ESI	Electrospray ionisation
et al.	*et alii* (Latin: and others)
FT	Fourier transform

FWHM	Full width at half-maximum
HESI-II	Heated electrospray ionisation
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear single-quantum correlation spectroscopy
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
Lit.	Literature
M	Molar
m.p.	Melting point
Mes	Mesityl
MPV	Meerwein–Ponndorf–Verley
MS	Mass spectrometry/mass spectra
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
Ph*	Pentamethylphenyl
PMP	*para*-Methoxyphenyl
Pyr	Pyridine
RT	Room temperature
SM	Starting material
t	Time
Temp	Temperature
TOCSY	Total Correlation Spectroscopy
UV/Vis	Ultraviolet/visible light
VCP	Vinylcyclopropane
XantPhos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

The Iridium-Catalysed Alkylation of Aromatic Ketones via Hydrogen Borrowing

A thesis submitted for the degree of Doctor of Philosophy
Choon Boon Cheong
Magdalen College, Trinity Term 2018

Abstract

This dissertation explores how the scope of hydrogen borrowing reactions can be further expanded to use both primary and secondary alcohols to form α-, β- and α,β-branched aryl ketones. *ortho* Substituents were critical in enabling the hydrogen borrowing alkylation by inducing a non-coplanar geometry of the aryl–ketone motif, which provides various beneficial effects that contribute to the success of the reaction.

The versatility of the hydrogen borrowing reaction was further improved by introducing a vinylcyclopropane rearrangement into the reaction manifold prior to enone reduction. Control studies and modified substrate provide insight into the mechanism of the reaction.

The synthetic utility of pentamethylphenyl (Ph*) ketones was enhanced through electrophilic cleavage to form various carboxylic acid derivatives. Phenol derivatives of Ph* ketones were also found to undergo a related oxidative cleavage of the derivatised Ph* group to form esters and carboxylic acids.

Phenol and aniline derivatives of Ph* ketones formed tetrasubstituted α-keto centres in the hydrogen borrowing reaction, a remarkable result that could not have been possible using conventional aldol chemistry. Attempts were made to explore the formation of tetrasubstituted α-keto centres in the hydrogen borrowing reaction with other aryl ketone derivatives.

Structural changes were observed by X-ray crystallography that were consistent with the alleviation of steric interactions between the aryl group and ketone substituent, providing evidence that *ortho*-substitution provides multiple benefits that drive the hydrogen borrowing reaction. Substituents at the *meta* and *para* positions of the aryl ring result in structural distortions that are directly responsible for the "buttressing" effect. IR, ^{13}C and ^{15}N NMR spectroscopy were also employed to study the effects of non-coplanar geometries of the amino, nitro and carbonyl groups.

Chapter 1. The *ortho* Effect

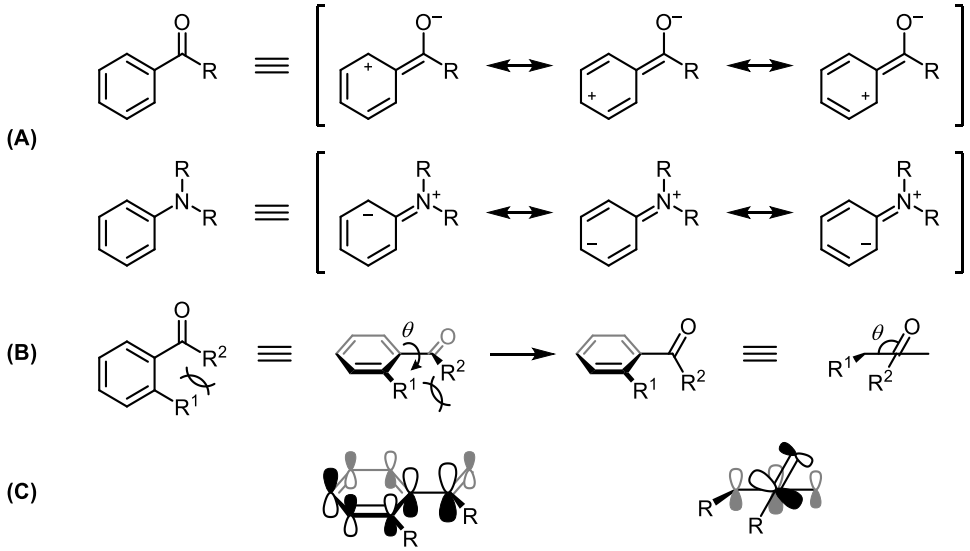
The *ortho* effect is a manifestation of anomalous reactivity as well as physical or chemical properties of *ortho*-substituted aryl compounds that deviate from expected trends when compared to their *meta*-, *para*- or unsubstituted counterparts. The *ortho* effect has been extensively studied over the past century through experimentation as well as using analytical techniques such as UV-vis, NMR and IR spectroscopy. This introductory chapter will very briefly highlight notable aspects of the *ortho* effect.

1.1 The Steric Inhibition of Resonance

When two groups exist in spatial proximity, they experience electrostatic repulsion from each other due to the local electron density of each group. For an aromatic ring with two substituents, the steric interaction between them would be greatest if the groups are adjacent to each other (Scheme 1.1). To minimise this steric interaction, the substituents could distort and move away from each other, a highly unfavourable process. However, if either or both groups could undergo a bond rotation, then the steric interaction would be minimised and the substituent would prefer to exist in a rotated conformation. If these substituents are planar, then upon rotation the plane of these groups will form a torsional or dihedral angle θ with the plane of the aromatic ring. The degree of steric interaction, and therefore the average value of θ, would be dependent on the size of both groups.[1]

Many substituents can experience favourable mesomeric interactions with the aryl ring, which results in changes in the electronic character of both the aromatic system and the substituent. The pre-requisite for conjugation is the coplanarity of the substituent and the aromatic ring, as the *p* or π-orbitals on the substituent must be in a coplanar geometry to form bonding interactions with the aromatic π-system. The introduction of *ortho*

substituents can result in a loss of coplanarity as just described, and this interaction is weakened or lost altogether. This steric inhibition of resonance, also known as the steric inhibition of conjugation, is the basis of the *ortho* effect.



Scheme 1.1 *(A) Substituents bearing p or π-orbitals can be conjugated with the aromatic π-system, which affects the electron density of both the aromatic ring as well as the substituent itself. (B) The presence of one or more ortho substituent introduces steric interactions that induce a rotation to give a non-coplanar geometry with a torsional or dihedral angle of θ. (C) The coplanar geometry of both the substituent and the aromatic ring is a geometrical requirement for conjugation to enable constructive overlap between the orbitals, but a less or non-coplanar geometry significantly reduces or negates this interaction.*

1.2 The Acidity and Basicity of Aromatic Acids and Bases

The increased acidity of *ortho*-substituted benzoic acids over their *meta*- or *para*-counterparts is one of the most characteristic features of the *ortho* effect and is well-studied in literature.[2–4] The wide availability of pK_a data in the literature, such as the exhaustive list by Jover et al.,[5] facilitates the comparison between the different substituents and substitution pattern of the benzoic acids in several solvents. The di-*ortho*-substituted benzoic acids were particularly acidic (Table 1.1), and this increased acidity is thought to arise from a combination of substituent electronic effects, steric inhibition of resonance as well as intramolecular hydrogen bonding.

Substituents	pK_a Value		
	H_2O	MeOH	DMSO
H	4.21	9.41	11.00
4-Me	4.38	9.61	11.42
3-Me	4.24	9.47	-
2-Me	3.91	9.31	11.07
2,6-Me	3.25	8.57	10.68
4-OMe	4.25	9.79	11.80
3-OMe	4.12	9.30	11.10
2-OMe	4.09	9.26	-
2,6-OMe	3.44	8.57	11.29
4-OH	4.55	9.99	-
3-OH	4.03	9.58	-
2-OH	2.77	7.92	-
2,6-OH	1.22	-	-
4-NO_2	3.43	8.36	9.04
3-NO_2	3.46	8.32	9.17
2-NO_2	2.19	7.59	8.18
2,6-NO_2	1.14	6.49	6.72
4-Ac	3.74	8.84	-
3-Ac	3.83	8.87	10.22
2-Ac	4.13	9.28	-

Substituents	pK_a Value		
	H_2O	MeOH	DMSO
H	4.21	9.41	11.00
4-F	4.15	9.23	-
3-F	3.88	8.87	-
2-F	3.57	8.41	-
2,6-F	-	7.39	8.59
4-Cl	4.00	9.09	10.10
3-Cl	3.80	8.83	9.51
2-Cl	2.92	8.31	9.16
2,6-Cl	1.82	7.26	8.31
4-Br	3.99	8.93	10.20
3-Br	3.81	8.80	9.68
2-Br	2.85	8.19	9.57
2,6-Br	-	7.14	8.61
4-I	3.98	9.04	-
3-I	3.82	8.89	10.16
2-I	2.96	8.24	9.90
2,6-I	-	7.29	8.75
4-CN	3.53	8.49	9.27
3-CN	3.60	8.53	9.44
2-CN	3.08	8.15	-

Table 1.1 *pK_a values of various benzoic acids in H_2O, MeOH or DMSO. Smaller values correspond to stronger acids. The di-ortho-substituted benzoic acids have significantly lower pK_as than expected.*

The *ortho* effect does not directly affect the pK_a value of phenols, but instead it results in steric inhibition of resonance for some mesomeric substituents that lead to a diminished electron-withdrawing effect (Table 1.2).[6,7] Having two methyl substituents *ortho* or *meta* to the phenol increased the pK_a due to their electron-donating nature, with a slightly greater effect for the *ortho*-methyl case due to steric interactions between the flanking methyl groups and the solvating molecules around the phenol. The linear cyano group was not significantly affected by the methyl substituents, but when the nitro group was flanked by methyl groups the phenol became less acidic, suggesting that a steric inhibition of resonance was at play.

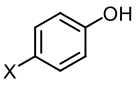
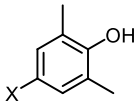
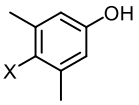
X	pK_a Value (H_2O)		
			
H	9.99	10.58	10.18
CN	7.95	8.27	8.21
NO_2	7.16	7.22	8.25

Table 1.2 *pK_a values of various phenol derivatives in H_2O.*

There are also many experimental pK_a studies of anilines in literature.[8–13] In this case, the effect of *ortho* substitution on the pK_a values of anilines was dependent on the degree of *N*-substitution (Table 1.3). If the amine is mono- or unsubstituted, then the presence of an *ortho* substituent resulted in a decrease in basicity. However, for the case of *N*,*N*-dimethylanilines, the presence of an *ortho* substituent led to an increase in basicity, but the introduction of a second *ortho* substituent resulted in a significant *decrease* in basicity (Table 1.4). The unusual divergence in the effect of *ortho* substituents is attributed to a significant size-dependent steric interaction that disfavours protonation of the nitrogen, but at the same time exhibiting steric inhibition of resonance.

Solvent	pK_aH Value					
	H_2O			30% EtOH	50% EtOH	
Substituents	NH_2	NHMe	NMe_2	NMe_2	NH_2	NMe_2
H	4.62	4.85	5.06	4.76	4.25	4.26
4-Me	5.12	5.33	5.50	5.29	-	4.77
3-Me	4.69	4.94	5.24	4.86	-	-
2-Me	4.39	4.59	5.86	5.42	3.98	5.07
2-*t*-Bu	3.78	-	-	-	-	4.32
4-OMe	5.29	-	-	-	-	5.16
3-OMe	4.20	-	-	-	-	-
2-OMe	4.49	-	-	-	-	5.49

Table 1.3 *pK_aH values of various anilines with one aryl substituent. Smaller values correspond to stronger acids, and therefore larger values correspond to stronger bases. See text for references.*

Aryl substituents	pK_aH Value (50% aq. EtOH)	
	NH_2	NMe_2
3,5-Me	4.48	4.48
2,4-Me	4.61	5.28
2,5-Me	4.17	5.19
2,6-Me	3.42	4.69

Table 1.4 *pK_aH values of various methyl-substituted arenes with a Group V substituent. Smaller values correspond to stronger acids, and therefore larger values correspond to stronger bases.*[11]

Interestingly, the *N*,*N*-dimethylphosphine analogue behaved similarly to the anilines, with the mesitylphosphine being a surprisingly much stronger base than the anilines (Table 1.5). However, the mesitylarsine derivative was a much weaker base than the phosphine or the aniline counterpart.

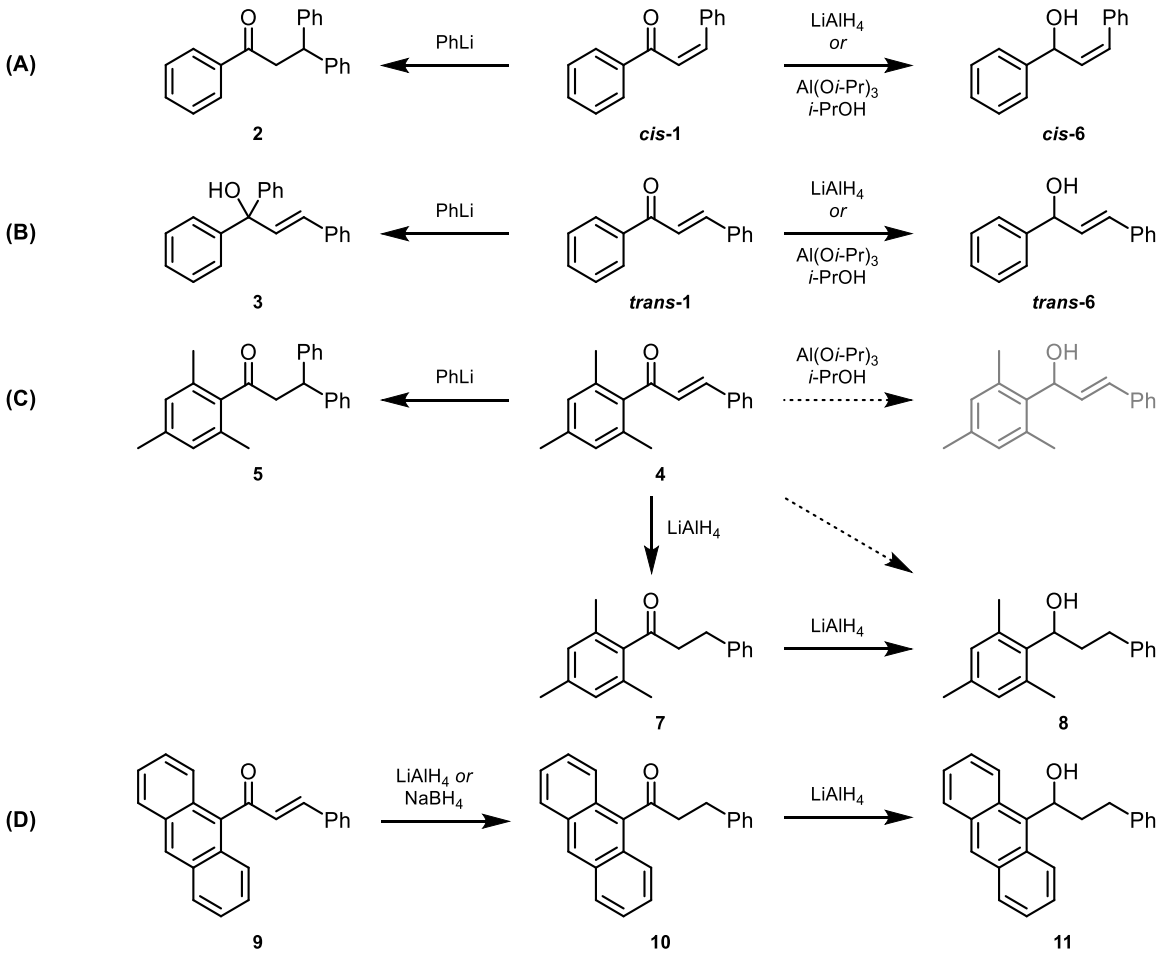
Aryl substituent(s)	pK_aH Value (50% aq. EtOH)		
	NMe_2	PMe_2	$AsMe_2$
H	4.26	4.32	< 2[a]
4-Me	4.77	4.66	-
2,5-Me	4.17	4.40	-
2,4,6-Me	5.15	6.51	2.11

Table 1.5 *pK_aH values of various methyl-substituted arenes with a Group V substituent. Smaller values correspond to stronger acids, and therefore larger values correspond to stronger bases. [a]The arsine was too weakly basic for accurate measurement of pK_aH by titration with dilute HCl.*[9]

1.3 Nucleophilic Reactions of Aromatic Ketones and Enones

The presence of two *ortho* substituents on the aromatic ring has a profound effect on the reduction of aryl enones and ketones.[14] Lutz and Weiss observed that *cis*-chalcone *cis*-**1** gave predominantly the 1,4-addition product **2** with phenyllithium while *trans*-chalcone *trans*-**1** gave predominantly the 1,2-addition product **3**, but *trans*-mesityl enone **4** gave the 1,4-addition product **5** exclusively (Scheme 1.2). The reductions of these enones were also particularly interesting. The Meerwein–Ponndorf–Verley (MPV) reduction of the chalcones *cis*-**1** and *trans*-**1** afforded the allylic alcohols *cis*-**6** and *trans*-**6** respectively with

the olefin geometries unchanged. The *cis*-chalcone *cis*-**1** required a longer reaction time than *trans*-chalcone *trans*-**1** while mesityl enone **4** was unreactive, suggesting that sterics was slowing down or altogether preventing the reduction of the carbonyl group. When $LiAlH_4$ was used as the reducing agent, both chalcones *cis*-**1** and *trans*-**1** also formed their corresponding allylic alcohols *cis*-**6** and *trans*-**6** respectively. However, mesityl enone **4** underwent a 1,4-reduction to give the mesityl ketone **7** instead with no trace of any benzylic alcohol, although mesityl ketone **7** itself could be reduced to the benzylic alcohol **8** when resubjected to $LiAlH_4$. Similarly, the 9-anthracenyl enone **9** underwent 1,4-reduction to give ketone **10**, which could only be reduced by strong reducing agents to give alcohol **11**.[15]

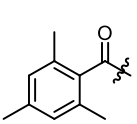
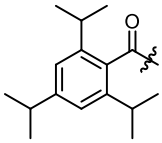


Scheme 1.2 *Differences in reactivity towards nucleophilic reagents for (A) cis-chalcone cis-**1**, (B) trans-chalcone trans-**1**, (C) trans-mesityl enone **4**, and (D) 9-anthracenyl enone **9**.*

Lutz and Weiss suggested that steric interactions from both the di-*ortho*-methyl substituents and from the styrene phenyl group played a significant role in the reaction rates and outcomes.[14] Williams suggested that the *peri*-hydrogens were responsible for restricting free rotation about the carbonyl group, as well as hindering nucleophilic attack along the "π-axis of the carbonyl carbon", now more accurately known as the Bürgi–Dünitz trajectory.[15–17] Similar studies about the effects of *ortho* substitution on the rates of alkaline hydrolysis of benzoate esters and formanilides are also found in literature.[18–20]

1.4 The Rotational Barrier about the Aryl–Carbonyl Ketone Bond

A key part of the steric interaction between the *ortho* substituents and the carbonyl substituents is the relative size of these groups. Although many studies focus on the aryl substituents, largely to amass data for the calculation of stereoelectronic parameters of these groups, for the consideration of the *ortho* effect it is equally important to consider the ketone substituent. Casarini et al. undertook this aspect of the study to provide valuable data on the Gibbs free energy of activation for the enantiotopomerisation of aryl ketones (Table 1.6).[21] This was made possible with the use of Pirkle's alcohol to create a chiral environment, or through prochiral motifs such as the isopropyl group that obviates the need for a chiral environment.[22] The data can be interpreted in part as the barrier of rotation about the aryl–CO bond, and therefore reflect the conformational preference of these compounds for a non-coplanar geometry.

Ketone substituent	ΔG* (kcal mol^{-1})	
		
	(1.9)[a]	(2.75)[a]
	6.1	12.2
	7.2	13.5
	9.1	14.9
	19.2	24.1[b]
	10.6	16.4

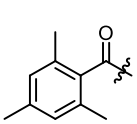
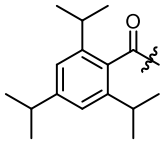
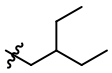
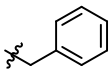
Ketone substituent	ΔG* (kcal mol^{-1})	
		
	7.2	13.5
	9.1	14.9
	-	14.2
	-	13.9
	9.0	14.8
	-	13.7

Table 1.6 *Gibbs free energy of activation (ΔG*) for the enantiotopomerisation of various aryl ketones.* [a]*Calculated values were based on molecular mechanics (MMPI). The lowest energy structure of mesitylaldehyde was predicted to be planar, while the triisopropyl analogue was predicted to have an orthogonal conformation;* [b]*The value was extrapolated due to experimental limitations.*[22]

The triisopropylphenyl compounds have significantly higher activation energies compared to their mesityl counterparts, indicating a very large steric interaction that is associated with the size of the *ortho* substituent. Larger ketone substituents lead to rapidly increasing barriers, with the degree of substitution at the α-keto carbon having the most significant effect. Moving the steric bulk one carbon away leads to a decrease in activation energy, and for the case of the *tert*-butyl substituent the effect was particularly dramatic.

1.5 The Aryl–Substituent Dihedral Angle

Amongst the extraordinary efforts undertaken to investigate the effects of substituents on the aromatic systems,[23] there is a significant number of reports that studied the *ortho* effect and attempted to measure the dihedral angle θ about the aryl–carbonyl motif.[24–26] These

attempts employed analytical methods such an NMR and IR spectroscopy, X-ray diffractometry, as well as *ab initio* calculations.

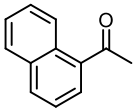
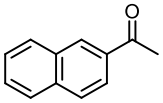
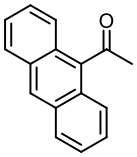
Aryl substituents	^{17}O NMR δ (ppm)		Dihedral Angle θ (°)
	δ (ppm)	Δδ (ppm)	
H	552	0	1
2-Me	582	30	27
4-Me	546	–6	1
2,4-Me	576	24	27
2,5-Me	582	30	26
3,4-Me	545	–7	1
2,4,5-Me	575	23	26
2,4,6-Me	601	49	57
2,3,5,6-Me	607	55	82
2,4,6-*i*-Pr	596	44	63
	585	33	38
	553	1	2
	613	61	69

Table 1.7 *^{17}O NMR chemical shift values for the carbonyl oxygen atom of various acetophenones and related compounds, as well as the dihedral angle θ derived from the data.*[27]

Oakley and Boykin employed ^{17}O NMR to study the impact of *ortho* substituents on the chemical shift values of the carbonyl oxygen atom in acetophenones (Table 1.7),[27] while Dhami and Stothers investigated the ^{13}C chemical shift of the carbonyl carbon atom for a broad range of acetophenones (Table 1.8).[28]

Aryl substituent(s)	^{13}C NMR Δδ (ppm)	Dihedral Angle θ (°)
H	0	-
2-Me	3.3	24
3-Me	–0.5	-
4-Me	0	-
2,3-Me	4.6	29
2,4-Me	2.6	21
2,5-Me	2.5	21
2,6-Me	9.7	44
2,4,5-Me	2.3	20
2,4,6-Me	10.2	46
2,3,4,6-Me	10.3	46
2,3,5,6-Me	11.0	48
2,3,4,5,6-Me	10.9	48

Aryl substituent(s)	^{13}C NMR Δδ (ppm)	Dihedral Angle θ (°)
H	0	-
2-Et	3.7	25
2,6-Et	9.8	44
2-*i*-Pr	4.8	29
2,6-*i*-Pr	10.3	46
2,4,6-*i*-Pr	10.6	47
2,5-*t*-Bu	12.0	51
2-Ph	6.4	34
2-OMe	1.8	17
2-Cl	2.7	22
2-Br	3.3	24
2-I	4.8	29
2-NO_2	2.3	20

Table 1.8 *^{13}C NMR chemical shift values for the carbonyl carbon atom of various acetophenones, as well as the dihedral angle θ derived from the data.*[28]

Both ^{13}C and ^{17}O NMR studies revealed that alkyl and heteroatom *ortho* substituents resulted in significant increases to the chemical shifts of the carbon and oxygen atoms on the aryl carbonyl group compared to their *meta*- or *para*- counterparts. These were translated to significantly large values for θ, clearly indicating their non-coplanar geometry. Compounds with two alkyl *ortho* substituents displayed a dramatic increase in chemical shifts and dihedral angles, which highlights their preference for a non-coplanar geometry.

Fiedler and Exner also studied the impact of the *ortho* effect on the IR stretching frequencies of acetophenones and methyl benzoates (Table 1.9).[29] The preference for a non-coplanar geometry is greatest when two *ortho* substituents were present, but there was negligible effect from only one *ortho* substituent. Compared with the results from the ^{13}C and ^{17}O NMR studies, the conclusions derived from the IR stretches only corroborate for the di-*ortho*-substituted compounds. In addition, there is significant discrepancy between the dihedral angles obtained from both NMR studies, which prompted a comment from Fiedler and Exner that many of the literature values for θ "are not reliable".

Aryl substituent(s)	$\nu_{C=O}$ (cm^{-1})		^{13}C NMR		^{17}O NMR	
	$COCH_3$	$COOCH_3$	Δδ (ppm)	θ (°)	Δδ (ppm)	θ (°)
-	1690.6	1728.1	0	-	0	1
2-Me	1688.6	1726.4	3.3	24	30	27
3-Me	1689.1	1726.2	–0.5	-	-	-
4-Me	1686.6	1726.1	3.3	-	–6	1
2,3-Me	1691.6	1726.6	4.6	29	-	-
2,4-Me	1684.0	1724.4	2.6	21	24	27
2,5-Me	1686.3	1726.2	2.5	21	30	26
2,6-Me	**1706.8**	**1733.0**	**9.7**	**44**	**-**	**-**
3,4-Me	1685.9	1724.3	-	-	–7	1
3,5-Me	1686.2	1725.6	-	-	-	-
2,3,4-Me	1686.5	1724.0	-	-	-	-
2,4,6-Me	**1703.3**	**1730.7**	**10.2**	**46**	**49**	**57**
3,4,5-Me	1686.4	1722.9	-	-	-	-
2,3,5,6-Me	**1704.0**	**1733**	**11.0**	**48**	**55**	**82**

Table 1.9 *IR stretching frequencies of the C=O bond for methyl-substituted acetophenones and methyl benzoates. Numbers in bold are the only data points from IR spectroscopy that give any clear indication of an ortho effect.[29] Relevant data from Tables 1.7 and 1.8 are included for convenience of comparison.*

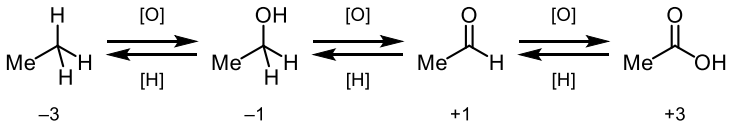
1.6 Conclusion

There remain some unresolved issues with the dihedral angles reported in literature, such as the incongruence of the various observed spectral data and the dihedral angles θ derived from them. Fiedler and Exner suggested that it is more realistic to classify the associated compounds into two groups, “planar” and “non-planar”. Nevertheless, the *ortho* effect is very real, given the significant impact on the reactivity and chemical properties of these *ortho*-substituted aromatic compounds. In this dissertation, the *ortho* effect plays a very significant role in the hydrogen borrowing reactions being developed. In Chapter 7, the analytical data obtained from the compounds synthesised throughout the course of this dissertation work are assembled and studied to verify the presence of the *ortho* effect and elucidate its role in the reactions.

Chapter 2. The Hydrogen Borrowing Reaction

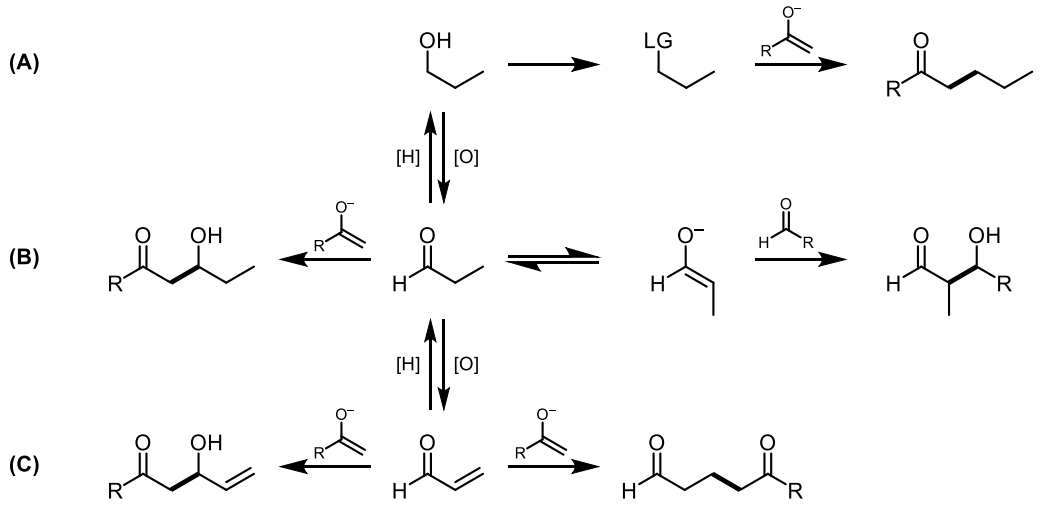
2.1 Oxidation and Reduction Reactions in Organic Chemistry

In organic chemistry, oxidation and reduction reactions typically involve the change in oxidation state of a carbon atom. An oxidation reaction increases the number of (bonds to) more electronegative atoms such as oxygen on the carbon centre, while a reduction process increases the number of more electropositive atoms such as hydrogen (Scheme 2.1).



Scheme 2.1 *Oxidation and reduction reactions alter the oxidation state of the carbon centre by varying the number of bonds between electronegative and electropositive atoms.*

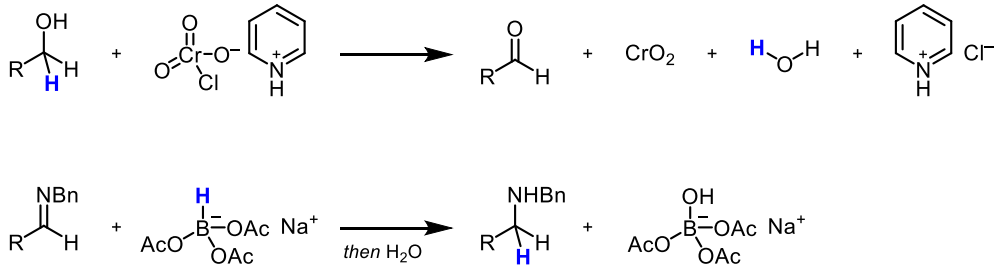
Oxidations and reductions allow an organic chemist to manipulate the electronics of functional groups to control their reactivity for bond formation (Scheme 2.2). For example, an alcohol group can be suitably modified to become a leaving group, which is susceptible to nucleophilic attack from an enolate to form a C–C bond. The oxidation of an alcohol to a ketone enables nucleophilic attack on the carbonyl group. At the same time, the α-keto protons also become more acidic, and deprotonation gives rise to a nucleophilic carbon centre in the form of an enolate. i.e. the adjacent carbon is now activated towards electrophilic attack. Further oxidation results in an α,β-unsaturated ketone, which has two electron-deficient centres that are both susceptible to nucleophilic attack. The judicious use of oxidation and reduction reactions will provide the desired reactivity of the precursors to achieve a desired synthetic outcome.



Scheme 2.2 *Oxidation and reduction reactions alter the reactivity of carbon centres that enable the formation of a wide variety of products.*

2.2 Methods for Oxidation and Reduction

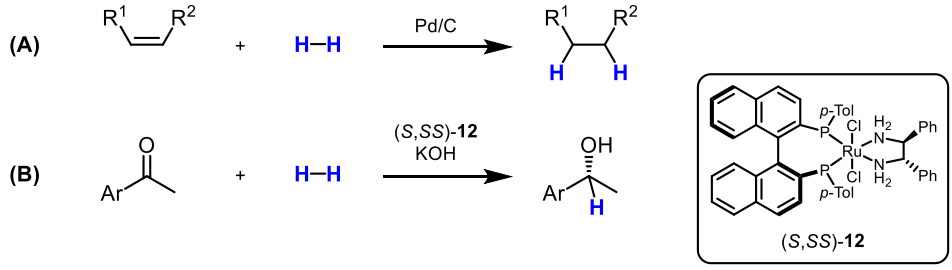
There are innumerable number of methods to achieve oxidation and reduction for all kinds of functional groups, with many reviews and books being published on this aspect of organic chemistry.[30] For example, oxidation and reduction reactions can be achieved with the use of stoichiometric reagents such as pyridinium chlorochromate (PCC) or $NaBH(OAc)_3$ for the formation or reduction of aldehydes and its derivatives (Scheme 2.3).



Scheme 2.3 *Oxidation and reduction reactions with stoichiometric reagents such as PCC and $NaBH(OAc)_3$ respectively.*

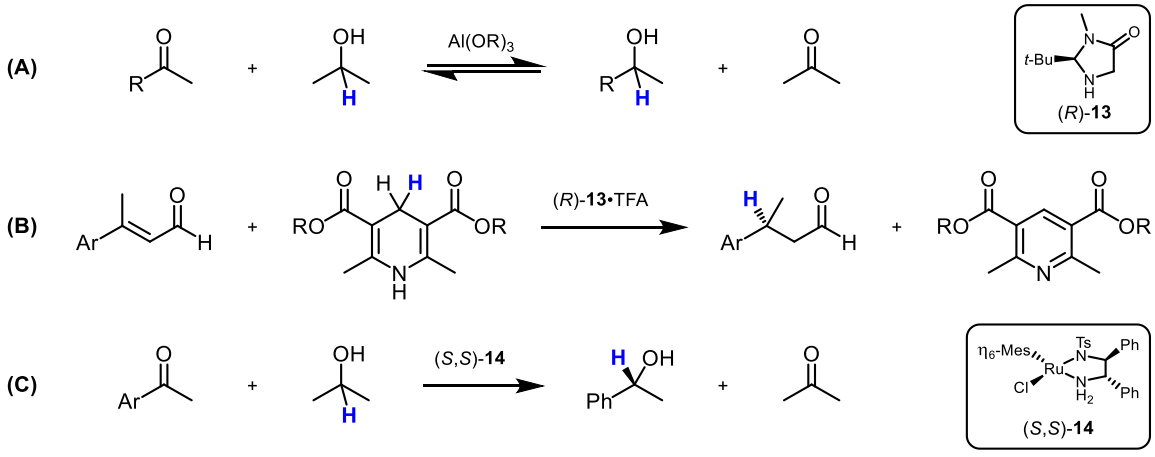
The use of stoichiometric reducing agents such as $NaBH(OAc)_3$ suffers from the generation of stoichiometric waste products as well as an extremely poor mass efficiency, with $NaBH(OAc)_3$ having a molecular mass of 212 that delivers a hydride (molecular mass of 1). The ideal reducing agent with perfect atom economy is H_2 gas, which is used with

heterogeneous catalysts such as palladium on carbon, or with homogeneous catalysts such as those employed in the Noyori asymmetric hydrogenation (Scheme 2.4).[31,32]



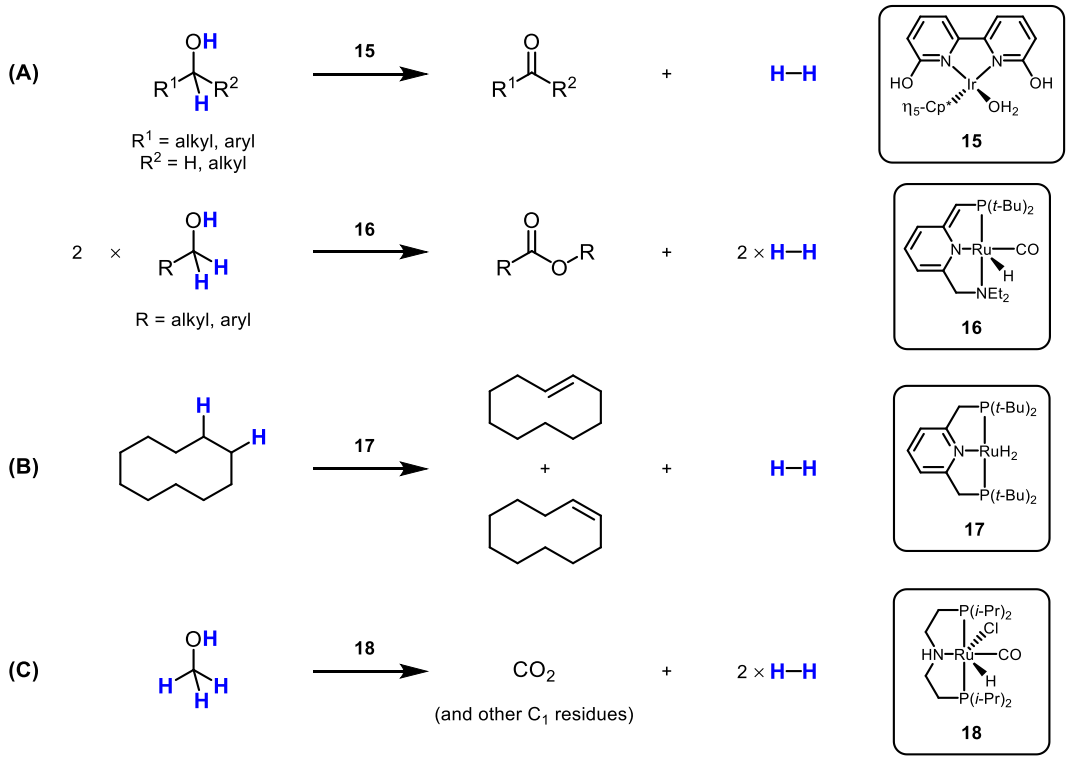
Scheme 2.4 *(A) Heterogeneous catalytic hydrogenation of alkenes to alkanes with Pd/C, and (B) Noyori asymmetric reduction of ketones to secondary alcohols with a chiral homogeneous catalyst.*[31]

There are some technical difficulties associated with the use of H_2 gas, such as the need for high-pressure vessels and gas-handling equipment. A suitable compromise between efficiency, cost and waste generation is transfer hydrogenation, which is an Oppenauer oxidation/MPV reduction-type process (see also Section 1.3, Scheme 1.2). The Oppenauer oxidation/MPV reduction reactions use aluminium alkoxides to effect the transformations, whereas transfer hydrogenation employ organocatalysts or transition metal catalysts with the potential for asymmetric reduction (Scheme 2.5).[31–36]



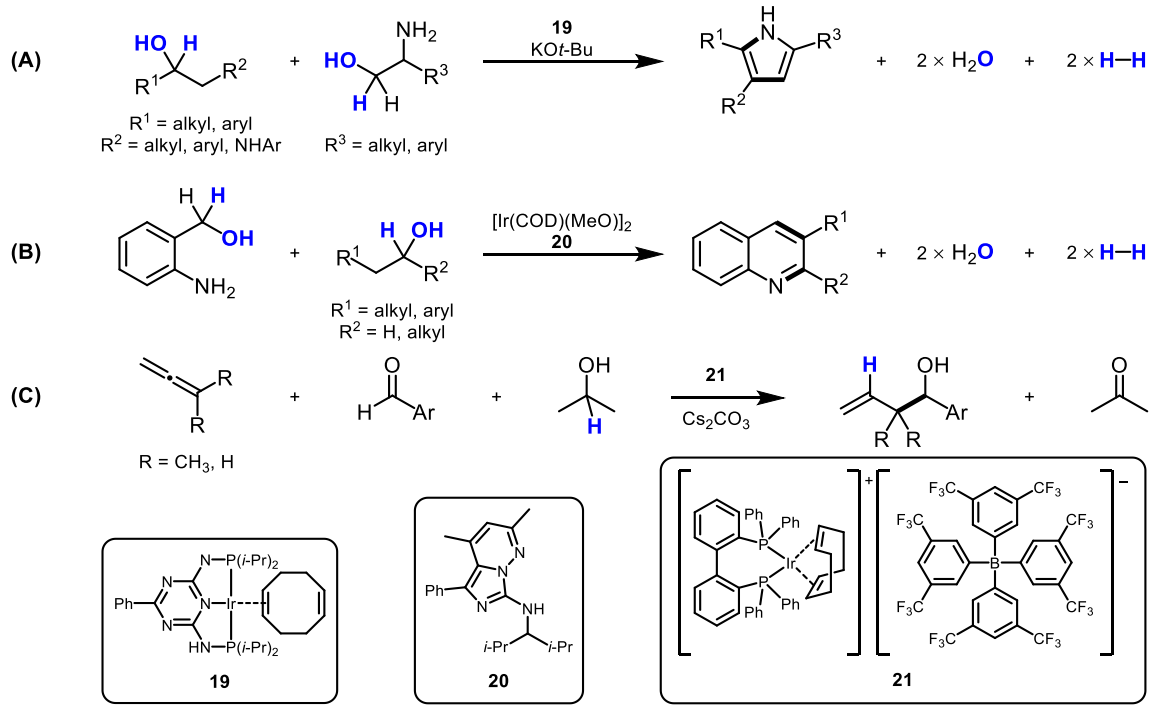
Scheme 2.5 *(A) Oppenauer oxidation/MPV reduction with acetone or isopropanol mediated by aluminium alkoxides. Examples of (B) chiral organocatalysts and (C) chiral transition metal catalysts for the asymmetric reduction of enals and ketones respectively.*

Compared to the catalytic reduction of alkenes, the oxidation of alkanes to alkenes is very difficult due to a lack of any significant dipoles for nucleophilic or electrophilic attack, as well as issues with chemoselectivity. This form of oxidation, also known as acceptorless dehydrogenation (or simply, dehydrogenation), would be highly atom-economical and would generate far less waste as no stoichiometric oxidant is used, with only H_2 being formed as the sole byproduct. The acceptorless dehydrogenation has been used to form aldehydes, ketones and esters from alcohols, as well as alkenes from alkane dehydrogenation (Scheme 2.6).[37–40] This system has also been used to directly oxidise aqueous methanol in the presence of base to give H_2 and CO_2, which could lend itself to clean energy applications of hydrogen storage and generation.[41]



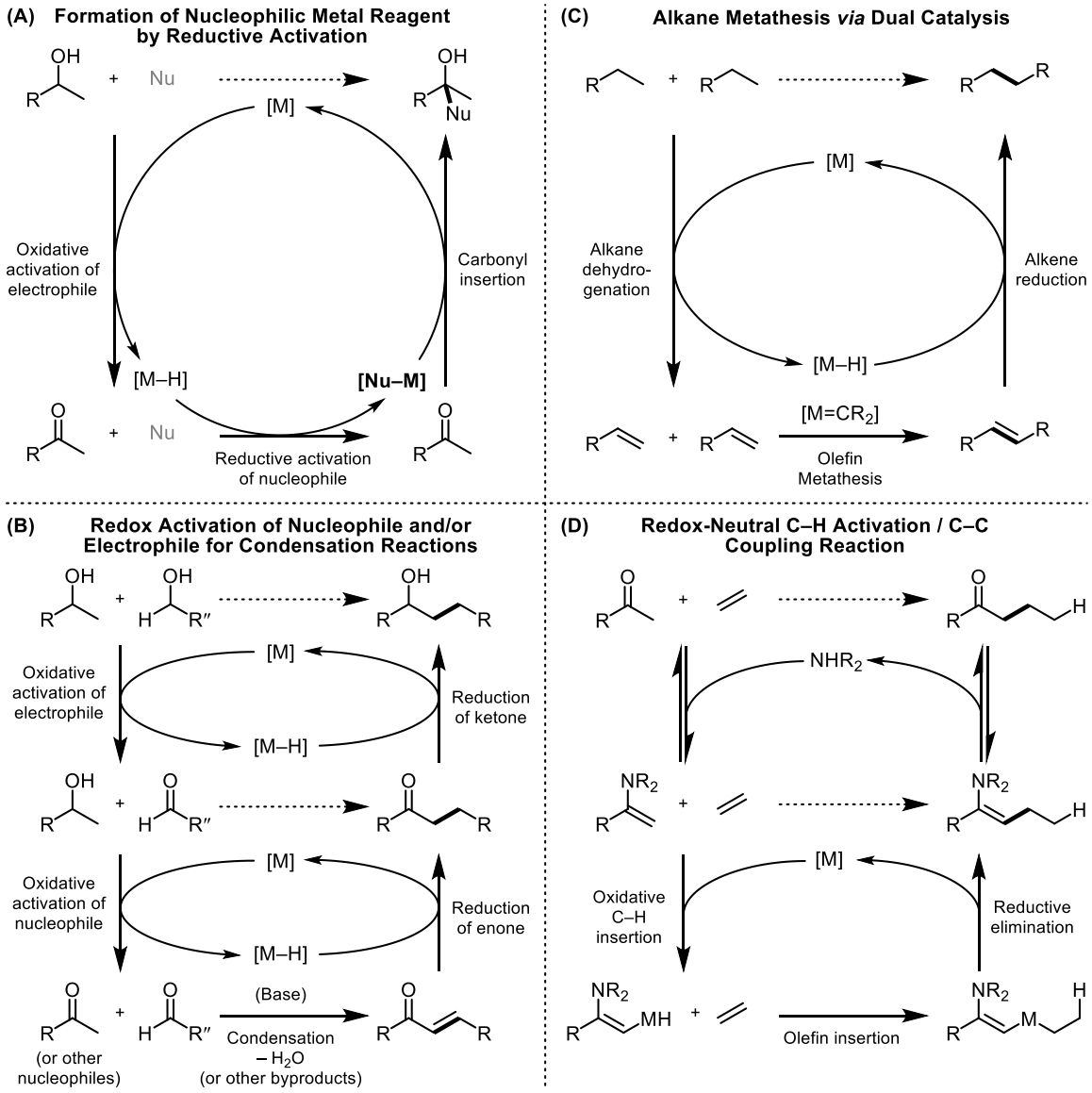
Scheme 2.6 *(A) Acceptorless dehydrogenation reaction of alcohols to give aldehydes, ketones and esters. (B) Alkane dehydrogenation to give alkenes and aromatic compounds. (C) Acceptorless dehydrogenation of methanol as a method for generating H_2 gas. See text for references.*

The acceptorless dehydrogenation and transfer hydrogenation reactions can also be involved in C–C and C–N bond formations to give heterocycles and homoallylic alcohols (Scheme 2.7). For example, the oxidation process activates the alcohols to form reactive aldehyde or ketone electrophiles and enolate nucleophiles, enabling aldol and Mannich-type condensation reactions to occur.[39,42–44] The reduction process could also activate an olefinic species to give an allylic nucleophile that subsequently attacks a carbonyl electrophile to give an alcohol product.[45–48] The reductive activation of the olefin can also employ H_2 as the reductant and allyl acetates as the precursor for the allylic nucleophile.



Scheme 2.7 *C–C and C–N bond formation can also be incorporated into acceptorless dehydrogenation and transfer hydrogenation reactions to give (A) pyrroles, (B) quinolines and (C) homoallylic alcohols. See text for references.*

2.3 Combining Oxidation and Reduction into a Reaction Sequence – Redox-Neutral C–C and C–N Coupling Reactions



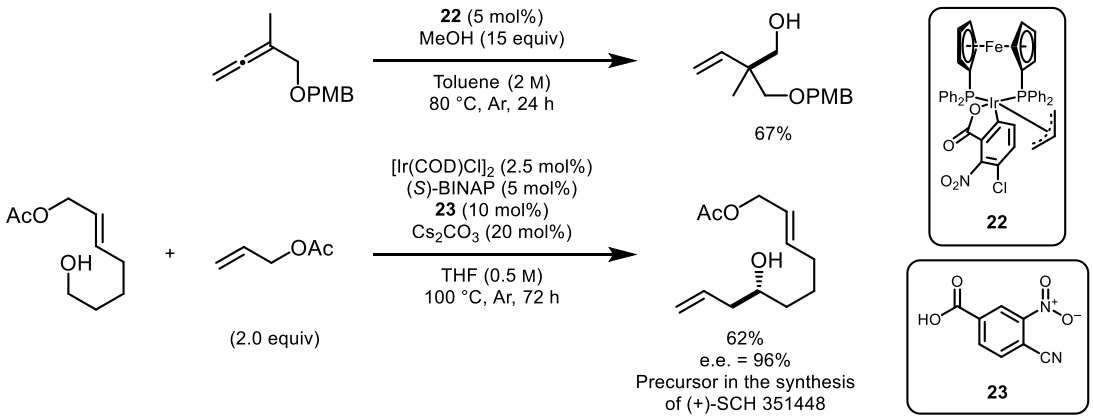
Scheme 2.8 *Redox-neutral C–C and C–N coupling reactions, also known as hydrogen borrowing or hydrogen autotransfer reactions, occur through the formation of a metal hydride intermediate. Reactions involved in (B) may also proceed directly via the intermediates with only one catalytic cycle taking place.*

The acceptorless dehydrogenation, C–C/N bond coupling and transfer hydrogenation processes can be further combined into a single reaction sequence, known as a hydrogen borrowing or hydrogen autotransfer reaction (Scheme 2.8). A nucleophile and/or electrophile could be activated in catalytic quantities by oxidising or "borrowing" the hydrogen from one precursor, forming a metal hydride intermediate. The metal hydride

species bearing the "borrowed" hydrogen could then either activate an olefin pro-nucleophile to enable C–C/N bond coupling, or reduce the π-bond formed after condensation between the nucleophile and electrophile, thereby "returning" the hydrogen. Other forms of redox-neutral C–C coupling reactions include alkane metathesis *via* dual catalysis, as well as olefin insertion *via* C–H activation. The hydrogen borrowing process would therefore represent a perfect hydrogen economy that does not evolve H_2 or require any additional hydrogen/hydride source.

2.3.1 Redox-Neutral Allylations of Ketones and Aldehydes

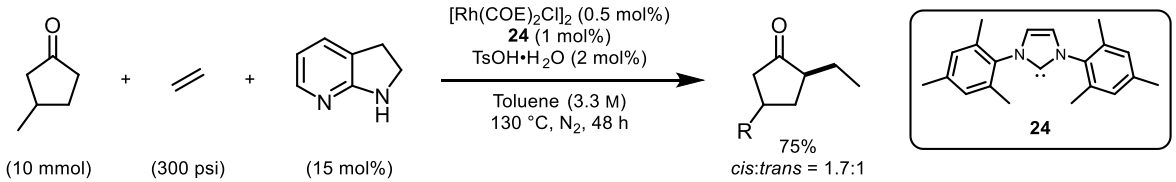
It was previously shown that the nucleophilic allyl species can be generated by activation of an allene through transfer hydrogenation (see Scheme 2.7). The Krische group has further improved this methodology by obviating the need for an additional reductant, with the alcohol substrate serving both as the precursor for the electrophile and as a hydrogen source for the activation of the allene. This was demonstrated by the reaction of allenes with methanol as the electrophilic precursor that forms formaldehyde *in situ* (Scheme 2.9).[49] The reaction can also be performed asymmetrically with allyl acetates as the precursor for the nucleophilic allyl species. This methodology was applied in the total synthesis of (+)-SCH 351448 to establish a stereocentre of an early-stage precursor in excellent enantioselectivity.[47,50] A similar reaction using an alkyne as the olefinic partner was also described by Obora et al.[51]



Scheme 2.9 *Synthesis of homoallylic alcohols from allenes or allyl acetates and alcohols.*

2.3.2 Redox–Neutral C–H Activation

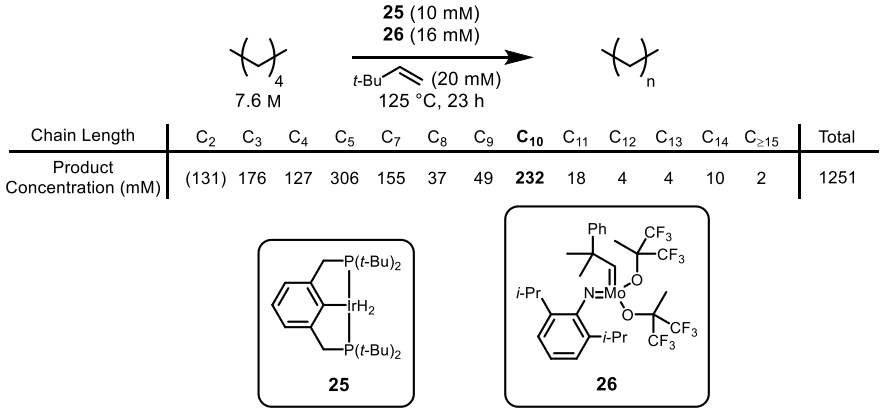
C–H activation typically requires an oxidant to re-oxidise the metal hydride species to regenerate the catalyst. Mo and Dong reported the redox-neutral α-alkylation of ketones with an olefin through C–H insertion into an enamine that is formed *in situ* (Scheme 2.10).[52] The metal hydride is consumed by olefin insertion, and the metal catalyst is regenerated through reductive elimination, thereby obviating the need for an oxidant and rendering the reaction redox-neutral. This reaction makes an interesting contrast to the formation of homoallylic alcohols through a nucleophilic allyl species (see Section 2.3.1). In the case of the C–H activation reaction, the nucleophilic ketone/enamine is "activated" to react with an electron-*rich* alkene in an apparent reversal in electronic character, whereas in the formation of homoallylic alcohols, the olefinic species is activated *by* alkene insertion to give a nucleophilic allyl metal species that attacks the electron-*deficient* carbonyl centre while still retaining their respective electronic character.



Scheme 2.10 *α-Alkylation of a ketone by redox-neutral C–H activation of an enamine formed in situ.*[52]

2.3.3 Alkane Metathesis *via* Dual Catalysis

Short-chain hydrocarbons can be obtained from long-chain hydrocarbons by high temperature cracking processes,[53,54] or by the Fisher–Tropsch process in which CO and H_2 are converted into alkanes at high temperatures in the presence of metal catalysts.[55] However, there is no process in which short-chain alkanes can be upgraded to give long-chain alkanes. Goldman et al. described the formation of long-chain hydrocarbons from *n*-hexane in the presence of an iridium catalyst as well as a Shrock-type olefin metathesis catalyst (Scheme 2.11).[56] This dual catalytic system gave a surprisingly selective formation of *n*-decane, which must necessarily arise from the metathesis of olefins derived from *n*-hexane or other alkanes of longer lengths.



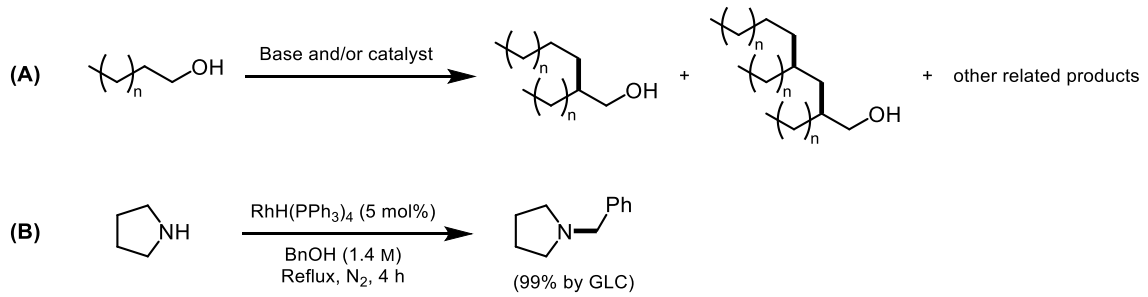
Chain Length	C_2	C_3	C_4	C_5	C_7	C_8	C_9	**C_{10}**	C_{11}	C_{12}	C_{13}	C_{14}	$C_{\geq 15}$	Total
Product Concentration (mM)	(131)	176	127	306	155	37	49	**232**	18	4	4	10	2	1251

Scheme 2.11 *Alkane metathesis through alkane dehydrogenation with an iridium catalyst, followed by olefin metathesis with a Shrock-type catalyst, and subsequent reduction of new olefin intermediate. Concentrations were determined by GC. Numbers in parentheses were extrapolated due to difficulties in quantifying ethane under the reaction conditions.*[56]

2.3.4 Hydrogen Borrowing Reactions Involving Condensation Reactions with Carbonyl Derivatives

The Guerbet reaction, which was discovered in 1909, is probably the earliest synthetic reaction that utilises alcohols as alkylating agents.[57] Under strong basic conditions, primary alcohols bearing a β-methylene carbon underwent dimerisation to give oligomeric alcohol products (Scheme 2.12). The reaction is rapidly catalysed by the presence of metal catalysts

such as nickel, palladium and rhodium. The Guerbet reaction is highly complex, with many studies on its mechanism being carried out over the past century.[58,59] There is increasing interest in the metal-catalysed Guerbet reactions for accessing advanced biofuels due to the current prevalence of bioethanol.[60–63]



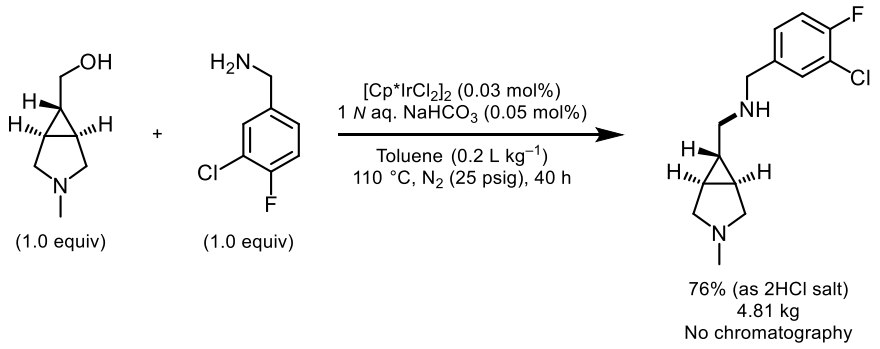
Scheme 2.12 *(A) The Guerbet reaction involves the dimerisation of primary alcohols in the presence of base and/or catalyst to give β-branched alcohols.[57] (B) An example of N-alkylation with a primary alcohol as reported by Grigg et al.[64]*

In 1981, Grigg et al. reported the alkylation of amines with alcohols in very high yields using a rhodium hydride catalyst, representing the first modern transition metal-catalysed hydrogen borrowing reaction that involved a condensation reaction of a nucleophile with an electrophilic carbonyl intermediate followed by subsequent reduction of the π-bond.[64] Since then, there has been an extraordinary number of reviews written on this area in the span of 40 years.[37–41,48,65–81] For this reason, this section will be deliberately kept short, and will only highlight the different types of reactions and products that can be formed.

2.3.4.1 *N*-Alkylation of Amines with Alcohols

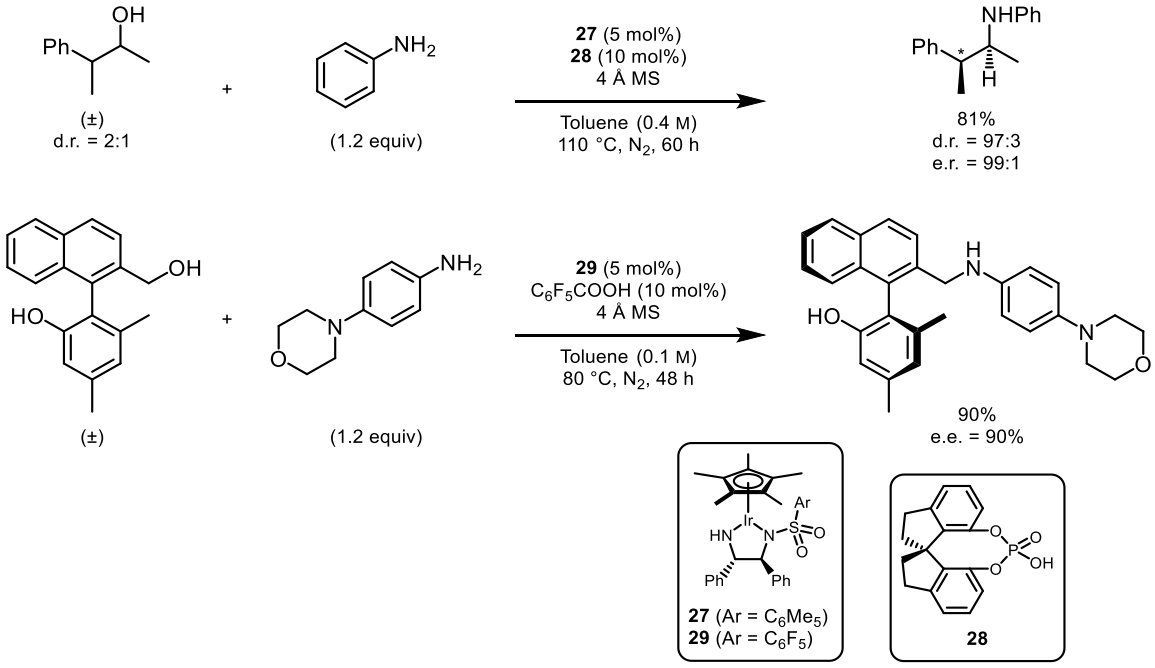
Although this dissertation is predominantly focused on C–C bond formation in hydrogen borrowing reactions, it is worth mentioning that pharmaceutical companies have taken interest in the use of iridium catalysis for *N*-alkylation with alcohols. For example, in the synthesis of PF-03463275, a GlyT1 inhibitor that has potential applications in schizophrenia therapy, the cyclopropylmethanol fragment was successfully coupled with a

benzylamine derivative using an iridium catalyst to give the diamine in excellent yield without any chromatographic purification (Scheme 2.13).[77,82]



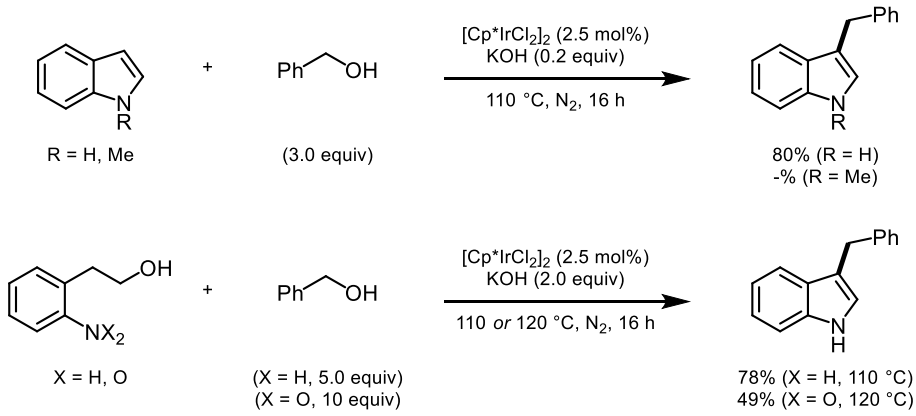
Scheme 2.13 *N-alkylation of a benzylamine with a cyclopropylmethanol derivative in the process development of PF-03463275.*[82]

An important development in the *N*-alkylation of amines is the application of dynamic kinetic resolution to obtain asymmetric products from racemic alcohols, as demonstrated by Rong et al. and Lim et al. (Scheme 2.14).[83,84] This concept was further extended by Zhang and Wong to the atropo- and enantioselective synthesis of (biaryl)methylamines from racemic (biaryl)methanols.[85]



Scheme 2.14 *Dynamic kinetic resolution was applied in hydrogen borrowing reactions to obtain atropo- and/or enantioselective syntheses of amine products.*[83,85]

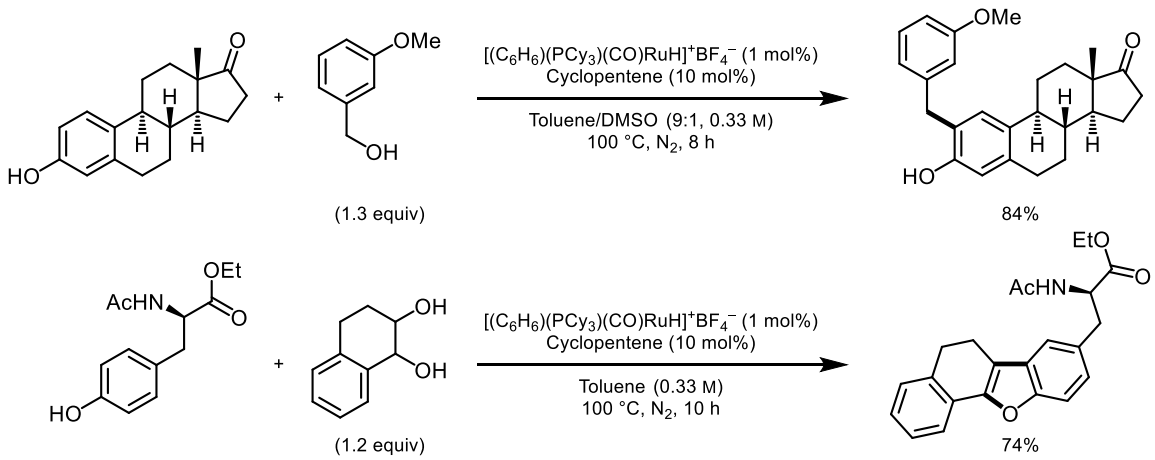
2.3.4.2 *C*-Alkylation of Aromatic Compounds



Scheme 2.15 *C-alkylation of indoles by hydrogen borrowing, as well as the concomitant reduction of nitro groups and formation of indoles in situ.*[86]

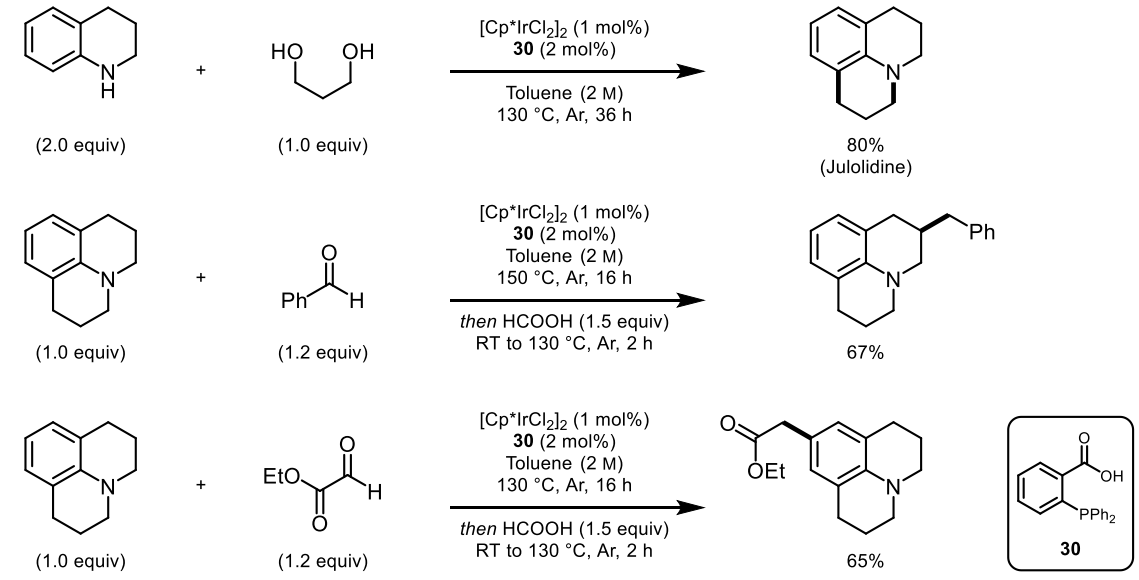
Aromatic compounds can also be alkylated at the nucleophilic carbon centre by hydrogen borrowing reactions. Whitney et al. demonstrated the ability for unprotected indoles to be selectively alkylated at the C3-position by primary alcohols in good yields without any *N*-alkylation observed (Scheme 2.15).[86] Unusually, *N*-methylindole failed to undergo the alkylation reaction. The indole could even be formed *in situ* from an aniline or even a nitrobenzene precursor, which highlights the lability of the nitro group in the hydrogen borrowing reaction. A similar reaction of indoles with ethanolamines was also described by Bartolucci et al.[87]

Lee et al. described the *C*-alkylation of phenols with primary and secondary alcohols in the presence of a ruthenium hydride catalyst (Scheme 2.16).[88] The reaction of estrone with 3-methoxybenzyl alcohol afforded the *C*-alkylated product in excellent yield with no trace of any reaction on the α-position of the ketone. Interestingly, the use of 1,2-diols resulted in the formation of annulated benzofurans. The reactions with cyclopentanol and other cycloalkyl alcohols can also be driven to form the alkenylated products using excess cyclopentene, which turns the reaction into a transfer hydrogenation (see also Scheme 2.5).



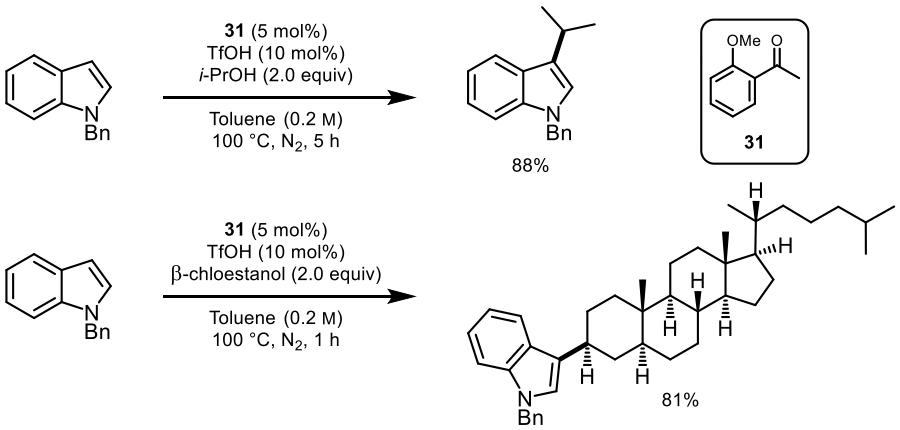
Scheme 2.16 *C-alkylation of phenols with primary alcohols by transition metal-catalysed hydrogen borrowing reactions to give C2-alkylated or annulated benzofurans.*[88]

Labed et al. reported the *N*- and *C*-alkylation of tetrahydroquinoline with propane-1,3-diol to form julolidine products (Scheme 2.17).[89] Interestingly, julolidine itself could also be oxidised to form an enamine, which could react with aldehydes followed by subsequent reduction with the addition of formic acid to give C3-alkylated products. However, the aromatic ring was also highly nucleophilic, and could give alkylation products at the *para*-position relative to the aniline.



Scheme 2.17 *N- and C-alkylation of tetrahydroquinoline with propane-1,3-diol to give julolidine. Julolidine could undergo in situ oxidation to form a reactive enamine group that can react with aldehydes.*[89]

Han and Wu described a "redox chain reaction" in which a catalytic quantity of a (sacrificial) ketone would couple with *N*-benzylindole, and the indolinium intermediate would oxidise the alcohol present to (re)generate the ketone to re-initiate another cycle of redox reaction (Scheme 2.18).[90] The reaction was also highly effective when β-cholestanol was used as the alkylating agent to afford the C3-alkylated product as a single diastereomer. This reaction differs from other hydrogen borrowing reactions in that the reaction conditions are acidic in nature, and the intermediate itself is directly involved in the redox process but not the ketone catalyst. In contrast, other hydrogen borrowing reactions have neutral or basic reaction conditions, and the catalysts are directly involved in the redox processes.

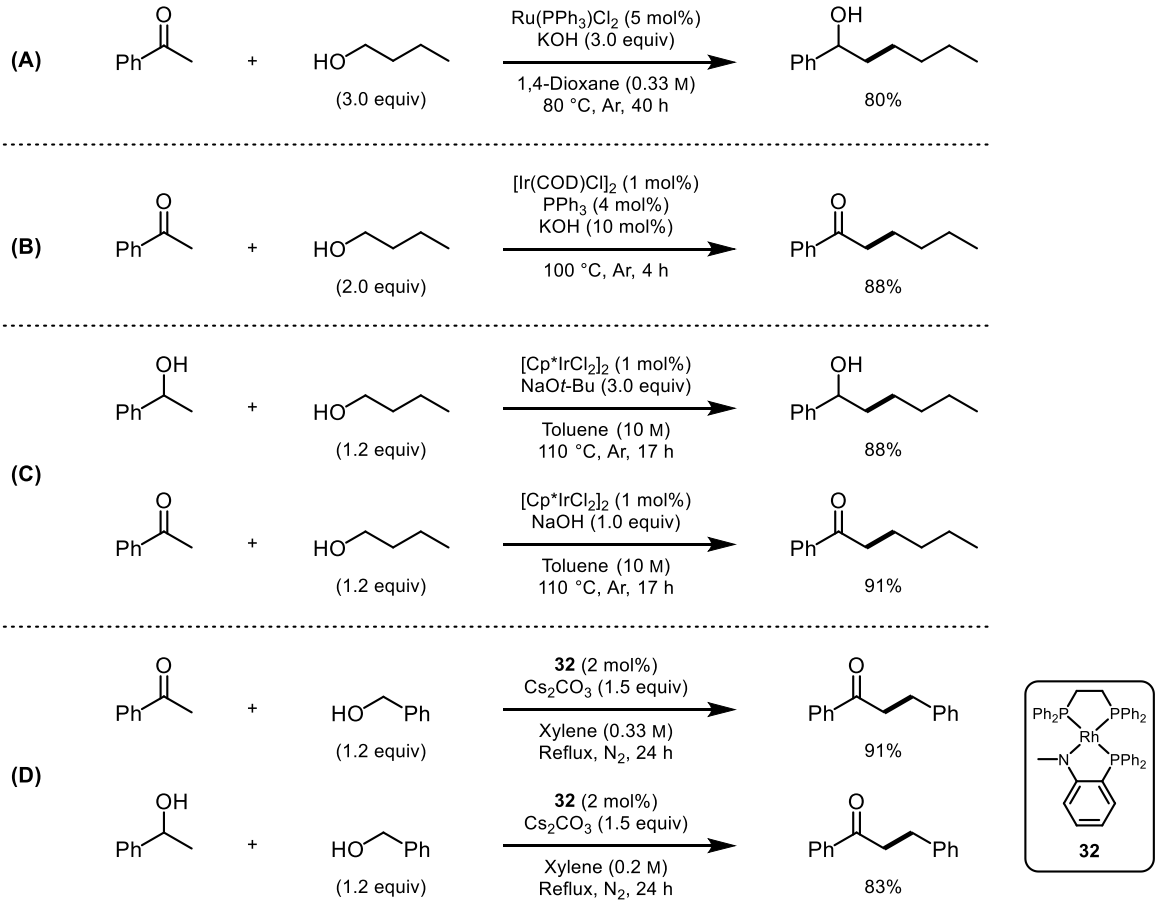


Scheme 2.18 *The ketone-catalysed C3-alkylation of N-benzylindole as describe by Han and Wu, which operates via a "redox chain reaction".*[90]

2.3.4.3 α-Alkylation of Ketones and Related Enolates with Alcohols

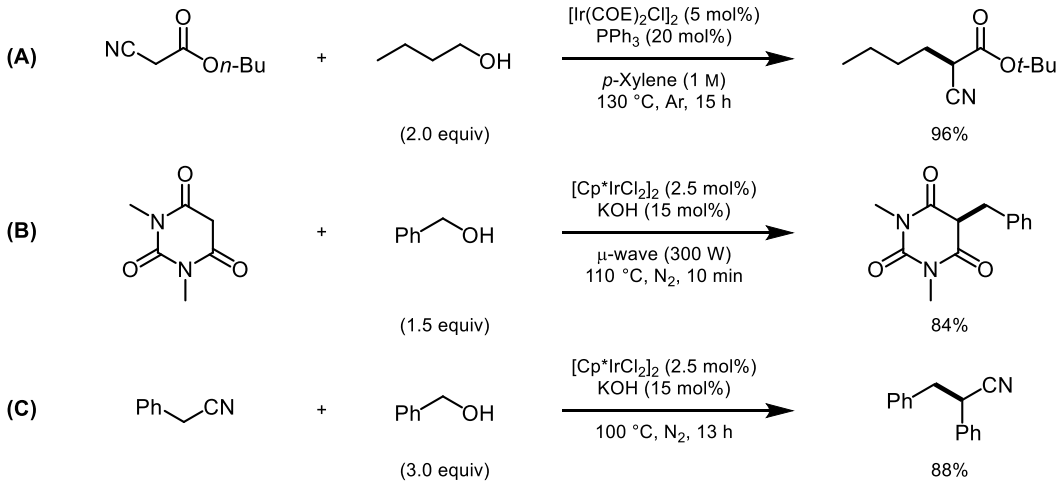
The α-alkylation of ketones with alcohols is very well-studied, with numerous reviews covering these reactions (*vide supra*). Cho et al. reported that acetophenone reacts with 3 equiv of primary alcohols in the presence of a ruthenium catalyst to give the alkylated benzylic alcohol (Scheme 2.19).[91] On the other hand, Taguchi et al. reported that performing the same reaction with 2 equiv of the alcohol in the presence of an Ir(I) catalyst gave predominantly the aryl ketone product and only a small amount of the corresponding benzylic alcohol.[92] Fujita et al. later described the alkylation of secondary alcohols with

only 1.2 equiv of primary alcohol in the presence of an Ir(III) to give the corresponding secondary alcohol products, but reaction of the analogous ketone led to the formation of the corresponding ketone product.[93] Unusually, Yu et al. reported that the reaction of benzyl alcohol and a rhodium catalyst gave the ketone product regardless of whether the nucleophilic starting material was a ketone or a benzylic secondary alcohol.[94] These reports suggest that the presence of excess primary alcohol could drive the reduction of the ketone products, but this extraneous reduction could also be interrupted, with an undetermined process enabling the turnover of the catalyst from the metal-hydride species.



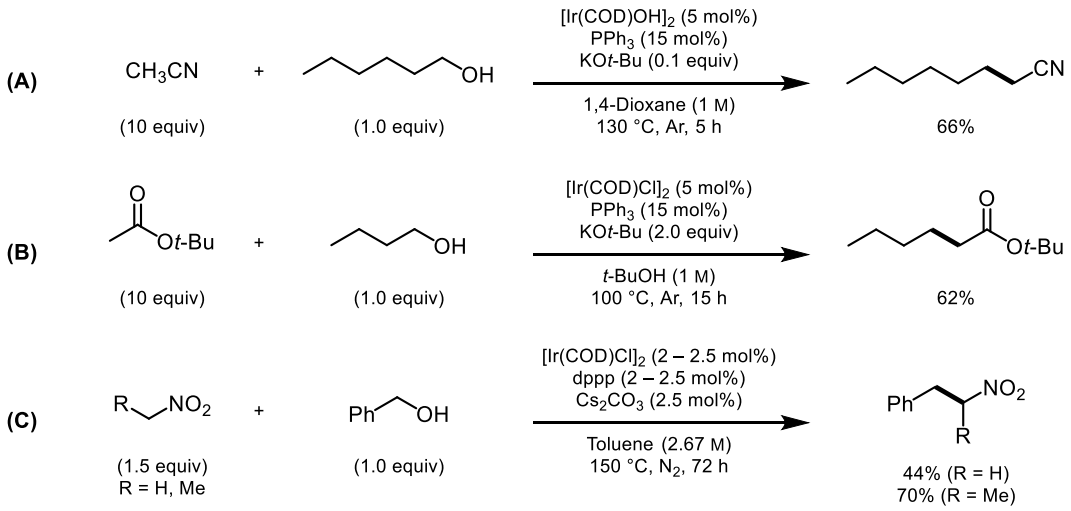
Scheme 2.19 *α-Alkylation of ketones and/or benzylic alcohols with primary alcohols as reported by (A) Cho et al.,[91] (B) Taguchi et al.,[92] (C) Fujita et al.,[93] and (D) Yu et al.[94]*

Enolates derived from activated methylenes are highly effective nucleophiles in hydrogen borrowing reactions. Morita et al. reported the reaction of 2-cyanoacetates with primary alcohols to give branched α-alkylated ketones (Scheme 2.20).[95] Notably, this reaction was base-free, highlighting the enhanced reactivity of these nucleophiles. Löfberg et al. also reported the reactions of barbituric acids and phenylacetonitriles with primary alcohols to give α-branched products, although these reactions required catalytic base to proceed.[96,97] Similar reactions of malonates have also been reported by Black et al.[98] These reactions are amongst the few reported in literature to successfully give α-branched ketones.



Scheme 2.20 *Formation of α-branched products through hydrogen borrowing reactions of (A) 2-cyanoacetates,[95] (B) barbituric acids,[96] and (C) arylacetonitriles with primary alcohols.[97]*

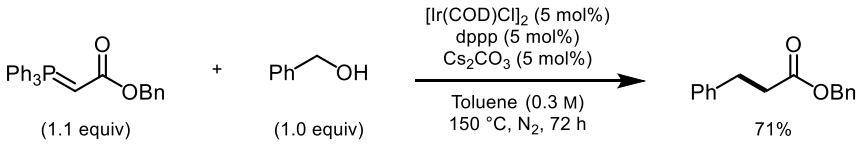
Sawaguchi and Obora reported the remarkable alkylation of acetonitrile with primary and secondary alcohols,[99] while Iuchi et al. described the alkylation of *tert*-butyl acetate with primary alcohols (Scheme 2.21). These methodologies would encourage the use of cheap and widely available chemical feedstocks to access more complex chemicals, and would obviate additional hydrolysis and decarboxylation steps compared to using malonates or malononitriles as the nucleophilic partner.[100] Similar reactions of acetonitrile and acetamides with primary alcohols were also reported by Anxionnat et al. and Guo et al.[101,102]



Scheme 2.21 *α-Alkylation of (A) acetonitrile,[99] (B) tert-butyl acetate,[100] and (C) nitroalkanes with primary alcohols.[98]*

On the other hand, Black et al. demonstrated the utility of nitroalkanes as nucleophiles for the hydrogen borrowing reaction (see Scheme 2.21C). These reactions are complementary to those that employ acetonitrile and *tert*-butyl acetate, as the nitro group not only provides access to branched primary amines, but could also be converted to carbonyl groups *via* the Nef reaction, thereby resulting in an umpolung hydrogen borrowing reaction.[98]

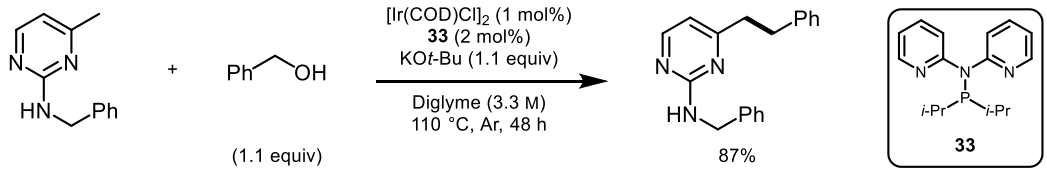
Edwards and Williams described the formation of esters and nitriles from electron-deficient phosphoranes and primary alcohols, presumably *via* a Wittig reaction to form the C–C bond (Scheme 2.22).[103] Similar reactions of iminophosphoranes and phosphonoacetates with primary alcohols have also been reported by the Williams group to give amines and ketone products analogous to the hydrogen borrowing reactions of esters and amines.[98,104]



Scheme 2.22 *Hydrogen borrowing reaction of an electron-deficient phosphorane with benzyl alcohol.[103]*

The benzylic positions of electron-deficient heterocycles could also serve as the nucleophilic site. Blank and Kempe reported the reaction of a 4-methylpyrimidine with

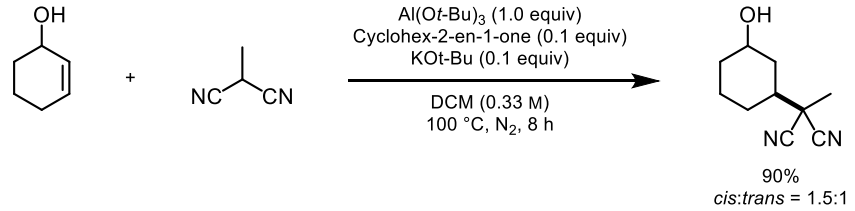
primary alcohols to give the corresponding pyrimidine derivative without *N*-alkylation being observed (Scheme 2.23).[105] Methyl-substituted pyrazines, pyridazines and pyridines were also suitable substrates, although 3-methylpyridine was unreactive under the reaction conditions. Obora et al. also reported a similar reaction with methyl-substituted quinolines, quinoxalines and benzoxazoles.[106]



Scheme 2.23 *The alkylation of benzylic sites for electron-deficient heterocycles via hydrogen borrowing.*[105]

2.3.4.4 Activation of Allylic Alcohols for Conjugate Addition

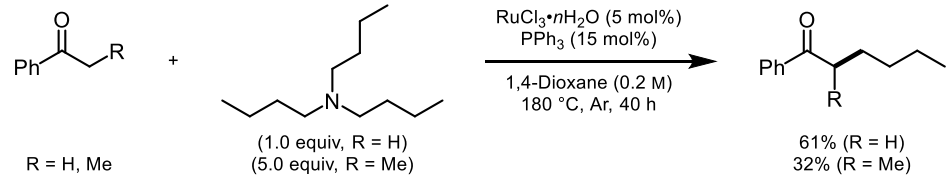
Black et al. described the activation of an allylic alcohol by hydrogen borrowing for conjugate addition with a nucleophile (Scheme 2.24). The presence of the methyl group on the malononitrile nucleophile prevents condensation reactions on the carbonyl group. Although the use of stoichiometric aluminium reagent and superheating of the low boiling solvent makes the reaction less practical, the methodology possesses great flexibility in controlling both local and remote functionalisation of the alcohol centre.[107,108]



Scheme 2.24 *An unreactive allylic alcohol is activated by the hydrogen borrowing process to form an electrophilic enone in situ, which undergoes conjugate addition with a nucleophile followed by ketone reduction to complete the catalytic cycle.*[107,108]

2.3.4.5 α-Alkylation of Ketones with Amines

Interestingly, Cho et al. reported that trialkylamines could also be used for the α-alkylation of ketones in the absence of a base, albeit at a significantly higher temperature than those reported for the hydrogen borrowing reactions of ketones with alcohols (Scheme 2.25).[109] Control experiments suggest that the reaction proceeds *via* an iminium intermediate. The reaction was also able to furnish an α-branched product in modest yield, a rare example of the formation of α-branched ketones that are not derived from compounds with activated methylenes.



Scheme 2.25 *α-Alkylation of aryl ketones using amines via hydrogen borrowing.*[109]

2.4 Conclusion

Hydrogen borrowing reactions have gained significant attention due to their numerous advantages. The discovery and development of hydrogen borrowing reactions leading to the syntheses of α-, β- and α,β-branched aryl ketones will be discussed in Chapter 3. Further improvements to the hydrogen borrowing process by introduction of a fourth reaction prior to the reduction will be detailed in Chapter 4. The synthesis and attempted hydrogen borrowing reactions of numerous heteroatom derivatives of aryl ketones will be discussed in Chapters 5 and 6. Finally, Chapter 7 will provide analytical data to show how the *ortho* effect has played a pivotal role in the success of the hydrogen borrowing reactions in this dissertation, as well as in the formation of unexpected products from these reactions.

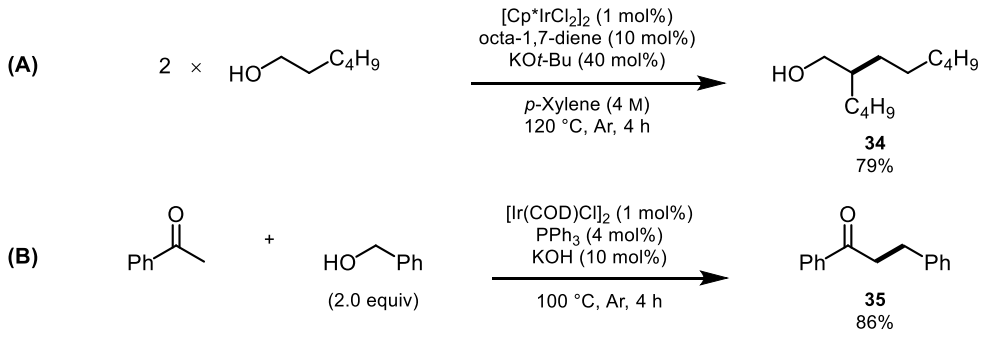
Chapter 3. The Synthesis of α- and β-Branched Aryl Ketones *via* Iridium-Catalysed Hydrogen Borrowing Reactions

In this chapter, the following questions will be answered:

- Can primary and secondary higher alcohols be employed in hydrogen borrowing reactions to form α-, β- and α,β-branched ketones?
- How do the *ortho* substituents affect the hydrogen borrowing reaction?

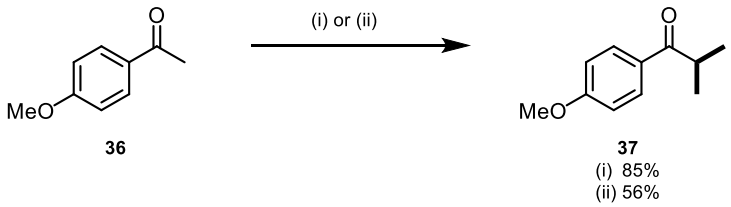
3.1 Introduction

Hydrogen borrowing processes operate by the telescoping of a three-step process, namely the oxidation of an alcohol, condensation of a nucleophilic substrate with the carbonyl electrophile formed *in situ*, and reduction of the newly-formed unsaturated bond. These reactions are typically catalysed by transition metals such as iridium or rhodium. For example, Matsu-ura et al. reported an iridium-catalysed Guerbet-type reaction involving a primary or secondary alcohol self-condensation to give homodimeric products,[60] and Taguchi et al. reported the hydrogen borrowing alkylation of ketones with primary alcohols (Scheme 3.1, see also Section 2.3.4.3).[92]



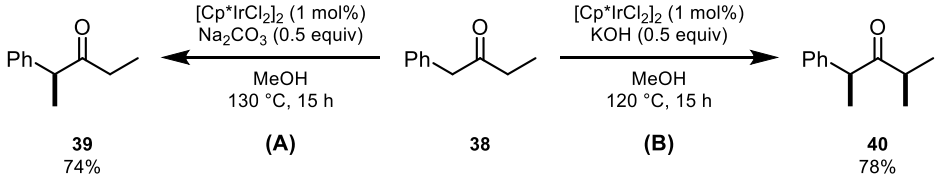
Scheme 3.1 *Representative examples of iridium-catalysed hydrogen borrowing reactions, including (A) a Guerbet-type reaction as reported by Matsu-ura et al.,[60] and (B) ketone α-alkylation with alcohols as reported by Taguchi et al.[92]*

Methanol is the simplest primary alcohol in organic chemistry. It is cheap, renewable, readily available and of important commercial value, thus there is significant interest in the use of methanol for hydrogen borrowing alkylation. Ogawa and Obora as well as Chan et al. have reported the di-alkylation of ketones such as **36** with methanol (Scheme 3.2).[110,111]



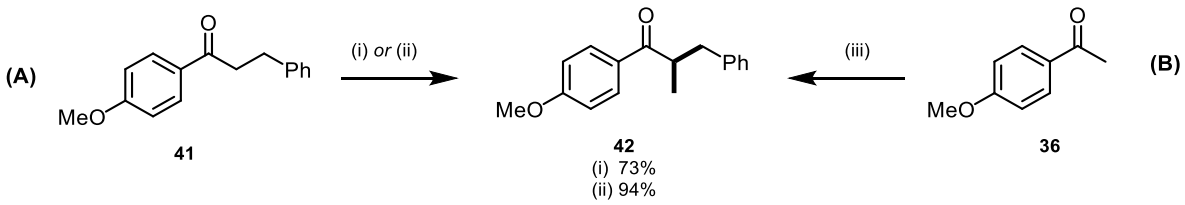
Scheme 3.2 *An example of di-alkylation of a methyl ketone as reported by (i) Ogawa and Obora,[110] and (ii) Chan et al.[111] (i) [Cp*IrCl$_2$]$_2$ (5 mol%), KOH (0.5 equiv), MeOH (0.67 M), 120 °C, Ar, 5 h; (ii) [Cp*RhCl$_2$]$_2$ (5 mol%), Cs$_2$CO$_3$ (5.0 equiv), MeOH (0.2 M), 65 °C, O$_2$, 24 h.*

Additionally, Ogawa and Obora demonstrated the ability to control the mono- or di-alkylation of a substrate with methanol through judicious choice of base (Scheme 3.3).[110]



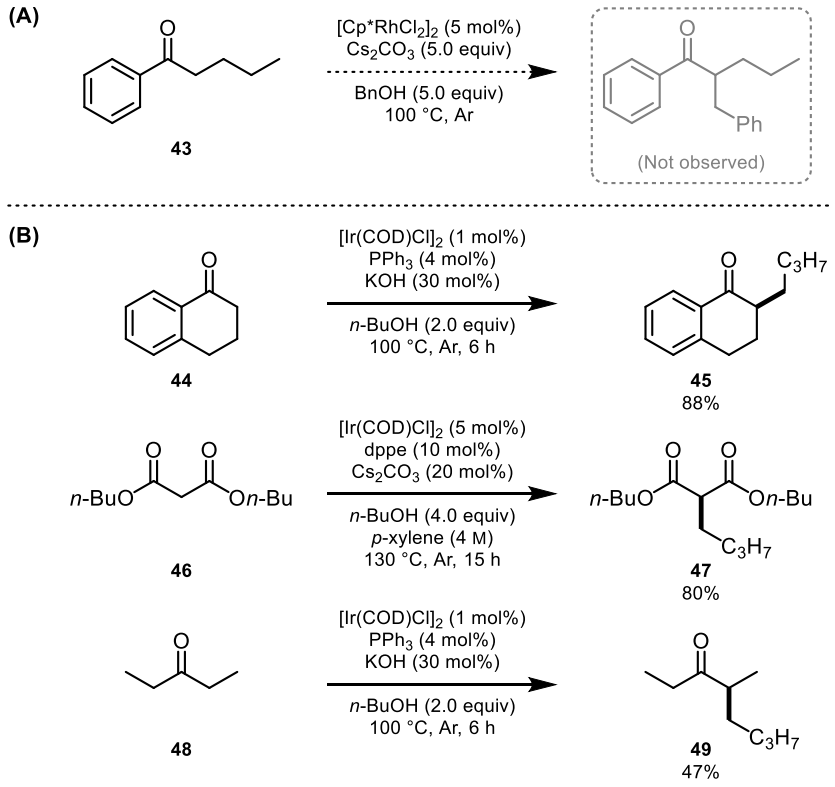
Scheme 3.3 *Examples of selective (A) mono-methylation vs (B) di-methylation through varying the base as reported by Ogawa and Obora. The relative stereochemistry of **40** was not determined.[110]*

On the other hand, Shen et al. was able to synthesise a variety of α-branched substrates with methanol using rhodium or iridium catalysts (Scheme 3.4).[111] They also showed that it was possible to perform sequential hydrogen borrowing alkylation with different alcohols.[112]



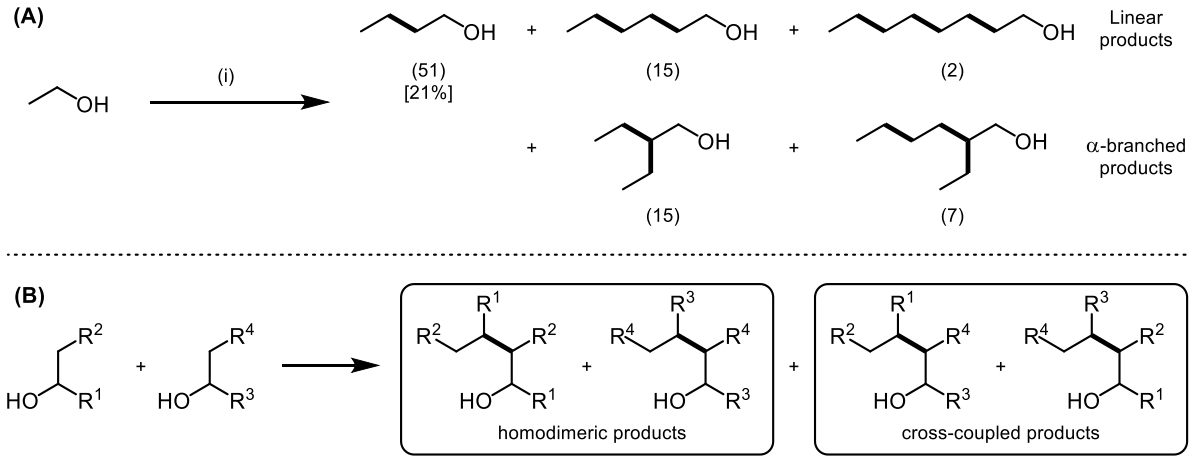
Scheme 3.4 *Representative examples by Donohoe et al. for (A) alkylation via Rh or Ir catalysis, and (B) sequential di-alkylation with different alcohols.[111,112] (i) [Cp*RhCl$_2$]$_2$ (5 mol%), Cs$_2$CO$_3$ (5.0 equiv), MeOH (0.2 M), 65 °C, O$_2$, 24 h; (ii) [Ir(COD)Cl]$_2$ (1 mol%), PPh$_3$ (4 mol%), KOH (2.0 equiv), MeOH (0.2 M), 65 °C, O$_2$, 48 h; (iii) [Ir(COD)Cl]$_2$ (1 mol%), PPh$_3$ (4 mol%), KOH (10 mol%), BnOH (2.0 equiv), 100 °C, Ar, 6 h, then PPh$_3$ (4 mol%), KOH (3.0 equiv), MeOH (0.2 M), 65 °C, O$_2$, 48 h.*

The hydrogen borrowing methodology is not without shortcomings. Previous attempts by the Donohoe group to access α-branched products with benzyl alcohol using rhodium catalysis were unsuccessful, and this difficult transformation became a key challenge in this field (Scheme 3.5).[113] The α-alkylation of ketones with alcohols has mainly been carried out with methanol, and cases involving higher alcohols (e.g. ethanol, *n*-butanol or benzyl alcohol) are sporadic in the literature, typically only being successful with either cyclic ketones, or activated methylenes (see also Section 2.3.4.3).[91,92,95,114,115]



Scheme 3.5 *(A) Unsuccessful hydrogen borrowing reaction with benzyl alcohol performed by Dr. Darren Poole.[113] (B) Representative examples of successful hydrogen borrowing alkylation reactions with higher alcohols to form α-branched products as reported by Morita et al. and Taguchi et al.[92,95] Yields quoted are GC yields.*

Guerbet-type hydrogen borrowing reactions also encounter issues with cross-substrate coupling, for example giving statistical mixtures even when starting from ethanol alone (Scheme 3.6).[61] This would frustrate any attempts to effectively couple two different secondary alcohols, ketones or a combination thereof. Ironically, some of the products from the Guerbet-type reaction of ethanol include α-branched products (after carbonyl reduction), which suggests that there may yet be hope in enabling the use of higher alcohols to access α-branched products.



Scheme 3.6 *Formation of statistical mixtures as an illustration of potential selectivity issues with cross-substrate coupling for (A) primary alcohols such as ethanol,[61] and (B) secondary alcohols (the starting materials and products could be ketones as well). Numbers in parentheses are GC ratios, and yield in square parentheses represents GC yield. (i) [Ir(COD)(acac)] (0.01 mol%), NaOEt (5 mol%), 120 °C, 15 h.*

To advance the utility of the hydrogen borrowing reaction, the following questions need to be addressed.

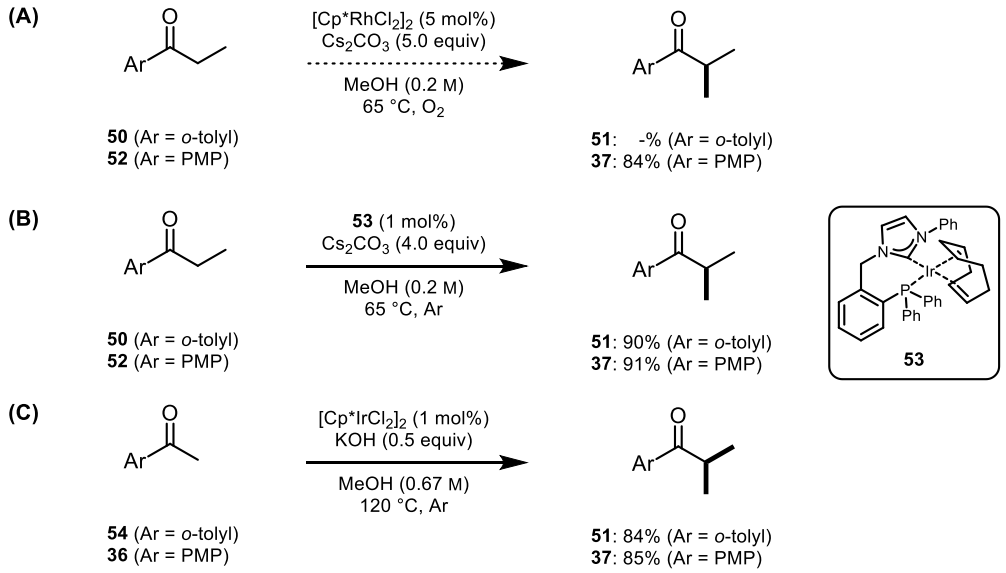
1. Can the current methodology be modified to use higher alcohols to form α-branched ketones?

2. Can aldol reactions in the synthesis of β-branched ketones *via* hydrogen borrowing be controlled to deliver only one crossed-aldol product?

3.2 The Synthesis of α-Branched Aryl Ketones

3.2.1 Initial Discovery

Soon after the start of the project, Quan et al. published a paper that described the branching α-alkylation of aryl ketones with methanol using an iridium catalyst,[116] a transformation closely related to those that Chan et al. had reported earlier using a rhodium catalyst (Scheme 3.7).[111] Ogawa and Obora had also previously reported the successful di-alkylation of acetophenones with methanol and an iridium catalyst to give similar products (see Scheme 3.2).[110] A close comparison revealed that *ortho*-tolyl ketone **50** suffered from poor conversion only when subjected to the rhodium catalysis conditions reported by the Donohoe group. However, all three methods were able to perform alkylation with methanol on *para*-methoxy-substituted ketones **52** or **36**.

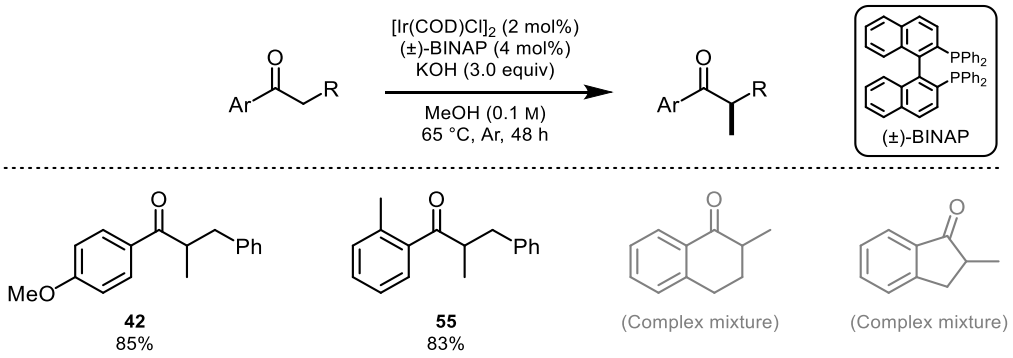


Scheme 3.7 *Comparison of results from hydrogen borrowing reactions by (A) Chan et al.,[111] (B) Quan et al.,[116] and (C) Ogawa et al.[110]*

Upon comparison with the literature reports of branched α-alkylation with higher alcohols, it was noted that iridium catalysts were also employed in the successful alkylation with *n*-butanol to give α-branched products, whereas the use of a rhodium catalyst was not successful when benzyl alcohol was attempted (see Scheme 3.5). While it was tempting to directly attribute these differences in reactivity to the catalyst used, a more in-depth study into the effects of catalyst, alcohol, reagents and reaction conditions was necessary to investigate this discrepancy. This would then bring the project closer to the ultimate goal of performing a general hydrogen borrowing reaction with higher alcohols to synthesise α-branched ketones.

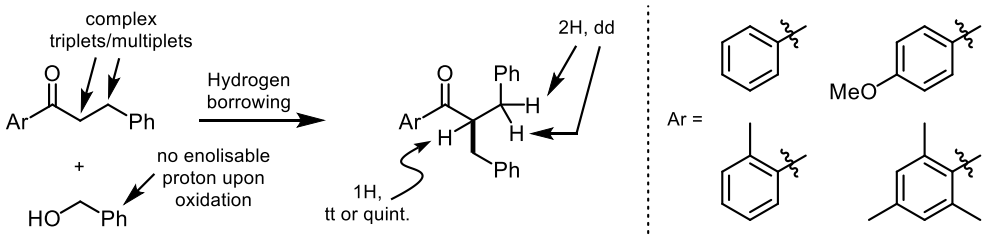
3.2.2 Preliminary Substrate Screen

With the aim of reducing the temperature required to perform hydrogen borrowing alkylation, the Donohoe group had previously developed an iridium-based catalytic system modelled upon the work from the Obora and Ishii groups (*vide supra*). The first step was to subject a small set of substrates to these conditions and determine if they behaved similarly to those from the Obora and Ishii group (Scheme 3.8). Both *para*-anisyl (**42**) and *ortho*-tolyl (**55**) ketones were formed in good yield, but cyclic ketone substrates gave a complex mixture of products. This suggested that an unusual substituent effect was at play that affected the reactivity of the substrates.



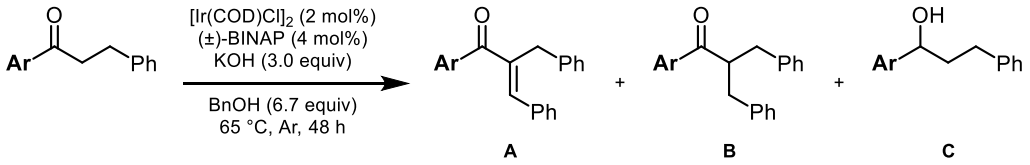
Scheme 3.8 *Preliminary substrate study on the hydrogen borrowing alkylation with methanol.*

Advancing on to higher alcohols, given the substrate effect observed in the rhodium catalysis, it seemed prudent to also screen a small set of substrates against an alcohol of choice to find a hit. For this investigation, substrates derived from chalcones with varying substituents were chosen to quickly probe steric and electronic effects (Scheme 3.9). Benzyl alcohol was chosen as the lack of enolisable protons in the aldehyde intermediate would minimise side product formation under the basic conditions, thereby facilitating analysis and purification. Furthermore, in combination with the chalcone derivatives, the products would be symmetrical and thus be readily distinguished from the substrates by ^{1}H NMR analysis of the crude mixture.



Scheme 3.9 *The choice of reagents used in the attempted hydrogen borrowing reaction with a higher alcohol would form symmetric α-branched products that facilitates purification and analysis.*

The results of the initial screen were remarkably informative (Table 3.1). Firstly, the phenyl (**35**) and *para*-anisyl (**41**) substrates, which had previously worked well for hydrogen borrowing with methanol, gave only traces of the desired product. In contrast, the sterically more demanding *ortho*-tolyl (**56**) and mesityl (**7**) substrates gave acceptable to good yields of the benzylated products **59** and **62** respectively. The presence of mesityl enone **61** supported a mechanism of an *in situ* oxidation of the alcohol to an aldehyde followed by condensation to give the corresponding enone. There was significant formation of benzylic alcohols **57**, **58** and **60** that likely arose from the undesired reduction of the starting material by the metal catalyst, although their yields did not appear to fit any trends in substituent effects.



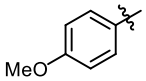
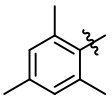
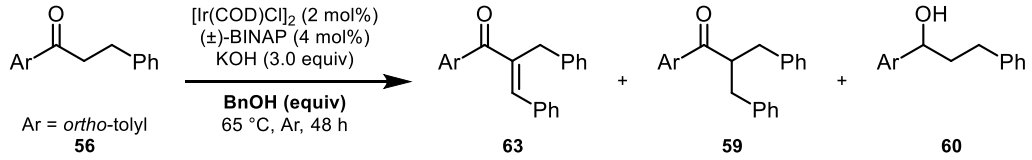
Entry	Ar	Yields (%)			
		SM	**A**	**B**	**C**
1	 **35**	7	-	Traces	90 (**57**)
2	 **41**	39	-	Traces	58 (**58**)
3	 **56**	Traces	Traces	38 (**59**)	62 (**60**)
4	 **7**	4	20 (**61**)	75 (**62**)	-

Table 3.1 *Preliminary substrate study on the hydrogen borrowing alkylation with benzyl alcohol.*

Between the two positive hits in the screen, the *ortho*-tolyl substrate **56** was chosen for optimisation as it would provide an opportunity to investigate and suppress the ketone reduction aspect of the reaction that would not be visible if mesityl substrate **7** were used. This would hopefully translate into a more rigorous optimisation process.

3.2.3 Optimisation

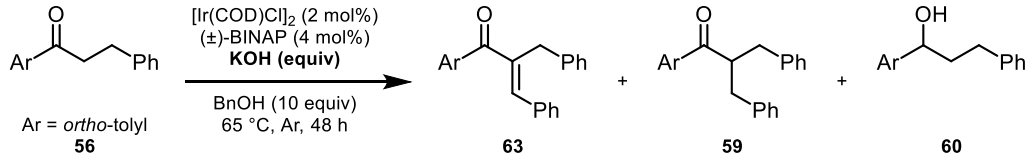
The optimisation process started by varying the loading of the alcohol (Table 3.2). Decreasing the loading of benzyl alcohol appeared to decrease the amount of ketone **59** formed (Entries 1 and 2). An increase in alcohol loading led to a modest decrease in undesired ketone reduction (Entry 3 vs 4), whilst excessive amounts of the alcohol not only compromised the conversion of starting material and enone intermediate, but also made purification considerably more difficult (Entries 5 and 6). An optimal loading of 10 equiv of benzyl alcohol gave 46% of the desired product **59**.



Entry	BnOH (equiv)	Yields (%)			
		56	**63**	**59**	**60**
1	2	2	Traces	33	58
2	5	1	Traces	31	62
3	6.7	Traces	Traces	38	62
4	**10**	**Traces**	**Traces**	**46**	**54**
5	25	29	23	24	24
6	50	50	27	8	15

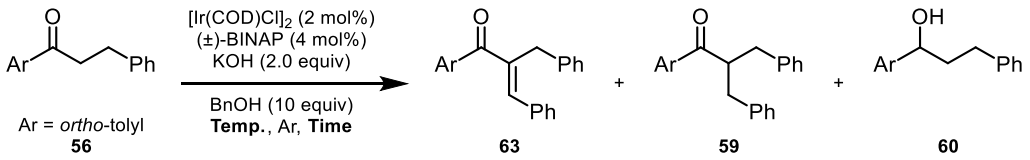
Table 3.2 *Optimisation of the loading of benzyl alcohol.*

Moving on to optimise the amount of KOH used, increasing the base loading led to significantly increased formation of undesired benzylic alcohol **60** (Table 3.3, Entry 5). Decreasing the base loading to 2 equiv reduced the formation of alcohol **60** and gave a modest increase in yield of ketone **59** with some build-up of enone **63** (Entry 3). However, a further decrease in base loading led to poorer conversion of ketone **56**, with virtually no reaction in the absence of base (Entries 1 and 2). This result is consistent with the critical role of the base in the aldol condensation for enolate formation and $E1_{CB}$. It also appears that the base is playing a role in the undesired ketone reduction pathway (*vide infra*).



Entry	KOH (equiv)	Yields (%)			
		56	**63**	**59**	**60**
1	-	94	-	-	6
2	1	30	18	24	28
3	**2**	**5**	**13**	**50**	**32**
4	3	Traces	Traces	46	54
5	5	Traces	Traces	28	72

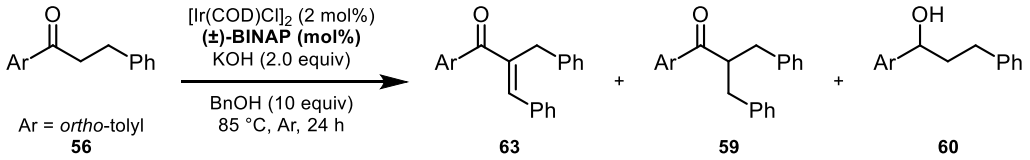
Table 3.3 *The effects of base loading on the hydrogen borrowing reaction.*



Entry	Temperature (°C)	Reaction time (h)	Yields (%)			
			56	**63**	**59**	**60**
1	25	48	86	7	Traces	7
2	65	48	5	13	50	32
3	**85**	**24**	**-**	**Traces**	**64**	**34**
4	105	12	-	Traces	60	40

Table 3.4 *Investigating the effect of temperature on the hydrogen borrowing reaction.*

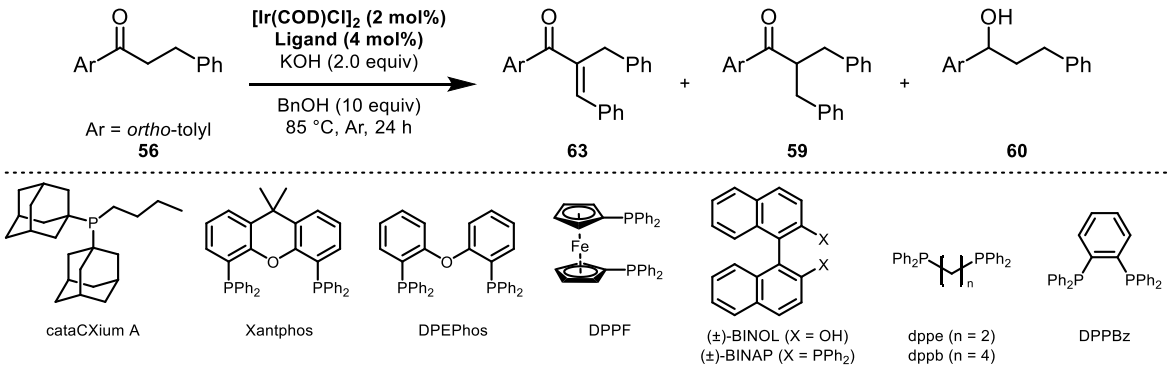
Temperature proved to be a critical variable in this reaction (Table 3.4). While negligible formation of ketone **59** was observed at RT (Entry 1), raising the temperature to 85 °C gave an increased yield of 67% and decreased the reaction time to 24 h (Entry 3). A subsequent increase in the temperature further accelerated the reaction, albeit at the cost of a more competitive ketone reduction (Entry 4).



Entry	(±)-BINAP (mol%)	Yields (%)			
		56	**63**	**59**	**60**
1	-	4	6	16	74
2	1	-	1	59	40
3	2	-	Traces	60	40
4	**4**	**-**	**Traces**	**64**	**34**
5	8	-	Traces	67	32

Table 3.5 *Optimising the amount of ligand required by the catalyst for the reaction.*

Following on, the amount of ligand used was then varied (Table 3.5). Reducing the ligand loading resulted in a small decrease in formation of ketone **59** (Entries 2 and 3). This effect was amplified when the ligand was entirely omitted (Entry 1). A further increase in ligand loading did not give a significant improvement to the yield of ketone **59** (Entry 5).

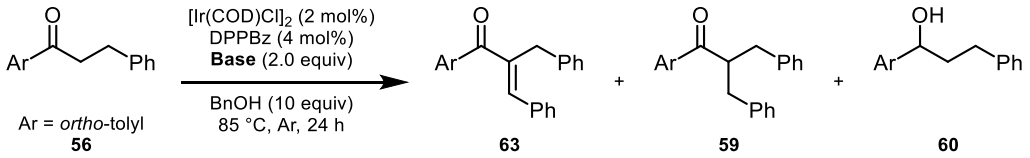


Entry	Ligand/ Catalyst	Yields (%)			
		56	**63**	**59**	**60**
1	P(*o*-tolyl)$_3$	Traces	3	42	55
2	cataCXium A	Traces	5	45	50
3	P(*n*-Bu)$_3$	2	12	45	41
4	PPh_3	2	6	48	44
5	PCy_3	Traces	5	52	43
6	P(OPh)$_3$	1	12	53	34
7	P(OEt)$_3$	1	3	62	34
8	$P(O)Ph_3$	2	7	15	76
9	XantPhos	1	15	35	48
10	DPEPhos	2	15	44	39
11	DPPF	1	3	57	39
12	dppe	-	Traces	59	41
13	dppb	Traces	1	63	36
14	(±)-BINAP	-	Traces	64	34
15	**DPPBz**		**-**	**71**	**29**
16	(±)-BINOL	2	3	15	79
17	-	4	6	16	74
18	$[Cp^*IrCl_2]_2$	Traces		63	34
19	$[Cp^*RhCl_2]_2$	Traces	5	65	30

Table 3.6 *Ligand screen for the hydrogen borrowing reaction.*

Next, a ligand screen comprising a variety of both monodentate and bidentate ligands was performed (Table 3.6). Both triphenylphosphine oxide and (±)-BINOL gave very similar results to a ligand-free system (Entries 8, 16 and 17), suggesting that phosphine ligands are critical for modulating the catalyst reactivity whereas oxygen-based ligands were ineffective. There did not appear to be any strong correlation between any particular ligand

parameter and the reaction outcomes (see Appendix 10.1). In this case the optimal ligand is DPPBz, which gave a marginally higher yield of 71% (Entry 15). It was also worth mentioning that both $[Cp^*IrCl_2]_2$ and $[Cp^*RhCl_2]_2$ performed comparably well (Entries 18 and 19).

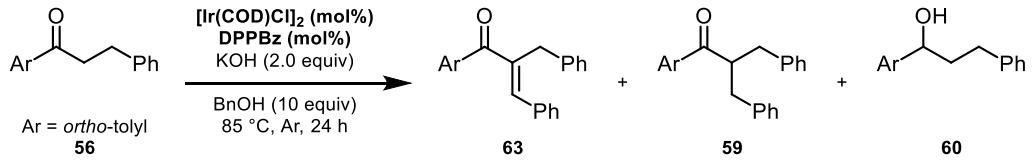


Entry	Base	Yields (%)			
		56	**63**	**59**	**60**
1	**KOH**	**-**	**-**	**71**	**29**
2	KOMe	-	3	40 (21)[a]	29
3	KO*t*-Bu	2	12	60	26
4	K_3PO_4	32	20	23	25
5	K_2CO_3	72	1	Traces	27

Table 3.7 *Base screen for the hydrogen borrowing reaction. [a]Yield in parentheses is that of ketone **55**.*

A screen to identify the most suitable base for the reaction gave very interesting results (Table 3.7). The comparatively stronger base KO*t*-Bu gave a slightly poorer yield of ketone **59** due to the incomplete conversion of enone **63** (Entry 3). Weaker bases such as K_3PO_4 gave significantly poorer conversion, with K_2CO_3 giving only traces of **59** or **63** (Entries 4 and 5). However, all the bases employed gave comparable levels of undesired alcohol **60**. The use of KOMe was complicated by the oxidation of methoxide/methanol, competing with benzyl alcohol for coupling (Entry 2). A disproportionately high yield of methylated product was observed given the amount of benzyl alcohol used (21% of **55** vs 40% of **59**, compared with five times more BnOH than MeOH/KOMe used). Given that formaldehyde has a *higher* oxidation potential (270 mV) than benzaldehyde (197 mV) i.e. formaldehyde would oxidise benzyl alcohol,[117] the facile hydrogen borrowing reaction with MeOH likely

involves a more efficient aldol condensation reaction with formaldehyde and/or a greater ease at reducing the enone intermediate following aldol condensation with formaldehyde.

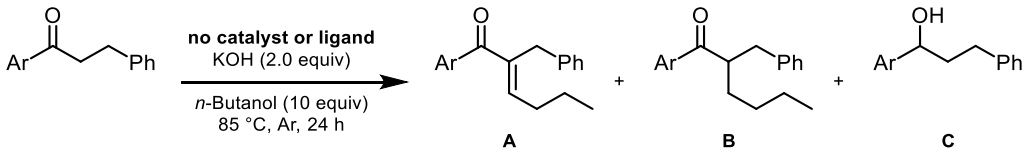


Entry	[Ir(COD)Cl]$_2$ (mol%)	DPPBz (mol%)	Yields (%)			
			56	**63**	**59**	**60**
1	4	8	-	-	70	30
2	2	4	-	-	71	29
3	**1**	**2**	**-**	**Traces**	**70**	**30**
4	0.5	1	-	4	66	30
5	-	-	4	30	38	28
6	-	4	3	18	47	32
7	2	-	4	6	16	74

Table 3.8 *Effects of varying catalyst and ligand loading.*

At this juncture it seemed appropriate to test the efficacy of the catalytic system and perform a series of controls to verify that this hydrogen borrowing reaction is indeed an iridium-catalysed process (Table 3.8). Increasing the catalyst and ligand loading concurrently did not result in any beneficial increase in yield (Entry 1). Encouragingly, decreasing their loadings did not drastically affect the reaction, with 1 mol% iridium catalyst and 2 mol% dppBz representing a more cost-efficient system without compromising the efficiency of the process (Entry 3).

Intriguingly, experiments performed without catalyst and/or ligand gave a significant amount of product **59** and intermediate **63** (Entries 5 and 6). These catalyst-free controls held true despite the use of fresh reagents and apparatus with careful metal-free handling. The role of the ligand is clearly to modulate the chemoselectivity of the catalyst, as performing the reaction with [Ir(COD)Cl]$_2$ in the absence of ligand led to a significant increase in formation of alcohol **60** (Entry 3 vs 7).



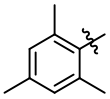
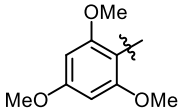
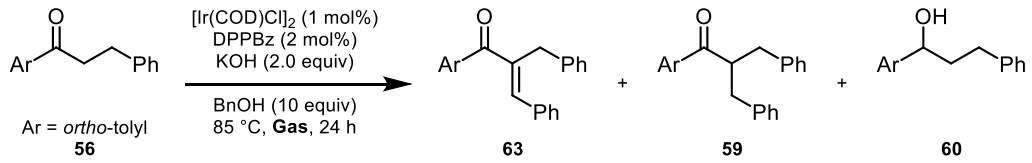
Entry	Ar	NMR Ratio (%)			
		SM	**A**	**B**	**C**
1[a]		4	30	38	28
2		40	6	10	44
3		3	-	-	97
4		96	4	-	-
5		100	-	-	-

Table 3.9 *Catalyst-free control experiments performed for different substrates with n-butanol. [a]Experiment performed with BnOH (see also Table 3.8).*

When a different alcohol, *n*-butanol, was used under catalyst-free conditions, only a small amount of product was formed (Table 3.9, Entry 1 vs 2). However, a significant amount of undesired ketone reduction still took place, suggesting a case of base-mediated reduction that also displayed alcohol-specific reactivity.

A series of other substrates were also subjected to these catalyst-free conditions. The phenyl substrate was almost fully reduced to the benzylic alcohol (Entry 3), whereas the di-*ortho*-substituted substrates did not form any of the benzylic alcohols (Entries 4 and 5). There was also consistently no coupling with the alcohol for these substrates. These findings are in line with recent literature that describe the base-mediated, transition metal-free alkylation processes with primary alcohols.[90,118–123]



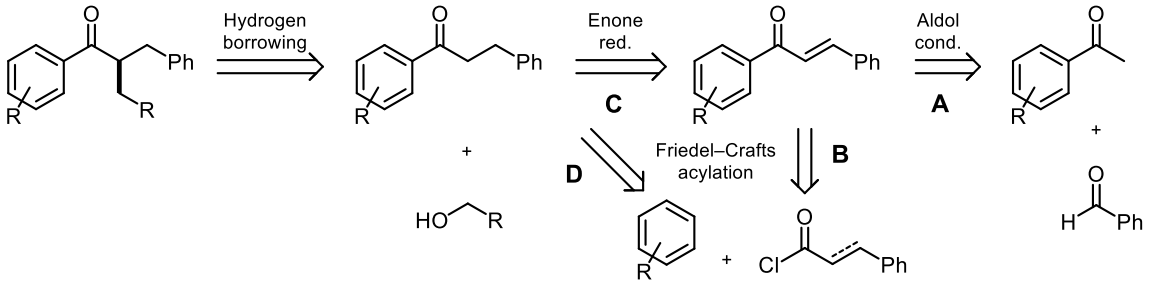
Entry	Gas	Yields (%)			
		56	**63**	**59**	**60**
1	**Ar**	**-**	**Traces**	**70**	**30**
2	Air	-	-	45	55
3	O_2	-	58	-	-

Table 3.10 *Effects of the composition of the atmosphere on the hydrogen borrowing reaction.*

Previous work on hydrogen borrowing with methanol showed that there was a beneficial effect of performing the reaction under an atmosphere of O_2,[111] but this was shown not to be the case here (Table 3.10). A headspace of air was detrimental to the yield (Entry 2), while an atmosphere of O_2 appeared to completely shut down the reduction pathway, with only the enone being isolated but with loss of mass recovery (Entry 3). This suggests that oxygen is interacting with the catalyst and interfering with the reduction of the enone.

3.2.4 Substrate Synthesis

With the optimised conditions in hand, a large variety of chalcone derivatives were synthesised to probe the steric and electronic effects of aryl substituents on the hydrogen borrowing reaction (Scheme 3.10). These substrates were prepared from the corresponding methyl ketone *via* aldol condensation (A) and hydrogenation (C), or from the respective arene *via* Friedel–Crafts acylation with cinnamoyl chloride (B) or hydrocinnamoyl chloride (D).



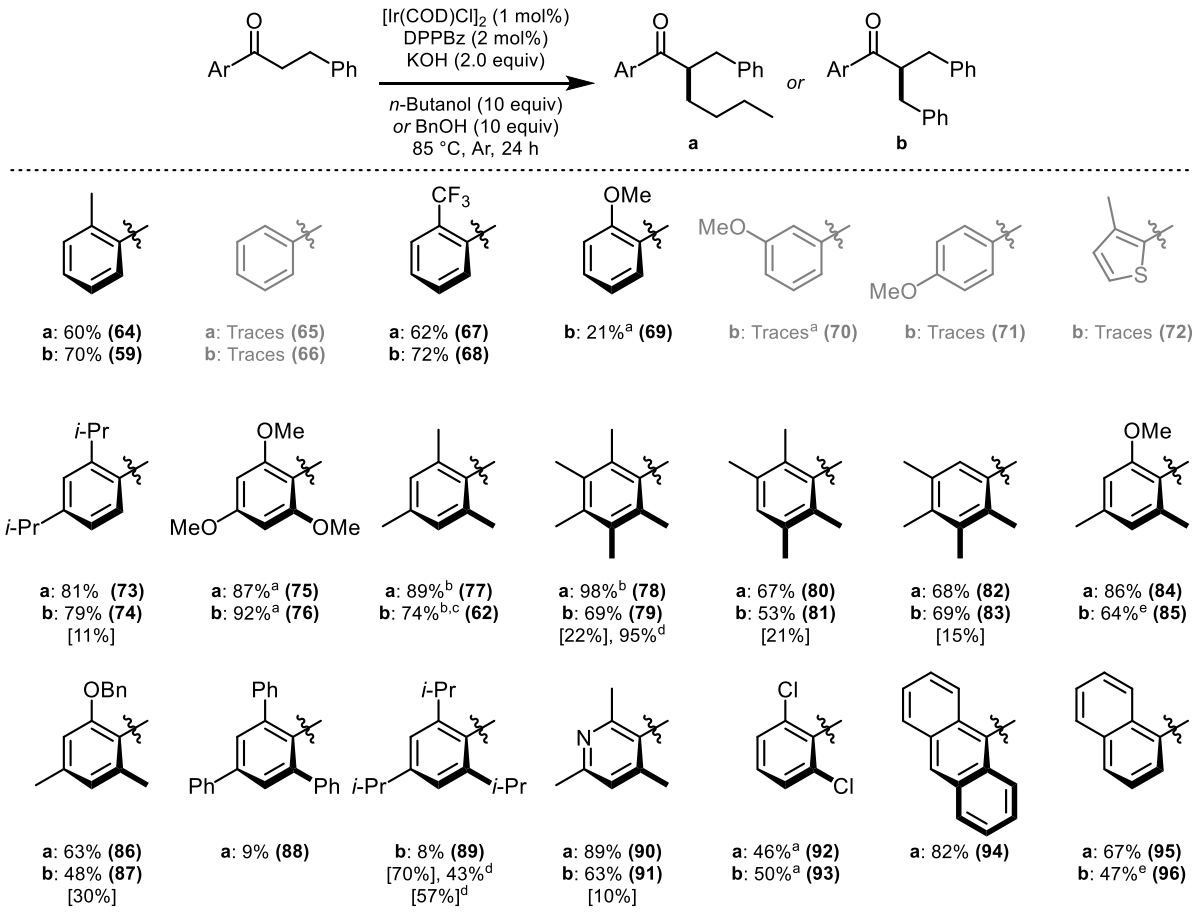
Scheme 3.10 *Retrosynthesis of α-branched products and the chalcone-derived precursors.*

The use of cinnamoyl chloride presents multiple advantages for Friedel–Crafts acylation over other reagents. Being a solid, it can also be conveniently weighed out in the open air, and is less sensitive to moisture than liquid acetyl halides or hydrocinnamoyl chloride. It does not undergo an intramolecular Friedel–Crafts reaction that is particularly competitive for sterically demanding substrates with 2,4,6-triisopropylphenyl or 1,3,5-triphenylphenyl group when hydrocinnamoyl chloride is used, and is also significantly cheaper than hydrocinnamoyl chloride.[*] Finally, it dispenses the need to perform an aldol condensation compared to if acetyl halides were used.

The reduction of the enone can be easily achieved through catalytic hydrogenation or sodium borohydride reduction. It should be noted that 9-anthracenyl enone **9** gave a complex mixture when subjected to catalytic hydrogenation, possibly due to the reactivity of the central anthracene ring. All the di-*ortho*-substituted substrates, including the anthracenyl substrate, did not suffer from any over-reduction to the alcohol, while the mono-*ortho*-substituted substrates started to display ketone reduction upon prolonged exposure to catalytic hydrogenation conditions. The full list of substrates may be found in Appendix 10.2.

[*] The average cost of cinnamoyl chloride is £0.16/g (Sigma-Aldrich), whereas for hydrocinnamoyl chloride it is £2.50/g (Sigma-Aldrich).

3.2.5 Substrate Scope



Scheme 3.11 *Substrate scope for the hydrogen borrowing reaction. Numbers in square parentheses indicate the yield of the enone obtained from the reaction with benzyl alcohol. For a complete list of substrates, see Appendix 10.2.* [a]*The starting material was provided by Dr. James Frost;* [b]*Reaction was performed by Dr. James Frost;* [c]*The rest of the mass balance was the enone;* [d]*Reaction done at 105 °C;* [e]*The enone was not isolated.*

The exploration of the substrate scope was jointly carried out by Choon Boon Cheong and Dr. James Frost.

The effect of an *ortho* substituent on the yield of the reaction is striking (Scheme 3.11). Removal of all substituents resulted in only traces of products **65** or **66** as observed by ^{1}H NMR of the crude mixture. The *ortho*-trifluoromethyl group was just as effective as the *ortho*-methyl group, giving **67** and **68** in comparable yields. The methoxy group seemed ineffective, with only the *ortho*-methoxy group capable of giving a low yield of product **69**. No desired product **72** was observed for the heteroaromatic thienyl ketone.

A more sterically-demanding *ortho*-isopropyl group was superior to the *ortho*-methyl group, giving an improved 81% yield of ketone **73**, suggesting a steric effect is in play. Performing the same reaction with benzyl alcohol gave a comparable yield, but the corresponding enone could also be isolated in 11% yield. This persistence of the enone intermediate derived from reactions with benzyl alcohol was observed for many of the other substrates as well, particularly the di-*ortho*-substituted examples.

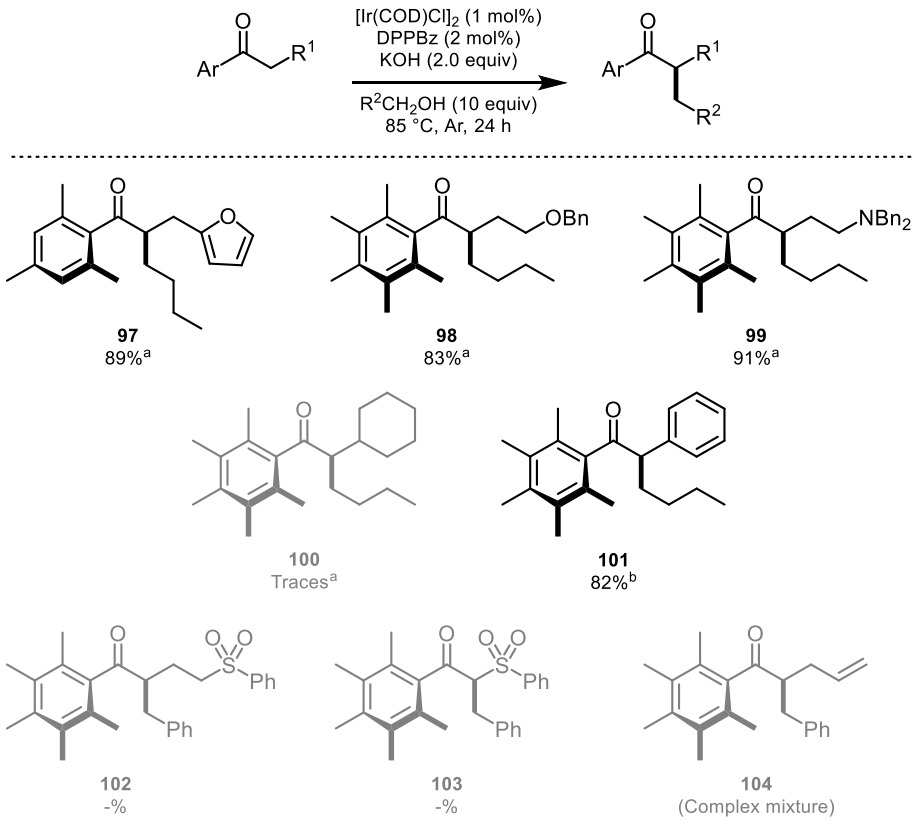
It was very apparent that di-*ortho*-substituted aryl substrates were generally superior to the mono-*ortho*-substituted examples in the hydrogen borrowing reaction. The effect of the second *ortho* group is clearly highlighted by the markedly higher yields of products bearing the trimethoxyphenyl (**75** and **76**), mesityl (**77** and **62**) and duryl (**80** and **81**) groups compared to the respective monosubstituted analogues. In addition, there was also no trace of any benzylic alcohol, suggesting that the undesirable ketone reduction pathway has been shut down. The pentamethylphenyl group, nicknamed Ph* by analogy to the pentamethylcyclopentadienyl group (Cp*), was particularly effective, giving ketones **78** and **79** in near-quantitative yields. Both ketones **82** and **83** that bear the phrenitene group, which has one fewer *ortho*-methyl group than the Ph* analogue, had similar yields the *ortho*-tolyl products **64** and **59**, again clearly highlighting the critical effect of a second *ortho* substituent.

It was interesting to note that the yield of mesityl ketone **62** was virtually identical to that from the initial screen, which retrospectively vindicated the choice of using *ortho*-tolyl substrate **56** for a more rigorous optimisation.

The di-*ortho*-substituted ketone products bearing one or more *ortho*-methyl groups (2-OMe: **84** and **85**, 2-OBn: **86** and **87**, mesityl: **77** and **62**) had slightly lower yields compared to the trimethoxyphenyl ketones **75** and **76**. The presence of *meta*-methyl groups also appeared to exacerbate this effect, as evident from the yields of the duryl (**80** and **81**) and Ph* (**78** and **79**) ketones. However, the additional methyl groups did not affect the yield of the mono-*ortho*-substituted prehnitene ketones **82** and **83**. The use of very large *ortho* substituents led to very poor yields of the desired products, with the meagre yield of 1,3,5-triphenylphenyl product **88** being particularly telling. The yield for triisopropylphenyl ketone **89** was also very low compared to the mesityl analogue **62** unless the reaction was heated to 105 °C, although there was very good overall conversion to the corresponding enone.

The hydrogen borrowing reaction was also able to tolerate certain heteroatom functionalities. Products bearing the electron-withdrawing pyridine ring (**90** and **91**) could be formed in good yield. The successful formation of di-*ortho*-chlorophenyl products **92** and **93** is quite remarkable. The reduced yield could be attributed to the gradual hydrolysis and decomposition of the chloro groups, possibly by an S_NAr pathway. However, it cannot be ruled out that there may be undesirable interactions between the iridium catalyst and the C–Cl bond, or any electronic effects on the aromatic ring.

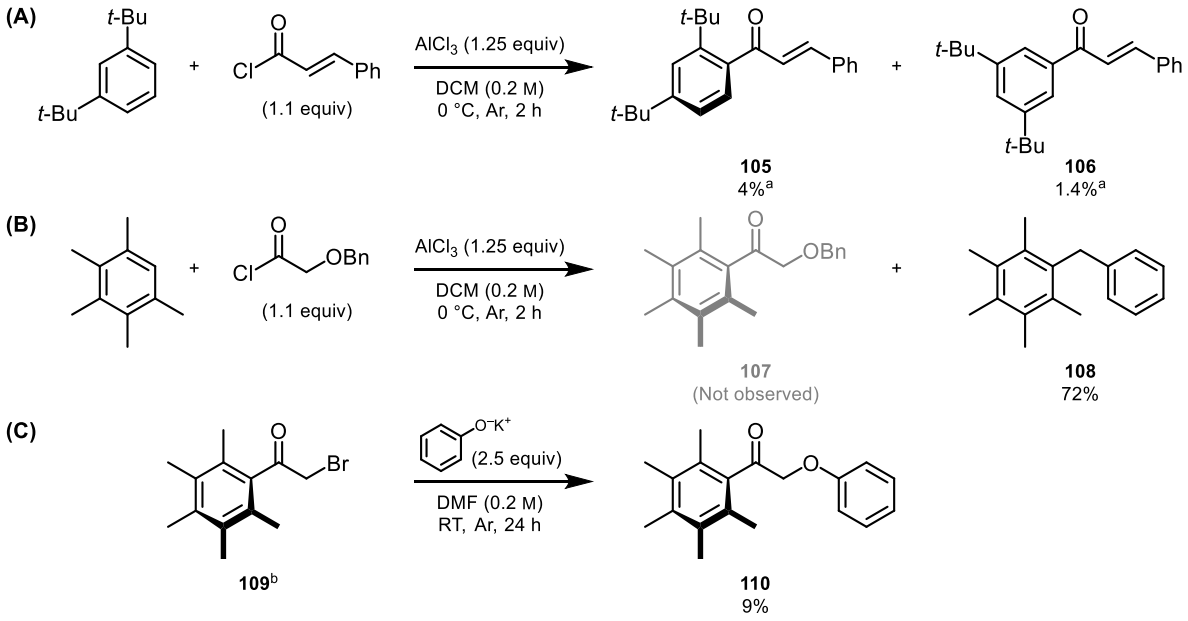
An interesting form of *ortho* substitution is illustrated by the formation of 9-anthracenyl and 1-naphthyl ketones **94**, **95** and **96** respectively. The extended aryl groups away from the central ring appear to be just as effective as methyl groups.



Scheme 3.12 *Side chain variations for the substrate scope study of the hydrogen borrowing reaction.* [a]*Work by Dr. James Frost;* [b]*Work by Sean Guggari;* [c]*BnOH was used instead.*

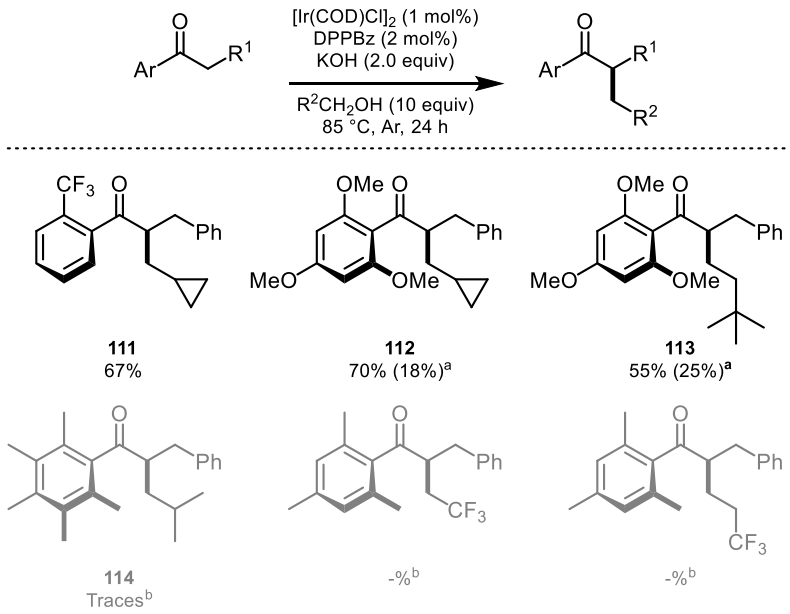
The alkyl pendant of the ketone substrate was a suitable motif to investigate functional group tolerance (Scheme 3.12). Work by Dr. James Frost showed that the hydrogen borrowing reaction could tolerate heteroaromatic functionalities such as a furan group (**97**), as well as benzyl-protected heteroatom functionalities (**98** and **99**), but the presence of a β-substituent led to negligible conversion, such as the case of α-cyclohexylmethyl ketone **100**. Interestingly, work by Sean Guggari showed that an α-phenylketone, which bore an sp^2 β-substituent, could be alkylated to give ketone **101** in very good yield. This difference in reactivity could possibly be attributed to a reduced pK_a of the α-keto proton due to the α-phenyl group (see also Section 3.4.1 and Table 3.11). A steric argument is also possible, as the phenyl group can twist out of plane to alleviate any steric clash during enolate formation, whereas the cyclohexyl group is unable to do so.

Disappointingly, attempts to form the α-branched ketones **102** and **103** bearing a phenylsulfonyl group were unsuccessful, and only decomposition was observed, with no trace of starting material, enone, product or reduced ketone observed. A complex mixture was also observed in the attempted formation of ketone **104**, possibly due to multiple side reactions such as reduction of the alkene. These functional groups are likely incompatible with this hydrogen borrowing methodology.



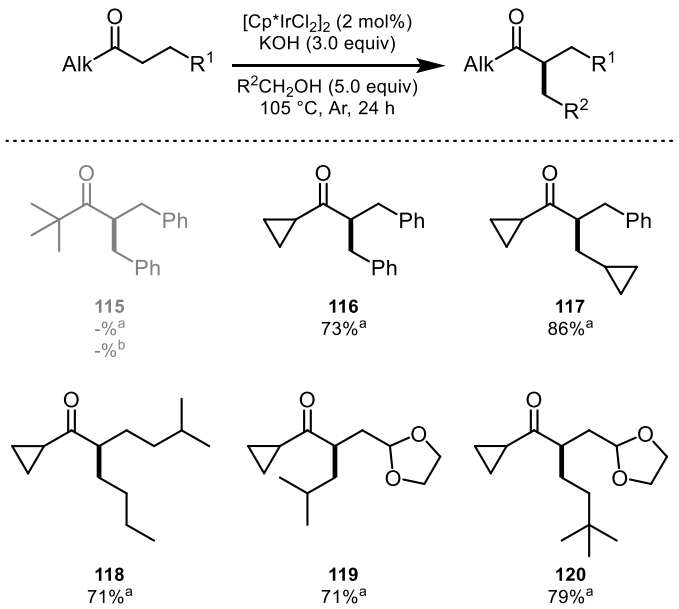
Scheme 3.13 *Unsuccessful attempts at (A) formation of ortho-tert-butyl substrate via Friedel–Crafts acylation, and formation of Ph* α-oxyketones via (B) Friedel–Crafts acylation and (C) Williamson ether synthesis. [a]Isolated as an inseparable mixture; [b]Material was provided by Dr. James Frost.*

Unfortunately, a small number of substrates could not be synthesised, which limited the exploration of the substrate scope (Scheme 3.13). An attempted Friedel–Crafts reaction of 1,3-di-*tert*-butylbenzene gave an inseparable mixture of **105** and **106** in low yield. An attempt to form α-benzyloxyketone **107** by a Friedel–Crafts reaction also failed to give any desired product as the Ph* ring had attacked the benzyl group to give diarylmethane **108** instead. In addition, the formation of α-phenoxyketone **110** from α-bromo ketone **109** was low yielding. As a result, the steric effects of a mono-*ortho*-*tert*-butyl substitution and the electronic effects of an α-oxyketones on hydrogen borrowing could not be investigated.



Scheme 3.14 *Exploring the types of alcohol that can be used for the hydrogen borrowing reaction.* [a]*Number in parentheses indicate the yield of the corresponding enone;* [b]*Work by Dr. James Frost.*

Aside from benzyl alcohol and *n*-butanol, the hydrogen borrowing reaction could also be performed with cyclopropylmethanol and neopentylmethanol (e.g. ketones **111**, **112** and **113**, Scheme 3.14). However, work by Dr. James Frost revealed that when the hydrogen borrowing reaction was attempted with isobutanol, only traces of the product **114** were formed, suggesting that steric bulk on the alcohol chain is compromising the hydrogen borrowing reaction, possibly impacting the oxidation of the alcohol or the formation of the enone intermediate. Attempts to use trifluoroethanol or 3,3,3-trifluoropropan-1-ol were also unsuccessful. Sam et al. had attributed this poor reactivity of fluorinated alcohols to a more difficult β-hydride elimination during the oxidation step of the hydrogen borrowing pathway.[124]

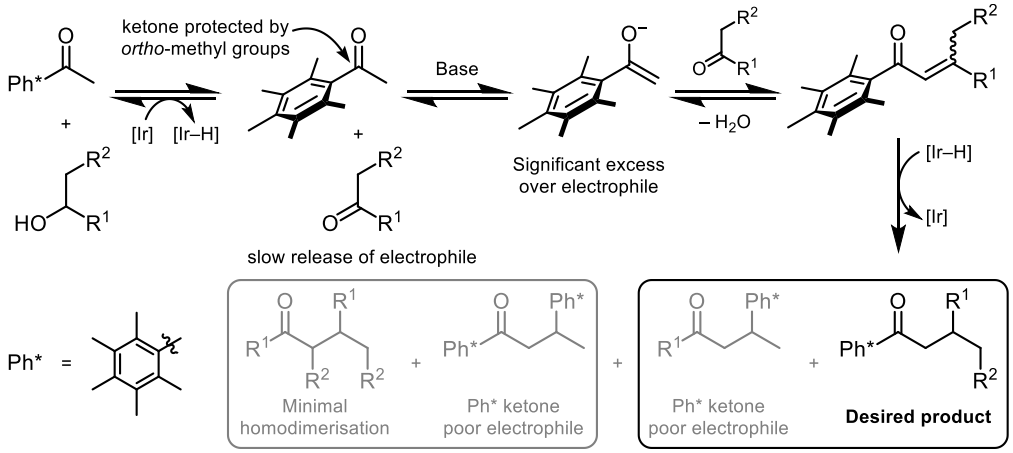


Scheme 3.15 *Alkyl ketones attempted for hydrogen borrowing reaction with higher alcohols.* [a]*Work by Wasim Akhtar;* [b]*Conditions from Scheme 3.11 were used instead.*

Dialkyl ketones were also explored to see if this hydrogen borrowing reaction could also give α-branched ketone products (Scheme 3.15). Although *tert*-butyl ketone **115** did not give any desired product, Wasim Akhtar discovered that a range of cyclopropyl ketones could undergo the hydrogen borrowing process in good yields, in this case using $[Cp^*IrCl_2]_2$ as the catalyst under very similar conditions. Interestingly, isobutanol could be used to perform the hydrogen borrowing alkylation to give a good yield of ketone **119**, unlike the attempted formation of ketone **114**. Given that the size of the cyclopropyl motif is significantly smaller than the Ph* group, it may suggest that the effectiveness of the cyclopropyl ketone could be due to an electronic effect, although a contributing steric effect (or lack of sterics) cannot be ruled out. Further work on the use of dialkyl ketones for hydrogen borrowing is currently being carried out by the Donohoe group.

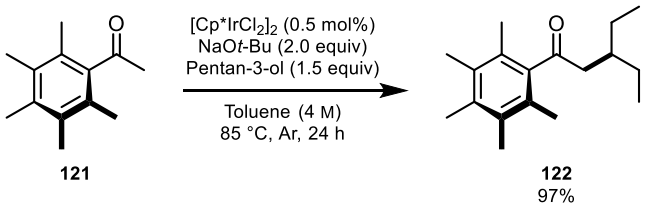
3.3 Synthesis of β- and α,β-Branched Ketones

3.3.1 Controlling the Outcome of the Hydrogen Borrowing Reaction with Secondary Alcohols



Scheme 3.16 *Use of a di-ortho-substituted phenyl ketone (e.g. Ph* ketone) and the gradual release of ketone electrophile by hydrogen borrowing to control the outcome of an aldol sequence. Products are assumed to be ketones in this scheme.*

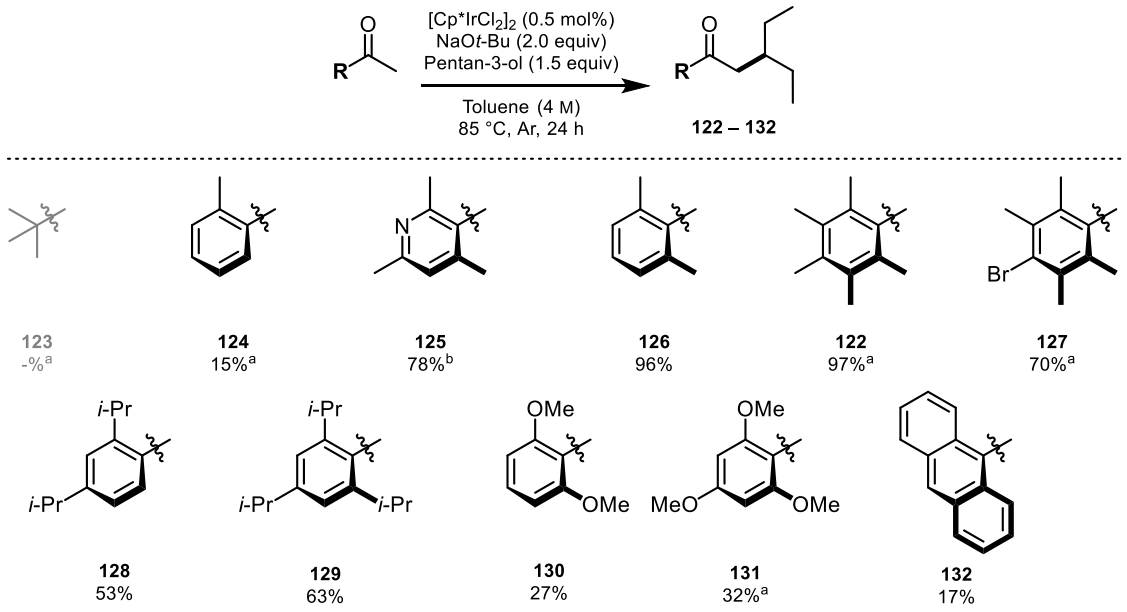
The next goal in hydrogen borrowing catalysis was to effectively synthesise β-branched compounds. In the previous section it was observed that the di-*ortho*-substituted substrates did not undergo any ketone reduction, something that the mono-*ortho* or unsubstituted substrates suffered from. This protective effect could be exploited to protect the carbonyl of the ketone substrate from nucleophilic attack or reduction (Scheme 3.16). In addition, the catalytic oxidation of the secondary alcohol slowly releases small amounts of the ketone electrophile thereby suppressing Guerbet-type homodimersation. The di-*ortho*-substituted ketone would form the enolate in relative excess to and react with the small amount of ketone electrophile generated at any one point of time, thus controlling the outcome of the reaction.



Scheme 3.17 *Optimised conditions developed by Wasim Akhtar for the hydrogen borrowing reaction with secondary alcohols.*

Using Ph* methyl ketone as the substrate and pentan-3-ol as the alkylating agent, the optimisation was carried out by Wasim Akhtar to give β-branched ketone **122** with an optimised yield of 97% (Scheme 3.17).

3.3.2 Substrate Scope

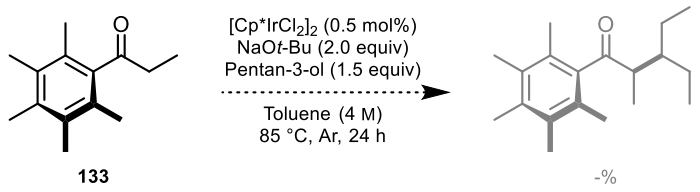


Scheme 3.18 *Investigations into the variation of the aryl group for the hydrogen borrowing reaction with secondary alcohols. [a]Reaction performed by Wasim Akhtar; [b]Reaction performed by Dr. James Frost.*

The exploration of the substrate scope was jointly carried out by Wasim Akhtar, Choon Boon Cheong and Dr. James Frost.

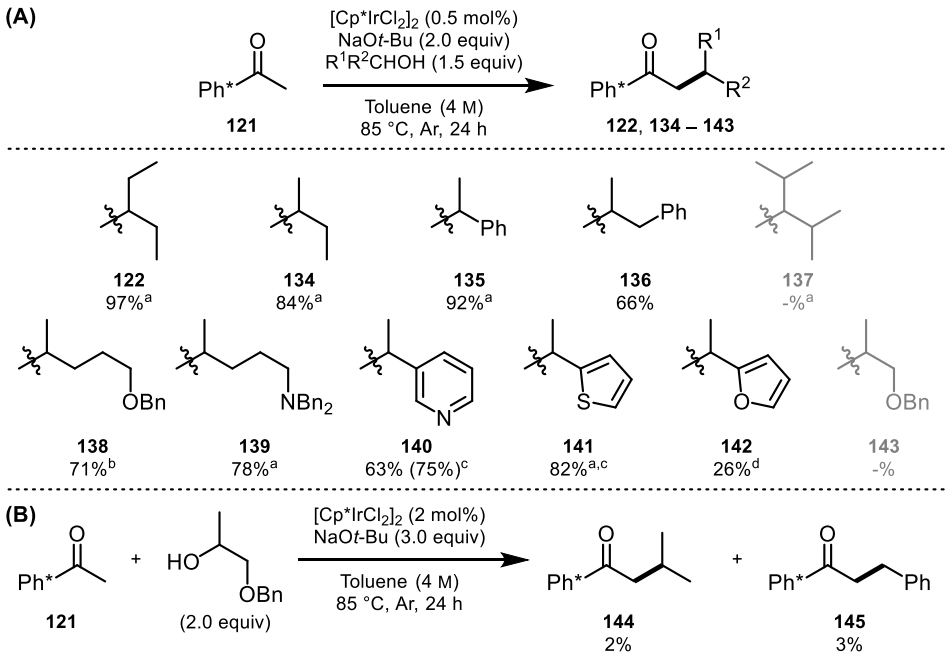
The first step of the substrate scope study was to compare the effects of the substituents and substitution patterns on the aryl group with those from Scheme 3.11, and the results were striking (Scheme 3.18). When pinacolone was attempted as the substrate, there was no desired product formed. The *ortho*-tolyl substrate now fared exceedingly poorly, giving a mediocre 15% yield of ketone **124** compared to the α-alkylation reaction that had a much better yield of 70% (see Scheme 3.11). Nevertheless, the effect of the second *ortho*-methyl group was particularly impressive, as indicated by the good yields of the products with the trimethylpyridine (**125**), dimethylphenyl (**126**) and Ph* (**122**) groups. Pleasingly, ketone **127** bearing the *para*-bromo analogue of Ph* could be formed in a respectable yield of 70%.

The yield for 2,4-diisopropylphenyl product **128** was comparatively higher than that of the *ortho*-tolyl substrate, a situation akin to the α-alkylation with primary alcohols, while the introduction of a second *ortho*-isopropyl group (**129**) resulted in further improvement to the yield. Disappointingly, the dimethoxyphenyl (**130**), trimethoxyphenyl (**131**) and 9-anthryl (**132**) products were all formed in very poor yields. These results deviate significantly from those of the α-alkylation, and will be discussed in detail in Section 3.4.



Scheme 3.19 *Attempted hydrogen borrowing reaction using Ph* ethyl ketone as substrate. Reaction was performed by Dr. James Frost.*

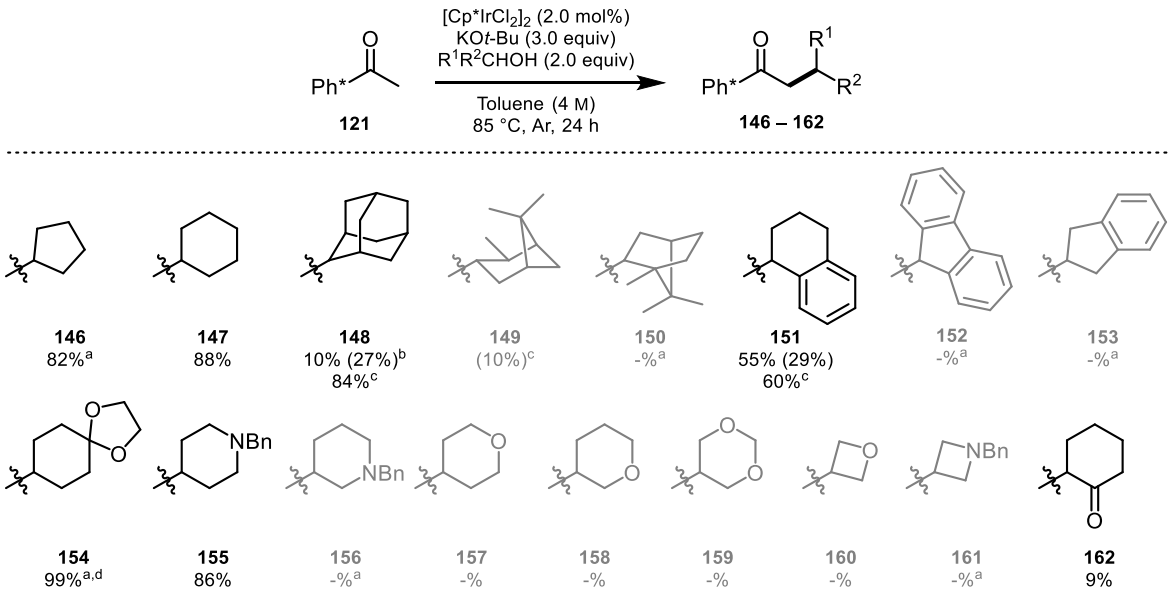
Disappointingly, Dr. James Frost found that no conversion was observed when the hydrogen borrowing reaction of ethyl ketone **133** with pentan-3-ol was attempted, suggesting that the synthesis of α,β-substituted compounds by this methodology is currently unfeasible (Scheme 3.19).



Scheme 3.20 *(A) β-branched ketones formed by the hydrogen borrowing reaction of* ***121*** *with acyclic secondary alcohols. (B) Degradation was observed for the reaction with a 2-benzyloxy alcohol. [a]Reaction performed by Wasim Akhtar; [b]Reaction performed by Dr. James Frost; [c]Reaction performed with [Cp*IrCl2]2 (2 mol%), NaOt-Bu (3.0 equiv) and alcohol (2.0 equiv); [d]Reaction performed with [Cp*IrCl2]2 (2 mol%), KOt-Bu (3.0 equiv) and alcohol (2.0 equiv).*

A wide range of secondary alcohols were next subjected to the reaction conditions with Ph* substrate **121** to probe the functional group tolerance of the reaction. The wide commercial availability of secondary alcohols with a variety of functional groups and structural motifs greatly facilitated the investigation (Scheme 3.20).

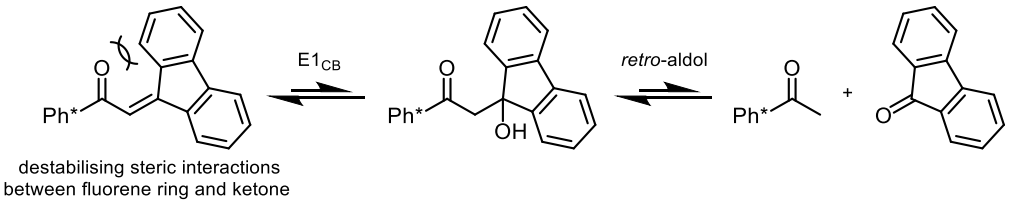
Products with alkyl (**122** and **134**), aryl (**135**) and benzyl (**136**) groups at the β-position were formed in excellent yields. However, no reaction was observed when there were alkyl substituents at the 2-position of the alcohol (**137**), again suggesting that sterics have a significant effect on the hydrogen borrowing reaction (see also Scheme 3.22). Several protected heteroatoms (**138** and **139**) and heteroaromatics (**140** and **141**) were well-tolerated, but ketone **142** bearing a 2′-furyl group had a poor yield. The use of a 2-benzyloxy alcohol gave a highly complex mixture, and an attempted purification of the mixture revealed traces of ketones **144** and **145**, their formation indicating the loss and subsequent undesired participation of the benzyloxy group in the hydrogen borrowing reaction.



Scheme 3.21 *β-Branched ketones formed from the hydrogen borrowing reaction of* ***122*** *with cyclic secondary alcohols. Numbers in parentheses indicate the yield of the corresponding enone. [a]Reaction performed by Wasim Akhtar; [b]Reaction performed with NaOt-Bu (3.0 equiv); [c]Reaction performed at 105 °C; [d]Reaction performed with [Cp*IrCl2]2 (0.5 mol%), NaOt-Bu (2.0 equiv) and alcohol (1.5 equiv).*

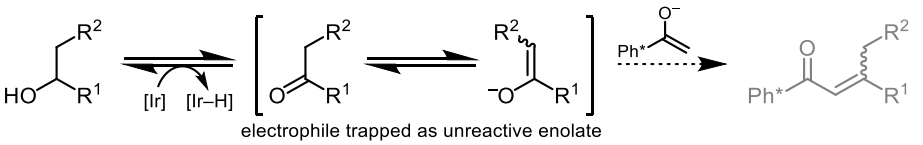
The use of cyclic secondary alcohols in the hydrogen borrowing reaction gave significantly more varied results (Scheme 3.21). Simple aliphatic cyclic alcohols gave good yields (**146** and **147**), while more bulky alcohols such as adamantan-2-ol, which has two bridgehead tertiary centres at the 2-position of the alcohol, required elevated temperatures for effective conversion to ketone **148**. In contrast, attempts at using bulky terpenoid alcohols such as (+)-isopinocampheol and (–)-borneol, bearing tertiary and quaternary centres at their respective 2-positions relative to the alcohol, resulted in little or no conversion to **149** or **150**.

The benzylic alcohol α-tetralinol furnished ketone **151** smoothly, but 9-fluorenol failed to give any trace of the product, an unusual result given the reactivity of the acyclic benzylic alcohols seen earlier (see Scheme 3.18). This could possibly be due to the *cis*-vinylene effect that would destabilise the enone and disfavour its formation, thereby promoting a *retro*-aldol reaction (Scheme 3.22).[1]



Scheme 3.22 *The cis-vinylene effect deters the formation of the enone intermediate, thereby promoting the retro-aldol process.*

The homobenzylic alcohol 2-indanol (**153**) was unreactive under hydrogen borrowing conditions, which contrasts with the acyclic homobenzylic alcohol (**136**, see Scheme 3.20). This could be attributed to the surprisingly low pK_a of 2-indanone (Table 3.11, see also Appendix 10.3),[125] resulting in the conversion of the electrophile to the unreactive enolate and thus cannot undergo aldol condensation with the enolate of Ph* methyl ketone.



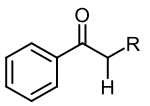
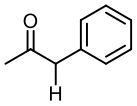
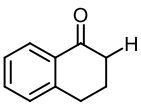
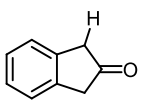
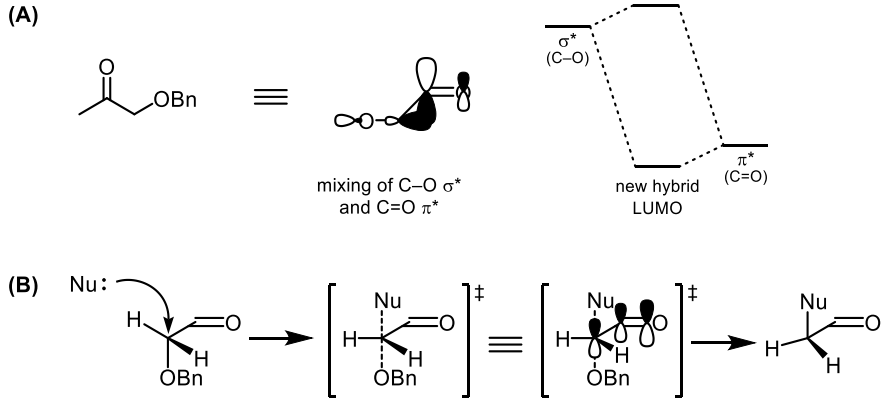
Ketone					
pK_a (DMSO)	26.5	24.7 (R = H) 24.4 (R = Me) 23.5 (R = Bn)	19.8	24.7	16.9

Table 3.11 *pK_a values of several ketone electrophiles formed in situ during hydrogen borrowing. Acetone is included as reference. A lower pK_a increases deprotonation and reduces the amount of electrophile present.*

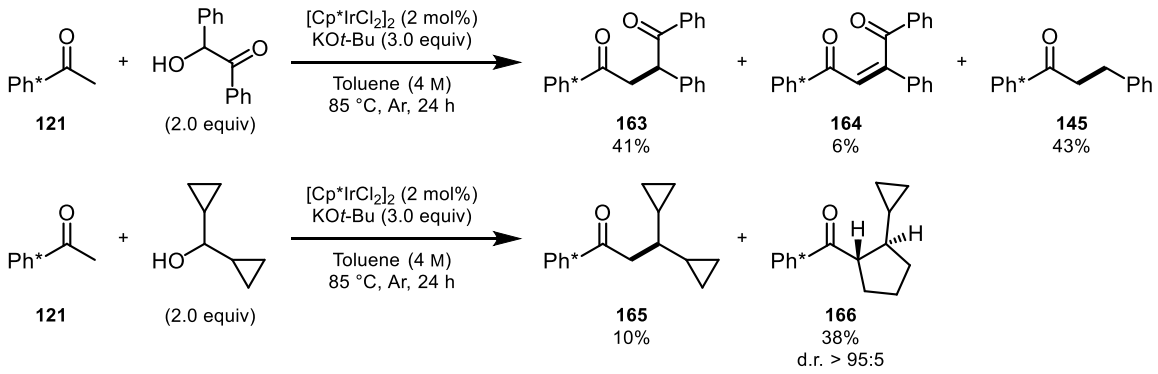
There were only a few heteroatom substitutions within the cyclic secondary alcohol skeleton that were tolerated. An acetal-protected ketone and a protected piperidine at the 4-position of the alcohols could furnish the alkylated products **154** and **155** respectively in excellent yield (see Scheme 3.21). However, no reaction was observed with an isomeric diol substituted with nitrogen at the 3-position. In addition, no product was observed if the 4-position of the carbon skeleton was substituted with an oxygen atom. An extended $E1_{CB}$ elimination could occur when the enone intermediate is deprotonated, so it is surprising that piperidine product **155** could be cleanly formed but not the tetrahydropyran (**157**).

Oxygen substitutions at the 3-position (**158** and **159**) both gave very complex mixtures, further suggesting the lability of ether substituents at the 2-position of the alcohol. The 3-oxa- and 3-azacyclobutanol analogues also did not give any desired reaction. This could also partly be attributed to a difficult oxidation of electron-deficient alcohols similar to the case of trifluoroethanol (see Scheme 3.14).[124] Having a carbonyl group at the 2-position resulted in a meagre 10% yield of dione **162**, although this represents a significant improvement over the rest of the substrates with heteroatom substitutions at the 2-position. It is unclear if the dione or the α-hydroxyketone served as the electrophile in this case.



Scheme 3.23 *(A) Interactions of the C=O π*-orbital with C–O σ* orbital leading to a new lower energy hybrid LUMO, and (B) interactions of the C=O π-orbital with the forming p-orbital, leading to a stabilisation in the transition state for the S_N2 displacement of an α-ether ketone.*

The lability of ether groups at the 2-position of the alcohol (see Scheme 3.20B) could be rationalised by the observation that heteroatoms at the α-position of the ketone are significantly more reactive towards S_N2 (Scheme 3.23). The σ* orbital for the C–O bond could mix with the π* of the C=O bond to give a new lower energy hybrid LUMO.[126] In addition, the forming *p*-orbital in the transition state of the S_N2 reaction can interact with the π-orbital of the C=O group, leading to a stabilisation of the transition state.[127] This greatly lowers the activation energy of the reaction, thus even poor leaving groups like ethers could become labile under the strongly basic reaction conditions and elevated temperatures.

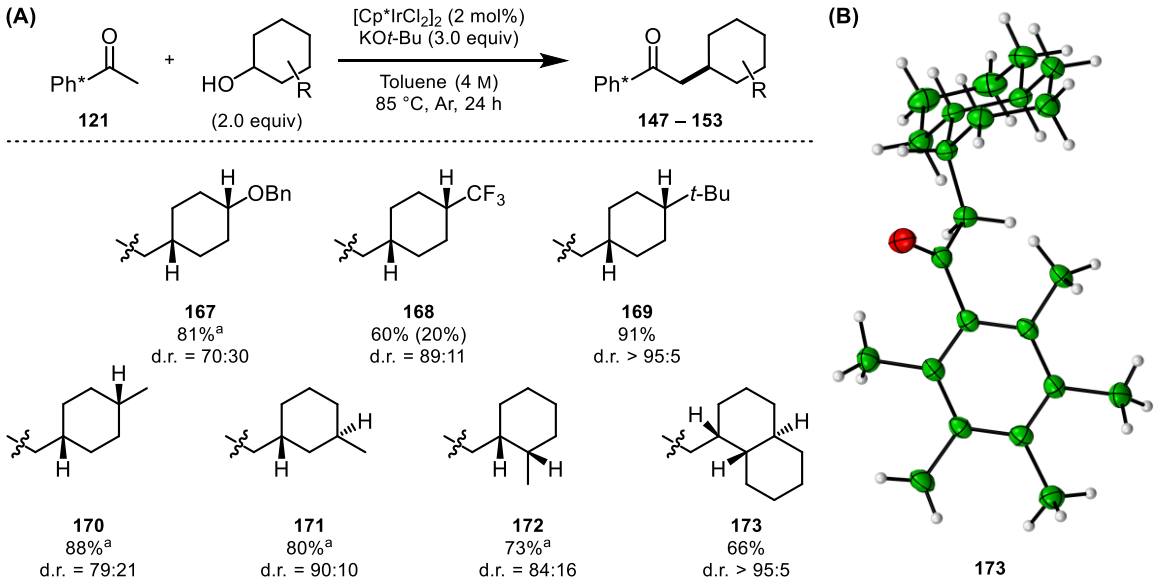


Scheme 3.24 *Unusual outcomes from the attempted formation of β-branched ketones via hydrogen borrowing.*

There were unusual results observed for two secondary alcohols attempted (Scheme 3.24). An attempt to use benzoin as the secondary alcohol resulted in a modest yield of dione **163**, however it also appears that the alcohol or intermediates derived from it had fragmented, giving the primary alcohol coupling product **145** in comparable yield. It is difficult to ascertain the role of the iridium catalyst or the nature of the species involved in the cleavage, given that 2-oxocyclohexanol gave quite contrasting results (see Scheme 3.19).

Perhaps even more intriguing is the reaction of dicyclopropylmethanol in hydrogen borrowing. A low yield of the β,β-dicyclopropyl ketone **165** was obtained, but surprisingly cyclopentane **166** was also obtained in comparatively higher yield. This unusual result will be discussed in Chapter 4.

Collectively, these observations suggest that steric and electronic effects at the 2-position of the alcohol may impact the hydrogen borrowing reaction. Additionally, accessible C–O bonds, such as oxygen groups at the α-position of the ketone electrophile formed *in situ*, may pose lability issues under the reaction conditions and are not reliable substrates.

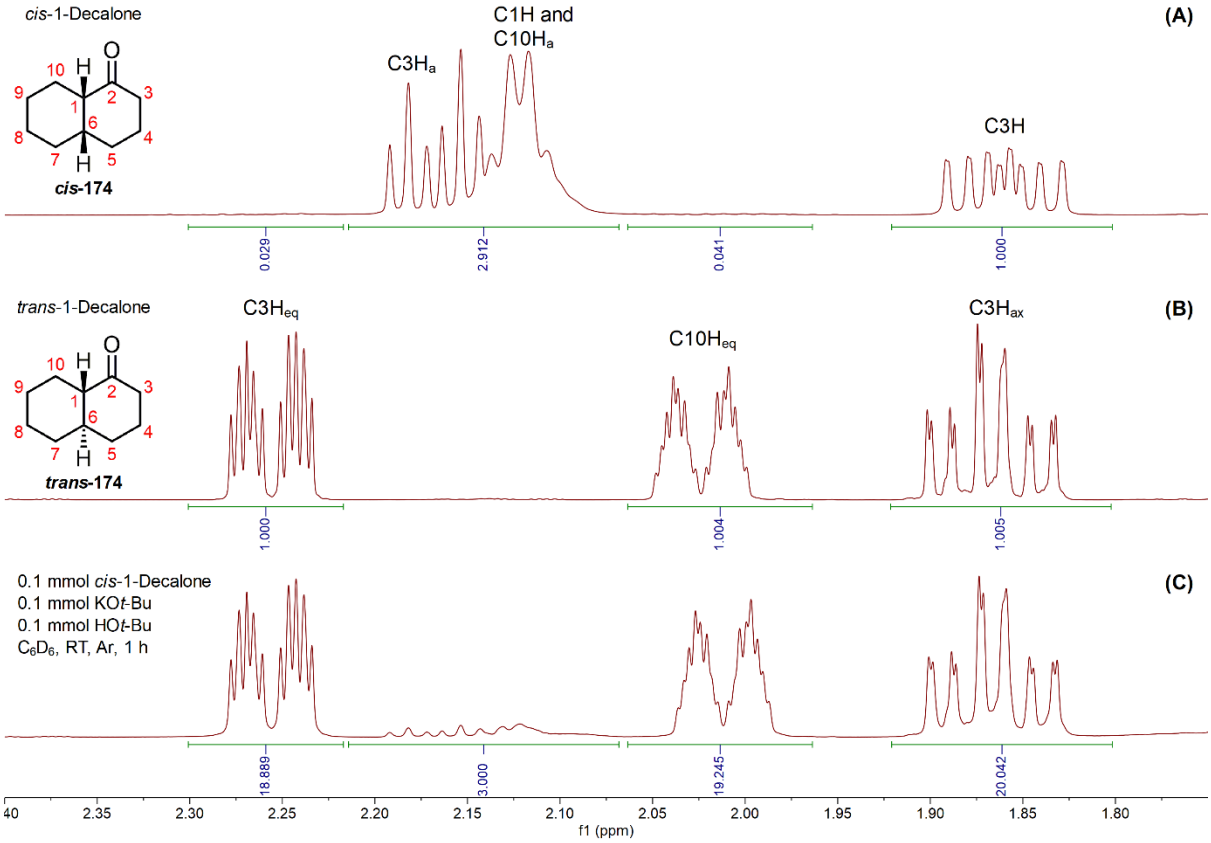


Scheme 3.25 *(A) Investigation into the stereochemical outcome of cyclic β-branched ketones formed via hydrogen borrowing. The d.r.s were obtained by integration of the ^{1}H NMR spectra of the respective crude mixtures. Numbers in parentheses indicate the yield of the corresponding enone. (B) The relative stereochemistry of ketone* ***153*** *was confirmed by X-ray crystallographic analysis. [a]Work by Wasim Akhtar.*

A range of substituted cyclohexanols were attempted to determine the stereochemical outcome of the hydrogen borrowing process, as well as to further gauge the functional group tolerance of the reaction (Scheme 3.25). The benzyloxy and trifluoromethyl groups at the 4-position were well-tolerated, giving the *cis*-cyclohexanes **167** and **168** in good yields. The diastereomeric ratio appears to correlate with the size of the substituent on the 4-position, as evident from the excellent diastereomeric ratio of the 4-*tert*-butylcyclohexane product **169**. The major diastereomers for the 2- and 4-methyl substituted products **170** and **172** were the *cis*-isomers, but when the methyl group is at the 3-position, the *trans*-isomer **171** was obtained instead.

The most impressive result was the use of *cis*-decan-1-ol to give bicyclic ketone **173** containing three consecutive stereocentres in good yield and with excellent diastereoselectivity. The *cis* configuration between the ring junction and the pendant ketone is consistent with the 2- and 3-substituted substrates. However, the product has a *trans*-

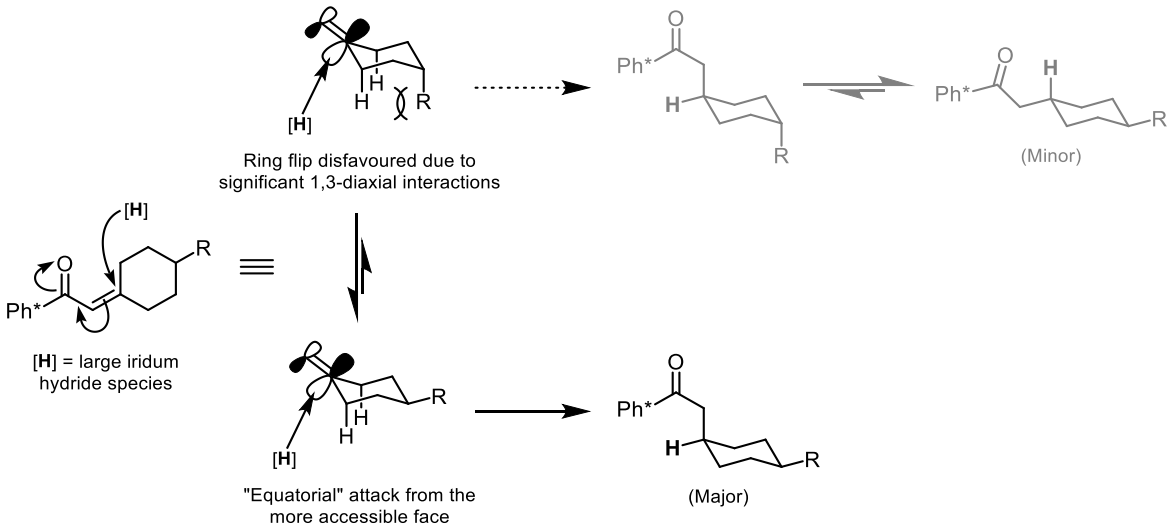
bicyclic ring instead of the *cis*-decalin ring from the starting material. The relative stereochemistry was confirmed by single crystal X-ray crystallography (see Scheme 3.25B).



Scheme 3.26 *Stacked ^{1}H NMR spectra of (A) cis-1-decalone, (B) trans-1-decalone, and (C) cis-1-decalone subjected to conditions intended to mimic the reaction conditions, apart from being performed at RT instead of 85 or 105 °C. tert-Butanol was intended to mimic the alcohol present in the reaction. The cis:trans ratio of isomeric 1-decalones after stirring at RT for 1 h was approximately 5:95.*

Under the basic conditions, the *cis*-1-decalone *cis*-**174** formed *in situ* could have isomerised to the thermodynamically more stable *trans*-isomer *trans*-**174**. Indeed, when pure *cis*-1-decalone (d.r. > 95:5) was subjected to conditions intended to mimic the reaction conditions, within an hour at room temperature the ratio of *cis*- to *trans*-isomers was approximately 5:95, suggesting a very facile *cis-trans* isomerisation (Scheme 3.26). However, this does not exclude the possibility of epimerisation by γ-deprotonation and reprotonation of the *cis*-decalin enone intermediate.

The stereochemical outcome of the hydrogen borrowing reaction appears consistent with an equatorial attack of a large iridium hydride species onto the *exo*-enone, with the diastereoselectivity congruent to the size of the substituent based on A-values of the substituents on the 4-position (Table 3.12).[128,129] Larger substituents encounter greater 1,3-diaxial interactions that disfavour the reactive conformer leading up to the formation of the minor isomer. Incidentally, this trend can also be visualised by taking the natural logarithm of the diastereomeric ratios of the respective products to give a result that mirrors their respective A-values reasonably well. This approximation is sufficiently useful to predict the stereochemical outcome of the major product.

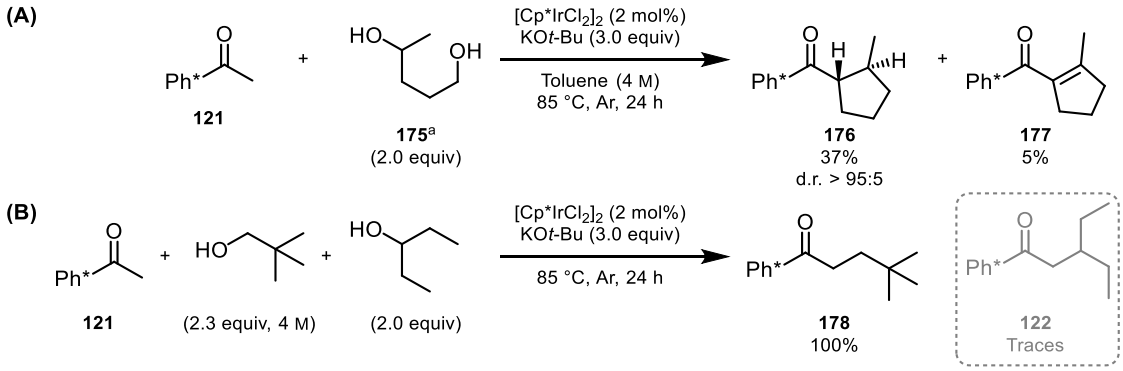


	OEt[a]	Me	CF_3	*t*-Bu
A-value	0.9	1.7	2.1	> 4.5
d.r.	70:30[b]	79:21	89:11	> 95:5
ln(d.r.)	0.85	1.3	2.1	> 2.9[c]

Table 3.12 *A model for the reduction of the enone intermediate to predict the stereochemistry of the products. The stereoselectivity of the reaction is influenced by the size of the second substituent on the ring depicted by their A-values, and is consistent with that for the attack of by a large nucleophile.*[128,129] *[a]A-values for OBn were unavailable, and were instead approximated by OEt instead; [b]d.r. is that for the OBn substituted product. [c]The apparent low value is due to limitations of integration by NMR, with the true value likely much higher, given that for a 99:1 ratio, ln(99) = 4.5.*

3.3.3 Towards the Synthesis of α,β-Substituted Ketones

In the quest to further improve the capabilities of the hydrogen borrowing reaction, the ability to access α,β-branched ketones is a goal that has proven difficult to reach. The formation of α-branched ketones could not utilise secondary alcohols and did not tolerate some substrates with substituents on the β position (see Scheme 3.12). The formation of β-branched ketones could only be performed with the methyl ketone and failed when the ethyl ketone was attempted (see Scheme 3.19).



Scheme 3.27 *(A) Hydrogen borrowing reaction with a diol to form a cyclic α,β-branched ketone. (B) The hydrogen borrowing reaction was chemoselective for primary alcohols.* [a]*The reagent was provided by Dr. James Frost.*

One of the strategies often used to promote a difficult reaction is to tether the two reacting groups together, so that there is less entropic cost in the reaction. Following that line of thought, a diol substrate **175** containing a secondary alcohol and a primary alcohol motif was attempted (Scheme 3.27). Pleasingly, the substrate could perform two consecutive hydrogen borrowing reactions to give cyclopentyl ketone **176** in modest yield and with excellent diastereoselectivity.

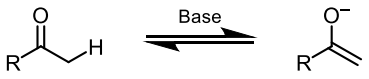
To determine if the hydrogen borrowing first occurs on the primary or the secondary alcohol, a modification was made to the reaction conditions. A limited amount of the bulky neopentyl alcohol was employed in place of toluene to maintain the same overall volume of the reaction. Despite the similar stoichiometry of both alcohols, the hydrogen borrowing reaction proceeded with near-complete selectivity for neopentyl alcohol to furnish ketone **178** in quantitative yield, with only baseline traces of the β-branched product **122** observed by ^{1}H NMR analysis of the crude mixture. This suggests that the hydrogen borrowing reaction proceeds from the primary alcohol first, followed by a successful intramolecular hydrogen borrowing reaction of a secondary alcohol to give a cyclic α,β-branched ketone product. Work on this reaction is currently being pursued by the Donohoe group.

3.4 Discussion

Given that *ortho*-substituted substrates have proven to be particularly successful, it is worth looking into the roles of the various manifestations of the *ortho* effect and comparing with the literature precedents reported by Morita et al. and Taguchi et al.[92,95] A detailed discussion on the factors influencing the *ortho* effect will be reserved for Chapter 7.

3.4.1 Generation of Enolate

The report on the successful formation of α-branched ketones with *n*-butanol by Morita et al. was achieved with the highly acidic dibutyl malonate using catalytic Cs_2CO_3 as the base.[95] The large difference in pK_a values between the malonate and acetophenones could be a contributing factor for the lack of any reaction when Cs_2CO_3 was used as base in the exploratory work by Dr. Darren Poole (Table 3.13, see also Scheme 3.5).[113] The substrates employed for the α- and β-alkylation of ketones earlier were *ortho*-substituted, which may have decreased the pK_a of the α-keto proton. This is supported by the characteristic pK_a modulation property of the *ortho* effect caused by the steric inhibition of resonance, for example *ortho*-toluic acid being more acidic than *meta*- or *para*-toluic acid (see Section 1.2 and Appendix 10.3). Since the benzoic acids are isoelectronic to the acetophenones, it is likely that the *ortho* effect is also lowering the pK_a of the α-keto proton for the ketones.



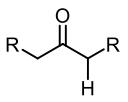
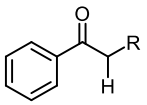
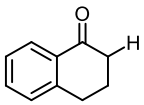
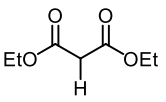
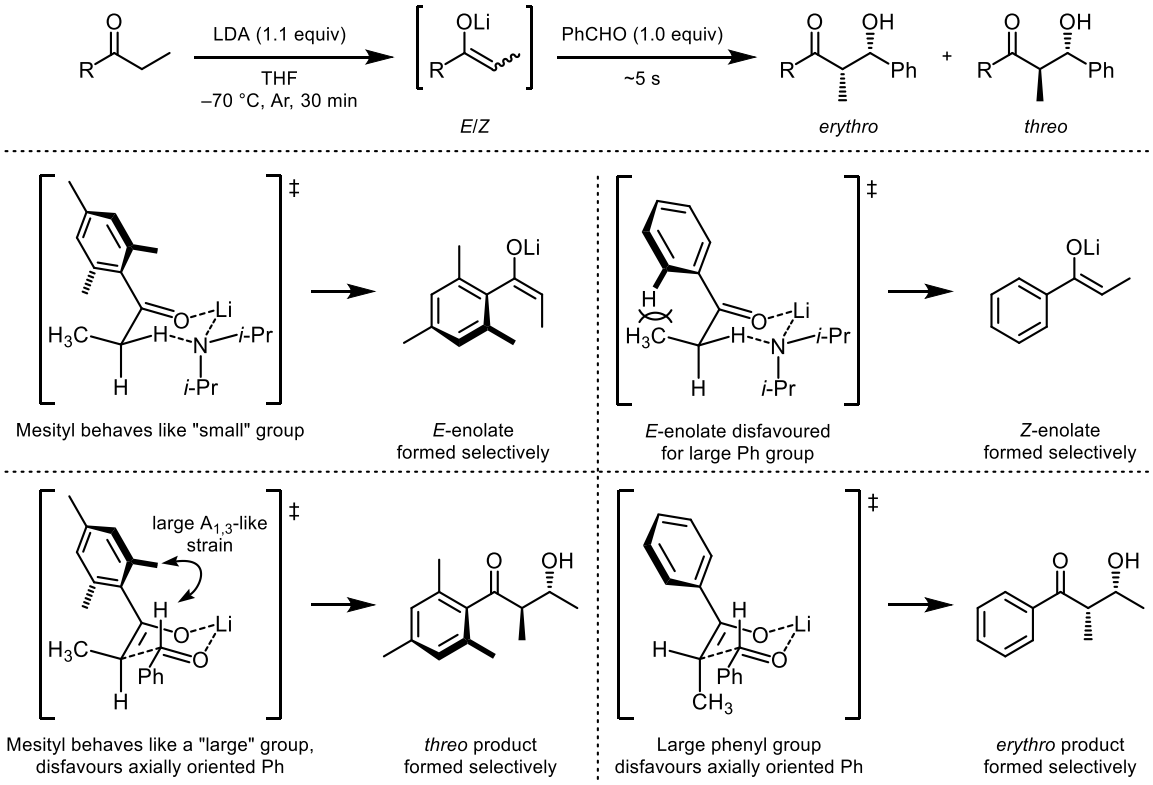
Ketone				
pK_a (DMSO)	26.4 (R = H) 27.1 (R = Me)	24.7 (R = H) 24.4 (R = Me) 23.5 (R = Bn)	24.7	16.4

Table 3.13 *pK_a values of several ketones used for hydrogen borrowing with higher alcohols. See Appendix 10.3 for references. See also Section 1.2.*

3.4.2 Aldol Adduct Stability and E1$_{CB}$



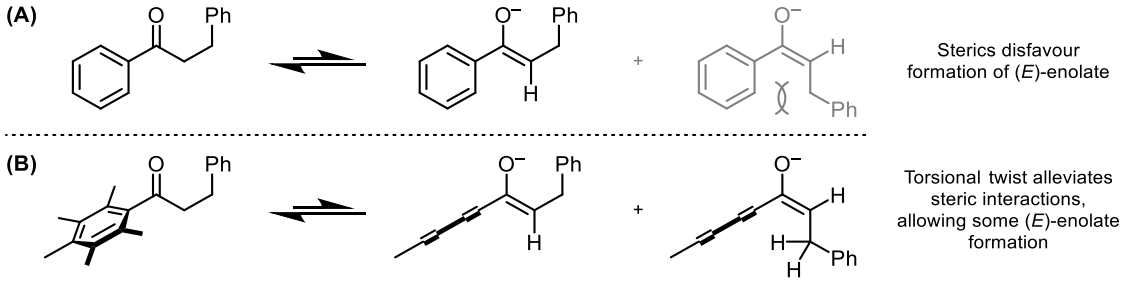
R	Et	*t*-Bu	Mesityl	Ph
E/*Z*	70/30	< 2/98	95/5	< 2/98
erythro/*threo*	64/36	> 98/2	8/92	88/12

Table 3.14 *Enolate formation and outcome of aldol reaction with benzaldehyde for phenyl and mesityl ketones under kinetic conditions as reported by Heathcock et al.*[130]

One of the interesting manifestations of the *ortho* effect is a paradoxical "reduction" in steric behaviour arising from the torsional twist of the aryl ring despite the increased steric bulk around the *ipso* centre. The effect of this behaviour on enolate chemistry was noted by Heathcock et al., who suggested that the mesityl group was "smaller" in size compared to the phenyl group due to the torsional twist in the molecule (Table 3.14).[130] This allowed it to selectively form the *E*-enolate and provide high levels of *threo* selectivity in the subsequent aldol reaction – an outcome superior to other small groups such as the ethyl group. On the other hand, the unsubstituted phenyl group displayed excellent selectivity

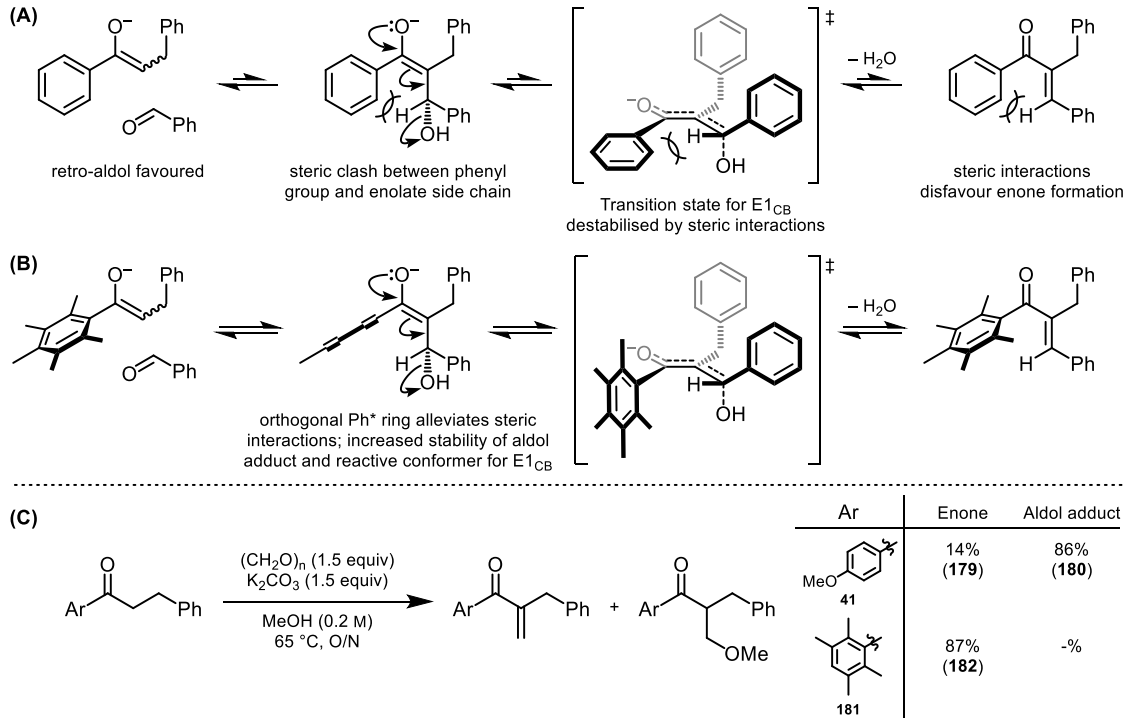
for generation of *E*-enolate and formation of *erythro* adduct in the aldol reaction, a behaviour consistent with a large group such as a *tert*-butyl group.

By a similar argument, compared to the phenyl enolate which encounters significant eclipsing interactions when attempting to form the *E*-enolate, the orthogonal geometry of substrates that manifest the *ortho* effect (e.g. Ph* ketones) creates a cavity that could accommodate the benzyl group (Scheme 3.28). Some amount of the *E*-enolate could then be formed under thermodynamic conditions. This agrees with observations by Heathcock et al. that, under dissociating conditions with hexamethylphosphoramide, the mesityl *E*-enolate isomerised to give an *E*/*Z* ratio of 66/34 within 5 min.[130]



Scheme 3.28 *(A) Steric clash between phenyl group and enolate side chain disfavours the formation of the E-enolate under thermodynamic conditions. (B) The orthogonal nature of the Ph* to the enolate creates a cavity that can easily accommodate the benzyl group, which could promote the formation of the E-enolate.*

The orthogonal geometry of a di-*ortho*-substituted aryl ring to the enolate could also have a beneficial effect towards the stability of the aldol adduct and the $E1_{CB}$ process (Scheme 3.29). In the absence of such a torsional strain, the phenyl group would likely be in the plane of the enolate due to it being conjugated with the ketone prior to deprotonation. This results in eclipsing interactions that would destabilise the reactive conformer leading to $E1_{CB}$ along with the transition state of the $E1_{CB}$ process and the enone intermediate, thus favouring the *retro*-aldol process instead. The molecule would have to rotate the phenyl group out of the plane of the enolate to promote the $E1_{CB}$ process.



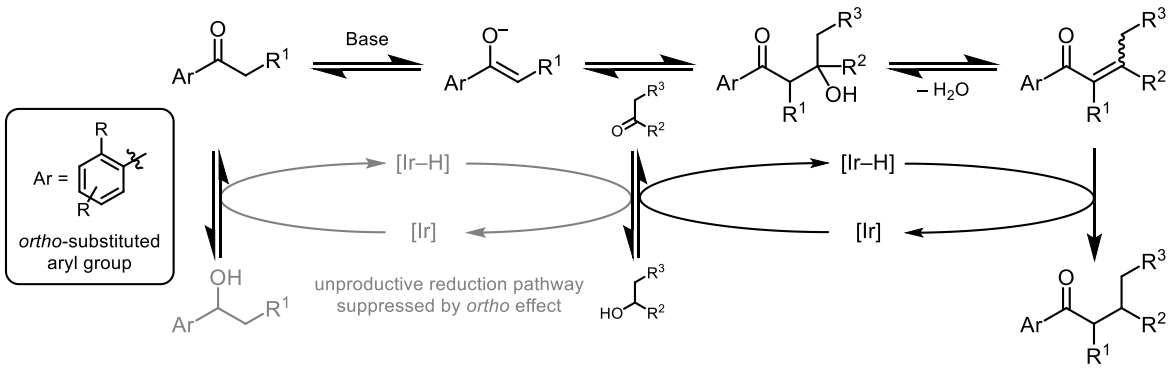
Scheme 3.29 *(A) Steric clash between phenyl group and enolate side chain destabilises the aldol adduct and enone, favouring retro-aldol process instead. (B) The orthogonal geometry of the Ph* group to the enolate creates a cavity to accommodate the benzyl and hydroxy motifs, thus facilitating the $E1_{CB}$ process. (C) ortho-methyl substituents appear to disfavour the formation of aldol adducts and promote $E1_{CB}$.*

The effect on the effective size of the aryl group can be seen by the outcome of aldol condensation reactions with formaldehyde. For *para*-anisyl ketone **36**, significantly more methoxy adduct **180** was formed than enone **179**, whereas for duryl ketone **181** only enone **182** was formed in good yield. This suggests that $E1_{CB}$ is significantly more facile when *ortho* substituents are present on the aryl ring.

3.4.3 Ketone Reduction and Enone Reactivity

Perhaps the most striking observation from the reactions of *ortho*-substituted substrates is the lack of or significantly reduced formation of undesired benzylic alcohols from the substrates. This protective nature of the *ortho* substituents results in the near-complete inertness of the carbonyl group of di-*ortho*-substituted ketones to reduction that is usually accompanied by an increase in yield of the hydrogen borrowing reaction. Literature reports of the difficult reduction of di-*ortho*-substituted ketones support this characteristic role of

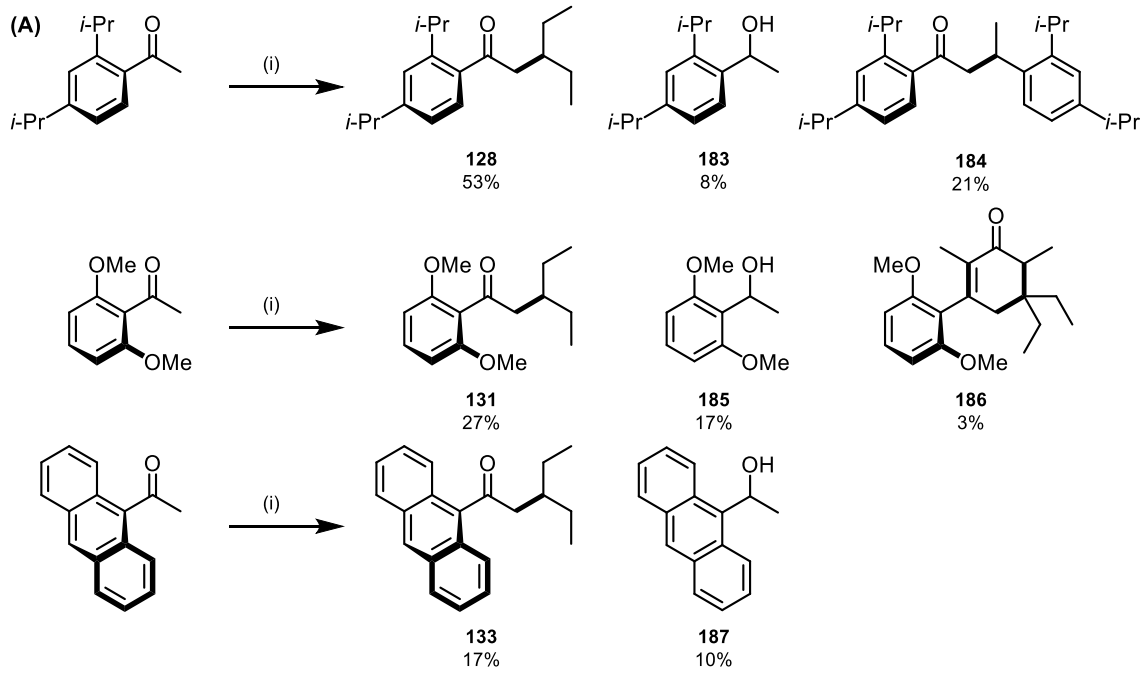
the *ortho* effect (see Sections 1.3 and 5.2.2). It is likely that suppression of the unproductive ketone reduction pathway by the *ortho* effect is funnelling the substrate towards the desired aldol reaction (Scheme 3.30).



Scheme 3.30 *The use of ortho-substituted phenyl ketones (e.g. Ph* ketone) suppresses the undesired ketone reduction for the substrate, driving the equilibrium towards enone formation.*

Based on the small differences in yields for the α-alkylation of higher alcohols between the *ortho*-methyl, *ortho*-trifluoromethyl and the *ortho*-methoxy aryl ketone substrates (both mono- and disubstituted, see Scheme 3.11), the protective nature of the *ortho* effect is not likely to be an electronic effect but rather a steric one. This is supported by the observation that substrates with a bulky *ortho*-isopropyl group gave a better yield than the *ortho*-methyl examples for both the α- and β-alkylation reactions (see also Scheme 3.18).

On the other hand, the protective *ortho* effect was significantly poorer for the methyl ketones when there was only one *ortho* substituent (e.g. 15% for *ortho*-tolyl **124** and 53% for 2,4-diisopropylphenyl **74**), or when the *ortho* substituents were small (e.g. trimethoxy **132** and 9-anthryl **133**) when compared to the larger phenethyl ketones employed for α-alkylation that all had yields above 60% (see Schemes 3.11 and 3.18). The isolation of dimeric side products such as **184** and **186**, as well as the presence of benzylic alcohols **183**, **185** and **187**, is particularly indicative of this reduced manifestation of the *ortho* effect when methyl ketones are used (Scheme 3.31).

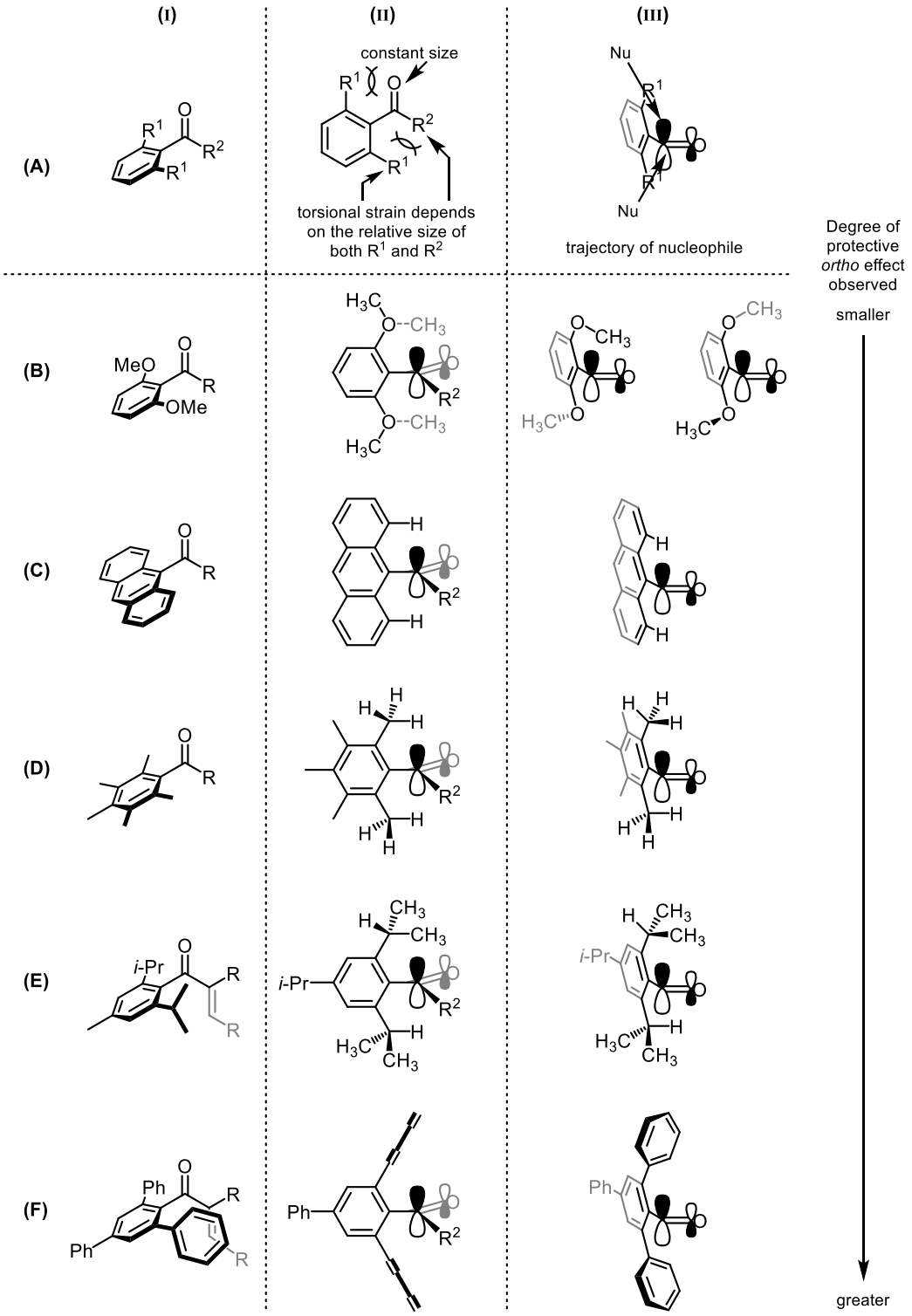


Scheme 3.31 *Isolation of dimeric side products and reduced starting material for several substrates with relatively poor yields under hydrogen borrowing conditions, indicating a reduced protective ability of the ortho effect. (i) [Cp*IrCl$_2$]$_2$ (0.5 mol%), NaOt-Bu (2.0 equiv), pentan-3-ol (1.5 equiv), toluene (4 M), 85 °C, Ar, 24 h.*

In contrast, the *ortho* effect was equally effective for both substrates when two *ortho*-methyl groups were present, but when the size of the *ortho* substituents was further increased as in the case of the di-*ortho*-isopropyl substrate, the yield was poorer for the phenethyl ketone instead. This suggests that the protective nature of the *ortho* effect depends on the size of both the *ortho* substituent and the ketone alkyl group.[21]

3.4.4 The Role of the *ortho* Effect

Based on the above observations and conclusions, the most likely role of the *ortho* effect in the hydrogen borrowing reaction is the protection of the ketone group against nucleophilic attack and reduction. For di-*ortho*-substituted aryl ketones, this could occur by the projection of the *ortho* substituents over the π* orbital of the carbonyl group, which sterically obstructs the approach of any nucleophile species (Scheme 3.32).



Scheme 3.32 *Perspective drawings of di-ortho-substituted ketones (I) facing the plane of the ketone, (II) facing the plane of the aryl group, and (III) horizontally along the ketone C=O bond (R^2 is omitted here for clarity). (A) The ortho effect is caused by steric interactions between the ortho substituents (R^1), the ketone or enolate oxygen (of constant size), and the ketone alkyl group (R^2) of varying size. Alleviation of this steric interaction is achieved by a torsional twist in the aryl-ketone bond. The projection of the ortho substituents over the π* of the carbonyl disrupts the approach of any nucleophilic species. See text for detailed descriptions of (B) to (F).*

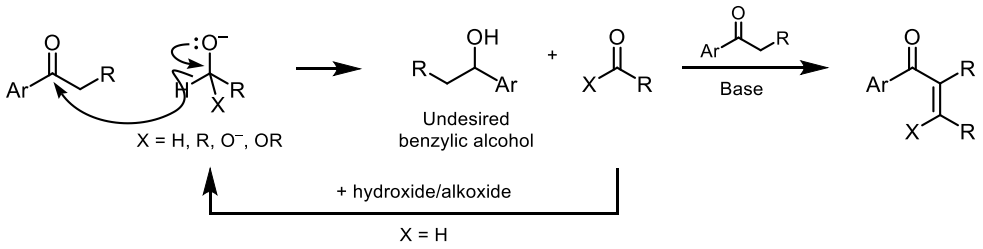
The origin of the *ortho* effect is the torsional strain arising from the steric interaction between the *ortho* substituent(s) on the aryl ring, and both the ketone or enolate oxygen (which is constant) and the ketone alkyl group, the latter becoming key to the manifestation of the *ortho* effect. These are depicted in Scheme 3.32. Compared to a methyl group, a larger alkyl group such as the phenethyl group exerts greater steric interactions with the *ortho* substituents and therefore induces greater torsional strain. This results in a larger population of molecules that is more significantly twisted away from the plane of the aryl ring, which then protects the ketone group from nucleophilic attack, thus funnelling them away from the undesired ketone reduction or related side reactions towards the desired aldol reaction. Cyclic or unhindered substrates such as α-tetralone do not have this twist and are rapidly reduced by the metal hydride.

The *ortho*-methoxy groups (B) have a large degree of freedom, so the degree of steric interactions with the ketone alkyl group would depend on the orientation of the methyl group, or be based on eclipsing interactions with the oxygen. The 9-anthracenyl group (C) exerts its steric effect through interactions with the *peri* C–H bonds. Both cases (B) and (C) require R^2 to be larger than CH_3 to significantly manifest the *ortho* effect. The *ortho*-methyl groups (D) are a very effective source of the *ortho* effect, its nature being superior to the 9-anthracenyl group likely due to the longer aryl–CH_3 bond and the larger effective size of the CH_3 group. This sensitivity to the distance of the *ortho* group from the ketone is further exemplified by the lack of any protective or enabling effect in thienyl ketones (see Scheme 3.11). If the size of the *ortho* group is too large such as for the isopropyl (E) or phenyl (F) substituents, they may obstruct the α and β centres, interfering with nucleophilic attack and enone reduction respectively. In contrast, the smaller methyl group on the ketone would experience significantly less steric interactions with these substituents and enable reduction of the enone.

Although the inhibition of ketone reduction is likely to be the key role that the *ortho* effect plays towards hydrogen borrowing, it would be difficult to gauge the relative contribution of the other factors mentioned in Sections 3.4.1 and 3.4.2 towards the results of the hydrogen borrowing reaction observed. The hydrogen borrowing reaction encompasses a very large number of individual transformations, and the presence of a nearby *ortho* substituent could potentially induce multiple stereochemical changes that will influence each transformation to varying degrees. This is relevant for situations where the protective property is incomplete, and particularly so for the mono-*ortho*-substituted aryl ketones where the different orientations of the aryl ring further complicate matters. An analysis into the relative degree of *ortho* effect manifested by aryl ketones from varying substituent effects is reserved for Chapter 7.

3.4.5 The Base-Mediated Reduction of Ketones with Alcohols

The formation of undesired benzylic alcohols would likely have contributions from both catalyst-mediated and catalyst-free pathways. Given that the base-mediated reduction is both concentration (see Tables 3.2 and 3.3) and substrate and alcohol dependent (see Tables 3.1 and 3.9), with electron-rich carbonyl groups being less susceptible to reduction (provided the carbonyl group is not protected by two *ortho* substituents), an intermolecular Cannizzaro or Tishchenko reaction-type process is probably at play here (Scheme 3.33). The true Cannizzaro and Tishchenko reactions would then occur when an aldehyde species is present.



Scheme 3.33 *A base-mediated Cannizzaro reaction-type process (X = H, R) could be responsible for the undesired catalyst-free ketone reduction. The resulting aldehyde or ketone could either re-participate in the reaction in a Cannizzaro (X = O⁻) or Tishchenko (X = OR) reaction, or perform an aldol condensation to provide an apparent synergistic effect to the hydrogen borrowing reaction.*

It is unclear if and to what extent the base-mediated reduction assists the reduction of the enone intermediate, but it is possible that this mode of action is responsible for the catalyst-free, base-mediated alkylation products observed in Tables 3.2 and 3.9. Nevertheless, this background reaction, particularly the undesired ketone reduction, will likely continue to be a bane for the development of hydrogen borrowing reactions with large amounts of base as it will compromise the scope of ketones substrates that can be employed despite the synergistic effect observed for some cases.

A mechanistic consideration of the iridium-catalysed oxidation and reduction processes will be reserved for Chapter 4 (see Section 4.6).

3.5 Conclusion

The methodology of alkylation with alcohols *via* hydrogen borrowing has been extended to synthesise α-branched, β-branched, and cyclic α,β-branched ketones. Key to the success of these methodologies was the use of *ortho*-substituted phenyl ketones that, through the *ortho* effect, suppressed the undesirable ketone reduction pathway and indirectly lead to a successful hydrogen borrowing reaction. Unfortunately, the current methodology is still unable to access acyclic α,β-branched ketones, which is largely due to the difficulties in the aldol condensation to form acyclic trisubstituted and tetrasubstituted ketones.

The hydrogen borrowing reaction is indeed catalysed by $[Ir(COD)Cl]_2$, but it requires a phosphine/phosphite ligand to suppress the ketone reduction pathway. Interestingly, the use of benzyl alcohol revealed a significant background non-metal-catalysed alkylation that was not observed with *n*-butanol.

This work serves as an excellent stepping stone further exploration of the hydrogen borrowing reaction and the use of *ortho*-substituted aryl ketones. In Chapter 4, the unusual formation of cyclopentanes from the hydrogen borrowing reaction with dicyclopropylmethanol will be studied in detail and exploited to form interesting and synthetically challenging scaffolds. Given that the Ph* group has proven to be highly effective in the hydrogen borrowing reaction, the next step would be to attempt to modify and make heteroatom analogues of Ph*. In addition, the ability to remove the Ph* motif would also help transform the products of the hydrogen borrowing reactions into synthetically more useful compounds. These aspects will be discussed in Chapter 5. The behaviour of these derivatives of Ph* ketones in the hydrogen borrowing reactions, particularly those involving heteroatom substitutions at the *ortho* position, will be studied in Chapter 6. Finally, Chapter 7 will cover the application of analytical techniques in the investigation into the manifestation of the *ortho* effect when substituents and substitution patterns are varied.

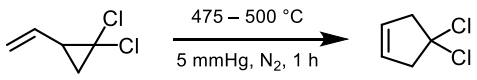
Chapter 4. The Vinylcyclopropane Rearrangement/Hydrogen Borrowing Reaction

In this chapter, the following questions will be answered:

- Can another transformation be introduced into the hydrogen borrowing sequence, one that could both tolerate and operate under the reaction conditions?
- What products can be obtained from this vinylcyclopropane rearrangement/hydrogen borrowing process?
- How does the vinylcyclopropane rearrangement operate within the hydrogen borrowing process?

4.1 Introduction

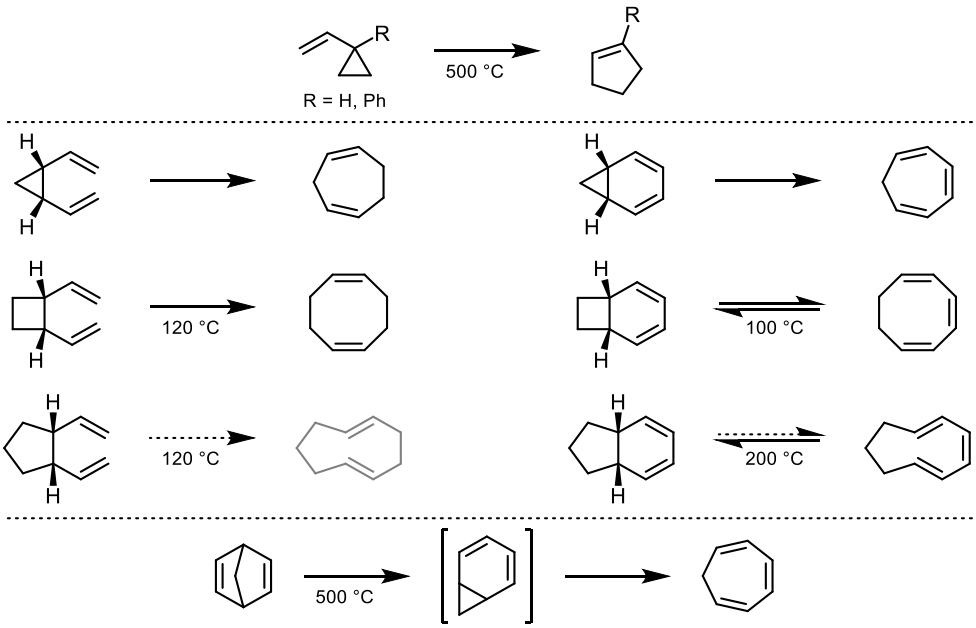
The vinylcyclopropane (VCP) rearrangement is a transformation that involves the formation of a cyclopentene structure from a cyclopropyl-substituted olefin. The reaction was first discovered by Neureiter in 1959, in which a vinyl *gem*-dichlorocyclopropane was pyrolysed to give a *gem*-dichlorocyclopentene (Scheme 4.1).[131] Since then, the reaction has fascinated chemists for over half a century, with numerous reviews being published on this reaction.[132–144] For this reason, this introduction will be deliberately kept brief, and only selected carbon-based examples that describe the different classes of this reaction will be mentioned instead.



Scheme 4.1 *The VCP rearrangement discovered by Neureiter in 1959.*[131]

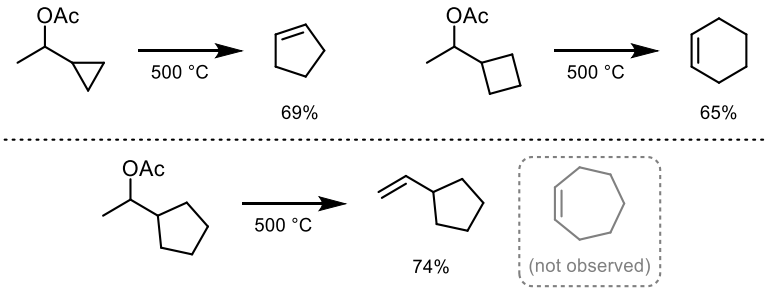
4.1.1 Thermal VCP Rearrangement Reactions

The thermal VCP rearrangement typically involves pyrolysis of vinylcyclopropanes at very high temperatures (> 300 °C). Following the discovery of the reaction by Neureiter, in 1960, Vogel described the rearrangement of similar vinylcyclopropanes to give cyclopentenes (Scheme 4.2). In the same publication, Vogel also described the related divinylcyclopropane rearrangement that proceeded at a significantly lower temperature, as well as the analogous divinylcyclobutane rearrangement, but the corresponding divinylcyclopentane rearrangements did not proceed as expected. Vogel suggested that the formation of cycloheptatriene from thermolysis of norbornadiene proceeded by a *retro*-VCP rearrangement followed by a divinylcyclopropane rearrangement. [145] Further discussion of this reaction lies outside the scope of this dissertation.



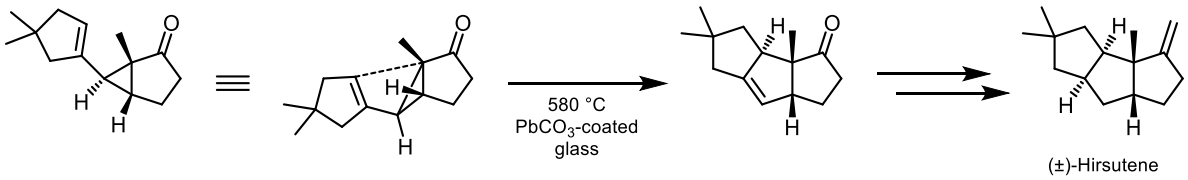
Scheme 4.2 *VCP and divinylcycloalkane rearrangement reactions reported by Vogel in 1960.*[145]

In the same year, Overberger and Borchert reported the pyrolysis of cyclopropyl acetates to give cyclopentene in high yield, which they proposed to go *via* the VCP rearrangement of vinylcyclopropane that they also observed in the reaction mixture (Scheme 4.3). They were also able to effect a similar vinylcyclobutyl rearrangement, but 1-(cyclopentyl)ethyl acetate gave vinylcyclopentane instead with no traces of cycloheptene observed.[146]



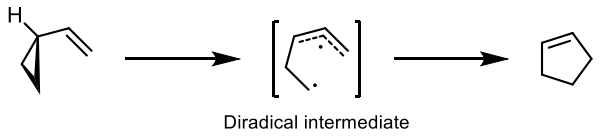
Scheme 4.3 *Pyrolysis of 1-cycloalkylethyl acetates to give cycloalkenes.*[146]

The utility of the thermal VCP rearrangement lies in its stereoselective and predictable reaction outcome, and is exemplified by its numerous applications in total syntheses. For example, in the total synthesis of (±)-hirsutene, Hudlický et al. employed the thermal VCP rearrangement to form the key central five-membered ring that forms a new stereocentre while leaving the two pre-defined stereocentres unchanged (Scheme 4.4).[147]



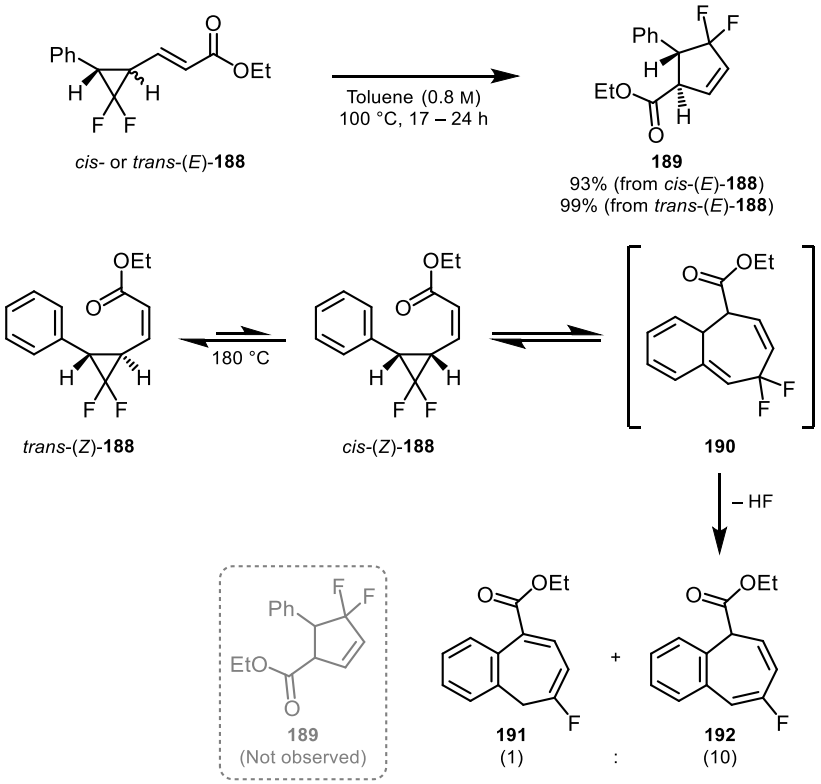
Scheme 4.4 *Stereoselective synthesis of (±)-hirsutene with the thermal VCP rearrangement as the key step in forming the central ring.*[147]

The thermal VCP rearrangement reaction has been studied by DFT calculations by Houk et al., and they suggested that the reaction proceeds by a diradical mechanism (Scheme 4.5).[148] Other computational studies have also been conducted to compare the effects of substitution on the thermal VCP rearrangement.[149,150]



Scheme 4.5 *The thermal VCP reaction is proposed to proceed by a diradical intermediate.*[148]

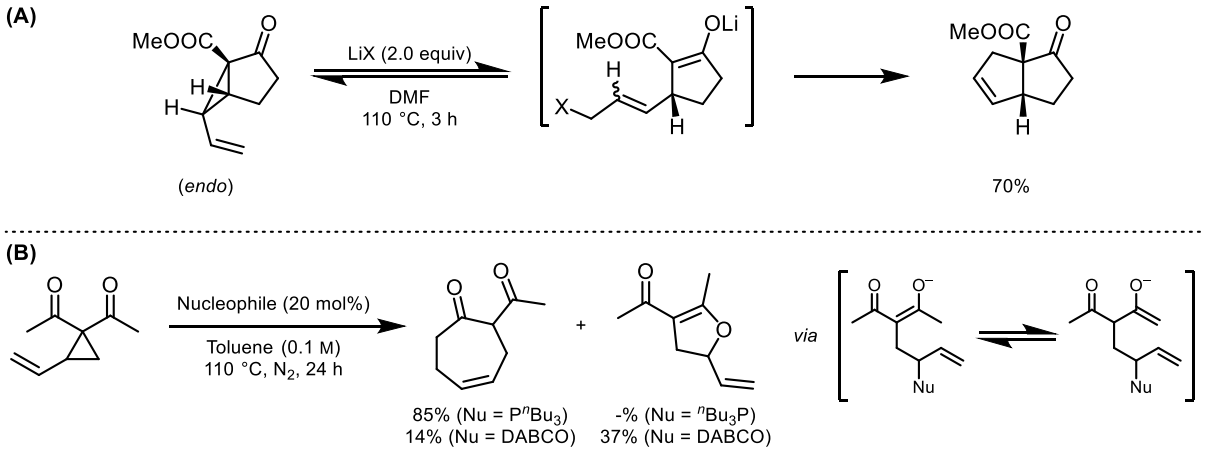
Recently, Orr et al. described the VCP rearrangement of a *gem*-difluorocyclopropyl (*E*)-enonates (*E*)-**188** to give cyclopentene **189** at a markedly lower temperature compared to the pyrolytic conditions in the earlier reports (Scheme 4.6).[151] Interestingly, the (*Z*)-enoate (*Z*)-**188** did not undergo the VCP rearrangement, but instead they underwent divinylcyclopropane rearrangement at a higher temperature to form seven-membered ring systems, with the phenyl group acting as a second olefin component for the divinylcyclopropane rearrangement.



Scheme 4.6 *Thermal VCP rearrangement could be carried out on gem-difluorocyclopropyl (E)-enoates, while the corresponding (Z)-enoates underwent divinylcyclopropane rearrangement instead. Numbers in parentheses are* ^{19}F *NMR ratios.*[151]

4.1.2 Nucleophile-Mediated VCP Rearrangement

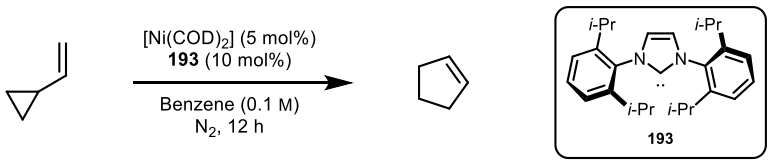
A formal VCP rearrangement can also occur through homoconjugate addition into the cyclopropane, followed by intramolecular displacement to generate the cyclopentene. This was demonstrated by Hashimoto et al. using anhydrous lithium halides in DMF at elevated temperatures (Scheme 4.7).[152] The lithium ion was critical for the success of the reaction, as the use of sodium salts resulted in the formation of complex mixtures. Wu et al. also reported a similar transformation using 20 mol% of a phosphine or an amine nucleophile.[153]



Scheme 4.7 *Nucleophile-mediated formal VCP rearrangement effected by (A) lithium halides,[152] or (B) phosphine or amine catalysts.[153]*

4.1.3 Transition Metal-Catalysed VCP Rearrangement

Given the very high temperatures required for the thermal VCP rearrangement, transition metal catalysts could provide alternative pathways to effect the VCP rearrangement at lower temperatures. Transition metals such as Ni(0), Rh(I) and Pd(0) have successfully been used to perform the VCP rearrangement.[136] In particular, Zuo and Louie reported that the use of a Ni(0) catalyst together with an NHC ligand enabled the VCP rearrangement to proceed near room temperature.[154] Through experimental work and DFT calculations, Wang et al. discovered that the Ni(0)-catalysed VCP rearrangement was highly sensitive to the substitution pattern of the alkene and the electronics of the aryl ring (Table 4.1).[155]



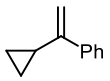
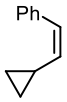
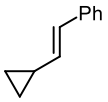
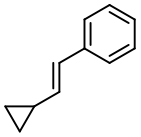
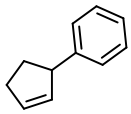
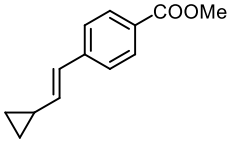
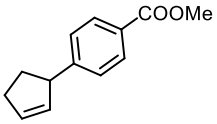
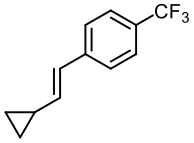
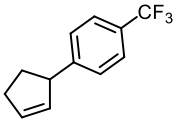
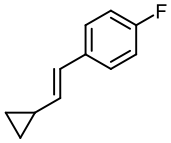
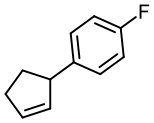
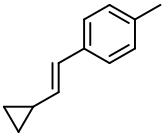
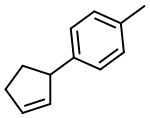
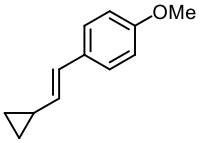
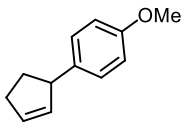
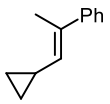
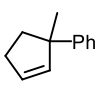
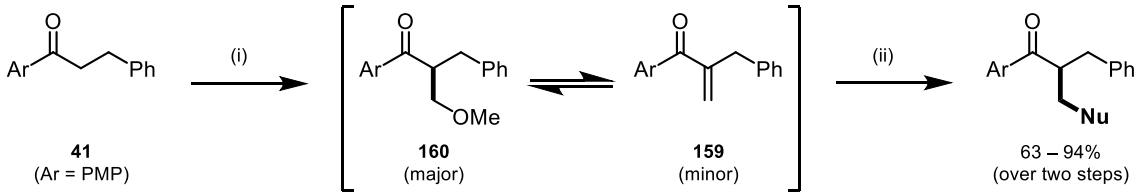
Entry	Substrate	Product	Temperature (°C)	Rate (10^{-3} s^{-1})
1			27	25.1
2			27	19.8
3			60	26.2
4			60	98.6
5			60	85.1
6			60	32.7
7			60	23.1
8			60	11.7
9			60	-[a]

Table 4.1 *The Ni(0)-catalysed VCP rearrangement reactions were highly sensitive to the substitution pattern of the alkene.* [a]*No reaction was observed.*[155]

4.2 The VCP Rearrangement and the Hydrogen Borrowing Reaction

It has been shown in previous chapters that the hydrogen borrowing process is able to telescope three steps into a single reaction, with the key condensation reaction involving carbonyl chemistry such as the aldol reaction (see Chapters 2 and 3). However, it is worth recognising that the enone intermediate formed has a distinct reactivity that could be further exploited. For example, the Donohoe group demonstrated the ability to interrupt the hydrogen borrowing process and trap the enone intermediate by conjugate addition to access a wider variety of α-branched substrates in a one-pot, two-step sequence (Scheme 4.8).[112]



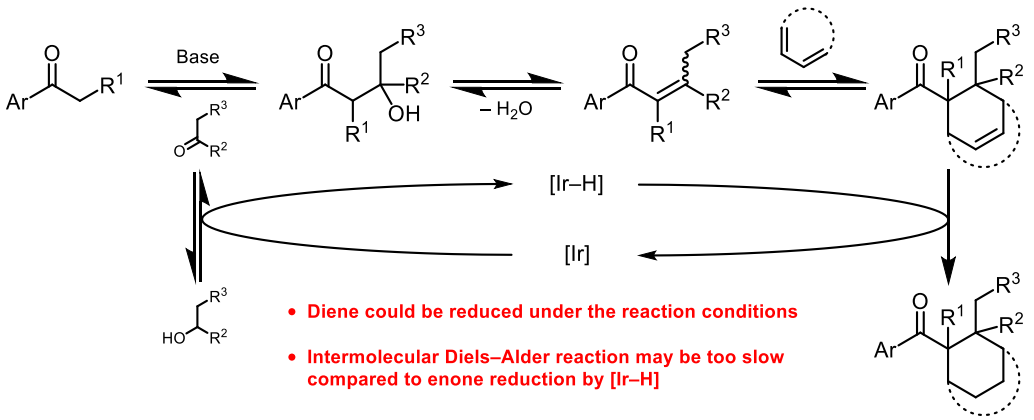
Scheme 4.8 *Representative examples by Chan et al. for interrupted hydrogen borrowing reaction followed by nucleophilic trapping. (i) [Ir(COD)Cl]$_2$ (2 mol%), cataCXium A (8 mol%), KOH (3.0 equiv), MeOH (0.1 M), 65 °C, O_2, 24 h; (ii) concentrate, SilaMetS DMT resin, then base, nucleophile.*

4.2.1 Adding a Reaction into the Hydrogen Borrowing Sequence – A Thought Experiment

One of the drawbacks of the methodology described in Scheme 4.8 is the interruption of the catalytic cycle, in this case using O_2 as an oxidant, that defeats the purpose of hydrogen *borrowing*. A more elegant but challenging idea would be to introduce an additional step in which either (a) another reactant is present in the reaction mixture that is able to tolerate the reaction conditions and react with the enone intermediate, or (b) the enone intermediate is set up for an intramolecular transformation such as a rearrangement. In addition, this additional transformation must provide an avenue to turn over the catalytic cycle e.g. a suitable unsaturated group must be present after the transformation. Given that the use of

di-*ortho*-substituted aryl ketones renders the carbonyl group inert to reduction, an addition reaction from a nucleophile would consume the only accessible double bond for an enone and thus would be consider an unsuitable transformation.

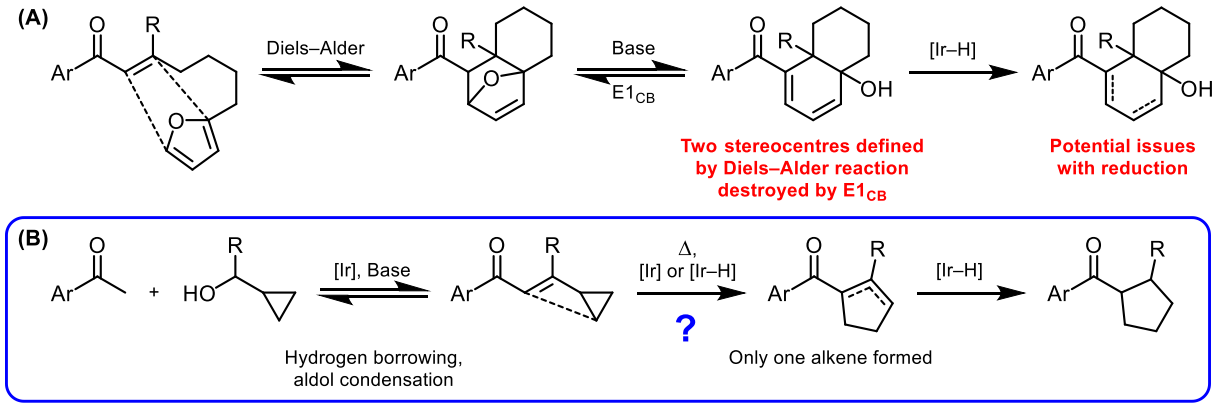
Given the presence of the π-system in the enone intermediate, pericyclic reactions are very simple and attractive candidates for the additional step in the hydrogen borrowing sequence. For example, for the Diels–Alder reaction requires only a diene as an additional reagent, is often thermally promoted, and the enone intermediate serves a suitable dienophile (Scheme 4.9). However, the key disadvantage is that additional π-systems such as the diene could be reduced by the metal catalyst, which would greatly restrict the choice of reagents or functionalities and thereby limit the substrate scope and utility of these transformations. The intermolecular Diels–Alder reaction may also be too slow and the enone may be reduced before the transformation has taken place.



Scheme 4.9 *The enone intermediate formed during the hydrogen borrowing process could be intercepted with a diene in a Diels–Alder reaction to give more advanced products.*

To overcome these challenges, an intramolecular masked π-system would be necessary to resist reduction under the hydrogen borrowing conditions and yet be able to rapidly participate in the desired transformation before the enone is reduced. Two suitable motifs were identified, which include aromatic groups for Diels–Alder reactions, and cyclopropanes for VCP rearrangements (Scheme 4.10). While the Diels–Alder reaction

could potentially install more stereocentres than the VCP rearrangement, it could also suffer from complications such the loss of desired stereocentres and/or the presence of multiple unsaturated groups that would compete for reduction.



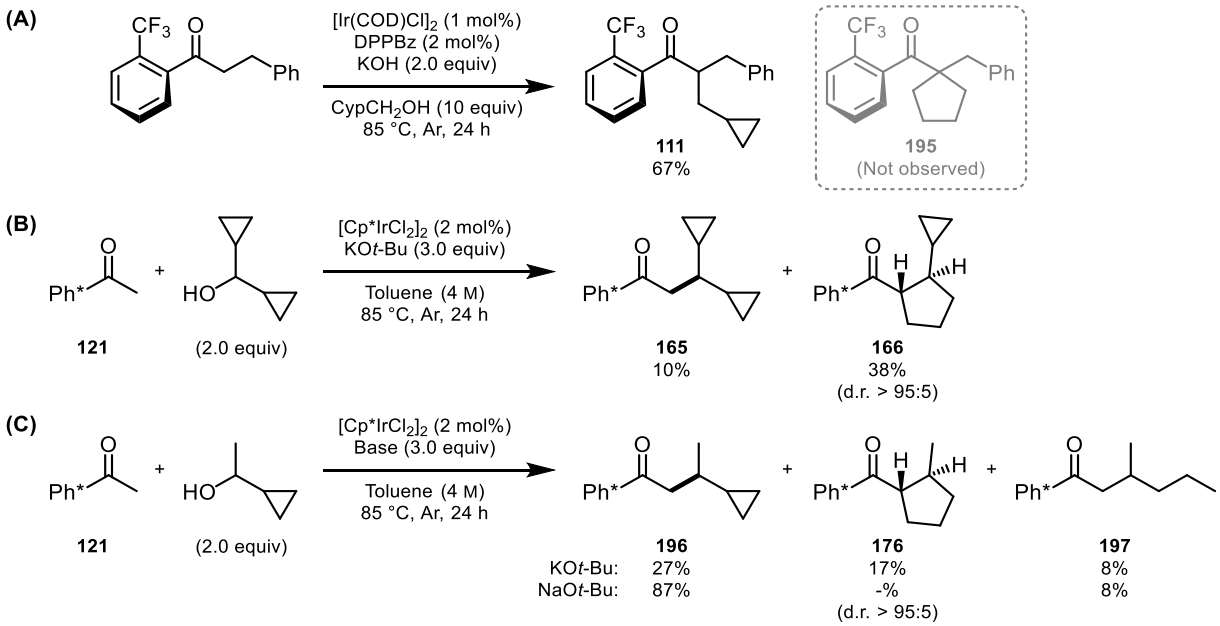
Scheme 4.10 *The intramolecular Diels–Alder reaction (A) and the VCP rearrangement (B) are potential transformations of the enone prior to metal-catalysed reduction. Substituents have been omitted for clarity. (A) The use of a heteroarene leads to the formation of a β-oxygenated centre that would be prone to E1$_{CB}$, leading to the formation of a dienone that presents a similar issue with reduction and undesirable loss of two predefined stereocentres. (B) The VCP rearrangement represents a highly suitable transformation of the enone as a fourth transformation to incorporate into the hydrogen borrowing sequence.*

Given that there is literature precedent for transition metal-catalysed VCP rearrangement (see Section 4.1.3), and that there is an enone being formed as an intermediate of the hydrogen borrowing reaction, the VCP rearrangement became the reaction of choice to be incorporated as a fourth transformation within the hydrogen borrowing sequence. The hypothesis is that the enone intermediate could be transformed by the VCP rearrangement into a cyclopentene before it is reduced by the catalytic reaction.

4.2.2 Initial Discovery

Initial attempts at triggering a VCP rearrangement started during the exploration of substrate scope in the formation of α-branched and β-branched ketones (Scheme 4.11). For the synthesis of α-branched ketones, the use of cyclopropylmethanol smoothly furnished α-branched ketones in good yield, but no trace of any form of rearrangement product such as cyclopentyl ketone **195** was observed (see also Scheme 3.14). However, during the

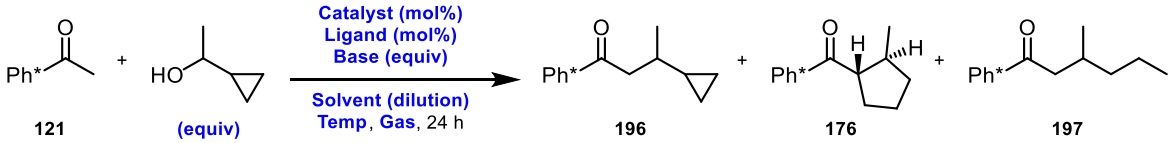
synthesis of β-branched ketones, the use of dicyclopropylmethanol gave a modest yield of a cyclopentane product **166** (see also Scheme 3.24).



Scheme 4.11 *Initial discovery of VCP-type rearrangement with hydrogen borrowing. (A) The attempted VCP rearrangement from the formation of α-branched ketones with cyclopropylmethanol was unsuccessful, but (B) a cyclopentane product **147** was observed for the formation of β-branched ketones with dicyclopropylmethanol. (C) An attempt with 1-cyclopropylethanol gave a poorer yield of cyclopentane **156**, while replacing the base with NaOt-Bu led to a very high yield of β-branched ketone **176** but no trace of rearrangement product **156**.*

A repeat of the reaction with 1-cyclopropyethanol gave slightly greater yield of direct coupling product **196**, comparatively less rearranged product **176**, and a third β-branched product **197** that appeared to have undergone cyclopropyl ring-opening. Interestingly, the use of NaO*t*-Bu instead of KO*t*-Bu gave very high yields of the direct coupling product, with no trace of rearranged product **176** observed. The diastereomeric ratio of the rearranged product **176** was also very high (d.r. > 95:5), with the *trans*-product being formed selectively. The determination of this stereochemical relationship will be discussed in Section 4.4.3.

4.3 Optimisation



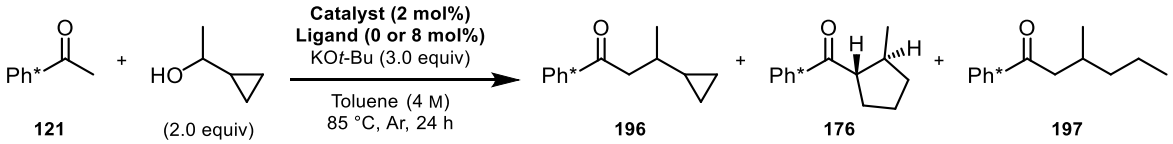
Scheme 4.12 *The lead reaction for optimisation, highlighting all the variables to be investigated.*

For the optimisation reaction, it was decided that the simplest secondary cyclopropyl alcohol, 1-cyclopropylethanol, would be the substrate for optimisation. This alcohol presents several advantages over dicyclopropylmethanol. The methyl group would not impart any electronic effects compared to the π-like cyclopropyl group. The distinctive ^{1}H NMR signals also simplified the analysis of the reaction, and it was significantly cheaper than dicyclopropylmethanol. [*] Furthermore, the purification of the reaction with dicyclopropylmethanol was significantly more difficult due to the presence of traces of multiple product-like signals in the ^{1}H NMR spectra for both ketones **165** and **166**.

The reaction would be optimised for the yield of cyclopentane **176**, and would aim to minimise direct coupling product **176** and ring-opening product **197** (Scheme 4.12). All the reactions would be run for 24 h for consistency. Due to the similar polarity of the various products, it was much more convenient and accurate to combine all the fractions containing ketones **121**, **196**, **176** and **197** together and perform quantitative ^{1}H NMR analysis to calculate and obtain the isolated yields of the various components (see experimental section).

[*] The average cost of 1-cyclopropylethanol is £2.47/g (Sigma-Aldrich), whereas for dicyclopropylmethanol it is £17.30/g (Tokyo Chemical Industry).

4.3.1 Catalyst Screen

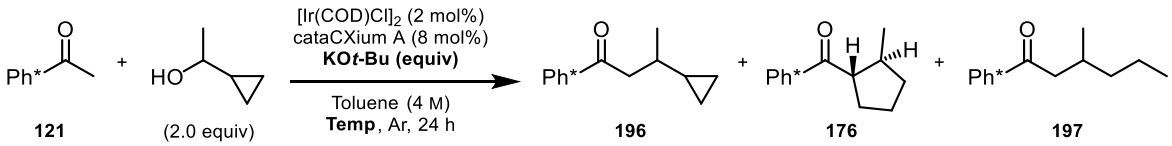


Entry	Catalyst	Ligand	Yields (%)[a]			
			121	**196**	**176**	**197**
1	$[Ir(COD)Cl]_2$	-	13	27	17	8
2	**$[Ir(COD)Cl]_2$**	**cataCXium A**	**-**	**12**	**24**	**3**
3	$[Cp^*IrCl_2]_2$	-	17	12	17	2
4	$[Rh(COD)Cl]_2$	-	22	23	4	10
5	$[Rh(COD)Cl]_2$	cataCXium A	12	-	-	37
6	$[Cp^*RhCl_2]_2$	-	11	8	16	2

Table 4.2 *Initial catalyst and ligand screen for the hydrogen borrowing-mediated VCP rearrangement reaction. [a]Isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^1H NMR analysis.*

The optimisation of the lead reaction started with an initial screen of transition metal catalysts with and without a phosphine ligand present (Table 4.2). Although the yields were generally quite low, it was immediately apparent that the Rh(I) catalyst gave significantly less rearrangement product **176** compared to the Ir(I) catalyst (Entries 1 and 2 vs Entries 4 and 5). The effects of a phosphine ligand, in this case cataCXium A, was dramatically changing the selectivity of the reaction for Ir(I) and Rh(I) catalysts. The ligand increased the yield of rearrangement product **176** when $[Ir(COD)Cl]_2$ was used compared to when it was absent (Entry 1 vs 2). However, the ligand promoted the formation of ring-opening product **197** instead when $[Rh(COD)Cl]_2$ was used (Entry 4 vs 5). In contrast, the Ir(III) and Rh(III) catalysts gave similar yields of cyclopentane **176** (Entries 3 and 6), but were both poorer than the combination of $[Ir(COD)Cl]_2$ and cataCXium A.

4.3.2 Temperature and Base Loading Screen



Entry	KO*t*-Bu (equiv)	Temperature (°C)	Yields (%)[a]			
			121	**196**	**176**	**197**
1	3	85	-	12	24	3
2	1	85	6	63	22	3
3	1	65	8	71	3	2
4	**1**	**105**	**-**	**38**	**45**	**-**
5	1	115	-	26	44	4
6	2	105	-	15	37	3
7	0.5	105	38	34	8	-
8	0.5	115	40	33	12	2

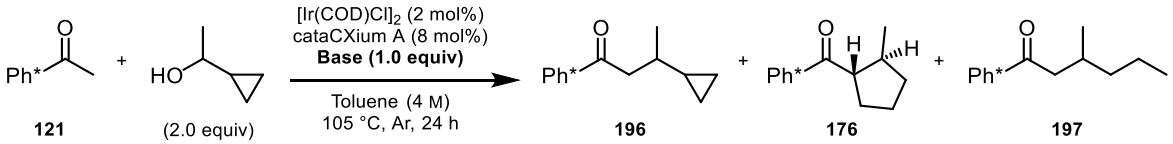
Table 4.3 *Both the temperature and base loading were critical variables in this reaction. [a]Isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^{1}H NMR analysis.*

The poor mass recovery from the purification of the reaction was a critical issue that took priority for optimisation. It was hypothesised that the base and/or the high temperature was degrading the substrates or intermediates. When the loading of KO*t*-Bu was decreased to 1 equiv, the mass recovery dramatically increased, but the yield of cyclopentane **176** was relatively similar (Table 4.3, Entry 1 vs 2).

The temperature of the reaction proved to be key to promoting the formation of cyclopentane **176**. Decreasing the reaction temperature resulted in negligible formation of cyclopentane **176** (Entry 3), whereas raising the temperature to 105 °C led to a significantly increased yield of 45% (Entry 4). A further increase in reaction temperature not only did not provide a beneficial effect to the formation of cyclopentane **176**, but it also caused the overall mass recovery to decrease (Entry 5). Attempting to increase the base loading at this juncture led to a decrease in mass recovery (Entry 6), while a further decrease in the base loading led to significantly poorer conversion as well as formation of cyclopentane **176**

(Entry 7). Unfortunately, this decreased conversion could not be rescued by a further increase in temperature (Entry 8), implying that there is a fine balance between the base loading and temperature of the reaction. The results also suggest that a base is involved in promoting the formation of rearranged product **176** over direct coupling product **196**.

4.3.3 Base Screen



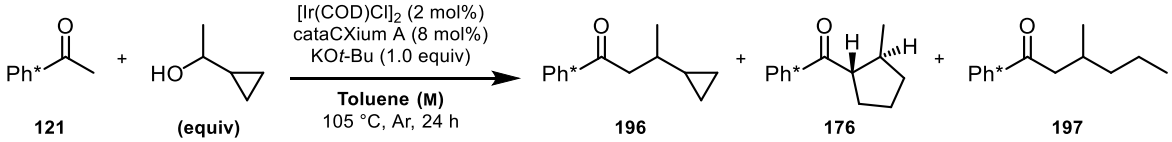
Entry	Base	Yields (%)[a]			
		121	**196**	**176**	**197**
1	**KO*t*-Bu**	**-**	**38**	**45**	**-**
2	$KOSi(Me)_3$	58	14	3	4
3	K-Phthalimide	100	-	-	-
4	KOH	49	38	8	5
5	K_3PO_4	100	-	-	-
6	K_2CO_3	100	-	-	-
7	Cs_2CO_3	100	-	-	-
8	$BaCO_3$	100	-	-	-
9	DBU	100	-	-	-
10	Proton sponge	100	-	-	-

Table 4.4 *A base screen revealed that only KOt-Bu proved to be suitable for this reaction. [a]Isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^{1}H NMR analysis.*

From the initial results with NaO*t*-Bu it was clear that the choice of base appeared to have a significant effect on the outcome of the reaction, and that NaO*t*-Bu was not likely to be a suitable base to give the desired outcome of the reaction. As such, a range of other organic and inorganic bases were screened, but KO*t*-Bu proved to be the superior option (Table 4.4, Entry 1). The silyl analogue potassium trimethylsiloxylate was significantly poorer (Entry 2), while no conversion was observed for the mild amide base K-phthalimide (Entry 3). Of all the inorganic bases, only KOH gave any significant conversion (Entry 4), but it did not

strongly promote the formation of rearrangement product **176**. Other mild inorganic and organic bases also failed to promote the conversion of the substrates to any of the products (Entries 5 – 10), suggesting a difficult aldol condensation reaction compared to the synthesis of α-branched ketones with primary alcohols (see also Table 3.8).

4.3.4 Alcohol Loading and Dilution Screen



Entry	Alcohol (equiv)	Concentration (M)	Yields (%)[a]			
			121	**196**	**176**	**197**
1	2	1	20	25	28	-
2	2	2	1	33	38	-
3	**2**	**4**	**-**	**38**	**45**	**-**
4	2	8	1	43	43	-
5	2	-	-	53	27	-
6	1.1	4	8	19	41	6
7	3	4	3	57	35	-
8	1.1	4[b]	5	11	42	3
9	3	4[b]	2	58	34	-

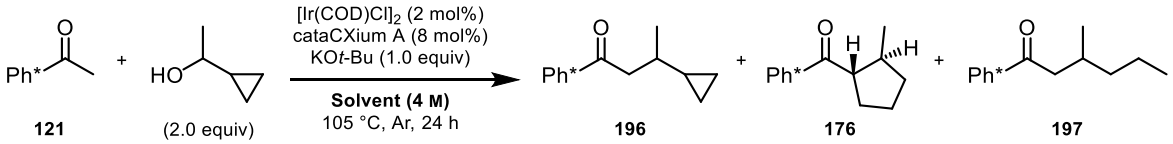
Table 4.5 *Investigations into the effects of dilution and alcohol loading. [a]Isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^{1}H NMR analysis; [b]Adjustments were made to the amount of toluene added so that the total volume of the reaction mixture was unchanged.*

Turning to investigate the effect of dilution on the reaction, diluting the reaction mixture led to increasingly formation of rearrangement product **176** and poorer conversion of starting material (Table 4.5, Entries 1 and 2 vs Entry 3), while a more concentrated reaction mixture did not significantly affect the reaction (Entry 4). However, the absence of a solvent was detrimental to the selectivity of the reaction for cyclopentane **176**.

At this point, it was appropriate to investigate the loading of alcohol as the total volume of the reaction mixture could be affected. Reducing the alcohol loading did not improve the

outcome of the reaction, while increasing the alcohol loading led to significantly increased formation of direct coupling product **196** (Entries 6 and 7). Isovolumetric adjustments to the reaction mixture verified that these changes were reflective of the effects from varying the amount of alcohol used (Entries 8 and 9). These results also indicated that the reaction was able to tolerate small inaccuracies in the volume of solvent added.

4.3.5 Solvent Screen



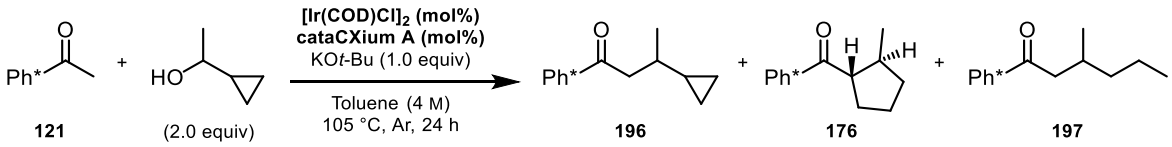
Entry	Solvent	Yields (%)[a]			
		121	**196**	**176**	**197**
1	Heptane	11	49	22	-
2	1,4-Dioxane	10	37	34	-
3	Diglyme	8	39	37	5
4	Chlorobenzene	13	36	34	-
5	Diphenyl ether	5	36	45	2
6	**Toluene**	**-**	**38**	**45**	**-**
7	*m*-Xylene	12	35	36	-
8	Naphthalene	4	40	45	4
9	*t*-AmOH	12	68	7	-
10	*N*,*N*-Diisopropylethylamine	6	46	33	3
11	Pyridine	100	-	-	-
12	Sulfolane	100	-	-	-
13	α,α,α-Trifluorotoluene	7	43	38	2
14	Perfluorotoluene	100	-	-	-

Table 4.6 *Solvent screen encompassing high boiling alkane, alkyl ether, halogenated, aromatic, polar, protic and fluorinated solvents. [a]Isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^{1}H NMR analysis.*

A solvent screen was next performed to identify the most suitable solvent for the reaction (Table 4.6). High-boiling alkane (Entry 1), alkyl ether (Entries 2 and 3) and halogenated solvents (Entries 4) did not give good selectivity for rearrangement product **176**. While diphenyl ether was equally good as toluene (Entries 5 and 6), the high-boiling aromatic

solvent *meta*-xylene did not give complete conversion (Entry 7), but the use of naphthalene as a high-boiling analogue of benzene also gave a very comparable result to toluene (Entry 8). The selectivity of the reaction for cyclopentane **176** suffered greatly when a tertiary alcohol was employed (Entry 9). Amine solvents such as Hünig's base started to have a detrimental effect on the yield of cyclopentane **176** (Entry 10), while even more polar solvents such as pyridine and sulfolane inhibited the reaction (Entries 11 and 12). Interestingly, the partially fluorinated analogue of toluene was able to promote conversion of the starting material although it was not very selective for the desired product (Entry 13), but the use of the perfluorinated analogue resulted in no reaction being observed. Between toluene, diphenyl ether and naphthalene, toluene was chosen as the other two solvents could not be easily removed and would hamper purification.

4.3.6 Catalyst and Ligand Loading



Entry	$[Ir(COD)Cl]_2$ (mol%)	cataCXium A (mol%)	Yields (%)[a]			
			121	**196**	**176**	**197**
1	2	4	3	38	44	-
2	2	8	-	38	45	-
3	2	16	2	42	45	-
4	**1**	**4**	**-**	**36**	**50**	**Traces**
5	4	16	3	58	28	11
6	-	-	29	52	-	-

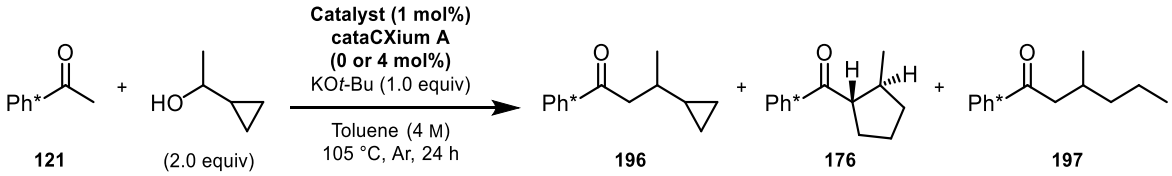
Table 4.7 *Investigations into the catalyst and ligand loading. [a]Isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^1H NMR analysis.*

With the other reagents optimised, the next step was to investigate the optimal catalyst and ligand loading for the reaction. The reaction appeared insensitive to the amount of ligand used, with little change in the yield of rearrangement product **176** observed (Table 4.7,

Entries 1 – 3). While keeping the metal:ligand ratio unchanged (1:2), a decrease in catalyst loading led to an improved selectivity for cyclopentane **176** (Entry 4), whereas an increase in catalyst loading was not only detrimental to the selectivity of the products formed, but it also promoted the undesirable ring-opening of the cyclopropane (Entry 5). This result suggests that the enone reduction, vinylcyclopropane rearrangement and ring opening of the cyclopropane are likely competing reactions that are mediated by the metal catalyst, and that the processes leading to the formation of ketones **196** and **197** appear to be more responsive to changes in the catalyst loading.

The omission of the catalytic system resulted in no formation of the cyclopentane **176**, suggesting the direct participation of an iridum catalytic species in the VCP rearrangement. However, a very significant amount of the non-metal-catalysed direct coupling process was in operation, forming the direct coupling product **196** in high yield (Entry 6), an outcome that was previously observed in the formation of α-branched ketones with benzyl alcohol *via* hydrogen borrowing (see Tables 3.7, 3.8 and 3.9). The incomplete mass recovery of this result also indicates a significant amount of inevitable degradation or polymerisation of the substrates (see Section 4.3.3), as evident from significant tarring in the reaction vials.

4.3.7 A Second Catalyst Screen

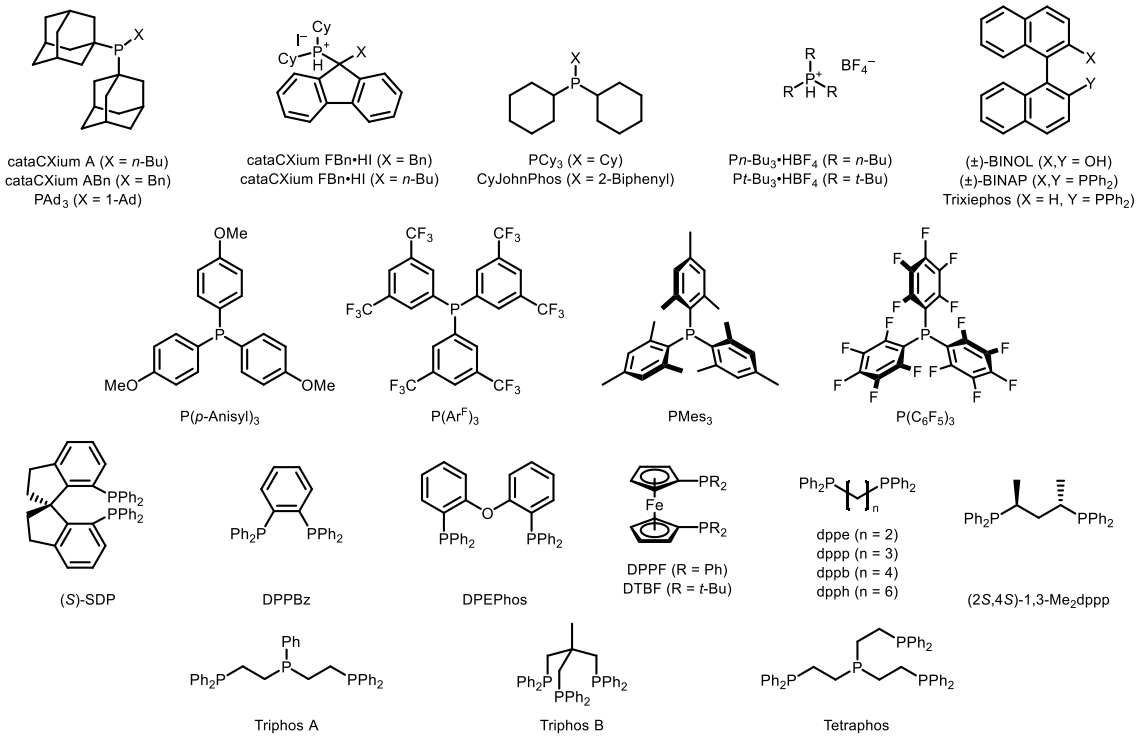


Entry	Catalyst	cataCXium A (mol%)	Yields (%)[a]			
			121	**196**	**176**	**197**
1	$[Cp^*IrCl_2]_2$	-	-	65	22	11
2	$[Cp^*IrI_2]_2$	-	-	68	22	10
3	$[Cp^*IrCl_2]_2$	4	-	63	26	Traces
4	$[Ir(COD)Cl]_2$	-	-	43	38	-
5	**$[Ir(COD)Cl]_2$**	**4**	**-**	**36**	**50**	**Traces**
6	$[Ir(COD)(Pyr)(PCy_3)]PF_6$	4	-	49	40	-
7	$[Ir(COD)(indenyl)]_2$	4	-	36	37	-
8	$[Ir(COD)_2]BF_4$	4	-	39	38	5

Table 4.8 *A screen for iridium catalysts with or without cataCXium A. [a]Isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^1H NMR analysis.*

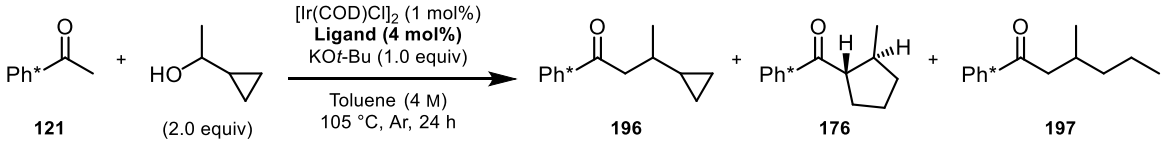
A second screen for the most suitable iridium catalyst was carried out to further boost the selectivity of the reaction for rearranged product **176** (Table 4.8). The use of Ir(III) catalysts gave consistently poor yield of cyclopentane **176** regardless of the bridging halide (Entry 1 vs 2). Interestingly, the use of $[Cp^*IrCl_2]_2$ in combination with cataCXium A suppressed the ring-opening of the cyclopropane (Entry 1 vs 3). In contrast, the Ir(I) catalysts consistently provided better selectivity for cyclopentane **176** than the Ir(III) catalysts. The omission of cataCXium A was detrimental to the selectivity for cyclopentane **176** (Entry 4), and $[Ir(COD)Cl]_2$ gave the best outcome amongst the four commercially available Ir(I) catalysts (Entries 5 – 8).

4.3.8 Ligand Screen



Scheme 4.13 *Ligands used in Table 4.9.*

An extensive ligand screen was carried out to identify the most suitable ligand that would promote the formation of rearrangement product **176**, comprising a broad range of commercially available monodentate, bidentate and several polydentate ligands that are common employed in catalysis (Table 4.9). There does not seem to be a clear correlation between the various ligand parameters and the yield of cyclopentane **176** (see Appendix 10.1).



Entry	Ligand	NMR Ratio (%)[a]			
		121	**196**	**176**	**197**
1	cataCXium A	- (-)[c]	0.7 (36)[c]	1 (50)[c]	Traces (Traces)[c]
2	cataCXium ABn	0.12	1	0.82	0.26
3	PAd_3	0.09	0.79	1	Traces
4	cataCXium FBn•HI	0.22	0.9	1	Traces
5	cataCXium FBu•HI	0.13	0.83	1	Traces
6	PCy_3	0.13	0.85	1	0.23
7	P*t*-Bu_3•HBF_4	0.27	0.93	1	-
8	P*n*-Bu_3•HBF_4	0.2	1	0.55	0.41
9	CyJohnPhos	0.18	1	1	0.24
10	TrixiePhos	0.12	1	0.97	Traces
11	PPh_3	Trace	1	0.76	0.29
12	P(*p*-Anisyl)$_3$	0.7	1	0.48	0.19
13	$P(Ar^F)_3$	0.65	1	0.33	0.21
14	$PMes_3$	0.15	0.87	1	Traces
15	$P(C_6F_5)_3$	1.21	1	0.67	0.15
16	$P(OPh)_3$	0.43	0.87	1	Traces
17	(*S*)-SDP	0.08	0.85	1	0.11
18	DPPBz	-	1	0.34	0.22
19	DPEPhos	-	1	0.12	0.22
20	(±)-BINAP	0.06	1	0.75	0.16
21	DPPF	-	1	0.34	0.19
22	DTBF	0.29	0.89	1	-
23	dppe	-	1	0.11	0.15
24	dppp	-	1	0.19	0.23
25	dppb	-	1	0.32	0.17
26	dpph	Trace	1	0.29	0.21
27	(2*S*,4*S*)-1,3-Me_2dppp	-	1	0.23	0.22
28	$(Ph_2PCH_2CH_2)_2PPh$ [Triphos A][b]	Trace	1	1	Traces
29	$(Ph_2PCH_2)_3CCH_3$ [Triphos B][b]	0.05	1	0.81	0.23
30	$P(CH_2CH_2(PPh_2))_3$ [Tetraphos]	0.31	1	-	-

Table 4.9 *Ligand screen, comprising monodentate, bidentate and polydentate ligands. [a]Ratios were obtained by quantitative ^1H NMR analysis of crude mixture; [b]The labels A and B are added to differentiate between duplicates in commercial names; Numbers in parentheses indicate isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^1H NMR analysis.*

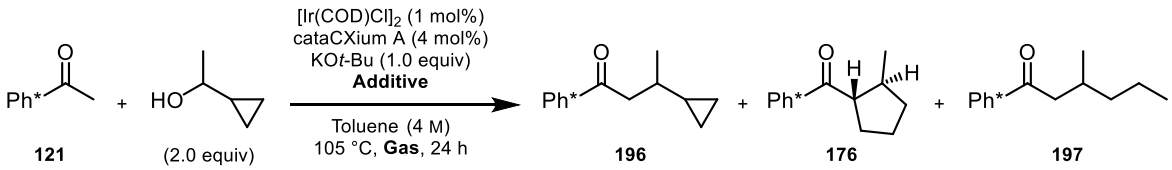
A striking observation was that compared to triphenylphosphine, both electron-donating *and* electron-withdrawing triphenylphosphine analogues suffered from unusually poor conversion and selectivity for cyclopentane **176** (Entry 11 vs Entries 12 and 13), with the perfluorinated analogue being a particularly acute case (Entry 15).

The reactions with bidentate ligands generally had good conversion of starting material, but most were particularly poor at promoting the formation of cyclopentane **176**. A key observation was the particularly poor selectivity. Only (±)-BINAP, DTBF and (*S*)-SDP had substantial selectivity for cyclopentane **176** (Entries 17, 20 and 22).

Of the three polydentate ligands attempted, the most remarkable result was that the formation of cyclopentane **176** was completely inhibited by Tetraphos (Entry 30), whereas both tridentate ligands could offer significant formation of cyclopentane **176** (Entries 28 and 29). The structural similarity between Triphos A and dppe makes the comparatively better result of Triphos A quite puzzling (Entry 23 vs 28).

From this ligand screen, it appears that cataCXium A remains the superior ligand to promote the formation of cyclopentane **176** *via* the hydrogen borrowing reaction.

4.3.9 Water Content and Reaction Atmosphere



Entry	Additive	Gas	Yields (%)[a]			
			121	**196**	**176**	**197**
1	-	Ar	- (-)	36 (0.70)	50 (1)	Traces (Traces)
2	H_2O (1.0 equiv)	Ar	36	42	15	Traces
3	4 Å MS (200 wt%)	Ar	-	76	17	-
4	COD (1.0 equiv)	Ar	12	71	-	18
5	Norbornene (2.0 equiv)	Ar	40	38	-	9
6	-	Air	(0.59)	(1)	(0.74)	(-)
7	-	H_2	Trace (0.04)	30 (0.55)	53 (1)	Traces (Traces)
8[b]	**-**	**H_2**	**Trace**	**26**	**54**	**Traces**

Table 4.10 *Investigations into effects of moisture, hydride acceptor additives and reaction atmosphere. Numbers in parentheses represent ^{1}H NMR ratios from the crude mixture. [a]Isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^{1}H NMR analysis; [b]This run is a repeat of Entry 7.*

Having investigated most of the variables in the reaction, the relatively poor yield of rearrangement product **176** was worrisome. One of the possibilities considered was that water could be interfering with the reaction, as the hydrogen borrowing reaction produces stoichiometric water as byproduct. Accordingly, the moisture content of the reaction was increased by the artificial addition of 1 equiv of water (Table 4.10, Entry 2). Not only did the additional water content result in a decrease in conversion, which was expected as it would favour the *retro*-aldol condensation, but it also made the reaction less selective for cyclopentane **176**. However, when activated molecular sieves was added to remove moisture from the system, the conversion of starting material was restored but the selectivity for cyclopentane **176** was *even poorer* (Entry 3). These results suggest that for

the VCP rearrangement reaction there are additional levels of complexity to the multiple equilibria already present within the hydrogen borrowing process.

Another possible cause for the poor yield of cyclopentane **176** was the presence of contaminating oxygen, which could potentially oxidise the catalytic species such as an iridium hydride complex. This hypothesis was studied from two approaches. The first was to introduce hydride acceptors that would compete for and abstract the hydride species. Two different high-boiling hydride acceptors were attempted, cycloocta-1,5-diene as well as norbornene (Entries 4 and 5). Interestingly, these hydride acceptors completely inhibited the formation of cyclopentane **176**, and the use of superstoichiometric norbornene led to a significant decrease in conversion of starting material. However, these additives did not fully suppress the formation of direct coupling product **196**, which would have arisen from the reduction of the enone intermediate by an iridium hydride species. A second reduction pathway is likely to be operating, which could be attributed to a background base-mediated catalyst-free alkylation previously observed for the formation of α-branched ketones (see Tables 3.9 and 3.10).[90,118–123]

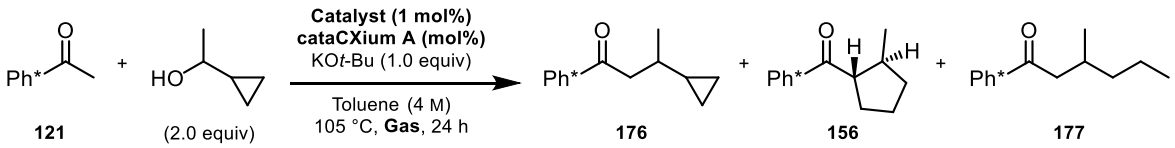
The second approach was to directly vary the reaction atmosphere. When the balloon of Ar was replaced with a balloon of air, the reaction became less selective for cyclopentane **176** and suppressed the conversion of starting material, supporting the detrimental effect of oxygen and moisture on the overall reaction (Entry 6).

In an attempt to "increase" the amount of putative iridium hydride species in the reaction, the atmosphere in the balloon was replaced with H_2. Surprisingly, the reaction became more selective for cyclopentane **176** which translated to a small increase in its yield (Entry 7). A repeat of the reaction verified the apparent beneficial effect of an atmosphere of H_2 (Entry 8).

4.3.10 A Second Variable Screen with H_2 as Reaction Atmosphere

Following the discovery of the beneficial properties of a reaction atmosphere of H_2, a second round of optimisation was undertaken to confirm the validity of the previous optimisation steps. Since the use of H_2 would likely only affect the catalytic species, only the catalyst, ligand and the ligand loading were reinvestigated.

When the reaction was attempted with an Ir(III) catalyst, the positive impact of an atmosphere of H_2 was not very pronounced in the absence of cataCXium A (Table 4.11, Entries 1 – 3). On the other hand, in the presence of cataCXium A, the reaction was significantly more selective for cyclopentane **176** under an atmosphere of H_2 than when it was performed under an atmosphere of Ar, albeit with a slightly lower conversion (Entry 2 vs 4).



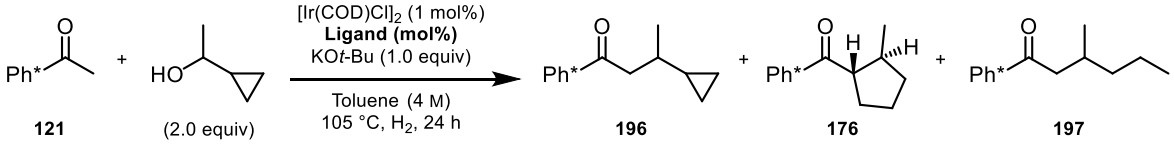
121 (2.0 equiv) **176** **156** **177**

Entry	Catalyst	cataCXium A (mol%)	Gas	NMR Ratio[a]/Yields (%)[b]			
				121	**196**	**176**	**197**
1	$[Cp^*IrCl_2]_2$	-	H_2	-	1	0.25	-
2	$[Cp^*IrCl_2]_2$	4	H_2	0.31	1	0.86	-
3	$[Cp^*IrCl_2]_2$	-	Ar	Trace	1	0.34	0.28
4	$[Cp^*IrCl_2]_2$	4	Ar	0.04	1	0.47	Trace
5	$[Ir(COD)Cl]_2$	-	H_2	0.25 (Traces)	0.83 (36)	1 (43)	- (-)
6	**$[Ir(COD)Cl]_2$**	**4**	H_2	**0.04 (Traces)**	**0.55 (30)**	**1 (53)**	**Traces (-)**
7	$[Ir(COD)Cl]_2$	-	Ar	0.08 (Traces)	1 (43)	0.96 (38)	- (-)
8	$[Ir(COD)Cl]_2$	4	Ar	- (-)	0.7 (36)	1 (50)	Traces (Traces)

Table 4.11 *A second investigation into the catalyst when performed under a reaction atmosphere of Ar or H_2. [a]Quantitative ^1H NMR ratios from the crude mixture; [b]Numbers in parentheses indicate isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^1H NMR analysis.*

The Ir(I) catalyst was still significantly better at promoting the formation of rearrangement product **176** than the Ir(III) catalyst (Entries 1 – 4 vs Entries 5 – 8). However, the impact of an atmosphere of H_2 on the reaction outcome was considerably less pronounced with or without cataCXium A present (Entries 5 and 6 vs Entries 7 and 8), with only subtle improvements to the yield of cyclopentane **176**.

These results suggest that the impact of H_2 on the catalysis is real for both Ir(I) and Ir(III) catalysts, which justifies the re-optimisation process to ensure the validity of the conclusion when performing the reaction under an atmosphere of H_2. Nevertheless, the conclusion that the best catalytic system was the combination of $[Ir(COD)Cl]_2$ and cataCXium A remains unchanged. The possible role(s) of H_2 in the reaction will be discussed in Section 4.5.

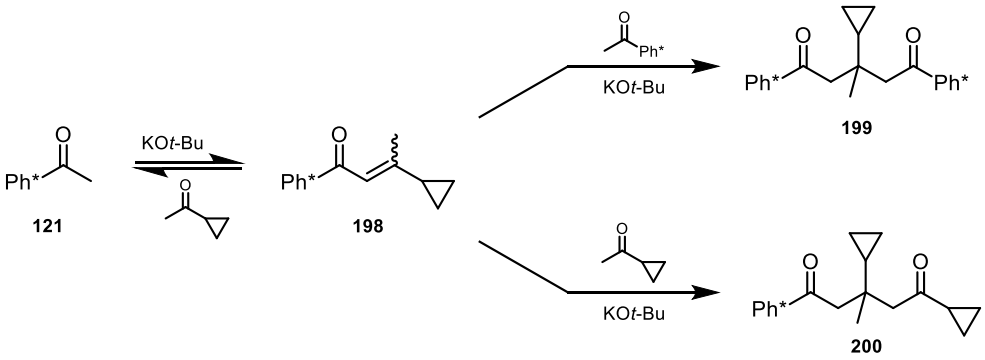


Entry	Catalyst	Ligand (mol%)	NMR Ratio[a]/Yields (%)[b]			
			121	**196**	**176**	**197**
1	$[Ir(COD)Cl]_2$	-	0.25	0.83	1	-
2	$[Ir(COD)Cl]_2$	cataCXium A (2)	0.08	0.59	1	-
3	$[Ir(COD)Cl]_2$	cataCXium A (4)	0.04 (Traces)	0.55 (30)	1 (53)	Traces (-)
4	**$[Ir(COD)Cl]_2$**	**cataCXium A (8)**	**0.05 (Traces)**	**0.46 (25)**	**1 (56)**	**Traces (-)**
5	$[Ir(COD)Cl]_2$	cataCXium A (12)	0.16	0.57	1	-
6	$[Ir(COD)Cl]_2$	PAd_3 (8)	0.10	0.62	1	Traces
7	$[Ir(COD)Cl]_2$	P*t*-Bu_3•HBF_4 (8)	0.29	0.81	1	Traces
8	$[Ir(COD)Cl]_2$	PCy_3 (8)	0.22	0.87	1	Traces
9	$[Ir(COD)Cl]_2$	$P(Mes)_3$ (8)	0.25	0.72	1	Traces
10	$[Ir(COD)Cl]_2$	$P(OPh)_3$ (8)	0.76	0.87	1	Traces
11	$[Ir(COD)Cl]_2$	DTBF (4)	0.30	0.72	1	Traces

Table 4.12 *A second investigation into the ligand and ligand loading performed under a reaction atmosphere of H_2. [a]Quantitative ^1H NMR ratios from the crude mixture; [b]Numbers in parentheses indicate isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative ^1H NMR analysis.*

Turning again to the ligand loading and the ligand itself, aside from a slight boost to yield of rearrangement product **176** when the loading of cataCXium A was increased, there was no significant deviation in the reaction outcome when the reaction was performed under an atmosphere of H_2 (Table 4.12, Entry 4). The optimal ligand for the reaction remained as cataCXium A (Entry 5 vs Entries 6 – 11, see also Table 4.9).

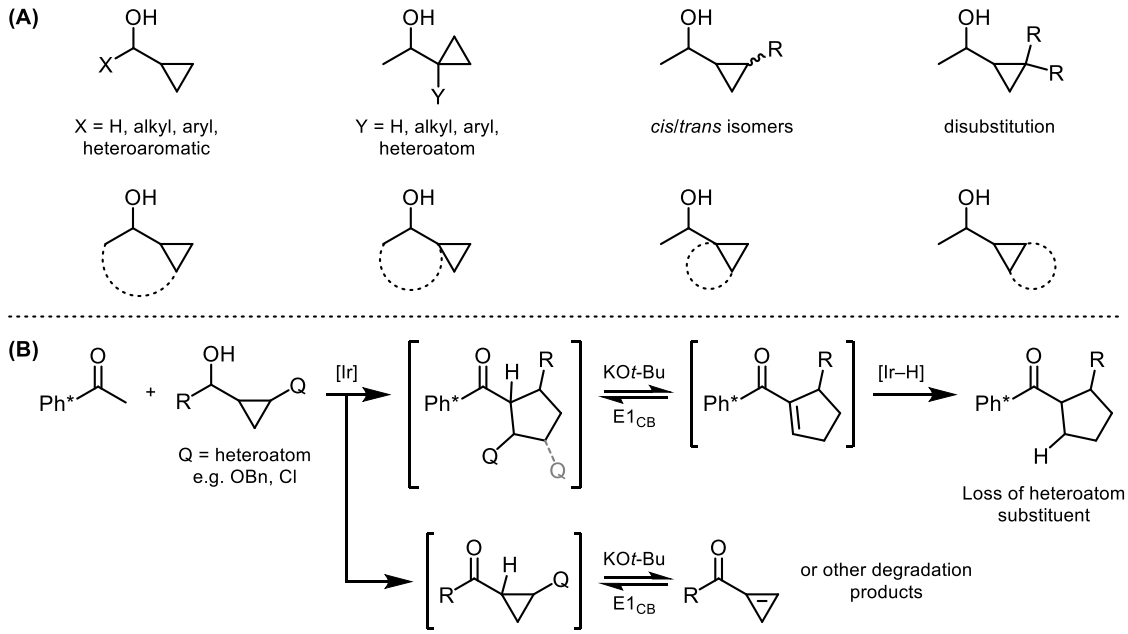
It is worth pointing out that traces of homo- and heterodimeric diones **199** and **200** have been observed in trace quantities (< 5%) in the reaction throughout the course of the optimisation process (Scheme 4.14). The isolation of these products suggest that an aldol condensation must have occurred to form enone **198**, which is then trapped by conjugate addition of the enolates of either ketone **121** or cyclopropyl methyl ketone.



Scheme 4.14 *Isolation of homo- and heterodimeric diones **199** and **200** suggests the formation of enone **198**, which are then trapped by conjugate addition with the respective enolates.*

4.4 Exploration of Substrate Scope

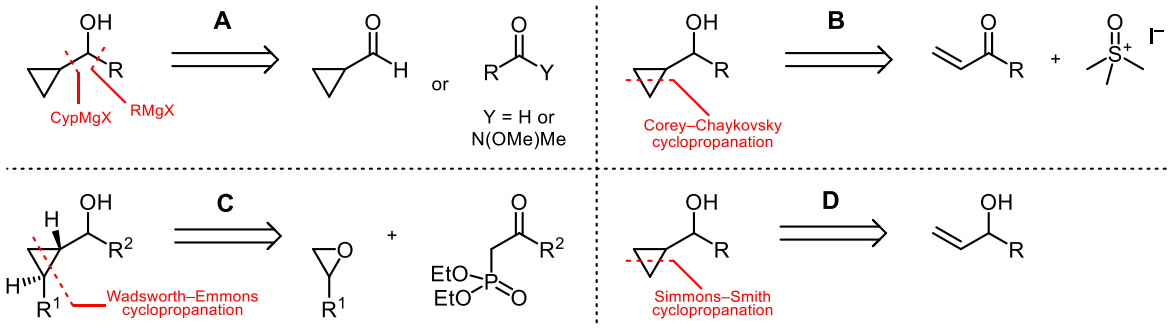
Having concluded the two rounds of optimisation, the next step was to investigate the effects of sterics, electronics and substitution at key sites of the alcohol substrate (Scheme 4.15). The tethering of key positions was of particular interest as it would reveal any geometric restrictions imposed by the reaction. However, given the likelihood of $E1_{CB}$ occurring for the rearrangement product or the cyclopropyl ketone formed *in situ*, heteroatom substituents on the 2′-positions of the cyclopropane would be unsuitable for the reaction.



Scheme 4.15 *(A) Strategy for design of substrates used for the investigation into the VCP rearrangement occurring within the iridium-catalysed hydrogen borrowing reaction. (B) Heteroatom substituents at the 2′-position of the cyclopropane could end up at a position liable to $E1_{CB}$ and/or degradation.*

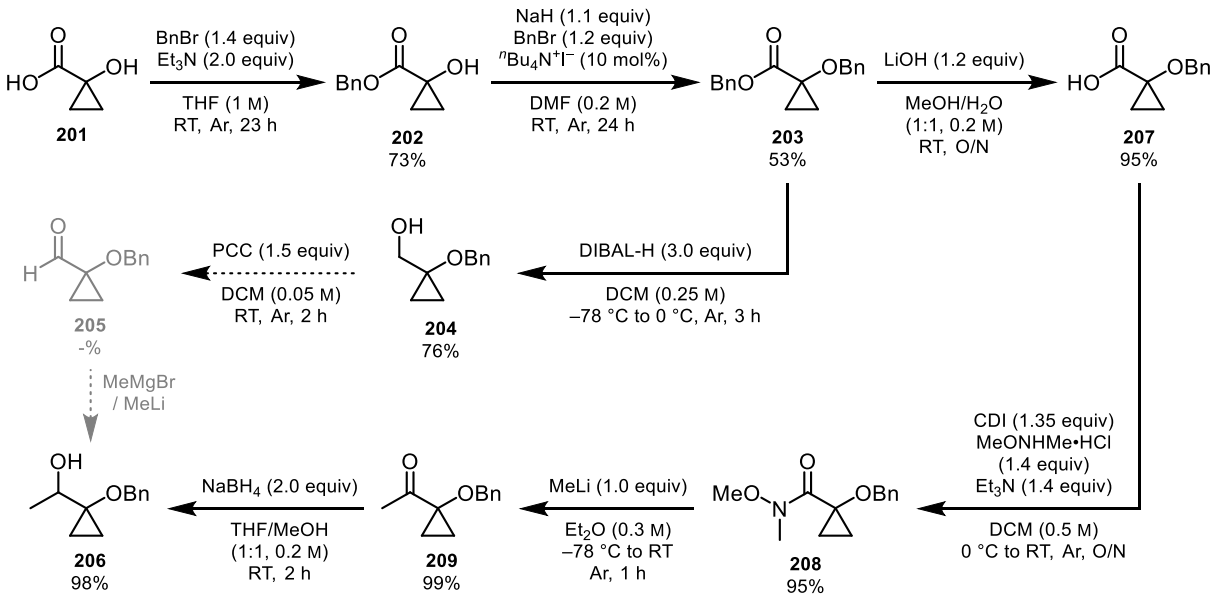
4.4.1 Synthesis of Substrates

The alkyl and benzyl cyclopropyl alcohols could be easily synthesised by organometallic addition into an appropriate aldehyde, or into a Weinreb amide followed by ketone reduction (Scheme 4.16). Other methods employed to access the cyclopropane motif include the Simmons–Smith cyclopropanation, the Corey–Chaykovsky cyclopropanation, and the Wadsworth–Emmons cyclopropanation. The commercial availability of numerous functionalised cyclopropane precursors greatly facilitated the syntheses of several substrates.



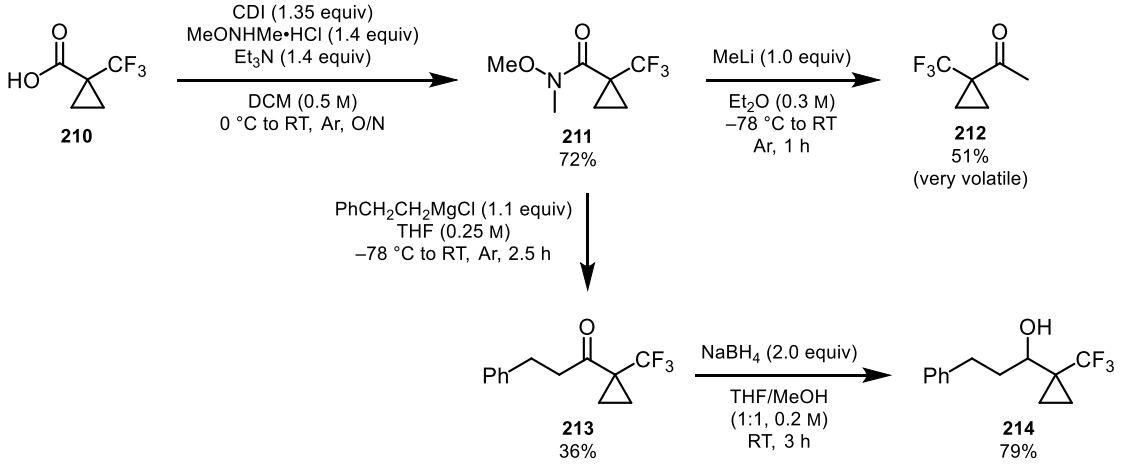
Scheme 4.16 *Retrosynthesis of cyclopropyl alcohol substrates through (A) organometallic addition to an appropriate carbonyl derivative, (B) Corey–Chaykovsky reaction, (C) Wadsworth–Emmons cyclopropanation, and (D) Simmons–Smith reaction.*

The synthesis of cyclopropyl alcohols bearing an electron-donating benzyloxy group on the 1′-position of the cyclopropane started from the unprotected carboxylic acid **201**, which was smoothly dibenzylated over two steps to give ester **203** (Scheme 4.17).[156,157] An initial plan to access secondary alcohol **206** by organometallic addition into aldehyde **205** was thwarted by the decomposition of alcohol **204** upon oxidation with PCC, with considerable quantities of benzaldehyde being produced. As a result, a lengthy but high-yielding detour was employed, involving formation of Weinreb amide **208** followed by addition of MeLi to give ketone 20**9**. A final reduction with $NaBH_4$ furnished the desired alcohol **206** in 88% yield over four steps from ester **203**.



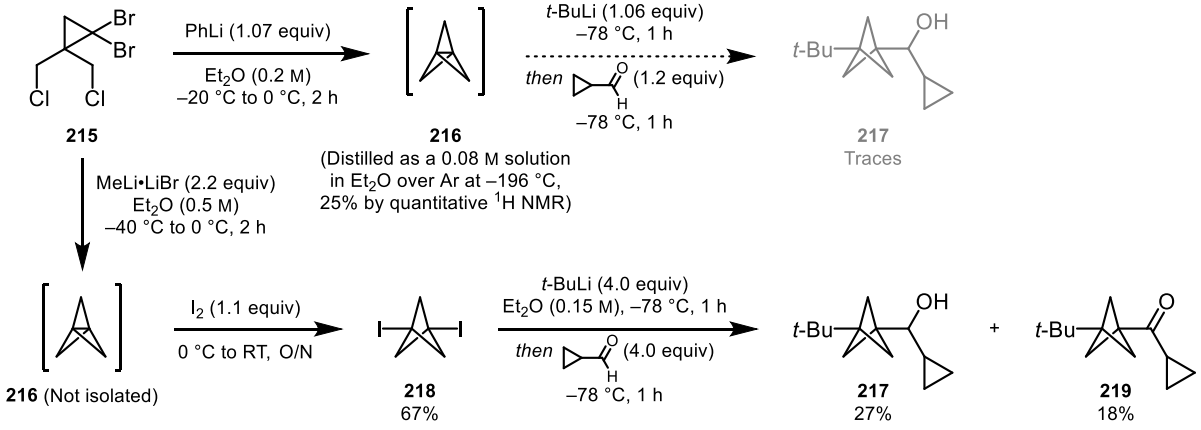
Scheme 4.17 *Synthesis of secondary alcohol* ***206*** *bearing a 1′-benzyloxylcyclopropyl group. The longer synthetic route was employed due to the unsuccessful oxidation of primary alcohol* ***204****.*

The synthesis of an analogous alcohol with an electron-withdrawing CF_3 group at the 1′-position started with the formation of Weinreb amide **211** from the corresponding acid **210** (Scheme 4.18) Although ketone **212** could be synthesised from Weinreb amide **211** in reasonable yield, the compound was very volatile, and it would likely evaporate into the headspace of the reaction vial under the hydrogen borrowing reaction conditions when generated *in situ*. The phenethyl group was installed instead to give ketone **213** in modest yield, which was then reduced with $NaBH_4$ to furnish the desired alcohol **214**.



Scheme 4.18 *Synthesis of secondary alcohol* ***214*** *bearing a 1′-benzyloxylcyclopropyl group. The significant volatility of methyl ketone* ***212*** *made the substrate unviable for the hydrogen borrowing reaction.*

The bicyclo[1.1.1]pentane (BCP) group has recently gained popularity for being a *tert*-butyl or phenyl bioisostere.[158,159] It would be interesting to incorporate this motif into a substrate and gauge the stability of the strained system under the hydrogen borrowing reaction conditions when placed next to the reactive centre. The commercially available *gem*-dibromocyclopropane **215** underwent two iterations of a reaction sequence consisting of a halogen-lithium exchange (Halex reaction) followed by intramolecular displacement of chloride to generate crude [1.1.1]-propellane **216** (Scheme 4.19).[160] The reaction mixture was then subjected to cryogenic distillation over an atmosphere of Ar to give a low yield of propellane **216** as a solution in Et_2O.[161] Unfortunately, an attempted addition of *t*-BuLi across the central propellane bond followed by trapping with cyclopropanecarboxaldehyde resulted in very little formation of cyclopropyl alcohol **217**.[162]

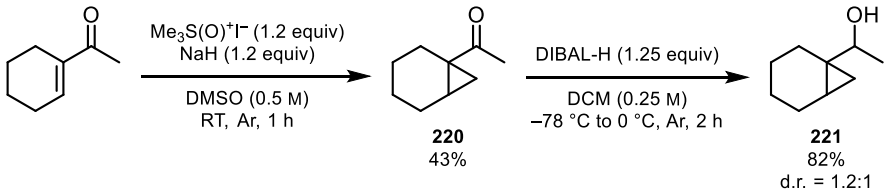


Scheme 4.19 *Synthesis of secondary alcohol **217** bearing a BCP group. The convenient generation of [1.1.1]-propellane **216** from 1,3-diiodo-BCP **218** obviated the problematic distillation procedure.*

The cause of the low yield of alcohol **216** could be due to the distillation process, which was not only low yielding, but also introduced multiple opportunities for the condensation of water that would destroy the organometallic reagent. The need for distillation was due to the presence of bromobenzene that would undergo Halex reaction with *t*-BuLi. While it was possible to conduct the entire sequence with a large excess of *t*-BuLi (minimum 5 equiv), this method would be impractically dangerous due to the highly pyrophoric nature

of *t*-BuLi. Instead, propellane **196** was generated *in situ* from 1,3-diiodo-BCP **218** and reacted with 4 equiv *t*-BuLi, which represents an acceptable stoichiometry of *t*-BuLi used in the reaction. The subsequent addition of an excess of cyclopropanecarboxaldehyde furnished alcohol **217** in modest yield as well as the corresponding ketone **219**. The overall cost of this synthetic route was minimised by the convenient in-house preparation of 1,3-diiodo-BCP **218** instead of a commercial purchase.[160*]

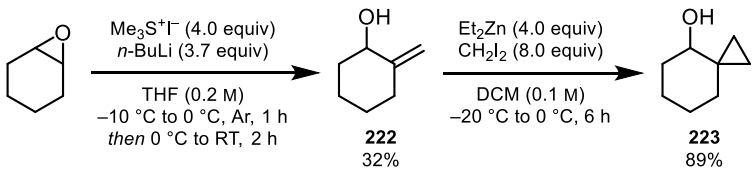
The synthesis of bicyclic alcohol **221** bearing a quaternary carbon at the 1′-position of the cyclopropane was readily achieved by Corey–Chaykovsky cyclopropanation of 1-acetyl-1-cyclohexene with trimethysulfoxonium iodide to give ketone **220** (Scheme 4.20).[163,164] Reduction of the ketone with DIBAL-H smoothly afforded alcohol **221** as an inconsequential mixture of diastereomers.



Scheme 4.20 *Synthesis of bicyclic secondary alcohol* ***221*** *bearing a quaternary 1′-carbon on the cyclopropane.*

The spirocyclic alcohol **223** was conveniently prepared by transformation of cyclohexene oxide into allylic alcohol **222** in modest yield,[165,166] then a Simmons–Smith reaction smoothly furnished the desired alcohol **223** (Scheme 4.21).[167]

[*] The lowest average cost of *gem*-dibromocyclopropane **215** is £3.20/g (£0.95/mmol, Fluorochem), while the lowest average cost of 1,3-diiodo-BCP **218** is £355.20/g (£93.16/mmol, Fluorochem). The cheapest available BCP compound suitable for derivatisation, BCP-carboxylic acid, costs £1665/g (£186.70/mmol, Apollo Scientific).

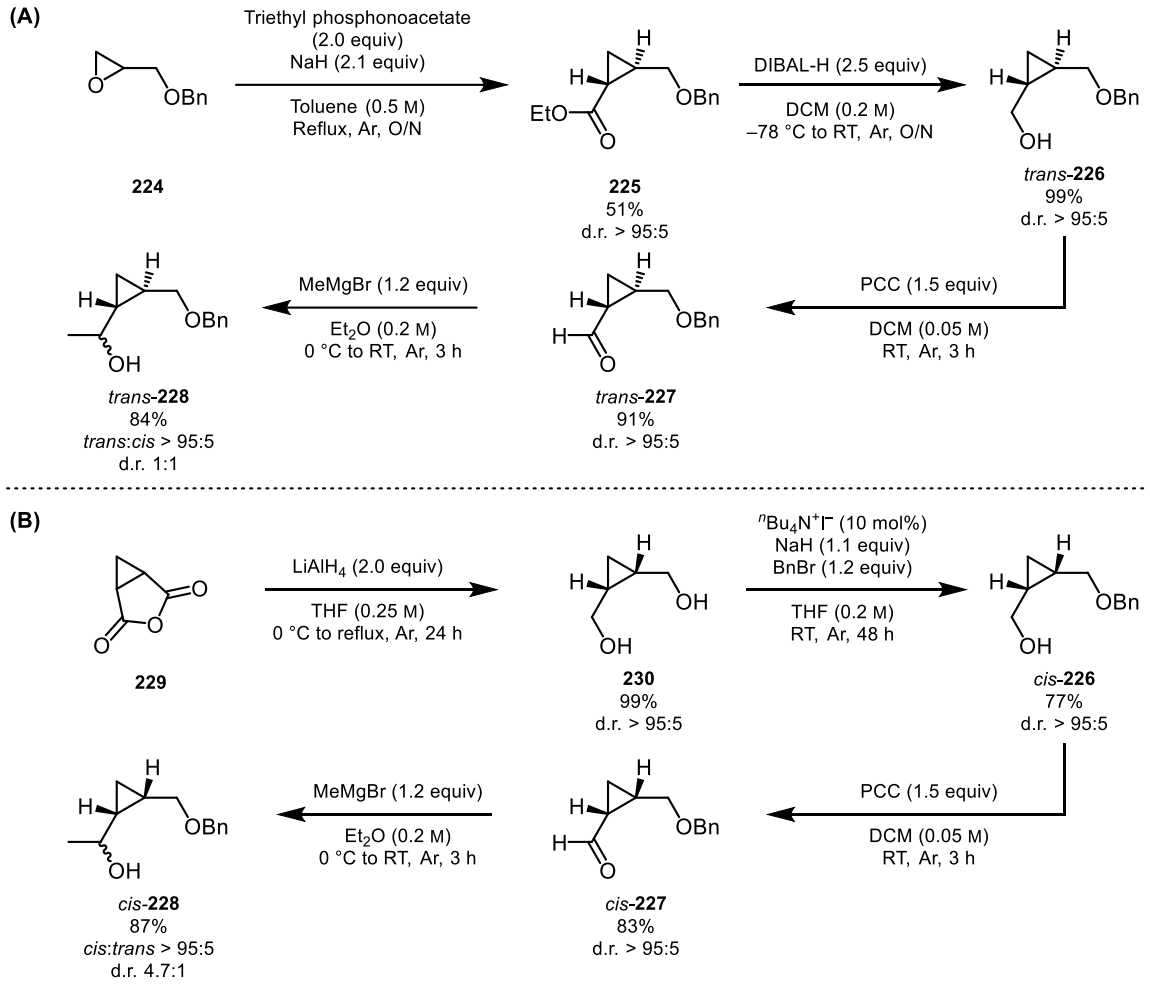


Scheme 4.21 *Synthesis of spirocyclic secondary alcohol* ***223****.*

To determine if *cis*-1,2-disubstituted cyclopropane substrates would give a similar reactivity as the *trans*-1,2-disubstituted counterpart, the substrates *cis*-**228** and *trans*-**228** bearing the BOM substituent on the 2′-position of the cyclopropane were synthesised. The choice of the BOM group involved many considerations. It is inert under basic conditions, and is unlikely to impart any significant electronic or steric bias that may affect the stereochemical outcome of the reaction. The BOM group also provides multiple distinct signals on the ^{1}H NMR spectrum that would not interfere with those from any of the products or enone intermediates. The reliability and stereospecific nature of the reactions involved in their preparation as well as the commercial availability and low cost of the starting materials, including enantiopure precursors, make the syntheses of the isomeric and potentially enantiopure BOM-substituted cyclopropane substrates highly attractive. Furthermore, the convergence of both routes towards epimeric intermediates would provide valuable analytical data for comparison and identification of any potential epimerisation process. Few other motifs can fulfil the considerations for availability and cost of precursors, quality of the products formed, and synthetic strategy for *both* isomers.

The synthesis of alcohol *trans*-**228** proceeded with the Wadsworth–Emmons cyclopropanation reaction of benzyl-protected glycidol **224** to form *trans*-configured ester **225** in reasonable yield with no trace of the *cis*-isomer,[168] followed by reduction with DIBAL-H to give monoprotected diol *trans*-**238** in near-quantitative yield (Scheme 4.22A). Oxidation of alcohol *trans*-**226** was achieved using PCC to give aldehyde *trans*-**227** with no signs of epimerisation, which was then converted to the desired *trans*-configured

cyclopropyl alcohol *trans*-**228** in excellent yield as an inseparable mixture of diastereomers and with no trace of the *cis*-configured diastereomers.



Scheme 4.22 *Synthesis of (A) cis- and (B) trans-1,2-disubstituted cyclopropane substrates.*

The synthesis of alcohol *cis*-**228** commenced from the reduction of anhydride **229** with $LiAlH_4$ under refluxing conditions to afford *cis*-configured diol **230** with essentially no *trans*-isomer observed (Scheme 4.22B).[169] Mono-benzylation with BnBr afforded monoprotected diol *cis*-**226** in good yield,[170] which was oxidised with PCC to give aldehyde *cis*-**227**, again with no signs of epimerisation. However, carbonyl addition with MeMgBr resulted in the formation of traces of the abovementioned *trans*-configured cyclopropyl alcohols *trans*-**228**, suggesting that the *cis*-configured aldehyde was much more prone to epimerisation under the basic reaction conditions. Fortunately, these

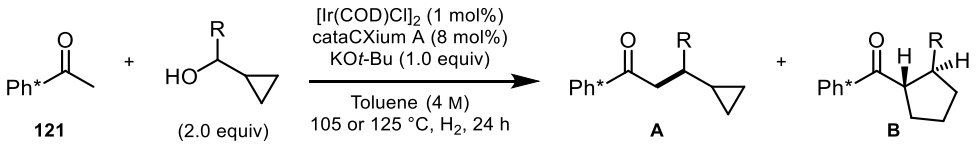
diastereomers had significantly different R_f values, and the *trans*-configured alcohols could be easily removed by flash column chromatography to afford *cis*-configured cyclopropyl alcohol *cis*-**228** in excellent yield and purity. Interestingly, the Grignard addition proceeded with some degree of stereoselectivity (d.r. = 4.7:1), and the diastereomers of *cis*-**228** could also be readily separated by flash column chromatography.

4.4.2 Substrate Scope Study

The exploration of the substrate scope started with variation in the side chain of the secondary alcohol (Table 4.13). A general observation was the need to increase the reaction temperature to 125 °C for improved yield the rearrangement product. This is likely a combination of improved conversion of starting material and enone intermediate.

Great caution must be exercised when interpreting the ratio of rearrangement to direct-coupled products due to variations in mass balance. Despite the best attempts at purification, it is difficult to account for the build-up of the various enone intermediates and any related side products (see Appendix 10.4), as well as degradation pathways that result in the pervasive tarring of the reaction vessels. For example, an increase in temperature was not beneficial for the optimisation substrate (Entry 1, see also Table 4.3), which may be partly attributed to the relatively low boiling point of the cyclopropyl ketone formed *in situ*.

An ethyl group was able to provide better selectivity and yield for the cyclopentane **232** over the direct coupling product **231** compared to the methyl substrate (Entry 1 vs 2). Although this trend of improved selectivity for rearrangement products held true for most of the alcohols with bulkier side chains, the yields were much more varied. The presence of α-branching such as the isopropyl substituent gave a very poor yield of cyclopentane **233** (Entry 3), while moving the branching one carbon away gave a comparatively better but nevertheless lacklustre yield of 29% for cyclopentane **234** (Entry 4).



Entry	R	Yield (%)[a]		
		A	**B**	**A**:**B**
1		25%, 19%[c] (**196**)	56%, 52%[c] (**176**)	1:2.3 1:2.8[c]
2		8%[b], 8%[c] (**231**)	50%[b], 67%[c] (**232**)	1:6.6 1:8.3[c]
3		Traces	6% (**233**)	-
4		-%, -%[a]	15%, 29%[b] (**234**)	-
5[d]		3%, 6%[c] (**165**)	32%, 56%[c] (**166**)	1:13.2 1:8.7[c]
6		5%[b] (**235**)	71%[b] (**236**)	1:15.5
7		-%	5% (**237**)	-
8		-%	Traces	-

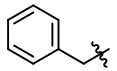
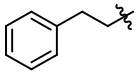
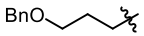
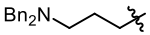
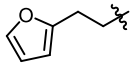
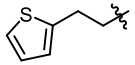
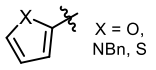
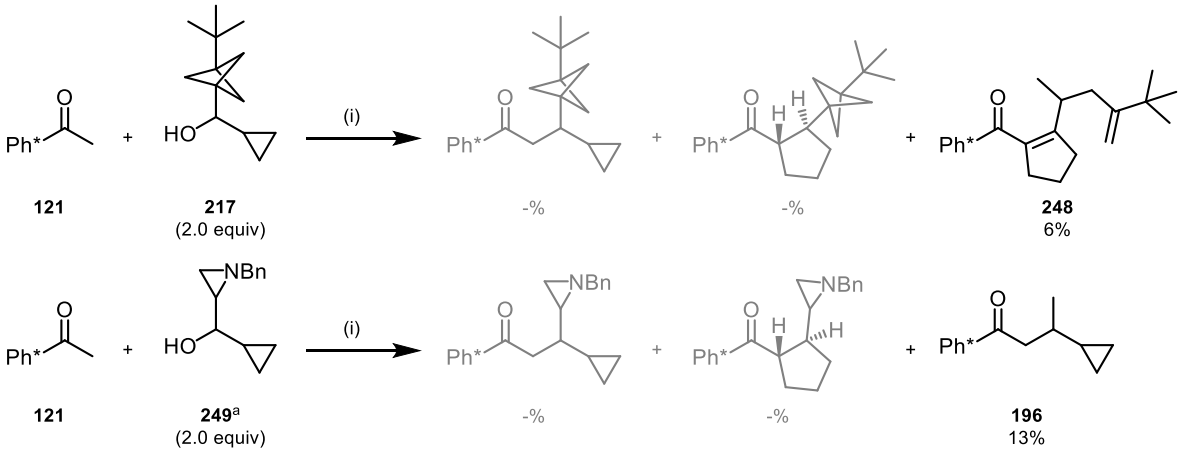
Entry	R	Yield (%)[a]		
		A	**B**	**A**:**B**
9[e]		6%, 8%[c] (**238**)	41%, 57%[c] (**239**)	1:5.2 1:10.0[c]
10		-%	-%	-
11[e]		9%, 20%[c] (**240**)	45%, 51%[c] (**241**)	1:4.7 1:2.5[c]
12		2%[c] (**242**)	74%[c] (**243**)	1:31.2[c]
13		-%[c]	72%[b,c] (**244**)	-
14[e]		7%[c] (**245**)	45%[c] (**246**)	1:6.0[c]
15		7%[b,c] (**247**)	-%[c]	-
16		-%[c]	-%[c]	-

Table 4.13 *Side chain variations in the substrate scope for the VCP rearrangement in the hydrogen borrowing reaction. For a complete list of substrates, and products and side products observed and isolated, see Appendix 10.4. With the exception of commercially available alcohols for entries 1, 5 and 9, all other alcohol substrates were provided by Dr. James Frost.* [a]*Yields correspond to the components of an inseparable mixture of products after chromatographic purification, calculated by quantitative* ^{1}*H NMR analysis (see experimental section for details on quantitative analysis). The identity of each compound was confirmed after further careful chromatographic purification to obtain analytically pure samples;* [b]*Complete separation by chromatographic purification was achieved in these cases;* [c]*Reaction was performed at 125 °C;* [d]*11% and 13% of the cyclopropane ring-opened isomer of* ***166*** *was also present in the chromatographic mixture when the reaction was performed at 105 and 125 °C respectively;* [e]*The corresponding cyclopropyl ketone derived from the oxidation of the alcohol was also present in the mixture obtained after chromatographic purification, see experimental section for details.*

Small ring substituents such as the cyclopropyl and cyclobutyl groups gave very respectable yields (Entries 5 and 6), although the slightly lower yield from the cyclopropyl group was due to a significant level of cyclopropane ring-opening (see Appendix 10.4). Further increase in ring size caused a dramatic decrease in conversion, with virtually no reaction being observed for the cyclohexyl substituent (Entries 7 and 8).

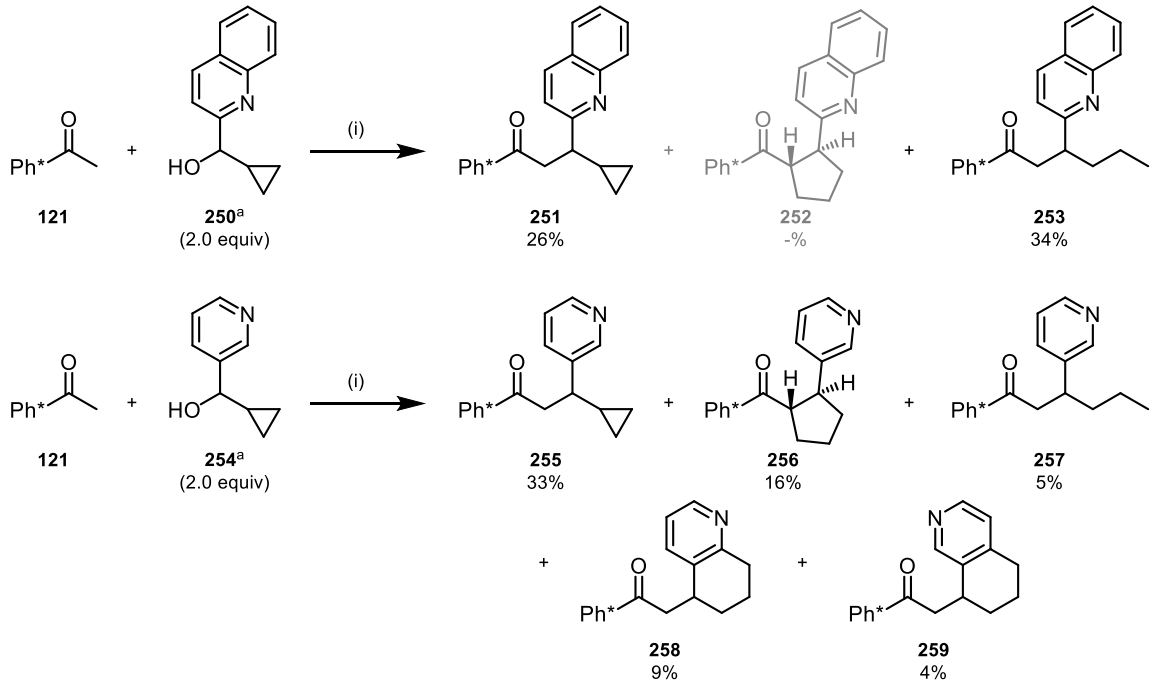
The phenyl group was well-tolerated in the reaction, giving a good selectivity and yield of rearrangement product **239** at elevated temperatures (Entry 9). Although the phenethyl substituent also gave respectable levels of rearrangement product **241**, the benzyl variant failed to effect any conversion at all (Entry 10 vs 11).

The benzyloxy and dibenzylamino groups on the side chain were well-tolerated, giving excellent yields of rearrangement products **243** and **244** respectively with no traces of debenzylation (Entries 12 and 13). However, there was limited viability for heteroaromatic motifs on the side chain, with only the 2′-furylethyl group giving a reasonable yield of cyclopentane **246** (Entry 14). In contrast, the 2′-thienylethyl group gave a very limited yield of the direct coupling product **247**, with no trace of any rearranged product being observed (Entry 15, see also Appendix 10.4). Unfortunately, all the heteroaryl alcohols failed to give any desired rearrangement product (Entry 16). Extensive decomposition and polymerisation observed for the furyl and thienyl substrates, whereas the *N*-benzylpyrrole alcohol was inert under the reaction conditions.



Scheme 4.23 *Decomposition outcomes for the cyclopropyl alcohols with the BCP and N-benzylaziridine side chain. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 125 °C, H_2, 24 h. [a]Material was provided by Dr. James Frost.*

There were a few substituents on the alcohol side chain that gave intriguing results (Scheme 4.23). The alcohol **217** bearing an unusual BCP motif gave no traces of the desired direct coupling or rearrangement product, instead giving a complex mixture by TLC analysis. An attempted purification revealed the presence of cyclopentene **248**, which suggests that the BCP group had decomposed under the reaction conditions. The *N*-benzylaziridine group also decomposed under the reaction conditions, giving no trace of the expected products. Bizarrely, the optimisation direct coupling product **196** was isolated in low yield, although there was also no trace of the optimisation cyclopentane product **176**.

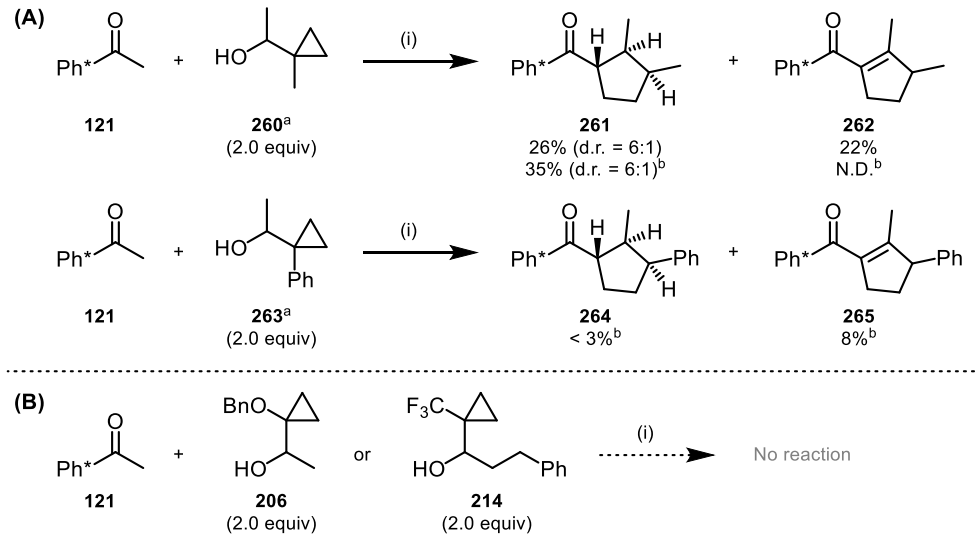


Scheme 4.24 *Unusual outcomes for the hydrogen borrowing reaction with cyclopropyl alcohols bearing the 2-quinolinyl and 3-pyridyl side chains. Yields quoted are based on calculations by quantitative ^{1}H NMR analysis of multiple fractions due to difficult chromatographic purification. The identity of each compound was confirmed after further careful chromatographic purification to obtain analytically pure samples. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 125 °C, H$_2$, 24 h. [a]Material was provided by Dr. James Frost.*

In contrast to the inert *N*-benzylpyrrole alcohol or the unstable *N*-benzylaziridine (see Table 4.13, Entry 16 and Scheme 4.23), the 2′-quinolinyl alcohol **250** was able to furnish some direct coupling product **251** as well as a large amount of cyclopropane ring-opening product **253**, but no trace of cyclopentane **252** could be observed (Scheme 4.24). It appears that having heteroatoms on the 2-position relative to the alcohol results in highly undesirable outcomes for the VCP rearrangement/hydrogen borrowing reaction.

On the other hand, the electron-deficient 3′-pyridyl alcohol **254** was able to give a small amount of rearrangement product **256** with a surprisingly large amount of direct coupling product **255**. However, the cyclopropane ring-opening product **257** was isolated alongside two unexpected quinoline-type products **258** and **259**. It appears that electron-deficient heteroaromatic groups could result in inhibition of the rearrangement process similar to that observed in electron-deficient quinoline substrate **250**, as well as some unexpected side

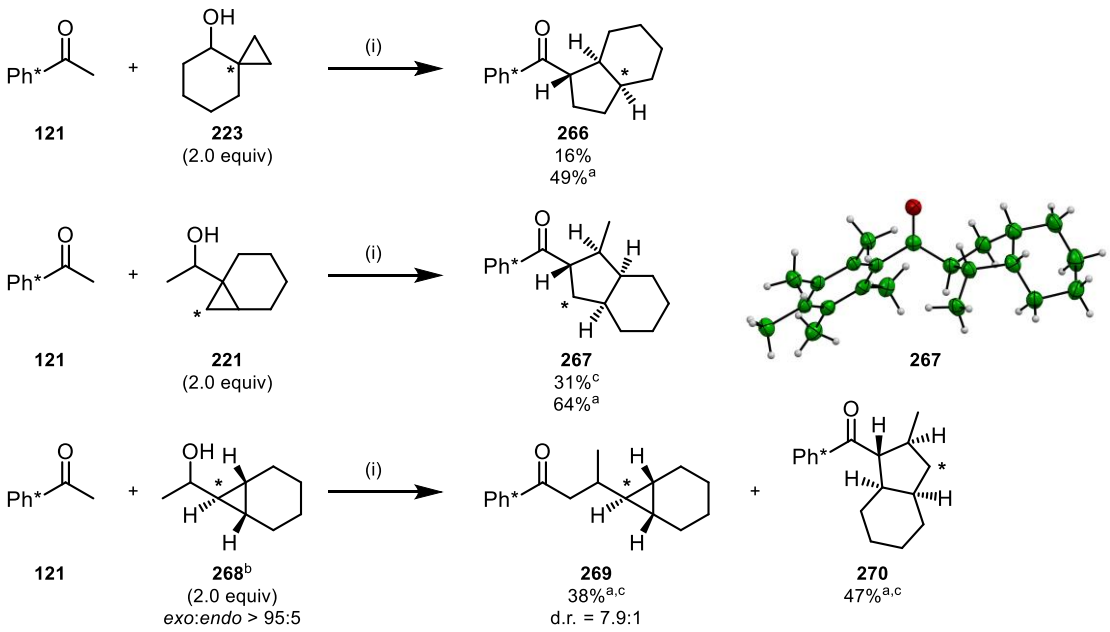
reactions. It is also possible that these heteroaromatic groups cause the β-carbon to be more electron-deficient, which may favour the direct reduction process either by the catalyst-mediated or base-mediated pathways (see Section 3.4.5).



Scheme 4.25 *Reactions involving 1′-substituted cyclopropyl alcohols in the VCP rearrangement/hydrogen borrowing reaction. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 105 or 125 °C, H_2, 24 h. N.D. = not determined. (A) Alkyl and aryl substituents on the 1′-position of the cyclopropyl group could give low yields of the rearrangement products and the corresponding enones. (B) The 1′-benzyloxy and 1′-trifluoromethyl groups render the alcohols inert to oxidation. [a]Material was provided by Dr. James Frost; [b]Reaction was performed at 125 °C.*

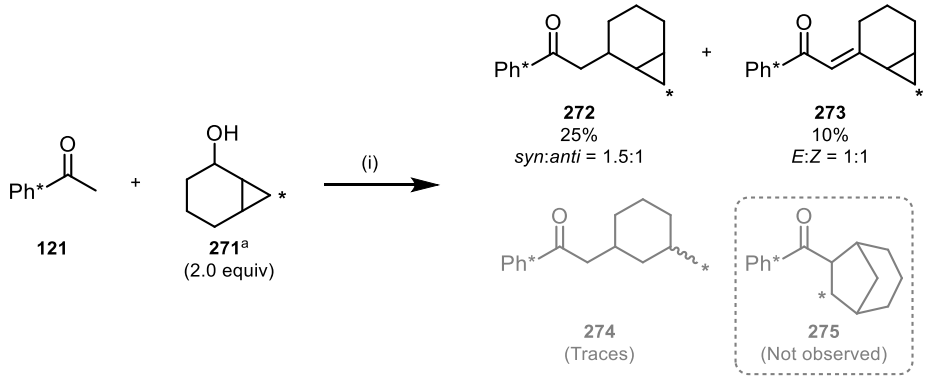
Turning to alcohols bearing a tetrasubstituted 1′-cyclopropyl position, the 1′-methylcyclopropyl alcohol **260** was able to give low yields of the rearrangement product **261** together with a significant amount of the corresponding enone **262** (Scheme 4.25). A modest increase in yield could be achieved by performing the reaction at a higher temperature. However, the 1′-phenyl substrate **263** gave extremely poor conversion, with only a very small amount of rearrangement product **264** observed together with slightly greater quantity of the corresponding enone **265**. In both cases, there was no trace of any direct coupling product.

Unfortunately, no reaction was observed with substrates bearing electron-donating or withdrawing groups on the 1′-position of the cyclopropane (**206** and **214**). This inert behaviour could be attributed to a difficult oxidation of the alcohol as previously observed for substrates with heteroatoms vicinal to the hydroxy group that render the *alcohol* electron-deficient (see Section 3.2.5 and 3.3.2).



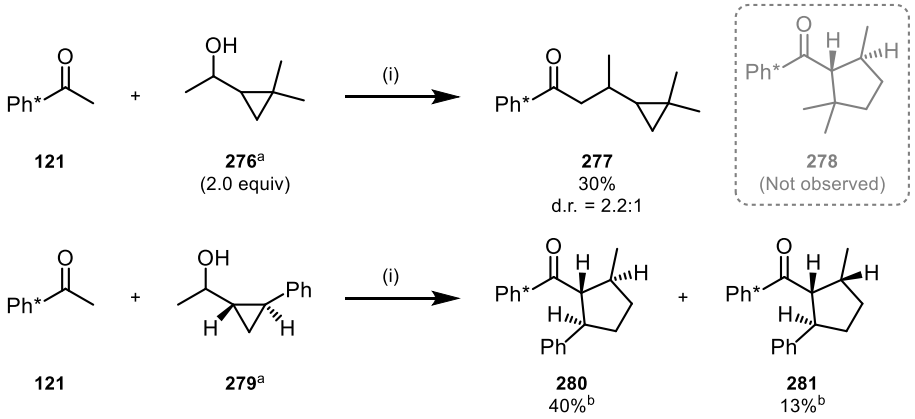
Scheme 4.26 *Reactions bicyclic cyclopropyl alcohols in the VCP rearrangement/hydrogen borrowing reaction that were able to give rearranged products. The asterisks (*) are included for clarity. The stereochemistry of* ***267*** *is confirmed by X-ray crystallographic analysis. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 105 or 125 °C, H_2, 24 h. [a]Reaction was performed at 125 °C; [b]Material was provided by Dr. James Frost; [c]Yields quoted are based on calculations by quantitative ^{1}H NMR analysis of multiple fractions due to difficult chromatographic purification. The identity of each compound was confirmed after further careful chromatographic purification to obtain analytically pure samples.*

The bicyclic cyclopropyl alcohols turned out to be amongst the most informative and successful substrates in this substrate scope study. The tethering of key positions was done such that all the substrates would possess the bicyclo[4.1.0]heptane skeleton. When the 1′-position of the cyclopropane was linked to the side chain or to the 2′-position of the cyclopropane ring, very good yields of the rearrangement products **266** and **267** were obtained with no trace of any direct coupling product observed (Scheme 4.26). This appears to agree with previous observations that the formation of rearranged products is greatly favoured by alkyl substitution at the 1′-position (see Scheme 4.25). In contrast, the tethering of both 2′-positions of the cyclopropane ring did not offer significant benefit to the selectivity for the rearrangement product, giving rearrangement product **270** in good yield together with a significant amount of direct coupling product **269**.



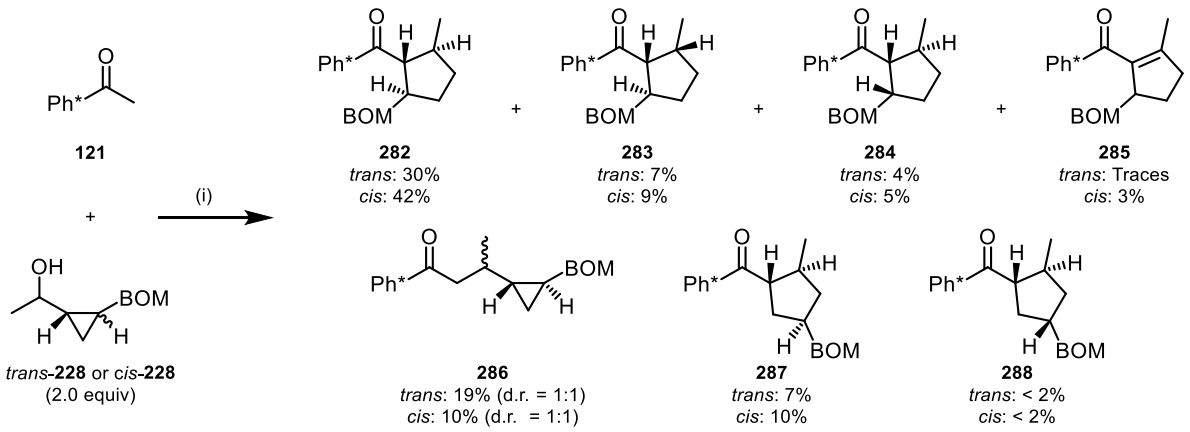
Scheme 4.27 *The tethering of the side chain and the 2′-position of the cyclopropane led to the formation of direct coupling product only. The asterisk (*) is included for clarity. Yields quoted are based on calculations by quantitative ^{1}H NMR analysis of multiple fractions due to difficult chromatographic purification. The identity of each compound was confirmed after further careful chromatographic purification to obtain analytically pure samples. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 105 °C, H_2, 24 h. [a]Material was provided by Dr. James Frost.*

However, when the side chain and the 2′-position of the cyclopropane was tethered together, the corresponding cyclohexanol derivative gave low yields of direct coupling product **272** as well as small amounts of the corresponding enones **273** (Scheme 4.27). Disappointingly, there was no trace of putative rearrangement product **275**, although there were traces of the cyclopropane ring-opening product **274** that were observed in the ^{1}H NMR spectrum of the crude material.



Scheme 4.28 *Investigating the effects of one or two substituents at the 2′-position of the cyclopropane. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 125 °C, H$_2$, 24 h. [a]Material was provided by Dr. James Frost; [b]Yields quoted are based on calculations by quantitative ^{1}H NMR analysis of multiple fractions due to difficult chromatographic purification. The identity of each compound was confirmed after further careful chromatographic purification to obtain analytically pure samples.*

The final aspect of the substrate scope study involved substituents at the 2′-position of the cyclopropane (Scheme 4.28). The *gem*-dimethyl alcohol **276** was able to furnish direct coupling product **277** in modest yield, but there was no trace of rearrangement product **278** formed. The *trans*-2′-phenyl-substituted alcohol **279** afforded epimeric rearrangement products **280** and **281** in modest yields, albeit as an inseparable mixture. Attempts to further identify other isomeric or side products were hampered by difficulties in the purification of this reaction.

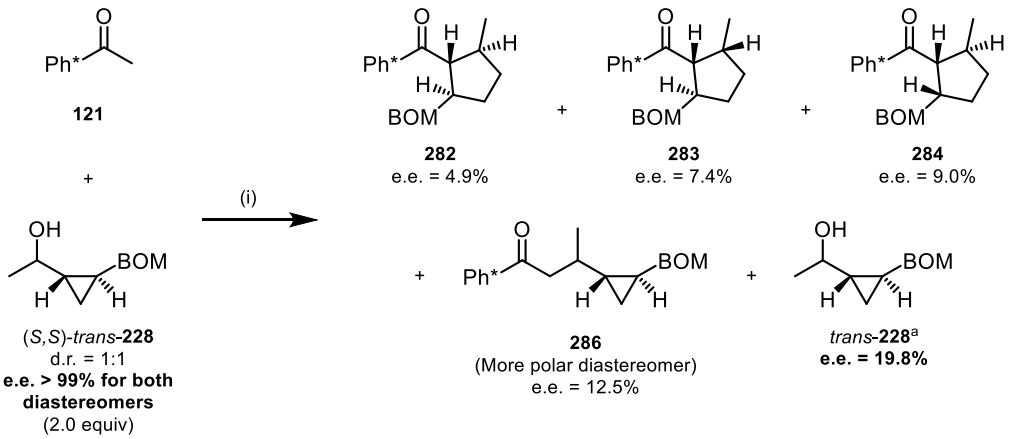


Scheme 4.29 *Investigating the effects of cis- and trans-BOM substituents at the 2′-position of the cyclopropane. Both trans-**228** and cis-**228** were observed in the ^{1}H NMR spectra of the crude mixtures even though each reaction started with either the trans- or the cis-isomers only. Yields quoted are based on calculations by quantitative ^{1}H NMR analysis of multiple fractions due to difficult chromatographic purification. The identity of each compound was confirmed after further careful chromatographic purification to obtain analytically pure samples. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KO*t*-Bu (1.0 equiv), toluene (4 M), 125 °C, H_2, 24 h.*

Turning to the *cis*- and *trans*-2′-BOM-substituted cyclopropyl alcohols, both substrates gave identical products, albeit with somewhat different distributions (Scheme 4.29). Both *cis*- and *trans*-alcohols **228** gave exclusively the *trans*-isomer of the direct coupling product **286**, suggesting that, when oxidised to form the ketone *in situ*, the proton on the 1′-position of the cyclopropane is sufficiently acidic under the reaction conditions to be deprotonated by KO*t*-Bu, thus leading to *cis*-*trans* isomerisation. This is further supported by the observation of all four possible diastereomers of the 2′-BOM-substituted cyclopropyl alcohols *cis*-**228** and *trans*-**228** in the ^{1}H NMR spectra of the crude mixture for *both* reactions. Since only one diastereomer of *cis*-**228** was used, it also shows that the oxidation and reduction of the alcohol is a reversible process.

Fortunately, the BOM group provided some polarity differences between the products that facilitated purification by flash column chromatography to a small degree. Both *cis*- and *trans*-**228** gave five different isomers of the rearrangement product, three of which were the highest yielding (**282**, **283** and **284**) and involved the putative migration of the more substituted cyclopropane bond, and two others which were formed in smaller quantities

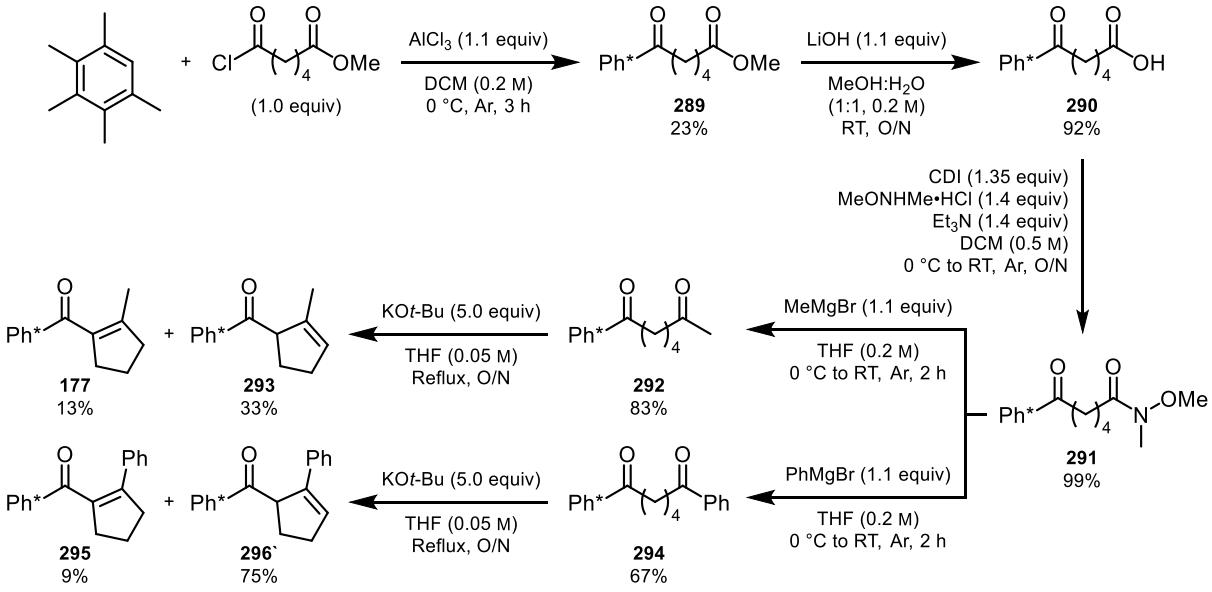
(**287** and **288**) and represented the putative migration from the less-substituted cyclopropane bond. The corresponding enone of the major isomers, enone **285**, could also be isolated in small amounts. The *cis*-alcohol *cis*-**228** gave a greater selectivity for the rearrangement products over the direct coupling products compared to the *trans*-alcohol *trans*-**228**. An overall 3:1 selectivity for the dominant product **282** over the pair of epimers **283** and **284** was observed for both isomeric alcohols *cis*-**228** and *trans*-**228**.



Scheme 4.30 *The use of enantiopure 2′-BOM-substituted alcohol in the hydrogen borrowing reaction led to the formation of products as well as the recovered alcohol substrate that were significantly racemised. Note that the products shown are for compounds in which the enantiomers of the compounds could be adequately purified by chromatographic purification and completely resolved by HPLC. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 125 °C, H_2, 24 h. [a]The cis isomer was also observed by ^{1}H NMR of the crude mixture.*

When the enantiopure version of the 2′-BOM-substituted cyclopropyl alcohol (*S*,*S*)-*trans*-**228** was subjected to the reaction conditions, the ^{1}H NMR of the crude mixture appeared identical to the reaction with racemic alcohol. Due to difficulties in purification as well as separation of mixtures of enantiomers on the HPLC, a full analysis of the enantiomers could not be performed. Nevertheless, it was clear that the products and alcohols themselves had also racemised significantly (Scheme 4.30). This implies that it is not possible to have useful levels of chirality transferred from an alcohol substrate with multiple stereocentres on the cyclopropane, although it is unclear which cyclopropane derivative (e.g. alcohol, ketone, enone etc.) was involved in the racemisation process (see also Section 4.5).

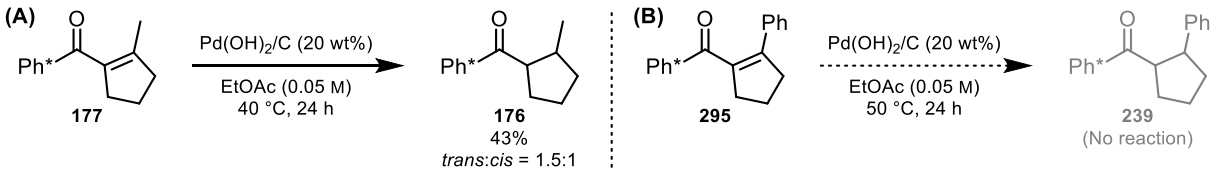
4.4.3 Predicting the Outcome of the VCP Rearrangement/Hydrogen Borrowing Reaction



Scheme 4.31 *Synthesis of cyclic enones* ***177*** *and* ***295*** *gave an unexpectedly large amount of skipped enones* ***293*** *and* ***296****.*

The major diastereomer of the rearrangement products are *trans*-1,2-cyclopentanes. This can be confirmed by X-ray crystallographic analysis,[*] as well as by NMR spectroscopy of the *cis*- and *trans*-cyclopentanes. To access the *cis*-isomers of cyclopentanes **176** and **239** by catalytic hydrogenation, keto-acid **290** was obtained by Friedel–Crafts acylation and subsequent ester hydrolysis in appreciable yield, then converted into Weinreb amide **291** as a common precursor for the organometallic addition with either MeMgBr or PhMgBr to give diones **292** and **294** in good yield (Scheme 4.31). Intramolecular aldol condensation furnished smaller quantities of conjugated enones **177** and **295**, with skipped enones **293** and **296** being the predominant products of the cyclisation.[171]

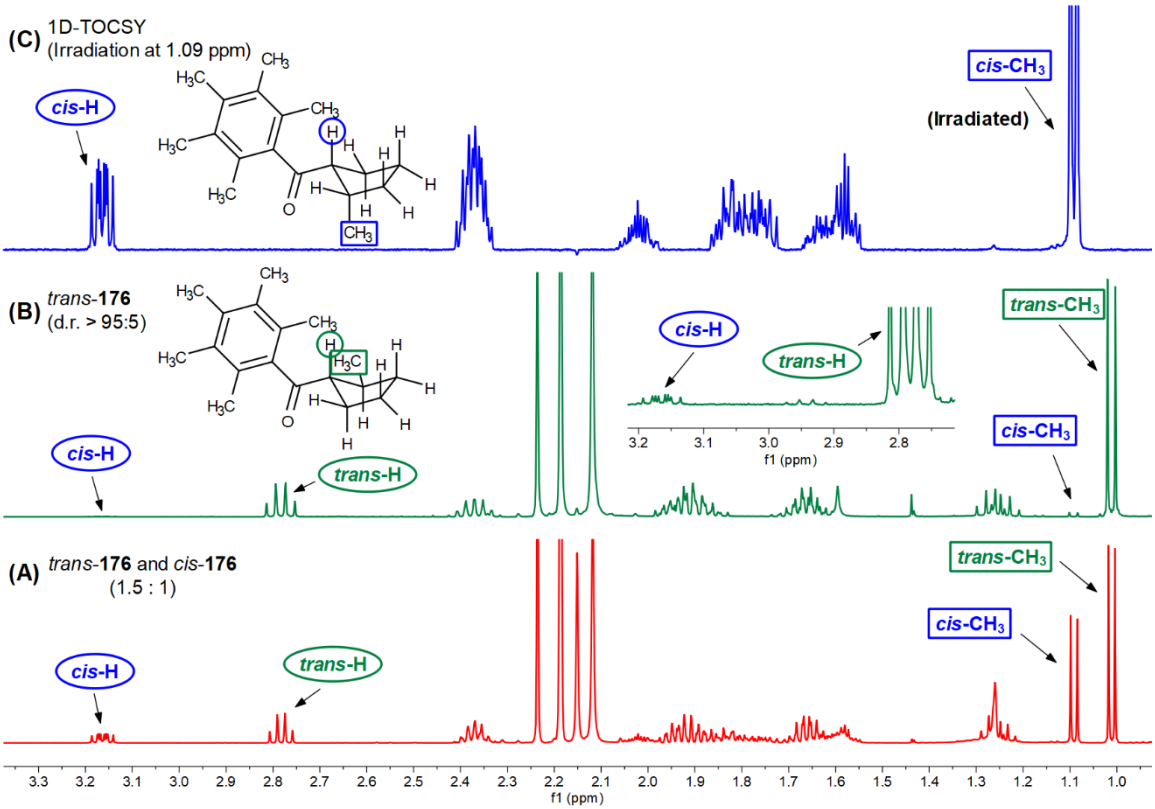
[*] Suitable single crystals of ethyl analogue **232** were prepared by Dr. James Frost through slow evaporation from Et_2O. Data collection, analysis and refinement were carried out by Dr. Kirsten Christensen.



Scheme 4.32 *(A) Catalytic hydrogenation of conjugated enone afforded cyclopentane **176** as a mixture of cis- and trans-isomers. (B) Catalytic hydrogenation of enone **295** failed to give the cis-isomer of cyclopentane **239**.*

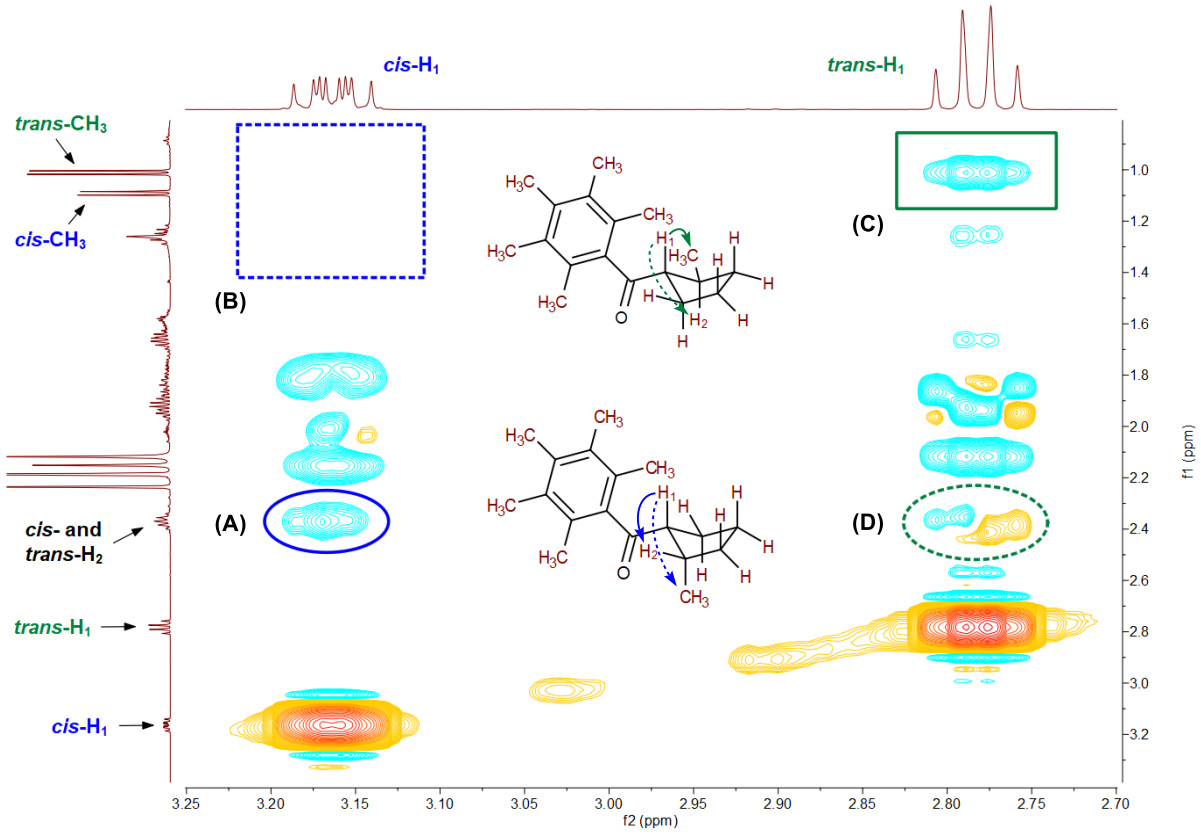
The catalytic reduction of conjugated enone **177** resulted in the formation of a mixture of *cis*- and *trans*-**176**, while enone **295** proved to be inert even at elevated temperatures (Scheme 4.32). The unexpected epimerisation of cyclopentane **176** could be due to the mildly basic nature of $Pd(OH)_2$ that could deprotonate the acidic α-keto proton under elevated temperatures.

Despite the inability to secure a relatively pure sample of *cis*-**176**, the mixture served as a useful sample for ^{1}H NMR characterisation of *cis*-**176**. Assignment of the ^{1}H NMR spectrum of the mixture was aided by comparison with the ^{1}H NMR spectrum of *trans*-**176** (Scheme 4.33). In addition, a 1D-TOCSY experiment was able to selectively identify the protons on the *cis*-cyclopentane ring through excitation of the cyclopentane CH_3 protons at δ_H = 1.09 ppm followed by coherence transfer to all vicinal protons during a 500 ms mixing period prior to acquisition.



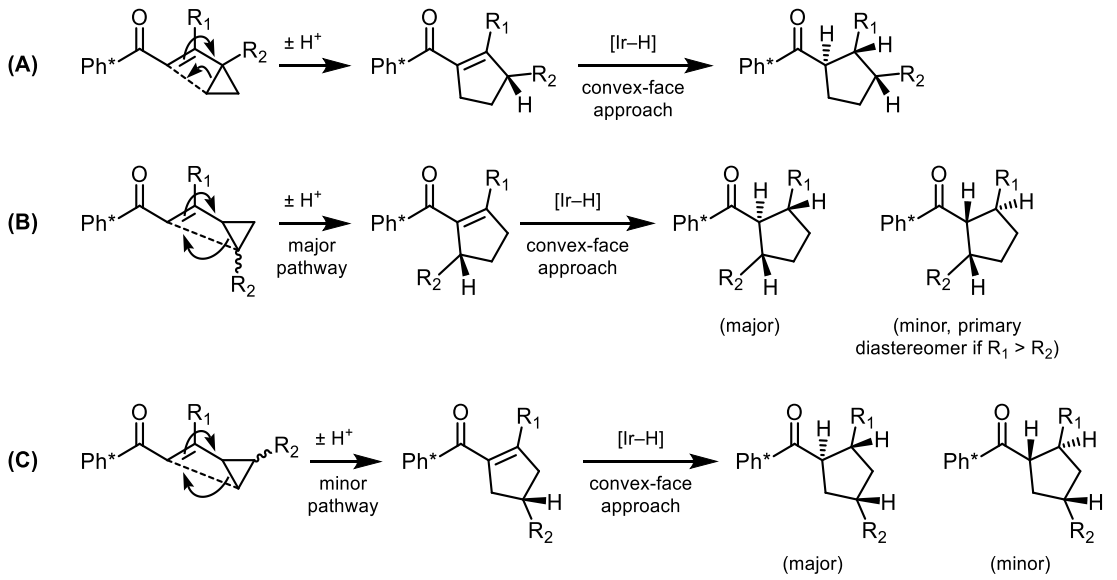
Scheme 4.33 *(A) ^{1}H NMR of a 1.5:1 mixture of trans- and cis-cyclopentanes* ***176****. (B) ^{1}H NMR spectrum of trans-****156*** *isolated from a typical hydrogen borrowing reaction. (C) 1D-TOCSY of the same mixture in (A) to identify the protons on the cyclopentane ring. The cyclopentane methyl group at 1.09 ppm was selectively excited with a mixing time of 500 ms prior to a 128-scan acquisition.*

The relative stereochemistries of *cis*-**176** and *trans*-**176** were confirmed by a 2D-NOESY experiment with the same mixture of *cis*- and *trans*-alcohols **176** (Scheme 4.34). In particular, the presence of an NOE between the α-keto proton (H_1) and the adjacent proton (H_2) as well as the lack of any significant NOE between H_1 and the methyl group on the *cis*-cyclopentane ring suggests a *cis*-relationship between H_1 and H_2. On the other hand, for the *trans*-isomer, the proton H_1 experiences an NOE with the methyl group on the cyclopentane ring, while the clear antiphase signal suggests a lack of any strong NOE against the scalar coupling to proton H_2, thus suggesting a *trans*-relationship between H_1 and H_2. All other cyclopentane products displayed NOEs consistent for the *trans*-isomers.



Scheme 4.34 *2D-NOESY of a 1.5:1 mixture of trans- and cis-**176**. The cis-relationship between H_1 and H_2 of cis-**176** is confirmed by (A) an NOE between H_1 and H_2 (which is overlapped with H_2 on the trans-isomer), as well as by (B) a lack of NOE between H_1 and the CH_3 proton on the cyclopentane ring. Similarly, the trans-relationship between H_1 and H_2 of trans-**176** is confirmed by (C) an NOE between H_1 and the CH_3 proton on the cyclopentane ring, as well as (D) the clear antiphase pattern of strong scalar coupling between H_1 and H_2 with a lack of any significant NOE present.*

Based on the product distributions observed from the substrate scope, the substitution pattern and stereochemistry of the major product from the VCP rearrangement/hydrogen borrowing reaction of a cyclopropyl alcohol with multiple substituents can be predicted by the following empirical model (Scheme 4.35).



Scheme 4.35 *A simple empirical model to predict the products of the VCP rearrangement/hydrogen borrowing reaction with (A) 1′-substituted cyclopropyl alcohols, and (B and C) 2′-substituted cyclopropyl alcohols, in which the putative migration of the more substituted bond (B) is the predominant pathway.*

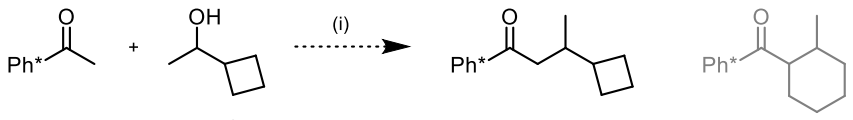
The VCP rearrangement reaction can be visualised as a cyclopropyl enone that performs a metathesis between the olefin and the more-substituted cyclopropyl bond (if applicable), giving a cyclopentene intermediate that becomes conjugated to the ketone under the basic conditions. The enone then undergoes reduction by a large hydride nucleophile *via* a convex-face approach, establishing the *cis*-relationship between R_1 and R_2. The α-keto stereocentre establishes a *trans*-relationship with R_1 and/or R_2 akin to forming a thermodynamic product. For the predominant pathway (Scheme 4.35B), the primary minor product for the 2′-substituted cyclopropyl alcohols is determined by the relative size of R_1 and R_2, with the larger substituent establishing a *trans*-relationship with the Ph* ketone motif. For the minor pathway (Scheme 4.35C), the major product is also the thermodynamic product.

4.5 Insights into the Mechanism of the VCP Rearrangement

Having concluded the substrate scope study, the next step is to gain a deeper understanding into the VCP rearrangement taking place in the hydrogen borrowing reaction. A series of experiments were carried out to answer the following questions:

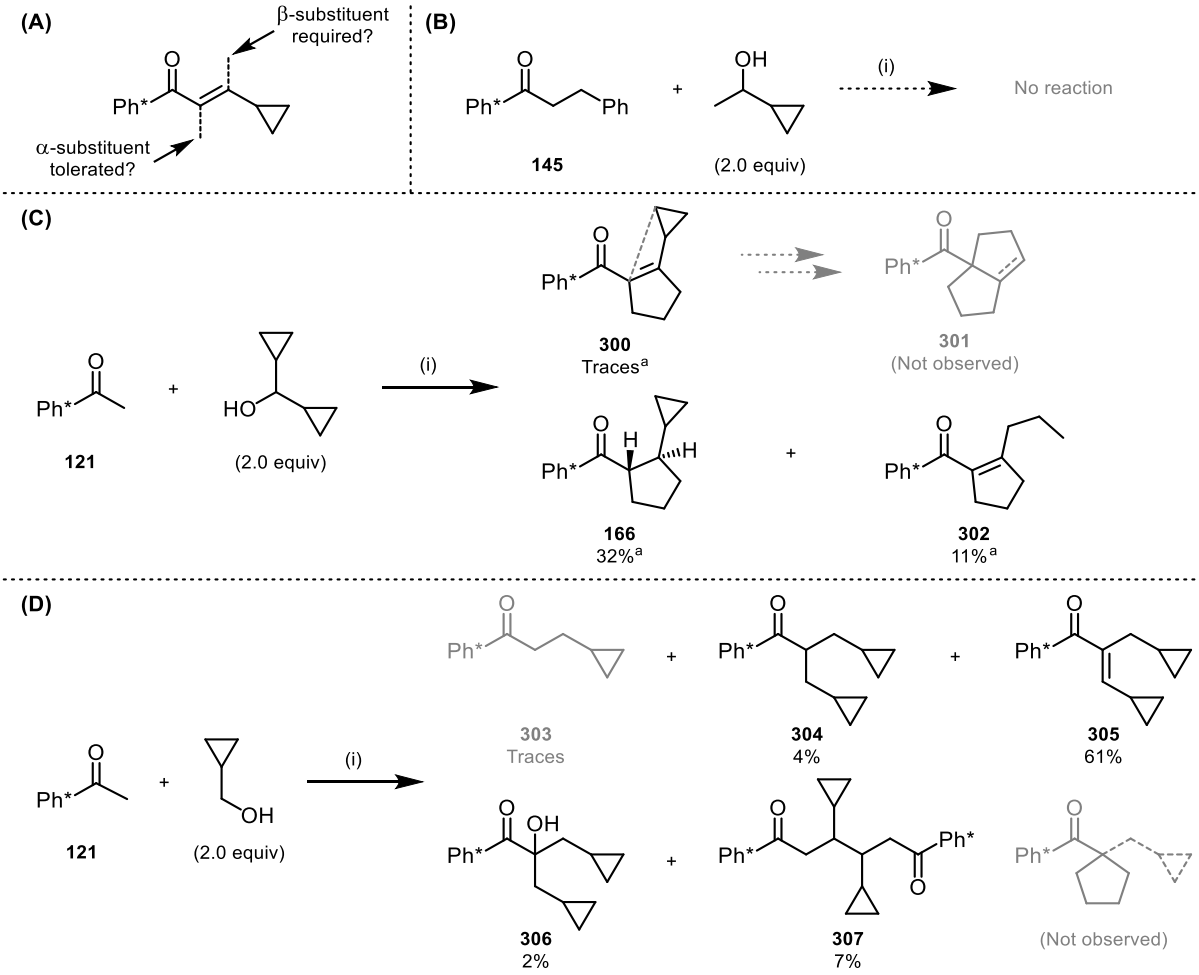
- Does the reaction work when the substitution pattern of the alkene is modified or when the carbonyl group is absent?
- Is the observed transformation truly a metal-catalysed VCP rearrangement, instead of some form of formal VCP rearrangement-like process that gives an analogous outcome?
- What is the nature or role of the metal catalyst?

4.5.1 Reactions with Modified Alcohol Substrates



Scheme 4.36 *No vinylcyclobutane rearrangement reaction was observed. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 105 °C, H_2, 24 h.* [a]*Material was provided by Dr. James Frost.*

One of the first considerations was whether the rearrangement could be extended to cyclobutanes in a potential vinylcyclobutane rearrangement (see also Scheme 4.3).[172] The hydrogen borrowing reaction with alcohol **297** gave a good yield of direct coupling product **298**, but there was no trace of any product bearing a cyclohexane skeleton such as **299**.

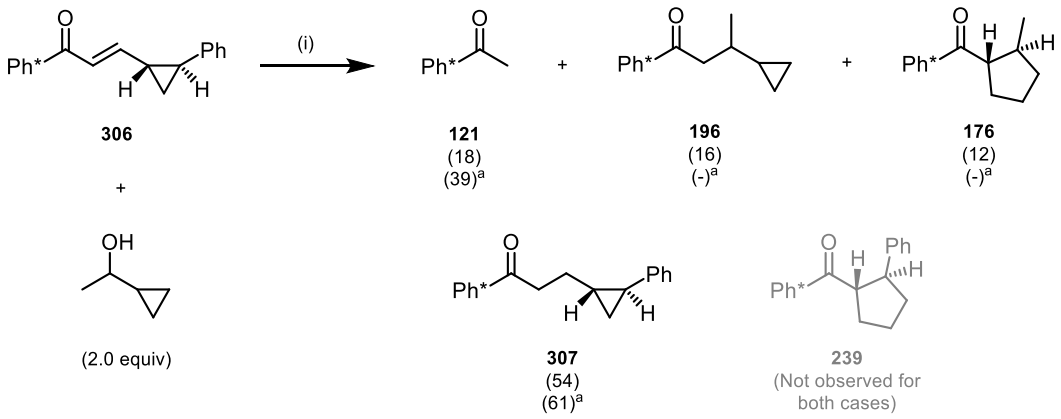


Scheme 4.37 *(A) Attempted investigations into the effects of additional α- and β-substituents at the enone on the VCP rearrangement. (B) The presence of an additional substituent on the ketone and/or alcohol led to the unsuccessful hydrogen borrowing reaction between ketone* ***145*** *and 1-cyclopropylethanol. (C) Only one VCP rearrangement was observed when dicyclopropylmethanol was used for the hydrogen borrowing reaction. (D) Omission of a β-substituent on the enone through the use of a primary alcohol resulted in no formation of rearrangement products. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (4 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 105 °C, Ar, 24 h. [a]Yields quoted are based on calculations by quantitative ^{1}H NMR analysis of multiple fractions due to difficult chromatographic purification. The identity of each compound was confirmed after further careful chromatographic purification to obtain analytically pure samples.*

In Section 4.2.2 it was noted that there was no sign of VCP rearrangement taking place when cyclopropylmethanol was used in the synthesis of α-branched ketones. The inability for the VCP rearrangement process to take place could be due to the substitution pattern of the enone intermediate. The VCP rearrangement could either require a β,β-disubstituted alkene, or could not tolerate an α,α-disubstituted alkene (Scheme 4.37). However, an attempt to investigate the tolerance of α-substituents is then complicated by the fact that formation of acyclic α,β-disubstituted ketones by the hydrogen borrowing process is

extremely difficult (see Schemes 3.12 and 3.19). This was confirmed by the lack of reaction between chalcone derivative **145** and 1-cyclopropylethanol. Nevertheless, it was noted that the hydrogen borrowing reaction with dicyclopropylmethanol only resulted in one VCP rearrangement reaction, but a second potential rearrangement to form a fused-ring compound such as **301** did not occur. This may suggest that an α-substituent is not tolerated for this VCP rearrangement.

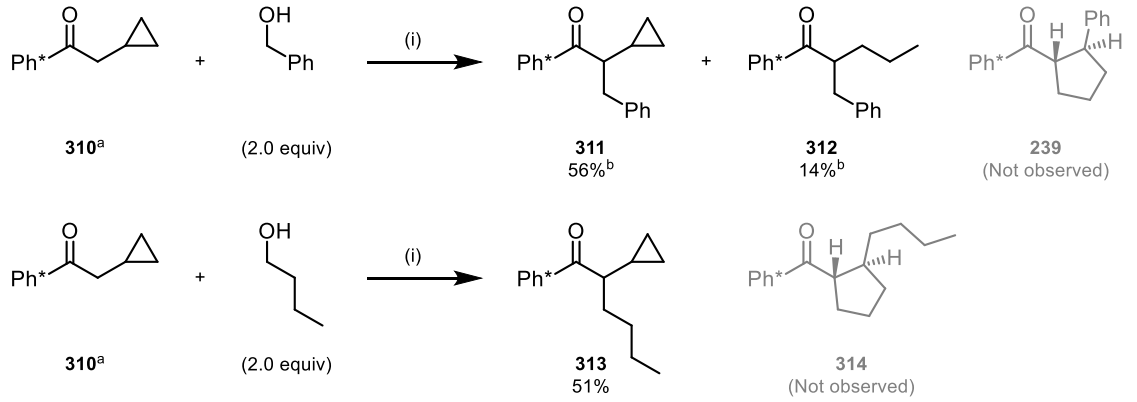
To investigate the effect of the β-substituent, cyclopropylmethanol was employed in the hydrogen borrowing reaction. A small amount of the double direct coupling product **304** was isolated, with only traces of single direct coupling product **303** being observed. Strangely, most of the product mass was comprised of enone **305**, and traces of an α-hydroxy compound were also isolated (see also Scheme 6.4), as well as an unusual homodimerisation product **307**. Nevertheless, the lack of any cyclopentane formation was the key result of this reaction, clearly suggesting that the β-substituent is a key requirement in this VCP rearrangement.



Scheme 4.38 *The omission of a β-substituent resulted in very facile enone reduction, with no desired VCP rearrangement observed. Numbers in parentheses represent approximate ^{1}H NMR ratios from the crude mixtures. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 105 °C, Ar, 24 h. [a]Reaction performed without 1-cyclopropylethanol and with a reaction atmosphere of H_2 instead of Ar as hydride source instead.*

The difficult aldol reaction and the need for a second β-substituent to trigger the VCP rearrangement is again highlighted by the hydrogen borrowing reaction of *trans*-1,2-

disubstituted enone **308** with 1-cyclopropylethanol as the hydride source (Scheme 4.38). Although ketone **309** was formed in good yield as expected, there was no trace of any rearrangement products **239** or **176**, indicating the essential role of the second β-substituent. In addition, the presence of the $E1_{CB}$ process was confirmed by the isolation of Ph* methyl ketone **121**, with virtually no trace of any product derived from 1-cyclopropylethanol. This suggests that the hydrogen borrowing reaction greatly favours the primary cyclopropyl alcohols, in agreement with observations made in the investigations towards the formation of α,β-branched products (see Scheme 3.27).

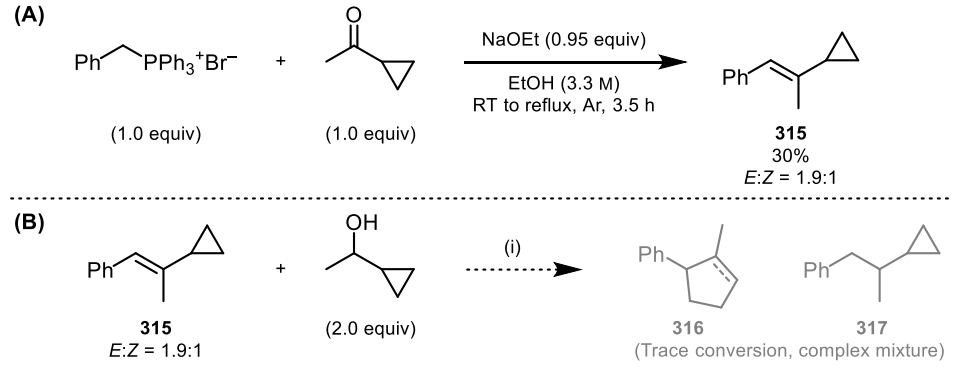


Scheme 4.39 *An α-cyclopropyl ketone was able to undergo hydrogen borrowing reaction with primary alcohols, but failed to effect a VCP rearrangement. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 105 °C, H_2, 24 h. [a]Material was provided by Dr. James Frost; [b]Yields quoted are based on calculations by quantitative ^{1}H NMR analysis of multiple fractions due to difficult chromatographic purification. The identity of each compound was confirmed after further careful chromatographic purification to obtain analytically pure samples.*

The next modification involves moving the cyclopropyl group to the α-position of the enone, fulfilling the disubstitution requirement on the olefin carbon bearing the cyclopropane but with different overall electronic behaviour on the vinylcyclopropane. Accordingly, α-cyclopropylketone **310** was subjected to the reaction conditions, but with benzyl alcohol and *n*-butanol as the alcohol substrate (Scheme 4.39). The direct coupling products **311** and **313** were isolated in appreciable yields together with some cyclopropane ring-opening product **312**, but no form of rearrangement product such as **239** or **314** was

observed. This suggests that electronics on the enone is a key factor in this VCP rearrangement reaction.

To confirm the impact of alkene electronics on the rearrangement reaction, the Ph* carbonyl group would be replaced with a simple phenyl group. Accordingly, the vinylcyclopropane **315** was synthesised by Wittig reaction in low yield, then subjected to identical hydrogen borrowing reaction conditions (Scheme 4.40). Analysis of the reaction mixture by ^{1}H NMR spectroscopy revealed that the dominant species in the reaction mixture was vinylcyclopropane **315** with its *E*/*Z* ratio unchanged. However, there were innumerable peaks close to the baseline that made attempts to identify potential products such as **316** difficult. This problem was exacerbated by possible Guerbet-type dimerisation reactions of the cyclopropyl alcohol.

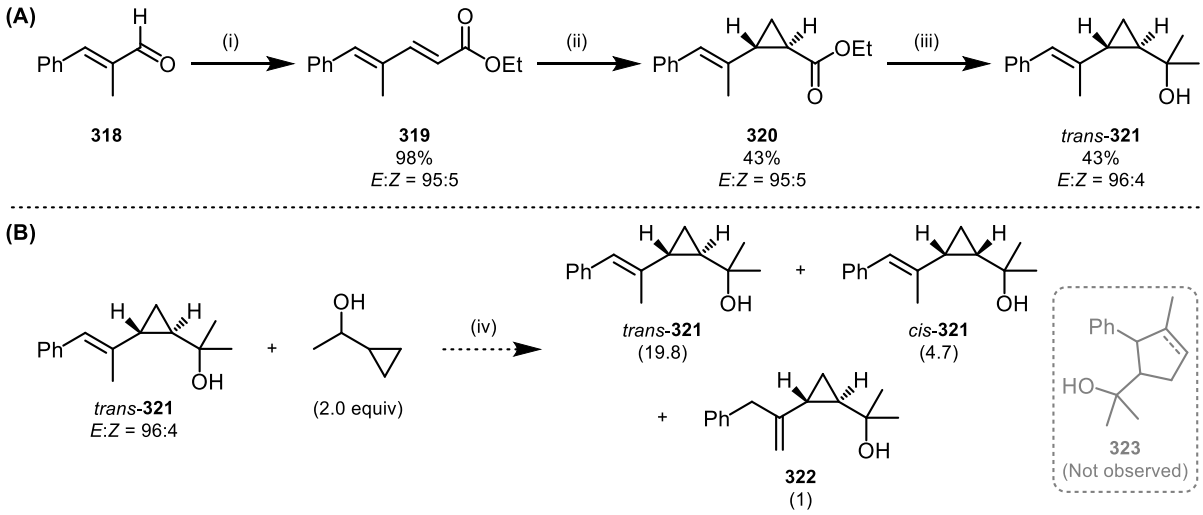


Scheme 4.40 *(A) Synthesis of vinylcyclopropane **315** without an electron-withdrawing carbonyl group. (B) No reaction was observed when vinylcyclopropane **315** was subjected to the hydrogen borrowing reaction. (i) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 105 °C, H_2, 24 h.*

It is worth noting the relatively inert behaviour of the alkene due to the absence of signals in the ^{1}H NMR spectrum that would be consistent with the structure of cyclopropane **317**, suggesting that the reduction of trisubstituted alkenes without any significant electronic influence is quite difficult under the hydrogen borrowing reaction conditions. This is compared to the successful reduction of *tetrasubstituted* enones to give the various products in the substrate scope study.

Collectively, the outcomes from these attempted VCP rearrangement reactions suggest that this VCP reaction is not operating in a fashion akin to the Ni(0)-catalysed VCP rearrangement (see Section 4.1.3). A full mechanistic study would need to be performed to understand the nature of the active catalytic species and how the VCP rearrangement operates.

One of the possible concerns regarding the VCP rearrangement was that the reactive intermediate responsible for interaction with the iridium catalyst was not actually the enone, but rather a β-hydroxyketone species (i.e. the aldol adduct), with the hydroxy group being a transient functionality. Since the β-hydroxyketone would be very prone to *retro*-aldol and hence difficult to accurately assess its reactivity, vinylcyclopropane *trans*-**321** was designed to include a tertiary alcohol akin to the β-hydroxyketone except that it cannot be eliminated (Scheme 4.41).[173]



Scheme 4.41 *(A) Synthesis of vinylcyclopropane trans-**321** containing a tertiary alcohol. (B) Cyclopropane and alkene isomerisations were observed when alcohol trans-**321** was subjected to the hydrogen borrowing reaction. Numbers in parentheses are ^{1}H NMR ratios. (i) Triethyl phosphonoacetate (1.1 equiv), NaH (1.1 equiv), THF (0.8 M), RT, Ar, 12 h;(ii) trimethylsulfoxonium iodide (1.2 equiv) NaH (1.2 equiv), DMSO (0.5 M), RT, Ar, 1 h; (iii) MeMgBr (2.1 equiv), THF (0.2 M), 0 °C to RT, Ar, 2 h (iv) [Ir(COD)Cl]$_2$ (1 mol%), cataCXium A (8 mol%), KOt-Bu (1.0 equiv), toluene (4 M), 105 °C, H_2, 24 h.*

When alcohol *trans*-**321** was subjected to the hydrogen borrowing reaction, analysis of the reaction mixture by ^{1}H NMR spectroscopy indicated that there were significant traces of

cyclopropane *cis*-*trans* isomerisation (*cis*- and *trans*-**321**) as well as olefin isomerisation (**322**), but there was no trace of potential rearrangement product **323**. This result reaffirms the observation of significant racemisation when enantiopure 2′-BOM-substituted cyclopropyl alcohol (*S*,*S*)-*trans*-**228** was used in the hydrogen borrowing reaction (see Scheme 4.30), and suggests that there may be an iridium–alcohol coordination that promotes a metal-cyclopropane interaction. Although the immediate relevance of this cyclopropane isomerisation to the VCP rearrangement has yet to be shown, it raises the possibility of the participation of the hydroxy group in the VCP rearrangement.

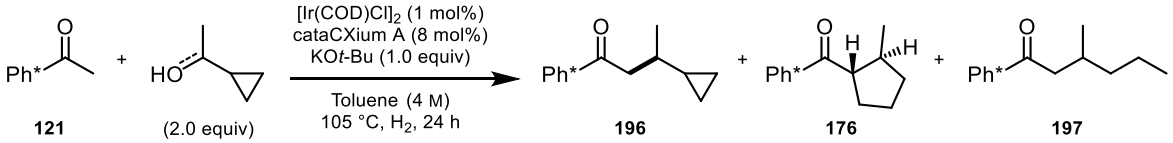
Based on the studies with modified substrates, the following conclusions can be drawn.

- The β-cyclopropylenone bearing a second β-substituent appears to be a privileged structure for the VCP rearrangement *via* the iridium-catalysed hydrogen borrowing reaction, as modifications to the substitution pattern of the enone is not well-tolerated. Removal of the second β-substituent or relocating it to the α-position will result in no rearrangement products being formed, although it has yet to be shown if the reaction is able to tolerate an additional α-substituent.
- The electronic character of the vinylcyclopropane is critical for the VCP rearrangement, as having the cyclopropyl group geminal to the aryl ketone results in no rearrangement product being formed. Removal of the carbonyl group results in no desired rearrangement reaction or reduction of the alkene, the latter suggesting that electronic bias assists the reduction process.
- The role of the enone in the VCP rearrangement has yet to be conclusively shown, although based on literature precedents it remains possible that the enone directly participates in the VCP rearrangement.

- A catalytic species is interacting with the cyclopropane group, leading to cyclopropane *cis*/*trans*-isomerisation as well as degradation of enantiopurity derived from stereocentres on the cyclopropane ring. It is possible that the transient β-hydroxyketone species (aldol adduct) is implicated in the rearrangement process, but this has yet to be conclusively proven.

4.5.2 Control Experiments

An extensive series of control experiments were carried out to identify the key components of the reaction that enable the hydrogen borrowing process and the VCP rearrangement to occur (Table 4.14).



Entry	Catalyst (mol%)	Ligand (mol%)	Base (equiv)	Alc/Ket (equiv)	Gas	NMR Ratio[a]/Yields (%)[b]			
						121	**196**	**176**	**197**
1	1	8	1	2	H_2	-	25	56	Trace
2	1	8	-	2	H_2	100	-	-	-
3	-	-	1	2	Ar	37	47	-	-
4	-	-	1	2	H_2	29	52	-	-
5	-	-	1	2 (Ket)[c]	Ar	(100)	-	-	-
6	1	8	1	2 (Ket)[c]	Ar	(100)	-	-	-
7	1	8	1	2 (Ket)[c]	H_2	(53)	(20)	(27)	(Trace)
8	1	8	-	2 (Ket)[d]	H_2	(100)	-	-	-

Table 4.14 *Control experiments involving ketone* ***121****, 1-cyclopropylethanol and cyclopropyl methyl ketone.* [a]*Numbers in parentheses indicate quantitative* ^{1}*H NMR ratios from the crude mixture;* [b]*Isolated yields as a mixture of all four components after chromatographic purification, with the amount of each component calculated by quantitative* ^{1}*H NMR analysis;* [c]*1-Cyclopropylethanol was observed in the* ^{1}*H NMR spectrum of the reaction mixture;* [d]*No trace of 1-cyclopropylethanol was observed in the* ^{1}*H NMR spectrum of the reaction mixture (see Section 4.5.3).*

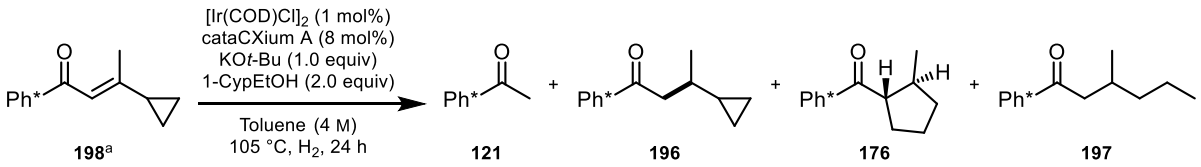
No reaction was observed when the reaction was performed in the absence of base, which agrees with the role of the base in enolate formation and aldol condensation (Entry 2). The omission of catalyst and ligand in an atmosphere of Ar or H_2 resulted in exclusive and

extensive formation of direct coupling product **196**, confirming the role of the catalyst for the VCP rearrangement as well as the persistent presence of the catalyst-free alkylation process (Entries 3 and 4, see also Section 4.3.6).

When the reaction was performed with cyclopropyl methyl ketone under an atmosphere of Ar with or without any ligand or catalyst, the lack of a hydride source resulted in no observable reaction (Entries 5 and 6). More importantly, no cyclopropyl enone or cyclopentene was formed, suggesting that the *retro*-aldol process was significantly more favourable than the aldol condensation, and that any cyclopropyl enone formed is unlikely to be thermally rearranging to the cyclopentene.

Both direct coupling and rearrangement products were observed when H_2 was present as a hydride source (Entry 7) However, traces of cyclopropyl alcohol could also be observed suggesting that the ketone was reduced by H_2. Therefore, this cannot conclusively show that H_2 is the only source of hydride for the catalyst due to potential cross-talk between the catalyst, alcohol/ketone and H_2. Interestingly, base was needed to effect the reduction of cyclopropyl methyl ketone as there was no trace of the corresponding alcohol, although it is not clear if this role is applicable to the reduction of enones (Entry 8).

It is now clear that the reaction is indeed iridium-catalysed and unlikely to be a purely thermal process. In addition, the base is needed for both the aldol reaction as well as for the reduction of ketone/enone under a H_2 atmosphere. The next step is to verify if the enone is indeed a key intermediate that is involved in the VCP rearrangement, with the expectation that the results should be generally consistent with those from Table 4.14. It is necessary to point out that this was likely to be a difficult exploration due to the very facile *retro*-aldol reaction of the enone (see Table 4.14, Entries 5 and 6).



Entry	Catalyst (mol%)	Ligand (mol%)	Base (equiv)	Alcohol (equiv)	Gas	NMR Ratio[b]/Yield (%)[c]				
						198	**121**	**196**	**176**	**197**
1	-	-	-	-	H_2	100	-	-	-	-
2	-	-	-	2	H_2	100	-	-	-	-
3	-	-	1	-	H_2	-	100	-	-	-
4	-	8	-	-	H_2	100	-	-	-	-
5	-	-	1	2	H_2	-	-	(68)	-	-
6	1	8	-	-	Ar	100	-	-	-	-
7	1	8	1	-	Ar	100	-	-	-	-
8	1	8	-	2	Ar	100	-	-	-	-
9	**1**	**8**	**-**	**-**	**H_2**	**-**	**-**	**20**	**-**	**80**
10	**1**	**8**	**1**	**-**	**H_2**	**-**	**71**	**13**	**16**	**-**

Table 4.15 *Control experiments involving enone **198**. Reactions were performed on 0.150 mmol scale. [a]Material was provided by Dr. James Frost; [b]Quantitative ^{1}H NMR ratios from the crude mixture; [c]The number in parentheses indicate isolated yield.*

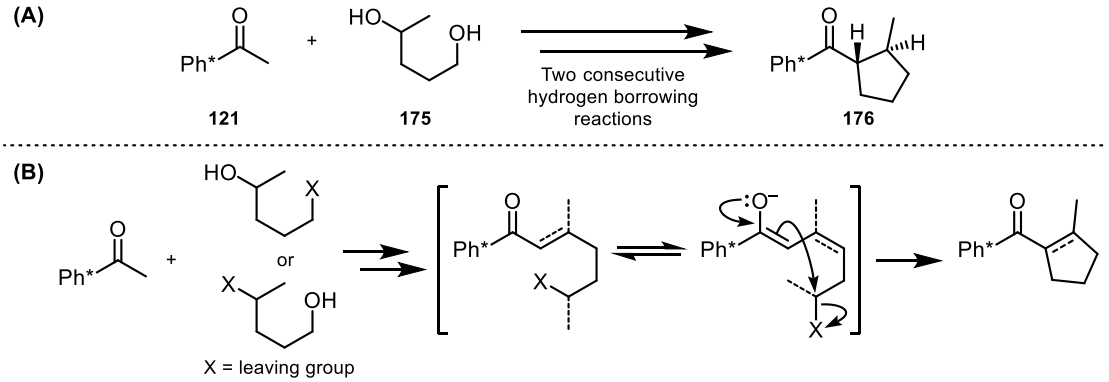
When enone **198** was heated with or without any alcohol present, no reaction was observed, suggesting that either the VCP rearrangement is not likely a purely thermal process (Table 4.15, Entries 1 and 2). Heating enone **198** with KO*t*-Bu alone resulted in a *retro*-aldol process that gave ketone precursor **121** exclusively, a result consistent with that previous seen (Entry 3, see also Table 4.14, Entries 5 and 6). The ligand alone also did not result in any conversion of the enone (Entry 4). Subjecting enone **198** to base and alcohol alone resulted in the formation of direct coupling product **196** exclusively (entry 5), a result consistent with the catalyst-free direct coupling process (see Tables 3.8 and 3.9 and text).

In the absence of any hydride source, the catalyst and ligand were not able to convert enone **198** to any rearranged products with or without KO*t*-Bu present, suggesting that the active catalytic species for VCP rearrangement is not $[Ir(COD)Cl]_2$ or its immediate monomeric counterparts (Entries 6 and 7). The use of the alcohol as the sole hydride source but with

KO*t*-Bu absent resulted in no observable reaction, confirming the active role of base in the reduction/VCP rearrangement process (Entry 8, see also Table 4.14, Entries 7 and 8).

When H_2 was used as the hydride source instead in the absence of base, the enone and cyclopropane groups were reduced to give ring-opening product **197** as the major component of the reaction mixture and direct coupling product **196** as the minor component, but no rearrangement product **176** could be observed (Entry 9). This clearly indicates the participation of both the iridium catalyst in the reaction with the enone being the key intermediate, although it leads to the undesired products.

The introduction of KO*t*-Bu to the catalytic system with H_2 as the only hydride source led to the modest formation of ketones **196** and **176** (Entry 10). Nevertheless, the pervasive *retro*-aldol process (see entry 3) and the possibility of cross-talk between the catalyst, alcohol/ketone and H_2 (see Table 4.14, entry 7 and Scheme 4.43) means that one cannot firmly conclude that H_2 is also capable of acting as the hydride source for the hydrogen borrowing reaction and the VCP rearrangement.



Scheme 4.42 *Formation of cyclopentane **176** could occur from side products derived from the ring-opening of the cyclopropyl ketone or alcohol such as (A) diol **175**, or (B) through a single hydrogen borrowing reaction followed by intramolecule displacement of a leaving group.*

An additional concern was the possibility of the ring-opening of the cyclopropane by nucleophiles that could result in the formation of cyclopentane **176** by a different route such as through two consecutive hydrogen borrowing reactions of diol **175** or some form of intramolecular displacement (Scheme 4.42). However, none of the reactions or control experiments produced any amount of diol **175** or related acyclic species despite the relatively large amount of nucleophilic KO*t*-Bu present. Therefore, it is highly unlikely that the reaction is proceeding by a conjugate addition/intramolecular displacement pathway.

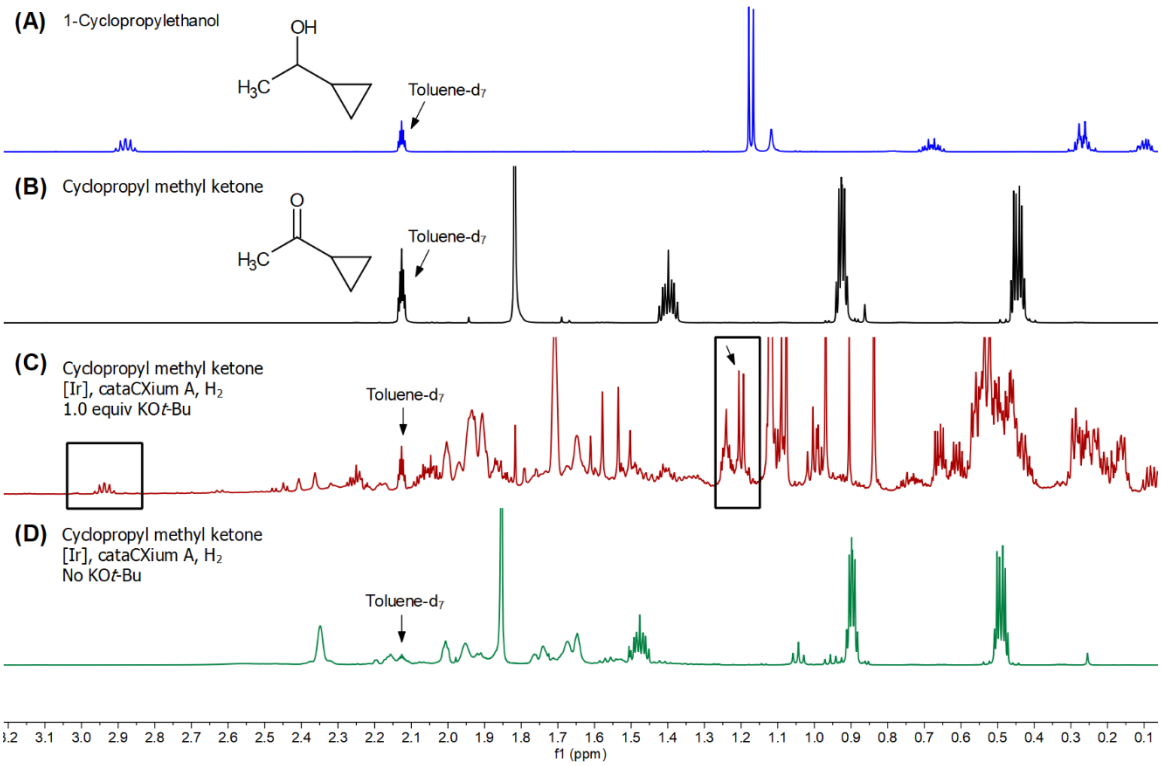
In summary, the following conclusions can be drawn from the control experiments and from the optimisation process.

- The VCP rearrangement is catalysed by an iridium species, potentially an iridium-hydride complex or a more advanced catalytic species. The ligand is not strictly necessary for the VCP rearrangement. It has a real but relatively small impact on the outcome of the reaction (see Sections 4.3.6 and 4.3.8). The rearrangement is not likely to be a purely thermal process or mediated by external nucleophiles.
- The base is critical for both the aldol condensation and catalytic reduction process. It is also likely required for the VCP rearrangement, the omission of which results in the reduction of both the enone and cyclopropane motifs. However, the base is also responsible for the competing non-catalytic direct coupling process.
- The hydride source for the catalyst can be either the alcohol or H_2. The catalyst is able to utilise H_2 to reduce the ketone to the alcohol, but the ability for a similar combination to reduce the enone and effect the VCP rearrangement cannot be conclusively proved due to cross-talk between the catalyst, alcohol, ketone and H_2.

- The enone cannot be conclusively proven to be the key intermediate prior to the VCP rearrangement due to its difficult formation as well as the constant pervasiveness of the *retro*-aldol reaction. The enone itself does not undergo a thermal VCP rearrangement process, but the possibility of a related species undergoing VCP rearrangement by a purely thermal process cannot be ruled out.

4.5.3 NMR Experiments

A short series of NMR experiments were conducted with two primary aims. The first was to verify the presence of any iridium hydride species, and the second was to observe any changes to this hydride species under conditions similar to those in the control experiments (see Table 4.1).

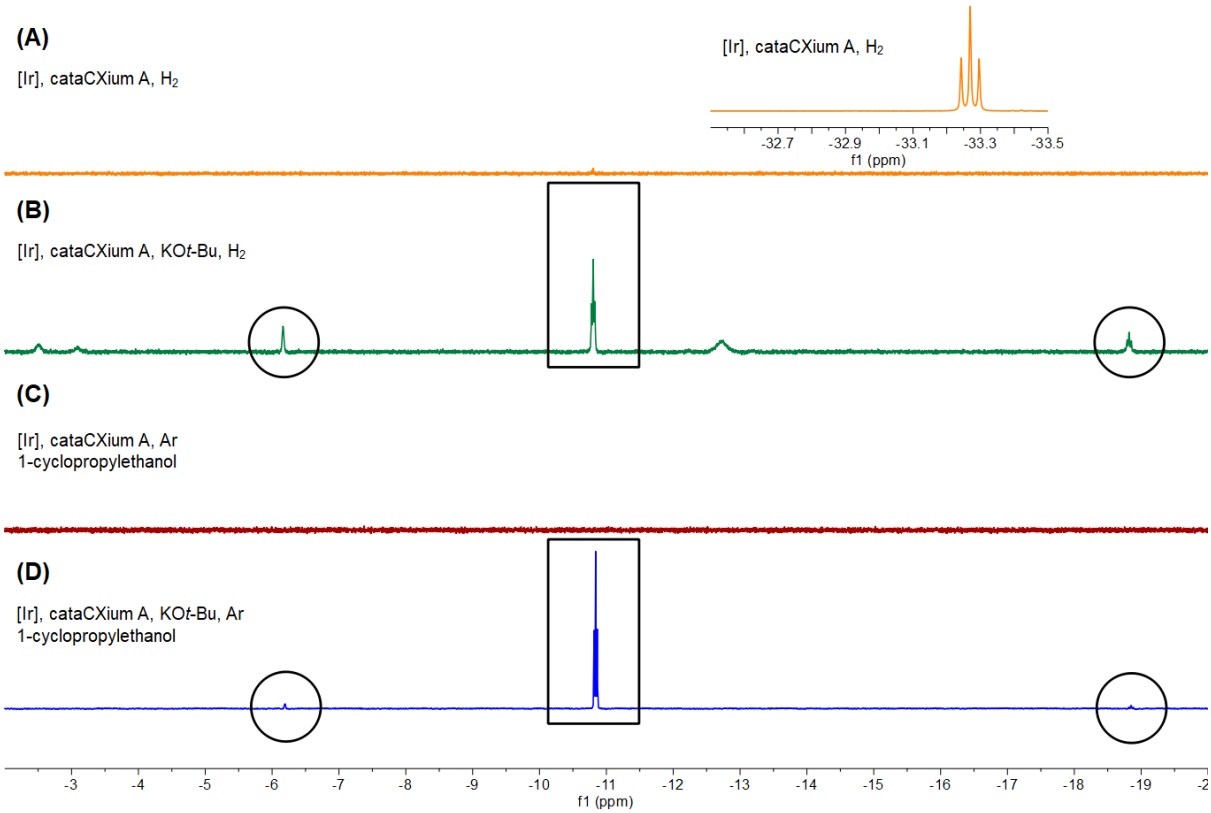


Scheme 4.43 *^{1}H NMR of (A) 1-cyclopropylethanol and (B) cyclopropyl methyl ketone in toluene-d_8. (C and D) Cyclopropyl methyl ketone was subjected to conditions identical to the hydrogen borrowing reaction with or without KOt-Bu for 4 h. (C) The presence of 1-cyclopropylethanol suggests that the catalyst was able to use H_2 as a source of hydride in the presence of a base to reduce the ketone. There was also significant degradation and polymerisation of the ketone/alcohol. (D) In the absence of KOt-Bu, virtually no reaction was observed. The rest of the signals were from the catalyst and ligand.*

To highlight the reduction of ketones in the presence of the iridium catalyst and base (see Table 4.14, Entries 7 and 8), cyclopropyl methyl ketone was exposed to $[Ir(COD)Cl]_2$ and cataCXium A in toluene-d_8 under an atmosphere of H_2 with or without KO*t*-Bu added (Scheme 4.43). No reaction was observed in the absence of KO*t*-Bu, but when the base was added, in addition to extremely significant amounts of degradation products, 1-cyclopropylethanol was also clearly observed. Therefore, any study with cyclopropyl enones or ketones would be complicated by a crosstalk between the catalyst, alcohol and H_2. Nevertheless, this also shows that base is essential for the iridium-catalysed reduction of ketones with H_2.

Since the hydrogen borrowing reaction is iridium-catalysed and likely involves a metal-hydride, the next step would be to confirm the presence of such a metal hydride. In addition, since the presence of KO*t*-Bu appears to alter the reactivity of the catalyst, in particular enabling the VCP rearrangement of enone **178** in the presence of the base while only performing reduction and cyclopropane ring-opening in its absence, it is worth studying the changes in behaviour of the catalytic species, particularly the metal hydride species, by ^{1}H NMR spectroscopy.

When a mixture of $[Ir(COD)Cl]_2$ and cataCXium A in toluene-d_8 was heated to 105 °C for 4 h under an atmosphere of H_2 and in the absence of KO*t*-Bu, a triplet was observed in the ^{1}H NMR spectrum at δ_H = –33.27 ppm (J = 13.3 Hz), but no other significant species was present between –2 and –20 ppm (Scheme 4.44). The addition of KO*t*-Bu to this H_2 system resulted in the formation of a triplet at –10.8 ppm (J = 11.9 Hz) as the dominant signal. A few other comparatively minor signals could also be observed, such as a singlet at δ_H = –6.16 ppm and a triplet at δ_H = –18.82 ppm (J = 15.9 Hz).



Scheme 4.44 *^{1}H NMR of a mixture of [Ir(COD)Cl]$_2$ and cataCXium A in toluene-d$_8$ heated at 105 °C for 4 h with H$_2$ or 1-cyclopropylethanol as hydride source with or without KOt-Bu present. The quantities used were identical to reaction conditions. (A) A triplet at –33.27 ppm (J = 13.3 Hz) was observed, but no other significant species are present between –2 and –20 ppm. (B) The addition of KOt-Bu to the system in (A) resulted in the formation of a triplet at –10.9 ppm (J = 11.9 Hz). (C) No signals was observed in the same region. (D) The addition of KOt-Bu to the system in (C) also resulted in the formation of a similar triplet observed in (B).*

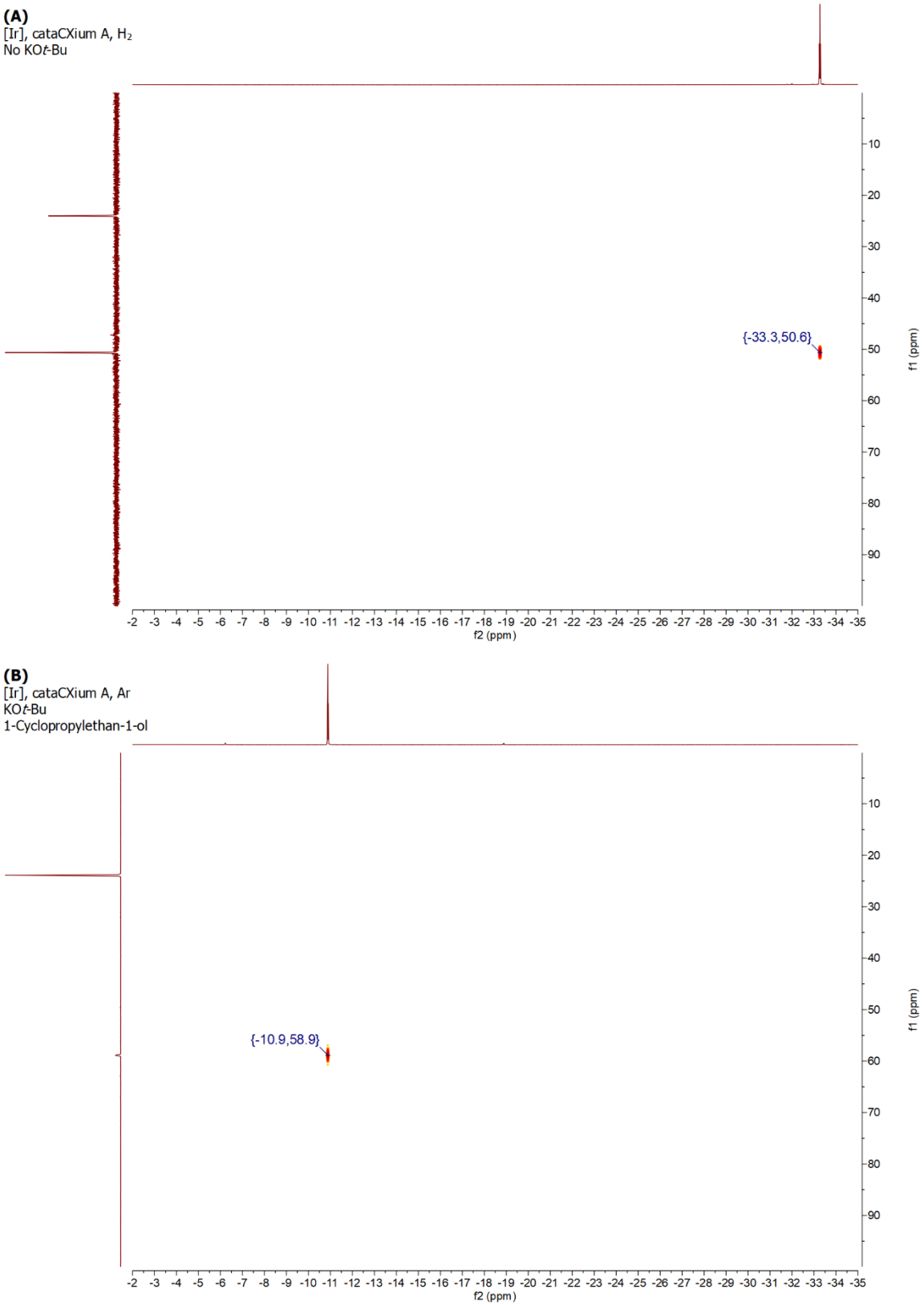
When the atmosphere of H_2 was replaced with Ar and 1-cyclopropylethanol was used as the hydride source in the absence of KO*t*-Bu, no signals were observed in the same region as expected (see Table 4.14, Entry 2, as well as Table 4.15, Entry 8). The addition of KO*t*-Bu to this alcohol system also resulted in the formation of a triplet at –10.8 ppm (J = 11.8 Hz) as the main species. Two other much weaker signals could also be observed, a singlet at δ_H = –6.19 ppm and a triplet at δ_H = –18.85 ppm (J = 16.6 Hz). Interestingly, these signals were very similar to those observed in the H_2 system. This suggests that the base was not only changing the nature of the iridium catalyst under an atmosphere of H_2, but was also responsible for enabling the oxidation of the alcohol to form several iridium hydride species that are very similar to those generated from the H_2 system. Since the

alcohol and H_2 could be considered as equivalent sources of hydride for the hydrogen borrowing and VCP rearrangement, the crosstalk between the catalyst, alcohol and H_2 is probably not a complicating factor in the control studies, and therefore the results therein are likely to be valid.

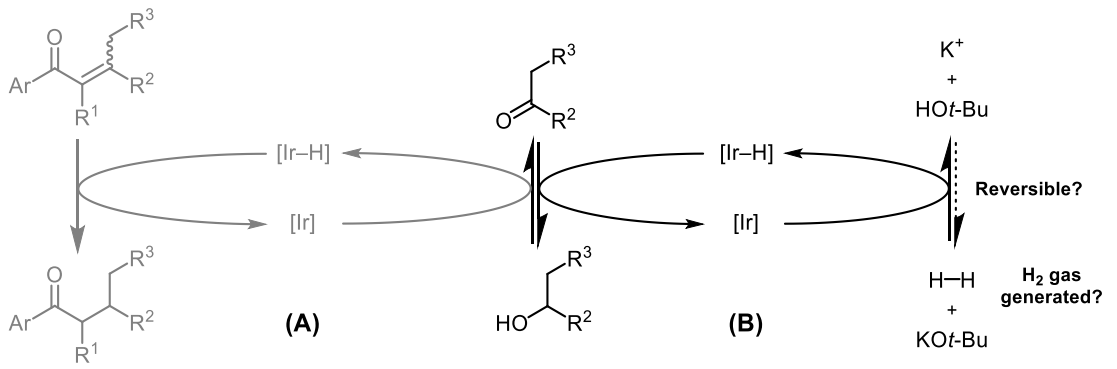
Further analyses of these samples suggest that, in the presence or absence of base, the observed iridium hydride complexes have two phosphorus ligands bound to them, likely in a *cis* or *cis*-like geometry due to the small coupling constants in the ^{1}H NMR. This observation is further confirmed by ^{1}H-^{31}P HMBC experiments that show a correlation between the hydride signal and a distinct ^{31}P signal (Scheme 4.45). However, the greatly reduced intensity of the key phosphorus signal in the presence of base suggest that there is a highly complex interaction between the phosphorus-bound metal hydride complex and the base. It is possible that the base can act as a ligand that would competitively displace the cataCXium A ligand, or form stable complexes with the iridium centre that would reduce the amount of iridium metal available for catalysis.

Attempts at deducing the structure of these complexes proved difficult due to the large number of signals present in the solution. Based on the multiplicity and chemical shift of the signals observed as well as from several structures in literature reports, the signal at –10.9 ppm likely corresponds to [IrH(COD)(cataCXium A)$_2$] or a related compound.[174,175] The participation of the COD ligand in the catalysis cannot be ruled out.

As these NMR experiments were performed at room temperature, it is likely that the signals observed correspond to the resting or more stable states of the complexes, and may not be indicative of the actual catalytic species present in the reaction at 105 °C. Further studies on the isolation, structure and reactivity of the iridium catalyst in hydrogen borrowing/VCP rearrangement reactions were halted here due to time and resource constraints.



Scheme 4.45 *^{1}H-^{31}P HMBC experiments for (A) entry A and (B) entry D in Scheme 4.44. The signal on the ^{31}P NMR at around 24.0 ppm corresponds to free cataCXium A. Note the markedly reduced intensity of the phosphorus signal correlating to the proton signal in (B) as compared to the intensity of the free cataCXium A signal. The NMR experiments were performed at RT, and may not reflect the state of the complexes in the reaction.*



Scheme 4.46 *(A) In the hydrogen borrowing reaction, the iridium hydride species would reduce the enone to form the desired ketone product and turning over the catalyst to oxidise the alcohol. (B) As enones have been often detected, the turning over of the iridium hydride by the (reversible) loss of H_2 is a possible scenario.*

An interesting implication of the convergence of hydride species from different hydride sources NMR studies was that H_2 gas could be generated in this fashion (Scheme 4.46). Enone intermediates have often been observed during the various substrate scope studies of the hydrogen borrowing-mediated α-alkylation, β-alkylation and VCP rearrangement reactions (see Schemes 3.11, 3.21 and 4.37 for examples). The iridium hydride species, which would have been generated from the alcohol substrate or from H_2 present in the reaction atmosphere as previously shown, should be reducing the enone intermediate to furnish the desired ketone product. Since the catalysts had been able to turn over despite not reducing the enones in the presence of super-stoichiometric alcohol or H_2 as reductant, it must imply that either a contaminating oxidant such as oxygen is present, or that the hydride is reducing an electrophilic species, for example a protic solvent and releasing H_2 gas. Studies on this auto-oxidative process is currently being carried out in the Donohoe group.

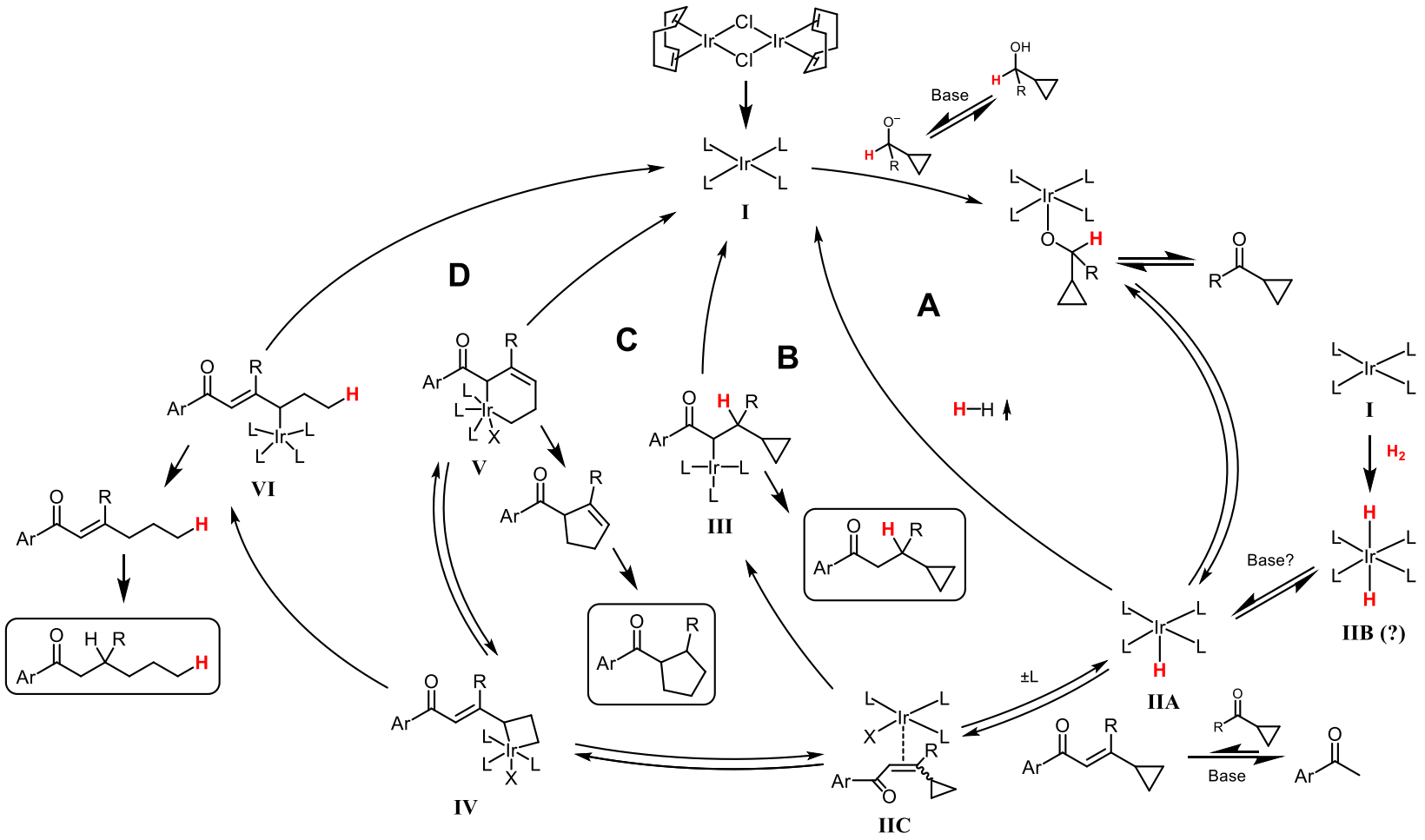
4.6 Mechanistic Proposal

A simple mechanism can now be proposed that is consistent with the reaction outcomes of various substrates observed in the hydrogen borrowing and VCP rearrangement reactions (Scheme 4.47).

The precatalyst $[Ir(COD)Cl]_2$ dissociates under the reaction conditions to form an active catalytic species **I**. Deprotonation of the alcohol to the alkoxide by a base enables a β-hydride elimination to give the ketone/aldehyde and a putative iridium hydride **IIA**. Based on the convergence of iridium hydride signals observed by ^1H NMR (see Scheme 4.44), it is likely that complex **IIA** can be generated under basic conditions with H_2, potentially *via* a putative iridium dihydride species **IIB**.

The fate of iridium hydride **IIA** depends on the electrophile it encounters (Scheme 4.47A). It can reduce the ketone to the alcohol, which accounts for the formation of both diastereomers of *cis*-**228** in the reaction mixture despite using only one diastereomer for the reaction (see Scheme 4.28). It could also potentially lose its hydride by protonation to release H_2 gas (i.e. a dehydrogenation reaction), thereby turning over the catalytic cycle and accounting for the observed build-up of enones in hydrogen borrowing reactions.

The iridium hydride **IIA** could undergo a ligand exchange and coordinate with a vinylcyclopropyl enone molecule to give complex **IIC**. From here, two paths are possible. The first is a migratory insertion/hydroiridation reaction into the enone, with the hydride migrating to the β-position and the iridium on the α-position (Scheme 4.47B). This is supported by the observed stereoselectivity in forming 1,4-*cis*-cyclohexanes such as ketone **169** (see Table 3.12). Ligand exchange/demetallation then affords the hydrogen borrowing alkylation product.



Scheme 4.47 *Proposed mechanism for the iridium catalysed hydrogen borrowing/VCP rearrangement reaction. X = H or L; L = ligand. The structure, generation and cross-interaction of iridium hydride species **IIA** and **IIB** is currently unclear. (A) Regeneration of active catalytic species **I** by protonation and loss of H_2 gas. (B) Migratory insertion followed by demetallation to give the hydrogen borrowing alkylation product. (C) Oxidative addition into cyclopropane bond, followed by allylic shift and subsequent reductive elimination to give the rearranged cyclopentane product (after enone reduction). (D) A premature reductive elimination in the VCP rearrangement sequence results in the ring-opened alkylation product (after enone reduction).*

A second pathway for complex **IIC** is an oxidative addition reaction into the cyclopropane bond to give an iridocyclobutane complex **IV**. The iridium centre could migrate to the α-position to form a less strained six-membered iridocyclohexane complex **V** Reductive elimination then regenerates the active catalyst **I** and affords a skipped enone intermediate that is subsequently isomerised and reduced to give the VCP rearrangement ketone product (Scheme 4.47C). The iridocyclobutane complex **IV** also encounters a second possible route, which is a reductive elimination to give complex **IV** that, upon demetallation and reduction, produces the ring-opened product.

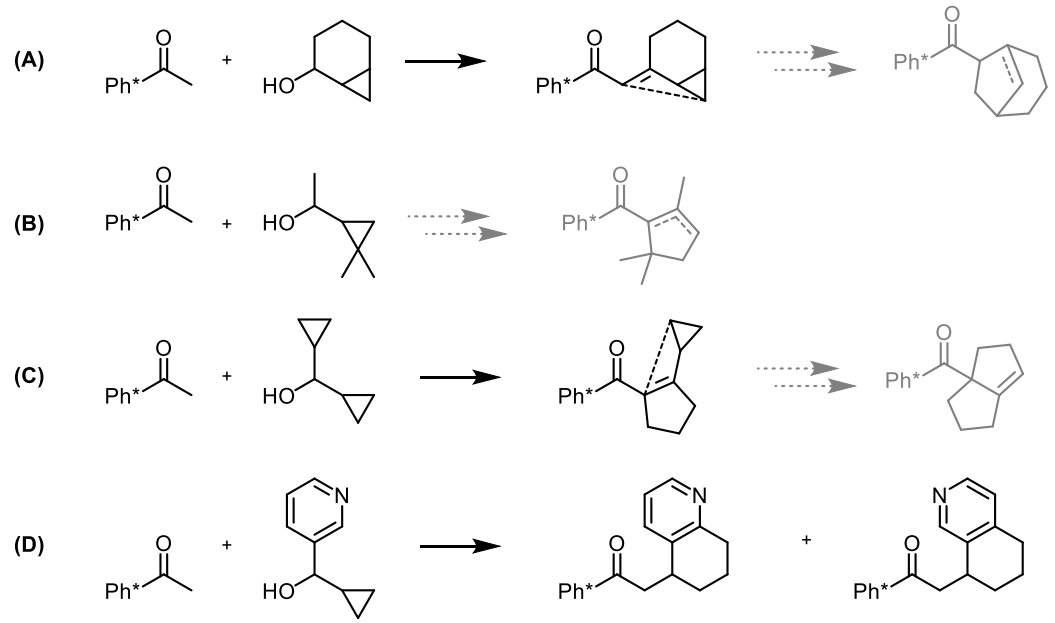
The inability to form ketone **275** could be rationalised as it would form a strained bridgehead alkene, thus iridocyclobutane **IV** proceeds back to complex **IIC** (path B), or undergoes reductive elimination (path D) to give acyclic products only (see Scheme 4.27). In addition, the introduction of *gem*-dimethyl groups on the 2′-position of the cyclopropane could sterically inhibit the oxidative addition process, which would account for the absence of ketone **278** (see Scheme 4.28). The racemisation of alcohol (*S*,*S*)-*trans*-**228** could be attributed to a β-hydride elimination process from complex **IV** or **V** (see Scheme 4.29), followed by a migratory insertion back into the alkene from the opposite face.

The proposed mechanism is not yet able to account for the reactivity of Ir(III) catalysts in hydrogen borrowing reactions and their poor performance for VCP rearrangement due to a lack of data on the structure and reactivity of the catalysts. The mechanism is also not able to explain the reactivity of the catalyst under a hydrogen gas atmosphere in the absence of base, in particular why it only proceeds *via* path B and D to give acyclic alkylated products from enone **198**, but not path C to give any cyclopentane or cyclopentene products. More importantly, this mechanism assumes that the vinylcyclopropyl enone is the key intermediate, but control experiments have yet to conclusively show this to be the case.

4.7 Conclusion

The VCP rearrangement was successfully introduced into the hydrogen borrowing process to give a four-step sequence, serving as a proof of concept for the interception and transformation of the enone into more complex frameworks prior to reduction. It permits the formation of cyclic α,β-branched ketones *via* hydrogen borrowing, an endeavour that has proven to be quite difficult (see Section 3.3.3). There is potential for the Diels–Alder reaction to be incorporated into the hydrogen borrowing sequence, although there may be some issues with the stereochemistry of the product formed.

The reaction was able to tolerate a limited number of heteroaromatic functionalities and install up to four stereocentres in a single reaction. It is possible that more functionalities could be effective for the VCP rearrangement step but are restricted by the harsh conditions from the hydrogen borrowing reaction.



Scheme 4.47 *(A) The simplified model describing the VCP rearrangement could predict the lack of formation of any rearrangement product due to the possible formation of bridgehead alkenes. However, (B) the unsuccessful VCP rearrangement for the gem-dimethylcyclopropyl alcohol and (C) the inability to perform a second VCP rearrangement for the cyclopentene illustrates the current lack of understanding of the mechanistic details. (D) The formation of cyclisation side products from the 3'-pyridyl alcohol substrate suggests the participation from other functionalities that add an additional layer of complexity to the reaction.*

Several cyclopropyl alcohol substrates did not effect the intended transformation or underwent unexpected side reactions (Scheme 4.47). A simplified model was able to predict the inability to form the [3.2.1]-bicyclooctane skeleton due to the possible formation of a strained bridgehead olefin. However, the presence of a second 2′-substituent on the cyclopropane ring resulted in the inhibition of the VCP rearrangement whereas 2′-monosubstituted cyclopropyl alcohols were successful in their transformation. In addition, the second consecutive VCP rearrangement for the reaction with dicyclopropylmethanol also did not occur, a disappointing result which could have led to the formation of a quaternary α-keto centre that could not have been possible with conventional hydrogen borrowing chemistry (see Chapter 6). These results highlight the current lack of knowledge of the intricate details for this reaction. The presence of cyclisation products in the reaction with the 3′-pyridyl alcohol substrate adds an additional level of complexity to this reaction mechanism.

Mechanistically, the VCP rearrangement requires an iridium catalyst, base and a hydride source such as the alcohol used for hydrogen borrowing or H_2 gas. Although the enone intermediate and related side products have been observed in these reactions, the persistent and favourable *retro*-aldol process greatly hinders any investigation into the role of the enone. Attempts with modified substrates reveal that the reaction is sensitive to substitution pattern and substituent effects, but the reaction does not appear to behave like those known in literature (e.g. the Ni(0) catalysed variants). The racemisation of an enantiopure substrate suggest a possible role of the alcohol in the interaction of the cyclopropane with the catalytic species and thereby implicating the β-hydroxyketone intermediate, but the relevance of this interaction and the true identity of the species that participates in the VCP rearrangement has yet to be clarified.

Chapter 5. Synthesis and Transformations of Ph* Ketone and its Derivatives

In this chapter, the following questions will be answered:

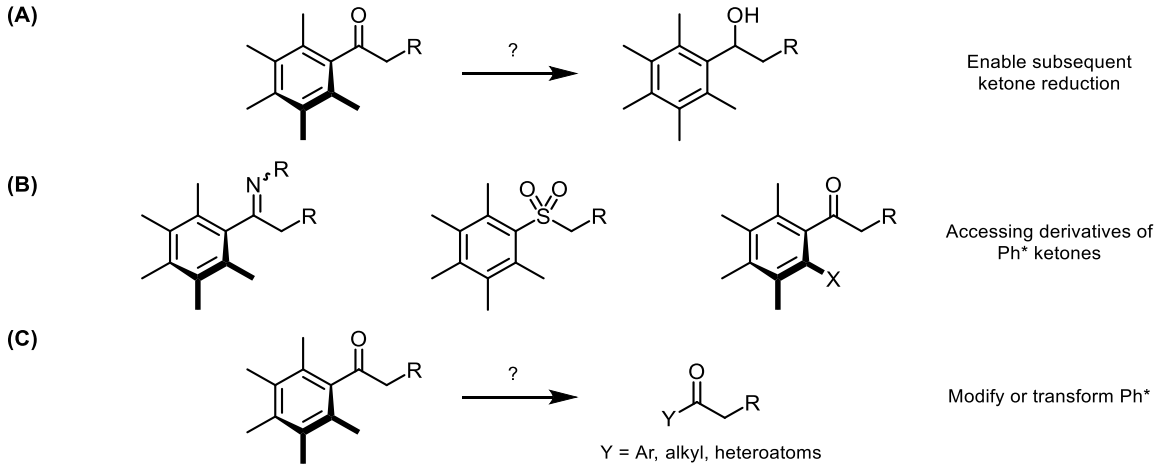
- What synthetic strategies are available to access derivatives of Ph* ketone?
- How can we remove or manipulate the Ph* group and its heteroatom derivatives?
- What is the impact of the *ortho* effect on the reactivity of the aryl ring?

5.1 The Practical Aspects of Ph*

Di-*ortho*-substituted phenyl groups have been shown to be highly effective at enabling the hydrogen borrowing reactions of aryl ketones with primary and secondary alcohols, and also for protection of the ketone group from undesired reduction. Throughout the course of our investigations, it was also observed that many compounds possessing the di-*ortho*-substituted phenyl groups are solids. In particular, compounds with the Ph* group are all crystalline high-melting solids, which would facilitate handling and enable large-scale purification by recrystallisation. These practical aspects make it attractive for use in industrial syntheses.

The use of Ph* presents multiple synthetic challenges (Scheme 5.1). The inhibition of reduction by di-*ortho*-substituted groups in general could cripple a subsequent transformation of that ketone into an alcohol or other functionalities. The reactivity of heteroatom derivatives of Ph* ketones with respect to hydrogen borrowing and their manifestation of the *ortho* effect are also unclear. It would first be necessary to access these derivatives prior to investigating their reactivity. Finally, the Ph* group possesses some intrinsic issues. It has limited additional utility as the numerous methyl groups could be redundant and difficult to remove or functionalise. As an enabling group for the hydrogen

borrowing methodology its mass efficiency and atom economy leaves much to be desired, having five more carbon atoms and 91% greater mass than a simple phenyl group. It would be ideal for Ph* to become a modular unit that can be easily removed to enable a parallel and diversifiable synthesis, thus making it more attractive to industries.

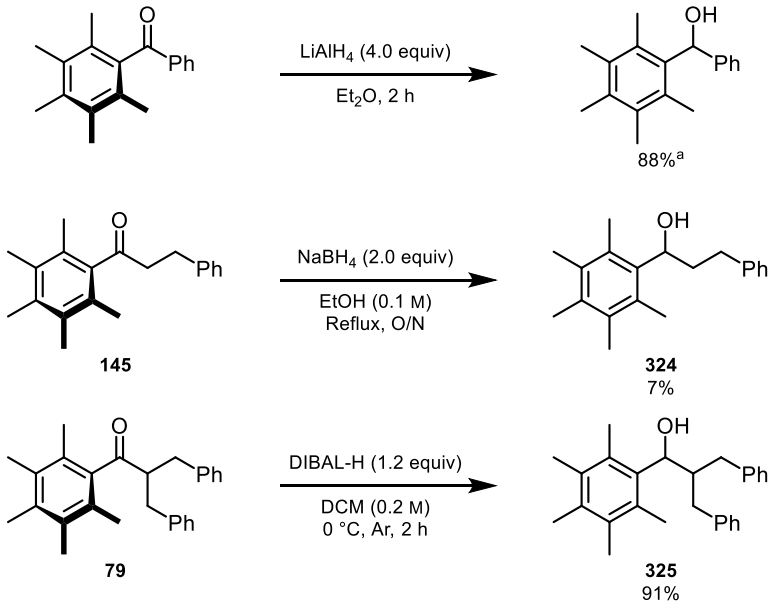


Scheme 5.1 *Challenges posed by the use of the Ph* group. (A) The ability to reduce the ketone adjacent to a Ph* group. (B) Access to heteroatom derivatives of Ph* ketones. (C) The modification and transformation of Ph*, possibly as a modular unit.*

5.2 Accessing Derivatives of Ph* Ketones

5.2.1 Reduction of Ph* Ketone

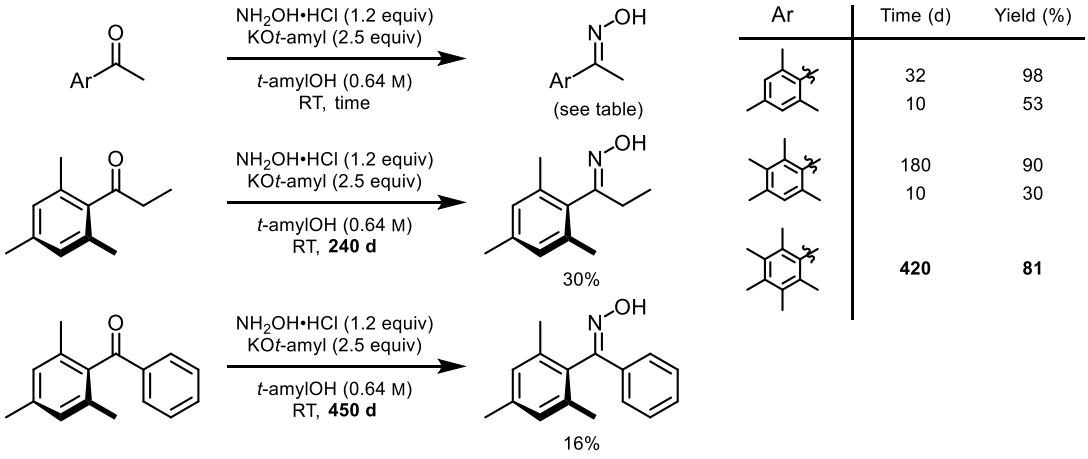
The first step was to find a set of conditions that would successfully reduce the ketone group adjacent to a Ph* moiety. Although Smith and Thompson have reported such a reduction with the powerful reducing agent $LiAlH_4$,[176] it would be ideal to find a milder set of conditions to achieve this reaction (Scheme 5.2). Conventional reduction methods such as $NaBH_4$ led to minimal conversion of ketone **145** to alcohol **324** even under refluxing conditions. Pleasingly, the use of DIBAL-H could smoothly reduce ketone **79** to benzylic alcohol **325** in excellent yield. These results were very similar to those observed by Williams for the 9-anthracenyl ketones (see Section 1.3).[15]



Scheme 5.2 *Reduction of Ph* ketones to the corresponding benzylic alcohols with various reducing agents.* [a]*Literature conditions by Smith and Thompson.*[176]

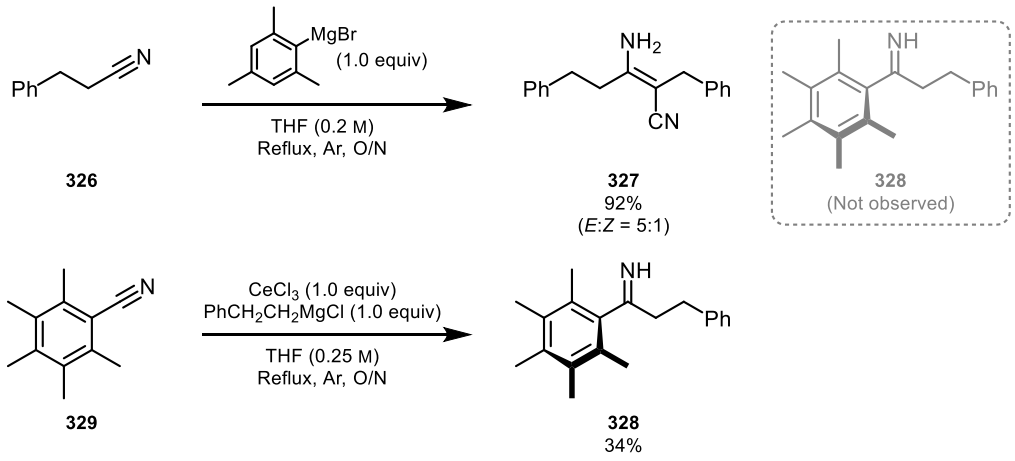
5.2.2 Synthesis of a Ph* Imine

Pearson and Keaton as well as Zaitsev et al. noted that the oxime formation from mesityl and Ph* methyl ketones and hydroxylamine was *extremely* sluggish, requiring *months* to give a good yield (Scheme 5.3).[177,178] The reaction time grew with increasing number of methyl substituents on the aryl ring, as well as with increasing size of the other ketone group,[21] clearly showing the reduced reactivity of *ortho*-substituted ketones towards nucleophiles.



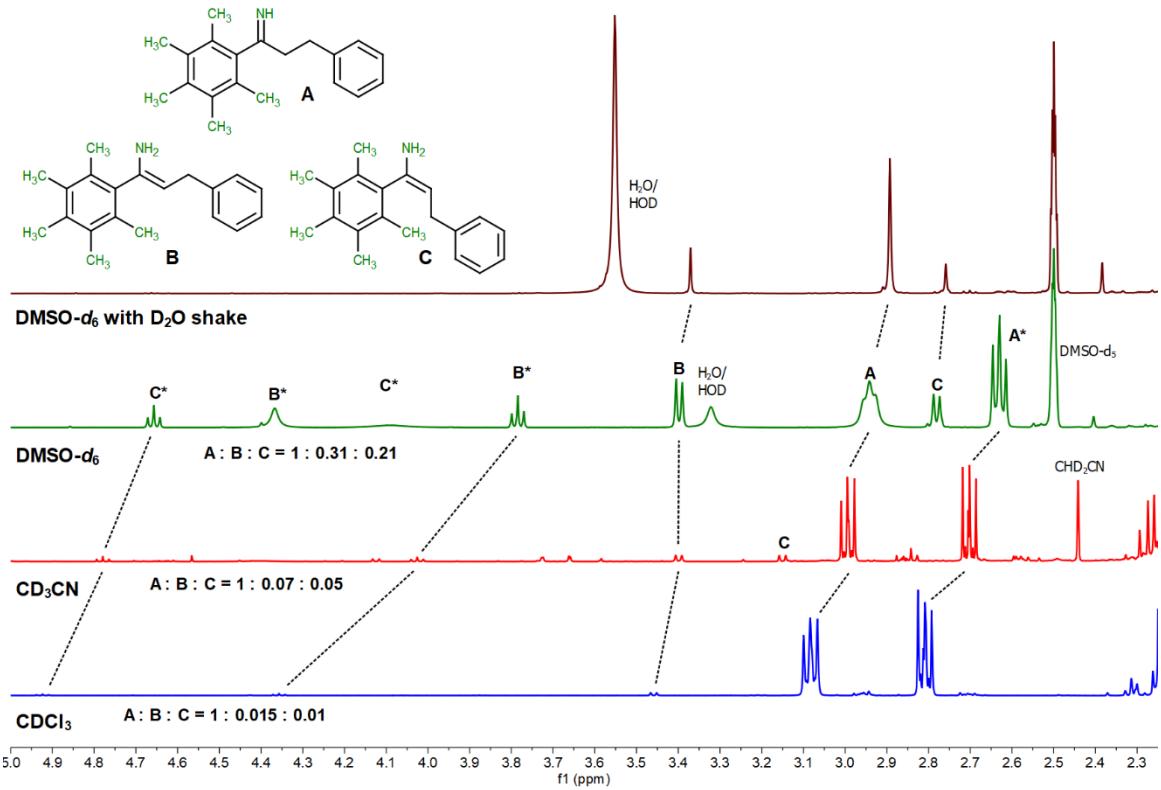
Scheme 5.3 *The reported condensations of hydroxylamine with di-ortho-methyl substituted phenyl ketones was extremely slow.*[177,178]

An attempted reaction between nitrile **326** and 2-mesitylmagnesium bromide led to the homodimerisation of the nitrile instead, suggesting that the Grignard reagent was a poor nucleophile (Scheme 5.4). By having the nitrile on the aryl ring (**329**) and increasing the nucleophilicity of the organometallic species through formation of an organocerium reagent,[179,180] the issue of homodimerisation was alleviated and imine **328** was formed in acceptable yield.



Scheme 5.4 *Formation of imine* ***328*** *by nucleophilic addition into nitriles.*

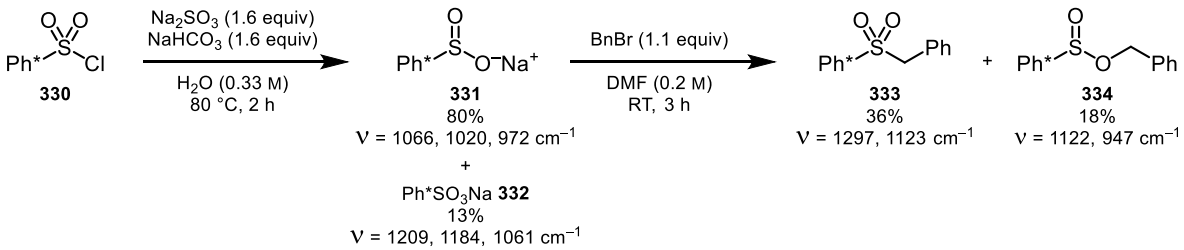
The ^{1}H NMR spectra of imine **328** was particularly interesting (Scheme 5.5). In a $CDCl_3$ solution the imine is the main species observed with virtually no enamine tautomer present, whereas in CD_3CN and DMSO-d_6 more significant amounts of tautomerisation is observed, albeit in differing levels. This agrees with observations by Clark et al. and Kostochka et al. that polar solvents such as DMSO-d_6 promote enamine formation.[181,182] It is worth noting that the dynamic equilibration between imine and enamine is extremely rapid in DMSO. A D_2O shake followed by ^{1}H NMR acquisition within 5 min resulted in complete deuteration of the *N*- and *C*-protons accompanied by loss of coupling information from the benzylic protons.



Scheme 5.5 *^{1}H NMR of imine **328** in various deuterated solvents. Blue: $CDCl_3$. Red: CD_3CN. Green: DMSO-d_6. Maroon: DMSO-d_6 with D_2O shake. Exchangeable signals are labelled with an asterisks (*). The same batch of imine **328** was used to prepare all the solutions for NMR spectroscopy.*

5.2.3 Synthesis of a Ph* Sulfone

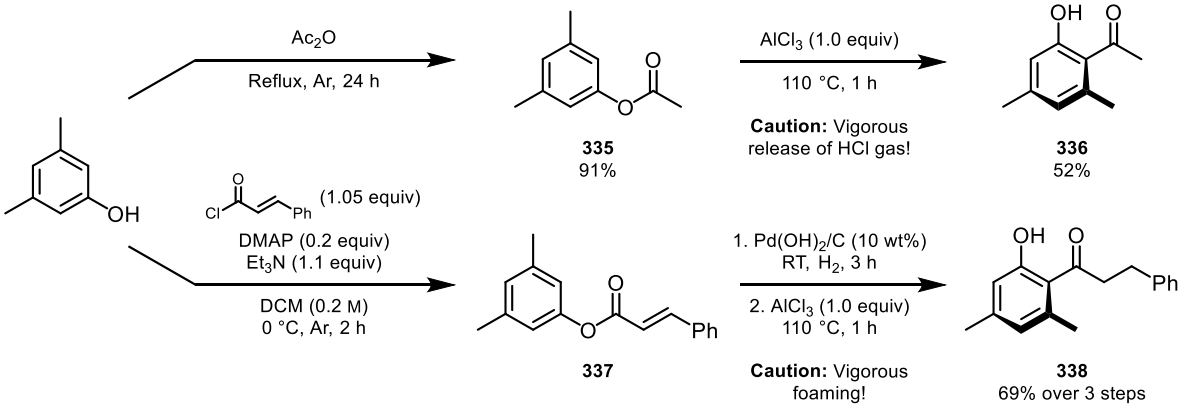
The synthesis of Ph* sulfones proceeded from the commercially available sulfonyl chloride **330**, which was reduced with Na_2SO_3 to give sulfinate **331** (Scheme 5.6).[183] Nucleophilic substitution with benzyl bromide gave the *S*-alkylated product **333** together with a small amount of *O*-alkylated product **334**, suggesting that the tetrahedral sulfinate centre is not as well-protected by the *ortho*-methyl groups compared to the trigonal planar ketone.



Scheme 5.6 *Synthesis of a Ph* aryl sulfone **333** from the corresponding sulfonyl chloride.[183] The IR stretching frequencies were highly diagnostic for the formation of the desired products.*

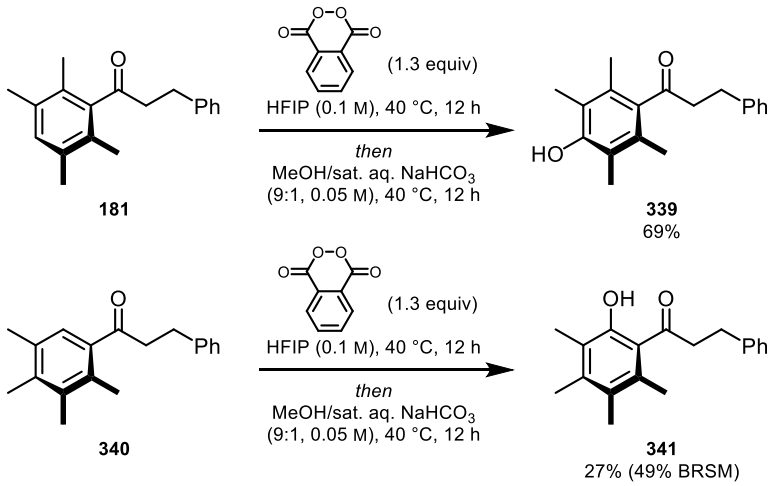
5.2.4 Synthesis of Di-*ortho*-Substituted Phenols and Anilines

The next challenge was to substitute key methyl groups on the di-*ortho*-substituted aryl substrates with other functionalities such as hydroxy, nitro and amine groups.



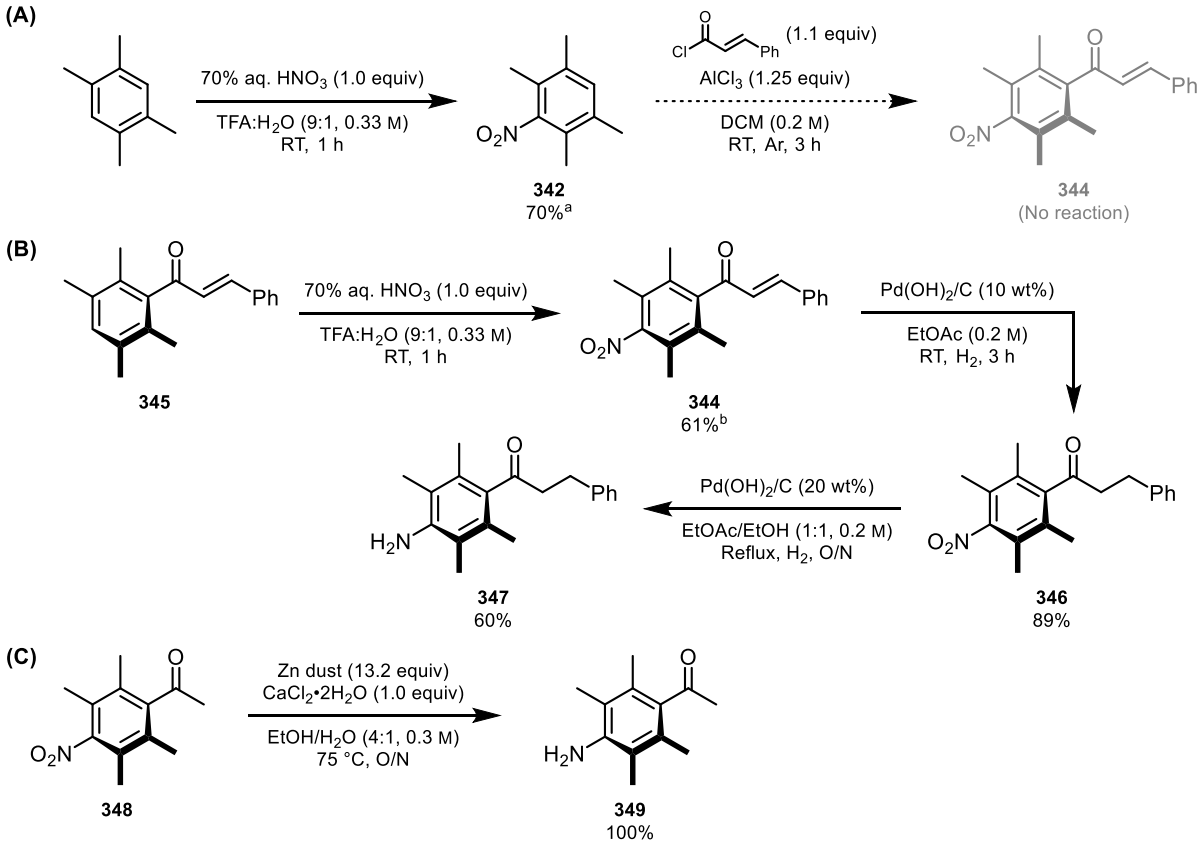
Scheme 5.7 *Synthesis of ortho-hydroxy analogues* ***336*** *and* ***338*** *via the Fries rearrangement.*[184]

Initial attempts to access the *ortho*-phenol analogues **336** and **338** from the commercially available 3,5-dimethylphenol *via* the Fries rearrangement revealed that the reaction was exceedingly vigorous, unpleasant to perform and difficult to work up (Scheme 5.7).[184] Although the mesityl analogue was prepared through this route in good yield, the non-commercial availability of tetramethylphenols and the hazardous nature of this reaction deterred any further attempts with this route.



Scheme 5.8 *Synthesis of phenol analogues* ***339*** *and* ***341*** *by direct aryl oxidation.*[185]

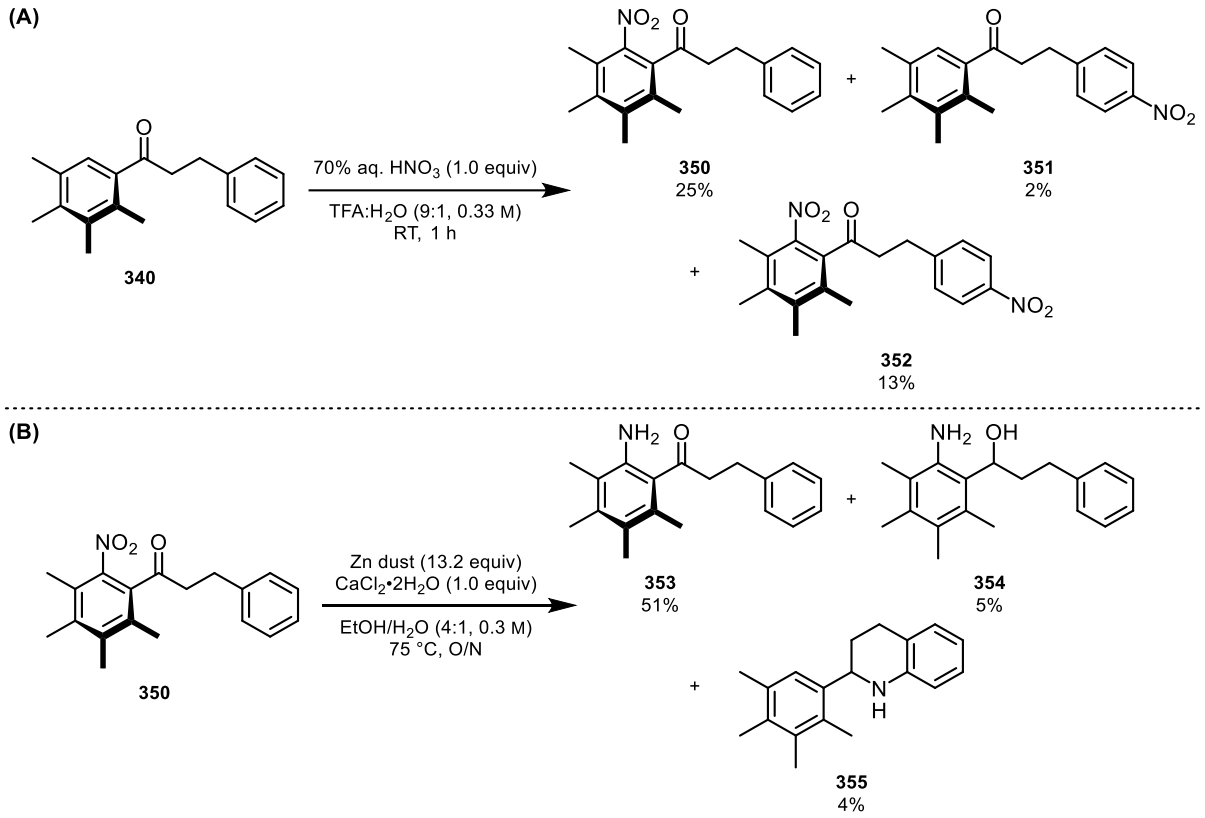
Fortunately, a mild protocol reported by Yuan et al. was able to directly oxidise arenes to phenols.[185] Gratifyingly, the tetramethylarenes were selectively oxidised over the phenyl ring on the alkyl pendant to give the desired phenols **339** and **341** in reasonably good yields (Scheme 5.8).



Scheme 5.9 *(A) Attempted synthesis of para-nitro analogue **344** via Friedel–Crafts acylation, and (B) successful synthesis through arene nitration and subsequent reduction. (C) Reduction of the sterically hindered nitro group could be achieved quantitatively by reduction with zinc dust. [a]The corresponding 1,4-dinitrodurene **343** was also isolated in 2% yield; [b]The corresponding methyl or phenethyl duryl ketones could also be nitrated under identical conditions to give nitroarenes **348** and **346** in 72% and 57% yields respectively.*

It was envisioned that the di-*ortho*-substituted anilines could be accessed through reduction of the corresponding nitroarenes. A Friedel–Crafts reaction of nitrodurene **342** was unsuccessful, suggesting that the aryl ring was too electron deficient for electrophilic substitution. Nitration of durene enone **345** was able to afford the desired nitroenone **344**

in reasonable yield,[186*] but reduction of both the enone and nitro groups *via* catalytic hydrogenation required forcing conditions. The steric bulk from the flanking methyl groups appeared to be retarding any reduction process. Gratifyingly, reduction of the sterically crowded nitro group could also be achieved using zinc dust under mild acidic conditions.[187]



Scheme 5.10 *Poor chemoselectivities were observed during (A) electrophilic nitration to form ortho-nitro analogue* ***350****, and during (B) reduction of the nitro group to form the ortho-aniline analogue* ***353****.*

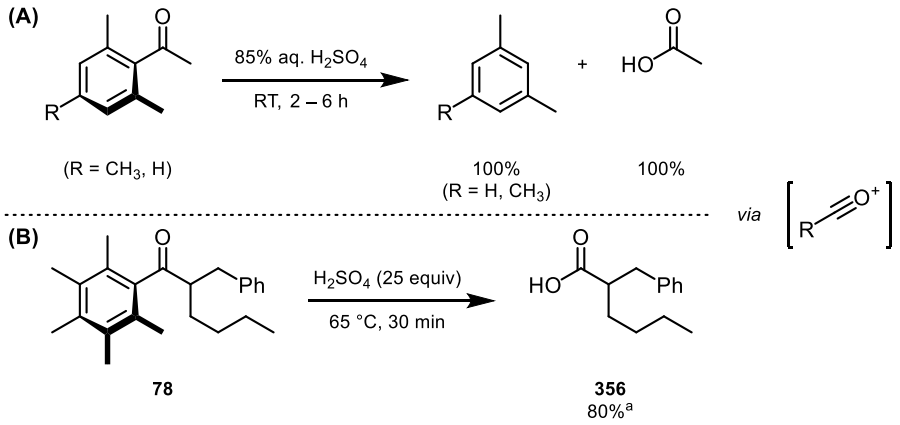
The situation for installing an amine at the *ortho* position was different. Nitration of prehnitene ketone gave several differently nitrated products, leading to a poor overall yield of **350** (Scheme 5.10). The reduction with zinc dust was also not very selective, giving small amounts of benzylic alcohol **354** as well as an unusual tetrahydroquinoline side product **355**.

[*] The corresponding methyl or phenethyl duryl ketones could also be nitrated under identical conditions to give nitroarenes **348** and **346** in 72% and 57% yields respectively.

5.3 The Manipulation of the Ph* Group

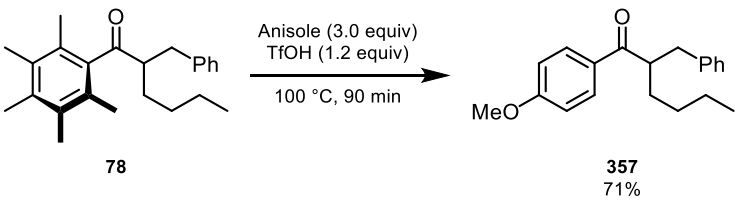
5.3.1 Acid-mediated Cleavage of Ph*

The ability to remove or transform the Ph* motif is a key objective in improving the synthetic utility of the Ph* group. A literature search revealed that Schubert and Latourette had described the cleavage of 2,6-dimethylacetophenone and acetylmesitylene with H_2SO_4 to give the corresponding arene and acetic acid (Scheme 5.11).[188] They also noted that the mesitylene derivative cleaved 66 times faster than the *meta*-xylene derivative. Work by Dr. James Frost showed that these conditions were able to remove the Ph* group from ketone **78** and furnish acid **356** in 80% yield. The mechanism was suggested to proceed *via* an acylium ion which was subsequently trapped by water to give an acid.



Scheme 5.11 *(A) Quantitative cleavage of di-ortho-methylacetophenones as reported by Schubert and Latourette.[188] (B) Acid-mediated removal of Ph* motif from hydrogen borrowing product **78** to form acid **356**. [a]Work by Dr. James Frost.*

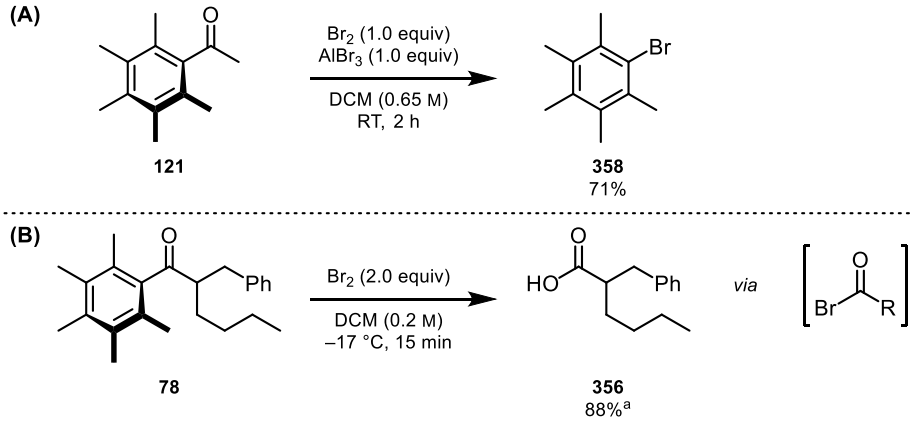
El-Khawaga et al. had also reported that acetylmesitylene was able to react with anisole in the presence of TfOH to give 4-acetylanisole.[189] Work by Dr. James Frost showed that these conditions could indeed provide the corresponding *para*-anisyl ketone **357** in good yield (Scheme 5.12). This transacylation reaction would therefore provide an indirect access to a large range of α-branched aryl ketones.



Scheme 5.12 *Trans-acylation reaction of **78** under acidic conditions to replace the Ph* motif with a para-anisyl group as reported by Dr. James Frost.*

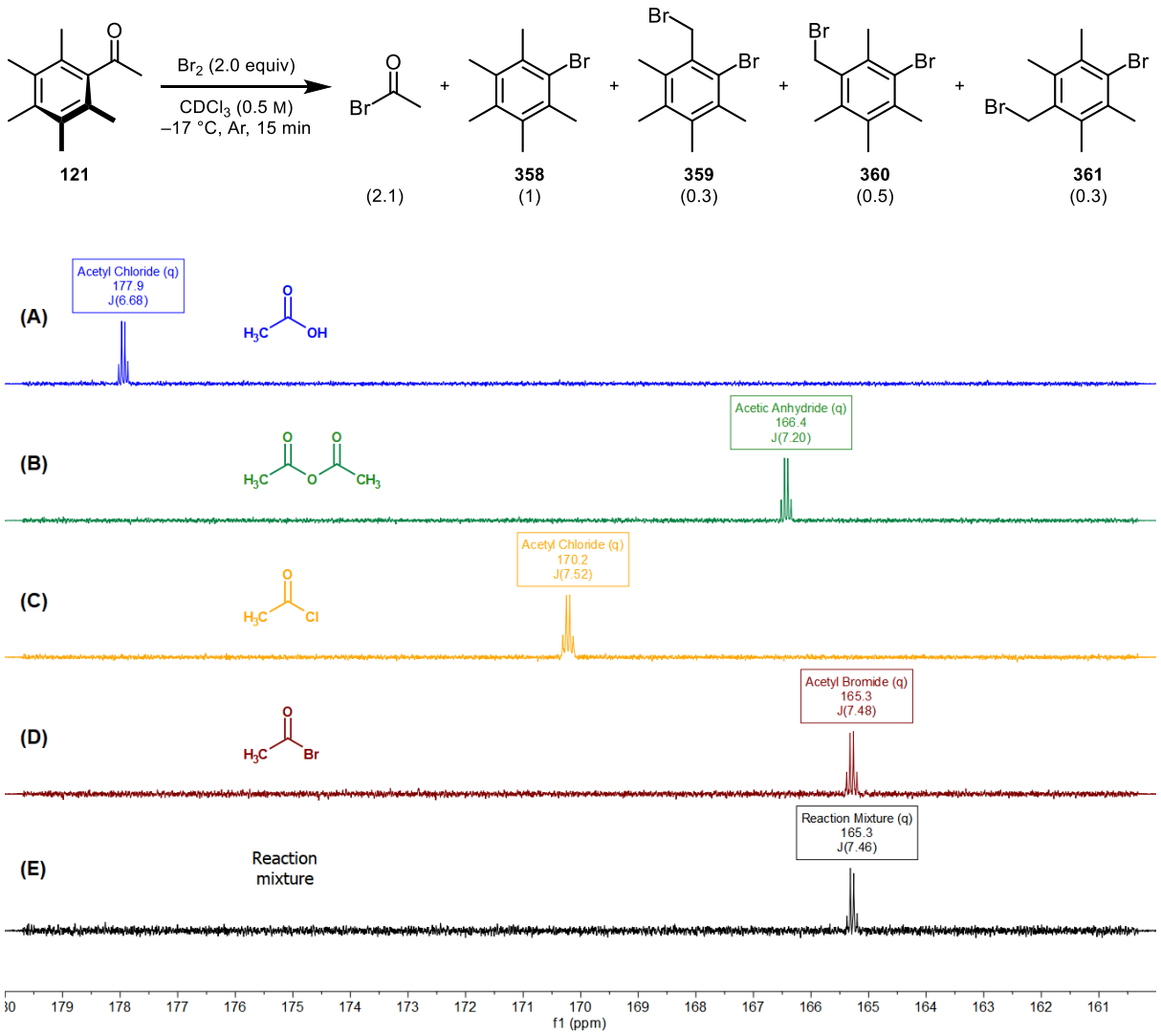
5.3.2 Br_2-Mediated Cleavage of Ph*

Despite the good yields of the acid-mediated cleavage and transacylation reaction, the harsh conditions needed for these reactions are rather undesirable and are incompatible with acid-sensitive functionalities. Fortunately, Matsuura et al. had also reported that ketone **121** could react with Br_2 and $AlBr_3$ to give bromoarene **358** (Scheme 5.13).[190] Further optimisation by Dimitri Caputo revealed that Br_2 alone was able to effect this cleavage to give acid **356** in good yield after aqueous workup.



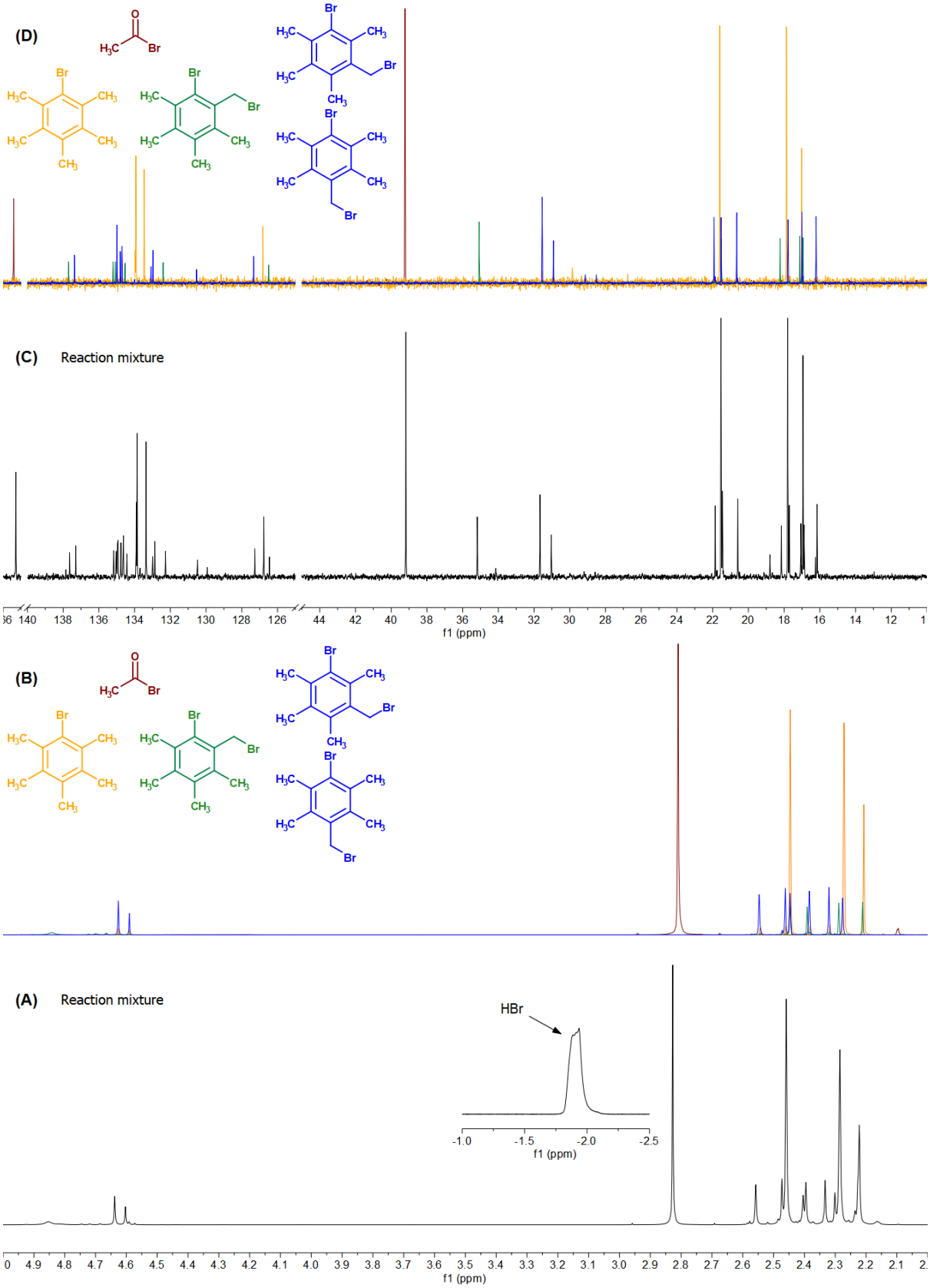
Scheme 5.13 *(A) Friedel–Crafts deacylation/bromination as reported by Matsuura et al.[190] (B) Br_2-mediated removal of Ph* group from ketone **78** to form acid **356**. [a]Work by Dimitri Caputo.*

The presence of an acyl bromide intermediate was confirmed by a quartet ($^2J_{CH}$ = 7.5 Hz) at 165.3 ppm in the ^{13}C NMR spectrum (without ^1H decoupling) that matched a commercial sample of AcBr against other carboxylic acid derivatives (Scheme 5.14).



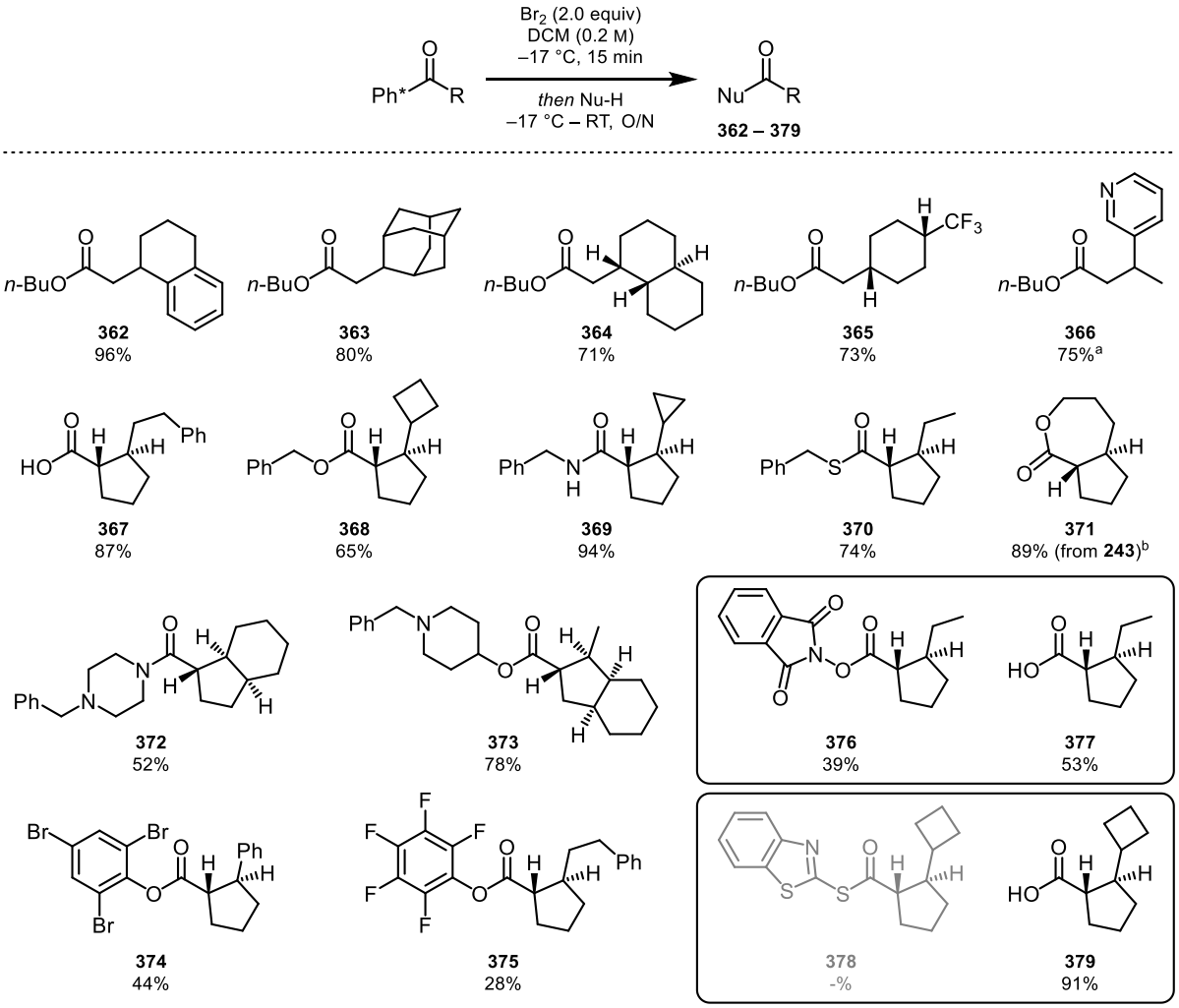
Scheme 5.14 *Friedel–Crafts deacylation/bromination as developed by Dmitri Caputo. Numbers in parentheses represent approximate ^{1}H NMR ratios after spectral deconvolution (see Scheme 5.15A). Non-^{1}H-decoupled ^{13}C NMR of (A) AcOH, (B) Ac_2O, (C) AcCl, (D) AcBr, and (E) the reaction mixture from the reaction described above.*

The Br_2-mediated cleavage reaction was extremely clean. The other byproducts of the reaction were mono- and dibromopentamethylbenzene, as well as HBr. The spectrum of the reaction mixture could be reconstructed from the individual components (Scheme 5.15).



Scheme 5.15 *(A and B) ^{1}H NMR and (C and D) ^{13}C NMR of a Friedel–Crafts deacylation/bromination reaction that was developed by Dmitri Caputo (see Scheme 5.13). (A) and (C) are spectra of the actual reaction mixture, while (B) and (D) are reconstructions from the individual components.*

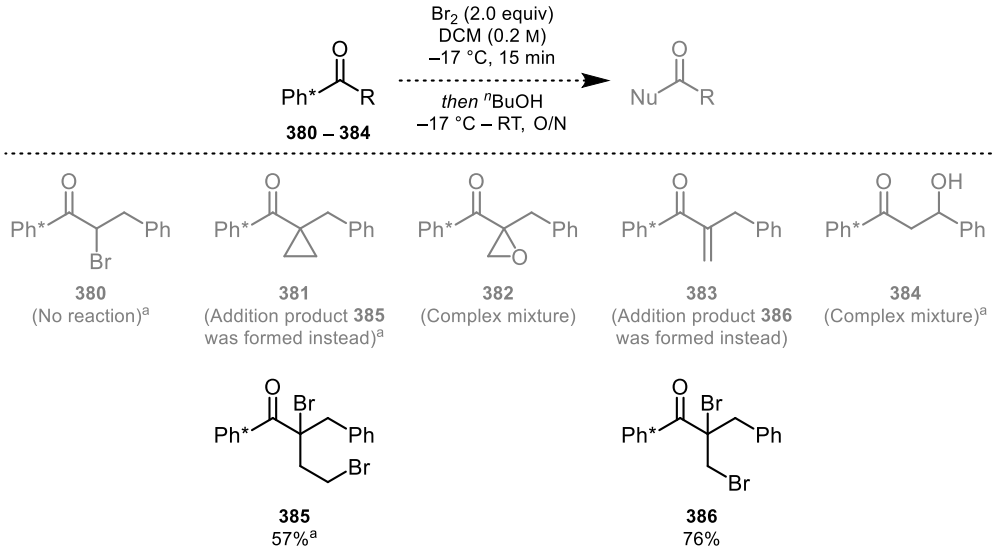
A wide variety of products obtained by the hydrogen borrowing methodology were then subjected to bromine-mediated cleavage (Scheme 5.16). Initial attempts with *n*-butanol as a nucleophile gave very good yields of the butyl esters. The reaction was even able to tolerate a pyridine motif present in the substrate to give ester **366**, and pleasingly no undesired bromination was observed for ester **362**.



Scheme 5.16 *Substrate scope for the removal and transformation of Ph* group into carbonyl derivatives.* [a]*4.0 equiv of Br_2 was used instead;* [b]*The reaction was quenched after 2 h without added nucleophile.*

Other nucleophiles were also attempted to furnish various carbonyl derivatives, including water, alcohols, amines, hydroxylamines and thiols. Although the benzyloxy group on ketone **243** was deprotected under these conditions, the exposed hydroxy group served to trap the acid bromide to form lactone **371**. The poor solubility of *N*-hydroxyphthalide was the likely cause of the poor yield of ester **376**, and a significant amount of acid **377** was also obtained. Weaker nucleophiles such as phenols gave significantly poorer yields, with acid **379** being formed instead of benzothiazole **378**.

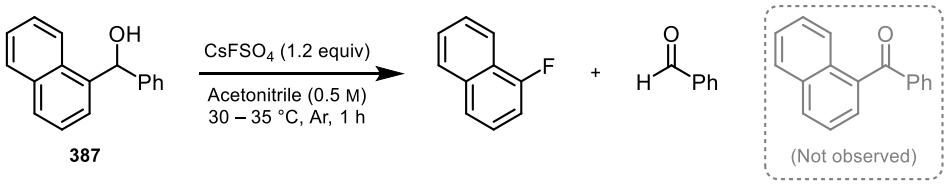
While it would be expected that these conditions would not be tolerated by alkenes, alkynes or electron rich arenes that would be readily brominated, it would be good to further probe the tolerance of other functional groups in the reaction. Disappointingly, substrates bearing α-bromo (**380**), cyclopropyl (**381**), epoxide (**382**) and vinyl (**383**) functionalities failed to undergo cleavage of the Ph* group (Scheme 5.17). The isolation of dibrominated products **385** and **386** suggest that bromine had added across the cyclopropane and the electron-deficient enone. The benzylic alcohol **384** also did not survive the reaction conditions, with a complex mixture being formed.



Scheme 5.17 *Unsuccessful attempts at Br_2-mediated deacylation. [a]Work by Dr. James Frost.*

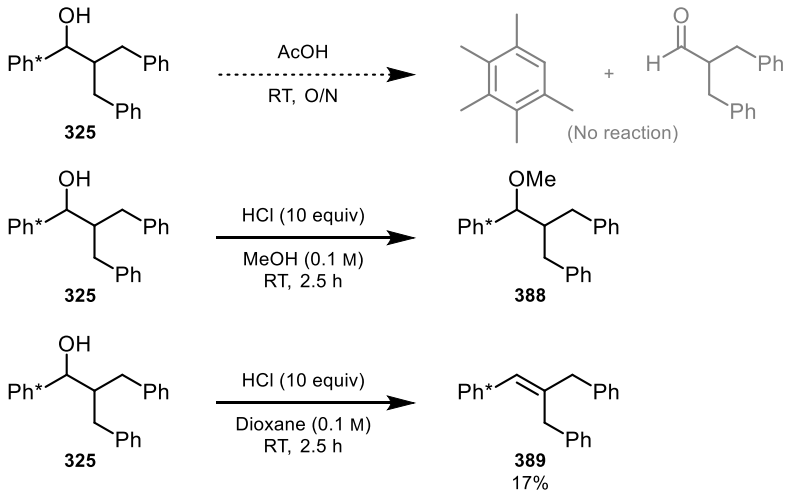
5.3.3 Attempted Electrophilic Cleavage of Ph* Alcohol

The next attempt at electrophilic cleavage of the Ph* motif was inspired by a report by Stavber et al. that described the deacylation of benzylic alcohol **387** with an electrophilic fluorine source, cesium fluoroxysulfate ($CsFSO_4$), to give benzaldehyde and 1-fluoronaphthalene instead of performing an oxidation (Scheme 5.18).[191] The oxygen on the alcohol would be more nucleophilic than the oxygen of the carbonyl group, so having a benzylic alcohol could accelerate the slow cleavage step. However, bromine was deemed unsuitable as it could oxidise the aldehyde formed.



Scheme 5.18 *Dearylation of **387** to form 1-fluoronaphthalene and benzaldehyde.*[191]

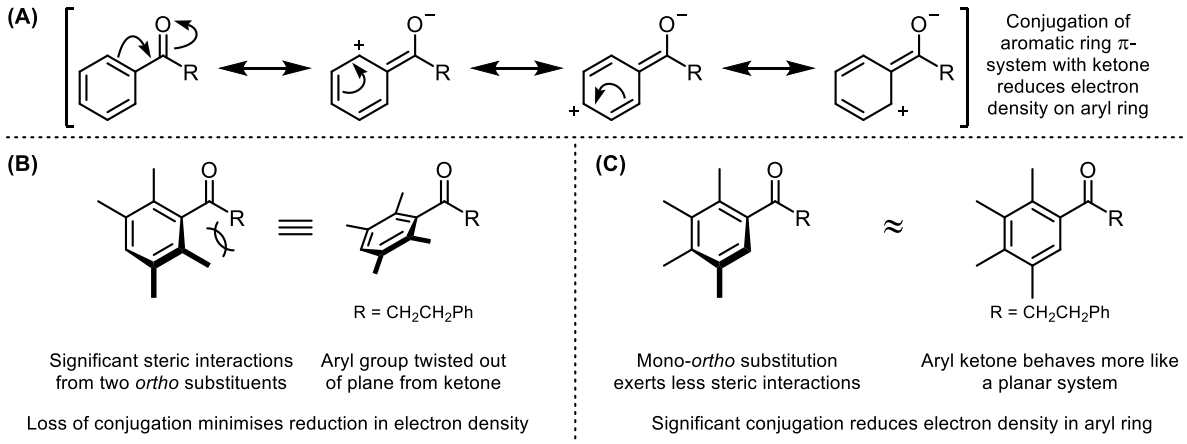
Having previously accessed benzylic alcohol **325** by reduction of the ketone with DIBAL-H, a series of conditions were screened to effect an acid-mediated cleavage (Scheme 5.19). Unfortunately, the alcohol was inert to weak acids such as AcOH, whereas use of HCl in aprotic or protic media resulted in dehydration (**389**) or solvent exchange (**388**).



Scheme 5.19 *Attempted cleavage of benzylic alcohol **325** under mild acidic conditions.*

5.3.4 The Impact of the *ortho* Effect on the Reactivity of the Aryl Ring

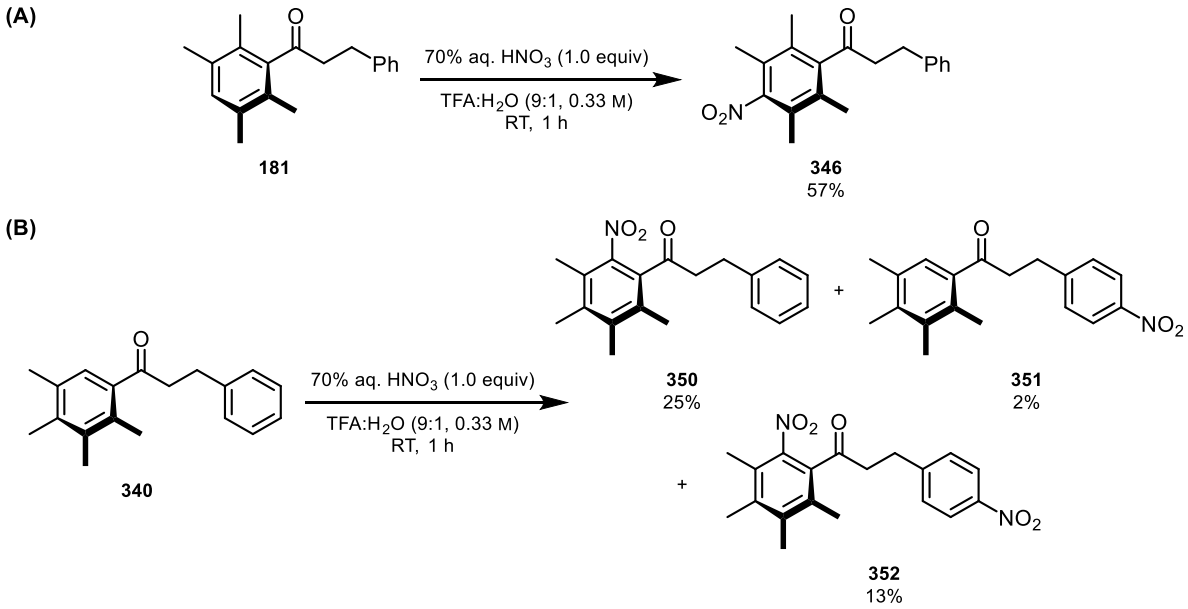
In Section 1.5 it was shown *ortho* substituents causes the aryl ring to be twisted away from the plane of the ketone, resulting in a significantly altered reactivity of the ketone group due to steric inhibition of resonance. This steric effect also has an impact on the electronics of the aryl ring, as the reduced degree or loss of conjugation between the carbonyl group and the aromatic ring will also cause the aryl ring to be less electron deficient than expected (Scheme 5.20, see also Section 1.2).* The inhibited electronic modulation of the aryl ring is most clearly exemplified by the successful cleavage of the Ph* group with bromine. The ability to perform electrophilic bromination/deacylation reactions without the need of a Lewis acid to activate the halogen suggests that the Ph* group has a significantly large electron density.



Scheme 5.20 *(A) Conjugation of the aromatic ring with an adjacent carbonyl group results in a decrease in electron density on the aryl ring. (B) When the carbonyl group is flanked by two ortho substituents, the torsional strain twists the carbonyl group out of plane from the ketone and thus the aryl ring does not experience significant reduction of electron density. (C) When only one ortho substituent is present, the aryl-carbonyl system behaves more like a planar conjugated system and thus the aryl ring has decreased electron density.*

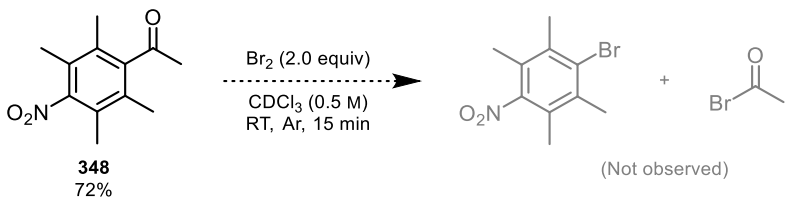
* It is worth pointing out that although the *ortho* effect typically refers to the impact of steric-dependent torsional strain on the reactivity of the adjacent functional group (that is flanked by the *ortho* substituents), it also directly results in the accompanying change in electronics of the aryl ring. Therefore, these changes in electronics should also be considered a manifestation of the *ortho* effect.

The extent of electronic modulation of the aryl ring depends on the degree of steric interactions exerted by the *ortho* substituents. This can be observed by the electrophilic nitration of duryl ketone **181** and phrenitene ketone **340** (Scheme 5.21, see also Schemes 5.9 and 5.10 and footnote in text). The high yield and selectivity of the nitration on the duryl ring of ketone **181** suggests that the duryl ring is more electron-rich than the pendant phenyl ring. This is most likely due to a combination of the electron-donating effects of four methyl groups outweighing the reduced mesomeric electron-withdrawing effect of the ketone group that is no longer conjugated with the aryl ring. On the other hand, the phrenitene ketone **340**, which only has one *ortho*-methyl substituent exerting torsional steric interactions, displayed a significantly reduced manifestation of the *ortho* effect (see Scheme 3.11). Consequentially, the phrenitene ring is likely considerably less electron-rich despite having four methyl substituents, and thus the nitration is not selective for the phrenitene ring and occurs on the pendant phenyl group as well. Investigations into the amount of torsional angle present in the variously-substituted aryl ketones will be discussed in Chapter 7.



Scheme 5.21 *(A) Nitration of duryl ketone was considerably more successful than (B) the corresponding phrenityl ketone.*

The diminished electron-withdrawing character of substituents influenced by the *ortho* effect did not appear to lend itself to the Br_2-mediated cleavage of the *para*-nitro ketone (Scheme 5.22). One possibility is that the nitro group is too small to offer significant steric interactions with the flanking methyl groups. Another possibility is that the nitro group is still able to exert an inductive electron-withdrawing effect that is sufficient to disfavour subsequent Friedel–Crafts reactions with electrophiles. Exner and Krygowski suggested that electron-withdrawing property of the nitro group has minimal contribution from mesomeric effects.[192] Further investigations into the relative manifestation of the *ortho* effect in nitrobenzenes are discussed in Section 7.2.4.

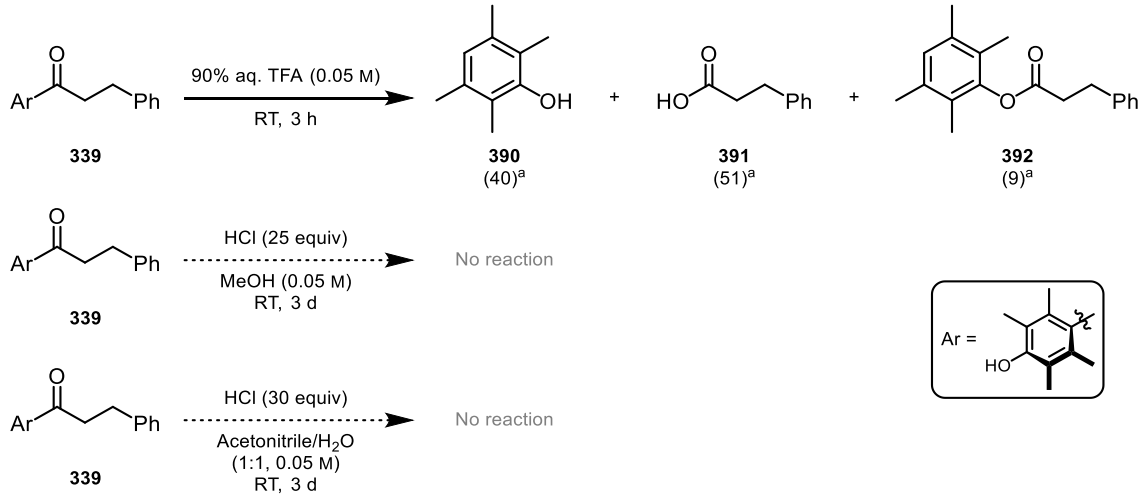


Scheme 5.22 *The para-nitro ketone* ***348*** *did not undergo Br_2-mediated deacylation.*

5.4 The Oxidative Cleavage of Phenol Derivatives of Ph*

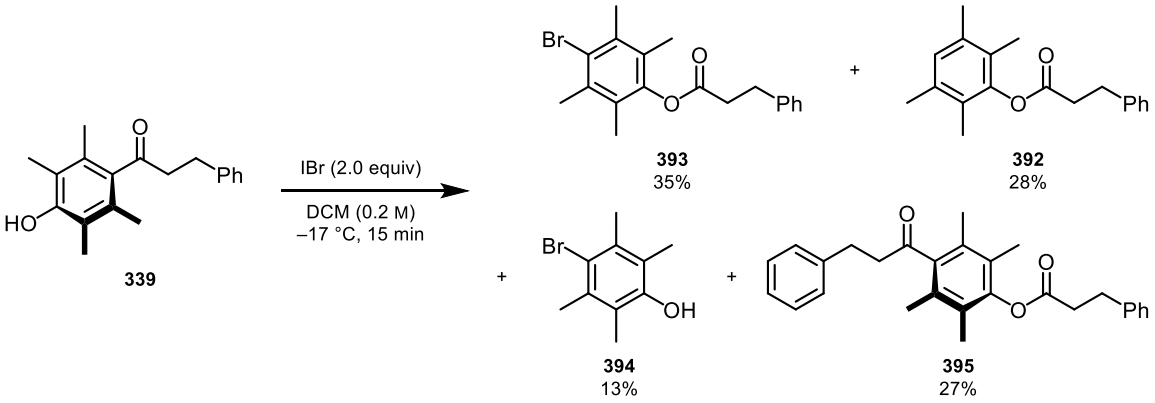
5.4.1 Electrophilic Cleavage of Phenol Derivatives of Ph*

The next strategy for cleavage of the Ph* group was to employ electron-donating substituents to facilitate aryl cleavage. The plan was to increase the electrophilicity of the ring through the installation of a *para*-hydroxy group, which would promote the formation of the Wheland intermediate and the subsequent deacylation reaction. Accordingly, phenol **339** was subjected to a screen of acidic media (Scheme 5.23). Disappointingly, solutions of HCl failed to give any reaction, and only a 90% aq. TFA solution was able to effect the acyl cleavage. While it is a significant step down from the powerful acid H_2SO_4, the use of TFA as solvent can hardly be considered as a mild set of conditions.



Scheme 5.23 *Attempted cleavage of phenol* ***339*** *under various acidic conditions.* [a]*Ratios of products as observed by* [1]*H NMR.*

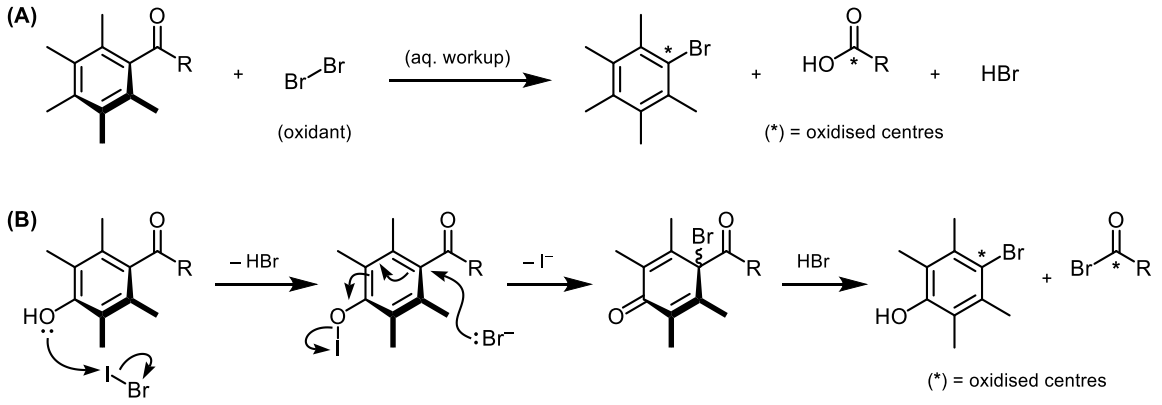
The halogen-mediated acyl cleavage methodology turned out to be unsuitable for use with the phenol derivatives of Ph* ketones (Scheme 5.24). This is because the formation of the acid bromide results in the formation of the phenoxy esters **393** and **395** along with some phenol **394**. Some dehalogenated ester **392** was also observed, although unusually no iodinated compounds were observed.



Scheme 5.24 *Cleavage of phenol derivative* ***339*** *with IBr results in the formation of a mixture of products.*

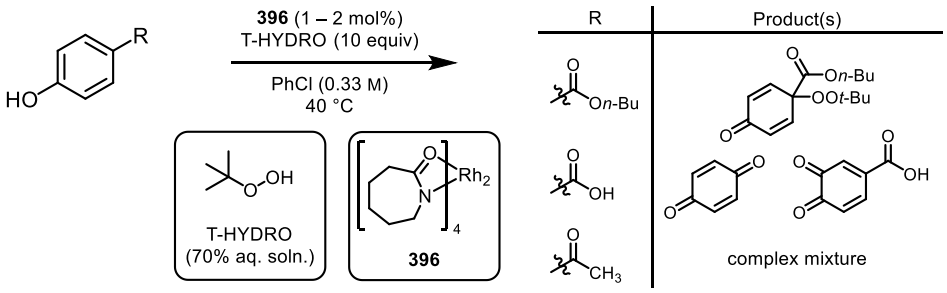
While considering possible reagents and mechanisms to elicit the cleavage of the Ph* motifs, it was recognised that Br_2 was not only serving as a Lewis acid, but also as an oxidant (Scheme 5.25). The formation of brominated products **393** and **394** and the lack of

any iodinated products was particularly interesting they suggested a second mode in which IBr could act as an oxidant.



Scheme 5.25 *(A) The electrophilic cleavage of Ph* with bromine may also be viewed as an oxidative cleavage. (B) The formation of brominated phenol* ***394*** *could occur via a phenol oxidation-like mechanism.*

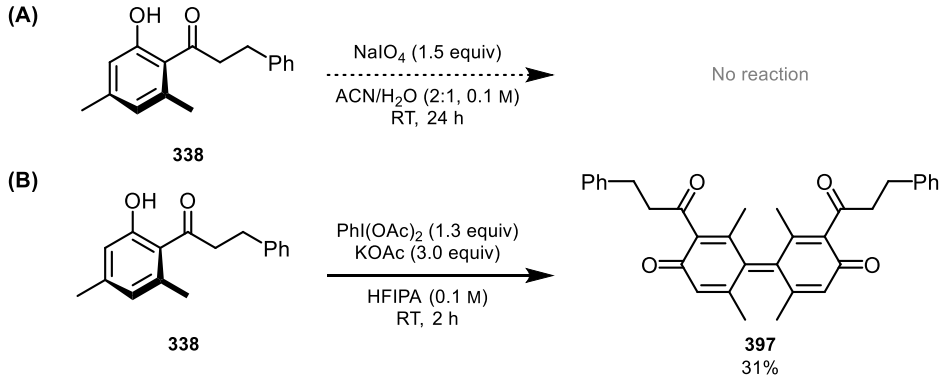
Phenols are well-known to undergo oxidation reactions, such as the Wessely oxidation and the related Adler–Becker oxidation,[193,194] but oxidations of phenols possessing a *para*-carbonyl group are rare in the literature. Ratnikov et al. reported a similar oxidation with aq. *tert*-butyl hydroperoxide and a rhodium catalyst (Scheme 5.26).[195] When an ester was used a semiquinone was formed with the ester group still intact, and when a carboxylic acid was used the intermediate had decarboxylated and formed a quinone instead. However, Ratnikov et al. also reported that performing the reaction with the corresponding acetophenone gave a complex mixture. The reported decarboxylation is very similar to the dearylative cleavage of Ph* groups, so perhaps a suitable oxidising agent would be able to effect the cleavage of the phenol derivative of Ph* while avoiding the formation of the complex mixture.



Scheme 5.26 *Oxidations various phenols with various carbonyl groups on the 4-position as reported by Ratnikov et al.*[195]

5.4.2 Oxidant Screen

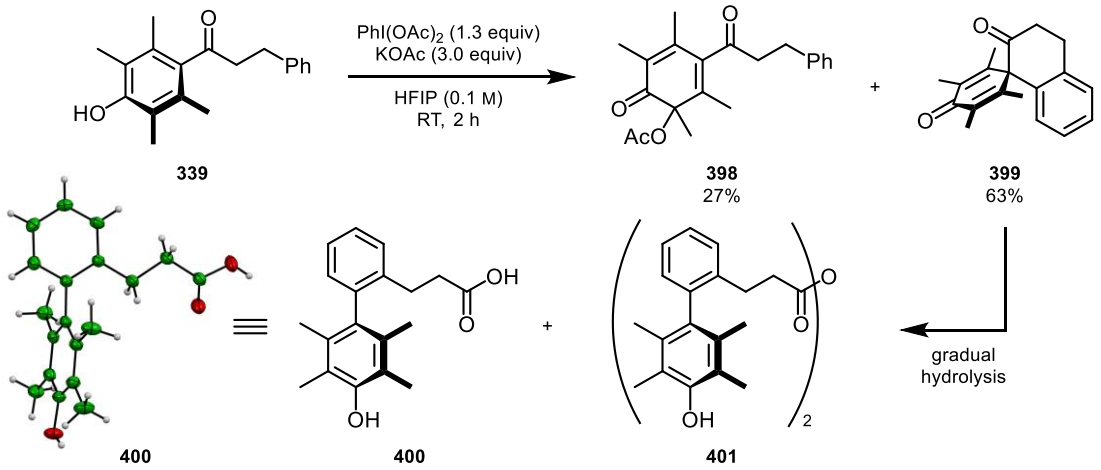
The search for a suitable oxidant started with hypervalent iodine reagents, which are often employed in phenol oxidations (Scheme 5.27). Sodium periodate gave no reaction when attempted with *ortho*-phenol **338**. Disappointingly, despite switching to an organic hypervalent iodine reagent with KOAc as a nucleophilic trap, the only product observed was dimer **397**. The substrate had undergone dimerisation at the *para* position with respect to the phenol.[194,196,197]



Scheme 5.27 *Attempted oxidative cleavage of ortho-phenol **338** with (A) inorganic or (B) organic hypervalent iodine reagents.*

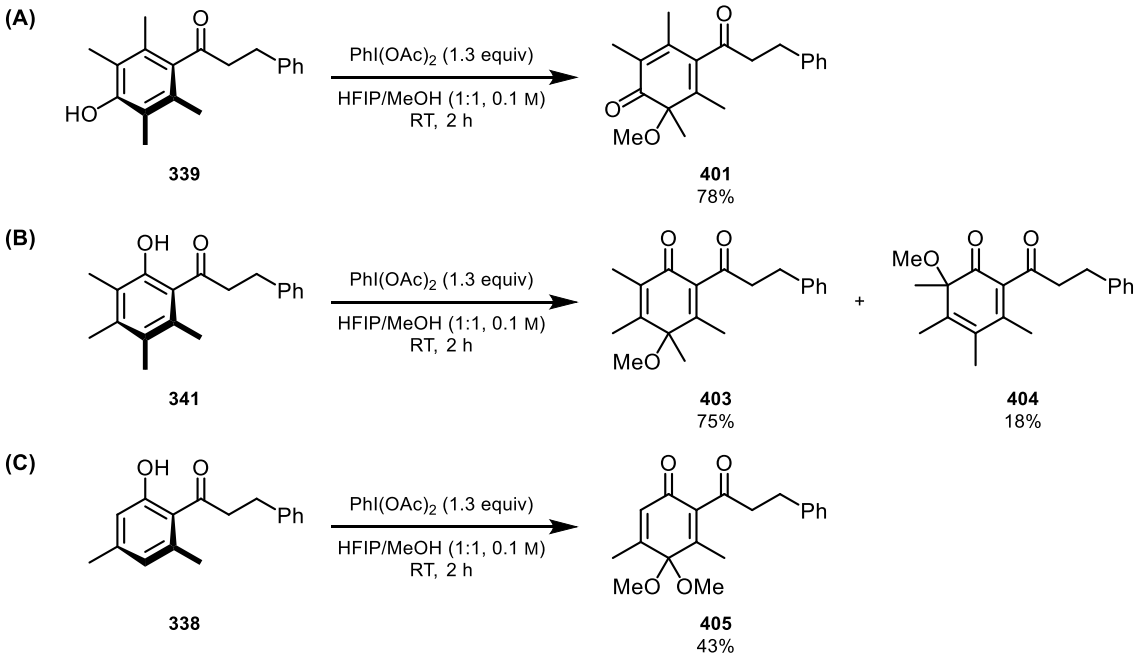
More unusually, when *para*-phenol **339** was reacted with PIDA in the presence of KOAc, only a small amount of *ortho*-substituted acetate **398** was formed, with the major product being spirocycle **399** (Scheme 5.28). The spirocyclic compound was observed to slowly hydrolyse over time to acid **400** and anhydride **401**, the structure of the latter being

confirmed by X-ray crystallography. The formation of acid **400** and anhydride **401** serves as a proof of concept for the acyl cleavage pathway. Such spirocyclisations are only known in the literature for *N*-phenylamides to form 5-membered spirolactams.[198–200]



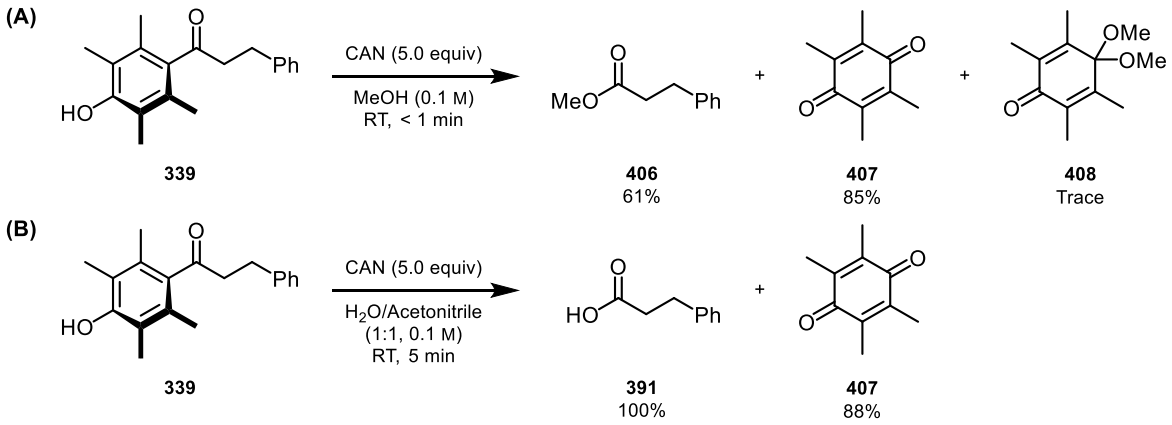
Scheme 5.28 *Attempted oxidative cleavage of para-phenol* ***339*** *with PIDA in the presence of KOAc as a nucleophilic trap gave spirocycle* ***399*** *as the major product, which gradually hydrolysed to acid* ***400*** *and anhydride* ***401****. The structure of acid* ***400*** *was confirmed by X-ray crystallographic analysis.*

Disappointingly, when methanol was used as a co-solvent in hope of promoting an intermolecular attack on the *ipso* carbon at the 4-position, the major product observed was the *ortho*-substituted product **402** instead (Scheme 5.29). To add to the frustration, subjecting the isomeric *ortho*-phenol **341** to PIDA in a methanolic solution gave mainly the *para*-substituted product **403** instead. Crucially, the minor product **402** is substituted at the methyl *ipso* carbon instead of the acyl *ipso* carbon. The phenol **338** also exhibited a similar reactivity, giving *para*-quinone dimethyl acetal **405** as the major product. Oxidations of phenols hypervalent iodine reagents such as PIDA are known to exhibit preferential reactivity at the 4-position, so it appears that interference from the acyl group is switching that preference to the 2-position.[193]



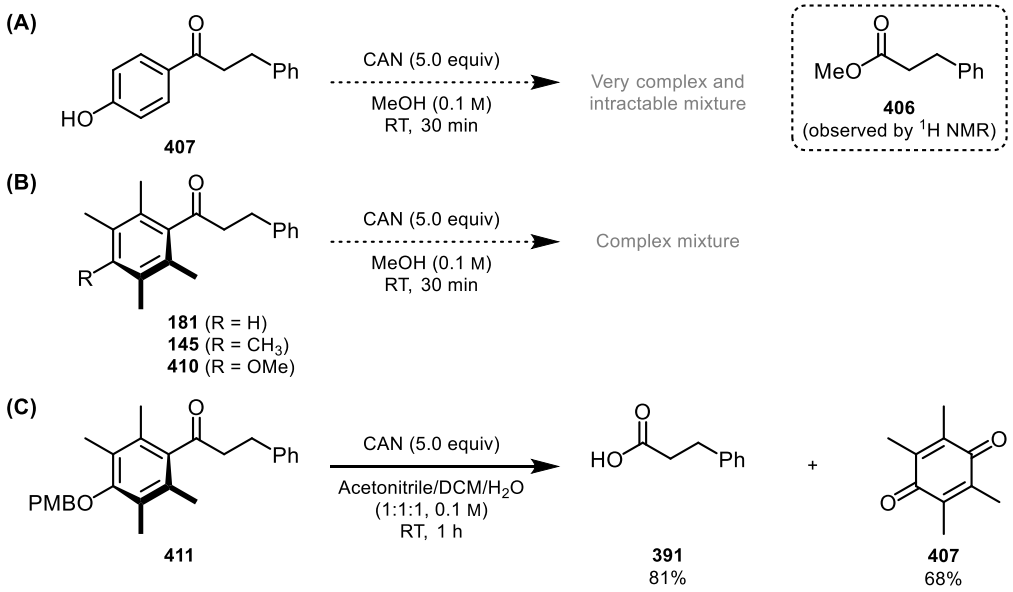
Scheme 5.29 *Attempted oxidative cleavage of isomers (A) para-phenol **339** and (B) ortho-phenol **341** with PIDA in a methanolic solvent. Unlike the formation of **399**, the attack at the acyl ipso carbon was not observed here. (C) Attempted oxidative cleavage of ortho-phenol **338** under identical conditions gave a similar para-oxidation product, in this case the para-quinone dimethoxy acetal **405**.*

Turning to other oxidising agents commonly used for phenolic substrates, the low toxicity, ease of handling and convenient waste disposal made ceric ammonium nitrate (CAN) far more attractive compared to other reagents such as DDQ. Very pleasingly, a methanolic solution of CAN elicited the cleavage of the *para*-phenol **339** very cleanly to give very good yields of the methyl ester **406** together with duroquinone **407** and its dimethoxy acetal **408** (Scheme 5.30). What was especially striking was the *very* rapid rate of the reaction, essentially being a titration reaction with visible decolourisation of the orange CAN solution and the reaction mixture taking up a pale yellow colour brought about by duroquinone **407**. The volatility of ester **406** is likely the cause for its poor yield. The reaction can also be carried out in an aqueous/organic biphasic mixture to give acid **391** in quantitative yield.



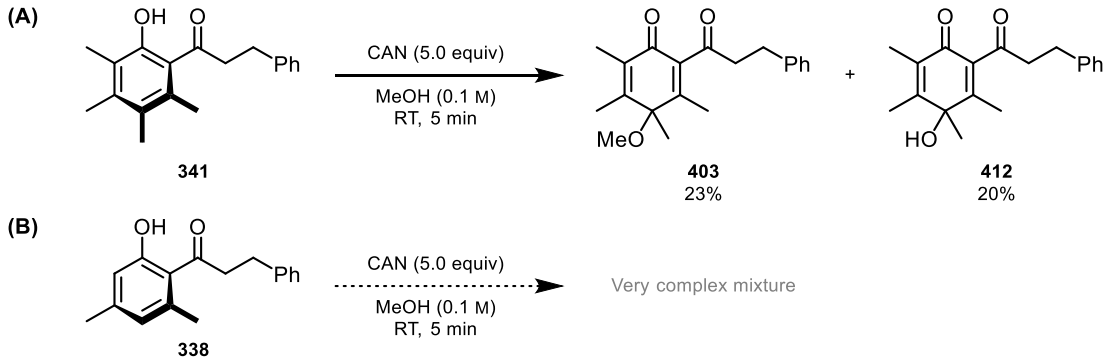
Scheme 5.30 *(A) Cleavage of para-phenol **339** with methanolic CAN gave ester **404**, duroquinone **407** and acetal **408**. (B) Cleavage of para-phenol **339** with aqueous CAN give acid **391** in good yield.*

The *para* substitution pattern and the presence of the methyl groups turned out to be critical for the reaction (Scheme 5.31). Although acyl cleavage was observed when the *ortho*- and *meta*-methyl groups were removed (**409**), the reaction also gave a highly intractable black tar (see Scheme 5.22). Replacing the phenol with a hydrogen (**181**), methyl (**145**) or methoxy (**410**) group resulted in varying degrees of conversion to highly complex mixtures. A PMB-protected phenol (**411**) was also a suitable substrate, with PMB deprotection and concomitant cleavage proceeding smoothly albeit over a much longer duration.



Scheme 5.31 *The oxidation of (A) para-phenol **409** and (B) several Ph* ketone derivatives with PIDA in a methanolic solvent all led to the formation of complex mixtures. (C) Concomitant PMB deprotection and oxidative cleavage of PMB-protected phenol **411**. Acetonitrile was added to aid solubility of phenol **411**.*

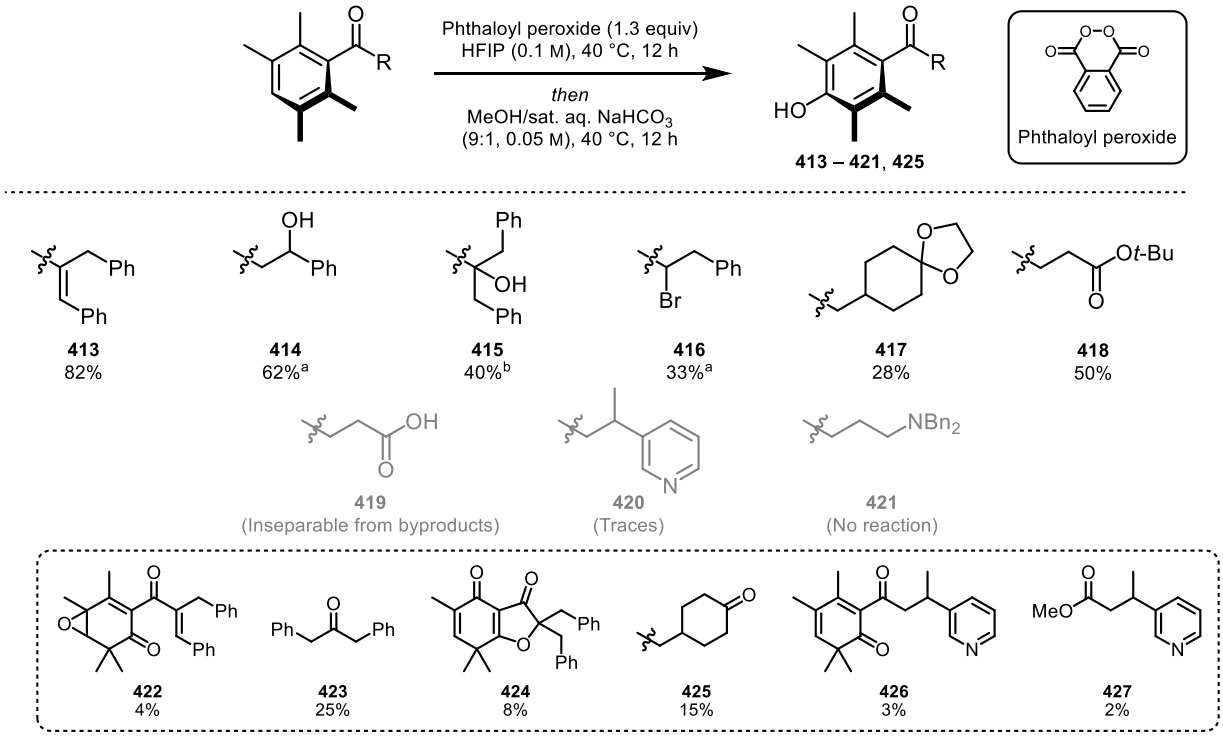
When the *ortho*-phenol **341** was used, the predominant products formed were the *para*-substituted cyclohexadienones **403** and **412** instead, again highlighting the strong *para* regioselectivity (Scheme 5.32). The suppression of side reactions by the *ortho* and *para* substituents is illustrated by the attempted cleavage of *ortho*-phenol **338**, which gave a highly complex mixture.



Scheme 5.32 *Attempted oxidative cleavage of ortho-phenols containing (A) four methyl groups (**341**) and (B) two methyl groups (**338**) with PIDA in a methanolic solvent. The additional methyl groups at the ortho and para positions likely suppressed undesired side reactions for phenol **341**.*

5.4.3 Functional Group Compatibility

The next step was to investigate the functional group tolerance of this methodology as compared to the Br_2-mediated cleavage of Ph*. Several substrates with different functionalities were synthesised by direct aryl oxidation with phthaloyl peroxide (Scheme 5.33).

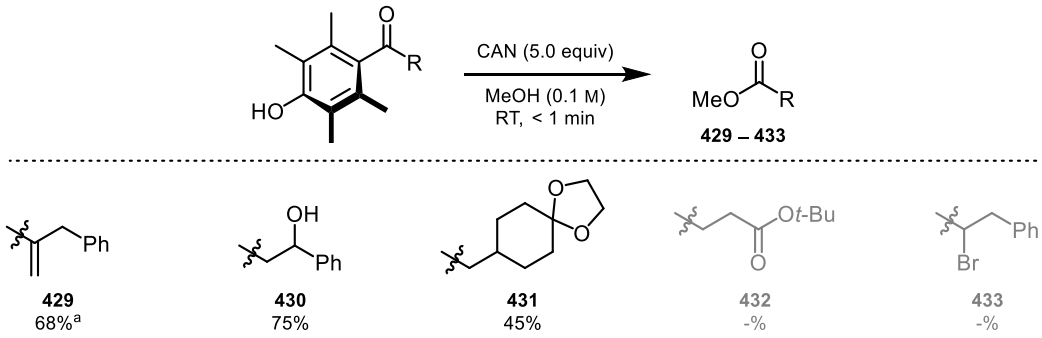


Scheme 5.33 *Synthesis of phenol analogues by direct aryl oxidation. The formation of numerous side products and the frequent low yields hamper the utility of this method and the CAN oxidative cleavage.* [a]*Starting material was provided by Dr. James Frost;* [b]*See Section 6.1.1 for synthesis of the starting material.*

The reaction was able to selectively oxidise an aryl ring to give **413** in excellent yield without interfering with an enone functionality. The α-hydroxy and α-bromoketone substrates also afforded ketones **414** and **415** in modest yields respectively. The α-hydroxyketone substrate **415** suffered from unexpected cleavage at the alkyl side of the ketone to form 1,3-diphenylacetone **423**. The acid **419**, unfortunately, was inseparable from the phthalic acid/monomethyl phthalate byproducts. The mild acidic conditions also resulted in the partial deprotection of acetal **417** to give ketone **425**,[*] however the acid-sensitive *tert*-butyl ester **418** was still obtained in good yield. Attempts to make pyridine **420** and dibenzylamine **421** suffered significantly from poor conversion, with traces of ester **427** being formed that, ironically, indicates that the desired oxidative cleavage of the

[*] The deprotected starting material **428** was also obtained in 16% yield.

phenol had occurred in the reaction. Traces of oxidative rearrangement products **422**, **424** and **426** could also be observed.[201]



Scheme 5.34 *Substrate scope for the oxidative cleavage of the phenolic Ph* motif with CAN. [a]Yield as observed by NMR after flash column chromatography, as the product was inseparable from the duroquinone byproduct.*

The phenolic substrates were then subjected to oxidative cleavage with a methanolic solution of CAN (Scheme 5.34). The enone and benzylic alcohol were cleaved in good yields to give esters **429** and **430** respectively. The acetal group on **417** stayed intact to afford **431** in acceptable yield given the acidic nature of the reaction mixture, however the *tert*-butyl ester **418** did not survive these conditions. Disappointingly, the α-bromo ketone **416** was unreactive, and upon heating a complicated mixture was obtained instead.

5.5 Conclusion

The synthetic utility of the Ph* group in aryl ketones lies in its ability to protect the carbonyl centre, enabling the hydrogen borrowing reaction, and allowing selective crossed-aldol processes to occur in the presence of other secondary alcohols or ketones. The ability to reduce the Ph* ketone with DIBAL-H provides subsequent users a set of reagents to plan synthetic routes and employ orthogonal protecting groups. The modular nature of the Ph* group, through aryl cleavage with Br_2 and subsequent trapping with nucleophiles, greatly enhance the potential value of the Ph* group.

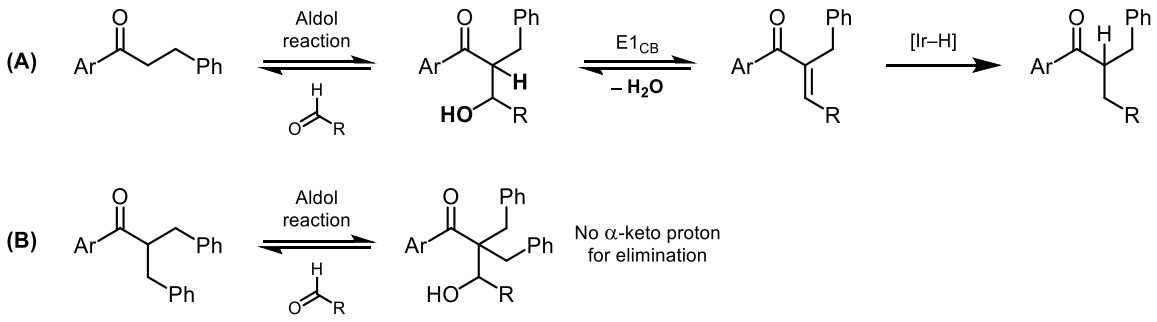
The access to heteroatom derivatives of Ph* ketone also enabled further attempts at improving the modular nature of Ph*, such as the use of CAN in the oxidative cleavage of the phenolic derivative of Ph*. With these derivatives in hand, the investigations into their behaviour in the hydrogen borrowing reactions will be discussed in the next chapter, together with the impact of these heteroatom modifications on the *ortho* effect.

Chapter 6. The Reactivity of Ph* Ketone Analogues, and Attempts towards the Formation of Tetrasubstituted α-Keto Centres *via* Hydrogen Borrowing

In this chapter, the following questions will be answered:

- Can heteroatom derivatives of Ph* ketones undergo hydrogen borrowing reactions?
- Can we access tetrasubstituted carbons directly from the hydrogen borrowing reaction?
- What roles does the *ortho* effect play for heteroatom derivatives of Ph* ketone?

6.1 Tetrasubstituted α-Keto Centres

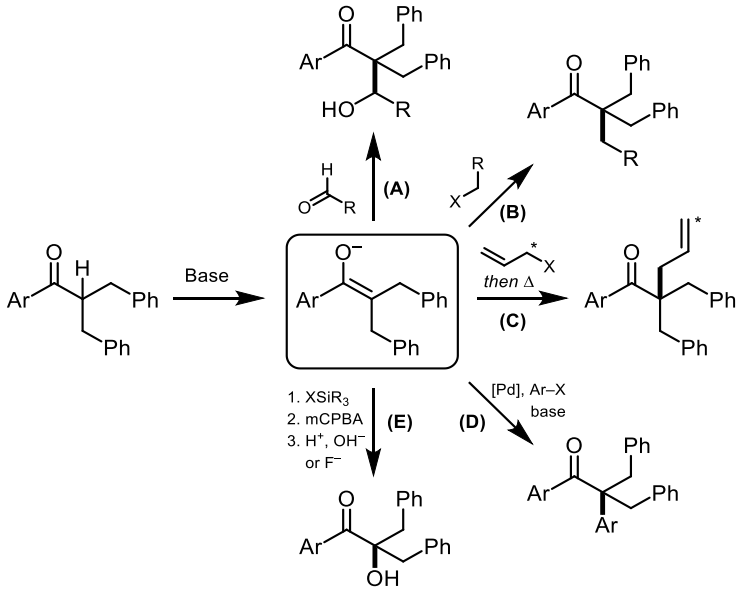


Scheme 6.1 *(A) An aldol condensation reaction requires an enolisable α-keto proton to perform $E1_{CB}$, so trisubstituted α-keto centres can be formed via hydrogen borrowing. (B) Under thermodynamic conditions, an α-branched ketone lacks an α-keto proton to perform $E1_{CB}$ required to make an enone, so only a retro-aldol process can occur.*

In an aldol condensation, a ketone reacts with an aldehyde to form a β-hydroxyketone, which dehydrates *via* $E1_{CB}$ to give an enone. A subsequent reduction, whether using reducing agents such as $NaBH_4$ or from the third reduction step in hydrogen borrowing, produces a trisubstituted stereocentre. A hydrogen must be removed to form the enone, so while an α-branched ketone could form a β-hydroxyketone with a tetrasubstituted α-keto centre, an $E1_{CB}$ process cannot take place and a *retro*-aldol occurs instead under

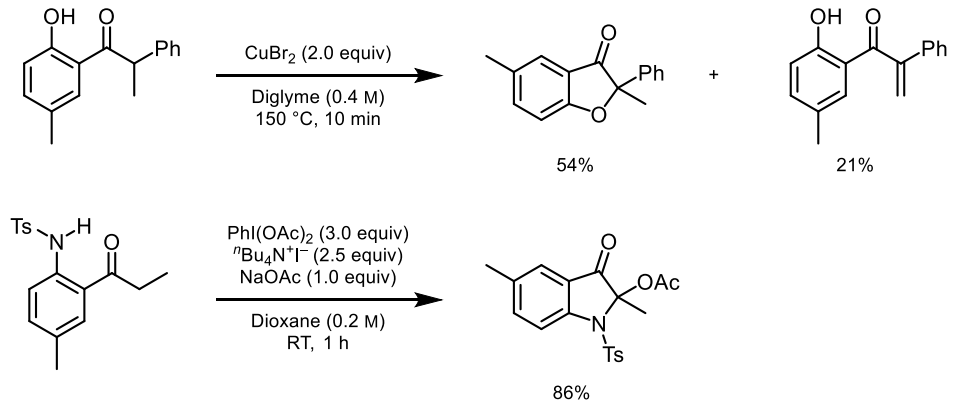
thermodynamic conditions (Scheme 6.1). In this regard, one cannot form a tetrasubstituted α-keto centre by hydrogen borrowing since no conceivable $E1_{CB}$ process can occur.

6.1.1 Methods to Form Tetrasubstituted α-Keto Centres



Scheme 6.2 *Formation of tetrasubstituted α-keto centres by (A) aldol reaction under kinetic conditions, (B) enolate C-alkylation with an alkyl halide, (C) Claisen rearrangement, (D) enolate arylation, and (E) electrophilic heteroatom functionalisation methods such as the Rubottom oxidation.*

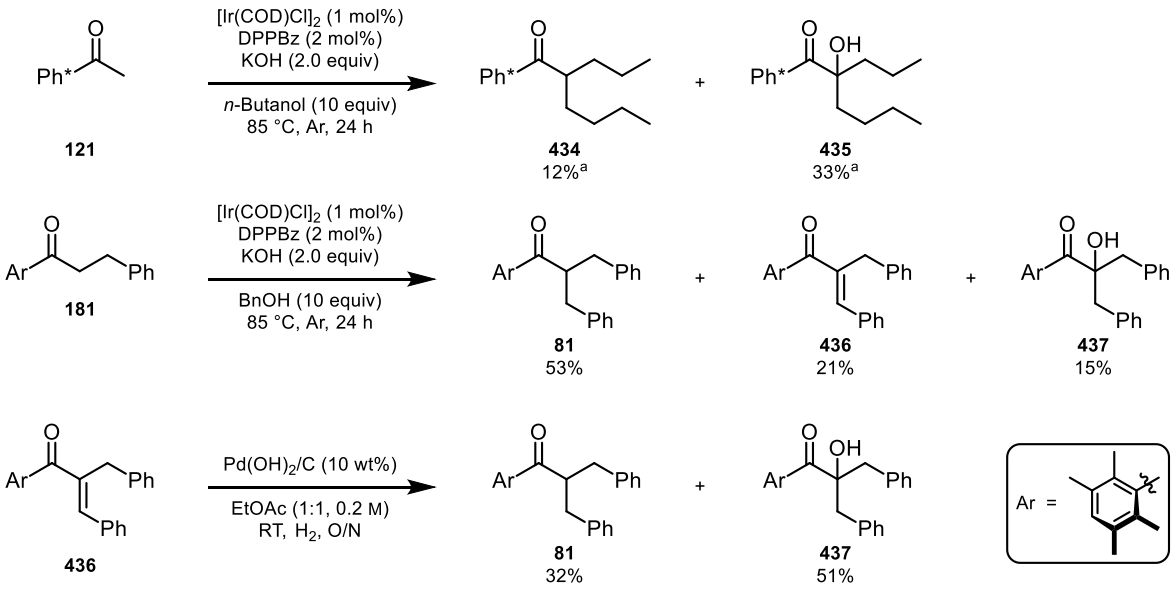
The most common method of quaternisation of an α-keto centre takes advantage of the electronics of the α-centre to perform enolate substitutions with a suitable electrophile (Scheme 6.2). Examples include the aldol reaction under kinetic conditions and alkylation with an alkyl halide. There are also pericyclic methods such as the Claisen rearrangement to give the desired α-allyl ketone. The formation of sp^3–sp^2 bonds is also possible by metal-catalysed processes such as the palladium-mediated enolate arylation. It is also possible to install heteroatom functionalities at the α-keto centre with electrophilic heteroatom reagents, for example with mCPBA in the Rubottom oxidation to give α-hydroxyketones.



Scheme 6.3 *Examples of oxidative cyclisation reactions reported in literature.*[202,203]

The ability for hydrogen borrowing reactions to do the impossible – the formation of quaternary centres beyond the oxidation/aldol condensation/reduction manifold – would take the utility of the reaction to a completely different level. Given the basic conditions of the reaction as well as the redox processes present, it was envisioned that the formation of such a centre would likely either involve an enolate substitution or a metal-catalysed enolate arylation/alkylation, potentially an oxidative or reductive coupling. There are several examples of oxidative cyclisation reactions in the literature, such as the use of Cu(II) salts to form an isobenzofuranone,[202] or with hypervalent iodine reagents to give 2-indolinones (Scheme 6.3).[203]

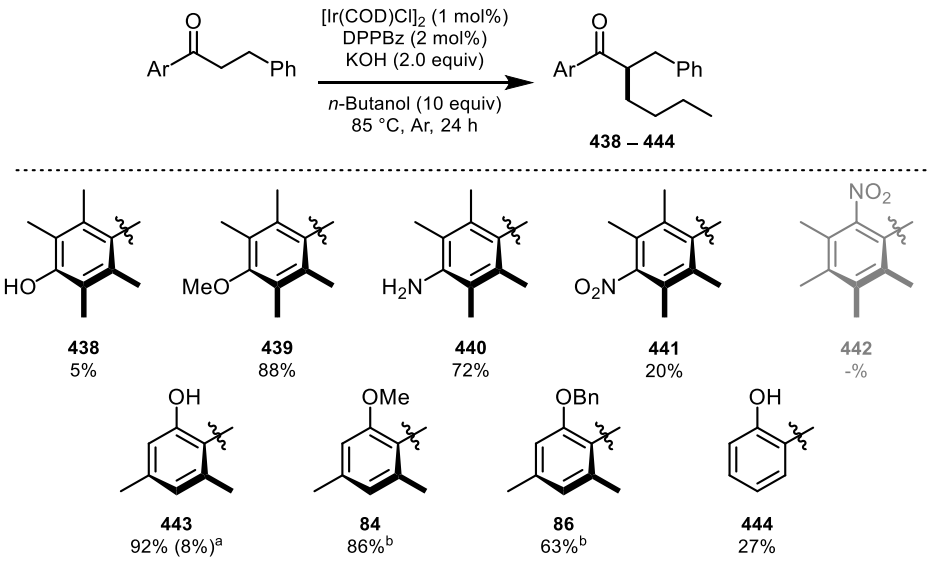
The first clues came from occasional observation of polar side products in hydrogen borrowing reactions as well as during the catalytic hydrogenation of trisubstituted enone **436** with $Pd(OH)_2/C$ (Scheme 6.4). Further analysis revealed them to be the tetrasubstituted α-hydroxy ketones. However, the capricious nature of their formation deterred further study into them.



Scheme 6.4 *Observed formation of α-hydroxyketones from hydrogen borrowing reactions and from a catalytic hydrogenation reaction. [a]Work by Wasim Akhtar.*

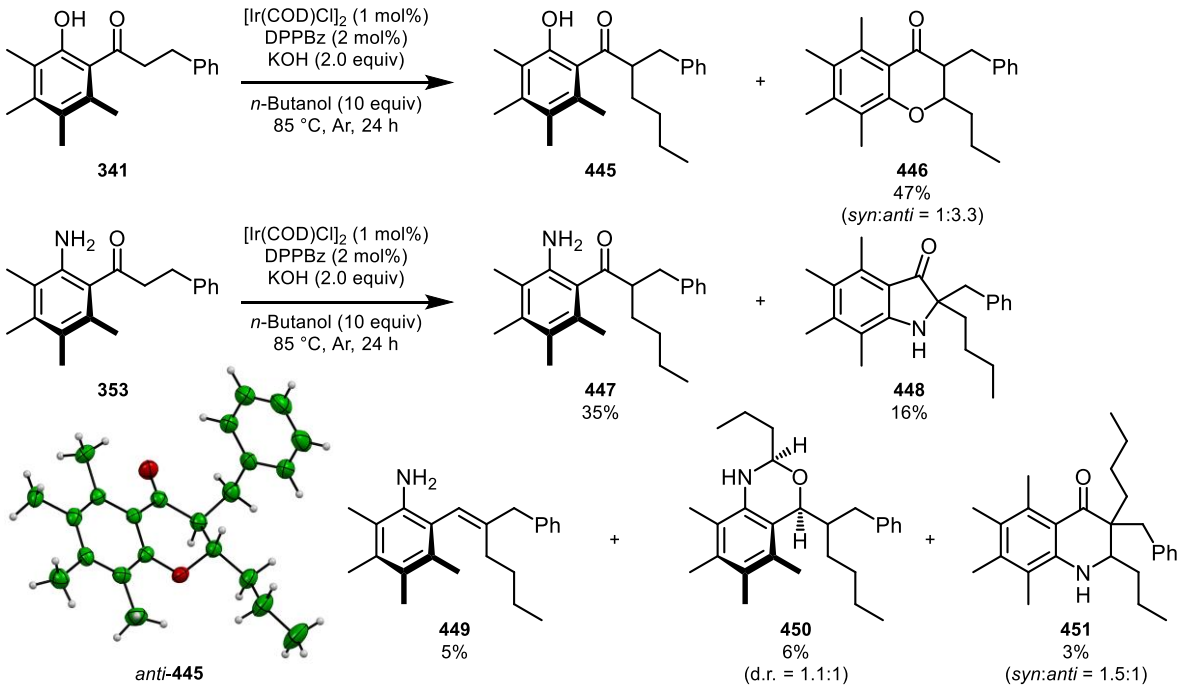
6.1.2 Hydrogen Borrowing Reactions of Heteroatom Derivatives of Ph* Ketones

Having previously synthesised a series of heteroatom-substituted aryl ketones (see Section 5.2.4), the next step was to investigate their reactivity in the hydrogen borrowing reactions. When *n*-butanol was used as the alkylating agent, the *para*-phenol **339** gave virtually no reaction, likely due to the formation of a negatively charged phenoxide that consumes one equivalent of base while deterring a second deprotonation at the α-keto centre (Scheme 6.5). Methylation of the oxygen restores the reactivity of the ketone to give **439** in excellent yield. In contrast, the *para*-aniline **347** could be alkylated in good yield to give **440** with no *N*-alkylation observed. Unfortunately, the *para*-nitroarene **441** was obtained in low yield, while *ortho*-nitroarene **350** completely decomposed, suggesting that the hydrogen borrowing conditions could not tolerate nitro groups.



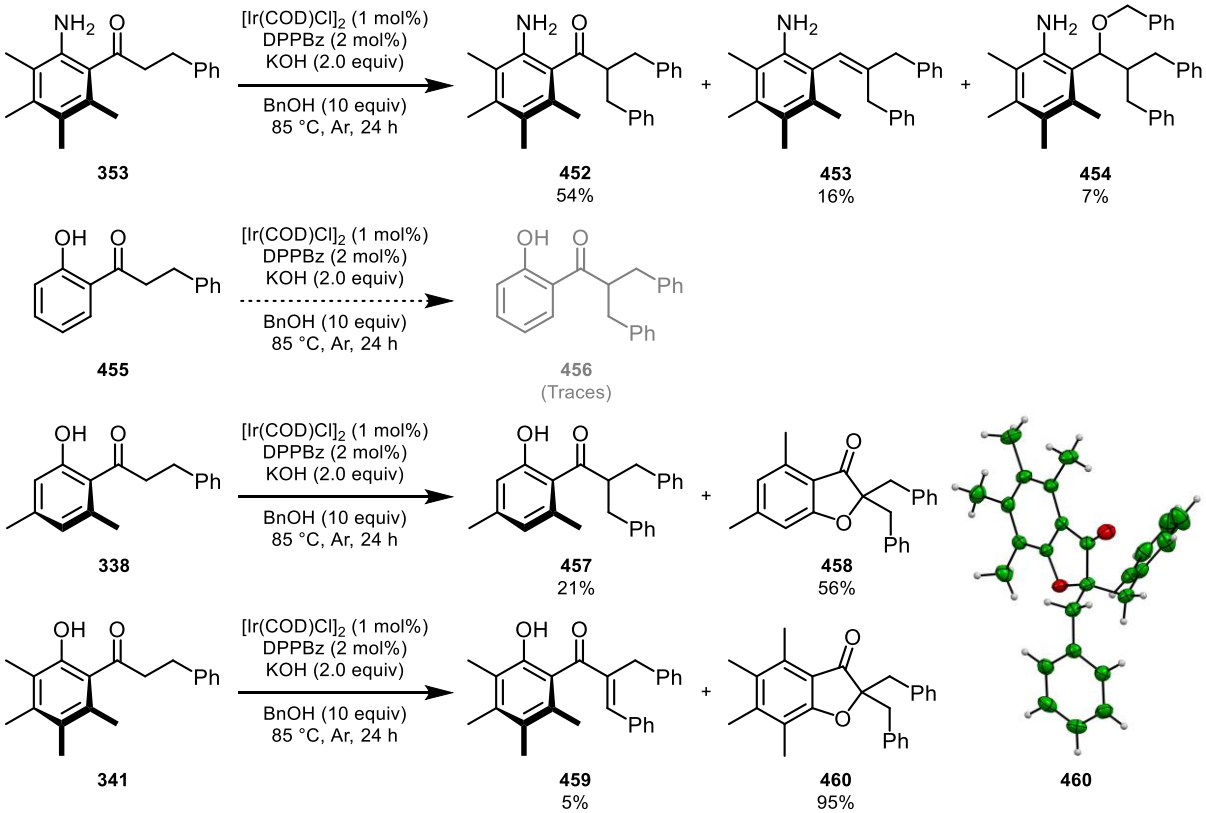
Scheme 6.5 *Hydrogen borrowing reactions of Ph* ketone substrates with heteroatom substituents.* [a]*Yield in parentheses is that of the corresponding enone.* [b]*See Scheme 3.11.*

Given the poor reactivity of the *para*-phenol substrate **339**, it was surprising to find that the *ortho*-phenol **443** could be obtained in excellent yield that surpassed the *O*-alkyl analogues **84** and **86** (see also Scheme 3.11) The hydrogen borrowing reaction could also work in the absence of an *ortho*-methyl group, with **444** being furnished in a modest 27% yield.



Scheme 6.6 *Unusual results from the hydrogen borrowing reactions of ortho-phenol* ***341*** *and ortho-aniline* ***353****. The structure of chromanone anti-****446*** *was confirmed by X-ray crystallographic analysis.*

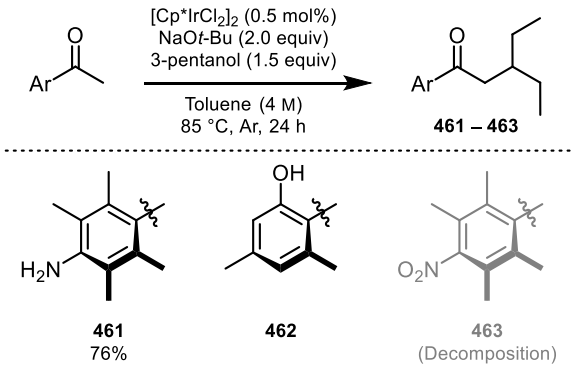
The *ortho*-phenol **339**, containing four methyl groups on the aryl ring, behaved differently from their *para*-substituted (**337**) or dimethyl (**336**) counterparts (Scheme 6.6). Only a relatively small amount of *ortho*-phenol **444** was obtained, but a larger quantity of chromanone **445** was formed as a 1:3.3 mixture of *syn*:*anti* isomers, with the structure of *anti*-chromanone *anti*-**445** being confirmed by X-ray crystallographic analysis. The reaction with *ortho*-aniline **351** was significantly more complicated, giving a mixture of the desired ketone **446** as well as various *N*-alkylated side products **449** and **450** that arose from the condensation of the aniline and *n*-butanal formed *in situ* followed by intramolecular trapping with an internal nucleophile. The loss of the ketone group in **448** and **449** suggests a weakened protective effect from this di-*ortho*-substituted system. Surprisingly, indolinone **447** was also obtained in a low yield, the first successful example of the formation of a tetrasubstituted α-keto centre by hydrogen borrowing.



Scheme 6.7 *Unusual results from the hydrogen borrowing reactions of ortho-aniline* ***353*** *as well as ortho-phenols* ***455***, ***338*** *and* ***341****. The structure of benzofuranone* ***460*** *was confirmed by X-ray crystallographic analysis.*

Pleased with the formation of the indolinone, the *ortho*-aniline **353** and *ortho*-phenols **455**, **338** and **341** were also subjected to the hydrogen borrowing reaction with benzyl alcohol (Scheme 6.7). Disappointingly, no indolinone formation was observed in this case. Instead, the α-alkylated product **452** was observed in good yield together with two side products **453** and **454** formed from the reduction of the ketone group.

Astoundingly, the *ortho*-phenol substrates could form benzofuranones in varying yields. In the absence of methyl groups on the aryl ring (**455**), only traces of the α-alkylated product **456** could be observed. The introduction of an *ortho*-methyl group gave significantly more α-alkylated product **457** together with a good yield of benzofuranone **458**. When four methyl groups are present, the benzofuranone **46** was formed in near-quantitative yield together with a small amount of the enone intermediate **459**. The structure of benzofuranone **460** was confirmed by X-ray crystallographic analysis (see also Section 7.1).

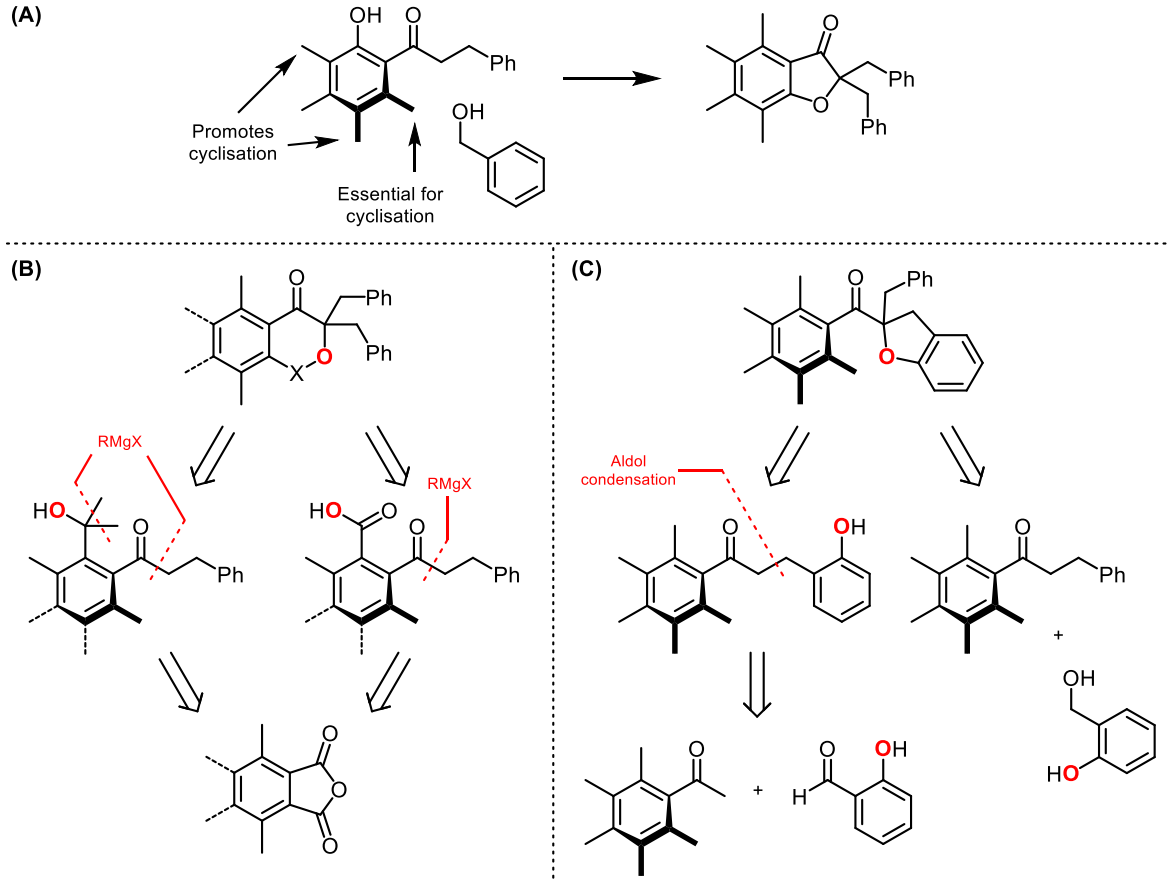


Scheme 6.8 *Hydrogen borrowing reactions of para-aniline **349**, ortho-phenol **336** and para-nitroarene **348** to form β-branched ketones.*

Several di-*ortho*-substituted aryl ketones with heteroatom substituents were also subjected to the hydrogen borrowing reaction to form β-branched ketones (Scheme 6.8). Only *para*-aniline **461** was obtained in good yield, whereas *ortho*-phenol **336** gave a poor mass recovery and only 10% of the desired phenol **462**. The extensive decomposition of *para*-

nitroarene **348** further reinforces the suggestion of the incompatibility of the nitro group with these hydrogen borrowing conditions.

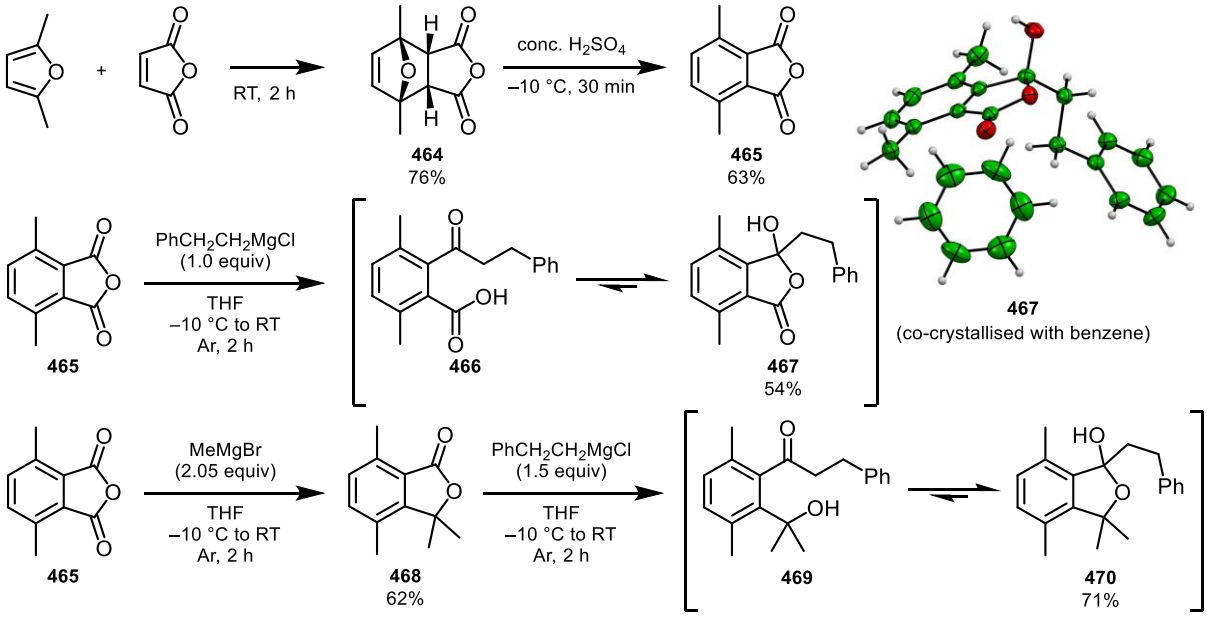
6.1.3 Investigations into the Formation of Tetrasubstituted α-Keto Centres from Hydrogen Borrowing



Scheme 6.9 *(A) Synthetic strategies to probe the intramolecular cyclisation and formation of tetrasubstituted α-keto centre. The methyl groups on the aryl ketone are observed to be critical for the cyclisation to occur. (B) An analogue that extends the oxygen away by one atom could take the form of a tertiary alcohol or a carboxylic acid, both of which could be derived from a common anhydride. (C) A cyclisation from an oxygen atom from the ketone aryl motif could involve moving the oxygen on the pendant phenyl group, or onto the primary alcohol.*

With a few successful examples of formation of tetrasubstituted α-keto centres by hydrogen borrowing, the next step was to investigate the conditions required to achieve this transformation (Scheme 6.9). It was clear that the *ortho*-methyl group was critical to the formation of the benzofuranone, and that additional adjacent methyl groups further enhanced the formation of the benzofuran over the reduction of the enone that would have

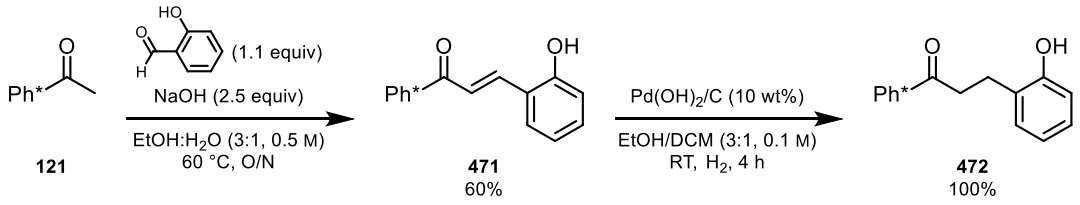
formed the α-branched ketone. One possible variation was to introduce a linker atom between the oxygen and the aryl group so that a six-membered chromanone would form instead. This could take the form of a carboxylic acid or a tertiary alcohol, both of which could be easily synthesised from a common anhydride precursor. The other possibility was to have the cyclisation occur away from the aryl motif on the ketone such that it would form a dihydrofuran. The oxygen atom involved in the cyclisation could be located on the pendant phenyl ring or on the alcohol used for hydrogen borrowing.



Scheme 6.10 *Synthesis of anhydride **465** that serves as a common precursor to acid **466** and tertiary alcohol **469**. Both **466** and **469** greatly favour their respective cyclic forms **467** and **470**. The structure of **467** was confirmed by ^{13}C NMR as well as from X-ray crystallographic analysis of a co-crystal with benzene (the benzene molecule is oriented to the foreground).*

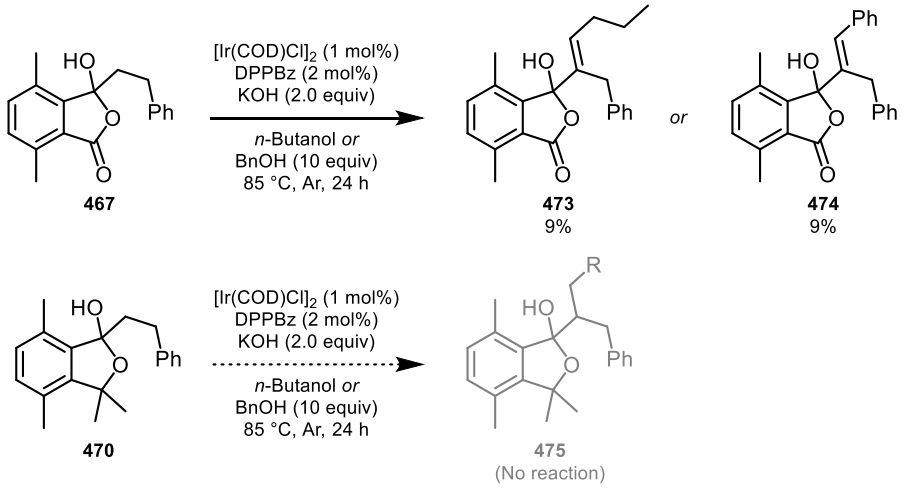
The desired tetramethylphthalic anhydride is not readily accessible, but the dimethyl analogue can be easily synthesised by a two-step process involving a Diels–Alder reaction between 2,5-dimethylfuran and maleic anhydride to give the *endo*-adduct **464**, which is then readily dehydrated by sulfuric acid to give the desired phthalic anhydride **465** in excellent yield (Scheme 6.10).[204] The unique reactivity of this anhydride allows the synthesis of benzoic acid **466** or the lactone **468** with 1 and 2 equiv of Grignard reagent respectively without the formation of any symmetric dione observed (see also Section

6.2.3).[205–209] Subsequent addition of another Grignard reagent to lactone **468** afforded the tertiary alcohol **469**, which is resistant to further attack by nucleophiles, again due to the equilibrium favouring the cyclic hemiacetal **470** over the ring-opened tertiary alcohol **469**. This behaviour is readily observed both in solution by ^{1}H and ^{13}C NMR spectroscopy, as well as in the solid state by X-ray crystallographic analysis of **467**.



Scheme 6.11 *Synthesis of phenol **472**.*

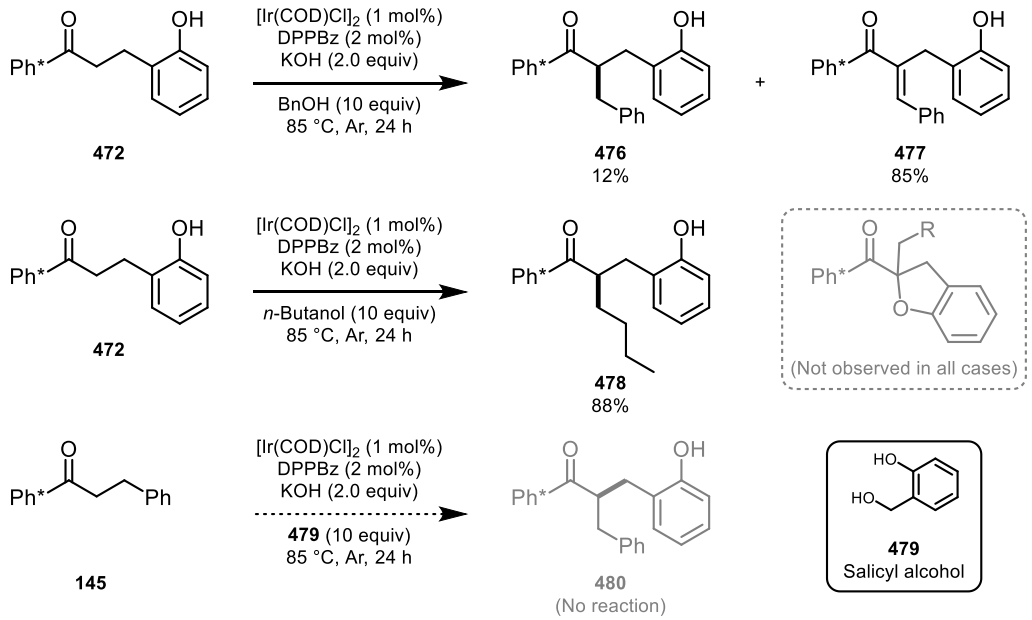
The synthesis of the pendant phenol substrate was readily achieved by aldol condensation with salicaldehyde to give enone **471**, followed by catalytic hydrogenation to afford the phenol **472** in quantitative yield (Scheme 6.11).



Scheme 6.12 *Hydrogen borrowing reactions with hemiacetals **467** and **470** were largely unsuccessful.*

When the modified substrates were subjected to hydrogen borrowing conditions using benzyl alcohol or *n*-butanol, the results were disappointing. Both hemiacetals **467** and **470** failed to give any oxidative cyclisation substrate or hydrogen borrowing alkylation

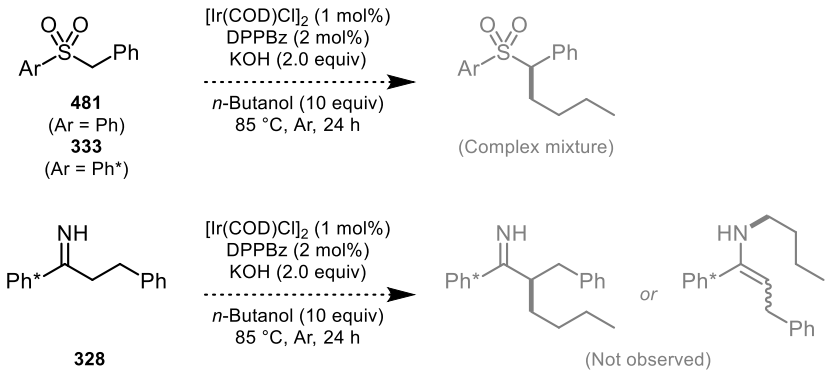
products (Scheme 6.12). Traces of the aldol condensation products **473** and **474** could be observed for the case of lactone **467**.



Scheme 6.13 *Hydrogen borrowing reactions with phenol **472** gave predominantly enone **477** when performed with BnOH, but when n-butanol was used instead the ketone **478** was obtained in good yield. Attempted hydrogen borrowing reaction with salicyl alcohol **479** failed to give any reaction.*

The phenol **472** gave excellent yields for alkylation *via* hydrogen borrowing, while the reaction with salicyl alcohol **479** gave no conversion, presumably due to the neutralisation of the base given the excess amount of acidic phenol present (Scheme 6.13). Unfortunately, all of these reactions did not give any trace of any cyclisation product.

6.1.4 Attempted Hydrogen Borrowing Reactions of Ph* Sulfone and Imine



Scheme 6.14 *Attempted hydrogen borrowing reactions of sulfones* ***481*** *and* ***333*** *as well as imine* ***328****.*

Disappointingly, when the sulfone (**333**) and imine (**328**) derivatives of Ph* ketone were subjected to the hydrogen borrowing reaction, no desired product was observed (Scheme 6.14). Both Ph* and phenyl sulfones **481** and **333** gave a complex mixture with severe loss of mass recovery. Frustratingly, although Ph* imine **328** was able to survive the hydrogen borrowing conditions, there was also no trace of any form of alkylation product, thus precluding the use of Ph* imines under this set of hydrogen borrowing reaction conditions.

6.2 Discussion

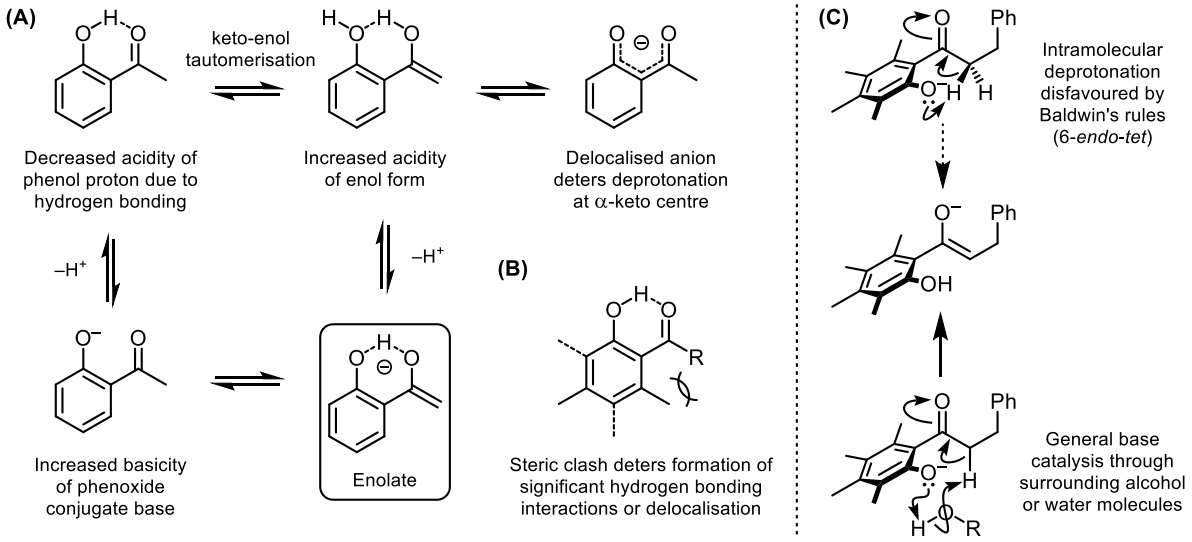
It is apparent that heteroatom substituents at the *ortho* position cause a deviation in behaviour during the hydrogen borrowing reaction. Not only do the *ortho*-phenol substrates successfully react under the reaction conditions when the *para*-phenol substrates failed to, but they also do so with better efficiency than their alkoxy counterparts (see Scheme 6.5). In addition, only certain functionalities on the *ortho* positions can intercept the reaction pathway and result in the formation of cyclic products with a tetrasubstituted α-keto centre (see Schemes 6.6 and 6.7). Could these results be yet another consequence of the *ortho* effect?

6.2.1 The Role of the *ortho*-Phenol as a Base

In Section 3.4.4 it was shown that the success of di-*ortho*-substituted ketones was largely attributed to the steric shielding of the ketone group, with mono-*ortho*-substituted ketones performing significantly poorer due to the limited steric interactions. The *ortho*-hydroxy group, being comparatively smaller in size than the alkoxy groups, deviates from this trend. Coupled with the ability to perform deprotonation at the α-keto centre despite the basic conditions and deterring subsequent deprotonation, this phenomenon deserves close attention.

One property commonly associated with the *ortho* effect is the stabilisation of the phenol proton by internal hydrogen bonding with the ketone (Scheme 6.15). For example, the phenol proton on *ortho*-hydroxyacetophenone has a higher pK_a (10.3) than the *para* analogue (8.1).[210] Although this affects the *phenol* proton, it also causes the corresponding conjugate base to be more basic and potentially contribute to the deprotonation of the α-keto proton. The converse is also potentially true – that the enolate could be stabilised by internal hydrogen bonding with the phenol proton thus decreasing the pK_a of the *enol*.

However, the phenoxide could also delocalise into the carbonyl group, deterring deprotonation of the α-keto proton. Nevertheless, given that any hydrogen bonding or delocalisation will require a geometry that results in a reduced dihedral angle between the aryl ring and ketone/enolate, the ensuing steric interactions between the other *ortho*-methyl group would minimise these effects, so these considerations are probably more relevant for *ortho*-phenol **454**, which lacks a second *ortho*-methyl group yet was able to give a very modest yield for hydrogen borrowing reaction.



Scheme 6.15 *(A) The ortho-hydroxy group can form multiple interactions with the ketone that can affect the effective pK_a of the α-keto proton. (B) These interactions, however, require the aryl-keto system to be planar, which would be disfavoured due to steric interactns from the ortho-methyl group and the other ketone substituent. (C) The ortho-hydroxy group can also facilitate deprotonation through either intramolecular deprotonation or general base catalysis.*

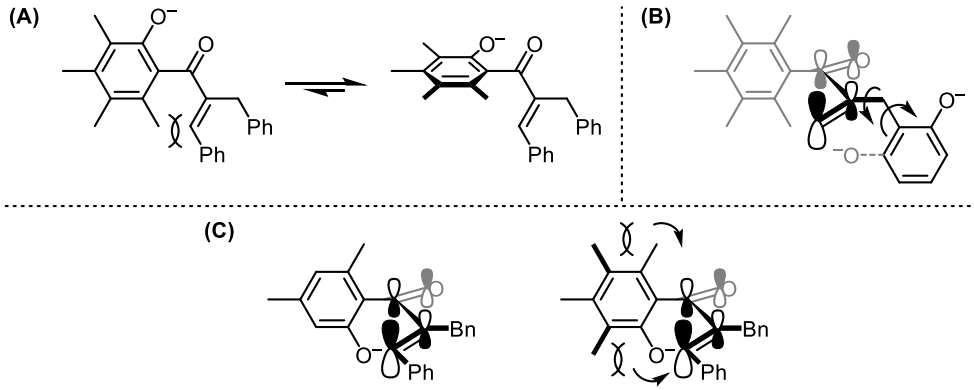
A second and more likely explanation is the *ortho*-phenol on either the ketone or pendant aryl ring exerting a proximity effect that accelerates deprotonation. This effect has been observed for reactions involving *ortho*-hydroxyacetophenones and *ortho*-carboxyacetophenones in buffered solutions.[210–213] It is also worth pointing out that although the α-keto proton is also likely to be in close proximity to the phenoxide in the conformation leading up to the generation of the enolate, this intramolecular deprotonation would be disfavoured by Baldwin's rules (6-*endo*-*tet*). Instead, general base catalysis is

more likely to be at play here, in which the phenoxide deprotonates a nearby alcohol molecule (e.g. from the solvation shell) that relays the delivery of the charge to the α-keto proton.

The amalgamation of these factors results in a lower effective pK_a of the α-keto proton. The end result is that *ortho*-phenols not only perform better than their *para*-phenol counterparts in the hydrogen borrowing reaction, but are also more effective substrates for aldol condensation.

6.2.2 The Role of the Methyl Groups in Conformational Control

Although the facilitated deprotonation for both *ortho*-phenols **338** and **341** could lead to higher yields of their respective products, the fact that only the hydroxy and amino groups on the ketone aryl ring participate in the cyclisation suggests a predisposition towards this reaction. This could be attributed to the *ortho* effect that induces a conformational preference of the aryl ring to be orthogonal to the ketone, and thus the phenol oxygen would be in much greater proximity to any potential reactive intermediate such as the enone or enolate (Scheme 6.16). In contrast, the phenol on the alkyl pendant would be freely rotating and would have to pay an entropic cost to interact with the reactive site.



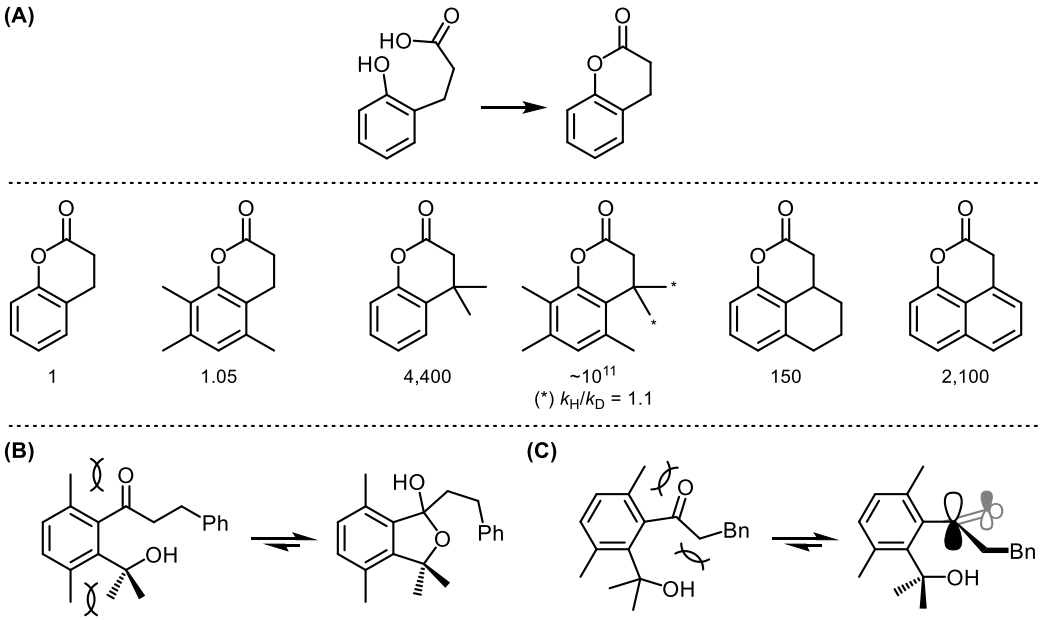
Scheme 6.16 *(A) The steric interactions exerted by the ortho-methyl group restricts the aryl-keto system to an orthogonal geometry, thus promoting cyclisation reactions. (B) In contrast, the pendant ortho-phenol has two additional degrees of rotational freedom that increases the entropic cost for cyclisation. (C) The meta-methyl groups distort and push the ortho substituents closer to the enone, further promoting cyclisation reactions.*

The predisposed participation of the hydroxy group on the ketone aryl ring is further supported by the observation that removal of the *meta*-methyl groups in the case of phenol **338** results in a decreased propensity to form benzofuranone **458**. In addition, dimethylphenol **338** reacted with *n*-butanol to give phenol **443** in excellent yield, whereas tetramethylphenol **341** gave a significant amount of chromanone **446**. This could be due to steric deformation of the aryl ring or adjacent substituents, also known as the "buttressing" effect (see Scheme 6.16).[214,215] The steric bulk of these methyl groups causes the phenol to be brought even closer to the reactive centre of the key intermediate, thereby further promoting the cyclisation reactions that gave chromanone **446** and benzofuranone **460** (see Schemes 6.6 and 6.7). A study on the structure of di-*ortho*-substituted substrates and the buttressing effects of the *meta*-methyl groups will be discussed in Section 7.1.

6.2.3 The Role of the Methyl Groups in Conformational Control – The Trimethyl Lock

The extremely poor reactivity of the lactols in the hydrogen borrowing reaction limits the amount of information that can be obtained from the investigation into the formation of tetrasubstituted α-keto centres. This lack of reactivity is likely due to the extreme preference

for the lactol form, also known as the "trimethyl lock" effect, thus disfavouring enolate formation (Scheme 6.17).[206,207] This behaviour stems from a combination of conformational control of the tertiary alcohol or carboxylic acid group that drives the cyclisation to form the hemiacetals, as well as an accompanying relief in steric interactions.[216] The presence of bulky groups adjacent to the ketone induces a torsional twist on the aryl-ketone bond, aligning the hydroxy groups towards the ketone and facilitating lactolisation.[205*] As a result, very little ring-opened ketone/enolate would exist at any one time thus giving an extremely poor result. However, it is difficult to gauge if the alcohol or carboxy groups would be effective intramolecular bases for the hydrogen borrowing reaction (see Section 6.2.1), or if the formation of a tetrasubstituted α-keto centre could occur for the case of a six-membered ring.



Scheme 6.17 *(A) Relative rates of lactonisation reported by Milstein and Cohen as well as Danforth et al. demonstrating the "trialkyl lock" effect.[206,207,216] The extreme preference for lactolisation is attributed to (B) strain relief from the interactions between the alkyl groups, and (C) torsional strain from the adjacent groups that orientates the ketone away from the plane of the aryl ring and in doing so, aligns the π* of the ketone towards the nucleophilic alcohol or carboxylic acid.*

[*] Hillery and Cohen also noted that the carbonyl centre involved in lactol formation is resistant to further nucleophilic attack, but the oxygens are readily isotopically labelled upon mixing with alkali $H_2{}^{18}O$. The authors suggest that this is likely an even more extreme case of the trialkyl effect due to one less degree of rotational freedom being present for the formation of a 5-membered ring.

6.2.4 Di-*ortho*-Substituted Aryl Ketones with Heteroatom Substituents and the Protective Nature of the *ortho* Effect

The last observations concern the protective nature of the *ortho* effect. The methyl groups flanking the amine for *para*-aniline **347** and **349** appear to be protecting the amine from condensation and/or subsequent reduction to form any *N*-alkylated products similar to how the di-*ortho*-substituted aryl ketones are not reduced under the reaction conditions (see Section 3.4.4).

Compared to methyl groups, however, the amino and hydroxy groups are not effective at exerting steric interactions that contribute to the protection of the ketone. This is clearly highlighted by *ortho*-phenol **462** being formed in a mediocre yield that is comparable to *ortho*-methyl ketone **124** (see Scheme 3.18). In some of the reactions internal hydrogen bonding could overcome a part of the torsional strain, particularly for *ortho*-amine **353** as it lacks acidic protons unlike *ortho*-phenols. Therefore, it is not unreasonable that the dihedral angle between the aryl ring and the ketone is smaller than expected, exposing the ketone towards reduction. Given that the situation is further complicated by the potential roles of these groups as bases, the results of these reactions cannot be interpreted simply based on the "size" of these groups.

6.3 Conclusion

Heteroatom derivatives of di-*ortho*-substituted aryl ketones behave significantly differently in the hydrogen borrowing reaction, with only a limited number of these derivatives being tolerated or surviving the reaction conditions. The unexpected reactivity of heteroatom substituents on the *ortho* position accounts for some of the surprisingly high yields from the hydrogen borrowing reactions, and enabled the unexpected cyclisation reaction to afford tetrasubstituted α-keto centres that would have been impossible to achieve by the usual hydrogen borrowing sequence alone. Attempts to modify the substituents and substitution pattern to emulate a similar cyclisation were unsuccessful and is likely attributed to conformation reasons. It is also worth pointing out that the vinylcyclopropane rearrangement was unable to form a quaternary α-keto centre when dicyclopropylmethanol was used, as the cyclopentene intermediate proved to be inert to a second rearrangement (see Section 4.5). In this regard, the access of tetrasubstituted α-keto centres by hydrogen borrowing reactions remains a challenge given the specific substitution pattern and the limited substrate scope required.

In the next chapter, various analytical data will be presented to discuss how substituents on the aryl group and on the α-keto centre affect the structure and electronic properties of aryl ketones, which would provide a structural basis for their observed reactivity in hydrogen borrowing reactions.

Chapter 7. The Effects of Substitution on Aryl Ketones

In this chapter, the following questions will be answered:

- How can the manifestation of the *ortho* effect in Ph* ketones and its derivatives be observed by spectroscopic or crystallographic methods, and are there trends that can be observed?
- What is the role of the methyl groups in the *meta* and *para* positions of Ph*?
- Can the differences in reactivity of di-*ortho*-substituted aryl ketones and nitrobenzenes in electrophilic substitution be rationalised by spectroscopic techniques?

The presence of *ortho* substituents results in deviations in reactivity of many aryl functional groups such as esters, acids and anilines, an effect broadly termed the *ortho* effect, with numerous studies in literature attributing this effect to a non-coplanar geometry of the aryl ketone that results in a steric inhibition of resonance (Chapter 1). The presence of *ortho* substituents was shown to enable the hydrogen borrowing reaction with higher alcohols by protecting the carbonyl group of aryl ketones against nucleophilic attack due to the orthogonal geometry of the aryl–ketone motif, and this protective nature was dependent on the size of the *ortho* substituents as well as on the other ketone substituent (Chapter 3). The *ortho* effect also resulted in changes to the electronics of the aromatic ring often associated with the steric inhibition of resonance, but this effect did not seem to be effective for the nitro group (Chapter 5). In addition, the presence of hydroxy or amino substituents at *ortho* positions of the aryl ketones led to the formation of interesting products in hydrogen borrowing reactions (Chapter 6). The reactivity of these *ortho*-hydroxy and *ortho*-amino ketones appeared to be influenced by flanking methyl groups *via* the “buttressing effect”.

Analytical techniques such as IR and NMR spectroscopy are excellent for providing detailed information about the structure and bonding of compounds. In addition, X-ray crystallography can provide precise measurements of bond lengths and angles, which are essential clues to understanding the nature of intra- and intermolecular bonding interactions in the compounds. These analytical techniques provide valuable information regarding the electronics, conformational preferences and any potential structural distortions to the compounds that may relate to the *ortho* and "buttressing" effects, and in turn provide a structural basis for the observed reactivity of the aryl ketones in hydrogen borrowing reactions.

7.1 Structural Studies of Aryl Ketones by X-Ray Crystallography

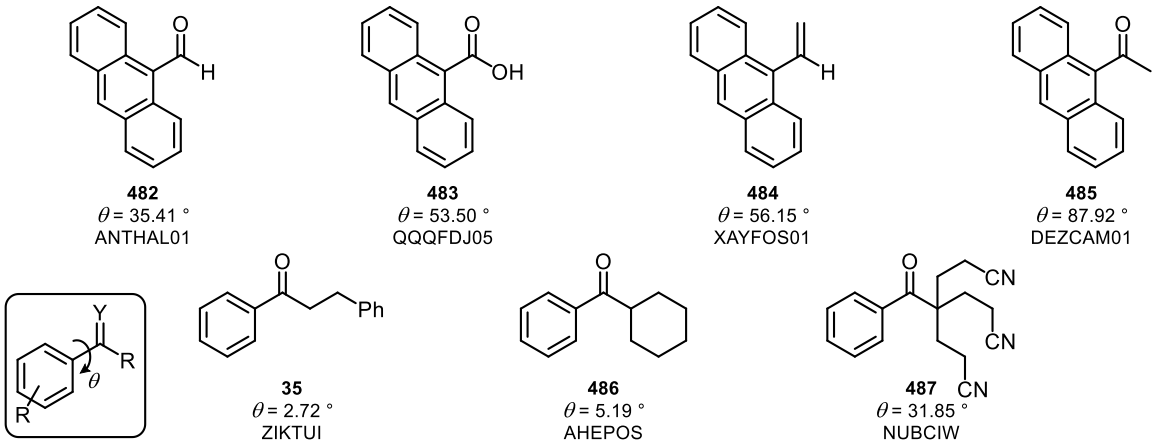
7.1.1 The Interdependence of the Conformation of Aryl Ketones on Steric Interactions between *ortho* and α-Keto Groups

The *ortho* substituents on aryl ketones experience steric interactions with the ketone group, resulting in torsional strain that raises the energy of the coplanar geometry. The preferred conformation of the aryl ketone is one that is, simply, not coplanar, which is the physical basis of the numerous manifestations of the *ortho* effect (see Chapter 1). This conformational preference is most readily and directly studied by X-ray crystallography. However, the average torsional angle between the aryl plane and the carbonyl plane is not likely to be the same for all compounds. Given the crystalline nature of many of these compounds, particularly those with two *ortho* substituents, as well as a wealth of crystallographic data in the Cambridge Crystallography Database Centre,[*] the hydrogen borrowing projects provide an excellent opportunity to further the conformational effects from substitution at the ketone and aryl ring.[†]

The relationship between the size of ketone substituent to the torsional angle θ is best depicted by the anthracene derivatives (Scheme 7.1). The aldehyde possesses a surprisingly large torsional angle, while switching to an acid or a vinyl group increases the torsional angle closer towards an orthogonal geometry. The use of an acetyl substituent, however, results in a virtually perpendicular orientation of the aryl and ketone planes. It is likely that the *peri* hydrogens are the source of the steric interactions with the carbonyl or vinyl groups.

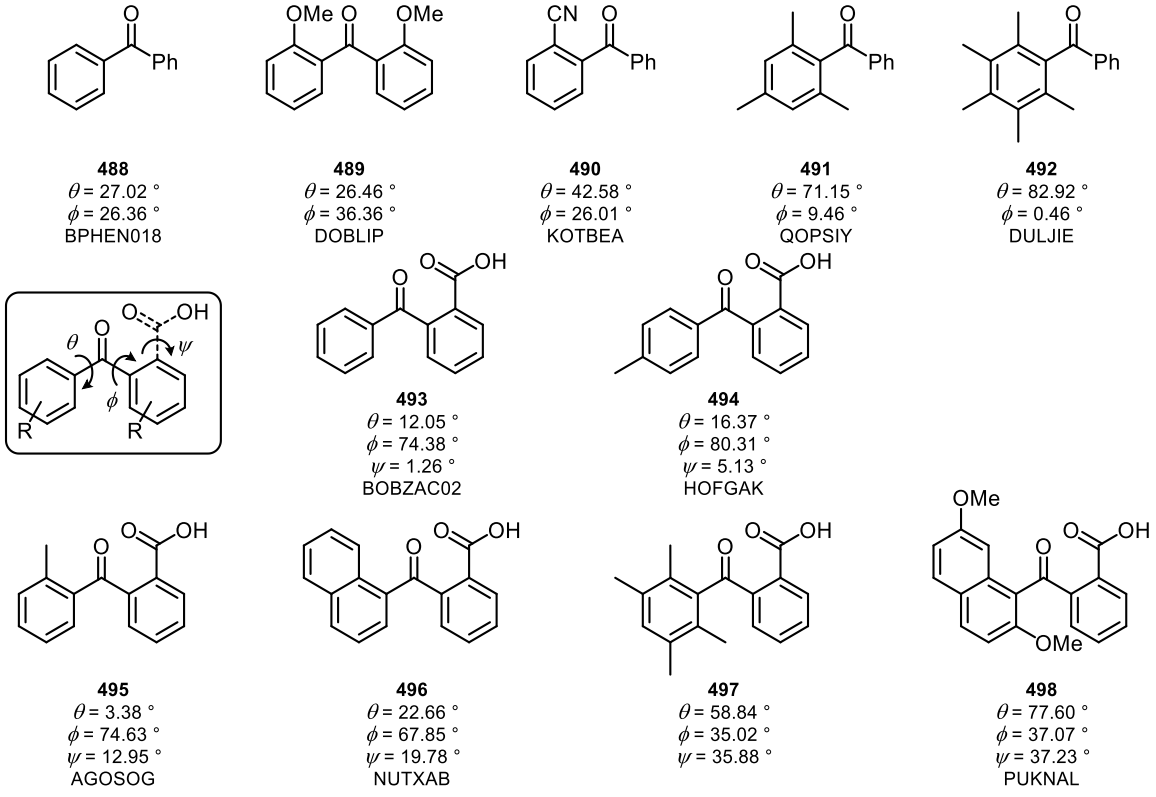
[*] CCDC Database Identifiers have been included for compounds whose data were obtained from the CCDC.

[†] Regrettably, the available data largely clustered around di-*ortho*-substituted aryl ketones due to the low-melting nature of many of the mono-*ortho*-substituted compounds that rendered the preparation and analysis of their single crystals difficult. The skew of data points was not helped by the fact that the hydrogen borrowing reactions performed most favourably on the di-*ortho*-substituted aryl ketones.



Scheme 7.1 *The size of the carbonyl group has a direct impact on the torsional angle θ.*

However, an excessively bulky ketone substituent can complicate matters. For the unsubstituted phenyl ketones, the expected coplanar geometry of the aryl–keto system is not observed for the case of a tetrasubstituted α-keto centre, whereas less bulky ketone groups caused the aryl ketone to display the expected conformation.



Scheme 7.2 *The torsional angles θ, ϕ and ψ are interdependent, and are also affected by the presence of ortho substituents.*

The effect of the size of the *ortho* substituent on θ show an interesting trend for benzophenones (Scheme 7.2). In this case, there are two possible aryl–keto torsional angles, with the torsional angle of the constant benzoyl group defined as ϕ. In the absence of any substituents, both θ and ϕ are relatively small non-zero angles of about 26 – 27 ° and are of *the same sign* (i.e. both rings rotate counter-clockwise *away* from each other). The presence of an *ortho*-methoxy group on both arenes slightly increased the angle of one of the aryl–keto torsional angles, while the other remained very similar.[*] A similar observation was made when an *ortho*-cyano group was present on only one aromatic ring. However, the mesityl and Ph* analogues have a much larger value for θ, while ϕ rapidly approached zero. This not only suggests that the size of the *ortho* substituents influence the torsional angle θ due to steric interactions between both aryl groups, but also that both groups respond to each other to minimise steric interactions.

The derivatives of 2-benzoylbenzoic acids generally displayed conformations consistent with the benzophenones, this time with a third torsional angle ψ. Aryl groups lacking any or possessing only one *ortho* substituent had relatively small torsional angles for θ, although unusually, the *ortho*-methyl analogue had an unexpectedly near-coplanar conformation. The presence of two *ortho* substituents resulted in a significant increase to the torsional angle θ. On the other hand, an increase in the torsional angle θ results in a general decrease in the torsional angle of the other aryl–keto motif, and a general increase in the torsional angle ϕ between the ketone carbonyl group and the aromatic ring of the benzoic acid. The torsional angle about the aryl–carboxylate motif ψ appears to be directly related to the torsional angle θ and inversely related to the angle ϕ. The carboxylic acid appears to be maintaining a proximity of around 2.8 – 3.3 Å (oxygen to oxygen) to the

[*] Regretfully, there is no crystallographic data available for the corresponding benzophenone with the *ortho*-methoxy group present on only one phenyl group.

ketone, although it is longer than the intermolecular dimeric hydrogen bonding distance of about 2.6 – 2.7 Å. The carboxylic acid group of the dimethoxynaphthalene derivative also fits into the cavity between the ketone and the distal methoxy group, suggesting a given amount of steric minimisation between the carboxylic acid and the proximal methoxy group.

7.1.2 A Survey on the Preferred Conformations of Aryl Ketones

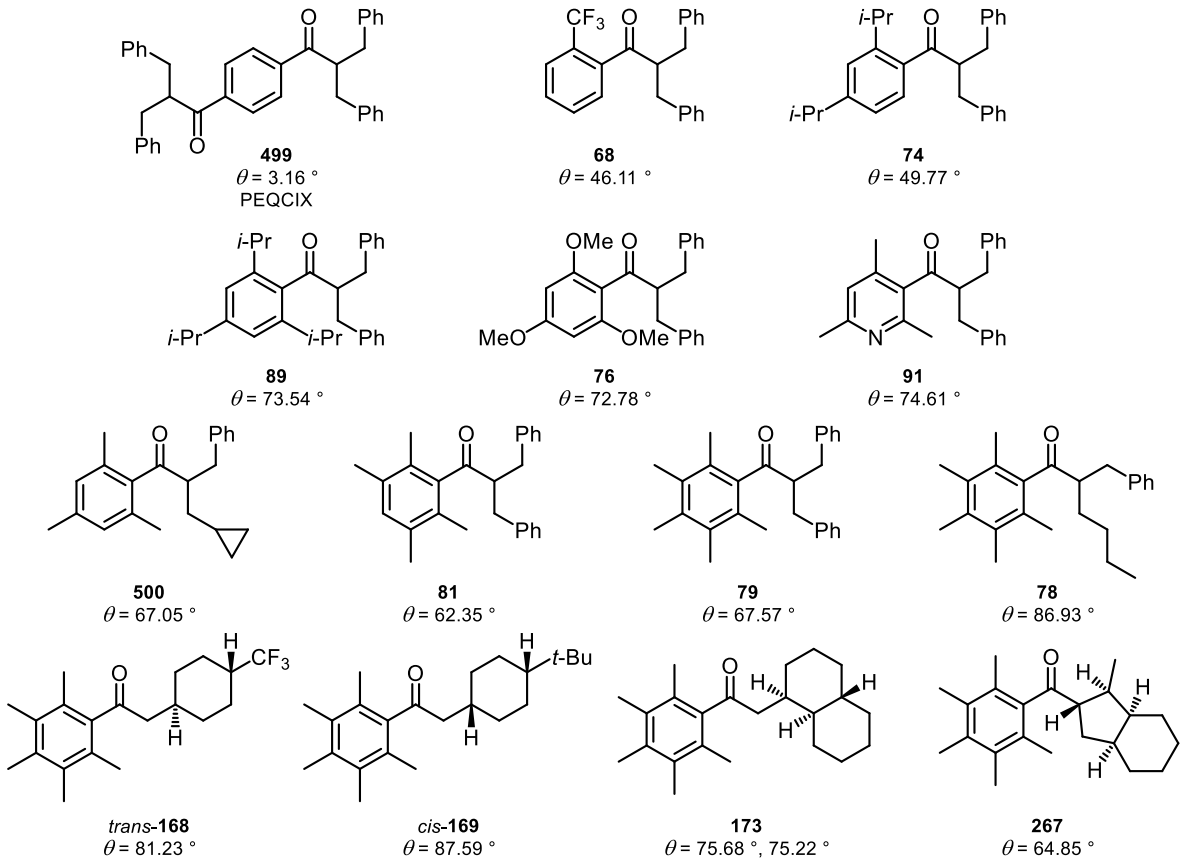
Based on the structural data available, all the compounds and their torsional angles θ (made by the aryl ring and the carbonyl group) generally fall into two categories:

(1) $\theta \leq 50$ °, which includes compounds with no or only one *ortho* substituent, and

(2) $\theta > 50$ °, which comprises all the di-*ortho*-substituted compounds.

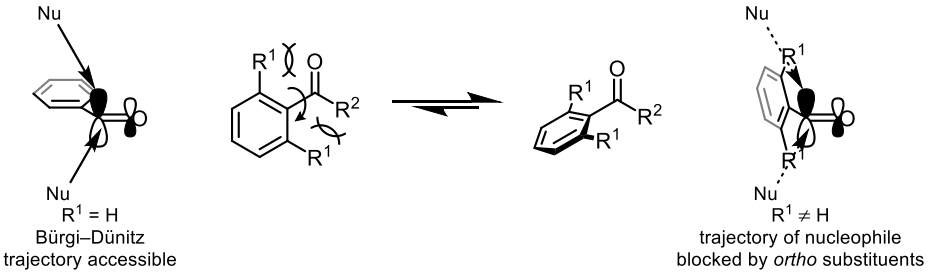
The structures are also classed into four groups. The first group comproses α-, β- and α,β-branched aryl ketone derived from hydrogen borrowing reactions, as well as several 9-anthracenyl and unsubstituted phenyl ketone derivatives. The second group of compounds are enone intermediates from hydrogen borrowing reactions or their precursors. The third set are derivatives of di-*ortho*-methyl aryl ketones that bear a tetrasubstituted α-keto centre. The last set comprises all compounds capable of forming hydrogen bond interactions.

In general, there is no trend that correlates the absolute value of θ with the structural properties of the aryl group or the ketone substituent, with the only obvious observation being the relatively smaller value of θ for mono- or unsubstituted ketones compared to the di-*ortho*-substituted ones.



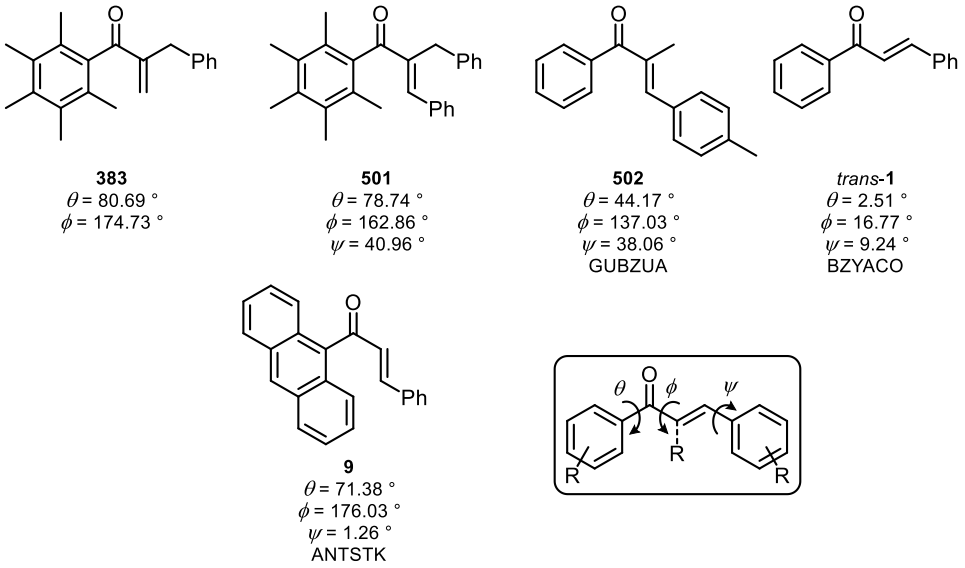
Scheme 7.3 *Torsional angle θ as observed by X-ray crystallographic analysis for α-, β- and α,β-branched products of hydrogen borrowing reactions.*

For di-*ortho*-substituted α- and β-branched aryl ketones, the lack of an observable trend between the size of the *ortho* substituents and the magnitude of θ imply that the precise torsional angles derived from X-ray crystallographic data cannot be used to corroborate the observed reactivity of the various aryl ketones in the hydrogen borrowing reaction (Scheme 7.3, see Schemes 3.11 and 3.18). Nevertheless, this preference of di-*ortho*-substituted aryl ketones to adopt a significantly non-coplanar geometry further reinforces the argument that the *ortho* substituents "protect" the ketone in hydrogen borrowing reactions by sterically shielding nucleophiles from attacking the carbonyl group (Scheme 7.4, see also Scheme 3.32).



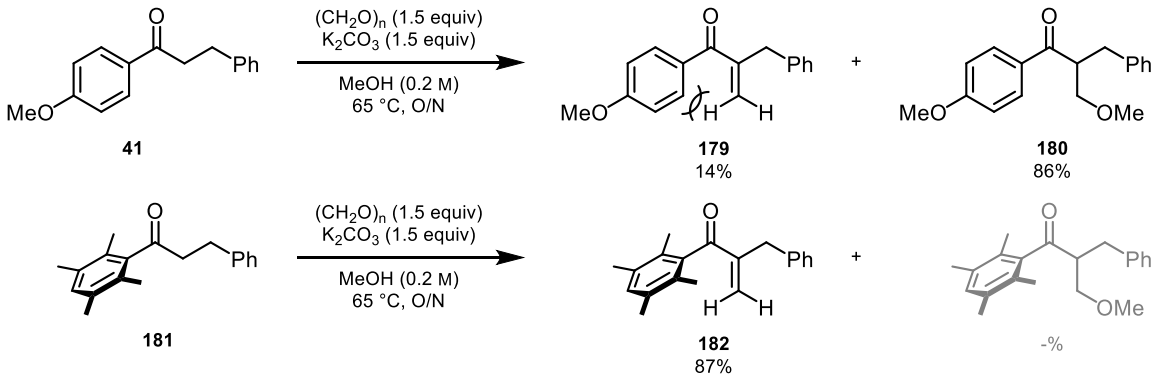
Scheme 7.4 *ortho substituents induce an orthogonal aryl–keto geometry that projects the ortho groups over the π* of the carbonyl group, thereby blocking the approach of nucleophiles.*

An interesting observation for α,β-unsaturated ketones was that the enone motifs were generally coplanar (Scheme 7.5). However, the trisubstituted enone deviated significantly from co-planarity despite possessing no *ortho* substituent, a behaviour very similar to benzophenone. In addition, although the enone for chalcone adopted a cisoid geometry ($\phi \approx 0$ °), the anthracenyl derivative and the 1,1-disubstituted enones possess a transoid conformation instead ($\phi \approx 180$ °). It is unclear whether the transoid geometry for the anthracenyl enone is due to packing effects or the minimisation of steric interactions with the aryl group on the ketone in a similar fashion to the benzophenones. Unusually, the styrene motif in the trisubstituted enones deviated from coplanarity compared to the disubstituted enones. It is possible that packing and lattice interactions could distort the conformation of the styrene given that the benzyl pendant is oriented in an orthogonal or antiperiplanar geometry to the olefin, which would preclude intramolecular steric interactions as the source of this distortion.



Scheme 7.5 *Torsional angles θ, ϕ and ψ for various enones. Note: a planar cisoid geometry about the enone is defined by its torsional angle ϕ = 0 °.*

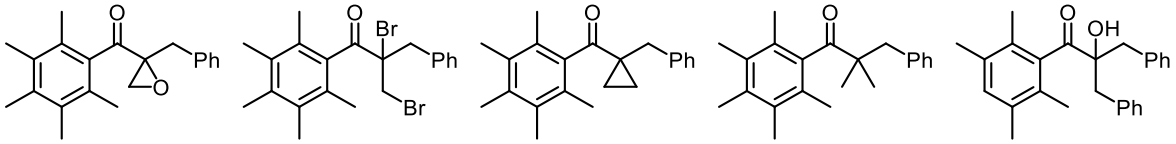
The co-rotational behaviour of the enones and benzophenones is indicative of steric interactions between the aryl ring and the enone system (see Schemes 7.2 and 7.5), and would provide a structural basis for the favourable formation of enones by di-*ortho*-substituted aryl ketones under thermodynamic conditions compared to their non-*ortho*-substituted counterparts (Scheme 7.6, see also Schemes 3.22 and 3.29).



Scheme 7.6 *The presence of ortho-methyl substituents appears to disfavour the formation of aldol adducts and promote $E1_{CB}$, which could be attributed to destabilising steric interactions between the aryl ring and the enone in the absence of ortho substituents.*

The torsional angles θ for the α-tetrasubstituted ketones are large, indicating their preference for non-coplanar conformations about the aryl ketone (Scheme 7.7). The α-keto heteroatoms were oriented either orthogonally to the plane of the ketone as in the case of

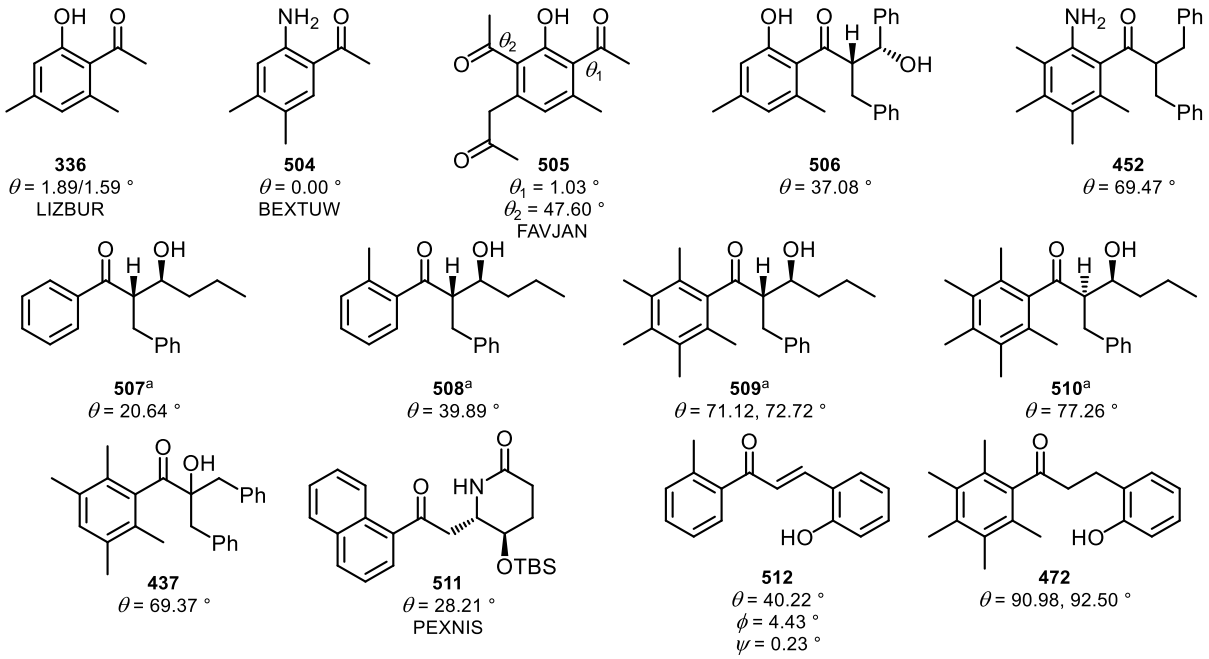
the bromide, or in an antiperiplanar geometry to the carbonyl group as in the cases of the α-oxyketones. The cyclopropane appeared to behave like an enone, with one of the cyclopropyl C–C bonds being oriented nearly antiperiplanar to the carbonyl group in a fashion very similar to the methylene enone precursor. In contrast, the *gem*-dimethyl ketone did not exhibit any unusual conformation observed in the other cases. It is worth noting that almost all these ketones have their alkyl groups oriented in synperiplanar, orthogonal or antiperiplanar geometries relative to the carbonyl group that would potentially minimise steric interactions with the ketone aryl group.



382 θ = 80.32 ° **385** θ = 76.71 ° **381** θ = 77.94 ° **503** θ = 80.55 ° **437** θ = 69.37 °

Scheme 7.7 *Torsional angle θ for tetra- and pentamethyl-substituted phenyl ketones with tetrasubstituted α-keto centres.*

The presence of intramolecular hydrogen bonding from adjacent hydroxy or amino groups results in acetyl groups adopting a near-coplanar geometry even with the presence of another *ortho*-methyl group (Scheme 7.8). In the presence of only one hydrogen donor but multiple hydrogen acceptors, the non-hydrogen bonded ketone with a flanking alkyl group was not coplanar. Similarly, the α-branched tetramethylaniline and *ortho*-phenols deviated significantly from coplanarity, suggesting that in this case the large α-branched ketone group was responsible for the increased steric interaction that results in the deviation from coplanarity.

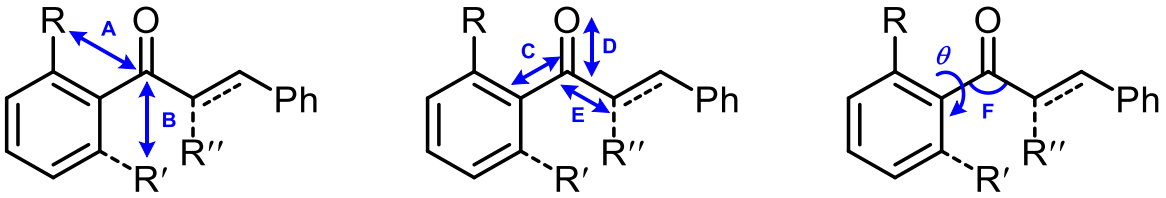


Scheme 7.8 *Torsional angles θ, ϕ and ψ for ketones with hydrogen bonding interactions present. [a]The compounds were synthesised and suitable single crystals prepared by Dr. James Frost.*

A small number of suitable structures with a hydrogen bond donor in a 1,3-relationship to the carbonyl group could be used for comparison of the effects of hydrogen bonding from the ketone substituents. The *ortho* substituents increased θ in a similar fashion to the previous groups. For the butanal aldol adducts, the unsubstituted phenyl analogue did not have a coplanar geometry although the value of θ was relatively small. Similar observations were made for other hydrogen bonding partners in 1,2-, 1,3- and 1,5-relationships to the ketone.

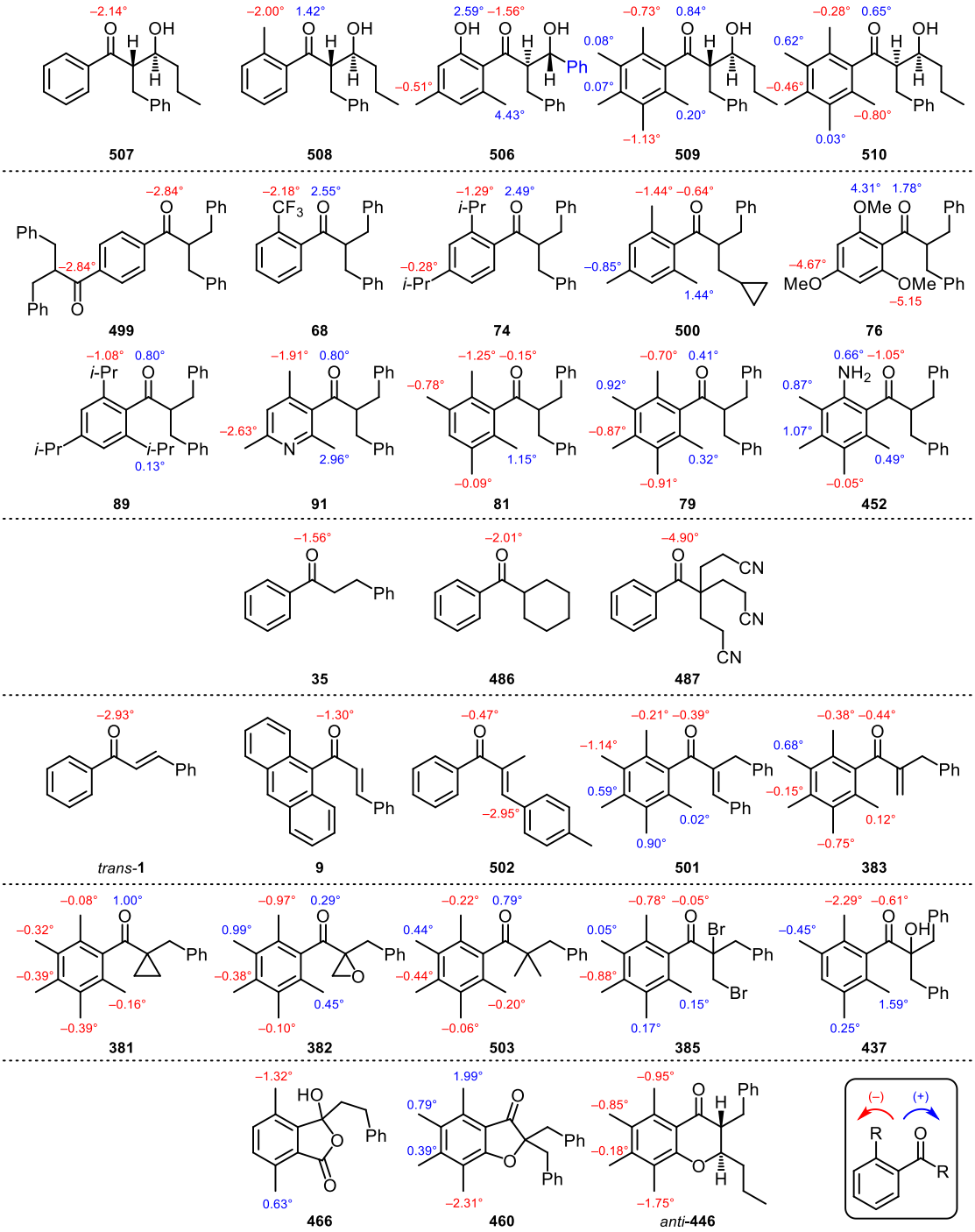
7.1.3 Structural Deformations at the Aromatic Ring as Indicators of the *ortho* and "Buttressing" Effects

X-ray diffractometry is often regarded as the gold standard for structural determination of compounds as it can determine the arrangement of atoms and provide their bond lengths and angles to very high precision. The availability of structural data for numerous aryl ketones and enones of similar structures presents an excellent opportunity to study the impact of the *ortho* and "buttressing" effects on the structure of the aryl ketone (Table 7.1).



No.	Dihedral Angle θ (°)[a]	Σ Aryl Bonds (Å)	Inter-substituent Distance (Å)[b]		Bond Lengths (Å)			Angle (°)
			A	**B**	**C**	**D**	**E**	**F**
507	20.64	8.343	-	-	1.497	1.218	1.524	120.28
508	39.89	8.358	3.013	-	1.499	1.217	1.530	119.52
506	37.08	8.380	(2.969)	2.974	1.483	1.228	1.533	121.22
509	71.12	8.402	2.954	2.887	1.509	1.210	1.534	116.56
	72.72	8.411	2.938	2.905	1.513	1.210	1.533	115.71
510	77.26	8.412	2.930	2.882	1.511	1.217	1.531	115.33
499	3.16	8.268	-	-	1.485	1.217	1.512	120.06
68	46.11	8.338	(3.044)	-	1.506	1.214	1.522	119.13
74	49.77	8.376	(3.032)		1.502	1.217	1.526	118.00
76	72.78	8.352	(2.780)	(2.680)	1.503	1.215	1.522	116.61
500	73.54	8.380	2.955	2.932	1.511	1.212	1.533	118.34
89	74.61	8.270	3.009	2.943	1.505	1.219	1.525	117.79
91	67.05	8.370	2.944	2.974	1.512	1.211	1.531	116.96
81	62.35	8.396	2.937	2.939	1.508	1.213	1.532	116.84
79	67.57	8.411	2.935	2.904	1.509	1.209	1.530	117.23
452	69.47	8.423	(2.822)	2.910	1.507	1.217	1.527	117.72
35	2.72	8.259	-	-	1.494	1.219	1.493	119.70
486	5.19	8.339	-	-	1.503	1.227	1.516	120.55
487	31.85	8.308	-	-	1.505	1.222	1.551	122.97
trans-**1**	2.51	8.308	-	-	1.498	1.204	1.479	118.44
9	71.38	8.447	(2.904)	(2.940)	1.507	1.214	1.458	119.70
502	44.17	8.343	-	-	1.495	1.225	1.494	119.67
501	78.74	8.410	2.910	2.899	1.513	1.220	1.494	119.62
383	80.69	8.411	2.900	2.917	1.512	1.215	1.494	117.14
381	77.94	8.416	2.928	2.889	1.513	1.218	1.491	119.22
382	80.32	8.412	2.934	2.881	1.512	1.209	1.511	118.78
503	80.55	8.411	2.936	2.891	1.511	1.213	1.551	119.30
385	80.32	8.408	2.953	2.905	1.505	1.211	1.554	119.32
437	69.37	8.392	2.961	2.951	1.516	1.216	1.551	119.39

Table 7.1 *Bond lengths, angles and torsional angle θ for variously substituted aryl ketones (see Scheme 7.9. for their structures). Values in parentheses indicate non-CH_3 groups.*



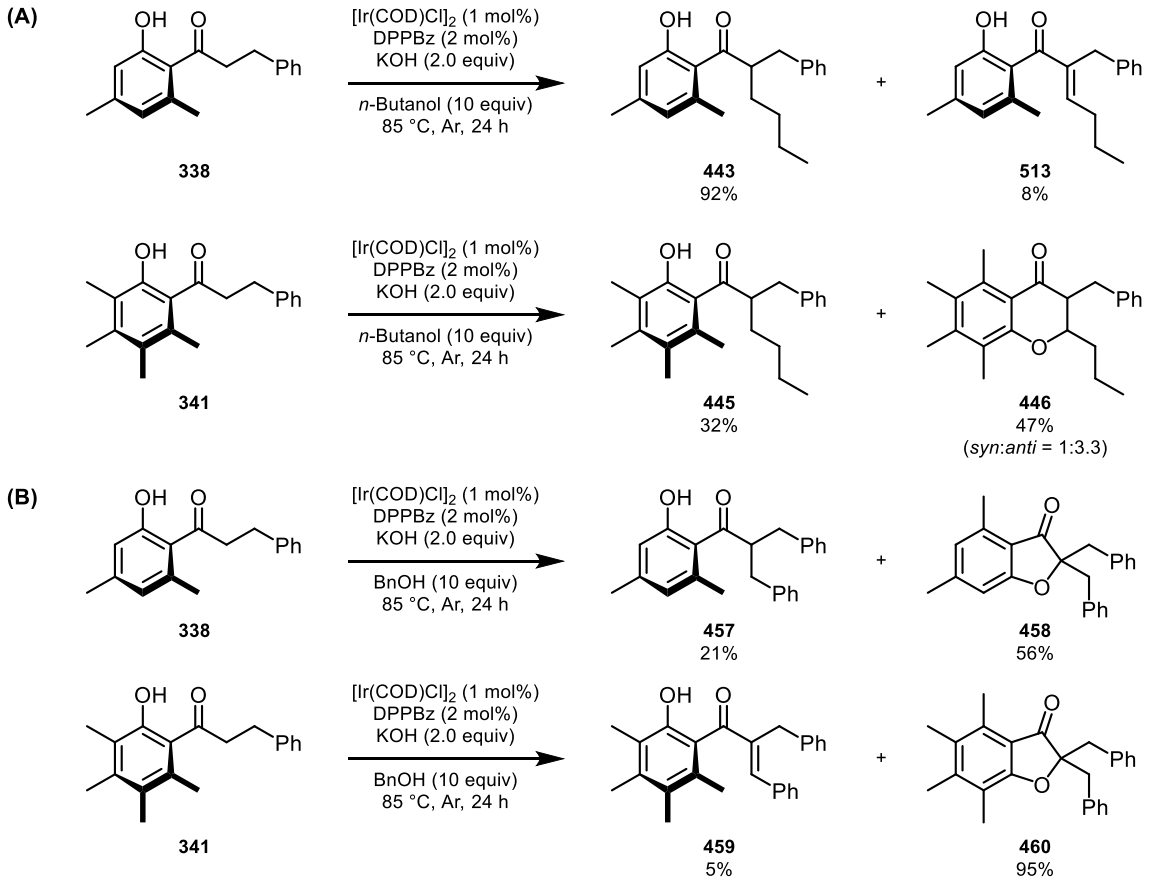
Scheme 7.9 *Structures of compounds in Table 7.1, and their angular displacements from 180 °. Positive values (in blue) indicate a clockwise angular displacement as drawn, and negative values (in red) indicate an anticlockwise displacement. See Schemes 7.1, 7.2, 7.3, 7.5 and 7.8 for their respective CCDC Database identifiers.*

The aromatic ring is gradually expanded with increasing number of substituents as indicated by the sum of all aryl bonds, with the pyridine and anthracene derivatives as the only exceptions to this series of compounds due to their different bonding properties. In addition, for the *ortho*-methyl substituted arenes, an increase in number of substituents results in a generally shorter distance between the *ortho*-methyl carbon and the carbonyl centre, suggesting a structural basis for the "buttressing" effect of the *meta* and *para* substituents.

Although a single measurement of individual single crystals by X-ray diffraction cannot easily indicate how flexible or "buttressed" the *ortho* substituents are, the structural data can be used to infer the presence or absence of significant distortions in substituent geometry from their expected positions. Any deviations in the aryl–substituent bond angles arising from steric repulsion between the *ortho* groups and the ketone could be suppressed by the flanking or "buttressing" *meta*- and *para*- substituents. Indeed, the introduction of *meta*- and *para*-methyl groups led to reduced deviations in the bond angles about the *ipso* carbons of the *ortho* substituents and the ketones. The comparatively larger CF_3 group experienced significant angular displacements, but a similar effect was not observed for the isopropyl groups as the methine hydrogens are oriented towards the ketone, thereby minimising steric interactions. The *ortho*-methoxy groups were pushed unusually far back, while the small size of the *ortho*-amino group and the presence of intramolecular hydrogen bonding caused it to be displaced significantly towards the ketone. The short C–N bond on the pyridine caused a greater angular displacement of the adjacent *ortho*-methyl group away from the ketone.

Very interestingly, the carbonyl substituent for all the non-*ortho*-substituted aryl ketones have a smaller angle on the oxygen side of the carbonyl group, suggesting that the oxygen atom is indeed smaller than the substituents on the ketone. This behaviour is also observed for the enones, including their styrene aryl groups.

A similar deviation in bond angles was also observed for several cyclic products. The presence of four methyl groups on the aromatic ring of the benzofuranone results in a significant displacement of the outer methyl groups towards the cavity between the five- and six-membered rings. On the other hand, the lactol does not have two inner methyl groups, and displayed a displacement *away* from the five-membered ring. Interestingly, all four methyl substituents of the chromanone were displaced in the same direction away from the carbonyl motif and towards the cavity adjacent to the phenoxy oxygen atom. These results show that adjacent methyl groups directly "buttress" each other, and it is reasonable to suggest that this "buttressing" effect from flanking methyl groups is the cause of the increased yield of benzofuranone **459** compared to benzofuranone **458** as well as the isolation of chromanone **446** when phenols **338** and **341** were subjected to the hydrogen borrowing reactions (Scheme 7.10).



Scheme 7.10 *Comparison of reaction outcome of ortho-hydroxy ketones in hydrogen borrowing reactions in (A) n-butanol, and (B) benzyl alcohol.*

7.1.4 Structural Changes about the Carbonyl Group due to *ortho* and α-Keto Substitutions

Compounds with generally coplanar aryl–keto geometry have slightly shorter aryl–keto bonds (c.a. 0.01 – 0.02 Å) than those that deviate from coplanarity, particularly in the presence of *ortho* substituents, although this variation in length is miniscule and unlikely to be of significance. In contrast, the C=O bond was essentially in the same region of 1.21 Å for all the compounds surveyed. The enones displayed similar to slightly longer carbonyl bond lengths, with the only exception being chalcone that displayed a shorter bond length despite an expected *decrease* in bond order given the high degree of coplanarity between the carbonyl, arene and olefin groups.

The C–C bond between the carbonyl group and the α-keto carbon also displayed a corresponding decrease in bond length with increased bond order. The number of α-keto substituents had a significant impact on the length of this bond, whereas the presence of *ortho* substituents had negligible effect on its length. This is clearly observed in the enones and the unsubstituted phenyl ketones. Very interestingly, the α-epoxy and *gem*-dimethyl ketones behaved like α-tetrasubstitued ketones whereas the α-keto cyclopropyl group had a bond length between that of the enone and the α-tetrasubstituted ketone. The cause of this intermediate bond length is likely attributed to the partial π-like character of the cyclopropane.

Increasing the number of substituents on the α-keto centre increases the C–C(O)–C carbonyl bond angle, as expected from a greater steric bulk associated with a larger ketone substituent. However, the presence of *ortho* substituents on the aromatic ring *decreases* this angle, implying that the aromatic ring become "smaller". This unusual behaviour indicates an alleviation in steric interactions between the ketone substituent and the *ortho*-substituted aromatic ring, which is consistent with the observation by Heathcock et al. on the unusually "small" size of the mesityl group in the formation of lithium enolates (see Section 3.4.2).[130]

Unfortunately, the π-systems for the enones and benzophenones rotate in response to steric interactions from each other, which complicates the analysis of the bond lengths and angles about the carbonyl centre.

In summary, based on the observed torsional angles, bond lengths and bond angles derived from X-ray crystallographic analysis of aryl ketones, the following key observations were made:

- The aryl–ketone torsional angle θ is affected by size, conformation and sterics from *ortho* groups (if present) *and* the ketone substituent. Consequentially, unsubstituted aryl ketones do not necessarily have a near-zero value for θ.
- Torsional angles θ, ϕ and ψ are interdependent.
- Unsubstituted or mono-*ortho*-substituted aryl ketones have comparatively smaller torsional angles (≤ 50 °) than di-*ortho*-substituted aryl ketones (> 50 °).
- In some cases, hydrogen bonding can induce a coplanar aryl–ketone geometry.
- Substituents on the aromatic ring cause the aryl ring to expand slightly.
- The length of the carbonyl–α-keto bond generally correlates to the bond order. However, the carbonyl C=O bond length was much less responsive to changes in bond order.
- Substitution at the α-keto centre lengthens the carbonyl–α-keto bond, whereas *ortho* substituents on the aryl group did not contribute to this effect.
- Substitution at the α-keto sp^3 centre increases the C–C(O)–C bond angle about the carbonyl group, whereas *ortho* substitution on the aromatic ring *decreases* this angle.

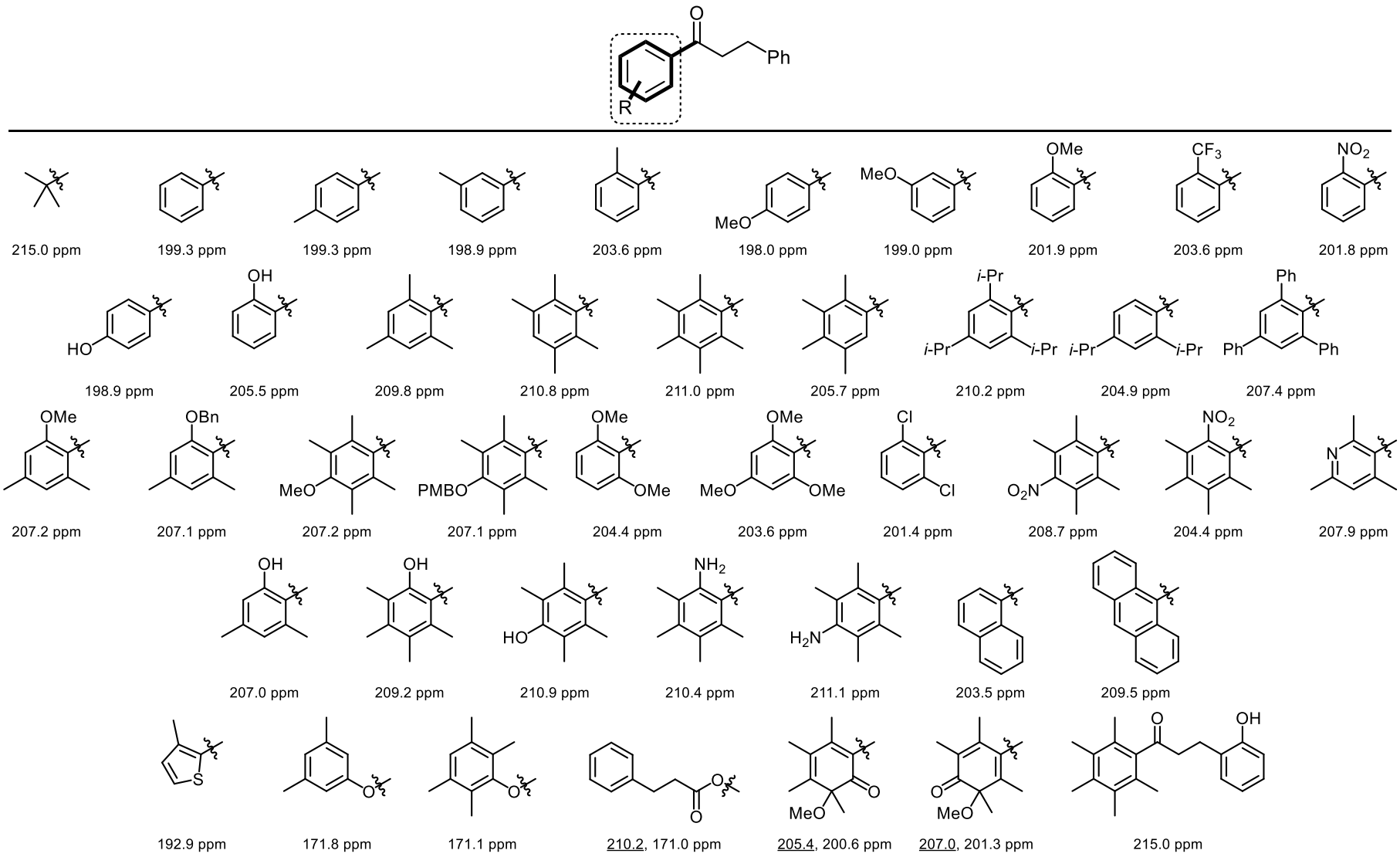
7.2 Studies on the *ortho* Effect using IR, ^{13}C and ^{15}N NMR Spectroscopy

One of the drawbacks of X-ray crystallography is that it can only analyse a given polymorph of the compound in the solid state, and so the conformation of the structures in the unit cell is an amalgamation of multiple factors that would not necessarily be representative of the interactions experienced in a disordered bulk phase or in solution. In this respect, NMR and IR spectroscopy can provide more relevant data, but these methods are more indirect as they observe the chemical shifts and the bond stretching frequencies of the carbonyl groups that respond to the conformation of the aryl ketone.

Nevertheless, NMR and IR spectroscopy could enable the assessment of any electronic effects that would not necessarily be obvious by X-ray diffractometry. In addition, these techniques are very easy and quick to perform, and the data processing and analysis is significantly less complex than X-ray diffractometry. Therefore, a broad range of isomers can be systematically investigated to minimise any undesired effects from variations in remote parts of the structure.

7.2.1 Analysis of ^{13}C NMR Chemical Shifts of the Carbonyl Group in Aryl Ketones

Compared to the *tert*-butyl ketone, the phenyl ketone has a considerably lower chemical shift (Scheme 7.11). The introduction of methyl or methoxy groups in the *para* or *meta* positions has negligible influence on the carbonyl group, but substitution at the *ortho* position results in very significant changes to the chemical shift of the carbonyl group. The introduction of the *ortho*-trifluoromethyl group was equally effective, while the *ortho*-nitro and *ortho*-methoxy exert a slightly smaller effect. The hydroxy motif also displayed similar effects, although the deceptively higher chemical shift of the *ortho*-hydroxy ketone is likely attributed to intramolecular hydrogen bonding to the carbonyl group (*vide infra*).



Scheme 7.11 *^{13}C NMR data various aryl ketones and related analogues in $CDCl_3$.*

The introduction of a second *ortho*-alkyl group further increases the chemical shift of the carbonyl group, while the presence of additional alkyl substituents at the other positions appear to boost the *ortho* effect slightly. The removal of one *ortho*-methyl or isopropyl group decreases the chemical shift of the carbonyl by over 5 ppm. The unusually shielded carbonyl group of the 1,3,5-triphenylphenyl derivative could be due to the anisotropy of the *ortho*-phenyl groups that would prefer to be in an orthogonal conformation to the central aromatic ring, thus leading to an upfield shift.

When one *ortho*-methyl group was replaced with an *ortho*-alkoxy group, the increase in chemical shift is smaller than for the case with two *ortho*-methyl substituents, while the di-*ortho*-methoxy and di-*ortho*-chlorophenyl ketones have very similar carbonyl chemical shifts to the mono-*ortho*-substituted aryl ketones. In contrast, replacement of the *para*-methyl group with *para*-alkoxy groups caused negligible variation in the chemical shift. The *para*-nitro analogue of the Ph* ketone only had a modest difference with its parent compound, whereas the *ortho*-nitro analogue also had a carbonyl chemical shift similar to a mono-*ortho*-substituted aryl ketone. These observations suggest that the nitro, methoxy and chloro motifs are less effective at inducing steric inhibition of resonance compared to the methyl groups. Unusually, the pyridyl ketone also had a smaller increase in chemical shift, which might be attributed to small structural changes associated with a shorter C–N bond within the aryl ring.

Interestingly, the trimethoxyphenyl ketone had a lower chemical shift than the dimethoxy analogue whereas the *para*-alkoxy analogues were unchanged, indicating that electronic effects from substituents may not be completely suppressed but are dependent on the *ortho* substituents present. Because the observed chemical shift carbonyl group is a time-averaged value of all the conformers in their respective population distributions, it is

possible that the *ortho*-methoxy groups are less effective at inducing steric inhibition of resonance, with a larger population of the molecules having a more coplanar conformation in which the mesomeric effects from the substituents are in play.

The replacement of *ortho*- or *para*-methyl groups with the hydroxy or amino motifs also resulted in comparatively higher carbonyl chemical shifts compared to their mono-*ortho*-substituted counterparts, although the presence of possible intra- and intermolecular hydrogen bonding effects will complicate attempts to interpret the effectiveness of these motifs at inducing steric inhibition of resonance (*vide infra*). On the other hand, the naphthyl and anthracenyl ketones were analogous to mono- and di-*ortho*-methyl-substituted phenyl ketones in their ability to induce steric inhibition of resonance.

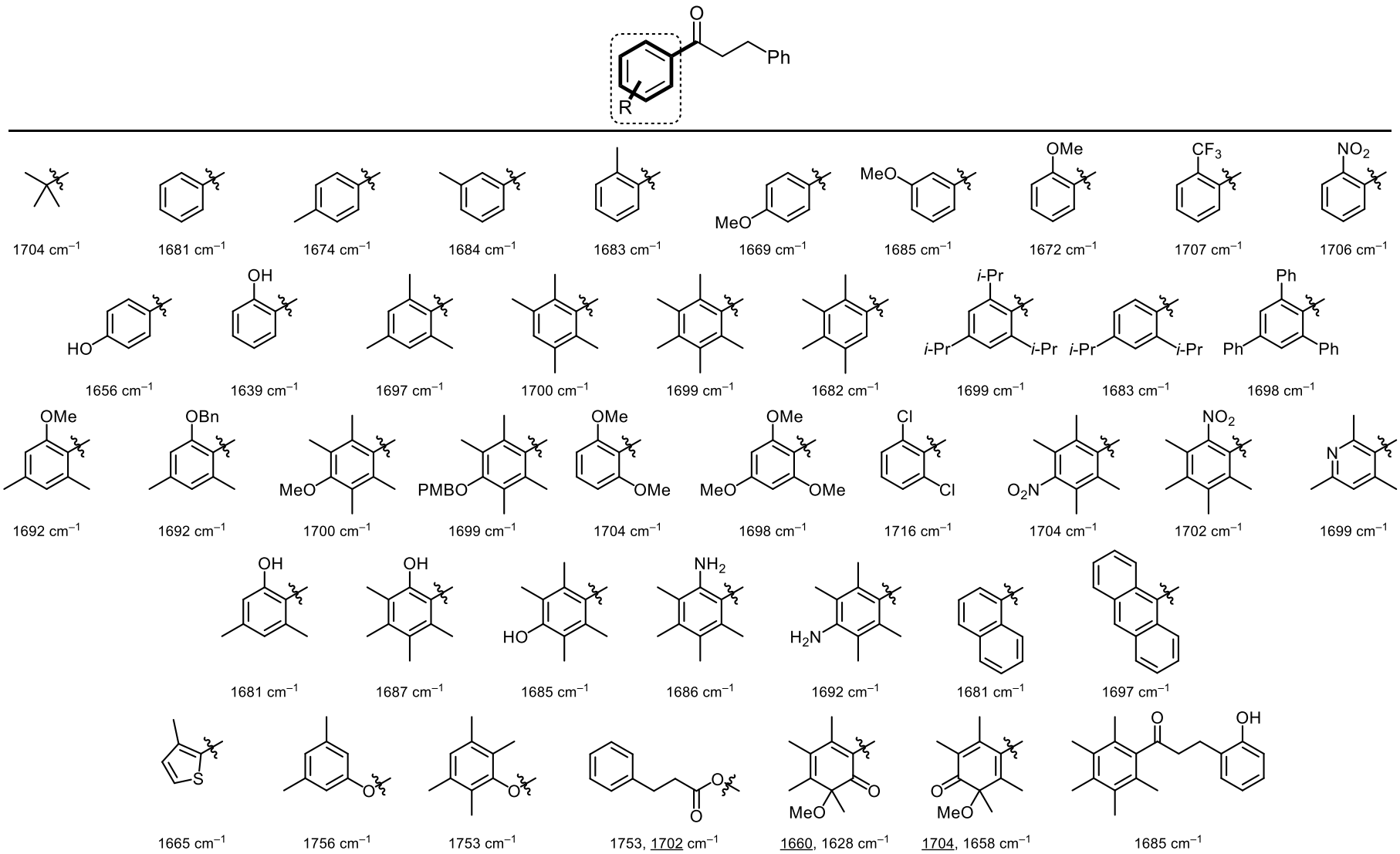
The electron-rich thiophene derivative not only did not effect any steric inhibition of resonance, but also instead weakened the carbonyl group leading to an even lower chemical shift, indicating the crucial role of geometry in enabling the *ortho* effect. The *ortho*-methyl substituents did not affect the chemical shifts of the ester derivatives, although for the cyclohexadienone systems they could inhibit conjugation between the endocyclic olefin and the exocyclic carbonyl group even when the aromatic ring is disrupted, which would otherwise have resulted in a conjugated enone system. The effect of intramolecular hydrogen bonding is best exemplified by the 2′-hydroxyphenyl derivative of the Ph* ketone, which gives a further increase in chemical shift of the carbonyl group by 4 ppm.

These observed trends are consistent with the increase in carbonyl bond order from the steric inhibition of resonance induced by the *ortho* substituents, and are in agreement with those in literature, such as those for the acetophenones (see Section 1.5).

7.2.2 Analysis of IR Stretching Frequencies of the Carbonyl Group in Aryl Ketones

The C=O stretching frequency data largely reflect the trends observed in the ^{13}C NMR analysis, the primary difference being the greater sensitivity to electronic effects for the mono-*ortho*-substituted aryl ketones (Scheme 7.12). The effectiveness of the *ortho*-methyl groups at silencing electronic effects from other mesomeric substituents compared to *ortho*-methoxy groups is further exemplified here, although the comparatively higher stretching frequency of 2,6-dimethoxyphenyl ketone indicates that the *ortho*-methoxy groups also present a strong inductive effect. Unusually, the *para*-nitro ketone displays a higher stretching frequency than the corresponding Ph* ketone despite the silencing effects of the two *ortho* substituents. This anomalous behaviour will be discussed in Section 7.5. The presence of hydrogen bonding results in a decrease in stretching frequency, as opposed to the increase in chemical shift of the carbonyl group in ^{13}C NMR, so it becomes clear that the presence of flanking methyl groups and *ortho*-methyl substituents limit the effectiveness of intra- and intermolecular hydrogen bonding.

Both ^{13}C NMR and IR spectroscopic data support the presence of the *ortho* effect that favours the non-coplanar conformation of the *ortho*-substituted ketones, which relates to the yield of these ketone substrates in the hydrogen borrowing reaction with alcohols (see Scheme 3.11). Based on IR spectroscopic analysis, it is noteworthy that di-*ortho*-substituted aryl ketones present a more orthogonal geometry and that mono-*ortho*-substituted aryl ketones appear to have a more coplanar geometry and behave like unsubstituted aryl ketones, which is in line with the observations by Fiedler and Exner.[29]



Scheme 7.12 *Thin-film IR data for various aryl ketones and related analogues.*

7.2.3 The Amino Group and the *ortho* Effect

One of the unusual outcomes of the hydrogen borrowing reaction was the formation of ketone reduction and cyclisation side products when an *ortho*-amino group is present on the aryl ketone. The formation of these side products suggests that the average population of the ketone and aryl rings are not as significantly twisted out of plane compared to the di-*ortho*-methylphenyl ketones, resulting in a decreased protective effect of the ketone.

A survey of the ^{13}C NMR and IR stretching frequency data of the carbonyl group for the relevant derivatives indicates a complex interaction at play (Table 7.2). The ^{13}C NMR data appear to show that the *ortho*-amino group exerts some degree of steric effect that, in combination with four other methyl substituents on the aromatic ring, increases the chemical shift of the carbonyl centre, surpassing the additive effect of the individual cases.

On the other hand, the electron-donating amino group results in a weakening of the carbonyl bond that causes the stretching frequency to significantly decrease, an effect which is not reflected in the ^{13}C NMR data. The presence of four methyl groups at the other positions has negligible effect on the carbonyl stretching frequency, but the appropriate combination of both the amino and methyl groups result in a further increase in the stretching frequency. The possible formation of hydrogen bonding interactions between the *ortho*-amino group and the ketone would complicate the interpretations of the steric effects of the amino group on the chemical shift and stretching frequency of the carbonyl group.

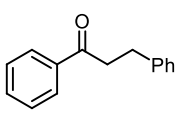
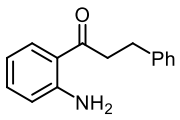
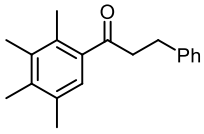
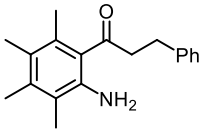
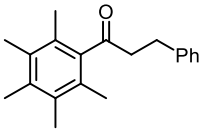
Compound					
^{13}C NMR	199.3	201.5	205.7	210.4	211.0
IR (C=O)	1681	1650	1682	1686	1699

Table 7.2 *Comparison of NMR and IR data on the impact of the ortho effect on the electronics of aryl ketones with or without* ortho-*amino substituents is complicated by the effects of hydrogen bonding.*

A slightly different approach would have to be taken to illustrate the small "size" of the amino group without interference from intramolecular hydrogen bonding. In this case, the ^{15}N chemical shift of the amine nitrogen and the ^{13}C chemical shifts of the aromatic ring carbons are studied to highlight the effective size required to induce any *ortho* effect (Table 7.3).

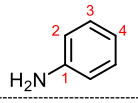
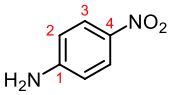
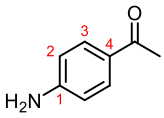
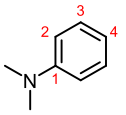
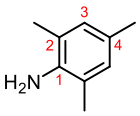
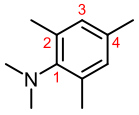
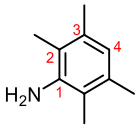
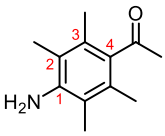
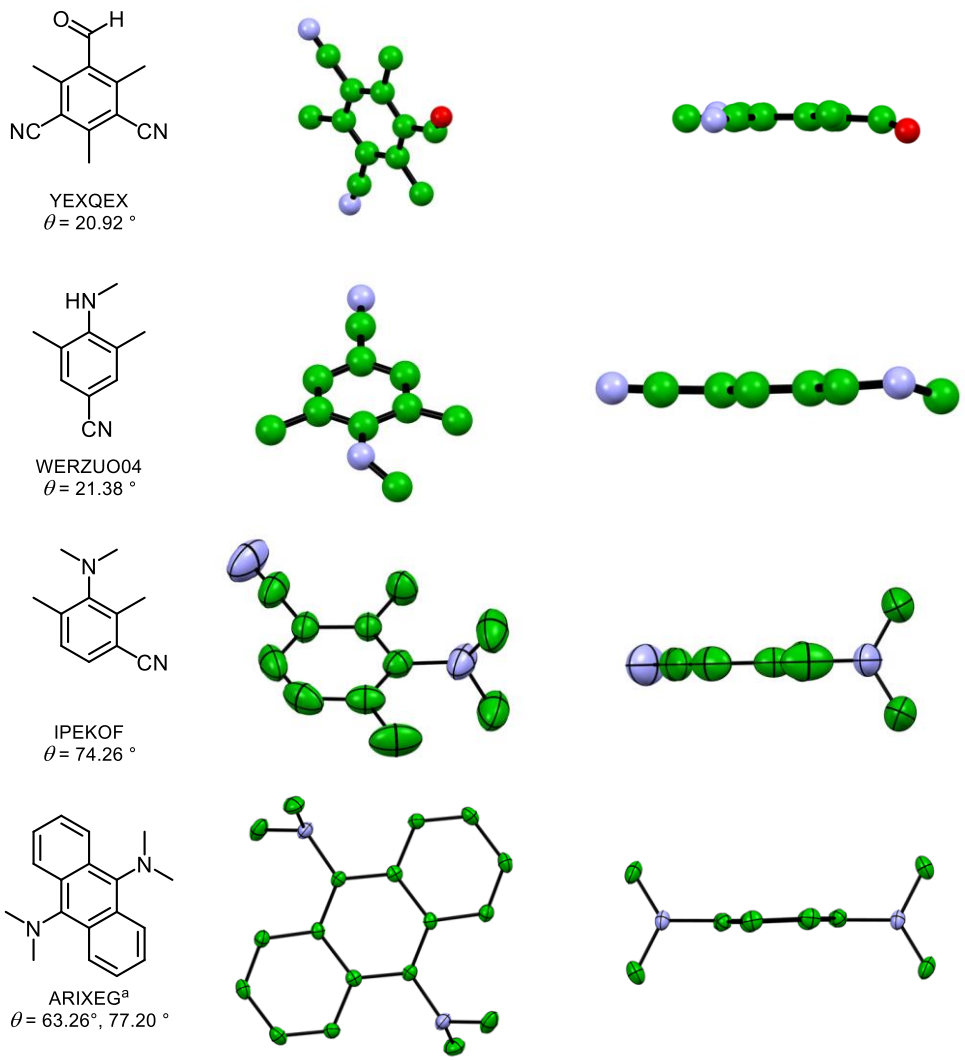
Entry	Compound	^{13}C NMR					^{15}N NMR	IR (C=O)
		C1	C2	C3	C4	C=O		
1		146.5	115.1	129.3	118.6	-	55.2	-
2		152.6	113.5	126.5	139.2	-	65.7	-
3		151.6	113.6	130.8	127.3	196.7	63.3	1650
4		150.7	112.7	129.1	116.7	-	44.8	-
5		140.2	121.9	128.9	127.1	-	48.4	-
6		147.2	137.1	134.3	129.6	-	16.0	-
7		142.8	118.1	133.8	122.1	-	51.6	-
8		143.0	118.3	128.1	134.5	210.3	53.5	1688

Table 7.3 *Comparison of NMR and IR data on the impact of the ortho effect on anilines.*

Compared to the parent unsubstituted aniline (Entry 1), electron-withdrawing groups at the *para*-position deshield the amino nitrogen and the corresponding C1-carbon. In contrast, methyl substituents on the nitrogen or aromatic ring increase the shielding around the nitrogen. These observations are consistent with the changes in electron density on the

nitrogen atom. Remarkably, the combined presence of methyl substituents on both *ortho* positions and the nitrogen result in a drastic decrease in nitrogen chemical shift as well as significantly increased deshielding character about the C2 and C3 carbons exceeding the additive effects of each individual case.



Scheme 7.13 *Torsional angles of di-ortho-substituted aldehydes and anilines. Hydrogen atoms have been omitted for clarity. Thermal ellipsoid data was not available for this compound.*

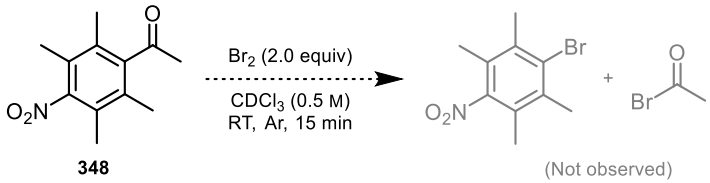
A final piece of evidence for the small size of the unsubstituted amino group comes from X-ray crystallographic data of *N*-methyl and *N*,*N*-dimethylanilines. The presence of only one *N*-methyl group on the aniline resulted in a small torsional angle that was comparable to the di-*ortho*-methyl substituted benzaldehyde (Scheme 7.13). However, the introduction

of a second *N*-methyl group led to a near-orthogonal conformation of the aniline, which suggests that the unsubstituted amino group is small compared to the ketone group and would not likely exert a significant steric effect on an *ortho*-ketone group, whereas the *N*,*N*-dimethylamino group is comparatively larger and experiences steric inhibition of resonance due to the *ortho* effect. The same effect was also observed for the anthracene derivative.

Collectively, these results are in very good agreement with the conclusions made by Burgers et al. based on their data from electronic absorption spectroscopy, that *N*,*N*-dialkylated anilines are significantly twisted out of conjugation by the *ortho* substituents whereas unsubstituted or *N*-monosubstituted anilines are not significantly affected.[13]

7.2.4 The Impact of the *ortho* Effect on Nitrobenzenes

In Chapter 5, it was shown that the Br_2-mediated cleavage of the acyl group was unsuccessful for nitrobenzene **348**, suggesting that the aryl rings were more electron-deficient compared to the ketone analogues (Scheme 7.14, see also Scheme 5.22). This result suggests that the nitro group was either not twisted out of co-planarity with the phenyl ring, or that it has a potent inductive effect.

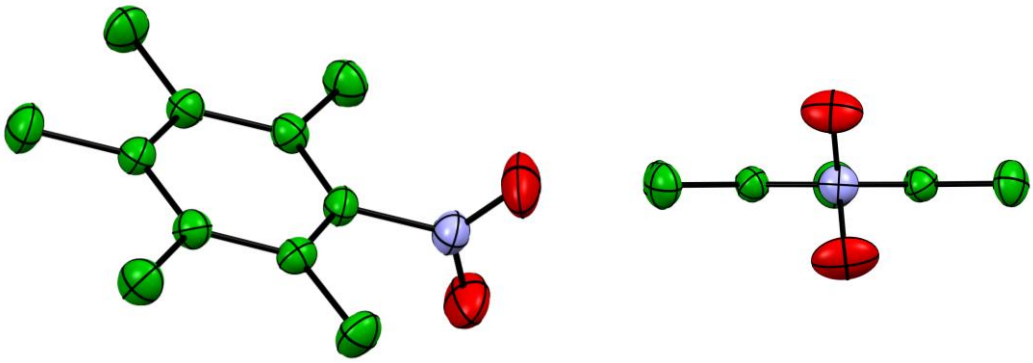


Scheme 7.14 *The para-nitro ketone* ***348*** *did not undergo* Br_2*-mediated deacylation.*

X-ray crystallographic analysis of 1-nitropentamethylbenzene (CCDC 747416) revealed that, in the solid state, the nitro group is twisted out of plane from the aryl group, with a torsional angle of 85.28 ° (Scheme 7.15). This orthogonal geometry is attributed to the torsional strain between the oxygen atoms on the nitro group and the flanking methyl

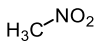
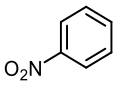
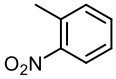
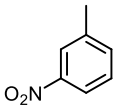
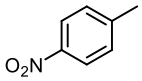
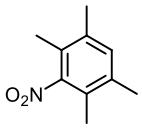
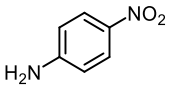
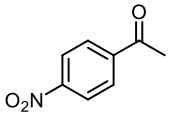
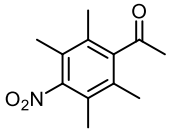
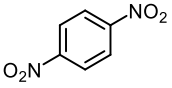
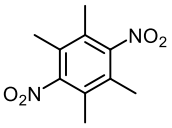
groups, a classic manifestation of the *ortho* effect. This suggests that any mesomeric effect operating in di-*ortho*-substituted nitrobenzenes would be significantly limited.

Exner and Krygowski suggest that, contrary to popular belief, the electron-withdrawing effect is predominantly inductive in nature with negligible contribution from any mesomeric effect.[192] This would imply that any steric inhibition of resonance caused by the *ortho* effect would have negligible impact on the electronics and reactivity of the ring, a result very different from that observed for the carbonyl group.



Scheme 7.15 *Thermal ellipsoids of 1-nitropentamethylbenzene (CCDC 747416) at 50% probability level, displayed in two different perspectives. Hydrogen atoms have been omitted for clarity.*

IR spectroscopy is well-suited to verify the statement by Exner and Krygowski, as any mesomeric interactions of the nitro group with the aromatic ring would result in a general weakening of the nitro group that would be disrupted by steric inhibition of resonance. Because the symmetric stretches were frequently overlapped with other signals in the fingerprint region, they are excluded from this analysis, and it is necessary to acknowledge that the analysis below would therefore be incomplete.

Entry	Compound	^{15}N NMR	X=O (IR)
1		377.6	1554 1376
2		370.2	1519 1343
3		375.2	1518 1343
4[a]		370.9	1527 1350
5		370.4	1512 1343
6		382.8	1512 1378
7		65.7 370.7	1470 1295
8		367.8	(1691) 1524 1343
9		381.2	(1704) 1528 1353
10		364.5	1552 1346
11		379.9	1530 1367

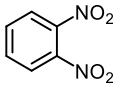
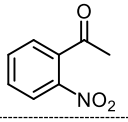
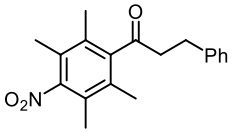
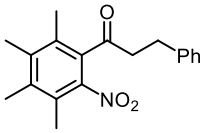
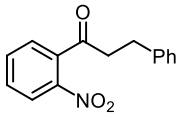
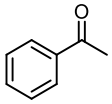
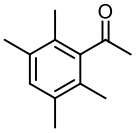
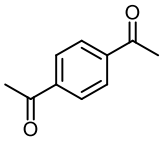
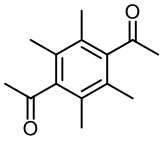
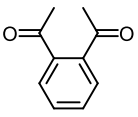
Entry	Compound	^{15}N NMR	X=O (IR)
12		364.2	1527 1354
13		369.7	(1702) 1524 1346
14		-	(1704) 1525 1382
15		376.9	(1703) 1523 1358
16[b]		-	(1707) 1528 1346
17		(198.3)	(1681)
18		(210.0)	(1693)
19		(197.2)	(1676)
20[c]		(209.2)	(1694)
21		(201.8)	(1672)

Table 7.4 *Comparison of NMR and IR data to study the impact of the ortho effect on the electronics of nitrobenzenes. Data for the carbonyl groups are marked in parentheses, and are included for comparison of the presence of ortho effect.* [a]*Ref 217;* [b]*Data was provided by Dr. James Frost;* [c]*Ref 218.*

Compared to nitromethane, switching the methyl group to a phenyl ring weakened the N=O bond by 35 cm^{-1}. A mesomeric electron-donating *para* substituent such as an amino group greatly weakens the N=O bond, decreasing the stretching frequency by 49 cm^{-1}, while a

mesomeric electron-withdrawing *para* substituent such as an acetyl group only increases the stretching frequency slightly (5 cm^{-1}). Interestingly, a *para*-nitro substituent significantly increases the N=O stretching frequency to a level comparable with nitromethane. On the other hand, the N=O stretching frequency for *ortho*-dinitrobenzene has a much smaller deviation of 8 cm^{-1} compared to nitrobenzene, strongly suggesting a significant inductive component for its electron-withdrawing ability with a comparatively minor mesomeric component. In contrast, the presence of a second *para*-acetyl substituent on acetophenone provides a small and *opposite* effect to the C=O stretching frequency, decreasing it by 5 cm^{-1}. An *ortho*-acetyl substituent further decreases the stretching frequency to 9 cm^{-1}. This highlights the different electronic behaviours of the carbonyl and the nitro group.

The *ortho* effect manifests itself in all the acetophenone derivatives, increasing their stretching frequencies by approximately 10 – 20 cm^{-1}, which is indicative of a loss of conjugation between the carbonyl group and the aryl ring thus highlighting the mesomeric behaviour of the carbonyl group. On the other hand, the presence of the *ortho*-methyl groups has a relatively minor impact on the stretching frequencies of the nitro groups on almost all the nitrobenzene derivatives and their tetramethyl-substituted analogues. A key outlier to this trend is 1,4-dinitrodurene, which has a lower N=O stretching frequency by 22 cm^{-1} compared to 1,4-dinitrobenzene, suggesting that the *ortho*-methyl groups are *weakening* the N=O bonds. Therefore, unlike the carbonyl group, the nitro group does not experience an *ortho* effect associated with the steric inhibition of resonance likely attributed to a predominantly inductive electron-withdrawing effect. Consequentially, the aromatic ring on nitrodurene remains too electron-deficient for any significant degree of electrophilic attack, and so the Friedel–Crafts acylation of nitrodurene was unsuccessful.

Because the chemical shift of the carbonyl group in the ^{13}C NMR spectrum changes significantly due to the steric inhibition of resonance from the *ortho* substituents, the use of ^{15}N NMR spectroscopy to study the ^{15}N nucleus of the nitro group could yield clues to the solution state conformation of di-*ortho*-substituted nitrobenzenes.

Contrary to the trends observed with the ^{15}N NMR chemical shifts of anilines, electron-donating or withdrawing *para* substituents such as an amine, nitro or ketone motifs did not significantly alter the nitrogen chemical shift of the nitro group, and also displayed the opposite behaviour i.e. electron-donating groups display an apparent *deshielding* effect, while electron-withdrawing groups appear to *shield* the nitro group. Furthermore, while the *ortho* effect drastically shields the dimethylamino group of *N*,*N*,2,4,6-pentamethylaniline consistent with an increase in electron density on the amine associated with a steric inhibition of resonance, the nitro group is *deshielded* by the *ortho*-methyl substituents instead, similar to the effect of *ortho*-substitution of aryl ketones.

Comparing between isomers of nitrotoluenes, dinitrobenzenes and nitroacetophenones, the *ortho*- and *para*-isomers of dinitrobenzene have very similar ^{15}N chemical shifts, whereas an *ortho*-acetyl group slightly increases the nitrogen chemical shift. This effect was even more pronounced for the nitrotoluenes, with an *ortho*-methyl group giving a very significant increase in chemical shift, while a second *ortho*-methyl group further increases the chemical shift additively to a result very similar to the non-aromatic nitromethane, suggesting that there is indeed an *ortho* effect at play. Axenrod et al. suggests that the changes in the ^{15}N NMR chemical shift are likely due to effects on the π-electron density of the nitrogen atom, as well as changes in the hybridisation state in the case of the anilines.[219] The strong dependence of the ^{15}N chemical shift on the π-electron density was also noted by Craik et al.[220]

Although these results are very similar to those from ^{13}C NMR observation of the carbonyl group for aryl ketones (see Section 7.2.1), the latter set of results could be corroborated with the corresponding data from IR spectroscopy that suggest a steric inhibition of resonance. However, in the case of nitrobenzenes, the data from IR spectroscopy is incomplete and appears to contradict the suggestion that there is loss of mesomeric effect of the nitro group due to *ortho*-substitution. Since the non-coplanar geometry of di-*ortho*-substituted nitrobenzenes has been observed by X-ray crystallography, some caution is advised in the use of ^{15}N NMR to observe or predict any torsional twist in the nitro group.

7.3 Conclusion

Analytical techniques such as NMR and IR spectroscopy can rapidly provide valuable information on the substrates and products to determine whether there is a structural basis to unusual reaction outcomes between different substrates. Powerful techniques such as X-ray crystallography can study these structures in high levels of detail and precision. The attentive mind would exploit the abundance of data from these techniques obtained even during routine characterisation of compounds at every possible instance.

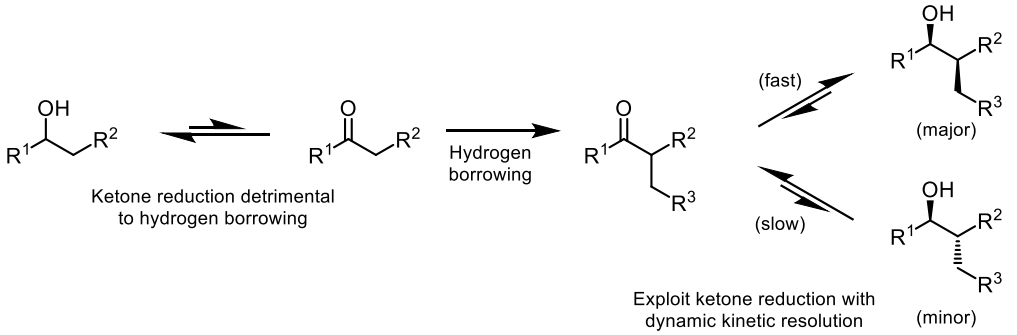
Aryl substituents that give rise to the *ortho* and "buttressing" effects cause deviations in bond lengths, angles and conformations, which in turn provide an explanation for the observed reactivity of these aryl ketones in hydrogen borrowing reactions. There is a good correlation between the presence of *ortho* substituents and changes in electronic and bonding properties associated with the steric inhibition of resonance. The comparatively small size of the amino motif compared to the methyl or acetyl groups was further shown by ^{13}C and ^{15}N NMR spectroscopy, with the *ortho* effect only operating in the presence of *N*-methyl substituents. The anomalous behaviour of the nitro group with regards to its electron-withdrawing ability was also investigated by IR and NMR spectroscopy, and shown to be predominantly inductive in nature and not operating by a mesomeric effect.

8. Future Work

The strength of the hydrogen borrowing reaction lies in its simplicity – performing three simple reactions in a single reaction vessel. This strength is also a weakness, in that the products formed are also very simple and mundane unless one uses complex substrates. The key challenge, therefore, is to engineer the hydrogen borrowing reaction to introduce complexity into molecules, thereby increasing the synthetic value of the methodology and the products that can be formed. The best way to achieve this is to introduce a fourth transformation into the hydrogen borrowing process, such as the VCP rearrangement discussed in Chapter 4, that would exploit the reactivity of the functional groups present.

8.1 Dynamic Kinetic Resolution

One of the notable aspects about the mono-*ortho*- or unsubstituted aryl ketone substrates for hydrogen borrowing reactions is that there is extensive ketone reduction observed. While is poses a problem for the current system, one could potentially exploit this reaction in the form of a dynamic kinetic resolution instead of trying to fight or block this seemingly undesirable reaction (Scheme 8.1). This could potentially have a much broader range of applications as the substrate scope would no longer be restricted to di-*ortho*-substituted aryl ketones for the current hydrogen borrowing system describes in earlier chapters.

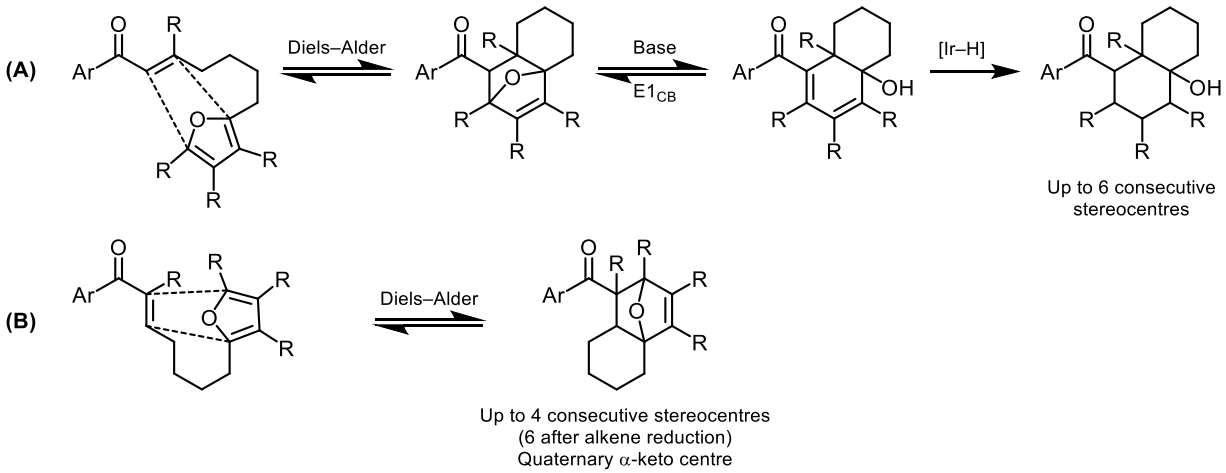


Scheme 8.1 *Exploiting the undesirable ketone reduction present in hydrogen borrowing reactions to perform dynamic kinetic resolution.*

8.2 Intramolecular Diels–Alder Reaction

In Chapter 4, the VCP rearrangement was chosen over the intramolecular Diels–Alder reaction as it appeared to be a simpler reaction to study (see Scheme 4.10). However, the products have such similar and low polarity that purification becomes an issue. Furthermore, the VCP rearrangement process itself is non-trivial and its mechanism is difficult to probe.

As such, the intramolecular Diels–Alder is the next goal to achieve, as the Diels–Alder reaction is highly reliable and easy to predict, and the stereogenic tertiary alcohol present in the product would impart sufficient polarity difference to facilitate chromatographic purification. The decalin systems are also very reliable for stereochemical analysis by NMR experiments. Furthermore, the substrates for the hydrogen borrowing reaction and the key intermediates for the study of the Diels–Alder reaction are easy to synthesise with conventional chemistry.



Scheme 8.2 *The intramolecular Diels–Alder reaction to be incorporated into the hydrogen borrowing reaction with (A) secondary alcohols or (B) primary alcohols.*

If a primary alcohol were to be used, there is also the possibility of forming a tetrasubstituted α-keto centre, a goal that was pursued in Chapter 6 (see Scheme 8.2B).

8.3 The Mechanism of the Iridium-Catalysed Hydrogen Borrowing and Vinylcyclopropane Rearrangement Reactions

Although significant progress has been made with the study of the hydrogen borrowing/VCP rearrangement reaction, the mechanism of the reaction (or its individual components) has proven difficult to elucidate. The main reasons include the general instability of the enone intermediate under the reaction conditions, the complex results from the control experiments, as well as the unusual stoichiometry of the catalytic system. Computational modelling of the reaction could provide valuable insight into the structure of the catalytic species, as well as control over the rearrangement process. Other potentially useful mechanistic experiments include deuterium labelling, although the stereospecific incorporation of deuterium into key sites on the cyclopropane is a non-trivial task, and the cost of D_2 gas used in studying the role of hydrogen gas in the reaction could be a major impediment.

Another key limitation of the hydrogen borrowing/VCP rearrangement reaction is that chiral cyclopropyl alcohols (with substitution on the cyclopropane ring) cannot be employed due to severe racemisation. The induction of asymmetry, therefore, should not be induced from the substrate, but rather *via* ligand control.

References

[1] Förster, H.; Vögtle, F. *Angew. Chem. Int. Ed*. **1977**, *16* (7), 429–441.

[2] Bowden, K.; Manser, G. E. *Can. J. Chem.* **1968**, *46* (18), 2941–2944.

[3] Böhm, S.; Exner, O. *Chem. Eur. J.* **2000**, *6* (18), 3391–3398.

[4] Böhm, S.; Fiedler, P.; Exner, O. *New. J. Chem.* **2004**, *28* (1), 67–74.

[5] Jover, J.; Bosque, R.; Sales, J. *QSAR Comb. Sci.* **2008**, *27* (5), 563–581.

[6] Wheland, G. W.; Brownell, R. M.; Mayo, E. C. *J. Am. Chem. Soc.* **1948**, *70* (7), 2492–2495.

[7] Thomas Tribble, M.; Traynham, J. G. *J. Am. Chem. Soc*. **1969**, *91* (2), 379–388.

[8] Hall, N. F.; Sprinkle, M. R. *J. Am. Chem. Soc.* **1932**, *54* (9), 3469–3485.

[9] Davies, W. C.; Addis, H. W. *J. Chem. Soc.* **1937**, 1622–1627.

[10] Thomson, G. *J. Chem. Soc.* **1946**, 1113–1116.

[11] Brown, H. C.; Cahn, A. *J. Am. Chem. Soc.* **1950**, *72* (7), 2939–2943.

[12] Taylor, H. T. *Nature* **1958**, *181*, 265.

[13] Burgers, J.; Hoefnage, M. A.; Verkade, P. E.; Wepster, B. M. Recl. Trav. Chim. Pays-Bas **1958**, *77* (6), 491–530; **1958**, *77* (11), 1080–1088.

[14] Lutz, R. E.; Weiss, J. O. *J. Am. Chem. Soc.* **1955**, *77* (7), 1814–1818.

[15] Williams, H. J. *J. Chem. Soc., Perkin Trans. I* **1973**, 1852–1855.

[16] Balasubramaniyan, V. *Chem. Rev.* **1966**, *66* (6), 567–641.

[17] Bürgi, H. B.; Dünitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30* (12), 1563–1572.

[18] Bauerová, I.; Ludwig, M. *Collect. Czech. Chem. Commun.* **2001**, *66* (5), 770–784.

[19] Nummert, V.; Piirsalu, M.; Mäemets, V.; Koppel, I. *Collect. Czech. Chem. Commun.* **2006**, *71* (1), 107–128.

[20] Desai, S. D.; Kirsch, L. E. *Int. J. Chem. Kinet.* **2015**, *47* (8), 471–488.

[21] Casarini, D.; Lunazzi, L.; Verbeek, R. *Tetrahedron* **1996**, *52* (7) 2471–2480.

[22] Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42* (2), 384–387.

[23] Topsom, R. D.; The Nature and Analysis of Substituent Electronic Effects. In *Progress in Physical Organic Chemistry, Volume 12*; Taft, R. W., Ed.; Wiley-Interscience: New York, 1971; pp 1–20.

[24] Charton, M. *J. Org. Chem.* **1983**, *48* (7), 1011–1015.

[25] Charton, M.; The Quantitative Treatment of the *Ortho* Effect. In *Progress in Physical Organic Chemistry, Volume 8*; Streitweiser Jr., A., Taft, R. W., Eds.; Wiley-Interscience: New York, 1971; pp 235–317.

[26] Fujita, T.; Nisshioka, T. The Analysis of the *Ortho* Effect. In *Progress in Physical Organic Chemistry, Volume 12*; Taft, R. W., Ed.; Wiley-Interscience: New York, 1971; pp 49–89.

[27] Oakley, M. G.; Boykin, D. W. *J. Chem. Soc., Chem. Commun.* **1986**, 439–441.

[28] Dhami, K. S.; Stothers, J. B. *Tetrahedron Lett.* **1964**, *5* (12), 631–639; *Can. J. Chem.* **1965**, *43* (2), 479–497.

[29] Fiedler, P.; Exner, O. *Collect. Czech. Chem. Commun.* **2004**, *69* (4), 797–810.

[30] Donohoe, T. J.; *Oxidations and Reductions in Organic Synthesis*; Oxford University Press: Oxford, U.K., 2000.

[31] Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30* (2), 97–102.

[32] Noyori, R.; Ohkuma, T. *Angew. Chem. Int. Ed.* **2001**, *40* (1), 40–73.

[33] Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74* (5), 567–580.

[34] Ouelett, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40* (12), 1327–1339.

[35] Bartoszewicz, A.; Ahlsten, N.; Martín-Matute, B. *Chem. Eur. J.* **2013**, *19* (23), 7274–7302.

[36] Wang, D.; Astruc, D. *Chem. Rev.* **2015**, *115* (13), 6621–6686.

[37] Choi, J.; MacArther, A. H. R.; Brookhard, M.; Goldman, A. S. *Chem. Rev.* **2011**, *111* (3), 1761–1779.

[38] Gunanathan, C.; Milstein, D. *Science* **2013**, *341* (6143), 1229712.

[39] Crabtree, R. H. *Chem. Rev.* **2017**, *117* (13), 9228–9246.

[40] Sharninghausen, L. S.; Crabtree, R. H. *Isr. J. Chem.* **2017**, *57* (10–11), 937–944.

[41] Nielsen, M.; Alberico, E.; Baumann, W.; Drexler, H.-J.; Junge, H. et al. *Nature* **2013**, *495*, 85–89.

[42] Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140–144.

[43] Zhang, M.; Fang, X.; Neumann, H.; Beller, M. *J. Am. Chem. Soc.* **2013**, *135* (30) 11384–11388.

[44] Ruch, S.; Irrgang, T.; Kempe, R. *Chem. Eur. J.* **2014**, *20* (41), 13279–13285.

[45] Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129* (49) 15134–15135.

[46] Bower, J. F.; Patman, R. L.; Krische, M. J. *Org. Lett.* **2008**, *10* (5), 1033–1035.

[47] Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130* (20), 6340–6341; **2008**, *130* (44), 14891–14899.

[48] Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem. Int. Ed.* **2008**, *48* (1), 34–46.

[49] Moran, J.; Preetz, A.; Mesch, R. A.; Krische, M. J. *Nat. Chem.* **2011**, *3*, 287–290.

[50] Wang, G.; Krische, M. J. *J. Am. Chem. Soc.* **2016**, *138* (26), 8088–8091.

[51] Obora, Y.; Hatanaka, S.; Ishii, Y. *Org. Lett.* **2009**, *11* (15), 3510.

[52] Mo, F.; Dong, G. *Science* **2014**, *345* (6192), 68–72.

[53] Corma, A.; Wojciechowski, B. W. *Catal. Rev.* **1985**, *27* (1), 29–150.

[54] Gao, J.; Xu, C. *Petrol. Sci. Technol.* **1999**, *17* (5–6), 471–490.

[55] de Klerk, A.; Fischer–Tropsch Process. In *Kirk–Othmer Encyclopedia of Chemical Technology*; Kroschwitz, J. I., Seidel, A., Eds.; Wiley-VCH, 2013.

[56] Goldman, A. S.; Roy, A. H.; Huang, Z.; Ahuja, R.; Schinski, W.; Brookhart, M. *Science* **2006**, *312* (5771), 257–261.

[57] Guerbet, M. C. R. Acad. Sci. **1909**, *49*, 129–132.

[58] Veibel, S.; Nielsen, J. I. *Tetrahedron* **1967**, *23* (4), 1723–1733.

[59] Gabriëls, D.; Hernández, W. Y.; Sels, B.; van der Voort, P.; Verberckmoes, A. *Catal. Sci. Technol.* **2015**, *5* (8), 3876–3902.

[60] Matsu-ura, T.; Sakaguchi, S.; Obora, Y.; Ishii, Y. *J. Org. Chem.* **2006**, *71* (21), 8306–8308.

[61] Koda, K.; Matsu-ura, T.; Obora, Y.; Ishii, Y. *Chem. Lett.* **2009**, *38* (8), 838–839.

[62] Dowson, G. R. M.; Haddow, M. F.; Lee, J.; Wingad, R. L.; Wass, D. F. *Angew. Chem.* **2013**, *125* (34), 9175–9178; *Angew. Chem. Int. Ed.* **2013**, *52* (34), 9005–9008.

[63] Aitchison, H.; Wingad, R. L.; Wass, D. F. *ACS Catal.* **2016**, *6* (10), 7125–7132.

[64] Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611–612.

[65] Black, P. J.; Cami-Kobeci, G.; Edwards, M. G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Org. Biomol. Chem.* **2006**, *4* (1), 116–125.

[66] Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem. Int. Ed.* **2007**, *46* (14), 2358–2364; *Chem. Rev.* **2010**, *110* (3), 1611–1641.

[67] Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349* (10), 1555–1575.

[68] Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 753–762.

[69] Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110* (2), 681–703.

[70] *Iridium Catalysis*; Andersson, P. G., Ed.; Springer-Verlag, 2011.

[71] Obora, Y.; Ishii, Y. *Synlett* **2011**, 30–51.

[72] Bähn, S.; Imm, S.; Neubert, L.; Zhang, M.; Neumann, H.; Beller, M. *ChemCatChem* **2011**, *3* (12), 1853–1864.

[73] Ketcham, J. M.; Shin, I.; Montgomery, T. P.; Krische, M. J. *Angew. Chem. Int. Ed.* **2014**, *53* (35), 9142–9150.

[74] Obora, Y. *ACS Catal.* **2014**, *4* (11), 3972–3981.

[75] Shimizu, K.-I. *Catal. Sci. Technol.* **2015**, *5*, 1412–1427.

[76] Yang, Q.; Wang, Q.; Yu, Z. *Chem. Soc. Rev.* **2015**, *44*, 2305–2329.

[77] Leonard, J.; Blacker, A. J.; Marsden, S. P.; Jones, M. F.; Mulholland, K. R.; Newton, R. *Org. Process Res. Dev.* **2015**, *19* (10), 1400–1410.

[78] Nandakumar, A.; Midya, S. P.; Landge, V. G.; Balaraman, E. *Angew Chem. Int. Ed.* **2015**, *54* (38), 11022–11034.

[79] Obora, Y. *Top. Curr. Chem.* **2016**, *374* (2), 11.

[80] Quintard, A.; Rodriguez, J. *Chem. Commun.* **2016**, *52* (69), 10456–10473.

[81] Corma, A.; Navas, J.; Sabater, M. J. *Chem. Rev.* **2018**, *118* (4), 1410–1459.

[82] Berliner, M. A.; Duban, S. P. A.; Makowski, T.; Ng, K.; Sitter, B. et al. *Org. Process Res. Dev.* **2011**, *15* (5), 1052–1062.

[83] Rong, Z.-Q.; Zhang, Y.; Chua, R. H. B.; Pan, H.-J.; Zhao, Y. *J. Am. Chem. Soc.* **2015**, *137* (15), 4944–4947.

[84] Lim, C. S.; Quach, T. T.; Zhao, Y. *Angew. Chem.* **2017**, *129* (5), 7282–7286; *Angew. Chem. Int. Ed.* **2017**, *56* (25), 7176–7180.

[85] Zhang, J.; Wang, J. *Angew. Chem. Int. Ed.* **2018**, *57* (2), 465 –469.

[86] Whitney, S.; Grigg, R.; Derrick, A.; Keep, A. *Org. Lett.* **2007**, *9* (17), 3299–3302.

[87] Bartolucci, S.; Mari, M.; Bedini, A.; Piersanti, G.; Spadoni, G. *J. Org. Chem.* **2015**, *80* (6), 3217–3222.

[88] Lee, D.-H.; Kwon, K.-H.; Yi, C. S. *J. Am. Chem. Soc.* **2012**, *134* (17), 7325–7328.

[89] Labed, A.; Jiang, F.; Labed, I.; Lator, A.; Peters, M. et al. *ChemCatChem* **2015**, *7* (7), 1090–1096.

[90] Han, X.; Wu, J. *Angew. Chem. Int. Ed.* **2013**, *52* (17), 4637–4640.

[91] Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Org. Chem.* **2001**, *66* (26), 9020–9022.

[92] Taguchi, K.; Nakagawa, H.; Hirabayashi, T.; Sakaguchi, S.; Ishii, Y. *J. Am. Chem. Soc.* **2004**, *126* (1), 72–73.

[93] Fujita, K.; Asai, C.; Yamaguchi, T.; Hanasaka, F.; Yamaguchi, R. *Org. Lett.* **2005**, *7* (18), 4017–4019.

[94] Yu, X.; Wang, Q. Y.; Wu, Q. J.; Wang, D. W. *Russ. J. Gen. Chem.* **2016**, *86* (1), 178–183.

[95] Morita, M.; Obora, Y.; Ishii, Y. *Chem. Commun.* **2007**, 2850–2852.

[96] Löfberg, C.; Grigg, R.; Keep, A.; Derrick, A.; Sridharan, V.; Kilner, C. *Chem. Commun.* **2006**, 5000–5002.

[97] Löfberg, C.; Grigg, R.; Whittaker, M. A.; Keep, A.; Derrick, A. *J. Org. Chem.* **2006**, *71* (21), 8023–8027.

[98] Black, P. J.; Cami-Kobeci, G.; Edwards, M. G.; Slatford, P. A.; Whittlesey, M. K.; Williams, J. M. J. *Org. Biomol. Chem.* **2006**, *1* (1), 116–125.

[99] Sawaguchi, T.; Obora, Y. *Chem. Lett.* **2011**, *40* (9), 1055–1057.

[100] Iuchi, Y.; Obora, Y.; Ishii, Y. *J. Am. Chem. Soc.* **2010**, *132* (8), 2536–2537.

[101] Anxionnat, B.; Gomez Pardo, D.; Ricci, G.; Cossy, J. *Org. Lett.* **2011**, *13* (15), 4084–4087.

[102] Guo, L.; Liu, Y.; Yao, W.; Leng, X.; Huang, Z. *Org. Lett.* **2013**, 15 (5), 1144–1147.

[103] Edwards, M. G.; Williams, J. M. J. *Angew. Chem. Int. Ed.* **2002**, *41* (24), 4740–4743.

[104] Cami-Kobeci, G.; Williams, J. M. J. *Chem. Commun.* **2004**, 1072–1073.

[105] Blank, B.; Kempe, R. *J. Am. Chem. Soc.* **2010**, *132* (3), 924–925.

[106] Obora, Y.; Ogawa, S.; Yamamoto, N. *J. Org. Chem.* **2012**, *77* (20), 9429–9433.

[107] Black, P. J.; Harris, W.; Williams, J. M. J. *Angew. Chem. Int. Ed.* **2001**, *40* (23), 4475–4476.

[108] Black, P. J.; Edwards, M. G.; Williams, J. M. J. *Tetrahedron* **2005**, *61* (5), 1363–1374.

[109] Cho, C. S.; Kim, B. T.; Lee, M. J.; Kim, T.-J.; Shim, S. C. *Angew. Chem. Int. Ed.* **2001**, *40* (5), 958–960.

[110] Ogawa, S.; Obora, Y. *Chem. Commun.* **2014**, *50* (19), 2491−2493.

[111] Chan, L. K. M.; Poole, D. L.; Shen, D.; Healy, M. P.; Donohoe, T. J. *Angew. Chem. Int. Ed.* **2014**, *53* (3), 761–765.

[112] Shen, D.; Poole, D. L.; Shotton, C. C.; Kornahrens, A. F.; Healy, M. P.; Donohoe, T. J. *Angew. Chem. Int. Ed.* **2015**, *54* (5), 1642–1645.

[113] Poole, D. L. Studies Towards the Nucleophilic Dearomatisation of Electron-Deficient Heteroaromatics and Hydrogen Borrowing Reactions of Methanol. DPhil. Thesis, University of Oxford, 2014.

[114] Li, F.; Zou, X.; Wang, N. *Adv. Synth. Catal.* **2015**, *357* (7), 1405–1415.

[115] Cho, C. S.; Kim, B, K.; Kim, T.-J.; Shim, S. C. *Tetrahedron Lett.* **2002**, *43* (44), 7987–7989.

[116] Quan, X.; Kerdphon, S.; Andersson, P. G. *Chem. Eur. J.* **2015**, *21* (9), 3576–3579.

[117] Adkins, H.; Elofson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc.* **1949**, *71* (11), 3622–3639.

[118] Allen, L. J.; Crabtree, R. H. *Green Chem.* **2010**, *12* (8), 1362–1364.

[119] Liang, Y.-F.; Zhou, X.-F.; Tang, S.-Y.; Huang, Y.-B.; Feng, Y.-S.; Xu, H.-J. *RSC Adv.* **2013**, *3* (21), 7739–7742.

[120] Xu, Q.; Chen, J.; Tian, H.; Yuan, X.; Li, S. et al. *Angew. Chem. Int. Ed.* **2014**, *53* (1), 225–229.

[121] Li, Q.-Q.; Xiao, Z.-F.; Yao, C.-Z.; Zheng, H.-X.; Kang, Y.-B. *Org. Lett.* **2015**, *17* (21), 5328–5331.

[122] Li, Z.; Li, S.; Li, Q.; Dong, X.; Li, Y. et al. *Tetrahedron* **2016**, *72* (2), 264–272.

[123] Xiong, B.; Zhang, S.; Jiang, H.; Zhang, M. *Org. Lett.* **2016**, *18* (4), 724–727.

[124] Sam, B.; Luong, T.; Krische, M. J. *Angew. Chem. Int. Ed.* **2015**, *54* (18), 5465–5469.

[125] Bordwell, F. G.; Fried, H. E. *J. Org. Chem.* **1991**, 56 (13), 4218–4223.

[126] Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. *Organic Chemistry*, 1st Edition; Oxford University Press: Oxford, U.K., 2001; pp 422–423.

[127] Carrion, F.; Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106* (12), 3531–3539.

[128] Hirsch, J. A.; Table of Conformational Energies—1967. In *Topics in Stereochemistry, Volume 1*; Allinger, N. L., Eliel, E. L., Eds.; John Wiley & Sons, Inc., 1967; pp 199–222.

[129] Jensen, F. R.; Bushweller, C. H. *Adv. Alicyclic Chem.* **1971**, *3*, 139–194.

[130] Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C., Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, 45 (6), 1066–1081.

[131] Neureiter, N. *J. Org. Chem.* **1959**, *24* (12), 2044–2046.

[132] Mil'vitskaya, E. M.; Tarakanova, A. V.; Plate, A. F. *Russ. Chem. Rev.* **1976**, *45* (5), 469–478.

[133] Goldschmidt, Z.; Crammer, B. *Chem. Soc. Rev.* **1988**, *17*, 229–267.

[134] Khusnutdinov, R. I.; Dzhemilev, U. M. *J. Organomet. Chem.* **1994**, *471* (1–2), 1–18.

[135] Hudlický, T.;Kutchan, T. M.; Naqvi, S. M.; The Vinylcyclopropane–Cyclopentene Rearrangement; In *Organic Reactions*; Kende, A. S., Ed.; John Wiley & Sons, Inc., 1985; Vol. 33, pp 247–335.

[136] Baldwin, J. E. *Chem. Rev.* **2003**, *103* (4), 1197–1212.

[137] Wang, S. C.; Tantillo, D. J. *J. Organometallic Chem.* **2006**, *691* (21), 4386–4392.

[138] Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107* (7), 3117–3179.

[139] Hudlický, T.; Reed, J. W. *Angew Chem. Int. Ed.* **2010**, *49* (29), 4864–4876.

[140] Jiao, L.; Yu, Z.-X. *J. Org. Chem.* **2013**, *78* (14), 6842–6848.

[141] Krüger, S.; Gaich, T. Beilstein *J. Org. Chem.* **2014**, *10*, 163–193.

[142] Thakur, A.; Louie, J.; Vinylcyclopropane–Cyclopentene Rearrangement; In *Molecular Rearrangements in Organic Synthesis*; Rojas, C. M. Ed.; Johm Wiley & Sons, Inc., 2015; Chapter 11, pp 323–362.

[143] Ganesh, V.; Chandrasekaran, S. *Synthesis* **2016**, *48* (24), 4347–4380.

[144] Meazza, M.; Guo, H.; Rios, R. *Org. Biomol. Chem.* **2017**, *15* (12), 2479–2490.

[145] Vogel, E. *Angew. Chem.* **1960**, *72* (1), 4–26.

[146] Overberger, C. G.; Borchet, A. E. *J. Am. Chem. Soc.* **1960**, *82* (4), 1007–1008.

[147] Hudlický, T.; Kutchan, T. M.; Wilson, S. R.; Mao, D. T. *J. Am. Chem. Soc.* **1980**, *102* (20), 6351–6353.

[148] Houk, K. N.; Nendel, M.; Wiest, O.; Storer, J. W. *J. Am. Chem. Soc.* **1997**, *119* (43), 10545–10546.

[149] Dewar, M. J. S.; Fonken, G. J.; Kirschner, S.; Minter, D. E. *J. Am. Chem. Soc.* **1975**, *97* (23), 6750–6753.

[150] Sperling, D.; Fabian, J. *Eur. J. Org. Chem.* **1999**, 215–220.

[151] Orr, D.; Percy, J. M.; Tuttle, T.; Kennedy, A. R.; Harrison, Z. A. *Chem. Eur. J.* **2014**, 20 (44), 14305–14316.

[152] Hashimoto, S.; Shinoda, T.; Ikegami, S. *Tetrahedron Lett.* **1986**, *27* (25), 2885–2888.

[153] Wu, J.; Tang, Y. *Angew. Chem. Int. Ed.* **2018**, *57* (21), 6284–6288

[154] Zuo, G.; Louie, J. *Angew. Chem. Int. Ed.* **2004**, *43* (17), 2277–2279.

[155] Wang, S. C.; Troast, D. M.; Conda-Sheridan, M.; Zuo, G. LaGarde, D. et al. *J. Org. Chem.* **2009**, *74* (20), 7822–7833.

[156] Ohta, T.; Komoriya, S.; Yoshino, T.; Uoto, K.; Nakamoto, Y. et al. Diamine Derivatives. EP1405852 (A1), April 7, 2004.

[157] Cogan, D.; Hao, M.-H.; Kamhi, V. M.; Miller, C. A.; Netherton, M. R.; Swinamer, A. D. 3-′4-Heterocyclyl-1,2,3,-Triazol-1-yl!-*N*-Aryl-Benzamides as Inhibitors of the Cytokines Production for the Treatment of Chronic Inflammatory Diseases. WO2005090333 (A1), September 29, 2005.

[158] Pellicciari, R.; Raimondo, M.; Marinozzi, M.; Natalini, B.; Constantino, G.; Thomsen, C. *J. Med. Chem.* **1996**, *39* (15), 2874–2876.

[159] Stepan, A. F.; Subramanyam, C.; Efremov, I. V.; Dutra, J. K.; O'Sullivan, T. J. et al. *J. Med. Chem.* **2012**, *55* (7), 3414–3424.

[160] Goh, Y. L.; Tam, E. K. W.; Bernardo, P. H.; Cheong, C. B.; Johannes, C. W. et al. *Org. Lett.* **2014**, *16* (7), 1884–1887.

[161] Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malin, L. R.; Pan, C.-M. et al. *J. Am. Chem. Soc.* **2017**, *139* (8), 3209–3226.

[162] Della, E. W.; Taylor, D. K. *J. Org. Chem.* **1994**, *59* (11), 2986–2996.

[163] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87* (6), 1353–1364.

[164] Degnan, A. P.; Maxwell, D.; Hill, M. D.; Fang, H.; Parker, M. F. et al. Oxazolidinone as Modulators of mGluR5. WO2015054103 (A1), April 16, 2015.

[165] Alcaraz, L.; Harnett, J.; Mioskowski, C.; Martel, J. P.; Gall, T. L. et al. *Tetrahedron Lett.* **1994**, *35* (30), 5449–5452.

[166] Alcaraz, L.; Cridl, A.; Kinchin, E. *Org. Lett.* **2001**, *3* (25), 4051–4053.

[167] Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron* **1968**, *24* (1), 53–58.

[168] Jorand-Lebrun, C.; Lan, R.; Chen, A.; Clark, R. C. Heteroaryl Compounds as IRAK Inhibitors and Uses Thereof. WO2017049068 (A1), March 23, 2017.

[169] Endo, Y.; Bäckvall, J.-E. *Chem. Eur. J.* **2011**, *17* (45), 12596–12601.

[170] Riss, P. J.; Rösch, F. *Org. Biomol. Chem.* **2008**, *6* (24), 4567–4574.

[171] Clausen, C.; Wartchow, R.; Butenschön, H. *Eur. J. Org. Chem.* **2001**, 93–113.

[172] Berson, J. A.; Patton, J. W. *J. Am. Chem. Soc.* **1962**, *84* (17), 3406–3407.

[173] Garayalde, D.; Gómez-Bengoa, E.; Guang, X.; Goeke, A.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132* (13), 4720–4730.

[174] Schnabel, R. C.; Roddick, D. M. *Organometallics* **1993**, *12* (3), 704–711.

[175] Wahidur Rahaman, S. M.; Daran, J.-C.; Manoury, E.; Poli, R. *J. Organometallic Chem.* **2017**, *829*, 14–21.

[176] Smith, H. A.; Thompson, R. G. *J. Am. Chem. Soc.* **1955**, *77* (7), 1778–1783.

[177] Pearson, D. E.; Keaton, O. D. *J. Org. Chem.* **1963**, *28* (6), 1557–1558.

[178] Zaitsev, A. B.; Méallet-Renault, R.; Schmidt, E. Y.; Mikhaleva, A. I.; Badré, S. et al. *Tetrahedron* **2005**, *61* (10), 2683–2688.

[179] Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111* (12), 4392–4398.

[180] Kohara, T.; Hashimoto, Y.; Shioya, R.; Saigo, K. *Tetrahedron: Asymmetry* **1999**, *10* (24), 4831–4840.

[181] Clark, R. A.; Parker, D. C. *J. Am. Chem. Soc.* **1971**, *93* (15) 7257–7261.

[182] Kostochka, L. M.; Lezina, V. P. *Chem. Heterocycl. Compd.* **1994**, *30* (3) 335–339.

[183] Skillinghaug, B.; Sköld, C.; Rydfjord, J.; Svensson, F. Behrends, M. et al. *J. Org. Chem.* **2014**, *79* (24), 12018–12032.

[184] Lubish, W.; Raschack, M.; von Philipsborn, G. *p*-Hydroxy Phenone Derivatives and the Use Thereof. US5118682 (A), June 02, 1992.

[185] Yuan, C.; Eliasen, A. M.; Camelio, A. M.; Siegel, D.; *Nat. Protoc.* **2014**, *9* (11), 2624–2629.

[186] Clemens, A. H.; Ridd, J. H.; Sandall, J. P. B. *J. Chem. Soc., Perkin Trans. II* **1985**, 1227–1231.

[187] Cao, P.; Khorev, O.; Devaux, A.; Sägesser, L.; Kunzmann, A. et al. *Chem. Eur. J.* **2016**, *22* (12), 4046–4060.

[188] Schubert, W. M.; Latourette, H. K. *J. Am. Chem. Soc.* **1952**, *74* (7), 1829–1834.

[189] El-Khawaga, A. M.; Roberts, R. M.; Sweeney, K. M. *J. Org. Chem.* **1985**, *50* (12), 2055–2058.

[190] Matsuura, K.; Kimura, Y.; Takahashi, H.; Morita, T.; Takahashi, I. et al. *Bull. Chem. Soc. Jpn.* **1994**, *67* (3), 757–765.

[191] Stavber, S.; Košir, I.; Zupan, M. *J. Org. Chem.* **1997**, *62* (15), 4916–4920.

[192] Exner, O.; Krygowski, T. M. *Chem. Soc. Rev.* **1996**, *25* (1), 71–75.

[193] Yoshimura, A.; Zhdankin, V. V. *Chem. Rev.* **2016**, *116* (5), 3328−3435.

[194] Wang, X.; Studer, A. *Acc. Chem. Res.* **2017**, *50* (7), 1712–1724.

[195] Ratnikov, M. O.; Farkas, L. E.; McLaughlin, E. C.; Chiou, G.; Choi, H. et al. *J. Org. Chem.* **2011**, *76* (8), 2585–2593.

[196] Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108* (12), 5299–5358.

[197] Zhdankin, V. V. *ARKIVOC* **2009**, (i) 1–62.

[198] Yu, Z.; Ju, X.; Wang, J.; Yu, W. *Synthesis* **2011**, 860–866.

[199] Hayashi, K.; Takayama, J.; Xuan, M.; Suda, M.; Teramae, H.; Sakamoto, T. *Heterocycles* **2016**, *92* (10), 1785–1795.

[200] Guo, X.; Xing, Q.; Lei, K.; Zhang-Negrerie, D.; Du, Y.; Zhao, K. *Adv. Synth. Catal.* **2017**, *359* (24), 4393–4398.

[201] Yuan, C.; Axelrod, A.; Varela, M.; Danysh, L.; Siegel, D. *Tetrahedron Lett.* **2011**, *52* (20), 2540–2542.

[202] Miyake, H.; Nishimura, A.; Yago, M.; Sasaki, M. *Chem. Lett.* **2007**, *36* (2), 332–333.

[203] Sun, Y.; Fan, R. *Chem. Commun.* **2010**, *46* (36), 6834–6836.

[204] Newman, M. S.; Lord, B. T. *J. Am. Chem. Soc.* **1944**, *66* (5), 733–735.

[205] Hillery, P. S.; Cohen, L. A. *J. C. S. Chem. Commun.* **1972**, 403.

[206] Milstien, S.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94* (26), 9158–9165.

[207] Bochardt, R. T.; Cohen, L. A. *J. Am. Chem. Soc.* **1972**, *94* (26), 9166–9174.

[208] Smith, J. G.; Wikman, R. T. *Tetrahedron* **1974**, *30* (16), 2603–3611.

[209] Chan, T.-L.; Mak, T. C. W.; Poon, C.-D.; Wong, H. N. C.; Jia, J. H.; Wang, L. L. *Tetrahedron* **1986**, *42* (2), 655–661.

[210] Bell, R. P.; Earls, D. W. *J. Chem. Soc., Perkin Trans. II* **1976**, 45–46.

[211] Bell, R. P.; Earls, D. W.; Timimi, B. A. *J. Chem. Soc., Perkin Trans. II* **1974**, 811–817.

[212] Bell, R. P.; Earls, D. W.; Henshall, J. B. *J. Chem. Soc., Perkin Trans. II* **1976**, 39–44.

[213] Backstrom, N.; Burton, N. A.; Turega, S.; Watt, C. I. F. *J. Phys. Org. Chem.* **2008**, *21* (7–8), 603–613.

[214] Wolf, C.; Hochmuth, D. H., König, W. A.; Roussel, C. *Liebigs Ann. Chem.***1994**, 781–786.

[215] Mazzanti, A.; Lunazzi, L.; Minzoni, M.; Anderson, J. E. *J. Org. Chem.* **2006**, *71* (15), 5474–5481.

[216] Danforth, C.; Nicholson, A. W.; James, J. C.; Loudon, G. M. *J. Am. Chem. Soc.* **1976**, *98* (14), 4275–4281.

[217] Pandiarajan, K.; Kabilan, S.; Sankar, P.; Kolehmainen, E.; Nevalainen, T.; Kauppinen, R. *Bull. Chem. Soc. Jpn.* **1994**, *67* (10), 2639–2646.

[218] Akhtar, W. M.; Cheong, C. B.; Frost, J. R.; Christensen, K. E.; Stevenson, N. G.; Donohoe, T. J. *J. Am. Chem. Soc.* **2017**, *139* (7), 2577–2580.

[219] Axenrod, T.; Pregosin, P. S.; Wieder, M. J.; Becker, E. D.; Bradley, R. B.; Milne, G. W. A. *J. Am. Chem. Soc.* **1971**, *93* (24), 6536–6541.

[220] Craik, D. J.; Levy, G. C.; Brownlee, R. T. C. *J. Org. Chem.* **1983**, *48* (10), 1601–1606.