University College London

Hydroacylation of N=N bonds *via* aerobic C-H activation of aldehydes, and reactions of the products thereof

by

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Submitted in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

Declaration

I, Ahmed Raqib Akhbar, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Ahmed Raqib Akhbar

June 2014

I WISH TO DEDICATE THIS THESIS TO

MY GRANDMOTHER

Asifa Orya

...the bravest, most sincere mother I have had the honour and privilege of being cared by

MY PARENTS

Mohammed and Suhaila Akhbar

...forever in your debt for all your love, patience and sacrifices in getting us to where we are

Abstract

The development of methods to construct new chemical bonds efficiently and selectively whilst minimising energy usage and waste production is of high importance in organic chemistry. Many current methods employ inefficient, costly and often toxic multi step protocols to generate new chemical bonds. The hydroacylation reaction is one method of reducing such inefficiencies. The development of an aerobic hydroacylation protocol in the Caddick group has recently allowed the functionalisation of aldehydes with a wide array of electron deficient alkenes. This process relies on trapping an acyl radical intermediate, from the auto-oxidation of aldehydes to acids, with a suitable alkene. Since aldehyde auto-oxidation takes place readily in the presence of atmospheric oxygen, the aerobic hydroacylation reaction can be conducted in aqueous media in the absence of any additional reagents.

Following on from previous work in the group, this thesis describes studies towards expanding the scope of this novel methodology in the formation of C-N bonds. It also assesses the scalability of this reaction in order to make acyl hydrazides for further chemical transformations; as such, the development of protocols for the conversion of acyl hydrazides to carboxylic acid derivatives and to ketones will also be described. Chapter 1 provides an introduction to and a general overview of current methods of hydroacylation and acid derivative syntheses. Chapter 2 describes the development of conditions for, and application of aerobic hydroacylation towards C-N bond formation, and the scalability of the hydroacylation reaction. Chapter 3 will focus on solving the failures of previous attempts for the conversion of acyl hydrazides to tertiary amides. Chapter 4 will demonstrate the applicability of acyl hydrazides to the synthesis of carboxylic esters and describe some of its limitations. Finally, chapter 5 will reveal acyl hydrazides as a new class of precursors for the chemoselective synthesis of ketones.

Contents

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Abbreviations

$[\alpha]_D$	Specific rotation
Ac	Acetyl
AZ	AstraZeneca
b.p.	Boiling point
BBN	Borabicyclo[3.3.1]-nonane
BHT	2,6-Di-*tert*-butyl-4-methylphenol
BMIM	1-Butyl-3-methylimidazolium
Bn	Benzyl
Bu	Butyl
CDI	*N*,*N*-Carbonyldiimidazole
CI	Chemical ionisation
COD	1,5-Cyclooctadiene
COST	Change one single variable at a time
Cp	Cyclopentadienyl
Cy	Cyclohexyl
d	Doublet
dba	Dibenzylideneacetone
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DEPT	Distortionless enhancement by polarisation transfer
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminium hydride
DMF	*N*,*N*-Dimethylformamide
DMHA	*N*,*O*-dimethyl hydroxylamine
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
E	Entgegen (opposite, *trans*)
EDG	Electron donating group
ee	Enantiomeric excess
Et	Ethyl

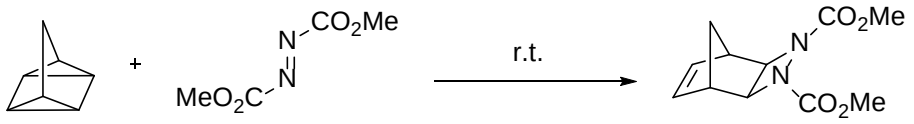
EI	Electron ionisation
EPR	Electron paramagnetic resonance
ES	Electrospray
EWG	Electron withdrawing group
FAB	Fast atom bombardment
HPLC	High performance liquid chromatography
KHMDS	Potassium hexamethyldisilazide
LDA	Lithium diisopropylamide
m	Multiplet
MIBK	Methyl isobutyl ketone
m.p.	Melting point
MTBE	Methyl *t*-butyl ether
Me	Methyl
MW	Microwave
NBS	*N*-Bromosuccinimide
NHPI	*N*-Hydroxyphthalimide
NMP	*N*-Methylpyrrolidone
NMR	Nuclear magnetic resonance
PFP	Pentafluorophenyl
Ph	Phenyl
Pr	Propyl
q	Quartet
rt	Room temperature
s	Singlet
sat.	Saturated
t	Triplet
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
TCP	Trichlorophenyl
TCT	2,4,6-Trichloro-1,3,5-triazine
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
THF	Tetrahydrofuran

TLC	Thin layer chromatography	UCL University College London
UV	Ultraviolet	
Z	Zusammen (together, *cis*)	

Chapter 1 Introduction

1.1 Atom-economic processes

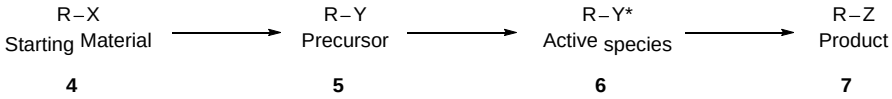
The development of methods to construct new chemical bonds efficiently and selectively whilst minimising energy usage and waste production has, arguably, never been of greater importance.[1] As such, current methods of synthesis must evolve to keep abreast of the ever-growing complexity of target molecules. Of utmost importance is reducing environmental impact by developing "greener", more versatile, selective and scalable reactions with high atom-economy and minimal waste-production.[1] The pericyclic, 2s + 2s + 2p cycloaddition of quadricyclane **1** with azodicarboxylate **2** is an example of a highly desirable, atom economic process; occurring under neat, stoichiometric reaction conditions (Scheme 1).[2] Moreover, even "greener" photochemical and thermal processes which proceed in the absence of external reagents and/or using sub-stoichiometric catalysis have also recently emerged.[3-5]



1 **2** **3**

Scheme 1. 2s + 2s + 2p cycloaddition reaction of quadricyclane **1** with azodicarboxylate **2**[3-5]

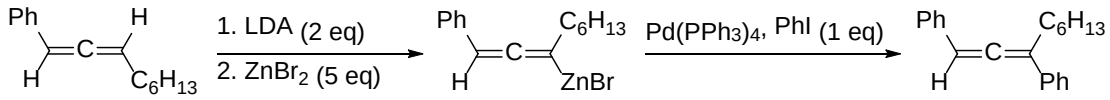
Despite recent work on development of more efficient chemical processes, it is still the case that an inherently inefficient multi-step approach of synthesis is employed to add chemical complexity. Generally, conversion of a starting material **4** to a desired product **7** is achieved *via* a number of intermediates, **5** and **6** (Scheme 2). The overall efficiency of this transformation relies on the efficiencies of the individual steps; 1) ease with which precursor **5** can be generated from starting material **4**, 2) efficiency of generating active species **6** from **5** and 3) efficiency and selectivity of the reaction to convert active species **6** to desired product **7**.



4 **5** **6** **7**

Scheme 2. Example of an inefficient multi-step approach to chemical synthesis

Unfortunately, excessive use of reagents and ultimate generation of additional waste at each step reduces the overall atom-economy and renders this multi-step approach highly inefficient. For example, the elegant conversion of propadiene **8** to trisubstituted allene **10** proceeds through a Negishi-type coupling of allene **9** to iodobenzene. However, it does require the use of additional equivalents of reagents at each step, generating undesired organometallic waste.[6]



8 **9** **10**

Scheme 3. Use of Negishi-coupling to generate allene **10** from propadiene **8**[6]

In spite of these shortcomings, however, the use of multi-step protocols is widespread in the chemical literature, perhaps, due to their distinguished power in reliably affecting some otherwise problematic chemical transformations. Metal-catalysed couplings[7] and metathesis[8-12] reactions are primary examples of multi-step transformations where alternative routes are either unavailable and/or highly un-economical.

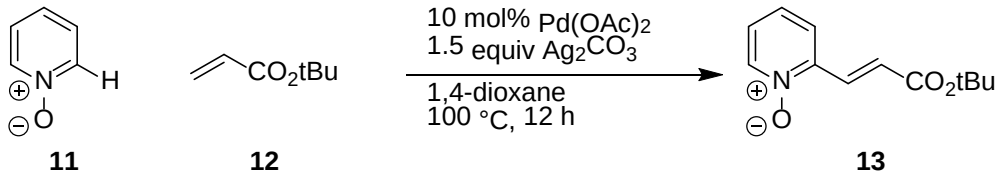
1.1.1 Formation of C-N bonds

Nitrogen containing compounds are of high importance because of their abundance in various natural products as well as in numerous pharmaceutically active agents.[13] As mentioned previously, discovery of benign methods for the construction of C-N bonds remains an ongoing challenge to chemists.[14] In the past decades, transition-metal catalysed C-N bond forming protocols have continued to gain traction;[15-16] in the 1990s, Buchwald[17] and Hartwig[18] independently demonstrated Pd- and Cu-catalysed N-arylation protocols in the presence of suitable phosphine or diamine ligands. Ultimately, current C-N bond forming strategies rely on a multi-step pre-activation of starting materials such as (hetero)aryl (pseudo)halides to react with amines.[13] As effective as they may be, the generation of stoichiometric amounts of metal salts as waste, harsh reaction conditions and ultimately poor atom-economy

mean milder, inexpensive and environmentally benign C-N bond formation protocols are still much sought after. Amongst the plethora of strategies explored, C-H activation has been, by far the most promising alternative and subject of most interest.

1.1.2 C-H activation

C-H activation involves preferential functionalisation of certain carbon-hydrogen bonds over others thus potentially alleviating the need for a multi-step protocol. The driving force for such activations can be the increased native acidity of a particular site (*i.e.* pK_a) or the effect of a local directing group., *i.e.* complex induced proximity effect, CIPE.[19] For example, a combination of C-H acidity and steric hindrance is proposed to contribute to achieve C-H activation and functionalisation of pyridine *N*-oxide **11** using Pd(II) (Scheme 4).

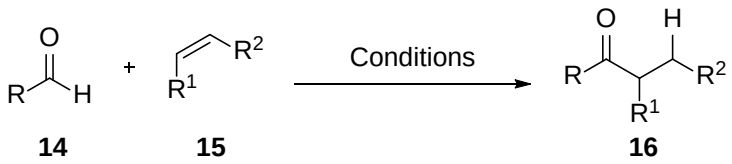


Scheme 4. Palladium catalysed C-H activation of *N*-oxide **11**[20]

C-H activation-promoted reactions usually rely on metal catalysts; oxidative insertion of a metal species into a C-H bond often activates it for reaction. Following reaction with a suitable reaction partner the metal catalyst can reductively eliminate, releasing the desired product. Of particular relevance to this thesis is the C-H activation of aldehydes for hydroacylation.

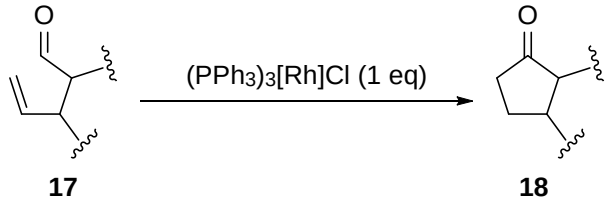
1.2 Hydroacylation

Hydroacylation is a specific example of C-H activation whereby an aldehyde and double or triple bond are combined to generate a ketone *via* activation of the aldehydic C-H bond. For example, the addition of an aldehyde **14** across alkene **15** generates ketone **16** with concomitant formation of a new C-C and C-H bond (Scheme 5).



Scheme 5. General schematic representing the concept of hydroacylation

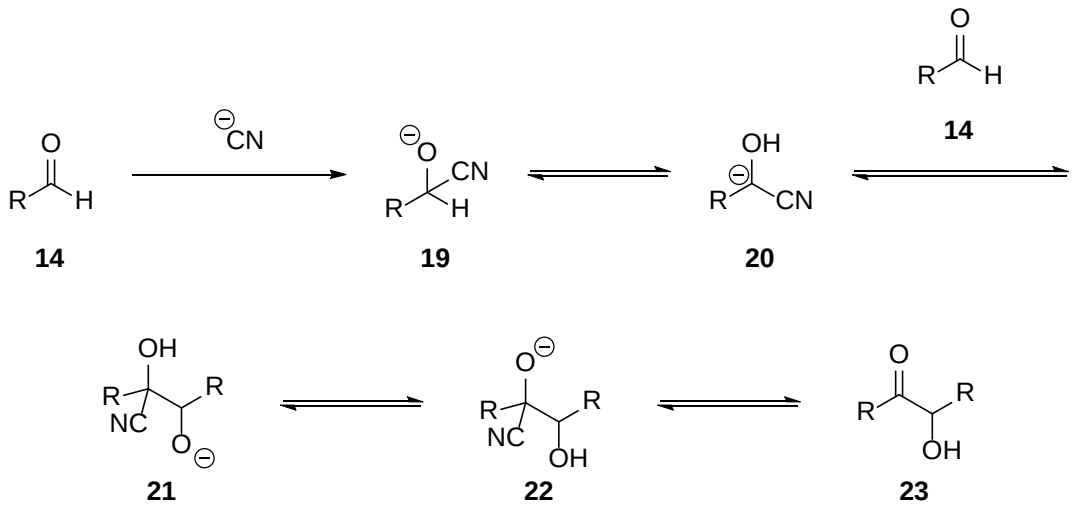
Such inversion of electrophilicity of the carbonyl group into a nucleophile, using transition metals, was first reported 1972.[21] Sakai and co-workers demonstrated the intramolecular alkene hydroacylation of penten-4-al systems with stoichiometric amounts of Rhodium catalyst to form cyclopentanones (Scheme 6). However, aldehyde umpolung chemistry was first described as far back as 1832 by W'ohler and Liebig in their paper describing the benzoin condensation (which forms the basis of the Stetter reaction).[22] Given their direct relevance to this thesis, a brief review of this and related aldehyde umpolung chemistry, in the context of hydroacylation, will now be presented.



Scheme 6. First example of a metal-catalysed hydroacylation reaction[22]

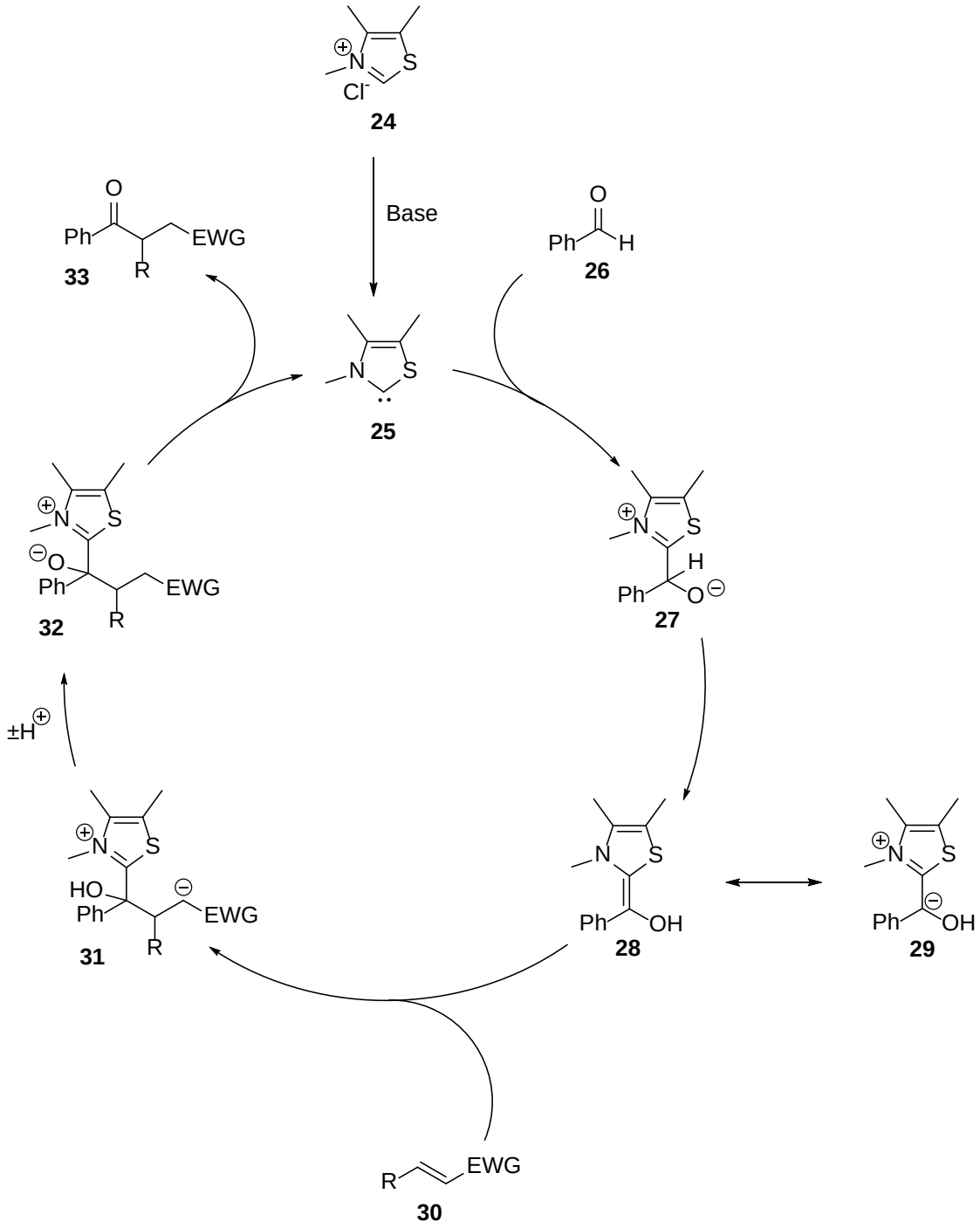
1.2.1 The Stetter reaction

Almost one hundred years after Wohler and Liebig's 1832 paper describing the cyanide catalysed benzoin condensation, Lapworth[23] proposed the now widely accepted mechanism of this reaction (Scheme 7); attack on aldehyde **14,** by the cyanide anion, results in the formation of alkoxide **19** which, after proton transfer, generates acyl anion equivalent **20**. Reaction of this species with electrophilic aldehyde **14**, proton exchange and subsequent elimination of cyanide generates α-hydroxyketone **23.**



Scheme 7. General schematic illustrating the mechanism of the benzoin condensation[23]

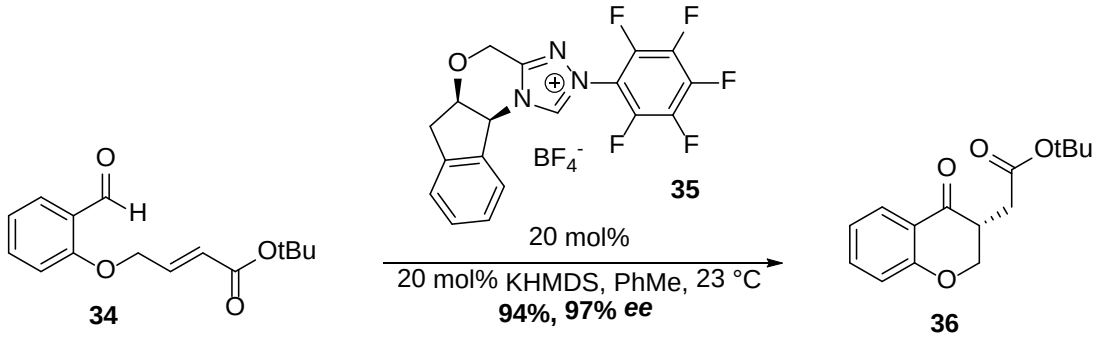
Soon after, Ukai carried out the same transformation using base-activated thiazolium catalysts.[24] In 1973, Stetter expanded this aldehyde umpolung chemistry to utilise Michael acceptors as the electrophilic partner for a wide variety of aromatic and aliphatic aldehydes. By employing cyanide or thiazolylidene carbene catalysts, α,β-unsaturated carboxylic esters,[25] ketones[26] and nitriles[27] were converted to γ-oxo carboxylic esters, γ-diketones and γ-oxo nitriles, respectively.[28] Although studies modelling the mechanism for the Stetter reaction have not yet been reported, currently accepted proposals are based on that elucidated by Breslow for the thiazolium catalysed benzoin reaction (Scheme 8).[29] Carbene **25** is formed *in situ* by deprotonation of the thiazolium salt **24**; this adds to aldehyde **26** to form alkoxide **27**. Proton transfer generates acyl anion equivalent **29** which attacks into Michael acceptor **30** to form carbanion **31** – *i.e.* forming a C-C bond. A second proton transfer is followed by collapse of tetrahedral intermediate **32** to form ketone **33**, accompanied by regeneration of active catalyst.



Scheme 8. General schematic illustrating the proposed mechanism of the Stetter reaction[29]

The advent of *N*-heterocyclic carbenes has been accompanied with an upsurge in examples of novel reactions, new modes of reactivity and even chiral catalyst systems pertaining to the Stetter reaction.[30] For example, Rovis and co-workers illustrated an asymmetric variant of the intramolecular Stetter reaction in 2008,

employing chiral pre-catalyst **35** (Scheme 9); aldehyde **34** underwent cyclization to afford cyclic ketone **36** with excellent yield and enantioselectivity.[31-32]

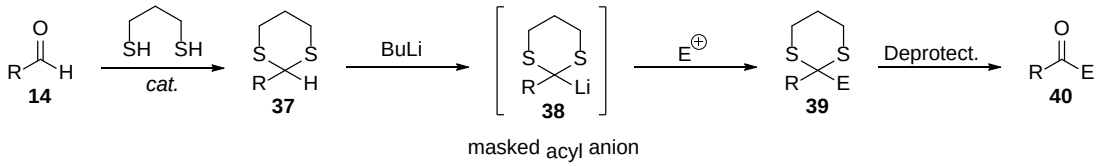


Scheme 9. Rovis' asymmetric intramolecular Stetter reaction[31-32]

Nevertheless, despite recent advances, the Stetter umpolung is limited by a number of factors. The multi-step approach and need for elaborate catalyst systems make this protocol highly inefficient and expensive, in the hydroacylation arena. Furthermore, aldehyde self-condensation and limited alkene scope – electron deficient C-C double bonds – remains a significant obstacle for this methodology.

1.2.2 Dithiane Chemistry – The Corey-Seebach reaction

The Corey-Seebach reaction also allows a reversal of the normal reactivity of acyl carbon atoms, such as aldehydes, *via* a dithiane species.[33] Conversion of aldehyde **14** to dithiane species **37** activates a C-H bond sufficiently that the hydrogen atom can be abstracted by *n*-butyllithium to generate metalated species **38** (Scheme 10). With a pK_a value of *ca.* 30, this acyl anion equivalent can then attack an electron deficient species to generate thioacetal **39** which, in turn, can be deprotected to reveal ketone **40** using suitable deprotection protocols such as hypervalent iodine species[34] or mercuric acetate.[35]



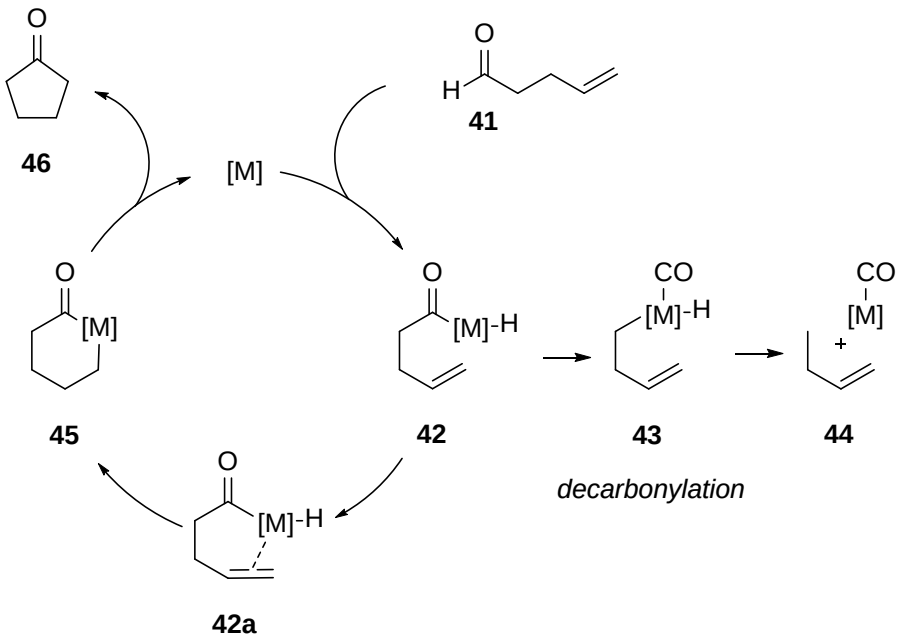
Scheme 10. General schematic representing the Corey-Seebach reaction[33]

The differential acidity of hydrogen atoms adjacent to oxygen, compared to divalent sulphur, comes about from the greater polarisability of sulphur and the relatively

longer sulphur carbon bond; less *d*-orbital contribution. However, despite the elegance of this protocol, its low atom-economy – due to its multi-step nature, intolerability to sensitive functional groups – due to strongly basic conditions and harsh deprotection conditions, and generation of significant amounts of waste have meant uptake of this chemistry, for hydroacylation has been limited. Furthermore, examples of this reaction involving heteroatomic electrophiles are non-existent, if not very limited.[35]

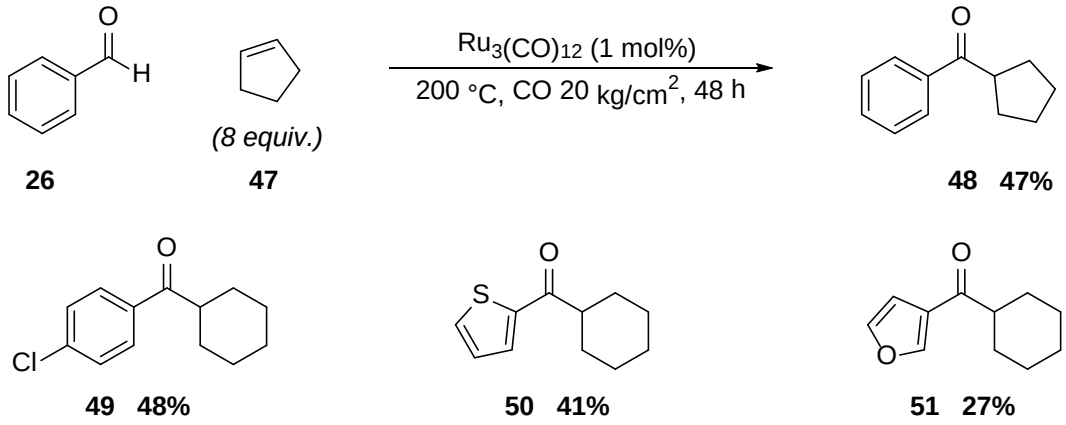
1.2.3 Transition metal catalysed hydroacylations

Since the first report of transition-metal catalysed hydroacylation by Sakai[21] and co-workers in 1972, numerous examples of metal-catalysed activation and subsequent functionalisation of aldehyde C-H bonds have followed. There have been multiple reports on the mechanism of this catalysis; collectively, there is agreement on a simplified catalytic cycle (Scheme 11). Oxidative insertion of the metal – most commonly rhodium, ruthenium, nickel or cobalt – into the aldehydic C-H bond generates acyl metal hydride **42**, which then co-ordinates with and inserts across alkene as in **42a**. Reductive elimination from species **45** regenerates the metal catalyst and ketone **46**.[36] However, the efficiency of this catalytic cycle, with respect to hydroacylation, is diminished by the propensity of metal species **42** to undergo decarbonylation to poorly active carbonylated catalyst **43** and hydrocarbon **44**.[37]



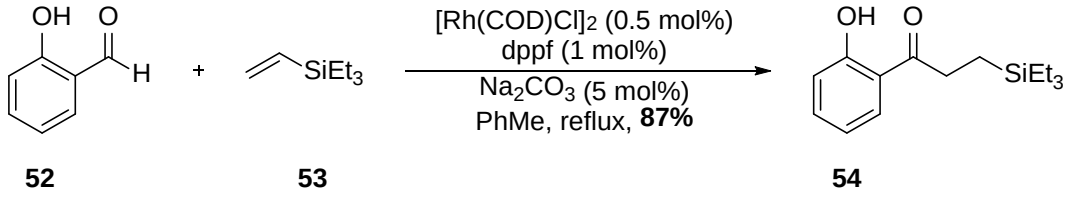
Scheme 11. Simplified catalytic cycle to illustrate the mechanism for a transition metal catalysed hydroacylation reaction

Although this facile decarbonylation forms the basis of many synthetically useful methodologies.[38] Significant advances towards obviating decarbonylation have opened up this field of research greatly, contributing to major advancements in metal-catalysed hydroacylation chemistry.[37,39] In general, a majority of methodologies rely on coordinatively saturating the acyl metal centre. Saturation of reaction solvents with 'dummy' ligands such as ethylene has served well to coordinatively saturate the metal centre; however, more commonly, high pressures of ligands such as carbon monoxide have been employed. For example, Watanabe demonstrated that the complex $Ru_3(CO)_{12}$ required high CO pressures of almost 20 bar and a temperature of 200 °C to affect the hydroacylation of alkene **47** with aldehyde **26** (Scheme 12). Moderate yields of a variety of ketones, **48-51** were obtained using a range of (hetero)aromatic aldehydes.[40-41]



Scheme 12. Ruthenium catalysed hydroacylation reaction of aromatic aldehydes with a range of alkenes[40-41]

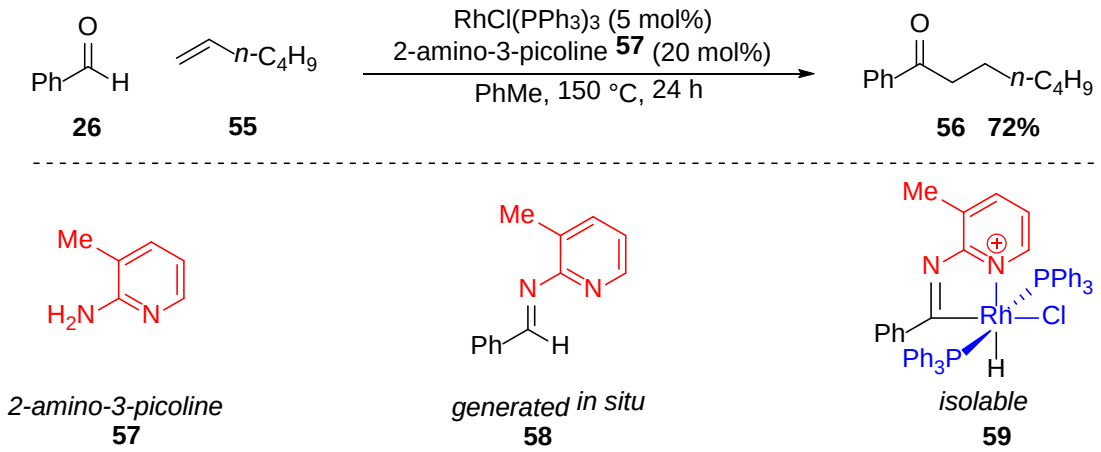
Groups have also invoked intramolecular chelating moeities to coordinatively saturate the metal centres using C-,[42] N-,[43] O-,[44] P-,[45] and S-coordinating motifs.[46-48] Although this strategy is restricted to suitably functionalised aldehydes, elegant examples have, nevertheless, emerged.[45] For example, Miura and co-workers took advantage of an *ortho*-hydroxyl group in salicylaldehyde **52** as an intramolecular chelating substrate for hydroacylation of triethylvinylsilane **53** using a $[Rh(COD)Cl]_2$/dppf catalyst system (Scheme 13).[49] Unfortunately, reactivity towards most other alkenes was very poor; thus, co-catalysts such as $AgClO_4$ were found to be vital to obtaining good yields.[50]



Scheme 13. Intramolecular chelation assisted hydroacylation reaction using salicylaldehyde **52**[49]

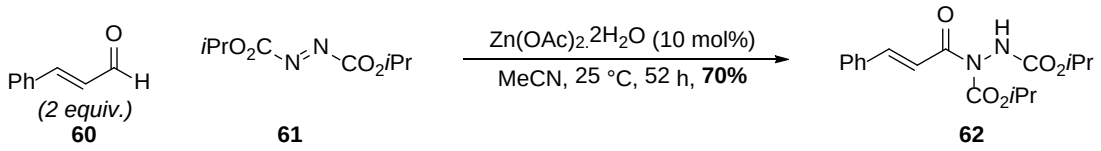
More recently, Willis has demonstrated removal of coordinating β-sulphide and β-thioketal groups, post-hydroacylation, by elimination or cleavage using Raney Ni; thus, expanding aldehyde scope.[37,46] However, a more significant improvement in aldehyde scope has been brought about by Jun, who developed a 2-amino-3-picoline co-catalyst system capable of facilitating intermolecular hydroacylation using, theoretically, any aldehyde (Scheme 14). Rhodium complex **59** has been isolated and

is postulated to be a possible intermediate in the transformation of **26** to **56**, utilising *in-situ* generated precursor **58**.[43,51]



Scheme 14. 2-amino-3-picoline assisted hydroacylation[43]

Examples of C-C double bond forming hydroacylation using metals are numerous; however, hydroacylation of heteroatomic unsaturated bonds are very scarce. Nonetheless, there are some examples of Cu-,[52] Ru-,[53] Rh-,[53] and Zn-catalysed hydroacylation reactions of N-N double bonds.[54] One recent example is presented by Qin; $Zn(OAc)_2$ hydrate was found to be an effective catalyst for the hydroacylation of diisopropyl azodicarboxylate **61** with aldehyde **60** to afford acyl hydrazide **62** in good yields (Scheme 15).[54]



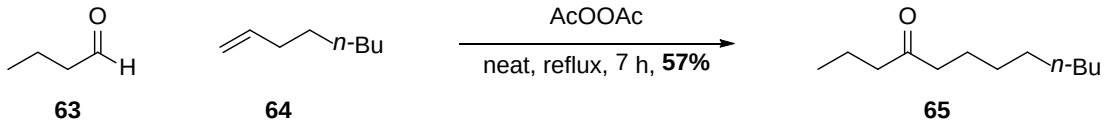
Scheme 15. Hydroacylation reaction of diisopropyl azodicarboxylate **61** using Zinc catalysis[54]

Collectively, the hydroacylation strategies described thus far are no doubt, powerful and elegant, and unsurprisingly, commonly utilised. However, there are key limitations associated with individual strategies that have hindered their uptake for more widespread use. Umpolung methodologies such as the Stetter reaction and dithiane chemistry are limited by their harsh reaction conditions, low atom economy, incompatibility with sensitive functional groups and their multi-step nature. Transition metal-catalysis suffers from the use of expensive metals, harsh reaction

conditions, production of significant amounts of waste, poor versatility and employment of an inefficient multi-step protocol. As such, acyl radical-mediated hydroacylation has received considerably more attention in recent years.

1.2.4 Hydroacylation *via* acyl radicals

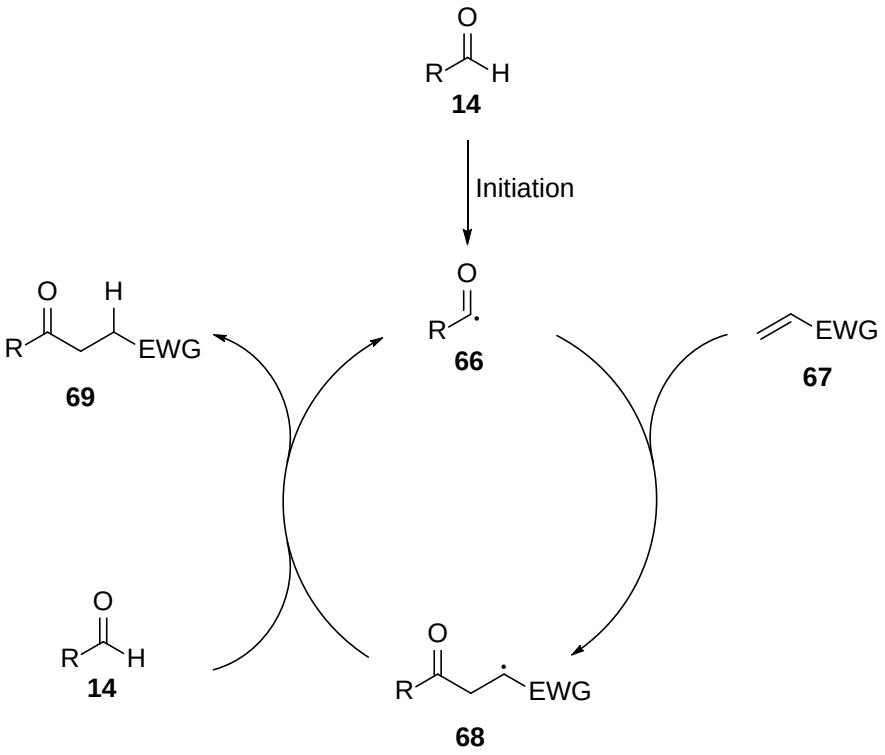
Hydroacylation methodologies employing acyl radicals have been subject to considerable interest in the chemical literature.[55] In the earliest report, Kharasch disclosed the hydroacylation of terminal alkene **64** with *n*-butanal **63** to obtain unsymmetrical ketone **65** under free-radical reaction conditions (initiated by the thermal decomposition of diacetyl peroxide).[56]



63 **64** **65**

Scheme 16. Peroxide-induced hydroacylation of alkene **64** by Kharasch[56]

There has been much work done to elucidate the mechanism of the acyl radical mediated chain process. Generally, there is much agreement that this chain process proceeds *via* the addition of an acyl radical **66** to an alkene **67** to generate intermediate radical species **68**; which generates ketone **69** by abstracting a formyl hydrogen while, concomitantly, regenerating the acyl radical (Scheme 17).



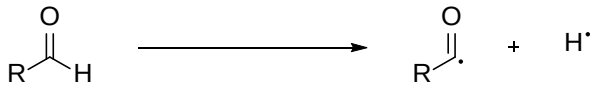
Scheme 17. General schematic illustrating the mechanism for an acyl radical mediated hydroacylation reaction

Addition of acyl radicals to alkenes represents a highly atom-economic, thus, relatively more efficient hydroacylation strategy (*cf.* previously discussed processes, **1.2.1** to **1.2.3**). It is noteworthy however, that the major inefficiencies associated with this protocol stem from the actual generation of acyl radicals and their precursors. Consequently, many of the significant advances in radical hydroacylation chemistry have involved developing novel methodologies for the generation of said acyl radicals, or precursors thereof. It is therefore justified, given their augmented potential for further development, to provide a more in-depth review of acyl radical hydroacylation chemistry with respect to said generation methodologies; albeit, after a brief overview the physical properties of acyl radicals.

1.2.4.1 Properties of acyl radicals

An acyl radical is believed to be an sp^2 hybridised, σ-type radical because, as evident from EPR studies, its unpaired electron occupies an orbital with considerable 2s character.[55] Furthermore, there is little or no delocalisation of the unpaired electron onto any neighbouring aromatic or vinylic systems.[57] This means that the C-H bond

dissociation enthalpies of the corresponding aldehydes are practically independent of the R-group in RC(O)-H (Table 1).[57-59]

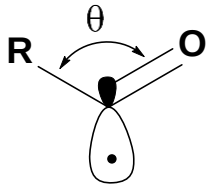


14 **66** **70**

RC(O)-H	D° (kcal mol^{-1})
$CH_3C(O)$-H	89.3
$CH_3CH_2C(O)$-H	89.5
CH_2=CHC(O)-H	89.1
PhC(O)-H	88.9

Table 1. Dissociation enthalpies for a range of aldehydes to their corresponding acyl radicals[57-59]

Additionally, Guerra has conducted *in-silico* studies which conclude that the α-substituent has very little, if any influence on the magnitude of angle θ in acyl radical **66a** (Table 2).[60]



66a

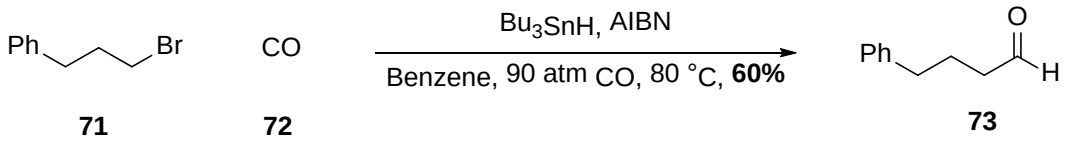
R	Angle θ (°)
H	126.6
CH_3	129.4
NH_2	130.8
$OC(CH_3)_3$	128.6
F	128.1

Table 2. Bending angles θ for various acyl radicals with substituents **R**[60]

1.2.4.2 Generation of acyl radicals

Theoretically, three general methods may be envisaged for the generation of acyl radicals.[55] The first is fragmentation of a C-C bond as, for example, in the Norrish-type I photocleavage of a CO-C bond. The second involves carbonylation of a carbon-centred radical ($R^{\bullet}$) with CO and the third, by far the most commonly applied method, is the homolytic rupture of a RC(O)-X bond. Of the three methods, the first

is most important for generation of acyl radicals for mechanistic and spectroscopic studies and will not be discussed herein. Although the second has recently gained prominence, its uptake has been somewhat impeded by its need for undesired additives (such as tributyltin) and high pressure of carbon monoxide. For example, employing a high pressure of CO in the presence of radical initiator AIBN, bromo-alkane **71** can be converted to aldehyde **73** (Scheme 18). It is perhaps for these reasons that the third method, homolytic fission of the C-X bond in RC(O)-X, has become the preferred method for the generation of acyl radicals.[55,61]

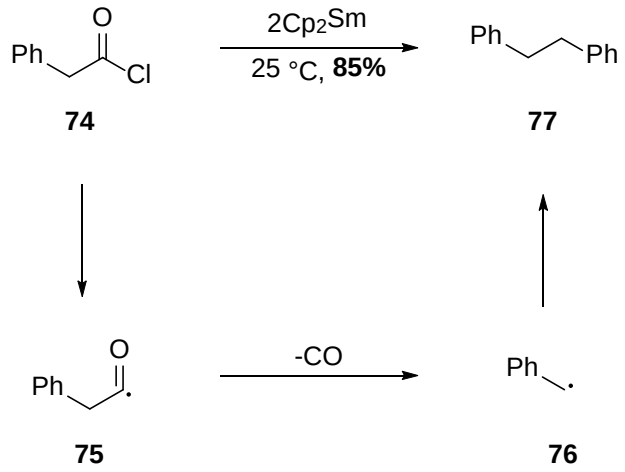


71 **72** **73**

Scheme 18. Generation of acyl radicals *via* carbonylation of a C-centred radical[45]

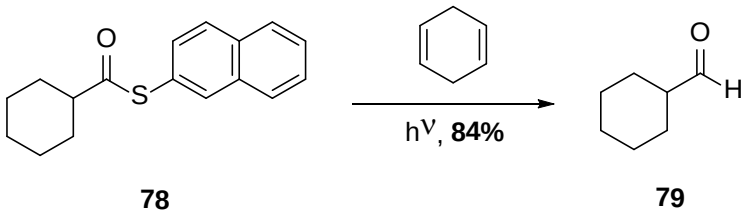
1.2.4.2.1 Generation of Acyl Radicals from RC(O)-X

In this method, group X in RC(O)-X may be any group such that the C-X bond is labile enough to undergo homolytic rupture. Generally, the precursors are divided in two groups: i) X is non-hydrogen group; this includes halogens, chalcogens and various metals, and ii) X is hydrogen. Of the precursors in the first group, acid chlorides, thioesters and selenoesters are among the most commonly employed. There is however, a plethora of other precursors such as telluroesters, metal carbene complexes and acylcobalt (III) derivatives. By way of example, when phenylacetyl chloride **74** was exposed to dicyclopentadienylsamarium at room temperature, an 85% yield of diphenylethane **77** was obtained, presumably *via* acyl radical **75** (Scheme 19).[62] However, the use of acid chloride precursors has been plagued by the formation of by-products, typically esters, as a result of over-reduction of aldehyde and reaction of metal-alkoxides with the acid chlorides



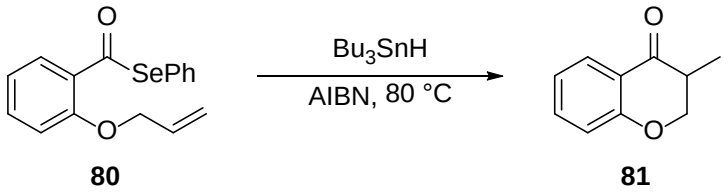
Scheme 19. Acyl chloride precursor for the generation of acyl radical **75**[62]

Following successful thermal and photochemical homolytic cleavage of acyl-SPh bonds, Penn and co-workers demonstrated the use of *S*-(2-napthyl) thioesters as another photochemical source of acyl radicals.[63-66] Under photolytic conditions and employing cyclohexa-1,4-diene as a hydrogen donor, the authors were able to convert thioester **78** into aldehyde **79** in excellent yield (Scheme 20).[63] However, simple thioesters are not sufficiently reactive towards homolytic cleavage under photolytic, as well as stannane-mediated conditions.



Scheme 20. Generation of acyl radicals from thioesters[63]

Selenoesters, with their weaker RC(O)-SeR' bond, do not suffer from poor reactivity. Unlike thioesters, C-Se bonds react readily with stannyl radicals to generate acyl radicals. For example, exposure of acyl selenide **80** to tributyl tin radicals affords cyclic ketone **81** presumably *via* radical hydroacylation of the pendant allyl ether.[67-69]



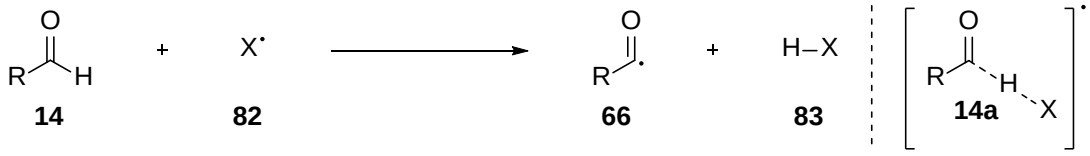
80 **81**

Scheme 21**.** Seleno-ester precursor for the generation of ketone **81**[67-69]

Despite their merits, the use of RC(O)-X precursors – where X is not hydrogen – suffers from the use of undesired and often toxic additives such as tributyltin compounds. It is for this reason that generation of acyl radicals from aldehydes, *i.e.* where X is hydrogen, has attracted more interest in the literature.

1.2.4.2.2 Generation of Acyl Radicals from aldehydes

Given its relevance to this thesis, generation of acyl radicals from aldehydes will be discussed in significant detail. Homolytic scission of an aldehydic C-H bond in **14** to generate acyl radical **66** is most commonly achieved by employing an abstracting radical **82** (Scheme 22); although examples of such radicals are numerous,[55,61] oxygen centred-radicals are by far the most commonly employed initiators.[55,70] It is believed that generation of acyl radicals in this manner proceeds *via* a polarised transition state **14a**. Thus, this process is most efficient when the radical abstracting the aldehydic hydrogen is electrophilic; employment of a nucleophilic alkyl radical, for example, retards the homolytic fission considerably.

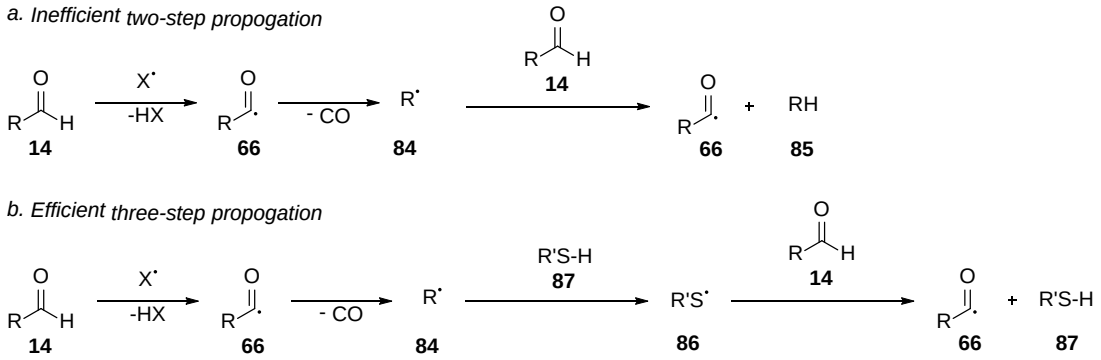


14 **82** **66** **83** **14a**

Scheme 22. General illustration of aldehyde C-H bond fission

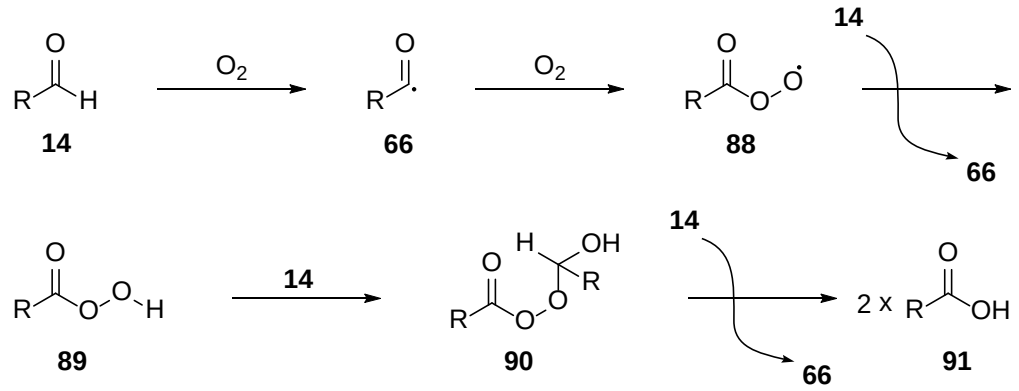
Better understanding of this polar effect has been a key driving force in the development of more efficient chain transfer processes. One such development is well illustrated by the thermally initiated, peroxide-induced, decarbonylation of aldehyde **14**; this chain process is highly inefficient since it relies on a nucleophilic alkyl radical **84**, produced from decarbonylation of acyl radical **66**, to abstract an aldehydic hydrogen atom (Scheme 23a). However, as initially disclosed by Harris and Waters,[71-72] and later developed by others,[73] by employing a thiol, the inefficient two-step propagation can be substituted for a much more efficient reaction sequence.

The success of this methodology stems from what has now become known as polarity reversal catalysis; electrophilic thiyl radical **86** far supersedes the efficiency of alkyl radical **84** – in fact, even aryl radicals[74] – at abstracting aldehydic hydrogen atoms (Scheme 23b).



Scheme 23. General concept of polarity reversal catalysis

As mentioned previously, generation of aldehydic acyl radicals by oxygen centred radicals is by far the most commonly employed methodology. Initiation of oxygen radical-mediated reactions can be achieved by photochemical irradiation of, or thermal decomposition of peroxides (c*f.* Section 1.2.4) or in a more indirect way; namely, aerobic auto-oxidation. The aerobic auto-oxidation of an aldehyde **14** to carboxylic acid **91** is known to proceed *via* an acyl radical **66** (Scheme 24).[55] In the pathway, an aldehyde **14** is converted to an acyl radical **66** which is trapped by molecular oxygen to give peracyl radical **88**. This acts as a chain carrier by abstracting a hydrogen atom from the parent aldehyde **14** to regenerate acyl radical **66** and peroxy acid **89**. Nucleophilic attack of peroxy acid **89** on aldehyde **14** forms intermediate **90** which then forms 2 equivalents of acid **91** after rupture of the O-O bond. The intermediacy of acyl radical **66** and peroxyacyl radical **88** in the aerial oxidation of aldehydes is well established. However, the precise mechanistic details for the formation of acyl radical **66** from aldehyde **14** are yet to be entirely unravelled – especially as the direct abstraction of hydrogen by dioxygen is highly endothermic.[55]

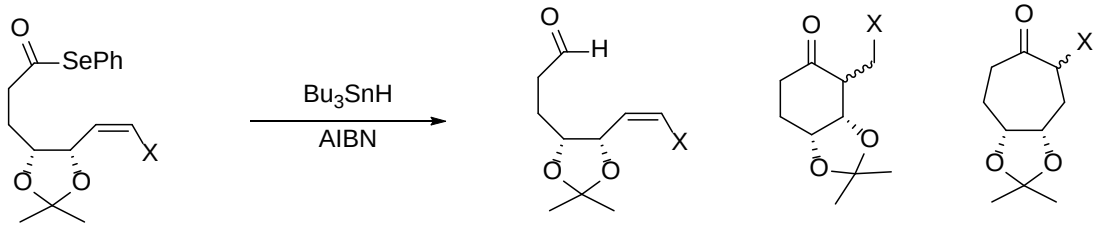


Scheme 24. Auto-oxidation of aldehyde **14** *via* acyl radical **66**[55]

1.2.4.3 Hydroacylation reactions of various unsaturated bonds

1.2.4.3.1 Intramolecular hydroacylation *via* acyl radicals

Although the radical mediated intramolecular hydroacylation of a C-C double bond represents a highly atom-economic methodology for the synthesis of cycloalkanones, there are some inherent complications posed by the possible formation of regioisomeric (endo/exo)–mixtures. Nevertheless, extensive investigations into the thermodynamic equilibration of β-acylalkyl radicals have enabled somewhat better control and thus numerous examples of acyl radical cyclizations have ensued.[55] For example, although AIBN-initiated cyclization of selenoester **92a** is highly efficient, the exo/endo-ratio was found to be as low as 4/5 (Scheme 25). However, when the selenoester is substituted at the alkene terminus as in **92b**, the exo/endo-ratio increases considerably and an excellent yield of **94b** is observed.[61]

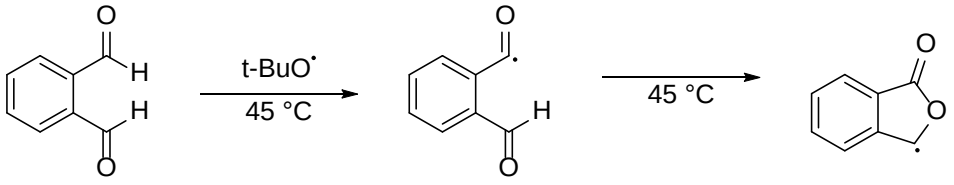


92 **93** **94** **95**

92a X = H	7%	41%	51%
92b X = Me	7%	91%	3%

Scheme 25. Comparison of 7-endo vs 6-exo cyclizations[61]

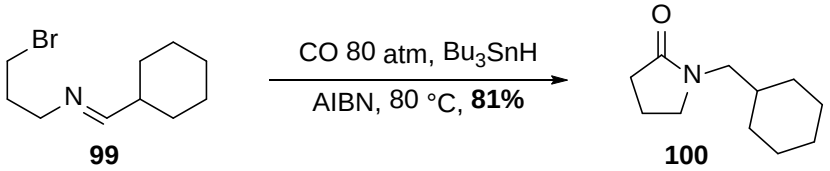
There also exist examples of intramolecular acyl radical additions to carbonyl groups and C-N multiple bonds. For example the formal 5-endo-trig cyclization of *o*-thalaldehyde **96** to **98** *via* acyl radical **97** was reported by Mendenhall and co-workers (Scheme 26).[75]



96 **97** **98**

Scheme 26. Intramolecular acyl radical addition to a carbonyl[75]

Cyclizations onto C-N multiple bonds can involve nitriles, oximes, hydrazones as well as imines. Given the generally nucleophilic character of acyl radicals, quite unusually, these cyclizations involve addition to more electron-rich nitrogen atoms. For example, using radical carbonylation to generate the relevant acyl radicals, Ryu and co-workers employed a [4+1] cyclization of imines such as **99** to generate a range of γ-lactams, including **100** (Scheme 27).[76]



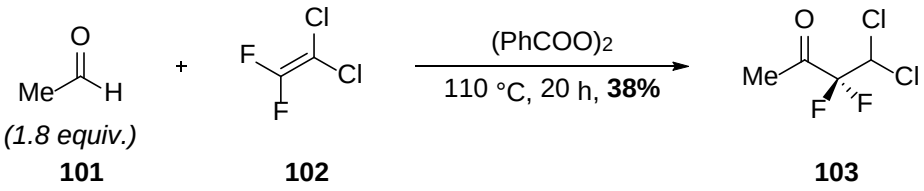
99 **100**

Scheme 27. Intramolecular acyl radical addition to a C-N double bond[76]

1.2.4.3.2 Intermolecular hydroacylation of C-C double bonds *via* acyl radicals

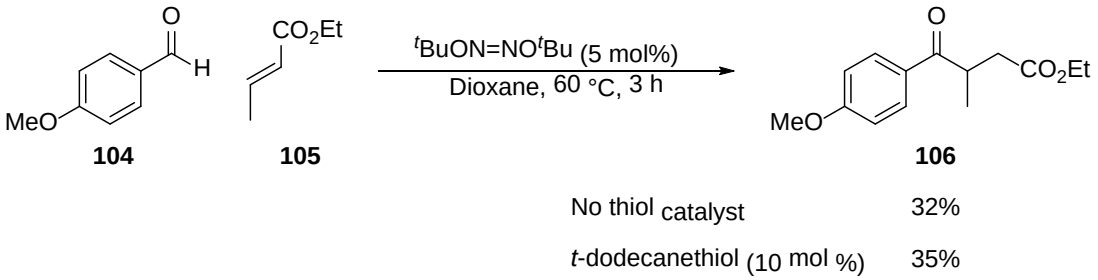
Acyl radicals add more efficiently to electron-deficient alkenes and are, therefore, regarded as nucleophilic radicals. Their intermolecular addition to electron poor alkenes represents an efficient and clean method for the synthesis of unsymmetrical ketones. As previously described, following initiation, the addition of an acyl radical to an alkene generates an intermediate radical species which generates a ketone by abstracting a formyl hydrogen atom from an aldehyde whilst, concomitantly, regenerating the acyl radical (c*f.* Scheme 17). In the case that the said intermediate radical species does not find an appropriate C-H bond, *e.g.* formyl hydrogen, to abstract, radical polymerization may ensue. As such, it is usually the case that an

excess of the aldehyde component is employed. For example, in the regioselective formation of 1,1-difluoro-2,2-dichloro alkyl ketones such as **103**, despite employing a highly electron-deficient alkene such as **102**, an almost two-fold excess of the aldehyde counterpart is required for an appreciable conversion.[77]



Scheme 28. Regioselective hydroacylation reaction of acetaldehyde **101** with alkene **102**[77]

As previously indicated, employing thiols as polarity reversal catalysts can result in dramatic improvements in the efficiency of such radical chain processes. However, polarity reversal catalysis does not always result in improvements as exemplified by the addition of *p*-anisaldehyde **104** to ethyl crotonate **105** with and without thiol catalyst; almost no improvement was observed in the yield of product **106** in the presence of the thiol catalyst (Scheme 29). Perhaps hydrogen abstraction from aldehyde by the resultant electrophilic intermediate radical would be so fast that thiol catalysis may not play a meaningful role.[78]

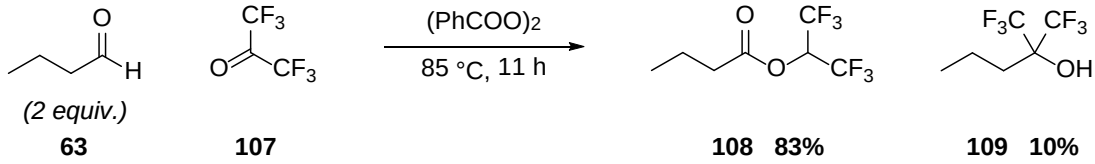


Scheme 29. Effect of thiol catalysis on hydroacylation reaction of aldehyde **104** and alkene **105**[78]

1.2.4.3.3 Intermolecular addition of acyl radicals into non C-C double bonds

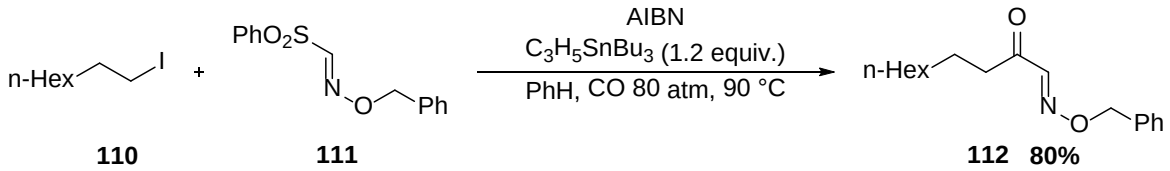
In addition to the intramolecular examples presented earlier, acyl radicals can add across non C-C double bonds intermolecularly too; albeit less commonly. Carbonyl groups, imines and azo- compounds can all undergo acyl radical mediated hydroacylation. For example, Urry and co-workers reported the acyl-radical

mediated oxygen-philic addition of *n*-butanal **63** to hexafluoroacetone **107** (Scheme 30).[79] Re-emphasizing the importance of polar effects, it is interesting to note that the addition of an alkyl radical, such as that derived from the decarbonylation of the acyl radical, occurs in a carbo-philic manner to generate tertiary alcohol **109**.



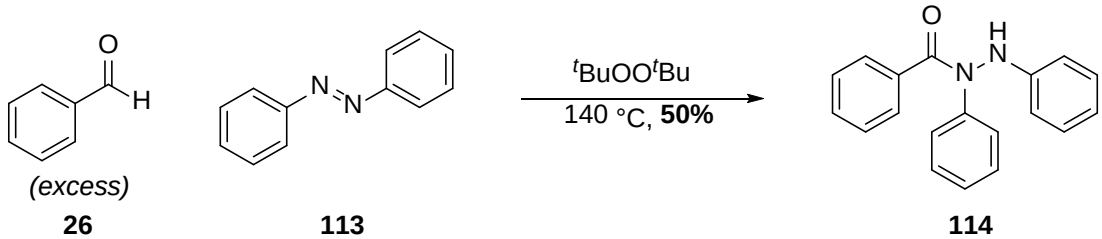
Scheme 30. Intermolecular addition of an acyl radical to a carbonyl[79]

In contrast to efficient intramolecular additions described previously, intermolecular additions of acyl radicals to C-N double bonds are more troublesome. Nevertheless, Kim and co-workers have succeeded in employing a three-component coupling reaction with sulphonyl oxime ether **111** to access oxime **112** following carbonylation of alkyl iodide **110**.[80]



Scheme 31. Intermolecular addition of an acyl radical to an unsaturated C-N bond[80]

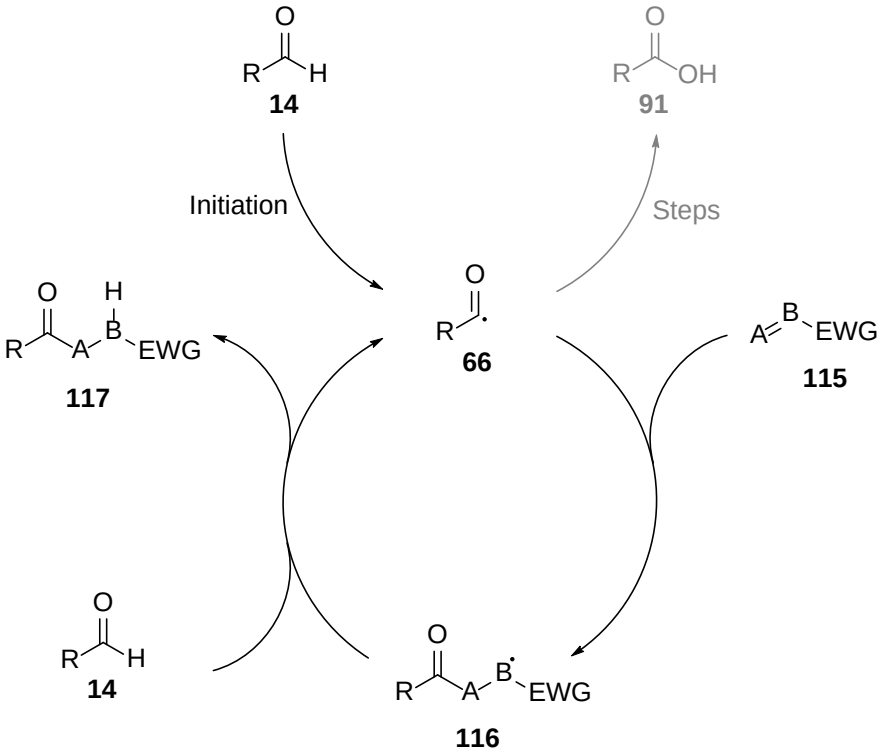
Perhaps of most relevance to this thesis is the intermolecular addition of acyl radicals to N-N double bonds; although known for a while, examples of this transformation are scarce.[81-83] Nonetheless, Kharasch and co-workers have successfully demonstrated the acyl radical mediated hydroacylation of azobenzene **113** with benzaldehyde **26** to obtain monobenzoylhydrazobenzene **114**; however, despite employing a ten-fold excess of the aldehyde, the reaction failed to proceed in the absence of a peroxide initiator.[81]



Scheme 32. Intermolecular addition of an acyl radical to an unsaturated N-N double bond[81]

1.2.4.3.4 Hydroacylation work within the Caddick group

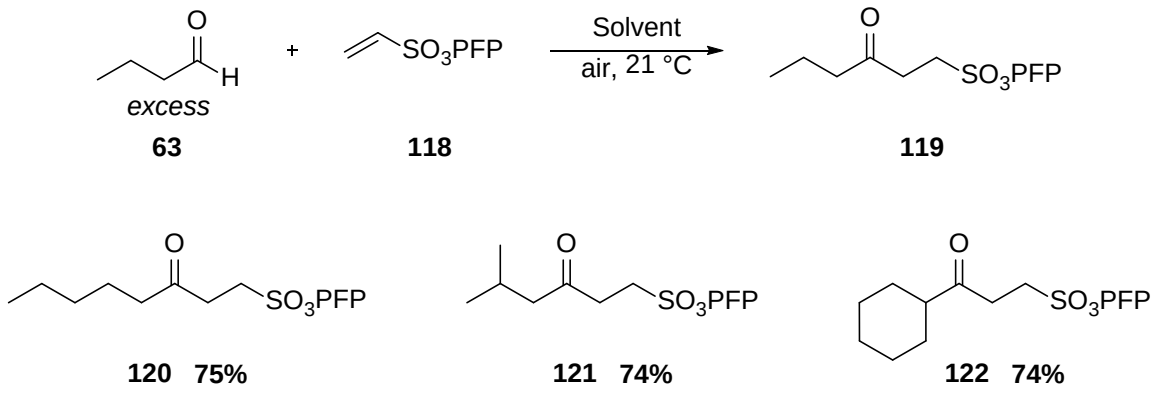
Conceivably, among some of the most useful contributions made to acyl radical mediated hydroacylation is the aerobic hydroacylation methodology developed in the Caddick group. Identifying the generation of said acyl radicals as the key limitation, Caddick and co-workers successfully took advantage of the aerobic aldehyde auto-oxidation pathway as a benign source of acyl radicals to affect clean hydroacylation of vinyl sulfonates,[84] sulfones and phosphonates,[85-86] α,β-unsaturated esters[87] and azodicarboxylates.[88] In general, as aldehyde **14** decomposes to carboxylic acid **91**, the intermediate acyl radical **66** is trapped by an electron deficient alkene **115** (Scheme 33). The intermediate β-radical **116** can then abstract an H-atom from aldehyde **14** to generate adduct **117** and thereby forming a radical chain process. In all of their reported cases, the reactions were inhibited by BHT; implying a radical process.[89]



Scheme 33. General schematic illustrating the mechanism for aerobic hydroacylation reaction of alkene **115**[89]

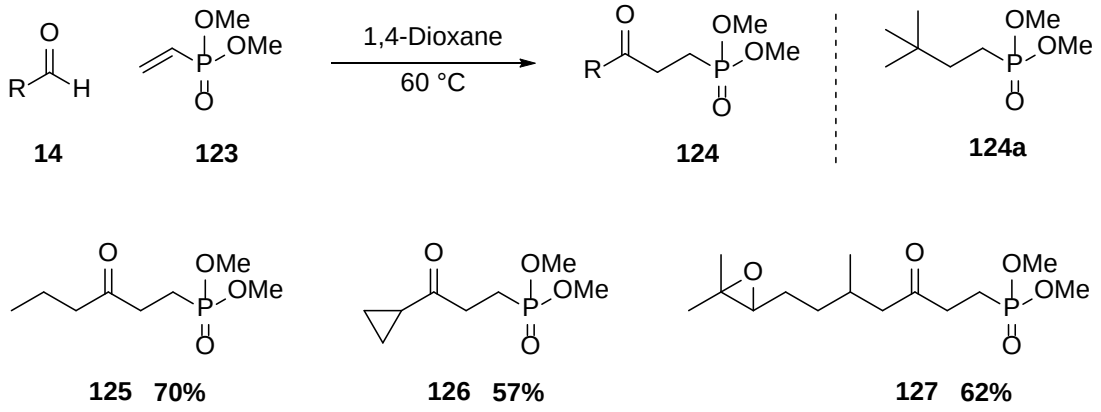
Given the efficiency of vinyl sulfonates to act as radical acceptors,[90] Caddick and co-workers disclosed the hydroacylation of PFP vinyl sulfonate **118** using a variety of aliphatic aldehydes to form unsymmetrical ketones (Scheme 34). Employing a 5-fold

excess of aldehyde in ethereal solvents such as 1,4-dioxane and, interestingly, only 2-fold excess of aldehyde in water, the authors were able to obtain ketone products in up to high yields. The increased efficiency of this carbon-carbon bond-forming reaction in water was rationalised by the increased concentration of the reagents, due to the hydrophobic effect; thereby reducing the longevity of the radical intermediates and consequently the likelihood of unimolecular degradation pathways, such as decarbonylation.[84]



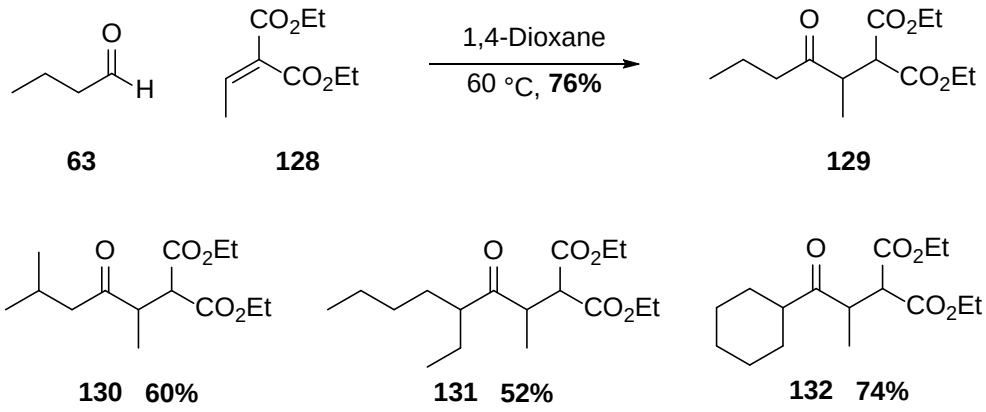
Scheme 34. Hydroacylation reaction of PFP vinyl sulfonate **118** to give a range of ketones, including ketones **120 - 122**[84]

Attempts in the group, to affect the hydroacylation of vinyl phosphonates under similar conditions, to the sulfonates, resulted in poor yields of the corresponding γ-ketophosphonate. Despite reactions in water being unsuccessful, lowering the concentration of dissolved molecular oxygen in the organic solvent by increasing the reaction temperature to 60 °C, and by reducing the surface area exposed to open air, resulted in a dramatic increase in ketone yield. Thus, a variety of aliphatic aldehydes were successfully added to vinyl phosphonate **123** to access synthetically useful γ-ketophosphonates in high yields (Scheme 35).[86] However, despite complete conversion, pivaldehyde underwent unimolecular decarbonylation prior to addition; thereby resulting in corresponding products such as **124a**.



Scheme 35. Hydroacylation reaction of vinyl phosphonate **123**[86]

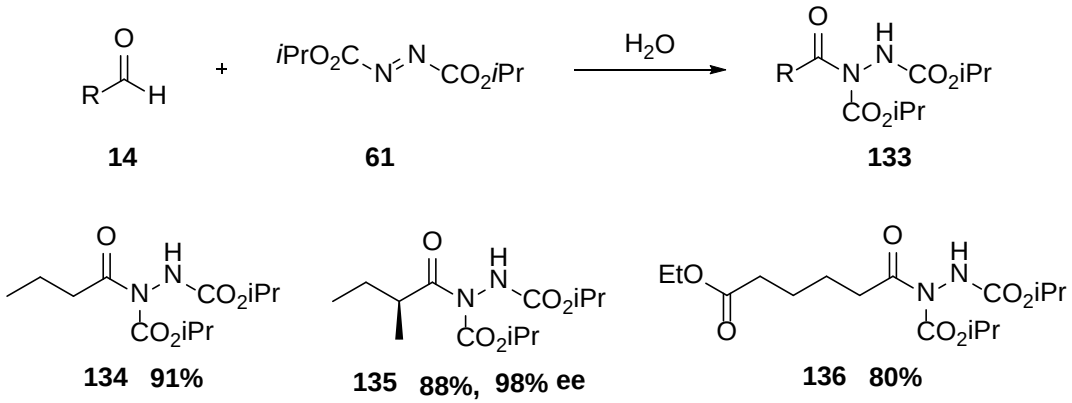
Similar to the vinyl phosphonates, attempts for hydroacylation of α-β-unsaturated esters in water were met with failure. As with vinyl phosphonates, reactions in 1,4-dioxane required elevated temperatures, 60 °C, and surface area:volume ratio optimisation to diminish the concentration of molecular oxygen thereby giving alkene **128** the opportunity to undergo hydroacylation. Thus a range of aliphatic aldehydes were successfully converted to their corresponding 1,4-dicarbonyls in up to 87% yield (Scheme 36). Consistent with the group's previous studies, rapidly auto-oxidising and/or rapidly degrading aldehydes, such as pivaldehyde, yielded little or no desired 1,4-dicarbonyls. Interestingly, additions to the alkenes were independent of *E/Z* geometry.[87]



Scheme 36. Hydroacylation reaction of diester **128**[87]

Another class of radical acceptors explored by the group included azodicarboxylates; diethylazodicarboxylate, DEAD, and diisopropylazodicarboxylate, DIAD, both showed superior reactivity and underwent hydroacylation in aqueous, *i.e.* water, as well as organic, *i.e.* 1,4-dioxane, solvents. Furthermore, owing to the efficiency of

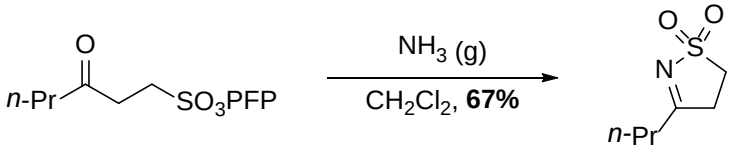
azodicarboxylates as radical acceptors, the group successfully demonstrated the first example of such reactions where the aldehyde is employed as the limiting reagent. Accordingly, a range of aldehydes, bearing a range of functional groups, were successfully converted to their corresponding acyl hydrazides in excellent yields of up to 91%.[88]



Scheme 37. Hydroacylation reaction of diisopropyl azodicarboxylate **61**[88]

1.2.4.3.4.1 Synthetic utility of the hydroacylation products

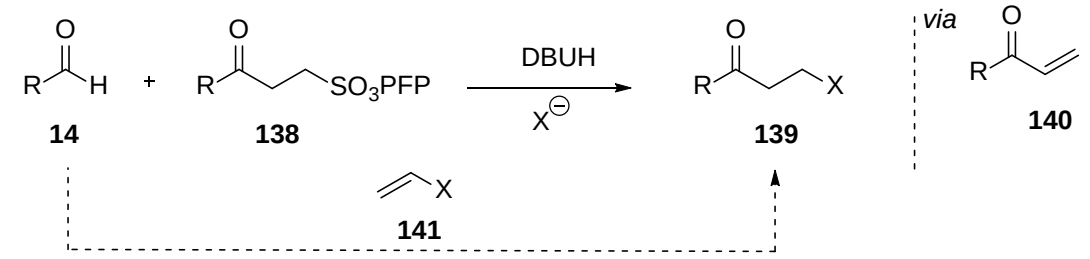
Aside from the inherent utility of the carbonyl group, hydroacylation of vinyl sulfonates, vinyl phosphonates and azodicarboxylates add further functionality and utility to the aldehyde. For example, Caddick and co-workers were able convert γ-keto-sulfonate **119** into cyclic *N*-Sulfonyl imine **137** by treatment with ammonia gas (Scheme 38); thus circumventing an otherwise multi step and inefficient protocol.[85]



Scheme 38. Conversion of sulfonate **119** into imine **137**[85]

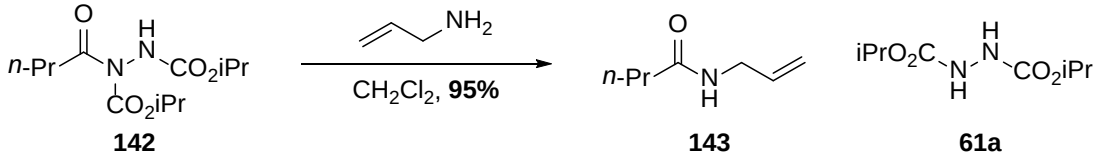
Another useful utility demonstrated by the group was an elimination-addition protocol. Treatment of γ-keto-sulfonate **138** with DBU and a relevant nucleophile resulted in the formation of ketone **139**. Having confirmed the formation of enone **140** the authors concluded that the reaction proceeds *via* a 1,4-addition of the

nucleophile. This mode of reactivity provides an indirect alternative to achieve hydroacylation of electron rich alkenes (Scheme 39).[85]



Scheme 39. Indirect alternative to hydroacylation of electron-rich alkene **141**[85]

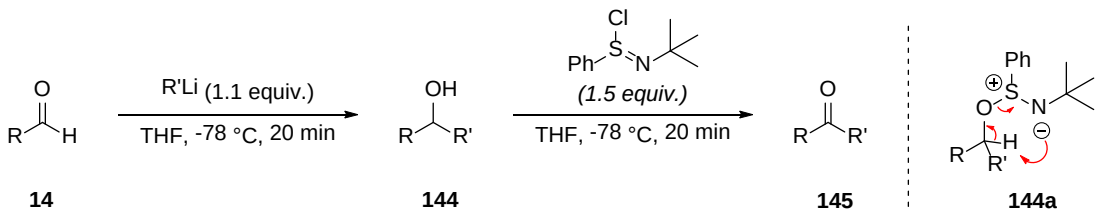
Caddick and co-workers also demonstrated the acyl donating capability of acyl hydrazides. Treatment of acyl hydrazide **142** with a range of primary amines resulted in the formation of secondary amides such as **143**. However, poor yields were observed on application of secondary and bulky primary amines.[88]



Scheme 40. Conversion of hydrazide **142** into secondary amide **143**[88]

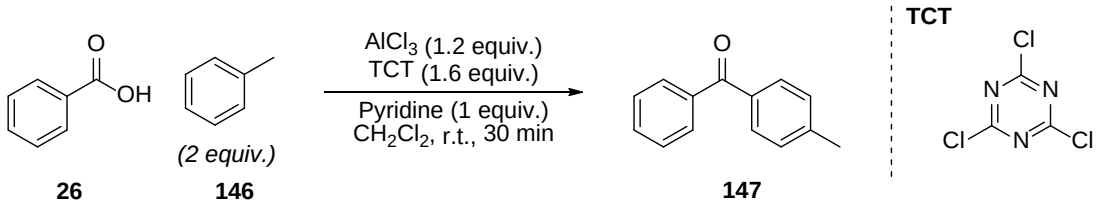
1.3 Synthesis of Ketones

Ketones have served as important versatile building blocks for the synthesis of various natural products, pharmaceuticals, agrochemicals and other functional materials.[91-94] There are numerous methods for their syntheses, perhaps the simplest of which is the oxidation of secondary alcohols to ketones. For example, Liu has reported the one-pot conversion of aldehydes such as **14** to ketones **145** *via* oxidation of secondary alcohol **144** by *N*-*tert*-butylbenzenesulfinimidoyl chloride as in **144a** (Scheme 45). However, despite its merits, this methodology most often suffers from functional group intolerance due to harsh reaction conditions and the need for an excess of oxidant.[95]



Scheme 45. Oxidation of secondary alcohol **144** to ketone **145**[95]

Conceptually, employing a Friedel-Crafts acylation protocol can also allow access to ketones. Although a well known and reliable methodology for the conversion of activated carboxylic acid derivatives and aldehydes to ketones **147**, this protocol frequently suffers from the need for stoichiometric amounts of Lewis acid and sometimes additional additives (Scheme 46). Furthermore, Friedel-Crafts acylation protocols have untunable regioselectivity and poor functional group tolerance.[96]

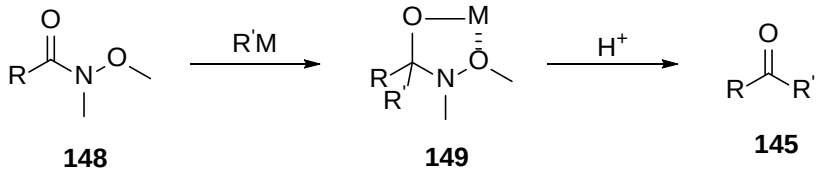


Scheme 46. Ketone synthesis *via* Friedel-Crafts acylation[96]

Direct addition of an organometallic reagent to activated carboxylic acid derivatives such as anhydrides and acid chlorides also provides access to ketones. However, owing to the reactive nature of the product ketones, this methodology suffers from over-addition, resulting in the formation of undesired tertiary alcohol products.[93,97-98] However, Weinreb amides are notable exceptions to this class of derivatives.

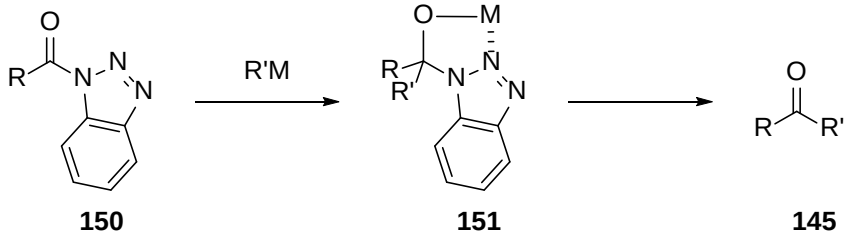
1.3.1 Synthesis of ketones *via* Weinreb amides

Treatment of a Weinreb amide such as **148** with a suitable organometallic reagent provides the corresponding ketone **145** selectively, in high yields without significant over-addition (Scheme 47).[99-100] This selectivity stems from the formation of a tetrahedral metal-chelate intermediate **149** which is stable under the reaction conditions and only destroyed upon protic work-up; preventing over-addition of the nucleophile.



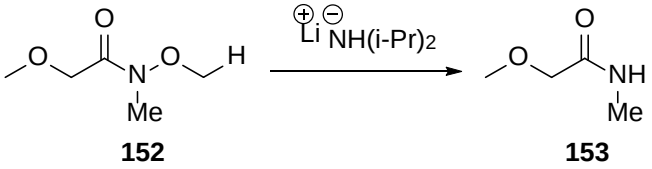
Scheme 47. Key intermediate **149** in the Weinreb ketone synthesis[99-100]

The advent of Weinreb amides has sparked a series of investigations into alternative chelating moieties for the synthesis of ketones. One such example is the use of N-acylbenzotriazole **150** as a ketone precursor (Scheme 48).[101] Similar to its Weinreb counterpart, reaction of benzotriazole **150** is believed to proceed *via* a stable tetrahedral complex **151** (albeit chelating through a nitrogen as opposed to an oxygen atom) which can be destroyed during work-up to release ketone **145**.



Scheme 48. Proposed transition state in ketone synthesis using *N*-acylbenzotriazoles[101]

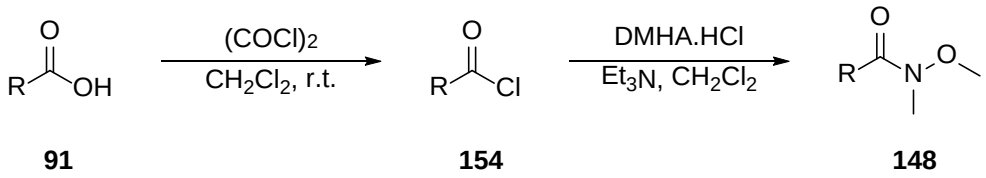
Conversion of Weinreb amides to ketones represents a highly facile and selective protocol for the synthesis of ketones. It does however, suffer from some undesired, thus impeding side reactions. One such reaction is the decomposition of Weinreb amide **152** to N-methylamide **153** and formaldehyde observed following elimination which is promoted by hindered and/or strongly basic nucleophiles (Scheme 49).[102]



Scheme 49. Side reaction observed in Weinreb ketone synthesis[102]

Although the decomposition problem has been addressed to some extent by the arrival of Weinreb mimetics such as benzotriazoles (c*f*. Scheme 48) there remains one inherent problem that even these mimics suffer from, the multi step protocol required for their synthesis. Weinreb amides are usually prepared by the reaction of

an activated carboxylic acid derivative **154** with a hydrochloride salt of *N,O*-dimethyl hydroxylamine (DMHA); a protocol that, unfortunately, diminishes the elegance of this useful methodology (Scheme 50). Such synthetic routes often employ either toxic and expensive reagents, laborious multi-step transformations and/or excessive generation of waste.[100]



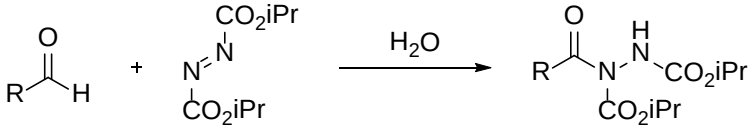
91 **154** **148**

Scheme 50. Multi-step synthesis of Weinreb amide **148**[100]

1.4 Aims

Thus far, there have been a very limited number of studies on the scalability of the hydroacylation reactions. Given the stringent environmental and safety regulations imposed upon the agrochemical, pharmaceutical, and the fine chemical industry as a whole, successful scalability of this highly atom economic and environmentally benign aerobic hydroacylation protocol would be of noticeable interest to these industries. This would be of even more interest if it can be demonstrated that the products of the hydroacylation protocol can act as efficient precursors for further synthetic manipulation.

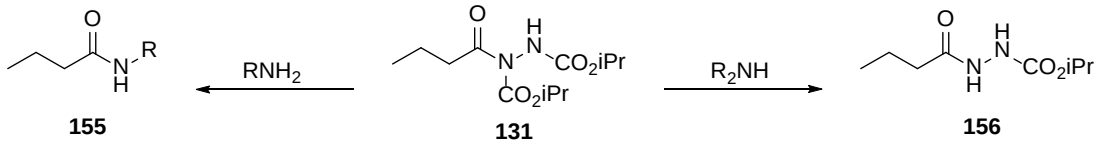
The primary aim of this project was to assess the scalability of present examples of DIAD hydroacylation (Scheme 51). Limited work had been completed thus far in examining the tolerance of the aerobic hydroacylation methodology to aromatic aldehydes. Given the prominence of the (hetero)aromatic moiety in the fine chemical industry, an attempt was to be made to extend the scope of this powerful chemistry with respect to (hetero)aromatic aldehydes.



14 **61** **125**

Scheme 51. Hydroacylation reaction of diisopropyl azodicarboxylate **61**[88]

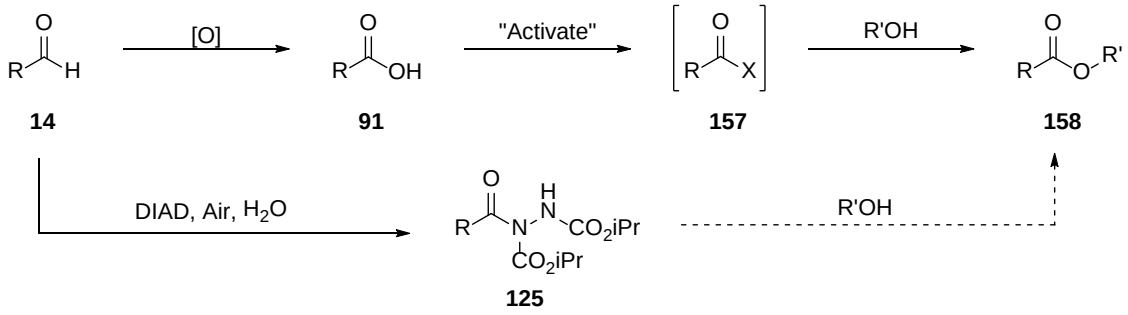
Previous work in the Caddick group had revealed that the hydrazide products of DIAD hydroacylation are efficient acyl donors for the synthesis of secondary amides such as **155**. However, attempts to extend this methodology to the synthesis of tertiary amides were met with failure due to a side reaction resulting in hydrazide **156** (Scheme 52). As such, a study was to be conducted to examine the failure of this transformation and attempt to solve it.



155 **131** **156**

Scheme 52. Initial attempts to synthesis tertiary amides from acyl hydrazide **131**

The highly economical and benign nature of the aerobic C-H activation protocol, together with the acyl donating capability of the hydrazide products thereof provides a valuable opportunity to access carboxylic acid derivatives from aldehydes with ease. Therefore, an investigation was to be conducted to assess the possibility of converting acyl hydrazides **125** to esters **158** by reaction with alcohols (Scheme 53). Such an approach would provide an alternative to an otherwise inefficient multi step protocol for accessing esters from aldehydes.

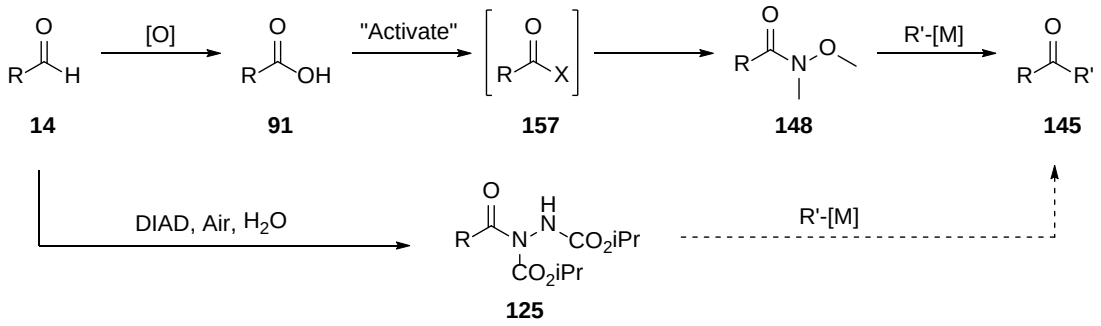


14 **91** **157** **158** **125**

Scheme 53. Alternative esterification methodology *via* easily accessible acyl hydrazides

Finally, given the similarities between acyl hydrazides and Weinreb amides including the fact they have multiple sites available for forming a stable metal chelate and have been shown to be acyl donors, a study was to be conducted to ascertain if acyl hydrazides could potentially serve as effective acyl donors for the synthesis of ketones. Once again, such a transformation would be highly desirable due to the facile and mild nature in which aldehydes can be readily transformed into

acyl hydrazides in a single step; thus overcoming an otherwise inefficient, multi-step protocol for accessing Weinreb amides from aldehydes (Scheme 54).



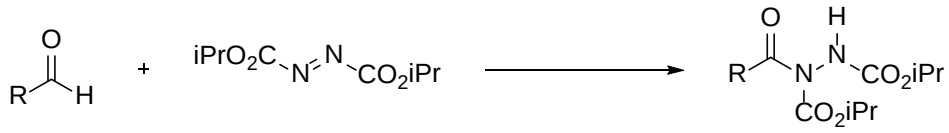
14 **91** **157** **148** **145** **125**

Scheme 54. Comparison of Weinreb amide **148** ketone syntheses to potential acyl hydrazide **125** mediated protocol for the synthesis of ketones **145**

Chapter 2 Hydroacylation of Azodicarboxylates

2.1 Background

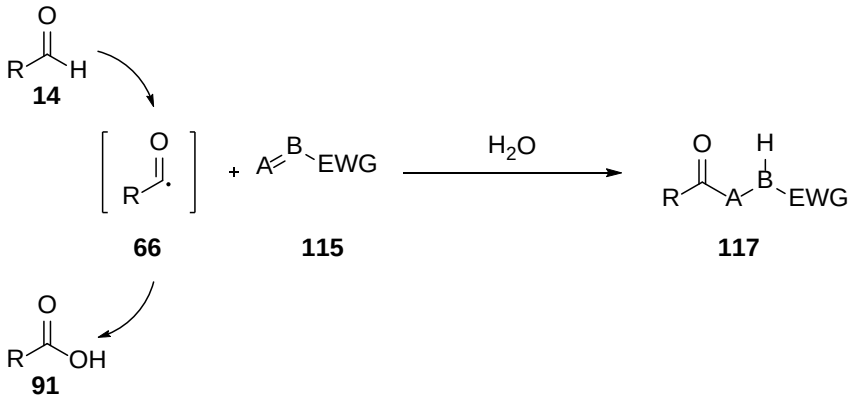
As described in Chapter 1, carbon-nitrogen bond-forming reactions are of great importance in organic chemistry. It is well established that dialkyl azodicarboxylates, *e.g.* diisopropylazodicarboxylate (DIAD), are excellent electrophiles that are highly accessible, with a large number being commercially available. Owing to their electrophilicity, a hydroacylation reaction which involves the use of azodicarboxylates as electrophiles has recently been used for carbon-nitrogen bond formation; thus, under suitable conditions, aldehyde **14** is able to add across the nitrogen-nitrogen double bond of DIAD **61** to form hydrazide product **125** (Scheme 55).[103]



14 **61** **125**

Scheme 55. Efficient hydroacylation of DIAD **61** to form hydrazine imide **125**

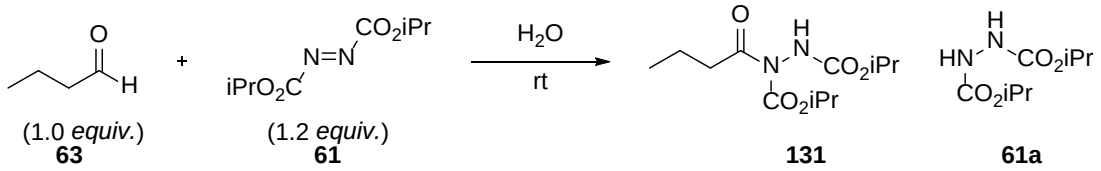
This new methodology is regarded as a highly efficient methodology for direct activation and subsequent functionalisation of the aldehydic C-H bond with dialkyl azodicarboxylates to form a variety of hydrazine imides. Although numerous conditions have been explored to affect this valuable transformation, the reaction usually results in relatively low yields, utilises costly precious metals and requires extended reaction times (especially when aromatic aldehydes are employed).[5,37,53] In light of this, the aerobic hydroacylation protocol recently developed in the Caddick group, shows promise to develop the efficiency of this transformation while extending the scope of the substrates without the use of costly reagents. The aerobic hydroacylation methodology relies on the use of aldehyde auto-oxidation as a benign source of acyl radicals like **66**; thus enabling efficient hydroacylation of electron deficient alkenes (Scheme 56).



Scheme 56. Aerobic hydroacylation of electron-deficient alkene **61** *via* acyl radical **66**

2.2 Further optimisation of previous work

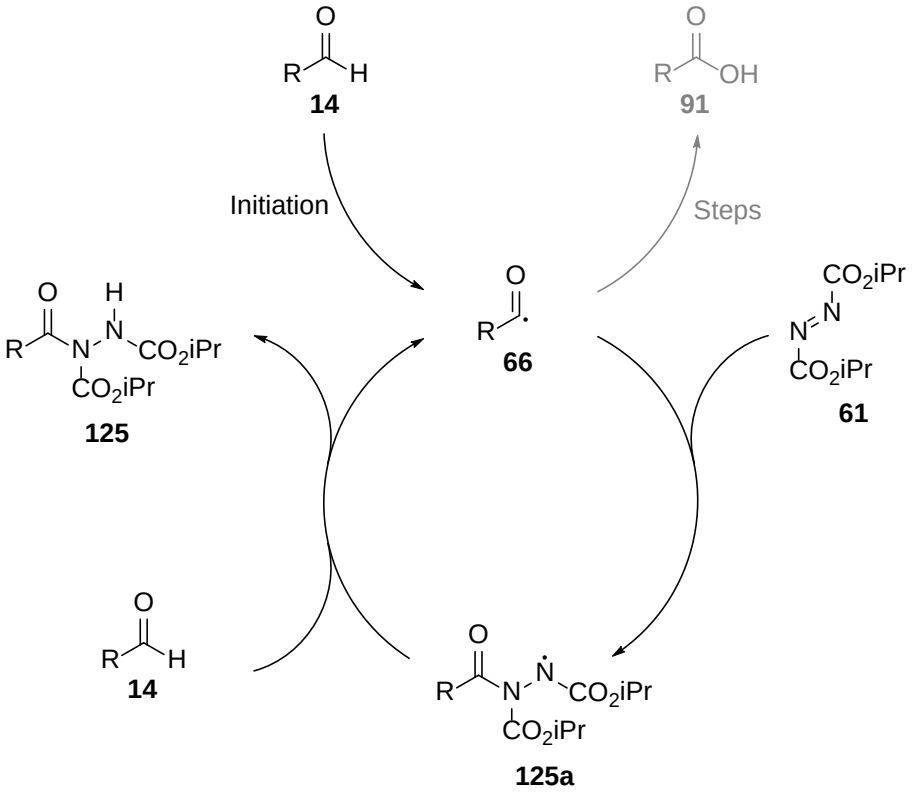
As discussed, the Caddick group has developed a benign method of C-H activation for aerobic hydroacylation. This was a major contribution to the field of acyl radical mediated hydroacylation, enabling the hydroacylation of a wide variety of alkenes. More recently, the Caddick group reported the hydroacylation of DIAD **61** under similar aerobic hydroacylation conditions. They observed that the reaction was highly efficient and clean; this led the group to identify conditions where the aldehyde is employed as the limiting reagent (Scheme 57). This is in sharp contrast with previous hydroacylation protocols and other alkene substrates where the aldehyde is employed as the reagent in excess.[89]



Scheme 57. Aerobic hydroacylation reaction of *n*-butanal 'on-water' in the presence of atmospheric oxygen

The hydroacylation of DIAD with *n*-butanal was completely inhibited in the presence of radical inhibitor, BHT (5 mol%); consistent with previous hydroacylation protocols developed in the Caddick group, this suggests the possibility of a radical mediated reaction. It is believed that the mechanism for this acyl radical mediated chain process is similar to that generally accepted for addition of acyl radicals to alkenes. It is well known that aldehyde **14** decomposes to carboxylic acid

91 in the presence of atmospheric oxygen *via* acyl radical **66**. Thus, it is proposed that the nucleophilic intermediate acyl radical **66** adds to the electron deficient nitrogen-nitrogen double bond of DIAD **61** (Scheme 58). The intermediate β-radical **125a** is then well polarity matched to abstract an H-atom from aldehyde **14** to re-generate acyl radical **66** and adduct **125**, thereby forming a radical chain process.[89]



Scheme 58. Proposed mechanism for the acyl radical mediated hydroacylation reaction of DIAD **61** with aldehyde **14**

In an attempt to detect the presence of radical intermediate **125a**, the hydroacylation reaction of *n*-butanal with DIAD **61** was subjected to an electron paramagnetic resonance, EPR, study. Unfortunately however, no peaks were observed even after 200 scans (Figure 1). It is possible that this is due to at least two reasons. Firstly, this may be due to a short life span of the nitrogen centred intermediate radical **125a**. Secondly, during the EPR study, the sample under investigation is placed in a sealed tube; it is possible that this may deprive the reaction of atmospheric oxygen, thus stopping the reaction.

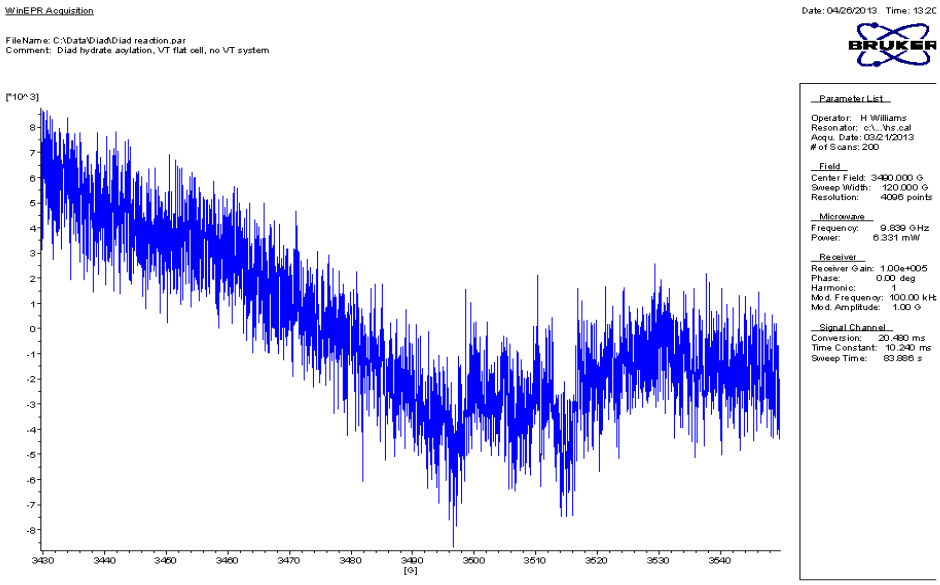


Figure 1. Electron paramagnetic resonance spectrum of the reaction of *n*-butanal with DIAD **61**; no peaks were observed. See experimental section for experiment parameters.

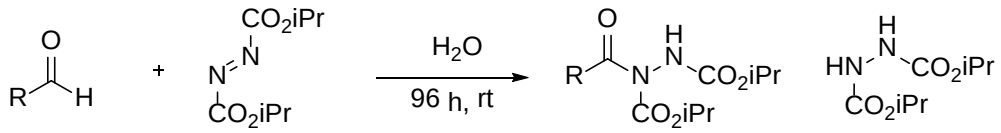
2.3 Aldehyde scope

Although previous studies in the group have successfully demonstrated the applicability of the aerobic hydroacylation protocol to a wide variety of aldehydes, there has been very little work undertaken on investigating the scalability of the reaction. Furthermore, scope for the hydroacylation of aromatic aldehydes, using the aerobic protocol, has thus far been somewhat limited.

Initially, to enable scalability of the hydroacylation reaction to 10 mmol, a brief study was carried out and it was found that an extended reaction time, 96 h, was necessary for sufficient conversion. Overall, a very slight decrease in yield was observed on scaling up the reactions, employing aliphatic aldehydes, from 1 mmol to 10 mmol scale. This was mainly due to difficulties experienced in separating the hydrazide products from hydrazine diisopropyldicarboxylate **61a**, formed as a result of DIAD **61** decomposing under the reaction conditions. Nevertheless, linear saturated as well as branched aliphatic aldehydes underwent hydroacylation reaction with DIAD **61** to afford their hydroacylation products in excellent yields of 65-90% (Table 3, entries 1 to 9).

Previous attempts in the group, to affect the hydroacylation of alkenes such as vinyl sulfonates with pivaldehyde failed; this was due to the propensity of the pivaloyl acyl radical to undergo rapid decarbonylation.[104] However, on reaction with DIAD, it has been shown that hydroacylation with pivaldehyde proceeded to give hydrazide product **165** in up to 64% yield; thus suggesting that intermolecular addition of a pivaloyl acyl radical to DIAD is more facile than its unimolecular decarbonylation to give a tertiary alkyl radical.[104-105] Gratifyingly, when the reaction was scaled up as part of the current study, the yield remained similar to that observed on small scale (Table 3, entry 8).

The hydroacylation reaction of α,β-unsaturated aldehydes with alkenes was previously shown to be problematic due to polymerisation; however, the Caddick group was successful in demonstrating the hydroacylation reaction of α,β-unsaturated aldehydes with DIAD.[86] Interestingly, despite its low rate of auto-oxidation, octynal was successfully functionalised to hydrazide **166** in a modest, 55% yield (Table 3, entry **9**). Although this is in contrast to previously poor yields observed with other alkenes, the yield obtained herewith was in agreement with that obtained previously on smaller scale. This implies that DIAD is a more efficient acceptor and/or its intermediate radical is a better chain propagator, thus requiring only a small amount of acyl radical to initiate the reaction.[89]



14 **61** **125** **61a**

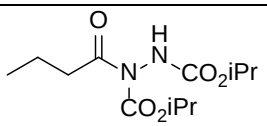
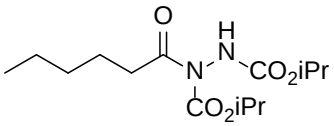
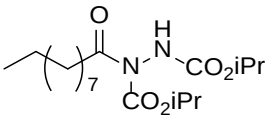
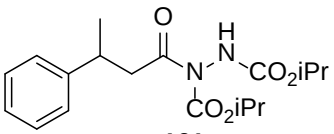
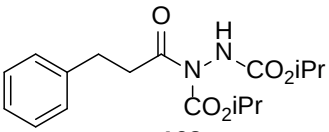
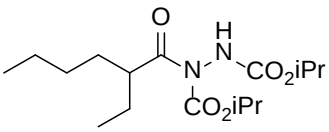
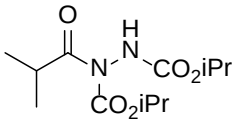
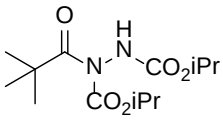
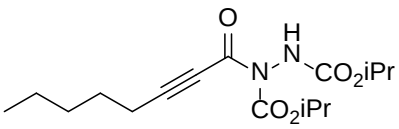
Entry	Hydrazide	% Yield at 1 mmol scale	% Yield at 10 mmol scale
1	 **131**	91	88
2	 **159**	82	76
3	 **160**	85	85
4	 **161**	97	90
5	 **162**	78	85
6	 **163**	95	86
7	 **164**	79	75
8	 **165**	69	65
9	 **166**	55	50

Table 3. Aliphatic aldehyde tolerance to aerobic hydroacylation reaction conditions

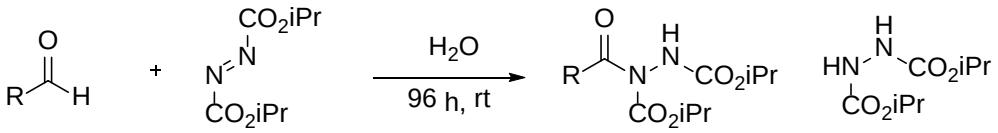
Next, a study was conducted to probe the applicability of aromatic aldehydes to the aerobic hydroacylation protocol. Thus, an electron neutral, a range of electron rich (Table 4, entries 1 to 5) and electron deficient (Table 4, entries 7 to 17) aldehydes were subjected to the reaction conditions; aldehydes were selected such that functionalities releasing and withdrawing electrons inductively and by resonance were represented. Previous attempts to functionalise aromatic aldehydes with alkenes such as vinyl sulfonates, -phosphonates and diester alkenes were met with failure.[86-87,89,105] One of the reasons postulated for these failures and/or inefficiencies was the limited solubility of solid aldehydes in the water-based reactions.[89,104] As such, it was pleasing to find that, on application of solid aldehydes such as 3-nitro-, 4-cyano-, and 2,3,4-trimethoxybenzaldehydes, hydroacylation reaction with DIAD **61** took place to give the corresponding hydrazides in comparable yields to non-solid aldehyde precursors (Table 4, entries 5, 15 and 16). This was partly made possible by DIAD **61** acting as an organic solvent to dissolve the aldehyde; thus enabling an "on-water" homogenous reaction mixture.

It was found that substitutions were tolerated well on all positions; *ortho*, *meta* and *para*. In fact, di- and tri-substituted aromatic aldehydes also underwent hydroacylation reaction to acyl hydrazides; with some aldehydes such as 2,6-dimethyl, 2,6-dichloro, and 2,3,4-trimethoxybenzaldehyde further demonstrating the tolerance of this reaction towards increased steric hindrance near to the acyl radical centre (Table 4, entries 3, 5 and 9). The success of a varied range of aldehyde electronics and sterics represented signifies the robustness of this novel methodology; thus suggesting that relative to previously employed alkenes, DIAD **61** may be a more superior acyl radical acceptor and/or its intermediate β-radical may be a better chain propagator.

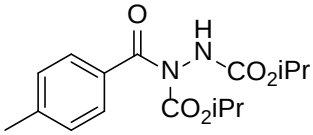
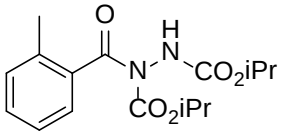
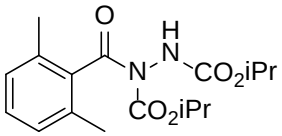
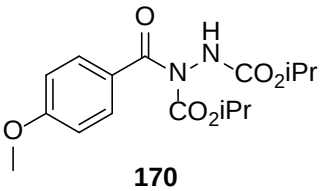
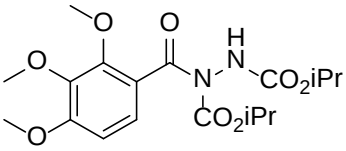
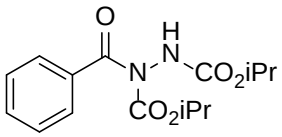
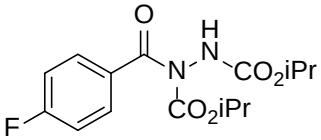
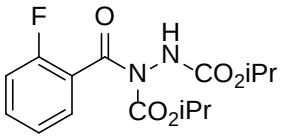
Also demonstrated was the applicability of the reaction conditions towards a range of functionalities; for example, nitro, cyano, ester and ether groups as well as halogens were all tolerated on aromatic aldehydes, thus furnishing their corresponding hydrazides in very good yields (Table 4). Unfortunately, attempts to affect the hydroacylation of heteroaromatic aldehydes such as nicotinaldehyde, furfural and *N*-methyl-pyrrole-2-carbaldehyde were met with failure (Table 4, entries 19 to 21). However, it was encouraging to find that thiophene-2-carbaldehyde underwent

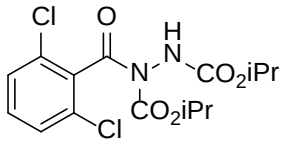
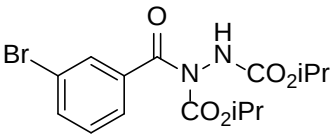
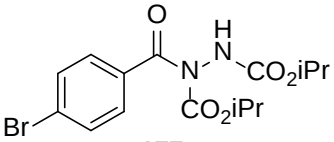
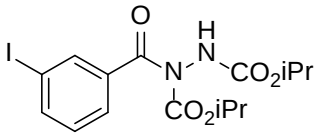
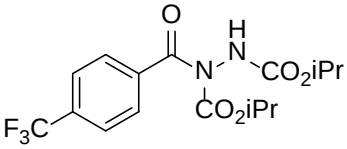
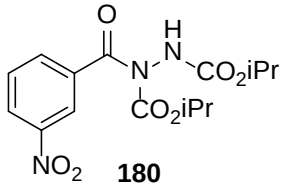
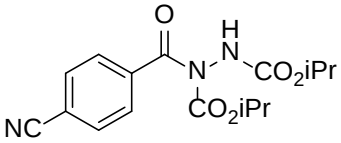
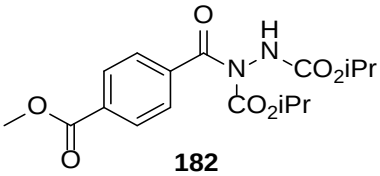
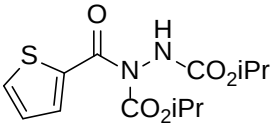
hydroacylation reaction with DIAD **61** to provide its corresponding hydrazide **183** in 65% yield (Table 4, entry **18**). The failure of these heteroaromatic aldehydes to undergo hydroacylation reaction with DIAD **61** is yet to be explained and is currently under investigation. However, one possibility may be the propensity of the product hydrazides to undergo hydrolysis under the reaction conditions. In support of this, upon analysis of the crude ^{1}H and ^{13}C NMR spectra of these reactions, in addition to the carboxylic acids, a significantly higher amount of hydrazine diisopropyldicarboxylate **61a**, in comparison to other substrates, was observed in all cases. Furthermore, syntheses and/or isolation of the hydrazide products of these aldehydes, **184-186**, are yet to be reported in the literature; thienyl hydrazide **183**, on the other hand, has been recently reported in the literature.[54]

Another significant obstacle in the functionalisation of aldehydes with DIAD **61** was the difficulty encountered in the separation of product hydrazides from hydrazine diisopropyldicarboxylate **61a**. Pleasingly, this was less of a problem with aromatic hydrazides compared to aliphatic substrates due to the relative ease with which they crystallised, thus allowing separation from hydrazine diisopropyldicarboxylate **61a**; this is most likely due to stacking of their aromatic rings in the crystallisation process.[106] It was highly encouraging to observe that, in all cases, the yields obtained on small scale, 1 mmol, were translated to reactions on larger scale, 10 mmol.



14 **61** **125** **61a**

Entry	Hydrazide	% Yield at 1 mmol scale	% Yield at 10 mmol scale
1	 **167**	62	60
2	 **168**	57	62
3	 **169**	63	69
4	 **170**	63	65
5	 **171**	41	45
6	 **172**	67	70
7	 **173**	75	78
8	 **174**	62	63

9	 **175**	53	56
10	 **176**	60	61
11	 **177**	60	59
12	 **178**	61	60
13	 **179**	61	59
14	 **180**	57	62
15	 **181**	64	71
16	 **182**	45	42
17	 **183**	65	65

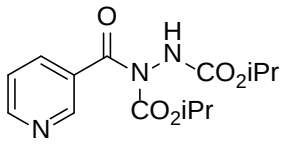
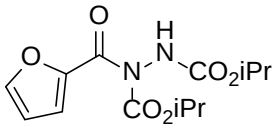
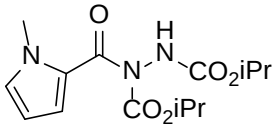
18	 **184**	0	-
19	 **185**	0	-
20	 **186**	0	-

Table 4. Tolerance of hydroacylation reaction conditions towards aromatic aldehydes

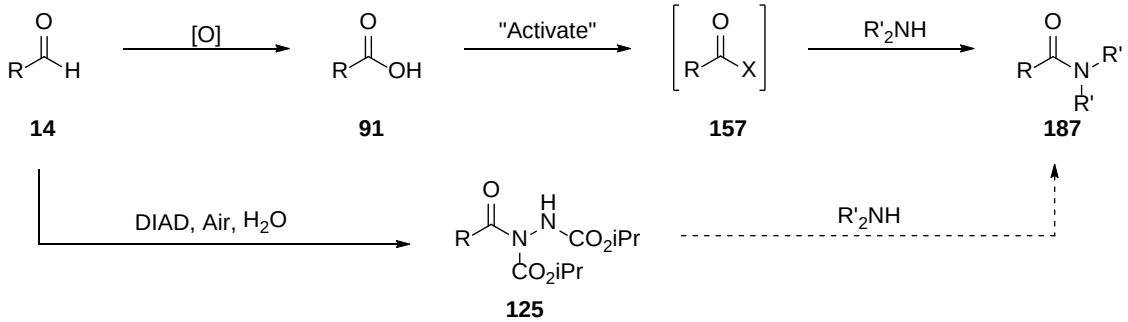
2.4 Conclusions

In summary, the aerobic hydroacylation methodology, developed in the Caddick group, has been extended to include a wide variety of aromatic aldehydes as substrates for hydroacylation of diisopropyl azodicarboxylate. With minimal optimisation, successful scalability of this reaction has also been demonstrated at a 10 mmol scale. This methodology provides a highly atom-economic protocol for functionalisation of aldehydes and because it can be carried out using just water and atmospheric oxygen as reagent, it is relatively benign. In contrast to previous hydroacylation examples, the hydroacylation of azodicarboxylates in the presence of water has been demonstrated to proceed with the aldehyde as the limiting reagent. It is envisaged that this methodology, given its versatility, will be of particular interest to industrial processes where atom economy and environmental impact are of paramount importance.

Chapter 3 Synthesis of Amides

3.1 Background

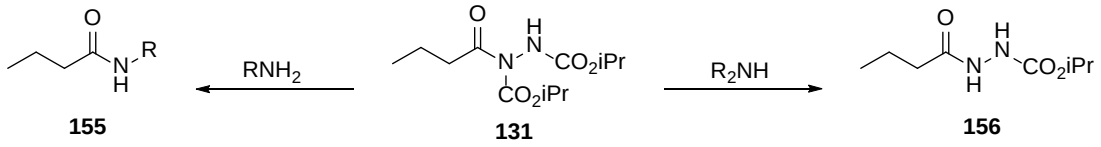
Nitrogen containing compounds are of high importance, especially because of their abundance in various natural products.[13] In fact, it has been estimated that the amide bond is present in as much as 25% of all synthetic pharmaceutical drugs.[107] Amides are most commonly synthesised from the reaction of amines with acylating agents such as acyl chlorides or acyl anhydrides.[108] They can also be synthesised from carboxylic acids following *in situ* activation with coupling reagents.[107] However, despite the reliability of these presented methods and numerous other literature preparations, if one is to avoid the often toxic nature of coupling reagents such as DCC and the multi-step preparation associated with elaborate reagents/catalysts such as boronic acids, development of alternative acyl donors is required.[109] Given the acyl donor capability of acyl hydrazides, mentioned in Chapter 1, it was envisaged that acyl hydrazides could serve as effective acyl donors for the synthesis of amides (Scheme 59). Such an approach would circumvent the need for prior oxidation of aldehydes to acids, and would be highly desired given the ease with which acyl hydrazides can be prepared from aldehydes. Although the synthesis of secondary amides from acyl hydrazides has been shown in the Caddick group previously, attempts to synthesise tertiary amides have so far been met with failure.[88] Thus the aim of this chapter was to identify conditions under which tertiary amides could be obtained from acyl hydrazides.



Scheme 59. Alternative amidation methodology *via* easily accessible acyl hydrazides

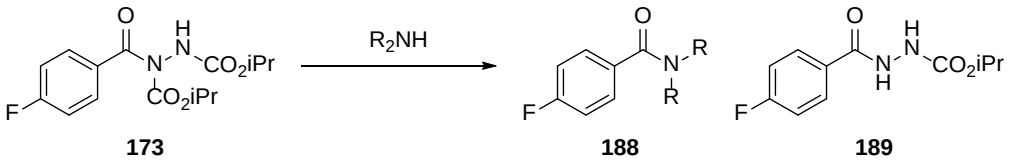
3.2 Optimisation

As reported previously, the conversion of an acyl hydrazide, such as *n*-butyl hydrazide **131**, into a secondary amide **155** can be achieved by treatment with a primary amine (Scheme 60).[88-89] Synthesis of a tertiary amide by treatment with a secondary amine, however, was met with failure; instead only decarboxylated hydrazide **156** was isolated. This suggested that nucleophilic attack of the amine on one of the carbamate esters was predominating for bulkier amines.



Scheme 60. Initial attempts to synthesis tertiary amides from acyl hydrazide **131**

A study was initiated to tackle the un-favourable side reaction observed in the reaction of secondary amines with acyl hydrazides. To begin with, an alternative hydrazide, diisopropyl 1-(4-fluorobenzoyl) hydrazine-1,2-dicarboxylate **173**, was selected as a model for optimisations; this would allow for reliable analysis of the reaction using quantitative ^{19}F NMR spectroscopy; 3,5-difluorobromobenzene was used as an external standard. It was decided that the selectivity of this reaction towards desired amide **188** would be measured by moles of amide **188** formed as a percentage of total conversion to product **188** and decarboxylated hydrazide **189**, *i.e.* not necessarily overall reaction conversion (Equation 1).

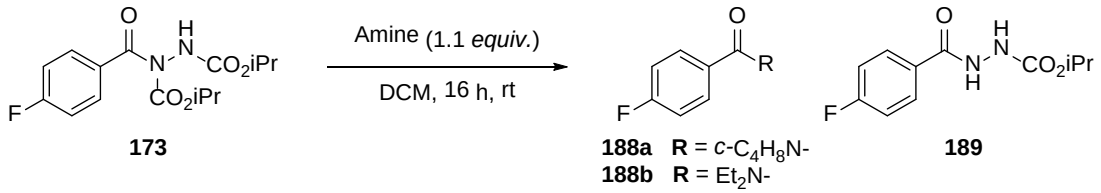


$$Selectivity\ (\%) = 100 \times \frac{moles\ of\ amide\ \mathbf{188}}{(moles\ of\ amide\ \mathbf{188} + moles\ of\ hydrazide\ \mathbf{189})}$$

Equation 1. Equation for determining % selectivity for amide **188**

A brief study was then conducted to establish whether there was any discriminatory reactivity between cyclic and acyclic amines (Table 5). Although treatment of hydrazide **173** with diethylamine resulted in only 20% selectivity for amide **188b**, employing pyrrolidine gave a much higher 48% selectivity for its corresponding amide **188a**. It is possible that this may be due to the relatively lower steric bulk and

higher nucleophilicity of cyclic amines when compared to their acyclic counterparts (*e.g.* diethylamine). Although not ideal, the mild improvement in selectivity towards desired product **188a** was encouraging and this reaction was selected for further optimisation studies (Table 5, entry 1).



173

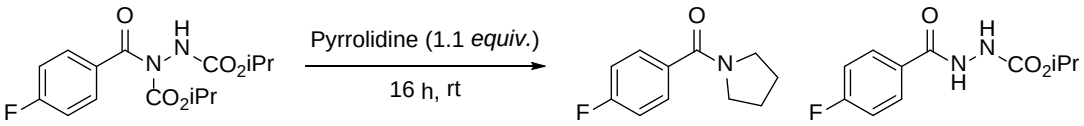
188a **R** = *c*-C_4H_8N-
188b **R** = Et_2N-

189

Entry	Amine	Solvent	Conversion /%	Product **188** /%	Hydrazide **189** /%	Selectivity /%
1	Pyrrolidine	DCM	95	44	48	48
2	Diethylamine	DCM	95	19	75	20

Table 5. Use of cyclic amines *vs* acyclic amines in amidation of hydrazide **173**

Following the slight improvement observed in selectivity for desired amide **188a**, when a cyclic amine was employed, a solvent screen was conducted to assess the possibility of tuning reaction of hydrazide **173** and pyrrolidine to form more of the desired product **188a** (Table 6).

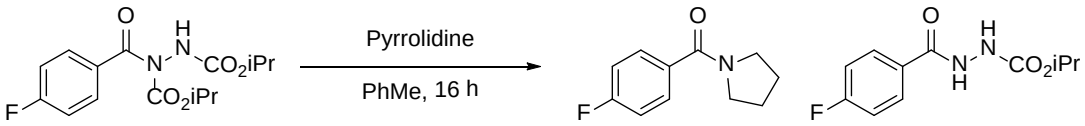


173 **188a** **189**

Entry	Solvent	Dipole /D	Conversion /%	Product 188a /%	Hydrazide 189 /%	Selectivity /%
1	PhMe	0.4	95	48	45	52
2	$CHCl_3$	1.0	94	42	53	44
3	MTBE	1.2	89	37	48	44
4	DCM	1.6	95	44	48	48
5	Me-THF	1.8	87	33	53	38
6	MIBK	2.8	72	27	43	39
7	DMF	3.8	88	19	48	28
8	MeCN	3.9	100	43	58	43

Table 6. Solvent screen for amidation of hydrazide **173** with pyrrolidine

In all cases, sufficient conversion was observed so as to allow for reliable analysis of the reaction mixtures. Generally, yield of amide **188a** increased with decreasing solvent polarity. Conversely, the yield of undesired hydrazide **189** was higher when the polarity of the solvent was higher. The highest yield of amide, 48%, and selectivity, 52%, was observed when toluene was employed as solvent. Attempts to conduct the reaction in less polar solvents such as cyclohexane and *n*-hexanes failed due to poor solubility of the hydrazide **173** in these solvents. Although very marginal, the small increase in selectivity was considered sufficient to warrant further studies. Consequently, a brief study was conducted to assess if temperature could be used to tune the selectivity of the reaction. Encouragingly, reducing the temperature from 25 to 0 °C increased the selectivity for desired amide **188a** from 52% to 56%. Interestingly, however, reducing the temperature further, to -30 °C, reduced the selectivity back to 52%. Despite increasing conversion, an elevated temperature of 50 °C, had very little effect on the selectivity.



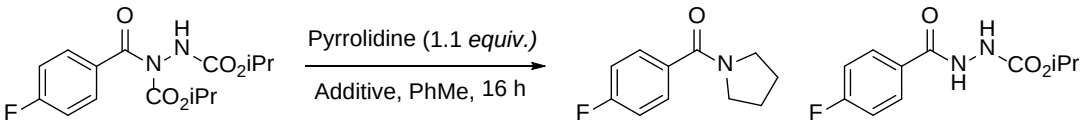
173 **188a** **189**

Entry	Pyrrolidine /equiv.	Temp. /°C	Conversion /%	Product 188a /%	Hydrazide 189 /%	Selectivity /%
1	1.1	-30	26	13	12	52
2	1.1	0	86	45	36	56
3	1.1	25	95	48	45	52
4	1.1	50	100	50	48	52

Table 7. Investigation into effect of temperature on selectivity for amide **188a**

It was envisaged that further improvements may be possible by employing a nucleophilic and/or Lewis-acid catalyst. To examine this, the optimum conditions thus far (Amine 1.1 equiv., Toluene, 0 °C, 16 h) were applied to hydrazide **173** in the presence of a range of nucleophilic (Table 8, entries 2 to 4) and Lewis-acidic (Table 8, entries 5 to 10) catalysts.

Reaction in the presence of any of the nucleophilic catalysts resulted in no significant change to both conversion and yield of amide (Table 8, entries 1 to 4). In the case of Lewis-acids, however, there was a general decrease in conversion of hydrazide and yield of amide. Conceptually, two explanations may be provided for the marked decrease in these conversions; 1) a lower rate of reaction or 2) amine-halogen exchange on the metal chlorides. Given the stoichiometric amount of pyrrolidine employed, the latter would preclude a considerable amount of amine from reacting with acyl hydrazide. Evidence for this came in two forms: 1) an instantaneous colour change was observed upon addition of amine to the reaction mixtures containing metal chlorides; and 2) when $BF_3.OEt_2$ was employed, which is not known to undergo such exchange, the reduction in conversion was less significant (Table 8, entry 10). Significantly, there was also an overall increase in selectivity for the desired amide **188a** with almost all Lewis-Acid additives. It is noteworthy that such increases were more significant in the cases of $AlCl_3$ and $TiCl_4$.

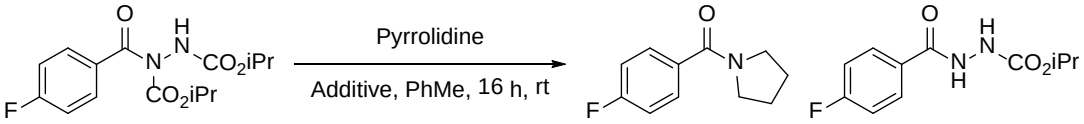


173 **188a** **189**

Entry	Additive	Temp. /°C	Conversion /%	Product 188a /%	Hydrazide 189 /%	Selectivity /%
1	None	0	86	45	36	56
2	DMAP	0	80	43	37	54
3	Imidazole	0	81	44	37	54
4	Lutidine	0	82	46	36	56
5	$InCl_3$	0	13	7	6	54
6	$AlCl_3$	0	14	11	2	85
7	$ZnCl_2$	0	11	8	3	73
8	$TiCl_4$	0	13	12	1	92
9	$BF_3.OEt_2$	0	57	20	14	59

Table 8. Investigation into effect of additives on selectivity for amide **188a**

Encouraged by the markedly higher selectivities exhibited by employing metal catalysts, it was concluded that, to increase overall amide yield, the reaction conversion would need to be improved when employing such catalysts. Firstly, it was decided to investigate if a lower rate of reaction was responsible for the low conversion observed in the case of metal catalysts. As such three reactions with the highest selectivities ($AlCl_3$, $ZnCl_3$ and $TiCl_4$), were chosen for a brief study at a higher reaction temperature (Table 9). Unfortunately, increasing temperature from 0 to 25 °C resulted in only a modest increase in conversion. Moreover, at higher temperature, the selectivity exhibited by $ZnCl_3$ and $AlCl_3$ was significantly lower. However, it was reassuring to find that selectivity for the product remained high in the case of $TiCl_4$ (Table 9, entry 4).

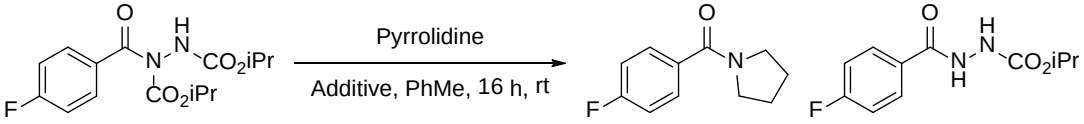


173 **188a** **189**

Entry	Additive	Amine /equiv.	Conversion /%	Product 188a /%	Hydrazide 189 /%	Selectivity /%
1	None	1.1	88	43	38	53
2	$ZnCl_2$	1.1	44	26	18	59
3	$AlCl_3$	1.1	35	7	6	54
4	$TiCl_4$	1.1	27	15	1	94

Table 9. Investigation into effect of additives on selectivity for amide **173**

To improve conversion further, employing even higher reaction temperature was one option, however, this was considered energy inefficient and it was decided that a higher stoichiometry of amine would be investigated instead. Moreover, a large enough excess, 5 equivalents, of the amine was employed, such that if there was any amine-halogen exchange, there would be sufficient excess of the amine remaining in the reaction mixture. Pleasingly, all reactions were pushed to >90% completion within 16 h on increasing pyrrolidine stoichiometry to 5.0 equivalents (Table 10). Furthermore, it was reassuring to observe that selectivity for amide **188a** remained high at 91% with $TiCl_4$ (Table 10, entry 4).



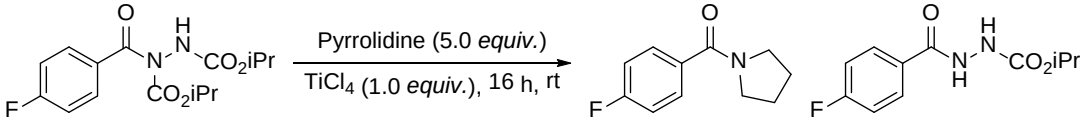
173 **188a** **189**

Entry	Additive	Amine /equiv.	Conversion /%	Product 188a /%	Hydrazide 189 /%	Selectivity /%
1	None	5.0	96	48	46	51
2	$ZnCl_2$	5.0	98	48	48	50
3	$AlCl_3$	5.0	98	63	34	65
4	$TiCl_4$	5.0	95	71	7	91

Table 10. Investigation into effect of additives on selectivity for amide **188a**

In a final attempt to increase the yield of desired amide **188a** further, a brief solvent screen was conducted. Thus, three solvents (*i.e.* toluene, Me-THF and DMF) were appraised based on their broad range of polarities. A limited change was observed in

amide selectivity as solvent polarity increased. However, employing DMF resulted in a noticeably lower conversion and product yield. Although reactions with both toluene and Me-THF proceeded equally well, Me-THF was selected due to its relatively superior robustness and environmentally benign nature.[110]

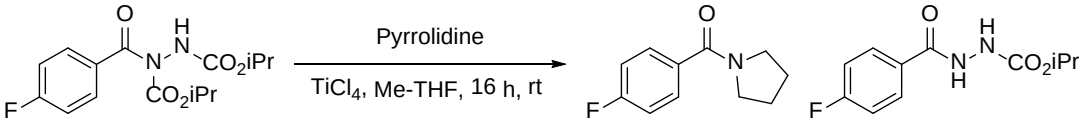


173 **188a** **189**

Entry	Solvent	Dipole /D	Conversion /%	Product 188a /%	Hydrazide 189 /%	Selectivity /%
1	PhMe	0.4	95	71	7	91
2	Me-THF	1.8	94	74	7	91
3	DMF	3.8	76	49	6	89

Table 11. Solvent screen for amidation of hydrazide **173** with pyrrolidine

The next step in the study was to investigate the stoichiometry of $TiCl_4$. To do this, a study was conducted where the stoichiometry of $TiCl_4$ was varied between 0.2 and 1.2 equivalents (Table 12). Overall reaction conversion remained mostly unaffected as the stoichiometry of $TiCl_4$ was reduced from 1.2 to 0.2 equivalents. The amount of undesired hydrazide **189** decreased significantly as $TiCl_4$ equivalents were increased; thus resulting in higher selectivity for the desired amide **188a** (*i.e.* from 38% at 0.2 equivalents, to 91% at 1.0 equivalent). Increasing the amount of $TiCl_4$ further, to 1.2 equivalents, did not have any significant effect on yield and/or conversion. As such, the reaction employing 1.0 equivalent of $TiCl_4$ was selected as the optimum for the conversion of acyl hydrazides to tertiary amides.

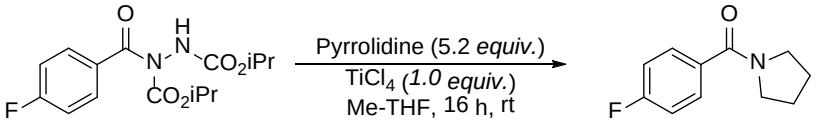


173 **188a** **189**

Entry	$TiCl_4$ /equiv.	Amine /equiv.	Conversion /%	Product 188a /%	Hydrazide 189 /%	Selectivity /%
1	0.2	5.0	98	37	61	38
2	0.4	5.0	97	53	36	60
3	0.6	5.0	94	66	25	73
4	0.8	5.0	78	66	11	86
5	1.0	5.0	90	74	7	91
6	1.2	5.0	95	72	9	89

Table 12. Investigation into effect of $TiCl_4$ stoichiometry on selectivity for amide **188a**

To confirm the results of the study, hydrazide **173** was treated with pyrrolidine under the optimised reaction conditions, and the product isolated. Gratifyingly this resulted in 75% yield of amide **188a**, thus confirming the validity of the optimised conditions.



173 **188a** **75%**

Scheme 61. Conversion of hydrazide **173** to tertiary amide **188a**

At this juncture, to understand the interdependency of the parameters on each other and to confirm the optimised conditions, a Factorial Experimental Design study was conducted.

3.3 Design of Experiment (DoE)

3.3.1 Background

'Design of Experiment' (DoE) is a revolutionary statistical method for designing experiments to enable more efficient screening and optimisation of experimental parameters. In contrast to an intuitive approach of 'change one separate factor at a time' (COST), DoE offers an organised approach that connects experiments in a statistical manner giving more precise information from fewer experiments. Design of experiment was first utilised by Fisher and has since been used in engineering, agriculture and biotechnology, amongst other disciplines.[111-112] Design of experiment can be used as a standalone method or as a supplement to COST to better understand and confirm an optimised system with multiple parameters; it is very information rich, thus after only a few experiments, much information can be obtained about the system under investigation.[113] For example, for the conversion of a starting material to a product, under a conventional COST approach, one particular reaction condition is altered while all other conditions are kept constant (Figure 2a). The optimum conditions obtained therefore depend on the starting point of the study. However, under a rational, statistical approach, points are chosen throughout a cube to fully represent the entire reaction space, thus reducing the need for many experiments (Figure 2b).[114]

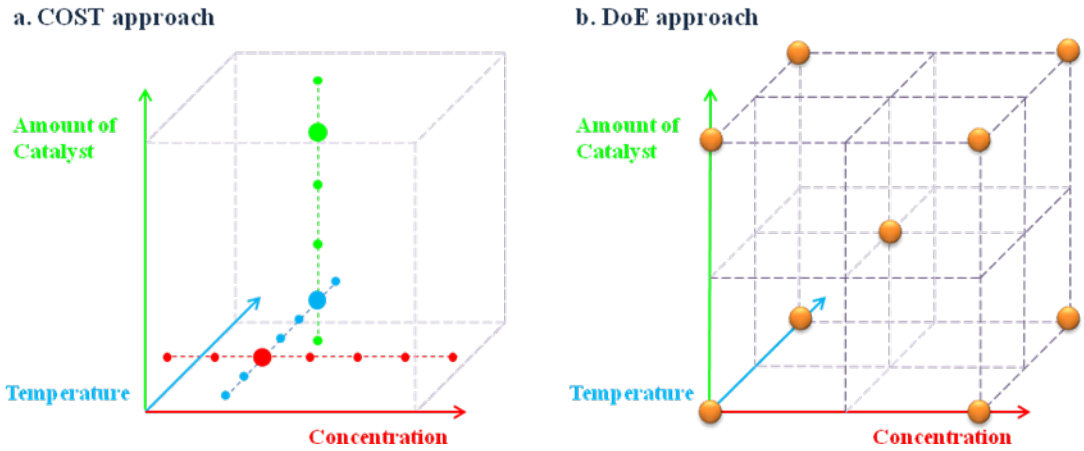
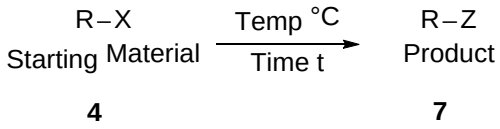


Figure 2. Comparison of a COST approach for optimisation to a DoE approach

It is often the case that optimised conditions obtained through a COST approach are not necessarily the real optimum conditions. For example, for the conversion of species **4** to product **7**, a COST approach may reveal 240 mins at 106 °C to be the optimum conditions for maximum yield of *ca.* 80% (Figure 3). However, the reaction may in fact behave differently; thus, the true optimised conditions may well lie quite further away (Figure 4). Therefore, by employing a DoE approach, a more accurate result may be obtained for the conditions required to affect a transformation. Moreover, a statistical analysis, such as DoE, has the potential to reveal interactions between the factors under investigation.[111-113]



4 **7**

Scheme 62. Conversion of species **4** to product **7**

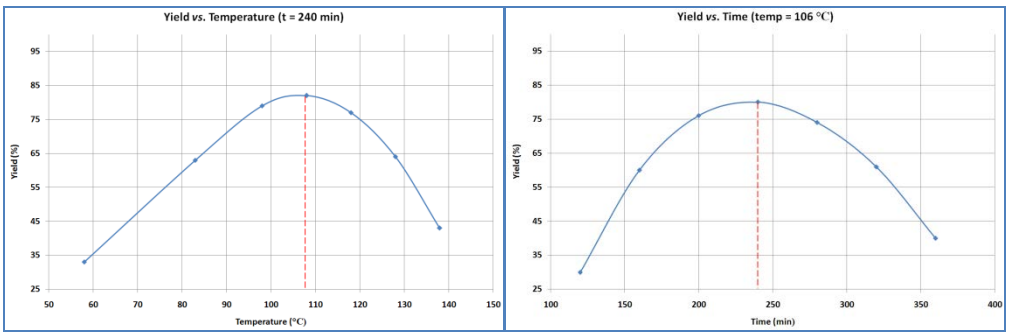


Figure 3. A COST approach to optimising a reaction

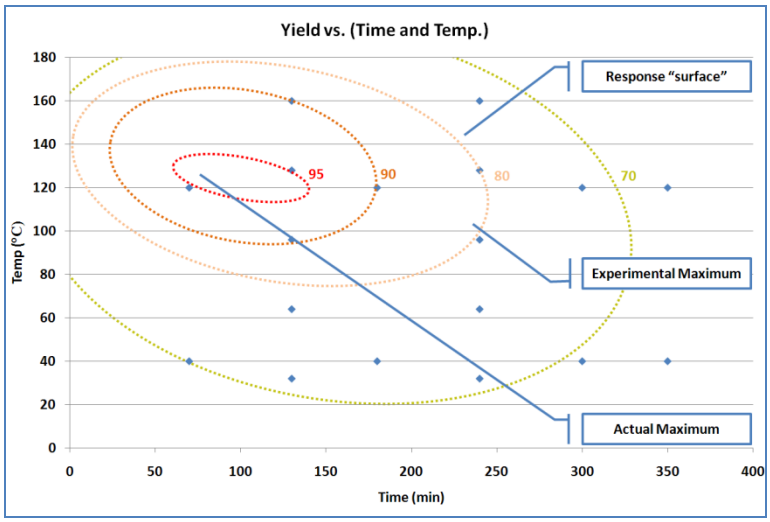


Figure 4. Response surface representing yields obtained through DoE

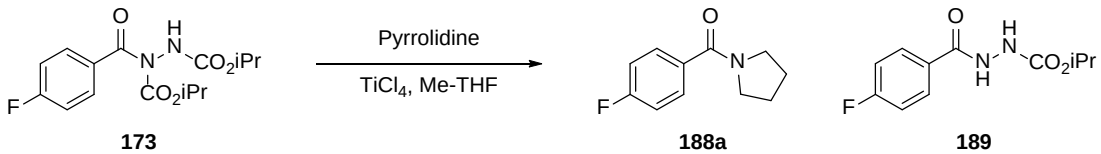
One of the major obstacles, however, in the employment of a powerful tool such as DoE in organic chemistry, has been the requirement for the experiments to be conducted in parallel; thus the need for automated systems.[111,113] Nevertheless, there are multiple examples of the application of DoE to the development and validation of conditions for organic transformations.[113,115] Although there are a number of types of experimental design, the most commonly used and easiest to understand is the fractional factorial design or factorial experimental design (FED). In this method, each corner of a cube, enclosing the reaction space, represents a combination of the factors being investigated in the experiment (see Figure 2 above). Employing a centre point, that is replicated at least two times, ensures reproducibility and helps detect any non-linear relationships.

When conducting an FED study, several considerations have to be made followed by certain steps:

1. Identification of a suitable experimental design *e.g.* FED;
2. Identification of factors to be investigated *e.g.* temperature, stoichiometry;
3. Identification of responses *e.g.* yield of product, conversion;
4. Generation of a design matrix to establish which experiments to conduct;
5. Carrying out the experiments;
6. Generating plots to describe the trends and relationships in the responses; and
7. Drawing conclusions

3.3.2 FED study into amidation of acyl hydrazides

An FED study was instigated in order to appraise the optimised conditions identified for the amidation of hydrazide **173** with pyrrolidine (Scheme 63). It was envisaged that such a study will also reveal any interdependencies and interactions between the factors.



173 **188a** **189**

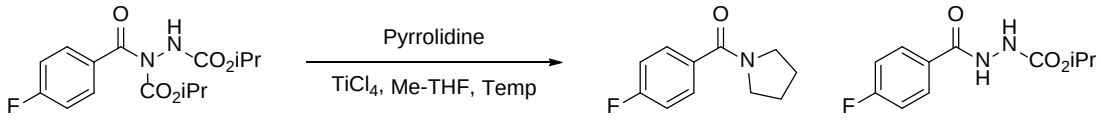
Scheme 63. General scheme for amidation of hydrazide **173**

3.3.2.1 Identification of a suitable experimental design

It was decided that a Fractional Factorial design with two levels, two repeats and resolution = IV, was the most suitable since it was simple and was capable of revealing any interactions between the parameters. To investigate 4 factors, 8 experiments corresponding to each corner of a cube and 2 duplicate experiments corresponding to the centre of the cube were required; totalling to 10 experiments.

3.3.2.2 Factors to be investigated

Four factors were selected for investigation (Table 13). In order to maximise the experimental space covered, a broad range (settings) was used.



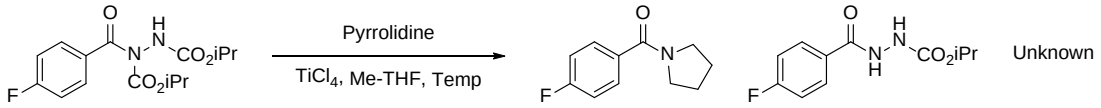
173 **188a** **189**

Entry	Factor	Abbr.	Units	Settings
1	Temperature	Temp	°C	0 to 50
2	Amine Charge	Ami_C	Mol equiv.	1.2 – 5.2
3	Me-THF Charge	Sol_C	Rel vols.	20 – 100
4	$TiCl_4$	Ti_C	Mol equiv.	0.5 – 1.5

Table 13. Identification of factors to be investigated

3.3.2.3 Identification of responses

Three specific responses were identified initially; these were amount of product **188a**, amount of decarboxylated hydrazide **189** and amount of starting material **173**, to represent conversion (Table 14, entries 1 to 3). However, as the study progressed it was found that there was a fourth response that should also be analysed. Unfortunately, the identity of this compound was not known at the time, and as such this was referred to as unknown compound **Y** (Table 14, entry 4). All responses were measured by integration of ^{19}F NMR spectra using 1-Bromo-3,5-difluorobenzene as an external standard with a resonance peak at -107.98 ppm.



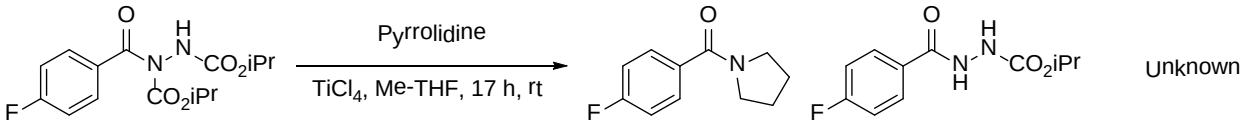
173 **188a** **189** **Y**

Entry	Response	Abbr.	Units
1	Starting Material	%SM (**173)**	%
2	Product	%Prod (**188a**)	%
3	Decarboxylated hydrazide	%DH (**189**)	%
4	Unknown Y	%Y (**Y)**	%

Table 14. Identification of responses to be measured

3.3.2.4 Generation of a design matrix and Results

Designs were generated and analysed using the software package MODDE v. 9.0. Experiments were conducted in parallel using the 'STEM Integrity 10 reaction station'. The design matrix generated consisted of 10 experiment runs, with two mid-point duplicates. Once randomised, the experiments were conducted strictly in the run order prescribed by the design. Although data was collected at different time points, only data obtained at 17 h was used for further analysis as the trends observed were similar. Furthermore, this was the point where sufficient conversion had taken place in all experiments.



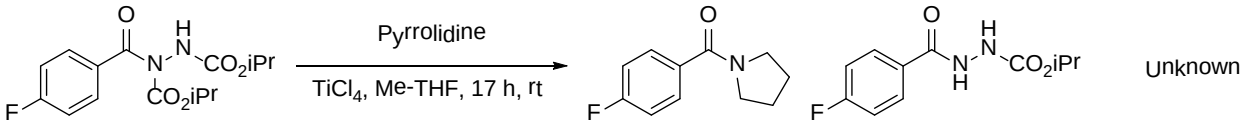
173 **188a** **189** **Y**

Run Order	Temp. /°C	Ami_C /mol equiv.	Sol_C /rel. vols	Ti_C /mol equiv.	% SM 173 /%	% Prod 188a /%	% DH. 189 /%	%Y /%
1	50	5.2	100	1.5	8	74	8	0
2	0	1.2	20	0.5	80	4	1	0
3	0	1.2	100	1.5	54	1	2	43
4	25	3.2	60	1	39	34	15	0
5	50	5.2	20	0.5	3	55	34	0
6	25	3.2	60	1	43	33	3	0
7	50	1.2	20	1.5	0	3	6	68
8	0	5.2	100	0.5	8	45	33	6
9	0	5.2	20	1.5	20	60	3	0
10	50	1.2	100	0.5	59	3	0	13

Table 15. Design matrix generated by DoE software package MODDE and the results obtained

3.3.2.5 Identification of unknown compound Y

As described previously (c*f.* Section **1.3.2.3**), as the study progressed it was found that there was an additional peak on the ^{19}F NMR, corresponding to a fourth response. When the crude ^{1}H NMR spectra were analysed, aside from small amounts of product **188a**, decarboxylated hydrazide **189** and unreacted hydrazide **173**, a small amount of carboxylic acid was observed. This led to the conclusion that unknown compound **Y** may be an intermediate of some sort which hydrolyses to the acid and liberates leaving group **61b** upon protic work up. To test this notion, the reaction yielding the greatest amount of unknown **Y**, 68%, was repeated and upon completion, treated with a further 4.0 equivalents of pyrrolidine (Table 16, entry 3). This resulted in a decrease in the amount of unknown **Y** and considerable increase in product **188a**; thus supporting the possibility that compound **Y** may be an intermediate in the reaction conditions.



173 **188a** **189** **Y**

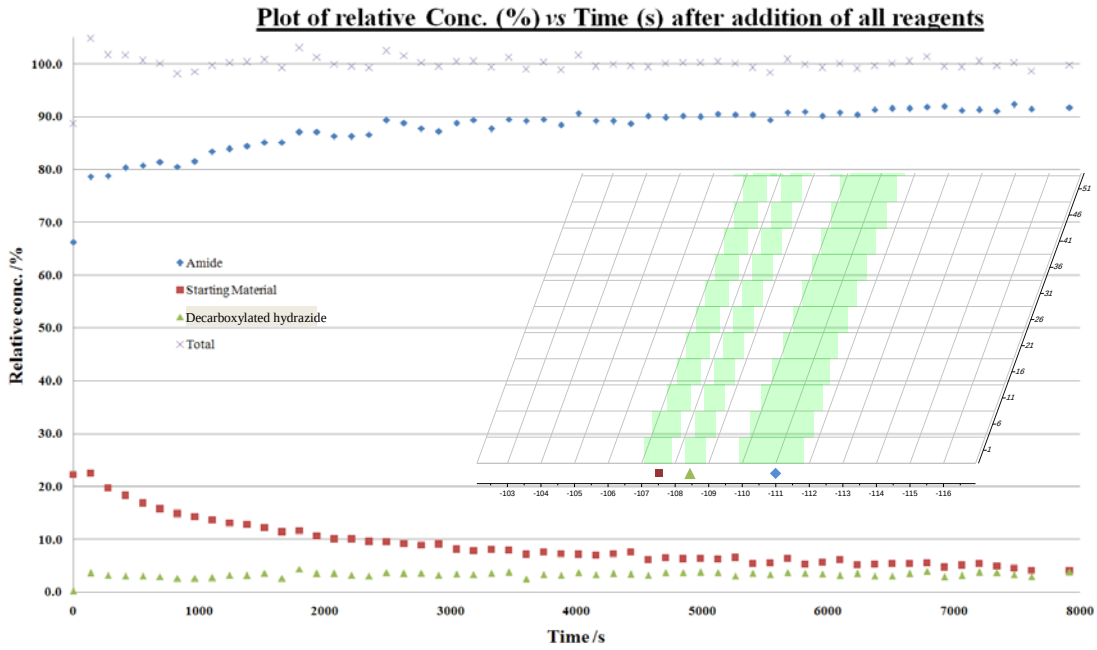
Run Order	Temp. /°C	Ami_C /mol equiv.	Sol_C /rel. vols	Ti_C /mol equiv.	% SM /%	% Prod /%	% DH. 189 /%	%Y /%
1	50	5.2	20	1.5	0	71	6	3
2	50	1.2	20	1.5	0	3	6	68
3	50	1.2 then 4.0	20	0.5	0	65	5	5

Table 16. Stepwise addition of pyrrolidine to the reaction mixture (entry 3)

To further confirm that unknown **Y** was in fact an intermediate in the reaction, an attempt was made to profile the reaction, as reagents were charged. To do this, hydrazide **173** was dissolved in d_8-toluene in an NMR sample tube at 300 K and both ^{1}H NMR and ^{19}F NMR spectra were obtained. To start with, the ^{19}F NMR spectra showed the starting material as two distinct peaks at -107.5 ppm in a ratio of 1:4 to represent the two rotamers.

On addition of $TiCl_4$ to the reaction mixture, a rapid color change, colorless to yellow, was observed. Upon ^{1}H and ^{19}F NMR analysis, a downfield shift and broadening of the ^{1}H NMR spectra was observed. The ^{19}F NMR showed the formation of three, non-baseline, distinct peaks further downfield, -103.5 ppm, from the two, now broad, poorly-defined starting material peaks at -107.5 ppm.

Upon addition of pyrrolidine an immediate darkening of the reaction mixture was observed. On analysis of the ^{19}F NMR over 2 h, it was found that most reaction had taken place prior to the first sampling point (*ca.*5 min. after addition). The newly formed peaks at -103.5 ppm had disappeared completely and a new a peak at -110.8 ppm was formed, corresponding to the product amide **188a** (Graph 1). Over the next 2 h, the small portion of hydrazide **173** that remained, at -107.5 ppm, was slowly consumed; meanwhile, relative concentration of product amide **188a** increased.



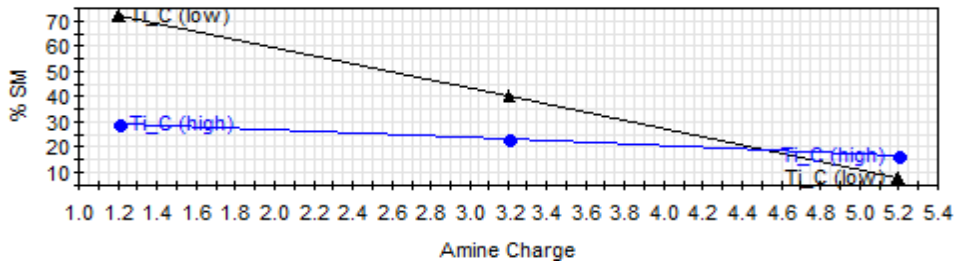
Graph 1. Plot of relative conc. *vs* time – monitored by ^{19}F NMR over *ca.* 2 h. The peaks at -103.5 have disappeared before the first NMR scan is completed.

3.3.3 FED Results

The outcomes analysed were %SM (starting material), %Product, %DH (decarboxylated hydrazide) and %Y (assumed to be an intermediate). Only the 17 h results were analysed in this FED; earlier samples had been taken but overall, these gave the same trends. Interactions included in models were chosen, based on chemical knowledge, and are assumed to cause the effect observed, although this is not definitively known.

3.3.3.1.1 To maximise yield of unreacted starting material 173, %SM

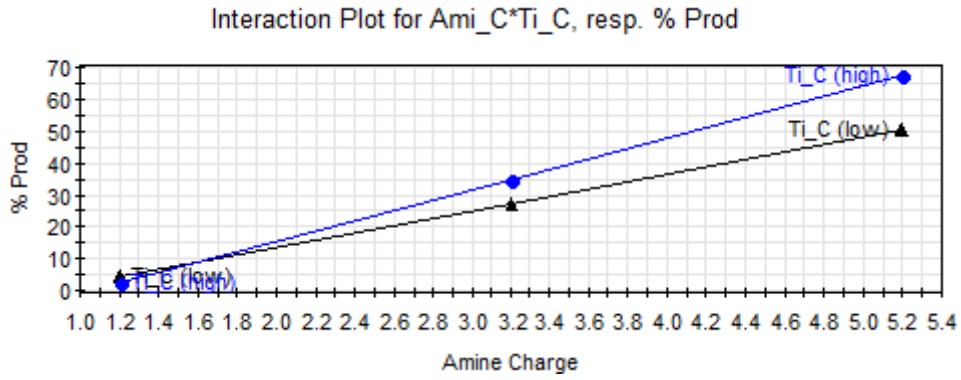
Aside from low temperature, to maximise the yield of starting hydrazide **173**, 80%, it would be necessary to employ a low amine charge together with a low $TiCl_4$ charge (Graph 2).When $TiCl_4$ charge was high, amine charge had very little effect on the yield of starting material **173**; thus %SM remained at *ca.* 12%. However, when $TiCl_4$ charge was low (0.5 equiv.), to maximise %SM, a low amine charge has to be employed.



Graph 2. Plot showing Amine charge *vs* %SM at high and low $TiCl_4$ charge

3.3.3.1.2 To maximise product yield, %prod 188a

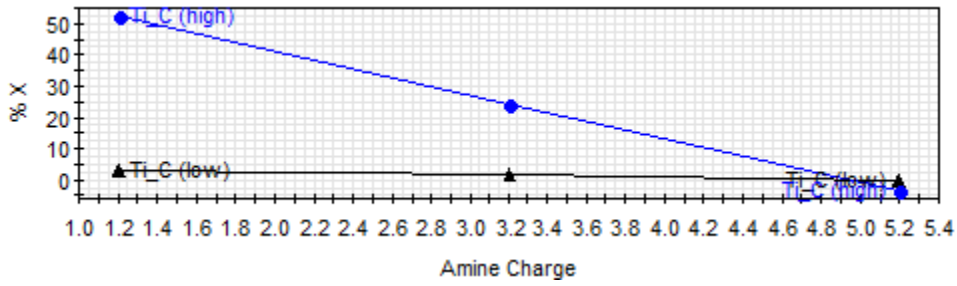
The main factor affecting product yield, %Prod, was found to be amine charge; although a high amine charge, 5.2 equivalents, was needed for achieving maximum yield of product, increasing $TiCl_4$ charge above 1.0 equivalent had very little effect on yield. Moreover, based on the interactions observed, to maximise product yield, 74%, it would be necessary to employ a high amine charge, 5.2 equivalents, together with an increased $TiCl_4$ charge of at least 1.0 equivalent (Graph 3).



Graph 3. Plot showing Amine charge *vs* %Prod at high and low $TiCl_4$ charge

3.3.3.1.3 To maximise yield of intermediate Y, %Y

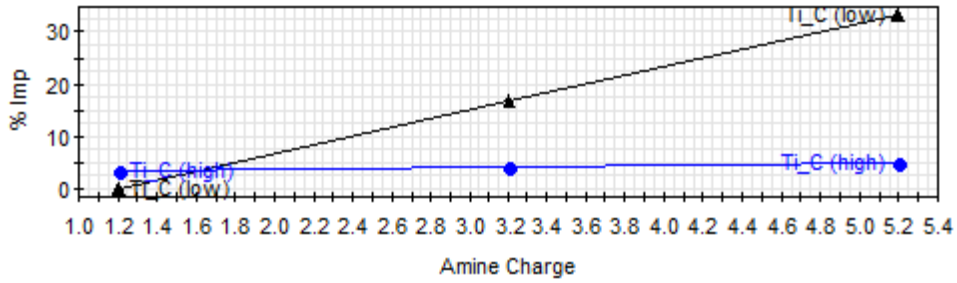
To maximise the yield of intermediate Y, 68%, it would be necessary to employ a low amine charge together with an increased $TiCl_4$ charge (Graph 4).When $TiCl_4$ charge was low, amine charge had very little effect on the yield of intermediate Y; thus %Y remained at *ca.*2%. However, when $TiCl_4$ charge was high, 1.5 equivalents, to maximise %Y, a high amine charge has to be employed.



Graph 4. Plot showing Amine charge *vs* %Y at high and low $TiCl_4$ charge

3.3.3.1.4 To maximise decarboxylated hydrazide yield, %DH 189

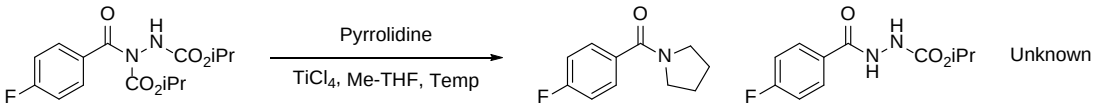
To maximise the yield of decarboxylated hydrazide **189**, 34%, it would be necessary to employ a high amine charge together with a decreased/low $TiCl_4$ charge (Graph 5).When $TiCl_4$ charge was high, amine charge had very little effect on the yield of hydrazide **189**; thus %DH remained at *ca.* 3%. However, when $TiCl_4$ charge was low (below 1.0 equivalent), to maximise %DH, a high amine charge has to be employed.



Graph 5. Plot showing Amine charge *vs* %DH at high and low $TiCl_4$ charge

3.3.3.2 FED Conclusions

In conclusion, no interactions were observed between temperature and concentration (solvent charge). Concentration had very little effect on any of the responses whilst temperature had a noticeable effect only on conversion; higher temperatures led to higher conversions of starting material **173**. The only interactions observed were between amine charge and $TiCl_4$ charge; for each of the 4 main outcomes possible, a different combination of amine charge and $TiCl_4$ charge was identified (Table 17).

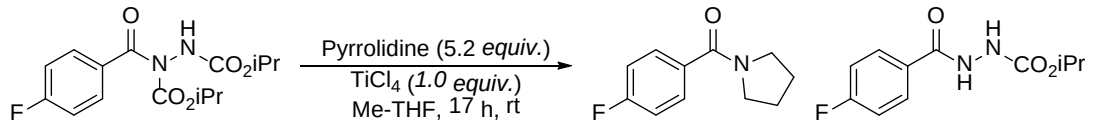


173 188a 189 Y

H - high, L - low level	Temp °C	Amine Charge /mol eq	TiCl4 Charge /mol eq	Solvent Volume / rel. vols	Response range (%)
To Increase unreacted SM	**L**	**L**	**L**	**H or L**	**0 to 80**
To Maximise Product	**H or L**	**H**	**H**	**H or L**	**1 to 74**
To Maximise Intermediate 'Y'	**H or L**	**L**	**H**	**H or L**	**0 to 68**
To Maximise decarboxylated hydrazide	**H or L**	**H**	**L**	**H or L**	**0 to 34**

Table 17. Summary of factors and responses for amidation of hydrazide **173**

Therefore, in order to maximise amide **188a** yield in the reaction of hydrazide **173** and pyrrolidine, two things have to be avoided: 1) Conditions giving maximum decarboxylated hydrazide %DH, *i.e.* high amine charge and low $TiCl_4$ charge, and 2) Conditions giving maximum unreacted starting material, %SM, *i.e.* low amine charge and low $TiCl_4$ charge. Although intermediate Y has been shown to be favourable since it can be converted into desired amide **188a**, such a conversion would require further equivalents of amine in any case. As such, to maximise the yield of amide **188a**, a high amine charge and a high $TiCl_4$ charge (at least 1.0 equivalent) are necessary. Although this is in strong agreements with the results obtained by the COST approach described already, the study has revealed the presence of an intermediate and the interdependencies of conditions employed.

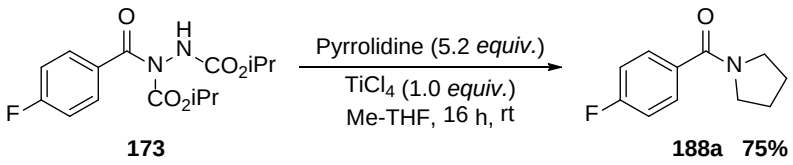


173 188a 189

Scheme 64. Confirmed, optimum conditions for amidation of hydrazide **173**

3.4 Summary and conclusions

In summary, a set of optimised conditions were determined for the amidation of hydrazide **173** with a secondary amine to access a tertiary amide **188a**. In the absence of a catalyst, only temperature and solvent polarity had a modest impact on improving selectivity for the product **188a**. However, in the presence of $TiCl_4$, there was a significant improvement in selectivity allowing for the isolation of tertiary amide **188a** in 75% isolated yield.



173 **188a** **75%**

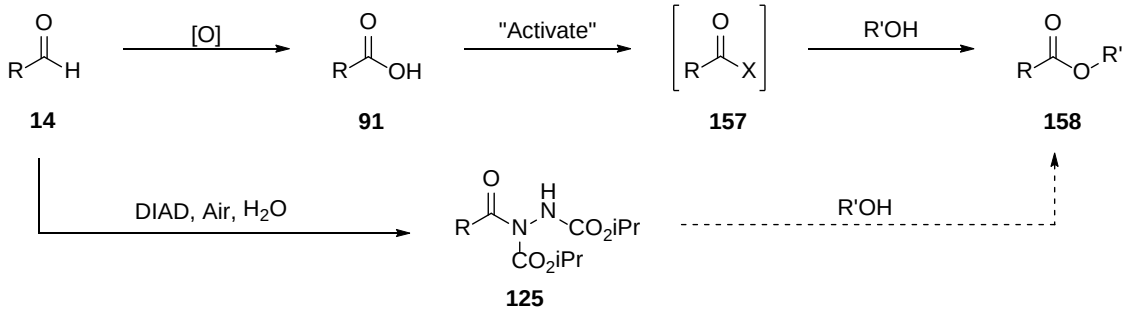
Scheme 65. Conversion of hydrazide **173** to tertiary amide **188a**

In order to confirm the optimised conditions, a brief FED study was conducted. By carrying out only 10 experiments it was confirmed that the conditions obtained were indeed true, to the best of our knowledge and to the limitations of the study itself. The FED study also revealed the presence of, what is believed to be an intermediate, in the amidation process.

Chapter 4 Synthesis of esters from hydrazides

4.1 Background

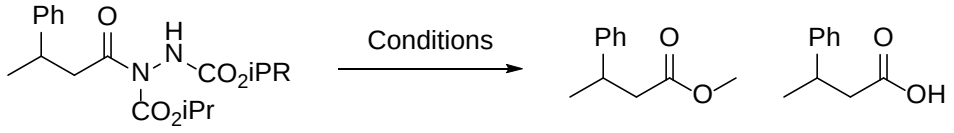
Esters are among the most common functional groups;[116] they are found in a range of natural products,[117] agrochemicals[117-118] and pharmaceuticals. As described in Chapter 1, esters can be synthesized from the reaction of alcohols with acylating agents such as acyl chlorides or anhydrides.[108] However, the synthesis of acyl chlorides and anhydrides is problematic due to inefficiencies associated with their multi-step preparation. Esters can also be synthesised from carboxylic acids and alcohols following *in situ* activation by acid catalysis. However, since this methodology is an equilibrium process, it relies on either the use of a dehydrating agent, the removal of one of the products or the use of an excess of one of the reagents; all of which seriously reduces the efficiency and economy of the reaction. Direct oxidative esterification of aldehydes is also an attractive method of esterification.[119-120] However, recent examples of this methodology involve the use of high temperatures and a vast excess of the alcohol; thus rendering it sub-optimal for volatile and/or valuable alcohols.[121] As such, given the acyl donating capabilities of acyl hydrazides, outlined in Chapters 1 and 2, it was envisaged that acyl hydrazides could serve as effective acyl donors for the synthesis of esters (Scheme 66). Such an approach would be highly desired given the ease with which acyl hydrazides can be prepared from aldehydes.



Scheme 66. Alternative esterification methodology *via* easily accessible acyl hydrazides

4.2 Optimisation

To assess the feasibility of converting acyl hydrazides into esters, initially hydrazide **161** was treated with a vast excess of methanol (Table 18, entry 1). Unfortunately, this resulted in very little conversion even after 36 h with complete recovery of starting hydrazide **161**. Encouragingly, however, in the presence of $^{t}BuNH_2$ and employing methanol as solvent, conversion increased to almost 100%, and 96% of ester **190** was isolated (Table 18, entry 3). Also identified in the crude reaction mixture was carboxylic acid **191**, presumably as a result of hydrazide **161** undergoing hydrolysis under the reaction conditions. Interestingly, other related amine bases did not have the same effect with both conversion and yield of ester **190** being very low when diethylamine, triethylamine and DBU were employed (Table 18, entries 4-7).



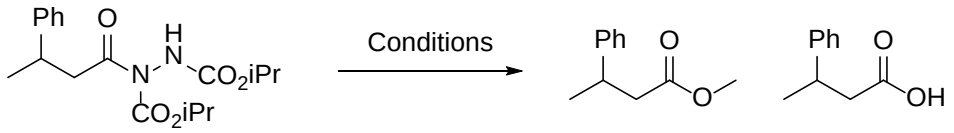
161 **190** **191**

Entry	Base	Base /equiv.	MeOH /equiv.	Time /h	Conversion /%	Ester[a] 190 /%	Acid[b] 191 /%
1	-	-	1000	15	0	0	0
2	-	-	1000	36	5	0	4
3	$^{t}BuNH_2$	1.0	1000	15	>99	96	3
4	Et_2NH	1.0	1000	15	12	9	2
5	NEt_3	1.0	1000	15	10	10	0
6	DBU	1.0	1000	15	<10	0	5
7	DBU	1.0	1000	36	<10	0	5

Table 18. Amine base screen for esterification of hydrazide **161**

In order to reduce the alcohol stoichiometry, a brief study was conducted to assess the tolerance of the reaction to lower equivalents of alcohol (Table 19). Both, conversion and yield of ester remained unchanged as alcohol stoichiometry was reduced to 100 equivalents. However, lower equivalents of alcohol resulted in considerably lower conversion of hydrazide and yield of ester, even when employing a longer reaction time of 36 h. To investigate concentration effects, the reaction with

10 equivalents was repeated in the presence of minimal amount of solvent and it was found that both conversion and yield of ester remained unchanged (Table 19, entry 8).

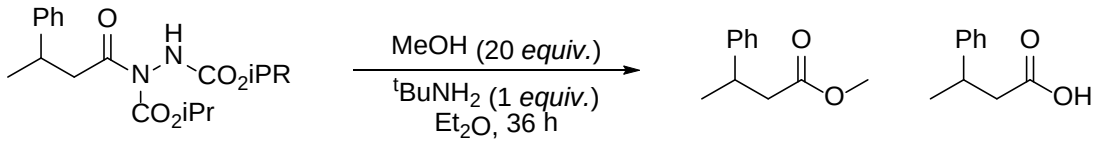


161 **190** **191**

Entry	Base	Conc. mol/L	Alcohol /equiv.	Time /h	Conversion /%	Ester[a] 190 /%	Acid[b] 191 /%
1	$^{t}BuNH_2$	0.025	1000	15	>99	96	3
2	$^{t}BuNH_2$	0.025	1000	36	>99	96	3
3	$^{t}BuNH_2$	0.025	100	15	>99	95	3
4	$^{t}BuNH_2$	0.025	100	36	>99	96	3
5	$^{t}BuNH_2$	0.025	50	36	80	70	5
6	$^{t}BuNH_2$	0.025	20	36	60	49	5
7	$^{t}BuNH_2$	0.025	10	36	54	45	4
8	$^{t}BuNH_2$	0.416	10	36	54	45	5

Table 19. Esterification of hydrazide **161** under varying alcohol stoichiometry

In an attempt to increase conversion and yield of ester **190** further, an investigation into the effect of catalytic additives was instigated (Table 20). Two scenarios were envisaged; 1) activation of the carbonyl of interest or 2) employment of a suitable nucleophilic catalyst to assist in the nucleophilic substitution process. As such, Lewis acid, $BF_3.OEt_2$, and nucleophilic catalyst, DMAP were selected for this brief investigation. However, no improvements were observed upon addition of DMAP or $BF_3.OEt_2$ into the reaction mixture.



161 **190** **191**

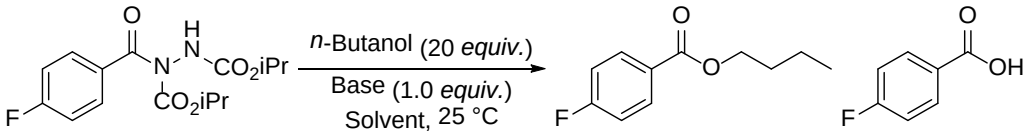
Entry	Additive	Additive /equiv.	Alcohol /equiv.	Time /h	Conversion /%	Ester[a] 190 /%	Acid[b] 191 /%
1	-	-	20	36	60	45	5
2	$BF_3.OEt_2$	0.5	20	36	51	39	3
3	$BF_3.OEt_2$	1.0	20	36	55	35	5
4	DMAP	0.5	20	36	59	42	5
5	DMAP	1.0	20	36	59	39	5

Table 20. Esterification of hydrazide **161** in the presence of catalysts

It is possible that the dependency of the reaction on an excess of alcohol to achieve a high yield and the failure of catalysts to promote ester formation may be due to an equilibrium process where the alcohol adds to the carbonyl reversibly; this would be consistent with other esterification methods such as the Fischer esterification. Therefore, to combat the sub-optimal conversion observed with $^tBuNH_2$, it was envisaged that an alternative, more potent base may be required. It should be noted that elevated temperatures may also have promoted conversion and ester yield, however, this was not investigated as it is not in fitting with providing an energy efficient protocol and it would also preclude the use of low-boiling alcohols.

Consequently, caesium carbonate was selected for further studies, and given the higher solubility of caesium carbonates in dipolar aprotic solvents; DMF was selected as the optimum solvent for this reaction.[122] To reduce the likelihood of side reactions resulting from possible alpha deprotonation of hydrazide **161** aromatic hydrazide **173** was selected as the model in this study.[123] 4-Fluoro substituted hydrazide **173**, would provide the additional opportunity for reaction analysis by quantitative ^{19}F NMR. Furthermore, to compensate for the loss in molecular mass of anticipated esters, a less volatile alcohol, *n*-butanol, was employed. As such, hydrazide **173** was initially treated with *n*-butanol under previously optimised conditions with $^tBuNH_2$ to ensure suitability of the model system (Table 21, entry 1).

Treatment of hydrazide **173** with caesium carbonate resulted in considerable improvements in conversion and yield of ester (Table 21). Additionally, it was found that employing a shorter reaction time of 15 h had a negligible effect on yield and conversion (Table 21, entry 3).

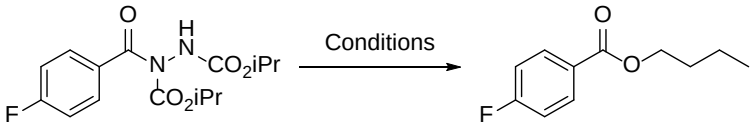


173 **192** **193**

Entry	Base	Base /equiv.	Solvent	Time /h	Conversion /%	Ester[a] 192 /%	Acid[b] 193 /%
1	$^{t}BuNH_2$	1.0	Et_2O	36	64	48	5
2	Cs_2CO_3	1.0	DMF	36	92	86	5
3	Cs_2CO_3	1.0	DMF	15	93	88	5

Table 21. Investigation into an alternative base for esterification of **173**

Selecting 15 h as the optimum length of time for reaction to take place, a brief study was conducted to appraise lowering the alcohol stoichiometry without affecting yield. Pleasingly, conversion and yield of ester remained high as alcohol stoichiometry was reduced from 20 to 1.1 equivalents (Table 22, entries 1 to 5). Next, to reduce the stoichiometry of the base, the reaction was repeated with sub-stoichiometric amount of caesium carbonate. Unfortunately, however, reducing the stoichiometry of the base to 0.5 equivalents significantly reduced the conversion of hydrazide **173** and yield of ester **192** to 39% and 31% respectively (Table 22, entry 6).



173 **192**

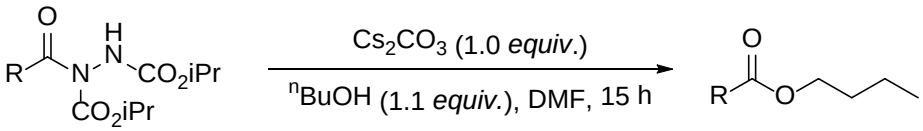
Entry	Base	Base /equiv.	*n*-Butanol /equiv.	Time /h	Conversion /%	Ester[a] 192 /%
1	Cs_2CO_3	1.0	20	15	>90	95
2	Cs_2CO_3	1.0	10	15	>90	92
3	Cs_2CO_3	1.0	5	15	>90	92
4	Cs_2CO_3	1.0	2.5	15	>90	90
5	Cs_2CO_3	1.0	1.1	15	>90	87
6	Cs_2CO_3	0.5	1.1	15	39	31

Table 22. Esterification of hydrazide **173** with varying alcohol stoichiometry

4.2.1 Hydrazide scope

The aerobic hydroacylation of azo-dicarboxylates, described earlier, provides a highly efficient method for the functionalisation of aldehydes to acyl hydrazides. As such, a representative selection of hydrazides was chosen from those synthesised in Chapter 2 to investigate the applicability of acyl hydrazides for the formation of esters.

Application of the optimised conditions (1.0 equivalents Cs_2CO_3, 1.1 equivalents alcohol, DMF, 15 h, 25 °C) to tertiary aliphatic hydrazide **165**, resulted in smooth conversion to its corresponding ester **194c** in 62% isolated yield (Table 23, entry 3). However, when primary and secondary alkyl hydrazides **131** and **163** were subjected to the same conditions, no ester was furnished. Analysis of the crude ^{1}H NMR spectra revealed that this was due to limited conversion of hydrazide.



125 **194**

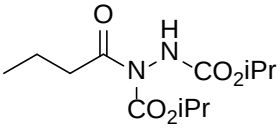
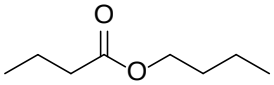
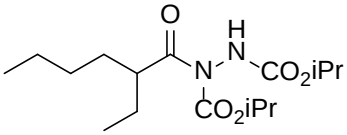
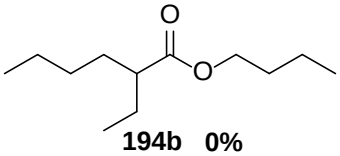
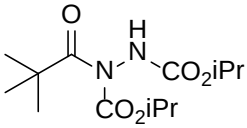
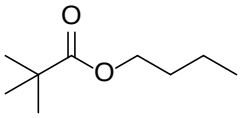
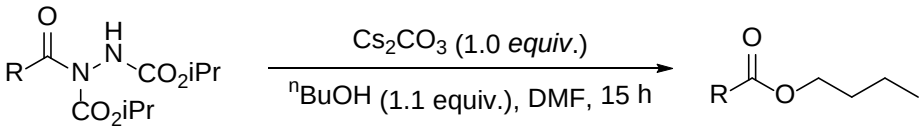
Entry	Hydrazide /%	Ester Yield /%
1	 **131**	 **194a 0%**
2	 **163**	 **194b 0%**
3	 **165**	 **194c 62%**

Table 23. Esterification of alkyl hydrazides

Given the success of tertiary hydrazide **165** to undergo esterification, it was postulated that the failure of primary **131** and secondary hydrazide **163** to undergo esterification may be due to α-deprotonation under the basic reaction conditions rather than steric hindrance. To evaluate this hypothesis, hydrazide **163** was subjected to the reaction conditions followed by quenching with deuterium oxide. This resulted in a 22% "consumption" of hydrazide **163** with respect to integration of the alpha proton; presumably due to exchange with deuterium. Although an exchange of this magnitude does not provide enough evidence for a solid conclusion, it does suggest that hydrazide **163** is deprotonated, at least to a certain extent, under the reaction conditions so as to become a factor in the failure of hydrazide **163** to undergo esterification.

Both, electron rich aromatic hydrazides **168** and **167**, and electron neutral hydrazide **172**, were tolerant of the optimised conditions to furnish their corresponding esters (Table 24, entries 1-4). However, hydrazides bearing 2- and/or 6-substitution gave a lower yield of ester. For example, the yield of ester for 2-substituted hydrazide **168**

was lower than that observed for hydrazides **167** and **172**, which presented no substitutions in the 2- position. Furthermore, when 2,6-disubstituted hydrazide **169** was subjected to the reaction conditions, the reaction failed to exhibit any conversion of hydrazide altogether. Given the similarities in the electronics of all three methyl-substituted hydrazides, it was concluded that their varying propensities to undergo esterification was due to the diverse steric hindrance about the reacting carbonyl.



125 **194**

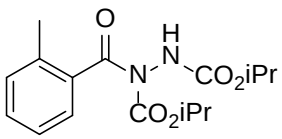
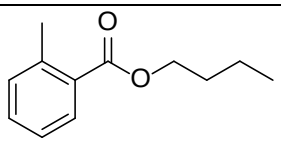
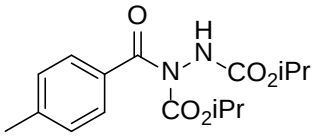
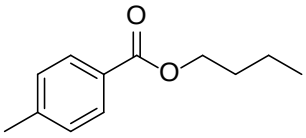
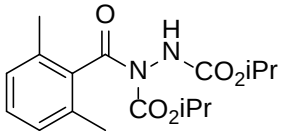
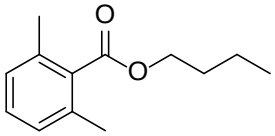
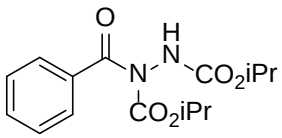
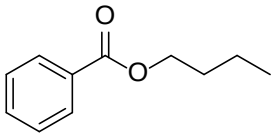
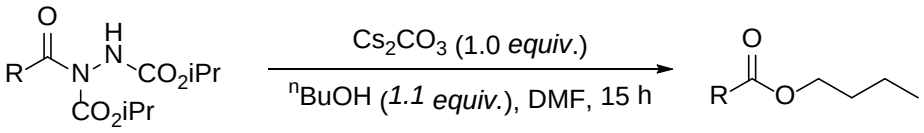
Entry	Hydrazide /%	Ester[a] Yield /%
1	 **168**	 **194d 26%**
2	 **167**	 **194e 85%**
3	 **169**	 **194f 0%**
4	 **172**	 **194g 78%**

Table 24. Esterification of electron rich and electron neutral hydrazides

The protocol also proved to tolerate halide functionalities and the reactions resulted in an excellent yield of fluoro- and bromo- substituted esters **192** and **194j**. As with 2,6-disubstituted hydrazide **169**, 2,6-diclorosubstituted hydrazide **175** also failed to furnish any ester. From analysis of the crude ^{1}H NMR spectra, it was clear that this was due to poor conversion. Once again, this was attributed to the steric inaccessibility of the carbonyl of interest in hydrazide **175** to *n*-butanol. More encouragingly, the esterification of nitro and cyano functionalised hydrazides **180** and **181** proceeded smoothly to give esters **194l** and **194k**, respectively, in excellent yield (Table 26, entries 6 and 7).



125 **194**

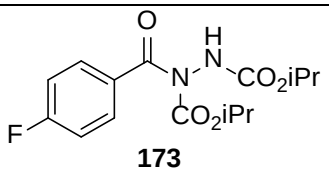
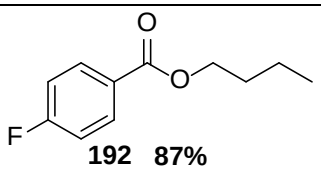
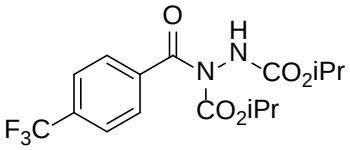
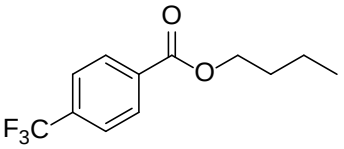
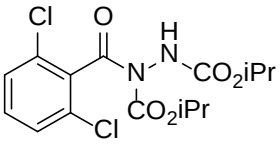
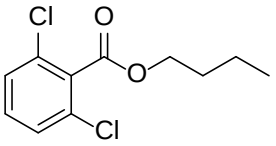
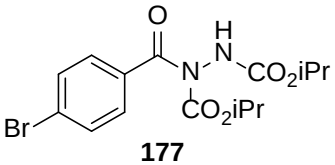
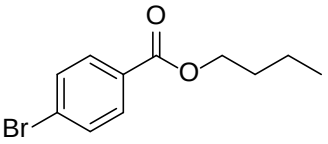
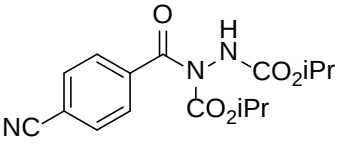
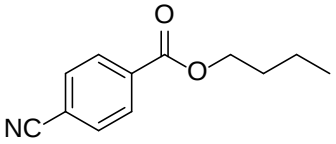
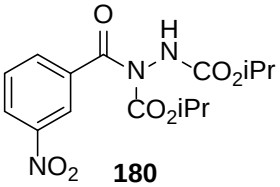
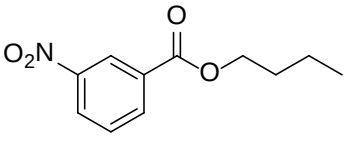
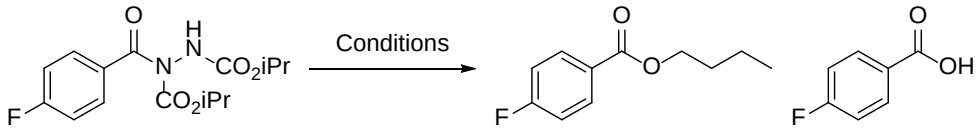
Entry	Hydrazide	Ester Yield /%
1	 **173**	 **192 87%**
2	 **179**	 **194h 79%**
3	 **175**	 **194i 0%**
5	 **177**	 **194j 85%**
6	 **181**	 **194k 77%**
7	 **180**	 **194l 80%**

Table 25. Esterification of electron deficient hydrazides

To assess the possibility of circumventing the limitations associated with the failed hydrazides, it was postulated that perhaps pre-formation of the alkoxide may expedite esterification. Substituting caesium carbonate for potassium *tert*-butoxide, ^{t}BuOK, using diethyl ether as solvent, in the reaction employing 20 equivalents of alcohol resulted in almost quantitative yield of the corresponding ester (Table 26, entry 1). It was found that employing a lower stoichiometry of the base, 0.5 equiv., had a negligible effect on conversion of hydrazide **173** and yield of ester **192**. As alcohol stoichiometry was reduced from 20 to 1.1 equivalents, although overall conversion remained high, yield of ester gradually decreased (Table 26, entries 1 to 6). Also observed was a gradual increase in the amount of acid **193** from 4 to 40%. Assuming this was as a result of hydrolysis caused by the water present in the reaction mixture, the reaction at 1.1 equivalents of alcohol was repeated under inert reaction conditions and flame-dried glassware (Table 26, entry 7). This resulted in a sharp increase in the yield of ester **192**, 75%, and a considerable decrease in yield of acid **193**.



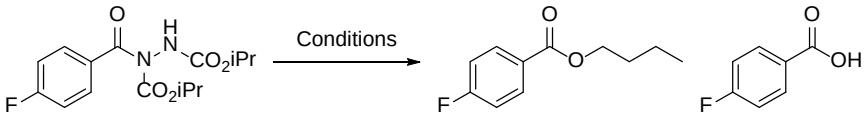
173 **192** **193**

Entry	Base	Base /equiv.	Alcohol /equiv.	Time /h	Conversion /%	Ester[a] 192 /%	Acid[b] 193 /%
1	^{t}BuOK	1.0	20	15	>99	96	3
2	^{t}BuOK	0.5	20	15	>99	96	2
3	^{t}BuOK	0.5	10	15	>99	89	10
4	^{t}BuOK	0.5	5	15	>99	62	22
5	^{t}BuOK	0.5	2.5	15	>99	50	32
6	^{t}BuOK	0.5	1.1	15	>99	53	36
7	^{t}BuOK	0.5	1.1	15	>99	75	12

Table 26. Esterification of hydrazide **173** with varying alcohol stoichiometry

Application of the optimum condition (0.5 equivalents ^{t}BuOK, 1.1 equivalents alcohol, under dry reaction conditions) to aromatic hydrazide **173** served as a control, thus resulting in smooth conversion and formation of the corresponding ester **192** in 75% isolated yield (Table 27, entry 1). However, when 2,6-disubstituted hydrazides

175 and **169,** and alpha-substituted hydrazide **163** were subjected to the optimised conditions, once again, no corresponding esters were furnished (Table 27, entries 2 to 5). In each case, only unreacted starting materials could be identified in the corresponding ^{1}H NMR and ^{13}C NMR spectra.



173 **192** **193**

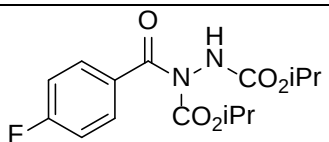
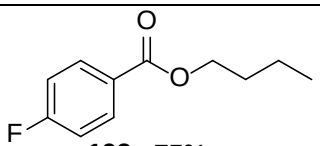
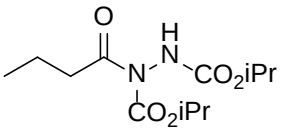
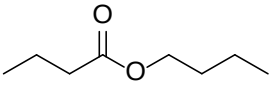
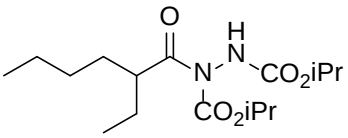
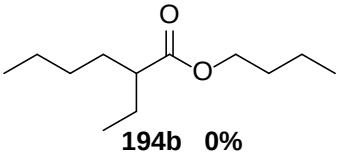
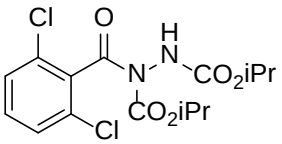
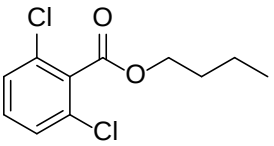
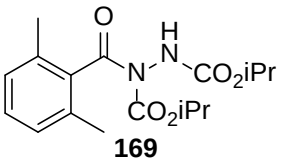
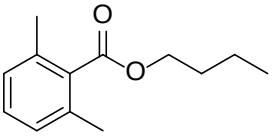
Entry	Hydrazide	Ester Yield /%
1	 **173**	 **192 75%**
2	 **131**	 **194a 0%**
3	 **163**	 **194b 0%**
4	 **175**	 **194i 0%**
5	 **169**	 **194f 0%**

Table 27. Esterification of hydrazides with ^{t}BuOK

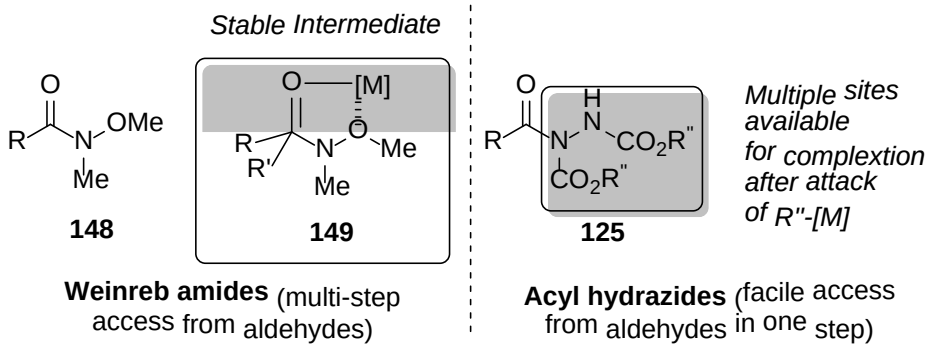
4.3 Conclusions

In summary, the work described herein represents a novel approach to the synthesis of esters; a range of acyl hydrazides were employed as acyl donors to access a range of esters under stoichiometric conditions. This is particularly attractive in view of the facile, atom-economic and benign manner in which acyl hydrazides may be prepared from various aldehydes. Moreover, ester formation has been shown to proceed under mild conditions, which has allowed for the tolerance of sensitive functional groups such as a nitrile and a nitro for the synthesis of functionalised esters.

Chapter 5 Synthesis of Ketones

5.1 Background

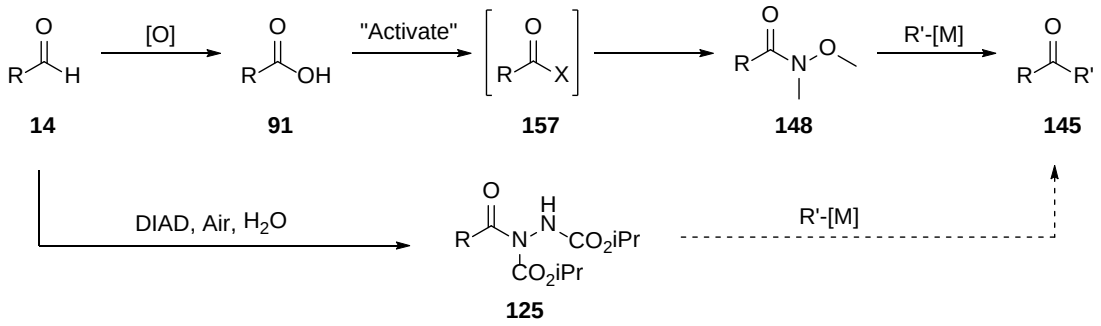
As discussed in Chapter 1, ketones are important building blocks for the synthesis of various natural products, pharmaceuticals, agrochemicals and other functional materials.[91-94] Syntheses of ketones by oxidation of secondary alcohols and Friedal-Crafts acylation suffer from various problems *e.g.* functional group intolerance and untunable regioselectivity. Direct addition of organometallic reagents to activated acid derivatives usually suffers from poor chemoselectivity; over-addition of organometallic reagent to the ketone product, forming tertiary alcohol.[99] Weinreb amides provide clean and selective routes to a variety of ketones. However, they too suffer from functional group intolerance and undesired side reactions in the presence of strongly basic and/or bulky nucleophiles. Given the similarities between acyl hydrazides and Weinreb amides (Scheme 67) including the fact they have multiple sites available for forming a stable metal chelate and have been shown to be highly stable and effective acyl donors, it was envisaged that acyl hydrazides could potentially serve as effective acyl donors for the synthesis of ketones.



Scheme 67. Similarities between Weinreb amides and acyl hydrazides

Additionally, such a transformation would be highly desirable due to the facile and mild nature in which aldehydes can be readily transformed into acyl hydrazides in a single step. The conversion of an aldehyde to a Weinreb amide, in contrast, typically requires multiple steps, elaborate metal catalysts and/or relatively harsh oxidants such as peroxides.[124] Thus, conversion of an aldehyde **14** to a ketone **145** *via* an acyl

hydrazide **66** may represent a more atom-economical and a relatively benign approach compared to the multi-step route *via* Weinreb amide **148** (Scheme 68).

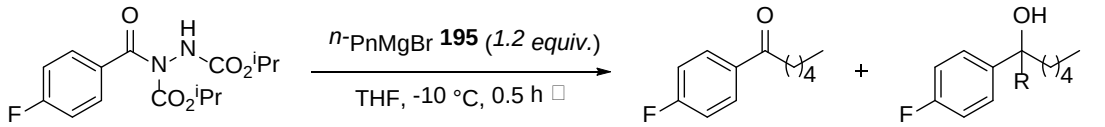


14 **91** **157** **148** **145** **125**

Scheme 68. Comparison of Weinreb amide ketone synthesis to potential Acyl hydrazide-mediated protocol

5.2 Optimisation

The feasibility of converting acyl hydrazides into ketones was initially investigated by assessing the reactivity of acyl hydrazide **173** towards *n*-PnMgBr **195** under typical Weinreb reaction conditions (Scheme 69).[100] Given the facile reactivity of ketones towards Grignard reagents to give tertiary alcohols, it was encouraging observing that the reaction of hydrazide **173** resulted in the formation of 21% of the desired ketone **196**.

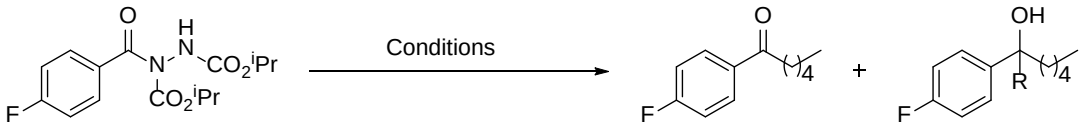


173 **196** 21% R = *n*-Pn **197** 14% R = H **198** 28%

Scheme 69. Treatment of hydrazide **173** with Grignard **195** under Weinreb reaction conditions[125]

As expected, increasing the equivalents of Grignard **195** resulted in the formation of considerably more tertiary alcohol **197** with no ketone being observed (Table 28, Entry 2), suggesting that perhaps any stable intermediate formed is now being overwhelmed by the increased amount of Grignard reagent. It was anticipated that a lower reaction temperature may increase the longevity of any intermediate complex formed. The reaction at lower temperatures of -40 °C and -78 °C with 1.2 and 2 equivalents of Grignard reagent **195** resulted in a gradual overall decrease in the

amount of alcohols **197** and **198**, and a significant increase in the amount of ketone **196**. The maximum yield of ketone, 64%, was observed at -78°C with 2 equivalents of Grignard (Table 28, entry 6).

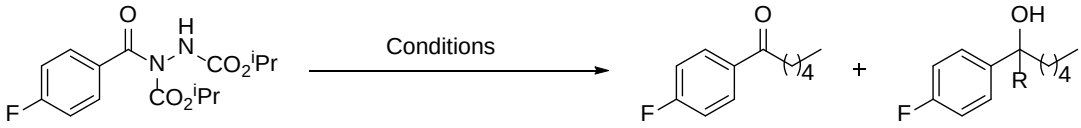


173 **196** **197** **198**

Entry	Temp /°C	Time /h	195 /equiv.	Conversion /%	Ketone 196 /%	2° Alc. 198 /%	3° Alc. 197 /%
1	-10	0.5	1.2	84	21	14	28
2	-10	0.5	2	100	0	12	42
3	-40	0.5	1.2	64	41	10	10
4	-40	0.5	2	95	32	11	21
5	-78	0.5	1.2	34	21	2	0
6	-78	0.5	2	74	64	4	2

Table 28**.** Effect of temperature on yields of ketone **196** and alcohols **197** and **198**

In an attempt to increase conversion and yield of ketone **196** further, an investigation into the effect of longer reaction times was instigated (Table 29). However, no improvements were observed by the extended reaction times; both conversion and ketone yield remained comparable to that observed at 30 mins.



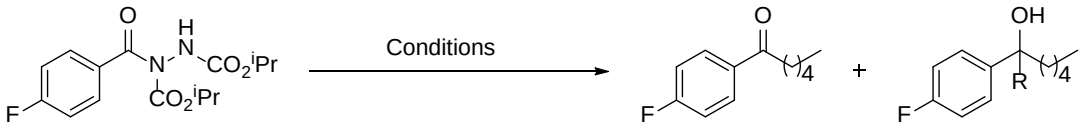
173 **196** **197** **198**

Entry	Temp /°C	Time /h	195 /equiv.	Conversion /%	Ketone 196 /%	2° Alc. 198 /%	3° Alc. 197 /%
1	-78	1	2	77	61	5	1
2	-78	2	2	75	60	3	2
3	-78	3	2	80	62	4	2

Table 29**.** Effect of reaction time on yield of ketone **196**

In an attempt to push the reaction to completion, it was envisaged that a higher stoichiometry of Grignard may be required. Gratifyingly, increasing the number of equivalents from 2 to 2.5 resulted in a noticeable increase in conversion of hydrazide

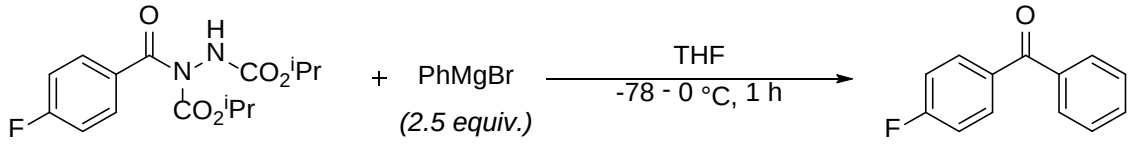
173 to 89%. Pleasingly, this also led to increase in the ketone yield from 64% to 78%. Increasing Grignard stoichiometry further had little effect on ketone yield, despite increasing conversion (Table 30, entries 3 to 6).



Entry	Temp /°C	Time /h	195 /equiv.	Conversion /%	Ketone 196 /%	2° Alc. 198 /%	3° Alc. 197 /%
1	-78	0.5	2	74	64	4	2
2	-78	0.5	2.5	89	78	7	3
3	-78	0.5	3	91	72	7	6
4	-78	0.5	4	92	71	8	6
5	-78	0.5	5	94	69	12	5
6	-78	0.5	6	100	72	11	8

Table 30. Effect of Grignard stoichiometry on yields of ketone **196**

The optimised conditions (2.5 equivalents *n*-PnMgBr **195**, 30 min, -78 °C) were then applied to the reaction of acyl hydrazide **173** with phenyl magnesium bromide **199** to assess their applicability for the synthesis of diaryl ketones. Unfortunately, very low conversion of **173**, 12%, and a minimal yield of ketone **200**, 7%, was observed. This could be explained by the lower nucleophilicity of **199.** To tackle this, the reaction was warmed up from -78 °C to 0 °C following addition of **199** leading to formation of desired ketone **200** in 78% yield (Scheme 70).



Scheme 70. Optimised conditions for the synthesis of diaryl ketones

5.3 Acyl Hydrazide Scope

As described in Chapter 2, the aerobic hydroacylation of azo-dicarboxylates, developed within the Caddick group, provides an efficient method for the functionalisation of aldehydes to acyl hydrazides. Therefore, to investigate the applicability of acyl hydrazides for formation of ketone, acyl hydrazides were synthesised using the efficient aerobic hydroacylation protocol.

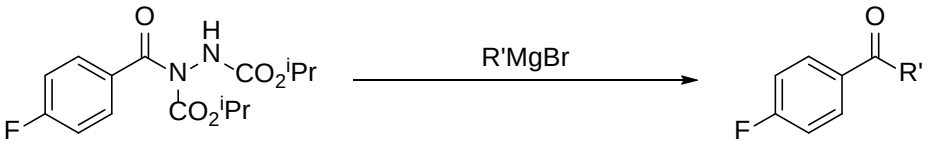
5.3.1 Aryl acyl hydrazides

A wide variety of aryl acyl hydrazides incorporating a range of different functional groups were assessed for ketone formation (Table 31). Each hydrazide was reacted with *n*-pentyl magnesium bromide **195** and phenyl magnesium bromide **199** under their corresponding optimised conditions. Generally, in the case of both Grignard reagents, excellent yields were observed with electron poor, electron neutral and electron rich aryl acyl hydrazides to form their corresponding ketones. Furthermore, the reactions exhibited remarkable tolerance for a wide range of functionalities (Table 31).

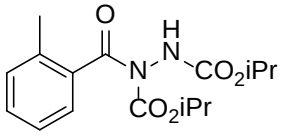
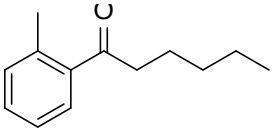
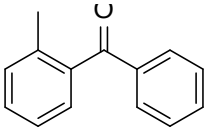
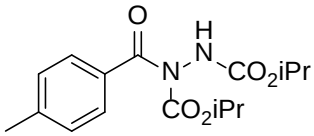
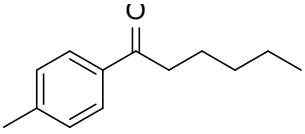
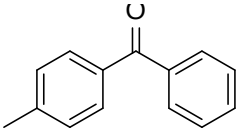
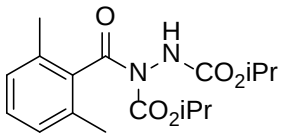
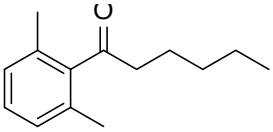
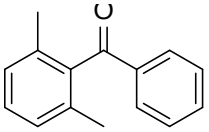
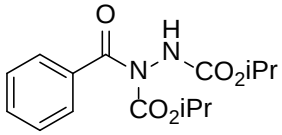
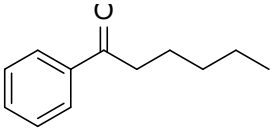
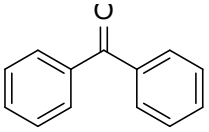
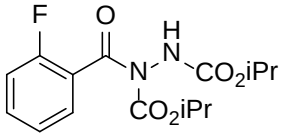
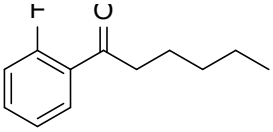
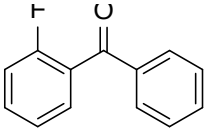
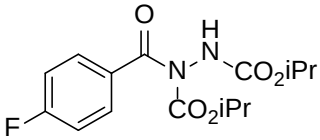
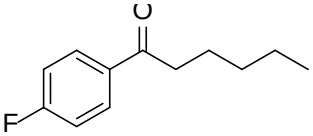
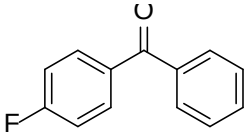
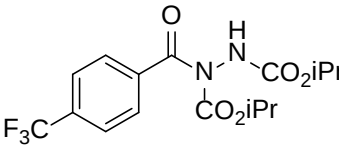
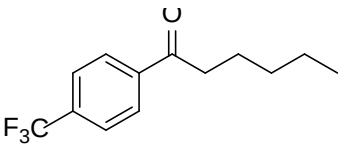
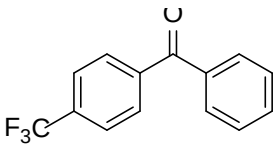
It was found that substitution of any kind in the 2- and/or 6- positions had a negative impact on the yield of ketone, especially in the hexanone series. For example, reaction of hydrazide **168** and hydrazide **174** resulted in considerably lower yields of hexanones **195a**, 36%, and **195e**, 44%. On close inspection of the reaction mixtures by ^{13}C NMR, it was evident that these reactions suffered from very poor conversion rather than over reaction to alcohols. Furthermore, although conversion to phenones **199a** and **199e** were unaffected by 2-substitution, 2,6-dimethyl- **169** and 2,6-dichloro hydrazides **175** both failed to furnish any ketones, hexanone or phenone. Given the differing electronics of hydrazides **169**, electron rich, and **175**, electron poor, it was concluded that this inefficiency was most likely as a result of steric hindrance.

Pleasingly, halogen substituted hydrazides also underwent smooth conversion without any noticeable trans-metallation with the Grignard reagent; fluoro- (**173**,**174**), bromo- (**176**, **177**), and iodo- (**178**) hydrazides were converted to their respective ketones in very good yields (Table 31).

Owing to the mildness of the reaction conditions required for effective conversion, the use of acyl hydrazides bearing functionalities that were not tolerant of Weinreb amide ketone synthesis conditions, *i.e*. nitro- and cyano groups (Table 31, entries 12 and 13) were appraised. Unfortunately, reaction of nitro and cyano substituted hydrazides with *n*-pentyl magnesium bromide **195** resulted in complex reaction mixtures with inseparable products. Analysis of the reaction mixtures by LCMS confirmed complete conversion of the starting hydrazides **180** and **181**, the absence of ketone **195k** and **195l**, and absence of any alcohol derivatives thereof. Given the absence of any nitro and cyano groups on IR spectra of the respective reaction mixtures, it was concluded that reaction had taken place exclusively on the respective functional groups. Pleasingly however, diaryl ketones **199k** and **199l** were isolated in excellent yields on application of PhMgBr **199**, demonstrating to some extent the mildness and advantage of this protocol over competing methodologies. The conversion of heterocyclic acyl hydrazide, **183**, to aryl alkyl and diaryl ketone was also demonstrated in excellent yields upon reaction with *n*-pentyl magnesium bromide **195** and PhMgBr **199**, respectively (Table 31, entry 14).



173 **201**

Entry	Hydrazide	*n*-PnMgBr 195[a]	PhMgBr 199[b]
1	 **168**	 **195a 44%**	 **199a 73%**
2	 **167**	 **195b 68%**	 **199b 70%**
3	 **169**	 **195c 0%**	 **199c 0%**
4	 **172**	 **195d 71%**	 **199d 73%**
5	 **174**	 **195e 36%**	 **199e 74%**
6	 **173**	 **196 78%**	 **200 78%**
7	 **179**	 **195f 77%**	 **199f 87%**

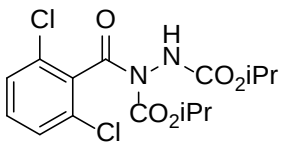
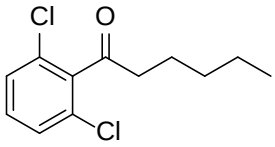
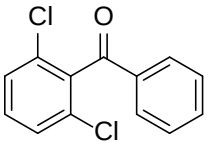
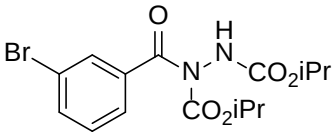
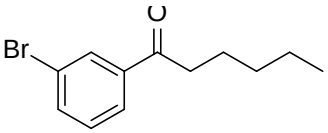
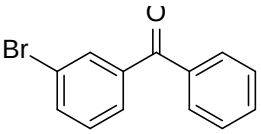
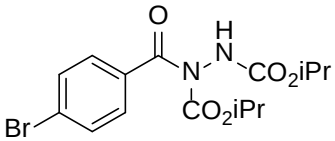
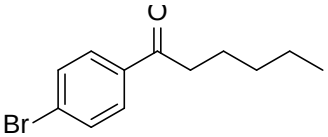
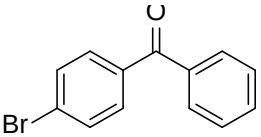
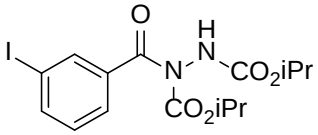
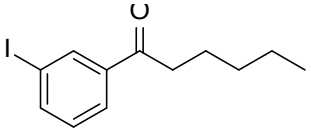
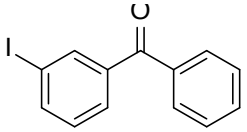
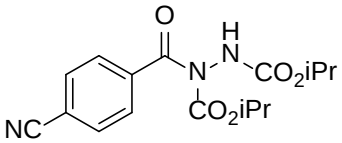
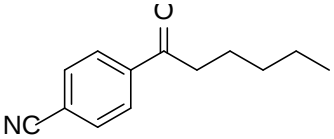
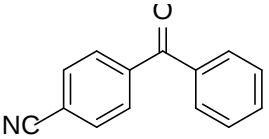
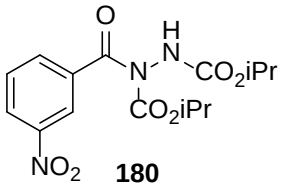
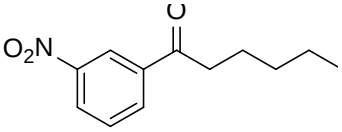
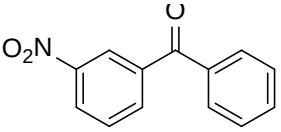
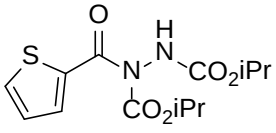
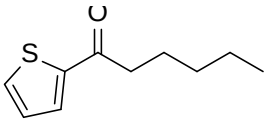
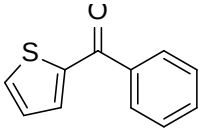
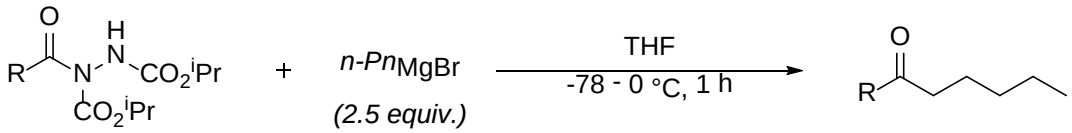
8	 **175**	 **195g 0%**	 **199g 0%**
9	 **176**	 **195h 72%**	 **199h 92%**
10	 **177**	 **195i 79%**	 **199i 71%**
11	 **178**	 **195j 76%**	 **199j 72%**
12	 **181**	 **195k 0%**	 **199k 76%**
13	 **180**	 **195l 0%**	 **199l 77%**
14	 **183**	 **195m 74%**	 **199m 76%**

Table 31. Hydrazide scope for synthesis of aryl-alkyl and aryl-aryl ketones

5.3.2 Alkyl acyl hydrazides

Encouraged by the selectivity exhibited by acyl hydrazides for ketone formation, the optimized conditions were then applied to the alkyl acyl hydrazides to assess their feasibility for selective conversion to their corresponding dialkyl ketones. However, treatment of all the alkyl hydrazides attempted, with *n*-PnMgBr **195** failed to furnish any ketone and exhibited very poor conversion (Table 32, entries 1 to 3). In the case of butyl hydrazide **131** and alpha-substituted hydrazide **163**, the starting materials were isolated from the reaction mixture in almost quantitative yields. It was rationalized that this may be as a result of deprotonation at the alpha position, by the Grignard, to form their corresponding inactive enolates, and subsequent reprotonation upon acidic workup. The failure of tertiary hydrazide **165** to undergo reaction was attributed to the possible inaccessibility of the carbonyl to the incoming nucleophile due to the steric bulk of the pivaloyl group despite not being a problem in the case of ester synthesis (See Chapter 4).



125 **195**

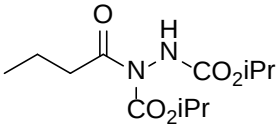
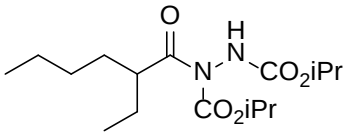
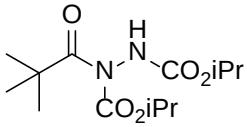
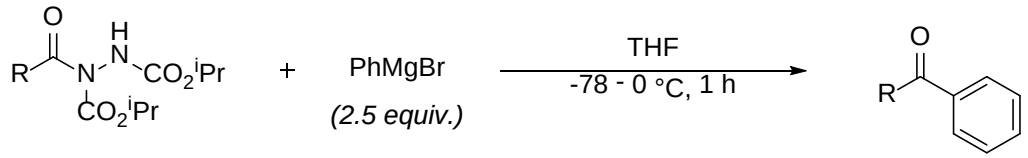
Entry	Hydrazide	Temp /°C	Time /h	195 /equiv.	Conversion /%	Ketone /%
1	 **131**	-78	0.5	2.5	<5	**195n** 0
2	 **163**	-78	0.5	2.5	<5	**195o** 0
3	 **165**	-78	0.5	2.5	<5	**195p** 0

Table 32. Treatment of alkyl hydrazides with alkyl Grignard **195**

It was envisaged that using a relatively less nucleophilic Grignard such as aromatic Grignard **199** may reduce the extent of deprotonation. However, although treatment

of alkyl hydrazides **163** and **165**, with PhMgBr **199** resulted in negligible conversion, hydrazide **131** underwent 15% conversion, and some ketone **199n** was detected by ^{13}C NMR spectroscopy (Table 33).



125 **199**

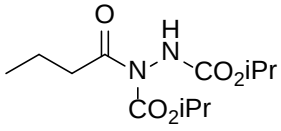
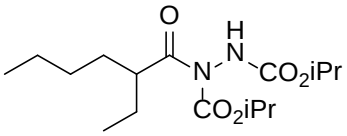
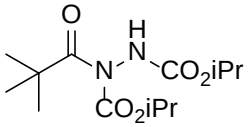
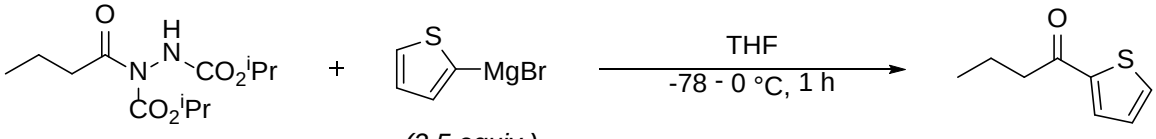
Entry	Hydrazide	Temp /°C	Time /h	199 /equiv.	Conversion /%	Ketone /%
1	 **131**	-78	0.5	2.5	<15	**199n** trace
2	 **163**	-78	0.5	2.5	<5	**199o** 0
3	 **165**	-78	0.5	2.5	<5	**199p** 0

Table 33. Treatment of alkyl hydrazides with aryl Grignard **199**

Taking advantage of the planar and lower nucleophilicity of thienyl Grignard **202**, a final attempt to reduce the extent of deprotonation and steric hindrance was made. Although, very little conversion was observed for secondary hydrazide **163** and tertiary hydrazide **165**, once again, butyl hydrazide **131** underwent reasonable conversion to furnish ketone **203** in 30% isolated yield.

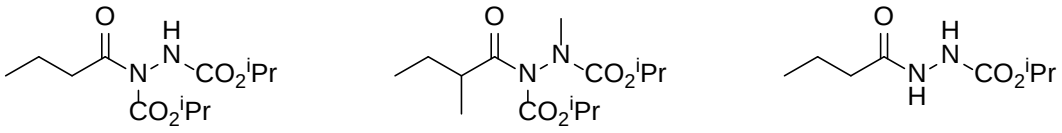


131 **202** **203** **30%**

Scheme 71. Treatment of alkyl hydrazide **131** with thienyl Grignard **202**

In an attempt to confirm that the low conversion of alkyl hydrazides was due to deprotonation , the reaction of hydrazide **131** with *n*-PnMgBr was carried out again but this time, quenched with an excess of methyl iodide instead of NH_4Cl.

Unfortunately, reaction with even a single equivalent of the Grignard resulted in a complex inseparable reaction mixture which was difficult to analyze; theoretically at least three possible products can be envisaged to be present in the reaction mixture; 1) Starting material **131**, 2) *N*-methylated 2-methyl butanal hydrazide **204** and 3) hydrazide **205** which may be formed as a result of initial attack on one of the carbamate esters. In all cases the closely related polarity of the products may explain why it was difficult to isolate the compounds from the mixture. Furthermore the presence of multiple N-Me groups, thus multiple rotameric species, complicated the proton NMR sufficiently that a reliable estimation of relative yields could not be made.

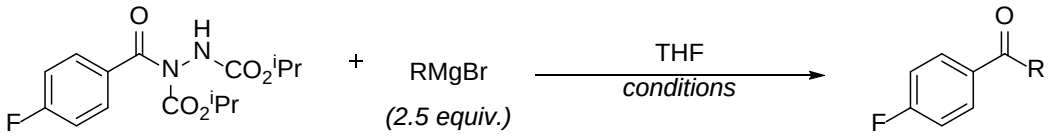


131 **204** **205**

Scheme 72. Possible products present in the reaction mixture following quenching reaction with methyl iodide.

5.4 Grignard Scope

Having successfully demonstrated good tolerance of acyl hydrazides for the formation of diaryl and aryl alkyl ketones on application of Grignards **195** and **199**, a study was initiated to explore compatibility of alternative Grignard reagents to this protocol (Table 34). Thus, acyl hydrazide **173** was reacted with alkynyl, thiophenyl and isopropyl magnesium bromides. Gratifyingly, this afforded excellent yields of corresponding ketones ranging from 70% to 78 % (Table 34).



173

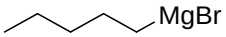
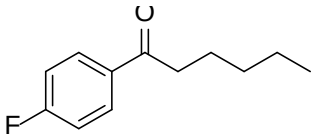
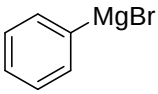
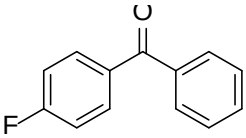
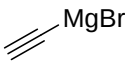
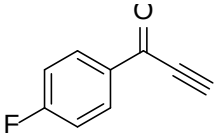
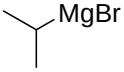
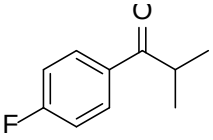
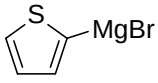
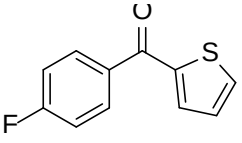
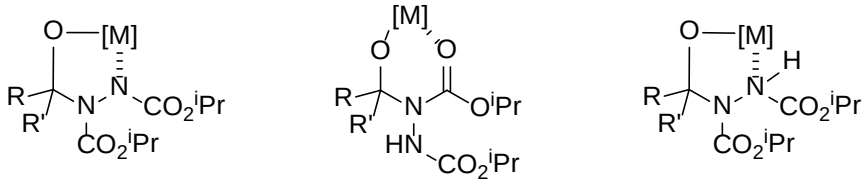
Entry	Grignard	Ketone
1		 **196 78%**
2		 **200 78%**
3		 **206 76%**
4		 **207 70%**
5		 **208 71%**

Table 34. Tolerance of hydrazide **173** towards various Grignard reagents

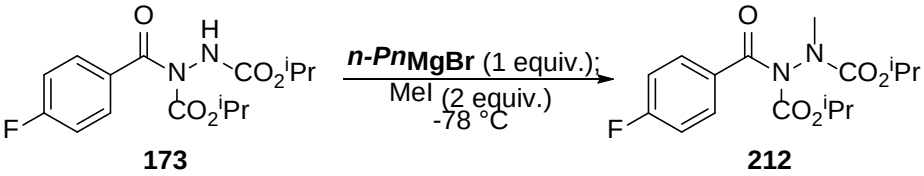
5.5 Mechanistic Studies

It was rationalised that in order for yield of ketone to be so high, there must be some form of complexation that stabilises the respective adduct that is formed upon nucleophilic addition of the Grignard reagent to the acyl hydrazide. Conceptually, three possibilities were envisaged for affecting such a complex (Fig. 3): (i) deprotonated hydrazide, **209**; (ii) ester carbonyl, **210**; or (iii) *N*-lone pair, **211**.



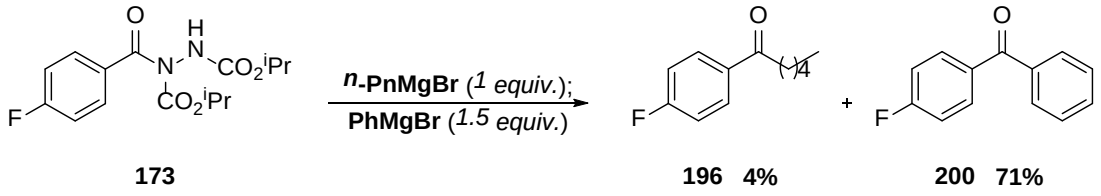
Scheme 73. Potential stable intermediates

In order to elucidate the identity of the complex it was important to establish whether an acyl hydrazide would be deprotonated under the reaction conditions owing to the inherent acidity of the N–H bond. Thus, acyl hydrazide **173** was reacted with a single equivalent of Grignard **195**, followed by addition of methyl iodide at -78 °C. The reaction was then quenched with ammonium chloride (Scheme 74). As this resulted in the formation of a significant amount of methylated hydrazide **212**, 87%, it was felt appropriate to conclude that an acyl hydrazide would be significantly deprotonated under the reaction conditions; making it unlikely that the complex is intermediate **211**.



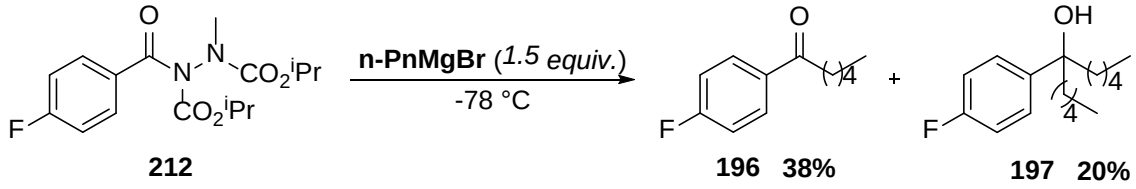
Scheme 74. Reaction confirming NH deprotonation of hydrazide **173** under the reaction conditions

Further evidence that the first equivalent of Grignard was acting as a base was obtained from reaction of acyl hydrazide **173** with *n*-PnMgBr **195** (1 equiv.) followed by addition of PhMgBr **199** (1.5 equiv.). This afforded primarily diaryl ketone **200**, 71%, and only a modest amount of ketone **196**.



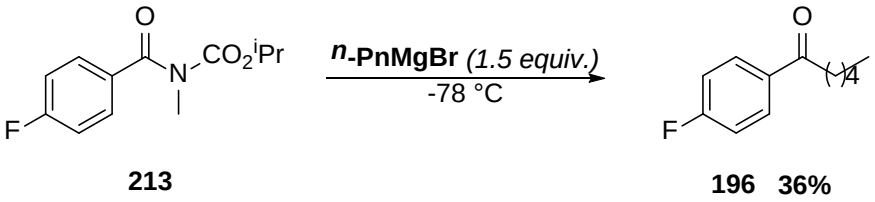
Scheme 75. Reaction confirming NH deprotonation of hydrazide **173** under the reaction conditions

To investigate the importance of deprotonation for efficient ketone synthesis, methylated hydrazide **212** was reacted with 1.5 equivalents of **195** (Scheme 76). This resulted in a poor yield of ketone, 38%, with a significant amount of tertiary alcohol being observed, 20%, perhaps indicating that deprotonation is important for efficient ketone formation to occur.



Scheme 76. Importance of deprotonation for efficient ketone synthesis

To investigate if complexation by carbonyl groups played a key role in formation of a stable intermediate, carbamate **213,** missing the carbamate group on the α-nitrogen, was analysed as the hydrazide component. This was especially relevant in view of a report on the reaction of Grignard reagents with N-Boc protected β-, γ- and δ-lactams for the synthesis of ketones.[126] Carbamate **213** was synthesised as previously described and reacted with 1.5 equivalents of *n*-PnMgBr **195**. However, reaction of **213** with **195** only afforded ketone in 36% yield, again due to the formation of a significant amount of tertiary alcohol (Scheme 77). Thus, it seems reasonable to conclude the high yield of ketone observed in the present protocol is most likely due to the formation of a persistent intermediate of the form of **209** (see Scheme 73).



213 **196** **36%**

Scheme 77. Investigation into carbonyl complexation for ketone synthesis

5.6 Conclusions

In summary, the work described herein represents a novel approach to the chemoselective synthesis of ketones. A range of acyl hydrazides were employed as acyl donors to access a variety of diaryl and aryl-alkyl ketones. This is particularly useful in view of the facile, atom-economic and benign manner in which acyl hydrazides may be prepared from various aldehydes. Moreover, ketone formation has been shown to proceed under mild conditions, which has allowed for the tolerance of sensitive functional groups such as a nitrile and a nitro for the synthesis of diaryl ketones.

Conclusions

The development of an aerobic hydroacylation protocol in the Caddick group has recently allowed the functionalisation of aldehydes with a wide array of electron deficient alkenes including diisopropylazodicarboxylate (DIAD). This process relies on trapping an acyl radical intermediate, from the auto-oxidation of aldehydes to acids, with a nitrogen-nitrogen double bond. Since aldehyde auto-oxidation takes place readily in the presence of atmospheric oxygen, the aerobic hydroacylation reaction can be conducted in aqueous media in the absence of any additional reagents.

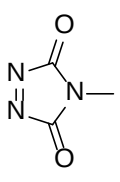
Following on from previous work in the group, this thesis describes studies towards expanding the scope of this novel C-H activation methodology in the formation of C-N bonds. It successfully demonstrates tolerance of the aerobic hydroacylation methodology towards a range of previously unexplored aromatic aldehydes. Although most heteroaromatic aldehydes attempted failed to undergo hydroacylation reaction under this methodology, it was encouraging to find 2-thienyl carboxaldehyde underwent smooth conversion to its hydroacylation product under the same conditions. The scalability of the methodology was also demonstrated when all reactions were shown to be tolerant of being scaled up to a 10 mmol scale.

The failure of previous attempts in the group for the synthesis of tertiary amides from acyl hydrazides was overcome; thus, conditions were identified where treatment of an acyl hydrazide with a secondary amine can furnish its corresponding tertiary amide in very good yield. The applicability of the acyl hydrazides to the synthesis of carboxylic esters was also demonstrated. Although limited to non-enolisable substrates, a range of esters were accessed from acyl hydrazides while employing stoichiometric amounts of the alcohol component.

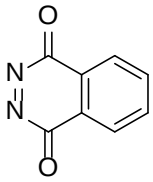
Finally, it was demonstrated that acyl hydrazides can act as a new class of precursors for the chemoselective synthesis of ketones. Analogous to the Weinreb chemistry it is believed that an intermediate chelate is responsible for the selectivity observed. Given the merits associated with the aerobic hydroacylation protocol, this is particularly exciting as it circumvents an otherwise inefficient and multi step approach to Weinreb amides.

Further work

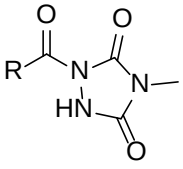
As demonstrated through work within the Caddick group and through this thesis, there are numerous opportunities worth exploring with respect to this project. For example, employing cyclic azo compounds such as **214** and **215** as alternative acceptors would result in hydrazides such as **216** and **217**. These cyclic hydrazides are likely to have better reactivity profiles with respect to their acyl donating capabilities; thus, they may solve the limitations observed with aliphatic acyl hydrazides as acyl donors.



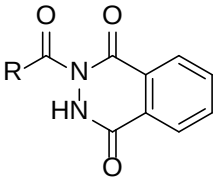
214



215

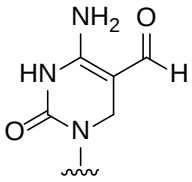


216



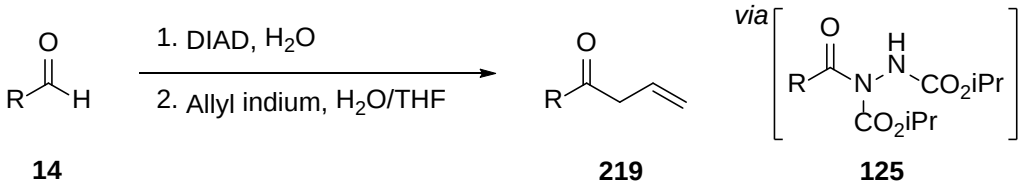
217

Given the prominence of heteroaromatic groups in the fine chemical industry, it would be highly desirable if the aldehyde scope for this aerobic hydroacylation reaction can be extended further to include the unsuccessful heteroaromatic aldehydes described in this thesis. Solving this problem may also extend the applicability of this chemistry to biological systems; for example to functionalise recently discovered 5-formylcytosine **218**.[127]



218

Finally, exploring the use of milder organometallics such as organo Indiums are likely to provide opportunities for even more environmentally benign transformations. For example, given that allyl indium reagents are tolerant of aqueous media, it may be possible develop a one-pot procedure for the conversion of aldehydes to ketones (Scheme 78).[128]



14 **219** **125**

Scheme 78. Potential one-pot synthesis of ketones from aldehydes

Experimental

General Experimental

Chemicals

All reagents were purchased from Aldrich or AlfaAesar and were used as received without further purification unless otherwise stated. All reactions were carried out with HPLC gradient grade water (demineralised) purchased from Fisher Scientific.

Solvents

Solvents were used as supplied unless otherwise stated. Where described below, petrol refers to petroleum ether (b.p. 40-60 °C).

Chromatography

All reactions were monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates (254 μm). Flash column chromatography was carried out with Kiesegel 60M 0.04/0.063 mm (200-400 mesh) silica gel.

Spectroscopy

^{1}H NMR spectra were recorded at 400 MHz, 500 MHz and 600 MHz and ^{13}C NMR at 100 MHz, 125 MHz and 150 MHz on Bruker AMX400, AMX500 and AMX600 spectrometers. ^{19}F NMR spectra were recorded at 376 MHz on Bruker AMX400 at ambient temperature unless otherwise stated, in $CDCl_3$ or d_6-DMSO (see below). The chemical shifts (δ) for ^{1}H and ^{13}C are quoted relative to residual signals of the solvent on the ppm scale. Coupling constants (*J* values) are reported in Hertz (Hz) and are H-H coupling constants unless otherwise stated. Signal multiplicities in ^{13}C NMR were determined using the distortionless enhancement by phase transfer (DEPT) spectral editing technique. Where applicable, only the peaks for the major rotamers of acyl hydrazides and ketones are assigned in the ^{1}H and ^{19}F NMR spectra. Mass spectra were obtained on a VG70-SE mass spectrometer. Infrared spectra were obtained on a Perkin Elmer Spectrum 100 FTIR Spectrometer operating in ATR

mode. Melting points were measured with a Gallenkamp apparatus and are uncorrected. Electron paramagnetic resonance (EPR) spectra were obtained on site at AstraZeneca pharmaceuticals (Macclesfield) on a Bruker machine with following parameters; 6.33 mW microwave power, 9.84 GHz frequency, 1.00 G modulation amplitude, 3490.00 G field centre, 120.00 sweep width and 200 scans.

Miscellaneous

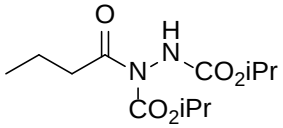
Melting points were measured with a Gallenkamp apparatus and are uncorrected. All hydroacylation reactions were carried out in carousel tubes (15 cm × 2 cm) equipped with an octagon-shaped magnetic stirrer bar (12.7 mm × 3 mm).

Experimental for Chapter 2

General Procedure for the hydroacylation of DIAD with various aldehydes

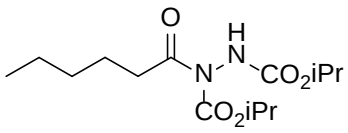
Aldehyde (1.0 mmol) was added to a mixture of azodicarboxylate (1.2 mmol) and H_2O (500 μL) and the reaction mixture stirred at 300 rpm at 21 °C in a stoppered carousel tube for 96 h. The solvent was removed *in vacuo* and the product purified as described below.

Diisopropyl 1-butyrylhydrazine-1,2-dicarboxylate[88] (131)



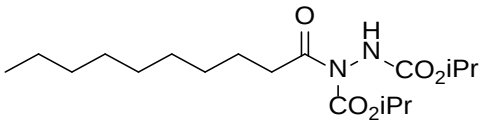
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-butyrylhydrazine-1,2-dicarboxylate as a colourless oil (250 mg, 0.91 mmol, 91%). **^{1}H NMR (500 MHz, CDCl3)** δ 6.62-6.34 (br s, NH, 1H), 5.03 (septet, *J* = 6.5 Hz, 1H), 4.97 (septet, *J* = 6.5 Hz, 1H), 2.94-2.74 (m, 2H), 1.69 (sextet, *J* = 7.5 Hz, 2H), 1.34-1.17 (m, 12H), 0.96 (t, *J* = 7.5 Hz, 3H); **^{13}C NMR (125 MHz, CDCl3)** δ 173.9 (C), 155.2 (C), 152.8 (C), 72.2 (CH), 70.5 (CH), 39.1 (CH2), 22.0 (CH_3), 21.8 (CH_3), 18.2 (CH_2), 13.8 (CH_3); **IR** (thin film) 3317, 2982, 2938, 1736, 1717 cm^{-1}; **LRMS (CI)** 275 (100, $[M+H]^+$); **HRMS (CI)** calcd for $C_{12}H_{23}N_2O_5$ $[M+H]^+$ 275.1607, observed 275.1609.

Diisopropyl 1-hexanoylhydrazine-1,2-dicarboxylate (159)



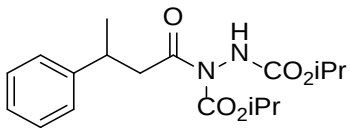
Purification by column chromatography (5-25% Et_2O/Petrol) gave Diisopropyl 1-hexanoylhydrazine-1,2-dicarboxylate as a clear oil (249 mg, 0.82 mmol, 82%). **^{1}H NMR (400 MHz, 100 °C, DMSO)** δ 9.1 (br s, NH, 1H), 4.99 (septet, *J* = 6.3 Hz, 1H), 4.87 (septet, *J* = 6.3 Hz, 1H), 2.74 (t, *J* = 7.3 Hz, 2H), 1.60 (m, 2H), 1.32 (m, 4H), 1.29 (d, *J* = 6.3 Hz, 6H), 1.24 (d, *J* = 6.3, 6H), 0.92 (m, 3H); **^{13}C NMR (150 MHz, DMSO)** δ 172.9 (C), 155.0 (C), 152.4 (C), 71.2 (CH), 68.8 (CH), 36.1 (CH_2), 30.6 (CH_2), 24.0 (CH_2), 21.9 (CH_2), 21.91 (CH_3), 21.81 (CH_3), 21.5 (CH_3), 21.4 (CH_3), 13.9 (CH_3); **HRMS (CI)** calcd for $C_{14}H_{27}N_2O_5$ $[M+H]^+$ 303.19200 observed 303.19240. Spectroscopic data in accordance with the literature.[53]

Diisopropyl 1-decanoylhydrazine-1,2-dicarboxylate (160)



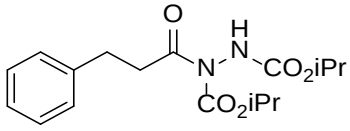
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-decanoylhydrazine-1,2-dicarboxylate as a clear oil (305 mg, 0.85 mmol, 85%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 6.61-6.53 (br s, NH, 1H), 5.03 (septet, *J* = 6.5 Hz, 1H), 4.97 (septet, *J* = 6.5 Hz, 1H), 2.96-2.84 (m, 2H), 1.69-1.62 (m, 2H), 1.37-1.15 (m, 24H), 0.88 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 174.0 (C), 155.2 (C), 152.8 (C), 72.2 (CH), 70.5 (CH), 37.2 (CH2), 32.0 (CH2), 29.6 (CH2), 29.5 (CH2), 29.4 (CH2), 29.2 (CH2), 24.7 (CH2), 22.8 (CH2), 22.0 (CH3), 21.8 (CH3), 14.2 (CH3); **IR** (thin film) 3323, 2982, 2924, 2855, 1737, 1720 cm^{-1}; **LRMS (FAB)** 381 (100, $[M+Na]^+$); **HRMS (FAB)** calcd for $C_{18}H_{34}N_2NaO_5$ [M+Na]+ 381.2365.

Diisopropyl 1-(3-phenylbutanoyl)hydrazine-1,2-dicarboxylate (161)



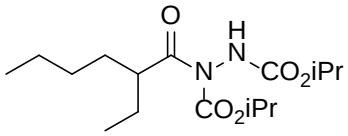
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(3-phenylbutanoyl)hydrazine-1,2-dicarboxylate as a white solid (341 mg, 0.97 mmol, 97%). **^{1}H NMR (400 MHz, 100°C, DMSO)** δ 9.13 (br s, NH, 1H), 7.23 (m, 5H), 4.98 (sept., J = 6.3Hz, 1H), 4.87 (sept., *J* = 6.3 Hz, 1H), 3.32 (sxt., *J* = 7.2 Hz, 1H), 3.10 (dd, *J* = 16.5, 6.0 Hz, 1H), 3.02 (dd, *J* = 16.5, 7.8 Hz, 1H), 1.27 (m, 9H), 1.22 (d, *J* = 6.2, 6H); **^{13}C NMR (150 MHz, DMSO)** δ 171.5 (C), 155.0 (C), 154.3 (C), 152.5 (C), 146.2 (C), 128.4 (CH), 126.8 (CH), 126.76 (CH), 126.1 (CH), 71.3 (CH), 68.8 (CH), 44.25 (CH_2), 35.5 (CH_3), 35.3 (CH_3), 21.8 (CH_3), 21.79 (CH_3), 21.5 (CH_3). **HRMS (CI)** calcd for $C_{18}H_{27}N_2O_5$ $[M+H]^+$ 351.19200, observed 351.19236. m.p. 81-83 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(3-phenylpropanoyl)hydrazine-1,2-dicarboxylate (162)



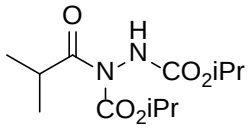
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(3-phenylpropanoyl)hydrazine-1,2-dicarboxylate as a white solid (263 mg, 0.78 mmol, 78%). **^{1}H NMR (400 MHz, 100°C, DMSO)** δ 9.16 (br s, NH, 1H), 7.30 (m, 5H), 5.00 (septet, *J* = 6.3 Hz, 1H), 4.87 (septet, *J* = 6.3 Hz, 1H), 3.09 (m, 2H), 2.91 (m, 2H), 1.28 (d, *J* = 6.3 Hz, 6H), 1.23 (d, *J* = 6.3 Hz, 6H); **^{13}C NMR (150 MHz, DMSO)** δ 172.2 (C), 155.0 (C), 152.4 (C), 140.8 (C), 128.4 (CH), 128.4 (CH), 126 (CH), 71.3 (CH), 68.8 (CH), 38.1 (CH_2), 30.1 (CH_2), 21.8 (CH_3), 21.8 (CH_3), 21.47 (CH_3), 21.44 (CH_3); **HRMS (CI)** calcd for $C_{17}H_{25}N_2O_5$ $[M+H]^+$ 337.17635, observed 337.17611. m.p. 82-87 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(2-ethylhexanoyl)hydrazine-1,2-dicarboxylate (163)



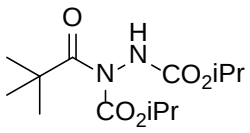
Purification by column chromatography (5-25% Et_2O/Petrol) gave Diisopropyl 1-(2-ethylhexanoyl)hydrazine-1,2-dicarboxylate as a clear oil (315 mg, 0.95 mmol, 95%). **^{1}H NMR (400 MHz, 100°C, DMSO)** δ 9.1 (br s, NH, 1H), 4.99 (septet, *J* = 6.3Hz, 1H), 4.87 (septet, *J* = 6.3Hz, 1H), 3.36 (m, 1H), 1.62 (m, 2H), 1.54 (m, 2H), 1.29 (m, 4H), 1.28 (d, *J* = 6.28, 6H), 1.22 (d, *J* = 6.24, 6H), 0.88 (m, 6H); **^{13}C NMR (150 MHz, DMSO)** δ 176.25 (C), 155.08 (C), 152.49 (C), 71.25 (CH), 71.21 (CH), 68.69 (CH), 31.19 (CH_2), 28.75 (CH_2), 24.99 (CH_2), 22.22 (CH_2), 21.80 (CH_3), 21.71 (CH_3), 21.61 (CH_3), 21.4 (CH_3), 13.85 (CH_3), 11.40 (CH_3); **IR** (thin film) 3329, 2979, 2931, 1738, 1635 cm^{-1}; **HRMS (CI)** calcd for $C_{16}H_{31}N_2O_5$ $[M+H]^+$ 331.22330 observed 331.22367.

Diisopropyl 1-isobutyrylhydrazine-1,2-dicarboxylate (164)



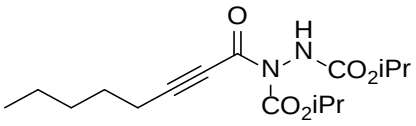
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-isobutyrylhydrazine-1,2-dicarboxylate as a white solid (217 mg, 0.79 mmol, 79%). **^{1}H NMR (600 MHz, CDCl3)** δ 6.76 (br s, NH, 1H), 5.00 (septet, *J* = 6.5 Hz, 1H), 4.93 (septet, *J* = 6.5 Hz, 1H), 3.60 (septet, *J* = 7.0 Hz, 1H), 1.33-1.12 (m, 18H); **^{13}C NMR (125 MHz, CDCl3)** δ 178.4 (C), 155.3 (C), 152.7 (C), 72.2 (CH), 70.4 (CH), 34.4 (CH), 22.0 (CH_3), 21.8 (CH_3), 19.4 (CH_3); **IR** (thin film) 3322, 2982, 2938, 1736, 1718, 1640 cm^{-1}; **LRMS (CI)** 275 (100, $[M+H]^+$); **HRMS (CI)** calcd for $C_{12}H_{23}N_2O_5$ $[M+H]^+$ 275.1607, observed 275.1598.

Diisopropyl 1-pivaloylhydrazine-1,2-dicarboxylate (165)



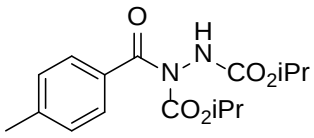
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-pivaloylhydrazine-1,2-dicarboxylate as a white solid (200 mg, 0.69 mmol, 69%). **^{1}H NMR (400 MHz, 100 °C, DMSO)** δ 9.2 (br s, NH, 1H), 4.95 (m, 2H), 1.25 (m, 21H); **^{13}C NMR (150 MHz, DMSO)** δ 178.7 (C), 155.9 (C), 152.6 (C), 71.1 (CH), 69.0 (CH), 41.2 (C), 27.2 (CH_3), 27.2 (CH_3), 21.8 (CH_3), 21.5 (CH_3). **HRMS (CI)** calcd for $C_{13}H_{25}N_2O_5$ $[M+H]^+$ 289.17635 observed 289.1768; m.p. 80-89 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(oct-2-ynoyl)hydrazine-1,2-dicarboxylate (166)



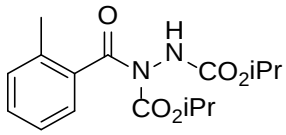
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(oct-2-ynoyl)hydrazine-1,2-dicarboxylate as a clear oil (192 mg, 0.55 mmol, 55%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 6.67-6.59 (br s, NH, 1H), 5.08 (septet, *J* = 6.5 Hz, 1H), 4.99 (septet, *J* = 6.5 Hz, 1H), 2.39 (t, *J* = 7.0 Hz, 2H), 1.62-1.55 (m, 2H), 1.42-1.22 (m, 16H), 0.90 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 154.7 (C), 152.4 (C), 151.4 (C), 98.8 (C), 74.3 (C), 72.8 (CH), 70.8 (CH), 31.1 (CH_2), 27.3 (CH_2), 22.2 (CH_2), 22.0 (CH_3), 21.8 (CH_3), 19.4 (CH_2), 14.0 (CH_3); **IR** (thin film) 3314, 2983, 2936, 2873, 2229, 1741, 1724, 1687 cm^{-1}; **LRMS (FAB)** 349 (100, $[M+Na]^+$); **HRMS (FAB)** calcd for $C_{16}H_{26}N_2NaO_5$ $[M+Na]^+$ 349.1739, observed 349.1733.

Diisopropyl 1-(4-(methyl)benzoyl)hydrazine-1,2-dicarboxylate (167)



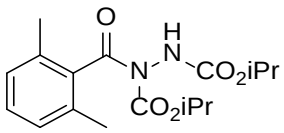
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(4-(methyl)benzoyl)hydrazine-1,2-dicarboxylate as a white solid (200 mg, 0.62 mmol, 62%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.66-7.50 (m, 2H), 7.21 (d, *J* = 7.9 Hz, 2H), 6.89-6.82 (br s, NH, 1H), 5.03-4.98 (m, 1H), 4.90-4.88 (m, 1H), 2.40 (s, 3H), 1.29 (d, *J* = 6.3, 6H), 1.09 (d, *J* = 6.2, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 171.3 (C), 155.4 (C), 153.2 (C), 142.9 (C), 130.3 (CH), 129.3 (CH), 128.9 (CH), 128.6 (CH), 72.5 (CH), 70.8 (CH), 22.1 (CH_3), 21.8 (CH_3), 21.5 (CH_3); **IR** (thin film) 3307, 2982, 1736, 1704, 1375, 1246, 1145, 1102 cm^{-1}; **LRMS (CI)** 323 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{16}H_{23}N_2O_5$ $[M+H]^+$ 323.1607, observed 323.1615; m.p. 99-101°C (recrystallized from *n*-heptane). Spectroscopic data in accordance with the literature.[129]

Diisopropyl 1-(2-methylbenzoyl)hydrazine-1,2-dicarboxylate (168)



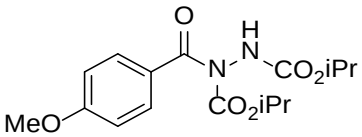
Purification by column chromatography (5-25% Et_2O: Et_2O/Petrol) gave diisopropyl 1-(2-methylbenzoyl)hydrazine-1,2-dicarboxylate as a white solid (184 mg, 0.57 mmol, 57%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.39-7.35 (m, 1H), 7.34-7.30 (m, 1H), 7.24-7.16 (m, 2H), 6.90 (br s, NH, 1H), 5.06-4.97 (m, 1H), 4.87-4.79 (m, 1H), 2.39 (s, 3H), 1.30 (d, *J* = 5.7 Hz, 6H), 1.02-0.98 (m, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 171.0 (C), 155.3 (C), 152.3 (C), 136.3 (C), 135.4 (C), 130.4 (CH), 130.1 (CH), 126.4 (CH), 125.5 (CH), 72.5 (CH), 70.8 (CH), 22.1 (CH_3), 21.3 (CH_3), 19.3 (CH_3); **IR** (thin film) 3308, 2982, 1707, 1248, 1102 cm^{-1}; **LRMS (CI)** 323 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{16}H_{22}N_2O_5$ $[M+H]^+$ 323.1607, observed 323.1602; m.p. 82-84 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(2,6-dimethylbenzoyl)hydrazine-1,2-dicarboxylate (169)



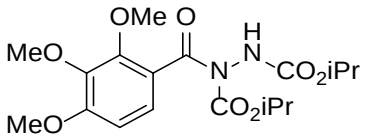
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(2,6-dimethylbenzoyl)hydrazine-1,2-dicarboxylate as a white solid (238 mg, 0.63 mmol, 63%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.18 (t, *J* = 7.6 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 2H), 6.66 (br s, NH, 1H), 5.03 (apparent s, 1H), 4.85 (br s, 1H), 2.28 (br s, 6H), 1.32 (br s, 6H), 0.97 (br s, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 170.3 (C), 152.2 (C), 151.7 (C), 137.0 (C), 133.5 (C), 129.0 (CH), 127.2 (CH), 72.5 (CH), 70.8 (CH), 22.1 (CH_3), 21.2 (CH_3), 19.2 (CH_3); **IR** (thin film) 3307, 2983, 2937, 1702, 1589, 1246, 1219, 1101, 769, 733 cm^{-1}; **LRMS (CI)** 133 (100, $[M–C_8H_{15}N_2O_4]^+$; **HRMS (CI)** calcd. for $C_{17}H_{25}N_2O_5$ $[M+H]^+$ 377.1764, observed 377.1771; m.p. 89-91 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(4-methoxybenzoyl)hydrazine-1,2-dicarboxylate (170)



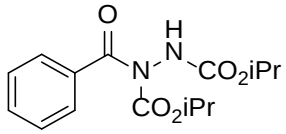
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(4-methoxybenzoyl)hydrazine-1,2-dicarboxylate as a white solid (214 mg, 0.63 mmol, 63%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.74-7.72 (m, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 6.84-6.58 (m, 1H), 5.00 (septet, *J* = 6.2 Hz, 1H), 4.94-4.90 (m, 1H), 3.86 (s, 3H), 1.29 (d, *J* = 4.6 Hz, 6H), 1.13 (d, *J* = 4.7 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.1 (C), 155.5 (C), 153.3 (C), 131.2 (CH), 131.2 (C), 127.0 (C), 113.5 (CH), 72.4 (CH), 70.7 (CH), 55.6 (CH_3), 22.1 (CH_3), 21.6 (CH_3); **IR** (thin film) 3317, 2983, 2941, 1736, 1700, 1605, 1578, 1249, 1104, 1030, 846 cm^{-1}; **LRMS (CI)** 135 (100, $[M–C_8H_{16}N_2O_4]^+$); **HRMS (CI)** calcd. for $C_{16}H_{23}N_2O_6$ $[M+H]^+$ 339.1556, observed 339.1559; m.p. 69-71 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(2,3,4-trimethoxybenzoyl)hydrazine-1,2-dicarboxylate (171)



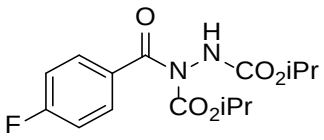
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(2,3,4-trimethoxybenzoyl)hydrazine-1,2-dicarboxylate as a colourless oil (164 mg, 0.41 mmol, 41%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.24-7.13 (m, 1H), 6.90-6.68 (m, 1H), 6.68-6.67 (d, *J* = 8.7 Hz, 1H), 4.99-4.91 (m, 2H), 3.91 (s, 3H), 3.88 (s, 3H), 3.86 (s, 3H), 1.25-1.15 (m, 12H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 168.0 (C), 156.3 (C), 155.1 (C), 152.5 (C), 151.4 (C), 141.7 (C), 124.3 (CH), 122.9 (C), 107.0 (CH), 72.3 (CH), 70.5 (CH), 62.1 (CH_3), 61.1 (CH_3), 56.2 (CH_3), 22.0 (CH_3), 21.6 (CH_3); **IR** (thin film) 3307, 2982, 2940, 1737, 1709, 1241, 1098, 1064 cm^{-1}; **LRMS (CI)** 195 (100, $[M–C_8H_{16}N_2O_4]^+$); **HRMS (CI)** calcd. for $C_{18}H_{27}N_3O_8$ $[M+H]^+$ 399.1767, observed 399.1758; m.p. 82-85 °C (recrystallized from *n*-heptane).

Diisopropyl 1-benzoylhydrazine-1,2-dicarboxylate[130] (172)



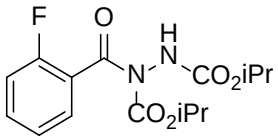
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-benzoylhydrazine-1,2-dicarboxylate as a white solid (206 mg, 0.67 mmol, 67%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.73-7.58 (m, 2H), 7.51 (t, *J* = 8.5 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 6.97 (br s, NH, 1H), 5.00 (septet, *J* = 6.1 Hz, 1H), 4.89-4.85 (m, 1H), 1.29 (d, *J* = 6.1 Hz, 6H), 1.05 (d, *J* = 6.1 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 171.4 (C), 155.4 (C), 153.0 (C), 135.3 (CH), 128.3 (CH), 128.0 (CH), 72.6 (CH), 70.8 (CH), 22.0 (CH_3), 21.4 (CH_3); **IR** (thin film) 3308, 2982, 1707, 1248, 1102 cm^{-1}; **LRMS (CI)** 309 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{15}H_{21}N_2O_5$ $[M+H]^+$ 309.1451, observed 309.1450; m.p. 118-120 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(4-fluorobenzoyl)hydrazine-1,2-dicarboxylate[130] (173)



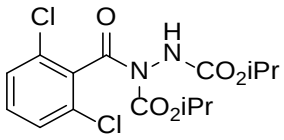
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(4-fluorobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (245 mg, 0.75 mmol, 75%). **^{1}H NMR (400 MHz, 100 °C, d_6-DMSO)** δ 9.43 (br s, NH, 1H), 7.68-7.64 (m, 2H), 7.29-7.24 (m, 2H), 4.89-4.80 (m, 2H), 1.22 (d, J = 6.2 Hz, 6H), 1.13 (d, J = 6.3 Hz, 6H); **^{13}C NMR (150 MHz, d_6-DMSO)** δ 169.3 (C), 164.9 (CH), 164.1 (d, $J_{C\text{-}F}$ = 249.0 Hz, C), 155.3 (C), 152.6 (C), 131.5 (CH), 130.6 (d, $J_{C\text{-}F}$ = 9.0 Hz, CH), 115.5 (d, $J_{C\text{-}F}$ = 9.0 Hz, CH), 71.7 (CH), 69.1 (CH), 21.8 (CH_3), 21.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -106.7 (s); **IR** (thin film) 3379, 1709, 1603, 1259, 1103 cm^{-1}; **LRMS (CI)** 327 (40, $[M+H]^+$), 307 (30), 241 (70), 227 (33), 199 (100); **HRMS (CI)** calcd. for $C_{15}H_{20}FN_2O_5$ $[M+H]^+$ 327.1356, observed 327.1355; m.p. 100-102 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(2-fluorobenzoyl)hydrazine-1,2-dicarboxylate (174)



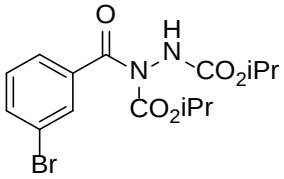
Purification by column chromatography (5-25% Et_2O/Petrol) gave as diisopropyl 1-(2-fluorobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (202 mg, 0.62 mmol, 62%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.60-7.45 (m, 2H), 7.21 (t, J = 7.6 Hz, 1H), 7.08 (t, J = 9.2 Hz, 1H), 6.82-6.59 (m, NH, 1H), 4.97 (m, 2H), 1.32-1.14 (m, 12H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 166.2 (C), 159.2 (d, $J_{C\text{-}F}$ = 249.7 Hz, C), 155.1 (C), 152.1 (C), 133.5 (d, $J_{C\text{-}F}$ = 7.4 Hz, CH), 129.9 (CH), 129.9 (C), 124.3 (d, $J_{C\text{-}F}$ = 3.3 Hz, CH), 115.5 (d, $J_{C\text{-}F}$ = 22.1 Hz, CH), 72.9 (CH), 70.9 (CH), 22.0 (CH_3), 21.5 (CH_3); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -114.1 (m, 1F); **IR** (thin film) 3308, 2983, 1710, 1709, 1231, 1099 cm^{-1}; **LRMS (CI)** 327 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{15}H_{20}FN_2O_5$ $[M+H]^+$ 327.1356, observed 327.1349; m.p. 128-130 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(2,6-dichlorobenzoyl)hydrazine-1,2-dicarboxylate (175)



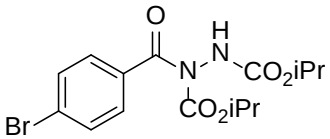
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(2,6-dichlorobenzoyl)hydrazine-1,2-dicarboxylate as a colourless oil (211 mg, 0.56 mmol, 56%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.31-7.27 (m, 3H), 6.80 (br s, NH, 1H), 5.07-5.03 (m, 1H), 4.94-4.90 (m, 1H), 1.32-1.08 (m, 12H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 164.4 (C), 154.7 (C), 151.1 (C), 136.3 (C), 130.6 (CH), 127.7 (C), 127.7 (CH), 73.0 (CH), 70.9 (CH), 22.0 (CH_3), 21.3 (CH_3); **HRMS (ESI)** calcd. for $C_{15}H_{18}C_{l2}N_2O_5$ $[M+Na]^+$ 399.0490, observed 399.0499. Spectroscopic data in accordance with the literature.[53]

Diisopropyl 1-(3-bromobenzoyl)hydrazine-1,2-dicarboxylate (176)



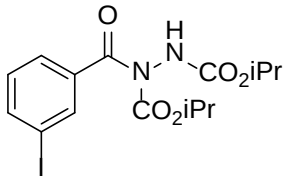
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(3-bromobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (231 mg, 0.60 mmol, 60%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.84-7.72 (m, 1H), 7.66-7.53 (m, 2H), 7.30 (t, *J* = 6.1 Hz, 1H), 6.88 (br s, NH, 1H), 5.01 (septet, *J* = 6.2 Hz, 1H), 4.96-4.87 (m, 1H), 1.29 (d, *J* = 6.2, 6H), 1.10 (d, *J* = 6.2, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 169.8 (C), 155.3 (C), 152.6 (C), 137.2 (CH), 134.9 (CH), 131.0 (CH), 129.9 (C), 126.7 (CH), 122.2 (C), 73.0 (CH), 71.0 (CH), 22.0 (CH_3), 21.5 (CH_3); **IR** (thin film) 3311, 2983, 1707, 1245, 1244, 1099 cm^{-1}; **LRMS (CI)** 389 (15, $[M^{81}Br+H]^+$), 387 (15, $[M^{79}Br+H]^+$), 185 (100, $[M^{81}Br\text{-}C_8H_{15}N_2O_4]^+$), 183 (100, $[M^{79}Br\text{-}C_8H_{15}N_2O_4]^+$); **HRMS (CI)** calcd. for $C_{15}H_{20}BrN_2O_5$ $[M^{79}Br+H]^+$ 387.0556, observed 387.0561; m.p. 139-140 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(4-bromobenzoyl)hydrazine-1,2-dicarboxylate[131] (177)



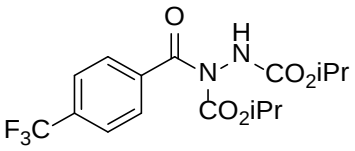
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(4-bromobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (232 mg, 0.60 mmol, 60%). **^{1}H NMR (600 MHz,$CDCl_3$)** δ 7.57-7.50 (m, 4H), 6.82 (br s, NH, 1H), 5.03 (septet, *J* = 6.2 Hz, 1H), 4.93-4.89 (m, 1H), 1.30 (d, *J* = 6.2, 6H), 1.13 (d, *J* = 6.2, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 170.5 (C), 155.4 (C), 152.8 (C), 134.1 (C), 131.6 (CH), 129.9 (CH), 126.9 (C), 72.9 (CH), 71.0 (CH), 22.0 (CH_3), 21.5 (CH_3); **IR** (thin film) 3305, 2982, 1708, 1589, 1255, 1101, 919 cm^{-1}; **LRMS (CI)** 389 (10, $[M^{81}Br+H]^+$), 387 (10, $[M^{79}Br+H]^+$), 185 (100, $[M^{81}Br\text{-}C_8H_{15}N_2O_4]^+$), 183 (100, $[M^{79}Br\text{-}C_8H_{15}N_2O_4]^+$); **HRMS (CI)** calcd. for $C_{15}H_{20}BrN_2O_5$ $[M^{79}Br+H]^+$ 387.0556, observed 387.0566; m.p. 102-105 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(3-iodobenzoyl)hydrazine-1,2-dicarboxylate (178)



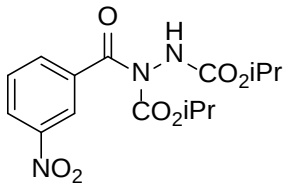
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(3-iodobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (265 mg, 0.61 mmol, 61%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.00 (s, 1H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.66-7.59 (m, 1H), 7.17 (t, *J* = 7.7 Hz, 1H), 6.83-6.58 (m, NH), 5.01 (septet, *J* = 6.2 Hz, 1H), 4.95-4.89 (m, 1H), 1.30 (d, *J* = 5.8 Hz, 6H), 1.10 (d, *J* = 5.2 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 169.6 (C), 157.1 (C), 152.6 (C), 140.8 (CH), 136.7 (CH), 130.8 (C), 129.9 (CH), 127.3 (CH), 93.5 (C), 73.0 (CH), 71.1 (CH), 22.1 (CH_3), 21.5 (CH_3); **IR** (thin film) 3317, 2981, 1709, 1250, 1101 cm^{-1}; **LRMS (CI)** 435 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{15}H_{20}IN_2O_5$ $[M+H]^+$ 435.0417, observed 435.0421; m.p. 156-159 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(4-(trifluoromethyl)benzoyl)hydrazine-1,2-dicarboxylate (179)



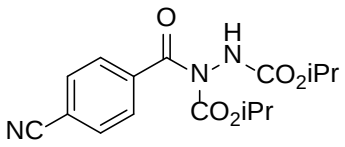
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(4-(trifluoromethyl)benzoyl)hydrazine-1,2-dicarboxylate as a white solid (229 mg, 0.61 mmol, 61%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.80-7.75 (m, 2H), 7.74-7.66 (m, 2H), 6.89-6.82 (br s, NH, 1H), 5.03-5.00 (m, 1H), 4.92-4.89 (m, 1H), 1.30 (d, *J* = 6.3, 6H), 1.09 (d, *J* = 6.2 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 170.2 (C), 155.3 (C), 152.6 (C), 138.8 (C), 133.3 (q, $J_{C\text{-}F}$ = 32.0 Hz, C), 128.3 (CH), 123.7 (q, $J_{C\text{-}F}$ = 271 Hz, C), 125.3 (CH), 73.1 (CH), 71.1 (CH), 22.0 (CH_3), 21.5 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -63.5 (s, CF_3, 3F); **IR** (thin film) 3305, 2985, 1708, 1620, 1323, 1245, 1168, 1127, 1100, 1064, 919 cm^{-1}; **LRMS (CI)** 377 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{16}H_{20}F_3N_2O_5$ $[M+H]^+$ 377.1324, observed 377.1332; m.p. 91-93 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(3-nitrobenzoyl)hydrazine-1,2-dicarboxylate (180)



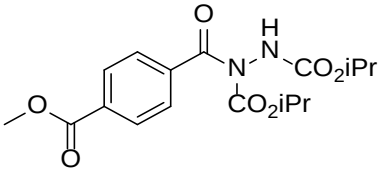
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(3-nitrobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (202 mg, 0.57 mmol, 57%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.54-8.43 (m, 1H), 8.40-8.36 (m, 1H), 8.05-7.91 (m, 1H), 7.69-7.60 (m, 1H), 6.67 (br s, NH, 1H), 5.08-4.99 (m, 1H), 4.98-4.91 (m, 1H), 1.31 (d, *J* = 5.7, 6H), 1.15 (d, *J* = 4.5, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 169.0 (C), 155.2 (C), 152.5 (C), 147.9 (C), 136.8 (C), 133.9 (CH), 129.5 (CH), 126.3 (CH), 123.2 (C), 73.3 (CH), 71.3 (CH), 22.0 (CH_3), 21.6 (CH_3); **IR** (thin film) 3310, 2984, 1715, 1534, 1350, 1258, 1102 cm^{-1}; **LRMS (CI)** 354 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{15}H_{20}N_3O_7$ $[M+H]^+$ 354.1301, observed 354.1319; m.p. 114-116 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(4-cyanobenzoyl)hydrazine-1,2-dicarboxylate (181)



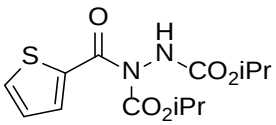
Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(4-cyanobenzoyl)hydrazine-1,2-dicarboxylate as a white solid (213 mg, 0.64 mmol, 64%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.79-7.71 (m, 4H), 6.86-6.62 (m, NH, 1H), 5.00-4.95 (m, 2H), 1.30-1.12 (m, 12H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 169.7 (C), 155.2 (C), 152.4 (C), 139.5 (C), 132.9 (CH), 132.1 (CH), 128.4 (CH), 126.3 (CH), 118.1 (C), 115.2 (C), 73.3 (CH), 71.3 (CH), 22.0 (CH_3), 21.5 (CH_3); **IR** (thin film) 3307, 2984, 2232, 1707, 1232, 1099, 850 cm^{-1}; **LRMS (CI)** 334 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{16}H_{20}N_3O_5$ $[M+H]^+$ 334.1403, observed 334.1402; m.p. 82-86 °C (recrystallized from *n*-heptane).

Diisopropyl 1-(4-(methoxycarbonyl)benzoyl)hydrazine-1,2-dicarboxylate (182)



Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(4-(methoxycarbonyl)benzoyl)hydrazine-1,2-dicarboxylate as a colourless oil (165 mg, 0.45 mmol, 45%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.09 (d, *J* = 8.0 Hz, 2H), 7.74 (d, *J* = 6.9 Hz, 2H), 6.85 (br s, NH, 1H), 5.04-4.99 (m, 1H), 4.90-4.88 (m, 1H), 3.94 (s, 3H), 1.30 (d, *J* = 5.7 Hz, 6H), 1.08-1.07 (m, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 170.6 (C), 166.3 (C), 155.3 (C), 152.6 (C), 139.5 (C), 132.8 (C), 129.51 (CH), 127.9 (CH), 73.0 (CH), 71.1 (CH), 52.6 (CH_3), 22.0 (CH_3), 21.5 (CH_3); **IR** (thin film) 3343, 3311, 2983, 1726, 1265, 1049 cm^{-1}; **LRMS (CI)** 367 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{17}H_{23}N_2O_7$ $[M+H]^+$ 367.1505, observed 367.1509.

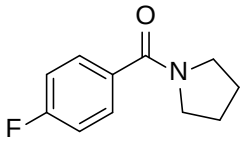
Diisopropyl 1-(thiophene-2-carbonyl)hydrazine-1,2-dicarboxylate (183)



Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(thiophene-2-carbonyl)hydrazine-1,2-dicarboxylate as pink oil (107 mg, 0.34 mmol, 34%). **^{1}H NMR (600 MHz, DMSO-d_6)** δ 10.14 (s, NH, 1H), 7.98 (dd, *J* = 5.0, 1.2 Hz, 1H), 7.82 (dd, *J* = 3.8, 1.3 Hz, 1H), 7.20 (dd, *J* = 4.8, 4.0 Hz, 1H), 4.92 (septet, *J* = 6.2 Hz, 1H), 4.85 (septet, *J* = 6.1 Hz, 1H), 1.24-1.20 (m, 12H); **^{13}C NMR (150 MHz, DMSO-d_6)** δ 162.1 (C), 155.6 (C), 154.7 (C), 152.1 (C), 135.2 (CH), 135.0 (CH), 127.7 (CH), 71.8 (CH), 69.4 (CH), 21.9 (CH_3), 21.4 (CH_3); **IR** (thin film) 3311, 2982, 1712, 1236, 1106, 1046 cm^{-1}; **LRMS (CI)** 315 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{13}H_{19}N_2O_5S$ $[M+H]^+$ 315.1015, observed 315.1007.

Experimental for Chapter 3

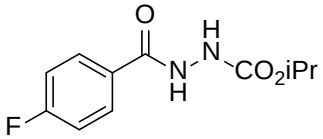
(4-Fluorophenyl)(pyrrolidin-1-yl)methanone[132] (188a)



Pyrrolidine (2.5 mmol, 5.0 eq) was added to a solution of diisopropyl 1-(4-fluorobenzoyl)hydrazine-1,2-dicarboxylate (0.5 mmol, 1.0 eq) and $TiCl_4$ in dichloromethane (0.5 mmol, 1.0 eq) in Me-THF (3 mL). After 16 h, the reaction was quenched with a solution of saturated NH_4Cl (3 mL), extracted with ether (3 x 20 mL), organic layers combined, dried ($MgSO_4$), filtered, and the solvent removed in *vacuo*. Purification of the resulting residue by column chromatography (50%-80% Et_2O/Petrol) gave (4-fluorophenyl)(pyrrolidin-1-yl)methanone as a white solid (145 mg, 0.75 mmol, 75%). **^{1}H NMR (500 MHz, d_6-DMSO)** δ 7.61-7.58 (m, 2H), 7.27-7.24 (m, 4H), 3.46 (t, *J* = 6.9 Hz, 2H), 3.39 (t, *J* = 6.5 Hz, 2H), 1.90-1.79 (m, 4H); **^{13}C NMR (125 MHz, d_6-DMSO)** δ 167.2 (C), 162.6 (d, $J_{C\text{-}F}$ = 246.7 Hz, C), 133.6 (d, $J_{C\text{-}F}$ = 3.2 Hz, CH), 129.6 (d, $J_{C\text{-}F}$ = 8.6 Hz, CH), 115.1 (d, $J_{C\text{-}F}$ = 21.6 Hz, C),

48.9 (CH_2), 45.9 (CH_2), 26.0 (CH_2), 23.9 (CH_2); **^{19}F NMR (470 MHz, DMSO-d_6)** δ -111.03 (1F); m.p. 87-89 °C (recrystallized from *n*-heptane).

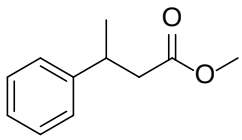
Isopropyl 2-(4-fluorobenzoyl)hydrazine-1-carboxylate (189)



Purification by column chromatography (5-25% Et_2O/Petrol) gave isopropyl 2-(4-fluorobenzoyl)hydrazine-1-carboxylate as colourless oil. **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.84-7.81 (m, 2H), 7.13-7.09 (m, 2H), 5.00 (septet, J = 6.3 Hz, 1H), 1.30-1.26 (m, 6H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 165.0 (C), 164.2 (d, J_{C-F} = 247.0 Hz, C), 156.0 (C), 133.0 (d, J_{C-F} = 23.0 Hz, CH), 130.1 (d, J_{C-F} = 9.0 Hz, C), 115.5 (d, J_{C-F} = 21.8 Hz, CH), 68.0 (CH), 21.9 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -108.3 (s, 1F); **IR** (thin film) 3379, 1709, 1603, 1259, 1103 cm^{-1}; **HRMS (CI)** calcd. For $C_{11}H_{13}FN_2O_3$ $[M+Na]^+$ 263.0819, observed 263.0816; m.p. 189-191 °C (recrystallized from *n*-heptane).

Experimental for Chapter 4

Methyl 3-phenylbutanoate (190)



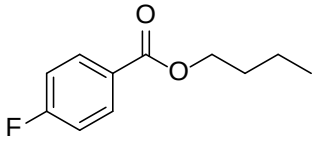
To a stirring solution of hydrazide (50 mg, 0.14 mmol, 1.0 eq) in methanol (58 µL, 14.3 mmol, 100 eq) was added tert-butylamine (20 µL, 0.14 mmol, 1.0 eq). The reaction was stirred at room temperature overnight and the solvent was then removed in *vacuo*. Purification by column chromatography (Eluent: 1% EtOAc: Petroleum Ether) yielded **190** as a clear oil (24.2 mg, 95%). **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 (m, 5H), 3.64 (s, CH_3, 3H), 3.33 (sxt., J = 7.0Hz, CH, 1H), 2.68 (dd, J = 6.88, 15.12Hz, CH_2 1H), 2.58 (dd, J = 15.16, 8.24Hz, CH_2, 1H), 1.33 (d, J = 7.0Hz, CH_3, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 173.0 (C), 145.8 (C), 128.6 (CH), 126.8 (CH), 126.5 (CH), 51.7 (CH), 42.8 (CH_2), 36.5 (CH_3), 21.9 (CH_3). **HRMS**

(CI) calcd for $C_{11}H_{14}O_2$ $[M+H]^+$ 178.09883, observed 178.09902. Spectroscopic data in accordance with the literature.[133]

General procedure for ester synthesis

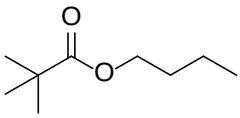
Appropriate hydrazide was added to a stirring solution of Cs_2CO_3 (163 mg, 0.5 mmol, 1.0 eq) and *n*-butanol in dimethylformamide (0.5 mL). After 15 h, the reaction mixture was diluted with diethyl ether (20 mL) and extracted with saturated solution of LiCl (3 x 20 mL). The organic layer was then extracted with brine, dried ($MgSO_4$), filtered under vacuum and the solvent was removed in *vacuo*. The resultant crude residue was purified as described below.

***n*-Butyl 4-fluorobenzoate (192)**



Purification by column chromatography (1-5% EtOAc/Petrol) yielded *n*-butyl 4-fluorobenzoate as a clear oil (85 mg, 0.44 mmol, 87%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.07-8.04 (m, 2H), 7.12-7.08 (m, 2H), 4.32 (t, J = 6.6 Hz, 2H), 1.75 (quintet., J = 7.1 Hz, 2H), 1.47 (sxt., J = 7.5 Hz, 2H), 0.98 (t, J = 7.3 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 165.9 (C), 165.8 (d, J_{C-F} = 210.1 Hz, C), 132.2 (d, J_{C-F} = 7.7 Hz, CH), 126.8 (d, J_{C-F} = 4.4 Hz, C), 115.5 (d, J_{C-F} = 18.2 Hz, CH), 65.1 (CH_2), 30.9 (CH_2), 19.4 (CH_2), 13.9 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -106.5 (s, 1F); **IR** (thin film) 2960, 2875, 1726, 1601, 1509, 608, 502 cm^{-1}. Spectroscopic data in accordance with the literature.[134]

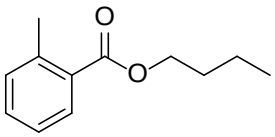
***n*-Butyl pivalate (194c)**



Purification by column chromatography (1-5% EtOAc/Petrol) yielded *n*-butyl pivalate as a clear oil (49 mg, 0.31 mmol, 62%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 4.00 (t, J = 6.6 Hz, 2H), 1.59-1.54 (m, 2H), 1.37-1.31 (m, 2H), 1.15 (s, 9H), 0.91-0.87 (m, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 178.8 (C), 64.3 (CH_2), 38.8 (CH), 30.8 (CH_2),

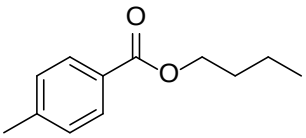
27.3 (CH_2), 19.2 (CH_3), 13.8 (CH_3). Spectroscopic data in accordance with the literature.[135]

***n*-Butyl 2-methylbenzoate (194d)**



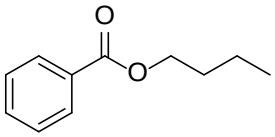
Purification by column chromatography (1-5% EtOAc/Petrol) yielded *n*-butyl 2-methylbenzoate as a clear oil (25 mg, 0.13 mmol, 26%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.91-7.90 (m, 1H), 7.39 (dt, *J* = 7.5 Hz, *J* = 1.3 Hz, 1H), 7.26-7.23 (m, 2H), 4.30 (t, *J* = 6.6 Hz, 2H), 2.60 (s, 3H), 1.75 (m, 2H), 1.47 (sxt., *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 167.8 (C), 140.0 (C), 131.8 (CH), 131.7 (CH), 130.5 (CH), 130.0 (C), 125.7 (CH), 64.6 (CH_2), 30.8 (CH_2), 21.8 (CH_3), 19.4 (CH_2), 13.8 (CH_3); **IR** (thin film) 2980, 1726, 1261, 836 cm^{-1}. Spectroscopic data in accordance with the literature.[136]

***n*-Butyl 4-methylbenzoate (194e)**



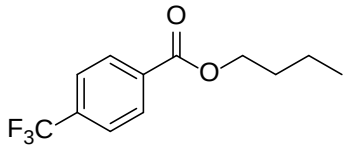
Purification by column chromatography (1-5% EtOAc/Petrol) yielded *n*-butyl benzoate as a clear oil (82 mg, 0.43 mmol, 85%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 7.93 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 4.30 (t, *J* = 6.5 Hz, 2H), 2.41 (s, 3H), 1.75 (m, 2H), 1.47 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.8 (C), 143.4 (C), 129.6 (CH), 129.0 (CH), 127.8 (C), 64.7 (CH_2), 30.8 (CH_2), 21.7 (CH_3), 19.3 (CH_2), 13.8 (CH_3); **IR** (thin film) 2980, 1769, 1261, 835 cm^{-1}. Spectroscopic data in accordance with the literature.[137]

***n*-Butyl benzoate (194g)**



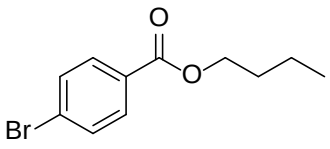
Purification by column chromatography (1-5% EtOAc/Petrol) yielded *n*-butyl benzoate as a clear oil (70 mg, 0.39 mmol, 78%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.06-8.04 (m, 2H), 7.57-7.54 (m, 1H), 7.45-7.42 (m, 2H), 4.33 (t, *J* = 6.6 Hz, 2H), 1.76 (m, 2H), 1.48 (sxt., *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 166.7 (C), 132.8 (CH), 130.6 (C), 129.6 (CH), 128.3 (CH), 64.9 (CH_2), 30.8 (CH_2), 19.3 (CH_2), 13.8 (CH_3); **IR** (thin film) 2961, 1725, 1270, 705 cm^{-1}. Spectroscopic data in accordance with the literature.[138]

***n*-Butyl 4-(trifluoromethyl)benzoate (194h)**



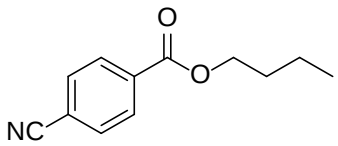
Purification by column chromatography (1-5% EtOAc/Petrol) yielded *n*-butyl 4-(trifluoromethyl)benzoate as a clear oil (97 mg, 0.40 mmol, 79%). **^{1}H NMR (500 MHz, $CDCl_3$)** δ 8.15 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 4.36 (t, *J* = 6.7 Hz, 2H), 1.77 (m, 2H), 1.48 (sxt., *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (125 MHz, $CDCl_3$)** δ 165.5 (C), 134.3 (d, J_{C-F} = 32.4 Hz, C), 133.7 (d, J_{C-F} = 1.3 Hz, C), 129.9 (CH), 125.4 (q, J_{C-F} = 4.0 Hz, CH), 123.5 (d, J_{C-F} = 271.1 Hz, C), 65.4 (CH_2), 30.7 (CH_2), 19.3 (CH_2), 13.8 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -64.1 (s, 1F); **IR** (thin film) 2980, 1752, 1261, 830 cm^{-1}. Spectroscopic data in accordance with the literature.[134]

***n*-Butyl 4-bromobenzoate (194j)**



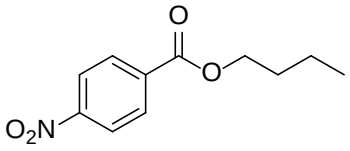
Purification by column chromatography (1-5% EtOAc/Petrol) yielded *n*-butyl 4-(trifluoromethyl)benzoate as a clear oil (109 mg, 0.43 mmol, 85%).**^{1}H NMR (500 MHz, 300 K, $CDCl_3$)** 7.91-7.89 (m, 2H), 7.59-7.57 (m, 2H), 4.34 (t, *J* = 6.6 Hz, 2H), 1.78-1.72 (m, 2H), 1.47 (sxt., *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.5 Hz, 3H); ; **^{13}C NMR (125 MHz, 300 K, $CDCl_3$)** 166.0 (C), 131.7 (CH), 131.1 (CH), 129.4 (C), 127.9 (C), 65.2 (CH_2), 30.7 (CH_2), 19.3 (CH_2), 13.8 (CH_3); **IR (thin film)** 2960, 2873, 1720, 1590, 1485, 1397 cm^{-1}. Spectroscopic data in accordance with the literature.[139]

***n*-Butyl 4-cyanobenzoate (194k)**



Purification by column chromatography (1-5% EtOAc/Petrol) yielded *n*-Butyl 4-cyanobenzoate as a clear oil (78 mg, 0.39 mmol, 77%).**^{1}H NMR (500 MHz, $CDCl_3$)** 8.14 (d, *J* = 8.6 Hz, 2H), 7.74 (d, *J* = 8.7 Hz, 2H), 4.36 (t, *J* = 6.7 Hz, 2H), 1.80-1.74 (m, 2H), 1.48 (sxt., *J* = 7.5 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (125 MHz, 300 K, $CDCl_3$)** 165.0 (C), 134.4 (C), 132.2 (CH), 130.1 (CH), 118.1 (C), 116.3 (C), 65.7 (CH_2), 30.7 (CH_2), 19.3 (CH_2), 13.8 (CH_3); **IR (thin film)** 2961, 2870, 2234,1710, 1462, 1408, 1020, 860, 768, 738, 692 cm^{-1}. Spectroscopic data in accordance with the literature.[139]

***n*-Butyl 4-nitrobenzoate (194l)**



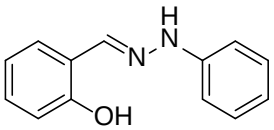
Purification by column chromatography (1-5% EtOAc/Petrol) yielded *n*-Butyl 4-cyanobenzoate as a clear oil (89 mg, 0.40 mmol, 80%). **^{1}H NMR (500 MHz, 300 K, $CDCl_3$)** 8.87-8.86 (m, 1H), 8.43-8.41 (m, 1H), 8.35-8.33 (m, 1H), 7.67-7.64 (m, 1H), 4.39 (t, *J* = 6.7 Hz, 2H), 1.82-1.76 (m, 2H), 1.49 (sxt., *J* = 7.5 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR (125 MHz, 300 K, $CDCl_3$)** 164.6 (C), 148.3 (C), 135.3 (CH), 132.3 (CH), 129.6 (CH), 127.3 (CH), 124.6 (CH), 65.8 (CH_2), 30.7 (CH_2), 19.2 (CH_2), 13.8 (CH_3); **IR (thin film)** 2959, 2878, 1723, 1601, 1355, 1279 cm^{-1}. Spectroscopic data in accordance with the literature.[139]

Experimental for Chapter 5

General method for the titration of Grignard reagents

Grignard reagents were titrated against salicylaldehydephenylhydrazone. An accurately weighed sample of salicylaldehydephenylhydrazone was dissolved in dry THF (10 mL) and stirred at room temperature under an inert nitrogen atmosphere. Grignard reagent was carefully added, drop wise using a gas tight syringe. A yellow color (mono anion) formed initially, the end point was apparent from the intense orange color change. Experiments were performed in triplicate.

Salicylaldehydephenylhydrazone[140]



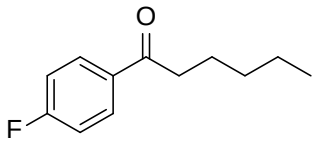
Phenylhydrazine (2.92 g, 27.0 mmol, 1 eq) was dissolved in 95% ethanol (10 mL) and stirred while salicylaldehyde (3.30 g, 27.0 mmol, 1 eq) in 95% ethanol (15 mL) was added in one portion. A white precipitate formed after 1 min. The reaction was stirred for 30 min and then cooled to –15 °C. The greenish solid was collected by vacuum filtration and washed with ice-cold ethanol to afford the product as a light

green solid (4.60 g, 21.7 mmol, 80%). **^{1}H NMR (600 MHz, d_6-DMSO)** δ 10.52 (s, 1H), 10.41 (s, 1H), 8.14 (s, 1H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.24 (t, *J* = 7.8 Hz, 2H), 7.18-7.16 (m, 1H), 6.97 (d, *J* = 7.9 Hz, 2H), 6.88-6.75 (m, 2H), 6.76 (t, *J* = 7.3 Hz, 1H); **^{13}C NMR (150 MHz, d_6-DMSO)** δ 155.6 (C), 144.8 (C), 137.1 (CH), 129.3 (CH), 129.2 (CH), 127.2 (CH), 120.5 (C), 119.4 (CH), 119.0 (CH), 115.9 (CH), 111.7 (CH); m.p. 139-141 °C.

Grignard reaction of diisopropyl 1-(4-fluorobenzoyl)hydrazine-1,2-dicarboxylate 173 under standard Weinreb conditions[100]

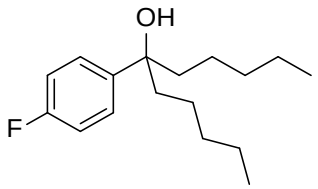
To a flame-dried three-necked flask, under an inert atmosphere, was added a solution of acyl hydrazide (0.5 mmol) in THF (10 mL). *n*-Pentylmagnesium bromide (0.6 mmol) was then added to the stirring solution in one portion at –10 °C. After 30 min, the reaction was quenched with pre-cooled (*ca.* 4 °C) saturated ammonium chloride solution (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers combined, dried ($MgSO_4$), filtered under vacuum and the solvent was removed in *vacuo*. The resultant crude residue was purified as described below to isolate **196**, **197** and **198**.

1-(4-Fluorophenyl)hexan-1-one[141] **(196)**



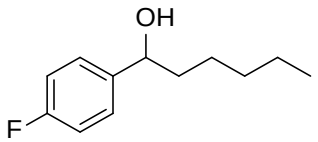
Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(4-fluorophenyl)hexan-1-one as a white solid (76 mg, 0.39 mmol, 78%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.98-7.95 (m, 2H), 7.11-7.08 (m, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.74-1.69 (m, 2H), 1.35-1.32 (m, 4H), 0.91-0.88 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.0 (C), 165.7 (d, $J_{C\text{-}F}$ = 252.7 Hz, CF), 133.6 (d, $J_{C\text{-}F}$ = 3.0 Hz, CH), 130.7 (d, $J_{C\text{-}F}$ = 9.5 Hz, CH), 115.7 (d, $J_{C\text{-}F}$ = 21.7 Hz, C), 38.6 (CH_2), 31.6 (CH_2), 24.1 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -106.2 (s, 1F); **IR** (thin film) 1675, 1507, 1452, 1017 cm^{-1}; **LRMS (EI)** 194 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{12}H_{15}FO$ $[M]^+$ 194.1107, observed 194.1110; m.p. 41-43 °C (recrystallized from *n*-heptane).

6-(4-Fluorophenyl)undecan-6-ol (197)



Purification by column chromatography (1-15% Et_2O/Petrol) of the crude residue in the reaction for the formation of 1-(4-fluorophenyl)hexan-1-one also gave 6-(4-fluorophenyl)undecan-6-ol as a clear oil. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.36-7.33 (m, 2H), 7.05-7.00 (m, 2H), 1.84-1.72 (m, 4H), 1.66-1.56 (m, 2H), 1.32-1.18 (m, 8H), 1.08-1.00 (m, 2H), 0.87-0.83 (m, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 161.5 (d, J_{C-F}= 242.7 Hz, CF), 142.2 (d, J_{C-F} = 2.8 Hz, C), 127.0 (d, J_{C-F} = 7.8 Hz, CH), 114.8 (d, J_{C-F} = 20.8 Hz, CH), 43.1 (CH_2), 32.3 (CH_2), 23.2 (CH_2), 22.7 (CH_2), 14.2 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -117.9 (s, 1F); **IR** (thin film) 3356, 2960, 1600, 1510, 1445, 1369, 1091, 1044, 975 cm^{-1}; **LRMS (CI)** 289 (100, $[M+Na]^+$); **HRMS (CI)** calcd. for $C_{17}H_{28}FO$ $[M+H]^+$ 267.2046, observed 267.2051.

1-(4-Fluorophenyl)hexan-1-ol (198)

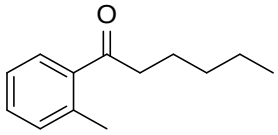


Purification by column chromatography (1-15% Et_2O/Petrol) of the crude residue in the reaction for the formation of 1-(4-fluorophenyl)hexan-1-one also gave 1-(4-fluorophenyl)hexan-1-ol as a colourless oil. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.32-7.26 (m, 2H), 7.04-7.01 (m, 2H), 4.65 (t, J = 6.7 Hz, 1H), 1.80-1.74 (m, 2H), 1.69-1.63 (m, 1H), 1.41-1.36 (m, 1H), 1.30-1.21 (m, 4H), 0.88-0.85 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 163.0 (d, J_{C-F} = 243.6 Hz, CF), 140.7 (d, J_{C-F} = 3.0 Hz, C), 127.7 (d, J_{C-F} = 8.0 Hz, CH), 115.4 (d, J_{C-F} = 21.2 Hz, CH), 74.2 (CH), 39.3 (CH_2), 31.8 (CH_2), 25.6 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -115.7 (s, 1F); **IR** (thin film) 3356, 2960, 1600, 1510, 1445, 1369, 1210, 1150, 1091, 1044, 975 cm^{-1}; **LRMS (CI)** 219 (100, $[M+Na]^+$); **HRMS (CI)** calcd. for $C_{12}H_{18}FO$ $[M+H]^+$ 197.1342, observed 197.1346. Spectroscopic data in accordance with the literature.[142]

General procedure for alkyl aryl ketone synthesis

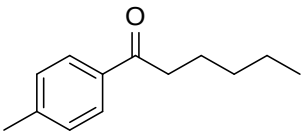
To a flame-dried three-necked flask, under an inert atmosphere, was added a solution of acyl hydrazide (0.5 mmol) in THF (10 mL). *n*-Pentylmagnesium bromide (1.25 mmol) was then added to the stirring solution in one portion at –78 °C. After 30 min, the reaction was quenched with pre-cooled (*ca.* 4 °C) saturated ammonium chloride solution (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers combined, dried ($MgSO_4$), filtered under vacuum and the solvent was removed in *vacuo.* The resultant crude residue was purified as described below.

1-(*o*-Tolyl)hexan-1-one (195a)



Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(*o*-tolyl)hexan-1-one as a colourless oil (42 mg, 0.22 mmol, 44%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.61 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.25 (m, 2H), 2.88 (t, *J* = 7.4 Hz, 2H), 1.72-1.67 (m, 2H), 2.48 (s, 3H), 1.33-1.32 (m, 4H), 0.93-0.88 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 205.2 (C), 138.5 (C), 137.9 (C), 132.0 (CH), 131.1 (CH), 128.4 (CH), 125.7 (CH), 41.8 (CH_2), 31.6 (CH_2), 24.2 (CH_2), 22.7 (CH_2), 21.3 (CH_3), 14.1 (CH_3); **IR** (thin film) 2956, 2926, 2857, 1656, 1455, cm^{-1}; **LRMS (CI)** 191 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{13}H_{19}O$ $[M+H]^+$ 191.1430, observed 191.1429. Spectroscopic data in accordance with the literature.[143]

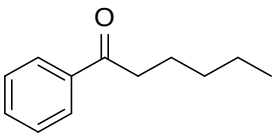
1-(*p*-Tolyl)hexan-1-one (195b)



Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(*p*-tolyl)hexan-1-one as a colourless oil (65 mg, 0.34 mmol, 68%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.85 (d, *J* = 7.9 Hz, 2H), 7.23 (d, *J* = 7.9 Hz, 2H), 2.92 (t, *J* = 7.4 Hz, 2H), 2.40 (s, 3H), 1.72-1.69 (m, 2H), 1.37-1.34 (m, 4H), 0.92-0.89 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 200.4 (C), 143.7 (C), 137.7 (C), 129.3 (CH), 128.3 (CH), 38.6 (CH_2), 31.7

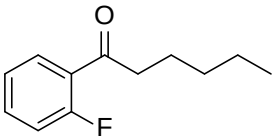
(CH_2), 24.3 (CH_2), 22.7 (CH_2), 21.7 (CH_3), 14.1 (CH_3); **IR** (thin film) 2984, 1665, 1017, 830 cm^{-1}; **LRMS (EI)** 190 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{13}H_{18}O$ $[M]^+$ 190.1358, observed 190.1364. Spectroscopic data in accordance with the literature.[141]

1-Phenylhexan-1-one (195d)



Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-phenylhexan-1-one as clear oil (63 mg, 0.36 mmol, 71%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.98-7.94 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 1.75-1.72 (m, 2H), 1.38-1.34 (m, 4H), 0.93-0.89 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 200.8 (C), 137.2 (C), 133.0 (CH), 128.7 (CH), 128.2 (CH), 38.7 (CH_2), 31.7 (CH_2), 24.2 (CH_2), 22.7 (CH_2), 14.1 (CH_3); **IR** (thin film) 1737, 1657, 1415, 984 cm^{-1}; **LRMS (EI)** 176 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{12}H_{16}O$ $[M]^+$ 176.1201, observed 176.1211. Spectroscopic data in accordance with the literature.[144]

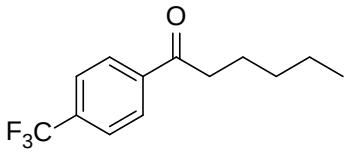
1-(2-Fluorophenyl)hexan-1-one (195e)



Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(2-fluorophenyl)hexan-1-one as a colourless oil (35 mg, 0.18 mmol, 36%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.84 (dt, *J* = 7.6 Hz, J_{H-F} = 1.6 Hz, 1H), 7.52-7.48 (m, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.14-7.11 (m, 1H), 2.97 (dt, *J* = 7.4 Hz, J_{H-F} = 2.9 Hz, 2H), 1.74-1.69 (m, 2H), 1.36-1.33 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.3 (d, J_{C-F} = 4.2 Hz, C), 162.4 (d, J_{C-F} = 252.6 Hz, CF), 134.4 (d, J_{C-F} = 9.0 Hz, CH), 130.7 (d, J_{C-F} = 2.7 Hz, CH), 126.0 (d, J_{C-F} = 13.2 Hz, C), 124.5 (d, J_{C-F} = 3.4 Hz, CH), 116.7 (d, J_{C-F} = 23.8 Hz, CH), 43.7 (d, J_{C-F} = 6.9 Hz, CH_2), 31.6 (CH_2), 23.8 (d, J_{C-F} = 1.7 Hz, CH_2), 22.6 (CH_2), 14.1 (CH_3); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -109.7 (s, 1F); **IR** (thin film) 2934, 1675, 1507, 1452, 1017 cm^{-1}; **LRMS**

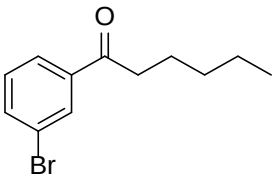
(EI) 194 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{12}H_{15}FO$ $[M]^+$ 194.1107, observed 194.1110. Spectroscopic data in accordance with the literature.[145]

1-(4-(Trifluoromethyl)phenyl)hexan-1-one (195f)



Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(4-(trifluoromethyl)phenyl)hexan-1-one as a white solid (94 mg, 0.39 mmol, 77%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.05 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 2.98 (t, *J* = 7.4 Hz, 2H), 1.77-1.72 (m, 2H), 1.36-1.35 (m, 4H), 0.92-0.90 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.7 (C), 139.8 (C), 134.2 (q, J_{C-F} = 129.7 Hz, C), 128.5 (q, J_{C-F} = 167.7 Hz, CH), 123.7 (q, J_{C-F} = 271.4 Hz, CF_3), 125.8 (q, J_{C-F} = 3.7 Hz, CH), 39.0 (CH_2), 31.5 (CH_2), 23.9 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -104.4 (m, 3F); **IR** (thin film) 2985, 1682, 1410, 1329, 1167, 1130, 1069, 1014, 831 cm^{-1}; **LRMS (EI)** 244 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{13}H_{15}F_3O$ $[M]^+$ 244.1075, observed 244.1070; m.p. 31-35 °C (recrystallized from petroleum ether). Spectroscopic data in accordance with the literature.[146]

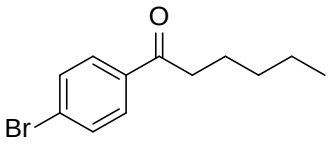
1-(3-Bromophenyl)hexan-1-one (195h)



Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(3-bromophenyl)hexan-1-one as a colourless oil (92 mg, 0.36 mmol, 72%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.07 (t, *J* = 1.7 Hz, 1H), 7.88-7.85 (m, 1H), 7.68-7.65 (m, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 2.92 (t, *J* = 7.4 Hz, 2H), 1.73-1.70 (m, 2H), 1.36-1.32 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.2 (C), 138.9 (C), 135.8 (CH), 131.2 (CH), 130.3 (CH), 126.7 (CH), 123.1 (C), 38.8 (CH_2), 31.6 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **IR** (thin film) 2952, 1676, 1586, 819 cm^{-1}; **LRMS (CI)** 256 (100, $[M^{81}Br]^+$), 254 (100, $[M\ ^{79}Br]^+$); **HRMS (CI)** calcd. for

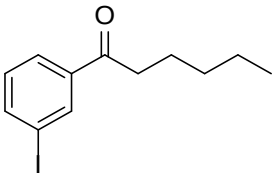
$C_{12}H_{15}BrO$ $[M^{79}Br]^+$ 254.0306, observed 254.0301. Spectroscopic data in accordance with the literature.[141]

1-(4-Bromophenyl)hexan-1-one (195i)



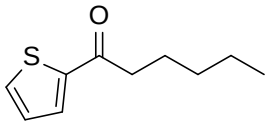
Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(4-bromophenyl)hexan-1-one as a colourless oil (102 mg, 0.40 mmol, 79%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.81-7.79 (m, 2H), 7.57 (d, *J* = 9.0 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.72-1.68 (m, 2H), 1.36-1.32 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.6 (C), 135.9 (C), 132.0 (CH), 129.7 (CH), 128.1 (C), 38.7 (CH_2), 31.6 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **IR** (thin film) 2964, 1676, 1585, 1401, 1201, 819 cm^{-1}; **LRMS (EI)** 256 (100, $[M^{81}Br]^+$), 254 (100, $[M^{79}Br]^+$); **HRMS (EI)** calcd. for $C_{12}H_{15}BrO$ $[M^{79}Br]^+$ 254.0306, observed 254.0304. Spectroscopic data in accordance with the literature.[147]

1-(3-Iodophenyl)hexan-1-one (195j)



Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(3-iodophenyl)hexan-1-one as a colourless oil (115 mg, 0.38 mmol, 76%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.26 (t, *J* = 1.6 Hz, 1H), 7.89-7.85 (m, 2H), 7.19 (t, *J* = 7.8 Hz, 1H), 2.91 (t, *J* = 7.4 Hz, 2H), 1.72-1.69 (m, 2H), 1.36-1.32 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 199.2 (C), 141.7 (CH), 138.9 (C), 137.2 (CH), 130.4 (CH), 127.3 (CH), 94.5 (C), 38.7 (CH_2), 31.6 (CH_2), 24.0 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **IR** (thin film) 2912, 1670, 1590, 1201, 901 cm^{-1}; **LRMS (EI)** 302 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{12}H_{15}IO$ $[M]^+$ 302.0168, observed 302.0163.

1-(Thiophen-2-yl)hexan-1-one 5 (195m)

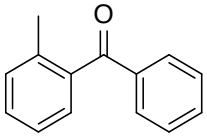


Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(thiophen-2-yl)hexan-1-one as a colourless oil (0.67 mg, 0.37 mmol, 74%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.71 (d, *J* = 3.7 Hz, 1H), 7.62 (d, *J* = 4.9 Hz, 1H), 7.12 (t, *J* = 4.3 Hz, 1H), 2.89 (t, *J* = 7.5 Hz, 2H), 1.76-1.72 (m, 2H), 1.37-1.33 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 193.9 (C), 144.6 (C), 133.5 (CH), 131.9 (CH), 128.2 (CH), 39.5 (CH_2), 31.6 (CH_2), 24.6 (CH_2), 22.6 (CH_2), 14.1 (CH_3); **IR** (thin film) 2955, 2927, 2858, 1658, 1518, 1459, 1237, 1058 cm^{-1}. Spectroscopic data in accordance with the literature.[148]

General procedure for diaryl ketone synthesis

To a flame-dried, three necked flask, under an inert atmosphere, was added a solution of acyl hydrazide (0.5 mmol) in THF (10 mL). Phenylmagnesium bromide (1.25 mmol) was then added to the stirring solution in one portion at –78 °C. After 30 min, the reaction was warmed to 0 °C over 30 min. After this time, the reactions was quenched with pre-cooled (*ca.* 4 °C) saturated ammonium chloride solution (10 mL). The aqueous layer was washed with diethyl ether (3 x 10 mL), the organic layers combined, dried ($MgSO_4$), filtered under vacuum and solvent removed in *vacuo.* The crude residue was purified as described below.

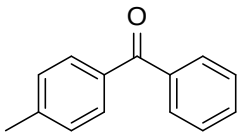
Phenyl(o-tolyl)methanone (199a)



Purification by column chromatography (1-5% Et_2O/Petrol) gave phenyl(*o*-tolyl)methanone as a clear oil (72 mg, 0.37 mmol, 73%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.82-7.79 (m, 2H), 7.61-7.57 (m, 1H), 7.47-7.44 (m, 2H), 7.42-7.38 (m, 1H), 7.32-7.28 (m, 2H), 7.27-7.24 (m, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 198.8 (C), 138.7 (C), 137.8 (C), 136.9 (C), 133.3 (CH), 131.1 (CH), 130.4 (CH), 128.6 (CH), 128.6 (CH), 128.4 (CH), 125.3 (CH), 20.1 (CH_3); **IR** (thin film) 1654, 1603,

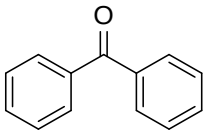
1339, 1262, 937, 729 cm^{-1}; **LRMS (EI)** 196 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{14}H_{12}O$ $[M]^+$ 196.0888, observed 196.0883. Spectroscopic data in accordance with the literature.[149]

Phenyl(p-tolyl)methanone (199b)



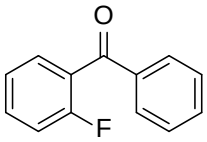
Purification by column chromatography (1-5% Et_2O/Petrol) gave phenyl(*p*-tolyl)methanone as a clear oil (69 mg, 0.35 mmol, 70%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.79-7.76 (m, 2H), 7.72 (d, *J* = 8.1 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 2.44 (s, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 196.6 (C), 143.4 (C), 138.1 (C), 135.0 (C), 132.3 (CH), 130.4 (CH), 130.0 (CH), 129.1 (CH), 128.3 (CH), 21.8 (CH_3); **IR** (thin film) 1654, 1604, 1275, 698 cm^{-1}; **LRMS (EI)** 196 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{14}H_{12}O$ $[M]^+$ 196.0888, observed 196.0883. Spectroscopic data in accordance with the literature.[150]

Benzophenone (199d)



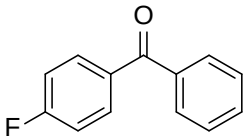
Purification by column chromatography (1-5% Et_2O/Petrol) gave benzophenone as a clear oil (67 mg, 0.37 mmol, 73%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.82-7.80 (m, 4H), 7.60-7.57 (m, 2H), 7.49-7.47 (m, 4H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 196.9 (C), 137.69 (C), 132.6 (CH), 130.2 (CH), 128.4 (CH); **IR** (thin film) 1656, 1577, 1317, 1275, 701 cm^{-1}; **LRMS (EI)** 182 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{13}H_{10}O$ $[M]^+$ 182.0732, observed 182.0727. Spectroscopic data in accordance with the literature.[151]

(2-Fluorophenyl)(phenyl)methanone (199e)



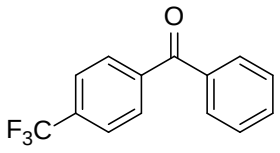
Purification by column chromatography (1-5% Et_2O/Petrol) gave (2-fluorophenyl)(phenyl)methanone as a colourless oil (74 mg, 0.37 mmol, 74%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.85-7.82 (m, 2H), 7.61 (dt, J = 7.4 Hz, J_{H-F} = 1.0 Hz, 1H), 7.57-7.52 (m, 2H), 7.49-7.46 (m, 2H), 7.27 (dt, J = 7.5 Hz, J_{H-F} = 1.0 Hz, 1H), 7.17 (t, J = 9.0 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 193.6 (C), 160.2 (d, J_{C-F} = 250.8 Hz, C), 137.5 (C), 133.6 (CH), 133.2 (d, J_{C-F} = 8.2 Hz, CH), 130.9 (d, J_{C-F} = 2.8 Hz, CH), 129.9 (CH), 128.6 (CH), 127.1 (d, J_{C-F} = 14.7 Hz, C), 124.4 (d, J_{C-F} = 3.5 Hz, CH) 116.4 (d, J_{C-F} = 21.5 Hz, CH); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -111.0 (s, 1F)**; IR** (thin film) 1685, 1584, 1440, 1313, 922, 731 cm^{-1}; **LRMS (EI)** 201 (100, $[M+H]^+$); **HRMS (EI)** calcd. for $C_{13}H_{10}FO$ $[M+H]^+$ 201.0716, observed 201.0710. Spectroscopic data in accordance with the literature.[152]

(4-Fluorophenyl)(phenyl)methanone (200)



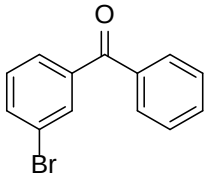
Purification by column chromatography (1-5% Et_2O/Petrol) gave (4-fluorophenyl)(phenyl)methanone as a colourless oil (78 mg, 0.39 mmol, 78%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.85-7.82 (m, 2H), 7.78-7.75 (m, 2H), 7.61-7.57 (m, 1H), 7.49-7.45 (m, 2H), 7.17-7.13 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 195.4 (C), 166.5 (d, J_{C-F} = 252.6 Hz, C), 137.6 (C), 133.9 (d, J_{C-F} = 2.9 Hz, C), 132.8 (d, J_{C-F} = 9.1 Hz, CH), 132.6 (CH), 130.0 (CH), 128.5 (CH), 115.6 (d, J_{C-F} = 21.8 Hz, CH); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -106.0 (s, 1F); **IR** (thin film) 1656, 1598, 1446, 1275, 698 cm^{-1}; **LRMS (EI)** 200 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{13}H_9FO$ $[M]^+$ 200.0637, observed 200.0635. Spectroscopic data in accordance with the literature.[153]

Phenyl(4-(trifluoromethyl)phenyl)methanone (199f)



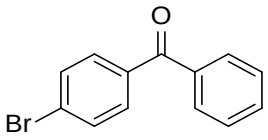
Purification by column chromatography (1-5% Et_2O/Petrol) gave phenyl(4-(trifluoromethyl)phenyl)methanone as a clear solid (109 mg, 0.43 mmol, 87%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.89 (d, *J* = 8.0 Hz, 2H), 7.82-7.88 (m, 2H), 7.75 (d, *J* = 8.1 Hz, 2H), 7.65-7.61 (m, 1H), 7.51 (t, *J* = 7.7 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 195.7 (C), 140.8 (C), 136.8 (C), 133.8 (q, J_{C-F} = 32.5 Hz, C), 133.3 (CH), 130.3 (m, CH), 128.7 (CH), 125.5 (q, J_{C-F} = 3.7 Hz, CH), 123.5 (q, J_{C-F} = 270.9 Hz, C); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -63.0 (s, CF_3, 3F); **IR** (thin film) 1654, 1604, 1275, 729 cm^{-1}; **LRMS (CI)** 250 (100, $[M]^+$); **HRMS (CI)** calcd. for $C_{14}H_9F_3O$ $[M]^+$ 250.0601, observed 250.0615; m.p. 110-113 °C (recrystallized from *n*-heptane). Spectroscopic data in accordance with the literature.[154]

(3-Bromophenyl)(phenyl)methanone (199h)



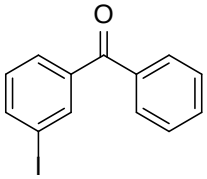
Purification by column chromatography (1-5% Et_2O/Petrol) gave (3-bromophenyl)(phenyl)methanone as a clear oil (120 mg, 0.46 mmol, 92%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.93 (t, *J* = 1.6 Hz, 1H), 7.79-7.77 (m, 2H), 7.71 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.62-7.59 (m, 1H), 7.50-7.48 (m, 2H), 7.35 (t, *J* = 7.9 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 195.3 (C), 139.6 (C), 137.0 (C), 135.4 (CH), 133.0 (CH), 132.9 (CH), 130.2 (CH), 130.0 (CH), 128.7 (CH), 128.6 (CH), 122.7 (C); **IR** (thin film) 1649, 1599, 1260, 937, 729 cm^{-1}; **LRMS (EI)** 262 (100, $[M^{81}Br]^+$), 260 (100, $[M^{79}Br]^+$); **HRMS (EI)** calcd. for $C_{13}H_9BrO$ $[M^{79}Br]^+$ 259.9837, observed 259.9835. Spectroscopic data in accordance with the literature.[155]

(4-Bromophenyl)(phenyl)methanone (199i)



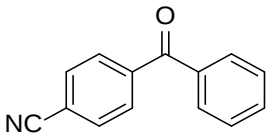
Purification by column chromatography (1-5% Et_2O/Petrol) gave (4-bromophenyl)(phenyl)methanone as a clear oil (92 mg, 0.36 mmol, 71%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.79-7.76 (m, 2H), 7.68-7.65 (m, 2H), 7.63-7.58 (m, 3H), 7.50-7.47 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 195.8 (C), 137.3 (C), 136.4 (C), 132.8 (CH), 131.7 (CH), 131.7 (CH), 130.1 (CH), 128.5 (CH), 127.6 (CH); **IR** (thin film) 1649, 1600, 1250, 922, 729 cm^{-1}; **LRMS (EI)** 262 (100, $[M^{81}Br]^+$), 260 (100, $[M^{79}Br]^+$); **HRMS (EI)** calcd. for $C_{13}H_9BrO$ $[M^{79}Br]^+$ 259.9837, observed 259.9835. Spectroscopic data in accordance with the literature.[156]

(3-iodophenyl)(phenyl)methanone (199j)



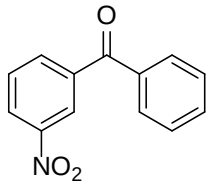
Purification by column chromatography (1-5% Et_2O/Petrol) gave (3-iodophenyl)(phenyl)methanone as a colourless oil (111 mg, 0.36 mmol, 72%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.14-8.11 (m, 1H), 7.92-7.89 (m, 1H), 7.79-7.76 (m, 2H), 7.74-7.68 (m, 1H), 7.62-7.59 (m, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.22 (t, J = 7.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 195.2 (C), 141.3 (CH), 139.6 (C), 138.7 (CH), 137.0 (C), 133.0 (CH), 130.2 (CH), 130.1 (CH), 129.3 (CH), 128.6 (CH), 94.2 (C); **IR** (thin film) 1680, 1580, 1313, 937, 698 cm^{-1}; **LRMS (ES^+)** 308 (100, $[M+H]^+$); **HRMS (ES^+)** calcd. for $C_{13}H_{10}IO$ $[M+H]^+$ 308.9776, observed 308.9770. Spectroscopic data in accordance with the literature.[157]

4-Benzoylbenzonitrile (199k)



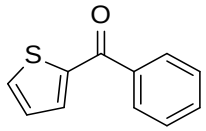
Purification by column chromatography (1-5% Et_2O/Petrol) gave 4-benzoylbenzonitrile as a clear oil (79 mg, 0.38 mmol, 76%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.87-7.86 (m, 2H), 7.79-7.77 (m, 4H), 7.65-7.62 (m, 1H), 7.52-7.50 (m, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 195.2 (C), 141.3 (C), 136.4 (C), 133.5 (CH), 132.3 (CH), 130.4 (CH), 130.2 (CH), 128.8 (CH), 118.2 (C), 115.8 (C); **IR** (thin film) 2227, 1648, 1595, 1309, 1279, 693 cm^{-1}; **LRMS (EI)** 207 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{14}H_9NO$ $[M]^+$ 207.0684, observed 207.0682. Spectroscopic data in accordance with the literature.[154]

(3-Nitrophenyl)(phenyl)methanone (199l)



Purification by column chromatography (1-5% Et_2O/Petrol) gave (3-nitrophenyl)(phenyl)methanone as a clear oil (87 mg, 0.39 mmol, 77%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.61 (t, *J* = 1.9 Hz, 1H), 8.43 (dq, *J* = 8.3 Hz, 1.0 Hz, 1H), 8.15-8.11 (m, 1H), 7.81-7.75 (m, 2H), 7.70 (t, *J* = 7.9 Hz, 1H), 7.66-7.62 (m, 1H), 7.52 (t, *J* = 7.8 Hz, 2H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 194.3 (C), 148.2 (C), 139.1 (C), 136.3 (C), 135.6 (CH), 133.5 (CH), 130.1 (CH), 129.8 (CH), 128.9 (CH), 126.9 (CH), 124.8 (CH); **IR** (thin film) 1664, 1532, 1348, 1274, 1090, 708 cm^{-1}; **LRMS (EI)** 227 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{13}H_9NO_3$ $[M]^+$ 227.0582, observed 227.0580. Spectroscopic data in accordance with the literature.[158]

Phenyl(thiophen-2-yl)methanone (199m)

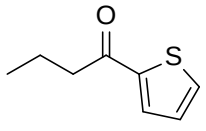


Purification by column chromatography (1-5% Et_2O/Petrol) gave phenyl(thiophen-2-yl)methanone as a clear oil (72 mg, 0.38 mmol, 76%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.87-7.85 (m, 2H), 7.73 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.52-7.48 (m, 2H), 7.65 (dd, *J* = 3.8, 0.9 Hz, 1H), 7.61-7.58 (m, 1H), 7.17 (dd, *J* = 4.9, 3.8 Hz, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 188.4 (C), 143.8 (C), 138.2 (C), 135.0 (CH), 134.4 (CH), 132.4 (CH), 129.3 (CH), 128.5 (CH), 128.1 (CH); **IR** (thin film) 3099, 1630, 1597, 1410, 1352, 1284, 1052 cm^{-1}. Spectroscopic data in accordance with the literature.[159]

General procedure for alkyl aryl ketone synthesis from alkyl hydrazide

To a flame-dried, three necked flask, under an inert atmosphere, was added a solution of acyl hydrazide (0.5 mmol) in THF (10 mL). 2-thienylmagnesium bromide (1.25 mmol) was then added to the stirring solution in one portion at –78 °C. After 30 min, the reaction was warmed to 0 °C over 30 min. After this time, the reactions was quenched with pre-cooled (*ca.* 4 °C) saturated ammonium chloride solution (10 mL). The aqueous layer was washed with diethyl ether (3 x 10 mL), the organic layers combined, dried ($MgSO_4$), filtered under vacuum and solvent removed in *vacuo.* The crude residue was purified as described below.

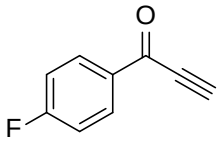
1-(Thiophen-2-yl)butan-1-one (203)



Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(thiophen-2-yl)butan-1-one as a colourless oil (23 mg, 0.15 mmol, 30%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.71 (d, *J* = 3.2 Hz, 1H), 7.62 (d, *J* = 4.1 Hz, 1H), 7.12 (t, *J* = 3.6 Hz, 1H), 2.88 (t, *J* = 6.1 Hz, 2H), 1.81-1.75 (m, 2H), 1.00 (t, *J* = 6.2 Hz, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 193.6 (C), 144.7 (C), 133.5 (CH), 131.8 (CH), 128.2 (CH), 41.4

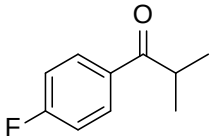
(CH_2), 18.3 (CH_2), 14.0 (CH_3); **IR** (thin film) 2955, 2927, 2858, 1658, 1518, 1459, 1237, 1058 cm^{-1}. Spectroscopic data in accordance with the literature.[148]

1-(4-Fluorophenyl)prop-2-yn-1-one (206)



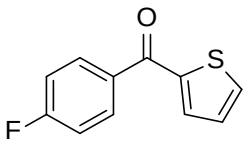
Applied general procedure for the diaryl ketone synthesis (see above). Purification by column chromatography (1-8% Et_2O/Petrol) gave 1-(4-fluorophenyl)prop-2-yn-1-one as a white solid (58 mg, 0.38 mmol, 76%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 8.22-8.18 (m, 2H), 7.20-7.16 (m, 2H), 3.45 (s, 1H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 175.9 (C), 166.2 (d, J_{C-F} = 256.0 Hz, C), 132.8 (d, J_{C-F} = 2.7 Hz, C), 132.6 (d, J_{C-F} = 9.7 Hz, CH), 116.1 (d, J_{C-F} = 22.1 Hz, C), 81.1 (C), 80.1 (CH); **^{19}F NMR (282 MHz, $CDCl_3$)** δ -102.3 (s, 1F); **IR** (thin film) 3211, 2092, 1650, 1592, 1503, 1409, 1252, 1232, 1015 cm^{-1}; **LRMS (CI)** 149 (100, $[M+H]^+$); **HRMS (CI)** calcd. for C_9H_6FO $[M+H]^+$ 149.0403, observed 149.0398, m.p. 50-53 °C (recrystallized from *n*-heptane). Spectroscopic data in accordance with the literature.[160]

1-(4-Fluorophenyl)-2-methylpropan-1-one (207)



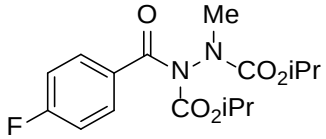
Applied general procedure for the alkyl aryl ketone synthesis (see above). Purification by column chromatography (1-5% Et_2O/Petrol) gave 1-(4-fluorophenyl)-2-methylpropan-1-one as a colourless oil (58 mg, 0.35 mmol, 70%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.99-7.96 (m, 2H), 7.16-7.10 (m, 2H), 3.51 (septet, *J* = 6.8 Hz, 1H), 1.20 (d, *J* = 6.8 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 203.0 (C), 166.5 (d, J_{C-F} = 252.7 Hz, C), 132.6 (d, J_{C-F} = 3.0 Hz, C), 131.0 (d, J_{C-F} = 9.1 Hz, CH), 115.8 (d, J_{C-F} = 21.6 Hz, CH), 35.4 (CH), 19.2 (CH_3); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -105.8; **IR** (thin film) 1681, 1595, 1219, 1152, 845 cm^{-1}; **LRMS (EI)** 166 (100, $[M]^+$); **HRMS (EI)** calcd. for $C_{10}H_{11}FO$ $[M]^+$ 166.0794, observed 166.0790. Spectroscopic data in accordance with the literature.[161]

(4-Fluorophenyl)(thiophen-2-yl)methanone (208)



Applied general procedure for the diaryl ketone synthesis (see above). Purification by column chromatography (1-5% Et_2O/Petrol) gave (4-fluorophenyl)(thiophen-2-yl)methanone as a colourless oil (73 mg, 0.36 mmol, 71%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.92-7.88 (m, 2H), 7.74 (d, *J* = 4.9 Hz, 1H), 7.63 (d, *J* = 4.8 Hz, 1H), 7.20-7.17 (m, 3H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 186.9 (C), 165.5 (d, J_{C-F} = 252.3 Hz, C), 143.5 (C), 134.8 (CH), 134.4 (CH), 134.4 (d, J_{C-F} = 3.5 Hz, C), 131.9 (d, J_{C-F} = 9.0 Hz, CH), 128.1 (CH), 115.7 (d, J_{C-F} = 21.6 Hz, CH); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -106.2 (s, 1F); **IR** 3025, 1285, 1240, 1230, 1150, 1049, 758 cm^{-1}; **LRMS (CI)** 207 (100, $[M+H]^+$); **HRMS (CI)** calcd. for $C_{11}H_8FOS$ $[M+H]^+$ 207.0258, observed 207.0276; m.p. 88-93 °C (recrystallized from *n*-heptane). Spectroscopic data in accordance with the literature.[162]

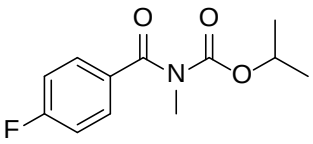
Diisopropyl 1-(4-fluorobenzoyl)-2-methylhydrazine-1,2-dicarboxylate (212)



To a solution of hydrazide **173** (1.63 g, 5.0 mmol) in DMF (40 mL) was added caesium carbonate (1.95 g, 6.0 mmol) and methyl iodide (374 µL, 6.0 mmol). The reaction was complete after 21 h. Purification by column chromatography (5-25% Et_2O/Petrol) gave diisopropyl 1-(4-fluorobenzoyl)-2-methylhydrazine-1,2-dicarboxylate as a colourless oil (1.19 g, 3.50 mmol, 70%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.71-7.59 (m, 2H), 7.11-7.05 (m, 2H), 4.98-4.87 (m, 2H), 3.25-3.21 (m, 3H), 1.33-1.08 (m, 12H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 169.0 (C), 164.1 (C), 155.4 (d, J_{C-F} = 268.1 Hz, CF), 152.4 (C), 152.3 (C), 131.4 (d, J_{C-F} = 3.2 Hz, C), 130.4 (d, J_{C-F} = 9.0 Hz, CH), 115.5 (d, J_{C-F} = 22.0 Hz, CH), 72.4 (CH), 70.6 (CH), 36.6 (CH_3), 22.2 (CH_3), 22.1 (CH_3), 21.6 (CH_3); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -107.4 (m, 1F); **IR** (thin film) 1709, 1579, 1231, 1115 cm^{-1}; **LRMS (ES^+)** 341.1525

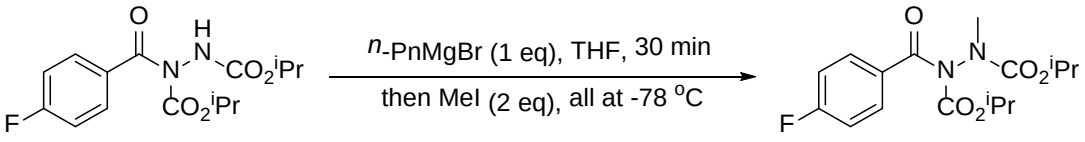
(100, $[M+H]^+$); **HRMS (ES^+)** calcd. for $C_{16}H_{22}FO_5$ $[M+H]^+$ 341.1513, observed 341.1525. Spectroscopic data in accordance with the literature.[163]

Isopropyl (4-fluorobenzoyl)(methyl)carbamate (213)



Sodium hydride (660 mg, 16.5 mmol) was added to a stirring solution of *N*-methylbenzamide (500 mg, 3.30 mmol) in THF (10 mL) at -78 °C. The mixture was slowly warmed to room temperature and isopropyl chloroformate (13 mL, 13.2 mmol) was added in one portion. After 2 h, the reaction was quenched with saturated ammonium chloride solution (10 mL). The organic layer was extracted with Et_2O (3 x 20 mL) and dried ($MgSO_4$). The solvent was then removed *in vacuo* and the crude residue purified by column chromatography (10%-25% Et_2O/Petrol) to afford isopropyl (4-fluorobenzoyl)(methyl)carbamate as a colourless oil (765 mg, 3.20 mmol, 97%). **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.56-7.52 (m, 2H), 7.19-7.15 (m, 2H), 4.83 (septet, J = 6.2 Hz, 1H), 3.32 (s, 3H), 1.03 (d, J = 6.2 Hz, 6H); **^{13}C NMR (150 MHz, $CDCl_3$)** δ 172.5 (C), 164.5 (d, $J_{C\text{-}F}$ = 250.2 Hz, C), 154.6 (C), 133.5 (d, $J_{C\text{-}F}$ = 3.3 Hz, C), 130.1 (d, $J_{C\text{-}F}$ = 35.6 Hz, CH), 115.2 (d, $J_{C\text{-}F}$ = 21.9 Hz, CH), 71.4 (CH), 32.9 (CH_3), 21.5 (CH_3); **^{19}F NMR (376 MHz, $CDCl_3$)** δ -108.1 (s, 1F); **IR** (thin film) 1718, 1600, 1216 cm^{-1}; **LRMS (ES^+)** 240 (100, $[M+H]^+$); **HRMS (ES^+)** calcd. for $C_{12}H_{15}FNO_3$ $[M+H]^+$ 240.1036, observed 240.1040. Spectroscopic data in accordance with the literature.[163]

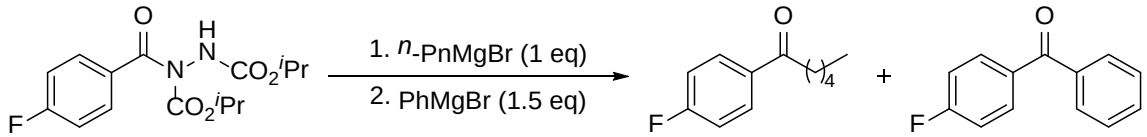
Reaction detailed in Scheme 74



To a flame-dried three-necked flask, under an inert atmosphere, was added a solution of acyl hydrazide **1a** (163 mg, 0.5 mmol) in THF (10 mL). *n*-Pentylmagnesium bromide (93 µL, 0.5 mmol) was then added to the stirring solution in one portion at –78 °C. After 30 min, methyl iodide (62 µL, 1.0 mmol) was added and the reaction stirred at –78 °C for a further 30 min. The reaction was then quenched with pre-

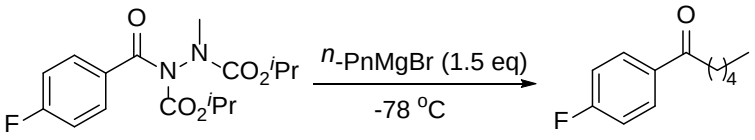
cooled (*ca.* 4 °C) saturated ammonium chloride solution (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers combined, dried ($MgSO_4$), filtered under vacuum and the solvent was removed in *vacuo.* The resultant crude residue was purified by column chromatography (5%-25% Et_2O/Petrol) to give diisopropyl 1-(4-fluorobenzoyl)-2-methylhydrazine-1,2-dicarboxylate as a colourless oil (148 mg, 0.43 mmol, 87%). Data for this compound matched that as described for diisopropyl 1-(4-fluorobenzoyl)-2-methylhydrazine-1,2-dicarboxylate **212**.

Reaction detailed in Scheme 75



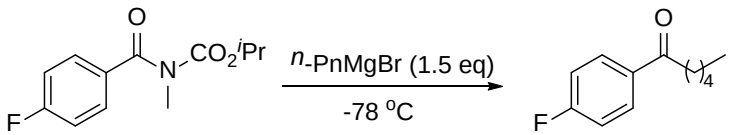
To a flame-dried three-necked flask, under an inert atmosphere, was added a solution of acyl hydrazide **173** (163 mg, 0.5 mmol) in THF (10 mL). *n*-Pentylmagnesium bromide (93 µL, 0.5 mmol) was then added to the stirring solution in one portion at –78 °C. After 30 min, phenylmagnesium bromide (119 µL, 0.75 mmol) was added and the reaction stirred at 0 °C for a further 30 min. The reaction was then quenched with pre-cooled (*ca.* 4 °C) saturated ammonium chloride solution (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers combined, dried ($MgSO_4$), filtered under vacuum and the solvent was removed in *vacuo.* The resultant crude residue was purified by column chromatography (5%-25% Et_2O/Petrol) to give 1-(4-fluorophenyl)hexan-1-one as a white solid (4 mg, 0.02 mmol, 4%) and (4-fluorophenyl)(phenyl)methanone as a colourless oil (72 mg, 0.36 mmol, 71%). Data for these compounds matched that as described for 1-(4-fluorophenyl)hexan-1-one **196** and (4-fluorophenyl)(phenyl)methanone **200**.

Reaction detailed in Scheme 76



To a flame-dried three-necked flask, under an inert atmosphere, was added a solution of diisopropyl 1-(4-fluorobenzoyl)-2-methylhydrazine-1,2-dicarboxylate **212** (170 mg, 0.5 mmol) in THF (10 mL). *n*-Pentylmagnesium bromide (119 µL, 0.75 mmol) was then added to the stirring solution in one portion and the reaction stirred for 30 min at –78 °C. The reaction was then quenched with pre-cooled (*ca.* 4 °C) saturated ammonium chloride solution (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers combined, dried ($MgSO_4$), filtered under vacuum and the solvent was removed in *vacuo*. The resultant crude residue was purified by column chromatography (5%-25% Et_2O/Petrol) to give 1-(4-fluorophenyl)hexan-1-one as a white solid (39 mg, 0.19 mmol, 38%). Data for this compound matched that as described for 1-(4-fluorophenyl)hexan-1-one **196**.

Reaction detailed in Scheme 77



To a flame-dried three-necked flask, under an inert atmosphere, was added a solution of isopropyl (4-fluorobenzoyl)(methyl)carbamate **13** (120 mg, 0.5 mmol) in THF (10 mL). *n*-Pentylmagnesium bromide (119 µL, 0.75 mmol) was then added to the stirring solution in one portion and the reaction stirred for 30 min at –78 °C. The reaction was then quenched with pre-cooled (*ca.* 4 °C) saturated ammonium chloride solution (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL), the organic layers combined, dried ($MgSO_4$), filtered under vacuum and the solvent was removed in *vacuo*. The resultant crude residue was purified by column chromatography (5%-25% Et_2O/Petrol) to give 1-(4-fluorophenyl)hexan-1-one as a white solid (37 mg, 0.18 mmol, 36%). Data for this compound matched that as described for 1-(4-fluorophenyl)hexan-1-one **196**.

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Appendix

Some of the work conducted as part of this thesis has been included in two separate publications.

Chudasama, V.; Akhbar, A. R.; Bahou, K. A.; Fitzmaurice, R. J.; Caddick, S. *Organic and Biomolecular Chemistry* **2013**, *11*, 7301.

Akhbar, A. R.; Chudasama, V.; Fitzmaurice, R. J.; Powell, L.; Caddick, S. *Chem Commun* **2013**, *50*, 743.