Synthesis of Valuable Compounds Through a Cobalt-catalysed C-H Functionalisation Approach

Paula Giorgiana Chirila

A thesis submitted in partial fulfilment of the requirements of Sheffield Hallam University
for the degree of Doctor of Philosophy

March 2021

Candidate Declaration

I hereby declare that:

1. I have not been enrolled for another award of the University, or other academic or professional organisation, whilst undertaking my research degree.

2. None of the material contained in the thesis has been used in any other submission for an academic award.

3. I am aware of and understand the University's policy on plagiarism and certify that this thesis is my own work. The use of all published or other sources of material consulted have been properly and fully acknowledged.

4. The work undertaken towards the thesis has been conducted in accordance with the SHU Principles of Integrity in Research and the SHU Research Ethics Policy.

5. The word count of the thesis is 37, 909.

Name	*Paula Giorgiana Chirila*
Date	*March 2021*
Award	*PhD*
Faculty	*Health and Wellbeing*
Director(s) of Studies	*Dr. Chrisopher John Whiteoak, Dr. Alexander Hamilton, Dr. Keith Miller*

Abstract

Directed C-H functionalisation protocols have attracted significant interest in recent years as they offer the possibility of forming new bonds selectively *via* C-H bond cleavage, without requiring pre-functionalised substrates whilst reducing waste production. Precious metals such as palladium and rhodium have been utilised to make considerable advancements in the field. However, recently there has been a shift towards the use of more environmentally friendly and cost-effective 3d-transition metals. High valent cobalt (Co)-catalysed C-H functionalisation has emerged as a tool for the development of a variety of protocols for the formation of novel C-C or C-heteroatom bonds.

Of particular interest to this thesis is the formation of important C-N bonds using Co(III)-catalysed C-H amidation protocols. Furthermore, utilising the products of the C-H amidation reaction for synthesis of new nitrogen-based heterocycles is desirable due to their prevalence in biologically active compounds and agrochemicals.

The focus of this thesis is developing efficient routes to valuable nitrogen containing heterocycles starting from a key Co(III)-catalysed C-H amidation step. In this context, the use of Cp*Co(III) catalysts for the amidation of benzamide and *N*-phenylisobutyramide type of substrates is reported using 1,4,2-dioxazol-5-ones as amidating agents. The isolable amidated products are thereafter converted to the valuable 1,2,3-benzotriazin-4(*3H*)-ones and *N*-acetylbenzotriazoles utilising *tert*-butyl nitrite (TBN) under mild conditions. Furthermore, another interest for this thesis is the development of Co(III)-catalysed C-H amidation protocols for more challenging alkenyl substrates. There is limited information about the mechanism by which these Co(III)-catalysed C-H amidation protocols proceed thus, DFT calculations and experimental mechanistic investigations are employed to elucidate the reaction mechanisms.

Lastly, 1,2,3-benzotriazin-4-(*3H*)-ones are reacted with various coupling partners in an attempt to provide new synthetic starting points for preparation of other potentially valuable heterocyclic compounds *via* denitrogenation under low-valent metal catalysis.

It was posible to develop facile one-pot routes towards the synthesis 1,2,3-benzotriazin-4(*3H*)-ones and *N*-acetylbenzotriazoles starting from readily available substrates, using Co(III)-catalysed C-H amidation reactions as initials steps. Expanding the scope to alkenyl substrates was more challenging due to limited availability of starting materials and the poor reactivity of the substrates with substituents at the β-position. Finally, DFT studies have revealed that the migratory insertion step is most likely the rate limiting step for the Co(III)-catalysed C-H amidation reactions.

Acknowledgments

Firstly, I would like to thank my supervisors Dr. Christopher John Whiteoak, Dr. Alexander Hamilton and Dr. Keith Miller for their continuous support and guidance throughout this project and the Biomolecular Sciences Research Centre (BMRC) at Sheffield Hallam University for funding. Furthermore, I would like to thank Dr Xavi Ribas for mentoring me during the 6-week scientific visit at the University of Girona and the COST action CHAOS for financial support. Many thanks to my PGRT, Dr Catherine Duckett, whose advice and assistance have been greatly appreciated.

I would like to extend my appreciation for the technical team who have supported me on numerous occasions. I am also very thankful to my colleagues in the BMRC for their friendship and for endlessly lifting my spirits during the last few years.

Finally, I owe my deepest gratitude to my family for their love, moral support and for always motivating me to accomplish my goals.

List of Abbreviations

(D)-Bz-Hpg-OH	(*R*)-2-(Boc-amino)-5-hexynoic acid
1,2-DCE	1,2-Dichloroethane
Ac	Acetic
Å	Ångstrom
AgOTf	Silver trifluoromethanesulfonate
ASAP	Atmospheric Solids Analysis Probe
BINOL	1,1′-Bi-2-naphthol
calcd	Calculated
CCA	Chiral Carboxylic Acids
CMD	Concerted Metalation-Deprotonation
Cp	Cyclopentadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
CsOPiv	Caesium pivalate
dacoda	1,5-diazacyclooctane-*N*,*N*'-diacetic acid
DCM	Dichloromethane
DFT	Density Functional Theory
DG	Directing Group
Dha	Dehydroalanine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
dppb	1,4-Bis(diphenylphosphino)butane
dppbenz	1,2-Bis(diphenylphosphino)benzene
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electrospray ionization
Et	Ethyl
EtOH	Ethanol
FDA	Food and Drug Administration
HFIP	1,1,1,3,3,3-Hexafluoro-2-propanol
HOPiv	Pivalic acid
HRMS	High Resolution Mass Spectrometry
Int	Intermediate

KIE	Kinetic isotope effect
Me	Methyl
NaOAc	Sodium acetate
NaOEt	Sodium ethoxide
NaOPiv	Sodium pvalate
NBP	*N*-bromophthalimide
NIS	*N*-iodosuccinimide
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
RT	Room Temperature
SET	Single Electron Transfer
SPINOL	1,1'-Spirobiindane-7,7'-diol
TBN	*tert*-Butyl nitrite
TCA	Trichloroacetic acid
Tf	Triflate
TFE	2,2,2-Trifluoroethanol
THF	Tetrahydrofuran
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TS	Transition State
UV	Ultraviolet

List of Figures

List of Schemes

List of Tables

Table of Contents

Chapter 1. Introduction

For more than 100 years synthetic chemists have focused on developing new methodologies to provide access to novel valuable molecules for a variety of areas such as medicinal chemistry or agrochemistry, amongst many others. In the past, most of the synthetic chemist's toolbox consisted of traditional organic chemistry approaches, which were used to build desired compounds, often by multi-step synthesis starting from pre-functionalised materials (**Figure 1-1a**). However, these conventional methods can be time consuming and unsuccessful in providing the desired molecules in good yield. Thus, the development of transition metal catalysed cross-coupling reactions has emerged as a more atom efficient and economical alternative (**Figure 1-1b**).

Palladium-catalysed cross-coupling reactions have had a distinct impact on the field of organic chemistry.[1] Indeed, this synthetic methodology has allowed access to complex molecules in a rapid, convenient and stereoselective fashion. The impact of palladium-catalysed cross coupling reactions has been highlighted by the awarding of the Nobel prize to Heck, Negishi and Suzuki.[2]

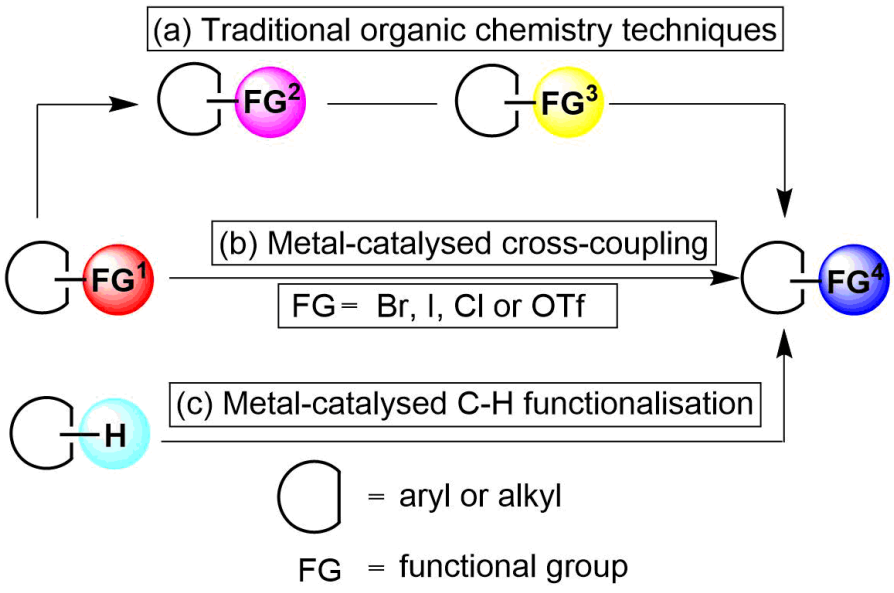


Figure 1-1: Overview of different methodologies for the synthesis of functionalised compounds.

However, there are drawbacks to transition metal catalysed cross coupling reactions particularly the requirement for pre-functionalised substrates and therefore the significant toxic waste generated.[3,4]

As a result, synthetic chemists have turned their attention to transition metal catalysed directed C-H bond functionalisation techniques which offered the possibility of forming new bonds selectively *via* direct C-H bond cleavage, without requiring pre-functionalised substrates (**Figure 1-1c**). Once again, precious metals such as palladium and subsequently rhodium have been utilised to make significant advancements in the field by developing methodologies which employ a direct C-H activation step.

1.1 Cobalt-catalysed C-H functionalisation

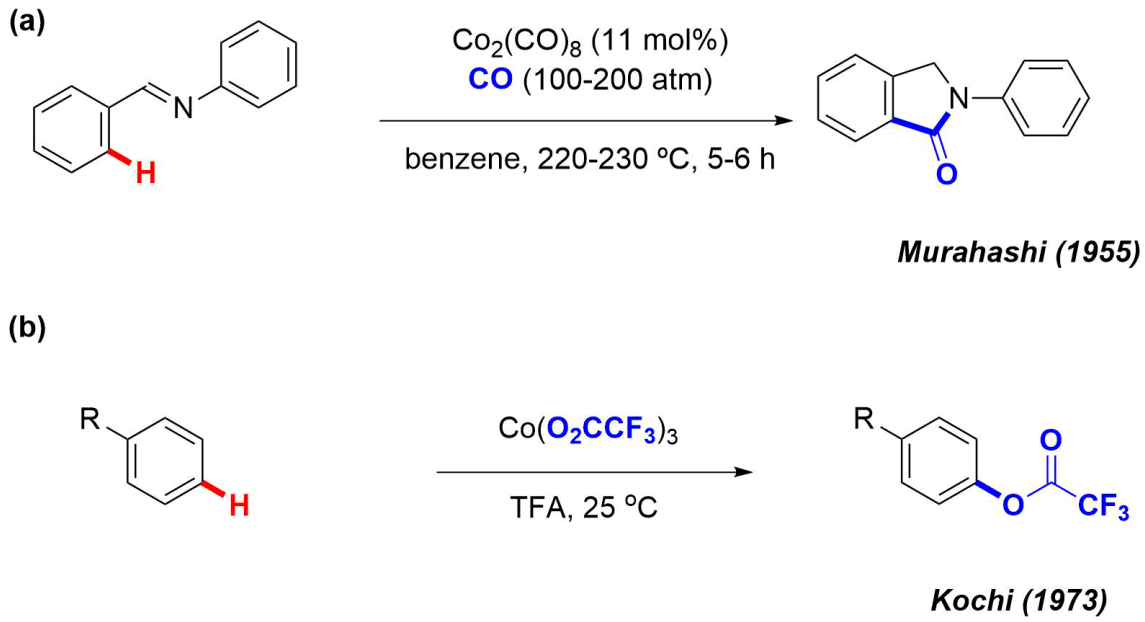
Organometallic C-H activation, like many organic chemistry processes, has recently shifted towards the use of more environmentally friendly and cost-effective reagents and catalysts. In this sense, substituting costly precious metals with earth-abundant 3d-transition metals such as cobalt (Co) or nickel (Ni)[5–7] as catalysts has attracted significant attention in recent years. Rh-catalysed C-H functionalisation has already shown great promise for several processes, therefore, the recognition of Co as a suitable metal for C-H activation is not unexpected.[8,9] Furthermore, while attempting to reproduce some of the processes established with Rh using Co-catalysts as an alternative, new reactivities have been observed. This is due to the reduced electronegativity of cobalt compared to rhodium, which results in a more nucleophilic system that can access new reactivities with improved chemo- and regioselectivities.[7]

There are two categories of Co-catalysed C-H functionalisation depending on the oxidation state of the catalyst: low-valent approach, where the active catalyst species is either in the Co^0 or Co^I oxidation state [10] and high-valent approach, where the active Co-catalyst species is usually in the Co^{III} oxidation state. [7,11] Until 2014 the Co-catalysed C-H functionalisation field was dominated by low-valent approaches, however since 2014 the focus has shifted increasingly towards the utilisation of high-valent Co-catalysts. High-valent

cobalt catalysts have the advantage of being applicable under less strict reaction conditions as they do not decompose under atmospheric conditions due to their 18-electron configuration.

1.2 Early examples of cobalt-catalysed couplings

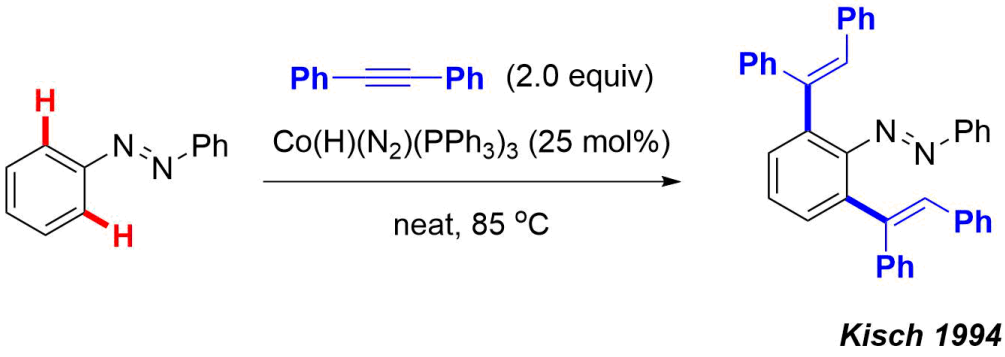
The first example of Co-catalysed C-C bond formation was illustrated in 1941 by Kharasch and Fields, who reported the coupling of organic halides with Grignard reagents.[12] Although this was not a C-H functionalisation protocol, it provided the foundation for utilisation of Co-catalysts for C-C coupling. In 1955, Murahashi reported the earliest example of low-valent Co-catalysed C-H functionalisation (**Scheme 1-1a**), which describes the carbonylation reaction between Schiff bases and carbon monoxide using $Co_2(CO)_8$ as catalyst, providing access to phthalimides derivatives.[13]



Scheme 1-1: Early examples of cobalt-catalysed C-H functionalisation reported by (a) Murahashi [13] and (b) Kochi.[16]

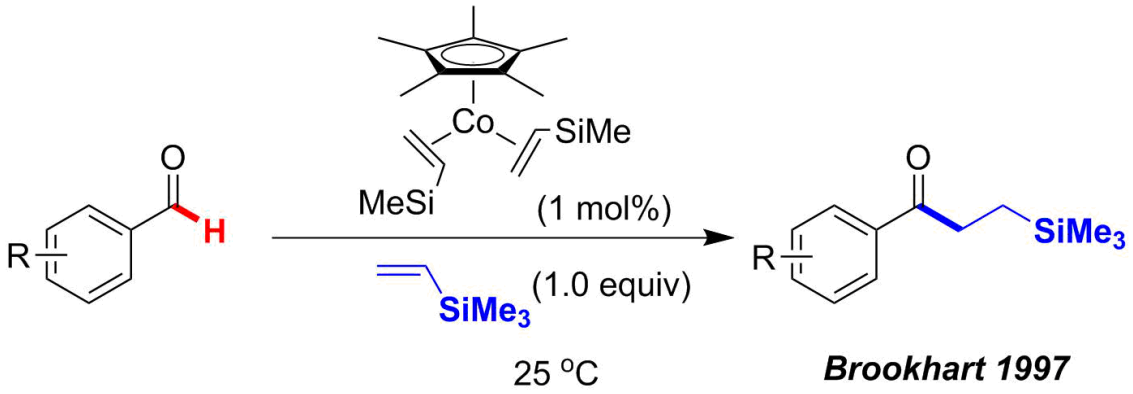
Following the initial breakthrough of low-valent Co-catalysed C-H functionalisation, several protocols were developed that utilised cobalt as an alternative to noble metals. The most significant applications were in the fields of hydroformylation and the Pauson-Khand reaction.[14,15] The first high-valent Co-catalysed approach was only described eighteen years later in 1973, Kochi

and co-workers reported the synthesis of trifluoroacetates through the Co-catalysed C-H functionalisation of aromatic substrates (**Scheme 1-1b**).[16] This was a stoichiometric protocol, as two equivalents of Co(III)$(OTf)_3$ for each molecule of substrate were necessary. Furthermore, this was the first reported example of Single Electron Transfer (SET) mechanism for a Co-catalysed C-H functionalisation protocol.



Scheme 1-2: Co(I)-mediated *ortho*-alkenylation of phenyldiazenes reported by Kisch.[17]

In 1994 Kisch and co-workers restored interest to the field of low-valent Co-catalysed C-H functionalisation by reporting the *ortho*-alkenylation of phenyldiazenes using a Co(I)-catalysed protocol (**Scheme 1-2**).[17] This has proven to be a versatile approach with a significant number of potential coupling reactions depending on the substituents of the aromatic rings.[10,18,19]



Scheme 1-3: Co(I)-mediated hydroacylation of olefins with aromatic aldehydes reported by Brookhart.[19]

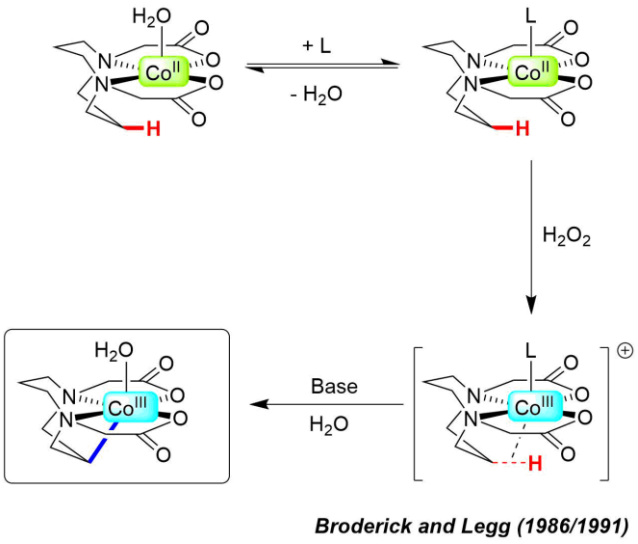
Brookhart also reported several Co(I)-mediated C-H activation methodologies including the hydroacylation of olefins with aromatic aldehydes (**Scheme 1-3**), C-H activation of vinyl(dimethyl)silyl amines and of benzene.[19,20] However,

low-valent Co-catalysed protocols will not be the focal point of this thesis, the focus will be the development of high-valent valent Co-catalysed approaches.

1.3 High-valent Co-catalysed C-H activation

1.3.1 Early examples of stoichiometric high-valent C-H activation

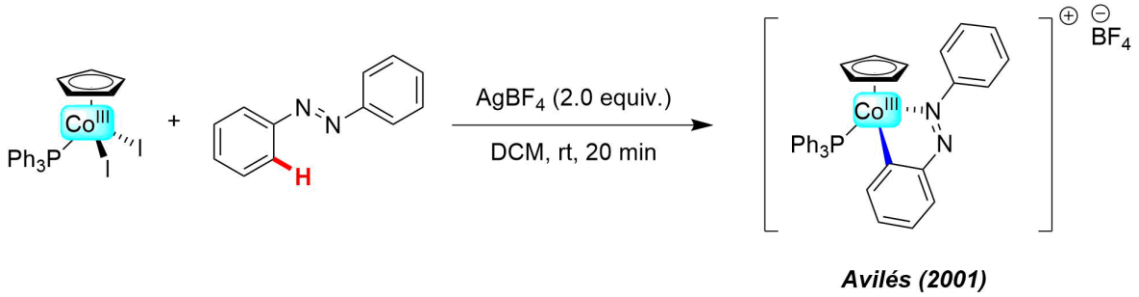
The first example of a stoichiometric high-valent Co-mediated C-H activation protocol was reported as a proof-of-concept by Broderick/Legg and co-workers in 1986. In their first report the authors isolated a Co(III)-organometallic complex using the quadridentate macrocycle ligand ''dacoda''(1,5-diazacyclooctane-*N*,*N*'-diacetic acid).[21] Later, in 1991, in a follow-up study the authors detected a weak agostic interaction between the Co(III)-complex and the C-H bond to be activated (**Scheme 1-4**).[22] It was possible to identify the structure of the Co(III) coordination compound using X-ray crystallography. This study proved that the Co(III)-species activated the C-H bond through a weak three center, two electron intermediate.



Scheme 1-4: Stepwise high-valent Co-mediated C-H activation described by Boderick/Legg and co-workers.[21-22]

A further high-valent Co-catalysed C-H activation stoichiometric example was provided by Avilés and co-workers in 2001 (**Scheme 1-5**).[23] This was the first example of C-H activation using a CpCo(III)-type complex, specifically

[$CpCo(PPh_3)I_2$]. The cobalt complex was reacted with diphenyldiazene and the organometallic product could be observed using X-ray crystallography. In 2003 Jackson and co-workers also reported an example of cobalt chelation-assisted high-valent C-H activation.[24]

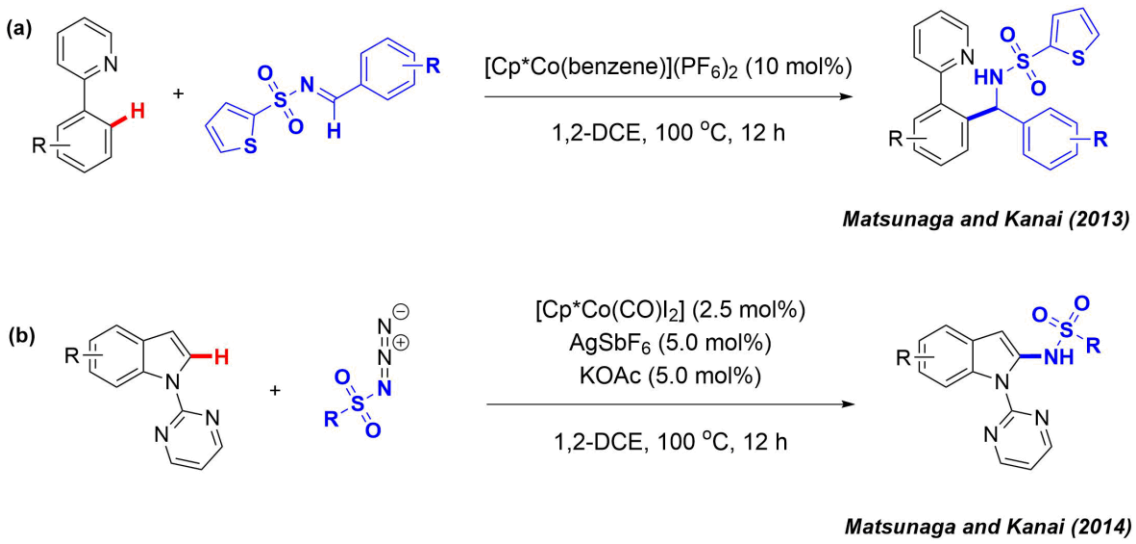


Avilés (2001)

Scheme 1-5: Stoichiometric example of high-valent Co-mediated C-H activation reported by Avilés and co-workers.[23]

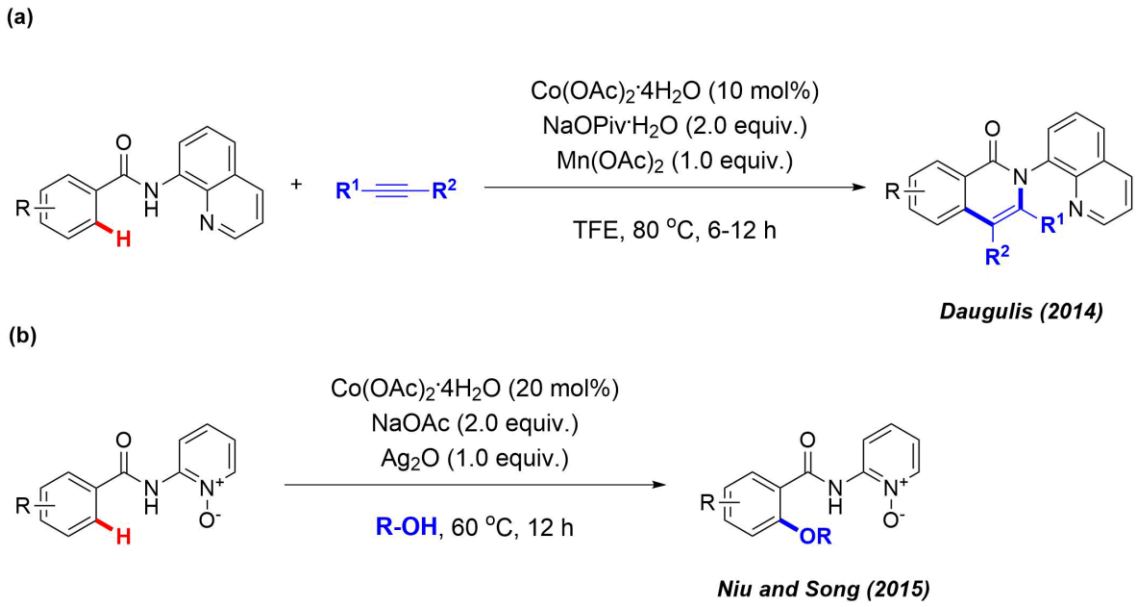
1.3.2 Early examples of catalytic high-valent C-H activation

In 2013 Matsunaga/Kanai and co-workers made a significant breakthrough and introduced high-valent Co(III)-catalysed synthetic reactions. The group reported the Cp*Co(III)-catalysed coupling of 2-arylpyridine with variety of electrophiles such as sulfonyl imines (**Scheme 1-6a**) and α,β-unsaturated ketones using the [Cp*Co(benzene)]$(PF_6)_2$ complex as catalyst.[25] A year later, in 2014, the same group introduced the [$Cp^*Co(CO)I_2$] pre-catalyst, which in combination with $AgSbF_6$ displayed high reactivity for the formation of a C-N bond starting from indole-type substrates (**Scheme 1-6b**).[26] The complex was the equivalent of the already established Cp*Rh(III)-type catalyst.[8]



Scheme 1-6: First examples of Cp*Co(III)-type catalytic protocol reported by Matsunaga and Kanai.[25-26]

In 2014, Daugulis and co-worker identified a different pathway for high-valent Co-catalysed C-H functionalisation. In this instance the insertion of C-C unsaturated bonds into the bidentate 8-aminoquinoline moiety was studied (**Scheme 1-7a**) using Co(II) salts as pre-catalysts.[27] In contrast to what was observed when employing Co(III) pre-catalysts, where the mechanism proceeds directly by Concerted Metalation-Deprotonation (CMD) pathway, when utilising Co(II) salts as pre-catalysts the Co(II) species is first oxidised using an external oxidant, in this case $Mn(OAc)_2$. Subsequently, the electrophilic Co(III)-centre initiated the C-H activation by the CMD route observed previously for Cp*Co(III) catalysts. An aryl-Co(III) species is observed which has a nucleophilic character and can react with coupling partners such as unsaturated C-C bonds.



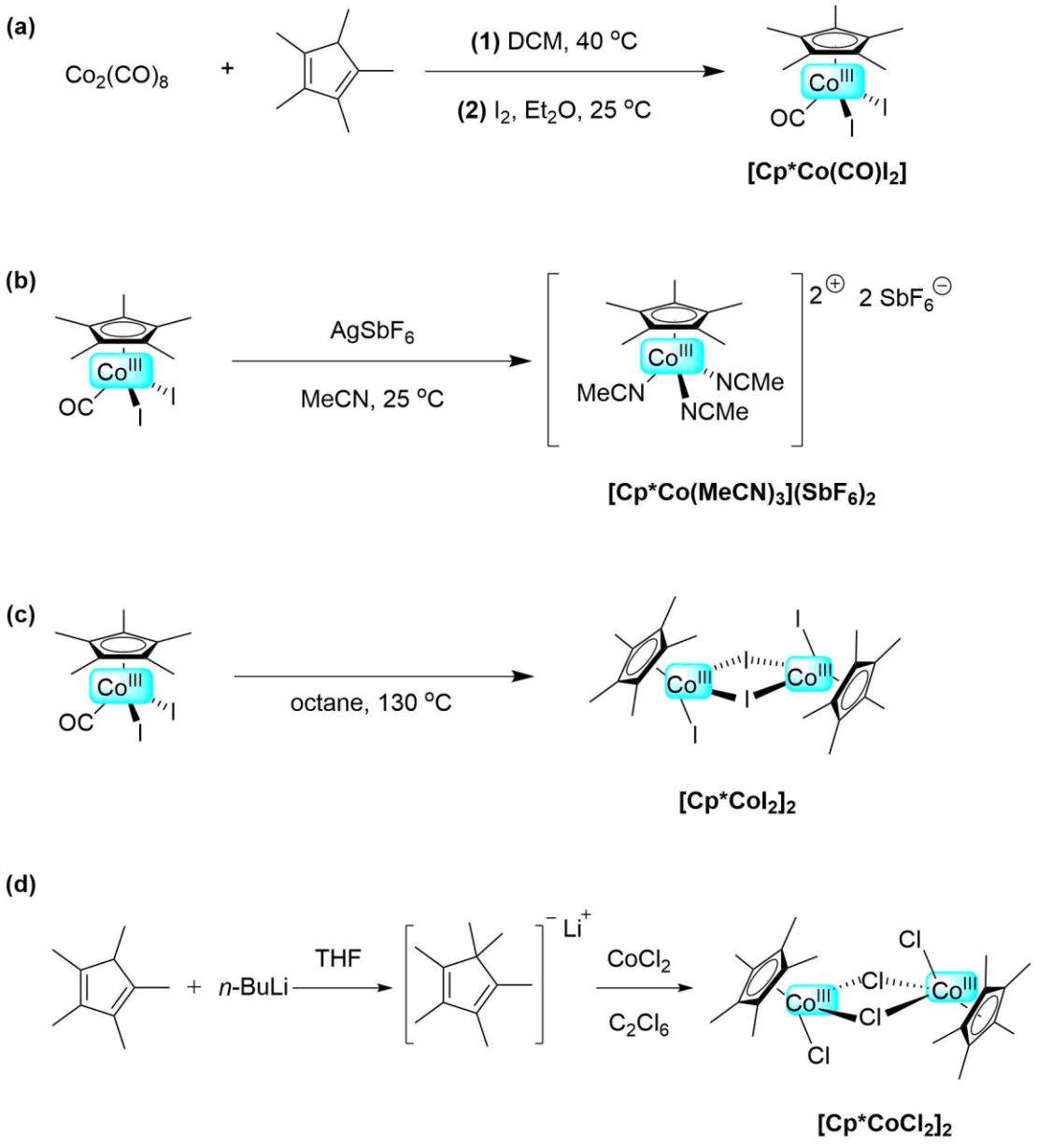
Scheme 1-7: Examples of high-valent cobalt-catalysed C-H functionalisation protocols. (a) First example of an 8-aminoquinoline assisted cobalt-catalysed protocol reported by Daugulis [27] (b) First example of a cobalt-catalysed SET approach.[28]

Whilst both of these approaches are proposed to proceed by a Concerted Metalation Deprotonation (CMD) process during the C-H activation step, in 2015 Niu/Song and co-workers reported an example of a high-valent Co-catalysed SET-based C-H functionalisation protocol. The study illustrates the coupling of aromatic amides with alcohols using a pyridine-*N*-oxide directing group (**Scheme 1-7b**).[28] During mechanistic studies the authors reported a k_H/k_D value of 1, which was unusual for most C-H functionalisation procedures, where a value considerably higher than 1 is usually observed due to the increased strength of the C-D bond compared to the C-H bond. In a later study, Niu/Wei investigated further the reaction mechanism of this transformation and concluded that the reaction most likely takes place through a SET mechanism.[29]

1.4 Cp*Co(III)-catalysed C-H functionalisation

Cp*Co(III)-type of catalysts have shown great potential for a variety of transformations since the first example reported by Matsunaga/Kanai in 2013.[25] In this first example, as previously revealed, the $[Cp^*Co(benzene)](PF_6)_2$ was introduced as a catalyst for the coupling of arylpyridine substrates with sulfonyl imines. A year later, the same group disclosed the $[Cp^*Co(CO)I_2]$ complex,

which showed improved activity for the development of a C-N bond forming procedure.[26] Since the publication of this work, there has been significant interest in developing catalytic protocols using the [Cp*Co(Co)I_2] catalyst and other related complexes (**Scheme 1-8a-c**).[30,31] Catalysts with chloro ligands have been synthesised as well (**Scheme 1-8d**) however, fewer examples of C-H functionalisation protocols have been reported using this type catalyst.[31]



Scheme 1-8: (a) Preparation of [Cp*Co(CO)I_2] from $Co_2(CO)_8$.[30] (b) Preparation of [Cp*Co(MeCN)$_3$](SbF$_6$)$_2$ from [Cp*Co(CO)I_2].[30] (c) Preparation of [Cp*CoI$_2$]$_2$ from [Cp*Co(CO)I_2].[31] (d) Preparation of [Cp*CoCl$_2$]$_2$ from $CoCl_2$.[31]

This introduction will focus on highlighting the protocols that have been developed using the Cp*Co(III)-complexes illustrated previously: [Cp*Co(CO)I_2],

$[Cp^*Co(MeCN)_3](SbF_6)_2$ and $[Cp^*CoI_2]_2$. Furthermore, this chapter will focus particularly on C-N bond formation protocols.

1.4.1 Terminal couplings using Cp*Co(III) catalysis

In this section, a variety of examples of terminal couplings using Cp*Co(III) catalysis will be illustrated. These protocols have been grouped by type of bond coupling and substrate type.

1.4.1.1 C-C couplings using Cp*Co(III) catalysis

1.4.1.1.1 C-C coupling with indole-type substrates

To date, indole derivatives with pyridine or pyrimidine directing groups have provided a variety of examples for C-C terminal couplings using the $[Cp^*Co(CO)I_2]$-type of catalyst.[7,32] These substrates can be easily synthesised in high yield by reacting indole with either 2-bromopyridine or 2-chloropyrimidine in the presence of sodium hydride.[33] Additionally, the directing group can be removed by heating with sodium ethoxide in DMSO.[34] Adding the directing group to the indole moiety provides new selectivity by coordinating coupling at the 2-position, compared to traditional electrophilic substitutions reactions which occur at the 3-position (**Figure 1-2**).

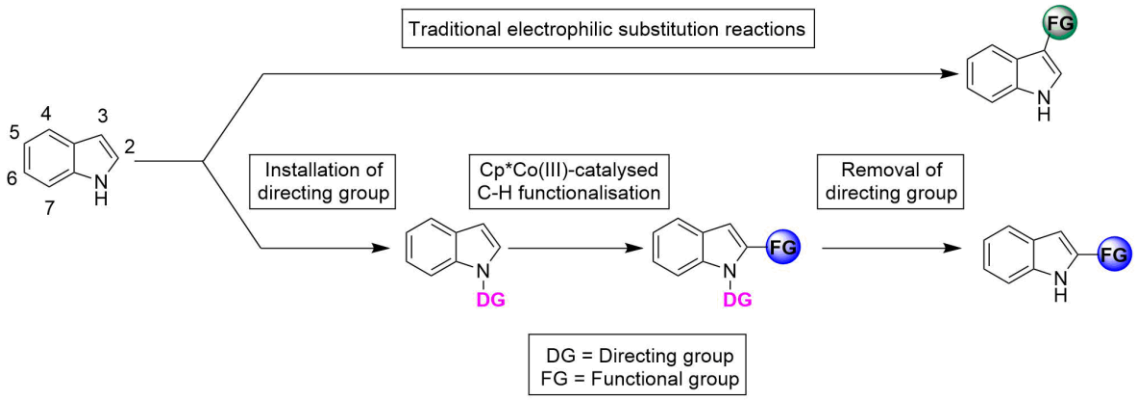
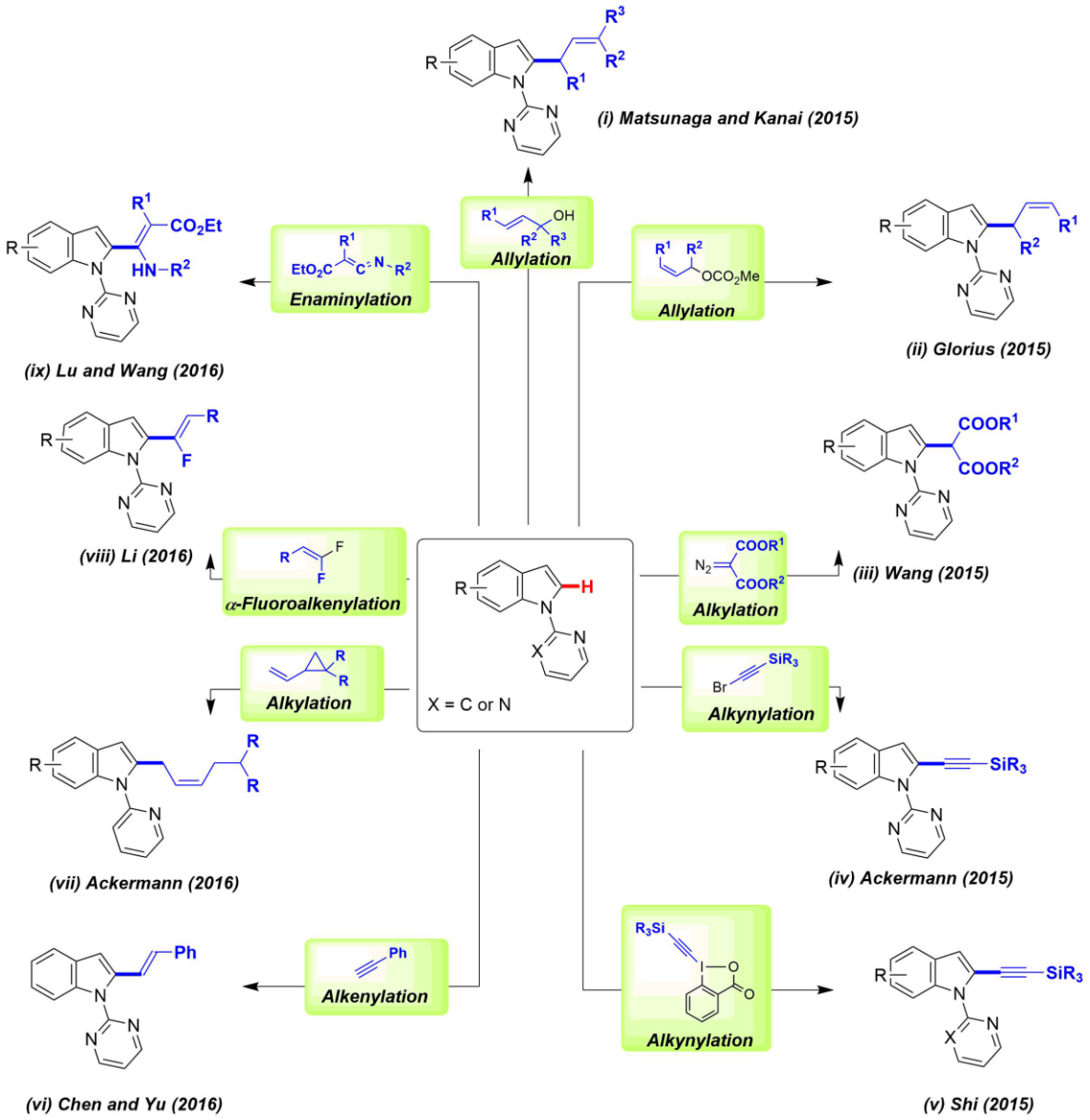


Figure 1-2: Overview of contrast between electrophilic substitution reactions which occur at 3-positions and Cp*Co(III)-catalysed C-H functionalisation reactions, which occur at the 2-position.



Scheme 1-9: Examples of reported C–C couplings using indole-based substrates in 2015 and 2016. General conditions for each example: (i) 5.0 mol% $[Cp^*Co(CO)I_2]$.[35] (ii) 0.5 mol% $[Cp^*Co(CO)I_2$.[36] (iii) 5.0 mol% $[Cp^*Co(CO)I_2]$.[37] (iv) 2.5 mol% $[Cp^*CoI_2]_2$.[39] (v) 5.0 mol% $[Cp^*Co(CO)I_2$.[41] (vi) 5.0 mol% $[Cp^*Co(CO)I_2]$.[42] (vii) 10 mol% $[Cp^*Co(CO)I_2$.[43] (viii) 5.0 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$.[44] (ix) 2.5 mol% $[Cp^*Co(CO)I_2$.[46]

The first C–C coupling to indoles using the $[Cp^*Co(CO)I_2]$ catalyst was reported by Matsunaga/Kanai and co-workers in 2015. This article described the allylation of indoles using allylic alcohols (**Scheme 1-9i**).[35] The $[Cp^*Co(CO)I_2]$ catalyst demonstrated higher reactivity compared with the corresponding $[Cp^*RhCl_2]_2$ catalyst. This is possibly due to the increased oxophillicity of the $[Cp^*Co]^{2+}$ cation compared with the $[Cp^*Rh]^{2+}$ cation, which promotes the

dehydrative C–H allylation with allyl alcohols through a β-hydroxide elimination pathway, rather than a typical β-hydride elimination pathway. The substrate scope demonstrates that the reaction proceeds smoothly with good to excellent yields with a variety substituted indole substrates and allylic alcohols, both terminal and internal. It was possible to convert a pyrrole bearing a pyrimidine directing group, however, this resulted in a double functionalisation at the 2 and 5-positions. Furthermore, 1-phenyl-pyrazole was also successfully converted in good yield under the optimised reaction conditions.

Shortly after this initial report, Glorius and co-workers extended the scope of this allylation protocol to the use of allyl carbonates as coupling partners (**Scheme 1-9ii**).[36] A variety of substituted allyl carbonates could be employed for the allylation of pyrimidylindoles. Besides methyl carbonates, *tert*-butyl carbonates and even allylic alcohol could be utilised as allyl sources. The authors reported that when the methyl carbonate was replaced with *tert*-butyl carbonate, the *E/Z* ratio could be enhanced. This indicated that the conformation of the carbonate at the step of olefin insertion to the organometallic cobaltacycle determines the relative configuration of cobalt and carbonate in the following intermediate and hence the geometry of the final olefin product.

The first example of an alkylation protocol was reported by Wang and co-workers using α-diazomalonates as coupling partners (**Scheme 1-9iii**).[37] These coupling partners have previously shown high reactivity as carbene precursors in transition-metal-catalysed carbene transfer reactions.[38] The substrate scope of this cobalt-catalysed alkylation has shown tolerance of various substituted indoles. Furthermore, *N*-arylpyrazoles and pyrrole could also be successfully converted, although another common substrate class, 2-arylpyridines, were unsuccessful. Interestingly, when β-methylindole was employed as a substrate, an unexpected route towards the mono-ester through a proposed decarbalkoxylation step was reported.

Besides allylation and alkylation, there are also reports of alkynylation protocols using the [Cp*Co(CO)I_2] catalysts. Both the groups of Ackermann and Shi have contributed to this field. Ackermann and co-workers reported an alkynylation

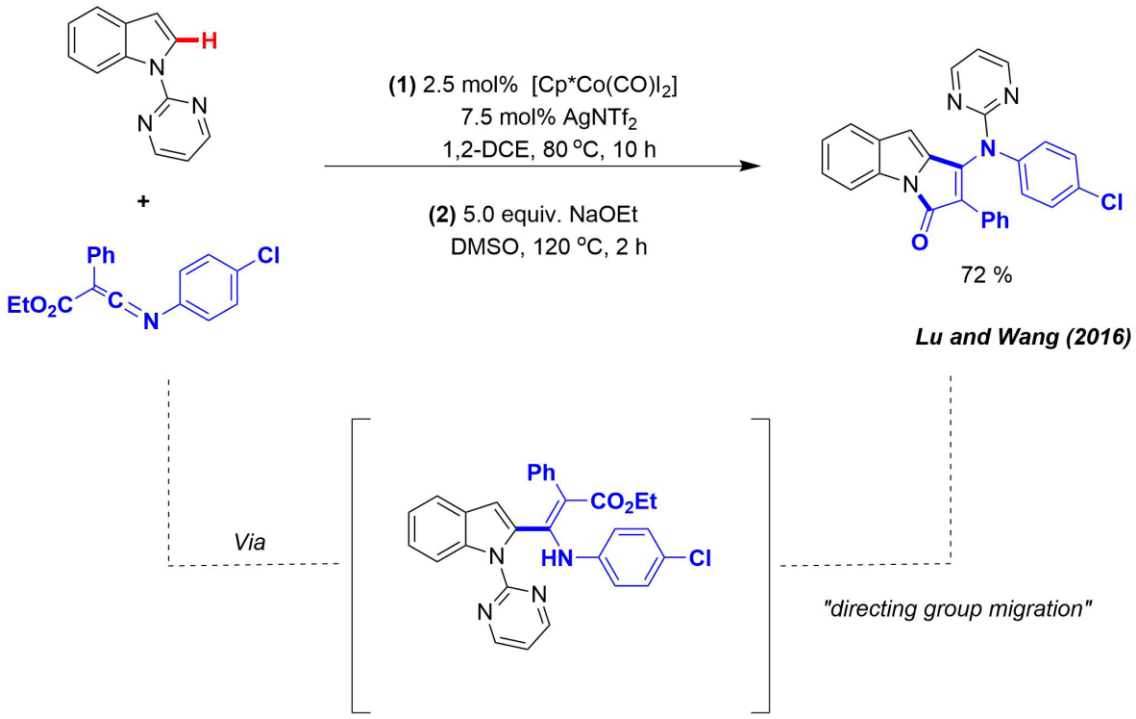
methodology using bromoalkynes as coupling partners (**Scheme 1-9iv**).[39] This protocol operates at room temperature and allowed for direct functionalisation of a wide range of indole-based substrates. The versatile Cp*Co(III)-catalyst was also able to convert pyrroles with similar success upon further increasing the bromoalkyne from 1.1 to 2.0 equivalents. Shi and co-workers demonstrated that the protocols which were previously reported by Li and co-workers using the $[Cp^*RhCl_2]_2$ catalyst [40] could be replicated using the $[Cp^*Co(CO)I_2]$ catalyst. The group achieved this by using hyper-valent iodine-alkyne reagents as coupling agents (**Scheme 1-9v**).[41] The substrate scope illustrated tolerance to a wide range of functionalised indoles, including β-cyanoindole. The drawback to this methodology was the elevated temperature when compared to the protocol of Ackermann and co-workers which operates at room temperature.

The first example of indole-based C-H alkenylation was provided by Chen/Yu in 2016. The authors reported that alkenylation was possible when using phenylacetylene as the coupling partner (**Scheme 1-9vi**).[42] This reaction proceeded extremely rapidly, with almost quantitative yield after only 10 minutes at room temperature.

Also in 2016, Ackermann and co-workers developed the first $[Cp^*Co(CO)I_2]$ catalysed C-H alkylation using vinylcyclopropanes as coupling partners. The authors presented an example of the coupling of vinylcyclopropanes with indole-based substrates bearing a pyridyl directing group (**Scheme 1-9vii**).[43] The methodology notably, delivers the thermodynamically less stable *Z*-alkenes with excellent selectivity. Furthermore, the percentage of *Z*-alkene observed is significantly higher when using the $[Cp^*Co(CO)I_2]$ catalyst compared with analogous rhodium catalyst. Further DFT mechanistic studies indicated that the higher percentage of *Z*-alkene using cobalt catalysis results from a shorter Co-C bond length in the *Z*-organometallic intermediate species.

Fluorine containing compounds are known to play an important role in a variety of areas, particularly in pharmaceutical and medicinal sciences. Thus, the inclusion of fluorine atoms into organic molecules remains an important challenge in synthetic chemistry. Li and co-workers were able to provide an example of a Co(III)-catalysed α-fluoroalkenylation of a variety of hetero(arenes)

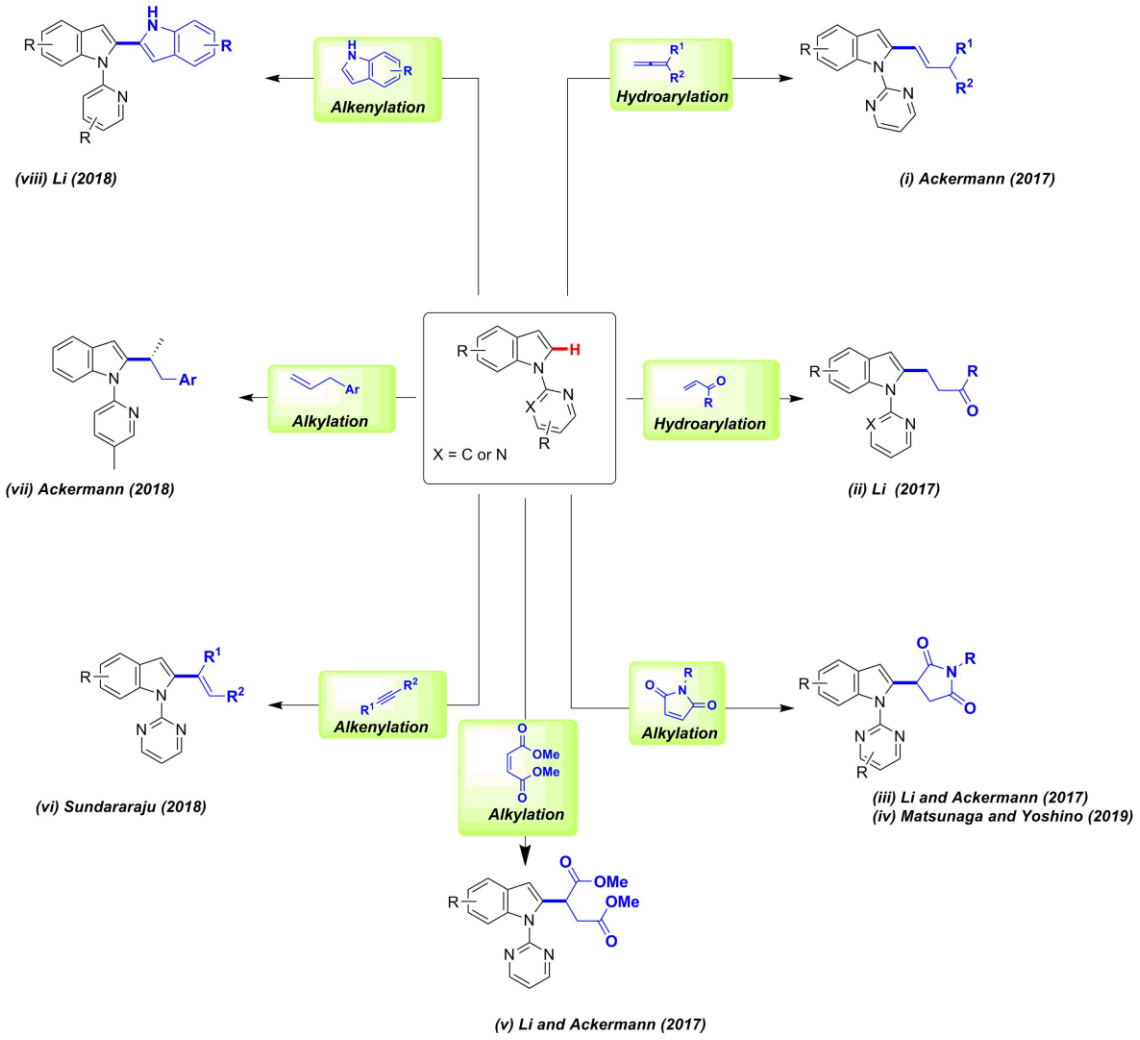
using *gem*-difluorostyrenes as coupling partners (**Scheme 1-9viii**).[44] This protocol is highly efficient and provides monofluoroalkenes with excellent *Z*-selectivity and yield. In this instance the $[Cp^*Co(MeCN)_3](SbF_6)_2$ single component catalyst is used in order to eliminate the need for addition of a silver salt. The mechanism is proposed to proceed *via* a key β-F elimination step and is comparable to the $[Cp^*Rh(MeCN)_3](SbF_6)_2$ catalysed fluoroalkenylation reported previously by Feng/Loh and co-worker.[45]



Scheme 1-10: Example of a facile one-pot preparation of *3H*-pyrrolo[1,2-a]indol-3-ones using cobalt-catalysed C–H functionalisation as the key step.[46]

Lu/Wang and co-workers reported the use of ketenimines as coupling partners for the C-H enaminylation of pyrimidinyl-substituted arenes (**Scheme 1-9ix)**.[46] The indole derivates obtained from this protocol could be easily converted into *3H*-pyrrolo[1,2-a]indol-3-ones, which are a class of compounds that are important in medicinal chemistry, through a base-promoted cyclisation reaction in a second separate or a one-pot procedure (**Scheme 1-10**). This protocol demonstrates the potential of one-pot reactions for construction of compounds with high molecular complexity, using an initial cobalt-catalysed C–H functionalisation step. In addition, the protocol is also able to convert indoline,

pyrrole and phenyl substrates bearing the pyrimidine directing group. However, in the case of indoline the conversion proceeds in relatively modest yield.



Scheme 1-11: Examples of reported C–C couplings using indole-based substrates from 2017 until 2019. General conditions for each example: (i) 5.0 mol% $[Cp^*Co(CO)I_2]$.[47] (ii) 2.5 mol% $[Cp^*Co(CO)I_2]$.[48] (iii) 5.0 mol% $[Cp^*Co(CO)I_2]$.[49] (iv) 5.0 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$.[50] (v) 10 mol% $[Cp^*Co(CO)I_2$.[49] (vi) 5.0 mol% $[Cp^*Co(CO)I_2]$.[51] (vii) 10 mol% $[Cp^*Co(CO)I_2$.[52] (viii) 2.5 mol% $[Cp^*Co(CO)I_2]$.[53]

In 2017 both research groups of Ackermann and Li reported $[Cp^*Co(CO)I_2]$ catalysed hydroarylation protocols (**Scheme 1-11i** and **ii** respectively). Allenes were employed as coupling partners by Ackermann and co-workers providing α,β-unsaturated products (**Scheme 1-11i**).[47] In this report, the authors provide a detailed mechanistic and computational study, which combine to provide evidence for a mechanism which involves C–H cobaltation of the substrate, migratory insertion of the allene, intermediate isomerisation and a final

proto-demetallation step. It was also possible to convert β-methylindole derivatives and 2-phenylpyridine substrates using the same protocol. Meanwhile, Li and co-workers demonstrated that a variety of α,β-unsaturated ketones and glyoxylate could be used as coupling partners (**Scheme 1-11ii**).[48] Again, it was possible to convert β-substituted indole derivatives and the pyrrole derivative, though in moderate yield.

In 2017, Li/Ackermann and co-workers introduced the use of maleimides for the Cp*Co(III)-catalysed C-C bond formation using indoles as substrates (**Scheme 1-11iii**).[49] This strategy offered a wide range of succinimide-containing products in high yield using mild, oxidant free reaction conditions. Furthermore, it was possible to convert several heteroarenes using the developed methodology including 2-pyridylpropene for which a mixture of the 1,4-addition product and the olefin migration product was observed. Matsunaga/Yoshino and co-workers were able to expand this protocol further by reporting the enantioselective 1,4-addition reaction of indoles and maleimides using the single component catalyst, $[Cp^*Co(MeCN)_3](SbF_6)_2$ alongside chiral carboxylic acids (**Scheme 1-11iv**).[50] In this example as well, indoles bearing both electron-withdrawing and electron-donating groups at the 4-, 5-, and 6-position could be successfully converted in high yield and with good enantioselectivity. However, the group reported that when a methyl substituent at the 7-position was employed, a low enantioselectivity was observed.

Li/Ackermann and co-workers also reported the use of maleate ester as coupling partner for the Cp*Co(III)-catalysed C-H alkylation of indoles (**Scheme 1-11v**).[49] Thus, indolyl-substituted succinates were produced in moderate yields. Sundararaju and co-workers likewise, reported moderate to low yields for the Cp*Co(III)-catalysed C-H alkenylation of indoles when utilizing alkynes as coupling partners, under mild conditions (**Scheme 1-11vi)**.[51] It was further noted that possibly due to steric hindrance lower yields were obtained when using diphenylacetylene compared to 5-decyne.

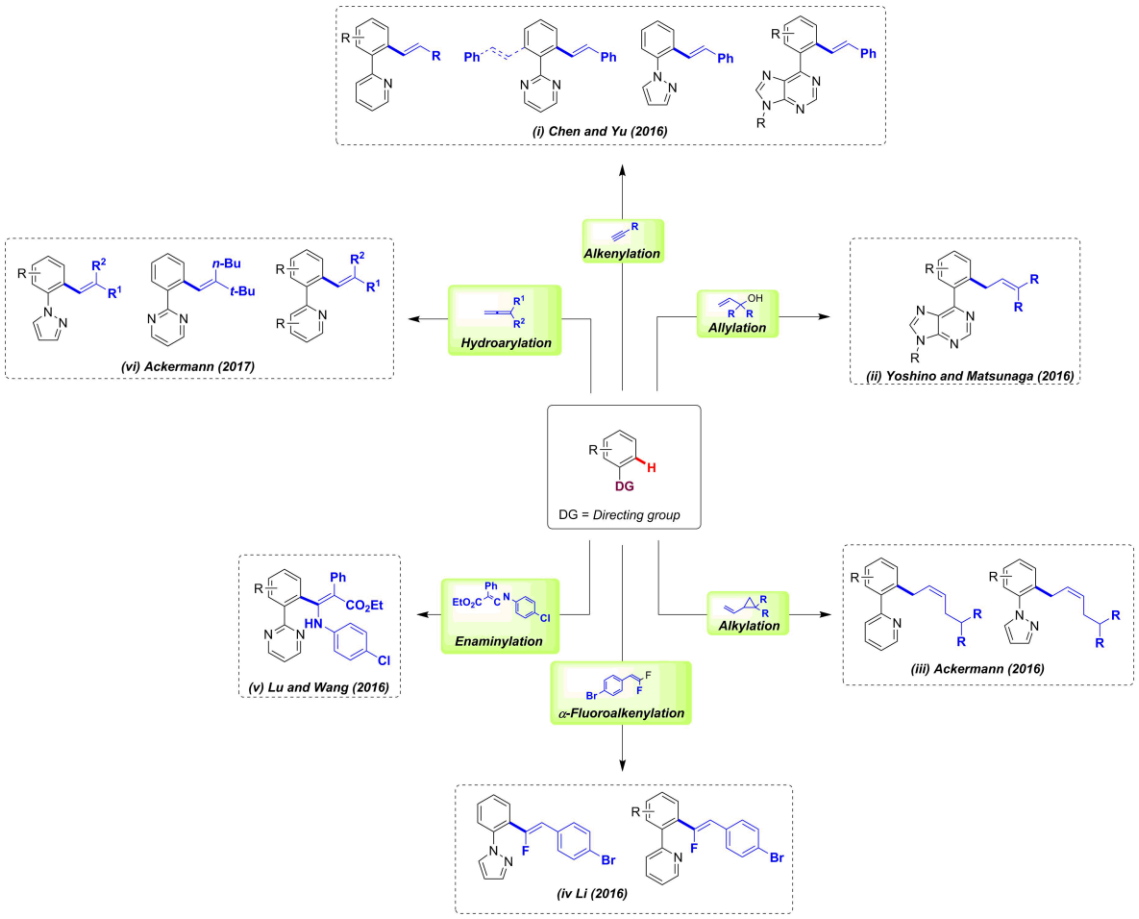
Ackermann and co-workers were the first group to report an enantioselective Cp*Co(III)-catalysed C-H alkylation protocol enabled by chiral carboxylic acids alongside an Amberlyst 15 additive (**Scheme 1-11vii**).[52] High

enantioselectivities were reported for a variety of substituted indoles with good functional group tolerance. The synthetic functionality of the protocol was further demonstrated by the facile removal of the directing group without impacting the enantiomeric excess.

Most recently, in 2018 Li and co-workers reported an example of cross-dehydrogenative coupling of *N*-(2-pyridyl)-based substrates with free indoles (**Scheme 1-11viii**) that allows the construction of unsymmetrical 2,2-bisindoles, which have shown to be ubiquitous compounds in medicinal sciences.[53] The protocol demonstrates good tolerance for a variety of functional groups for both *N*-(2-pyridyl) and free indoles. Mechanistic investigations revealed that the C-H cleavage on the *N*-(2-pyridyl) was not the rate-determining step with a K_H/K_D value of 1.05 being observed. A high value of 4.05 was observed for the K_H/K_D C-H cleavage on the free indole which suggested this might be the rate-determining step. Furthermore, it was possible to remove the directing group to allow the synthesis of unsymmetrical 2,2-biindoles.

1.4.1.1.2 C-C couplings with 2-aryl pyridine and related substrates

2-Arylpyridine and arylpyrimidine related substrates have been utilised as proof-of-concept substrates for many transition metal-catalysed C-H functionalisation protocols to report novel bond formation reactions for both C-C and C-heteroatom bonds. These substrates are relatively easy to convert due to the rigid nature of the aromatic rings and the available coordination site for directed C-H activation. In the last few years, a variety of Cp*Co(III)-catalysed C-H functionalisation protocols have been reported using 2-arylpyridine and related substrates.



Scheme 1-12: Examples of reported C–C couplings using 2-aryl pyridine-based substrates from 2016 and 2017. General conditions for each example: (i) 5.0 mol% $[Cp^*Co(CO)I_2]$.[42] (ii) 5.0 mol% $[Cp^*Co(CO)I_2]$.[54] (iii) 10 mol% $[Cp^*Co(CO)I_2]$.[43] (iv) 5.0 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$.[44] (v) 2.5 mol% $[Cp^*Co(CO)I_2]$.[46] (vi) 5.0 mol% $[Cp^*Co(CO)I_2]$.[47]

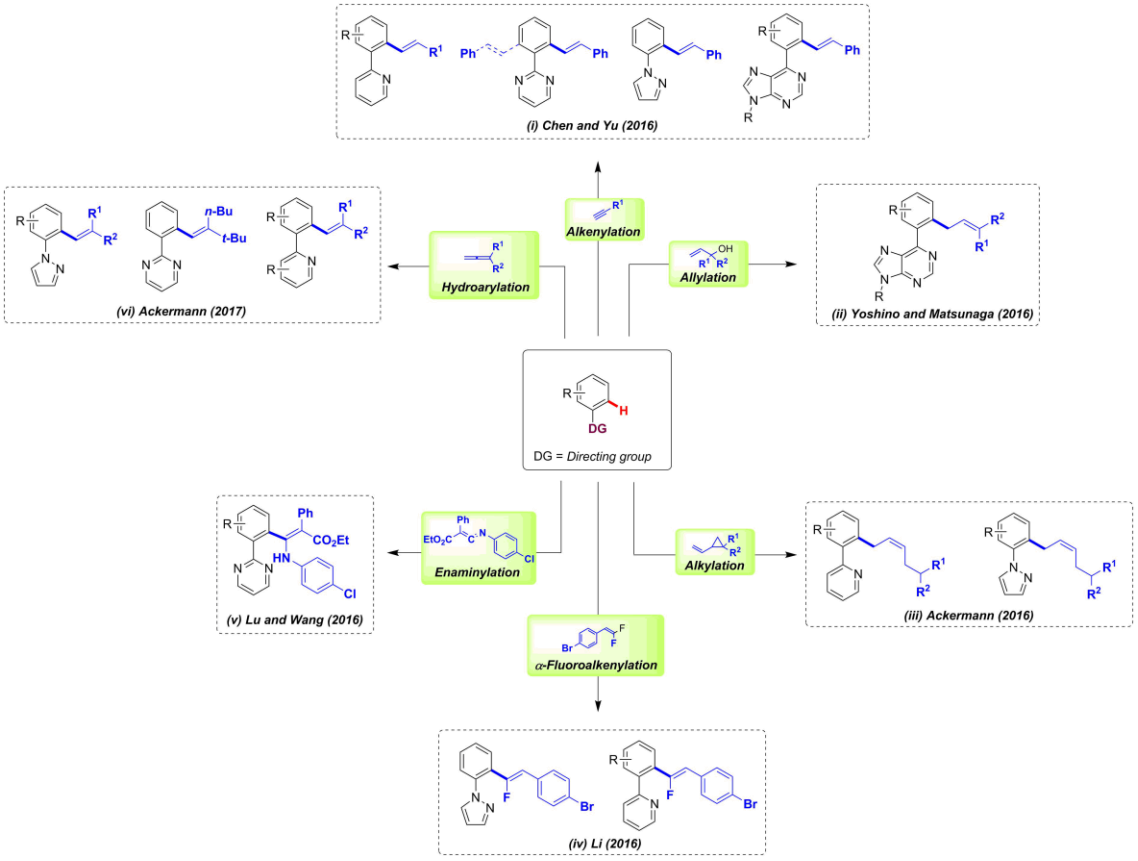
The first example of a Cp*Co(III)-catalysed C-C bond formation using 2-arylpyridine and related substrates was reported by Chen/Yu and co-workers in 2016. The authors reported a wide substrates scope for the alkenylation of 2-arylpyridines with terminal alkynes using the $[Cp^*Co(CO)I_2]$ catalyst (**Scheme 1-12i**).[42] When 2-arylpyrimidine substrates were employed, mixtures of mono- and di-functionalisation products were obtained and when the loading of phenylacetylene was doubled, the yield of the di-functionalised product was increased, although a mixture of both products was still observed. The alkenylation protocol could also be transferred successfully to 6-arylpurine derivatives. Furthermore, the protocol could be scaled at least tenfold without significant loss in yield.

Yoshino/Matsunaga and co-workers reported the dehydrative CpCo(III)-catalysed C–H allylation of 6-aryl purines using allyl alcohols as coupling partners (**Scheme 1-12ii**).[54] The use of fluorinated solvent was found to be key, as the conversion was significantly reduced when using other solvents.

Ackermann and co-workers extend their protocol for alkylation of indoles to 2-arylpyridines and 2-arylpyrazoles (**Scheme 1-12iii**).[43] The substrate scope illustrated high yields for substituted 2-arylpyridines and 2-arylpyrazole with good Z-selectivity. Furthermore, only mono-functionalised arenes were furnished. In contrast, it was noted that when Rh catalysts were employed mono- and di-functionalised products were recovered

Both Li and Lu/Wang and have also extended the application of their C-H α-fluoroalkenylation and C-H enaminylation protocols, to include 2-arylpyridine type of substrates.[44,46] The α-fluoroalkenylation (**Scheme 1-12iv**) takes place under mild conditions and proceeds for 2-arylpyridine and 2-arylpyrazole. However, the enaminylation protocol reported by Lu/Wang and co-workers only provided products in modest yield compared with indole-based substrates containing a pyrimidine directing group (**Scheme 1-12v**).

In a similar way, Ackermann and co-workers transferred their hydroarylation protocol to 2-aryl pyridine and 2-arylpyrimidine substrates (**Scheme 1-12vi**),[47] although again observing reduced yields compared to the same conversions with indole-based substrates containing pyrimidine directing groups.



Scheme 1-13: Examples of reported C–C couplings using 2-aryl pyridine-based substrates from 2018 and 2019. General conditions for each example: (i) 5.0 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$.[55] (ii) 5.0 mol% $[Cp^*Co(CO)I_2]$.[56] (iii) 10 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$.[57] (iv) 5.0 mol% $[Cp^*Co(CO)I_2]$.[51] (v) 5.0 mol% $[Cp^*Co(CO)I_2]$.[58] (vi) 5.0 mol% $[Cp^*Co(CO)I_2]$.[58]

More recently, in 2018 Matsunaga/Yoshino and co-workers reported that the substrate scope of the fluoroalkenylation reaction could be expanded by applying the protocol to 6-arylpurine substrates as well (**Scheme 1-13i**).[55] Similar, to the procedure described by Li and co-workers,[44] the single component catalyst $[Cp^*Co(MeCN)_3](SbF_6)_2$ was found to be optimal, alongside hexafluoro-2-propanol as solvent. A variety of *gem*-difluoroalkenes were employed for the synthesis of monofluoroalkenes and good functional group tolerance was observed. Additionally, the authors also described the allylation of 6-arylpurines using allyl fluorides. This reaction also proceeded in good yields and its functionality was further demonstrated by performing a large-scale reaction.

Clavier and co-workers developed a Cp*Co(III)-catalysed C-H allylation protocol using vinylazirides as coupling partners (**Scheme 1-13ii**).[56] A range of arenes

could be converted in high yield under the optimised reaction conditions including *para*-functionalised 2-phenylpyridines and a pyrazole-containing substrate. Furthermore, the group tested the limitations of the protocol by broadening the variety of vinylazirides used. It was possible to convert 2-phenylpyridine using a broad range of vinylazirides however, low *E/Z* selectivity was observed regardless of which coupling partners or arenes were employed.

The single component catalyst $[Cp^*Co(MeCN)_3](SbF_6)_2$ also facilitated the acylmethylation of 2-arylpyridines using sulfoxonium ylides, as reported by Wang and co-workers (**Scheme 1-13iii**).[57] The reaction protocol tolerated a broad range of both 2-arypyridines and sulfoxonium ylides with good to excellent yields being observed.

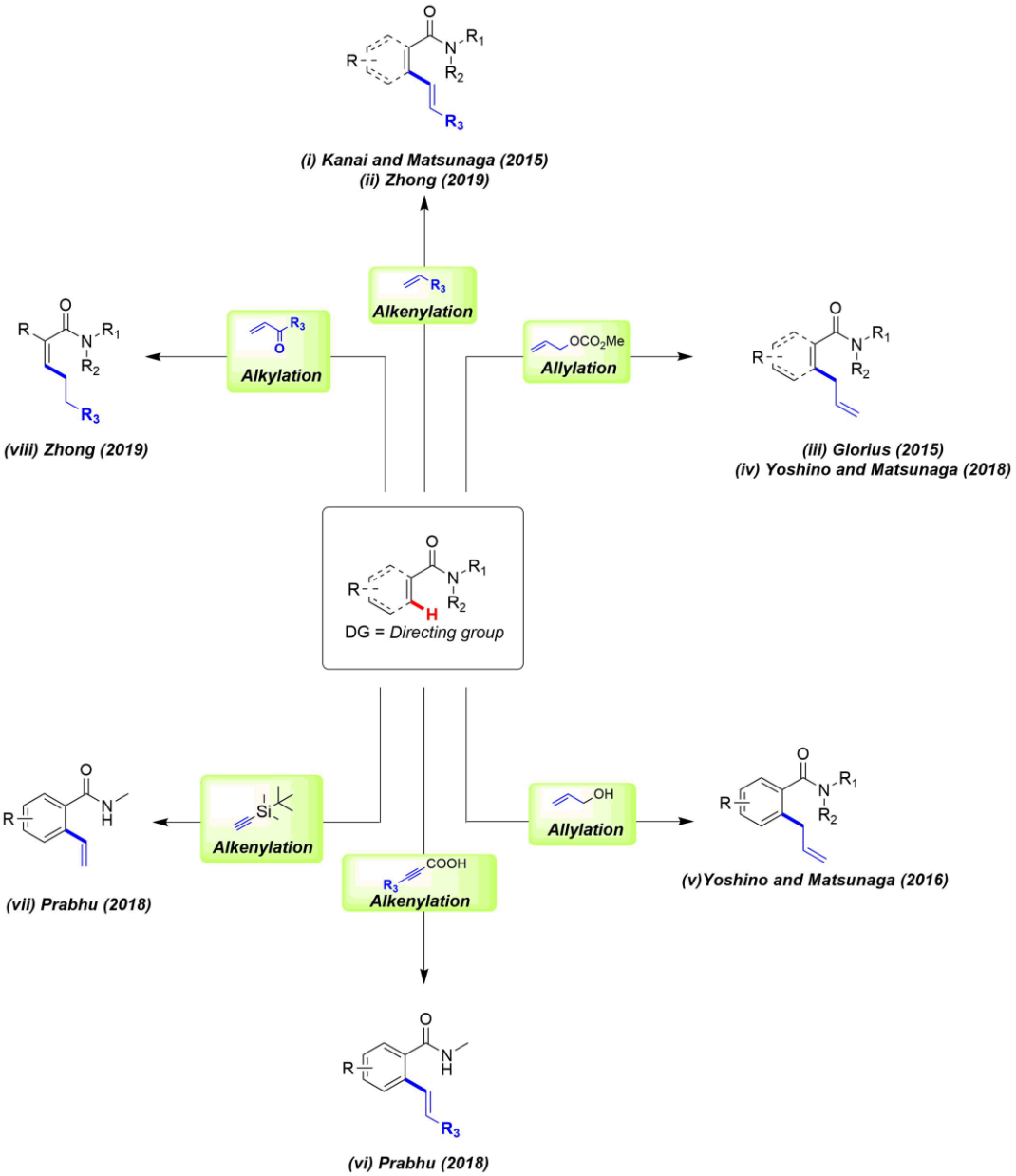
Sundararaju and co-workers developed the Cp*Co(III) C-H alkenylation of 2-arylpyrazoles using alkynes under mild conditions (**Scheme 1-13iv**).[51] Compared to the C-H alkenylation of indoles, 2-arylpyrazoles could be converted in higher yields, with a broad range of functional groups being tolerated. The group were able to isolate the Cp*Co(III)-alkenyl intermediate after the alkyne insertion step, which was analysed by X-ray crystallography, NMR spectroscopy and mass spectrometry.

In 2019, Prabhu and co-workers reported the cobalt-catalysed C-H alkenylation of 2-arylpyrazoles using arylalkynylsilane derivatives (**Scheme 1-13v**) and arylalkynyl carboxylic acids (**Scheme 1-13vi**) as coupling agents.[58] A range of substituted alkenylated products could be obtained through decarboxylation and desilylation mechanisms.

1.4.1.1.3 C-C couplings with benzamide-type substrates

Besides the use of indole-based and 2-aryl pyridine/related substrates, Cp*Co(III)-catalysed C-H functionalisation couplings have also been successfully developed using simple benzamide-based substrates. In this section, an overview of these couplings will be presented. Whilst cobalt-catalysed C–H functionalisation of benzamides is relatively well established using cobalt(II) salts, as a result of the ground breaking work of

Daugulis and co-workers using the 8-aminoquinoline directing group,[27] there are fewer examples of terminal additions using the [Cp*Co(CO)I_2].

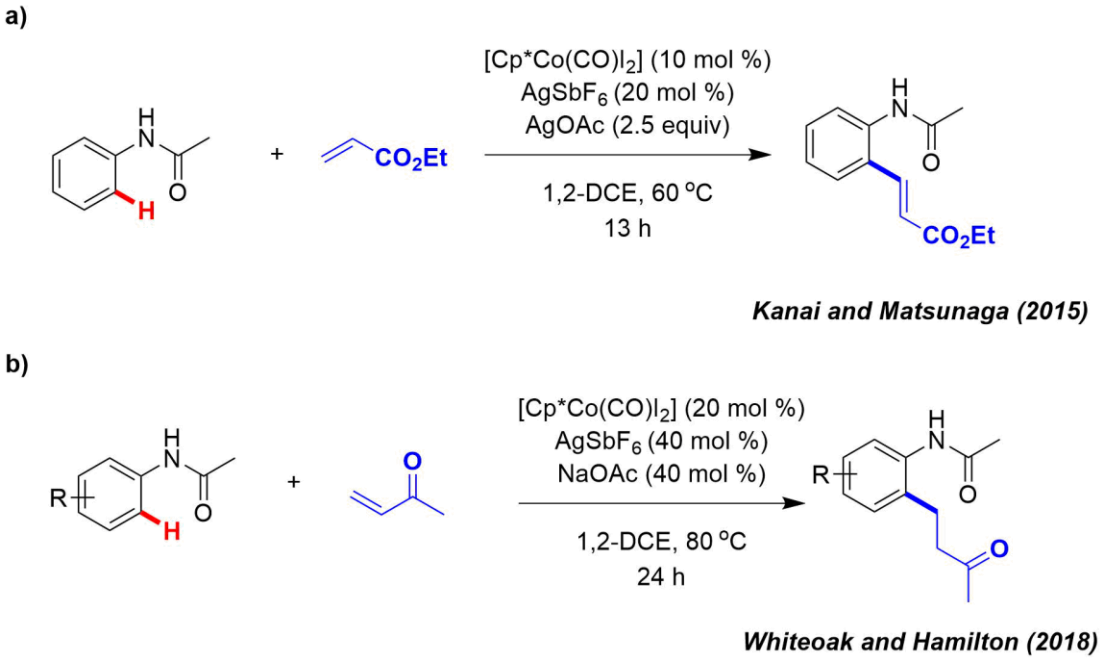


Scheme 1-14: Examples of terminal couplings using benzamide. General conditions for each example: (i) 10 mol% [Cp*Co(CO)I_2].[59] (ii) 10 mol% [Cp*Co(CO)I_2].[61] (iii) 2.5 mol% [Cp*CoI_2]$_2$.[36] (iv) 10 mol% [Cp*Co(CO)I_2].[62] (v) 5.0 mol% [Cp*Co(CO)I_2].[54] (vi) 5.0 mol% [Cp*Co(CO)I_2.[63] (vii) 5.0 mol% [Cp*Co(CO)I_2].[63] (viii) 10 mol% [Cp*Co(CO)I_2].

In 2015 Kanai/Matsunaga and co-workers presented an example of C-H alkenylation of benzamides using ethyl acrylate as coupling partner (**Scheme 1-14i**).[59] In this example the authors propose that rather than the typical redox

neutral catalytic cycle proposed in the majority of protocols using [Cp*Co(CO)I_2], the reaction proceeds through is a reductive elimination step and hence super-stoichiometric AgOAc oxidant was required. This coupling was also able to be applied to acetanilides (**Scheme 1-15a**). Whiteoak/Hamilton and co-workers also reported a protocol that employed acetanilides and the alkylation was found to be challenging due to the unfavourable coordination of the coupling partner to the organometallic intermediate (**Scheme 1-15b**).[60]

More recently, in 2019 Zhong and co-workers expanded the scope of this protocol by reporting the C-H alkenylation of acrylamides using broad scope of acrylates as coupling partners (**Scheme 1-14ii**).[61] The reaction takes place *via* the same reductive elimination step with AgOAc being used as the external oxidant. Interestingly, the group reported that by carefully selecting coupling partners and performing the reaction without AgOAc it was possible for the acrylamides to undergo a C-H alkylation reaction instead (**Scheme 1-14viii**). When unsaturated ketones are used as coupling partners the reaction proceeds through a redox-neutral mechanism *via* a proto-demetallation step.



Scheme 1-15: a) Cp*Co-catalysed alkenylation of acetanilide using a) ethyl acrylate as coupling partner reported by Kanai/Matsunaga [59] b) 3-buten-2-one reported by Whiteoak/Hamilton.[60]

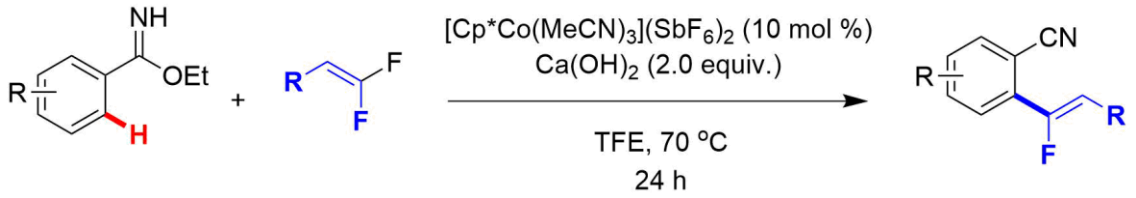
Glorius and co-workers reported a different reaction pathway by replacing the acrylate coupling partners with allyl carbonates (**Scheme 1-14iii**).[36] This

protocol was able to convert both benzamides and acrylamides, although significantly lower yields were observed for the acrylamides. In 2018, Matsunaga/Yoshino and co-workers reported a variety of C-H functionalisation protocols using synthetically useful Weinreb amides which included a C-H allylation procedure using allyl carbonates (**Scheme 1-14iv**).[62] Matsunaga/Yoshino and co-workers have also provided a methodology for allylating benzamide substrates using alcohols as allylating agents (**Scheme 1-14v**).[54] A moderate yield was observed when employing a Weinreb amide due to its weak coordinating ability.

In 2018, Prabhu and co-worker developed the C-H alkenylation of *N*-methyl benzamide derivatives using alkynyl carboxylic acids as coupling agents *via* decarboxylation of the corresponding acids (**Scheme 1-14vi**).[63] This protocol yields solely the linear alkenylation product; the potential cyclic product was not observed. Moreover, the same group reported another example for C-H alkenylation of *N*-methyl benzamides using alkynylsilanes as coupling agents through a novel SbF_6^- triggered desilylation (**Scheme 1-14vii**).

1.4.1.1.4 C-C coupling with other substrates

Although indoles, 2-aryl pyridine and benzamides related substrates have been utilised more often for the development of C-H activation reactions due to their versatility, novel coupling reactions have also been reported using other classes of substrates. This section is a summary of C-C couplings using miscellaneous substrates.

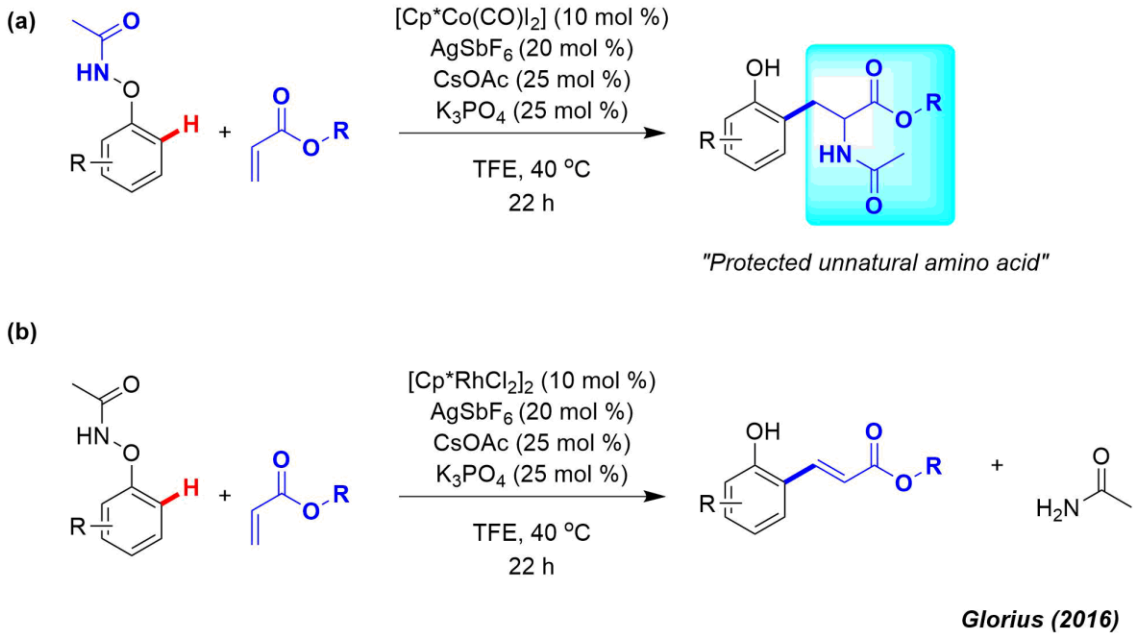


Li (2016)

Scheme 1-16: Coupling of alkylbenzimidates with *gem*-difluoroalkenes reported by Li and co-workers.[44]

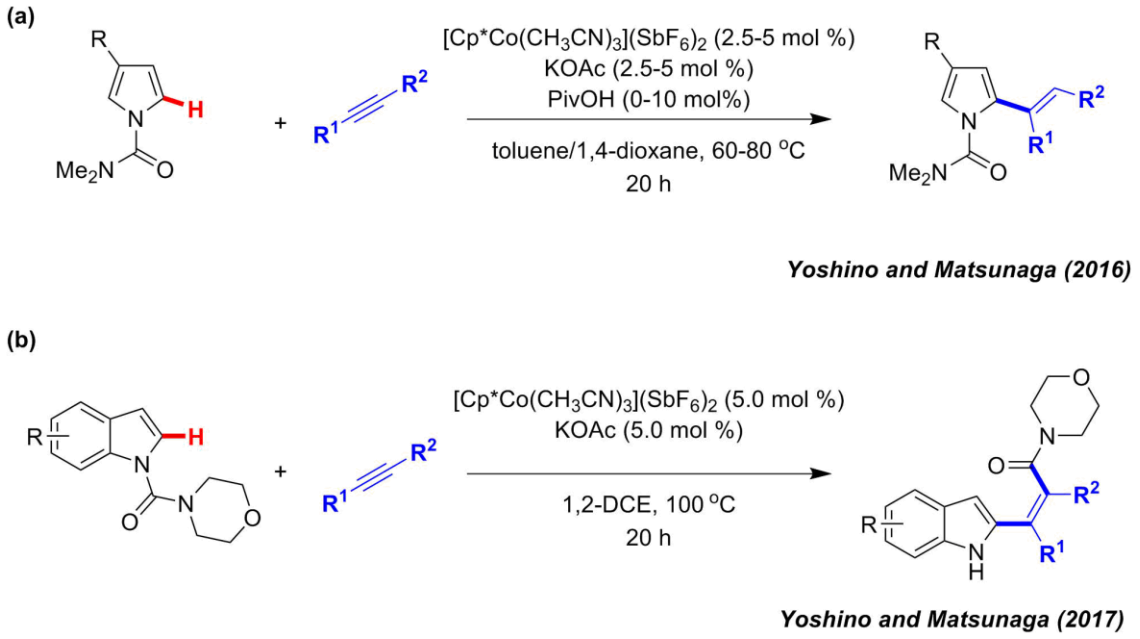
Whilst Li and co-workers were exploring the potential of their α-fluoroalkenylation using alkylbenzimidates as coupling partners, the authors observed an unusual product outcome (**Scheme 1-16**).[44] Rather than providing

a simple terminal coupling as would be expected, the final product was a substituted benzonitrile, demonstrating further applicability of their protocol.



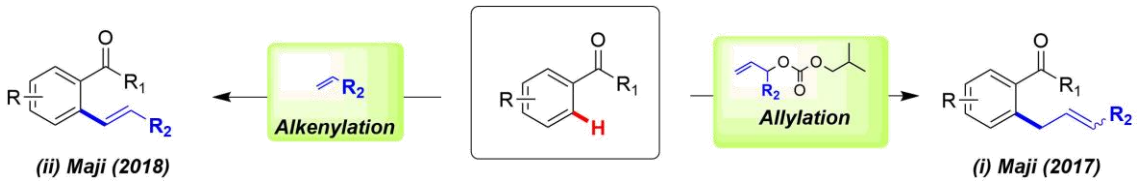
Scheme 1-17: Example of differential outcome when coupling phenoxyacetamides with alkylacrylates using either cobalt or rhodium catalysts, reported by Glorius and co-workers.[64]

Glorius and co-workers have demonstrated application of the [Cp*Co(CO)I_2] catalyst for the facile formation of potentially valuble unnatural protected amino acids (**Scheme 1-17**).[64] The reaction proceeds by an intermolecular carboamination of the alkene, with the participating amine coming from a transfer from within the substrate itself. The authors also report contrasting reaction outcomes using Cp*Co(Ⅲ) and Cp*Rh(Ⅲ) catalysis, which results from the increased tendency for β-H elimination when utilising rhodium catalysts.



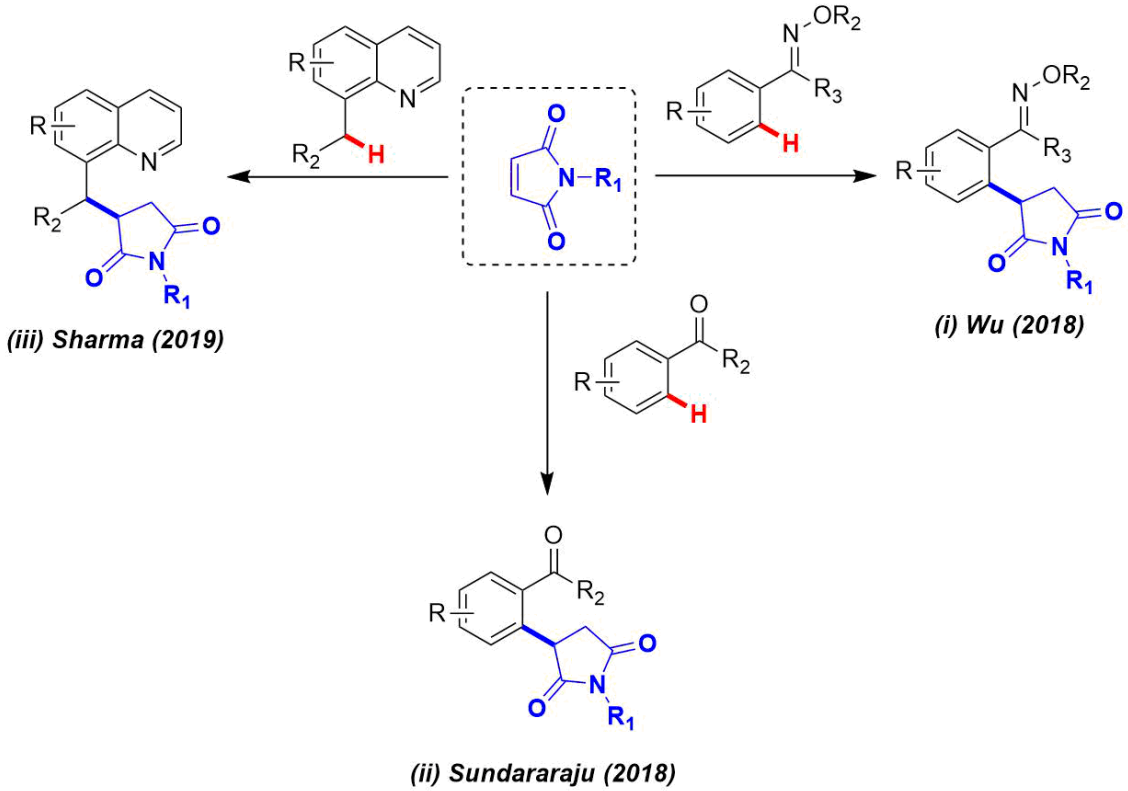
Scheme 1-18: Alkyne coupling to (a) pyrrole [65] and (b) indole, using carbonyl directing groups.[66]

In 2016, Yoshino/Matsunaga and co-workers reported on the alkenylation of dimethylcarbamoyl-protected pyrroles (**Scheme 1-18a**).[65] The protocol was found to only mono-alkenylate at the 2-position or 5-position when unsymmetrically substituted pyrroles were employed. Under the optimised reaction conditions rhodium catalysts do not display any activity, again showing the distinct reactivity of Cp*Co(III) catalyst. More recently, the same group provided a new coupling protocol with indole substrates bearing a carbonyl directing group with a range of alkynes. This new example also involved a directing group migration, providing access to a new family of tetrasubstituted alkenes (**Scheme 1-18b**).[66] This reactivity pattern could not be observed using Rh catalysts, although this new report is in contrast to previous work where the same substrate was converted to pyrroloindolones using the $[Cp^*Co(benzene)](PF_6)_2$ catalyst.[66]



Scheme 1-19: Examples of C-H functionalisation using ketones as substrates reported by Maji and co-workers.[67]

Maji and co-workers reported two examples of cobalt-catalysed C-H functionalisation using weakly coordinating ketones as directing groups (**Scheme 1-19**). Regioselective C-H allylation of a broad range of arenes was achieved using allyl isobutyl carbonate.[67] The group also developed a C-H alkenylation protocol to further expand the scope of ketones as directing groups.[68] Once again it was possible to convert a broad range of aromatic ketones using acrylates as coupling partners. The practicality of both these reactions was demonstrated by the synthesis of potentially valuable compounds starting from the C-H functionalisation products.

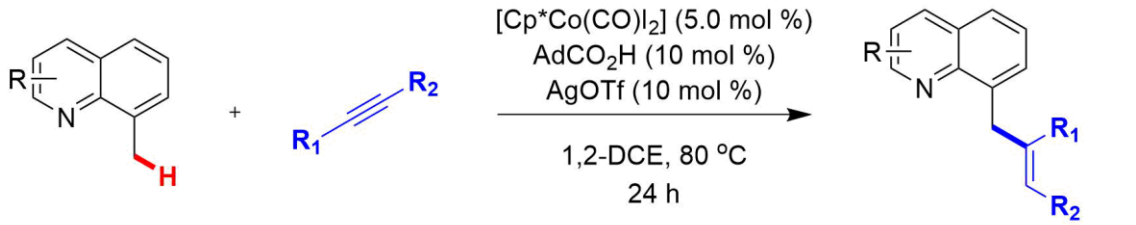


Scheme 1-20: Examples of C-H functionalisation reactions using maleimides as coupling partners. [69-71]

In the last two years there have been several examples of C-H functionalisation reactions using maleimides as coupling partners reported. Wu and co-workers developed a methodology for the synthesis of succinimide derivatives employing the Cp*Co(III)-catalysed 1,4-addition reaction of aryl ketoximines and maleimides (**Scheme 1-20i**).[69] The reaction takes place in the absence of base and it showed good tolerability for a broad range of functional groups. The novel succinimide derivatives could be further transformed into several valuable compounds.

Sundararaju and co-workers also explored the synthesis of succinimides which are frequently used as antidepressants and anticonvulsants. In this instance aromatic ketones and esters with weakly coordinating groups were employed alongside maleimides (**Scheme 1-20ii**).[70] The Cp*Co(CO)I_2 catalyst showed high activity for a large number of substituted ketones and maleimides. Furthermore, the reaction proceeded in good yield when esters were examined as substrates however, in this case trifluoroethanol (TFE) was found to be the optimal solvent instead of 1,2-DCE. The competition reaction between strong and weakly coordinating groups using *aza*-indolyl-substituted arylketone demonstrated that the ketone is preferred as directing group over pyridine. This could be explained by the increased stability of a 5-membered metallocycle compared to a 6-memered one.

In 2019, Sharma and co-workers reported a rare example of C-H functionalisation of C(sp^3)–H bonds, using 8-methylquinoline as substrates alongside maleimides (**Scheme 1-20iii**).[71] The developed method could be applied to over forty substituted 8-methylquinolines substrates with good functional groups tolerance. This protocol is of interest as it can transform also secondary C(sp^3)–H bonds.



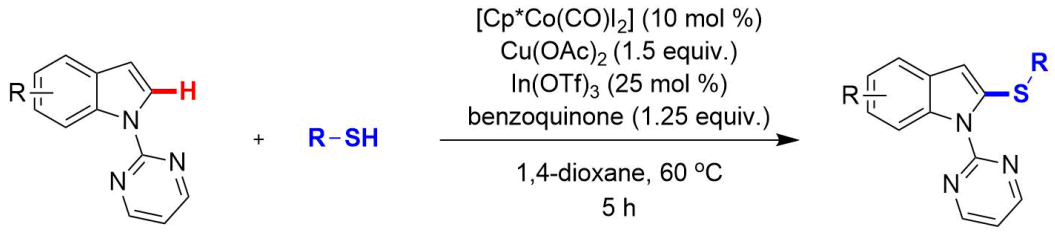
Scheme 1-21: C(sp^3)–H functionalisation of 8-methylquinolines with alkynes, reported by Sundararaju and co-workers.[72]

C-H activation of C(sp^3)–H bonds using first row transition metals has proven to be challenging in the past, with only a few examples of methodologies being available in the literature. In 2016, Sundararaju and co-workers reported the first example C-H functionalisation of C(sp^3)–H bonds using 8-methylquinoline as substrates alongside alkynes as coupling agents for the development of a Cp*Co(III) C-H alkenylation reaction (**Scheme 1-21**).[72]

1.4.1.2 C-S couplings using Cp*Co(III) catalysis

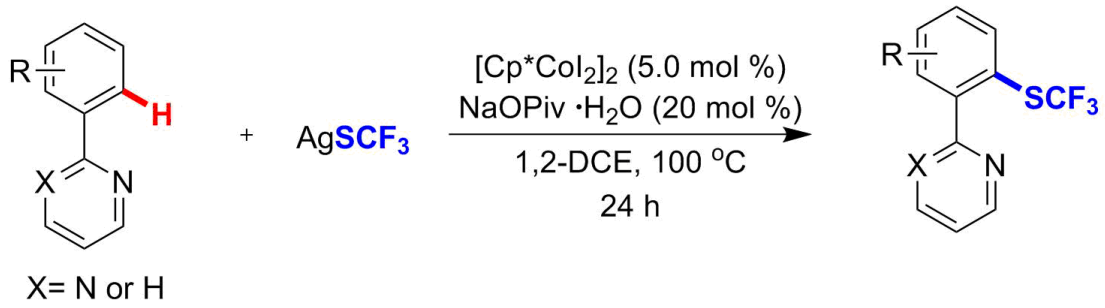
In 2016, Glorius and co-workers reported the first Cp*Co(III)-catalysed thiolation protocol through the dehydrogenative cross-coupling reaction between indoles and thiols (**Scheme 1-22**).[73] In addition to thiolation, this report also contains an example of selenation through use of diphenyl diselenide as coupling partner. The unique role of the Cp*Co(III)-catalyst is confirmed as only traces of the thiolation product were observed when the Cp*Rh-catalyst or cobalt salts were utilised as catalysts. The report underlines the importance of using the [Cp*Co(CO)I_2] catalyst further by performing a reaction in the absence of a cobalt catalyst and observing that β-thiolation products were selectively obtained instead of the α-thiolation products.

In addition, the authors also attempted to provide insight into possible reaction intermediates, by monitoring the reaction mixture after 5 minutes using ESI mass spectroscopy which revealed the presence of organometallic cobalt(III) intermediates.



Scheme 1-22: Dehydrogenative cross-coupling reaction between indoles and thiols, reported by Glorius and co-workers.[73]

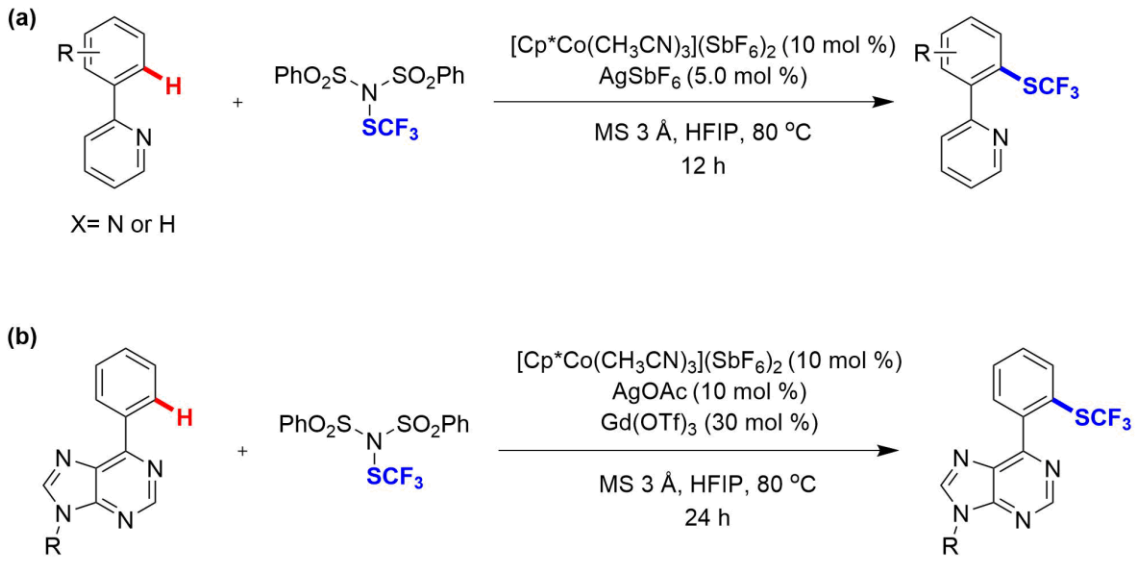
In 2017, Wang and co-workers have presented the first trifluoromethylthiolation using the dimer organometallic complex, [Cp*CoI_2]$_2$, as catalyst (**Scheme 1-23**).[74] This conversion was found to only proceed with 2-arylpyridine and 2-arylpyrimidine substrates with a range of other common classes of substrate (e.g. indole-based substrates containing a pyrimidine directing group) being employed unsuccessfully.



Wang (2017)

Scheme 1-23: Trifluoromethylthiolation of 2-arylpyridine and 2-arypyrimidine using $AgSCF_3$, reported by Wang and co-workers.[73]

The optimised protocol provided a range of differently substituted trifluoromethylthiolated products in moderate yield. Furthermore, the report highlights that both $[Cp^*Rh(III)Cl_2]_2$ and $[Cp^*Ir(III)Cl_2]_2$ catalysts showed no conversion under the optimised conditions, demonstrating once again the uniqueness in the reactivity of Cp*Co(III)-catalysts.



Yoshino and Matsunaga (2017)

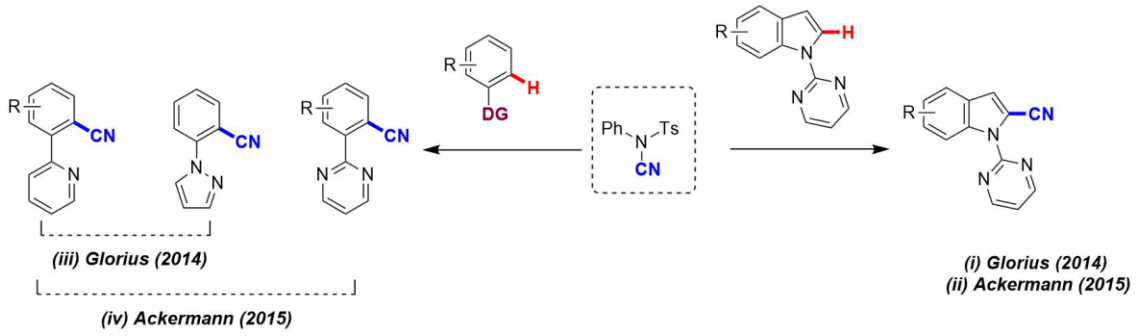
Scheme 1-24: Trifluoromethylthiolation of (a) 2-arylpyridine and (b) 6-arylpurine using *N*-trifluoromethylthiodibenzenesulfonimide, reported by Yoshino/Matsunaga and co-workers.[75]

Soon after that, Yoshino/Matsunaga and co-workers also reported the trifluoromethylthiolation of 2-arylpyridines using *N*-trifluoromethyl-thiodibenzenesulfonimide as coupling agents (**Scheme 1-24a**). The group have extended the substrate scope further and also included 6-arylpurines as

substrates (**Scheme 1-24b**).[75] In this example, the single component catalyst, $[Cp^*Co(MeCN)_3](SbF_6)_2$, showed higher reactivity compared to the $[Cp^*Co(CO)I_2]/AgSbF_6$ catalyst system.

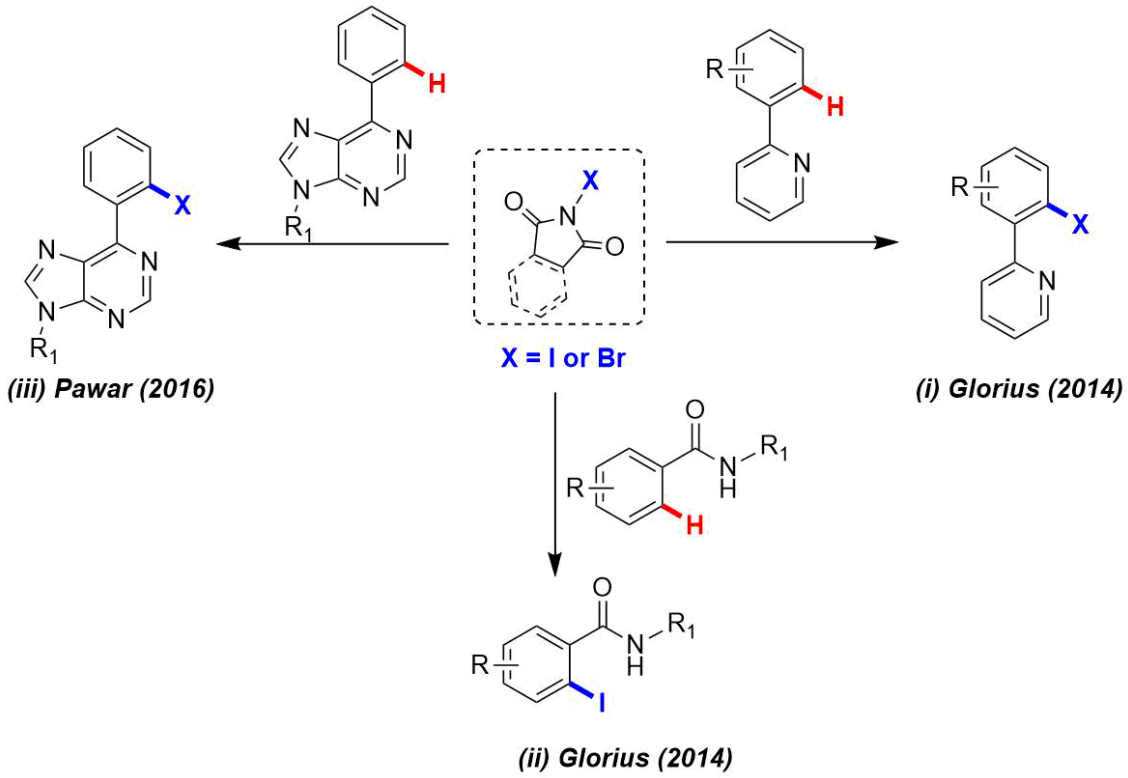
1.4.1.3 C-X couplings using Cp*Co(III) catalysis

In late 2014, both the groups of Glorius and Ackermann simultaneously reported $[Cp^*Co(CO)I_2]$ catalysed cyanation protocols for indole and 2-arylpyridine based substrates using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as cyanating agent (**Scheme 1-25**).[76,77] In both examples the catalyst system tolerates a wide variety of substituted indoles, 2-arylpyridines and related substrates and β-methylindole. In addition, Ackermann and co-worker demonstrated that pyrrole and thiophenes could also be cyanated using the optimised catalytic protocol in good to quantitative yields.



Scheme 1-25: C-H cyanation of indoles and 2-arylpyridine based substrates using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide as a cyanating agent, reported by Glorius and Ackermann.[76-77]

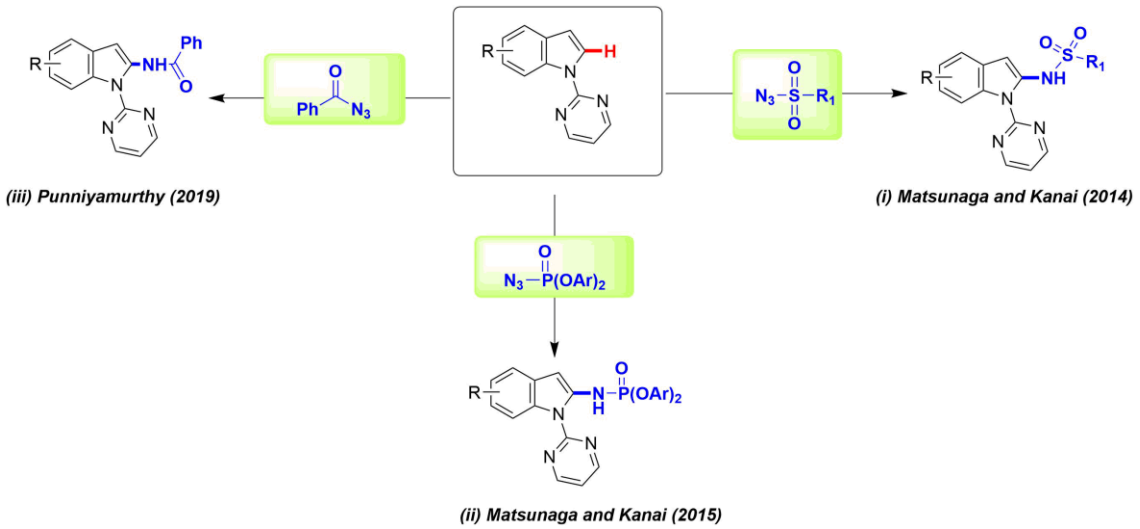
Glorius and co-workers have also reported an example of iodination and bromination of 2-aryl pyridines, although yields of the bromination product were found to be low (**Scheme 1-26i**).[76] In this example, *N*-iodosuccinimide (NIS) and *N*-bromophthalimide (NBP) were employed as iodinating and brominating agents respectively. The group also reported the C-H halogenation of benzamides under the same conditions with modest yields being observed (**Scheme 1-26ii**).



Scheme 1-26: Examples of C-H halogenation reactions. General conditions: 10 mol% $[Cp^*Co(CO)I_2]$.[76] (ii) 10 mol% $[Cp^*Co(CO)I_2]$.[76] (iii) 5.0 mol% $[Cp^*CoI_2]_2$.[78]

Further development and application of halogenation protocols has been reported by Pawar and co-worker (**Scheme 1-26iii**).[78] This report describes the iodination and bromination of 6-arylpurines. Not only could the developed protocol covert 6-arylpurines, but it was also able to convert 2-thiophenepurines, although other heterocyclic purines could not be successfully converted.

1.4.1.4 C-N couplings using Cp*Co(III) catalysis

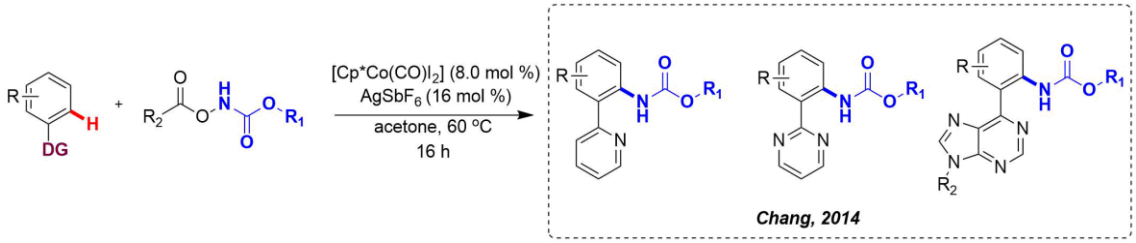


Scheme 1-27: Examples of Cp*Co (III)-catalysed C-H amidation reactions using indoles as substrates and azides as coupling partners. General conditions: (i) 2.5 mol% $[Cp^*Co(CO)I_2]$.[79] (ii) 5.0 mol% $[Cp^*CoI_2]_2$.[81] (iii) 5.0 mol% $[Cp^*Co(CO)I_2]$.[82]

As mentioned earlier, the first example where the $[Cp^*Co(CO)I_2]$ complex was used as a catalyst for a C–H functionalisation protocol was reported by Matsunaga/Kanai and co-workers, in 2014. The authors described the C-H amidation of indoles bearing a pyrimidine directing group using aryl/alkyl sulfonyl azides as coupling partners. This report demonstrated for the first time the increased efficiency of the $[Cp^*Co(CO)I_2]$ catalyst over the previously utilised $[Cp^*Co(benzene)](PF_6)_2$ catalyst (**Scheme 1-27i**).[79] A similar protocol had been reported formerly by Zhou/Li and co-workers in 2012 using the $[Cp^*Rh(MeCN)_3](SbF_6)_2$ complex as a catalyst.[80] The developed procedure enabled the coupling of a wide range of substituted indoles and aryl/alkyl sulfonyl azides.

A year later, in 2015 the same research group reported a similar protocol for the C-H amidation of indoles, this time using the dimer catalyst $[Cp^*CoI_2]_2$ alongside phosphoryl azides as coupling partners. (**Scheme 1-27ii**).[81] This phosphoramidation reaction also proceeded in high yields for a variety of 2-pyrimidyl-protected indoles.

More recently, in 2019 Punniyamurthy and co-workers also presented the Cp*Co(III)-catalysed C-H amidation of indoles using acyl azides (**Scheme 1-27iii**). The reaction proceeds with high yields for a variety of substituted indoles and azides.[82]

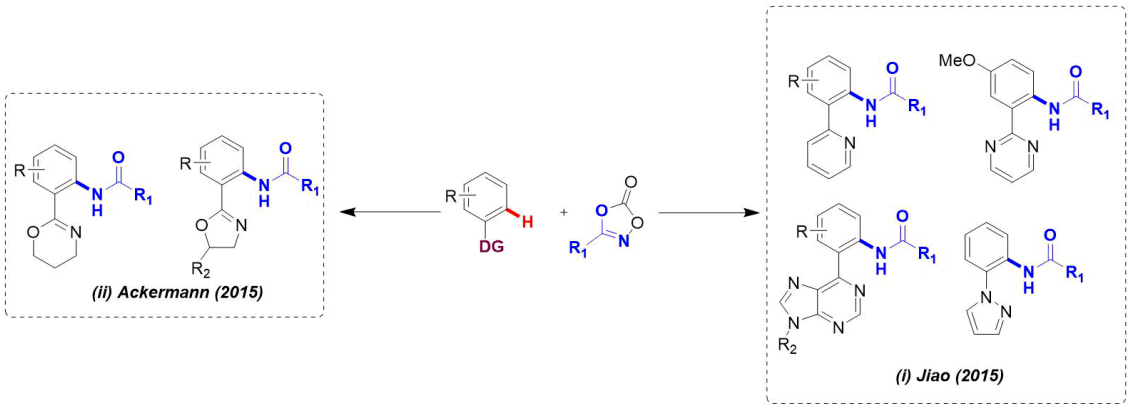


Scheme 1-28: [Cp*Co(CO)I_2]-catalysed C-H amidation of pyridine related substrates using acetoxycarbamates as coupling partners, reported by Chang and co-workers.[83]

The Cp*Co(III)-catalysed amidation of pyridine-type substrates was first reported by Chang and co-worker in 2014 (**Scheme 1-28**).[83] The authors describe that the C-H amidation of pyridine related substrates was not possible using the sulfonyl azide coupling partners, which were previously utilised for indoles. This provides a good example of the limitations of transferring developed protocols to different classes of substrates. In this report, acetoxycarbamates are utilised instead as the reactive source of amide. This transformation provided a wide substrate scope with good functional group tolerance on the aryl group. Furthermore, the presented protocol also enabled the conversion of 6-arylpurine derivatives bearing sensitive functional groups, which further increases the future relevance of the protocol.

1.4.1.5 C-N couplings using 1,4,2-dioxazol-5-ones as coupling partners

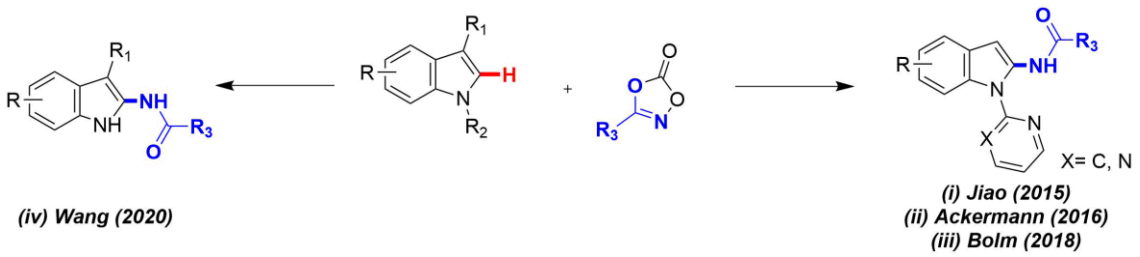
In the last few years 1,4,2-dioxazol-5-ones have emerged as highly effective amidation agents in the field of Cp*Co(III)-catalysed C-H activation. This can be explained by the higher coordination attraction to the metal center displayed by 1,4,2-dioxazol-5-ones compared to organic azides. Furthermore, these amidation agents are easy to prepare, with only CO_2 being extruded as by-product.



Scheme 1-29: Examples of Cp*Co-catalysed C-H amidation reactions of 2-arylpyridine related substrates using 1,4,2-dioxazol-5-one as coupling partners. General conditions: (i) 5.0 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$.[84] (ii) 5.0 mol% $[Cp^*CoI_2]_2$.[85]

The first example of a Cp*Co(III)-catalysed C-H amidation protocol where 1,4,2-dioxazol-5-ones were used as the active amide source was reported by Jiao and co-workers, in 2015 (**Scheme 1-29i**).[84] This protocol describes the C-H amidation of 2-aryl pyridines and 6-arylpurine substrates, with excellenttolerance for various substituents. Additionally, the same protocol was successfully applied to a substrate using an oxime ether as directing group. In this report the single component catalyst $[Cp^*Co(MeCN)_3](SbF_6)_2$ was found to display superior efficiency compared to the $[Cp^*Co(CO)I_2/AgSbF_6$ pair.

Ackermann and co-workers further expanded the utility of this C-H amidation methodology in 2015 by using the oxazoline moiety as directing group (**Scheme 1-29ii**). Oxazolines are found in several bioactive compounds, thus enhancing the efficiency of this methodology.[85] In this report, the authors use 1,4,2-dioxazol-5-one as amidation agent alongside the $[Cp^*Co(CO)I_2]$ catalyst.

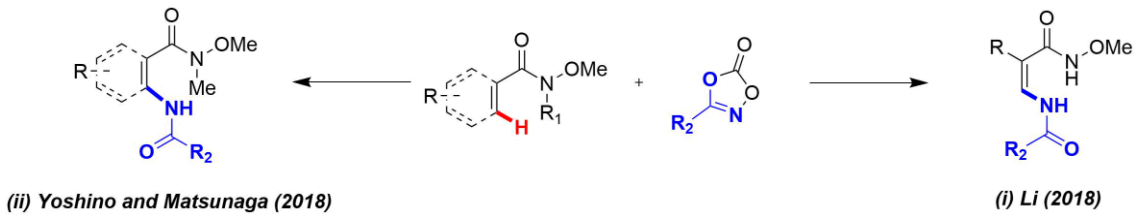


Scheme 1-30: Examples of Cp*Co-catalysed C-H amidation reactions of indoles using 1,4,2-dioxazol-5-one as coupling partners. General conditions: (i) 2.5 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$.[84] (ii) 2.5–5.0 mol% $[Cp^*Co(CO)I_2]$.[85] (iii) 2.5 mol% $[Cp^*Co(CO)I_2]$.[86] (iv) 5.0 mol% $[Cp^*Co(CO)I_2]$.[87]

Jiao and co-workers also described the Cp*Co(III)-catalysed coupling of indoles with 1,4,2-dioxazol-5-ones (**Scheme 1-30i**).[84] This methodology was further expanded by Ackermann and co-workers in 2016 for several substituted indoles (**Scheme 1-30ii**).[85]

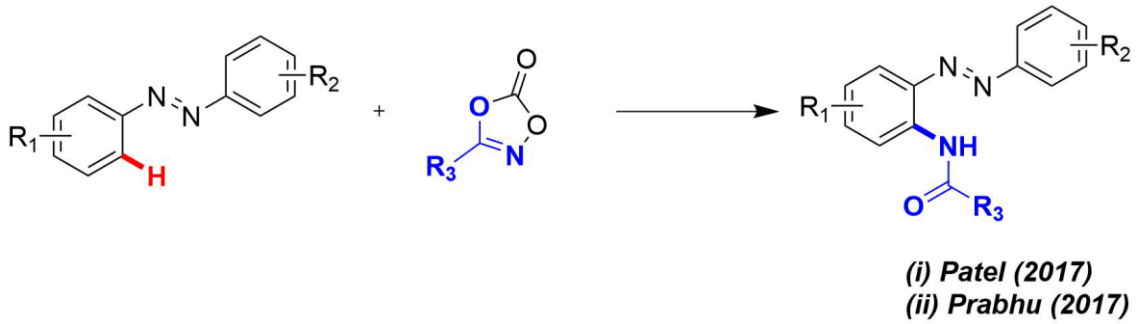
In 2018, Bolm and co-workers presented the advantages of mechanochemical techniques for development of C-H functionalisation reactions. The group reported high yields for the same Cp*Co(III)-catalysed C-H amidation reaction of indoles previously reported by Jiao and Ackermann, in the absence of heat and solvent (**Scheme 1-30iii**).[86] The C-H amidation reaction was achieved by using ball milling in shorter reaction times compared to those previously described. This report reveals a solvent free protocol to access 2-amidated indoles.

More recently, Wang and co-workers developed a procedure for the C-H amidation of free indoles at the C2-position using ketones as a directing group (**Scheme 1-30iv**).[87] This is the first report where the site selectivity was determined by a C3 directing group. The protocol tolerates a wide variety of functional groups for both indoles and 1,4,2-dioxazol-5-ones. The group demonstrated the efficiency of the protocol by performing a gram scale synthesis and obtaining the amidated product in comparable yield to the small-scale example.



Scheme 1-31: Examples of Cp*Co-catalysed C-H amidation reactions of amide-based substrate using 1,4,2-dioxazol-5-one as coupling partners. General conditions: (i) 5.0 mol% $[Cp^*Co(CO)I_2]$.[88] (ii) 10 mol% $[Cp^*Co(CO)I_2]$.[62]

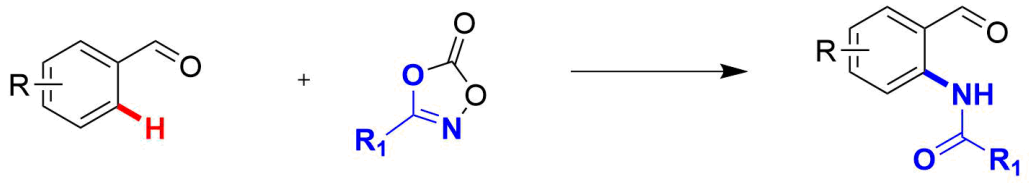
The 1,4,2-dioxazol-5-one coupling partners have also been employed in the cobalt-catalysed C-H amidation of olefinic C-H bonds as decribed by Li and co-workers, in 2018 (**Scheme 1-31i**).[88] The report describes a broad substrate scope for the synthesis of various enamides using the $[Cp^*Co(CO)I_2]$ catalyst alongside $AgNTf_2$ at low temperatures. Interestingly, the group reported that at higher temperatures and when using a lower loading of catalyst and silver salt the carbonyl group of the enamides undergoes intramolecular nuclephilic attack to furnish cyclic pyrimidones. In a similar protocol, Matsunaga/Yoshino and co-workers decribed the C-N bond formation between Weinreb amides and 1,4,2-dioxazol-5-one (**Scheme 1-31ii**).[62]



Scheme 1-32: Examples of Cp*Co-catalysed C-H amidation reactions of azobenzene substrates using 1,4,2-dioxazol-5-one as coupling partners. General conditions: (i) 5.0 mol% $[Cp^*Co(CO)I_2]$.[89] (ii) 5.0 mol% $[Cp^*Co(CO)I_2]$.[90]

Both Patel and Prabhu reported in 2017 the Cp*Co(III)-catalysed C-H amidation of azobenzenes with 1,4,2-dioxazol-5-one (**Scheme 1-32**).[89,90] Both groups focused initially on symmetrical azobenzene derivatives which afforded high yields with good functional group tolerance. Patel and co-workers reported that when a methyl substituent is employed at the *meta*-position, two products are observed with the amidation reaction taking place at the most hindered

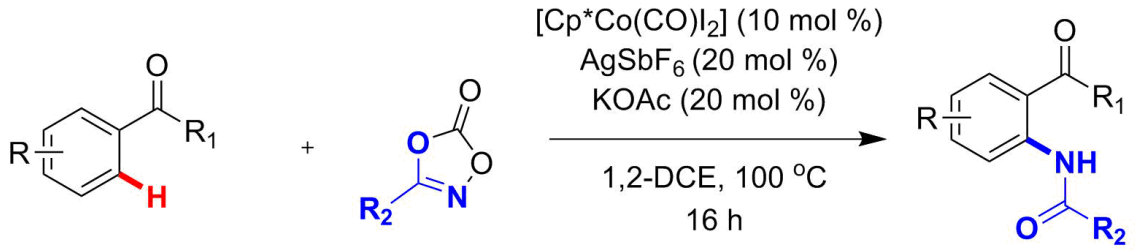
position.[89] When asymmetrical azobenzenes were employed, a mixture of monoamidated regioisomers was observed. However, Prabhu and co-workers reported that the formation of a regioselective product was possible when employing bulkier substituents or highly electron-donating groups.[90]



(i) Wu and Li (2019)
(ii) Sundararaju (2020)

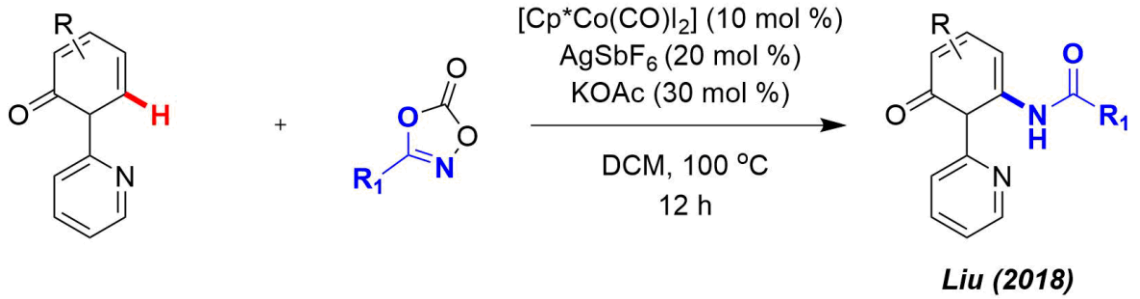
Scheme 1-33: Examples of Cp*Co-catalysed C-H amidation reactions of benzaldehydes with 1,4,2-dioxazol-5-one as coupling partners, using transient directing group strategy. General conditions: (i) 10 mol% $[Cp^*Co(MeCN)_3](SbF_6)_2$.[91] (ii) 10 mol% $[Cp^*Co(CO)I_2]$.[92]

The C-H functionalisation of benzaldehydes using transition metal catalysts has proven to be challenging since aldehydes are weak ligands and thus are poor directing groups (DG). The transient directing group strategy overcomes this limitation by reversible in-situ conversion of weak DG into strong DG such as imines *via* Schiff base condensation. Both the groups of Wu/Li and Sundararaju used this strategy for cobalt-catalysed C-H amidation of benzaldehydes using 1,4,2-dioxazol-5-ones as coupling agents (**Scheme 1-33**). [91,92] Li and co-workers used *p*-chloroaniline as the transient directing group and were able to generate a variety of multi-substituted amidated benzaldehydes (**Scheme 1-33i**). They further demonstrated the applicability of their protocol by the synthesis of C1r serine protease inhibitor and elastase inhibitor. Sundararaju and co-workers found aniline to be the optimal transient directing group alongside the $[Cp^*Co(CO)I_2]$ catalyst (**Scheme 1-33ii**). They also demonstrated the utility of this procedure by transforming the amidated aldehydes into various potentially valuble products.



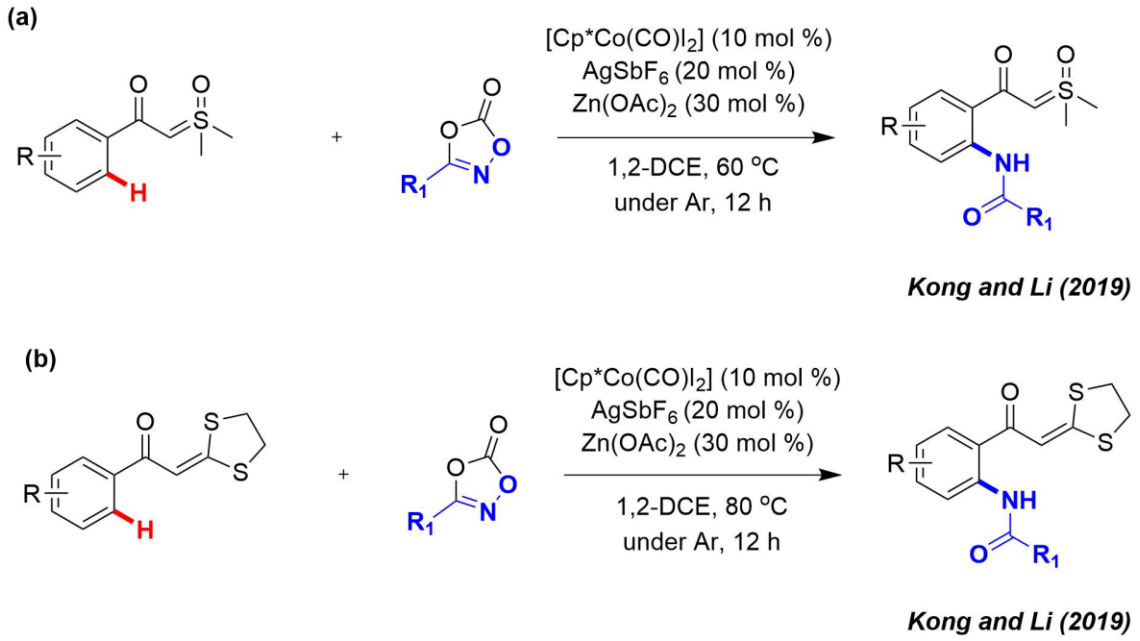
Scheme 1-34: Cp*Co-catalysed C-H amidation of ketones using 1,4,2-dioxazol-5-one as coupling partner, reported by Maji and co-workers. The group applied two sets of reaction conditions.[93]

In 2019, Maji and co-workers introduced a cobalt-catalysed C-H amidation reaction using weakly coordinating ketone directing groups (**Scheme 1-34**).[93] The work compared the reactivity of the $[Cp^*Co(CO)I_2]$ catalyst with the $[Cp^*RhCl_2]_2$ catalyst and found that the resulting yields were comparable. The group demonstrated the practicality of their protocol by synthesising biologically useful acridone derivatives starting from the C-H amidation products. Furthermore, the significance of the amide products was further proven by the synthesis various key heterocycles.



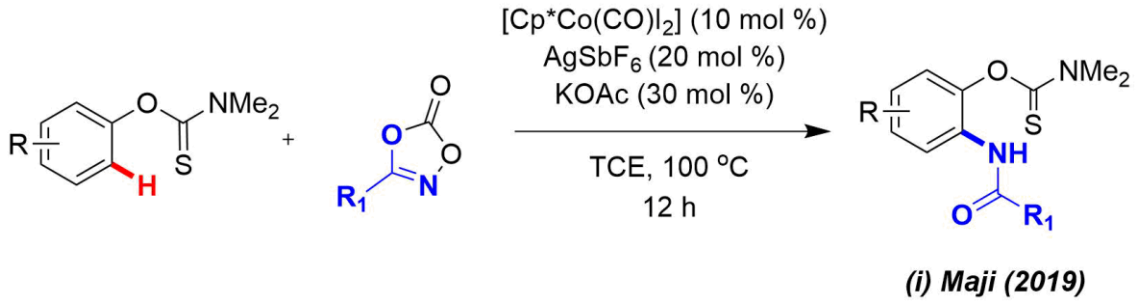
Scheme 1-35: Cp*Co-catalysed C-H amidation of pyridones using 1,4,2-dioxazol-5-one as coupling partner, reported by Liu and co-workers.[94]

Liu and co-workers further demonstrated that the 1,4,2-dioxazol-5-one amidation agents alongside Cp*Co(III)-catalysts can be effective for the formation of novel C-N bonds by reporting the C-H amidation of pyridones (**Scheme 1-35**).[94] The work provides a robust methodology for the transformation of a variety of substituted pyridones, in high yield. This is an additional example of a basic protocol for the conversion of key heterocyclic scaffolds found in various biologically active molecules.



Scheme 1-36: Cp*Co-catalysed C-H amidation of (a) sulfoxonium ylides and (b) benzoylketene dithioacetals using 1,4,2-dioxazol-5-one as coupling partner, reported by Kong/Li and co-worker.[95]

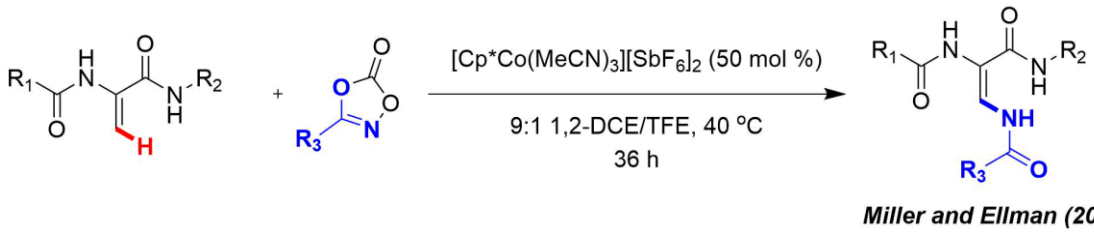
Recently, Kong and Li described the C-H amidation of sulfoxonium ylides and α-benzoylketene dithioacetals enabled by weakly coordinating groups (**Scheme 1-36**).[95] This approach resulted in the formation of *ortho*-amidated sulfur-containing products in significant yield.



Scheme 1-37: Cp*Co-catalysed C-H amidation of carbamates using 1,4,2-dioxazol-5-one as coupling partner, reported by Maji and co-worker.[96]

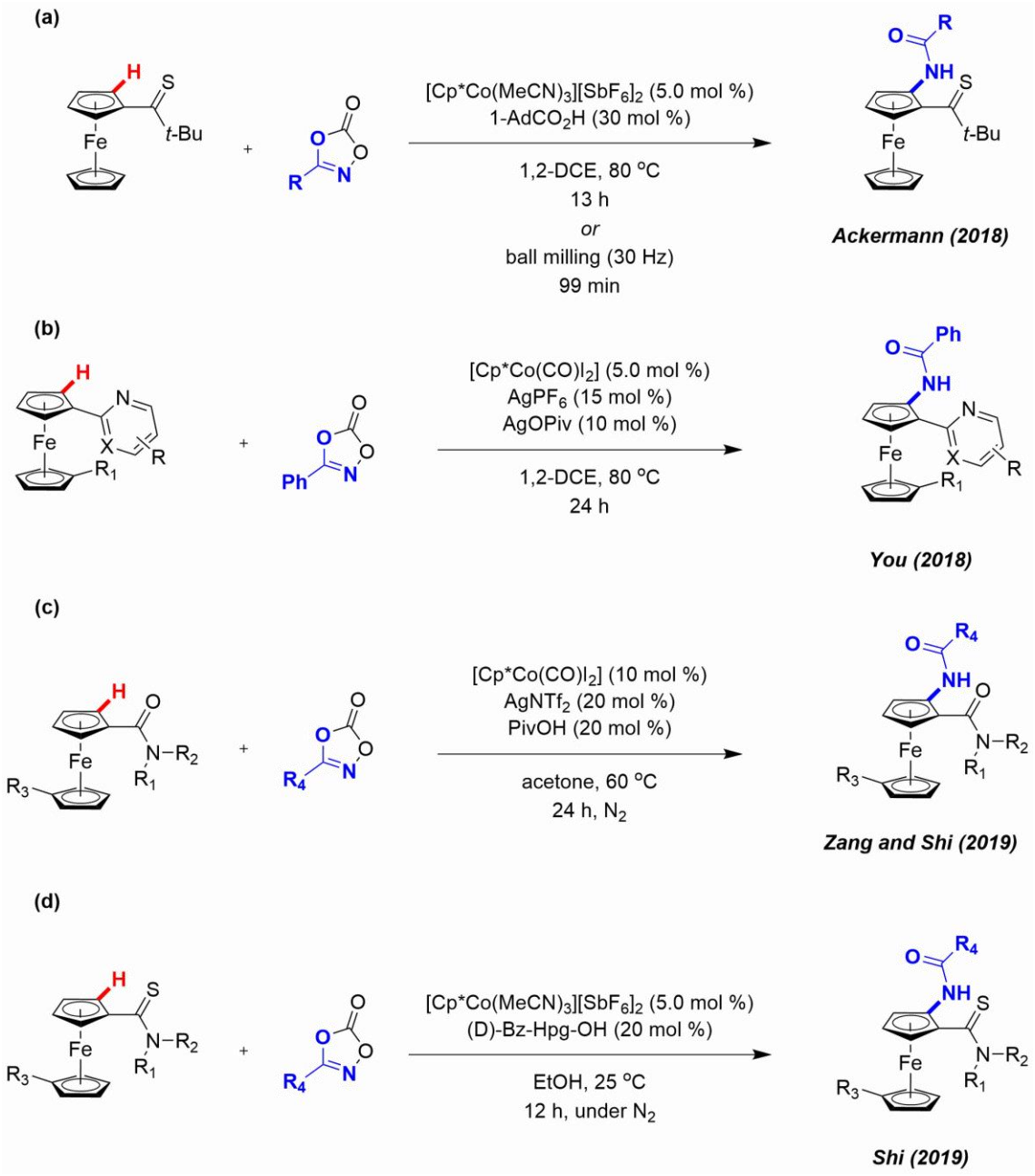
Carbamate directed amidation reactions although highly desirable, have proven to be challenging in the past. Recently, Maji and co-worker were able to successfully develop a Cp*Co(III)-catalysed C-H amidation reaction with carbamate derivatives by modifying the directing group to thiocarbamate (**Scheme 1-37**).[96] The reaction takes place in high yield and gives access to a variety of amidated BINOL and SPINOL amidated scaffolds. The

functionalisation of these ligands represents an important progress for potential novel asymmetric catalysis. The functionality of this method was further demonstrated by the C-H amidation of L-tyrosine under the developed reaction conditions.



Scheme 1-38: Cp*Co-catalysed C-H amidation of thiostrepton using 1,4,2-dioxazol-5-one as coupling partner, reported by Miller/Ellman and co-workers.[97]

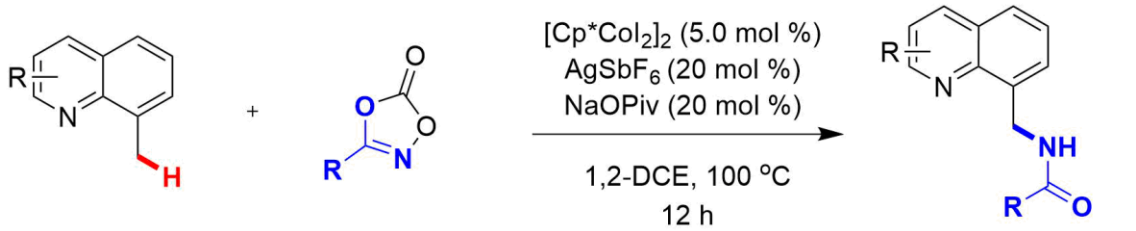
Thiostrepton is an oligopeptide which is effective against a range of Gram-positive bacteria, however it is mainly used as an active ingredient in veterinary antibiotics since its poor aqueous solubility makes it unsuitable for human use. Miller/Ellman and co-workers were able to utilise a Cp*Co(III)-catalyst for the first time to functionalise the Dha active site present on thiostrepton (**Scheme 1-38**).[97] The Co-catalysed C-H amidation with 1,4,2-dioxazol-5-ones facilitated the formation of a range of amidated analogues. This represents the first example where the alkene functionality of the Dha site was preserved during functionalisation. The work showed that the antibiotic properties of the novel thiostrepton derivatives were maintained and greater aqueous solubility was observed due to the incorporated amides.



Scheme 1-39: Examples of Cp*Co-catalysed C-H amidation of ferrocenes using 1,4,2-dioxazol-5-one as coupling partner.[98-101]

In recent years, several groups have reported directed Cp*Co(III)-catalysed C-H amidation reactions enabled by 1,4,2-dioxazol-5-one using ferrocenes as substrates. In 2018, Ackermann and co-workers presented a weakly coordinating thiocarbonyl-assisted C-H amidation of ferrocene (**Scheme 1-39a**) using both thermal and mechanochemical reaction conditions.[98] The developed protocol showed high reactivity for several substituents and displayed high functional group tolerance. During the same year, You and co-workers reported using pyridine derivatives as directing groups for the Cp*Co(III)-catalysed C-H

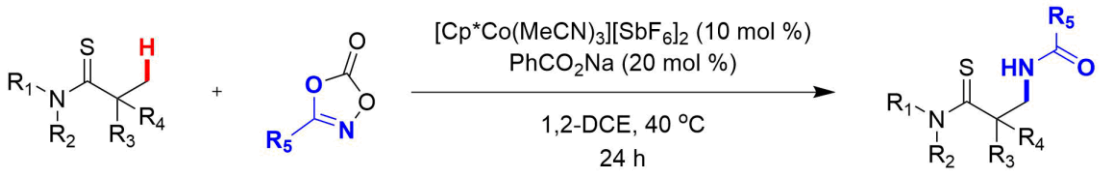
amidation of ferrocenes (**Scheme 1-39b**).[99] This protocol enabled the formation of a variety of potentially useful *N,N*-bidentated ferrocene derivatives in high yield. Likewise, Zhang/Shi and co-workers reported another example of C-H amidation of ferrocene bearing amides as directing groups (**Scheme 1-39c**).[100] Their methodology provides access to various amidated ferrocenes, including paracyclophane substituted ferrocene which is a broadly used framework in organic synthesis. Shi and co-workers further developed an asymmetric methodology by designing an enantioselective protocol using mono protected amino acids (MPAAs) as chiral ligands (**Scheme 1-39d)**.[101] The reaction proceeds under mild conditions using a variety of substituted ferrocenes and 1,4,2-dioxazol-5-ones and enantioselectivity is achieved.



Sundararaju, 2016

Scheme 1-40: Cp*Co-catalysed C(sp^3)-H amidation of 8-methylquinoline using 1,4,2-dioxazol-5-one as coupling partner.[102]

Directed C-H amidation of C(sp^3)−H bonds is highly desirable particularly because of their significance in natural products and biologically active compounds. However, C(sp^3)−H bonds are generally less reactive with transition metals. In agreement with that, examples of cobalt-catalysed C-H functionalisation reactions are extremely rare. In 2016, Sundararaju and co-workers described the first example of a Cp*Co(III)-catalysed C-H amidation reaction using 8-methylquinolines as substrates (**Scheme 1-40**).[102]



Scheme 1-41: Cp*Co-catalysed C(sp^3)-H amidation of thioamides using 1,4,2-dioxazol-5-one as coupling partner reported by Dixon and Seayad.[103]

Dixon/Seayad and co-workers described another example of a 1,4,2-dioxazol-5-one enabled Cp*Co(III)-catalysed C(sp^3)-H amidation in 2017, using thioamides as directing group (**Scheme 1-41**).[103] The protocol was successfully applied to substituted thioamides using various 1,4,2-dioxazol-5-ones. Computational studies supported the observed regioselectivity and suggested that the cyclometallation step proceeded with an external carboxylic acid.

1.5 Synthesis of heterocycles *via* Cp*Co(III)-catalysed C-H activation approaches

Heterocyclic fragments are very common and important structural components in many valuable chemicals and have applications in a variety of areas as agrochemicals, dyes, sanitisers, corrosion inhibitors and antioxidants. Heterocycles are particularly significant in the pharmaceutical industry both as fragments of active ingredients and of pharmaceutical excipients.[104] Their importance is emphasised by the prevalence of heterocyclic moiety in most FDA approved drugs. This is illustrated by the FDA approved drugs report from 2019 which shows that small molecules containing heterocyclic moieties represent 63% (29 drugs) of the total of drugs approved in 2019. Furthermore, nitrogen-based heterocycles are of particular importance in drug design, being present in most of the approved drugs (**Figure 1-3**).[105]

Thus, synthesising new heterocycles or modifying existing ones has been significant for the development of drugs with better solubility, lipophilicity. polarity and other properties that can improve drug candidates. The synthesis of new nitrogen-based compounds has been of particular importance due to their

prevalence in FDA approved drug molecules and as a result many metal-catalysed cross-coupling and hetero-coupling reactions have been developed to provide access to a broad range of heterocycles.[106]

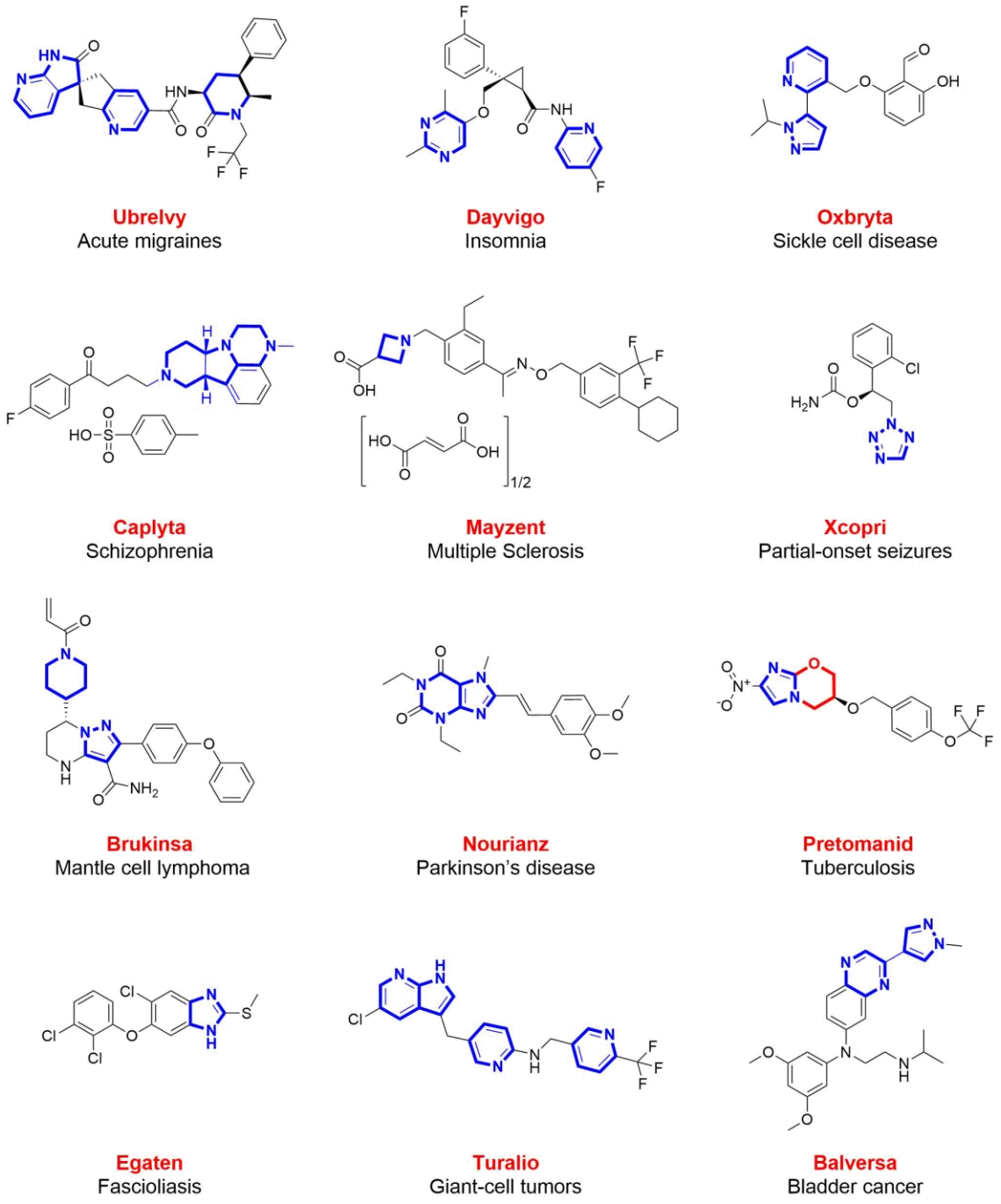


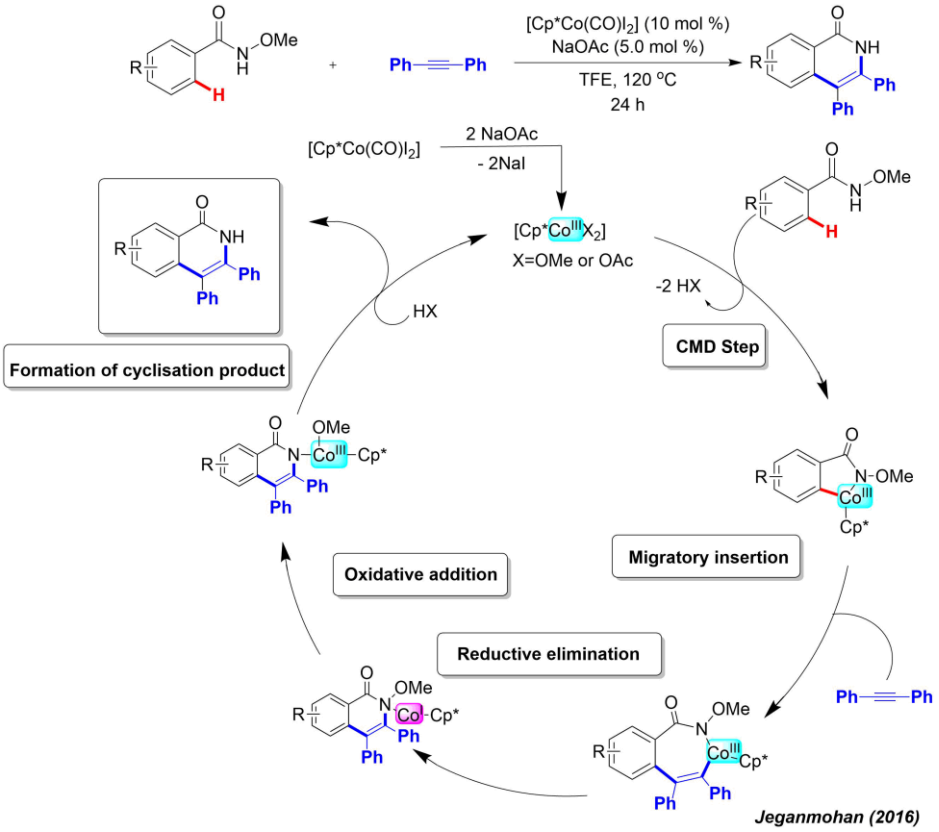
Figure 1-3: Examples of FDA approved drugs in 2019.[105]

This section will focus on examples of different approaches for the synthesis of nitrogen-containing heterocycles using Cp*Co(III)-catalysed protocols. Particularly, two different type of methodologies will be described depending on the redox potential of the catalytic reaction mechanism by which the

heterocycles are formed. Furthermore, examples will be presented where the heterocycles are formed using Cp*Co(III)-catalysed C-H activation as the first step, followed by the addition of another reactant in a one-pot manner.

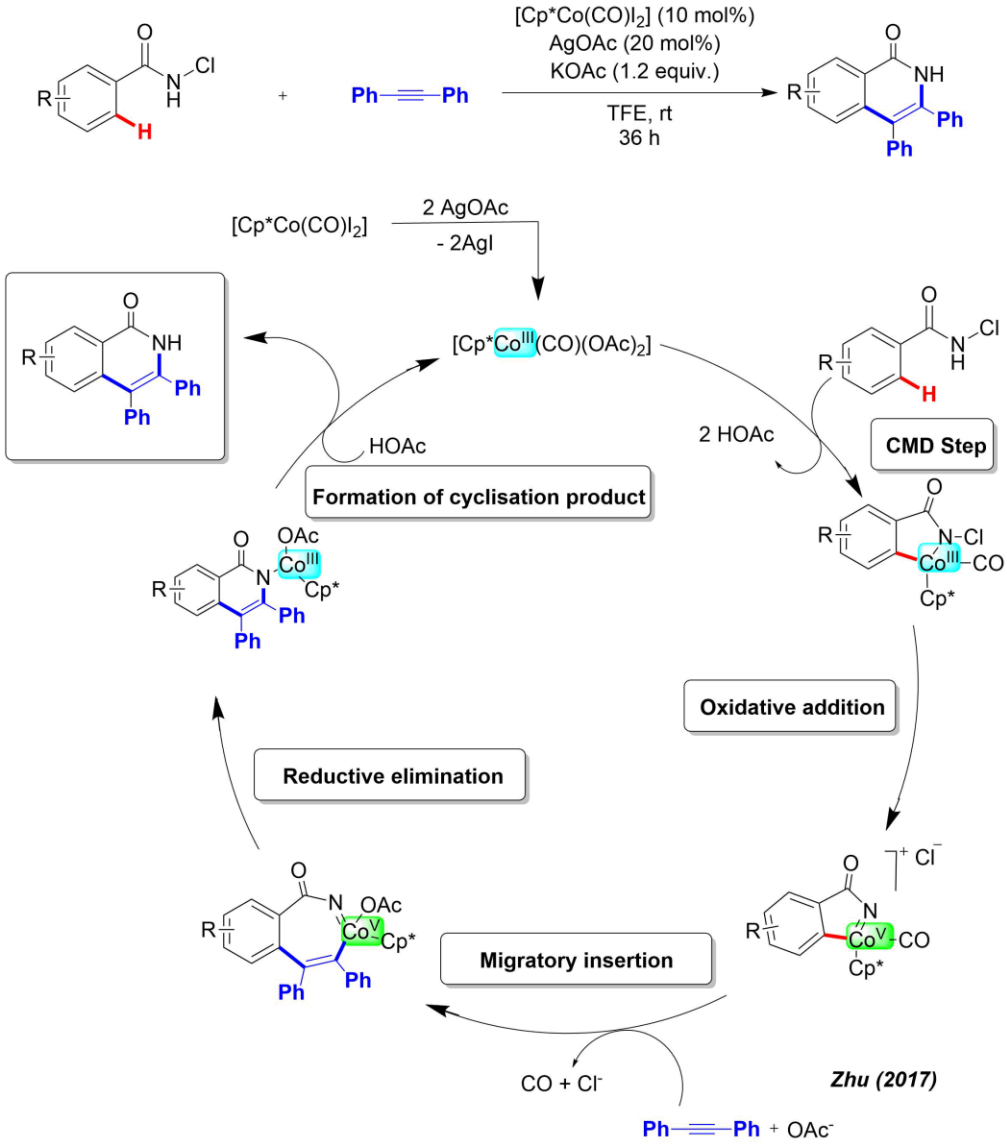
1.5.1 Synthesis of nitrogen-containing heterocycles using a redox-active annulative approach

The redox-active annulative approach for the synthesis of isoquinolones has been presented by both Jeganmohan in 2016 (**Scheme 1-42**) and Zhu in 2017 (**Scheme 1-43**) with both examples using the directing group as oxidising agent.[107,108] Jeganmohan and co-workers reported the annulation reaction between *N*-methoxy benzamides and alkynes (**Scheme 1-42**) where the N-OMe bond acts as directing group but also as oxidising agent to facilitate the re-oxidation of the Cp*Co(I) species back to the catalytically active Cp*Co(III) complex.



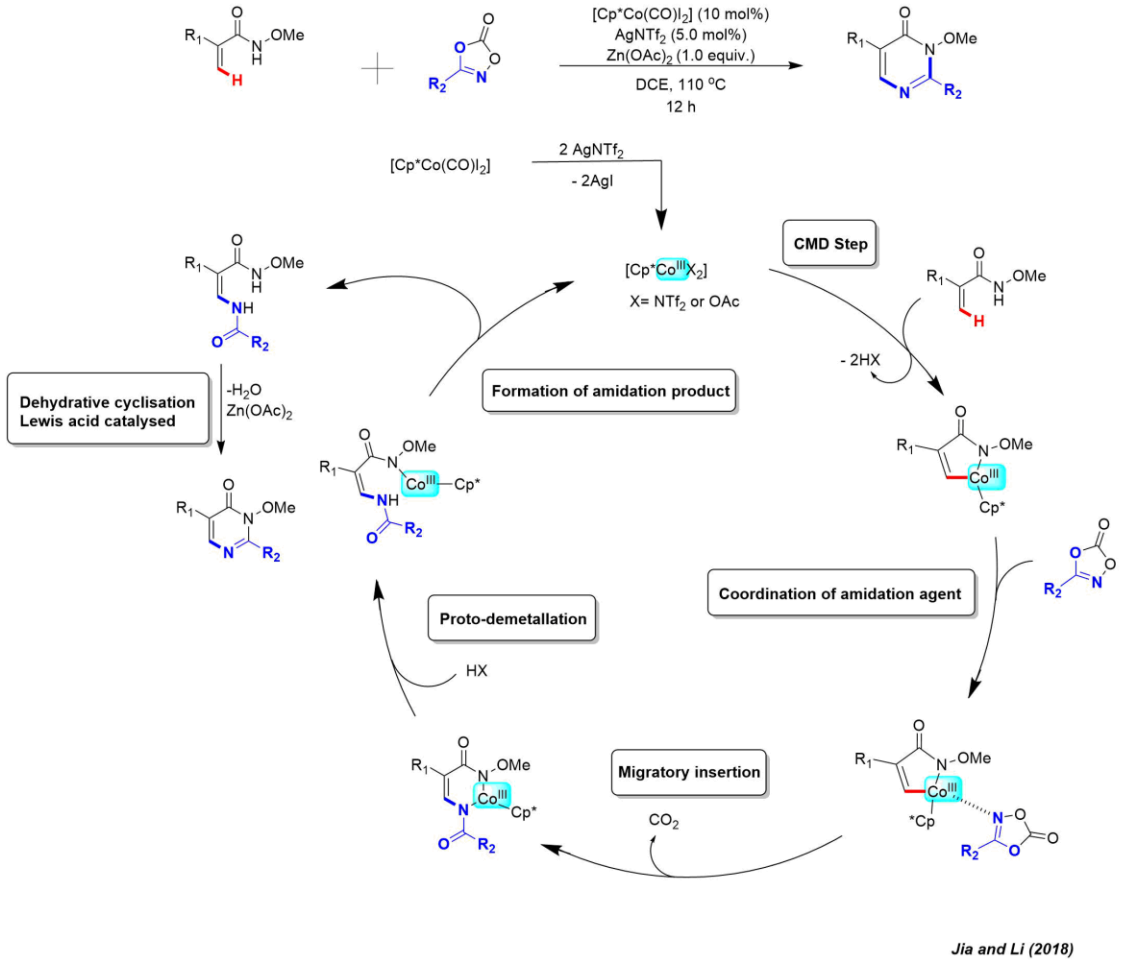
Scheme 1-42: Cp*Co(III)-catalysed synthesis of isoquinolones using *N*-methoxy benzamides as substrates with alkynes as coupling agents reported by Jaganmohan and co-workers. Proposed mechanism *via* a redox-active annulative pathway.[107]

In contrast in the report that Zhu and co-workers presented the Co(III) complex is oxidised to a Co(V) across the N-Cl bond (**Scheme 1-43**). Furthermore, the authors were able to isolate and identify by single crystal X-Ray crystallography the five-membered cobaltacycle intermediate. These two examples are particularly interesting as the same product is obtained starting using different directing groups and *via* different mechanistic pathways.



Scheme 1-43: Cp*Co(III)-catalysed synthesis of isoquinolones using *N*-chloro benzamides as substrates with alkynes as coupling agents reported by Zhu and co-workers, with loss of CO after the first catalytic cycle. Proposed mechanism *via* a redox active annulative pathway.[108]

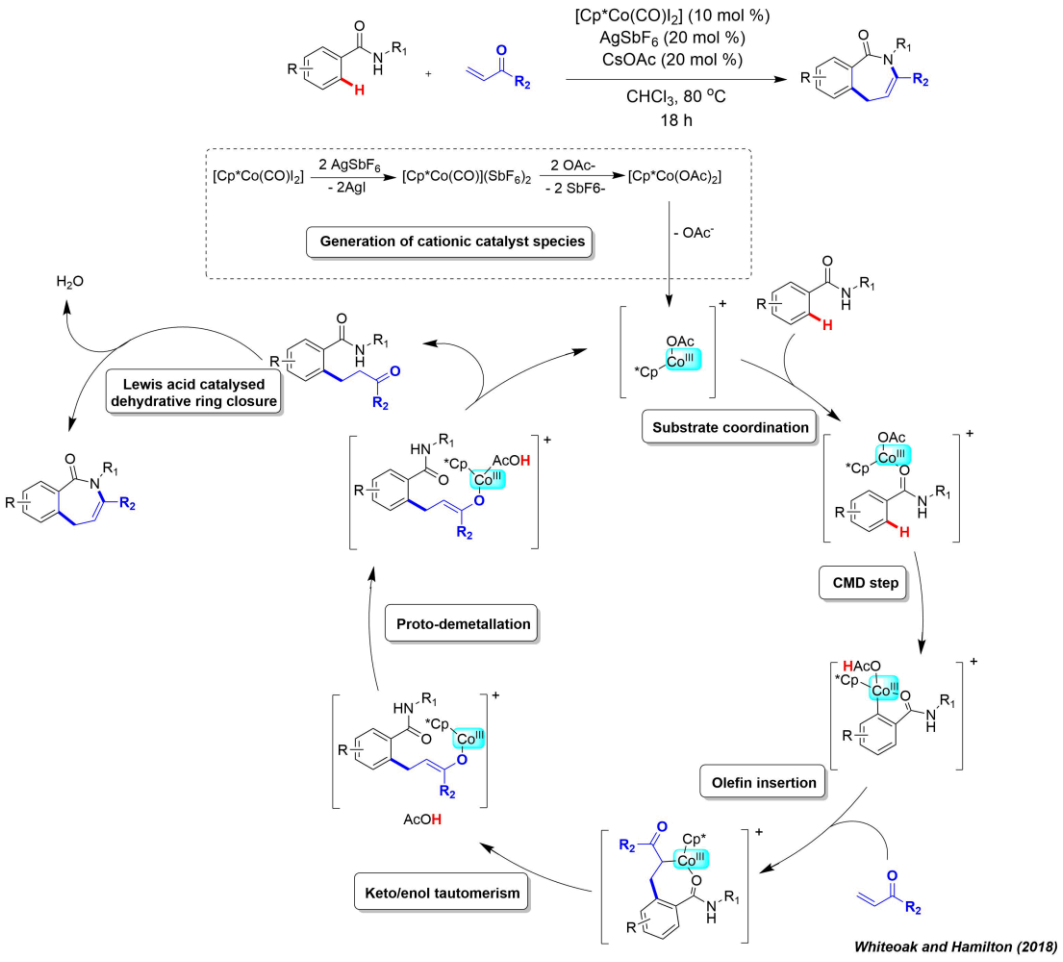
1.5.2 Synthesis of nitrogen-containing heterocycles using a redox neutral cascade approach



Scheme 1-44: Cp*Co(III)-catalysed synthesis of pyrimidone using *N*-methoxy acrylamides as substrates with 1,4,2-dioxazol-5-ones as coupling agents reported by Li and co-workers. Proposed mechanism *via* a redox neutral cascade pathway.[88]

High-valent Cp*Co(III) catalysts are active in their oxidation state thus, protocols which utilise these catalysts only need oxidant if there is a reductive elimination or a β-hydride elimination step in the mechanistic pathway by which the reaction takes place. Instead, the Cp*Co(III) catalysts are usually regenerated *via* a redox neutral proto-demetallation step. Jia/Li and co-workers reported the Cp*Co(III)-catalysed synthesis of pyrimidones starting from acrylamides and 1,4,2-dioxazol-5-ones through a redox-neutral cascade type of mechanism (**Scheme 1-44**).[88] The group were able to isolate both linear (enamides) and cyclic products (pyrimidones) by changing the reaction temperature and catalytic loading. When mild conditions are employed only enamides are

afforded however, when applying a higher reaction temperature and under lower catalytic loading, the enamides undergo dehydrative cyclisation to afford the cyclic products. Furthermore, the pyrimidones can undergo a secondary C-H amidation reaction when a higher loading of amidation agent is utilised.



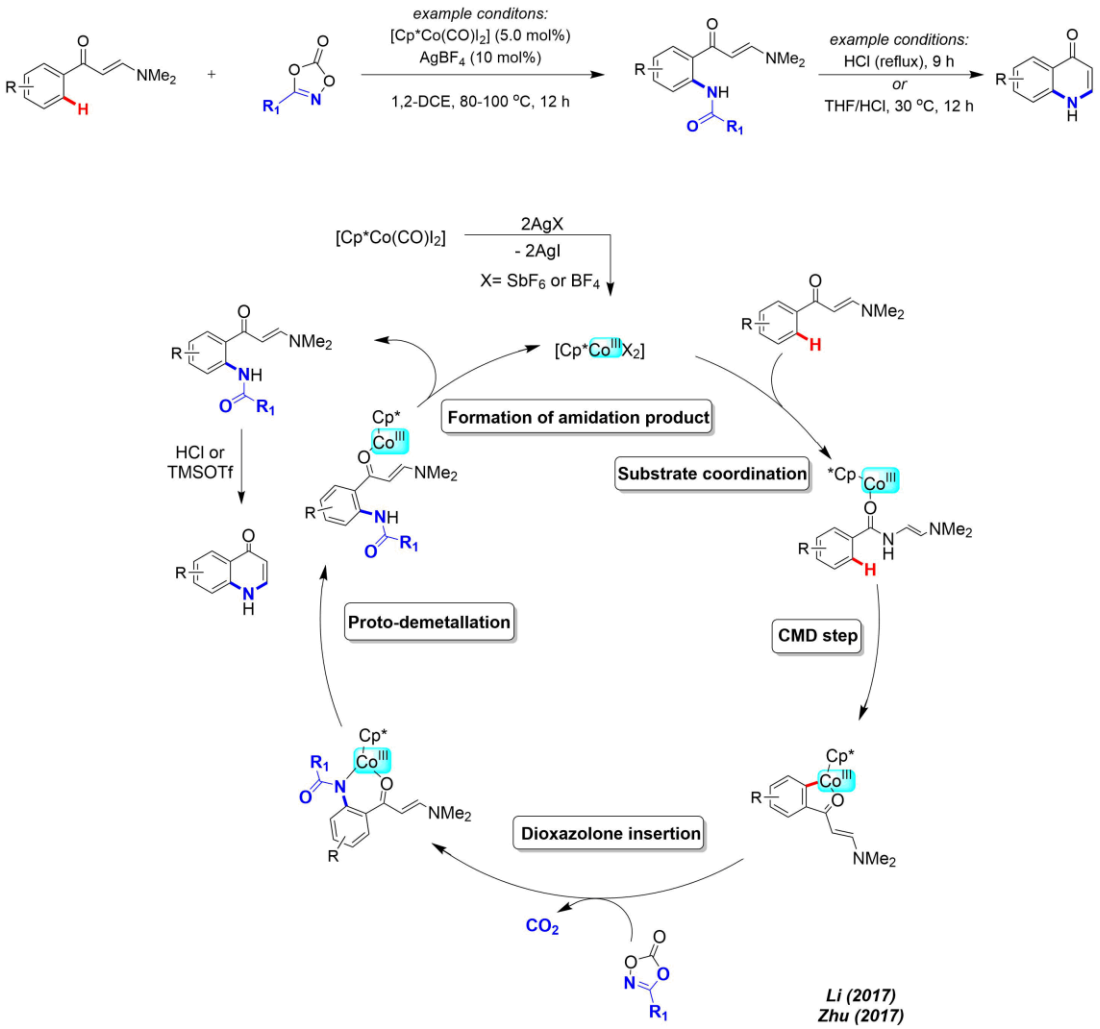
Scheme 1-45: Cp*Co(III)-catalysed synthesis of azepinones using benzamides as substrates with acrolein as coupling agents reported by Whiteoak/Hamilton and co-workers. The mechanism takes place *via* a redox neutral cascade pathway and is elucidated using DFT calculations.[109]

Whiteoak/Hamilton and co-workers also described a C-H functionalisation protocol which proceeds *via* a redox neutral cascade pathway (**Scheme 1-45**). The procedure provides facile access to azepinones using an initial key Cp*Co(III)-catalysed C-H alkylation step. DFT calculations offered good insights into the mechanism by which the C-H alkylation reaction proceeds. The computational studies described that, as a result of a proto-demetallation step after the migratory insertion of the olefin, aliphatic ketones are observed as

products instead of α,β-unsaturated ketones which are typically observed as a result of a β-hydride elimination step in Heck-type reactions. This key step is not detected when employing α,β-unsaturated esters, resulting in formation of olefinic products.[109] When employing acrolein as a coupling partner, azepinones are obtained as products as a result of intramolecular dehydration of the amide and the newly installed aldehyde.

1.5.3 Synthesis of nitrogen-containing heterocycles using a redox-neutral one-pot approach

Other examples of redox neutral Cp*Co(III)-catalysed C-H amidation were reported simultaneously by the groups of Li and Zhu, in 2017 (**Scheme 1-46**).[110,111] Both groups described the preparation of quinolones using a one-pot sequential method starting from the C-H amidation of enaminones. This is followed by the addition of either HCl or TMSOTf, without isolating the C-H amidation intermediate, to generate the cyclic product. The one-pot strategy is highly desirable as it provides access to the products without lengthy intermediate work-up or separation processes. Also, one-pot reactions minimise reaction times, chemical waste and can increase the yield of the overall reaction.



Scheme 1-46: One-pot synthesis of quinolones *via* a Cp*Co(III)-catalysed approach using enaminones as substrates with 1,4,2-dioxazol-5-ones as coupling agents reported by both Li and Zhu.[110,111]

1.6 Summary

Over the past few years, there has been an extensive interest in use of [Cp*Co(CO)I_2] catalysts for directed C–H bond functionalisation protocols, since the initial report by Kanai and Matsunaga in 2014. The cost and relative low toxicity make cobalt a desirable metal for development of more sustainable procedures. Furthermore, the lower electronegativity and increased Lewis acidity of cobalt compared to rhodium has enabled unique reactivities to be observed which were complementary to reactivities observed with the established rhodium catalysts. Significant progress has been made with C-C

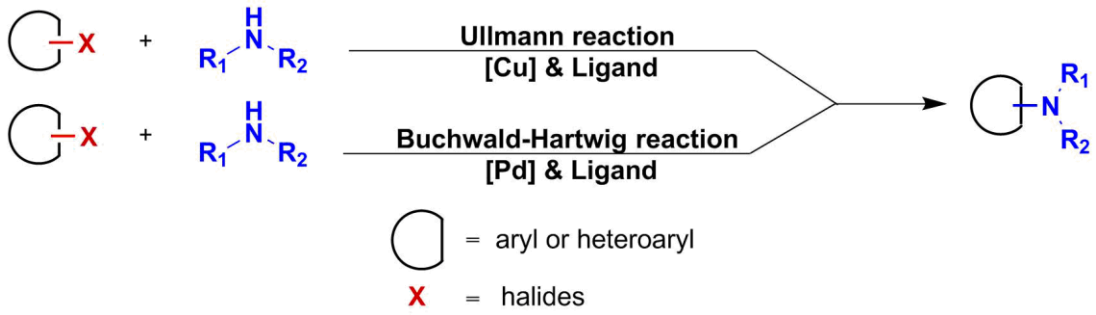
and C-heteroatom couplings, with many proof-of-concept protocols being reported. Particularly, advancements in Cp*Co(III)-catalysed C-N bond formation using 1,4,2-dioxazo-5-ones as coupling partners have been discussed in this introduction. These coupling partners have proven to be incredibly versatile for a variety of substrates and have even been integrated in one-pot procedures to provide facile access to nitrogen-containing heterocycles. Further development of reaction protocols to access heterocycles is of great interest thus, inspired by the examples of Li and Zhu this work focuses mainly on synthesis of potentially valuable nitrogen containing heterocycles *via* a key Cp*Co(III)-catalysed step.

There are limited examples where computational studies are used to elucidate the mechanism by which Co-catalysed C-H functionalisation reactions proceed. DFT calculations are particularly valuable as a complementary tool to experimental studies that could be used in the future to help improve reactivity thus, continuing to explore computational methods is key to the development of this field.

Chapter 2. One-pot preparation of 1,2,3-Benzotriazin-4(*3H*)-ones Employing a Key Cp*Co(III)-catalysed C-H Amination Step

2.1 Introduction

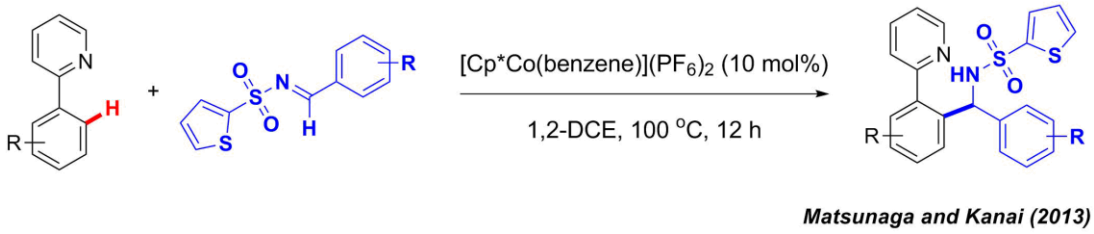
Formation of C-N bonds is one of the most important, yet challenging, transformations in synthetic organic chemistry.[112] Traditionally, both Ullman and Buchwald-Hartwig cross-couplings have provided the most successful routes for the preparation of these important bonds (**Scheme 2-1**).[113,114] Although well established and used extensively, these methodologies suffer a major drawback, in that a pre-functionalised starting material is required. In this context, and with the explosion of research in the field of direct C-H functionalisation,[115–120] much attention is now beginning to focus on the development of novel C-N bond forming reactions through directed C-H activation approaches.[121,122]



Scheme 2-1: Examples of established procedures for C-N bond formation.

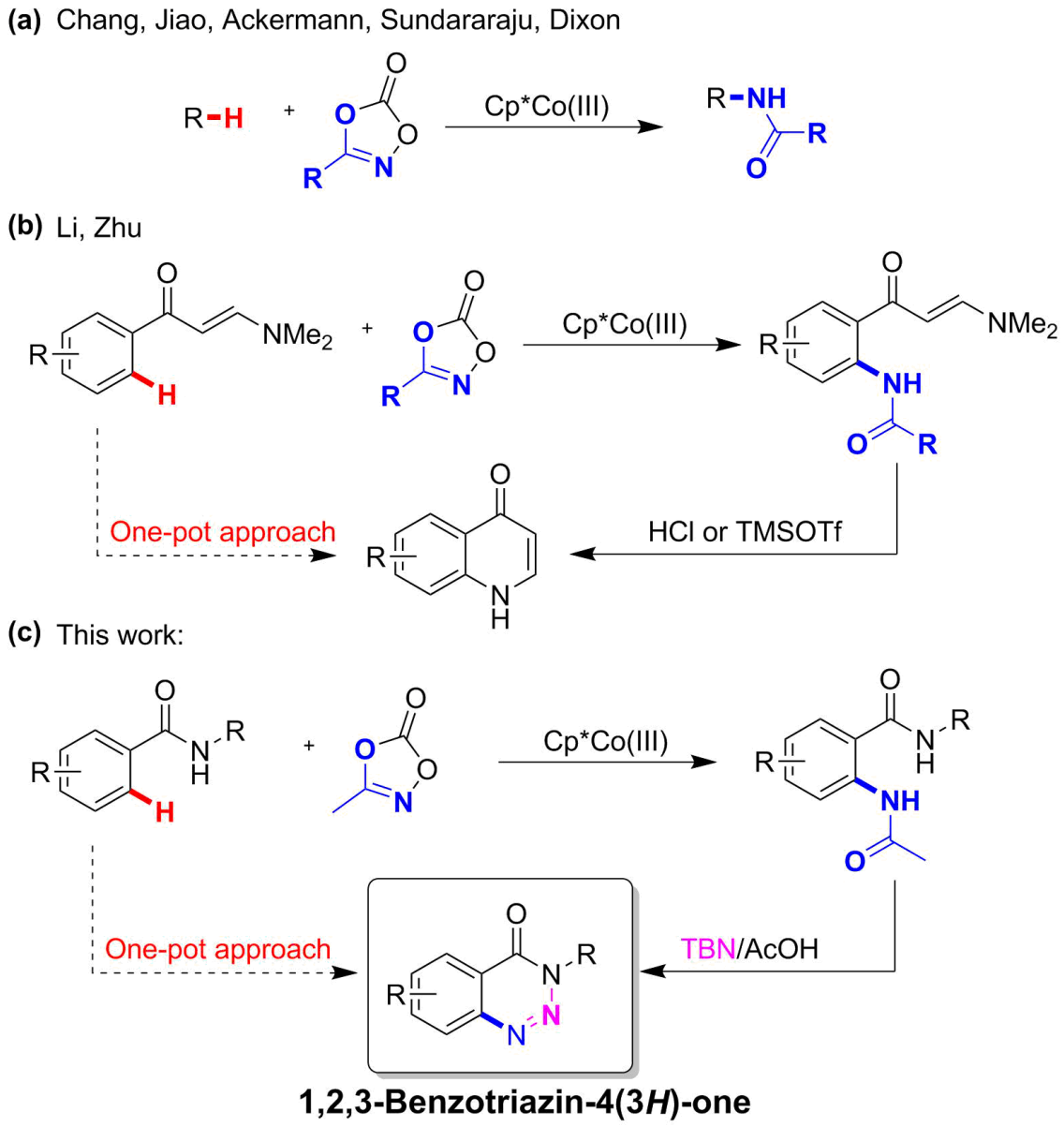
Bearing in mind that the well-established Buchwald-Hartwig methodology is based on relatively expensive palladium catalysis, more recently, focus has also begun to switch to the application of cheaper, more abundant first row transition metals, such as iron, nickel and cobalt.[123] As a result of this, particularly since

the publication by Kanai and Matsunaga on the powerful Cp*Co(III) catalyst for C-H functionalisation protocols in 2013 (**Scheme 2-2**),[25] high-valent cobalt-catalysed C-H functionalisation has started to attract significant attention, providing a wide range of coupling protocols.[7,32,124–127] In the field of C-N bond formation, several groups have successfully developed and applied Cp*Co(III)-catalysed protocols.[20–33]



Scheme 2-2: First example of Cp*Co(III)-type catalytic protocol.[25]

Some of the most intriguing protocols to be developed involve the use of readily available, easy to handle and bench-top stable, 1,4,2-dioxazol-5-ones (**Scheme 2-3a**).[23-33] These coupling partners are easily prepared on a gram scale and when employed in C-H functionalisation protocols, only carbon dioxide is released as waste. Recently, both the groups of Li and Zhu simultaneously reported the one-pot preparation of quinolone compounds using Cp*Co(III) catalysis, aryl enaminone substrates and 1,4,2-dioxazol-5-ones (**Scheme 2-3b**).[110,111] It was possible to isolate the intermediate amidation products, before a facile second reaction takes place, which furnishes the quinolone products.



Scheme 2-3: a) general scheme for Cp*Co(III)-catalysed amidation of C-H bonds with 1,4,2-dioxazol-5-ones.[23-33] (b) Example of one-pot approaches to preparation of quinolone products simultaneously reported by Li and Zhu.[110,111] (c) The sequential one-pot protocol reported.[135]

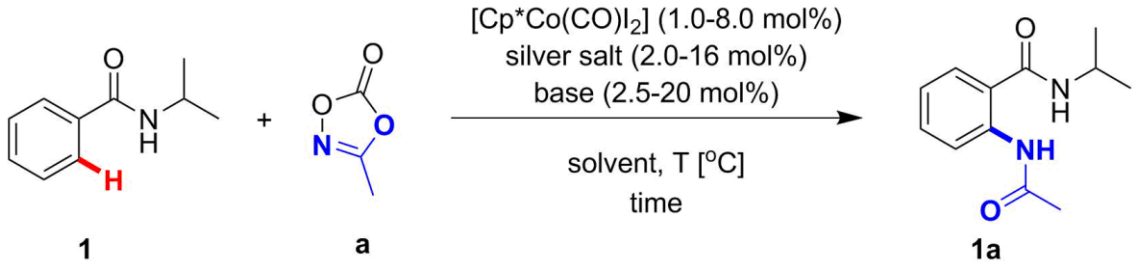
With this approach in mind, this chapter is focused on the further development of the Cp*Co(III)-catalysed amidation of readily available benzamides, reported by Chang and co-workers,[132] before developing a second reaction which could then be combined in a one-pot manner to provide a potentially valuable heterocycle (**Scheme 2-3c**).[135] This work provides a novel sequential one-pot procedure for the preparation of valuable 1,2,3-benzotriazin-4*(3H)*-ones using *tert*-butyl nitrite as key reagent in the second reaction.

1,2,3-Benzotriazin-4(*3H*)-ones are a family of heterocyclic compounds, which have been recognised for their potential application as pesticides and medicines, although their synthesis can be challenging.[136] Besides their use as pesticides and medicines, they have also been studied as useful precursors for Ni(0)-catalysed heterocycle preparation.[35–140] Previously, these compounds have been synthesised using a variety of complex multi-step routes or from substrates which show limited potential for diversity. The new facile approach for their preparation described in this report would therefore present an attractive proposition and improve their accessibility, likely resulting in widened applications.

2.2 Results and discussion

2.2.1 Optimisation studies of the C-H amidation reaction

The study was initiated with the optimisation of the C-H amidation coupling of *N*-isopropyl benzamide, **1**, with 3-methyl-1,4,2-dioxazol-5-one using the [Cp*Co(CO)I_2] pre-catalyst. The optimisation study focused on silver salts, bases, solvents, reaction temperature, time of reaction and loading of reactants (**Scheme 2-4**). Yields for the C-H amidation product **1a** were determined by ^{1}H NMR using mesitylene as internal standard.



Scheme 2-4: Optimisation studies for Cp*Co(III)-catalysed synthesis of 2-acetamido-*N*-isopropylbenzamide.

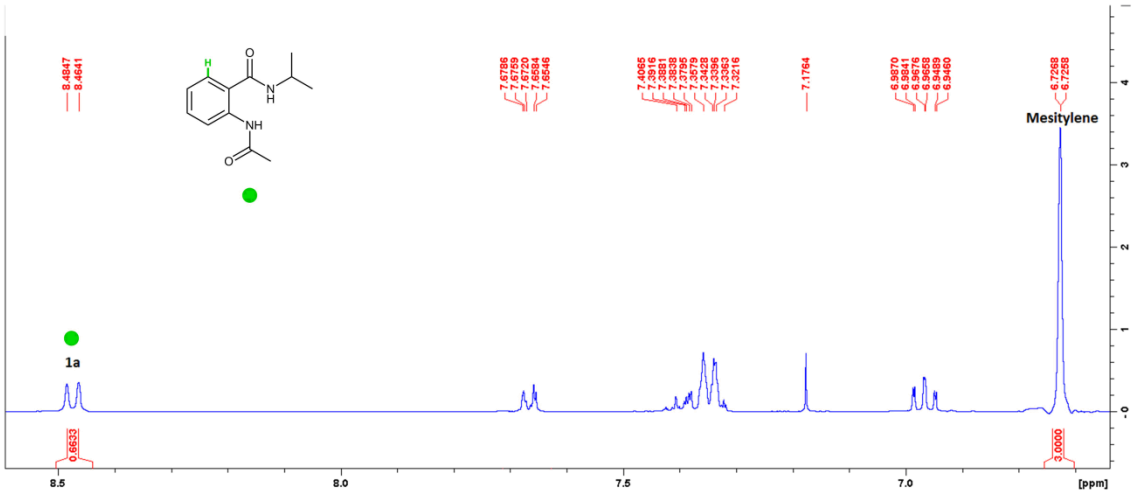


Figure 2-1: Example of ^{1}H NMR spectrum for the optimisation of the C-H amidation reaction. Yield of **1a** was determined using mesitylene as internal standard.

The methyl substituted 1,4,2-dioxazol-5-one was selected, although Chang and co-workers previously observed that this was not the optimal 1,4,2-dioxazol-5-one.[132] The objective of this study was to further react the amide in a second reaction and through use of the methyl, the mass loss was reduced, increasing the sustainability of the process. For note, the 3-phenyl-1,4,2-dioxazol-5-one afforded a lower yield (68 %) compared to the optimised reaction with 3-methyl-1,4,2-dioxazol-5-one (77 %).

Silver salts were employed as additives for the abstraction of iodine from the Cp*Co(III) pre-catalyst to obtain the active cationic catalyst. Thus, as expected, no product was observed without the addition of silver salts (**Table 2-1**). Furthermore, weakly coordinating silver salts appeared to be very beneficial to the reaction as silver hexafluoroantimonate ($AgSbF_6$), silver bis (trifluoromethanesulfonyl) imide ($AgNTf_2$) and silver tetrafluoroborate ($AgBF_4$) afforded the highest yields of 66%, 64% and 65% respectively.

Table 2-1: Silver salt optimisation [a]

Entry	Silver salt	1a [%][b]
1	$AgNTf_2$	64
2	AgOTf	23
3	$AgBF_4$	65
4	Ag_2O	None
6	**$AgSbF_6$**	**66**
5	-	None

[a] General conditions: 0.25 mmol **1**, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, 8.0 mol% [Cp*Co(CO)I_2], 16 mol% silver salt, 20 mol% NaOAc, in 2.0 mL 1,2-DCE, 80 °C, 16h.[b] Yields of **1a** calculated from ^{1}H NMR using mesitylene as internal standard.

No increase in yield was observed when substituting sodium acetate (NaOAc) with other bases (**Table 2-2**). Overall, sodium and potassium bases showed better activity compared to the caesium bases. It should be mentioned that the reaction proceeds in the absence of a base however, in lower yield.

Table 2-2: Base optimisation [a]

Entry	Base	1a [%][b]
1	**NaOAc**	**65**
2	Na_2CO_3	64
3	NaOPiv	42
4	K_2CO_3	55
5	K_3PO_4	50
6	KOPiv	18
7	CsOAc	23
8	Cs_2CO_3	36
9	CsOPiv	None
10	-	40

[a] General conditions: 0.25 mmol 1, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, 8.0 mol% [Cp*Co(CO)I_2], 16 mol% $AgSbF_6$, 20 mol% base, in 2.0 mL 1,2-DCE, 80 °C, 16h.[b] Yields of **1a** calculated from ^{1}H NMR using mesitylene as internal standard.

Following the optimisation of base, the focus shifted towards solvent optimisation. From the screening, 1,2-dichloroethane (1,2-DCE) was the optimal

solvent for the reaction to take place in (**Table 2-3**). The reaction proceeds also in toluene, cyclohexane and 1,4-dioxane nonetheless, the yields are significantly lower when using these solvents. The protocol appears not to be amenable to protic solvents or coordinating ones. It was also observed that increasing the temperature of reaction did not improve the obtained yield (**Table 2-3,** entry 10).

Table 2-3: Solvent optimisation [a]

Entry	Solvent	Temp. [°C]	1a [%][b]
1	acetone	80	None
2	MeCN	80	None
3	cyclohexane	80	8
4	**1,2-DCE**	**80**	**66**
5	1,4-dioxane	80	13
6	MeOH	80	None
7	THF	80	None
8	toluene	80	19
9	TFE	80	None
10	1,2-DCE	90	62

[a] General conditions: 0.25 mmol **1**, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, 8.0 mol% $[Cp^*Co(CO)I_2]$, 16 mol% $AgSbF_6$, 20 mol% NaOAc, in 2.0 mL solvent, 80 °C, 16h.[b] Yields of **1a** calculated from ^1H NMR using mesitylene as internal standard.

The reaction was completed in only 4 hours and by increasing the volume of 1,2-DCE from 2 mL to 4 mL the obtained yield for **1a** increased from 66% to 77% (**Table 2-4**).

Table 2-4: Time of reaction optimisation [a]

Entry	Time [h]	1a [%][b]
1	2	62
2	**4**	**66 (77)[c]**
2	16	66
4	20	64
5	24	60

[a] General conditions: 0.25 mmol **1**, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, 8.0 mol% $[Cp^*Co(CO)I_2]$, 16 mol% $AgSbF_6$, 20 mol% NaOAc, in 2.0 mL 1,2-DCE, 80 °C, time.[b] Yields of **1a** calculated from ^1H NMR using mesitylene as internal standard.[c] Yield obtained using 4 mL of 1,2-DCE.

Lastly, the catalyst and reactant loadings were investigated, and it was observed that decreasing catalyst loading to 1.0 mol% resulted in lower yields (**Table 2-5**). This was not a surprising finding when considering the reduced time of reaction compared to Chang's protocol.[132]

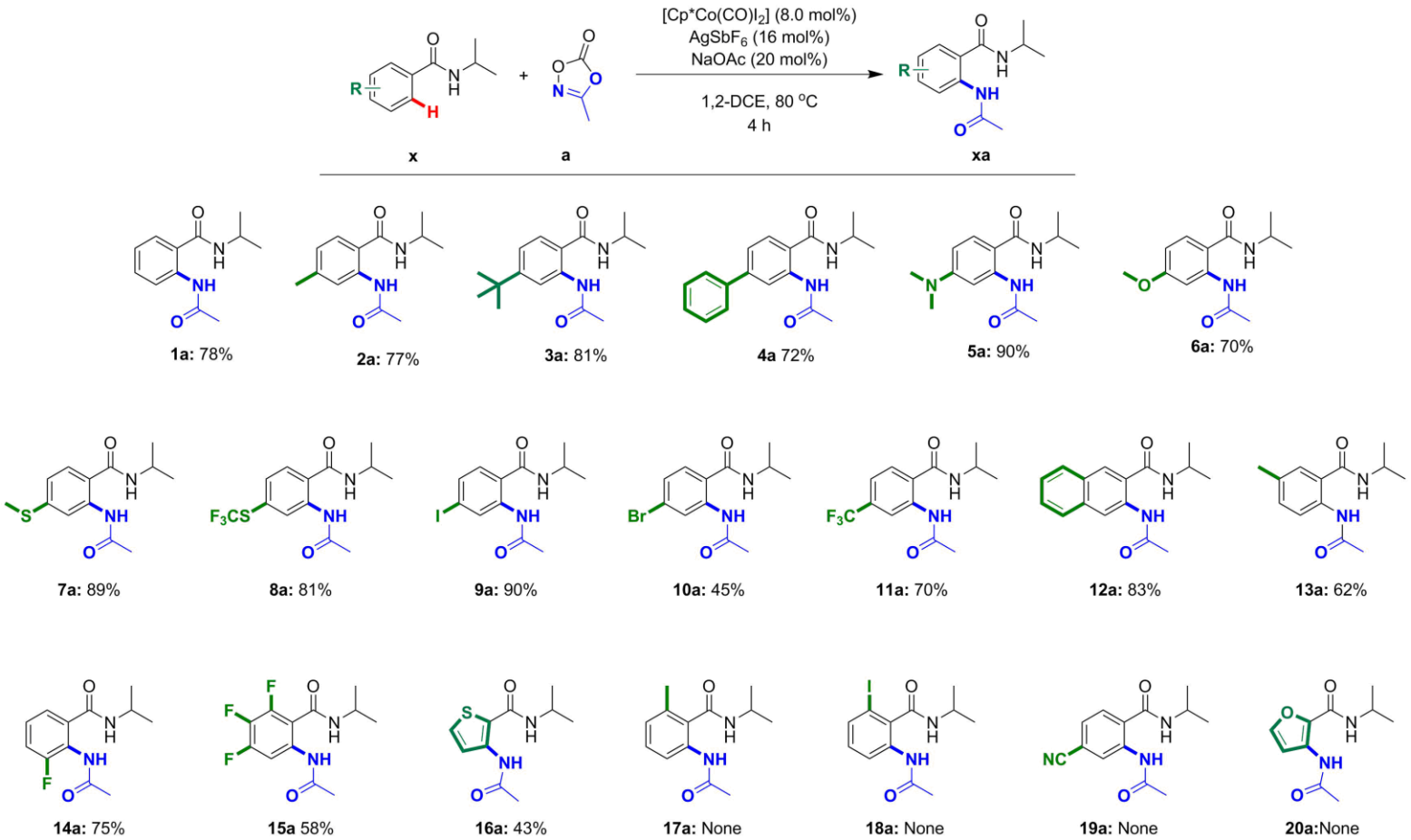
Table 2-5: Optimisation of loading of reactants [a]

Entry	[Cp*Co(CO)I_2] [mol%]	$AgSbF_6$ [mol%]	NaOAc [mol%]	1a [%][b]
1	**8.0**	**16**	**20**	**66**
2	4.0	8.0	10	60
3	2.5	5.0	6.3	51
4	1.0	2.0	2.5	36

[a] General conditions: 0.25 mmol **1**, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, [Cp*Co(CO)I_2], $AgSbF_6$, NaOAc, in 2.0 mL 1,2-DCE, T [80 °C], 4h.[b] Yields of **1a** calculated from ^{1}H NMR using mesitylene as internal standard.

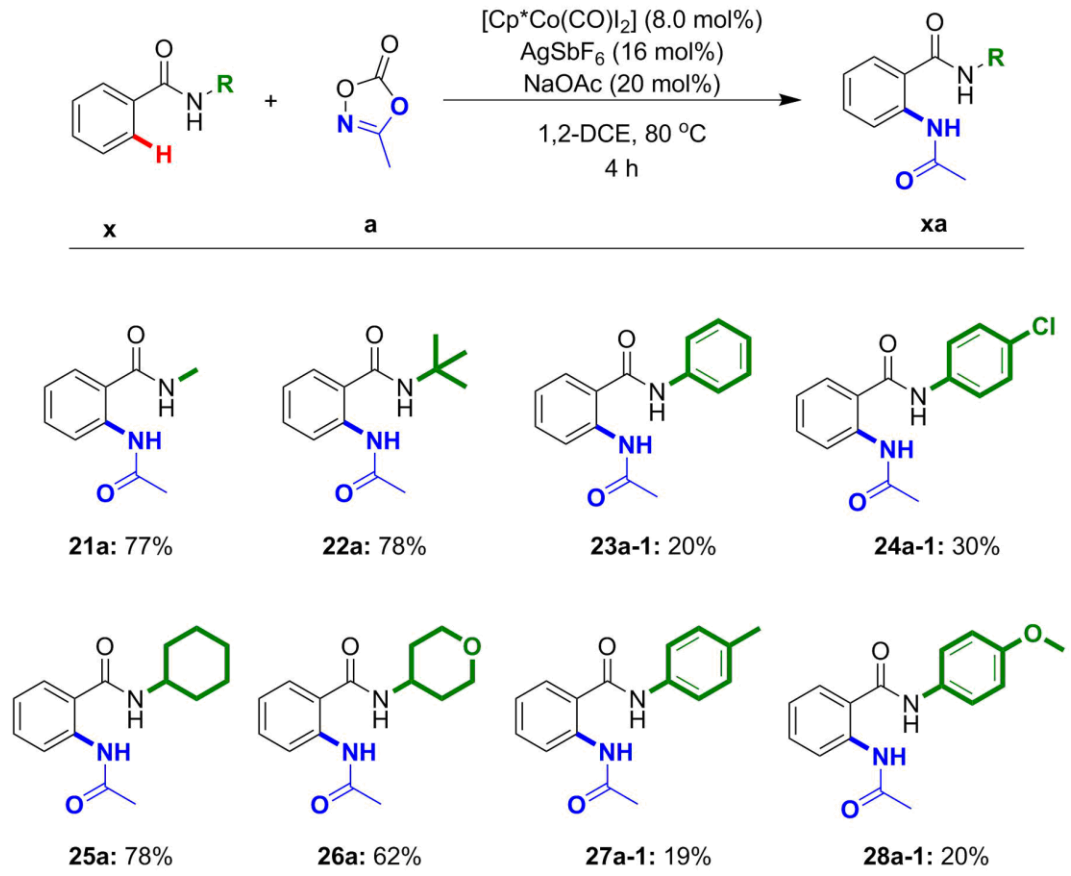
2.2.2 Substrate scope for the C-H amidation reaction

With the optimised conditions in hand, the substrate scope was studied (**Scheme 2-5**). Electron-withdrawing groups at the *para*-position afforded good to excellent yields for both weakly (**8a**, **9a** and **10a**) and highly deactivating groups (**11a**). The addition of electron-donating groups at the *para* position also delivered high yields of amidation products for weakly (**2a**, **3a**, **4a** and **12a**) and highly (**5a**, **6a**) activating groups. However, inclusion of cyano at the *para*-position prevented the formation of the desired amidation product, **19a**. This is likely due to the competitive coordination of CN to the Cp*Co(III) catalyst, thus inhibiting the amidation reaction



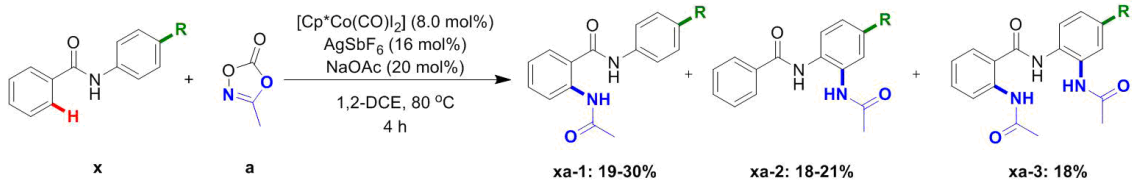
Scheme 2-5: Substrate scope studying the effect of variation in substituent on the aromatic moiety of the *N*-isopropyl benzamide under the optimised reaction conditions; Isolated yields of (xa) reported. General conditions: 1.5 mmol benzamide substrate (x), 8.0 mol% [Cp*Co(CO)I_2], 16 mol% $AgSbF_6$, 20 mol% NaOAc, 1.2 equiv. 3-methyl-1,4,2-dioxazol-5-one, 24 mL 1,2-DCE, 80 °C, 4 hours.

The protocol also displayed *meta*-substituent tolerance affording high yields for both fluoro- and methyl-substitution in a regioselective manner (**13a**, **14a**). The fluoro-substituted substrate was found to react at the most sterically hindered site, whereas the methyl-substituted substrate was found to react at the least sterically hindered C-H. This regioselectivity is the same observed previously for the Cp*Co(III) coupling of methyl vinyl ketone with benzamides and has been previously reported by several groups working with *meta*-substituted aromatic compounds.[36,109,141,142] In addition, the thiophene derivative could also be converted to furnish the corresponding amidation product, **16a**. When substituents were included in the *ortho*-position of the benzamide substrate, in the case of methyl- or iodo- (**17** and **18**), no amidation product was obtained. However, when the size of substituent was decreased to fluoro, the amidation reaction proceeded in good yield (**15a**). This indicated an important steric constraint at the *ortho* position.



Scheme 2-6: Substrate scope studying the effect of variation in substituent on the nitrogen atom of the benzamide under the optimisd reaction conditions. General conditions: 1.5 mmol benzamide substrate, 8.0 mol% $[Cp^*Co(CO)I_2]$, 16 mol% $AgSbF_6$, 20 mol% NaOAc, 1.20 equiv. 3-methyl-1,4,2-dioxazol-5-one, 24 mL 1,2-DCE, 80 °C, 4 hours.

Thereafter, the effect of replacing the isopropyl amide with other substituents was studied (**Scheme 2-6**). Methyl, *tert*-butyl, cyclohexyl and tetrahydropyranyl were tolerated providing the corresponding amidated products, **21a**, **22a**, **25a** and **26a**, in similar yield to the isopropyl derivative. On the other hand, aromatic substituents provided the desired amides, **23a-1**, **24a-1**, **27a-1** and **28a-1**, in relatively poor yield. It was found that at the end of the reaction, there was a complex mixture between the desired amidation product and by-products. (**Scheme 2-7**).



Scheme 2-7: Detected by-products for substrates with phenyl derived substituents on the nitrogen atom of the benzamide. General conditions: 1.5 mmol benzamide substrate, 8.0 mol% $[Cp^*Co(CO)I_2]$, 16 mol% $AgSbF_6$, 20 mol% NaOAc, 1.20 equiv. 3-methyl-1,4,2-dioxazol-5-one, 24 mL 1,2-DCE, 80 °C, 4 hours.

Most of these products could be isolated and characterised. The results illustrated that the selectivity could be slightly controlled to afford a higher yield of the desired product by the addition of an electron-withdrawing group at the *para*-position of the phenylamine, although still not synthetically useful. Consequently, adding a halogen at the *para* position affords a higher yield of **24a-1** compared to **23a-1**.

2.2.3 Synthesis of 1,2,3-benzotriazin-4(*3H*)-ones

With a library of 2-acetamido benzamides in hand and with an interest in conversions utilizing *tert*-butyl nitrite (TBN), it was observed that upon reacting 2-acetamido-*N*-isopropylbenzamide (**1a**) with TBN in acetic acid (AcOH) at 75 °C, an intriguing and unexpected transformation towards the cyclic 1,2,3-benzotriazin-4(*3H)*-one was observed, in excellent yield (98%). Reducing the temperature at which this conversion is carried out, decreases the yield of 1,2,3-benzotriazin-4(*3H*)-one obtained (**Table 2-6**).

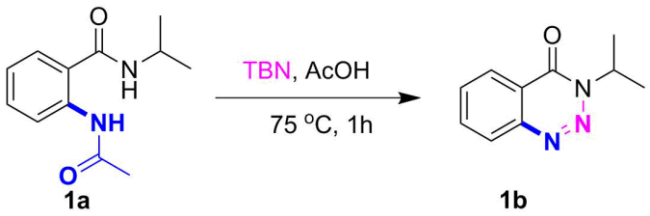
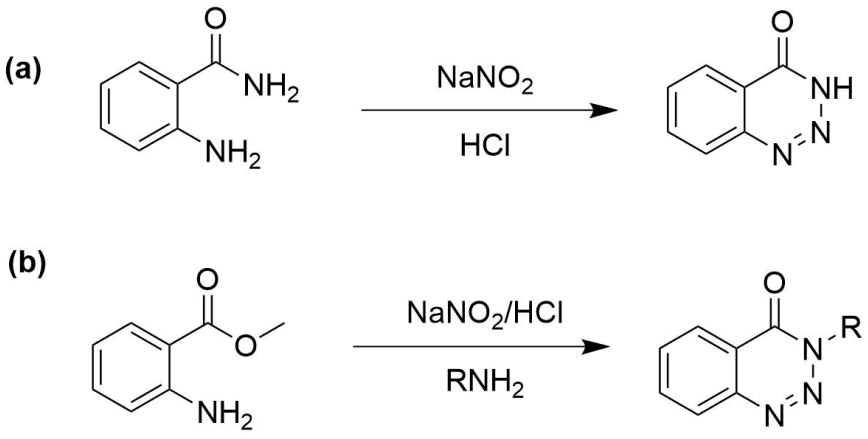


Table 2-6: Optimisation of temperature for the synthesis of 1,2,3-benzotriazin-4(*3H*)-one [a]

Entry	T [°C]	Yield of 1b [%][b]
1	25	25
2	50	75
3	**75**	**98**

[a] General conditions: 1.5 mmol **1a**, 3.0 equiv. TBN, 3.0 mL AcOH, T, 1 hour. [b] Yields of **1b** calculated from crude ^{1}H NMR using mesitylene as internal standard.

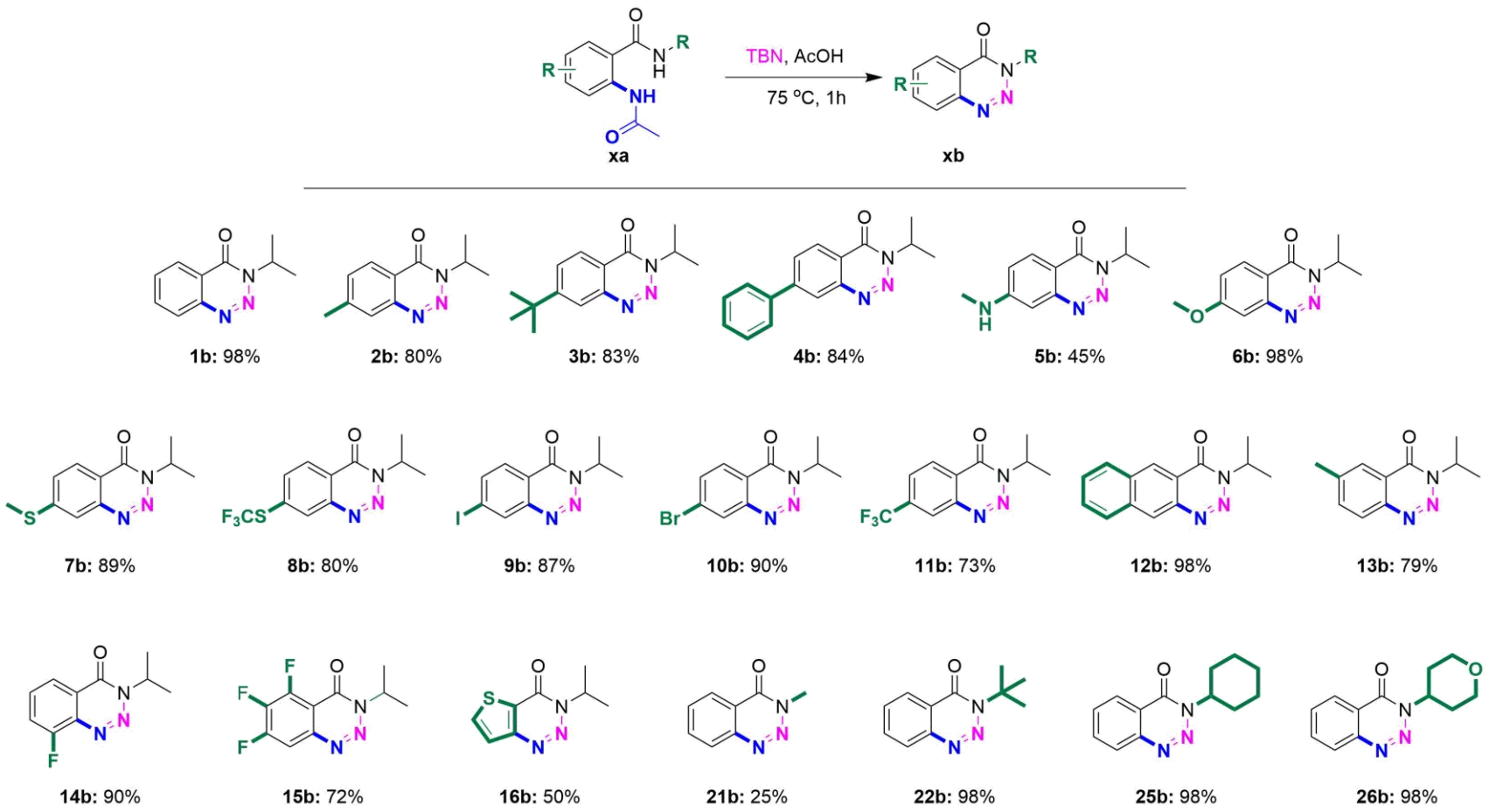
Acetic acid was chosen as the optimal solvent as it was previously observed that highly reactive species are formed from the degradation of *tert*-butyl nitrite to nitric oxide.[143] Typically 1,2,3-benzotriazin-4(*3H*)-ones can be prepared through diazotisation of 2-aminobenzamides or methyl anthranilate using sodium nitrite.[144-145] However, these reactions required low temperatures and the use of strong acids.



Scheme 2-8: Common approaches for synthesis of 1,2,3-benzotriazin-4(*3H*)-ones *via* diasotization of (a) 2-aminobenzamides or (b) methyl anthranilate.

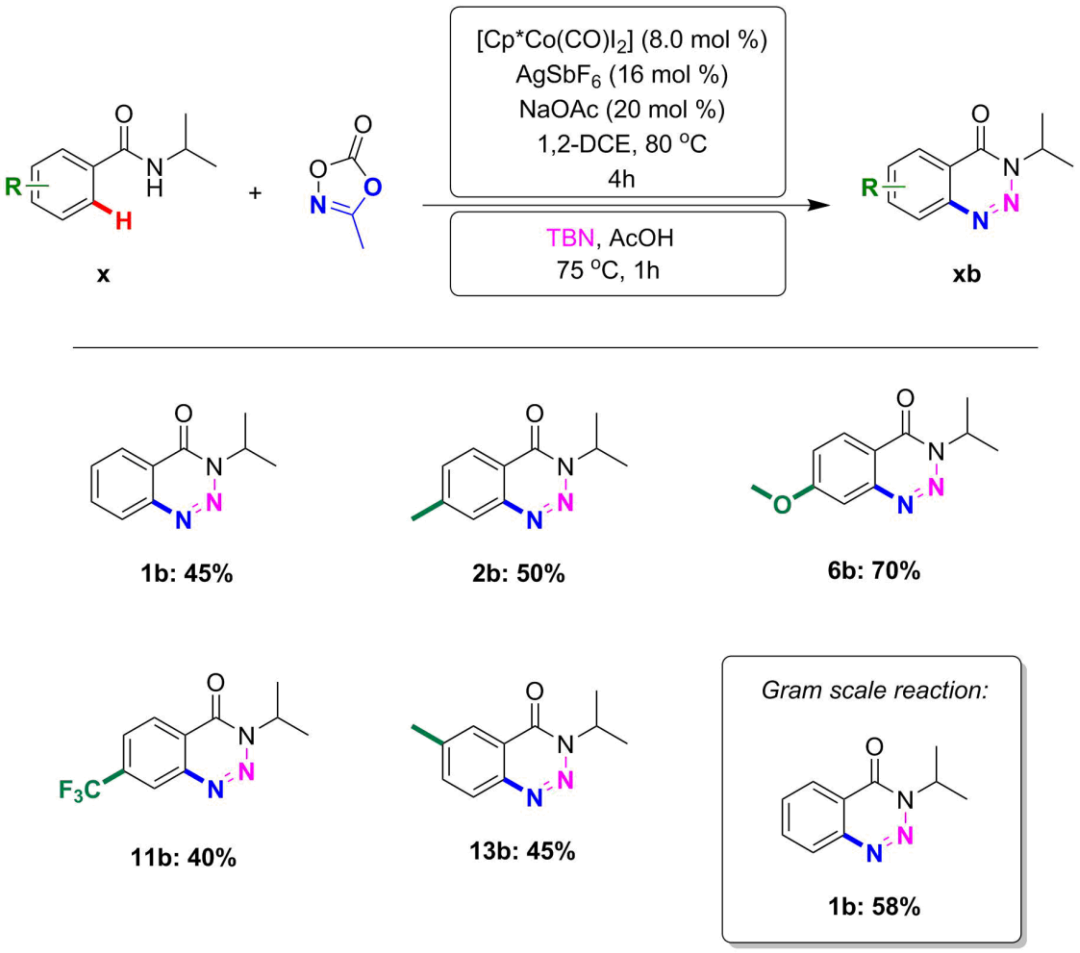
This route limits the facile inclusion of substituents on the aromatic ring, whereas the newly developed protocol described in this report provides a methodology for a wide substituent scope.

With the new facile protocol for the conversion of 2-acetamido-*N*-isopropylbenzamide, **1a**, to 1,2,3-benzotriazin-4(*3H*)-one developed, all the remaining 2-acetamido benzamides previously obtained were converted (**Scheme 2-9**). Substituents at the *para*-position of the original benzamide afforded excellent yields of the desired products (**2b**, **3b**, **4b**, **6b**, **7b**, **8b**, **9b**, **10b** and **11b**). Furthermore, multi-substituted substrates could also be converted in high yields (**12b**, **15b**) Intriguingly, **5b** was obtained as the secondary amine which may result from dealkylation of the dimethylamine in the presence of *tert*-butoxy anion.[146] High yields of 1,2,3-benzotriazin-4(*3H*)-one were also obtained for compounds bearing *meta*-substituents (**13b**, **14b**). A lower yield of 50% was observed when the thiophene substrate was applied. Furthermore, **21b** was converted in low yield compared to **1b** and **22b** however, **25b** and **26b** could be converted in high yields. This is proposed to result from a less stable intermediate after the reaction with TBN.



Scheme 2-9: Substrate scope studying the effect of variation in substituent on the aromatic moiety of the *N*-isopropyl benzamide and substituent on the nitrogen atom of the benzamide under the optimised reaction conditions; Isolated yields reported. General conditions: 1.0 mmol amidated benzamide, 3.0 equiv. TBN, 3.0 mL AcOH, 75 °C, 1 hour.

Inspired by the work of Zhu and Li,[110,111] some of the target molecules were synthesised in a sequential one-pot protocol, to eliminate the need for intermediate work-up (**Scheme 2-10**). The development of one-pot protocols is highly attractive and has received significant attention because these processes provide access to desired products without intermediate work-up or separation processes.[147] The obtained yields after one-pot reaction with **1b**, **2b**, **6b**, **11b**, and **13b** (**Scheme 5**) were comparable to the overall yields of the combined individual steps and exemplify the application of a facile sequential one-pot protocol for the preparation of 1,2,3-benzotriazin-4(*3H*)-ones using Cp*Co(III) C-H functionalisation catalysis as the key step.



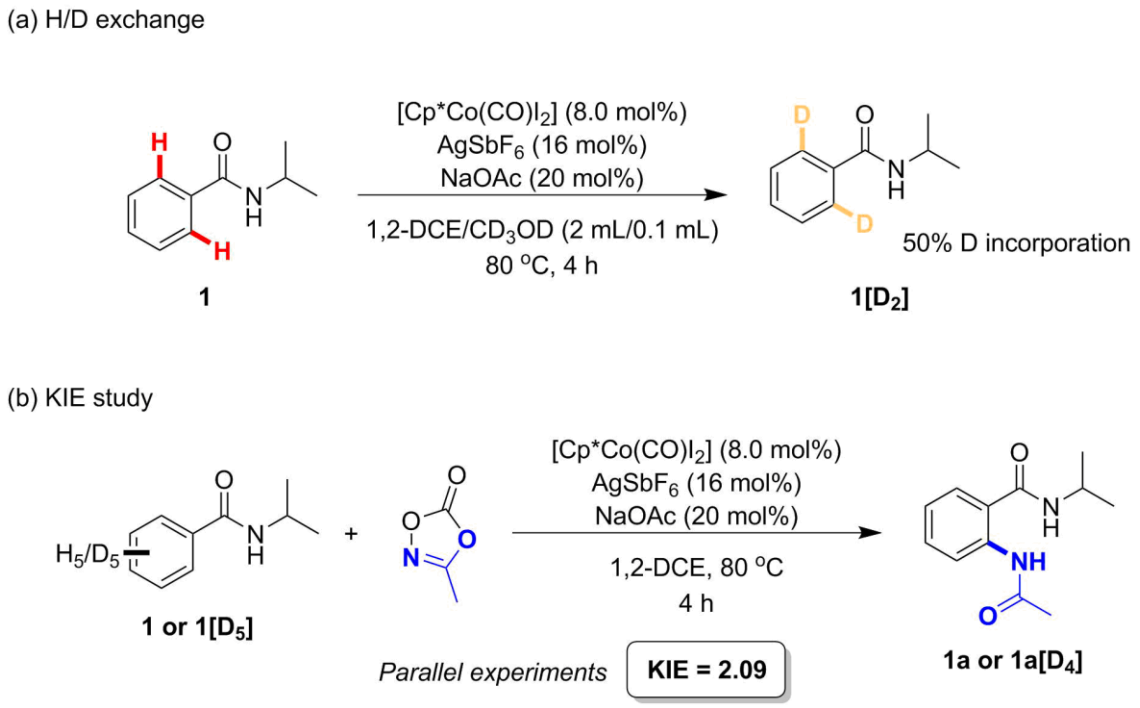
Scheme 2-10: Examples of conversions of benzamides towards 1,2,3-benzotriazin-4(*3H*)-ones by a sequential one-pot protocol developed in this work (including a gram scale synthesis of **1b** from 1.0 g of benzamide **1**). Isolated yields reported. General conditions: Optimised reaction conditions for each individual step.

To explore the scalability of the new sequential one-pot protocol, a gram scale conversion was attempted. An overall yield of 58% was observed for **1b**, which highlighted the potential of this new synthetic protocol. The yield is slightly higher than the smaller scale reaction (45%) likely because of the easier isolation of larger amounts of product.

2.2.4 Mechanistic investigations

2.2.4.1 Experimental mechanistic investigations

To further understand the initial Cp*Co(III)-catalysed amidation step, both deuterium exchange and parallel Kinetic Isotope Effect (KIE) experiments were performed (**Scheme 2-11**). The results obtained demonstrate that the C-H activation step is clearly reversible and that C-H cobaltation could be relevant in the rate-determining step of the mechanism with a KIE value of 2.09.



Scheme 2-11: Experimental insights into mechanism of the Cp*Co(III)-catalysed C-H amidation step.

2.2.4.2 Computational mechanistic investigations

In addition to the experimental results, and in order to gain an in-depth insight into the mechanism of formation for the new C-N bond, DFT calculations were carried out (**Figure 2-2**). The formation of the cationic active catalyst $[Cp^*Co(OAc)]^+$ species is observed as a result of the loss of acetate ion from the neutral $[Cp^*Co(OAc)]_2$ pre-catalyst and requires an energy of 9.99 kcal mol^{-1}.[148]

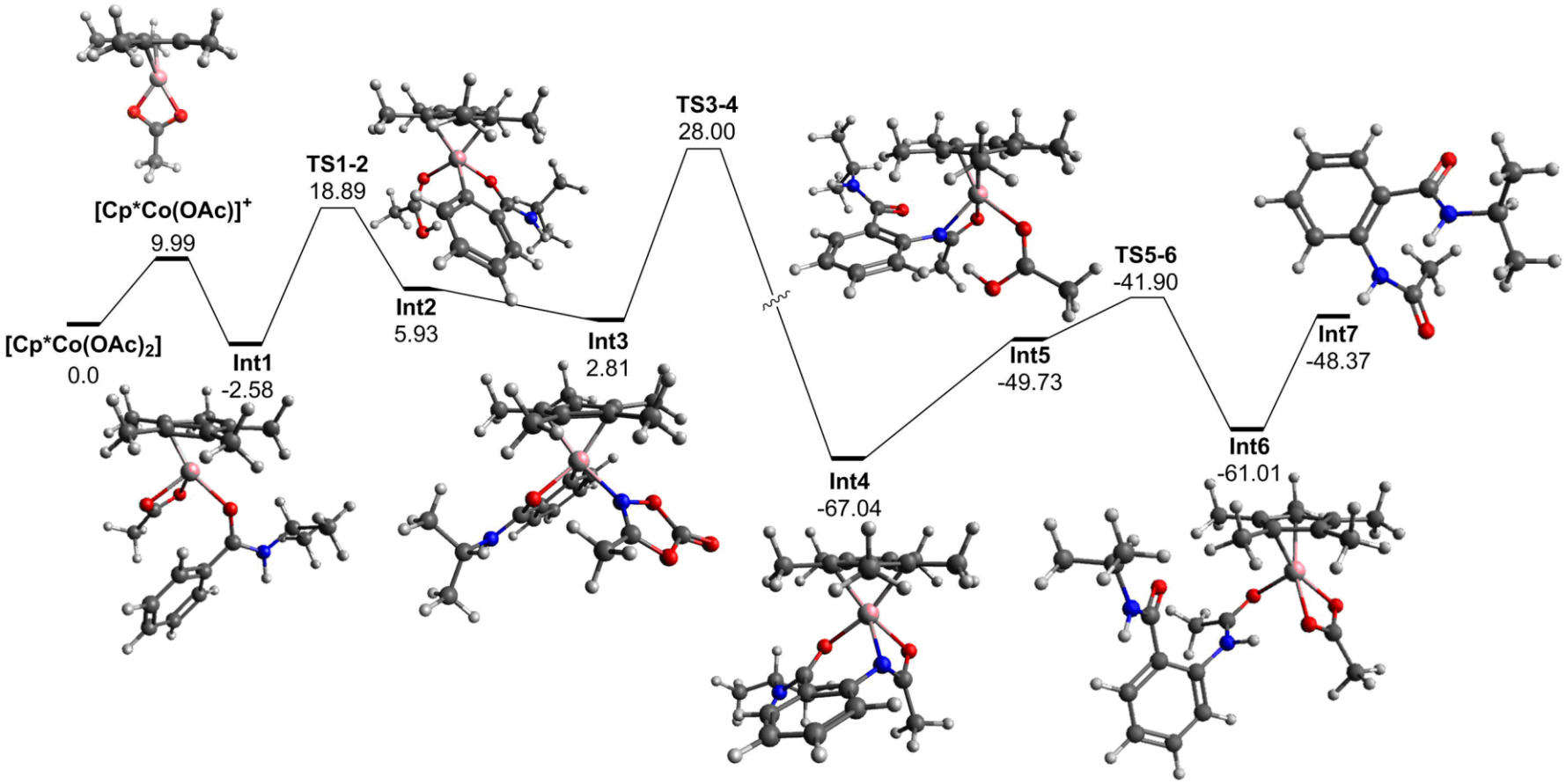


Figure 2-2: Solvent corrected Free Energy Surface (ΔG_{298} kcal mol^{-1}) for the amidation of isopropyl benzamide with 3-methyl-1,4,2-dioxazol-5-one. Free energies taken relative to the [Cp*Co(III)$(AcO)_2$] pre-catalyst and associated reagents.

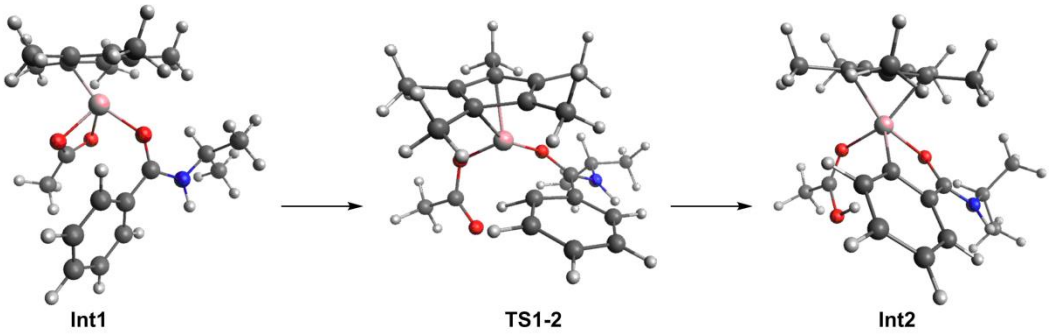


Figure 2-3: Calculated structures for **Int1**, **TS1-2** and **Int2**

Subsequently, the $[Cp^*Co(OAc)]^+$ coordinates to the lone pair of the oxygen of the isopropyl benzamide substrate to form the first intermediate (**Int1**). This is in agreement with a previous DFT study reported by Whiteoak/Hamilton and co-workers.[109] Next, C-H activation leads to the 5 membered cobaltacycle, **Int2** *via* an energy barrier of 21.5 kcal mol^{-1}. The distance between the cobalt centre and the aromatic carbon decreases from 3.75 Å (**Int1**) to 1.93 Å (**Int2**) to form the cobaltacycle (**Table 2-7**). The C_{sp}^2-H bond is cleaved, and the proton is abstracted by the acetate group.

Table 2-7: Selected bond lengths (Å) for Int1, TS1-2, Int2

Atoms	Int1	TS1-2	Int2
Co-C_{sp}^2	3.75	2.09	1.93
H-$O_{acetate}$	2.79	1.41	1.00
C_{sp}^2-H	1.09	1.27	1.93

The favourable loss of acetic acid by 3.1 kcal mol^{-1} and coordination of the amidating agent 1,4,2-dioxazol-5-one, yields **Int3**. The following migratory insertion of the amidation agent, with formation of the new C-N bond and concomitant loss of CO_2 to furnish **Int4** is the rate determining step for the reaction with a barrier of 25.2 kcal mol^{-1}. The calculated transition state (**TS3-4**) illustrates the loss of CO_2 by the cleavage of the N-O and O-C bonds of the amidation agent (**Table 2-8**). It should be noted that a stepwise barrier has also been calculated and is only 0.5 kcal mol^{-1} higher in the energy so it cannot be discounted.

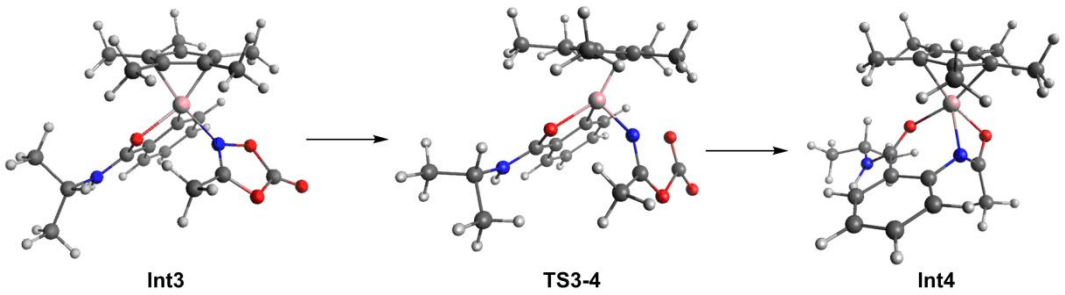


Figure 2-4: Calculated structures for **Int3**, **TS3-4** and **Int4**

Interestingly, both the Cp*Co(III)-catalysed concerted and stepwise mechanisms are significantly higher in energy than the equivalent Cp*Ir(III)-catalysed CO_2 extrusion reported by Chang for the same benzamide substrates.[149] At first glance this proposal of the migratory insertion being the rate determining step contradicts the experimentally obtained KIE results, however taking into account the reversibility of the initial C-H activation step having the potential to limit the equilibrium concentration of the following intermediates prior to this migratory insertion, a small KIE is not unexpected.[150]

Table 2-8: Selected bond lengths (Å) for Int3, TS3-4, Int4

Atoms	Int3	TS3-4	Int4
$N\text{-}C_{sp^2}$	2.71	2.69	1.40
$N\text{-}O_{\text{amid. ag.}}$	1.44	2.14	-
$O\text{-}C_{\text{amid. ag.}}$	1.40	1.78	-

The migratory insertion step leads to **Int4** with a significant stabilisation in energy. This agrees with the observed irreversibility of the reaction after the loss of CO_2.

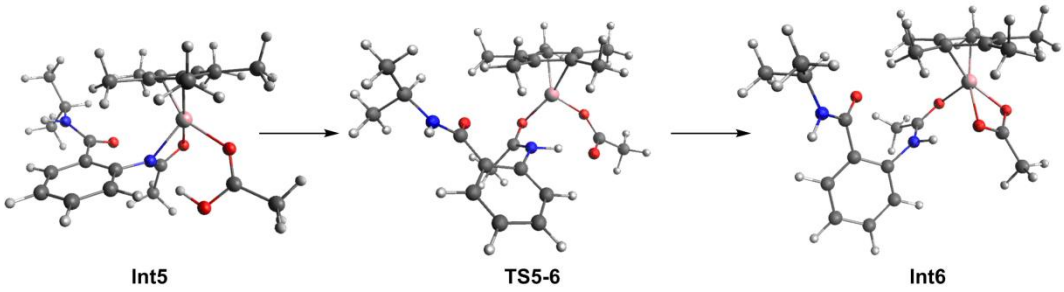


Figure 2-5: Calculated structures for **Int5**, **TS5-6** and **Int6**

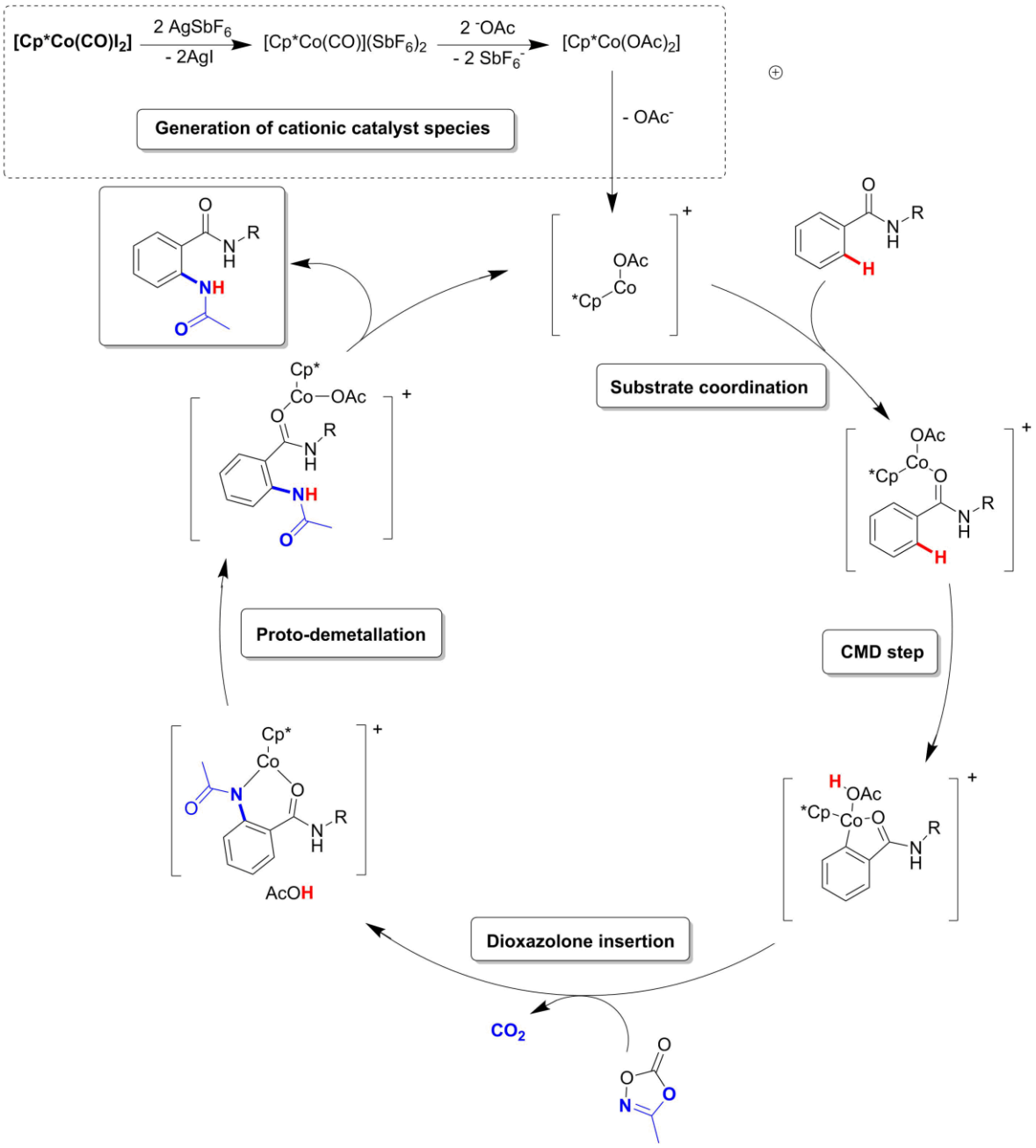
Entropically unfavourable addition of an acetic acid to the coordination site weakly associated to the benzamide oxygen affords **Int5**. Coordination of the acetic acid facilitates the last step of the reaction, which is the protonation of the newly installed amide group, with a barrier of 7.8 kcal mol^{-1}, forming **Int6**. The distance between the nitrogen of the amidation agent and the cobalt centre increases as the catalyst cleaves from the product (**Table 2-9**).

Table 2-9: Selected bond lengths (Å) for Int5, TS5-6, Int5

Atoms	Int5	TS5-6	Int6
N-$H_{acetate}$	1.65	1.10	1.03
N-Co	2.02	2.58	3.25

Dissociation of **Int6** releases the 2-acetamido benzamide product and regenerates the active $[Cp^*Co(OAc)]^+$ catalyst, completing the catalytic cycle. This mechanism is also in agreement with the DFT study provided by Kim and Chang for the amidation of arylpyridines under Cp*Rh(III) catalysis using the same 1,4,2-dioxazol-5-one amidating agents, although the energies are not directly comparable due to the different substrates and methodologies being used.[151]

Scheme 2-12 summarises the proposed catalytic cycle for the formation of 2-acetamido benzamides using both the experimental and the DFT results obtained in this study.



Scheme 2-12: Proposed catalytic cycle for Cp*Co(III)-catalysed coupling of diozaxolones and benzamides for the preparation of 2-acetamido benzamides.

Calculations were also undertaken on the triplet state of each intermediate. The triplet surface was found to be significantly higher in energy throughout the reaction pathway excluding the possibility for conical intersections connecting the energy surfaces. **Figure 2-6** illustrates the Free Energy Surfaces for both the singlet and triplet states.

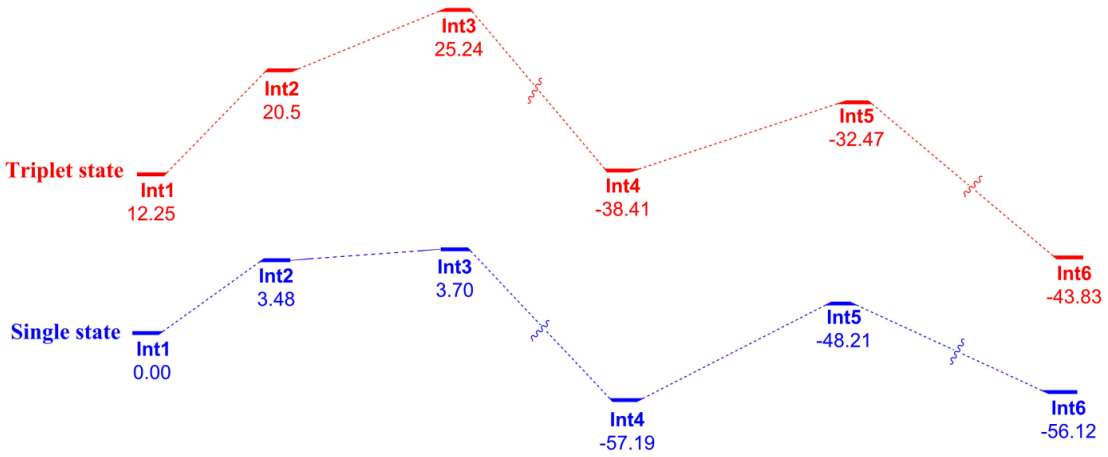
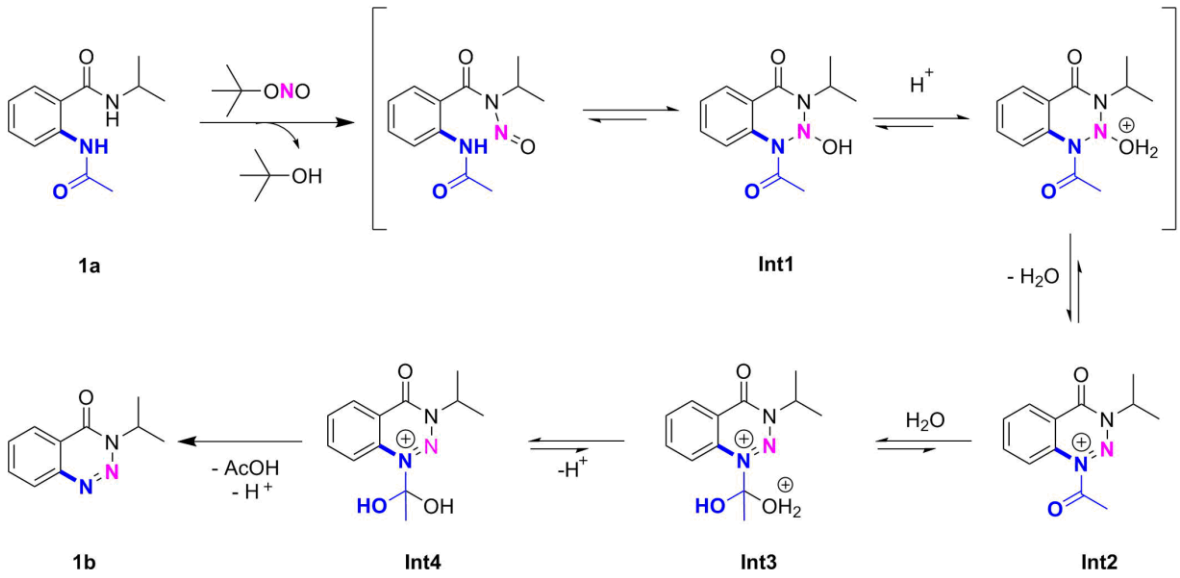


Figure 2-6: Comparison between single and triple state Free Energy Surface (ΔG 298 kcal mol-^{1}) for the intermediates of the amidation of isopropyl benzamide with 3-methyl-1,4,2-dioxazol-5-one. Free energies taken relative to intermediate **Int1** and associated reagents in singlet state.

The mechanism for the conversion of 2-acetamido benzamides to the corresponding 1,2,3-benzotriazin-4(*3H*)-ones is less clear. It is well known that alkyl nitrites are a source of nitric oxide (NO).[152] This mechanism proposes that the NO species reacts with one of the amides of the 2-acetamido benzamides generating a highly reactive *N*-nitrosoamide intermediate (**Int1**) reported recently by Bhanage [153], which releases water to furnish **Int2**. The final cyclic product (**1b**) is obtained after the addition of water and the formation of the N-N double bond (**Int3**) followed by loss of acetic acid.



Scheme 2-13: Proposed mechanism for the synthesis of 1,2,3-benzotriazin-4(*3H*)-one by reacting 2-acetamido benzamides with TBN.

2.3 Summary

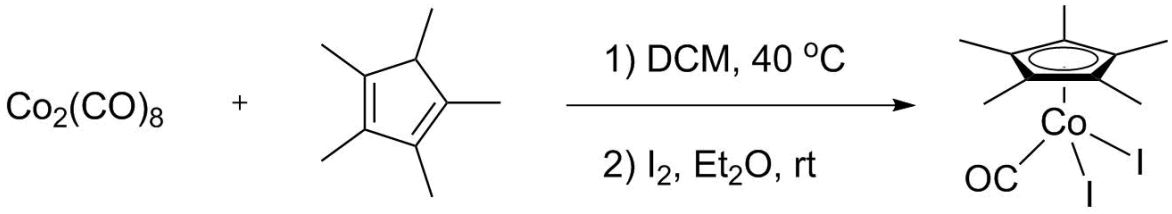
In summary, a wide library of substituted benzamides could be successfully amidated using a Cp*Co(III)-catalysed protocol and employing the readily available 1,4,2-dioxazol-5-one as coupling partner. Furthermore, the C-H amidation products (2-acetamido-*N*-benzamides) could be converted into potentially valuable 1,2,3-benzotriazin-4(3*H*)-ones through a single step reaction using TBN. The two steps can be combined to provide a sequential one-pot synthesis of 1,2,3-benzotriazin-4(*3H*)-ones, starting from the readily available and cheap benzamides. Finally, the mechanism of the Cp*Co(III)-catalysed C−H amidation step has been elucidated for the first time using DFT studies, wherein it has been found that despite an experimentally obtained KIE of 2.09, the migratory insertion is the rate limiting step. This observable KIE could potentially arise from the reversibility of the C−H cobaltation step. The results from this chapter were further utilised to develop further protocols for both Cp*Co(III)-catalysed C-H amidation reactions and formation of heterocycles.

2.4 Experimental procedures

2.4.1 General Experimental Considerations

All reagents and solvents were purchased from Sigma Aldrich, Fisher Scientific, Fluorochem and Acros Organics and used without further purification. ^{1}H (400 MHz, 298K), ^{13}C $\{^{1}H\}$ (100 MHz, 298K), ^{19}F $\{^{1}H\}$ NMR (376 MHz, 298K) and 2D NMR were recorded on a Bruker AV-400 spectrometer and referenced to the residual deuterated solvent signals. High Resolution Mass Spectra (HRMS) were recorded on a Xevo G2-Xs QTof Mass Spectrometer.

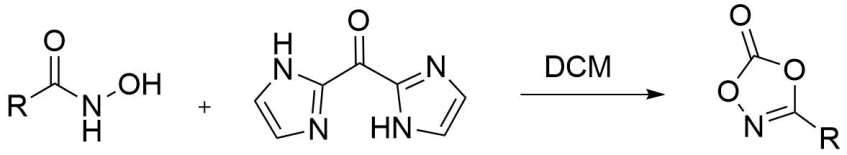
2.4.2 Procedure for the synthesis of the [Cp*Co(CO)I_2] pre-catalyst



Scheme 2-14: Procedure for the synthesis of the [Cp*Co(CO)I_2] pre-catalyst.

$Co_2(CO)_8$ (5.00 g, 14.6 mmol), anhydrous DCM (100 mL) and pentamethylcyclopentadiene (5.55 mL, 35.4 mmol) were added to an oven dried 500 mL two neck round bottom flask. The mixture was refluxed at 40 °C nder nitrogen for 6 h. Afterwards, the mixture was cooled to room temperature and the solvent was removed under vacuum. The residue was dissolved in anhydrous Et_2O (50 mL) and then a solution of iodine (9.0 g, 35.5 mmol) dissolved in dry Et_2O (50 mL) was added dropwise while stirring. Afterward, the mixture was left to stir for 1 h at room temperature (the reaction was exothermic and CO gas was observed). The solvent was evaporated under vacuum and the crude mixture was purified by silica gel column chromatography using hexane then DCM/hexane=4/1. A dark purple powder (11.0 g, 79% yield) was isolated. The ^{1}H NMR spectrum was consistent with that reported by Kanai and Matsunaga.[26]

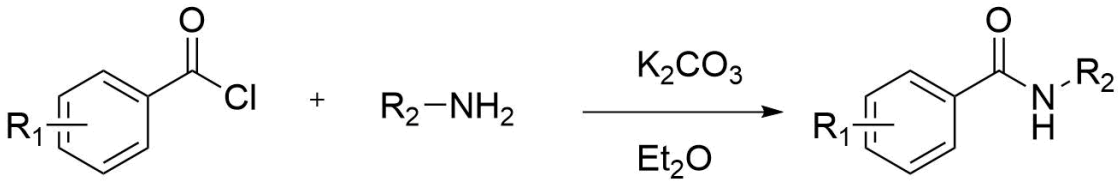
2.4.3 General procedure for the synthesis of the 1,4,2-dioxazol-5-ones



Scheme 2-15: General procedure for the synthesis of the 1,4,2-dioxazol-5-ones.

1,1'-Carbonyldiimidazole (10.0 mmol) was added to a solution of hydroxamic acid (10.0 mmol) in DCM (100 mL). The mixture was stirred overnight at room temperature. After this time, the reaction mixture was quenched with 1.0 M aqueous HCl (70 mL). The organic layer was extracted with DCM (100 mL x 3) and dried over $MgSO_4$. The solvent was removed under vacuum to afford 3-substituted 1,4,2-dioxazol-5-ones. The NMR spectra were consistent with those reported by Chang.[132]

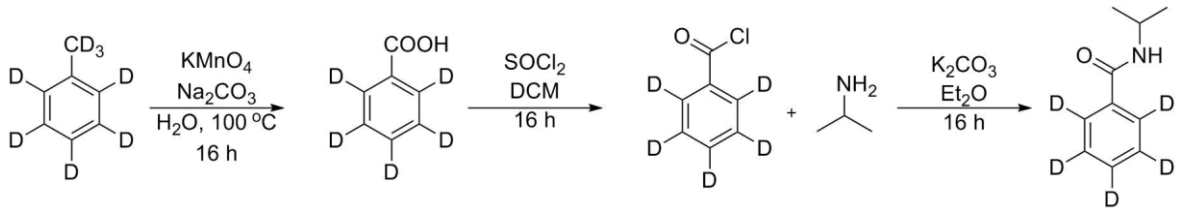
2.4.4 General procedure for synthesis of benzamide substrates



Scheme 2-16: General procedure for synthesis of benzamide substrates.

To a solution of acyl chloride (1.0 equiv.) in Et_2O (50 mL) was added K_2CO_3 (2.5 equiv.) After the mixture had been cooled in an ice bath, the amine (1.5 equiv.) was added. The mixture was stirred overnight at room temperature. After this time, the mixture was extracted using EtOAc (3 x 100 mL) and washed with H_2O (50 mL) and then aqueous HCl (1.0 M, 50 mL)). The organic phase was dried over $MgSO_4$, filtered and the solvent removed was removed under vacuum. The crude mixture was purified by silica gel column chromatography if necessary, using hexane/EtOAc (1/1) to provide analytically pure benzamides.

2.4.5 Procedure for synthesis of benzamide-d_5



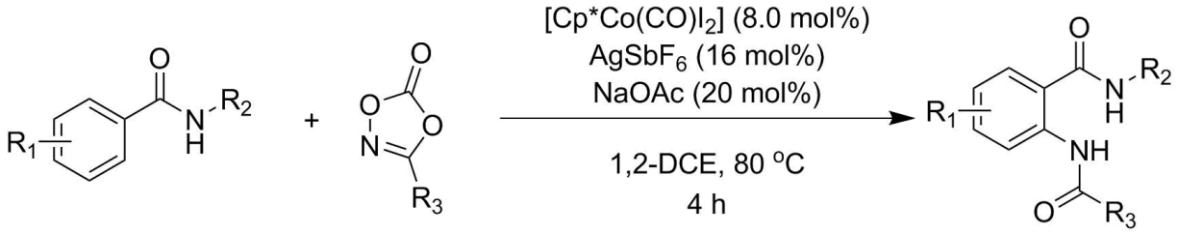
Scheme 2-17: Procedure for synthesis of benzamide-d_5.

Toluene-d_8 (5 g, 50 mmol), KMnO4 (20.0 g, 125 mmol), Na_2CO_3 (5.28 g, 50 mmol), and H_2O (150 mL) were added to a round bottom flask. The reaction mixture was refluxed at 120 °C for 16 h and then cooled to room temperature. The mixture was filtered through a pad of Celite, and the filtrate was acidified with 2M HCl until precipitate was observed. The crude was extracted with DCM (3 × 200 mL) and the solvent removed was removed under vacuum. The crude product was recrystallised from water to give benzoic acid-d_5 as white solid (3.00 g, 47% yield)

Benzoic acid-d_5 (3.00 g, 23.6 mmol), DCM (50 mL) and thionyl chloride (8.41 g, 71 mmol) were added to a round bottom flask. The reaction mixture was stirred for 16h at room temperature. After this time, the mixture was washed with H_2O (50 mL), the organic layer was extracted with DCM (100 mL x 2) and concentrated under vacuum to give benzoyl chloride-d_5 as a colourless oil (2.8 g, 81%).

To a solution of benzoyl chloride-d_5 (19.2 mmol) in Et_2O (50 mL) was added K_2CO_3 (49 mmol). After the mixture had been cooled in an ice bath, the isopropyl amine (28.8 mmol) was added. The mixture was stirred overnight at room temperature. After this time, the mixture was extracted with EtOAc (3 x 100 mL) and washed with H_2O (50 mL) and then aqueous HCl (1.0 M, 50 mL). The organic phase was dried over magnesium sulfate, filtered and the solvent removed under reduced pressure to yield isopropyl benzamide-d_5 as a white amorphous solid (2.50 g, 78%).

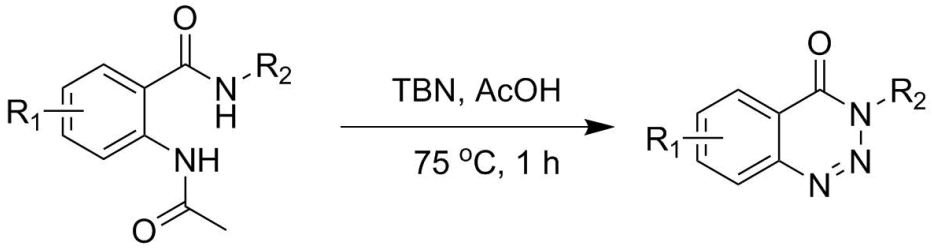
2.4.6 General procedure for Cp*Co(III)-catalysed amidation reactions



Scheme 2-18: General procedure for Cp*Co(III)-catalyzed C-H amidation reactions.

Benzamide substrate (1.5 mmol), $[Cp^*Co(CO)I_2]$ (8.0 mol%, 0.12 mmol), $AgSbF_6$ (16 mol%, 0.24 mmol), NaOAc (20 mol%, 0.30 mmol), 1,4,2-dioxazol-5-one (1.2 equiv., 1.8 mmol) and 1,2-DCE (24 mL) were added to a 40 mL vial under air. The vial was sealed, and the mixture stirred at 80 °C for 4 hours. The solvent was removed under vacuum and the crude was purified by column chromatography, using hexane/EtOAc (8/2) as eluent to provide the analytically pure amidation products.

2.4.7 General procedure for synthesis of 1,2,3-benzotriazin-4*(3H)*-ones

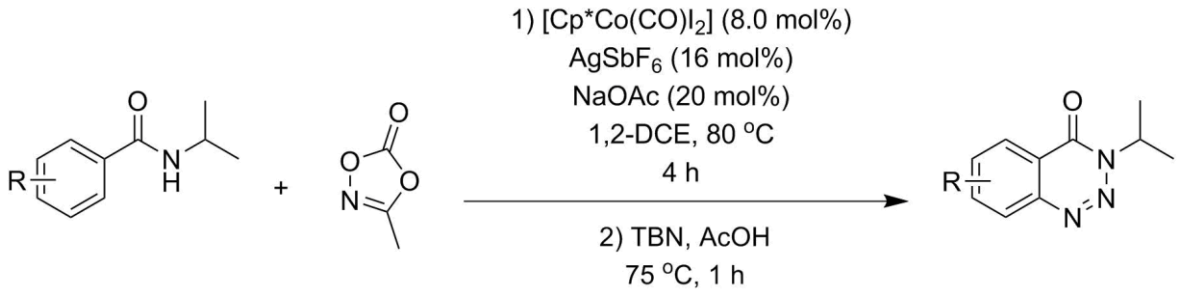


Scheme 2-19: General procedure for synthesis of 1,2,3-benzotriazin-4(*3H*)-ones.

2-Acetamido-benzamide (1.0 mmol), AcOH (3.0 mL) and *tert*-butyl nitrite (3.0 equiv., 3.0 mmol) were added to an 8 mL vial. The vial was sealed, and the reaction mixture was stirred at 75 °C for 1 hour. After this period, the acetic acid was removed under reduced pressure and the crude reaction mixture was purified

by column chromatography using hexane/EtOAc (1/1) as eluent to provide the analytically pure 1,2,3-benzotriazin-4(*3H*)-one products.

2.4.8 General procedure for sequential one-pot reaction for synthesis of 1,2,3-benzotriazin4(*3H*)-ones



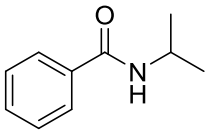
Scheme 2-20: General procedure for sequential one-pot reaction for synthesis of 1,2,3-benzotriazin-4(*3H*)-ones.

Benzamide (1.5 mmol), [Cp*Co(CO)I_2] (8.0 mol%, 0.12 mmol), $AgSbF_6$ (16 mol%, 0.24 mmol), NaOAc (20 mol%, 0.30 mmol), 3-methyl-1,4,2-dioxazol-5-one (1.2 equiv., 1.8 mmol) and 1,2-DCE (24 mL) were added to a 20 mL vial. The vial was sealed and the mixture was stirred at 80 °C for 4 hours. After this time, the solvent was evaporated under vacuum and TBN (3.0 equiv., 4.5 mmol) and AcOH (3.0 mL-5.0 mL) were added to the crude reaction mixture. The reaction was then stirred at 75 °C for a further 1 hour. The AcOH was then removed under reduced pressure and the crude was purified by silica gel column chromatography using hexane/EtOAc (8/2) as eluent to provide the analytically pure 1,2,3-benzotriazin-4(*3H)*-one.

2.5 Characterisation of synthesised compounds

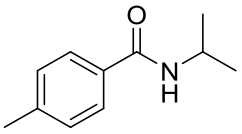
2.5.1 Characterisation of substrates

N-Isopropylbenzamide (1)



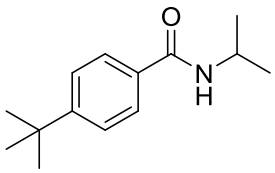
This compound was prepared in accordance to the general synthesis described for benzamides starting from benzoyl chloride (2.00 g, 14.2 mmol) to yield a white amorphous solid (1.87 g, 81%). **^{1}H NMR ($CDCl_3$);** δ: 7.77-7.75 (m, 2H), 7.51-7.47 (m, 1H), 7.44-7.40 (m, 2H), 6.02 (br s, 1H), 4.34-4.26 (m, 1H), 1.27 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 166.7, 134.9, 131.2, 128.5, 126.8, 41.9, 22.8. **HR-MS (ASAP, m/z)** calcd. from $C_{10}H_{13}NO+H]^+$: 164.1075; found 164.1077. R_f = 0.53 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[154]

N-Isopropyl-4-methylbenzamide (2)



This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-methylbenzoyl chloride (2.00 g, 12.9 mmol) to yield a white amorphous solid (1.67 g, 73%). **^{1}H NMR ($CDCl_3$);** δ: 7.65 (d, 2H, $^3J_{HH}$ = 8.1 Hz), 7.21 (d, 2H, $^3J_{HH}$ = 8.1 Hz), 5.97 (br s, 1H), 4.36-4.28 (m, 1H), 2.42 (s, 3H), 1.29 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 166.6, 141.6, 132.1, 129.1, 126.83, 41.8, 22.9, 21.4. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NO+H]^+$: 178.1232; found: 178.1239. R_f = 0.46 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[154]

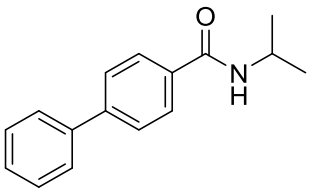
4-(*tert*-Butyl)-*N*-isopropyl benzamide (3)



This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-(*tert*-Butyl)benzoyl chloride (2.00 g, 10.17 mmol) to yield a white amorphous solid (1.84 g, 82%). **^{1}H NMR ($CDCl_3$)**: δ 7.70 (d, 2H, $^3J_{HH}$ = 8.6 Hz), 7.44 (d, 2H, $^3J_{HH}$ = 8.6 Hz), 5.91 (br s, 1H), 4.30-4.25

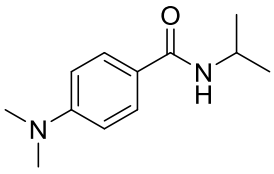
(m, 1H), 1.33 (s, 9H), 1.26 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$, 100 MHz, 298K);** δ: 166.6, 154.7, 132.1, 126.6, 125.4, 41.8, 34.9, 31.2, 22.9. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{21}NO+H]^+$: 220.1701; found: 220.1709. R_f = 0.62 (EtOAc/Hexane 40/60).

***N*-Isopropyl-[1,1'-byphenyl]-4-carboxamide (4)**



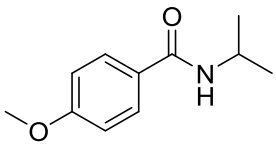
This compound was prepared in accordance to the general synthesis described for benzamides starting from [1,1'-biphenyl]-4-carbonyl chloride (2.00 g, 9.23 mmol) to yield a white amorphous solid (1.84 g, 83%). **^{1}H NMR ($CDCl_3$);** δ: 7.87 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.68 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 7.65 (d, 2H, $^3J_{HH}$ = 8.0 Hz), 7.50 (dd, $^3J_{HH}$ = 7.2 Hz, $^3J_{HH}$ = 7.8 Hz), 7.42 (t, 1H, $^3J_{HH}$ = 7.3 Hz), 6.03 (br s, 1H), 4.40-4.32 (m, 1H), 1.33 (d, 6H, $^3J_{HH}$ = 6.5). **^{13}C NMR ($CDCl_3$);** δ: 166.4, 144.1, 140.1, 133.65, 128.9, 128.0, 127.4, 127.2, 41.9, 22.4. **HR-MS (ASAP, m/z)** calcd. from $[C_{16}H_{17}NO+H]^+$: 240.1388; found: 240.1382. R_f = 0.46 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[155]

4-(Dimethylamino)-*N*-isopropyl benzamide (5)



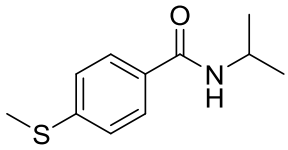
This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-(dimethylamino)benzoyl chloride (1.00 g, 5.45 mmol) to yield a light orange amorphous solid (1.01 g, 90%). **^{1}H NMR ($CDCl_3$);** δ: 7.67 (d, 2H, $^3J_{HH}$ = 9.0 Hz), 6.97 (d, 2H, $^3J_{HH}$ = 9.0 Hz), 5.79 (br s, 1H), 4.33-4.24 (m, 1H), 3.02 (s, 6H), 1.25 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 166.6, 152.3, 128.2, 121.8, 111.0, 41.5, 40.1, 23.1. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{18}N_2O+H]^+$: 207.1497; found: 207.1504. R_f = 0.15 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[156]

***N*-Isopropyl-4-methoxybenzamide (6)**



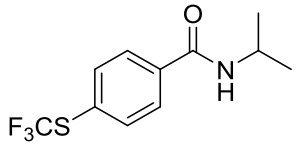
This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-methoxybenzoyl chloride (1.00 g, 5.89 mmol) to yield a light green amorphous solid (1.0 g, 90%). **^{1}H NMR ($CDCl_3$)**; δ: 7.75 (d, 2H, $^{3}J_{HH}$ = 8.9 Hz), 6.95 (d, 2H, $^{3}J_{HH}$ = 8.9 Hz), 5.91 (br s, 1H), 4.36-4.27 (m, 1H), 3.88 (s, 3H), 1.29 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$)**; δ: 166.2, 162.0, 128.5, 127.2, 113.7, 55.4, 41.80, 23.0. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NO_2+H]^+$:194.1181; found: 194.1175. R_f = 0.25 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[157]

***N*-Isopropyl-4-(methylthio)benzamide (7)**



This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-(methylthio)benzoyl chloride (2.00 g, 10.71 mmol) to yield a white amorphous solid (1.79 g, 80%). **^{1}H NMR ($CDCl_3$);** δ: 7.68 (d, 2H, $^{3}J_{HH}$ = 8.7 Hz), 7.25 (d, 2H, $^{3}J_{HH}$ = 8.7 Hz), 5.94 (br s, 1H), 4.33-4.24 (m, 1H), 2.51 (s, 3H), 1.27 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 166.1, 143.1, 131.1, 127.2, 125.5, 41.9, 22.9, 15.1. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NO_2+H]^+$: 210.0953; found: 210.0955. R_f = 0.31 (EtOAc/Hexane 40/60).

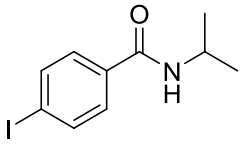
***N*-Isopropyl-4-((trifluoromethyl)thio)benzamide (8)**



This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-(trifluoromethyl)thio)benzoyl chloride (1.00 g, 4.16 mmol) to yield a white amorphous solid (0.76 g, 70%). **^{1}H NMR ($CDCl_3$);** δ: 7.80 (d, 2H, $^{3}J_{HH}$ = 8.5 Hz), 7.72 (d, 2H, $^{3}J_{HH}$ = 8.4 Hz), 5.98 (br s, 1H), 4.34-4.26 (m, 1H), 1.28 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 165.6, 137.2, 136.1, 133.9, 129.4, (q, $^{1}J_{CF}$ = 305.6 Hz) 127.9, 42.2, 22.8. **^{19}F NMR ($CDCl_3$);** δ:

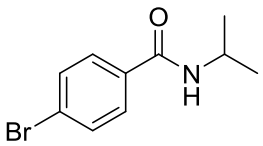
−42.2. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{12}NOS+H]^+$: 264.0670; found: 264.0680. R_f = 0.56 (EtOAc/Hexane 40/60).

4-Iodo-*N*-isopropylbenzamide (9)



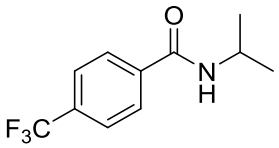
This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-iodobenzoyl chloride (2.00 g, 7.51 mmol) to yield a white amorphous solid (1.90 g, 88%). **^{1}H NMR ($CDCl_3$);** δ: 7.78 (d, 2H, $^3J_{HH}$ = 8.5), 7.48 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 5.90 (br s, 1H), 4.32-4.23 (m, 1H), 1.27 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 165.9, 137.7, 134.4, 128.5, 98.1, 42.1, 22.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{12}INO+H]^+$: 290.0042; found: 290.0042. R_f = 0.50 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[154]

4-Bromo-*N*-isopropylbenzamide (10)



This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-bromobenzoyl chloride (1.00 g, 4.55 mmol) to yield a white amorphous solid (0.83 g, 77%). **^{1}H NMR ($CDCl_3$)**; δ: 7.66 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.59 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 5.91 (br s, 1H), 4.35-4.27 (m, 1H), 1.30 (d, 6H, $^3J_{HH}$ = 6.5 Hz) **^{13}C NMR ($CDCl_3$)**; δ: 165.73, 133.80, 131.75, 128.48, 125.92, 42.10, 22.85. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{12}BrNO+H]^+$: 242.0181; found: 242.0192. R_f = 0.46 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[158]

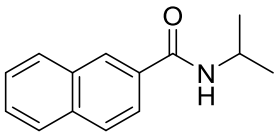
***N*-Isopropyl-4-(trifluoromethyl)benzamide (11)**



This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-(trifluoromethyl)benzoyl chloride (2.00 g, 9.59 mmol) to yield a white amorphous solid (1.85 g, 84%). **^{1}H NMR ($CDCl_3$);** δ: 7.86 (d, 2H, $^3J_{HH}$ = 8.1 Hz), 7.68 (d, 2H, $^3J_{HH}$ = 8.1 Hz), 6.01 (br s, 1H), 4.34-4.25 (m, 1H), 1.28 (d,

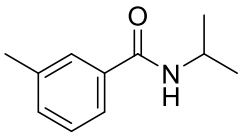
6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 165.4, 138.2, 133.0 (q, $^{2}J_{CF}$ = 32.3 Hz), 127.3, 125.6 (q, $^{3}J_{CF}$ = 3.7 Hz), 123.7 (q, $^{1}J_{CF}$ = 273.1 Hz), 42.25, 22.79. **^{19}F NMR ($CDCl_3$);** δ: −60.9. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{12}F_3NO+H]^+$: 232.0949; found: 232.0956. R_f = 0.50 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[159]

***N*-Isopropyl-2-naphthamide (12)**



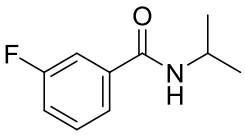
This compound was prepared in accordance to the general synthesis described for benzamides starting from 2-naphthoyl chloride (2.00 g, 10.5 mmol) to yield a light green amorphous solid (1.97 g, 88%). **^{1}H NMR ($CDCl_3$);** δ: 8.28 (s, 1H), 7.93-7.82 (m, 4H), 7.59-7.52 (m, 2H), 6.14 (br s, 1H), 4.41-4.33 (m, 1H), 1.33 (d, 6H, $^{3}J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 166.6, 134.5, 132.0, 128.7, 128.3, 127.6, 127.4, 127.0, 126.6, 123.5, 41.9, 22.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{15}NO+H]^+$: 214.1232; found: 214.1241. R_f = 0.43 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[154]

***N*-Isopropyl-3-methylbenzamide (13)**



This compound was prepared in accordance to the general synthesis described for benzamides starting from 3-methylbenzoyl chloride (1.00 g, 6.46 mmol) to yield a white amorphous solid (0.93 g, 81%). **^{1}H NMR ($CDCl_3$);** δ: 7.59 (s, 1H), 7.54-7.52 (m, 1H), 7.33-7.30 (m, 2H), 5.94 (br s, 1H), 4.34-4.25 (m, 1H), 2.40 (s, 3H), 1.27 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 167.1, 138.5, 135.2, 131.2, 128.6, 127.8, 123.9, 42.0, 23.1, 21.5. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NO+H]^+$: 178.1232; found: 178.1240. R_f = 0.46 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[160]

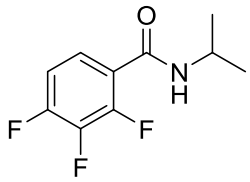
3-Fluoro-*N*-isopropylbenzamide (14)



This compound was prepared in accordance to the general synthesis described for benzamides starting from

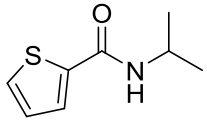
3-fluorobenzoyl chloride (2.00 g, 12.51 mmol) to yield a white amorphous solid (1.85 g, 81%). **^{1}H NMR ($CDCl_3$);** δ: 7.52-7.46 (m, 2H), 7.42-7.36 (m, 1H), 7.18 (ddd, 1H, $^{3}J_{HH}$ = 8.3 Hz, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HF}$ = 2.7 Hz), 6.03 (br s, 1H), 4.32-4.24 (m, 1H), 1.27 (d, 6H, $^{3}J_{HH}$ = 6.4 Hz). **^{13}C NMR ($CDCl_3$);** δ: 165.4(d, $^{4}J_{CF}$ = 2.1 Hz), 162.7 (d, $^{1}J_{CF}$ = 247.9 Hz), 137.3 (d, $^{3}J_{CF}$ = 6.7 Hz), 130.2 (d, $^{3}J_{CF}$ = 7.3 Hz), 122.3 (d, $^{4}J_{CF}$ = 2.9 Hz), 118.3 (d, $^{2}J_{CF}$ = 21.3 Hz), 114.3 (d, $^{2}J_{CF}$ = 22.3 Hz), 42.1, 22.8. **^{19}F NMR ($CDCl_3$);** δ: –120.0. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{12}FNO+H]^+$: 182.0981 found: 182.0988. R_f = 0.43 (EtOAc/Hexane 40/60).

2,3,4-Trifluoro-*N*-Isopropylbenzamide (15)



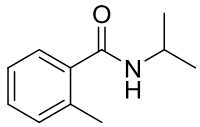
This compound was prepared in accordance to the general synthesis described for benzamides starting from 2,3,4-trifluorobenzoyl chloride (1.00 g, 5.14 mmol) to yield a white amorphous solid (0.78 g, 70%). **^{1}H NMR ($CDCl_3$);** δ: 7.83-7.77 (m, 1H), 7.08-7.02 (m, 1H), 6.38 (br s, 1H), 4.31-4.24 (m, 1H), 1.25 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{19}F {^{1}H}** δ:168.4, 134.6, 131.4, 128.5, 126.9, 26.9. **HR-MS (ASAP, m/z)** calcd. from $[C_8H_9NO+H]^+$: 136.0762; found: 136.0767. R_f = 0.26 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[161]

***N*-Isopropylthiophene-2-carboxamide (16)**



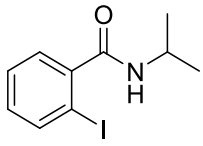
This compound was prepared in accordance to the general synthesis described for benzamides starting from thiophene-2-carbonyl chloride (1.00 g, 6.82 mmol) to yield a white amorphous solid (0.90 g, 78%). **^{1}H NMR ($CDCl_3$);** δ: 7.49 (dd, 1H, $^{3}J_{HH}$ = 3.7, $^{4}J_{HH}$ = 0.9), 7.46 (dd, 1H, $^{3}J_{HH}$ = 5.0, $^{4}J_{HH}$ = 1.0), 7.07 (dd, 1H, $^{3}J_{HH}$ = 5.1, $^{3}J_{HH}$ = 3.7) 5.83 (br s, 1H), 4.31-4.22 (m, 1H), 1.27 (d, 6H, $^{3}J_{HH}$ = 6.5). **^{13}C NMR ($CDCl_3$);** δ: 161.0, 139.4, 129.6, 127.7, 127.5, 42.0, 22.9. **HR-MS (ASAP, m/z)** calcd. from $[C_8H_{11}NOS+H]^+$: 170.0640; found: 170.0647. R_f = 0.67 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[10]

_N_-Isopropyl-2-methylbenzamide (17)



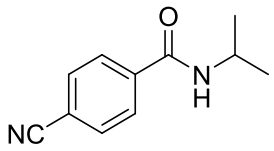
This compound was prepared in accordance to the general synthesis described for benzamides starting from 2-methylbenzoyl chloride (2.00 g, 12.94 mmol) to yield a light yellow amorphous solid (1.98 g, 87%). **^{1}H NMR ($CDCl_3$);** δ: 7.34-7.29 (m, 2H), 7.23-7.18 (m, 2H), 5.69 (br s, 1H), 4.32-4.24 (m, 1H), 2.45 (s, 3H), 1.27 (d, 6H, $^{3}J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.4, 137.0, 135.7, 130.9, 129.6, 126.6, 125.7, 41.7, 22.8, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NO+H]^+$: 178.1232; found: 178.1240. R_f = 0.64 (EtOAc/Hexane 40/60).

2-Iodo-_N_-Isopropylbenzamide (18)



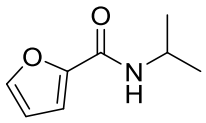
This compound was prepared in accordance to the general synthesis described for benzamides starting from 2-iodobenzoyl chloride (2.0 g, 7.51 mmol) to yield a white amorphous solid (1.97 g, 91%). **^{1}H NMR ($CDCl_3$);** δ: 7.84 (d, 2H, $^{3}J_{HH}$ = 7.7), 7.39-7.34 (m, 2H), 7.08 (ddd, 1H, $^{3}J_{HH}$ = 8.0 Hz, $^{3}J_{HH}$ = 6.1 Hz, $^{4}J_{HH}$ = 3.0 Hz), 5.63 (br s, 1H), 4.34-4.25 (m, 1H), 1.29 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 168.6, 142.6, 139.8, 130.95, 128.2, 128.2, 92.4, 42.2, 22.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{12}INO+H]^+$: 290.0042; found; 290.0050. R_f = 0.58 (EtOAc/Hexane 40/60).

4-Cyano-_N_-isopropyl benzamide (19)



This compound was prepared in accordance to the general synthesis described for benzamides starting from 4-cyanobenzoyl chloride (1.00 g, 6.04 mmol) to yield a white amorphous solid (1.0 g, 89%). **^{1}H NMR ($CDCl_3$);** δ: 7.85 (d, 2H, $^{3}J_{HH}$ = 8.5 Hz), 7.72 (d, 2H, $^{3}J_{HH}$ = 8.7 Hz), 6.01 (br s, 1H), 4.35-4.24 (m, 1H), 1.28 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 164.9, 138.9, 132.4, 127.6, 118.1, 114.9, 42.4, 22.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{12}N_2O+H]^+$: 189.1028; found: 189.1034. R_f = 0.47 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[11]

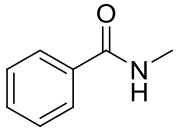
***N*-Isopropylfuran-2-carboxamide (20)**



This compound was prepared in accordance to the general synthesis described for benzamides starting from furan-2-carbonyl chloride (1.00g, 7.66 mmol) to yield a white amorphous solid (0.93 g, 80%). **^{1}H NMR ($CDCl_3$);** δ: 7.42 (dd, 1H, $^{3}J_{HH}$ = 1.8 Hz, $^{4}J_{HH}$ = 0.8 Hz), 7.09 (dd, 1H, $^{3}J_{HH}$ = 3.6 Hz, $^{4}J_{HH}$ = 0.8 Hz), 6.48 (dd, 1H, $^{3}J_{HH}$ = 3.6 Hz, $^{4}J_{HH}$ = 1.7 Hz) 6.20 (br s, 1H), 4.30-4.21 (m, 1H), 1.25 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 157.6, 148.3, 143.6, 113.9, 112.1, 41.2, 22.9. **HR-MS (ASAP, m/z)** calcd. from $[C_8H_{11}NO_2+H]^+$: 154.0868; found: 154.0871.

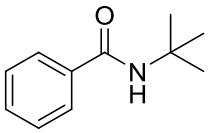
Rf = 0.44 (EtOAc/Hexane 40/60).

***N*-Methylbenzamide (21)**



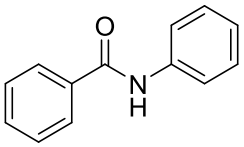
This compound was prepared in accordance to the general synthesis described for benzamides starting from benzoyl chloride (1.00 g, 7.11 mmol) to yield a white amorphous solid (0.75 g, 78%). **^{1}H NMR ($CDCl_3$);** δ: 7.79-7.76 (m, 2H), 7.50-7.45 (m, 1H), 7.42-7.38 (m, 2H), 6.58 (br s, 1H), 2.99 (d, 3H, $^{3}J_{HH}$ = 4.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 168.4, 134.6, 131.4, 128.5, 126.9, 26.9. **HR-MS (ASAP, m/z)** calcd. from $[C_8H_9NO+H]^+$: 136.0762; found: 136.0767. R_f = 0.26 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[12]

***N*-(*tert*-Butyl)benzamide (22)**



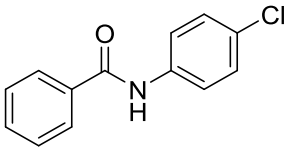
This compound was prepared in accordance to the general synthesis described for benzamides starting from benzoyl chloride (1.00 g, 7.11 mmol) to yield a white amorphous solid (0.97 g, 77%). **^{1}H NMR ($CDCl_3$);** δ: 7.72-7.70 (m, 2H), 7.47-7.43 (m, 1H), 7.42-7.37 (m, 2H), 5.98 (br s, 1H), 1.46 (s, 9H). **^{13}C NMR ($CDCl_3$);** δ: 167.0, 135.9, 131.1, 128.5, 126.7, 51.6, 28.9. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NO+H]^+$: 177.1154; found: 177.1158. R_f = 0.85 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[154]

***N*-Phenylbenzamide (23)**



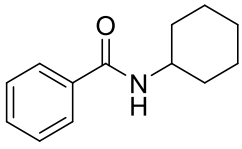
This compound was prepared in accordance to the general synthesis described for benzamides starting from benzoyl chloride (1.00 g, 7.11 mmol) to yield a white amorphous solid (1.26 g, 90%). **^{1}H NMR ($CDCl_3$);** δ: 7.90-7.87 (m, 2H), 7.86 (br s, 1H), 7.66 (d, 2H, $^{3}J_{HH}$ = 7.7 Hz), 7.59-7.55 (m, 1H), 7.52-7.48 (m, 2H), 7.41-7.37 (m, 2H), 7.19-7.15 (m, 1H) **^{13}C NMR ($CDCl_3$);** δ: 165.8, 137.9, 135.0, 131.9, 129.1, 128.8, 127.0, 124.6, 120.2. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{11}NO+H]^{+}$: 198.0919 found: 198.0918. Rf = 0.85 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[154]

***N*-(4-Chlorophenyl)benzamide (24)**



This compound was prepared in accordance to the general synthesis described for benzamides starting from benzoyl chloride (1.00 g, 7.11 mmol) to yield a white amorphous solid (1.31 g, 80%). **^{1}H NMR ($CDCl_3$);** δ: 7.89-7.87 (m, 2H), 7.82 (br s, 1H), 7.63 (d, 2H, $^{3}J_{HH}$ = 8.8 Hz), 7.58-7.57 (m, 1H), 7.53-7.50 (m, 2H), 7.36 (d, 2H, $^{3}J_{HH}$ = 8.8 Hz). **^{13}C NMR ($CDCl_3$);** δ: 165.7, 136.5, 134.7, 132.1, 129.6, 129.2, 128.9, 127.0, 121.4. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{10}ClNO+H]^{+}$: 232.0529 found: 232.0528. R_f = 0.82 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[161]

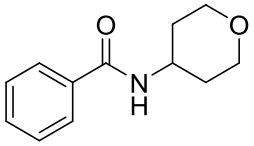
***N*-Cyclohexylbenzamide (25)**



This compound was prepared in accordance to the general synthesis described for benzamides starting from benzoyl chloride (1.00 g, 7.11 mmol) to yield a white amorphous solid (1.21 g, 84%). **^{1}H NMR ($CDCl_3$);** δ: 7.76 (dd, 2H, $^{3}J_{HH}$ =7.0 Hz, $^{4}J_{HH}$ =1.5 Hz), 7.51-7.47 (m, 1H), 7.43 (ddd, 2H, $^{3}J_{HH}$ =7.5 Hz, $^{3}J_{HH}$ =7.0 Hz, $^{4}J_{HH}$ =1.5 Hz), 6.02 (br s, 1H), 4.04-3.94 (m, 1H), 2.06-2.02 (m, 2H), 1.82-1.73 (m, 2H), 1.69-1.64 (m, 1H), 1.49-1.38 (m, 2H), 1.29-1.20 (m, 3H) **^{13}C NMR**

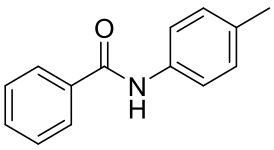
($CDCl_3$); δ:166.7, 135.1, 131.3, 128.5, 126.9, 48.7, 33.3, 25.6, 24.9. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{17}NO+H]^+$: 204.1388 found: 204.1388. R_f = 0.61 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[154]

***N*-(Tetrahydro-2H-pyran-4-yl)benzamide (26)**



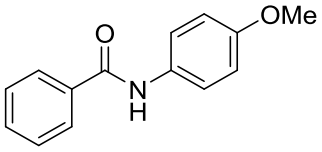
This compound was prepared in accordance to the general synthesis described for benzamides starting from benzoyl chloride (1.00 g, 7.11 mmol) to yield a white amorphous solid (0.99 g, 68%). **^{1}H NMR ($CDCl_3$);** δ: 7.78-7.76 (m, 2H), 7.53-7.49 (m, 1H), 7.47-7.42 (m, 2H), 6.03 (br s, 1H), 4.27-4.18 (m, 1H), 4.04-3.99 (m, 2H), 3.58-3.51 (td, 2H, $^3J_{HH}$ = 11.8 Hz, $^4J_{HH}$ = 2.2 Hz), 2.05-2.00 (m, 2H), 1.63-1.53 (m, 2H). **^{13}C NMR ($CDCl_3$);** δ: 166.9, 134.6, 131.6, 128.6, 126.9, 66.9, 46.2, 33.3. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{15}NO_2+H]^+$: 206.1181 found: 206.1176. R_f = 0.18 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[162]

***N*-(*p*-Tolyl)benzamide (27)**



This compound was prepared in accordance to the general synthesis described for benzamides starting from benzoyl chloride (1.0 g, 7.11 mmol) to yield a light yellow amorphous solid (1.02 g, 68%). **^{1}H NMR ($CDCl_3$);** δ: 7.92-7.89 (m, 2H), 7.80 (br s, 1H), 7.61-7.54 (m, 4H), 7.53-7.50 (m, 1H), 7.22 (d, 2H, $^3J_{HH}$ = 8.2 Hz), 2.38 (s, 3H). **^{13}C {^{1}H} NMR ($CDCl_3$);** δ: 165.6, 135.4, 135.1, 134.3, 131.8, 129.6, 128.8, 127.0, 120.3, 20.9. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{13}NO+H]^+$: 212.1075 found: 212.1069. R_f = 0.88 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[161]

***N*-(4-Methoxyphenyl)benzamide (28)**

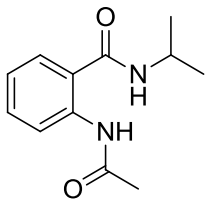


This compound was prepared in accordance to the general synthesis described for benzamides starting

from benzoyl chloride (1.00 g, 7.11 mmol) to yield a light purple amorphous solid (1.35 g, 84%). **^{1}H NMR ($CDCl_3$,);** δ: 7.88 (d, 2H, $^{3}J_{HH}$ = 8.5 Hz), 7.75 (br s, 1H), 7.58-7.55 (m, 3H) 7.51-7.48 (m, 2H), 6.93 (d, 2H, $^{3}J_{HH}$ = 8.8 Hz), 3.83 (s, 3H) **^{13}C NMR ($CDCl_3$);** δ: 156.7, 135.1, 131.8, 131.0, 128.8, 127.0, 122.1, 114.3, 114.3, 55.5. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{13}NO_2+H]^+$: 228.1025 found: 228.1024. R_f = 0.76 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[161]

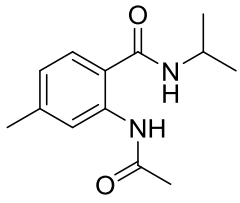
2.5.2 Characterisation of amidation products:

2-Acetamido-*N*-isopropylbenzamide (1a)



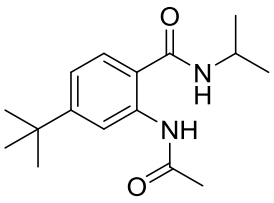
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **1** (1.50 mmol) to yield a light yellow amorphous solid (257 mg, 78%). **^{1}H NMR ($CDCl_3$);** δ: 11.04 (br s, 1H), 8.55 (d, 1H, ^{3}J =8.1 Hz), 7.47-7.42 (m, 2H), 7.07-7.03 (m, 1H), 6.19 (br s, 1H), 4.29-4.20 (m, 1H), 2.19 (s, 3H), 1.29 (d, 6H, $^{3}J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.1, 168.3, 139.5, 132.4, 126.4, 122.6, 121.5, 120.7, 42.1, 25.4, 22.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{13}NO_2+H]^+$: 221.1290 found: 221.1288. R_f = 0.62 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[163]

2-Acetamido-*N*-isopropyl-4-methylbenzamide (2a)



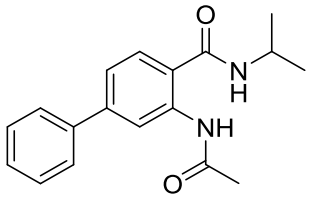
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **2** (1.50 mmol) to yield a white amorphous solid (270 mg, 77%). **^{1}H NMR ($CDCl_3$);** δ: 11.19 (br s, 1H), 8.40 (s, 1H,), 7.32 (d, 1H, $^{3}J_{HH}$ = 8.0 Hz), 6.83 (d, 1H, $^{3}J_{HH}$ = 8.0 Hz), 6.24 (br s, 1H), 4.26-4.18 (m, 1H), 2.35 (s, 3H), 2.17 (s, 3H), 1.27 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$,);** δ: 169.0, 168.4, 143.2, 139.6, 126.4, 123.4, 121.7, 117.6, 42.0, 25.4, 22.7, 21.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{18}N_2O_2+H]^+$: 235.1447; found: 235.1451. R_f = 0.60 (EtOAc/Hexane 40/60).

2-Acetamido-4-(*tert*-Butyl)-*N*-isopropylbenzamide (3a)



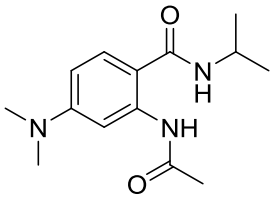
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **3** (1.50 mmol) to yield a light yellow amorphous solid (335 mg, 81%). **^{1}H NMR ($CDCl_3$);** δ: 11.22 (br s, 1H), 8.72 (s, 1H), 7.37 (d, 1H, $^3J_{HH}$ = 8.2 Hz), 7.06 (dd, 1H, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 2.0 Hz), 6.11 (br s, 1H), 4.28-4.20 (m, 1H), 2.20 (s, 3H), 1.32 (s, 9H), 1.27 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.1, 168.2, 156.4, 139.8, 126.0, 119.7, 118.6, 117.5, 41.9, 35.2, 31.0, 25.4, 22.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{16}H_{24}N_2O_2+H]^+$: 277.1916 found: 277.1910. R_f = 0.83 (EtOAc/Hexane 40/60).

3-Acetamido-*N*-isopropyl-[1,1'-biphenyl]-4-carboxamide (4a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **4** (1.50 mmol) to yield a white amorphous solid (320 mg, 72%). **^{1}H NMR ($CDCl_3$);** δ: 11.23 (br s, 1H), 8.92 (s, 1H), 7.67-7.64 (m, 2H), 7.50-7.43 (m, 3H), 7.41-7.37 (m, 1H), 7.30 (dd, 1H, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.8 Hz), 6.10 (br s, 1H), 4.31-4.22 (m, 1H), 2.24 (s, 3H), 1.31 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.2, 168.1, 145.3, 140.2, 139.8, 128.9, 128.2, 127.4, 126.8, 121.1, 120.0, 119.0, 42.0, 25.4, 22.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{18}H_{20}N_2O_2+H]^+$: 297.1603 found: 297.1600. R_f = 0.69 (EtOAc/Hexane 40/60).

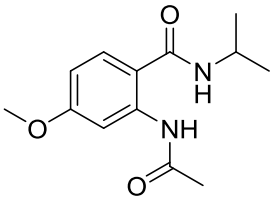
2-Acetamido-4-(dimethylamino)-*N*-isopropylbenzamide (5a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **5** (1.50 mmol) to yield a light yellow amorphous solid (355 mg, 90%). **^{1}H NMR ($CDCl_3$);** δ: 11.78 (br s, 1H), 8.09 (d, 1H, $^4J_{HH}$ = 2.5 Hz), 7.25 (d, 1H, $^3J_{HH}$ = 9.0 Hz), 6.28 (dd, 1H, $^3J_{HH}$ = 9.0 Hz, $^4J_{HH}$ = 2.6 Hz), 5.86 (br s, 1H), 4.23-4.15 (m, 1H), 3.00 (s, 6H), 2.18 (s,

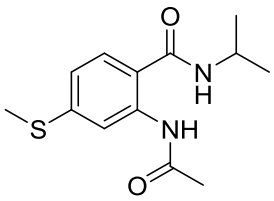
3H), 1.23 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.3, 168.6, 153.1, 141.9, 127.6, 106.8, 105.6, 103.2, 41.6, 40.1, 25.7, 22.9. **HR-MS (ASAP, m/z)** calcd. from $[C_{14.}H_{21}N_3O_2+H]^+$: 264.1712 found: 264.1711. R_f = 0.46 (EtOAc/Hexane 40/60).

2-Acetamido-*N*-isopropyl-4-methoxybenzamide (6a)



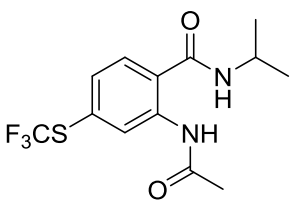
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **6** (1.50 mmol) to yield a light yellow amorphous solid (262 mg, 70%). **^{1}H NMR ($CDCl_3$);** δ: 11.58 (br s, 1H), 8.27 (d, 1H, $^4J_{HH}$ = 1.9 Hz), 7.36 (d, 1H, $^3J_{HH}$ = 8.7 Hz), 6.51 (dd, 1H, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.0 Hz), 6.20 (br s, 1H), 4.22-4.17 (m, 1H), 3.80 (s, 3H), 2.17 (s, 3H), 1.25 (d, 6H, $^3J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.3, 168.7, 142.0, 127.8, 112.2, 109.3, 105.2, 55.4, 41.9, 25.5, 22.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{18}N_2O_3+M]^+$: 250.1317 found: 250.1315. R_f = 0.58 (EtOAc/Hexane 40/60).

2-Acetamido-*N*-isopropyl-4-(methylthio)benzamide (7a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **7** (1.50 mmol) to yield a light yellow amorphous solid (355 mg, 89%). **^{1}H NMR ($CDCl_3$);** δ: 11.40 (br s, 1H), 8.60 (d, 1H, $^4J_{HH}$ = 1.9 Hz), 7.30 (d, 1H, $^3J_{HH}$ = 8.4 Hz), 6.90 (dd, 1H, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 2.0 Hz), 5.87 (br s, 1H), 4.28-4.20 (m, 1H), 2.52 (s, 3H), 2.22 (s, 3H), 1.29 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.2, 168.0, 145.2, 140.5, 126.3, 119.5, 116.5, 115.8, 42.0, 25.5, 22.8, 14.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{18}N_2O_2S+H]^+$: 267.1167 found: 267.1158. R_f = 0.62 (EtOAc/Hexane 40/60).

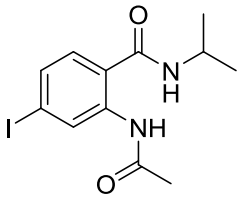
2-Acetamido-*N*-isopropyl-4-((trifluoromethyl)thio)benzamide (8a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from

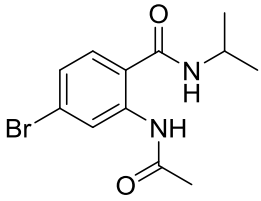
substrate **8** (1.50 mmol) to yield a white amorphous solid (389 mg, 81%). **^{1}H NMR ($CDCl_3$);** δ: 11.04 (br s, 1H), 8.92 (d, 1H, $^{4}J_{HH}$ = 1.6 Hz), 7.47 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz), 7.30 (dd, 1H, $^{3}J_{HH}$ = 8.1, $^{4}J_{HH}$ = 1.5 Hz), 6.28 (br s, 1H), 4.29-4.21 (m, 1H), 2.19 (s, 3H), 1.30 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.2, 167.3, 140.0, 129.4 (q, $^{1}J_{CF}$ = 308.2 Hz), 129.2, 129.2, 129.0, 127.2, 122.1, 42.4, 25.3, 22.6. **^{19}F NMR ($CDCl_3$);** δ: −41.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{15}F_3N_2O_2S+H]^+$: 321.0885 found: 321.0885. R_f = 0.81 (EtOAc/Hexane 40/60).

2-Acetamido-4-iodo-*N*-isopropylbenzamide (9a)



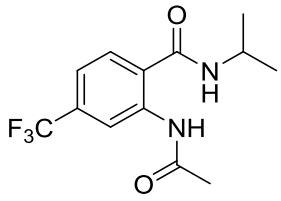
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **9** (1.50 mmol) to yield a white amorphous solid (467 mg, 90%). **^{1}H NMR ($CDCl_3$);** δ: 11.00 (br s, 1H), 8.92 (d, 6H, $^{4}J_{HH}$ = 1.6 Hz), 7.38 (dd, 1H, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 1.7 Hz), 7.11 (d, 1H, $^{3}J_{HH}$ = 8.2 Hz), 6.18 (br s, 1H), 4.28-4.19 (m, 1H), 2.18 (s, 3H), 1.29 (d, 6H, $^{3}J_{HH}$ = 6.5). **^{13}C NMR ($CDCl_3$);** δ: 169.1, 167.8, 140.2, 131.7, 130.0, 127.5, 119.6, 99.1, 42.2, 25.3, 22.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{15}IN_2O_2+H]^+$: 347.0256 found: 347.0259. R_f = 0.76 (EtOAc/Hexane 40/60).

2-Acetamido-4-bromo-N-isopropylbenzamide (10a)



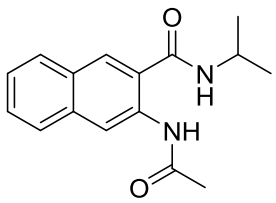
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **10** (1.50 mmol) to yield a white amorphous solid (201 mg, 45%). **^{1}H NMR ($CDCl_3$,);** δ: 11.15 (br s, 1H), 8.83 (d, 1H, $^{4}J_{HH}$ = 2.0 Hz), 7.26 (d, 1H, $^{3}J_{HH}$ = 8.4 Hz), 7.17 (dd, 1H, $^{3}J_{HH}$ = 8.4 Hz, $^{4}J_{HH}$ = 2.0 Hz), 6.07 (br s, 1H), 4.25-4.20 (m, 1H), 2.19 (s, 3H), 1.27 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C {^{1}H} NMR ($CDCl_3$);** δ: 169.1, 167.6, 140.6, 127.5, 126.9, 125.6, 124.1, 118.9, 42.3, 25.4, 22.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{15}BrN_2O_2+H]^+$: 299.0395 found: 299.0390. R_f = 0.76 (EtOAc/Hexane 40/60).

2-Acetamido-*N*-isopropyl-4-(trifluoromethyl)benzamide (11a)



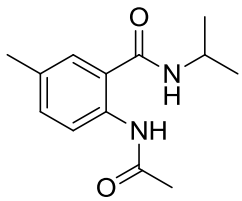
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **11** (1.50 mmol) to yield a white amorphous solid (302 mg, 70%). **^{1}H NMR ($CDCl_3$);** δ: 11.06 (br s, 1H), 8.88 (s, 1H), 7.53 (d, 1H, $^3J_{HH}$ = 8.2 Hz), 7.24 (d, 1H, $^3J_{HH}$ = 8.2 Hz), 6.41 (br s, 1H), 4.29-4.21 (m, 1H), 2.52 (s, 3H), 1.30 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.2, 167.2, 139.8, 133.8 (q, $^2J_{CF}$ = 32.6 Hz), 127.1, 123.4 (q, $^1J_{CF}$ = 272.5 Hz), 123.3, 119.0 (q, $^3J_{CF}$ = 3.5 Hz), 118.2 (q, $^3J_{CF}$ = 3.7 Hz), 42.4, 25.3, 22.5. **^{19}F NMR ($CDCl_3$);** δ: −66.2. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{15}IN_2O_2F_3+H]^+$: 289.1164 found: 289.1166. R_f = 0.79 (EtOAc/Hexane 40/60).

3-Acetamido-*N*-isopropyl-2-naphthamide (12a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **12** (1.50 mmol) to yield a white amorphous solid (336 mg, 83%). **^{1}H NMR ($CDCl_3$);** δ: 10.79 (br s, 1H), 8.96 (s, 1H), 7.93 (s, 1H), 7.81 (d, 1H, $^3J_{HH}$ = 8.1 Hz), 7.76 (d, 1H, $^3J_{HH}$ = 8.0 Hz), 7.52 (t, 1H, $^3J_{HH}$ = 7.4 Hz), 7.42 (t, 1H, $^3J_{HH}$ = 7.5 Hz), 6.37 (br s, 1H), 4.32-4.28 (m, 1H), 2.21 (d, 3H, $^3J_{HH}$ = 3.8 Hz), 1.36 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.0, 168.5, 135.2, 134.9, 128.6, 128.3, 127.9, 127.8, 127.3, 125.6, 122.3, 118.3, 42.3, 25.4, 22.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{16}H_{18}N_2O_2+H]^+$: 271.1447 found: 271.1450. R_f = 0.58 (EtOAc/Hexane 40/60).

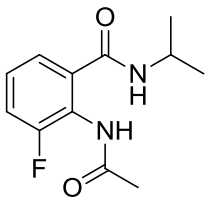
2-Acetamido-*N*-isopropyl-5-methylbenzamide (13a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **13** (1.50 mmol) to yield a white amorphous solid (217 mg, 62%). **^{1}H NMR ($CDCl_3$);** δ: 10.91 (br s, 1H), 8.44 (d, 1H, $^3J_{HH}$ = 8.2 Hz), 7.26 (d, 1H, $^3J_{HH}$ = 8.3 Hz), 7.20 (s, 1H), 6.05 (br

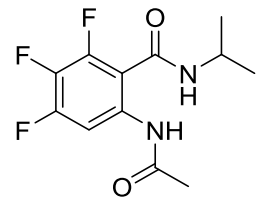
s, 1H), 4.29-4.22 (m, 1H), 2.34 (s, 3H), 2.19 (s, 3H), 1.30 (d, 6H, $^3J_{HH}$ = 6.6). **^{13}C NMR ($CDCl_3$);** δ: 169.0, 168.4, 143.2, 139.6, 126.4, 123.4, 121.7, 117.6, 41.9, 25.4, 22.7, 21.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{18}N_2O_2+H]^+$: 235.1447 found: 235.1438. R_f = 0.53 (EtOAc/Hexane 40/60).

2-Acetamido-3-fluoro-*N*-isopropylbenzamide (14a)



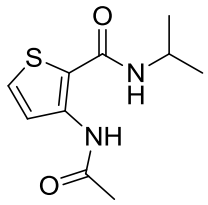
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **14** (1.50 mmol) to yield a white amorphous solid (268 mg, 75%). **^{1}H NMR ($CDCl_3$);** δ: 8.70 (br s, 1H), 7.22-7.19 (m, 3H), 6.20 (br s, 1H), 4.24-4.15 (m, 1H), 2.20 (s, 3H), 1.25 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 169.3, 166.7, 157.2 (d, $^1J_{CF}$ =252.1), 132.5, 127.0 (d, $^3J_{CF}$ =8.3 Hz), 124.0 (d, $^2J_{CF}$ =14.5 Hz), 122.4 (d, $^3J_{CF}$ =3.4 Hz), 118.7 (d, $^2J_{CF}$ =21.2 Hz), 42.2, 23.5, 22.5. **^{19}F NMR ($CDCl_3$);** δ: −14.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{15}FN_2O_2+H]^+$: 239.1196 found: 239.1190. R_f = 0.16 (EtOAc/Hexane 40/60).

6-Acetamido-2,3,4-trifluoro-*N*-isopropylbenzamide (15a)



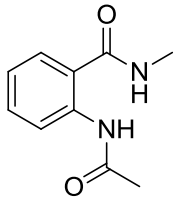
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **15** (1.50 mmol) to yield a white amorphous solid (238 mg, 58%). **^{1}H NMR ($CDCl_3$);** δ: 11.41 (br s, 1H), 8.48 (dd, 1H, $^3J_{HF}$= 13.1 Hz, $^4J_{HF}$ = 7.2 Hz), 6.52 (br s, 1H), 4.31-4.27 (m, 1H), 2.21 (s, 3H), 1.31 (d, 6H, $^3J_{HH}$ = 6.3 Hz). **^{19}F NMR ($CDCl_3$):** δ: −126.9 (dd, $^3J_{FF}$ = 22.8, $^4J_{FF}$ = 12.2), −134.6 (dd, $^3J_{FF}$ = 23.3, $^4J_{FF}$ = 11.3), −166.1 (dd, $^3J_{FF}$ = 22.0 $^3J_{FF}$ = 22.0). **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{13}F_3N_2O_2+H]^+$: 275.1007; found: 275.1010. R_f = 0.78 (EtOAc/Hexane 40/60).

3-Acetamido-*N*-isopropylthiophene-2-carboxamide (16a)



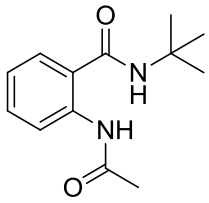
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **16** (1.50 mmol) to yield a white amorphous solid (145 mg, 43%). **^{1}H NMR ($CDCl_3$);** δ: 11.00 (br s, 1H), 8.16 (d, 1H, $^3J_{HH}$ = 5.3 Hz), 7.29 (d, 1H, $^3J_{HH}$ = 5.2 Hz), 5.53 (br s, 1H), 4.25-4.20 (m, 1H), 2.21 (s, 3H), 1.27 (d, 6H, $^3J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 167.9, 163.6, 143.5, 126.5, 123.4, 112.3, 41.9, 24.6, 22.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{14}N_2O_2S+H]^+$: 227.0854 found: 227.0854. R_f = 0.72 (EtOAc/Hexane 40/60).

2-Acetamido-*N*-methylbenzamide (21a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **21** (1.50 mmol) to yield a light yellow amorphous solid (222 mg, 77%). **^{1}H NMR ($CDCl_3$);** δ: 11.07 (br s, 1H), 8.61 (d, 1H, $^3J_{HH}$ = 7.6- Hz), 7.52-7.45 (m, 2H), 7.10 (ddd, 1H, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.1 Hz), 6.32 (br s, 1H), 3.04 (s, 3H), 2.24 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.7; 169.1, 139.4, 132.5, 126.4, 122.7, 121.6, 120.4, 26.8, 25.3. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{12}N_2O_2+H]^+$: 193.0977 found: 193.0987. R_f = 0.62 (EtOAc/Hexane 40/60).

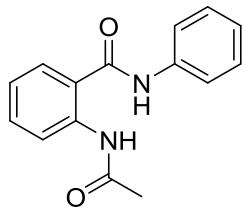
2-Acetamido-*N*-(*tert*-butyl)benzamide (22a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **22** (1.50 mmol) to yield a white amorphous solid (274 mg, 78%). **^{1}H NMR ($CDCl_3$);** δ: 10.92 (br s, 1H), 8.54 (d, 1H, $^3J_{HH}$ = 8.3 Hz), 7.46-7.42 (m, 1H), 7.39 (dd, 1H, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.4 Hz), 7.05 (ddd, $^3J_{HH}$ = 7.6 Hz, $^3J_{HH}$ = 7.8 Hz, $^4J_{HH}$ = 1.0 Hz), 6.06 (br s, 1H), 2.20 (s, 3H), 1.49 (s, 9H). **^{13}C NMR ($CDCl_3$);** δ: 169.0, 168.8, 139.3, 132.2, 126.4, 122.6, 121.9, 121.6, 52.1, 28.8, 25.3. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{18}N_2O_2+H]^+$: 235.1447

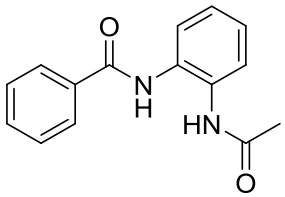
found: 235.1451. R_f = 0.75 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[163]

2-Acetamido-*N*-phenylbenzamide (23a-1)



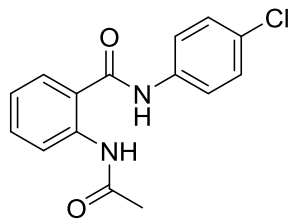
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **23** (1.50 mmol) to yield a white amorphous solid (76.0 mg, 20%). **^{1}H NMR ($CDCl_3$);** δ: 10.61 (br s, 1H), 8.46 (br s, 1H), 8.43 (dd, 1H, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ =0.8 Hz), 7.66 (dd, 2H, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ =1.0 Hz), 7.55 (dd, 1H, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ =1.5 Hz), 7.45-7.38 (m, 3H), 7.24-7.20 (m, 1H), 7.09 (td, 1H, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ =1.1 Hz), 2.18 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.5, 167.4, 138.7, 137.7, 132.3, 129.3, 127.3, 125.0, 122.8, 121.9, 121.7, 120.6, 25.30 . **HR-MS (ASAP, m/z)** calcd. from $[C_{15}H_{14}N_2O_2+H]^+$: 225.1134 found: 225.1133. R_f = 0.75 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[164]

***N*-(2-Acetamidophenyl)benzamide (23a-2)**



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **23** (1.50 mmol) to yield a white amorphous solid (76.0 mg, 20%). **^{1}H NMR (DMSO-d_6);** δ: 9.86 (br s, 1H), 9.75 (br s, 1H), 7.96 (d, 1H, $^3J_{HH}$ = 8.1 Hz), 7.67-7.50 (m, 5H), 7.22-7.20 (m, 2H), 2.09 (s, 3H). **^{13}C NMR (DMSO-d_6,);** δ: 169.2, 164.9, 134.4, 131.7, 131.2, 130.4, 128.5, 127.5, 125.9, 125.3, 124.9, 124.5, 23.5. **HR-MS (ASAP, m/z)** calcd. from $[C_{15}H_{14}N_2O_2+H]^+$: 225.1134 found: 225.1127. R_f = 0.16 (EtOAc/Hexane 40/60).

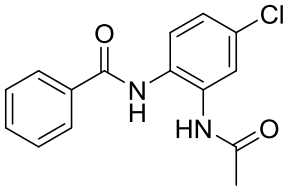
2-Acetamido-*N*-(4-chlorophenyl)benzamide (24a-1)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **24** (1.50 mmol) to yield a white amorphous solid (129 mg, 30%). **^{1}H NMR (DMSO-d_6);** δ: 10.52 (br s, 1H),

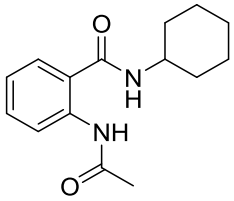
10.29 (br s, 1H), 8.05 (d, 1H, $^3J_{HH}$ = 8.2), 7.76 (d, 2H, $^3J_{HH}$ = 8.9 Hz), 7.72 (dd, 1H, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.3 Hz), 7.51 (ddd, 1H, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.4 Hz), 7.42 (d, 2H, $^3J_{HH}$ = 8.9 Hz), 7.22 (ddd, 1H, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.1 Hz), 2.04 (s, 3H). **^{13}C NMR (DMSO-d$_6$);** δ: 168.2, 166.8, 137.9, 137.5, 131.5, 128.6, 128.5, 127.7, 127.4, 124.9, 123.2, 122.0, 24.2. **HR-MS (ASAP, m/z)** calcd. from $[C_{15}H_{13}ClN_2O_2+H]^+$: 289.0744 found: 289.0737. R_f = 0.86 (EtOAc/Hexane 40/60).

***N*-(2-Acetamido-4-chlorophenyl)benzamide (24a-2)**



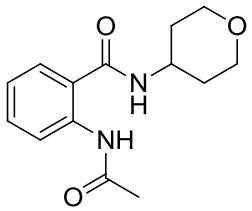
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **24** (1.50 mmol) to yield a white amorphous solid (86.0 mg, 20%). **^{1}H NMR (DMSO-d$_6$,);** δ: 9.79 (br s, 2H), 7.98 (d, 2H, $^3J_{HH}$ = 8.5 Hz), 7.74 (d, 1H, $^4J_{HH}$ = 2.4 Hz), 7.63-7.59 (m, 2H), 7.56-7.52 (m, 2H), 7.25 (dd, 1H, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 2.4 Hz), 3.35 (s, 3H). **^{13}C {^{1}H} NMR (DMSO-d$_6$);** δ: 169.2, 165.4, 134.2, 133.1, 131.8, 128.9, 128.7, 128.4, 127.7, 124.2, 123.5, 23.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{15}H_{13}ClN_2O_2+H]^+$: 289.0744 found: 289.0740. R_f = 0.36 (EtOAc/Hexane 40/60).

2-Acetamido-*N*-cyclohexylbenzamide (25a)



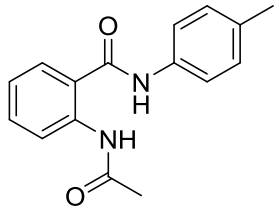
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **25** (1.50 mmol) to yield a white amorphous solid (304 mg, 78%). **^{1}H NMR (CDCl$_3$);** δ: 11.03 (br s, 1H), 8.55 (d, 1H, $^3J_{HH}$ = 8.3 Hz), 7.46-7.41 (m, 2H), 7.04-7.00 (m, 1H), 6.23 (br s, 1H), 3.96-3.89 (m, 1H), 2.18 (s, 3H), 2.05-2.02 (m, 2H), 1.81-1.77 (m, 2H), 1.69-1.66 (m, 1H), 1.49-1.40 (m, 2H), 1.33-1.21 (m, 3H). **^{13}C NMR (CDCl$_3$);** δ: 169.1, 168.2, 139.5, 126.4, 122.4, 122.6, 121.5, 120.7, 48.9, 33.0, 25.5, 25.4, 24.9. **HR-MS (ASAP, m/z)** calcd. from $[C_{15}H_{20}N_2O_2+H]^+$: 261.1603 found: 261.1597. R_f = 0.75 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[163]

2-Acetamido-*N*-(tetrahydro-2H-pyran-4-yl)benzamide (26a)



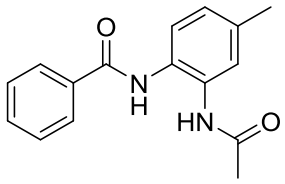
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **26** (1.50 mmol) to yield a white amorphous solid (243 mg, 62%). **^{1}H NMR ($CDCl_3$);** δ: 10.96 (br s, 1H), 8.55 (d, 1H, $^3J_{HH}$ = 8.0 Hz), 7.48-7.43 (m, 2H), 7.09-7.05 (m, 1H), 6.29 (br s, 1H), 4.17-4.15 (m, 1H), 4.04-4.01 (m, 2H), 3.55 (t, 2H, $^3J_{HH}$ = 11.3 Hz) 2.19 (s, 3H) 2.03-2.00 (m, 2H), 1.64-1.60 (m, 2H). **^{13}C NMR ($CDCl_3$);** δ:169.1, 168.4, 139.5, 132.7, 126.5, 122.7, 121.6, 120.3, 60.8, 46.4, 33.0. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{18}N_2O_3+H]^+$: 263.1396 found: 263.1398. R_f = 0.47 (EtOAc/Hexane 40/60).

2-Acetamido-*N*-(p-tolyl)benzamide (27a-1)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **27** (1.50 mmol) to yield a white amorphous solid (76.0 mg, 19%). **^{1}H NMR ($CDCl_3$);** δ: 10.63 (br s, 1H), 8.54 (br s, 1H), 8.39 (dd, 1H, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ =0.7 Hz), 7.56-7.51 (m, 3H), 7.36 (ddd, 1H, $^3J_{HH}$ = 7.9 Hz, $^3J_{HH}$ =8.0 Hz, $^4J_{HH}$ =1.5 Hz), 7.23 (d, 2H, $^3J_{HH}$ = 8.2 Hz), 7.05 (ddd, 1H, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 7.6 Hz, $^4J_{HH}$ = 1.1 Hz), 2.38 (s, 3H), 2.16 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.4, 167.3, 138.8, 135.0, 134.8, 132.3, 129.7, 127.1, 122.8, 121.8, 121.6, 120.8, 25.3, 21.0**. HR-MS (ASAP, m/z)** calcd. from $[C_{16}H_{16}N_2O_2+H]^+$: 269.1290 found: 269.1294. R_f = 0.75 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[165]

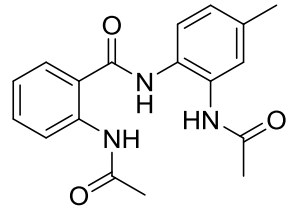
***N*-(2-Acetamido-4-methylphenyl)benzamide (27a-2)**



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **27** (1.50 mmol) to yield a white amorphous solid (84.0 mg, 21%). **^{1}H NMR (DMSO-d_6);** δ: 9.77 (br s, 2H), 7.94 (d, 2H, $^3J_{HH}$ = 7.0 Hz), 7.62-7.58 (m, 1H), 7.55-7.51 (m, 3H), 7.32 (d, 1H, $^4J_{HH}$ =1.1 Hz), 7.02 (dd, 1H, $^3J_{HH}$ = 8.2 Hz, $^4J_{HH}$ = 1.3 Hz), 2.30 (s, 3H), 2.07 (s, 3H). **^{13}C NMR**

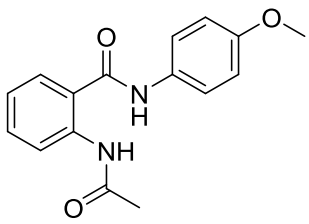
(DMSO-d_6); δ: 169.1, 164.9, 134.5, 134.4, 131.6, 131.1, 128.5, 127.8, 127.4, 125.8, 125.5, 124.7, 23.5, 20.6**. HR-MS (ASAP, m/z)** calcd. from $[C_{16}H_{16}N_2O_2+H]^+$: 269.1290 found: 269.1292. R_f = 0.36 (EtOAc/Hexane 40/60).

2-Acetamido-*N*-(2-acetamido-4-methylphenyl)benzamide (27a-3)



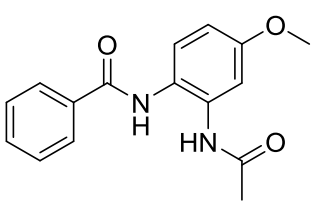
This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **27** (1.50 mmol) to yield a white amorphous solid (87.0 mg, 18%). **^{1}H NMR (DMSO-d_6,);** δ: 10.40 (br s, 1H), 9.88 (br s, 1H), 9.55 (br s, 1H), 8.09 (d, 1H, $^3J_{HH}$ = 8.1 Hz), 7.85 (d, 1H, $^3J_{HH}$ = 7.4 Hz), 7.60-7.56 (m, 2H), 7.47 (d, 1H, $^3J_{HH}$ =8.1 Hz), 7.29 (t, 1H, $^3J_{HH}$ =7.5 Hz), 7.06 (d, 1H, $^3J_{HH}$ = 7.8 Hz), 2.36 (s, 3H), 2.14 (s, 3H), 2.11 (s, 3H). **^{13}C NMR (DMSO-d_6);** δ: 168.9, 168.5, 167.0, 137.7, 135.1, 132.3, 131.6, 128.46, 126.6, 126.5, 125.01, 124.04, 123.32, 121.7, 121.7, 24.3, 23.6, 20.7**. HR-MS (ASAP, m/z)** calcd. from $[C_{18}H_{19}N_3O_3+H]^+$: 326.1505 found: 326.1503. R_f = 0.19 (EtOAc/Hexane 40/60).

2-Acetamido-*N*-(4-methoxyphenyl)benzamide (28a-1)



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **28** (1.50 mmol) to yield a white amorphous solid (85.0 mg, 20%). **^{1}H NMR ($CDCl_3$);** δ: 10.70 (br s, 1H), 8.45 (dd, 1H, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ =0.7 Hz), 8.31 (br s, 1H), 7.56-7.54 (m, 3H), 7.41 (ddd, 1H, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ =8.0 Hz, $^4J_{HH}$ =1.4 Hz), 7.08 (ddd, 1H, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ =8.0 Hz, $^4J_{HH}$ =1.4 Hz), 6.98 (d, 2H, $^3J_{HH}$ = 8.4 Hz), 3.85 (s, 3H), 2.18 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.4, 167.3, 157.1, 139.1, 132.5, 130.4, 126.9, 122.8, 122.7, 121.8, 121.4, 114.4, 55.6, 25.3. **HR-MS (ASAP, m/z)** calcd. from $[C_{16}H_{16}N_2O_3+H]^+$: 285.1239 found: 285.1242. R_f = 0.58 (EtOAc/Hexane 40/60).

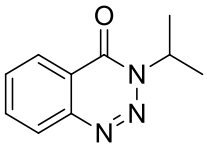
***N*-(2-Acetamido-4-methoxyphenyl)benzamide (28a-2)**



This compound was prepared in accordance to the general synthesis described for the amidation reaction starting from substrate **28** (1.50 mmol) to yield a white amorphous solid (85.0 mg, 20%). **^{1}H NMR (DMSO-d$_6$);** δ: 9.68 (br s, 2H), 7.95 (d, 2H, $^{3}J_{HH}$ = 7.2 Hz), 7.59-7.53 (m, 3H), 7.46 (d, 1H, $^{3}J_{HH}$ = 8.9 Hz), 7.20 (d, 1H, $^{4}J_{HH}$ = 2.7 Hz), 6.79 (dd, 1H, $^{3}J_{HH}$ = 8.9 Hz, $^{4}J_{HH}$ = 2.7 Hz), 3.75 (s, 3H), 2.07 (s, 3H). **^{13}C NMR (DMSO-d$_6$);** δ: 169.1, 165.1, 156.6, 134.4, 132.9, 131.6, 128.4, 127.5, 127.3, 122.8, 110.3, 109.0, 55.2, 23.6 . **HR-MS (ASAP, m/z)** calcd. from $[C_{16}H_{16}N_2O_3+H]^+$: 285.1239 found: 285.1242. R_f = 0.22 (EtOAc/Hexane 40/60).

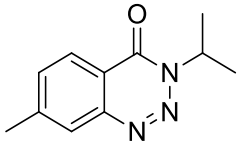
2.5.3 Characterisation of 1,2,3-benzotriazin-4(3*H*)-ones:

3-Isopropylbenzo[d][1,2,3]triazin-4*(3H)*-one (1b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **1a** (1.00 mmol) to yield a light yellow amorphous solid (185 mg, 98% yield). **^{1}H NMR (CDCl$_3$);** δ: 8.39 (dd, 1H, $^{3}J_{HH}$ = 8.0 Hz, $^{4}J_{HH}$ =1.0 Hz), 8.16 (d, 1H, $^{3}J_{HH}$ = 8.1 Hz), 7.94 (ddd, 1H, $^{3}J_{HH}$ = 7.2 Hz, $^{3}J_{HH}$ = 7.2 Hz, $^{4}J_{HH}$ = 1.3 Hz), 7.79 (ddd, 1H, $^{3}J_{HH}$ = 7.6, $^{3}J_{HH}$ = 7.6 Hz, $^{4}J_{HH}$ = 1.0 Hz), 5.49-5.42 (m, 1H), 1.60 (d, 6H, $^{3}J_{HH}$ = 6.7 Hz). **^{13}C NMR (CDCl$_3$);** δ: 155.1, 144.0, 134.7, 132.1, 128.1, 125.3, 119.6, 49.6, 21.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{11}N_3O+H]^+$: 190.0980 found: 190.0986. R_f = 0.56 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[166]

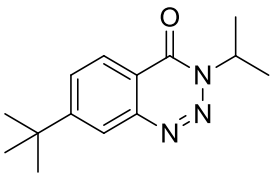
3-Isopropyl-7-methylbenzo[d][1,2,3]triazin-4*(3H)*-one (2b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **2a** (1.0 mmol) to

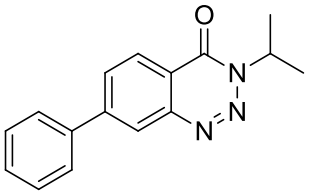
yield a light yellow amorphous solid (162 mg, 80% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.21 (d, 1H, $^{3}J_{HH}$ = 8.1 Hz), 7.90 (s, 1H), 7.58 (dd, 1H, $^{3}J_{HH}$ = 8.1 Hz, $^{4}J_{HH}$ = 1.1 Hz), 5.45-5.39 (m, 1H), 2.58 (s, 3H), 1.57 (d, 6H, $^{3}J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 155.1, 145.9, 144.2, 132.1, 125.0, 122.5, 117.3, 49.4, 22.0, 21.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{13}N_3O+H]^+$: 204.1137 found: 204.1139. R_f = 0.58 (EtOAc/Hexane 40/60).

7-(*tert*-Butyl)-3-isopropylbenzo[d][1,2,3]triazin-4*(3H)*-one (3b)



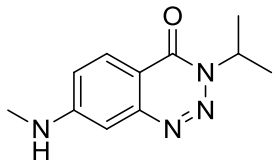
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **3a** (1.0 mmol) to yield a light yellow amorphous solid (203 mg, 83% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.26 (d, 1H, $^{3}J_{HH}$ = 8.5 Hz), 8.10 (d, 1H, $^{4}J_{HH}$ = 1.7 Hz), 7.83 (dd, 1H, $^{3}J_{HH}$ = 8.5 Hz, $^{4}J_{HH}$ = 1.8 Hz), 5.47-5.40 (m, 1H), 1.57 (d, 6H, $^{3}J_{HH}$ = 6.7 Hz), 1.42 (s, 9H). **^{13}C NMR ($CDCl_3$);** δ: 159.0, 155.1, 144.3, 130.2, 124.9, 124.1, 117.2, 49.3, 35.6, 31.0, 21.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{19}N_3O+H]^+$: 246.1606 found: 246.1606. R_f = 0.64 (EtOAc/Hexane 40/60).

3-Isopropyl-7-phenylbenzo[d][1,2,3]triazin-4*(3H)*-one (4b)



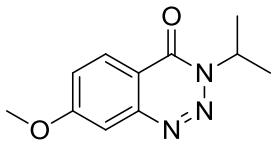
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **4a** (1.0 mmol) to yield a light yellow amorphous solid (222 mg, 84% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.39 (d, 1H, $^{3}J_{HH}$ = 8.3 Hz), 8.32 (d, 1H, $^{4}J_{HH}$ = 1.4 Hz), 8.00 (dd, 1H, $^{3}J_{HH}$ = 8.4 Hz, $^{4}J_{HH}$ = 1.6 Hz) 7.72-7.71 (m, 2H), 7.55-7.51 (m, 2H), 7.48-7.45 (m, 1H), 5.50-5.43 (m, 1H), 1.61 (d, 6H, $^{3}J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 155.0, 147.8, 144.5, 138.7, 131.1, 129.3, 129.0, 127.5, 125.8, 125.8, 118.2, 49.5, 21.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{16}H_{15}N_3O+H]^+$: 266.1293 found: 266.1297. R_f = 0.56 (EtOAc/Hexane 40/60).

3-Isopropyl-7-(methylamino)benzo[d][1,2,3]triazin-4(*3H*)-one (5b)



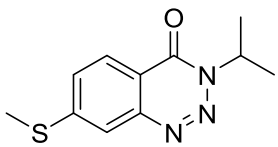
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **5a** (1.0 mmol) to yield a light yellow amorphous solid (98 mg, 45% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.45 (d, 1H, $^3J_{HH}$ = 8.9 Hz), 8.25 (dd, 1H, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.2 Hz), 8.11 (d, 1H, $^4J_{HH}$ = 2.2 Hz), 5.50-5.43 (m, 1H), 3.56 (s, 1H), 1.61 (d, 6H, $^3J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ:154.4, 147.3, 145.1, 127.2, 121.8, 117.5, 114.8, 49.8, 30.1, 21.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{14}N_4O]^+$: 218.1168 found: 218.1166. R_f = 0.30 (EtOAc/Hexane 40/60).

3-Isopropyl-7-methoxybenzo[d][1,2,3]triazin-4(3*H*)-one (6b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **6a** (1.0 mmol) to yield a light yellow amorphous solid (214 mg, 98% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.23 (d, 1H, $^3J_{HH}$ = 8.9 Hz), 7.46 (d, 1H, $^4J_{HH}$ = 2.4 Hz), 7.32 (dd, 1H, $^3J_{HH}$ = 8.9 Hz, $^4J_{HH}$ = 2.4 Hz), 5.48-5.38 (m, 1H), 3.99 (s, 3H), 1.57 (d, 6H, $^3J_{HH}$ = 6.8 Hz). **^{13}C NMR ($CDCl_3$, 100 MHz, 298K);** δ: 164.6, 154.9, 146.2, 126.8, 122.3, 113.3, 107.9, 56.0, 49.3, 21.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{14}N_3O_2+H]^+$: 220.1086 found: 220.1084. R_f = 0.43 (EtOAc/Hexane 40/60).

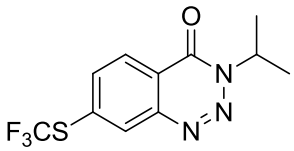
3-Isopropyl-7-(methylthio)benzo[d][1,2,3]triazin-4*(3H)*-one (7b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **7a** (1.0 mmol) to yield a light yellow amorphous solid (209 mg, 89% yield). **^{1}H NMR ($CDCl_3$,);** δ: 8.17 (d, 1H, $^3J_{HH}$ = 8.5 Hz), 7.80 (d, 1H, $^4J_{HH}$ = 1.7 Hz), 7.57 (dd, 1H, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.7 Hz), 5.45-5.38 (m, 1H), 2.62 (s, 3H), 1.57 (d, 6H, $^3J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 154.9, 148.7, 144.5, 129.7, 125.1, 121.7, 116.0, 49.5, 21.6, 14.9.

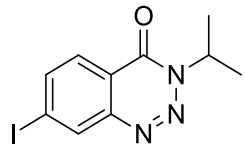
HR-MS (ASAP, m/z) calcd. from $[C_{11}H_{13}N_3OS+H]^+$: 236.0858 found: 236.0854. R_f = 0.46 (EtOAc/Hexane 40/60).

3-Isopropyl-7-((trifluoromethyl)thio)benzo[d][1,2,3]triazin-4*(3H)*-one (8b)



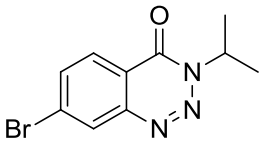
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **8a** (1.0 mmol) to yield a light yellow amorphous solid (231 mg, 80% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.44 (d, 1H, $^4J_{HH}$ = 1.4 Hz), 8.40 (d, 1H, $^3J_{HH}$ = 8.3 Hz), 7.98 (dd, 1H, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 1.5 Hz), 5.47-5.40 (m, 1H), 1.60 (d, 6H, $^3J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 154.3, 144.0, 137.6, 134.9, 132.5, 129.0 (q, $^1J_{CF}$ = 306.5), 126.6, 120.7, 50.1, 21.6. **^{19}F NMR ($CDCl_3$);** δ: –41.1. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{10}F_3N_3OS+H]^+$: 290.0575 found: 290.0581. R_f = 0.61 (EtOAc/Hexane 40/60).

7-Iodo-3-isopropylbenzo[d][1,2,3]triazin-4*(3H)*-one (9b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **9a** (1.0 mmol) to yield a light yellow amorphous solid (274 mg, 87% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.53 (d, 1H, $^4J_{HH}$ = 1.3 Hz), 8.08 (dd, 1H, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.5 Hz), 8.03 (d, 1H, $^3J_{HH}$ = 8.2 Hz), 5.45-5.38 (m, 1H), 1.58 (d, 6H, $^3J_{HH}$ = 6.8 Hz). **^{13}C {^{1}H} NMR ($CDCl_3$);** δ: 154.8, 144.41, 141.1, 136.9, 126.3, 118.9, 101.6, 49.9, 21.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{10}IN_3O+H]^+$: 315.9947 found: 315.9944. R_f = 0.58 (EtOAc/Hexane 40/60).

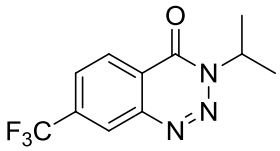
7-Bromo-3-isopropylbenzo[d][1,2,3]triazin-4(3*H*)-one (10b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **10a** (1.0 mmol) to yield a light yellow amorphous solid (233 mg, 90% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.32

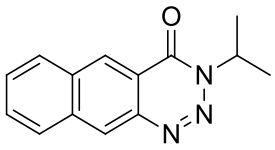
(d, 1H, $^4J_{HH}$ = 1.8 Hz), 8.22 (d, 1H, $^3J_{HH}$ = 8.5 Hz), 7.89 (dd, 1H, $^3J_{HH}$ = 8.5 Hz, $^4J_{HH}$ = 1.8 Hz), 5.46-5.39 (m, 1H), 1.59 (d, 6H, $^3J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 154.6, 144.7, 135.5, 130.6, 129.4, 127.0, 118.4, 49.9, 21.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{11}BrN_3O+H]^+$: 268.0085 found: 268.0085. R_f = 0.58 (EtOAc/Hexane 40/60).

3-Isopropyl-7-(trifluoromethyl)benzo[d][1,2,3]triazin-4*(3H)*-one (11b)



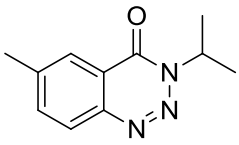
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **11a** (1.0 mmol) to yield a light yellow amorphous solid (223 mg, 73% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.48 (d, 1H, $^3J_{HH}$ = 8.3 Hz), 8.42 (s, 1H), 7.98 (dd, 1H, $^3J_{HH}$ = 8.4 Hz, $^4J_{HH}$ = 1.5 Hz), 5.47-5.40 (m, 1H), 1.60 (d, 6H, $^3J_{HH}$ = 6.8 Hz). **^{13}C NMR ($CDCl_3$);** δ: 154.1, 143.7, 136.5 (q, $^2J_{CF}$ = 33.4), 128.0 (q, $^3J_{CF}$ = 3.3), 126.7, 125.7 (q, $^3J_{CF}$ = 4.0 Hz), 123.1 (q, $^1J_{CF}$ = 273.9 Hz), 122.0, 50.1, 21.6. **^{19}F NMR ($CDCl_3$);** δ: –63.2. **HR-MS (ASAP, m/z)** calcd. from $C_{11}H_{10}F_3N_3O+H]^+$: 258.0854 found: 258.0860. R_f = 0.64 (EtOAc/Hexane 40/60).

3-Isopropylnaphtho[2,3-d][1,2,3]triazin-4*(3H)*-one (12b)



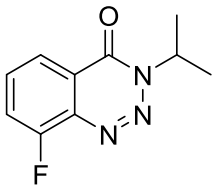
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **12a** (1.0 mmol) to yield a light yellow amorphous solid (234 mg, 98% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.92 (s, 1H), 8.68 (s, 1H), 8.16-8.12 (m, 2H), 7.74-7.68 (m, 2H), 5.51-5.44 (m, 1H), 1.62 (d, 6H, $^3J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 155.4, 140.4, 136.0, 134.3, 129.4, 129.1, 129.1, 128.8, 128.2, 126.7, 117.1, 49.0, 21.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{13}N_3O+H]^+$: 240.1137 found: 240.1135. R_f = 0.51 (EtOAc/Hexane 40/60).

3-Isopropyl-6-methylbenzo[d][1,2,3]triazin-4*(3H)*-one (13b)



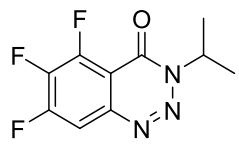
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **13a** (1.0 mmol) to yield a light yellow amorphous solid (160 mg, 79% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.14 (d, 1H, $^{4}J_{HH}$ = 1.7 Hz), 8.04 (d, 1H, $^{3}J_{HH}$ = 8.3 Hz), 7.74 (dd, 1H, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HH}$ = 1.7 Hz), 5.47-5.41 (m, 1H), 2.58 (s, 3H), 1.58 (d, 6H, $^{3}J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 155.2, 143.3, 142.4, 136.1, 128.0, 124.5, 119.5, 49.9, 21.9, 21.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{13}N_3O+H]^+$: 204.1137 found: 204.1142. R_f = 0.51 (EtOAc/Hexane 40/60).

8-Fluoro-3-isopropylbenzo[d][1,2,3]triazin-4*(3H)*-one (14b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **14a** (1.0 mmol) to yield a light yellow amorphous solid (186 mg, 90% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.13 (d, 1H, $^{3}J_{HH}$ = 8.1 Hz), 7.78-7.72 (m, 1H), 7.63 (ddd, 1H, $^{3}J_{HH}$ = 8.5 Hz, $^{3}J_{HH}$ = 8.5 Hz, $^{4}J_{HH}$ = 1.1 Hz), 5.47-5.40 (m, 1H), 1.59 (d, 6H, $^{3}J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 158.8, 155.2 (d, $^{1}J_{CF}$ =206.1 Hz), 133.7 (d, $^{2}J_{CF}$ = 10.4 Hz), 132.9 (d, $^{3}J_{CF}$ = 8.0 Hz), 121.3, 120.8 (d, $^{3}J_{CF}$ = 4.8 Hz), 120.5 (d, $^{2}J_{CF}$ = 18.2 Hz), 50.0, 21.6. **^{19}F NMR ($CDCl_3$);** δ: –122.0. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{10}FN_3O+H]^+$: 208.0886 found: 208.0886. R_f = 0.38 (EtOAc/Hexane 40/60).

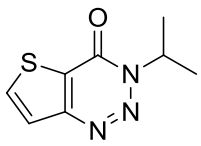
5,6,7-Trifluoro-3-isopropylbenzo[d][1,2,3]triazin-4*(3H)*-one (15b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **15a** (1.0 mmol) to yield a light yellow amorphous solid (175 mg, 72% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.78 (m, 1H), 5.44-5.37 (m, 1H), 1.58 (d, 6H, $^{3}J_{HH}$ = 6.7 Hz). **^{19}F**

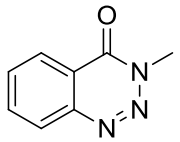
NMR ($CDCl_3$); -120.6 (dd, $^3J_{FF}$ = 21.4 Hz, $^4J_{FF}$ = 12.8 Hz), -129.9 (dd, $^3J_{FF}$ = 18.4 Hz, $^4J_{FF}$ = 12.5 Hz), -150.8 (dd, $^3J_{FF}$ = 18.0 Hz, $^3J_{FF}$ = 18.7 Hz). **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_8F_3N_3O+H]^+$: 244.0698 found: 244.0702. R_f = 0.64 (EtOAc/Hexane 40/60).

3-Isopropylthieno[3,2-d][1,2,3]triazin-4(3*H*)-one (16b)



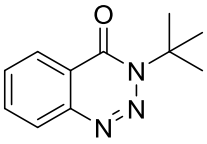
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **16a** (1.0 mmol) to yield a light yellow amorphous solid (82 mg, 50% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.89 (d, 1H, $^3J_{HH}$ = 5.3 Hz), 7.69 (d, 1H, $^3J_{HH}$ = 5.3 Hz) 5.55-5.45 (m, 1H), 1.60 (d, 6H, $^3J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 153.9, 153.1, 134.0, 126.4, 124.7, 49.8, 21.9. **HR-MS (ASAP, m/z)** calcd. from $[C_8H_{10}N_3OS+H]^+$: 196.0545 found: 196.0542. R_f = 0.80 (EtOAc/Hexane 40/60).

3-Methylbenzo[d][1,2,3]triazin-4(3*H*)-one (21b)



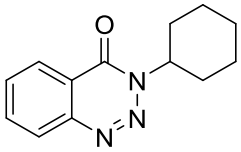
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **21a** (1.0 mmol) to yield a light yellow amorphous solid (40 mg, 25% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.38 (dd, 1H, $^3J_{HH}$ = 8.1 Hz, $^4J_{HH}$ = 1.0 Hz), 8.17 (d, 1H, $^3J_{HH}$ = 8.1 Hz), 7.96 (ddd, 1H, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.4 Hz), 7.82 (ddd, 1H, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.3 Hz), 4.08 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 156.0, 144.6, 134.8, 132.4, 128.3, 125.0, 119.7, 37.4. **HR-MS (ASAP, m/z)** calcd. from $[C_8H_7N_3O+H]^+$: 162.0667 found: 162.0664. R_f = 0.73 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[137]

3-(*tert*-Butyl)benzo[d][1,2,3]triazin-4*(3H)*-one (22b)



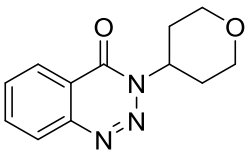
This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **22a** (1.0 mmol) to yield a light yellow amorphous solid (199 mg, 98% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.34 (d, 1H, $^3J_{HH}$ = 7.8 Hz), 8.11 (d, 1H, $^3J_{HH}$ = 8.0 Hz), 7.91 (dd, 1H, $^3J_{HH}$ = 7.4 Hz, $^3J_{HH}$ = 7.4 Hz), 7.76 (dd, 1H, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 7.5 Hz), 1.82 (s, 9H). **^{13}C NMR ($CDCl_3$);** δ: 156.2, 143.8, 134.5, 131.8, 127.6, 125.0, 120.8, 65.1, 28.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{13}N_3O+H]^+$: 204.1137 found: 204.1130. R_f = 0.91 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[166]

3-Cyclohexylbenzo[d][1,2,3]triazin-4*(3H)*-one (25b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **25a** (1.0 mmol) to yield a light yellow amorphous solid (224 mg, 98% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.35 (dd, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.0 Hz), 8.13 (dd, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.5 Hz), 7.93 (dd, 1H, $^3J_{HH}$ = 7.2 Hz, $^4J_{HH}$ = 1.5 Hz), 7.78 (t, 1H, $^3J_{HH}$ = 7.7 Hz, $^4J_{HH}$ = 1.1 Hz), 5.07-5.00 (m, 1H), 2.05-1.93 (m, 6H), 1.80-174 (m, 1H), 1.58 (m, 2H), 1.38-1.27 (m, 1H). **^{13}C NMR ($CDCl_3$);** δ: 155.1, 143.9, 134.7, 132.0, 128.0, 125.3, 119.6, 56.7, 31.9, 25.8, 25.3. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{15}N_3O+H]^+$: 230.1293 found: 230.1293. R_f = 0.87 (EtOAc/Hexane 40/60). This characterisation is in agreement with previously published data.[166]

3-(Tetrahydro-pyran-4-yl)benzo[d][1,2,3]triazin-4*(3H)*-one (26b)



This compound was prepared in accordance to the general synthesis described for the for preparation of 1,2,3-benzotriazin-4*(3H)*-ones starting from **26a** (1.0 mmol) to yield a light yellow amorphous solid (226 mg, 98% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.35 (dd, 1H, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 0.9 Hz), 8.15 (d, 1H, $^3J_{HH}$ = 7.6

Hz), 7.97-7.31 (m, 1H), 7.82-7.78 (m, 1H), 5.29-5.23 (m, 1H), 4.17 (dd, 2H, $^{3}J_{HH}$ = 11.6 Hz, $^{4}J_{HH}$ = 4.7 Hz), 3.63 (td, 2H, $^{3}J_{HH}$ =12.2 Hz, $^{3}J_{HH}$ =12.2 Hz, $^{4}J_{HH}$ =2.0 Hz), 2.45-2.34 (m, 2H), 1.97-1.93 (m, 2H). **^{13}C NMR ($CDCl_3$);** δ: 155.2, 143.8, 134.9, 132.3, 128.2, 125.3, 119.5, 67.3, 53.9, 31.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{14}N_3O_2+H]^+$: 232.1086 found: 232.1082. R_f = 0.54 (EtOAc/Hexane 40/60.

Chapter 3. One-pot Preparation of Benzotriazoles Employing a Key Cp*Co(III)-catalysed C-H Amidation Step

3.1 Introduction

The development of novel Cp*Co(III)-catalysed C-H amidation protocols using 1,4,2-dioxazol-5-ones has been of great interest with many procedures being reported over that last few years, as discussed in **Chapter 1**. However, most of these methodologies were proof-of-concept protocols, which resulted in the installation of a new amide, which were not utilised further. For this work, emphasis has been placed on utilising Cp*Co(III)-catalysed C-H amidation reaction as a key first step for one-pot synthesis of nitrogen containing heterocycles.

Benzotriazoles are versatile compounds that have applications in a variety of fields as corrosion inhibitors, pharmaceuticals, polymers, dyes etc.[167–170] In organic synthesis, the benzotriazole moieties have been beneficial for a variety of synthetic protocols as synthetic auxiliaries or as good leaving groups. *N*-acylbenzotriazoles have attracted particular interest due to their use as acylating agents for N-, O-, C-, and S acylations.[171] Furthermore, a variety of other protocols have been reported where benzotriazoles scaffolds act as activating groups, ligands, polymers, electron donors and precursors for radicals.[172–181]

However, the benzotriazole scaffold has been particularly useful for the design of novel biologically active molecules, as substituted benzotriazole can exhibit a variety of biological properties as antitumour, antibacterial and antiemetic agents amongst others (**Figure 3-1**). [170]

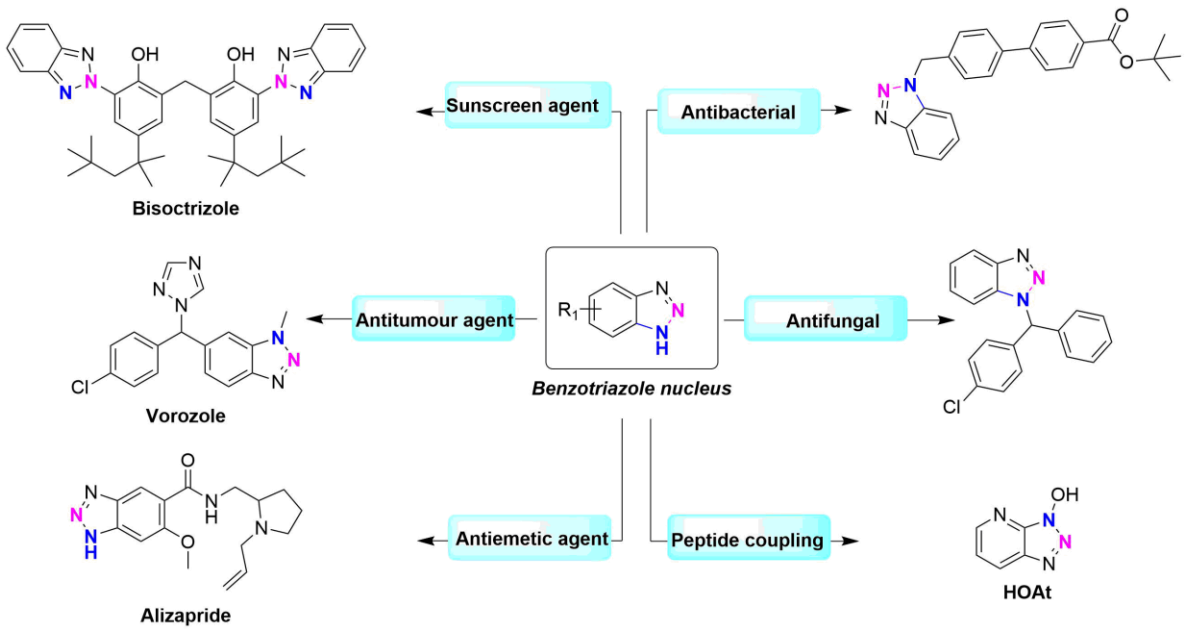
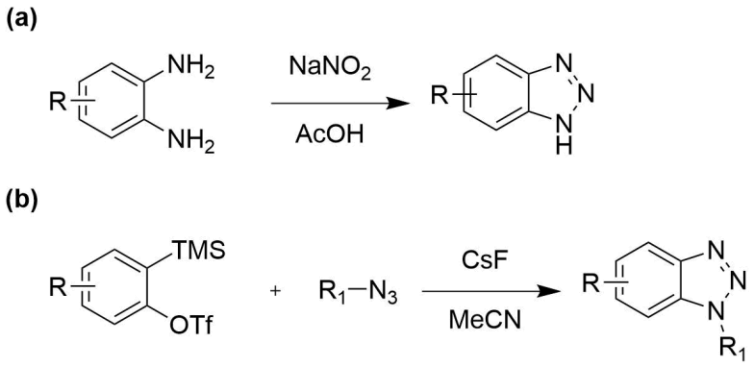


Figure 3-1: Uses of benzotriazole scaffolds as biologically active molecules.[170]

Typically, benzotriazoles are synthesised *via* diazotisation of *o*-phenylenediamine or [3 + 2] cycloaddition of azides to benzynes (**Scheme 3-1**), although other methods have been reported more recently.[182–186] However, these reactions require high temperatures or long reaction time thus, the development of milder, shorter reactions is of interest.



Scheme 3-1: Common approaches for synthesis of benzotriazoles *via* diazotisation of (a) *o*-phenylenediamine or (b) [3+2] cycloaddition of azides with benzynes.[182-186]

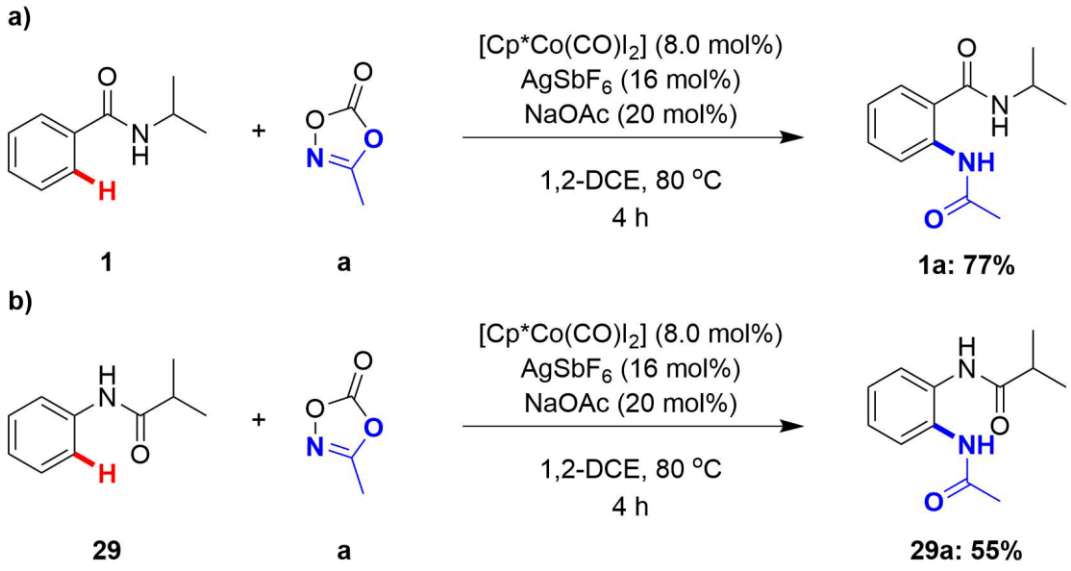
This chapter focuses on developing a novel methodology for the synthesis of benzotriazole starting from the Cp*Co(III)-catalysed C-H amidation of *N*-phenylisobutyramide using 1,4,2-dioxazol-5-ones as amidation partners. The

products are subsequently reacted with *tert*-butyl nitrite in a one-pot manner to yield a variety of substituted acylbenzotriazoles.

3.2 Results and discussion

3.2.1 Optimisation studies of the C-H amidation reaction

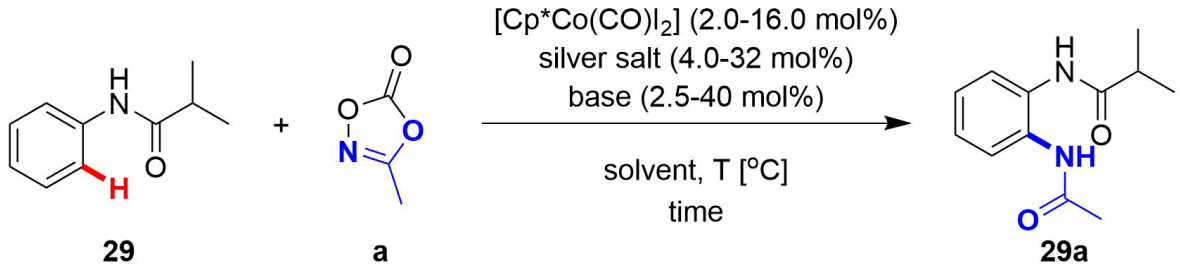
The amidation of *N*-phenylisobutyramide *via* a Cp*Co(III)-catalysed C-H amidation approach was initiated starting from the optimised conditions reported in **Chapter 2** for the corresponding amidation of benzamides. However, in this case the previously optimised conditions afforded a yield of only 55% which was lower than the yield observed for the C-H amidation of benzamides (**Scheme 3-2**). Consequently, reaction conditions were further optimised to improve the observed yield for the C-H amidation of *N*-phenylisobutyramides.



Scheme 3-2: Comparison of yields for the Cp*Co(III)-catalysed amidation of *N*-isopropylbenzamide and *N*-phenylisobutyramide using the optimised reaction conditions from Chapter 2.

The initial optimisation study for the C-H amidation of *N*-phenylisobutyramide focused on variation of the same parameters as the previously reported for the Cp*Co(III)-catalysed C-H amidation of benzamides: silver salts, bases, solvents, reaction temperature, time of reaction and loading of reactants (**Scheme 3-3**). The

yields for **29a** were determined using the same method from **Chapter 2**, where the conversion was determined using ^{1}H NMR spectroscopy in the presence of mesitylene as internal standard.



Scheme 3-3: Optimisation studies for the Cp*Co(III)-catalysed amidation of *N*-phenylisobutyramide using 3-methyl-1,4,2-dioxazol-5-one as amidating agent.

Table 3-1: Solvent optimisation [a]

Entry	Solvent	Temp. [°C]	29a [%][b]
1	$CHCl_3$	60	40
2	$CHCl_3$	80	42
3	$CHCl_3$	100	40
4	MeCN	60	None
5	cyclohexane	60	21
6	1,2-DCE [2 mL]	60	50
7	**1,2-DCE [4 mL]**	**60**	**55**
8	1,4-dioxane	60	22
9	THF	60	None
10	toluene	60	29
11	toluene	100	29

[a] General conditions: 0.25 mmol substrate, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, 8.0 mol% $[Cp^*Co(CO)I_2]$, 16 mol% $AgSbF_6$, 20 mol% NaOAc, in 2.0 mL solvent, temperature, 24 h. [b] Yields of **29a** calculated from ^{1}H NMR using mesitylene as internal standard.

A variety of other solvents besides 1,2-DCE were investigated during the optimisation process. However, none of these afforded higher yields compared to the previously optimised reaction conditions (**Table 3-1**, entry 7, 55% yield). The aim of the optimisation of solvent was not only to increase the yield of **29a** but also to substitute 1,2-DCE as it is not an ideal solvent due to its known toxicity.[97] It should be noted that the reaction also proceeded in $CHCl_3$ (**Table 3-1**, entries 1-3) although the best obtained yield was lower (42%) when using this solvent and reactivity did not increase at higher or lower temperatures. Furthermore, significantly lower yields were observed in the presence of other common solvents (**Table 3-1,** entries 4, 5, 8, 9 and 10).

Table 3-2: Base optimisation [a]

Entry	Base	29a [%][b]
1	LiOAc	53
2	**NaOAc (20 mol%)**	**55**
3	KOAc	47
4	CsOAc	32
5	K_2CO_3	46
6	Cs_2CO_3	34
7	NaOPiv	41
8	CsOPiv	28
10	K_3PO_4	41
11	$Cu(OAc)_2$	48
12	$Zn(OAc)_2$	50
13	NaOAc (40 mol%)	53
14	-	33

[a] General conditions: 0.25 mmol substrate, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, 8.0 mol% [Cp*Co(CO)I_2], 16 mol% $AgSbF_6$, 20 mol% base, in 4.0 mL 1,2-DCE, 80 °C, 24 h.[b] Yields of **29a** calculated from ^{1}H NMR using mesitylene as internal standard.

Regarding the optimisation of base, no improvement in reactivity over the use of NaOAc was observed in the presence of a variety of other bases (**Table 3-2**). Caesium bases which showed the lowest activity (**Table 3-2**, entries 4 and 6: 32% and 34%), afforded similar yields to when the reaction takes place without base. Similarly to what was observed for the corresponding amidation of benzamides, the highest activity was displayed by the acetate bases particularly Na and Li bases. Furthermore, increasing the loading of NaOAc did not increase the obtained yield (**Table 3-2**, entries 2 *vs*. 13).

Table 3-3: Silver salt optimisation [a]

Entry	Silver salt	29a [%][b]
1	$AgNO_3$	None
2	AgOTf	8
3	$AgBF_4$	35
4	Ag_2O	None
6	**$AgSbF_6$**	**55**
5	AgOAc	None
6	$AgNO_3$	None
7	-	None

[a] General conditions: 0.25 mmol substrate, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, 8.0 mol% [Cp*Co(CO)I_2], 16 mol% silver salt, 20 mol% NaOAc, in 4.0 mL 1,2-DCE, 80 °C, 24 h.[b] Yields of **29a** calculated from ^{1}H NMR using mesitylene as internal standard.

No conversion was observed in the absence of silver salt, as this is needed for the abstraction of halide to generate the active cationic catalyst.

Table 3-3 illustrated that the only silver salts to show activity were the weakly coordinating ones (entries 3 and 6). None of the other salts from the screening were successful for the Cp*Co(III)-catalysed C-H amidation of *N*-phenylisobutyramide. It is worth mentioning that increasing the time of reaction above 4 hours did not improve the yield of the reaction (**Table 3-4**).

Table 3-4: Time of reaction optimisation

Entry	Time [h]	29a [%][b]
1	24	55
2	**4**	**55**
3	2	50

[a] General conditions: 0.25 mmol substrate, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, 8.0 mol% [Cp*Co(CO)I_2], 16 mol% $AgSbF_6$, 20 mol% NaOAc, in 4.0 mL 1,2-DCE, 60 °C, time.[b] Yields of **29a** calculated from ^{1}H NMR using mesitylene as internal standard.

Subsequently, the temperature of reaction was optimised and it was observed that temperature variation had little effect on the obtained yield for **29a**. Lower temperatures, (**Table 3-5**, entries 4 and 5) afforded similar yields of 50% and respectively 55% however, increasing temperature to 120 °C decreased yield to 40% (**Table 3-5**, entry 1).

Table 3-5: Temperature of reaction optimisation [a]

Entry	Temp [°C]	29a [%] [b]
1	120	40
2	100	57
3	**80**	**55**
4	60	50
5	40	52

[a] General conditions: 0.25 mmol substrate, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, 8.0 mol% [Cp*Co(CO)I_2], 16 mol% silver salt, 20 mol% NaOAc, in 4.0 mL 1,2-DCE, temperature, 24 h.[b] Yields of **29a** calculated from ^{1}H NMR using mesitylene as internal standard.

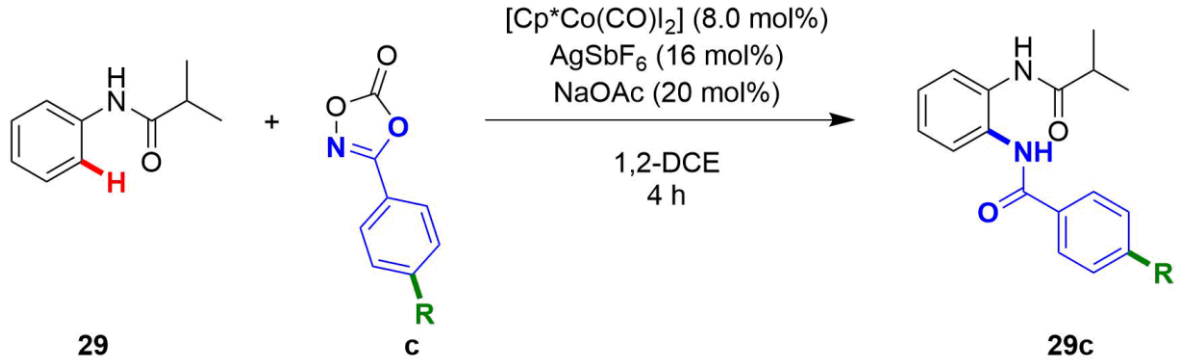
The need to increase catalyst loading has previously been reported for the Cp*Co(III)-catalysed C-H functionalisation of acetanilides.[59,60] However, as illustrated by entry 5 **(Table 3-6),** in this instance no improvement was observed when a higher loading of reactants was employed.

Table 3-6: Optimisation of loading of reactants [a]

Entry	[Cp*Co(CO)I_2] [mol%]	$AgSbF_6$ [mol%]	NaOAc [mol%]	29a [%] [b]
1	2.0	4.0	2.5	41
2	4.0	8.0	10	50
3	6.0	12	15	50
4	**8.0**	**16**	**20**	**55**
5	16	32	40	54

[a] General conditions: 0.25 mmol substrate, 0.3 mmol 3-methyl-1,4,2-dioxazol-5-one, [Cp*Co(CO)I_2], $AgSbF_6$, NaOAc, in 4.0 mL 1,2-DCE, 80 °C, 24 h.[b] Yields of **29a** calculated from ^{1}H NMR using mesitylene as internal standard.

Unfortunately, it was not possible to obtain a yield higher than 55% after the initial screening of the above standard parameters, so attention was shifted to a new set of parameters, in particular to variation of the amidation agent and the Cp*Co(III) pre-catalyst. Aryl amidation agents with different *para*-functional groups were employed for the next set of reactions to examine the effect that different electronic properties have on C-H amidation reaction. Furthermore, aryl amidation agents were used instead of the alkyl as it is easier to install new functionalities on the aryl moiety.



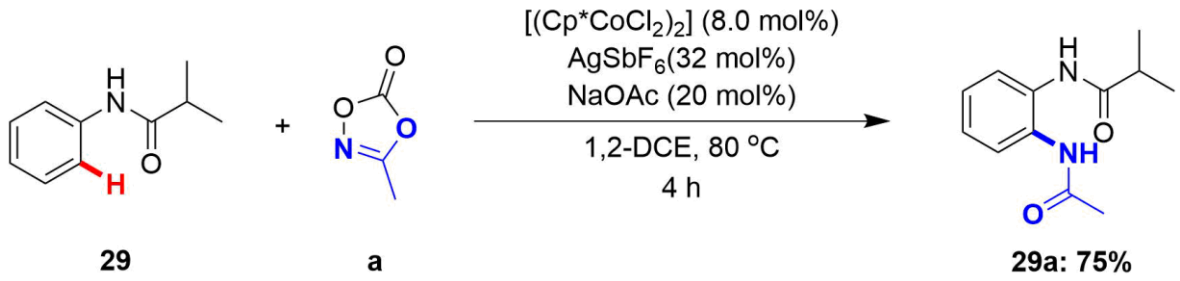
Scheme 3-4: Optimisation studies for the Cp*Co(III)-catalysed amidation of *N*-phenylisobutyramide using substituted 3-phenyl-1,4,2-dioxazol-5-ones.

Table 3-7: Optimisation of amidation agent [a]

Entry	R	Temp. [°C]	29c [%][b]
1	H	80	Mixture of prod.
2	**H**	**40**	**50**
3	CF_3	40	None
4	OMe	40	34
5	Cl	40	24
6	Me	40	40

[a] General conditions: 0.25 mmol substrate, 0.3 mmol 1,4,2-dioxazol-5-one, 8.0 mol% [Cp*Co(CO)I_2], 16 mol% $AgSbF_6$, 20 mol% NaOAc, in 4.0 mL 1,2-DCE, 24 h.[b] Yields of products calculated from ^{1}H NMR using mesitylene as internal standard.

In this regard, substituted 3-phenyl-1,4,2-dioxazol-5-one amidation agents were screened to establish whether the presence of an aromatic ring instead of a methyl group would increase reactivity. When applying the same reaction conditions optimised previously for the amidation of *N*-phenylisobutyramide using 3-phenyl-1,4,2-dioxazol-5-one a mixture of products was observed (**Table 3-7**, entry 1). Reducing the reaction temperature from 80 °C to 40 °C affords only the desired product, which agreed with the report of Chang and co-worker,[132] who also described an increase in yield at milder temperatures for the Cp*Co(III)-catalysed C-H amidation of *N*-phenylpivalamide with 3-phenyl-1,4,2-dioxazol-5-one. However, even when using milder temperatures, the substrate could only be converted in a yield of 50% (**Table 3-7**, entries 1 and 2). Furthermore, the effect of amidation agents with both electron donating (**Table 3-7**, entries 4 and 6) and electron-withdrawing (**Table 3-7**, entries 3 and 5) effect were studied. None of the substituted 3-phenyl-1,4,2-dioxazol-5-one had a positive effect on reactivity, with the highest yield recorded being 34% when using the OMe substituted amidation agent (**Table 3-7**, entry 4). Employing an amidation agent with a highly electron-withdrawing CF_3 group at the *para*-position was particularly unsuccessful, with no product being observed.

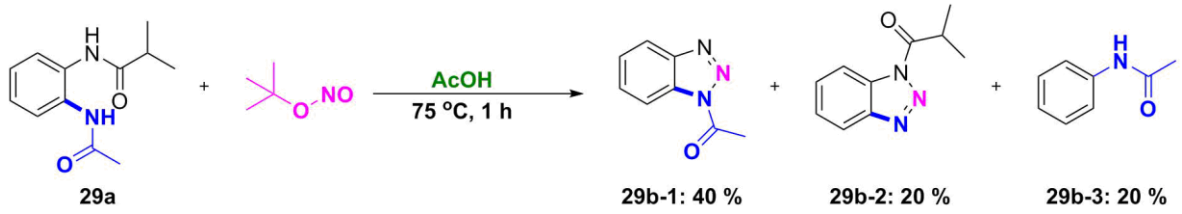


Scheme 3-5: Synthesis of *N*-(2-acetamidophenyl)isobutyramide (**29a**) using [(Cp*$CoCl_2$)$_2$] pre-catalyst.

The last parameter to be investigated was the cobalt source (**Scheme 3-5**). The [(Cp*$CoCl_2$)$_2$] complex was synthesised using the method described by Matsunaga and Kanai.[25] This dimeric pre-catalyst has been previously used by Chang and co-worker for the amidation of substituted pivalanilides.[132] The product yield increased to 75% in the presence of the dimer pre-catalyst, using the 3-methyl-1,4,2-dioxazol-5-one as the amidation agent. It is worth noting that since the effect of adding two equivalents of the monomeric pre-catalyst, [Cp*Co(CO)I_2], was also tested (**Table 3-6**, entry 6), the observed increase in yield when utilising the dimer pre-catalyst was not due to the having two equivalents of Cp*Co-catalyst available.

3.2.2 One-pot synthesis of acetylbenzotriazole

After the Cp*Co(III)-catalysed C-H amidation reaction was optimised for a variety of substituted *N*-phenylisobutyramide the main interest was to isolate the benzotriazole heterocycles resulted from the reaction with *tert*-butyl nitrite (TBN). In order the achieve that, the cyclisation reaction was optimised starting from the reaction conditions applied for the synthesis of 1,2,3-benzotriazin-4(*3H*)-ones in **Chapter 2**. To begin with, *N*-(2-acetamidophenyl)isobutyramide **29a** was reacted with TBN in acetic acid at 75 °C for 1 hour.



Scheme 3-6: Detected products from reacting *N*-(2-acetamidophenyl)isobutyramide (**29a**) with TBN in AcOH at 75 °C for 1 h.

After the reaction was completed, a mixture of three products was observed (**Scheme 3-6**). It was possible to isolate all three products, with the major product being **29b-1** in a yield of 40%.

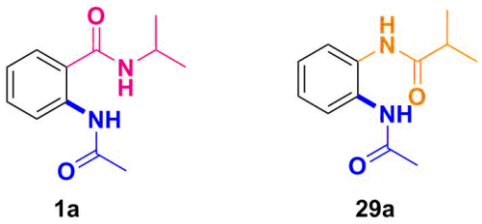


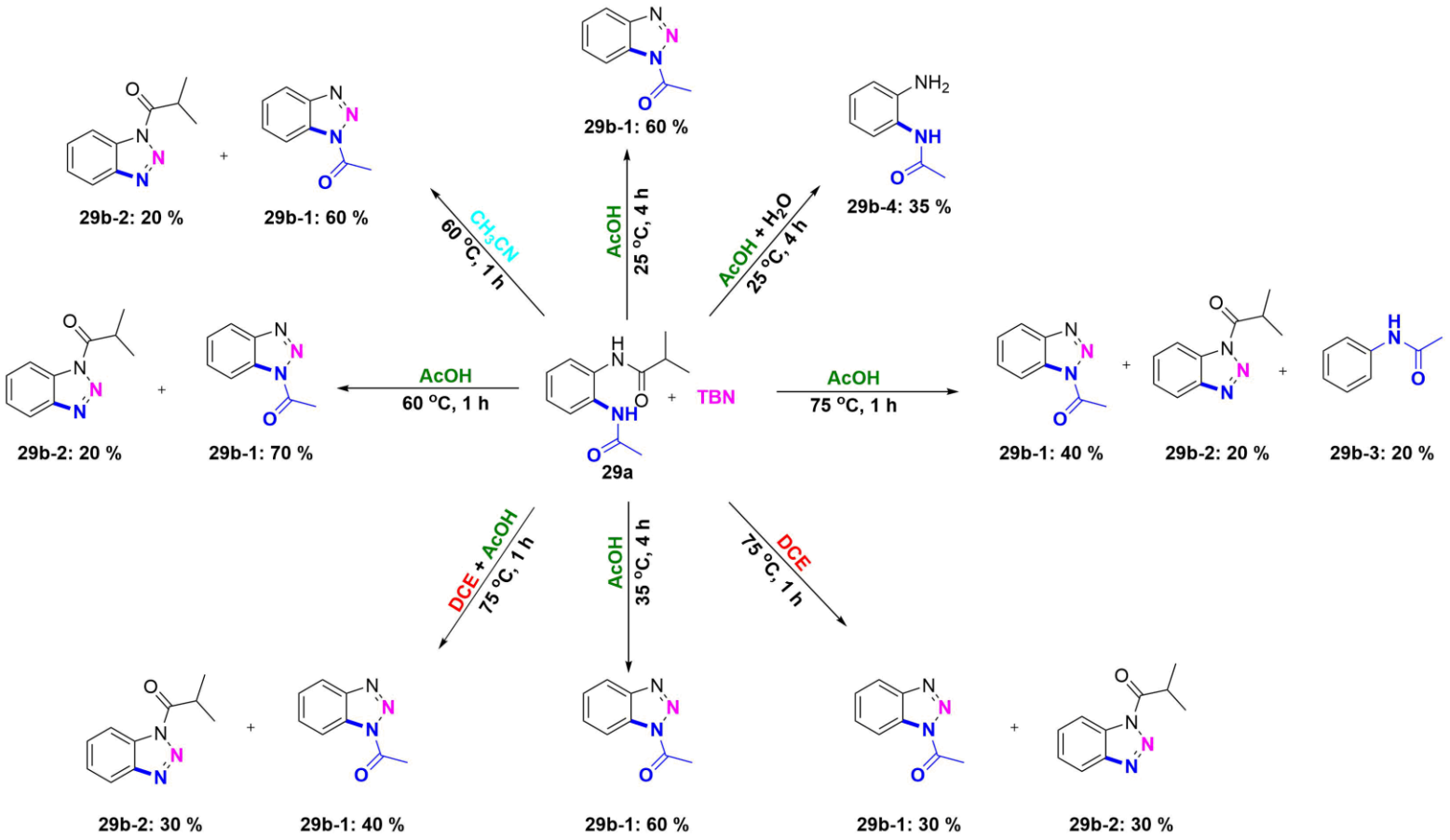
Figure 3-2: The amides of 2-acetamido-*N*-isopropylbenzamide (**1a**) and *N*-(2-acetamidophenyl)isobutyramide (**29a**) prepared using the Cp*Co(III)-catalysed amidation procedure.

The presence of **29b-2** is due to the similar nature of the two amides present in compound **29a** compared to the distinctly different amides present in the

corresponding amidated benzamide species **1a** (**Figure 3-2**). Thus, the nitroso group no longer attacks selectively one of the amides, resulting in the formation of the two products. The third isolated product **29b-3** was the result of decomposition of the cyclic product **29b-1** due to the increased instability of the acetylbenzotriazole at higher temperatures compared to the 1,2,3-benzotriazin-4(*3H*)-ones.

The cyclisation reaction was optimised in order to obtain synthetically useful yields (**Scheme 3-7**). Decreasing the temperature of reaction to 60 $^{\circ}$C increases the yield of **29b-1** to 70%, with no acetanilide product (**29b-3**) being observed. However, reducing the temperature further to 35 $^{\circ}$C and 25 $^{\circ}$C decreases the yield to 60%.

Ideally, the reaction would have taken place in 1,2-DCE to have continuity from the first reaction. However, a lower yield of 30% was observed when 1,2-DCE was used as solvent. The yield of **29b-1** was increased sightly to 40% when a mixture of AcOH and 1,2-DCE was used. Furthemore, it was also observed that using a mixture of AcOH and H_2O furnishes **29b-4** in 35% yield. Finally, the reaction proceeds in good yield when using CH_3CN (60% yield), however, the most optimal solvent to obtain **29b-1** remained AcOH with a reaction temperature of 60 $^{\circ}$C and reaction time of 1 hour.



Scheme 3-7: Optimisation studies for the synthesis of acetylbenzotriazoles. General conditions: 0.50 mmol **29a**, 3.0 equiv. TBN, 4.0 mL solvent. Yields of products calculated from ^{1}H NMR using mesitylene as internal standard.

With the optimised conditions in hand for the cyclisation reaction the focus moved to the potential for scope and limitations of the one-pot synthesis of *N*-acetylbenzotriazoles. It was possible to isolate 40% of the unsubstituted product (**29b-1**). This was comparable to the yields that were observed in **Chapter 2** for one-pot synthesis of 1,2,3-benzotriazin-4(*3H*)-ones.

N-unsubstituted benzotriazoles have been known to exhibit two tautomeric forms which are in equilibrium.[187–189] The *1H*-tautomer is believed the more predominant in solution due to its increased aromaticity and higher polarity.[187,188]

1H-benzo[d][1,2,3]triazole *2H*-benzo[d][1,2,3]triazole

Scheme 3-8: Structures of the two tautomers for benzotriazole.

For several of the synthesised substituted acetylbenzotriazoles it was possible to identify the *1H*-acetylbenzotriazole as well as the *2H*-acetylbenzotriazole structural isomers *via* ^{1}H NMR (**Figure 3-3**).

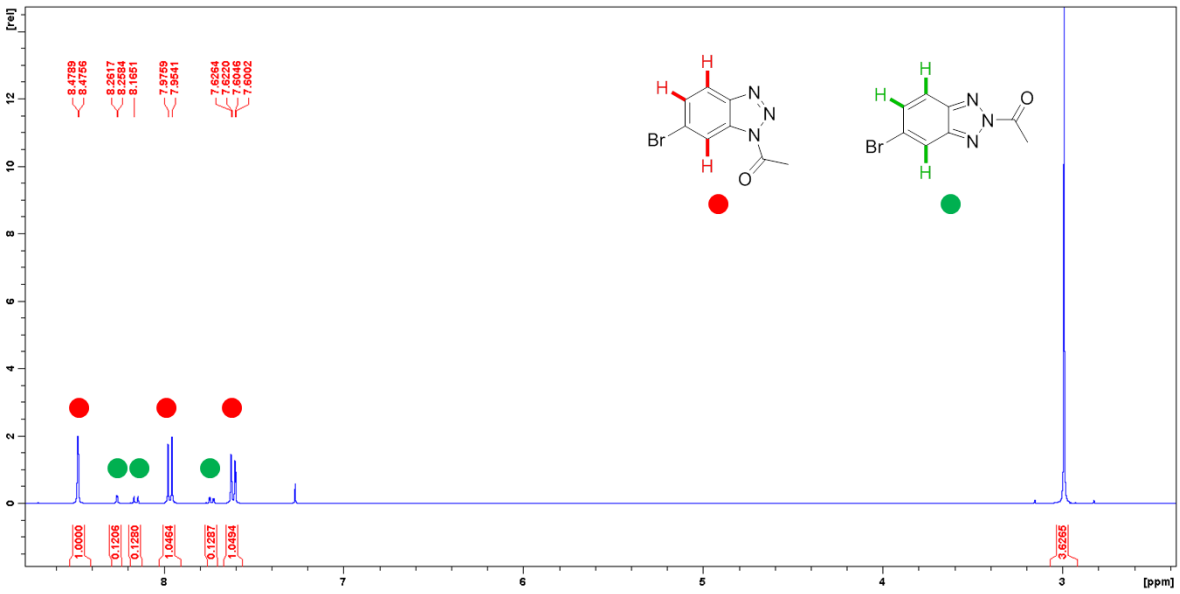


Figure 3-3: Example of ^{1}H NMR to illustrate the presence of both structural isomers with 6-bromo-*1H*-acetylbenzotriazole in red and 5-bromo-*2H*-acetylbenzotriazole in green.

In order to establish which one of the isomers was the major product, crystals of the bromo-substituted acetylbenzotriazole, **37b**, suitable for single crystal X-ray diffraction studies were obtained by vapour diffusion of pentane into concentrated chloroform solution. The acquired structure (**Figure 3-4**) identified the 6-bromo-*1H*-acetylbenzotriazole as the predominant isomer.

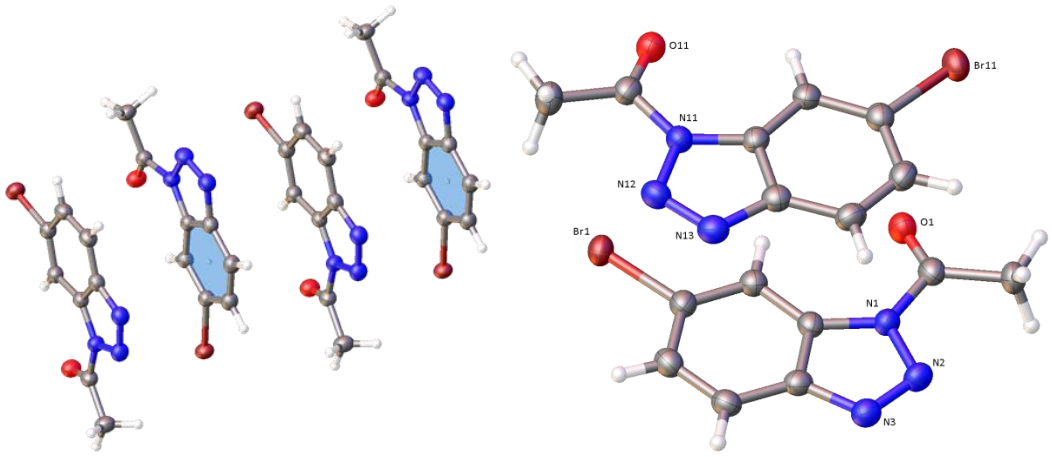
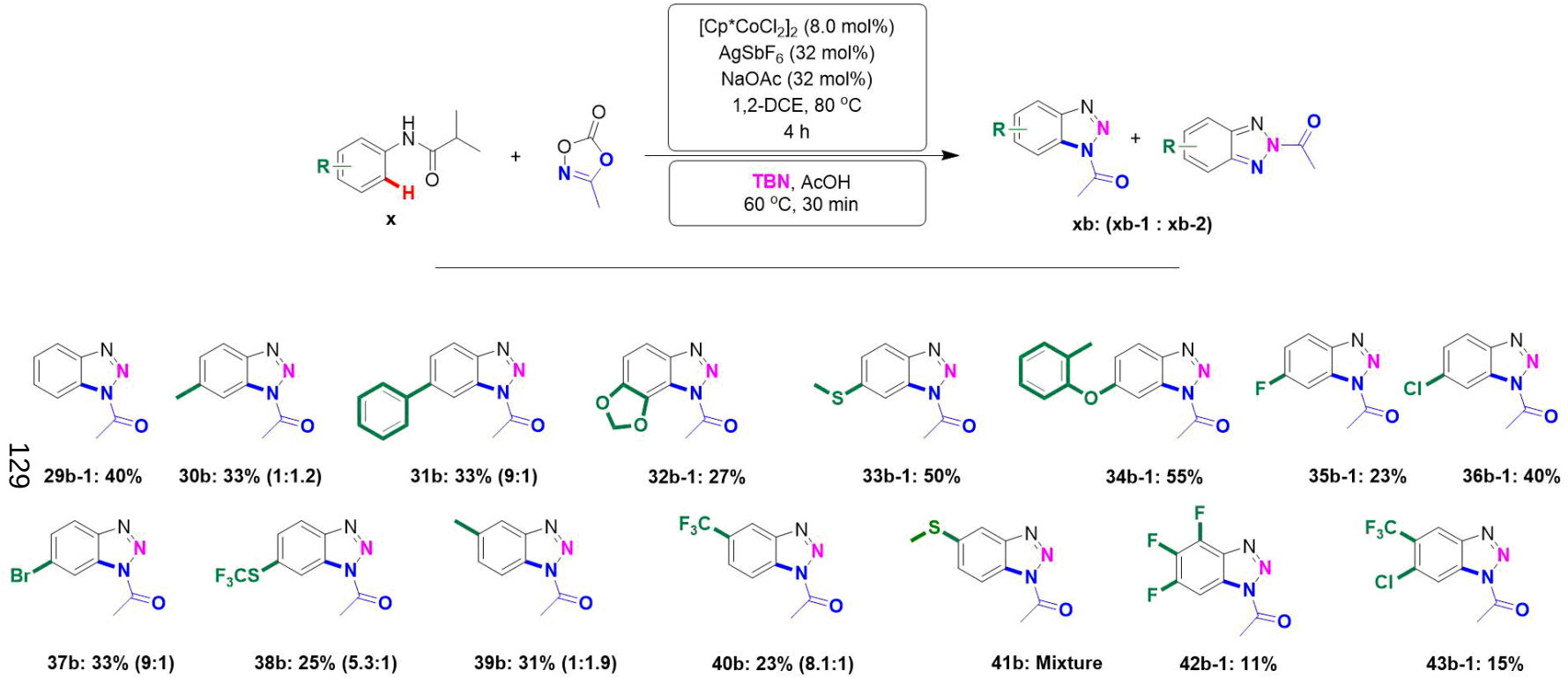


Figure 3-4: Molecular structure of 6-bromo-*1H*-acetylbenzotriazole (**37b**), analysed by the EPSRC National Crystallography Service. Two independent molecules which interact through $\pi-\pi$ stacking were observed in the asymmetric unit.

With regards to the effect of various substituents on the aromatic ring (**Scheme 3-9**) it was observed that the overall yields obtained for the one-pot synthesis of acetylbenzotriazoles were lower compared to the yields obtained for the one-pot synthesis of 1,2,3-benzotriazin-4(*3H*)-ones. The decline in yields was mainly due to the formation of side products (**Scheme 3-6**). Good yields were observed when substrates with electron-donating substituents were employed (**30b**, **31b**, **32b-1**, **33b-1**, **34b-1**). Only one isomer was observed for substituents which are medium to highly electron-donating **32b-1**, **33b-1** and **34b-1** whilst, when employing weakly electron-donating groups both (**30b**, **31b**) isomers could be observed. Interestingly, the inclusion of methyl at the *para*-position results in an almost even mixture of isomers **30b**. The incorporation of weakly electron-withdrawing groups (**35b-1**, **36b-1**, **37b**) affords good yields, furnishing predominantly the *1H*-acetylbenzotriazole isomer. The selectivity for a single isomer decreases with

the inclusion of a highly electron-withdrawing group (**38b**). The highest yield obtained for substrates with *meta*-substituents was observed for the methyl substituted compound (**39b**), however, the *2H*-acetylbenzotriazole isomer was the predominant compound in this instance. It was not possible to isolate **41b** as a mixture of products was observed. Finally, double substituted substrates **42b-1** and **43b-1** were converted in low yields 11% and 15%, respectively.



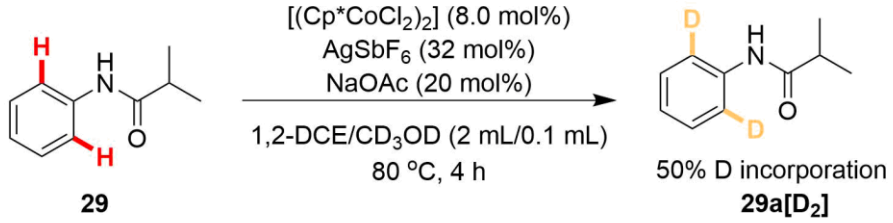
Scheme 3-9: Substrate scope studying the effect of variation in substituent on the aromatic moiety for the one-pot synthesis of substituted acetylbenzotriazole. General conditions: optimised reaction conditions for each individual step.

3.2.3 Mechanistic investigations

3.2.3.1 Experimental mechanistic investigations

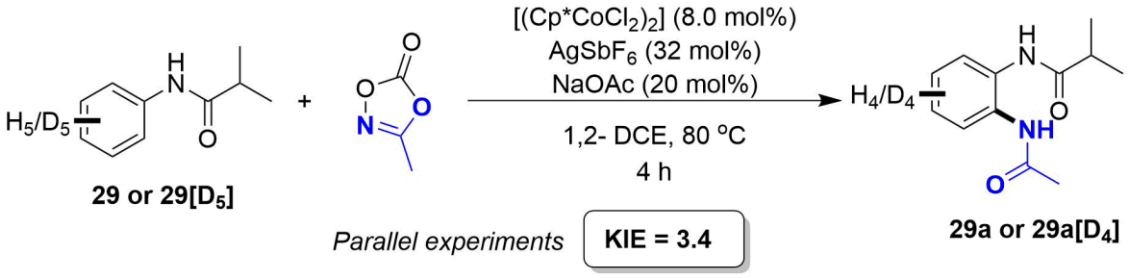
Deuterium exchange and parallel Kinetic Isotope Effect (KIE) experiments were performed for the *N*-phenylisobutyramides (**Scheme 3-10**) in order to reveal information about the C-H activation step. Regarding the reversibility of the C-H activation, when the deuterium exchange experiment was performed 50% deuterium incorporation was observed. This suggests that the C-H activation step is reversible when employing *N*-phenylisobutyramides, in similarity to the benzamides in **Chapter 2**. The KIE experiment showed a higher rate between the hydrogen and deuterium isotopes compared to what was observed for the benzamides. The high KIE rate (k_H/k_D = 3.4) could indicate that the C-H activation step is the rate limiting step of this reaction however, this is in disagreement with what was observed during computational studies.

(a) H/D exchange



29 **29a[D_2]**

(b) KIE study



29 or 29[D_5] **29a or 29a[D_4]**

Scheme 3-10: Experimental mechanistic studies for the Cp*Co(III) C-H amidation step.

3.2.3.2 Computational mechanistic investigations

To gain further insight into the mechanism involved in the C-H amidation of *N*-phenylisobutyramides, DFT calculations were carried out (**Figure 3-5**). Solvated free energies were calculated using M06 as functional and def2-TZVP as a basis set (See computational details for further information). This computational methodology has been applied previously to successfully elucidate Co-catalysed reactions.[29,109,190] Similarly to the mechanistic studies conducted for the C-H amidation reaction using isopropyl benzamide, the [Cp*Co(OAc)$_2$] pre-catalyst was used as reference point and the formation of the [Cp*Co(OAc)]$^+$ acetate was observed as a result of the loss of acetate ion with an energy barrier of 9.99 kcal/mol (**Figure 3-5**).[148]

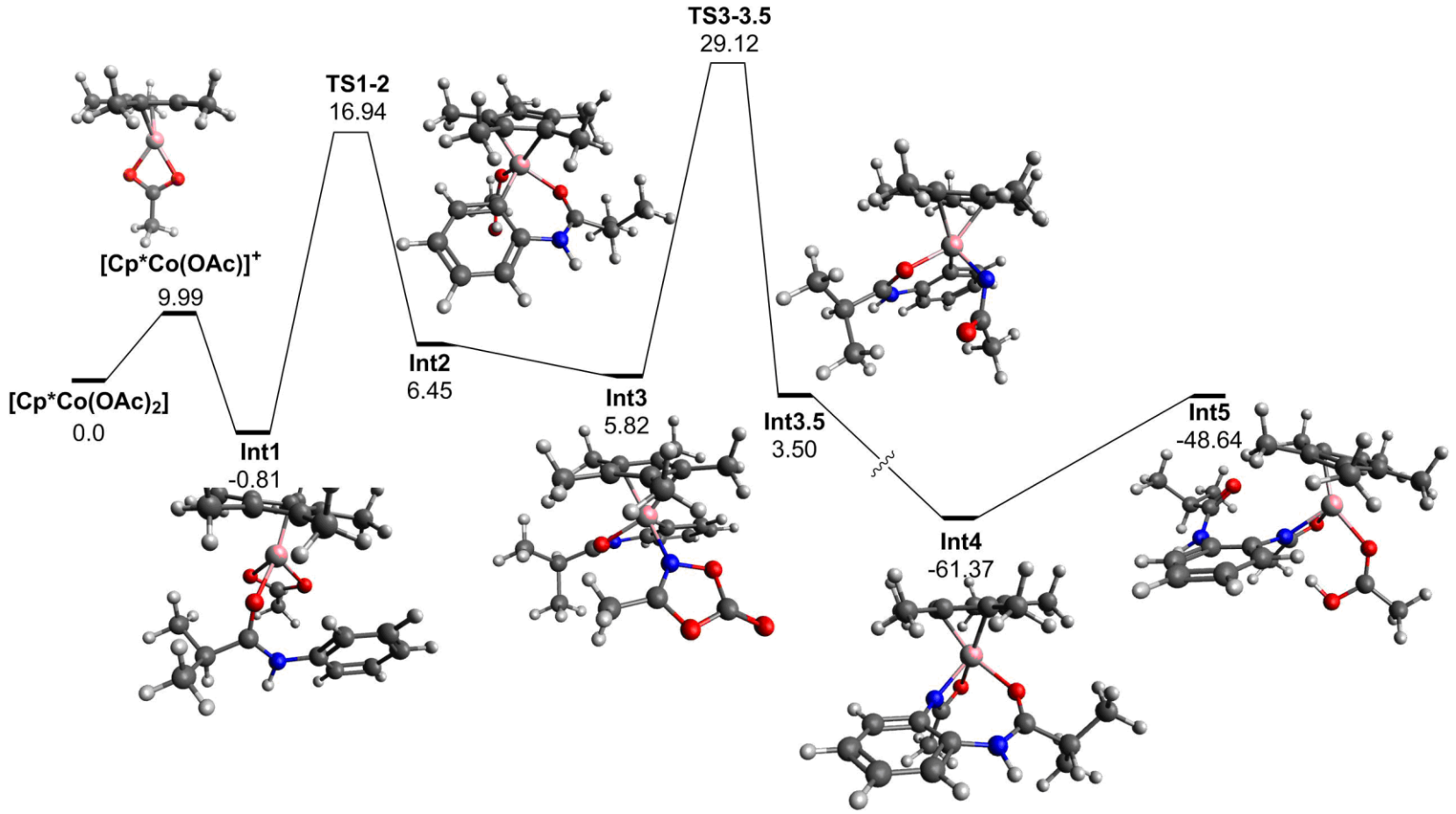
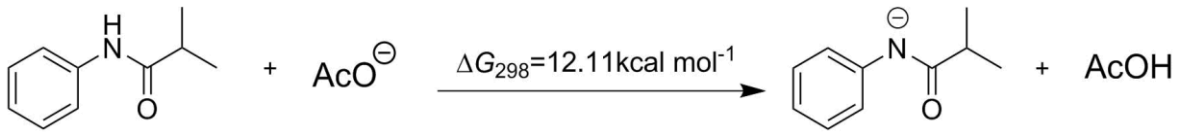


Figure 3-5: Solvent corrected Free Energy Surface (ΔG_{298} kcal mol^{-1}) for the amidation of *N*-phenylisobutyramide with 3-methyl-1,4,2-dioxazol-5-one. Free energies taken relative to the [Cp*Co(III)$(AcO)_2$] pre-catalyst and associated reagents.

In line with the benzamide functionalisation Co(III)-O chelation is observed for the functionalisation of *N*-phenylisobutyramide to furnish **Int1**. This is also in agreement with previous DFT studies for C-H functionalisation of acetanilides.[60] Acid base equilibrium calculations further supported the unlikeliness of Co(III)-N chelation, with a significant energy barrier of 12.11 kcal mol^{-1} being observed for the deprotonation of *N*-phenylisobutyramide (**Scheme 3-11**).



Scheme 3-11: DFT calculated equilibrium for *N*-phenylisobutyramide.

The formation of the 6-membered organometallic cobaltacycle was observed (**Int2)** *via* an energy barrier of 17.8 kcal mol^{-1}. The energy barrier of the C-H activation step is lower by approximately 3.5 kcal mol^{-1} compared to the benzamide C-H activation step. This was surprising when considering the slightly lower yields observed for the C-H amidation reaction when employing *N*-phenylisobutyramides. As the 6-membered ring is formed the distance between the aromatic carbon and the cobalt centre decreases from 3.55 Å (**Int1**) to 1.93 Å (**Int2**) (**Table 3-8**). The C_{sp}^2-H bond is broken, and the proton is abstracted by the acetate group, with the distance between H-$O_{acetate}$ decreasing from 3.47 Å to 1.00 Å.

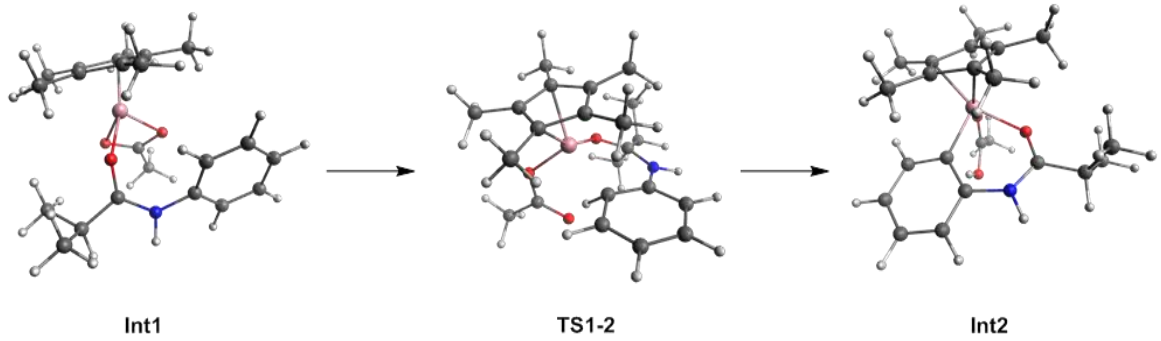


Figure 3-6: Calculated structures for Int1, TS2-3 and Int2.

Table 3-8: **Selected bond lengths (Å), dihedral angles (°) for Int1, TS1-2, Int2**

Atoms	Int1	TS1-2	Int2
Co-C_{sp}^2	3.55	2.07	1.93
H-$O_{acetate}$	3.47	1.37	1.00
C_{sp}^2-H	1.09	1.27	1.92
Co-O-C-N	62.30	2.23	15.96

The computational studies revealed that when employing *N*-phenylisobutyramide, it is not possible to observe the concerted migratory insertion step to form the new C-N bond (**Figure 3-7**). Instead, the migratory insertion takes place stepwise with **Int3.5** being formed as a result of loss of CO_2 from the amidation agent *via* an energy barrier of 23.3 kcal/mol^{-1}. This represents the rate limiting step of the reaction and it is followed by the formation of **Int4** where the C-N bond is formed with a bond length of 1.41 Å (**Table 3-9**). The proto-demetallation step was also explored however, it was not possible to find the optimised structure for **TS4-5**.

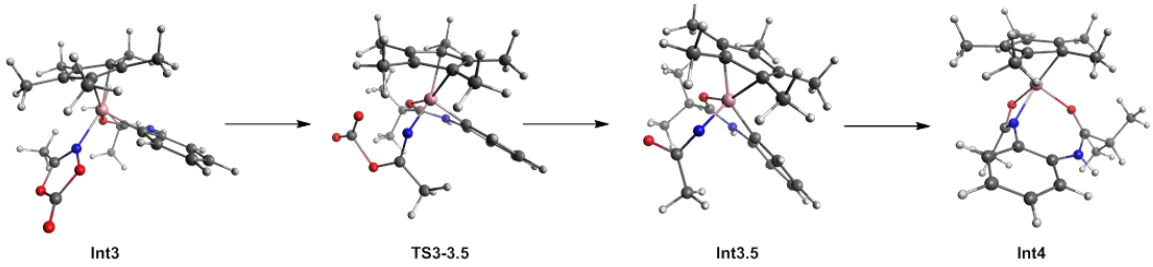
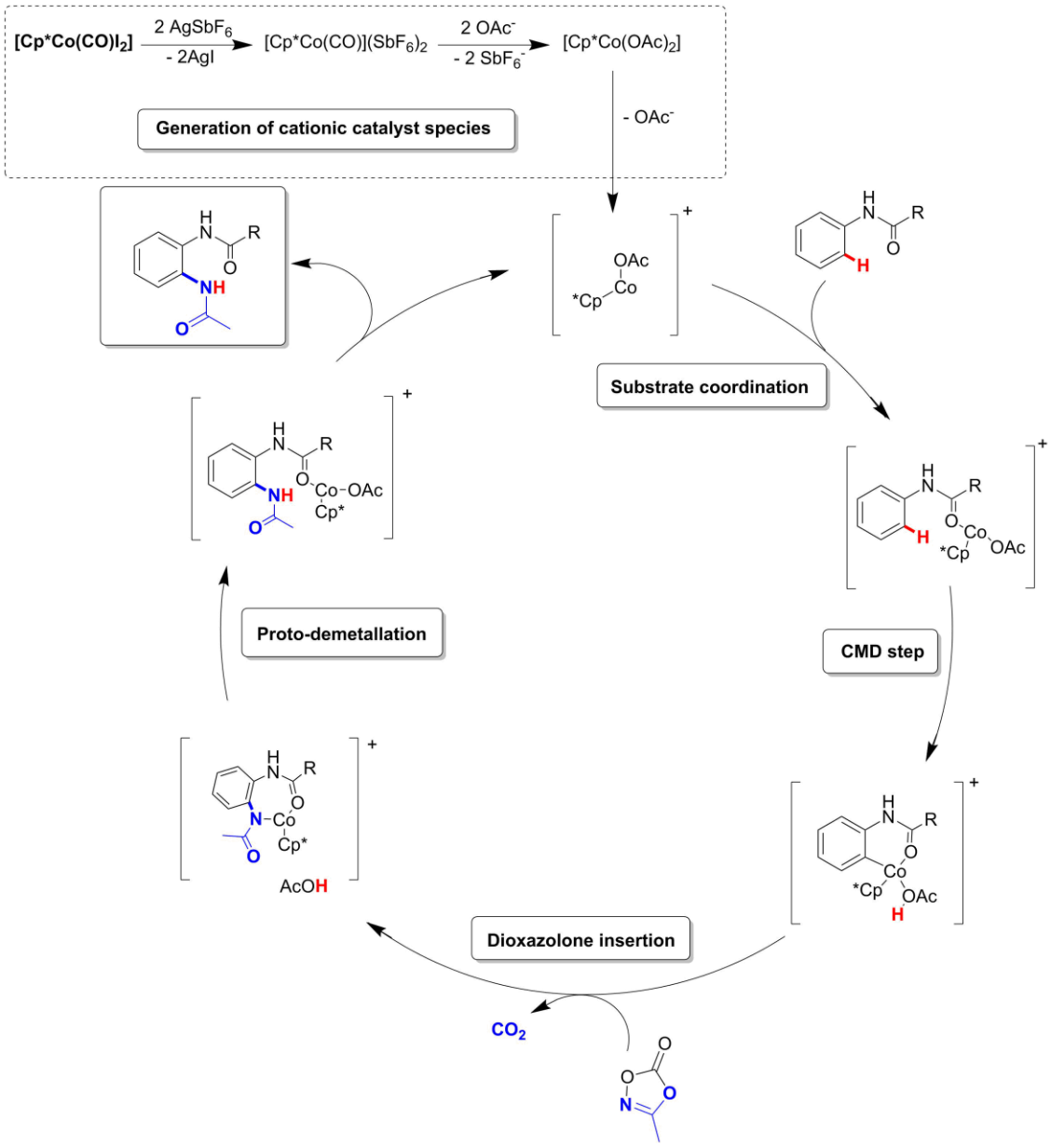


Figure 3-7: Calculated structures for Int3, TS3-3.5, Int3.5 and Int4.

Table 3-9: **Selected bond lengths (Å), dihedral angles (°) for Int3, TS3.5, Int3.5, Int4**

Atoms	Int3	TS3-3.5	Int3.5	Int4
$N\text{-}C_{sp^2}$	2.80	2.77	2.64	1.41
$N\text{-}O_{\text{amid. ag.}}$	1.44	2.10	-	-
$O\text{-}C_{\text{amid. ag.}}$	1.40	1.66	-	-

Scheme 3-12 summarises the proposed catalytic cycle for the formation 2-acetamidophenyl isobutyramide using both the experimental and the DFT results obtained in this study.



Scheme 3-12: Proposed catalytic cycle for Cp*Co(III)-catalysed coupling of 1,4,2-diozaxol-5-ones and phenylisobutyramide for the preparation of 2-acetamidophenyl isobutyramide.

3.3 Summary

In summary, it was possible to apply the Cp*Co(III) C-H amidation protocol developed in **Chapter 2** to phenylisobutyramide substrates however, lower yields were observed compared to isopropyl benzamides. Employing the [Cp^*CoCl_2] dimer resulted in a synthetically useful yield (75%) thus, this optimised procedure

could be successfully applied to a variety of substituted phenylisobutyramides. The synthesis of benzotriazoles was also more challenging, with a mixture of products being observed when of 2-acetamidophenyl isobutyramide was reacted with TBN. The cyclisation reaction was optimised and it was possible to combine the two steps to provide a one-pot sequential protocol for the synthesis of acetylbenzotriazoles, though in lower yields compared to 1,2,3-benzotriazin-4(*3H*)-ones.

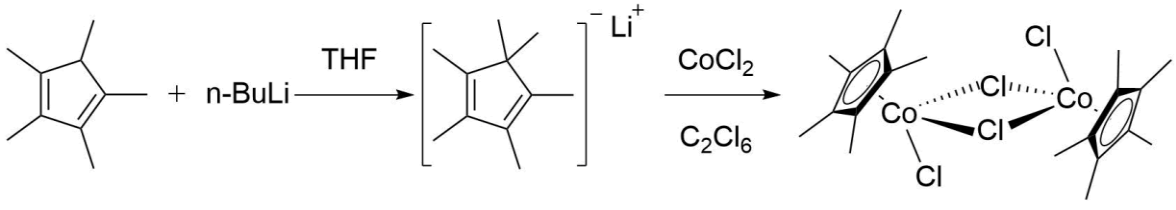
The mechanism by which the Cp*Co(III)-catalysed C−H amidation reaction takes place was studied experimentally and using DFT calculations. The experimental studies revealed that the C-H activation step was reversible and a k_H/k_D value of 3.4 was observed. The KIE value indicates that the C-H activation step could be the rate limiting step however, this in in disagreement with what was observed computationally, where the loss of CO_2 is the rate limiting step.

3.4 Experimental procedures

3.4.1 General experimental considerations

All reagents and solvents were purchased from Sigma Aldrich, Fisher Scientific, Fluorochem and Acros Organics and used without further purification. ^{1}H (400 MHz), ^{13}C {1H} (100 MHz), ^{19}F {1H} (376 MHz) and 2D NMR were recorded on a Bruker AV-400 spectrometer and referenced to the residual deuterated solvent signals. High Resolution Mass Spectra (HRMS) was recorded on a Xevo G2-Xs QTof Mass Spectrometer.

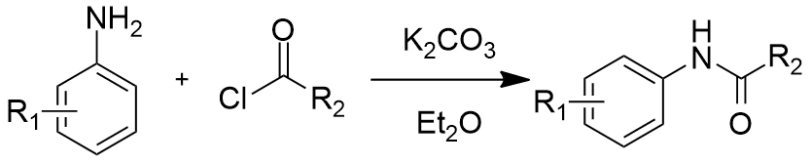
3.4.2 Procedure for the synthesis of the $[Cp^*CoCl_2]_2$ pre-catalyst [25]



Scheme 3-13: Procedure for the synthesis of $[Cp^*CoCl_2]_2$ pre-catalyst.

1,2,3,4,5-Pentamethyl-1,3-cyclopentadiene (1.00 g, 7.3 mmol) and anhydrous tetrahydrofuran (35 mL) were added to an oven dried and previously degassed Schlenk flask. The reaction flask was cooled to −78 °C and *n*-BuLi in hexane (2.5 M, 2.93 mL, 7.3 mmol) was added to the solution slowly. The mixture was stirred for 1.5 h at room temperature to provide a white suspension of pentamethylcyclopentadienyllithium. To the resulting mixture $CoCl_2$ (0.87 g, 6.67 mmol) was added under nitrogen atmosphere. After stirring for 15 min at room temperature, the solvent was removed under vacuum slowly. Hexane was added to the residue (70 mL) and the extracts were filtered using a filter cannula under nitrogen atmosphere. Hexachloroethane (3.17 g, 13.7 mmol) was added to the filtrate and the mixture was stirred for 15 min at room temperature. Green powder was collected by filtration, washed with hexane (100 mL), and then dried under vacuum afford 0.90 g of $[Cp^*CoCl_2]_2$ (25% yield).

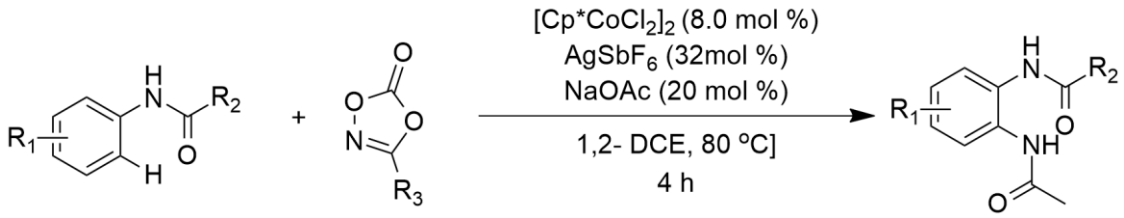
3.4.3 General procedure for synthesis of *N*-phenylisobutyramide substrates



Scheme 3-14: General procedure for synthesis of *N*-phenylisobutyramide substrates.

To a solution of acyl chloride (1.0 equiv.) in diethyl ether (50 mL) was added K_2CO_3 (2.5 equiv.) After the mixture had been cooled in an ice bath, the correspondent aniline (1.5 equiv.) was added. The mixture was stirred for 16 hours at room temperature. After this time, the mixture was diluted with EtOAc (3 x 100 mL) and washed with H_2O (50 mL) then aqueous 1M HCl (1.0 M, 50 mL) three times. The organic phase was dried over $MgSO_4$, filtered and the solvent removed under vacuum. The crude mixture was purified by silica gel column chromatography if necessary, using hexane/EtOAc (1/1) to provide analytically pure *N*-phenylisobutyramides.

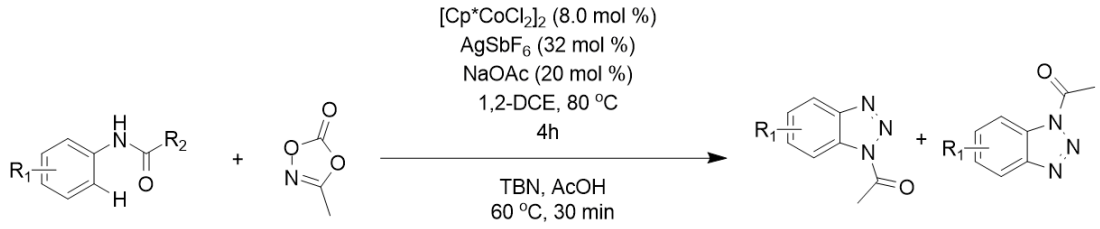
3.4.4 General procedure for Cp*Co(III)-catalysed amidation reactions.



Scheme 3-15: General procedure for Cp*Co(III)-catalysed amidation reactions.

N-phenylisobutyramide substrate (0.25 mmol), $[Cp^*CoCl_2]_2$ (8.0 mol%, 0.02 mmol), $AgSbF_6$ (32 mol%, 0.08 mmol), NaOAc (20 mol%, 0.05 mmol), 1,4,2-dioxazol-5-one (1.2 equiv., 0.3 mmol) and 1,2-DCE (4.0 mL) were added to a 10 mL vial under air. The vial was sealed, and the mixture stirred at 80 °C for 4 hours. Mesitylene (0.25 mmol) was added to the reaction mi and used as internal standard to determine percentage yield of the amidated products by ^{1}H NMR.

3.4.5 General procedure for sequential one pot reaction for synthesis of benzotriazoles

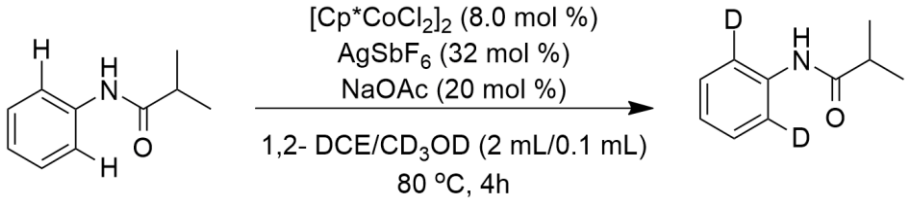


Scheme 3-16: General procedure for sequential one pot reaction for synthesis of benzotriazoles.

N-Phenylisobutyramide (1.5 mmol), $[Cp^*CoCl_2]_2$ (8.0 mol%, 0.12 mmol), $AgSbF_6$ (32 mol%, 0.48 mmol), NaOAc (20 mol%, 0.30 mmol), 3-methyl-1,4,2-dioxazol-5-one (1.2 equiv., 1.8 mmol) and 1,2-DCE (24 mL) were added to a 20 mL vial. The vial was sealed, and the mixture was stirred at 80 °C for 4 hours. After this time, the solvent was evaporated under reduced pressure and TBN (3.0 equiv., 4.5 mmol) and AcOH (3.0 mL- 5 mL) were added to the crude

reaction mixture. The reaction was then stirred at 60 °C for a further 1 hour. The AcOH was then removed under reduced pressure and the crude was purified by silica gen column chromatography using hexane/EtOAc (8/2) as eluent to provide the analytically pure benzotriazoles.

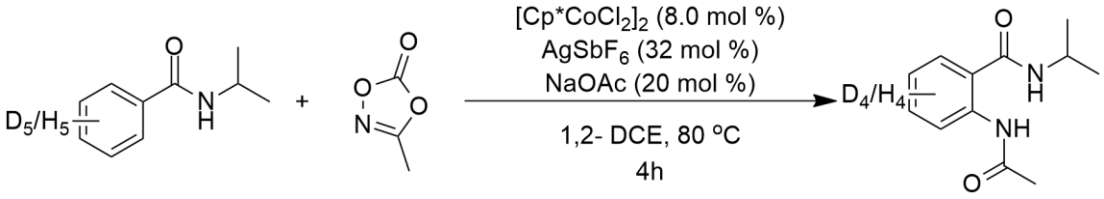
3.4.6 Procedure for deuterium exchange experiment



Scheme 3-17: Procedure for deuterium exchange experiment.

The *N*-phenylisobutyramide substrate (0.25 mmol), $[Cp^*CoCl_2]_2$ (8.0 mol%, 0.02 mmol), $AgSbF_6$ (32 mol%, 0.08 mmol), NaOAc (20 mol%, 0.05 mmol) and 1,2-DCE/CD_3OD (2 mL/0.1 mL) were added to a 10 mL vial. The vial was sealed, and the mixture stirred at 80 °C for 4 hours. After the solvent was reduced under pressure, mesitylene (0.25 mmol) was added to the reaction mixture and used as internal standard for ^1H NMR to determine percentage yield of deuterium incorporated and loss of hydrogen.

3.4.7 Procedure for Kinetic Isotope Effect experiment



Scheme 3-18: Procedure for Kinetic Isotope Effect experiment.

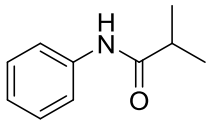
N-phenylisobutyramide substrate (0.25 mmol), $[Cp^*CoCl_2]_2$ (8.0 mol%, 0.02 mmol), $AgSbF_6$ (32 mol%, 0.08 mmol), NaOAc (20 mol%, 0.05 mmol), 1,4,2-dioxazo-5-one (1.2 equiv., 0.3 mmol) and 1,2-DCE (4 mL) were added to a 10 mL vial under air. *N*-phenylisobutyramide-d_5 was simultaneously loaded in a separate vial with the

same reagents and both reactions were stirred at 80 °C for 4 h. After this time, mesitylene (0.25 mmol) was added to the crude and used as internal standard to determine difference between the rate of reaction when using *N*-phenylisobutyramide and *N*-phenylisobutyramide-d_5.

3.5 Characterisation of synthesised compounds

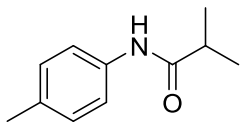
3.5.1 Characterisation of substrates

N-Phenylisobutyramide (29)



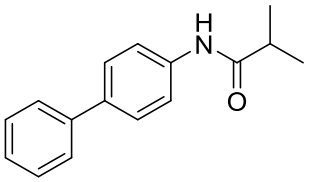
This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from aniline (14.1 mmol) to yield a white amorphous solid (85% yield). **^{1}H NMR ($CDCl_3$, 400 MHz, 298K);** δ: 7.62 (br s, 1H), 7.57 (d, 2H, $^3J_{HH}$ = 7.7 Hz), 7.31 (at, 2H, $^3J_{HH}$ = 7.6 Hz), 7.10 (t, 1H, $^3J_{HH}$ = 7.4 Hz), 2.58-2.51 (m, 1H), 1.25 (d, 6H, $^3J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ:175.6, 138.2, 128.9, 124.1, 119.9, 36.6, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{13}NO+H]^+$: 164.1075; found: 164.1074 . R_f = 0.80 (EtOAc/Hexane 50/50). This characterisation in agreement with previously published data.[191]

N-(*p*-Tolyl)isobutyramide (30)



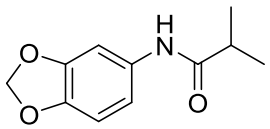
This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from *p*-toluidine (14.1 mmol) to yield a white amorphous solid (73% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.42 (d, 2H, $^3J_{HH}$ = 8.3 Hz), 7.37 (br s, 1H), 7.11 (d, 2H, $^3J_{HH}$ = 8.2 Hz), 2.54-2.47 (m, 1H), 2.32 (s, 3H), 1.25 (d, 6H, $^3J_{HH}$ = 6.8 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.4, 135.5, 133.7, 129.4, 120.0, 36.6, 20.8, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NO+H]^+$: 178.1232; found: 178.1231. R_f = 0.80 (EtOAc/Hexane 50/50). This characterisation in agreement with previously published data.[192]

***N*-([1,1'-Biphenyl]-4-yl)isobutyramide (31)**



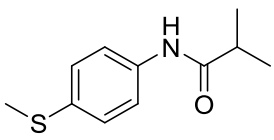
This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from [1,1'-biphenyl]-4-amine (14.1 mmol) to yield a gray amorphous solid (58% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.64 (d, 2H, $^{3}J_{HH}$ = 8.5 Hz), 7.60-7.56 (m, 4H), 7.46-7.42 (m, 3H), 7.35 (t, 1H, $^{3}J_{HH}$ = 7.3 Hz), 2.60-2.53 (m, 1H), 1.30 (d, 6H, $^{3}J_{HH}$ = 6.8 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.5, 140.5, 137.4, 137.0, 128.8, 127.6, 127.1, 126.8, 120.1, 36.7, 19.7. **HR-MS (ASAP, m/z)** calcd. from $[C_{16}H_{17}NO+H]^{+}$: 240.1388; found: 240.1388. R_f = 0.75 (EtOAc/Hexane 50/50).

***N*-(Benzo[d][1,3]dioxol-5-yl)isobutyramide (32)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from benzo[d][1,3]dioxol-5-amine (14.1 mmol) to yield a dark brown amorphous solid (67% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.40 (br s, 1H), 7.25 (d, 1H, $^{4}J_{HH}$ = 2.0 Hz), 6.81 (dd, 1H, $^{3}J_{HH}$ = 8.4 Hz, $^{4}J_{HH}$ = 2.0 Hz), 6.72 (d, 1H, $^{3}J_{HH}$ = 8.3 Hz), 5.93 (s, 2H), 2.53-2.50 (m, 1H), 1.24 (d, 6H, $^{3}J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.0, 147.8, 144.1, 132.3, 113.0, 108.0, 102.9, 101.2, 36.6, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{13}N_3O+H]^{+}$: 208.0974; found: 208.0975. R_f = 0.74 (EtOAc/Hexane 50/50).

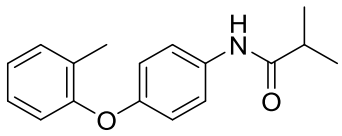
***N*-(4-(Methylthio)phenyl)isobutyramide (33)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 4-(methylthio)aniline (14.1 mmol) to yield a light purple amorphous solid (76% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.49 (d, 2H, $^{3}J_{HH}$ = 8.2 Hz), 7.25 (d, 2H, $^{3}J_{HH}$ = 8.4 Hz), 7.20 (br s, 1H), 2.55-2.50 (m, 1H), 2.48 (s, 3H), 1.27 (d, 6H, $^{3}J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.2, 135.7, 133.3, 128.1, 120.4, 36.7, 19.6,

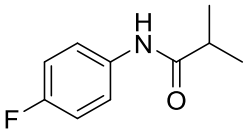
16.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NO_2+H]^+$: 210.0953; found: 210.0951. R_f = 0.81 (EtOAc/Hexane 50/50).

***N*-(4-(*o*-Tolyloxy)phenyl)isobutyramide (34)**



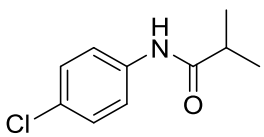
This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 4-(o-tolyloxy)aniline (14.1 mmol) to yield a white amorphous solid (50% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.47 (d, 2H, $^3J_{HH}$ = 8.9 Hz), 7.41 (br s, 1H), 7.25 (d, 1H, $^3J_{HH}$ = 7.2 Hz), 7.16 (at, 1H, $^3J_{HH}$ = 7.7 Hz), 7.06 (at, 1H, $^3J_{HH}$ = 7.3 Hz), 6.88-6.86 (m, 3H), 2.56-2.49 (m, 1H), 2.26 (s, 3H), 1.26 (d, 6H, $^3J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$, 100 MHz);** δ: 175.4, 154.8, 154.2, 132.8, 131.4, 129.7, 127.1, 123.8, 121.7, 119.2, 117.9, 36.5, 19.7, 16.2. **HR-MS (ASAP, m/z)** calcd. from $[C_{17}H_{19}NO_2+H]^+$: 270.1494; found: 270.1490. R_f = 0.75 (EtOAc/Hexane 50/50).

***N*-(4-Fluorophenyl)isobutyramide (35)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 4-fluoroaniline (14.1 mmol) to yield a white amorphous solid (60% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.82 (br s, 1H), 7.48 (dd, 2H, $^3J_{HH}$ = 8.2 Hz, $^4J_{HF}$ = 4.8 Hz), 6.97 (at, 2H, $^3J_{HH}$ = 8.7 Hz, $^3J_{HF}$ = 8.7 Hz), 2.55-2.50 (m, 1H), 1.27 (d, 6H, $^3J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.8, 159.3 (d, $^1J_{CF}$ = 240.3), 134.1 (d, $^4J_{CF}$ = 2.7), 121.9 (d, $^3J_{CF}$ = 7.7), 115.4 (d, $^2J_{CF}$ = 22.3), 36.6, 19.6. **^{19}F NMR ($CDCl_3$);** δ: −118.3. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{12}FNO+H]^+$: 182.0981; found: 182.0983. R_f = 0.60 (EtOAc/Hexane 50/50). This characterisation in agreement with previously published data.[193]

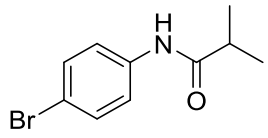
***N*-(4-Chlorophenyl)isobutyramideyl)isobutyramide (36)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 4-chloroaniline (14.1 mmol) to yield a white amorphous solid

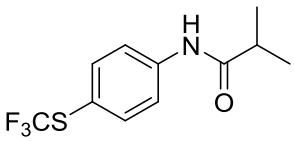
(86% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.50 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 7.42 (br s, 1H), 7.27 (d, 2H, $^3J_{HH}$ = 8.8 Hz), 2.55-2.29 (m, 1H), 1.25 (d, 6H, $^3J_{HH}$ = 6.8 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.5, 136.6, 129.1, 129.0, 121.2, 36.7, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{12}ClNO+H]^+$: 198.0686; found: 198.0685. R_f = 0.80 (EtOAc/Hexane 50/50). This characterisation in agreement with previously published data.[194]

***N*-(4-Bromophenyl)isobutyramide (37)**



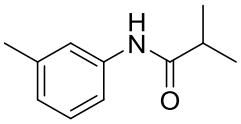
This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 4-bromoaniline (14.1 mmol) to yield a gray amorphous solid (74% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.46-7.40 (m, 5H), 2.55-2.48 (m, 1H), 1.25 (d, 6H, $^3J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.5, 137.1, 131.9, 121.5, 116.7, 36.7, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{12}BrNO+H]^+$: 242.0181; found: 242.0176. R_f = 0.75 (EtOAc/Hexane 50/50). This characterisation in agreement with previously published data.[193]

***N*-(4-((Trifluoromethyl)thio)phenyl)isobutyramide (38)**



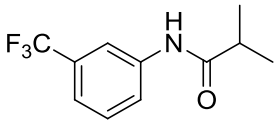
This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 4-((trifluoromethyl)thio)aniline (14.1 mmol) to yield a cream amorphous solid (81% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.65-7.59 (m, 5H), 2.59-2.52 (m, 1H), 1.26 (d, 6H, $^3J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.7, 140.7, 137.5, 129.5 (q, $^1J_{CF}$ = 307.1), 120.3, 118.6, 36.8, 19.5. **^{19}F NMR ($CDCl_3$);** δ: –43.4. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{12}FNOS+H]^+$: 264.0670; found: 264.0680. R_f = 0.87 (EtOAc/Hexane 50/50).

***N*-(*m*-Tolyl)isobutyramide (39)**



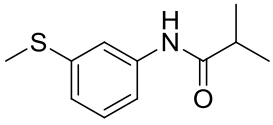
This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from *m*-toluidine (14.1 mmol) to yield a light purple amorphous solid (72% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.74 (br s, 1H), 7.44 (s, 1H), 7.34 (d, 1H, $^{3}J_{HH}$ = 8.1 Hz), 7.18 (at, 1H, $^{3}J_{HH}$ = 7.9 Hz), 6.91 (d, 1H, $^{3}J_{HH}$ = 7.7 Hz), 2.58-2.50 (m, 1H), 2.31 (s, 3H), 1.24 (d, 6H, $^{3}J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.5, 138.8, 138.0, 128.7, 124.9, 120.6, 117.0, 36.6, 21.5, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NO+H]^+$: 178.1232; found: 178.1236. R_f = 0.80 (EtOAc/Hexane 50/50). This characterisation in agreement with previously published data.[195]

***N*-(3-(Trifluoromethyl)phenyl)isobutyramide (40)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 3-(trifluoromethyl)aniline (14.1 mmol) to yield an orange amorphous solid (81% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.07 (br s, 1H), 7.88 (s, 1H), 7.73 (d, 1H, $^{3}J_{HH}$ = 8.0 Hz), 7.39 (at, 1H, $^{3}J_{HH}$ = 7.9 Hz), 7.33 (d, 1H, $^{3}J_{HH}$ = 7.9 Hz), 2.60-2.53 (m, 1H), 1.24 (d, 6H, $^{3}J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 176.3, 138.6, 131.2 (q, $^{2}J_{CF}$ = 32.4 Hz), 129.4, 123.9 (q, $^{1}J_{CF}$ = 273.0 Hz), 123.2, 120.7 (q, $^{3}J_{CF}$ = 3.8 Hz), 116.9 (q, $^{3}J_{CF}$ = 3.8 Hz), 36.5, 19.4. **^{19}F NMR ($CDCl_3$);** δ: –62.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{12}F_3NO+H]^+$: 232.0949; found: 232.0940. R_f = 0.81 (EtOAc/Hexane 50/50).

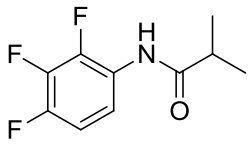
***N*-(3-(Methylthio)phenyl)isobutyramide (41)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 3-(methylthio)aniline (14.1 mmol) to yield a gray amorphous solid (79% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.83 (br s, 1H), 7.60 (s, 1H), 7.24 (d, 1H, $^{3}J_{HH}$ = 8.1 Hz), 7.18 (at, 1H, $^{3}J_{HH}$ = 7.9 Hz), 6.97 (d, 1H, $^{3}J_{HH}$ = 7.7 Hz), 2.56-2.50 (m, 1H), 2.44 (s, 3H), 1.23 (d, 6H, $^{3}J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.9,

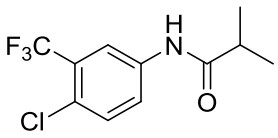
139.4, 138.7, 129.1, 122.1, 117.6, 116.5, 36.6, 19.6, 15.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{15}NOS+H]^+$: 210.0953; found: 210.0961. R_f = 0.73(EtOAc/Hexane 50/50).

***N*-(2,3,4-Trifluorophenyl)isobutyramide (42)**



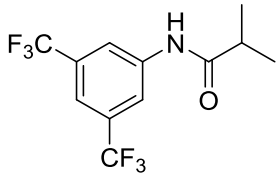
This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 2,3,4-trifluoroaniline (14.1 mmol) to yield a grey amorphous solid (78% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.08-8.01 (m, 1H), 7.26 (br s, 1H), 7.00-6.94 (m, 1H), 2.62-2.55 (m, 1H), 1.29 (d, 6H, $^3J_{HH}$ = 6.8 Hz). **^{19}F NMR ($CDCl_3$);** −140.2 (dd, $^3J_{FF}$ = 21.0 Hz, $^4J_{FF}$ = 3.4 Hz), −150.1 (dd, $^3J_{FF}$ = 20.5 Hz, $^4J_{FF}$ = 2.7 Hz), −160.1 (at, $^3J_{FF}$ = 20.3 Hz). **HR-MS (ASAP, m/z)** calcd. from $[C_{10}H_{10}F_3NO+H]^+$: 218.0793; found: 218.0801. R_f = 0.85 (EtOAc/Hexane 50/50).

***N*-(4-Chloro-3-(trifluoromethyl)phenyl)isobutyramide (43)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 4-chloro-3-(trifluoromethyl)aniline (14.1 mmol) to yield an orange amorphous solid (65% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.79 (d, 1H, $^4J_{HH}$ = 2.6 Hz), 7.65 (dd, 1H, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 2.5 Hz), 7.59 (br s, 1H), 7.43 (d, 1H, $^3J_{HH}$ = 8.8 Hz), 2.49-2.42 (m, 1H), 1.18 (d, 6H, $^3J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.8, 136.9, 131.9, 128.7 (q, $^2J_{CF}$ = 31.5 Hz), 126.7, 123.8, 122.5 (q, $^1J_{CF}$ = 273.5 Hz). 118.9 (q, $^3J_{CF}$ = 5.6 Hz), 36.6, 19.5. **^{9}F {^{1}H} NMR ($CDCl_3$, 376 MHz, 298K);** δ: −62.84 **HR-MS (ASAP, m/z)** calcd. from $[C_{11}H_{11}ClF_3NO+H]^+$: 266.0560; found: 266.0560. R_f = 0.77 (EtOAc/Hexane 50/50).

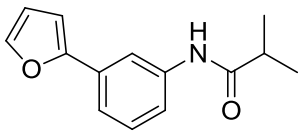
***N*-(3,5-Bis(trifluoromethyl)phenyl)isobutyramide (44)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 3,5-bis(trifluoromethyl)aniline (14.1 mmol) to yield a white amorphous solid (70% yield). **^{1}H NMR ($CDCl_3$, 400 MHz,**

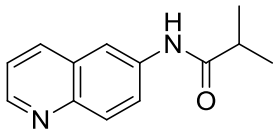
298K); δ: 8.07 (s, 2H), 7.61 (s, 1H), 7.53 (br s, 1H), 2.60-2.53 (m, 1H), 1.30 (d, 6H, $^{3}J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$,);** δ: 175.7, 139.4, 132.3 (q, $^{2}J_{CF}$ = 33.2 Hz), 123.07 (q, $^{1}J_{CF}$ = 272.2 Hz), 119.4, 117.4 (q, $^{3}J_{CF}$ = 3.7 Hz), 36.7, 19.4. **^{19}F NMR ($CDCl_3$);** δ: −63.1. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{11}F_6NO+H]^+$: 300.0823 found: 300.0824. R_f = 0.77 (EtOAc/Hexane 50/50).

***N*-(3-(Furan-2-yl)phenyl)isobutyramide (45)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from 3-(furan-2-yl)aniline (14.1 mmol) to yield a dark orange amorphous solid (66% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.91 (s, 1H), 7.45-7.40 (m, 4H), 7.32 (at, 1H, $^{3}J_{HH}$ = 7.9 Hz), 6.67 (d, 1H, $^{3}J_{HH}$ = 3.2 Hz), 6.47 (dd, 1H, $^{3}J_{HH}$ = 3.2 Hz, $^{4}J_{HH}$ = 1.7 Hz), 2.58-2.51 (m, 1H), 1.27 (d, 6H, $^{3}J_{HH}$ = 6.8 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.5, 153.5, 142.1, 138.5, 131.6, 129.3, 119.6, 118.7, 115.1, 111.7, 105.5, 36.7, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{15}NO_2+H]^+$: 230.1181; found: 230.1169. R_f = 0.80 (EtOAc/Hexane 50/50).

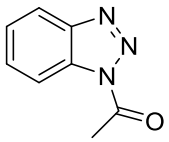
***N*-(Quinolin-6-yl)isobutyramide (46)**



This compound was prepared in accordance to the general synthesis described for *N*-phenylisobutyramide starting from quinolin-6-amine (14.1 mmol) to yield a brown amorphous solid (60% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.85 (dd, 1H, $^{3}J_{HH}$ = 4.2 Hz, $^{4}J_{HH}$ = 1.7 Hz), 8.47 (d, 1H, $^{4}J_{HH}$ = 1.8 Hz), 8.14 (d, 1H, $^{3}J_{HH}$ = 7.7 Hz), 8.07 (d, 1H, $^{3}J_{HH}$ = 8.8 Hz), 7.57 (m, 2H), 7.41 (dd, 1H, $^{3}J_{HH}$ = 8.2 Hz, $^{3}J_{HH}$ = 4.2 Hz), 2.65-2.57 (m, 1H), 1.32 (d, 6H, $^{3}J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 175.7, 149.1, 145.1, 136.2, 136.0, 129.8, 128.9, 123.3, 121.7, 116.0, 36.8, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{14}N_2O+H]^+$: 215.1184; found: 215.1182. R_f = 0.17 (EtOAc/Hexane 50/50). This characterisation in agreement with previously published data.[196]

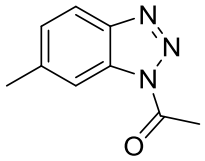
3.5.2 Characterisation of benzotriazoles:

31-(1H-Benzo[d][1,2,3]triazol-1-yl)ethan-1-one (29b-1)



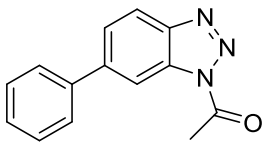
This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-phenylisobutyramide (1.5 mmol) to yield a white amorphous solid (40% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.32 (dd, 1H, $^{3}J_{HH}$ = 8.2 Hz, $^{4}J_{HH}$ = 0.9 Hz), 8.15 (dd, 1H, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HH}$ = 0.9 Hz), 7.69 (ddd, 1H, $^{3}J_{HH}$ = 7.1 Hz, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HH}$ = 1.0 Hz), 7.54 (ddd, 1H, $^{3}J_{HH}$ = 7.16 Hz, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HH}$ = 1.0 Hz), 3.03 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.6, 146.3, 131.0, 130.4, 126.2, 120.2, 114.4, 23.3. **HR-MS (ASAP, m/z)** calcd. from $[C_5H_5N_3+H]^+$: 120.0562; found: 120.0572. Mass observed for the deacetylated product. R_f = 0.60 (EtOAc/Hexane 20/80).

1-(5-Methyl-1H-benzo[d][1,2,3]triazol-1-yl)ethenone (30b)



This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N-(p*-tolyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (33% yield 1:1.2). **^{1}H NMR ($CDCl_3$);** δ: 8.15 (d, 1H, $^{3}J_{HH}$ = 8.5 Hz), 7.88 (d, 1H, $^{4}J_{HH}$ = 0.8 Hz), 7.48 (dd, 1H, $^{3}J_{HH}$ = 8.3 Hz, $^{4}J_{HH}$ = 1.1 Hz), 2.99 (s, 3H), 2.55 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.5, 146.9, 136.4, 132.3, 129.4, 119.3, 113.8, 23.2, 21.5. **HR-MS (ASAP, m/z)** calcd. from $[C_7H_7N_3+H]^+$: 134.0718; found: 134.0720. Mass observed for the deacetylated product. R_f = 0.65 (EtOAc/Hexane 20/80).

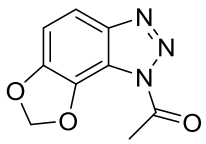
1-(6-Phenyl-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (31b)



This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-([1,1'-biphenyl]-4-yl)isobutyramide (1.5 mmol) to yield a white amorphous solid (33% yield 9:1). **^{1}H NMR ($CDCl_3$);** δ: 8.49 (d, 1H, $^{4}J_{HH}$ = 1.5 Hz), 8.17 (d, 1H, $^{3}J_{HH}$ = 8.6 Hz), 7.77 (dd, 1H, $^{3}J_{HH}$ = 8.6 Hz, $^{4}J_{HH}$ = 1.6 Hz), 7.70-7.68 (m, 2H), 7.53-7.49 (m, 2H), 7.46-7.44 (m, 1H), 3.03 (s, 3H). **^{13}C NMR ($CDCl_3$,**

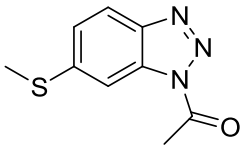
100 MHz, 298K); δ: 169.7, 145.6, 144.2, 140.0, 131.8, 129.0, 128.3, 127.8, 126.3, 120.2, 112.5, 23.3. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_9N_3+H]^+$: 196.0875; found: 196.0874. Mass observed for the deacetylated product. R_f = 0.61 (EtOAc/Hexane 20/80).

1-(1H-[1,3]Dioxolo[4',5':3,4]benzo[1,2-d][1,2,3]triazol-1-yl)ethan-1-one (32b-1)



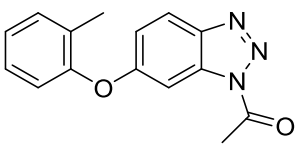
This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(benzo[d][1,3]dioxol-5-yl)isobutyramide (1.5 mmol) to yield a white amorphous solid (27% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.64 (d, 2H, $^3J_{HH}$ = 8.6 Hz), 7.09 (d, 2H, $^3J_{HH}$ = 8.6 Hz), 6.20 (s, 2H), 2.95 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ:167.8, 149.6, 144.6, 131.9, 115.9, 114.0, 109.2, 102.6, 23.0. **HR-MS (ASAP, m/z)** calcd. from $[C_7H_5N_3O_2+H]^+$: 164.0460; found: 164.0464. Mass observed for the deacetylated product. R_f = 0.36 (EtOAc/Hexane 20/80).

1-(6-(Methylthio)-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (33b-1)



This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(4-(methylthio)phenyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (50% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.05 (d, 1H, $^4J_{HH}$ = 1.3 Hz), 7.98 (d, 1H, $^3J_{HH}$ = 8.8 Hz), 7.38 (dd, 1H, $^3J_{HH}$ = 8.7 Hz, $^4J_{HH}$ = 1.7 Hz), 3.00 (s, 3H), 2.62 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ:169.8, 144.2, 144.0, 132.0, 125.1, 119.8, 109.1, 23.3, 15.5. Mass observed for the deacetylated product. **HR-MS (ASAP, m/z)** calcd. from $[C_7H_8N_3S+H]^+$: 166.0439; found: 166.0436. R_f = 0.57 (EtOAc/Hexane 20/80).

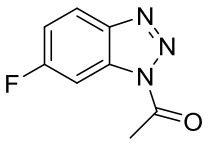
1-(6-(*o*-Tolyloxy)-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (34b-1)



This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(4-(o-tolyloxy)phenyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (55% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.02 (d, 1H, $^3J_{HH}$ = 9.0

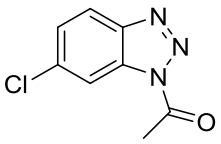
Hz), 7.59 (d, 1H, $^4J_{HH}$ = 2.2 Hz), 7.30 (d, 1H, $^3J_{HH}$ = 7.0 Hz), 7.24 (ddd, 1H, $^3J_{HH}$ = 7.7 Hz, $^3J_{HH}$ = 7.5 Hz, $^4J_{HH}$ = 1.7 Hz), 7.19-7.14 (m, 2H), 6.99 (dd, 1H, $^3J_{HH}$ = 7.9 Hz, $^4J_{HH}$ = 1.2 Hz), 2.94 (s, 3H), 2.21 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.6, 160.7, 153.3, 142.1, 132.3, 131.9, 130.3, 127.6, 125.4, 121.1, 120.6, 117.7, 100.3, 23.2, 16.1. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{11}N_3O+H]^+$: 226.0980; found: 226.0982. Mass observed for the deacetylated product. R_f = 0.61(EtOAc/Hexane 20/80).

1-(6-Fluoro-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (35b-1)



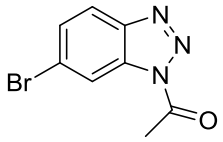
This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(4-fluorophenyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (23% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.00 (dd, 1H, $^3J_{HH}$ = 9.0 Hz, $^4J_{HF}$ = 4.6 Hz), 7.88 (dd, 1H, $^3J_{HF}$ = 8.1 Hz, $^4J_{HH}$ = 2.2 Hz), 7.19 (ddd, 1H, $^3J_{HH}$ = 9.0 Hz, $^3J_{HF}$ = 9.0 Hz, $^4J_{HH}$ = 2.4 Hz), 2.92 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.4, 163.9 (d, $^1J_{CF}$ = 240.3 Hz), 142.9, 131.7 (d, $^3J_{CF}$ = 14.8 Hz), 121.6 (d, $^3J_{CF}$ = 11.2 Hz), 115.7 (d, $^2J_{CF}$ = 26.8 Hz), 101.0 (d, $^2J_{CF}$ = 29.3 Hz), 23.1. **^{9}F NMR ($CDCl_3$);** δ: −107.4. **HR-MS (ASAP, m/z)** calcd. from $[C_6H_4FN_3+H]^+$: 138.0468; found: 138.0480. Mass observed for the deacetylated product. R_f = 0.60 (EtOAc/Hexane 20/80).

1-(6-Chloro-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (36b-1)



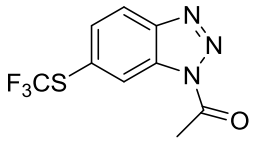
This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(4-chlorophenyl)isobutyramideyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (40% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.31 (d, 1H, $^4J_{HH}$ = 1.6 Hz), 8.04 (d, 1H, $^3J_{HH}$ = 8.8 Hz), 7.49 (dd, 1H, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.9 Hz), 3.00 (s, 3H). **^{13}C {^{1}H} NMR ($CDCl_3$);** δ: 169.3, 144.8, 137.1, 131.6, 127.3, 121.0, 114.4, 23.2. **HR-MS (ASAP, m/z)** calcd. from $[C_6H_4ClN_3+H]^+$: 154.0172; found: 154.0177. Mass observed for the deacetylated product. R_f = 0.64 (EtOAc/Hexane 20/80).

1-(6-Bromo-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (37b)



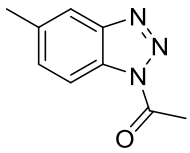
This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-4-bromophenyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (33% yield 9:1). **^{1}H NMR ($CDCl_3$);** δ: 8.41 (d, 1H, $^{4}J_{HH}$ = 1.2 Hz), 7.90 (d, 1H, $^{3}J_{HH}$ = 8.8 Hz), 7.55 (dd, 1H, $^{3}J_{HH}$ = 8.7 Hz, $^{4}J_{HH}$ = 1.7 Hz), 2.92 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.3, 145.1, 131.9, 129.9, 125.2, 121.2, 117.5, 23.2. **HR-MS (ASAP, m/z)** calcd. from $[C_6H_4BrN_3+H]^+$: 197.9667; found: 197.9669. Mass observed for the deacetylated product. R_f = 0.64 (EtOAc/Hexane 20/80).

1-(6-((Trifluoromethyl)thio)-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (38b)



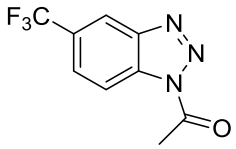
This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(4-((trifluoromethyl)thio)phenyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (25% yield 5.3:1). **^{1}H NMR ($CDCl_3$);** δ: 8.58 (d, 1H, $^{4}J_{HH}$ = 1.0 Hz), 8.10 (d, 1H, $^{3}J_{HH}$ = 8.6 Hz), 7.70 (dd, 1H, $^{3}J_{HH}$ = 8.6 Hz, $^{4}J_{HH}$ = 1.2 Hz), 2.95 (s, 3H). **^{13}C NMR ($CDCl_3$,);** δ: 169.3, 147.0, 133.2, 131.2, 129.2 ($^{1}J_{CF}$ = 309.0 Hz), 127.5, 122.5, 120.9, 23.2. **^{19}F NMR ($CDCl_3$);** δ: –63.106. **HR-MS (ASAP, m/z)** calcd. from $[C_7H_4F_3N_3S+H]^+$: 220.0156; found: 220.0166. Mass observed for the deacetylated product. R_f = 0.67 (EtOAc/Hexane 20/80).

1-(5-Methyl-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (39b)



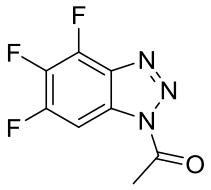
This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(*m*-tolyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (31% yield 1:1.9). **^{1}H NMR ($CDCl_3$);** δ: 8.08 (d, 1H, $^{4}J_{HH}$ = 1.4 Hz), 7.98 (d, 1H, $^{3}J_{HH}$ = 8.4 Hz), 7.33 (dd, 1H, $^{3}J_{HH}$ = 8.4 Hz, $^{4}J_{HH}$ = 1.1 Hz), 2.99 (s, 3H), 2.57 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.7, 144.9, 132.3, 131.4, 128.1, 119.5, 113.9, 23.3, 22.1. **HR-MS (ASAP, m/z)** calcd. from $[C_7H_7N_3+H]^+$: 134.0718; found: 137.0724. Mass observed for the deacetylated product. R_f = 0.64(EtOAc/Hexane 20/80).

1-(5-(Trifluoromethyl)-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (40b)



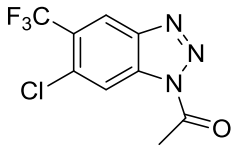
This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(3-(trifluoromethyl)phenyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (23% 8.1:1). **^{1}H NMR ($CDCl_3$);** δ: 8.36-8.34 (m, 2H), 7.82 (dd, 1H, $^{3}J_{HH}$ = 8.4 Hz, $^{4}J_{HH}$ = 1.4 Hz), 2.96 (s, 3H). **^{13}C NMR ($CDCl_3$, 100 MHz, 298K);** δ: 169.4, 145.6, 132.6, 128.9 (q, $^{2}J_{CF}$ = 33.2 Hz), 127.12 (q, $^{3}J_{CF}$ = 3.07 Hz), 123.6 (q, $^{1}J_{CF}$ = 272.3 Hz), 118.2 (q, $^{3}J_{CF}$ = 4.3 Hz), 115.4 (q, $^{3}J_{CF}$ = 3.8 Hz), 23.2. **^{19}F NMR ($CDCl_3$);** δ: −61.7. **HR-MS (ASAP, m/z)** calcd. from $[C_7H_4F_3N_3+H]^+$: 188.0436; found: 188.0447. Mass observed for the deacetylated product. R_f = 0.67 (EtOAc/Hexane 20/80).

1-(4,5,6-Trifluoro-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one (41b-1)



This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(2,3,4-trifluorophenyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (11% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.00-7.96 (m, 1H), 3.03 (s, 3H). **^{19}F NMR ($CDCl_3$);** −124.7 (dd, $^{3}J_{FF}$ = 20.2- Hz, $^{4}J_{FF}$ = 8.9 Hz), −142.6 (dd, $^{3}J_{FF}$ = 19.1 Hz, $^{4}J_{FF}$ = 8.2 Hz), −160.1 (t, $^{3}J_{FF}$ = 20.1 Hz). **HR-MS (ASAP, m/z)** calcd. from $[C_6H_2F_3N_3+H]^+$: 174.0279; found: 174.0288. Mass observed for the deacetylated product. R_f = 0.64 (EtOAc/Hexane 20/80).

1-(6-Chloro-5-(trifluoromethyl)-1H-benzo[d][1,2,3]triazol-1-yl)ethan-1-one



(42b-1) This compound was prepared in accordance to the general one pot synthesis described for benzotriazoles starting from *N*-(4-chloro-3-(trifluoromethyl)phenyl)isobutyramide (1.5 mmol) to yield a white amorphous solid (15% yield). **^{1}H NMR ($CDCl_3$);** δ: 8.50 (s, 1H), 8.48 (s, 1H), 3.03 (s, 3H). **^{13}C NMR ($CDCl_3$);** δ: 169.1, 143.8, 134.6, 132.7, 126.9 (q, $^{2}J_{CF}$ = 32.6 Hz), 122.3 (q, $^{1}J_{CF}$ = 273.5 Hz), 120.2 (q, $^{3}J_{CF}$ = 6.0 Hz, 117.4, 23.13. **^{19}F NMR ($CDCl_3$);** −140.2. **HR-MS (ASAP, m/z)** calcd.

from $[C_7H_3ClF_3N_3+H]^+$: 222.0046; found: 222.0050. Mass observed for the deacetylated product. R_f = 0.64 (EtOAc/Hexane 20/80).

Chapter 4. Cp*Co(III)-catalysed C-H Bond Amidation of Acrylamides

4.1 Introduction

Cp*Co(III) catalysed C-H functionalisation has emerged as a remarkable, straightforward tool for the formation of novel C-C or C-heteroatom bonds, offering a more environmentally friendly and economical approach to traditional cross coupling reactions. Over the past few years several protocols have been reported which employ DG-assisted Cp*Co(III) C-H functionalisation using a variety of substrates as discussed in **Chapter 1**.[7,32] However, most protocols focus on aryl C-H activation with only a few examples of alkenyl C-H activation reactions being described.

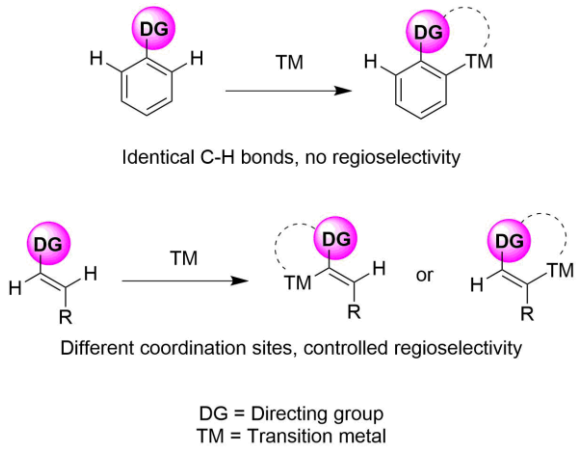


Figure 4-1: Contrast between aryl and alkenyl C-H functionalisation.

This is due to the strong π-coordinating properties of olefinic compounds to metals which could inhibit the C-H activation step and different potential coordination sites (**Figure 4-1**). Furthermore, side reactions are more common when using olefins particularly Diels–Alder or cyclopropanation reactions.[197] However, alkene

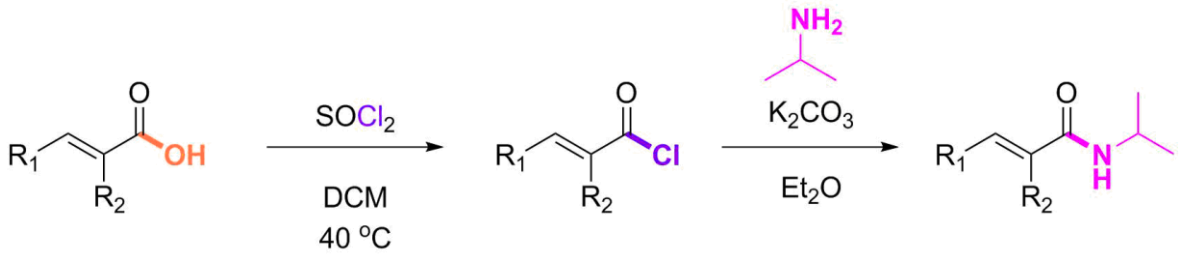
derivatives are highly desirable in material sciences and pharmaceuticals. Particularly, building new C-N bonds using olefinic compounds is of interest as a vast number of nitrogen-based compounds have demonstrated biological activities.[121] A few examples of Cp*Co(III)-catalysed alkenyl C-N bond formation methodologies were discussed in **Chapter 1** reported by the groups of Ellman ,[97] Jia/Li[88] and Matsunaga/Yoshino,[62] all of which employed 1,4,2-dioxazol-5-ones as amidation partners for the amidation of thiostreptoon, enamides and Weinreb amieds respectively.

In this chapter it was possible to expand the Cp*Co(III) C-H amidation protocol developed previously to *N*-isopropylmethacrylamides substrates, although the synthesis of these substrates was more challenging. Furthermore, the reaction mechanism was investigated using DFT calculations with emphasis on the C-H activation step.

4.2 Results and discussion

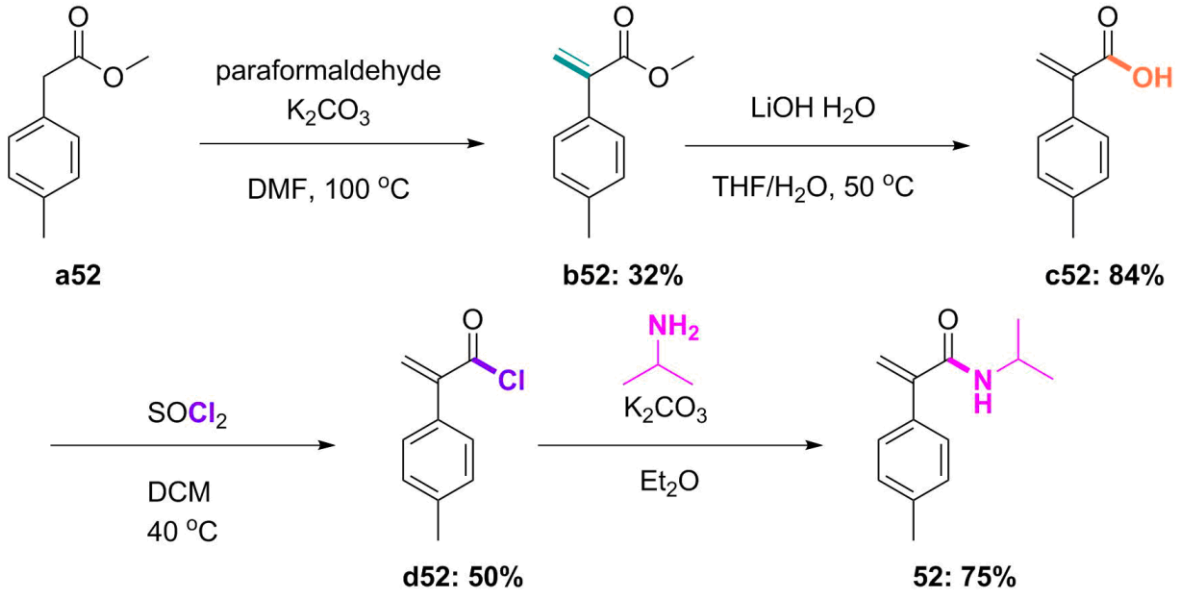
4.2.1 Synthetic pathways for the preparation of substrates

The studies were initiated with the synthesis of a library of acrylamide substrates. Compared with the benzamides, synthesising a vast library of acrylamides was more challenging due to poor availability of the corresponding acyl chloride starting materials. Most substrates were as a result prepared by a two-step procedure (**Scheme 4-1**) starting from acrylic acids, which converted to the corresponding acyl chloride through reaction with thionyl chloride under reflux. The acyl chlorides were thereafter converted into amides following the procedures described in **Chapter 2** for synthesis of the benzamide substrates.



Scheme 4-1: Synthetic pathway for the preparation of acrylamides starting from acrylic acids.

As a result of generally low commercial availability of acrylic acids, in some cases it was necessary to develop a new synthetic pathway in order to expand the variation of substrates available for the scope of the C-H amidation reaction. A four step synthetic pathway was developed for the synthesis of isopropyl-2-(*p*-tolyl)acrylamide (**52**) starting from 2-(*p*-tolyl)acetate (**a52**).[198]



Scheme 4-2: First synthetic pathway developed for the preparation of isopropyl-2-(*p*-tolyl)acrylamide (**52**) starting from methyl 2-(*p*-tolyl)acetate.

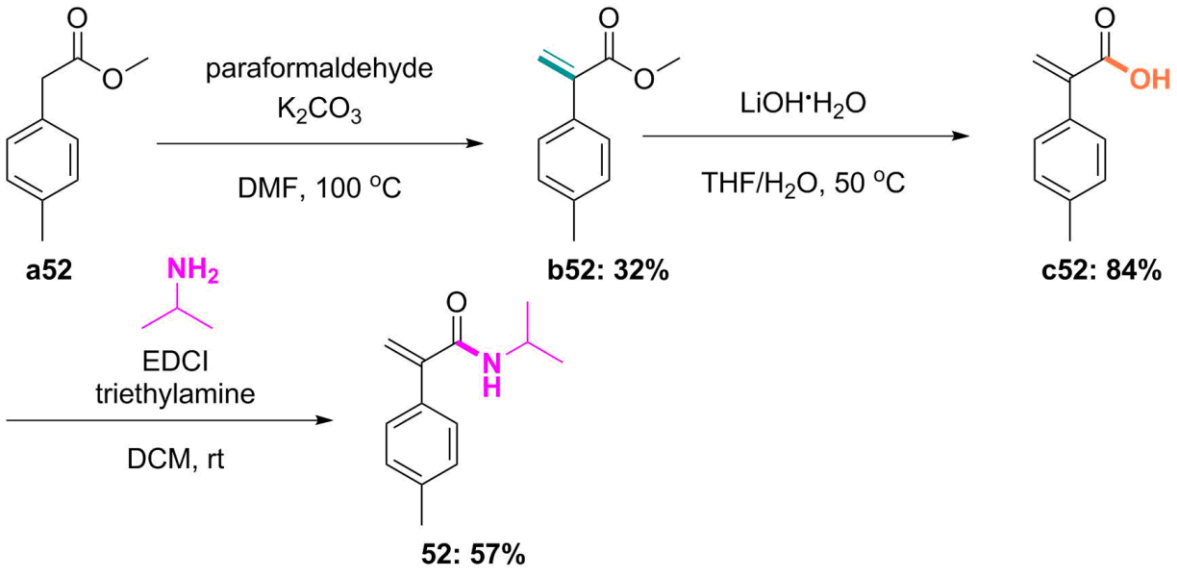
The alkene moiety (**b52**) was added by reacting the ester with paraformaldehyde. However, the generated yield for the desired methyl-2-(*p*-tolyl) acrylate was low (32%). In an interest to increase the yield of this reaction, temperature was optimised however, this was unsuccessful with no increase in yield being observed regardless of temperature of reaction (**Table 4-1**). Furthermore, reactivity was also

not improved when formaldehyde along with a phase transfer catalyst (tetrabutylammonium bisulfate) was employed.

Table 4-1: Optimisation of temperature for the synthesis of methyl 2-(*p*-tolyl)acrylate (b52) [a]

Entry	Temp. [°C]	b52 [%]
1	60	25
2	80	30
3	100	32
4	120	30

General conditions: 7.0 mmol **a52**, 1.5 equiv. paraformaldehyde, 7.0 mmol K_2CO_3, 5.0 mL DMF, 16 hours.



Scheme 4-3: Final synthetic pathway developed for the preparation of isopropyl-2-(*p*-tolyl)acrylamide (**52**) starting from methyl 2-(*p*-tolyl)acetate (**a52**).

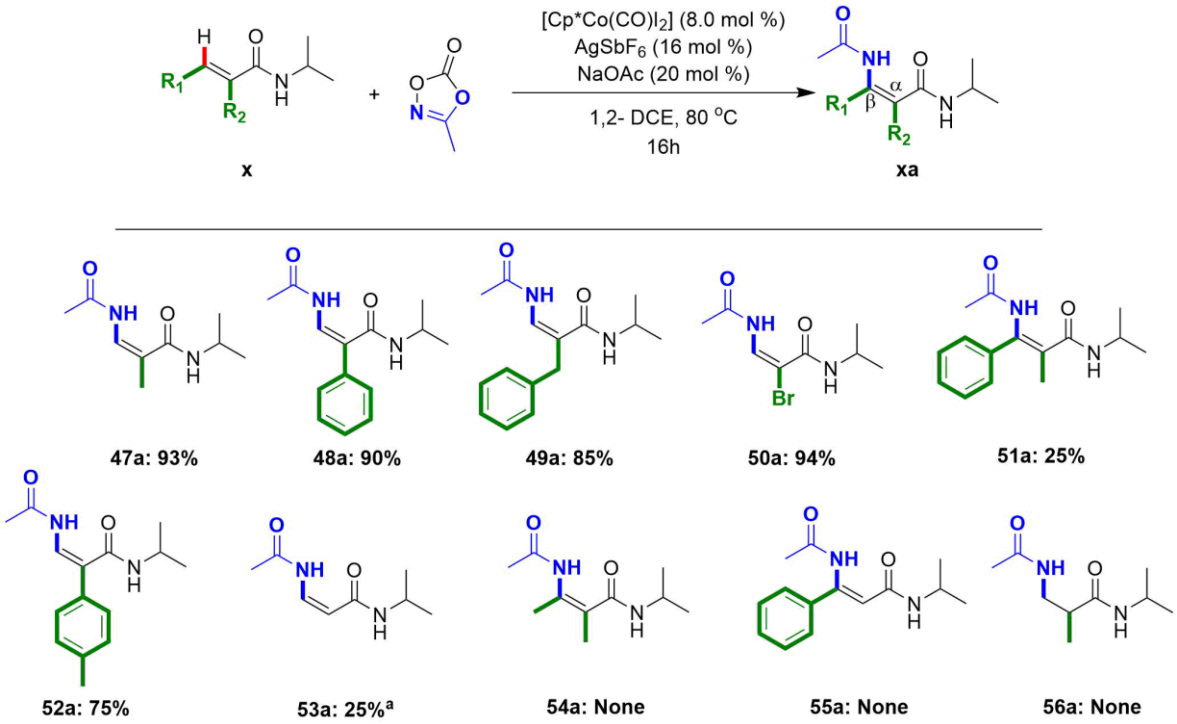
As a consequence of the low yields obtained from the first (32%) and third step (50%) of the synthetic pathway to synthesise **b52** and **d52** respectively, the overall yield obtained for the *N*-isopropyl-2-(*p*-tolyl)acrylamide (**52**) was only 9% (**Scheme 4-3**). This could be slightly increased to 15% by directly converting the acrylic acid

into the acrylamide using EDCI, thus removing the potentially unselective reaction with thionyl chloride (**Scheme 4-3**).

4.2.2 Substrate scope for the Cp*Co(III)-catalysed C-H bond amidation reaction

With a library of substrates in hand, the previously optimised conditions for the benzamides were tested to functionalise *N*-isopropylmethacrylamide (**Scheme 4-4**; **47)**. An excellent yield of 93% was observed, thus no further optimisation studies were performed.

The developed protocol was further applied to several substituted acryalamides in order to test the limitations of the reaction (**Scheme 4-4**). Acrylamides with substituents at the α-position afforded good to excellent yields for all substituents (**48, 49** and **52**). Electron-withdrawing substituents at the α-position also had a positive effect; high yields were observed for the bromo-substituted substrate (**50**). However, substituents at the β−position were not well tolerated. The presence of substituents at the β−position completely hinders reactivity, as is observed for **54** and **55**. Furthermore, the only substrate with a substituent at the β−position that could be converted, albeit in low yield was **51**. This is likely due to the resonance effect of the phenyl substituent. The absence of a methyl substituent at the α-position significantly decreased the reactivity **53** could only be converted in 25% yield. No product was observed when an aliphatic substrate was employed (**56**).



Scheme 4-4: Substrate scope studying the effect of variation in substituents on the *N*-isopropylmethacrylamide under the optimisd reaction conditions; Isolated yields reported. General conditions: 1.5 mmol benzamide substrate, 8.0 mol% $[Cp^*Co(CO)I_2]$, 16 mol% $AgSbF_6$, 20 mol% NaOAc, 1.2 equiv. 3-methyl-1,4,2-dioxazol-5-one, 24 mL 1,2-DCE, 80 °C, 4 hours. [a] Yields of **53a** calculated from ^1H NMR using mesitylene as internal standard due to difficulty in purification.

4.2.3 Mechanistic investigations

In addition to the experimental results, to gain an in-depth insight into the mechanism of formation for the new C-N bond and to understand better the effect of the substitutes at the β−position DFT calculations were carried out (**Figure 4-2**). The cationic unsaturated active catalyst $[Cp^*Co(OAc)]^+$ is formed as a result of dissociation of the acetate anion. The isopropylmethacrylamide coordinates to the cobalt centre through pair of the oxygen resulting in **Int1**. This is in agreement with previous DFT study for **Chapter 2** and **Chapter 3**.

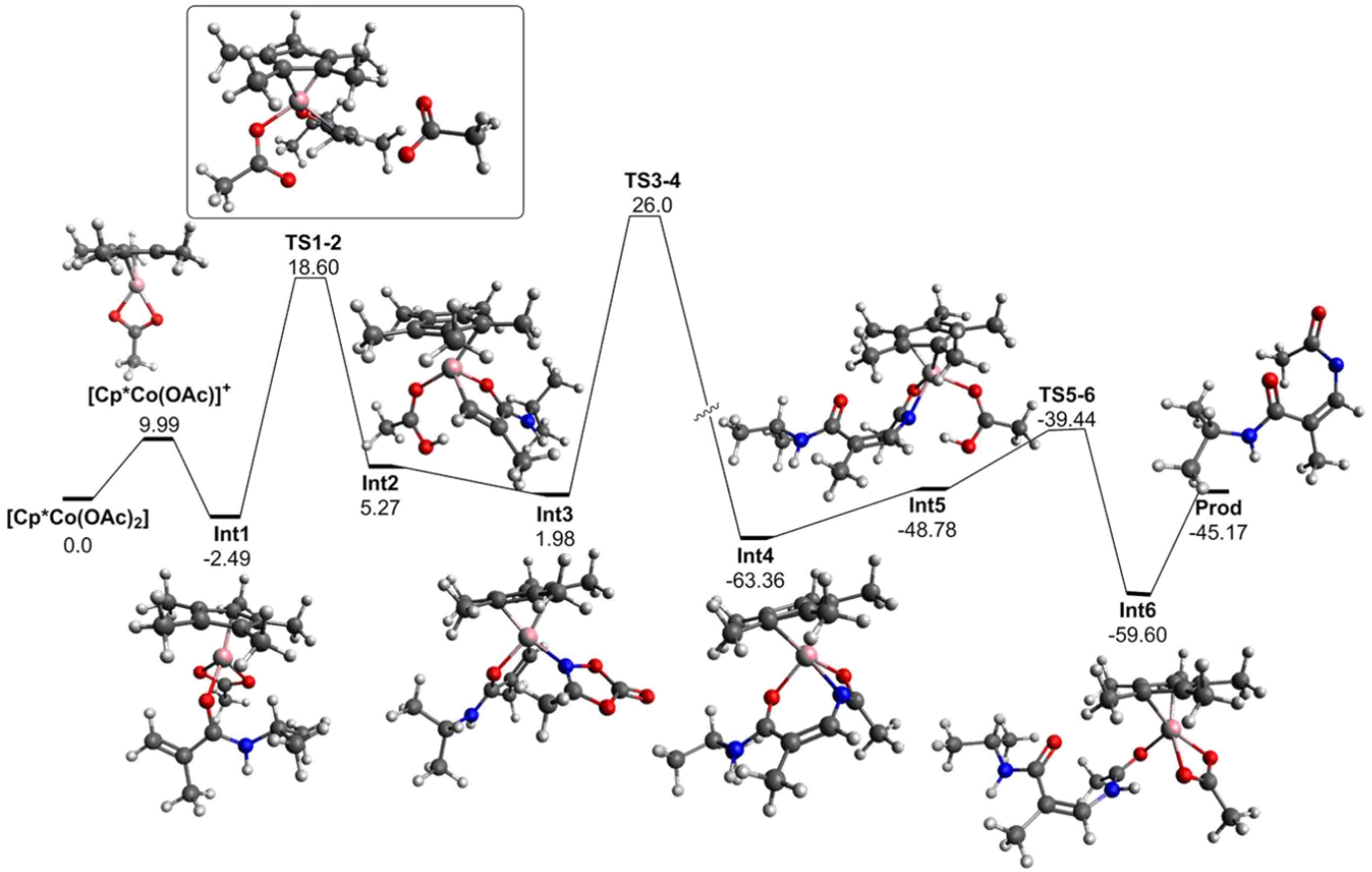


Figure 4-2: Solvent corrected Free Energy Surface (ΔG_{298} kcal mol^{-1}) for the amidation of *N*-isopropylmethacrylamide with 3-methyl-1,4,2-dioxazol-5-one. Free energies taken relative to the [Cp*Co(III)$(AcO)_2$] pre-catalyst and associated reagents.

Subsequently, the 5 membered cobaltacycle (**Int2**) is formed *via* an energy barrier of 20.9 kcal mol^{-1}. The observed energy barrier for this step is similar to the one observed when employing benzamides as substrates. However, formation of the 5 membered cobaltacycle was not possible without the presence of an external base which possibly interacts with one of the hydrogens of the alkene, thus making the remaining more acidic and reactive. This could explain the loss of activity when substrates with substituents at the β-position are employed as the interaction with the external acetate is no longer possible. With the formation of the 5 membered ring a loss in the distance between the cobalt centre and the sp^2 carbon is observed from 4.22 Å (**Int1**) to 1.90 Å (**Int2**) (**Table 4-2**). The $C_{sp}{}^2$-H bond is cleaved, and the proton is abstracted by the acetate group coordinated to the cobalt centre.

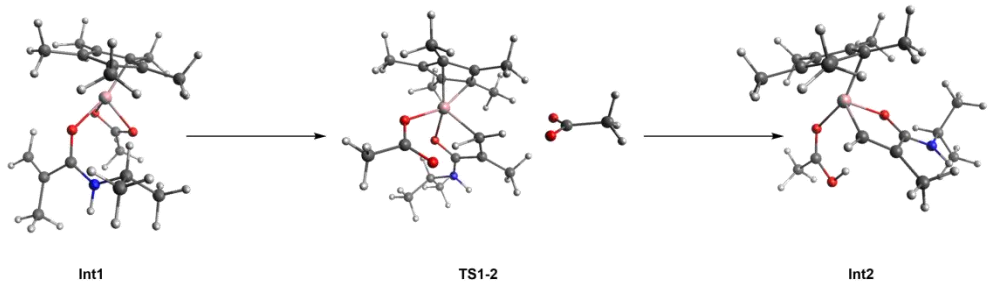


Figure 4-3: Calculated structures for **Int1**, **TS1-2** and **Int2**

Table 4-2: Selected bond lengths (Å), dihedral angles (°) for Int1, TS1-2, and Int2

Atoms	Int1	TS1-2	Int2
Co-$C_{sp}{}^2$	4.22	2.01	1.90
H-$O_{acetate}$	2.95	1.35	1.00
$C_{sp}{}^2$-H	1.09	1.30	1.93
Co-O-C-N	60.26	-173.3	-177.1
H-$O_{ext.acetate}$	-	1.90	-

After the amidation agent coordinates to the cobalt centre to afford **Int3**, the migratory insertion step take place to furnish **Int4** *via* a comparable energy barrier

with the one observed for the benzamide substrate of 24.02 kcal mol^{-1} (**Figure 4-4**).

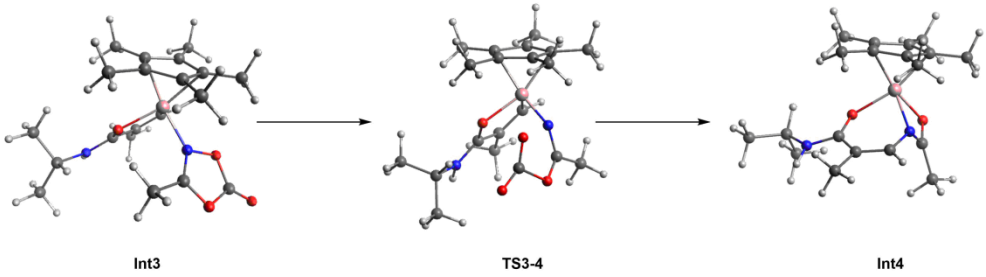


Figure 4-4: Calculated structures for **Int3**, **TS3-4** and **Int4**

Table 4-3: Selected bond lengths (Å), angles (°) and dihedral angles (°) for Int3, TS3-4, and Int4

Atoms	Int3	TS3-4	Int4
N-C_{sp^2}	2.71	2.77	1.39
N-$O_{amid.\ ag.}$	1.45	2.10	-
O-$C_{amid.\ ag.}$	1.40	1.69	-
$O_{amid.\ ag.}$-$N_{amid.\ ag.}$-Co-C_{sp^2}	51.76	-136.55	-
$N_{amid.\ ag.}$-Co-C_{sp^2}	91.08	97.70	22.39

The six membered ring formed as the result of the migratory insertion step is broken followed by the addition of an acetic acid to the cobalt centre to afford **Int5**. The newly installed amide group is protonated (**Int6**) with an energy barrier of 9.34 kcal mol^{-1} (**Figure 4-5**).

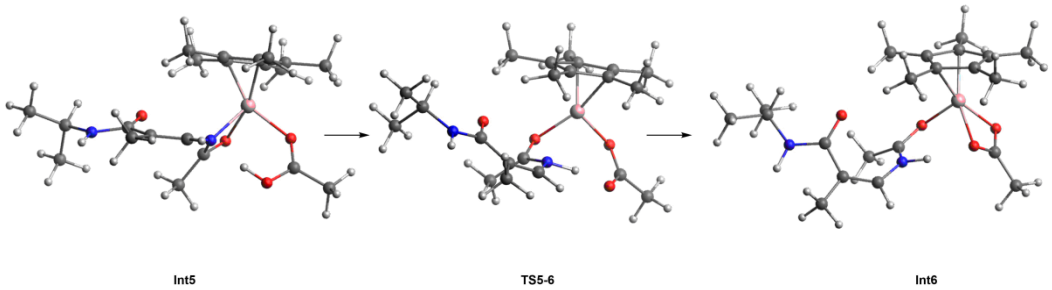


Figure 4-5: Calculated structures for **Int5**, **TS5-6** and **Int6**

Table 4-4: Selected bond lengths (Å), angles (°) and dihedral angles (°) for Int5, TS5-6 and Int6

Atoms	Int5	TS5-6	Int6
N-$H_{acetate}$	1.65	1.12	1.03
N-Co	2.04	2.58	3.20
Co-O	4.53	-	-
N-O-Co-$O_{acetate}$	96.36	92.71	40.40

The loss of reactivity when substrates with substituents at the β-position were employed was also studied *via* DFT calculations. The methyl substituted substrate (**55**) was used to investigate the effect of a substituent at the β-position on the C-H activation step (**Figure 4-6**). The energy barrier observed for this step was 2.2 kcal mol^{-1} higher than the related α-substituted substrate. However, this energy difference is no significant enough to account for the difference in reactivity observed experimentally.

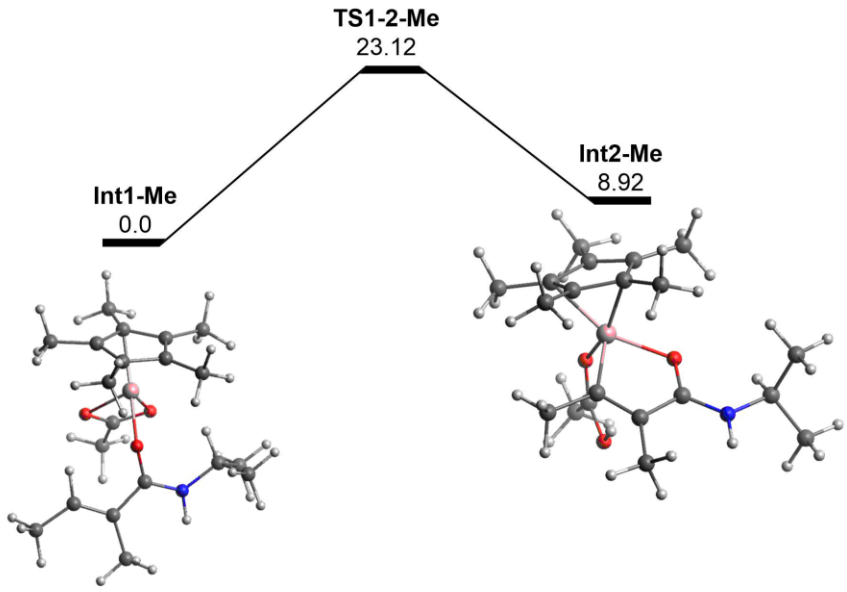


Figure 4-6: Solvent corrected Free Energy Surface (ΔG_{298} kcal mol^{-1}) for **Int1-Me**, **TS1-2-Me** and **Int2-Me** the amidation of *N*-isopropyl-2-methylbut-2-enamide with 3-methyl-1,4,2-dioxazo-5-one. Free energies taken relative to **Int1** and associated reagents.

Substituting the methyl group at the β-position with the highly electron withdrawing CF_3 group reduces the energy barrier of the C-H activation step significantly, to 14.84 kcal mol^{-1} (**Figure 4-7**). The presence of the CF_3 group increases the acidity of the adjacent proton and thus its reactivity. Although the observed computational results are not in complete agreement with the experimental results some evidence was observed which suggests that the interaction between an external acetate group and the geminal proton is necessary for the C-H activation reaction to take place. Further investigations of later steps, particularly the migratory insertion step could potentially elucidate the limits of the mechanism.

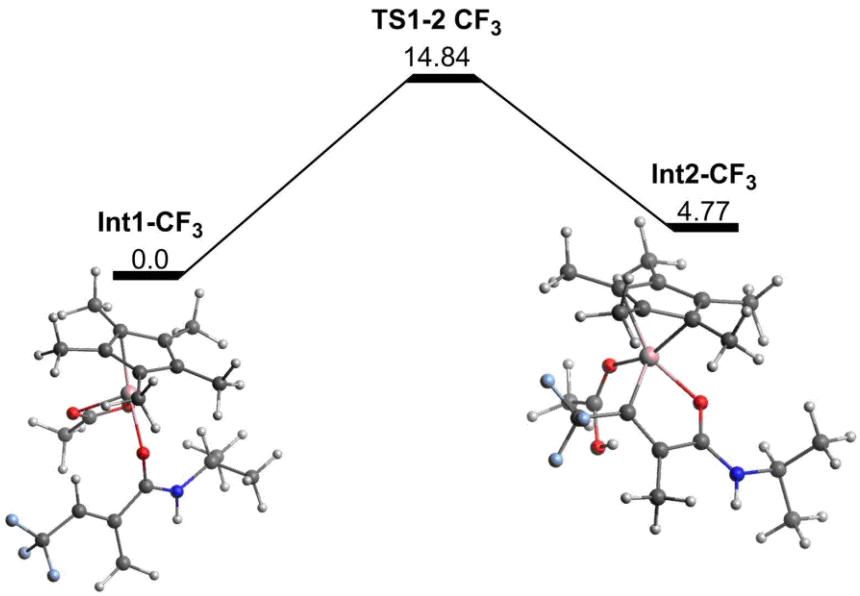
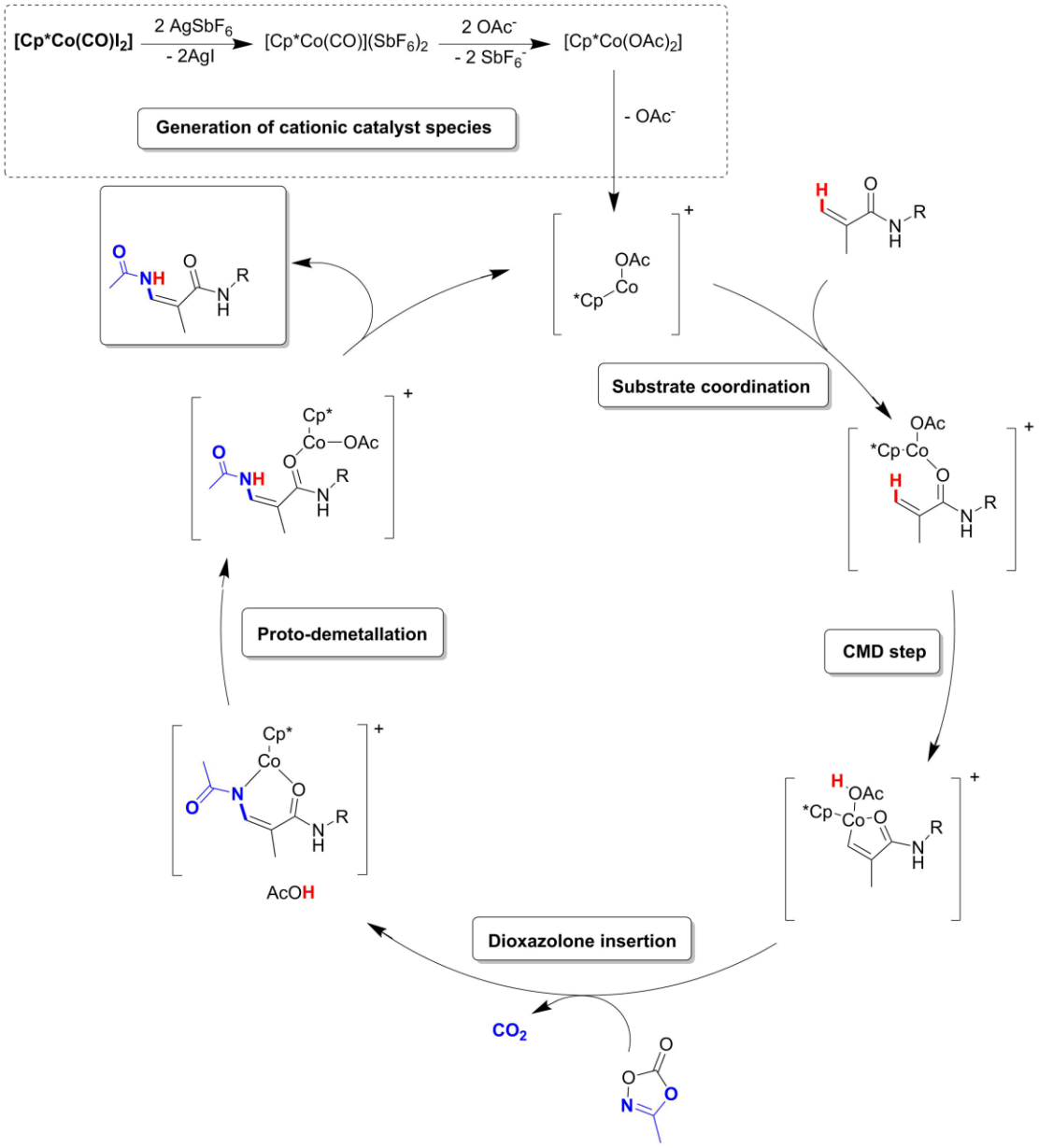


Figure 4-7: Solvent corrected Free Energy Surface (ΔG_{298} kcal mol^{-1}) for **Int1-CF_3**, **TS1-2 CF_3** and **Int2-CF_3** the amidation of 4,4,4-trifluoro-*N*-isopropyl-2-methylbut-2-enamide with 3-methyl-1,4,2-dioxazol-5-one. Free energies taken relative to **Int1-CF_3** and associated reagents.

Scheme 4-5 summarises the proposed catalytic cycle for the formation 1-acetamidoprop-1-en-2-yl isobutyramide using the DFT results obtained in this study.



Scheme 4-5: Proposed catalytic cycle for Cp*Co(III)-catalysed coupling of diozaxolones and prop-1-en-2-yl isobutyramide for the preparation of 1-acetamidoprop-1-en-2-yl isobutyramide.

4.3 Summary

It was possible to expand the substrate scope of the C-H amidation reaction developed in **Chapter 2** to functionalise olefinic acrylamides however, the synthesis of these substrates was more challenging due to limited availability of linear acyl chlorides. Furthermore, the substrates with substitutes at the β-position could not be converted except for the phenyl substituent, albeit in low yield. DFT calculations revealed that the C-H activation step was not possible

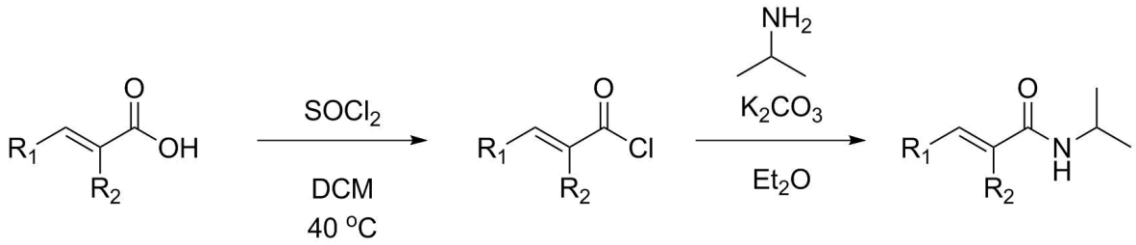
without the interaction of the hydrogen at the β-position with an external acetate base, which could explain the lack of reactivity in the presence of substituents at the β-position.

4.4 Experimental procedures

4.4.1 General experimental considerations

All reagents and solvents were purchased from Sigma Aldrich, Fisher Scientific, Fluorochem and Acros Organics and used without further purification. ^{1}H (400 MHz), ^{13}C {1H} (100 MHz), ^{19}F {1H} (376 MHz) and 2D NMR were recorded on a Bruker AV-400 spectrometer and referenced to the residual deuterated solvent signals. High Resolution Mass Spectra (HRMS) was recorded on a Xevo G2-Xs QTof Mass Spectrometer.

4.4.2 General procedure for synthesis of acrylamide substrates



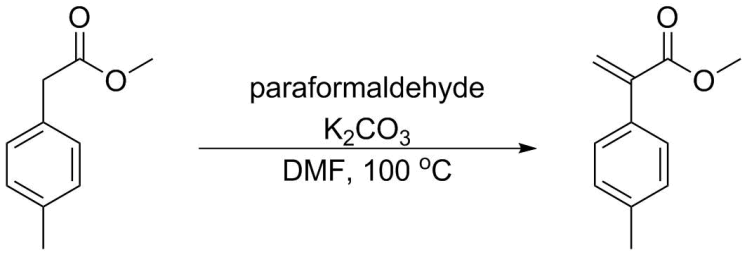
Scheme 4-6: General procedure for synthesis of acrylamide substrate.

To a solution of the corresponding acrylic acid (9.6 mmol) dissolved in DCM (10 mL), thionyl chloride (3.0 equiv.) was added. The mixture was refluxed at 40 ºC for 16 hours and then washed with H_2O (20 mL). The organic layer was extracted using EtOAc (3 x 20 mL) then dried over $MgSO_4$, filtered and the solvent was removed under vacuum along with any residual thionyl chloride. The resulting acyl chloride was used in the second step of the synthesis without further purification.

To a solution of the previously obtained acyl chloride (1.0 equiv.), in Et_2O (50 mL) was added K_2CO_3 (2.5 equiv.) After the mixture had been cooled in an ice bath, the amine (1.5 equiv.) was added. The mixture was stirred for 16 hours at room temperature. After this time, the mixture was diluted with EtOAc and

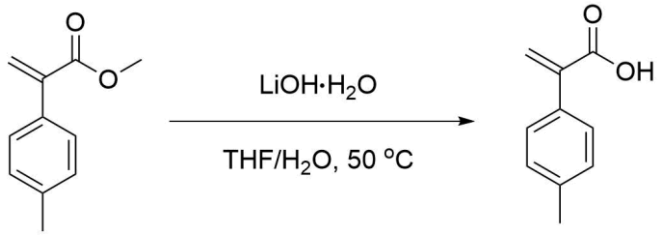
washed with H_2O (50 mL) and then aqueous HCl (1.0 M, 50 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography if necessary, using hexane/EtOAc (1/1) to provide analytically pure acrylamides.

4.4.3 Procedure for synthesis of 52 substrate



Scheme 4-7: Procedure for synthesis of methyl 2-(*p*-tolyl)acrylate.

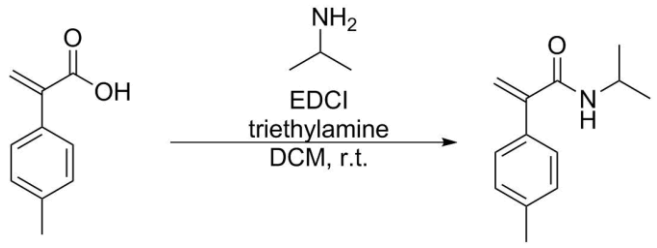
Methyl 2-(*p*-tolyl)acetate (1.15 g, 7.0 mmol), paraformaldehyde (0.315 g, 10.5 mmol) and K_2CO_3 (0.967 g, 7.0 mmol) and DMF (5 mL) were added to a round bottom flask and heated at 100 °C for 16 hours. The mixture was cooled to room temperature, diluted in H_2O (20 mL) and Et_2O (40 mL). The organic layer was separated carefully to avoid formation of an emulsion then washed with brine (3 x 20 mL) followed by H_2O (1 x 20 mL) and dried over $MgSO_4$, filtered and the solvent was removed under vacuum. The crude mixture was purified by silica gel column chromatography Hexane/Et_2O (from 100:0 to 90:10) to provide 400 mg of methyl-2-(*p*-tolyl)acrylate as a colorless oil (32% yield). This is in agreement with previous literature. [198]



Scheme 4-8: Procedure for synthesis of methyl 2-(*p*-tolyl)acrylic acid.

To a solution of the methyl 2-(*p*-tolyl)acrylate (2.27 mmol) in THF/H_2O (1:1, 20 mL) was added LiOH·H_2O (11.4 mmol, 5.0 equiv.). The reaction flask was heated at 50 °C for 16 hours. After this time, the reaction was allowed to cool down and the organic layer was extracted using Et_2O (25 mL). The aqueous

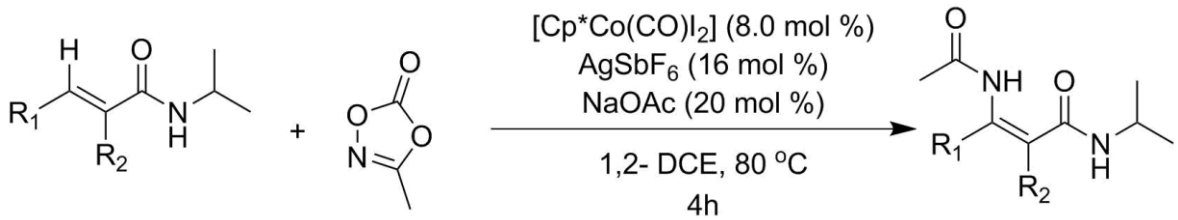
phase was acidified with aqueous 2M HCl until a white precipitate was observed. The organic layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were dried over dried over $MgSO_4$, filtered and the solvent was removed under vacuum to obtain 310 mg of grey amorphous powder (84% yield). This is in agreement with previous literature. [198]



Scheme 4-9: Procedure for synthesis of methyl *N*-isopropyl-2-(*p*-tolyl)acrylamide.

To a mixture of the isopropyl amine (113 mg, 1.91 mmol), EDCI (549 mg, 2.87 mmol) and triethylamine (261 mg, 2.57 mmol) in DCM (20 mL) was added the previously obtained 2-(*p*-tolyl)acrylic acid (1.91 mmol, 310 mg,) at 0 $^{\circ}$C. The reaction mixture was warmed to room temperature and stirred for 16 hours. After quenching the reaction with saturated aqueous ammonium chloride (50 mL), the resulting mixture was extracted with EtOAc (3 x 40 mL). The combined organic extracts were washed with brine, $MgSO_4$, filtered and the solvent was removed under vacuum and purified by silica gel column chromatography using Hexane/EtOAc (85/15) to obtain 350 mg of isopropyl-2-(p-tolyl)acrylamide as a white powder was obtained (57% yield). This is in agreement with previous literature.[198]

4.4.4 General procedure for Cp*Co(III)-catalysed C-H amidation reactions



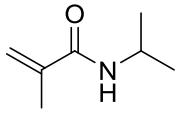
Scheme 4-10: General procedure for Cp*Co(III)-catalysed amidation reactions.

The acrylamides substrate (1.5 mmol), [Cp*Co(CO)I_2] (8.0 mol%, 0.12 mmol), $AgSbF_6$ (16 mol%, 0.24 mmol), NaOAc (20 mol%, 0.30 mmol), 1,4,2-dioxazol-5-one (1.2 equiv., 1.8 mmol) and 1,2-DCE (24 mL) were added to a 40 mL vial under air. The vial was sealed, and the mixture stirred at 80 °C for 4 hours. The reaction mixture was concentrated under vacuum and purified by silica gel column chromatography, using hexane/EtOAc (8/2) as eluent to provide the analytically pure amidation products.

4.5 Characterisation of synthesised compounds

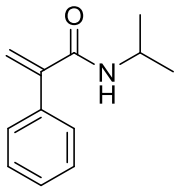
4.5.1 Characterisation of substrates

N-Isopropylmethacrylamide (47)



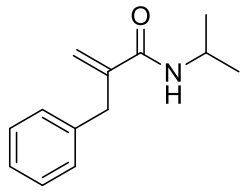
This compound was prepared in accordance to the general synthesis described for linear amides starting from the corresponding acyl chloride (9.6 mmol) to yield a white amorphous solid (76% yield). **^{1}H NMR ($CDCl_3$);** δ: 5.68 (br s, 1H),5.63 (s, 1H Hz), 5.28 (s, 1H), 4.16-4.07 (m, 1H), 1.93 (s, 3H), 1.17 (d, 6H, $^3J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 167.7, 140.4, 119.0, 41.5, 22.7, 18.7. **HR-MS (ASAP, m/z)** calcd. from $[C_7H_{13}NO+H]^+$: 128.1075; found: 128.1075 . R_f = 0.38 (EtOAc/Hexane 30/70). This characterisation is in agreement with previously published data.[199]

N-Isopropyl-2-phenylacrylamide (48)



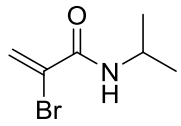
This compound was prepared in accordance to the general synthesis described for linear amides starting from the corresponding acrylic acid (9.6 mmol) to yield a white amorphous solid (45% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.41-7.34 (m, 5H), 6.10 (br s, 1H), 5.60 (d, 1H, $^2J_{HH}$ = 1.3 Hz), 5.54 (d, 1H, $^2J_{HH}$ = 1.3 Hz), 4.23-4.18 (m, 1H), 1.16 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 166.5, 145.06, 137.1, 128.7, 128.5, 128.1, 121.7, 41.8, 22.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{15}NO+H]^+$: 190.1232; found: 190.1239. R_f = 0.70 (EtOAc/Hexane 30/70).

2-Benzyl-*N*-isopropylacrylamide (49)



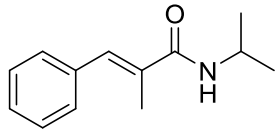
This compound was prepared in accordance to the general synthesis described for linear amides starting from the corresponding acrylic acid (9.6 mmol) to yield a white amorphous solid (58% yield). **^{1}H NMR ($CDCl_3$, 400 MHz, 298K);** δ: 7.36-7.31 (m, 2H), 7.27-7.23 (m, 3H), 5.73 (d, 1H, $^{2}J_{HH}$ = 1.0 Hz) 5.64 (br s, 1H), 5.23 (d, 1H, $^{2}J_{HH}$ = 1.0 Hz), 4.12-4.07 (m, 1H), 3.69 (s, 2H), 1.13 (d, 6H, $^{3}J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 167.5, 144.8, 138.5, 128.9, 128.6, 126.5, 119.2, 41.4, 38.8, 22.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{17}NO+H]^+$: 204.1388; found: 204.1387. R_f = 0.44 (EtOAc/Hexane 30/70).

2-Bromo-*N*-isopropylacrylamide (50)



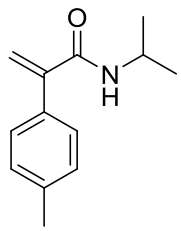
This compound was prepared in accordance to the general synthesis described for linear amides starting from the corresponding acrylic acid (9.6 mmol) to yield a white amorphous solid (55% yield). **^{1}H NMR ($CDCl_3$);** δ: 6.98 (d, 1H, $^{2}J_{HH}$ = 1.5 Hz), 6.46 (br s, 1H), 6.01 (d, 1H, $^{2}J_{HH}$ = 1.5 Hz), 4.12-4.03 (m, 1H), 1.21 (d, 6H, $^{3}J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 160.1, 127.3, 123.1, 42.7, 22.4. **HR-MS (ASAP, m/z)** calcd. from $[C_6H_{10}BrNO+H]^+$: 192.0024; found: 192.0024. R_f = 0.68 (EtOAc/Hexane 30/70).

***N*-Isopropyl-2-methyl-3-phenylacrylamide (51)**



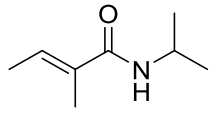
This compound was prepared in accordance to the general synthesis described for linear amides starting from the corresponding acrylic acid (9.6 mmol) to yield a white amorphous solid (73% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.29-7.17 (m, 6H), 5.79 (br s, 1H), 4.15-4.07 (m, 1H), 1.99 (d, 3H, $^{4}J_{HH}$ = 1.3 Hz), 1.14 (d, 6H, $^{3}J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 168.9, 136.3, 133.5, 132.4, 129.3, 128.3, 127.7, 41.8, 22.8, 14.3. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{17}NO+H]^+$: 204.1388; found: 204.1385. R_f = 0.38 (EtOAc/Hexane 30/70). This characterisation is in agreement with previously published data.[200]

***N*-Isopropyl-2-(*p*-tolyl)acrylamide (52)**



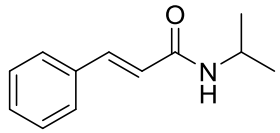
This compound was prepared in accordance to the general synthesis described for linear amides starting from the corresponding ester (7.0 mmol) to yield a white amorphous solid (15% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.29 (d, 2H, $^3J_{HH}$ = 8.0 Hz), 7.21 (d, 2H, $^3J_{HH}$ = 8.0 Hz), 6.08 (d, 1H, $^2J_{HH}$ = 1.2 Hz), 5.58 (d, 1H, $^2J_{HH}$ = 1.1 Hz), 4.26-4.17 (m, 1H), 2.40 (s, 3H), 1.18 (d, 6H, $^3J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 166.7, 144.9, 138.4, 134.2, 129.4, 128.0, 121.2, 41.7, 22.6, 21.2. **HR-MS (ASAP, m/z)** calcd. from $[C_{13}H_{17}NO+H]^+$: 204.1388; found: 204.1388. R_f = 0.50 (EtOAc/Hexane 30/70).

***N*-Isopropyl-2-methylbut-2-enamide (54)**



This compound was prepared in accordance to the general synthesis described for linear amides starting from the corresponding acrylic acid (9.6 mmol) to yield a white amorphous solid (83% yield). **^{1}H NMR ($CDCl_3$);** δ: 6.39 (dd, 1H, $^3J_{HH}$ = 7.0 Hz, $^4J_{HH}$ = 1.4 Hz), 5.52 (br s, 1H), 4.17-4.08 (m, 1H), 1.83 (d, 3H, $^4J_{HH}$ = 1.4), 1.74 (d, 3H, $^3J_{HH}$ = 7.0 Hz), 1.18 (d, 6H, $^3J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 168.6, 132.1, 130.1, 41.4, 22.8, 13.9, 12.4. **HR-MS (ASAP, m/z)** calcd. from $[C_8H_{15}NO+H]^+$: 142.1232; found: 124.1233. R_f = 0.40 (EtOAc/Hexane 30/70).

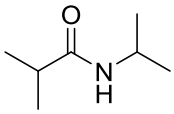
***N*-Isopropylcinnamamide (55)**



This compound was prepared in accordance to the general synthesis described for linear amides starting from the corresponding acrylic acid (9.6 mmol) to yield a white amorphous solid (72% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.63 (d, 1H, $^3J_{HH}$ = 15.6 Hz), 7.51-7.49 (m, 2H), 7.38-7.34 (m, 3H), 6.39 (d, 1H, $^3J_{HH}$ = 15.6 Hz), 5.58 (br s, 1H), 4.27-4.22 (m, 1H), 1.24 (d, 6H, $^3J_{HH}$ = 6.9 Hz). **^{13}C NMR ($CDCl_3$);** δ: 165.1, 140.6, 135.0, 129.5, 128.8, 127.7, 121.2, 41.6, 22.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{12}H_{15}NO+H]^+$: 190.1232; found: 190.1232. R_f = 0.36

(EtOAc/Hexane 30/70). This characterisation is in agreement with previously published data.[200]

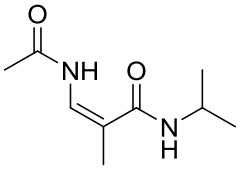
_N_-Isopropylisobutyramide (56)



This compound was prepared in accordance to the general synthesis described for linear amides starting from the corresponding acyl chloride (9.6 mmol) to yield a white amorphous solid (90% yield). **^{1}H NMR ($CDCl_3$);** δ: 5.32 (br s, 1H), 4.09-4.01 (m, 1H), 2.30-2.24 (m, 1H), 1.13 (d, 6H, $^{3}J_{HH}$ = 6.6 Hz), 1.12 (d, 6H, $^{3}J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 176.1, 41.0, 35.7, 22.8, 19.6. **HR-MS (ASAP, m/z)** calcd. from $[C_7H_{15}NO+H]^+$:130.1232; found: 130.1231. R_f = 0.34 (EtOAc/Hexane 30/70). This characterisation is in agreement with previously published data.[201]

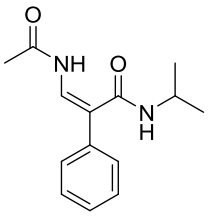
4.5.2 Characterisation of amidation products:

3-Acetamido-_N_-isopropyl-2-methylacrylamide (47a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction described for the amidation reaction starting from substrate **47** (1.5 mmol) to yield a white amorphous solid (93% yield). **^{1}H NMR ($CDCl_3$);** δ: 11.36 (br s, 1H), 7.27 (dd, 1H, ^{3}J =10.6 Hz, ^{4}J =1.3 Hz), 5.42 (br s, 1H), 4.20-4.12 (m, 1H), 2.19 (s, 3H), 1.87 (d, 3H, $^{4}J_{HH}$ = 1.2 Hz), 1.25 (d, 6H, $^{3}J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ:168.7, 168.3, 132.8, 104.7, 41.3, 23.7, 22.8, 16.5. **HR-MS (ASAP, m/z)** calcd. from $[C_9H_{16}N_2O_2+H]^+$: 185.1290 found: 185.1299. R_f = 0.20 (EtOAc/Hexane 30/70).

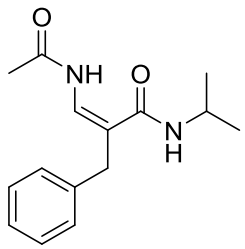
3-Acetamido-_N_-isopropyl-2-phenylacrylamide (48a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction described for the amidation reaction starting from substrate **48** (1.5 mmol) to yield a white amorphous solid (90% yield). **^{1}H NMR ($CDCl_3$);** δ: 11.40 (br s, 1H), 7.32-7.25 (m, 4H), 7.21-7.19 (m, 2H), 5.37 (br s, 1H), 4.09-4.00 (m, 1H), 2.83 (s, 3H), 1.04 (d, 6H, $^{3}J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 168.6, 167.8, 136.5, 134.3, 129.8, 129.1, 128.1, 113.5, 41.5, 23.8,

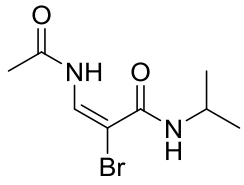
22.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{14}H_{18}N_2O_2+H]^+$: 247.1447 found: 247.1458. R_f = 0.18 (EtOAc/Hexane 30/70).

3-Acetamido-2-benzyl-*N*-isopropylacrylamide (49a)



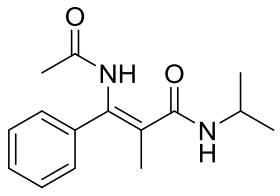
This compound was prepared in accordance to the general synthesis described for the amidation reaction described for the amidation reaction starting from substrate **49** (1.5 mmol) to yield a white amorphous solid (85% yield). **^{1}H NMR ($CDCl_3$);** δ: 11.52 (br d, 1H, ^3J =9.5), 7.44 (d, 1H, ^3J =10.5 Hz), 7.38-7.35 (m, 2H), 7.31-7.25 (m, 3H), 5.28 (br s, 1H), 4.00-3.92 (m, 1H), 3.57 (s, 2H), 2.18 (s, 3H), 0.97 (d, 6H, $^3J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ: 168.6, 168.2, 138.6, 134.6, 129.1, 128.0, 127.2, 108.2, 41.2, 37.5, 23.8, 22.4. **HR-MS (ASAP, m/z)** calcd. from $[C_{15}H_{20}N_2O_2+H]^+$: 261.1603 found: 261.1603. R_f = 0.24 (EtOAc/Hexane 30/70).

3-Acetamido-2-bromo-*N*-isopropylacrylamide (50a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction described for the amidation reaction starting from substrate **50** (1.5 mmol) to yield a white amorphous solid (94% yield). **^{1}H NMR ($CDCl_3$, 400 MHz, 298K);** δ: 11.36 (br d, 1H, ^3J =7.1 Hz), 7.76 (d, 1H, ^3J =10.6 Hz), 6.27 (br s, 1H), 4.09-4.01 (m, 1H), 2.13 (s, 3H), 1.23 (d, 6H, $^3J_{HH}$ = 6.6 Hz). **^{13}C NMR ($CDCl_3$);** δ:167.7, 164.1, 136.1, 93.8, 42.3, 23.5, 22.5. **HR-MS (ASAP, m/z)** calcd. from $[C_8H_{13}BrN_2O_2+H]^+$: 249.0239 found: 249.0254. R_f = 0.50 (EtOAc/Hexane 30/70).

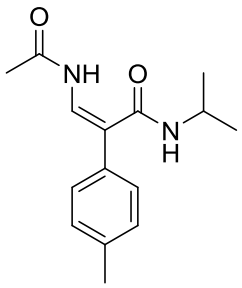
3-Acetamido-*N*-isopropyl-2-methyl-3-phenylacrylamide (51a)



This compound was prepared in accordance to the general synthesis described for the amidation reaction described for the amidation reaction starting from substrate **51** (1.5 mmol) to yield a white amorphous solid (25% yield). **^{1}H NMR ($CDCl_3$);** δ: 11.93 (br s, 1H), 7.27-7.24 (m, 3H), 7.27-7.24 (m, 2H), 5.68 (br s, 1H), 4.25-4.15 (m, 1H), 2.07 (s, 3H), 1.71 (s, 3H), 1.27 (d,

6H, $^{3}J_{HH}$ = 6.6 Hz). **^{13}C {^{1}H} NMR ($CDCl_3$);** δ: 169.6, 168.3, 146.1, 136.5, 128.1, 128.1, 128.0, 107.6, 41.5, 24.8, 22.8, 14.8. **HR-MS (ASAP, m/z)** calcd. from $[C_{15}H_{20}N_2O_2+H]^+$: 261.1603 found: 261.1608. R_f = 0.26 (EtOAc/Hexane 30/70).

***(Z)*-3-Acetamido-*N*-isopropyl-2-(*p*-tolyl)acrylamide (52a)**



This compound was prepared in accordance to the general synthesis described for the amidation reaction described for the amidation reaction starting from substrate **52** (1.5 mmol) to yield a white amorphous solid (75% yield). **^{1}H NMR ($CDCl_3$);** δ: 11.40 (br d, 1H, $^{3}J_{HH}$ = 10.3 Hz), 7.24 (d, 1H, $^{3}J_{HH}$ = 10.7 Hz), 7.21-7.06 (m, 4H), 5.40 (br s, 1H), 4.08-3.99 (m, 1H), 2.30 (s, 3H), 2.07 (s, 3H), 1.04 (d, 6H, $^{3}J_{HH}$ = 6.7 Hz). **^{13}C NMR ($CDCl_3$);** δ: 168.6, 167.8, 136.5, 134.3, 129.8, 129.1, 128.1, 113.5, 41.5, 23.8, 22.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{15}H_{20}N_2O_2+H]^+$: 261.1603 found: 261.1610. R_f = 0.20 (EtOAc/Hexane 30/70).

Chapter 5. Synthesis of novel compounds *via* low valent metal-catalysed denitrogenation of 1,2,3-benzotriazin-4-(*3H*)-ones

5.1 Introduction

Benzotriazin-4(*3H*)-ones are a family of heterocyclic compounds, which have been recognised for their potential application as pesticides and medicines.[136] These compounds have been investigated as anti-cancer, anaesthetic, anti-hypertensive and anti-depressant agents (**Figure 5-1**).

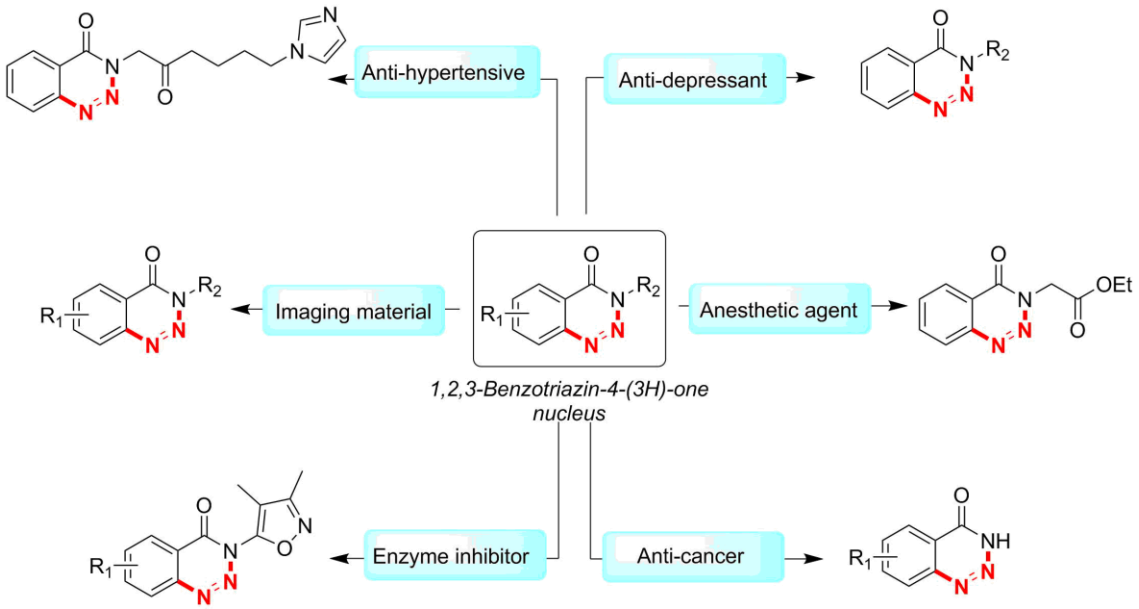
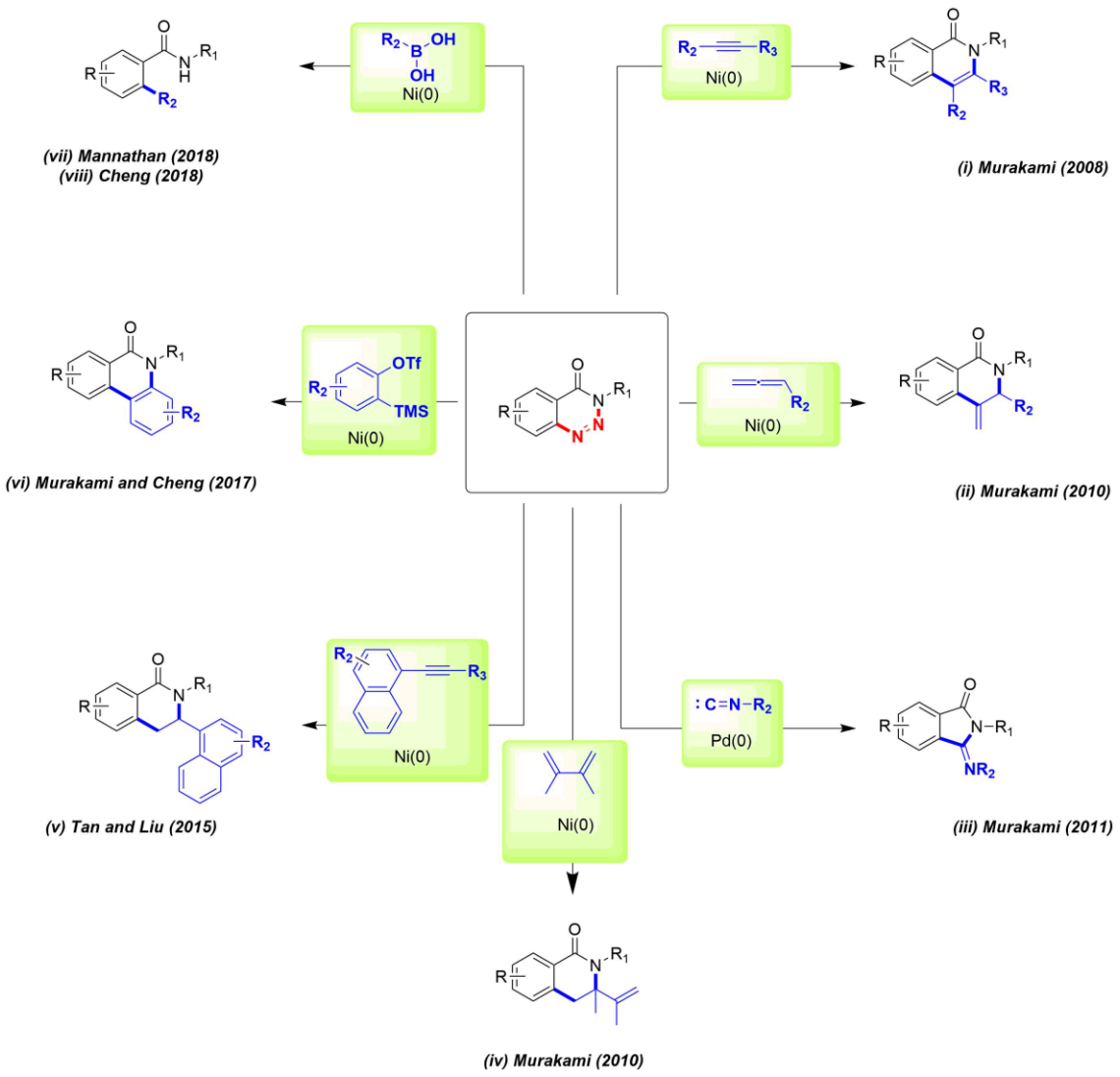


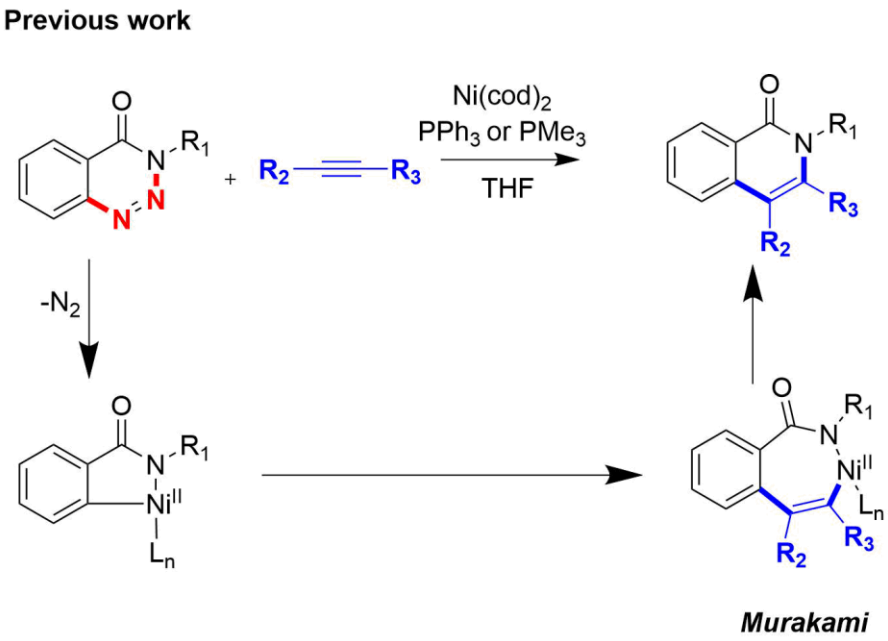
Figure 5-1: Uses of benzotriazin-4(*3H*)-ones scaffolds as biologically active molecules.[136]

Besides these uses, the groups of Murakami, Cheng, Tan, Liu, amongst others have shown that 1,2,3-benzotriazin-4-(*3H*)-ones can react with various coupling partners as a route to provide new synthetic starting points for preparation of other potentially valuable heterocyclic compounds under low-valent metal catalysis, specifically Ni(0) and Pd(0) (**Scheme 5-1**).[137,140,202–207]



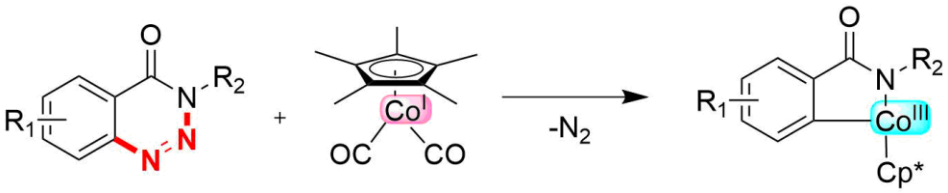
Scheme 5-1: Examples of reported couplings *via* low valent-catalysed denitrogenation of substituted 1,2,3-benzotriazin-4-(*3H*)-ones. [137,140,202–207]

The mechanism of these reactions proceeds *via* the oxidative insertion of the low valent nickel (Ni) or palladium (Pd) complexes into the triazinone moiety followed by the loss of N_2. Murakami and co-workers were the first to report a Ni(0)-mediated denitrogenative activation of the triazinone moiety.[137] The 1,2,3-benzotriazin-4-(*3H*)-ones were coupled with internal and terminal alkynes in the presence of a Ni(0)/phosphine catalyst system to afford a variety of substituted 1(*2H*)-isoquinolones (**Scheme 5-2**).



Scheme 5-2: Mechanism proposed by Murakami and co-workers for the synthesis of 1(2*H*)-Isoquinolones by the Ni(0)-catalysed denitrogenative coupling of 1,2,3-benzotriazin-4-(*3H*)-ones with alkynes.

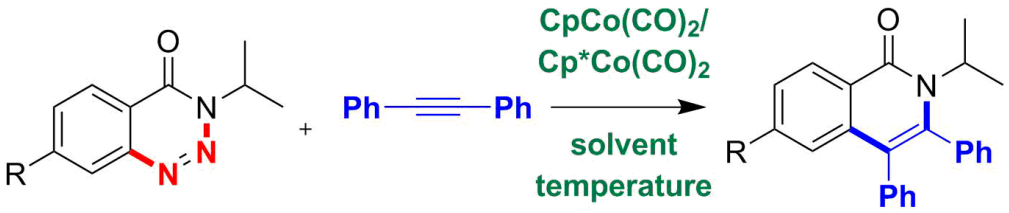
The aim of this chapter was to attempt to replicate the Ni(0)-type reactivity of substituted 1,2,3-benzotriazin-4-(*3H*)-ones using a Co(I) catalyst, specifically [$CpCo(CO)_2$] or [$Cp^*Co(CO)_2$]. Furthermore, the isolation of the Co(III) organometallic intermediate was of interest in order to gain insight into the mechanism by which the reaction proceeds (**Scheme 5-3**) and as an alternative to the cobaltacycle reported by Perez Temprano which was isolated *via* oxidative addition of Co(I) with 2-phenylpyridine.[208]



Scheme 5-3: Proposed strategy for isolation of the Co(III) organometallic intermediate.

5.2 Results

The initial optimisation studies focused on the reaction between 3-isopropylbenz[1,2,3]triazin-4(*3H*)-one (**1b**) and diphenylacetylene, in the presence of a [$CpCo(CO)_2$] or [$Cp^*Co(CO)_2$] catalyst. The aim was to replicate the synthesis of the 1(*2H*)-isoquinolone (**1c**) type of compounds prepared by Murakami using a Co(I)-catalyst instead of Ni(0). Reproducing the reaction conditions that Murakami and co-workers used did not afford **1c**, with no product being observed (**Table 5-1**, entry 1). **Table 5-1** illustrates the effect of the optimisation of solvent and temperature of reaction, whereby the desired product was not observed by changing temperature of the reaction or the solvents in which the reaction took place. Furthermore, all the starting material was recovered in all cases, as observed by ^1H NMR using 1,3,5-trimethoxybenzene as internal standard. Subsequently, the effect of substituents on the reactivity was considered, with the effect of substrates with a strong electron withdrawing groups (CF_3) or strong electron donating groups (OMe) being tested. Again, no product was observed in the presence of either of these substituents as well (**Table 5-1**, entries 12-13). Furthermore, applying stoichiometric amounts of the CpCo(I)-type of catalyst did not improve reactivity (**Table 5-1**, entry 14).



xb **c** **xc**

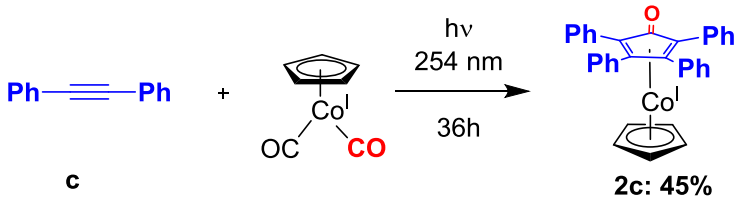
Table 5-1: Optimisation studies for attempted Co(I)-catalysed synthesis of 1(*2H*)-isoquinolone.[a]

Entry	R (compound)	Solvent	Temp. [°C]	[XCo^{I}(CO)$_2$] complex	xc [%][b]
1	H (1b)	THF	80	Cp	None
2	H (1b)	THF	100	Cp	None
3	H (1b)	THF	140	Cp	None
4	H (1b)	THF	140	Cp*	None
5	H (1b)	1,4-dioxane	100	Cp	None
6	H (1b)	1,2-DCE	100	Cp	None
7	H (1b)	TFE	100	Cp	None
9	H (1b)	TFE	100	Cp*	None
10	H (1b)	1,2-DCE	100	Cp*	None
11	H (1b)	toluene	100	Cp*	None
12	CF_3 (11b)	THF	100	Cp	None
13	OMe (6b)	THF	100	Cp	None
14	H (1b)	THF	100	Cp (1.0 equiv.)	None

[a] General conditions: 0.05 mmol of **xb**, 1.2 equiv. of **coupling agent**, 10 mol% of [XCo^{I}(CO)$_2$] (X = Cp or Cp*),1.0 mL solvent, T [°C], 16 hours. [b)] Yields of **xc** calculated from crude ^{1}H NMR using 1,3,5-trimethoxybenzene as internal standard.

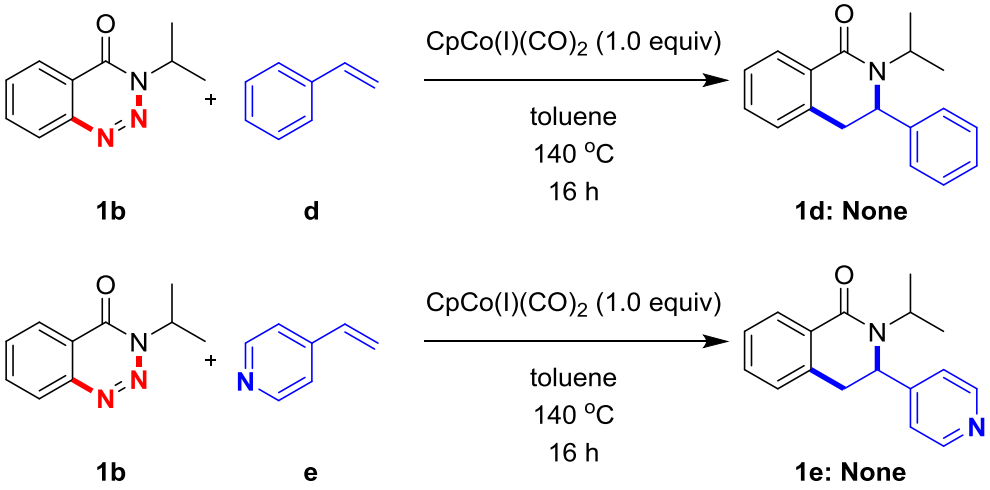
No product was observed during the initial optimisation and it was postulated that using heat was not likely to promote dissociation of the carbonyl ligands, which is required to form the more reactive 14 or 16 electron Co-species. Photochemistry has previously been used to promote the dissociation of the carbonyl groups from the metal center.[209] Therefore, the substrate and alkyne along with the [CpCo(CO)$_2$] catalyst were irradiated under UV-light (254 nm) for

36 h to promote the formation of the more unstable 14 or 16 electron reactive Co-complex, which was proposed would thereafter react with the triazinone moiety *via* oxidative addition, in similarity to the mechanism for Ni(0) proposed by Murakami (**Scheme 5-2**). Under these conditions, new peaks were indeed observed in the ^{1}H NMR spectrum of the crude reaction mixture. The novel product was isolated by column chromatography and after analysis by both 1D, 2D NMR techniques and HRMS it was concluded that the product observed was the result of the reaction between the [CpCo(CO)$_2$] and the diphenyl acetylene which furnished, by cycloaddition, the stable 18-electron Co(I)-complex **2c** (**Scheme 5-4**). This reactivity has previously been observed by Hamilton and co-workers when reacting the [CpCo(CO)$_2$] with diarylacetylenes using microwave irradiation.[210] To further demonstrate that the presence of the triazinone compound did not have an impact on the formation of Co(I)-complex **2c**, the reaction was performed in the absence of substrate **1a** and the same Co-complex (**2c)** was obtained in 45% yield.



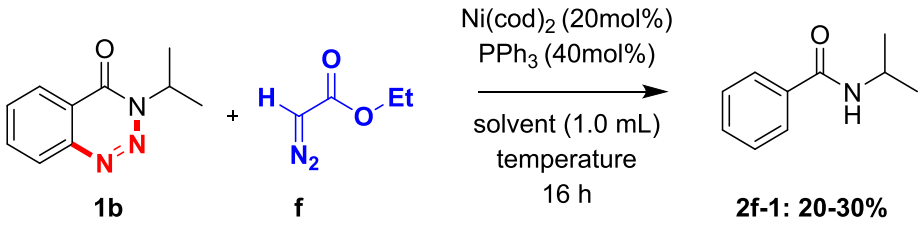
Scheme 5-4: Photochemical preparation of the Co^{I}-complex by reacting CpCo^{I}(CO)$_2$ with diphenyl acetylene.

As a result of no reactivity being observed between the 1,2,3-benzotriazin-4-(*3H)*-ones and diphenylacetylene using [CpCo(I)(CO)$_2$] as catalyst, attention was shifted to alkenes as coupling partners to obtain the related annulation products (**Scheme 5-5**). However, both of these reactions were also unsuccessful when styrene and 4-vinylpyridine were reacted with **1b** using stoichiometric amounts of [CpCo(CO)$_2$]. Furthermore, it was not possible to observe any proof that the metal species had added into the triazinone moiety by oxidative insertion at any point for any of the attempted reactions. This was unexpected as oxidative addition of [CpCo(CO)$_2$] should be possible, given that oxidative addition of I_2 to [Cp*Co(CO)$_2$] provides the [Cp*Co(CO)I_2] catalyst.



Scheme 5-5: Strategy for reaction between 3-isopropylbenz[1,2,3]triazin-4(3*H*)-one and alkenes using [$CpCo(CO)_2$] catalyst.

Thus, attention was shifted to the Ni(0)-catalyst, which has previously shown reactivity for a variety of coupling partners with the intent of studying new coupling partners for 1,2,3-benzotriazin-4-(*3H)*-ones using $Ni(cod)_2$ as catalyst. Highly reactive carbenes, and ethyl diazoacetate (EDA) were selected as coupling partners for substrate **1b** using $Ni(cod)_2/PPh_3$ as a catalyst under various temperatures with 1.0 mL of THF or toluene as a solvent (**Scheme 5-6**).[211] No reaction was detected between the substrate and the EDA however, 30% yield of the isopropyl benzamide obtained from a proto-demetalation event was observed *via* ^1H NMR. This suggested that the $Ni(cod)_2/PPh_3$ catalyst was able to insert the triazonone moiety.



Scheme 5-6: Synthesis of isopropyl benzamide by activation of the triazinone cycle.

Subsequently, the effect of various phosphine ligands was tested. Surprisingly, when switching to bidentate phosphine ligands (**Table 5-2**) the reaction afforded moderate yields of the dimerised product **2f-2** alongside the initial observed product **2f-1**. However, no reaction was observed between the 1,2,3-benzotriazin-4-(*3H)*-one and EDTA. Similar experiments were conducted, under the same conditions using 1-cyanocyclohexene as a potential coupling

agent. Correspondingly, no reactivity was observed with the nitrile functionality either. The dimerisation product was observed in this instance as well, which further confirmed that none of the coupling agents contributed to the reaction which furnished **2f-2**.

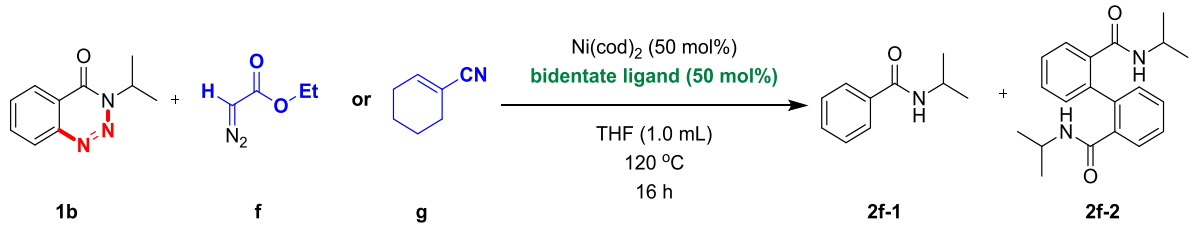
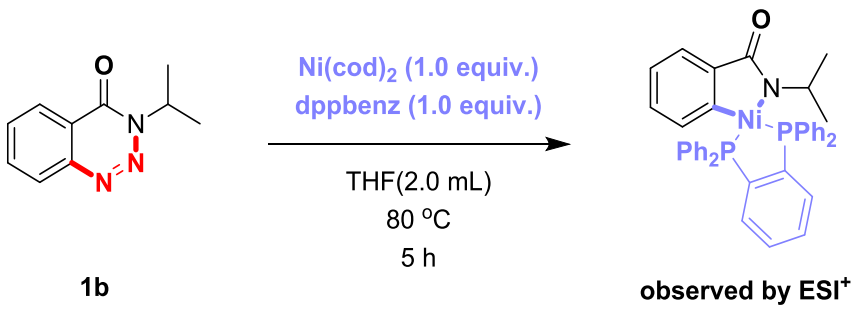


Table 5-2: Optimisation studies using **f** or **g** as possible coupling agents alongside $Ni(cod)_2$ catalyst and various bidentate phosphine ligands.[a]

Entry	Coupling partner	Ligand	2f-1 [%][b]	2f-2 [%][b]
1	f	dppb	23	25
2	f	dppbenz	20	16
3	f	dppf	20	33
4	g	dppb	35	20
5	g	dppbenz	30	28
6	g	dppf	30	25

[a] General conditions: 0.05 mmol of **1b**, 1.2 equiv. for **g**, 50 mol% $Ni(cod)_2$, 50 mol% ligand, 1.0 mL THF, 120 °C, 16 hours. [b)] Yields of **2f-1** and **2f-2** calculated from crude ^1H NMR using 1,3,5-trimethoxybenzene as internal standard.

The synthesis of the Ni(II) organometallic intermediate was desirable and it was attempted by reacting the $Ni(cod)_2$/dppbenz with the substrate **1b**. It was possible to detect the organometallic intermediate by mass spectrometry (ESI+) at m/z of 666.2 (**Figure 5-2**) however, it could not be separated from the oxidised phosphine by-product.



Scheme 5-7: Ni(II)-organometallic intermediate observed by ESI^+.

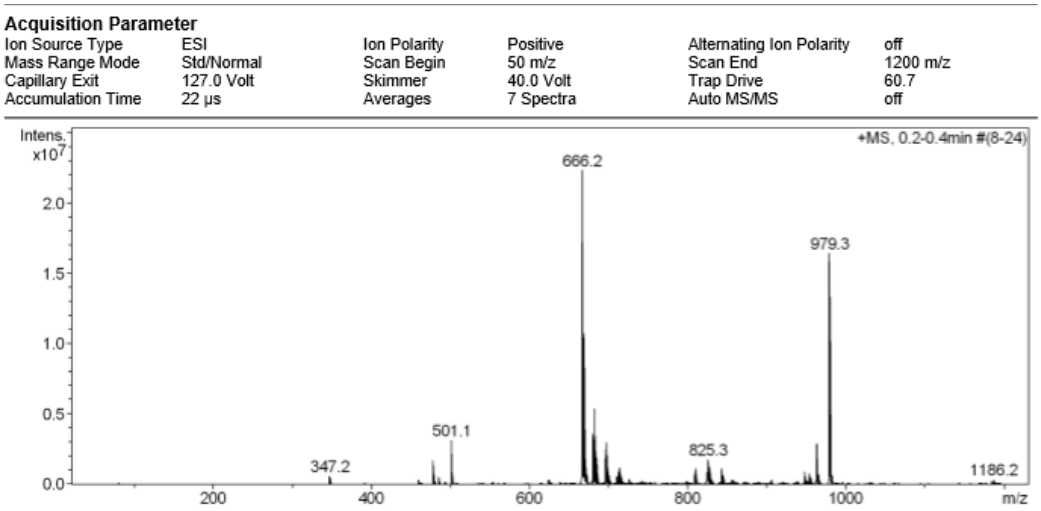


Figure 5-2: Mass spectrometry (ESi^+) spectrum of the Ni(II)-organometallic intermediate.

5.3 Summary

In conclusion it was not possible to activate the triazinone ring using the $[CpCo(CO)_2]$ and $[Cp^*Co(CO)_2]$ complexes. Nevertheless, an elusive cyclopentadienone–Co(I)Cp complex was isolated by reacting the $CpCo(CO)_2$ complex with diphenyl acetylene under UV light. Furthermore, it was possible to activate the triazinone ring using the $Ni(cod)_2$ in combination with phosphine ligands, but no novel coupling partners could be inserted into the moiety. Surprisingly, the dimerisation product was observed when bidentate phosphine ligands were employed.

5.4 Experimental procedures

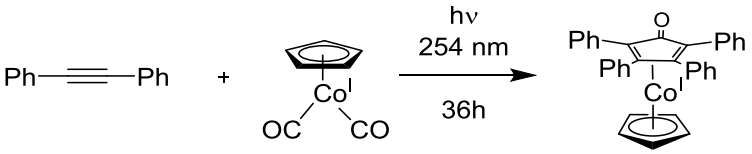
5.4.1 General experimental considerations

All reagents and solvents were purchased from Sigma Aldrich, Fisher Scientific, Fluorochem and Acros Organics and used without further purification. ^{1}H (400 MHz), ^{13}C $\{^{1}H\}$ (100 MHz),) and 2D NMR were recorded on a Bruker AV-400 spectrometer and referenced to the residual deuterated solvent signals. Low resolution mass spectra were recorded on Bruker Esquire 6000 mass spectrometer. High resolution mass spectra (HRMS) were recorded on a micrOTOF-Q mass spectrometer.

5.4.2 General procedure for optimisation studies using [$XCo(CO)_2$] catalysts (X= Cp or Cp*)

In an N_2-filled glove-box, the corresponding 1,2,3-benzotriazin-4-(*3H)*-one (0.05 mmol), the coupling agent (0.06 mmol), 10-100% of $CpCo(CO)_2$ or $Cp^*Co(CO)_2$ and solvent (1.0 mL) were added to an oven-dried vial equipped with a stir bar. The vial was sealed, removed from the glove-box and the reaction mixture was left to heat and stir at various temperatures for 16 hours. After this time, the reaction mixture was diluted with ethyl acetate (5.0 mL) and resulting mixture was passed through a pad of silica. The solvent was removed under vacuum and 1,3,5-trimethoxybenzene was added to the crude and used as internal standard to determine percentage yield of products by ^{1}H NMR.

5.4.3 Procedure for the preparation of the cobalt-complex 2c



Scheme 5-8: Procedure for synthesis of cobalt-complex **2c.**

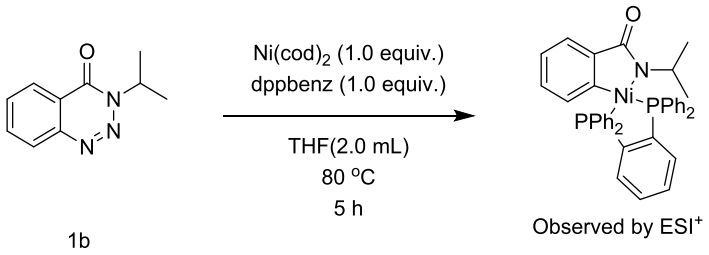
In an N_2-filled glove-box, diphenylacetylene (0.2 mmol), $CpCo(CO)_2$ (0.1 mmol) and THF (2.0 mL) were were added to an oven-dried vial equipped with a stir bar. The vial was sealed, removed from the glove-box and the reaction mixture was irradiated under UV-light (254 nm) for 36 h. After this time, the reaction

mixture was diluted with ethyl acetate (10 mL) and resulting mixture was passed through a pad of silica. The solvent was removed under vacuum and the crude was purified by preparative thin-layer chromatography (hexane/EtOAc 5:1) to give the product **2c** (60.6 mg, 45% yield) as an amorphous red solid.

5.4.4 General procedure for optimisation studies using $Ni(cod)_2$ catalyst

In an N_2-filled glove-box, the corresponding 1,2,3-benzotriazin-4-(*3H)*-one (0.05 mmol), the coupling agent (0.06 mmol), 50 mol% of $Ni(cod)_2$ and solvent (1.0 mL) were added to an oven-dried vial equipped with a stir bar. The vial was sealed, removed from the glove-box and the reaction mixture was left to heat and stir at various temperatures for 16 hours. After this time, the reaction mixture was diluted with ethyl acetate (5.0 mL) and resulting mixture was passed through a pad of silica. The solvent was removed under reduced pressure and 1,3,5-trimethoxybenzene was added to the crude and used as internal standard to determine percentage yield products by ^{1}H NMR.[202]

5.4.5 Procedure for the isolation of Ni(II)-organometallic intermediate

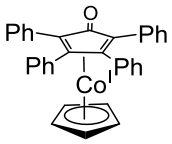


Scheme 5-9: Procedure for observation of Ni(II)-organometallic intermediate.

In an N_2-filled glove-box, **1b** (0.2 mmol) and THF (1.0 mL) were added to an oven-dried vial equipped with a stir bar. $Ni(cod)_2$ (1.0 equiv.) and dppbenz (1.0 equiv.) were dissolved in THF (1.0 mL) and added to the vial after. The vial was sealed, removed from the glove-box heated and stirred at 80 °C for 5 h. The solvent was removed under vacuum and crude was analysed by ESI^+ Mass Spectrometry.[202]

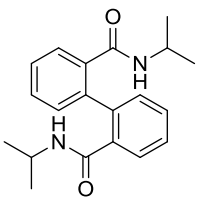
5.5 Characterisation of synthesised compounds

Cp*Co(Ph_4C_5O) complex (2c)



This compound was prepared in accordance with the procedure for the preparation of the cobalt-complex **2c** starting from $CpCo(CO)_2$ (0.1 mmol) to yield a red amorphous solid (45% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.64-7.62 (m, 4H), 7.27-7.25 (m, 8H), 7.19-7.14 (m, 8H), 4.95 (s, 5H). **^{13}C NMR ($CDCl_3$);** δ:132.9, 131.9, 130.68, 127.79, 127.18, 85.6. **HR-MS (ASAP, m/z)** calcd. from $[C_{34}H_{25}CoO+H]^+$: 509.1310; found: 509.1319. R_f = 0.40 (EtOAc/Hexane 50/50). This characterisation in agreement with previously published data.

N2,N2'-Diisopropyl-[1,1'-biphenyl]-2,2'-dicarboxamide (2f-2)



This compound was prepared in accordance to the general synthesis described for general procedure for optimisation studies using $Ni(cod)_2$ catalyst starting from 3-isopropylbenzo[*d*][1,2,3]triazin-4(*3H*)-one (0.1 mmol) to yield a white amorphous solid (33% yield). **^{1}H NMR ($CDCl_3$);** δ: 7.55-7.35 (m, 2H), 7.42-7.34 (m, 4H), 7.14-7.12 (m, 2H), 6.90 (s, br, 2H), 4.02-3.96 (m, 2H), 1.05 (d, 6H, $^3J_{HH}$ = 6.4 Hz), 0.83 (d, 6H, $^3J_{HH}$ = 6.5 Hz). **^{13}C NMR ($CDCl_3$);** δ: 138.9, 129.3, 127.8, 126.7, 41.5, 22.5, 22.0. **MS (ESI^+, m/z)** calcd. from $[C_{20}H_{24}N_2O_2+H]^+$: 325.2; found: 325.2. R_f = 0.51 (EtOAc/Hexane 50/50).

References

1 K. Kohler, K. Wussow and A. S. Wirth, *Palladium-Catalysed Coupling Reactions*, Wiley, Hoboken, 2013.

2 C. C. Johansson-Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chemie Int. Ed.*, 2012, **51**, 5062–5085.

3 X. Chen, K. M. Engle, D. Wang and J.-Q Yu, *Angew. Chemie Int. Ed.*, 2009, **48**, 5094–5115.

4 T. Gensch, M. N. Hopkinson, F. Glorius and J. Wencel-Delord, *Chem. Soc. Rev.*, 2016, **45**, 2900–2936.

5 S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, **509**, 299-309.

6 X. X. Guo, D. W. Gu, Z. Wu and W. Zhang, *Chem. Rev.*, 2015, **115**, 1622–1651.

7 M. Moselage, J. Li and L. Ackermann, *ACS Catal.*, 2016, **6**, 498–525.

8 G. Song, F. Wang and X. Li, *Chem. Soc. Rev.*, 2012, **41**, 3651–3678.

9 G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48**, 1007–1020.

10 K. Gao and N. Yoshikai, *Acc. Chem. Res.*, 2014, **47**, 1208–1219.

11 P. G. Chirila and C. J. Whiteoak, *Dalton Trans.*, 2017, **46**, 9721–9739.

12 M. S. Kharasch and E. K. Fields, *J. Am. Chem. Soc.*, 1941, **63**, 2316-2320.

13 S. Murahashi, *J. Am. Chem. Soc.*, 1955, **77**, 6403–6404.

14 F. Hebrard and P. Kalck, *Chem. Rev.*, 2009, **109**, 4272–4282.

15 J. B.-Urgoiti, L. Añorbe, L. P.-Serrano, G. Domínguez and J. Pérez-Castells, *Chem. Soc. Rev.*, 2004, **33**, 32–42.

16 J. K. Kochi, R. T. Tang and T. Bernath, *J. Am. Chem. Soc.*, 1973, **95**, 7114–7123.

17 G.Halbritter, F. Knoch, A. Wolski and H. Kisch, *Angew. Chem. Int. Ed.*, 1994, **33**, 1603–1605.

18 D. Tilly, G. Dayaker and P. Bachu, *Catal. Sci. Technol.*, 2014, **4**, 2756-2777.

19 C. P. Lenges, P. S. White and M. Brookhart, *J. Am. Chem. Soc.*, 1998, **120**, 6965–6979.

20 C. P. Lenges and M. Brookhart, *J. Am. Chem. Soc.*, 1997, **119**, 3165-3166.

21 K. Kanamori, W. E. Broderick, R. F. Jordan, R. D. Willett and J. I. Legg, *J. Am. Chem. Soc.*, 1986, **108**, 7122–7124.

22 W. E. Broderick, K. Kanamori, R. D. Willett and J. I. Legg, *Inorg. Chem.*, 1991, **30**, 3875–3881.

23 T. Avilés, A. Dinis, M. J. Calhorda, P. Pinto, V. Félix and M. G. B. Drew, *J. Organomet. Chem.*, 2001, **625**, 186–194.

24 X. Zhou, A. I. Day, A. C. Willis and W. G. Jackson, *Chem. Commun.*, 2003, **3**, 2386–2387.

25 T. Yoshino, H. Ikemoto, S. Matsunaga and M. Kanai, *Angew. Chemie Int. Ed.*, 2013, **52**, 2207–2211.

26 B. Sun, T. Yoshino, S. Matsunaga and M. Kanai, *Adv. Synth. Catal.*, 2014, **356**, 1491–1495.

27 L. Grigorjeva and O. Daugulis, *Angew. Chem. Int. Ed.*, 2014, **53**, 10209-10212.

28 L. B. Zhang, X. Q. Hao, S. K. Zhang, Z. J. Liu, X. X. Zheng, J. F. Gong, J. L. Niu and M. P. Song, *Angew. Chem. Int. Ed.*, 2015, **54**, 272–275.

29 X. K. Guo, L. B. Zhang, D. Wei and J. L. Niu, *Chem. Sci.*, 2015, **6**, 7059-7071.

30 D. G. Yu, T. Gensch, F. De Azambuja, S. Vásquez-Céspedes and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17722–17725.

31 B. Sun, T. Yoshino, S. Matsunaga and M. Kanai, *Chem. Commun.*, 2015, **51**, 4659–4661.

32 P. G. Chirila and C. J. Whiteoak, *Dalton Trans.*, 2017, **46**, 9721–9739.

33 G. W. Gribble, *J. Chem. Soc. Perkin Trans. 1*, 2000, 1045–1075.

34 Y. Zhao, U. K. Sharma, F. Schröder, N. Sharma, G. Song and E. V. Van Der Eycken, *RSC Adv.*, 2017, **7**, 32559–32563.

35 Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga and M. Kanai, *Angew. Chem. Int. Ed.*, 2015, **54**, 9944–9947.

36 T. Gensch, S. Vásquez-Céspedes, D. G. Yu and F. Glorius, *Org. Lett.*, 2015, **17**, 3714–3717.

37 X. G. Liu, S. S. Zhang, J. Q. Wu, Q. Li and H. Wang, *Tetrahedron Lett.*, 2015, **56**, 4093–4095.

38 F. Hu, Y. Xia, C. Ma, Y. Zhang and J. Wang, *Chem. Commun.*, 2015, **51**, 7986–7995.

39 N. Sauermann, M. J. González and L. Ackermann, *Org. Lett.*, 2015, **17**,

5316–5319.

40 F. Xie, Z. Qi, S. Yu and X. Li, *J. Am. Chem. Soc.*, 2014, **136**, 4780–4787.

41 Z. Z. Zhang, B. Liu, C. Y. Wang and B. F. Shi, *Org. Lett.*, 2015, **17**, 4094-4097.

42 S. Wang, J. T. Hou, M. L. Feng, X. Z. Zhang, S. Y. Chen and X. Q. Yu, *Chem. Commun.*, 2016, **52**, 2709–2712.

43 D. Zell, Q. Bu, M. Feldt and L. Ackermann, *Angew. Chem. Int. Ed.*, 2016, **55**, 7408–7412.

44 L. Kong, X. Zhou and X. Li, *Org. Lett.*, 2016, **18**, 6320–6323.

45 P. Tian, C. Feng and T. P. Loh, *Nat. Commun.*, 2015, **6**, 1–7.

46 X. Zhou, Z. Fan, Z. Zhang, P. Lu and Y. Wang, *Org. Lett.*, 2016, **18**, 4706–4709.

47 S. Nakanowatari, R. Mei, M. Feldt and L. Ackermann, *ACS Catal.*, 2017, **7**, 2511–2515.

48 J. Li, Z. Zhang, W. Ma, M. Tang, D. Wang and L. H. Zou, *Adv. Synth. Catal.*, 2017, **359**, 1717–1724.

49 Z. Zhang, S. Han, M. Tang, L. Ackermann and J. Li, *Org. Lett.*, 2017, **19**, 3315–3318.

50 T. Kurihara, M. Kojima, T. Yoshino and S. Matsunaga, *Asian J. Org. Chem.*, 2020, **9**, 368–371.

51 M. Sen, N. Rajesh, B. Emayavaramban, J. R. Premkumar and B. Sundararaju, *Chem. - Eur. J.*, 2018, **24**, 342–346.

52 F. Pesciaioli, U. Dhawa, J. C. A. Oliveira, R. Yin, M. John and L. Ackermann, *Angew. Chem. Int. Ed.*, 2018, **57**, 15425–15429.

53 T. Li, Y. Yang, B. Li and P. Yang, *Chem. Commun.*, 2019, **55**, 353–356.

54 Y. Bunno, N. Murakami, Y. Suzuki, M. Kanai, T. Yoshino and S. Matsunaga, *Org. Lett.*, 2016, **18**, 2216–2219.

55 N. Murakami, M. Yoshida, T. Yoshino and S. Matsunaga, *Chem. Pharm. Bull.*, 2018, **66**, 51–54.

56 L. Kong, B. Biletskyi, D. Nuel and H. Clavier, *Org. Chem. Front.*, 2018, **5**, 1600–1603.

57 S. Ji, K. Yan, B. Li and B. Wang, *Org. Lett.*, 2018, **20**, 5981–5984.

58 A. Kumar, N. Muniraj and K. R. Prabhu, *Eur. J. Org. Chem.*, 2019, **2019**, 2735–2739.

59 Y. Suzuki, B. Sun, T. Yoshino, M. Kanai and S. Matsunaga, *Tetrahedron*, 2015, **71**, 4552–4556.

60 A. Kenny, A. Pisarello, A. Bird, P. G. Chirila, A. Hamilton and C. J. Whiteoak, *Beilstein J. Org. Chem.*, 2018, **14**, 2366–2374.

61 T. Li, C. Shen, Y. Sun, J. Zhang, P. Xiang, X. Lu and G. Zhong, *Org. Lett.*, 2019, **21**, 7772–7777.

62 K. Kawai, Y. Bunno, T. Yoshino and S. Matsunaga, *Chem. Eur. J.*, 2018, **24**, 10231–10237.

63 N. Muniraj and K. R. Prabhu, *Adv. Synth. Catal.*, 2018, **360**, 1370–1375.

64 A. Lerchen, T. Knecht, C. G. Daniliuc and F. Glorius, *Angew. Chem. Int. Ed.*, 2016, **55**, 15166–15170.

65 R. Tanaka, H. Ikemoto, M. Kanai, T. Yoshino and S. Matsunaga, *Org. Lett.*, 2016, **18**, 5732–5735.

66 H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga and M. Kanai, *J. Am. Chem. Soc.*, 2014, **136**, 5424–5431.

67 M. R. Sk, S. S. Bera and M. S. Maji, *Org. Lett.*, 2018, **20**, 134–137.

68 M. R. Sk, S. S. Bera and M. S. Maji, *Adv. Synth. Catal.*, 2019, **361**, 585-590.

69 X. Chen, J. Ren, H. Xie, W. Sun, M. Sun and B. Wu, *Org. Chem. Front.*, 2018, **5**, 184–188.

70 R. Mandal, B. Emayavaramban and B. Sundararaju, *Org. Lett.*, 2018, **20**, 2835–2838.

71 R. Kumar, R. Kumar, D. Chandra and U. Sharma, *J. Org. Chem.*, 2019, **84**, 1542–1552.

72 M. Sen, B. Emayavaramban, N. Barsu, J. R. Premkumar and B. Sundararaju, *ACS Catal.*, 2016, **6**, 2792–2796.

73 T. Gensch, F. J. R. Klauck and F. Glorius, *Angew. Chem. Int. Ed.*, 2016, **55**, 11287–11291.

74 X. G. Liu, Q. Li and H. Wang, *Adv. Synth. Catal.*, 2017, **359**, 1942–1946.

75 M. Yoshida, K. Kawai, R. Tanaka, T. Yoshino and S. Matsunaga, *Chem. Commun.*, 2017, **53**, 5974–5977.

76 D. G. Yu, T. Gensch, F. De Azambuja, S. Vásquez-Céspedes and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17722–17725.

77 J. Li and L. Ackermann, *Angew. Chem. Int. Ed.*, 2015, **54**, 3635–3638.

78 A. B. Pawar and D. M. Lade, *Org. Biomol. Chem.*, 2016, **14**, 3275–3283.

79 B. Sun, T. Yoshino, S. Matsunaga and M. Kanai, *Adv. Synth. Catal.*, 2014, **356**, 1491–1495.

80 J. Shi, B. Zhou, Y. Yang and Y. Li, *Org. Biomol. Chem.*, 2012, **10**,

8953-8955.

81 B. Sun, T. Yoshino, S. Matsunaga and M. Kanai, *Chem. Commun.*, 2015, **51**, 4659–4661.

82 T. A. Shah, P. B. De, S. Pradhan, S. Banerjee and T. Punniyamurthy, *J. Org. Chem.*, 2019, **84**, 16278–16285.

83 P. Patel and S. Chang, *ACS Catal.*, 2015, **5**, 853–858.

84 Y. Liang, Y. F. Liang, C. Tang, Y. Yuan and N. Jiao, *Chem. Eur. J.*, 2015, **21**, 16395–16399.

85 R. Mei, J. Loup and L. Ackermann, *ACS Catal.*, 2016, **6**, 793–797.

86 H. Cheng, J. G. Hernández and C. Bolm, *Adv. Synth. Catal.*, 2018, **360**, 1800–1804.

87 X. Shi, W. Xu, R. Wang, X. Zeng, H. Qiu and M. Wang, *J. Org. Chem.*, 2020, **85**, 3911–3920.

88 Y. Liu, F. Xie, A. Q. Jia and X. Li, *Chem. Commun.*, 2018, **54**, 4345–4348.

89 G. Borah, P. Borah and P. Patel, *Org. Biomol. Chem.*, 2017, **15**, 3854-3859.

90 A. E. Hande, N. Muniraj and K. R. Prabhu, *ChemistrySelect*, 2017, **2**, 5965–5969.

91 J. Huang, J. Ding, T. M. Ding, S. Zhang, Y. Wang, F. Sha, S. Y. Zhang, X. Y. Wu and Q. Li, *Org. Lett.*, 2019, **21**, 7342–7345.

92 B. Khan, V. Dwivedi and B. Sundararaju, *Adv. Synth. Catal.*, 2020, **362**, 1195–1200.

93 S. S. Bera, M. R. Sk and M. S. Maji, *Chem. Eur. J.*, 2019, **25**, 1806-1811.

94 F. Gao, X. Han, C. Li, L. Liu, Z. Cong and H. Liu, *RSC Adv.*, 2018, **8**, 32659–32663.

95 Q. Jia, L. Kong and X. Li, *Org. Chem. Front.*, 2019, **6**, 741–745.

96 S. S. Bera and M. S. Maji, *Org. Lett.*, 2020, **22**, 2615–2620.

97 R. J. Scamp, E. deRamon, E. K. Paulson, S. J. Miller and J. A. Ellman, *Angew. Chem. Int. Ed.*, 2020, **59**, 890–895.

98 S. R. Yetra, Z. Shen, H. Wang and L. Ackermann, *Beilstein J. Org. Chem.*, 2018, **14**, 1546–1553.

99 S. B. Wang, Q. Gu and S. L. You, *J. Catal.*, 2018, **361**, 393–397.

100 D. Y. Huang, Q. J. Yao, S. Zhang, X. T. Xu, K. Zhang and B. F. Shi, *Org. Lett.*, 2019, **21**, 951–954.

101 Y. H. Liu, P. X. Li, Q. J. Yao, Z. Z. Zhang, D. Y. Huang, M. D. Le, H.

Song, L. Liu and B. F. Shi, *Org. Lett.*, 2019, **21**, 1895–1899.

102 N. Barsu, M. A. Rahman, M. Sen and B. Sundararaju, *Chem. Eur. J.*, 2016, **22**, 9135–9138.

103 P. W. Tan, A. M. Mak, M. B. Sullivan, D. J. Dixon and J. Seayad, *Angew. Chem. Int. Ed.*, 2017, **56**, 16550–16554.

104 S. Sabir, M. I. Alhazza and A. A. Ibrahim, *Catal. Sustain. Energy*, 2016, **2**, 99–115.

105 Novel Drug Approvals for 2020: U.S. Food & Drug, https://*www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020, (accessed August 2021).*

106 J. Jampilek, *Molecules*, 2019, **24**, 10–13.

107 G. Sivakumar, A. Vijeta and M. Jeganmohan, *Chem. Eur. J.*, 2016, **22**, 5899–5903.

108 X. Yu, K. Chen, S. Guo, P. Shi, C. Song and J. Zhu, *Org. Lett.*, 2017, **19**, 5348–5351.

109 P. G. Chirila, J. Adams, A. Dirjal, A. Hamilton and C. J. Whiteoak, *Chem.-A Eur. J.*, 2018, **24**, 3584.

110 F. Wang, L. Jin, L. Kong and X. Li, *Org. Lett.*, 2017, **19**, 1812–1815.

111 P. Shi, L. Wang, K. Chen, J. Wang and J. Zhu, *Org. Lett.*, 2017, **19**, 2418–2421.

112 R. Hili and A. K. Yudin, *Nat. Chem. Biol.*, 2006, **2**, 284–287.

113 G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054-3131.

114 P. Ruiz-Castillo and S. L. Buchwald, *Chem. Rev.*, 2016, **116**, 12564-12649.

115 J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369–375.

116 H. M. L. Davies and D. Morton, *J. Org. Chem.*, 2016, **81**, 343–350.

117 J. J. Li, *C-H Bond Activation in Organic Synthesis*, CRC Press, Boca Raton, 2015.

118 H. Yi, G. Zhang, H. Wang, Z. Huang, J. Wang, A. K. Singh and A. Lei, *Chem. Rev.*, 2017, **117**, 9016–9085.

119 J. P. Wan, L. Gan and Y. Liu, *Org. Biomol. Chem.*, 2017, **15**, 9031–9043.

120 Y. Qin, L. Zhu and S. Luo, *Chem. Rev.*, 2017, **117**, 9433–9520.

121 J. Jiao, K. Murakami and K. Itami, *ACS Catal.*, 2016, **6**, 610–633.

122 K. Shin, H. Kim and S. Chang, *Acc. Chem. Res.*, 2015, **48**, 1040–1052.

123 G. Pototschnig, N. Maulide and M. Schnürch, *Chem. Eur. J.*, 2017, **23**, 9206–9232.

124 D. Wei, X. Zhu, J. L. Niu and M. P. Song, *ChemCatChem*, 2016, **8**, 1242-1263.

125 T. Yoshino and S. Matsunaga, *Adv. Synth. Catal.*, 2017, **359**, 1245–1262.

126 S. Wang, S.-Y. Chen and X.-Q. Yu, *Chem. Commun.*, 2017, **53**, 3165-3180.

127 S. Prakash, R. Kuppusamy and C. H. Cheng, *ChemCatChem*, 2018, **10**, 683–705.

128 F. Wang, H. Wang, Q. Wang, S. Yu and X. Li, *Org. Lett.*, 2016, **18**, 1306-1309.

129 N. Barsu, M. A. Rahman, M. Sen and B. Sundararaju, *Chem. Eur. J.*, 2016, **22**, 9135–9138.

130 X. Yu, Q. Ma, S. Lv, J. Li, C. Zhang, L. Hai, Q. Wang and Y. Wu, *Org. Chem. Front.*, 2017, **4**, 2184–2190.

131 J. Huang, Y. Huang, T. Wang, Q. Huang, Z. Wang and Z. Chen, *Org. Lett.*, 2017, **19**, 1128–1131.

132 J. Park and S. Chang, *Angew. Chem. Int. Ed.*, 2015, **54**, 14103–14107.

133 Y. Liang, Y. F. Liang, C. Tang, Y. Yuan and N. Jiao, *Chem. Eur. J.*, 2015, **21**, 16395–16399.

134 X. Wang, A. Lerchen and F. Glorius, *Org. Lett.*, 2016, **18**, 2090–2093.

135 P. G. Chirila, L. Skibinski, K. Miller, A. Hamilton and C. J. Whiteoak, *Adv. Synth. Catal.*, 2018, **360**, 2324–2332.

136 Z. Khalid, H. A. Ahmad, M. A. Munawar, M. U. A. Khan and S. Gul, *Heterocycles*, 2017, **94**, 3–54.

137 T. Miura, M. Yamauchi and M. Murakami, *Org. Lett.*, 2008, **10**, 3085-3088.

138 T. Miura, M. Morimoto, M. Yamauchi and M. Murakami, *J. Org. Chem.*, 2010, **75**, 5359–5362.

139 N. Wang, S. C. Zheng, L. L. Zhang, Z. Guo and X. Y. Liu, *ACS Catal.*, 2016, **6**, 3496–3505.

140 V. H. Thorat, N. S. Upadhyay, M. Murakami and C. H. Cheng, *Adv. Synth. Catal.*, 2018, **360**, 284–289.

141 J. Li and L. Ackermann, *Chem. Eur. J.*, 2015, **21**, 5718–5722.

142 Y. Bunno, N. Murakami, Y. Suzuki, M. Kanai, T. Yoshino and S.

Matsunaga, *Org. Lett.*, 2016, **18**, 2216–2219.

143 C. J. Whiteoak, O. Planas, A. Company and X. Ribas, *Adv. Synth. Catal.*, 2016, **358**, 1679–1688.

144 T. S. Ibrahim, A. A. Rashad, Z. K. Abdel-Samii, S. A. El-Feky, M. K. Abdel-Hamid and W. Barakat, *Med. Chem. Res.*, 2012, **21**, 4369–4380.

145 E. V. Heyningen, *J. Am. Chem. Soc.*, **77**, 6562–6564.

146 G. Verardo, A. G. Giumanini and P. Strazzolini, *Tetrahedron*, 1990, **46**, 4303–4332.

147 Y. Hayashi, *Chem. Sci.*, 2016, **7**, 866–880.

148 S. Qu and C. J. Cramer, *J. Org. Chem.*, 2017, **82**, 1195–1204.

149 Y. Hwang, Y. Park and S. Chang, *Chem. Eur. J.*, 2017, **23**, 11147–11152.

150 E. M. Simmons and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2012, **51**, 3066–3072.

151 Y. Park, K. T. Park, J. G. Kim and S. Chang, *J. Am. Chem. Soc.*, 2015, **137**, 4534–4542.

152 X. Pang, L. Zhao, D. Zhou, P. Y. He, Z. An, J. X. Ni and R. Yan, *Org. Biomol. Chem.*, 2017, **15**, 6318–6322.

153 S. L. Yedage and B. M. Bhanage, *J. Org. Chem.*, 2017, **82**, 5769–5781.

154 Y. S. Seo, D. S. Kim and C. H. Jun, *Chem. - An Asian J.*, 2016, **11**, 3508-3512.

155 S. C. Chuang, V. Rajeshkumar, C. A. Cheng, J. C. Deng and G. W. Wang, *J. Org. Chem.*, 2011, **76**, 1599–1604.

156 D. C. and Z. R. W. Juana Garcia, J. Sorrentino, E. J. Diller, *Synth Commun.*, 2016, **46**, 475.

157 J. Kraïem and T. Ollevier, *Green Chem.*, 2017, **19**, 1263–1267.

158 S. Sharma, E. Park, J. Park and I. S. Kim, *Org. Lett.*, 2012, **14**, 906–909.

159 C. G. Jørgensen, B. Frølund, J. Kehler and A. A. Jensen, *ChemMedChem*, 2011, **6**, 725–736.

160 U. Gross, P. Koos, M. O'Brien, A. Polyzos and S. V. Ley, *European J. Org. Chem.*, 2014, **2014**, 6418–6430.

161 V. K. Das, R. R. Devi and A. J. Thakur, *Appl. Catal. A Gen.*, 2013, **456**, 118–125.

162 R. Sakamoto, S. Sakurai and K. Maruoka, *Chem. Commun.*, 2017, **53**, 9030.

163 G. N. Hermann and C. Bolm, *ACS Catal.*, 2017, **7**, 4592–4596.

164 K. D. Hesp, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2011, **133**, 11430–11433.

165 N. Kuroda, N. Hird and D. G. Cork, *J. Comb. Chem.*, 2006, **8**, 505–512.

166 Y. Yan, H. Li, B. Niu, C. Zhu, T. Chen and Y. Liu, *Tetrahedron Lett.*, 2016, **57**, 4170–4173.

167 C. Sease, *Stud. Conserv.*, 1978, **23**, 76–85.

168 M. Finšgar and I. Milošev, *Corros. Sci.*, 2010, **52**, 2737–2749.

169 Y. Ren, *Med. Chem. (Los Angeles)*, 2014, **4**, 640–662.

170 I. Briguglio, S. Piras, P. Corona, E. Gavini, M. Nieddu, G. Boatto and A. Carta, *Eur. J. Med. Chem.*, 2015, **97**, 612–648.

171 A. R. Katritzky, S. R. Tala, N. E. Abo-Dya, K. Gyanda, B. E. D. M. El-Gendy, Z. K. Abdel-Samii and P. J. Steel, *J. Org. Chem.*, 2009, **74**, 7165–7167.

172 A. R. Katritzky, S. Rachwal and G. J. Hitchings, *Tetrahedron*, 1991, **47**, 2683–2732.

173 A. R. Katritzky, X. Lan, J. Z. Yang and O. V Denisko, *Chem. Rev.*, 1998, **98**, 409–548.

174 A. R. Katritzky and B. V Rogovoy, *Chem. Eur. J.*, 2003, **9**, 4586–4593.

175 A. R. Katritzky, K. Manju, S. K. Singh and N. K. Meher, *Tetrahedron*, 2005, **61**, 2555–2581.

176 A. R. Katritzky, L. Xie, D. Toader and L. Serdyuk, *J. Am. Chem. Soc.*, 1995, **117**, 12015–12016.

177 A. R. Katritzky, S. A. Henderson and B. Yang, *J. Heterocycl. Chem.*, 2009, **35**, 1123–1159.

178 R. R. Kale, V. Prasad, P. P. Mohapatra and V. K. Tiwari, *Monatsh. Chem.*, 2010, **141**, 1159–1182.

179 X. Wang, Y. Liu and Y. Zhang, *Tetrahedron*, 2003, **59**, 8257–8263.

180 S. Talukdar, R.-J. Chen, C. Chen, L. Lo and J. Fang, *J. Comb. Chem.*, 2001, **3**, 341–345.

181 G. Boche, P. Andrews, K. Harms, M. Marsch, K. S. Rangappa, M. Schimeczek and C. Willeke, *J. Am. Chem. Soc.*, 1996, **118**, 4925–4930.

182 V. Gurram, H. K. Akula, R. Garlapati, N. Pottabathini and M. K. Lakshman, *Adv. Synth. Catal.*, 2015, **357**, 451–462.

183 J. Fu, Y. Yang, X. W. Zhang, W. J. Mao, Z. M. Zhang and H. L. Zhu, *Bioorganic Med. Chem.*, 2010, **18**, 8457–8462.

184 J. Zhou, J. He, B. Wang, W. Yang and H. Ren, *J. Am. Chem. Soc.*, 2011,

133, 6868–6870.

185 F. Shi, J. P. Waldo, Y. Chen and R. C. Larock, *Org. Lett.*, 2008, **10**, 2409-2412.

186 S. Azeez, P. Chaudhary, P. Sureshbabu, S. Sabiah and J. Kandasamy, *Org. Biomol. Chem.*, 2018, **16**, 6902–6907.

187 W. Roth, D. Spangenberg, C. Janzen, A. Westphal and M. Schmitt, *Chem. Phys.*, 1999, **248**, 17–25.

188 J. Poznański, A. Najda, M. Bretner and D. Shugar, *J. Phys. Chem. A*, 2007, **111**, 6501–6509.

189 N. Jagerovic, M. Luisa Jimeno, I. Alkorta, J. Elguero and R. María Claramunt, *Tetrahedron*, 2002, **58**, 9089–9094.

190 Y. Wang, C. Du, Y. Wang, X. Guo, L. Fang, M. P. Song, J. L. Niu and D. Wei, *Adv. Synth. Catal.*, 2018, **360**, 2668–2677.

191 L. Zhang, W. Wang, A. Wang, Y. Cui, X. Yang, Y. Huang, X. Liu, W. Liu, J. Son, H. Oji and T. Zhang, *Green Chem.*, 2013, **15**, 2680.

192 A. R. Massah, R. J. Kalbasi, M. Khalifesoltani and F. Moshtagh Kordesofla, *ISRN Org. Chem.*, 2013, **2013**, 1–12.

193 R. Guo, C. Zhu, Z. Sheng, Y. Li, W. Yin and C. Chu, *Tetrahedron Lett.*, 2015, **56**, 6223–6226.

194 M. Li, L. Hu, X. Cao, H. Hong, J. Lu and H. Gu, *Chem. Eur. J.*, 2011, **17**, 2763–2768.

195 B. T. Gowda and J. K. Lakshmipathy, 2006, 2–6.

196 K. Dooleweerdt, B. P. Fors and S. L. Buchwald, *Org. Lett.*, 2010, **12**, 2350–2353.

197 B. Liu, L. Yang, P. Li, F. Wang and X. Li, *Org. Chem. Front.*, 2021, **8**, 1085–1101

198 B. Jiang, M. Zhao, S. Sen Li, Y. H. Xu and T. P. Loh, *Angew. Chem. Int. Ed.*, 2018, **57**, 555–559.

199 J. Zhang and T. P. Loh, *Chem. Commun.*, 2012, **48**, 11232–11234.

200 M. K. Haj, S. M. Banik and E. N. Jacobsen, *Org. Lett.*, 2019, **21**, 4919-4923.

201 M. Hashimoto, Y. Obora, S. Sakaguchi and Y. Ishii, *J. Org. Chem.*, 2008, **73**, 2894–2897.

202 M. Yamauchi, M. Morimoto, T. Miura and M. Murakami, *J. Am. Chem. Soc.*, 2010, **132**, 54–55.

203 T. Miura, M. Morimoto, M. Yamauchi and M. Murakami, *J. Org. Chem.*, 2010, **75**, 5359–5362.

204 T. Miura, M. Yamauchi, A. Kosaka and M. Murakami, *Angew. Chem. Int. Ed.*, 2010, **49**, 4955–4957.

205 T. Miura, Y. Nishida, M. Morimoto, M. Yamauchi and M. Murakami, *Org. Lett.*, 2011, **13**, 1429–1431.

206 Z. J. Fang, S. C. Zheng, Z. Guo, J. Y. Guo, B. Tan and X. Y. Liu, *Angew. Chem. Int. Ed.*, 2015, **54**, 9528–9532.

207 M. Hari Balakrishnan, K. Sathriyan and S. Mannathan, *Org. Lett.*, 2018, **20**, 3815–3818.

208 J. Sanjosé-Orduna, D. Gallego, A. Garcia-Roca, E. Martin, J. Benet-Buchholz and M. H. Pérez-Temprano, *Angew. Chemie Int. Ed.*, 2017, **56**, 12137–12141.

209 M. Wrighton, *Chem. Rev.*, 1974, **74**, 401–430.

210 E. M. Harcourt, S. R. Yonis, D. E. Lynch and D. G. Hamilton, *Organometallics*, 2008, **27**, 1653–1656.

211 O. Planas, S. Roldán-Gómez, V. Martin-Diaconescu, T. Parella, J. M. Luis, A. Company and X. Ribas, *J. Am. Chem. Soc.*, 2017, **139**, 14649-14655.

212 F. Neese, *WIREs Comput. Mol. Sci.*, 2012, **2**, 73–78.

213 F. Neese, F. Wennmohs, A. Hansen and U. Becker, *Chem. Phys.*, 2009, **356**, 98–109.

214 A. D. Becke, *Phys. Rev. A*, 1988, **4**, 3098.

215 J. P. Perdew, *Phys. Rev. B*, 1986, 8822–8824.

216 J. P. Perdew, *Phys. Rev. B*, 1986, **34**, 7406.

217 F. Weigend and R. Ahlrichs, *Phys. Chem. Chem. Phys.*, 2005, **7**, 3297-3305.

218 A. Schäfer, H. Horn and R. Ahlrichs, *J. Chem. Phys.*, 1992, **97**, 2571-2577.

219 Y. Zhao and D. G. Truhlar, *Theor. Chem. Acc.*, 2008, **120**, 215–241.

220 S. Sinnecker, A. Rajendran, A. Klamt, M. Diedenhofen and F. Neese, *J. Phys. Chem. A*, 2006, **110**, 2235–2245.

221 A.-R. Allouche, *J. Comput. Chem.*, 2011, **32**, 174.

222 R. López, *Adv. Math.*, 2014, **262**, 476–483.

223 G. M. Sheldrick, *Acta Crystallogr. Sect. A Found. Adv.*, 2015, **71**, 3–8.

224 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339–341.

225 G. M. Sheldrick, *Acta Crystallogr. Sect. C Struct. Chem.*, 2015, **71**, 3–8.

Annex

Computational Details

DFT calculations undertaken using the ORCA 3.03 computational software.[212] Optimisations were performed at the RI-BP86-D3BJ/def2-TZVP level of theory[213–216] and single point energies and solvation corrections calculated at RIJCOSX-M06/def2-TZVP using default settings for integration grid.[75–77] Frequencies calculations approximated the ZPE correction and entropic contributions to the free energy term as well as confirming all intermediate were true with no imaginary modes and all transition states had the correct critical frequency of decomposition (imaginary mode). Solvation correction was implemented with the COSMO [220] model for 1,2-DCE. Graphical visualisation using Gabedit 2.4.8 [221] and Avogadro 1.2.0 [222] programs.

General Calculated Structures

AcOH (-229.03 Eh)

C	0.07314062571764	0.39572173448082	0.08039171199520
O	1.24834503036206	0.36480072992513	0.38251116466215
O	-0.62346203314231	-0.72539872128957	-0.27658616421262
H	0.01984355239347	-1.46398387771840	-0.22399919101996
C	-0.78875934242156	1.63183919555068	0.04978177403677
H	-1.81693483017188	1.41431142021261	-0.25598148763634
H	-0.33864209041947	2.35714339224073	-0.64117089827268
H	-0.78398991231795	2.08722812659800	1.04910309044746

AcO^- (-228.56 Eh)

C	0.03598607385040	0.29685776359975	0.05511216778790
O	1.24642324127849	0.43030892687872	0.39046838938669
O	-0.59263483990739	-0.74820378331687	-0.27136091447641
C	-0.79308750064602	1.63367755651974	0.04924493905048
H	-1.83889776463871	1.47018902877139	-0.25380416156695
H	-0.32228645864540	2.35673393006308	-0.63766940877994
H	-0.77066303692124	2.08651073459101	1.05467090000639

AgOAc (-5428.32 Eh)

C	0.25315202600428	-0.36464359006794	-0.11425909200623
O	1.48496100851511	-0.32847676045819	0.21261970832772
O	-0.37088846693423	-1.42632533530502	-0.44172432598208
C	-0.51112232693026	0.94982802513432	-0.10806238149700
H	-1.55371905650363	0.80218642391744	-0.40637819544471
H	-0.02133068597900	1.65615131952636	-0.79189883006478
H	-0.46752523599471	1.38785908805536	0.89847736908813
Ag	1.60464873782244	-2.63719217080232	-0.11648425242103

$AgSbF_6$ (--12115.00 Eh)

Sb	-0.06067880002312	0.08980692244763	0.04307952851391
F	-1.74762501280623	0.52110203593808	0.77506620420186
F	1.79377738160266	-0.13816214312118	-0.57016927416065
F	0.81003321214130	0.41235621731370	1.77665724042206
F	-0.69872583809947	-0.07007024818585	-1.72745651299273
F	0.33943391974667	1.99469584897506	-0.23893270102413
F	-0.19528843133265	-1.75562262791544	0.42201883821105
Ag	2.55667856877085	1.76499399454801	0.74453467682863

Amidating agent (-396.43 Eh)

C	-0.85337060731739	1.20552160262476	-0.00420701505938
O	0.48334848912315	1.16948043955392	0.42051660028679
C	0.87981785238113	-0.12765297170049	0.26325799345954
N	-0.02957492507740	-0.91558292554657	-0.20415220044925
O	-1.17248051170537	-0.06808685210253	-0.38778803397436
O	-1.55629407708555	2.16949745625374	-0.01939162072346
C	2.26109208306498	-0.51321999907581	0.62454073902032
H	2.39708749569383	-1.58358602991133	0.43476276990856
H	2.45038732782376	-0.30090336699265	1.68632576145120
H	2.98455687309886	0.05966464689697	0.02852400608003

CO_2 (-188.59 Eh)

C	1.49403779672939	0.13860154127029	0.41402977465009
O	1.39324546617214	1.29545681429889	0.56912478558740
O	1.59492473709847	-1.01825235556918	0.25898543976251

SbF_6^- (-6915.29 Eh)

Sb	-3.67992632051867	6.03797383596487	-9.03757582241826
F	-2.81847311854004	4.70676385986016	-10.12559385137536
F	-4.54417717613647	7.36630449859634	-7.94820120022293
F	-3.31867958965395	7.36951072019612	-10.37720632440826
F	-1.99941895483180	6.43278224664650	-8.19010162269145
F	-4.04379011506592	4.70888088896509	-7.69634391369860
F	-5.36028872525316	5.64447994977091	-9.88600226518513

[Cp*Co(III)OAc]$^{+}$ (-2000.77 Eh)

Co	0.98417452445472	-1.55154633671616	1.03382410819974
C	0.38348598124991	-1.08085806586443	2.88984959386938
C	0.53248269271206	-2.52652275011278	2.76210748463042
C	1.88000087763379	-2.78711244999296	2.38180959230683
C	2.57792251781877	-1.50377148767554	2.28675835464876
C	1.66039233192406	-0.45886736396026	2.62458919237865
C	1.92896840464291	1.00588785751504	2.63126032066688
H	2.84798019889235	1.25545955438671	2.08883667929965
H	2.04351253958611	1.36008853414174	3.66769267660681
H	1.10367275658335	1.57012580462784	2.17845364957831
C	3.98901173016382	-1.33517118292548	1.85679978689079
H	4.18767835406460	-0.32698408387611	1.47663825803326
H	4.27388210412669	-2.06738059527343	1.08999084289307
H	4.65401501467720	-1.50282609316472	2.72181279477845
C	2.48017744811512	-4.11342749506034	2.08043212592261
H	3.20439837354852	-4.05658328547986	1.25711770621035
H	1.71805159685779	-4.85763257100249	1.82321067537163
H	3.02422858868540	-4.48335141458388	2.96597220022162
C	-0.55578601507655	-3.52585565261090	2.93601916141632
H	-0.34499421329534	-4.45499259453577	2.39518258959504
H	-1.52252358247156	-3.13817606699802	2.59178092715557
H	-0.66244923841387	-3.77444862336219	4.00418547998189
C	-0.87594242099707	-0.36999143211076	3.21984221502902
H	-0.88375864416734	0.65497140710560	2.83180209519047
H	-0.97334265143006	-0.30698644129865	4.31826915738419
H	-1.76033184221468	-0.90222566146729	2.84884450827216
C	0.22463019664009	-1.30938180449407	-1.11466452675993

O	0.78220315317825	-0.34297204011753	-0.46293683158785
O	0.10537363830367	-2.41488916670002	-0.45374000815906
C	-0.26356882031229	-1.15755317325534	-2.50532170576319
H	-0.18484030111324	-2.10955139319407	-3.04397559795494
H	0.28109092633358	-0.35804050304729	-3.01955649840599
H	-1.32962822070075	-0.88039542889658	-2.46730300790091

Cp*Co(III)$(OAc)_2$ (-2229.39 Eh)

Co	1.07615934347659	-1.43758851541960	1.28428257928123
C	0.39082877445472	-0.99738874950653	3.15682503256086
C	0.41213380714687	-2.41214201518510	2.94762687514825
C	1.76370223178281	-2.80319365081618	2.60535340739562
C	2.58530781051292	-1.61901180808370	2.66115547604196
C	1.74425669517078	-0.50121752052151	2.96795415167494
C	2.18650138603048	0.92001589779279	3.03336978576444
H	2.78446552647261	1.15917447622620	2.14236422233080
H	2.80123362364542	1.09299688510355	3.93170289133804
H	1.32985639681623	1.60330869374150	3.07077950625135
C	4.05560504736525	-1.57457785648491	2.42744289675716
H	4.37269082682106	-0.58387771243497	2.08830544434038
H	4.35810740563028	-2.30778344185214	1.66915664433562
H	4.58460057700734	-1.82169908872123	3.36309036180265
C	2.23602896357335	-4.17879526605155	2.27556663339245
H	2.96564142470899	-4.15243754827107	1.45511207909371
H	1.40513915678134	-4.82530143090694	1.96590589667651
H	2.72298427162433	-4.64921651675090	3.14606017300646
C	-0.75777623651138	-3.33581148493537	2.97184776944389
H	-0.77051021486275	-3.98101376712168	2.08300526049626

H	-1.70709686387896	-2.78876646662462	2.99987391340030
H	-0.71198409055904	-3.98402572406697	3.86191386825623
C	-0.80000002681996	-0.15468082877708	3.46968052893250
H	-0.75670598225172	0.80020931443234	2.93074591439664
H	-0.84985412761584	0.06715668094559	4.54753167817328
H	-1.73313260985463	-0.65614431444771	3.18511713562633
C	-0.60863250166111	-0.91162734654151	-0.28259660702422
O	0.08087274520936	0.00053814419816	0.28807975804081
O	-0.41112432104233	-2.11668020375447	0.09752287108441
C	-1.57884211292302	-0.58580849042974	-1.37871854715708
H	-1.06875532990941	-0.70574036763543	-2.34610924446512
H	-1.92010760881888	0.45206207887754	-1.29310257593178
H	-2.43008679848284	-1.27680615939621	-1.35501446267835
C	3.05820915493773	-0.70721846077733	-0.56769353134888
O	2.23134148020894	-1.66636579681457	-0.22475748547588
O	3.28498789143179	0.32970329899755	0.06260557372638
C	3.74823599278465	-0.98095332658904	-1.90097859462008
H	4.76507709752787	-0.57137259719138	-1.88057626085434
H	3.18996824198886	-0.45761275994350	-2.69128994627767
H	3.76481395208130	-2.05033125426226	-2.14141107293609

Calculated Structures for Chapter 2

Calculated Structures for single state

iPr-Substrate (-518.54 Eh)

C	-3.13821301815115	-2.97055309700632	-0.55837356922019
N	-2.95182184174973	-1.53029621275897	-0.80613443721635
C	-2.07296955736953	-0.73389365835035	-0.12596036054088

O	-1.32006527642434	-1.15579551098839	0.75644972796873
C	-2.08117755908339	0.71914518645285	-0.52248354943748
C	-1.63777372402852	1.64883454250051	0.42867036701749
C	-1.61848508862599	3.01007344706662	0.12999721615357
C	-2.02474546247545	3.45723017273275	-1.13156509087905
C	-2.44722235592591	2.53576498780364	-2.09303296148590
C	-2.47818064779957	1.17340810457317	-1.78944719564795
H	-1.30798830661809	1.27336614991505	1.39750394243241
H	-1.28133581026148	3.72645525172958	0.88050875446221
H	-2.00275879913083	4.52195414269852	-1.36896021422422
H	-2.74449154259152	2.87790466709601	-3.08513850557296
H	-3.91099759443645	-3.27696197629526	-1.28161302464159
C	-3.66297704060144	-3.24044684322048	0.85764851771093
C	-1.85924426123588	-3.75702958052091	-0.86286441855652
H	-4.59360524165085	-2.68618067879549	1.04333722131947
H	-2.91775809568270	-2.93384933190022	1.60192637753493
H	-3.86959990048660	-4.31271759003693	0.98451768235797
H	-1.06095360200244	-3.46916959876130	-0.16838833593563
H	-1.51808467271752	-3.56398824157205	-1.88959310278355
H	-2.04944911802868	-4.83491633428004	-0.75781552655799
H	-2.77450367597961	0.46239117482073	-2.56293248776979
H	-3.63528980694235	-1.06606717290269	-1.39313002648764

Int1 (-2519.34 Eh)

C	2.40753001758866	-3.10527563852997	1.12635142031733
Co	-1.63064197061710	-3.62740517929759	2.97468431276650
N	2.01357647649611	-4.49855577279667	1.38176461791363
C	0.96462348970295	-4.86782742312158	2.13116394531823

O	0.30435040531157	-3.98061451103622	2.75302176022674
C	0.68474082974972	-6.31981663974303	2.22006455594440
C	0.22874483749931	-6.85201595448392	3.43525368383600
C	-0.00007864043210	-8.22068493456448	3.55451481435619
C	0.21055948681179	-9.06489016453828	2.45969545897734
C	0.65224683570807	-8.53848159570602	1.24142863316651
C	0.89280878516943	-7.17056809675258	1.12076314244059
H	0.06147998927710	-6.18530414338927	4.27970042798787
H	-0.34586187293481	-8.63180570825280	4.50280557413869
H	0.02576322569522	-10.13553117619760	2.55408710153261
H	0.80104767799846	-9.19373508618531	0.38300445328504
H	1.47563905255303	-2.52673450618705	1.19179497874918
C	2.98381320214121	-3.00272805349508	-0.28425361423979
C	3.38165123908874	-2.61413882126485	2.20108395188142
H	2.25617046790690	-3.33124513369483	-1.03807061858115
H	3.89383887938786	-3.61377511879886	-0.38304064129679
H	3.26099491924634	-1.96355865528627	-0.50298563377941
H	4.32268060676814	-3.18125011718095	2.16504520932870
H	2.94964169765026	-2.72885886918271	3.20442500279959
H	3.61867483319469	-1.55348775107968	2.04302928083719
C	-2.45091034004649	-1.77342206867332	2.70456643365079
C	-3.34840970075727	-2.67419610162766	3.39822246492834
C	-2.69604646709891	-3.08477716164204	4.62448171096464
C	-1.39556497129011	-2.48695439931824	4.65905130019469
C	-1.25048392049419	-1.66099734473998	3.47233062263022
C	-0.03828284019656	-0.86680554686325	3.13701122003575
H	0.87190018176098	-1.46122933719278	3.29189907086012
H	0.02788122948578	0.01711149528654	3.78989181039266

H	-0.05362450517427	-0.51589160885131	2.09886171466796
C	-0.34786559094364	-2.66727086227953	5.70180668481522
H	0.64409524985328	-2.78309670330199	5.24614558720066
H	-0.54504572170439	-3.54462358232594	6.32813869839334
H	-0.30974243356650	-1.78489166496958	6.36125405130059
C	-3.26997494569231	-4.03418298708447	5.61485634655880
H	-2.50562423514397	-4.43174900336794	6.29158730481353
H	-3.76325686669026	-4.87961895087935	5.11684182458426
H	-4.02736181194753	-3.51791968423794	6.22622533611205
C	-4.71348505560384	-3.07164041901118	2.95382208765194
H	-4.98503218674289	-4.06285407247451	3.33561397424716
H	-4.79023054944541	-3.08632526813618	1.85900630121146
H	-5.46074911696613	-2.35424865265187	3.32901016414068
C	-2.72339954863030	-1.14931588754096	1.38195774048442
H	-1.80216632192885	-0.81712033160164	0.89049758958864
H	-3.37481044085649	-0.27008311087430	1.51224980138029
H	-3.23910209199247	-1.84892581361210	0.71157131010570
H	1.20108564219638	-6.75740314866318	0.15895447742449
H	2.62790347618255	-5.23544061439117	1.04302809296539
C	-2.33546231827835	-5.46823930335622	1.67215055931612
O	-1.97889343595913	-4.35880129179127	1.13706944448474
O	-2.30189237177879	-5.50023304745312	2.95420640183108
C	-2.73806495926225	-6.65780353297958	0.86856822902597
H	-1.98484267726603	-7.44878651463426	1.00122384130682
H	-2.81766993887935	-6.39988458836891	-0.19241211287260
H	-3.69485788610387	-7.04937983962519	1.23815309769749

TS1-2 (-2519.30 Eh)

C	1.37247423498986	-2.87590048324255	1.63295420233284
Co	-2.46833501193658	-5.30950886137453	3.12780553689065
N	1.29195767927932	-4.28522709350735	2.06088180136706
C	0.15682689779057	-4.89410111058190	2.41245123719704
O	-0.94463967171417	-4.25310429176603	2.42554160343270
C	0.12985161119315	-6.31941104144524	2.77756562077072
C	-1.16764139228629	-6.89459370040520	2.71670178691200
C	-1.28862551538675	-8.26574808466806	2.99981042994522
C	-0.17814227089683	-9.01965947190772	3.38148439575381
C	1.08265074041659	-8.42018245292390	3.48688839563585
C	1.24021997173582	-7.06771476211679	3.17560146797015
H	-1.83671012249835	-6.59427889313708	1.67631965574237
H	-2.25695093615749	-8.75432662295751	2.88309822825985
H	-0.29016261717827	-10.08366342950138	3.59458073393484
H	1.94332143936829	-9.00892330439586	3.80341220632985
H	0.64119560712620	-2.33701867583475	2.25312516660297
C	0.97352896420005	-2.73842127732603	0.16106851876834
C	2.77890251240296	-2.35766906555385	1.91940670923430
H	-0.03750319075966	-3.13003928660173	-0.00897628646670
H	1.67542125810048	-3.28299535196382	-0.48669988743703
H	0.98722722366296	-1.68065566851118	-0.13365480733909
H	3.52937136060420	-2.91360007472831	1.33649573625253
H	3.03034493140200	-2.44169326064726	2.98557476150923
H	2.85721535597527	-1.30196177867466	1.63079814828479
C	-4.28591646036609	-4.90964732771729	4.04542415253187
C	-3.74740520254275	-6.15949322230976	4.50430262655377
C	-2.47095627317336	-5.88303003641841	5.14001338311023

C	-2.20816253925464	-4.48828659624212	5.00652304804956
C	-3.32041278802531	-3.87650564006730	4.30495052702624
C	-3.44043616063274	-2.43587967753961	3.94735626022361
H	-2.46971277814055	-2.01812474033364	3.65179936450074
H	-3.80657855153893	-1.85371107105940	4.80856818881546
H	-4.14183798440841	-2.28779750362888	3.11806230150478
C	-0.99649574191113	-3.77709954760623	5.49619447018435
H	-0.73870244475537	-2.92768156245673	4.85238493980413
H	-0.12945465240203	-4.44646169594161	5.56141030279633
H	-1.18240821117040	-3.38124732638037	6.50744168188515
C	-1.62841507439767	-6.85110214253590	5.89501081520596
H	-0.55679093566081	-6.68286152155548	5.72697444669086
H	-1.85268373173748	-7.88804421514194	5.62698895440994
H	-1.81785342189269	-6.73158230463363	6.97434590149103
C	-4.45168018132458	-7.47289432333599	4.46789854326694
H	-3.75522097967675	-8.31286258620456	4.56916084906874
H	-5.01749088244218	-7.60354376467904	3.53625236848253
H	-5.17106404446687	-7.53853909971283	5.30063049886468
C	-5.59408033960545	-4.72272767627999	3.36554796216935
H	-5.52475839962001	-3.98440097937328	2.55782903874643
H	-6.33463427238261	-4.35976201824701	4.09648481179714
H	-5.97036190406450	-5.66114946783111	2.94412604970519
H	2.22525041501983	-6.60547434505135	3.27183231905006
H	2.11827595918508	-4.86507339884235	1.93668643001492
C	-3.09989831695609	-5.57721334863302	0.38596049036745
O	-3.38706637387543	-4.93573385832912	1.46294093202904
O	-2.24145304082443	-6.50125696970198	0.33329081832860
C	-3.86955840975783	-5.20350910674119	-0.85508864205725

H	-3.22686044866453	-5.29804240256660	-1.73743412919744
H	-4.27520013836766	-4.19035249422503	-0.77304136727276
H	-4.70493174959896	-5.90924898490443	-0.97101970003192

Int2 (-2519.32 Eh)

C	1.40981270254217	-2.95916076757562	1.45965780372143
Co	-2.33919171098814	-5.43012897785322	3.10157408934164
N	1.35857490231300	-4.36760993654902	1.89258114051253
C	0.24631753506773	-4.99859500068708	2.27778347075221
O	-0.87251837613697	-4.38223996291466	2.28959679479180
C	0.23259793757314	-6.41826494516341	2.65353101411136
C	-1.07405109193613	-6.87683959721852	2.98110104569970
C	-1.23179411817900	-8.25331730203377	3.20591395003322
C	-0.13602614827287	-9.12219674317637	3.16404565529379
C	1.15024212922213	-8.63929540442480	2.89238809829352
C	1.33398889822939	-7.28557593932529	2.62203320302197
H	-1.49190814918400	-7.10057192476488	1.10831808584931
H	-2.22245648446825	-8.66374312244583	3.40846248222909
H	-0.28537087006143	-10.18807849910541	3.34444417286735
H	1.99943755086138	-9.32161635389768	2.87199225818073
H	0.42893119185087	-2.75245902384848	1.00792402781965
C	2.50477495370713	-2.80712342836832	0.40776723843894
C	1.61098592512212	-2.03088667440412	2.65877593821177
H	2.32612775495205	-3.46186195350648	-0.45545745700710
H	3.49388544537200	-3.04380599165428	0.83044536525148
H	2.54137448549776	-1.77088091952570	0.04969300462347
H	2.58064283861091	-2.21502407408984	3.14472763237106
H	0.81735368262625	-2.17341197688323	3.40429034829366

H	1.58811403976500	-0.98233429773331	2.33242014489731
C	-4.10092117763568	-4.44795141157257	3.82230382540505
C	-3.97837266559173	-5.83125289297332	4.27343895895496
C	-2.77860655277044	-5.93717011964815	5.05147951247230
C	-2.09145055020686	-4.67636405816486	4.96204228497915
C	-2.94999962467876	-3.74456122276827	4.23695964742274
C	-2.58927014292712	-2.32877812407516	3.94493866248932
H	-1.62194856190174	-2.27900474452280	3.42482005374622
H	-2.49859523451575	-1.75387876834234	4.87879160035406
H	-3.33766557315565	-1.83646708275537	3.31371970187504
C	-0.78783112471060	-4.34671179474392	5.60266171497522
H	-0.26879685821667	-3.54386686352429	5.06502317864008
H	-0.12828227646357	-5.22347094134066	5.63916830230057
H	-0.94151598437632	-4.00492613375611	6.63884289052880
C	-2.36013654651023	-7.08855881960214	5.89883355143642
H	-1.27241770207733	-7.22493620784566	5.90686120321150
H	-2.82240347481945	-8.02975830290902	5.58240574667882
H	-2.68289291820457	-6.89796461433121	6.93509681861866
C	-4.99945055364521	-6.89612707980594	4.06155903209559
H	-4.57056283396994	-7.89825269752143	4.18667484352723
H	-5.44105770772723	-6.83343882012304	3.05891443075042
H	-5.82129732347552	-6.79424088893672	4.78923606922776
C	-5.23317981249233	-3.93507576107346	3.00286579122710
H	-5.07017968840147	-2.90034258540474	2.68165559357966
H	-6.16934256246526	-3.97030647435304	3.58075850355846
H	-5.37425821978863	-4.55217550824721	2.10502084374865
H	2.33547418357499	-6.92250767234141	2.37778091249531
H	2.22973783453383	-4.89083324324277	1.90129775679447

C	-2.93796593347835	-6.20525826787645	0.29429941562600
O	-3.24868370926239	-5.60577438190994	1.34153250239728
O	-1.90738714381384	-7.02741887035257	0.20000235576191
C	-3.72206081852896	-6.04305315992508	-0.96763340118451
H	-3.07436912861858	-5.61236729192933	-1.74477995848909
H	-4.58304259159254	-5.39104355982593	-0.79996458077516
H	-4.04957404617233	-7.02648581710575	-1.33066227202991

Int3 (-2686.73 Eh)

C	-5.56978276789837	-5.75189429900301	3.27653684013308
Co	-0.90245727340752	-4.99192354108797	2.49169279103474
N	-4.41165860977308	-6.32729273022913	3.98152115809576
C	-3.13420429426638	-6.05033862728882	3.70347110945824
O	-2.84868609263744	-5.19703907635387	2.78955575315078
C	-2.02020543387327	-6.66104885304195	4.42437108979235
C	-0.75827846952187	-6.21229066557144	3.97005365473223
C	0.37800427672923	-6.64339040628377	4.65754208607054
C	0.26539407013087	-7.53230992498125	5.73079446065664
C	-0.98779489652211	-8.00029833826942	6.14836205453457
C	-2.13531919702098	-7.55663002079431	5.50142979592306
H	1.36776317553224	-6.28324779182310	4.37553102046275
H	1.16489907339525	-7.85977425085873	6.25422288721720
H	-1.06341549230709	-8.69414968472736	6.98519917589828
H	-5.25439030351021	-4.74776953894896	2.95800273033029
C	-6.73793712964175	-5.64047577451719	4.25280902689588
C	-5.91339641759348	-6.58222879406184	2.03748757357377
H	-6.48030702495123	-5.01741831743305	5.11956935417597
H	-7.04410553797915	-6.63427488414733	4.61450841089746

H	-7.60653177007537	-5.19313679257256	3.75327260650249
H	-6.21645364205716	-7.60059963134636	2.31988631466666
H	-5.05095432748745	-6.65366191054201	1.36155788482649
H	-6.74442892174277	-6.11864842562060	1.48908764762944
C	-0.07491891219590	-3.91733340663552	0.86343909456293
C	0.87528629259387	-4.84737847548607	1.46756961746849
C	0.34316630754490	-6.17412920969736	1.32193589755576
C	-0.96391701976194	-6.05734415510193	0.74680827380758
C	-1.19865310408650	-4.65348559487474	0.42584578093616
C	-2.44181695436831	-4.13217568617785	-0.21093286049998
H	-3.33389650454496	-4.48986147850757	0.32325637549466
H	-2.51981488910128	-4.48394562975347	-1.25096743392746
H	-2.46225113663024	-3.03569508422828	-0.22981186213835
C	-1.89319343289381	-7.17964858360009	0.43687500367343
H	-2.93994980992903	-6.86537532042294	0.52912101105324
H	-1.72834663477495	-8.03719660924956	1.10039776786166
H	-1.74235077498465	-7.52617633460265	-0.59837956831252
C	1.04743635227308	-7.45111292580767	1.62695204906522
H	0.37321471804552	-8.20465059445650	2.04941934583659
H	1.87778306037852	-7.30704450200282	2.32721905947428
H	1.46946371661809	-7.85837446254788	0.69457141588165
C	2.23020385629093	-4.49371234628411	1.97867761334714
H	2.56805747328526	-5.19053128596919	2.75556169228376
H	2.26022151688408	-3.48135643485112	2.39755151156570
H	2.96607757977823	-4.53341786880071	1.15877234384641
C	0.13029864600017	-2.44358243155201	0.76048373496989
H	-0.81472586221181	-1.90528726188505	0.62087462886387
H	0.77579082328221	-2.21132436904368	-0.10108452959763

H	0.63206996964339	-2.04165040978229	1.65053126958785
H	-3.11088186592435	-7.90363189319427	5.85075279197433
H	-4.59559175062361	-7.03322505693981	4.68940966507012
C	-1.50403332701904	-2.47639526724188	3.95917867026325
O	-0.97324490209823	-1.69148438322809	4.92817973031261
C	0.24050152442693	-2.28807945257828	5.31854030203210
O	0.37524828437484	-3.42103332097086	4.55575215864264
N	-0.77540915544662	-3.51608847039049	3.68724377178632
O	0.99219449238298	-1.87917671805168	6.14013173229815
C	-2.78043163951162	-2.09476423395434	3.32726590669263
H	-3.05280268539010	-2.84295530600934	2.57656458464687
H	-2.68572987457381	-1.10028706443075	2.86880090913426
H	-3.57011037125316	-2.03796909218503	4.08992511782772

TS3-4 (-2686.69 Eh)

C	-5.47512478377405	-6.33853636196843	3.08882217141834
Co	-0.99016972522522	-4.84043934334055	2.37650854661951
N	-4.25784242841585	-6.67684900312690	3.84908545542450
C	-3.03994706807342	-6.19155358929265	3.60838427813739
O	-2.85598950726596	-5.37348834635470	2.63419725333828
C	-1.87149680947650	-6.54604303865759	4.40359805603141
C	-0.68613597886966	-5.94039681702853	3.93801400507888
C	0.49506504709646	-6.12338327040589	4.64965556796376
C	0.49842371928752	-6.93326051079784	5.79119040626243
C	-0.67309006196212	-7.55771716557994	6.23846959258392
C	-1.86382215552057	-7.35939997609735	5.54988076377153
H	1.41049508490211	-5.61619640399963	4.35580752587714
H	1.42722930556286	-7.06488255740173	6.34807154682576

H	-0.65436353808359	-8.17889775688570	7.13326732666341
H	-5.12252840309750	-6.00058478600954	2.10460853565338
C	-6.23192262517644	-5.19596754383285	3.76983069913538
C	-6.32515406933759	-7.59720772067988	2.92870289912387
H	-5.59454159937293	-4.30845927492890	3.87196158075150
H	-6.57650787200901	-5.49492116849351	4.76978957981820
H	-7.11371635555484	-4.91981682193574	3.17645306387014
H	-6.66860924962421	-7.96871984896525	3.90653502582009
H	-5.76570953892188	-8.39800536125955	2.42717595575627
H	-7.21833630360196	-7.37422118524891	2.33141382010464
C	0.08912155284885	-3.89232425367200	0.82564069848764
C	0.84552428036128	-4.98974998588062	1.39978268251635
C	0.10980411320668	-6.20846988946811	1.16943472423936
C	-1.10104041948996	-5.85429721500060	0.49626344703517
C	-1.11963166853966	-4.42104128485888	0.28497344898555
C	-2.21044073070528	-3.66539103234927	-0.39340423684820
H	-3.19668147968891	-4.07850068164790	-0.14348108316652
H	-2.09853805949071	-3.72586603193376	-1.48828023104488
H	-2.19956429252131	-2.60415618796108	-0.11726389305219
C	-2.17514764628467	-6.79143411941138	0.07467659835916
H	-3.16814109261255	-6.34945498631262	0.22027395718416
H	-2.12695759783140	-7.73986461455484	0.62084896834253
H	-2.06659851597893	-7.01699613668529	-0.99842790852470
C	0.56586132714181	-7.59051535739892	1.49238198487878
H	-0.27751988519871	-8.25499501088741	1.71747104880749
H	1.24257043116254	-7.60345023706001	2.35470298798802
H	1.10564558144995	-8.01472080493341	0.63066224727020
C	2.21384154546204	-4.86343645406500	1.97017872517243

H	2.53670460488537	-5.78263856075416	2.46959462083641
H	2.27958335268769	-4.02722581821984	2.67803877373831
H	2.92739808210604	-4.66317966636282	1.15446670730977
C	0.52598930185345	-2.47131966646566	0.83394911840569
H	-0.31075104847723	-1.78739968999628	0.65262292289352
H	1.27470199229914	-2.30835658389392	0.04233540801108
H	0.98645761662967	-2.20473784436497	1.79385796868033
H	-2.78063652883397	-7.82737142414955	5.91711438329928
H	-4.36238061544212	-7.29601406949847	4.64956389909516
C	-1.75821287420915	-2.62407915361897	4.11881635429206
O	-1.35251195482972	-2.10021115917897	5.20800941026275
C	0.37115367307849	-2.52252643933668	5.49136109175162
O	0.72522076271205	-3.05671972145794	4.43879559284039
N	-1.05667073681211	-3.35343132997078	3.29189973025673
O	0.68951977020931	-2.17254356358415	6.57567578090489
C	-3.16667532637788	-2.29339096637448	3.65311354995646
H	-3.43513069762602	-2.82770837663860	2.73690411468110
H	-3.22598722661463	-1.20830299728091	3.49502048525505
H	-3.85538967401503	-2.56595183248019	4.46390326486930

Int4 (-2498.25 Eh)

C	-6.81371559940506	-7.81541716722338	0.98177738324747
Co	-2.41858343757069	-6.10664992919429	0.74272152507460
N	-5.76411809085466	-8.23208168091930	1.93033147754347
C	-4.50681122221817	-7.76331558343179	1.91039630172346
O	-4.19752158201109	-6.90502780082494	1.02558187385047
C	-3.56814944492838	-8.27546374694352	2.94256873421694
C	-2.17756053429494	-8.30680053247790	2.66937581591650

C	-1.28796129483036	-8.78171632662474	3.63938500872144
C	-1.76404285253861	-9.22954957050664	4.87184765156512
C	-3.13218352782349	-9.18328223143940	5.15729428617905
C	-4.02475868635131	-8.70755927397633	4.19858036526472
H	-0.22271784789688	-8.79351865574662	3.40845275337109
H	-1.06286462481891	-9.60124793238758	5.61937782355280
H	-3.50179349983984	-9.50473490646921	6.13026537269248
H	-6.66590129574391	-6.73640669800539	0.82770183383814
C	-8.17639628673687	-8.06426751511223	1.62232272124040
C	-6.64352774256514	-8.53332222108786	-0.36001618873523
H	-8.28162799017245	-7.51660380282462	2.56829386909181
H	-8.33147292693647	-9.13691638910042	1.81652733377778
H	-8.97463586727628	-7.73479827239015	0.94542657662981
H	-6.76495760804113	-9.61943262551289	-0.23801506353080
H	-5.65310228678784	-8.33132048714558	-0.78798855456913
H	-7.40264418826812	-8.18229281593220	-1.07213450249155
C	-1.98279879897358	-4.40998679495447	-0.32803901694914
C	-3.12690938905793	-4.18558089342864	0.49124703395057
C	-2.74824892820795	-4.45005919494260	1.87195870455911
C	-1.35856762578553	-4.80544625064550	1.89126610349831
C	-0.88317936540322	-4.82133347729450	0.52886102284072
C	0.49573197024665	-5.15423861630738	0.07271572881818
H	1.00710650056804	-5.81448805809162	0.78430173117701
H	1.09874462799542	-4.23729992433516	-0.02554303292030
H	0.48267237887405	-5.65012829319570	-0.90525412112267
C	-0.56375218830848	-5.15785475023513	3.09996089682505
H	0.25048353051819	-5.85194196066397	2.85963967260844
H	-1.18746990526907	-5.61563634263486	3.87779246120679

H	-0.11260233397771	-4.24872332182349	3.52800312527614
C	-3.65342690288582	-4.35120859154707	3.05195632643226
H	-3.33946511157924	-5.02308831898577	3.86019192402373
H	-4.68894976482524	-4.59320785740110	2.78156575452228
H	-3.64982915094918	-3.32434366800523	3.45171778576765
C	-4.49627985459222	-3.80652783584599	0.04390974533980
H	-5.25891411784258	-4.39814396306669	0.56853997503383
H	-4.62938402824921	-3.95841052739044	-1.03348635149143
H	-4.69129868336879	-2.74495457100700	0.26307538822857
C	-1.91153195539090	-4.33575828255063	-1.81363144253824
H	-1.38043745120007	-5.20339873766605	-2.22660805543148
H	-1.36001363301233	-3.43209904378074	-2.11955221937935
H	-2.90632658575789	-4.29382776065158	-2.27050072935059
H	-5.08414185492424	-8.63436686331350	4.45075095764316
H	-5.97221354240934	-9.00318630701230	2.55910545849299
C	-1.81314560583958	-8.34826061012324	0.25493455957119
O	-1.99758884948011	-7.47962096609777	-0.67226848055251
N	-1.71799555905267	-7.77508853435926	1.45782991070570
C	-1.76648065748052	-9.81455495664024	-0.01953564009834
H	-1.44178765639844	-10.37966199575539	0.86179849719635
H	-1.08455250967178	-10.00779061544828	-0.85827578297108
H	-2.76478556039810	-10.16158894952169	-0.32377028908356

Int5 (-2727.25 Eh)

C	-6.97973398399873	-7.74669736988933	0.93474011076637
Co	-1.20848378975580	-6.15491557380697	0.68582959744887
N	-5.88761142146513	-7.97354816216314	1.89134895651099
C	-4.64592332449667	-8.38976011474833	1.51895397590461

O	-4.31038139597682	-8.43713927868747	0.32528659175906
C	-3.71579962952470	-8.72066919500282	2.64660765244212
C	-2.32379846403208	-8.45599993844690	2.56649248681300
C	-1.53874366817499	-8.60277604108476	3.72440811182257
C	-2.07751896144107	-9.08862451676141	4.91139786646313
C	-3.42858002690485	-9.44045243057691	4.96748676256199
C	-4.23005582387707	-9.24241192977379	3.84691161470824
H	-0.47964893672416	-8.34655915777745	3.67543902878624
H	-1.43789637139546	-9.21482444327526	5.78519261917642
H	-3.85437042741876	-9.86230510601014	5.87739377718376
H	-6.48879115664631	-7.45203353280751	-0.00345929611383
C	-7.86233058894761	-6.60813636253193	1.44047892683614
C	-7.76428598089106	-9.03965523671501	0.69359679328660
H	-7.28574023780510	-5.68229174402133	1.57570834199060
H	-8.33128729132389	-6.86709779715130	2.40301450019567
H	-8.66984666787029	-6.40817348840168	0.72509908802384
H	-8.23728656110322	-9.39038942846483	1.62299318916479
H	-7.10333330992704	-9.83133979778894	0.31710410144551
H	-8.55723975888607	-8.87144802021859	-0.04795227072964
C	-1.75840035354211	-4.46083786842629	-0.33128443917568
C	-2.86157754912541	-4.97896096989599	0.46104258012498
C	-2.44663779494537	-4.98091482756071	1.83732435789643
C	-1.08497972171855	-4.52012687725921	1.89780186117428
C	-0.68739372098751	-4.14493033313048	0.55464749443594
C	0.63764656547290	-3.58767677742115	0.17691222882782
H	1.43530613087442	-3.96813518560386	0.82627540888755
H	0.61623175184540	-2.49060741190790	0.28308998045220
H	0.89878037123963	-3.81948293434693	-0.86180981176586

C	-0.26261738437511	-4.37291268542295	3.13258035439317
H	0.80359775530304	-4.53635419914946	2.92911186982129
H	-0.57992368052887	-5.07913328578301	3.90989105586164
H	-0.36460541407610	-3.35571859558906	3.54600298168057
C	-3.26578102356369	-5.37267345921705	3.01487133606257
H	-2.69352582964870	-5.97839954766599	3.73025183147456
H	-4.16093871799140	-5.93339394385948	2.72645031719248
H	-3.59306377483003	-4.46339273981745	3.54401750241805
C	-4.19802243711292	-5.33915621154102	-0.08582606383552
H	-4.87112220783645	-5.70166210149095	0.69818099192897
H	-4.12432033828614	-6.12392848672596	-0.84962202801819
H	-4.65764651060066	-4.45271969201981	-0.55032806666400
C	-1.77648767041473	-4.31806177993030	-1.81290932669108
H	-0.76506792090709	-4.25352792035708	-2.22977895867187
H	-2.31512914284161	-3.39907559235231	-2.09742534207633
H	-2.29222996944383	-5.16445669100178	-2.28380149484651
H	-5.28216826200451	-9.52824022620640	3.89512474485447
H	-6.11322844165441	-7.94040448168695	2.88139346711764
C	-1.87921188491780	-8.43138052199887	0.13760062641351
O	-1.58896503470003	-7.53224994443110	-0.72097630272307
N	-1.68420381500146	-7.97626451730700	1.40797622572460
C	-2.04323993496978	-9.86168586271325	-0.24656597542299
H	-2.48986905578396	-10.44650847520619	0.56362718186176
H	-1.04530282823758	-10.26950011362731	-0.47535433709918
H	-2.66462196851837	-9.93451246041284	-1.14447071952124
C	1.42538993755222	-7.52233418300066	0.83932846090108
O	0.74212131708225	-6.52781021428279	0.51140637469575
O	0.92298337935603	-8.56853454838657	1.45726313899032

H	-0.09533245619045	-8.40513649258666	1.53871159145960
C	2.88767945896160	-7.59085519639256	0.53781221868415
H	3.43972628630249	-7.93379632143336	1.42242345086659
H	3.25604990042575	-6.61805758068997	0.20146736792498
H	3.05060376892581	-8.33527107605549	-0.25601866206250

TS5-6 (-2727.24 Eh)

C	-4.49011743687682	-11.58245715770757	1.61333386929771
Co	-0.75987878741088	-6.95592316108774	-0.14753919755587
N	-3.03697862779119	-11.68137542294463	1.80508864323718
C	-2.13310050594181	-11.15300680440149	0.94296812580268
O	-2.49442094823427	-10.44673373156097	-0.01823934385550
C	-0.69515458477866	-11.42212742361965	1.25510933449125
C	0.32932367231039	-10.52608299961063	0.85828658881951
C	1.64660213730767	-10.73155855653936	1.30319844773514
C	1.97219342232491	-11.84155790995538	2.07517160661763
C	0.98583722783236	-12.77545233202867	2.40683821734178
C	-0.32688183016313	-12.55620011285550	2.00294118217641
H	2.41328123496760	-10.01371474910476	1.01018705829274
H	3.00316060616903	-11.99216773470034	2.39537463374608
H	1.23994145854029	-13.67045546427995	2.97398720485255
H	-4.66737158205816	-10.60488203025812	1.13832261323082
C	-5.17546102262784	-11.62066339584116	2.97663900668376
C	-4.98889475672180	-12.67913986445400	0.66826402972802
H	-4.81866217224105	-10.81197247733123	3.63036059603382
H	-4.99582726073038	-12.58234760772315	3.48373145447154
H	-6.26104157225978	-11.51166489197501	2.85756119641509
H	-4.81654515257236	-13.67432363772149	1.10403180422278

H	-4.47051392533321	-12.62353703964189	-0.29710806295946
H	-6.06674214279078	-12.56688411769451	0.48747146134710
C	-2.15016334322572	-5.53276446004751	-0.27015877299185
C	-2.76689520959049	-6.74989085549370	0.24084224105752
C	-2.08046389702079	-7.10831996647520	1.43402844451951
C	-1.03534303524130	-6.11755672585825	1.68008058592064
C	-1.12577984538006	-5.11572832377586	0.67035468676712
C	-0.27276458899910	-3.90730204644972	0.52305722635238
H	0.56272502059659	-3.90756753830959	1.23215800505276
H	-0.87768661442893	-3.00585128468993	0.70839985267552
H	0.13789333202488	-3.83548985588608	-0.49179500016483
C	-0.05984626746246	-6.18063385258518	2.80316824395330
H	0.82513286880231	-5.56305476808092	2.61208176578438
H	0.27177998223424	-7.21130138575546	2.98311976847604
H	-0.52954958105571	-5.81936711028156	3.73288100768626
C	-2.36062600672945	-8.25996546999160	2.33250978153128
H	-1.46187205511784	-8.86783907954251	2.50873800436314
H	-3.14097789877005	-8.90891247619205	1.92523522183006
H	-2.69103260905315	-7.88152588192613	3.31265445101262
C	-3.87897734458154	-7.49883316558471	-0.40453573527370
H	-3.80514955313641	-8.57461272835010	-0.20021668712417
H	-3.87521819175458	-7.35895860455045	-1.49244377331474
H	-4.84476666516402	-7.12829510901060	-0.02445813554814
C	-2.52471537194655	-4.80804888824153	-1.51096641145615
H	-1.66378446328694	-4.28687174571499	-1.94665976916518
H	-3.28986600810399	-4.04804764569155	-1.27683942544620
H	-2.94748976113799	-5.48125845594947	-2.26619644126615
H	-1.08216524956763	-13.30368544776482	2.24806762442652

H	-2.70144541052782	-12.19275260068986	2.61520676799777
C	-0.56323576652298	-9.39387510944384	-1.14596393026111
O	-0.93946652572847	-8.27044876416634	-1.57927956192383
N	0.08763424734862	-9.38033124057509	0.06870675800737
C	-0.60603975476262	-10.58811179500795	-2.03785170299907
H	-0.42981877015487	-11.51836367905179	-1.49115555166768
H	0.19296842281518	-10.46128224451586	-2.78732072403316
H	-1.56639532333239	-10.63332425488788	-2.55984974164564
C	1.97960955607854	-6.76329211080481	-0.67555275108726
O	0.82387070788790	-6.25867923123268	-0.96255148425311
O	2.14379486936425	-7.76592519089951	0.06703658247917
H	0.91495892743389	-8.65756863908161	0.10535074923625
C	3.17336161885865	-6.07977410173007	-1.29399311055779
H	3.91363529384980	-5.86520318540616	-0.51229481886158
H	2.88973773324963	-5.15979452384045	-1.81352357021227
H	3.64469508031921	-6.77164983342940	-2.00655914004881

Int6 (-2727.27 Eh)

C	-4.06658446275792	-11.52425064759811	2.36229530924966
Co	-0.64995964124523	-6.57334302931116	0.01662516951993
N	-2.65633081854033	-11.79885006320801	2.05854797533464
C	-2.04380453043079	-11.40893702624231	0.91177472154384
O	-2.58518334703201	-10.67487774570349	0.07162798011157
C	-0.64651867665410	-11.93694256196778	0.73652039326307
C	0.40024614401717	-11.10969254053654	0.28535134166242
C	1.69197360893983	-11.62157371698838	0.14266981584546
C	1.95559663382342	-12.96483475513596	0.41385752516856
C	0.92080621595363	-13.80184166898804	0.83398442948556

C	-0.36491764148505	-13.28654985942074	0.99933775813141
H	2.48740272748744	-10.95499412705882	-0.19149484429612
H	2.96501573594003	-13.35625827678498	0.28848648003370
H	1.11312096920858	-14.85647330628646	1.03110127098443
H	-4.33277523107787	-10.66170460905771	1.73422025294843
C	-4.21035715954876	-11.15731475474221	3.83795623347868
C	-4.94299008570752	-12.71461528637383	1.96217932475849
H	-3.57970838433008	-10.29644097485865	4.09852661995851
H	-3.92722145497981	-12.00137878564412	4.48635384546817
H	-5.25376505309804	-10.90469967179709	4.06734516310082
H	-4.68643269712130	-13.60678309652669	2.55308309017843
H	-4.81569438630187	-12.95119436896495	0.89764590690828
H	-6.00325099907599	-12.48649379470039	2.13994651301384
C	-2.11437656101651	-5.41249290560047	-0.77537604189184
C	-2.69533170974766	-6.62378127515536	-0.24970600128387
C	-2.33837224602674	-6.73040233396522	1.13447430407584
C	-1.58644257204247	-5.53797287369933	1.49401799395940
C	-1.46074071554461	-4.72548279906795	0.32084916237592
C	-0.73145643687773	-3.43375011980090	0.20673369219116
H	-0.04362997022811	-3.27495550519261	1.04501628450134
H	-1.45322683344927	-2.60124181390568	0.19962580696650
H	-0.15308569581144	-3.38208020901524	-0.72412932212606
C	-1.03429195966605	-5.25031609160213	2.84688723613688
H	-0.25453668187428	-4.47983568521629	2.81396164773184
H	-0.60598653875815	-6.15148201042752	3.30404752645030
H	-1.83636723266978	-4.88809540904670	3.50968360462823
C	-2.68200187560383	-7.85347669167395	2.05015618901051
H	-1.89079011533169	-8.02098914487624	2.79190383208163

H	-2.84260063338334	-8.78195164027418	1.48858364144390
H	-3.60697271125961	-7.62219483124473	2.60391503168663
C	-3.47213799255608	-7.61931473231816	-1.03347842564777
H	-3.38981663635422	-8.63101948217505	-0.61867008940849
H	-3.15271189094190	-7.64043321329353	-2.08204714267040
H	-4.53656996699609	-7.33021878526868	-1.01974995080414
C	-2.20191375810535	-4.93804492506244	-2.18409742124200
H	-1.38495839139290	-4.24851010082812	-2.42752019291624
H	-3.15188737239512	-4.40361708922535	-2.35042207255696
H	-2.16506386501797	-5.77598616430289	-2.89146508418711
H	-1.17520574521405	-13.94927793163979	1.30824583884295
H	-2.13603146650618	-12.38815943289122	2.70340300191167
C	-0.26251670764269	-9.22692480864200	-1.15525817552886
O	-0.47489765537589	-7.98914196018480	-1.31879693618644
N	0.17903893117058	-9.72155456339172	0.01167421445930
C	-0.52048619981817	-10.15479423721402	-2.30009076270108
H	0.25010882999944	-10.93179960096628	-2.37764344843454
H	-0.57726960814940	-9.57780256616008	-3.22768367427132
H	-1.48471355198719	-10.65154607968003	-2.11417219857049
C	1.68725484844085	-6.60427790482541	0.46499876402287
O	1.17767121509222	-5.88000729824346	-0.44811597042727
O	0.85459218922884	-7.29127766634770	1.17688875344641
H	0.43371886871847	-9.02032318954025	0.72232557109510
C	3.16037257438655	-6.68410320708899	0.69625077571761
H	3.37537909852856	-6.71364784439591	1.77132416261821
H	3.66957391166128	-5.83829030414115	0.22239312284315
H	3.54302336453428	-7.61566590451200	0.25261347680574

Int7 (-726.48 Eh)

C	-5.50206246558616	-7.41400324414213	-0.84574620267106
N	-4.70546574983149	-7.58770150535760	0.37133927597531
C	-5.09551946477162	-8.39147767696842	1.39689415426810
O	-6.18996568232210	-8.96367660535129	1.41707801074947
C	-4.13551209372874	-8.51824380184057	2.55794635841962
C	-2.72709469818789	-8.46573059917588	2.47881016503669
C	-1.96239249654042	-8.52436116973650	3.65316104385678
C	-2.57477489730594	-8.64804363977190	4.89812296978940
C	-3.96649825962404	-8.75016744897718	4.97967731419915
C	-4.72911573977099	-8.69566711051422	3.81663135641244
H	-0.87378849664581	-8.49569742468291	3.57281427095448
H	-1.96351056022287	-8.68853151190304	5.80039821209735
H	-4.45454958859193	-8.86950866168760	5.94730823703683
H	-6.01010845489138	-8.37691230198340	-1.01589046021987
C	-4.56369047125198	-7.10985352787738	-2.01209665362815
C	-6.57316395493409	-6.33647861610776	-0.65366563596098
H	-3.81246408869567	-7.90039661112372	-2.14496126096102
H	-4.03307352636824	-6.15782525621210	-1.84998543999076
H	-5.13559785854182	-7.01386572441467	-2.94469808693299
H	-6.10826289478215	-5.35670467078413	-0.46777662862289
H	-7.21747264318180	-6.58915288213240	0.19822111846292
H	-7.20200941867560	-6.25422547962808	-1.55223229710400
H	-5.81624467339235	-8.77442496595481	3.84827443747788
H	-3.76788309105716	-7.19656418293703	0.39752958530864
C	-2.03810166975063	-9.23966902671113	0.16506968800242
O	-1.31965715812025	-9.01226580607209	-0.80226254946735
N	-2.04153177717195	-8.34726970406237	1.23777123084304

C	-2.93055765443257	-10.45486211240539	0.25902237961668
H	-3.91703563079919	-10.22962031476820	-0.16918814932669
H	-3.08582367586327	-10.79332995894285	1.29055671692628
H	-2.47350114754199	-11.24977593820946	-0.33980484448297
H	-1.25402401741791	-7.70100351956379	1.20233468393519

Calculated Structures for triple state

Int1 (-2520.51 Eh)

C	1.91482631035232	-3.07528364819352	1.04111060987193
Co	-1.32715497632000	-3.77882269541047	3.19122707932028
N	1.82432900515809	-4.50121178779529	1.39261570027902
C	1.07776249320261	-5.00607598130706	2.36927043568505
O	0.53825457398914	-4.22766804766581	3.23680957589981
C	0.90472090235795	-6.46950085689664	2.45940052243977
C	0.58295744749662	-7.03355541603823	3.70410738508952
C	0.38503715756640	-8.40691979830707	3.81681399248214
C	0.49244377307344	-9.22508619138304	2.68792747145065
C	0.79629120737058	-8.66735555397352	1.44159827341870
C	1.00206149805706	-7.29469464319089	1.32501241073920
H	0.49779301192041	-6.38421737498578	4.57437030549954
H	0.14401775714597	-8.84310933355268	4.78604250975390
H	0.33106162317738	-10.29998473181203	2.77680595919137
H	0.86008972907628	-9.30211307257873	0.55776296318055
H	1.21431363863348	-2.57171953338425	1.71843526028795
C	1.45048470623476	-2.89371928776380	-0.40486996592723
C	3.33179837438056	-2.55903631181471	1.29239602032671
H	0.42935914917114	-3.27440220464909	-0.53588099504497
H	2.11909840954497	-3.42027878742643	-1.10284659215106

H	1.46925452949562	-1.82912765929406	-0.67266892962348
H	4.06287279132684	-3.08764640628426	0.66351283175640
H	3.62045489145140	-2.69113214951748	2.34366762482173
H	3.39187458761130	-1.49036304691418	1.04697062600186
C	-1.98339810626198	-1.74316119737098	2.74631848590459
C	-3.04564969959801	-2.61167664627738	3.15206052062273
C	-2.79915433628758	-3.03947124930790	4.54072036799979
C	-1.56786570753870	-2.48171095061508	4.94493233643357
C	-1.04058849777802	-1.71839366986100	3.82050416492213
C	0.25943520118161	-0.99438019080942	3.85478880644744
H	1.07510942550911	-1.65740097800733	4.17525780604927
H	0.20721536257092	-0.17072090081798	4.58481413857147
H	0.51841548484004	-0.55908759316758	2.88268503852481
C	-0.87986600089229	-2.63428182854315	6.25994000879404
H	0.18599569292974	-2.87091895173339	6.13320126181985
H	-1.33657102614049	-3.42563879879496	6.86577433880002
H	-0.93642375719610	-1.69667220690670	6.83610130615738
C	-3.72008625687206	-3.90698956207936	5.32763497613909
H	-3.26077830762388	-4.24082892105921	6.26443244991865
H	-4.01076910717725	-4.79589827604088	4.75053864780105
H	-4.64295189060685	-3.36096181011690	5.57865125533483
C	-4.26759039834887	-2.94190244739840	2.36883265451213
H	-4.62232387066333	-3.95647990623149	2.58894721112709
H	-4.09478209374811	-2.85355671288557	1.28888709166309
H	-5.07920942177646	-2.24475455449608	2.63447959816136
C	-1.85628272602464	-1.08186439533568	1.41435261795164
H	-0.82535457208822	-0.76512908367206	1.21604034656242
H	-2.49506146970036	-0.18744150768863	1.35709813958227

H	-2.15825374081045	-1.76273903608186	0.60767816991546
H	1.18384257263843	-6.86461921225330	0.33858833234523
H	2.31424005971309	-5.16086700355302	0.79076648890589
C	-2.05778186472129	-5.43612131801465	1.52567205966290
O	-1.43315015866285	-4.45275175211512	1.03329718808339
O	-2.24892814810418	-5.45135669638261	2.80687477569709
C	-2.56877593308212	-6.57706165783648	0.70126392541063
H	-2.03717196031730	-7.49317246507714	0.99489426140011
H	-2.40964655436572	-6.38403936020713	-0.36475791572866
H	-3.63583578447017	-6.74021863912258	0.90231006975791

Int2 (-2520.50 Eh)

C	1.29094245947885	-2.83618569483587	1.49258499365417
Co	-2.42477792094360	-5.71378968057839	3.04930186321655
N	1.29206389905902	-4.24886577433747	1.90598896239855
C	0.19332797136163	-4.95861434406296	2.19643580571205
O	-0.96408681007875	-4.44427513315384	2.12411759242492
C	0.29256276832674	-6.37705788689957	2.59526029321534
C	-0.94408077300933	-6.93691525720592	3.01205512168824
C	-0.97513520505982	-8.30274970068870	3.33215031451482
C	0.18054052984151	-9.08588174665560	3.24347274719966
C	1.39736006453432	-8.51421963671197	2.85297693114978
C	1.45359980277756	-7.16113832196816	2.52575237495245
H	-1.39178306203246	-7.06158720914185	1.04780944172007
H	-1.90748753550992	-8.77283175653184	3.64962655453152
H	0.13339575261001	-10.14878057351661	3.48499567080694
H	2.29581571105556	-9.12798603784409	2.79169763758099
H	0.25961806457471	-2.63010240439010	1.17470715164361

C	2.24614705521327	-2.65460280761709	0.31441370974701
C	1.64418277374935	-1.93549954822120	2.67839096330199
H	1.96456085796055	-3.29743465057912	-0.52974894974234
H	3.28148688786035	-2.89267435635519	0.60539278870538
H	2.23236429534480	-1.61104531666967	-0.02556066044613
H	2.66637953504742	-2.13483411796667	3.03312932377961
H	0.94989608775893	-2.09382712291919	3.51444316238375
H	1.59001449490659	-0.87886831631347	2.38296477149403
C	-4.06123603327740	-4.40500090200497	3.84607502651242
C	-4.17843626748084	-5.72627752174091	4.36849410142510
C	-2.94200422685648	-6.03302423967623	5.04039545679392
C	-2.09293431147300	-4.84251500985518	4.98437796996172
C	-2.80152093915500	-3.84229834374001	4.27219723648937
C	-2.33137548537849	-2.46296939783681	3.96417050656512
H	-1.27081045036330	-2.33940580358420	4.20869454939471
H	-2.90078517198127	-1.72274821779595	4.54734098752574
H	-2.46260993490275	-2.21875428295021	2.90184508890198
C	-0.75743887507398	-4.69599846338651	5.63326997594328
H	-0.10966628607788	-4.01676260334972	5.06394467548504
H	-0.24271919805643	-5.65950602499696	5.72675744887730
H	-0.86185517848475	-4.27697367674782	6.64686630482971
C	-2.67601637069555	-7.23036889436299	5.88817548920113
H	-1.61246511945200	-7.49683787982049	5.90400145422332
H	-3.24792540145893	-8.10665488530301	5.55781016360308
H	-2.98042790784366	-7.01721191709607	6.92597453556860
C	-5.34884770481797	-6.64165900565281	4.21705692051778
H	-5.04881272489912	-7.69712018555682	4.25963574012406
H	-5.87393784077524	-6.47538602809808	3.26700732923011

H	-6.07973241001043	-6.47781190093540	5.02590016765620
C	-5.07498069832052	-3.69056189677402	3.01995629303222
H	-4.59959373373073	-3.05006001746476	2.26529944138015
H	-5.69656958971518	-3.04018936339306	3.65673705879887
H	-5.74551755302155	-4.38882410573253	2.50512749242060
H	2.40364039789586	-6.73715015370819	2.19162298203915
H	2.19478294208249	-4.70307721634678	2.01707811649788
C	-2.92000720355060	-6.33783567106809	0.19655281739959
O	-3.33794782710870	-5.80659863485219	1.24309649642616
O	-1.79730214045962	-7.03427769956880	0.13424157074483
C	-3.66531545639271	-6.24582252323505	-1.09445925391923
H	-3.00674341726355	-5.83302123761545	-1.87105468954608
H	-4.55247099388299	-5.61894645743002	-0.97478803467683
H	-3.95578859284502	-7.25392944315537	-1.42180298505998

Int3 (-2688.00 Eh)

C	-5.62162761280395	-6.28729707486983	2.96843489035941
Co	-1.14630389795596	-4.89940096867430	2.24711405114492
N	-4.40459435634889	-6.74842907628627	3.66548622936164
C	-3.17681902819507	-6.31607900697198	3.39275526555501
O	-2.98251168457601	-5.54146743762166	2.38590799718558
C	-2.01373601993917	-6.67408216527046	4.20012792216729
C	-0.84590688561762	-5.98861677574393	3.81582159631422
C	0.30580727144488	-6.10627148425964	4.58406366506544
C	0.31180246439150	-6.96200442744909	5.69275538384582
C	-0.83227281734519	-7.68833707448287	6.04480483399539
C	-2.00265885581971	-7.53538530916692	5.30758528674713
H	1.19965302573793	-5.52790616228810	4.35098348209037

H	1.21858348307037	-7.05618664231088	6.29231492366654
H	-0.81244976236946	-8.35397502247891	6.90721973103175
H	-5.32026676004824	-6.12358939306171	1.92394597834052
C	-6.10185591587650	-4.96086480643151	3.56401980463002
C	-6.67422277643638	-7.38969290982631	3.03565366737047
H	-5.30394194197322	-4.20791971913151	3.53593305039279
H	-6.41347755169160	-5.09354864830359	4.60978251776050
H	-6.96335685841998	-4.58632564802893	2.99494971600547
H	-6.96708508913481	-7.59152414942681	4.07745657359850
H	-6.30984911376257	-8.32358268155939	2.58734895531179
H	-7.57778782397382	-7.07871688020016	2.49685081845879
C	-0.24385804732588	-3.91513301759583	0.57520776915184
C	0.71852629868362	-4.72101363160226	1.30586433323059
C	0.32543845923185	-6.10878899433129	1.18850710940028
C	-0.91304812276695	-6.14351023798657	0.49436412496222
C	-1.26885498521181	-4.78242875122865	0.10987448348699
C	-2.50152335032880	-4.41515122755444	-0.64113154754479
H	-3.38888796850624	-4.87320760283041	-0.18179634789441
H	-2.44147926009343	-4.78061099069351	-1.67816172519888
H	-2.65328987419347	-3.33067350589956	-0.67225445760958
C	-1.72298254863193	-7.35331085761435	0.19088220598631
H	-2.79620784795318	-7.12845158707831	0.21830891939117
H	-1.51518262698774	-8.16668272820780	0.89645373814427
H	-1.48750840964045	-7.72255967785356	-0.82056786448971
C	1.10850279100577	-7.28887310885509	1.64656435428016
H	0.45784044323826	-8.12484959551672	1.92729419202297
H	1.74516112775528	-7.05259659393332	2.50584037655975
H	1.76301049308211	-7.63036244603937	0.82855281789953

C	1.97523215530296	-4.20274370577193	1.91346258415128
H	2.44842124790926	-4.94149279210111	2.57045448588309
H	1.79553833135127	-3.28636895076490	2.49021830217945
H	2.69963386240834	-3.95694674743260	1.12025953001182
C	-0.15356002695947	-2.44050583283338	0.39112677561797
H	-1.12781238946112	-1.99857743549579	0.15536744448799
H	0.53381856358079	-2.20846290886539	-0.43779615243186
H	0.23632150964692	-1.95007229393154	1.29149767819320
H	-2.89838294926988	-8.08616559349049	5.60345504754834
H	-4.53037766756651	-7.28568895816148	4.51961162382328
C	-2.02187675989400	-3.01561649435189	4.31383506372775
O	-2.81267198728194	-3.76569975812403	4.91206778067388
N	-1.32173500790757	-3.49591220493073	3.25093288916241
C	-1.79168028945333	-1.57876172129461	4.70075705075754
H	-1.20848060467916	-1.04533512726565	3.94038946209508
H	-1.24503842993173	-1.55310820895335	5.65496574789315
H	-2.75786462150832	-1.08076324756530	4.85420786404755

Int4 (-2499.42 Eh)

C	-7.01542654404625	-7.68661924635703	1.40487555050691
Co	-2.67314578399560	-6.20700702094807	0.60292147894604
N	-5.86661748475112	-8.19107399800385	2.18228406488923
C	-4.60986341115262	-7.75648708939803	2.04174478530932
O	-4.39306872836738	-6.84160586952679	1.17342448272876
C	-3.56754064731968	-8.36747377567212	2.89688701379640
C	-2.23718600308623	-8.49166081864735	2.40864981658452
C	-1.29133107166217	-9.19109620818558	3.17710107676375
C	-1.64270346182100	-9.73589867196184	4.40932370835344

C	-2.93863677771456	-9.57534693936918	4.91405192642373
C	-3.89036000503240	-8.89900797816942	4.15772527679349
H	-0.27136353692695	-9.27628845725406	2.80355949428683
H	-0.89180931181147	-10.26611893718371	4.99584372886561
H	-3.19929826039772	-9.96442120287186	5.89712545362494
H	-6.84618099469878	-6.60610888235944	1.28840614234905
C	-8.28998943106492	-7.92979886782340	2.20874168248905
C	-7.05451473012072	-8.33689381480189	0.01920484070715
H	-8.24756382802850	-7.44113804350874	3.19110942909677
H	-8.46310483131892	-9.00694777570373	2.35574505953778
H	-9.15536070431103	-7.52894499699400	1.66644514054190
H	-7.21302531194764	-9.42163521731846	0.10330033628786
H	-6.11969917116910	-8.15852043798573	-0.52768005102009
H	-7.88216810664799	-7.91514826376457	-0.56674531893461
C	-1.89869694780464	-4.47501979398095	-0.39540191687392
C	-3.12924701393581	-4.13088421287044	0.23851017269386
C	-2.96523112823469	-4.25653170861852	1.68468625371427
C	-1.68473580868195	-4.78500418731651	1.93293233320107
C	-1.01976513477341	-4.95829865296792	0.63906075906626
C	0.39201586591572	-5.39729696665346	0.46147191136373
H	0.66858200247280	-6.16838853990278	1.19226929250919
H	1.06938641610066	-4.54196524620606	0.62014088878546
H	0.56878564229217	-5.78806385468836	-0.54642598452125
C	-1.07488561926175	-5.12342059045946	3.25107767199746
H	-0.52217168535879	-6.07110707566301	3.20509993373380
H	-1.83132098424841	-5.21081846951423	4.04070441129642
H	-0.35791754624350	-4.34442805862560	3.55644269711986
C	-4.03446690735346	-3.96590916532407	2.67921005244845

H	-3.73660939683267	-4.25671725953761	3.69314661869489
H	-4.96571593416711	-4.49465387803209	2.42838998302940
H	-4.26948586291973	-2.89030641248643	2.69131532102770
C	-4.37027397776693	-3.63538423473884	-0.42253791840652
H	-5.26896174199138	-4.07024286676343	0.03593468296103
H	-4.38327883114807	-3.86703492639983	-1.49437365599932
H	-4.44942507055802	-2.54095115123372	-0.31528122941019
C	-1.57176173525250	-4.40429346371738	-1.84936865850878
H	-1.09173991575213	-5.32996821456808	-2.19152118026886
H	-0.88042415588365	-3.56994398184109	-2.04671926331482
H	-2.46859784652638	-4.24168846053487	-2.45880527349757
H	-4.89052793572783	-8.75051665408646	4.56934766766521
H	-6.02195578920516	-8.99122801284894	2.79057513178243
C	-1.43131084394256	-8.33615588125832	0.06253851477402
O	-1.54996565700005	-7.51890742333036	-0.90450241502446
N	-1.91801411720773	-7.86691663303429	1.21670777084487
C	-0.81100467881689	-9.68866883021173	-0.11145780681501
H	-1.17840897003505	-10.40660862533082	0.63273826988008
H	0.28092651685529	-9.60702164524437	-0.00102783803763
H	-1.01822706961366	-10.05394940820109	-1.12418931683892

Int5 (-2728.58 Eh)

C	-7.10613012941880	-7.90408707609642	1.32414310634694
Co	-1.11225279661544	-6.20133860228419	0.69641037609016
N	-5.98155262789746	-8.18405272216811	2.23004319320494
C	-4.70112552522052	-8.28641850660474	1.79942412465602
O	-4.41413486143019	-8.08412784655889	0.60474502930036
C	-3.65971441648932	-8.56851826716059	2.84274370649083

C	-2.28903617455898	-8.26465257455899	2.61201391512431
C	-1.39365515581259	-8.29137774292486	3.69905780030395
C	-1.79439979957948	-8.70114400764283	4.96416885654296
C	-3.11564538205687	-9.10961479720341	5.16986790178030
C	-4.02496729891804	-9.03095709016594	4.12028353860256
H	-0.35422464361542	-8.01280644611463	3.51768430729013
H	-1.07266175018865	-8.73217451226093	5.78064816985524
H	-3.43625434758894	-9.48065282292181	6.14261840566362
H	-6.71317235257717	-7.21616729714475	0.55973114878737
C	-8.21572650106624	-7.21722704732254	2.11593185576138
C	-7.57756566938393	-9.18344793984692	0.62769181556271
H	-7.86222447259099	-6.28579274183497	2.57917876079875
H	-8.60436643285565	-7.87674983404102	2.90823292521012
H	-9.05484054452747	-6.97218614462413	1.45327726158980
H	-7.96364612376218	-9.90666856225994	1.36085233592790
H	-6.75199206207583	-9.64839450841009	0.07407544054961
H	-8.38204686306009	-8.95200339505206	-0.08373378448569
C	-1.30742407781445	-4.36168905096855	-0.32672932969399
C	-2.61058783404362	-4.77739131956294	0.05120257429635
C	-2.60947341195448	-4.89850399096000	1.49187671007966
C	-1.33149494754808	-4.45496808369621	2.01029460646683
C	-0.51905897329217	-4.14405103202886	0.89631311028687
C	0.88353421437671	-3.64469807067148	0.91198965242883
H	1.35815051262874	-3.77691036508476	1.89209866426235
H	0.90288517088063	-2.56872197639304	0.67466819298391
H	1.49532407389476	-4.15436516226320	0.15615304901428
C	-0.97834473627699	-4.36188596850047	3.45766210031676
H	0.10706828867779	-4.38677340962237	3.61550327436315

H	-1.42915015836725	-5.18104259705168	4.03403555967715
H	-1.35235158397104	-3.41894250543591	3.88926292824987
C	-3.79085143596865	-5.21967970892353	2.33456108317193
H	-3.54120399549167	-5.88726403056402	3.17038364688568
H	-4.59487942814948	-5.67187372101270	1.74600890628515
H	-4.17533937979173	-4.28602233782574	2.77709849040421
C	-3.76343620347364	-5.09035779147575	-0.84065466759008
H	-4.25044749663369	-6.02834697378185	-0.54259953672535
H	-3.44454274409304	-5.19516141391688	-1.88352533040044
H	-4.51295895444814	-4.28293125517256	-0.79710970492406
C	-0.79771065180077	-4.13847027588368	-1.70873106876347
H	0.23036742655153	-4.50809027683761	-1.82026555543777
H	-0.78594431315804	-3.06205279310537	-1.94404746965479
H	-1.42371729387732	-4.64124182339971	-2.45417495867117
H	-5.04870802503739	-9.35951757307784	4.30367860027460
H	-6.18652711832505	-8.27407351396519	3.21916072059877
C	-2.08922510922551	-8.47463347014325	0.14490310993113
O	-1.79808001797911	-7.74867076824297	-0.83099572168804
N	-1.74100732703373	-7.90588384806467	1.36895300497868
C	-2.44291589361623	-9.92087717664857	-0.00649028273219
H	-2.83774164128920	-10.35872305188083	0.91534587537012
H	-1.52566024450016	-10.46151963098655	-0.28940604311026
H	-3.17032390724218	-10.03198042683369	-0.81725458652522
C	1.34802903976648	-7.68531325399422	0.25643438269370
O	0.70094448787133	-6.64232150701444	0.01577592496632
O	0.88489952704828	-8.66306079542728	1.00865899668724
H	-0.07391435258851	-8.42920847097502	1.27855134749487
C	2.71326994935314	-7.90302192346022	-0.30606514161179

H	3.39510891393263	-8.25055253132716	0.48092807702804
H	3.08803563063308	-6.98584622342686	-0.76775515317225
H	2.65855395266646	-8.69882841518961	-1.06429922944986

Int6 (-2728.59 Eh)

C	-4.00521379323741	-11.43863191602395	2.35768599489810
Co	-0.54900582911465	-6.63198739725810	-0.18597433877512
N	-2.61489142342789	-11.77384478021480	2.02400368436275
C	-2.01040935261325	-11.41295361510751	0.86444176838051
O	-2.53998070642183	-10.66532734704572	0.02825888935221
C	-0.63597377836318	-11.99025536118650	0.66572012027677
C	0.42248435918269	-11.20598561043400	0.16898982074579
C	1.69426762074789	-11.75607179031758	-0.00075390195816
C	1.92425850407261	-13.10193750125657	0.28836916638153
C	0.87757392147086	-13.89879251809915	0.75488074550821
C	-0.38703396781333	-13.34214092934123	0.94733193607960
H	2.49928386211980	-11.11834950223113	-0.36651498632696
H	2.91756321590032	-13.52606226256611	0.14236554400381
H	1.04434228420791	-14.95472821857542	0.96757499563340
H	-4.24799553504428	-10.56359458526892	1.73717564556020
C	-4.09987209352130	-11.06813759310262	3.83632152555417
C	-4.94108627526794	-12.58866866504677	1.97487747989864
H	-3.42381016527858	-10.23810352046776	4.08237483083431
H	-3.84239018323046	-11.92569038486451	4.47762094773172
H	-5.12510913502815	-10.76756462759992	4.08860093094680
H	-4.71196676870976	-13.49231429428206	2.55957652906148
H	-4.84635981974693	-12.82844831984953	0.90769872867408
H	-5.98629645247680	-12.31431361215416	2.17493682676913

C	-2.26932638107896	-5.37606464973056	-0.84378375071694
C	-2.70481709746845	-6.62890761423548	-0.27012868462994
C	-2.26074655914297	-6.70332587144092	1.10381773220132
C	-1.46855229304440	-5.54753417893029	1.34833423339211
C	-1.46795622690443	-4.72545192568149	0.12704410751131
C	-0.76122132969378	-3.42176346620204	-0.00360834854676
H	0.27686374743395	-3.50051433105496	0.34521777545716
H	-1.26092157794576	-2.65740930882382	0.61229242426029
H	-0.74684447692722	-3.06681061257897	-1.04026280293269
C	-0.81918498506238	-5.16480852327037	2.63325384720297
H	0.10556209388033	-4.59687327809854	2.46756862152552
H	-0.58570252208936	-6.04504424265462	3.24405324245377
H	-1.49537640275607	-4.51793538196459	3.21646160106517
C	-2.55370987204452	-7.81038546383034	2.06010918997940
H	-1.72623702434143	-7.95641612610854	2.76632407988803
H	-2.72638243388301	-8.75387735734127	1.52705364876715
H	-3.45766705818331	-7.58391980182184	2.64846609819704
C	-3.53580272766169	-7.64348919378860	-0.96911510016999
H	-3.39782461057145	-8.64889773902486	-0.55449368760765
H	-3.31621271113511	-7.67083247684675	-2.04395880063231
H	-4.60085171598252	-7.37355964954492	-0.86125690800954
C	-2.56558981191396	-4.92093147996576	-2.23305665025468
H	-1.93186985403943	-4.07731736385978	-2.52986129085025
H	-3.61493267878808	-4.59647555367119	-2.31595314752181
H	-2.42116004456695	-5.72929626943772	-2.96340682783858
H	-1.20702104863410	-13.97418097986350	1.29284116035334
H	-2.10008498774178	-12.36799751254841	2.66873707374212
C	-0.24027798086345	-9.33549628445154	-1.27034302630950

O	-0.47144235964313	-8.09138545994126	-1.42216708386044
N	0.23175122635073	-9.81589793252789	-0.12019683294592
C	-0.52813836173480	-10.25360949046907	-2.41291515491285
H	0.20697220255969	-11.06419144205900	-2.48249581482610
H	-0.55718547414310	-9.67851593475992	-3.34341803881407
H	-1.51532357553631	-10.70417747803962	-2.22996070556849
C	1.68976305614590	-6.72869885678248	0.91884130498685
O	1.25565597848717	-5.94432784641022	-0.00742349260392
O	0.90477667945627	-7.61293640651988	1.38131373199687
H	0.47056047108202	-9.10924377710658	0.60157852840722
C	3.09324956364916	-6.57356194623083	1.41901823091238
H	3.11734620911657	-6.69874737269429	2.50880838778938
H	3.51079635704253	-5.60350009970746	1.12950315288384
H	3.71569610991130	-7.36807296768577	0.98110009298620

Calculated Structures for Chapter 3

***N*-phenylisobutyramide substrate** (-518.54 Eh)

C	-0.71413350612954	0.82701653972448	-0.60469106024815
C	0.38521471889756	1.00348856116506	0.25189543463807
C	1.04305489863844	-0.12313180341837	0.77598858536220
C	0.61290260671421	-1.40705439510503	0.45197926659274
C	-0.48043703759528	-1.58754741213907	-0.39982896556014
C	-1.13219607062207	-0.46714647982575	-0.91924439872845
H	-1.21877993818013	1.70020666922268	-1.00703031220728
H	1.90011564696301	0.01419691376107	1.44099778620940

H	1.13635679428438	-2.26919632268818	0.86659667520608
H	-0.81952956004012	-2.59159786792553	-0.65506934042440
H	-1.98768935930084	-0.59629048060202	-1.58413480197914
N	0.87614947773128	2.26907471506262	0.62524499256190
C	0.45245608348502	3.52493959517639	0.24039561837028
O	-0.48788517328096	3.72822836731006	-0.52230993375262
H	2.76643891484843	4.65043539907138	-0.77884652078570
H	2.65021040007142	6.19647160122856	0.09849737001831
H	1.37929695142693	5.72935643806951	-1.06228057829191
C	2.06937431291262	5.35057599025456	-0.29583530233563
C	1.27588363074843	4.67444123442476	0.83264350072987
H	1.98974919554578	4.27297114705428	1.57421126846535
C	0.34066668499407	5.66664899532701	1.53363618186449
H	-0.40719545736083	6.04046354006806	0.82113500140419
H	0.91111986597634	6.52081856751353	1.92460768156872
H	-0.19292472237827	5.19584887144288	2.37131748427506
H	1.66969464165013	2.25017961582705	1.25921036704676

Int 1 (-2519.34 Eh)

Co	2.23913558352437	-0.63731650644662	0.93258792104737
C	3.62955275121398	0.76830057983476	1.25290207052480
C	3.23622352798868	0.78057577018067	-0.14112376156453
C	1.82816344799005	1.02465340618899	-0.20479923164216

C	1.34116164663407	1.19790731401072	1.15398277682280
C	2.44973706289838	1.05262516746714	2.04614874208898
C	2.41774880500808	1.09315566137523	3.53285943947919
H	1.39405095145190	1.13867913043295	3.91846257363998
H	2.95938213514070	1.98114813605488	3.89557313557690
H	2.90506182174633	0.20682434517866	3.96154802365204
C	-0.07264849114628	1.49823162355905	1.51021164804117
H	-0.77196788086241	0.89807224202433	0.91376160384539
H	-0.29044520264965	2.55710429199982	1.29625472495563
C	0.97176467011826	1.07073732594248	-1.42174291172772
H	0.06131677751960	0.47320144617517	-1.27919557879516
H	1.49670932465225	0.69196014520855	-2.30577336809837
H	0.66234664833274	2.10673943465793	-1.62973419696117
C	4.14336552327812	0.49199287220913	-1.28417090763170
H	3.58767119091538	0.22895016389538	-2.19096476484824
H	4.82731080245241	-0.33297803662579	-1.04725367664724
H	4.75574769557867	1.38081135671851	-1.50616057928762
C	5.00389794126216	0.54374620681156	1.78018042024638
H	4.97991987585225	0.06210474250439	2.76520759079525
H	5.53036238719003	1.50522295302413	1.89199856201190
H	5.59698319991147	-0.08025618861507	1.09988290818046
C	3.35531412822233	-2.64482970192587	1.51205583574340
O	2.74027863098638	-1.92569394163192	2.37489810707659

O	3.34390823744096	-2.20272261213887	0.30798217217890
C	4.04787043355831	-3.91179008126818	1.89127401177818
H	3.53970956982080	-4.37988837073616	2.74234958271525
H	5.07779343918058	-3.67801947540844	2.19972252925806
H	4.09661115141744	-4.59561259042010	1.03575666454050
N	0.11396035774074	-3.51944647457840	1.41190797711096
C	0.09647012495627	-3.08289492435004	2.76542658617803
C	0.45825277843586	-4.00438333428327	3.75404088467147
C	0.42544290176659	-3.62858611246199	5.09546072741819
C	0.02749965592036	-2.33738938415610	5.45179780092098
C	-0.35388266152542	-1.43165051326601	4.45875284508049
C	-0.32341891757634	-1.79510199570713	3.11329949201073
H	0.76741263821479	-5.01263401587674	3.47145561061250
H	0.70747143073642	-4.34800270506632	5.86415614957951
H	-0.00252398054073	-2.04454968789155	6.50122935091192
H	-0.69986189866423	-0.43572371832375	4.73768776169520
H	-0.63565209525956	-1.09801381780546	2.34075572676387
H	-0.09075325563769	-4.50648795453284	1.26848705306576
H	-0.27637340020729	1.32639266590158	2.57263717273501
C	0.28164691487174	-2.79555535543462	0.28604006567397
O	0.61072824066023	-1.57958216637326	0.28181893558029
H	-2.19254793284524	-3.24197167357449	-0.81451113600656
H	-1.63200490514827	-3.52772918384931	-2.47881982673296

H	-1.37593761580369	-1.93988284965567	-1.71980268431488
C	-1.39205801947212	-3.02241916937954	-1.53430203834870
C	-0.01516818284247	-3.49476668365811	-1.02605032611759
H	-0.06995818663673	-4.58074114932371	-0.83636386603643
C	1.09311132149694	-3.21424201052387	-2.04715966558771
H	1.13946483806351	-2.13972619524535	-2.26782626925284
H	0.88402423438489	-3.75099741083582	-2.98135162212088
H	2.07793882828313	-3.52339598998564	-1.67447677248558

TS1-2 (-2519.31 Eh)

Co	-4.16217493531207	-4.42029153751657	3.22334109206043
C	-1.71258015296222	-5.93795396646652	3.66636805809565
O	-2.94652346842130	-5.95499215194858	3.43660093458153
C	-1.47519605848455	-3.48802775080074	4.03063571140289
C	-2.84233463588436	-3.25361495002511	4.31602814402032
C	-3.20178780745509	-1.93383230078083	4.66880899824103
C	-2.27864648524249	-0.89264386033447	4.67176728192095
C	-0.94884243412450	-1.14962860258061	4.31863710223212
C	-0.54184672770883	-2.44792141290565	4.00771661047628
H	-3.28371833150895	-4.10616072996006	5.14888780490798
H	-4.22986840177898	-1.74243349458836	4.97870387088941
H	-2.58274085012835	0.11385541149470	4.95947970302147
H	-0.21728472995722	-0.34144961570249	4.30939618209993

C	-5.92983981092577	-4.37363762892620	2.12214457833504
C	-5.38123543372297	-3.04747995892196	2.27793493709855
C	-4.08074102111021	-3.03564395997505	1.64556975779988
C	-3.80086740013404	-4.35731148656512	1.18873364743405
C	-4.95162229454527	-5.19465962528253	1.48178502562257
C	-5.06389030679435	-6.64597785886331	1.17052497086542
H	-4.10624031820265	-7.15800440607397	1.32801174353068
H	-5.34911281628312	-6.79154579936015	0.11626486792125
H	-5.81969700219025	-7.13473455956805	1.79513421803369
C	-2.56126611605230	-4.79260402024124	0.48721504387333
H	-2.35968549898342	-5.85833060940691	0.64928498875144
H	-1.68779378651856	-4.21326668524106	0.81342272888692
H	-2.66902252307566	-4.64040544725834	-0.59920534349747
C	-3.21416427674914	-1.84817358466048	1.41396028554378
H	-2.14933743217145	-2.09313461495453	1.51333638878973
H	-3.44282313884229	-1.02820077219987	2.10042779262381
H	-3.37346733999890	-1.48531319329422	0.38559847671032
C	-6.11440142478245	-1.87273718891826	2.82938048097180
H	-5.43644760749951	-1.04728998223358	3.07034642577817
H	-6.68012058626274	-2.13447051023375	3.73310649764411
H	-6.84098751719746	-1.50099449322841	2.08836404842835
C	-7.27166223466214	-4.79960237360594	2.59987149145539
H	-7.32931283378434	-5.88355071615252	2.74718326232352

H	-8.03079123018454	-4.51448998986361	1.85348014209666
H	-7.53116635322552	-4.31146071003751	3.54663593003951
H	0.50524977278199	-2.65305528809545	3.77179337905273
C	-4.78665568568792	-5.29153304862936	5.85617408262227
O	-5.25627823018499	-5.12087547654411	4.67434950933791
O	-3.63200230455604	-4.90673963557596	6.21049758261959
C	-5.67431501430526	-5.97261713969101	6.86507647442661
H	-5.14289817256205	-6.83468183236930	7.28896203959170
H	-6.61482645844505	-6.29625097541475	6.41018083413173
H	-5.87655578911175	-5.27698404084289	7.69084215191198
N	-0.99735301264825	-4.80507424245595	3.85361725472054
H	0.00531913170438	-4.93311743400759	3.97079465422185
H	-1.21951056692236	-7.31374784722713	5.95820524272247
H	-0.83925787776805	-8.88116821644592	5.20147729830508
H	-2.47191065562862	-8.18492551444978	5.04069352851788
C	-1.40108272364397	-7.94660092065509	5.07917725853324
C	-0.96652678143930	-7.25120224959910	3.77384903493887
H	0.11200167695737	-7.02765109508109	3.83616906105129
C	-1.22212187651807	-8.13289870861443	2.54515504010638
H	-2.28974131449357	-8.37348200950150	2.46125224691693
H	-0.66717724729751	-9.07456704788262	2.64091010455235
H	-0.89583354736299	-7.64219213973511	1.61706434070808

Int2 (-2519.32 Eh)

C	-1.36880043698558	0.23027861000256	-0.12009488050436
C	-0.20601180337034	0.59167321139760	0.64564861851231
C	-0.16076471365401	-0.25593305721850	1.83268626576936
C	-1.32543944889272	-1.04772070352810	1.84065938827123
C	-2.11169734722270	-0.72006425614885	0.65279374324415
C	-3.38719034018305	-1.39533871105203	0.28009817522205
H	-3.18623241523429	-2.41888624103191	-0.07547842529891
H	-3.91333134350264	-0.86771302515422	-0.52393283626304
C	-1.66223692671920	0.70728807105667	-1.50108406512127
H	-1.09089953201348	0.09570209395589	-2.21682781591551
H	-1.36428214048548	1.75353940088096	-1.64282951013009
C	0.85497743441680	1.54717846906940	0.21497687735755
H	1.43411590966294	1.91909587394707	1.06820709396812
H	0.42950061788227	2.40615140858435	-0.32000921245105
H	1.56272939825412	1.05148513265457	-0.46984098109229
C	0.90934732854966	-0.20330765776830	2.86662400537999
H	0.73759853860346	-0.92986897793314	3.66834876570452
H	0.95920118298747	0.79560940771093	3.32470449936645
H	1.89201219259145	-0.41417261122725	2.41927299560969
C	-1.75682958983057	-2.02645406432380	2.87629984256680
H	-1.80821262251074	-3.03802916213756	2.44512075024403
H	-2.75899792227661	-1.77724110675507	3.25275327179805

H	-1.07048012149220	-2.05454847724866	3.73036675451868
Co	-1.87134220096632	1.02129331346239	1.72129480770533
O	-4.29156723595541	2.66530334577652	3.27814038267816
O	-3.28377440835999	0.64834965931047	3.09104933750749
O	-1.02883093347014	2.26477380968638	2.97026910278628
C	-4.07946070869805	1.41798502849265	3.66359999026167
C	-0.72504093249887	3.46669037876187	2.74785388602041
N	-1.21607293579589	4.16754108074007	1.70990848114846
C	-4.86890915982949	0.99082890694753	4.85806783867909
H	-4.71364618932453	-0.07304259166629	5.05594516211274
H	-5.93489086169686	1.20484393813820	4.70146309922049
H	-4.54590834830147	1.57832522569864	5.72972449181600
H	-0.91876646042024	5.13880130467366	1.64781048059357
C	-2.26708677416713	3.78675455188784	0.83552213971993
C	-2.81774243648660	4.80572655975816	0.04085776226786
C	-3.92572449782571	4.54450730481186	-0.75839344949216
C	-4.49910593060717	3.26954811852290	-0.74422723565683
C	-3.92387791674196	2.26041193966091	0.02976031435236
C	-2.77533929549317	2.47030430029530	0.81849476126135
H	-2.38776606250874	5.81038879984097	0.06945565004191
H	-4.35272345135949	5.33914580586806	-1.36939847755358
H	-5.39047248054704	3.06157459633542	-1.33656373694543
H	-4.38793886105260	1.27240097151826	0.03000615469473

H	-2.72320458298986	0.62012568127322	-1.75854223390096
H	-4.06005086979944	-1.47779878236660	1.14417108120455
H	-3.79000773997417	2.79992777306391	2.41862466441456
H	-1.00765094757117	3.97331531236090	5.45046089012320
H	0.70825983797396	4.30499277038094	5.78183721479107
H	0.20055199382240	2.68288246453693	5.25075831502188
C	0.01924353838581	3.75846671192797	5.12577875230416
C	0.24902453186665	4.17758749968579	3.66972345973390
H	0.06285964410855	5.26085486477543	3.57586331293949
C	1.69544220637316	3.89958990773310	3.21872903349240
H	1.93055339400585	2.82957090383712	3.30883931137394
H	2.39409479815634	4.45186258370975	3.86003637923309
H	1.87087837917423	4.21060733282715	2.17952155529242

Int3 (-2686.73 Eh)

C	-1.39138880007776	0.26574971436936	-0.09425312815112
C	-0.17176054574331	0.56279187374884	0.59768578760245
C	-0.04453323537753	-0.36740283968150	1.71334107379103
C	-1.20361972160483	-1.16506795590067	1.75239643086253
C	-2.08013269227643	-0.74272523987856	0.66058571835489
C	-3.35851705824545	-1.40627570758487	0.27637841752599
H	-3.14521659251794	-2.30351244004208	-0.32786275553759
H	-3.99208593486486	-0.74971059611433	-0.33191823836538
C	-1.80222723521807	0.83563538628483	-1.40861268506180

H	-1.34990480059466	0.23533228076555	-2.21372594148845
H	-1.46169865720205	1.87113052892851	-1.53102748914862
C	0.86960617075633	1.53308844168803	0.15516225342761
H	1.43393977796510	1.93326717632078	1.00634654173209
H	0.43319466935556	2.37032096807705	-0.40313857474870
H	1.59573433843079	1.03554437305398	-0.50848214863778
C	1.12395214197941	-0.44708943400266	2.63200594074209
H	0.89621269951642	-1.02440095015946	3.53540875050304
H	1.46382619398253	0.55013103881368	2.93778549363319
H	1.96980033771550	-0.93760631996566	2.12421938194652
C	-1.45171015099945	-2.30619579542843	2.68345977702859
H	-0.83880189324378	-3.16726971869644	2.37382275791236
H	-2.49883991650827	-2.62324685767165	2.67540854576351
H	-1.17592511576891	-2.06443041053680	3.71770836998257
Co	-1.75505388174656	0.92928329497923	1.84596475520966
O	-0.72428119604453	2.12127086197517	3.03180259699857
C	-0.38919294668954	3.30802830077049	2.76353385922970
N	-0.94909531898425	4.02315684880861	1.77227320730111
C	0.62037790177883	4.02115102579398	3.64352976073844
H	0.92574764286388	4.94218884451471	3.11986185280673
H	-0.60116597976617	4.97241687066978	1.65668440158321
C	-2.13682602927966	3.71042152459230	1.05594185639561
C	-2.77773942392659	4.78327511463291	0.41477748731093

C	-4.01216339862014	4.59115451084045	-0.19780035340554
C	-4.61194004666806	3.32973908088037	-0.14794976161620
C	-3.94778292472957	2.26857216100835	0.47294077905486
C	-2.68460199962712	2.41959933736067	1.06168947069136
H	-2.31567408132586	5.77422480514766	0.41997355660350
H	-4.50859760416186	5.42470848623380	-0.69336485127344
H	-5.59231629432553	3.16998566356715	-0.59725799415355
H	-4.43254549406387	1.29064216464500	0.49633109350700
H	-2.88863926993585	0.81938843497064	-1.54766107062991
H	-3.93262721734467	-1.72988100648412	1.15244642889053
O	-3.74584620751619	-0.52733784314740	3.36794057940577
C	-4.81396902411414	-0.40436107404729	4.22434556439989
O	-4.90340796645709	0.95355245061803	4.53724950401510
C	-3.91450031223998	1.58933476348172	3.85390175820246
N	-3.18567793606903	0.77660456329695	3.14333091528284
O	-5.51550456148516	-1.27798834602269	4.61712147416569
C	-3.81788464732277	3.05623151745727	3.98380957952489
H	-4.13464136511371	3.34811609586889	4.99277812648899
H	-4.48172125320083	3.54105646753335	3.25269937811510
H	-2.79563774840450	3.39108726257941	3.80423269219165
C	1.86045237680239	3.16512976525425	3.90980410936451
H	2.57000574133142	3.72216283854615	4.53563475895634
H	2.37585348108679	2.89480735319896	2.97770949190587

H	1.58678998519461	2.24477099041408	4.44137120431075
C	-0.08584834219037	4.41777790030945	4.95638056568110
H	0.60681589543135	4.98042392634134	5.59612003719606
H	-0.40672185327599	3.52052380732054	5.50281196273438
H	-0.96537867931803	5.05045771970236	4.77102894314700

TS3-3.5 (-2686.69 Eh)

C	-1.38821533119334	2.46643709819780	4.63951251279582
C	-0.76829774265986	3.33614527532011	3.66949044845073
C	-1.78864856728889	3.78036242181207	2.77416914028495
C	-3.06119381863204	3.24453135612609	3.22468128063160
C	-2.81288111386189	2.45201112743761	4.38444618208776
C	-3.81355520917995	1.73617960823560	5.21861205262722
H	-3.96187102571335	2.28750314593174	6.16075678902613
H	-3.46930578247284	0.72683634424284	5.47598147946840
C	-0.73651794580464	1.82696007658162	5.81593040712365
H	-0.95482644581579	2.41517442467636	6.72219555267332
H	0.35351703279908	1.77972623029968	5.71230419589023
C	0.65098010230518	3.78541027584277	3.65288394984779
H	1.04724249254592	3.85425524662738	2.63252488037984
H	1.30445461224938	3.11855890436218	4.22384552874989
H	0.71098366877265	4.78802295285089	4.10587068685627
C	-1.59427319203216	4.68783669231314	1.61103895006066

H	-2.34545914315338	4.50776417746307	0.83218430734601
H	-0.59454976071238	4.57808409261132	1.17212893197872
H	-1.70020203454901	5.73765479066312	1.93012306675142
C	-4.37794926433147	3.49993447324074	2.58356814020043
H	-4.78223477038198	4.46426589742743	2.93204033670689
H	-5.09964398103962	2.71202189211206	2.82186827699874
H	-4.28396869147799	3.55639302851891	1.49213493344794
Co	-1.72662685529678	1.67101982596602	2.71965659890597
O	-2.44478799159071	1.65551687721322	0.90360124367755
C	-1.83551395769052	1.72518111709704	-0.19578298092971
N	-0.49704268669556	1.69734685243321	-0.28887721565696
C	-2.63573059181204	1.76514744791456	-1.48001318577223
H	-2.00362996953215	2.24601075627099	-2.24682500838897
H	-0.11378128703140	1.76227961923970	-1.22981297817172
C	0.41958625672695	1.33060567889219	0.72859562070260
C	1.73361584943304	1.05494412734266	0.30967176590097
C	2.68340683868402	0.60485383665229	1.21909703974247
C	2.31625876596294	0.40647682455109	2.55171279692191
C	1.01195506574979	0.69593038200940	2.96065528881490
C	0.05016502367829	1.19017779232144	2.07290450665648
H	2.00004927257061	1.18293388406610	-0.74246288396160
H	3.69855299757457	0.39515527203291	0.88417666127512
H	3.04045701116650	0.03019334849133	3.27472457250290

H	0.74278219439264	0.52946224964212	4.00279965618987
H	-1.12238931902826	0.81419491414627	5.98854843541579
H	-4.77807285954245	1.64689574388793	4.71082685377108
O	-4.39501792724837	0.20242033356655	2.60980926079742
C	-4.53975133447079	-0.53683728861725	1.62152110484228
O	-3.25465714012605	-1.59513767943010	1.63218989189486
C	-2.26830377677729	-1.10929135143174	2.30351004655030
N	-2.29380181987935	0.01811535470438	2.97185156314373
O	-5.27182971653703	-0.73269901947687	0.69905321802679
C	-1.01438537123486	-1.94555257209871	2.36968207207542
H	-1.31049401900911	-2.98266030772935	2.57458803456005
H	-0.31960727867744	-1.58823479615497	3.13337576611898
H	-0.52091600391244	-1.90551146688618	1.38838813149767
C	-3.93162680037752	2.56173726248161	-1.31285557811306
H	-4.46029870471199	2.60959111472276	-2.27309312446771
H	-3.73738397452216	3.59145161320539	-0.98152961839371
H	-4.59060918026575	2.07367256533720	-0.58370236195776
C	-2.91716919940089	0.30781375205890	-1.91150782542371
H	-3.45105394104980	0.31190340399769	-2.87089093810722
H	-3.55090873467910	-0.19961227167858	-1.17175854813968
H	-1.99036892321121	-0.26752972963575	-2.04027591288554

Int3.5 (-2498.14 Eh)

C	-1.38635142401415	2.51960492398567	4.65452835845556
C	-0.78435918700791	3.41370705291580	3.68256537958810
C	-1.81054896429253	3.84940748619965	2.80053234865348
C	-3.06157316074026	3.25045965306044	3.22912257288863
C	-2.79978611357032	2.46012470849764	4.39338248009416
C	-3.78372001543942	1.68232543160200	5.19295046295085
H	-3.98487660083887	2.19883879578202	6.14437454260533
H	-3.39346479450713	0.68410604891149	5.42881847811352
C	-0.71606133281665	1.88401912877843	5.82224819158519
H	-0.97316700620116	2.43629766746796	6.74052673083503
H	0.37596582149334	1.89284760651796	5.72984759206580
C	0.63048508988387	3.87778628230103	3.67117316134683
H	1.00183881544743	4.02853045536020	2.65013004428592
H	1.30241944850424	3.17357310620737	4.17270803331527
H	0.69664005714102	4.84233484876689	4.19921446285011
C	-1.64579973174949	4.77260507891676	1.64390833931813
H	-2.32708041218718	4.51330126943567	0.82345153753765
H	-0.61716060002512	4.76632357408600	1.26422028133337
H	-1.88048382290710	5.80628809978412	1.94557792588297
C	-4.38522222619999	3.45716171681738	2.58378147291624
H	-4.88377684673087	4.33594074505243	3.02415829385820
H	-5.04331507958522	2.59182545848468	2.72579769029737

H	-4.28082611770580	3.64018124247102	1.50839656351833
Co	-1.69293077925024	1.70810503352539	2.72140284157203
O	-2.40647438423078	1.71539255816176	0.92891895118620
C	-1.80385254860435	1.67857953792643	-0.17554573924080
N	-0.46953171776898	1.59369197873810	-0.28064945180108
C	-2.61990279091274	1.64202003128565	-1.44950953910507
H	-1.96668933047942	1.97250131960432	-2.27529473586606
H	-0.09834615582564	1.57478427322591	-1.22833107658172
C	0.45266109571941	1.28346568080107	0.74938875660698
C	1.76693199851163	0.99608756327063	0.34059115535923
C	2.71681592026438	0.58078103897650	1.26649584669119
C	2.34842259495329	0.42772594855059	2.60445676774973
C	1.04352539326352	0.72862373069813	3.00365367460845
C	0.08781266082722	1.20176429636613	2.09905300085528
H	2.03293250419071	1.08788383276004	-0.71547775015319
H	3.73190592933499	0.35877402658509	0.93943988066896
H	3.07056816551736	0.07086661012344	3.33919703292647
H	0.76800395788364	0.58520805465117	4.04676495003189
H	-1.05401739853642	0.84886340268059	5.96176989156483
H	-4.73457895203845	1.56149933353882	4.66297931877884
O	-3.35840092998832	-1.07958364918792	1.73028496924822
C	-2.22308127723496	-0.98829099270054	2.23360888079723
N	-2.08680174668755	0.05785812273030	3.08305564330655

C	-1.10636436750750	-1.96806077561512	2.03163356251959
H	-1.52552195854935	-2.95077318201845	1.78158045376265
H	-0.47195437337478	-2.04027376037043	2.92500349443796
H	-0.46982818794546	-1.62591679359305	1.20137705140776
C	-3.83943036765795	2.56254913306655	-1.36858166178345
H	-4.39677567330050	2.51954828837650	-2.31305777923931
H	-3.54954865798378	3.60896092646890	-1.19627486842779
H	-4.50850387517508	2.24264205847308	-0.55963789118176
C	-3.02695889870282	0.17133567982355	-1.69155359196581
H	-3.62723355985643	0.10521274795427	-2.60856439971422
H	-3.62269863409122	-0.20479725051472	-0.84920578872560
H	-2.14867745071416	-0.47747018576531	-1.81092579459020

Int4 (-2498.25 Eh)

C	0.23171147754268	4.06819971544468	2.33541444249099
C	-0.87397519893818	4.63017843378700	3.05311055459555
C	-0.71824976223970	4.29661965525566	4.46064379503428
C	0.46272306329361	3.50840753894362	4.59303253541594
C	1.04619262409152	3.33342694484305	3.27559685376311
C	2.29064891797513	2.57247513804770	2.96968187479211
H	3.17563852680510	3.21925131485738	3.08099498322557
H	2.28541795650194	2.19157245954506	1.94135426391698
C	0.47693047085230	4.18897884945043	0.87232784250144

H	1.07189926196098	5.09470701493936	0.67144317497977
H	-0.45793024512920	4.27363933040452	0.30445827926169
C	-1.98645615407504	5.43347030125884	2.47232718887991
H	-2.93441147214715	5.23384373069845	2.98813328794317
H	-2.12013811975082	5.22427582870775	1.40338212071442
H	-1.77610896091486	6.51058411244421	2.57699435624442
C	-1.65712730950178	4.69709891351682	5.54532298168030
H	-1.54059500785446	4.06770772881663	6.43484788441323
H	-2.70125757325606	4.63053136330091	5.21393356293448
H	-1.47167648308227	5.74094597897228	5.84418294540989
C	0.98204035336287	2.87576948218598	5.83682545703590
H	1.90439122021079	3.38461013175378	6.15725974672791
H	1.22547844535296	1.81792176718258	5.66828729450156
H	0.25869157410554	2.93288882632317	6.65845836568378
Co	-0.83149245183888	2.60551913380477	3.27461564612936
O	-2.75195212869419	2.36784614461511	3.46480063242724
C	-3.70823332741113	2.13265270330473	2.69050864756282
N	-3.66976801390101	1.90862070229420	1.34956156370216
C	-5.09808063985951	2.05005659627571	3.30957521080163
H	-5.84309075524403	2.00181707832189	2.49771412976929
H	-4.60750473301756	1.82068275462041	0.96322239761077
C	-2.68049313783525	1.75197285179303	0.33753863645777
C	-3.12372023565392	1.92503028920913	-0.98214671724505

C	-2.27584562268045	1.68648466640481	-2.06021629783427
C	-0.96387408482680	1.26346017690133	-1.83289221295325
C	-0.50904611605348	1.10868301798754	-0.52575000272400
C	-1.34936440163143	1.34472629647613	0.57267116335192
H	-4.15277181882648	2.24386501606659	-1.16234934090392
H	-2.64375208325508	1.82728911148825	-3.07599955668146
H	-0.29568984112931	1.06508466980094	-2.67035551908857
H	0.51591779635043	0.79784547628517	-0.32179624777585
H	1.03797211968571	3.33225793157448	0.48158895600260
H	2.41151746145420	1.72280341665237	3.65163056597567
C	-5.38490472258107	3.28551677312088	4.16958954553246
H	-6.40047800005514	3.22660058542620	4.58173010596386
H	-5.31010802896278	4.21460255503375	3.58633016340876
H	-4.67877112502733	3.33922776922527	5.00839862448084
C	-5.18597954892467	0.75206700034787	4.13327311760720
H	-6.18062802867335	0.66739244621651	4.58986865600888
H	-4.43526944312649	0.75926267156824	4.93480338617178
H	-5.02118725436125	-0.13688597046757	3.50896668411372
N	-0.85243934025979	1.28240865773748	1.87175262411304
C	-0.77933361148642	0.27785470558172	2.73162295661022
O	-0.56314871911606	0.70559968566964	3.92890999230264
C	-0.96612573873111	-1.16883969365979	2.41700895023391
H	-0.17970251615187	-1.75924298675629	2.90511147725644

H	-0.95020104793483	-1.34631710164823	1.33557138914451
H	-1.92971746540556	-1.50983369195212	2.82307388032047

Int5 (-2727.26 Eh)

C	1.29231024235231	-8.94801961329091	2.02285231030837
Co	-3.69825787772030	-5.49595801921801	1.01051906919190
C	-0.12845070457022	-8.63492395703791	1.56171834104139
N	-1.07898915542883	-9.54503581731239	1.96319551380264
C	-2.40630708471947	-9.66456316658573	1.47637632124440
C	-3.35956275367635	-8.61461850039466	1.41117849384542
C	-4.62657240494447	-8.91781269072021	0.86487650982464
C	-4.98236512469865	-10.19293489491376	0.45296433229680
C	-4.05483070971060	-11.23202451134889	0.56871736828069
C	-2.78884137932170	-10.95394980952212	1.06746860898530
H	-5.34136217635446	-8.09821965102044	0.78749265707819
H	-5.97774034131510	-10.37825034632509	0.05005046800637
H	-4.30684175963388	-12.24393245618691	0.25400561169641
H	1.24038389678015	-9.59684328171269	2.91401280469220
C	2.04465496401381	-7.66381290291823	2.37618130369045
C	2.00071876708925	-9.72207712669368	0.89253946340473
H	1.57970339483263	-7.13544207557597	3.22055174264509
H	2.05825098720553	-6.98288486785564	1.51508941025643
H	3.08083620789404	-7.89660858326106	2.65445200389773

H	2.05748254110808	-9.10224180334198	-0.01259255436909
H	1.47531175234847	-10.65383782191494	0.63958871180623
H	3.02267421501684	-9.98121048537532	1.19838450488727
C	-3.26855145355837	-3.74004519419602	0.04765161630987
C	-2.33231454067116	-4.78690983543748	-0.32589877628604
C	-3.08335822560391	-5.86096704957361	-0.91750232331226
C	-4.48217404744623	-5.50028835878994	-0.88362274068135
C	-4.57656160067859	-4.16932782471173	-0.33155414989808
C	-5.83854668135141	-3.40862558037213	-0.13901696549434
H	-6.69649213442852	-4.07512286019747	0.00493174137958
H	-6.03580321953384	-2.80187619901968	-1.03820947850278
H	-5.78026799473610	-2.72658446599403	0.71707690546171
C	-5.61544231031845	-6.29559217998598	-1.43707727025136
H	-6.52761504405633	-6.17770034981953	-0.83837179993478
H	-5.37056271656369	-7.36248209539048	-1.49074944443969
H	-5.84989273144135	-5.95847152426967	-2.45956418192613
C	-2.51848858026083	-7.12004456379255	-1.46877966788478
H	-3.26473089829386	-7.92388695177946	-1.49138238631908
H	-1.65714278559057	-7.45522512019355	-0.87774915300412
H	-2.18512563219035	-6.94266258413196	-2.50405436283032
C	-0.85823335702252	-4.71396165796948	-0.15035529123771
H	-0.39484033370987	-5.70508801288087	-0.16627905373077
H	-0.59649460487975	-4.22993876374288	0.79930572083114

H	-0.42468609546457	-4.10668404500547	-0.96267024355064
C	-2.90513861415513	-2.45439973262252	0.70479685074488
H	-3.75837262281916	-2.01089405260750	1.23150135122359
H	-2.56255091110714	-1.72702889163817	-0.04894050209476
H	-2.08819519112090	-2.59363204168955	1.42415433592063
H	-2.04379210474406	-11.75054718476116	1.12412124108803
O	-0.40897083058014	-7.66357163637696	0.86058644491643
C	-2.44923246858208	-6.67627792602074	2.73332219865214
O	-2.48463335098625	-5.39692035543177	2.60613650631217
N	-3.20689106795283	-7.27621154423788	1.80586287821327
C	-1.77085653837455	-7.29329128806965	3.91040275331217
H	-2.10006560245914	-8.32265307981495	4.08287556439811
H	-1.98248616749097	-6.67554213829342	4.79298603105550
H	-0.68270633025532	-7.28833905923605	3.75699307243197
C	-5.79970099631736	-5.76581583591116	3.12282953201445
O	-5.27173888126163	-5.13829795131248	2.18438420580821
O	-5.43223936154041	-6.98453260059056	3.47959717683495
H	-4.66329634411914	-7.25017569887858	2.88723279276338
C	-6.90814907848841	-5.18121851212333	3.93577005052437
H	-7.72491479546358	-5.90762799673087	4.03891452423492
H	-7.26668993249402	-4.25487073235207	3.48029202038651
H	-6.53273706893726	-4.96910529024121	4.94766447964114
H	-0.72272324949733	-10.37543085127889	2.43034580040631

Calculated structures for Chapter 4

***N*-isopropylmethacrylamide substrate** (-404.27 Eh)

C	-0.50161421354036	1.23873428309792	-0.95195062164624
C	0.00237820655734	1.23714929245144	0.46801372812492
H	-1.27853390013140	2.00533555416451	-1.11049550721034
C	0.68768565125402	2.45963371026554	1.03297085701923
O	1.14539738076780	2.50152378072894	2.17804817810770
N	0.78324514009665	3.52599342051217	0.17944554897149
H	0.34153481185150	3.47801275692861	-0.73243285503312
H	2.64733644055757	4.89309463021110	-1.20013571477129
H	2.41573901586012	6.45262048417136	-0.37144914195990
H	1.09949882400841	5.77265971813157	-1.34592692287019
C	1.92120720279253	5.51486681791168	-0.65773034927835
C	1.39363777534343	4.79361204011838	0.58103498536124
H	2.23210818904411	4.52276465505653	1.24042572256561
C	0.41009656959481	5.65082897460725	1.38645304823050
H	-0.45720713084757	5.93280211956740	0.77003832939403
H	0.89653984663318	6.57279506120233	1.73606769091816
H	0.05600723772593	5.09321055077080	2.26265318025131
C	-0.12448241697566	0.17723473717412	1.27773623274048
H	-0.60472281379906	-0.74230900564974	0.94121201899412

H	0.25954798521695	0.22818012588992	2.29642270790344
H	-0.94497655857903	0.26773378540416	-1.20680020855278
H	0.30864575656874	1.43439150728401	-1.67211590726001

Int 1 (-2405.07 Eh)

C	1.36277350398280	-3.30182726171922	1.08317269444863
Co	-1.56084597123380	-3.62482872508602	3.14812672944494
N	1.47695941438573	-4.68467495772327	1.56543250384238
C	0.93334680422698	-5.18720428334146	2.68132581454372
O	0.17062558320548	-4.51449256540696	3.44051179062560
C	1.27708356557683	-6.59483825298474	3.03046824047653
C	0.54989473803183	-7.18568820109656	3.99234250312051
H	-0.25740981943471	-6.64746338238287	4.48578028554710
H	0.49505171695372	-2.87852524089557	1.60380490402636
C	1.09788944244053	-3.30608167479053	-0.41987384245089
C	2.62636839755477	-2.52198453102105	1.45971975967204
H	0.16544470696932	-3.83688243918394	-0.64594022188129
H	1.92741668887043	-3.77974838037098	-0.96746989615150
H	1.00822533677299	-2.27550938144053	-0.78751637581272
H	3.51033636074370	-2.94015394573926	0.95654035897580
H	2.80119598488456	-2.54813635642048	2.54314697521050
H	2.53159006921802	-1.47354355555722	1.14698843623743
C	-2.07468933626108	-1.67120521654522	2.91403743919323
C	-3.20281066950833	-2.47957316134351	3.32750814883827

C	-2.87208770510709	-3.06755062829577	4.60875826400930
C	-1.54233046342553	-2.66729490808276	4.95704256433000
C	-1.04951949040052	-1.79201159678156	3.90676766359283
C	0.28238860866563	-1.12594034400059	3.90923898868558
H	1.05649979387822	-1.77961655908124	4.32941093328795
H	0.24246997210407	-0.21907525773898	4.53353873260909
H	0.59467362136970	-0.81928787868871	2.90431319780783
C	-0.76290004369811	-3.08296518653432	6.15488636414420
H	0.26922853358698	-3.33872591036981	5.88279595676885
H	-1.21094694933138	-3.95305309434115	6.64770897725024
H	-0.72347485122737	-2.26163639825985	6.88844240065254
C	-3.74784668087965	-4.00582197988580	5.36023693014904
H	-3.20230066706448	-4.53228673800616	6.15054559324225
H	-4.19031366428601	-4.75377774815580	4.68870846938883
H	-4.57348961712990	-3.44772143299967	5.82911919913967
C	-4.48793296864265	-2.63840739393196	2.59197740373498
H	-4.96152264415349	-3.60500169207803	2.80699302600006
H	-4.34344092132862	-2.55577466308807	1.50724991071186
H	-5.19667698073117	-1.84940227202296	2.89267422850415
C	-1.98904929644562	-0.91795902024293	1.63289595772028
H	-0.96012067176650	-0.61779991272821	1.40405404242201
H	-2.59968604263442	-0.00361726356284	1.69331228959303
H	-2.37149654108648	-1.51744908446637	0.79596836245132

H	2.09404290345584	-5.29842665564790	1.03669333062144
C	-2.16186426327831	-5.29775978977475	1.57825391444581
O	-1.64715016739945	-4.17593595855208	1.22057835095137
O	-2.37983117896286	-5.43847424550985	2.83021032833040
C	-2.44912605932779	-6.38476961355053	0.59565375959425
H	-1.66448276881001	-7.15244808066324	0.67589931050395
H	-2.46163887736398	-5.99109805107004	-0.42624162662200
H	-3.40547636220818	-6.86726999454693	0.83314430404776
C	2.38995087453973	-7.29152827888796	2.29329072011959
H	2.55746797751270	-8.29164765683699	2.70818211499682
H	3.33802760707982	-6.73582770964572	2.36520237069796
H	2.15769598252309	-7.42315430951067	1.22292311173590
H	0.74415748459402	-8.21504117941038	4.29260530647423

TS1-2 (-2633.59 Eh)

C	-3.05050928618743	-1.91273440098631	1.00579566451383
Co	-1.88003235359917	-5.92800255763559	3.25631507685315
N	-1.71141855246966	-2.39948585229632	1.35155821103468
C	-1.47502286740254	-3.59361518064142	1.92471897353542
O	-2.46179187011557	-4.34114471960879	2.25146897804141
C	-0.11833025025459	-4.06602876308335	2.17350515083221
C	-0.07306742590872	-5.39112230573927	2.53296782360808
H	-0.59121657237659	-6.21200301203750	1.65392912823968

H	-3.71660092526127	-2.29303105376600	1.79470869421174
C	-3.51174638048627	-2.48818276859442	-0.33827001638140
C	-3.04788435628644	-0.38656908105058	1.02359358538571
H	-3.48868554335907	-3.58546716559912	-0.31248676859471
H	-2.85991541885384	-2.14086588870335	-1.15340071510977
H	-4.53932499533847	-2.16642639786845	-0.55888801402150
H	-2.35863760911420	0.01525426002853	0.26418129247327
H	-2.74565676612388	0.00068990527804	2.00620624330362
H	-4.05067110735533	-0.00230685840788	0.79460424290581
C	-3.23488375712847	-6.68049500286430	4.65643913650609
C	-1.99115983532560	-7.43154265208940	4.64281782124783
C	-0.92319729479040	-6.54538019899130	4.99523309163925
C	-1.47732552705219	-5.21974718033169	5.13776879342634
C	-2.91280170372694	-5.32722335511477	4.95703120846772
C	-3.86674600563395	-4.18322235227974	5.01621997664464
H	-3.39465842121700	-3.25957110662242	4.66051008516886
H	-4.18890403983666	-4.01397326214413	6.05567404260189
H	-4.76057892095547	-4.36778112375533	4.40783607924467
C	-0.71704452581138	-3.98692988213646	5.48875510019827
H	-1.14213872799185	-3.10386675285819	4.98994138110682
H	0.34392585411878	-4.07186809191547	5.20111324551671
H	-0.76782025291860	-3.80361216958098	6.57509143640864
C	0.49325854518938	-6.93456070637297	5.22809073340448

H	1.15542171341781	-6.05922932673479	5.23903161809792
H	0.86710191678407	-7.62675860984460	4.46405389199105
H	0.56072663951623	-7.44435606911833	6.20434292950123
C	-1.86679442268621	-8.89007454568680	4.36199537026661
H	-0.85710166857190	-9.14296042271223	4.01688471147568
H	-2.58801947495467	-9.20746614699085	3.59748346451027
H	-2.06443463214694	-9.47701555838085	5.27440394809665
C	-4.57686291146342	-7.24553661675693	4.33961368957031
H	-5.32750894331831	-6.45569392041806	4.21181387390628
H	-4.91908276083552	-7.91208564581094	5.14761111505339
H	-4.53753041473893	-7.83229861489324	3.41106373952797
H	-0.90156758392327	-1.87641184980727	1.02908658449646
C	-2.06514734604283	-7.35069842022147	0.81473445518879
O	-2.71478343734806	-7.04461659401557	1.87025937564735
O	-0.88741522944245	-6.95222873301111	0.56479684944813
C	-2.73854252203977	-8.26259909491658	-0.18323078055008
H	-2.60936166476864	-7.86403678500730	-1.19740284919140
H	-3.80146590539160	-8.37994264515335	0.05124348312136
H	-2.24606921103332	-9.24487478144697	-0.15118363615945
C	1.08453138318107	-3.18169426637460	2.07952765446870
H	1.68826944510598	-3.34406833663660	2.99545120921070
H	0.82962220255300	-2.11289622480335	2.00657903112358
H	1.72081379458682	-3.45270308350604	1.22344265338406

H	0.93409781903144	-5.79421443319692	2.79040547908897
C	3.15841250104977	-5.16130727395295	4.03966430975084
O	2.41705904544566	-4.32031577824093	4.64226244860251
O	2.80287542711652	-5.94356999081008	3.11048632243294
C	4.61904292880200	-5.26366604139751	4.51127335695590
H	5.27328279235156	-5.59288436932197	3.69383419821356
H	4.67593299168655	-6.01527483182777	5.31459304397417
H	4.96359542165074	-4.30534231123512	4.92029477638213

Int2 (-2405.05 Eh)

C	1.35967378084907	-2.96153887812867	1.35122091457165
Co	-2.35807605902744	-5.37273755201786	3.14941318720730
N	1.29495070111567	-4.36980102768859	1.78242685735319
C	0.19566394170561	-4.96090711358137	2.26139188061045
O	-0.91015256299487	-4.31561216069565	2.32436228640842
C	0.19907805536044	-6.36199034755076	2.69938812692572
C	-1.04516757034615	-6.75114647791125	3.10588282919773
H	-1.34273175793585	-6.88347083161040	1.20086866730000
H	0.36552415736981	-2.73134553335466	0.94174304779824
C	2.41521024345995	-2.82673170317054	0.25797211279772
C	1.62967328405246	-2.04733409140136	2.54868205347076
H	2.19053045540490	-3.47446533581394	-0.59980366284029
H	3.41508001769115	-3.08445744426080	0.64121347714880

H	2.45765313292751	-1.78972651168293	-0.09742820587110
H	2.61854787190751	-2.25292738318829	2.98452046034323
H	0.86901893347333	-2.18654886937437	3.32845201448013
H	1.60899150305956	-0.99526147347599	2.23365430436994
C	-4.13679663137344	-4.39190992238579	3.84981416887687
C	-4.04370204253895	-5.79182044853309	4.25117019744692
C	-2.86410620853547	-5.94886929059987	5.04908858791996
C	-2.16230608724033	-4.68794862857039	5.03821798214369
C	-2.99010047889395	-3.72124229491066	4.32523655493670
C	-2.60311499937943	-2.30110319670905	4.09488108718933
H	-1.61085985850090	-2.24602773562071	3.62545000458574
H	-2.55392985396900	-1.75660970309765	5.04989296967349
H	-3.31529014715682	-1.78316860446815	3.44285532071160
C	-0.87911596468205	-4.38428086710701	5.73203668567580
H	-0.30348167285758	-3.62144089140778	5.19259063551858
H	-0.25634334501163	-5.28168886788638	5.83334004499780
H	-1.07207313912477	-3.99669638948418	6.74532264775894
C	-2.46409510678455	-7.16989761079963	5.80350491204066
H	-1.37417569098908	-7.25480641832410	5.89908945143015
H	-2.84438994725877	-8.08545101221565	5.33416445235287
H	-2.88327425581944	-7.12408031838824	6.82046496385549
C	-5.06813991561541	-6.83483979440617	3.96166995657254
H	-4.64661799634105	-7.84569873273122	4.02092781472704

H	-5.50481077402662	-6.70028146085078	2.96384718837758
H	-5.89218150945778	-6.77418230076959	4.69166780425569
C	-5.23780735706816	-3.83255477690507	3.01782030307208
H	-5.04279840562831	-2.79470816454011	2.72545294332238
H	-6.18779841027359	-3.85744373398012	3.57344075223004
H	-5.37408044174183	-4.42533599070967	2.10283896620937
H	2.15392046030305	-4.91410246753732	1.76231335688465
C	-2.88626450748092	-6.18534732144411	0.36223963167869
O	-3.25697860952534	-5.59512070552039	1.39575816065448
O	-1.78193363800440	-6.90792472155306	0.29515505071720
C	-3.67751796643903	-6.12999644279153	-0.90414770235207
H	-3.06122348774098	-5.69193351982539	-1.70191656839463
H	-4.58229367806972	-5.53367755853223	-0.76207644217248
H	-3.93780124702921	-7.14923128907008	-1.22066596702284
C	1.44553569238739	-7.20137590265265	2.66486495470679
H	1.24093825254401	-8.20902682266966	3.04554214524016
H	2.24301101666816	-6.76574066326531	3.28871295174382
H	1.84155447070214	-7.30650954450088	1.64209131434079
H	-1.18851564611891	-7.78069015032889	3.45894736682220

Int3 (-2572.46 Eh)

C	-5.57985899438055	-5.54790379902745	3.35623543857054
Co	-0.91767431055218	-5.01933474845829	2.41163374281637

N	-4.42231879435843	-6.19513318385274	3.99732551349238
C	-3.14743312585062	-6.00183419748599	3.63865163474713
O	-2.86375535601580	-5.15302123497435	2.71406081701520
C	-2.05073620194684	-6.71562229867260	4.28396139389091
C	-0.85028508107574	-6.33671072132632	3.78353425980445
H	-5.24701161225560	-4.53321353731209	3.09192319589612
C	-6.72325201224223	-5.47026429232084	4.36385422681189
C	-5.96902838099229	-6.29099302794052	2.07512988416976
H	-6.43093085812251	-4.91000825906077	5.26209413607311
H	-7.04651615336876	-6.47725300070555	4.66946973687907
H	-7.59033679810675	-4.97045711066729	3.91430426623608
H	-6.29896361591112	-7.31484673388289	2.30219996766388
H	-5.11838193201674	-6.34539600926023	1.38236068578649
H	-6.79309945791072	-5.77064128956659	1.56894011367563
C	-0.17389321996593	-3.90118531367448	0.75406953960809
C	0.85179201601112	-4.70988088979543	1.40528662080953
C	0.46061809046830	-6.08706979910914	1.31427449832935
C	-0.84565229427676	-6.12920050145638	0.71143268601769
C	-1.20602433651395	-4.76820855991809	0.32969222192281
C	-2.48914401101019	-4.40036964549351	-0.33299670709114
H	-3.34560696888330	-4.79195535036651	0.23494321364468
H	-2.53655643348583	-4.83536770078435	-1.34247857154003
H	-2.60653309216427	-3.31501860865470	-0.43044241373308

C	-1.65516423996022	-7.34787850019553	0.42793087767947
H	-2.72875048150319	-7.14718488711663	0.53692488428440
H	-1.38869780835972	-8.17060639667076	1.10152162074523
H	-1.48673593744229	-7.69162706735939	-0.60547674354262
C	1.28158750707959	-7.25992956660224	1.72841594802130
H	0.65926218047173	-8.09821773598359	2.06441654664802
H	1.98050552668286	-7.00145521335030	2.53300101786891
H	1.87923638852958	-7.61080493422695	0.87241340784565
C	2.14219912855110	-4.19779138500143	1.94998635447696
H	2.50689218358060	-4.81409874061405	2.78076561757278
H	2.05427734895976	-3.16434760648564	2.30589389221508
H	2.91398854649900	-4.20885236091668	1.16279232575315
C	-0.10340910714983	-2.42057960201257	0.58009941108668
H	-1.08272390289878	-1.98991472220961	0.34070125310458
H	0.58222375913381	-2.16558435296600	-0.24295831623191
H	0.28391565699289	-1.92277503344705	1.47963044418546
H	-4.60569398123903	-6.90152213089704	4.70596584410908
C	-1.40994768346753	-2.54817914321944	3.99362306137216
O	-0.89385963645172	-1.87731854843314	5.05117229642258
C	0.23598519553877	-2.60011497238018	5.48247261459845
O	0.33793005374672	-3.68631964076846	4.64999037900202
N	-0.74478859967961	-3.62211087835049	3.69502216968904
O	0.94984047909444	-2.31320428540002	6.38514733122771

C	-2.60843974064469	-2.02782343623025	3.31009675809508
H	-2.91177329195435	-2.72591849335902	2.52350545344614
H	-2.39540291058489	-1.03621411286732	2.88647504005426
H	-3.42707369719835	-1.91334780427611	4.03429947921745
H	0.07843996392387	-6.76155622129859	4.18065859581592
C	-2.29295708265017	-7.71749883460821	5.37995081115387
H	-1.34308658967029	-8.13095871138820	5.73822082558098
H	-2.91092559462109	-8.56191246688256	5.03360415747140
H	-2.79968769838126	-7.26107640071545	6.24572153953379

TS3-4 (-2572.46 Eh)

C	-5.57903190190377	-4.97859413023495	2.86576489241350
Co	-0.86424916892703	-5.01581486177604	2.39722541729026
N	-4.59640115170082	-5.82467916400992	3.57497367731142
C	-3.28904046566084	-5.83712530543550	3.32411894021728
O	-2.81088192741828	-5.11806089141631	2.37010385455487
C	-2.33880212174178	-6.61168834948683	4.12134558850616
C	-1.06312661490015	-6.31883414915185	3.78278902056403
H	-4.98363318100334	-4.20601964746694	2.36111264199613
C	-6.50002478156005	-4.32101858255996	3.88861609196865
C	-6.33277289421098	-5.80620851510570	1.82338687779224
H	-5.93204069251446	-3.70050453388209	4.59383701748832
H	-7.07508584274019	-5.07419786358047	4.45072905978254

H	-7.21936167322611	-3.67110175230665	3.37408642703400
H	-6.91852699466366	-6.60517271974886	2.30148283694135
H	-5.64053637025819	-6.26555778051607	1.10476156200326
H	-7.02880029840671	-5.16352536816840	1.26762710938831
C	0.25302229457467	-4.08595324540095	0.79819449570034
C	1.08100727972720	-4.93731541606668	1.62440409559793
C	0.57055702200332	-6.28254667557032	1.53415171232983
C	-0.62141245066853	-6.24512648921744	0.73657651583098
C	-0.81102747464930	-4.87794044589437	0.27848350829847
C	-1.94837433907161	-4.41889776620088	-0.56260508637082
H	-2.89812230484096	-4.80355980599828	-0.16704845641951
H	-1.83780038009578	-4.79524524420281	-1.59162344457636
H	-2.01534947758658	-3.32644861078732	-0.59634445593926
C	-1.49119739740534	-7.40159264287246	0.38831938968900
H	-2.53518182472650	-7.09008509395960	0.26638421320534
H	-1.44746871531449	-8.18711440420651	1.15280590941732
H	-1.16453891058170	-7.84586779036244	-0.56570637091517
C	1.21312632303961	-7.50304167544701	2.09328535331101
H	0.47858784637403	-8.28730357534230	2.31148960518622
H	1.78286928621162	-7.29131978322331	3.00643461548388
H	1.92287680166435	-7.90796235259177	1.35409612637620
C	2.30508078516391	-4.50123926103917	2.35096915262557
H	2.54355940409869	-5.16785180597444	3.18842049022335

H	2.19723520892354	-3.48005623978449	2.73580899362722
H	3.16924986887519	-4.50666285288652	1.66659078866998
C	0.48213451896178	-2.63228320098588	0.58451938446468
H	-0.36641180960409	-2.15241655949867	0.08828165145588
H	1.37863082625621	-2.48804674439245	-0.03910258490379
H	0.65093901403024	-2.11287570706428	1.53663708738578
H	-4.93827007873707	-6.42200943541045	4.32485609373456
C	-1.34827461118371	-3.16539361857571	4.56434396447948
O	-2.32189520053256	-2.33432604139782	4.69695720763459
C	-2.99160493366814	-1.99688767875690	3.18778065522093
O	-2.11477856870769	-2.27049944636232	2.35007299908317
N	-0.86516004457476	-3.57960748398234	3.42180620553366
O	-4.10975920633828	-1.59468367863782	3.28063866891420
C	-0.66258077685059	-3.64965194436384	5.81837268236864
H	-1.41235578898679	-4.12497665082602	6.46387643846909
H	-0.25375346744993	-2.77524639778981	6.34328470170311
H	0.14148188934256	-4.35563538783800	5.59121859702154
H	-0.21122268405248	-6.77467615782049	4.29685501067583
C	-2.78247950621768	-7.56054367177187	5.19833762142241
H	-1.91731648673888	-8.03163009355302	5.67921271574156
H	-3.41935378942991	-8.36338056186883	4.79449028599630
H	-3.35576406039722	-7.04160674722785	5.98395744699459

Int4 (-2383.98 Eh)

C	-6.83215435459688	-7.60498575946210	1.07287126408686
Co	-2.38903287947891	-6.12427071745703	0.66386882381020
N	-5.77627777555149	-8.06119017256595	1.99397869387869
C	-4.47158700254902	-7.76702019670542	1.85238312669742
O	-4.13787110876292	-6.99134866391550	0.89837806863410
C	-3.53794143048740	-8.37523835793009	2.82934880044789
C	-2.20714293314429	-8.38438442334865	2.56171921323176
H	-6.57222097143167	-6.57038492566794	0.80554400923931
C	-8.16743429353414	-7.62987325703305	1.81136037277048
C	-6.84013084286307	-8.45601604735522	-0.20074902007201
H	-8.14406163681291	-6.99837864622825	2.70958977179609
H	-8.43318905330999	-8.65574293057906	2.10913420712193
H	-8.96591214551315	-7.26259832548502	1.15465458615259
H	-7.08336666494277	-9.50281982511947	0.03330054583296
H	-5.86303934853654	-8.42055430103470	-0.69927290491939
H	-7.59802509041835	-8.07793909011961	-0.90016281129636
C	-1.98927360878748	-4.40968090269554	-0.39501165188267
C	-3.17875036631467	-4.23862588445876	0.36998412796618
C	-2.85262344769485	-4.47651371081081	1.76796093807787
C	-1.44881823463248	-4.76185230878556	1.85246395281739
C	-0.91010675921714	-4.75719371661645	0.51501866360413
C	0.50474981352110	-5.01688002473575	0.12626968569196

H	1.01269734769538	-5.66146083244840	0.85475628829217
H	1.06531571855943	-4.06994428153870	0.07242956391159
H	0.56541319649436	-5.49694561450059	-0.85769228379602
C	-0.68996974778277	-5.07074612663644	3.09597766602542
H	0.15982128909464	-5.73391373505078	2.89456297831878
H	-1.32698872492786	-5.54494946983588	3.85291285787738
H	-0.29274692904150	-4.14056454689971	3.53191462413128
C	-3.81518422899607	-4.40580963182665	2.90381314655198
H	-3.48898451746785	-5.02323246848616	3.74973033293251
H	-4.81772706523263	-4.73326234409134	2.60119687098344
H	-3.90442354946005	-3.36921692687974	3.26551902161428
C	-4.54493704819356	-3.94157973769523	-0.14082120186008
H	-5.28376525103915	-4.61885519279090	0.30887234269782
H	-4.60657192054328	-4.04603147935557	-1.23033529095760
H	-4.83656403370857	-2.91192084663131	0.11893724020493
C	-1.85570203963360	-4.33897497813022	-1.87643862086334
H	-1.27763977893758	-5.18959887019146	-2.26140375030587
H	-1.32356886601220	-3.41781489079815	-2.16388124524629
H	-2.83110946183506	-4.33492030403692	-2.37483419682154
H	-6.03675922090707	-8.73670539592488	2.70753508475485
C	-1.54481347198339	-8.30382790555378	0.23124250340726
O	-1.72551215317455	-7.44337991978113	-0.70125355878308
N	-1.66690311407244	-7.75514289936384	1.44660583897513

C	-1.30054222449319	-9.74881037933726	-0.05108317934288
H	-0.75613487055919	-10.23324276384856	0.76868220753945
H	-0.73895982247968	-9.84809130583839	-0.98788551208707
H	-2.26415830869717	-10.26434312410055	-0.18174854651256
H	-1.51450498686111	-8.85665387450411	3.26806486307259
C	-4.08024357012552	-9.01573181047342	4.07833291698981
H	-3.25912363738590	-9.38783509610670	4.70279330872762
H	-4.72570264100595	-9.88153478671297	3.85390835113042
H	-4.66848423222788	-8.30710827252031	4.68083891475026

Int5 (-2612.98 Eh)

C	-7.39455436752486	-8.27780604230675	1.57726438479601
Co	-1.15630736582788	-5.93349693637718	0.54002435376908
N	-6.15731574641193	-8.46262397643734	2.34676695080652
C	-4.96354498398577	-7.93369071491673	1.97936035335908
O	-4.85051536304892	-7.22130027298717	0.96222674359750
C	-3.81932665937912	-8.21157377606975	2.90002938321668
C	-2.52604153599740	-7.98475760162703	2.54765272109041
H	-7.28349200832709	-7.30738524517630	1.07265838930306
C	-8.57915760984386	-8.23412069044126	2.53928995233574
C	-7.54119095083747	-9.37234232039733	0.51605045604065
H	-8.47138699817292	-7.42219583368624	3.27143830849113
H	-8.68121276931120	-9.18549448055665	3.08551869905843

H	-9.51263681764818	-8.07410104052350	1.98472746031750
H	-7.62352427017793	-10.36416255698336	0.98470517494457
H	-6.67724189685727	-9.37601990997054	-0.16145546557160
H	-8.44590419760943	-9.20241854682573	-0.08368388008870
C	-1.17699622992152	-4.12579066433409	-0.41308972251807
C	-2.46334227200448	-4.40090227608116	0.20512978727926
C	-2.25109560292944	-4.56086788823163	1.61363227628971
C	-0.83412267960105	-4.42734858593310	1.87601185373418
C	-0.19118382035608	-4.10027194569142	0.62671713481622
C	1.26311362740902	-3.85404778919752	0.44157413866315
H	1.86300195446358	-4.35642983258133	1.20893035928772
H	1.45982984935813	-2.77256950257568	0.51873126499316
H	1.61054245186415	-4.18672849246280	-0.54292066728853
C	-0.17756265500305	-4.51342585529745	3.21225381070428
H	0.85875203935324	-4.86445462272904	3.13308131453006
H	-0.71969067823082	-5.19181250282024	3.88328888840923
H	-0.15415757904572	-3.52207583501778	3.69359858879083
C	-3.31036043195558	-4.78434013611564	2.63049480468764
H	-2.93531618157993	-5.33609278436838	3.50024661961335
H	-4.16034987969410	-5.32915938221722	2.20524083650318
H	-3.66993819609575	-3.80644960255143	2.98989620167387
C	-3.77150598417176	-4.49313194184671	-0.49633927226948
H	-4.41398512346236	-5.25729345323329	-0.04014956353403

H	-3.64266421315218	-4.73480371086990	-1.55780123281112
H	-4.29039361735693	-3.52184825149818	-0.43338105051280
C	-0.94933974094356	-3.90547245777734	-1.86791992507016
H	0.10040693850861	-4.05832518838742	-2.14404102554301
H	-1.22125653236317	-2.87394864981983	-2.14405881225912
H	-1.56613978349263	-4.58215131294502	-2.47307740174020
H	-6.19902662747493	-9.05839690962127	3.16841371610567
C	-2.43592994046231	-7.95900731878858	0.08539034475138
O	-2.00656787219668	-7.15430873134036	-0.80458653895920
N	-1.98230110665674	-7.62615638237209	1.32209324098209
C	-3.16024420625284	-9.20638998730317	-0.28277363700881
H	-3.32126552307536	-9.85282686642596	0.58690098930839
H	-2.57865374803239	-9.74015384857926	-1.04740295151341
H	-4.13167679554234	-8.93475430151839	-0.71542695715841
C	1.11938754575636	-7.81602403702931	0.51361629949931
O	0.62760856085973	-6.71799979451584	0.17138658630655
O	0.46433320173589	-8.70594908382781	1.22660503886811
H	-0.49225105507390	-8.34456554534311	1.34441622063042
C	2.51141806619424	-8.19770116123343	0.12691338267984
H	3.07023932995501	-8.51642783446916	1.01703404849111
H	3.01603462366998	-7.36186241157822	-0.36545422862809
H	2.47009987578828	-9.05990057957385	-0.55460137739467
H	-1.77116043394012	-8.07898859890268	3.33589759030041

C	-4.10671087879510	-8.68647560209738	4.30174724287846
H	-3.18626189947702	-8.73147417550033	4.89736724811027
H	-4.53496142605222	-9.70279981863410	4.31252366332924
H	-4.81675480956299	-8.02317240147922	4.81976988652590

TS5-6 (-2612.97 Eh)

C	-4.13520150536653	-11.47574364693686	2.25519527726321
Co	-0.60279655256401	-6.56128914441856	0.02549770149464
N	-2.71528774338747	-11.78061842559709	2.02432299390433
C	-2.06926306714691	-11.48054471609286	0.87064464323322
O	-2.61580318280191	-10.87942299357273	-0.06444707867287
C	-0.62361618192914	-11.91616247775256	0.82074012493212
C	0.34203256899564	-11.04826752928767	0.47750716437338
H	-4.33136004272580	-10.54086648469950	1.70818326376292
C	-4.36061237207754	-11.25544109037426	3.74863564485097
C	-5.02748412306768	-12.57459733631106	1.67273668487130
H	-3.72156150811847	-10.44940735885282	4.13587143343992
H	-4.15004307755974	-12.17191723161095	4.32189326932420
H	-5.40740967962528	-10.98589054647898	3.93844882214962
H	-4.84728617820967	-13.53380941179789	2.17998209472332
H	-4.83328898993677	-12.70056463256937	0.59989202835027
H	-6.08717880420782	-12.31363917212332	1.80302880443240
C	-2.16015191606388	-5.49577098182074	-0.73023528101185

C	-2.65451575391618	-6.71690394260160	-0.13938210610385
C	-2.22559048735723	-6.75970487279089	1.22707308787672
C	-1.51430389629712	-5.52176432090232	1.51175856860355
C	-1.48734587408345	-4.74429287438511	0.30880548120608
C	-0.82218484280748	-3.42777615980543	0.11483323603664
H	-0.06230623488813	-3.23429324143159	0.88017041456425
H	-1.57246713414893	-2.62258759045956	0.16961097361032
H	-0.33967794225674	-3.36728602445824	-0.86817488670627
C	-0.91392916357512	-5.16459103686045	2.82685343431682
H	-0.20305484507245	-4.33489475863271	2.73800003114496
H	-0.38969290434145	-6.02062997500924	3.27139262356375
H	-1.70426019558807	-4.85565339480908	3.52909265925470
C	-2.46298547430404	-7.86500688385447	2.19841247308478
H	-1.60058800966192	-8.00718944098301	2.86317004622045
H	-2.66831605574982	-8.81034822431674	1.68251024742332
H	-3.33109345608399	-7.62973339545539	2.83546963321677
C	-3.42107223735120	-7.77106506219357	-0.85273890026092
H	-3.26145630385710	-8.76943026807291	-0.42820450357044
H	-3.16215840894351	-7.80237488612057	-1.91767107133459
H	-4.49743751739464	-7.54003663377753	-0.78193095325328
C	-2.34406235987243	-5.06570349204827	-2.14400024688564
H	-1.50993936758291	-4.44133011311187	-2.48768954359341
H	-3.26741475769634	-4.47187914248804	-2.24579206616417

H	-2.42842326035095	-5.92746538958164	-2.81698048200881
H	-2.21609695487954	-12.28691338754095	2.75030402937032
C	-0.23130194017299	-9.22573886730642	-1.07791803452280
O	-0.39753458488007	-7.98820581553614	-1.29376069632483
N	0.11502290699993	-9.68412875571037	0.13886673772362
C	-0.42987721728807	-10.18676907012046	-2.20535857421484
H	0.37032109546458	-10.93872835552164	-2.23353621661343
H	-0.46861191413671	-9.63459731248480	-3.14875027115935
H	-1.38086122158146	-10.71392462940491	-2.03713804324500
C	1.74398285716620	-6.52279572843779	0.40968106546847
O	1.18556535772973	-5.81049942970710	-0.48429538592665
O	0.95125694965439	-7.22760001944888	1.14963135266101
H	0.42894080407540	-8.95359994582740	0.79520263845775
C	3.22580792735013	-6.57222238409599	0.58300243711731
H	3.48474836797813	-6.76168843636239	1.63086779786783
H	3.68335816751533	-5.64133003558744	0.22941683267602
H	3.62632861362037	-7.39872689663768	-0.02411605193415
C	-0.29678490451134	-13.34721061542052	1.14018259519993
H	-0.77806539923741	-14.01944186046388	0.41378758375817
H	-0.66312181037004	-13.64863466351553	2.13292235270862
H	0.78580547270907	-13.52220518733258	1.11161133722694
H	1.38988126576852	-11.36515429908954	0.48562677204225

Int6 (-2613.00 Eh)

C	-4.42570229155069	-12.38467822570190	1.55966635504046
Co	-0.56336816913320	-6.43893314849117	-0.04733980043577
N	-2.96685835906932	-12.40961451787556	1.73784908935849
C	-2.18859255681844	-11.30398030400704	1.64418171436691
O	-2.66995102569569	-10.18387928605385	1.39842800187871
C	-0.72577375551362	-11.51706321601485	1.90857108896446
C	0.21489668472647	-10.62197859949319	1.53306836940620
C	-0.29855986699890	-12.72062825153193	2.71000096346481
H	-4.75819275469000	-11.41940260289346	1.96917112611524
C	-5.04328761618029	-13.52783324074734	2.36082594180783
C	-4.79423746528833	-12.44237804525689	0.07425377596099
H	-4.78435426327147	-13.45663086117373	3.42627529187330
H	-4.70456033282299	-14.50499084298726	1.98153995570071
H	-6.13748723079474	-13.50386017151226	2.27302172201765
H	-4.44128629982691	-13.38049517183249	-0.37883639624494
H	-4.34759675518859	-11.59899928829767	-0.46758999068945
H	-5.88467529803593	-12.39084035176470	-0.05073782669962
C	-2.14933773101786	-5.28936545953973	-0.58375389214660
C	-2.59354824165078	-6.33002614159371	0.30557414001522
C	-1.83511679324492	-6.24278695920123	1.52439132297326
C	-0.96384349923759	-5.08433311896704	1.41550143293537
C	-1.15791302802384	-4.49879991843138	0.12325345862928

C	-0.45105086501686	-3.31488095849880	-0.43624881201911
H	0.47616773247737	-3.09507043939704	0.10476980784042
H	-1.10136267784870	-2.42813878276900	-0.36364452807859
H	-0.20429921963692	-3.45998549088678	-1.49511875732095
C	-0.00807703197396	-4.62713368286504	2.46075955002061
H	0.76071132772477	-3.96253024000460	2.04945850970191
H	0.49367833723498	-5.47433597722911	2.94335576075864
H	-0.55027473878328	-4.07032655066760	3.24212609280148
C	-1.94996014318290	-7.15256530709035	2.69796333628032
H	-1.01581509604395	-7.18348222920183	3.27347313771302
H	-2.20995351626453	-8.17506543499246	2.39101678827517
H	-2.74073555584614	-6.79372232193931	3.37811160565115
C	-3.61393365963633	-7.36449481046993	-0.01030202417128
H	-3.45614933836065	-8.28775773889375	0.55978446860911
H	-3.62412717991886	-7.60576237245602	-1.08007961613552
H	-4.61068128163367	-6.97075313548564	0.25001185550259
C	-2.63319897234941	-5.03877729263036	-1.96948050315367
H	-1.82750498527777	-4.66553348244933	-2.61425998742656
H	-3.43206021188720	-4.27864968711198	-1.96179335550123
H	-3.04213566426589	-5.94858481665981	-2.42326880851696
H	-0.87840886116641	-12.80982458440601	3.63971268586413
H	-2.52923072030011	-13.30821471568113	1.91881001744427
C	-0.64014271501772	-9.32517942173422	-0.41279395705689

O	-0.81014247516264	-8.17423810113260	-0.90872140553432
N	0.06098362660222	-9.48396617518465	0.73182383481378
C	-1.15081918703681	-10.49666182712928	-1.18778447210153
H	-0.74583458221045	-11.44684329154685	-0.82637807187304
H	-0.88557904031044	-10.34530115051522	-2.24191430394317
H	-2.24532853856152	-10.52310429693856	-1.11172656870871
C	1.78177690466294	-6.55774051442082	-0.44926312830188
O	0.97377574453101	-6.04858347782904	-1.28824332311409
O	1.26444326595371	-6.96197609795344	0.66600562791111
H	0.59934202321870	-8.64459317314187	0.99731788313702
C	3.24103497848516	-6.70701298770030	-0.72787354119558
H	3.82435944827370	-6.51695238011845	0.18145196990779
H	3.54837323913639	-6.03137205467355	-1.53321533798501
H	3.44081784259272	-7.74186633900784	-1.04471243905948
H	0.76484029557874	-12.66121908682042	2.97340401374744
H	-0.43055984334277	-13.65815108973660	2.14383089247473
H	1.23809298389109	-10.75013975926203	1.89495525845037

Substrate-Me (-443.55Eh)

C	1.44282355342512	-3.31962231180122	1.02958039179866
N	1.51667460234957	-4.71573413855373	1.45690864272565
C	0.94624564139477	-5.15510046182122	2.62299535853819
O	0.28931651704603	-4.39581159575534	3.34303572001722

C	1.16481091638624	-6.61374184213062	2.94059458561583
C	0.62748374907204	-7.05183079435359	4.09476917497998
H	0.09176690766569	-6.29270926804148	4.67384930406542
H	0.44598371823157	-2.96887279570014	1.33622696304893
C	1.57155339760244	-3.24946313536613	-0.49039083693059
C	2.49270319139713	-2.46264158793943	1.74515638057119
H	0.79220512661505	-3.84582427623625	-0.98448668290542
H	2.55492455525373	-3.62185852985648	-0.82153546133359
H	1.48190857555474	-2.21051640833849	-0.83497298412433
H	3.50984153172087	-2.79435053282852	1.48444123767869
H	2.36396777345286	-2.53905580081038	2.83277733496340
H	2.39235310955418	-1.40583069942367	1.45684070131262
H	2.12058247640315	-5.34111954515693	0.93401962294743
C	1.94309043449576	-7.47306543029514	1.97986540787777
H	1.99969038216706	-8.51286428958861	2.32179514607610
H	2.98043090581901	-7.11823360910031	1.86200608137621
H	1.47997527548729	-7.48357280296090	0.97983114582496
C	0.67089273519379	-8.42710671719986	4.67113209104687
H	1.14375047719995	-8.41133963328352	5.66664432756835
H	1.21409108636444	-9.15005486069481	4.04923872666901
H	-0.35090263985248	-8.81027193276322	4.82558462059143

Int1-Me (-2444.34 Eh)

C	1.47631977952296	-3.27368851011680	1.10528647910096
Co	-1.53049840218326	-3.62562041444212	3.13601423666365
N	1.54340757471289	-4.66481425897922	1.57039384831788
C	0.96724842953963	-5.15729017607919	2.67583066060227
O	0.24340616591903	-4.43037221978700	3.43159197345802
C	1.22221641627432	-6.58087433481570	3.00328723315781
C	0.45595937392705	-7.11665402016349	3.97990128235039
H	-0.27094313254887	-6.44129876695033	4.43733855741204
H	0.61149045749167	-2.83350761092233	1.61600234592515
C	1.23602926260047	-3.25531730999255	-0.40200769807034
C	2.74987118204146	-2.52712769403623	1.51375524576801
H	0.29307414577182	-3.75846589974681	-0.64792305544621
H	2.06024954547531	-3.74684428514680	-0.94194847836650
H	1.18034449878506	-2.21941311766324	-0.76111728848735
H	3.63422285068461	-2.96160124179236	1.02524411667331
H	2.90113566376559	-2.56758243303560	2.60059127837581
H	2.68481764795776	-1.47389800800332	1.20962652446554
C	-2.15587913278946	-1.70314203720783	2.92033821635550
C	-3.22690856393551	-2.57118465973106	3.35942919732613
C	-2.83083503512936	-3.14416392630434	4.63022958318550
C	-1.51861551512768	-2.66871398763214	4.94739562992007
C	-1.09700065891112	-1.77340794888542	3.88363187296916

C	0.20437734139574	-1.04964891171649	3.84680356009035
H	1.01582182155364	-1.67017974200951	4.24616854000177
H	0.14581263510171	-0.14161002922790	4.46795273888654
H	0.47530639622008	-0.73628385294616	2.83181518738284
C	-0.68473112025933	-3.04322529468612	6.12201938828057
H	0.31710869306512	-3.36180060512495	5.80427523439324
H	-1.13804054072368	-3.85931555374550	6.69580671469113
H	-0.56568530137759	-2.17978355600885	6.79523085305837
C	-3.63205131689918	-4.13272837945106	5.40065839047592
H	-3.03746707020307	-4.62445206073848	6.17827909153100
H	-4.04345397791504	-4.90608925607956	4.73839200793264
H	-4.47981731814217	-3.62702540817845	5.88916741527520
C	-4.51842144058585	-2.80556125584498	2.65526277635101
H	-4.89624530746291	-3.81934990606334	2.83793612250720
H	-4.41699581046894	-2.66137645080252	1.57250117582391
H	-5.28213951095404	-2.09711703478020	3.01450267087874
C	-2.14469787510109	-0.94079450735095	1.64164225951970
H	-1.14547283798080	-0.56175688560739	1.39996482443711
H	-2.82299082773904	-0.07636915185267	1.71706775215759
H	-2.49039751080140	-1.56383611355274	0.80637590052061
H	2.13286663909730	-5.29623393430716	1.03169445785495
C	-2.04137425421625	-5.28944737936525	1.52447093390962
O	-1.56893938225065	-4.14057313965803	1.19765804830146

O	-2.27555851029719	-5.46511587408270	2.76923799673600
C	-2.25767608650394	-6.36834456398034	0.51485343487319
H	-1.36981413983702	-7.01886308178699	0.49889340139135
H	-2.39504088691561	-5.94122848776623	-0.48443361256746
H	-3.11963638166410	-6.98635759546296	0.79345388725342
C	2.27545568909045	-7.32565684458804	2.22613957824646
H	2.44065473901413	-8.32847877152137	2.63247879796952
H	3.24470361898808	-6.80362646150266	2.25466419935250
H	1.99389876293492	-7.45749980545700	1.16763791313499
C	0.46899423671836	-8.51120699067187	4.49294922925929
H	0.65675930991143	-8.51186959702803	5.57913669048234
H	1.21040089302312	-9.15921715493873	4.01247333458775
H	-0.52641992165959	-8.96805350068097	4.36288034336237

TS1-2-Me (-2444.73 Eh)

C	-3.12197677356084	-2.00642635635728	1.03389620353414
Co	-1.78241634509831	-5.98653014258678	3.26192402478729
N	-1.76226110408895	-2.43143719748332	1.41344517031354
C	-1.46900682180486	-3.62779336236321	1.93761526620429
O	-2.40606194168501	-4.45574972019979	2.20535458133114
C	-0.07857187091224	-4.01239080712687	2.19702408650664
C	0.07288026141573	-5.34943108313336	2.46571474261925
H	-0.60922724632891	-6.05499032424763	1.70078386864620

H	-3.79099777604427	-2.47224845601704	1.77154115922801
C	-3.47693690910463	-2.53242388422688	-0.36010622377037
C	-3.20809649476284	-0.48673892750425	1.13612490582288
H	-3.38417639704514	-3.62573664552112	-0.40041765575543
H	-2.81630058149035	-2.09447318128066	-1.12208094022665
H	-4.51157196565815	-2.26346327725897	-0.61177771358521
H	-2.51990069992508	-0.00291775746209	0.42561091191622
H	-2.96766264893139	-0.13701084596643	2.14935010262872
H	-4.22282193697477	-0.14947642784583	0.88952586647750
C	-3.23050336775955	-6.61432449684733	4.59133231959891
C	-2.04659527591985	-7.44336080978274	4.70546773933320
C	-0.95333811617005	-6.60314371478994	5.08297879297825
C	-1.43277205656945	-5.24005005010854	5.15644111236910
C	-2.84748117332326	-5.26561431399798	4.88932321408727
C	-3.75067427914957	-4.08310356547320	4.87366140968111
H	-3.21096296206199	-3.15968664527633	4.63318017991137
H	-4.20255347232100	-3.95465207076220	5.87023957699932
H	-4.56610715018822	-4.20841295263037	4.15118048276580
C	-0.64121593973428	-4.04171773876963	5.55475278770017
H	-0.98696286567249	-3.14116194641159	5.03090537376118
H	0.42705063289997	-4.16985357697023	5.34188346663666
H	-0.74576846739748	-3.85233687404369	6.63514104347872
C	0.40281481935530	-7.07755755010930	5.46988787548842

H	1.16164158836199	-6.29248103935164	5.38733874299765
H	0.72603216539175	-7.94509037444183	4.88196445220772
H	0.37066089933116	-7.39692473175335	6.52430188197433
C	-2.00826535410321	-8.91512947402758	4.49169957728522
H	-0.98819789214803	-9.27531813537117	4.31501227510240
H	-2.63240254440036	-9.20271867611730	3.63597889189115
H	-2.39898996614570	-9.43663913364435	5.38061741815048
C	-4.58550692012977	-7.10412883221145	4.22293933599311
H	-5.25823869497295	-6.28171641267214	3.95347369028865
H	-5.03548698004166	-7.64549497912404	5.07070605069231
H	-4.52769253399866	-7.79619504653143	3.37262743726985
H	-0.98613358250836	-1.84115796351944	1.12422295324428
C	-1.98910956830647	-7.32547063704473	0.77693538948071
O	-2.54348118525226	-7.18441098441684	1.93166873125338
O	-0.92198427434907	-6.74656323898710	0.44266781773366
C	-2.66674999181140	-8.26018834584946	-0.19448345239327
H	-2.70849177647633	-7.79278546360632	-1.18582803337891
H	-3.67095048461618	-8.52684788456610	0.14772416823373
H	-2.05869292432917	-9.17139503171014	-0.28562987851124
C	1.02801021582798	-3.00930168280347	2.08217794416956
H	1.97338368009287	-3.41217282435966	2.46040147290941
H	0.80504360862890	-2.08935648233999	2.64447311384773
H	1.20242889790524	-2.72261416324084	1.03086118980084

C	1.42177385321911	-5.98516668865767	2.62579618452512
H	1.96875669129316	-5.93220550940038	1.67072646338097
H	1.34252755567227	-7.04499848468994	2.88764695730645
H	2.04182944387701	-5.48199907700708	3.38108549307707

Int2-Me (-2444.33 Eh)

C	1.39351142301084	-2.96571840817674	1.50835500733033
Co	-2.35673172776322	-5.41529662388914	3.15020941154415
N	1.31848178349125	-4.37627512670974	1.92772019516004
C	0.19700718893530	-4.99115410191987	2.32285099010033
O	-0.91393819566912	-4.34909899322776	2.34498036939097
C	0.17996971675364	-6.41029475387659	2.66940533723894
C	-1.07403361186184	-6.84030025483134	3.03515229448919
H	-1.16557935904462	-6.65115917059999	1.03995885256700
H	0.40367945474841	-2.72847178543924	1.09270047051203
C	2.45683284058719	-2.82829472573960	0.42221630766922
C	1.66033070165035	-2.05847346454519	2.71141134377834
H	2.23340524201138	-3.46889750834004	-0.44117714832922
H	3.45278503354351	-3.09510401620672	0.80945166806022
H	2.50789403814492	-1.78901586713126	0.07446330216523
H	2.64150007218824	-2.27674003281949	3.15850040284336
H	0.88985022702883	-2.19073310264352	3.48293084057427
H	1.65569730513941	-1.00507341600434	2.40000106796077

C	-4.13979098204320	-4.42325458931134	3.81826367657124
C	-4.01641207129477	-5.78984485565771	4.31788732523428
C	-2.82667328668248	-5.86432604137765	5.11122652337384
C	-2.14506183282541	-4.60277568407903	4.99002962037384
C	-3.00229102095951	-3.69851501020030	4.22907519829491
C	-2.64754159980545	-2.28909656351138	3.90251705246074
H	-1.67447281090884	-2.24665697715111	3.39245906047289
H	-2.57035768500559	-1.69061552008094	4.82273876533615
H	-3.39325446139029	-1.81787511846867	3.25196231872508
C	-0.85148352242248	-4.24326928816031	5.63564022742934
H	-0.32520843841894	-3.46647054480542	5.06770080613087
H	-0.19321224780004	-5.11765647370394	5.71842669761122
H	-1.01927377299986	-3.85476399345163	6.65299138643693
C	-2.42401575680247	-6.98041088461926	6.01314993363421
H	-1.33447016336103	-7.06263168750624	6.10838689834475
H	-2.82587991853142	-7.94620758045270	5.68923903754007
H	-2.82529392222940	-6.78059751892420	7.01973690324653
C	-5.03179400711308	-6.86423724881823	4.12730658026142
H	-4.61575770548444	-7.85727588894776	4.33802624463510
H	-5.42364210020911	-6.86581080151143	3.10229385269533
H	-5.88670394696518	-6.71240776232923	4.80615096668898
C	-5.26438762799493	-3.94536013501575	2.96693570185696
H	-5.07884103166605	-2.94104276139404	2.56961889977559

H	-6.19792402328385	-3.91353043444324	3.54956648232026
H	-5.42581670894171	-4.62508136092882	2.11976168481711
H	2.18003799771996	-4.91633712456997	1.93231209374432
C	-2.85728882874982	-6.17359715569422	0.33218737996664
O	-3.27209568661710	-5.73959382567548	1.42398662539663
O	-1.64442649827687	-6.67398934506885	0.15745809068311
C	-3.71130526881632	-6.16901491839875	-0.89375289671292
H	-3.25611148152273	-5.51471623223180	-1.65131197286866
H	-4.71714373023093	-5.81362436201772	-0.65563235744189
H	-3.75231024843819	-7.17949640661847	-1.32234268489945
C	1.43053638332229	-7.24421905647382	2.56790928029921
H	1.23936020619185	-8.28623707181674	2.84581604394499
H	2.21299236722160	-6.87061311791490	3.24894113945132
H	1.84894867240958	-7.24503441244627	1.54834646451302
C	-1.38232209386599	-8.28870822167258	3.26585320561118
H	-0.90133833663747	-8.93178705367461	2.51136665053227
H	-2.46088920437511	-8.48843690843795	3.23670640538606
H	-1.01228473708972	-8.62769871033699	4.24542497507134

Substrate-CF_3 (-741.35 Eh)

C	1.44672062626689	-3.30987487462505	1.03506721129425
N	1.53970071809153	-4.71014797742565	1.45381343695294
C	0.97800190813757	-5.16355979077522	2.61087394449364

O	0.32581330918164	-4.42872346777776	3.35568775946970
C	1.20029820013747	-6.64114954213889	2.90944553395863
C	0.64032393664521	-7.05130665781763	4.05784841951173
H	0.09774268096752	-6.29737829796709	4.63509550232106
H	0.45438298736400	-2.96827579582071	1.36561044902483
C	1.54081737228537	-3.23344466255983	-0.48684472337444
C	2.50857354532260	-2.45508515953477	1.73382891154290
H	0.75337952097604	-3.83138443052151	-0.96582635486010
H	2.51912570424248	-3.59573727019090	-0.84254439161523
H	1.43505571710888	-2.19347427476609	-0.82286290796675
H	3.52075624404004	-2.77972070656954	1.44758272867997
H	2.40603145693899	-2.53703684112390	2.82381334965875
H	2.39615369714427	-1.39756013766093	1.45413847266516
H	2.11431766955927	-5.33474465047140	0.89817916455603
C	1.98985821571107	-7.46968470863216	1.93479419398473
H	2.05901733531299	-8.51619216501330	2.23573133242201
H	3.01642783545531	-7.08166381903015	1.83725813606922
H	1.52566434533226	-7.43707329166183	0.93598205497363
C	0.62410464217894	-8.39607726902245	4.70456260373252
F	1.12957328706845	-8.31487221254287	5.97047691322029
F	1.32353027084741	-9.37734497724891	4.07031716578188
F	-0.65920622631617	-8.84908201910144	4.82387709350267

Int1-CF_3 (-2742.14 Eh)

C	1.47738374762209	-3.25380869925264	1.08185984460602
Co	-1.53027997563992	-3.62222673567036	3.16149463095664
N	1.57246728599432	-4.63975876620911	1.56313592093010
C	0.99131775914194	-5.12943153572209	2.66205158913189
O	0.26022286997306	-4.42600298475697	3.42091333471359
C	1.24562292777845	-6.56941319186045	2.98197922226310
C	0.42987615359314	-7.10206777744223	3.90815187756863
H	-0.33948464541649	-6.48157361768572	4.36464777516060
H	0.62330519759649	-2.81809191452919	1.61449936952492
C	1.19280510091493	-3.25820002500912	-0.41777830394660
C	2.75604201029974	-2.49374404176930	1.44644680499089
H	0.24664579948490	-3.77092615406725	-0.62935266062726
H	2.00475727647301	-3.74988343570514	-0.97546462154229
H	1.11881842271395	-2.22710302564797	-0.78703318335981
H	3.63042954022412	-2.92744713568975	0.93989325919696
H	2.93664867080255	-2.51652974155484	2.52919060853077
H	2.67327041160907	-1.44597746030306	1.12901858412442
C	-2.13426977756216	-1.69497738226285	2.92317156483361
C	-3.21547736139884	-2.55157983057830	3.36565879728678
C	-2.83211597772750	-3.11359287639286	4.64501268002572
C	-1.51504333539753	-2.65013916948505	4.96118152057592
C	-1.08256781313083	-1.76406326072806	3.89283163757576

C	0.22409662468407	-1.05031420610935	3.85408870469954
H	1.03378026744514	-1.67586277253468	4.24934194498069
H	0.17313991630094	-0.14486970016031	4.47953291797263
H	0.49281701470323	-0.73365367735024	2.83959308318957
C	-0.69649000032020	-3.02110554506124	6.14752749836011
H	0.34170245665378	-3.23353850533385	5.86173173074928
H	-1.09906080648206	-3.90440734059474	6.65599286004990
H	-0.68154596964764	-2.19188701374380	6.87322972003752
C	-3.64679055271517	-4.08381568120467	5.42380182557277
H	-3.06028353282874	-4.57773847458104	6.20589643297982
H	-4.07125888697972	-4.85647309956866	4.76917886349165
H	-4.48575951079432	-3.55966200647633	5.90812115115799
C	-4.50519911452556	-2.77946786971495	2.65705504747519
H	-4.91105688569980	-3.77599398611550	2.87120519365215
H	-4.39153960451626	-2.67432673607658	1.57082112102879
H	-5.25360217304891	-2.03992222991234	2.98528719162778
C	-2.11430035722873	-0.94518563252452	1.63734186754540
H	-1.11368544259448	-0.56890264203758	1.39710689559610
H	-2.79234323567432	-0.07954213738586	1.70016097121597
H	-2.45742634906882	-1.57595160348608	0.80654648613517
H	2.16761603280517	-5.26914053371983	1.02716522482997
C	-2.06366064819195	-5.32811746044288	1.60147779770404
O	-1.59155820930312	-4.19073399111062	1.23481353990403

O	-2.27409732704971	-5.46574657359544	2.85638836372187
C	-2.31143143499124	-6.43515172208269	0.63169713036399
H	-1.50300358597160	-7.17680552192792	0.72305552599505
H	-2.33531757684216	-6.05469203813273	-0.39490874618500
H	-3.25090335260684	-6.94789681449562	0.87395286273055
C	2.32948058976168	-7.30722800352420	2.24731453238516
H	2.48420978161388	-8.31106466291581	2.65189672152924
H	3.28742675203403	-6.76905440884767	2.31448057900877
H	2.08084617264639	-7.42638049014213	1.17962409711795
C	0.45819850134656	-8.53546036994704	4.36338837443277
F	-0.49187217795649	-8.74917507096652	5.30338064595139
F	1.65755209978027	-8.88078676367927	4.90524590038688
F	0.21915223731424	-9.39846595217495	3.33485869008497

TS1-2-CF_3 (-2742.08 Eh)

C	-3.34121954818843	-2.25940502289246	1.01720520845499
Co	-2.01130307738200	-6.02386945750777	3.56358230236157
N	-1.97479552941917	-2.48237199705869	1.53293042341711
C	-1.60050611236418	-3.59708266318523	2.16477672836270
O	-2.45982179258275	-4.47934227572435	2.45827419889705
C	-0.15506582140923	-3.77513778595523	2.49792828438080
C	0.27226387506851	-5.05347553507516	2.44206098678348
H	-0.37352539941968	-5.80417886026859	1.93786515981093

H	-4.01191077485729	-2.69426829575297	1.77241003734386
C	-3.52991663405071	-3.00517752623278	-0.30652075133898
C	-3.58685234746594	-0.75852725322160	0.90505502401568
H	-3.29304829068849	-4.07101439054004	-0.19328534053948
H	-2.87852502968970	-2.58502877295830	-1.08618028574955
H	-4.57093340717352	-2.90943609152952	-0.64371089417227
H	-2.89887952039669	-0.29766186282714	0.17959672654850
H	-3.46794047999116	-0.25369547080634	1.87340733216985
H	-4.60800311904250	-0.57447506234423	0.54822448156859
C	-3.42428674660178	-6.48411188564797	4.88737114279883
C	-2.38261955047576	-7.48546716930595	4.95767404838658
C	-1.15999309321756	-6.81117903208316	5.26490662847786
C	-1.44381810467784	-5.39588913008246	5.46201980009543
C	-2.83588792381669	-5.19938315479615	5.24157305285934
C	-3.57103879606823	-3.90843671013907	5.30665768648787
H	-2.89771530879466	-3.05092708567946	5.19422170442331
H	-4.07021518407533	-3.81561302606573	6.28454317630533
H	-4.34676041247422	-3.84420224562740	4.53288223513346
C	-0.46240264998430	-4.35899775881002	5.88601385199284
H	-0.74260132741484	-3.36087505356132	5.52770417348279
H	0.54919309086313	-4.58139435609483	5.53091952926091
H	-0.42694866913001	-4.31270972822948	6.98674607448437
C	0.17129218269258	-7.45860419616386	5.40160584689296

H	0.99485119056483	-6.74760664882839	5.28282528422529
H	0.30497179001165	-8.27283995007488	4.67949426453811
H	0.25437277272317	-7.89630075538163	6.41070372006610
C	-2.56055487237636	-8.93328467763868	4.67205031538193
H	-1.61130576508863	-9.47595192348609	4.73029647024313
H	-2.97682012000475	-9.07629812787774	3.66455553540167
H	-3.25825676740309	-9.37905362433708	5.39711925904469
C	-4.84819017384404	-6.73502311515026	4.54875069795399
H	-5.31487436924855	-5.86156221627926	4.07741808169004
H	-5.41358704774958	-6.95414509563093	5.47061060951691
H	-4.95215297271580	-7.59572603602413	3.87816068346533
H	-1.24623256354396	-1.84076241688074	1.22866736877961
C	-2.19607869270521	-7.11246926990273	0.90661826004546
O	-2.44697708752281	-7.24237826480138	2.20175058245706
O	-1.43254325474424	-6.27637516202871	0.41881141702245
C	-2.92929336437959	-8.13360256168991	0.06334250259516
H	-2.70090776018284	-7.97710938390145	-0.99593128694167
H	-4.01226173942454	-8.05267115514840	0.23297120783399
H	-2.62671300639222	-9.14747933015772	0.35985758480578
C	0.68084339205759	-2.56301684930764	2.77848445340043
H	1.64634021513208	-2.82679519046948	3.21920226192757
H	0.16178310778357	-1.86368870409930	3.44898584146398
H	0.89875208868593	-2.02067487823316	1.84257161480911

C	1.69697824331707	-5.48646702174947	2.64515398527067
F	2.52082925902337	-4.97401083263276	1.69889195201111
F	1.79733717732729	-6.83520810389464	2.59532820402338
F	2.20089782292808	-5.09293884822619	3.86111355557204

Int2-CF_3 (-2781.44 Eh)

C	1.35882500787336	-2.93613400529870	1.48893298850190
Co	-2.36335727099536	-5.44865675652981	3.13849620077705
N	1.31203820210536	-4.33808717499030	1.94318340579689
C	0.20159017825533	-4.97516040140876	2.32361178338899
O	-0.93032119864170	-4.37755869055218	2.30181218296544
C	0.22933436106908	-6.39620376659402	2.70661436662717
C	-1.02728798431075	-6.83937245767331	3.02580805256191
H	-1.22569453733166	-6.69940876286586	1.01591846762313
H	0.36962348479086	-2.73453543537923	1.05355022271107
C	2.43518893152495	-2.80009126364782	0.41574092076936
C	1.58513297926470	-1.99652109234364	2.67519335854151
H	2.23978347486396	-3.46554759335969	-0.43549150609360
H	3.43107812695441	-3.03332279247998	0.82392893268805
H	2.46634460839522	-1.76833622843766	0.04418960976135
H	2.56526999865200	-2.17645922798237	3.14118379988045
H	0.80785184340150	-2.13167414705371	3.43984064327743
H	1.55561831097824	-0.95123455736309	2.33932342121114
C	-4.10312417974855	-4.39897781658979	3.79911042555701

C	-4.04838658302350	-5.76379399463685	4.30716981000205
C	-2.86790671639153	-5.89032163287867	5.10814756171221
C	-2.12563387326883	-4.66083973320086	4.98796266529293
C	-2.93610440183578	-3.72277927928815	4.22127168545468
C	-2.53282809514392	-2.32566474854034	3.90448754558437
H	-1.55156692509468	-2.31020762401200	3.40987448941501
H	-2.45177357718371	-1.73578804895492	4.83001083375822
H	-3.25338188675660	-1.82921121324224	3.24492740136244
C	-0.82646843789188	-4.35683386488972	5.64989077083032
H	-0.26116100570014	-3.59591832332031	5.09725567422767
H	-0.20618398990797	-5.25761696543473	5.73899206880235
H	-0.99346177878072	-3.96828213877796	6.66748261142022
C	-2.53073271559915	-7.01357466324898	6.02515497140055
H	-1.44980793028633	-7.14696104656440	6.14438925614188
H	-2.96814698453053	-7.96354307720996	5.70500992118727
H	-2.94275035110705	-6.77616848834616	7.01976318983821
C	-5.11919784403016	-6.78034246179277	4.11710310787036
H	-4.77689262780652	-7.78781036087469	4.37519699518071
H	-5.47500024772294	-6.79152215412403	3.07904405093811
H	-5.98351579563329	-6.54096858537511	4.75798101966104
C	-5.20243971673784	-3.86837667282452	2.94747612357374
H	-4.97460252983602	-2.87091820047811	2.55566023553781
H	-6.13356222685938	-3.80039556628102	3.53082046684776

H	-5.39398258598172	-4.53768295619726	2.09829519792241
H	2.18847254812920	-4.85312468893550	1.98236825660771
C	-2.91238422017470	-6.20181271505576	0.32794001991946
O	-3.31257778149662	-5.76739828391990	1.42522541670553
O	-1.69975699998207	-6.69504248216074	0.13697465856025
C	-3.78544384165252	-6.21233917554460	-0.88368440186716
H	-3.30134119118786	-5.64566825409684	-1.69118088675547
H	-4.76228268428479	-5.77957072842603	-0.65387564650494
H	-3.90265577187932	-7.24546191868711	-1.23913224931473
C	1.52144710539473	-7.16454595366968	2.65284202772052
H	1.40526344759839	-8.19410830889873	3.00014898889986
H	2.27894111658925	-6.68711696164538	3.29559357042992
H	1.92601788274350	-7.20167997701116	1.62893121928958
C	-1.25650146063129	-8.31689434978054	3.22803844462449
F	-0.78399273073745	-9.04598917364461	2.17095789165348
F	-2.57605104014638	-8.62849978709612	3.32987532107461
F	-0.64410088827282	-8.80086327038358	4.34815043844832

Crystallographic data information

Experimental. Single colourless cut block crystals of **37b** recrystallised by slow diffusion of pentane into concentrated chloroform solution. The crystal was analysed by the EPSRC National Crystallography Service. A suitable crystal with dimensions 0.400 × 0.160 × 0.060 mm^3 was selected and mounted on a MITIGEN holder in perfluoroether oil on a Rigaku 007HF equipped with Varimax

confocal mirrors and an AFC11 goniometer and HyPix 6000 detector diffractometer. The crystal was kept at a steady T = 100(2) K during data collection. The structure was solved with the **ShelXT** 2018/2 [223] solution program using dual methods and by using **Olex2** [224] as the graphical interface. The model was refined with **ShelXL** 2018/3 [225] using full matrix least squares minimisation on F^2.

Crystal Data $C_8H_6BrN_3O$, M_r = 240.07, monoclinic, $P2_1/c$ (No. 14), a = 7.46010(10) Å, b = 11.16990(10) Å, c = 21.0965(2) Å, β = 97.9460(10)°, $\alpha = \gamma$ = 90°, V = 1741.06(3) Å^3, T = 100(2) K, Z = 8, Z' = 2, μ(Cu K$_\alpha$) = 6.132 mm^{-1}, 29357 reflections measured, 3159 unique (R_{int} = 0.0409) which were used in all calculations. The final wR_2 was 0.0860 (all data) and R_1 was 0.0303 (I > 2(I)).

Bond Lengths in Å for 37b.

Atom	Atom	Length/Å
Br1	C3	1.896(2)
O1	C7	1.189(3)
N1	N2	1.382(3)
N1	C1	1.382(3)
N1	C7	1.426(3)
N2	N3	1.283(3)
N3	C6	1.392(3)
C1	C2	1.389(3)
C1	C6	1.393(3)
C2	C3	1.383(3)
C3	C4	1.412(3)
C4	C5	1.377(3)
C5	C6	1.403(3)

Atom	Atom	Length/Å
C7	C8	1.502(3)
Br11	C13	1.901(2)
O11	C17	1.191(3)
N11	N12	1.378(3)
N11	C11	1.382(3)
N11	C17	1.423(3)
N12	N13	1.287(3)
N13	C16	1.385(3)
C11	C12	1.397(3)
C11	C16	1.399(3)
C12	C13	1.383(3)
C13	C14	1.417(3)
C14	C15	1.380(4)
C15	C16	1.396(3)
C17	C18	1.493(3)

Bond Angles in ^{o} for 37a

Atom	Atom	Atom	Angle/$^{\circ}$
N2	N1	C1	109.60(18)
N2	N1	C7	121.37(18)
C1	N1	C7	128.96(19)
N3	N2	N1	109.02(17)
N2	N3	C6	108.81(18)
N1	C1	C2	133.7(2)
N1	C1	C6	103.70(19)

Atom	Atom	Atom	Angle/°
C2	C1	C6	122.6(2)
C3	C2	C1	114.7(2)
C2	C3	Br1	118.47(17)
C2	C3	C4	124.0(2)
C4	C3	Br1	117.54(17)
C5	C4	C3	120.2(2)
C4	C5	C6	116.9(2)
N3	C6	C1	108.87(19)
N3	C6	C5	129.6(2)
C1	C6	C5	121.6(2)
O1	C7	N1	118.7(2)
O1	C7	C8	126.5(2)
N1	C7	C8	114.8(2)
N12	N11	C11	109.72(18)
N12	N11	C17	121.27(18)
C11	N11	C17	129.00(19)
N13	N12	N11	109.04(18)
N12	N13	C16	108.84(19)
N11	C11	C12	133.5(2)
N11	C11	C16	103.48(19)
C12	C11	C16	123.0(2)
C13	C12	C11	114.0(2)
C12	C13	Br11	118.62(18)
C12	C13	C14	124.6(2)
C14	C13	Br11	116.73(17)
C15	C14	C13	119.7(2)
C14	C15	C16	117.3(2)

Atom	Atom	Atom	Angle/°
N13	C16	C11	108.9(2)
N13	C16	C15	129.7(2)
C15	C16	C11	121.4(2)
O11	C17	N11	118.0(2)
O11	C17	C18	126.1(2)
N11	C17	C18	115.9(2)