Transition Metal Catalyzed Alkylation And Synthesis of Biotin Derivatives

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Declaration

The work described in this thesis is entirely my own, except where I have either acknowledged help from a named person or given reference to a published source. Text taken from another source will be enclosed in quotation marks and a reference given.

Di Shen

Oxford, Michaelmas 2014

Contents

Abstract

Transition Metal Catalyzed Alkylation

We have reported methodology for the use of methanol as an alkylation reagent using catalytic rhodium or iridium species for the formation of branched products from methyl ketones. The synthetic utility of the dialkylated products was enhanced by performing a regioselective Baeyer-Villiger oxidation which allowed access to ester products. A range of different phosphine ligands were screened, and sterically hindered and electron rich phosphine ligands were found to favour the formation of enone and methoxy adducts under an O_2 atmosphere. This interrupted hydrogen borrowing reaction enabled the *in situ* addition of a nucleophile to give more complex products. A range of tetrasubsitituted pyridines were then synthesized from 1, 5-dicarbonyl compounds formed in the methylenation/conjugate addition sequence. Finally, deuteration experiments suggest that the reaction proceeds *via* a monohydride mechanism, and the possibilities for the beneficial effect of O_2 were discussed.

Synthesis of biotin derivatives

The streptavidin-biotin system was chosen for the studies of protein/ligand interactions at molecular level. A series of modified biotin ligands were designed and synthesized to introduce repulsive interations with streptavidin. The protein/ligand complexes were analyzed at high resolution by X-ray crystallography.

Acknowledgement

First of all, I would like to thank my supervisor, Professor Tim Donohoe, for his invaluable guidance and advice in directing my DPhil projects during the past 3 years. He is not only a brilliant academic, but also an enthusiastic mentor encouraging me to fight with difficulties. My thanks must also go to Professor Mark Howarth, our collaboration in the department of biochemistry. I really appreciate his patience for tutoring me biology knowledge, and helping me with the X-ray software.

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Last but the most important, I must thank my family for their selfless dedication. The support of my mum, dad, and my aunt are essential to help me get through the difficulties.

Abbreviations

Ac	Acetyl
Acac	Acetylacetonate
aq.	Aqueous solution
Ar	Aromatic group/Argon
atm	Atmosphere pressure
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
Bu	Butyl
Bz	Benzoyl
cat.	Catalytic
conc.	Concentrated
CataCXium A	Di-(1’-adamantyl)-n-butylphosphine
cod	1,5-Cyclooctadiene
Cp*	Pentamethylcyclopentadienyl
Cy	Cyclohecxyl
DCM	Dichloromethane
DMAP	4-(Dimethyl)aminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
dppb	1,4-bis(Diphenylphosphino)butane
dppe	1,4-bis(Diphenylphosphino)ethane
dr	Diastereomeric ratio
EDC• HCl	*N*-(3-Dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride
ee	Enantiomeric excess
eq.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
et al.	And others
FCC	Flash column chromatography
g	Gram(s)

h	Hour(s)
HRMS	High resolution mass
Hz	Hertz
*i*Pr	Isopropyl
i	Iso
IR	Infra red
J	Coupling constant
L	Litre / generic ligand
LDA	Lithium diisopropylamide
Lit.	Literature value
m	*Meta*
mol	Mole
M	Molar
*m*CPBA	*Meta*-chloroperbenzoic acid
m.p.	Melting point
Me	Methyl
MS	Mass spectrometry or molecular sieves
min	Minute(s)
mg	Milligram(s)
mL	Millilitre(s)
mmol	Millimole(s)
MW	Microwave
m/z	Mass to charge ratio
NMR	Nuclear magnetic resonance
n/o	Not observed
o	*Ortho*
p	*Para*
Ph	Phenyl
PMB	*para*-Methoxybenzyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
Pr	Propyl
PIDA	(Diacetoxyiodo)benzene
Rbf	Round-bottomed flask

RSM	Recovered starting material
r.t.	Room temperature
sat.	Saturated
SM	starting material
T	Temperature
t/*tert*-	tertiary-
TFA	Trifluoroacetic acid
TLC	Thin layer chromatography
TM	Transition metal
THF	tetrahydrofuran
UV	ultraviolet
vide infra	See below

Chapter 1:

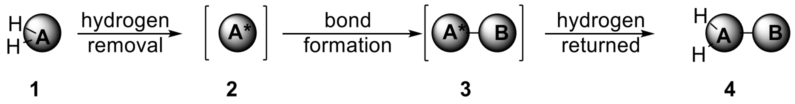
Introduction-Transition Metal Catalyzed Alkylation

1 Introduction – transition metal catalyzed alkylation

1.1 Hydrogen borrowing chemistry

Hydrogen borrowing for reactions of alcohols is a powerful method for functional group interconversion which involves reversible changes in the oxiditation state of the reacting partners. A catalyst temporarily removes two hydrogens from the substrate **1** to form the more reactive intermediate **2**, which undergoes a range of transformations with reacting partner **B** permitting new bond formation to occur. Finally, the intermediate **3** is reduced with redelivery of two hydrogen atoms, affording product **4** without a change in the overall oxidation state (Scheme 1.1).

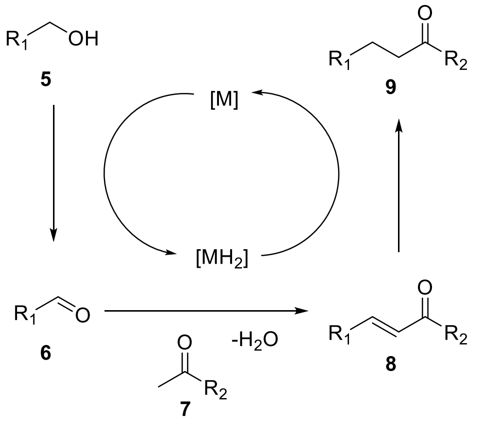
Scheme 1.1 *Concepts of hydrogen borrowing chemistry*



1.1.1 α-Alkylation of ketones with alcohols

The α-alkylation of ketones with alkyl halides or tosylates is the most frequently used method for the synthesis of ketones. These reactions require the use of high molecular weight strong bases (typically LDA), toxic alkylating agents, and result in formation of inorganic waste. However in recent years, alcohols have been widely studied as alternative alkylating agents by activation with a number of transition metal catalysts. A general pathway includes the initial removal of hydrogen from the alcohol **5** to generate aldehyde **6**, which then undergoes an aldol condensation reaction with ketone **7** affording the α,β-unsaturated ketone **8**. The saturated ketone product **9** is obtained by returning of hydrogens in the catalytic cycle (Scheme 1.2).

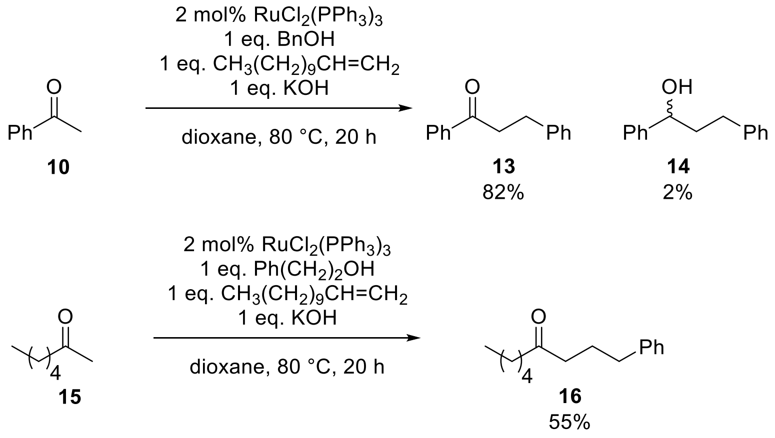
Scheme 1.2 *Alkylation of ketones with alcohols*



1.1.1.1 Ru catalyzed ketone alkylation

Transition metal catalysts that could be employed in the alkylation reactions are diverse. Cho, Shim and co–workers have reported a $RuCl_2(PPh_3)_3$ catalyzed regioselective α-alkylation of ketones with primary alcohols in the presence of 1-dodecene as a hydrogen acceptor (Scheme 1.3).[1]

Scheme 1.3 *$RuCl_2(PPh_3)_3$ catalyzed ketone alkylation*

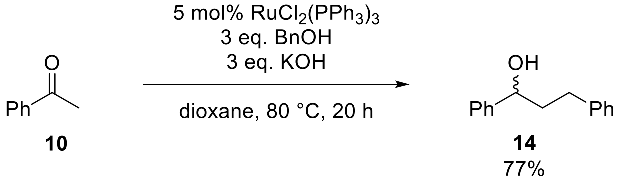


Treatment of an equimolar amount of acetophenone (**10**) with benzyl alcohol (**11**) in dioxane in the presence of $RuCl_2(PPh_3)_3$ (2 mol%) and KOH (1 eq.) together with 1-dodecene (**12**) at

80 ˚C for 20 h afforded 1,3-diphenylpropan-1-one (**13**) in 82% isolated yield and a small amount of further hydrogenated product 1,3-diphenylpropan-1-ol (**14**, 2%). In the case of dialkyl ketones, the alkylation took place selectively at the less hindered methyl group, although with a lower yield (55%, Scheme 1.3).

In the absence of a hydrogen acceptor, Cho and Shim *et al.* also developed a ruthenium catalyzed transfer hydrogenation of ketones with alcohols accompanied by C-C bond formation.[2] Acetophenone (**10**) was treated with 3 eq. benzyl alcohol (**11**) with a higher loading of $RuCl_2(PPh_3)_3$ (5 mol%) and KOH (3 eq.), affording 1,3-diphenylpropan-1-ol in 77% yield (Scheme 1.4).

Scheme 1.4 *$RuCl_2(PPh_3)_3$ catalyzed transfer hydrogenation of ketones with alcohols accompanied by C-C bond formation*

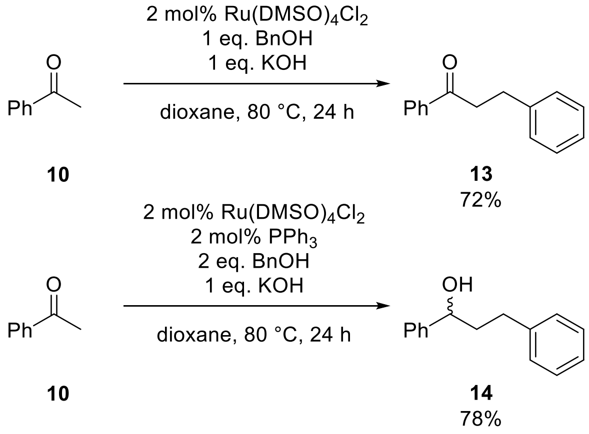


10

14
77%

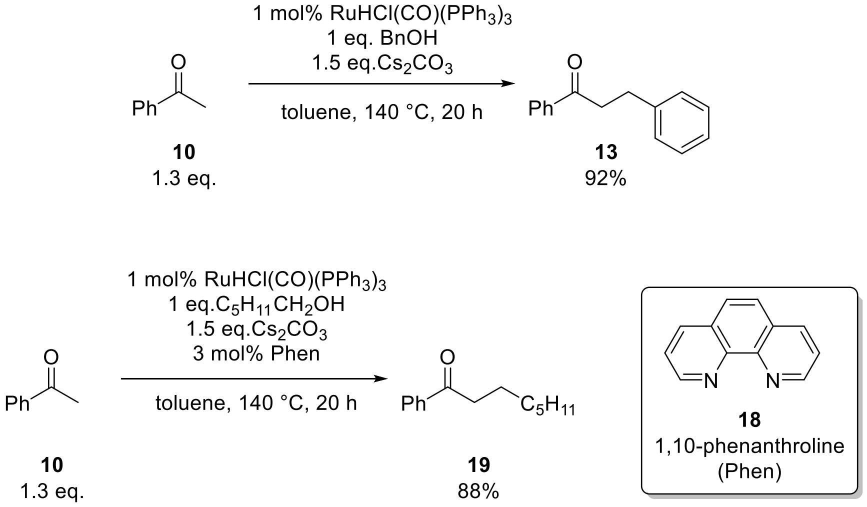
Related chemistry has been reported by Yus and co-workers using $Ru(DMSO)_4Cl_2$ as the catalyst.[3] The desired 1,3-diphenylpropan-1-one (**13**) was obtained in 72% yield by mixing equimolecular amounts of acetophenone (**10**), benzyl alcohol (**11**) and KOH in the presence of $Ru(DMSO)_4Cl_2$ (2 mol%). The reaction can also be forced to obtain the over reduced alcohol product **14** (78%) with the addition of 2 mol% PPh_3 ligand and double the amount of benzyl alcohol (2 eq., **11**), and it was suggested that the excess alcohol could act as the reducing agent (Scheme 1.5).[4]

Scheme 1.5 *Ru(DMSO)$_4$Cl$_2$ catalyzed ketone alkylation*



Another piece of work by Ryu and co-workers is shown in Scheme 1.6 where acetophenone (**10**) was alkylated with benzyl alcohol (**11**) in 92% yield by using RuHCl(CO)(PPh$_3$)$_3$ as a catalyst in the presence of Cs$_2$CO$_3$.[5] While the reaction of aliphatic primary alcohols such as 1-hexanol (**17**) with acetophenone (**10**) was sluggish compared with that of benzylic alcohols, and a catalytic amount of 1,10-phenanthroline (Phen, **18**) dramatically accelerated the reaction giving the desired product **19** in 88% yield (Scheme 1.6).

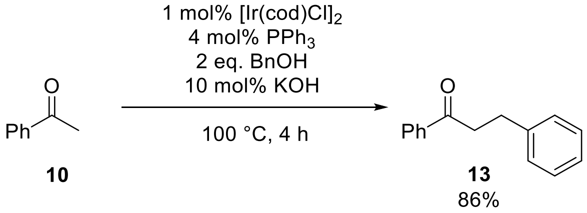
Scheme 1.6 *RuHCl(CO)(PPh$_3$)$_3$ catalyzed ketone alkylation*



1.1.1.2 Ir catalyzed ketone alkylation

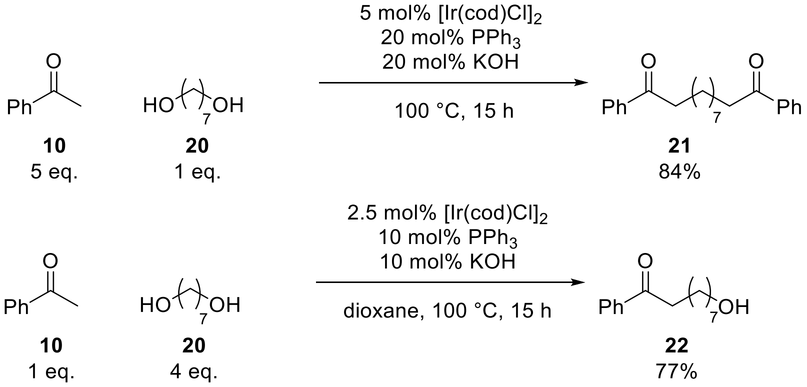
Several groups have reported the use of iridium catalysts to be effective as well for the alkylation of ketones with primary alcohols. It was demonstrated by Ishii and co-workers that the combination of $[Ir(cod)Cl]_2$, PPh_3, and KOH efficiently catalyzed the α-alkylation of ketones without solvent. Alkylation of acetophenone (**10**) was achieved in benzyl alcohol (**11**) with a yield of 86% under influence of catalytic amount of $[Ir(cod)Cl]_2$ (1 mol%), PPh_3 (4 mol%) and KOH (10 mol%) as a base (Scheme 1.7).

Scheme 1.7 *$[Ir(cod)Cl]_2$/ PPh_3/ KOH system catalyzed ketone alkylation*



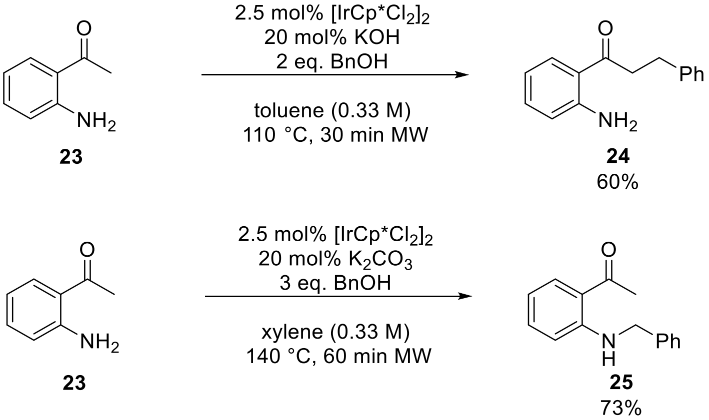
Later on, the scope of this $[Ir(cod)Cl]_2$/ PPh_3/ KOH system was extended to the synthesis of diketones and ω-hydroxy ketones from methyl ketones and diols.[6] The reaction of acetophenone (**10**) with 1,7-heptanediol (**20**) in the presence of 5 mol% $[Ir(cod)Cl]_2$, 20 mol% PPh_3 and 20 mol% KOH was found to produce the diketone **21** in 84% isolated yield. The same reaction with large excess of 1,7-heptanediol (**20**, 4 eq.) in dioxane gave the corresponding ω-hydroxy ketone **22** in 77% yield (Scheme 1.8).

Scheme 1.8 *$[Ir(cod)Cl]_2$/ PPh_3/ KOH system catalyzed ketone alkylation*



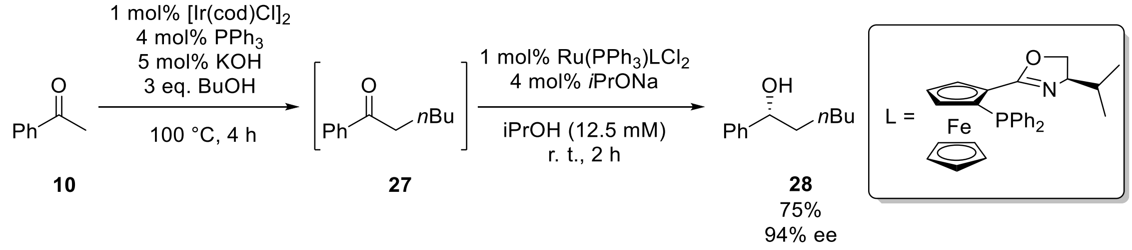
A chemoselective alkylation of 2’-aminoacetophenone with primary bezylic alcohols under microwave conditions was demonstrated by Sridharan and co-workers.[7] Initially the alkylation reaction of 2’-aminoacetophenone **23** (1 eq.) with benzyl alcohol (11, 2 eq.), KOH (20 mol%) and $[IrCp^*Cl_2]_2$ (2.5 mol%) in toluene (0.33 M) at 110 ˚C for 30 min in the microwave affored the mono *C*-alkylated product **24** in 60% yield as the sole product. On the other hand, the *N*-alkylated product **25** was achieved in 73% yield when 2’-aminoacetophenone (**10**, 1 eq.) was treated with benzyl alcohol (**11,** 3 eq.), K_2CO_3 (20 mol%), $[IrCp^*Cl_2]_2$ (2.5 mol%) in xylene (0.33 M) at 140 ˚C for 60 min in the microwave (Scheme 1.9).

Scheme 1.9 *Chemoselective alkylation of 2’-aminoacetophenone*



An asymmetric α-alkylative reduction of ketones with alcohols has been reported by Nishibayashi and co-workers.[8] Acetophenone (**10**) was first alkylated with *n*-butanol (**26**) using $[Ir(cod)Cl]_2$ catalyst, followed by the addition of an enantiomerically pure ruthenium catalyst and isopropanol as the reducing agent to give (*R*)-**28** in 75% yield and 94% ee (Schem 1.10).

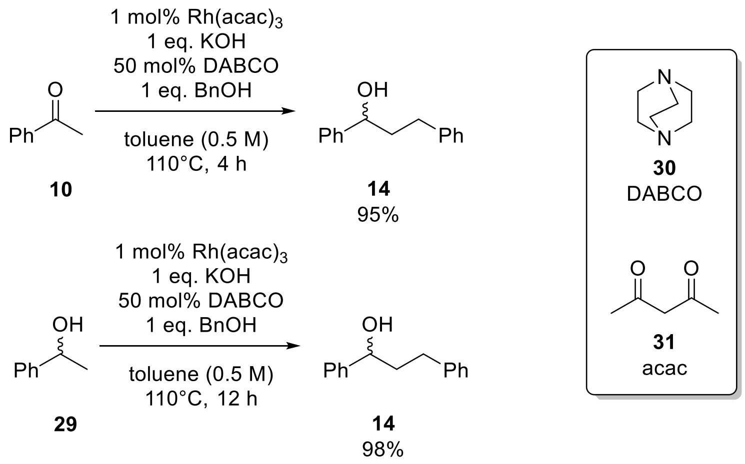
Scheme 1.10 *Ir and Ru catalyzed sequential asymmetric α-alkylative reduction of ketones with alcohols*



1.1.1.3 Rh catalyzed ketone alkylation

The Rh catalyzed α-alkylation of ketones has been reported by Maheswaran and co-workers.[9] Successful α-alkylation of acetophenone (**10**), followed by transfer hydrogenation to afford alcohol product **14** was achieved by using $Rh(acac)_3$ (1 mol%), KOH (1 eq.), and DABCO (0.5 eq.) as a ligand. The same alcohol product **14** could also be formed starting from the corresponding secondary alcohol **29** which was oxidised to acetophenone *in situ* (Scheme 1.11).

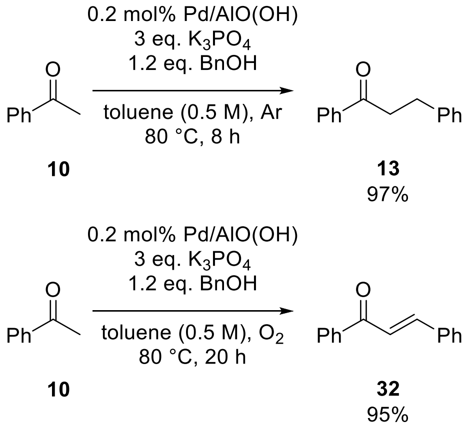
Scheme 1.11 *Rh(acac)$_3$ catalyzed α-alkylation of ketones and β-alkylation of secondary alcohols*



1.1.1.4 Pd catalyzed ketone alkylation

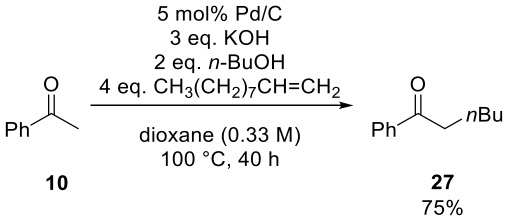
There are several examples of heterogeneous palladium catalysts for the alkylation at the α-position of ketones including the use of Pd/AlO(OH),[10] palladium nanoparticles,[11] or palladium on carbon.[12] Park and co-workers reported a palladium catalyst, Pd/AlO(OH), that is composed of palladium nanoparticles entrapped in aluminium hydroxide.[13] 1,3-Diphenylpropan-1-one was obtained in 97% yield in the reaction of acetophenone (**10**) with benzyl alcohol (**11**, 1.2 eq.) in the presence of Pd/AlO(OH) (0.2 mol% Pd) and K_3PO_4 (3 eq.) for 8 h at 80 ˚C under an Ar atmosphere. However, the same reaction under an O_2 atmosphere produced chalcone (**32**) in 95% yield after 20 h, presumably because of the reaction of H_2 with O_2 rather than reduction of the unsaturated ketone (Scheme 1.12).[10]

Scheme 1.12 *Pd/AlO(OH) catalyzed α-alkylation of ketones with alcohols*



Pd/C is also reported to be efficient for the ketone α-alkylation by Cho *et al.*.[12] Treatment of acetophenone (**10**) with 2 eq. *n*-butanol (**26**) in dioxane in the presence of a catalytic amount of Pd/C (5 mol%), KOH (3 eq.), and 1-decene (4 eq., **33**) as a sacrificial hydrogen acceptor afforded the desired ketone in 75% yield (Scheme 1.13).

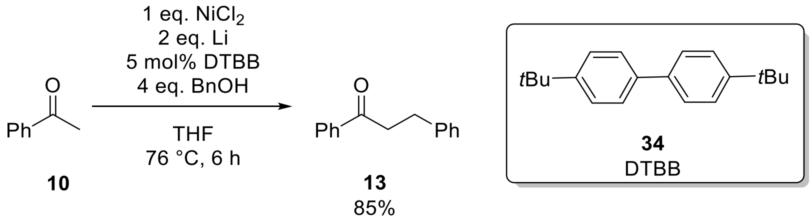
Scheme 1.13 *Pd/C catalyzed α-alkylation of ketones with alcohols*



1.1.1.5 Other metal catalysts for the α-alkylation of ketones

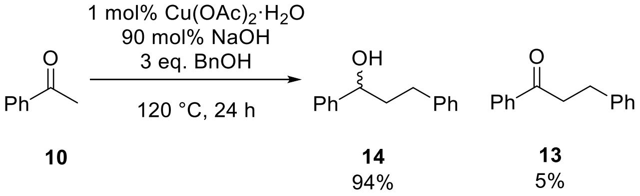
Nickel nanoparticles have been found by *Yus et al.* to activate primary alcohols used for the α-alkylation of ketones.[14] Acetophenone (**10**) was alkylated with benzyl alcohol (**11**, 4 eq.) in 85% yield with the use of nickel(0) nanoparticles (NiNPs) which were generated *in situ* from anhydrous nickel(II) chloride (1 eq.), lithium powder (2 eq.) and 4,4’-di-*tert*-butylbiphenyl (**34**, 5 mol%, DTBB) in THF (Scheme 1.14).

Scheme 1.14 *Ni nanoparticles catalyzed α-alkylation of ketones*



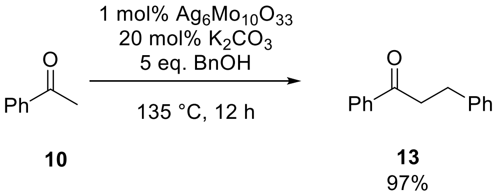
It was reported by Xu *et al.* that aerobic conditions give a more effective alcohol activation process as acetophenone (**10**) was effectively benzylated by treatment with $Cu(OAc)_2{\cdot}H_2O$ (1 mol%), NaOH (90 mol%) under air, giving the alcohol product **14** in 94% yield (Scheme 1.15).[15]

Scheme 1.15 *Cu catalyzed α-alkylation of ketones*



The use of Ag/Mo catalyst ($Ag_6Mo_{10}O_{33}$) was demonstrated by Shi and co-workers.[16] With this system, methyl ketones were alkylated with benzylic alcohols using catalytic K_2CO_3 (20 mol%) at 135 ˚C. In the benzylation of acetophenone, the expected product **13** was obtained in 97% yield (Scheme 1.16).

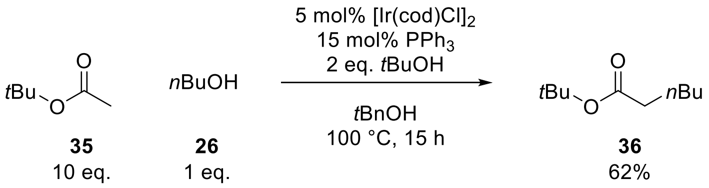
Scheme 1.16 *Ag/Mo catalyzed α-alkylation of ketones*



1.1.2 α-Alkylation of esters

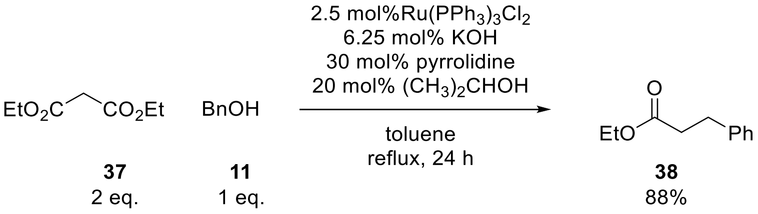
Alkylations of ketones with primary alcohols using hydrogen borrowing methodology have been widely studied, while the α-alkylation of esters with alcohols are still challenging. Ishii *et al.* reported the first example for the alkylation of *tert*-butyl acetate (**35**) with a combination of $[Ir(cod)Cl]_2$ (5 mol%), PPh_3 (15 mol%) and KO*t*Bu, although the reactions were limited to *tert*-butyl acetate and required a large excess of this ester (10 eq. to alcohol, Scheme 1.17).[17] They suggested that the ester exchange between *tert*-butyl acetate (**35**) and *n*BuOH (**26**) proceeded faster than the alkylation, and since *t*BuOH was used in excess amount as a solvent, the desired *tert*-butyl ester product **36** was regenerated.

Scheme 1.17 *α-Alkylation of tbutyl acetate*



As an alternative route to form ester products, Williams and co-workers reported the use of malonate half esters as convenient reagents for alkylation reactions with the decarboxylation occurring *in situ* (Scheme 1.18).[18] The reaction proved to be successful for a range of benzylic alcohols, and in the case of benzyl alcohol, 88% yield was achieved with the use of $Ru(PPh_3)_3Cl_2$ (2.5 mol%), KOH (6.25 mol%), pyrrolidine (30 mol%), and isopropanol (20 mol%)

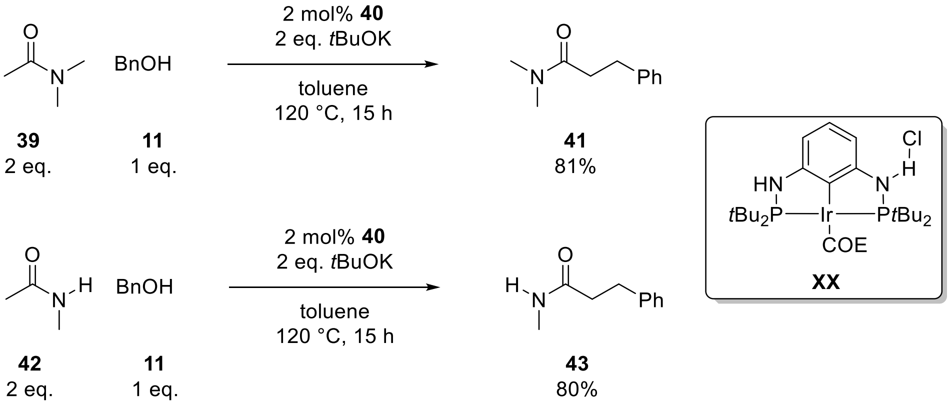
Scheme 1.18 *Alkylation of malonate half esters*



1.1.3 α-Alkylation of amides

α-Alkylation of *N*,*N*-disubstituted acetamide (**39**) with primary alcohols using pincer iridium complexes **40** has been developed by Huang and co-workers. Selective α-alkylation of secondary amides with alcohols also occurred using this protocol (Scheme 1.19).[19]

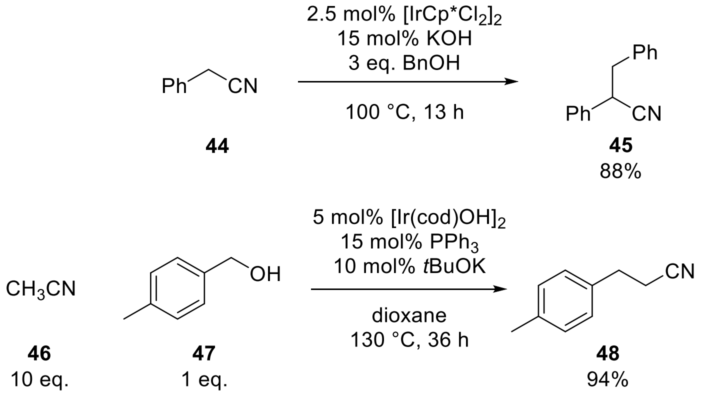
Scheme 1.19 *α-Alkylation of amides*



1.1.4 Alkylation of nitriles

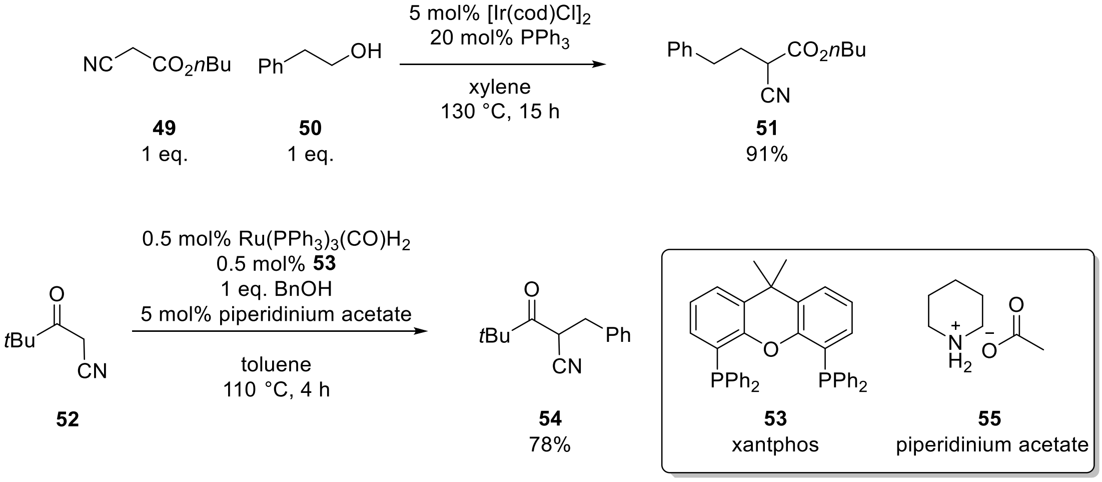
Other substrates than carbonyl compounds have also been used in the hydrogen borrowing strategy. Examples include the alkylation of arylacetonitriles such as **44** with benzylic alcohols, reported by Grigg. [20] Additionally, acetonitrile, an important feedstock in the chemical industry, was reported by Obora *et al.* to be alkylated with alcohols for the synthesis of substituted nitriles (Scheme 1.20).[21]

Scheme 1.20 *Alkylation of nitriles*



The alkylation of ester nitriles **49** has been reported by Ishii with a range of primary alcohols and benzylic alcohols using [Ir(cod)Cl]$_2$ catalyst.[22] Examples of the alkylation of ketonitrile **52** with benzylic alcohols was demonstrated by Williams *et al.* using a combination of Ru(PPh$_3$)$_3$(CO)H$_2$ catalyst and bidentate ligand **53**.[23] The addition of the xantphos ligand significantly enhanced the catalyst reactivity, allowing for a faster reaction and lower catalyst loading (0.5 mol%, Scheme 1.21).

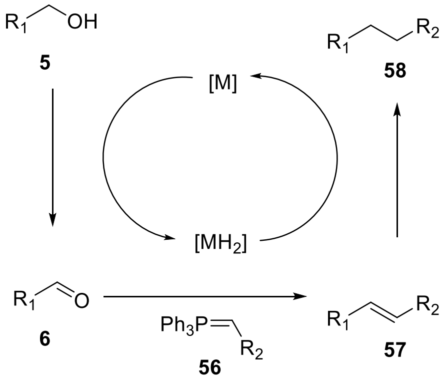
Scheme 1.21 *Alkylation of ester nitriles and ketonitriles*



1.1.5 Indirect Wittig reaction of alcohols

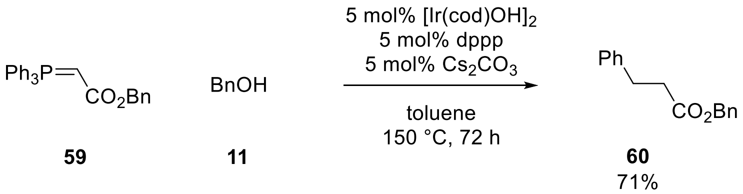
An indirect Wittig reaction has been developed by Williams group *via* dehydrogenation of alcohols **5** to afford the aldehyde **6**, followed by *in situ* reaction with stabilised Wittig ylides **56** and subsequent reduction of the alkene **57**, providing the alkane product **58** (Scheme 1.22).[24]

Scheme 1.22 *Indirect Wittig reaction of alcohols*



Alkane **60** was formed in 71% yield in the reaction of benzyl alcohol (**11**) and ylide **59** under influence of 5 mol% $[Ir(cod)Cl]_2$, 5 mol% dppp and 5 mol% Cs_2CO_3 (Scheme 1.23).

Scheme 1.23 *Indirect Wittig reaction of alcohols*

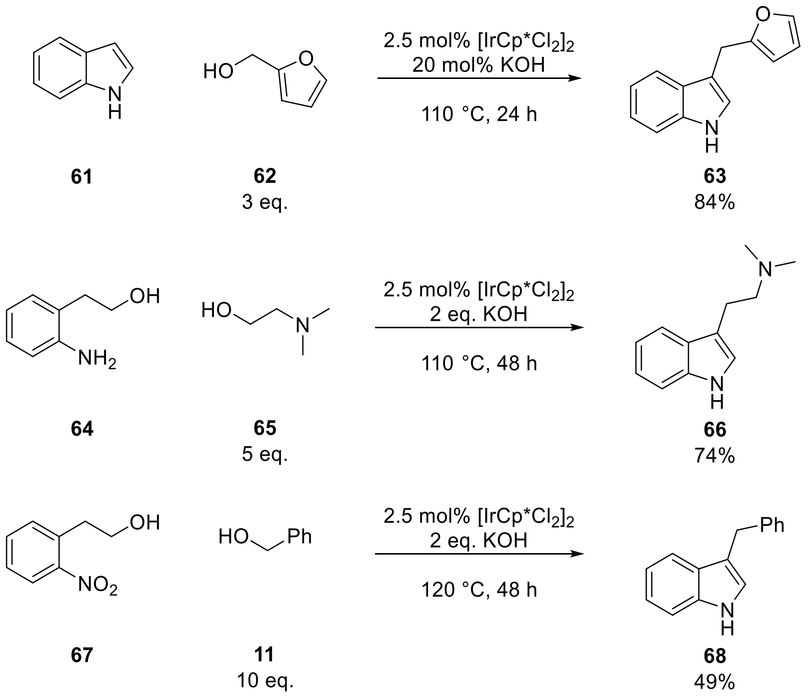


1.1.6 Alkylation of hetero-aromatic compounds

The indole ring is a privileged structure found in many structurally diverse natural products and pharmaceutical agents, and it was presented by Grigg for the iridium catalyzed reactions that afforded substituted indoles *via* the C-3 selective alkylation of indoles with alcohols.

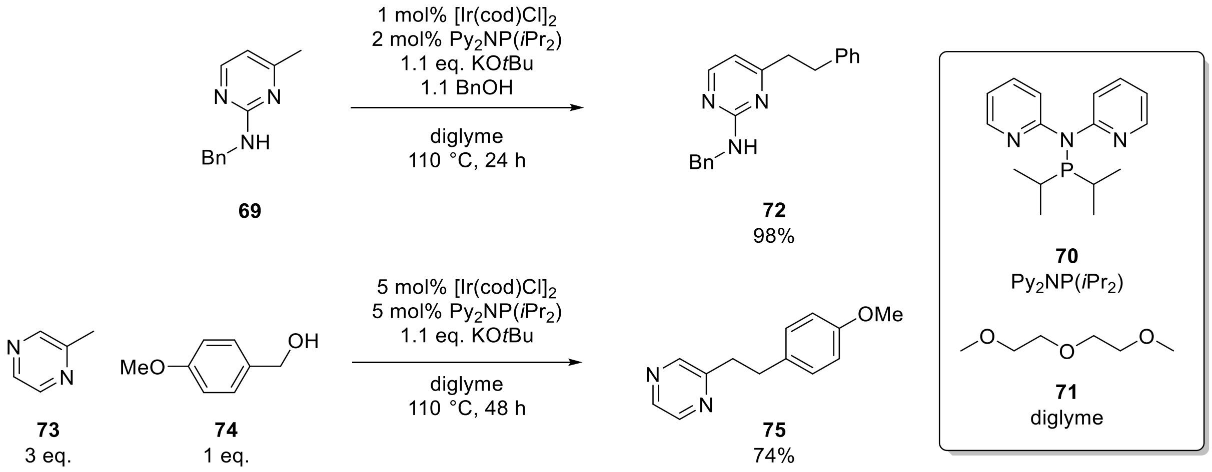
Indole (**61**) was readily alkylated with aromatic, heteroaromatic, and aliphatic alcohols under solvent free conditions to give a variety of 3-substituted indoles, and 84% yield of **63** was achieved when excess 2-furylmethanol (**62**) was employed.[25] They have also successfully extended their system in combination with Fujita's work[26] to the synthesis of C-3 substituted indoles from 2-amino- or 2-nitro-phenyl ethyl alcohols **64**, **67**, incorporating oxidative cyclization and C-3 alkylation (Scheme 1.24).

Scheme 1.24 *C-3 Alkylation of indoles and one-pot synthesis from 2-amino- or 2-nitro-phenyl ethyl alcohols*



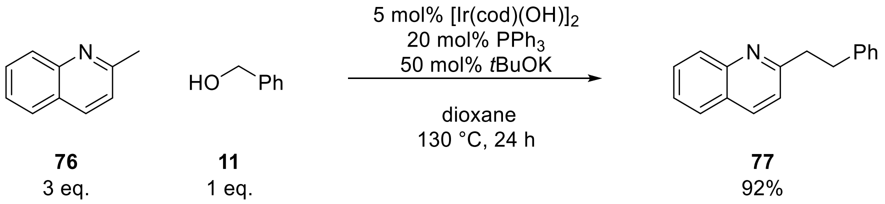
A range of methyl-substituted heteroaromatic substrates in hydrogen borrowing chemistry were studied by Kempe *et al.*.[27] C-alkylation of the methyl groups in *N*-benzylated 4-methylpyrimidin-2-ylamine (**69**) or pyrizine **73** were observed when $[Ir(cod)Cl_2]_2$ was employed with a P, N-ligand **70** and KO*t*Bu in diglyme (**71**) (Scheme 1.25).

Scheme 1.25 *Alkylation of methyl-N-heteroaromatics with alcohols*



Furthermore, the methyl alkylation of methylquinolines using alcohols as akylating agents in the presence of $[Ir(cod)(OH)]_2$ and PPh_3 was reported by Obora and co-workers.[28] Benzyl alcohol (**11**) was treated with excess amount (3 eq.) of 2-methylquinoline (**76**), 5 mol% Ir catalyst, 20 mol% PPh_3, 50 mol% *t*BuOK in dioxane at 130 ˚C for 24 h, providing the desired benzylated product **77** in 92% yield (Scheme 1.26).

Scheme 1.26 *Alkylation of 2-methylquinoline (**76**)*

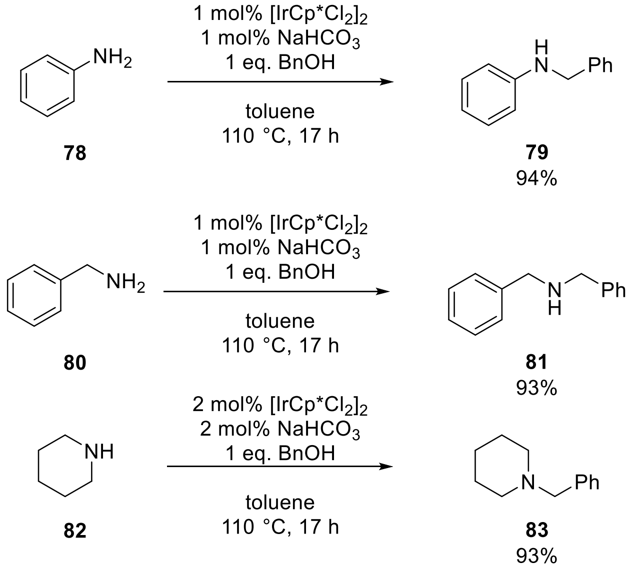


1.1.7 *N*-Alkylation of amines

The examples of homogeneously catalyzed *N*-alkylation of amines have been reported by several research groups involving ruthenium or iridium catalysts. Primary and secondary amines, aliphatic and aromatic, and also amides have been used as substrates for the *N*-alkylation using hydrogen borrowing methodology. Fujita and Yamaguchi have reported a *N*-

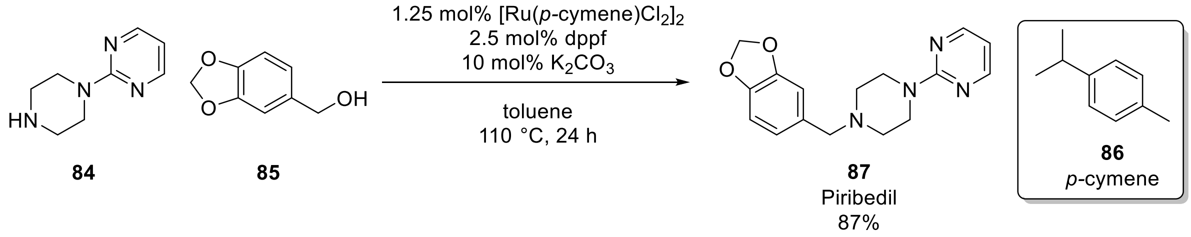
alkylation of anilines with various primary and secondary alcohols. The reaction is also successful for alkylamines and secondary amines (Scheme 1.27).[29]

Scheme 1.27 *N-Alkylation of amines*



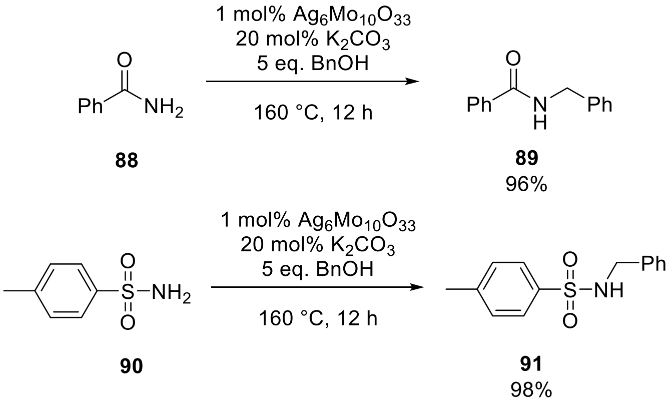
Williams et al. have used cyclic amines such as morpholine, piperidine and pyrrolidine, which were alkylated with various primary alcohols catalyzed by a Ru catalyst. The pharmaceutically important compound Piribedil (**87**) was synthesized from commercially available 1-(2-pyrimidyl)piperazine (**84**) and piperonyl alcohol (**85**) under this conditions (Scheme 1.28). [30]

Scheme 1.28 *Synthesis of Piribedil*



The alkylation of amides or sulphonamides is reported by Shi *et al.* using the Ag/Mo catalyst ($Ag_6Mo_{10}O_{33}$), 5 eq. alcohols at 160 ˚C (Scheme 1.29).[16]

Scheme 1.29 *Ag/Mo catalyzed α-alkylation of amides and sulfonamides*

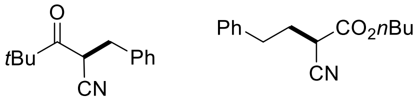


1.2 Formation of α-branched carbonyl compounds using hydrogen borrowing methodology

Among all the examples shown before, the α-alkylation of carbonyl compounds with primary alcohols only occurs once and is mostly limited to methyl ketones, providing linear mono-alkylated products. There are only a handful of examples for the α-branched products being formed in previous literature.

The first category includes the α-alkylation of ketonitriles[23] or ester nitriles[31] (section 1.1.4), presumably because of the lower pKa of the α-protons adjacent to both carbonyl and nitrile groups, allowing faster aldol step (Figure 1.1).

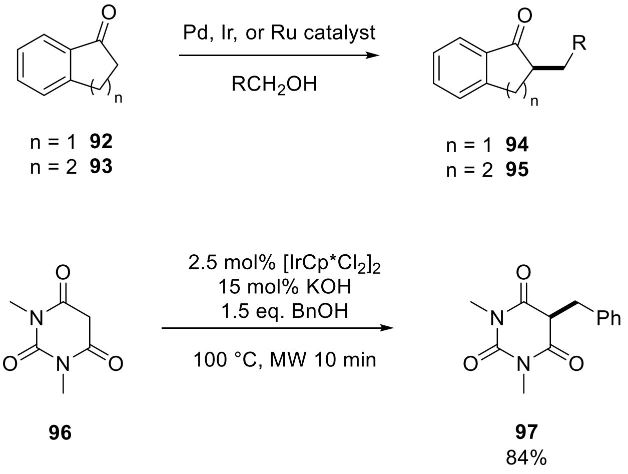
Figure 1.1 *Examples for formation of branched carbonyl compounds*



54 **51**

Cyclic ketones 3,4-dihydronaphthalen-1(2*H*)-one (**92**) and 2,3-dihydro-1*H*-inden-1-one (**93**) are found to be good substrates for the α-alkylation with alcohols, catalyzed by Pd,[10] Ru,[1] or Ir.[32] Grigg and co-workers have used 1,3-dimethylbarbituric acid (**96**) in the microwave assisted monoalkylation with alcohols.[33] The desired product **97** was achieved in 84% yield when **96** was treated with benzyl alcohol (1.5 eq.), $[IrCp^*Cl_2]_2$ (2.5 mol%), KOH (15 mol%) at 100 ˚C for 10 min (Scheme 1.30).

Scheme 1.30 *Alkylation of cyclic ketones*



1.3 Oxidation of MeOH and its use in hydrogen borrowing chemistry

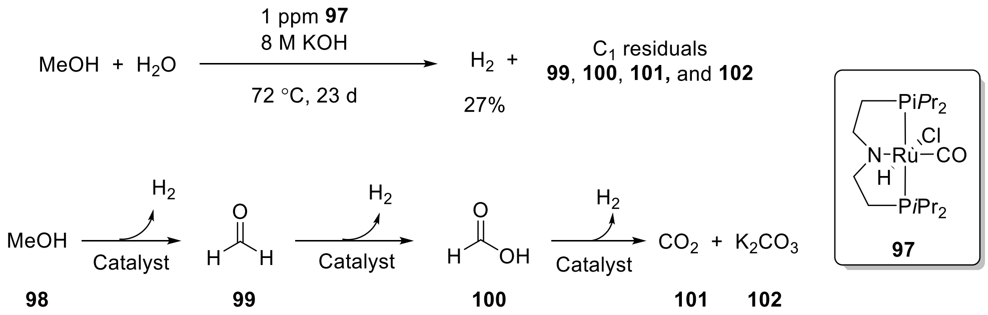
From the above survey of the literature in relation to hydrogen borrowing and related methodologies, it is clear that alkylation reactions of alcohols are predominantly based on benzylic and longer chain aliphatic alcohols.

Methanol is a highly abundant chemical feedstock, which can be produced industrially on a large scale, and each day more than 180,000 tons of methanol is used as a chemical feedstock or as a transportation fuel.[34] As one of the most basic chemicals, methanol can be converted into key building blocks, such as formaldehyde, acetic acid, and olefins, and can also be used as a fuel source for hydrogen production.[35] The use of methanol in hydrogen borrowing chemistry has proved to be difficult as the energetic demand of methanol dehydrogenation (ΔH = +84 kJ mol^{-1}) is relative higher than that of higher alcohols (ethanol: ΔH = +68 kJ mol^{-1}). [36] Herein, we have summarised the examples from literature which have employed the oxidation of methanol.

1.3.1 Dehydrogenation of methanol

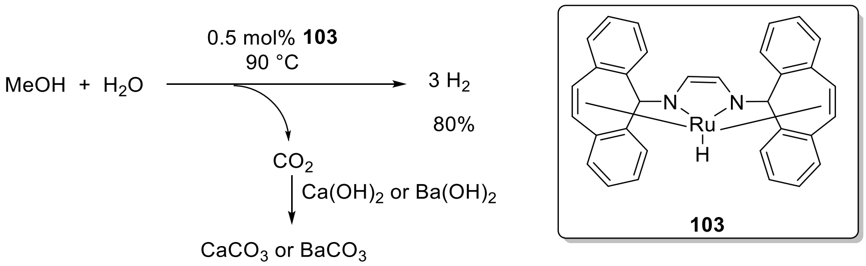
Methanol has been considered as a very good renewable source for hydrogen production. Traditional reaction typically proceeds using heterogeneous catalysts under high pressure and in a temperature range of 200-300 ˚C. Under these conditions, carbon monoxide can contaminate the product gas and may poison the fuel cell catalyst. Therefore, a number of low temperature processes have now been developed for the dehydrogenation of methanol, using homogeneous catalysts. Recently, Beller reported a homogeneous pincer ruthenium catalyzed methanol dehydrogenation reaction at 72 ˚C.[37] The process includes the initial dehydrogenation of methanol to hydrogen and formaldehyde, water promoted dehydrogenation of formaldehyde to formic acid and hydrogen, and final dehydrogenation of formic acid to hydrogen and carbon dioxide, leading to an overall yield of three molecules of hydrogen (Scheme 1.31). When performing the experiment in neat methanol, 1.6 ppm loading of catalyst **97**, and potassium hydroxide (0.8 M), a high turnover frequency of approximately 4720 h^{-1} was obtained in the first several hours (each molecule of hydrogen is counted as resembling one turnover). In 9:1 MeOH/H_2O solution, the catalyst is reactive even after 23 days although with considerably decreased turnover frequency over time and low overall methanol conversion (27%).

Scheme 1.31 *Dehydrogenation of methanol catalyzed by ruthenium pincer catalysts*



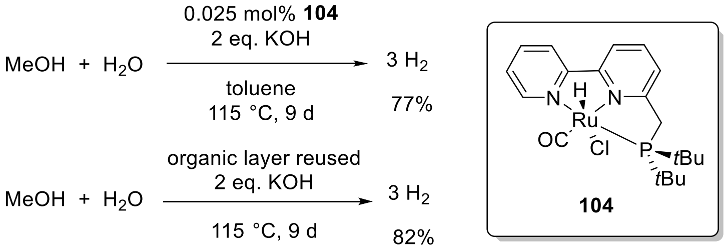
Later on, Grützmacher presented another example of generation of hydrogen from methanol and water mixture.[38] Three equivalent of hydrogen was achieved from each equivalent of methanol being oxidised with 0.5 mol% loading of **103** at 90 ˚C (Scheme 1.32).

Scheme 1.32 *Dehydrogenation of methanol reported by Grützmacher*



Early this year, Milstein reported a reusable homogeneous catalyst system, with no need of catalyst isolation and purification, offering production of hydrogen from methanol and water mixture.[39] Treating 10:1 MeOH/H_2O with KOH (2 eq.), 0.025 mol% catalyst **104**, and toluene as a solvent, 77% yield of hydrogen was achieved over 9 days. The organic layer was separated after the reaction and reused directly without addition of more catalyst **104** or toluene to give an 82% yield of hydrogen after another 9 days (Scheme 1.33).

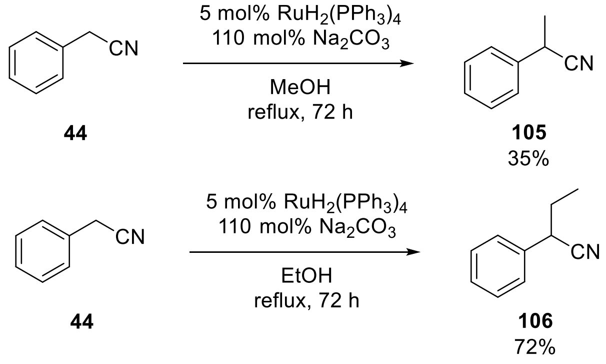
Scheme 1.33 *Dehydrogenation of methanol reported by Milstein*



1.3.2 Alkylation of nitriles with methanol

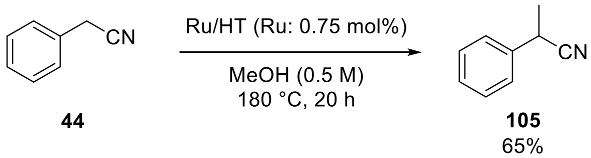
The monoalkylation of arylacetonitriles with primary alcohols catalyzed by $RuH_2(PPh_3)_4$ catalyst in the presence of Na_2CO_3 (110 mol%) was reported by Grigg in 1981.[40] Benzylnitrile (**44**) in boiling methanol gave only a poor yield of **105** (35%), however, the alkylation of the same substrate with ethanol afforded the corresponding product **106** in 72% yield (Scheme 1.34).

Scheme 1.34 *Alkylation of arylacetonitrile* ***44***



Another example was shown by Kaneda *et al.* for the alkylation of arylacetonitriles using hydrotalcite (HT, $Mg_6Al_2(OH)_{16}CO_3$) supported ruthenium catalyst.[41] Benzyl nitrile (**44**), the only example employed methanol in this work, was successfully methylated in 65% yield at 180 ˚C after 20 h (Scheme 1.35).

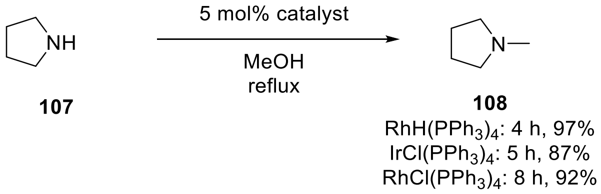
Scheme 1.35 *Methylation of benzylnitrile (**44**)*



1.3.3 C-N bond formation using methanol

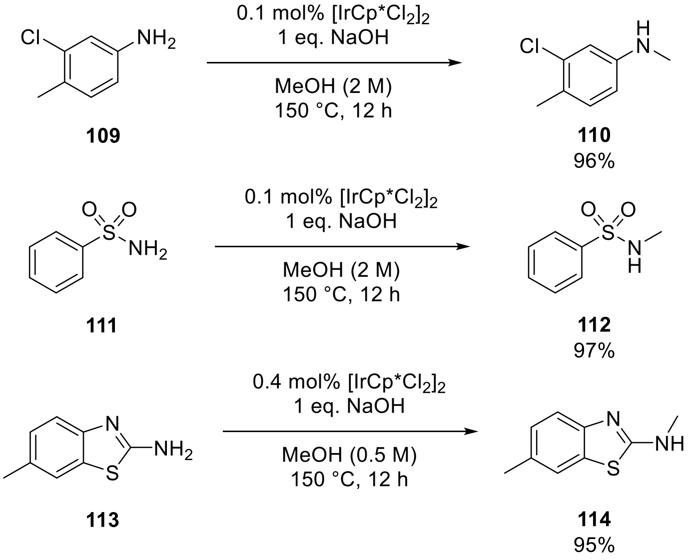
The *N*-methylation of pyrrolidine with methanol has been shown by Grigg and co-workers using different catalysts.[42] The desired *N*-methylpyrrolidine was formed in high yields in the presence of Rh or Ir catalysts within hours (Scheme 1.36).

Scheme 1.36 *N-Methylation of pyrrolidine*



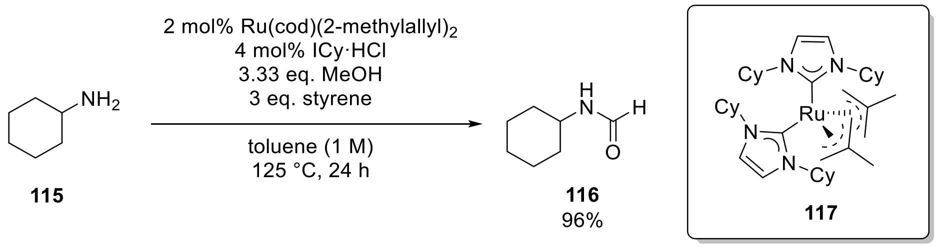
Recently, Li and co-workers presented a more general method for the *N*-methylation of aromatic primary amines with methanol. [43] In this work, anilines, sulfonamides, and amino azoles were all methylated in high yields using only 0.1-0.4 mol% $[IrCp^*Cl_2]_2$ and NaOH as base (Scheme 1.37).

Scheme 1.37 *N-Methylation of anilines, sulfonamides, and amino azoles*



In contrast to the methylation of amines, Glorius and co-workers reported a *N*-formylation of primary or secondary amines catalyzed by a ruthenium complex **117**, the dehydrogenative coupling of amines and methanol was achieved by addition of styrene as a sacrificial hydrogen acceptor.[35] The catalyst **117** was formed *in situ* by stirring Ru(cod)(2-methylallyl)$_2$ and dicyclohexylimidazolium chloride (ICy·HCl) in toluene for 12 h before addition of the amine **115**, methanol and styrene. Further reaction at 125 ˚C for 24 h gave the desired *N*-cyclohexylformamide (**116**) in 96% yield (Scheme 1.38).

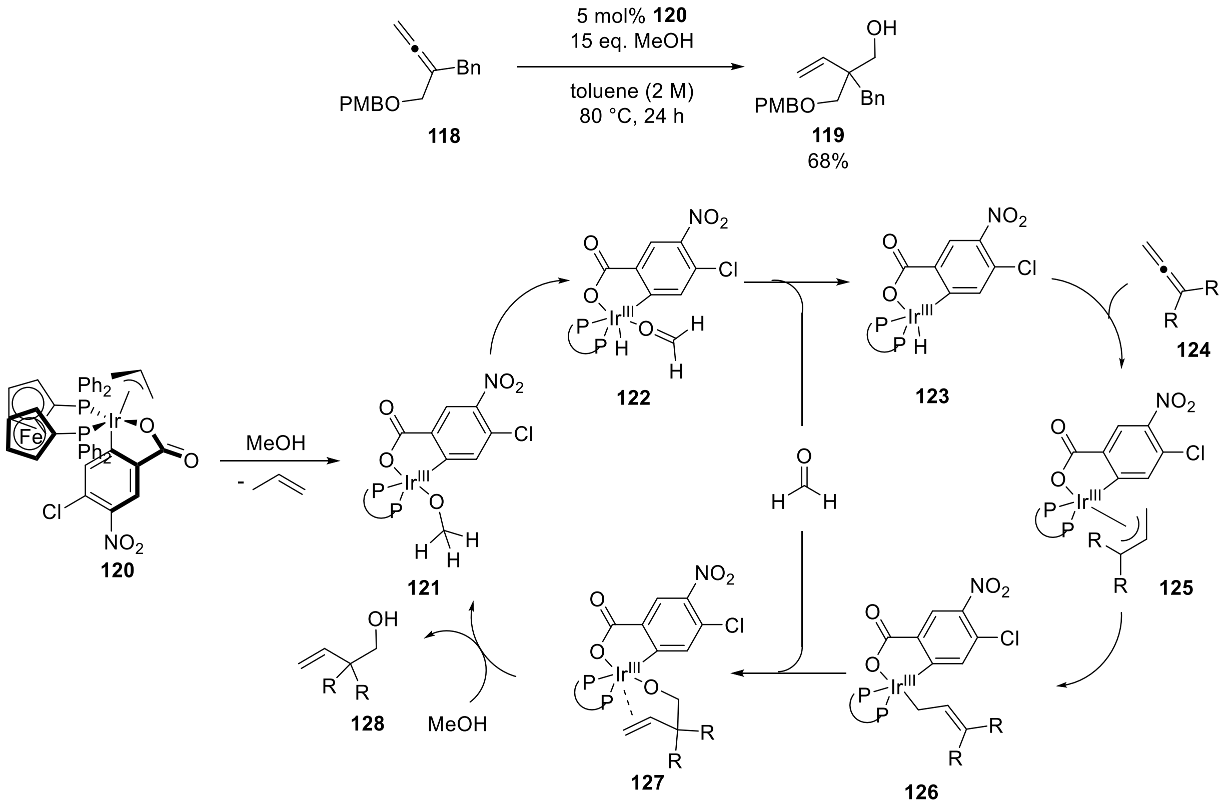
Scheme 1.38 *N-Formylation of amines with methanol*



1.3.4 C-C coupling of allenes and methanol

In 2011, Krische and co-workers reported an iridium catalyzed direct C-C bond coupling of 1,1-disubstituted allenes with methanol to yield homoallylic neopentyl alcohols.[36] The reaction was initiated by coordination of methoxide to Ir for the formation of an iridium methoxide species **121**, followed by β-hydride elimination, generating an iridium hydride complex **123** with the concomitant release of formaldehyde. Allene hydrometallation followed by addition of the resulting allyliridium intermediate **126** to formaldehyde affords the homoallylic iridium alkoxide, which exchanges with methoxide to close the catalytic cycle (Scheme 1.39).

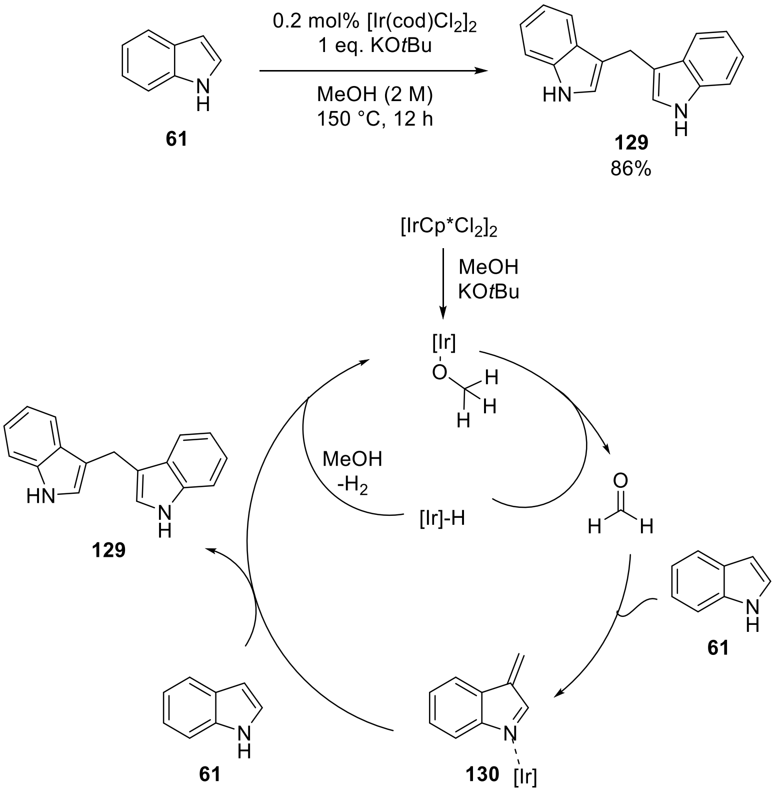
Scheme 1.39 *C-C coupling of allenes and methanol*



1.3.5 Coupling of indoles with methanol

It was developed by Li and co-workers for the first example of direct coupling of indoles and methanol catalyzed by $[IrCp^*Cl_2]_2$ to form 3,3'-bisindolylmethanes.[44] It was suggested that an enamine intermediate **130** was formed from reaction of indole **61** and formaldehyde, which was generated from dehydrogenation of methanol. The addition of a second indole to the enamine **130** afforded the desired 3,3'-bisindolylmethane **129** in 86% yield, and hydrogen was released to regenerate the catalyst (Scheme 1.40).

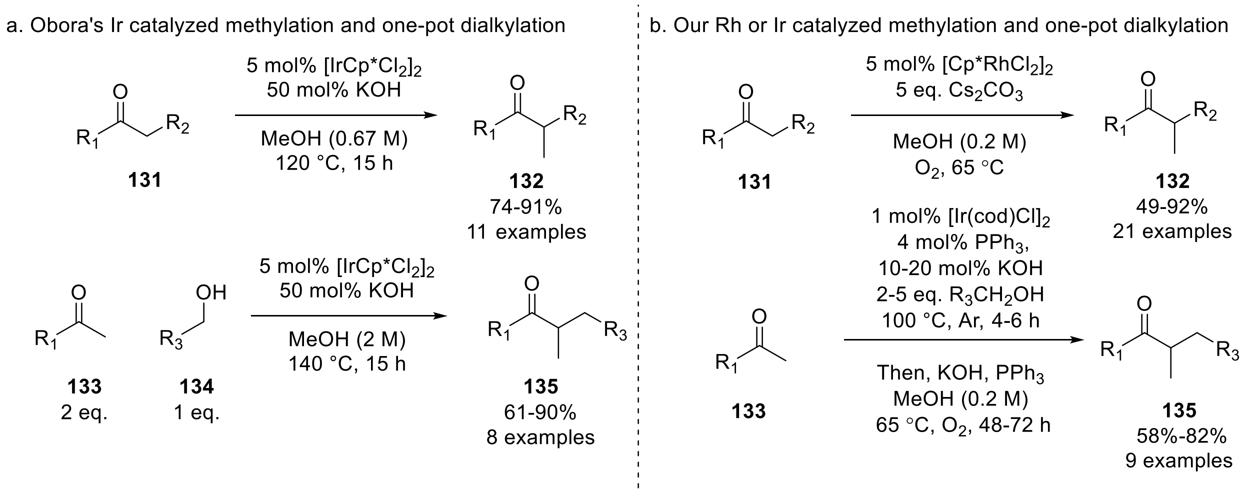
Scheme 1.40 *C-C coupling of indoles with methanol*



1.3.6 α-Methylation of ketones with methanol

The methylation α to ketones was first reported by our group, and use of methanol for branched products formation will be discussed in this thesis (Chapter 2). Subsequent to the our work on the Rh catalyzed methylation, Obora and co-workers reported an Ir catalyzed α-methylation of ketones with methanol, with an extension of their catalytic system to a one-pot synthesis of dialkylated products from methyl ketones, primary alcohols and methanol.[45] However, almost at the same time, a similar Ir catalyzed double alkylation of methyl ketones using lower loading of catalyst at a lower temperature was developed in our group (Scheme 1.41).

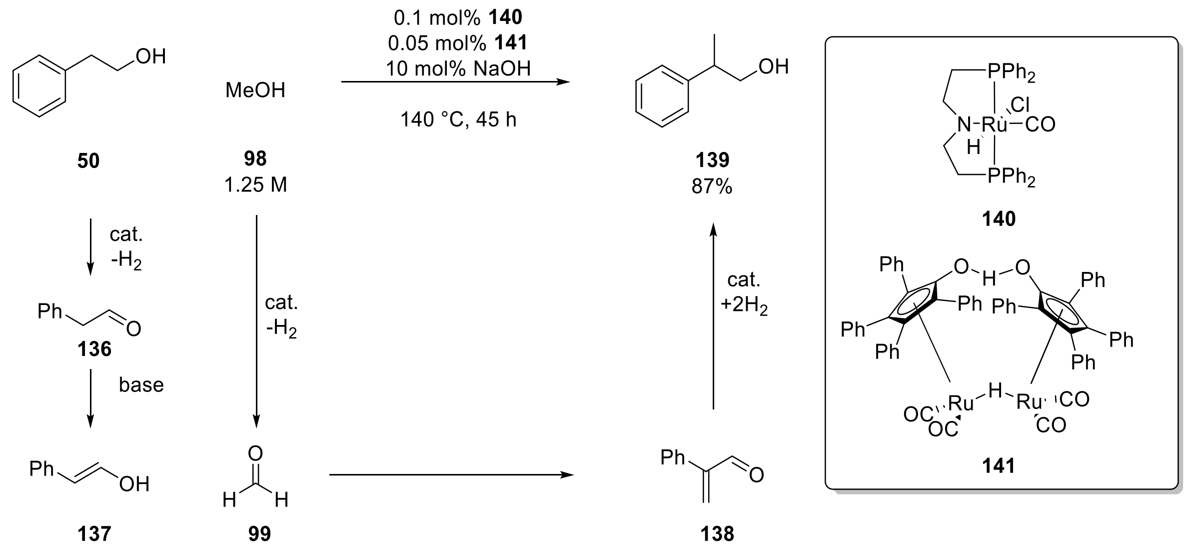
Scheme 1.41 *α-Methylation of ketones with methanol*



1.3.7 β-Methylation of alcohols with methanol

Based on their previous work of catalytic methanol dehydrogenation, Beller reported a cross coupling of methanol and primary alcohols earlier this year (Scheme 1.42).[46] By employing a dual catalytic system comprising of **140** and **141**, both methanol and primary alcohol **50** were oxidised to formaldehyde and enolizable aldehyde **136**, which underwent an aldol condensation to afford the α,β-unsaturated aldehyde **138**. Finally, the reduction of both the alkene and the carbonyl group provides the desired β-methylated alcohol **139** in 87% yield.

Scheme 1.42 *β-methylation of alcohols*



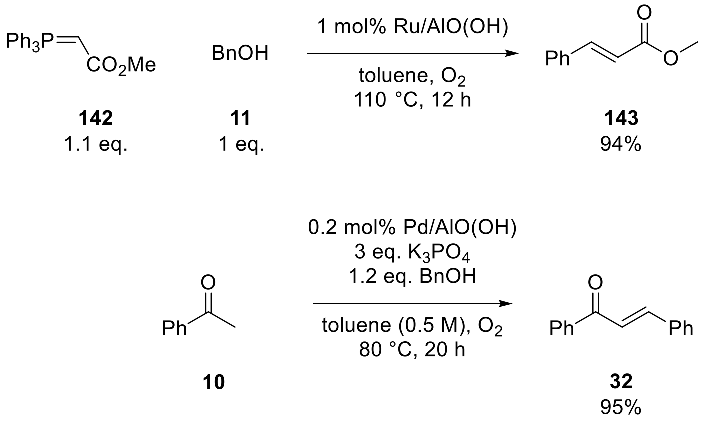
1.4 Interupted hydrogen borrowing and hydride acceptors

Traditionally, in the transition metal catalyzed alcohol dehydrogenation reactions, stoichiometric oxidant such as O_2,[47] H_2O_2,[48] olefins,[49] and sacrificial ketones (Oppenauer-type reaction)[50] are needed. In the last decade, there are a few examples of employing such hydride acceptors in the hydrogen borrowing sequence to intercept the reduction step, allowing formation of products at a more oxidised level.

Williams and co-workers reported the synthesis of dihydrocinnamate derivatives by a one-pot process, wherein coupling of the resulting aldehydes obtained from dehydrogenation of primary benzylic alcohols with stabilized Wittig ylides were achieved by using $[IrCl(cod)]_2$ in the presence of Cs_2CO_3 at 150 °C for 72 h. However, dihydrocinnamate derivatives were obtained as the major products in good yields as a result of hydrogenation by iridium hydride intermediates (section 1.1.5). With the addition of an O_2 balloon, Park *et al.* developed a method for heterogeneous metal catalysts[51], which are composed of Ru nanoparticles entrapped in highly porous aluminum oxyhydroxide (Ru/AlO(OH)), for a one-pot oxidation–

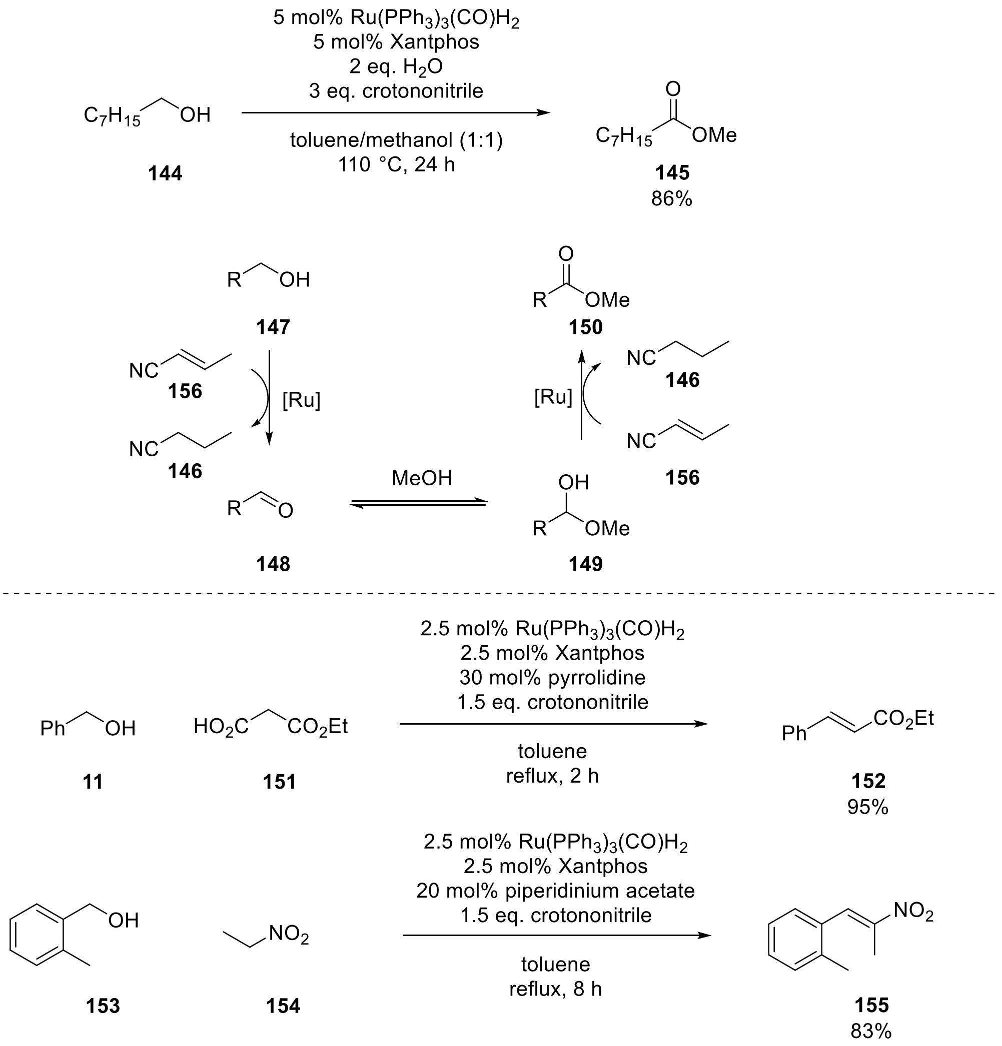
Wittig reaction affording α,β-unsaturated esters (Scheme 1.43). Additionally, The Pd/AlO(OH) catalyzed benzylation of acetophenone, reported by the same group, under O_2 produced the unsaturated ketone in 95% yield (Section 1.1.1.4).

Scheme 1.43 *Formation of unsaturated esters or ketones using O_2 as a hydride acceptor*



Crotononitrile (**156**) has been used as a hydrogen acceptor in the ruthenium-catalysed oxidation of alcohols to methyl esters by Williams and co-workers. In this chemistry, an alcohol **147** is initially oxidised to an aldehyde **148** which reacts reversibly with methanol to form a hemiacetal **149** and further oxidation leads to the formation of the ester **150**.[52] They could also use this hydride acceptor to intercept other hydrogen borrowing reactions, such as alkylation of malonate half esters or nitroalkanes, by transferring hydrogen to crotononitrile (**156**), providing a route for the conversion of alcohols into alkenes (Scheme 1.44).[53]

Scheme 1.44 *Crotononitrile (156) as hydrogen acceptor*



1.5 Aim of the project

The use of methanol in hydrogen borrowing chemistry remains challenging, especially in the area of alkylation of ketones. Besides, formation of branched carbonyl products using hydrogen borrowing methodology is limited to nitriles, cyclic ketones or esters. Therefore, our first aim was to investigate the possibilities of using methanol as an alkylating agent, and extend the scope to branched ketone products. We also aimed at taking advantage of the unsaturated products formed, in an interrupted hydrogen borrowing process, and combine it with nucleophilic addition to form more complex products.

Chapter 2:

Results and Discussion-Transition Metal Catalyzed Alkylation

2 Results and Discussion-Transition metal catalyzed alkylation

2.1 Introduction: previous work in the Donohoe group[*]

As discussed in Chapter 1, α-alkylation of carbonyl compounds with alcohols using hydrogen borrowing is achieved by use of transition metal catalysts, but is limited to methyl ketones, with the reaction stopping after mono-alkylation. Typically, benzylic or long chain primary alcohols are used, generating the corresponding ketone products with no branching at the α-position. Generally, this type of alkylation reaction requires high reaction temperatures (≥100 ˚C). Previous work in the Donohoe group resulted in the development of rhodium catalyzed ketone methylation methodology to form α-branched products from more substituted carbonyl starting materials using methanol as an alkylating reagent at a lower temperature (65 ˚C).

Valerophenone (**157**) was chosen as a model substrate, with different metal catalysts screened, in the presence of Cs_2CO_3, an atmosphere of O_2 in methanol at 65 ˚C.[†] Early experiments using $[IrCp^*Cl_2]_2$ or $[RuCp^*Cl_2]_n$ (Table 2.1, entry 1, 2) gave a mixture of several different compounds: the desired methylated ketone **157a**, enone **157b**, methoxy adduct **157c**, and dimer **157d**. The distribution of products indicated that the reduction of enone **157b** was interrupted by nucleophilic addition. It was clear that methoxy adduct **157c** was formed by the addition of methoxide to enone **157b**, whilst dimer **157d**[‡] was derived from the addition of the enolate of starting ketone. Previous literature had shown rhodium to be an effective catalyst for the 1,4-reduction of enones, so it was screened in a search for a more efficient reduction reaction.[54] Pleasingly, when 5 mol% $[RhCp^*Cl_2]_2$ was employed (Table 2.1, entry 3), α-methylated ketone **157a** was afforded in an excellent 98% yield after 48 hours.

---

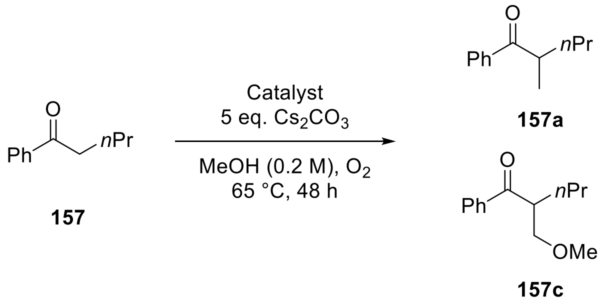
[*] Work by Dr. L. K. M. Chan and Dr. D. L. Poole

[†] Methanol was used as received from Sigma Aldrich, and not dried prior to use.

[‡] isolated as an approximately 1:1 *anti*:*syn* ratio of inseparable diastereomers

Treatment of valerophenone **157** using the same conditions but instead under an atmosphere of Ar (Table 2.1, entry 4) afforded methylated product **157a** in only 57% yield after 48 h. In addition to this, 9% of dimer **157d** was also isolated. Subjection of valerophenone (**157**) to these reaction conditions in the absence of $[RhCp^*Cl_2]_2$ catalyst resulted in 98% recovery of starting material (Table 2.1, entry 5). This control experiment indicated that the $[RhCp^*Cl_2]_2$ catalyst was essential for the reaction to occur, with an oxygen atmosphere also being a key requirement to improve the isolated yield of the desired product.[§]

Table 2.1 *Catalyst screening*

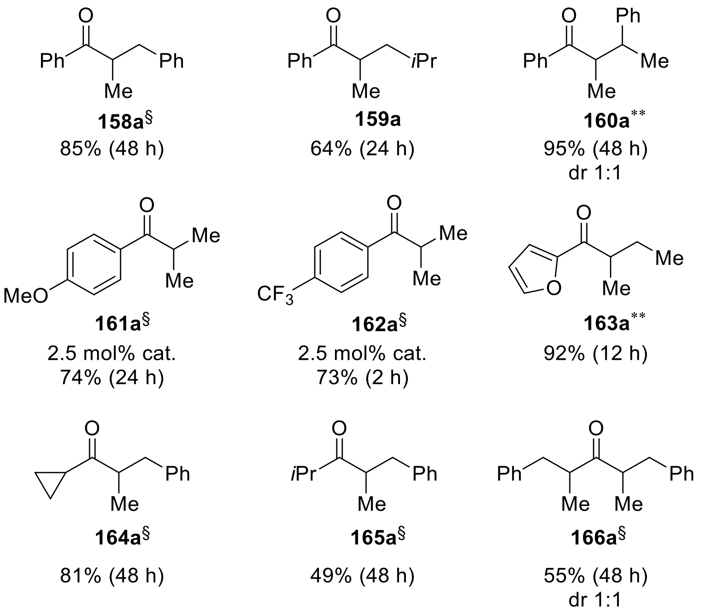


Entry	Catalyst	**157** (%)	**157a** (%)	**157b** (%)	**157c** (%)	**157d** (%)
1	$[IrCp^*Cl_2]_2$ 5 mol%	n/o	42	14	27	12
2	$[RuCp^*Cl_2]_n$ 5 mol%	n/o	<2	23	39	19
3	$[RhCp^*Cl_2]_2$ 5 mol%	n/o	98	n/o	n/o	n/o
4	$[RhCp^*Cl_2]_2$ 5 mol%, Ar	n/d	57	n/o	n/o	9
5	No catalyst	98	n/o	n/o	n/o	n/o

With the optimised conditions (Table 2.1, entry 3) in hand for the methylation of valerophenone (**157**), attention was then turned to exploring the substrate scope of the methylation reaction (Scheme 2.1).

[§] The four products derived from the starting ketone were numbered as follows: **a**. methylated ketone; **b**. enone; **c**. methoxy adduct; **d**. dimer

Scheme 2.1 *Substrate scope; products of methylation are shown*



The reaction conditions were found to be compatible with other alkyl chains including homobenzyl ketone **158**[**] and isopentyl ketone **159** which were methylated in 85% and 64% yields to give **158a** and **159a** respectively. β-Substitution on the alkyl chain was also tolerated on the alkyl chain, with β-methyl ketone **160** [††] alkylated in 95% yield. Unfortunately, no diastereoselectivity was observed in the methylation of **160**, presumably due to the epimerization of product under the basic reaction conditions. Variation of the electronic properties of the aromatic ring by introducing electron-rich (**161**[**]) or electron-poor (**162***[*]) *para* substituents led to good yields, as did a substrate incorporation of a furan moiety (163[††]). With a range of different aromatic ketones in hand, the group also studied methylation reactions of alkyl-alkyl ketones. Cyclopropyl ketone **164**[**] was methylated in 81% yield with no alkylation occurring at the secondary centre. However, replacement of the cyclopropyl substituent in **164** with an isopropyl group resulted in a relatively low yield of 49% after 48 h. The slower reaction appeared to result in the decomposition of both substrate and

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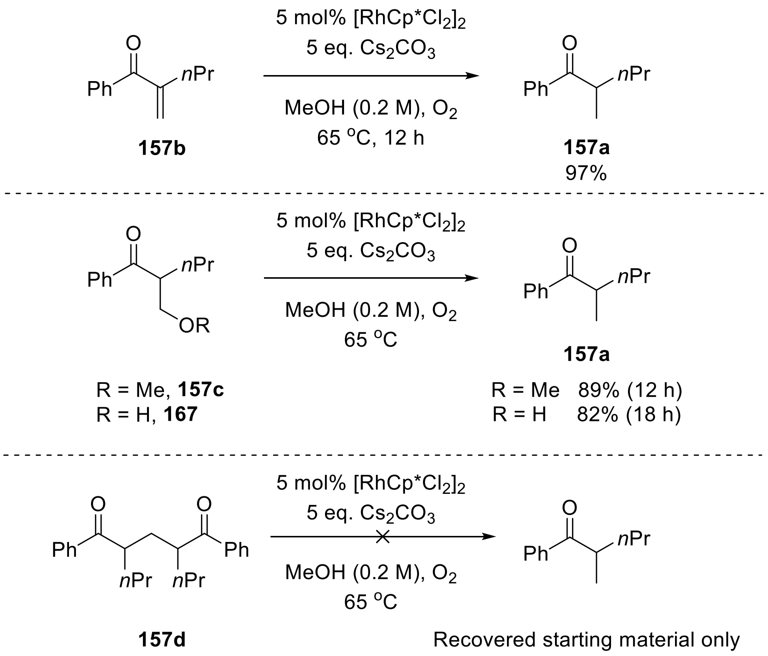
[**] Examply by Dr. D. L. Poole

[††] Example by Dr. L. K. M. Chan, dr calculated from HPLC

product under the reaction conditions. 1,5-Diphenylpentan-3-one (**166****) was doubly methylated in 55% yield, with no 1,3-diastereoselectivity observed, affording methylated ketones *syn*- and *anti*-**166a** in 1:1 dr. Although this ketone was methylated in a moderate 55% yield, this is still equal to a yield of approximately 75% per methylation, which is comparable to the methylation of other ketones.

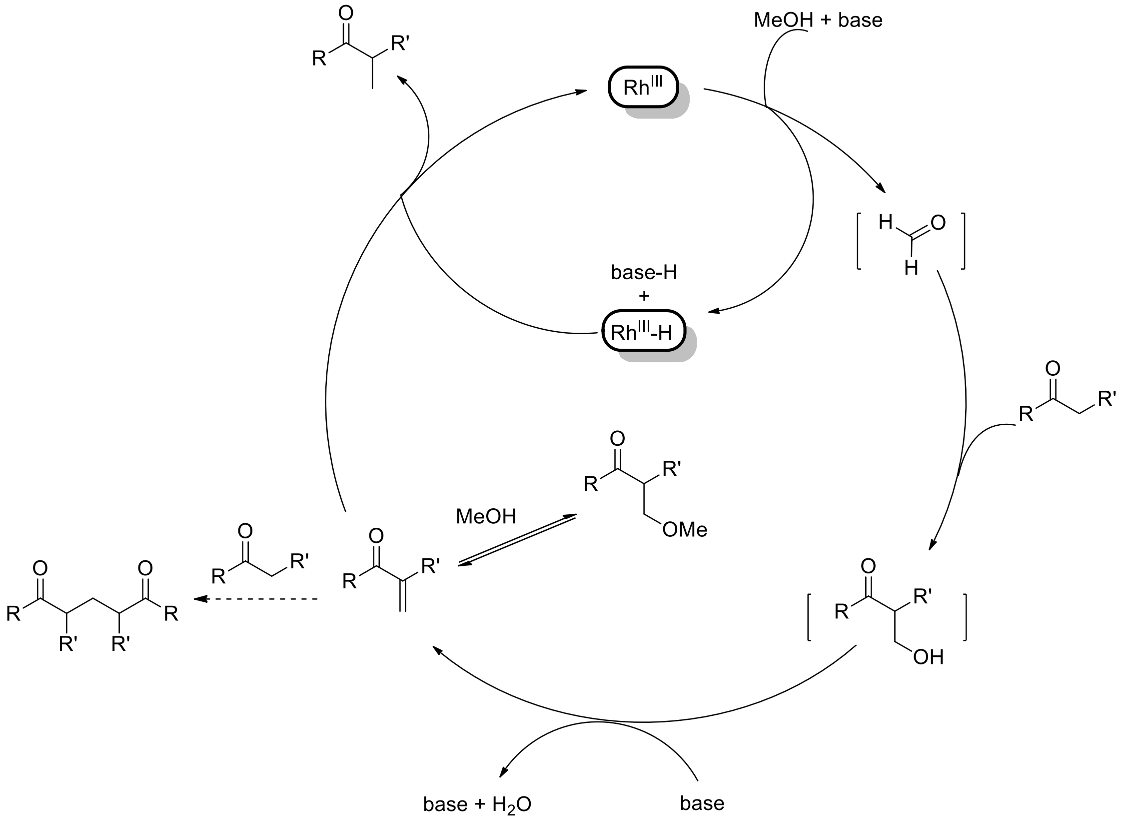
In order to gain further insight into the reaction mechanism, a series of experiments were carried out by Dr. D. L. Poole whereby isolated intermediates from the reaction were resubjected to the conditions. As previously mentioned, enone **157b** was assumed to be formed *via* an aldol reaction/elimination sequence prior to reduction to from methylated compound **157a**. The methoxy adduct **157c** and dimer **157d** resulted from a conjugate addition of either methoxide or enolate of starting ketone **157** to enone **157b**. They also postulated the existence of adduct **167** (Scheme 2.2), formed *via* an aldol reaction with formaldehyde, but this compound has never been isolated from the reaction mixture. As a result, the aldol adduct was synthesized and subjected to the optimised conditions as well.

Scheme 2.2 *Resubjection experiments*



Under the methylation conditions, enone **157b** afforded methylated ketone **157a** in 97% yield after 12 h. Similarly, the methylated ketone **157a** was obtained in 89% yield after 12 h from methoxy adduct **157c**. The aldol product **167** was also converted into the desired methylated product in 82% yield after 18 h. These results strongly suggested that these three species were involved in the reaction pathway, with methanol adduct **157c** and aldol product **167** presumably consumed by respective elimination of methanol or water to form enone **157b** followed by reduction by a rhodium-hydride species. However, resubjection of dimer **157d** to the methylation conditions resulted in only the recovery of starting material, suggesting that the formation of this product was a dead-end in the reaction pathway (Scheme 2.2). These studies led us to propose the mechanism shown in Scheme 2.3. Methanol is oxidised by the catalyst to formaldehyde, followed by an aldol reaction/elimination sequence to form enone. Reduction of the enone by a metal-hydride species is then competitive with the conjugate addition of either methanol or the enolate of starting ketone (Scheme 2.3).

Scheme 2.3 *Proposed mechanism*

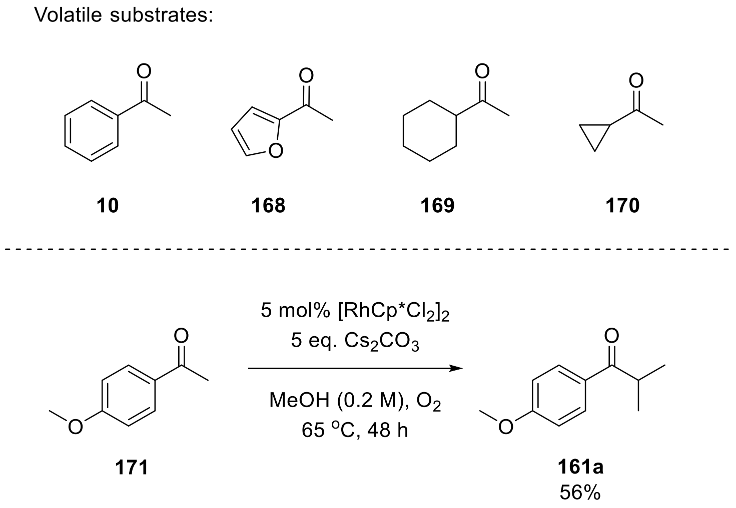


2.2 Results: double alkylation of methyl ketones

2.2.1 Rh catalyzed dimethylation of methyl ketones

At this point, I joined the project with the prior insight of the Rh catalyzed methylation methodology. Since α-branched products are rarely formed from alkylation of ketones with alcohols other than methanol, we decided to examine the possibility of performing a double methylation reaction on methyl ketones. Additionally, methyl ketones are ideal starting substrates due to their wide commercial accessibility. As a result, the double methylation of methyl ketones under the previously optimized reaction conditions was first investigated (Scheme 2.4).

Scheme 2.4 *Substrates for the double methylation of methyl ketones*

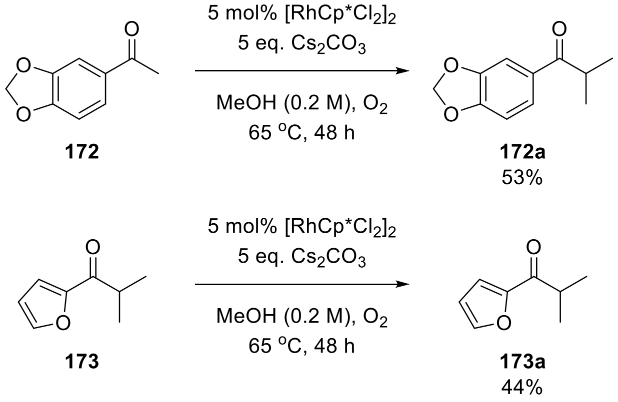


Commercially available acetophenone (**10**), 1-(furan-2-yl)ethanone (**168**), 1-cyclopropylethanone (**169**), and 1-cyclohexylethanone (**170**) were treated with 5 mol% $[RhCp^*Cl_2]_2$, 5 eq. Cs_2CO_3, MeOH (0.2 M) and O_2 at 65 ˚C for 48 h. Unfortunately, the mass recovery was poor for those reactions due to the volatility of both the starting ketones and dimethylated products. Therefore, we turned our attention to the use of methyl ketones with higher boiling points.

When 4'-methoxy acetophenone (**171**) was subjected to the standard conditions, isopropyl ketone **161a** was obtained in 56% yield. The structure of dimethylated ketone **161a** was confirmed by ^{1}H NMR spectroscopy, with a 1H septet at 3.45 ppm, corresponding to the ketone α-proton, and a 6H doublet at 1.13 ppm, consistent with previously reported literature data.[55]

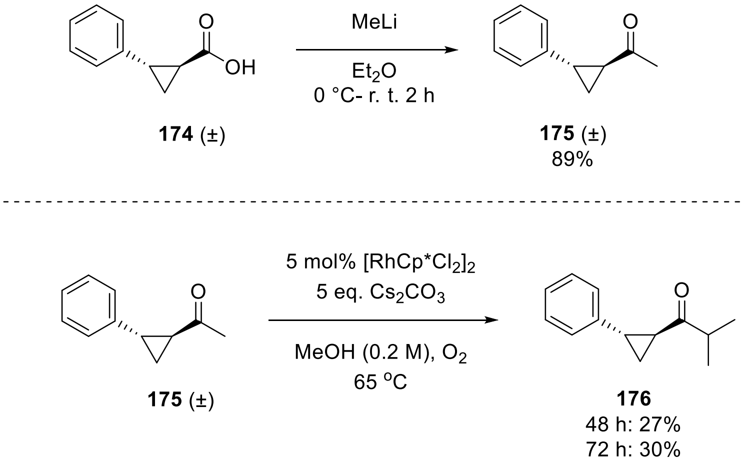
Using the same conditions, isopropyl ketones **172a** and **173a** were also accessed directly from the commercially available starting materials in 53% and 44% yields respectively. The moderate yields for the dimethylation reactions indicated yields of 67-75% per methylation, which were consistent with the mono-methylation yields reported previously (Scheme 2.5).

Scheme 2.5 *Double methylation of methyl ketones*



We have successfully performed double methylation reactions on aryl-methyl ketones, and as a next stage, we wanted to further expand the scope to alkyl-methyl ketones. It appeared that cyclopropyl ketones offered good reactivity in the previous reported Rh-catalyzed methylation methodology (section 2.1), and so we decided to investigate the double methylation of a more substituted and less volatile cyclopropyl-methyl ketone. We chose to synthesize *trans*-2-phenylcyclopropylethanone (**175**), which was prepared by the addition of MeLi to *trans*-2-phenyl-1-cyclopropane carboxylic acid (**174**) in 89% yield. However, the attempted double methylation reaction only afforded the desired product in 27% yield with unconsumed starting material present (23%) after 48 h. The yield was not improved by leaving the reaction for 72 h, affording 30% product with 21% recovered starting material, and it was hard to identify the rest of the mass (Scheme 2.6). The stereochemistry of **176** was not determined at this stage due to the poor conversion of the reaction.

Scheme 2.6 *Double methylation of substituted cyclopropyl-methyl ketone*

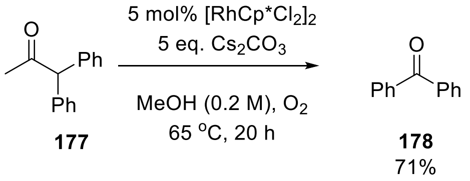


However, double methylation was achieved for aryl-methyl ketones **171**, **172**, **173** in 44-56% yields, while the reaction of alkyl-methyl ketone **175** was slow with only *ca.* 50% mass recovery. It was noticed that there was a missing mass issue for all of the double methylation reactions, and it might help us to improve the conditions if we could identify the side products of these reactions.

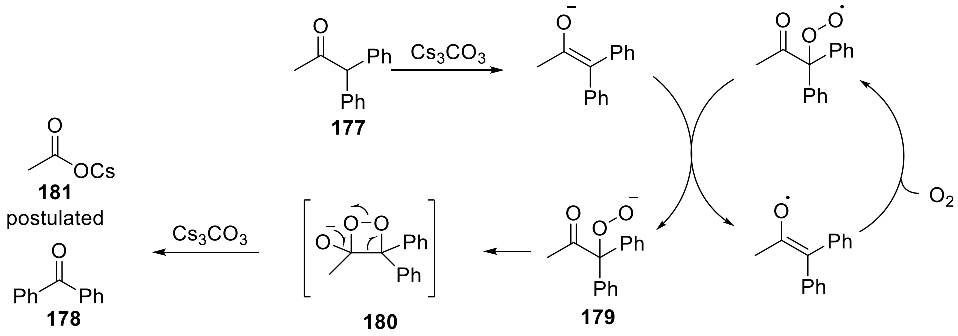
An unexpected result led us to consider a plausible side reaction that might occur under the dimethylation conditions. During the reaction of 1,1-diphenylacetone (**177**), instead of forming the dimethylated compound, benzophenone (**178**) was isolated in 71% yield as the sole product detected (Scheme 2.7a). In order to account for this observation, we propose an oxidative rearrangement mechanism. We believe that the substrate was initially deprotonated at the dibenzylic position to form the enolate, which then reacted with O_2 to give the peroxide anion (**179**). This in turn formed a four-membered intermediate **180** which rearranged to provide benzophenone **178** and formic salt **181** (Scheme 2.7b). Such a mechanism is supported by work by Sakurai and co-workers where the α-peroxide species **179** was detected by GC during the gold nanocluster promoted aerobic oxidation of 1,1-diphenylacetone **177**.[56] Richardson *et al.* also suggested a cyclic mechanism involving 1,2-dioxetane intermediates for the cleavage of α-hydroperoxy ketones into the corresponding aryl ketone and acid under aerobic conditions.[57] Originally, the hydroperoxide cyclizes with the carbonyl moiety to generate a 1,2-dioxetane **183**, which subsequently decomposes to yield an acid and a carbonyl compound (Scheme 2.7c).

Scheme 2.7 *Aerobic oxidation of benzylic ketones*

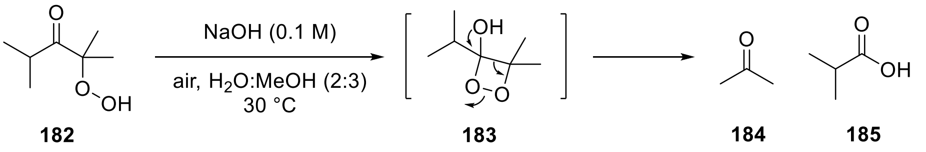
a. Unexpected formation of benzophenone



b. Proposed mechanism

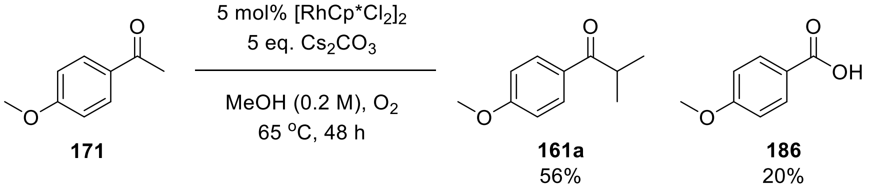


c. Base catalyzed decomposition of α-hydroperoxy ketones in the literature



We suggest that the oxidative cleavage is a general side reaction for all the ketones under the methylation conditions, which would result in formation of corresponding acids through a similar mechanism. The slower the methylation is, the more decomposition would occur.

Scheme 2.8 *Isolation of 4-methoxyphenyl benzoic acid*



In order to support this hypothesis, the dimethylation of 4-methoxyacetophenone (**171**) was revisited, and the crude mixture was quenched with water following complete reaction. The aqueous phase was separated and acidified to pH = 1, extracted with ethyl acetate. Concentration of the organic phase revealed 4-methoxyphenyl benzoic acid (**186**) in 20% yield (Scheme 2.8). Since oxidative cleavage occurs under basic and aerobic conditions, and both Cs_2CO_3 and O_2 are essential for a successful methylation, the formation of side products is unavoidable. The more acidic ketones such as 1,1-diphenylacetone (**177**) are more likely to undergo oxidative side reaction, while we were still able to achieve reasonable yields of the dimethylated products for the less acidic ketones **171**, **172**, and **173**.

In the end, we also investigated if the reaction could be stopped at the mono-methylated stage. During the methylation of 4'-methoxyactophenone, TLC analysis indicated that both the mono- and doubly methylated compounds were present after 12 h, with complete conversion to the doubly methylated product after 48 h. Attempts to stop the reaction after a shorter period of time in order to isolate pure mono-methylated material were in vain, with doubly methylated product always being present. Lowering the amount of Cs_2CO_3 was also attempted, but this tactic only resulted in slower reaction with incomplete consumption of starting material (32%). Mono- and doubly methylated product **161**, **161a** were isolated as an inseparable mixture with approximately 20% and 30% conversion respectively.[‡‡] The use of

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[‡‡] Yields calculated from ^{1}H NMR spectroscopy

other bases such as KOH led to decomposition of both starting material and products, whilst Li_2CO_3, which is not soluble in MeOH, resulted in the sole recovery of starting material (94%, Scheme 2.9).

Scheme 2.9 *Attempts to stop the reaction at mono-methylation stage*

171

	161	**161a**	**RSM**
2.5 eq. Cs_2CO_3	20%	30%	32%
5 eq. KOH	trace	16%	n/o
5 eq. Li_2CO_3	n/o	n/o	94%

In summary, the double methylation, which could not be stopped at the mono-methylation stage, was successfully applied to the reactions of aryl-alkyl ketones in good yields, with an oxidative cleavage side reaction being observed.

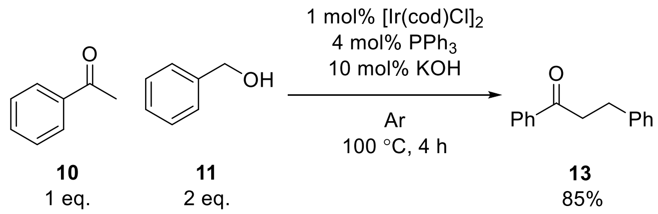
2.2.2 One-pot sequential Ir/Rh catalyzed dialkylation

As mentioned earlier, there are many literature reactions for the alkylation of methyl ketones with benzylic or long chain primary alcohols catalyzed by Ir,[32] Ru,[1, 3-5] Rh,[9] Pd,[10-12, 58] or Ag/Mo oxides,[16] but branched products could not be afforded under those conditions. Methanol is the only alcohol that has been observed to alkylate more substituted ketones for the formation of branched products. Therefore we chose to combine one of literature procedures for the alkylation of methyl ketones with our Rh catalyzed methylation methodology in a one-pot protocol to further expand the scope of branched products.

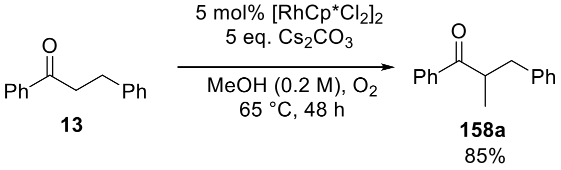
The solvent-free alkylation conditions reported by Ishii using a combination of $[Ir(cod)Cl]_2$, PPh_3, and KOH appeared attractive for this purpose since there was no need for a solvent change or complex workup.[32] In order to test this, the stepwise reactions were first performed. Subjection of acetophenone (**10**) and benzyl alcohol to the Ishii conditions at 100 ˚C firstly provided 3-phenylpropiophenone (**13**) in 85% yield. Armed with the knowledge that this product reacted smothly under the Rh catalyzed conditions (section 2.1.2), we then chose to attempt a one-pot procedure. Once the first alkylation was completed and cooled, $[RhCp^*Cl_2]_2$, Cs_2CO_3, MeOH, and an O_2 balloon were added to the crude mixture. This was heated to 65 ˚C for 14.5 h, giving the desired dialkylated ketone **158a** in 67% yield with the structure confirmed by observation of peaks in ^{1}H NMR at 3.85-3.75 ppm (m, 1H) corresponding to the α-proton of ketone, 3.21 ppm (dd, *J* = 13.7, 6.3 Hz, 1H), 2.73 (1H, dd, *J* = 13.7, 7.9 Hz) for the two diastereotopic β-protons , and 1.24 ppm (d, *J* = 6.9 Hz, 3H) for the methyl group (Scheme 2.10).

Scheme 2.10 *Ir/Rh catalyzed dialkylation of acetophenone*

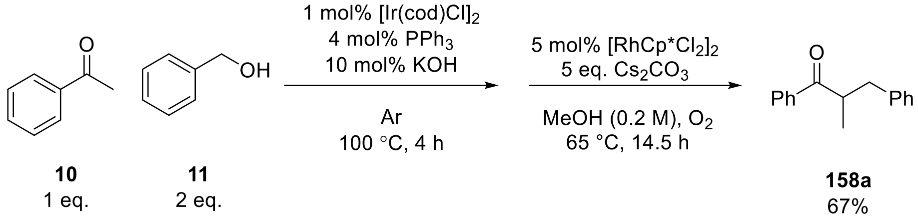
a) Ir catalyzed first alkylation



b) Rh catalyzed methylation



c) One-pot Ir/Rh catalyzed dialkylation



A set of control experiments were carried out in order to rule out the possibility that the Ir catalyst was also responsible for the second methylation step (Scheme 2.11). 3-Phenylpropiophenone was treated with 1 mol% [Ir(cod)Cl]$_2$, 4 mol% PPh$_3$, 10 mol% KOH in methanol (0.2 M) under Ar or O$_2$ at 65 ˚C, and only starting material was observed. With hindsight, we know that the reason that this reaction did not work was related to the amount of base added (see section 2.2.4). Furthermore, after the first alkylation was finished, if 5 mol% [Ir(cod)Cl]$_2$, 5 eq. Cs$_2$CO$_3$, methanol, and an O$_2$ balloon were added, only 8% of the desired dialkylated product was obtained along with the over reduced compound **14 (**71%)§§. The structure of 1,3-diphenylpropan-1-ol (**14**) was confirmed by the appearance of peaks in the ^{1}H NMR at 4.72-4.69 ppm (m, 1H) corresponding to the proton adjacent to the hydroxyl group,

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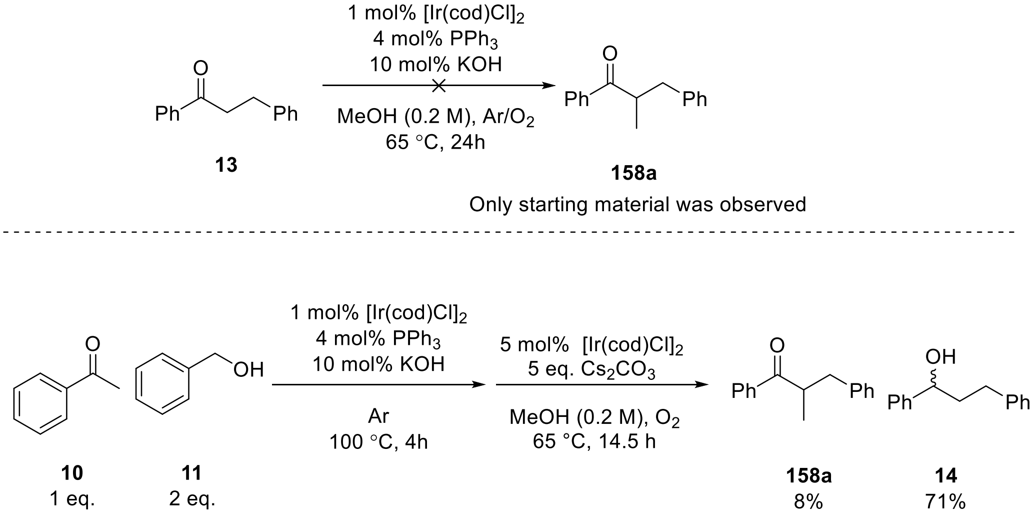
§§ Yield was calculated from ^{1}H NMR using1,2-dimethoxybenzene as an internal standard

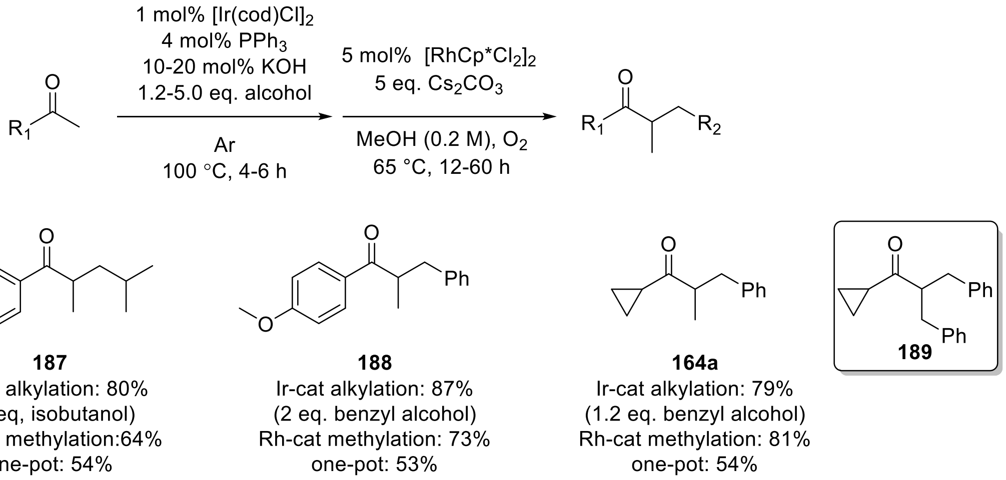
2.83-2.67 ppm (m, 2H), and 2.22-2.02 ppm (m, 2H) corresponding to the two sets of diastereotopic protons. The data were consistent with that reported in literature.[59]

Scheme 2.11 *Control experiments*



These control experiments confirmed that $[RhCp^*Cl_2]_2$ was essential for the second methylation step. In order to examine the general applicability of this one-pot procedure, several other methyl ketones were assessed. For example, acetophenone was alkylated with 5 eq. *iso*butanol, followed by methanol to generate the dialkylated ketone **187** in 54% yield. Similarly, doubly alkylated products from 4-methoxyacetophenone (**171**) and 1-cyclopropylethanone (**170**) were obtained in good yields.

Scheme 2.12 *dialkylation of methylketones*



187
Ir-cat alkylation: 80%
(5 eq, isobutanol)
Rh-cat methylation:64%
one-pot: 54%

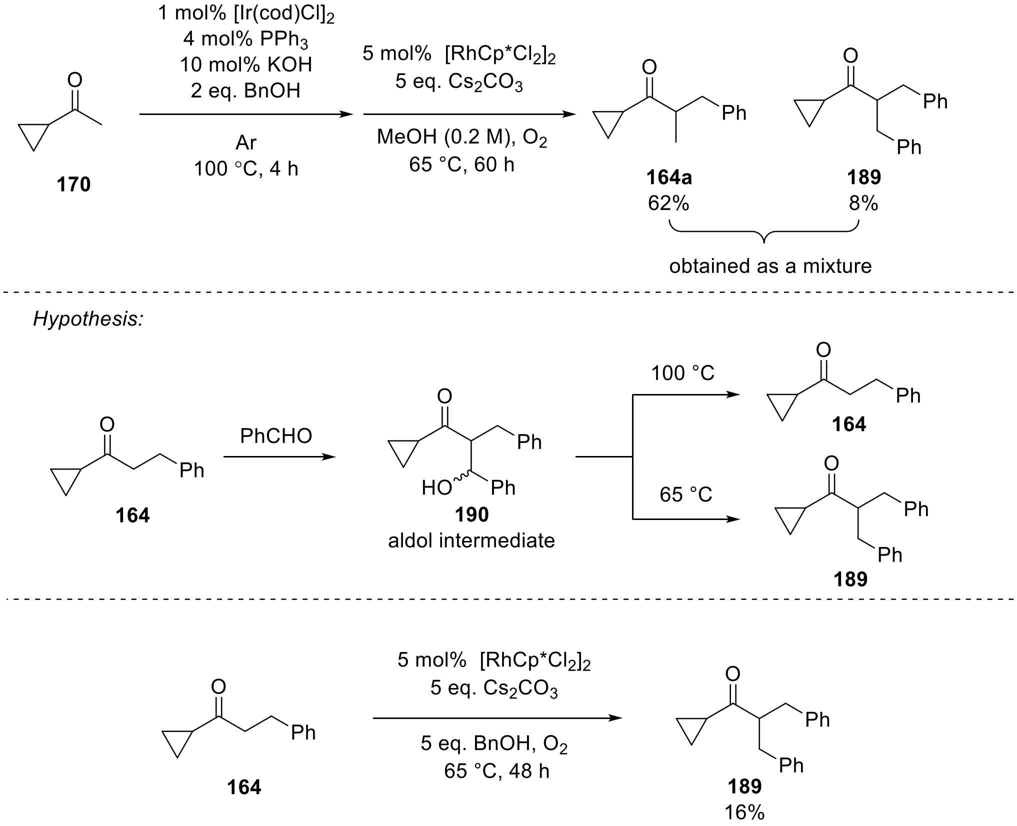
188
Ir-cat alkylation: 87%
(2 eq. benzyl alcohol)
Rh-cat methylation: 73%
one-pot: 53%

164a
Ir-cat alkylation: 79%
(1.2 eq. benzyl alcohol)
Rh-cat methylation: 81%
one-pot: 54%

It was noteworthy that only 1.2 equivalents of benzyl alcohol was used in the first alkylation of 1-cyclopropylethanone (**170**), since having an excess (2.0 eq.) resulted in the formation of *ca.* 8% of the dibenzylated compound **189,** which was inseparable from **164a** by column chromatography. The structure of **189** was supported by the presence of a peak at 287 ppm ($[M+Na]^+$) in the ESI^+ mass spectrum, as well as observation of peaks at 3.34-3.27 ppm (m, 1H) corresponding to the α-proton of ketone and 2.88-2.75 ppm (m, 2H) corresponding to a pair of the diastereotopic benzylic protons (the rest of peaks are overlapping with those of **164a**) .

To the best of our knowledge, double alkylation under hydrogen borrowing conditions using alcohols other than methanol has not been reported. The dibenzylated by-product observed here was not generated in either of the individual steps, but only observed in the one-pot procedure and was a unique occurance. We propose that mono-benzylated cyclopropyl ketone **164** reacted with a second equivalent of benzaldehyde to give the aldol intermediate **190**. However, **190** only underwent retro-aldol at 100 ˚C, while at a lower temperature (65 ˚C), the aldol intermediate **190** was able to eliminate H_2O and be reduced by M-H to give the dibenzylated product. Besides, retro-aldol is favoured by steric congestion, and the cyclopropyl group is a relatively small substituent which encourages the formation of dibenzylated product. The A value of cyclopropyl group is not available in the literature, but it should be between 1.75 (Et) and 2.15 kcal/mol(*i*Pr), while the A value for a phenyl group is 3.0 kcal/mol[60] (Scheme 2.13). The double alkylation (non-methanol) of sterically unhindered ketones is a promising topic for further investigation. The cyclopropyl group is a versatile one, capable of undergoing ring opening reactions allowing formation of more complicated ketone products. Attempt to optimise this promising result are currently underway in the Donohoe group, and 16% yield of the dibenzylated compound **189** was generated when employing 5 mol% $[RhCp^*Cl_2]_2$, 5 eq. Cs_2CO_3, 5 eq. BnOH at 65 ˚C under an oxygen atmosphere (Scheme 2.13). ***

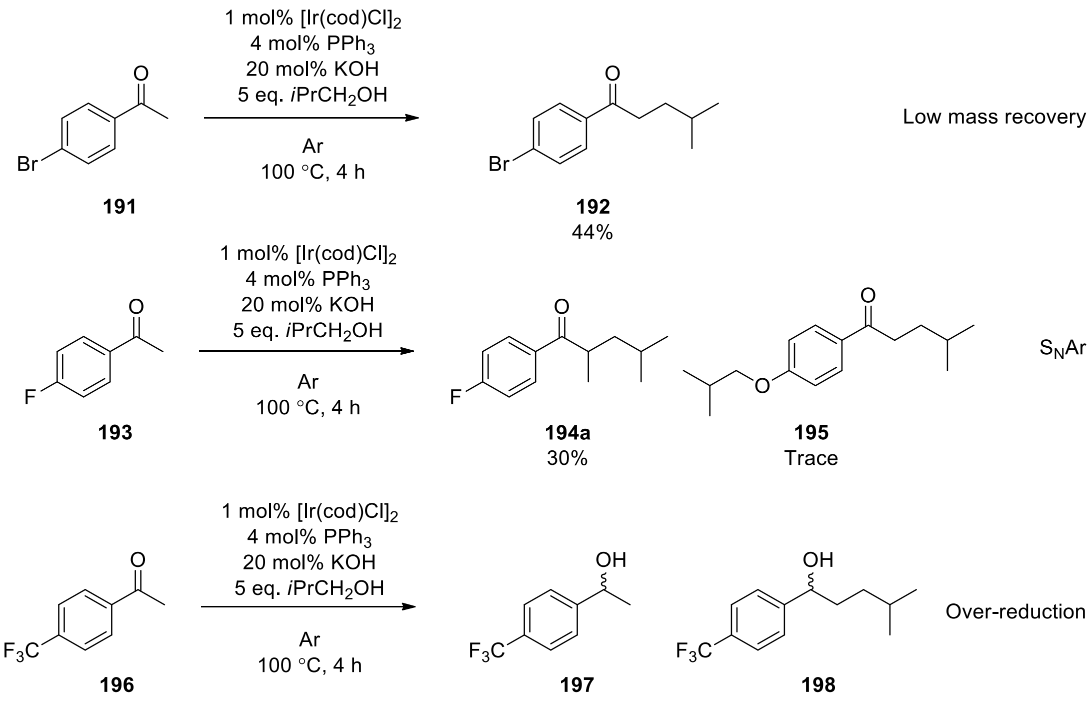
Scheme 2.13 *Observation of dibenzylated ketone*



*** L.M. Rakers

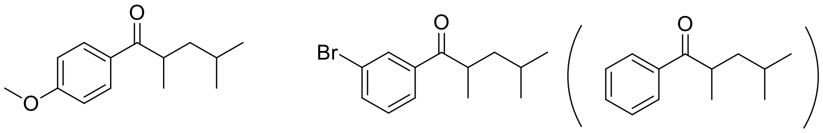
When expanding the substrate scope for the one-pot procedure, it became apparent that the Ishii alkylation reaction was somewhat limited in terms of functional group tolerance (Scheme 2.14). This concerned the substitution pattern of the aromatic ring, with the alkylation product from reaction of 4’-bromoacetophenone (**191**) with *iso*butanol being isolated in only 44% yield without other detectable products. A similar result was obtained with 4’-fluoroacetophenone (**193**) with a small amount of S_NAr product observed in addition to the desired product. For the reaction of 4’-trifluoromethylacetophenone (**196**), both starting material and product were over reduced to the corresponding alcohols, yields were not determined because of purification difficulties.

Scheme 2.14 *Unsuccessful reactions for Ishii alkylation*



4’-Methoxyacetophenone was successfully alkylated with *iso*butanol in 72% yield, but the subsequent methylation step was slow and only afforded 51% product. The one-pot procedure was found to be slower still, giving an inseparable mixture of mono- and dialkylated products. The first alkylation of 3’-bromoacetophenone was achieved in 82%, however during the methylation step, an inseparable debromination product **187** was also formed in addition to the desired dialkylated product **200a** (Figure 2.1). Such debromination had never been observed for substrates containing bromide in previous studies, and we suggest the debrominated product derived from the insertion of Rh into the C-Br bond followed by reductive elimination with hydride.

Figure 2.1 *Unsuccessful methylation step*



199
Ir-cat alkylation: 72%
Rh-cat methylation: 51%
one-pot: slow reaction

200a
Ir-cat alkylation:82%
Rh-cat methylation:
debromination observed

187

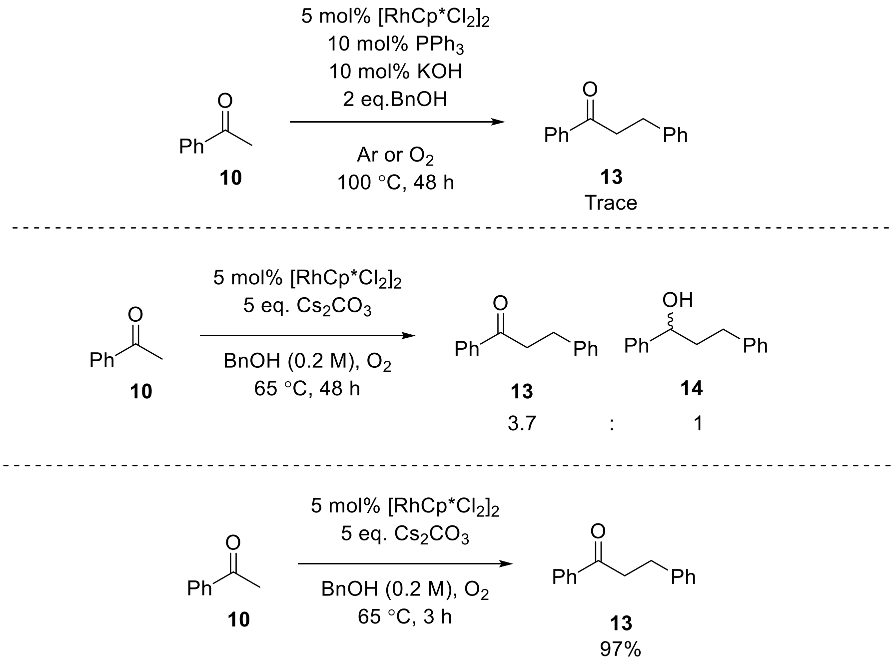
2.2.3 Rh catalyzed double alkylation

The Ir/Rh catalyzed tandem dialkylation methodology held considerable promise for the generation of complex carbonyl compounds from simple methyl ketones, but this route required two different catalysts with a high overall metal loading (2 mol% Ir +10 mol% Rh). As a result, we attempted to improve the conditions with the aim of using only one catalyst for both steps.

We first studied the ability of $[RhCp^*Cl_2]_2$ to catalyze the first alkylation of methyl ketones with alcohols other than methanol. Taking acetophenone and benzyl alcohol as a model system, Ishii’s conditions were repeated using $[RhCp^*Cl_2]_2$. Disappointingly, reactions under either an O_2 or Ar atmosphere gave only trace amounts of the desired product with mainly recovered starting material. Alternatively, the desired product **13** and over reduced product **14** **(**ratio of 3.7:1) were generated when $[RhCp^*Cl_2]_2$ and Cs_2CO_3 were employed under O_2 in

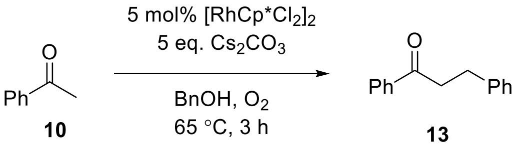
BnOH (0.2 M) at 65 ˚C after 48 h. Shortening the reaction time to 3 h gave only the desired product **13** in 97% yield (Scheme 2.15).

Scheme 2.15 *Rh catalyzed first alkylation*



Lowering the amount of BnOH to 0.6 M (*ca.* 16 eq.) also gave the desired product in 73% yield (Table 2.2, entry 2), but further reduction of the amount of BnOH resulted in poor yields because stirring the 5 eq. Cs_2CO_3 in BnOH became inefficient (Table 2.2, entry 3-5). The addition of a co-solvent such as THF or toluene with 2 eq. BnOH did not further improve the reaction (Table 2.2, entry 6, 7).

Table 2.2 *Effect of amount of BnOH*

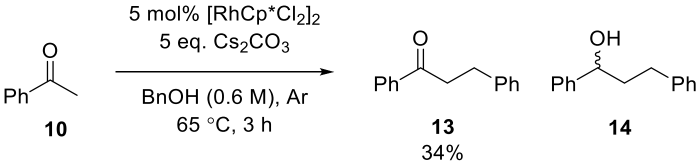


Entry	BnOH (eq.)	Yield (%)
1	48 (0.2 M)	97
2	16 (0.6 M)	73
3	10	51
4	5	27
5	2	25
6	2[a]	23
7	2[b]	36

a. THF (0. 6 M) was used as co-solvent; b. toluene (0.6 M) was used as co-solvent.

Repeating the conditions shown in entry 2 but under an Ar atmosphere only afforded 34% yield of the desired product, with the majority being the over reduced compound **14** (Scheme 2.16).

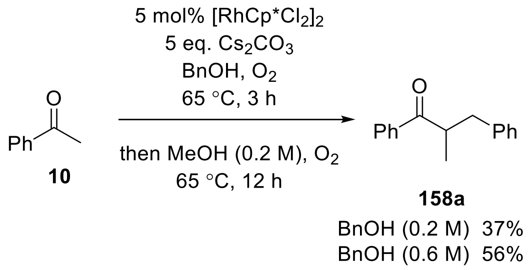
Scheme 2.16 *Rh catalyzed first alkylation under Ar*



Since the Rh catalyzed benzylation was achieved in 97% yield with a subsequent methylation in 85%, these two steps were combined in an one-pot procedure. Acetophenone was first alkylated with BnOH (0.2 M) using 5 mol% $[RhCp^*Cl_2]_2$, 5 eq. Cs_2CO_3 under O_2 at 65 ˚C for 3 h before MeOH was added. The mixture was then stirred for an additional 12 h under O_2 at

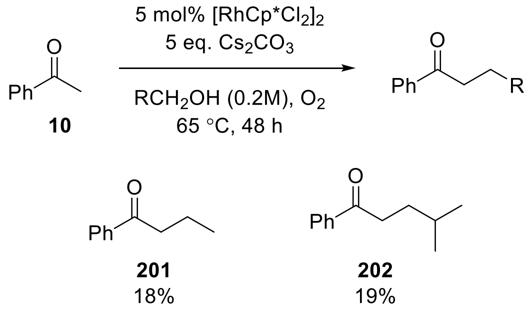
65 ˚C, resulting in the formation of dialkylated product **158a** in a modest 37% yield. Pleasingly, reducing the amount of BnOH to 0.6 M yielded the dialkylated product in an improved 56% yield. This was an excellent result considering it being a one-pot, two-step synthesis.

Scheme 2.17 *Rh catalyzed double alkylation*



To our disappointment, the Rh catalyzed double alkylation could not be applied to other alcohols such as *iso*butanol or ethanol as the first alcohol. The reactions did not go to completion even after 48 h, and only afforded the desired products in 18% and 19% yields respectively (Scheme 2.18). We could not suggest a simple reason for these unsuccessful reactions, although it should be noted that BnOH might be activated towards oxidation and elimination, due to conjugation. It seems that there are no general conditions for the Rh catalyzed alkylation with different alcohols, as a result, we chose to abandon further investigation of this procedure.

Scheme 2.18 *Rh catalyzed alkylation with other alcohols*



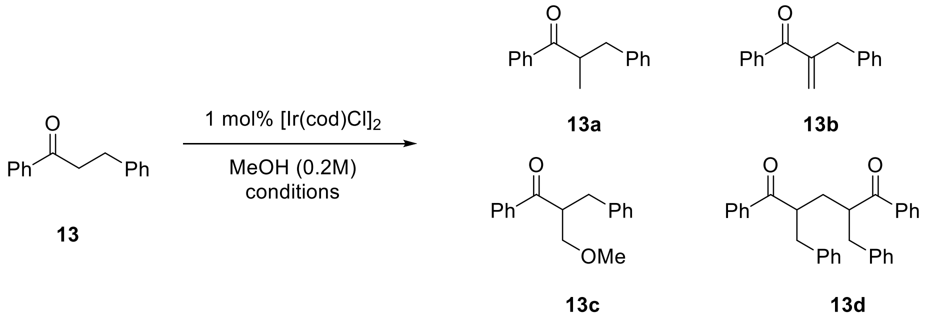
mainly starting material with poor mass recovery

2.2.4 Ir catalyzed methylation

As discussed earlier, the Ir/Rh catalysed sequential dialkylation and the Rh catalysed dialkylation reactions required high catalyst loading and the substrate scope was limited. Moreover, rhodium is one of the most expensive metals ($[RhCp^*Cl_2]_2$, £212619/mol, Alfa Aesar), so we decided to explore the possibilities of using the cheaper catalyst $[Ir(cod)Cl]_2$ (£80738/mol, Sigma Aldrich), used in Ishii alkylation chemistry, to catalyze the methylation step.

Taking 3-phenylpropiophenone (**13**) as a model substrate, we first repeated Ishii's alkylation conditions using methanol as an alkylating regent. This resulted in the sole recovery of starting material (Table 2.3, entry 1). With the prior insight that an O_2 atmosphere has beneficial effect on the rhodium catalyzed methylation reaction, we then tested to see if O_2 could facilitate the iridium system. When the reaction was performed under an O_2 atmosphere, a trace of the desired methylated product was detected by ^{1}H NMR with lower recovery of starting material (Table 2.3, entry 2). It seemed that the starting material decomposed at a higher temperature under O_2, and therefore the same reaction was carried out at 65 ˚C, but again only starting material was observed (Table 2.3, entry 3). Pleasingly, the reaction afforded 48% desired product (along with 5% starting material and 33% dimer) when treated with 2 eq. KOH under Ar after 48 h (Table 2.3, entry 4), while the reaction under O_2 was completed within 24 h to give the desired product in 69% yield with 30% dimer formation (Table 2.3 , entry 5).

Table 2.3 *Ir catalyzed methylation of 3'-phenylpropiophenone*



Entry	Conditions	RSM (%)	13a (%)	13b (%)	13c (%)	13d (%)
1	10% KOH, 4% PPh_3 100 °C, Ar, 24 h	>90	-	-	-	-
2	10% KOH, 4% PPh_3 100 °C, O_2, 24 h	62*	3*	-	-	-
3	10% KOH, 4% PPh_3 65 °C, O_2, 24 h	>90	-	-	-	-
4	2 eq. KOH, 4% PPh_3 65 °C, Ar, 48 h	5*	48*	-	-	33
5	2 eq. KOH, 4% PPh_3 65 °C, O_2, 24 h	-	69	-	-	30
6	2 mol% $[Ir(cod)Cl]_2$ 2 eq. KOH, 8% PPh_3 65 °C, O_2, 24 h	-	74	-	-	23
7	1 eq. KOH, 4% PPh_3 65 °C, O_2, 48 h	-	81	-		10
8	1 eq. KOH, 4% PPh_3 65 °C, O_2, 48 h (1 mmol)	-	83	-	-	9
9	1 eq. KOH, 4% PPh_3 65 °C, Ar, 48 h	17	47	-	-	4

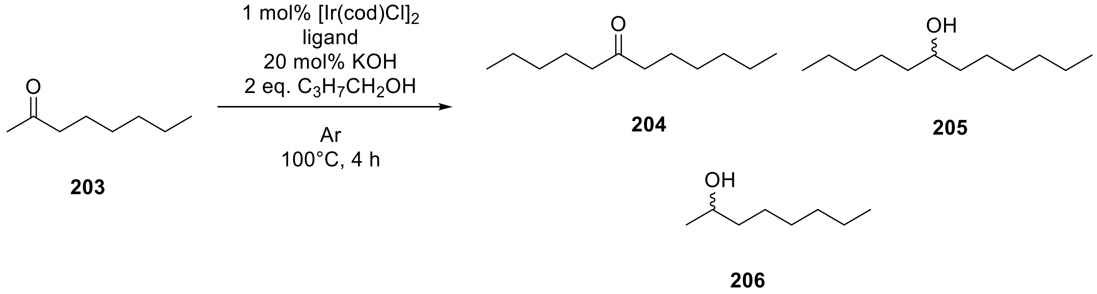
0.3 mmol 3'-phenylpioprophenone was stirred with $[Ir(cod)Cl]_2$, PPh_3, base in methanol (0.2 M). *Recovered starting material and methylated compound **13a** were obtained as inseparable mixture, yields calculated by ^1H NMR.

We suggested that dimerisation was favoured when formaldehyde was formed slowly, or too much enolate of starting ketone was present. With slow formation of formaldehyde, only a small amount of enone was generated, which could be trapped by large excess amount of starting material to yield the dimer. Therefore, we chose to double the amount of catalyst to facilitate the formation of formaldehyde. However, this only led to a minimal improvement in yield (Table 2.3, entry 6). Employing too much base would result in higher concentration of enolate of starting material to trap the enone, and also favours dimer formation. To our pleasure, the yield was improved to 81% by the addition of less KOH (Table 2.3, entry 7). We were also able to scale-up the reaction to 200 mg (0.95 mmol), which gave a consistently high yield (83%, Table 2.3, entry 8). As a control experiment, when 3-phenylpropiophenone was reacted with methanol under an Ar atmosphere, 47% product was obtained with 17% unreacted starting material and 4% dimer (Table 2.3, entry 9).

2.2.4.1 Effect of phosphine ligands

Ishii has reported that the alkylation of methylketones was considerably influenced by addition of ligands. While PPh_3 (Table 2.4, entry 1) was the best ligand followed by PBu_3 and PCy_3 (Table 2.4, entry 3 and 4), the bidentate ligands, dppe and dppp, promoted transfer hydrogenation from alcohols to ketones rather than the alkylation (Table 2.4, entry 5 and 6). They also reported that excess PPh_3 ($Ir:PPh_3 = 1:4$) inhibited the coordination of alcohols to the iridium complex; thus poor conversion was observed (Table 2.4, entry 2).[32]

Table 2.4 *Effect of ligands for Ishii's alkylation of 2-octanone with 1-butanol*

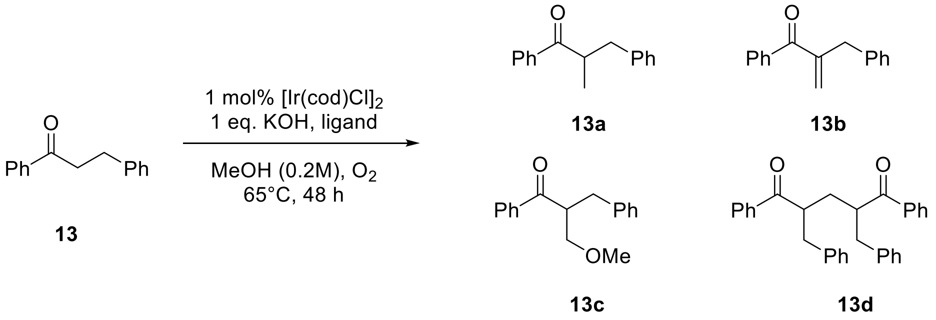


Entry	Ligand	Conv. (%)	204 (%)	205 (%)	206 (%)
1	4 mol% PPh_3	96	80	2	7
2	8 mol% PPh_3	38	2	n/d	6
3	4 mol% PBu_3	84	63	2	16
4	4 mol% PCy_3	82	48	2	15
5	2 mol% dppe	85	28	2	26
6	2 mol% dppp	92	23	3	27

203 (2 mmol) was reacted with 1-butanol (4 mmol) in the presence of $[Ir(cod)Cl]_2$ (0.02 mmol), KOH (0.2 mmol), and ligand at 100 ° C for 4 h without solvent.

The effect of different phosphine ligands on our methylation reaction was therefore examined with the the loading fixed at Ir:P = 1:2 in order to see if we could further optimize the conditions.

Table 2.5 *Effect of phosphine ligands*



Entry	Ligand	RSM (%)	13a (%)	13b (%)	13c (%)	13d (%)
1	4 mol% PPh$_3$	-	83	-	-	9
2	4 mol% P(2-furyl)$_3$	-	57	2	12	23
3	4 mol% P(*o*-tolyl)$_3$	-	56 (57)	-	7	37
4	4 mol% PBu$_3$	6	4	10	29	26
5	4 mol% PCy$_3$	-	8	6	33	34
6	2 mol% dppe	-	47	2	16	20
7	2 mol% dppb	-	72 (74)	Trace	Trace	10

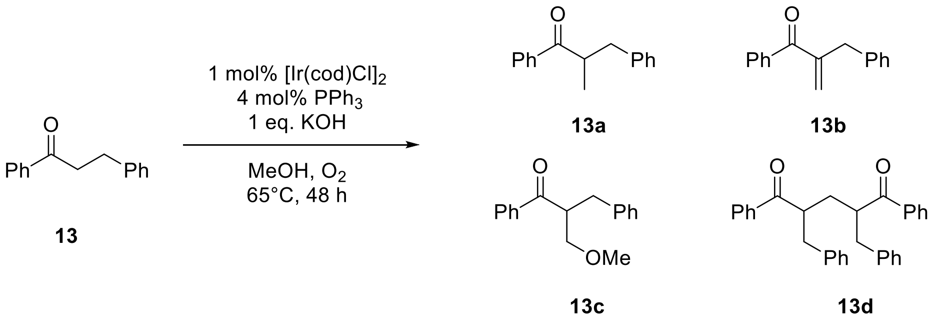
Yields were calculated from ^{1}H NMR with 1,2-dimethoxybenzene as an internal standard; Yields in brackets are isolated yields. NB 1 mol% [Ir(cod)Cl]$_2$ equals 2 mol% Ir metal.

Other aromatic substituted phosphine ligands such as tri(2-furyl)phosphine and tri(*o*-tolyl) phosphine (Table 2.5, entries 2 and 3) also gave good yields of the desired methylated product **13a** (57% and 56%). Interestingly, when alkyl phosphine ligands such as PBu$_3$ and PCy$_3$ were employed (Table 2.5, entry 4 and 5), enone **13b**, methoxy adduct **13c**, dimer **13d** were formed in good amount, indicating the interruption of reduction process. Transfer hydrogenation product was not observed with the addition of bidentate ligands, and high yield of desired methylated product was still obtained with dppb (72%, Table 2.5, entry 7). A lower yield was observed for dppe (47%, Table 2.5, entry 6), and we supposed that the short ethylene bridge between two phosphine atoms in dppe limited the bite angle (85 ° compared to 98 ° for dppb)[61] of the ligand, thereby restricting the flexibility of its binding to Ir and disfavouring the reaction. In summary, it is clear that the phosphine ligands play an important role on the product distribution, with PPh_3 (mono-dentate, electron poor) appears to be the best ligand for the formation of desired methylated product.

2.2.4.2 Effect of concentration

The dimer **13d** was found to be the major side product in the methylation reactions (9%, Table 2.6, entry 1), and we supposed that performing the reactions in more dilute methanol would lower the concentration of enolate, thus reduceing the formation of dimer.

Table 2.6 *Effect of concentration*



Entry	Conc. (M)	RSM (%)	13a (%)	13b (%)	13c (%)	13d (%)
1	0.2	-	83	-	-	9
2	0.1	8*	79*	-	-	12
3	0.67	-	36	-	-	45

*Recovered starting material and methylated compound **13a** were obtained as inseparable mixture, yields adjusted by ^{1}H NMR

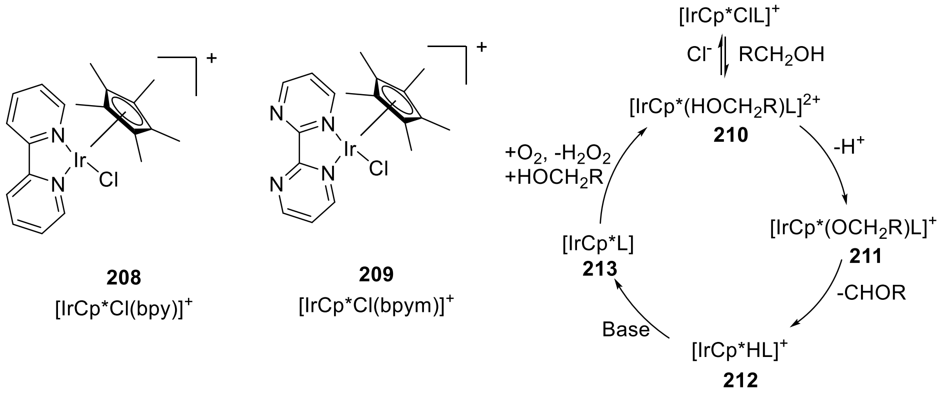
The reaction was slower when performed in 0.1 M methanol, providing 79% methylated compound **13a**, 8% unconsumed starting material **13**, and 12% dimer after the same amount of time (48 h, Table 2.6, entry 2). Performing the reaction under more concentrated conditions (0.67 M), not surprisingly, resulted in more dimer formation. In conclusion, 0.2 M was found to be the best concentration for methylation reactions. Higher concentrations would result in more dimer formation, while slower reaction was observed for lower concentrations.

2.2.4.3 Ir(I) and Ir(III) catalysts

As a next stage, we wanted to gain some insight of the active catalyst species during the methylation reaction to help us further optimize the conditions. It has been reported that $[Ir(cod)(PPh_3)_2]^+Cl^-$ is formed *in situ* when $[Ir(cod)Cl]_2$ (1 eq.), and PPh_3 (4 eq.) are stirred in cold alcohol (methanol or ethanol) under an inert atmosphere.[62] However, it was reported by Oro *et al.* that $[Ir(cod)(PPh_3)_2H]$ was isolated when $[Ir(cod)Cl]_2$ (1 eq.), PPh_3 (4 eq.) was stirred in methanolic solution of potassium hydroxide at room temperature under Ar. [63] In order to test which Ir complex was formed during the course of our methylation ractions, $[Ir(cod)Cl]_2$, PPh_3, and KOH were stirred in MeOH at 65 ˚C under Ar for 24 h to give a yellow suspension. At this point, a small sample (0.5 mL) of the mixture was taken out, filtered, and ^1H NMR of the resulting yellow solid showed peaks at 7.23-7.19 ppm (m, 12 H), 7.13-7.09 ppm (m, 6 H), 7.06-7.02 ppm (m, 12 H) corresponding to the two PPh_3, and peaks at 3.71 ppm (m, 2H), 3.37 ppm (m, 2H), 1.75 ppm (m, 4H), 1.46 ppm (m, 4H) corresponding to the 1,5-cyclooctadiene chelating to Ir. The ^1H NMR data were consistent with that reported for $[Ir(cod)(PPh_3)_2H]$,[63] but the complex was not stable and no more data was obtained to further comfirm the structure. The rest of the reaction mixture was continuously stirred under O_2 for 24 h to give a green suspension. A white solid was obtained after filtration, and the green filtrate was also collected and concentrated. ^1H NMR of either of the precipitate or the filtrate showed only peaks in the aromatic region (7.70-6.70 ppm) without any peaks related to 1,5-cyclooctadiene. The 1,5-cyclooctadiene could have dissociated from Ir and was removed during concentration. We could not identify the structure of the catalyst species under O_2 at this point because of the difficulties in isolating a pure iridium complex.

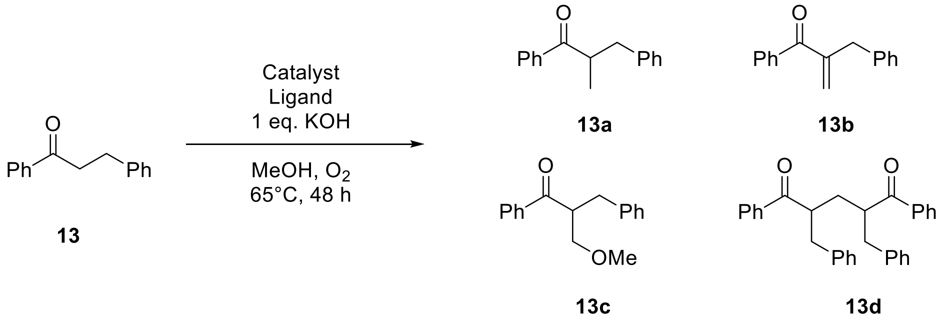
Gabrielsson and co-workers reported an aerobic oxidation of Ir(I)species to the Ir(III) complexes during the dehydrogenation of alcohols using [IrCp*Cl(bpym)]$^+$ and [IrCp*Cl(bpy)]$^+$ complexes.[64] Substitution of the halide by the alcohol and subsequent deprotonation gave an alkoxide complex which rapidly underwent β-hydride elimination to give hydride species **212**. Deprotonation of the acidic hydrides led to a highly oxygen sensitive Ir(I) species **213** that regenerated the Ir(III) complexes **210** upon oxidation with dioxygen. The reoxidation of the Ir^I complexes presumably formed hydrogen peroxide, which subsequently decomposed to molecular oxygen and H_2O (Scheme 2.19).

Scheme 2.19 *Air* o*xidation of Ir(I) species for the regeneration of Ir(III) complexes*



We supposed that the $[Ir(cod)Cl]_2$ catalyst could be oxidised to a Ir(III) species by O_2 during the course of reaction, and a Ir(III) catalyst with the same ligands might give the same or better reactivity. However, it was not the case when $Ir(III)Cl_3$ was employed in the methylation reaction with addition of 1,5-cyclooctadiene and PPh_3, and only starting material was obtained (Table 2.7, entry 2).

Table 2.7 *Ir(I) and Ir(III) catalysts*



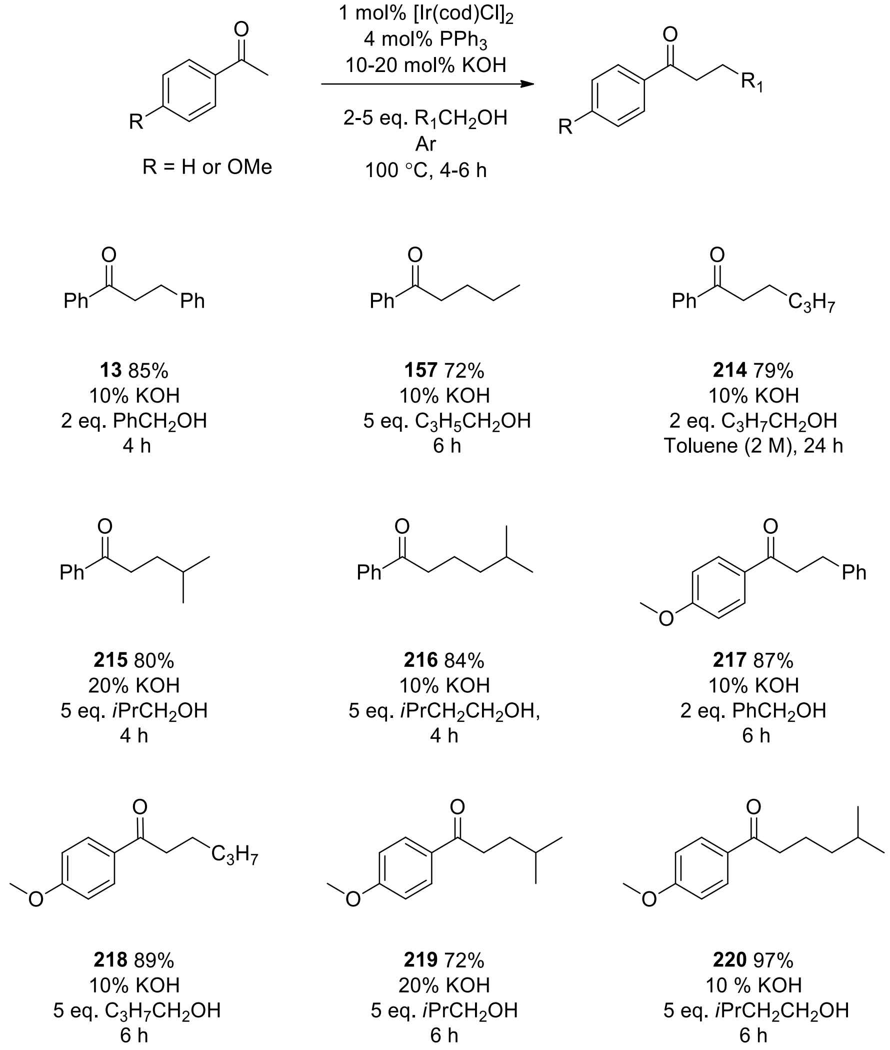
Entry	Catalyst, ligand	RSM (%)	13a (%)	13b (%)	13c (%)	13d (%)
1	1 mol% $[Ir(cod)Cl]_2$, 4 mol% PPh_3	-	83	-	-	9
2	2 mol% $IrCl_3$, 2 mol% cod, 4 mol% PPh_3	90	-	-	Trace	Trace

At this point, the identity of the true catalytic species has not been determined largely due to the difficulty in isolating any Ir related intermediates. Further mechanistic investigation is currently underway in the Donohoe group.

2.2.4.4 Substrate scope

From all of the experiments dicussed above, the best conditions for the methylation of 3-phenylpropiophenone **13** were found to be 1 mol% $[Ir(cod)Cl]_2$, 4 mol% PPh_3, 1 eq. KOH in MeOH (0.2M) at 65 °C under O_2. With these optimal conditions, our attention turned to expanding the substrate scope of the methylation reaction. As such, a variety of different ketones were prepared following Ishii’s alkylation procedure.

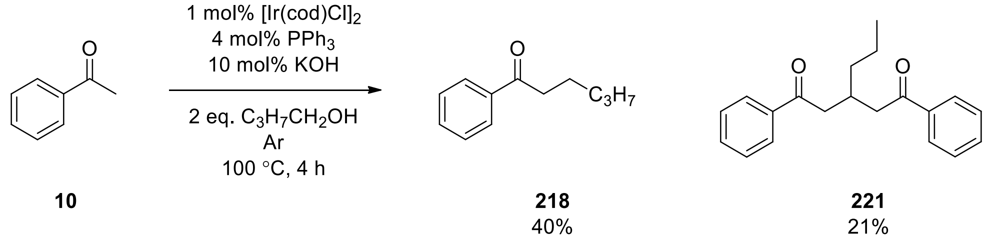
Scheme 2.20 *Preparation of ketone substrates*



Acetophenone was alkylated with different alcohols in the presence of [Ir(cod)Cl]$_2$, PPh$_3$, and KOH following procedures reported by Ishii. Only 2 eq. benzyl alcohol for the benzylation of acetophenone was needed, whilst a higher loading of 5 eq. of alcohols were required for other alkylations. This has again proved that the alkylation with BnOH is easier than that of other primary alcohols (see section 2.2.3, Rh system). Toluene was added as a co-solvent for the *n*butylation of acetophenone, because a dimer species **221** derived from the conjugate addition of acetophenone to the enone intermediate in neat *n*butanol was formed (Scheme 2.20). The dimer **221** has a peak at 295.1 ppm corresponding to [M+H]$^+$ species in the ESI$^+$

mass spectrum and multiplets at 3.17-2.97 ppm (4H, α-protons of ketone), 2.85-2.75 ppm (1H, C*H*) in the ^{1}H NMR (Scheme 2.21).

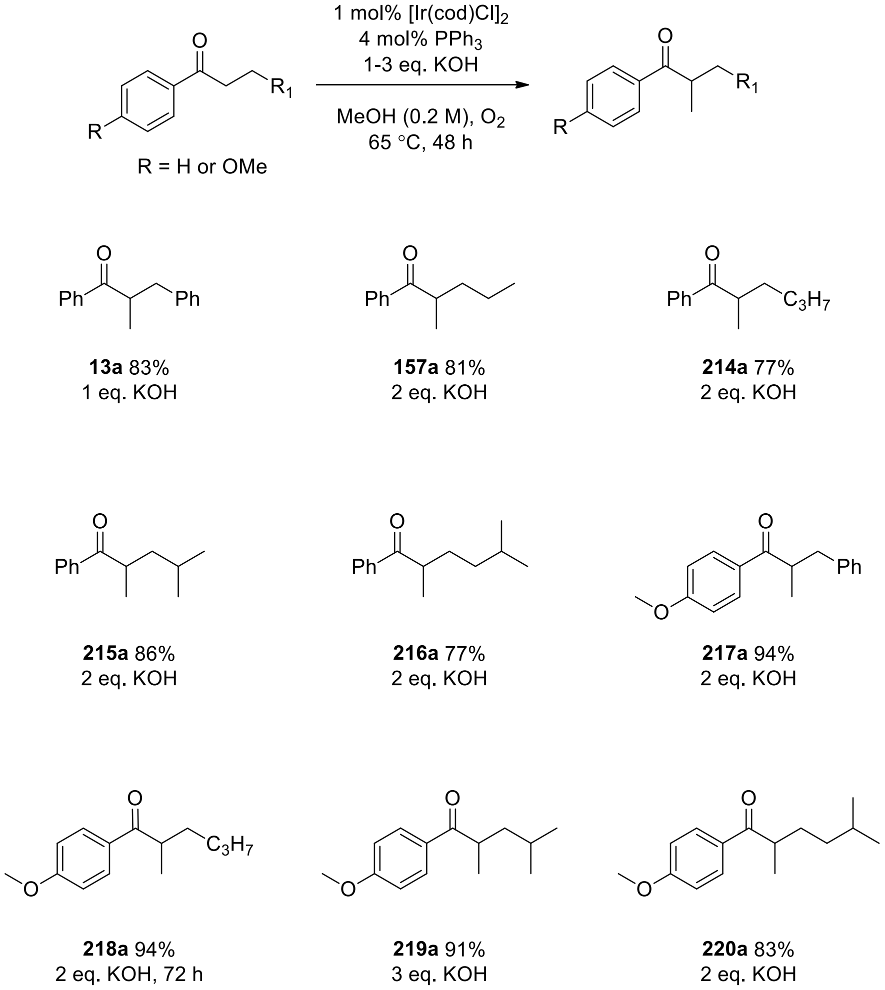
Scheme 2.21 *Dimerisation of acetophenone in neat n-butanol*



In the *iso*butylation of acetophenone, 20 mol% KOH was added to facilitate the reaction. The alkylations of 4’-methoxyacetophenone (pKa = 25.7 (DMSO), and for acetophenone, pKa = 24.7 (DMSO)) took longer reaction time since it is more difficult to deprotonate and subsequent reduce electron rich ketones. It was noted that among all the alkylation reactions, no double alkylation was observed.

With the range of ketones in hand, we next examined the efficiency of the methylation conditions (Scheme 2.22).

Scheme 2.22 *Ir catalyzed methylation reactions*

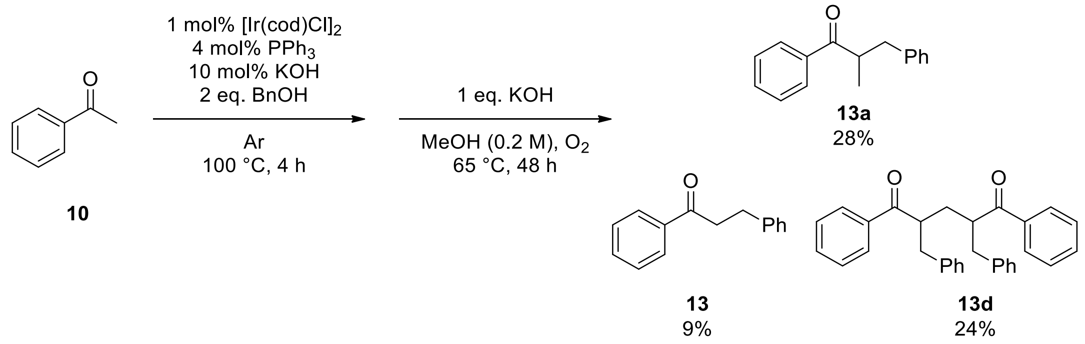


In general, 2 eq. KOH was needed for most of the substrates in order to achieve full conversion while our model substrate, 3'-phenylpropiophenone, only required 1 eq. KOH due to its greater acidity (Section 2.2.4). Ketone **219** bearing an *i*Pr branching group at the β-position required 3 eq. KOH in order to ensure complete reaction. The general observation was that increasing the amount of KOH made the slow substrate react faster, but resulted in more dimer for fast substrate (3'-phenylpropiophenone). Dimer by-products were not observed for 4’-methoxyphenyl ketones **217a-220a**, resulting in better yields than their parent phenyl analogue. We considered aryl ketones bearing a *para* methoxy group to be more versatile than other aromatic ketones since it gave the possibility for the formation of functionalised esters through a regioselective Baeyer-Villiger reaction (will be discussed in Section 2.2.6).

2.2.5 Ir catalyzed one-pot double alkylation

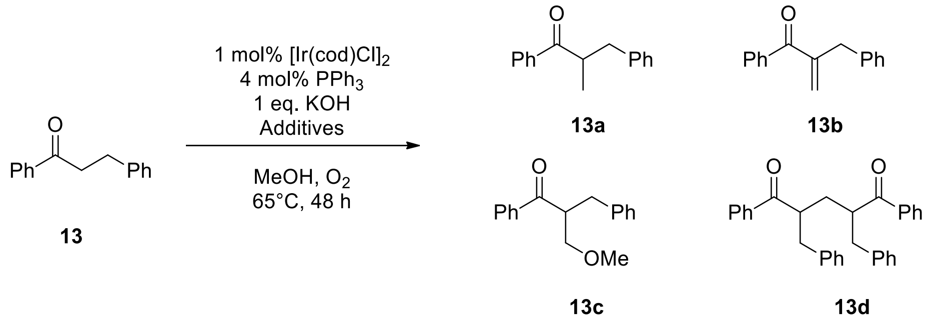
With conditions for the first alkylation of methyl ketones and subsequent methylation in hand, we once again studied the one-pot dialkylation reaction. Acetophenone was benzylated under the standard Ishii conditions to give the desired product, which following the completion of the reaction, was dissolved in MeOH (0.2 M) and KOH (1 eq.) added. This reaction was then heated to 65 ˚C under O_2 for 48 h.

Scheme 2.23 *First attempt at an Ir catalyzed one-pot dialkylation*



To our disappointment, only 28% of the desired dialkylated product **13a**, 9% benzylated product **13** and 24% dimer **13d** were obtained. We hypothesized that the benzaldehyde generated in the first step or possibly the excess amount of BnOH would have a negative effect on the methylation step. In order to rectify this, a series of test reactions were carried out where BnOH or benzaldehydewere added to the methylation reaction of 3-phenylpropiophenone (**13**).

Table 2.8 *Effect of BnOH or benzaldehyde on the methylation reaction*



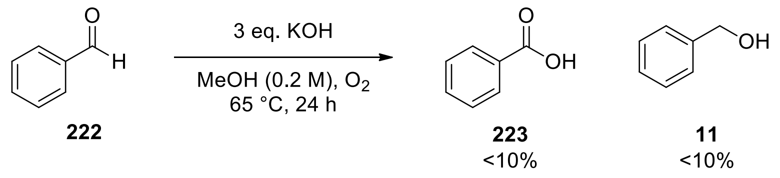
Entry	Additive	RSM (%)	13a (%)	13b (%)	13c (%)	13d (%)	BnOH (%)	PhCHO (%)
1	1 eq. BnOH	-	(76)	-	-	(8)	80	Trace
2	1 eq. Benzaldehyde	15	65	-	-	n/d	44	4
3	1 eq. BnOH 1 eq. Benzaldehyde	11	69	-	-	n/d	78	11
4	5 eq. benzaldehyde	57	3	-	22	-	15	22

Yields were calculated from ^{1}H NMR with 1,2-dimethoxybenzene as an internal standard; yields in brackets are isolated yields.

The addition of BnOH did not cause any harm to the reaction, and a trace of benzaldehyde was observed in the crude ^{1}H NMR (Table 2.8, entry 1). The methylation was slowed down with the formation of 44% benzyl alcohol when 1 eq. benzaldehyde was added, and only 4% benzaldehyde was recovered at the end of reaction (Table 2.8, entry 2). The results for the addition of both BnOH and benzaldehyde (Table 2.8, entry 3) were similar to that of entry 2 with 78% BnOH and 11% benzaldehyde recovered after the reaction. With the addition of 5 eq. benzaldehyde, the methylation was almost stopped with mostly staring material and 22% methoxy adduct being observed. We concluded that the presence of excess benzaldehyde was the main reason for the slow methylation step, and also that benzaldehyde was converted to benzyl alcohol under the reaction conditions.

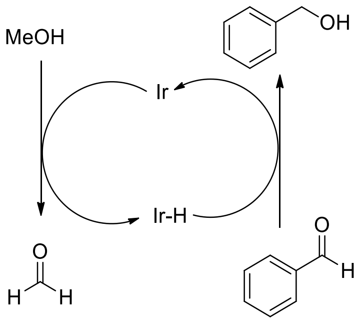
It occurred to us that a Cannizzaro reaction between benzaldehyde to form benzyl alcohol and the potassium salt of benzoic acid could be operating. To test this hypothesis, benzaldehyde and KOH was stirred in MeOH at 65 ˚C under O_2 for 24 h before water and ethyl acetate were added to quench the reaction. The aqueous phase was reacidified to pH = 1, extracted with ethyl acetate, and concentrated. The crude ^1H NMR showed mainly unreacted starting material, and the formation of a small amount of benzyl alcohol was confirmed by appearance of a peak at 4.63 ppm (benzylic CH_2) in the ^1H NMR and a peak at 65.4 ppm for the corresponding carbon in the ^{13}C NMR. The carboxylic OH of benzoic acid was not observed in the ^1H NMR, but the appearance of a peak at 171.7 ppm in the ^{13}C NMR is consistent with literature known data,[65] and confirmed the formation of benzoic acid. It appeared that the Cannizzaro reaction was possible at 65 ˚C in methanol, but only a small amount of the products were formed in this manner (Scheme 2.24).

Scheme 2.24 *Test reaction for the Cannizzaro pathway*



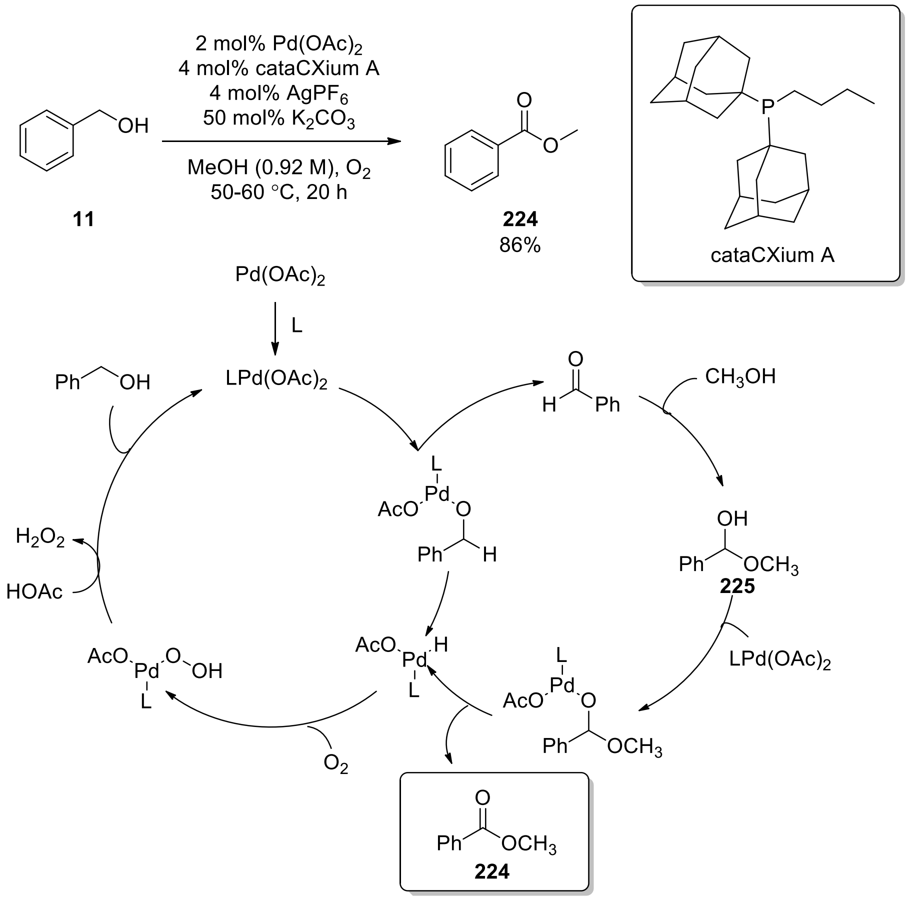
An alternative possibility involved transfer hydrogenation from methanol to benzaldehyde catalyzed by Ir to give benzyl alcohol and formaldehyde, since methanol was present in a large excess (Scheme 2.25).

Scheme 2.25 *Transfer hydrogenation from methanol to benzaldehyde*



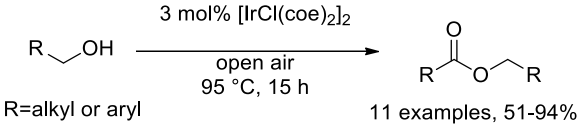
Thirdly, an esterification between methanol and benzaldehyde was also a possible pathway accounting for the low recovery of benzaldehyde (Table 2.8, entry 2-4). Beller and co-workers have reported a palladium catalyzed cross esterification reaction of benzyl alcohol and methanol under an O_2 atmosphere (Scheme 2.26).[66] Benzyl alcohol was first oxidised to benzaldehyde by the Pd catalyst, and a hemiacetal intermediate **225** was formed by addition of MeOH. Further oxidation of the hemiacetal gave a methyl ester **224** and a Pd-H species which was reoxidised by O_2 (Scheme 2.26).

Scheme 2.26 *Pd catalyzed cross esterification of alcohols*



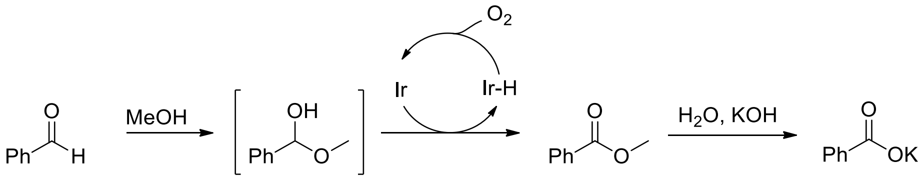
Additionally, Ishii *et al.* reported a dimerization of primary alcohols to esters catalyzed by $[IrCl(coe)_2]_2$ (Scheme 2.27), confirming the capability of Ir species to catalyze such reactions.[67]

Scheme 2.27 *Ir catalyzed dimerization of alcohols to esters*



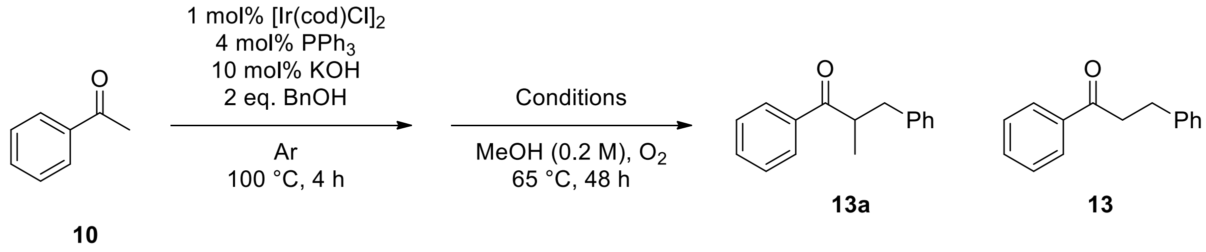
We proposed that benzaldehyde could undergo a similar esterification reaction with methanol under our optimised Ir catalyzed methylation conditions. The methyl ester could then be hydrolyzed with water under basic conditions to form the salt, thus consuming KOH and slowing down the methylation reaction (Scheme 2.28).

Scheme 2.28 *Proposed side reaction: esterification of benzaldehyde and methanol*



Taking account of these possible side reactions, it was assumed that more base was needed in the one-pot procedure as most of the KOH was sacrificed during the side reactions of benzaldehyde. As expected, the yield was improved to 45% when 2 eq. KOH was added in the second step (Table 2.9, entry 2). Further increasing the amount of base (3 eq.) did not result in a further improvement (Table 2.9, entry 3). To our surprise, when 2 mol% PPh_3 was added together with 2 eq. KOH, an overall yield of 58% was achieved (Table 2.9, entry 4). The yield dropped to 45% again 4 mol% PPh_3 was added (Table 2. 9, entry 5). We have considered the possibility that PPh_3 might have been oxidised to $Ph_3P{=}O$, but TLC analysis showed that $Ph_3P{=}O$ was not present in the reaction mixture. The role of PPh_3 was not evident, but clearly fresh PPh_3 ligand was required after the first alkylation step.

Table 2.9 *Optimisation of the one-pot Ir catalyzed dialkylation reactions*

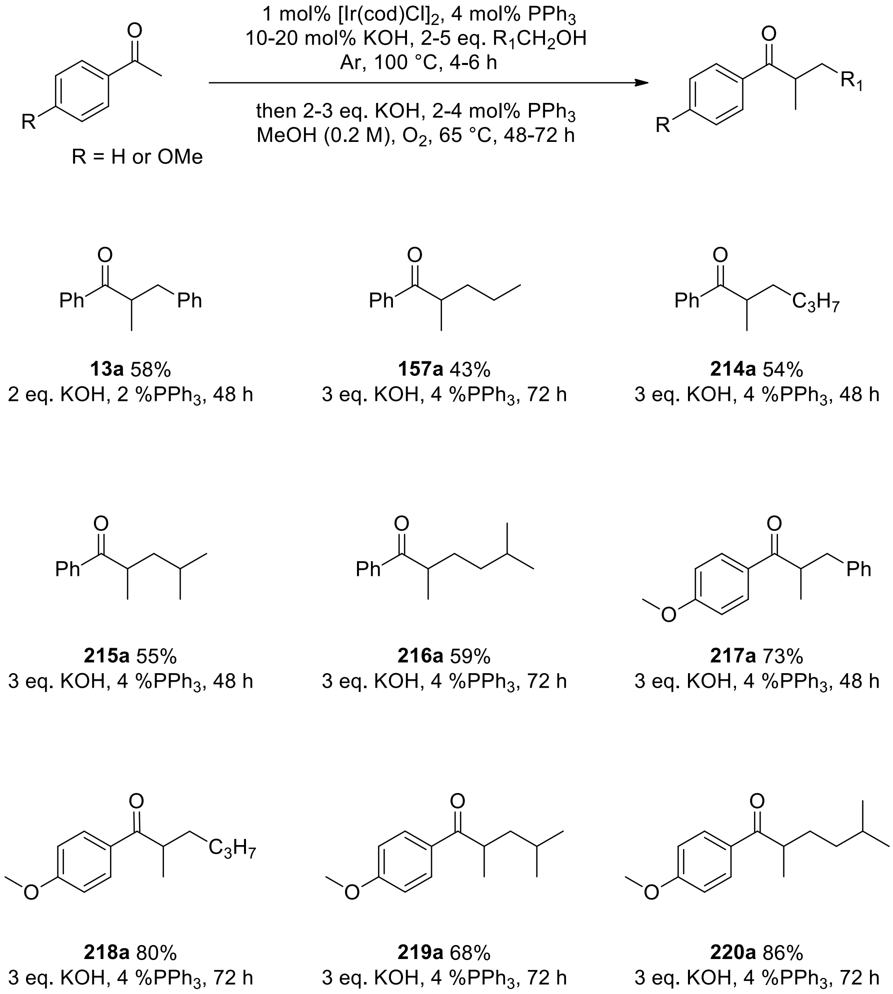


Entry	**Conditions**	**13a (%)**	**13 (%)**
1	1 eq. KOH	28	9
2	2 eq. KOH	45	Trace
3	3 eq. KOH	44	-
4	2 eq. KOH, 2 mol% PPh$_3$	**58**	-
5	2 eq. KOH, 4 mol% PPh$_3$	45	-

2.2.5.1 Substrate scope

With the optimum one-pot conditions in hand (Table 2.9, entry 4), we set out to explore the substrate scope. Acetophenone or 4’-methoxyacetophenone were first alkylated with various alcohols following the conditions discussed in section 2.2.4.4. Once the first step was finished, KOH, PPh$_3$, and methanol were added. The resulting mixture was stirred at 65 ˚C under O$_2$ for an additional 48-72 h. Compared to our model substrate **13**, a higher loading of KOH (3 eq.) and PPh$_3$ (4 mol%) were needed in the second methylation step for all other substrates, presumably because of their lower acidity. The second step also required a longer reaction time (72 h) for electron rich ketones **218-220.** Good to excellent overall dialkylation yields were achieved which were comparable to the multiples of individual stepwise yields.

Scheme 2.29 *Ir catalyzed one-pot dialkylation reactions*



13a 58%
2 eq. KOH, 2 %PPh$_3$, 48 h

157a 43%
3 eq. KOH, 4 %PPh$_3$, 72 h

214a 54%
3 eq. KOH, 4 %PPh$_3$, 48 h

215a 55%
3 eq. KOH, 4 %PPh$_3$, 48 h

216a 59%
3 eq. KOH, 4 %PPh$_3$, 72 h

217a 73%
3 eq. KOH, 4 %PPh$_3$, 48 h

218a 80%
3 eq. KOH, 4 %PPh$_3$, 72 h

219a 68%
3 eq. KOH, 4 %PPh$_3$, 72 h

220a 86%
3 eq. KOH, 4 %PPh$_3$, 72 h

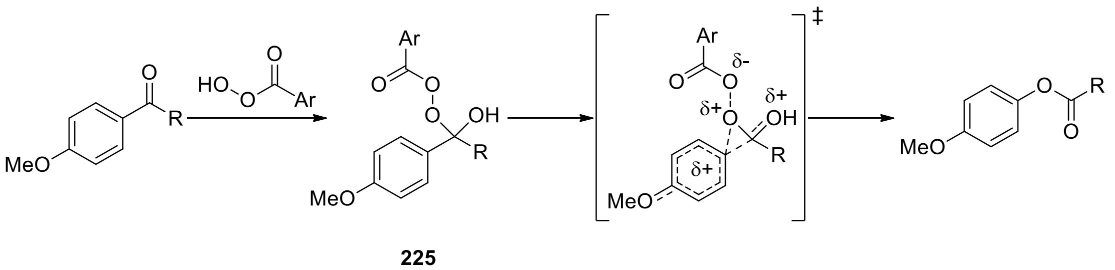
Dialkylation reactions of 4’-methoxy acetophenone (**171**) were found to give better yields than those reactions for acetophenone because the 4’-methoxyphenyl ketones **217**-**220** did not dimerize under the reaction conditions. Furthermore, results in the next section will show that the dialkylated products were ideal substrates for Baeyer-Villiger oxidation, allowing regioselective formation of 4’-methoxyphenyl esters.

2.2.6 Baeyer-Villiger Oxidation

It has been discussed in section 1.1.2 that the α-alkylation of esters with alcohols using hydrogen borrowing methodology remains challenging, and the subjection of esters into our methylation conditions only resulted hydrolysis of the ester group or trans-esterification with methanol without any methylation being observed.[68] It was important to extend the scope of this methodology beyond the reaction of ketones; therefore a Baeyer-Villiger oxidation was investigated to allow the formation of other carbonyl derivatives from the methylated ketones.

We suspected that 4’-methoxyphenyl-alkyl ketones would be able to give good regioselectivities because the electron rich group was more likely to migrate by virtue of its ability to stabilize the positive charge build up over the molecule. In terms of mechanism, Criegee postulated a nucleophilic attack of the peracid onto the ketone in the Baeyer-Villiger oxidation to generate the so-called “Criegee intermediate” **225** (Scheme 2.30). Then, the carboxylic acid moiety acts as a leaving group and, in a concerted fashion, the C=O bond was reformed and one substituent migrated from the carbonyl carbon atom to the partially positively charged oxygen atom.[69] The electron-rich groups were preferred for migration because their abilities to accommodate a positive charge thus stabilising the transition state for migration.

Scheme 2.30 *Mechanism for the Baeyer-Villiger oxidation*

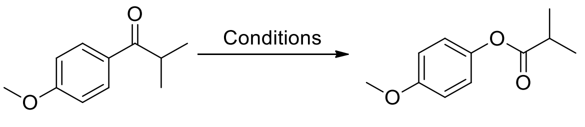


225
Criegee intermediate

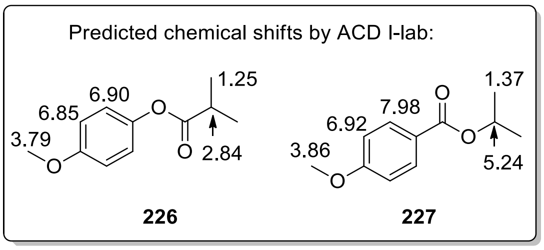
As we are intended to do a one-pot methylation and then Baeyer-Villiger reactions, initial studies involved performing the Baeyer-Villiger oxidation using similar conditions to the methylation reaction, and therefore 1-(4-methoxyphenyl)-2-methylpropan-1-one (**161a**) was treated with *m*CPBA[†††] in MeOH in the first instance. Treatment of 1-(4-methoxyphenyl)-2-methylpropan-1-one (**161a**) with *m*CPBA (2 eq.) in methanol at room temperature for 60 h gave solely staring material (Table 2.10, entry 1). Chamberlin and co-workers reported that the combination of trifluoroacetic acid (TFA) and *m*CPBA in dichloromethane oxidized both cyclic and acyclic ketones in much shorter reaction times and in higher yields than with *m*CPBA alone, presumably because the protonated carbonyl groups are more reactive towards *m*CPBA.[70] As such, TFA (1 eq.) was added together with *m*CPBA (2 eq.) to the starting ketone in methanol, but only a trace of the desired ester was formed at room temperature (Table 2. 10, entry 2). With a higher temperature, 40% conversion was achieved when the mixture was refluxed in methanol for 48 h (Table 2.10, entry 3). The addition of TFA did promote Baeyer-Villiger oxidation, but we were not able to achieve high conversion in methanol. The reaction was therefore performed in dichloromethane, providing the desired ester in 71% yield after 24 h, albeit with some contamination by unreacted starting ketone (Table 2.10, entry 4). Finally, doubling the amount of *m*CPBA and TFA yielded the ester in 97% with complete regioselectivity for the desired regioisomer at room temperature after 24 h (Table 2.10, entry 5).

[†††] 3-Chloroperoxybenzoic acid (*m*CPBA) was washed with phosphate buffer (pH =7-8) before being recrystalized from refluxing dichloromethane.

Table 2.10 *Baeyer-Villiger oxidation of 1-(4-methoxyphenyl)-2-methylpropan-1-one*



161a **226**

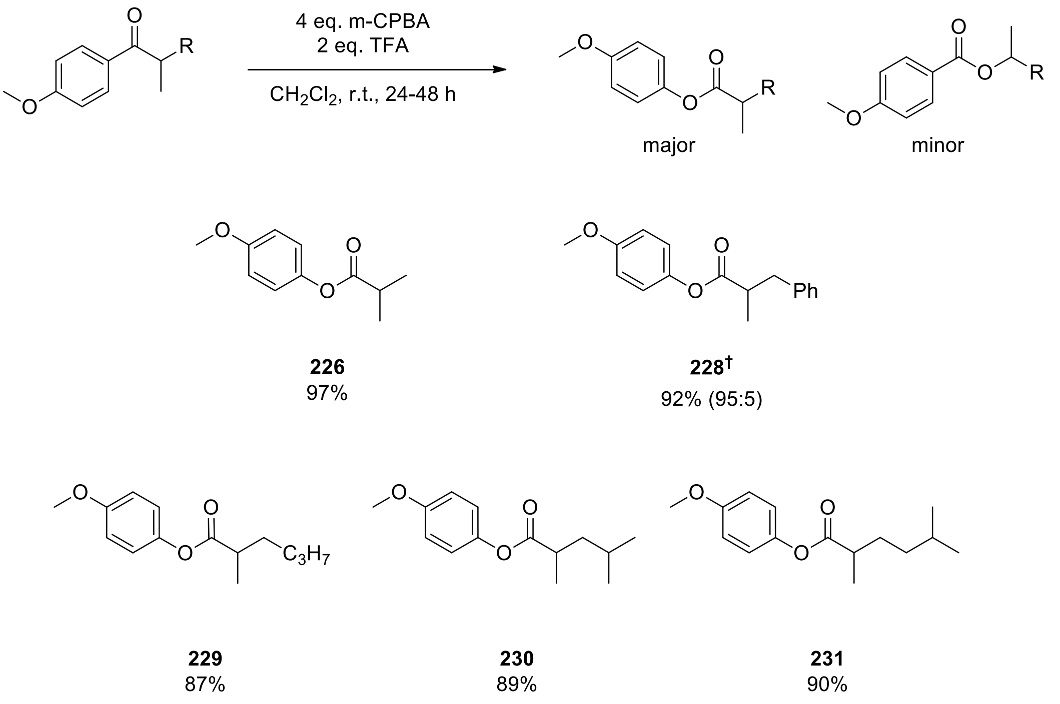


Entry	Conditions	Solvent	226 (%)
1	2 eq. *m*CPBA 60 h, r. t.	MeOH	-
2	2 eq. *m*CPBA, 1 eq. TFA 48 h, r. t.	MeOH	Trace
3	2 eq. *m*CPBA, 1 eq. TFA 48 h, reflux	MeOH	40
4	2 eq. *m*CPBA, 1 eq. TFA 24 h, r.t.	CH_2Cl_2	71
5	4 eq. *m*CPBA, 2 eq. TFA 24 h, r.t.	CH_2Cl_2	97

If the aryl group migrates, we would expect the ArC<u>H</u> *ortho* to the ester group to be less deshielded at around 6.90 ppm, and the C<u>H</u> of the isopropyl group to have a low chemical shift at 2.84 ppm; However, if the isopropyl group migrates, the isopropyl C<u>H</u> is more deshielded at 5.24 ppm, and the ArC<u>H</u> *ortho* to the carbonyl group is at a higher chemical shift 7.98 ppm.[‡‡‡] The regioisomer **226** was confirmed by observation of peaks in ^{1}H NMR at 6.91 (d, *J* 8.0 Hz, 2H), 6.81 (d, *J* 8.0 Hz, 2H), 3.72 (s, 3H) corresponding to the *para*-methoxyphenyl group, and peaks at 2.71 (sept, *J* 7.0 Hz, 1H), 1.23 (d, *J* 6.8 Hz, 6H) for the *i*Pr group, consistent with those previously reported. [71] Since the Baeyer-Villiger oxidation in methanol was slow, we were unable to perform a one-pot methylation and oxidation to form the ester. After the alkylation reactions were finished, 4'-methoxyphenyl ketone products were purified and treated with *m*CPBA, TFA in dichloromethane to yield various esters.

[‡‡‡] https://ilab.acdlabs.com/iLab2

Scheme 2.31 *Baeyer-Villiger oxidation*

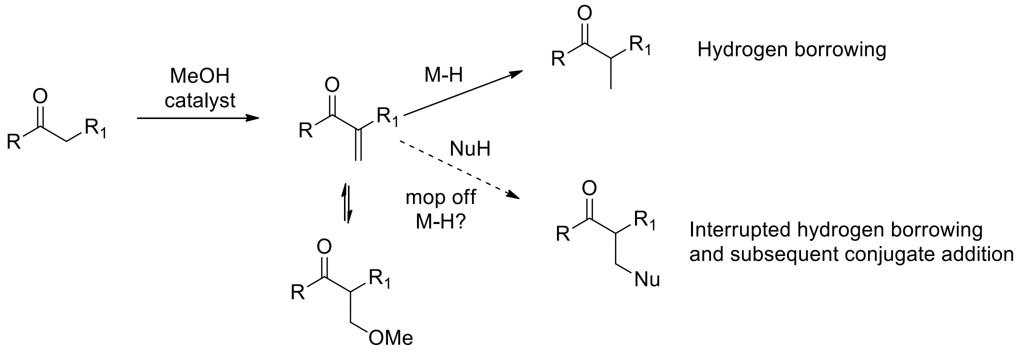


Baeyer-Villiger oxidation of 1-(4-methoxyphenyl)-2-methylhexan-1-one (**218a**), 1-(4-methoxyphenyl)-2,4-dimethylpentan-1-one (**219a**), and 1-(4-methoxyphenyl)-2,5-dimethylhexan-1-one (**220a**) also gave complete regioselectivity with the migration of the *para*-methoxy phenyl group, proved by ^{1}H NMR. Oxidation of 1-(4-methoxyphenyl)-2-methyl-3-phenylpropan-1-one (**217a**)*[*] gave trace amount of the other isomer as an inseparable mixture with the major regioisomer. The integration of peaks in ^{1}H NMR at 3.70 ppm, 3.77 ppm corresponding to the OMe groups of the major and minor regioisomers gave a ratio of 95: 5. In summary, the dialkylation and Baeyer-Villiger oxidation sequence had further expanded the scope to esters, thus introduced potential for the formation of more oxidised carbonyl group in the products.

2.3 Interrupted hydrogen borrowing

Upon surveying literature, it was clear that we were unlikely to produce branched products from the alkylation of ketones with alcohols other than methanol (Chapter 1). Resubjection experiments (Section 2.1.3) had shown that the methylation reaction proceeded *via* an enone intermediate, which was subsequently reduced by a metal hydride. It was postulated that if we could interrupt the hydrogen borrowing process by preventing enone reduction, the selective formation of enone followed by an *in situ* conjugate addition of different nucleophiles would allow the synthesis of a wide range of complex products (Scheme 2.32).

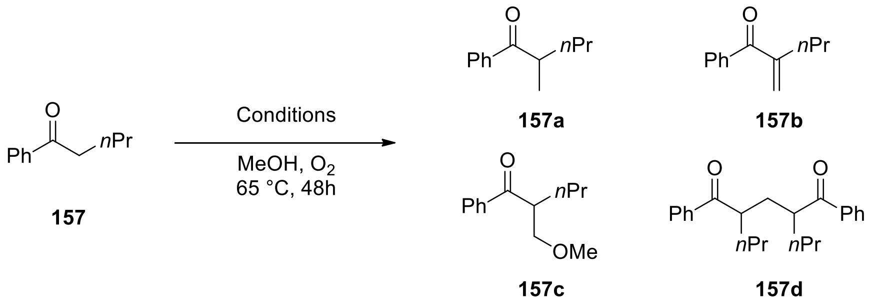
Scheme 2.32 *The concept of interrupted hydrogen borrowing*



The ligand-screening experiments discussed in section 2.2.4.1 showed that the choice of ligand played a crucial role in determining the distribution of products. Less than 10% yield of methylated product was observed when we employed alkyl phosphine ligands such as PBu_3 and PCy_3 (*vide infra*). It seemed that the electron rich alkyl phosphine ligands had the potential to stop enone reduction. With further screening of phosphine ligands in the Donohoe group,[§§§] we were able to selectively produce both the enone and methoxy adduct (Table 2.11).

[§§§] Dr. Darren L. Poole and Anne F. Kornahrens

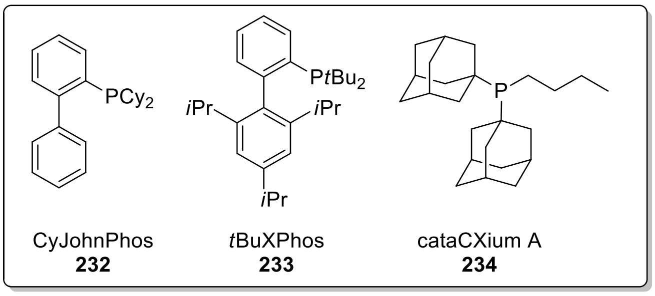
Table 2.11 *Screening of phosphine ligands for the selective formation of enone and methoxy adduct*[§§§]



Entry	Conditions	RSM (%)	157a (%)	157b (%)	157c (%)	157d (%)
1	1 mol% [Ir(cod)Cl]$_2$ 4 mol% PCy$_3$, 2 eq. KOH, 0.2 M	Trace	Trace	17	59	16
2	1 mol% [Ir(cod)Cl]$_2$ 4 mol% PCy$_3$, 2 eq. KOH, 0.1 M	12	Trace	7	62	Trace
3	1 mol% [Ir(cod)Cl]$_2$ 4 mol% PBu$_3$, 2 eq. KOH, 0.1 M	24	Trace	12	58	Trace
4	1 mol% [Ir(cod)Cl]$_2$ 4 mol% CyJohnPhos 2 eq. KOH, 0.1 M	22	9	12	52	Trace
5	1 mol% [[Ir(cod)Cl]$_2$ 4 mol% *t*BuXPhos 2 eq. KOH, 0.1 M	38	Trace	10	45	4
6	1 mol% [Ir(cod)Cl]$_2$ 4 mol% cataCXium A 2 eq. KOH, 0.1 M	32	Trace	11	49	Trace
7	2 mol% [Ir(cod)Cl]$_2$ 8 mol% PCy$_3$, 2 eq. KOH 0.1 M	8	5	23	56	Trace
8	2 mol% [Ir(cod)Cl]$_2$ 8 mol% cataCXium A 2 eq. KOH, 0.1 M	Trace	5	26	63	4

Initially, valerophenone (**157**) was treated with 1 mol% [IrCp*Cl$_2$]$_2$ 4 mol% PCy$_3$, and 2 eq. KOH in methanol (0.2 M), affording enone **157b** and methoxy adduct **157c** in a combined yield of 76% and 16% yield of dimer as the major side product (Table 2.11, entry 1). Halving the concentration of the reaction considerably reduced the amount of dimer, but 12% starting material was recovered in addition to 69% yield of the desired enone and methoxy adduct (Table 2.11, entry 2). The use of PBu$_3$ as a ligand gave a lower conversion with 24% of unreacted starting material being recovered, but it still afforded the enone **157b** and methoxy adduct **157c** in a combined yield of 70% (Table 2.11, entry 3). The (2-biphenyl)dicyclohexylphophine (**232**, CyJohnPhos), which was slightly less electron rich than PCy_3 due to the presence of the aromatic ring, gave slightly less enone and methoxy adduct in 64% combined yield, 22% recovered starting material, and 9% yield of methylated ketone **157a** (Table 2.11, entry 4).

Figure 2.2 *Bulky phosphine ligands screened*

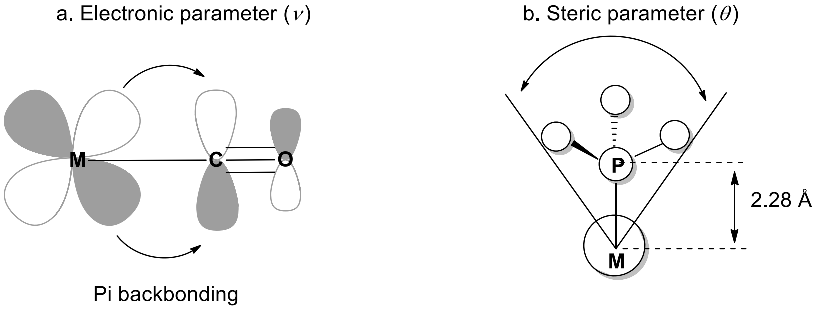


*t*BuXPhos **233** showed poor conversion with only 55% combined yield of desired products with 4% yield of dimer also observed (Table 2.11, entry 5). The bulky trialkyl phosphine di-(1-adamantyl)-*n*-butylphosphine (**234**, cataCXium A), developed by Beller,[72] afforded a combined yield of 60% of the desired compounds with 32% of unreacted starting material observed (Table 2.11, entry 6). Since only trace amounts of methylated compound **157a** or dimer **157d** was observed, cataCXium A showed promise to be able to selectively form enone and methoxy adduct, if we could improve conversion. We decided to increase the catalyst loading. Conducting the reaction with 2 mol% $[Ir(cod)Cl]_2$, 8 mol% PCy_3 and 2 eq. KOH in MeOH (0.1 M) afforded the enone **157b** and methoxy adduct **157c** in 79% combined yield, but still with 8% of the starting ketone recovered (Table 2.11, entry 7). To our satisfaction, reaction with cataCXium A under the same conditions gave the desired enone **157b** and methoxy adduct **157c** in a combined yield of 89%, with 5% methylated compound **157a** and 4% dimer **157d**. (Table 2.11, entry 8).

2.3.1 Electronic and steric properties of phosphine ligands

We proposed that the product distribution was influenced by both the electronic and steric properties of the phosphine ligand. Tolman suggests an experimental measure of electronic parameter (ν) by using the fundamental CO stretching frequency of [$Ni(CO)_3L$] complexes in CH_2Cl_2.[73] [$Ni(CO)_3L$] complexes were chosen as model compounds because they can be easily prepared by mixing $Ni(CO)_4$ and ligand in a 1:1 ratio. The metal forms a π backbond to the carbonyl ligand by donating electrons through its d orbitals into the empty π* anti-bonding orbitals on CO, thus strengthening the metal-carbon bond, while weakening the carbon-oxygen bond. Electron rich ligands increase the ability of backbond donation, and ν(CO) decreases with the weakening of the carbon-oxygen bond (Figure 2.3a).

Figure 2.3 *Tolman's electronic and steric parameters*



Tolman also defined a steric parameter (θ) paired to an electronic parameter. The size of a ligand was measured by the cone angle, θ, as defined by placing the metal at the vertex and the atoms at the perimeter of the cone with a metal-to-phosphorus distance of 2.28 Å, the standard Ni-P bond length in [$Ni(CO)_3L$] complexes (Figure 2.3b).[74]

Table 2.12 *Electronic and steric trends for phosphine ligands*[75]

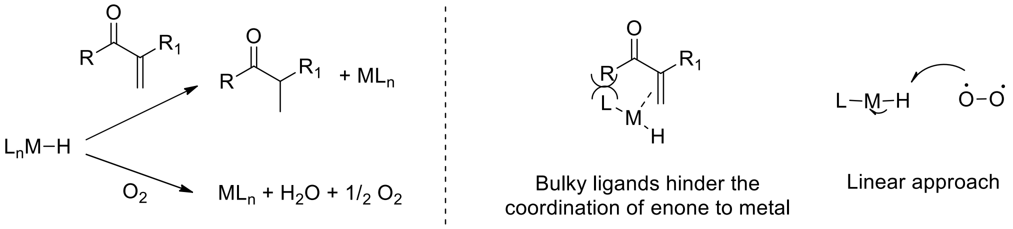
	PCy_3	PBu_3	$P(o\text{-}Tol)_3$	PPh_3
ν(CO)/cm^{-1}	2056.4	2060.3	2066.6	2068.9
	Electron rich	→		Electron poor

	$P(o\text{-}Tol)_3$	PCy_3	PPh_3	PBu_3
θ/deg	194	170	145	132
	More bulky	→		Less bulky

Comparing the results using PPh_3 (83% methylated, 9% dimer), $P(o\text{-}Tol)_3$ (56% methylated, 37% dimer, 7% methoxy adduct), PCy_3 (5% methylated, 79% enone and methoxy adduct), we believed that electron rich as well as sterically bulky phosphine ligands are good at interrupting the redelivery of M-H to the enone, and the electronic property plays a more important role. CataCXium A, with two bulky admantyl groups and one butyl alkyl substituent, proved to be the best ligand for the selective formation of enone and methoxy adducts. Although specific electronic and steric data of cataCXium A are not available, we postulate that the balance of electron rich with a particular type of bulky framework proved to be key.

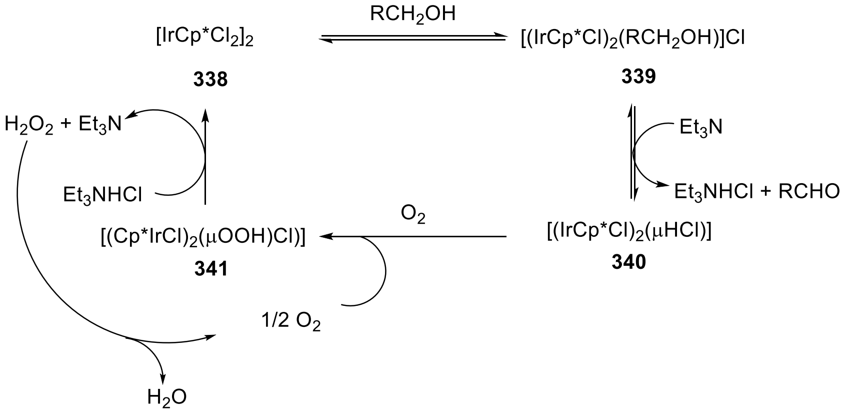
We hypothesized that the metal hydride had increased reducing ability when the metal core was chelated to an electron-donating phosphine ligand. Thus the metal hydride was more reactive towards reduction of enone or O_2. However, we suggest that the steric requirements for the two pathways are very different. The bulky ligand hinders the coordination of enone to the metal through π bonds, while O_2 approaches the σ^* orbital of the metal hydride to avoid the bulky phosphine ligands. Thus, most of the metal hydride was simply oxidized by dioxygen and the metal was returned back to catalytic cycle to continue the reaction.

Figure 2.4 *Possible explanation for the effect of electronic-rich bulky phosphine ligands*



The ability of O_2 to react with a metal hydride is supported by Ison and co-workers. They reported the beneficial effect of oxygen on the oxidation of primary and secondary alcohols by $[IrCp^*Cl_2]_2$, and a catalytic cycle was proposed whereby oxygen allowed the regeneration of the active catalyst by formation of hydrogen peroxide (Scheme 2.33).[76]

Scheme 2.33 *$[IrCp^*Cl_2]_2$ catalyzed aerobic oxidation of alcohols by Ison*



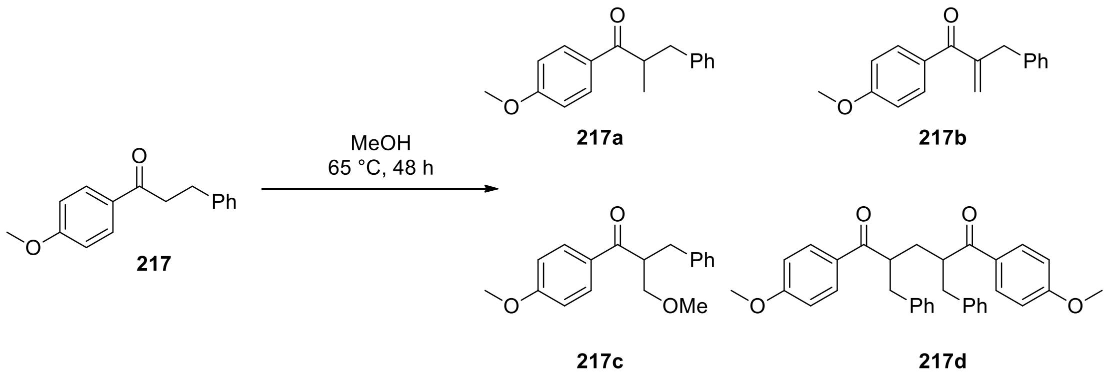
2.3.2 Methylenation of 4-methoxyphenyl ketones

As discussed in Section 2.2.6, 4’-methoxyphenyl ketones are more synthetically useful because they can be easily converted into ester derivatives *via* regioselective Baeyer-Villiger oxidation. Thus, the project turned next to the investigation of the methylenation of 4’-methoxyphenyl ketones.

1-(4-Methoxyphenyl)-3-phenylpropan-1-one (**217**) was treated with 2 mol% $[Ir(cod)Cl]_2$, 8 mol% cataCXium A and 3 eq. KOH in methanol (0.1 M) and heated at 65 ˚C under O_2 for 48 h. A higher loading of base was required because of the decreased acidity of the electron rich 4'-methoxyphenyl ketone compared to valerophenone. Enone **217b** and methoxy adduct **217c** were obtained in a combined yield of 81% with only 2% starting material **217** and 4% methylated compound **217a** (Table 2.14, entry 1). Interestingly, conducting the reaction under an Ar atmosphere gave poor conversion with only 50% of starting material consumed. Additionally, the undesired methylated compound was formed in 29% yield as the major product with only 14% combined yield of enone **217b** and methoxy adduct **217c** (Table 2.14, entry 2). The control experiments with no catalyst presence, but with cataCXium A or PPh_3 resulted in solely recovery of starting material (Table 2.14, entry 3 and 4).

The results of the reaction performed under Ar suggested that the metal hydride, with coordinated bulky ligands, was still able to reduce the enone **217b**, but that the overall reaction was slower. The possibilities for the role of oxygen will be discussed in detail in Section 2.4.2.

Table 2.14 *Methylenation of 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**)*

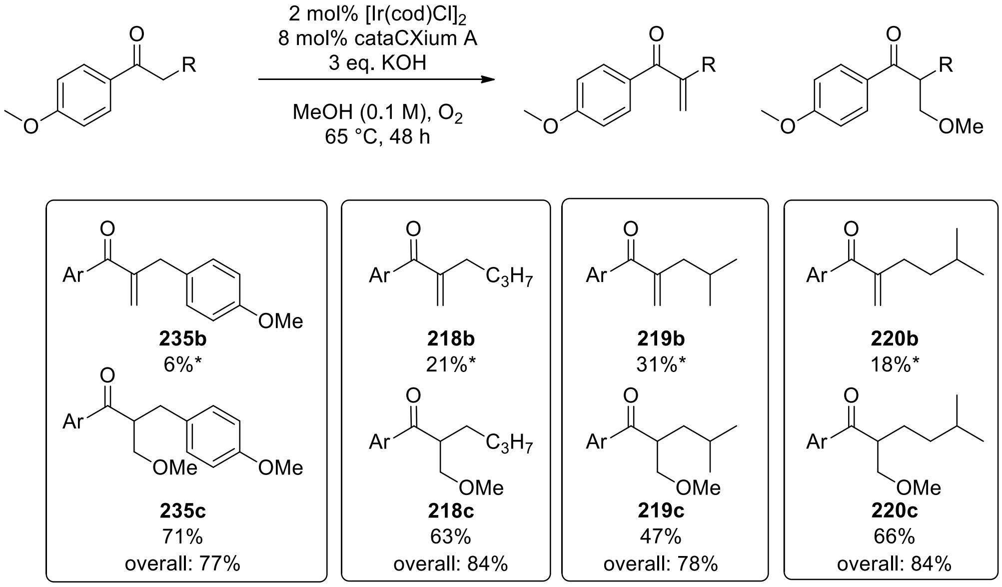


Entry	**Conditions**	**RSM** (%)	**217a** (%)	**217b** (%)	**217c** (%)	**217d** (%)
1	2 mol% [Ir(cod)Cl]$_2$ 8 mol% cataCXium A 3 eq. KOH, O_2, 0.1 M	2*	4*	6*	75	-
2	2 mol% [Ir(cod)Cl]$_2$ 8 mol% cataCXium A 3 eq. KOH, Ar, 0.1 M	50*	29*	1*	13	-
3	8 mol% cataCXium A 3 eq. KOH, O_2, 0.1 M	100	-	-	-	-
4	4 mol% PPh_3 2 eq. KOH, O_2, 0.2 M	98	-	-	-	-

Recovered starting material **217**, methylated product **217a** and enone **217b** were obtained as an inseparable mixture, and yields of material purified by chromatography were adjusted by calculation from molar ratios in ^{1}H NMR.

As a next step, we examined the efficiency of the interrupted hydrogen borrowing methylenation conditions with several 4’-methoxyphenyl ketones.

Scheme2.34 *Methylenation of 4’-methoxyphenyl ketones*



Ar = 4’-methoxyphenyl; *Enone was contaminated with a small amount of inseparable starting material and methylated product, and yields of material purified by chromatography were adjusted by calculation from molar ratios in the ^{1}H NMR spectrum.

1,3-Bis(4-methoxyphenyl)propan-1-one **235** was methylenated to give enone **235b** and methoxy adduct **235c** in a combined yield of 77%, although the enone was contaminated with 1% starting material and 3% methylated compound. Yields of 21% (enone **218b**) and 63% (methoxy adduct **218c**) were obtained from the methylenation of 1-(4-methoxyphenyl)hexan-1-one **218** which contained a linear alkyl side chain. A small amount of starting material (6%) and methylated product (10%) were also observed for this substrate. A 4’-methoxyphenyl ketone containing a branched alkyl chain **219** was also methylenated giving 78% combined yield of desired products with 7% unreacted starting material and 10% methylated side product. 1-(4-Methoxyphenyl)-5-methylhexan-1-one **220** was methylenated in 84% yield together with 4% starting material and 10% methylated product.

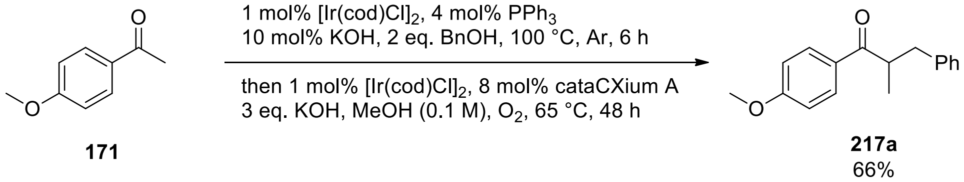
Control experiments by Dr. Darren Poole showed that the enone and methoxy adduct were in equilibrium,[77] and the ratio formed in each reaction depended on the substrate employed. Due to the reversible nature of methoxy adduct formation, we believed that both enone and methoxy adduct would be useful in subsequent reactions.

2.3.3 One-pot alkylation and methylenation

The 4'-methoxyphenyl ketone starting material used above in methylenation reactions were synthesized under Ishii's alkylation conditions from methyl ketones. We realized it would be ideal if we could combine these two steps into a one-pot sequence.

Facile benzylation of 4'-methoxyacetophenone **171** was enacted using our known procedure (Section 2.2.4.5), and upon completion of the reaction, 1 mol% $[Ir(cod)Cl]_2$, 8 mol% cataCXium A, 3 eq. KOH, methanol and an O_2 balloon were added. The mixture was stirred at 65 ˚C for 48 h to give a 66% yield of methylated compound **217a** with no desired enone or methoxy adduct, indicating that the PPh_3 ligand present in the first step was still able to facilitate the reduction of the enone in the second step.

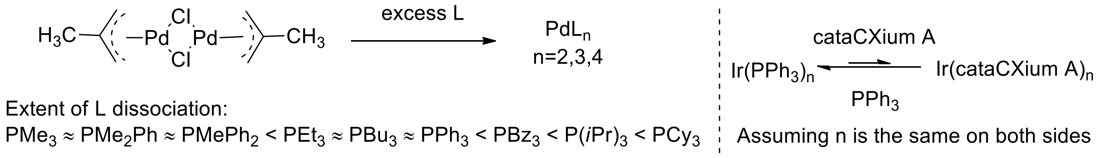
Scheme2.35 *First attempt towards the one-pot alkylation/methylenation*



This result suggested that the PPh_3 on the metal had not been replaced by cataCXium A as we hoped. Musco and co-workers have reported that the extent of ligand dissociation is dominated by steric effects. They prepared a series of Pd(0) tertiary phosphine complexes of the type PdL_n (n = 2,3,4) through displacement of the allyl ligand from $(2\text{-methylallylPdCl})_2$

with an excess of phosphine. With increasing steric hindrance, phosphines prefer to form complexes of lower co-ordination numbers (Scheme 2.36).[78]

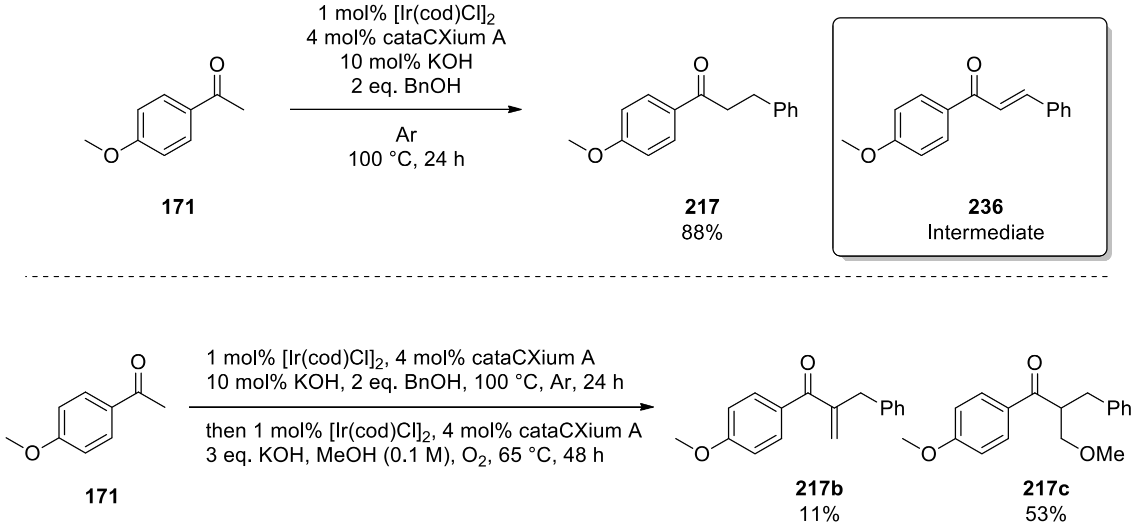
Scheme 2.36 *Ligand dissociation studies*



We suggest that in the one-pot alkylation/methylenation reaction, the equilibrium of Ir binding to either of the two phosphine ligands is skewed towards PPh$_3$, because cataCXium A is more sterically hindered and more likely to dissociate from Ir. This explains the results observed for the one-pot sequence, as the dominant Ir/PPh$_3$ system favours the formation of methylated compound.

In order to avoid the use of PPh$_3$ in the first alkylation step, we studied the Ir/(cataCXium A) system in the benzylation of 4’-methoxyacetophenone **171**. TLC analysis showed that the unsaturated ketone **236** was formed as the major product after 6 h, and the desired benzylated ketone was isolated in 88% after 24 h (Scheme 2.37).

Scheme2.37 *Ir/(cataCXium A)- catalyzed alkylation and one-pot reactions*



171 **217** **236** **171** **217b** **217c**

With addition of 1 mol% $[Ir(cod)Cl]_2$, 4 mol% cataCXium A, 3 eq. KOH, methanol and an O_2 balloon to the modified alkylation, enone **217b** and methoxy adduct **217c** were obtained in a combined yield of 64% with only 7% methylated side product **217a** being formed.

However, the alkylations using Ir/(cataCXium A) with other alcohols such as *n*-butanol and *iso*-butanol were problematic, TLC showed that a small amount of unsaturated ketone was formed with mainly starting material being observed even after 24 h. The attempts to stir the reactions for another 24 h did not give any improvement. We suggested this was because *n*-butanol and *iso*-butanol are more difficult to oxidise than benzyl alcohol, resulting in slower reactions (*vide infra*). Besides, we have already suggested earlier that cataCXium A was inhibiting the redelivery of M-H to the enone, so the unsaturated ketones were observed to be the major products. Therefore, we decided to stop further investigation on this sequence.

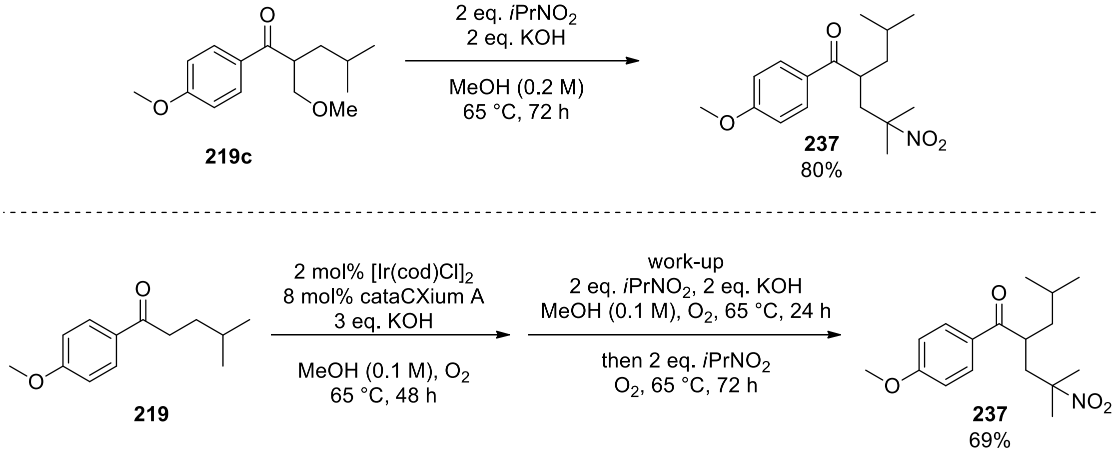
2.3.4 One-pot methylenation and conjugate addition

After the successful methylenation of 4’-methoxyphenyl ketones, our next goal was to produce branched ketone products through methylenation/conjugate addition sequence where the enone and methoxy adduct were not isolated but reacted *in situ* with an external nucleophile.

2.3.4.1 Conjugate addition of alphatic nitro compounds

The conjugate addition of alphatic nitro compounds to enones is a well-known process, first reported by Kohler and co-workers in 1916.[79] To test the conjugate addition of a nitro compound to our *p*-methoxyphenyl enones, 2 eq. *i*$PrNO_2$ and 2 eq. KOH were added to 1 eq. methoxy adduct **219c** in MeOH, and after 72 h of stirring afforded 80% yield of the desired product with a trace of enone and methoxy adduct observed. The conjugate addition of *i*$PrNO_2$ to 2-(methoxymethyl)-1-(4-methoxyphenyl)-4-methylpentan-1-one **219c** was slow presumably due to the branched isopropyl side chain hindering nuleophilic attack. In the one-pot sequence, direct addition of *i*$PrNO_2$ after the methylenation step resulted in an even slower reaction with poor conversions, and we were only able to perform a “semi” one-pot procedure for this substrate. Therefore, after the standard methylenation step, the mixture was diluted with Et_2O, filtered through SiO_2, and concentrated *in vacuo*. The mixture was redissolved in MeOH (0.2 M) and 2 eq. of 2-nitropropane and 2 eq. of KOH were added. The reaction was heated at 65 ˚C for 24 h, and another 2 eq. of 2-nitropropane was added and heated at 65 ˚C for a further 72 h. This gave a yield of 69% with the structure of the product confirmed by the appearance of two new singlets in the ^1H NMR at 1.57 ppm and 1.34 ppm corresponding to the two germinal methyl groups (Scheme 2.38).

Scheme2.38 *2-Nitropropane addition and one-pot reaction*



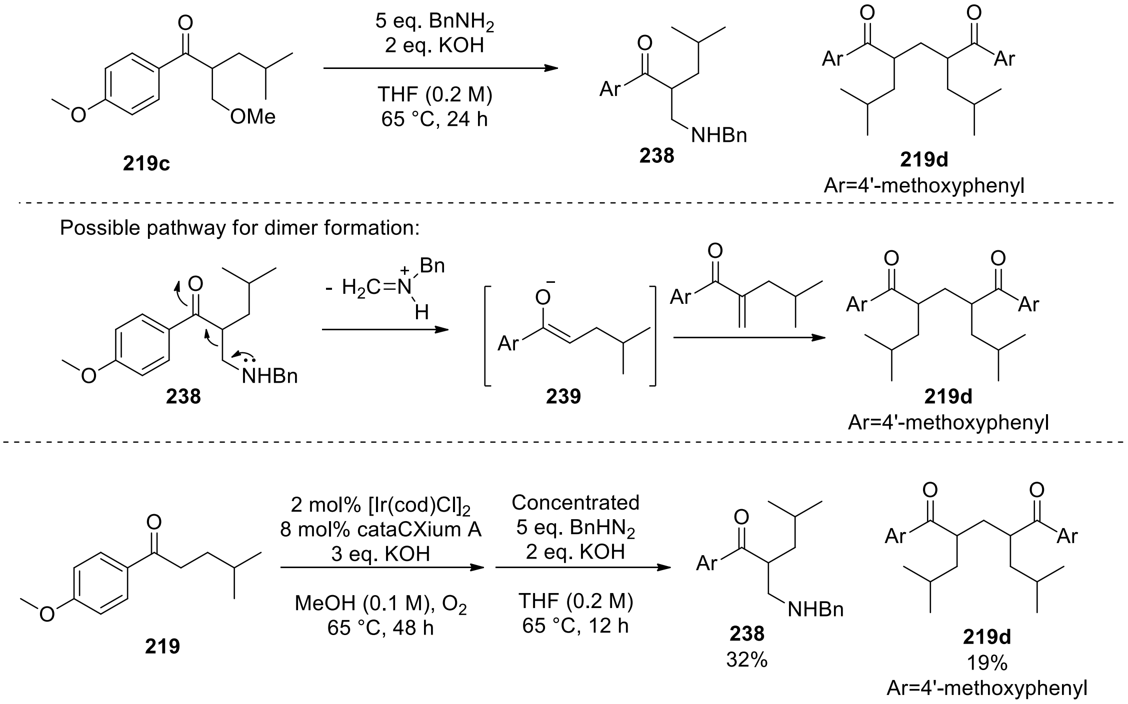
work-up: Diluted with Et_2O, filtered through SiO_2, and concentrated *in vacuo*.

2.3.4.2 Conjugate addition of amines

Compounds incorporating a β-amino ketone functionality are prevalent in many natural products of biological importance and can serve as building blocks for the preparation of nitrogen-containing molecules.[80] As such, we also wanted to explore conjugate addition reaction using benzylamine as a nucleophile.

Addition of benzylamine to 2-(methoxymethyl)-1-(4-methoxyphenyl)-4-methylpentan-1-one (**219c**) gave a complicated crude mixture with mostly unreacted enone and methoxy adduct formed. To our surprise, in addition to the formation of desired product **238,** the reaction gave dimer species **219d** (as observed by ESI^+ mass spectrum with a peak at 425.3 ppm ($[M+H]^+$); yields were not determined due to purification difficulties). We proposed that the product **238** underwent a retro-Mannich reaction to give the enolate **239** which then reacted with enone **219b** to form the dimer **219d**. To explore one-pot protocol, the crude methylenation mixture was concentrated to remove excess formaldehyde and redissolved in THF before stirring with 5 eq. $BnNH_2$ and 2 eq. KOH at 65 ˚C for 12 h. We were able to isolate the desired amine product **238** in 32% yield and also 19% yield of dimer **219d**.

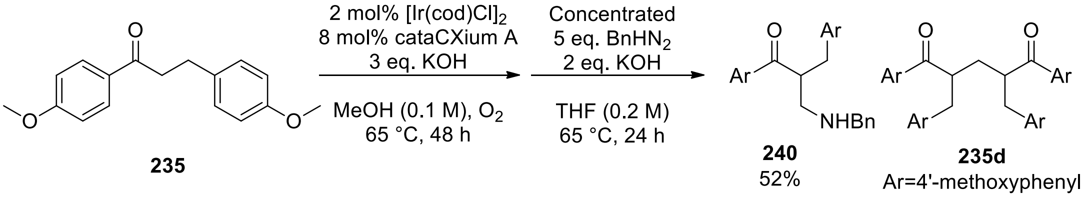
Scheme2.39 *Benzylamine addition and one-pot reaction*



It was worth noting that the dimer **219d** was never observed during the course of methylenation step, so it was formed after benzylamine was added. The structure of the desired product **238** was confirmed by ^{1}H NMR with a characteristic peak at 3.69 ppm (s, 2H) corresponding to the benzylic CH_2. The expected broad singlet for the NH was not clearly observed as it overlapped with peaks for the alkyl side chain in the region of 1.62-1.40 ppm.

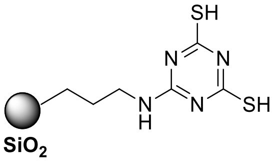
The same reaction conditions were employed for another substrate: 1,3-bis(4-methoxyphenyl)propan-1-one **235**. The solvent was removed when the methylenation step was finished to remove excess formaldehyde, and the resulting mixture was redissolved in THF. Conducting the reaction at 65 ˚C for another 24 h after the addition of 5 eq. $BnNH_2$ and 2 eq. KOH gave the desired product in a moderate 52% yield. Again the dimer species was observed as a yellow spot on TLC plate when stained with vanilin but the yield was not determined because of purification difficulties (Scheme 2.40).

Scheme2.40 *Benzylamine addition*



It has been reported that functionalized SiO_2 resins can be used for the scavenging of transition metals during purification processes.[81] We hypothesized that the conjugate addition step would proceed more smoothly, without any metal-catalyzed reactions, if iridium was scavenged from the solution after the methylenation step. Dr. Darren Poole in the group found that with some nucleophiles it was beneficial to treat the methylenated crude reaction mixture with a metal scavenging resin (SiliaMetS DMT **241**, Figure 2.5) while stirring the vessel open to the atmosphere for 1h to remove excess formaldehyde before the addition of base and the external nucleophile.[77]

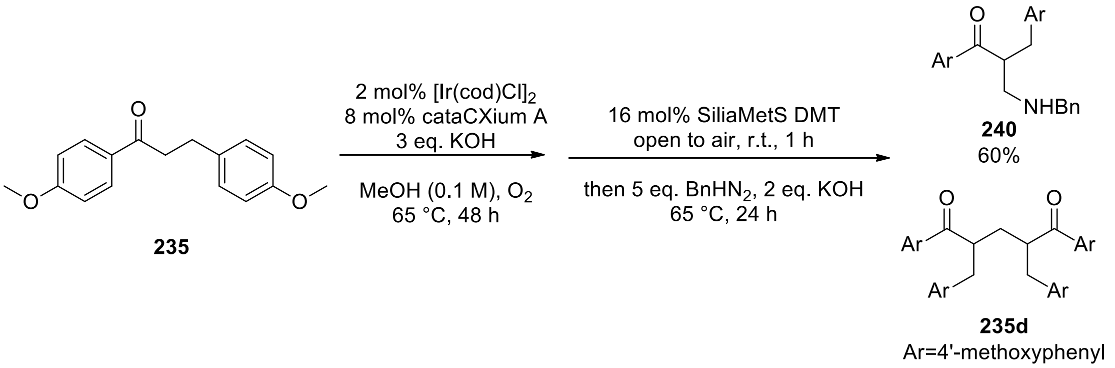
Figure 2.5 *SiliaMetS DMT*



SiliaMetS DMT
241

In order to test if the addition of scavenger resin would improve the yields, 4’-methoxyphenyl ketone **235** was subjected to the standard methylenation conditions, followed by the addition of 16 mol% SiliaMetS DMT **241**. After stirring the mixture open to air for 1 h at room temperature, 5 eq. $BnNH_2$ and 2 eq. KOH were added and the reaction was stirred at 65 ˚C for 24 h (Scheme 2.41). The scavenger may have some positive effect on the conjugate addition of benzylamine, as the yield of desired product **240** was slightly improved to 60%, though the dimer **235d** was still observed by TLC.

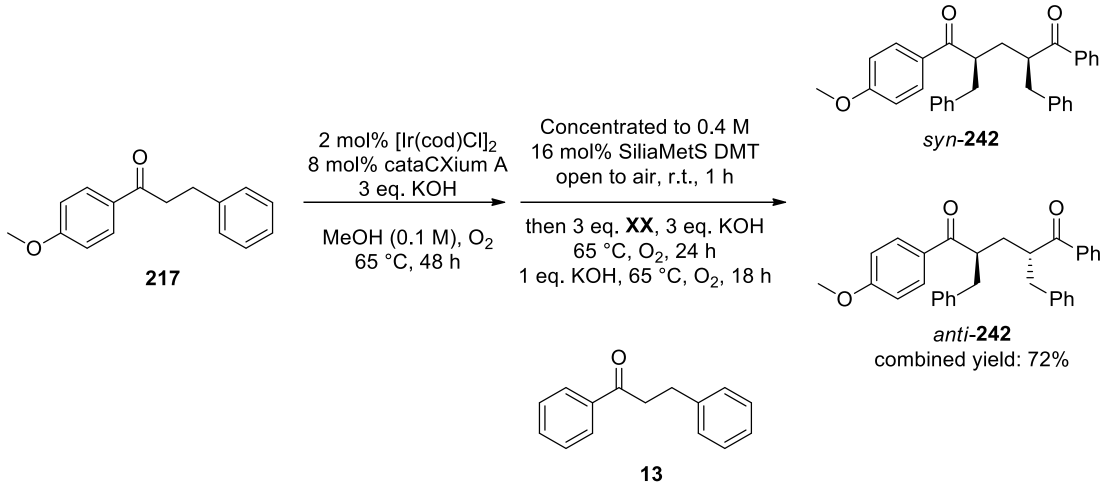
Scheme2.41 *Benzylamine addition with scavenger resin*



2.3.4.3 Conjugate addition of a second ketone

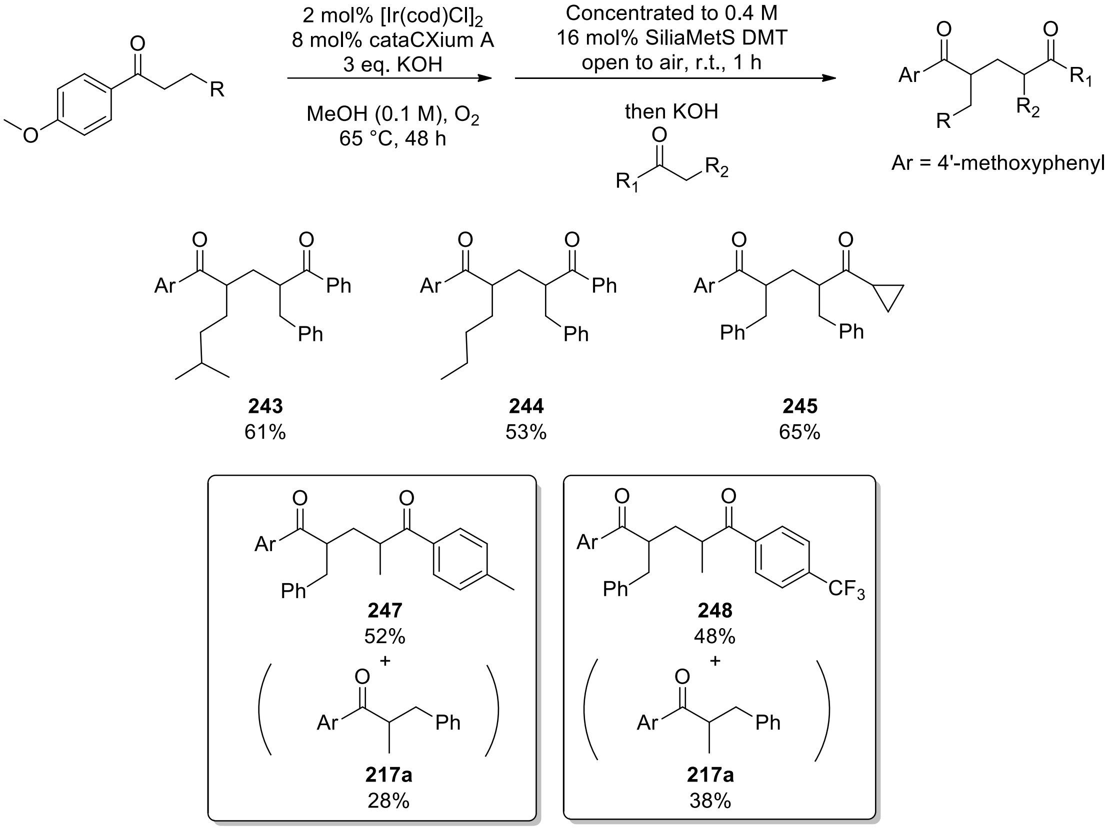
1,5-Dicarbonyl compounds are interesting intermediates which allow access to pyridines with a wide range of substitution patterns. Thus, we envisaged that using the enolate of a second ketone as nucleophile would allow us to synthesize 1,5-diketones. We considered that we could use the beneficial metal scavenger to remove most of the Ir metal from the reaction solution after the methylenation step to avoid the reactions of the second ketone with formaldehyde generated from methanol. After the methylenation of 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**), the mixture was concentrated to 0.4 M (previous work had suggested that formation of dimer species were favoured in more concentrated solutions, see Section 2.2.4.3). SiliaMetS DMT **241** (16 mol%) was added and stirred open to air for 1 h at room temperature before the addition of 3 eq. 3-phenylpropiophenone (**13**) and 3 eq. KOH (Scheme 2.42). Pleasing, the mixture was heated at 65 ˚C under O_2 for 24 h before another 1 eq. KOH was added and heated for 18 h. The desired product was obtained as a inseparable 1:1 mixture of two diasteroisomers in 72% yield. The two protons of the methylene bridge for *anti*-**242** appeared as one multiplet in the ^{1}H NMR at 2.15-2.12 ppm, while the protons for *syn*-**242** were split into two multiplets away from each other at 2.43-2.38 ppm and 1.77-1.72 ppm, allowing the ratio of *syn*- and *anti*-**242** to be determined (Scheme 2.42).

Scheme 2.42 *Addition of 3-phenylpropiophenone*



The reactions were also performed on 1-(4-methoxyphenyl)-5-methylhexan-1-one (**220**) and 1-(4-methoxyphenyl)hexan-1-one (**218**) using 3-phenylpropiophenone (**13**) as the nucleophile with 61% and 52% yields respectively, the lower isolated yields were because of the purification difficulties. Other ketones were also examined as nucleophiles. The alkyl-alkyl ketone, 1-cyclopropyl-3-phenylpropan-1-one (**164**), was able to react with methylenated 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**) to afford **245** in 66% yield. When 4'-methylpropiophenone (**246**) was used, besides 52% yield of the desired product, the methylated product of the 4'-methoxyphenyl ketone was isolated in 28%. This result implied that the scavenger did not remove all the Ir metal from solution, and so the enone was still getting reduced during the second step. We first supposed that 4'-methylpropiophenone (**246**) was less acidic than 3-phenylpropiophenone (**13**), resulting in slower conjugate addition step. However, the use of more acidic 4'-trifluoromethylpropiophenone (**162**) gave similar results with 48% yield of desired hetero-dimer **248** and 38% of the methylated 4'-methoxyphenyl ketone **217a** (Scheme 2.43). At this point, it was not clear why the reduction was turned back on when ethyl ketones were added.

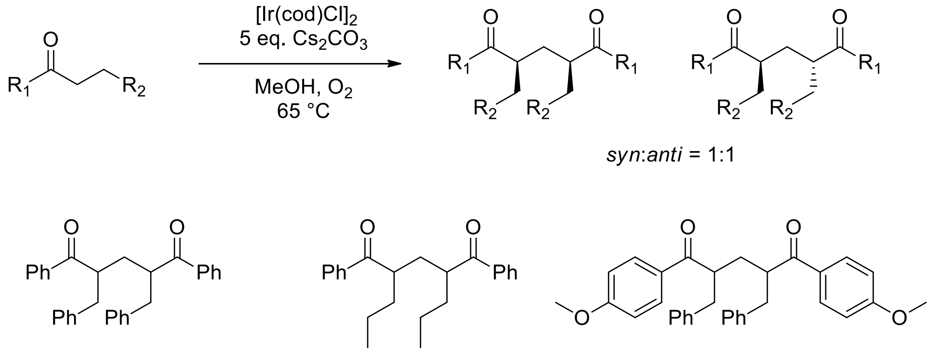
Scheme 2.43 *Formation of hetero-dimers*



2.3.4.4 Homo-dimer formation and functionalisation

During our optimization of the methylenation conditions, we noticed that the homo-dimer formation was favoured in the slow methylenation process when no phosphine ligand was added. The homo-dimer derived from matching the rates of methylenation and enolate addition reactions, and since each substrate had a slightly different pKa, the best conditions for dimer formation were different for each ketone. Herein, we examined the homo-dimer formation reactions on three different ketones (Scheme 2.44). For the reaction of valerophenone, when 1 mol% [Ir(cod)Cl]$_2$ was added to 0.2 M methanol, only 48% yield of the desired dimer was obtained using 5 eq. Cs$_2$CO$_3$ and 43% yield using 5 eq. KOH after 48 h, with the rest being enone and methoxy adduct. In order to slow down the methylenation process, a lower loading of $[Ir(cod)Cl]_2$ (0.5 mol%) and 5 eq. Cs_2CO_3 were employed at 65 ˚C under O_2 to give the desired homo-dimer in 74% yield after 72 h. Dimerisation of the more acidic ketone, 3-phenylpropiophenone (**13**) was achieved in 81% yield under the same conditions but with a shorter reaction time of 48 h. For electron rich 4’-methoxyphenyl ketone **217**, 1 mol% $[Ir(cod)Cl]_2$ was employed in 0.4 M methanol, affording the desired dimer in 83% yield.[****] The *anti*- and *syn*-diastereroisomers were also obtained as a 1:1 mixture in each case (Scheme 2.44).

Scheme 2.44 *Formation of homo-dimers*



13d
0.5% $[Ir(cod)Cl]_2$
[0.2M], 48 h, 81%

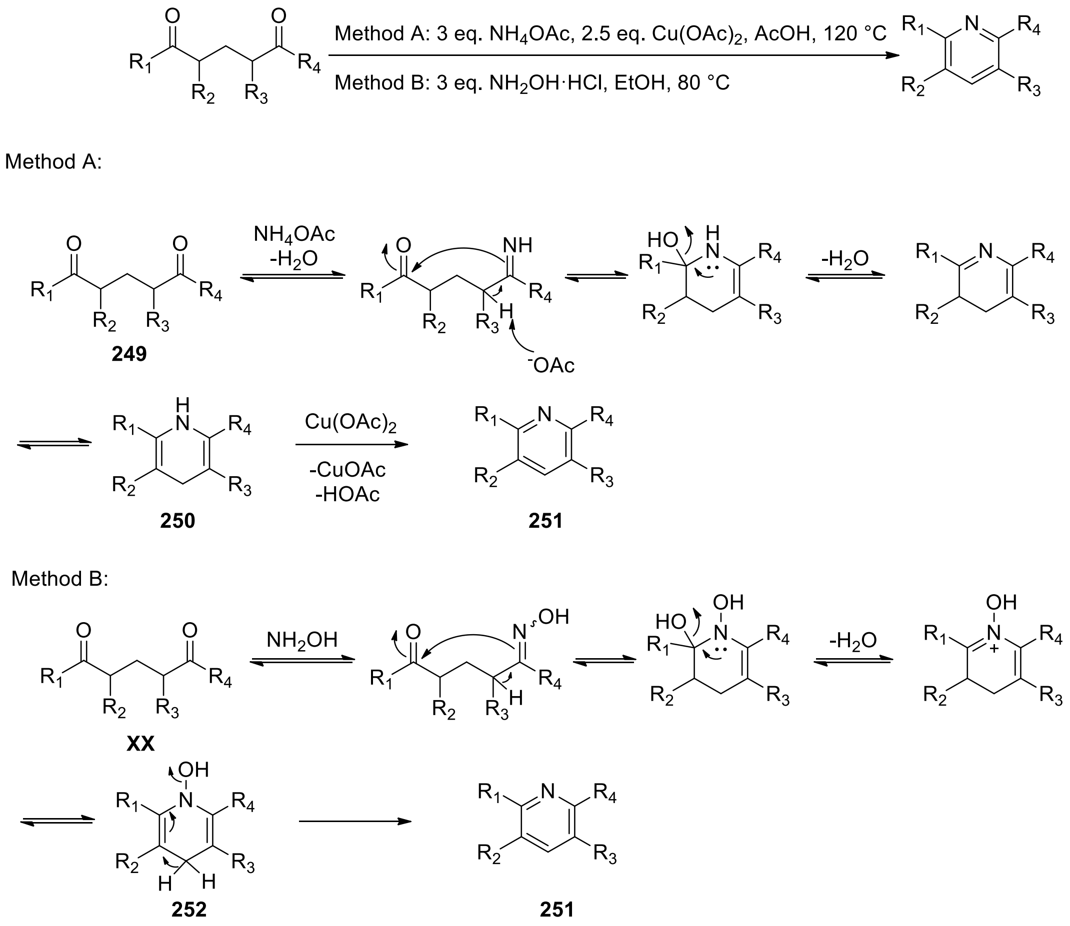
157d
0.5% $[Ir(cod)Cl]_2$
[0.2M], 72 h, 74%

217d
1% $[Ir(cod)Cl]_2$
[0.4M], 48 h, 83%

With all the 1,5-dicarbonyl compounds in hand, we now turned our interest to pyridine synthesis. The dimer species were treated with either ammonium acetate and $Cu(OAc)_2$[82] or hydroxylamine hydrochloride[83] to afford the corresponding tetra-substituted pyridines in excellent yields (Scheme 2.45).

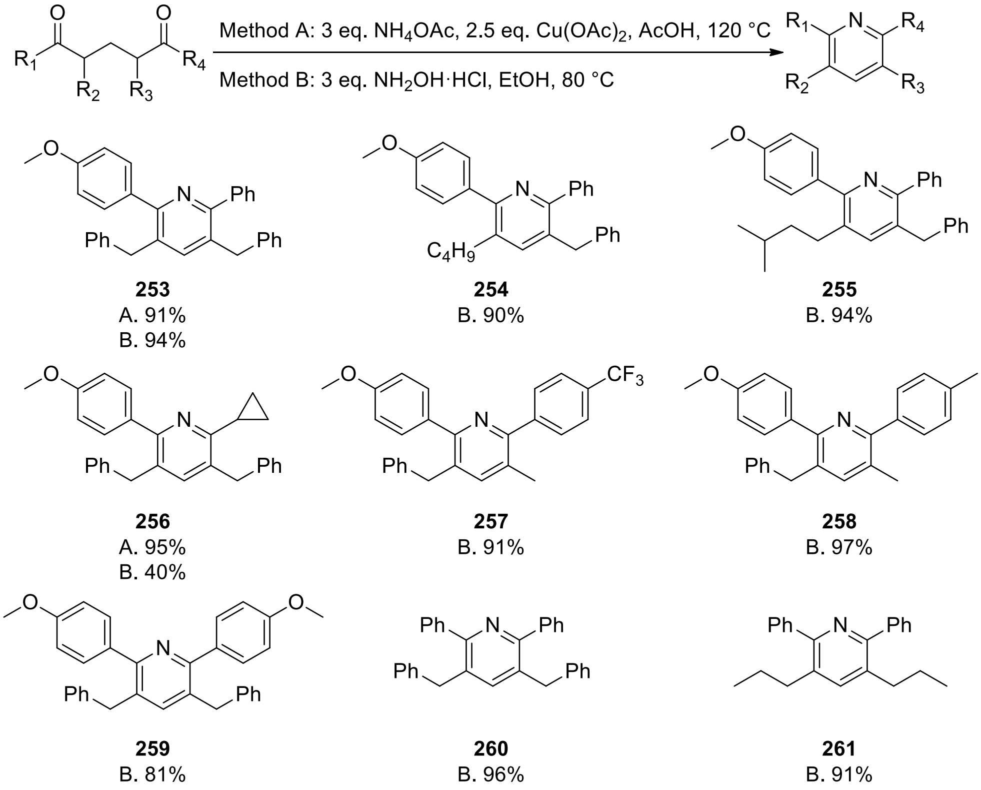
[****] Example by Anne Kornahrens

Scheme 2.45 *Pyridine synthesis*



In the first method, condensation between the 1,5-diketone **249** and ammonia acetate first afforded the dihydropyridine **250** which was subsequently oxidised by Cu(II)(OAc)₂, providing the desired pyridine **251**. Alternatively, the 1,5-diketone **249** condensed with hydroxylamine followed by rearomatisation to give the same pyridine product **251**.

Scheme 2.46 *Pyridine synthesis*

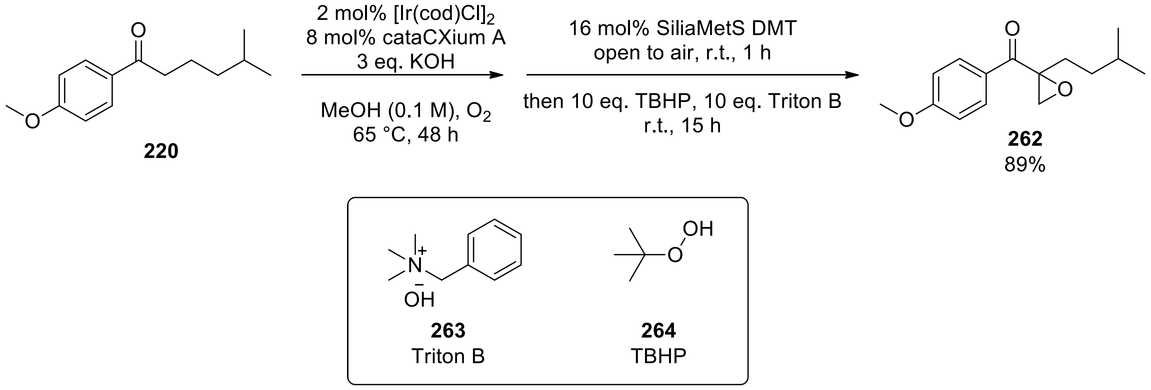


(±)(2*SS*,4*RS*)-2,4-Dibenzyl-1-(4-methoxyphenyl)-5-phenylpentane-1,5-dione (**242**) was treated with 3 eq. NH_4OAc and 2.5 eq. $Cu(OAc)_2$ in acetic acid at 120 ˚C for 24 h to give the desired pyridine **253** in 91%. Alternatively, the same pyridine could be synthesized from the reaction of dimer **242** with 3 eq. $NH_2OH·HCl$ in ethanol at 80 ˚C. The formation of pyridine was confirmed by the disappearance of C=O stretching peaks in the IR spectrum at 1673 cm^{-1} compared to the starting diketone. Since the workup procedure for method B was easier than that of method A which required an ammonia wash, most of the diketones were subjected to method B to afford high yields of pyridine products. However, the reaction of (±)(2*RS*,4*SS*)-2,4-Dibenzyl-1-cyclopropyl-5-(4-methoxyphenyl)pentane-1,5-dione (**245**) using hydroxylamine hydrochloride gave only 40% of desired product **256**. It seems that the cyclopropyl ring was opened by hydroxylamine to give a very polar product which stuck to silica gel upon purification. Conducting the reaction with method A for this substrate afforded pyridine **256** in a yield of 95% (Scheme 2.46).

2.3.4.5 Conjugate addition of other nucleophiles developed in the Donohoe group**

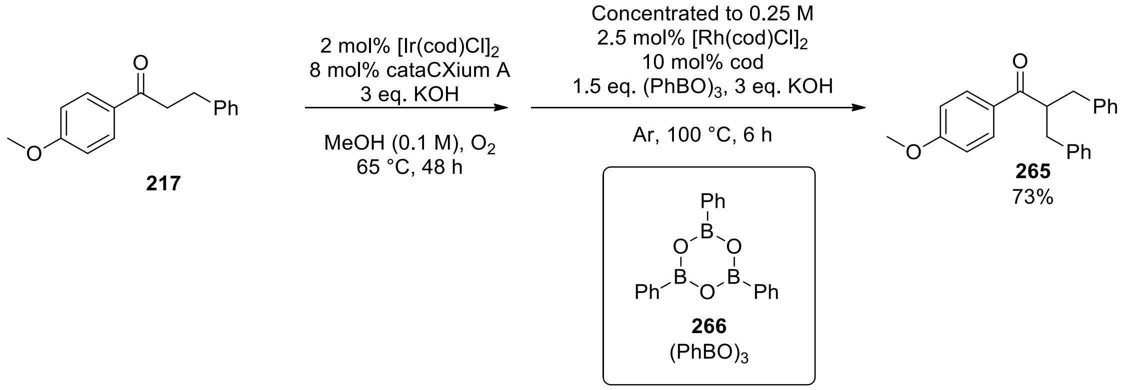
Dr. Darren L. Poole in the group showed the possibility of a one-pot methylenation/epoxidation reaction where a nucleophilic epoxidation reagent, *tert*-butylhydroperoxide (TBHP), was used in the second step.[77] 4'-Methoxyphenyl ketone **220** was exposed to the standard methylenation conditions, stirred for 1 h at room temperature with 16 mol% SiliaMetS DMT **241**, and then 10 eq. 70% aq. TBHP and 10 eq. benzyltrimethylammonium hydroxide (Triton B) were added. The reaction was subsequently stirred for 24 h to form the desired epoxide **262** in 89% yield (Scheme 2.47).

Scheme 2.47 *Epoxide formation*



He also developed a protocol using boronic acid derivatives for conjugate addition.[77] After the methylenation step of 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**), the reaction was concentrated to 0.25 M before adding 2.5 mol% [Rh(cod)Cl]$_2$, 10 mol% 1,5-cyclooctadiene, 3 eq. KOH and 1.5 eq. 1,3,5-triphenylboroxine. The mixture was degassed with Ar and heated at 100 °C for 6 h to give the addition product in 73% yield (Scheme 2.48).

Scheme 2.48 *Boronic acid derivative conjugate addition*

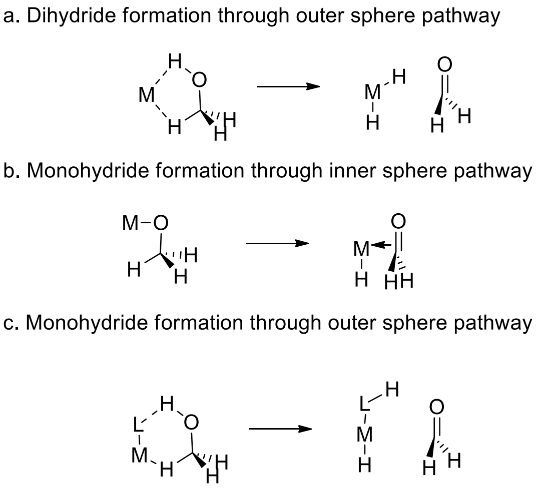


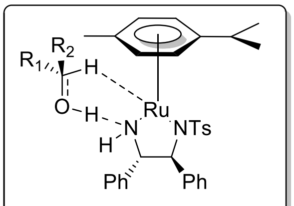
In conclusion, this methylenation/conjugate addition sequence is an extension of our previous Rh or Ir catalyzed methylation methodology, allowing the formation of products that are not previously accessible *via* the hydrogen-borrowing alkylation reactions of ketones. We have successfully synthesized a wide range of branched products using an interrupted hydrogen borrowing reaction with methanol to form an enone, followed by *in situ* nucleophilic addition.

2.4 Mechanistic studies

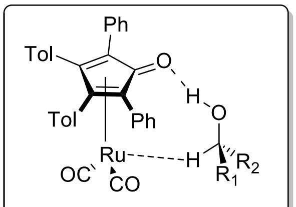
During the hydrogen borrowing reactions, transition metal catalysts generally operate through a hydridic route where a metal hydride species is involved as a key intermediate.[84] This can be further divided into monohydridic (MH) or dihydridic (MH_2) routes. The dihydride mechanism proceeds through the outer sphere of the metal where the two hydrogens (one hydride deriving from the hydroxyl group, and one from a methyl C-H bond) become equivalent after being transferred to the metal (Scheme 2.49a). For catalysts operating through the monohydride mechanism, two pathways have been suggested. One possibility may involve the formation of a transition metal alkoxide followed by β-elimination to give the M-H (Scheme 2.49b). In this mechanism the hydride transfer occurs in the inner sphere of the metal. Alternatively, this reaction may also proceed through the outer sphere of the metal without coordination of the alcohol to the metal, and the hydrogen of the hydroxyl group is transferred to the hydrogen accepter in the ligand (Scheme 2.49c). Catalysts operating through this mechanism are often called metal-ligand bifunctional catalyst such as **267** (Noyori's catalyst, the NH unit of a diamine ligand forms a hydrogen bond with the hydroxyl group)[85] and **268** (Shvo type catalyst, the cyclohexanone carbonyl forms a hydrogen bond with the hydroxyl group).[86] In both pathways, the hydride delivered would derive from one of the C-H bonds of the methanol CH_3 group.

Scheme 2.49 *mono- or dihydride mechanism*





267
Noyori's catalyst



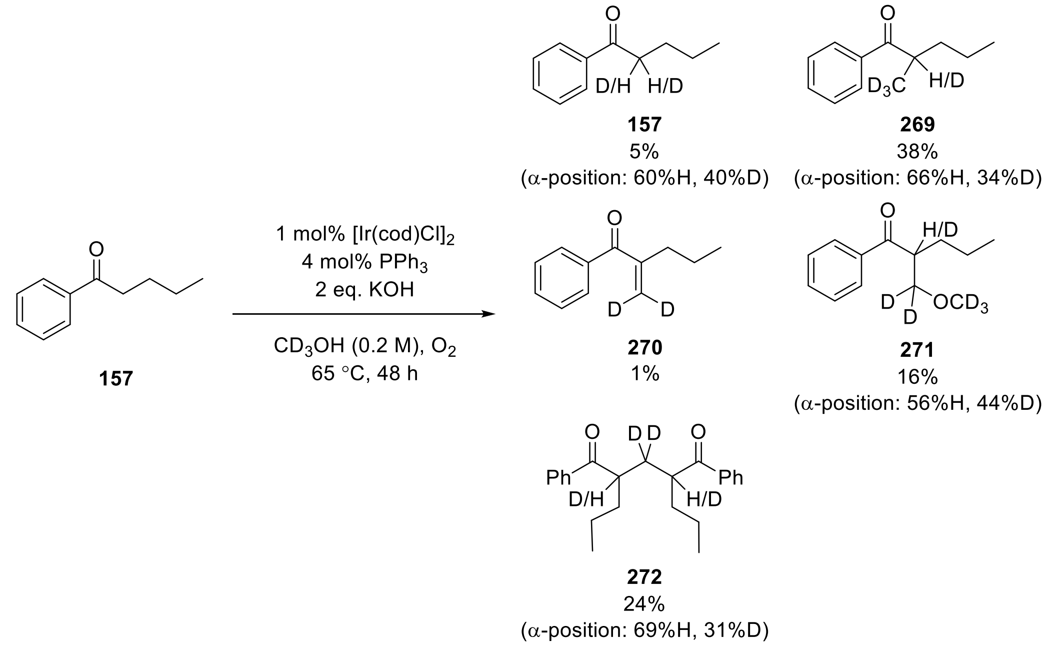
268
Shvo type catalyst

2.4.1 Reactions in CD_3OH

In order to investigate whether the Ir catalyzed reactions were proceeding *via* a mono- or dihydride mechanism, an experiment was designed where the methylation reaction was conducted in CD_3OH (99.8%). A similar reaction has been previously performed by Dr. Darren Poole for the $[RhCp^*Cl_2]_2$ catalyzed methylation, and it was postulated that if the reaction were to proceed *via* a Ir monohydride, then only deuterium would be observed in the product methyl group, whereas we would expect a mixture of both hydrogen and deuterium to be present in the methyl group if the reaction were to proceed *via* a dihydride species.

Valerophenone was subjected to the optimised methylation conditions (see section 2.2.4.5) in CD_3OH for 48h (Scheme 2.50). The desired methylated compound **269** was obtained in a much lower yield (38%) compared to 81% yield for the reaction in non-deuterated solvent. Moreover, the methylated ketone was isolated as an inseparable mixture with a small amount of unreacted starting material (5%) and enone (1%), whereas methoxy adduct **271** and dimer **272** were also isolated in 16% and 24% yields respectively (Scheme 2.50).

Scheme 2.50 *Methylation reaction of valerophenone in* CD_3OH



Complete deuteration of the methyl group in the methylated product **269** had occurred, as shown by the disappearance of a doublet at 1.12 ppm in the ^{1}H NMR. Furthermore, the α-proton of the ketone, which exhibits a sextet at 3.48 ppm for the non-deuterated ketone **157a**, showed a change in multiplicity to a triplet, due to the loss of coupling to the methyl CH_3 protons. The structure was further proved by observation of a singlet at 1.16 ppm in the ^{2}H NMR for the CD_3 group as well as a singlet at 3.47 ppm corresponding to the α-proton of the ketone, indicating partial deuteration at the α-position. The percentage of deuterium at the α-position (34%) was calculated by comparing the integration of peaks in the ^1H NMR spectrum for the α-proton and the terminal CH_3 of the valeryl side chain, which should normally be 1:3 if no deuterium had been incorporated.

For enone **270**, two broad singlets at 5.85 and 5.58 ppm were observed in the ^2H NMR spectrum corresponding to the terminal alkene deuteriums, and the same peaks were absent in the ^1H NMR, showing complete deuteration at this position.

In the case of the methoxy adduct **271**, the ^2H NMR spectrum showed the presence of broad singlets corresponding to the CD_2OCD_3 group at 3.70, 3.49, and 3.26 ppm in a ratio of 1:1:3. Such peaks were not observed in the ^1H NMR, and the α-proton, previously a complex multiplet in the region 3.75−3.60 ppm, was now present as a triplet at 3.77 ppm, due to the absence of coupling to the diastereotopic $C\underline{H}_2OCH_3$ protons. The integration of this triplet compared to that of the valeryl CH_3 also revealed 44% deuterium incorporation at the α-position.

Complete deuteration of the methylene bridge in the dimer species was confirmed by the presence of broad singlets in the ^2H NMR spectrum at 2.26 and 1.60 ppm for the *syn*-**272** as well as 2.04 ppm for *anti*-**272**. Peaks in this region had disappeared in the ^1H NMR, and the multiplicity of the α-protons in both *anti*- and *syn*-**272** were changed to triplets at 3.37 and 3.53 ppm due to the loss of coupling to the protons of the methylene bridge.Intergration studies also showed 31% deuterium present at the α-position.

We proposed two potential causes for the high percentage of deuterium present at the α-position of the carbonyls. The first possibility was a result of deprotonation of an acidic Ir-D species by either methoxide or hydroxide (see section 2.2.4.3, for example, the pKa of

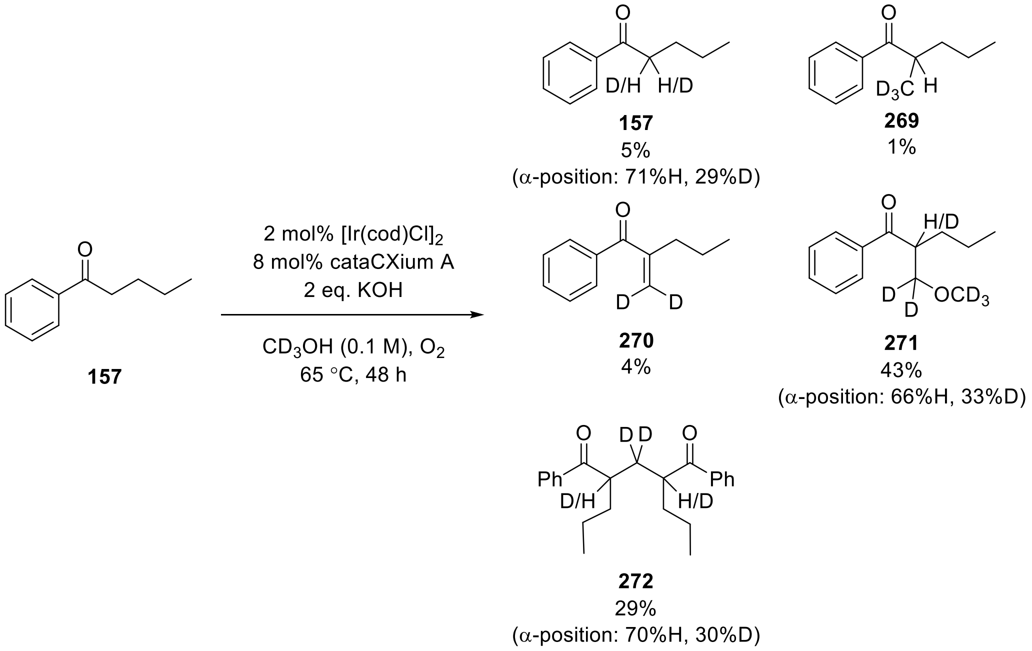
[IrCp*H(bpym)] **209** and [IrCp*H(bpy)] **208** was determined to be *ca.* 6 in MeCN/H_2O), thus leading to formation of CD_3OD or DOH *in situ*, which would compete with CD_3OH for protonation of the enolate of products **269**, **271**, **272**. The second possibility was the insertion of O_2 into an Ir-D species (see section 2.3.1), resulting in formation of HOOD which might decompose to give DOH and half an equivalent of O_2. Whatever the mechanism, given that the amount of deuterium at the α-position is very similar for all compounds isolated, it may have reached equilibrium at this position.

The introduction of deuterium at the α-position is interesting, but it is consistent with a mono-hydride mechanism followed by H/D exchange. The complete deuteration of the new methyl group formed in the methylated product **269**, although with a lower yield compared to the results in CH_3OH, has confirmed that only M-D was generated and the Ir catalyst participates in a mono-hydride mechanism.

It was considered that there were two potential reasons for the different product distribution of the reaction conducted in CD_3OH compared with CH_3OH. First of all, reduction of enone **270** with Ir-D could be slower than with Ir-H due to a kinetic isotope effect, resulting in an increased chance of trapping the enone with starting material enolate, and hence an increased yield of dimer **272**. Secondly, slower oxidation of CD_3OH compared to CH_3OH, again caused by a kinetic isotope effect, was also possible. This would result in a lower concentration of formaldehyde and Ir-D, which would lead to a lower concentration of enone **270** able to be trapped by large excess of starting material enolate affording dimer **272**.

In order to test the slow step in the reaction pathway, valerophenone was also subjected to the methylenation conditions (section 2.3) where no reduction of the enone should occur (Scheme 2.51).

Scheme 2.51 *Methylenation reaction of valerophenone in CD_3OH*

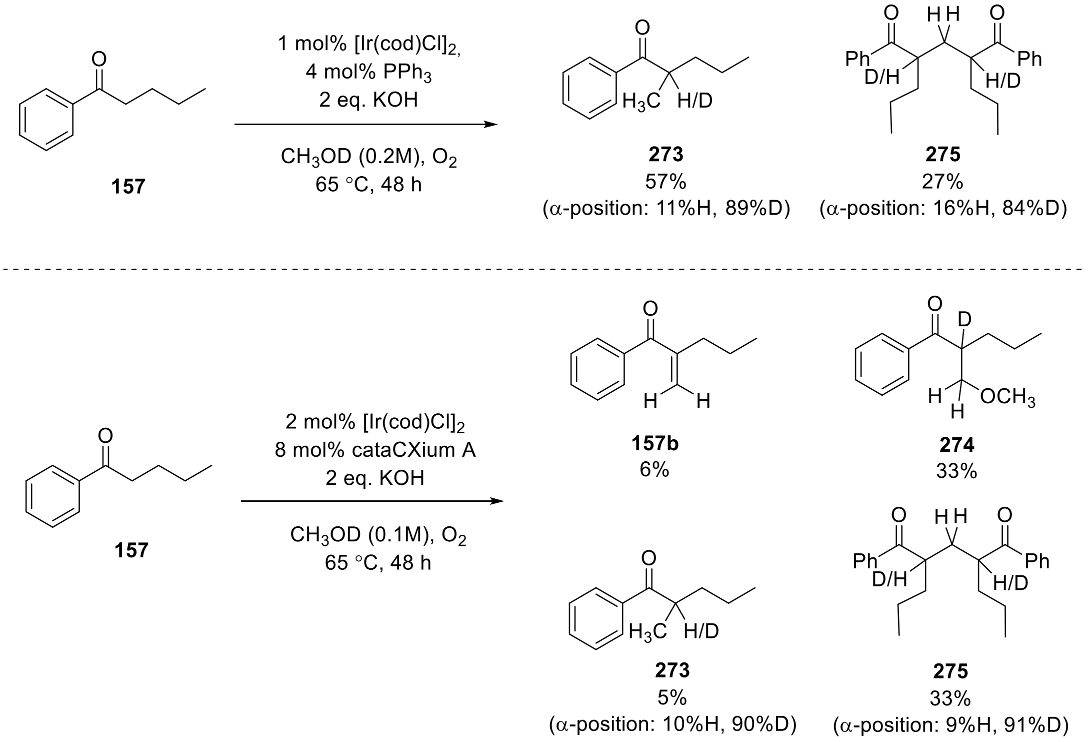


A lower combined yield of enone **270** and methoxy adduct **271** (47%) was obtained in CD_3OH compared to 89% combined yield of these two compounds in non-deuterated methanol. Deuterium incorporation (*ca.* 30%) at the α-position of ketones were also observed for all starting material **157**, methoxy adduct **271**, and dimer **272**. Again, this is consistent with a source of D^+ being present in the reaction as before again. Unreacted starting material **157** (5%), methylated compound **269** (1%) and enone **270** (4%) were collected as an inseparable mixture, and the yields were calculated from ^1H and ^2H NMR spectrum. The undesired dimer species **272** was still isolated in a relatively high yield (29%). Once again, the large degree of dimer formation in the methylenation reaction suggested that the oxidation of CD_3OH was slower compared to CH_3OH, leading to low concentration of formaldehyde and Ir-D, therefore enone **270** was trapped by excess starting material enolate.

2.4.2 Reactions in CH_3OD

As a complementary set of experiments, both the methylation and methylenation of valerophenone were conducted in CH_3OD (99%), and in this case a mono-hydride mechanism implies that deuterium should only be observed at α-position of each ketone product, with hydrogen present on the newly formed methyl or methylene group.

Scheme 2.52 *Methylation and methylenation reaction of valerophenone in CH_3OD*



Under these methylation conditions, 57% of the desired methylated compound **273** was isolated, giving a broad singlet at 3.49 ppm corresponding to the α-deuterium in the ^2H NMR. However, the ^1H NMR spectrum revealed that the α-position was partially deuterated with 11% of a proton being incorporated, since the sext at 3.41 ppm was still present. The undesired dimer species was formed in 27% yield, providing two broad singlets at 3.54 and 3.37 ppm correlating to the α-deuterium of *syn*- and *anti*- **275** in the ^2H NMR. However, peaks at 3.53 and 3.73 ppm in the ^1H NMR showed 16% of proton present at the α-position (Scheme 2.52).

For the methylenation reaction, the desired enone **157b** and methoxy adduct **274** were obtained in 44% yield, in addition to 5% yield of methylated compound **273** and 33% yield of dimer **275**. Complete deuteration of the α-position was observed for methoxy adduct **274** with a broad singlet at 3.77 ppm in the ^2H NMR and the absence of such a peak in the ^1H NMR. A small amount of proton was also present at the α-position for both methylated compound **273** and dimer **275** (10% and 9% respectively).

The presence of proton at the α-position was because of the deuterium exchange with acidic Ir-H or its reaction with O_2, as suggested earlier, affording CH_3OH or H_2O. Despite this complication, the fact that deuterium was only observed at the α-position but not the newly formed methyl group in methylated product confirmed the monohydride mechanism.

The large amount of dimer formation in either methylation or methylenation reactions suggested that the oxidation of CH_3OD was still slower than that of CH_3OH. Howver, since the methylation of valerophenone in CH_3OD gave a better yield of the desired methylated product **273** and a simplier product distribution, it still seems that the oxidation of CH_3OD is faster than that of CD_3OH.

The H/D ratio at the α-position of products formed from reactions in CD_3OH (H/D ≈ 4/6) or CH_3OD (H/D ≈ 1/9) was not exactly opposite, and more deuterium incorporation was observed in CD_3OH (40%) than the proton incorporation in CH_3OD (10%). These results did not fit with what we were expecting and are unexplained. Ir-H is more acidic than Ir-D because of the kinetic isotope effect, and thus more Ir-H is deprotonated in solution, resulting in a larger concentration of H^+, and thus more incorporation of a proton in CH_3OD should occur compared to the deuterium incorporation in CD_3OH. This is opposite to that observed. Alternatively, if CH_3OD is oxidised faster than CD_3OH, we would expect faster formation of Ir-H in the CH_3OD experiment, also leading to higher concentration of H^+. We suggest that the different observations arise from the thermodynamic equilibrium between H^+ and D^+, and a different ratio of H/D would be observed at varying times during the course of the reaction. The faster oxidation of CH_3OD compared to CD_3OH would lead to higher concentration of formaldehyde which would be trapped by methanol to give the hemiacetal **276**. Further oxidation and hydrolysis would lead to formation of formic acid which lowered the pH (see section 2.2.5 and 2.4.3, scheme 2.54). Therefore, it would take longer time for the H/D exchange to reach equilibrium in the less basic reaction with CH_3OD, and less proton incorporation was observed after 48 h. Due to time constrains, we were unable to investigate the mechenisms further, and the studies are being continued in the Donohoe group.

2.4.3 The role of O_2

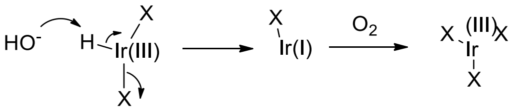
Throughout these studies, an atmosphere of O_2 has proved to be beneficial for both methylation and methylenation reactions, and we reasoned that there are three possible pathways involving O_2 in the $[Ir(cod)Cl]_2$ catalyzed reactions presented earlier.

(1) α-Elimination of Ir-H species followed by oxidition

Gabrielsson proposed the reoxidation of an Ir(I) complex formed by deprotonation and α-elimination of an acidic Ir(III)-H species by oxygen, thus regenerating the active Ir(III) catalyst to continue the reaction (section 2.2.4.4, Scheme 2.53).[64] Although $Ir(III)Cl_3/cod/PPh_3$ showed no reactivity in catalyzing the methylation reation (section

2.2.4.3), we cannot rule out possibility of formation of Ir(III) species during the course of the $[Ir(cod)Cl]_2$ catalyzed reactions.

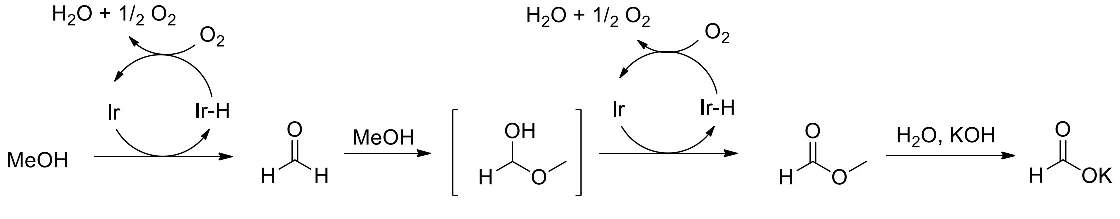
Scheme 2.53 *α-Elimination*



(2) Insertion of O_2 into an Ir-H species

As previous discussed in section 2.3.1, Ison have proposed the formation of hydrogen peroxide by insertion of O_2 into an Ir-H species, thus regenerated the active catalyst.[87] We considered that this was the major role of O_2 in the methylenation reactions, essentially mopping up the Ir-H so that no enone reduction occurs. This pathway was also possible for the methylation reactions, as the dehydrogenative coupling of methanol may have occurred. As mentioned in section 2.2.5, Ishii *et al.* have reported an aerobic dimerization of primary alcohols to esters catalyzed by $[IrCl(coe)_2]_2$.[67] In our mechanism, we supposed that methanol was first oxidised to formaldehyde by the Ir catalyst, and a hemiacetal intermediate **276** was formed by addition of MeOH. Further oxidation of the hemiacetal gave a methyl ester **277** and a Ir-H species which was reoxidised by O_2. The hydrolysis of the methyl ester under basic conditions gave a formic salt reducing the pH, which explained the requirement of super stoichiometric amount of KOH for the reactions (Scheme 2.54).

Scheme 2.54 *Proposed Ir catalyzed dehydrogenative coupling of methanol*

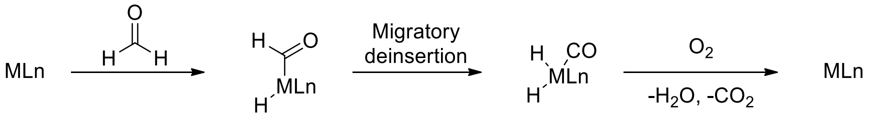


276 **277** **278**

(3) Carbon monoxide species

Last but not least, we suggested that an inactive [Ir]-CO species could be formed by the dehydrogenation of formaldehyde, and was reactivated under an atmosphere of O_2 by oxidation to carbon dioxide (Scheme 2.54). In support of this idea, Saito and co-workers reported that the catalytic activity of [Ru(OAc)Cl($PEtPh_2$)$_3$] decreased over time for the dehydrogenation reaction of methanol, and that a [RuClH(CO)($PEtPh_2$)$_3$] complex was isolated from the deactivated solution. [88] It was also suggested by Iwashita and co-workers that O_2 was able to oxidise a [Rh]-CO complex ([$Rh_2(CO)_4(PPh_3)_4$]) into a [Rh]-CO_2 complex ([$Rh_2(CO)_2(CO_2)(PPh_3)_3C_6H_6$]).[89]

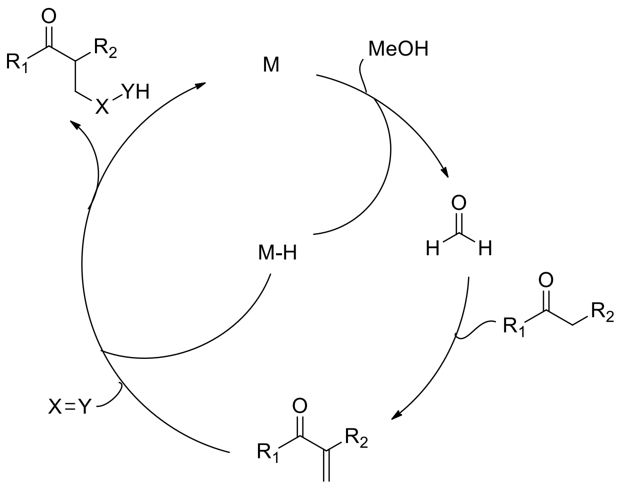
Scheme 2.55 *Proposed dehydrogenation of formaldehyde for the formation of M-CO complex and its reactivation by* O_2



2.5 Future work

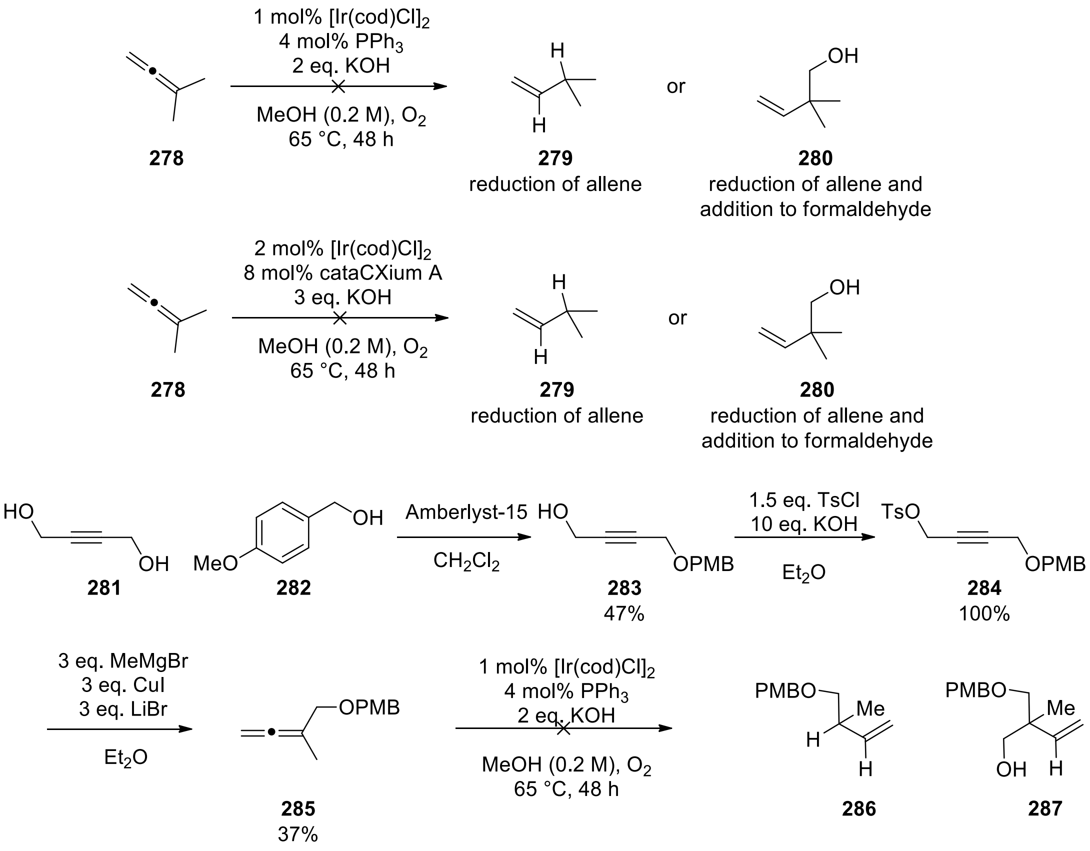
The reduction of an enone by a metal hydride species was interrupted during the methylenation process, and it would be more advantageous if we could take advantage of the metal hydride for the activation of a ‘pronucleophile’, which may then add back in to the enone (Scheme 2.56). We have considered allenes as a good pronucleophile following inspiration by work developed by Krische and co-workeres where allenes were reduced and added to formaldehyde affording hydrohydroxymethylated products (see section 1.3.4). [36]

Scheme 2.56 *Potential activation of a pronucleophile X=Y followed by addition to enones*



In preliminary experiments, commercially available allene **278** was added to both the methylation and methylenation conditions to see if the [Ir(cod)Cl]$_2$ catalyst was able to transfer hydrogen from methanol to the allene; however we could not monitor the reaction due to the volatility of the starting material. Therefore, we synthesized allene **285** which was used in Krische's work. Mono-protection of 2-butyne-1,4-diol with *para*-methoxybenzyl alcohol resulted in a moderate yield of **283**, and tosylation of the second hydroxyl group was achieved in quantitative yield. Finally, Grignard addition to **284** afforded 37% yield of the desired allene **285**, which has peaks in the ^{1}H NMR at 4.69 - 4.58 ppm (m, 2 H) corresponding to the two terminal allene protons, and 1.67 ppm (t, J = 3.1 Hz, 3 H) corresponding to the methyl group. Subjection of this allene **285** to the methylation conditions resulted in sole recovery of starting material (Scheme 2.57).

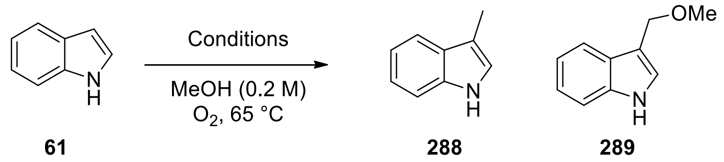
Scheme 2.57 *Reactions with allenes*



Although the first attempts to reduce the allenes failed, time constraints meant that a full investigation was not carried out, and the concept of activating a ‘pronucleophile’ is still being studied in the Dohonoe group.

The other goal of future work is to apply our hydrogen borrowing methodology using methanol to substrates other than ketones. Grigg and co-workers had developed a $[IrCp^*Cl_2]_2$ catalyzed alkylation reaction of indoles, but methanol could not be employed as an alkylating agent in those reactions (see section 1.1.6).[25] As such, indole (**61**) was subjected to our methylation conditions using $[Ir(cod)Cl]_2$ (Table 2.15, entry 1), and pleasingly, both the desired methylated product **288** (17%) with a peak at 2.32 ppm for the methyl group and the methoxy adduct **289** (34%) with two singlets at 4.66 (2H) and 3.39 (3H) ppm corresponding to the CH_2OCH_3 were observed in the crude ^1H NMR. The desired methylated product was isolated in 47% yield when 2.5 mol% $[IrCp^*Cl_2]_2$ was employed after 24 h. The methoxy adduct **289** was not isolated from the reaction mixture presumably because of its instability, and a 31% yield was determined from its crude ^1H NMR (Table 2.15, entry 2). Further stirring the reaction for 48 h did not improve the yield of the methylated product **288**, but only led to poorer yield of the methoxy adduct **289** (Table 2.15, entry 3).

Table 2.15 *Methylation or methylenation of indole*

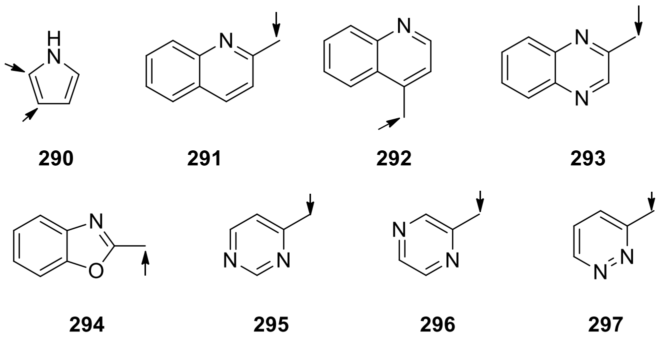


Entry	**Conditions**	**288** (%)	**289** (%)
1	1 mol% $[Ir(cod)Cl]_2$ 4 mol% PPh_3, 3 eq. KOH, 48 h	17	34
2	2.5 mol% $[IrCp^*Cl_2]_2$ 3 eq. KOH, 24 h	(47)	31
3	2.5 mol% $[IrCp^*Cl_2]_2$ 3 eq. KOH, 48 h	51	12

Yields were calculated from ^1H NMR with 1,2-dimethoxybenzene as an internal standard; Yields in brackets are isolated yields.

The indole substrates have the potential to either be methylated or undergo methylenation/conjugate addition sequence for the formation of more complex products. Further optimisation of the conditions is still underway in the group. Other potential substrates mentioned in section 1.1.6 such as pyrrole **290**,[90] methylquinolines **291** and **292**, 2-methylquinoxaline **293**, 2-methylbenzoxazole **294**[28], methylpyrimidine **295**, methylpyrazine **296**, and methylpyridazine **297**[27] are also being studied (Scheme 2.58).

Scheme 2.58 *Other potential heterocycles for hydrogen borrowing using methanol*



2.6 Conclusion

We have reported methodology for the use of methanol as an alkylation reagent using catalytic rhodium or iridium species. A rhodium catalyzed double methylation of methyl ketones was first achieved, and then the scope was expanded to a Ir/Rh consecutive one-pot double alkylation reactions in combination with Ishii alkylation conditions. Later on, after the optimisation of $[Ir(cod)Cl]_2$ catalyzed methylation reactions, the double alkylation was accomplished with a low loading of iridium catalyst (1 mol%). The synthetic utility of the dialkylated products was enhanced by performing a regioselective Baeyer-Villiger oxidation which allowed access to ester products.

A range of different phosphine ligands were screened for optimal activity in the methylation reaction, and we were pleased to find that sterically hindered and electron rich phosphine ligand favoured the formation of enone and methoxy adducts under an O_2 atmosphere. This interrupted hydrogen borrowing reaction enabled the *in situ* addition of a nucleophile to give more complex products. A range of tetrasubsitituted pyridines were then synthesized from 1, 5-dicarbonyl compounds formed in the methylenation/conjugate addition sequence.

Finally, deuteration experiments suggest that the reaction proceeds *via* a monohydride mechanism, and the possibilities for the beneficial effect of O_2 were discussed.

Chapter 3:

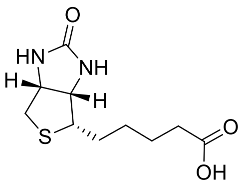
Introduction-Synthesis of biotin derivatives

3 Introduction-Synthesis of biotin derivatives

3.1 Biotin

Biotin is a vitamin that is present in small amounts in all living cells and is critical for a number of biological processes.[91] Biotin is abundant in certain plant and animal tissues such as currants, sunflower seeds, egg yolk, pig kidney, liver and blood.[92] The structure of biotin, which contains urea and thiophene ring with valeric acid attached, was first determined by Vincent du Vigneaud in 1942 (Figure 3.1).[93] Biotin can be conjugated to many proteins and other molecules without significantly altering their biological activity, and the valeric acid side chain of the biotin molecule can be derivatized in order to incorporate various functional groups. The highly specific interaction proteins with biotin make it a useful tool in assay systems designed to detect and target biological analytes.

Figure 3.1 *Structure of biotin*



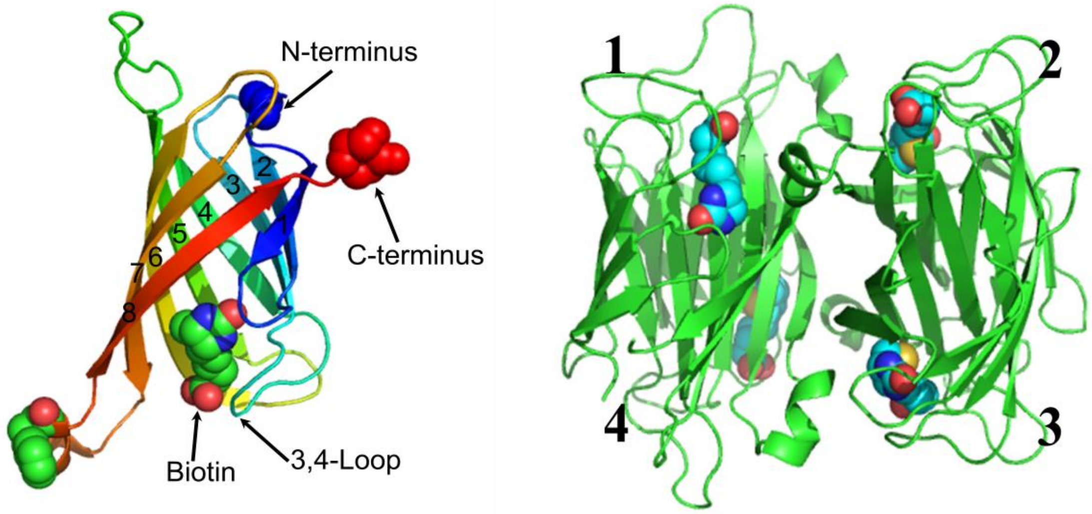
3.2 Streptavidin

Streptavidin is a tetrameric protein produced by *Streptomyces avidinii*, and it is structurally similar to the protein avidin found in chicken eggs. Strepravidin was first isolated in 1964 by Tsusig and Wolf from fermentation filtrates of streptomycetes, which binds to the vitamin biotin with an extremely high affinity (dissociation constant of 4×10^{-14} M).[94] Streptavidin and avidin are among the most stable proteins known as they are resistant to high temperatures (melting temperature for streptavidin: 75 °C, and 83 °C for avidin),[95] extremes of pH, organic denaturants, and proteolytic enzymes.[96] These characteristics make streptavidin and avidin ideal models in studying high affinity macromolecule-ligand interactions and the structural stability of proteins in general.

3.3 Streptavidin and biotin complex

The X-ray studies performed by Salemme revealed that each streptavidin subunit consists of eight β-strands,[97] forming a very stable β-barrel structure with a simple antiparallel topology (Figure 3.2A). Four subunits are positioned in dihedral D_2 symmetry (the binding sites of subunits 1, 2 point in the same direction, and 1,3 sites point away from each other) to form a tetramer, which can be viewed as a dimer of a stable subunit dimer. The biotin-binding site of streptavidin is located at one end of each β-barrel subunit. Each tetrameric streptavidin molecule can therefore bind four biotin molecules (Figure 3.2B, PDB code: 1SWE).

Figure 3.2 *Streptavidin structure*[*]



A. Streptavidin monomer

B. Streptavidin tetramer

The high affinity of the noncovalent interaction between biotin and streptavidin results from several factors. First of all, a number of amino acid residues make contact with biotin,

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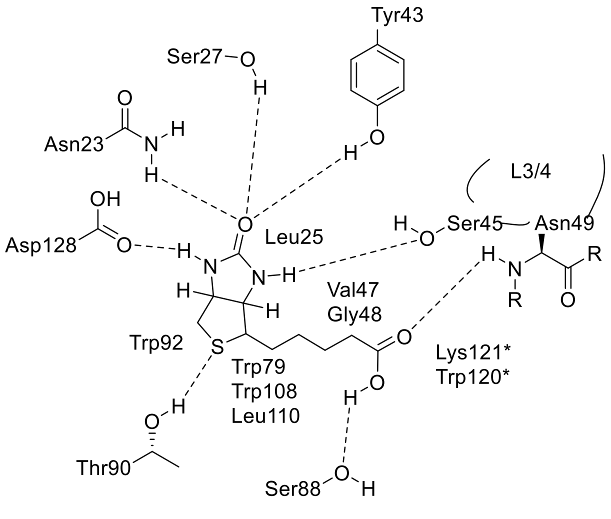
[*] Figures provided by the Howarth group

providing the extremely high stability of the streptavidin-biotin complex. The amino acid residues that make hydrogen bonds or strong van der Waals contacts with biotin are shown schematically in Figure 3.3. The eight amino acid residues make hydrogen bonds with different parts of the biotin include: Asn23, Ser27, and Tyr43 with the ureido oxygen of biotin; Ser45 and Asp128 with each of the ureido amino groups; Thr90 with the thiophene sulfur; and Asn49 and Ser88 with the carboxyl oxygens. Secondly, several aromatic or aliphatic residues create the hydrophobic environment required for the hydrophobic ligand biotin and this factor contributes most to the tight binding. Four tryptophan residues, Trp79, 92, 108, and 120, together with Leu25, Val47, and Leu110, interact with the thiophene ring and the alkyl chain of biotin through van der Waals forces. It is noted that both Lys121 and Trp120 are provided by an adjacent subunit, and these intersubunit contacts play key roles in the extremely tight biotin binding by this tetrameric protein (Figure 3.3).

Figure 3.3 *Hydrogen bond or van der Waals contacts between streptavidin and biotin*



Thirdly, a loop consists of the sequence from Ser45 to Ala50 is likely to be relatively flexible. But after the biotin binding has taken place, the conformation of the loop between β-strands 3 and 4 becomes defined, where Val47, Gly48, and Asn49 on the loop make strong electrostatic and van der Waals interactions with biotin. The last factor contributing to the tight binding is the shape complementarily of the binding pocket with the ligand. In the absence of bound biotin, five water molecules mimic a biotin molecule in the binding pocket.[91]

3.4 Streptavidin mutants

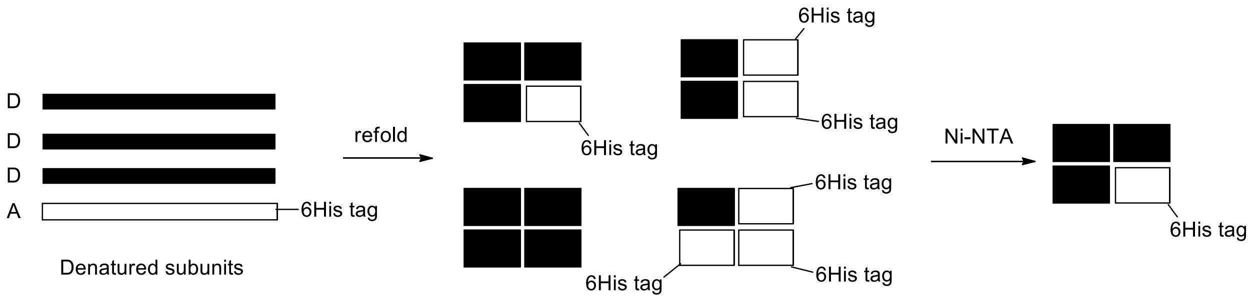
The gene of streptavidin in *Escherichia coli* was cloned and expressed using the bacteriophage T7 expression system by Cantor in 1986.[96] Since then, the establishment of efficient expression and purification systems for streptavidin has allowed modification of streptavidin by genetic engineering to fully understand the structural and functional characteristics of this protein. Mutagenesis not only allows changes to individual amino acid residues, but also makes it possible to introduce changes in its structure and topology. For example, new residues can be inserted, parts of protein can be deleted and the order the residues can be altered. The development of genetically engineered streptavidin has broadened the spectrum of its potential applications.

3.5 Preparation of monovalent streptavidin by using streptavidin mutants

The tetrameric streptavidin can sometimes tetramerize the biotin conjugates to which they bind, thus interfere with normal biomolecule function or complicate affinity measurements, limiting the applications of the system. Much effort has been made to develop monomeric streptavidin, such as disrupting the tetramer interface[98] or titrating in three equivalents of biotin per tetramer. However, the former method is always accompanied by a dramatic decrease in biotin affinity as the biotin binding site lies at the interface between subunits *vide infra*, and the latter method always generates a mixture of mono-, di-, tri- and tetravalent strepavidins.

The Howarth group has reported a new method for generating monovalent streptavidin, of which three subunits are unable to bind biotin and one subunit binds biotin as well as wild-type streptavidin.[99] They found that triple mutated (N23A, S27D, S45A) streptavidin reduced biotin affinity dramatically but left the tetramer structure intact. Asn23 and Ser27, which form hydrogen bonds with biotin ureido oxygen were converted to alanine (N23A) and aspartate (S27D) respectively, and Ser45 which forms a hydrogen bond with biotin ureido nitrogen was converted to alanine (S45A). The biotin affinity of this mutant (composed of 'dead' subunits, D) has an approximate dissociation constant of 1.2×10^{-3} M (10^{11} fold less than that of wild-type streptavidin). In order to produce the monovalent streptavidin, a 6His tag was attached to the wild-type subunit ('alive' subunit, A), then combined D and A subunits at a molar ratio of 3:1 in guanidinium hydrochloride and refolded them by rapidly diluting the mixture into phosphate buffered saline (PBS). This refold generated a statistical mixture of tetramers of different composition which was purified using a nickel–nitrilotriacetic acid (Ni-NTA) column, eluting according to the number of 6His tags with increasing concentrations of imidazole. The desired monovalent A1D3 streptavidin was obtained in about 30% yield (Scheme 3.1).

Schem 3.1 *Production of monovalent A1D3 streptavidin*



Electrospray ionization mass spectrometry confirmed that A1D3 streptavent was monovalent, with only a single biotin binding. The biotin binding affinity was determined by measuring the competition with wild-type streptavidin, and the 6His tag in monovalent A1D3 did not affect biotin binding, as the measured affinity was 4.8×10^{-14} M, similar to the untagged wild-type affinity of 4.0×10^{-14} M.

3.6 Divalent streptavidins

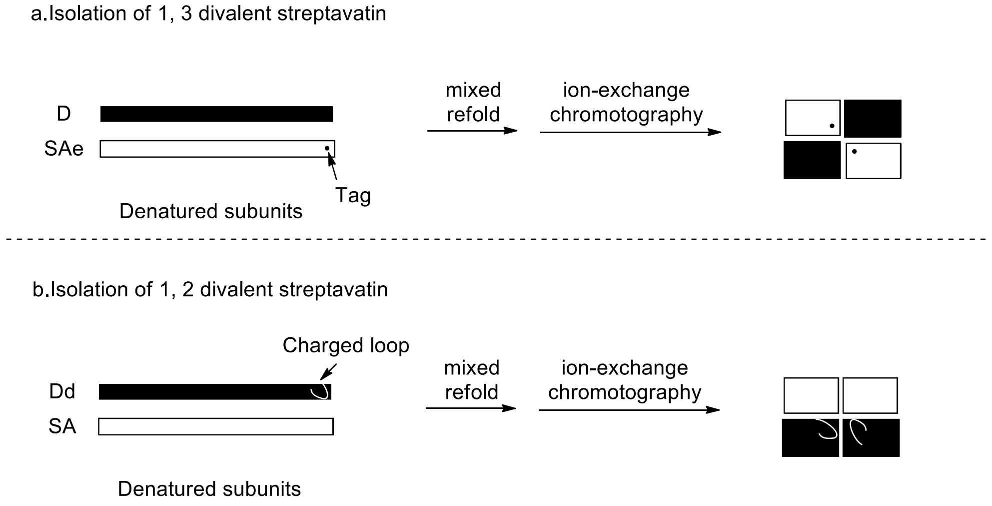
Tetramers with two functional and two dead subunits (divalent streptavidins) can assemble in three different arrangements: 1,2, 1,3, and 1,4 divalent forms of streptavidin. In the 1,2 arrangement the biotin-binding sites of streptavidin are in a cis configuration as the binding sites both point in the same direction. However, in the 1,3 arrangement, both sites are in a trans configuration, pointing away from each other. A mixture of all three arrangements would not be suitable for applications where defined spatial control is necessary. The Howarth group demonstrated a method for the simple isolation of streptavidin variants with precise *cis*-divalent or 1,3 *trans*-divalent arrangements.[100]

The C-termini are close together between subunits 1 and 3 (27 Å) but far apart between subunits 1 and 2 (57 Å) or subunits 1 and 4 (50 Å), so a hexaglutamate tag was placed at the

C-terminus of core streptavidin monomer (SAe). When SAe was refolded together with dead (D) streptavidin (N23A, S27D, S45A), the 1, 3 divalent streptavatin was easily purified from the ion-exchange column at a later time after the 1,2 and 1,4 divalents were co-eluted (Scheme 3.2a).

To separate the 1,2 divalent streptavidin, aspartate was introduced into the loop between β-strands 3 and 4 of the dead subunits (Dd). The negatively charged loops are apposed in 1,2 arrangement, while in the 1,3 or 1,4 arrangements, they are far apart. The aspartate units were inserted to the dead units because the loops are important for biotin binding affinity. Similarly, the ion-exchange chromatography of a mixed refold of streptavidin (SA) and Dd allowed efficient separation of the 1,2 divalent streptavidin after the 1,3 and 1,4 divalents were co-eluted (Scheme 3.2b).

Schem 3.2 *Isolation of 1,3 or 1,2 divalent streptavatin*



3.7 Methods for the study of how force changes structure and reactivity at molecular level

Atomic Force Microscopy (AFM), is a set of techniques for the study of the binding forces between individual molecules. The AFM technique allows mapping of the surface characteristics at sub-nanometer resolution. In a typical AFM pulling experiment, molecules of interest are attached between the sample surface and the cantilever tip. A piezoelectric controller then pulls up the cantilever increasing the separation between the cantilever and the sample surface. The force on the molecule is provided by the cantilever deflection which is measured by the position of a laser beam. The main drawbacks and limitations of AFM stem from the large size and relatively high stiffness of the cantilevers, which impose a lower limit on the useful force range. It is also difficult to discriminate interactions of the AFM tip with the molecule of interest from nonspecific interactions or inappropriate contacts with the molecule of interest.[101]

Protein-ligand simulations have been developed to compute the binding affinity of a ligand to a known binding site.[102] The computational calculations suggests that there are new molecular interactions made as ligands are extracted from the binding site by an external force. However, simulation often use simplifications to binding partners and there is limited experimental verification of such results.

X-ray crystallography is the most widely used method for high resolution analysis of ligand binding interactions. The crystalline atoms cause a beam of incident X-rays to diffract into many specific directions. By measuring the angles and intensities of these diffracted beams, a three-dimensional picture of the density of electrons within the crystal can be produced, thus, allowing determination of the mean positions of the atoms in the crystal as well as other chemical information.

3.8 Aim of the project

The aim of this project is to use crystallography to gain molecular insight into how force affected ligand interactions through the synthesis of a series of modified ligands.

As introduced before, the strepatavidin-biotin system is ideal for our studies due to their high affinities. Monomeric streptavidin, or divalent streptavidin were used in some cases to avoid theinteraction between ligands binding to adjacent sites where certain mutated streptavidin was used when the ligand binding affinities need to be decreased.

Chapter 4:

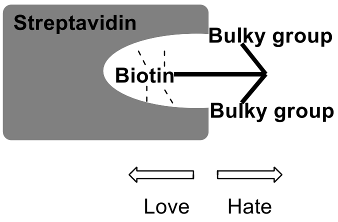
Results and Discussion-Synthesis of Biotin Derivatives

4 Results and Discussion - synthesis of biotin derivatives

4.1 Design of the first Love-Hate ligand

In order to study how force affected the ligand binding interactions, we decided to design ligands with the appropriate balance of attraction and repulsion (Figure 4.1). The attraction was achieved by interaction of a biotin head with the binding pocket of streptavidin (Love). Therefore, the biotin core should not be modified, as we required the fundamental hydrogen bonding network between ligands and the protein to be retained. Repulsive interactions were introduced through a steric clash of a bulky moiety with the streptavidin surface at a position distant from the binding site (Hate).

Figure 4.1 *Love-Hate ligand concept*

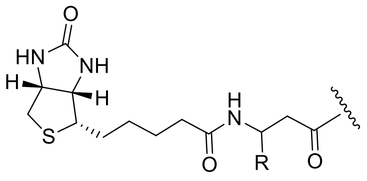


Biotin itself has a solubility of 20 mg/100 mL in water, and since the following crystallisation experiments will be conducted in phosphate buffered saline solution (PBS) with 10% DMSO, we wanted to further increase the water solubility of the ligands by introducing heteroatoms.

We first avoided having the large moiety within one or two atoms of the biotin carboxylate, based on prior insight into such biotin conjugates designed to be resistant to biotinidase cleavage. Wilbur and co-workers have reported that biotin conjugates which have functional groups (R) of varying size α to the biotinamide bond remained bound to streptavidin when treated with large excess of biotin, indicating their high binding affinities (Figure 4.2).[103]

However, our goal was to gradually decreacing the binding affinity with larger bulky groups in order to study the interaction changes. Therefore, the type of biotin conjugate shown in Figure 4.2 should be avoided as they still retain high binding affinity with biger R group.

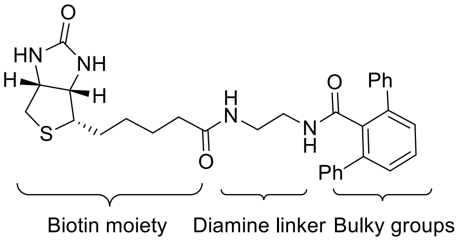
Figure 4.2 *Biotin conjugates with functional groups α to the biotinamide bond*



R = CH_3, CH_2OH, CH_2COOH, or COOH

Considering these points, we designed the ligand LH1 which contains a 4-atom linker between biotin and a sterically hindered di-*ortho*-phenyl benzamide moiety. It was synthetically accessible from commercially available compounds, and by changing the size of di-*ortho* groups, we could easily tune the streptavidin repulsion (Figure 4.3).

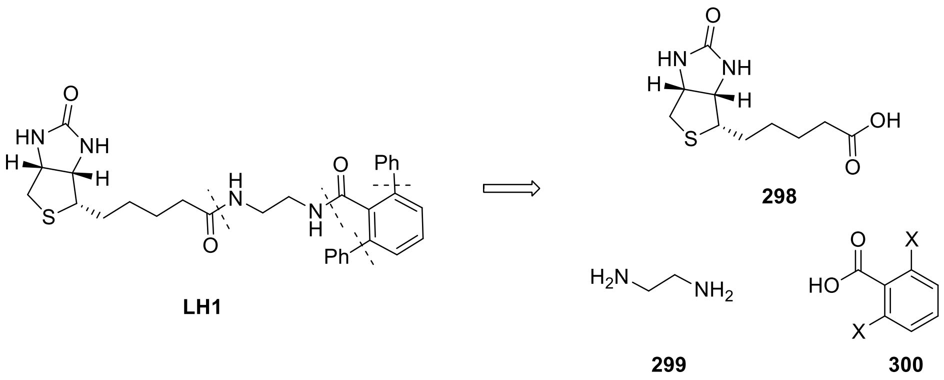
Figure 4.3 *Structure of ligand LH1*



LH1

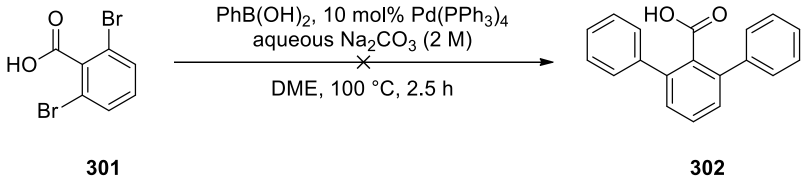
4.2 Synthesis of the first Love-Hate ligand

Scheme 4.1 *Retrosynthetic analysis of ligand LH1*



The approach was divided into two parts with the first being the synthesis of the bulky end group and linker by employment of Suzuki coupling and amide bond forming techniques, and the second being the final coupling of the bulky group to the biotin moiety (Scheme 4.1). Previous work in the Donohoe group had shown that direct coupling of phenylboronic acid to 2,6-dibromobenzoic acid (**301**) proved unsuccessful due to difficulties in isolating the polar carboxylic acid **302** (Scheme 4.2).*

Scheme 4.2 *Suzuki coupling of phenylboronic acid **303** to 2.6-dibromobenzoic acid **301***



To rectify the problem, the Suzuki coupling on amides **308** was then attempted. Mono-Boc protected amine **305** was first synthesized by slow addition of ethylenediamine (**304**) to a solution of di-*tert*-butyl dicarbonate in CH_2Cl_2. The protected amine **305** was then coupled to diiodobenzoic acid **307** which was synthesized through palladium-catalyzed *ortho* iodination

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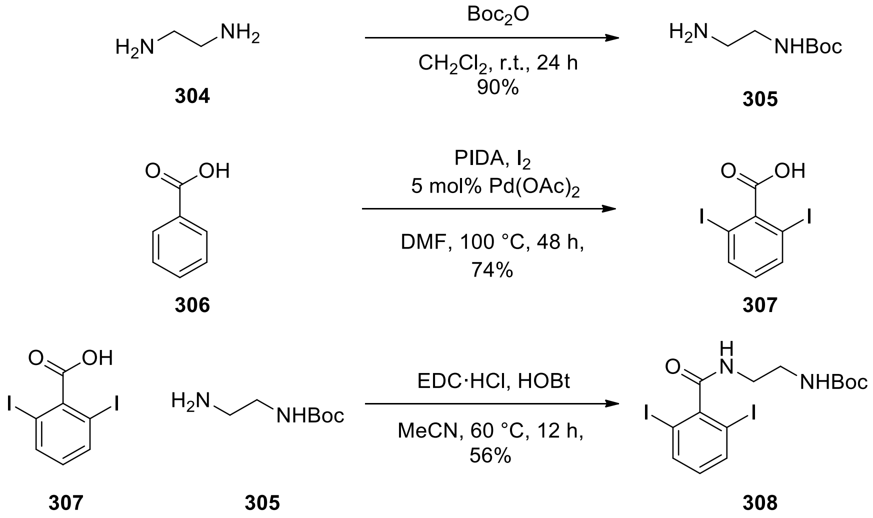
* Gemma Adams

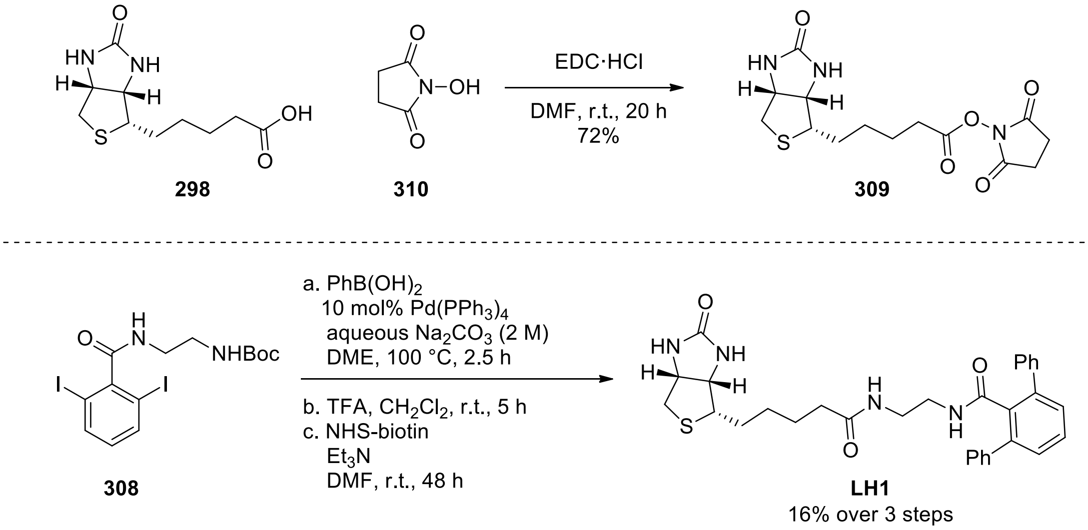
of benzoic acid (**306**) to give **308** in 56%.[104] The structure of **308** was confirmed by observation of peak in the ^{1}H NMR at 7.73 ppm (d, J = 7.9 Hz, 2H), 6.68 ppm (t, J = 7.9 Hz, 1H) corresponding to the phenyl protons, 6.70 ppm (br s, 1H), 5.20 ppm (br s, 1H), 3.55-3.52 ppm (m, 2H), 3.43-3.41 ppm (m, 2H) matching the diamine linker and 1.39 ppm (s, 9H) for the tBu group (Scheme 4.3).

Scheme 4.3 *Synthesis of the amide for Suzuki coupling*



Activated (+)-biotin *N*-hydroxysuccinimide ester (NHS-biotin **309)** was synthesized from the EDC promoted coupling of (+)-biotin and *N*-hydroxysuccimide in DMF with a yield of 72%. Suzuki coupling of **308** and phenylboronic acid was then successfully performed and without further purification the crude material was treated with TFA to release the free amine which was finally attached to NHS-biotin ester to afford **LH1** in 16% yield over 3 steps. The structure of **LH1** was confirmed by the observation of peaks in ^{1}H NMR at 4.50 ppm (dd, J = 7.7, 4.6 Hz, 1H), 4.30 ppm (dd, J = 7.9, 4.4 Hz, 1H), 3.21-3.19 ppm (m, 1H), 2.93 ppm (dd, J = 12.8, 4.9 Hz, 1H), and 2.72 ppm (d, J = 12.6 Hz, 1H) corresponding to the 5 protons in the biotin head, and peaks at 2.99-2.97 ppm (m, 2H), and 2.85-2.84 ppm (m, 2H) related to the two CH_2 groups in the diamine linker. The appearance of peaks at 176.0 ppm, 172.4 ppm, and 166.1 ppm in the ^{13}C NMR also confirmed the presence of three different carbonyl groups. Furthermore, a peak in the high resolution mass spectrum at 565.2223 ppm corresponding to the $[M+Na]^+$ species was observed (Scheme 4.4).

Scheme 4.4 *Synthesis of ligand LH1*



4.3 Crystal structure of Streptavidin bound to LH1[†]

This project was carried out in collaboration with the Howarth group (Department of Biochemistry) for the crystallography studies. Crystals of streptavidin/ligand complexes were obtained by the sitting drop crystallization method. Protein (1 mM) was incubated with ligand (2 mM) for 1 h at r.t. in PBS with 10% DMSO. Samples were centrifuged to remove any precipitate. The protein ligand solution was then mixed with cyrstallization buffer (75% ammonium sulfate, 25% 1 M sodium acetate, pH = 4.5) in a sitting drop 2 well Swissci plate. Crytals were obtained after a few hours at r.t. and reached a maximum size after 1-2 days.

LH1 gave a 1.1 Å structure in complex with streptavidin, with both binding sites in the asymmetric unit containing well defined ligand (Figure 4.4 A,B). Despite the di-*ortho* phenyl

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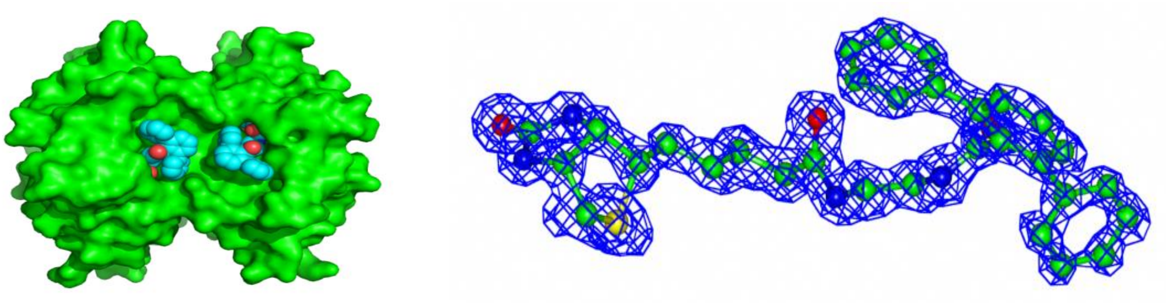
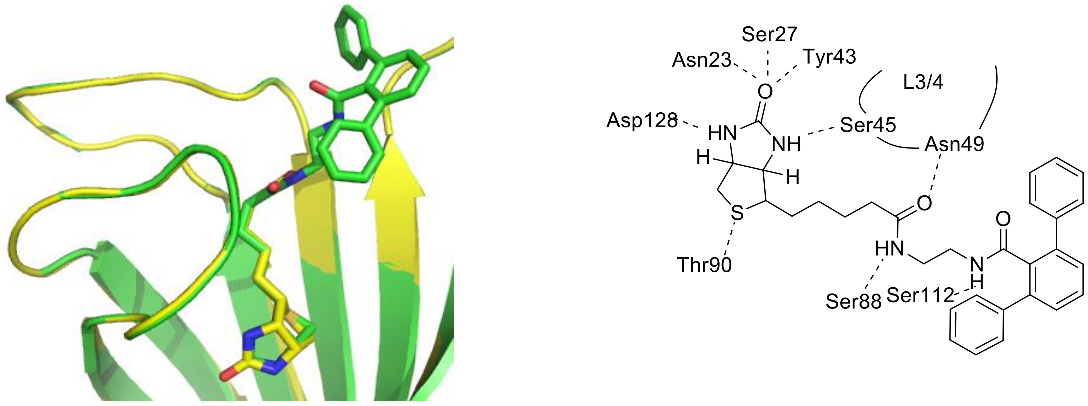
[†] All the X-Ray experiments and refinement of data were performed by Dr Michael Fairhead

groups, the loop between β-strands 3 and 4 (L3/4) of streptavidin was shut and all hydrogen bond contacts to biotin were preserved, with minimal difference to complexes with biotin itself, and an extra potential hydrogen bond from the amine linker to Ser112 (Figure 4.4 C, D).

Figure 4.4 *Crystal structure of* ***LH1*** *and comparison with biotin*[‡]



A. Crystal structure of **LH1** B. Electron density around **LH1** contoured at 1 σ



C. Overlay with biotin D. Hydrogen bond contacts

The X-ray results suggested that the binding of **LH1** to streptavidin was almost identical to that of biotin itself. Moreover, **LH1**, compared to biotin, showed a minimal difference in equilibrium binding with streptavidin (this will be further discussed in Section 4.10). We proposed that this was because the 4-atom ethylene diamine spacer of **LH1** allowed

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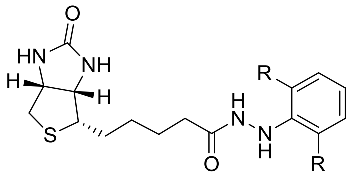
[‡] Crystallography analysis pictures were provided by Dr Michael Fairhead

flexibility in positioning of the repulsive moieties and therefore a Love-Hate ligand with a shorter linker was needed.

4.4 Design of the second series of Love-Hate ligands

Consequently, we designed a second series of Love-Hate ligands which contained a 2-atom hydrazide linker. This linkerwas chosen because (1) the two nitrogen atoms would increase the water solubility of the ligands; (2) their readily accessibility from cheap commercially available compounds (Figure 4.5).

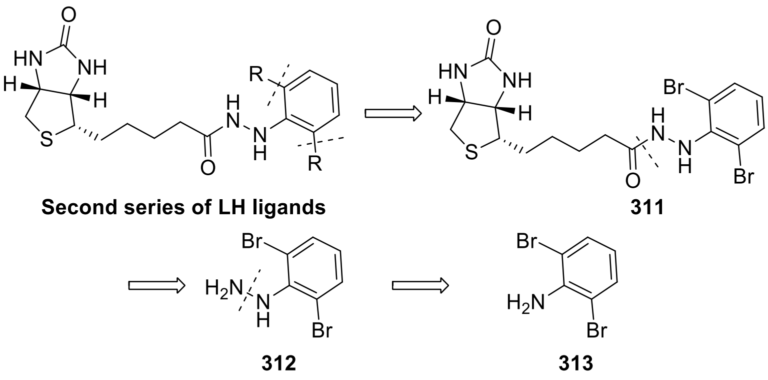
Figure 4.5 *Structure of the second series of Love-Hate ligands*



4.5 Synthesis of the second series of Love-Hate ligands

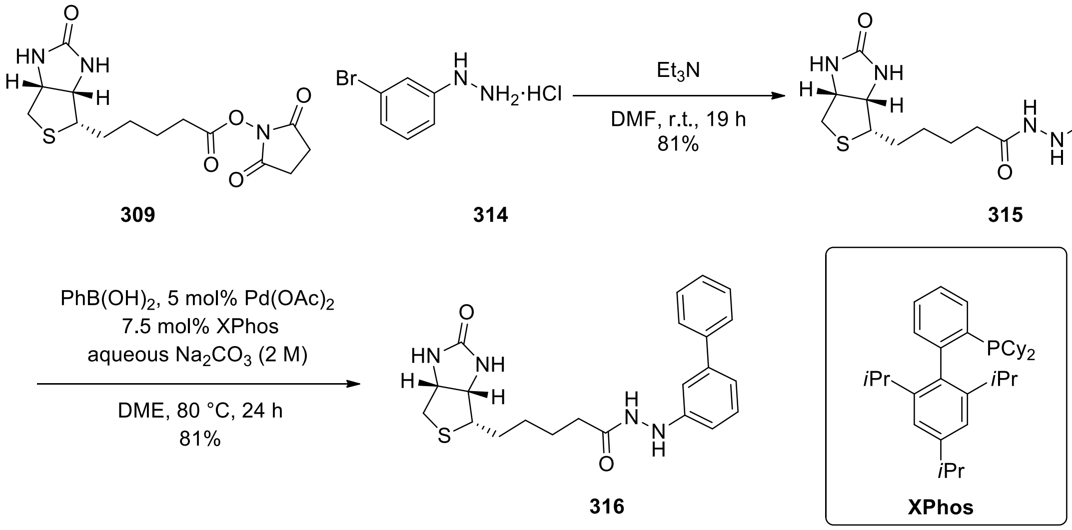
The synthesis of the second series of Love-Hate ligands utilized a cross-coupling strategy allowing diversification at the latest stage possible.

Scheme 4.5 *Retrosynthetic analysis of the second series of Love-Hate ligands*



A model substrate **316**, which was synthesized easily from commercially available 3-bromophenylhydrazine hydrochloride (**314**) and (+)-biotin *N*-hydroxysuccinimide ester (**309**), was shown to undergo Suzuki coupling cleanly in 81%. This suggested that the planned route was feasible as the Suzuki conditions tolerated functionalities on biotin, as well as the key aromatic hydrazide linker (Scheme 4.6).

Scheme 4.6 *Investigation on a model substrate*

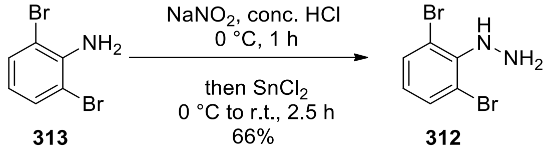


The structure of product was proved by observation of peaks in the ^{1}H NMR at 4.30 ppm (dd, J = 4.9, 7.8 Hz, 1 H), 4.06 ppm (dd, J = 4.4, 7.8 Hz, 1 H), 3.03 - 2.94 ppm (m, 1 H), 2.74 ppm (dd, J = 4.9, 12.7 Hz, 1 H), 2.56 ppm (d, J = 12.7 Hz, 1 H) corresponding to the biotin moiety, and 9 aromatic protons determined by integration of peaks in the region of 7.51 – 6.66 ppm.

With the successful synthesis of model compound in hand, we turned our interest to the real system. The synthesis of the 2,6-dibromophenylhydazine (**312**) was achieved by starting from commercially available 2,6-dibromoaniline (**313**). Diazotization using 2 equivalents of $NaNO_2$ followed by reduction with $SnCl_2$ resulted in hydrazine formation in 66% yield.[105]

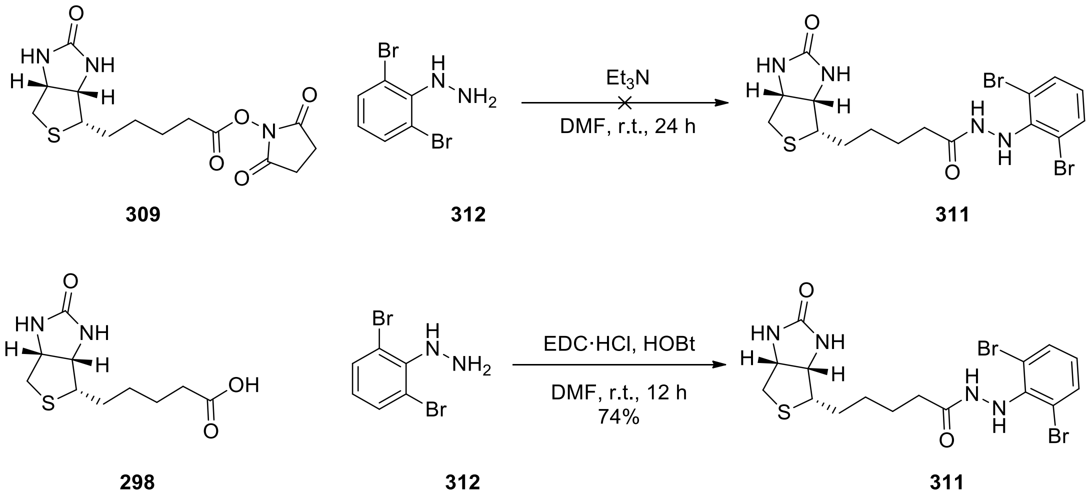
Although only one broad singlet was observed at 4.91 ppm (br s, 3H, $\mathrm{N}\underline{H}\mathrm{N}\underline{H}_2$) in its ^{1}H NMR spectrum in methanol-*d*4, the structure of hydrazine **312** was confirmed by observation of a peak at 264.8981 ppm in the high resolution mass spectrum corresponding to the $[M+H]^+$ species. The hydrazine was highly reactive towards acetone, ethyl acetate and acetonitrile, and decomposition was also observed in methanol. Thus, careful handling, including rinsing all the glassware and rotary evaporator with diethyl ether, was crucial to obtain pure material.

Scheme 4.7 S*ynthesis of the hydrazine*



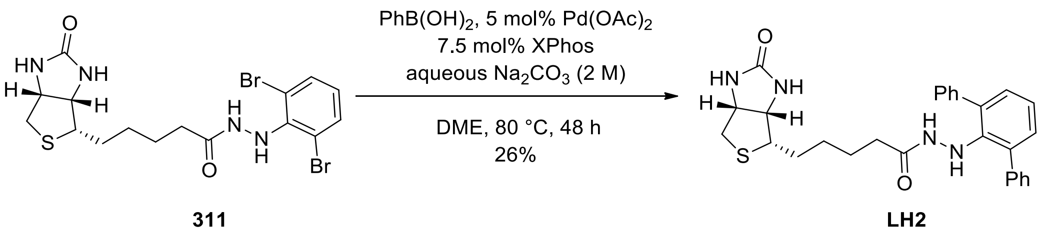
The following amide coupling using hydrazine **312** and (+)-biotin *N*-hydroxysuccinimide ester (**309**) was sluggish, whereas the coupling of (+)-biotin (**298**) and hydrazine **312** was successful with EDC·HCl, and HOBt in DMF at room temperature to give 74% of the desired dibromohydrazone **311**, which had a peak at 512.9553 ppm ($[M+Na]^+$) in the high resolution mass spectrum. Furthermore, DMF was found to be the ideal solvent for this reaction due to the high solubility of the starting material and the direct precipitation of the product at room temperature.

Scheme 4.8 *Synthesis of the dibromohydrozone* ***311***



With the dibromohydrazone **311** in hand, Suzuki coupling under optimized conditions afforded 26% yield of **LH2** along with unreacted starting material and mono-Suzuki product which was observed by a peak at 411.2 ppm ($[M+H]^+$) in the ESI^+ mass spectrum. We reasoned that the low yield was due to the large steric hinderance caused by the *ortho*-substitution pattern as well as decomposition of the starting hydrazone. Other palladium catalysts such as $Pd(PPh_3)_4$ and $Pd(dba)_2$ were also examined in this reaction, but neither of them gave better reactivity.

Scheme 4.8 *Suzuki coupling for the formation of* ***LH2***



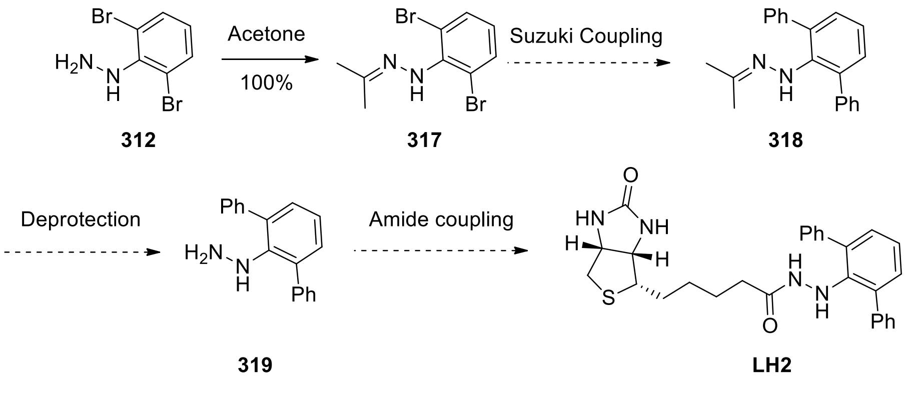
The structure of **LH2** was confirmed by the observation of peaks in ^1H NMR at 7.57-7.55 ppm (m, 4H), 7.47 ppm (t, J = 7.7 Hz, 4H), 7.39-7.37 (m, 2H), 7.17-7.15 (m, 2H), 7.09-7.06 (m, 1H) corresponding to the three phenyl rings, and peaks at 4.44-4.42 ppm (m, 1H), 4.20-

4.18 ppm (m, 1H), 3.05-3.02 ppm (m, 1H), 2.83 ppm (dd, J = 12.8, 4.9 Hz, 1H), and 2.63 ppm (d, J = 12.6 Hz, 1H) corresponding to the 5 protons in the biotin head. The appearance of peaks at 171.3 ppm, 163.6 ppm in the ^{13}C NMR also confirmed the presence of two different carbonyl groups. Furthermore, a peak in the high resolution mass spectrum at 509.1974 ppm corresponding to the $[M+Na]^+$ species was observed.

The above route enabled us to synthesize **LH2** in sufficient quantities even though the yield of the last Suzuki step was low. Before we moved to make more analogues of **LH2**, we decided to investigate other possible routes further.

As mentioned earlier, hydrazine **312** was highly active towards acetone to give the protected hydrazone **317**. We were inspired to perform the Suzuki coupling in the beginning on the protected hydrazone **317**, and with subsequential deprotection and amide coupling steps, attached the hydrazine to biotin moiety in the end. (Scheme 4.9)

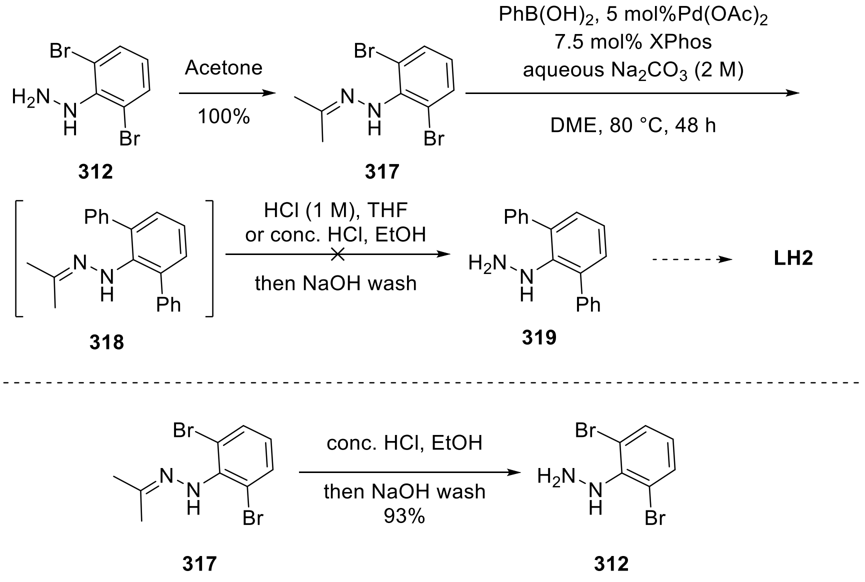
Scheme 4.9 *Planned alternative route towards the synthesis of* ***LH2***



Therefore, 2,6-dibromophenylhydrazine (**312**) was protected as the hydrazone, using acetone, which subsequently underwent smooth Suzuki coupling indicated by TLC and crude ^{1}H

NMR. [§] Unfortunately, the purification of the product was problematic because of decomposition. Attempts at deprotecting the crude Suzuki product were also unsuccessful using hydrochloric acid, although in a test reaction, 2,6-dibromophenylhydrazine (**312**) was obtained in 93% yield by treating protected dibromohydrazone **317** with concentrated hydrochloric acid in ethanol, following by solvent removal, base wash and extraction with Et_2O.

Scheme 4.10 *Alternative route towards the synthesis of* ***LH2***



Due to the difficulties in handling the reactive intermediates, this second route failed to give the desired product. We decided to return to the previous route whereby a Suzuki coupling was carried out as a last step between dibromohydrazide **311** and boronic acids.

In order to further increase the bulkiness of the Hate group, **LH3** containing *tert*-butyl groups on the the phenyl rings was also synthesized through Suzuki coupling of the dibromohydrazide **311** and (4-(*tert*-butyl)phenyl)boronic acid (**320**). The biotin moiety in

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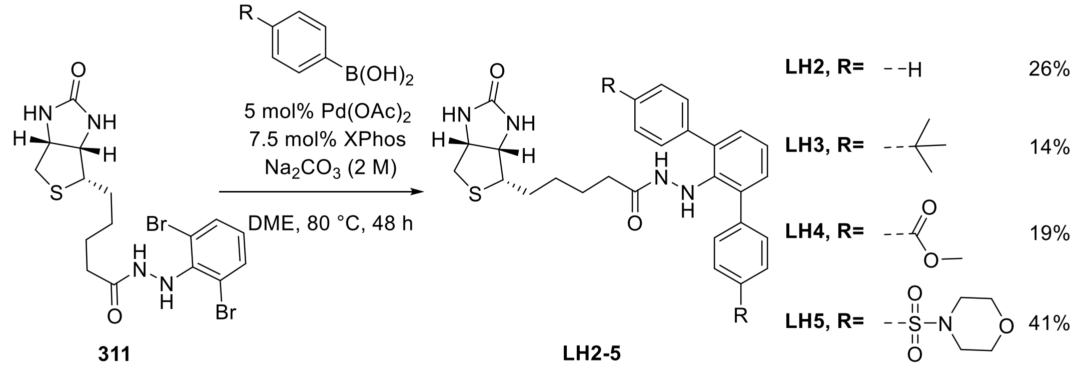
[§] Dr. Louis Chan

LH3 showed similar peaks to those of **LH2** at 4.45 ppm (dd, *J* = 7.6, 5.0 Hz, 1H), 4.20 ppm (dd, *J* = 7.7, 4.6 Hz, 1H), 3.08-3.04 ppm (m, 1H), 2.86 ppm (dd, *J* = 12.8, 4.9 Hz), 2.67 ppm (d, *J* = 12.9 Hz, 1H), a singlet at 1.38 ppm (s,18H) correlating to the two *tert*-butyl groups was also observed in the ^{1}H NMR of **LH3**. Both **LH2** and **LH3** were given to the Howarth lab for X-ray studies, but they were not able to obtain well-resolved crystals of **LH2** and **LH3**, due to their low water solubility. Therefore, we introduced methyl ester groups for **LH4** and morpholinosulfonyl groups for **LH5** to increase their water solubility as well as steric hindrance. We reasoned that these groups would be easily introduced by using the corresponding commercially available boronic acids in the Suzuki coupling.

Scheme 4.11 *Formation of* ***LH2-5***



As such, **LH4** was synthesized in 19% yield through Suzuki coupling of dibromohydrazide **311** and 4-methoxycarbonylphenyl boronic acid (**321**) with the appearance of peaks in the ^{13}C NMR at 171.6 ppm, 166.9 ppm, and 163.3 ppm for the three different carbonyl groups. Pleasingly, a 41% yield was obtained for the synthesis of **LH5** using dibromohydrazide **311** and 4-(4-morpholinylsulfonyl)phenylboronic acid (**322**). Two peaks at 3.78-3.76 ppm (m, 8H) and 3.08-3.06 ppm (m, 8H) in the ^{1}H NMR were observed for the morpholinyl groups.

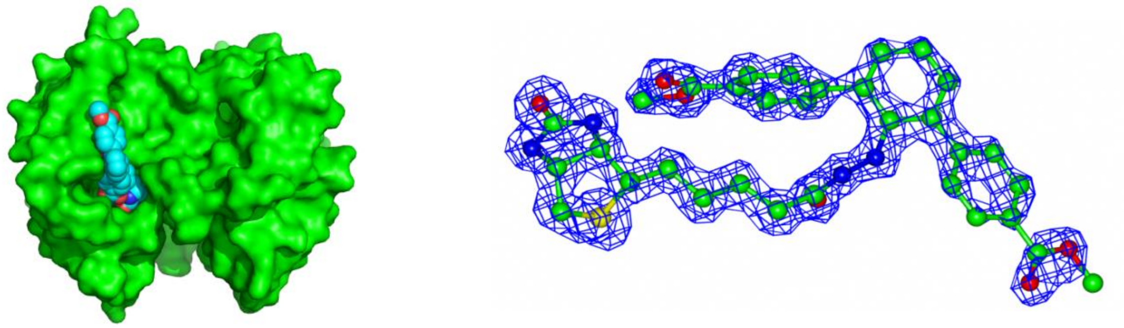
In conclusion, despite the moderate yields obtained in the Suzuki reaction, we were able to prepare the key compounds **LH2-5**, and use them for streptavidin binding studies.

4.6 Crystal structure of Streptavidin bound to the second series of Love-Hate ligands LH4, LH5†

Pleasingly, the Howarth lab were able to obtain a 1.1 Å resolution crystal structure for **LH4** bound to wild-type streptavidin tetramer (see Section 3.3). In one subunit, **LH4** was clearly resolved in all its regions (Figure 4.6A). The di-*ortho* bulky groups of the ligand had displaced L3/4 of streptavidin and prevented Asn49 (bond length between the carbonyl of Ser88 and biotin hydrazide is 7.868 Å)[**] and Ser88 (bond length between the NH_2 of Asn49 and biotin hydrazide is 11.796 Å) from forming hydrogen bonds with biotin (Figure 4.6D). The conformation of the rings had led the carbonyl of the methylester to be within hydrogen bonding distance of the cis-NH of biotin (3.060 Å). Normally the cis-NH of biotin hydrogen-bonds to Ser45 (Figure 4.1), but the displaced Ser45 may be able to form an alternative hydrogen bond (3.287 Å) to the carbonyl of this same methylester (Figure 4.6D, for comparasion with hydrogen bonding interaction with biotin see Figure 3.3). Cation–π interaction is a noncovalent molecular interaction between the face of an electron-rich π system and an adjacent cation. Take benzene for example, the electron-rich π system above and below the benzene ring hosts a partial negative charge and a counterbalancing positive charge is associated with the plane of the benzene atoms, resulting in an electric quadrupole. The negatively charged region of the quadrupole can then interact favorably with positively charged species. The positively charged guanidino group of Arg84 is well positioned for a putative cation-π interaction with the central phenyl ring of **LH4** as the length between the cation centre and the ring centre is only 3.596 Å (Figure 4.6E).[106]

[**] Bond length calculated from CCP4MG software

Figure 4.6 *Crystal structure of* ***LH4*** *and comparison with biotin‡*

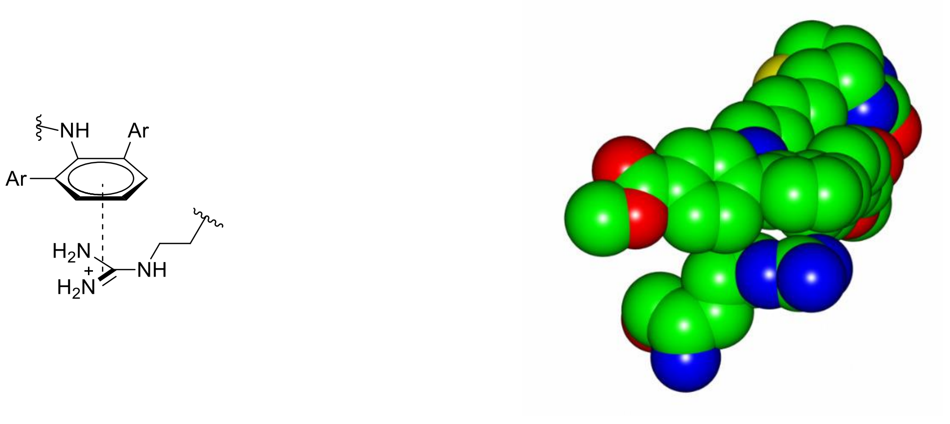


A. Crystal structure of **LH4**

B. Electron density around **LH4** contoured at 1 σ

C. Overlay with biotin

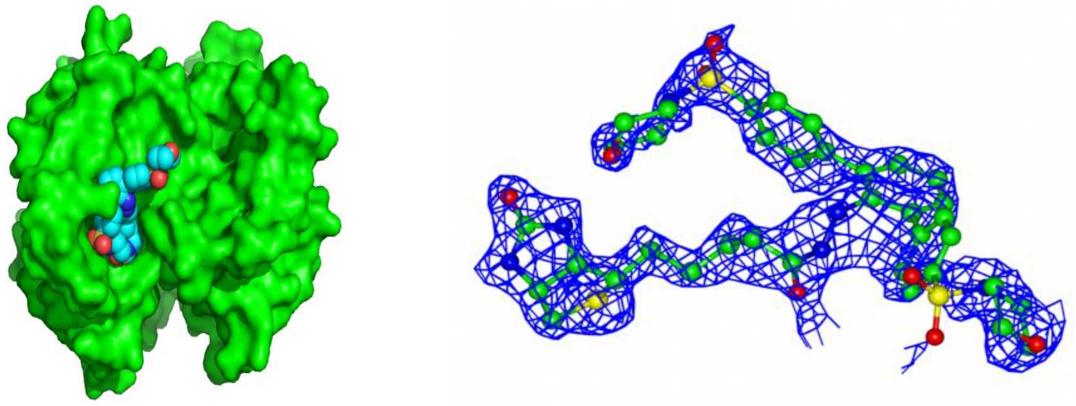
D. Hydrogen bond contacts



E. Putative cation-π interaction of Arg84 of streptavidin with **LH4**

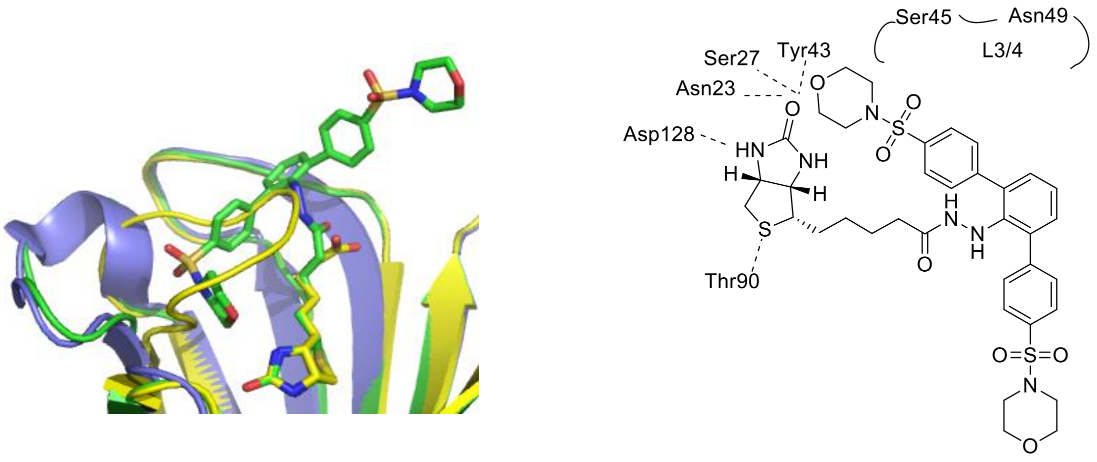
LH5, with the largest headgroup, morpholinosulfonyl, on each phenyl ring, did not yield crystals with wild-type streptavidin. However, **LH5** was able to form a 1.6 Å crystals with trans-divalent streptavidin (see Section 3.6). In a trans-divalent streptavidin, only the 1 and 3 subunits on opposite sides of the tetramer could bind biotin ligands thus avoiding any clash between adjacent ligands.[100] The density of the biotin core of **LH5** was well resolved (Figure 4.7B). The electron density of part of the central phenyl ring and one of the pendant phenyl rings of **LH5** were seen clearly but the rest of **LH5** had substantial disorder (Figure 4.7B). **LH5** also yielded major changes to the binding site: L3/4 was displaced and **LH5** failed to form the three hydrogen bonds to Ser45, Asn49 and Ser88 (Figure 4.7D) which normally hydrogen bonding to biotin (Figure 4.1).

Figure 4.7 *Crystal structure of **LH5** and comparison with biotin*‡



A. Crystal structure of **LH5**

B. Electron density around **LH5** contoured at 1 σ

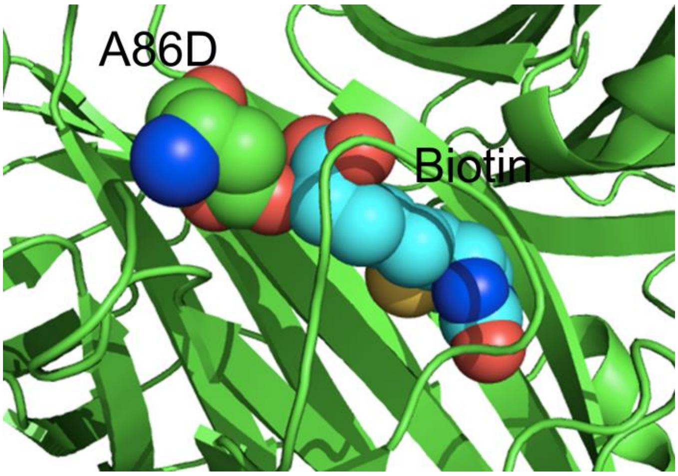


C. Overlay with biotin

D. Hydrogen bond contacts

The rotation of the pendant arms in **LH5** still allowed avoidance of steric congestion with streptavidin. Therefore the Howarth's group employed an A86D streptavidin mutant, where alanine 86 was mutated to asparagine. The Asp 86 were found to cause a clash with the carboxylate group of biotin which lowered the affinity. They hoped the Asp 86 would cause a similar clash with **LH5**, so favoring the desired repulsive interactions from van der Waals clash of the diphenyl branches with the surface of streptavidin.

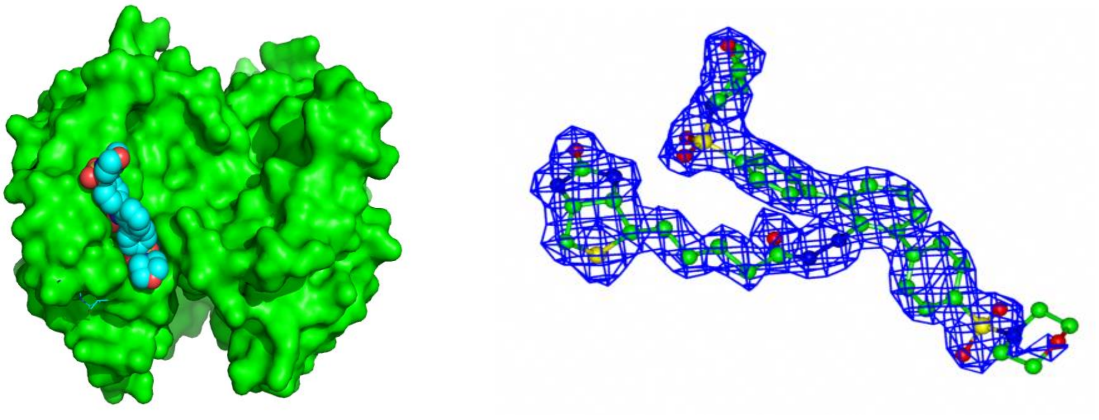
Figure 4.8 *Steptavidin A86D mutant with biotin*[††]



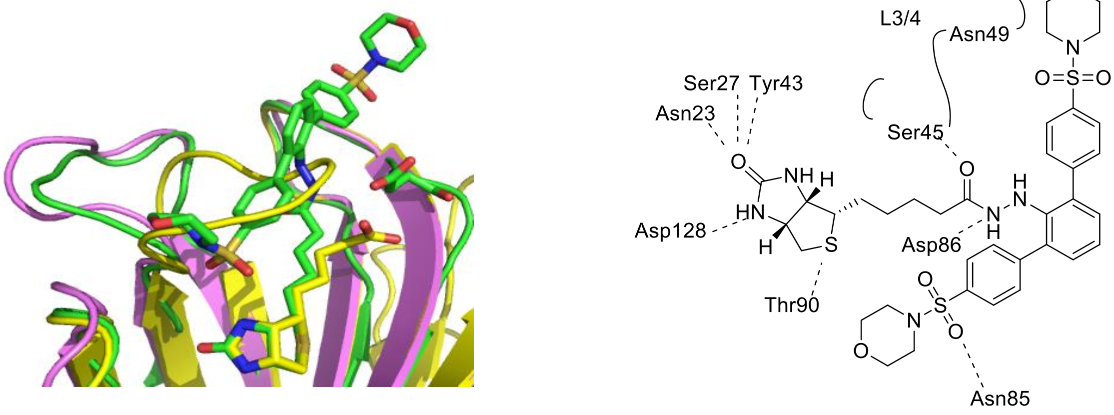
LH5 was able to form a 1.5 Å crystals with A86D streptavidin. The structure of the complex showed clear density for two of the four copies of **LH5** present in the asymmetric unit (Figure 4.9A,B). The pendant arms had a different orientation for **LH5**:A86D compared to **LH5**:trans-divalent streptavidin. The valeryl tail for **LH5**:A86D projected well away from the classic orientation for biotin (Figure 4.9C). L3/4 was again displaced into an open conformation, with loss of Asn49 and Ser88 hydrogen bonds. However, novel putative hydrogen bonds were formed: from Asn85 to one of the sulfonyl groups (bonth length 2.669 Å), and from Asp86 to one of the hydrazide NH groups (bond length 2.870 Å). One of the sulfonyl oxygens was close enough to form an intra-ligand hydrogen bond to the cis-NH of biotin (Figure 4.9D).

[††] Diagram provided by the Howarth group

Figure 4.9 *Crystal structure of Streptavidin A86D:**LH5** complex‡*



A. Crystal structure of A86D:**LH5** B. Electron density around **LH5**



C. Overlay with biotin D. Hydrogen bond contacts

4.7 Comparison of Love-Hate:Streptavidin Complex Structures

Overlaying the Love-Hate ligand complex structures with the streptavidin:biotin structure, the organization of the biotin head moiety in each structure was unchanged, within error, to biotin itself (Figure 4.10). Focusing on the L3/4 loop shows how the loop was shut with **LH1** (Figure 4.4C) just as for biotin, but pushed into different open conformations in the presence of **LH4** (Figure 4.6C), **LH5** (Figure 4.7C) or **LH5** bound to the A86D mutant (Figure 4.9C). The valeryl tail was unchanged compared to biotin for **LH1** but gradually more distorted from biotin in **LH4**, **LH5** and **LH5**/A86D.

Figure 4.10 *Overlay of the Love-Hate ligand complex structures with the streptavidin:biotin structure*

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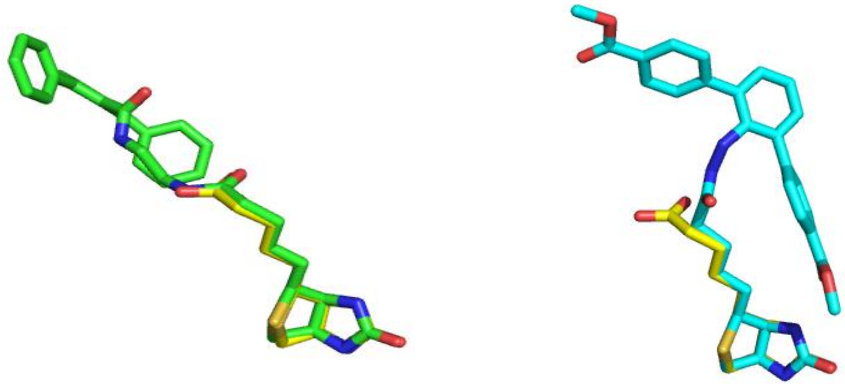


A. **LH1** vs biotin

B. **LH4** vs biotin

C. **LH5** vs biotin

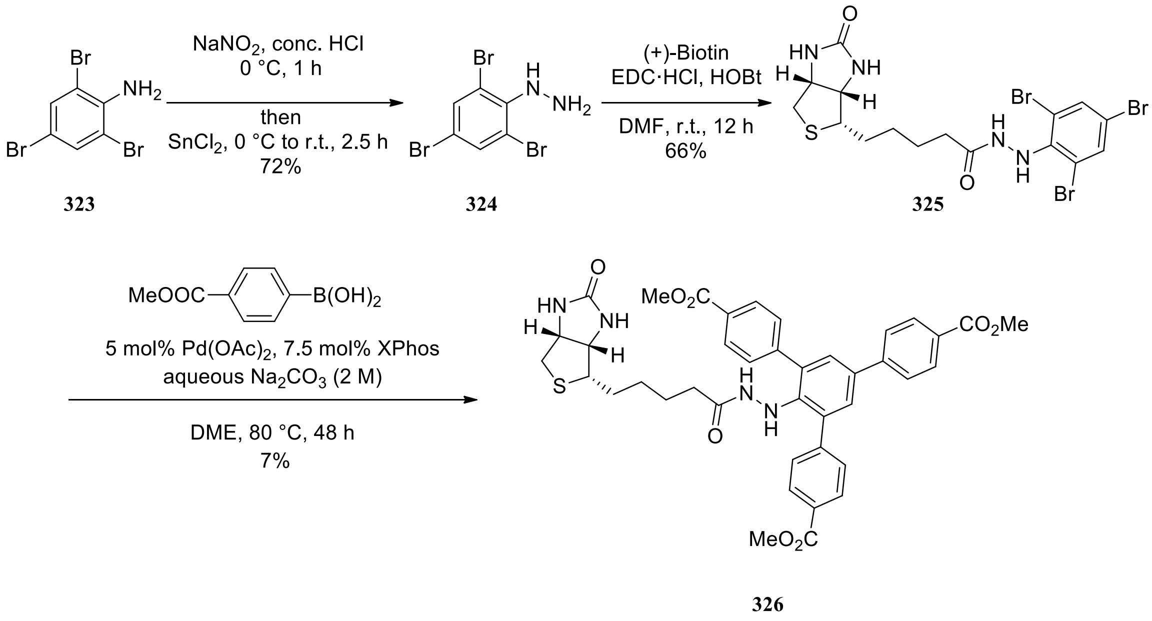
D. **LH5** (A96D) vs biotin

4.8 Design and synthesis of other Love-Hate ligands

Although L3/4 was forced into an open conformation, **LH4** and **LH5** still bound to streptavidin to some extent because the rotation of the di-*ortho* arms in **LH4** and **LH5** still allow for avoidance of the steric clash with streptavidin. Thus, we then decided to introduce another bulky arm on the *para* position in order to further increase steric congestion. Despite the rotation of the di-*ortho* arms, the *para* arm, pointing away from the biotin head, should start to cause significant repulsive interactions of van der Waals clash with the surface of streptavidin.

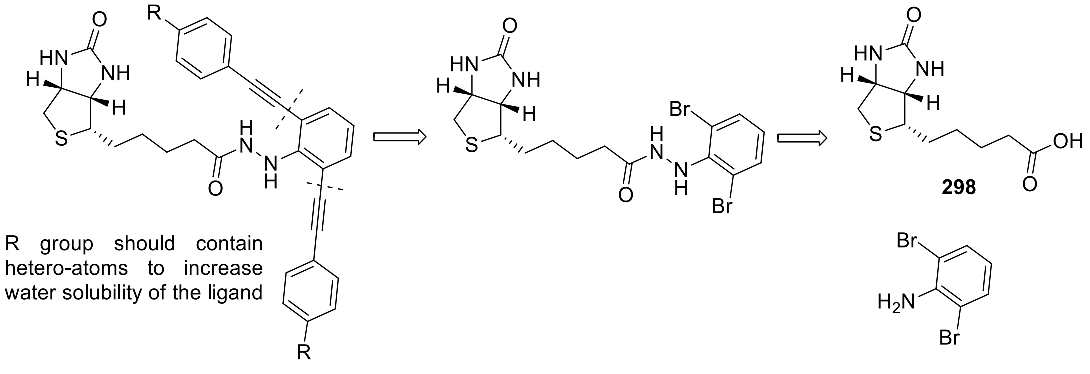
Therefore, **326** was synthesized following the route developed before (Scheme 4.12): First diazotization of 2,4,6-tribromoaniline (**323**) with $NaNO_2$, followed by the reduction using $SnCl_2$ gave hydrazine **324** in 72% yield. This was confirmed by the observation of two broad singlets in the ^{1}H NMR at 5.42 and 3.86 ppm. The following amide coupling was successfully achieved using EDC·HCl, HOBt in DMF at room temperature. Suzuki coupling yielded the desired compound in 7% yield. Four doublets were observed in the ^{1}H NMR at 8.09 ppm (d, J = 8.2 Hz, 4H), 7.99 ppm (d, J = 8.4 Hz, 2H), 7.63 ppm (d, J = 8.4 Hz, 4H), 7.57 ppm (d, J = 8.5 Hz, 2H) for the aromatic protons of the three pendent arms, and a peak at 7.38 ppm (s, 2H) for protons on the central phenyl ring (Scheme 4.12).

Scheme 4.12 *Synthesis of 2,4,6-trisubstituted ligand **326***



The crystallographic studies of this compound are still being carried out in the Howarth group. An alternative solution was to introduce an alkyne group between the central phenyl ring and side arms to force the three rings to lie in the same plane, therefore restricting the freedom of rotation. We were hoping the restricted side arms would cause van der Waals clash with the surface of strepativadin (Scheme 4.13).

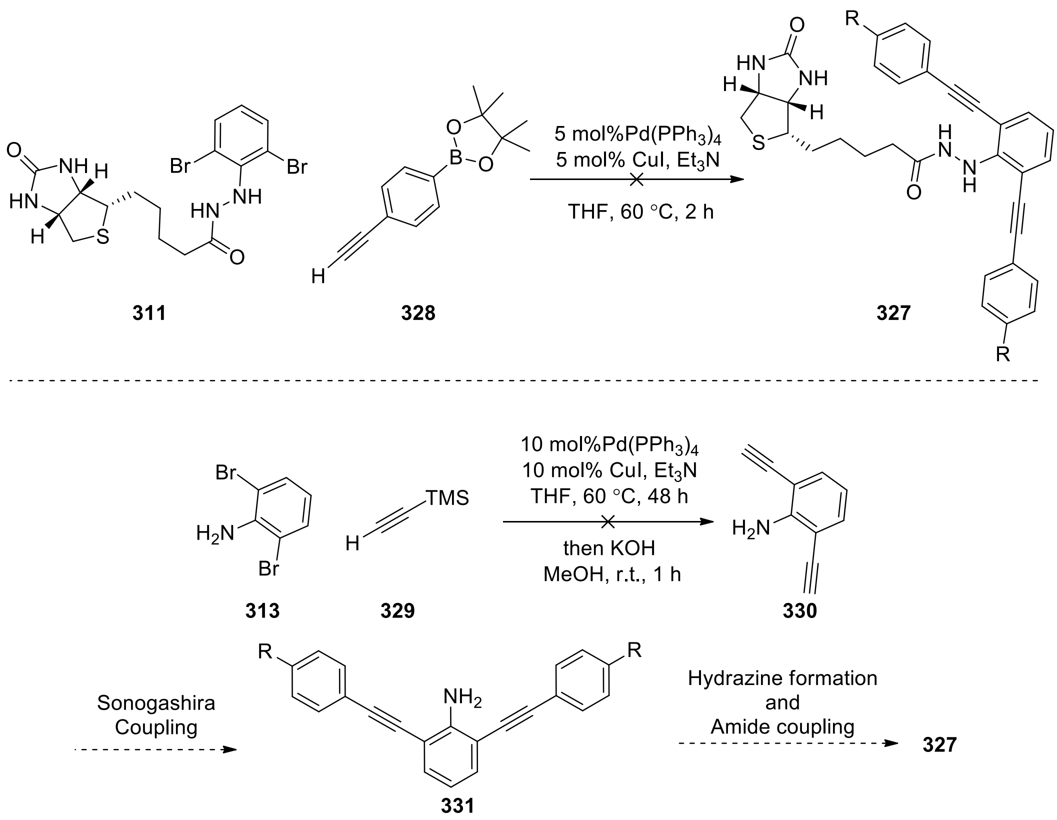
Scheme 4.13 *Design of alkyne group containing Love-Hate ligands*



327 **311** **313**

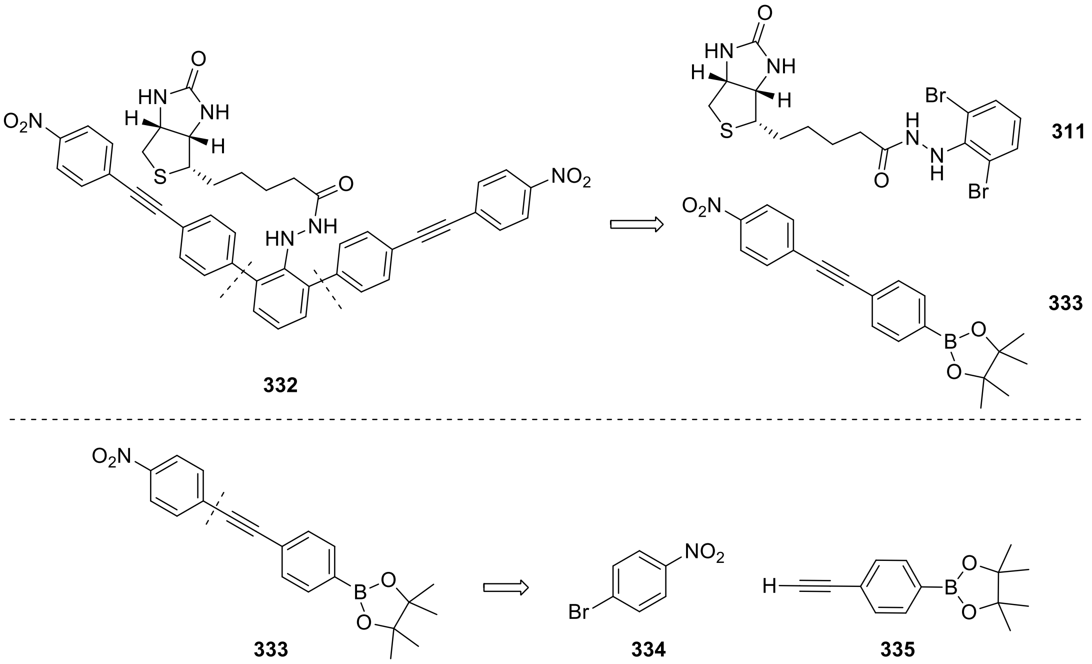
An attempt of coupling 4-ethylnyl phenyl boronic acid pinacol ester (**328)** to the dibromohydrazone **311** only led to decomposition of both starting materials (Scheme 4.14). Therefore, we decided to attach the side arms at the beginning of the synthetic sequence. Sonogashira coupling of 2,6-dibromoaniline (**313**) and (trimethylsilyl)acetylene (**329**) with simultaneous deprotection of the TMS group was attempted following Stang and co-workers' procedure (Scheme 4.14). [107] However, due to low yields and hard purification, a sufficient amount of material for the next steps could not be isolated. Due to time constraints, no further investigation into this route was carried out.

Scheme 4.14 *Attempts to synthesize **327***



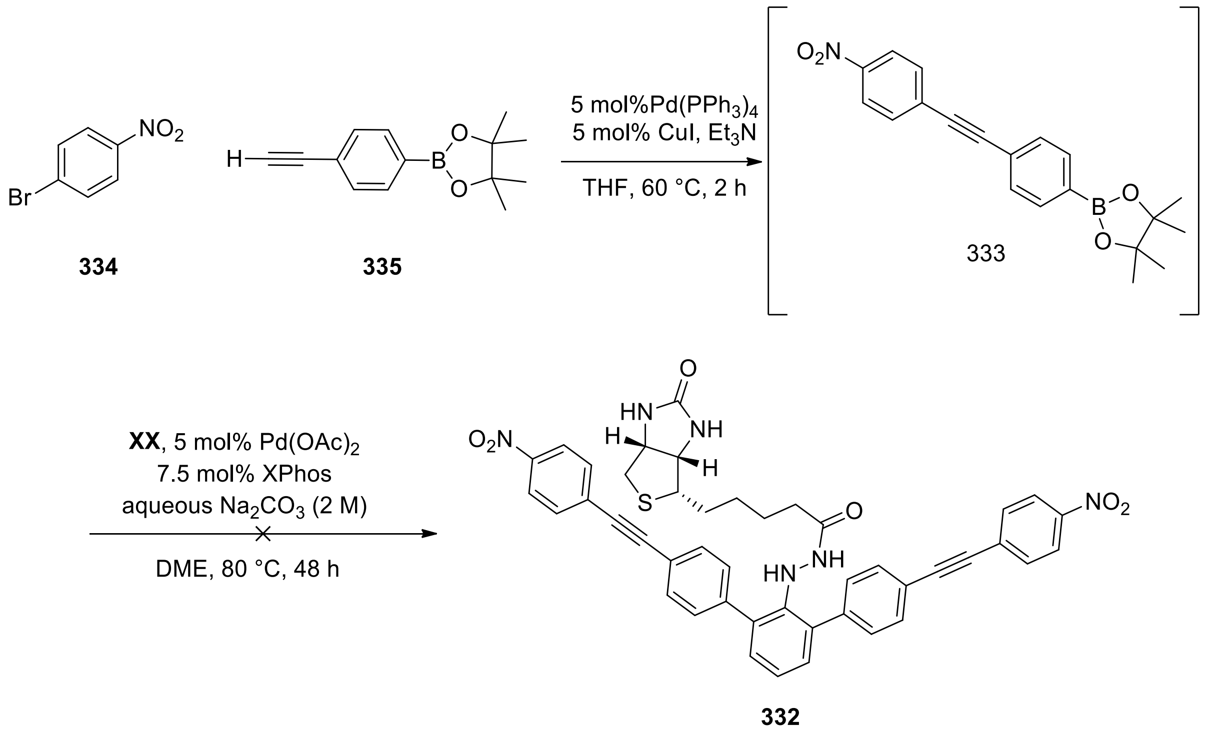
Another molecule **332** was designed which encompassed a Suzuki coupling as a last step similar to the route planned for the second series of Love-Hate ligands. The key step was to synthesize the alkyne containing boronic acid pinacol ester **333** (Scheme 4.15).

Scheme 4.15 *Design of alkyne group containing Love-Hate ligands*



4-Ethylnyl phenyl boronic acid pinacol ester **335** and 1-bromo-4-nitrobenzene **334** were coupled using $Pd(PPh_3)_4$ and CuI in THF: Et_3N (1:1) mixture at 60 ˚C under argon. TLC clearly showed the disappearance of both starting material after 2 hours and formation of a new spot. A crude NMR also confirmed the formation of the desired product **333** with the observation of four doublets at 8.16 ppm (2H, J = 9.0 Hz), 7.75 ppm (2H, J = 8.3 Hz), 7.60 ppm (2H, J = 9.0 Hz), and 7.49 ppm (2H, J = 8.3 Hz) corresponding to the four different ArCH protons, and another singlet at 1.29 ppm (12H) belonging to the methyl groups. However, compound **333** was not stable, and decomposed upon isolation after chromatography. As such, we decided not to isolate the product but use the crude mixture for the next step. After the Sonogashira coupling, the resulting yellow suspension was filtered through a plug of cotton wool, concentrated, and directly used for the subsequent Suzuki coupling step. But this sequence had led to the complete decomposition of the dibromohydrozone **311**, and the desired product was not observed (Scheme 2.16).

Scheme 4.16 *Synthesis towards ligand **332***



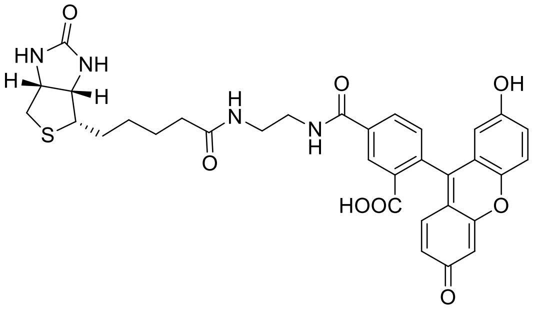
In conclusion, we were not able to synthesize ligands containing alkyne groups at this stage, and further investigation was stopped on this route.

4.9 Binding strength of Love-Hate ligand series[‡‡]

Co-workers in the Howarth group characterized the dissociation constant of the ligand series for streptavidin, and obtained relative K_d values using an equilibrium competition assay, based on the amount of biotin-4-fluorescein dissociation at increasing ligand concentration.

[‡‡] Dr. Michael Fairhead and Ed D. Lowe

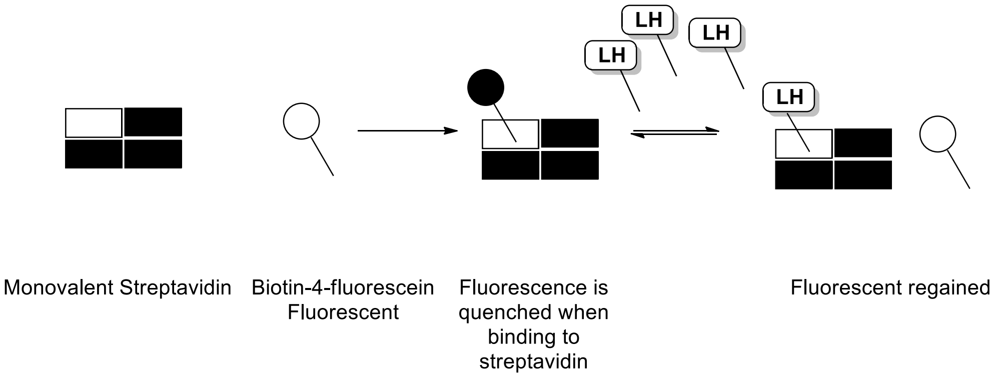
Figure 4.12 *Structure of biotin-4-fluorescein*



336
Biotin-4-fluorescein

To avoid any interaction between bulky ligands binding to adjacent streptavidin binding sites, ligand binding was tested on a monovalent streptavidin with three subunits which do not bind biotin and one subunit that binds biotin with wild-type affinity. The fluorescence of biotin-4-fluorescein is quenched ~90% upon binding to streptavidin, while fluorescence is regained upon release.[108]

Scheme 4.17 *Biotin 4-fluorescein dissociation assay*



Biotin-4-fluorescein was incubated with streptavidin and then the Love-Hate ligand was added to complete with biotin-4-fluorescein (Scheme 4.17). Fluorescence was regained if biotin-4-fluorescein was released from streptavidin, and fluorescence at each ligand concentration was measured. EC_{50} was defined as the concentration of ligand for 50%

dissociation of biotin-4-fluorescein. The EC_{50} for the ligand was divided by the EC_{50} for biotin to give the relative decrease in binding affinity.[109]

Table 4.1 *Love-Hate ligands binding affinity*

Ligand	Biotin	**LH1**	**LH2**	**LH4**	**LH5**
EC_{50}/nM	28	31	251	178	138
Fold-decrease in affinity	1	1.1	9	6.4	4.9

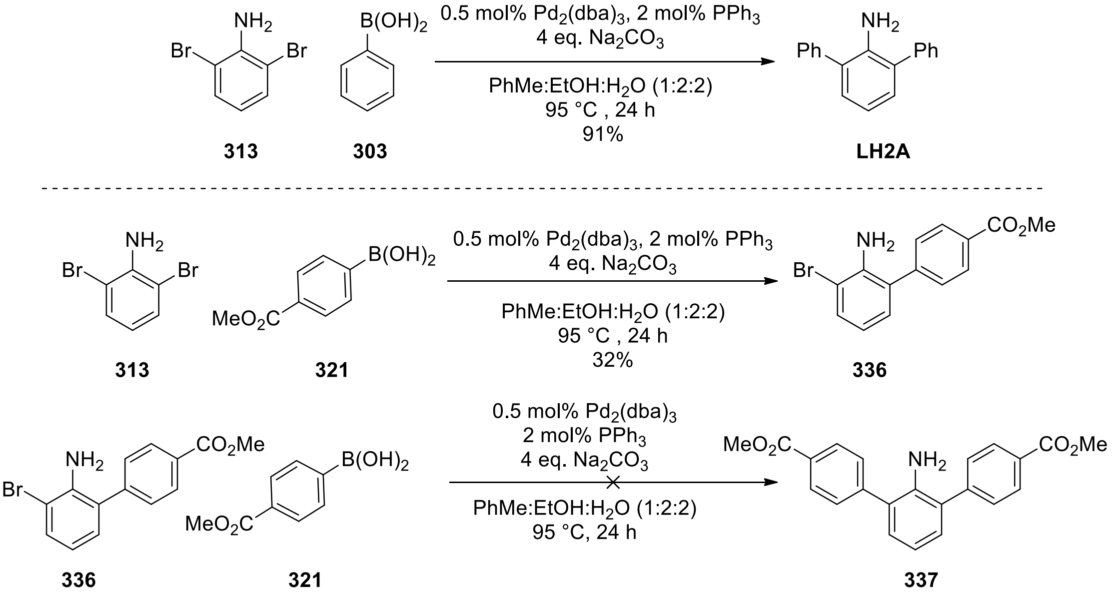
Biotin itself was used in the assay as a reference ligand, with K_d of 4×10^{-14} M at pH = 7.25.[110] Despite the bulky substituents, **LH1** showed a minimal difference in equilibrium binding to biotin, with a 1.1 fold reduction in affinity (Table 4.17). **LH2**, **LH4**, **LH5** showed reduced affinity compared to biotin but the effect was smaller than would be expected based on the major changes in the binding interface from the crystal structures.

4.10 Control experiments involving the large Hate ligand without the biotin moiety

Despite the decrease in binding affinity with the large substituents, each ligand still bound with high affinity to streptavidin and so it was clear that the principal reason for the binding of the Love-Hate ligands was the presence of the biotin moiety rather than specific interactions with the bulky arms. In order to prove this, we set out to synthesize a biotin-less analogue of Love-Hate ligands.

Suzuki coupling of 2,6-dibromoaniline (**313**) with phenyl boronic acid (**303**) was performed using $Pd_2(dba)_3$ to yield 91% of **LH2A**.[111] The spectroscopic data of **LH2A** were consistent with those previously reported.[112] On the contrary, when (4-(methoxycarbonyl)phenyl)boronic acid (**321**) was used, only the mono-Suzuki product was formed in 32% yield. Two peaks in the high resolution mass spectrum at 306.0120 ppm, and 308.0098 ppm with approximately a 1:1 ratio indicated the presence of one bromide. **336** was resubjected to the reaction conditions, and only starting material was recovered with poor mass recovery.

Scheme 4.18 *Synthesis of biotin-less analogue of Love-Hate ligands*



Our collaborators[§§] were able to perform the same affinity experiment discussed in Section 4.10 using **LH2A**, and as expected, **LH2A** had negligible binding in our competition assay. These results showed that the high affinity of each ligand to stretavidin was achieved through the biotin motiety rather than the bulky end groups.

4.11 Conclusions

We have successfully synthesized a modular series of ligands to introduce repulsive interations with streptavidin, and analyzed the protein/ligand complexes at high resolution by X-ray crystallography. The hydrogen bonds surrounding the biotin head were retained for all

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[§§] Dr. Michael Fairhead

ligands **LH1, LH4, LH5**, but the valeryl tail could change orientation and L3/4 loop could be displaced by the bulky arms of the ligands. **LH1** had a similar affinity, while **LH2**, **LH4**, **LH5** showed reduced binding affinity to streptavidin compared to biotin.

Chapter 5:
Experimental Section

5 Experimental Section

5.1 Experimental Techniques

Tetrahydrofuran, dichloromethane, acetonitrile, toluene, benzene and diethyl ether were purified prior to use by filtration through two activated alumina columns (grade: DD-2, Alcoa – THF; activated basic aluminium oxide, Brockmann I, standard grade, ~ 150 mesh, 58 Å, Aldrich – dichloromethane, acetonitrile, toluene, diethyl ether). Reagents obtained from Acros, Aldrich, Avocado, TCI, Fluka and Lancaster fine chemicals suppliers were used directly as supplied All non-aqueous reactions were carried out under an atmosphere of argon using oven- or flame- dried glassware. Syringes and needles, for the transfer of moisture sensitive reagents, were oven-dried and cooled in a dessicator over self-indicating silica gel.

Flash column chromatography was carried out according to the method of Still using silica gel 60 (0.040-0.063 mm) (Merck) using head pressure by means of head bellows. Thin layer chromatography was performed on commercially available pre-coated aluminium-backed plates (0.25 mm silica gel with fluorescent indicator UV254). Compounds were visualised either by the quenching of UV fluorescence or by staining with a potassium permanganate, ammonium molybdate, or vanillin solution.

^{1}H NMR spectra were recorded on a Bruker AC200 (200 MHz), Bruker AVANCE AV400 (400 MHz), Bruker DPX400 (400 MHz) or on a Bruker AVANCE AV500 (500 MHz) spectrometer in $CDCl_3$, $(CD_3)_2CO$, CD_3OD, C_6D_6 or $(CD_3)_2SO$. Signal positions were recorded in ppm with the abbreviations s, d, dd, t, dt, td, q, quint, app sext, ddt, dddd, br and m denoting singlet, doublet, doublet of doublets, triplet, doublet of triplets, triplet of doublets, quartet, quintet, sextuplet, double doublet of triplet, double doublet of double doublet, broad and multiplet respectively. ^{13}C NMR spectra were recorded on a Bruker AVANCE AV400

(101 MHz) or on a Bruker AVANCE AV500 (125 MHz) spectrometer. All NMR chemical shifts were referenced to residual solvent peaks. All coupling constants, *J*, are quoted in Hz. Signals in both the ^{1}H and ^{13}C spectra were assigned with the aid of COSY (correlated spectroscopy), HMQC (heteronuclear multiple-quantum correlation) and HMBC (heteronuclear multiple-bond correlation).

Infra-red spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Spectra were analysed as thin films between NaCl plates. Absorption maxima are quoted in wavenumbers (cm^{-1}).

Mass spectra (m/z) under the conditions of electrospray ionisation (ESI) were recorded on a Fisons Platform II. Accurate mass (HRMS) data were recorded under conditions of ESI on a Micromass LCT (resolution = 5000 FWHM) using a lock-spray source in MeOH unless otherwise stated. The lock-mass used for calibration was tetraoctylammonium bromide in positive ion and sodium dodecyl sulfate in negative ion. m/z and HRMS data were recorded under conditions of electron impact ionisation (EI) on a Micromass GCT (resolution = 7000 FWHM).

Optical rotations were recorded on a Perkin Elmer 241 polarimeter (using the sodium D line, 589 nm) and $[\propto]_{D}^{20}$ are given in units of $10^{-1}\cdot\text{deg}\cdot\text{dm}^{2}\cdot\text{g}^{-1}$.

Melting points were obtained using a Leica VMTG heated-stage microscope or Griffin melting point apparatus with a mercury thermometer, and are uncorrected.

The result of ACD/IUPAC Name v8.05 was obtained using the ACD/I-Lab service.

"Petrol" refers to the fraction boiling in the range 30-40 ºC unless otherwise stated.

5.2 General Procedures

Procedure A: Rh-catalyzed methylation

Under an open atmosphere, $[RhCp^*Cl_2]_2$ and base were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol and starting ketone. The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 ºC for the period of time stated. The reaction was quenched by diluting with water, and extracted with CH2Cl2. The combined organic layers were dried with anhydrous MgSO4, filtered and concentrated. Purification by FCC afforded product.

Procedure B: Ir-catalyzed alkylation

Following literature procedure (Iuchi, Y.; Obora, Y.; Ishii, Y. *J. Am. Chem. Soc.* 2010, *132*, 2536) with some modification where stated: Under an open atmosphere, $[Ir(cod)Cl]_2$, KOH and PPh_3 were added to a Biotage® microwave vial equipped with a stir bar, followed by methyl ketone and alcohol. The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed via a needle with a balloon of Ar. The mixture was stirred at 100 oC for the time stated. Purification (where necessary) by FCC afforded product.

Procedure C: Ir-catalyzed methylation

Under an open atmosphere, $[Ir(cod)Cl]_2$, KOH and PPh_3 were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol and starting ketone. The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 °C for the period of time stated. The reaction was quenched by diluting with diethyl ether and filtering through a pad of silica gel. Purification by FCC afforded product.

Procedure D: Ir-catalyzed methylenation

Under an open atmosphere, $[Ir(cod)Cl]_2$, KOH and cataCXium® A were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol and starting ketone. The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 ˚C for the period of time stated. The reaction was quenched by diluting with diethyl ether and filtering through a pad of silica gel. Purification by FCC afforded product.

Procedure E: Baeyer Villiger oxidation

Under an open atmosphere, starting ketone, mCPBA, trifluoroacetic acid and CH_2Cl_2 were added to a Biotage® microwave vial equipped with a stir bar. The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and stirred at rt for 48 h. The organic phase was washed with sat. aq. $NaHCO_3$ (3 x 10mL), extracted with CH_2Cl_2, dried over Na_2SO_4, filtered, and the solvent removed *in vacuo*. Purification by FCC afforded product.

Procedure F: Pyridine formation using $NH_2OH{\cdot}HCl$

Under an open atmosphere, stating diketone (30 mg, 1 equiv.), hydroxylamine hydrochloride (3 equiv.) were added to a Biotage® microwave vial equipped with a stir bar, followed by ethanol (0.15 mL). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and was heated to 80 ˚C for 24 h. The reaction was quenched by adding $NaHCO_3$ (sat.), extracted with CH_2Cl_2, then washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*. Purification by FCC afforded product.

Procedure G: Pyridine formation using NH_4OAc

Under an open atmosphere, stating diketone (30 mg, 1 equiv.), ammonium acetate (3 equiv.), copper (II) acetate monohydrate (2.5 equiv.) were added to a Biotage® microwave vial equipped with a stir bar, followed by acetic acid (0.16 mL). The vial was sealed with a microwave vial cap (containing a Reseal™ septum), degassed with argon and heated to 120 ˚C for 24 h. The reaction was quenched by adding ammonia solution (28%-30%, 0.7 mL), extracted with EtOAc, then washed with brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*. Purification by FCC afforded product.

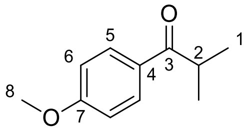
Procedure H: Suzuki coupling

N'-(2,6-Dibromophenyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanehydrazide (**311**, 50.0 mg, 0.102 mmol, 1 equiv.), boronic acid (0.306 mmol, 3 equiv.), $Pd(OAc)_2$ (1.1 mg, 0.00508 mmol, 0.05 equiv.), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (3.6 mg, 0.00765 mmol, 0.075 equiv.), aqueous Na_2CO_3 (2 M, 0.32 m), and 1,2-dimethoxyethane (0.64 mL) were placed in a sealed tube, and degassed with argon. The suspension was then heated at 80 °C for 48 h, and the crude mixture was directly purified by column chromatography (CH_2Cl_2: MeOH, 95:5).

5.3 Experimental

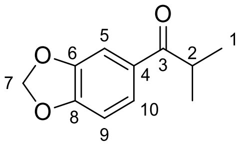
5.3.1 Experimental: Transition metal catalyzed alkylation

1-(4-Methoxyphenyl)-2-methylpropan-1-one, 161a



4’-Methyoxyacetophenone (45.0 mg, 0.300 mmol, **171**), [RhCp*Cl$_2$]$_2$ (9.3 mg, 5 mol%), Cs$_2$CO$_3$ (488 mg, 1.50 mmol) and methanol (1.5 mL) were subjected to general procedure A for 48 h. Purification by FCC (Petrol/Et$_2$O 9:1) afforded **161a** (30.0 mg, 0.170 mmol, 56 %) as a colourless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.94-7.84 (m, 2H, C(5)$\underline{H}$×2), 6.93-6.81 (m, 2H, C(6)$\underline{H}$×2), 3.79 (s, 3H, C(8)$\underline{H}_3$), 3.45 (sept, *J* = 6.8 Hz, 1H, C(2)$\underline{H}$), 1.13 (d, *J* = 6.8 Hz, 6H, C(1)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, CDCl$_3$) δ 203.1 ($\underline{C}$(3)O), 163.3, 130.6 ($\underline{C}$(5)H×2), 129.1, 113.7 ($\underline{C}$(6)H×2), 55.5 ($\underline{C}$(8)H$_3$), 35.0 ($\underline{C}$(2)H), 19.3 ($\underline{C}$(1)H$_3$×2). Spectroscopic data were consistent with those previously reported.[55]

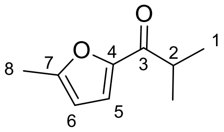
1-(Benzo[*d*][1,3]dioxol-5-yl)-2-methylpropan-1-one, 172a



3’,4’-(Methylenedioxy)acetophenone (49.0 mg, 0.300 mmol), [RhCp*Cl$_2$]$_2$ (9.3 mg, 5 mol%), Cs$_2$CO$_3$ (488 mg, 1.50 mmol) and methanol (1.5 mL) were subjected to general procedure A for 48 h. Purification by FCC (Petrol/Et$_2$O 9:1) afforded **172a** as a light yellow oil (30.5 mg, 0.159 mmol, 53 %). IR ν_{max} (cm^{-1}) 2971, 1672, 1438, 1243, 1035; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.49 (dd, *J* = 8.1, 1.7 Hz, 1H, C(10)$\underline{H}$), 7.37 (d, *J* = 1.7 Hz, 1H, C(5)$\underline{H}$), 6.78 (d, *J* = 8.3 Hz, 1H, C(9)$\underline{H}$), 5.97 (s, 2H, C(7)$\underline{H}_2$), 3.39 (sept, *J* = 6.8 Hz, 1H, C(2)$\underline{H}$), 1.12 (d, *J* = 6.9 Hz, 6H, C(1)$\underline{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 202.6 ($\underline{C}$(3)O), 151.5, 148.2, 131.0, 124.3

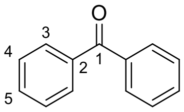
(<u>C</u>(10)H), 108.3 (<u>C</u>(5)H), 107.9 (<u>C</u>(9)H), 101.8 (<u>C</u>(7)H_2), 35.1 (<u>C</u>(2)H), 19.4 (<u>C</u>(1)H_3×2); HRMS (ESI$^+$) calculated for $[C_{11}H_{12}O_3+Na]^+$ 215.0679, found 215.0670, (Δ 4.1 ppm).

1-(5-Methylfuran-2-yl)ethanone, 173a



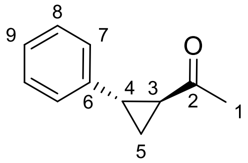
1-(5-Methylfuran-2-yl)ethanone (37.0 mg, 0.300 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol) and methanol (1.5 mL) were subjected to general procedure A for 20 h. Purification by FCC (Petrol/Et_2O 9:1) afforded **173a** (20.0 mg, 0.130 mmol, 44% yield) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (d, *J* = 3.5, 1H, C(5)<u>*H*</u>), 6.07 (dd, *J* = 3.3, 0.8 Hz, 1H, C(6)<u>*H*</u>), 3.20 (sept, *J* 6.9 Hz, 1H, C(2)<u>*H*</u>), 2.33 (s, 3H, C(8)<u>*H*</u>$_3$), 1.13 (d, *J* = 6.6 Hz, 6H, C(1)<u>*H*</u>$_3$×2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.0 (<u>C</u>(3)O), 157.6, 150.8, 119.0 (<u>C</u>(5)H), 108.7 (<u>C</u>(6)H), 35.8 (<u>C</u>(2)H), 19.0 (<u>C</u>(8)H_3), 14.0 (<u>C</u>(1)H_3×2). Spectroscopic data were consistent with those previously reported.[113]

Benzophenone, 178



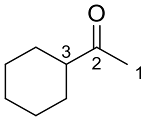
1,1-Diphenylacetone (63.1 mg, 0.300 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol) and methanol (1.5 mL) were subjected to general procedure A for 20 h. Purification by FCC (Petrol/Et_2O 9:1) afforded **178** (38.7 mg, 0.212 mmol, 71% yield) as a yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ 7.83-7.81 (m, 2H, C(3)H×2), 7.62-7.58 (m, 1H, C(5)H), 7.51-7.47 (m, 2H, C(4)H×2); ^{13}C NMR (101 MHz, CDCl3) δ 196.8 (<u>C</u>(1)O), 137.6 (<u>C</u>(2)), 132.4 (<u>C</u>(5)H), 130.1 (<u>C</u>(3)H), 128.3 (<u>C</u>(4)H). Spectroscopic data were consistent with those previously reported.[114]

trans-2-Phenylcyclopropyl)ethanone, 175



trans-2-Phenyl-1-cyclopropane carboxylic acid (500 mg, 3.08 mmol) was dissolved in diethyl ether (10 mL) and cooled to -78˚C when MeLi (1.6 M in Et_2O, 4.2 mL) was added dropwise under Ar. The mixture was allowed to warm up to room temperature and stirred for 2 h before ice was added to quench the reaction. The crude material was extracted with Et_2O, dried over Na_2SO_4, concentrated, and purified by FCC (Petrol/Et_2O 9:1) afforded **175** (440 mg, 89%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.30 (m, 2H, C(8)*H*×2), 7.26-7.24 (m, 1H, C(9)*H*), 7.13 (d, *J* = 7.3 Hz, 2H, C(7)*H*×2), 2.56 (ddd, *J* = 17.0, 6.5, 4.1 Hz, 1H, C(3)*H*), 2.34 (s, 3H, C(1)H_3), 2.26-2.24 (m, 1H, C(4)*H*), 1.71 (ddd, *J* = 17.0, 5.1, 4.2 Hz, 1H, C(5)*H*H), 1.41 (ddd, *J* = 19.0, 6.6, 4.2 Hz, 1H, C(5)H*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.8 (*C*(2)O), 140.4 (*C*(6)), 128.5 (*C*(8)H×2), 126.5 (*C*(9)H), 126.0 (*C*(7)H×2), 32.9 (*C*(3)H), 30.9 (*C*(1)H_3), 29.0 (*C*(4)H), 19.2 (*C*(5)H_2). Spectroscopic data were consistent with those previously reported.[115]

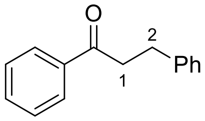
1-Cyclohexylethanone, 169



Cyclohexane carboxylic acid (500 mg, 3.90 mmol) was dissolved in diethyl ether (10 mL) and cooled to -78˚C when MeLi (1.6 M in Et_2O, 5.4 mL) was added dropwise under Ar. The mixture was allowed to warm up to room temperature and stirred for 2 h before ice was added to quench the reaction. The crude material was extracted with Et_2O, dried over Na_2SO_4, concentrated, and purified by FCC (Petrol/Et_2O 9:1) afforded **169** (373 mg, 75%). ^{1}H NMR

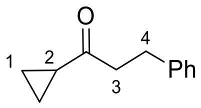
(400 MHz, $CDCl_3$) δ 2.30-2.26 (m, 1H, C(3)<u>*H*</u>), 2.08 (s, 3H, C(1)<u>*H*</u>$_3$), 1.83-1.80 (m, 2H), 1.73-1.71 (m, 2H), 1.63-1.60 (m, 1H), 1.30-1.10 (m, 5H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.1 (<u>*C*</u>(2)O), 51.4 (<u>*C*</u>(3)H), 28.4, 27.8 (<u>*C*</u>(1)H_3), 25.8, 25.6. Spectroscopic data were consistent with those previously reported.[116]

1,3-Diphenylpropan-1-one, 13



[Ir(cod)Cl]$_2$ (13.4 mg, 0.0199 mmol), KOH (11.2 mg, 0.200 mmol), PPh_3 (21.0 mg, 0.0801 mmol), acetophenone (0.23 mL, 2.0 mmol), and benzyl alcohol (0.42 mL, 4.0 mmol) were subjected to general procedure **B** for 4 h. Purification by FCC (Petrol/Et_2O 9:1) afforded **13** (358 mg, 1.70 mmol, 85%) as a colorless solid. Melting point = 64-66 °C (Lit: 64-65 °C)[117]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (m, 2H), 7.50-7.48 (m, 1H), 7.40-7.36 (m, 2H), 7.25-7.12 (m, 5H), 3.26-3.22 (m, 2H, C(1)<u>*H*</u>$_2$), 3.02-2.98 (m, 2H, C(2)<u>*H*</u>$_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2, 141.3, 136.9, 133.1, 128.6, 128.5, 128.4, 128.0, 126.2, 40.5 (<u>*C*</u>(1)H_2), 30.1 (<u>*C*</u>(2)H_2). Spectroscopic data were consistent with those previously reported.[118]

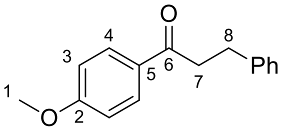
1-Cyclopropyl-3-phenylpropan-1-one, 164



[IrCl(cod)]$_2$ (6.7 mg, 0.010 mmol), KOH (6.1 mg, 0.10 mmol), PPh_3 (10.1 mg, 0.040 mmol), 1-cyclopropylethanone (99.0 mg, 1.00 mmol), and benzyl alcohol (1.3 mL, 1.2 mmol) were subjected to general procedure **B** for 4h. Purification by FCC (Petrol/Et_2O 9:1) afforded **164** (137 mg, 0.790 mmol, 79 %) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.21 (m, 5H), 2.98-2.89 (m, 4H, C(3)<u>*H*</u>$_2$, C(4)<u>*H*</u>$_2$), 1.95-1.93 (m, 1H, C(2)<u>*H*</u>), 1.06-1.04 (m, 2H), 0.90-

0.88 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9, 141.2, 128.4, 128.3, 126.0, 44.9, 29.9, 20.5, 10.7. All spectroscopic data were consistent with those previously reported.[119]

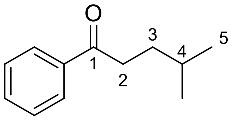
1-(4-Methoxyphenyl)-3-phenylpropan-1-one, 217



Benzylation with PPh_3: 4'-Methoxyacetophenone (300 mg, 2.00 mmol), $[IrCl(cod)]_2$ (13.4 mg, 1 mol%), KOH (11.2 mg, 0.200 mmol), PPh_3 (21.0 mg, 0.0800 mmol) and benzyl alcohol (416 μL) were subjected to general procedure **B** for 6 h. Purification by FCC (Petrol/Et_2O 10:1→4:1) afforded **217** (418 mg, 1.74 mmol, 87 %) as a colourless solid.

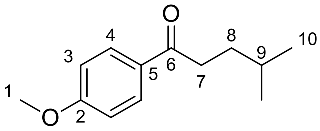
Benzylation with CataCXium A: To a mixture of 4'-Methoxyacetophenone (300 mg, 2.00 mmol), $[Ir(cod)Cl]_2$ (13.4 mg, 0.0199 mmol), KOH (11.2 mg, 0.200 mmol), cataCXium® A (28.7 mg, 0.0801 mmol) in a Biotage® microwave vial equipped with a stir bar was added benzyl alcohol (0.42 mL, 4.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 °C for 24 h. Purification by FCC (Petrol/Et_2O 8:2) afforded **217** (421 mg, 1.75 mmol, 88 %) as a colourless solid. Melting point = 95-97 °C (Lit: 96-98 °C)[120]; ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (d, J = 9.0 Hz, 2H, C(4)$\underline{H}$×2), 7.16-7.33 (m, 5H), 6.92 (d, J = 9.0 Hz, 2H, C(3)$\underline{H}$×2), 3.86 (s, 3H, C(1)$\underline{H}_3$), 2.25 (t, J = 7.8 Hz, 2H, C(7)$\underline{H}_2$), 3.05 (t, J = 7.8 Hz, 2H, C(8)$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) 197.8 (C(6)O), 163.4, 141.4, 130.3 ($\underline{C}$(4)H×2), 129.9, 128.5, 128.4, 126.0, 113.7 ($\underline{C}$(3)H×2), 55.4 ($\underline{C}$(1)H_3), 40.1 ($\underline{C}$(7)H_2), 30.3 ($\underline{C}$(8)H_2). All spectroscopic data were consistent with those previously reported.[120]

4-Methyl-1-phenylpentan-1-one, 215



$[IrCl(cod)]_2$ (2.0 mg, 0.003 mmol), KOH (3.4 mg, 0.06 mmol), PPh_3 (3.2 mg, 0.012 mmol), acetophenone (36.0 mg, 0.300 mmol), and 2-methyl-1-propanol (140 µL, 1.50 mmol) were subjected to general procedure **B** for 4 h. Purification by FCC (Petrol/Et_2O 9:1) afforded intermediate **215** as a yellow oil (42.0 mg, 0.240 mmol, 80 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89-7.86 (d, *J* = 8.0, 2H), 7.48-7.44 (m, 1H), 7.38-7.35 (m, 2H), 2.89-2.86 (m, 2H, C(2)$\underline{H}_2$), 1.62-1.50 (m, 3H, C(3)$\underline{H}_2$, C(4)$\underline{H}$), 0.86 (d, *J* = 6.6, 6H, C(5)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.7 ($\underline{C}$(1)O), 137.1, 132.9, 128.6, 128.1, 36.6 ($\underline{C}$(2)H_2), 33.2 ($\underline{C}$(3)H_2), 27.9 ($\underline{C}$(4)H), 22.5 ($\underline{C}$(5)H_3). All spectroscopic data were consistent with those previously reported.[121]

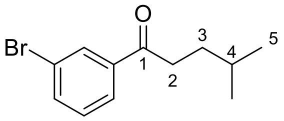
1-(4-Methoxyphenyl)-4-methylpentan-1-one, 219



$[IrCl(cod)]_2$ (13.4 mg, 0.020 mmol), KOH (22.4 mg, 0.40 mmol), PPh_3 (21.0 mg, 0.080 mmol), 4-methoxyacetophenone (300 mg, 2.0 mmol), and 2-methyl-1-propanol (0.93 mL, 10.0 mmol) were subjected to general procedure **B** for 6 h. Purification by FCC (9:1 petrol/ether) afforded **219** (298 mg, 1.43 mmol, 72%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.8 Hz, 2H, C(4)$\underline{H}$×2), 6.85 (d, *J* = 9.0 Hz, 2H, C(3)$\underline{H}$×2), 3.79 (s, 3H, C(1)$\underline{H}_3$), 2.85-2.81 (m, 2H, C(7)$\underline{H}_2$), 1.56-1.47 (m, 3H, C(8)$\underline{H}_2$, C(9)$\underline{H}$), 0.87 (d, *J* = 6.4 Hz, 6H, C(10)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.4 ($\underline{C}$(6)O), 163.3 ($\underline{C}$(5)), 130.3 $\underline{C}$(4)H×2), 130.2 ($\underline{C}$(2)), 113.7 ($\underline{C}$(3)H×2), 55.4 ($\underline{C}$(1)H_3), 36.3 ($\underline{C}$(7)H_2), 33.5 ($\underline{C}$(8)H_2), 27.9

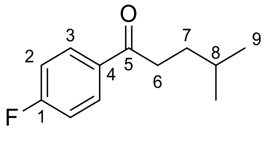
($\underline{C}$(9)H), 22.5 ($\underline{C}$(10)H_3). All spectroscopic data were consistent with those previously reported.[122]

1-(3-Bromophenyl)-4-methylpentan-1-one, 200



3-Bromoacetophenone (0.27 mL, 2.0 mmol), $[IrCl(cod)]_2$ (13.4 mg, 0.0200 mmol), KOH (22.4 mg, 0.400 mmol), PPh_3 (21.0 mg, 0.0800 mmol) and isobutanol (0.99 mL, 10 mmol) were subjected to general procedure **B** for 4 h. Purification by FCC (Petrol/Et_2O 20:1) afforded **200** (419 mg, 1.64 mmol, 82 %) as a colourless oil. IR ν_{max} (cm^{-1}) 2956, 2931, 2869, 1687, 1262, 1068, 762; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06-8.04 (m, 1H), 7.86-7.84 (m, 1H), 7.64 (ddd, *J* = 8.1, 2.0, 1.0 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 2.93-2.89 (m, 2H, C(2)$\underline{H}_2$), 1.64-1.57 (m, 3H, C(3)$\underline{H}_2$, C(4)$\underline{H}$), 0.93 (d, *J* = 6.3 Hz, 6H, C(5)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1 ($\underline{C}$(1)O), 138.8, 135.7, 131.1, 130.1, 126.6, 122.9, 36.6 ($\underline{C}$(2)H_2), 32.9 ($\underline{C}$(3)H_2), 27.8 ($\underline{C}$(4)H), 22.4 ($\underline{C}$(5)H_3×2); HRMS (ESI^+) calculated for $[C_{12}H_{15}OBr + Na]^+$ 277.0198, 279.0178, found 277.0207, 279.0187 (Δ -3.1 ppm).

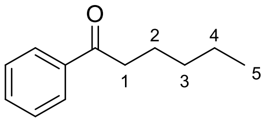
1-(4-Fluorophenyl)-4-methylpentan-1-one, 194



4'-Fluoroacetophenone (0.24 mL, 2.0 mmol), $[IrCl(cod)]_2$ (13.4 mg, 0.0200 mmol), KOH (22.4 mg, 0.400 mmol), PPh_3 (21.0 mg, 0.0800 mmol) and isobutanol (0.37 mL, 4.0 mmol) were subjected to general procedure B for 4 h. Purification by FCC (Petrol/Et_2O 20:1) afforded **194** (118 mg, 0.60 mmol, 30 %) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.98-7.95 (m, 2H, C(3)$\underline{H}$×2), 7.11-7.07 (m, 2H, C(2)$\underline{H}$×2), 2.93-2.89 (m, 2H, C(6)$\underline{H}_2$), 1.64-

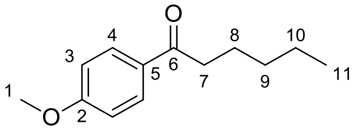
1.57 (m, 3H, C(7)*H*$_2$, C(8)*H*), 0.92 (d, *J* = 6.4 Hz, 6H, C(9)*H*$_3$×2); ^{19}F NMR (377 MHz, CDCl$_3$) δ -105.78; ^{13}C NMR (101 MHz, CDCl$_3$) δ 199.0 (*C*(5)O), 166.8 and 164.3 (J_{CF} = 252 Hz, *C*(1)), 133.5 and 133.4 (J_{CF} 3.2 Hz, *C*(4)), 130.7 and 130.6 (J_{CF} 9.5 Hz, *C*(3)H×2), 115.7 and 115.4 (J_{CF} 22 Hz, *C*(2)H×2), 36.5 (*C*(6)H$_2$), 33.2 (*C*(7)H$_2$), 27.8 (*C*(8)H), 22.4 (*C*(9)H$_3$×2) . Spectroscopic data are consistent with those previously reported.[123]

1-Phenylhexan-1-one, 214



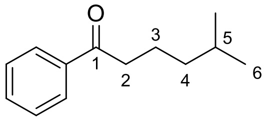
[Ir(cod)Cl]$_2$ (13.4 mg, 0.0199 mmol), KOH (11.2 mg, 0.200 mmol), PPh$_3$ (21.0 mg, 0.0801 mmol), acetophenone (0.23 mL, 2.0 mmol), 1-butanol (0.37 mL, 4.0 mmol), and toluene (1 mL) were added to a Biotage® microwave vial equipped with a stir bar. The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 °C for 24 h. Purification by FCC (Petrol/Et$_2$O 10:1) afforded **214** (279 mg, 1.56 mmol, 79%) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.91-7.89 (m, 2H), 7.48-7.44 (m, 1H), 7.39-7.35 (m, 2H), 2.90-2.86 (m, 2H, C(1)*H*$_2$), 1.70-1.64 (m, 2H, C(2)*H*$_2$), 1.33-1.28 (m, 4H, C(3)*H*$_2$, C(4)*H*$_2$), 0.88-0.84 (m, 3H, C(5)*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 200.2 (CO), 137.0, 132.8, 128.4, 128.0, 38.4 (*C*(1)H$_2$), 31. (*C*(2)H$_2$), 24.0 (*C*(3)H$_2$), 22.5 (*C*(4)H$_2$), 13.9 (*C*(5)H$_3$). Spectroscopic data are consistent with those previously reported.[124]

1-(4-Methoxyphenyl)hexan-1-one, 218



4’-Methoxyacetophenone (300 mg, 2.00 mmol), [Ir(cod)Cl]$_2$ (13.4 mg, 0.0199 mmol), KOH (11.2 mg, 0.200 mmol), PPh$_3$ (21.0 mg, 0.0801 mmol), and 1-butanol (0.92 mL, 10.0 mmol) were subjected to general procedure **B** for 6 h. Purification by FCC (Petrol/Et$_2$O 10:1) afforded **218** (366 mg, 1.78 mmol, 89 %) as a colourless solid. Melting point = 32-33 ^{o}C (Lit: 34-35 ^{o}C)[125]; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.84 (d, *J* = 8.0 Hz, 2H, C(4)$\underline{H}$×2), 6.82 (d, *J* = 8.0 Hz, 2H, C(3)$\underline{H}$×2), 3.75 (s, 3H, C(1)$\underline{H}_3$), 2.83-2.79 (m, 2H, C(7)$\underline{H}_2$), 1.65-1.61 (m, 2H, C(8)$\underline{H}_2$), 1.28-1.24 (m, 4H, C(9)$\underline{H}_2$, C(10)$\underline{H}_2$). 0.83-0.80 (m, 3H, C(11)$\underline{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 199.1 ($\underline{C}$(6)O), 163.3 ($\underline{C}$(5)), 130.3 ($\underline{C}$(4)H×2), 130.2 (C(2)), 113.6 ($\underline{C}$(3)H×2), 55.4 ($\underline{C}$(1)H$_3$), 38.2 ($\underline{C}$(7)H$_2$), 31.6 ($\underline{C}$(8)H$_2$), 24.3 ($\underline{C}$(9)H$_2$), 22.6 ($\underline{C}$(10)H$_2$), 14.0 ($\underline{C}$(11)H$_3$). Spectroscopic data are consistent with those previously reported.[124]

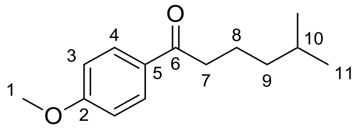
5-Methyl-1-phenylhexan-1-one, 216



[Ir(cod)Cl]$_2$ (13.4 mg, 0.0199 mmol), KOH (11.2 mg, 0.200 mmol), PPh$_3$ (21.0 mg, 0.0801 mmol), acetophenone (0.23 mL, 2.0 mmol), 3-methyl-1-butanol (1.1 mL, 10.0 mmol) were subjected to general procedure **B** for 4 h. Purification by FCC (Petrol/Et$_2$O 10:1) afforded **216** (319 mg, 1.68 mmol, 84%) as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97-7.95 (m, 2H), 7.55-7.51 (m, 1H), 7.46-7.42 (m, 2H), 2.95-2.91 (m, 2H, C(2)$\underline{H}_2$), 1.77-1.71 (m, 2H, C(3)$\underline{H}_2$), 1.61-1.55 (m, 1H, C(5)$\underline{H}$), 1.28-1.24 (m, 2H, C(4)$\underline{H}_2$), 0.9 (d, *J* = 6.6 Hz, 6H, C(6)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, CDCl$_3$) δ 200.1 ($\underline{C}$(1)O), 137.0, 132.8, 128.5, 128.0, 38.7

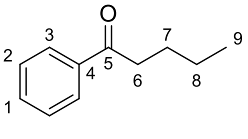
(<u>C</u>(2)H_2), 38.6 (<u>C</u>(4)H_2), 27.9 (<u>C</u>(5)H), 22.5 (<u>C</u>(6)H_3), 22.1 (<u>C</u>(3)H_2). Spectroscopic data were consistent with those previously reported.[126]

1-(4-Methoxyphenyl)-5-methylhexan-1-one, 220



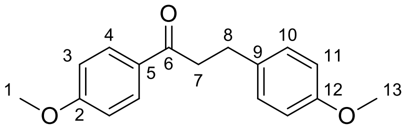
$[IrCl(cod)]_2$ (13.4 mg, 0.020 mmol), KOH (11.2 mg, 0.20 mmol), PPh_3 (21.0 mg, 0.080 mmol), 4-methoxyacetophenone (300 mg, 2.0 mmol), and 3-methyl-1-butanol (1.10 mL, 10.0 mmol) were subjected to general procedure **B** for 6 h. Purification by FCC (10:1 petrol/ether) afforded **220** (425 mg, 1.93 mmol, 97%) as a yellow oil. IR ν_{max} (cm^{-1}) 2954, 1675, 834, 807; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.6 Hz, 2H, C(4)<u>*H*</u>×2), 6.89 (d, *J* = 8.3 Hz, 2H, C(3)<u>*H*</u>×2), 3.82 (s, 3H, C(1)<u>*H*</u>3), 2.86 (t, *J* = 7.5 Hz, 2H, C(7)<u>*H*</u>2), 1.73-1.71 (m, 2H, C(8)<u>*H*</u>2), 1.61-1.54 (m, 1H, C(10)<u>*H*</u>), 1.28-1.22 (m, 2H, C(9)<u>*H*</u>2), 0.87 (d, *J* = 6.6 Hz, 6H, C(11)<u>*H*</u>3×2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.2 (<u>C</u>(6)O), 163.3 (<u>C</u>(5)), 130.3 (<u>C</u>(4)H×2), 130.2 (<u>C</u>(2)), 113.7 (<u>C</u>(3)H×2), 55.4 (<u>C</u>(1)H_3), 38.7 (<u>C</u>(7)H_2), 38.5 (<u>C</u>(9)H_2), 28.0 (<u>C</u>(10)H), 22.6 (<u>C</u>(11)H_3×2), 22.5 (<u>C</u>(8)H_2); HRMS (ESI^+) calculated for $[C_{14}H_{20}O_2+H]^+$ 221.1536, found 221.1540, (Δ -1.4 ppm).

Valerophenone, 157



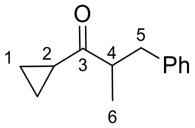
$[Ir(cod)Cl]_2$ (13.4 mg, 0.0199 mmol), KOH (11.2 mg, 0.200 mmol), PPh_3 (21.0 mg, 0.0801 mmol), acetophenone (0.23 mL, 2.0 mmol), 1-propanol (0.75 mL, 10.0 mmol) were subjected to general procedure **B** for 6 h. Purification by FCC (Petrol/Et_2O 15:1) afforded **157** (234 mg, 1.44 mmol, 72%) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86-7.84 (m, 2H, C(3)<u>*H*</u>×2), 7.43-7.41 (m, 1H, (C(1)$\underline{H}$), 7.34-7.32 (m, 2H, C(2)$\underline{H}$×2), 2.85-2.83 (m, 2H, C(6)$\underline{H}_2$), 1.63-1.59 (m, 2H, C(7)$\underline{H}_2$), 1.33-1.25 (m, 2H, C(8)$\underline{H}_2$), 0.85-0.81 (m, 3H, C(9)$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 200.4 ($\underline{C}$(5)O), 137.0 ($\underline{C}$(4)), 132.8 ($\underline{C}$(1)H), 128.5($\underline{C}$(3)H×2) , 128.0 ($\underline{C}$(2)H×2), 38.3 ($\underline{C}$(6)H_2), 26.4 ($\underline{C}$(7)H_2), 22.5 ($\underline{C}$(8)H_2), 14.0 ($\underline{C}$(9)H_3). Spectroscopic data were consistent with those previously reported.[127]

1,3-Bis(4-methoxyphenyl)propan-1-one, 235



$[IrCl(cod)]_2$ (13.4 mg, 0.0200 mmol), KOH (11.2 mg, 0.200 mmol), PPh_3 (21.0 mg, 0.0800 mmol), 4-methoxyacetophenone (300 mg, 2.00 mmol), and 4-methoxybenzyl alcohol (1.25 mL, 10.0 mmol) were subjected to general procedure **B** for 6 h. Purification by FCC (toluene/ Et_2O 10:1) afforded **235** (428 mg, 1.59 mmol, 79%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2H, C(4)$\underline{H}$×2), 7.04 (d, *J* = 8.6 Hz, 2H, C(10)$\underline{H}$×2), 6.78 (d, *J* = 9.1 Hz, 2H, C(3)$\underline{H}$×2), 6.71 (d, *J* = 8.6 Hz, 2H, C(11)$\underline{H}$×2), 3.71 (s, 3$\underline{H}$), 3.64 (s, 3$\underline{H}$), 3.13-3.01 (m, 2H, C(7)$\underline{H}_2$), 2.95-2.83 (m, 2H, C(8)$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.9 ($\underline{C}$(6)O), 163.4, 158.0, 133.5, 130.3 ($\underline{C}$(4)H×2), 130.0, 129.4 ($\underline{C}$(10)H×2), 113.9 ($\underline{C}$(3)H×2), 113.7 ($\underline{C}$(11)H×2), 55.4, 55.2 ($\underline{C}$(1)H_3, $\underline{C}$(13)H_3), 40.4 ($\underline{C}$(7)H_2), 29.5 ($\underline{C}$(8)H_2). Spectroscopic data are consistent with those previously reported.[128]

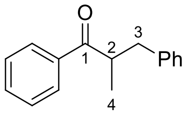
(±)1-Cyclopropyl-2-methyl-3-phenylpropan-1-one, 164a



Rh catalyzed methylation: 1-Cyclopropyl-3-phenylpropan-1-one (**164**, 52.0 mg, 0.300 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol) and methanol (1.5 mL) were subjected to general procedure **A** for 48 h. Purification by FCC (Petrol/Et_2O 20:1) afforded **164a** (46.0 mg, 0.240 mmol, 81 %) as a colourless oil.

Ir/Rh one-pot procedure: To a mixture of $[IrCl(cod)]_2$ (6.7 mg, 0.010 mmol), KOH (6.1 mg, 0.10 mmol), PPh_3 (10.1 mg, 0.0400 mmol) in a Biotage® microwave vial were added 1-cyclopropylethanone (99 mg, 1.0 mmol), and benzyl alcohol (1.3 mL, 1.2 mmol). The mixture was with a Biotage® microwave vial cap (containing a Reseal™ septum) and was degassed with Ar, then stirred at 100 °C for 4h. Then $[RhCp^*Cl_2]_2$ (30.9 mg, 0.0500 mmol), Cs_2CO_3 (1.6 g, 5.0 mmol), MeOH (3.0 mL) were added, and the mixture was stirred under O_2 at 65 °C for 60 h. Purification by FCC (Petrol/Et_2O 9:1) afforded **164a** (102 mg, 0.540 mmol, 54%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.13 (m, 5H), 3.05 (dd, *J* = 13.4, 6.6 Hz, 1H, C(5)*H*H), 2.97 (app sext, *J* = 7.2 Hz, 1H, C(4)*H*), 2.58 (dd, *J* = 13.4, 7.6 Hz, 1H, C(5)H*H*), 1.94-1.86 (m, 1H, C(2)*H*), 1.12 (d, *J* = 6.9 Hz, 3H, C(6)H_3), 1.00-0.90 (m, 2H, C(1)*H*H×2), 0.88-0.74 (m, 2H, C(1)H*H*×2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 213.8 (*C*(3)O), 139.9, 129.1, 128.3, 126.2, 48.9, 39.0, 19.7, 16.3, 10.9, 10.8. Spectroscopic data are consistent with those previously reported.[129]

(±)2-Methyl-1,3-diphenylpropan-1-one, 13a



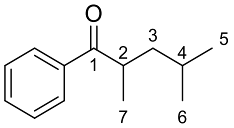
Rh catalyzed methylation: 3-Phenylpropiophenone (**13**, 63.0 mg, 0.300 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol) and methanol (1.5 mL) were subjected to general procedure **A** for 48 h. Purification by FCC (Petrol/Et_2O 30:1) afforded **13a** (53.5 mg, 0.240 mmol, 85 %) as a colourless oil.

Ir/Rh One-pot procedure: To a mixture of $[IrCl(cod)]_2$ (2 mg, 0.003 mmol), KOH (1.7 mg, 0.03 mmol), PPh_3 (3.2 mg, 0.012 mmol) in a Biotage® microwave vial were added acetophenone (36.0 mg, 0.300 mmol), benzyl alcohol (62 μL, 0.60 mmol). The mixture was sealed with a Biotage® microwave vial cap (containing a Reseal™ septum) and was degassed with Ar, then stirred at 100 °C for 4 h. Then $[RhCp^*Cl_2]_2$ (9.3 mg, 0.015 mmol), Cs_2CO_3 (488 mg, 1.50 mmol), MeOH (1.5 mL) were added, and the mixture was stirred under O_2 at 65 °C for 12 h. Purification by FCC (Petrol/Et_2O 9:1) afforded **13a** as a colourless oil (45.0 mg, 0.200 mmol, 67 %).

Ir catalyzed methylation: 1, 3-Phenylpropiophenone (**13**, 63.0 mg, 0.300 mmol), $[Ir(cod)Cl]_2$ (2.0 mg, 0.0030 mmol), KOH (17.0 mg, 0.303 mmol), PPh_3 (3.2 mg, 0.012 mmol), MeOH (1.5 mL) were subjected to general procedure **C** for 48 h. Purification by FCC (Petrol/Et_2O 10:1) afforded **13a** (54.7 mg, 0.244 mmol, 81%) as a colorless oil.

Ir one-pot dialkylation: To a mixture of acetophenone (120 mg, 1.00 mmol), $[Ir (cod) Cl]_2$ (6.7 mg, 0.010 mmol), KOH (5.6 mg, 0.10 mmol) and PPh_3 (10.5 mg, 0.0400 mmol) in a Biotage® microwave vial equipped with a stir bar was added benzyl alcohol (0.21 mL, 2.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 °C for 4 h before KOH (112 mg, 2.00 mmol), PPh_3 (5.3 mg, 0.020 mmol) and MeOH (5 mL) were added, and the mixture was stirred under O_2 at 65 °C for 48 h. Purification by FCC (Petrol/Et_2O 10:1) afforded **13a** (130 mg, 0.580 mmol, 58%) as a colorless oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.93 (m, 2H), 7.61-7.54 (m, 1H), 7.51-7.45 (m, 2H), 7.34-7.17 (m, 5H), 3.85-3.75 (m, 1H, C(2)<u>*H*</u>), 3.21 (dd, *J* = 13.7, 6.3 Hz, 1H, C(3)<u>*H*</u>H), 2.73 (1H, dd, *J* = 13.7, 7.9 Hz, C(3)H<u>*H*</u>), 1.24 (d, *J* = 6.9 Hz, 3H, C(4)$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.7 (<u>*C*</u>(1)O), 139.9, 136.4, 132.9, 129.1, 128.6, 128.3, 128.3, 126.2, 42.7 (C(2)H), 39.3 (C(3)H_2), 17.4 (C(4)H_3). Spectroscopic data were consistent with those previously reported.[130]

(±)2,4-Dimethyl-1-phenylpentan-1-one, 215a



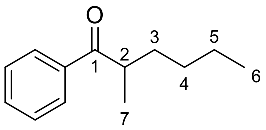
Rh catalyzed methylation: 4-Methyl-1-phenylpentan-1-one (**215**, 52.8 mg, 0.300 mmol), $[RhCp^*Cl_2]_2$ (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol) and methanol (1.5 mL) were subjected to general procedure **A** for 48 h. Purification by FCC (Petrol/Et_2O 9:1) afforded **215a** (36.0 mg, 0.190 mmol, 64 %) as a colourless oil.

Ir/Rh One-pot Procedure: To a mixture of $[IrCl(cod)]_2$ (2.0 mg, 0.003 mmol), KOH (3.4 mg, 0.06 mmol), PPh_3 (3.2 mg, 0.012 mmol) in a Biotage® microwave vial were added acetophenone (36.0 mg, 0.300 mmol), and 2-methyl-1-propanol (140 µL, 1.50 mmol). The mixture was sealed with a Biotage® microwave vial cap (containing a Reseal™ septum) and was degassed with Ar, then stirred at 100 ^{0}C for 4h before $[RhCp^*Cl_2]_2$ (9.3 mg, 0.015 mmol), Cs_2CO_3 (488 mg, 1.50 mmol), and MeOH (1.5 mL) were added, and the mixture was stirred under O_2 at 65 °C for 12 h. Purification by FCC (Petrol/Et_2O 9:1) afforded **215a** as a yellow oil (30.5 mg, 0.160 mmol, 54 %).

Ir catalyzed methylation: 4-Methyl-1-phenylpentan-1-one (**215**, 52.8 mg, 0.300 mmol), $[[Ir(cod)Cl]_2$ (2.0 mg, 0.0030 mmol), KOH (33.7 mg, 0.602 mmol), PPh_3 (3.2 mg, 0.012 mmol), MeOH (1.5 mL) were subjected to general procedure **C** for 48 h. Purification by FCC (Petrol/Et_2O 15:1) afforded **215a**(48.9 mg, 0.0.257 mmol, 86%) as a colorless oil.

Ir one-pot Procedure: To a mixture of acetophenone (120 mg, 1.00 mmol), [Ir (cod) Cl]$_2$ (6.7 mg, 0.010 mmol), KOH (11.2 mg, 0.200 mmol) and PPh$_3$ (10.5 mg, 0.0400 mmol) in a Biotage® microwave vial equipped with a stir bar was added 2-methyl-1-propanol (0.46 mL, 5.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 °C for 4 h before KOH (168 mg, 3.00 mmol), PPh$_3$ (10.5 mg, 0.040 mmol) and MeOH (5 mL) were added, and the mixture was stirred under O$_2$ at 65 °C for 48 h. Purification by FCC (Petrol/Et$_2$O 15:1) afforded **215a** (105 mg, 0.553 mmol, 55%) as a colorless oil. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.99-7.96 (m, 2H), 7.58-7.55 (m, 1H), 7.49-7.46 (m, 2H), 3.60-3.55 (m, 1H, C(2)$\underline{H}$), 1.75-1.62 (m, 2H, C(3)$\underline{H}$H, C(4)$\underline{H}$), 1.33-1.26 (m, 1H, C(3)H$\underline{H}$), 1.19 (d, J = 6.9, 3H, C(7)$\underline{H}_3$), 0.93 (d, J = 6.3, 3H, C(5)$\underline{H}_3$), 0.90 (d, J = 6.3, 3H, C(6)$\underline{H}_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 204.6 ($\underline{C}$(1)O), 136.7, 132.8, 128.6, 128.2, 42.7 ($\underline{C}$(3)H$_2$), 38.4 ($\underline{C}$(2)H), 25.9 ($\underline{C}$(4)H), 23.0, 22.3 ($\underline{C}$(5)H$_3$, $\underline{C}$(6)H$_3$), 17.5 ($\underline{C}$(7)H$_3$). Spectroscopic data were consistent with those previously reported.[131]

(±)2-Methyl-1-phenylhexan-1-one, 214a

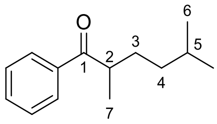


Ir catalyzed methylation: 1-Phenylhexan-1-one (**214**, 52.8 mg, 0. 300 mmol), [Ir(cod)Cl]$_2$ (2.0 mg, 0.0030 mmol), KOH (33.7 mg, 0.602 mmol), PPh$_3$ (3.2 mg, 0.012 mmol), MeOH (1.5 mL) were subjected to general procedure **C** for 48 h. Purification by FCC (Petrol/Et$_2$O 15:1) afforded **214a** (43.8 mg, 0.0.231 mmol, 77%) as a colorless oil.

Ir one-pot Procedure: To a mixture of acetophenone (120 mg, 1.00 mmol), [Ir (cod) Cl]$_2$ (6.7 mg, 0.010 mmol), KOH (5.6 mg, 0.10 mmol), PPh$_3$ (10.5 mg, 0.0400 mmol) and toluene (0.5

mL) in a Biotage® microwave vial equipped with a stir bar was added 1-butanol (0.19 mL, 2.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 ºC for 24 h and toluene removed *in vacuo* before KOH (168 mg, 3.00 mmol), PPh_3 (10.5 mg, 0.040 mmol) and MeOH (5 mL) were added, and the mixture was stirred under O_2 at 65 ^{0}C for 48 h. Purification by FCC (Petrol/Et_2O 15:1) afforded **214a** (102 mg, 0.537 mmol, 54%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.96 (m, 2H), 7.58-7.55 (m, 1H), 7.50-7.46 (m, 2H), 3.47 (app sext, *J* = 6.8 Hz, 1H, C(2)*H*), 1.83-1.78 (m, 1H, C(3)*H*H), 1.47-1.44 (m, 1H, C(3)H*H*), 1.33-1.31 (m, 4H, C(4)$\underline{H}_2$, C(5)$\underline{H}_2$), 1.20 (d, *J* = 6.8 Hz, 3H, C(7)$\underline{H}_3$), 0.90-0.87 (m, 3H, C(6)$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6, 136.8, 132.8, 128.6, 128.2, 40.6, 33.5, 29.6, 22.8, 17.3, 14.0. Spectroscopic data are consistent with those previously reported.[132]

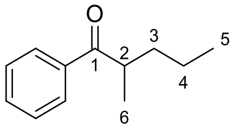
(±)2,5-Dimethyl-1-phenylhexan-1-one, 216a



Ir catalyzed methylation: 5-Methyl-1-phenylhexan-1-one (**216**, 57.0 mg, 0.300 mmol), [[Ir(cod)Cl]$_2$ (2.0 mg, 0.0030 mmol), KOH (33.7 mg, 0.602 mmol), PPh_3 (3.2 mg, 0.012 mmol), MeOH (1.5 mL) were subjected to general procedure **C** for 48 h. Purification by FCC (Petrol/Et_2O 20:1) afforded **216a** (46.9 mg, 0.0.230 mmol, 77%) as a colorless oil.

Ir one-pot Procedure: To a mixture of acetophenone (120 mg, 1.00 mmol), [Ir (cod) Cl]$_2$ (6.7 mg, 0.010 mmol), KOH (5.6 mg, 0.100 mmol) and PPh_3 (10.5 mg, 0.0400 mmol) in a Biotage® microwave vial equipped with a stir bar was added 3-methyl-1-butanol (0.54 mL, 5.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 °C for 4 h before KOH (168 mg, 3.00 mmol), PPh_3 (10.5 mg, 0.040 mmol) and MeOH (5 mL) were added, and the mixture was stirred under O_2 at 65 °C for 72 h. Purification by FCC (Petrol/Et_2O 20:1) afforded **216a** (112 mg, 0.549 mmol, 55%) as a colorless oil. IR ν_{max} (cm^{-1}) 2955, 1682, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 7.98-7.96 (m, 2H), 7.59-7.55 (m, 1H), 7.50-7.46 (m, 2H), 3.44 (app sext, *J* = 6.7 Hz, 1H, C(2)$\underline{H}$), 1.85-1.77 (m, 1H, C(3)$\underline{H}$H), 1.56-1.38 (m, 2H, C(3)H$\underline{H}$, C(5)$\underline{H}$), 1.21-1.19 (m, 5H, C(7)$\underline{H}_3$, C(4)$\underline{H}_2$), 0.89-0.85 (m, 6H, C(6)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 ($\underline{C}$(1)O), 136.8, 132.8, 128.6, 128.2, 40.8 ($\underline{C}$(2)H), 36.6 ($\underline{C}$(4)H_2), 31.6 ($\underline{C}$(3)H_2), 28.2 ($\underline{C}$(5)H), 22.6, 22.4 ($\underline{C}$(6)H_3×2), 17.3 ($\underline{C}$(7)H_3); HRMS (ESI^+) calculated for $[C_{14}H_{20}O + Na]^+$ 227.1406, found 227.1411, (Δ -1.6 ppm).

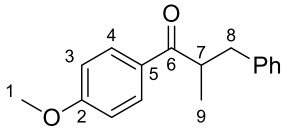
(±)2-Methyl-1-phenylpentan-1-one, 157a



Ir catalyzed methylation: Valerophenone (**157**, 162 mg, 1.00 mmol), $[[Ir(cod)Cl]_2$ (6.7 mg, 0.010 mmol), KOH (112 mg, 2.00 mmol), PPh_3 (10.5 mg, 0.0400 mmol), MeOH (5 mL) were subjected to general procedure **C** for 48 h. Purification by FCC (Petrol/Et_2O 15:1) afforded **157a** (143 mg, 0.812 mmol, 81%) as a colorless oil.

Ir One-pot Procedure: To a mixture of acetophenone (120 mg, 1.00 mmol), $[Ir (cod) Cl]_2$ (6.7 mg, 0.010 mmol), KOH (5.6 mg, 0.100 mmol) and PPh_3 (10.5 mg, 0.0400 mmol) in a Biotage® microwave vial equipped with a stir bar was added 1-propanol (0.38 mL, 5.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 °C for 6 h before KOH (168 mg, 3.00 mmol), PPh_3 (10.5 mg, 0.040 mmol) and MeOH (5 mL) were added, and the mixture was stirred under O_2 at 65 ^{0}C for 72 h. Purification by FCC (Petrol/Et_2O 15:1) afforded **157a** (75.4 mg, 0.428 mmol, 43%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92-7.84 (m, 2H), 7.52-7.34 (m, 3H), 3.41 (app sext, *J* = 6.8 Hz, 1H, C(2)*<u>H</u>*), 1.78-1.66 (m, 1H, C(3)*<u>H</u>*H), 1.42-1.13 (m, 3H, C(3)H*<u>H</u>*, C(4)*<u>H</u>*$_2$), 1.12 (d, *J* = 6.9 Hz, 3H, C(6)*<u>H</u>*$_3$), 0.83 (t, *J* = 7.2 Hz, 3H, C(5)*<u>H</u>*$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (*<u>C</u>*(1)O), 136.8, 132.8, 128.6, 128.2, 40.3 (*<u>C</u>*(2)H), 35.9 (*<u>C</u>*(3)H$_2$), 20.6 (*<u>C</u>*(4)H$_2$), 17.2 (*<u>C</u>*(6)H$_3$), 14.2 (*<u>C</u>*(5)H$_3$). Spectroscopic data are consistent with those previously reported[133]

(±)1-(4-Methoxyphenyl)-2-methyl-3-phenylpropan-1-one, 217a



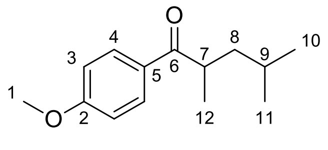
Rh catalyzed methylation: 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**, 72.0 mg, 0.300 mmol), [RhCp*Cl_2]$_2$ (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol) and methanol (1.5 mL) were subjected to general procedure **A** for 24 h. Purification by FCC (Petrol/Et_2O 10:1) afforded **217a** (56.0 mg, 0.220 mmol, 73 %) as a colourless oil.

Ir/Rh one-pot procedure: To a mixture of [IrCl(cod)]$_2$ (2.0 mg, 0.003 mmol), KOH (1.7 mg, 0.03 mmol), PPh_3 (3.2 mg, 0.012 mmol) in a Biotage® microwave vial were added 1-(4-methoxyphenyl)ethanone (45.1 mg, 0.3 mmol), and benzyl alcohol (62 μL, 0.60 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and the mixture was degassed with Ar, then stirred at 100 °C for 4h before [RhCp*Cl_2]$_2$ (9.3 mg, 0.015 mmol), Cs_2CO_3 (488 mg, 1.5 mmol), and MeOH (1.5 mL) were added, and the mixture was stirred under O_2 at 65 ^{0}C for 24 h. Purification by FCC (Petrol/Et_2O 9:1) afforded **217a** (41 mg, 0.16 mmol, 53 %) as a light yellow oil.

Ir catalyzed methylation: 1-(4-Methoxyphenyl)-3-phenylpropan-1-one (**217**, 72.0 mg, 0.300 mmol), $[Ir(cod)Cl]_2$ (2.0 mg, 0.0030 mmol), KOH (33.7 mg, 0.602 mmol), PPh_3 (3.2 mg, 0.012 mmol), MeOH (1.5 mL) were subjected to general procedure **C** for 48 h. Purification by FCC (Petrol/Et_2O 10:1) afforded **217a** (71.5 mg, 0.281 mmol, 94%) as a colorless oil.

Ir one-pot procedure: To a mixture of 4'-Methoxyacetophenone (150 mg, 1.00 mmol), $[Ir (cod) Cl]_2$ (6.7 mg, 0.010 mmol), KOH (5.6 mg, 0.10 mmol) and PPh_3 (10.5 mg, 0.0400 mmol) in a Biotage® microwave vial equipped with a stir bar was added benzyl alcohol (0.21 mL, 2.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 ^{o}C for 6 h before KOH (168 mg, 3.00 mmol), PPh_3 (10.5 mg, 0.0400 mmol) and MeOH (5 mL) were added, and the mixture was stirred under O_2 at 65 ^{0}C for 48 h. Purification by FCC (Petrol/Et2O 10:1) afforded **217a** (185 mg, 0.728 mmol, 73%) as a colorless oil.^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.9 Hz, 2H, C(4)$\underline{H}$×2), 7.13-7.28 (m, 5H), 6.91 (d, J = 8.9 Hz, 2H, C(3)$\underline{H}$×2), 3.84 (s, 3H, C(1)$\underline{H}_3$), 3.65-3.74 (m, 1H, C(7)$\underline{H}$), 3.15 (dd, J = 6.7, 13.6 Hz, 1H, C(8)$\underline{H}$H), 2.68 (dd, J = 7.9, 13.6 Hz, 1H, C(8)H$\underline{H}$), 1.19 (d, J = 6.9 Hz, 3H, C(9)$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2 ($\underline{C}$(6)O), 163.3, 140.0, 130.5 ($\underline{C}$(4)H×2), 129.3, 129.0, 128.3, 126.1, 113.7 ($\underline{C}$(3)H×2), 55.4 ($\underline{C}$(1)H_3), 42.3 ($\underline{C}$(7)H), 39.5 ($\underline{C}$(8)H_2), 17.5 ($\underline{C}$(9)H_3). Spectroscopic data are consistent with those previously reported.[134]

(±)1-(4-methoxyphenyl)-2,4-dimethylpentan-1-one, 219a



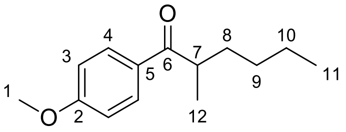
Rh catalyzed methylation: 1-(4'-methoxyphenyl)-4-methylpentan-1-one (**219**, 64.4 mg, 0.30 mmol), $[RhCp^{*}Cl_2]_2$, (9.3 mg, 5 mol%), Cs_2CO_3 (488 mg, 1.50 mmol) and methanol (1.5

mL) were subjected to general procedure **A** for 48 h. Purification by FFC (10:1 petrol/ether) afforded **219a** (34.0 mg, 0.150 mmol, 51%) as a colorless oil.

Ir catalyzed methylation: 1-(4'-methoxyphenyl)-4-methylpentan-1-one (**219**, 62.4 mg, 0.300 mmol), [Ir(cod)Cl]$_2$ (2.0 mg, 0.0030 mmol), KOH (33.7 mg, 0.602 mmol), PPh$_3$ (3.2 mg, 0.012 mmol), MeOH (1.5 mL) were subjected to general procedure **C** for 48 h. Purification by FCC (Petrol/Et$_2$O 10:1) afforded **219a** (60.9 mg, 0.274 mmol, 91%) as a colorless oil.

Ir one-pot procedure: To a mixture of 4'-Methoxyacetophenone (150 mg, 1.00 mmol), [Ir (cod) Cl]$_2$ (6.7 mg, 0.010 mmol), KOH (11.2 mg, 0.20 mmol) and PPh$_3$ (10.5 mg, 0.0400 mmol) in a Biotage® microwave vial equipped with a stir bar was added 2-methyl-1-propanol (0.46 mL, 5.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 ^{o}C for 6 h before KOH (168 mg, 3.00 mmol), PPh$_3$ (10.5 mg, 0.0400 mmol) and MeOH (5 mL) were added, and the mixture was stirred under O$_2$ at 65 ^{0}C for 72 h. Purification by FCC (Petrol/Et2O 10:1) afforded **219a** (150 mg, 0.676 mmol, 68%) as a colorless oil. IR ν_{max} (cm^{-1}) 2957, 1673, 1600, 1246, 892, 803; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.98-7.96 (m, 2H, C(4)$\underline{H}$×2)), 6.97-6.95 (m, 2H, C(3)$\underline{H}$×2), 3.87 (s, 3H, C(1)$\underline{H}_3$), 3.53 (app sext, *J* = 6.9 Hz, 1H, C(7)$\underline{H}$), 1.74-1.59 (m, 2H, C(8)$\underline{H}$H, C(9)$\underline{H}$), 1.28(ddd, *J* = 13.3, 7.2, 6.1 Hz, 1H, C(8)H$\underline{H}$), 1.16 (d, *J* = 6.8 Hz, 3H, C(12)$\underline{H}_3$), 0.92 (d, *J* = 6.6 Hz, 3H, C(10)$\underline{H}_3$), 0.89 (d, *J* = 6.6 Hz, 3H, C(11)$\underline{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 203.2 ($\underline{C}$(6)O), 163.3 ($\underline{C}$(5)), 130.5 ($\underline{C}$(4)H×2), 129.7 ($\underline{C}$(2)), 113.8 ($\underline{C}$(3)H×2), 55.4 ($\underline{C}$(1)H$_3$), 43.0 ($\underline{C}$(8)H$_2$), 38.0 ($\underline{C}$(7)H), 25.9 ($\underline{C}$(9)H), 23.1 ($\underline{C}$(12)H$_3$), 22.4, 17.7($\underline{C}$(10)H$_3$, $\underline{C}$(11)H$_3$). HRMS (ESI$^+$) calculated for $[C_{14}H_{20}O_2 +H]^+$ 221.1536, found 221.1544, (Δ -3.5 ppm).

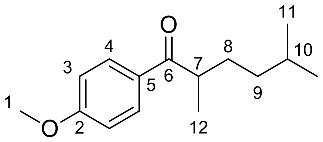
(±)1-(4-Methoxyphenyl)-2-methylhexan-1-one, 218a



Ir catalyzed methylation: 1-(4-Methoxyphenyl)hexan-1-one (**218**, 61.8 mg, 0.300 mmol), [Ir(cod)Cl]$_2$ (2.0 mg, 0.0030 mmol), KOH (33.7 mg, 0.602 mmol), PPh$_3$ (3.2 mg, 0.012 mmol), MeOH (1.5 mL) were subjected to general procedure **C** for 48 h. Purification by FCC (Petrol/Et$_2$O 10:1) afforded **218a** (62.3 mg, 0.283 mmol, 94%) as a colorless oil.

One-pot procedure: To a mixture of 4'-Methoxyacetophenone (150 mg, 1.00 mmol), [Ir (cod) Cl]$_2$ (6.7 mg, 0.010 mmol), KOH (5.6 mg, 0.10 mmol) and PPh$_3$ (10.5 mg, 0.0400 mmol) in a Biotage® microwave vial equipped with a stir bar was added 1-butanol (0.46 mL, 5.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 ^{o}C for 6 h before KOH (224 mg, 4.00 mmol), PPh$_3$ (10.5 mg, 0.0400 mmol) and MeOH (5 mL) were added, and the mixture was stirred under O$_2$ at 65 ^{0}C for 72 h. Purification by FCC (Petrol/Et2O 10:1) afforded **218a** (176 mg, 0.800 mmol, 80%) as a colorless oil. IR ν_{max} (cm^{-1}) 2932, 1672, 1599, 842, 734; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.95 (d, J = 9.0 Hz, 2H, C(4)$\underline{H}$×2), 6.94 (d, J = 9.0 Hz, 2H, C(3)$\underline{H}$×2), 3.86 (s, 3H, C(1)$\underline{H}_3$), 3.42 (app sext, J = 6.8 Hz, 1H, C(7)$\underline{H}$), 1.80-1.76 (m, 1H, C(8)$\underline{H}$H), 1.45-1.41 (m, 1H, C(8)H$\underline{H}$), 1.30-1.28 (m, 4H, C(9)H$_2$, C(10)$\underline{H}_2$), 1.17 (d, J = 6.8 Hz, 3H, C(12)$\underline{H}_3$), 0.87-0.85 (m, 3H, C(11)$\underline{H}_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 203.2 ($\underline{C}$(6)O), 163.3 ($\underline{C}$(5)), 130.5 ($\underline{C}$(4)H×2), 129.8 ($\underline{C}$(2)), 113.7 ($\underline{C}$(3)H×2), 55.5 ($\underline{C}$(1)H$_3$), 40.1 ($\underline{C}$(7)H), 33.7 ($\underline{C}$(8)H$_2$), 29.7, 22.8 ($\underline{C}$(9)H$_2$, $\underline{C}$(10)H$_2$), 17.4 ($\underline{C}$(12)H$_3$), 14.0 ($\underline{C}$(11)H$_3$); HRMS (ESI^{+}) calculated for $[C_{14}H_{20}O_2 + H]^{+}$ 221.1536, found 221.1539, (Δ -0.3 ppm).

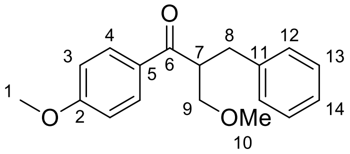
(±)1-(4-Methoxyphenyl)-2,5-dimethylhexan-1-one, 220a



Ir catalyzed methylation: 1-(4-Methoxyphenyl)-5-methylhexan-1-one (**220**, 66.0 mg, 0.300 mmol), [Ir(cod)Cl]$_2$ (2.0 mg, 0.0030 mmol), KOH (33.7 mg, 0.602 mmol), PPh$_3$ (3.2 mg, 0.012 mmol), MeOH (1.5 mL) were subjected to general procedure **C** for 48 h. Purification by FCC (Petrol/Et$_2$O 10:1) afforded **220a** (58.4 mg, 0.250 mmol, 83%) as a colorless oil.

Ir one-pot procedure: To a mixture of 4'-Methoxyacetophenone (150 mg, 1.00 mmol), [Ir (cod) Cl]$_2$ (6.7 mg, 0.010 mmol), KOH (5.6 mg, 0.10 mmol) and PPh$_3$ (10.5 mg, 0.0400 mmol) in a Biotage® microwave vial equipped with a stir bar was added 3-methyl-1-butanol (0.55 mL, 5.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 ^{o}C for 6 h before KOH (168 mg, 3.00 mmol), PPh$_3$ (10.5 mg, 0.0400 mmol) and MeOH (5 mL) were added, and the mixture was stirred under O$_2$ at 65 ^{0}C for 72 h. Purification by FCC (Petrol/Et$_2$O 10:1) afforded **220a** (192 mg, 0.821 mmol, 82%) as a colorless oil. IR ν_{max} (cm^{-1}) 2956, 1673, 843, 762; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.97-7.93 (m, 2H, C(4)$\underline{H}$×2), 6.96-6.92 (m, 2H, C(3)$\underline{H}$×2), 3.86 (s, 3H, C(1)$\underline{H}_3$), 3.39 (app sext, *J* = 6.8 Hz, 1H, C(7)$\underline{H}$), 1.85-1.71 (m, 1H, C(8)$\underline{H}$H), 1.53-1.41 (m, 2H, C(8)H$\underline{H}$, C(10)$\underline{H}$), 1.20-1.14 (m, 2H, C(9)$\underline{H}_2$), 1.18 (d, *J* = 6.8, 3H, C(12)$\underline{H}_3$), 0.88-0.82 (m, 6H, C(11)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, CDCl$_3$) δ 203.2 ($\underline{C}$(6)O), 163.3 ($\underline{C}$(5)), 130.5 ($\underline{C}$(4)H×2), 129.8 ($\underline{C}$(2)), 113.7 ($\underline{C}$(3)H×2), 55.4 ($\underline{C}$(1)H$_3$), 40.4, ($\underline{C}$(7)H), 36.7 ($\underline{C}$(9)H$_2$), 31.8 ($\underline{C}$(8)H$_2$), 28.2($\underline{C}$(10)H), 22.6, 22.4 ($\underline{C}$(11)H$_3$×2), 17.5 ($\underline{C}$(12)H$_3$); HRMS (ESI^{+}) calculated for $[C_{15}H_{22}O_2+Na]^{+}$ 257.1512, found 257.1524, (Δ -4.5 ppm).

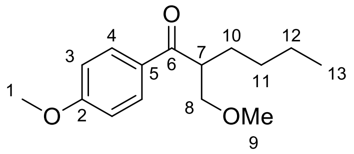
(±)2-Benzyl-3-methoxy-1-(4-methoxyphenyl)propan-1-one, 217c



Methylenation: 1-(4-Methoxyphenyl)-3-phenylpropan-1-one (**217**, 72.0 mg, 0.300 mmol), $[Ir(cod)Cl]_2$ (4.0 mg, 0.0060 mmol), KOH (50.0mg, 0.893 mmol), cataCXium® A (8.4 mg, 0.024 mmol), MeOH (3.0 mL) were subjected to general procedure **D** for 48 h. Purification by FCC (Petrol/Et_2O 8:2) afforded **217c** (64.3 mg, 0.226 mmol, 75%) as a colorless oil.

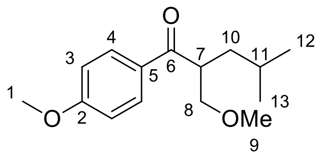
One-pot procedure: To a mixture of 4'-Methoxyacetophenone (150 mg, 1.00 mmol), [Ir (cod) Cl]$_2$ (6.7 mg, 0.010 mmol), KOH (5.6 mg, 0.10 mmol) and cataCXium® A (14.4 mg, 0.0400 mmol) in a Biotage® microwave vial equipped with a stir bar was added benzyl alcohol (0.21 mL, 2.0 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septa) and degassed *via* a needle with a balloon of Ar. The mixture was stirred at 100 ^{o}C for 24 h before KOH (168 mg, 3.00 mmol), [Ir (cod) Cl]$_2$ (6.7 mg, 0.010 mmol), cataCXium® A (14.4 mg, 0.0400 mmol) and MeOH (10 mL) were added, and the mixture was stirred under O_2 at 65 ^{0}C for 48 h. Purification by FCC (Petrol/Et_2O 8:2) afforded **217c** (149 mg, 0.525 mmol, 53%) as a colorless oil. IR ν_{max} (cm^{-1}) 2929, 1669, 1598, 1169, 842, 700; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 2H, C(4)$\underline{H}$×2), 7.25-7.15 (m, 5H), 6.89 (d, *J* = 9.0 Hz, 2H, C(3)$\underline{H}$×2), 3.98 (td, *J* = 7.1, 1.9 Hz, 1H, C(7)$\underline{H}$), 3.84 (s, 3H, C(1)$\underline{H}_3$), 3.72 (dd, *J* = 9.0, 7.4 Hz, 1H, C(9)$\underline{H}$H), 3.51 (dd, *J* = 9.0, 5.4 Hz, 1H, C(9)H$\underline{H}$), 3.28 (s, 3H, C(10)$\underline{H}_3$), 3.06 (dd, *J* = 13.8, 7.5 Hz, 1H, C(8)$\underline{H}$H), 2.88 (dd, *J* = 13.8, 6.7 Hz, 1H, C(8)H$\underline{H}$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.5 ($\underline{C}$(6)O), 163.5 ($\underline{C}$(2)), 139.3 ($\underline{C}$(11)), 130.7 ($\underline{C}$(4)H×2), 130.4 (($\underline{C}$(5)), 129.0, 128.4 ($\underline{C}$(12)H×2, $\underline{C}$(13)H×2), 126.3 ($\underline{C}$(14)H), 113.7 ($\underline{C}$(3)H×2), 73.7 ($\underline{C}$(9)H$_2$), 59.1 ($\underline{C}$(10)H$_3$), 55.4 ($\underline{C}$(1)H$_3$), 48.3 ($\underline{C}$(7)H), 35.5 ($\underline{C}$(8)H$_2$); HRMS (ESI$^+$) calculated for $[C_{18}H_{20}O_3+Na]^+$ 307.1305, found 307.1305, (Δ -0.3 ppm).

(±)2-(Methoxymethyl)-1-(4-methoxyphenyl)hexan-1-one, 218c



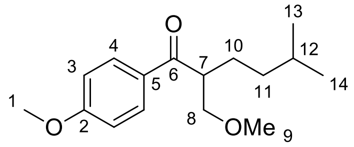
1-(4-Methoxyphenyl)hexan-1-one (**218**, 61.8 mg, 0.300 mmol), [Ir(cod)Cl]$_2$ (4.0 mg, 0.0060 mmol), KOH (50.0mg, 0.893 mmol), cataCXium® A (8.4 mg, 0.024 mmol), MeOH (3.0 mL) were subjected to general procedure **D** for 48 h. Purification by FCC (Petrol/Et$_2$O 8:2) afforded **218c** (46.9 mg, 0.188 mmol, 63%) as a colorless oil. IR ν_{max} (cm^{-1}) 2929, 1671, 1599, 1255, 1171, 843, 763; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, *J* = 8.8 Hz, 2H, C(4)$\underline{H}$×2), 6.94 (d, *J* = 8.8 Hz, 2H, C(3)$\underline{H}$×2), 3.87 (s, 3H, C(1)$\underline{H}_3$), 3.73-3.66 (m, 2H, C(7)$\underline{H}$, C(8)$\underline{H}$H), 3.51-3.46 (m, 1H, C(8)H$\underline{H}$), 3.29 (s, 3H, C(9)$\underline{H}_3$), 1.75-1.68 (m, 1H, C(10)$\underline{H}$H), 1.58-1.49 (m, 1H, C(10)H$\underline{H}$), 1.32-1.20 (m, 4H, C(11)$\underline{H}_2$, C(12)$\underline{H}_2$), 0.84 (t, *J* = 7.0 Hz, 3H, C(13)$\underline{H}_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 201.5 ($\underline{C}$(6)O), 163.5 ($\underline{C}$(5)), 130.7 ($\underline{C}$(2)), 130.7 ($\underline{C}$(4)H×2), 113.8 ($\underline{C}$(3)H×2), 74.4 ($\underline{C}$(8)H$_2$), 59.1 ($\underline{C}$(10)H$_3$), 55.4 ($\underline{C}$(1)H$_3$), 46.3 ($\underline{C}$(7)H), 29.7, 29.6, 22.9 ($\underline{C}$(10)H$_2$, $\underline{C}$(11)H$_2$, $\underline{C}$(12)H$_2$), 13.9 ($\underline{C}$(13)H$_3$); HRMS (ESI$^+$) calculated for [$C_{15}H_{22}O_3$+Na]$^+$ 273.1461, found 273.1458, (Δ 1.3 ppm).

(±)2-(Methoxymethyl)-1-(4-methoxyphenyl)-4-methylpentan-1-one, 219c



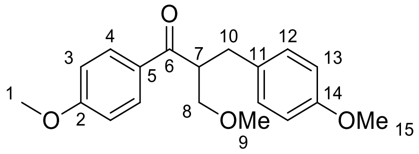
1-(4'-Methoxyphenyl)-4-methylpentan-1-one (**219**, 61.8 mg, 0.300 mmol), [Ir(cod)Cl]$_2$ (4.0 mg, 0.0060 mmol), KOH (50.0mg, 0.893 mmol), cataCXium® A (8.4 mg, 0.024 mmol), MeOH (3.0 mL) were subjected to general procedure **D** for 48 h. Purification by FCC (Petrol/Et$_2$O 8:2) afforded **219c** (35.4 mg, 0.142 mmol, 47%) as a colorless oil. IR ν_{max} (cm^{-1}) 2957, 1671, 1599, 1252, 1171, 842, 765; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.99 (d, *J* = 9.0 Hz, 2H, C(4)*H*×2), 6.94 (d, *J* = 9.0 Hz, 2H, C(3)*H*×2), 3.87 (s, 3H, C(1)*H*$_3$), 3.82-3.77 (m, 1H, C(7)*H*), 3.67 (t, *J* = 8.5 Hz, 1H, C(8)*H*H), 3.46 (dd, *J* = 8.8, 5.2 Hz, 1H, C(8)H*H*), 3.27 (s, 3H, C(9)*H*$_3$), 1.66 (ddd, *J* = 13.5, 8.1, 6.6 Hz, 1H, C(10)*H*H), 1.60-1.51 (m, 1H, C(11)*H*), 1.34 (ddd, *J* = 13.4, 7.5, 5.8 Hz, 1H, C(10)H*H*), 0.89 (d, *J* = 6.5 Hz, 3H, C(12)*H*$_3$), 0.87 (d, *J* = 6.5 Hz, 3H, C(13)*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 201,7 (*C*(6)O), 163.5 (*C*(5)), 130.8 (*C*(2)), 130.6 (*C*(4)H×2), 113.8 (*C*(3)H×2), 75.0 (*C*(8)H$_2$), 59.1 (*C*(9)H$_3$), 55.4 (*C*(1)H$_3$), 44.3 (*C*(7)H), 39.0 (*C*(10)H$_2$), 26.1 (*C*(11)H), 23.0, 22.6 (*C*(12)H$_3$, *C*(13)H$_3$); HRMS (ESI$^+$) calculated for [$C_{15}H_{22}O_3$+Na]$^+$ 273.1461, found 273.1464, (Δ -1.0 ppm).

(±)2-(Methoxymethyl)-1-(4-methoxyphenyl)-5-methylhexan-1-one, 220c



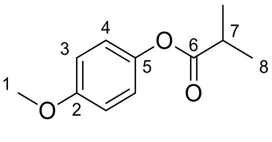
1-(4-Methoxyphenyl)-5-methylhexan-1-one (**220**, 66.0 mg, 0.300 mmol), Ir(cod)Cl]$_2$ (4.0 mg, 0.0060 mmol), KOH (50.0mg, 0.893 mmol), cataCXium® A (8.4 mg, 0.024 mmol), MeOH (3.0 mL) were subjected to general procedure **D** for 48 h. Purification by FCC (Petrol/Et$_2$O 8:2) afforded **220c** (52.2 mg, 0.200 mmol, 66%) as a colorless oil. IR ν_{max} (cm^{-1}) 2955, 1671, 1599, 1255, 1170, 834, 760; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.90 (d, *J* = 9.0 Hz, 2H, C(4)*H*×2), 6.87 (d, *J* = 9.0 Hz, 2H, C(3)*H*×2), 3.79 (s, 3H, C(1)*H*$_3$), 3.65-3.55 (m, 2H, C(7)*H*, C(8)*H*H), 3.44-3.38 (m, 1H, C(8)H*H*), 3.21 (s, 3H, C(9)*H*$_3$), 1.68-1.55 (m, 1H, C(10)*H*H), 1.52-1.37 (m, 2H, C(10)H*H*, C(12)*H*), 1.09-1.03 (m, 2H, C(11)*H*$_2$), 0.76 (d, *J* = 4.4 Hz, 3H, C(13)*H*$_3$), 0.74 (d, *J* = 4.4 Hz, 3H, C(14)*H*$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 201.5 (*C*(8)O), 163.5 (*C*(5)), 130.7 (*C*(2)), 130.6 (*C*(4)H×2, 113.7 (*C*(3)H×2), 74.5 (*C*(8)H$_2$), 59.1 (*C*(9)H$_3$), 55.4 (*C*(1)H$_3$), 46.5 (*C*(7)H), 36.5 (*C*(11)H$_2$), 28.2 (*C*(12)H), 27.8 (*C*(10)H$_2$), 22.4 (*C*(13)H$_3$, *C*(14)H$_3$); HRMS (ESI$^+$) calculated for [$C_{16}H_{24}O_3$+Na]$^+$ 287.1618, found 287.1617, (Δ 0.4 ppm).

(±)3-Methoxy-2-(4-methoxybenzyl)-1-(4-methoxyphenyl)propan-1-one, 235c



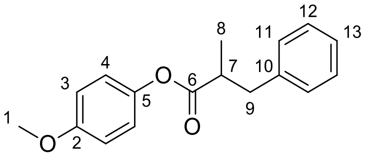
1,3-Bis(4-methoxyphenyl)propan-1-one (**235**, 81.0 mg, 0.300 mmol), [Ir(cod)Cl]$_2$ (4.0 mg, 0.0060 mmol), KOH (50.0mg, 0.893 mmol), cataCXium® A (8.4 mg, 0.024 mmol), MeOH (3.0 mL) were subjected to general procedure **D** for 48 h. Purification by FCC (Petrol/Et$_2$O 7:3) afforded **235c** (67.2 mg, 0.214 mmol, 71%) as a colorless oil. IR ν_{max} (cm^{-1}) 2932, 2837, 1669, 1245, 840, 818; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.89 (d, *J* = 8.8 Hz, 2H, C(4)$\underline{H}$×2), 7.08 (d, *J* = 8.6 Hz, 2H, C(12)$\underline{H}$×2), 6.89 (d, *J* = 9.0 Hz, 2H, C(3)$\underline{H}$×2), 6.77 (d, *J* = 8.6 Hz, 2H, C(13)$\underline{H}$×2), 3.97-3.90 (m, 1H, C(7)$\underline{H}$), 3.84 (s, 3H, C(1)$\underline{H}_3$), 3.75 (s, 3H, C(15)$\underline{H}_3$), 3.70 (dd, *J* = 8.8, 7.6 Hz, 1H, C(8)$\underline{H}$H), 3.51-3.48 (m, 1H, C(8)H$\underline{H}$), 3.28 (s, 3H, C(9)$\underline{H}_3$), 3.00 (dd, *J* = 13.8, 7.5, 1H, C(10)$\underline{H}$H), 2.81 (dd, *J* = 13.8, 6.7, 1H, C(10)H$\underline{H}$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 200.6 ($\underline{C}$(6)O), 163.4 ($\underline{C}$(5)), 158.1 ($\underline{C}$(11)), 131.3 ($\underline{C}$(2)), 130.7 ($\underline{C}$(4)H×2), 130.5 ($\underline{C}$(14)), 130.0 ($\underline{C}$(12)H×2), 113.8 ($\underline{C}$(3)H×2), 113.7 ($\underline{C}$(13)H×2), 73.6 ($\underline{C}$(8)H$_2$), 59.1 ($\underline{C}$(9)H$_3$), 55.4, 55.2 ($\underline{C}$(1)H$_3$, $\underline{C}$(15)H$_3$), 48.5 ($\underline{C}$(7)H), 34.7 ($\underline{C}$(10)H$_2$); HRMS (ESI$^+$) calculated for [$C_{19}H_{22}O_4$+H]$^+$ 315.1591, found 315.1585, (Δ -1.8 ppm).

4-Methoxyphenyl isobutyrate, 226



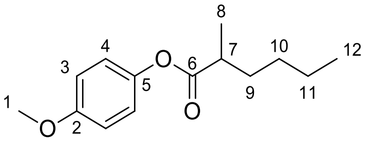
1-(4-Methoxyphenyl)-2-methylpropan-1-one (**161a**, 18.1 mg, 0.102 mmol), mCPBA (70.2 mg, 0.41 mmol), trifluoroacetic acid (16 µL, 0.20 mmol) were dissolved in CH$_2$Cl$_2$, (2 mL) and stirred at rt for 24 h. The organic phase was washed with sat. aq. NaHCO$_3$ (3 x 10mL), extracted with CH$_2$Cl$_2$, dried over Na$_2$SO$_4$, filtered, and the solvent removed *in vacuo*. Purification by FCC (Petrol/Et$_2$O 9:1) afforded **226** as a colourless oil (19.4 mg, 0.10 mmol, 98% yield). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.91 (d, *J* = 8.0 Hz, 2H, C(4)H×2), 6.81 (d, *J* = 8.0 Hz, 2H, C(3)H×2), 3.72 (s, 3H, C(1)H_3), 2.71 (sept, *J* = 7.0 Hz, 1H, C(7)H), 1.23 (d, *J* = 6.8 Hz, 6H, C(8)H_3×2); **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.0 ($\underline{C}$(6)O), 157.1 (*C*(5)), 144.4 ($\underline{C}$(2)), 122.2 ($\underline{C}$(4)H×2), 114.4 ($\underline{C}$(3)H×2), 55.6 ($\underline{C}$(1)H_3), 34.1 ($\underline{C}$(7)H), 19.0 ($\underline{C}$(8)H_3×2). Spectroscopic data were consistent with those previously reported.[71]

(±)4-Methoxyphenyl 2-methyl-3-phenylpropanoate, 228



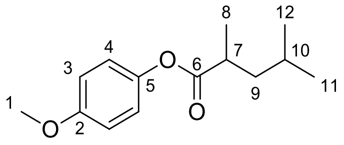
1-(4-Methoxyphenyl)-2-methyl-3-phenylpropan-1-one (**217a**, 30.0 mg, 0.120 mmol), mCPBA (80.0 mg, 0.480 mmol), trifluoroacetic acid (19 µL, 0.24 mmol) and CH_2Cl_2, (2.4 mL) were subjected to general procedure **E**. Purification by FCC (Petrol/Et_2O 20:1) afforded **228** as a colourless oil (29.5 mg, 0.110 mmol, 92 %). IR ν_{max} (cm^{-1}) 3063, 3028, 2973, 2935, 2837, 1751, 1606, 1597, 1505, 1455, 1248, 1192, 1137; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27-7.20 (m, 2H), 7.19-7.14 (m, 3H), 6.79-6.72 (m, 4H), 3.70 (s, 3H, C(1)$\underline{H}_3$), 3.04 (dd, *J* = 13.3, 7.6 Hz, 1H, C(9)$\underline{H}$H), 2.90 (app sext, *J* = 7.0 Hz, 1H, C(7)$\underline{H}$), 2.75 (dd, *J* =13.3, 7.2 Hz, 1H, C(9)H$\underline{H}$), 1.24 (d, *J* = 6.9 Hz, 3H, C(8)$\underline{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.9, 157.1, 144.1, 139.0, 129.1, 128.4, 126.5, 122.2, 144.3, 55.5 ($\underline{C}$(1)H_3), 41.6 ($\underline{C}$(9)H_2), 39.8 ($\underline{C}$(7)H), 16.9 ($\underline{C}$(8)H_3); HRMS (ESI$^+$) calculated for $[C_{17}H_{18}O_3+Na]^+$ 293.1148, found 293.1149.

(±)4-Methoxyphenyl 2-methylhexanoate, 229



1-(4-Methoxyphenyl)-2-methylhexan-1-one (**218a**, 50.0 mg, 0.227 mmol), mCPBA (157 mg, 0.909 mmol), trifluoroacetic acid (35 μL, 0.454 mmol) and CH_2Cl_2, (1.2 mL) were subjected to general procedure **E**. Purification by FCC (Petrol/Et_2O 10:1) afforded **229** as a colourless oil (46.8 mg, 0.198 mmol, 87%). IR ν_{max} (cm^{-1}) 2935, 1754, 1506, 1195, 819, 746; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 9.0 Hz, 2H, C(4)*H*×2), 6.89 (d, *J* = 9.0 Hz, 2H, C(3)*H*×2), 3.81 (s, 3H, C(1)H_3), 2.67 (app sext, *J* = 7.0 Hz, 1H, C(7)*H*), 1.85-1.75 (m, 1H, C(9)*H*H), 1.61-1.50 (m, 1H, C(9)H*H*), 1.48-1.30 (m, 4H, C(10)H_2, C(11)H_2), 1.29 (d, *J* = 6.9 Hz, 3H, C(8)H_3), 0.94 (t, *J* = 7.1 Hz, 3H, C(12)H_3); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8 (*C*(6)O), 157.1 (*C*(5)), 144.4 (*C*(2)), 122.3 (*C*(4)H×2), 114.4 (*C*(3)H×2), 55.6 (*C*(1)H_3), 39.6 (*C*(7)H), 33.5 (*C*(9)H_2), 29.4, 22.6 (*C*(10)H_2, *C*(11)H_2), 17.1 (*C*(8)H_3), 14.0 (*C*(12)H_3); HRMS (ESI^+) calculated for $[C_{14}H_{20}O_3+Na]^+$ 259.1305, found 259.1316, (Δ -4.5 ppm).

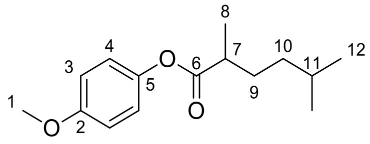
(±)4-Methoxyphenyl 2,4-dimethylpentanoate, 230



1-(4-Methoxyphenyl)-2,4-dimethylpentan-1-one (**219a**, 30 mg, 0.135 mmol), mCPBA (93.2 mg, 0.540 mmol), trifluoroacetic acid (21 μL, 0.270 mmol) and CH_2Cl_2, (2.4 mL) were subjected to general procedure **E**. Purification by FCC (Petrol/Et_2O 10:1) afforded **230** as a colourless oil (28.5 mg, 0.120 mmol, 89%). IR ν_{max} (cm^{-1}) 2957, 1752, 1505, 1194, 815, 757; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 9.0 Hz, 2H, C(4)*H*×2), 6.89 (d, *J* = 9.0 Hz, 2H, C(3)*H*×2), 3.81 (s, 3H, C(1)H_3), 2.75 (app sext, *J* = 7.1 Hz, 1H, C(7)*H*), 1.80-1.68 (m, 2H, C(9)*H*H, C(10)*H*), 1.40-1.34 (m, 1H, C(9)H*H*), 1.28 (d, *J* = 7.1 Hz, 3H, C(8)H_3), 0.98 (d, *J* = 6.5Hz, 3H, C(11)H_3), 0.95 (d, *J* 6.3 Hz, 3H, C(12)H_3) ; ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0 (*C*(6)O), 157.1 (*C*(5)), 144.3 (*C*(2)), 122.3 (*C*(4)H×2), 114.4 (*C*(3)H×2), 55.6 (*C*(1)H_3), 43.0

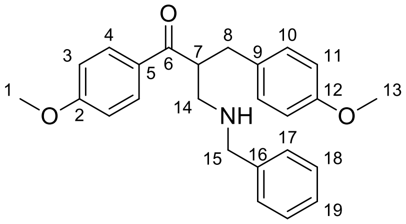
($\underline{C}$(7)H), 37.7 ($\underline{C}$(9)H$_2$), 26.0 ($\underline{C}$(10)H), 22.5, 22. 5 ($\underline{C}$(11)H$_3$, $\underline{C}$(12)H$_3$), 17.5 ($\underline{C}$(8)H$_3$); HRMS (ESI$^+$) calculated for [$C_{14}H_{20}O_3$+Na]$^+$ 259.1305, found 259.1314, (Δ -3.4 ppm).

(±)4-Methoxyphenyl 2,5-dimethylhexanoate, 231



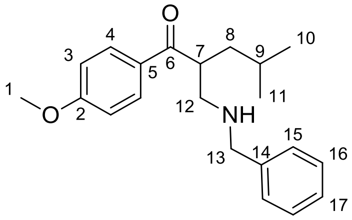
1-(4-Methoxyphenyl)-2,5-dimethylhexan-1-one (**220a**, 30 mg, 0.128 mmol), mCPBA (88.5 mg, 0.510 mmol), trifluoroacetic acid (20 µL, 0.256 mmol) and CH_2Cl_2, (2.3 mL) were subjected to general procedure **E**. Purification by FCC (Petrol/Et_2O 10:1) afforded **231** as a colourless oil (28.7 mg, 0.115 mmol, 90%). IR ν_{max} (cm^{-1}) 2955, 1754, 1506, 1195, 827, 816, 739; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 9.0Hz, 2H, C(4)$\underline{\mathit{H}}$×2), 6.89 (d, *J* = 9.1Hz, 2H, C(3)$\underline{\mathit{H}}$×2), 3.81 (s, 3H, C(1)$\underline{\mathit{H}}_3$), 2.64 (app sext, *J* = 7.0 Hz, 1H, C(7)$\underline{\mathit{H}}$), 1.82-1.76 (m, 1H, C(7)$\underline{\mathit{H}}$H), 1.62-1.52 (m, 2H, C(9)H$\underline{\mathit{H}}$, C(11)$\underline{\mathit{H}}$), 1.30-1.24 (m, 2H, C(10)$\underline{\mathit{H}}_2$), 1.29 (d, *J* = 6.9 Hz, 3H, C(8)$\underline{\mathit{H}}_3$), 0.93 (d, *J* = 6.6 Hz, 6H, C(12)$\underline{\mathit{H}}_3$×2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8 ($\underline{C}$(6)O), 157.1 ($\underline{C}$(5)), 144.4 ($\underline{C}$(2)), 122.3 ($\underline{C}$(4)H×2), 114.4 ($\underline{C}$(3)H×2), 55.6 ($\underline{C}$(1)H$_3$), 39.8, 36.4, 31.6, 28.0, 22.6 ($\underline{C}$(12)H$_3$×2), 17.1 ($\underline{C}$(8)H$_3$); HRMS (ESI$^+$) calculated for [$C_{15}H_{22}$-O_3+Na]$^+$ 273.1461, found 273.1464, (Δ -0.9 ppm).

(±)3-(Benzylamino)-2-(4-methoxybenzyl)-1-(4-methoxyphenyl)propan-1-one, 240



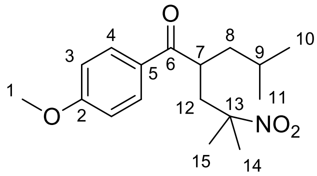
Under an open atmosphere, [Ir(cod)Cl]$_2$ (4.0 mg, 0.0060 mmol), KOH (50.0 mg, 0.900 mmol) and cataCXium® A (8.4 mg, 0.024 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (3 mL) and 1,3-bis(4-methoxyphenyl)propan-1-one (**235**, 81.0 mg, 0.300 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 48 h before SiliaMet S® DMT (77.0 mg, 0.0480 mmol) was added. The mixture was stirred at rt open to air for 1 h before $BnNH_2$ (0.16 mL, 1.5 mmol) and KOH (33.6 mg, 0.600 mmol) were added. The vial was sealed and heated at 65 ˚C for 24 h. Crude mixture was diluted with Et_2O, filtered through SiO_2, concentrated *in vacuo*. Purification by FCC (toluene/Et_2O 1.5:1, then toluene/Et_2O/TEA 1.5:1:0.01) afforded **240** as a light yellow oil (69.9 mg, 0.180 mmol, 60%). IR ν_{max} (cm^{-1}) 2934, 2836, 1667, 1599, 1511, 1245, 1170, 1031; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.76 (m, 2 H, C(4)$\underline{H}$×2), 7.23- 7.16 (m, 2 H), 7.15-7.10 (m, 3 H), 7.01-6.95 (m, 2 H, C(11)$\underline{H}$×2), 6.83-6.78 (m, 2 H, C(3)$\underline{H}$×2), 6.70-6.66 (m, 2 H, C(10)$\underline{H}$×2), 3.84-3.77 (m, 1 H, C(7)$\underline{H}$), 3.76 (s, 3 H, C(1)$\underline{H}_3$), 3.66 (s, 3 H, C(13)$\underline{H}_3$), 3.63 (s, 2 H, C(15)$\underline{H}_2$) 2.84 - 3.02 (m, 2 H, C(8)$\underline{H}$H, C(14)$\underline{H}$H), 2.62 - 2.76 (m, 2 H, C(8)H$\underline{H}$, C(14)H$\underline{H}$), 1.67 (br s, 1 H, N$\underline{H}$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 201.7 ($\underline{C}$(6)O), 163.5 ($\underline{C}$(5)), 158.1 ($\underline{C}$(9)), 140.1 ($\underline{C}$(16)), 131.5 ($\underline{C}$(12)), 130.7 ($\underline{C}$(4)H×2), 130.2 ($\underline{C}$(2)), 130.0 ($\underline{C}$(11)H×2), 128.4, 128.1, 126.9 ($\underline{C}$(17)H×2, $\underline{C}$(18)H×2, $\underline{C}$(19)H), 113.8, 113.8 ($\underline{C}$(3)H×2, $\underline{C}$(10)H×2), 55.5, 55.2 ($\underline{C}$(1)H_3, $\underline{C}$(13)H_3), 54.1 ($\underline{C}$(15)H_2), 50.8, 36.1 ($\underline{C}$(8)H_2, $\underline{C}$(14)H_2), 48.7 ($\underline{C}$(7)H); HRMS (ESI$^+$) calculated for $[C_{25}H_{27}NO_3+H]^+$ 390.2064, found 390.2065, (Δ -0.2 ppm).

(±)2-((Benzylamino)methyl)-1-(4-methoxyphenyl)-4-methylpentan-1-one, 238



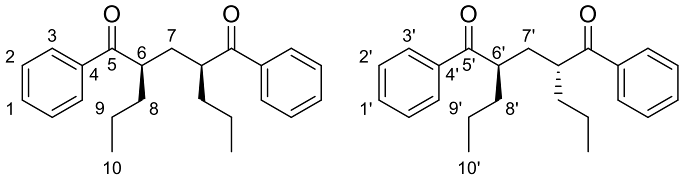
Under an open atmosphere, [Ir(cod)Cl]$_2$ (4.0 mg, 0.0060 mmol), KOH (50.0 mg, 0.900 mmol) and cataCXium® A (8.4 mg, 0.024 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (3 mL) and 1-(4-Methoxyphenyl)-4-methylpentan-1-one (**219**, 61.8 mg, 0.300 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O$_2$ was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 48 h and concentrated *in vacuo*. The mixture was redissolved in THF (1.5 mL) and BnNH$_2$ (0.16 mL, 1.5 mmol) and KOH (33.6 mg, 0.600 mmol) were added. The vial was sealed and heated at 65 ˚C for 12 h. Crude mixture was diluted with Et$_2$O, filtered through SiO$_2$, concentrated *in vacuo*. Purification by FCC (Petrol/Et$_2$O 4:1, then Petrol/Et$_2$O/TEA 4:1:0.01) afforded **238** as a yellow oil (31.0 mg, 0.0954 mmol, 32%). IR ν_{max} (cm^{-1}) 2954, 2906, 2850, 1668, 1599, 1249, 1170, 734, 698; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.90-7.88 (m, 2H, C(4)$\underline{H}$×2), 7.23-7.14 (m, 5H, C(15)$\underline{H}$×2, C(16)$\underline{H}$×2, C(17)*H*), 6.87-6.85 (m, 2H, C(3)$\underline{H}$×2), 3.79 (s, C(1)$\underline{H}_3$), 3.69 (s, 2H, C(13)$\underline{H}_2$), 3.68-3.63 (m, 1H, C(7)$\underline{H}$), 2.95 (dd, *J* = 11.8, 8.2 Hz, 1H, C(12)$\underline{H}$H), 2.65 (dd, *J* = 11.7, 4.8 Hz, C(12)H$\underline{H}$), 1.62-1.40 (m, 3H, C(8)$\underline{H}$H, C(9)$\underline{H}$, N$\underline{H}$), 1.29-1.26 (m, 1H, C(8)H$\underline{H}$), 0.83 (d, *J* = 6.5 Hz, 3H, C(10)$\underline{H}_3$), 0.79 (d, *J* = 6.5 Hz, 3H, C(11)$\underline{H}_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 206.2 ($\underline{C}$(6)O), 163.5 ($\underline{C}$(5)), 140.3 ($\underline{C}$(14)), 130.6 ($\underline{C}$(4)H×2), 130.4 ($\underline{C}$(2)), 128.4, 128.0, 126.9 ($\underline{C}$(15)H×2, $\underline{C}$(16)H×2, $\underline{C}$(17)H), 113.8 ($\underline{C}$(3)H×2), 55.5 ($\underline{C}$(1)H$_3$), 54.1 ($\underline{C}$(13)H$_2$), 51.6 ($\underline{C}$(12)H$_2$), 44.5 ($\underline{C}$(7)H), 40.3 ($\underline{C}$(8)H$_2$), 26.1 ($\underline{C}$(9)H), 22.9, 22.7 ($\underline{C}$(10)H$_3$, $\underline{C}$(11)H$_3$); HRMS (ESI$^+$) calculated for [C$_{21}$H$_{27}$NO$_2$+H]$^+$ 326.2115, found 326.2118, (Δ -1.2 ppm).

(±)2-*iso*Butyl-1-(4-methoxyphenyl)-4-methyl-4-nitropentan-1-one, 237



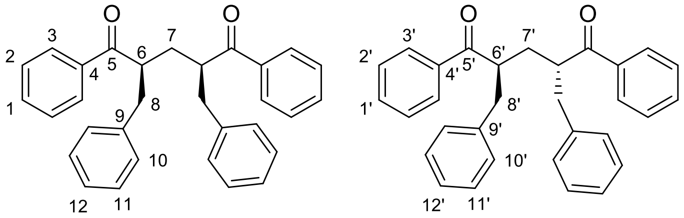
Under an open atmosphere, $[Ir(cod)Cl]_2$ (4.0 mg, 0.0060 mmol), KOH (50.0 mg, 0.900 mmol) and cataCXium® A (8.4 mg, 0.024 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (3 mL) and 1-(4-methoxyphenyl)-4-methylpentan-1-one (**219**, 61.8 mg, 0.300 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 48 h before diluted with Et_2O, filtered through SiO_2, and concentrated *in vacuo*. The mixture was redissolved in MeOH (1.5 mL) and 2-nitropropane (54 µL, 0.60 mmol) and KOH (33.6 mg, 0.600 mmol) were added. The vial was sealed and heated at 65 ˚C for 24 h, and another 2 equiv. of 2-nitropropane (54 µL, 0.60 mmol) was added and heated at 65 ˚C for another 72 h. Crude mixture was diluted with Et_2O, filtered through SiO_2, concentrated *in vacuo*. Purification by FCC (Petrol/Et_2O 9:1) afforded **237** as a colourless oil (63.5 mg, 0.207 mmol, 69%). IR ν_{max} (cm^{-1}) 2958, 2870, 1672, 1599, 1535, 1259, 1170, 843, 828; ^1H NMR (400 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H, C(4)$\underline{H}$×2), 6.96-6.94 (m, 2H, C(3)$\underline{H}$C2), 3.86 (s, 3H, C(1)$\underline{H}_3$), 3.42-3.36 (m, 1H, C(7)$\underline{H}$), 2.63 (dd, *J* = 14.3, 9.7 Hz, 1H, C(12)$\underline{H}$H), 2.19 (d, *J* = 14.7 Hz, 1H, C(12)H$\underline{H}$), 1.70-1.58 (m, 1H, C(9)$\underline{H}$), 1.57 (s, 3H, C(14)$\underline{H}_3$), 1.34 (s, 3H, C(15)$\underline{H}_3$), 1.36-1.20 (m, 2H, C(8)$\underline{H}$H, C(8)H$\underline{H}$), 0.89 (d, *J* = 6.6 Hz, 3H, C(10)$\underline{H}_3$), 0.85 (d, *J* = 6.6 Hz, 3H, C(11)$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.1 ($\underline{C}$(6)O), 163.8 ($\underline{C}$(5)), 130.6 ($\underline{C}$(4)H×2), 129.1 ($\underline{C}$(2)), 114.1 ($\underline{C}$(3)H×2), 88.4 ($\underline{C}$(13)), 55.5 ($\underline{C}(1)H_3$), 43.5 ($\underline{C}(8)H_2$), 41.2 ($\underline{C}(12)H_2$), 39.5 ($\underline{C}$(7)H), 28.2, 25.6 ($\underline{C}(14)H_3$, $\underline{C}(15)H_3$), 24.6 ($\underline{C}$(9)H), 23.3, 21.9 ($\underline{C}(10)H_3$, $\underline{C}(11)H_3$); HRMS (ESI^+) calculated for $[C_{17}H_{25}NO_4+Na]^+$ 330.1676, found 330.1679, (Δ -0.9 ppm).

(±)(2*RR*,4*RS*)-1,5-Diphenyl-2,4-dipropylpentane-1,5-dione, 157d



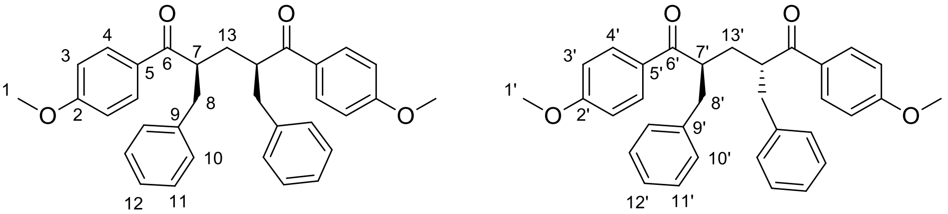
Under an open atmosphere, $[Ir(cod)Cl]_2$ (3.3 mg, 0.0050 mmol), Cs_2CO_3 (1.63 g, 5 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (5 mL) and valerophenone (166 μL, 1 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 °C for 72 h. The reaction was quenched by diluting with diethyl ether and filtering through a pad of silica gel. Purification by FCC afforded product as colourless oil (125 mg, 0.371 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.92 (m, 4H, C(3)$\underline{H}$×4), 7.62-7.60 (m, 4H, C(3')$\underline{H}$×4), 7.52-7.48 (m, 2H, C(1)$\underline{H}$×2), 7.44-7.40 (m, 4H, C(2)$\underline{H}$×4), 7.36-7.33 (m, 2H, C(1')$\underline{H}$×2), 7.21-7.17 (m, 4H, C(2')$\underline{H}$×4), 3.48-3.41 (m, 2H, C(6)$\underline{H}$×2), 3.41-3.26 (m, 2H, C(6')$\underline{H}$×2), 2.21 (dt, J = 14.0, 7.1 Hz, 1H, C(7)$\underline{H}$H), 1.99 (dd, J = 7.8, 6.4 Hz, 2H, C(7')$\underline{H}_2$), 1.70-1.54 (m, 5H, C(7)H$\underline{H}$, C(8)$\underline{H}$H×2, C(8')$\underline{H}$H×2), 1.40-1.06 (m, 12H, C(8)H$\underline{H}$×2, C(8')H$\underline{H}$×2, C(9)$\underline{H}_2$×2, C(9')$\underline{H}_2$×2), 0.77 (t, J = 7.3 Hz, 6H, C(10')$\underline{H}_3$×2), 0.71 (t, J = 7.2 Hz, 6H, C(10)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9 ($\underline{C}$(5')O×2), 203.9 ($\underline{C}$(5)O×2), 137.4 ($\underline{C}$(4')×2), 137.2 ($\underline{C}$(4)×2), 133.0 ($\underline{C}$(1)H×2), 132.8 ($\underline{C}$(1')H×2), 128.7 ($\underline{C}$(2)H×4), 128.5 ($\underline{C}$(2')H×4), 128.3 ($\underline{C}$(3)H×4), 128.0 ($\underline{C}$(3')H×4), 43.7 ($\underline{C}$(6')H×2), 43.4 ($\underline{C}$(6)H×2), 36.2 ($\underline{C}$(8)H_2×2), 36.2 ($\underline{C}$(8')H_2×2), 34.4 ($\underline{C}$(7')H_2), 34.0 ($\underline{C}$(7)H_2), 20.5 ($\underline{C}$(9')H_2×2), 20.4 ($\underline{C}$(9)H_2×2), 14.1 ($\underline{C}$(10')H_3×2), 14.1 ($\underline{C}$(10)H_3×2). Spectroscopic data are consistent with those previously reported. [135]

(±)(2*RS*,4*SS*)-2,4-Dibenzyl-1,5-diphenylpentane-1,5-dione, 13d



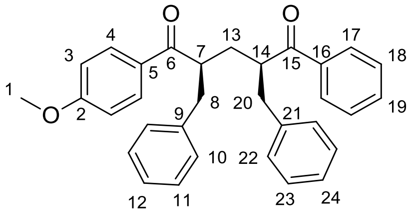
Under an open atmosphere, [Ir(cod)Cl]$_2$ (1.0 mg, 0.0015 mmol), Cs_2CO_3 (489 mg, 1.50 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (1.5 mL) and 3-phenylpropiophenone (66 mg, 0.3 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 °C for 48 h. The reaction was quenched by diluting with diethyl ether and filtering through a pad of silica gel. Purification by FCC afforded product as yellow oil (52.4 mg, 0.121 mmol, 81%). IR ν_{max} (cm^{-1}) 3062, 3027, 2923, 2855, 1677, 1447, 1181, 697; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 7.9 Hz, 4H), 7.58-7.55 (m, 6H), 7.48-7.44 (m, 4H), 7.39-7.35 (m, 2H), 7.23-7.09 (m, 20H), 7.00 (d, *J* = 7.3 Hz, 4H), 3.84-3.70 (m, 4H, C(6)$\underline{H}$×2, C(6')$\underline{H}$ ×2), 3.09-3.00 (m, 4H, C(8)$\underline{H}$H×2, C(8')$\underline{H}$H×2), 2.76-2.63 (m, 4H, C(8)H$\underline{H}$×2, C(8')H$\underline{H}$×2), 2.42 (dt, *J* = 14.0, 7.0 Hz, 1H, C(7)$\underline{H}$H), 2.15 (t, *J* = 7.0 Hz, 2H, C(7')$\underline{H}_2$), 1.76 (dt, *J* = 13.8, 6.8 Hz, 1H, C(7)H$\underline{H}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.9, 203.1, 139.3, 138.9, 137.2, 136.8, 133.2, 132.9, 129.0, 129.0, 128.7, 128.5, 128.4, 128.4, 128.4, 128.0, 126.4, 126.3, 46.0 ($\underline{C}$(6)H×2), 45.7 ($\underline{C}$(6')H×2), 39.8 ($\underline{C}$(8')H$_2$), 38.4 ($\underline{C}$(8)H$_2$), 34.6 ($\underline{C}$(7')H$_2$), 34.3 ($\underline{C}$(7)H$_2$); HRMS (ESI$^+$) calculated for $[C_{31}H_{28}O_2+H]^+$ 433.2162, found 433.2154, (Δ -1.8 ppm).

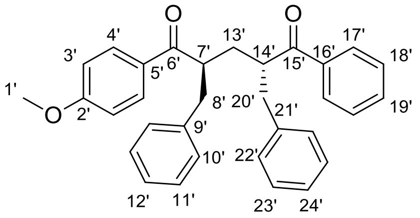
(±)(2*RS*,4*SS*)-2,4-Dibenzyl-1,5-bis(4-methoxyphenyl)pentane-1,5-dione, 217d



Under an open atmosphere, [Ir(cod)Cl]$_2$ (2.0 mg, 0.0030 mmol), Cs_2CO_3 (489 mg, 1.50 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by “wet” methanol (0.75 mL) and 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**, 72.1 mg, 0.300 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted *via* a needle through the septum. The reaction was heated to 65 °C for 48 h. The reaction was quenched by dilution with diethyl ether and filtering, first through a cotton filter and then through a pad of silica gel. Purification by FCC (Petrol/Et_2O 8:2) afforded **217d** (61.0 mg, 83%) as a yellow oil. IR ν_{max} (cm^{-1}) 2933, 2839, 1667, 1598, 1510, 1246, 1170, 1030, 836, 749, 700; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.7, 4H, C(4)*H*×4), 7.50 (d, *J* = 8.8, 4H, C(4’)*H*×4), 7.21-7.07 (m, 16H), 6.99 (d, *J* = 7.1, 4H), 6.92 (d, *J* = 9.0, 4H, C(3)*H*×4), 6.61 (d, *J* = 8.6, 4H, C(3’)*H*×4), 3.86 (s, 6H, C(1)*H*$_3$×2), 3.74 (s, 6H, C(1’)*H*$_3$×2), 3.76-3.71 (m, 2H, C(7)*H*×2), 3.67-3.60 (m, 2H, C(7’)*H*×2), 3.06-2.96 (m, 4H, C(8)*H*H×2, C(8’)*H*H×2), 2.74-2.62 (m, 4H, C(8)H*H*×2, C(8’)H*H*×2), 2.41-2.35 (m, 1H, C(13)*H*H), 2.12 (t, *J* = 7.1, 2H, C(13’)*H*$_2$), 1.75-1.69 (m, 1H, C(13)H*H*); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.4 (*C*(6)O), 201.6 (*C*(6’)O), 163.6 163.2, 139.6, 139.2, 130.8(*C*(4)H×4), 130.4(*C*(4’)H×4),, 130.4, 129.9, 129.0, 129.0, 128.5, 128.4, 126.3, 126.7, 113.9 (*C*(3)H×4), 113.5 (*C*(3’)H×4), 55.6 (*C*(1)H$_3$), 55.3 (*C*(1’)H$_3$), 45.6 (*C*(7)H×2), 45.2 (*C*(7’)H×2), 40.2, 38.5 (*C*(8)H$_2$×2, *C*(8’)H$_2$×2), 35.5 (*C*(13’)H$_2$), 34.8 (*C*(13)H$_2$); HRMS (ESI$^+$) calculated for $[C_{33}H_{32}O_4+H]^+$ 493.2373, found 493.2367 (Δ –1.3 ppm).

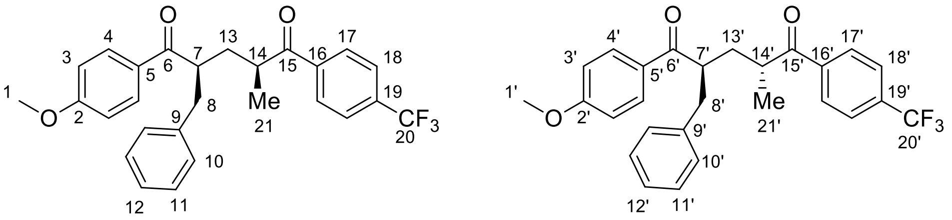
(±)(2*SS*,4*RS*)-2,4-Dibenzyl-1-(4-methoxyphenyl)-5-phenylpentane-1,5-dione, 242





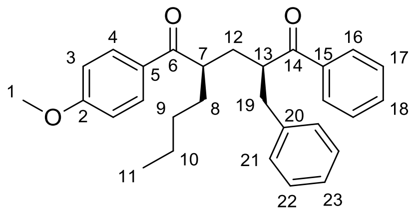
Under an open atmosphere, $[Ir(cod)Cl]_2$ (13.3 mg, 0.0200 mmol), KOH (167 mg, 3 mmol) and cataCXium® A (28.0 mg, 0.0800 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (10 mL) and 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**, 240.0 mg, 1 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 48 h before concentrated to 0.4 M and SiliaMet S® DMT (257 mg, 0.16 mmol) was added. The mixture was stirred at rt open to air for 1 h before 3-phenylpropiophenone (630 mg, 3 mmol) and KOH (167 mg, 3 mmol) were added. The vial was sealed and heated at 65 ˚C under O_2 for 24 h and another 1 equiv. KOH was added (56 mg, 1 mmol), heated for another 18 h. Crude mixture was diluted with Et_2O, filtered through SiO_2, concentrated *in vacuo*. Purification by FCC (Petrol/Et_2O 8:2) afforded **242** as a light yellow oil (333 mg, 0.721 mmol, 72%). IR ν_{max} (cm^{-1}) 3061, 3027, 2923, 2851, 2361, 2341, 1674, 1599, 1259, 1245, 1171, 699; ^1H NMR (500 MHz, $CDCl_3$) δ 7.90-7.87 (m, 4H), 7.58-7.51 (m, 5H), 7.46-7.43 (m, 2H), 7.39-7.35 (m, 1H), 7.22-7.08 (m, 18H), 7.01-6.99 (m, 4H), 6.94-6.92 (m, 2H), 6.64-6.63 (m, 2H), 3.87 (s, 3H), 3.84-3.66 (m, 4H, C(7)*H*, C(7')*H*, C(14)*H*, C(14')*H*), 3.74 (s, 3H), 3.07-2.98 (m, 4H, C(8)*H*H, C(8')*H*H, C(20)*H*H, C(20')*H*H), 2.75-2.63 (m, 4H, C(8)H*H*, C(8')H*H*, C(20)H*H*, C(20')H*H*), 2.43-2.38 (m, 1H, C(13)*H*H), 2.15-2.12 (m, 2H, C(13')$\underline{H}_2$), 1.77-1.72 (m, 1H, C(13)H*H*); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.9, 202.3 (C(6')O, C(15')O), 203.2, 201.5 (C(6)O, C(15)O), 163.6, 163.3, 139.5, 139.3, 139.1, 138.8, 137.2, 136.8, 133.1, 132.7, 130.7, 130.4, 129.8, 129.0, 128.9, 128.9, 128.7, 128.5, 128.4, 128.4, 128.4, 128.4, 128.3, 128.0, 126.4, 126.3, 126.3, 113.9, 113.5, 55.5, 55.4, 46.0, 45.6, 45.5, 45.2 ($\underline{C}$(7)H, $\underline{C}$(7’)H, $\underline{C}$(14)H, $\underline{C}$(14’)H), 39.9, 39.9 ($\underline{C}$(8’)H_2, $\underline{C}$(20’)H_2), 38.5, 38.3 ($\underline{C}$(8)H_2, $\underline{C}$(20)H_2), 34.9, 34.5 ($\underline{C}$(13)H_2, $\underline{C}$(13’)H_2) (3 carbon peaks were not observed due to overlapping); HRMS (ESI^+) calculated for $[C_{32}H_{30}O_3+H]^+$ 463.2268, found 463.2260 (Δ –1.6 ppm).

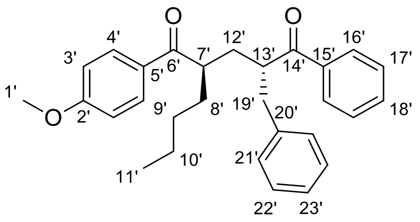
(±)(2*SS*,4*RS*)-2-Benzyl-1-(4-methoxyphenyl)-4-methyl-5-(4-(trifluoromethyl)phenyl)pentane-1,5-dione, 248



Under an open atmosphere, $[Ir(cod)Cl]_2$ (13.3 mg, 0.0200 mmol), KOH (167 mg, 3 mmol) and cataCXium® A (28.0 mg, 0.0800 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by “wet” methanol (10 mL) and 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**, 240.0 mg, 1 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 48 h before concentrated to 0.4 M and SiliaMet S® DMT (257 mg, 0.16 mmol) was added. The mixture was stirred at rt open to air for 1 h before 1-(4-(trifluoromethyl)phenyl)propan-1-one (607 mg, 3 mmol) and KOH (167 mg, 3 mmol) were added. The vial was sealed and heated at 65 ˚C under O_2 for 24 h. Crude mixture was diluted with Et_2O, filtered through SiO_2, concentrated *in vacuo*. Purification by FCC (Petrol/Et_2O 8:2) afforded **248** as a light yellow oil (217 mg, 0.478 mmol, 48%). IR ν_{max} (cm^{-1}) 2969, 2935, 1810, 1896, 1324, 1168, 1128, 1067; ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.0 Hz, 2 H), 8.00 - 7.94 (m, 2 H), 7.78 - 7.67 (m, 4 H), 7.63 - 7.56 (m, 2 H), 7.53 (d, *J* = 8.2 Hz, 2 H), 7.25 - 7.03 (m, 10 H), 6.98 - 6.90 (m, 2 H), 6.68 - 6.57 (m, 2 H), 3.88 (s, 3H), 3.94 - 3.84 (m, 1 H, C(7)$\underline{H}$), 3.80-3.72 (m, 1H, C(7’)$\underline{H}$), 3.71 (s, 3H), 3.49 - 3.31 (m, 2 H, C(14)$\underline{H}$, C(14')$\underline{H}$), 3.11-3.07 (m, 2 H, C(8)$\underline{H}$H, C(8')$\underline{H}$H), 2.78 (dd, *J* = 6.5, 13.6 Hz, 1 H, C(8')H$\underline{H}$), 2.67 (dd, *J* = 7.6, 13.8 Hz, 1 H, C(8)H$\underline{H}$), 2.42 (ddd, *J* = 5.7, 8.6, 13.9 Hz, 1 H, C(13)$\underline{H}$H), 2.17 (ddd, *J* = 4.1, 10.0, 13.6 Hz, 1 H, C(13')$\underline{H}$H), 2.04 - 1.92 (m, 1 H, C(13')H$\underline{H}$), 1.57 (ddd, *J* = 5.3, 8.4, 13.7 Hz, 1 H, C(13)H$\underline{H}$), 1.14 (d, *J* = 6.9 Hz, 3 H, C(21')$\underline{H}_3$), 1.09 (d, *J* = 6.8 Hz, 3 H, C(21)$\underline{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.1, 202.7, 202.7, 201.6, 163.8, 163.5, 139.2, 139.2, 139.0, 138.7, 134.3 (q, *J* = 31.5 Hz), 134.1 (q, *J* = 32.8 Hz), 130.8, 130.4, 129.9, 129.0, 128.9, 128.6, 128.5, 128.4, 126.5, 126.4, 125.7 (q, *J* = 3.8 Hz), 125.4 (q, *J* = 3.8 Hz), 123.7 (q, *J* = 272.2 Hz), 123.6 (q, *J* = 272.2 Hz), 114.0, 113.7, 55.6, 55.3, 45.2, 45.2 (C(7)H, C(7')H), 39.8 (C(8')H_2), 39.4 (C(8)H_2), 38.9, 38.8 (C(14)H, C(14')H), 36.5 (C(13')H), 35.4 (C(13)H_2), 19.1 (C(21')H_3), 16.5 (C(21)H_3) (2 carbon peaks were not observed due to overlapping); ^{19}F NMR (377 MHz, $CDCl_3$) δ -63.08, -63.14; HRMS (ESI$^+$) calculated for $[C_{27}H_{25}O_3F_3+H]^+$ 455.1829, found 455.1823 (Δ –1.3 ppm).

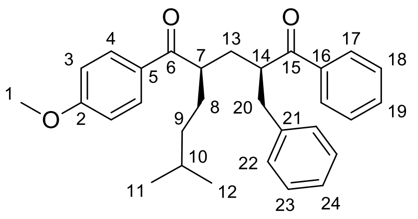
(±)(2*SS*,4*RS*)-2-Benzyl-4-butyl-5-(4-methoxyphenyl)-1-phenylpentane-1,5-dione, 244

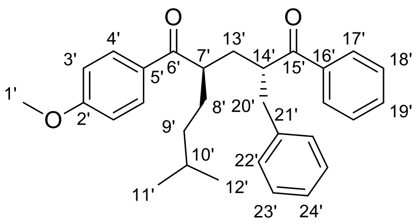




Under an open atmosphere, [Ir(cod)Cl]$_2$ (13.3 mg, 0.0200 mmol), KOH (167 mg, 3 mmol) and cataCXium® A (28.0 mg, 0.0800 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (10 mL) and 1-(4-methoxyphenyl)hexan-1-one (**218**, 206 mg, 1 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 48 h before concentrated to 0.4 M and SiliaMet S® DMT (257 mg, 0.16 mmol) was added. The mixture was stirred at rt open to air for 1 h before 3-phenylpropiophenone (630 mg, 3 mmol) and KOH (167 mg, 3 mmol) were added. The vial was sealed and heated at 65 ˚C under O_2 for 24 h and another 2 equiv. KOH (111 mg, 2 mmol) was added, heated for another 22 h. Crude mixture was diluted with Et_2O, filtered through SiO_2, concentrated *in vacuo*. Purification by FCC (Petrol/Et_2O 9:1) afforded **244** as a light yellow oil (227 mg, 0.530 mmol, 53%). IR ν_{max} (cm^{-1}) 3062, 3027, 2956, 2930, 2858, 1671, 1598, 1256, 1239, 1169, 698; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 - 7.91 (m, 2 H), 7.63 (d, *J* = 8.8 Hz, 2 H), 7.58 (d, *J* = 7.3 Hz, 2 H), 7.55 - 7.51 (m, 1 H), 7.47 - 7.42 (m, 1 H), 7.39 - 7.34 (m, 1 H), 7.22 - 7.17 (m, 4 H), 7.16 - 7.06 (m, 5 H), 7.03 (d, *J* = 6.9 Hz, 2 H), 6.97 (d, *J* = 8.8 Hz, 2 H), 6.70 (d, *J* = 8.8 Hz, 2 H), 3.88 (s, 3 H), 3.85 - 3.77 (m, 1 H, C(7)$\underline{H}$), 3.77 (s, 3H), 3.75 - 3.65 (m, 1 H, C(7')$\underline{H}$), 3.52 - 3.44 (m, 1 H, C(13)$\underline{H}$), 3.31 (dd, *J* = 5.4, 9.1 Hz, 1 H, C(13')$\underline{H}$), 3.11 (dd, *J* = 7.9, 13.6 Hz, 1 H, C(19)$\underline{H}$H), 3.03 (dd, *J* = 7.7, 13.7 Hz, 1 H, C(19')$\underline{H}$H), 2.81 - 2.69 (m, 2 H, C(19)H$\underline{H}$, C(19')H$\underline{H}$), 2.34 (td, *J* = 7.0, 14.1 Hz, 1 H, C(12)$\underline{H}$H), 2.09 (td, *J* = 4.5, 9.3 Hz, 2 H, C(12')$\underline{H}_2$), 1.74 - 1.58 (m, 3 H, C(12)H$\underline{H}$, C(8)$\underline{H}$H, C(8')$\underline{H}$H), 1.48 - 1.35 (m, 2 H, C(8)H$\underline{H}$, C(8')H$\underline{H}$), 1.30 - 1.06 (m, 8 H, C(9)$\underline{H}_2$, C(10)$\underline{H}_2$, C(9')$\underline{H}_2$, C(10)$\underline{H}_2$), 0.82 (t, *J* = 6.8 Hz, 3 H, C(11')$\underline{H}_3$), 0.77 (t, *J* = 7.1 Hz, 3 H, C(11)$\underline{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 203.7, 203.3, 202.6, 164.0, 163.7, 139.9, 139.4, 137.8, 137.4, 133.5, 133.2, 131.1, 130.8, 130.7, 130.6, 129.4, 129.3, 129.1, 129.0, 128.8, 128.8, 128.7, 128.5, 126.7, 126.6, 114.3, 114.0, 55.9, 55.8, 46.4 ($\underline{C}$(7)H), 46.1 ($\underline{C}$(7')H), 43.8 ($\underline{C}$(13')H), 43.6 ($\underline{C}$(13)H), 40.5 ($\underline{C}$(19')H_2), 38.5 ($\underline{C}$(19)H_2), 35.3 ($\underline{C}$(12')H_2), 35.0 ($\underline{C}$(12)H_2), 34.2, 32.7 ($\underline{C}$(8)H_2, $\underline{C}$(8')H_2), 29.9, 29.9, 23.2, 23.2 ($\underline{C}$(9)H_2, $\underline{C}$(9')H_2, $\underline{C}$(10)H_2, $\underline{C}$(10')H_2), 14.3, 14.3 ($\underline{C}$(11)H_3, $\underline{C}$(11')H_3); HRMS (ESI$^+$) calculated for $[C_{29}H_{32}O_3+H]^+$ 429.2424, found 429.2416 (Δ –1.9 ppm).

(±)(2*SS*,4*RS*)-2-Benzyl-4-isopentyl-5-(4-methoxyphenyl)-1-phenylpentane-1,5-dione, 243

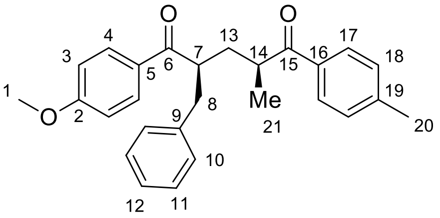


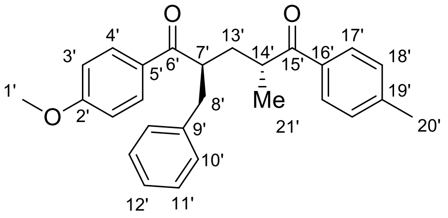


Under an open atmosphere, [Ir(cod)Cl]$_2$ (13.3 mg, 0.0200 mmol), KOH (167 mg, 3 mmol) and cataCXium® A (28.0 mg, 0.0800 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (10 mL) and 1-(4-methoxyphenyl)-5-methylhexan-1-one (**220**, 220 mg, 1 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O$_2$ was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 48 h before concentrated to 0.4 M and SiliaMet S® DMT (257 mg, 0.16 mmol) was added. The mixture was stirred at rt open to air for 1 h before 3-phenylpropiophenone (630 mg, 3 mmol) and KOH (167 mg, 3 mmol) were added. The vial was sealed and heated at 65 ˚C under O$_2$ for 24 h and another 2 equiv. KOH (111 mg, 2 mmol) was added, heated for another 22 h. Crude mixture was diluted with Et$_2$O, filtered through SiO$_2$, concentrated *in vacuo*. Purification by FCC (Petrol/Et$_2$O 9:1) afforded **243** as a light yellow oil (268 mg, 0.606 mmol, 61%). IR ν_{max} (cm^{-1}) 3062, 3027, 2954, 2868, 1671, 1598, 1258, 1240, 1169, 698; ^{1}H NMR (500MHz ,CDCl$_3$) δ 7.96 - 7.92 (m, 4 H), 7.63 (d, *J* = 8.8 Hz, 1 H), 7.59 - 7.51 (m, 3 H), 7.47 - 7.42 (m, 3 H), 7.22 - 7.17 (m, 3 H), 7.16 - 7.06 (m, 6 H), 7.03 (d, *J* = 7.3 Hz, 3 H), 6.97 (d, *J* = 8.8 Hz, 3 H), 6.70 (d, *J* = 8.8 Hz, 2 H), 3.89 (s, 3 H, C(1)*H*$_3$), 3.84 – 3.79 (m, 1 H, C(7)*H*), 3.78 (s, 3 H, C(1')*H*$_3$), 3.74 – 3.68 (m, 1 H, C(7')*H*), 3.50 - 3.44 (m, 1 H, C(14)*H*), 3.31 - 3.24 (m, 1 H, C(14')*H*), 3.10 (dd, *J* = 7.9, 13.9 Hz, 1 H, C(8)*H*H), 3.03 (dd, *J* = 7.6, 13.6 Hz, 1 H, C(8')*H*H), 2.81 - 2.68 (m, 2 H, C(8)H*H*, C(8')H*H*), 2.39 - 2.27 (m, 1 H, C(13)*H*H), 2.14 - 2.03 (m, 2 H, C(13')*H*$_2$), 1.76 - 1.58 (m, 3 H, C(13)H*H*, C(20)*H*H, C(20')H*H*), 1.48 - 1.33 (m, 4 H, C(10)*H*, C(10')*H*, C(20)H*H*, C(20')H*H*), 1.19 - 0.95 (m, 4 H, C(9)H$_2$, C(9')H$_2$,), 0.80 (dd, *J* = 6.8, 9.0 Hz, 6 H, C(11')*H*$_3$, C(12')*H*$_3$), 0.75

(dd, *J* = 6.9, 8.2 Hz, 6 H, C(11)$\underline{H}_3$, C(12)$\underline{H}_3$); ^{13}C NMR (126MHz , $CDCl_3$) δ 204.8, 203.8, 203.4, 202.6 ($\underline{C}$(6)O, $\underline{C}$(6’)O, $\underline{C}$(15)O, $\underline{C}$(15’)O), 164.0, 163.7, 139.9, 139.3, 137.8, 137.4, 133.5, 133.2, 131.1, 130.8, 130.7, 130.6, 129.4, 129.3, 129.1, 128.8, 128.8, 128.8, 128.5, 126.7, 126.6, 114.3, 114.0, 55.9, 55.8 ($\underline{C}$(7)H, $\underline{C}$(7’)H), 46.4, 46.1 ($\underline{C}$(14)H, $\underline{C}$(14’)H), 44.0, 43.9 ($\underline{C}$(8)H_2, $\underline{C}$(8’)H_2), 40.5, 38.5 ($\underline{C}$(13)H_2, $\underline{C}$(13’)H_2), 36.9, 36.8 ($\underline{C}$(9)H_2, $\underline{C}$(9’)H_2), 35.3, 35.1 ($\underline{C}$(20)H_2, $\underline{C}$(20’)H_2), 32.4, 30.7 ($\underline{C}$(10)H, $\underline{C}$(10’)H), 28.6, 28.5 , 22.8, 22.8 ($\underline{C}$(11)H_3, $\underline{C}$(11’)H_3, $\underline{C}$(12)H_3, $\underline{C}$(12’)H_3). (One aromatic carbon was not observed due to overlapping); HRMS (ESI$^+$) calculated for $[C_{30}H_{34}O_3+H]^+$ 443.2581, found 443.2571 (Δ –2.1 ppm).

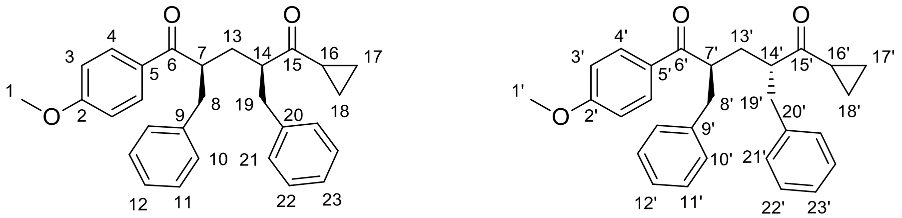
(±)(2*SS*,4*RS*)-2-Benzyl-1-(4-methoxyphenyl)-4-methyl-5-(p-tolyl)pentane-1,5-dione, 247





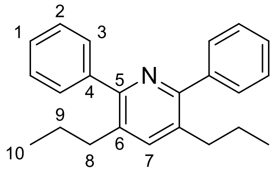
Under an open atmosphere, $[Ir(cod)Cl]_2$ (13.3 mg, 0.0200 mmol), KOH (167 mg, 3 mmol) and cataCXium® A (28.0 mg, 0.0800 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by “wet” methanol (10 mL) and 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**, 240.0 mg, 1 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 48 h before concentrated to 0.4 M and SiliaMet S® DMT (257 mg, 0.16 mmol) was added. The mixture was stirred at rt open to air for 1 h before 4’-methylpropiophenone (630 mg, 3 mmol) and KOH (167 mg, 3 mmol) were added. The vial was sealed and heated at 65 ˚C under O_2 for 24 h, and another 1 equiv. KOH (56.0 mg, 1 mmol) was added, heated for another 18 h. Crude mixture was diluted with Et_2O, filtered through SiO_2, concentrated *in vacuo*. Purification by FCC (Petrol/Et_2O 8:2) afforded **247** as a light yellow oil (210mg, 0.524 mmol, 52%). IR ν_{max} (cm^{-1}) 3028, 2967, 2932, 2840, 1672, 1598, 1244, 1169, 746, 699; ^{1}H NMR (500MHz ,CDCl$_3$) δ 7.99 (d, *J* = 8.8 Hz, 2 H), 7.88 (d, *J* = 8.2 Hz, 2 H), 7.63 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 8.2 Hz, 2 H), 7.30 - 7.25 (m, 2 H), 7.23 - 7.06 (m, 12 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.66 - 6.61 (m, 2 H), 3.89 - 3.75 (m, 2 H, C(7)*H*, C(7')*H*), 3.82 (s, 3H), 3.69 (s, 3 H), 3.58 - 3.46 (m, 1 H, C(14)*H*), 3.42 - 3.33 (m, 1 H, C(14')*H*), 3.10 (ddd, *J* = 5.4, 7.7, 13.4 Hz, 2 H, C(8)*H*H, C(8')*H*H), 2.81 (dd, *J* = 6.3, 13.6 Hz, 1 H, C(8')H*H*), 2.72 (dd, *J* = 6.6, 13.6 Hz, 1 H, C(8)H*H*), 2.46 - 2.37 (m, 1 H, C(13)*H*H), 2.41 (s, 3H), 2.32 (s, 3 H), 2.19 (ddd, *J* = 4.3, 9.9, 13.6 Hz, 1 H, C(13')*H*H), 1.96 (ddd, *J* = 4.3, 9.9, 13.6 Hz, 1 H, C(13')H*H*), 1.60 (td, *J* = 7.0, 13.7 Hz, 1 H, C(13)H*H*), 1.13 (d, *J* = 7.3 Hz, 3 H, C(20')*H*$_3$), 1.10 (d, *J* = 6.9 Hz, 3 H, C(20)*H*$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 204.0, 203.8, 203.2, 202.0, 164.0, 163.8, 144.3, 143.9, 139.9, 139.8, 134.3, 134.1, 131.1, 130.9, 130.8, 130.4, 129.8, 129.6, 129.4, 129.3, 129.0, 128.8, 128.8, 128.7, 126.7, 114.3, 114.0, 55.9, 55.7 (*C*(1)H$_3$, *C*(1')H$_3$), 45.8, 45.7 (*C*(7)H, *C*(7')H), 40.2, 39.2 (*C*(8)H$_2$, *C*(8')H$_2$), 38.8, 38.6 (*C*(14)H, *C*(14')H), 37.0, 36.5 (*C*(13)H$_2$, *C*(13')H$_2$), 22.1, 21.9 (*C*(20)H$_3$, *C*(20')H$_3$), 19.8, 17.7 (*C*(21)H$_3$, *C*(21')H$_3$); HRMS (ESI$^+$) calculated for $[C_{27}H_{28}O_3+H]^+$ 401.2111, found 401.2094 (Δ –4.3 ppm).

(±)(2*RS*,4*SS*)-2,4-Dibenzyl-1-cyclopropyl-5-(4-methoxyphenyl)pentane-1,5-dione, 245



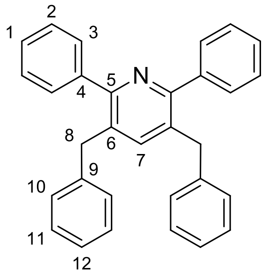
Under an open atmosphere, [Ir(cod)Cl]$_2$ (13.3 mg, 0.0200 mmol), KOH (167 mg, 3 mmol) and cataCXium® A (28.0 mg, 0.0800 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol (10 mL) and 1-(4-methoxyphenyl)-3-phenylpropan-1-one (**217**, 240.0 mg, 1 mmol). The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O$_2$ was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 48 h before concentrated to 0.4 M and SiliaMet S® DMT (257 mg, 0.16 mmol) was added. The mixture was stirred at rt open to air for 1 h before 1-cyclopropyl-3-phenylpropan-1-one (**164**, 523 mg, 3 mmol) and KOH (167 mg, 3 mmol) were added. The vial was sealed and heated at 65 ˚C under O_2 for 21 h, and another 2 equiv. KOH (112.0 mg, 1 mmol) was added, heated for another 24 h. Crude mixture was diluted with Et_2O, filtered through SiO_2, concentrated *in vacuo*. Purification by FCC (Petrol/Et_2O 8:2) afforded **247** as a light yellow oil (290 mg, 0.681 mmol, 68%). IR ν_{max} (cm^{-1}) 3062, 3027, 2934, 2841, 1598, 1259, 1169, 699; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8.8 Hz, 2 H), 7.84 (d, *J* = 9.0 Hz, 2 H), 7.30 - 7.10 (m, 18 H), 7.06 - 7.02 (m, 2 H), 6.92 (d, *J* = 8.8 Hz, 2 H), 6.88 (d, *J* = 8.8 Hz, 2 H), 3.86 - 3.82 (m, 3 H), 3.81 - 3.77 (m, 3 H), 3.77 - 3.64 (m, 2 H), 3.14 - 2.87 (m, 6 H), 2.80 - 2.69 (m, 3 H), 2.63 (dd, *J* = 6.7, 13.5 Hz, 1 H), 2.36 (td, *J* = 7.1, 14.1 Hz, 1 H, C(13')$\underline{H}$H), 2.14 - 2.05 (m, 1 H, C(13)$\underline{H}$H), 2.04 - 1.96 (m, 1 H, C(13)H$\underline{H}$), 1.94 - 1.84 (m, 1 H, cyclopropyl C$\underline{H}$), 1.67 (td, *J* = 6.6, 13.8 Hz, 1 H, C(13')H$\underline{H}$), 1.57 - 1.48 (m, 1 H, cyclopropyl C$\underline{H}$), 1.07 - 0.92 (m, 2 H, 2×cyclopropyl C$\underline{H}$H), 0.91 - 0.79 (m, 3 H, 3×cyclopropyl C$\underline{H}$H), 0.79 - 0.71 (m, 1 H, cyclopropyl C$\underline{H}$H), 0.65 - 0.51 (m, 2 H, 2×cyclopropyl C$\underline{H}$H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 213.7, 213.1, 202.0, 201.4 ($\underline{C}$(6)O, $\underline{C}$(6')O, $\underline{C}$(15)O, $\underline{C}$(15')O), 163.6, 163.5, 139.6, 139.4, 139.2, 138.9, 130.7, 130.6, 130.5, 129.8, 129.0, 129.0, 129.0, 128.5, 128.4, 128.4, 126.4, 126.3, 113.9, 113.8, 55.5, 55.4 ($\underline{C}$(1)H_3), $\underline{C}$(1')H_3), 52.8, 52.6, 45.7, 45.3 ($\underline{C}$(7)H, $\underline{C}$(7')H, $\underline{C}$(14)H, $\underline{C}$(14')H), 39.9, 39.3, 38.3, 38.1, 33.8, 33.7 ($\underline{C}$(8)H_2, $\underline{C}$(8')H_2, $\underline{C}$(13)H_2, $\underline{C}$(13')H_2, $\underline{C}$(19')H_2, $\underline{C}$(19)H_2), 20.9, 20.7 ($\underline{C}$(16)H, $\underline{C}$(16')H), 11.7, 11.5, 11.5, 11.5 ($\underline{C}$(17)H_2, $\underline{C}$(17')H_2, $\underline{C}$(18)H_2, $\underline{C}$(18')H_2) (4 aromatic carbons were not observed due to overlapping); HRMS (ESI$^+$) calculated for $[C_{29}H_{30}O_3+H]^+$ 427.2268, found 427.2259 (Δ –2.1 ppm).

2,6-Diphenyl-3,5-dipropylpyridine, 261



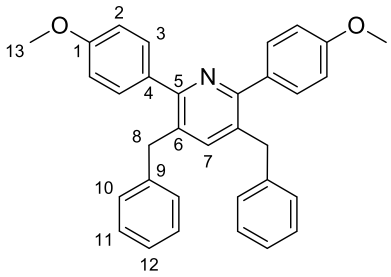
(±)(2*RR*,4*RS*)-1,5-Diphenyl-2,4-dipropylpentane-1,5-dione (**157d**, 30.0 mg, 0.0892 mmol), hydroxylamine hydrochloride (18.6 mg, 0.267 mmol) were subjected to general procedure F. Purification by FCC (toluene/Et_2O 20:1) afforded **261** as a white solid (25.6 mg, 0.0810 mmol, 91%). Melting point = 135-136 °C; ν_{max} (thin film)/cm^{-1} 2963, 2922, 2866, 1441, 755, 702; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 - 7.49 (m, 5 H, C(3)$\underline{H}$×4, C(7)$\underline{H}$), 7.45 - 7.39 (m, 4 H, C(2)$\underline{H}$×4), 7.39 - 7.33 (m, 2 H, C(1)$\underline{H}$×2), 2.73 - 2.60 (m, 4 H, C(8)$\underline{H}_2$×2), 1.68 - 1.53 (m, 4 H, C(9)$\underline{H}_2$×2), 0.91 (t, *J* = 7.3 Hz, 6 H, C(10)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.8 ($\underline{C}$(6)×2), 140.9, 138.7 ($\underline{C}$(7)H), 133.8, 129.2 ($\underline{C}$(3)H×4), 128.0 ($\underline{C}$(2)H×4), 127.5 ($\underline{C}$(1)H×2), 34.2 ($\underline{C}$(8)H_2×2), 24.2 ($\underline{C}$(9)H_2×2), 14.1 ($\underline{C}$(10)H_3×2); HRMS (ESI^+) calculated for $[C_{23}H_{25}N+H]^+$ 316.2060, found 316.2051 (Δ –2.6 ppm).

3,5-Dibenzyl-2,6-diphenylpyridine, 260



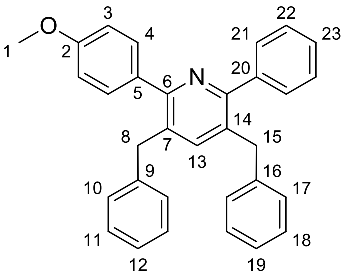
(±)(2*RS*,4*SS*)-2,4-Dibenzyl-1,5-diphenylpentane-1,5-dione (**13d,** 30 mg, 0.0693 mmol), hydroxylamine hydrochloride (14.5 mg, 0.208 mmol) were subjected to general procedure F. Purification by FCC (Petrol/Et_2O 8:2) afforded **260** as a white solid (27.3 mg, 0.0663 mmol, 96%). Melting point = 126-127 °C; ν_{max} (thin film)/cm^{-1} 2923, 1601, 1547, 1493, 696; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.40 (m, 4 H, C(3)$\underline{H}$×4), 7.33 - 7.24 (m, 7 H, C(7)$\underline{H}$, C(11)$\underline{H}_2$×2, C(12)$\underline{H}$×2), 7.19 - 7.13 (m, 4 H, C(2)$\underline{H}$×4), 7.12 - 7.07 (m, 2 H, C(1)$\underline{H}$×2), 6.91 (d, *J* = 7.3 Hz, 4 H, C(10)$\underline{H}_2$×2), 3.95 (s, 4 H, C(8)$\underline{H}_2$×2); ^{13}C NMR (126MHz ,CDCl$_3$) δ = 156.7 ($\underline{C}$(6)×2), 141.0 ($\underline{C}$(7)H), 140.5, 140.3 (C(4)×2, C(5)×2), 132.3 ($\underline{C}$(9)×2), 129.3 ($\underline{C}$(3)H×4), 128.8 ($\underline{C}$(10)H×4), 128.5 ($\underline{C}$(2)H×4), 128.1, 127.9 ($\underline{C}$(11)H×4, $\underline{C}$(12)H×2), 126.2 ($\underline{C}$(1)H×2), 38.2 ($\underline{C}$(8)H$_2$×2); HRMS (ESI$^+$) calculated for [$C_{31}H_{25}N$+H]$^+$ 412.2060, found 412.2052 (Δ –1.88 ppm).

3,5-Dibenzyl-2,6-bis(4-methoxyphenyl)pyridine, 259



(±)(2*RS*,4*SS*)-2,4-dibenzyl-1,5-bis(4-methoxyphenyl)pentane-1,5-dione (**217d**, 30 mg, 0.0609 mmol), hydroxylamine hydrochloride (12.7 mg, 0.183 mmol) were subjected to general procedure F. Purification by FCC (toluene/Et$_2$O 15:1) afforded **259** as an oily solid (23.2 mg, 0.0492 mmol, 81%). ν$_{max}$ (thin film)/cm^{-1} 3015, 2970, 1609, 1511, 1434, 1294, 1175, 1031, 839; ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.48 (d, *J* = 8.6 Hz, 4H, C(3)$\underline{H}$×4), 7.34 (s, 1H, C(7)$\underline{H}$), 7.25 (t, *J* = 7.7 Hz, 4H, C(11)$\underline{H}$×4), 7.18 (t, *J* = 6.8 Hz, 2H, C(12)$\underline{H}$×2), 7.02 (d, *J* = 7.6, 4H, C(10)$\underline{H}$×2), 6.93 (d, *J* = 8.6, 4H, C(2)$\underline{H}$×4), 4.04 (s, 4H, C(8)$\underline{H}_2$×2), 3.83 (s, 6H, C(13)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, CDCl$_3$) δ 159.6, 156.3, 141.4, 140.8, 132.9, 131.9, 130.7, 128.8, 128.6, 126.2, 113.6, 55.4 ($\underline{C}$(13)H$_3$×2), 38.4 ($\underline{C}$(8)H$_2$×2); HRMS (ESI$^+$) Calculated for [$C_{33}H_{29}NO_2$+H]$^+$ 472.2271, found 472.2264 (Δ –1.6 ppm).

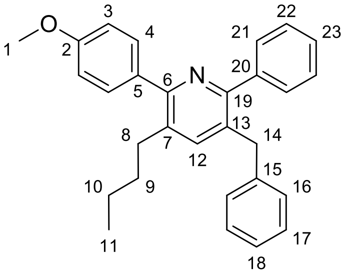
3,5-Dibenzyl-2-(4-methoxyphenyl)-6-phenylpyridine, 253



Procedure F: (±)(2*SS*,4*RS*)-2,4-Dibenzyl-1-(4-methoxyphenyl)-5-phenylpentane-1,5-dione (**242**, 30 mg, 0.0649 mmol), hydroxylamine hydrochloride (13.6 mg, 0.0974 mmol) were subjected to general procedure F. Purification by FCC (Petrol/Et_2O 8:2) afforded **253** as a colorless oil (26.9 mg, 0.0609 mmol, 94%).

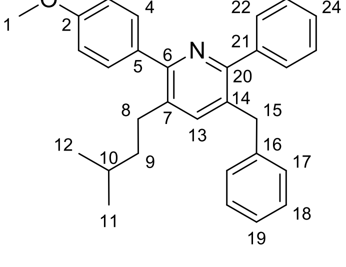
Procedure G: (±)(2SS,4RS)-2,4-Dibenzyl-1-(4-methoxyphenyl)-5-phenylpentane-1,5-dione (**242**, 30 mg, 0.0649 mmol), ammonium acetate (15.0 mg, 0.195 mmol), copper (II) acetate monohydrate (32.4, 0.162 mmol) were subjected to general procedure G for 24 h. Purification by FCC (Petrol/Et_2O 8:2) afforded **253** as a colourless oil (26.0 mg, 0.0588 mmol, 91%). ν_{max} (thin film)/cm^{-1} 3060, 3026, 2932, 2836, 1609, 1434, 1248, 1175, 728, 699; ^1H NMR (500MHz , $CDCl_3$) δ 7.42 (d, *J* = 7.6 Hz, 2 H), 7.38 (d, *J* = 7.9 Hz, 2 H, C(4)H×2), 7.33 - 7.24 (m, 4 H), 7.15 (q, *J* = 8.0 Hz, 4 H), 7.12 - 7.08 (m, 2 H), 6.93 (d, *J* = 7.6 Hz, 2 H), 6.90 (d, *J* = 7.4 Hz, 2 H), 6.83 (d, *J* = 8.4 Hz, 2 H, C(3)H×2), 3.96 (s, 2 H), 3.93 (s, 2 H), 3.74 (s, 3 H, C(1)H_3); ^{13}C NMR (126MHz , $CDCl_3$) δ 159.5, 156.5, 156.3, 141.2, 140.6, 140.2, 132.7, 140.5, 132.2, 132.0, 130.6, 129.3, 128.8, 128.8, 128.5, 128.5, 128.1, 127.9, 126.2, 126.2, 113.6, 55.4, 38.3, 38.2; HRMS (ESI$^+$) calculated for $[C_{32}H_{27}NO+H]^+$ 442.2165, found 442.2157 (Δ –1.97ppm).

3-Benzyl-5-butyl-6-(4-methoxyphenyl)-2-phenylpyridine, 254



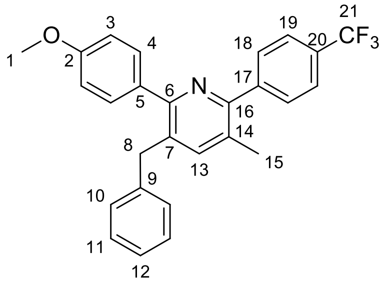
(±)(2*SS*,4*RS*)-2-Benzyl-4-butyl-5-(4-methoxyphenyl)-1-phenylpentane-1,5-dione (**244**, 30 mg, 0.0701 mmol), hydroxylamine hydrochloride (14.6 mg, 0.210 mmol) were subjected to general procedure F. Purification by FCC (toluene/Et_2O 15:1) afforded **254** as a yellow oil (25.8 mg, 0.0632 mmol, 90%). ν_{max} (thin film)/cm^{-1} 2956, 2929, 1610, 1494, 1434, 1247, 1174, 699; ^1H NMR (500MHz , $CDCl_3$) δ 7.44 - 7.38 (m, 4 H), 7.32 (s, 1 H, C(12)$\underline{H}$), 7.31 - 7.23 (m, 3 H), 7.22 - 7.16 (m, 2 H), 7.15 - 7.07 (m, 1 H), 6.98 (dd, *J* = 0.9, 7.8 Hz, 2 H), 6.89 - 6.85 (m, 2 H), 3.97 (s, 2 H, C(14)$\underline{H}_2$), 3.76 (s, 3 H, C(1)$\underline{H}_3$), 2.62 - 2.52 (m, 2 H, C(8)$\underline{H}_2$), 1.46 - 1.37 (m, 2 H, C(9)$\underline{H}_2$), 1.18 (m, 2 H, C(10)$\underline{H}_2$), 0.75 (t, *J* = 7.3 Hz, 3 H, C(11)$\underline{H}_3$); ^{13}C NMR (126MHz , $CDCl_3$) δ 158.2, 155.0, 154.9, 139.7, 139.5, 138.7, 133.2, 132.3, 130.6, 129.4, 128.2, 127.8, 127.4, 127.0, 126.7, 125.1, 112.4, 54.3 ($\underline{C}$(1)H_3), 37.1 ($\underline{C}$(14)H_2), 32.1 ($\underline{C}$(8)H_2), 30.8 ($\underline{C}$(9)H_2), 21.4 ($\underline{C}$(10)H_2), 12.8 ($\underline{C}$(11)H_3); HRMS (ESI$^+$) calculated for $[C_{29}H_{29}NO+H]^+$ 408.2322, found 408.2311 (Δ –2.57 ppm).

3-Benzyl-5-isopentyl-6-(4-methoxyphenyl)-2-phenylpyridine, 255



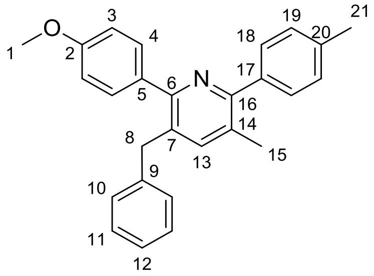
(±)(2*SS*,4*RS*)-2-Benzyl-4-isopentyl-5-(4-methoxyphenyl)-1-phenylpentane-1,5-dione (**243**, 30 mg, 0.0671 mmol), hydroxylamine hydrochloride (7.1 mg, 0.102 mmol) were subjected to general procedure F. Purification by FCC (toluene/Et$_2$O 20:1) afforded **255** as a colourless oil (26.9 mg, 0.0637 mmol, 94%). ν_{max} (thin film)/cm^{-1} 2955, 2931, 1576, 1512, 1435, 1248, 1174, 722, 699; ^{1}H NMR (500MHz , CDCl$_3$) δ 7.46 - 7.37 (m, 4 H), 7.32 (s, 1 H, C(13)<u>*H*</u>), 7.31 - 7.23 (m, 3 H), 7.22 - 7.18 (m, 2 H), 7.15 - 7.09 (m, 1 H), 6.98 (dd, *J* = 0.9, 8.0 Hz, 2 H), 6.91 - 6.83 (m, 2 H), 3.97 (s, 2 H, C(15)<u>*H*</u>$_2$), 3.76 (s, 3 H, C(1)<u>*H*</u>$_3$), 2.63 - 2.52 (m, 2 H, C(8)<u>*H*</u>$_2$), 1.44 - 1.36 (m, 1 H, C(10)<u>*H*</u>), 1.34 - 1.28 (m, 2 H, C(9)<u>*H*</u>$_2$), 0.73 (d, *J* = 6.5 Hz, 6 H, C(11)<u>*H*</u>$_3$×2); ^{13}C NMR (126MHz , CDCl$_3$) δ 159.3, 156.1, 156.0, 140.8, 140.5, 139.8, 134.5, 133.3, 131.7, 130.4, 129.3, 128.8, 128.5, 128.1, 127.7, 126.1, 113.5, 55.4 (<u>*C*</u>(1)H$_3$), 40.3 (<u>*C*</u>(9)H$_2$), 38.2 (<u>*C*</u>(15)H$_2$), 30.1 (<u>*C*</u>(8)H$_2$), 27.9 (<u>*C*</u>(10)H), 22.4 (<u>*C*</u>(11)H$_3$×2); HRMS (ESI$^+$) calculated for $[C_{30}H_{31}NO+H]^+$ 422.2478, found 422.2462 (Δ –3.85 ppm).

3-Benzyl-2-(4-methoxyphenyl)-5-methyl-6-(4-(trifluoromethyl)phenyl)pyridine, 258



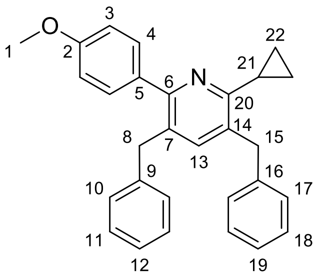
(±)(2*SS*,4*RS*)-2-Benzyl-1-(4-methoxyphenyl)-4-methyl-5-(4-(trifluoromethyl)phenyl)pentane-1,5-dione (**248**, 30 mg, 0.0660 mmol), hydroxylamine hydrochloride (13.8 mg, 0.198 mmol) were subjected to general procedure F. Purification by FCC (toluene/Et$_2$O 20:1) afforded **258** as a colourless oil (26.1 mg, 0.0601 mmol, 91%). ν_{max} (thin film)/cm^{-1} 2920, 2834, 1610, 1511, 1324, 1248, 1165, 1123, 1068, 1027, 839; ^{1}H NMR (400MHz , CDCl$_3$) δ 7.79 - 7.65 (m, 4 H), 7.50 - 7.44 (m, 2 H), 7.41 (s, 1 H), 7.35 - 7.28 (m, 2 H), 7.26 - 7.20 (m, 1 H), 7.14 - 7.06 (m, 2 H), 7.00 - 6.91 (m, 2 H), 4.09 (s, 2 H, C(8)<u>*H*</u>$_2$), 3.85 (s, 3 H, C(1)<u>*H*</u>$_3$), 2.34 (s, 3H, C(15)<u>*H*</u>$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 159.5, 156.2, 154.6, 144.2, 141.2, 140.5, 132.8, 132.7, 130.5, 129.8 (q, *J* = 32.8 Hz, <u>*C*</u>(20)), 129.6, 129.1, 128.9, 128.6, 126.3, 125.1 (q, *J* = 3.8 Hz, <u>*C*</u>(19)H×2), 124.3 (q, *J* = 272.2 Hz, <u>*C*</u>(21)F$_3$), 113.7, 55.4 (<u>*C*</u>(1)H$_3$), 38.2 (<u>*C*</u>(8)H$_2$), 19.6 (<u>*C*</u>(15)H$_3$); ^{19}F NMR (377 MHz, CDCl$_3$) δ -62.58; HRMS (ESI$^+$) calculated for $[C_{27}H_{22}NOF_3+H]^+$ 434.1726, found 434.1719 (Δ –1.66 ppm).

3-Benzyl-2-(4-methoxyphenyl)-5-methyl-6-(p-tolyl)pyridine, 257



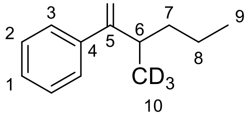
(±)(2*SS*,4*RS*)-2-Benzyl-1-(4-methoxyphenyl)-4-methyl-5-(p-tolyl)pentane-1,5-dione (**247**, 30 mg, 0.0749 mmol), hydroxylamine hydrochloride (15.6 mg, 0.225 mmol) were subjected to general procedure F. Purification by FCC (toluene/Et$_2$O 20:1) afforded **257** as a yellow oil (27.6 mg, 0.0728 mmol, 97%). ν_{max} (thin film)/cm^{-1} 3059, 2929, 2835, 1609, 1246, 1110, 806, 729, 697; ^{1}H NMR (500MHz ,CDCl$_3$) δ 7.52 (d, *J* = 8.0 Hz, 2 H), 7.50 - 7.47 (m, 2 H), 7.38 (s, 1 H), 7.33 - 7.28 (m, 2 H), 7.27 - 7.22 (m, 3 H), 7.11 (d, *J* = 7.4 Hz, 2 H), 6.94 (d, *J* = 8.8 Hz, 2 H), 4.08 (s, 2 H, C(8)<u>*H*</u>$_2$), 3.84 (s, 3 H, C(1)<u>*H*</u>$_3$), 2.41 (s, 3 H, C(21)<u>*H*</u>$_3$), 2.36 (s, 3 H, C(15)<u>*H*</u>$_3$); ^{13}C NMR (126MHz , CDCl$_3$) δ 159.3, 156.2, 155.8, 140.9, 140.8, 137.8, 137.5, 133.1, 131.6, 130.6, 129.2, 129.0, 128.9, 128.7, 128.6, 126.2, 113.5, 55.3 (<u>*C*</u>(1)H$_3$), 38.2 (<u>*C*</u>(8)H$_2$), 21.3 (<u>*C*</u>(21)H$_3$), 19.9 (<u>*C*</u>(15)H$_3$); HRMS (ESI$^+$) calculated for $[C_{27}H_{25}NO+H]^+$ 380.2009, found 380.2000 (Δ –2.15 ppm).

3,5-Dibenzyl-2-cyclopropyl-6-(4-methoxyphenyl)pyridine, 256



(±)(2*RS*,4*SS*)-2,4-Dibenzyl-1-cyclopropyl-5-(4-methoxyphenyl)pentane-1,5-dione (**245**, 30 mg, 0.0703 mmol), ammonium acetate (16.3 mg, 0.211 mmol), copper (II) acetate monohydrate (35.1 mg, 0.176 mmol) were subjected to general procedure G for 24 h. Purification by FCC (toluene/Et_2O 20:1) afforded **256** as a yellow oil (27.0 mg, 0.0667 mmol, 95%). ν_{max} (thin film)/cm^{-1} 3002, 1608, 1513, 1449, 1249, 1175, 840, 727, 698; ^{1}H NMR (500MHz , $CDCl_3$) δ 7.36 - 7.30 (m, 2 H), 7.22 - 7.04 (m, 9 H), 6.92 (dd, *J* = 0.9, 7.8 Hz, 2 H), 6.85 - 6.79 (m, 2 H), 4.03 (s, 2 H, C(8)$\underline{H}_2$), 3.91 (s, 2 H, C(15)$\underline{H}_2$), 3.74 (s, 3 H, C(1)$\underline{H}_3$), 2.04 - 1.91 (m, 1 H, C(21)$\underline{H}$), 1.08 - 0.97 (m, 2 H, C(22)$\underline{H}$H×2), 0.82 - 0.68 (m, 2 H, C(22)H$\underline{H}$×2); ^{13}C NMR (126MHz , $CDCl_3$) δ 159.3, 157.9, 155.5, 141.1, 140.1, 140.0, 133.4, 131.7, 130.5, 129.5, 128.7, 128.7, 128.5, 128.5, 126.2, 126.0, 113.4, 55.3 ($\underline{C}$(1)H_3), 38.2, 37.9 ($\underline{C}$(8)H_2, $\underline{C}$(15)H_2), 13.7 ($\underline{C}$(21)H), 9.0 ($\underline{C}$(22)H_2×2); HRMS (ESI$^+$) calculated for $[C_{29}H_{27}NO+H]^+$ 406.2165, found 406.2162 (Δ –0.72 ppm).

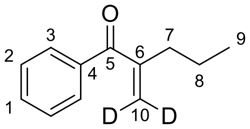
(±)2-(Methyl-*d*$_3$)-1-phenylpentan-1-one, 269



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99-7.93 (m, 2H, C(3)$\underline{H}$×2), 7.59-7.53 (m, 1H, C(1)$\underline{H}$), 7.50-7.44 (m, 2H, C(2)$\underline{H}$×2), 3.48 (t, *J* = 6.5 Hz, 1H, C(6)$\underline{H}$), 1.84-1.28 (m, 4H, C(7)$\underline{H}_2$, C(8)$\underline{H}_2$), 0.91 (t, *J* = 7.2 Hz, 3H, C(9)$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6, 136.8, 132.8, 128.6, 128.2, 40.1, 35.8, 20.6, 14.2 (CD_3 peak was not observed); ^{2}H NMR (77MHz, $CHCl_3$) δ 1.16

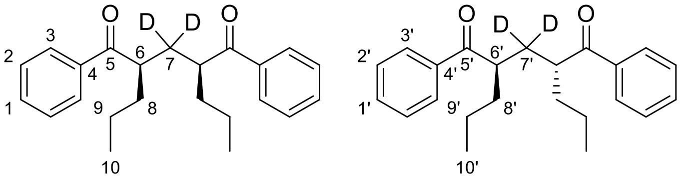
(br s). All spectroscopic data were consistent with that reported in Darren Poole's DPhil thesis.

2-(Methylene-d_2)-1-phenylpentan-1-one, 270



^{1}H NMR (400 MHz, CDCl$_3$) δ 7.79-7.74 (m, 2H, C(3)$\underline{H}$×2), 7.59-7.52 (m, 1H, C(1)$\underline{H}$), 7.50-7.41 (m, 2H, C(2)$\underline{H}$×2), 2.46 (t, *J* = 7.6 Hz, 2H, C(7)$\underline{H}_2$), 1.49-1.62 (m, 2H, C(8)$\underline{H}_2$), 0.98 (t, *J* = 7.4 Hz, 3H, C(9)$\underline{H}_3$); ^{2}H NMR (77MHz, CHCl$_3$) δ 5.88 (br s), 5.63 (br s). All spectroscopic data were consistent with that reported in Darren Poole's DPhil thesis.

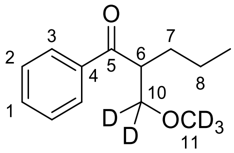
(±)-(2*RR*,4*RS*)-1,5-Diphenyl-2,4-dipropylpentane-1,5-dione-3, 3-d_2, 272



Anti-**272**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 7.71-7.67 (m, 4H), 7.46-7.39 (m, 2H), 7.31-7.24 (m, 4H), 3.36 (t, *J* = 6.5 Hz, 2H, C(6')$\underline{H}$×2), 1.80-1.58 (m, 4H), 1.49-1.37 (m, 2H), 1.36-1.11 (m, 2H), 0.85 (t, *J* = 7.2 Hz, 6H, C(10')$\underline{H}_2$×2); ^{13}C NMR (101 MHz, CDCl$_3$) δ 204.8, 137.4, 132.8, 128.5, 128.0, 43.6, 36.1, 34.3, 20.5, 14.1; ^{2}H NMR (77MHz, CHCl$_3$) δ 2.05 (br s).

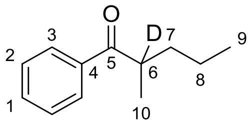
Syn-**272**: ^{1}H NMR (400 MHz, CDCl$_3$) δ 8.04-7.98 (m, 4H), 7.61-7.55 (m, 2H), 7.53-7.47 (m, 4H), 3.52 (dd, *J* = 5.5, 7.6 Hz, 2H, C(6)$\underline{H}$×2), 1.49-1.37 (m, 2H), 1.37-1.11 (m, 6H), 0.79 (t, *J* = 7.3 Hz, 6H, C(10)$\underline{H}_3$×2); ^{13}C NMR (101 MHz, CDCl$_3$) δ 204.0, 137.2, 133.0, 128.7, 128.3, 43.2, 36.1, 34.3 20.4, 14.1; ^{2}H NMR (77MHz, CHCl$_3$) δ 2.27 (br s), 1.61 (br s). All spectroscopic data were consistent with that reported in Darren Poole's DPhil thesis.

(±)2-((Methoxy-*d*$_3$)methyl-*d*$_2$)-1-phenylpentan-1-one, 271



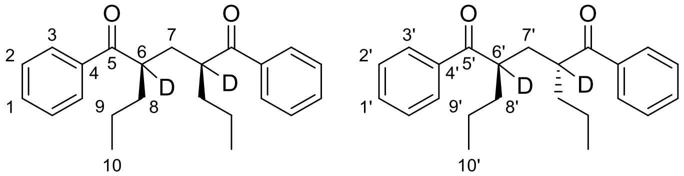
^{1}H NMR (400 MHz, CDCl$_3$) δ 8.01-7.99 (m, 2H, C(3)<u>*H*</u>×2), 7.60-7.56 (m, 1H, C(1)<u>*H*</u>), 7.51-7.47 (m, 2H, C(2)<u>*H*</u>×2), 3.77 (t, *J* = 6.7 Hz, 1H, C(6)<u>*H*</u>), 1.76-1.66 (m, 1H, C(7)<u>*H*</u>H), 1.56-1.46 (m, 1H, C(7)H<u>*H*</u>), 1.36-1.25 (m, 2H, C(8)<u>*H*</u>$_2$), 0.90 (t, *J* = 7.3 Hz, 3H, C(9)<u>*H*</u>$_3$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 203.2 (<u>*C*</u>(5)O), 137.7 (<u>*C*</u>(4)), 133.0 (<u>*C*</u>(1)H), 128.6, 128.3 (<u>*C*</u>(2)H×2, <u>*C*</u>(3)H×2), 46.4 (<u>*C*</u>(6)H), 32.0 (<u>*C*</u>(7)H$_2$), 20.6 (<u>*C*</u>(8)H$_2$), 14.2 (<u>*C*</u>(9)H$_3$) (C(10)D$_2$, and C(11)D$_3$ were not observed); ^{2}H NMR (77MHz, CHCl$_3$) δ 3.70 (br s), 3.49 (br s), 3.26 (br s). All spectroscopic data were consistent with that reported in Darren Poole's DPhil thesis.

(±)2-Methyl-1-phenyl(2-*d*)pentan-1-one, 273



^{1}H NMR (400 MHz, CDCl$_3$) δ 8.03 - 7.88 (m, 2 H, C(3)<u>*H*</u>×2), 7.61 - 7.52 (m, 1 H, C(1)<u>*H*</u>), 7.51 - 7.39 (m, 2 H, C(2)<u>*H*</u>×2), 1.79 (ddd, *J* = 6.3, 9.0, 13.0 Hz, 1 H, C(7)<u>*H*</u>H), 1.48 - 1.27 (m, 3 H, C(7)H<u>*H*</u>, C(8)<u>*H*</u>$_2$), 1.19 (s, 3 H, C(10)<u>*H*</u>$_3$), 0.91 (t, *J* = 7.2 Hz, 3 H, C(9)<u>*H*</u>$_3$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 204.6 (<u>*C*</u>(5)O), 136.8 (<u>*C*</u>(4)), 132.8 (<u>*C*</u>(1)H), 128.6 (<u>*C*</u>(2)H×2), 128.2 (<u>*C*</u>(3)H×2), 40.0 (m, <u>*C*</u>(6)D), 35.8 (<u>*C*</u>(7)H$_2$), 20.6 (<u>*C*</u>(8)H$_2$), 17.1 (<u>*C*</u>(10)H$_3$), 14.2 (<u>*C*</u>(9)H$_3$); ^{2}H NMR (77MHz, CHCl$_3$) δ 3.49 (br s). All spectroscopic data were consistent with that reported in Darren Poole's DPhil thesis.

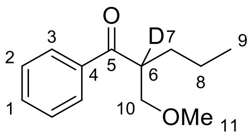
(±)-(2*RR*,4*RS*)-1,5-Diphenyl-2,4-dipropylpentane-1,5-dione-3, 2-*d*, 4-*d*, 275



Anti-**275**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 - 7.59 (m, 4 H, C(3’)*H*×4), 7.37 - 7.32 (m, 2 H, C(1’)*H*×2), 7.22 - 7.16 (m, 4 H, C(2’)*H*×4), 1.98 (s, 2 H, C(7’)*H_2*), 1.61 - 1.50 (m, 2 H, C(8)*H*H×2), 1.28-1.06 (m, 6H, C(8’)H*H*×2, C(9’)*H_2*×2), 0.79 - 0.75 (m, 6 H, C(10’)*H_3*×2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8 (*C*(5’)×2), 137.2 (*C*(4’)×2), 132.9 (*C*(1’)H×2), 128.5 (*C*(2’)H×4), 128.0 (*C*(3’)H×4), 43.4 (m, *C*(6’)D×2), 36.1 (*C*(8’)H_2×2), 33.9 (*C*(7’)H_2), 20.4 (*C*(9’)H_2×2), 14.1 (*C*(10’)H_3×2); ^{2}H NMR (77MHz, $CHCl_3$) δ 3.37 (br s).

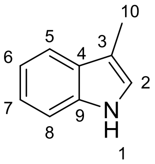
Syn-**275**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 - 7.90 (m, 4 H, C(3)*H*×4), 7.53 - 7.48 (m, 2 H, C(1)*H*×2), 7.45 - 7.40 (m, 4 H, C(2)*H*×4), 2.20 (d, *J* = 13.7 Hz, 1 H, C(7)*H*H), 1.65 (ddd, *J* = 5.5, 10.0, 13.4 Hz, 2 H, C(8’)*H*H×2), 1.55 (d, *J* = 13.6 Hz, 1 H, C(7)H*H*), 1.28-1.06 (m, 6H, C(8)H*H*×2, C(9)*H_2*×2), 0.71 (t, *J* = 7.3 Hz, 6 H, C(10)H_3×2); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.0 (*C*(5)×2), 137.4 (*C*(4)×2), 133.1 (*C*(1)H×2), 128.8 (*C*(2)H×4), 128.3 (*C*(3)H×4), 43.4 (m, *C*(6)D×2), 34.3 (*C*(8)H_2×2), 33.9 (*C*(7)H_2), 20.6 (*C*(9)H_2×2), 14.2 (*C*(10)H_3×2); ^{2}H NMR (77MHz, $CHCl_3$) δ 3.53 (br s). All spectroscopic data were consistent with that reported in Darren Poole’s DPhil thesis.

2-(Methoxymethyl)-1-phenyl(2-2*d*)pentan-1-one, 274



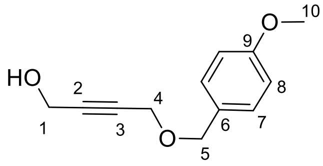
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 - 7.94 (m, 2 H, C(3)*H*×2), 7.61 - 7.53 (m, 1 H, C(1)*H*), 7.51 - 7.42 (m, 2 H, C(2)*H*×2), 3.72 (d, *J* = 8.8 Hz, 1 H, C(10)*H*H), 3.51 (d, *J* = 9.0 Hz, 1 H, C(10)H*H*), 3.29 (s, 3 H, C(11)$\underline{H}_3$), 1.76 - 1.68 (m, 1 H, C(7)*H*H), 1.55 - 1.48 (m, 1 H, C(7)H*H*), 1.31 (qd, *J* = 7.6, 15.2 Hz, 2 H, C(8)$\underline{H}_2$), 0.88 (t, *J* = 7.3 Hz, 3 H, C(9)$\underline{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 203.2 (*C*(5)O), 137.7 (*C*(4)), 133.0 (*C*(1)H), 128.6 (*C*(2)H×2), 128.3 (*C*(3)H×2), 74.2 (*C*(10)H_2), 59.1(*C*(11)H_3), 46.1(t, *J* = 20.0 Hz, *C*(6)D), 31.9 (*C*(7)H_2), 20.6 (*C*(8)H_2), 14.2 (*C*(9)H_3); ^{2}H NMR (77MHz, $CHCl_3$) δ 3.77 (br s). All spectroscopic data were consistent with that reported in Darren Poole's DPhil thesis.

3-Methyl-1H-indole, 288



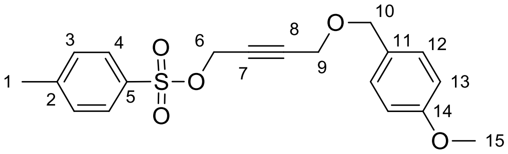
Under an open atmosphere, indole (35.1 mg, 0.300 mmol), $[IrCp^*Cl_2]_2$ (6.0 mg, 0.0075 mmol), KOH (50 mg, 0.900 mmol) were added to a Biotage® microwave vial equipped with a stir bar, followed by "wet" methanol. The vial was sealed with a microwave vial cap (containing a Reseal™ septum) and a balloon of O_2 was inserted via a needle through the septum. The reaction was heated to 65 ˚C for 24 h. The reaction was quenched by diluting with diethyl ether and filtering through a pad of silica gel. Purification by FCC (Petrol/Et_2O 8:2) to afford **288** as a colourless solid (18.6 mg, 0.142 mmol, 47%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1 H, N(1)*H*), 7.62 (dd, *J* = 0.5, 7.8 Hz, 1 H, C(5)*H*), 7.39 - 7.34 (m, 1 H, C(8)*H*), 7.22 (dt, *J* = 1.2, 7.5 Hz, 1 H, C(7)*H*), 7.18 - 7.11 (m, 1 H, C(6)*H*), 6.99 (dd, *J* = 1.1, 2.1 Hz, 1 H, C(2)*H*), 2.37 (d, *J* = 1.0 Hz, 3 H, C(10)$\underline{H}_3$); ^{13}C NMR (101MHz , $CDCl_3$) δ 136.3, 128.3, 121.9 (*C*(7)H), 121.6 (*C*(2)H), 119.1 (*C*(6)H), 118.9 (*C*(5)H), 111.8, 111.0 (*C*(8)H), 9.7 (*C*(10)H_3). Spectroscopic data were consistent with those previously reported.[136]

4-((4-Methoxybenzyl)oxy)but-2-yn-1-ol, 283



A mixture of 2-butyne-1,4-diol (**281**, 1.00 g, 11.6 mmol), 4-methoxybenzyl alcohol (1.58 mL, 12.8 mmol), and Amberlyst-15 (150 mg, 15 wt%), in anhydrous CH_2Cl_2 was refluxed for 21.5 h. The crude mixture was filtered, concentrated *in vacuo* and purified by FCC (Petrol/Et_2O 1:1) to afford **283** as a yellow oil (1.070 g, 5.19 mmol, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.4 Hz, 2 H, C(7)$\underline{H}$×2), 6.90 (d, *J* = 8.5 Hz, 2 H, C(8)$\underline{H}$×2), 4.54 (s, 2 H, C(5)$\underline{H}_2$), 4.30 (s, 2 H), 4.19 (s, 2 H), 3.80 (s, 3 H, C(10)$\underline{H}_3$), 3.13 (br s, 1 H, O$\underline{H}$); ^{13}C NMR (101MHz , $CDCl_3$) δ 159.4, 129.9, 129.3, 113.9, 85.1, 81.4, 71.3, 57.1, 55.3, 50.8. Spectroscopic data were consistent with those previously reported.[137]

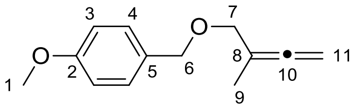
4-((4-Methoxybenzyl)oxy)but-2-yn-1-yl 4-methylbenzenesulfonate, 284



To a stirred solution of 4-((4-Methoxybenzyl)oxy)but-2-yn-1-ol (**283**, 1.07 g, 5.19 mmol) in dry Et_2O (26.0 mL) was added *p*-toluenesulfonyl chloride (1.09 g, 5.71 mmol) at 0 ˚C. KOH (2.91 g, 51.9 mmol) was added in three portions to the stirring solution at 0 ˚C. The yellow suspension was warmed up to room temperature and stirred for 30 min. The reaction was quenched by addition of water at 0 ˚C. The organic layer was washed with saturated aqueous NH_4Cl and brine, dried over $MgSO_4$, filtered, concentrated *in vacuo*. Purification by FCC (Petrol/Et_2O 1:1) afforded **284** as a yellow oil (1.86 g, 5.17 mmol, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 - 7.76 (m, 2 H), 7.34 (d, *J* = 8.1 Hz, 2 H), 7.26 - 7.21 (m, 2 H), 6.93 - 6.85 (m, 2 H), 4.77 (t, *J* = 1.8 Hz, 2 H), 4.42 (s, 2 H, C(10)$\underline{H}_2$), 4.04 (t, *J* = 1.8 Hz, 2 H), 3.81

(s, 3 H, C(15)$\underline{H}_3$), 2.42 (s, 3 H, C(1)$\underline{H}_3$); ^{13}C NMR (101MHz , $CDCl_3$) δ 159.5, 145.2, 133.1, 129.9, 129.8, 129.1, 128.1, 113.9, 85.6, 78.2, 71.3 ($\underline{C}$(10)H_2), 57.9, 56.7, 55.3 ($\underline{C}$(15)H_3), 21.7 ($\underline{C}$(1)H_3). Spectroscopic data were consistent with those previously reported.[36]

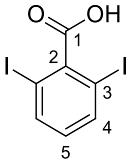
1-Methoxy-4-(((2-methylbuta-2,3-dien-1-yl)oxy)methyl)benzene, 285



To a flamed-dried round botton flask was added CuI (158.6 mg, 0.833 mmol), LiBr (72.3 mg, 0.833 mmol), and Et_2O (1 mL). The suspension was cooled to 0 ˚C, and MeMgBr (3 M in Et_2O, 0.28 mL) was added. The resulting yellow suspension was warmed up to room temperature and stirred for 15 min before 4-((4-methoxybenzyl)oxy)but-2-yn-1-yl 4-methylbenzenesulfonate (**284**, 100 mg, 0.278 mmol) in Et_2O (1.8 mL) was added at 0 ˚C. The mixture was stirred at room temperature for another 15 min, and was cooled to 0 ˚C again before water was added to quench the reaction. The two layers were separated, organic phase was washed with water and brine, dried over Na_2SO_4, filtered, concentrated *in vacuo*. Purification by FCC (Petrol/Et_2O 9:1) afforded **285** as a yellow oil (20.8 mg, 0.102 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.6 Hz, 2 H), 6.86 - 6.71 (m, 2 H), 4.69 - 4.58 (m, 2 H), 4.35 (s, 2 H), 3.90 (t, J = 2.2 Hz, 2 H), 3.73 (s, 3 H), 1.67 (t, J = 3.1 Hz, 3 H); ^{13}C NMR (101MHz , $CDCl_3$) δ 207.1, 159.2, 130.4, 129.5, 113.8, 95.8, 74.4, 71.6, 71.1, 55.3, 15.7. Spectroscopic data were consistent with those previously reported.[36]

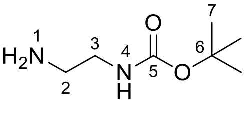
5.3.2 Experimental: Synthesis of Biotin Derivatives

2,6-Diiodobenzoic acid, 307



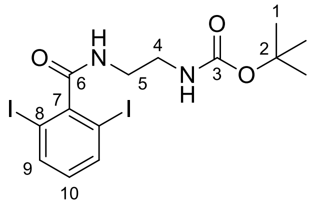
Benzoic acid (**306**) (500 mg, 4.09 mmol), $Pd(OAc)_2$ (45.9 mg, 0.20 mmol), iodobenzene diacetate (2.00 g, 6.14 mmol) and I_2 (1.56 g, 6.14 mmol) were dissolved in DMF (20 mL) under argon in a sealed tube. The reaction mixture was stirred at 100 °C for 48 h, then cooled to rt, diluted with ethyl acetate (50 mL) and washed with aqueous HCl (1 M, 50 mL × 4). The organic phase was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystallized from ethyl acetate and petrol (EtOAc: petrol, 10: 1) to give the product as a light yellow solid (1.13 g, 74%). Melting point = 179-180 ^{o}C (Lit: 184-187 ^{o}C,[138]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.9 Hz, 2H, C(4)<u>*H*</u> ×2), 6.82 (t, *J* = 7.9 Hz, 1H, C(5)<u>*H*</u>); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5 (<u>*C*</u>(1)), 144.4 (<u>*C*</u>(2)), 138.7 (<u>*C*</u>(4)H×2), 132.1 (<u>*C*</u>(5)H), 90.7 (<u>*C*</u>(3)×2). Spectroscopic data are consistent with those previously reported.[104]

tert-Butyl (2-aminoethyl)carbamate, 305



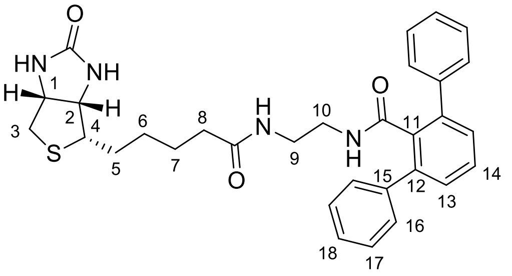
A solution of di-*tert*-butyl dicarbonate (2.10 mL, 9.20 mmol) in chloroform (45 mL) was added *via* a syringe pump over 3 h to a solution of ethylenediamine (3.10 mL, 45.8 mmol) in chloroform (50 mL) at 0 °C. The reaction was stirred for 24 h at rt to give a white suspension which was then washed with sat. Na_2CO_3 (100 mL ×3). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to yield the title compound as a colorless oil (1.32 g, 90%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.20 (br s, 1H, N(4)<u>*H*</u>), 3.12-3.08 (m, 2H), 2.74-2.70 (m, 2H), 1.37 (s, 9H, C(7)*H*$_3$×3), 1.26 (br s, 2H, N(1)*H*$_2$); ^{13}C NMR (101 MHz, CDCl$_3$) δ 156.2 (*C*(5)), 79.1 (*C*(6)), 43.4, 41.8, 28.4 (*C*(7)H$_3$×3). Spectroscopic data are consistent with those previously reported.[139]

tert-Butyl (2-(2,6-diiodobenzamido)ethyl)carbamate, 308



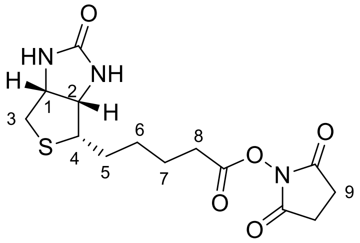
tert-Butyl (2-aminoethyl)carbamate (**305**, 400 mg, 2.50 mmol), 2,6-diiodobenzoic acid (**307**, 778 mg, 2.08 mmol), *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (399 mg, 2.08 mmol, Fluorochem) and 1-hydroxybenzotriazole (281 mg, 2.08 mmol) were dissolved in MeCN (25 mL) in a sealed tube and the reaction was stirred at 60 °C for 12 h. The crude mixture was filtered through a short pad of silica gel, eluted with ethyl acetate, then recrystallized with dichloromethane to yield the product as a white solid (600 mg, 56%). Melting point = 74-75 °C; ν_{max} (thin film)/cm^{-1} 3351, 3256, 2976, 2931, 2160, 2029, 766, 689; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.73 (d, *J* = 7.9 Hz, 2H, C(9)*H*×2), 6.70 (br s, 1H, N*H*), 6.68 (t, *J* = 7.9 Hz, 1H, C(10)*H*), 5.20 (br s, 1H, N*H*), 3.55-3.52 (m, 2H), 3.43-3.41 (m, 2H), 1.39 (s, 9H, C(1)H$_3$×3); ^{13}C NMR (126 MHz, CDCl$_3$) δ 170.4 (*C*(6)O), 156.6 (*C*(3)O), 147.0 (*C*(7)), 138.8 (*C*(9)H×2), 131.6 (*C*(10)H), 92.2 (*C*(8)×2), 79.6 (*C*(2)), 40.7, 39.8, 28.4 (*C*(1)H$_3$×3); HRMS (ESI$^+$) calculated for [$C_{14}H_{18}I_2N_2O_3$+Na]$^+$ 538.9299, found 538.9278 (Δ 3.9 ppm).

***N*-(2-(5-((3a*S*,4*S*,6a*R*)-2-Oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)ethyl)-[1,1':3',1''-terphenyl]-2'-carboxamide, LH1**



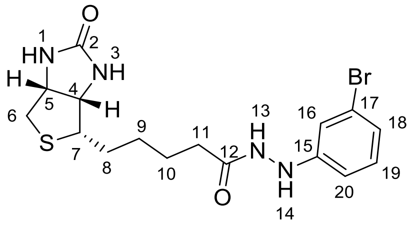
tert-Butyl (2-(2,6-diiodobenzamido)ethyl)carbamate (**308,** 50.0 mg, 0.0969 mmol), phenyl boronic acid (35.4 mg, 0.290 mmol), Pd(PPh$_3$)$_4$ (11.2 mg, 0.00969 mmol), aqueous Na$_2$CO$_3$ (2 M, 1 mL) and 1,2-dimethoxyethane (4 mL) were placed in a sealed tube, and the mixture was degassed with argon. The reaction mixture was then heated at 100 °C for 2.5 h, allowed to cool to rt, filtered through a short pad of silica gel, eluented with diethyl ether, and concentrated *in vacuo*. The crude material was redissolved in dichloromethane (0.3 mL) and TFA (74 μL, 1 mmol) was added. The yellow solution was stirred at rt for 5 h, concentrated *in vacuo* and then redissolved in DMF (0.3 mL) before (+)-biotin *N*-hydroxysuccinimide ester (33.1 mg, 0.0969 mmol), and triethylamine (176 μL, 1.26 mmol) were added. The mixture was further stirred at rt for 48 h, purified *via* column chromatography (CH$_2$Cl$_2$: MeOH, 9:1) to afford the product as a white solid (8.2 mg, 16%). Melting point = 134-136 °C; $[\propto]_D^{20}$ = +27.2 (*c* 0.25, CHCl$_3$); ν_{max} (thin film)/cm^{-1} 3313, 2925, 1697, 1647, 1541, 1457, 761, 702; ^{1}H NMR (500 MHz, MeOD) δ 7.56-7.54 (m, 1H, C(14)$\underline{H}$), 7.49-7.48 (m, 2H, ArC$\underline{H}$), 7.44-7.39 (m, 10H, ArC$\underline{H}$), 6.91 (br s, 1H, N*H*), 4.50 (dd, *J* = 7.7, 4.6 Hz, 1H, C(1)$\underline{H}$), 4.30 (dd, *J* = 7.9, 4.4 Hz, 1H, C(2)$\underline{H}$), 3.21-3.19 (m, 1H, C(4)$\underline{H}$), 2.99-2.97 (m, 2H, C(10)$\underline{H}_2$), 2.93 (dd, *J* = 12.8, 4.9 Hz, 1H, C(3)$\underline{H}$H), 2.85-2.84 (m, 2H, C(9)$\underline{H}_2$), 2.72 (d, *J* = 12.6 Hz, 1H, C(3)H$\underline{H}$), 2.07 (t, *J* = 7.6 Hz, 2H, C(8)$\underline{H}_2$), 1.75-1.39 (m, 6H, C(5)$\underline{H}_{2,}$ C(6)$\underline{H}_{2,}$ C(7)$\underline{H}_2$); ^{13}C NMR (126 MHz, MeOD) δ 176.0 ($\underline{C}$(O)), 172.4 ($\underline{C}$(O)), 166.1 ($\underline{C}$(O)), 142.0, 141.5, 136.9 ($\underline{C}$(11), $\underline{C}$(12), $\underline{C}$(15)), 130.2 ($\underline{C}$(14)), 130.0 ($\underline{C}$(13)×2), 130.2, 129.3, 128.7 ($\underline{C}$(16)×4, *C*(17)×4, *C*(18)×2), 63.4 (*C*(2)H), 61.6 (*C*(1)H), 57.0 (*C*(4)H), 41.1 (*C*(3)H$_2$), 39.9, 39.7 (*C*(9)H$_2$, *C*(10)H$_2$), 36.8 (*C*(8)H$_2$), 29.8, 29.5, 26.6 (*C*(5)H$_2$, *C*(6)H$_2$, *C*(7)H$_2$); HRMS (ESI$^+$) calculated for $[C_{31}H_{34}N_4O_3S+Na]^+$ 565.2244, found 565.2223(Δ 3.7 ppm).

(+)-Biotin N-hydroxysuccinimide ester, 309



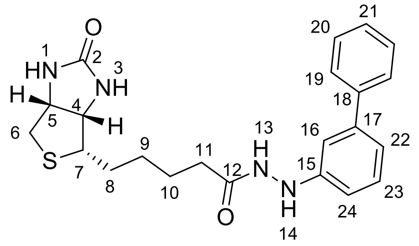
The suspension of (+)-Biotin (1.00 g, 4.09 mmol), *N*-hydroxysuccimide (0.570 g, 4.91 mmol), *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (0.940 g, 4.91 mmol) in DMF was stirred at rt. For 20 h. The resulting white suspension was filtered, rinsed with water to give the title compound as a white solid (1.01 g, 2.96 mmol. 72%). Melting point = 218-220 ^{0}C (lit.[140] 206-207 ^{0}C); ^{1}H NMR (400 MHz, DMSO-d6) δ 6.44 (br s, 1H, N*H*), 6.38 (br s, 1H, N*H*), 4.31 (dd, J = 7.6, 5.1 Hz, 1H, C(1)*H*), 4.17-4.14 (m, 1H, C(2)*H*), 3.14-3.06 (m, 1H, C(4)*H*), 2.86-2.83 (m, 1H, C(3)*H*H), 2.82 (s, 4H, C(9)*H*$_2$×2), 2.68 (t, *J* = 7.3 Hz, 2H, C(8)*H*$_2$), 2.58 (d, *J* = 12.2 Hz, 1H, C(3)H*H*), 1.69-1.35 (m, 6H, C(5)*H*$_2$, C(6)*H*$_2$, C(7)*H*$_2$); ^{13}C NMR (126 MHz, DMSO-d6) δ 170.3, 168.9, 162.7 (*C*O×3), 61.0 (*C*(2)H), 59.2 (*C*(1)H), 55.2 (*C*(4)H), 40.1 (*C*(3)H$_2$), 30.0, 27.8, 27.6, 24.3 (*C*(5)H$_2$, *C*(6)H$_2$, *C*(7)H$_2$, *C*(8)H$_2$), 25.4 (*C*(9)H$_2$×2). Spectroscopic data are consistent with those previously reported.[141]

N'-(3-Bromophenyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanehydrazide, 315



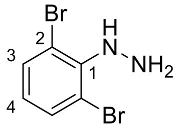
(+)-Biotin N-hydroxysuccinimide ester (**309**, 153 mg, 0.448 mmol) and Et_3N (75 µL, 0.538 mmol) were added to a solution of 3-bromophenylhydrazine hydrochloride (100 mg, 0.448 mmol) in DMF in round bottom flask at rt. The resulting yellow solution was stirred at rt for 19 h before water was added and extracted with EtOAc. The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. Purification by column chromatography (CH_2Cl_2: MeOH, 9:1) to give the title compound as a white solid (150.8 mg, 0.364 mmol, 81%). Melting point = 135-137 ^{0}C; ν_{max} (thin film)/cm^{-1} 3248, 2918, 2862, 1688, 1673, 1468, 773, 684, 660; $[\propto]_D^{20}$ = +32.4 (*c* 0.25, MeOH); ^1H NMR (500 MHz, DMSO-d_6) δ 9.61 (br s, 1 H, N(13)$\underline{H}$), 7.91 (br s, 1 H, N(14)$\underline{H}$), 7.01 (t, *J*=7.9 Hz, 1 H, C(19)$\underline{H}$), 6.71 - 6.79 (m, 2 H, C(16)$\underline{H}$, C(18)$\underline{H}$), 6.60 (dd, *J*=8.2, 1.3 Hz, 1 H, C(20)$\underline{H}$), 6.38 (br s, 1 H, N$\underline{H}$), 6.30 (br s, 1 H, N$\underline{H}$), 4.22 - 4.31 (m, 1 H, C(5)$\underline{H}$), 4.06 - 4.13 (m, 1 H, C(4)$\underline{H}$), 3.00 - 3.08 (m, 1 H, C(7)$\underline{H}$), 2.76 (dd, *J*=12.3, 5.0 Hz, 1 H, C(6)$\underline{H}$H), 2.52 (d, *J*=12.3 Hz, 1 H, C(6)H$\underline{H}$), 2.11 (t, *J*=7.4 Hz, 2 H, C(11)$\underline{H}_2$), 1.14 - 1.65 (m, 6 H, C(8)$\underline{H}_2$, C(9)$\underline{H}_2$, C(10)$\underline{H}_2$); ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.4 ($\underline{C}$(12)O), 163.1 ($\underline{C}$(2)O), 151.6 ($\underline{C}$(15), 131.0 ($\underline{C}$(19)H), 122.4 ($\underline{C}$(17), 121.0 ($\underline{C}$(18)H), 114.5 ($\underline{C}$(16)H), 111.4 ($\underline{C}$(20)H), 61.4 ($\underline{C}$(4)H), 59.6 ($\underline{C}$(5)H), 55.8 ($\underline{C}$(7)H), 40.4 ($\underline{C}$(6)H_2), 33.4 ($\underline{C}$(11)H_2), 28.6, 28.4, 25.5 ($\underline{C}$(8)H_2, $\underline{C}$(9)H_2, $\underline{C}$(10)H_2); HRMS (ESI$^+$) calculated for $[C_{16}H_{21}N_4O_2BrS+H]^+$ 413.0641, 415.0621, found 413.0634, 415.0613 (Δ-1.7 ppm).

N'-([1,1'-Biphenyl]-3-yl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanehydrazide, 316



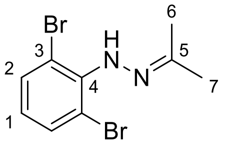
N'-(3-Bromophenyl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanehydrazide (**315**, 50.0 mg, 0.121 mmol), bezeneboronic acid (44.3 mg, 0.363 mmol), Pd(OAc)$_2$ (1.4 mg, 0.00605 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (4.5 mg, 0.00906 mmol), aqueous Na$_2$CO$_3$ (2 M, 0.32 mL), and 1,2-dimethoxyethane (0.64 mL) were placed in a sealed tube, and degassed with argon. The suspension was then heated at 80 ^{0}C for 24 h, and the crude mixture was directly purified by column chromatography (CH$_2$Cl$_2$: MeOH, 9:1) to yield the title compound as a white solid (40.2 mg, 0.0980, 81%). Melting point = 114-116 ^{0}C; ν$_{max}$ (thin film)/cm^{-1} 3353, 3285, 1696, 1667, 1497, 791,756, 696, 613; $[\propto]_D^{20}$ = +32.0 (*c* 0.25, MeOH); ^{1}H NMR (400 MHz, MeOD) δ 7.51 - 7.41 (m, 2H, C(19)*H*×2), 7.33 - 7.26 (m, 2 H, C(20)*H*×2), 7.23 - 7.17 (m, 1 H), 7.14 (t, *J* = 7.9 Hz, 1 H, C(21)*H*), 6.97 - 6.88 (m, 2 H), 6.71 - 6.66 (m, 1 H), 4.30 (dd, *J* = 4.9, 7.8 Hz, 1 H, C(5)*H*), 4.06 (dd, *J* = 4.4, 7.8 Hz, 1 H, C(4)*H*), 3.03 - 2.94 (m, 1 H, C(7)*H*), 2.74 (dd, *J* = 4.9, 12.7 Hz, 1 H, C(6)*H*H), 2.56 (d, *J* = 12.7 Hz, 1 H, C(6)H*H*), 2.20 (t, *J* = 7.2 Hz, 2 H, C(11)*H*$_2$), 1.71 - 1.29 (m, 6 H, C(8)*H*$_2$, C(9)*H*$_2$, C(10)*H*$_2$); ^{13}C NMR (126 MHz, MeOD) δ 176.3, 166.5, 150.9, 143.8, 143.2, 130.9, 130.2, 128.7, 128.4, 120.3, 113.7, 113.0, 63.7 (C(4)*H*), 62.0 (C(5)*H*, 57.3 (C(7)*H*), 41.4 (C(6)*H*$_2$), 35.1 (*C*(11)H$_2$), 30.2, 29.9, 27.1 (*C*(8)H$_2$, (*C*(9)H$_2$, (*C*(10)H$_2$); HRMS (ESI$^+$) calculated for [C$_{22}$H$_{26}$N$_4$O$_2$S+Na]$^+$ 433.1669, found 433.1660 (Δ-1.9ppm).

2,6-Dibromophenylhydrazine, 312



A solution of $NaNO_2$ (276 mg, 4.00 mmol) in H_2O (1.7 mL) was added dropwise to a white suspension of 2,6-dibromoaniline (500 mg, 2.00 mmol) in aqueous HCl (37%, 5 mL) while cooling with an ice-water bath. The reaction mixture was stirred at 0 °C for 1 h to give a yellow suspension. Then a solution of $SnCl_2$ (760 mg, 4.00 mmol) in aqueous HCl (37%, 1.2 mL) was added dropwise at 0 °C. The reaction was stirred for 30 min before being warmed to rt and further stirred for 2 h to give a thick yellow suspension. The reaction was cooled to 0 °C, and solid sodium hydroxide was added until the pH = 9. The resulting yellow suspension was extracted with diethyl ether, dried over sodium sulphate, concentrated *in vacuo*, and purified *via* column chromatography (petrol: ether, 9:1) to afford the product as a yellow solid (354 mg, 66%). Melting point = 79-82 °C; ν_{max} (thin film)/cm^{-1} 3228, 2416, 1427, 755, 716, 658; ^{1}H NMR (400 MHz, MeOD) δ 7.60 (d, *J* = 8.1 Hz, 2H, C(3)$\underline{H}$×2), 6.92 (t, *J* = 8.0 Hz, 1H, C(4)$\underline{H}$), 4.91 (br s, 3H, N$\underline{H}$); ^{13}C NMR (101 MHz, MeOD) δ 145.1 ($\underline{C}$(1)), 132.7 ($\underline{C}$(3)H×2), 126.1 ($\underline{C}$(4)H), 117.6 ($\underline{C}$(2) ×2); HRMS (ESI$^+$) calculated for $[C_6H_6Br_2N_2+H]^+$ 264.8970, found 264.8981 (Δ-3.2 ppm).

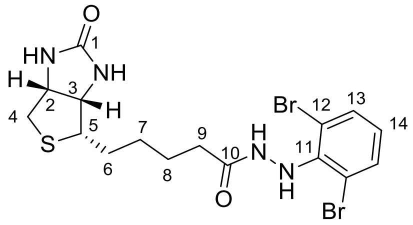
1-(2,6-Dibromophenyl)-2-(propan-2-ylidene)hydrazine, 317



2,6-Dibromophenylhydrazine (50.0 mg, 0.188 mmol) was dissolved in acetone, and then concentrated *in vacuo* to give the title compound as yellow oil (57.5 mg, 100%). ν_{max} (thin film)/cm^{-1} 3322, 2910, 2360, 1560, 1446, 765, 727; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J*

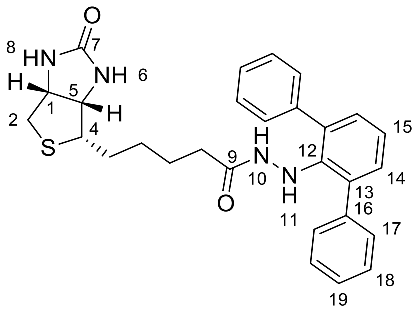
= 8.0 Hz, 2H, C(2)$\underline{H}$×2), 6.79 (t, *J* = 8.0 Hz, 1H, C(1)$\underline{H}$), 2.08, 2.04 (s×2, 6H, C(6)$\underline{H}_3$, C(7)$\underline{H}_3$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4 ($\underline{C}$(5)), 141.9 ($\underline{C}$(4)), 132.8 ($\underline{C}$(2)H×2), 125.3 ($\underline{C}$(1)H), 117.1 ($\underline{C}$(3)×2), 24.9, 16.6 ($\underline{C}$(6)H_3, $\underline{C}$(7)H_3); HRMS (ESI$^+$) calculated for $[C_9H_{10}Br_2N_2+H]^+$ 304.9283, found 304.9297 (Δ0.5 ppm).

***N*'-(2,6-Dibromophenyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanehydrazide, 311**



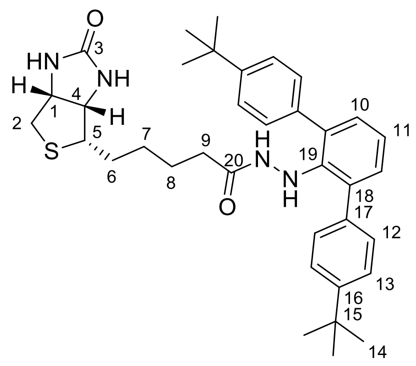
2,6-Dibromophenylhydrazine (302 mg, 1.14 mmol), D-biotin (185 mg, 0.757 mmol), *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (218 mg, 1.14 mmol), and 1-hydroxybenzotriazole anhydrous (154 mg, 1.14 mmol) were dissolved in DMF (15 mL). The yellow solution was stirred at rt for 18 h to give a white suspension which was then filtered to give the product as a white solid (287 mg, 74%). Melting point = 168-170 °C; $[\propto]_D^{20}$ = +21.6 (*c* 0.25, MeOH); ν_{max} (thin film)/cm^{-1} 3269, 2929, 2360, 2341, 1696, 1440; ^{1}H NMR (500 MHz, MeOD) δ 7.53 (d, *J* = 8.2 Hz, 2H, C(13)$\underline{H}$×2), 6.81 (t, *J* = 8.0 Hz, 1H, C(14)$\underline{H}$), 4.51-4.48 (m, 1H, C(2)$\underline{H}$), 4.29 (dd, *J* = 7.9, 4.4 Hz, 1H, C(3)$\underline{H}$), 3.20 (ddd, *J* = 8.7, 6.0, 4.6 Hz, 1H, C(5)$\underline{H}$), 2.94 (dd, *J* = 12.9, 5.0 Hz, 1H, C(4)$\underline{H}$H), 2.72 (d, *J* = 12.6 Hz, 1H, C(4)H$\underline{H}$), 2.25 (t, *J* = 7.2 Hz, 2H, C(9)$\underline{H}_2$), 1.81-1.53 (m, 4H, C(7)$\underline{H}_2$, C(8)$\underline{H}_2$), 1.50-1.38 (m, 2H, C(6)$\underline{H}_2$); ^{13}C NMR (126 MHz, MeOD) δ 175.0 ($\underline{C}$(10), 166.1 ($\underline{C}$(1)), 144.4 ($\underline{C}$(11)), 134.2 ($\underline{C}$(13)H×2), 125.6 ($\underline{C}$(14)H), 115.6 ($\underline{C}$(12)×2), 63.3 ($\underline{C}$(3)H), 61.6 ($\underline{C}$(2)H), 57.0 ($\underline{C}$(5)H), 41.1 ($\underline{C}$(4)H_2), 34.2 ($\underline{C}$(9)H_2), 29.8, 29.4 ($\underline{C}$(7)H_2, $\underline{C}$(8)H_2), 26.4 ($\underline{C}$(6)H_2); HRMS (ESI$^+$) calculated for $[C_{16}H_{20}Br_2N_4O_2S+Na]^+$ 512.9566, found 512.9553 (Δ1.2 ppm).

N'-([1,1':3',1''-Terphenyl]-2'-yl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanehydrazide, LH2



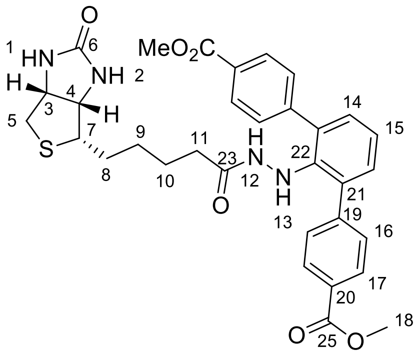
Phenylboronic acid (37.2 mg) was subjected to the general procedure H to give the title compound (13.1 mg, 26%) as a yellow solid. Melting point = 111-112 °C; $[\propto]_D^{20}$ = +75.6 (*c* 0.25, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3254, 3057, 2929, 2860, 1701, 1455, 1420, 758, 703; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57-7.55 (m, 4H, C(17)$\underline{H}$×4), 7.47 (t, *J* = 7.7 Hz, 4H, C(18)$\underline{H}$×4), 7.39-7.37 (m, 2H, C(19)$\underline{H}$×2), 7.17-7.15 (m, 2H, C(14)$\underline{H}$×2), 7.09-7.06 (m, 1H, C(15)$\underline{H}$), 6.44 (br s, 1H, N(10)$\underline{H}$), 6.27 (br s, 1H, N$\underline{H}$), 6.01 (br s, 1H, N$\underline{H}$), 5.30 (br s, 1H, N(11)$\underline{H}$), 4.44-4.42 (m, 1H, C(1)$\underline{H}$), 4.20-4.18 (m, 1H, C(5)$\underline{H}$), 3.05-3.02 (m, 1H, C(4)$\underline{H}$), 2.83 (dd, *J* = 12.8, 4.9 Hz, 1H, C(2)$\underline{H}$H) 2.63 (d, *J* = 12.6 Hz, 1H, C(2)H$\underline{H}$), 1.62-1.08 (m, 8H, C$\underline{H}_2$×4); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.3 ($\underline{C}$(9)), 163.6 ($\underline{C}$(7)), 142.8 ($\underline{C}$(12)), 140.4 ($\underline{C}$(16) ×2), 131.2 ($\underline{C}$(13) ×2), 130.4 ($\underline{C}$(14)H), 129.0, 128.8 ($\underline{C}$(17)H×4, $\underline{C}$(18)H×4), 127.3 ($\underline{C}$(19)H×2), 122.1 ($\underline{C}$(15)H), 61.7 ($\underline{C}$(5)H), 60.1 ($\underline{C}$(1)H), 55.3 ($\underline{C}$(4)H), 40.4 ($\underline{C}$(2)H_2), 33.2, 28.2, 28.0, 24.5 ($\underline{C}H_2$×4); HRMS (ESI$^+$) calculated for $[C_{28}H_{30}N_4O_2S+Na]^+$ 509.1982, found 509.1974 (Δ1.5 ppm).

N'-(4,4''-Di-tert-butyl-[1,1':3',1''-terphenyl]-2'-yl)-5-((3aS,4S,6aR)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanehydrazide, LH3



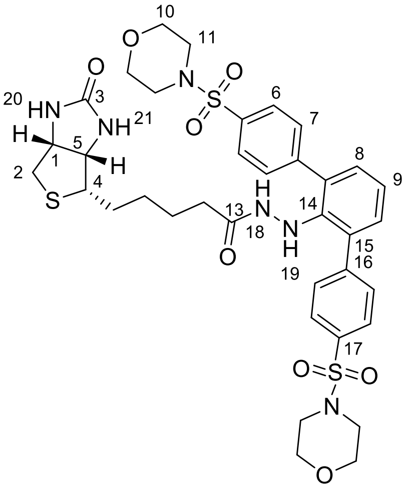
N'-(2,6-Dibromophenyl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanehydrazide (**311**, 40.0 mg, 0.081 mmol, 1 equiv.), 4-(tert-butyl)phenyl)boronic acid (43.4 mg, 0.240 mmol, 3 equiv.), Pd(OAc)$_2$ (0.9 mg, 0.004 mmol, 0.05 equiv.), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (3.0 mg, 0.006 mmol, 0.075 equiv.), aqueous Na$_2$CO$_3$ (2 M, 0.32 m), and 1,2-dimethoxyethane (0.64 mL) were placed in a sealed tube, and degassed with argon. The suspension was then heated at 80 °C for 48 h, and the crude mixture was directly purified by column chromatography (CH$_2$Cl$_2$: MeOH, 95:5) to give the title compound (6.7 mg, 14%) as a yellow solid. Melting point = 132-134 °C; $[\propto]_D^{20}$ = +21.3 (*c* 0.25, CHCl$_3$); ν_{max} (thin film)/cm^{-1} 3243, 2961, 2866, 1704, 1462; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.49 (s×2, 8H, C(12)*H*×4, C(13)*H*×4), 7.15 (d, *J* = 8.4 Hz, 2H, C(10)*H*×2), 7.06 (t, *J* = 8.3 Hz, 1H, C(11)*H*), 6.32 (br s, 1H), 4.45 (dd, *J* = 7.6, 5.0 Hz, 1H, C(1)*H*), 4.20 (dd, *J* = 7.7, 4.6 Hz, 1H, C(4)*H*), 3.08-3.04 (m, 1H, C(5)*H*), 2.86 (dd, *J* = 12.8, 4.9 Hz, C(2)*H*H), 2.67 (d, *J* = 12.9 Hz, 1H, C(2)H*H*), 1.58-1.18 (m, 8H, C(6)*H*$_2$, C(7)*H*$_2$, C(8)*H*$_2$, C(9)*H*$_2$), 1.38 (s, 18H, C(14)*H*$_3$×6); ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.0 (*C*(20)), 163.1 (*C*(3)), 150.2 (C(16) ×2), 142.8 (*C*(19)), 137.4, 130.8 (*C*(17)×2, *C*(18)×2), 130.3 (*C*(10)H×2), 128.6, 125.7 (*C*(12)H×4, *C*(13)H×4), 121.9 (*C*(11)H), 61.8 (*C*(4)H), 60.1 (*C*(1)H), 55.1 (*C*(5)H), 40.4 (*C*(2)H$_2$), 34.6 (*C*(15) ×2), 31.4 (*C*(14)H$_3$×6), 33.0, 28.2, 28.0, 24.3 (*C*(6)H$_2$, *C*(7)H_2, *C*(8)H_2, *C*(9)H_2); HRMS (ESI$^+$) calculated for $[C_{36}H_{46}N_4O_2S+Na]^+$ 621.3234, found 621.3227 (Δ1.5 ppm).

Dimethyl 2'-(2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)hydrazinyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate, LH4



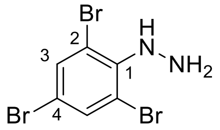
4-Methoxycarbonylphenyl boronic acid (54.0 mg) was subjected to the general procedure H to give the title compound (11.6 mg, 19%) as a colourless solid. Melting point = 93-95 °C; $[\propto]_D^{20}$ = +28.8 (*c* 0.25, $CHCl_3$); ν_{max} (thin film)/cm^{-1} 3299, 2949, 2363, 2342, 1706, 1400, 1278; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.5 Hz, 4H, C(17)*H*×4), 7.65 (d, *J* = 8.5 Hz, 4H, C(16)*H*×4), 7.19-7.17 (m, 2H, C(14)*H*×2), 7.13-7.10 (m, 1H, C(15)*H*), 6.48 (d, *J* = 4.1 Hz, 1H, N(12)*H*), 6.20 (d, *J* = 4.4 Hz, 1H, N(13)*H*), 5.83 (br s, 1H, N*H*), 5.01 (br s, 1H, N*H*), 4.45 (dd, *J* = 7.6, 5.0 Hz, 1H, C(3)*H*), 4.22-4.21 (m, 1H, C(4)*H*), 3.04-3.01 (m, 1H, C(7)*H*), 2.88 (dd, *J* = 12.9, 5.0 Hz, 1H, C(5)*H*H), 2.84 (d, *J* = 12.9 Hz, 1H, C(5)H*H*), 1.67-1.12 (m, 8H, C(8)*H*$_2$, C(9)*H*$_2$, C(10)*H*$_2$, C(11)*H*$_2$,); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6 (*C*(23)O), 166.9 (*C*(25)O), 163.3 (*C*(6)O), 145.2 (*C*(19) ×2), 142.7 (*C*(21) ×2), 130.8 (*C*(14)H×2), 130.4 (*C*(22)), 130.1 (*C*(17)H×4), 129.1 (*C*(20)×2), 129.0 (*C*(16)H×4), 122.4 (*C*(15)H), 61.7 (*C*(4)H), 60.0 (*C*(3)H), 55.3 (*C*(7)H), 52.3 (*C*(18)H_3×2), 40.4 (*C*(5)H_2), 33.0, 28.2, 28.0, 24.6 (*C*(8)H_2, *C*(9)H_2, *C*(10)H_2, *C*(11)H_2); HRMS (ESI$^+$) calculated for $[C_{32}H_{34}N_4O_6S+Na]^+$ 625.2091, found 625.2101 (Δ-1.5 ppm).

N'-(4,4''-Bis(morpholinosulfonyl)-[1,1':3',1''-terphenyl]-2'-yl)-5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanehydrazide, LH5



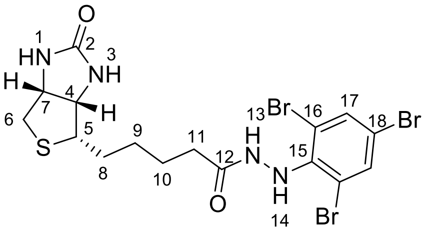
4-(4-Morpholinylsulfonyl)phenylboronic acid (83.0 mg) was subjected to the general procedure H to give the title compound (32.7 mg, 41%) as a yellow solid. Melting point = 162-165 °C; $[\propto]_D^{20}$ = +22.4 (*c* 0.25, CHCl$_3$); ν_{max} (thin film)/cm^{-1} 3326, 2921, 2859, 2247, 1698, 1165, 728; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.83 (d, *J* = 8.5 Hz, 4H, C(7)*H*×4), 7.75 (d, *J* = 8.5 Hz, 4H, C(6)*H*×4), 7.19-7.10 (m, 3H, C(8)*H*×2, C(9)*H*), 7.02 (br s, 1H, N(18)*H*), 6.10 (br s, 1H, N(21)*H*), 5.99 (br s, 1H, N(20)*H*), 5.13 (br s, 1H, N(19)*H*), 4.43 (dd, *J* = 7.6, 5.0 Hz, 1H, C(1)*H*), 4.21 (dd, *J* = 7.6, 4.7 Hz, 1H, C(5)*H*), 3.78-3.76 (m, 8H, C(10)*H*$_2$×4), 3.08-3.06 (m, 8H, C(11)*H*$_2$×4), 3.05-3.03 (m, 1H, C(4)*H*), 2.84 (dd, *J* = 12.9, 5.0 Hz, 1H, C(2)*H*H), 2.64 (d, *J* = 12.6, 1H, C(2)H*H*), 1.75-1.06 (m, 8H, C*H*$_2$×4); ^{13}C NMR (126 MHz, CDCl$_3$) δ 172.1 (*C*(13)O), 163.5 (*C*(3)O), 145.5(*C*(15)×2), 142.7 (*C*(14)) , 133.8 (*C*(17) ×2), 131.2 (*C*(8)H×2), 129.8 (*C*(6)H×4), 129.2 (*C* (16) ×2), 128.4 (*C*(7)H×4), 122.3 (*C*(9)H), 66.1 (*C*(10)H$_2$×4), 61.7 (*C*(5)H), 60.0 (*C*(1)H), 55.5 (*C*(4)H), 46.0 (*C*(11)H$_2$×4), 40.4 (*C*(2)H$_2$), 33.1, 28.2, 28.0, 24.6 (*C*H$_2$×4); HRMS (ESI$^+$ in MeCN) calculated for $[C_{36}H_{44}N_6O_8S_3+Na]^+$ 807.2275, found 807.2301 (Δ-3.3 ppm).

(2,4,6-Tribromophenyl)hydrazine, 324



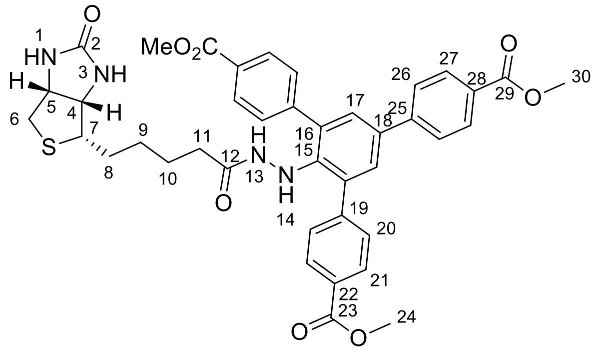
A solution of $NaNO_2$ (207 mg, 3.00 mmol) in H_2O (1.7 mL) was added dropwise to a white suspension of 2,4,6-tribromoaniline (**323**) (500 mg, 1.50 mmol) in aqueous HCl (37%, 5 mL) while cooling with an ice-water bath. The reaction mixture was stirred at 0 ^{0}C for 1 h to give a yellow suspension. Then a solution of $SnCl_2$ (569 mg, 3.00 mmol) in aqueous HCl (37%, 1.2 mL) was added dropwise at 0 °C. The reaction was stirred for 30 min before being warmed to rt and further stirred for 2 h to give a thick yellow suspension. The reaction was cooled to 0 °C, and solid sodium hydroxide was added until the pH = 9. The resulting yellow suspension was extracted with diethyl ether, dried over sodium sulphate, concentrated *in vacuo*, and purified *via* column chromatography (petrol: ether, 1:1) to afford the product as a white solid (373 mg, 72%). Melting point = 144-145 ^{0}C; ν_{max} (thin film)/cm^{-1} 3251, 3070, 1543, 1122, 856, 791; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (s, 2H, C(3)$\underline{H}$ ×2), 5.42 (br s, 1H, N$\underline{H}$), 3.86 (br s, 1H, N$\underline{H}$); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.6 ($\underline{C}$(1)), 135.1 ($\underline{C}$(3)H×2), 117.2 ($\underline{C}$(2) ×2), 116.1 ($\underline{C}$(4)); HRMS (ESI$^+$) calculated for $[C_6H_5Br_3N_2+H]^+$ 342.8076, found 342.8078 (Δ-2.1 ppm).

5-((3a*S*,4*S*,6a*R*)-2-Oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-N'-(2,4,6-tribromophenyl)pentanehydrazide, 325



(2,4,6-Tibromophenyl)hydrazine (**324**, 373 mg, 1.08 mmol), D-biotin (240 mg, 0.984 mmol), *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (188 mg, 0.984 mmol), and 1-hydroxybenzotriazole anhydrous (132 mg, 0.984 mmol) were dissolved in DMF (15 mL). The yellow solution was stirred at rt for 24 h, and diethyl ether (15 mL) was added to give a white suspension which was then filtered to give the product as a white solid (368 mg, 66%). Melting point = 175-177 ^{0}C; $[\propto]_D^{20}$ = +19.6 (*c* 0.25, MeOH); ν_{max} (thin film)/cm^{-1} 3255, 2924, 2857, 1698, 1661, 1436, 854; ^{1}H NMR (500 MHz, DMSO-d6) δ 9.95 (d, *J* = 2.0 Hz, 1H, N(13)*H*), 7.75 (s, 2H, C(17)*H*×2), 6.98 (d, *J* = 1.9 Hz, 1H, N(14)*H*), 6.43 (s, 1H, N(3)*H*), 6.37 (s, 1H, (N(1)*H*), 4.31 (dd, *J* = 7.6, 5.4 Hz, 1H, C(7)*H*), 4.13-4.12 (m, 1H, C(4)*H*), 3.08-3.06 (m, 1H, C(5)*H*), 2.82 (dd, *J* = 12.5, 5.2 Hz, 1H, C(6)*H*H), 2.58 (d, *J* =12.5 Hz, 1H, C(6)H*H*), 2.12-2.09 (m, 2H, C(11)H_2), 1.64-1.24 (m, 6H, C(8)H_2, C(9)H_2, C(10)H_2); ^{13}C NMR (126 MHz, DMSO-d6) δ 171.9 (*C*(12)O), 163.2 (*C*(2)O), 143.6 (*C*(15)), 135.1 (*C*(17)H×2), 114.0 (*C*(16) ×2), 113.4 (*C*(18)), 61.5 (*C*(4)H), 59.7 (*C*(7)H), 55.9 (*C*(5)H), 40.3 (*C*(6)H$_2$), 33.0 (*C*(11)H$_2$), 28.7, 28.5, 25.3 (*C*(8)H$_2$, *C*(9)H$_2$, *C*(10)H$_2$); HRMS (ESI$^+$) calculated for $[C_{16}H_{19}Br_3N_4O_2S+Na]^+$ 590.8671, found 590.8675 (Δ1.4 ppm).

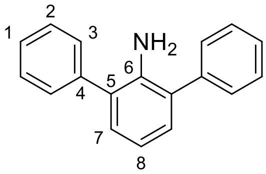
Dimethyl 5'-(4-(methoxycarbonyl)phenyl)-2'-(2-(5-((3a*S*,4*S*,6a*R*)-2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoyl)hydrazinyl)-[1,1':3',1''-terphenyl]-4,4''-dicarboxylate, 326



5-((3aS,4S,6aR)-2-Oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-N'-(2,4,6-tribromophenyl)pentanehydrazide (**325**, 50.0 mg, 0.0876 mmol), 4-methoxycarbonylphenyl boronic acid (63.0 mg, 0.350 mmol), Pd(OAc)$_2$ (1.0 mg, 0.00438 mmol), 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl (3.3 mg, 0.00657 mmol), aqueous Na$_2$CO$_3$ (2 M, 0.32 mL), and 1,2-dimethoxyethane (0.64 mL) were placed in a sealed tube, and degassed with argon. The suspension was then heated at 80 ^{0}C for 48 h, and the crude mixture was directly purified by column chromatography (CH$_2$Cl$_2$: MeOH, 95:5) to give the title compound (4.2 mg, 7%) as a yellow solid. Melting point = 134-136 ^{0}C; $[\propto]_D^{20}$ = +23.2 (*c* 0.125, CHCl$_3$); ν_{max} (thin film)/cm^{-1} 3331, 2950, 2360, 2342, 1717, 1278, 1113; ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.09 (d, *J* = 8.2 Hz, 4H, C(21)$\underline{H}$×4), 7.99 (d, *J* = 8.4 Hz, 2H, C(28)$\underline{H}$×2), 7.63 (d, *J* = 8.4 Hz, 4H, C(20)$\underline{H}$×4), 7.57 (d, *J* = 8.5 Hz, 2H, C(26)$\underline{H}$×2), 7.38 (s, 2H, C(17)$\underline{H}$×2), 6.35 (d, *J* = 4.1 Hz, 1H, N(13)$\underline{H}$), 6.14 (d, *J* = 4.1 Hz, 1H, N(14)$\underline{H}$), 5.48, 4.76 (br s ×2, 2H, N(1)$\underline{H}$, N(3)$\underline{H}$), 4.39-4.37 (m, 1H, C(5)$\underline{H}$), 4.16-4.13 (m, 1H, C(4)$\underline{H}$), 3.89 (s, 6H, C(24)$\underline{H}_3$×2), 3.85 (s, 3H, C(30)$\underline{H}_3$), 2.97-2.96 (m, s, C(7)$\underline{H}$), 2.79 (dd, *J* = 12.8, 5.0 Hz, 1H, C(6)$\underline{H}$H), 2.58 (d, *J* = 12.9 Hz, 1H, C(6)H$\underline{H}$), 1.60-1.07 (m, 8H, C(8)$\underline{H}_2$, C(9)$\underline{H}_2$, C(10)$\underline{H}_2$, C(11)$\underline{H}_2$); ^{13}C NMR (126 MHz, CDCl$_3$) δ 171.7 ($\underline{C}$(12)O), 167.0, 166.9 ($\underline{C}$(23)O, $\underline{C}$(30)O), 163.1 ($\underline{C}$(2)O), 144.9, 144.3, 143.0, 134.0, 130.8, 130.3 ($\underline{C}$(21)H×4), 130.2

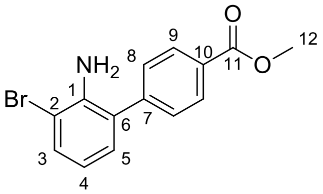
($\underline{C}$(27)H×2), 129.5 ($\underline{C}$(17)H×2), 129.4, 129.1 ($\underline{C}$(20)H×4), 128.8, 126.6 ($\underline{C}$(26)H×2), 61.8 ($\underline{C}$(4)H), 60.0 ($\underline{C}$(5)H), 55.3 ($\underline{C}$(7)H), 52.4 ($\underline{C}$(24)H_3×2), 52.2 ($\underline{C}$(30)H_3), 40.5 ($\underline{C}$(6)H_2), 33.0, 28.2, 28.1, 24.6 ($\underline{C}$(8)H_2, $\underline{C}$(9)H_2, $\underline{C}$(10)H_2, $\underline{C}$(11)H_2); HRMS (ESI^+) calculated for $[C_{40}H_{40}N_4O_8S+Na]^+$ 759.2459, found 759.2456 (Δ1.0 ppm).

2,6-Diphenylaniline, LH2A



2,6-dibromoaniline (50.2 mg, 0.200 mmol), phenylboronic acid (56.1 mg, 0.460 mmol), $Pd_2(dba)_3$ (0.9 mg, 0.001 mmol) and triphenylphosphine (1.1 mg, 0.004 mmol) were placed in a sealed tube and degassed with argon. Toluene (0.7 mL) was added and the resulting dark red mixture was stirred at room temperature for 10 min until the color became green. Ethanol (0.12 mL), water (0.12 mL) and Na_2CO_3 (84.8 mg, 0.800 mmol) were then added. The resulting mixture was stirred at 95 ^{0}C for 22 h and allowed to cool down to room temperature. Water (15 mL) was added and the aqueous layer was extracted with diethyl ether (3×15 mL). The organic layer was combined, dried over $MgSO_4$ and evaporated under vacuum. Purification by column chromatography (toluene: cyclohexane, 3:7) to give the title compound as a white solid (44.7 mg, 91%). Melting point = 70-71 ^{0}C (lit. 74 ^{0}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56-7.47 (m, 8H), 7.41-7.47 (m, 2H), 7.16 (d, *J* = 7.3 Hz, 2H, C(7)$\underline{H}$×2), 6.93-6.90 (m, 1H, C(8)$\underline{H}$), 3.76 (br s, 2H, N$\underline{H}_2$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.8 ($\underline{C}$(6)), 139.8 ($\underline{C}$(4) ×2), 129.8 ($\underline{C}$(7)H×2), 129.4 ($\underline{C}$(3)H×4), 128.9 ($\underline{C}$(2)H×4), 128.0 ($\underline{C}$(5)), 127.3 ($\underline{C}$(1)H×2) , 118.1 ($\underline{C}$(8)H). Spectroscopic data are consistent with those previously reported.[112]

Methyl 2'-amino-3'-bromo-[1,1'-biphenyl]-4-carboxylate, 336



2,6-dibromoaniline (50.2 mg, 0.200 mmol), 4-methoxycarbonylphenyl boronic acid (82.8 mg, 0.460 mmol), $Pd_2(dba)_3$ (0.9 mg, 0.001 mmol) and triphenylphosphine (1.1 mg, 0.004 mmol) were placed in a sealed tube and degassed with argon. Toluene (0.7 mL) was added and the resulting dark red mixture was stirred at room temperature for 10 min until the color became green. Ethanol (0.12 mL), water (0.12 mL) and Na_2CO_3 (84.8 mg, 0.800 mmol) were then added. The resulting mixture was stirred at 95 ^{0}C for 24 h and allowed to cool down to room temperature. Water (15 mL) was added and the aqueous layer was extracted with diethyl ether (3×15 mL). The organic layer was combined, dried over $MgSO_4$ and evaporated under vacuum. Purification by column chromatography (petrol: Et_2O, 8:2) to give the title compound as a light yellow solid (19.4 mg, 32%). Melting point = 94-96 ^{0}C (lit. 74 ^{0}C); ν_{max} (thin film)/cm^{-1} 3476, 3377, 1720, 1278, 782; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.04 (m, 2H, C(9)$\underline{H}$×2), 7.47-7.43 (m, 2H, C(8)$\underline{H}$×2), 7.37 (dd, *J* = 8.0, 1.3 Hz, 1H, C(3)$\underline{H}$), 6.98 (dd, *J* = 7.6, 1.5 Hz, 1H, C(5)$\underline{H}$), 6.62 (t, *J* = 7.8 Hz, 1H, C(4)$\underline{H}$), 4.13 (br s, 1H, N$\underline{H}$), 3.88 (s, 3H, C(12)$\underline{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8 ($\underline{C}$(11)O), 143.8 ($\underline{C}$(1)), 141.3 ($\underline{C}$(7)), 132.4 ($\underline{C}$(3)H), 130.3 ($\underline{C}$(9)H), 129.4 ($\underline{C}$(5)H), 129.4, 127.5 ($\underline{C}$(6), $\underline{C}$(10)), 129.1 ($\underline{C}$(8)H), 119.0 ($\underline{C}$(4)H), 110.1 ($\underline{C}$(2)), 52.2 ($\underline{C}$(12)H_3); HRMS (ESI$^+$) calculated for $[C_{14}H_{12}NO_2Br+H]^+$ 306.0124, found 306.0120 (Δ-1.5 ppm).

6 References

[1] C. S. Cho, B. T. Kim, T. J. Kim, S. C. Shim, *Tetrahedron Lett.* **2002**, *43*, 7987-7989.

[2] C. S. Cho, B. T. Kim, T. J. Kim, S. C. Shim, *J. Org. Chem.* **2001**, *66*, 9020-9022.

[3] R. Martinez, G. J. Brand, D. J. Ramon, M. Yus, *Tetrahedron Lett.* **2005**, *46*, 3683-3686.

[4] R. Martinez, D. J. Ramon, M. Yus, *Tetrahedron* **2006**, *62*, 8988-9001.

[5] T. Kuwahara, T. Fukuyama, I. Ryu, *Org. Lett.* **2012**, *14*, 4703-4705.

[6] K. Maeda, Y. Obora, S. Sakaguchi, Y. Ishii, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 689-696.

[7] S. Bhat, V. Sridharan, *Chem. Commun.* **2012**, *48*, 4701-4703.

[8] G. Onodera, Y. Nishibayashi, S. Uemura, *Angew. Chem., Int. Ed.* **2006**, *45*, 3819-3822.

[9] P. Satyanarayana, G. M. Reddy, H. Maheswaran, M. L. Kantam, *Adv. Synth. Catal.* **2013**, *355*, 1859-1867.

[10] M. S. Kwon, N. Khn, S. H. Seo, I. S. Park, R. K. Cheedrala, J. Park, *Angew. Chem., Int. Ed.* **2005**, *44*, 6913-6915.

[11] Y. M. A. Yamada, Y. Uozumi, *Org. Lett.* **2006**, *8*, 1375-1378.

[12] C. S. Cho, *Journal of Molecular Catalysis a-Chemical* **2005**, *240*, 55-60.

[13] M. S. Kwon, N. Kim, C. M. Park, J. S. Lee, K. Y. Kang, J. Park, *Org. Lett.* **2005**, *7*, 1077-1079.

[14] F. Alonso, P. Riente, M. Yus, *Eur. J. Org. Chem.* **2008**, 4908-4914.

[15] S. H. Liao, K. K. Yu, Q. Li, H. W. Tian, Z. P. Zhang, X. C. Yu, Q. Xu, *Org. Biomol. Chem.* **2012**, *10*, 2973-2978.

[16] X. Cui, Y. Zhang, F. Shi, Y. Deng, *Chemistry-a European Journal* **2011**, *17*, 1382-1382.

[17] Y. Iuchi, Y. Obora, Y. Ishii, *J. Am. Chem. Soc.* **2010**, *132*, 2536.

[18] S. J. Pridmore, J. M. J. Williams, *Tetrahedron Lett.* **2008**, *49*, 7413-7415.

[19] L. Guo, Y. H. Liu, W. B. Yao, X. B. Leng, Z. Huang, *Org. Lett.* **2013**, *15*, 1144-1147.

[20] C. Lofberg, R. Grigg, M. A. Whittaker, A. Keep, A. Derrick, *J. Org. Chem.* **2006**, *71*, 8023-8027.

[21] T. Sawaguchi, Y. Obora, *Chem. Lett.* **2011**, *40*, 1055-1057.

[22] M. Morita, Y. Obora, Y. Ishii, *Chem. Commun.* **2007**, 3306-3306.

[23] P. A. Slatford, M. K. Whittlesey, J. M. J. Williams, *Tetrahedron Lett.* **2006**, *47*, 6787-6789.

[24] M. G. Edwards, J. M. J. Williams, *Angew. Chem., Int. Ed.* **2002**, *41*, 4740-4743.

[25] S. Whitney, R. Grigg, A. Derrick, A. Keep, *Org. Lett.* **2007**, *9*, 3299-3302.

[26] K. Fujita, K. Yamamoto, R. Yamaguchi, *Org. Lett.* **2002**, *4*, 2691-2694.

[27] B. Blank, R. Kempe, *J. Am. Chem. Soc.* **2010**, *132*, 924.

[28] Y. Obora, S. Ogawa, N. Yamamoto, *J. Org. Chem.* **2012**, *77*, 9429-9433.

[29] K. I. Fujita, Y. Enoki, R. Yamaguchi, *Tetrahedron* **2008**, *64*, 1943-1954.

[30] M. Haniti, S. A. Hamid, J. M. J. Williams, *Tetrahedron Lett.* **2007**, *48*, 8263-8265.

[31] M. Morita, Y. Obora, Y. Ishii, *Chem. Commun.* **2007**, 2850-2852.

[32] K. Taguchi, H. Nakagawa, T. Hirabayashi, S. Sakaguchi, Y. Ishii, *J. Am. Chem. Soc.* **2004**, *126*, 72-73.

[33] C. Lofberg, R. Grigg, A. Keep, A. Derrick, V. Sridharan, C. Kilner, *Chem. Commun.* **2006**, 5000-5002.

[34] www.methanol.org.

[35] N. Ortega, C. Richter, F. Glorius, *Org. Lett.* **2013**, *15*, 1776-1779.

[36] J. Moran, A. Preetz, R. A. Mesch, M. J. Krische, *Nature Chemistry* **2011**, *3*, 287-290.

[37] M. Nielsen, E. Alberico, W. Baumann, H. J. Drexler, H. Junge, S. Gladiali, M. Beller, *Nature* **2013**, *495*, 85-89.

[38] R. E. Rodriguez-Lugo, M. Trincado, M. Vogt, F. Tewes, G. Santiso-Quinones, H. Grutzmacher, *Nature Chemistry* **2013**, *5*, 342-347.

[39] P. Hu, Y. Diskin-Posner, Y. Ben-David, D. Milstein, *Acs Catalysis* **2014**, *4*, 2649-2652.

[40] R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, *Tetrahedron Lett.* **1981**, *22*, 4107-4110.

[41] K. Motokura, N. Fujita, K. Mori, T. Mizugaki, K. Ebitani, K. Htsukawa, K. Kanedar, *Chemistry-a European Journal* **2006**, *12*, 8228-8239.

[42] R. Grigg, T. R. B. Mitchell, S. Sutthivaiyakit, N. Tongpenyai, *Journal of the Chemical Society-Chemical Communications* **1981**, 611-612.

[43] F. Li, J. J. Xie, H. X. Shan, C. L. Sun, L. Chen, *Rsc Advances* **2012**, *2*, 8645-8652.

[44] C. L. Sun, X. Y. Zou, F. Li, *Chemistry-a European Journal* **2013**, *19*, 14030-14033.

[45] S. Ogawa, Y. Obora, *Chem. Commun.* **2014**, *50*, 2491-2493.

[46] Y. Li, H. Li, H. Junge, M. Beller, *Chem. Commun.* **2014**, *50*, 14991-14994.

[47] M. J. Schultz, M. S. Sigman, *Tetrahedron* **2006**, *62*, 8227-8241.

[48] K. Sato, M. Aoki, J. Takagi, R. Noyori, *J. Am. Chem. Soc.* **1997**, *119*, 12386-12387.

[49] D. Morales-Morales, R. Redon, Z. H. Wang, D. W. Lee, C. Yung, K. Magnuson, C. M. Jensen, *Canadian Journal of Chemistry-Revue Canadienne De Chimie* **2001**, *79*, 823-829.

[50] F. Hanasaka, K. Fujita, R. Yamaguchi, *Organometallics* **2005**, *24*, 3422-3433.

[51] E. Y. Lee, Y. Kim, J. S. Lee, J. Park, *Eur. J. Org. Chem.* **2009**, 2943-2946.

[52] N. A. Owston, A. J. Parker, J. M. J. Williams, *Chem. Commun.* **2008**, 624-625.

[53] M. I. Hall, S. J. Pridmore, J. M. J. Williams, *Adv. Synth. Catal.* **2008**, *350*, 1975-1978.

[54] S. J. Taylor, M. O. Duffey, J. P. Morken, *J. Am. Chem. Soc.* **2000**, *122*, 4528-4529.

[55] C. C. Yuan, L. Yang, G. Z. Yue, T. Z. Yu, W. M. Zhong, B. Liu, *Tetrahedron Lett.* **2012**, *53*, 6972-6976.

[56] H. Sakurai, I. Kamiya, H. Kitahara, H. Tsunoyama, T. Tsukuda, *Synlett* **2009**, 245-248.

[57] Richards.Wh, V. F. Hodge, D. L. Stiggall, Yelvingt.Mb, Montgome.Fc, *J. Am. Chem. Soc.* **1974**, *96*, 6652-6657.

[58] Y. M. A. Yamada, Y. Uozumi, *Tetrahedron* **2007**, *63*, 8492-8498.

[59] M. Lamani, R. S. Guralamata, K. R. Prabhu, *Chem. Commun.* **2012**, *48*, 6583-6585.

[60] Hirsch, *Top. Stereochem.* **1967**, *3*, 199.

[61] P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek, P. Dierkes, *Chem. Rev.* **2000**, *100*, 2741-2769.

[62] aR. Spogliarich, G. Mestroni, M. Graziani, *J. Mol. Catal.* **1984**, *22*, 309-311; bC. E. Housecroft, *Coord. Chem. Rev.* **1996**, *152*, 141-156.

[63] M. J. Fernandez, M. A. Esteruelas, M. Covarrubias, L. A. Oro, *J. Organomet. Chem.* **1986**, *316*, 343-349.

[64] A. Gabrielsson, P. W. N. M. van Leeuwen, W. Kaim, *Chem. Commun.* **2006**, 4926-4927.

[65] A. Terakita, H. Matsunaga, T. Ueda, T. Eguchi, M. Echigoya, K. Umemoto, M. Godo, *Chem. Pharm. Bull.* **2004**, *52*, 546-551.

[66] S. Gowrisankar, H. Neumann, M. Beller, *Angew. Chem., Int. Ed.* **2011**, *50*, 5139-5143.

[67] A. Izumi, Y. Obora, S. Sakaguchi, Y. Ishii, *Tetrahedron Lett.* **2006**, *47*, 9199-9201.

[68] C. C. Shotton, *Part II Thesis, University of Oxford* **2014**.

[69] R. Criegee, *Annalen Der Chemie-Justus Liebig* **1948**, *560*, 127-135.

[70] S. S. C. Koch, A. R. Chamberlin, *Synth. Commun.* **1989**, *19*, 829-833.

[71] M. Miyashita, I. Shiina, S. Miyoshi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516-1527.

[72] A. Tewari, M. Hein, A. Zapf, M. Beller, *Synthesis-Stuttgart* **2004**, 935-941.

[73] C. A. Tolman, *J. Am. Chem. Soc.* **1970**, *92*, 2953

[74] C. A. Tolman, *J. Am. Chem. Soc.* **1970**, *92*, 2956.

[75] C. A. Tolman, *Chem. Rev.* **1977**, *77*, 313-348.

[76] B. Jiang, Y. Feng, E. A. Ison, *J. Am. Chem. Soc.* **2008**, *130*, 14462.

[77] D. L. Poole, *DPhil thesis, University of Oxford* **2014**.

[78] A. Musco, W. Kuran, A. Silvani, M. W. Anker, *Journal of the Chemical Society-Chemical Communications* **1973**, 938-939.

[79] E. P. Kohler, *J. Am. Chem. Soc.* **1916**, 889.

[80] D. Seebach, T. Kimmerlin, R. Sebesta, M. A. Campo, A. K. Beck, *Tetrahedron* **2004**, *60*, 7455-7506.

[81] SiliaMetS Metal Scavenger Portfolio. http://www.silicycle.com/eu/products/metal-scavengers/metal-scavengers-portfolio.

[82] N. S. Gill, K. B. James, F. Lions, K. T. Potts, *J. Am. Chem. Soc.* **1952**, *74*, 4923-4928.

[83] D. Sielemann, R. Keuper, N. Risch, *Journal Fur Praktische Chemie-Chemiker-Zeitung* **1999**, *341*, 487-491.

[84] J. S. M. Samec, J. E. Backvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237-248.

[85] R. Noyori, S. Hashiguchi, *Acc. Chem. Res.* **1997**, *30*, 97-102.

[86] Y. Blum, D. Czarkie, Y. Rahamim, Y. Shvo, *Organometallics* **1985**, *4*, 1459-1461.

[87] E. A. Ison, B. Jiang, Y. Feng, *Abstracts of Papers of the American Chemical Society* **2009**, *237.*

[88] H. Itagaki, S. Shinoda, Y. Saito, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2291-2294.

[89] Y. Iwashita, A. Hayata, *J. Am. Chem. Soc.* **1969**, *91*, 2525.

[90] X. P. Han, J. Wu, *Angew. Chem., Int. Ed.* **2013**, *52*, 4637-4640.

[91] O. H. Laitinen, V. P. Hytonen, H. R. Nordlund, M. S. Kulomaa, *Cell. Mol. Life Sci.* **2006**, *63*, 2992-3017.

[92] E. L. Smith, *Annu. Rev. Biochem.* **1954**, *23*, 245-274.

[93] U. Ragnarsson, *J. Pept. Sci.* **2007**, *13*, 431-433.

[94] Lichstei.Hc, J. Birnbaum, *Biochem. Biophys. Res. Commun.* **1965**, *20*, 41.

[95] M. Gonzalez, C. E. Argarana, G. D. Fidelio, *Biomol Eng* **1999**, *16*, 67-72.

[96] T. Sano, S. Vajda, G. O. Reznik, C. L. Smith, C. R. Cantor, *Enzyme Engineering Xiii* **1996**, *799*, 383-390.

[97] P. C. Weber, D. H. Ohlendorf, J. J. Wendoloski, F. R. Salemme, *Science* **1989**, *243*, 85-88.

[98] M. H. Qureshi, S. L. Wong, *Protein Expression Purif.* **2002**, *25*, 409-415.

[99] M. Howarth, D. J. F. Chinnapen, K. Gerrow, P. C. Dorrestein, M. R. Grandy, N. L. Kelleher, A. El-Husseini, A. Y. Ting, *Nat. Methods* **2006**, *3*, 267-273.

[100] M. Fairhead, D. Krndija, E. D. Lowe, M. Howarth, *J. Mol. Biol.* **2014**, *426*, 199-214.

[101] K. C. Neuman, A. Nagy, *Nat. Methods* **2008**, *5*, 491-505.

[102] R. O. Dror, R. M. Dirks, J. P. Grossman, H. F. Xu, D. E. Shaw, *Annual Review of Biophysics, Vol 41* **2012**, *41*, 429-452.

[103] D. S. Wilbur, M. K. Chyan, P. M. Pathare, D. K. Hamlin, M. B. Frownfelter, B. B. Kegley, *Bioconjugate Chem.* **2000**, *11*, 569-583.

[104] T. S. Mei, R. Giri, N. Maugel, J. Q. Yu, *Angew. Chem., Int. Ed.* **2008**, *47*, 5215-5219.

[105] W. Gu, S. F. Wang, *Eur. J. Med. Chem.* **2010**, *45*, 4692-4696.

[106] J. P. Gallivan, D. A. Dougherty, *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 9459-9464.

[107] J. B. Pollock, T. R. Cook, P. J. Stang, *J. Am. Chem. Soc.* **2012**, *134*, 10607-10620.

[108] G. Kada, H. Falk, H. J. Gruber, *Biochimica Et Biophysica Acta-General Subjects* **1999**, *1427*, 33-43.

[109] M. Fairhead, D. Shen, L. K. M. Chan, E. D. Lowe, T. J. Donohoe, M. Howarth, *Bioorg. Med. Chem.* **2014**, *22*, 5476-5486.

[110] N. M. Green, *Methods Enzymol.* **1990**, *184*, 51-67.

[111] S. Brenet, F. Berthiol, J. Einhorn, *Eur. J. Org. Chem.* **2013**, 8094-8096.

[112] S. Brenet, F. Berthiol, J. Einhorn, *Eur. J. Org. Chem.* **2013**, *2013*, 8094-8096.

[113] S. Scholz, H. Marschallweyerstahl, P. Weyerstahl, *Liebigs Ann. Chem.* **1985**, 1935-1950.

[114] P. Wang, J. Cai, J. B. Yang, C. L. Sun, L. S. Li, H. Y. Hu, M. Ji, *Tetrahedron Lett.* **2013**, *54*, 533-535.

[115] M. Hatzimarinaki, M. M. Roubelakis, M. Orfanopoulos, *J. Am. Chem. Soc.* **2005**, *127*, 14182-14183.

[116] Z. W. Chen, D. N. Ye, Y. P. Qian, M. Ye, L. X. Liu, *Tetrahedron* **2013**, *69*, 6116-6120.

[117] S. Kotani, K. Osakama, M. Sugiura, M. Nakajima, *Org. Lett.* **2011**, *13*, 3968-3971.

[118] P. Colbon, J. W. Ruan, M. Purdie, J. L. Xiao, *Org. Lett.* **2010**, *12*, 3670-3673.

[119] R. Fernandez, A. Ferrete, J. M. Llera, A. Magriz, E. Martin-Zamora, E. Diez, J. M. Lassaletta, *Chemistry-a European Journal* **2004**, *10*, 737-745.

[120] A. R. Hajipour, A. Zarei, L. Khazdooz, A. E. Ruoho, *Synth. Commun.* **2009**, *39*, 2702-2722.

[121] K. Fujita, C. Asai, T. Yamaguchi, F. Hanasaka, R. Yamaguchi, *Org. Lett.* **2005**, *7*, 4017-4019.

[122] S. J. Teague, *J. Org. Chem.* **2008**, *73*, 9765-9766.

[123] P. J. Wagner, E. J. Siebert, *J. Am. Chem. Soc.* **1981**, *103*, 7329-7335.

[124] J. W. Ruan, O. Saidi, J. A. Iggo, J. L. Xiao, *J. Am. Chem. Soc.* **2008**, *130*, 10510.

[125] P. S. Manchand, A. Schwartz, S. Wolff, P. S. Belica, P. Madan, P. Patel, S. J. Saposnik, *Heterocycles* **1993**, *35*, 1351-1369.

[126] J. J. Cao, F. Zhou, J. A. Zhou, *Angew. Chem., Int. Ed.* **2010**, *49*, 4976-4980.

[127] X. Y. Wang, M. C. Liu, L. Xu, Q. Z. Wang, J. X. Chen, J. C. Ding, H. Y. Wu, *J. Org. Chem.* **2013**, *78*, 5273-5281.

[128] P. Colbon, J. W. Ruan, M. Purdie, K. Mulholland, J. L. Xiao, *Org. Lett.* **2011**, *13*, 5456-5459.

[129] D. T. Ziegler, A. M. Steffens, T. W. Funk, *Tetrahedron Lett.* **2010**, *51*, 6726-6729.

[130] F. Wu, W. B. Lu, Q. Qian, Q. H. Ren, H. G. Gong, *Org. Lett.* **2012**, *14*, 3044-3047.

[131] F. Henin, A. Mboungoumpassi, J. Muzart, J. P. Pete, *Tetrahedron* **1994**, *50*, 2849-2864.

[132] L. J. Gazzard, W. B. Motherwell, D. A. Sandham, *Journal of the Chemical Society-Perkin Transactions 1* **1999**, 979-993.

[133] B. M. Trost, J. Y. Xu, T. Schmidt, *J. Am. Chem. Soc.* **2009**, *131*, 18343-18357.

[134] S. Samanta, B. K. Mishra, T. C. S. Pace, N. Sathyamurthy, C. Bohne, J. N. Moorthy, *J. Org. Chem.* **2006**, *71*, 4453-4459.

[135] L. K. M. Chan, D. L. Poole, D. Shen, M. P. Healy, T. J. Donohoe, *Angew. Chem., Int. Ed.* **2014**, *53*, 761-765.

[136] K. Okuro, J. Gurnham, H. Alper, *J. Org. Chem.* **2011**, *76*, 4715-4720.

[137] S. P. Chavan, K. R. Harale, V. G. Puranik, R. L. Gawade, *Tetrahedron Lett.* **2012**, *53*, 2647-2650.

[138] J. Kulhanek, O. Pytela, *Collect. Czech. Chem. Commun.* **1997**, *62*, 913-924.

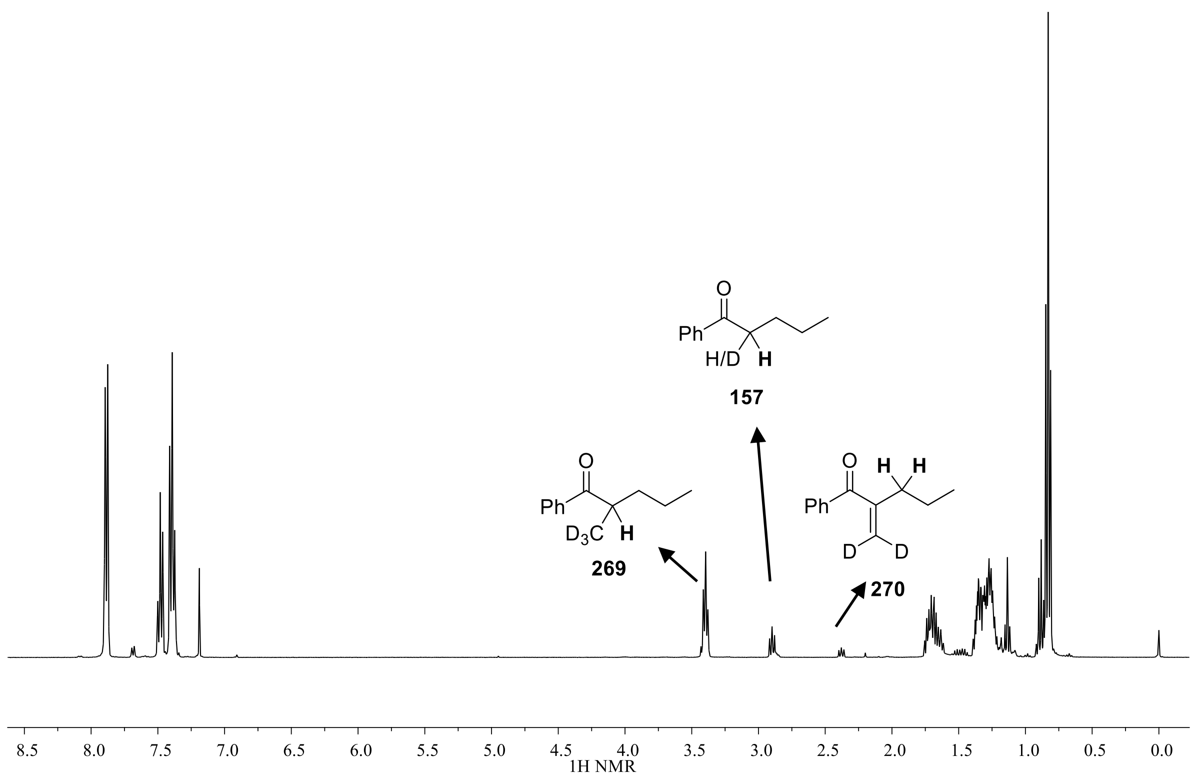
[139] T. Aubineau, J. Cossy, *Chem. Commun.* **2013**, *49*, 3303-3305.

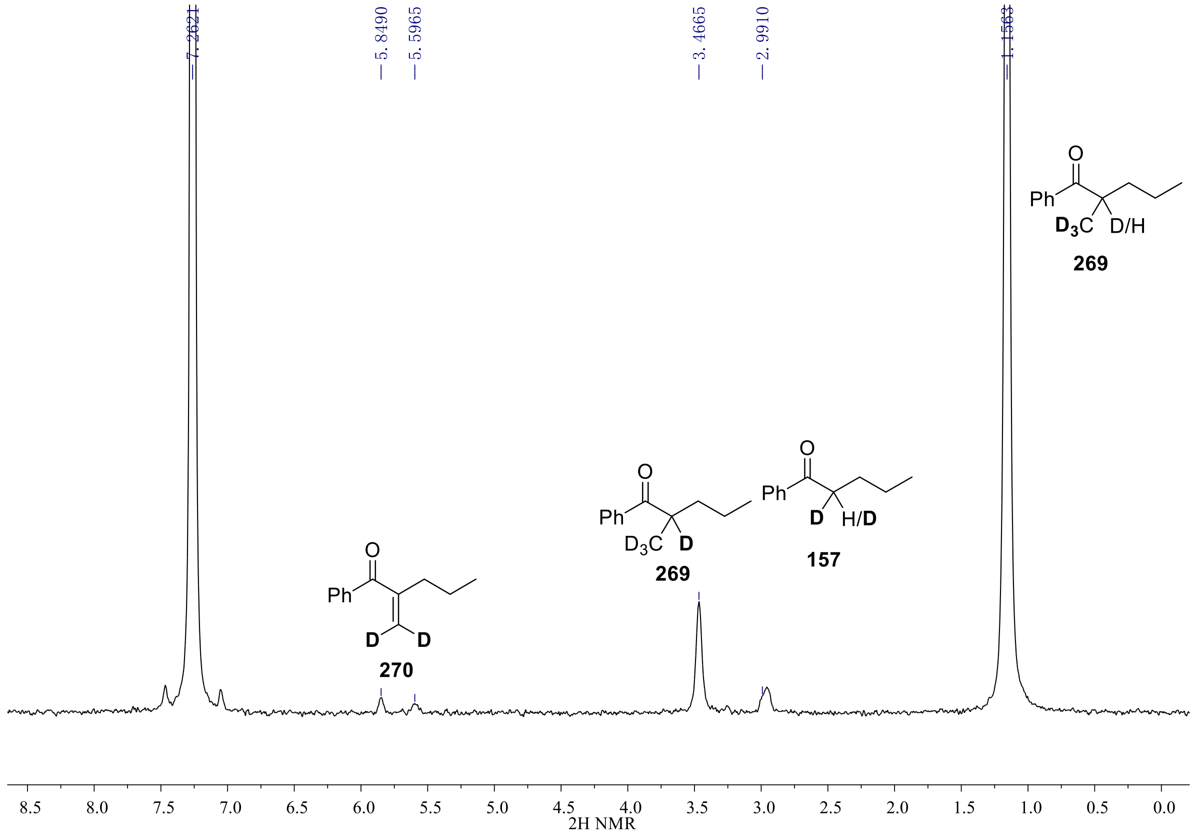
[140] A. Kayushin, A. Demekhina, M. Korosteleva, A. Miroshnikov, A. Azhayev, *Nucleosides Nucleotides & Nucleic Acids* **2011**, *30*, 490-502.

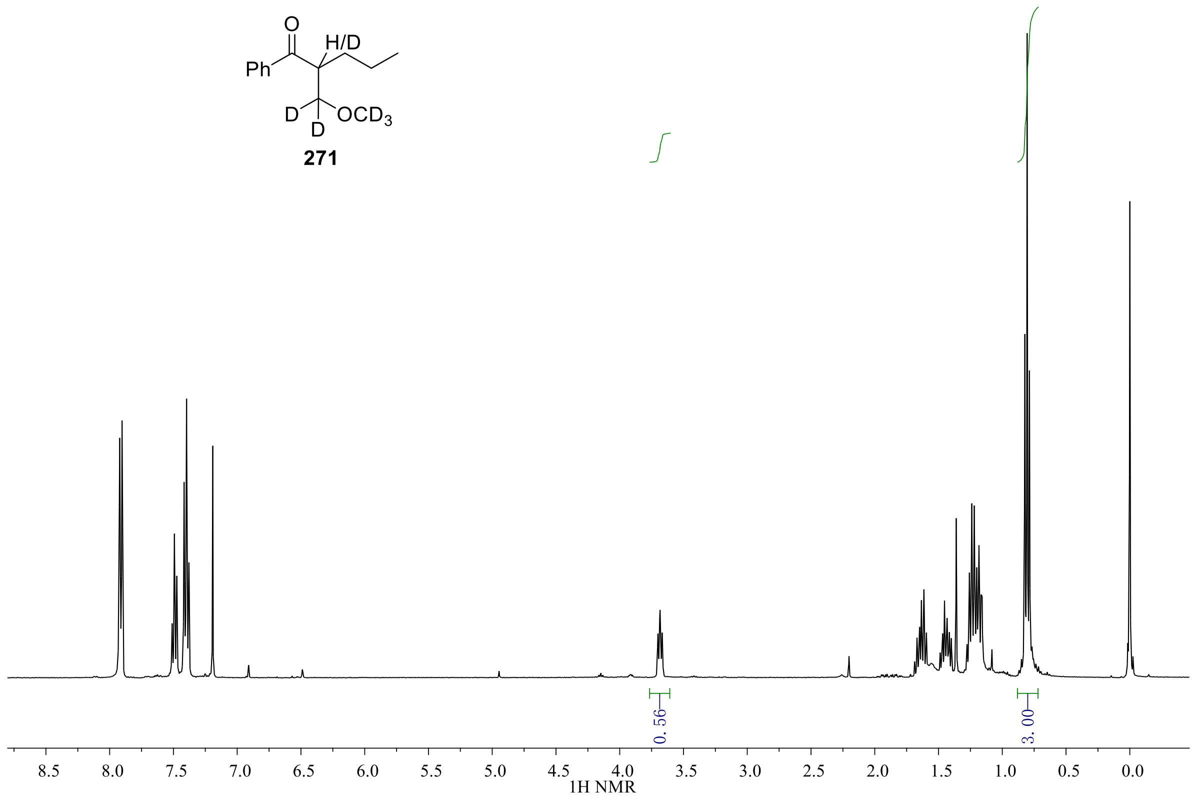
[141] E. Gerard, A. Meulle, O. Feron, J. Marchand-Brynaert, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 586-590.

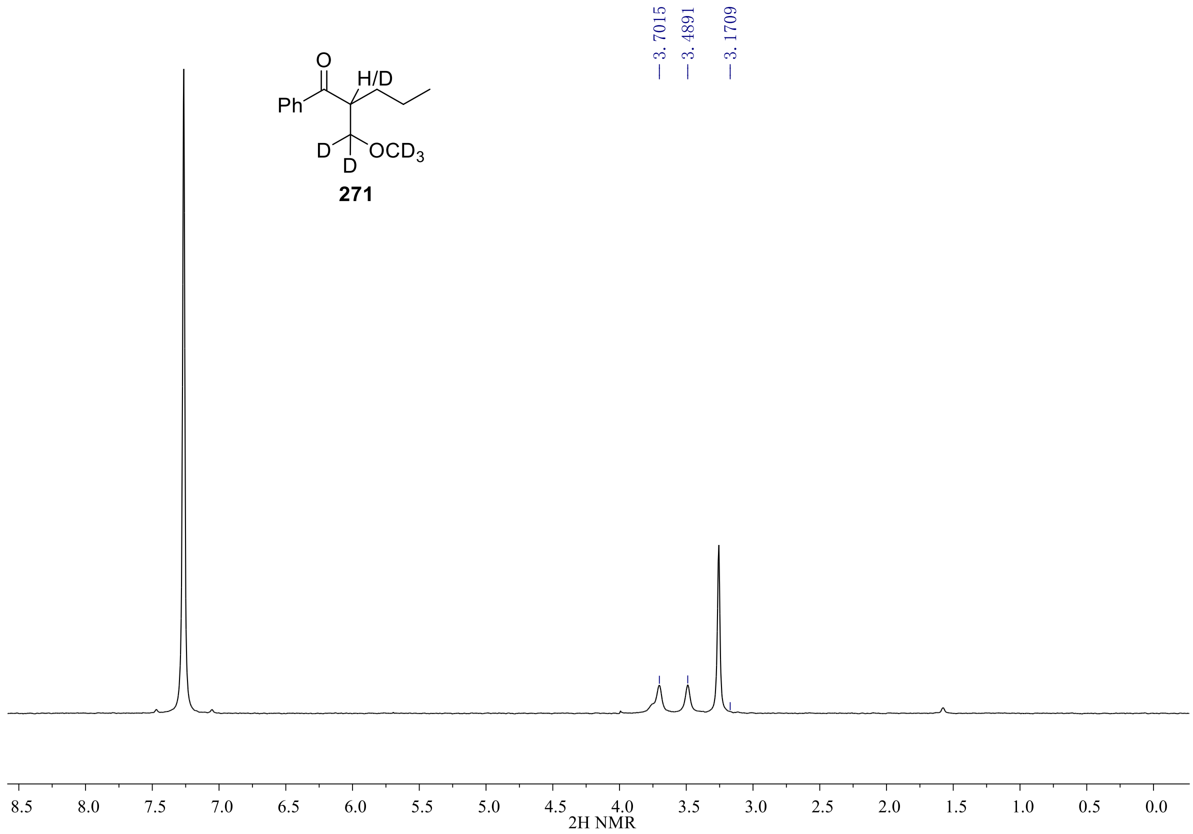
Appendix-Deuterium experiments

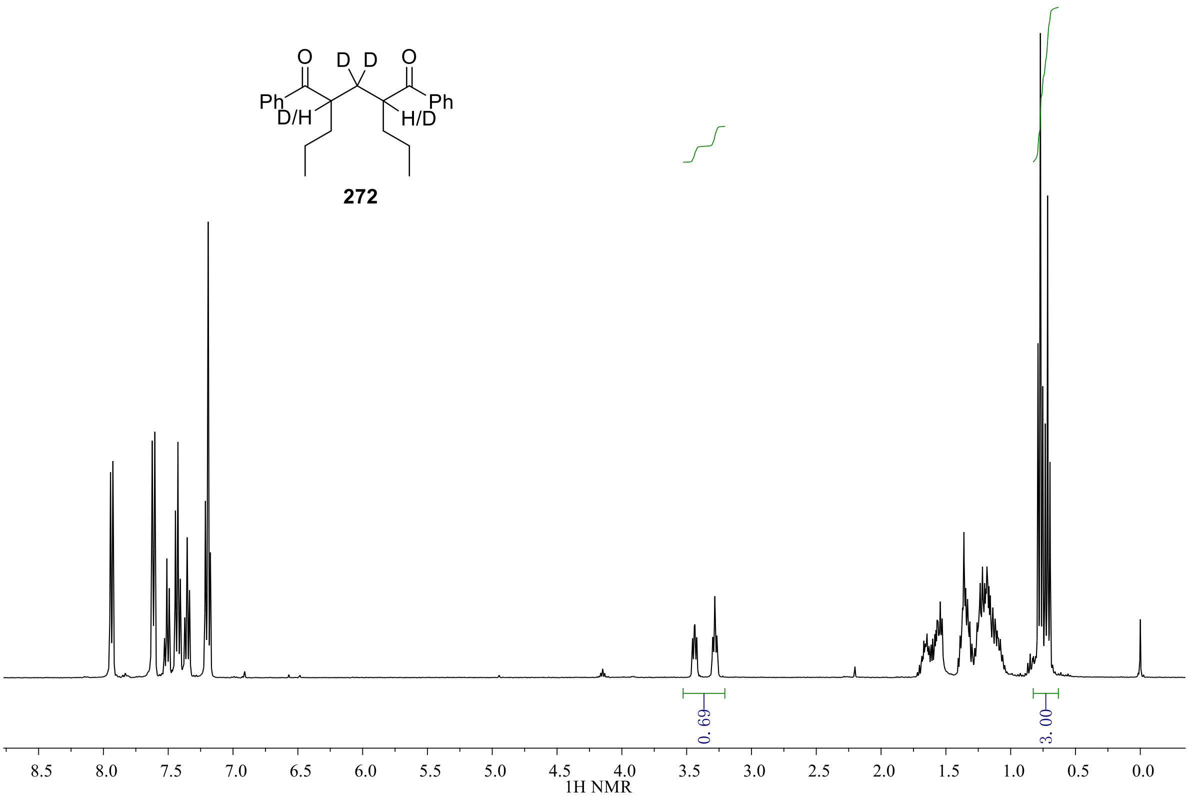
A1.1 Methylation reaction of valerophenone in CD3OH

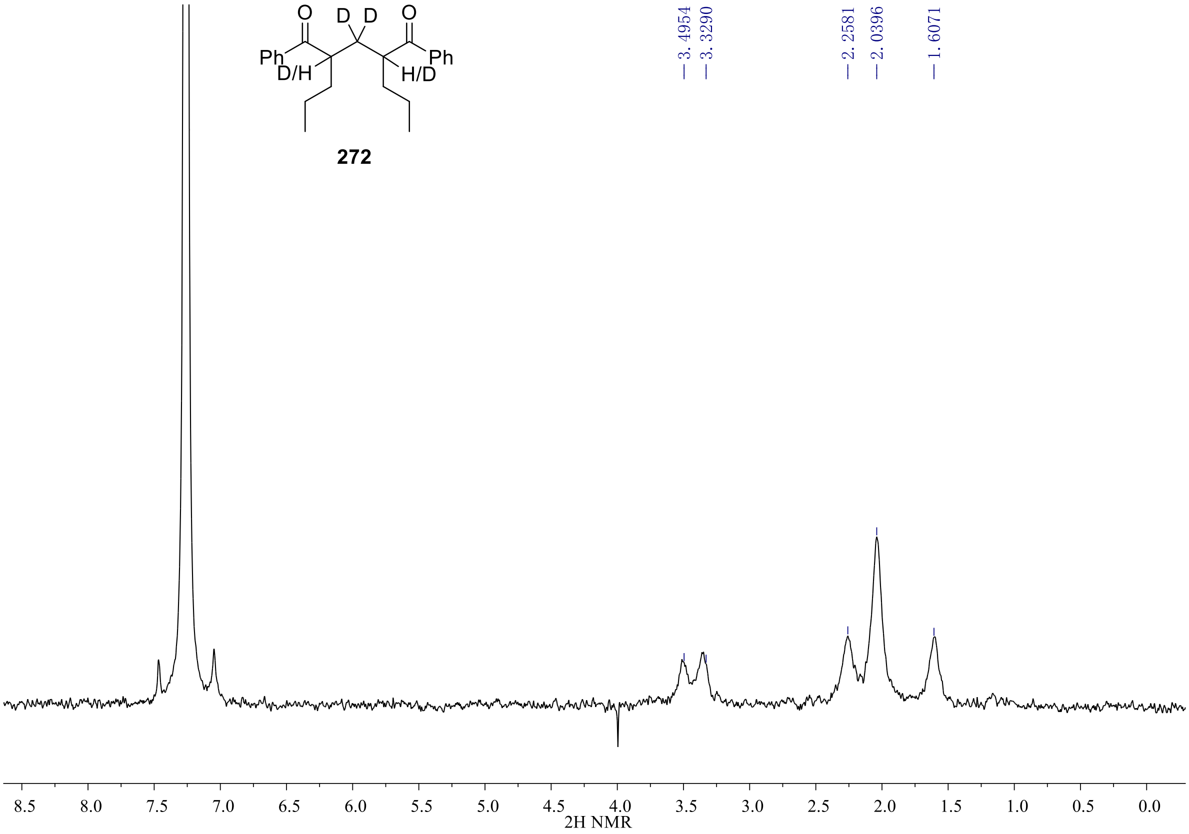




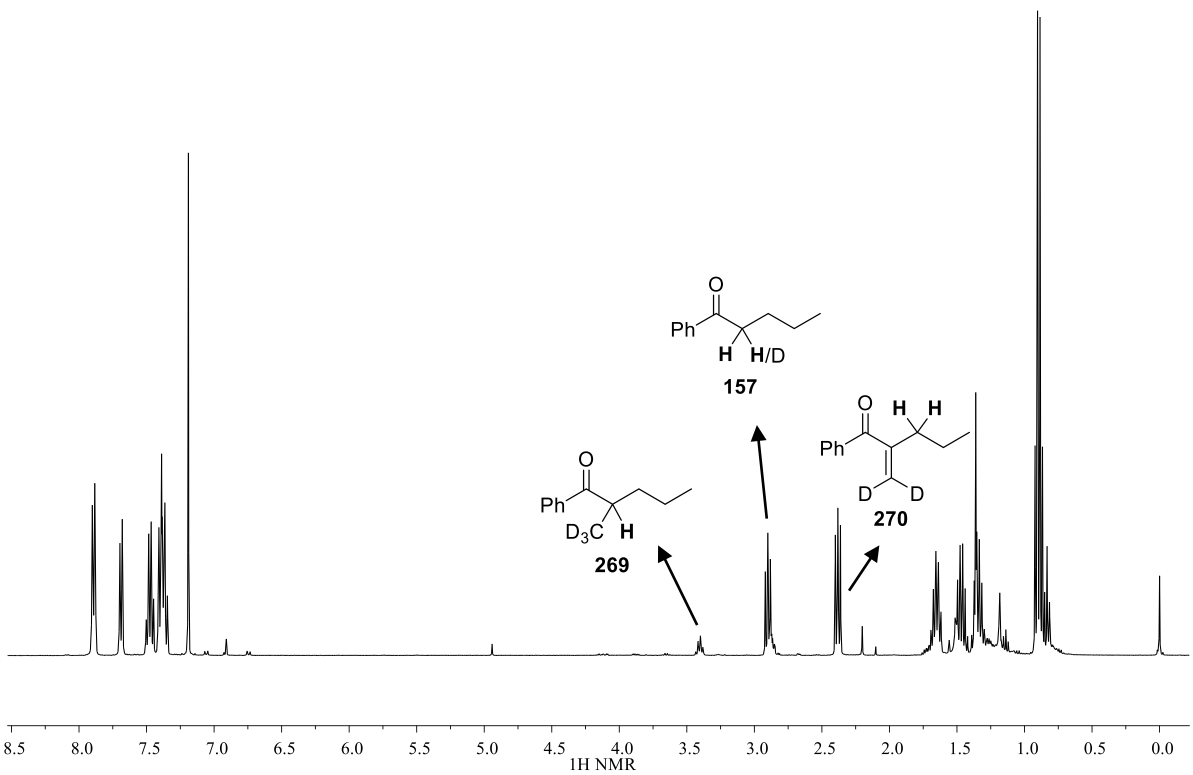

O
H/D
Ph
D
D
OCD3
271
0.56
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H NMR

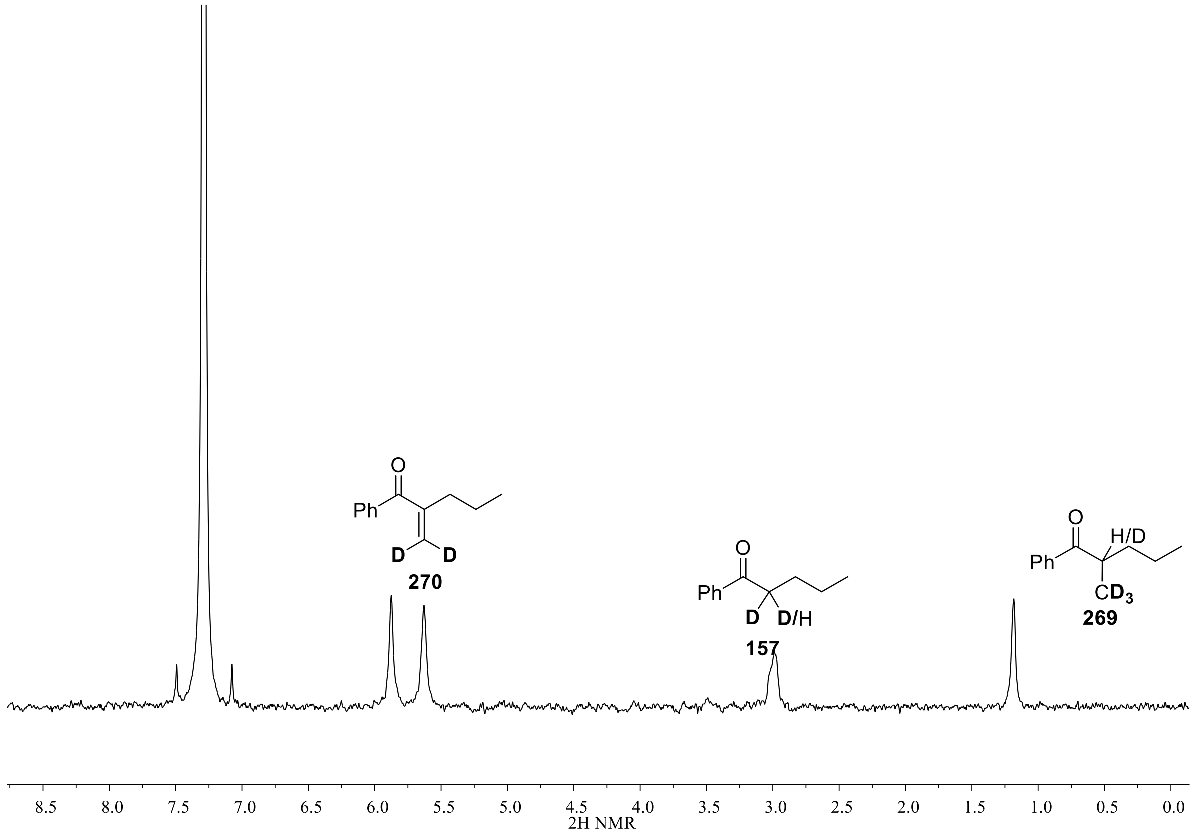

3.7015
3.4891
3.1709
O
H/D
Ph
D
D
OCD3
271
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2H NMR

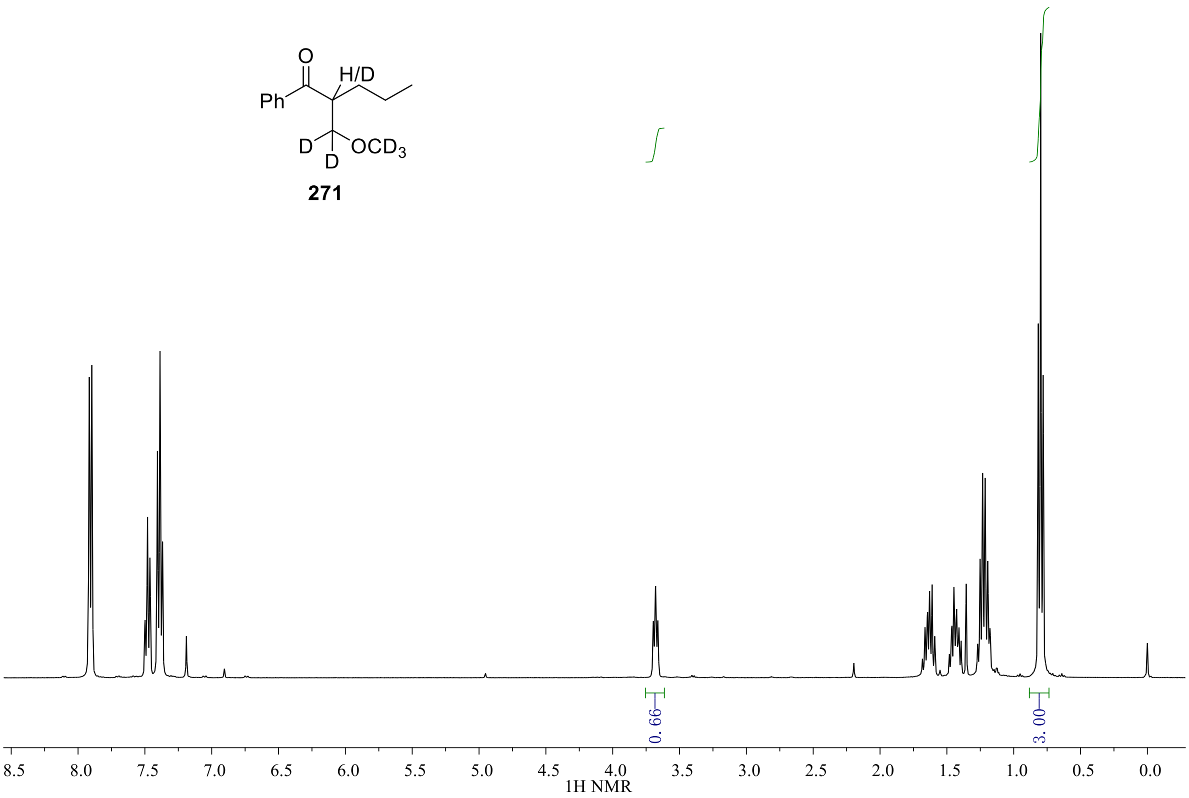

O
D D
O
Ph
D/H
H/D
Ph
272
0.69
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H NMR

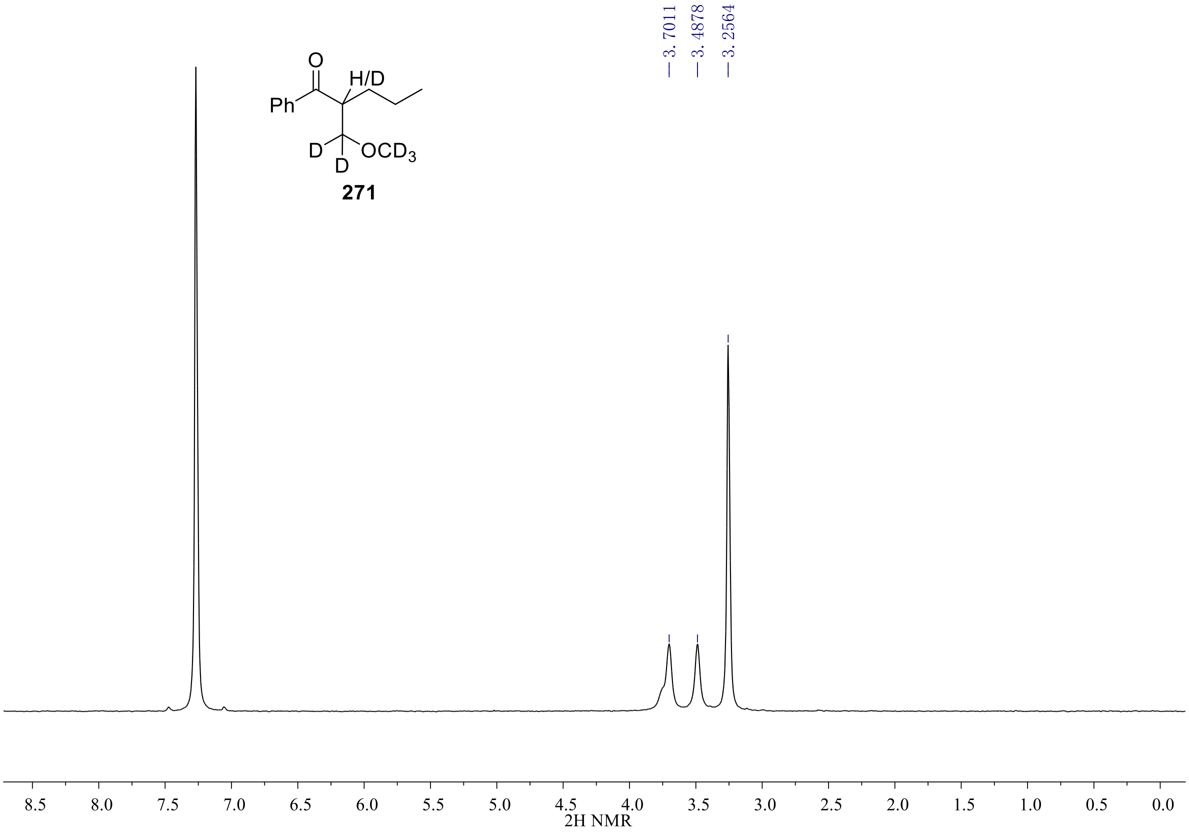

O
D D
O
Ph
D/H
H/D
Ph
272
3.4954
3.3290
2.2581
2.0396
1.6071
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2H NMR

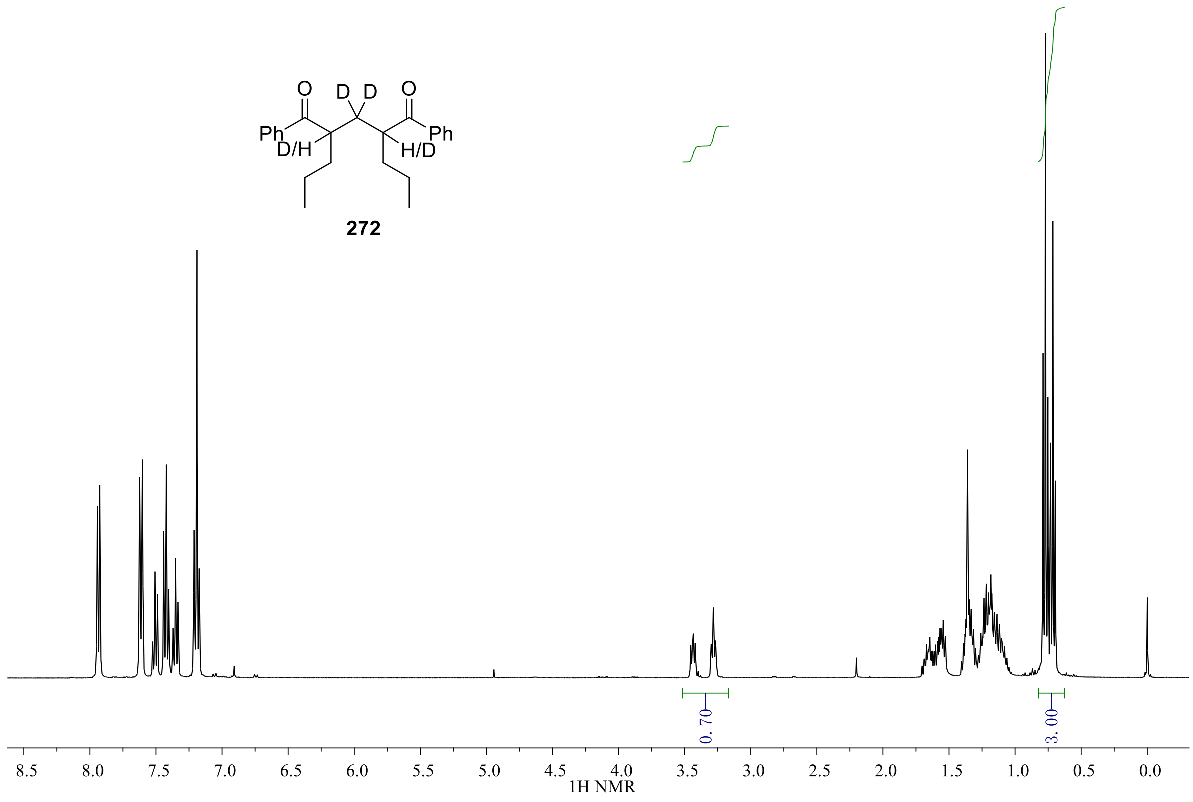
A1.2 Methylenation reaction of valerophenone in CD_3OH

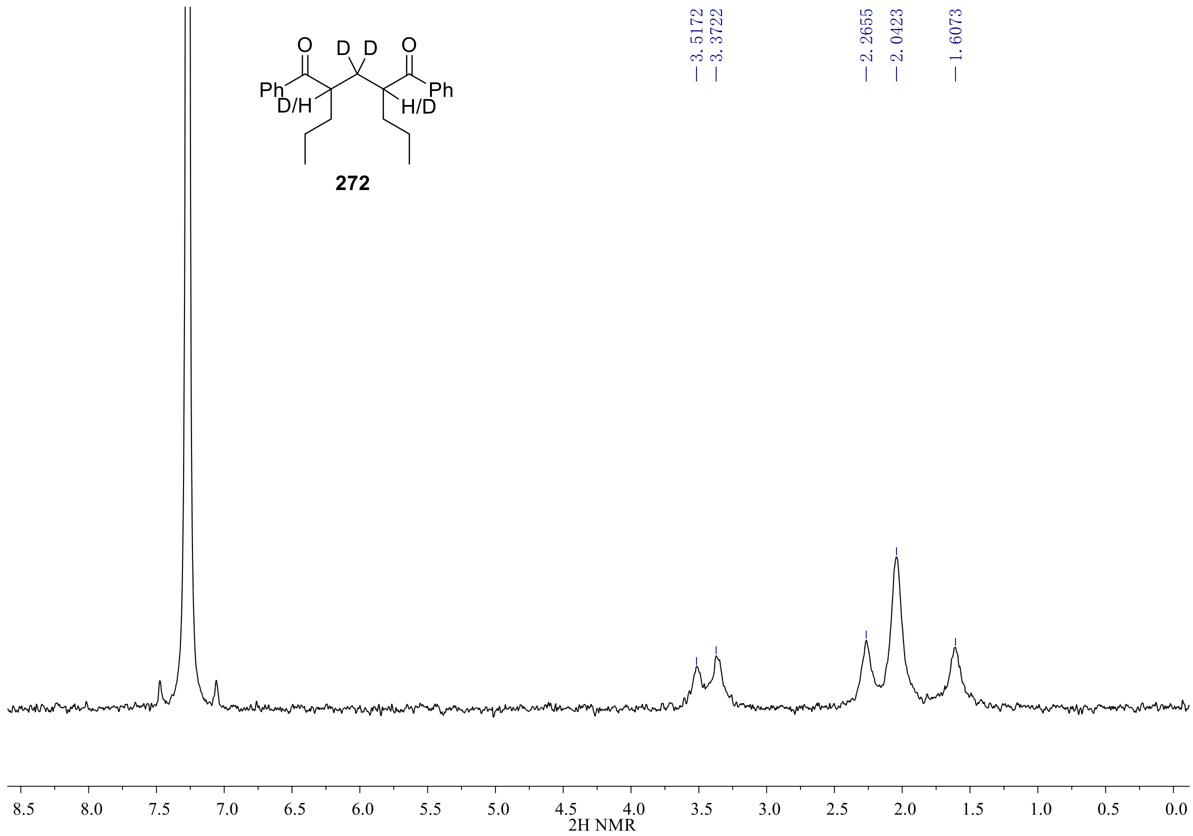




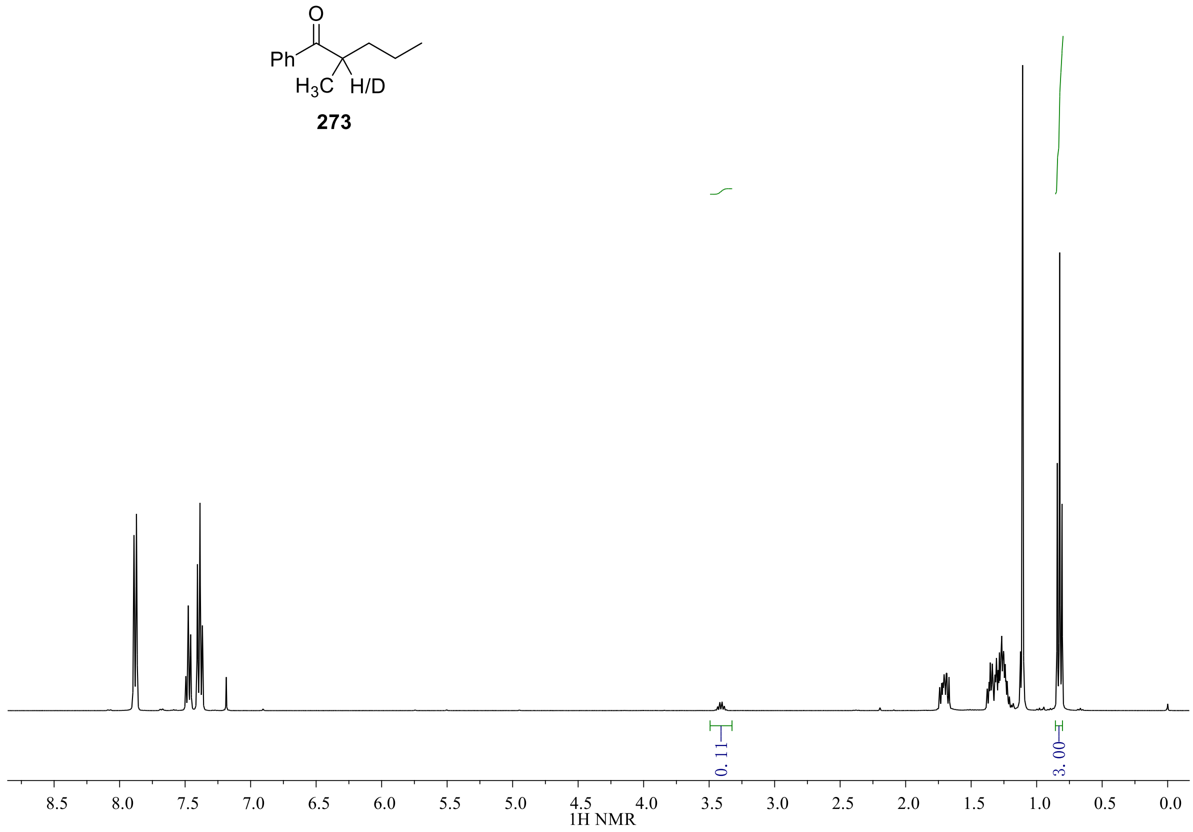

O
H/D
Ph
D
D
OCD$_3$
271
0.66
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H NMR

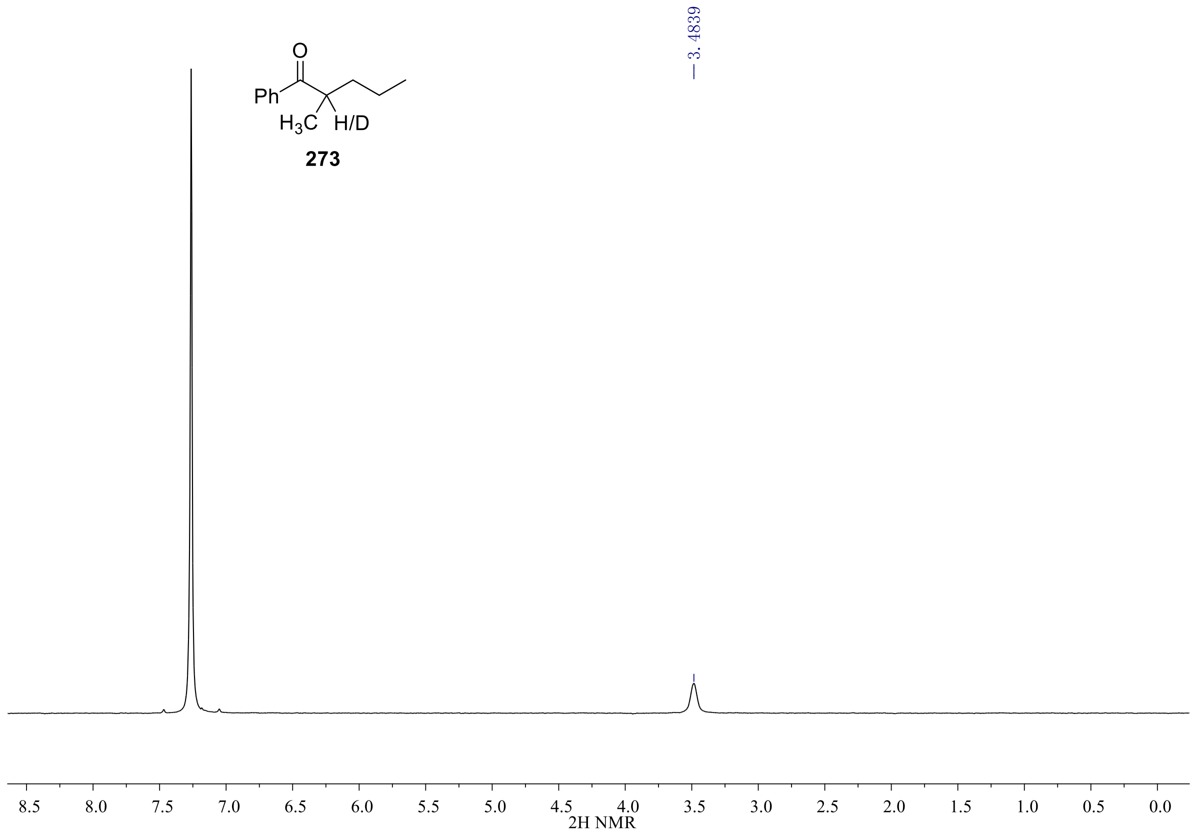

3.7011
3.4878
3.2564
O
H/D
Ph
D
D
OCD$_3$
271
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2H NMR

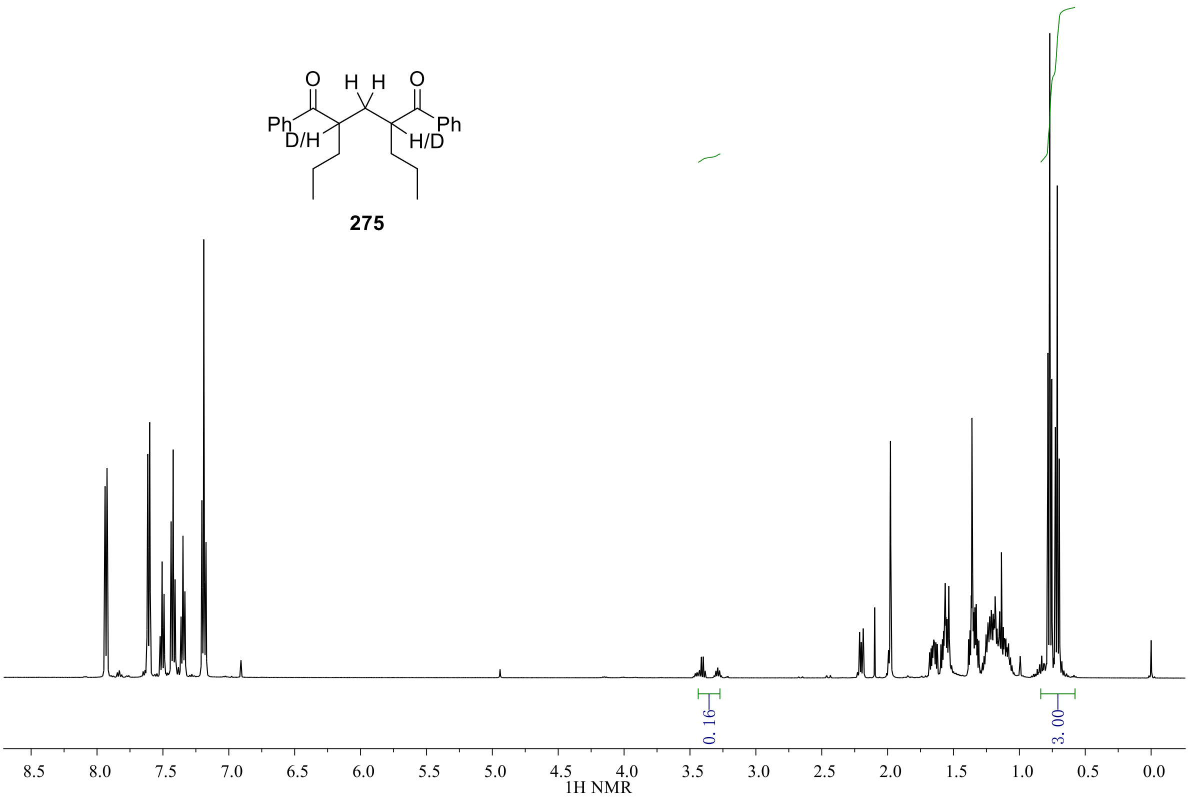

O
D D
O
Ph
D/H
Ph
H/D
272
0.70
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H NMR

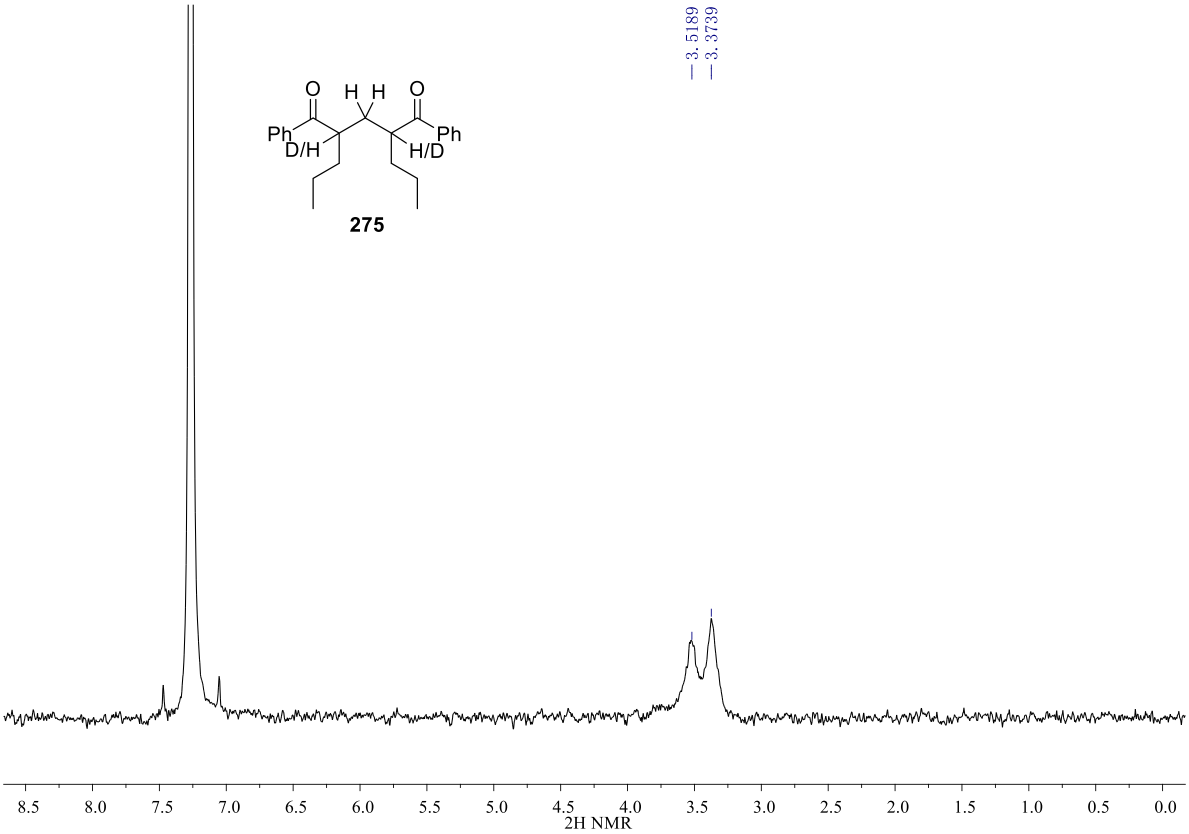

3.5172
3.3722
2.2655
2.0423
1.6073
O
D D
O
Ph
D/H
Ph
H/D
272
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2H NMR

A1.3 Methylation reaction of valerophenone in CH_3OD

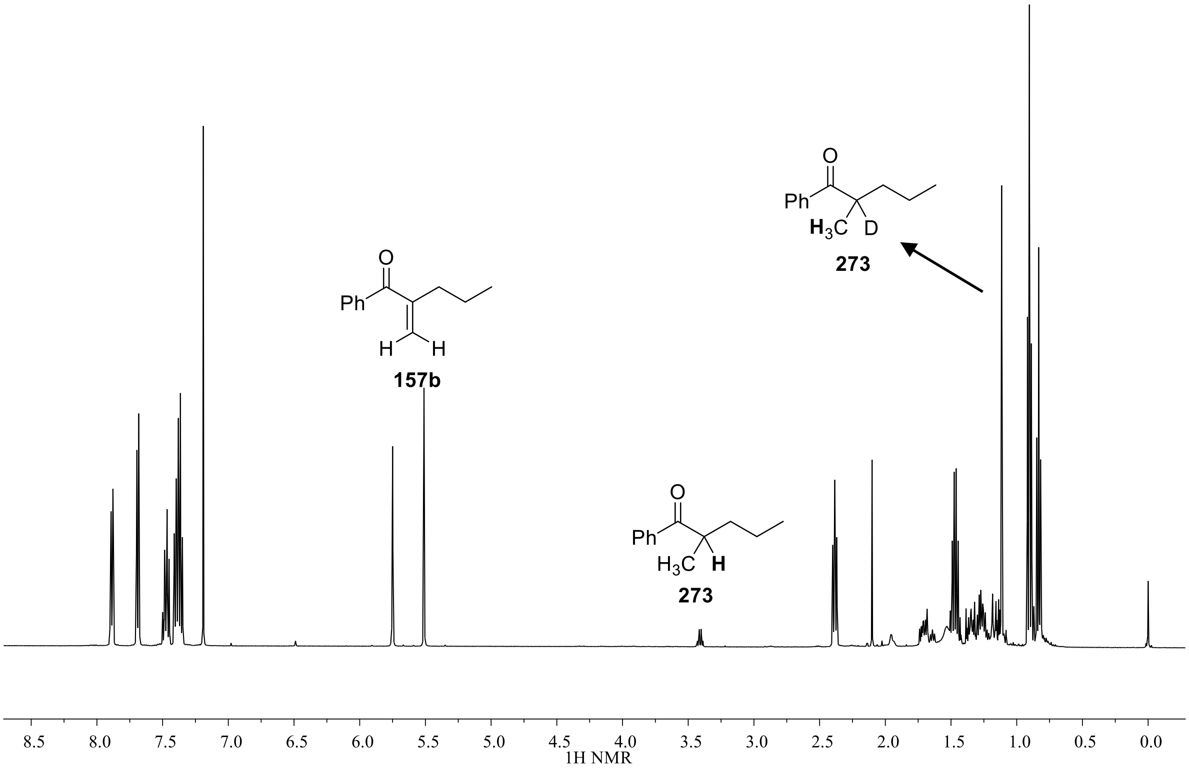


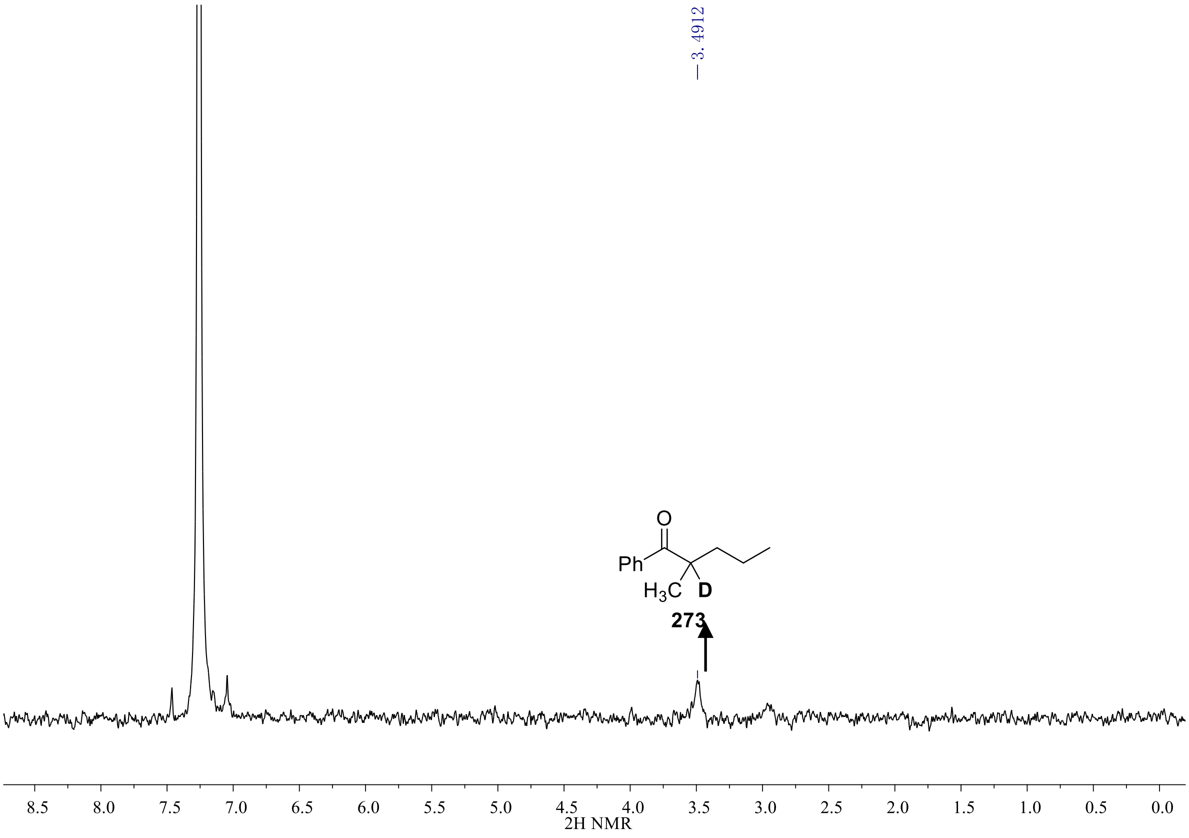


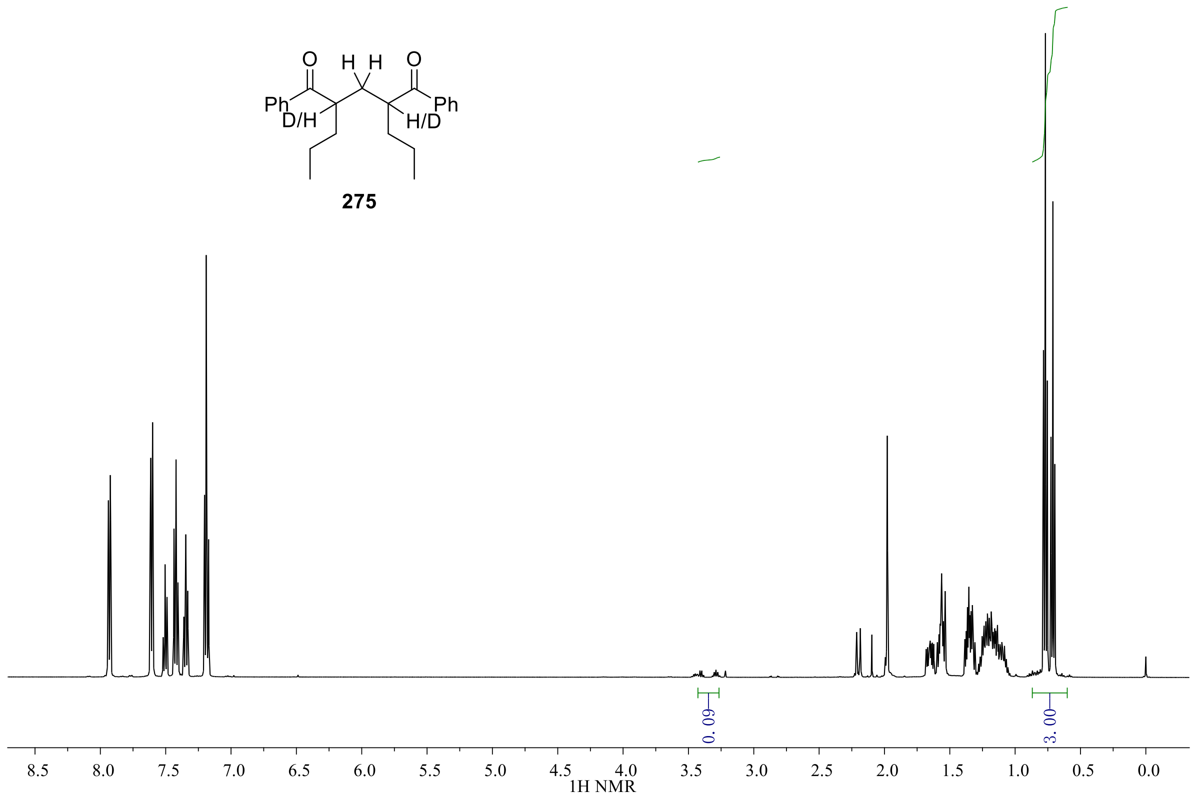

O
H H
O
Ph
Ph
D/H
H/D
275
0.16
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H NMR

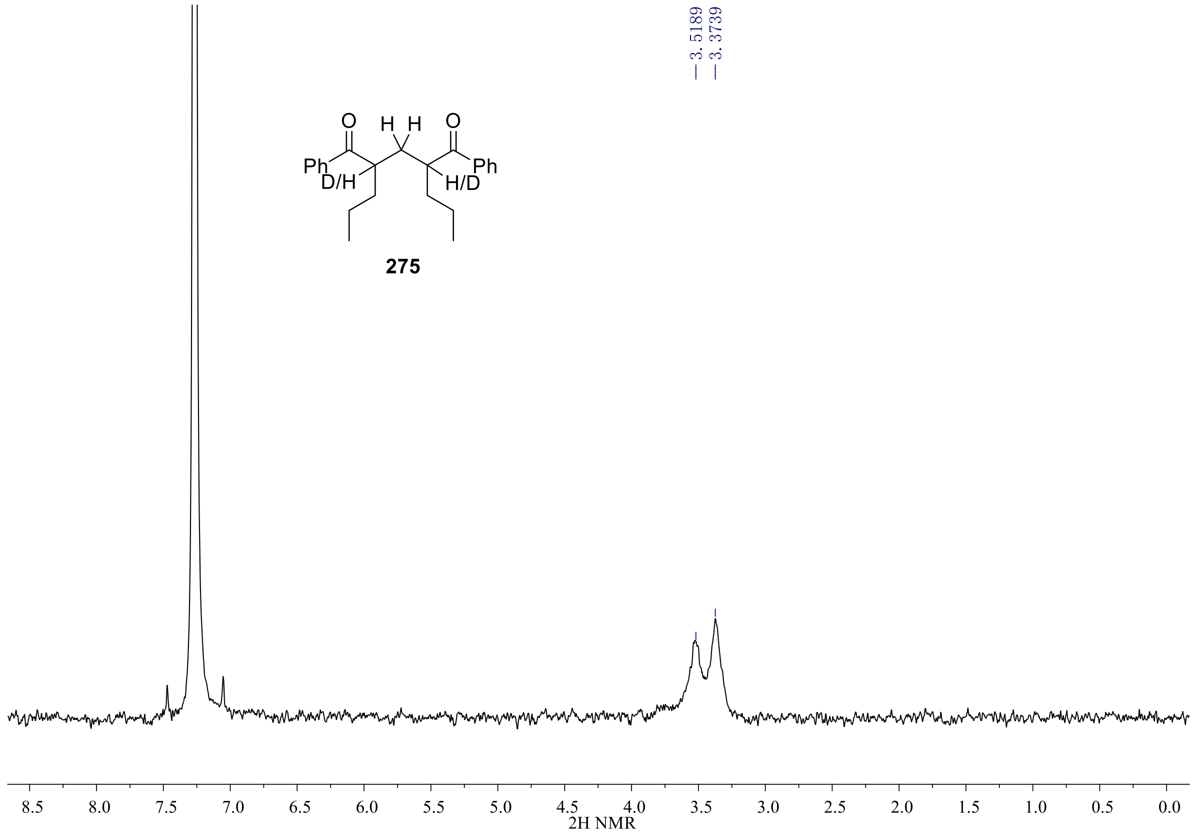

3.5189
3.3739
O
H H
O
Ph
Ph
D/H
H/D
275
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2H NMR

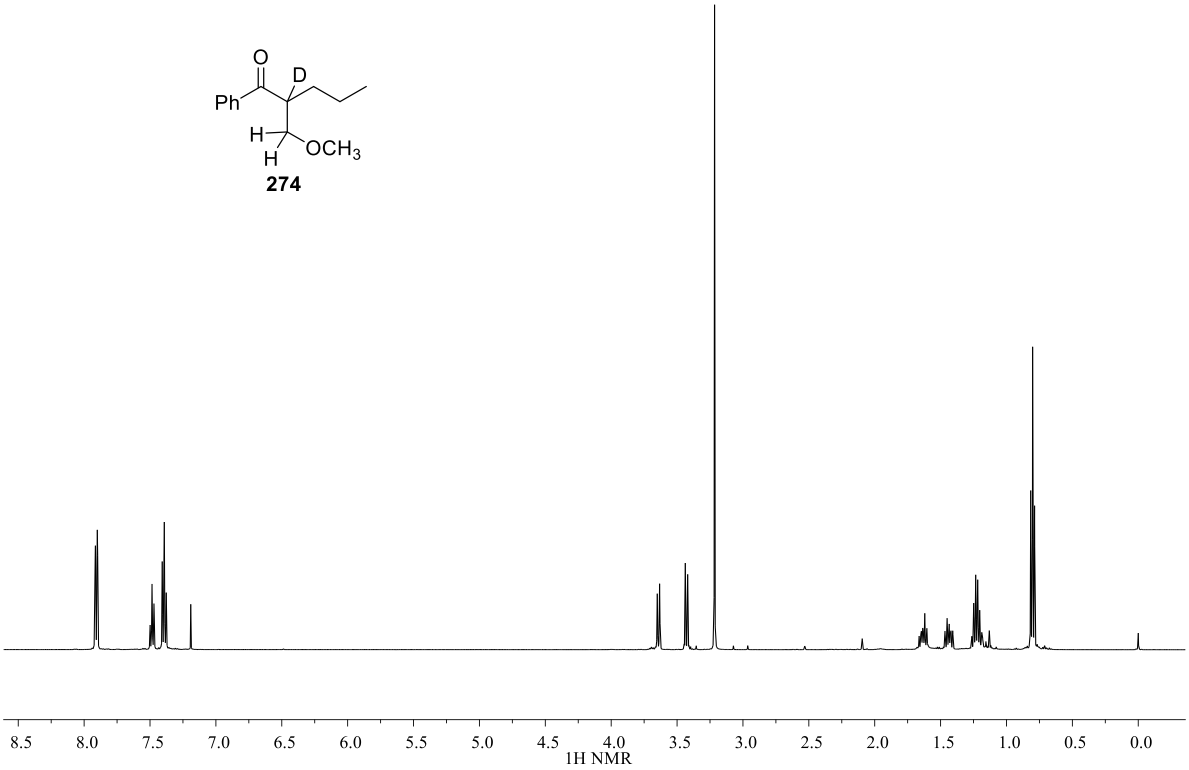
A1.4 Methylenation reaction of valerophenone in CH_3OD



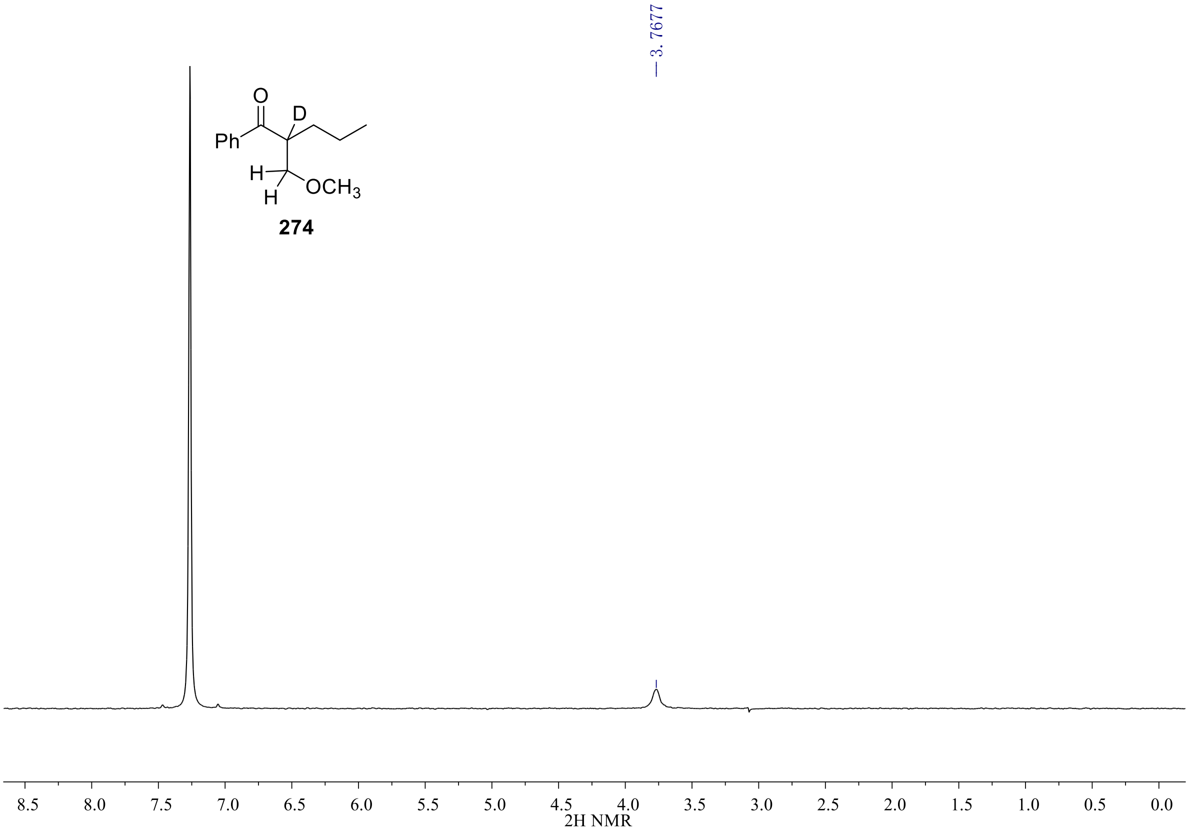



O
H H
O
Ph
D/H
H/D
Ph
275
0.09
3.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H NMR


3.5189
3.3739
O
H H
O
Ph
D/H
H/D
Ph
275
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2H NMR


O
Ph
D
H
H
OCH3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1H NMR

274


3.7677
O
Ph
D
H
H
OCH3
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
2H NMR

274