Discovery and Development of Novel Enantioselective C(sp^3)-H Functionalisations

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A thesis submitted in partial fulfilment of the requirement for the degree of Doctor of Philosophy (DPhil)

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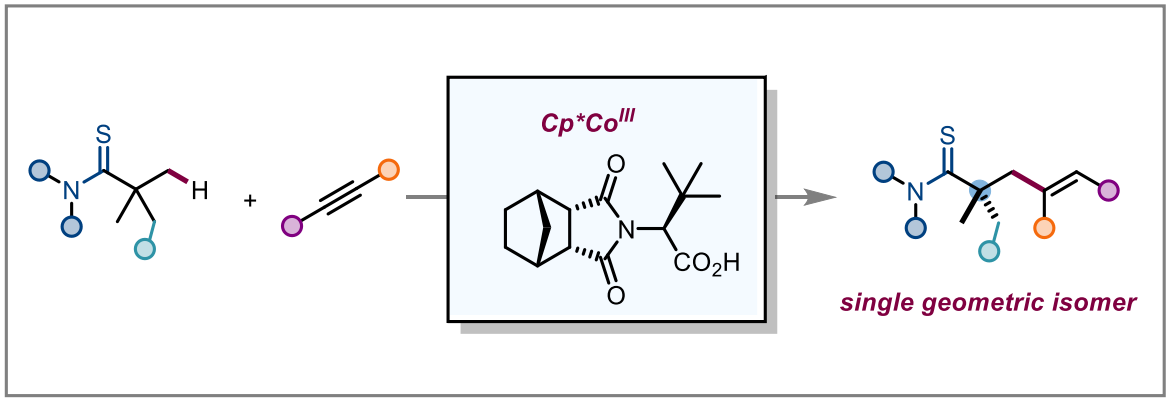
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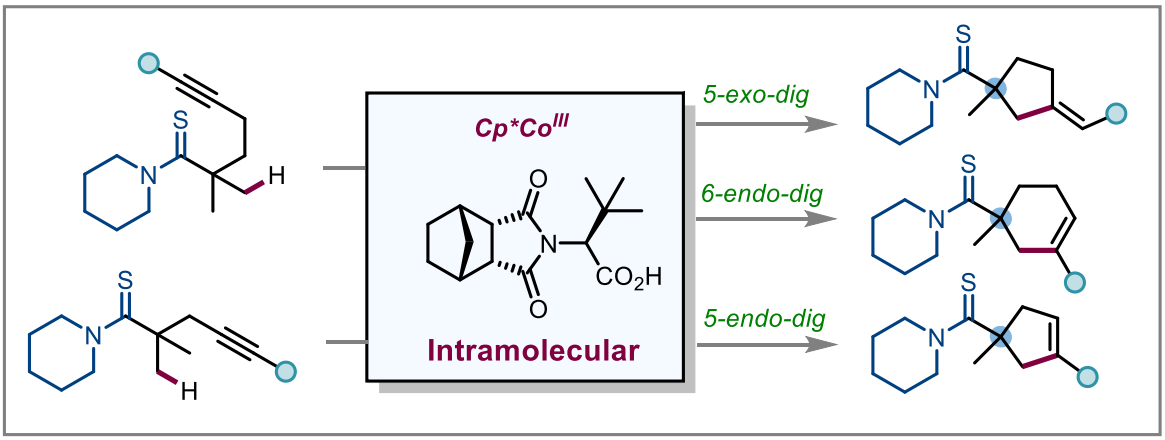
Abstract

Discovery and Development of Novel Enantioselective C(sp^3)–H Functionalisations



This thesis describes studies towards new enantioselective C–H activation reactions. In **chapter 2** the investigation towards a novel enantioselective cobalt-catalysed C(sp^3)–H alkenylation, directed by thioamides, with but-2-ynoates is described. In this method prochiral thioamides undergo asymmetric C(sp^3)–H functionalisation with but-2-ynoates in presence of a [Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ complex and chiral carboxylic acid, which allows the formation of chiral thioamides. The method provides alkenylated products as single regioisomers in excellent yields (up to 85%) and high enantiomeric ratios (up to 91:9 er, or up to >99:1 er after single recrystallisation). The protocol is operationally very simple with mild reaction conditions, which is not very common for C–H functionalisations, because the activation of naturally inactive C–H bonds often requires high reaction temperatures. The applicability of this methodology can be found in diverse downstream derivatisations of products, delivering a broad range of enantiopure pharmaceutically and agrochemically relevant scaffolds, such as various substituted heterocycles. Mechanistic investigations and state-of-the-art DFT calculations carried out in collaboration with Ken Yamazaki, Prof

Trevor A. Hamlin and Prof F. Matthias Bickelhaupt revealed that the pivotal C–H activation step is rate- and enantiodetermining step. DFT calculations explain the reaction mechanism, and stereochemical outcome of the products, as well as the unusual regioselectivity of the alkenylation reaction.



After successfully developing a novel thioamide-directed cobalt-catalysed enantioselective C(sp^3)–H alkenylation reaction, in **chapter 3** we investigated intramolecular variant of this new reaction. Taking into consideration the specific interactions between a Cp^*Co^{III} complex, thioamides and but-2-ynoates, with suitable substrates the formation of cyclic products should be straightforward, and this project would be a viable follow-up of our completed study.

Declarations

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford, from February 2018 until May 2022, under the supervision of Prof Darren J. Dixon. All the work is my own unless stated otherwise and has not been submitted previously for any other degree at this or any other university.



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List of Abbreviations

Å	Angstrom
acac	Acetylacetonate
AcOH	Acetic acid
Ad	Adamantyl
Ala	*L*-Alanine
AMLA	Ambiphilic Metal-Ligand Activation
Ar	Aryl
Asn	*L*-Asparagine
BIMP	Bifunctional Iminophosphorane
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
*n*Bu	*n*-Butyl
*t*Bu	*tert*-Butyl
Bz	Benzyl
Cbz	Benzyloxy carbamate
CIP	Chan-Ingold-Prelog
cm	centimetre
CMD	Concerted Metalation Deprotonation
Cp	Cyclopentadiene
Cp*	1,2,3,4,5-Pentamethylcyclopentadiene
CPME	Cyclopentyl methyl ether
Cy	Cyclohexyl
δ	Chemical shift
dba	Dibenzylideneacetone
*o*DCB	1,2-Dichlorobenzene
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFT	Density Functional Theory
DG	Directing group
DME	1,2-Dimethoxyethane
DMF	*N,N*-Dimethylformamide

dmpe	1,2-Bis(dimethylphosphino)ethane
DMPU	1,3-Dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone
DNA	Deoxyribonucleic acid
dppb	1,4-Bis(diphenylphosphino)butane
ee	Enantiomeric excess
eq	Equivalent
er	Enantiomeric ratio
ES	Electrophilic Substitution
ESI	Electrospray ionisation
Et	Ethyl
Fmoc	Fluorenylmethyloxycarbonyl
g	gram
Glu	*L*-Glutamic acid
Gly	*L*-Glycine
HFB	Hexafluorobenzene
HFIP	Hexafluoro-2-propanol
HMPA	Hexamethylphosporic triamide
HPLC	High Pressure Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
Ile	*L*-Isoleucine
IMesH	*N,N*-bis(mesityl)imidazolium
IPA	Isopropanol
J	Coupling constant
λ	Wavelength
LDA	Lithium diisopropylamide
LLHT	Ligand to Ligand Hydrogen Transfer
Leu	*L*-Leucine
M	Molar concentration
m-	meta
Me	Methyl
MeCN	Acetonitrile
Men	Menthol
MeOH	Methanol
MHz	megahertz

min	minute
mL	millilitre
mmol	millimoles
MP	Melting point
MPAA	mono-*N*-protected amino acid
MS	Molecular sieves
nbe	Norbornene
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
μ	micro
o-	ortho
p-	para
PCy_3	Tricyclohexylphosphine
PEPPSI	Pyridine-Enhanced Precatalyst Preparation Stabilization and Initiation
Ph	Phenyl
phen	1,10-Phenanthroline
PMP	*para*-Methoxyphenyl
por	Porphyrin
ppm	parts per million
Pro	*L*-Proline
Py	Pyridyl
R	Organic group
RT	Room temperature
RNA	Ribonucleic acid
SBM	Sigma Bond Metathesis
TBAI	Tetrabutylammonium iodide
TBME	*tert*-Butyl methyl ether
TEMPO	2,2,6,6-Tetramethylpiperidine-1-oxyl
TFB	Trifluoromethylbenzene
TFE	2,2,2-Trifluoroethanol
TFEtOAc	2,2,2-Trifluoroethyl acetate
THF	Tetrahydrofurane
TLC	Thin-layer chromatography
TMS	Trimethylsilane

TOAB	Tetraoctylammonium bromide
Tol	Tolyl
Trt	Trityl
Ts	Tosyl
Tyr	*L*-Tyrosine
Val	*L*-Valine
VTMS	Vinyltrimethyl silane

Chapter 1: Introduction

1.1 Chirality and Enantioselective Synthesis

1.1.1 Chirality and history

The founding grounds of enantioselective or asymmetric synthesis goes back in time to the discovery and explanation of chirality, which is based on the observation and discovery of optical activity. French physicist Francois Arago, was the first one to observe the rotation of the orientation of linearly polarised light in quartz crystals in 1811.[1] He also described thin film interference colours produced by sheets of mica between polarisers. However, it was Jean-Baptiste Biot who clarified the difference between quartz and mica polarisation. And not only that, he also discovered that a range of natural products that have the ability to rotate the plane of polarisation while in solution, which set up the basics of optical polarimetry.[2] Optical polarimetry is a method used to determine the optical activity of a molecule. From a chemical point of view, the founder of chirality was Luis Pasteur, who by hand, separated for the first time the two mirror-image isomers of sodium ammonium tartrate in 1848 (**Figure 1**).[3]

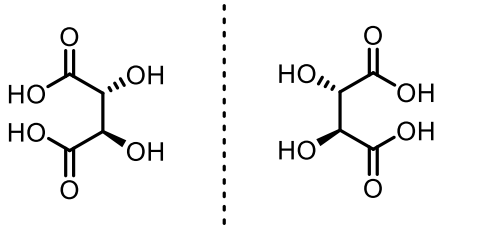


Figure 1. Structures of two mirror-image isomers of tartaric acid.

Majority of organic molecules that are formed in living organisms are chiral, therefore they may exist in two forms as two opposite enantiomers. These enantiomers are mirror images of each other, one rotates the plane of polarised light to the right and one to the left. It is important to mention that compounds that constitute the structural basis of living organisms and those that bear essential vital functions are mostly found in organisms in one of these two forms. A result of a substance containing unequal number of molecules in these two forms, is the rotation of the plane of polarisation of light by this substance, or optical activity. In living organisms, not just simple building blocks, but also more complicated scaffolds including protein polymers exhibit chirality. α-Amino acids, or their acid residues are the basic structural elements of proteins and polypeptides. Although plenty of amino acids are known, only 22 have been found to compose diverse proteins in living organisms, these for example include alanine **1-2** and serine **3-4** (**Figure 2**). All amino acids that are present in proteins are *L*(-)-configured (levorotatory), while for instance all nucleosides, which are the structural elements of nucleic acids RNA and DNA, consist only of *D*(+)-configured (dextrorotatory) sugar, ribose. Other important sugars that compose polysaccharides, glucose and fructose, are both present in their *d*(+)-form.[4]

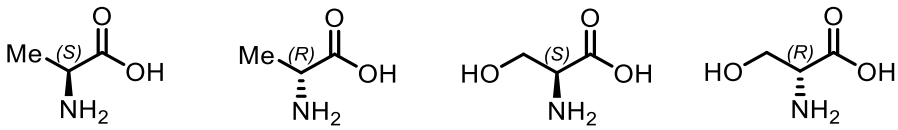


Figure 2. Structures of both mirror forms of Alanine and Serine.

Chirality plays a crucial role not only in living organisms, but also in pharmaceutical, agrochemical and other chemical industries. Currently 56% of the drugs on the market are chiral and 88% of the lately marketed ones are marketed as racemates (containing equimolar

mixture of two enantiomers). Even though the two enantiomers have the same chemical structure, their biological activities are, in most cases, different. They can differ in toxicology, pharmacology, pharmacokinetics, metabolic pathways, etc.[5]

One of the most well-known examples of enantiomers with different biological activities is thalidomide. Thalidomide was brought to market in the late 1950's by German pharmaceutical company Chemie-Grunenthal. It was marketed as a nonaddictive, nonbarbiturate sedative, and as it was very effective it was quickly discovered to be also an effective antiemetic and it started to be prescribed to treat morning sickness in pregnant women. Thalidomide was distributed in 46 countries around the world and it quickly became one of the world's largest selling drugs, as it was heavily marketed and advertised as perfectly safe, up until it was banned in November 1961. Not long after thalidomide's release, reports of severe birth defects and patients developing peripheral neuropathy started to appear. But it was not until 1961 when two clinicians Lenz (Germany) and McBride (Australia) confirmed the cause of the defects to be thalidomide. This is known to be the world's largest medical disaster in history caused by man with over 10,000 reports of severe birth defects in children. And what is the cause of this disaster? *R*(+)-Thalidomide **5** is an effective sedative while the *S*(-)-enantiomer **6** is teratogenic, and when ingested due to the physiological conditions inside the body, rapid interconversion between the two enantiomers occurs (**Figure 3**).[6]

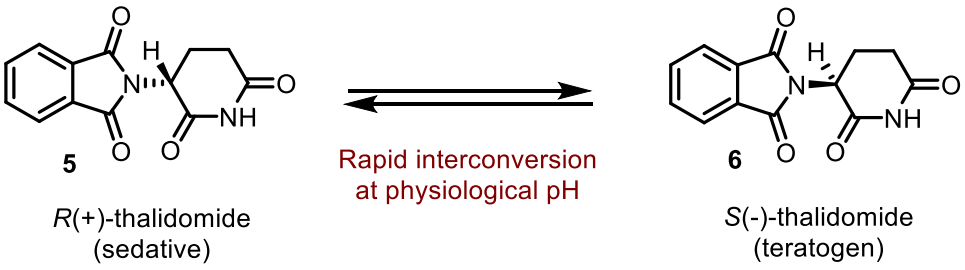


Figure 3. Structures of *R*-thalidomide and *S*-thalidomide.

The two enantiomers are best identified by their absolute configuration or their optical rotation. The absolute configuration is assign by Cahn-Ingold-Prelog (CIP) system using *R/S* descriptors, while optical rotation by (+)/(-) rather than *D/L* that are nowadays used for amino acids and sugars.[7] Experimentally, optical rotation is used more often simply because it is easier to determine than absolute configuration, optical rotation however does not provide information about the absolute configuration itself. Using a hypothetical interaction between the 2 enantiomers of a chiral drug and a receptor at the drug binding sites, the difference between the two mirror forms can be illustrated (**Figure 4**). In this example, one of the enantiomers is biologically active. Parts of the drug A, B and C have to bind with the corresponding regions a, b and c of the binding site in order for the drug to be effective. The 3-dimensional structure of the active enantiomer can be aligned with the binding site to form Aa, Bb and Cc, while the inactive one's cannot. In some cases, the chiral centre of the enantiomer can be in a different part of the molecule than the binding part, and in these case both enantiomers might display very similar pharmacology in their target site, but even in these cases the enantiomers can differ in their metabolic pathways.[8]

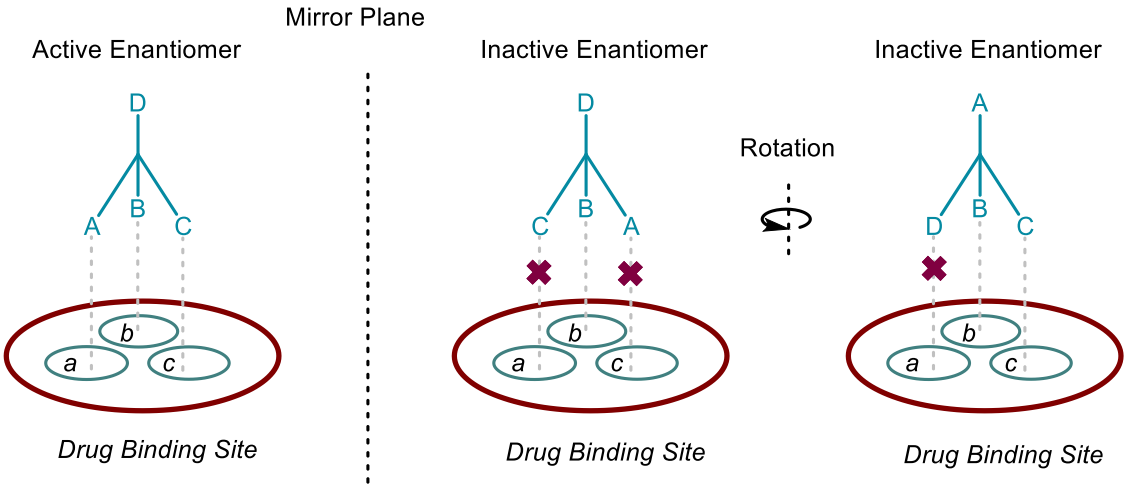


Figure 4. Easson-Stedman hypothetical interaction between the 2 enantiomers of a racemic drug with the receptor at the drug binding sites.

1.1.2 Overview of enantioselective synthesis

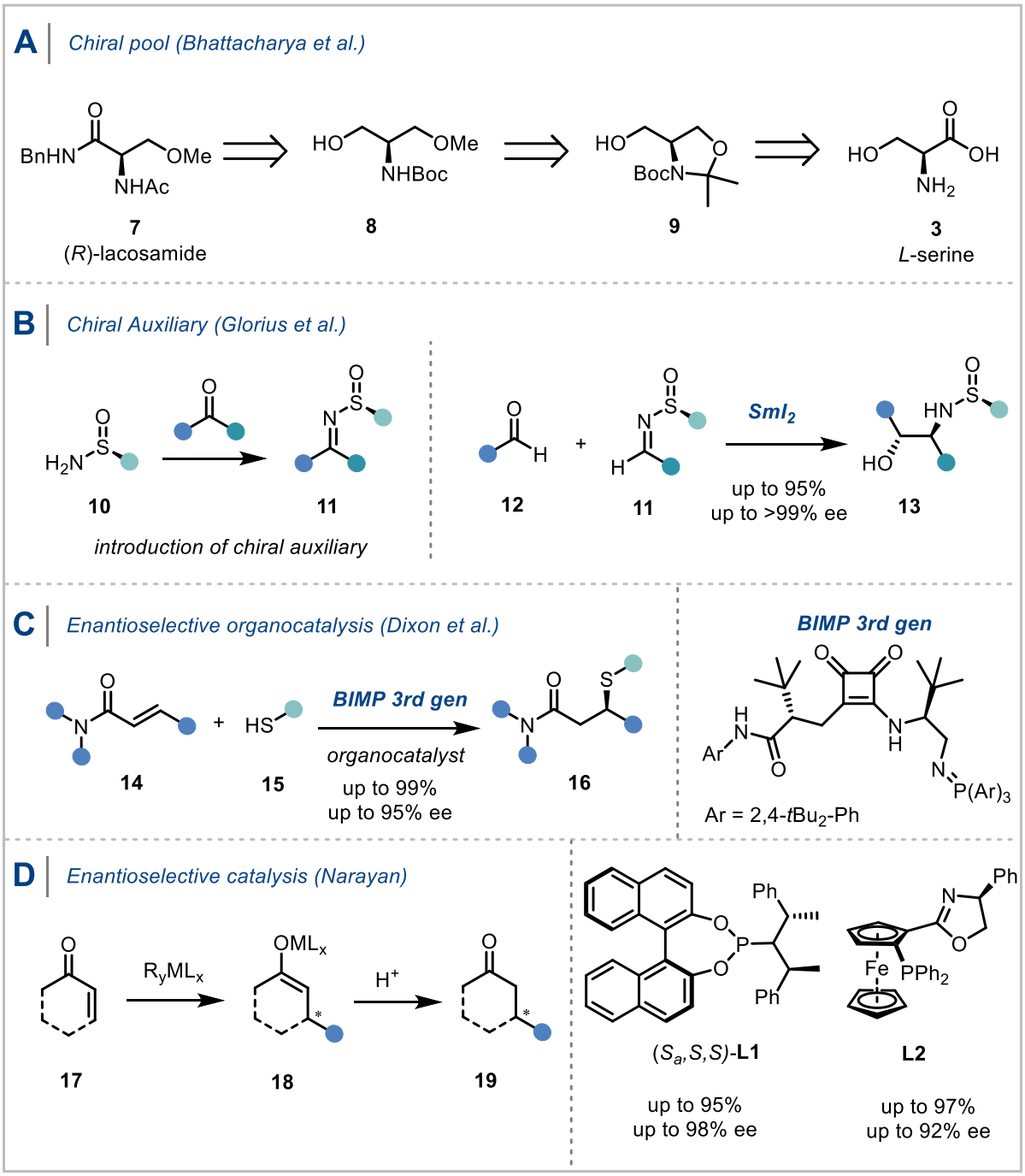
Enantioselective synthesis is often viewed as a subdiscipline of organic chemistry, however it is essential to all chemistry fields. Nowadays, asymmetric synthesis plays a crucial role in the synthesis of a wide variety of bioactive molecules. These methodologies vary from the traditional direct modifications of chiral naturally occurring molecules, to enantioselective catalysis where either metal complexes bearing or binding to chiral ligands or chiral metal-free organocatalysts are employed.[9]

There are multiple approaches for the synthesis of enantiopure materials. One of the oldest approaches is "chiral pool" synthesis, which relies on the stoichiometric application of naturally occurring chiral building blocks, such as amino acids, carbohydrates or small terpenes.[10] These simple chiral materials can be transformed into complicated chiral structures, or used as a chiral source in the synthesis of chiral ligands or reagents for asymmetric catalysis.[11–13] For example, Bhattacharya reported "chiral pool" synthesis of (*R*)-lactosamide **7** from readily available natural amino acid *L*-serine **3** (**Scheme 1A**).[14]

Another approach to asymmetric synthesis is *via* chiral auxiliaries **11**, in which case a pure enantiomer **10** is linked to the substrate, forming chiral starting material **11**, which controls the stereochemical course of the transformation and allows the formation of auxiliary-containing product **13**. Often chemical auxiliaries are introduced early in the synthesis, and are removed by simple transformations after the formation of enantiopure products. (**Scheme 1B**).[15]

Enantioselective catalysis or organocatalysis are two of the most important technologies in practise today. Often, it allows difficult processes to be completed with high efficacy and without a significant strain on the chemical and ecological resources. Catalytic transformations are offering access to broad range of valuable molecules with significant reduction of costs, compared to the stoichiometric transformations. Dixon reported enantioselective BIMP-catalysed Sulfa-Michael addition to unactivated α,β-unsaturated amides **14** allowing the formation of enantiopure amides **16** in up to 99% and 95% ee (**Scheme 1C**).[16]

In organic chemistry, transition metal catalysis holds a place of prominence, as transition metals showed to be most versatile for enantioselective catalysis. Transition metals are able to coordinate to a range of different ligands, which vastly expands the potential of transition metal catalysis. The purpose of ligands can vary from tuning the electronic nature of the metal centre to creating a chiral environment around it. The fact that chiral ligands can be combined with metal salts offers enormous scope to discover and develop enantioselective catalytic methodologies. An example could be enantioselective conjugate addition of organometallic reagents to *α,β*-unsaturated carbonyl compounds **17** (**Scheme 1D**).[17]

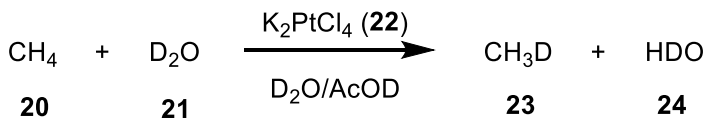


Scheme 1. A) (*R*)-Lacosamide synthesis via "chiral pool". B) Introduction and application of chiral auxiliary. C) Enantioselective organocatalysed Sulfa-Michael addition to unactivated *α,β*-unsaturated amides. D) Enantioselective conjugate addition of organometallic reagent to *α,β*-unsaturated carbonyl compounds.

1.2 C–H Functionalisation

1.2.1 Discovery of C–H functionalisation

Historically, first advances in the field of transition metal homogeneous catalysis for C–H activation and C–H functionalisation reactions date back to Fenton with his oxidation of tartaric acid in 1894.[18] The development of modern C–H activation methods however, dates back to the 1970's, when Shilov studied platinum chemistry. He applied platinum catalysis to olefin hydrogenation, with an understanding of the critical step of this transformation being C–H elimination from Pt alkyl to give Pt^{II}. The reversibility of this step was investigated, and it was discovered through H/D exchange of methane **20** and D_2O **21** that Pt^{II} **22** can react with C–H bonds (**Scheme 2**).[19]

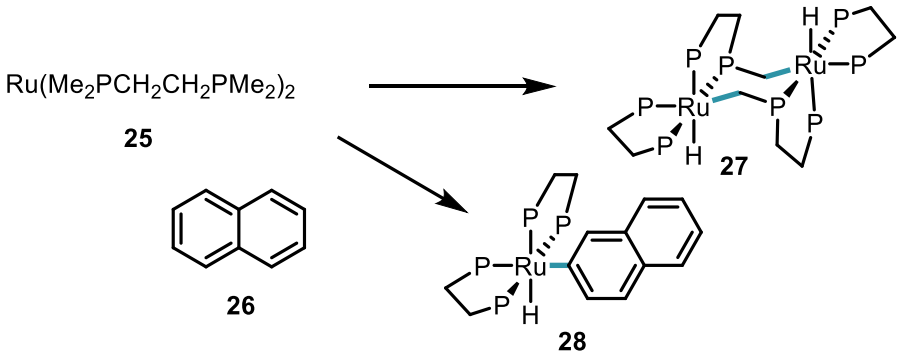


Scheme 2. H/D exchange between methane and D_2O in presence of Pt^{II}.

The driving force and continuing aspiration of C–H activation is to transform methane into useful products, for instance methanol. The need to explore C–H functionalisations only grew more with the rise of cracking, which is a technique that largely enhanced the global methane supplies.[20] Alkanes and saturated hydrocarbons are the main components of natural gas and petroleum, but there are not many processes for the direct conversion of these to more valuable products. The reason is the low reactivity of alkanes or in other words their "inertness", which arises from the constituent atoms all being held together by strong C–C and C–H bonds. These molecules do not have any empty low-energy orbitals or any filled high-energy orbitals that could readily engage in chemical transformations.[21]

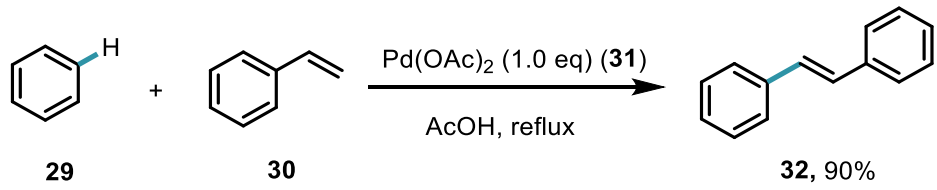
1.2.2 Transition metal-catalysed C–H activation

Transition metal-based systems have a long history in the activation of C–H bonds. One of the first reports of C–H activation with transition metal complex is associated with Chatt's $Ru^0(dmpe)_2$ **25** activation of ligand's phosphinomethyl C–H group **27** or the activation of one of naphthalene's C–H groups **28** (**Scheme 3**).[19,22]



Scheme 3. Chatt's C–H activation by $Ru^0(dmpe)_2$ complex.

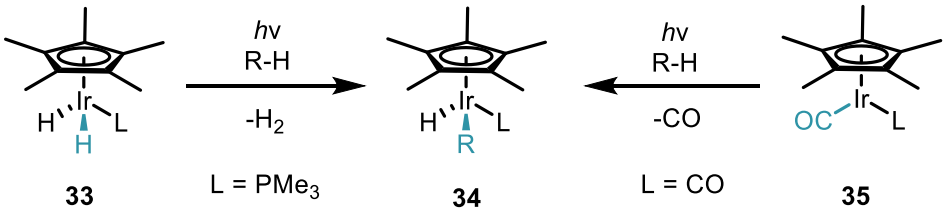
Another significant discovery was reported by Fujiwara in 1969, in which he described the stoichiometric $Pd(OAc)_2$ **31** catalysed synthesis of *trans*-stilbene **32** from benzene **29** and styrene **30** (**Scheme 4).**[23]



Scheme 4. Fujiwara's palladium catalysed C–H functionalisation.

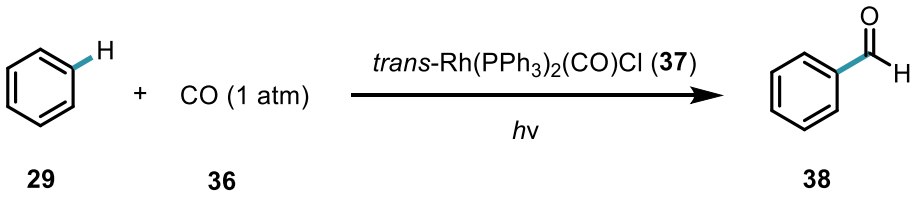
More than a decade later, in 1982, another stepping stone was when Bergman and Graham independently reported the first examples of intermolecular alkane C–H bond addition to create stable alkyl iridium hydrides (**Scheme 5**).[24,25] Probably, the most important finding

of Bergman's research is an outstanding selectivity between multiple C–H bonds. The metal centre of the reactive intermediate Cp*Ir(PMe_3) (Cp* = η^5-C_5Me_5) showed a striking inclination for the cleavage of stronger C–H bonds; aryl > 1° > 2° >> 3°.[26] Soon after this report, many chemists adapted these principles into their research and it became apparent that kinetics and thermodynamics of the addition of transition-metal complexes to C–H bonds were in favour for the least-substituted primary alkyl groups.[19]



Scheme 5. Bergman's (left) and Graham's (right) alkane C–H bond addition to the transition metal complex.

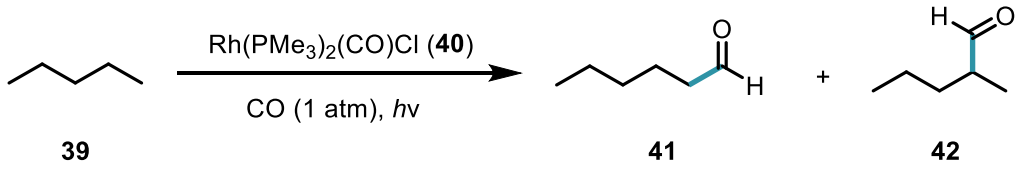
Out of many transition-metal catalysed transformations, in which alkyl transition metals are formed as intermediates, carbonylations are the ones with most importance. For example, in 1983, Eisenberg found that carbonylation of benzene **29** is photochemically catalysed by $Rh(PPh_3)_2(CO)Cl$ **36** (**Scheme 6**).[27,28]



Scheme 6. Eisenberg's photochemically catalysed carbonylation of benzene.

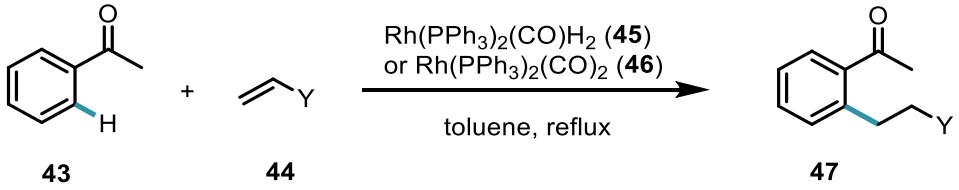
Bergman's previous studies of Cp*Ir(PR_3) complexes revealed selectivity differences between PPh_3 and PMe_3-containing complexes in carbonylations. These differences were noticed by Tanaka, who further investigated PMe_3 analogue of Eisenberg's catalyst $Rh(PPh)_3)_2(CO)Cl$ **37**. What he discovered was not only that $Rh(PMe)_3)_2(CO)Cl$ catalyst **40**

was more effective for benzene carbonylation, but it also allowed the carbonylation of alkanes **39** (**Scheme 7**). It was discovered that short-wavelength light induces the carbonylation of the terminal position of the alkane **39** forming linear aldehydes **41**, while longer-wavelengths primarily form branched aldehydes **42**.[19]



Scheme 7. Tanaka's photochemically catalysed carbonylation of pentane.

There are many transition-metal based systems that show low energetical barrier for olefin insertion into the carbon-metal bonds. However, there are also some examples of unsaturated molecules being inserted into the alkyl C–H bonds. The C–H bond strength difference between sp^2 and sp^3 is striking and most likely can only be partially attributed to the greater reactivity of sp^2 hybridised C–H bonds. Murai's report from 1993 is considered to be another breakthrough in the field of catalytic C–H activation as an example of directed C–H functionalisation. The Murai's group discovered, that $Ru(PPh_3)_3(CO)H_2$ **45** and $Ru(PPh_3)_3(CO)_2$ **46** catalyse olefins **44** insertion into the *ortho*-C–H bonds of aromatic ketones **43** (**Scheme 8**).[19,29]



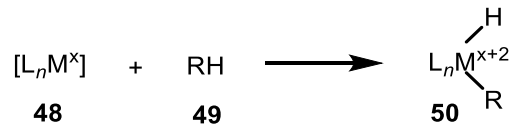
Scheme 8. Murai's ruthenium catalysed *ortho*-C–H olefination of aromatic ketones.

1.3 Mechanisms of C–H activation reactions

Historically, C–H activation processes have been divided into 5 different types of mechanisms. These can be described by a variety of factors, such as the use of early or late transition metals, whether the metal's oxidation state changes, whether there is a ligand involvement in the C–H bond cleavage during the transition state, and as well the type of the involved ligand. It is important to state, that in recent years the classification of mechanisms is changing due to new discoveries of transformations that do not fit within the historical categories.[30]

1.3.1 Oxidative addition

The transformations occuring *via* oxidative addition mechanism are common for the electron-rich complexes of low-valent transition metals, such as Ir, Rh, Pt, Re, Ru, Os or Fe. In this case, a reactive species $[L_nM^x]$ **48** is generated *in situ* by either thermal or photochemical decomposition of a viable precursor, and is almost always unstable due to its coordinatively unsaturated nature. In these reactions the metal's oxidation state is formally increased by two due to the C–H bond breakage (**Scheme 9**).[21,30]

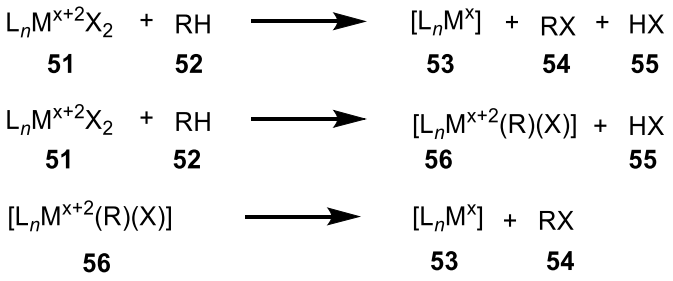


Scheme 9. Oxidative addition activation reaction.

1.3.2 Electrophilic activation

Electrophilic C–H activation dates back to Shilov and his mechanistic experiments of H/D exchange on methane in the presence of platinum. His work was over the years expanded by Shteinman, Labinger, Bercaw and many others.[31,32] The key feature of the electrophilic C–H activation mechanism is a proton abstraction during the transition state by the

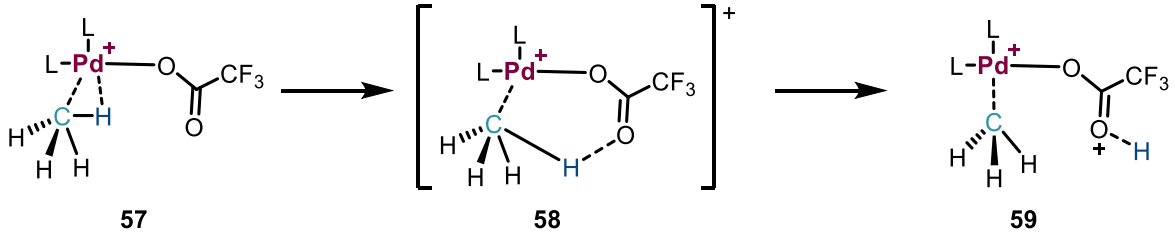
neighbouring heteroatom's lone pair. This also differentiates the electrophilic substitution mechanism from sigma bond metathesis, as both have four-centred transition states, however no lone pairs are involved in sigma bond metathesis.[30] Certain transformations that directly form functionalised alkanes, have been classified as electrophilic activation reactions. These can proceed without the observation of organometallic species even though their existance as intermediates is strongly suggested. In such a reaction [M^{x+2}] indicates a late- or post-transition metal species, (Pd^{2+}, Pt^{2+}, Pt^{4+}, Hg^{2+}, Tl^{3+}) usually in water or other strongly polar media like anhydrous acid. The suspected organometallic intermediate [L_nM^{x+2}(R)(X)] **56** would be formed through 'metal for a proton' substitution, and this intermediate would transform into product **54** (**Scheme 10**).[21]



Scheme 10. Electrophilic activation reaction.

Electrophilic C–H activation consists of a number of categories, such as electrophilic substitution (ES) that have been heavily researched by Goddard, Ess, Periana and many others,[33] electrophilic concerted metalation deprotonation (eCMD), a term introduced by Carrow,[34] or ligand to ligand hydrogen transfer (LLHT) that operates within the first row metals, proposed by Eisenstein and Perutz.[35] Ambiphilic metal-ligand activation (AMLA) presented by Macgregor and Davis,[36] and concerted metalation deprotonation (CMD) introduced by Fagnou,[37] are arguably the most significant categorisations of C–H activation. In both instances (AMLA/CMD), the C–H bond cleavage is aided by a base. During both

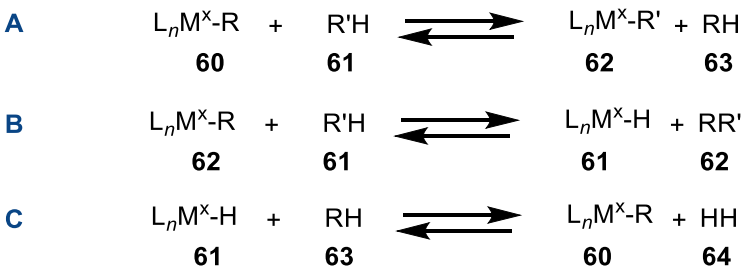
CMD and AMLA processes, a late transition metal such as Ir, Pt, Pd forms a sigma bond with an alkane and this sigma-complex **57** formation polarises the C–H bond, essentially making the proton more acidic. At this point a weak base, usually a carboxylate ligand, deprotonates the C–H bond and affords a new C–M bond and carboxylic acid (**Scheme 11**).[30]



Scheme 11. CMD/AMLA activation mechanism.

1.3.3 Sigma-bond metathesis

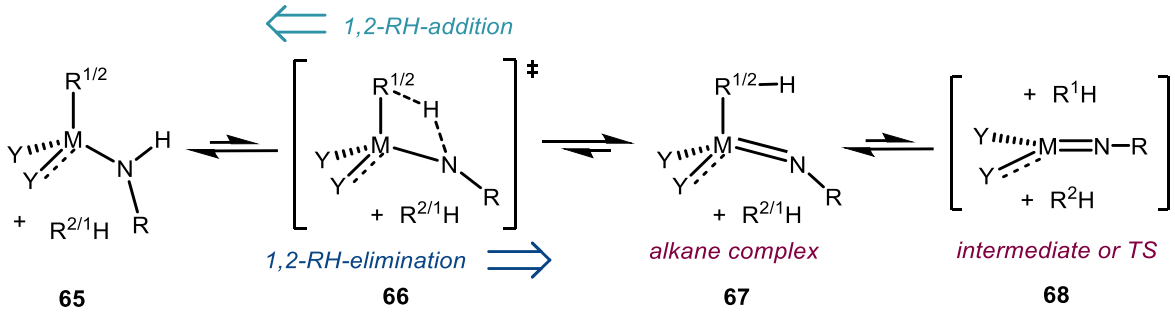
Early transition metals without available *d* electrons for oxidative addition are generally involved in sigma bond metathesis (SBM). In SBM the oxidation state of the metal does not change throughout the transformation. During SBM a four-centred transition state where proton from the C–H bond is transferred to the existing C–M bond is formed. The proton acceptor usually dissociates from the metal complex after proton transfer.[30] Transition metals, mostly from the group 3, with d^0 configuration (lanthanides, actinides, Sc) are viable for this reversible reaction (**Scheme 12A**), if complexed with alkyl or hydride ligands. Usually R and R' stand for alkyl groups, which means that the reaction extends only to alkyl-fragment interchange. C–C bond formation, and breakage through the alternative exchange is not observed (**Scheme 12B**), while in some instances the interconversion between dihydrogen and metal alkyl with alkane and metal hydride are known (**Scheme 12C**).[21]



Scheme 12. Sigma bond metathesis activation reaction.

1.3.4 1,2-Addition

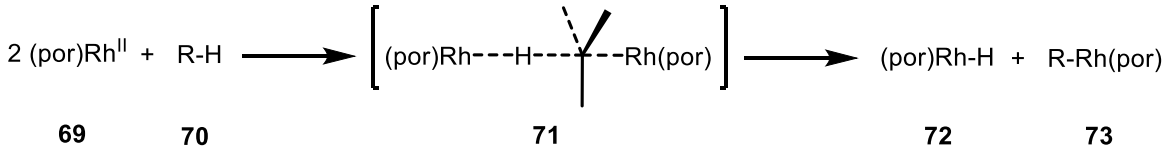
Commonly, early transition metals (Zr, Ti) are involved in the activation through 1,2-addition. Initially, the alkane binding occurs *via* a sigma complex to the d_n^2 orbital and the crucial interaction comes from the electron density donation from the metal-ligand dπ orbital to the σ* orbital of R–H, leading to a four-centred transition state similar to the one in sigma-bond metathesis and this results in the cleavage and hydrogen transfer (**Scheme 13**). The driving force of this mechanism is the overall bond strength of the M–R bond and this type of mechanism is observed for alkylidene, alkylidyne and imido metal complexes.[30,38]



Scheme 13. 1,2-addition activation reaction.

1.3.5 Metalloradical

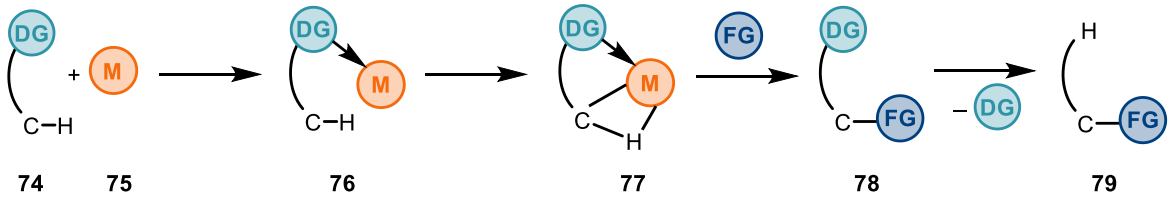
Porphyrin complexes of Rh^{II} and Ir^{II} that occur in monomer-dimer equilibria can reversibly break C–H bonds. The paramagnetic radical-like systems can cleave benzylic bonds, however are unreactive towards stronger aryl C–H bonds. This preference would normally suggest radical involvement in the mechanism, but even higher selectivity was found in much stronger C–H bonds of methane. Studies led to the explanation that a termolecular transition state operates, where one metal centre forms a bond with carbon **73** while the second one forms the bond with hydrogen **72** (**Scheme 14**).[19,39]



Scheme 14. Metalloradical activation reaction.

1.4 Directing groups for C–H functionalisation

Organic substrates are complex structures, that hold several different types of C–H bonds within the molecule. Normally, more reactive C–H bonds of the molecules are favoured for the C–H activation. Although when it comes to selectivity, it is very challenging to control reactivity on one single bond, and for this reason the use of directing groups (DGs) is wide spread strategy to enable selective activation of C–H bonds. Generally speaking, directing groups are Lewis basic ligands **74** that coordinate to the metal centre of the catalyst **75** in order to bring it closer to the targeted C–H bond **76**. One of the limitations of this strategy is the position of the directing group, which needs to be on the side of the substrate in order to achieve the activation. However, recently some DGs have been utilised in this strategy that can be efficiently removed by post-functionalisation to form DG-free products **79** (**Scheme 15**).[40]



Scheme 15. Mode of action of the directing group for selective C–H activation.

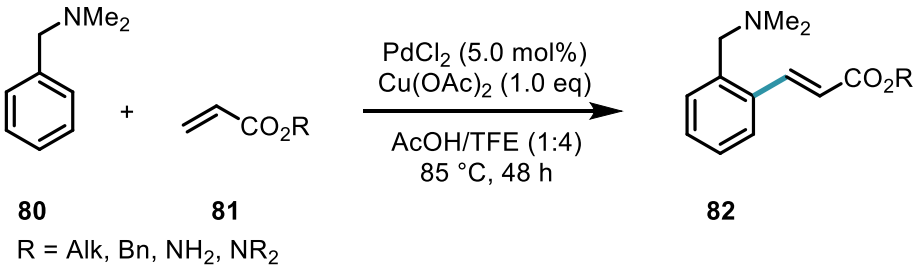
In order for a DG not to block the metal centre permanently, the directing group should act as a labile or semi-labile ligand, therefore substrates containing DGs must coordinate to the metal centre prior to the C–H activation either by a simple coordination or by ligand substitution.[40]

1.4.1 Nitrogen-based directing groups

The largest class of directing groups feature a nitrogen atom. This is generally attributed to the nitrogen possessing multiple binding modes, and to the fact that nitrogen's Lewis basicity can be tuned by up to three substituents. *N*-Based directing groups are usually stable and the ease of installation aids their popularity.[41]

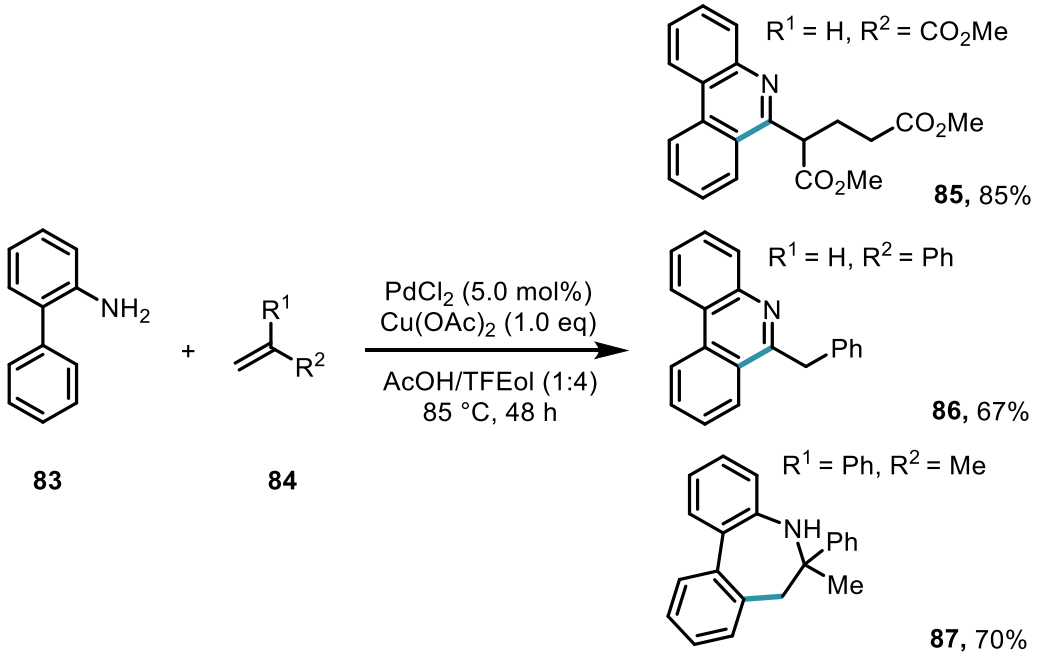
Amine-based directing groups for catalytic C–H functionalisation represent a challenge due to their strong σ-donating ability. The *N,N*-dimethylaminomethyl directing group has been widely used for the *ortho*-metalation by transition metal complexes to form metallacycles, however in the catalytic systems, substrates bearing amino groups bind strongly to the catalyst, which forbids the formation of empty coordinating sites around the catalyst centres. The first example of an amine-directed palladium-catalysed C–H functionalisation was reported by Shi in 2007. In this case, acrylate **81** was reacted with benzyl amine **80**, which under Pd-catalysis generates **82**, *via ortho*-C–H olefination. A specifically tuned solvent system of acetic acid/2,2,2-trifluoroethanol (1:4) was crucial for the success of the reaction

(**Scheme 16**). The role of acetic acid was in tuning the free amines concentration as well as assisting the anionic ligand dissociation from the catalyst centre to create reactive and coordinately unsaturated catalyst species.[41,42]



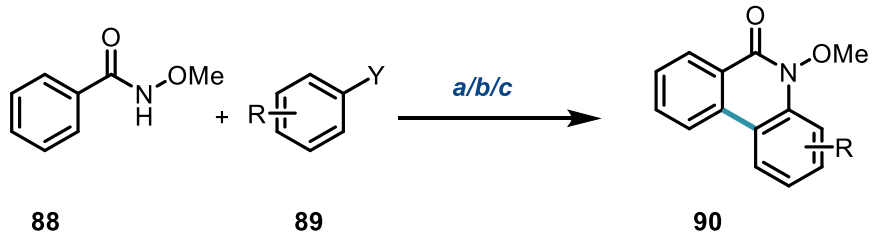
Scheme 16. First Pd-catalysed amine directed C–H functionalisation.

The use of free amines as directing groups for catalytic C–H activation reactions became established soon after. In 2012, a palladium-catalysed free-amine-directed alkylation of C(sp^2)–H bonds and cycloamination of aryl amine **83** was reported by Zhang (**Scheme 17**).[41,43]



Scheme 17. Pd-catalysed free-amine-directed C(sp^2)–H alkylation and cycloamination.

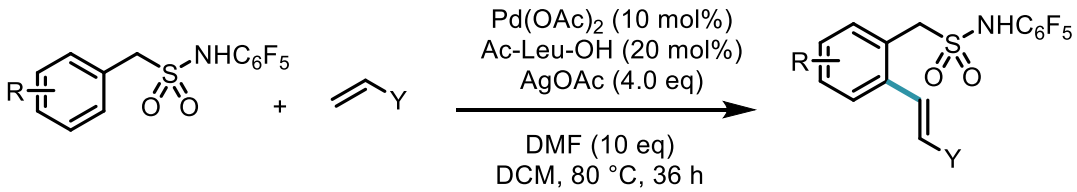
Another class of widely studied *N*-containing directing groups are *N*-substituted amides (CONHR). *N*-Methoxybenzamide **88** was used by Wang and Cheng in the Pd-catalysed one-pot cascade to afford phenanthridinone derivatives **90** with arenes or iodoarenes **89**.[44,45] Another example was published by Cheng, in which case phenanthridinone derivatives **90** were achieved by Rh^{III}-catalysed oxidative cyclisation of *N*-methoxybenzamides **88** with aryl boronic acids **89** (**Scheme 18**).[46]



88 **89** **90**

Scheme 18. Pd- or Rh^{III}-catalysed synthesis of phenanthridinones **90** via C–H activation. *a*) $Pd(OAc)_2$ (5 mol%), Ag_2O (2.0 eq), AcOH, 120 °C, 24 h, Y = I, R = Me, OMe, CO_2Me, halides, NO_2; *b*) $Pd(OAc)_2$ (5 mol%), $K_2S_2O_8$ (2.0 eq), TFA (20 eq), 25 °C, 16 h, Y = H, R = H, Me, OMe, Cl; *c*) $[Cp^*RhCl_2]_2$ (2 mol%), Ag_2O (4.0 eq), MeOH, 60 °C, 3 h, Y = $B(OH)_2$, R = Me, OMe, halide.

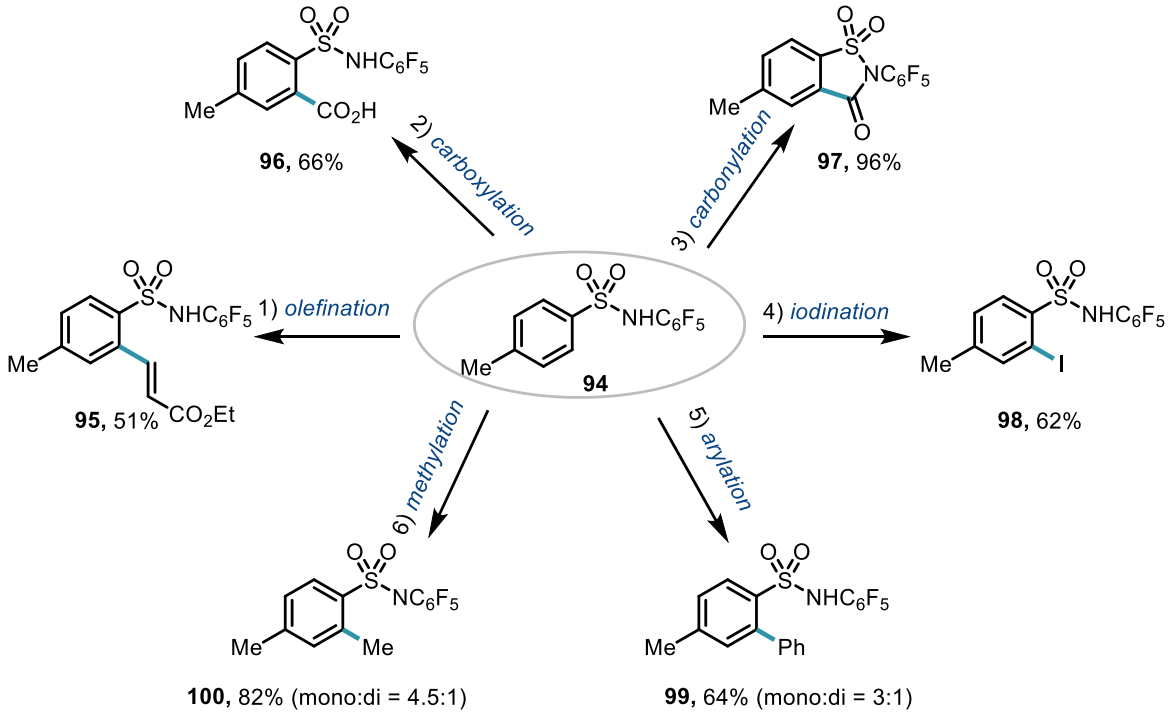
Sulfonamides were first employed as directing group in 2011 by Yu to form *ortho*-alkenylated products **93** by the palladium-catalysed C–H olefination of perfluoroaryl-substituted benzylsulfonamides **91** with acrylates or styrenes **92** (**Scheme 19**). In order to achieve high efficacy for this transformation, the utility of *N*-protected amino acid Ac-Leu-OH was crucial.[40,47]



91 Y = CO_2Et, Ph **92** **93,** 36-89%

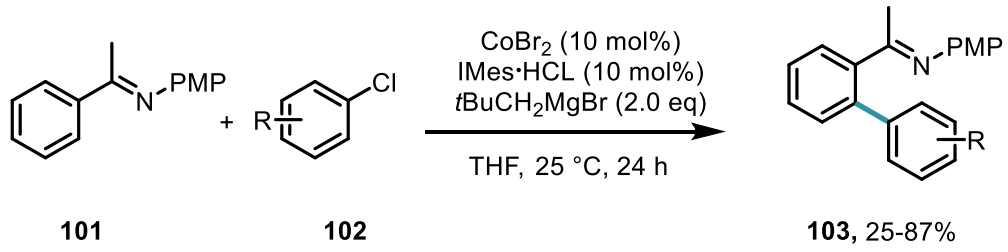
Scheme 19. Pd-catalysed sulfonamide directed $C(sp^2)$–H olefination.

In order to further establish the newly discovered DG, it was important to apply sulfonamide-containing starting material **94** to various carbon-carbon and carbon-heteroatom bond formations. Sulfonamides proved to be efficient in several *ortho*-C–H functionalisations. They were successfully applied in olefination to yield alkenylated product **95** in 51% yield, carboxylation to form **96** in 66% yield, carbonylation to form **97** in 96% yield, iodination to form **98** in 62% yield, arylation to achieve **99** in 64% yield and methylation to yield **100** in 82% (**Scheme 20**). Most of the previously reported directing groups proved to be applicable only to the limited set of these C–H transformations, while the broad application of sulfonamides proved how powerful this directing group is.[47]



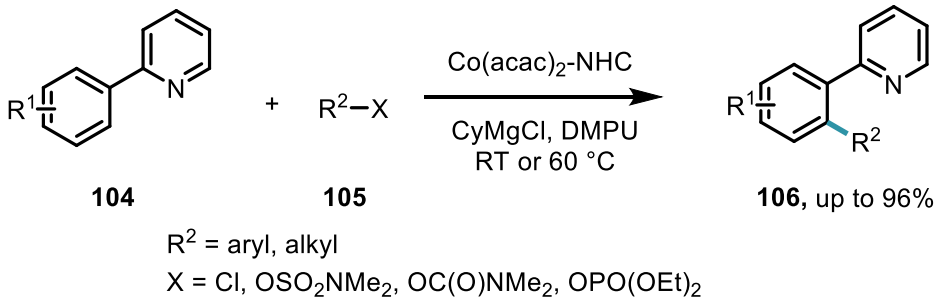
Scheme 20. Use of sulfonamide as directing group for C–H activation. 1) $Pd(OAc)_2$ 10 mol%, Ac-Leu-OH 20 mol%, AgOAc 4.0 eq, ethyl acrylate 4.0 eq, DMF 10 eq, DCM, 80 °C, 36 h; *2)* $Pd(OAc)_2$ 10 mol%, AgOAc 2.0 eq, TEMPO 2.0 eq, KH_2PO_4 2.0 eq, *n*-hexane, CO (1 atm), 130 °C, 24 h, 3) $Pd(OAc)_2$ 10 mol%, AgOAc 2.0 eq, KH_2PO_4 2.0 eq, *n*-hexane, CO (1 atm), 130 °C, 24 h; 4) $Pd(OAc)_2$ 10 mol%, $PhI(OAc)_2$ 3.0 eq, I_2 3.0 eq, DMF, 90 °C, 48 h; 5) $Pd(OAc)_2$ 10 mol%, BQ 10 mol%, pinacol phenylboronate 2.0 eq, K_2HPO_4 1.0 eq, Ag_2CO_3 2.0 eq, *t*-amylOH, 110 °C, 24 h; 6) $Pd(OAc)_2$ 10 mol%, BQ 10 mol%, $MeB(OH)_2$ 2.0 eq, K_2HPO_4 1.0 eq, Ag_2CO_3 2.0 eq, *t*-amylOH, 110 °C, 24 h

Discovery and development of *N*-based directing groups led to the development of directed C–H functionalisation with abundant and inexpensive first row transition metals (Mn, Fe, Co, Cu, Ni), and in particular cobalt catalysis attracted much attention due its similar reactivity to rhodium. In 2012, Yoshikai reported aromatic imines **101** as new directing group for Co^{II}-catalysed *ortho*-arylations with aryl chlorides **102**. In this case a cobalt-*N*-heterocyclic carbene with neopentyl Grignard reagent are crucial for the formation of arylated products **103**, which after acidic hydrolysis yielded arylated ketones (**Scheme 21**).[41,48]



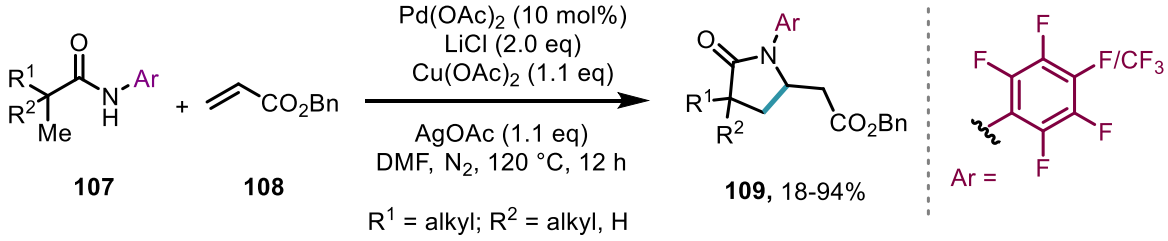
Scheme 21. Co-catalysed aromatic imines directed C(sp^2)–H arylation.

While exploring cobalt-catalysed C–H activation reactions, Ackermann discovered a pyridine-directed arylation and alkylation of arenes and heteroarenes **104** with aryl or alkyl chlorides **105**. The transformation was catalysed by an *N*-heterocyclic cobalt-carbene complex. Further studies led to the syntheses of biaryls **106**, which were achieved by pyridine-directed C–H activation followed by C–O bond cleavage, and as arylating agents they used carbamates, sulfamates or phosphates (**Scheme 22**).[49,50]



Scheme 22. Co-catalysed pyridine-directed C(sp^2)–H arylation and alkylation.

While C(sp^2)–H olefinations have been widely explored, the olefination of C(sp^3)–H bonds is reltively rare. Amides used as a directing group for C(sp^3)–H olefination have been reported by Yu in 2010. In this case, secondary amides **107** underwent olefination, and the amide products furnished the corresponding lactams **109** *via* a 1,4-type addition (**Scheme 23**). This protocol can also be applied to cyclopropyl methylene and other α-hydrogen containing substrates.[51] Amides as directing groups for C(sp^3)–H activation have been further studied, and Yu in 2012 reported a Pd^{II}-catalysed C(sp^3)–H arylation of methylene with aryl iodides directed by amides. This reaction was enabled by an electron-rich quinolone ligand.[52]



Scheme 23. Pd-catalysed amide-directed C(sp^3)–H olefination.

Other *N*-containing directing groups are for example triazenes employed in the Rh^{III}-catalysed C–H *ortho*-olefination with $Cu(OAc)_2 \cdot H_2O$ as the oxidant,[53] *N*-nitroso groups that directed Rh^{III}-catalysed *ortho*-olefination of arenes under mild conditions,[54] and other various *N*-heterocycles, oximes, hydroxamic acids or *N*-oxides (**Figure 5**).[41,55]

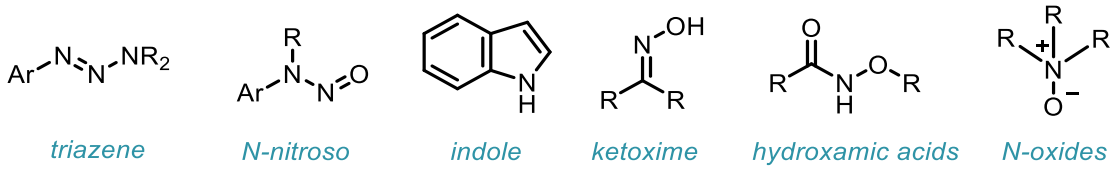
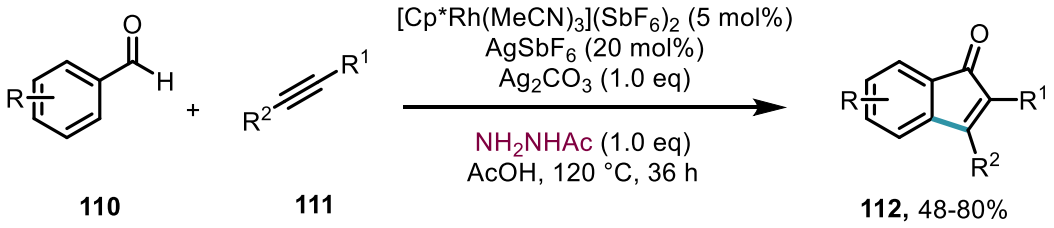


Figure 5. *N*-containing directing groups.

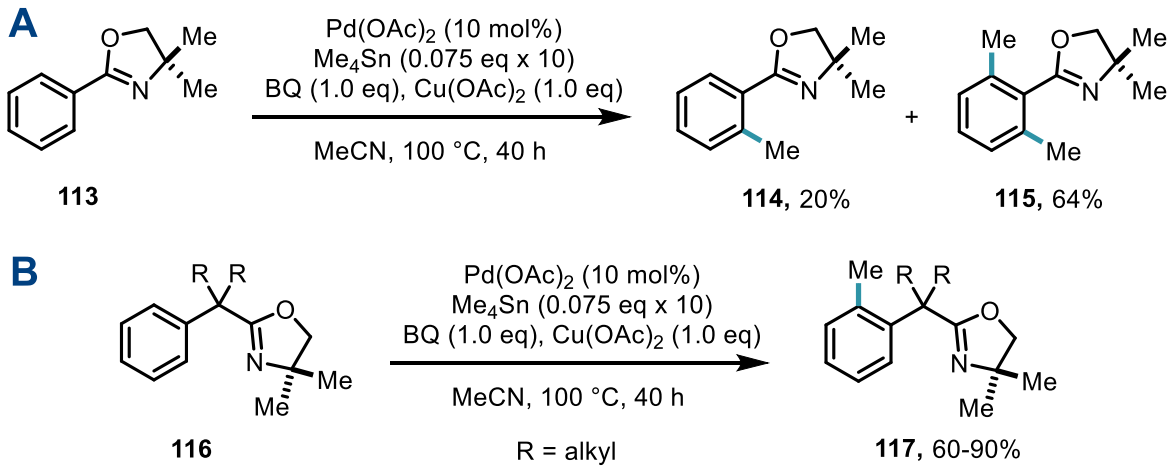
In 2013, Cheng reported direct annulation of aldehydes **110** with alkynes **111** to form indenones **112** catalysed by $[Cp^*Rh(MeCN)_3](SbF_6)_2$ complex. This efficient *ortho*-C–H activation is facilitated by the *in situ* formation of hydrazone (from acetylhydrazine) as a directing group, and after the activation, the removal of the DG by hydrolysis occurs (**Scheme 24**).[56]



Scheme 24. Rh-catalysed direct annulation of aldehydes.

The introduction of an oxazoline substituent as a directing group for C–H alkylations or arylations dates back to soon after its chelating properties were first observed and studied.[57] Some of the first examples of oxazoline-directed C–H activation reactions were iodination and oxygenation of methyl C–H bonds reported by Yu in 2005.[58] In 2006, Yu took this concept further and applied this chelating/directing group to the alkylation of aryl C–H bonds. Simple 2-oxazoline-substituted aryl **113** underwent directed Pd^{II}-catalysed C–H methylation in the presence of benzoquinone as an oxidant and continuous batch-wise additions of methyl-tin reagent, to allow the C–H activation and reoxidation steps to be completed. In the case of simple aryl-oxazoline substrates **113**, they observed the formation

of monomethylated product **114** in 20%, while the major product of the transformation was dimethylated aryl **115** achieved in 64% (**Scheme 25A**). To overcome the issue of dialkylation of the starting material, they found benzyl-oxazoline substrates **116** as an effective solution in the formation of monoalkylated aryls **117** (**Scheme 25B**).[59]

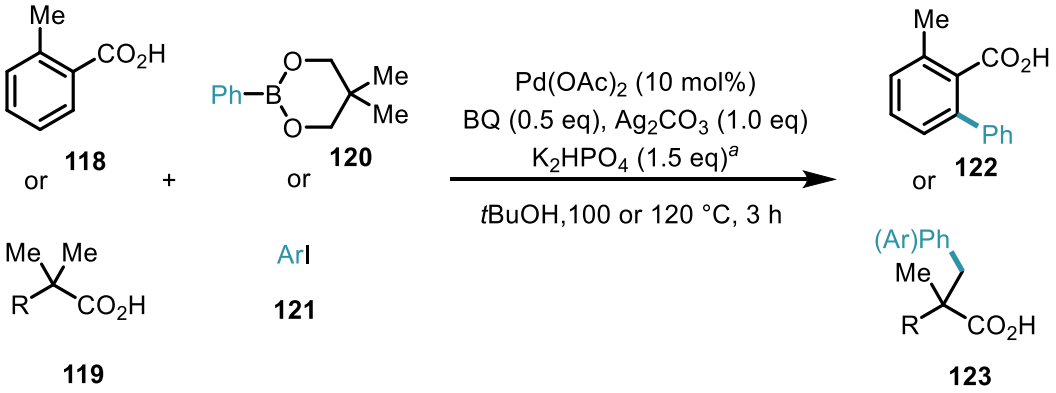


Scheme 25. Oxazoline as directing group for Pd-catalysed C–H alkylation.

1.4.2 Oxygen-based directing groups

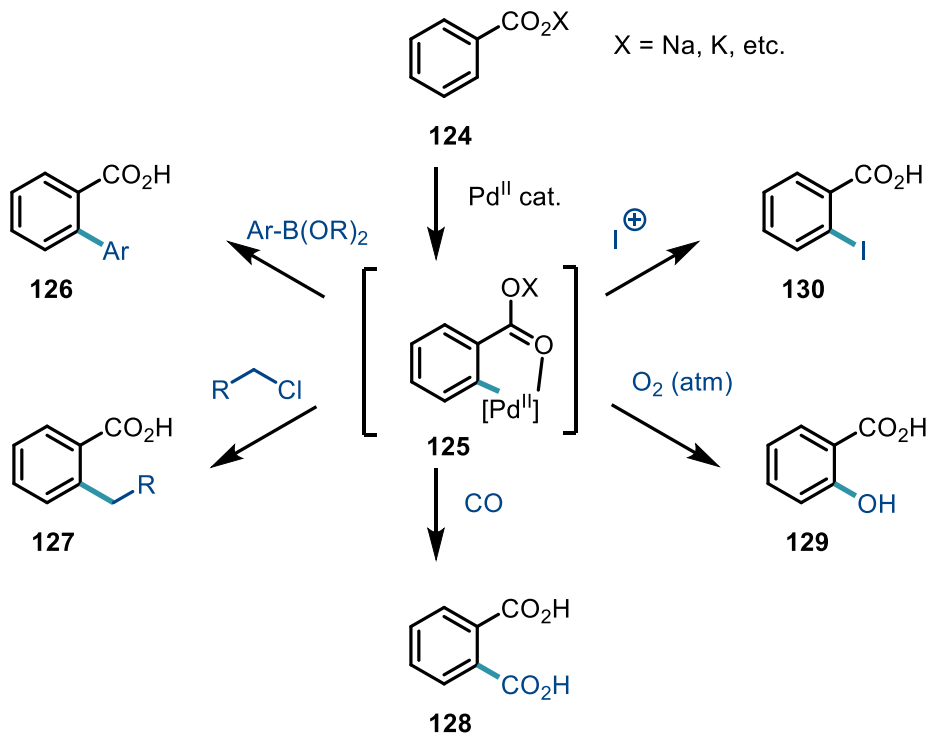
Another major class of directing groups are oxygen-based DGs, of which carboxylic acids and their salts were first discovered by Yu and Miura in 2007. Miura observed benzoic and naphthoic acids as effective substrates for *ortho*-alkenylation with acrylates under Pd-catalysis.[60] Studies towards new oxygen-based directing groups, like hydroxyls and carbonyls, commenced due to limitations of widely used *N*-containing DGs. These include the lack of versatility for further synthetic manipulations of pyridines, and the necessity of preinstallation and removal of oxazoline directing group, what restricts the substrate scope. In 2007, Yu reported his pioneering work on Pd^{II}/Pd^{0}-catalysed coupling of *ortho*-C(sp^2)–H bond of benzoic acids and β-C(sp^3)–H bonds with organoboron reagents, and further

generality of this approach was observed in β-C(sp^3)–H arylation of aliphatic acids with aryl iodide *via* Pd^{II}/Pd^{IV} catalysis (**Scheme 26**).[61,62]



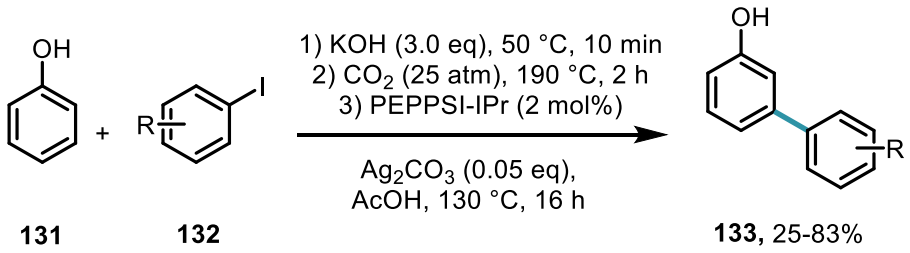
Scheme 26. Pd-catalysed carboxylate-directed C–H arylation of benzoic and aliphatic acids. *a*) Used in case of C(sp^3)–H activation of aliphatic acids **119.**

Since then, carboxylates as DGs have been studied extensively, and due to their weak coordination, their utility in ligand-controlled C–H activation reactions has been proven. Diverse reactivity and *ortho*-selectivity of carboxylates in palladium-catalysed C–H transformations have been summarised by Yu in 2012. Carboxylates **124** form a 5-membered palladacycle **125** with Pd^{II}, which can be arylated with aryl-boronic esters to form **126**, alkylated with alkyl halides to gain **127**, carboxylated with CO to form dicarboxylic acid **128**, oxygenated to achieve phenolcarboxylic acid **129** or iodinated to form **130** (**Scheme 27**).[63]



Scheme 27. Use of carboxylate as directing group for Pd-catalysed C(sp^2)–H functionalisations.

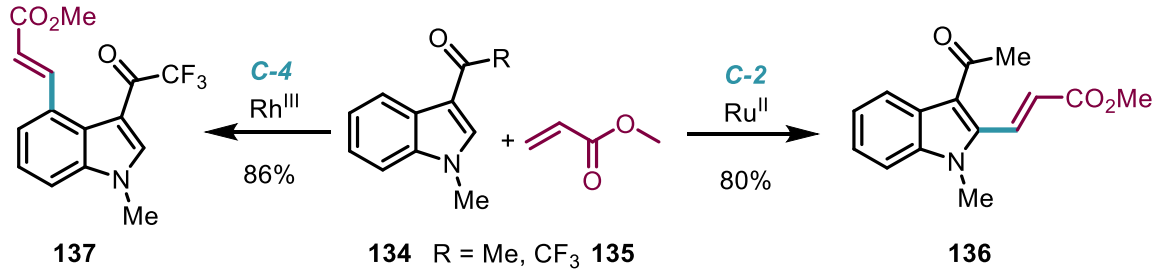
One of the advantages of carboxylic acid as a directing group is easy decarboxylation, leading to a traceless directing group strategy. Larrosa utilised this approach in his one-pot direct *meta*-arylation of phenols **131** with iodoarenes **132** (**Scheme 28**).[64]



Scheme 28. One-pot direct *meta*-arylation of phenols.

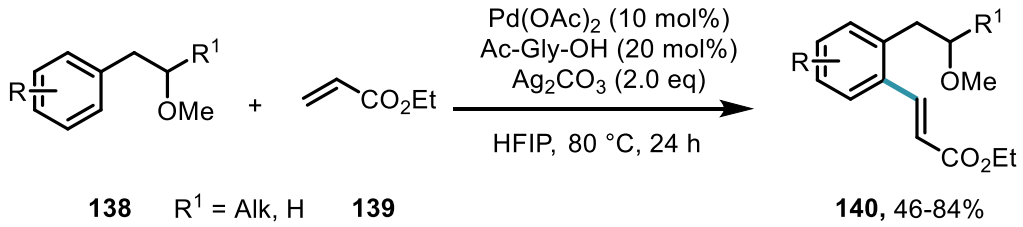
Carbonyl-derived directing groups are amongst the most versatile DGs, and only small differences in the electronic nature of the carbonyl group can dramatically change the selectivity of the reaction. One excellent example of such is Prabhu's report of site selective ketone directed alkenylation of indoles **134**, in which case methyl ketone appointed as DG

furnishes C-2 alkenylated products **136** exclusively, while trifluoromethyl ketone furnishes only C-4 alkenylated indoles **137** (**Scheme 29**). Further studies into the understanding of C-2/C-4 selectivity led to findings that weakly-coordinating directing groups are C-4 selective, and strongly-coordinating directing groups are responsible for C-2 selectivity.[65]



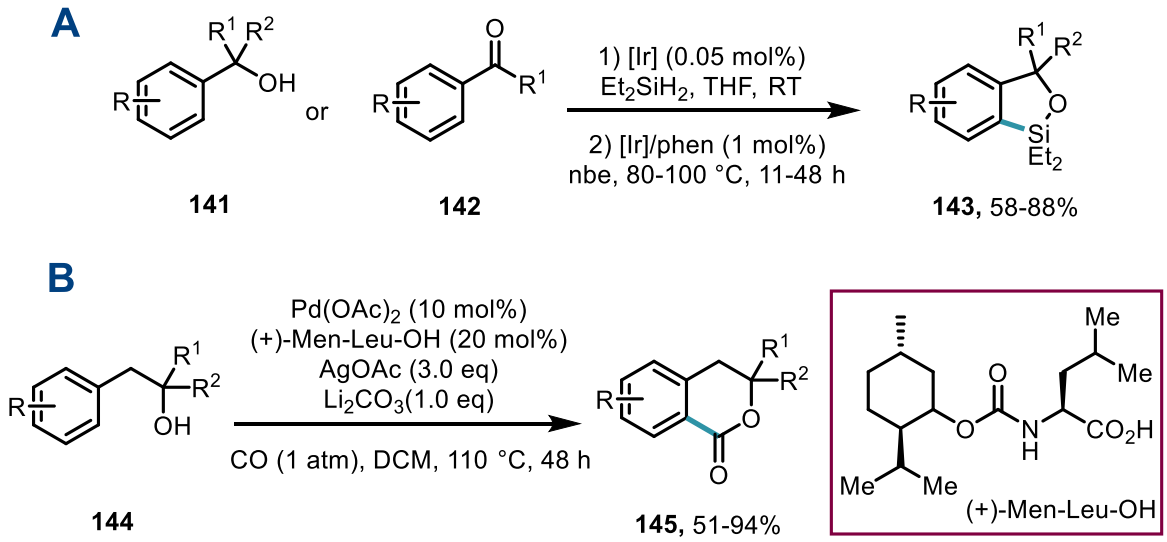
Scheme 29. Ketone as a directing group for Ru- or Rh-catalysed C-2/C-4 selective C–H alkenylation of indole. Conditions: $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%) or $[RhCp^*Cl_2]_2$ (2.5 mol%), $AgSbF_6$ (4 x cat. mol%), $Cu(OAc)_2$ H_2O (1.0 eq), DCE:AcOH (3:1) or DCE, 80 or 100 °C.

The utility of ether as a directing group would be synthetically useful as ethers are one of the most common motifs in both natural products and pharmaceuticals.. The problem with this functional group is its very poor coordination to transition metals, and therefore the first report of ether-directed C–H activation reaction only dates back to 2012, when Álvarez and Muñiz published their study of Pd^{II}-catalysed C–H amidation of a benzylic C–H bond directed by aryl-ether.[66] Inspired by this report, Yu took this concept further and in 2013 reported the first alkyl-ether-directed C–H olefination of aryls **138** with ethyl acrylate **139**, achieving new cinnamate derivatives **140** (**Scheme 30**). In order to overcome the poor coordination of alkyl-ethers, protected amino acid *N*-acetyl-glycine was used as a ligand to accelerate the transformation.[67]



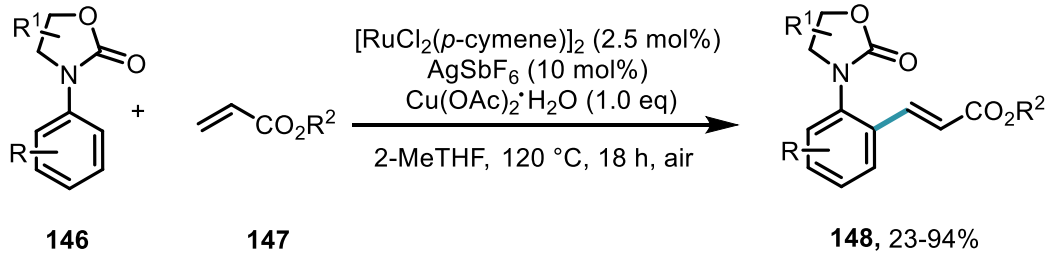
Scheme 30. Pd-catalysed alkyl-ether-directed C(sp^2)–H olefination.

Similarly, aromatic and aliphatic alcohols also form a major class of molecules widely used in the chemical industry, and are present in a large number of natural product scaffolds. One of the first reports utilising hydroxyl group as a directing group dates back to 2010, when Hartwig reported a regioselective Ir^{I}-catalysed formal hydroxyl-directed *ortho*-C–H silylation. In this case, benzyl alcohols **141** undergo *ortho*-silylation and hydroxyl group serves as the directing element for C–H activation *via* dehydrogenative cyclisation of diethyl(hydrido)silyl ethers generated *in situ* (**Scheme 31A**). Silanes are very attractive due to their low costs and low toxicity, while being available for a range of transformations to achieve useful molecules.[68] Yu took this concept and applied hydroxyl group in directing of Pd^{II}-catalysed carbonylation to achieve 1-isochromanones, which are biologically active 6-membered cyclic lactones found in mycotoxins. Reaction of phenyl ethyl alcohols **144** to form desired 6-membered cyclic lactones **145** regioselectively is enabled by mono-*N*-protected amino acid (+)-Men-Leu-OH, as these ligands can accelerate palladium-catalysed C–H olefinations (**Scheme 31B**).[69]



Scheme 31. Hydroxyl group-directed C(sp^2)–H activation reactions.

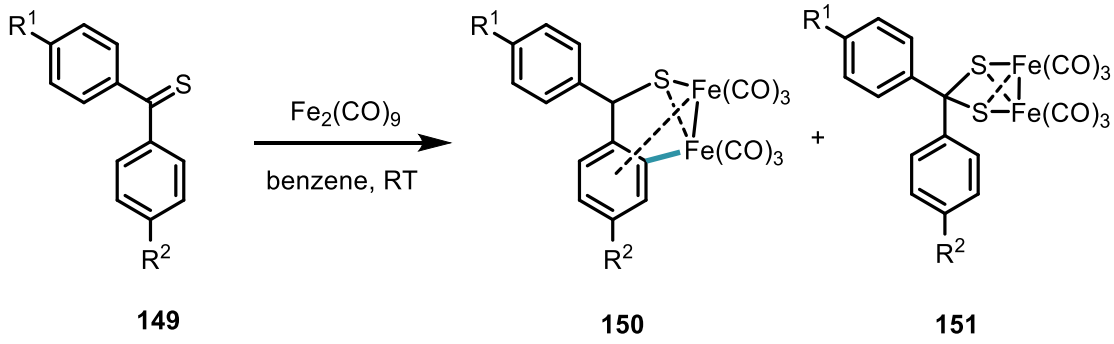
Molecules containing *N*-aryloxazolidinones attracted the synthetic community due to their biological activity and promising pharmaceutical properties. Being attached to the aryl ring makes oxazolidinones an interesting functional group for directing C–H functionalisations. Studies around weakly coordinating carbonyl directing groups grew rapidly, as with such chelating functionality already present in the substrate, regio- and enantioselective transformations become possible. One of the first reports utilising this directing group was Dong's Pd^{II}-catalysed *ortho*-arylation from 2010, when *N*-aryloxazolidinones were used as substrates with simple arenes. In 2016, Williams and Frost took this concept and applied it to olefinations. In this case, *N*-aryloxazolidinones **146** underwent Ru^{II}-catalysed C–H alkenylation with various acrylates **147** (**Scheme 32**).[70,71]



Scheme 32. Ru^{II}-catalysed oxazolidinone-directed $C(sp^2)$–H olefinations.

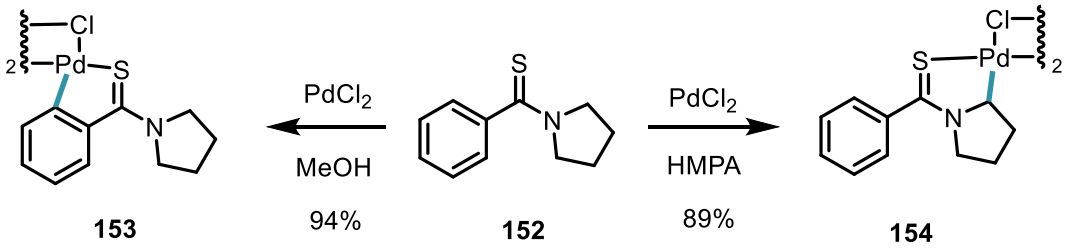
1.4.3 Sulfur-based directing groups

Amongst many directing groups available for C–H activation, sulfur-based functional groups show unique properties and therefore have a wide range of applications in the chemical and pharmaceutical industries. Studies using sulfur-containing directing groups however, have not been wide-spread due to sulfur's natural potential to poison many transition metal catalysts. Nonetheless, the development of sulfur-based DGs dates back to 1973, when Alper published his pioneering report of forming and isolating *ortho*-metalated complexes **150-151** from thiobenzophenones **149** and diiron nonacarbonyl (**Scheme 33**).[72,73] Soon after, Alper reported isolation of *ortho*-metalated ruthenium complexes formed in the similar manner from thiobenzophenones and triruthenium dodecacarbonyl $[Ru_3(CO)_{12}]$.[74]



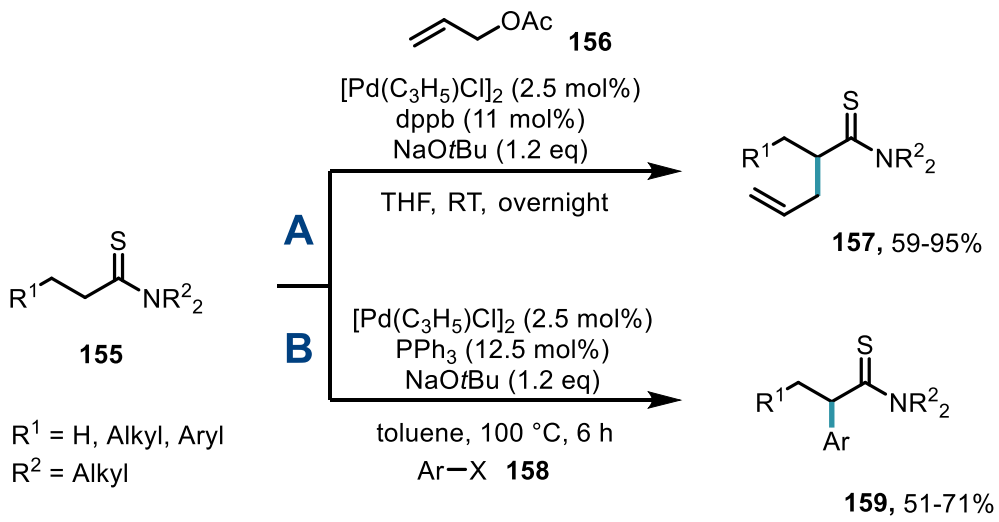
Scheme 33. Alper's first sulfur-directed C–H *ortho*-metalation.

Further advances in *S*-based directing groups were reported by Yoshida in 1981, when thioamides **152** were treated with a stoichiometric amount of $PdCl_2$ to form cyclopalladated complexes. When the reaction was run in methanol, *ortho*-palladated complex **153** was formed in 94% yield, while if HMPA was used, the formation of C(sp^3)–H palladated complex **154** was obtained in 89% (**Scheme 34**).[75]



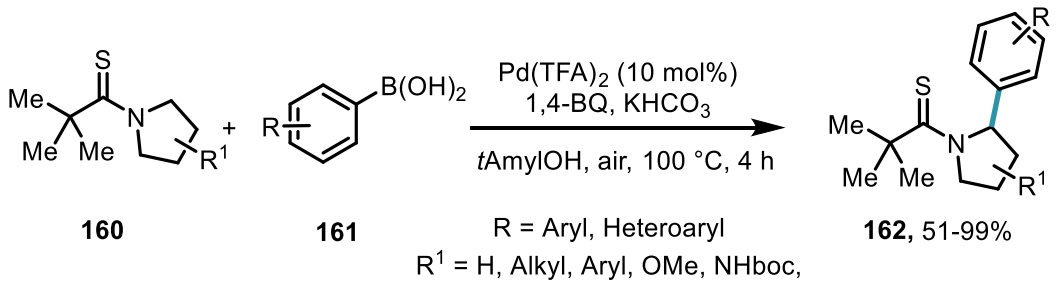
Scheme 34. Yoshida's first thioamide-directed C–H metalation.

One of the first examples of the use of thioamides in a coupling reaction dates to 2013, when Zhao reported his findings in Pd-catalysed C(sp^3)–H functionalisations. He found that aliphatic thioamides **155** can undergo alkylation with allyl acetate **156** to form α-allylated thioamides **157** in high yields and selectivity (**Scheme 35A**).[76] These substrates are also viable for arylations with aryl halides **158** to form broad range of α-arylated thioamides **159** in good yield (**Scheme 35B**).[77]



Scheme 35. Pd-catalysed thioamide-directed *α*-C–H alkylation and arylation.

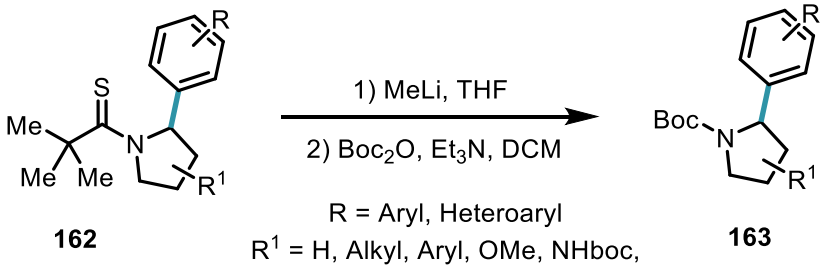
In 2015, Yu and co-workers reported a Pd^{II}-catalysed thioamide-directed α-C(sp^3)–H arylation of various azacycles and *N*-methylamines. This was the first example of a palladium-catalysed direct cross-coupling of methylene C–H bonds with organometallic reagents. In this report, they selectively arylated the α-amine position of pyrrolidines, piperidines, azepanes **160** and the methyl group of *N*-methylamines with arylboronic acids **161**, to form monoarylated thioamides **162** in moderate to excellent yields (**Scheme 36**).



Scheme 36. Pd-catalysed thioamide-directed *α*-C(sp^3)–H arylation.

These products can be easily transformed into *α*-arylated boc-carbamates **163** by deprotection of thioamide **162** with methyllithium and subsequent boc-protection (**Scheme**

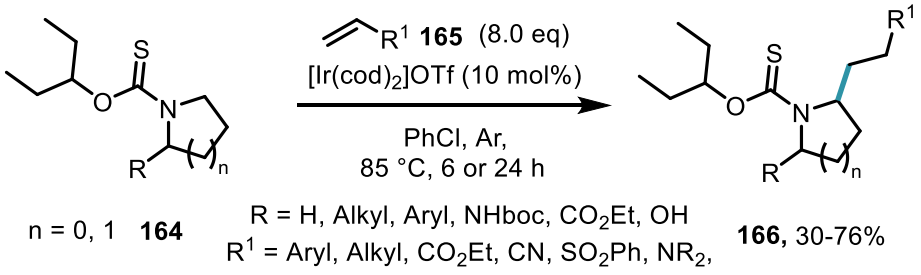
37). Boc-protected carbamates are synthetically relevant scaffolds due to their prevalence in natural products and pharmaceuticals.[78]



162 **163**

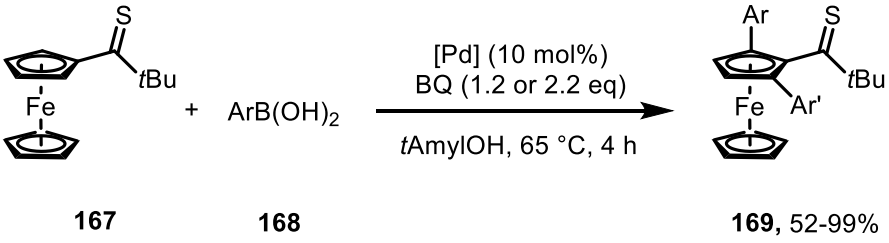
Scheme 37. Thioamide deprotection followed by Boc-protection.

The previously stated method towards *α*-substituted amines *via* thioamide-directed C–H activation was unfortunately limited to arylations, therefore Yu continued his investigation towards a more general method to obtain α-alkylated amines. Inspired by Hodgson's *tert*-butoxy thiocarbonyl directing group for α-lithiation of azetidine,[79] they discovered a new 3-pentoxy thiocarbonyl directing group to be effective for Ir^{I}-catalysed C(sp^3)–H alkylation of substituted pyrrolidines, piperidines and tetrahydroisoquinolines **164** with various alkenes **165** to afford α-alkylated thioamides **166** (**Scheme 38**). They also observed that in case of no substitution on the azacycle, dialkylated products were obtained in great yields. The practical utility of the new DG was demonstrated with easy installation and removal of this auxiliary. To prove the applicability of this method, simple amino acids such as *L*-proline were submitted to the reaction conditions and 2,5-dialkylated amino acid derivatives, which could not be obtained by any other C–H functionalisation, were isolated.[80]



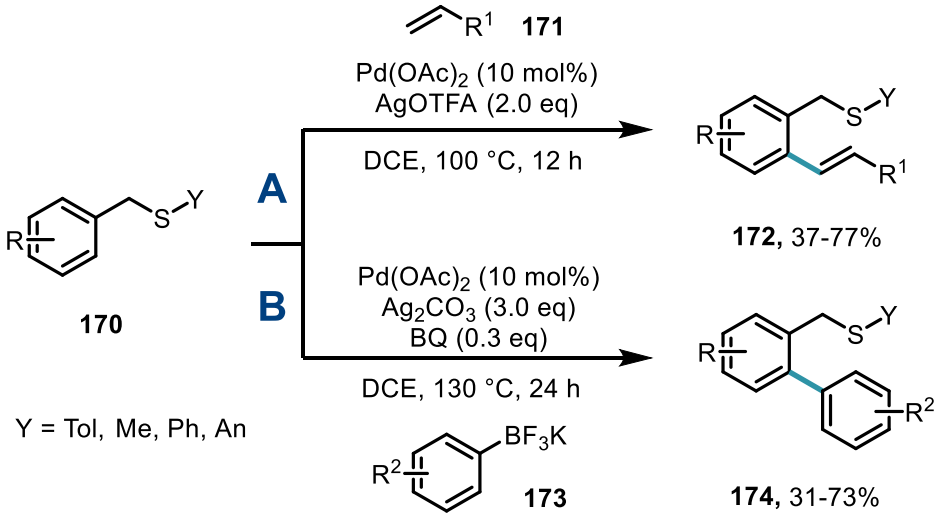
Scheme 38. Ir^{I}-catalysed alkoxythiocarbonyl-directed α-C(sp^3)–H alkylation.

Another *S*-based directing group was developed by You in 2018 for direct C–H arylation of ferrocenes. In this method, chelation of a thioketone allows for the Pd^{II}-catalysed C–H bond activation of ferrocenes **167** and subsequent addition of arylboronic acids **168** (**Scheme 39**). This methodology affords a variety of mono- and diarylated ferrocenes **169** in high yields and selectivity.[81]



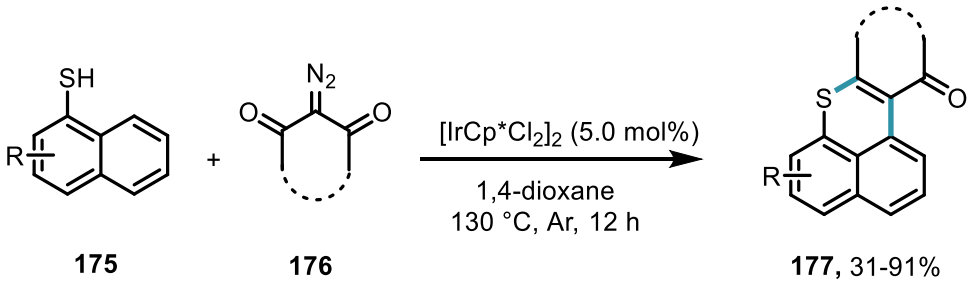
Scheme 39. Pd-catalysed thioketone-directed C–H arylation of ferrocenes.

In early 2012, Zhang introduced the thioether as a new directing element for C–H bond activation. The pioneering work presented Pd-catalysed arene olefination with various thioethers employed as a directing group (**Scheme 40A**),[82] however it was found that benzyl thioethers **170** were the best for this transformation and C–H bond cleavage is the rate-limiting step. Later that year, they employed thioethers as a directing group for Pd-catalysed *ortho*-C–H arylation of arenes **170** using potassium aryltrifluoroborates **173** to form *o*-arylated benzyl thioethers in moderate to good yields (**Scheme 40B**).[83]



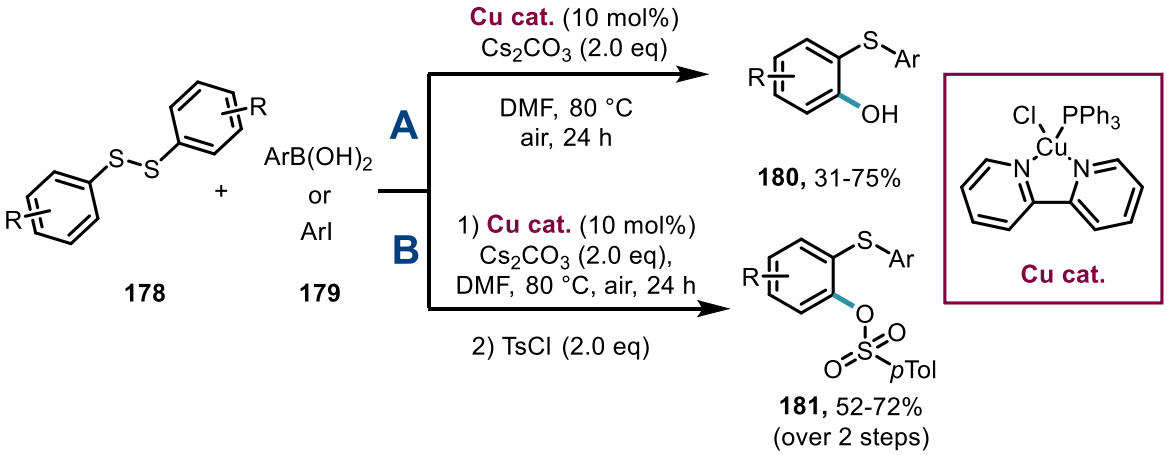
Scheme 40. Pd-catalysed thioether-directed *ortho*-C–H alkenylation and arylation.

Thiols (sulfhydryls) are the simplest sulfur-containing molecules, and are present in many natural products,[84] but their application as directing groups only dates back to 2019 when Wang disclosed his investigations of sulfhydryl as a directing element for C–H activation. They discovered that Ir-catalysed C–H activation of naphthalene-1-thiols **175** with diazo compounds **176**, which led to diazo coupling followed by a tandem annulation to furnish naphtho[1,8-*bc*]thiopyrans **177**, can be directed by a sulfhydryl group (**Scheme 41**). This method forms the desired naphtho[1,8-*bc*]thiopyrans in one step, making the synthesis of these molecules much more simple.[85]



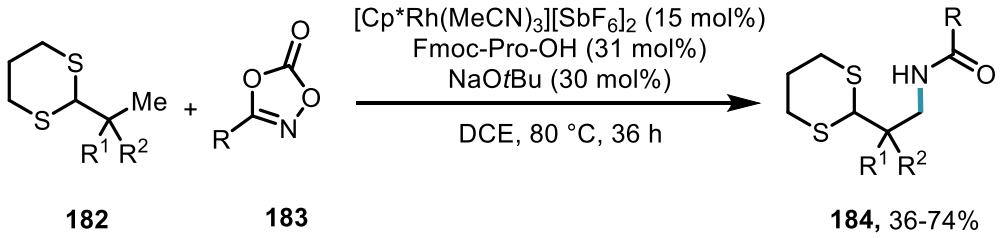
Scheme 41. First Ir-catalysed sulfhydryl-directed C–H/diazo coupling and tandem annulation.

In 2017, Wang and Li developed the first disulfide-directed Cu-catalysed C–H *ortho*-hydroxylation of aryl disulfides **178** with arylboronic acids and aryl iodides **179**, for the formation of sulfonyl diphenyl sulfides **181** and diaryl thiophenols **180**, employing oxygen as the oxidant (**Scheme 42**). The advantage of this protocol is that the method avoids the formation of sulfones and sulfoxides under the aerobic conditions.[86]



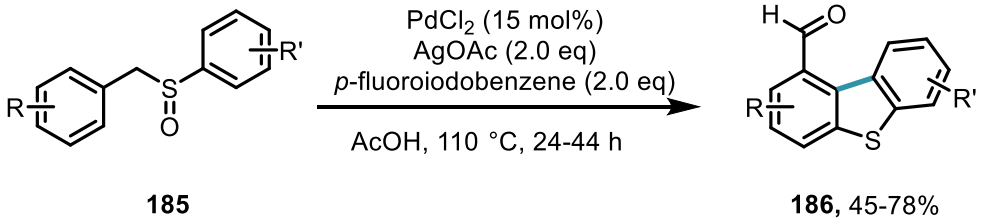
Scheme 42. First Cu-catalysed disulfide-directed C–H hydroxylation.

The dithiane functional group is not only a versatile building block for organic synthesis, it is also a masked carbonyl and umpolung synthon. This functional group was first employed as a directing group for regioselective C(sp^2)–H alkenylation by Satoh and Miura in 2015.[87] In 2019, Dixon reported the first Rh^{III}-catalysed direct C(sp^3)–H amidation of dithianes **182** with a wide range of dioxazolone coupling partners **183** (**Scheme 43**). They were able to achieve a broad scope of amidated dithianes **184** that could be transformed into other synthetically relevant molecules such as desulfurised amides or aldehydes.[88]



Scheme 43. Rh^{III}-catalysed dithiane-directed $C(sp^3)$–H amidation.

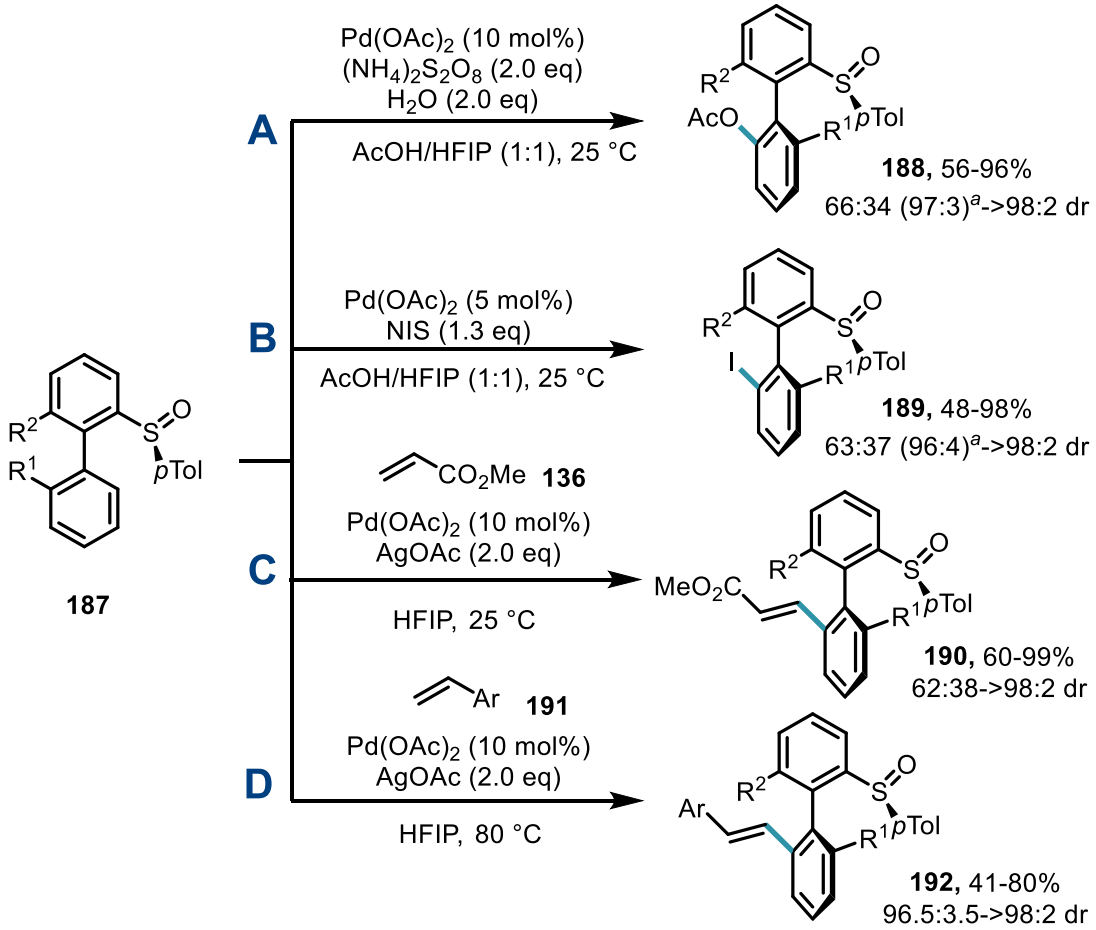
In 2011, Antonchick introduced a new traceless sulfur-containing directing group for C–H activation. Sulfoxides **185** have been employed as assisting group for highly regioselective Pd-catalysed double C–H activation to form dibenzothiophenes **186** (**Scheme 44**). Dibenzothiophenes are highly desirable scaffolds due to their biological activities.[89]



Scheme 44. First Pd-catalysed sulfoxide-directed double C–H functionalisation.

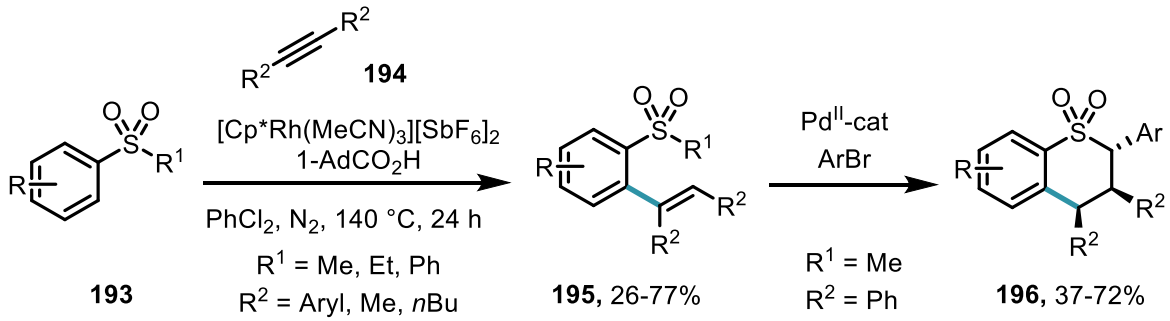
Enantiopure sulfoxides have been used by Wencel-Delord and Colobert as traceless directing groups, as well as chiral auxiliaries, to promote mild asymmetric C–H activation for the synthesis of atropoisomeric biaryls. Chiral biarylsulfoxides **187** underwent Pd-catalysed direct C–H acetoxylation (**Scheme 45A**) and iodination (**Scheme 45B**) through dynamic kinetic resolution to form atropoisomeric biaryls **188-189**. They also developed atroposelective sulfoxide-directed Fujiwara-Moritani reaction[90] of biarylsulfoxides **190** with methyl acrylate **136** and various styrenes **191** to afford chiral biaryls **192** in moderate to excellent yield and excellent atropo-stereoselectivity (up to >98:2 dr) (**Scheme 45C-D**). Interestingly, they discovered that 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) played a pivotal role in enabling higher yields and selectivity in sulfoxide-directed transformations.

Sulfoxide promptly forms a hydrogen-bonded complex with HFIP, which is believed to change the coordinating and steric properties of this directing group. [91,92]



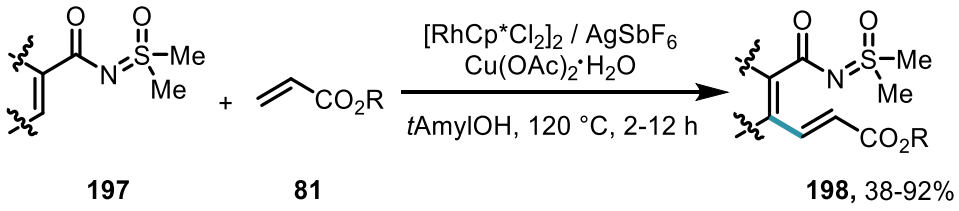
Scheme 45. Pd-catalysed asymmetric sulfoxide-directed C–H functionalisations. a) dr after recrystallisation.

The fully oxidised sulfonyl functional group has been utilised as a modifiable directing group for rhodium promoted *ortho*-C(sp^2)–H alkenylation of aryl sulfones **193** with symmetrical alkynes **194** to form alkyl aryl sulfones **195**, which can be further functionalised into the corresponding 2-arylthiochromane 1,1-dioxide derivatives **196**, occasionally seen in bioactive substances (**Scheme 46**).[93]



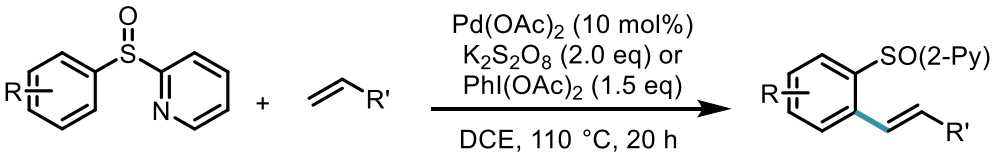
Scheme 46. Rh-catalysed sulfonyl-directed *ortho*-C–H alkenylation and further functionalisation.

Sulfoximines, have also been employed as directing groups for Rh-catalysed C(sp^2)–H alkenylations by Bolm. In 2014, selective *ortho*-C(sp^2)–H olefinations of *N*-acylsulfoximines and *N*-aroylsulfoximines **197** with acrylates **81** were disclosed, allowing the synthesis of sulfoximidoyl derivatives **198**, relevant for the pharmaceutical industry (**Scheme 47**).[94]



Scheme 47. Rh^{III}-catalysed sulfoximine-directed C(sp^2)–H olefination.

The pyridine sulfinyl group was first introduced as a directing group in 2011. This functionality was used to direct Pd-catalysed C(sp^2)–H *o*-olefinations of 2-pyridyl sulfoxides **199** in order to achieve *ortho*-substituted sulfoxides **201** in moderate to excellent yields (**Scheme 48**). This versatile directing group can be easily removed or transformed into the thiol.[95]



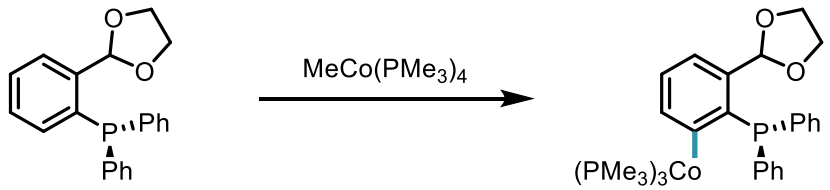
199 **200** **201,** 40-89%

R' = CO_2Bu,CO_2Me, Aryl, SO_2Ph, $P(O)(OMe)_2$

Scheme 48. Pd-catalysed pyridine sulfinyl-directed C(sp^2)–H olefination.

1.4.4 Other directing groups

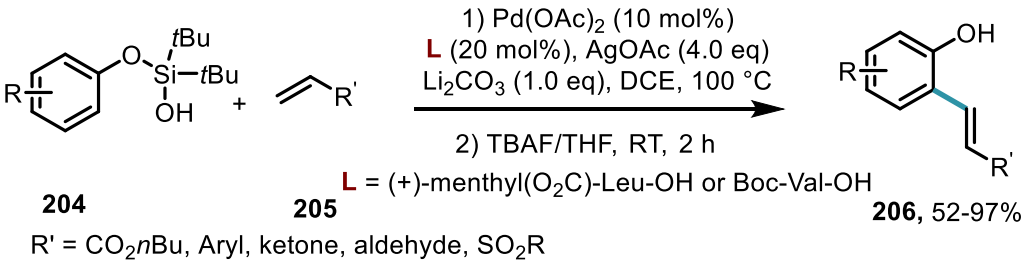
As well as the major heteroatoms used in directing groups (nitrogen, oxygen or sulfur), there are also examples using different directing elements, such as phosphine **202** directed *ortho*-metalation with $MeCo(PMe_3)_4$ to form Co-containing product **203** (**Scheme 49**).[96]



202 **203**

Scheme 49. Phosphine-directed *ortho*-cobaltation.

Another class of directing groups is based on silicon. Gevorgyan in 2011 developed Pd^{II}-catalysed silanol-directed C–H *ortho*-alkenylation of phenols. The phenol substrates are transformed into silanols **204**, which then undergo olefination with various different alkenes **205** and afford a wide range of *o*-alkenylated phenols **206** in moderate to excellent yields (**Scheme 50**). The silanol group can then be easily removed, which adds to the applicability of this method.[97]



Scheme 50. Pd-catalysed silanol-directed C–H *ortho*-alkenylation.

1.5 Cobalt catalysis in C–H functionalisation

Advances in recent years have established C–H functionalisation as a powerful tool for selective C–C and C–X bond formation, as these transformations represent simplified access to many natural products, pharmaceuticals, agrochemicals and feedstock chemicals.[98] Historically, most studies employ rather expensive second- and third-row transition metals for C–H catalysis, however in recent years, the development of first-row transition-metal catalysis improved significantly. These earth-abundant 3d transition metal complexes became an attractive alternative due to their lower cost compared with the traditionally used noble transition metals. Cobalt in particular received significant attention because of its great potential for homogeneous catalysis. Cobalt belongs to the group 9 transition metals and is the first and the lightest of this group, which also consists of rhodium, iridium and meitnerium. It is the thirtieth most earth-abundant element with 25 g/ton average concentration in the Earth's crust. Compared with its 4d (Rh) and 5d (Ir) homologues, which both have a concentration of 0.0001 g/ton in the Earth's crust.[96] Given the versatility of precious 4d and 5d transition metals, many studies have recently been undertaken towards the application of 3d cobalt for C–H activation. However, the electronic properties of cobalt with $3d^9$ electron configuration, such as its electronegativity and spin-orbit coupling, largely differ from those of its 4d and 5d homologues, which creates challenges in cobalt catalysis

(**Figure 6**). A result of cobalt's lower electronegativity is the formation of more nucleophilic intermediates, which allow better selectivity and new reaction pathways in C–H functionalisation.[99,100]

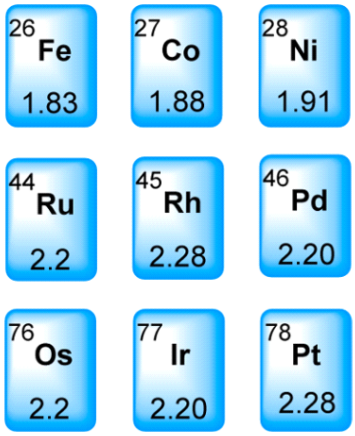


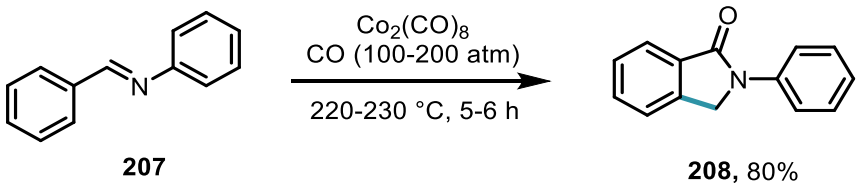
Figure 6. Group 8, 9, and 10 electronegativities according to Pauling scale.

The most common oxidation states of cobalt are -1, 0, +1, +2, and +3, however the majority of cobalt complexes used in catalysis have formal +1/+3 oxidation states. Generally speaking, most contemporary processes include a catalyst generation step, in which Co^{II} salts are added together with ligand and reductant, or any other additives, to generate a +1 oxidation state active species, which is ready to start the catalytic cycle. That being said, a vast number of Co^{III} complexes with cyclopentadienyl ligands are well established in C–H functionalisation.[100]

1.5.1 Low-valent Co-catalysed C–H functionalisations

One of the early examples of directed C–H functionalisation dates back to 1955, when Murahashi reported a cobalt-catalysed reaction of Schiff base **207** in benzene at high pressure and temperature to form phthalimidine **208** in 80% yield (**Scheme 51**).[96,101] It was later discovered that azobenzene can undergo similar carbonylative cyclisation to furnish

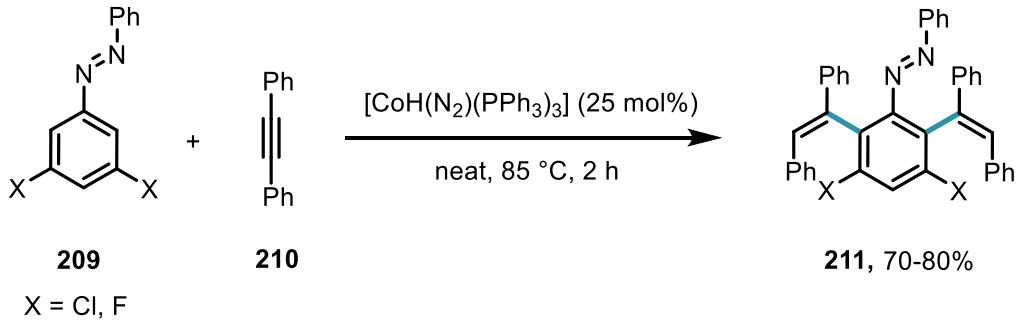
indazolones, and although these early examples showed the potential of cobalt catalysis, rather harsh reaction conditions widely limited further applications. Murahashi utilised in this transformation the 18-electron catalyst dicobalt octacarbonyl $Co_2(CO)_8$, which is the most important Co^0 molecule for synthesis and catalysis.[100]



207 **208,** 80%

Scheme 51. One of the first examples of Co-catalysed directed C–H functionalisation.

The development of modern C–H functionalisation began when, in 1994 Kisch, reported the first example of Co^I-catalysed C–H hydroarylation of alkynes **210** (**Scheme 52**), using Co^I complex with a labile N_2 ligand, which facilitated the generation of catalytically active species by substitution of labile N_2 with Lewis-basic azobenzene substrate **209**.[102]



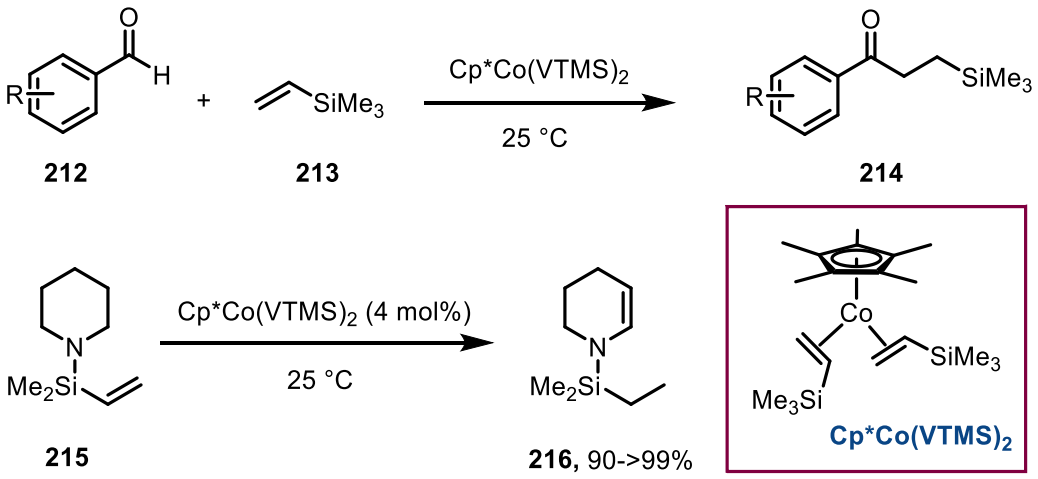
209 **210** **211,** 70-80%

X = Cl, F

Scheme 52. First Co-catalysed C(sp^2)–H hydroarylation.

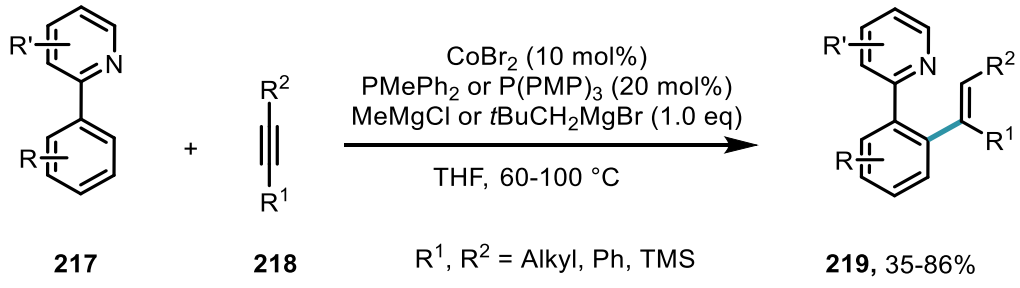
In 1997, Brookhart introduced a new low-valent Co^I complex with very labile vinyltrimethyl silane (VTMS) ligands Cp*Co(VTMS)$_2$, which successfully activated the C(sp^2)–H bond of aldehyde **212** and allowed hydroacylation of vinyltrimethyl silane **213** (**Scheme 53**). In 2007, application of the Cp*Co^I catalyst was extended to the synthesis of enamine **216** *via* C(sp^3)–H activation of the methylene C–H bond. To date, it has been indicated by both

computational and experimental studies that C(sp^3)–H bonds are not able to add to the 16-electron Co^I centre. [103,104]



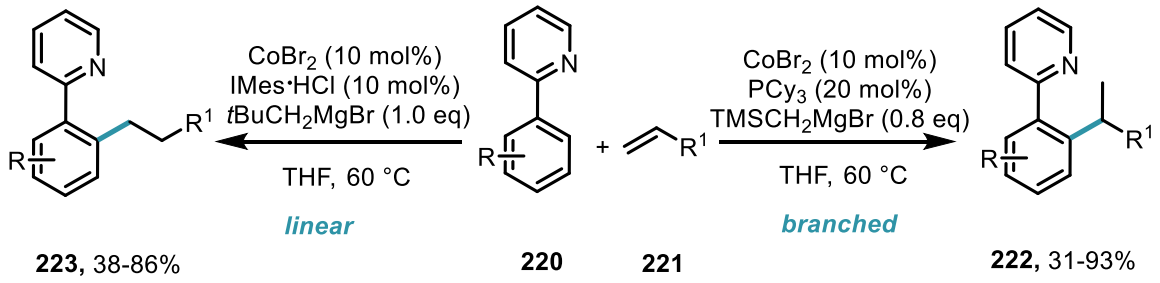
Scheme 53. Cp*Co^I-catalysed C–H hydroacylation.

In 2010, a ground-breaking report by Yoshikai introduced an *in situ* generated electron-rich low-valent active cobalt species from $CoBr_2$ with phosphine ligands and Grignard reagents for the C–H alkenylation of arenes **217**, assisted by pyridine or other *N*-based directing groups (**Scheme 54**). The low-valent active species of the catalyst is formed by organometallic reduction of Co^{II} salt with Grignard reagent, and subsequent pyridine-directed oxidative addition of the catalyst active species to the C–H bond generates a cobaltacycle ready for further functionalisation.[105]



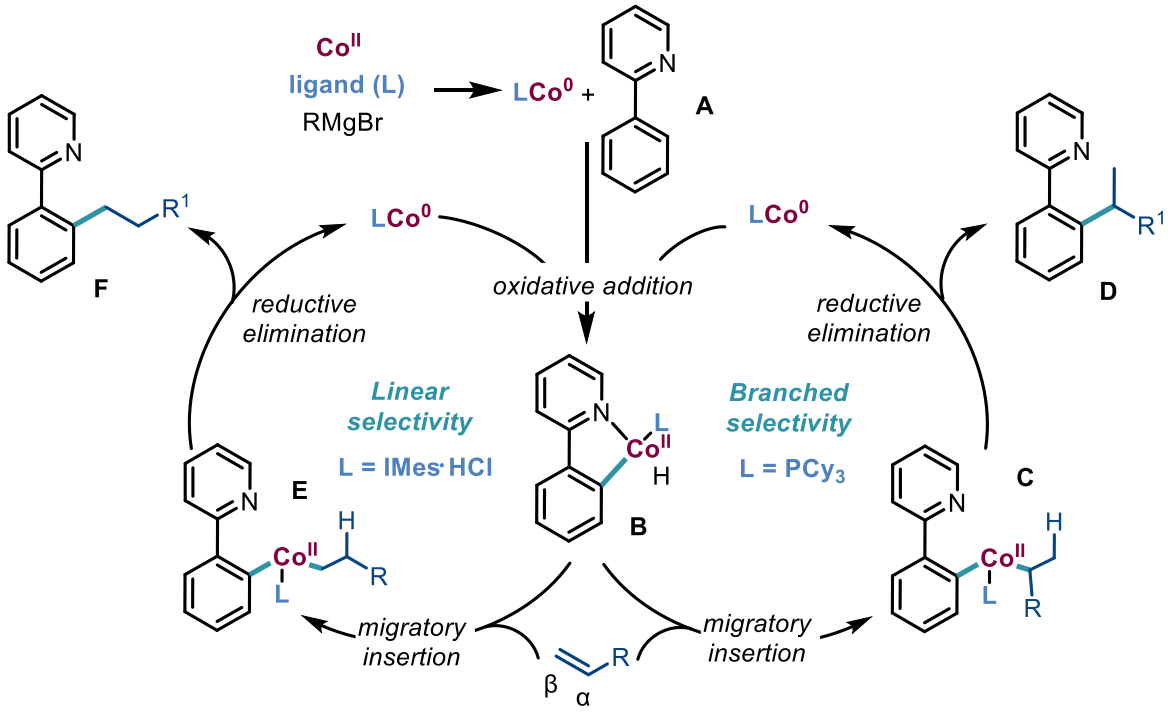
Scheme 54. *In situ* generated Co^I-catalysed C(sp^2)–H hydroarylation.

Since an initial report, multiple studies have been reported by Yoshikai, applying this catalytic system to C–H alkenylations and alkylations of various substrates with different ligands. In one of the reports, the authors demonstrated how the nature of the ligand can affect the regioselectivity in the hydroarylation of arenes **220** with styrenes **221**. For example, when using a phosphine ligand, such as tricyclohexylphosphine (PCy_3), branched alkylated products **222** were obtained, while employing an *N*-heterocyclic carbene as the ligand, such as 1,3-dimesitylimidazol-2-ylidene (IMes), linearly-alkylated products **223** were formed (**Scheme 55**).[106,107]



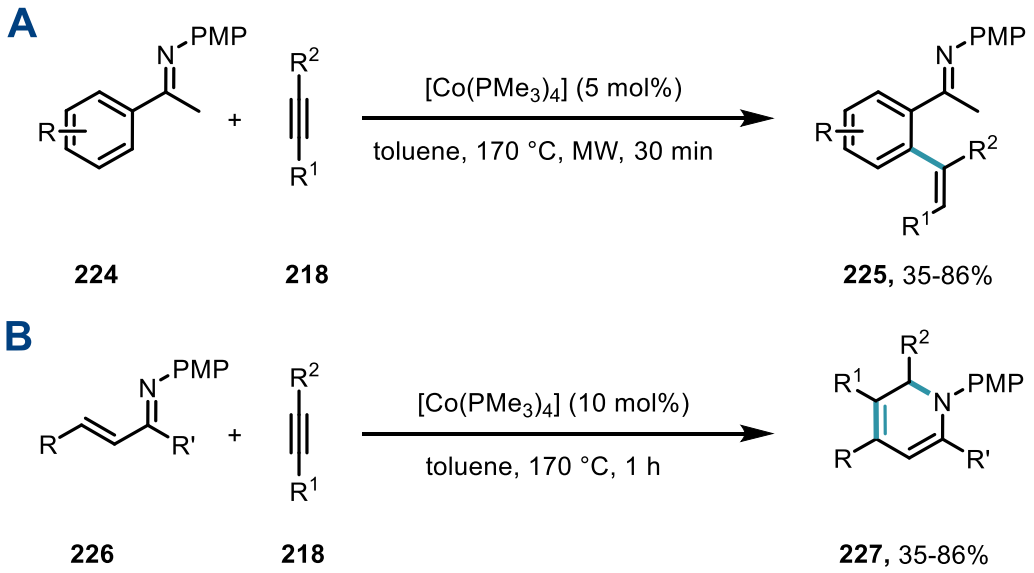
Scheme 55. Regioselectivity difference when employing PCy_3 and IMes·HCl ligands in Co-catalysed C(sp^2)–H hydroarylation.

The mechanism proposed for this transformation commences with the oxidative addition of the active Co^0 species into the C–H bond, forming aryl-Co^{II}-hydride intermediate **B**. Subsequent migratory insertion then proceeds differently, depending on the nature of the ligand. With the phosphine ligand PCy_3, migratory insertion proceeds in an *α,β*-fashion forming **C**, followed by the creation of branched product **D** after reductive elimination (**Scheme 56**). With carbene ligand IMes·HCl, the migratory insertion proceeds in a *β,α*-fashion generating **E** and subsequently affording linear product **F**.[107,108] In 2012, Ackermann disclosed C–H arylations and benzylations with sulfamates, carbamates and phosphates utilised through C–O bond cleavage, and in 2015 this strategy was expanded to include C–H alkenylations with alkyl acetates, carbonates, carbamates and phosphates.[49,109]



Scheme 56. Mechanism of regioselective Co-catalysed C(sp^2)–H hydroarylation.

While most of these C–H activation reactions proceed *via in situ* generated Co^I species, in 2015 Petit introduced the Co^0 complex [$Co(PMe_3)_4$] in the C–H alkenylation of aryl imines **224**, as well as in the C–H annulation of dienes **226** for the construction of dihydropyridine derivatives **227** (**Scheme 57**).[110,111]

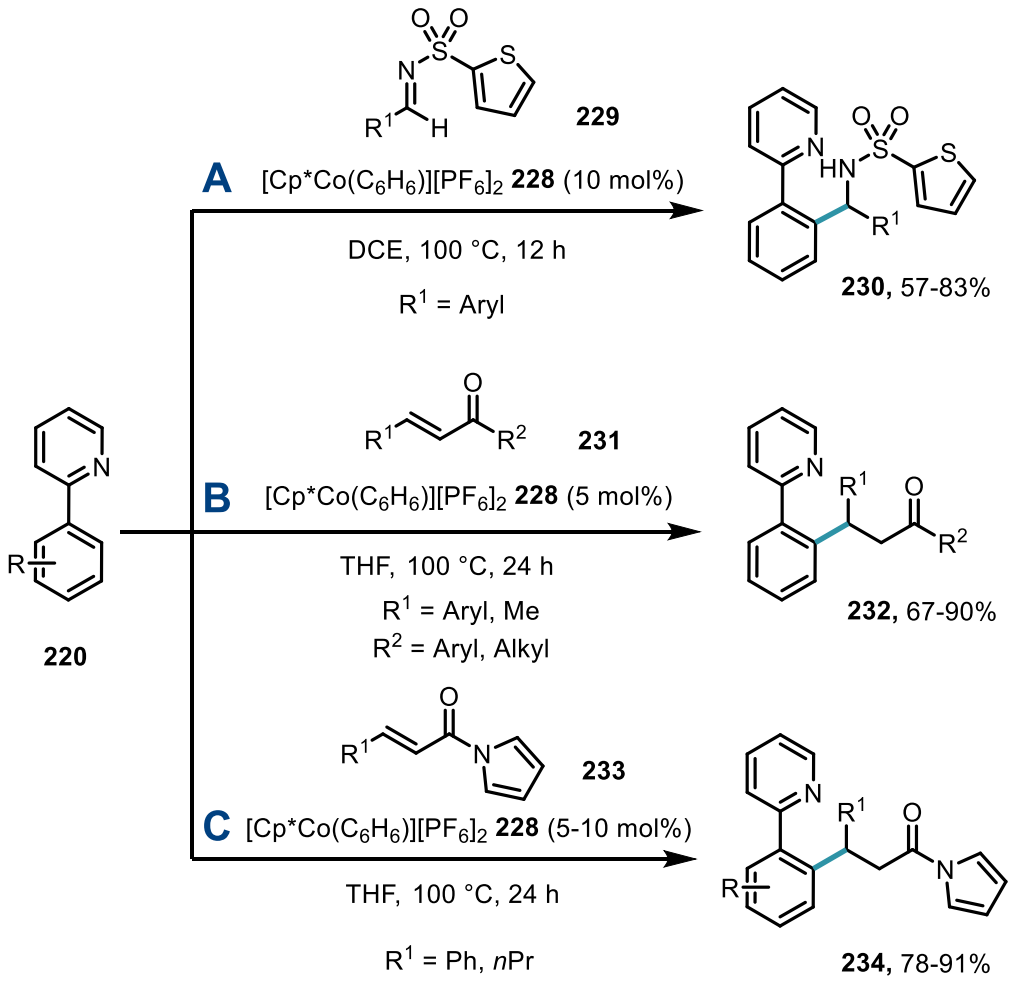


Scheme 57. Co^0-catalysed $C(sp^2)$–H alkenylation and annulation.

1.5.2 High-valent Co^{III}-catalysed C–H functionalisations

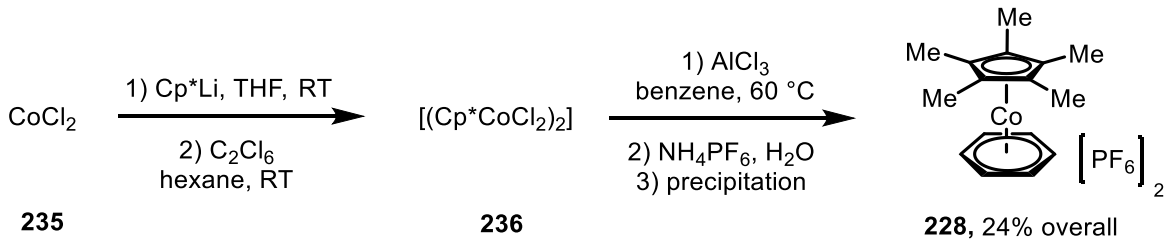
1.5.2.1 Cp^*Co^{III}-catalysed $C(sp^2)$–H activation reactions

The discovery of high-valent cobalt catalysts dates back only to 2013, when Matsunaga and Kanai disclosed their discovery of cationic Cp^*Co^{III} complexes that generate nucleophilic organometallic species. The first Cp^*Co^{III}-catalysed C–H functionalisation was addition of 2-phenylpyridines **220** to imines **229**, enones **231** and *N*-acyl pyrroles **233**, which led to the formation of *ortho*-alkylated 2-phenylpyridines **230, 232** and **234** respectively (**Scheme 58**).[112,113]



Scheme 58. First examples of Cp^*Co^{III}-catalysed $C(sp^2)$–H functionalisations.

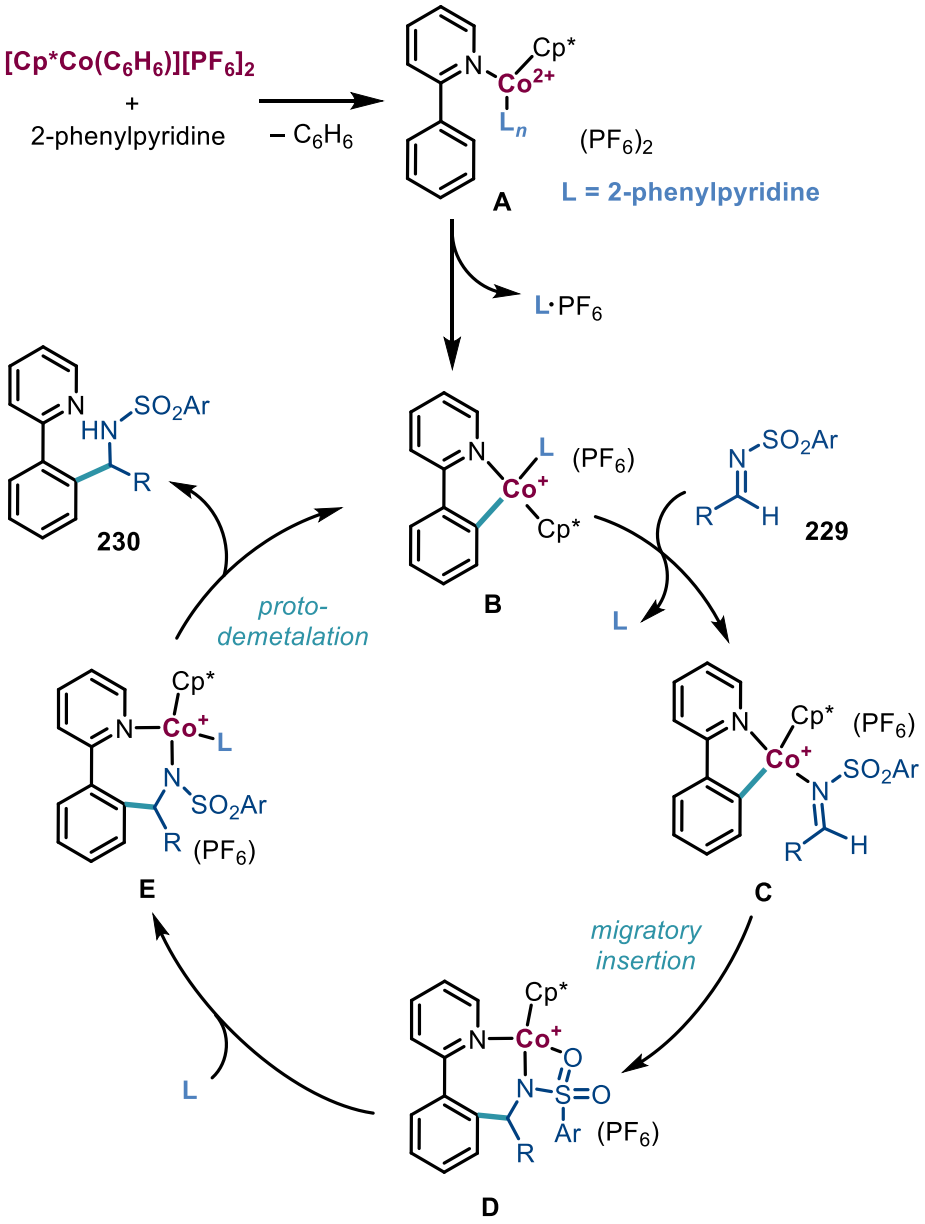
The C–H activation was successfully facilitated by $[Cp^*Co(C_6H_6)][PF_6]_2$ complex **228**, which was prepared from readily-available $CoCl_2$ salt **235** by addition of Cp*Li, followed by oxidation and counterion exchange through $AlCl_3$-promoted abstraction of chloride. The air-stable complex **228** was furnished in overall 24% yield (**Scheme 59**). Authors in this report disclosed another four more sterically hindered Cp^*Co^{III} complexes, but their activity was not sufficient for this C–H functionalisation. One of the major achievements of this report was demonstration of these Cp^*Co^{III} complexes as successful and cheaper alternatives to expensive Cp^*Rh^{III} catalysts.



235 **236** **228,** 24% overall

Scheme 59. Gram-scale synthesis of $[Cp^*Co(C_6H_6)][PF_6]_2$ **228**.

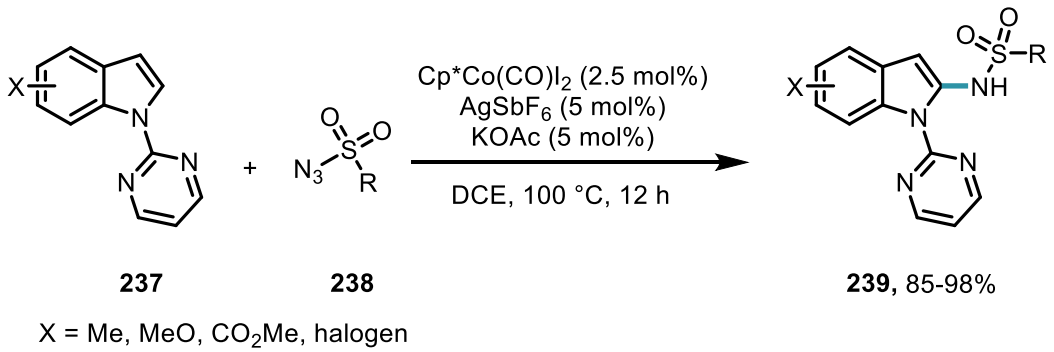
A plausible reaction mechanism was proposed based on the known mechanism of Cp^*Rh^{III}-catalysed C–H functionalisation.[114,115] Initiated by thermal dissociation of the benzene ligand from the Cp^*Co^{III} complex and addition of 2-phenylpyridine, the intermediate **A** is formed. Subsequent C–H activation to furnish cyclometalated complex **B** is proposed to proceed *via* electrophilic aromatic substitution or *via* a base-assisted concerted metalation-deprotonation (CMD) mechanism. Subsequent ligand exchange for the coupling partner **229** achieves intermediate **C**, which forms **D** after migratory insertion. Next, addition of a second 2-phenylphospine into the intermediate **D** achieves formation of **E**, proto-demetalation of which yields the *ortho*-substituted product **230** and regenerates the active cobalt species **B** for another catalytic cycle (**Scheme 60**).[113]



Scheme 60. Proposed mechanism of Cp*Co^{III}-catalysed C(sp^2)–H functionalisation.

One of the biggest contributions to the field of Cp*Co^{III} catalysed C–H activation was the introduction of the Cp*Co(CO)I$_2$ complex by Matsunaga and Kanai in 2014. This readily available air-stable cobalt diiodide complex was employed as a precatalyst for the directed C–H amidation of indoles **237** with sulfonyl azides **238** to afford C-2-amidated indoles **239** in excellent 85-98% yield (**Scheme 61**). The combination of Cp*Co(CO)I$_2$ with AgSbF$_6$ and

KOAc led to *in situ* generation of the active Cp*Co^{III} catalyst, which was able to effectively catalyse this transformation.[116]

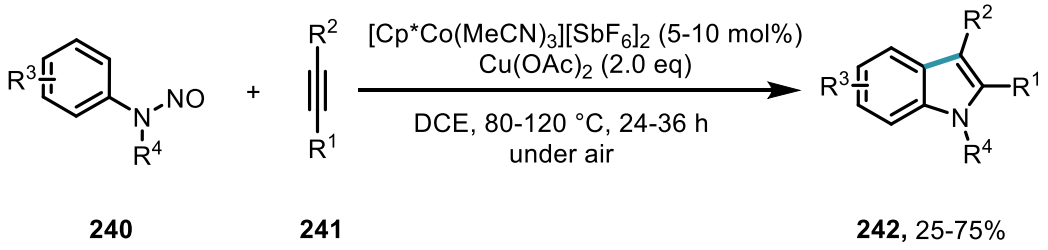


237 **238** **239,** 85-98%

X = Me, MeO, CO_2Me, halogen

Scheme 61. Cp*Co^{III}-catalysed C(sp^2)–H amidation.

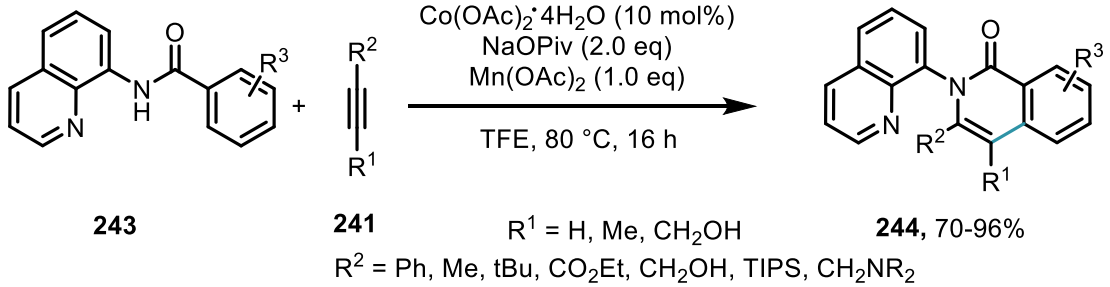
Since its introduction, this complex was used as a precursor to the active cationic Cp*Co^{III} catalyst for many transformations such as cyanations, halogenations, trifluoromethylthiolations, alkylations, alkenylations, allylations, and amidations with various different amidating agents.[117–120] High-valent Cp*Co^{III} complexes became heavily studied not only because of their lower cost compared to the Cp*Rh^{III} catalysts, but also because of their unique reactivity and selectivity. In 2016, Jiao reported regioselective C–H cyclisation of *N*-nitrosoanilines **240** with alkynes **241** for the formation of various *N*-substituted indoles **242** (**Scheme 62**). High regioselectivity was obtained when unsymmetrical *meta*-substituted *N*-nitrosoanilines were used. Furthermore, this Cp*Co^{III} catalyst proved efficient even for internal alkynes with electron-deficient functional groups, which were almost completely unreactive with Cp*Rh^{III} catalysts.[121]



Scheme 62. Cp*Co^{III}-catalysed regioselective direct C(sp^2)–H cyclisation.

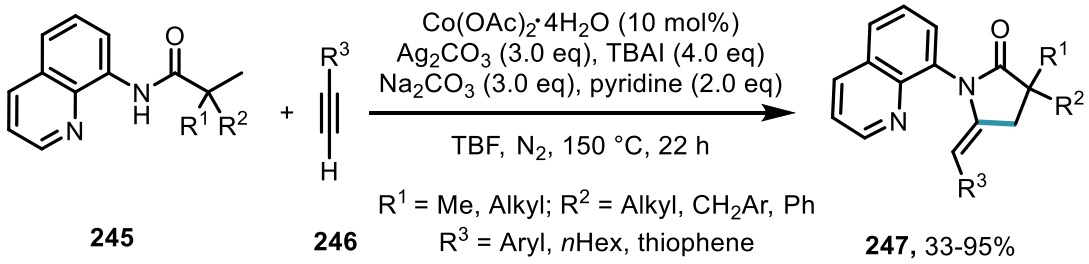
1.5.2.2 Oxidative Co^{III}-catalysed C–H activation reactions

Another approach towards high-valent cobalt catalysis was pioneered by Daugulis in 2014. The study presented Co^{III}-catalysed aminoquinoline- and picolinamide-directed C–H alkenylation of arylamides **243** with various internal and terminal alkynes **241**, which furnished 6-membered cyclic products **244** in good to excellent yields, with very high functional-group tolerance (**Scheme 63**). In this report, the high-valent Co^{III} catalyst was formed by oxidation of the Co^{II} precatalyst by an external oxidant. The active Co^{III} species then undergoes nonoxidative C–H activation *via* a CMD mechanism.[108,122]



Scheme 63. Co^{III}-catalysed aminoquinoline-directed C(sp^2)–H alkenylation.

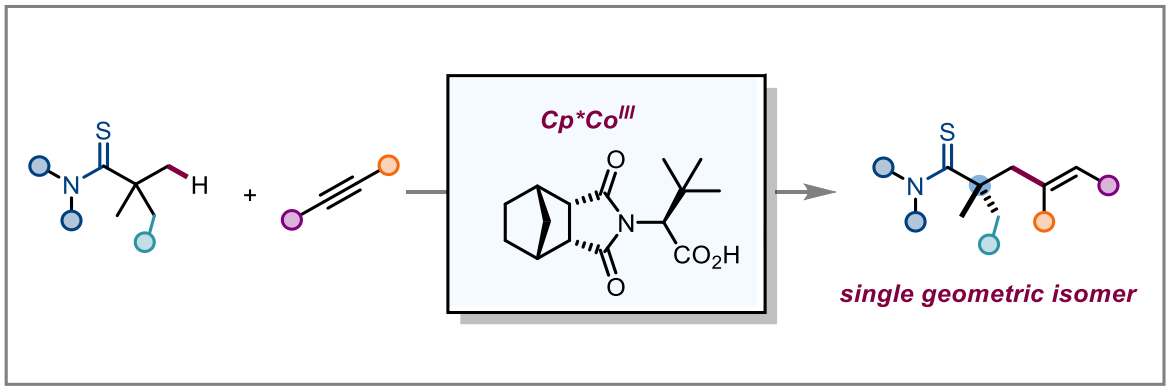
This work served as an inspiration for further research with 8-aminoquinoline as a directing group.[108] Zhang, for example applied this approach to the C(sp^3)–H alkenylation with terminal alkynes **246** to form 5-membered cyclic products **247** (**Scheme 64**).[123]



Scheme 64. Co^{III}-catalysed aminoquinoline-direct C(sp^3)–H alkenylation.

Chapter 2: Discovery and Development of the Cobalt-Catalysed Enantio- and Regioselective C(sp^3)–H Alkenylation of Thioamides

2.1 Chapter overview



Scheme 65. Thioamide directed cobalt-catalysed enantioselective C(sp^3)–H alkenylation.

A novel enantioselective cobalt-catalysed C(sp^3)–H alkenylation of thioamides with but-2-ynoates, using thioamide as a directing group is presented in this chapter. In this method prochiral thioamides are added with alkyl but-2-ynoates, which in presence of [Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ catalyst and chiral ligand allows enantioselective C(sp^3)–H alkenylation. The method is operationally simple and utilises mild reaction conditions, while providing a wide range of alkenylated products as single regioisomers in excellent yields (up to 85%) and high enantiomeric ratio (up to 91:9 er, or up to >99:1 er after single recrystallisation). Enantioselectivity is provided by assistance of chiral carboxylic acid (CCA) together with achiral Cp*Co^{III} catalyst. Diverse downstream derivatisations of the alkenylated enantiopure products are demonstrated, delivering a broad range of enantiopure scaffolds. Mechanistic investigations and DFT calculations revealed that the pivotal C–H

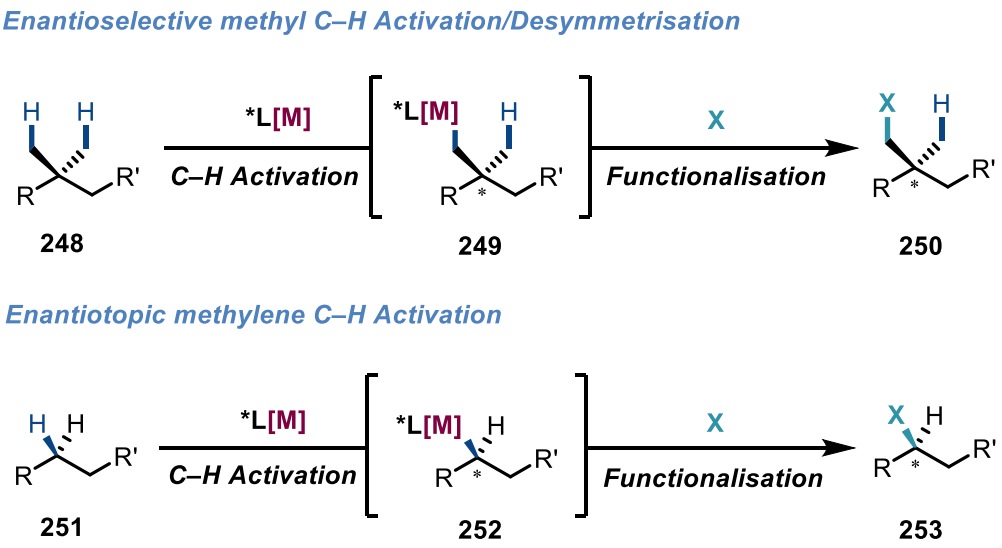
activation step is irreversible and enantiodetermining. DFT calculations support the reaction mechanism, the stereochemical configuration of products, as well as the unusual regioselectivity of the alkenylation reaction.

2.2 Introduction

2.2.1 Enantioselective C(sp^3)–H functionalisation

Selective functionalisation of ubiquitous C(sp^3)–H bonds have been a long-term focus of the synthetic community, because it could in theory allow any structural transformations, and therefore give access to a broad scope of molecules, that are otherwise prepared by long indirect multi-step syntheses. Development of methods that see inert C–H bonds as masked targets for various functionalisations would enable more step and atom-economical pathways, unveil new disconnections or shorten synthetic routes towards complex molecules. Especially, in drug design and drug discovery, these new approaches would enable late stage functionalisation of complicated substrates or give access to previously inaccessible C–H bonds. The major issue of general application of C–H functionalisations is selectivity. Although, in the last decade, there has been great progress in the regioselective C–H bond transformations, utilising various directing groups, stereoselective C–H activation still stays largely unexplored. Enantioselective C–H activation methodologies are of great importance, because chiral molecules are often main targets in the pharmaceutical or agrochemical industry. Development of these methodologies would allow not only for the formation of new stereocentres, but also for the precise modification of specifically targeted carbon centres. To this date, several different methodologies towards enantioselective C–H functionalisation have been developed, however our main focus relies within transition-metal induced processes, which are defined by a C–H bond cleavage prior to the formation of the carbon-metal bond.[124] There are two main methods employing this approach towards stereoselective C–H functionalisations. First approach is desymmetrisation of prochiral functionality such as isopropyl-substituted substrate **248**, in

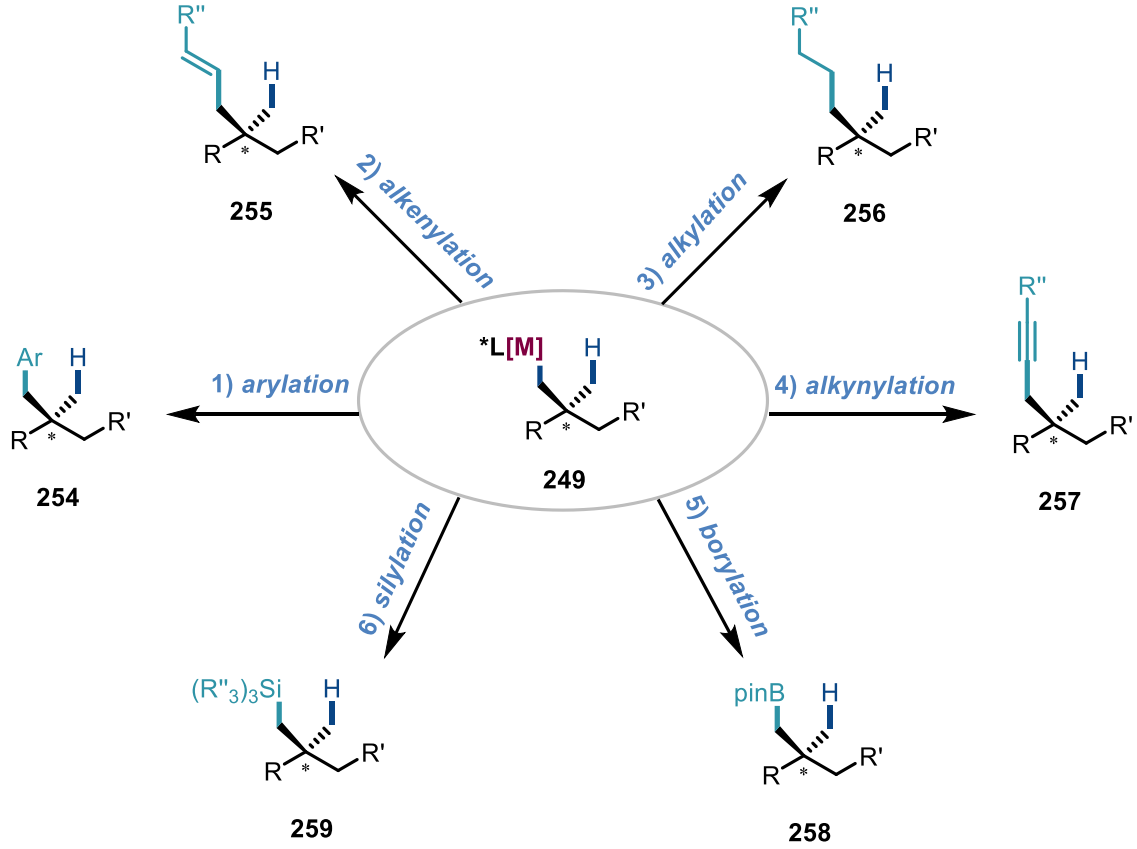
which case the transition metal is not bound directly to the chiral carbon stereocentre **249**. Second widely spread approach is C–H bond activation of enantiotopic methylene group **251** with the transition metal complex directly bound to the chiral carbon stereocentre **252** (**Scheme 66**). The development of transition-metal catalysed C(sp^3)–H functionalisations has been largely focused on selected noble transition metals, such as palladium, rhodium or iridium, however there are other preliminary examples utilising earth-abundant metals, for instance cobalt, nickel and iron. [125]



Scheme 66. Two main methods for enantioselective transition metal-catalysed C(sp^3)–H activation.

Focusing on enantioselective C(sp^3)–H activation/desymmetrisation method, diverse transformations have been enabled by transition metal complexes, such as arylations, alkenylations, alkylations, alkynylations, borylations and silylations (**Scheme 67**). In the early examples of enantioselective C–H activation, stereocontrol was established by the use of mono-*N*-protected amino acid (MPAA) ligands along with pyridine-containing substrates. Studies using MPAA ligands commenced due to their easy availability from

naturally occurring amino acids, their coordinatig ability to Pd^{II} and capability to act as chiral carboxylate surrogates and bidentate ancillary ligands.[126]

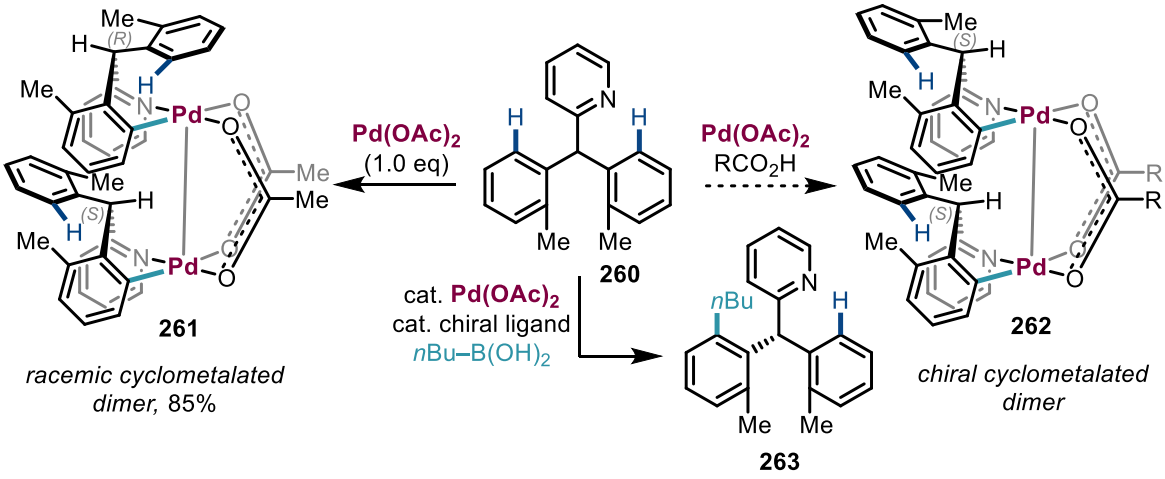


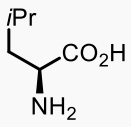
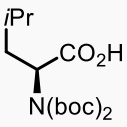
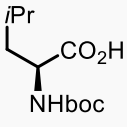
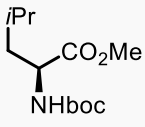
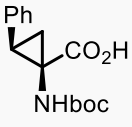
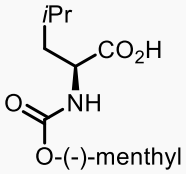
Scheme 67. Enantioselective transition metal-catalysed C(sp^3)–H activation/desymmetrisation enabled transformations.

Initial investigations with stoichiometric $Pd(OAc)_2$ allowed the formation of racemic cyclometalated dimer **261** in 85% yield (Table 1). Based on the structure of the racemic dimer with coordinated acetate ligands, the authors anticipated that the exchange of acetates for amino acids would lead to the formation of a chiral cyclometalated dimer. With unprotected *L*-leucine as chiral ligand no reaction was detected (Table 1, Entry 1), while with double *N*-boc-protected *L*-leucine the reaction occurred with almost no stereoselectivity (74% yield, 7% ee) (Table 1, Entry 2). When mono *N*-boc-protected *L*-

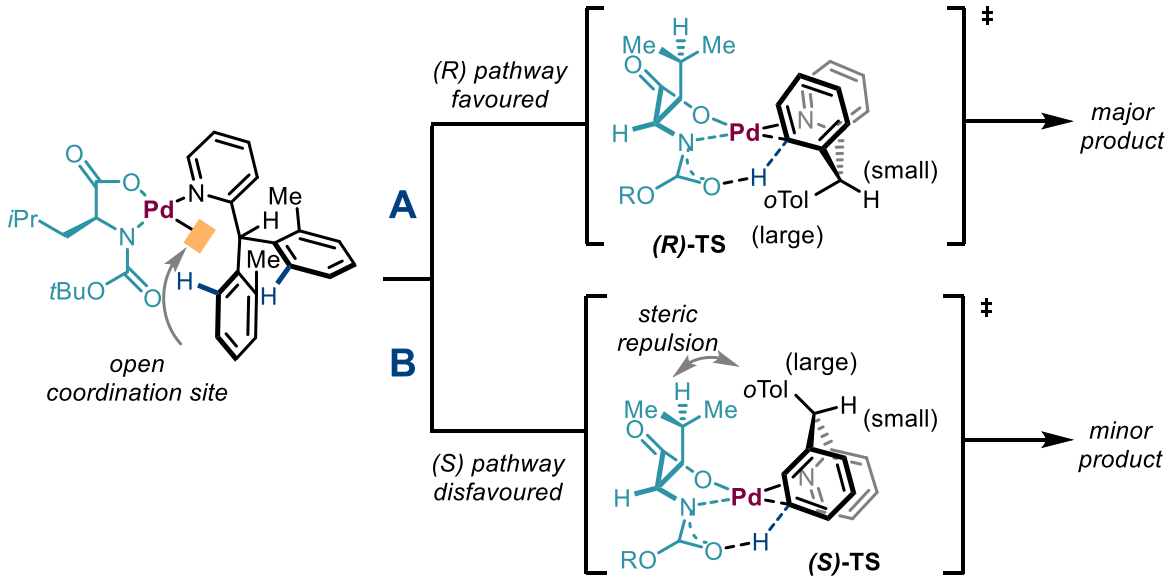
leucine was employed in the transformation, butylated product **263** was obtained in 63% and 90% ee (Table 1, Entry 3). To confirm whether it is indeed the carboxylic acid, that is needed to induce chirality, the corresponding methyl ester was tested, which resulted in racemic product **263** in 86% yield (Table 1, Entry 4). Surprisingly, using a C_2-symmetric cyclopropyl ligand, **263** was isolated in only 46% yield and 46% ee (Table 1, Entry 5), which was unexpected as C_2-symmetric ligands tend to dominate in transition metal-catalysed functionalisations. Further ligand design and development led to the (-)-menthol-derived mono-*N*-protected amino acid that yielded desired product **263** in high 91% yield and 87% ee (Table 1, Entry 6). All these experiments suggested that MPAA ligands induce stereo-control through bidentate coordination of both the mono-protected amine and carboxylate to the transition metal core.[125,127]

Table 1. Influence of MPAA ligands on enantioselectivity of Pd-catalysed C(sp^2)–H butylation.



Entry	1	2	3	4	5	6
chiral ligand						
*Yield **263** (%)*	nr	74	63	86	46	91
ee (%)	–	7	90	0	46	87

Further mechanistic and computational investigations towards the origins of enantioselectivity in this transformation led to a proposed model that is in line with the experimental observations. There are two possible pathways to proceed towards the pretransition state intermediate, in which both the directing group of the substrate and MPAA are bound to the palladium. While going through the *(S)*-pathway, steric repulsions present between the isopropyl group and second *ortho*-tolyl group of the substrate generate the higher energy transition state, that leads to the formation of disfavoured ***(S)*-TS** (**Scheme 68B**). Alternatively, going through the *(R)*-pathway, no steric repulsions are present between the chiral ligand and the substrate, which leads to the formation of favoured ***(R)*-TS** (**Scheme 68A**).[127,128]



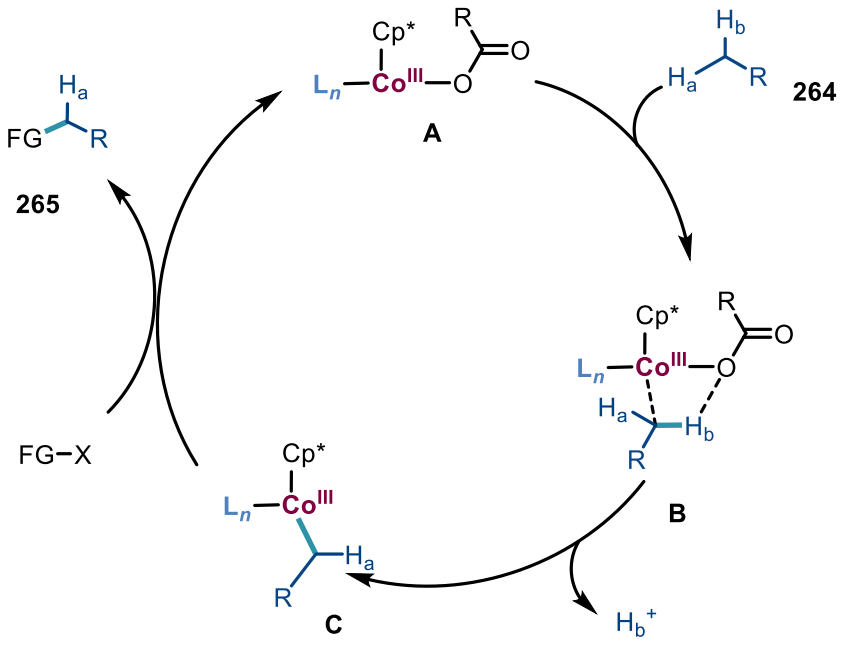
Scheme 68. Stereochemical models of MPAA ligand induced enantioselective C–H activation.

This pyridine-directed C(sp^2)–H alkylation proceeds even without the chiral ligand, underscoring one of the drawbacks of the standard directed C–H activation. Usually, innate directing groups, such as amines, alcohols, carboxylic acids and ethers do not interact sufficiently with transition metals to direct metalation, and therefore strongly coordinating directing groups have to be installed prior to the C–H activation step. In some instances, however, when strong directing groups like pyridine are present in the substrate, coordination to the metal centre, and ligand exchanges are facilitated, allowing the non stereoselective pathway to occur. One of the strategies to resolve this issue, is the use of weakly coordinating monodentate directing groups, which would not participate in the transformation without the chiral bidentate ligand. Therefore in ligand-design for asymmetric C–H activation reactions, ligands have to be able to form a steric environment that allows stereo-control, while also accelerating the reaction rate, and MPAAs had been proven to be capable of significantly accelerating various asymmetric C–H functionalisation reactions.[125,129,130]

2.2.2 Enantioselective Cp*Co^{III}-catalysed C–H functionalisation

2.2.2.1 Achiral Cp*Co^{III} catalysts with chiral ligands

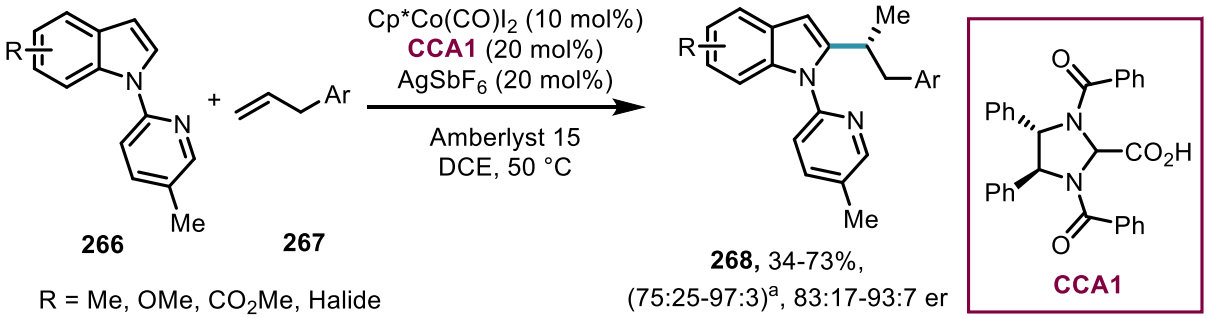
Based on the typical mechanism of enantioselective high-valent Co-catalysed C–H functionalisations, when the C–H activation step is enabled by a Co^{III} active species **A** *via* electrophilic activation, the resulting Co-C species **C** reacts with the coupling partner to furnish the reaction product **265** and regenerates the active Co^{III} intermediate **A** (**Scheme 69**). In this type of mechanism, an acid anion plays a crucial role in C–H metalation, therefore asymmetry can be achieved by the use of chiral acid additive together with achiral Cp*Co^{III} complex.[131]



Scheme 69. Mechanistic pathway of enantioselective Cp*Co^{III}-catalysed C–H functionalisation.

Enantioselectivity in high-valent Co-catalysed C–H functionalisations assisted by chiral carboxylic acids was pioneered by Ackermann in 2017. In this report, enantiopure mono-*N*-protected *L*-leucine promoted C–H alkylation of indole with terminal octene to achieve 2-

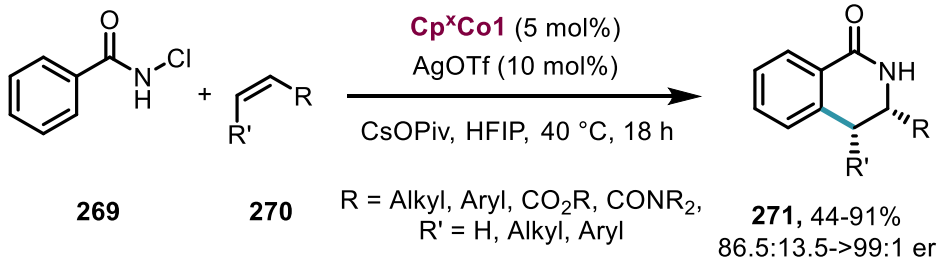
(octan-2-yl)-substituted indole in 37% yield and 26% ee.[132] This report provided a proof of concept and further research in the Ackermann group led to, in 2018, the introduction of a novel chiral carboxylic acid **CCA1**. This chiral acid was used together with an achiral Cp*Co^{III} complex to promote highly enantio-, regio- and C2-selective C–H alkylation of indoles **266** with alkenes **267** (**Scheme 70**). This catalytic system allowed very mild reaction conditions and high functional-group tolerance.[133]



Scheme 70. Chiral carboxylic acid promoted enantioselective Cp*Co^{III}-catalysed C–H alkylation. a) Markovnikov/ anti-Markovnikov selectivity in parentheses.

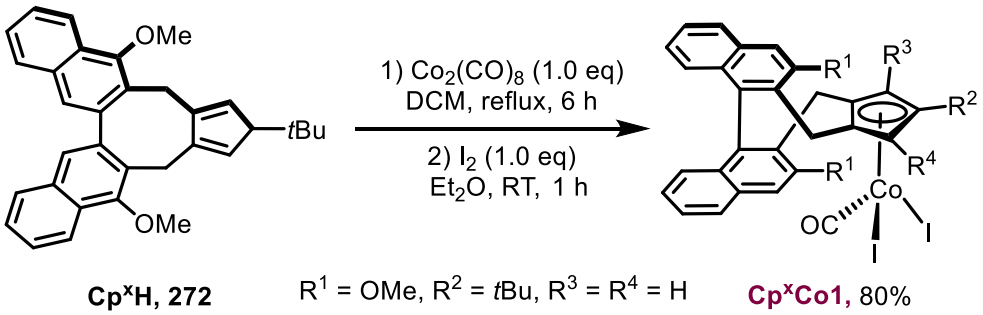
2.2.1.1 Chiral Cp^{x}Co^{III} catalysts for C–H activation

The development of chiral cyclopentadienyl (Cp) ligands for C–H activation reactions was pioneered by Cramer in 2012, with the formation of chiral Cp^{x}Rh^{III} catalysts and their application to enantioselective C–H additions.[134] Since then, Cramer and co-workers have introduced multiple generations of chiral Cp^x ligands and applied them to asymmetric transition-metal catalysed C–H functionalisations.[124,135–138] However, it was only in 2019 when Cramer reported a highly enantioselective C–H addition of olefines **270** to *N*-chlorobenzamides **269** catalysed by chiral **Cp^{x}Co1** complex (**Scheme 71**).



Scheme 71. First example of chiral Cp^xCo^{III}-catalysed C–H functionalisation.

This report disclosed multiple active chiral Cp^xCo^{III} complexes, however the highest stereoselectivity was achieved by **Cp^xCo1**. This sterically hindered catalyst**,** and other structurally-similar Co^{III} complexes were successfully synthesised from corresponding chiral Cp^xH **272** in 80% yield, by simple stirring of $Co_2(CO)_8$ with the chiral Cp^xH, followed by iodine oxidation (**Scheme 72**).[139]

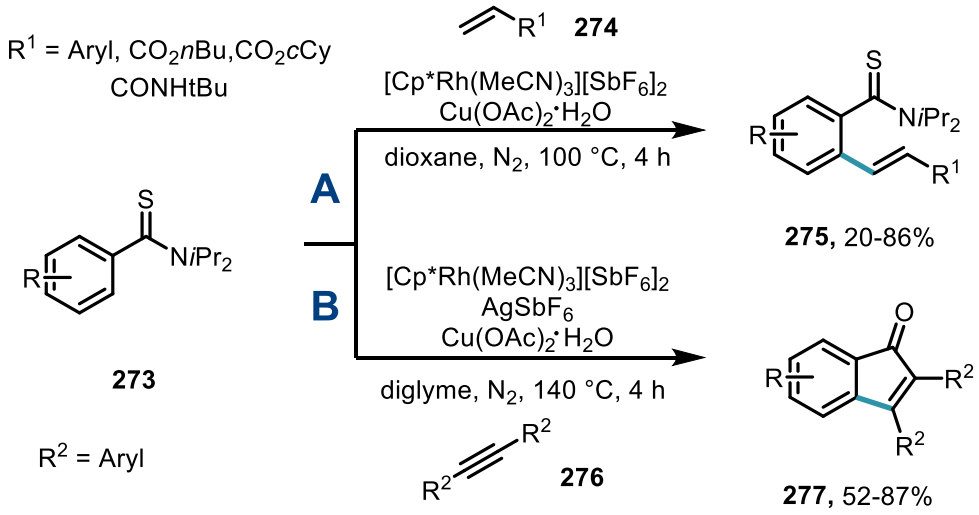


Scheme 72. Synthesis of chiral Cp^xCo^{III} complex.

2.2.3 Thioamide-directed C–H alkenylation

One of the most important modes of C–H functionalisation is functional group-directed C–H bond cleavage, which allows regio- and enantioselective transformations. While oxygen- and nitrogen-containing directing groups have been widely used and developed for decades, the utility of sulfur-based directing groups is limited, most likely due to strong coordination of sulfur to the metal core of the catalyst. Despite these challenges, the development of new transition-metal complexes enabled studies with *S*-based directing groups and thioamides

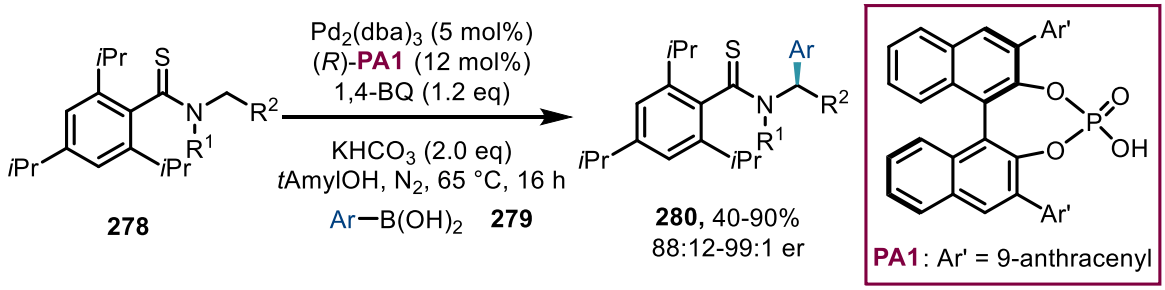
have become attractive candidates, due to their known biological activities.[140,141] In 2015, Satoh and Miura reported a Rh^{III}-catalysed alkenylation of benzothioamides. In this report, a Cp*Rh-complex is employed as the catalyst, due to its compatibility with a wide range of directing groups, as well as its diverse reactivity profile. Arylthioamides **273** undergo *ortho*-C–H activation directed by the thioamide group, and directly couple to alkenes **274** to form *ortho*-olefinated aromatic thioamides **275** (**Scheme 73A**). When reacted with alkynes **276,** they provide a range of various annulated thioamide species **277** (**Scheme 73B**) regioselectively.[142]



Scheme 73. Rh-catalysed thioamide-directed *ortho*-C–H alkenylation and annulation.

Combining the advances in thioamide-directed C–H functionalisations with asymmetric synthesis led to the development of new enantioselective C–H transformations. In 2017, Yu and co-workers developed one of the first examples of enantioselective thioamide-directed amine α-arylation reactions *via* Pd^0-catalysed C–H activation. To induce asymmetry, a chiral phosphoric acid **PA1** proved to be efficient anionic ligand for the enantioselective C–C bond formation between the α-carbon of amine **278** and aryl boronic acids **279** (**Scheme 74**). This

transformation proceeded with high enantioselectivity, and provided single regioisomeric products when two methylene groups were present in the substrate.[143]

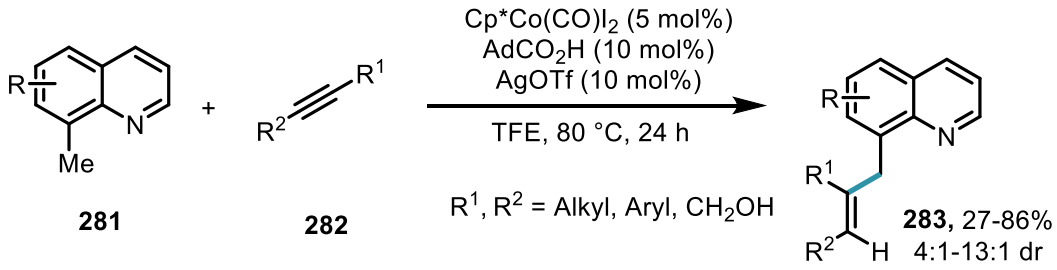


Scheme 74. Enantioselective Pd-catalysed thioamide-directed C–H arylation.

2.2.4 Cp*Co-catalysed directed C(sp^3)–H functionalisation

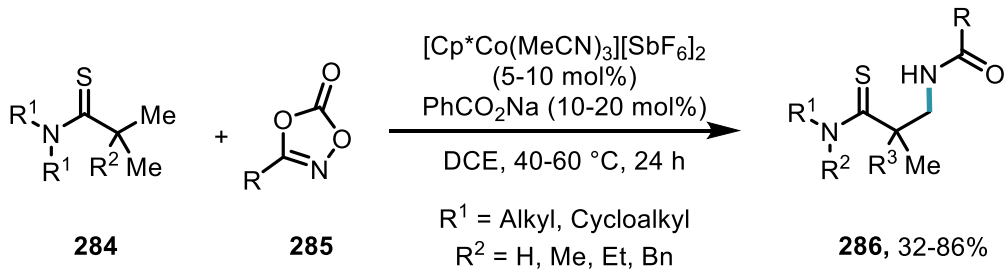
While the cobalt-catalysed activation of C(sp^2)–H bonds have been heavily studied, the activation of naturally benign C(sp^3)–H bonds is yet to be fully explored. One of the reactions that brought interest towards C(sp^3)–H activation studies was alkenylation, because it is considered to be both step- and atom-economical transformation. This type of reaction is commonly employed in activation of C(sp^2)–H bonds with rather expensive noble transition-metal catalysts. With the rising interest in earth-abundant transition metal-catalysed C–H functionalisations, cobalt complexes were targeted for development in this field. Especially high-valent Cp*Co^{III} complexes received substantial attention due to their excellent reactivity and stability, comparable with Rh^{III} and Ir^{III} analogues. These complexes have been employed in many C(sp^2)–H functionalisations, such as cyclisations, halogenations, imine additions, alkenylation, alkynylations and others.[99] However, only rarely are these catalysts utilised in the activation of C(sp^3)–H bonds. In 2016, Sundararaju disclosed his findings in the Cp*Co^{III}-catalysed stereo- and regioselective C(sp^3)–H alkenylation of 8-methylquinoline **281** with alkynes **282** (**Scheme 75**). The report features,

for the first time in C(sp^3)–H activation, a well-defined and air-stable Cp*Co(CO)I_2 catalyst.[144]



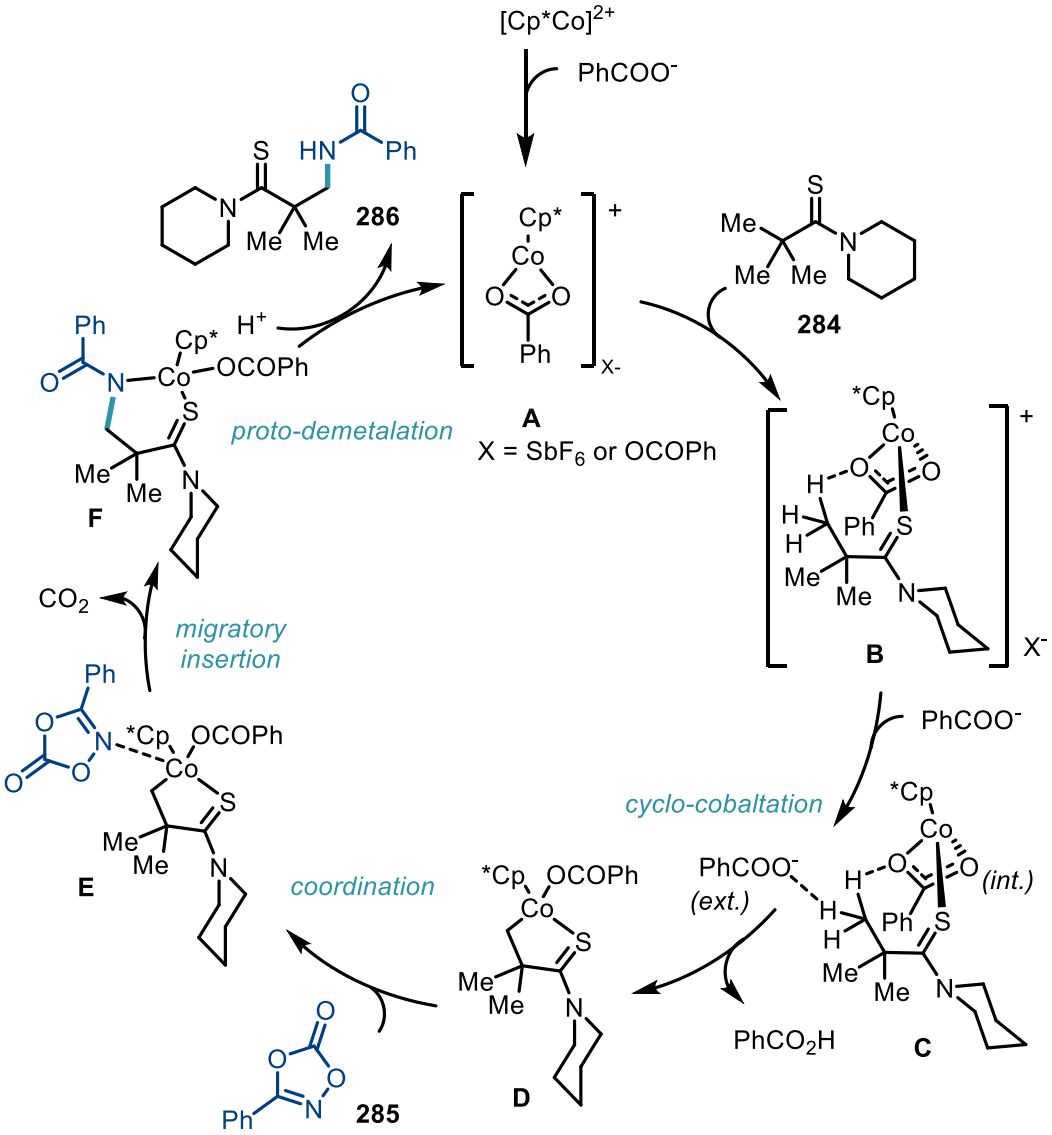
Scheme 75. First Cp*Co^{III}-catalysed 8-methylquinoline-directed C(sp^3)–H alkenylation.

With growing desire for earth-abundant transition-metal catalysts for the activation of ubiquitous C–H bonds, investigations towards transformations employing cobalt complexes became attractive due to their specific reactivity ranging from low-valent to high-valent Co-catalysed C–H functionalisations. Research in the Dixon group involving thioamide-directed C–H functionalisations dates back to 2017, when Dixon and Seayad reported the first example of a Cp*Co^{III}-catalysed thioamide-directed C(sp^3)–H amidation. In this transformation, the C(sp^3)–H bond of thioamide **284** is activated by a [Cp*Co(MeCN)$_3$][SbF_6]$_2$ complex, and with the addition of various oxazolones **285**, as amidating agents, amidated thioamide products **286** are generated in high yields and selectivity (**Scheme 76**). This method is reasonably mild and external oxidant-free, while effective to form a wide range of alkyl-, aryl- and heteroaryl-substituted amides.[145]



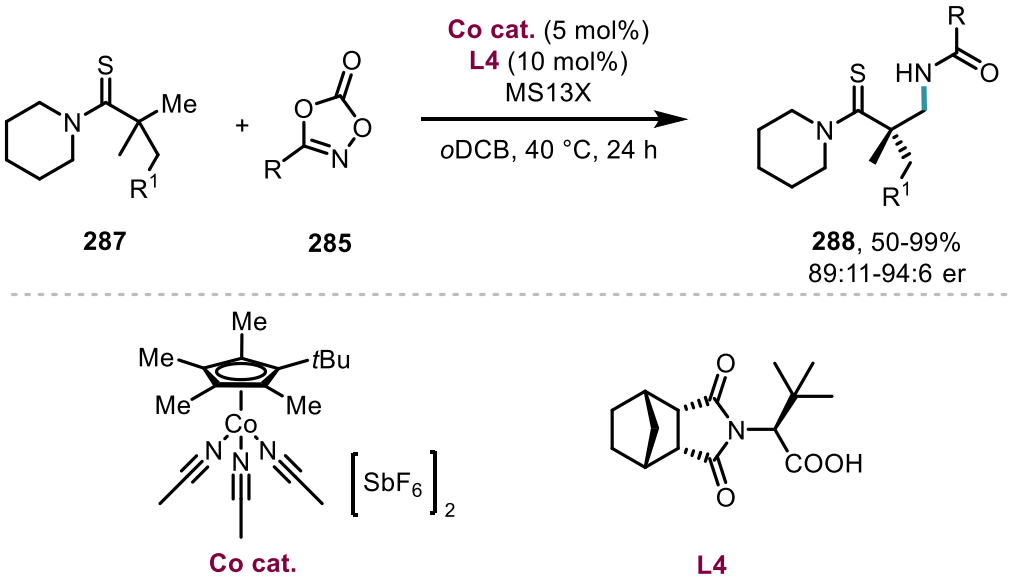
Scheme 76. Co-catalysed thioamide-directed C(sp^3)–H amidation.

The authors suggest that the catalytic cycle is initiated by the coordination of a benzoate anion to $[Cp^*Co]^{2+}$ in η^2 coordination mode, resulting in the formation of intermediate **A**. Subsequently, thioamide substrate **284** binds to **A** and forms complex **B**, to which a second external benzoate anion coordinates and aids the conversion of η^2 to η^1 ligand, resulting in the formation of intermediate **C**. Following cyclo-cobaltation leads to cobalacycle **D**, and coordination of dioxazolone **285** to **D**, after migratory insertion, results in the amide-containing cyclic intermediate **F** and loss of CO_2. Finally, proto-demetalation of **F** allows for the formation of amidated product **286**, and active species **A** is regenerated for another catalytic cycle (**Scheme 77**).[145]



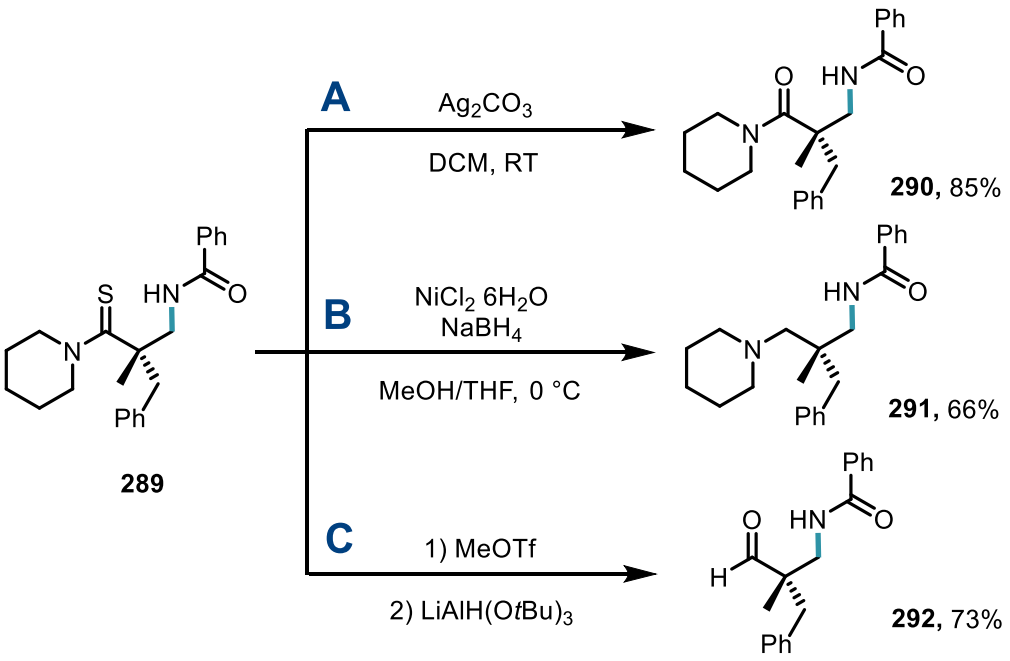
Scheme 77. A computed mechanism of the Co^{III}-catalysed thioamide-directed $C(sp^3)$–H amidation.

In 2019, Yoshino and Matsunaga reported the enantioselective variant of a similar Co^{III}-catalysed $C(sp^3)$–H amidation directed by thioamides. This asymmetric reaction utilises prochiral thioamides **287** with oxazolones **285**, and provides β-amidated thioamides **288** with an α-stereocentre in moderate to high yields and outstanding enantioselectivities (**Scheme 78**). To achieve such reactivity and enantioselectivity, a bulky achiral Co^{III} catalyst together with chiral carboxylic acid **L4** were used.[146]



Scheme 78. Enantioselective Co-catalysed thioamide-directed C(sp^3)–H amidation.

Moreover, synthetic utility of thioamide group was demonstrated by simple transformations of chiral thioamide product **289** into the corresponding amide **290**, amine **291** and aldehyde **292** in good to excellent yields (**Scheme 79**).[146]



Scheme 79. Transformations of a thioamide directing group.

2.3 Project aims

The aim of this project was to explore the realm of earth-abundant transition metal-catalysed C–H activation reactions, and to discover and further develop novel enantioselective C(sp^3)–H functionalisations catalysed with cobalt. We have focused on C(sp^3)–H activation methodologies utilising thioamide directing group, either with achiral Cp^*Co^{III} catalysts together with chiral ligands, such as chiral carboxylic acids, or by designing new chiral Cp^xCo^{III}-based complexes. Our efforts were also to understand the mechanistic pathways of asymmetric C(sp^3)–H activations, and uncover the origins of stereo- and regiocontrol in these transformations. We also wanted to investigate the thioamide moiety and its applicability towards the synthesis of various different functional groups.

2.4 Initial preliminary studies

2.4.1 Proposal for the development of cobalt-catalysed C(sp^3)–H activation reaction

The exploration and further development of earth-abundant transition-metal catalysed C–H activation reactions, utilising for example Co complexes, could provide a suitable alternative, to the traditionally used expensive noble transition-metal catalysts. Earth-abundant cobalt and high-valent Cp^*Co^{III} complexes became attractive due to the great stability, specific reactivity and high selectivity for a wide range of C–H functionalisations. Our initial investigation was commenced by focusing on identifying alternative coupling partners compatible with the concept of C(sp^3)–H activation directed by thioamides as shown in **Scheme 80**, where the C–H bond of one of the three methyl groups in the β-

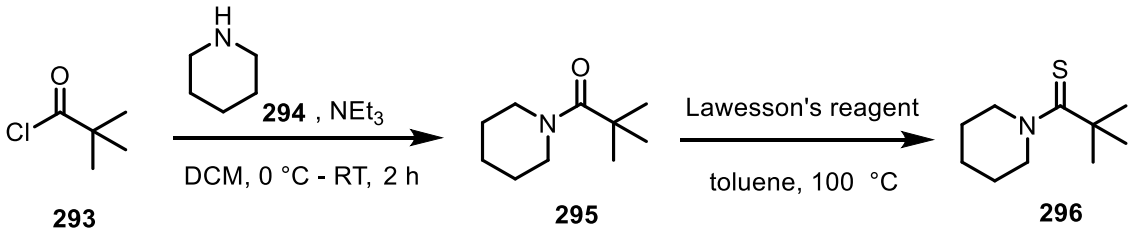
position of the thioamide gets activated by the Co^{III} catalyst, that allows for the formation of a new C–C or C–X bond between the starting material and the electrophilic coupling partner.



Scheme 80. Proposal for the new cobalt-catalysed C(sp^3)–H activation reaction.

2.4.2 Synthesis of thioamide model substrate

To investigate the viability of the proposed transformation, thioamide **296** was readily synthesised by acylation of piperidine **294** with pivaloyl chloride **293**, followed by a subsequent thionisation with Lawesson's reagent, which afforded the desired model starting material **296** (**Scheme 81**).[1]



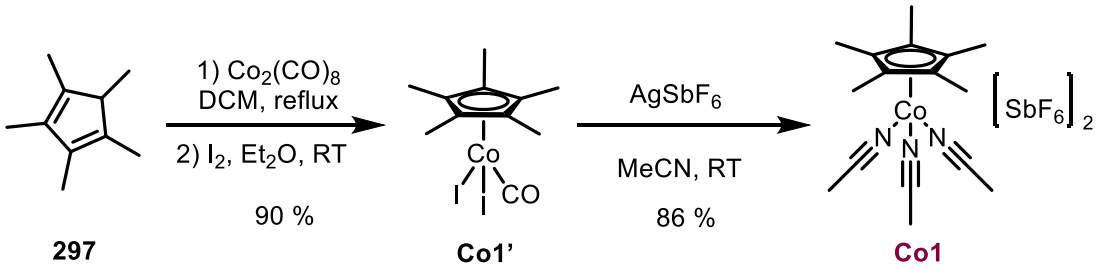
Scheme 81. Synthesis of 2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **296** as a model substrate.

2.4.3 Synthesis of Cp*Co^{III} complex

Before the initial preliminary studies, achiral $[CoCp^*(MeCN)_3][SbF_6]_2$ complex **Co1** had to be prepared by the complexation of pentamethylcyclopentadiene (Cp*) **297** with

[1] Synthesis performed by Dr Heyao Shi.

$Co_2(CO)_8$.[147] This was followed by oxidation with iodine, and finally ligand exchange on the Co^{III} complex afforded the desired catalyst **Co1** in 77% overall yield (**Scheme 83**).



Scheme 82. Synthesis of Cp*Co^{III} catalyst **Co1**.

2.4.4 Preliminary experiments and optimisation of Co^{III}-catalysed C(sp^3)–H activation reaction

Following up on previous findings in the Dixon group,[145] on the thioamide-directed Cp*Co^{III} catalysed C(sp^3)–H amidation, our study initially focused on finding alternative and useful electrophiles that could be employed in this type of transformation, such as olefins, alkynes, and enones.

During the initial screening campaign, methyl but-2-ynoate **298** proved to be a successful electrophilic coupling partner in the alkenylation of simple thioamide **296**, yielding monoalkylated product **299** as a rather unusual and unexpected single regioisomer in 18% yield. At this stage, we could see that the $[Cp^*Co(MeCN)_3][SbF_6]_2$ complex **Co1** allows for a rare C(sp^3)–H activation of one of the three pivalic acid derived methyl groups in *β*-position of the thioamide, which was probably made possible by the specific coordination of cobalt to the sulfur atom of the model substrate. It is important to note, that all optimisation was performed using **Co1** catalyst outside of a glovebox, however to our

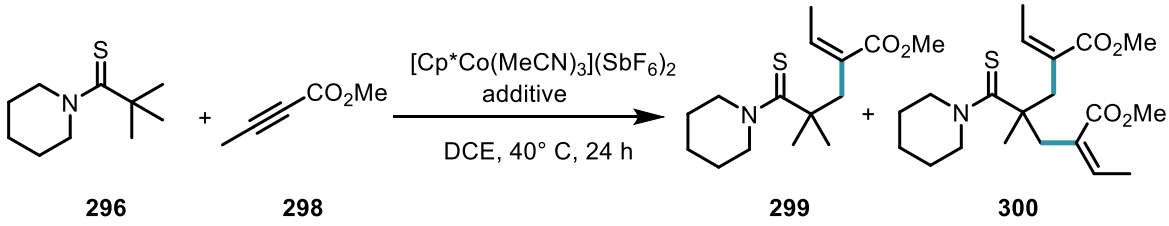
knowledge, all reports using this Cp^*Co^{III} complex, require the utilisation of glovebox techniques.

To improve the reaction yield, various additives were screened, and these results are summarised in **Table 2**. The study was commenced by using standard conditions as reported by Dixon and Seayad's.[145] Prochiral thioamide **296** was added with methyl but-2-ynoate **298,** 10 mol% of **Co1** complex and catalytic amount of sodium benzoate in 1,2-dichloroethane (DCE) as a solvent at 40° C under argon atmosphere. This model experiment afforded the desired product **299** in 18% yield (Table 2, Entry 1). The use of benzoic acid instead of sodium benzoate led to 21% and 34% yield respectively, when 20 and 40 mol% was added (Table 2, Entry 2 and 3), however, stoichiometric and superstoichiometric amounts did not lead to any improvements (Table 2, Entry 4 and 5). We noticed that the increase in catalyst loading from 10 mol% to 30 mol%, led to formation of desired product **299** in 24% yield together with double C–H activation product **300**, which was isolated as 1:1 mixture with **299** (Table 2, Entry 6). Encouraged by these results, further commonly used carboxylic acids were tested as additives. Firstly, the addition of 1.0 equivalent of 2,4,6-trimethyl benzoic acid afforded sluggish reactivity, while 40 mol% of Cbz-protected *L*-alanine yielded 10% of the desired product **299**, and 1.0 equivalent of both dimethylbutyric and adamantanecarboxilic acid led to 22% and 26% yield, respectively (Table 2, Entries 7-10).

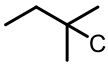
The trend in the amount of the acid additive proved to be similar as with benzoic acid, 2.0 equivalents led to 20%, and catalytic amounts (20 mol%) to 13% isolated yield (Table 2, Entry 11 and 12). We then explored whether various *in situ* formed benzoate salts could help

to boost the yield, however we only observed the formation of hydrolysed starting material to the amide (Table 1, Entries 13-15).

Table 2. Preliminary additive screening.



296 **298** **299** **300**

Entry	Additive	Catalyst loading (mol %)	Yield 299 (%)	Yield 300 (%)
1	$PhCO_2Na$ (10 mol%)	10	18	N/A
2	$PhCO_2H$ (20 mol%)	10	21	N/A
3[a]	$PhCO_2H$ (40 mol%)	10	34	N/A
4	$PhCO_2H$ (1 eq.)	10	33	N/A
5	$PhCO_2H$ (2 eq.)	10	23	N/A
6[a]	$PhCO_2H$ (1 eq.)	30	24	48[b]
7	2,4,6-triMe$PhCO_2H$ (1 eq.)	10	low conversion	N/A
8	Cbz-Ala-OH (40 mol%)	10	10	N/A
9	 (1 eq.)	10	22	N/A
10	$AdCO_2H$ (1 eq.)	10	26	N/A
11	$AdCO_2H$ (2 eq.)	10	20	N/A
12	$AdCO_2H$ (20 mol%)	10	13	N/A
13	$PhCO_2H$ (1 eq.) $Cu(OTf)_2$ (1 eq.)	10	0	0
14	$PhCO_2Na$ (1 eq.) $Cu(OTf)_2$ (1 eq.)	10	0	0
15	$PhCO_2H$ (1 eq.) Cs_2CO_3 (1 eq.)	10	0	0

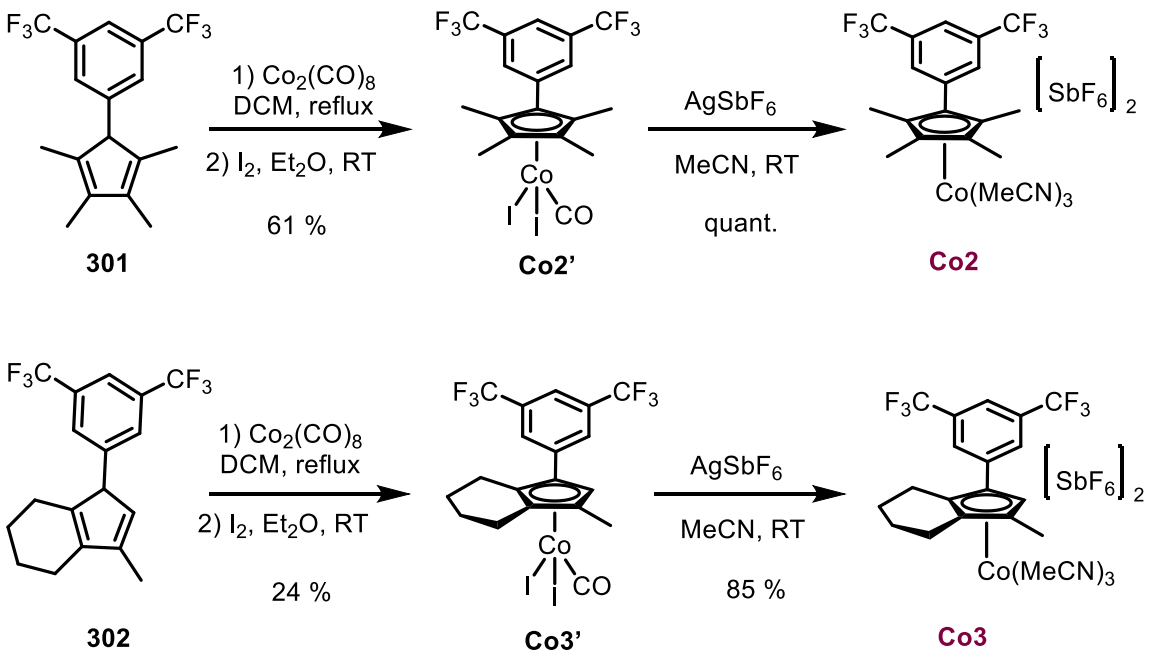
General conditions: **296** (0.05 mmol), **298** (0.10 mmol). [a] Reaction carried out for 48 h. [b] Isolated as a 1:1 mixture of **299** and **300**.

2.4.5 Design and application of new Co^{III}-Cp based catalysts

At the same time, we aimed to explore, design, synthesise and test new cobalt-based catalysts with a cyclopentadiene core, therefore we chose to prepare two achiral and two prochiral Cp ligands.

2.4.5.1 Synthesis and testing of achiral $CpCo^{III}$ catalysts

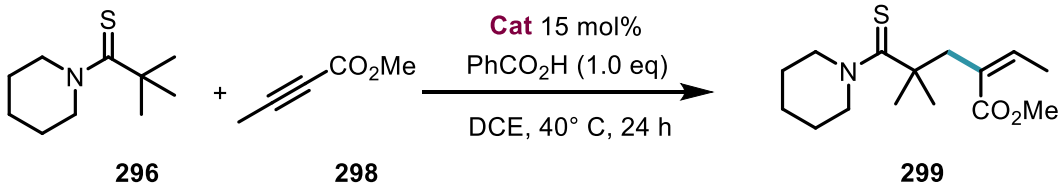
We thought that changing substitution on the cyclopentadiene ring could aid the transformation, and therefore two achiral ligands **301** and **302** were chosen for the subsequent cobalt complexation. Both ligands are sterically more demanding than Cp*, which may aid in the shielding of the metal centre and protect it from the catalyst deactivation. Both are however also more electron-deficient, which could potentially improve the catalyst's binding to the active species and alter the $C(sp^3)$–H activation efficacy.[139] Both ligands **301** and **302** were treated with dicobalt octacarbonyl, followed by an oxidation with iodine to furnish the precatalyst **Co2'** in 61% and **Co3'** in 24% yield. Subsequent ligand exchange of the cobalt core with silver hexafluoro antimonate allowed the formation of catalyst **Co2** quantitatively and **Co3** in 85% yield (**Scheme 83**).



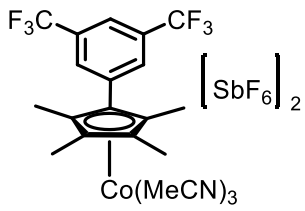
Scheme 83. Synthesis of new achiral $CpCo^{III}$ complexes **Co2** and **Co3**.

Both prepared catalysts were tested in the alkenylation reaction of thioamide **296** with methyl but-2-ynoate **298** in presence of benzoic acid additive in DCE at 40° C. Unfortunately, after 24 hours no trace of desired product **299** was observed (Table 3, Entry 1 and 2), suggesting that less electron-rich ligands, containing CF_3 groups, cannot catalyse this type of transformation.

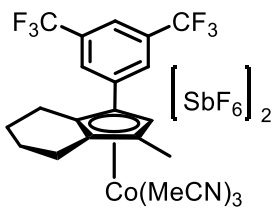
Table 3. Testing of new achiral $CpCo^{III}$ catalysts in $C(sp^3)$–H alkenylation of thioamide **296**.



296 **298** **299**



Co2



Co3

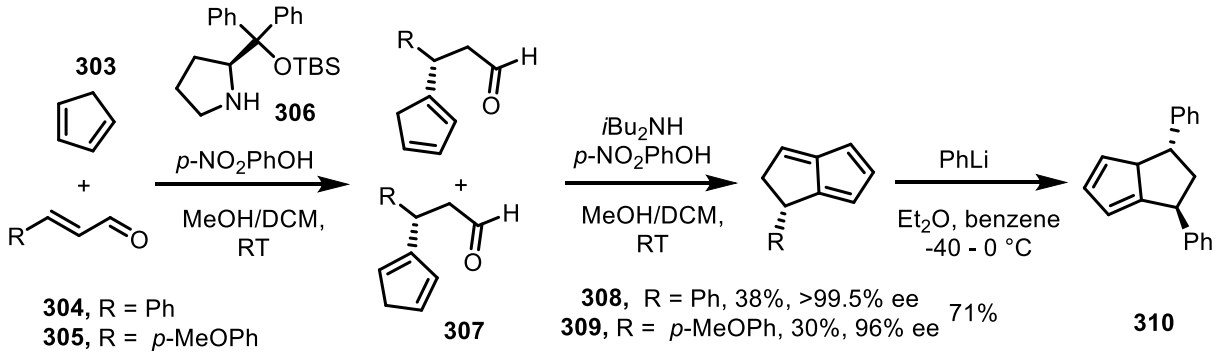
Entry	Catalyst	Yield 299 (%)
1	**Co2**	0
2	**Co3**	0

2.4.5.2 Synthesis of chiral Cp^xCo^{III} catalyst

For the synthesis of chiral Cp^xCo^{III} catalyst, first prochiral ligands had to be prepared, that could undergo complexation with a cobalt-based Lewis acid. We chose two prochiral cyclopentadiene-fused fulvenes previously reported by Hayashi[148] and Cramer.[137]

The two steps/one-pot synthesis was commenced with the addition of cyclopentadiene **303** to cinnamaldehydes **304** and **305** in the presence of Hayashi's catalyst **306**, which was previously synthesised from *L*-proline in 4 steps.[149,150] Regioisomeric mixture of aldehydes **307** was subsequently treated with diisobutylamine and *p*-nitrophenol, and *via* intramolecular condensation fulvenes **308** and **309** were formed in 30% and 38% yield and excellent 96 and >99.5% ee, respectively. Unfortunately, the addition of the *p*-methoxyphenyl lithium was unsuccessful, therefore as a model substrate we decided to

continue with the synthesis of (*S*)-1-phenyl-1,2-dihydropentalene **308**, in which case the diastereoselective addition of phenyl lithium afforded the C_2-symmetric ligand **310** in 71% yield (**Scheme 84**).



Scheme 84. Synthesis of prochiral Cp-fused fulvene ligands.

The reaction mechanism of Michael addition of the cyclopentadiene **303** to cinnamaldehyde **304** proceeds *via* iminium intermediate. Cinnamaldehyde **304** deprotonates *p*-nitrophenol and following addition of Hayashi's catalyst forms iminium intermediate **A** and water. At the same time Hayashi catalyst **306** deprotonates cyclopentadiene **303** and generates Cp anion-containing intermediate **B**. The intermediate **B** then exchanges Cp anion for the anion of **A**, which results in the formation of active intermediate **C** and regeneration of *p*-nitrophenol and catalyst **306**. The active intermediate **C** then undergoes asymmetric 1,4-addition *via* the transition state on **Figure 7**, and allows the formation of **D**, which after hydrolysis forms the desired chiral products **307** and regenerates the catalyst **306** for another catalytic cycle (**Scheme 85**).[151]

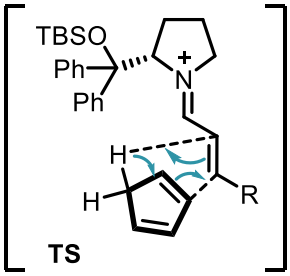
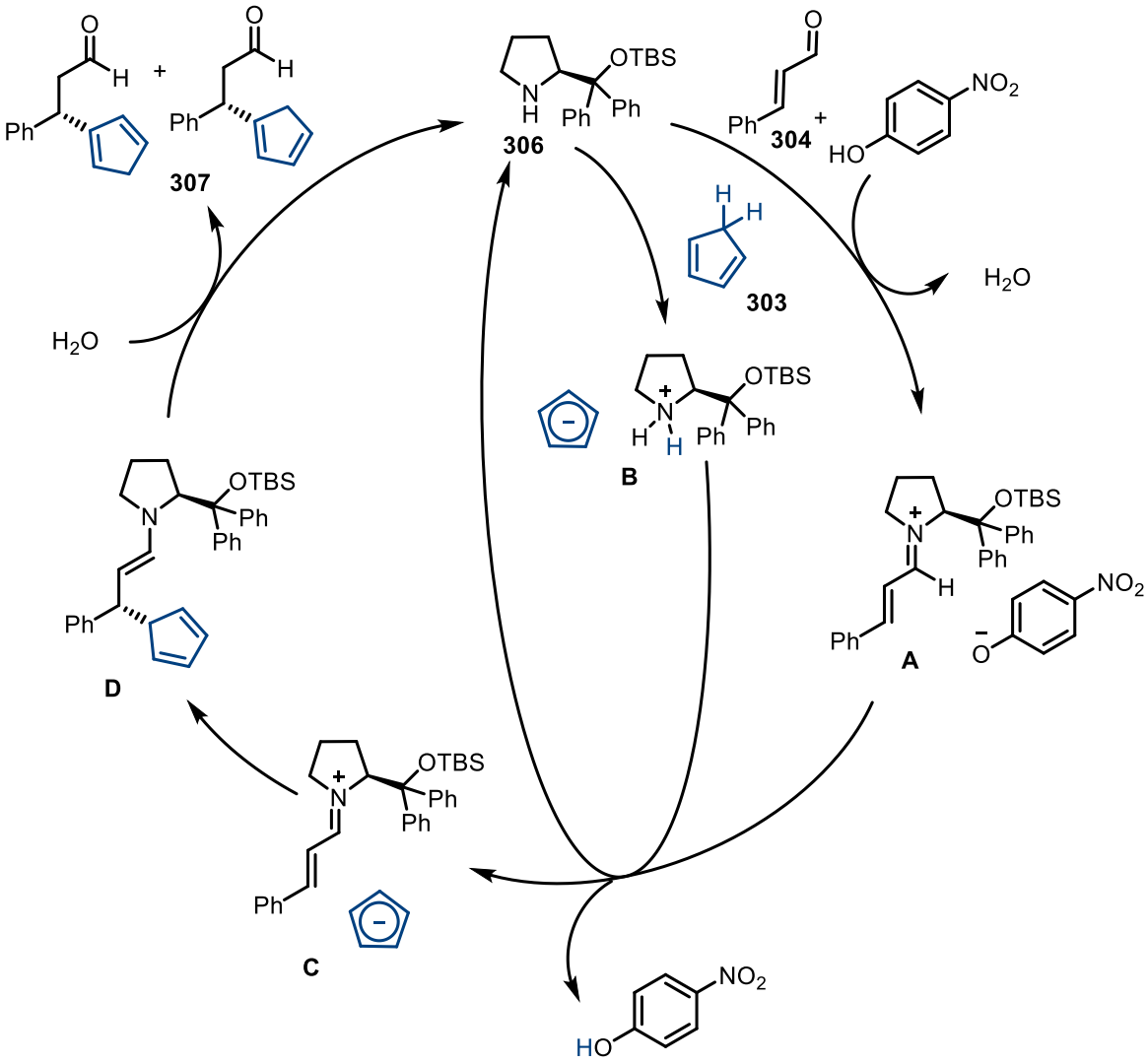
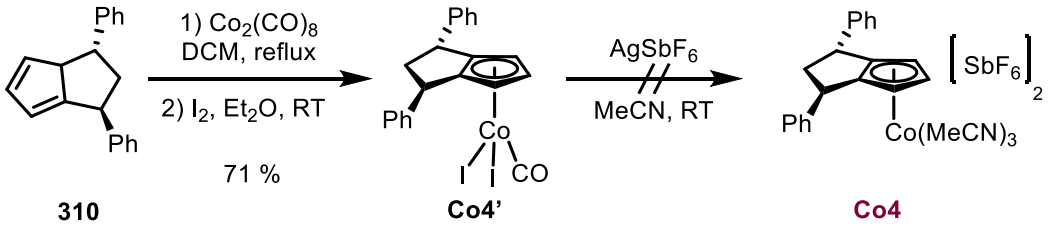


Figure 7. Transition state for the enantioselective Michael addition.



Scheme 85. Mechanism of the enantioselective Michael addition.

The coordination of cobalt onto the Cp-fused fulvene precatalyst **Co4'** was performed, using the previously mentioned method reported by Matsunaga and Kanai.[147] Prochiral ligand **310** was added to dicobalt octacarbonyl, followed by iodine oxidation to acquire chiral Cp^xCo^{III} precatalyst **Co4'** in 71%. Unfortunately, due to the air instability of compound **Co4**, ligand exchange on cobalt was not possible (**Scheme 86**). We observed the formation of purple Cp^xCo^{III} complex, however there was an instant colour change to blue/green upon contact with air.



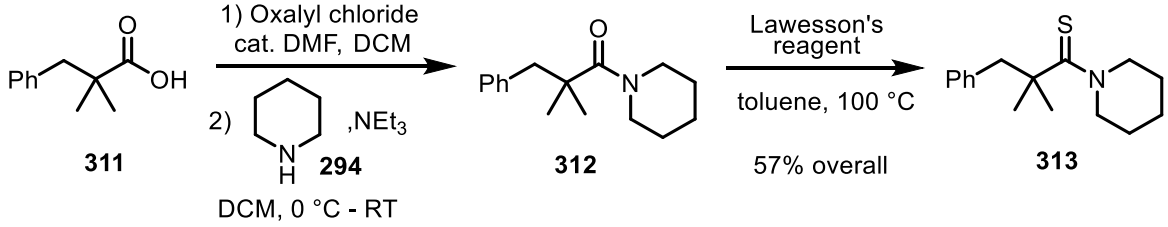
Scheme 86. Synthesis of new chiral Cp^xCo^{III} catalysts **Co4**.

2.5 Investigation

2.5.1 Initial optimisation of Co^{III}-catalysed C(sp^3)–H alkenylation of thioamides

After the initial hit with methyl but-2-ynoate as an electrophilic coupling partner and not much success with new $CpCo^{III}$ fused catalysts, we decided to continue with the optimisation of all other variables in the reaction mixture. Based on the nature of the substrate, we speculated that enantioselectivity could be established with the corresponding prochiral model substrate. Therefore, we prepared benzyl-substituted thioamide **313**, from previously prepared 2,2-dimethyl-3-phenylpropionic acid **311**,[152] After the corresponding tertiary amide **312** was obtained under standard conditions, using oxalyl chloride to generate the

more reactive acid chloride, **312** was readily transformed with Lawesson's reagent, to the desired prochiral thioamide **313** in overall 57% yield (**Scheme 87**).



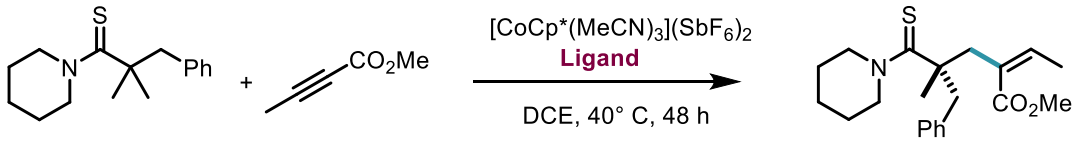
Scheme 87. Synthesis of prochiral model substrate for enantioselective C(sp^3)–H alkenylation.

With the prochiral model substrate **313** in hand, further ligand optimisation was performed (**Table 4**). Observing that acidic additives improved reactivity (Table 4, Entry 1 and 2), several *N*-protected amino acids were then tested. The first set of experiments using differently protected glycine derivatives revealed Fmoc as the optimal protecting group (Table 4, Entries 3-5). At this stage, we reasoned that if any enantioselectivity was to be established, we should be able to see small enantiomeric ratios with other protected amino acids, therefore we continued with 40 mol% and 80 mol% loading of Fmoc-*L*-alanine, that led to the desired single regioisomer **314** in 73% yield and encouraging 53:47 er (Table 4, Entry 8). A library of Fmoc-protected amino acids were then subjected to the reaction conditions, yielding product **314** in 51-61% yield and up to 54:46 er (Table 4, Entries 10-13). These important experiments demonstrated a proof of concept for the enantioselective C(sp^3)–H alkenylation directed by thioamides and led to the investigation of the effect of the unnatural amino acid derivatives **L1** and **L2**.[2] Both selected *L*-valine derived ligands in 40 mol% provided very encouraging 78% and 61% yields, with 64:36 and 59:41 er,

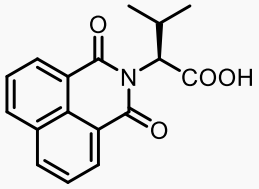
[2] Both ligands **L1** and **L2** were prepared by Dr Michele Formica.

respectively (Table 4, Entry 14 and 16), in which case the bulkier **L1** proved better for reactivity and selectivity.

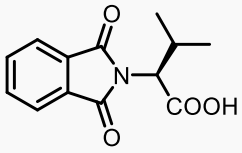
Table 4. Ligand screening.



313 **298** **314**



L1



L2

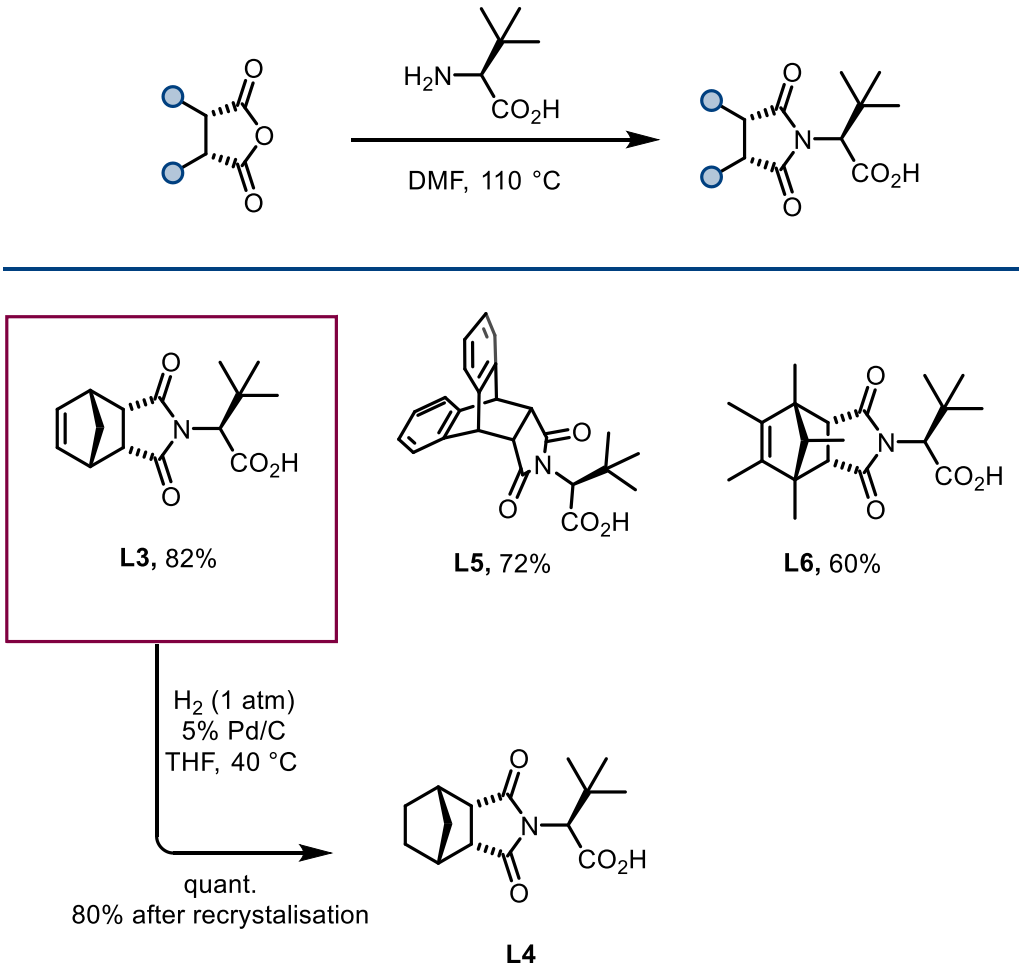
Entry	Ligand	Catalyst loading (mol %)	Yield 314[a] (%)	er[b]
1[c]	$PhCO_2H$ (40 mol%)	10	34	N/A
2[c]	$AdCO_2H$ (1 eq.)	10	26	N/A
3[c]	Boc-Gly-OH 80 mol%	10	44	N/A
4[c]	Cbz-Gly-OH 80 mol%	10	43	N/A
5[c]	Fmoc-Gly-OH 80 mol%	10	47	N/A
6[c]	Fmoc-Ala-OH 40 mol%	20	39	N/A
7[c]	Fmoc-Ala-OH 80 mol%	10	56	N/A
8	Fmoc-Ala-OH 80 mol%	20	73	53 : 47
9	Fmoc-Ala-OH 1 eq.	20	76[d]	53 : 47
10	Fmoc-Ile-OH 80 mol%	20	61[d]	52 : 48
11	Fmoc-Asn(Trt)-OH 80 mol%	20	51[d]	54 : 46
12	Fmoc-Tyr(*t*Bu)-OH 80 mol%	20	54[d]	50 : 50
13	Fmoc-Glu(OBzl)-OH 80 mol%	20	55[d]	50 : 50
13	Fmoc-Val-OH 80 mol%	20	60[d]	52 : 48
14	**L1** 40 mol%	20	78[d]	64 : 36
15	**L1** 80 mol%	20	63[d]	N/A
16	**L2** 40 mol%	20	61[d]	59 : 41

General conditions: **313** (0.05 mmol), **298** (0.10 mmol), DCE (0.2 M). [a] Isolated yield after silica gel column chromatopraphy. [b] Determined by chiral HPLC analysis. [c] Reaction carried out using thioamide **296** instead of prochiral **313.** [d] NMR yield calculated using *p*-nitrotoluene as internal standard.

2.5.2 Design and synthesis of amino acid-derived ligands

L-Valine derived cyclic imides **L1** and **L2**, improved the reactivity as well as enantioselectivity in this transformation, therefore we decided to study this group of ligands in more detail. Coincidentally, Yoshino and Matsunaga reported[146] enantioselective C(sp^3)–H amidations using analogous ligands, that further inspired and encouraged us to test them in our transformation.

Firstly, we started with the synthesis of **L3,** condensing commercially available cis-5-norbornene-endo-2,3-dicarboxylic anhydride with *L-tert*-leucine, achieving desired **L3** in 82%, that was subsequently hydrogenated to afford **L4** in 80% yield after recrystallisation (**Scheme 88**). Synthesis of ligand **L5** commenced with the anthracene anhydride formation *via* Diels-Alder reaction of anthracene and maleic anhydride, followed by the condensation with *L-tert*-leucine, which led to the desired ligand **L5** in 72% yield. Similarly, 1,2,3,4,5-pentamethylcyclopentadiene (Cp*) underwent Diels-Alder cyclisation with maleic anhydride, that was followed by *L-tert*-leucine condensation to form **L6** in 60% isolated yield (**Scheme 88**).



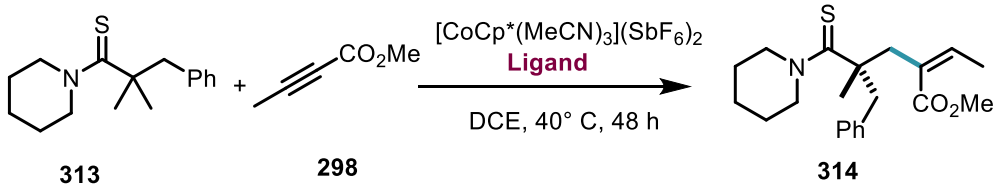
Scheme 88. Synthesis of chiral ligands for enantioselective C(sp^3)–H alkenylation.

2.5.3 Screening of new ligands and further optimisation of Co^{III}-catalysed C(sp^3)–H alkenylation of thioamides

With new and freshly prepared ligands in hand, we were ready to test them in our C–H activation methodology. Previously, in our best experiment, we were able to achieve 78% yield and 64:36 er of the chiral thioamide **314**, using *L*-valine derived ligand **L1** (Table 5, Entry 3). Using *L-tert*-leucine derived **L3** and **L4** affprded moderate 53% and 49% yield, with 74:26 and 76:24 er, respectively (Table 5, Entry 4 and 5). Using the newly designed ligand **L5** led to slightly lower reactivity and selectivity - 42% yield, 60:40 er (Table 5, Entry

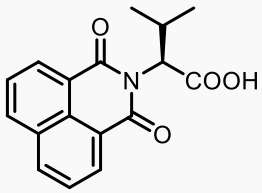
6), while ligand **L6** furnished the product in 48% yield and 68:32 er (Table 5, Entry 7). At the same time we were interested to see if Ackermann's ligand **L7** would increase reactivity or selectivity of this C–H alkenylation, however this type of chiral acid completely shut down the reaction (Table 5, Entry 8).

Table 5. Ligand screening.

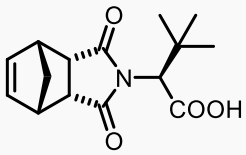


313 **298** **314**

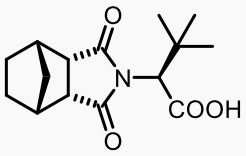
single geometric isomer



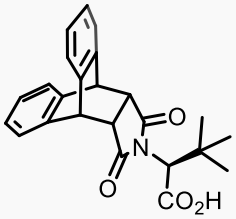
L1



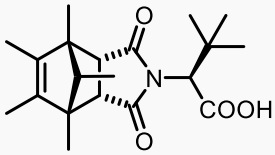
L3



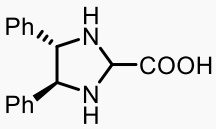
L4



L5



L6



L7

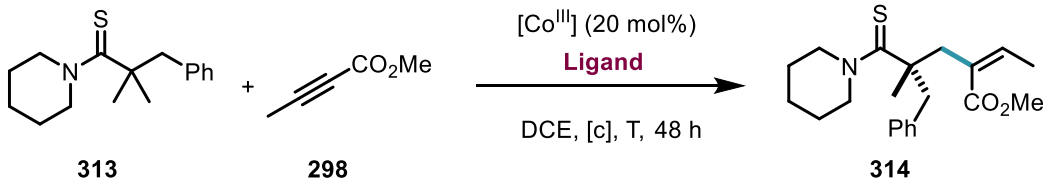
Entry	Ligand	Yield 314[a] (%)	er[b]
1	$PhCO_2H$ (1 eq.)	63	N/A
2	Fmoc-Ala-OH 80 mol%	73	53 : 47
3	**L1** 40 mol%	78[c]	64 : 36
4	**L3** 40 mol%	53	74 : 26
5	**L4** 40 mol%	49	76 : 24
6	**L5** 40 mol%	42	60 : 40
7	**L6** 40 mol%	48	68 : 32
8	**L7** 40 mol%	no reaction	N/A

General conditions: **313** (0.05 mmol), **298** (0.10 mmol), DCE (0.2 M) [a] Isolated yield after silica gel column chromatopraphy. [b] Determined by chiral HPLC analysis. [c] NMR yield calculated using *p*-nitrotoluene as internal standard.

All these experiments suggested that fully hydrogenated ligand **L4** proved to be the best in terms of enantioselectivity, however **L3** yielded the desired alkenylated thioamide **314** in slightly better yield, therefore we decided to continue the optimisation of our transformation with both, to see whether the trends continued (**Table 6**). In general, for C–H activation, it is usually necessary to use elevated temperature to promote the catalytic cycle, however our test reactions were performed at 40 °C, therefore we wanted to test the reaction at room temperature and at 0 °C. While running the reaction at room temperature, we observed a small boost in yield and no change in selectivity (Table 6, Entry 3 and 4). When the reaction mixure was cooled down to 0 °C, althought we saw a significant drop in reactivity, even after prolonged reaction times, we also observed an increase in enantioselectivity, achieving 78:22 er with 40 mol% of **L3** and 79:21 er with 40 mol% of **L4** (Table 6, Entry 5 and 6). Decreasing the loading of the ligand to 20 mol% resulted in a substantial drop in reactivity and no change in selectivity (Table 6, Entries 8-10). Seeing that overall, hydrogenated ligand **L4** provided slightly better enantiomeric ratios, we decided to continue the optimisation only with this ligand. Next, the effect of the amount of the alkyne coupling partner was screened, and we found that this variable did not have a significant effect on the yield of the reaction, but the selectivity changed substantially. When only 1.5 eq. of methyl but-2-ynoate **298** was used, the enantiomeric ratio decreased to 68:32 (Table 6, Entry 11). On the other hand, when the amount of the alkyne was increased to 5.0 or 10 equivalents, 80:20 and 86:14 er were achieved, respectively (Table 6, Entries 13 and 14). Although 10 eq. of methyl but-2-ynoate **298** boosted the selectivity, we aimed to find conditions under which the use of a large excess of the alkyne couling partner would be avoided, therefore we turned our attention to

concentration effects. When the reaction mixture was diluted [0.1 M], the selectivity dropped to 69:31 er (Table 6, Entry 15), while when more concentrated [0.5 M] we observed an increase to 83:17 er using 5.0 eq. of the alkyne (Table 6, Entry 16).

Table 6. Reaction optimisation.



313 **298** **314**

single geometric isomer

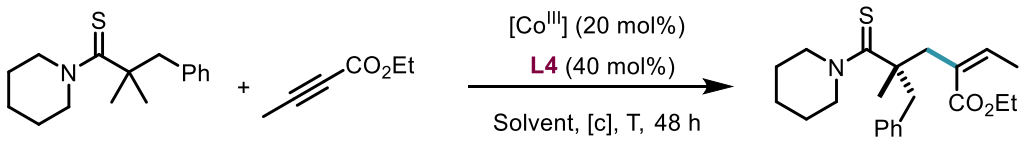
Entry	Ligand	T (°C)	Alkyne eq.	[c] (mol/L)	Yield 314[a] (%)	er[b]
1	**L3** 40 mol%	40	2	0.2	53	74 : 26
2	**L4** 40 mol%	40	2	0.2	49	76 : 24
3	**L3** 40 mol%	rt	2	0.2	61	75 : 25
4	**L4** 40 mol%	rt	2	0.2	46	76 : 24
5[c]	**L3** 40 mol%	0	2	0.2	25	78 : 22
6[d]	**L4** 40 mol%	0	2	0.2	14	79 : 21
7[e]	**L3** 40 mol%	40	2	0.2	56	73 : 27
8	**L3** 20 mol%	40	2	0.2	36	75 : 25
9	**L4** 20 mol%	40	2	0.2	42	76 : 24
10[f]	**L3** 20 mol%	40	2	0.2	32	76 : 24
11	**L4** 40 mol%	40	1.5	0.2	51	68 : 32
12	**L4** 40 mol%	40	3	0.2	55	75 : 25
13	**L4** 40 mol%	40	5	0.2	47	80 : 20
14	**L4** 40 mol%	40	10	0.2	49	86 : 14
15	**L4** 40 mol%	40	2	0.1	50	69 : 31
16	**L4** 40 mol%	40	5	0.5	39	83 : 17

General conditions: **313** (0.05 mmol). [a]Isolated yield after after silica gel column chromatopraphy [b]Determined by chiral HPLC analysis. [c] Reaction time 4 days. [d] Reaction time 3 days. [e]Reaction carried out at 0.2 mmol scale. [f] Reaction carried out using $[Cp^*Co(MeCN)_3][SbF_6]$ (0.005 mmol, 10 mol%).

In a bid to achieve higher selectivity, methyl but-2-ynoate **298** was replaced with the ethyl but-2-ynoate **315**, achieving under diluted conditions [0.2 M] 47% yield and 83:17 er (Table 7, Entry 1), the same selectivity as was afforded with **298** when the reaction wes carried out at higher concentration [0.5 M] (Table 6, Entry 16). This finding encouraged us to continue optimisation of the reaction conditions with ethyl but-2-ynoate **315**. Knowing that an increase of the concentration of the reaction had a positive effect on the enantioselectivity, we tested the reaction with 5.0 and 10 eq. of the alkyne **315** at 0.5 M concentration at 40 °C, achieving 86:14 and 87:13 er of desired **316** (Table 7, Entries 2 and 3). Next, the effect of the reaction temperature was studied, at room temperature **316** was obtained with 86:14 er and 88:12 er, when 5.0 and 10 eq. of **315** were added, respectively (Table 7, Entries 6 and 7). Following, the effect of the amount of alkyne under 1.0 M and 2.0 M concentration was tested. With 5.0 eq. of **315** in 1.0 M, 87:13 er was achieved (Table 7, Entry 4), while with 10 eq. of **315** in 2.0 M selectivity increased to 89:11 er (Table 7, Entry 5). However, such a large excess of one of the reagents was not desirable, so we continued the optimisation in order to find more adequate conditions. At this point, a thorough solvent screen commenced at both 40 °C and room temperature. Out of all the solvents tested at 40 °C, *o*DCB proved to act the best in terms of a combination of reactivity and selectivity with 56% yield and 87:13 er (Table 7, Entry 8), while Et_2O allowed for better selectivity, furnishing the product in 88:12 er and 47% yield (Table 7, Entry 15). DME afforded even better 90:10 er, but the yield dropped significantly to 32% (Table 7, Entry 17). This left us thinking about the effects of chlorinated and ether-type solvents, and we continued the solvent screen with examples from both groups at room temperature as the data suggested. Out of these experiments, the one that stand out was *o*DCB, which allowed the transformation in 76% yield with 88:12 er (Table 7, Entry 21), which, up to this point, was the best combination of reactivity and

selectivity for this C–H alkenylation. From this set of experiments, we were also able to identify other ether- and ester-type solvents that boosted selectivity; with Et_2O, CPME and EtOAc providing 90:10 er (Table 7, Entries 20, 23 and 24), and TBME affording the product **316** in 91:9 er (Table 7, Entry 22), and up to 92:8 er when DME was used (Table 7 Entry 26), but unfortunatelly all these solvents significantly reduced the yield of **316**.

Table 7. Reaction optimisation.



313 **315** **316**

Entry	Solvent	T (°C)	Alkyne eq.	[c] (mol/L)	Yield 316[a] (%)	er[b]
1	DCE	40	5	0.2	47	83 : 17
2	DCE	40	5	0.5	49	86 : 14
3	DCE	40	10	0.5	58	87 : 13
4	DCE	40	5	1.0	53	87 : 13
5	DCE	40	10	2.0	50	89 : 11
6	DCE	rt	5	0.5	55	86 : 14
7	DCE	rt	10	0.5	66	88 : 12
8	*o*DCB	40	5	0.5	56	87 : 13
9	TFE	40	5	0.5	37	85 : 15
10	HFIP	40	5	0.5	no reaction	N/A
11	1,4-dioxane	40	5	0.5	trace	N/A
12	THF	40	5	0.5	trace	N/A
13	DCM	40	5	0.5	58	84 : 16
14	DMF	40	5	0.5	no reaction	N/A
15	Et_2O	40	5	0.5	47	88 : 12
16	HFB	40	5	0.5	41	84 : 16
17	DME	40	5	0.5	32	90 : 10

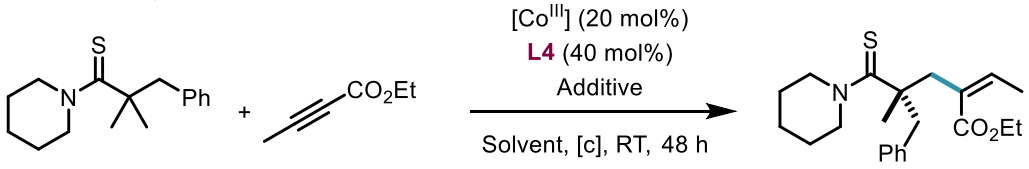
Entry	Solvent	T (°C)	Alkyne eq.	[c] (mol/L)	Yield 316[a] (%)	er[b]
18[c]	DCE	rt	5	0.5	74	86 : 14
19	DCE	rt	5	0.5	64	86 : 14
20	Et_2O	rt	5	0.5	53	90 : 10
21	*o*DCB	rt	5	0.5	76	88 : 12
22	TBME	rt	5	0.5	47	91 : 9
23	CPME	rt	5	0.5	30	90 : 10
24	EtOAc	rt	5	0.5	46	90 : 10
25	TFEtOAC	rt	5	0.5	58	89 : 11
26	DME	rt	5	0.5	23	92 : 8

General conditions: **313** (0.05 mmol). [a]Isolated yield after silica gel column chromatopraphy [b]Determined by chiral HPLC analysis. [c]Reaction time 36 h.

Our next step was to study whether different alkynes, used as solvents, would stabilise the coordination of cobalt catalyst into the thioamide, and subsequently increase the conversion of **313** to **316**, however none turned out to be successful (Table 8, Entries 1-4). At the same time, we considered the possibility of a trace amount of water, poisoning the catalyst during the reaction and if that being the reason, why we are not able to achieve better reactivity. Yoshino and Matsunaga reported[146] the utility of MS13X, as special type of molecular sieves powder, to aid the conversion in C–H amidation, therefore the addition of molecular sieves powder MS 4Å to the reaction mixture was tested. A small increase in yield of desired **316** was achieved, when THF was utilised as the reaction solvent, affording 31% yield and great 92:8 er (Table 8, Entry 5), while previously without MS 4Å only a trace product was observed.The addition of molecular sieves powder with *o*DCB as solvent afforded desired **316** in 78% yield and retained 88:12 er (Table 8, Entry 7). Interestingly, we noticed a trend,

that prolonged length of the ether-type solvent positively affected the selectivity. To confirm our observations, the reaction was run in diglyme, achieving excellent 94:6 er (Table 8, Entry 9). The data analysis suggested a two-solvent system, to find a perfect ratio between the reactivity and selectivity, therefore a set of experiments was performed with *o*DCB and TBME, diglyme and tetraglyme in 1:1 or 9:1 ratio. In correlation with our hypothesis, all of the solvent combinations led to 57-71% yield, 90:10 er (Table 8, Entries 11, 13-15), apart from *o*DCB/TBME (1:1) that afforded the product in 50% yield and 92:8 er (Table 8, Entry 10). Observing the encouraging effect of the ether-type solvents on selectivity, we focused on finding alternative additives that could exhibit similar effect as ether-type solvents, but reduce the negative impact on the reactivity. We realised that crown ethers, as solid additives, present a viable option due to the structural similarities with ether-type solvents. Therefore 18-crown-6 in 20, 50 and 100 mol% loading, was added into the reaction mixture, leading to 75%, 70% and 65% yield and 89:11, 89:11 and 90:10 er, respectively (Table 8, Entries 16-18). Seeing that the catalytic addition (20 mol%) of crown ether slightly improved the selectivity, while held the yield at 75%, the next step was screening the catalytic addition (20 mol%) of other readily available crown ethers, 15-crown-5 and dibenzo-18-crown-6, which yielded alkylated thioamide **316** in 61% and 74% and 88:12 er in both cases (Table 8, Entries 19 and 20). All the experiments led to the optimal conditions being; at room temperature, in *o*DCB with 20 mol% of 18-crown-6 and MS13X, and therefore our next step was to explore the possibilities of novel amino acid-derived ligands, in order to achieve even better selectivity.

Table 8. Reaction optimisation.



313 **315** **316**

Entry	Solvent	Additive	[c] (mol/L)	Yield 316[a] (%)	er[b]
1	4-octyne	none	0.5	no reaction	N/A
2	1-hexyne	none	0.5	no reaction	N/A
3	MeCN	none	0.5	no reaction	N/A
4	3-hexyne	none	0.5	15	86 : 14
5	THF	MS 4Å	0.5	31	92 : 8
6	TBME	MS 4Å	1.0	51	91 : 9
7	*o*DCB	MS 4Å	0.5	78	88 : 12
8	DME	MS 4Å	0.5	32	90 : 10
9	diglyme	MS 4Å	0.5	15	94 : 6
10	*o*DCB:TBME (1:1)	MS 4Å	0.5	50	92 : 8
11	*o*DCB:TBME (9:1)	MS 4Å	0.5	62	90 : 10
12	*o*DCB	MS13X	0.5	78	88 : 12
13	*o*DCB:diglyme (1:1)	MS13X	0.5	57	90 : 10
14	*o*DCB:diglyme (9:1)	MS13X	0.5	71	90 : 10
15	*o*DCB:tetraglyme (9:1)	MS13X	0.5	68	90 : 10

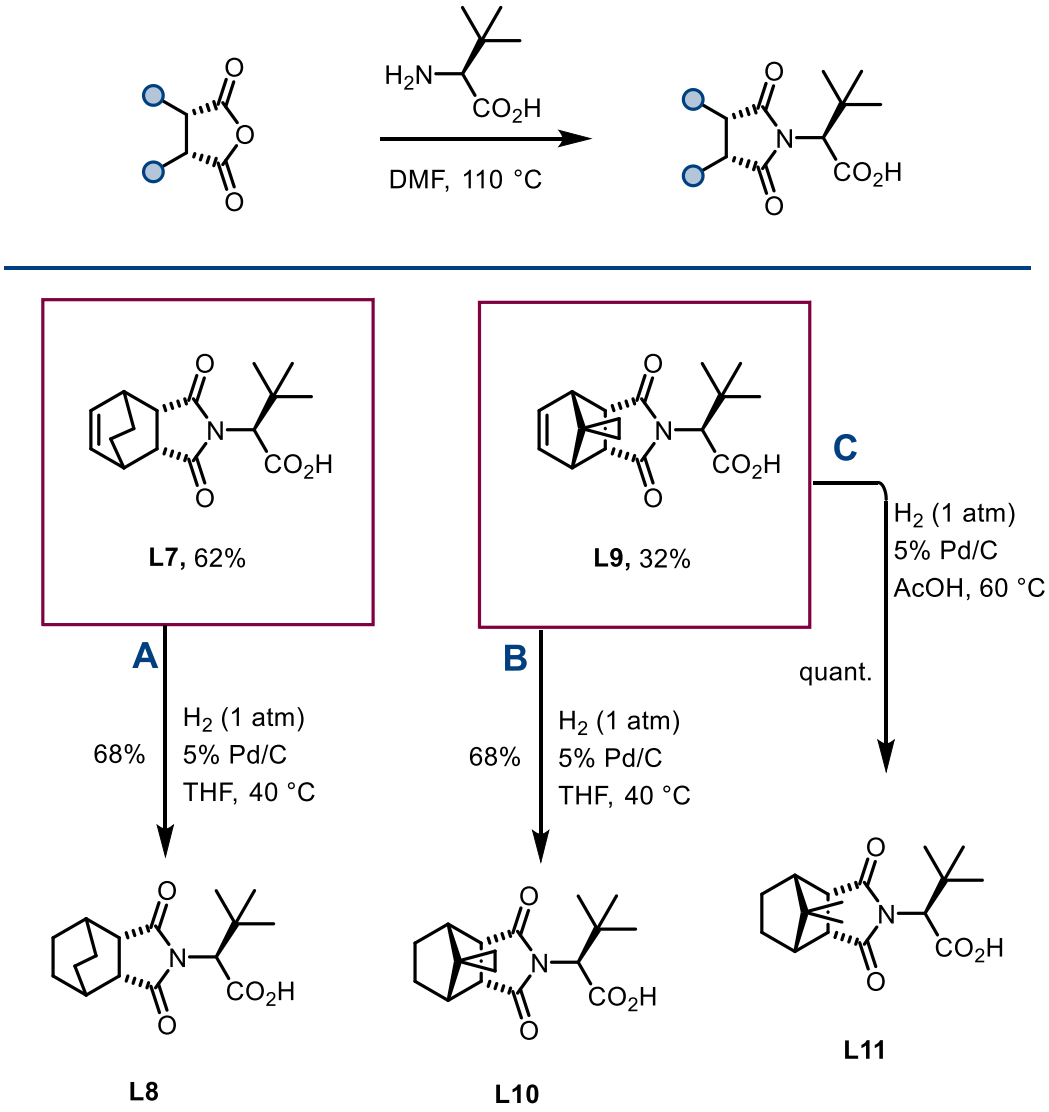
Entry	Solvent	Additive	[c] (mol/L)	Yield 316[a] (%)	er[b]
16	**oDCB**	**MS13X, 18-crown-6 20 mol%**	**0.5**	**75**	**89 : 11**
17	*o*DCB	MS13X, 18-crown-6 50 mol%	0.5	70	89 : 11
18	*o*DCB	MS13X, 18-crown-6 100 mol%	0.5	65	90 : 10
19[c]	*o*DCB	MS13X, 15-crown-5 20 mol%	0.5	61	88 : 12
20[c]	*o*DCB	MS13X Dibenzo-18-crown-6 20 mol%	0.5	74	88 : 12

General conditions: **313** (0.05 mmol), **315** (0.25 mmol). [a]Isolated yield after silica gel column chromatography [b]Determined by chiral HPLC analysis. [c]Performed at 33 °C.

2.5.4 Design and development of novel unnatural amino acid-derived ligands for Co^{III}-catalysed C(sp^3)–H alkenylation of thioamides

During the optimisation of reaction conditions, we considered new motifs for the same type of ligands as the current best *L-tert*-leucine derived ligands **L3** and **L4**. First, 1,3-cyclohexadiene was reacted with maleic anhydride to form desired anhydride species, that was consequently condensed with *L-tert*-leucine to form **L7** in 62% yield. Carboxylic acid **L7** was then submitted to hydrogenation catalysed by Pd on carbon, to yield **L8** in 68% (**Scheme 89A**). In a similar fashion, cyclopentadiene with spirocyclic cyclopropane was reacted with maleic anhydride to form the corresponding anhydride that was then condensed with *L-tert*-leucine to form ligand **L9** in 32% yield. **L9** Was then submitted to two different sets of hydrogenation conditions, to form **L10** under our standard conditions in 68% yield

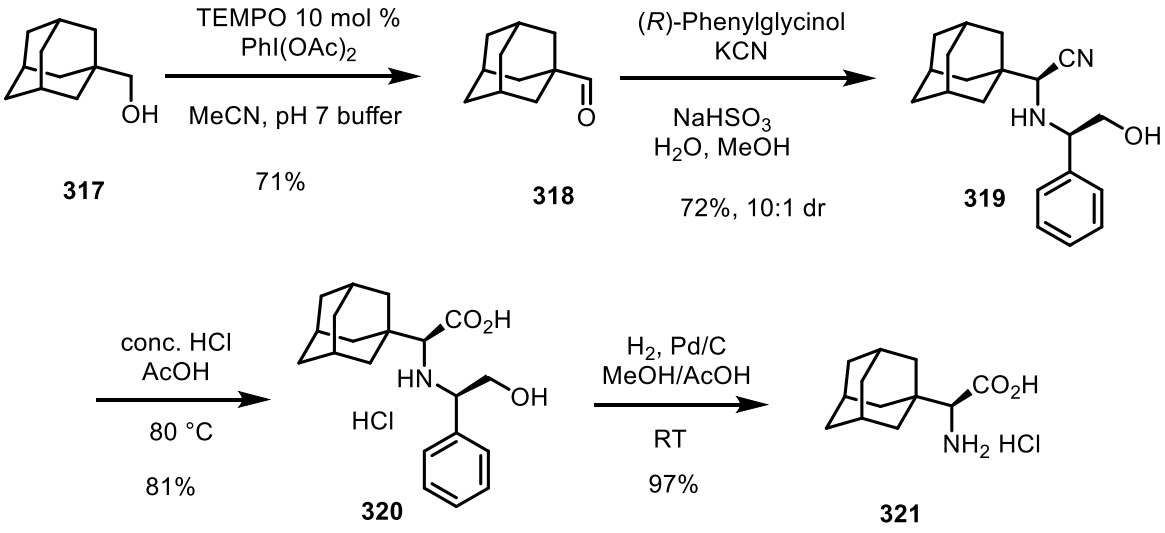
(**Scheme 89B**), and to form **L11** while running the reaction in acetic acid instead of THF at 60 °C quantitatively (**Scheme 89C**).



Scheme 89. Synthesis of novel chiral ligands for enantioselective C(sp^3)–H alkenylation.

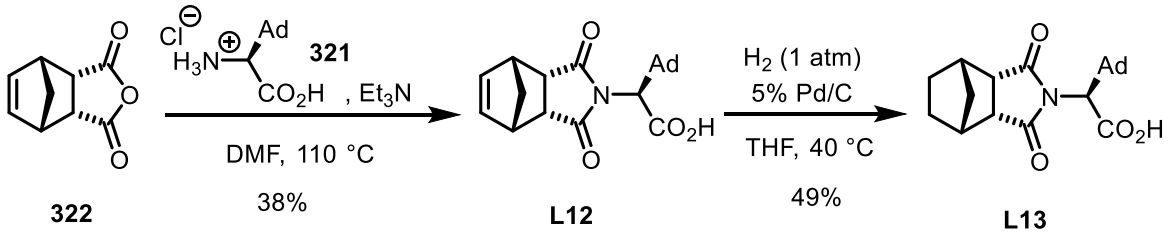
Next, we looked to exchange *L-tert*-leucine for different unnatural bulky amino acids, such as adamantanyl aminoacetic acid **321**. Therefore, firstly we needed to synthesise amino acid **321**. The synthesis was commenced with the radical oxidation of 1-adamantanemethanol **317** to adamantane-1-carbaldehyde **318** with TEMPO in 71% yield. This aldehyde was then transformed into secondary amine **319** *via* reductive amination with *(R)*-phenylglycinol in

72% and 10:1 dr. The nitrile group of the amine **319** was subsequently hydrolysed to afford the carboxylic acid **320** in 81% yield. Finally, hydrogenation over Pd/Cto revealed the desired hydrochloride salt of adamantanyl aminoacetic acid **321** in 97% yield (**Scheme 90**).



Scheme 90. Synthesis of adamantyl-derived amino acid **321**.

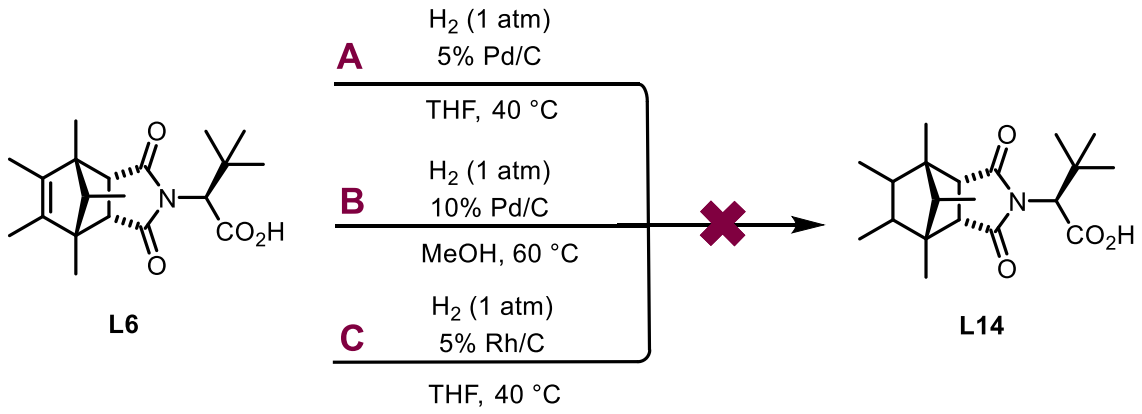
With **321** in hand, we then submitted it to the condensation with cis-5-norbornene-endo-2,3-dicarboxylic anhydride **322** to form ligand **L12** in 38%, which was followed by hydrogenation under our standard conditions, to afford **L13** in 49% yield (**Scheme 91**).



Scheme 91. Synthesis of novel chiral ligands **L12** and **L13**.

One of our efforts throughout the ligand synthesis was to fully hydrogenate the previously prepared bulky ligand **L6**. Under our standard conditions with 5 mol% of Pd/C the starting material we fully recovered (**Scheme 92A**), therefore 10 mol% of Pd/C in methanol at 60

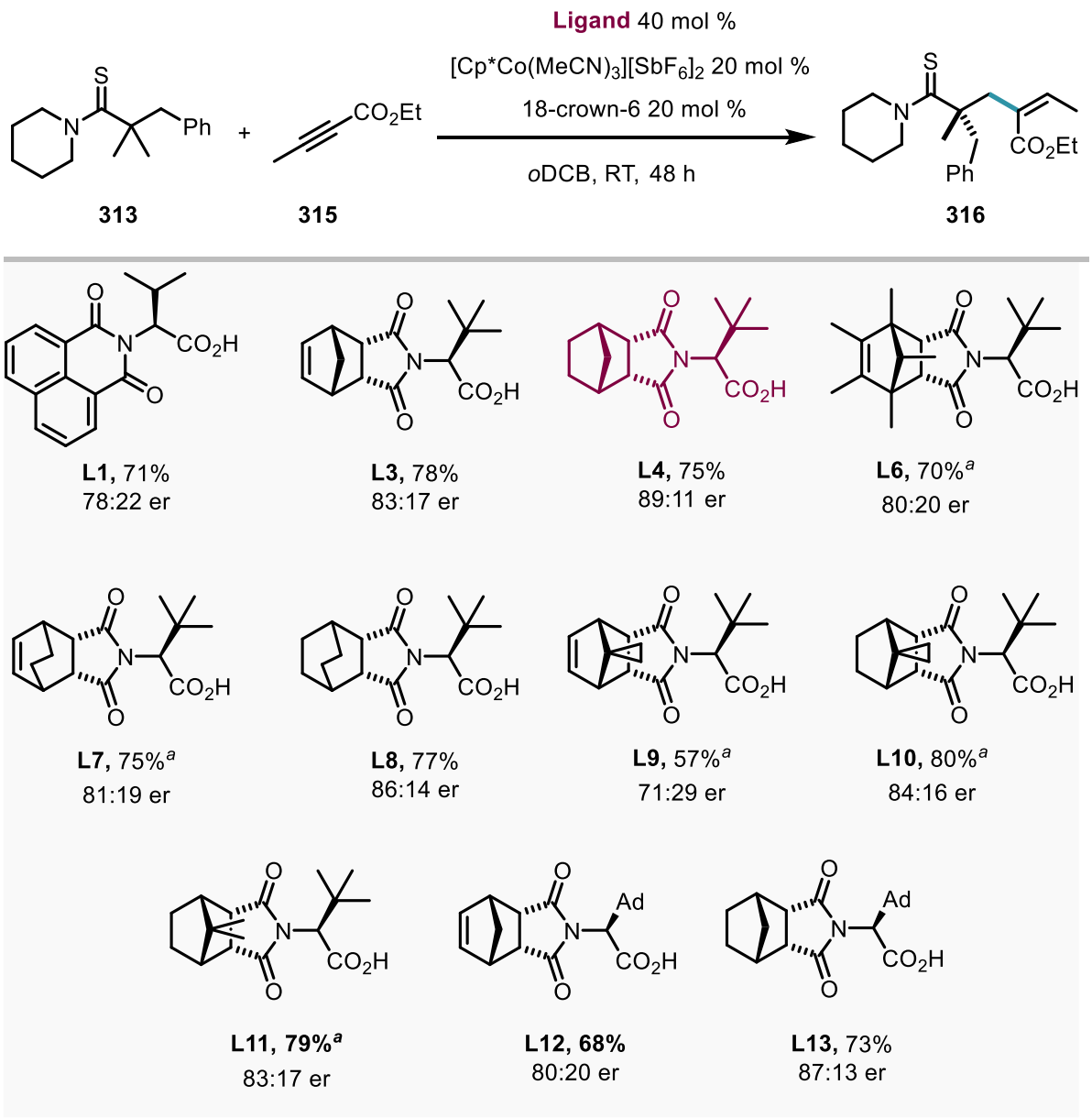
°C as well as 5 mol% of stronger Rh/C were tested (**Scheme 92B-C**). Unfortunately, none of these experiments led to the desired product **L14**, and as the initial enantiomeric ratio with **L6** was not the best out of our previous ligand screen, we decided to focus on different ligands.



Scheme 92. Unsuccessful attempts to hydrogenate **L6**.

Having a library of newly designed and prepared ligands, we were ready to test them under our current best conditions for this thioamide directed C(sp^3)–H alkenylation (**Scheme 93**). First, we tested *L*-valine derived ligand **L1**, with which we were able to achieve 71% yield and 78:22 er. Second, to this point, the best ligands **L3** and **L4** were tested, and yielded desired thioamide **316** in 78% and 75% yield, 83:17 and 89:11 er, respectively. We added to the screening previously tested **L6**, however we were only able to achieve 80:20 er. Structure-wise very similar to our current best ligand, **L7** and **L8** were screened, to form product **316** in 75%, 81:19 er with **L7** and 77%, 86:14 er with **L8**, implying that the incorporation of more symmetry into the ligand takes away its enantiocontrolling abilities. Therefore, the next set of ligands, instead of being more symmetrical on the bicyclic core, feature different substitution on the bridgehead of the 5-membered cycle. Ligand **L9** decreased the reactivity to 57% and selectivity to 71:29 er, while fully hydrogenated **L10**

and **L11** afforded 80% and 79%, and 84:16 and 83:17 er, of the desired thioamide **316**, respectively. Seeing that all manipulations around bicyclic core only resulted in lower enantiomeric ratio, we decided to keep the core from **L4** and exchange *L-tert*-leucine for different bulky amino acid. Based on previous experiments, we could see that sterically less demanding *L*-valine derived ligands were slightly less favoured for the enantioselectivity of our transformation. Steric occupancy of a *tert*-butyl group in space is only slightly bigger than that of an adamantyl group, therefore adamantanyl derived ligands **L12** and **L13** were synthesised, in the hope to gain better selectivity. As expected, **L12** yielded **316** in 68% and 80:20 er, while fully hydrogenated **L13** afforded great 73% and 87:13 er. Unfortunately, even ligand **L13** did not exceed the current best carboxylic acid **L4** (75%, 89:11 er), therefore we decided to finish the optimisation and employ **L4** in our transformation.



Scheme 93. Further ligand screening for enantioselective C(sp^3)–H alkenylation. General conditions: **313** (0.05 mmol), **315** (0.25 mmol). [a]*Without 18-crown-6.*

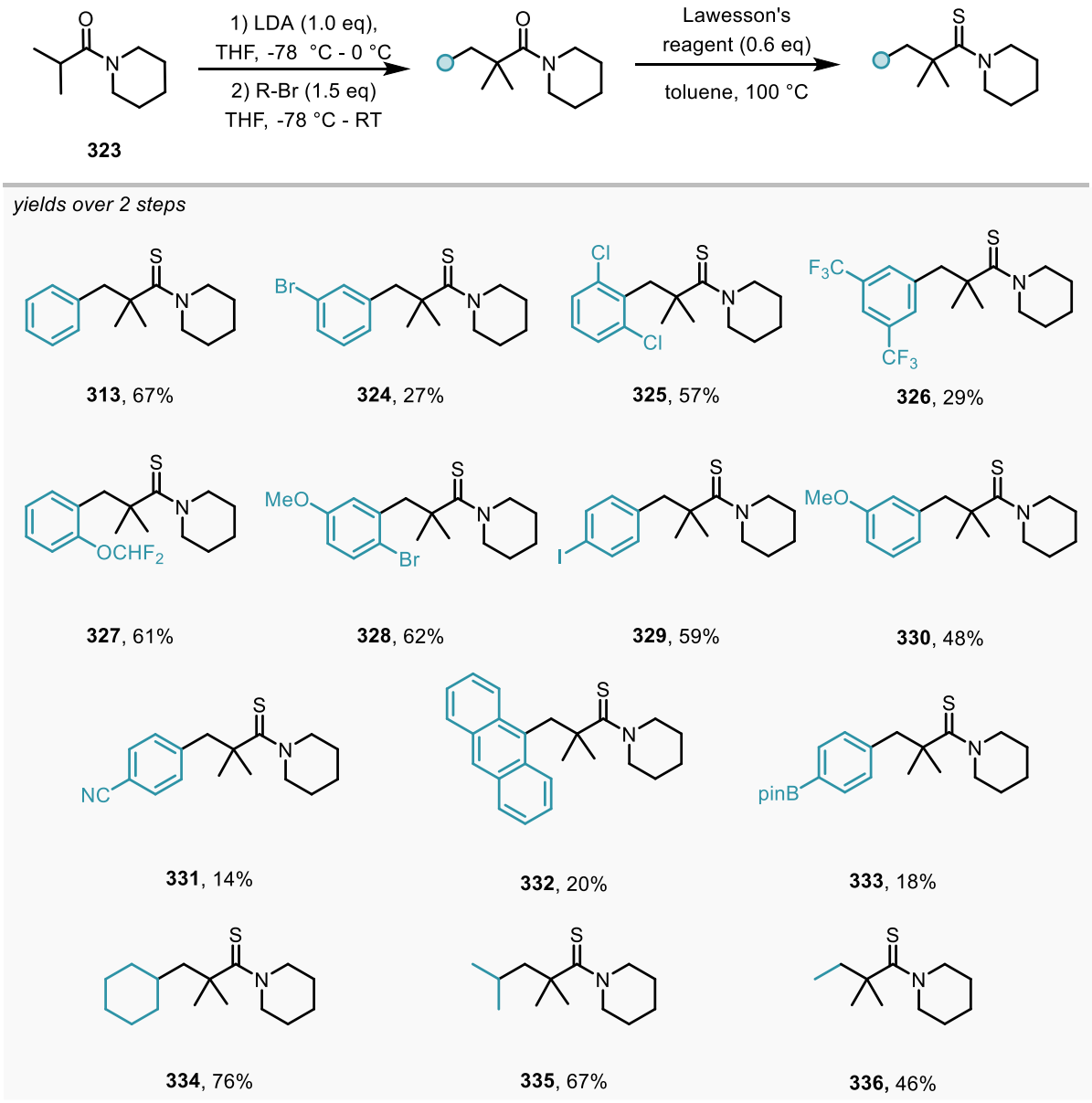
2.6 Reaction scope

2.6.1 Starting material synthesis

Having our transformation successfully optimised for the model substrate **313**, we were ready to test the applicability of our reaction on a broad scope of various thioamides. Therefore firstly, a library of differently substituted thioamides was synthesised.

Starting with variations of the *β*-position of the thioamide, 13 freshly prepared starting materials were obtained (**Scheme 94**). In general, 1-isobutyrylpiperidine **323** was deprotonated with LDA, which after the following addition of corresponding benzyl bromide furnished the desired amide, which was subsequently transformed to the corresponding thioamide with Lawesson's reagent. All yields are reported over the two-step sequence. With this strategy, a range of *ortho-, meta-* and *para-* substituted halogenated starting materials were prepared to probe mesomeric and steric effects. Starting materials, *meta*-bromobenzyl derivative **324**, *ortho*-di-chlorobenzyl derivative **325**, *meta*-di-trifluoromethylbenzyl derivative **326**, *ortho*-($OCHF_2$)-benzyl derived substrate **327**, as well as *ortho*-bromo-*meta*-methoxy benzyl derived substrate **328** and *para*-iodobenzyl derived **329** were readily synthesised. We were also able to prepare *meta*-methoxybenzyl derived substrate **330** in 48% yield, and surprisingly, even *para*-nitrile derived **331** was isolated, albeit in 14% yield. The low yield was due to the side reaction of Lawesson's reagent and nitrile group of the substrate, that led to the formation of another primary thioamide derived from the nitrile group. Using this method, we were also able to obtain bulky anthracene derived thioamide **332** in 20% yield, as well as pinacol boronate-containing substrate **333** in 18% yield. We also wanted to test our reaction on α-substituted alkyl derivatives, therefore

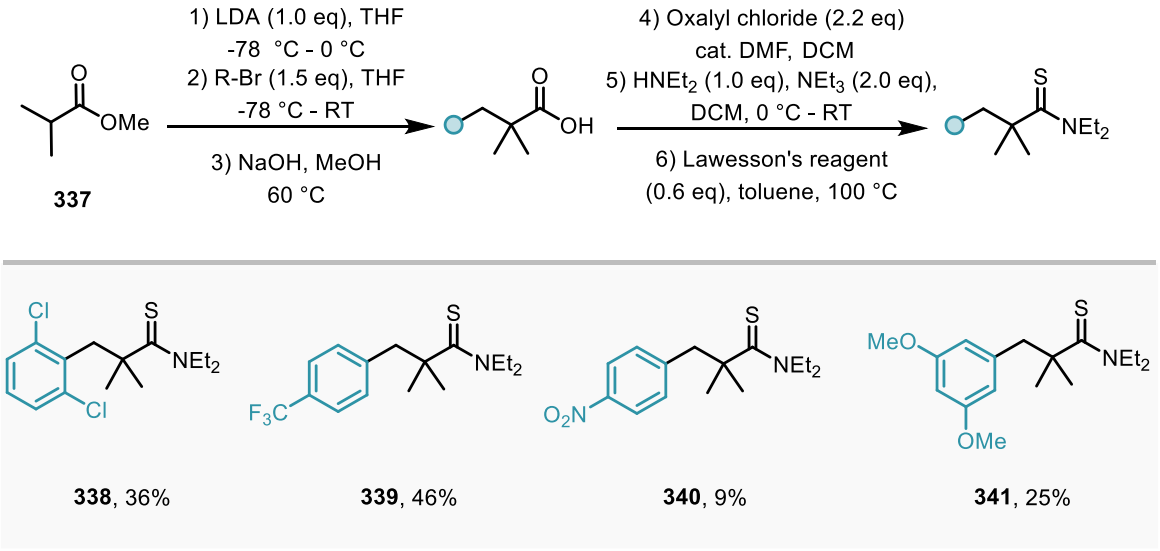
cyclohexyl- **334**, isopropyl- **335** and ethyl- **336** derived starting materials were synthesised in 67-76% yield.



Scheme 94. Synthesis of starting materials with variations to the *α*-benzyl position of the thioamide.

To explore the applicability of our method at an early stage, before enantioselective optimisation, we wanted to confirm the versatility of the transformation with respect to the substrate functionality. Therefore, a small substrate scope was prepared containing dichloro-

338, trifluoromethyl- **339**, nitro- **340** and methoxy- **341** functional groups in 36%, 46%, 9% and 25% yield, respectively (**Scheme 94**).[3]

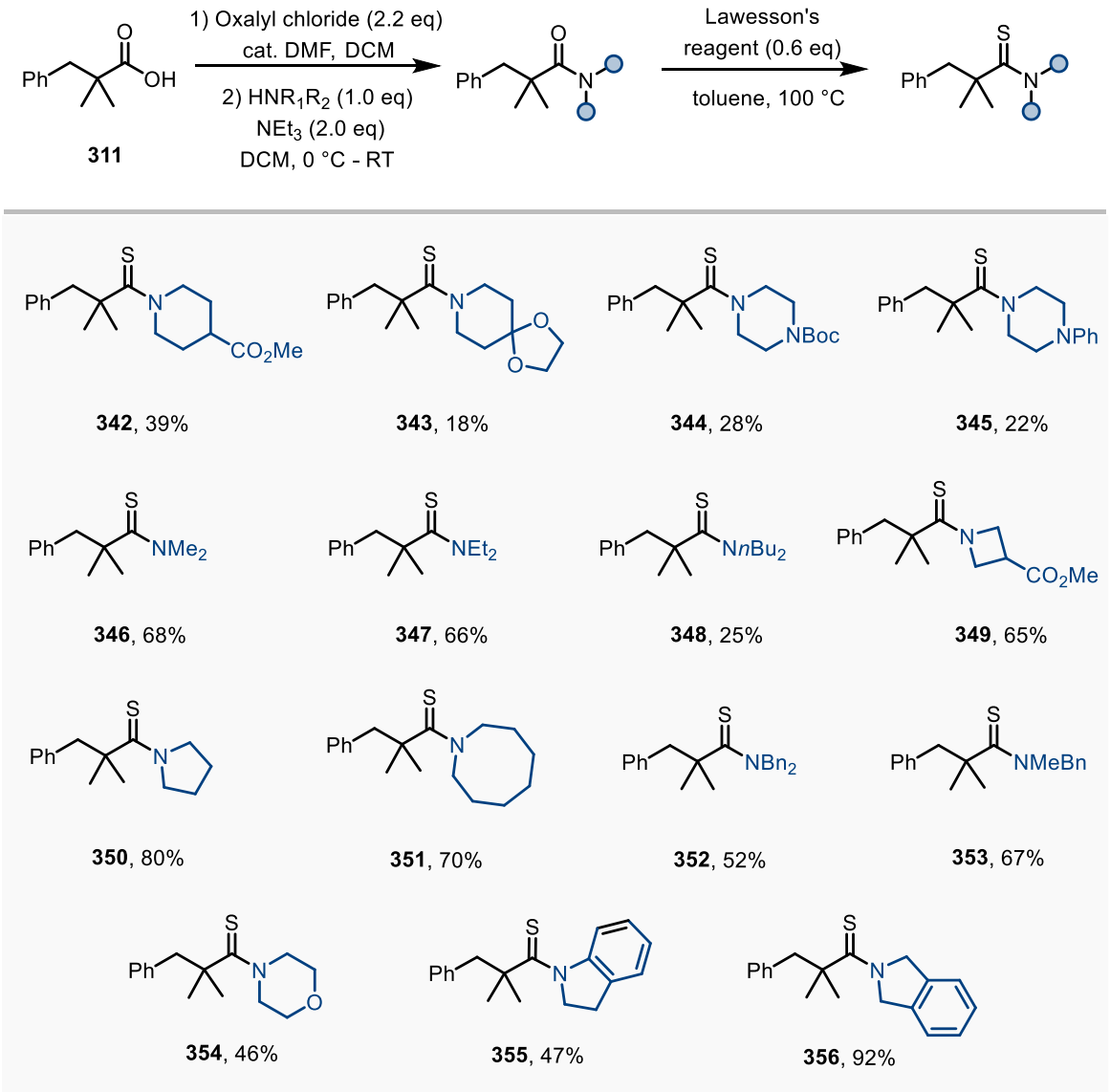


Scheme 95. Synthesis of starting materials with variations tothe *α*-benzyl position of the thioamide.

To probe the effects of the amide substituents, a library of differently-substituted amide derivatives was synthesised. These were all prepared using 2,2-dimethyl-3-phenylpropanoic acid **311**, which was promptly transformed into its highly reactive acid chloride. A nucleophilic substitution, using the corresponding amine then followed, what yielded the desired amide. Next, simple amide to thioamide transformation with Lawesson's reagent furnished substrates **342-356** (**Scheme 96**). We were able to prepare methyl ester functionalised piperidine **342** as well as diol-protected piperidine derived compound **343** in 39% and 18% yields, respectively. Furthermore, we were able to achieve *N*-boc **344** and *N*-Ph **345** protected piperazine substrates in 28% and 22% yield, respectively. The effect of the length of the alkyl chain on the thioamide functionality could be unveiled by comparing the

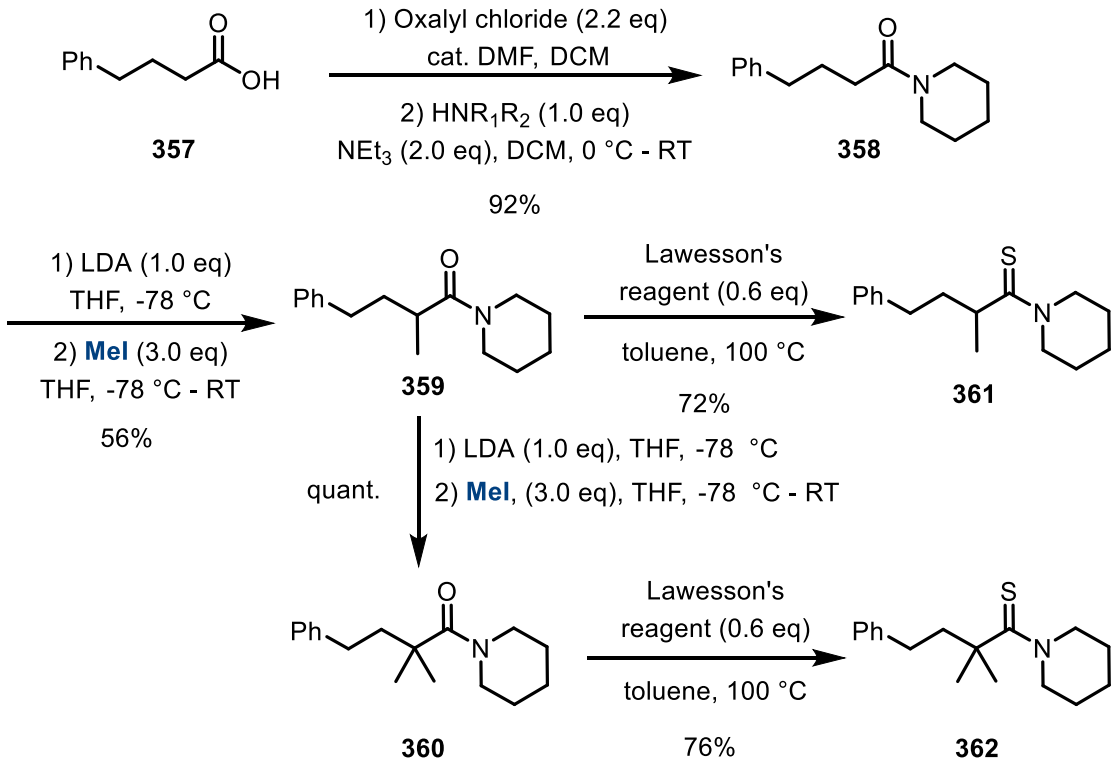
[3] Substrates were prepared in collaboration with Dr Heyao Shi and all results are included for completeness.

dimethyl- **346**, diethyl- **347**, *n*-butyl- derived **348**, as well as cyclic azetidine- **349**, pyrrolidine- **350**, azocane- **351** or dibenzyl functionalised substrate **352**. These were prepared in 68%, 66%, 25%, 65%, 80%, 70% and 52% yield, respectively. To probe the transformation when applied to an unsymmetrical substrate, thioamide **353** was prepared in 67%. To see the effect of different heterocyclic moieties, morpholine **354**, indoline **355** and isoindoline derivatives **356** were synthesised in 46%, 47% and 92% yield, respectively.



Scheme 96. Synthesis of starting materials with variations to the thioamide.

In order to test a longer alkyl chain in our methodology, a different approach was taken into consideration. Starting from phenylbutanoic acid **357**, which, was initially transformed to the corresponding amide **358** in 92% yield, *in situ* prepared LDA was then used to deprotonate the amide, and methyl iodide was added to form **359** in 56%, and this monomethylated amide was submitted to the LDA deprotonation, followed by a second methylation with MeI to gain dimethylated amide **360** quantitatively. Both amides were then transformed to the corresponding thioamides **361** and **362** in 72% and 76% yield, respectively (**Scheme 97**).



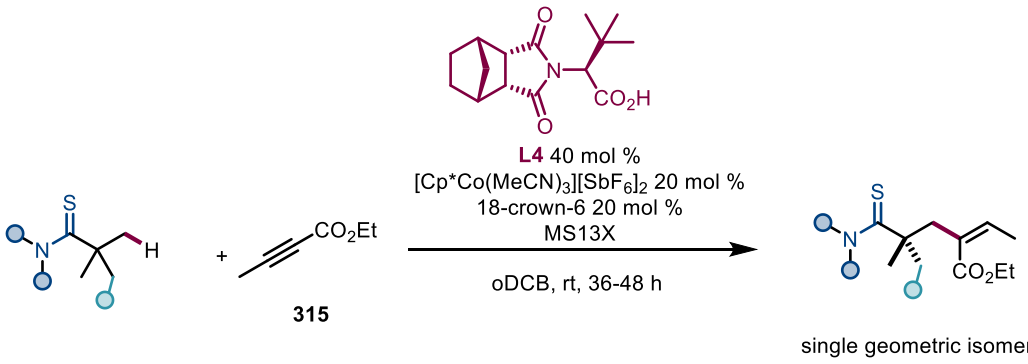
Scheme 97. Synthesis of substrates **361** and **362** for enantioselective C(sp^3)–H alkenylation.

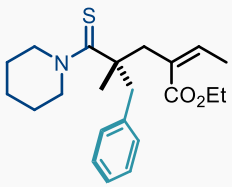
2.6.2 Application of starting materials with regards to the variation of the α-benzyl/alkyl substitution of thioamides

Having prepared a large variety of α-substituted starting materials, screening of the applicability of our transformation with respect to the prochiral thioamides was commenced (**Scheme 98**). All scope examples were obtained as single regioisomers, unless stated otherwise. Benzyl substituted thioamides bearing various electron-withdrawing and electron-donating functional groups on the aromatic ring were well tolerated, achieving the corresponding desymmetrised products in good yield and enantioselectivity. Halides in all *ortho-, meta-,* and *para-* positions allowed the formation of the corresponding products **363-367** in good to excellent 69-82% yields and 86:14–89:11 er. Direct comparison of **364** and **365** revealed a cyclic thioamide **325** to be more advantageous for enantioselectivity (89:11 er vs 86:14 er), while diethyl thioamide **338** allowed the formation of the desired product with better reactivity (71% vs 82%).

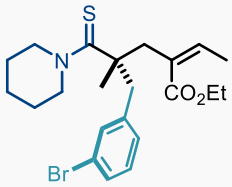
Trifluoromethyl-substituted aromatic rings **368** and **370** as well as *o*-$OCHF_2$ **369** gave 76%, 68% and 73% yield with 85:15, 88:12 and 87:13 er, respectively. Nitrogen containing functional groups on the benzyl group, such as nitrile and nitro, were tolerated under the reaction conditions and afforded alkenylated thioamides **371** and **372** both in 71% yield, and excellent 90:10 and 91:9 er. Both of these functional groups present important motifs, as various *N*-containing moieties are often present in pharmaceuticals[153] and agrochemicals.[154] Both 3-methoxy and 3,5-dimethoxy substituted products **373** and **374** were obtained in 69%, 73% yield with 89:11, 85:15 er, respectively. Sterically demanding anthracene derived substrate **333** was well tolerated, giving the desired alkenylated product **375** in good 68% yield and 89:11 er. Pleasingly, and despite potential incompatibility issues with boronic ester

bearing thioamide **334**, pinacol boronate-containing product **376** was delivered in 43% with 88:12 er, providing the opportunity for subsequent cross-coupling reactions, such as Suzuki couplings.[155]

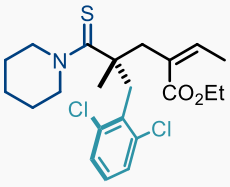




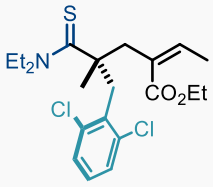
316, 75%
89:11 er



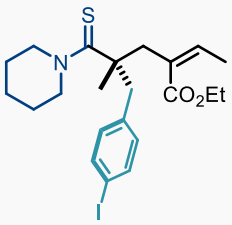
363, 72%
86:14 er



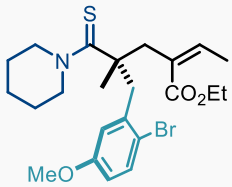
364, 71%
89:11 er, (>99:1 er)[a]



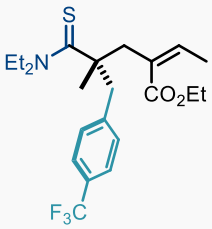
365, 82%
86:14 er



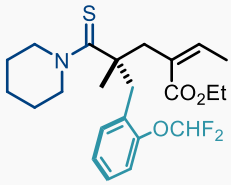
366, 69%
88:12 er



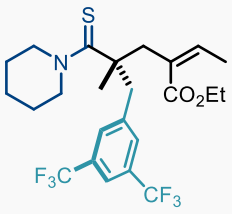
367, 80%
89:11 er, (>99:1 er)[a]



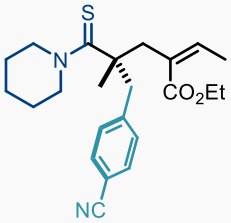
368, 76%
85:15 er



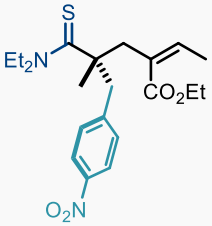
369, 73%
87:13 er, (>99:1 er)[a]



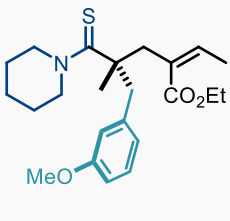
370, 68%
88:12 er



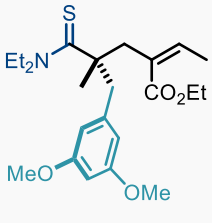
371, 71%
90:10 er



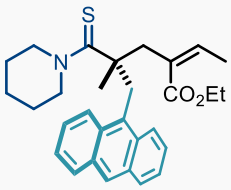
372, 71%
91:9 er



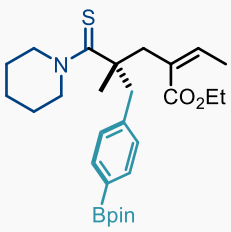
373, 69%
89:11 er



374, 73%
85:15 er



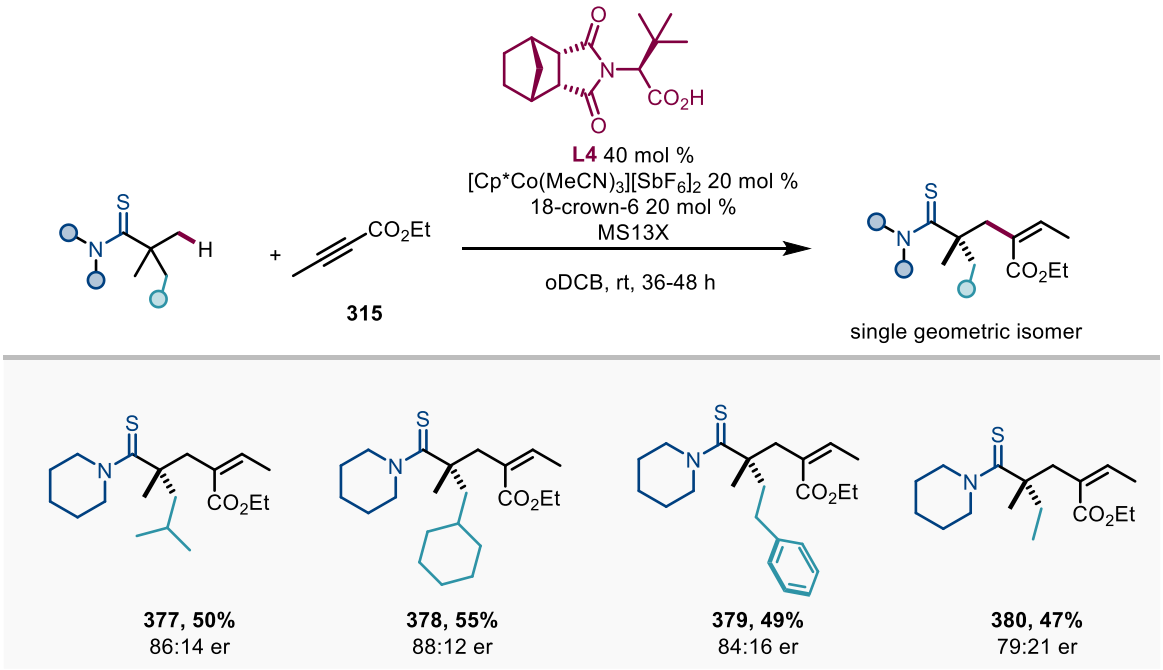
375, 68%
89:11 er



376, 43%
88:12 er

Scheme 98. Reaction scope of starting materials with variations to the *α*-benzyl position of the thioamide. General conditions: substrate (0.20 mmol), **315** (1.00 mmol) [a]After recrystallisation from Et_2O/pentane.

Furthermore, α-alkyl substituted thioamides were also successful in this methodology (**Scheme 99**). Isopropyl- **377**, cyclohexyl- **378** and 2-phenylethyl- **379** substituted thioamides provided the alkenylated products in 50%, 55% and 49% yield and 86:14, 88:12 and 84:16 er, respectively. Prochiral ethyl- substituted thioamide **337**, showed a slight decrease in reactivity (47% yield, 79:21 er), however no C–H functionalisation of the ethyl group was observed, highlighting the exquisite selectivity of present alkenylation.

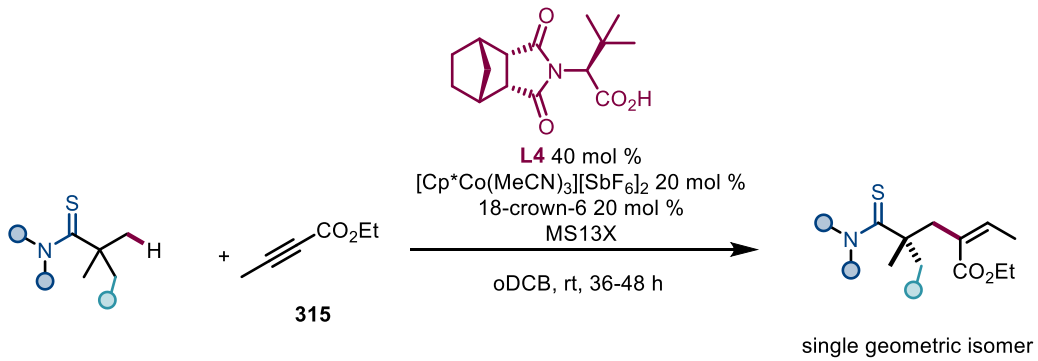


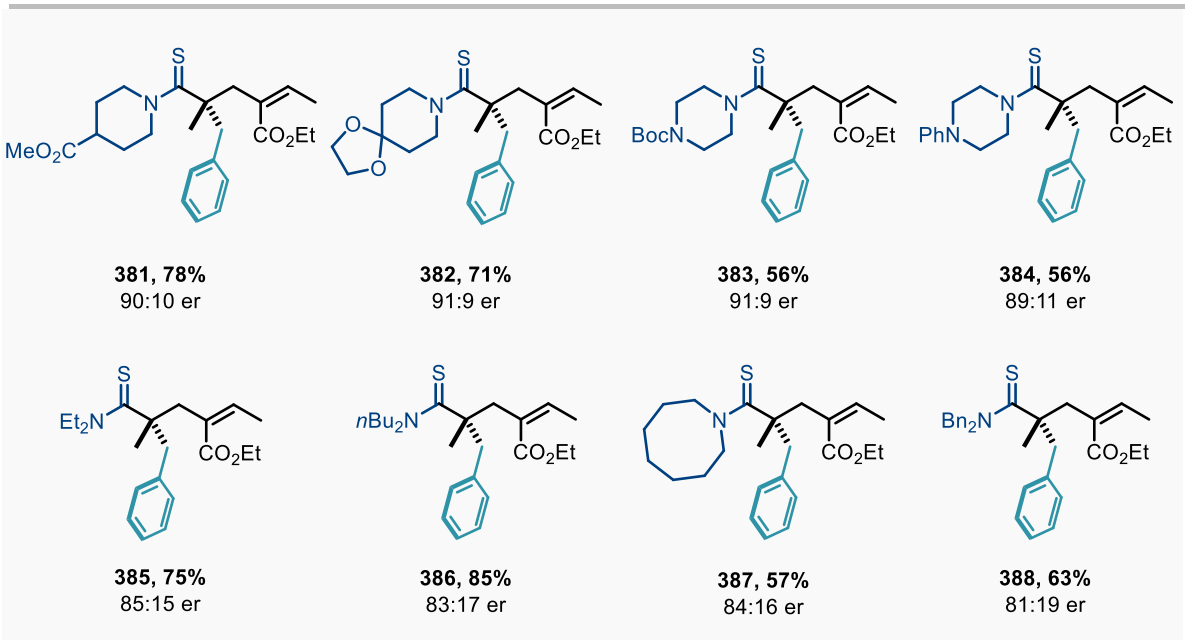
Scheme 99. Reaction scope of starting materials with variations to the *α*-alkyl position of the thioamide. General conditions: substrate (0.20 mmol), **315** (1.00 mmol).

2.6.3 Application of starting materials with regards to the variation of the thioamides

The scope with respect to the amide component of the thioamide was found to be broad, tolerating a wide range of different functional groups as well as differently sized cyclic and linear alkyl side chains (**Scheme 100**). Methyl ester **381** and dioxolane **382** functionality on the piperidine ring provided high 78% and 71% yields, with excellent 90:10 and 91:9 er,

respectively. *N*-Phenyl and *N*-boc protected piperazines **383** and **384** both afforded the corresponding products in moderate yield, with great selectivity, 91:9 and 89:11 er, respectively. Excellent reactivity was observed with ethyl- and *n*-butyl- derived thioamides (**347**, **348**), affording the corresponding alkenylated thioamides **385** and **386** in 75% and 85% yield with slightly diminished enantioselectivities (85:15 and 83:17 er). Cyclic azocane-derived substrate **351** and di-benzyl thioamide **352** were also successful in this transformation, affording the corresponding products in 57%, 63% yield, and 84:16 and 81:19 er, respectively.

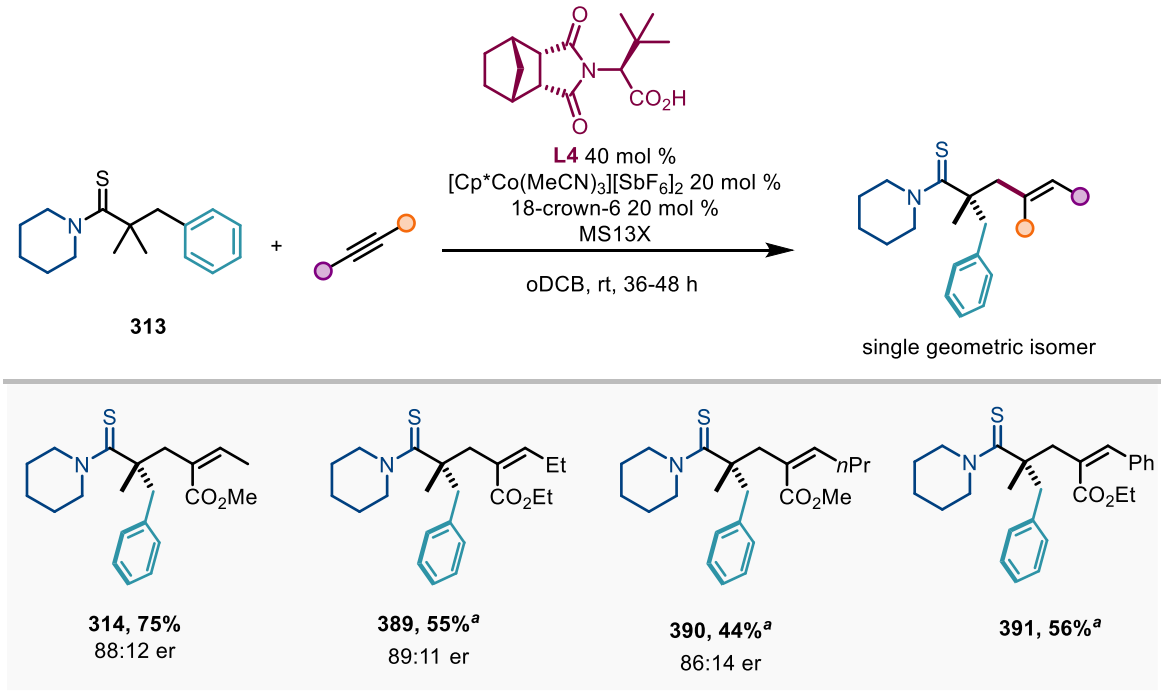




Scheme 100. Reaction scope of starting materials with variations to the thioamide. General conditions: substrate (0.20 mmol), **315** (1.00 mmol)

2.6.4 Application of different alkyne coupling partners

Finally, the reaction scope with respect to the alkyne coupling partners was evaluated (**Scheme 101**). Methyl but-2-ynoate **298** underwent the transformation similarly to the model system with ethyl but-2-ynoate **315**, displaying excellent yield (75%) and enantioselectivity of 88:12 er. Interestingly, when the methyl group on the alkyne was exchanged for the ethyl or *n*-propyl, reactivity was found to decreas significantly. However, doubling the catalyst loading afforded the desired thioamide **389** in 55% and product **390** in 44% yield, with 89:11 and 86:14 er, respectively. Using ethyl 3-phenylpropiolate as a coupling partner resulted in a 56% yield of **391**.

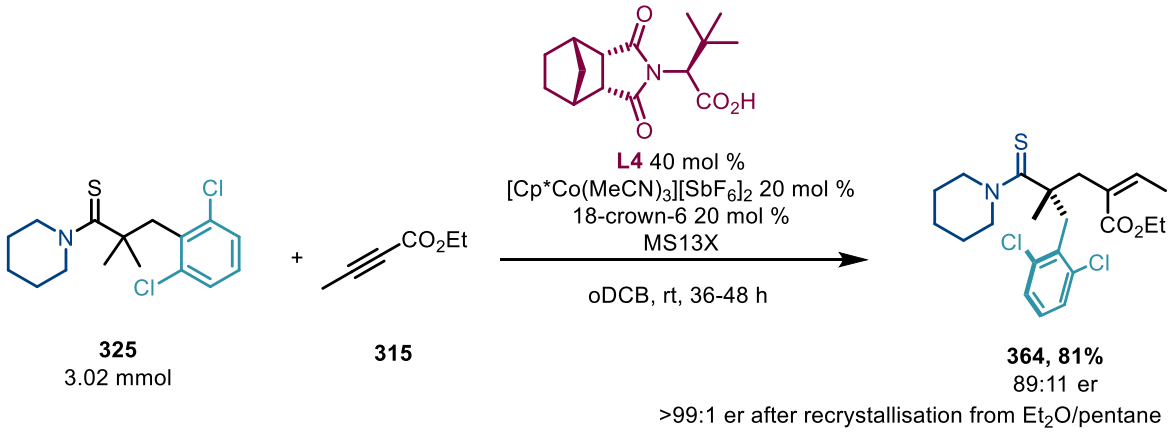


Scheme 101. Reaction scope of thioamide **313** with different alkynes. General conditions: **313** (0.20 mmol), alkyne (1.00 mmol) [a]With 40 mol% of catalyst.

2.6.5 Reaction scale-up

Having explored and established the reaction scope, the scalability of the transformation was explored. This was demonstrated on 1.0 g (3.02 mmol) scale using substrate **326** with ethyl

but-2-ynoate **315**. Performing the experiment on this scale allowed the formation of alkenylated thioamide **364** in an excellent 81% isolated yield and 89:11 er (**Scheme 102**). This experiment showcases the applicability of our methodology on a larger scale, providing a potential for industrial applications, as well as even larger scale transformations.



Scheme 102. Reaction scale-up to 3.02 mmol (1 g) and recrystallisation to >99:1 er.

2.6.6 X-Ray diffraction analysis

In order to confirm the relative and absolute configuration of our products, we faced a challenge to produce a single crystal suitable for X-ray diffraction. We found that a single recrystallisation of the rather amorphous solid of **364** led to the separation of the racemic and enantiopure material, furnishing >99:1 er. Unfortunately, in our case the racemate readily crystallised, providing single crystals suitable for X-ray analysis, while the enantiopure material remained in the mother liquor. Unfortunately, the same trend was observed during our attempts to recrystallise analogous products, therefore enantiomerically pure single crystals, suitable for the determination of the absolute stereochemical configuration, could not be obtained. Racemic single crystals, however, carry great value in the confirmation of the unusual regioselectivity of this method. The evaluated X-ray structures of selected scope examples **364**, **367**, and **369** are summarised in **Figure 7**.

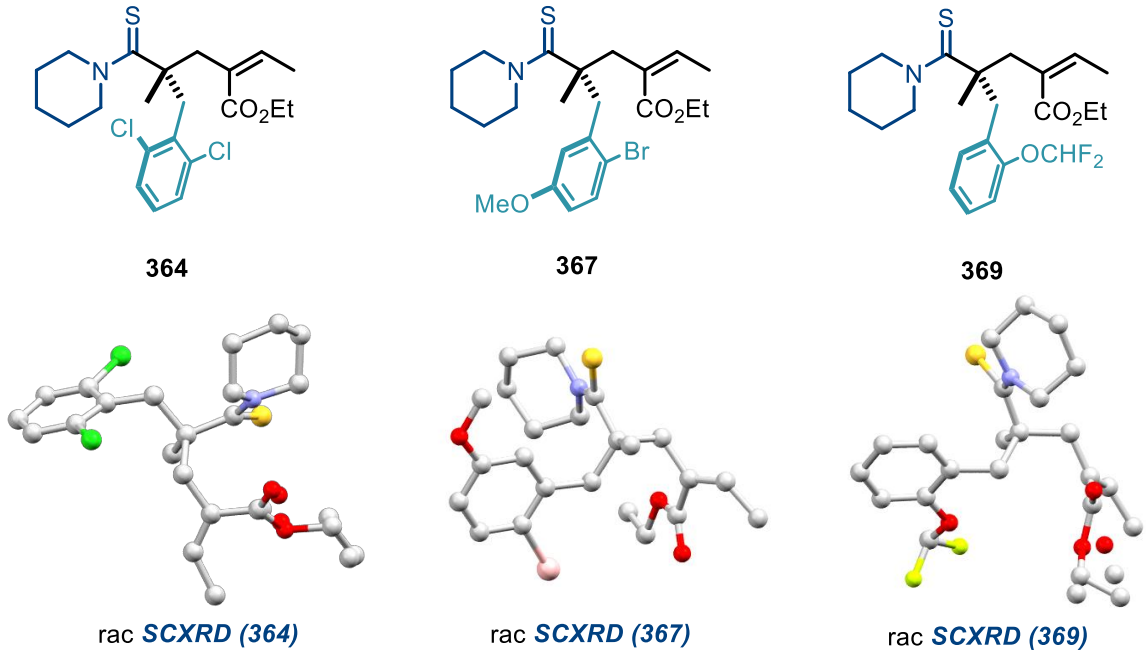
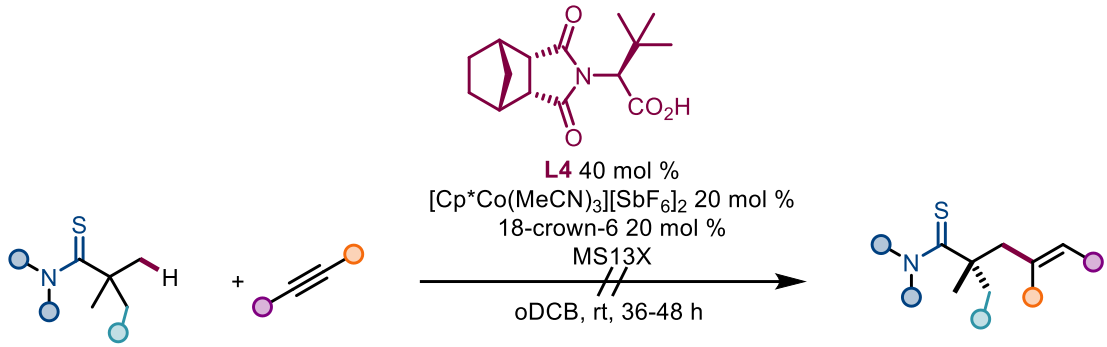


Figure 7. Single crystal X-ray diffraction of racemic products **364, 367, 369**.

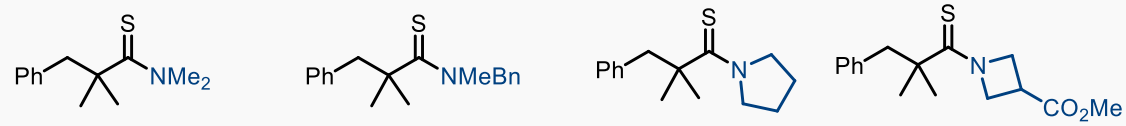
2.6.7 Unsuccessful scope examples

Out of all the thioamide starting materials submitted to the reaction conditions, some proved to be incompatible with our methodology (**Scheme 103A**). For instance, dimethyl thioamide **346** did not allow for the transformation to occur, furthermore *N,N*-benzyl-methyl thioamide **353** showed a similar diminished reactivity, suggesting that the presence of a methyl group changes the nucleophilicity of the substrate significantly. Similarly, pyrrolidine and azetidine derived substrates **350-351** are probably too nucleophilic on the nitrogen, and therefore stop the reaction. Further unsuccessful examples include different heterocyclic moieties on the thioamide, such as morpholine- **354**, indoline- **355** and isoindoline- **356**. Another unsuitable substrate is mono- methylated thioamide **361**, which showed no trace of the product in the reaction mixture. On the other hand, a range of various alkyne coupling partners were submitted to the reaction conditions and many proved to be inactive (**Scheme**

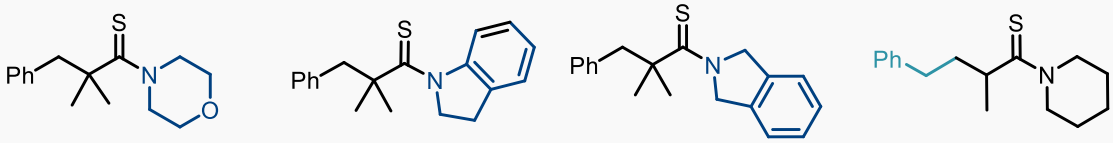
103B). Symmetrical dimethyl **392** and diethyl **393** but-2-ynedioates to our surprise did not form the products, similarly to secondary **394** and tertiary **395** amides on the alkyne. Exchanging shorter and smaller methyl- group in the but-2-ynoate for benzyl **396**, as well as for trifluoromethyl- **397** or trimethylsilyl- **398** also led to no product formation. Finally, allene-containing coupling partner **399**, proved to be incompatible with this methodology.



A *Unsuccessful thioamides*

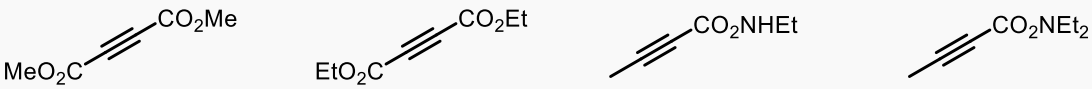


346 **353** **350** **349**



354 **355** **356** **361**

B *Unsuccessful alkynes*



392 **393** **394** **395**



396 **397** **398** **399**

Scheme 103. Unsuccessful reaction scope examples.

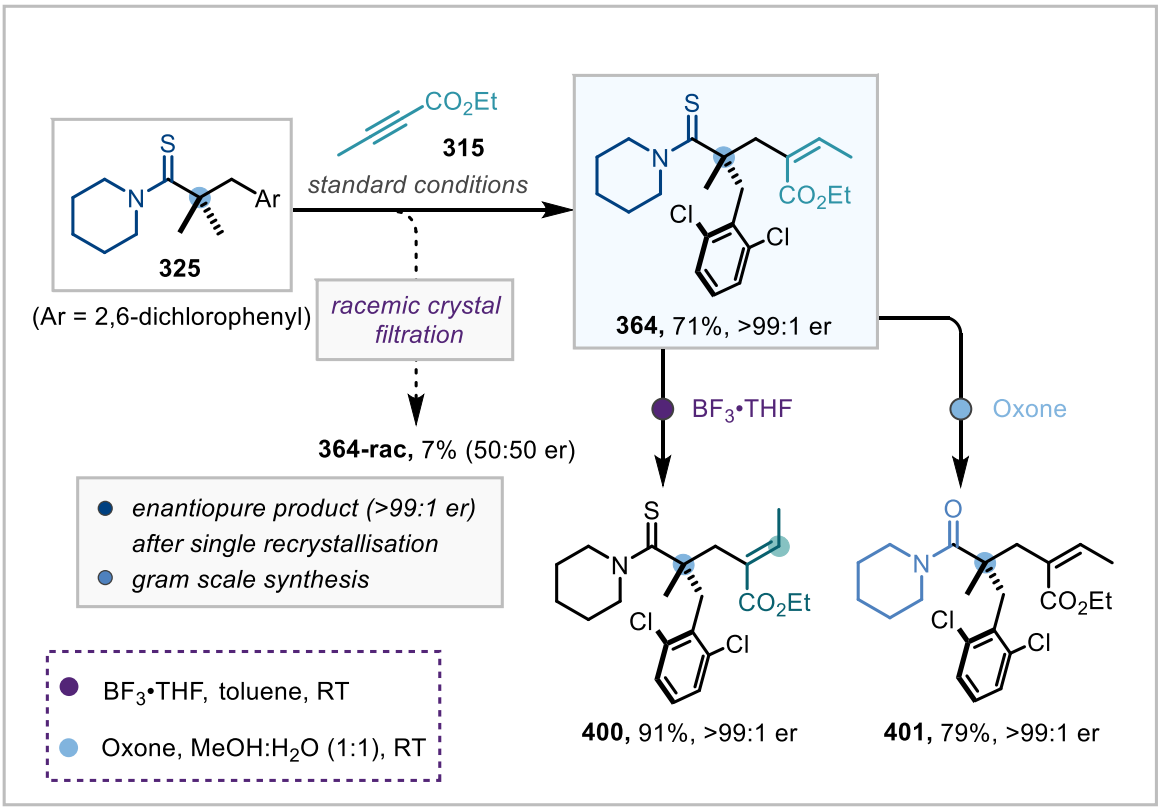
2.7 Derivatisations of the C(sp^3)–H alkenylation products[4]

After creating a broad scope of the reaction with various functional groups, a desire to demonstrate the synthetic utility of the newly made C–H activation products, led to the various downstream derivatisations of enantiopure **364**. Another drive to explore the reaction product's reactivity was to look for and find a crystalline product that would be suitable for single crystal X-ray diffraction to determine and confirm the absolute configuration of our prepared compounds.

2.7.1 Direct derivatisations of C(sp^3)–H alkenylation product

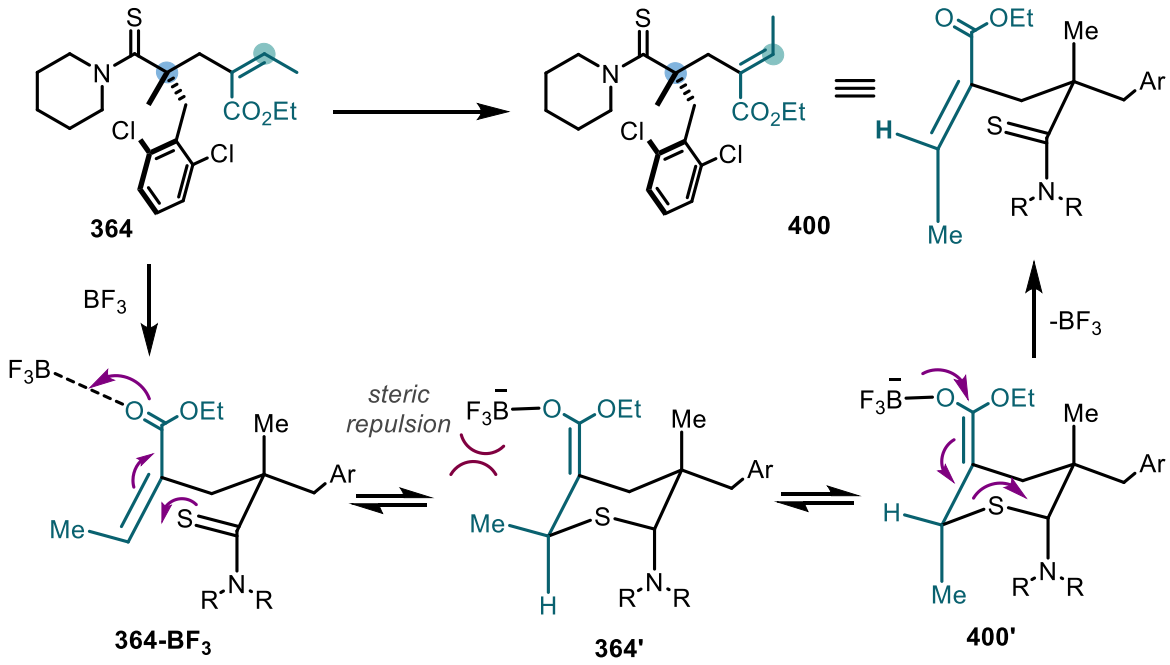
After acquiring product **364** on gram scale, we were able to crystallise out the racemic **364-rac** (7%) and obtain the enantiopure product in 71% yield, and with this material in hand we wanted to explore its reactivity (**Scheme 104**). What we found is, that using the Lewis acidic trifluoroborane tetrahydrofuran complex allows the Z → E isomerization of the C=C double bond and converts our *cis* alkene to the *trans* isomer **400** in outstanding 91% yiel, while keeping the enantioselectivity intact. Another simple transformation of our thioamide **364** was oxidative desulfurisation with oxone, which led to the formation of amide **401** as a single enantiomer in 79% yield.

[4] Derivatisations were conducted with contributions from Mr Ken Yamazaki and all results are included for completeness.



Scheme 104. Direct isomerisation and oxidation of **364**.

Our curiosity of why is this isomerisation occurring so rapidly, led us to the investigation of the reaction mechanism (**Scheme 105**). Firstly, the coordination of BF_3 onto the thioamide **364** formed **364-BF$_3$**, which generated the formation of cyclic intermediate **364'**. Due to the 1,3-allylic strain between equatorial methyl and BF_3 group, the energy of this intermediate is elevated.[156] As a result the isomerisation of the equatorial methyl to the axial position occurs, forming energetically favourable stable intermediate **400'**. Subsequent release of the trifluoroborane then allowed for the formation of product **400** (**Scheme 105**).



Scheme 105. Mechanism of the isomerisation of **364** to **400**.

To confirm the proposed mechanism, we used the computational modelling of the intermediate complex **400'**, which affirmed that this transformation occurs in order to avoid the steric repulsion (1,3-allylic strain) between the methyl group and BF_3 (**Figure 8**). The driving force of this isomerisation is the formation of less energetically demanding intermediate **400'**.

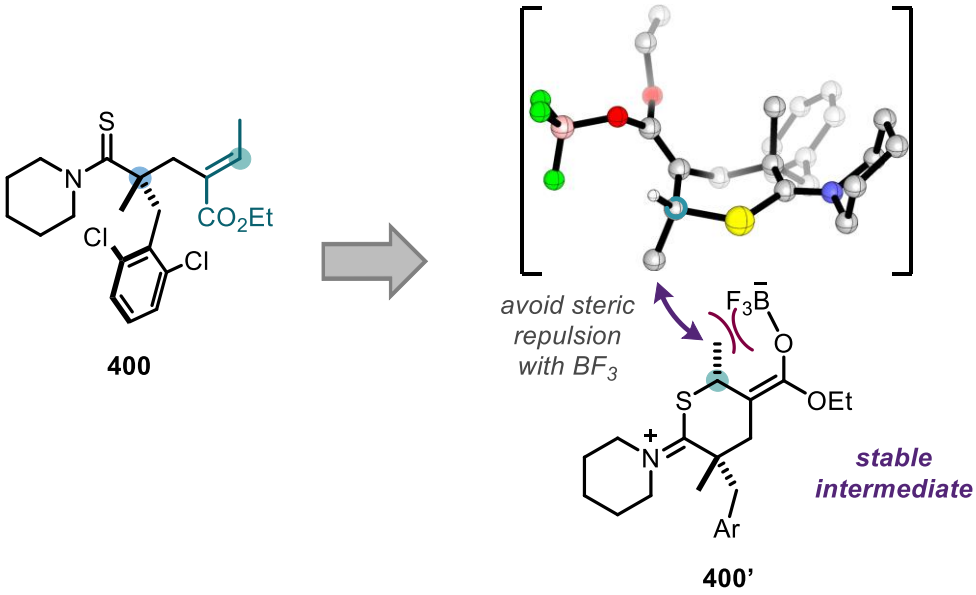
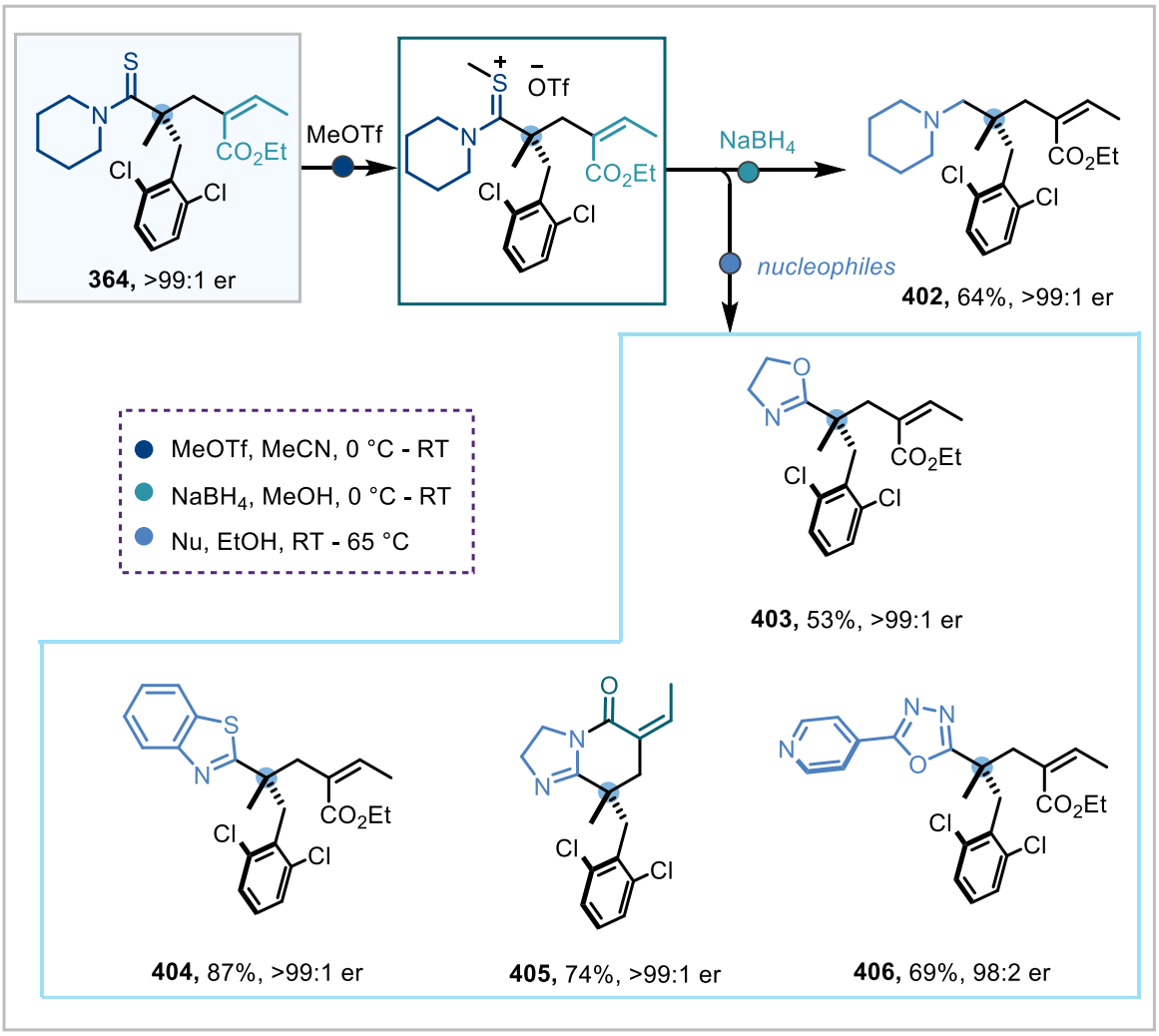


Figure 8. Computational model of isomerisation of **364** to **400**.

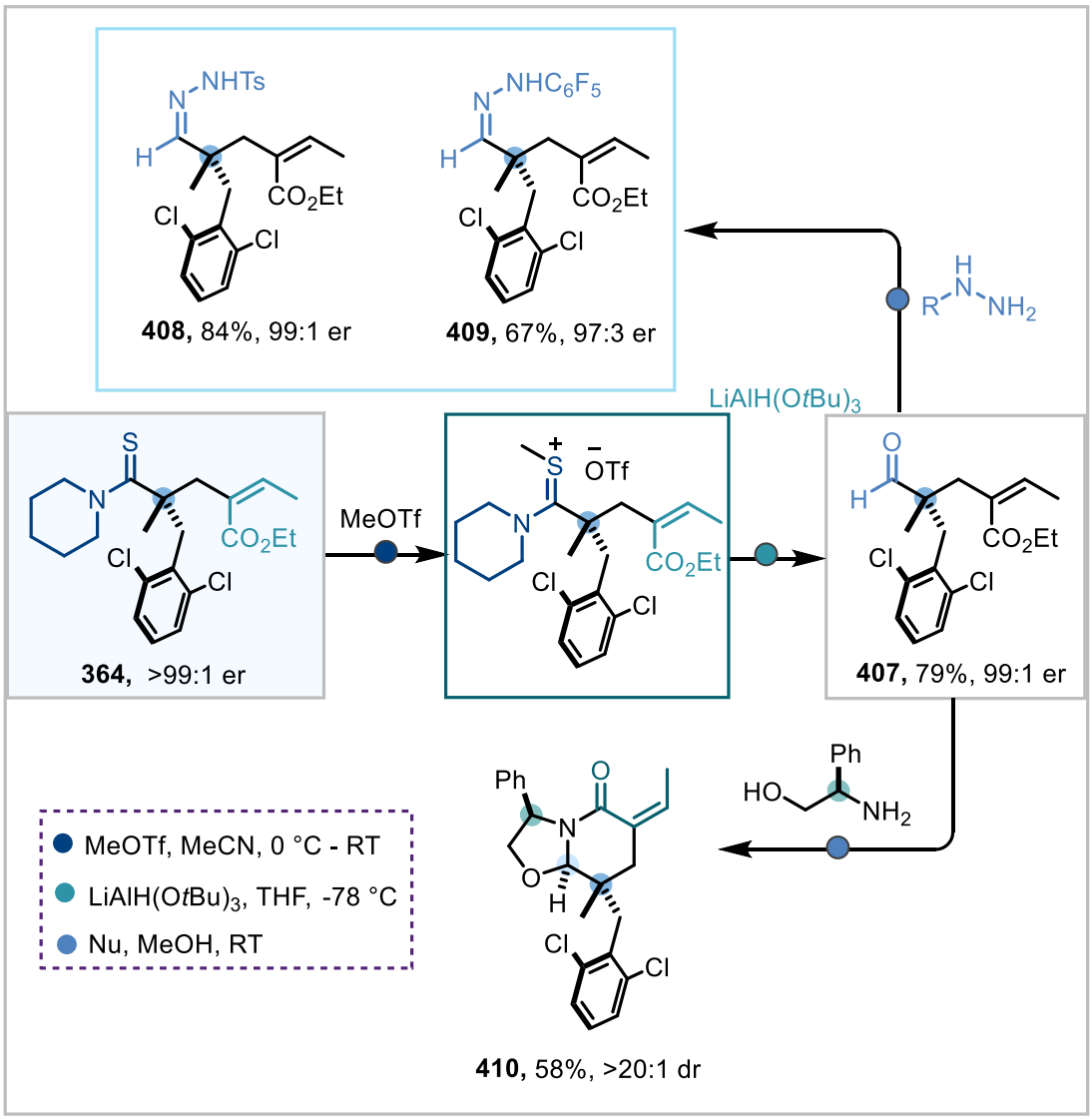
2.7.2 Derivatisations of C(sp^3)–H alkenylation product *via* imidate salts

Following up, inspired by Yoshino and Matsunaga's methylation of C–H amidation products,[146] we submitted **364** with MeOTf and found it forms a stable *S*-methylated piperidinium salt, which can undergo various transformations (**Scheme 106**). After reacting with sodium borohydride, we were able to achieve the fully reduced amine **402** in 64%. When this piperidinium salt was treated with a range of nucleophiles, various heterocyclic moieties were acquired, such as dihydrooxazole derived **403** in 53% yield, benzothiazole derived **404** in 87% yield and 1,3,4-oxadiazole derived **406** in 69% yield. Interestingly, when ethylenediamine was used as a nucleophile, a nitrogen-containing 5,6-fused bicyclic compound **405** was obtained by a subsequent cyclisation between an *in situ* formed imidazole and the ester group of the alkene.



Scheme 106. Derivatisations of enantiopure alkenylation products *via* thioimidate formation.

This imidate intermediate can also be partially reduced to form the aldehyde **407** in 79% yield as a single enantiomer, which was further reacted with different hydrazines to form synthetically relevant hydrazones **408** and **409** in 84% and 67% yield and 99:1 and 97:3 er, respectively. Enantiopure aldehyde **407** was further reacted with a chiral amino alcohol to furnish a complex bicyclic compound **410** with three stereocentres in 58% yield and outstanding diastereoselectivity (>20:1 dr) (**Scheme 107**). Overall, all of these transformations preserved the enantiopurity and demonstrated the synthetic utility of the thioamide as a powerful and useful directing group.



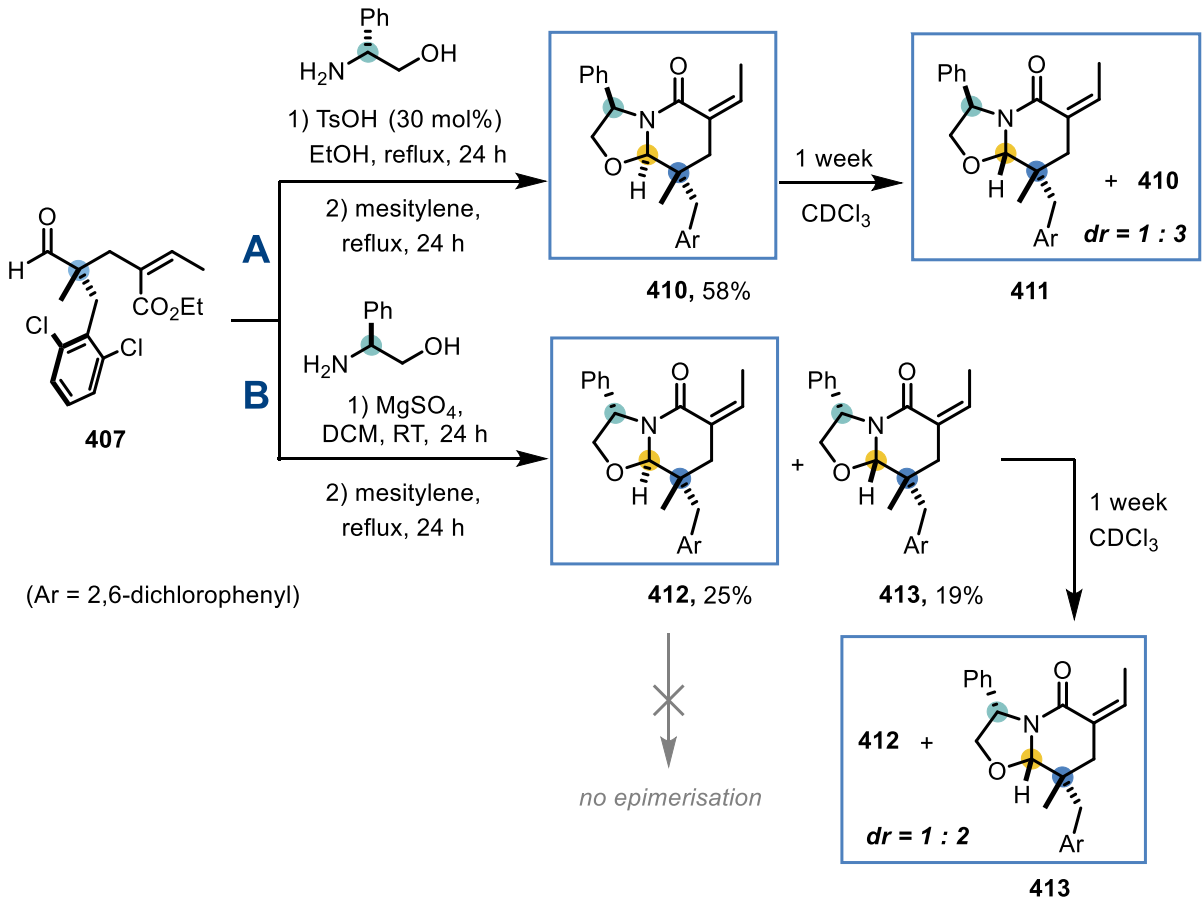
Scheme 107. Derivatisations of enantiopure alkenylation products *via* thioimidate formation.

2.7.3 Confirmation of the absolute configuration[5]

Because we were not able to derivatise the direct C–H alkenylation product to form single crystal suitable for X-ray analysis, we decided to take an alternative route and determine the absolute configuration through NMR experiments. During derivatisations, bicyclic three

[5] Analysis to confirm the absolute configuration was performed by Mr Ken Yamazaki, and data is included for completeness.

stereocenters-containing compound **410** was prepared, which possesed two new stereocentres when compared with the aldehyde **407**. One of the stereocentres is set by the nucleophile (*R*)-phenylglycinol, and the other is formed during the nucleophilic addition, followed by the intramolecular cyclisation. In order to determine the absolute configuration, all 4 possible diastereomers had to be prepared. Previously prepared **410** partially epimerised in chloroform after one week, providing diastereomer **411** for the analysis (**Scheme 108A**). Aldehyde **407** was treated with (*S*)-phenylglycinol to afford **412** in 25% and **413** in 19% yield (**Scheme 108B**).



Scheme 108. Synthesis of four diastereomers for the determination of absolute configuration.

With the four possible diastereomers in hand, the Nuclear Overhauser Effect Spectroscopy (NOESY) experiments have been performed, and their analysis provided insight into the 3D

spatial structure of molecules. All molecules were compared with known, structurally similar heterocycles.[157] In the case of the *cis*-fused heterocycle ***cis*-414**, with regards to two hydrogens, the chemical shift of the hemiaminal hydrogens is found at 4.92 ppm as a doublet of doublets. Two of our diastereomers (**410**, **412**) exhibit similar chemical shifts (4.88 and 5.02 ppm) with doublet of double splitting, therefore we looked at the spatial interactions of diastereotopic hydrogen between the two heteroatoms at NOESY spectrum. The yellow hydrogen of heterocycle **410** is in close proximity to benzylic hydrogens and one of the diastereotopic hydrogens of the 6-membered cycle, and does not interact with the methyl group. On the other hand, yellow hydrogen in heterocycle **412** shows interaction with the methyl group and one of the diastereotopic hydrogens of the cyclic core (**Figure 9**).

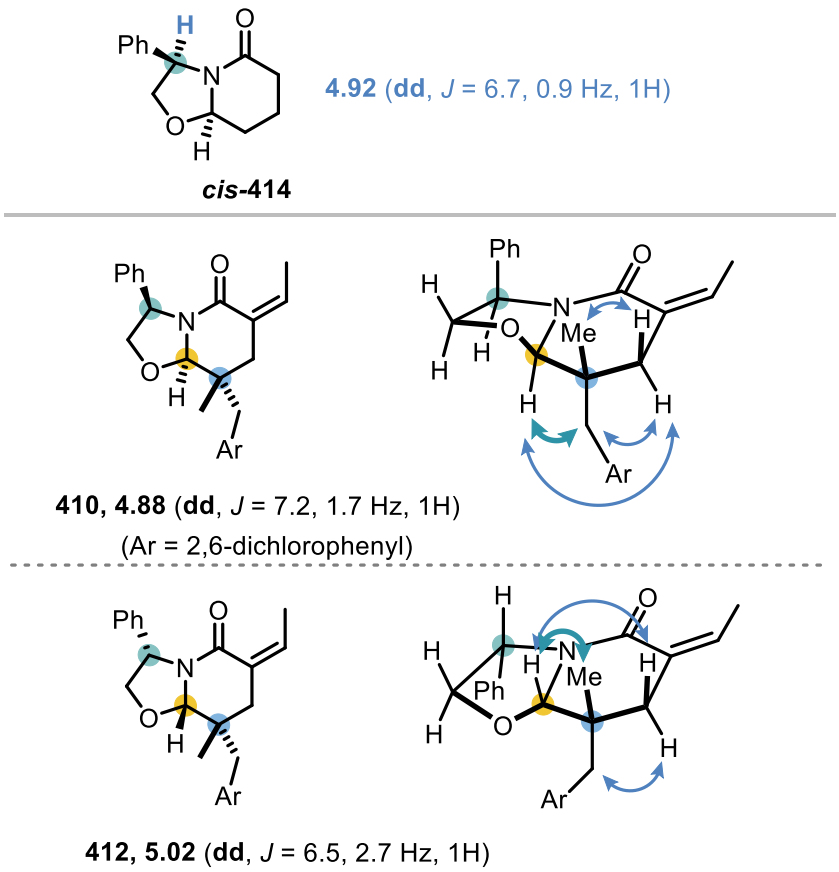


Figure 9. NOESY analysis of **410** and **412** for the determination of the absolute configuration.

In the case of the *trans*-fused heterocycle ***trans*-414** the chemical shift of marked proton is slightly higher (5.27 ppm), with splitting into a triplet, and the other two diastereomers (**411**, **413**) exhibit very similar chemical shifts (5.35 and 5.20 ppm) with splitting into the triplet. The yellow hydrogen of **411** is in close proximity of the methyl group while the yellow proton of heterocycle **413** is close to the benzylic hydrogens (**Figure 10**). Based on all interactions between the three stereocentres of our main derivatisation product **410**, we were able to assign configuration of all stereocentres, and through the analogy we were able to determine the absolute configuration of the C–H alkenylation products to be (*S*).

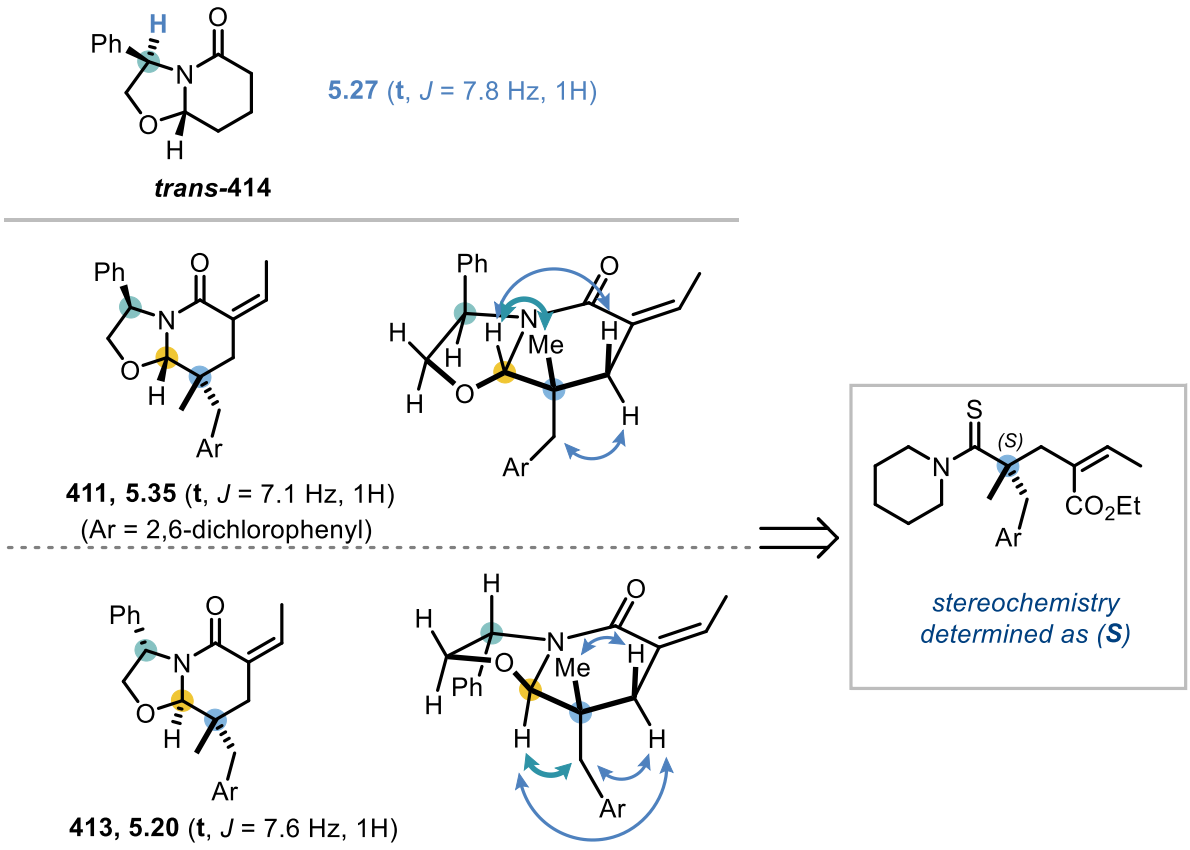
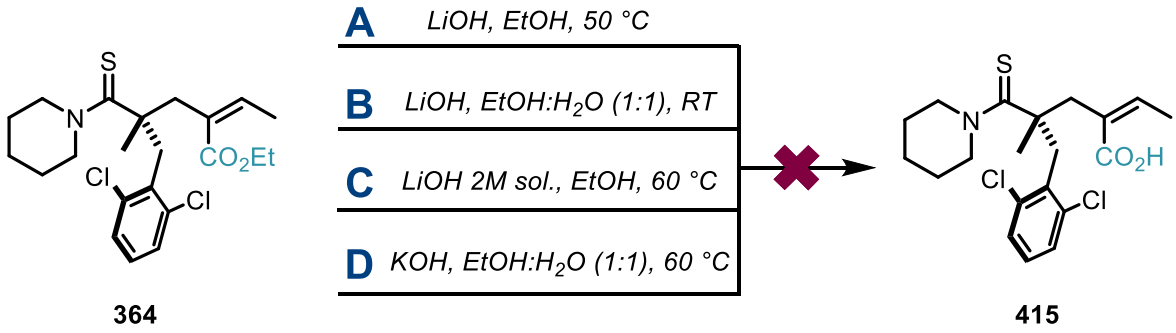


Figure 10. NOESY analysis of **411** and **413** for the determination of the absolute configuration.

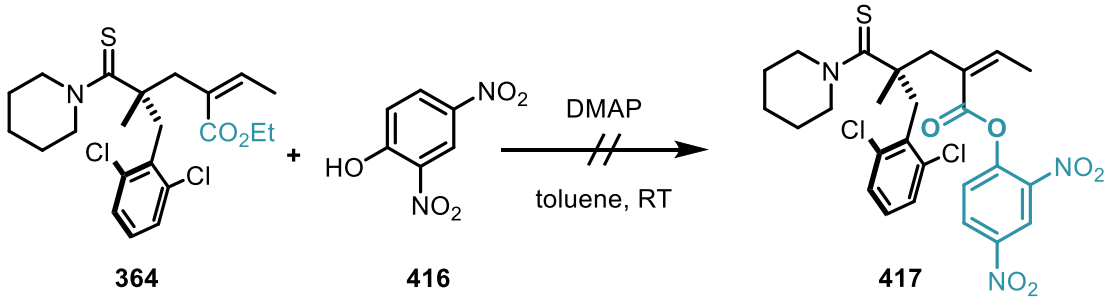
2.7.4 Unsuccessful derivatisations

During the studies into the reactivity of C–H alkenylation products, we encountered certain difficulties with some transformations. All our efforts to hydrolyse the ethyl ester group of **364** to the corresponding carboxylic acid **415** were unsuccessful (**Scheme 109**).



Scheme 109. Unsuccessful hydrolysis of **364**.

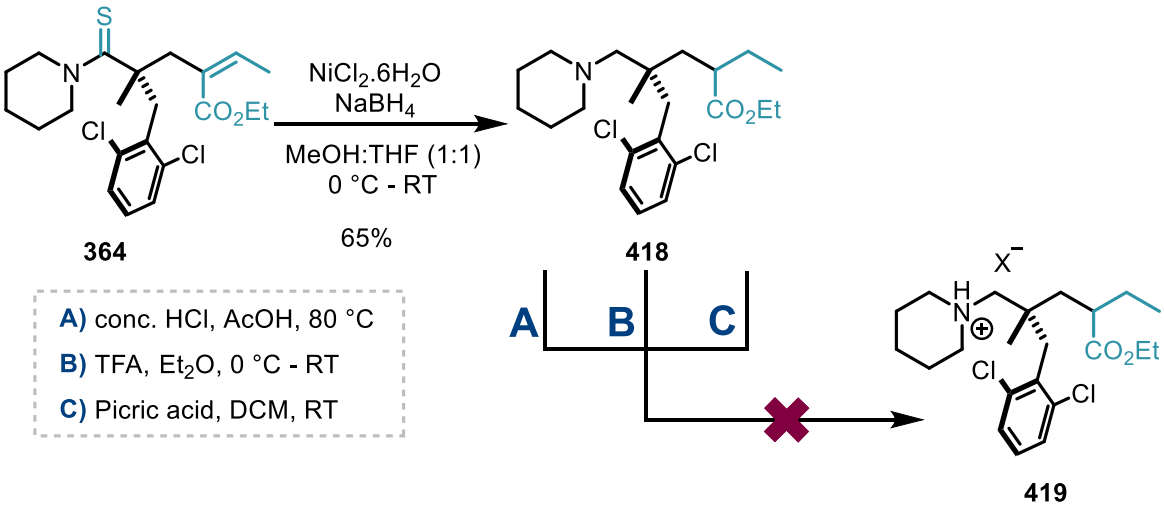
Similarly, our attempts to transesterify the ethyl ester with commonly highly crystalline 2,4-dintrophenyl ester **416**, were unsuccessful (**Scheme 110**). This left us thinking that there must be either some specific interactions within the ester group on the alkene or some interactions with the thioamide itself, or the steric effects of this quite busy product does not allow any sort of transformation at the carbonyl group of the ester functionality.



Scheme 110. Unsuccessful transesterification of **364**

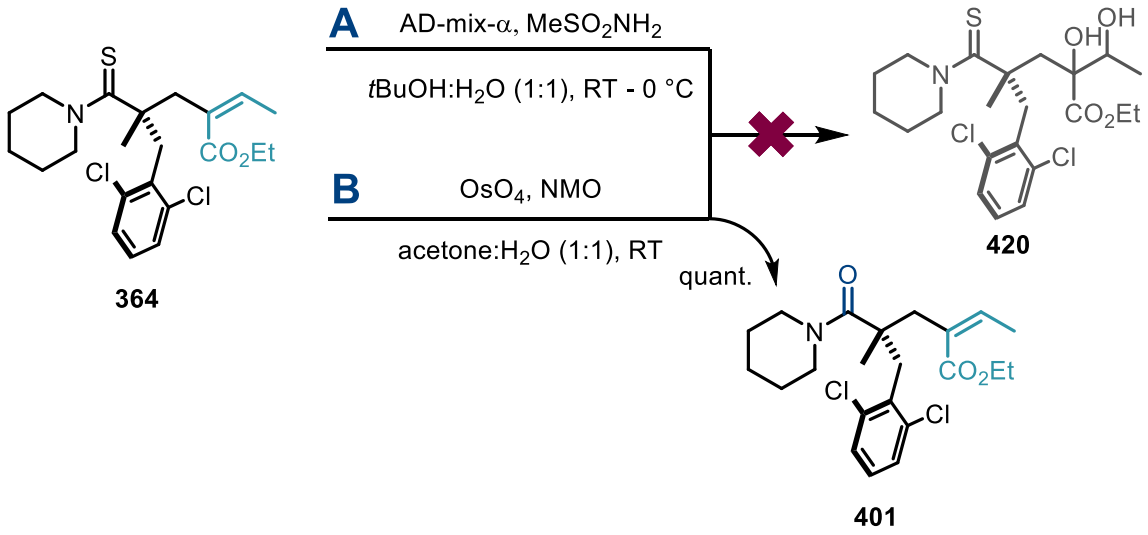
As our main goal during these experiments was to find a crystalline product that would be suitable for the single crystal X-ray diffraction to confirm the absolute configuration, our

next efforts moved to formation of crystalline salts. We successfully reduced the enantiopure thioamide **364** to the amine **418** in 65% yield, and we left this amine to react with various Brønsted acids, such as HCl, trifluoracetic or picric acid, however all these experiments did not lead to the desired piperidinium salts **419** (**Scheme 111**).



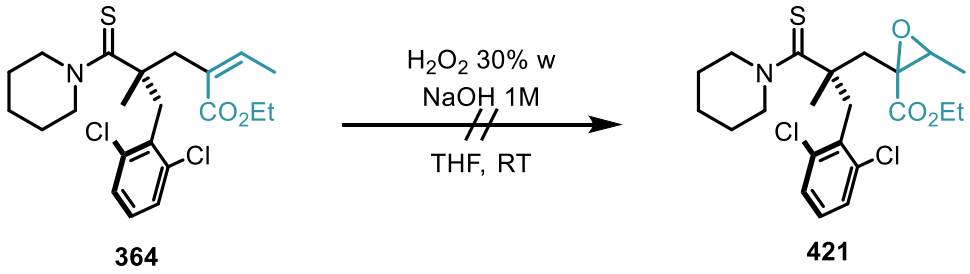
Scheme 111. *Unsuccessful piperidium salts formation.*

Knowing there is a double bond in the product our thoughts turned towards how we could transform this alkene into something else. Our first, and possibly the most obvious, choice was to do Sharpless asymmetric dihydroxylation and form the product **420**, however the dihydroxylated product was never obtained (**Scheme 112A**). Our next step was to test much harsher dihydroxylation conditions (osmium tetroxide), but instead of forming **420**, we were able to isolate only amide **401** in quantitative yield (**Scheme 112B**).



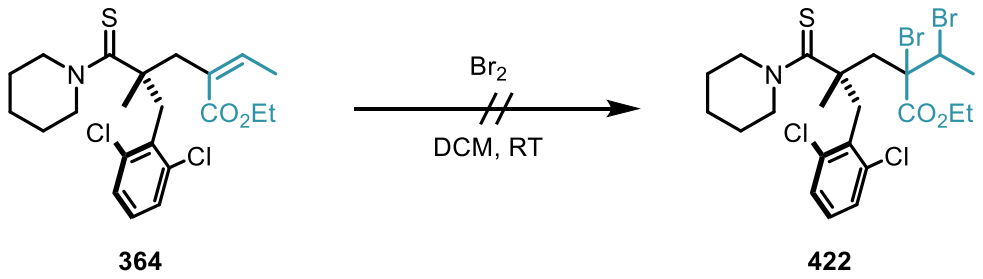
Scheme 112. Unsuccessful Sharpless dihydroxylation of alkenylated **364** hydroxylation with OsO_4 leading to amide **401**.

Unable to access the dihydroxylated product, we considered that epoxidation may be more facile. Therefore, we used hydrogen peroxide, but again we were not able to obtain the epoxidated **421** (**Scheme 113**).



Scheme 113. Unsuccessful epoxidation of **364**.

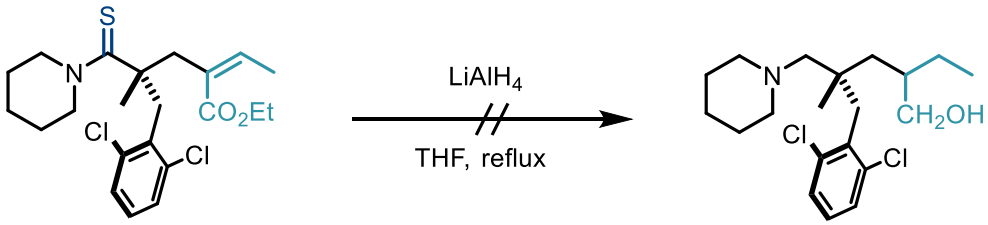
While none of the oxygen-containing additions into the double bond proved fruitful, we attempted the bromination using molecular bromine, but again this experiment did not lead to the desired dibrominated **422** (**Scheme 114**).



364 422

Scheme 114. Unsuccessful alkene bromination of **364**.

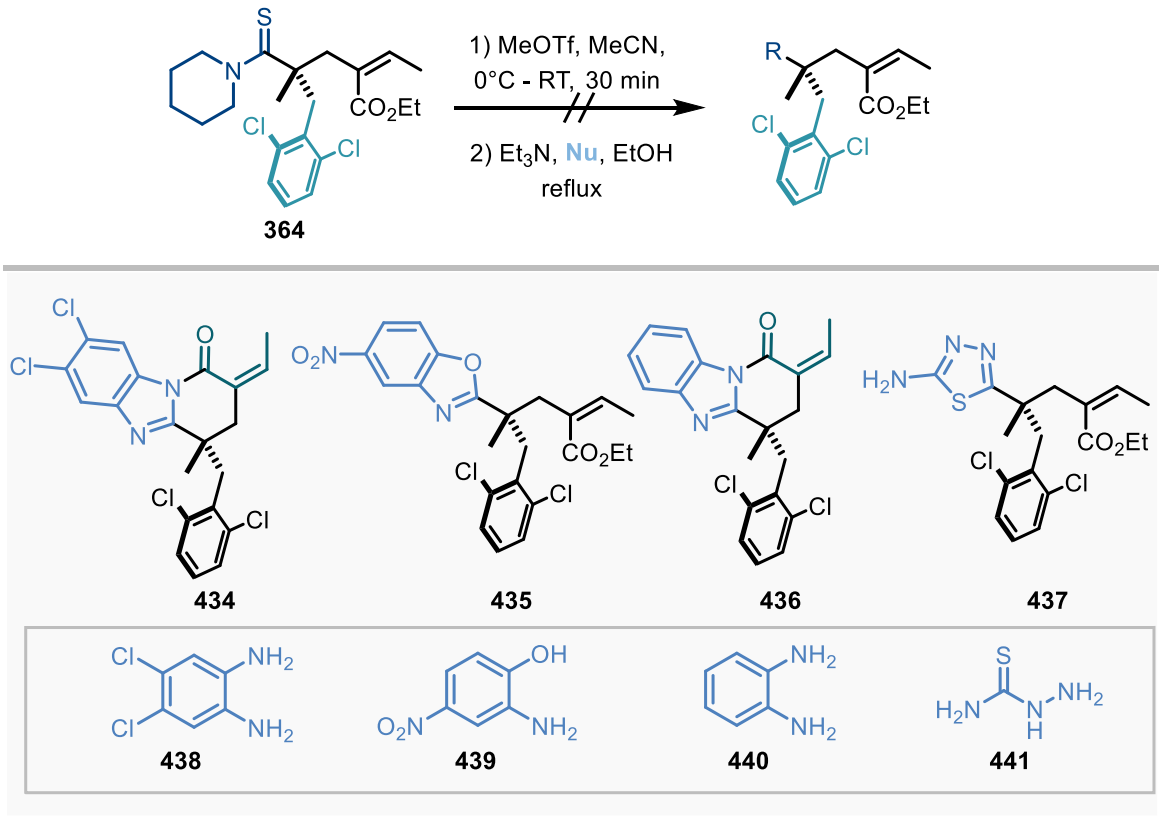
While none of our efforts to functionalise the alkene or ester group lead to positive results, we decided to try and fully reduce the **364** with lithium aluminium hydride. However, this led only to a complex mixture of various partially-reduced parts of our starting material and alcohol **423** could not be isolated (**Scheme 115**).



364 423

Scheme 115. Unsuccessful reduction of **364**

Furthermore, we also found that activated *S*-methylated piperidinium salt did not afford the corresponding products **434-437**, with aniline nucleophiles **438-440** or with hydrazine **441** (**Scheme 116**).

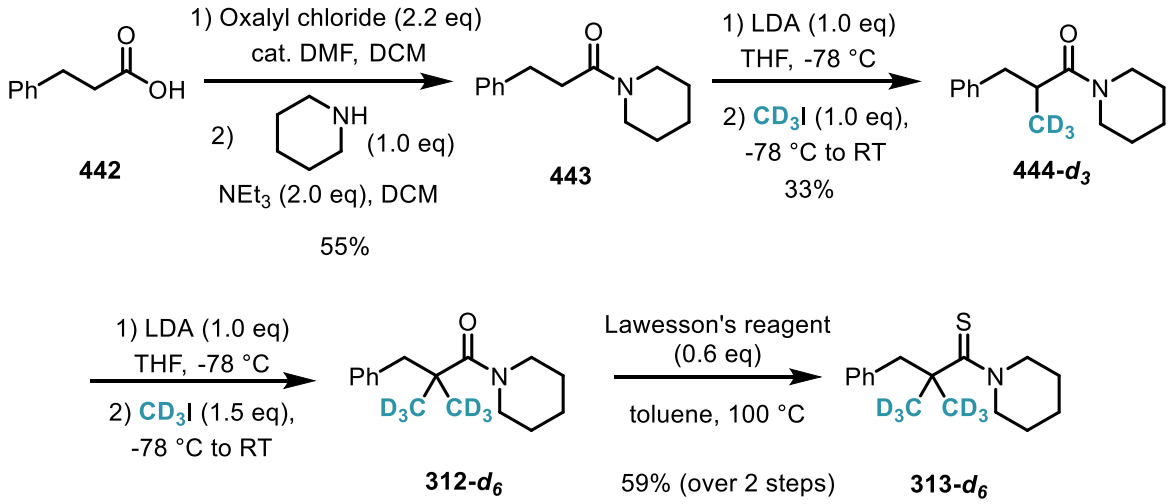


Scheme 116. Unsuccessful nucleophiles.

2.8 Mechanistic investigation and deuterium labelling studies

2.8.1 Synthesis of deuterium labelled substrate

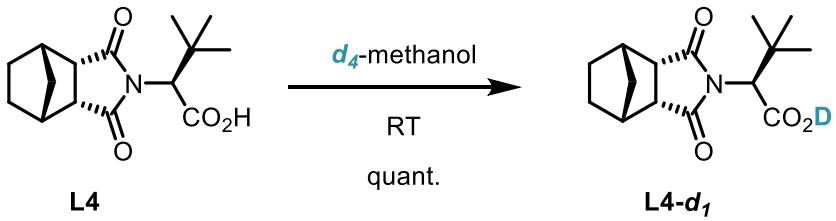
In order to probe the mechanistic pathway of the thioamide directed Cp*Co^{III}-catalysed C(sp^3)–H alkenylation, firstly a deuterium labelled substrate **313-*d*$_6$** had to be synthesised (**Scheme 117**). Carboxylic acid **442** was transformed to the corresponding amide **443**, which was then treated with LDA followed by deuterium labelled methyl iodide to furnish monomethylated amide **444-*d*$_3$** in 33% yield. Methylation with CD_3I was repeated to yield dimethylated amide **312-*d*$_6$**, which was transformed to the deuterated thioamide **313-*d*$_6$** in 59% over 2 steps.



Scheme 117. Synthesis of deuterium labelled substrate **313-d_6**.

2.8.2 Synthesis of deuterium labelled ligand

Secondly, to understand whether the proton present in the carboxylic acid of the ligand is incorporated in the product and therefore having a crucial role in the reaction mechanism, a deuterium-labelled ligand was prepared by a simple stirring of **L4** in deuterated methanol (**Scheme 118**).

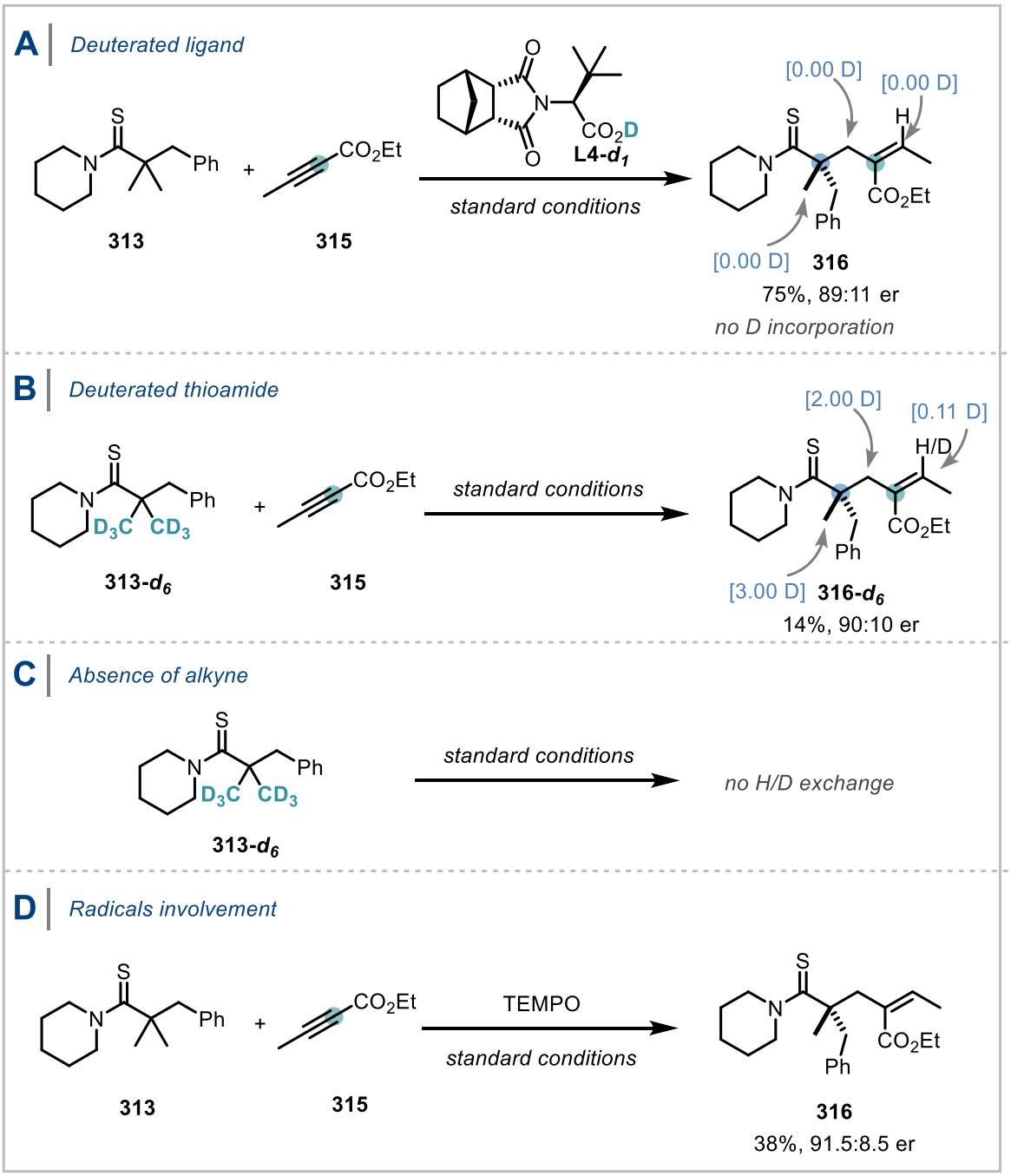


Scheme 118. Synthesis of deuterium labelled ligand **L4-d_1**.

2.8.3 Mechanistic investigation of enantioselective C(sp^3)–H alkenylation

With deuterium-labelled model substrate and ligand in hand, a series of experiments was performed in order to further understand the reaction pathway. First, when a deuterated carboxylic acid ligand was used, no deuterium incorporation was observed in the isolated

product, indicating clean H-transfer from C–H activated methyl group to the olefin (**Scheme 119A**). Next, to study the reversibility of the C–H activation, we submitted the deuterated starting material **313-*d*$_6$** to the optimal reaction conditions, both in the presence and absence of the coupling partner. In the presence of the electrophile **315**, deuterated product **316-*d*$_6$** was isolated in 14% yield and 90:10 er, containing 0.11 D/H ratio on the alkene (**Scheme 119B**). The significantly lower yield suggests that the energy barrier of C–D activation is much higher, and C–H bond functionalisation is therefore involved in the rate- and enantio-determining step. Submission of the deuterated starting material to the reaction conditions without the alkyne coupling partner resulted in only a very small D/H exchange, confirming the irreversibility of this step (**Scheme 119C**). We were also interested to see whether there was any evidence of the presence of the radical species during the reaction, therefore we added TEMPO to the reaction mixture, and we were able to isolate product **316** in 38%, 91.5:8.5 er (**Scheme 119D**), which confirmed that this C–H activation reaction does not proceed *via* radical mechanism.



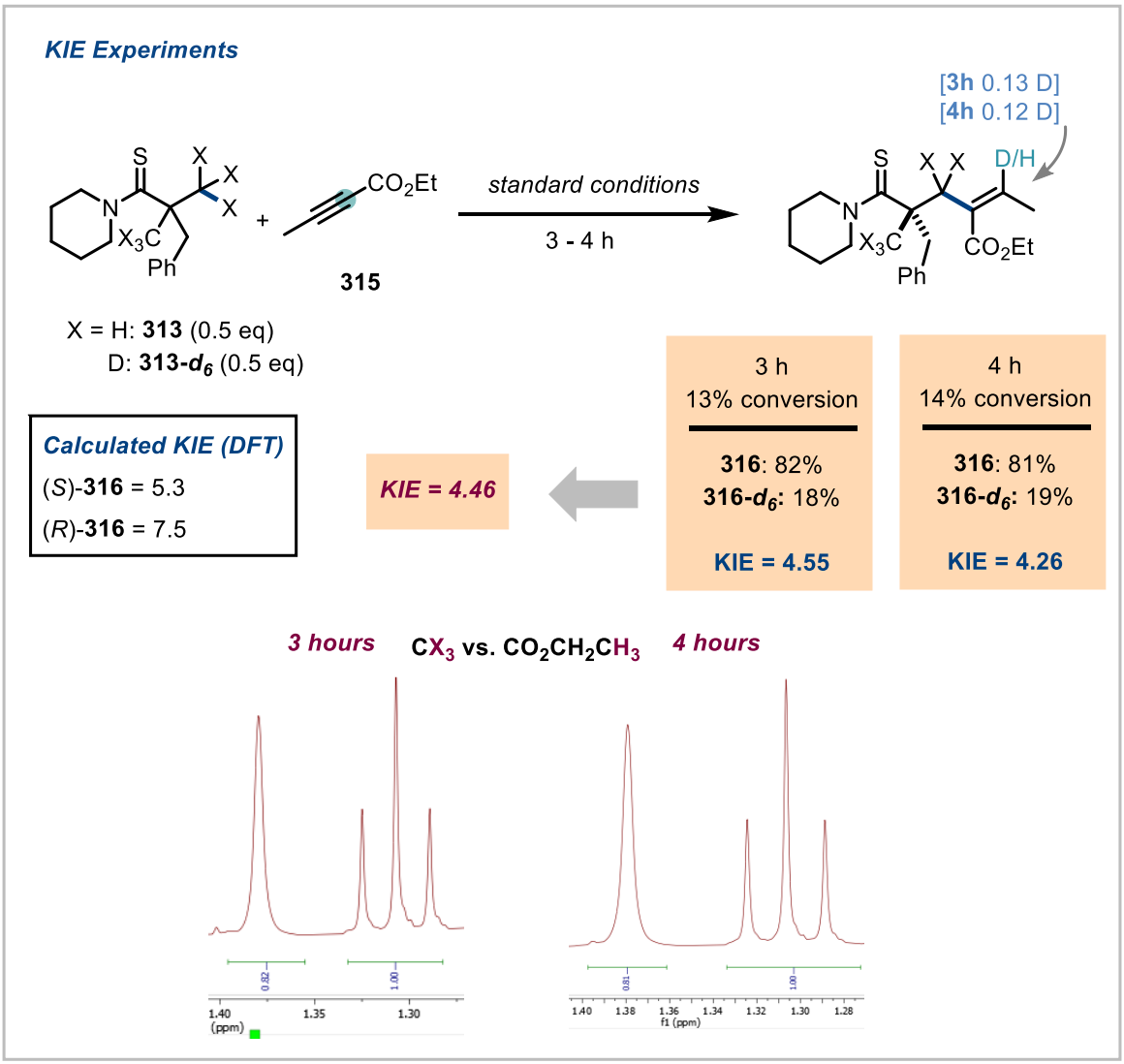
Scheme 119. Mechanistic investigation of enantioselective C(sp^3)–H alkenylation.

2.8.4 KIE Experiments

Finally, kinetic isotope effect (KIE) studies, to determine the rate limiting step, were performed. The KIE value represents a change in the reaction rate of the transformation

where one of the atoms (hydrogen) in the substrate is replaced by its isotope (deuterium). This effect is expressed by the ratio of k_H/k_D.[158] In order to determine the KIE value, we set up two parallel experiments with 0.5 equivalents of substrate **313** and 0.5 equivalents of deuterated substrate **313-*d*$_6$** and let the reactions run under the standard conditions for both 3 and for 4 hours (**Scheme 120**). We were then able to isolate products **316** and **316-*d*$_6$** as inseparable mixture, containing 0.13 and 0.12 H/D ratios on the alkene. This suggested that deuterium from C–D activation was mostly getting washed out either by the free MeCN groups from the catalyst ligand exchange of by the excessive amount of the alkyne. Afterwards, we compared the incorporation of deuterium in both products by looking at the peak integrations of CX_3 group that contained D and intact CO_2Et group. This allowed us to calculate KIE values of 4.55 (3 hours) and 4.26 (4 hours), which on average demonstrated a value of 4.41, suggesting that C–H activation is indeed the rate- and enantio-determining step of the cobalt-catalysed C(sp^3)–H alkenylation. We also wanted to compare the experimental value to the DFT calculated KIE for both (*S*)- and (*R*)- products to see whether it matches to our experimental data, and for product (*S*)-**316** we got the value 5.3 while for product and (*R*)-**316** the KIE value went up to 7.5. This result was in line with our experimental data, forming the (*S*)-enantiomer under the standard conditions.[6]

[6] All DFT calculations were performed by Mr Ken Yamazaki, and results are included for completeness.



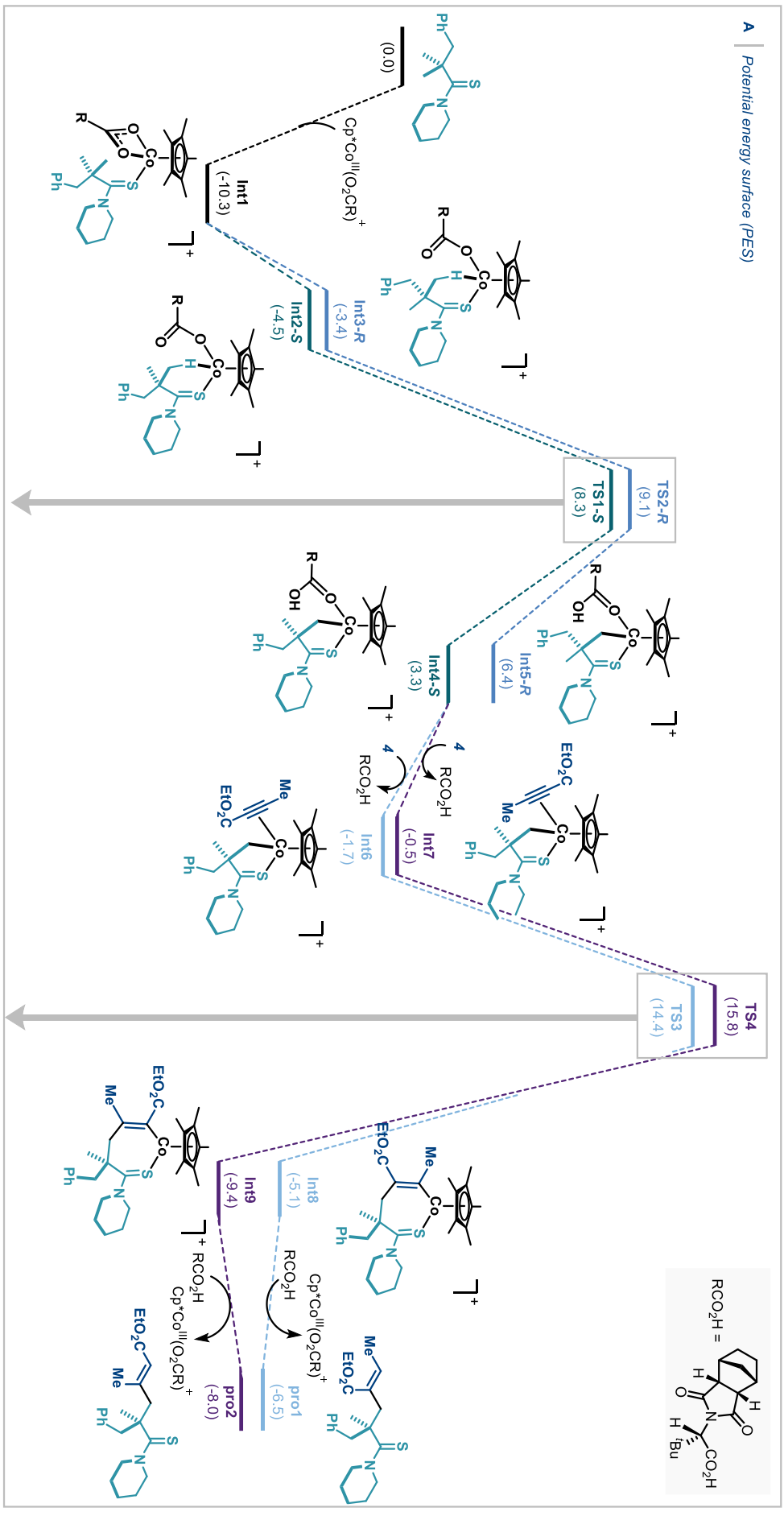
Scheme 120. KIE experiments of enantioselective C(sp^3)–H alkenylation.

2.9 Computational studies[7]

To elucidate the origin of the regio- and stereocontrol in the Co^{III}-catalysed C–H alkenylation of thioamides, we performed a state-of-the-art density functional theory (DFT) study on the complete catalytic cycle (**Scheme 121**). Previous work by Dixon and Seayad, proposed an active cobalt species $Cp^*Co(OAc)^+$ generated *in situ* in the presence of Cp^*Co^{III}

[7] Computational analysis was in full performed by Ken Yamazaki, and data is included for completeness.

species and an acetate source.[159] In a similar manner, the active species Cp*Co(O_2CR)$^+$ can be formed between the chiral acid ligand in our reaction conditions. The catalytic cycle begins with the thioamide complexation with a proposed active catalyst to form a complex **Int1**. An initial k^2–k^1-displacement of the carboxylate ligand by the *β*-hydrogen of the substrate is required to initiate the C–H activation step. The formed complexes **Int2-*S*** and **Int3-*R*** have an increased acidity of the *β*-hydrogen that can facilitate the ambiphilic metal-ligand activation/concerted metalation deprotonation (AMLA/CMD) mechanism through transition structures **TS1-*S*** and **TS2-*R***.[36] The C–H activation step preferably proceeds through **TS1-*S*** ($\Delta\Delta G^{\ddagger}$ = 0.8 kcal mol^{-1}), and this leads to the *S*-configured product, which matches with the experimentally confirmed stereochemistry. In order to quantitatively understand the origin of this kinetic preference of the AMLA/CMD, the activation strain model (ASM) was applied using Cp*Co(O_2CR)$^+$ and the thioamide substrate as the fragments (**Figure 11**).[160–165] The stereoselectivity of this reaction can be traced back to steric effects, involving the clash between the *t*Bu group of the chiral carboxylate ligand and the Ph group on the substrate. The preferred transition structure **TS1-*S*** benefits from a large distance between the ligand and the substrate Ph group that avoids steric clash and results in a less destabilizing strain energy ($\Delta\Delta E^{\ddagger}_{strain}$ = –2.5 kcal mol^{-1}). This strain energy is traced back to mainly the substrate fragment ($\Delta\Delta E^{\ddagger}_{strain[sub]}$ = –1.8 kcal mol^{-1}) and therefore the steric bulk of the ligand in this step controls the stereoselectivity. After the C–H activation step, the cobaltacycle **Int4-*S*** releases the carboxylic acid and generates a stable cobaltacycle **Int6-*S***. The next step is initiated with the coordination of the alkyne to **Int6-*S*** and generates either **Int7** or **Int8**. The migratory insertion of an alkyne preferably proceeds through **TS3** ($\Delta\Delta G^{\ddagger}$ = 1.4 kcal mol^{-1}), and the new C–C bond is formed between the *β*-position of the thioamide substrate and the *α*-position of the alkyne.



Scheme 121. (A) Computed potential energy surface (ΔG [kcal mol–1]) of the cobalt-catalyzed enantio- and regioselective C(sp^3)–H alkenylation of thioamides,

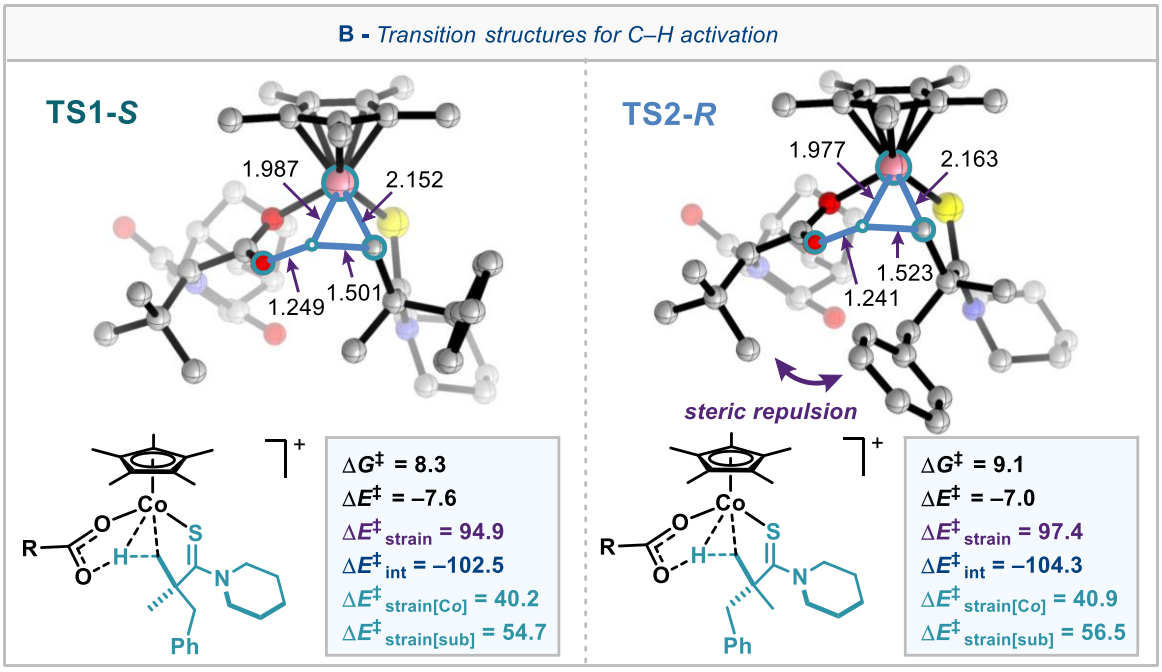


Figure 11. (B) C–H activation transition structures.

Analysis of the ASM using the five-membered cobaltacycle **Int6-*S*** and the alkyne as the fragments revealed that the less destabilizing strain energy for **TS3** compared to **TS4** ($\Delta\Delta E^{\ddagger}_{strain}$ = –2.1 kcal mol^{-1}) is decisive for setting the trend of the regioselectivity (**Figure 12**). This trend solely originates from the strain energy of the alkyne fragment as the methyl and ester groups must significantly bend to undergo the migratory insertion. The bend angle of the ester group is larger in **TS3**, while the bend angle of the methyl group is larger in **TS4**, indicating that the functional group on the alkyne closer to the substrate β-carbon atom bends to a larger degree due to the steric clash. Therefore, the regioselectivity is determined by the steric repulsion of the migratory insertion transition state.

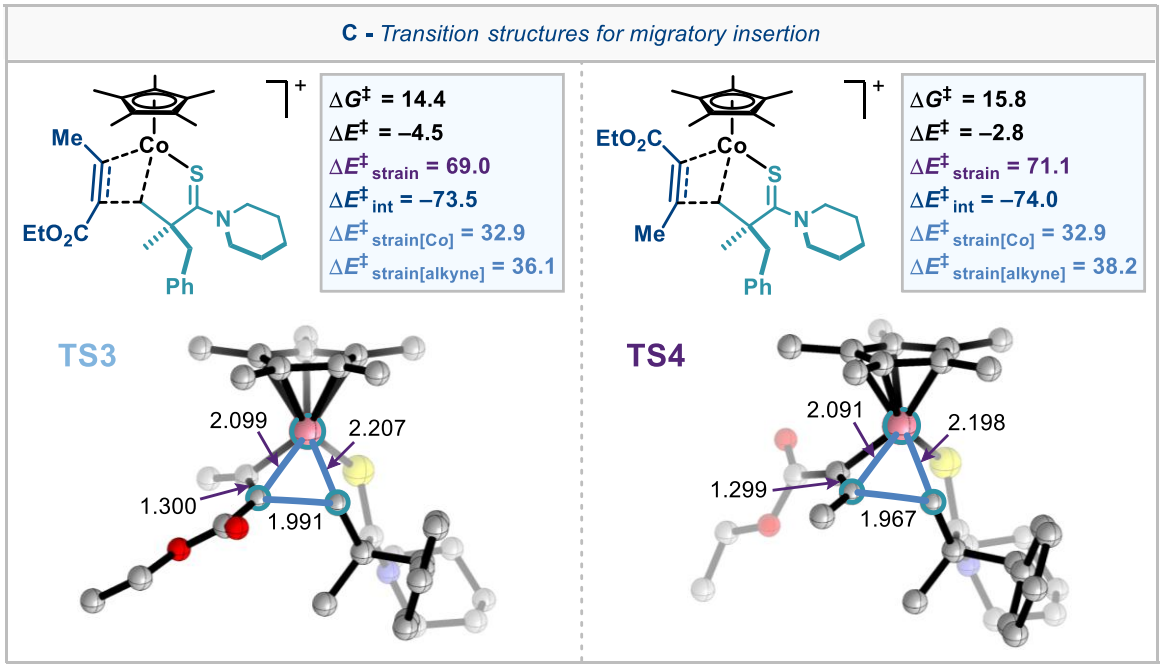


Figure 12. (C) migratory insertion transition structures computed at COSMO(DCB)-ZORA-M06/TZ2P//COSMO(DCB)-ZORA-BLYP-D3(BJ)/TZ2P level of theory. Energies (kcal mol–1) and bond lengths (Å) of the TS geometries are provided in the insert.

The complexity of the reaction mechanism is not completely covered in the modelling, as there is an inconsistency between the computations and the mechanistic experiments. The modelling suggested that the migratory insertion is the rate determining step of this transformation, while the KIE experiments suggested the C–H activation to be both rate- and enantio- determining step. However, the modelling does not consider a large excess of the alkyne present in the reaction mixture, which affected the enantiomeric ratios during the optimisation. We observed that less equivalents of the alkyne decreased the er, while larger excess of the but-2-ynoate boosted up the enantioselectivity. This could then explain that the reaction rate is directly connect with the amount of the alkyne. The energetical barrier of the C–H activation step would then be much higher in the presence of a large excess of the alkyne, and therefore the rate-determining step. Overall, the detailed DFT calculations on the catalytic cycle could explain the origins of the enantiocontrol in the C–H activation

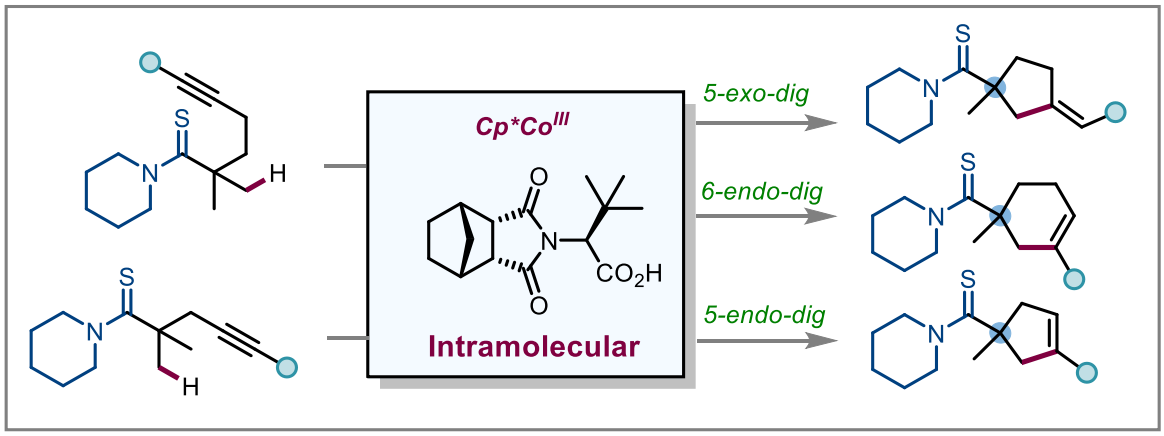
step and the regiocontrol in the migratory insertion step, however the complexity of the whole system is not fully covered.

2.10 Conclusions

In conclusion, a novel thioamide directed enantioselective Cp*Co^{III}-catalysed alkenylation *via* C(sp^3)–H activation furnishing unusual regioisomeric products has been discovered and developed. The method is highly tolerant of a wide range of α-dimethyl substituted thioamide partners, giving products in high yields and enantioselectivity. Furthermore, with a single recrystallisation of products, complete enantiopurity was achieved. Formation of enantiopure products was followed by diversification into a wide range of enantiopure scaffolds including heterocycles bearing an α-quaternary stereocentre. This method is the first example of Co^{III}-catalysed C(sp^3)–H alkenylation of thioamides with but-2-ynoates, and is significant for delivering an unusual regioselectivity that to the best of our knowledge has not yet been reported in the literature as a main regioisomeric product. This method is also very mild, running at room temperature and operationally easy, and for the first time using Cp*Co^{III} complex outside of the glovebox successfully. The origins of enantio- and regioselectivity of this reaction were elucidated using state-of-the-art DFT calculations on the complete catalytic cycle. The mild reaction conditions, ease of operation, broad substrate scope and diverse downstream functionalisation of products makes this an attractive methodology for both industry and academia.

Chapter 3: Preliminary Investigation of the Intramolecular Cobalt-Catalysed C(sp^3)–H Alkenylation of Thioamides

3.1 Chapter overview



Scheme 122. Proposed thioamide directed cobalt-catalysed enantioselective intramolecular C(sp^3)–H alkenylation.

Following the successful development of a novel thioamide-directed cobalt-catalysed C(sp^3)–H alkenylation, the potential for an intramolecular variant of this type of transformation presented itself. Due to the specific interaction between Cp*Co^{III} with thioamides and alkynes, with suitable substrates the formation of cyclic products containing a stereocentre could be straightforward, and if successful this methodology would lead to completely new cyclic chiral scaffolds.

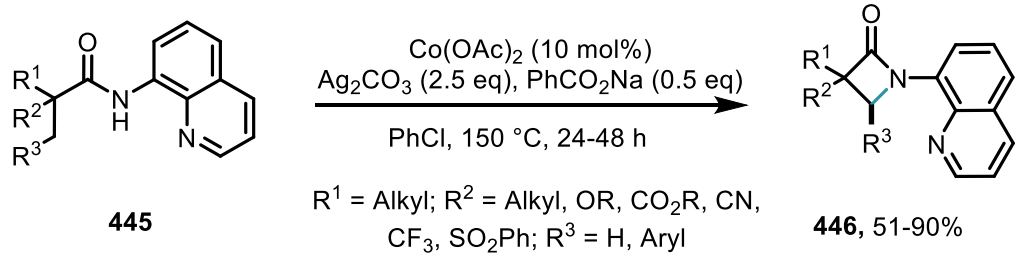
3.2 Introduction

3.2.1 Intramolecular C–H Activation

Over the past decade, C–H functionalisation became one of the fundamental methodologies for organic synthesis, due to multiple advantages, when compared with other types of transformations. Generally, C–H functionalisation represents a method that does not require prefunctionalisation of the substrate, making the synthesis more straightforward while also reducing the number of by-products. Furthermore, intramolecular reactions are more atom-economical and often require shorter reaction times, due to the favourable entropy and better proximity of the reaction centres.[166]

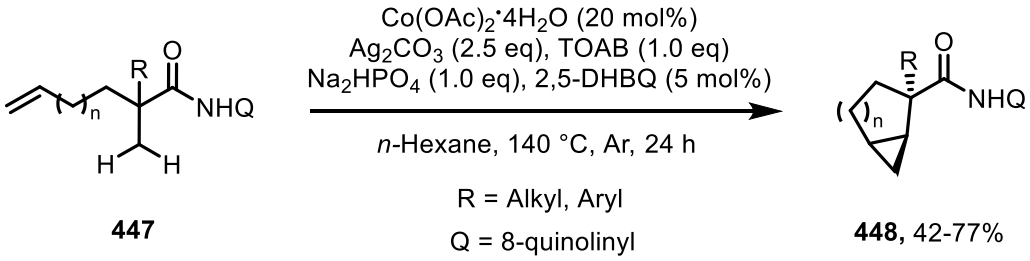
3.2.2 Intramolecular Co-catalysed C(sp^3)–H Functionalisation

The development around Co-catalysed C–H functionalisations was focused mainly on C(sp^2)–H activation reactions, and only a small number of reports is available for C(sp^3)–H functionalisations. Specifically, intramolecular transformations are largely undeveloped, with only small number of examples. Historically, one of the first to study such transformations was Brookhart, who in 2007 reported intramolecular Co^I-catalysed hydrogen transfer of cyclic enamines *via* C(sp^3)–H activation.[104] In 2015, inspired by the progress in bidentate ligand-directed transition metal-catalysed C–H functionalisations, Li disclosed his findings on a Co-catalysed intramolecular C–H transformation (**Scheme 123**). Site-selective Co-catalysed dehydrogenative C(sp^3)–H cyclisation of aliphatic amides **445**, assisted by bidentate directing group was presented, as a new methodology towards monocyclic lactams **446** and spiro *β*- or *γ*-lactams. The method proved to be highly regioselective, providing pharmaceutically relevant lactams in excellent yields.[167]



Scheme 123. Co^{III}-catalysed intramolecular dehydrogenative C(sp^3)–H amidation.

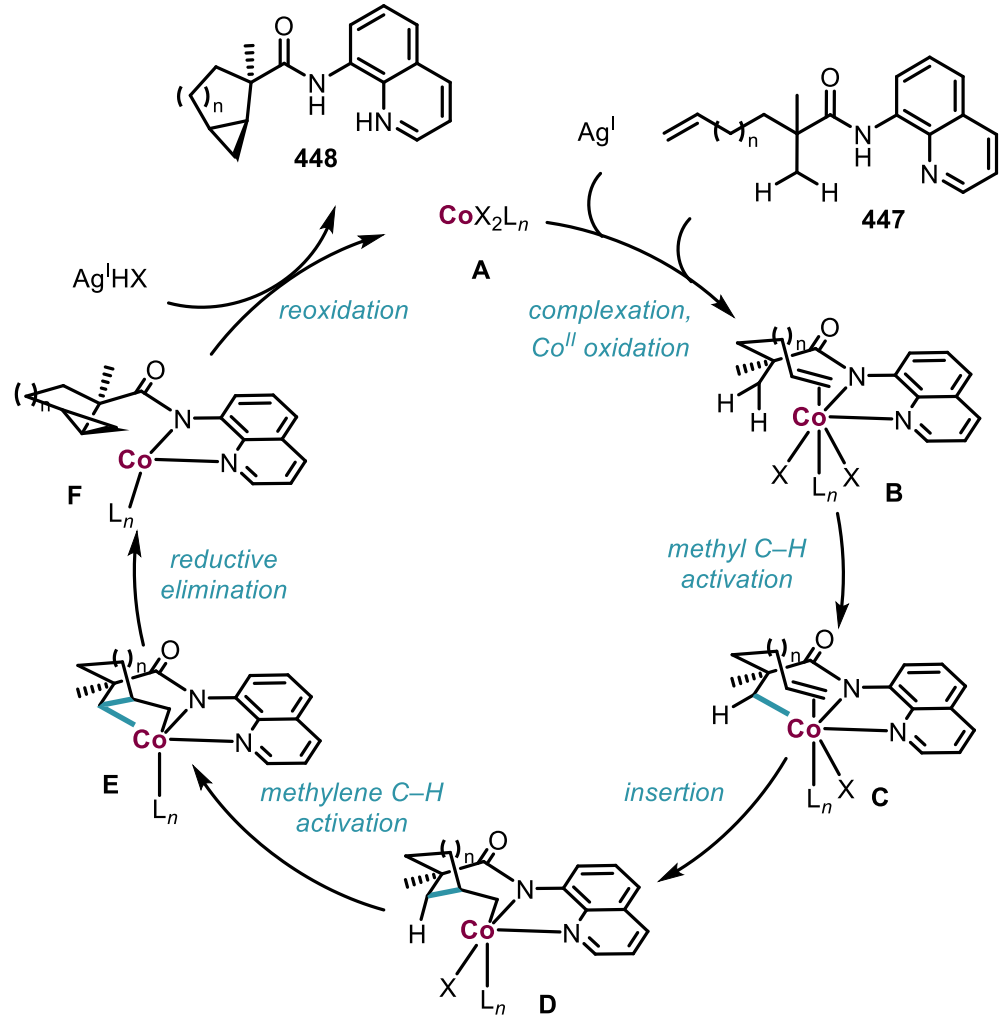
In 2017, Co-catalysed C(sp^3)–H activation towards bicyclic scaffolds was employed by Shi. In this study the authors focused on the development of a complementary strategy, that involves dual intramolecular C(sp^3)–H activation of aliphatic quinoline-protected amides **447**, in order to form bicyclo[4.1.0]heptanes and bicyclo[3.1.0]hexanes **448** (**Scheme 124**).[168,169]



Scheme 124. Co^{III}-catalysed dual intramolecular C(sp^3)–H functionalisations.

The authors proposed a catalytic cycle based on their mechanistic investigations and literature precedent. The cycle starts with Ag^I salt oxidation of Co^{II} complex **A** and its coordination to the starting material **447**, which forms intermediate **B**. Subsequently, one of the geminal methyl C–H bonds is activated, forming cobaltacycle **C**, into which the intramolecular terminal alkene is inserted, generating bicyclic intermediate **D**. Next, conformation induced methylene C(sp^3)–H activation of **D** leads to a second cobaltacycle intermediate **E**, which after reductive elimination affords **F**. Subsequent proto-demetalation

and Ag^{I} reoxidation of Co^{I} species **F** leads to the formation of bicyclic product **448** and regeneration of active Co^{III} species (**Scheme 125**).[169]



Scheme 125. Proposed mechanism of Co^{III}-catalysed dual C(sp^3)–H functionalisation.

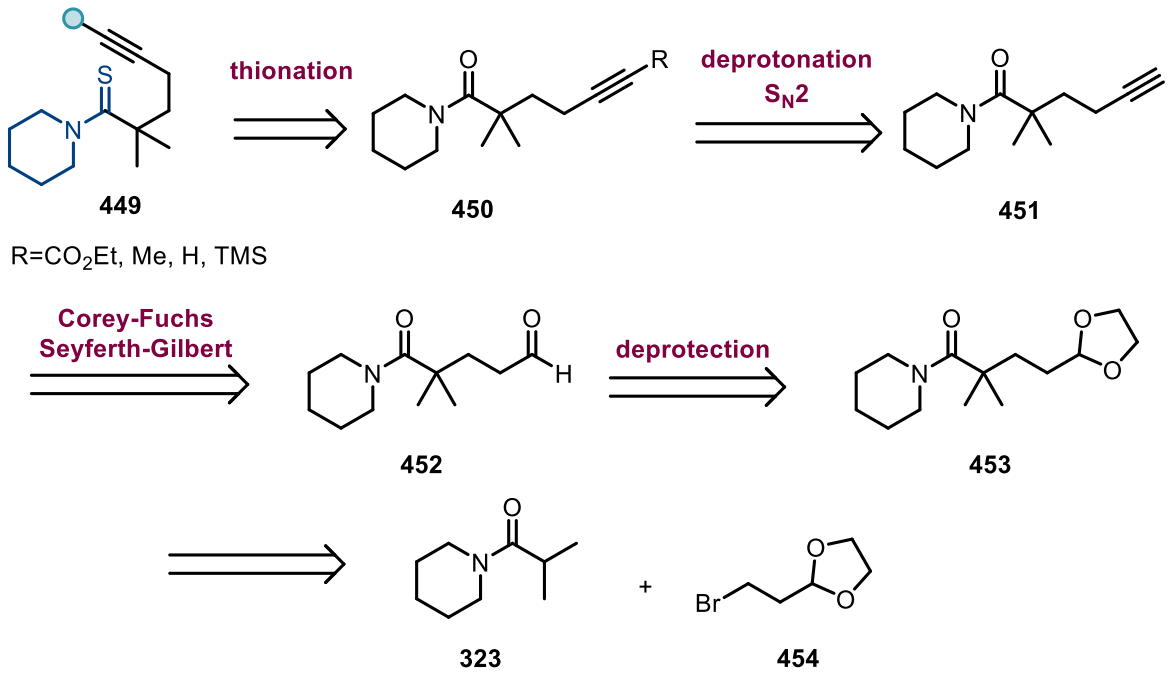
3.3 Project aims

The aim of this project was to further explore a largely undiscovered and undeveloped chemistry around cobalt catalysed C(sp^3)–H activation and to explore novel cyclic structural moieties with α-stereocentres acquired during the reaction.

This project is a direct follow up of the work described in chapter two, but in this case instead of using *β*-substituted thioamides with alkyne coupling partners, the aim is to design and build thioamide substrates to contain the alkyne within the molecule and therefore initiate intramolecular cobalt-catalysed C(sp^3)–H alkenylation directed by the thioamide group.

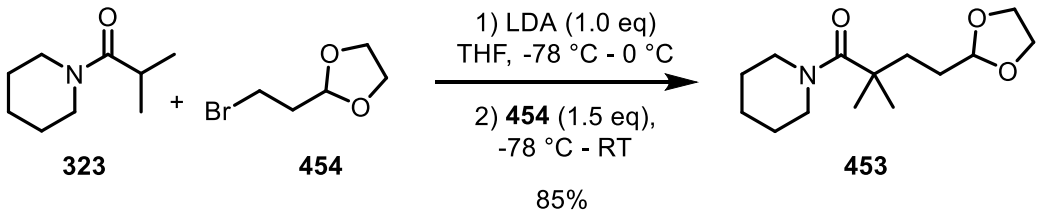
3.4 Initial preliminary studies towards the synthesis of alkyne containing substrates

Our investigation into the intramolecular Cp*Co^{III} catalysed C(sp^3)–H alkenylation started with the substrate design. For the starting material to contain the triple bond at the right place in the molecule, we had to look deeper into the various alkyne transformations. We started with the retrosynthetic analysis of our main substrate **449** (**Scheme 126**). Alkyne-containing thioamide **449** can be obtained from the corresponding amide **450**, which could be achieved by deprotonation followed by a nucleophilic addition of **451**. We considered that terminal alkyne group of **451** could be prepared from the corresponding aldehyde **452** *via* Corey-Fuchs[170] or Seyferth-Gilbert[171,172] reactions. In order to install the aldehyde **452** into our substrate, we could mask it by dioxolane protection and therefore, to form the amide-containing protected acetal **453**, we could use a simple nucleophilic substitution with amide **323** and bromoethyl dioxolane **454**. The reason we decided to use an aldehyde to install the alkyne group into the molecule instead of direct nucleophilic substitution of amide **323** with bromo alkyne, is the electronics of this bromo alkyne that would not allow the transformation for the substrate we desire.



Scheme 126. Retrosynthetic analysis of thioamide **449**.

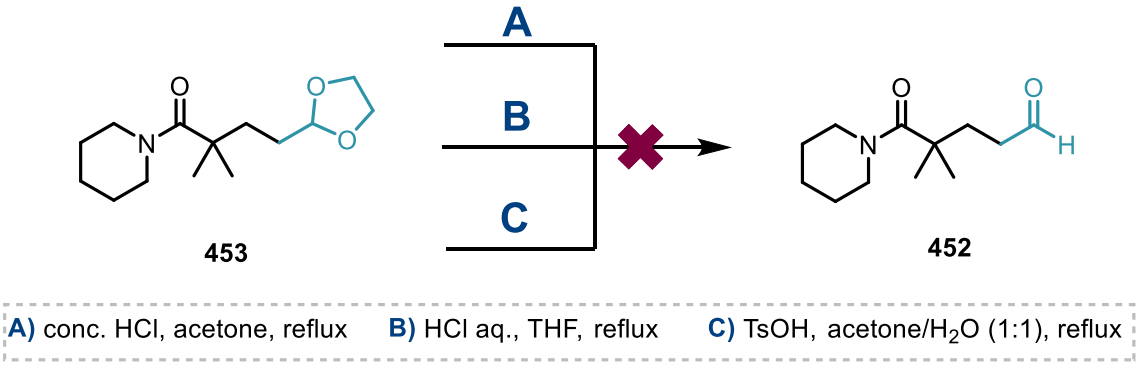
Following the retrosynthetic analysis, the synthesis of the desired starting material commenced. We started with the deprotonation of amide **323**, to which was added bromoalkyne **454**, which resulted in the formation of the dioxolane-containing amide **453** in excellent 85% yield (**Scheme 127**).



Scheme 127. Synthesis of amide **453**

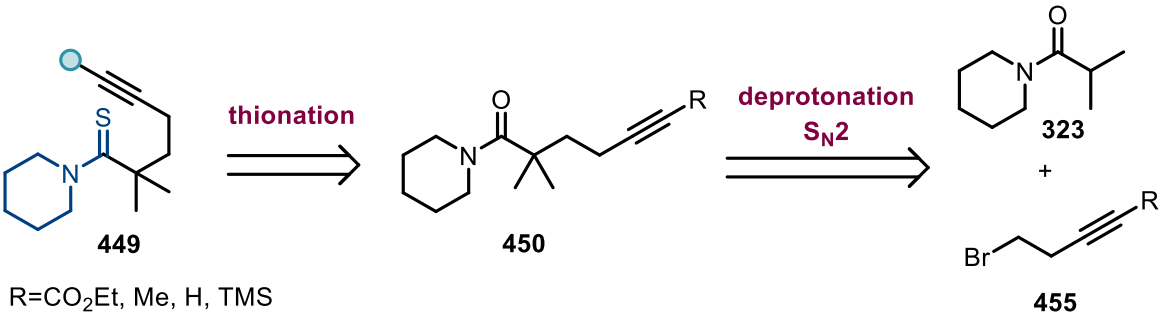
Having the amide **453** in hand, we were ready to transform it into the corresponding aldehyde **452** (**Scheme 128**). Deprotection of the dioxolane requires acidic conditions, and therefore we tried both concentrated and diluted hydrochloric acid, but unfortunately none led to the desired product. We also tried to deprotect this cyclic acetal with *p*-toluenesulfonic

acid, but we were not able to obtain the desired **452**, because conditions strong enough to deprotect the oxolane would also hydrolyse the amide group, and therefore we decided to change the approach to this synthesis.



Scheme 128. Unsuccessful aldehyde formation.

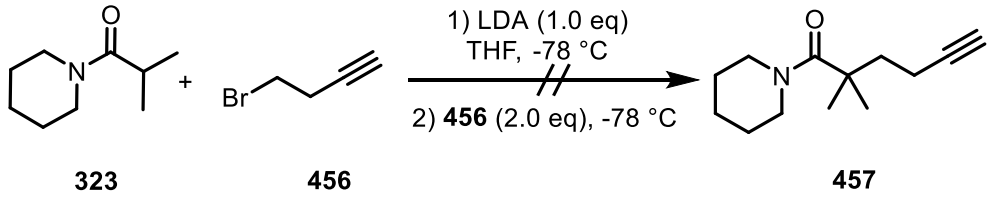
Returning to our retrosynthetic analysis of the desired thioamide **449**, we thought we could somehow manipulate the electronics of the bromo alkyne **455** and therefore allow the direct nucleophilic substitution of the amide **323** (**Scheme 129**).



Scheme 129. Retrosynthetic analysis of thioamide **449.**

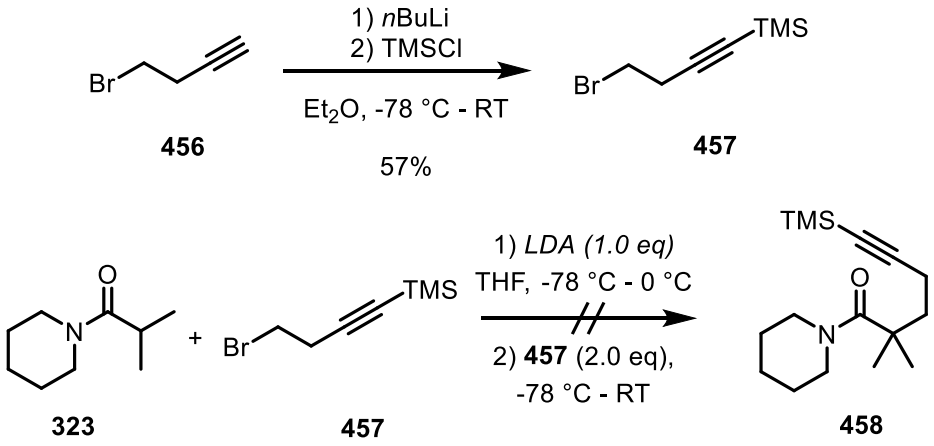
Even though we know that alkyne substrates like bromo alkyne **456** favour E2 reactions over the desired S_N2-type reaction when added with the corresponding enolate of **323**.[173] We wanted to test this reaction to see whether a small percentage of substrate could be transformed into the desired product **457**. Unfortunately, upon the reaction analysis, only the starting material was recovered from the transformation. This confirmed that **323** after

deprotonation formed an enolate that acts as a base, rather than a nucleophile and this enolate deprotonated the alkyne, causing it to eliminate (**Scheme 130**).



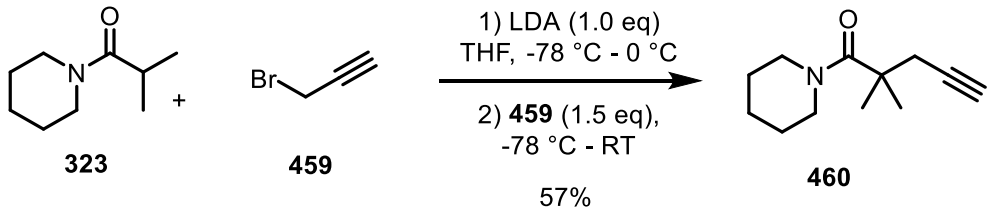
Scheme 130. Unsuccessful formation of amide **457**

Our next step was the formation of trimethylsilyl-containing alkyne **457**, which was obtained by a simple deprotonation of bromo alkyne **456** with *n*BuLi, followed by the TMSCl addition. This approach formed the alkyne **457** in 57% yield. We then took this alkyne and used it as a coupling partner in the next transformation. Unfortunately, the nucleophilic substitution between the amide **323** and bromo alkyne **457** did not occur, and similarly to the previous example, the E2 elimination was favoured and we were not able to form the desired amide **458** (**Scheme 131**), and due to the time constrains we decided to more forward with a different approach.



Scheme 131. Unsuccessful formation of amide **458.**

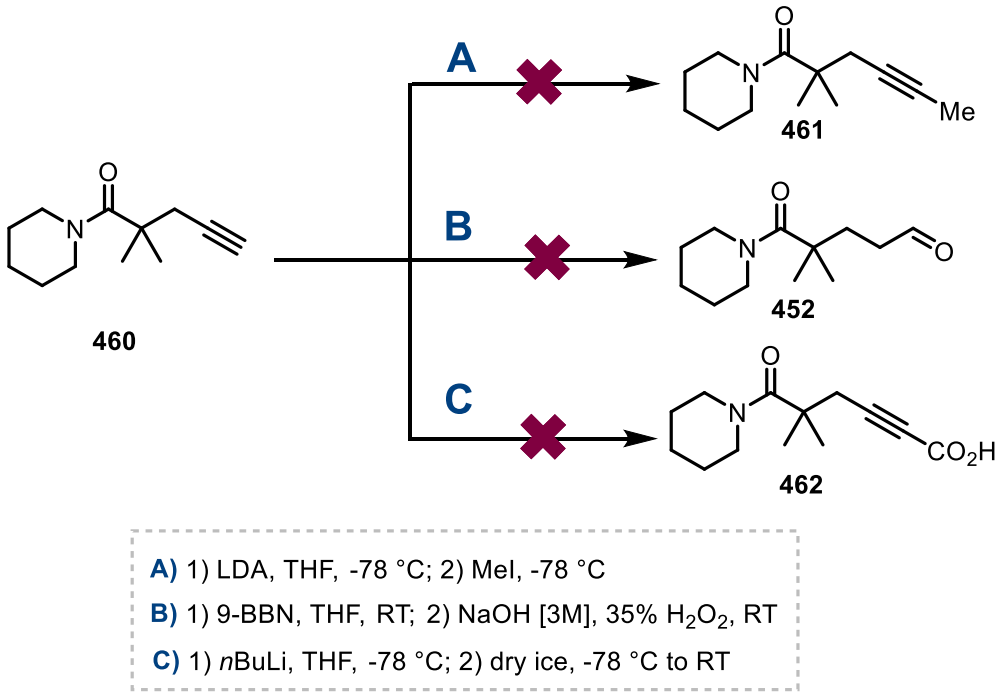
In any case, all of our attempts to install the alkyne group containing two extra CH_2 groups failed, we decided to shorten the alkyne and instead use bromopropyne **459**. The amide **323** was readily transformed into the corresponding enolate, to which was added bromopropyne **459** and the corresponding amide **460** was achieved in good 57% yield (**Scheme 132**).



323 459 460

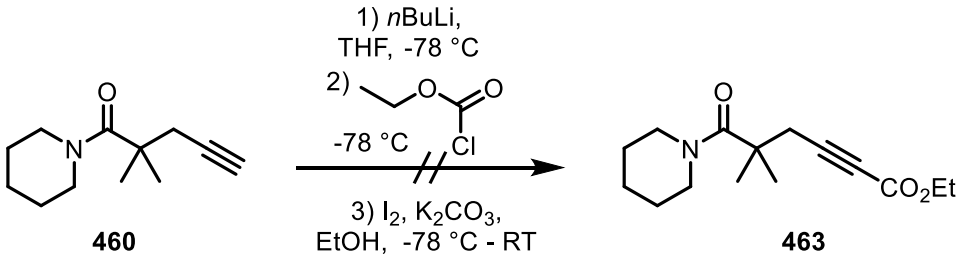
Scheme 132. Synthesis of amide **460.**

The plan was to use this amide to further derivatise its terminal sp hybridised carbon (**Scheme 133**). First, we wanted to methylate **460** to obtain amide **461**, but unfortunately this reaction led to a complex mixture of products, and we were not able to isolate compound **461**. Second, we wanted to use this alkyne for the formation of previously-designed aldehyde **452**, and therefore we trialled a Brown hydroboration followed by basic peroxide hydrolysis, but this again did not lead to the desired molecule. Lastly, we wanted to form a carboxylic acid functionalised amide **462**, and for that we deprotonated the terminal alkyne **460** and quenched the deprotection with dry ice, but we were not able to isolate the pure **462**.



Scheme 133. Unsuccessful transformations of amide **460.**

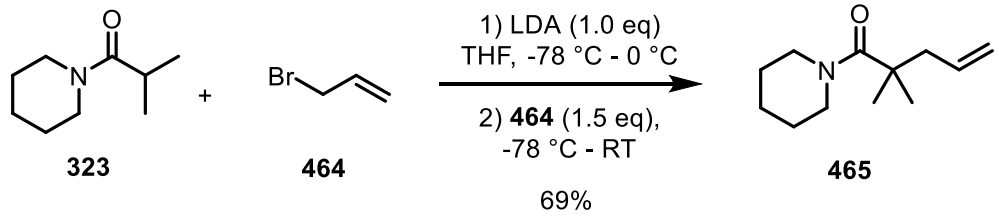
Not being able to transform the terminal alkyne group into any of the chosen functional groups led to our conclusion that perhaps functionalising it as an ethyl ester would make the compound **463** easier to afford and isolate, therefore we took the alkyne **460**, deprotonated and added ethyl chloroformate, but we were not able to isolate pure **463** (**Scheme 134).**



Scheme 134. Unsuccessful formation of amide **463.**

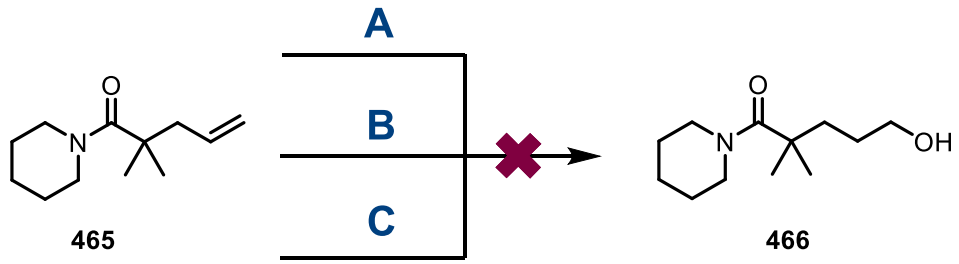
Being unsuccessful on so many fronts with the currently designed amide **460**, we decided to prepare terminal alkene functionalised amide **465** (**Scheme 135**). Amide **323** underwent the

S_N2 reaction with allyl bromide **464**, and we were able to isolate functionalised amide **465** in great 69% yield.



Scheme 135. Synthesis of amide **465**.

The reason to form this alkene-derived molecule **465** was the possibility to hydroxylate it using the Brown hydroboration method and form an oxidisable alcohol **466** (**Scheme 136**). Unfortunately, neither standard conditions with 9-BBN (**Scheme 136A**) nor an unusual ruthenium catalysed hydroxylation (**Scheme 136C**) did not lead to the required product, and we were only able to regenerate the starting material.

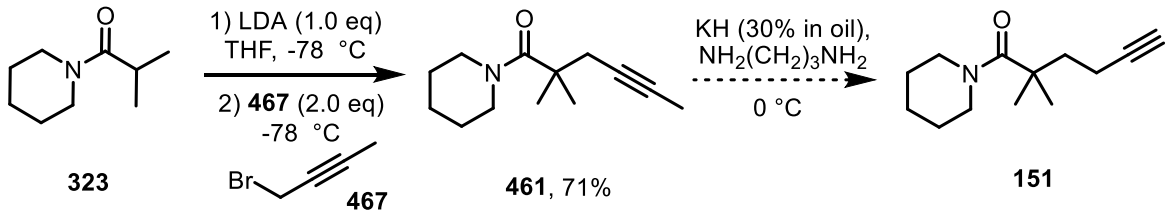


A) 1) 9-BBN, THF, RT; 2) NaOH [3M], 35% H_2O_2, RT
B) 1) $BF_3.Et_2O$, 2-methyl-2-butene, $NaBH_4$, THF, 0 °C;
2) alkene, RT, 2 h; 3) NaOH [3M], 30% H_2O_2, 70 °C
C) 1) H-Bpin, $[Ru(p\text{-cymene})Cl_2]_2$ neat, rt, 4h; 2) NaOH [3M], 30% H_2O_2, 70 °C

Scheme 136. Unsuccessful Brown hydroboration of amide **465.**

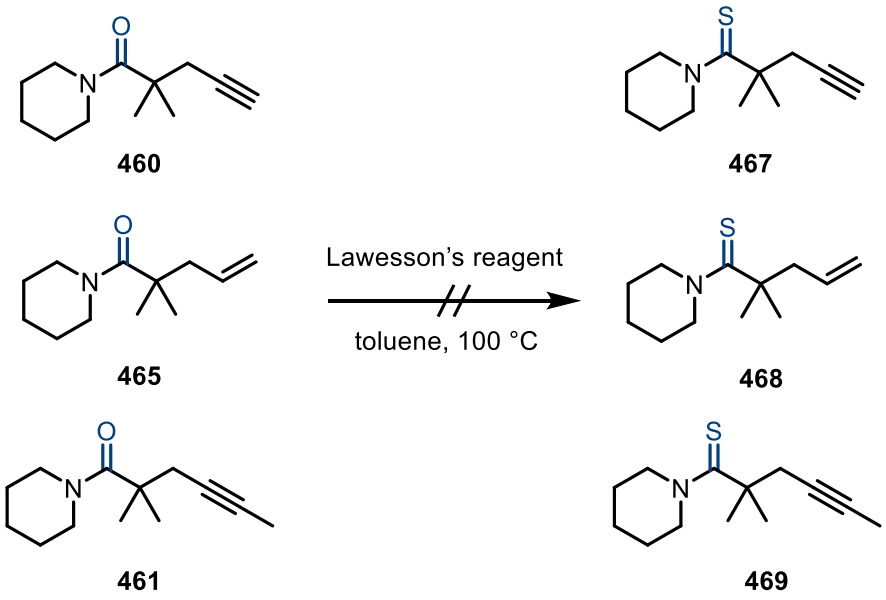
Expanding our search for possible transformations and how to deliver an alkyne group at the position we needed, we found that alkyne zipper reaction could allow the formation of the desired terminal alkyne, as this reaction involves isomerisation of a non-terminal alkyne

into the terminal. Therefore, we decided to prepare non-terminal alkyne **461** in the traditional fashion in 71% yield, but unfortunately due to time constraints the planned zipper reaction is yet to be tested (**Scheme 137**).



Scheme 137. Formation of amide **461** and following Alkyne zipper reaction.

Naturally, we wanted to test at least those amides/thioamides that we were able to prepare during the time working on this project (**Scheme 138**). However, what we found is that alkynes and alkenes of this type are not suitable to be transformed into the thioamide using the standard conditions with the Lawesson's reagent, and therefore different thionating agents need to be tested in order to furnish a small library of thioamides suitable for intramolecular C–H activation, however due to the time constrain we were not able to continue with these experiments.



Scheme 138. Unsuccessful attempts of the thioamide synthesis.

3.5 Conclusion and future work

In conclusion, we have designed new type of thioamides suitable for the intramolecular C–H activation reaction and some preliminary experiments were performed, but unfortunately in the limited time that we had we were not able to synthesise any of the desired thioamides. In the time we had left, we designed and tested multiple hypotheses towards the synthesis of desired alkyne-containing thioamides, however many of them turned unsuccessful. We were able to achieve 3 different amides with the potential to be successful for this transformation and we believe that the alkyne zipper reaction could be the key reaction in order to find a solution for the formation of terminal alkynes with a longer CH_2 chain in the molecule. Further work on this project can reveal a novel C–H activation reaction, which could be both academically interesting and have a potential use in the pharmaceutical and agrochemical industry.

Chapter 4: Final Remarks and Future Studies

During the course of this DPhil, a novel cobalt catalysed enantioselective C–H activation reaction with unusual regioselectivity has been discovered and developed and a direct follow-up project of an intramolecular variant of this transformation started.

In chapter 2, we have shown and demonstrated the novel enantioselective transformation of but-2-ynoates directed by thioamides to afford single unusual regioisomeric products in excellent yields of up to 85% and high enantiomeric ratio of up to 91:9 er, which can be, just by a single recrystallisation with Et_2O/pentane, transformed into enantiopure products (>99:1 er). Applicability of this transformation was demonstrated by diverse downstream derivatisations, affording a broad range of enantiopure scaffolds including medicinally relevant heterocycles such as oxazole, oxadiazole and benzothiazole. Mechanistic studies delivered the information of rate- and enantio- determining step of the catalytic cycle and the origins of enantio- and regio-selectivity of this reaction were elucidated using state-of-the-art DFT calculations on the complete catalytic cycle. This method is very mild, operationally easy as it does not require a glovebox like other methods using this $[Cp^*Co(MeCN)_3][SbF_6]_2$ complex. In chapter 3, we started our preliminary work towards an intramolecular variant of cobalt catalysed $C(sp^3)$–H functionalisation. We have designed a suitable thioamide starting material and tried various pathways to synthesise these substrates. Although, we were not able to achieve the thioamide compounds containing an alkyne group, we were able to prepare 3 amides that after the transformation to the thioamide could be suitable and possibly form the cyclic products. We believe that future work on this project could reveal and allow a new different C–H activation transformations and possibly expand this largely unexplored field.

Chapter 5: Experimental Section

5.1 General Experimental Details

5.1.1 Materials and Conditions

Reactions were carried out under a N_2 atmosphere in oven-dried glassware at room temperature (rt = 20 - 25 °C) unless stated otherwise. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. All reactions were performed using reagents obtained from MBRAUN-SPS solvent purification system, Sigma-Aldrich, Acros Organics, Alfa Aesar, STREM, Insight Biotechnology or Fluorochem without further purification unless stated. Anhydrous tetrahydrofuran, dichloromethane, toluene, 1,2-dichloroethane, 1,2-dichlorobenzene, dimethoxyethane were obtained by sitting over molecular sieves of the appropriate size under N_2 atmosphere. Diisopropylamine was dried by distillation over KOH and stored over KOH under N_2 atmosphere. Other solvents were used directly as received from commercial suppliers. Deuterated solvents were used as supplied. Solvents were removed under reduced pressure using Büchi Rotavapor apparatus.

5.1.2 Naming of compounds

Systematic names were generated using computer program ChemDraw in accordance with the guidelines specified by the International Union of Pure and Applied Chemistry (IUPAC).

5.1.3 Chromatography

Analytical thin-layer chromatography (TLC) was performed on aluminium backed sheets coated with Merck Kieselgel 60 F254 and visualised with UV light (λ_{max}= 254 or 365 nm),

$KMnO_4$, vanillin and/or ninhydrin solutions. Silica gel column chromatography was performed using 60 Å silica gel 40-63 μm purchased from VWR. The enantiomeric excess was determined by HPLC analysis on an Agilent 1200 Series instrument employing a chiral stationary phase column specified in the individual experiment and by comparing the samples with the appropriate racemic mixtures.

5.1.4 Mass Spectrometry

High-resolution mass spectra (ESI) were recorded on Bruker μTOF mass spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported (in ν_{max} (cm^{-1})).

5.1.5 Melting points

Melting points were obtained on a Leica Galen III hot-stage melting point microscope apparatus and are reported uncorrected (in °C).

5.1.6 NMR Spectroscopy

All ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded using a Bruker AVG400 (400/101 MHz), Bruker AVH400 (400/101 MHz), Bruker AVF400 (400/101 MHz), Bruker AVC500 (500/126 MHz), Bruker AVB500 (500/126 MHz), Bruker AVX500 (500/126 MHz), Bruker NEO600 (600/151) and Bruker AV600 (600/151) NMR spectrometers. Spectra were referenced in ppm with respect to the residual solvent peak ($CHCl_3$: δ_H 7.26, δ_C 77.16 ppm; C_6D_5H: δ_H 7.16, δ_C 128.06 ppm; CD_3COCD_2H: δ_H 2.05, δ_C 29.84 ppm; CD_2HCN: δ_H 1.94, δ_C 1.32 ppm; $C_6D_4HCD_3$: δ_H 7.09, δ_C 125.13 ppm; CHD_2OD: δ_H 3.31, δ_C 49). NMR data are presented in the following format: chemical shift (multiplicity [app = apparent, br = broad, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq =

doublet of quartets, ddd = doublet of doublet of doublets, m = multiplet], coupling constant (in Hz), number of equivalent nuclei by integration). Peaks were assigned based on chemical shifts, integrations, coupling constants, 2-D COSY and HSQC, HMBC and NOESY.

5.1.7 Polarimetry

Optical rotations were recorded using a Perkin Elmer 241 optical activity polarimeter at 25 $^{\circ}$C.

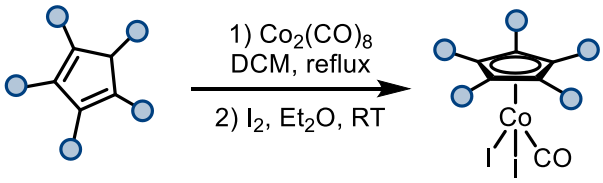
5.1.8 X-Ray Crystallography

Single crystal X-ray diffraction data were collected using an Enraf-Nonius KCCD diffractometer or an Oxford Diffraction SuperNova diffractometer at 150 K. Crystal structures were solved with SIR92 and refined with CRYSTALS by Dr. Heyao Shi (University of Oxford), with assistance of Dr. Amber L. Thompson and Dr. Kirsten E. Christensen (University of Oxford - Chemical Crystallography department).

5.2 Experimental Details for Chapter 2

5.2.1 Synthesis of catalysts

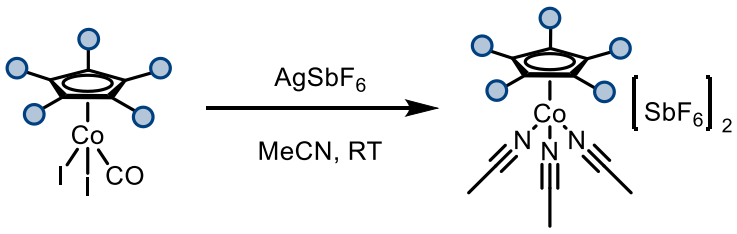
5.2.1.1 General procedure A: *Precatalyst synthesis*



Modified literature procedure.[116]

To a solution of $Co_2(CO)_8$ (1.00 eq.) in degassed DCM (0.15 M) was added corresponding cyclopentadiene (2.43 eq.), and the mixture was heated to reflux under an argon stream for 6 hours, cooled down to room temperature and the solvent was removed under vacuum. The residue was dissolved in degassed Et_2O (0.3 M) and iodine (2.43 eq.) in degassed Et_2O (0.3 M) was added dropwise at room temperature. After stirring the mixture for 2 hours, the solvent was removed *in vacuo* and the residue was purified by silica gel column chromatography (pentane then DCM/pentane) to yield corresponding $CpCo(CO)I_2$ complex.

5.2.1.2 General procedure B: *Catalyst synthesis*

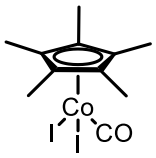


Modified literature procedure.[174]

To the suspension of corresponding $CoCp^*(CO)I_2$ (1.00 eq.) in anhydrous MeCN (0.1 M), a solution of $AgSbF_6$ (4.00 eq.) in dried MeCN (0.1 M) was added portion-wise, causing

AgI to precipitate immediately. The reaction mixture was allowed to stir under the argon stream for 3 hours at room temperature. The white solid was then filtered through a pad of Celite, washed with MeCN (3 x reaction solvent volume) and the residue was concentrated to approx. 1/10 of the volume. The product was then precipitated *via* a rapid addition of Et_2O (6 x reaction solvent volume). The purple solid was collected by suction filtration, washed twice with DCM and twice with Et_2O, collected and dried under reduced pressure to yield the desired product.

CoCp(CO)I₂ Precatalyst (Co1')*



Prepared according to **general procedure A**, using $Co_2(CO)_8$ (2.00 g, 5.8 mmol, 1.00 eq.) in degassed DCM (40.0 mL, 0.15 M), with pentamethylcyclopentadiene (2.2 mL, 14.2 mmol, 2.43 eq.). The residue dissolved in degassed Et_2O (20.0 mL, 0.3 M) was added with iodine (3.60 g, 14.2 mmol, 2.43 eq.) in degassed Et_2O (20.0 mL, 0.3 M). The crude residue was purified by silica gel column chromatography (pentane then 4/1 DCM/pentane) to yield $CoCp*(CO)I_2$ as black crystals (5.01 g, 90%).

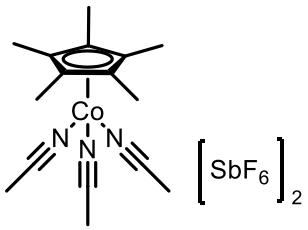
Analytical data is consistent with literature.[116]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 2.23 (s, 15H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 101.1 (Cp<u>C</u>), 11.6 (C(<u>C</u>H_3)$_5$).

IR (film) ν_{max}/cm^{-1}: 2981 (C-H), 2052 (C≡O), 1472, 1375, 1252, 1155, 1073, 954.

*[Cp*Co(MeCN)$_3$][SbF$_6$]$_2$ Catalyst Co1*

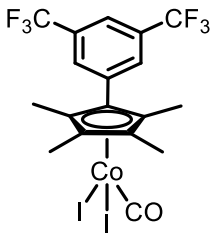


Prepared according to **general procedure B**, using CoCp*(CO)I$_2$ **Co1'** (4.76 g, 10.0 mmol, 1.00 eq.) in anhydrous MeCN (25.0 mL, 0.1 M), with a solution of AgSbF$_6$ (13.75 g, 40.0 mmol, 4.00 eq.) in dried MeCN (25.0 mL, 0.1 M). The title product was collected as a purple solid (6.75 g, 86%).

Analytical data is consistent with literature.[174]

^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 1.99 (s, 9H, 3N≡CC$\underline{H}_3$), 1.41 (s, 15H, C(C$\underline{H}_3$)$_5$).

Precatalyst Co2'



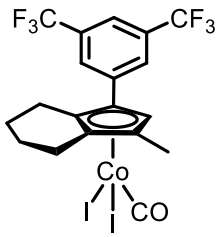
Prepared according to **general procedure A**, using $Co_2(CO)_8$ (100 mg, 0.29 mmol, 1.00 eq.) in degassed DCM (2.0 mL, 0.15 M), with a cyclopentadiene ligand (164 mg, 0.49 mmol, 1.70 eq.). The residue dissolved in degassed Et_2O (1.0 mL, 0.3 M) was added with iodine (58.8 mg, 0.59 mmol, 0.80 eq.) in degassed Et_2O (1.0 mL, 0.3 M). The crude residue was purified by silica gel column chromatography (pentane then 1/1 DCM/pentane) to yield **Co2'** as black crystals (93.1 mg, 60%).

Presence of complex was confirmed using IR spectroscopy (CO peak at 2055.32) and was used in a next step without further analysis, to avoid potential issues with air sensitivity.

IR (film) ν_{max}/cm^{-1}: 2980.59, 2055.32 (CO), 1462.60, 1378.77, 1345.04, 1278.14, 1175.93, 1132.96, 1018.06, 953.59, 902.10, 848.92, 824.23, 707.11, 673.18.

MP 71-73°C.

Precatalyst Co3'



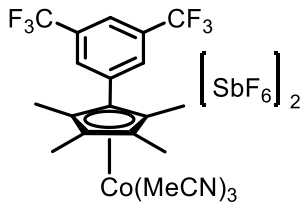
Prepared according to **general procedure A**, using $Co_2(CO)_8$ (100 mg, 0.29 mmol, 1.00 eq.) in degassed DCM (2.0 mL, 0.15 M) with cyclopentadiene ligand (203 mg, 0.59 mmol, 2.00 eq.). The residue dissolved in degassed Et_2O (1.0 mL, 0.3 M) was added with iodine (148 mg, 0.59 mmol, 2.00 eq.) in degassed Et_2O (1.0 mL, 0.3 M). The crude residue was purified by silica gel column chromatography (pentane then 1/1 DCM/pentane) to yield **Co3'** as black crystals (48.7 mg, 24%).

Presence of complex was confirmed using IR spectroscopy (CO peak at 2059.79) and was used in a next step without further analysis, to avoid potential issues with air sensitivity.

IR (film) ν_{max}/cm^{-1}: 2980.59, 2059.79 (CO), 1380.83, 1361.02, 1278.51, 1172.86, 1134.94, 682.30.

MP 66-70 °C.

Catalyst Co2



Prepared according to **general procedure B**, using **Co2'** (80 mg, 0.12 mmol, 1.00 eq.) in anhydrous MeCN (0.3 mL, 0.1 M), with a solution of $AgSbF_6$ (163 mg, 0.48 mmol, 4.00 eq.) in dried MeCN (0.3 mL, 0.1 M). The title product **Co2** was collected as a purple solid (116 mg, 99%).

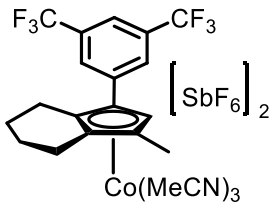
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.40 – 8.35 (m, 1H_{Ar}), 8.20 – 8.14 (m, 2H_{Ar}), 1.53 (s, 6H, 2 C(C_{Ar})-C(C$\underline{H}_3$)-C(CH_3)), 1.43 (s, 6H, 2 C(C_{Ar})-C(CH_3)-C(C$\underline{H}_3$)).

^{13}C NMR (101 MHz, Acetonitrile-d_3) δ 138.4, 133.5, 130.7, 109.4, 101.8 (N$\underline{C}$(CH_3), 11.5, 10.5, 1.9, 1.7.

IR (film) ν_{max}/cm^{-1}: 3607.01, 2283.76 (CN), 1623.62, 1348.28, 1282.65, 1184.10, 1139.44, 657.88.

MP 110-130 °C.

Catalyst Co3



Prepared according to **general procedure B**, using **Co3'** (30 mg, 0.04 mmol, 1.00 eq.) in anhydrous MeCN (0.1 mL, 0.1 M), with a solution of $AgSbF_6$ (60 mg, 0.18 mmol, 4.00 eq.) in dried MeCN (0.1 mL, 0.1 M). The title product **Co3** was collected as a purple solid (37.2 mg, 85%).

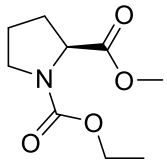
^{1}H NMR (400 MHz, Acetonitrile-d_3) δ 8.42 – 8.36 (m, $1H_{Ar}$), 8.23 – 8.14 (m, $2H_{Ar}$), 1.73 (m, 4H, $2C(C_{Cp})$-$C\underline{H_2}$-CH_2), 1.68 (m, 4H, $2C(C_{Cp})$-CH_2-$C\underline{H_2}$), 1.56 (s, 3H, $C(C\underline{H_3})$).

IR (film) ν_{max}/cm^{-1}: 2262.43 (CN), 1036.74, 833.40, 659.98.

MP 130 °C decomposition.

5.2.1.3 Synthesis of Hayashi's catalyst

1-Ethyl 2-methyl (S)-pyrrolidine-1,2-dicarboxylate (470)



Prepared according to literature,[150] *L*-proline (5.00 g, 43.4 mmol, 1.00 eq.) was dissolved in MeOH (100 mL) and K_2CO_3 (6.00 g, 43.5 mmol, 1.00 eq.) was added to the flask. The reaction mixture was cooled down to 0 °C and ethyl chloroformate (9.13 mL, 10.37 g, 95.5 mmol, 2.20 eq.) was added dropwise over 30 minutes. The mixture was then stirred for 4 hours at 0°C and overnight at room temperature. MeOH was removed under reduced pressure and 40 mL of water were added to the residual oil. The solution was then extracted with DCM and the combined organic layers were washed with brine and dried over Mg_2SO_4, filtered and evaporated to dryness to achieve the product **470** as pale yellow oil (8.63 g, 99%).

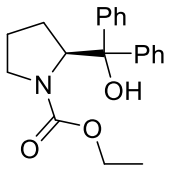
Analytical data is consistent with literature.[150]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.34 (dd, *J* = 8.6, 3.4 Hz, 1H), 4.27 (dd, *J* = 8.7, 3.9 Hz, 1H), 4.18 – 3.99 (m, 4H), 3.71 (s, 2H), 3.69 (s, 3H), 3.61 – 3.36 (m, 5H), 2.31 – 2.04 (m, 3H), 2.02 – 1.79 (m, 6H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 173.5, 173.4, 155.3, 154.7, 61.4, 61.3, 59.1, 58.9, 52.3, 52.2, 46.8, 46.4, 31.0, 30.0, 24.4, 23.6, 14.8, 14.7.

HRMS (ESI) $[C_9H_{16}NO_4]^+$ requires m/z: 202.1056, found m/z: 202.1058.

Ethyl (S)-2-(hydroxydiphenylmethyl)pyrrolidine-1-carboxylate (471)



According to literature,[150] Mg turnings (1.62 g, 66.6 mmol, 4.00 eq.) were suspended in THF (20 mL) and few crystals of I_2 were added. Phenyl bromide (7.09 ml, 10.46 g, 66.6 mmol, 4.00 eq.) was dissolved in THF (46.6 mL) and added dropwise into the reaction mixture over 30 minutes. The mixture was then heated to reflux for 1 hour to obtain phenylmagnesium bromide. The reaction mixture was cooled to 0 °C and protected *L*-proline **470** (3.35 g, 16.6 mmol, 1.00 eq.) dissolved in THF (25 mL) was added. The reaction mixture was stirred at 0 °C for 1 hour and overnight at room temperature. Subsequently, the mixture was cooled down to 0 °C and quenched with water. The mixture was filtered by suction filtration and washed with Et_2O. The filtrate was extracted with Et_2O and the combined organic layers were washed with brine, dried over Mg_2SO_4 and concentrated on vacuum. Purification by flash column chromatography (gradient EtOAc/pentane) resulted in the compound **471** (3.58 g, 66%) as a white solid.

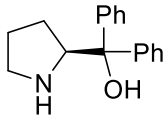
Analytical data is consistent with literature.[150]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.16 (m, 10H), 4.86 (dd, *J* = 8.9, 3.6 Hz, 1H), 4.15 – 3.82 (m, 2H), 3.34 (q, *J* = 8.7 Hz, 1H), 2.88 (s, 1H), 2.08 – 1.97 (m, 1H), 1.92 – 1.83 (m, 1H), 1.50 – 1.32 (m, 1H), 1.16 (t, *J* = 7.1 Hz, 3H), 0.73 (s, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.5, 143.8, 128.3, 128.0, 127.8, 127.6, 127.3, 127.3, 81.7, 62.1, 47.9, 29.8, 23.1, 14.8.

HRMS (ESI) $[C_{20}H_{24}NO_3]^+$ requires m/z: 326.1749, found m/z: 326.1750.

(S)-Diphenyl(pyrrolidin-2-yl)methanol (472)



According to literature,[150] KOH (6.16 g, 109.79 mmol, 10.00 eq.) was dissolved in MeOH (55 mL) and the protected prolinol amine **471** (3.57 g, 10.98 mmol, 1.00 eq.) was added to the mixture and heated to reflux overnight. Subsequently, the reaction mixture was concentrated on vacuum, quenched with water and 1 M HCl and extracted with DCM. The aqueous layer was then basified with KOH and extracted with DCM. The combined organic layers were washed with brine, dried over Mg_2SO_4, filtered and concentrated on vacuum to yield the corresponding unprotected amine **472** (1.56 g, 56%) as a pale yellow solid.

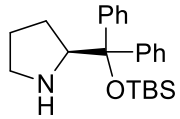
Analytical data is consistent with literature.[150]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.60 – 7.53 (m, 2H), 7.52 – 7.44 (m, 2H), 7.32 – 7.20 (m, 4H), 7.20 – 7.10 (m, 2H), 4.24 (t, *J* = 7.6 Hz, 1H), 3.06 – 2.87 (m, 2H), 1.81 – 1.52 (m, 4H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 148.3, 145.5, 128.4, 128.1, 126.6, 126.5, 126.0, 125.7, 77.2, 64.6, 46.9, 26.4, 25.6.

HRMS (ESI) $[C_{17}H_{20}NO]^+$ requires m/z: 254.1557, found m/z: 254.1558.

(S)-2-(((tert-Butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine (306)



According to literature,[149] to the unprotected amine **472** (0.500 g, 1.97 mmol, 1.00 eq.) in DCM (10 mL) 2,6-lutidine (1.15 mL, 9.87 mmol, 5.00 eq.) was added at 0 °C. TBSOTf (1.36 mL, 5.92 mmol, 3.00 eq.) was added portion-wise and the reaction was stirred overnight at room temperature. The mixture was quenched with NH_4Cl at 0 °C and the solution was extracted with DCM. The combined organic layer was washed with KOH (1 M, 25 mL), water and brine, dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The crude was purified via flash column chromatography (1/9 EtOAc/pentane) to give **306** (0.519 g, 72%) as pale yellow crystals.

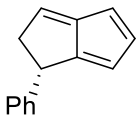
Analytical data is consistent with literature.[149]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.54 – 7.48 (m, 2H), 7.39 – 7.32 (m, 2H), 7.31 – 7.20 (m, 6H), 4.02 (t, *J* = 7.3 Hz, 1H), 2.82 (ddd, *J* = 10.0, 7.5, 6.2 Hz, 1H), 2.68 (ddd, *J* = 10.0, 7.5, 5.5 Hz, 1H), 1.70 (s, 1H), 1.64 – 1.46 (m, 3H), 1.30 – 1.15 (m, 1H), 0.95 (s, 9H), -0.22 (s, 3H), -0.46 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 146.6, 145.4, 129.4, 128.4, 127.7, 127.4, 127.2, 127.1, 83.2, 65.8, 47.3, 28.0, 26.5, 25.1, 19.2, -2.6, -3.2.

HRMS (ESI) $[C_{23}H_{34}NOSi]^+$ requires m/z: 368.2384, found m/z: 368.2383.

(S)-1-Phenyl-1,2-dihydropentalene (308)



According to literature,[137] (*S*)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine **306** (0.300 g, 0.82 mmol, 10 mol%) and p-nitrophenol (0.227 g, 1.63 mmol, 20 mol%) were dissolved in MeOH/DCM (8.2 mL/8.2 mL) and (*E*)-cinnamaldehyde (1.00 mL, 1.080 g, 8.17 mmol, 1.00 eq.) was added at room temperature. The reaction mixture was stirred for 1 minute before addition of cyclopentadiene (2.06 mL, 1.621 g, 24.52 mmol, 3.00 eq.). After stirring for 24 hours at room temperature excess of cyclopentadiene was azeotropically removed from the crude mixture with toluene. Subsequently, *p*-nitrophenol (1.137 g, 8.17 mmol, 1.00 eq.) and diisobutylamine (2.152 mL, 12.26 mmol, 1.50 eq.) were added to the crude mixture in MeOH/DCM (8.2 mL/8.2 mL) at room temperature and the solution was allowed to stir for 36 hours. The reaction was quenched with phosphate buffer pH 7.0 and extracted with DCM. The combined organic layer was washed with brine, dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (pentane to 1/100 DCM/pentane) to yield product **308** (0.551 g, 38%) as a bright orange solid.

Enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (100/1 hexane/*i*PrOH; flow rate 1.0 ml/min, λ=220 nm, τ_{Rmajor} = 9.43 min, τ_{Rminor} = 7.36 min).

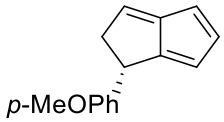
Analytical data is consistent with literature.[148]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.24 (m, 5H), 7.21 – 7.17 (m, 3H), 6.90 (dd, *J* = 5.1, 1.9 Hz, 1H), 6.82 (q, *J* = 2.6 Hz, 1H), 6.23 (d, *J* = 5.1 Hz, 1H), 5.91 (d, *J* = 2.1 Hz, 1H), 4.17 (d, *J* = 6.7 Hz, 1H), 3.69 (dd, *J* = 6.6, 2.8 Hz, 1H), 2.99 (t, *J* = 2.5 Hz, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.7, 153.7, 144.6, 142.4, 141.1, 128.7, 127.4, 126.4, 116.8, 112.5, 51.7, 42.3.

HRMS (ESI) $[C_{14}H_{13}]^{+}$ m/z: requires m/z: 181.0999, found m/z: 181.1000.

(S)-1-(4-Methoxyphenyl)-1,2-dihydropentalene (309)



According to literature,[137] (*S*)-2-(((tert-butyldimethylsilyl)oxy)diphenylmethyl)pyrrolidine **306** (22.7 mg, 0.06 mmol, 10 mol%) and *p*-nitrophenol (17.2 mg, 0.12 mmol, 20 mol%) were dissolved in MeOH/DCM (0.6 mL/0.6 mL) and *p*-methoxy-(*E*)-cinnamaldehyde (100 mg, 0.62 mmol, 1.00 eq.) was added at room temperature. The reaction mixture was stirred for 1 minute before addition of cyclopentadiene (155 µL, 122 mg, 1.85 mmol, 3.00 eq.). After stirring for 24 hours at room temperature excess of cyclopentadiene was azeotropically removed from the crude mixture with toluene. Subsequently, *p*-nitrophenol (85.8 mg, 0.62 mmol, 1.00 eq.) and diisobutylamine (162 µL, 0.92 mmol, 1.50 eq.) were added to the crude mixture in MeOH/DCM (0.6 mL/0.6 mL) at room temperature and the solution was allowed to stir for 22 hours. The reaction was quenched with phosphate buffer pH 7.0 and extracted with DCM. The combined organic layer was washed with brine, dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1/100 EtOAc/pentane) to yield product **309** (39.2 mg, 30%) as an orange solid.

Enantiomeric excess was determined by HPLC using a Chiralpak OD-H column (100/1 hexane/*i*PrOH; flow rate 1.0 ml/min, λ=220 nm, τ_{Rmajor} = 11.63, τ_{Rminor} = 8.64 min).

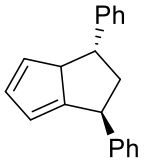
Analytical data is consistent with literature.[148]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.10 (m, 2H), 6.90 (dd, *J* = 5.2, 1.8 Hz, 1H), 6.86 – 6.80 (m, 3H), 6.22 (d, *J* = 5.1 Hz, 1H), 5.90 (d, *J* = 2.1 Hz, 1H), 4.13 (dt, *J* = 6.6, 2.2 Hz, 1H), 3.79 (s, 3H), 3.65 (ddd, *J* = 20.0, 6.5, 2.8 Hz, 1H), 2.96 – 2.94 (m, 1H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.2, 154.1, 153.7, 142.3, 141.2, 136.7, 128.3, 116.6, 114.0, 112.5, 55.4, 51.8, 41.5.

HRMS (ESI) $[C_{15}H_{15}O]^+$ requires m/z: 211.1096, found m/z: 211.1095.

(1S,3R)-1,3-Diphenyl-1,2,3,3a-tetrahydropentalene (310)



According to literature,[137] the solution of PhLi (1.25 mL, 1.67 M, 2.08 mmol, 7.50 eq.) in Bu_2O was added dropwise to the solution of bicyclo[3.3.0]octatriene **308** (50 mg, 0.28 mmol, 1.00 eq.) in anhydrous Et_2O (555 µL) and anhydrous benzene (277 µL) at -40 °C. The reaction mixture was stirred at -40 °C for 2 hours, and then allowed to slowly warm up to 0 °C. After stirring for 22 hours at 0 °C the reaction was quenched with water and the combined organic layer was extracted with Et_2O, washed with brine, dried over Mg_2SO_4, filtered and concentrated *in vacuo*. The crude mixture was purified via flash column chromatography (pentane to 1/100 Et_2O/pentane) to yield **310** (51 mg, 71%) as an orange solid.

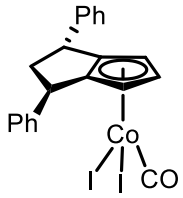
Analytical data is consistent with literature.[137]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.36 – 7.27 (m, 5H), 7.24 – 7.14 (m, 5H), 6.48 (d, *J* = 5.4 Hz, 1H), 6.39 (dt, *J* = 5.4, 1.8 Hz, 1H), 4.28 – 4.18 (m, 2H), 2.97 – 2.67 (m, 4H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 153.2, 152.9, 146.5, 145.6, 136.8, 129.3, 128.6, 128.5, 127.8, 127.5, 127.3, 126.2, 51.3, 47.8, 46.4, 36.9.

HRMS (ESI) $[C_{20}H_{19}]^+$ requires m/z: 259.1473, found m/z: 259.1474.

Precatalyst Co4'



Prepared according to **general procedure A**, using $Co_2(CO)_8$ (200 mg, 0.59 mmol, 1.00 eq.) in degassed DCM (4 mL, 0.15 M), with a chiral cyclopentadiene ligand **310** (302 mg, 1.17 mmol, 2.00 eq.). The residue dissolved in degassed Et_2O (2.0 mL, 0.3 M) was added with iodine (297 mg, 1.17 mmol, 2.00 eq.) in degassed Et_2O (2 mL, 0.3 M). The crude residue was purified by silica gel column chromatography (pentane then 1/1 Et_2O/pentane) to yield **Co4'** as black crystals (248.4 mg, 71%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 6.94 (m, 10H_{Ph}), 6.16 (s, 1H), 5.73 (s, 1H), 4.81 (d, 2H, C(C_{Ph})-C$\underline{H}_2$), 4.43 (s, 1H), 3.34 (q, *J* = 11.1, 10.6 Hz, 1H), 2.80 – 2.64 (m, 1H).

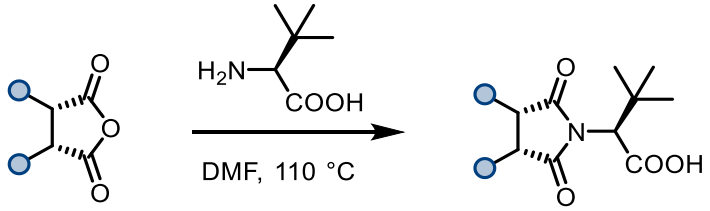
^{13}C NMR (101 MHz, Chloroform-*d*) δ 129.4 (2C_{Ph}), 128.4 (2C_{Ph}), 127.8 (2C_{Ph}), 127.3 (2C_{Ph}), 127.2 (2C_{Ph}), 97.3 (2C_{Cp}), 81.8 (2C_{Cp}), 73.6 (C_{Cp}), [44.2, 42.0, 41.3] ($\underline{C}$(C_{Ph})-$\underline{C}H_2$-$\underline{C}$(C_{Ph})).

IR (film) ν_{max}/cm^{-1}: 2980.62, 2888.97, 2065.75 (CO), 1494.76, 1448.68, 1380.64, 1251.74, 1152.70, 1079.96, 954.84, 761.18, 700.16.

MP 70-74 °C.

5.2.2 Synthesis of chiral carboxylic acid ligands

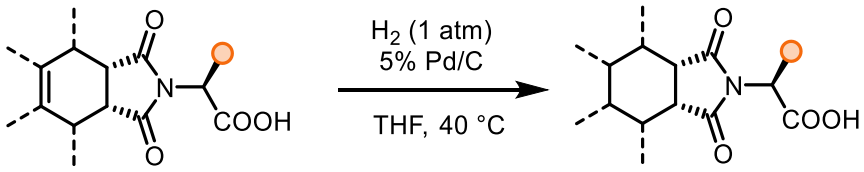
5.2.2.1 General procedure C: *Ligand Synthesis*



Modified literature procedure.[175]

An over dried round-bottom flask was charged with the anhydride (1.10 eq.) and *L-tert*-leucine (1.00 eq.). The mixture was dissolved in dry DMF (0.2 M) and heated for 24-48 hours at 110 °C. Upon completion, the reaction mixture was cooled down to room temperature, diluted with EtOAc, washed with brine (7 times), dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/pentane) to afford pure carboxylic acid ligands.

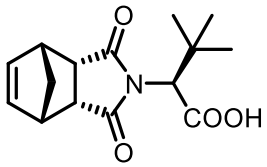
5.2.2.2 General procedure D: *Ligand Synthesis*



Modified literature procedure.[146]

The mixture of unsaturated carboxylic acid (1.00 eq.) and 5% palladium on carbon (0.80 eq.) was dissolved in THF (0.18 M) and stirred overnight under hydrogen atmosphere at 40 °C. The crude mixture was then filtered through a pad of Celite, washed with DCM and concentrated under reduced pressure to yield desired ligands. The products were either used directly or, if applicable, recrystallized from the listed solvent or solvent mixture.

(S)-2-((3aR,7aS)-1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-isoindol-2-yl)-3,3-dimethylbutanoic acid (L3)



Prepared according to **general procedure C**, using *cis*-5-Norbornene-endo-2,3-dicarboxylic anhydride (2.75 g, 16.8 mmol) and *L-tert*-leucine (2.00 g, 15.2 mmol). The crude mixture was purified by silica gel column chromatography (1/19 to 1/4 EtOAc/pentane). **L3** was isolated as light yellow powder (3.45 g, 82%).

Analytical data is consistent with literature.[146]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.19 – 6.08 (m, 2H), 4.37 (s, 1H), 3.46 – 3.39 (m, 2H), 3.38 – 3.29 (m, 2H), 1.75 (dt, *J* = 8.8, 1.7 Hz, 1H), 1.56 (d, 1H), 1.04 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 177.6 (amide C=O, 2C), 171.9 (acid C=O), 135.5 (CH=CH), 134.7 (CH=CH), 60.5 (N-CH-CO_2H), 52.7 (CH-CH_2-CH), 46.2 (NC(O)-CH), 45.9 (NC(O)-CH), 45.4 (NC(O)-CH-CH), 45.2 (NC(O)-CH-CH), 35.6 (C(CH_3)$_3$), 28.0 (C(CH_3)$_3$).

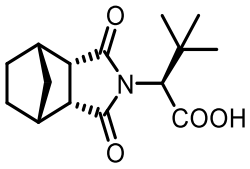
HRMS (ESI) [$C_{15}H_{20}O_4N$]+ requires m/z 278.1387, found m/z 278.1388.

MP 178 - 179 °C.

IR (film) ν_{max}/cm^{-1}: 3182, 2981, 1703, 1380, 1339, 1176.

$[\alpha]_D^{25}$ = -60 (c = 0.44, $CHCl_3$).

(S)-2-((3aR,4R,7S,7aS)-1,3-D -2H-4,7-methanoisoindol-2-yl)-3,3-dimethylbutanoic acid (L4)



Prepared according to **general procedure D**, using ligand **L3** (500 mg, 1.8 mmol) and 5% palladium on carbon (153 mg, 1.4 mmol). The crude product was purified by recrystallisation (EtOAc/hexane) to yield chiral carboxylic acid L4 as a white powder (269 mg, 54%).

Analytical data is consistent with literature.[146]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.53 (s, 1H), 3.21 – 3.09 (m, 2H), 2.84 – 2.73 (m, 2H), 1.70 – 1.45 (m, 5H), 1.40 – 1.30 (m, 1H), 1.12 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 178.4 (amide C=O), 178.2 (amide C=O), 172.1 (acid C=O), 60.3 (N-CH-CO_2H), 49.0 (NC(O)-CH), 42.8 (CH-CH_2-CH), 39.7 (NC(O)-CH-CH), 39.5 (NC(O)-CH-CH), 35.6 ($C(CH_3)_3$), 28.1 ($C(CH_3)_3$), 24.8 (CH_2-CH_2), 24.7 (CH_2-CH_2).

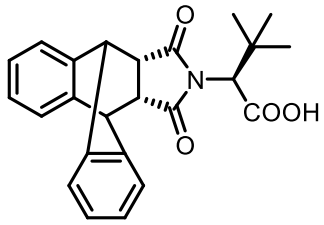
HRMS (ESI) $[C_{15}H_{22}O_4N]$+ requires m/z 280.1543, found m/z 280.1544.

MP 204 - 205 °C.

IR (film) ν_{max}/cm^{-1}: 3043, 2980, 2888, 1741, 1689, 1382, 1170.

$[\alpha]_D^{25}$ = -73.1 (c = 0.55, $CHCl_3$).

(S)-2-((11R,15S)-12,14-Dioxo-9,10-dihydro-9,10-[3,4]epipyrroloanthracen-13-yl)-3,3-dimethylbutanoic acid (L5)



According to literature,[176] a solution of anthracene (5.00 g, 28.0 mmol, 2.00 eq.) and maleic anhydride (2.50 g, 25.5 mmol, 1.00 eq.) in xylene (60.0 mL, 0.4 M) was refluxed for 8 h. The reaction mixture was then cooled down to the room temperature, which caused the precipitation of white solid. The precipitate was collected by vacuum filtration, washed with xylene and Et_2O, and then dried *in vacuo* to afford 9,10-dihydroanthracene-9,10-*α,β*-succinic anhydride as white powder (5.60 g, 80%), which was used in the next step crude.

Prepared according to **general procedure C**, using 9,10-dihydroanthracene-9,10-*α,β*-succinic anhydride (695 mg, 2.5 mmol) and *L-tert*-leucine (300 mg, 2.3 mmol). The crude mixture was purified by silica gel column chromatography (1/19 to 1/4 EtOAc/pentane). **L5** was isolated as white powder (636 mg, 72%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.34 (m, 2H, ArH), 7.33 – 7.26 (m, 2H, ArH), 7.19 – 7.13 (m, 2, ArH), 7.13 – 7.05 (m, 2H, ArH), 4.80 (t, *J* = 3.4 Hz, 2H, NC(O)-CH-CH), 4.19 (s, 1H, N-CH-CO_2H), 3.37 – 3.18 (m, 2H, NC(O)-CH), 0.67 (s, 9H, C(CH_3)$_3$).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 176.6 (amide C=O), 172.0 (acid C=O), 142.0 (ArC), 141.8 (ArC), 139.1 (ArC), 138.9 (ArC), 127.4 (ArC), 127.3 (ArC), 126.7 (ArC, 2C), 125.3 (ArC), 125.1 (ArC), 124.2 (ArC, 2C), 60.5 (N-CH-CO_2H), 47.2 – 46.9 (m, NC(O)-CH), 46.6 (NC(O)-CH), 45.3 (NC(O)-CH-CH, 2C), 34.8 (C(CH_3)$_3$), 27.3 (C(CH_3)$_3$).

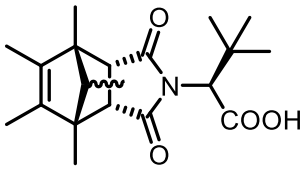
HRMS (ESI) $[C_{24}H_{24}O_4N]+$ requires m/z 390.1700, found m/z 390.1702.

MP 221 - 223 °C.

IR (film) ν_{max}/cm^{-1}: 2981, 1775, 1706, 1466, 1380, 1178, 1164, 878, 760, 731.

$[\alpha]_D^{25}$ = -37.8 (c = 0.67, $CHCl_3$).

(S)-3,3-Dimethyl-2-((3aR,4S,7R,7aS)-4,5,6,7,8-pentamethyl-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindol-2-yl)butanoic acid (L6)



According to literature,[177] a solution of 1,2,3,4,5-pentamethylcyclopentadiene (1.3 mL, 8.4 mmol, 1.10 eq.) and maleic anhydride (750 mg, 7.6 mmol, 1.00 eq.) were heated for 2 hours in toluene (3.0 mL, 2.5 M). Upon completion, the solvent was removed on rotary evaporator. The residue was recrystallized from hexane to give (*3aR,7aS*)-4,5,6,7,8-pentamethyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione as white crystals (913 mg, 51%).

Prepared according to **general procedure C**, using (3aR,7aS)-4,5,6,7,8-pentamethyl-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione (491 mg, 2.1 mmol) and *L-tert*-leucine (250 mg, 1.9 mmol). The crude mixture was purified by silica gel column chromatography (1/19 to 1/9 EtOAc/pentane). **L6** was isolated as light yellow powder (393 mg, 59%).

Isolated as mixture of diastereomers 1:4.5. Data given for the major diastereomer.

[i]All attempts to reduce the double bond has failed.

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.36 (s, 1H, N-C<u>H</u>-CO_2H), 3.03 – 2.95 (m, 2H, NC(O)-C<u>H</u>), 1.61 – 1.56 (m, 1H, C<u>H</u>), 1.52 – 1.46 (m, 6H, C<u>H</u>$_3$), 1.35 – 1.30 (m, 6H, C<u>H</u>$_3$), 1.03 (s, 9H, C(C<u>H</u>$_3$)$_3$), 0.60 (d, *J* = 6.4 Hz, 3H, CH-C<u>H</u>$_3$).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.8 (amide <u>C</u>=O), 177.5 (amide <u>C</u>=O), 172.4 (acid <u>C</u>=O), 134.7 (<u>C</u>=C), 133.0 (C=<u>C</u>), 66.4 (C-<u>C</u>H-C), 60.6 (brs, N-<u>C</u>H-CO_2H), 57.7 (NC(O)-

CH-CH), 57.4 (NC(O)-CH-CH), 53.5 (NC(O)-CH), 53.2 (NC(O)-CH), 35.5 ($C(CH_3)_3$), 27.9 ($C(CH_3)_3$), 15.0 (CH_3, 2C), 12.2 (CH_3, 2C), 7.6 (CH-CH_3).

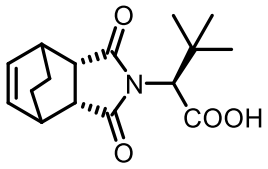
HRMS (ESI) $[C_{20}H_{30}O_4N]+$ requires m/z 348.2169, found m/z 248.2171.

MP 135 - 136 °C.

IR (film) ν_{max}/cm^{-1}: 2980, 1703, 1380, 1252, 1172, 954.

$[\alpha]_D^{25}$ = -35.4 (c = 0.4, $CHCl_3$).

(2S)-2-((3aR,7aS)-1,3-Dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-ethanoisoindol-2-yl)-3,3-dimethylbutanoic acid (L7)



According to literature,[178] a solution of 1,3-cyclohexadiene (1.1 mL, 11.2 mmol, 1.10 eq.) and maleic anhydride (1.00 g, 10.2 mmol, 1.00 eq.) in DCM (5.0 mL, 2 M) was added at room temperature and the mixture was heated to 55 °C and stirred for 5 hours. The reaction mixture was washed with water and the organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure, what afforded (*3aR,7aS*)-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1,3-dione as white solid (1.78 g, 75%). The crude product was used in the next step without further purification.

Prepared according to **general procedure C**, using (*3aR,7aS*)-3a,4,7,7a-tetrahydro-4,7-ethanoisobenzofuran-1,3-dione (403 mg, 2.3 mmol) and *L-tert*-leucine (270 mg, 2.1 mmol). The crude mixture was purified by silica gel column chromatography (1/19 to 1/4 EtOAc/pentane). **L7** was isolated as a white solid (372 mg, 62%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.26 – 6.13 (m, 2H, C<u>H</u>=C<u>H</u>), 4.44 (s, 1H, N-C<u>H</u>-CO_2H), 3.22 – 3.13 (m, 2H, NC(O)-CH-C<u>H</u>), 2.90 (qd, *J* = 8.4, 3.0 Hz, 2H, NC(O)-C<u>H</u>), 1.68 – 1.57 (m, 2H, C<u>H</u>$_2$-C<u>H</u>$_2$), 1.44 – 1.34 (m, 2H, C<u>H'</u>$_2$-C<u>H'</u>$_2$), 1.05 (s, 9H, C(C<u>H</u>$_3$)$_3$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 179.0 (amide <u>C</u>=O), 178.8 (amide <u>C</u>=O), 171.8 (acid <u>C</u>=O), 133.1 (<u>C</u>H=CH), 132.6 (CH=<u>C</u>H), 60.6 (N-<u>C</u>H-CO_2H), 44.5 (NC(O)-<u>C</u>H), 44.2 (NC(O)-<u>C</u>H), 35.9 (<u>C</u>(CH$_3$)$_3$), 32.0 (NC(O)-CH-<u>C</u>H), 31.8 (NC(O)-CH-<u>C</u>H), 28.0 (C(<u>C</u>H$_3$)$_3$), 23.9 (<u>C</u>H$_2$-CH$_2$), 23.8 (CH$_2$-<u>C</u>H$_2$).

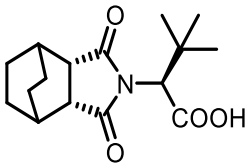
HRMS (ESI) $[C_{16}H_{22}O_4N]+$ requires m/z 292.1543, found m/z 292.1541.

MP 178 - 180 °C.

IR (film) ν_{max}/cm^{-1}: 2980, 1700, 1383, 1178, 732, 695.

$[\alpha]_D^{25}$ = -56.0 (c = 0.58, $CHCl_3$).

(S)-2-((3aR,7aS)-1,3-Dioxooctahydro-2H-4,7-ethanoisoindol-2-yl)-3,3-dimethylbutanoic acid (L8)



Prepared according to **general procedure D**, using ligand **L7** (250 mg, 0.9 mmol) and 5% palladium on carbon (73 mg, 0.7 mmol). The crude product was purified by recrystallisation (EtOAc/hexane) to yield chiral carboxylic acid **L8** as a white powder (170 mg, 68%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.58 (s, 1H, N-C<u>H</u>-CO_2H), 2.94 – 2.82 (m, 2H, NC(O)-C<u>H</u>), 2.20 (s, 2H, NC(O)-CH-C<u>H</u>), 1.77 – 1.68 (m, 2H, $C\underline{H}_2$-$C\underline{H}_2$), 1.62 (d, *J* = 10.8 Hz, 2H, $C\underline{H'}_2$-$C\underline{H'}_2$), 1.57 – 1.37 (m, 4H, $C\underline{H}_2$-$C\underline{H}_2$), 1.14 (s, 9H, $C(C\underline{H}_3)_3$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 180.0 (amide <u>C</u>=O, 2C), 172.8 (acid <u>C</u>=O), 60.3 (N-<u>C</u>H-CO_2H), 43.8 (NC(O)-<u>C</u>H, 2C), 35.7 ($\underline{C}(CH_3)_3$), 28.1 ($C(\underline{C}H_3)_3$), 26.3 (NC(O)-CH-<u>C</u>H), 26.2 (NC(O)-CH-<u>C</u>H), 25.2 ($\underline{C}H_2$-CH_2), 25.0 (CH_2-$\underline{C}H_2$), 21.5 ($\underline{C}H_2$-CH_2), 21.3 (CH_2-$\underline{C}H_2$).

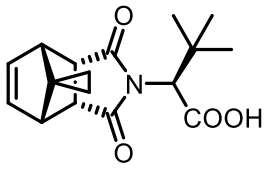
HRMS (ESI) $[C_{16}H_{24}O_4N]+$ requires m/z 294.1700, found m/z 294.1699.

MP 224 - 225 °C.

IR (film) ν_{max}/cm^{-1}: 3021, 2980, 1771, 1743, 1679, 1390, 1368, 1251, 1165, 744.

$[\alpha]_D^{25}$ = -72.6 (c = 0.47, $CHCl_3$).

(S)-2-((3a'R,4'S,7'R,7a'S)-1',3'-Dioxo-1',3',3a',4',7',7a'-hexahydro-2'H-spiro[cyclopropane-1,8'-[4,7]methanoisoindol]-2'-yl)-3,3-dimethylbutanoic acid (L9)



According to literature,[179] to a solution of maleic anhydride (200 mg, 2.0 mmol, 1.00 eq.) in chloroform (5.0 mL, 0.4 M) under argon atmosphere at 0 °C was added dropwise spiro[2.4]hepta-4,6-diene (204 µL, 2.0 mmol, 1.00 eq.) and the reaction was allowed to warm to room temperature and stirred for 20 hours in the dark. The solvent was evaporated *in vacuo* affording (*4'R,7'S*)-3a',4',7',7a'-tetrahydrospiro[cyclopropane-1,8'-[4,7]methanoisobenzofuran]-1',3'-dione as light yellow solid (387 mg, quant.). The crude product was used in the next reaction without any purification.

Prepared according to **general procedure C**, using (4'*R*,7'*S*)-3a',4',7',7a'-tetrahydrospiro[cyclopropane-1,8'-[4,7]methanoisobenzofuran]-1',3'-dione (375 mg, 2.0 mmol) and *L-tert*-leucine (235 mg, 1.8 mmol). The crude mixture was purified by silica gel column chromatography (1/19 to 3/17 EtOAc/pentane). **L9** was isolated as light yellow powder (174 mg, 32%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.29 – 6.16 (m, 2H, C<u>H</u>=C<u>H</u>), 4.40 (s, 1H, N-C<u>H</u>-CO_2H), 3.56 – 3.43 (m, 2H, NC(O)-C<u>H</u>), 2.86 – 2.74 (m, 2H, NC(O)-CH-C<u>H</u>), 1.06 (s, 9H, C($C\underline{H}_3$)$_3$), 0.66 – 0.55 (m, 2H, C-$C\underline{H}_2$-$C\underline{H}_2$), 0.54 – 0.45 (m, 2H, C-$C\underline{H'}_2$-$C\underline{H'}_2$).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 177.5 (amide <u>C</u>=O), 177.4 (amide <u>C</u>=O) , 171.8 (acid <u>C</u>=O), 135.4 (<u>C</u>H=CH), 134.7 (CH=<u>C</u>H), 60.6 (N-<u>C</u>H-CO_2H), 50.5 (NC(O)-CH-<u>C</u>H), 50.2

(NC(O)-CH-CH), 48.8 (CH-C-CH), 46.6 (NC(O)-CH), 46.3 (NC(O)-CH), 35.7 ($C(CH_3)_3$), 28.0 ($C(CH_3)_3$), 8.0 ($C-CH_2-CH_2$), 6.9 ($C-CH_2-CH_2$).

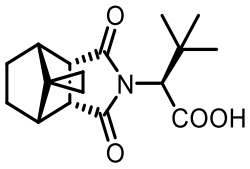
HRMS (ESI) $[C_{17}H_{22}O_4N]+$ requires m/z 304.1543, found m/z 304.1542.

MP 226 - 230 °C.

IR (film) ν_{max}/cm^{-1}: 2981, 2890, 1743, 1704, 1679, 1392, 1252, 1170, 954.

$[\alpha]_D^{25}$ = -60.8 (c = 0.2, $CHCl_3$).

(S)-2-((3a'R,4'S,7'R,7a'S)-1',3'-Dioxooctahydro-2'H-spiro[cyclopropane-1,8'-[4,7]methanoisoindol]-2'-yl)-3,3-dimethylbutanoic acid (L10)



Prepared according to **general procedure D**, using ligand **L9** (50 mg, 0.17 mmol) and 5% palladium on carbon (14 mg, 0.13 mmol). The product **L10** was obtained directly after filtration without further purification as white solid (34 mg, 68%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.55 (s, 1H, N-C<u>H</u>-CO_2H), 3.45 – 3.29 (m, 2H, NC(O)-C<u>H</u>), 2.01 (m, 2H, NC(O)-CH-C<u>H</u>), 1.89 – 1.70 (m, 2H, C<u>H_2</u>-C<u>H_2</u>), 1.64 – 1.54 (m, 1H, C<u>H'</u>$_2$-CH'$_2$), 1.51 – 1.40 (m, 1H, CH'$_2$-C<u>H'</u>$_2$), 1.13 (s, 9H, C(C<u>H_3</u>)$_3$), 0.66 – 0.53 (m, 4H, C-C<u>H_2</u>-C<u>H_2</u>).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.5 (amide <u>C</u>=O), 178.3 (amide <u>C</u>=O), 171.7 (acid <u>C</u>=O), 60.3 (N-<u>C</u>H-CO_2H), 49.1 (NC(O)-<u>C</u>H, 2C), 44.7 (NC(O)-CH-<u>C</u>H), 44.5 (NC(O)-CH-<u>C</u>H), 38.9 (CH-<u>C</u>-CH), 35.6 (<u>C</u>(CH_3)$_3$), 28.1 (C(<u>C</u>H_3)$_3$), 25.1 (<u>C</u>H_2-<u>C</u>H_2), 6.4 (C-<u>C</u>H_2-CH_2), 5.8 (C-CH_2-<u>C</u>H_2).

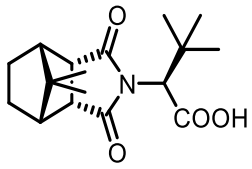
HRMS (ESI) [$C_{17}H_{24}O_4N$]+ requires m/z 306.1700, found m/z 306.1699.

MP 202 - 203 °C.

IR (film) ν_{max}/cm^{-1}:2981, 2888, 1705, 1381, 1253, 1167, 951.

$[\alpha]_D^{25}$ = -70.6 (c = 0.11, $CHCl_3$).

(S)-2-((3aR,4S,7R,7aS)-8,8-Dimethyl-1,3-dioxooctahydro-2H-4,7-methanoisoindol-2-yl)-3,3-dimethylbutanoic acid (L11)



According to modified literature procedure,[180] the solution of **L9** (38 mg, 0.12 mmol, 1.00 eq.) and 5% palladium on carbon (0.80 eq.) in acetic acid (710 μL, 0.18 M) was stirred overnight under hydrogen atmosphere at 60 °C. The crude mixture was cooled down to room temperature and filtered through a pad of Celite, washed with acetic acid and DCM. The residue was concentrated under reduced pressure to yield desired ligand **L11** (38 mg, quant.).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.51 (s, 1H, N-C<u>H</u>-CO_2H), 3.48 – 3.21 (m, 2H, NC(O)-C<u>H</u>), 2.17 – 2.11 (m, 2H, NC(O)-CH-C<u>H</u>), 1.91 – 1.69 (m, 2H, $C\underline{H}_2$-$C\underline{H}_2$), 1.52 – 1.40 (m, 1H, $C\underline{H}'_2$-CH'_2), 1.37 – 1.29 (m, 1H, CH'_2-$C\underline{H}'_2$), 1.12 (s, 12H, $C(C\underline{H}_3)_3$, $C\underline{H}_3$), 1.09 (s, 3H, $C\underline{H}_3$).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 179.4 (amide <u>C</u>=O), 179.3 (amide <u>C</u>=O), 172.0 (acid <u>C</u>=O), 60.6 (N-<u>C</u>H-CO_2H), 52.2 (CH-<u>C</u>-CH), 48.7 (NC(O)-<u>C</u>H, 2C), 46.7 (NC(O)-CH-<u>C</u>H), 46.5 (NC(O)-CH-<u>C</u>H), 35.6 ($\underline{C}(CH_3)_3$), 28.2 ($C(\underline{C}H_3)_3$), 24.2 ($\underline{C}H_2$-CH_2), 23.8 (CH_2-$\underline{C}H_2$), 21.2 ($\underline{C}H_3$), 20.8 ($\underline{C}H_3$).

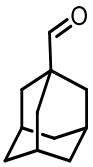
HRMS (ESI) $[C_{17}H_{26}O_4N]+$ requires m/z 308.1856, found m/z 308.1856.

MP 203 - 204 °C.

IR (film) ν_{max}/cm^{-1}: 3127, 2962, 1705, 1377, 1178.

$[\alpha]_D^{25}$ = -61.8 (c = 0.13, $CHCl_3$).

(3R,5R,7R)-Adamantane-1-carbaldehyde (318)



According to literature,[181] the 1-adamantanemethanol (5.00 g, 30.1 mmol, 1.00 eq.) was dissolved in MeCN (24.0 mL, 1.25 M) and pH 7 phosphate buffer (7.3 mL). TEMPO (470 mg, 3.0 mmol, 10 mol %) and $PhI(OAc)_2$ (10.7 g, 33.1 mmol, 1.10 eq.) were then added to the reaction mixture at 0 °C and stirred at this temperature for 1 hour, then for 19 hours at room temperature. Upon the reaction completion, the mixture was quenched with saturated aqueous solution of sodium thiosulfate and extracted with DCM. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (pentane to 1/9 EtOAc/pentane), resulting in desired product **318** as a white amorphous solid (3.53 g, 71%)

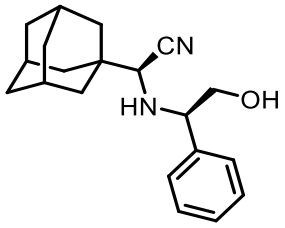
Analytical data is consistent with literature.[181]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 9.32 (s, 1H), 2.07 (s, 3H), 1.78 (d, *J* = 12.4, 3.3 Hz, 3H), 1.74 – 1.66 (m, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 206.1, 45.0, 36.7 (3C), 36.0 (3C), 27.5 (3C).

HRMS (ESI) $[C_{11}H_{17}O]+$ requires m/z 165.1274, found m/z 165.1275.

(S)-2-((3S,5S,7S)-Adamantan-1-yl)-2-(((R)-2-hydroxy-1-phenylethyl)amino)acetonitrile (319)



According to literature,[181] to the solution of (*3R,5R,7R*)-adamantane-1-carbaldehyde **318** (3.00 g, 18.3 mmol, 1.00 eq.) in water (48.0 mL, 0.38 M) were added sodium bisulfite (1.90 g, 18.3 mmol, 1.00 eq.) and potassium cyanide (1.24 g, 19.0 mmol, 1.04 eq.) at 0 °C. A solution of (R)-2-phenylglycinol (2.51 g, 18.3 mmol, 1.00 eq.) dissolved in MeOH (4.8 mL, 3.8 M) was then added dropwise. The reaction mixture was then stirred at room temperature for 30 minutes, then at 45 °C for 2 hours and then heated up to reflux overnight. After the reaction completion, the mixture was cooled down to the room temperature and extracted with EtOAc. The combined organic phases were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (1/9 EtOAc/pentane), yielding **319** as a light yellow powder (4.05 g, 72%).

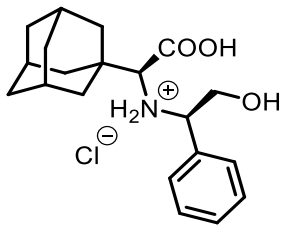
Analytical data is consistent with literature.[181]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.42 – 7.28 (m, 5H), 4.07 (dd, *J* = 9.3, 4.0 Hz, 1H), 3.80 (dt, *J* = 10.9, 3.9 Hz, 1H), 3.64 – 3.51 (m, 1H), 2.87 (s, 1H), 2.19 (brs, 1H), 2.09 – 1.97 (m, 3H), 1.81 – 1.62 (m, 10H), 1.61 – 1.57 (m, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 138.7 (C), 128.9 (2C), 128.3, 128.0 (2C), 119.3, 67.8, 63.3, 59.3, 38.9 (3C), 36.9 (3C), 35.9, 28.3 (3C).

HRMS (ESI) $[C_{20}H_{27}ON_2]$+ requires m/z 311.2118, found m/z 311.2115.

(R)-N-((S)-((3S,5S,7S)-Adamantan-1-yl)(carboxy)methyl)-2-hydroxy-1-phenylethan-1-aminium chloride (320)



According to literature,[181] a mixture of (S)-2-((3S,5S,7S)-adamantan-1-yl)-2-(((R)-2-hydroxy-1-phenylethyl)amino)acetonitrile **319** (2.00 g, 6.4 mmol, 1.00 eq.) in acetic acid (10.7 mL, 0.6 M) and 37% aqueous solution of HCl (43.0 mL, 0.15 M) was heated at 80 °C overnight. The reaction mixture was then cooled down to room temperature, then to 0 °C, which caused a formation of white precipitate. The precipitate was collected by suction filtration to achieve the desired salt as white solid **320** (1.90 g, 81%).

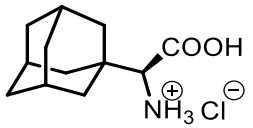
Analytical data is consistent with literature.[181]

^{1}H NMR (400 MHz, Methanol-d_4) δ 7.58 – 7.44 (m, 5H), 4.27 (dd, J = 8.9, 5.0 Hz, 1H), 4.22 – 4.11 (m, 1H), 3.97 (dd, J = 11.7, 5.1 Hz, 1H), 3.21 (s, 1H), 2.01 (s, 3H), 1.80 – 1.60 (m, 9H), 1.51 (d, J = 12.9 Hz, 3H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 169.5, 132.1, 131.7, 130.7 (2C), 130.2 (2C), 69.3, 66.9, 62.2, 39.1 (3C), 37.0 (3C), 36.3, 29.4 (3C).

HRMS (ESI) $[C_{20}H_{28}O_3N]$+ requires m/z 330.2064, found m/z 330.2068.

(S)-((3S,5S,7S)-Adamantan-1-yl)(carboxy)methanaminium chloride (321)



According to literature,[181] to the mixture of (R)-N-((S)-((3S,5S,7S)-adamantan-1-yl)(carboxy)methyl)-2-hydroxy-1-phenylethan-1-aminium chloride **320** (1.30 g, 3.6 mmol, 1.00 eq.) and 10% palladium on carbon (76 mg, 0.7 mmol, 20 mol %) was added acetic acid (2.2 mL, 1.6 M) and MeOH (10.8 mL, 0.33 M), and the mixture was stirred under hydrogen atmosphere overnight at room temperature. Upon completion, the reaction mixture was filtered through a pad of Celite, washed with MeOH and concentrated under reduced pressure. The residue was then triturated with Et_2O and filtered to provide the amino acid as white solid **321** (0.85 g, 97%).

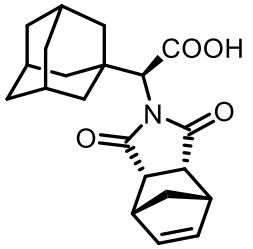
Analytical data is consistent with literature.[181]

^{1}H NMR (400 MHz, Methanol-d_4) δ 3.52 (s, 1H), 2.07 (s, 3H), 1.88 – 1.76 (m, 6H), 1.69 (ddt, J = 25.1, 12.5, 4.5 Hz, 6H).

^{13}C NMR (101 MHz, Methanol-d_4) δ 170.5, 63.6, 39.3 (3C), 37.3 (3C), 35.7, 29.6 (3C).

HRMS (ESI) $[C_{12}H_{20}O_2N]$+ requires m/z 210.1489, found m/z 210.1488.

(S)-2-((3S,5S,7S)-Adamantan-1-yl)-2-((3aR,4S,7R,7aS)-1,3-dioxo-1,3,3a,4,7,7a-hexahydro-2H-4,7-methanoisoindol-2-yl)acetic acid (L12)



An over dried round-bottom flask was charged with the *cis*-5-norbornene-endo-2,3-dicarboxylic anhydride (588 mg, 3.6 mmol, 1.10 eq.) and (*S*)-((*3S,5S,7S*)-adamantan-1-yl)(carboxy)methanaminium chloride **321** (800 mg, 3.3 mmol, 1.00 eq.). The mixture was dissolved in dry DMF (16.0 mL, 0.2 M), then Et_3N (453 µL, 3.3 mmol, 1.00 eq.) was added and the solution was allowed to stir for 48 hours at 110 °C. The reaction mixture was then cooled to the room temperature, then washed with HCl twice (0.5 M), extracted with DCM, washed with brine (7 times), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The residue was purified by flash column chromatography (1/9 to 3/7 EtOAc/pentane) to afford white crystalline solid **L11** (443 mg, 38%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.21 – 6.08 (m, 2H, C<u>H</u>=C<u>H</u>), 4.25 (s, 1H, N-C<u>H</u>-CO_2H), 3.48 – 3.40 (m, 2H, NC(O)-CH-C<u>H</u>), 3.40 – 3.29 (m, 2H, NC(O)-C<u>H</u>), 2.01 – 1.92 (m, 3H_{Ad}), 1.81 – 1.72 (m, 4H, 3H_{Ad}, CH-C<u>H</u>$_2$-CH), 1.71 – 1.59 (m, 9H_{Ad}), 1.56 (dd, *J* = 8.8, 1.6 Hz, 1H, CH-C<u>H</u>'$_2$-CH).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 178.2 (amide <u>C</u>=O, 2C), 171.3 (acid <u>C</u>=O), 135.5 (<u>C</u>H=CH), 134.8 (CH=<u>C</u>H), 61.7 (N-<u>C</u>H-CO_2H), 52.6 (CH-<u>C</u>H_2-CH), 46.0 (NC(O)-<u>C</u>H, 2C), 45.4 (NC(O)-CH-<u>C</u>H), 45.2 (NC(O)-CH-<u>C</u>H), 39.3 (3C_{Ad}), 37.7 (C_{Ad}), 36.7 (3C_{Ad}), 28.5 (3C_{Ad}).

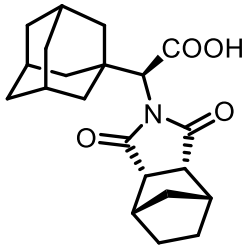
HRMS (ESI) $[C_{21}H_{26}O_4N]+$ requires m/z 356.1856, found m/z 356.1858.

MP 223 - 225 °C.

IR (film) ν_{max}/cm^{-1}: 2905, 1700, 1383, 1370, 1196, 1175, 908, 731.

$[\alpha]_D^{25}$ = -38.1 (c = 0.3, $CHCl_3$).

(S)-2-((3S,5S,7S)-Adamantan-1-yl)-2-((3aR,4R,7S,7aS)-1,3-dioxooctahydro-2H-4,7-methanoisoindol-2-yl)acetic acid (L13)



Prepared according to **general procedure D**, using ligand **L12** (400 mg, 1.1 mmol) and 5% palladium on carbon (96 mg, 0.9 mmol). The crude product was purified by flash column chromatography (1/19 EtOAc/pentane) to yield chiral carboxylic acid **L13** as a white powder (197 mg, 49%).

^{1}H NMR (600 MHz, Chloroform-*d*) δ 4.41 (s, 1H, N-C<u>H</u>-CO_2H)), 3.34 – 3.03 (m, 2H, NC(O)-C<u>H</u>), 2.92 – 2.68 (m, 2H, NC(O)-CH-C<u>H</u>), 1.98 (s, 3H_{Ad}), 1.93 – 1.82 (m, 3H, 2H_{Ad}, CH-C<u>H</u>$_2$-CH), 1.75 – 1.60 (m, 11H, 10H_{Ad}, CH-C<u>H'</u>$_2$-CH), 1.59 – 1.42 (m, 3H, C<u>H</u>$_2$-C<u>H</u>$_2$), 1.39 – 1.29 (m, 1H, CH_2-C<u>H'</u>$_2$).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 178.7 (amide <u>C</u>=O, 2C), 170.2 (acid <u>C</u>=O), 61.9 – 61.1 (m, N-<u>C</u>H-CO_2H), 49.1 (NC(O)-<u>C</u>H, 2C), 42.8 (C_{Ad}), 39.7 (NC(O)-CH-<u>C</u>H), 39.5 (2C_{Ad}, NC(O)-CH-<u>C</u>H, CH-<u>C</u>H_2-CH, 4C), 37.7 (C_{Ad}), 36.7 (3C_{Ad}), 28.5 (3C_{Ad}), 25.0 – 24.6 (m, <u>C</u>H_2-<u>C</u>H_2).

HRMS (ESI) [$C_{21}H_{28}O_4N$]+ requires m/z 358.2013, found m/z 358.2013.

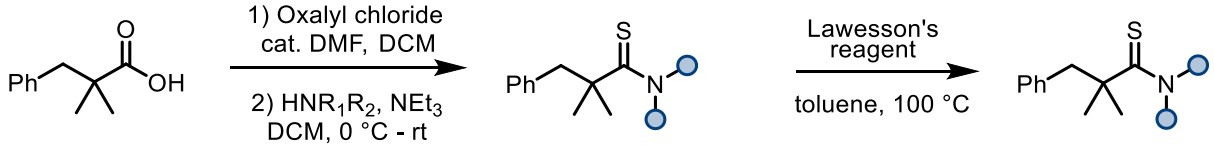
MP 230 - 231 °C.

IR (film) ν_{max}/cm^{-1}: 2905, 2851, 1700, 1382, 1369, 1173, 731.

$[\alpha]_D^{25}$ = -44.4 (c = 0.48, $CHCl_3$).

5.2.3 Synthesis of starting materials – thioamides

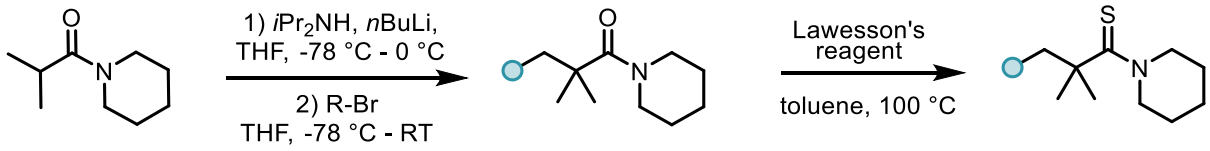
5.2.3.1 General procedure E: *Thioamide synthesis*



Modified literature procedure.[145]

To a solution of carboxylic acid (1.10 eq.) in DCM (0.5 M), oxalyl chloride (2.20 eq.) was added dropwise at 0 °C. Subsequently, 2-3 drops of DMF were added and the mixture was allowed to stir for 3 hours at room temperature. The solvent was then removed in vacuo to yield corresponding acid chloride, which was then added dropwise to a stirred solution of Et_3N (2.00 eq.) and corresponding secondary amine (1.00 eq.) in DCM (0.2 M) at 0 °C. The reaction was warmed to the room temperature and let to stir for 2 hours. Upon the reaction completion, the crude mixture was quenched with HCl (1 M) and extracted with DCM. The combined organic layers were washed with NaOH (1 M), brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The crude amide was dissolved in toluene (0.2 M) and Lawesson's reagent (0.60 eq.) was added. The mixture was heated to 100 °C and stirred overnight. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography (Et_2O/pentane) to result the thioamide products.

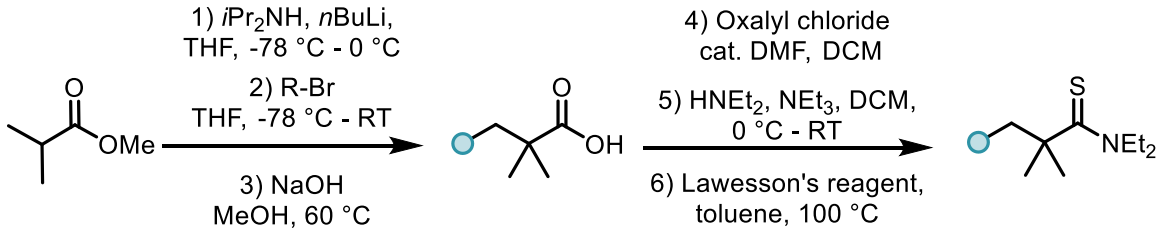
5.2.3.2 General procedure F: *Thioamide synthesis*



Modified literature procedure.[146]

A solution of LDA (1.00 eq.) in THF (1M) was prepared from diisopropylamine (1.07 eq.) and nBuLi in hexane (1.00 eq., 2.5 M) at -78 °C in 30 min. To this LDA solution, isobutyramide (1.00 eq.) was added dropwise at -78 °C and the mixture was warmed to 0 °C and stirred for 2 h at this temperature. Aryl halide (1.50 eq.) was then added dropwise to the solution at -78 °C. After the addition, the mixture was warmed to room temperature and stirred 20 - 62 h. The reaction was quenched with NH_4Cl (1 M), and extracted with EtOAc. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$ and filtered. After the solvent was removed in vacuo, the resultant crude amide was purified by column chromatography (Et_2O/pentane). Purified amide was then added with toluene (0.2 M). Lawesson's reagent (0.60 eq.) was subsequently added and the stirred reaction mixture was heated to 100 °C overnight. The reaction was cooled to room temperature and solvent was removed under reduced pressure. The crude residue was then purified via flash column chromatography (Et_2O/pentane) 1 – 3 times to afford the resultant thioamide products.

5.2.3.3 General procedure G: *Thioamide synthesis*

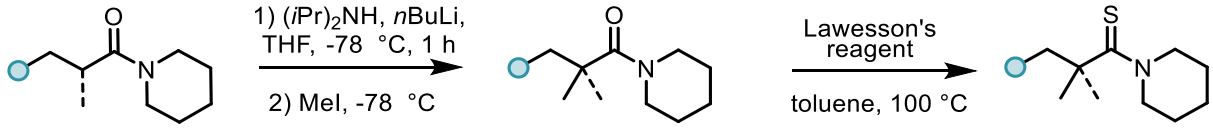


Modified literature procedure.[145]

A solution of LDA (1.00 eq.) in THF (1M) was prepared from diisopropylamine (1.07 eq.) and nBuLi in hexane (1.00 eq, 2.5 M) at -78 °C in 30 min. To this solution, methyl isobutyrate (1.00 eq.) was added dropwise at -78 °C and the mixture was stirred for 1 h at this temperature. Alkyl halide (1.50 eq.) was then at -78 °C added dropwise to the solution. After the addition, the mixture was warmed to room temperature and stirred overnight. The reaction was quenched with water at 0 °C, and extracted with Et_2O. The combined organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield in crude ester. To the crude ester was then added an aqueous solution of NaOH (2 M) and MeOH (1 M). The mixture was then stirred at 60 °C overnight. After the removal of MeOH in the vacuo, the mixture's pH was adjusted to 2 with HCl (1 M). The mixture was then saturated with NaCl and extracted with Et_2O. The combined organic layers were then separated, washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield in crude carboxylic acid, which was used in the next step without purification. The crude carboxylic acid (1.10 eq.) was dissolved in DCM (0.5 M) and oxalyl chloride (2.20 eq.) was added dropwise at 0 °C. Subsequently, 2-3 drops of DMF were added and the mixture was allowed to stir for 3 hours at room temperature. The solvent was then removed in vacuo to yield corresponding acid

chloride, which was then added dropwise to a stirred solution of Et_3N (2.00 eq.) and Et_2NH (1.00 eq.) in DCM (0.2 M) at 0 °C. The reaction was warmed to the room temperature and let to stir for 2 hours. Upon the reaction completion, the crude mixture was quenched with HCl (1 M) and extracted with DCM. The combined organic layers were washed with NaOH (1 M) and brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resultant crude amide was then added with toluene (0.2 M). Lawesson's reagent (0.60 eq.) was subsequently added and the stirred reaction mixture was heated to 100 °C overnight. The reaction was cooled to room temperature and solvent was removed under reduced pressure. The crude residue was then purified via flash column chromatography (Et_2O/pentane) twice times to afford the resultant thioamide products.

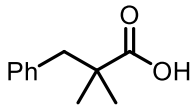
5.2.3.4 General procedure H: *Thioamide synthesis*



Modified literature procedure.[146,182]

A solution of LDA (1.00 eq.) in THF (1 M) was prepared from diisopropylamine (1.07 eq.) and nBuLi in hexane (1.00 eq., 2.5 M) at -78 °C in 30 min. To this LDA solution, isobutyramide (1.00 eq.) was added dropwise at -78 °C and the mixture was warmed to 0 °C and stirred for 2 h at this temperature. Methyl iodide (3.00 eq.) was then added dropwise to the solution at -78 °C. After the addition, the mixture was warmed to room temperature and stirred overnight. The reaction was quenched with NH_4Cl (1 M), and extracted with EtOAc. The organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$ and filtered. After the solvent was removed in vacuo, the resultant crude amide was purified by column chromatography (Et_2O/pentane). In case of double methylation, the whole process was repeated twice. Purified amide was then added with toluene (0.2 M). Lawesson's reagent (0.60 eq.) was subsequently added and the stirred reaction mixture was heated to 100 °C overnight. The reaction was cooled to room temperature and solvent was removed under reduced pressure. The crude residue was then purified via flash column chromatography (Et_2O/pentane) 1 – 3 times to afford the resultant thioamide products.

2,2-Dimethyl-3-phenylpropanoic acid (311)



According to literature,[152] a solution of LDA (1.00 eq.) in THF (26.5 mL, 1M) was prepared from diisopropylamine (3.96 mL, 28.3 mmol, 1.07 eq.) and nBuLi in hexane (10.58 mL, 26.4 mmol, 1.00 eq, 2.5 M) at -78 °C in 30 min. To this solution, methyl isobutyrate (3.03 mL, 26.4 mmol, 1.00 eq.) was added dropwise at -78 °C and the mixture was stirred for 1 h at this temperature. Benzyl bromide (4.72mL, 39.7 mmol, 1.50 eq.) was then at added dropwise to the solution -78 °C and the mixture was warmed to the room temperature and stirred overnight. The reaction was quenched with water at 0 °C, and extracted with Et_2O. The combined organic layer was separated, washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield in crude ester. To the crude ester was then added an aqueous solution of NaOH (21 mL, 2 M) and MeOH (26.5 mL, 1 M). The mixture was then stirred at 60 °C overnight. After the removal of MeOH in the vacuo, the mixture's pH was adjusted to 2 with HCl (1 M). The mixture was then saturated with NaCl and extracted with Et_2O. The combined organic layers were then separated, washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to yield in crude carboxylic acid, that was recrystalised to afford **311** as pale crystals (2.58, 55%).

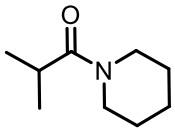
Analytical data is consistent with the literature.[152]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 1H), 7.28 – 7.23 (m, 1H), 7.22 – 7.17 (m, 2H), 2.92 (s, 2H), 1.24 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 183.5, 138.1, 130.6 (2C), 127.2 (2C), 126.9, 46.4, 44.0, 30.1 (2C),.

HRMS (ESI) $[C_{11}H_{15}O_2]^+$ requires m/z 179.1053, found m/z 179.1052.

2-Methyl-1-(piperidin-1-yl)propan-1-one (323)



According to literature,[145] isobutyryl chloride (11.7 mL, 111.5 mmol, 1.10 eq.) was added dropwise into the stirred solution of piperidine (10.0 mL, 101.3 mmol, 1.00 eq.) and Et_3N (28.2 mL, 202.6 mmol, 2.00 eq.) in DCM (500 mL, 0.2 M) at 0 °C. The reaction mixture was then warmed up to the room temperature and stirred for 2 hours. Upon completion, the crude mixture was quenched with 1 M HCl and extracted with DCM. The combined organic layers were washed with 1 M NaOH solution and extracted, washed with brine and dried over anhydrous $MgSO_4$ and filtered. The solvent was evaporated in vacuo and the crude amide was purified by flash column chromatography (10/90 Et_2O/pentane). Isobutyryl amide **323** was isolated as light yellow oil (14.72 g, 94%).

Analytical data is consistent with literature.[145]

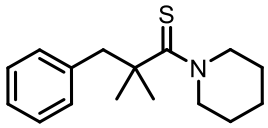
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.50 (brs, 4H, H5, H9), 2.79 (hept, *J* = 6.8 Hz, 1H, H3), 1.68 – 1.59 (m, 2H, H7), 1.59 – 1.49 (m, 4H, H6, H8), 1.12 (d, *J* = 6.7 Hz, 6H, H1-2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.4 (C4), 30.2 (C3), 26.4 (C6, C8), 24.9 (C7), 19.6 (C1-2).

*C5, C9 Not visible on ^{13}C NMR, rotameric.

HRMS (ESI) $[C_9H_{18}ON]^+$ requires m/z 156.1383, found m/z 156.1383.

2,2-Dimethyl-3-phenyl-1-(piperidin-1-yl)propane-1-thione (313)



Prepared according to **general procedure F**, using diisopropylamine (290 μL, 2.1 mmol), *n*BuLi in hexane (773 μL, 1.9 mmol), 1-isobutyrylpiperidine (313 μL, 1.9 mmol), benzyl bromide (345 μL, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (3/97 Et_2O/pentane). **313** was isolated as a pale yellow solid (338 mg, 67%).

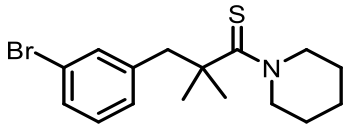
Analytical data is consistent with literature.[145]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.26 (m, 1H), 7.26 – 7.19 (m, 2H), 7.18 – 7.12 (m, 2H), 4.25 – 4.11 (m, 4H), 3.05 (s, 2H), 1.81 – 1.64 (m, 6H), 1.40 (s, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 211.0, 138.1, 130.6 (2C), 128.1 (2C), 126.6, 54.5 (2C), 48.0, 46.6, 30.1 (2C), 26.3 (2C), 24.5.

HRMS (ESI) $[C_{16}H_{24}N^{32}S]^+$ requires m/z 262.1624, found m/z 262.1625.

3-(3-Bromophenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione (324)



Prepared according to **general procedure F**, using diisopropylamine (193 μL, 1.4 mmol), *n*BuLi in hexane (515 μL, 1.3 mmol), 1-isobutyrylpiperidine (209 μL, 1.3 mmol), 3-bromobenzyl bromide (483 mg, 1.9 mmol) and Lawesson's reagent (313 mg, 0.8 mmol). The crude reaction mixture was purified by flash column chromatography (1/49 to 1/24 Et_2O/pentane). **324** was isolated as a light orange oil (117 mg, 27%).

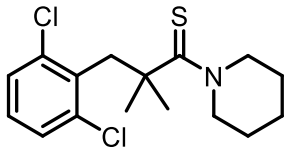
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 (ddd, *J* = 7.8, 2.0, 1.2 Hz, H_{Ar}), 7.29 (t, *J* = 1.8 Hz, H_{Ar}), 7.14 (t, *J* = 7.7 Hz, H_{Ar}), 7.07 (dt, *J* = 7.7, 1.4 Hz, H_{Ar}), 4.27 – 4.08 (m, 4H, N-C$\underline{H}_2$), 3.02 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.87 – 1.65 (m, 6H, N-CH$_2$-C$\underline{H}_2$-C$\underline{H}_2$), 1.40 (s, 6H, geminal C$\underline{H}_3$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.4 (C=S), 140.5 (C_{Ar}), 133.5 (C_{Ar}), 129.7 (C_{Ar}), 129.6 (C_{Ar}), 129.3 (C_{Ar}), 122.1 (C_{Ar}), 54.5 (N-$\underline{C}$H$_2$, 2C), 47.8 (NC(S)-$\underline{C}$), 46.5 (NC(S)-C-$\underline{C}$H$_2$), 30.0 (geminal $\underline{C}$H$_3$, 2C), 26.3 (N-CH$_2$-$\underline{C}$H$_2$, 2C), 24.5 (N-CH$_2$-CH$_2$-$\underline{C}$H$_2$).

HRMS (ESI) $[C_{15}H_{23}N^{79}Br^{32}S]^+$ requires m/z 340.0729, found m/z 340.0732.

IR (film) ν_{max}/cm^{-1}: 2935, 1473, 1419, 1247, 1221, 1108, 1072, 1019, 1002, 770, 702, 672.

3-(2,6-Dichlorophenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione (325)



Prepared according to **general procedure F**, using diisopropylamine (290 µL, 2.1 mmol), nBuLi in hexane (773 µL, 1.9 mmol), 1-isobutyrylpiperidine (313 µL, 1.9 mmol), 1,3-dichlorobenzyl bromide (695 mg, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/20 to 1/49 Et2O/pentane). **325** was isolated as a yellow powder (362 mg, 57%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 (d, *J* = 8.0 Hz, $2H_{Ar}$), 7.09 (dd, *J* = 8.4, 7.6 Hz, H_{Ar}), 4.34 – 4.13 (m, 4H, N-C$\underline{H_2}$), 3.45 (s, 2H, NC(S)-C-C$\underline{H_2}$), 1.87 – 1.69 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.45 (s, 6H, geminal C$\underline{H_3}$).

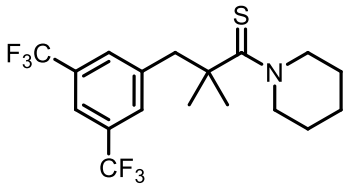
^{13}C NMR (101 MHz, Chloroform-*d*) δ 211.2 ($\underline{C}$=S), 137.0 ($2C_{Ar}$), 135.8 (C_{Ar}), 128.5 ($2C_{Ar}$), 128.2 (C_{Ar}), 54.5 (N-$\underline{C}H_2$, 2C), 48.3 (NC(S)-$\underline{C}$), 39.8 (NC(S)-C-$\underline{C}H_2$), 30.9 (geminal $\underline{C}H_3$, 2C), 26.4 (N-CH_2-$\underline{C}H_2$, 2C), 24.5 (N-CH_2-CH_2-$\underline{C}H_2$).

HRMS (ESI) $[C_{16}H_{22}N^{35}Cl_2{}^{32}S]^+$ requires m/z 330.0845, found m/z 330.0844.

IR (film) ν_{max}/cm^{-1}: 2936, 1433, 1249, 1230, 1110, 1020, 1003, 772, 758.

MP 104 - 105 °C.

3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione (326)



Prepared according to **general procedure F**, using diisopropylamine (193 µL, 1.4 mmol), *n*BuLi in hexane (515 µL, 1.3 mmol), 1-isobutyrylpiperidine (209 µL, 1.3 mmol), 3,5-(trifluoromethyl)benzyl bromide (354 µL, 1.9 mmol) and Lawesson's reagent (313 mg, 0.8 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/49 Et_2O/pentane wash, then 1/24 Et_2O/pentane). **326** was isolated as an amorphous orange solid (145 mg, 29%).

Analytical data is consistent with literature.[146]

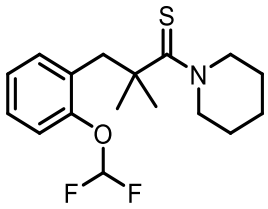
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (s, 1H), 7.57 (s, 2H), 4.27 – 4.09 (m, 4H), 3.22 (s, 2H), 1.86 – 1.66 (m, 6H), 1.43 (s, 6H).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -62.8 (6F).

^{13}C NMR (151 MHz, Chloroform-*d*) δ 209.2, 140.7, 131.2 (q, J = 33.1 Hz, 2C), 130.5 (brs, 2C), 123.5 (q, J = 272.8 Hz, 2C), 120.7 (hept), 54.6 (2C), 47.7, 47.2, 30.0 (2C), 26.3, 24.4 (2C).

HRMS (ESI) $[C_{18}H_{22}NF_6{}^{32}S]^+$ requires m/z 398.1372, found m/z 398.1366.

3-(2-(Difluoromethoxy)phenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione (327)



Prepared according to **general procedure F**, using diisopropylamine (290 μL, 2.1 mmol), *n*BuLi in hexane (773 μL, 1.9 mmol), 1-isobutyrylpiperidine (313 μL, 1.9 mmol), 2-(difluoromethoxy)benzyl bromide (442 μL, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (3/100 Et_2O/pentane). **327** was isolated as a pale yellow solid (384 mg, 61%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 – 7.23 (m, $2H_{Ar}$), 7.14 (td, *J* = 7.5, 1.2 Hz, H_{Ar}), 7.06 – 7.01 (m, H_{Ar}), 6.52 (t, *J* = 74.3 Hz, O-C<u>H</u>F_2), 4.36 – 4.21 (m, 4H, N-C<u>H$_2$</u>), 3.06 (s, 2H, NC(S)-C-C<u>H$_2$</u>), 1.83 – 1.68 (m, 6H, N-CH_2-C<u>H$_2$</u>-C<u>H$_2$</u>), 1.37 (s, 6H, geminal C<u>H$_3$</u>).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -79.5 (d, *J* = 74.5 Hz, 2F).

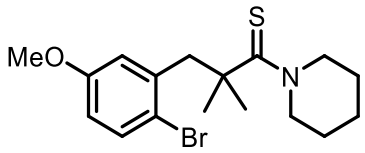
^{13}C NMR (126 MHz, Chloroform-*d*) δ 210.2 (<u>C</u>=S), 150.7 (t, *J* = 2.4 Hz, C_{Ar}), 133.7 (C_{Ar}), 128.8 (C_{Ar}), 128.3 (C_{Ar}), 124.8 (C_{Ar}), 116.9 (C_{Ar}), 116.5 (t, *J* = 257.2 Hz, O-<u>C</u>HF_2), 54.3 (N-<u>C</u>H_2, 2C), 48.2 (NC(S)-<u>C</u>), 38.7 (NC(S)-C-<u>C</u>H_2), 29.3 (geminal <u>C</u>H_3, 2C), 26.2 (N-CH_2-<u>C</u>H_2, 2C), 24.4 (N-CH_2-CH_2-<u>C</u>H_2).

HRMS (ESI) $[C_{17}H_{24}ONF_2{}^{32}S]^+$ requires m/z 287.1577, found m/z 287.1578.

MP 53 - 55 °C.

IR (film) ν_{max}/cm^{-1}: 2938, 1493, 1422, 1382, 1228, 1120, 1039, 758.

3-(2-Bromo-5-methoxyphenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione (328)



Prepared according to **general procedure F**, using diisopropylamine (290 µL, 2.1 mmol), *n*BuLi in hexane (773 µL, 1.9 mmol), 1-isobutyrylpiperidine (313 µL, 1.9 mmol), 1-bromo-4-methoxybenzyl bromide (812 mg, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/49 to 3/100 Et_2O/pentane). **328** was isolated as a pink solid (444 mg, 62%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 8.8 Hz, H_{Ar}), 6.85 (d, *J* = 3.0 Hz, H_{Ar}), 6.65 (dd, *J* = 8.8, 3.1 Hz, H_{Ar}), 4.28 – 4.16 (m, 4H, N-C$\underline{H_2}$), 3.75 (s, 3H, O-C$\underline{H_3}$), 3.22 (s, 2H, NC(S)-C-C$\underline{H_2}$), 1.81 – 1.64 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.48 (s, 6H, geminal C$\underline{H_3}$).

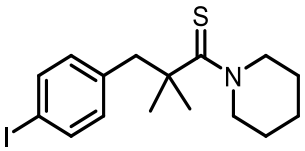
^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.6 (C=S), 158.6 (C_{Ar}), 138.8 (C_{Ar}), 133.4 (C_{Ar}), 117.5 (C12), 116.4 (C_{Ar}), 114.6 (C_{Ar}), 55.7 (O-$\underline{C}H_3$), 54.6 (N-$\underline{C}H_2$, 2C), 48.6 (NC(S)-$\underline{C}$), 45.2 (NC(S)-C-$\underline{C}H_2$), 30.6 (geminal $\underline{C}H_3$, 2C), 26.4 (N-CH_2-$\underline{C}H_2$, 2C), 24.5 (N-CH_2-CH_2-$\underline{C}H_2$).

HRMS (ESI) $[C_{17}H_{23}ON^{79}Br^{32}S]^+$ requires m/z 328.1541, found m/z 328.1540.

MP 70 - 72 °C.

IR (film) ν_{max}/cm^{-1}: 2936, 1468, 1418, 1280, 1239, 1222, 1166, 1108, 1018, 855, 808.

3-(4-Iodophenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione (329)



Prepared according to **general procedure F**, using diisopropylamine (290 μL, 2.1 mmol), *n*BuLi in hexane (773 μL, 1.9 mmol), 1-isobutyrylpiperidine (313 μL, 1.9 mmol), 4-iodobenzyl bromide (861 mg, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/20 and 3/100 Et_2O/pentane). **329** was isolated as a pale yellow solid (438 mg, 59%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.54 (m, $2H_{Ar}$), 6.93 – 6.85 (m, $2H_{Ar}$), 4.24 – 4.10 (m, 4H, N-C$\underline{H_2}$), 3.00 (s, 2H, NC(S)-C-C$\underline{H_2}$), 1.82 – 1.65 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.38 (s, 6H, geminal C$\underline{H_3}$).

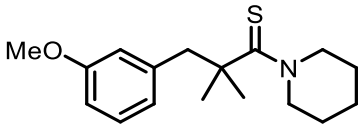
^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.4 ($\underline{C}$=S), 137.8 (C_{Ar}), 137.2 ($2C_{Ar}$), 132.6 ($2C_{Ar}$), 92.0 (C_{Ar}), 54.5 (N-$\underline{C}H_2$, 2C), 47.7 (NC(S)-$\underline{C}$), 46.5 (NC(S)-C-$\underline{C}H_2$), 30.0 (geminal $\underline{C}H_3$, 2C), 26.3 (N-CH_2-$\underline{C}H_2$, 2C), 24.5 (N-CH_2-CH_2-$\underline{C}H_2$).

HRMS (ESI) $[C_{16}H_{23}NI^{32}S]^+$ requires m/z 388.0590, found m/z 388.0591.

MP 100 - 102 °C.

IR (film) ν_{max}/cm^{-1}: 2981, 1483, 1419, 1388, 1247, 1220, 1153, 1005, 953.

3-(3-Methoxyphenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione (330)



Prepared according to **general procedure F**, using diisopropylamine (290 µL, 2.1 mmol), *n*BuLi in hexane (773 µL, 1.9 mmol), 1-isobutyrylpiperidine (313 µL, 1.9 mmol), 3-methoxybenzyl bromide (406 µL, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/49 to 2/23 Et_2O/pentane). **330** was isolated as a pink solid (270 mg, 48%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 (dd, J = 8.2, 7.5 Hz, H_{Ar}), 6.80 – 6.69 (m, $3H_{Ar}$), 4.18 (t, *J* = 5.0 Hz, 4H, N-C$\underline{H_2}$), 3.79 (s, 3H, O-C$\underline{H_3}$), 3.03 (s, 2H, NC(S)-C-C$\underline{H_2}$), 1.82 – 1.67 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.41 (s, 6H, geminal C$\underline{H_3}$).

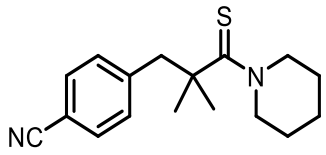
^{13}C NMR (101 MHz, Chloroform-*d*) δ 211.0 (<u>C</u>=S), 159.4 (C_{Ar}), 139.7 (C_{Ar}), 129.0 (C_{Ar}), 123.1 (C_{Ar}), 116.6 (C_{Ar}), 111.8 (C_{Ar}), 55.3 (O-<u>C</u>H_3), 54.5 (N-<u>C</u>H_2, 2C), 48.0 (NC(S)-<u>C</u>), 46.7 (NC(S)-C-<u>C</u>H_2), 30.3 (geminal <u>C</u>H_3, 2C), 26.3 (N-CH_2-<u>C</u>H_2, 2C), 24.5 (N-CH_2-CH_2-<u>C</u>H_2).

HRMS (ESI) $[C_{17}H_{26}ON^{32}S]^+$ requires m/z 292.1730, found m/z 292.1731.

MP 80 - 81 °C.

IR (film) ν_{max}/cm^{-1}: 2937, 1600, 1488, 1419, 1263, 1247, 1223, 1169, 1107, 1043, 1019, 1003, 780, 700.

4-(2,2-Dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)benzonitrile (331)



Prepared according to **general procedure F**, using diisopropylamine (290 μL, 2.1 mmol), nBuLi in hexane (773 μL, 1.9 mmol), 1-isobutyrylpiperidine (313 μL, 1.9 mmol), 4-(bromomethyl)benzonitrile (568 mg, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (3/25 Et2O/pentane). **331** was isolated as a bright yellow solid (75 mg, 14%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.51 (m, 2H_{Ar}), 7.29 – 7.21 (m, 2H_{Ar}), 4.27 – 4.09 (m, 4H, N-CH_2), 3.14 (s, 2H, NC(S)-C-CH_2), 1.84 – 1.67 (m, 6H, N-CH_2-CH_2-CH_2), 1.40 (s, 6H, geminal CH_3).

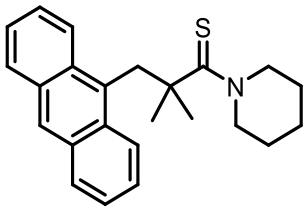
^{13}C NMR (126 MHz, Chloroform-*d*) δ 209.7 (C=S), 144.0 (C_{Ar}), 131.8 (2C_{Ar}), 131.3 (2C_{Ar}), 119.1 (C_{Ar}), 110.5 (C≡N), 54.6 (N-CH_2, 2C), 47.7 (NC(S)-C), 47.4 (NC(S)-C-CH_2), 30.0 (geminal CH_3, 2C), 26.3 (N-CH_2-CH_2, 2C), 24.4 (N-CH_2-CH_2-CH_2).

HRMS (ESI) $[C_{17}H_{23}N_2{}^{32}S]^+$ requires m/z 287.1577, found m/z 287.1578.

MP 81 - 83 °C.

IR (film) ν_{max}/cm^{-1}: 2936, 2227, 1607, 1421, 1247, 1222, 1109, 1019, 854.

3-(Anthracen-9-yl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione (332)



Prepared according to **general procedure F**, using diisopropylamine (290 μL, 2.1 mmol), *n*BuLi in hexane (773 μL, 1.9 mmol), 1-isobutyrylpiperidine (313 μL, 1.9 mmol), 9-antracenyl bromide (524 mg, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/49 Et_2O/pentane). **332** was isolated as an orange solid (94 mg, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.70 (m, H_{Ar}), 8.70 – 8.62 (m, H_{Ar}), 8.22 – 8.14 (m, H_{Ar}), 7.83 (dd, *J* = 7.8, 1.5 Hz, H_{Ar}), 7.67 (s, H_{Ar}), 7.66 – 7.56 (m, $4H_{Ar}$), 4.18 – 4.06 (m, 4H, N-C$\underline{H_2}$), 3.64 (s, 2H, NC(S)-C-C$\underline{H_2}$), 1.74 – 1.62 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.53 (s, 6H, geminal C$\underline{H_3}$).

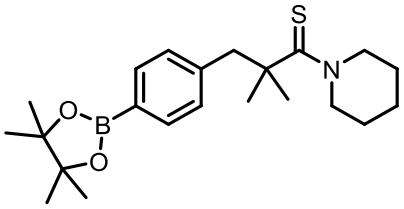
^{13}C NMR (126 MHz, $CDCl_3$) δ 211.5 (<u>C</u>=S), 133.1 (C_{Ar}), 132.4 (C_{Ar}), 131.5 (C_{Ar}), 130.8 (C_{Ar}), 129.9 (C_{Ar}), 129.1 (C_{Ar}), 128.4 (C_{Ar}), 126.8 (C_{Ar}), 126.6 (C_{Ar}), 126.5 (C_{Ar}), 126.3 (C_{Ar}) ,125.5 (C_{Ar}), 123.3 (C_{Ar}), 122.6 (C_{Ar}), 54.7 (N-<u>C</u>H_2, 2C), 48.9 (NC(S)-<u>C</u>), 42.7 (NC(S)-C-<u>C</u>H_2), 31.1 (geminal <u>C</u>H_3, 2C), 26.3 (N-CH_2-<u>C</u>H_2, 2C), 24.4 (N-CH_2-CH_2-<u>C</u>H_2).

HRMS (ESI) $[C_{24}H_{28}N^{32}S]^+$ requires m/z 362.1937, found m/z 362.1937.

MP 30 - 31 °C.

IR (film) ν_{max}/cm^{-1}: 2981, 1384, 1248, 1152, 1073, 954, 749.

2,2-Dimethyl-1-(piperidin-1-yl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-thione (333)



Prepared according to **general procedure F**, using diisopropylamine (290 μL, 2.1 mmol), *n*BuLi in hexane (773 μL, 1.9 mmol), 1-isobutyrylpiperidine (313 μL, 1.9 mmol), 2-(4-(bromomethyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (861 mg, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/20 and 3/100 Et_2O/pentane). **333** was isolated as an off-white solid (132 mg, 18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.68 (m, $2H_{Ar}$), 7.19 – 7.12 (m, $2H_{Ar}$), 4.25 – 4.10 (m, 4H, N-C$\underline{H}_2$), 3.06 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.81 – 1.66 (m, 6H, N-CH_2-C$\underline{H}_2$-C$\underline{H}_2$), 1.38 (s, 6H, geminal C$\underline{H}_3$), 1.34 (s, 12H, O-C(C$\underline{H}_3$)$_2$).

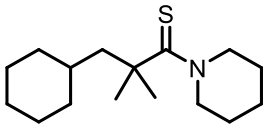
^{13}C NMR (126 MHz, $CDCl_3$) δ 210.8 ($\underline{C}$=S), 141.4 (C_{Ar}), 134.6 ($2C_{Ar}$), 130.1 ($2C_{Ar}$), 83.9 (O-$\underline{C}$(CH_3)$_2$), 54.5 (N-$\underline{C}H_2$, 2C), 47.9 (NC(S)-$\underline{C}$), 46.7 (NC(S)-C-$\underline{C}H_2$), 30.0 (geminal $\underline{C}H_3$, 2C), 26.3 (N-CH_2-$\underline{C}H_2$, 2C), 25.0 (O-C($\underline{C}H_3$)$_2$), 24.5 (N-CH_2-CH_2-$\underline{C}H_2$).

HRMS (ESI) $[C_{22}H_{35}O_2N^{11}B^{32}S]^+$ requires m/z 388.2477, found m/z 388.2483.

MP 145 - 148 °C.

IR (film) ν_{max}/cm^{-1}: 2980, 1611, 1361, 1250, 1144, 1090, 1021, 962, 859.

3-Cyclohexyl-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione (334)



Prepared according to **general procedure F**, using diisopropylamine (290 μL, 2.1 mmol), *n*BuLi in hexane (773 μL, 1.9 mmol), 1-isobutyrylpiperidine (313 μL, 1.9 mmol), (bromomethyl)cyclohexane (405 μL, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/100 and 1/49 Et_2O/pentane). **334** was isolated as a yellow oil (395 mg, 76%).

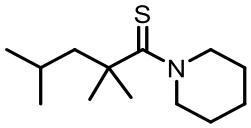
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 4H, N-C$\underline{H}_2$), 1.78 – 1.65 (m, 8H, N-CH_2-C$\underline{H}_2$-C$\underline{H}_2$, cyclohexyl C$\underline{H}$, CH-CH_2-CH_2-C$\underline{H}_2$), 1.66 – 1.53 (m, 6H, NC(S)-C-C$\underline{H}_2$; cyclohexyl C$\underline{H}_2$), 1.44 (s, 6H, geminal C$\underline{H}_3$), 1.29 – 1.02 (m, 3H, cyclohexyl C$\underline{H}_2$), 0.95 – 0.82 (m, 2H, H14b, cyclohexyl C$\underline{H}'_2$, CH-CH_2-CH_2-C$\underline{H}'_2$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2 (C=S), 54.2 (N-$\underline{C}H_2$, 2C), 48.9 (NC(S)-C-$\underline{C}H_2$), 47.3 (NC(S)-$\underline{C}$), 35.2 (cyclohexyl $\underline{C}H_2$, 2C), 34.8 (CH-CH_2-CH_2-$\underline{C}H_2$), 32.1 (geminal $\underline{C}H_3$, 2C), 26.5 (cyclohexyl $\underline{C}H_2$, 2C), 26.4 (cyclohexyl $\underline{C}$H), 26.2 (N-CH_2-$\underline{C}H_2$, 2C), 24.5 (N-CH_2-CH_2-$\underline{C}H_2$).

HRMS (ESI) $[C_{16}H_{30}N^{32}S]^+$ requires m/z 268.2093, found m/z 268.2094.

IR (film) ν_{max}/cm^{-1}: 2920, 2851, 1444, 1418, 1364, 1249, 1221, 1131, 1112, 1018, 898, 855.

2,2,4-Trimethyl-1-(piperidin-1-yl)pentane-1-thione (335)



Prepared according to **general procedure F**, using diisopropylamine (290 μL, 2.1 mmol), *n*BuLi in hexane (773 μL, 1.9 mmol), 1-isobutyrylpiperidine (313 μL, 1.9 mmol), 1-bromo-2-methylpropane (315 μL, 2.9 mmol) and Lawesson's reagent (469 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/49 Et_2O/pentane). **335** was isolated as a yellow oil (296 mg, 67%).

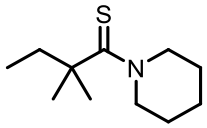
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (s, 4H, N-C$\underline{H}_2$), 1.84 – 1.75 (m, 1H, CH_3-C$\underline{H}$-CH_3), 1.75 – 1.66 (m, 6H, N-CH_2-C$\underline{H}_2$-C$\underline{H}_2$), 1.64 (d, J = 6.0 Hz, 2H, NC(S)-C-C$\underline{H}_2$), 1.45 (s, 6H, geminal C$\underline{H}_3$), 0.90 (d, J = 6.6 Hz, 6H, C$\underline{H}_3$-CH-C$\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0 ($\underline{C}$=S), 54.2 (N-$\underline{C}H_2$, 2C), 50.3 (NC(S)-C-$\underline{C}H_2$), 47.4 (NC(S)-$\underline{C}$), 32.2 (geminal $\underline{C}H_3$, 2C), 26.2 (N-CH_2-$\underline{C}H_2$, 2C), 25.5 (CH_3-$\underline{C}$H-CH_3), 24.7 ($\underline{C}H_3$-CH-$\underline{C}H_3$, 2C), 24.5 (N-CH_2-CH_2-$\underline{C}H_2$).

HRMS (ESI) $[C_{13}H_{26}N^{32}S]^+$ requires m/z 228.1780, found m/z 228.1782.

IR (film) ν_{max}/cm^{-1}: 2980, 1419, 1389, 1365, 1248, 1228, 1183, 1132, 1072, 1018, 1002, 951, 898.

2,2-Dimethyl-1-(piperidin-1-yl)butane-1-thione (336)



Prepared according to **general procedure E**, using piperidine (201 µL, 2.0 mmol), 2,2-dimethylbutanoic acid (260 mg, 2.2 mmol), oxalyl chloride (399 µL, 4.5 mmol), Et_3N (567 µL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/4 Et_2O/pentane). **336** was isolated as a light orange oil (188 mg, 46%).

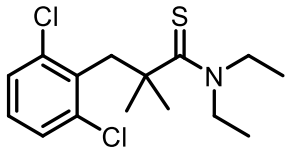
Analytical data is consistent with literature.[145]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.21 – 3.98 (m, 4H), 1.82 – 1.63 (m, 8H, H1), 1.41 (s, 6H), 0.91 (t, J = 7.5 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.5, 54.2 (2C), 47.5, 34.3, 30.4 (2C), 26.3 (2C), 24.5, 9.6.

HRMS (ESI) $[C_{11}H_{32}N^{32}S]^+$ requires m/z 200.1468, found m/z 200.1469.

3-(2,6-Dichlorophenyl)-N,N-diethyl-2,2-dimethylpropanethioamide (338)



Prepared according to **general procedure G**, using diisopropylamine (655 μL, 4.7 mmol), *n*BuLi in hexane (1.75 mL, 4.4 mmol), methyl isobutyrate (500 μL, 4.4 mmol), 2-(bromomethyl)-1,3-dichlorobenzene (1.57 g, 6.6 mmol), aqueous NaOH (3.5 mL, 2 M), Et_2NH (410 μL, 4.0 mmol), oxalyl chloride (775 μL, 8.7 mmol), Et_3N (1.1 mL, 7.9 mmol) and Lawesson's reagent (963 mg, 2.4 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/19 Et_2O/pentane). **338** was isolated as a light brown oil (455 mg, 36%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.29 (d, *J* = 8.0 Hz, $2H_{Ar}$), 7.08 (t, *J* = 8.0 Hz, H_{Ar}), 4.03 (brs, 4H, N-C$\underline{H_2}$), 3.42 (s, 2H, NC(S)-C-C$\underline{H_2}$), 1.44 (s, 6H, geminal C$\underline{H_3}$), 1.40 – 1.25 (m, 6H, N-CH_2-C$\underline{H_3}$).

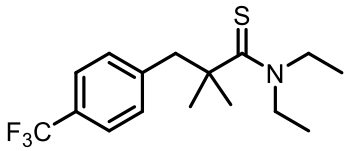
^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.8 ($\underline{C}$=S), 137.0 ($2C_{Ar}$), 135.7 (C_{Ar}), 128.5 ($2C_{Ar}$), 128.2 (C_{Ar}), 49.1* (brs, N-$\underline{C}H_2$, 2C), 48.4 (NC(S)-$\underline{C}$), 39.9 (NC(S)-C-$\underline{C}H_2$), 30.9 (geminal $\underline{C}H_3$, 2C), 13.9* (brs, N-CH_2-$\underline{C}H_3$, 2C), 11.0* (brs, N-CH_2-$\underline{C}H_3$, 2C).

*Rotamers observed.

HRMS (ESI) $[C_{15}H_{22}N^{35}Cl_2{}^{32}S]^+$ requires m/z 318.0844, found m/z 318.0846.

IR (film) ν_{max}/cm^{-1}: 2977, 1434, 1411, 1268, 1220, 1088, 1011, 770, 758.

N,N-Diethyl-2,2-dimethyl-3-(4-(trifluoromethyl)phenyl)propanethioamide (339)



Prepared according to **general procedure G**, using diisopropylamine (655 μL, 4.7 mmol), *n*BuLi in hexane (1.75 mL, 4.4 mmol), methyl isobutyrate (500 μL, 4.4 mmol), 1-(bromomethyl)-4-(trifluoromethyl)benzene (1.0 mL, 6.6 mmol), aqueous NaOH (3.5 mL, 2 M), Et_2NH (410 μL, 4.0 mmol), oxalyl chloride (775 μL, 8.7 mmol), Et_3N (1.1 mL, 7.9 mmol) and Lawesson's reagent (963 mg, 2.4 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/9 Et_2O/pentane). **339** was isolated as a light brown oil (579 mg, 46%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.46 (m, $2H_{Ar}$), 7.29 – 7.24 (m, $2H_{Ar}$), 3.92 (brs, 4H, N-C$\underline{H}_2$), 3.11 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.43 (s, 6H, geminal C$\underline{H}_3$), 1.29 (t, *J* = 6.9 Hz, 6H, N-CH_2-C$\underline{H}_3$).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -62.4 (3F).

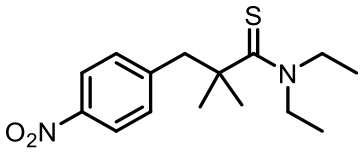
^{13}C NMR (176 MHz, Chloroform-*d*) δ 209.4 (C$\underline{}$=S), 142.3 (C_{Ar}), 130.8 ($2C_{Ar}$), 128.9 (q, *J* = 32.4 Hz, C_{Ar}), 124.9 (q, *J* = 3.8 Hz, $2C_{Ar}$), 124.4 (q, *J* = 271.6 Hz, C$\underline{F}_3$), 50.0* (brs, N-C$\underline{H}_2$, 2C), 48.0 (NC(S)-C$\underline{}$), 47.5* (brs, NC(S)-C-C$\underline{H}_2$, N-C$\underline{H}_2$, 3C), 30.5 (geminal C$\underline{H}_3$, 2C), 14.0* (brs, N-CH_2-C$\underline{H}_3$, 2C), 10.7* (brs, N-CH_2-C$\underline{H}_3$, 2C).

*Rotamers observed.

HRMS (ESI) $[C_{16}H_{23}NF_3{}^{32}S]^+$ requires m/z 318.1498, found m/z 318.1499.

IR (film) ν_{max}/cm^{-1}: 1412, 1323, 1272, 1162, 1116, 1067, 1018, 850.

N,N-Diethyl-2,2-dimethyl-3-(4-nitrophenyl)propanethioamide (340)



Prepared according to **general procedure G**, using diisopropylamine (655 μL, 4.7 mmol), *n*BuLi in hexane (1.75 mL, 4.4 mmol), methyl isobutyrate (500 μL, 4.4 mmol), 1-(bromomethyl)-4-nitrobenzene (1.42 g, 6.6 mmol), aqueous NaOH (3.5 mL, 2 M), Et_2NH (410 μL, 4.0 mmol), oxalyl chloride (775 μL, 8.7 mmol), Et_3N (1.1 mL, 7.9 mmol) and Lawesson's reagent (963 mg, 2.4 mmol). The crude reaction mixture was purified by flash column chromatography twice (3/17 Et_2O/pentane). **340** was isolated as a yellow solid (109 mg, 9%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.17 – 8.08 (m, $2H_{Ar}$), 7.36 – 7.28 (m, $2H_{Ar}$), 4.16 – 3.72 (m, 4H, N-C$\underline{H}_2$), 3.19 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.45 (s, 6H, geminal C$\underline{H}_3$), 1.30 (t, *J* = 6.9 Hz, 6H, N-CH_2-C$\underline{H}_3$).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 208.8 (<u>C</u>=S), 146.9 (C_{Ar}), 146.1 (C_{Ar}), 131.3 ($2C_{Ar}$), 123.2 ($2C_{Ar}$), 48.0 (NC(S)-<u>C</u>), 47.9 (NC(S)-C-<u>C</u>H_2), 30.6 (geminal <u>C</u>H_3, 2C).

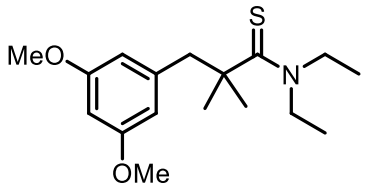
N-<u>C</u>H_2-<u>C</u>H_3 are not visible due to free rotation around the C-N bond.

HRMS (ESI) $[C_{15}H_{23}O_2N_2{}^{32}S]^+$ requires m/z 295.1475, found m/z 295.1475.

MP 67 - 68 °C.

IR (film) ν_{max}/cm^{-1}: 2981, 1519, 1345, 1271, 1150, 1074, 955.

3-(3,5-Dimethoxyphenyl)-N,N-diethyl-2,2-dimethylpropanethioamide (341)



Prepared according to **general procedure G**, using diisopropylamine (655 μL, 4.7 mmol), *n*BuLi in hexane (1.75 mL, 4.4 mmol), methyl isobutyrate (500 μL, 4.4 mmol), 1-(bromomethyl)-3,5-dimethoxybenzene (1.51 g, 6.6 mmol), aqueous NaOH (3.5 mL, 2 M), Et_2NH (410 μL, 4.0 mmol), oxalyl chloride (775 μL, 8.7 mmol), Et_3N (1.1 mL, 7.9 mmol) and Lawesson's reagent (963 mg, 2.4 mmol). The crude reaction mixture was purified by flash column chromatography twice (3/17 Et_2O/pentane). **341** was isolated as a light brown oil (308 mg, 25%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.43 – 6.20 (m, $3H_{Ar}$), 3.76 (s, 10H, N-C$\underline{H}_2$, O-C$\underline{H}_3$), 2.97 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.45 (s, 6H, geminal C$\underline{H}_3$), 1.27 (t, *J* = 7.0 Hz, 6H, N-CH_2-C$\underline{H}_3$).

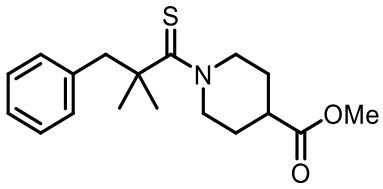
^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.3 (<u>C</u>=S), 160.4 ($2C_{Ar}$), 140.4 (C_{Ar}), 108.8 ($2C_{Ar}$), 98.4 (C_{Ar}), 55.4 (O-<u>C</u>H_3, 2C), 48.6* (brs, N-<u>C</u>H_2, 2C), 48.1 (NC(S)-<u>C</u>), 47.8 (NC(S)-C-<u>C</u>H_2), 30.9 (geminal <u>C</u>H_3, 2C), 13.9* (brs, N-CH_2-<u>C</u>H_3, 2C), 10.7* (brs, N-CH_2-<u>C</u>H_3, 2C).

*Rotamers observed.

HRMS (ESI) $[C_{17}H_{28}O_2N^{32}S]^+$ requires m/z 310.1835, found m/z 310.1833.

IR (film) ν_{max}/cm^{-1}: 2972, 1584, 1460, 1412, 1203, 1150, 1062, 1011, 838.

Methyl 1-(2,2-dimethyl-3-phenylpropanethioyl)piperidine-4-carboxylate (342)



Prepared according to **general procedure E**, using methyl piperidine-4-carboxylate (276 µL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 µL, 4.5 mmol), Et_3N (567 µL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/4 Et_2O/pentane). **342** was isolated as a light orange solid (252 mg, 39%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.26 (m, 1H, H_{Ar}), 7.26 – 7.19 (m, H_{Ar}), 7.16 – 7.11 (m, $2H_{Ar}$), 4.91 (d, *J* = 13.2 Hz, 2H, N-C$\underline{H}_2$), 3.72 (s, 3H, C(O)-O-C$\underline{H}_3$), 3.53 (ddd, *J* = 13.6, 10.7, 2.9 Hz, 2H, N-C$\underline{H}'_2$), 3.04 (s, 2H, NC(S)-C-C$\underline{H}_2$), 2.72 (hept, *J* = 9.8, 4.6 Hz, 1H, C(O)-C$\underline{H}$), 2.11 – 1.99 (m, 2H, N-CH_2-C$\underline{H}_2$), 1.98 – 1.82 (m, 2H, N-CH_2-C$\underline{H}'_2$), 1.40 (s, 6H, geminal C$\underline{H}_3$).

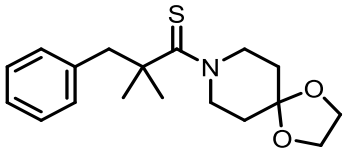
^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.2 ($\underline{C}$=S), 174.5 ($\underline{C}$=O), 138.0 (C_{Ar}), 130.6 ($2C_{Ar}$), 128.1 ($2C_{Ar}$), 126.7 (C_{Ar}), 52.3 (N-$\underline{C}H_2$, 2C), 52.1 (C(O)-O-$\underline{C}H_3$), 48.2 (NC(S)-$\underline{C}$), 46.8 (NC(S)-C-$\underline{C}H_2$), 40.5 (C(O)-$\underline{C}$H), 30.2 (geminal $\underline{C}H_3$, 2C), 28.3 (N-CH_2-$\underline{C}H_2$, 2C).

HRMS (ESI) $[C_{18}H_{26}O_2N^{32}S]^+$ requires m/z 320.1679, found m/z 320.1680.

MP 48 - 50 °C.

IR (film) ν_{max}/cm^{-1}: 1705, 1310, 1207, 1106, 1033, 908, 732.

2,2-Dimethyl-3-phenyl-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)propane-1-thione (343)



Prepared according to **general procedure E**, using 4-piperidinone ethylene acetal (262 μL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 μL, 4.5 mmol), Et_3N (567 μL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/4 Et_2O/pentane). **343** was isolated as a pale yellow solid (118 mg, 18%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.26 (m, H_{Ar}), 7.26 – 7.19 (m, $2H_{Ar}$), 7.17 – 7.10 (m, $2H_{Ar}$), 4.30 (t, *J* = 5.7 Hz, 4H, N-C$\underline{H}_2$), 4.01 (s, 4H, O-C$\underline{H}_2$), 3.05 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.89 – 1.79 (m, 4H, N-CH_2-C$\underline{H}_2$), 1.41 (s, 6H, geminal C$\underline{H}_3$).

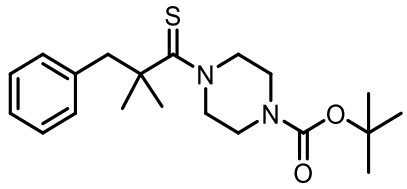
^{13}C NMR (101 MHz, Chloroform-*d*) δ 212.0 ($\underline{C}$=S), 138.0 (C_{Ar}), 130.6 ($2C_{Ar}$), 128.2 ($2C_{Ar}$), 126.7 (C_{Ar}), 106.8 (O-$\underline{C}$-O), 64.8 (O-$\underline{C}H_2$, 2C), 51.0 (N-$\underline{C}H_2$, 2C), 48.2 (NC(S)-$\underline{C}$), 46.9 (NC(S)-C-$\underline{C}H_2$), 35.4 (N-CH_2-$\underline{C}H_2$, 2C), 30.2 (geminal $\underline{C}H_3$, 2C).

HRMS (ESI) $[C_{18}H_{26}O_2N^{32}S]^+$ requires m/z 320.1679, found m/z 320.1679.

MP 88 - 90 °C.

IR (film) ν_{max}/cm^{-1}: 1418, 1219, 1098, 1032, 915, 703.

tert-Butyl 4-(2,2-dimethyl-3-phenylpropanethioyl)piperazine-1-carboxylate (344)



Prepared according to **general procedure E**, using tert-butyl piperazine-1-carboxylate (380 mg, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 µL, 4.5 mmol), Et_3N (567 µL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (3/17 Et_2O/pentane). **344** was isolated as a light yellow solid (207 mg, 28%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.32 – 7.20 (m, $3H_{Ar}$), 7.17 – 7.11 (m, $2H_{Ar}$), 4.16 (t, J = 5.3 Hz, 4H, N-C$\underline{H}_2$), 3.57 – 3.45 (m, 4H, N-CH_2-C$\underline{H}_2$), 3.04 (s, 1H, NC(S)-C-C$\underline{H}_2$), 1.48 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.43 (s, 6H, geminal C$\underline{H}_3$).

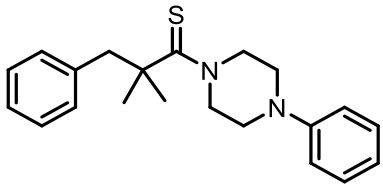
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 213.1 ($\underline{C}$=S), 154.7, 137.8 (C_{Ar}), 130.5 ($2C_{Ar}$), 128.2 ($2C_{Ar}$), 126.8 (C_{Ar}), 80.6 ($\underline{C}(CH_3)_3$), 52.6 (N-$\underline{C}H_2$, 2C), 48.5 (NC(S)-$\underline{C}$), 47.3 (NC(S)-C-$\underline{C}H_2$), 43.4 (N-CH_2-$\underline{C}H_2$, 2C), 30.5 (geminal $\underline{C}H_3$, 2C), 28.5 ($C(\underline{C}H_3)_3$).

HRMS (ESI) $[C_{20}H_{31}O_2N_2{}^{32}S]^+$ requires m/z 363.2101, found m/z 363.2102.

MP 86 - 87 °C.

IR (film) ν_{max}/cm^{-1}: 1696, 1413, 1286, 1219, 1119, 1007.

2,2-Dimethyl-3-phenyl-1-(4-phenylpiperazin-1-yl)propane-1-thione (345)



Prepared according to **general procedure E**, using 1-phenylpiperazine (312 μL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 μL, 4.5 mmol), Et_3N (567 μL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/9 Et_2O/pentane). **345** was isolated as a light yellow solid (153 mg, 22%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.33 – 7.21 (m, $5H_{Ar}$), 7.19 – 7.14 (m, $2H_{Ar}$), 6.98 – 6.88 (m, $3H_{Ar}$), 4.37 (t, J = 5.2 Hz, 4H, N-C$\underline{H_2}$), 3.38 – 3.23 (m, 4H, N-CH_2-C$\underline{H_2}$), 3.09 (s, 2H, NC(S)-C-C$\underline{H_2}$), 1.46 (s, 6H, geminal C$\underline{H_3}$).

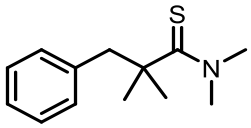
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 212.6 ($\underline{C}$=S), 150.4 (N-C_{Ar}), 137.9 (C_{Ar}), 130.6 ($2C_{Ar}$), 129.5 ($2C_{Ar}$), 128.2 ($2C_{Ar}$), 126.8 (C_{Ar}), 120.5 (C_{Ar}), 116.1 ($2C_{Ar}$), 52.6 (N-$\underline{C}H_2$, 2C), 49.0 (N-CH_2-$\underline{C}H_2$, 2C), 48.4 (NC(S)-$\underline{C}$), 47.3 (NC(S)-C-$\underline{C}H_2$), 30.4 (geminal $\underline{C}H_3$, 2C).

HRMS (ESI) $[C_{21}H_{27}N_2{}^{32}S]^+$ requires m/z 339.1890, found m/z 339.1888.

MP 52 - 55 °C.

IR (film) ν_{max}/cm^{-1}: 1600, 1418, 1280, 1220, 1106, 1023.

N,N,2,2-Tetramethyl-3-phenylpropanethioamide (346)



Prepared according to **general procedure E**, using dimethylamine (137 µL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 µL, 4.5 mmol), Et_3N (567 µL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/49 Et_2O/pentane). **346** was isolated as a pink solid (307 mg, 68%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.42 – 7.30 (m, $3H_{Ar}$), 7.27 – 7.23 (m, $2H_{Ar}$), 3.55 (s, 6H, N-C$\underline{H}_3$), 3.17 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.56 (s, 6H, geminal C$\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 211.6 (C$\underline{}$=S), 138.1 (C_{Ar}), 130.4 ($2C_{Ar}$), 128.1 ($2C_{Ar}$), 126.7 (C_{Ar}), 48.2 (NC(S)-C$\underline{}$), 47.2 (NC(S)-C-C$\underline{H}_2$), 30.3 (geminal C$\underline{H}_3$, 2C).

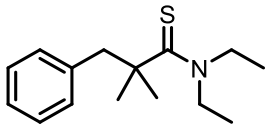
N-C$\underline{H}_3$ are not visible due to free rotation around the C-N bond.

HRMS (ESI) $[C_{13}H_{20}N^{32}S]^+$ requires m/z 222.1311, found m/z 222.1312.

MP 54 - 55 °C.

IR (film) ν_{max}/cm^{-1}: 1495, 1362, 1209, 1106, 1031, 746, 703.

N,N-Diethyl-2,2-dimethyl-3-phenylpropanethioamide (347)



Prepared according to **general procedure E**, using diethylamine (211 μL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 μL, 4.5 mmol), Et_3N (567 μL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/9 Et_2O/pentane). **347** was isolated as a light brown oil (336 mg, 66%).

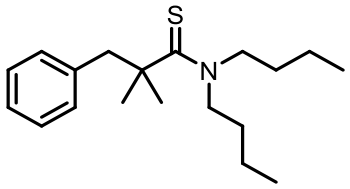
Analytical data is consistent with literature.[146]

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.29 – 7.18 (m, 3H), 7.19 – 7.14 (m, 2H), 3.88 (br s, 4H), 3.03 (s, 2H), 1.43 (s, 6H), 1.28 (t, J = 7.0 Hz, 6H).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 210.1, 138.0, 130.4 (2C), 127.9 (2C), 126.5, 53.4 (C2), 48.4 (2C), 48.1, 47.3 (2C), 30.6 (2C).

HRMS (ESI) $[C_{15}H_{24}N^{32}S]^+$ requires m/z 250.1624, found m/z 250.1624.

N,N-Dibutyl-2,2-dimethyl-3-phenylpropanethioamide (348)



Prepared according to **general procedure E**, using dibutylamine (344 μL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 μL, 4.5 mmol), Et_3N (567 μL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/19 Et_2O/pentane). **348** was isolated as an orange oil (155 mg, 25%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.30 – 7.19 (m, $3H_{Ar}$), 7.18 – 7.12 (m, $2H_{Ar}$), 4.10 – 3.44 (m, 4H, N-C$\underline{H}_2$), 3.02 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.78 – 1.62 (m, 4H, N-CH_2-C$\underline{H}_2$), 1.41 (s, 6H, geminal C$\underline{H}_3$), 1.34 (h, *J* = 7.4 Hz, 4H, N-CH_2-CH_2-C$\underline{H}_2$), 0.96 (t, *J* = 7.3 Hz, 6H, CH_2-C$\underline{H}_3$).

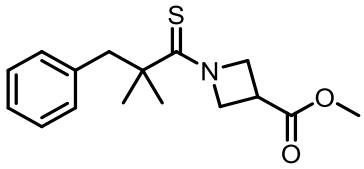
^{13}C NMR (176 MHz, Chloroform-*d*) δ 210.5 (C=S), 138.1 (C_{Ar}), 130.6 ($2C_{Ar}$), 128.1 ($2C_{Ar}$), 126.6 (C_{Ar}), 56.1* (brs, N-$\underline{C}H_2$, 2C), 53.8* (brs, N-$\underline{C}H_2$, 2C), 48.3 (NC(S)-C), 47.3 (NC(S)-C-$\underline{C}H_2$), 30.7* (brs, geminal $\underline{C}H_3$, N-CH_2-$\underline{C}H_2$, 4C), 27.4* (brs, N-CH_2-$\underline{C}H_2$, 2C), 20.4 (N-CH_2-CH_2-$\underline{C}H_2$, 2C), 14.0 (CH_2-$\underline{C}H_3$, 2C).

*Rotamers observed.

HRMS (ESI) $[C_{19}H_{32}N^{32}S]^+$ requires m/z 306.22500, found m/z 306.22510.

IR (film) ν_{max}/cm^{-1}: 2960, 2932, 2873, 1463, 1408, 1366, 1217, 1145, 1031, 745, 702.

Methyl 1-(2,2-dimethyl-3-phenylpropanethioyl)azetidine-3-carboxylate (349)



Prepared according to **general procedure E**, using methyl azetidine-3-carboxylate (1.133 g, 9.8 mmol), 2,2-dimethyl-3-phenylpropanoic acid (1.290 g, 10.8 mmol), oxalyl chloride (1.92 mL, 21.6 mmol), Et_3N (4.10 mL, 29.5 mmol) and Lawesson's reagent (2.388 g, 5.9 mmol). The crude reaction mixture was purified by flash column chromatography three times (1/5, 1/10 and 1/20 Et_2O/pentane). **349** was isolated as a colourless oil (1.871 g, 65%).

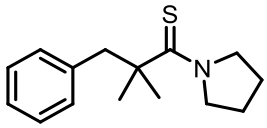
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.24 (m, $3H_{Ar}$), 7.22 – 7.15 (m, $2H_{Ar}$), 4.39 – 4.30 (m, 1H, N-C$\underline{H}_2$), 4.26 (ddd, *J* = 12.5, 6.2, 1.8 Hz, 1H, N-C$\underline{H}'_2$), 3.93 – 3.83 (m, 1H, N-C$\underline{H}_2$), 3.70 (s, 3H, O-C$\underline{H}_3$), 3.54 (ddd, *J* = 10.7, 9.1, 1.8 Hz, 1H, N-C$\underline{H}'_2$), 3.08 – 2.95 (m, 2H, NC(S)-C-C$\underline{H}_2$, N-CH_2-C$\underline{H}$), 2.86 (d, *J* = 13.0 Hz, 1H, NC(S)-C-C$\underline{H}'_2$), 1.45 (s, 3H, geminal $\underline{C}H_3$), 1.38 (s, 3H, geminal $\underline{C}H'_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.3 ($\underline{C}$=S), 172.1 (C9), 138.2 (C_{Ar}), 130.2 ($2C_{Ar}$), 128.1 ($2C_{Ar}$), 127.0 (C_{Ar}), 59.0 (N-$\underline{C}H_2$), 57.5 (N-$\underline{C}H'_2$), 52.5 (O-$\underline{C}H_3$), 50.0 (NC(S)-C-$\underline{C}H_2$), 49.1 (NC(S)-$\underline{C}$), 31.1 (N-CH_2-$\underline{C}$H), 29.7 (geminal $\underline{C}H_3$), 27.4 (geminal $\underline{C}H'_3$).

HRMS (ESI) $[C_{16}H_{22}O_2N^{32}S]^+$ requires m/z 292.1366, found m/z 292.1366.

IR (film) ν_{max}/cm^{-1}: 2981, 1737, 1472, 1436, 1361, 1205, 1177, 1071, 1027, 960, 743, 706.

2,2-Dimethyl-3-phenyl-1-(pyrrolidin-1-yl)propane-1-thione (350)



Prepared according to **general procedure E**, using pyrrolidine (168 μL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 μL, 4.5 mmol), Et_3N (567 μL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/9 Et_2O/pentane). **350** was isolated as a light orange solid (405 mg, 80%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.30 – 7.20 (m, $3H_{Ar}$), 7.19 – 7.16 (m, $2H_{Ar}$), 4.05 – 3.85 (m, 2H, N-C$\underline{H}_2$), 3.36 (t, J = 6.4 Hz, 2H, N-C$\underline{H}'_2$), 3.03 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.85 – 1.77 (m, 4H, N-CH_2-C$\underline{H}_2$), 1.50 (s, 6H, geminal C$\underline{H}_3$).

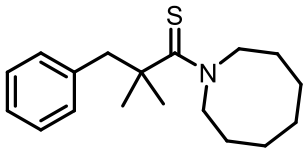
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 207.7 ($\underline{C}$=S), 138.4 (C_{Ar}), 130.3 ($2C_{Ar}$), 128.1($2C_{Ar}$), 126.7 (C_{Ar}), 58.6 (N-$\underline{C}H_2$), 53.2 (N-$\underline{C}H'_2$), 49.4 (NC(S)-$\underline{C}$), 48.5 (NC(S)-C-$\underline{C}H_2$), 30.2 (geminal $\underline{C}H_3$, 2C), 27.6 (N-CH_2-$\underline{C}H_2$), 23.2 (N-CH_2-$\underline{C}H'_2$).

HRMS (ESI) $[C_{15}H_{22}N^{32}S]^+$ requires m/z 248.1468, found m/z 248.1468.

MP 51 - 52 °C.

IR (film) ν_{max}/cm^{-1}: 1420, 1203, 1107, 1031, 705.

1-(Azocan-1-yl)-2,2-dimethyl-3-phenylpropane-1-thione (351)



Prepared according to **general procedure E**, using azocane (258 μL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 μL, 4.5 mmol), Et_3N (567 μL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/50 Et_2O/pentane). **351** was isolated as a light brown oil (426 mg, 70%).

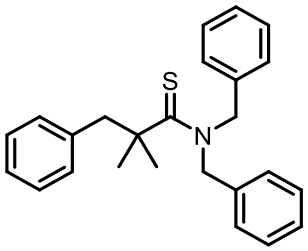
^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.32 – 7.19 (m, $3H_{Ar}$), 7.19 – 7.13 (m, $2H_{Ar}$), 4.04 (brs, 4H, N-C$\underline{H}_2$), 3.09 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.98 (brs, 4H, N-CH_2-C$\underline{H}_2$), 1.80 – 1.45 (m, 6H, C$\underline{H}_2$-C$\underline{H}_2$-C$\underline{H}_2$), 1.43 (s, 6H, geminal C$\underline{H}_3$).

^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 210.8 (C=S), 138.1 (C_{Ar}), 130.7 ($2C_{Ar}$), 128.1 ($2C_{Ar}$), 126.6 (C_{Ar}), 56.7 (N-CH_2, 2C), 48.3 (NC(S)-C), 46.7 (NC(S)-C-CH_2), 30.3 (geminal CH_3, 2C), 27.3 (N-$(CH_2)_3$-CH_2), 25.6 (N-CH_2-CH_2, 2C), 22.8 (N-CH_2-CH_2-CH_2, 2C).

HRMS (ESI) $[C_{18}H_{28}N^{32}S]^+$ requires m/z 290.1937, found m/z 290.1938.

IR (film) ν_{max}/cm^{-1}: 2925, 2854, 1470, 1406, 1362, 1288, 1217, 1112, 1037, 742, 702.

N,N-Dibenzyl-2,2-dimethyl-3-phenylpropanethioamide (352)



Prepared according to **general procedure E**, using dibenzylamine (410 μL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 μL, 4.5 mmol), Et_3N (567 μL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/19 Et_2O/pentane). **352** was isolated as an orange solid (393 mg, 52%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.41 – 7.27 (m, $6H_{Ar}$), 7.25 – 7.20 (m, $3H_{Ar}$), 7.19 – 7.12 (m, $6H_{Ar}$), 5.25 (s, 4H, N-C$\underline{H}_2$), 3.16 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.46 (s, 6H, geminal C$\underline{H}_3$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 215.1 ($\underline{C}$=S), 137.8 (C_{Ar}), 136.1 ($2C_{Ar}$), 130.9 ($4C_{Ar}$), 129.0 (brs, $4C_{Ar}$), 128.1 ($4C_{Ar}$), 127.8 ($2C_{Ar}$), 126.7 (C_{Ar}), 57.5* (brs, N-$\underline{C}H_2$), 56.1* (brs, N-$\underline{C}H_2$), 48.7 (NC(S)-$\underline{C}$), 47.2 (NC(S)-C-$\underline{C}H_2$), 30.2 (geminal $\underline{C}H_3$, 2C).

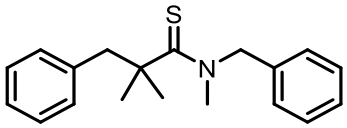
*Rotamers observed.

HRMS (ESI) $[C_{25}H_{28}N^{32}S]^+$ requires m/z 374.19370, found m/z 374.19372.

MP 110 - 112 °C.

IR (film) ν_{max}/cm^{-1}: 3028, 2980, 1495, 1451, 1398, 1217, 1146, 1078, 1030, 999, 737, 699.

N-Benzyl-N,2,2-trimethyl-3-phenylpropanethioamide (353)



Prepared according to **general procedure E**, using N-methyl-1-phenylmethanamine (263 µL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 µL, 4.5 mmol), Et_3N (567 µL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/49 Et_2O/pentane). **353** was isolated as a yellow oil (409 mg, 67%).

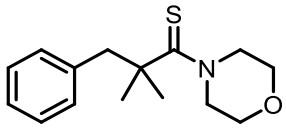
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.22 (m, $6H_{Ar}$), 7.22 – 7.14 (m, $4H_{Ar}$), 5.26 (s, 2H, N-C$\underline{H_2}$), 3.34 (s, 3H, N-C$\underline{H_3}$), 3.13 (s, 2H, NC(S)-C-C$\underline{H_2}$), 1.48 (s, 6H, geminal C$\underline{H_3}$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 213.3 ($\underline{C}$=S), 138.0 (C_{Ar}), 136.1 (C_{Ar}), 130.6 ($2C_{Ar}$), 129.0 ($2C_{Ar}$), 128.2 ($2C_{Ar}$), 127.8 (C_{Ar}), 127.3 (brs, $2C_{Ar}$), 126.7 (C_{Ar}), 60.7 (N-$\underline{C}H_2$), 48.5 (NC(S)-$\underline{C}$), 47.3 (NC(S)-C-$\underline{C}H_2$), 44.2 (N-$\underline{C}H_3$), 30.5 (geminal $\underline{C}H_3$, 2C).

HRMS (ESI)) $[C_{19}H_{24}N^{32}S]^+$ requires m/z 298,1624, found m/z 298,1625.

IR (film) ν_{max}/cm^{-1}: 2923, 1482, 1451, 1380, 1364, 1214, 1079, 1029, 735, 699.

2,2-Dimethyl-1-morpholino-3-phenylpropane-1-thione (354)



Prepared according to **general procedure E**, using morpholine (176 μL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 μL, 4.5 mmol), Et_3N (567 μL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/9 Et_2O/pentane). **354** was isolated as a light yellow solid (248 mg, 46%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ_H 7.36 – 7.19 (m, $3H_{Ar}$), 7.18 – 7.09 (m, $2H_{Ar}$), 4.33 – 4.17 (m, 4H, N-C$\underline{H}_2$), 3.91 – 3.69 (m, 4H, N-CH_2-C$\underline{H}_2$), 3.04 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.43 (s, 6H, geminal C$\underline{H}_3$).

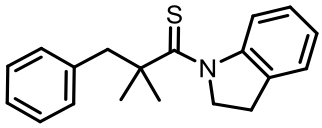
^{13}C NMR ($CDCl_3$, 101 MHz) δ_C 212.8 (C=S), 137.8 (C_{Ar}), 130.6 ($2C_{Ar}$), 128.2 ($2C_{Ar}$), 126.8 (C_{Ar}), 66.8 (N-CH_2-CH_2, 2C), 53.7 (N-CH_2, 2C), 48.2 (NC(S)-C), 47.1 (NC(S)-C-CH_2), 30.4 (geminal CH_3, 2C).

HRMS (ESI) $[C_{15}H_{22}ON^{32}S]^+$ requires m/z 264.1417, found m/z 264.1417.

MP 85 - 86 °C.

IR (film) ν_{max}/cm^{-1}: 1416, 1271, 1218, 1114, 1034, 702.

1-(Indolin-1-yl)-2,2-dimethyl-3-phenylpropane-1-thione (355)



Prepared according to **general procedure E**, using indoline (229 µL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 µL, 4.5 mmol), Et_3N (567 µL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography three times (1/19 to 1/4 Et_2O/pentane). **355** was isolated as a bright yellow solid (283 mg, 47%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.49 (d, *J* = 8.3 Hz, H_{Ar}), 7.32 – 7.26 (m, $4H_{Ar}$), 7.26 – 7.16 (m, $3H_{Ar}$), 7.08 (td, *J* = 7.4, 1.1 Hz, H_{Ar}), 3.85 (t, *J* = 7.4 Hz, 2H, N-C$\underline{H_2}$), 3.20 (s, 2H, NC(S)-C-C$\underline{H_2}$), 2.78 (t, *J* = 7.4 Hz, 2H, N-CH_2-C$\underline{H_2}$), 1.57 (s, 6H, geminal C$\underline{H_3}$).

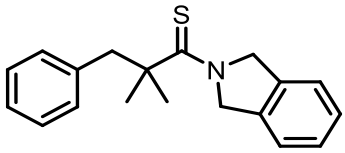
^{13}C NMR (126 MHz, Chloroform-*d*) δ 213.7 ($\underline{C}$=S), 145.9 (C_{Ar}), 138.7 (C_{Ar}), 135.4 (C_{Ar}), 130.5 ($2C_{Ar}$), 128.4 ($2C_{Ar}$), 126.8 (C_{Ar}), 125.9 (C_{Ar}), 125.6 (C_{Ar}), 124.7 (C_{Ar}), 121.9 (C_{Ar}), 56.8 (N-$\underline{C}H_2$), 51.9 (NC(S)-$\underline{C}$), 49.0 (NC(S)-C-$\underline{C}H_2$), 31.1 (geminal $\underline{C}H_3$, 2C), 29.5 (N-CH_2-$\underline{C}H_2$).

HRMS (ESI) $[C_{19}H_{22}N^{32}S]^+$ requires m/z 296.1468, found m/z 296.1469.

MP 77 - 78 °C.

IR (film) ν_{max}/cm^{-1}: 1475, 1360, 1324, 1257, 1165, 1044, 754, 703.

1-(Isoindolin-2-yl)-2,2-dimethyl-3-phenylpropane-1-thione (356)



Prepared according to **general procedure E**, using isoindoline (232 μL, 2.0 mmol), 2,2-dimethyl-3-phenylpropanoic acid (400 mg, 2.2 mmol), oxalyl chloride (399 μL, 4.5 mmol), Et_3N (567 μL, 4.1 mmol) and Lawesson's reagent (495 mg, 1.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/19 to 1/4 Et_2O/pentane). **356** was isolated as a light yellow solid (558 mg, 92%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, $2H_{Ar}$), 7.26 – 7.08 (m, $7H_{Ar}$), 5.35 (s, 2H, N-C$\underline{H}_2$), 4.82 (s, 2H, N-C$\underline{H}'_2$), 3.11 (s, 2H, NC(S)-C-C$\underline{H}_2$), 1.59 (s, 6H, geminal C$\underline{H}_3$).

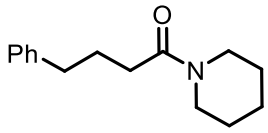
^{13}C NMR (126 MHz, Chloroform-*d*) δ 209.1 ($\underline{C}$=S), 138.0 (C_{Ar}), 136.2 (C_{Ar}), 134.6 (C_{Ar}), 130.3 ($2C_{Ar}$), 128.1 ($2C_{Ar}$), 128.0 (C_{Ar}), 127.7 (C_{Ar}), 126.8 (C_{Ar}), 122.3 (C_{Ar}), 122.2 (C_{Ar}), 64.5 (N-$\underline{C}H_2$), 57.5 (N-$\underline{C}H_2$), 49.5 (NC(S)-$\underline{C}$), 48.4 (NC(S)-C-$\underline{C}H_2$), 30.2 (geminal $\underline{C}H_3$, 2C).

HRMS (ESI) $[C_{19}H_{22}N^{32}S]^+$ requires m/z 296.1468, found m/z 296.1466.

MP 100 - 102 °C.

IR (film) ν_{max}/cm^{-1}: 1399, 1362, 1324, 1089, 1024, 745, 702.

4-Phenyl-1-(piperidin-1-yl)butan-1-one (358)



Prepared according to modified **general procedure E**, using piperidine (1.094 mL, 11.1 mmol), 4-phenylbutanoic acid (2.00 g, 12.2 mmol), oxalyl chloride (2.164 mL, 24.4 mmol), Et_3N (3.078 mL, 22.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/9 Et_2O/pentane). **358** was isolated as a light brown oil (2.36 g, 92%).

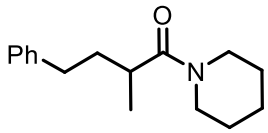
Analytical data is consistent with the literature.[183]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.33 (m, 2H), 7.32 – 7.24 (m, 3H), 3.70 – 3.59 (m, 2H), 3.46 – 3.36 (m, 2H), 2.83 – 2.72 (m, 2H), 2.46 – 2.37 (m, 2H), 2.06 (tt, J = 8.7, 6.8 Hz, 2H), 1.79 – 1.66 (m, 2H), 1.66 – 1.56 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 142.0, 128.6, 128.5, 126.0, 46.7, 42.8, 35.6, 32.7, 27.0, 26.7, 25.7, 24.7.

HRMS (ESI) $[C_{15}H_{22}ON]^+$ requires m/z 232.1696, found m/z 232.1695.

2-Methyl-4-phenyl-1-(piperidin-1-yl)butan-1-one (359)



Prepared according to **general procedure H**, using diisopropylamine (1.348 mL, 9.6 mmol), *n*BuLi in hexane (3.728 mL, 9.3 mmol), 4-phenyl-1-(piperidin-1-yl)butan-1-one (1.000 mL, 4.2 mmol), iodomethane (0.791 mL, 12.7 mmol). The crude reaction mixture was purified by flash column chromatography (1/10 Et_2O/pentane). **359** was isolated as a yellow oil (580 mg, 56%).

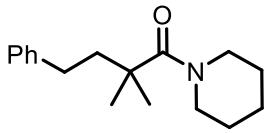
Analytical data is consistent with the literature.[184]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (ddd, *J* = 8.6, 6.5, 0.8 Hz, 2H), 7.18 (tt, *J* = 6.5, 1.2 Hz, 3H), 3.64 (dt, *J* = 13.2, 5.8 Hz, 1H), 3.59 – 3.48 (m, 1H), 3.40 – 3.23 (m, 2H), 2.74 – 2.53 (m, 3H), 2.07 (dddd, *J* = 13.7, 8.7, 7.5, 6.3 Hz, 1H), 1.73 – 1.60 (m, 3H), 1.52 (dt, *J* = 16.8, 5.9 Hz, 4H), 1.13 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 142.1, 128.5, 128.3, 125.8, 46.4, 42.9, 35.6, 34.3, 33.5, 26.8, 25.8, 24.7, 17.7.

HRMS (ESI) $[C_{16}H_{24}ON]^+$ requires m/z 246.1852, found m/z 246.1853.

2,2-Dimethyl-4-phenyl-1-(piperidin-1-yl)butan-1-one (360)



Prepared according to **general procedure H**, using methylated amide **359** (300 mg, 1.2 mmol), diisopropylamine (257 μL, 1.8 mmol), *n*BuLi in hexane (736 μL, 1.8 mmol) and iodomethane (152 μL, 2.4 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/10 Et_2O/pentane). **360** was isolated as a yellow oil (316 mg, quant.).

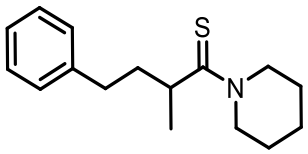
Analytical data is consistent with literature.[146]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.25 (m, 2H), 7.20 – 7.12 (m, 3H), 4.24 – 4.01 (m, 4H), 2.64 (dt, 2H), 2.02 (dt, 2H), 1.82 – 1.67 (m, 6H), 1.50 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 142.7, 128.6, 128.5, 126.2, 54.4, 47.6, 44.2, 31.6, 31.0, 26.4, 24.7.

HRMS (ESI) $[C_{17}H_{26}ON]^+$ requires m/z 260.2011, found m/z 260.2010.

2-Methyl-4-phenyl-1-(piperidin-1-yl)butane-1-thione (361)



Prepared according to **general procedure H**, using diisopropylamine (1.348 mL, 9.6 mmol), *n*BuLi in hexane (3.728 mL, 9.3 mmol), 4-phenyl-1-(piperidin-1-yl)butan-1-one (1.000 mL, 4.2 mmol), iodomethane (0.791 mL, 12.7 mmol). The crude reaction mixture was purified by flash column chromatography (1/10 Et_2O/pentane). The pure methylated amide (193 mg, 0.8 mmol) was added with Lawesson's reagent (191 mg, 0.5 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/20 Et_2O/pentane). **361** was isolated as a yellow oil (148 mg, 40%; over the two steps).

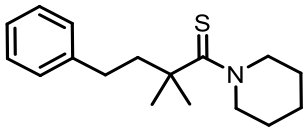
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.23 (m, $2H_{Ar}$), 7.22 – 7.13 (m, $3H_{Ar}$), 4.40 – 4.24 (m, 2H, N-C$\underline{H}_2$), 3.65 – 3.52 (m, 2H, N-C$\underline{H}'_2$), 2.98 (h, *J* = 6.7 Hz, 1H, NC(S)-C$\underline{H}$), 2.72 – 2.54 (m, 2H, NC(S)-CH-CH_2-C$\underline{H}_2$), 2.26 (dddd, *J* = 13.6, 8.4, 7.4, 6.3 Hz, 1H, NC(S)-C-C$\underline{H}_2$), 1.84 (ddt, *J* = 13.2, 8.7, 6.5 Hz, 1H, NC(S)-C-C$\underline{H}'_2$), 1.75 – 1.64 (m, 4H, N-CH_2-C$\underline{H}_2$-C$\underline{H}_2$), 1.60 – 1.50 (m, 2H, N-CH_2-C$\underline{H}'_2$-CH_2), 1.24 (d, *J* = 6.7 Hz, 3H, C$\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9 (C$\underline{}$=S), 142.1 (C_{Ar}), 128.7 ($2C_{Ar}$), 128.5 ($2C_{Ar}$), 126.0 (C_{Ar}), 52.0 (N-C$\underline{H}_2$), 50.3 (N-C$\underline{H}'_2$), 40.7 (NC(S)-C$\underline{H}$), 39.1 (NC(S)-C-C$\underline{H}_2$), 33.6 (NC(S)-CH-CH_2-C$\underline{H}_2$), 27.3 (N-CH_2-C$\underline{H}_2$), 25.6 (N-CH_2-C$\underline{H}'_2$), 24.6 (N-CH_2-CH_2-C$\underline{H}_2$), 21.4 (C$\underline{H}_3$).

HRMS (ESI) $[C_{16}H_{24}N^{32}S]^+$ requires m/z 262.1624, found m/z 262.1624.

IR (film) ν_{max}/cm^{-1}: 2923, 2851, 1482, 1441, 1282, 1260, 1236, 1021, 773.

2,2-Dimethyl-4-phenyl-1-(piperidin-1-yl)butane-1-thione (362)



Prepared according to **general procedure H**, using diisopropylamine (1.348 mL, 9.6 mmol), *n*BuLi in hexane (3.728 mL, 9.3 mmol), 4-phenyl-1-(piperidin-1-yl)butan-1-one (1.000 mL, 4.2 mmol), iodomethane (0.791 mL, 12.7 mmol). The crude reaction mixture was purified by flash column chromatography (1/10 Et_2O/pentane). The process was then repeated with methylated amide (300 mg, 1.2 mmol), diisopropylamine (257 µL, 1.8 mmol), *n*BuLi in hexane (736 µL, 1.8 mmol), iodomethane (152 µL, 2.4 mmol) and Lawesson's reagent (297 mg, 0.7 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/20 and 1/50 Et_2O/pentane). **362** was isolated as a yellow oil (240 mg, 42%; over the three steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.24 (m, $2H_{Ar}$), 7.21 – 7.13 (m, $3H_{Ar}$), 4.24 – 4.05 (m, 4H, N-C$\underline{H_2}$), 2.69 – 2.60 (m, 2H, NC(S)-C-CH_2-C$\underline{H_2}$), 2.07 – 1.98 (m, 2H, NC(S)-C-C$\underline{H_2}$), 1.79 – 1.66 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.52 (s, 6H, geminal C$\underline{H_3}$).

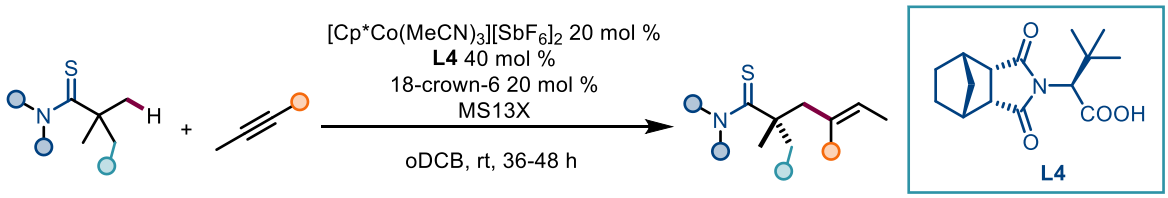
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.9 ($\underline{C}$=S), 142.6 (C_{Ar}), 128.6 ($2C_{Ar}$), 128.4 ($2C_{Ar}$), 126.0 (C_{Ar}), 54.2 (N-$\underline{C}H_2$, 2C), 47.3 (NC(S)-$\underline{C}$), 44.1 (NC(S)-C-$\underline{C}H_2$), 31.6 (C11), 31.0 (geminal $\underline{C}H_3$, 2C), 26.4 (N-CH_2-$\underline{C}H_2$, 2C), 24.5 (N-CH_2-CH_2-$\underline{C}H_2$).

HRMS (ESI) $[C_{17}H_{26}N^{32}S]^+$ requires m/z 276.1780, found m/z 276.1780.

IR (film) ν_{max}/cm^{-1}: 2981, 2939, 1389, 1249, 1111, 1003, 979.

5.2.4 The enantio- and regio-selective Co^{III}-catalysed $C(sp^3)$–H alkenylation of thioamides

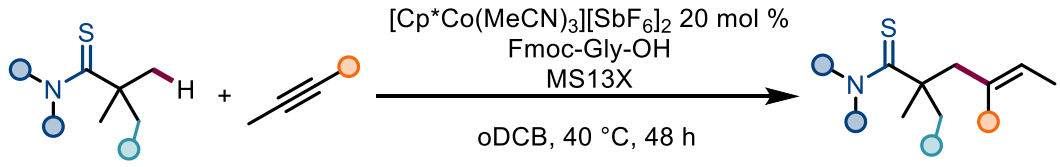
5.2.4.1 General procedure I: *Enantioselective C–H Alkenylation*



To the mixture of thioamide (0.20 mmol, 1.00 eq.), $[CoCp^*(MeCN)_3][SbF_6]_2$ (0.04 mmol, 20 mol %), chiral carboxylic acid **L4** (0.08 mmol, 40 mol %) and 18-crown-6 (0.04 mmol, 20 mol %) was added alkyne (1.00 mmol, 5.00 eq.) and MS13X (40 mg). The mixture was then dissolved in *o*DCB (0.5 M) and allowed to stir under an argon atmosphere for 36 - 48 hours at room temperature. Upon the reaction completion, the solvent was removed in vacuo and the crude reaction mixture was purified by flash column chromatography (Et_2O/pentane) resulting in the alkylated thioamide products. The two enantiomers were then separated by chiral HPLC, with conditions specified for each individual product.

*Some products were isolated with inseparable purple oil stain invisible on the NMR and MS.

5.2.4.2. General Procedure J: *Racemic C-H Alkenylation*

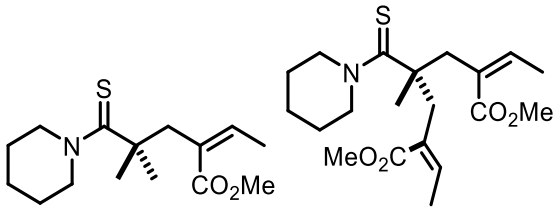


The mixture of thioamide (0.05 mmol, 1.00 eq.), $[CoCp^*(MeCN)_3][SbF_6]_2$ (0.01 mmol, 20 mol %), Fmoc-glycine (0.05 mmol, 1.00 eq.), alkyne (0.15 mmol, 3.00 eq.) and MS13X (10

mg) was dissolved in *o*DCB (0.5 M) and allowed to stir under an argon atmosphere for 48 hours at 40 °C. Upon the reaction completion, the solvent was removed in vacuo and the crude mixture was purified by flash column chromatography (Et_2O/pentane) resulting in the racemic alkylated thioamide products. The two enantiomers were then separated by chiral HPLC, with conditions specified for each individual product.

*Some products were isolated with inseparable purple oil stain invisible on the NMR and MS.

Methyl (E)-3,5,5-trimethyl-6-(piperidin-1-yl)-6-thioxohex-2-enoate (299) and Dimethyl (2E,7E)-3,5,7-trimethyl-5-(piperidine-1-carbonothioyl)nona-2,7-dienedioate (300)



The mixture of thioamide **296** (10 mg, 53.95 nmol, 1.00 eq.), $[CoCp^*(MeCN)_3][SbF_6]_2$ (12.8 mg, 16.19 nmol, 30 mol %), benzoic acid (6.6 mg, 53.95 nmol, 1.00 eq.) and alkyne **298** (15.9 mg, 161.87 nmol, 3.00 eq.) was dissolved in DCE (1.0 mL) and allowed to stir under Ar for 24 hours at 40 °C. Upon completion, the solvent was removed *in vacuo* and the crude mixture was purified by flash column chromatography (1/9 Et_2O/pentane) resulting in the product **299** (3.7 mg, 24 %) as a dark blue solid and product **300** (8.5 mg, 48 %) as a 1/1 mixture with monoalkenylated thioamide. NMR analysis was only performed for the monoalkenylated thioamide **299**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.03 (q, *J* = 7.2, 1.0 Hz, 1H, C=C<u>H</u>), 4.19 (d, *J* = 6.5 Hz, 4H, N-C<u>H$_2$</u>), 3.73 (s, 3H, O-C<u>H$_3$</u>), 2.71 – 2.67 (m, 2H, C-C<u>H$_2$</u>-C$_{Alk}$), 1.98 – 1.94 (m, 3H, CH-C<u>H$_3$</u>), 1.77 – 1.66 (m, 6H, N-CH$_2$-C<u>H$_2$</u>-C<u>H$_2$</u>), 1.34 (s, 6H, 2(C-C<u>H$_3$</u>)).

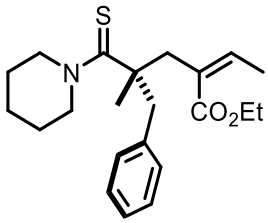
^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.9 (<u>C</u>=S), 169.2 (ester <u>C</u>=O), 140.6 (<u>C</u>=CH), 129.4 (C=<u>C</u>H), 51.5 (O-<u>C</u>H$_3$), 47.6 (N-<u>C</u>H$_2$, 2C), 43.6 (NC(S)-<u>C</u>), 29.8 (C-<u>C</u>H$_3$), 29.6 (N-CH$_2$-<u>C</u>H$_2$, C-<u>C</u>H$_3$, 3C), 24.5 (N-CH$_2$-CH$_2$-<u>C</u>H$_2$), 16.2 (CH-<u>C</u>H$_3$).

HRMS (ESI) $[C_{15}H_{26}CoI_2O]^+$ requires m/z 284.1679, found m/z 284.1680.

IR (film) ν_{max}/cm^{-1}: 2980, 2937, 1716, 1423, 1387, 1238, 1188, 1155, 1136, 1074, 1021, 1002, 952.

MP 58 - 60 °C.

Ethyl (Z)-4-benzyl-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (316)



Prepared according to the **general procedure I**, using 2,2-dimethyl-3-phenyl-1-(piperidin-1-yl)propane-1-thione **313** (52.4 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **316** was isolated as pale yellow oil (56.2 mg, 75%, 89/11 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 9.41 min, τ_{Rminor} = 12.90 min, 89/11 er).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.25 – 7.15 (m, $3H_{Ar}$), 7.11 (d, *J* = 6.9, 1.8 Hz, $2H_{Ar}$), 6.02 (q, *J* = 7.1 Hz, 1H, C=C<u>H</u>), 4.37 – 3.99 (m, 6H, N-C<u>H$_2$</u>, O-C<u>H$_2$</u>-CH_3), 3.43 (d, *J* = 14.0 Hz, 1H, C-C<u>H$_a$</u>H_b-C_{Ar}), 2.95 (d, *J* = 14.0 Hz, 1H, C-C<u>H$_a$</u>H_b-C_{Alk}), 2.80 (d, *J* = 14.0 Hz, 1H, C-CH_a<u>H$_b$</u>-C_{Alk}), 2.71 (d, *J* = 13.9 Hz, 1H, C-CH_a<u>H$_b$</u>-C_{Ar}), 1.94 (d, *J* = 7.2 Hz, 3H, CH-C<u>H$_3$</u>), 1.79 – 1.65 (m, 6H, N-CH_2-C<u>H$_2$</u>-C<u>H$_2$</u>), 1.38 (s, 3H, C-C<u>H$_3$</u>), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H$_3$</u>).

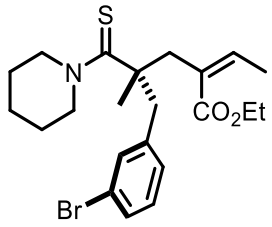
^{13}C NMR (126 MHz, Chloroform-*d*) δ 209.1 (<u>C</u>=S), 168.9 (ester <u>C</u>=O), 139.6 (C=<u>C</u>H), 137.9 (<u>C</u>=CH), 130.4 ($2C_{Ar}$), 129.7 (C_{Ar}), 128.1 ($2C_{Ar}$), 126.6 (C_{Ar}), 60.6 (O-<u>C</u>H_2-CH_3), 54.5 (brs, N-<u>C</u>H_2, 2C), 52.5 (NC(S)-<u>C</u>), 45.5 (C-<u>C</u>$H_a$$H_b$-$C_{Ar}$), 44.4 (C-<u>C</u>$H_a$$H_b$-$C_{Alk}$), 29.5 (C-<u>C</u>$H_3$), 26.1 (N-$CH_2$-<u>C</u>$H_2$, 2C), 24.4 (N-$CH_2$-$CH_2$-<u>C</u>$H_2$), 16.1 (CH-<u>C</u>$H_3$), 14.4 (O-$CH_2$-<u>C</u>$H_3$).

HRMS (ESI) $[C_{22}H_{32}O_2N^{32}S]^+$ requires m/z 374.2148, found m/z 374.2144.

IR (film) ν_{max}/cm^{-1}: 2979, 2936, 1709, 1455, 1418, 1382, 1244, 1143, 1096, 1010, 702.

$[\alpha]_D^{25}$ = 7.76 (c = 0.92, $CHCl_3$).

Ethyl (Z)-4-(3-bromobenzyl)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (363)



Prepared according to the **general procedure I**, using 3-(3-bromophenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **324** (32.5 mg, 0.10 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (15.8 mg, 0.02 mmol), chiral carboxylic acid **L4** (11.2 mg, 0.04 mmol), 18-crown-6 (5.3 mg, 0.02 mmol), ethyl but-2-ynoate (56.0 mg, 0.50 mmol) and MS13X (20 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **363** was isolated as pale yellow oil (32.5 mg, 72%, 86/14 er). Chiral HPLC (Chiralpak IB, 1/99 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 12.49 min, τ_{Rminor} = 14.42 min, 86/14 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 (dt, *J* = 7.6, 1.9 Hz, 1H, H_{Ar}), 7.28 – 7.26 (m, 1H, H_{Ar}), 7.09 (t, *J* = 7.6 Hz, 1H, H_{Ar}), 7.05 (dt, *J* = 7.7, 1.5 Hz, 1H, H_{Ar}), 6.10 – 6.01 (m, 1H, C=C$\underline{H}$), 4.26 – 4.07 (m, 6H, N-C$\underline{H_2}$, O-C$\underline{H_2}$-CH_3), 3.47 (d, *J* = 14.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 2.92 (d, *J* = 14.1 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.82 (d, *J* = 14.0 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Alk}), 2.63 (d, *J* = 14.0 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Ar}), 1.96 (d, *J* = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.81 – 1.64 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.36 (s, 3H, C-C$\underline{H_3}$), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 208.8 (C=S), 168.9 (ester C=O), 140.4 (C=CH), 140.0 (C=CH), 133.4 (C_{Ar}), 129.6 (C_{Ar}), 129.6 (C_{Ar}), 129.5 (C_{Ar}), 129.0 (C_{Ar}), 122.1 (C_{Ar}), 60.6 (O-CH_2-CH_3), 54.6 (brs, N-CH_2, 2C), 52.6 (NC(S)-C), 45.4 (C-CH_aH_b-C_{Ar}), 44.6 (C-

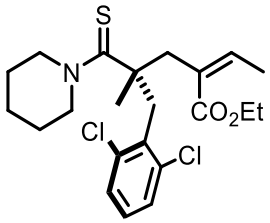
$\underline{C}H_aH_b$-C_{Alk}), 29.2 (C-$\underline{C}H_3$), 26.2 (N-CH_2-$\underline{C}H_2$, 2C), 24.4 (N-CH_2-CH_2-$\underline{C}H_2$), 16.1 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{22}H_{31}O_2N^{79}Br^{32}S]^+$ requires m/z 452.1253, found m/z 452.1252.

IR (film) ν_{max}/cm^{-1}: 2936, 1709, 1474, 1417, 1382, 1242, 1143, 1010, 772.

$[\alpha]_D^{25}$ = -2.41 (c = 0.66, $CHCl_3$).

Ethyl (Z)-4-(2,6-dichlorobenzyl)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (364)



Prepared according to the **general procedure I**, using 3-(2,6-dichlorophenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **325** (66.1 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **364** was isolated as pale yellow oil (62.7 mg, 71%, 89/11 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 11.58 min, τ_{Rminor} = 21.23 min, 89/11 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (d, *J* = 8.1 Hz, $2H_{Ar}$), 7.07 (dd, *J* = 8.4, 7.6 Hz, H_{Ar}), 5.97 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.99 – 3.71 (m, 6H, N-C<u>H$_2$</u>, O-C<u>H$_2$</u>-CH$_3$), 3.54 (d, *J* = 13.9 Hz, 1H, C-C<u>H$_a$</u>H$_b$-C$_{Ar}$), 3.42 (d, *J* = 13.9 Hz, 1H, C-CH$_a$<u>H$_b$</u>-C$_{Ar}$), 3.18 (d, *J* = 13.8 Hz, 1H, C-C<u>H$_a$</u>H$_b$-C$_{Alk}$), 2.81 (d, *J* = 13.8 Hz, 1H, C-CH$_a$<u>H$_b$</u>-C$_{Alk}$), 1.94 (d, *J* = 7.2 Hz, 3H, CH-C<u>H$_3$</u>), 1.89 – 1.72 (m, 6H, N-CH$_2$-C<u>H$_2$</u>-C<u>H$_2$</u>), 1.29 (t, *J* = 7.1 Hz, 3H, O-CH$_2$-C<u>H$_3$</u>), 1.22 (s, 3H, C-C<u>H$_3$</u>).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.3 (<u>C</u>=S), 168.7 (ester <u>C</u>=O), 140.2 (C=<u>C</u>H), 137.0 ($2C_{Ar}$), 136.2 (C_{Ar}), 129.6 (<u>C</u>=CH), 128.4 ($2C_{Ar}$), 128.2 (C_{Ar}), 60.5 (O-<u>C</u>H$_2$-CH$_3$), 54.4 (brs, N-<u>C</u>H$_2$, 2C), 50.9 (NC(S)-<u>C</u>), 45.5 (C-<u>C</u>H$_a$H$_b$-C$_{Alk}$), 40.0 (C-<u>C</u>H$_a$H$_b$-C$_{Ar}$), 28.5 (C-

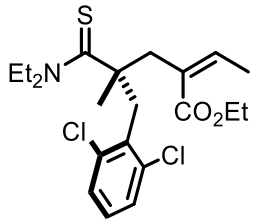
$\underline{C}H_3$), 26.1 (brs, N-CH_2-$\underline{C}H_2$, 2C), 24.5 (N-CH_2-CH_2-$\underline{C}H_2$), 16.2 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{22}H_{30}O_2N^{35}Cl_2{}^{32}S]^+$ requires m/z 442.1369, found m/z 442.1368.

IR (film) ν_{max}/cm^{-1}: 2981, 1706, 1581, 1435, 1382, 1247, 1149, 1087, 1014, 952, 758.

$[\alpha]_D^{25}$ = 36.69 (c = 2.10, $CHCl_3$).

Ethyl (Z)-4-(2,6-dichlorobenzyl)-5-(diethylamino)-2-ethylidene-4-methyl-5-thioxopentanoate (365)



Prepared according to the **general procedure I**, using 3-(2,6-dichlorophenyl)-*N,N*-diethyl-2,2-dimethylpropanethioamide **338** (63.7 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (2/23 Et_2O/pentane) and **365** was isolated as pale yellow oil (70.4 mg, 82%, 86/14 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 9.78 min, τ_{Rminor} = 14.29 min, 86/14 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 (d, *J* = 8.0 Hz, $2H_{Ar}$), 7.07 (dd, *J* = 8.5, 7.6 Hz, H_{Ar}), 5.97 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.36 – 4.07* (m, 4H, N-C<u>H</u>$_2$, O-C<u>H</u>$_2$-CH_3), 4.07 – 3.73* (m, 2H, N-C<u>H</u>'$_2$), 3.53 – 3.39 (m, 2H, C-C<u>H$_a$H$_b$</u>-C_{Ar}), 3.20 (d, *J* = 13.9 Hz, 1H, C-C<u>H$_a$</u>H$_b$-C_{Alk}), 2.83 (d, *J* = 13.9 Hz, 1H, C-CH$_a$<u>H$_b$</u>-C_{Alk}), 1.93 (d, *J* = 7.2 Hz, 3H, CH-C<u>H</u>$_3$), 1.50 – 1.39* (m, 3H, N-CH_2-C<u>H</u>$_3$), 1.36 – 1.25* (m, 6H, N-CH_2-C<u>H</u>'$_3$, O-CH_2-C<u>H</u>$_3$), 1.22 (s, 3H, C-C<u>H</u>$_3$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.1 (<u>C</u>=S), 168.6 (ester <u>C</u>=O), 140.2 (C=<u>C</u>H), 137.0 (<u>C</u>=CH), 136.2 (C_{Ar}), 129.5 ($2C_{Ar}$), 128.4 ($2C_{Ar}$), 128.2 (C_{Ar}), 60.4 (O-<u>C</u>H_2-CH_3), 51.2 (NC(S)-<u>C</u>), 50.0* (brs, N-<u>C</u>H_2), 48.7* (brs, N-<u>C</u>H'$_2$), 45.8 (C-<u>C</u>H$_a$H$_b$-C_{Alk}), 40.4 (C-<u>C</u>H$_a$H$_b$-

C_{Ar}), 28.5 (C-$\underline{C}H_3$), 16.1 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$), 13.7* (brs, N-CH_2-$\underline{C}H_3$), 11.3* (brs, N-CH_2-$\underline{C}H'_3$).

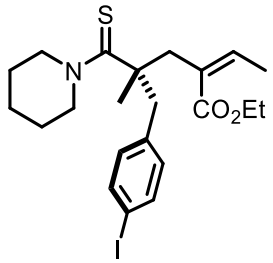
HRMS (ESI) $[C_{21}H_{30}O_2N^{35}Cl_2{}^{32}S]^+$ requires m/z 430.1369, found m/z 430.1368.

*Rotamers observed.

IR (film) ν_{max}/cm^{-1}: 2980, 1708, 1382, 1252, 1152, 1086, 954.

$[\alpha]_D^{25}$ = 39.40 (c = 1.29, $CHCl_3$).

Ethyl (Z)-2-ethylidene-4-(4-iodobenzyl)-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (366)



Prepared according to the **general procedure I**, 3-(4-iodophenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **329** (77.5 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **366** was isolated as pale yellow oil (69.0 mg, 69%, 88/12 er). Chiral HPLC (Chiralpak AD-H, 3/97 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 9.24 min, τ_{Rminor} = 10.06 min, 88/12 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.57 – 7.49 (m, $2H_{Ar}$), 6.91 – 6.82 (m, $2H_{Ar}$), 6.04 (q, *J* = 7.1 Hz, 1H, C=C<u>H</u>), 4.27 – 4.04 (m, 6H, N-C<u>H_2</u>, O-C<u>H_2</u>-CH_3), 3.43 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 2.91 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.80 (d, *J* = 14.0 Hz, 1H, C-CH_a<u>H_b</u>-C_{Alk}), 2.61 (d, *J* = 14.0 Hz, 1H, C-CH_a<u>H_b</u>-C_{Ar}), 1.95 (d, *J* = 7.2 Hz, 3H, CH-C<u>H_3</u>), 1.81 – 1.64 (m, 6H, N-CH_2-C<u>H_2</u>-C<u>H_2</u>), 1.34 (s, 3H, C-C<u>H_3</u>), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H_3</u>).

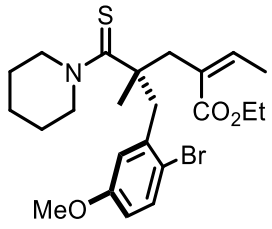
^{13}C NMR (101 MHz, Chloroform-*d*) δ 208.7 (<u>C</u>=S), 168.7 (ester <u>C</u>=O), 139.8 (C=<u>C</u>H), 137.6 (C_{Ar}), 137.0 ($2C_{Ar}$), 132.2 ($2C_{Ar}$), 129.4 (<u>C</u>=CH), 91.8 (C_{Ar}), 60.5 (O-<u>C</u>H_2-CH_3), 54.5 (brs, N-<u>C</u>H_2, 2C), 52.2 (NC(S)-<u>C</u>), 45.0 (C-<u>C</u>$H_a$$H_b$-$C_{Ar}$), 44.4 (C-<u>C</u>$H_a$$H_b$-$C_{Alk}$), 29.1 (C-<u>C</u>$H_3$), 26.0 (N-$CH_2$-<u>C</u>$H_2$, 2C), 24.2 (N-$CH_2$-$CH_2$-<u>C</u>$H_2$), 16.0 (CH-<u>C</u>$H_3$), 14.3 (O-$CH_2$-<u>C</u>$H_3$).

HRMS (ESI) $[C_{22}H_{31}O_2NI^{32}S]^+$ requires m/z 500.1115, found m/z 500.1111.

IR (film) ν_{max}/cm^{-1}: 2981, 1709, 1382, 1243, 1150, 1007, 953.

$[\alpha]_D^{25}$ = 0.62 (c = 1.19, $CHCl_3$).

Ethyl (Z)-4-(2-bromo-5-methoxybenzyl)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (367)



Prepared according to the **general procedure I**, 3-(2-bromo-5-methoxyphenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **328** (74.1 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **367** was isolated as pale yellow oil (77.4 mg, 80%, 89/11 er). Chiral HPLC (Chiralpak IA, 1/99 IPA/hexane, 1.0 mL/min, $\lambda = 230$ nm) $\tau_{Rmajor} = 10.88$ min, $\tau_{Rminor} = 11.84$ min, 89/11 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 (d, *J* = 8.8 Hz, H_{Ar}), 6.94 (d, *J* = 3.0 Hz, H_{Ar}), 6.61 (dd, *J* = 8.8, 3.0 Hz, H_{Ar}), 6.05 (q, *J* = 7.2 Hz, 1H, C=C$\underline{H}$), 4.42 – 4.02 (m, 6H, N-C$\underline{H_2}$, O-C$\underline{H_2}$-CH_3), 3.72 (s, 3H, O-C$\underline{H_3}$), 3.44 (d, *J* = 15.6 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 3.10 (d, *J* = 15.7 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Ar}), 2.94 (d, *J* = 13.9 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.83 (d, *J* = 13.9 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Alk}), 1.97 (d, *J* = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.75 – 1.59 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.47 (s, 3H, C-C$\underline{H_3}$), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.0 (C=S), 168.8 (ester C=O), 158.7 (C_{Ar}), 140.4 (C=CH), 138.7 (C_{Ar}), 133.2 (C_{Ar}), 129.3 (C=CH), 116.4 (C_{Ar}), 116.0 (C_{Ar}), 114.8 (C_{Ar}), 60.6 (O-CH_2-CH_3), 55.8 (O-CH_3), 54.6 (brs, N-CH_2, 2C), 52.4 (NC(S)-C), 44.7 (C-CH_aH_b-C_{Alk}),

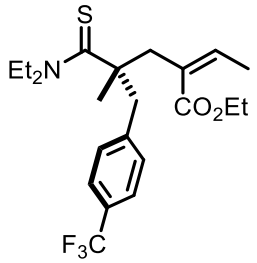
44.5 (C-$\underline{C}H_aH_b$-C_{Ar}), 29.5 (C-$\underline{C}H_3$), 26.2 (N-CH_2-$\underline{C}H_2$, 2C), 24.4 (N-CH_2-CH_2-$\underline{C}H_2$), 16.2 (CH-$\underline{C}H_3$) 14.4 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{23}H_{33}O_3N^{79}Br^{32}S]^+$ requires m/z 482.1359, found m/z 482.1357.

IR (film) ν_{max}/cm^{-1}: 2981, 2972, 2918, 1383, 1152.

$[\alpha]_D^{25}$ = 35.56 (c = 1.53, $CHCl_3$).

Ethyl (Z)-5-(diethylamino)-2-ethylidene-4-methyl-5-thioxo-4-(4-(trifluoromethyl)benzyl)pentanoate (368)



Prepared according to the **general procedure I**, using 2,2-dimethyl-3-phenyl-1-(piperidin-1-yl)propane-1-thione **339** (63.5 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid L4 (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **368** was isolated as pale yellow oil (65.5 mg, 76%, 85/15 er). Chiral HPLC (Chiralpak IB, 2/98 IPA/hexane, 1.0 mL/min, λ = 240 nm) τ_{Rmajor} = 6.42 min, τ_{Rminor} = 7.16 min, 85/15 er).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.46 (d, *J* = 8.0 Hz, $2H_{Ar}$), 7.28 (d, *J* = 8.0 Hz, $2H_{Ar}$), 6.10 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.21 (q, *J* = 7.1 Hz, 2H, O-C<u>H_2</u>-CH_3), 4.17 – 3.73 (m, 4H, N-C<u>H_2</u>), 3.70 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 3.04 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.83 (d, *J* = 14.0 Hz, 1H, C-CH_a<u>H_b</u>-C_{Alk}), 2.71 (d, *J* = 14.0 Hz, 1H, C-CH_a<u>H_b</u>-C_{Ar}), 1.95 (d, *J* = 7.2 Hz, 3H, CH-C<u>H_3</u>), 1.37 (s, 3H, C-C<u>H_3</u>), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H_3</u>), 1.23 (t, *J* = 7.0 Hz, 6H, N-CH_2-C<u>H_3</u>).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -62.41 (3F).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 207.6 (<u>C</u>=S), 168.8 (ester <u>C</u>=O), 142.3 (C=<u>C</u>H), 139.8 (<u>C</u>=CH), 130.5 ($2C_{Ar}$), 129.4 (C_{Ar}), 128.7 (q, *J* = 32.3 Hz, C_{Ar}), 124.8 (q, *J* = 3.8 Hz,

$2C_{Ar}$), 124.3 (q, *J* = 271.8 Hz, $\underline{C}F_3$), 60.5 (O-$\underline{C}H_2$-CH_3), 52.8 (NC(S)-$\underline{C}$), 50.5* (brs, N-$\underline{C}H_2$), 47.2* (brs, C-$\underline{C}H_aH_b$-C_{Ar}, N-$\underline{C}H'_2$, 2C), 45.9 (C-$\underline{C}H_aH_b$-C_{Alk}), 28.0 (C-$\underline{C}H_3$), 16.0 (CH-$\underline{C}H_3$), 14.3 (O-CH_2-$\underline{C}H_3$), 13.8* (brs, N-CH_2-$\underline{C}H_3$), 10.6* (brs, N-CH_2-$\underline{C}H'_3$).

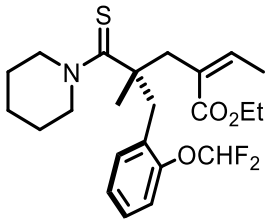
*Rotamers observed.

HRMS (ESI) $[C_{22}H_{31}O_2NF_3{}^{32}S]^+$ requires m/z 430.2022, found m/z 430.2020.

IR (film) ν_{max}/cm^{-1}: 2980, 1710, 1412, 1383, 1325, 1255, 1162, 1120, 1068, 1019.

$[\alpha]_D^{25}$ = -8.60 (c = 0.65, $CHCl_3$).

Ethyl (Z)-4-(2-(difluoromethoxy)benzyl)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (369)



Prepared according to the **general procedure I**, using 3-(2-(difluoromethoxy)phenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **327** (65.5 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **369** was isolated as pale yellow oil (64.0 mg, 73%, 87/13 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, $\lambda = 240$ nm) $\tau_{Rmajor} = 11.90$ min, $\tau_{Rminor} = 19.23$ min, 87/13 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.18 (m, $2H_{Ar}$), 7.15 – 7.06 (m, H_{Ar}), 7.02 (d, $J = 8.1$ Hz, H_{Ar}), 6.49 (t, $J = 74.2$ Hz, $C\underline{H}F_2$), 5.91 (q, $J = 7.1$ Hz, 1H, C=C$\underline{H}$), 4.42 – 4.06 (m, 6H, N-C$\underline{H}_2$, O-C$\underline{H}_2$-CH_3), 3.17 (d, $J = 14.4$ Hz, 1H, C-C$\underline{H}_a$$H_b$-$C_{Ar}$), 3.13 – 3.01 (m, 2H, C-C$\underline{H}_a$$H_b$-$C_{Alk}$, C-$CH_a\underline{H}_b$-$C_{Ar}$), 2.54 (d, $J = 14.1$ Hz, 1H, C-$CH_a\underline{H}_b$-C_{Alk}), 1.90 (d, $J = 7.1$ Hz, 3H, CH-C$\underline{H}_3$), 1.81 – 1.63 (m, 6H, N-CH_2-C$\underline{H}_2$-C$\underline{H}_2$), 1.40 (s, 3H, C-C$\underline{H}_3$), 1.27 (t, $J = 7.2$ Hz, 3H, O-CH_2-C$\underline{H}_3$).

^{19}F NMR (377 MHz, $CDCl_3$) δ -78.8 – -80.2 (m, 2F).

^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6 (C=S), 168.8 (ester C=O), 150.5 (t, $J = 2.3$ Hz, C_{Ar}), 139.2 (C=CH), 132.8 (C_{Ar}), 129.7 (C_{Ar}), 129.2 (C=CH), 128.1 (C_{Ar}), 125.0 (C_{Ar}), 117.6

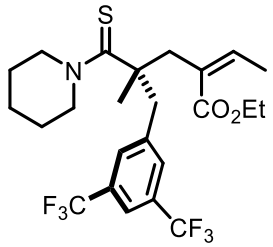
(C_{Ar}), 116.6 (t, J = 257.7 Hz, $\underline{C}HF_2$), 60.5 (O-$\underline{C}H_2$-CH_3), 54.5 (brs, N-$\underline{C}H_2$, 2C), 52.1 (NC(S)-$\underline{C}$), 42.8 (C-$\underline{C}H_aH_b$-C_{Alk}), 38.2 (C-$\underline{C}H_aH_b$-C_{Ar}), 29.6 (C-$\underline{C}H_3$), 26.1 (N-CH_2-$\underline{C}H_2$, 2C), 24.4 (N-CH_2-CH_2-$\underline{C}H_2$), 16.0 (CH-$\underline{C}H_3$), 14.3 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{23}H_{32}O_3NF_2{}^{32}S]^+$ requires m/z 440.2065, found m/z 440.2060.

IR (film) ν_{max}/cm^{-1}: 2981, 1708, 1382, 1250, 1144, 954, 757.

$[\alpha]_D^{25}$ = 14.00 (c = 0.56, $CHCl_3$).

Ethyl (Z)-4-(3,5-bis(trifluoromethyl)benzyl)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (370)



Prepared according to the **general procedure I**, using 3-(3,5-bis(trifluoromethyl)phenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **326** (39.8 mg, 0.10 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (15.6 mg, 0.02 mmol), chiral carboxylic acid **L4** (11.2 mg, 0.04 mmol), 18-crown-6 (5.3mg, 0.02 mmol), ethyl but-2-ynoate (56.2 mg, 0.50 mmol) and MS13X (20 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **370** was isolated as pale yellow oil (34.9 mg, 68%, 88/12 er). Chiral HPLC (Chiralpak IB, 1/99 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 6.34 min, τ_{Rminor} = 6.99 min, 88/12 er).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.69 (s, 1H, H_{Ar}), 7.57 (s, $2H_{Ar}$), 6.13 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.26 – 4.12 (m, 6H, N-C<u>H$_2$</u>, O-C<u>H$_2$</u>-CH$_3$), 3.75 (d, *J* = 14.0 Hz, 1H, C-C<u>H$_a$</u>H$_b$-C_{Ar}), 2.94 (d, *J* = 14.0 Hz, 1H, C-C<u>H$_a$</u>H$_b$-C_{Alk}), 2.85 (d, *J* = 14.0 Hz, 1H, C-CH$_a$<u>H$_b$</u>-C_{Alk}), 2.71 (d, *J* = 14.0 Hz, 1H, C-CH$_a$<u>H$_b$</u>-C_{Ar}), 2.00 (d, *J* = 7.2 Hz, 3H, CH-C<u>H$_3$</u>), 1.82 – 1.67 (m, 6H, N-CH$_2$-C<u>H$_2$</u>-C<u>H$_2$</u>), 1.42 (s, 3H, C-C<u>H$_3$</u>), 1.33 (t, *J* = 7.1 Hz, 3H, O-CH$_2$-C<u>H$_3$</u>).

^{19}F NMR (377 MHz, Chloroform-*d*) δ -62.8 (d, *J* = 5.5 Hz, 6F).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 208.1 (<u>C</u>=S), 168.8 (ester <u>C</u>=O), 141.1 (C=<u>C</u>H), 140.6 (<u>C</u>=CH), 131.1 (q, *J* = 33.0 Hz, $2C_{Ar}$), 130.6 – 130.4 (m, $2C_{Ar}$), 129.0 (C_{Ar}), 123.5 (q, *J* = 272.6 Hz, CF_3, 2C), 120.8 – 120.4 (m, C_{Ar}), 60.8 (O-<u>C</u>H$_2$-CH$_3$), 54.6 (brs, N-<u>C</u>H$_2$, 2C),

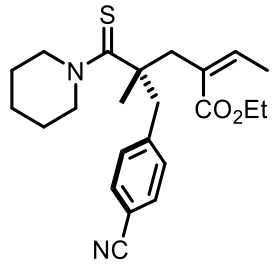
52.6 (NC(S)-C), 45.5 (C-CH_aH_b-C_{Ar}), 44.5 (C-CH_aH_b-C_{Alk}), 28.7 (C-CH_3), 26.2 (N-CH_2-CH_2, 2C), 24.3 (N-CH_2-CH_2-CH_2), 16.3 (CH-CH_3), 14.4 (O-CH_2-CH_3).

HRMS (ESI) $[C_{24}H_{30}O_2NF_6{}^{32}S]^+$ requires m/z 510.1896, found m/z 510.1895.

IR (film) ν_{max}/cm^{-1}: 2981, 1711, 1376, 1277, 1169, 1131, 1024, 953.

$[\alpha]_D^{25}$ = -35.37 (c = 0.19, $CHCl_3$).

Ethyl (Z)-4-(4-cyanobenzyl)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (371)



Prepared according to the **general procedure I**, using 4-(2,2-dimethyl-3-(piperidin-1-yl)-3-thioxopropyl)benzonitrile **331** (28.6 mg, 0.10 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (15.8 mg, 0.02 mmol), chiral carboxylic acid **L4** (11.2 mg, 0.04 mmol), 18-crown-6 (5.3 mg, 0.02 mmol), ethyl but-2-ynoate (56.0 mg, 0.50 mmol) and MS13X (20 mg). The crude reaction mixture was purified by flash column chromatography (1/4 Et_2O/pentane) and **371** was isolated as pale yellow oil as inseparable mixture with starting material (28.3 mg, 71%, 90/10 er). Chiral HPLC (Chiralpak AS-H, 4/96 IPA/hexane, 1.0 mL/min, $\lambda = 230$ nm) τ_{Rmajor} = 32.47 min, τ_{Rminor} = 41.22 min, 90/10 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 – 7.47 (m, $2H_{Ar}$), 7.25 – 7.19 (m, $2H_{Ar}$), 6.13 – 6.03 (m, 1H, C=C$\underline{H}$), 4.27 – 4.04 (m, 6H, N-C$\underline{H_2}$, O-C$\underline{H_2}$-CH_3), 3.62 (d, J = 14.0 Hz, C-C$\underline{H_a}H_b$-C_{Ar}), 2.92 – 2.81 (m, 2H, C-C$\underline{H_a H_b}$-C_{Alk}), 2.70 (d, J = 14.1 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Ar}), 1.97 (d, J = 7.3 Hz, 3H, CH-C$\underline{H_3}$), 1.81 – 1.66 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.34 (s, 3H, C-C$\underline{H_3}$), 1.31 (t, J = 7.2 Hz, 3H, O-CH_2-C$\underline{H_3}$).

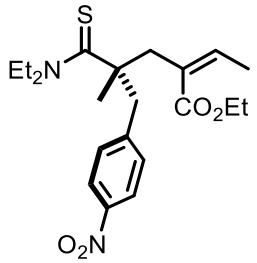
^{13}C NMR (101 MHz, $CDCl_3$) δ 208.4 (C=S), 168.8 (ester C=O), 144.0 (C_{Ar}), 140.5 (C=CH), 131.8 ($2C_{Ar}$), 131.1 ($2C_{Ar}$), 129.2 (C=CH), 119.1 (C_{Ar}), 110.4 (C≡N), 60.7 (O-CH_2-CH_3), 54.6 (N-CH_2, 2C), 52.4 (NC(S)-C), 45.9 (C-CH_aH_b-C_{Ar}), 44.7 (C-CH_aH_b-C_{Alk}), 29.0 (C-CH_3), 26.2 (N-CH_2-CH_2, 2C), 24.3 (N-CH_2-CH_2-CH_2), 16.2 (CH-CH_3), 14.4 (O-CH_2-CH_3).

HRMS (ESI) $[C_{23}H_{31}O_2N_2{}^{32}S]^+$ requires m/z 399.2101, found m/z 399.2099.

IR (film) ν_{max}/cm^{-1}: 2981, 1710, 1382, 1249, 1152, 1038, 954.

$[\alpha]_D^{25}$ = -25.42 (c = 0.31, $CHCl_3$).

Ethyl (Z)-5-(diethylamino)-2-ethylidene-4-methyl-4-(4-nitrobenzyl)-5-thioxopentanoate (372)



Prepared according to the **general procedure I**, using *N,N*-diethyl-2,2-dimethyl-3-(4-nitrophenyl)propanethioamide **340** (22.4 mg, 0.09 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (12.0 mg, 0.02 mmol), chiral carboxylic acid **L4** (9.5 mg, 0.03 mmol), 18-crown-6 (4.0 mg, 0.02 mmol), ethyl but-2-ynoate (42.7 mg, 0.38 mmol) and MS13X (20 mg). The crude reaction mixture was purified by flash column chromatography (3/17 Et_2O/pentane) and **372** was isolated as pale yellow oil (21.9 mg, 71%, 91/9 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 20.05 min, τ_{Rminor} = 18.31 min, 91/9 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.10 – 8.03 (m, $2H_{Ar}$), 7.39 – 7.32 (m, $2H_{Ar}$), 6.12 (q, *J* = 7.1, 6.7 Hz, 1H, C=C$\underline{H}$), 4.23 (q, *J* = 7.2 Hz, 2H, O-C$\underline{H_2}$-CH_3), 4.18 – 3.61 (m, 5H, C-C$\underline{H_a}H_b$-C_{Ar}, N-C$\underline{H_2}$), 3.02 (d, *J* = 14.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.86 (d, *J* = 14.0 Hz, 1H, $CH_a\underline{H_b}$-C_{Alk}), 2.74 (d, *J* = 14.0 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Ar}), 1.96 (dd, *J* = 7.2, 0.9 Hz, 3H, CH-C$\underline{H_3}$), 1.37 (s, 3H, C-C$\underline{H_3}$), 1.32 (t, *J* = 7.2 Hz, 3H, O-CH_2-C$\underline{H_3}$), 1.24 (t, *J* = 7.0 Hz, 6H, N-CH_2-C$\underline{H_3}$).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 207.3 (C=S), 168.8 (ester C=O), 146.8 (C_{Ar}), 146.4 (C_{Ar}), 140.4 (C=CH), 131.2 ($2C_{Ar}$), 129.3 (C=CH), 123.2 ($2C_{Ar}$), 60.7 (O-CH_2-CH_3), 53.1 (NC(S)-C), 50.7* (brs. N-CH_2), 47.4* (brs, C-CH_aH_b-C_{Ar}, N-CH'_2, 2C), 46.1 (C-CH_aH_b-

C_{Alk}), 27.9 (C-$\underline{C}H_3$), 16.1 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$C\underline{H_3}$), 14.0* (brs, N-CH_2-$\underline{C}H_3$), 10.8* (brs, N-CH_2-$\underline{C}H'_3$).

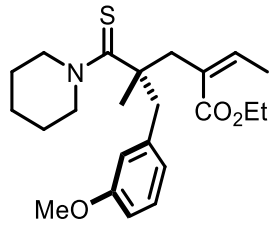
*Rotamers observed.

HRMS (ESI) $[C_{21}H_{31}O_4N_2{}^{32}S]^+$ requires m/z 407.1999, found m/z 407.1993.

IR (film) ν_{max}/cm^{-1}: 1710, 1519, 1345, 1257, 1145, 1026, 859.

$[\alpha]_D^{25}$ = -18.10 (c = 0.39, $CHCl_3$).

Ethyl (Z)-2-ethylidene-4-(3-methoxybenzyl)-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (373)



Prepared according to the **general procedure I**, using 3-(3-methoxyphenyl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **330** (58.3 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (3/22 Et_2O/pentane) and **373** was isolated as pale yellow oil (55.8 mg, 69%, 89/11 er). Chiral HPLC (Chiralpak AS-H, 3/97 IPA/hexane, 1.0 mL/min, λ = 220 nm) τ_{Rmajor} = 13.16 min, τ_{Rminor} = 11.47 min, 89/11 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 – 7.09 (m, 1H, H_{Ar}), 6.76 – 6.66 (m, 3H_{Ar}), 6.02 (q, *J* = 6.7, 6.2 Hz, 1H, C=C$\underline{H}$), 4.29 – 4.05 (m, 6H, N-C$\underline{H_2}$, O-C$\underline{H_2}$-CH_3), 3.76 (s, 3H, O-C$\underline{H_3}$), 3.43 (d, *J* = 14.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 2.94 (d, *J* = 14.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.80 (d, *J* = 14.0 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Alk}), 2.68 (d, *J* = 14.0 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Ar}), 1.95 (d, *J* = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.79 – 1.65 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.38 (s, 3H, C-C$\underline{H_3}$), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.3 (C=S), 168.9 (ester C=O), 159.4 (C_{Ar}), 139.6 (C=CH), 139.5 (C=CH), 129.7 (C_{Ar}), 129.0 (C_{Ar}), 122.8 (C_{Ar}), 116.0 (C_{Ar}), 112.1 (C_{Ar}), 60.6 (O-CH_2-CH_3), 55.3 (O-CH_3), 54.6 (brs, N-CH_2, 2C), 52.5 (NC(S)-C), 45.7 (C-CH_aH_b-C_{Ar}),

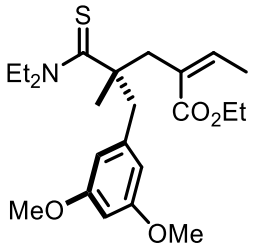
44.6 (C-$\underline{C}H_aH_b$-C_{Alk}), 29.5 (C-$\underline{C}H_3$), 26.2 (N-CH_2-$\underline{C}H_2$, 2C), 24.4 (N-CH_2-CH_2-$\underline{C}H_2$), 16.1 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{23}H_{34}O_3N^{32}S]^+$ requires m/z 404.2254, found m/z 404.2250.

IR (film) ν_{max}/cm^{-1}: 2936, 1709, 1601, 1418, 1382, 1245, 1153, 1011.

$[\alpha]_D^{25}$ = 13.76 (c = 1.12, $CHCl_3$).

Ethyl (Z)-5-(diethylamino)-4-(3,5-dimethoxybenzyl)-2-ethylidene-4-methyl-5-thioxopentanoate (374)



Prepared according to the **general procedure I**, using 3-(3,5-dimethoxyphenyl)-*N,N*-diethyl-2,2-dimethylpropanethioamide **341** (61.9 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (3/17 Et_2O/pentane) and **374** was isolated as pale yellow oil (61.9 mg, 74%, 85/15 er). Chiral HPLC (Chiralpak AD-H, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 20.17min, τ_{Rminor} = 18.31 min, 85/15 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.34 (d, *J* = 2.3 Hz, $2H_{Ar}$), 6.29 (t, *J* = 2.3 Hz, H_{Ar}), 6.07 (q, *J* = 7.1 Hz, 1H, C=C<u>H</u>), 4.21 (q, *J* = 7.1 Hz, 2H, O-C<u>H_2</u>-CH_3), 4.16 – 3.75 (m, 4H, N-C<u>H_2</u>), 3.73 (s, 6H, O-C<u>H_3</u>), 3.53 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 3.05 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.81 (d, *J* = 14.0 Hz, 1H, CH_a<u>H_b</u>-C_{Alk}), 2.61 (d, *J* = 14.0 Hz, 1H, C-CH_a<u>H_b</u>-C_{Ar}), 1.93 (d, *J* = 7.3 Hz, 3H, CH-C<u>H_3</u>), 1.41 (s, 3H, C-C<u>H_3</u>), 1.31 (t, *J* = 7.1 Hz, 3H, H6 O-CH_2-C<u>H_3</u>), 1.23 (t, *J* = 7.0 Hz, 6H, N-CH_2-C<u>H_3</u>).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 208.5 (<u>C</u>=S), 169.0 (ester <u>C</u>=O), 160.4 ($2C_{Ar}$), 140.4 (<u>C</u>=CH), 139.4 (C=<u>C</u>H), 129.8 (C_{Ar}), 108.4 ($2C_{Ar}$), 98.7 (C_{Ar}), 60.5 (O-<u>C</u>H_2-CH_3), 55.4 (O-<u>C</u>H_3, 2C), 53.0 (NC(S)-<u>C</u>), 50.7* (brs, N-<u>C</u>H_2), 47.6* (brs, C-<u>C</u>$H_a$$H_b$-$C_{Ar}$, N-<u>C</u>H'$_2$, 2C), 46.3

(C-$\underline{C}H_aH_b$-C_{Alk}), 28.5 (C-$\underline{C}H_3$), 16.0 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$C\underline{H_3}$), 13.9* (brs, N-CH_2-$\underline{C}H_3$), 10.8* (brs, N-CH_2-$\underline{C}H'_3$).

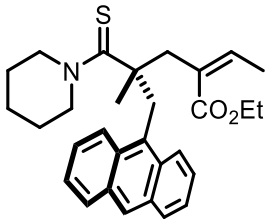
*Rotamers observed.

HRMS (ESI) $[C_{23}H_{36}O_4N^{32}S]^+$ requires m/z 422.2360, found m/z 422.2350.

IR (film) ν_{max}/cm^{-1}: 2980, 1709, 1595, 1462, 1382, 1254, 1203, 1150, 1066, 954.

$[\alpha]_D^{25}$ = 11.28 (c = 1.03, $CHCl_3$).

Ethyl (Z)-4-(anthracen-9-ylmethyl)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (375)



Prepared according to the **general procedure I**, using 3-(anthracen-9-yl)-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **332** (62.3 mg, 0.17 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (27.2 mg, 0.03 mmol), chiral carboxylic acid **L4** (19.3 mg, 0.07 mmol), 18-crown-6 (9.1 mg, 0.03 mmol), ethyl but-2-ynoate (96.6 mg, 0.86 mmol) and MS13X (35 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **375** was isolated as light yellow solid (55.2 mg, 68%, 89/11 er). Chiral HPLC (Chiralpak IB, 4/96 IPA/hexane, 1.0 mL/min, λ = 240 nm) τ_{Rmajor} = 19.10 min, τ_{Rminor} = 21.79 min, 89/11 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 – 8.69 (m, H_{Ar}), 8.68 – 8.60 (m, H_{Ar}), 8.07 – 8.02 (m, H_{Ar}), 7.82 – 7.74 (m, $2H_{Ar}$), 7.68 – 7.51 (m, $4H_{Ar}$), 6.07 (q, *J* = 7.2 Hz, 1H, C=C$\underline{H}$), 4.46 – 4.15 (m, 4H, N-C$\underline{H_2}$, O-C$\underline{H_2}$-CH_3), 4.12 – 4.01 (m, 2H, N-C$\underline{H'_2}$), 3.88 (d, *J* = 16.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 3.45 (d, *J* = 16.0 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Ar}), 3.11 (d, *J* = 13.9 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.99 (d, *J* = 13.9 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Alk}), 1.98 (d, *J* = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.65 – 1.49 (m, 9H, C-C$\underline{H_3}$, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.32 (t, *J* = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.7 (C=S), 169.1 (ester C=O), 140.0 (C=CH), 132.3 (C_{Ar}), 132.2 (C_{Ar}), 131.6 (C_{Ar}), 130.7 (C_{Ar}), 129.7 (C=CH), 129.6 (C_{Ar}), 128.5 (C_{Ar}), 127.9 (C_{Ar}), 126.8 (C_{Ar}), 126.6 (C_{Ar}), 126.4 (C_{Ar}), 126.2 (C_{Ar}), 124.5 (C_{Ar}), 123.3 (C_{Ar}), 122.4 (C_{Ar}), 60.7 (O-CH_2-CH_3), 54.6 (brs, N-CH_2, 2C), 52.4 (NC(S)-C), 45.7 (C-CH_aH_b-C_{Alk}), 41.4 (C-

$\underline{C}H_aH_b$-C_{Ar}), 29.7 (C-$\underline{C}H_3$), 26.0 (N-CH_2-$\underline{C}H_2$, 2C), 24.3 (N-CH_2-CH_2-$\underline{C}H_2$), 16.2 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

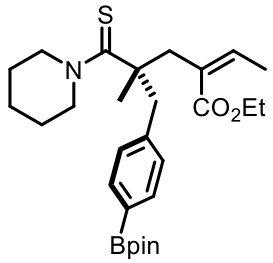
HRMS (ESI) $[C_{30}H_{36}O_2N^{32}S]^+$ requires m/z 474.2461, found m/z 474.2458.

MP 27 - 30 °C

IR (film) ν_{max}/cm^{-1}: 2981, 1710, 1382, 1251, 1152, 1073, 954.

$[\alpha]_D^{25}$ = 45.86 (c = 0.28, $CHCl_3$).

Ethyl (Z)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)-5-thioxopentanoate (376)



Prepared according to the **general procedure I**, using 2,2-dimethyl-1-(piperidin-1-yl)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propane-1-thione **333** (77.5 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **376** was isolated as pale yellow oil (43.0 mg, 43%, 88/12 er). Chiral HPLC (Chiralcel OD-H, 2/98 IPA/hexane, 1.0 mL/min, $\lambda = 230$ nm) $\tau_{Rmajor} = 9.18$ min, $\tau_{Rminor} = 7.93$ min, 88/12 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.62 (m, $2H_{Ar}$), 7.16 – 7.07 (m, $2H_{Ar}$), 6.01 (q, $J = 7.1$ Hz, 1H, C=C$\underline{H}$), 4.26 – 4.05 (m, 6H, N-C$\underline{H_2}$, O-C$\underline{H_2}$-CH_3), 3.44 (d, $J = 13.9$ Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 2.94 (d, $J = 14.0$ Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.79 (d, $J = 14.1$ Hz, 1H, C-$CH_a\underline{H_b}$-C_{Alk}), 2.72 (d, $J = 13.8$ Hz, 1H, C-$CH_a\underline{H_b}$-C_{Ar}), 1.94 (d, $J = 7.2$ Hz, 3H, CH-C$\underline{H_3}$), 1.79 – 1.64 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.37 (s, 3H, C-C$\underline{H_3}$), 1.32 (s, 12H, O-C-(C$\underline{H_3}$)$_2$), 1.32 – 1.28 (m, 3H, O-CH_2-C$\underline{H_3}$).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.0 (C=S), 168.9 (ester C=O), 141.3 (C_{Ar}), 139.7 (C=CH), 134.6 ($2C_{Ar}$), 129.8 ($2C_{Ar}$), 129.6 (C=CH), 83.8 (O-C-$(CH_3)_2$, 2C), 60.6 (O-CH_2-CH_3), 54.6 (N-CH_2, 2C), 52.4 (NC(S)-C), 45.6 (C-CH_aH_b-C_{Ar}), 44.4 (C-CH_aH_b-C_{Alk}), 29.6 (C-CH_3),

26.1 (N-CH_2-$\underline{C}H_2$, 2C), 25.0 (O-C-($\underline{C}H_3$)$_2$, 4C), 24.4 (N-CH_2-CH_2-$\underline{C}H_2$), 16.1 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

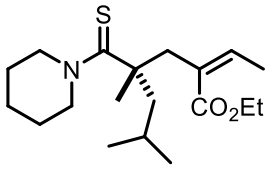
*B-C_{Ar} not visible on NMR

HRMS (ESI) $[C_{26}H_{44}O_4N^{11}B^{32}\ SNa]^+$ requires m/z 500.2979, found m/z 500.2998.

IR (film) ν_{max}/cm^{-1}: 2981, 1706, 1381, 1251, 1146, 1089, 955.

$[\alpha]_D^{25}$ = -2.64 (c = 0.22, $CHCl_3$).

Ethyl (Z)-2-ethylidene-4,6-dimethyl-4-(piperidine-1-carbonothioyl)heptanoate (377)



Prepared according to the **general procedure I**, using 2,2,4-trimethyl-1-(piperidin-1-yl)pentane-1-thione **335** (45.5 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/49 Et_2O/pentane) and **377** was isolated as pale yellow oil (31.9 mg, 47%, 86/14 er). Chiral HPLC (Chiralpak IA, 1/99 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 7.06 min, τ_{Rminor} = 7.95 min, 86/14 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.44 – 3.86 (m, 6H, N-C<u>H$_2$</u>, O-C<u>H$_2$</u>-CH$_3$), 2.83 (d, *J* = 13.9 Hz, 1H, C-C<u>H$_a$</u>H$_b$-C$_{Alk}$), 2.55 (d, *J* = 13.9 Hz, 1H, C-CH$_a$<u>H$_b$</u>-C$_{Alk}$), 1.93 (d, *J* = 7.1 Hz, 3H, CH-C<u>H$_3$</u>), 1.91 – 1.86 (m, 1H, C-C<u>H$_a$</u>H$_b$-C$_{Me}$), 1.78 – 1.67 (m, 7H, N-CH$_2$-C<u>H$_2$</u>-C<u>H$_2$</u>, <u>H</u>C(CH$_3$)$_2$), 1.48 (s, 3H, C-C<u>H$_3$</u>), 1.30 (t, *J* = 7.1 Hz, 3H, O-CH$_2$-C<u>H$_3$</u>), 1.26 – 1.21 (m, 1H, C-CH$_a$<u>H$_b$</u>-C$_{Me}$), 0.88 (d, *J* = 6.6 Hz, 3H, HC(C<u>H$_3$</u>)$_2$), 0.82 (d, *J* = 6.7 Hz, 3H, HC(C<u>H'$_3$</u>)$_2$).

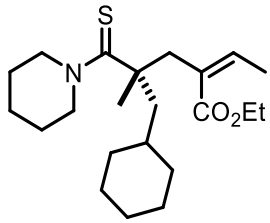
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.4 (<u>C</u>=S), 168.9 (ester <u>C</u>=O), 139.6 (C=<u>C</u>H), 129.8 (<u>C</u>=CH), 60.4 (O-<u>C</u>H$_2$-CH$_3$), 54.2 (brs, N-<u>C</u>H$_2$, 2C), 51.7 (NC(S)-<u>C</u>), 47.6 (C-<u>C</u>H$_a$H$_b$-C$_{Me}$), 44.7 (C-<u>C</u>H$_a$H$_b$-C$_{Alk}$), 31.0 (C-<u>C</u>H$_3$), 26.0 (N-CH$_2$-<u>C</u>H$_2$, 2C), 25.3 (H<u>C</u>(CH$_3$)$_2$), 25.2 (HC(<u>C</u>H$_3$)$_2$), 24.4 (N-CH$_2$-CH$_2$-<u>C</u>H$_2$), 24.1 (HC(<u>C</u>H'$_3$)$_2$), 16.0 (CH-<u>C</u>H$_3$), 14.4 (O-CH$_2$-<u>C</u>H$_3$).

HRMS (ESI) $[C_{19}H_{34}O_2N^{32}S]^+$ requires m/z 340.2305, found m/z 340.2305.

IR (film) ν_{max}/cm^{-1}: 2981, 1708, 1383, 1251, 1153, 1073, 954.

$[\alpha]_D^{25}$ = 21.21 (c = 0.38, $CHCl_3$).

Ethyl (Z)-4-(cyclohexylmethyl)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (378)



Prepared according to the **general procedure I** using 3-cyclohexyl-2,2-dimethyl-1-(piperidin-1-yl)propane-1-thione **334** (53.5 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/49 Et_2O/pentane) and **378** was isolated as pale yellow oil (41.4 mg, 55%, 88/12 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 220 nm) τ_{Rmajor} = 6.33 min, τ_{Rminor} = 7.13 min, 88/12 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.40 – 3.90 (m, 6H, N-C<u>H$_2$</u>, O-C<u>H$_2$</u>-CH$_3$), 2.81 (d, *J* = 13.9 Hz, 1H, C-C<u>H$_a$</u>H$_b$-C$_{Alk}$), 2.54 (d, *J* = 13.9 Hz, 1H, C-CH$_a$<u>H$_b$</u>-C$_{Alk}$), 1.92 (d, *J* = 7.2 Hz, 3H, CH-C<u>H$_3$</u>), 1.87 (dd, *J* = 14.4, 6.2 Hz, 1H, C-C<u>H$_a$</u>H$_b$-C$_{Cyh}$), 1.78 – 1.68 (m, 6H, N-CH$_2$-C<u>H$_2$</u>-C<u>H$_2$</u>), 1.66 – 1.51 (m, 4H, Cyclohexyl C<u>H$_2$</u>), 1.46 (s, 3H, C-C<u>H$_3$</u>), 1.40 – 1.33 (m, 1H, Cyclohexyl C<u>H</u>), 1.29 (t, *J* = 7.1 Hz, 3H, O-CH$_2$-C<u>H$_3$</u>), 1.26 – 0.98 (m, 3H, C-CH$_a$<u>H$_b$</u>-C$_{Cyh}$, Cyclohexyl C<u>H$_2$</u>), 0.94 – 0.71 (m, 4H, Cyclohexyl C<u>H$_2$</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ 209.6 (<u>C</u>=S), 168.9 (ester <u>C</u>=O), 139.5 (C=<u>C</u>H), 129.8 (<u>C</u>=CH), 60.4 (O-<u>C</u>H$_2$-CH$_3$), 54.2 (brs, N-<u>C</u>H$_2$, 2C), 51.5 (NC(S)-<u>C</u>), 46.4 (C-<u>C</u>H$_a$H$_b$-C$_{Cyh}$), 44.6 (C-<u>C</u>H$_a$H$_b$-C$_{Alk}$), 35.6 (Cyclohexyl <u>C</u>H$_2$), 34.7 (Cyclohexyl <u>C</u>H), 34.5 (Cyclohexyl <u>C</u>H$_2$), 31.1 (C-<u>C</u>H$_3$), 26.5 (Cyclohexyl <u>C</u>H$_2$), 26.5 (Cyclohexyl <u>C</u>H$_2$), 26.4 (Cyclohexyl

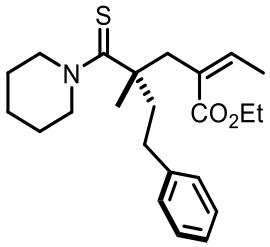
$\underline{C}H_2$), 26.0 (brs, N-CH_2-$\underline{C}H_2$, 2C), 24.4 (N-CH_2-CH_2-$\underline{C}H_2$), 16.0 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{22}H_{38}O_2N^{32}S]^+$ requires m/z 380.2618, found m/z 380.2618.

IR (film) ν_{max}/cm^{-1}: 2922, 2852, 1712, 1446, 1418, 1382, 1246, 1139, 1010, 856.

$[\alpha]_D^{25}$ = 17.47 (c = 1.05, $CHCl_3$).

Ethyl (Z)-2-ethylidene-4-methyl-6-phenyl-4-(piperidine-1-carbonothioyl)hexanoate (379)



Prepared according to the **general procedure I**, using 2,2-dimethyl-4-phenyl-1-(piperidin-1-yl)butane-1-thione **362** (55.1 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **379** was isolated as dark yellow oil (38.0 mg, 49%, 84/16 er). Chiral HPLC (Chiralcel IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 220 nm) τ_{Rmajor} = 9.32 min, τ_{Rminor} = 11.18 min, 84/16 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.21 (m, $2H_{Ar}$), 7.19 – 7.10 (m, $3H_{Ar}$), 6.01 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.39 – 4.05 (m, 6H, N-C<u>H$_2$</u>, O-C<u>H$_2$</u>-CH_3), 2.85 (d, *J* = 13.9 Hz, 1H, C-C<u>H$_a$</u>H_b-C_{Alk}), 2.74 – 2.60 (m, 2H, C-CH_aH_b-C<u>H$_a$</u>H_b-C_{Ar}, C-CH_a<u>H$_b$</u>-C_{Alk}), 2.51 (td, *J* = 13.2, 4.6 Hz, 1H, C-CH_aH_b-CH_a<u>H$_b$</u>-C_{Ar}), 2.33 (td, *J* = 13.1, 4.7 Hz, 1H, C-C<u>H$_a$</u>H_b-CH_aH_b-C_{Ar}), 1.94 (d, *J* = 7.2 Hz, 3H, CH-C<u>H$_3$</u>), 1.73 (s, 6H, N-CH_2-C<u>H$_2$</u>-C<u>H$_2$</u>), 1.69 – 1.60 (m, 1H, C-CH_a<u>H$_b$</u>-CH_aH_b-C_{Ar}), 1.54 (s, 3H, C-C<u>H$_3$</u>), 1.24 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H$_3$</u>).

^{13}C NMR (126 MHz, $CDCl_3$) δ 208.4 (<u>C</u>=S), 168.9 (ester <u>C</u>=O), 142.5 (C_{Ar}), 139.9 (C=<u>C</u>H), 129.6 (<u>C</u>=CH), 128.5 ($2C_{Ar}$), 128.3 ($2C_{Ar}$), 125.9 (C_{Ar}), 60.5 (O-<u>C</u>H$_2$-CH_3), 54.2 (brs, N-<u>C</u>H$_2$, 2C), 51.5 (NC(S)-<u>C</u>), 44.0 (C-<u>C</u>H$_a$$H_b$-$C_{Alk}$), 41.5 (C-<u>C</u>$H_aH_b$-$CH_aH_b$-$C_{Ar}$), 31.1 (C-

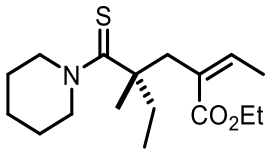
CH_aH_b-$\underline{C}H_aH_b$-C_{Ar}), 29.4 (C-$\underline{C}H_3$), 26.3 (N-CH_2-$\underline{C}H_2$, 2C), 24.4 (N-CH_2-CH_2-$\underline{C}H_2$), 16.1 (CH-$\underline{C}H_3$), 14.3 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{23}H_{34}O_2N^{32}S]^+$ requires m/z 388.2305, found m/z 388.2303.

IR (film) ν_{max}/cm^{-1}: 2981, 1711, 1631, 1436, 1383, 1251, 1152, 1086, 955.

$[\alpha]_D^{25}$ = -21.45 (c = 1.13, $CHCl_3$).

Ethyl (Z)-2-ethylidene-4-methyl-4-(piperidine-1-carbonothioyl)hexanoate (380)



Prepared according to the **general procedure I**, using 2,2-dimethyl-1-(piperidin-1-yl)butane-1-thione **336** (39.9 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **380** was isolated as pale yellow oil (28.6 mg, 46%, 79/21 er). Chiral HPLC (Chiralpak AS-H, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 9.22 min, τ_{Rminor} = 8.31 min, 79/21 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.00 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.38 – 4.02 (m, 6H, N-C<u>H</u>$_2$, O-C<u>H</u>$_2$-CH$_3$), 2.82 (d, *J* = 13.9 Hz, 1H, C-C<u>H</u>$_a$H$_b$-C$_{Alk}$), 2.64 (d, *J* = 13.9 Hz, 1H, C-CH$_a$<u>H</u>$_b$-C$_{Alk}$), 2.03 (dq, *J* = 14.7, 7.4 Hz, 1H, C-C<u>H</u>$_a$H$_b$-C$_{iPr}$), 1.94 (d, *J* = 7.2 Hz, 3H, CH-C<u>H</u>$_3$), 1.79 – 1.63 (m, 6H, N-CH$_2$-C<u>H</u>$_2$-C<u>H</u>$_2$), 1.42 (s, 3H, C-C<u>H</u>$_3$), 1.41 – 1.33 (m, 1H, C-CH$_a$<u>H</u>$_b$-C$_{iPr}$), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH$_2$-C<u>H</u>$_3$), 0.86 (t, *J* = 7.4 Hz, 3H, C-CH$_2$-C<u>H</u>$_3$).

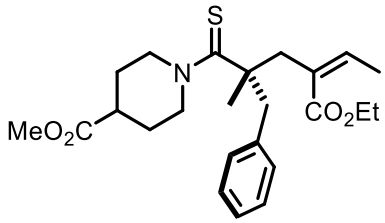
^{13}C NMR (101 MHz, Chloroform-*d*) δ 208.7 (<u>C</u>=S), 168.9 (ester <u>C</u>=O), 139.6 (C=<u>C</u>H), 129.9 (<u>C</u>=CH), 60.5 (O-<u>C</u>H$_2$-CH$_3$), 54.2 (brs, N-<u>C</u>H$_2$, 2C), 51.9 (NC(S)-<u>C</u>), 43.8 (C-<u>C</u>H$_a$H$_b$-C$_{Alk}$), 31.9 (C-<u>C</u>H$_a$H$_b$-C$_{iPr}$), 29.1 (C-<u>C</u>H$_3$), 26.3 (N-CH$_2$-<u>C</u>H$_2$, 2C), 24.5 (N-CH$_2$-CH$_2$-<u>C</u>H$_2$), 16.0 (CH-<u>C</u>H$_3$), 14.4 (O-CH$_2$-<u>C</u>H$_3$), 9.5 (C-CH$_2$-<u>C</u>H$_3$).

HRMS (ESI) $[C_{17}H_{30}O_2N^{32}S]^+$ requires m/z 312.1992, found m/z 312.1990.

IR (film) ν_{max}/cm^{-1}: 2936, 1711, 1420, 1383, 1231, 1155, 1010.

[α]$_D^{25}$ = -12.00 (c = 0.36, $CHCl_3$).

Methyl (Z)-1-(2-benzyl-4-(ethoxycarbonyl)-2-methylhex-4-enethioyl)piperidine-4-carboxylate (381)



Prepared according to the **general procedure I**, using 1-(2,2-dimethyl-3-phenylpropanethioyl)piperidine-4-carboxylate **342** (32.0 mg, 0.10 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (15.8 mg, 0.02 mmol), chiral carboxylic acid **L4** (11.2 mg, 0.04 mmol), 18-crown-6 (5.3 mg, 0.02 mmol), ethyl but-2-ynoate (56.2 mg, 0.50 mmol) and MS13X (20 mg). The crude reaction mixture was purified by flash column chromatography (1/4 Et_2O/pentane) and **381** was isolated as pale yellow oil (33.5 mg, 78%, 90/10 er). Chiral HPLC (Chiralpak IA, 3/97 IPA/hexane, 1.0 mL/min, $\lambda = 230$ nm) $\tau_{Rmajor} = 13.76$ min, $\tau_{Rminor} = 15.19$ min, 90/10 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.14 (m, $3H_{Ar}$), 7.13 – 7.07 (m, $2H_{Ar}$), 6.02 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 5.02 – 4.77 (m, 2H, N-C<u>H</u>$_2$), 4.20 (q, *J* = 7.1 Hz, 2H, O-C<u>H</u>$_2$-CH_3), 3.70 (s, 3H, O-C<u>H</u>$_3$), 3.54 – 3.45 (m, 2H, N-C<u>H</u>'$_2$), 3.42 (d, *J* = 14.2 Hz, 1H, C-C<u>H</u>$_a$H$_b$-C_{Ar}), 2.97 (d, *J* = 14.0 Hz, 1H, C-C<u>H</u>$_a$H$_b$-C_{Alk}), 2.82 – 2.64 (m, 3H, C-CH$_a$<u>H</u>$_b$-C_{Alk}, C-CH$_a$<u>H</u>$_b$-C_{Ar}, C(O)-C<u>H</u>), 2.09 – 1.97 (m, 2H, N-CH_2-C<u>H</u>$_2$), 1.94 (d, *J* = 7.2 Hz, 3H, CH-C<u>H</u>$_3$), 1.92 – 1.80 (m, 2H, N-CH_2-C<u>H</u>'$_2$), 1.38 (s, 3H, C-C<u>H</u>$_3$), 1.31 (t, *J* = 7.2 Hz, 3H, O-CH_2-C<u>H</u>$_3$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.5 (<u>C</u>=S), 174.6 (Me ester <u>C</u>=O), 168.9 (Et ester <u>C</u>=O), 139.6 (C=<u>C</u>H), 137.8 (<u>C</u>=CH), 130.4 ($2C_{Ar}$), 129.6 (C_{Ar}), 128.1 ($2C_{Ar}$), 126.7 (C_{Ar}), 60.6 (O-<u>C</u>H_2-CH_3), 52.7 (NC(S)-<u>C</u>), 52.3 (brs, N-<u>C</u>H_2, 2C), 52.1 (O-<u>C</u>H_3), 45.8 (C-<u>C</u>H$_a$H$_b$-

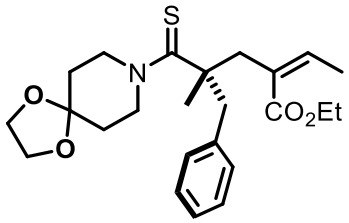
C_{Ar}), 44.9 (C-$\underline{C}H_aH_b$-C_{Alk}), 40.4 (C(O)-$\underline{C}H$), 29.3 (C-$\underline{C}H_3$), 28.2 (N-CH_2-$\underline{C}H_2$), 28.1 (N-CH_2-$\underline{C}H'_2$), 16.1 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{24}H_{34}O_4N^{32}S]^+$ requires m/z 432.2203, found m/z 432.2202.

IR (film) ν_{max}/cm^{-1}: 2952, 1732, 1709, 1417, 1381, 1256, 1199, 1172, 1149, 1034, 702.

$[\alpha]_D^{25}$ = -0.36 (c = 0.44, $CHCl_3$).

Ethyl (Z)-4-benzyl-2-ethylidene-4-methyl-5-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)-5-thioxopentanoate (382)



Prepared according to the **general procedure I**, using 2,2-dimethyl-3-phenyl-1-(1,4-dioxa-8-azaspiro[4.5]decan-8-yl)propane-1-thione **343** (63.9 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/4 Et_2O/pentane) and **382** was isolated as pale yellow oil (61.0 mg, 71%, 91/9 er). Chiral HPLC (Chiralpak AD-H, 3/97 IPA/hexane, 1.0 mL/min, λ = 220 nm) τ_{Rmajor} = 19.84 min, τ_{Rminor} = 26.68 min, 91/9 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.17 (m, 3H_{Ar}), 7.12 – 7.06 (m, 2H_{Ar}), 6.03 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.36 – 4.24 (m, 4H, N-C<u>H_2</u>), 4.20 (q, *J* = 7.2 Hz, 2H, O-C<u>H_2</u>-CH_3), 4.00 (s, 4H, O-C<u>H_2</u>), 3.42 (d, *J* = 13.9 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 2.94 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.81 (d, *J* = 14.0 Hz, 1H, C-CH_a<u>H_b</u>-C_{Alk}), 2.70 (d, *J* = 13.9 Hz, 1H, C-CH_a<u>H_b</u>-C_{Ar}), 1.95 (d, *J* = 7.3 Hz, 3H, CH-C<u>H_3</u>), 1.88 – 1.77 (m, 4H, N-CH_2-C<u>H_2</u>), 1.39 (s, 3H, C-C<u>H_3</u>), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H_3</u>).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.1 (<u>C</u>=S), 168.7 (ester <u>C</u>=O), 139.5 (C=<u>C</u>H), 137.6 (<u>C</u>=CH), 130.2 (2C_{Ar}), 129.5 (C_{Ar}), 128.0 (2C_{Ar}), 126.5 (C_{Ar}), 106.7 (O-<u>C</u>-O), 64.6 (O-<u>C</u>H_2, 2C), 60.5 (O-<u>C</u>H_2-CH_3), 52.6 (NC(S)-<u>C</u>), 50.9 (brs, N-<u>C</u>H_2, 2C), 45.7 (C-<u>C</u>$H_a$$H_b$-

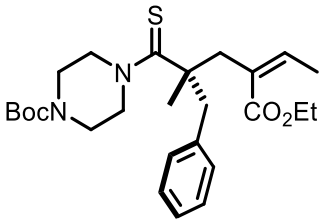
C_{Ar}), 44.7 (C-<u>C</u>H_aH_b-C_{Alk}), 35.1 (N-CH_2-CH_2-<u>C</u>H_2), 29.3 (C-<u>C</u>H_3), 16.0 (CH-<u>C</u>H_3), 14.3 (O-CH_2-<u>C</u>H_3).

HRMS (ESI) $[C_{24}H_{34}O_4N^{32}S]^+$ requires m/z 432.2203, found m/z 432.2202.

IR (film) ν_{max}/cm^{-1}: 2976, 2929, 1708, 1416, 1239, 1145, 1092, 1031, 944, 703.

$[\alpha]_D^{25}$ = -4.77 (c = 0.71, $CHCl_3$).

tert-Butyl (Z)-4-(2-benzyl-4-(ethoxycarbonyl)-2-methylhex-4-enethioyl)piperazine-1-carboxylate (383)



Prepared according to the **general procedure I**, using 4-(2,2-dimethyl-3-phenylpropanethioyl)piperazine-1-carboxylate **344** (18.1 mg, 0.05 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (7.9 mg, 0.01 mmol), chiral carboxylic acid **L4** (5.6 mg, 0.02 mmol), 18-crown-6 (2.6 mg, 0.01 mmol), ethyl but-2-ynoate (28.0 mg, 0.25 mmol) and MS13X (10 mg). The crude reaction mixture was purified by flash column chromatography (3/17 Et_2O/pentane) and **383** was isolated as pale yellow oil (13.2 mg, 56%, 91/9 er). Chiral HPLC (Chiralpak IB, 2/98 IPA/hexane, 1.0 mL/min, $\lambda = 220$ nm) $\tau_{Rmajor} = 24.75$ min, $\tau_{Rminor} = 22.65$ min, 91/9 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.17 (m, $3H_{Ar}$), 7.14 – 7.08 (m, $2H_{Ar}$), 6.02 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.24 – 4.06 (m, 6H, O-C<u>H_2</u>-CH_3, C(S)-N-C<u>H_2</u>), 3.57 – 3.47 (m, 4H, C(O)-N-C<u>H_2</u>), 3.43 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 3.06 (d, *J* = 14.6 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.72 (dd, *J* = 14.0, 4.2 Hz, 2H, CH_a<u>H_b</u>-C_{Alk}, C-CH_a<u>H_b</u>-C_{Ar}), 1.93 (d, *J* = 7.2 Hz, 3H, CH-C<u>H_3</u>), 1.47 (s, 9H, C(C<u>H_3</u>)$_3$), 1.40 (s, 3H, C-C<u>H_3</u>), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H_3</u>).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 211.2 (<u>C</u>=S), 169.0 (ester <u>C</u>=O), 154.7 (amide <u>C</u>=O), 139.4 (C=<u>C</u>H), 137.6 (<u>C</u>=CH), 130.3 ($2C_{Ar}$), 129.7 (C_{Ar}), 128.2 ($2C_{Ar}$), 126.8 (C_{Ar}), 80.5 (<u>C</u>$(CH_3)_3$), 60.7 (O-<u>C</u>H_2-CH_3), 53.0 (NC(S)-<u>C</u>), 52.6 (C(S)-N-<u>C</u>H_2, 2C), 46.5 (C-<u>C</u>$H_a$$H_b$-

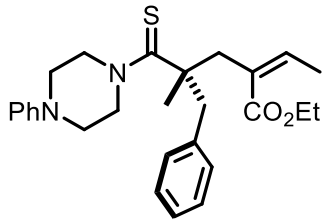
C_{Ar}), 45.7 (C-$\underline{C}H_aH_b$-C_{Alk}), 42.9 (C(O)-N-CH_2-$\underline{C}H_2$, 2C), 29.1 (C-$\underline{C}H_3$), 28.5 (C($\underline{C}H_3$)$_3$), 16.1 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{26}H_{39}O_4N_2{}^{32}S]^+$ requires m/z 475.2625, found m/z 475.2626.

IR (film) ν_{max}/cm^{-1}: 2978, 1697, 1455, 1407, 1366, 1242, 1167, 1122, 1020, 702.

$[\alpha]_D^{25}$ = -1.19 (c = 0.36, $CHCl_3$).

Ethyl (Z)-4-benzyl-2-ethylidene-4-methyl-5-(4-phenylpiperazin-1-yl)-5-thioxopentanoate (384)



Prepared according to the **general procedure I**, using2,2-dimethyl-3-phenyl-1-(4-phenylpiperazin-1-yl)propane-1-thione **345** (33.9 mg, 0.10 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (15.8 mg, 0.02 mmol), chiral carboxylic acid **L4** (11.2 mg, 0.04 mmol), 18-crown-6 (5.3 mg, 0.02 mmol), ethyl but-2-ynoate (56.2 mg, 0.50 mmol) and MS13X (20 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **384** was isolated as pale yellow oil (25.2 mg, 56%, 89/11 er). Chiral HPLC (Chiralpak IB, 10/90 IPA/hexane, 1.0 mL/min, $\lambda = 230$ nm) $\tau_{Rmajor} = 13.95$ min, $\tau_{Rminor} = 21.00$ min, 89/11 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.32 – 7.26 (m, $2H_{Ar}$), 7.26 – 7.16 (m, $3H_{Ar}$), 7.15 – 7.10 (m, $2H_{Ar}$), 6.94 – 6.84 (m, $3H_{Ar}$), 6.11 – 6.00 (m, 1H, C=C$\underline{H}$), 4.49 – 4.29 (m, 4H, C(S)-N-C$\underline{H_2}$), 4.22 (q, *J* = 7.1 Hz, 2H, O-C$\underline{H_2}$-CH_3), 3.47 (d, *J* = 13.1 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 3.31 (t, *J* = 5.2 Hz, 4H, C_{Ar}-N-C$\underline{H_2}$), 3.03 (d, *J* = 14.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.83 (d, *J* = 14.0 Hz, 1H, $CH_a\underline{H_b}$-C_{Alk}), 2.74 (d, *J* = 14.0 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Ar}), 1.95 (d, *J* = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.42 (s, 3H, C-C$\underline{H_3}$), 1.32 (t, *J* = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 210.7 (C=S), 169.0 (ester C=O), 150.3 (C_{Ar}), 139.6 (C=CH), 137.7 (C=CH), 130.3 ($2C_{Ar}$), 129.6 (C_{Ar}), 129.4 ($2C_{Ar}$), 128.2 ($2C_{Ar}$), 126.7 (C_{Ar}), 120.2 (C_{Ar}), 115.8 ($2C_{Ar}$), 60.7 (O-CH_2-CH_3), 52.9 (NC(S)-C), 52.7 (C(S)-N-CH_2, 2C), 48.6

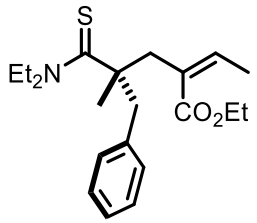
(C_{Ar}-N-$\underline{C}H_2$, 2C), 46.2 (C-$\underline{C}H_aH_b$-C_{Ar}), 45.4 (C-$\underline{C}H_aH_b$-C_{Alk}), 29.3 (C-$\underline{C}H_3$), 16.1 (CH-$\underline{C}H_3$), 14.5 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{27}H_{35}O_2N_2{}^{32}S]^+$ requires m/z 451.2414, found m/z 451.2405.

IR (film) ν_{max}/cm^{-1}: 2979, 1703, 1600, 1496, 1455, 1414, 1386, 1256, 1223, 1147, 1020, 756, 699.

$[\alpha]_D^{25}$ = -12.82 (c = 0.33, $CHCl_3$).

Ethyl (Z)-4-benzyl-5-(diethylamino)-2-ethylidene-4-methyl-5-thioxopentanoate (385)



Prepared according to the **general procedure I**, using *N,N*-diethyl-2,2-dimethyl-3-phenylpropanethioamide **347** (25.0 mg, 0.10 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (15.8 mg, 0.02 mmol), chiral carboxylic acid **L4** (11.2 mg, 0.04 mmol), 18-crown-6 (5.3 mg, 0.02 mmol), ethyl but-2-ynoate (56.2 mg, 0.50 mmol) and MS13X (20 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **385** was isolated as pale yellow oil (27.2 mg, 75%, 85/1 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 7.43 min, τ_{Rminor} = 8.21 min, 85/15 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.17 (m, $3H_{Ar}$), 7.17 – 7.13 (m, $2H_{Ar}$), 6.06 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.21 (q, *J* = 7.1 Hz, 2H, O-C<u>H_2</u>-CH_3), 4.15 – 3.59 (m, 4H, N-C<u>H_2</u>), 3.53 (d, *J* = 13.9 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 3.08 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.82 (d, *J* = 14.2 Hz, 1H, C-CH_a<u>H_b</u>-C_{Alk}), 2.69 (d, *J* = 13.9 Hz, 1H, C-CH_a<u>H_b</u>-C_{Ar}), 1.93 (d, *J* = 7.2 Hz, 3H, CH-C<u>H_3</u>), 1.40 (s, 3H, C-C<u>H_3</u>), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H_3</u>), 1.23 (t, *J* = 7.0 Hz, 6H, N-CH_2-C<u>H_3</u>).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 208.3 (<u>C</u>=S), 169.0 (ester <u>C</u>=O), 139.3 (C=<u>C</u>H), 138.0 (<u>C</u>=CH), 130.4 ($2C_{Ar}$), 129.9 (C_{Ar}), 128.0 ($2C_{Ar}$), 126.6 (C_{Ar}), 60.5 (O-<u>C</u>H_2-CH_3), 53.0 (NC(S)-<u>C</u>), 50.4* (brs, N-<u>C</u>H_2, 2C), 47.4* (brs, N-<u>C</u>H_2, 2C), 47.2 (C-<u>C</u>$H_a$$H_b$-$C_{Ar}$), 46.0 (C-<u>C</u>$H_a$$H_b$-$C_{Alk}$), 28.4 (C-<u>C</u>$H_3$), 16.0 (CH-<u>C</u>$H_3$), 14.4 (O-$CH_2$-<u>C</u>$H_3$), 13.9* (brs, N-$CH_2$-<u>C</u>$H_3$, 2C), 10.7* (brs, N-$CH_2$-<u>C</u>$H_3$, 2C).

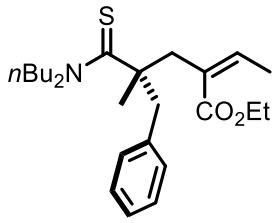
*Rotamers observed.

HRMS (ESI) $[C_{21}H_{32}O_2N^{32}S]^+$ requires m/z 362.2148, found m/z 362.2145.

IR (film) ν_{max}/cm^{-1}: 2981, 1711, 1462, 1410, 1382, 1254, 1150, 1029, 955, 703.

$[\alpha]_D^{25}$ = -2.30 (c = 0.46, $CHCl_3$).

Ethyl (Z)-4-benzyl-5-(dibutylamino)-2-ethylidene-4-methyl-5-thioxopentanoate (386)



Prepared according to the **general procedure I**, using *N,N*-dibutyl-2,2-dimethyl-3-phenylpropanethioamide **348** (43.1 mg, 0.14 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (22.3 mg, 0.03 mmol), chiral carboxylic acid **L4** (15.8 mg, 0.06 mmol), 18-crown-6 (7.5 mg, 0.03 mmol), ethyl but-2-ynoate (79.1 mg, 0.71 mmol) and MS13X (30 mg). The crude reaction mixture was purified by flash column chromatography (1/19 Et_2O/pentane) and **386** was isolated as pale yellow oil (50.0 mg, 85%, 83/17 er). Chiral HPLC (Chiralpak ID, 2/98 IPA/hexane, 1.0 mL/min, λ = 275 nm) τ_{Rmajor} = 9.57min, τ_{Rminor} = 8.38 min, 83/17 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.18 (m, 3H_{Ar}), 7.18 – 7.12 (m, 2H_{Ar}), 6.06 (q, *J* = 7.2 Hz, 1H, C=C$\underline{H}$), 4.20 (q, *J* = 7.2 Hz, 2H, O-C$\underline{H_2}$-CH_3), 4.06 – 3.41 (m, 5H, C-C$\underline{H_a}H_b$-C_{Ar}, N-C$\underline{H_2}$), 3.13 (d, *J* = 14.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.79 (d, *J* = 14.1 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Alk}), 2.70 (d, *J* = 13.8 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Ar}), 1.92 (d, *J* = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.74 – 1.47 (m, 4H, N-CH_2-C$\underline{H_2}$), 1.38 (s, 3H, C-C$\underline{H_3}$), 1.33 – 1.20 (m, 7H, O-CH_2-C$\underline{H_3}$, N-CH_2-CH_2-C$\underline{H_2}$), 0.92 (t, *J* = 7.3 Hz, 6H, N-CH_2-CH_2-CH_2-C$\underline{H_3}$).

^{13}C NMR (176 MHz, Chloroform-*d*) δ 208.5(C=S), 169.0 (ester C=O), 138.9 (C=CH), 138.2 (C=CH), 130.5 (2C_{Ar}), 130.1 (C_{Ar}), 128.0 (2C_{Ar}), 126.6 (C_{Ar}), 60.5 (O-CH_2-CH_3), 56.8* (brs, N-CH_2, 2C), 53.6* (brs, N-CH_2, 2C), 53.3 (NC(S)-C), 47.7 (C-CH_aH_b-C_{Ar}), 46.3 (C-CH_aH_b-C_{Alk}), 30.7* (brs, N-CH_2-CH_2, 2C), 28.2 (C-CH_3), 27.3* (brs, N-CH_2-CH_2, 2C), 20.4 (N-CH_2-CH_2-CH_2), 16.0 (CH-CH_3), 14.4 (O-CH_2-CH_3), 13.9 (N-CH_2-CH_2-CH_2-CH_3).

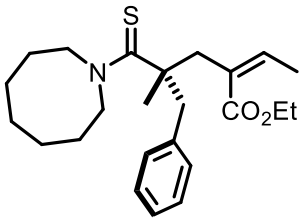
*Rotamers observed.

HRMS (ESI) $[C_{25}H_{34}O_2N^{32}S]^+$ requires m/z 418.2774, found m/z 418.2768.

IR (film) ν_{max}/cm^{-1}: 2959, 2933, 2873, 1711, 1456, 1408, 1380, 1250, 1219, 1146, 1028, 703.

$[\alpha]_D^{25}$ = -4.25 (c = 0.51, $CHCl_3$).

Ethyl (Z)-5-(azocan-1-yl)-4-benzyl-2-ethylidene-4-methyl-5-thioxopentanoate (387)



Prepared according to the **general procedure I**, using 1-(azocan-1-yl)-2,2-dimethyl-3-phenylpropane-1-thione **351** (57.9 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/19 Et_2O/pentane) and **387** was isolated as pale yellow oil (45.9 mg, 57%, 84/16 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 8.13 min, τ_{Rminor} = 11.84 min, 84/16 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.26 – 7.17 (m, $3H_{Ar}$), 7.17 – 7.11 (m, $2H_{Ar}$), 6.07 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.20 (q, *J* = 7.1 Hz, 2H, O-C<u>H_2</u>-CH_3), 4.19 – 3.74 (m, 4H, N-C<u>H_2</u>), 3.50 (d, *J* = 13.8 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 3.06 (d, *J* = 14.1 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.85 (d, *J* = 14.1 Hz, 1H, C-CH_a<u>H_b</u>-C_{Alk}), 2.78 (d, *J* = 13.8 Hz, 1H, C-CH_a<u>H_b</u>-C_{Ar}), 2.11 – 1.76 (m, 7H, CH-C<u>H_3</u>, N-CH_2-C<u>H_2</u>), 1.72 – 1.46 (m, 6H, N-CH_2-CH_2-C<u>H_2</u>-C<u>H_2</u>), 1.40 (s, 3H, C-C<u>H_3</u>), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H_3</u>).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 208.8 (<u>C</u>=S), 169.0 (ester <u>C</u>=O), 139.7 (C=<u>C</u>H), 138.0 (<u>C</u>=CH), 130.5 ($2C_{Ar}$), 129.8 (C_{Ar}), 128.1 ($2C_{Ar}$), 126.6 (C_{Ar}), 60.5 (O-<u>C</u>H_2-CH_3), 57.3* (brs, N-<u>C</u>H_2, 2C), 56.7* (brs, N-<u>C</u>H_2, 2C), 53.1 (NC(S)-<u>C</u>), 46.3 (C-<u>C</u>$H_a$$H_b$-$C_{Ar}$), 45.2 (C-<u>C</u>$H_a$$H_b$-$C_{Alk}$), 28.9 (C-<u>C</u>$H_3$), 27.2 (N-$CH_2$-$CH_2$-<u>C</u>$H_2$-<u>C</u>$H_2$, 3C), 25.7* (brs, N-$CH_2$-<u>C</u>$H_2$, 2C), 25.2* (brs, N-$CH_2$-<u>C</u>$H_2$, 2C), 16.1 (CH-<u>C</u>$H_3$), 14.4 (O-$CH_2$-<u>C</u>$H_3$).

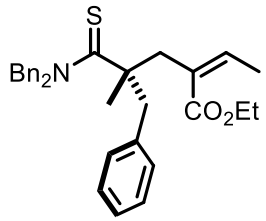
*Rotamers observed.

HRMS (ESI) $[C_{24}H_{36}O_2N^{32}S]^+$ requires m/z 402.2461, found m/z 402.2462.

IR (film) ν_{max}/cm^{-1}: 2981, 1711, 1382, 1252, 1152, 1069, 955, 703.

$[\alpha]_D^{25}$ = -1.26 (c = 0.85, $CHCl_3$).

Ethyl (Z)-4-benzyl-5-(dibenzylamino)-2-ethylidene-4-methyl-5-thioxopentanoate (388)



Prepared according to the **general procedure I**, using *N,N*-dibenzyl-2,2-dimethyl-3-phenylpropanethioamide **352** (74.7 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (31.6 mg, 0.04 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl but-2-ynoate (112.4 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/19 Et_2O/pentane) and **388** was isolated as pale yellow oil (61.5 mg, 63%, 81/19 er). Chiral HPLC (Chiralpak AD-H, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 12.20 min, τ_{Rminor} = 11.50 min, 81/19 er).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.31 – 7.25 (m, $6H_{Ar}$), 7.24 – 7.18 (m, $5H_{Ar}$), 7.14 – 6.91 (m, $4H_{Ar}$), 6.15 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 5.62 – 4.67 (m, 4H, N-C<u>H_2</u>), 4.16 (app qd, *J* = 7.1, 2.2 Hz, 2H, O-C<u>H_2</u>-CH_3), 3.77 (d, *J* = 13.6 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 3.28 (d, *J* = 13.8 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.96 (d, *J* = 13.8 Hz, 1H, C-CH_a<u>H_b</u>-C_{Alk}), 2.76 (d, *J* = 13.6 Hz, 1H, C-CH_a<u>H_b</u>-C_{Ar}), 1.93 (d, *J* = 7.1 Hz, 3H, CH-C<u>H_3</u>), 1.43 (s, 3H, C-C<u>H_3</u>), 1.24 (t, *J* = 7.2 Hz, 3H, O-CH_2-C<u>H_3</u>).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 213.6 (<u>C</u>=S), 169.0 (ester <u>C</u>=O), 139.7 (C=<u>C</u>H), 137.9 (<u>C</u>=CH), 136.0 ($2C_{Ar}$), 130.8 ($2C_{Ar}$), 130.1 (C_{Ar}), 128.8 ($4C_{Ar}$), 128.1 ($2C_{Ar}$), 127.5 ($2C_{Ar}$), 127.4 (brs, $4C_{Ar}$), 126.7 (C_{Ar}), 60.5 (O-<u>C</u>H_2-CH_3), 58.1* (brs, N-<u>C</u>H_2, 2C), 55.5* (brs, N-<u>C</u>H_2, 2C), 55.0 (NC(S)-<u>C</u>), 49.1 (C-<u>C</u>$H_a$$H_b$-$C_{Ar}$), 47.4 (C-<u>C</u>$H_a$$H_b$-$C_{Alk}$), 26.9 (C-<u>C</u>$H_3$), 16.0 (CH-<u>C</u>$H_3$), 14.4 (O-$CH_2$-<u>C</u>$H_3$).

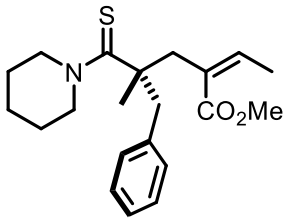
*Rotamers observed.

HRMS (ESI) $[C_{31}H_{36}O_2N^{32}S]^+$ requires m/z 486.2461, found m/z 486.2458.

IR (film) ν_{max}/cm^{-1}: 2926, 1711, 1495, 1452, 1228, 1147, 1030, 735, 700.

$[\alpha]_D^{25}$ = -44.94 (c = 0.48, $CHCl_3$).

Methyl (Z)-4-benzyl-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (314)



Prepared according to the **general procedure I**, using 2,2-dimethyl-3-phenyl-1-(piperidin-1-yl)propane-1-thione **313** (26.2 mg, 0.10 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (15.8 mg, 0.02 mmol), chiral carboxylic acid **L4** (11.2 mg, 0.48 mmol), 18-crown-6 (5.3 mg, 0.02 mmol), methyl but-2-ynoate (49.2 mg, 1.00 mmol) and MS13X (20 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **314** was isolated as a purple oil (27.0 mg, 75%, 88/12 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 220 nm) τ_{Rmajor} = 9.13 min, τ_{Rminor} = 11.99 min, 88/12 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.15 (m, 3H_{Ar}), 7.15 – 6.96 (m, 2H_{Ar}), 6.01 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.40 – 4.05 (m, 4H, N-C<u>H_2</u>), 3.73 (s, 3H, O-C<u>H_3</u>), 3.41 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 3.04 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.78 – 2.67 (m, 2H, C-CH_a<u>H_b</u>-C_{Alk}, C-CH_a<u>H_b</u>-C_{Ar}), 1.93 (d, *J* = 7.2 Hz, 3H, CH-C<u>H_3</u>), 1.75 – 1.63 (m, 6H, N-CH_2-C<u>H_2</u>-C<u>H_2</u>), 1.37 (s, 3H, C-C<u>H_3</u>).

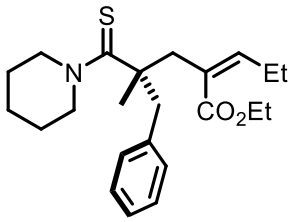
^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.1 (<u>C</u>=S), 169.3 (ester <u>C</u>=O), 139.6 (C=<u>C</u>H), 137.9 (<u>C</u>=CH), 130.4 (2C_{Ar}), 129.6 (C_{Ar}), 128.1 (2C_{Ar}), 126.6 (C_{Ar}), 54.6 (N-<u>C</u>H_2, 2C), 52.4 (NC(S)-<u>C</u>), 51.5 (O-<u>C</u>H_3), 45.9 (C-<u>C</u>$H_a$$H_b$-$C_{Ar}$), 44.7 (C-<u>C</u>$H_a$$H_b$-$C_{Alk}$), 29.5 (C-<u>C</u>$H_3$), 26.1 (N-$CH_2$-<u>C</u>$H_2$, 2C), 24.4 (N-$CH_2$-$CH_2$-<u>C</u>$H_2$), 16.1 (CH-<u>C</u>$H_3$).

HRMS (ESI) $[C_{21}H_{30}O_2N^{32}S]^+$ requires m/z 360.1992, found m/z 360.1991.

IR (film) ν_{max}/cm^{-1}: 2936, 1712, 1418, 1382, 1240, 1193, 1143, 1010, 702.

$[\alpha]_D^{25}$ = 9.06 (c = 0.32, $CHCl_3$).

Ethyl (Z)-2-(2-benzyl-2-methyl-3-(piperidin-1-yl)-3-thioxopropyl)pent-2-enoate (389)



Prepared according to the **general procedure I**, using 2,2-dimethyl-3-phenyl-1-(piperidin-1-yl)propane-1-thione **313** (52.4 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (63.1 mg, 0.08 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl pent-2-ynoate (126.2 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (3/47 Et_2O/pentane) and **389** was isolated as pale yellow oil (42.7 mg, 55%, 89/11 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 220 nm) τ_{Rmajor} = 8.02 min, τ_{Rminor} = 13.84 min, 89/11 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.15 (m, $3H_{Ar}$), 7.15 – 7.08 (m, $2H_{Ar}$), 5.89 (t, *J* = 7.5 Hz, 1H, C=C$\underline{H}$), 4.27 – 4.04 (m, 6H, N-C$\underline{H_2}$, O-C$\underline{H_2}$-CH_3), 3.42 (d, *J* = 13.9 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 2.97 (d, *J* = 14.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.75 (dd, *J* = 15.5, 13.9 Hz, 2H, C-C$H_a\underline{H_b}$-C_{Alk}, C-C$H_a\underline{H_b}$-C_{Ar}), 2.37 (p, *J* = 7.5 Hz, 2H, CH-C$\underline{H_2}$-CH_3), 1.80 – 1.65 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.38 (s, 3H, C-C$\underline{H_3}$), 1.30 (t, *J* = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$), 1.01 (t, *J* = 7.5 Hz, 3H, CH-CH_2-C$\underline{H_3}$).

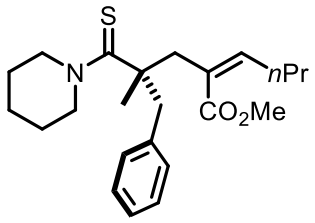
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2 (C=S), 169.0 (ester C=O), 146.5 (C=CH), 137.9 (C=CH), 130.4 ($2C_{Ar}$), 128.2 (C_{Ar}), 128.1 ($2C_{Ar}$), 126.6 (C_{Ar}), 60.5 (O-CH_2-CH_3), 54.5 (brs, N-CH_2, 2C), 52.5 (NC(S)-C), 45.7 (C-CH_aH_b-C_{Ar}), 44.4 (C-CH_aH_b-C_{Alk}), 29.5 (C-CH_3), 26.1 (N-CH_2-CH_2, 2C), 24.4 (N-CH_2-CH_2-CH_2), 23.4 (CH-CH_2 -CH_3), 14.4 (O-CH_2-CH_3), 14.1 (CH-CH_2-CH_3).

HRMS (ESI) $[C_{23}H_{34}O_2N^{32}S]^+$ requires m/z 388.2305, found m/z 388.2303.

IR (film) ν_{max}/cm^{-1}: 2935, 1710, 1455, 1418, 1380, 1237, 1152, 1095, 1010, 744, 702.

$[\alpha]_D^{25}$ = 14.71 (c = 0.38, $CHCl_3$).

Methyl (Z)-2-(2-benzyl-2-methyl-3-(piperidin-1-yl)-3-thioxopropyl)hex-2-enoate (390)



Prepared according to the **general procedure I**, using 2,2-dimethyl-3-phenyl-1-(piperidin-1-yl)propane-1-thione **313** (52.4 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (63.1 mg, 0.08 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), methyl hex-2-ynoate (126.2 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (3/47 Et_2O/pentane) and **390** was isolated as pale yellow oil (34.1mg, 44%, 86/14 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 8.76 min, τ_{Rminor} = 14.85 min, 86/14 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.16 (m, $3H_{Ar}$), 7.15 – 7.09 (m, $2H_{Ar}$), 5.89 (t, J = 7.5 Hz, 1H, C=C$\underline{H}$), 4.29 – 4.03 (m, 4H, N-C$\underline{H_2}$), 3.71 (s, 3H, O-C$\underline{H_3}$), 3.40 (d, J = 13.9 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 3.06 (d, J = 14.1 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.73 (dd, J = 16.7, 13.9 Hz, 2H, C-C$H_a\underline{H_b}$-C_{Alk}, C-C$H_a\underline{H_b}$-C_{Ar}), 2.33 (q, J = 7.4 Hz, 2H, CH-C$\underline{H_2}$-CH_2-CH_3), 1.80 – 1.64 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.48 – 1.39 (m, 2H, CH-CH_2-C$\underline{H_2}$-CH_3), 1.38 (s, 3H, C-C$\underline{H_3}$), 0.91 (t, J = 7.4 Hz, 3H, CH-CH_2-CH_2-C$\underline{H_3}$).

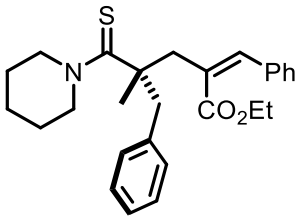
^{13}C NMR (101 MHz, $CDCl_3$) δ 209.1 (C=S), 169.4 (ester C=O), 145.0 (C=CH), 137.9 (C=CH), 130.4 ($2C_{Ar}$), 128.6 (C_{Ar}), 128.1 ($2C_{Ar}$), 126.6 (C_{Ar}), 54.5 (brs, N-CH_2, 2C), 52.4 (NC(S)-C), 51.5 (O-CH_3), 46.0 (C-CH_aH_b-C_{Ar}), 44.8 (C-CH_aH_b-C_{Alk}), 32.0 (CH-CH_2-CH_2-CH_3), 29.4 (C-CH_3), 26.1 (N-CH_2-CH_2, 2C), 24.4 (N-CH_2-CH_2-CH_2), 22.7 (CH-CH_2-CH_2-CH_3), 14.0 (CH-CH_2-CH_2-CH_3).

HRMS (ESI) $[C_{23}H_{34}O_2N^{32}S]^+$ requires m/z 388.2305, found m/z 388.2302.

IR (film) ν_{max}/cm^{-1}: 2980, 1715, 1418, 1380, 1223, 1151, 1094, 1010, 952, 748, 702.

$[\alpha]_D^{25}$ = 13.31 (c = 0.42, $CHCl_3$).

Ethyl (S,Z)-4-benzyl-2-benzylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (391)



Prepared according to the **general procedure I**, using 2,2-dimethyl-3-phenyl-1-(piperidin-1-yl)propane-1-thione **313** (52.4 mg, 0.20 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (63.1 mg, 0.08 mmol), chiral carboxylic acid **L4** (22.4 mg, 0.08 mmol), 18-crown-6 (10.6 mg, 0.04 mmol), ethyl 3-phenylpropiolate (174.3 mg, 1.00 mmol) and MS13X (40 mg). The crude reaction mixture was purified by flash column chromatography (1/20 Et_2O/pentane) and **391** was isolated as pale yellow oil (48.4 mg, 56%, 86/14 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 8.76 min, τ_{Rminor} = 14.85 min, 86/14 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 6H_{Ar}), 7.21 – 7.17 (m, 4H_{Ar}), 6.75 (s, 1H, C=C$\underline{H}$), 4.25 (p, J = 7.3 Hz, 2H), 4.16 – 3.95 (m, 4H, N-C$\underline{H_2}$), 3.51 – 3.36 (m, 2H, C-C$\underline{H_a}H_b$-$C_{Ar,}$ C-C$\underline{H_a}H_b$-C_{Alk}), 2.88 (d, J = 13.8 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Ar}), 2.78 (dd, J = 14.2, 1.0 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Alk}), 1.70 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.53 (s, 3H, C-C$\underline{H_3}$), 1.03 (t, J = 7.2 Hz, 3H, O-CH_2-C$\underline{H_3}$).

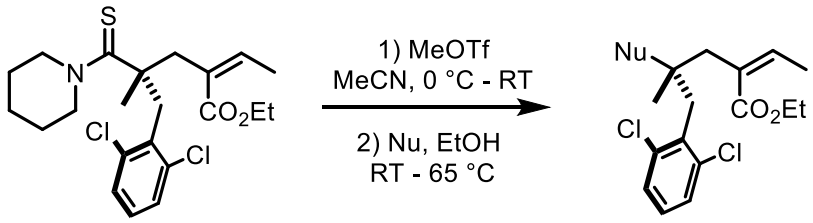
^{13}C NMR (101 MHz, $CDCl_3$) δ 208.8 ($\underline{C}$=S), 170.2 (ester $\underline{C}$=O), 137.7 ($\underline{C}$=CH), 137.3 (C=$\underline{C}$H), 130.5 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 128.4 (C_{Ar}), 128.2 (2C_{Ar}), 128.1 (2C_{Ar}), 127.8 (C_{Ar}), 126.7 (C_{Ar}), 60.9 (O-$\underline{C}H_2$-CH_3), 54.6 (brs, N-$\underline{C}H_2$, 2C), 52.8 (NC(S)-$\underline{C}$), 46.8 (C-$\underline{C}H_aH_b$-C_{Ar}), 46.4 (C-$\underline{C}H_aH_b$-C_{Alk}), 29.0 (C-$\underline{C}H_3$), 26.1 (N-CH_2-$\underline{C}H_2$, 2C), 24.3 (N-CH_2-CH_2-$\underline{C}H_2$), 13.7 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{27}H_{34}O_2N^{32}S]^+$ requires m/z 463.2305, found m/z 463.2310.

IR (film) ν_{max}/cm^{-1}: 2982, 1718, 1420, 1222, 1151, 1090, 1007, 951.

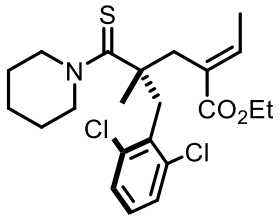
5.2.5 Derivatisations of C(sp^3)–H alkenylation products

5.2.5.1 General procedure K: *Formation of heterocycles.*



According to the modified literature procedure,[146] to a solution of **364** (1.00 eq.) in CH_3CN (0.1 M) was added MeOTf (1.10 eq.) at 0 ºC and the resulting mixture was warmed to room temperature and stirred for 30 min. The solvent was then removed *in vacuo*, and EtOH (0.1 M) and the nucleophile (1.10 eq.) was added. The resulting mixture was stirred at room temperature for 3 h and then heated for 1 hour at 65 °C. The mixture was concentrated *in vacuo* and sat. aq. $NaHCO_3$ and EtOAc was added. The organic layer was separated and dried over anhydrous $MgSO_4$. After filtration and evaporation, the crude mixture was purified by silica gel column chromatography (pentane/EtOAc) to give heterocyclic products. The two enantiomers were then separated by chiral HPLC, with conditions specified for each individual product.

Ethyl (E)-4-(2,6-dichlorobenzyl)-2-ethylidene-4-methyl-5-(piperidin-1-yl)-5-thioxopentanoate (400)



According to a modified literature procedure,[185] to a solution of **364** (18.2 mg, 0.041 mmol, 1.00 eq., >99:1) in toluene (0.4 mL, 0.1 M) was added trifluoroborane tetrahydrofuran complex solution (4.5 μL, 0.041 mmol, 1.00 eq.) and the mixture was stirred at room temperature for 24 h. The reaction was quenched by water and poured into the EtOAc. The combined organic layers were separated and dried over anhydrous $MgSO_4$. After filtration and the evaporation of the solvent, the crude mixture was purified by silica gel column chromatography (1/10 Et_2O/pentane) to give **400** (16.6 mg, 91% >20:1 *E/Z*, >99/1 er) as a colorless oil. Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm, τ_{Rmajor} = 6.4 min, τ_{Rminor} = 11.7 min, >99:1 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.27 (d, J = 7.7 Hz, $3H_{Ar}$), 7.07 (t, J = 8.0 Hz, H_{Ar}), 6.92 (q, J = 7.2 Hz, 1H, C=C$\underline{H}$), 5.26-4.79 (bs, 1H, N-C$\underline{H_2}$), 4.68-4.32 (bs, 1H, N-C$\underline{H_2}$), 4.25 – 4.05 (m, 2H, O-C$\underline{H_2}$-CH_3), 4.35-3.87 (bs, 1H, N-C$\underline{H_2}$), 3.84-3.56 (bs, 1H, N-C$\underline{H_2}$), 3.62 (d, J = 13.8 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 3.50 (d, J = 13.9 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Ar}), 3.13 (d, J = 13.6 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 3.01 (d, J = 13.6 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Alk}), 1.96-1.68 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.78 (d, J = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.27 (t, J = 7.2 Hz, 3H, O-CH_2-C$\underline{H_3}$), 1.17 (s, 3H, C-C$\underline{H_3}$).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.42, 168.48, 139.83, 136.79, 136.45, 130.76, 128.18, 128.07, 60.57, 51.19, 40.27, 37.51, 29.70, 28.43, 25.89, 24.37, 15.62, 14.32.

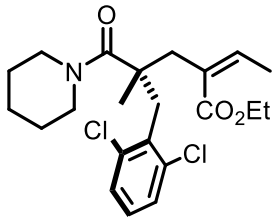
^{13}C NMR (101 MHz, Chloroform-*d*) δ 209.5 (C=S), 168.6 (ester C=O), 140.0 (C=CH), 136.9 ($2C_{Ar}$), 136.6 (C_{Ar}), 130.9 (C=CH), 128.3 ($2C_{Ar}$), 128.2 (C_{Ar}), 60.7 (O-CH_2-CH_3), 54.6 (brs, N-CH_2, 2C), 51.3 (NC(S)-C), 40.4 (C-CH_aH_b-C_{Alk}), 37.6 (C-CH_aH_b-C_{Ar}), 28.6 (C-CH_3), 26.0 (brs, N-CH_2-CH_2, 2C), 24.5 (N-CH_2-CH_2-CH_2), 15.8 (CH-CH_3), 14.5 (O-CH_2-CH_3).

HRMS (ESI) $[C_{22}H_{30}O_2N^{35}Cl_2{}^{32}S]^+$ requires m/z 442.1369, found m/z 442.1368.

IR (film) ν_{max}/cm^{-1}:2981, 2937, 1707, 1435, 1249, 1145, 1014, 953, 775.

$[\alpha]_D^{25}$ = 9.06 (c = 0.24, $CHCl_3$).

Ethyl (Z)-4-(2,6-dichlorobenzyl)-2-ethylidene-4-methyl-5-oxo-5-(piperidin-1-yl)pentanoate (401)



According to literature,[185] oxone (312.6 mg, 1.02 mmol, 5.00 eq.) was added to a stirred solution of **364** (90.0 mg, 0.20 mmol, 1.00 eq, >99:1 er) in MeOH/water (1:1, 8 mL) at room temperature. The resulting mixture was stirred at rt for 72 h. The reaction mixture was then diluted with EtOAc and washed with water and brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography (1/4 Et_2O/pentane) and **401** was isolated as transparent oil (68.2 mg, 79%, >99:1 er). Chiral HPLC (Chiralpak IA, 5/95 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 10.03 min, τ_{Rminor} = 16.28 min, >99/1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J = 8.1 Hz, $2H_{Ar}$), 7.11 – 7.03 (m, H_{Ar}), 5.95 (q, J = 7.2 Hz, 1H, C=C$\underline{H}$), 4.18 (q, J = 7.1 Hz, 2H, O-C$\underline{H_2}$-CH_3), 3.85 – 3.51 (m, 4H, N-C$\underline{H_2}$), 3.48 (d, J = 14.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 3.30 (d, J = 14.0 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Ar}), 3.01 (d, J = 13.9 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.77 (d, J = 13.9 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Alk}), 1.91 (d, J = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.73 – 1.52 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.29 (t, J = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$), 0.99 (s, 3H, C-C$\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3 (amide $\underline{C}$=O), 168.8 (ester $\underline{C}$=O), 138.8 (C=$\underline{C}$H), 136.9 ($2C_{Ar}$), 135.8 ($\underline{C}$=CH), 130.3 (C_{Ar}), 128.4 ($2C_{Ar}$), 128.2 (C_{Ar}), 60.4 (O-$\underline{C}H_2$-CH_3), 47.1

(NC(S)-C), 44.1 (C-CH_aH_b-C_{Alk}), 38.4 (C-CH_aH_b-C_{Ar}), 26.0 (N-CH_2-CH_2, 2C), 24.9 (N-CH_2-CH_2-CH_2), 22.4 (C-CH_3), 16.1 (CH-CH_3), 14.4 (O-CH_2-CH_3).

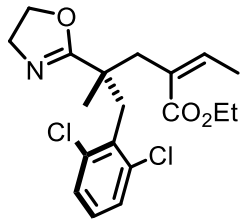
*N-CH_2 not visible on C NMR

HRMS (ESI) $[C_{22}H_{30}O_3N^{35}Cl_2]^+$ requires m/z 426.1597, found m/z 426.1597.

IR (film) ν_{max}/cm^{-1}: 2981, 1735, 1707, 1435, 1382, 1247, 1149, 1104, 955, 755.

$[\alpha]_D^{25}$ = -27.48 (c = 0.29, $CHCl_3$).

Ethyl (Z)-5-(2,6-dichlorophenyl)-4-(4,5-dihydrooxazol-2-yl)-2-ethylidene-4-methylpentanoate (403)



Prepared according to the **general procedure J**, using thioamide **364** (39.8 mg, 0.090 mmol) in CH_3CN (0.9 mL) with MeOTf (11.2 μL, 0.099 mmol), 2-aminoethan-1-ol (1.3 μL, 0.022 mmol) in EtOH (0.2 mL). The crude mixture was purified by silica gel column chromatography (1/4 Et_2O/pentane) to give **403** (18.3 mg, 53%, >99:1 er) as a colorless oil. Chiral HPLC (Chiralpak AD-H, 1/99 IPA/hexane, 1.0 mL/min, λ = 230 nm, τ_{Rmajor} = 25.8 min, τ_{Rminor} = 35.9 min, >99:1 er).

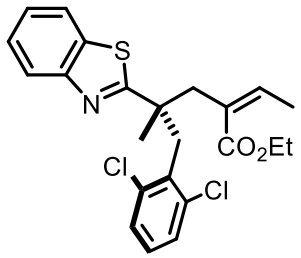
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.0 Hz, $2H_{Ar}$), 7.06 (dd, *J* = 8.4, 7.6 Hz, $1H_{Ar}$), 5.99 (q, J = 7.2 Hz, 1H, C=C$\underline{H}$), 4.26 – 4.07 (m, 4H, N-C$\underline{H_2}$-C$\underline{H_2}$-O), 3.84 – 3.69 (m, 2H, O-C$\underline{H_2}$-CH_3), 3.34 (d, *J* = 13.9 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 3.24 (d, *J* = 13.9 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Ar}), 2.91 (d, *J* = 13.5 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.71 (dt, *J* = 13.4, 0.9 Hz, 1H, C-C$H_a\underline{H_b}$-C_{Alk}), 1.91 (dd, *J* = 7.2, 0.8 Hz, 3H, CH-C$\underline{H_3}$), 1.29 (t, *J* = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$), 1.14 (s, 3H, C-C$\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3 (O$\underline{C}$=N), 168.7 (ester $\underline{C}$=O), 138.9 (C=$\underline{C}$H), 137.0 ($2C_{Ar}$), 134.9 ($\underline{C}$=CH), 130.0 (C_{Ar}), 128.5 ($2C_{Ar}$), 128.2 (C_{Ar}), 67.2 (2C, N-$\underline{C}H_2$-$\underline{C}H_2$-O), 60.3 (O-$\underline{C}H_2$-CH_3), 54.7 (NC(S)-$\underline{C}$), 43.4 (C-$\underline{C}H_aH_b$-C_{Alk}), 39.4 (C-$\underline{C}H_aH_b$-C_{Ar}), 20.8 (C-$\underline{C}H_3$), 16.0 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{19}H_{24}O_3N^{35}Cl_2]^+$requires m/z 384.1128, found m/z 384.1124.

IR (film) ν_{max}/cm^{-1}: . 2985, 1733, 1705, 1439, 1252, 1153, 1104, 955, 758.

Ethyl (Z)-4-(benzo[d]thiazol-2-yl)-5-(2,6-dichlorophenyl)-2-ethylidene-4-methylpentanoate (404)



Prepared according to the **general procedure J**, using thioamide **364** (8.8 mg, 0.020 mmol) in CH_3CN (0.2 mL) with MeOTf (2.4 μL, 0.022 mmol), 2-aminobenzenethiol (2.4 μL, 0.022 mmol,), Et_3N (5.6 μL, 0.040 mmol), in EtOH (0.2 mL). The crude mixture was purified by silica gel column chromatography (1/4 Et_2O/pentane) afforded **404** (7.8 mg, 87%, >99:1 er) as a colorless oil. Chiral HPLC (Chiralpak AD-H, 1/99 IPA/hexane, 1.0 mL/min, λ = 230 nm, τ_{Rmajor} = 12.90 min, τ_{Rminor} = 12.22 min, >99:1 er).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 (ddd, J = 8.2, 1.2, 0.6 Hz, $1H_{Ar}$), 7.84 (ddd, J = 8.0, 1.3, 0.6 Hz, $1H_{Ar}$), 7.46 (ddd, J = 8.3, 7.2, 1.3 Hz, $1H_{Ar}$), 7.35 (ddd, J = 8.2, 7.2, 1.2 Hz, $1H_{Ar}$), 7.27 – 7.21 (m, $2H_{Ar}$), 7.08 (dd, J = 8.5, 7.5 Hz, $1H_{Ar}$), 5.93 – 5.85 (q, J = 7.2 Hz, 1H, C=C$\underline{H}$), 3.94 (qd, J = 7.2, 1.3 Hz, 2H, O-C$\underline{H_2}$-CH_3), 3.68 – 3.54 (m, 2H C-C$\underline{H_a}\underline{H_b}$-$C_{Ar}$), 3.37 (d, J = 13.5 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 3.05 (d, J = 13.5 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Alk}), 1.81 (d, J = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.46 (s, 3H, C-C$\underline{H_3}$), 1.13 (t, J = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$).

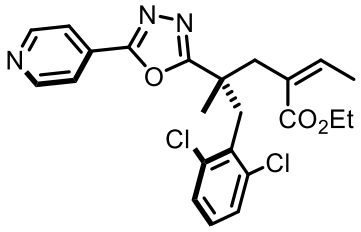
^{113}C NMR (101 MHz, $CDCl_3$) δ 178.8 (S$\underline{C}$=N), 168.5 (ester $\underline{C}$=O), 153.3 (C_{Ar}), 139.5 (C=$\underline{C}$H), 137.0 ($2C_{Ar}$), 135.3 ($\underline{C}$=CH), 134.4 (C_{Ar}), 129.6 (C_{Ar}), 128.4 (C_{Ar}), 128.2 ($2C_{Ar}$), 125.7 (C_{Ar}), 124.5 (C_{Ar}), 122.8 (C_{Ar}), 121.4 (C_{Ar}), 60.2 (O-$\underline{C}H_2$-CH_3), 47.2 (NC(S)-$\underline{C}$), 45.8 (C-$\underline{C}H_aH_b$-C_{Alk}), 42.4 (C-$\underline{C}H_aH_b$-C_{Ar}), 22.4 (C-$\underline{C}H_3$), 15.7 (CH-$\underline{C}H_3$), 14.0 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{23}H_{24}O_2N^{35}Cl_2{}^{32}S]^+$ requires m/z 448.0899, found m/z 448.0898.

IR (film) ν_{max}/cm^{-1}: 2918, 1712, 1560, 1435, 1384, 1230, 1150, 1025.

$[\alpha]_D^{25}$ = 4.05 (c = 0.60, $CHCl_3$).

Ethyl (R,Z)-5-(2,6-dichlorophenyl)-2-ethylidene-4-methyl-4-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)pentanoate (406)



Prepared according to the **general procedure J**, using thioamide **364** (27.2 mg, 0.061 mmol) in CH_3CN (0.6 mL) with MeOTf (7.7 μL, 0.068 mmol), Et_3N (23.1 μL, 0.123 mmol), isonicotinohydrazide (25.7 μL, 0.184 mmol), in EtOH (0.2 mL). The crude mixture was purified by silica gel column chromatography (1/1 Et_2OAc/pentane) affording **406** 19.4 mg, 69%, 98:21 er) as a colorless oil. Chiral HPLC (Chiralpak IA, 20/80 IPA/hexane, 1.0 mL/min, λ = 230 nm τ_{Rmajor} = 10.2 min, τ_{Rminor} = 14.3 min, 98/2 er).

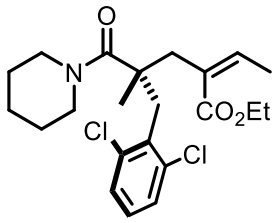
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 – 8.75 (m, $2H_{Ar}$), 7.82 – 7.74 (m, $2H_{Ar}$), 7.28 (d, *J* = 0.6 Hz, $2H_{Ar}$), 7.11 (dd, *J* = 8.6, 7.4 Hz, $1H_{Ar}$), 6.02 (q, J = 7.1 Hz, 1H, C=C$\underline{H}$), 4.06 (qd, *J* = 7.1, 3.2 Hz, 2H, O-C$\underline{H_2}$-CH_3), 3.54 – 3.41 (m, 2H, C-C$\underline{H_aH_b}$-C_{Ar}), 3.24 – 3.15 (m, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 3.02 (dt, *J* = 13.8, 0.9 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Alk}), 1.88 (d, J = 7.1 Hz, 3H, CH-C$\underline{H_3}$), 1.48 (s, 3H, C-C$\underline{H_3}$), 1.22 (t, *J* = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1 (0$\underline{C}$=N), 168.3 (ester $\underline{C}$=O), 163.0 (N=$\underline{C}$O), 151.0 ($2C_{Ar}$), 140.4 (C=$\underline{C}$H), 137.0 ($2C_{Ar}$), 137.0 ($\underline{C}$=CH), 133.4 (C_{Ar}), 131.4 (C_{Ar}), 128.9 (C_{Ar}), 128.8 ($2C_{Ar}$), 120.4 ($2C_{Ar}$), 60.6 (O-$\underline{C}H_2$-CH_3), 44.1 (C-$\underline{C}H_aH_b$-C_{Alk}), 41.8 (NC(S)-$\underline{C}$), 40.9 (C-$\underline{C}H_aH_b$-C_{Ar}), 21.0 (C-$\underline{C}H_3$), 16.0 (CH-$\underline{C}H_3$), 14.3 (O-CH_2-$\underline{C}H_3$).

HRMS (ESI) $[C_{23}H_{24}O_3N_3{}^{35}Cl_2{}^{32}S]^+$ requires m/z 460.1195, found m/z 460.1189.

IR (film) ν_{max}/cm^{-1}: 2935, 2895, 1701, 1635, 1399, 1270, 1251, 1228, 1150, 955.

Ethyl (Z)-4-(2,6-dichlorobenzyl)-2-ethylidene-4-methyl-5-oxo-5-(piperidin-1-yl)pentanoate (407)



According to literature,[185] oxone (312.6 mg, 1.02 mmol, 5.00 eq.) was added to a stirred solution of **364** (90.0 mg, 0.20 mmol, 1.00 eq, >99:1 er) in MeOH/water (1:1, 8 mL) at rt. The resulting mixture was stirred at room temperature for 72 h. The reaction mixture was then diluted with EtOAc and washed with water and brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure to give the crude product. The crude product was purified by flash column chromatography (1/4 Et_2O/pentane) and **407** was isolated as transparent oil (68.2 mg, 79%, >99:1 er). Chiral HPLC (Chiralpak IA, 5/95 IPA/hexane, 1.0 mL/min, λ = 230 nm, τ_{Rmajor} = 10.03 min, τ_{Rminor} = 16.28 min, >99/1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.1 Hz, $2H_{Ar}$), 7.11 – 7.03 (m, H_{Ar}), 5.95 (q, *J* = 7.2 Hz, 1H, C=C$\underline{H}$), 4.18 (q, *J* = 7.1 Hz, 2H, O-C$\underline{H_2}$-CH_3), 3.85 – 3.51 (m, 4H, N-C$\underline{H_2}$), 3.48 (d, *J* = 14.0 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Ar}), 3.30 (d, *J* = 14.0 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Ar}), 3.01 (d, *J* = 13.9 Hz, 1H, C-C$\underline{H_a}H_b$-C_{Alk}), 2.77 (d, *J* = 13.9 Hz, 1H, C-$CH_a\underline{H_b}$-C_{Alk}), 1.91 (d, *J* = 7.2 Hz, 3H, CH-C$\underline{H_3}$), 1.73 – 1.52 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$), 1.29 (t, *J* = 7.1 Hz, 3H, O-CH_2-C$\underline{H_3}$), 0.99 (s, 3H, C-C$\underline{H_3}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3 (amide C=O), 168.8 (ester C=O), 138.8 (C=CH), 136.9 ($2C_{Ar}$), 135.8 (C=CH), 130.3 (C_{Ar}), 128.4 ($2C_{Ar}$), 128.2 (C_{Ar}), 60.4 (O-CH_2-CH_3), 47.1

(NC(S)-C), 44.1 (C-CH_aH_b-C_{Alk}), 38.4 (C-CH_aH_b-C_{Ar}), 26.0 (N-CH_2-CH_2, 2C), 24.9 (N-CH_2-CH_2-CH_2), 22.4 (C-CH_3), 16.1 (CH-CH_3), 14.4 (O-CH_2-CH_3).

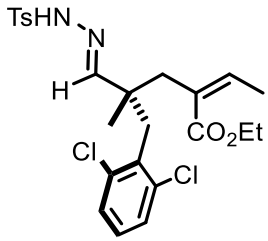
*N-CH_2 not visible on C NMR

HRMS (ESI) $[C_{22}H_{30}O_3N^{35}Cl_2]^+$ requires m/z 426.1597, found m/z 426.1597.

IR (film) ν_{max}/cm^{-1}: 2981, 1735, 1707, 1435, 1382, 1247, 1149, 1104, 955, 755.

$[\alpha]_D^{25}$ = -27.48 (c = 0.29, $CHCl_3$).

Ethyl (R,2Z,5E)-4-(2,6-dichlorobenzyl)-2-ethylidene-4-methyl-5-(2-tosylhydrazineylidene)pentanoate (408)



According to literature,[186] to a solution of aldehyde **407** (7.6 mg, 0.022 mmol, 1.0 eq, >99:1 er) in MeOH (0.04 mL, 0.5 M) was added tosylhydrazide (4.1 mg, 0.022 mmol, 1.0 eq.) and the reaction mixture was stirred at room temperature overnight. Solvent was then removed in vacuo and crude mixture was purified by silica gel chromatography (1/4 EtOAc/pentane) to give **408** as white solid (9.5 mg, 84%, 99:1 er). Chiral HPLC (Chiralpak AD-H, 15/85 IPA/hexane, 1.0 mL/min, λ = 220 nm) τ_{Rmajor} = 14.58 min, τ_{Rminor} = 10.68 min, 99/1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.64 (m, $2H_{Ar}$), 7.27 (s, Ts-N<u>H</u>), 7.22 – 7.17 (m, $2H_{Ar}$), 7.07 (d, *J* = 8.0 Hz, $2H_{Ar}$), 7.03 (s, 1H, <u>H</u>C=N), 6.99 – 6.94 (m, H_{Ar}), 5.96 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.23 – 4.08 (m, 2H, O-C<u>H_2</u>-CH_3), 3.04 (d, *J* = 13.7 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 2.95 (d, *J* = 13.7 Hz, 1H, C-CH_a<u>H_b</u>-C_{Ar}), 2.76 (d, *J* = 13.6 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.45 (d, *J* = 13.6 Hz, 1H, C-CH_a<u>H_b</u>-C_{Alk}), 2.42 (s, 3H, Ts C<u>H_3</u>), 1.90 (d, *J* = 7.2 Hz, 3H, CH-C<u>H_3</u>), 1.29 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H_3</u>), 1.00 (s, 3H, C-C<u>H_3</u>).

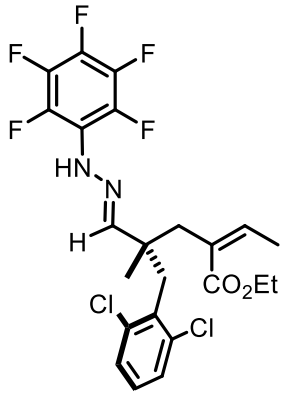
^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (ester <u>C</u>=O), 156.8 (H<u>C</u>=N), 143.7 (C_{Ar}), 140.3 (C=<u>C</u>H), 136.3 ($2C_{Ar}$), 135.5 (C_{Ar}), 133.9 (C_{Ar}), 129.5 ($2C_{Ar}$), 129.1 (<u>C</u>=CH), 128.7 ($2C_{Ar}$), 128.0 ($3C_{Ar}$), 60.7 (O-<u>C</u>H_2-CH_3), 45.1 (NC(S)-<u>C</u>), 44.5 (C-<u>C</u>$H_a$$H_b$-$C_{Alk}$), 40.1 (C-<u>C</u>$H_a$$H_b$-$C_{Ar}$), 21.8 (Ts <u>C</u>$H_3$), 19.7 (C-<u>C</u>$H_3$), 16.1 (CH-<u>C</u>$H_3$), 14.4 (O-$CH_2$-<u>C</u>$H_3$).

HRMS (ESI) $[C_{24}H_{29}O_4N_2{}^{35}Cl_2{}^{32}S]^+$ requires m/z 511.1220, found m/z 511.1219.

IR (film) ν_{max}/cm^{-1}: 2981, 2889, 1382, 1252, 1154, 1073, 955.

$[\alpha]_D^{25}$ = 11.67 (c = 0.6, $CHCl_3$).

Ethyl (2Z,5E)-4-(2,6-dichlorobenzyl)-2-ethylidene-4-methyl-5-(2-(perfluorophenyl)hydrazineylidene)pentanoate (409)



According to literature,[186] to a solution of aldehyde **407** (8.7 mg, 0.025 mmol, 1.0 eq, >99:1 er) in MeOH (0.05 mL, 0.5 M) was added (perfluorophenyl)hydrazine (5.0 mg, 0.025 mmol, 1.0 eq.) and the reaction mixture was stirred at room temperature overnight. Solvent was then removed *in vacuo* and crude mixture was purified by silica gel chromatography (1/9 Et_2O/pentane) to give **409** as dark yellow amorphous solid (9.1 mg, 67%, 97:3 er). Chiral HPLC (Chiralpak IA, 3/97 IPA/hexane, 1.0 mL/min, λ = 254 nm τ_{Rmajor} = 6.98 min, τ_{Rminor} = 9.52 min, 97:3 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.0 Hz, $2H_{Ar}$), 7.14 (t, *J* = 1.8 Hz, 1H, H<u>C</u>=N), 7.07 (dd, *J* = 8.4, 7.7 Hz, H_{Ar}), 6.72 (t, *J* = 3.1 Hz, 1H, Ar-N<u>H</u>), 6.04 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.25 – 4.07 (m, 2H, O-C<u>H_2</u>-CH_3), 3.20 – 3.07 (m, 2H, C-C<u>H_a</u>H_b-C_{Ar}, C-CH_a<u>H_b</u>-C_{Ar}), 2.88 (d, *J* = 13.6 Hz, 1H, C-C<u>H_a</u>H_b-C_{Alk}), 2.52 (d, *J* = 13.6 Hz, 1H, C-CH_a<u>H_b</u>-C_{Alk}), 1.95 (d, *J* = 7.2 Hz, 3H, CH-C<u>H_3</u>), 1.27 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H_3</u>), 1.08 (s, 3H, C-C<u>H_3</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8 (ester <u>C</u>=O), 152.9 (H<u>C</u>=N), 139.8 (C=<u>C</u>H), 136.6 ($2C_{Ar}$), 134.4 (C_{Ar}), 129.6 (<u>C</u>=CH), 128.8 ($2C_{Ar}$), 128.3 (C_{Ar}), 60.5 (O-<u>C</u>H_2-CH_3), 44.9

(NC(S)-C, C-$\underline{C}H_aH_b$-C_{Alk}, 2C), 40.5 (C-$\underline{C}H_aH_b$-C_{Ar}), 20.2 (C-$\underline{C}H_3$), 16.1 (CH-$\underline{C}H_3$), 14.4 (O-CH_2-$\underline{C}H_3$).

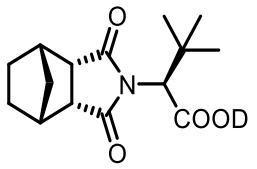
HRMS (ESI) $[C_{23}H_{22}O_2N_2{}^{35}Cl_2F_5]^+$ requires m/z 523.0973, found m/z 523.0974.

IR (film) ν_{max}/cm^{-1}: 2981, 2889, 1383, 1252, 1153, 1073, 955.

$[\alpha]_D^{25}$ = 3.00(c = 0.09, $CHCl_3$).

5.2.6 Synthesis of deuterium labelled ligand

(S)-2-((3aR,4R,7S,7aS)-1,3-dioxooctahydro-2H-4,7-methanoisoindol-2-yl)-3,3-dimethylbutanoic acid-d (L4-d_1)

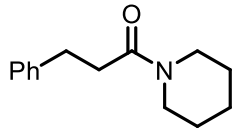


According to modified literature procedure,[187] ligand **L4** (75 mg, 0.27 mmol, 1.00 eq.) was dissolved in methanol-d_4 (0.27 mL, 1 M) and stirred at room temperature for 1 hour. The solvent was evaporated under reduced pressure and the cycle was repeated 5 times to afford **L4-*d_1*** as white solid (75 mg, quant.).

^{1}H NMR (400 MHz, C_6D_6) δ 4.65 (s, 1H), 2.53 – 2.39 (m, 2H), 2.35 (q, *J* = 4.2 Hz, 2H), 1.61 – 1.26 (m, 3H), 1.17 (s, 10H), 1.11 (t, *J* = 7.0 Hz, 2H).

5.2.7 Synthesis of deuterium labelled starting material – thioamide

3-Phenyl-1-(piperidin-1-yl)propan-1-one (443)



Prepared according to modified **general procedure E**, using piperidine (1.196 mL, 12.1 mmol), 3-phenylpropanoic acid (2.00 g, 13.3 mmol), oxalyl chloride (2.366 mL, 26.6 mmol), Et_3N (3.366 mL, 24.2 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/9 Et_2O/pentane). **443** was isolated as a light brown oil (1.46 g, 55%).

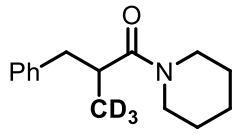
Analytical data is consistent with the literature.[188]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.24 – 7.17 (m, 3H), 3.61 – 3.51 (m, 2H), 3.38 – 3.27 (m, 2H), 3.01 – 2.93 (m, 2H), 2.66 – 2.57 (m, 2H), 1.61 (tdd, J = 8.2, 4.7, 1.5 Hz, 2H), 1.57 – 1.41 (m, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 141.7, 128.6, 128.6, 126.2, 46.7, 42.8, 35.3, 31.8, 26.5, 25.7, 24.7.

HRMS (ESI) $[C_{14}H_{20}ON]^+$ requires m/z 218.1539, found m/z 218.1540.

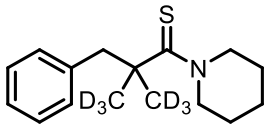
2-Benzyl-1-(piperidin-1-yl)propan-1-one-3,3,3-d_3 (444-d_3)



Prepared according to **general procedure H**, using diisopropylamine (1.142 mL, 8.1 mmol), *n*BuLi in hexane (3.258 mL, 8.1 mmol), 3-phenyl-1-(piperidin-1-yl)propan-1-one (1.207 mL, 5.4 mmol), iodomethane-d_3 (0.507 mL, 8.1 mmol). The crude reaction mixture was purified by flash column chromatography (1/10 Et_2O/pentane). **444-d_3** was isolated as light brown solid (423 mg, 33%)

Used in the next step without further analysis.

2-Benzyl-2-(methyl-d_3)-1-(piperidin-1-yl)propane-1-thione-3,3,3-d_3 (313-d_6)



Prepared according to **general procedure H**, using methylated amide **444-*d_3*** (420 mg, 1.8 mmol), diisopropylamine (0.377 mL, 1.8 mmol), *n*BuLi in hexane (1.075 mL, 1.8 mmol), iodomethane-*d_3* (0.167 mL, 2.7 mmol) and Lawesson's reagent (435 mg, 1.1 mmol). The crude reaction mixture was purified by flash column chromatography twice (1/20 and 1/50 Et_2O/pentane). **313-*d_6*** was isolated as a yellow solid (281 mg, 59%, over two steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.19 (m, $3H_{Ar}$), 7.18 – 7.10 (m, $2H_{Ar}$), 4.28 – 4.10 (m, 4H, N-C$\underline{H_2}$), 3.04 (s, 2H, NC(S)-C-C$\underline{H_2}$), 1.84 – 1.67 (m, 6H, N-CH_2-C$\underline{H_2}$-C$\underline{H_2}$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 211.0 (<u>C</u>=S), 138.1 (C_{Ar}), 130.6 ($2C_{Ar}$), 128.1 ($2C_{Ar}$), 126.6 (C_{Ar}), 54.5 (N-<u>C</u>H_2), 47.6 (NC(S)-<u>C</u>), 46.5 (NC(S)-C-<u>C</u>H_2), 26.3 (N-CH_2-<u>C</u>H_2, 2C), 24.5 (N-CH_2-CH_2-<u>C</u>H_2).

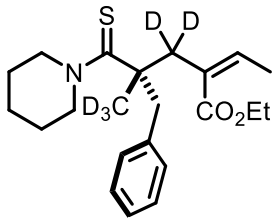
HRMS (ESI) $[C_{16}H_{18}D_6N^{32}S]^+$ requires m/z 268.2001, found m/z 268.2000.

MP 60 - 62 °C.

IR (film) ν_{max}/cm^{-1}: 2919, 2850, 1456, 1419, 1221, 773.

5.2.8 Deuterium labelled product

Ethyl (Z)-4-benzyl-2-ethylidene-4-(piperidine-1-carbonothioyl)pentanoate-3,3,5,5,5-d_5 (313-d_6)



Prepared according to the **general procedure I**, using 2-benzyl-2-(methyl-d_3)-1-(piperidin-1-yl)propane-1-thione-3,3,3-d_3 **444-d_3** (26.8 mg, 0.10 mmol), $[CoCp^*(MeCN)_3][SbF_6]_2$ (15.8 mg, 0.02 mmol), chiral carboxylic acid **L4** (11.2 mg, 0.04 mmol), 18-crown-6 (5.3 mg, 0.02 mmol), ethyl but-2-ynoate (56.2 mg, 0.50 mmol) and MS13X (20 mg). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) and **313-d_6** was isolated as pale yellow oil (5.1 mg, 14%, 90/10 er). Chiral HPLC (Chiralpak IA, 2/98 IPA/hexane, 1.0 mL/min, λ = 230 nm) τ_{Rmajor} = 8.68 min, τ_{Rminor} = 11.31 min, 90/10 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.15 (m, 3H_{Ar}), 7.15 – 7.08 (m, 2H_{Ar}), 6.02 (q, *J* = 7.2 Hz, 1H, C=C<u>H</u>), 4.27 – 4.06 (m, 6H, N-C<u>H_2</u>, O-C<u>H_2</u>-CH_3), 3.42 (d, *J* = 14.0 Hz, 1H, C-C<u>H_a</u>H_b-C_{Ar}), 2.70 (d, *J* = 13.9 Hz, 1H, C-CH_a<u>H_b</u>-C_{Ar}), 1.94 (d, *J* = 7.2 Hz, 3H, CH-C<u>H_3</u>), 1.78 – 1.66 (m, 6H, N-CH_2-C<u>H_2</u>-C<u>H_2</u>), 1.31 (t, *J* = 7.1 Hz, 3H, O-CH_2-C<u>H_3</u>).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.2 (<u>C</u>=S), 168.9 (ester <u>C</u>=O), 139.7 (C=<u>C</u>H), 137.9 (<u>C</u>=CH), 130.4 (2C_{Ar}), 129.6 (C_{Ar}), 128.1 (2C_{Ar}), 126.6 (C_{Ar}), 60.6 (O-<u>C</u>H_2-CH_3), 54.5 (brs, N-<u>C</u>H_2, 2C), 52.1 (NC(S)-<u>C</u>), 45.4 (C-<u>C</u>$H_a$$H_b$-$C_{Ar}$), 26.2 (N-$CH_2$-<u>C</u>$H_2$, 2C), 24.4 (N-$CH_2$-$CH_2$-<u>C</u>$H_2$), 16.1 (CH-<u>C</u>$H_3$), 14.4 (O-$CH_2$-<u>C</u>$H_3$).

HRMS (ESI) $[C_{22}H_{27}D_5O_2N^{32}S]^+$ requires m/z 379.2462, found m/z 379.2464.

IR (film) ν_{max}/cm^{-1}: 2981, 2889, 1382, 1251, 1154, 1073, 955.

$[\alpha]_D^{25}$ = 15.67 (c = 0.18, $CHCl_3$).

5.2.9 Single crystal X-ray diffraction data

Single crystal X-ray diffraction for 364

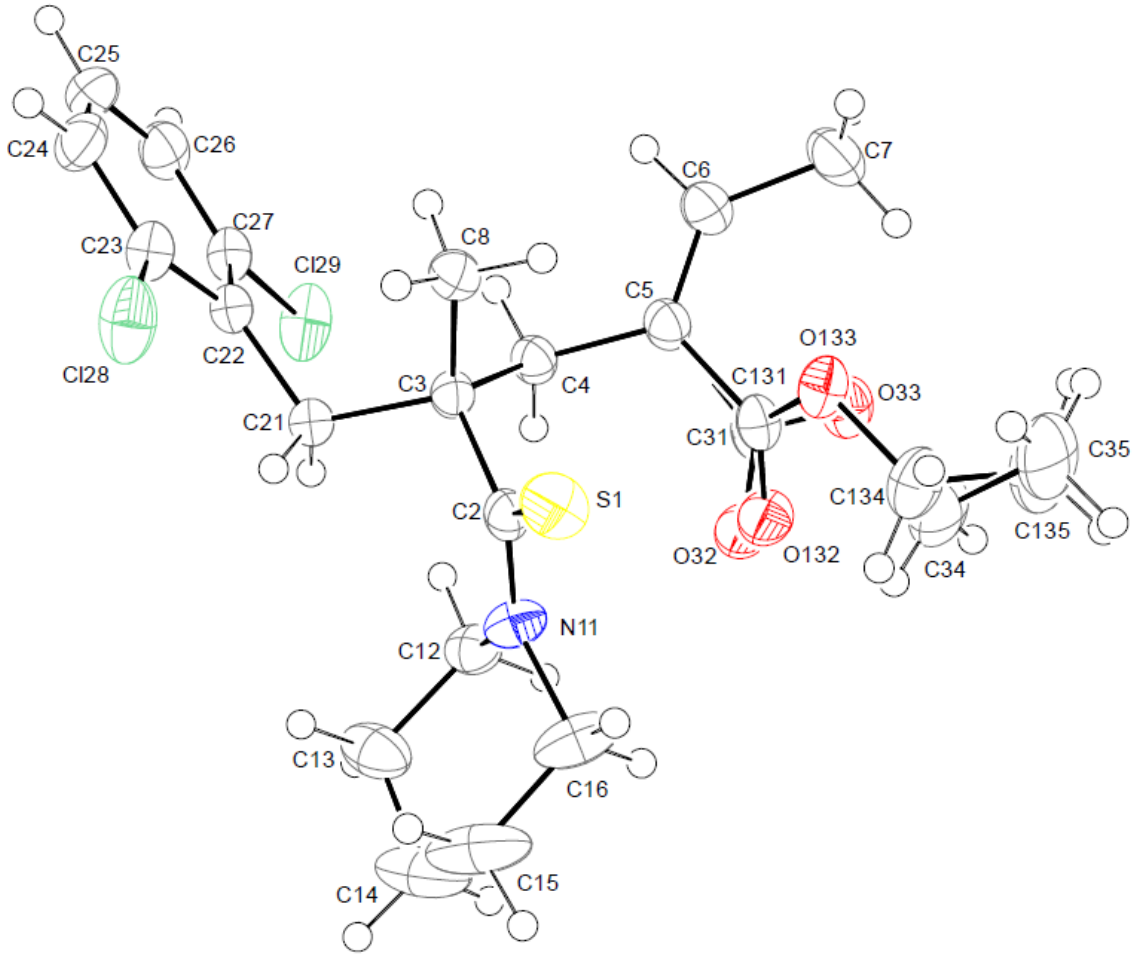


Table 1. Crystal data and structure refinement for 7297.

Identification code	7297	
Empirical formula	C22 H29 Cl2 N O2 S	
Formula weight	442.45	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P b c a	
Unit cell dimensions	a = 14.8096(2) Å	α= 90°.
	b = 13.1006(2) Å	β= 90°.
	c = 23.4093(4) Å	γ = 90°.
Volume	4541.75(12) $Å^3$	
Z	8	
Density (calculated)	1.294 Mg/m^3	
Absorption coefficient	3.563 mm^{-1}	
F(000)	1872	
Crystal size	0.22 x 0.21 x 0.19 mm^3	
Theta range for data collection	4.816 to 77.411°.	
Index ranges	-18<=h<=18, -16<=k<=15, -27<=l<=29	
Reflections collected	17206	
Independent reflections	4765 [R(int) = 0.034]	
Completeness to theta = 75.862°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.51 and 0.48	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4765 / 0 / 281	
Goodness-of-fit on F^2	0.9950	
Final R indices [I>2sigma(I)]	R1 = 0.0378, wR2 = 0.0943	
R indices (all data)	R1 = 0.0437, wR2 = 0.1001	
Largest diff. peak and hole	0.65 and -0.50 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 7297. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	5387(1)	7397(1)	6649(1)	44
C(2)	4865(1)	8029(1)	6121(1)	29
C(3)	4126(1)	8833(1)	6272(1)	26
C(4)	4384(1)	9917(1)	6050(1)	29
C(5)	5237(1)	10363(1)	6303(1)	31
C(6)	5212(1)	11153(1)	6663(1)	37
C(7)	5975(2)	11742(2)	6920(1)	49
C(8)	4025(1)	8941(1)	6923(1)	33
N(11)	5073(1)	7850(1)	5575(1)	37
C(12)	4653(1)	8262(1)	5054(1)	36
C(13)	4246(2)	7403(2)	4700(1)	50
C(14)	4951(2)	6610(2)	4544(1)	71
C(15)	5454(2)	6263(2)	5077(1)	74
C(16)	5820(2)	7161(2)	5413(1)	60
C(21)	3195(1)	8448(1)	6018(1)	30
C(22)	2357(1)	8890(1)	6292(1)	27
C(23)	1906(1)	8401(1)	6741(1)	33
C(24)	1169(1)	8820(2)	7019(1)	40
C(25)	841(1)	9752(2)	6840(1)	42
C(26)	1225(1)	10244(2)	6379(1)	38
C(27)	1964(1)	9802(1)	6111(1)	31
Cl(28)	2258(1)	7197(1)	6971(1)	51
Cl(29)	2376(1)	10424(1)	5506(1)	48
O(33)	6755(2)	9907(3)	6420(1)	43
C(34)	7613(2)	9515(4)	6208(2)	58
C(35)	8267(3)	9614(4)	6689(2)	70
C(134)	7483(4)	9115(6)	6544(4)	44
O(133)	6618(4)	9611(5)	6648(3)	35
C(135)	8197(7)	9884(12)	6447(6)	70
O(32)	6180(2)	9742(3)	5540(1)	40
O(132)	6351(6)	9678(8)	5709(3)	40

C(131)	6148(12)	9840(13)	6182(6)	30
C(31)	6087(4)	9977(4)	6039(2)	30

Table 3. Bond lengths [Å] and angles [°] for 7297.

S(1)-C(2)	1.6766(17)	C(15)-H(152)	0.993
C(2)-C(3)	1.560(2)	C(16)-H(161)	0.944
C(2)-N(11)	1.336(2)	C(16)-H(162)	0.956
C(3)-C(4)	1.560(2)	C(21)-C(22)	1.512(2)
C(3)-C(8)	1.537(2)	C(21)-H(211)	0.958
C(3)-C(21)	1.583(2)	C(21)-H(212)	0.953
C(4)-C(5)	1.512(2)	C(22)-C(23)	1.401(2)
C(4)-H(41)	0.966	C(22)-C(27)	1.396(2)
C(4)-H(42)	0.965	C(23)-C(24)	1.384(2)
C(5)-C(6)	1.337(2)	C(23)-Cl(28)	1.7469(18)
C(5)-C(31)	1.489(7)	C(24)-C(25)	1.379(3)
C(5)-C(6)	1.337(2)	C(24)-H(241)	0.916
C(5)-C(131)	1.538(19)	C(25)-C(26)	1.381(3)
C(6)-C(7)	1.494(2)	C(25)-H(251)	0.937
C(6)-H(61)	0.969	C(26)-C(27)	1.388(2)
C(7)-H(71)	0.957	C(26)-H(261)	0.919
C(7)-H(72)	0.946	C(27)-Cl(29)	1.7429(17)
C(7)-H(73)	0.965	O(33)-C(34)	1.458(4)
C(8)-H(81)	0.964	O(33)-C(31)	1.336(5)
C(8)-H(82)	0.963	C(34)-C(35)	1.489(5)
C(8)-H(83)	0.971	C(34)-H(341)	0.988
N(11)-C(12)	1.470(2)	C(34)-H(342)	0.975
N(11)-C(16)	1.478(2)	C(35)-H(353)	0.962
C(12)-C(13)	1.522(3)	C(35)-H(352)	0.965
C(12)-H(121)	0.972	C(35)-H(351)	0.961
C(12)-H(122)	0.961	C(134)-O(133)	1.456(8)
C(13)-C(14)	1.518(4)	C(134)-C(135)	1.477(16)
C(13)-H(131)	0.987	C(134)-H(1341)	0.964
C(13)-H(132)	0.978	C(134)-H(1342)	0.965
C(14)-C(15)	1.524(4)	O(133)-C(131)	1.327(14)
C(14)-H(141)	0.959	C(135)-H(1351)	0.965
C(14)-H(142)	0.981	C(135)-H(1352)	0.965
C(15)-C(16)	1.514(4)	C(135)-H(1353)	0.959
C(15)-H(151)	0.955	O(32)-C(31)	1.218(6)

O(132)-C(131)	1.167(19)	H(81)-C(8)-H(83)	110.5
		H(82)-C(8)-H(83)	109.7
S(1)-C(2)-C(3)	119.34(12)	C(2)-N(11)-C(12)	129.18(15)
S(1)-C(2)-N(11)	120.85(13)	C(2)-N(11)-C(16)	121.67(17)
C(3)-C(2)-N(11)	119.81(15)	C(12)-N(11)-C(16)	109.15(16)
C(2)-C(3)-C(4)	111.55(12)	N(11)-C(12)-C(13)	110.36(16)
C(2)-C(3)-C(8)	110.79(14)	N(11)-C(12)-H(121)	112.3
C(4)-C(3)-C(8)	105.67(13)	C(13)-C(12)-H(121)	110.2
C(2)-C(3)-C(21)	108.06(12)	N(11)-C(12)-H(122)	105.7
C(4)-C(3)-C(21)	112.24(13)	C(13)-C(12)-H(122)	109.1
C(8)-C(3)-C(21)	108.51(13)	H(121)-C(12)-H(122)	109.1
C(3)-C(4)-C(5)	115.26(13)	C(12)-C(13)-C(14)	111.4(2)
C(3)-C(4)-H(41)	107.1	C(12)-C(13)-H(131)	109.6
C(5)-C(4)-H(41)	106.6	C(14)-C(13)-H(131)	108.1
C(3)-C(4)-H(42)	109.2	C(12)-C(13)-H(132)	107.6
C(5)-C(4)-H(42)	108.6	C(14)-C(13)-H(132)	110.6
H(41)-C(4)-H(42)	110.0	H(131)-C(13)-H(132)	109.5
C(4)-C(5)-C(6)	121.47(16)	C(13)-C(14)-C(15)	109.99(18)
C(4)-C(5)-C(31)	114.4(3)	C(13)-C(14)-H(141)	108.0
C(6)-C(5)-C(31)	123.2(3)	C(15)-C(14)-H(141)	107.6
C(4)-C(5)-C(6)	121.47(16)	C(13)-C(14)-H(142)	111.7
C(4)-C(5)-C(131)	119.3(7)	C(15)-C(14)-H(142)	111.0
C(6)-C(5)-C(131)	119.1(7)	H(141)-C(14)-H(142)	108.4
C(5)-C(6)-C(7)	129.21(18)	C(14)-C(15)-C(16)	111.6(2)
C(5)-C(6)-H(61)	116.2	C(14)-C(15)-H(151)	110.1
C(7)-C(6)-H(61)	114.5	C(16)-C(15)-H(151)	107.1
C(6)-C(7)-H(71)	109.6	C(14)-C(15)-H(152)	110.0
C(6)-C(7)-H(72)	111.4	C(16)-C(15)-H(152)	109.8
H(71)-C(7)-H(72)	108.8	H(151)-C(15)-H(152)	108.1
C(6)-C(7)-H(73)	111.0	C(15)-C(16)-N(11)	109.8(2)
H(71)-C(7)-H(73)	108.2	C(15)-C(16)-H(161)	112.2
H(72)-C(7)-H(73)	107.7	N(11)-C(16)-H(161)	109.3
C(3)-C(8)-H(81)	107.3	C(15)-C(16)-H(162)	108.9
C(3)-C(8)-H(82)	110.2	N(11)-C(16)-H(162)	106.9
H(81)-C(8)-H(82)	108.2	H(161)-C(16)-H(162)	109.5
C(3)-C(8)-H(83)	110.7	C(3)-C(21)-C(22)	115.63(13)

C(3)-C(21)-H(211)	105.3	C(35)-C(34)-H(342)	112.3
C(22)-C(21)-H(211)	108.2	H(341)-C(34)-H(342)	109.8
C(3)-C(21)-H(212)	110.2	C(34)-C(35)-H(353)	110.3
C(22)-C(21)-H(212)	107.7	C(34)-C(35)-H(352)	110.8
H(211)-C(21)-H(212)	109.6	H(353)-C(35)-H(352)	110.9
C(21)-C(22)-C(23)	122.39(15)	C(34)-C(35)-H(351)	107.3
C(21)-C(22)-C(27)	122.76(15)	H(353)-C(35)-H(351)	108.4
C(23)-C(22)-C(27)	114.84(15)	H(352)-C(35)-H(351)	109.1
C(22)-C(23)-C(24)	123.24(17)	O(133)-C(134)-C(135)	110.6(7)
C(22)-C(23)-Cl(28)	120.09(13)	O(133)-C(134)-H(1341)	109.0
C(24)-C(23)-Cl(28)	116.66(14)	C(135)-C(134)-H(1341)	110.2
C(23)-C(24)-C(25)	119.05(17)	O(133)-C(134)-H(1342)	108.6
C(23)-C(24)-H(241)	120.2	C(135)-C(134)-H(1342)	109.9
C(25)-C(24)-H(241)	120.8	H(1341)-C(134)-H(1342)	108.5
C(24)-C(25)-C(26)	120.40(17)	C(134)-O(133)-C(131)	115.2(10)
C(24)-C(25)-H(251)	120.3	C(134)-C(135)-H(1351)	109.3
C(26)-C(25)-H(251)	119.3	C(134)-C(135)-H(1352)	109.2
C(25)-C(26)-C(27)	118.94(18)	H(1351)-C(135)-H(1352)	109.2
C(25)-C(26)-H(261)	120.9	C(134)-C(135)-H(1353)	110.1
C(27)-C(26)-H(261)	120.1	H(1351)-C(135)-H(1353)	109.7
C(22)-C(27)-C(26)	123.29(16)	H(1352)-C(135)-H(1353)	109.3
C(22)-C(27)-Cl(29)	120.04(13)	C(5)-C(131)-O(133)	114.2(12)
C(26)-C(27)-Cl(29)	116.64(14)	C(5)-C(131)-O(132)	118.7(10)
C(34)-O(33)-C(31)	116.3(3)	O(133)-C(131)-O(132)	127.0(15)
O(33)-C(34)-C(35)	106.2(3)	C(5)-C(31)-O(33)	111.9(4)
O(33)-C(34)-H(341)	111.1	C(5)-C(31)-O(32)	125.4(4)
C(35)-C(34)-H(341)	109.1	O(33)-C(31)-O(32)	122.7(5)
O(33)-C(34)-H(342)	108.4		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x 10^3$) for 7297. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	46(1)	41(1)	45(1)	1(1)	-14(1)	10(1)
C(2)	25(1)	23(1)	37(1)	0(1)	-1(1)	-3(1)
C(3)	24(1)	25(1)	29(1)	-1(1)	1(1)	-2(1)
C(4)	28(1)	25(1)	35(1)	-1(1)	-2(1)	-1(1)
C(5)	30(1)	27(1)	35(1)	-1(1)	-1(1)	-4(1)
C(6)	39(1)	33(1)	40(1)	-6(1)	2(1)	-7(1)
C(7)	54(1)	45(1)	47(1)	-13(1)	0(1)	-17(1)
C(8)	33(1)	37(1)	29(1)	-4(1)	0(1)	-4(1)
N(11)	39(1)	35(1)	38(1)	-2(1)	7(1)	10(1)
C(12)	44(1)	32(1)	32(1)	1(1)	9(1)	-2(1)
C(13)	75(2)	41(1)	33(1)	-3(1)	9(1)	-11(1)
C(14)	121(2)	46(1)	46(1)	-13(1)	24(1)	3(2)
C(15)	113(2)	48(1)	61(2)	-5(1)	30(2)	31(2)
C(16)	61(1)	61(2)	59(1)	-2(1)	17(1)	30(1)
C(21)	25(1)	32(1)	33(1)	-6(1)	1(1)	-3(1)
C(22)	23(1)	29(1)	30(1)	-2(1)	-2(1)	-3(1)
C(23)	27(1)	35(1)	37(1)	6(1)	-1(1)	-2(1)
C(24)	31(1)	55(1)	34(1)	1(1)	6(1)	-5(1)
C(25)	28(1)	52(1)	47(1)	-15(1)	5(1)	3(1)
C(26)	30(1)	32(1)	53(1)	-3(1)	-7(1)	4(1)
C(27)	27(1)	34(1)	33(1)	3(1)	-3(1)	-5(1)
Cl(28)	38(1)	41(1)	73(1)	24(1)	-3(1)	-5(1)
Cl(29)	36(1)	61(1)	48(1)	27(1)	-8(1)	-7(1)
O(33)	30(1)	57(2)	41(1)	-4(1)	-7(1)	1(1)
C(34)	33(2)	85(3)	55(2)	-4(2)	-5(1)	8(2)
C(35)	37(2)	101(4)	71(3)	-4(3)	-24(2)	9(2)
C(134)	30(3)	47(4)	55(5)	10(3)	-3(3)	5(3)
O(133)	27(2)	35(3)	42(3)	7(2)	1(2)	-2(2)
C(135)	37(2)	101(4)	71(3)	-4(3)	-24(2)	9(2)
O(32)	35(1)	58(1)	27(2)	-2(1)	-1(1)	0(1)
O(132)	35(1)	58(1)	27(2)	-2(1)	-1(1)	0(1)

C(131)	28(1)	27(2)	35(3)	3(2)	-4(2)	-5(1)
C(31)	28(1)	27(2)	35(3)	3(2)	-4(2)	-5(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 7297.

	x	y	z	U(eq)
H(41)	3898	10372	6155	34
H(42)	4447	9897	5640	35
H(61)	4617	11399	6767	41
H(71)	5869	12458	6872	73
H(72)	6038	11600	7314	74
H(73)	6539	11574	6736	73
H(81)	3601	9485	6992	48
H(82)	4594	9128	7092	48
H(83)	3811	8308	7090	47
H(121)	4197	8774	5138	41
H(122)	5135	8574	4842	44
H(131)	3767	7060	4921	59
H(132)	3986	7708	4356	58
H(141)	5383	6926	4294	84
H(142)	4683	6027	4343	85
H(151)	5957	5847	4974	89
H(152)	5047	5851	5323	89
H(161)	6131	6953	5745	72
H(162)	6218	7543	5173	72
H(211)	3193	7725	6077	37
H(212)	3166	8590	5619	37
H(241)	907	8482	7319	48
H(251)	352	10055	7029	51
H(261)	995	10852	6247	46
H(341)	7832	9922	5881	70
H(342)	7527	8807	6092	69
H(353)	8847	9349	6579	104
H(352)	8315	10315	6811	104
H(351)	8040	9209	7000	104
H(1341)	7633	8696	6869	53

H(1342)	7426	8682	6213	53
H(1351)	8773	9545	6414	104
H(1352)	8215	10347	6767	104
H(1353)	8074	10261	6105	104

Table 6. Hydrogen bonds for 7297 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(42)...C(12)	0.96	2.56	3.210(5)	125
C(12)-H(121)...O(32)#1	0.97	2.57	3.209(5)	123

Single crystal X-ray diffraction for 367

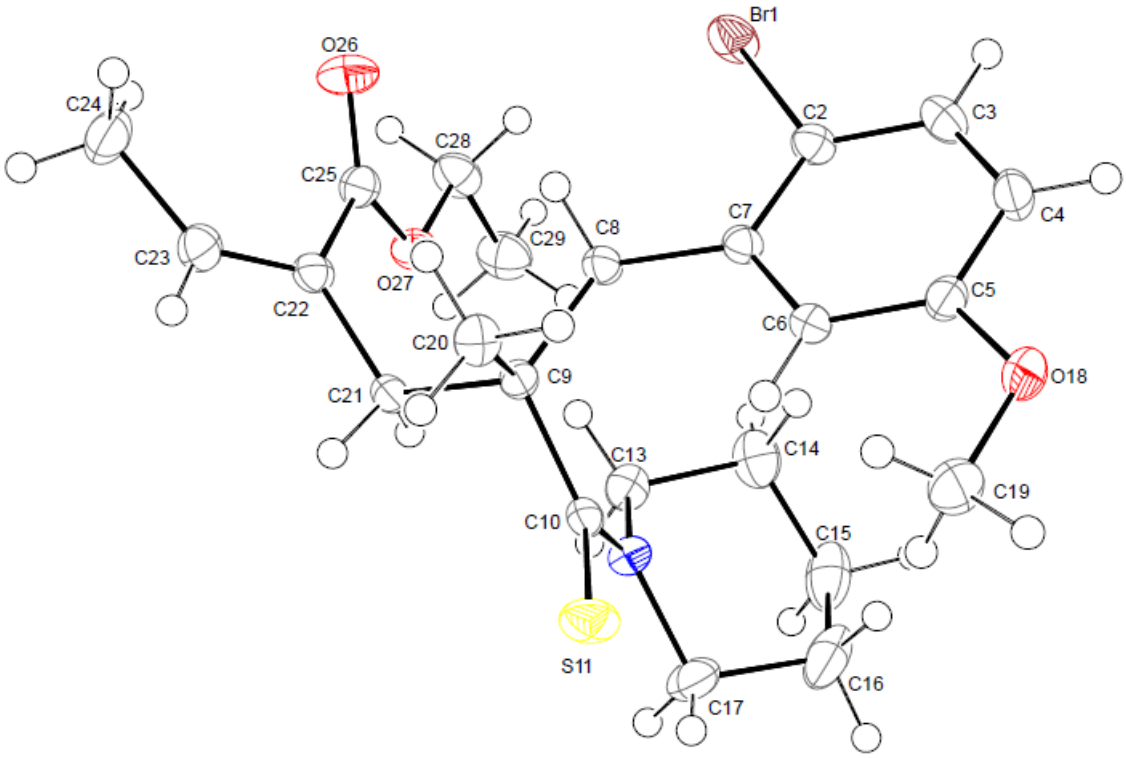


Table 1. Crystal data and structure refinement for 7284.

Identification code	7284	
Empirical formula	C23 H32 Br N O3 S	
Formula weight	482.48	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.6554(3) Å	α= 71.381(3)°.
	b = 10.4415(3) Å	β= 83.115(2)°.
	c = 11.8934(3) Å	γ = 80.784(2)°.
Volume	1118.60(6) $Å^3$	
Z	2	
Density (calculated)	1.432 Mg/m^3	
Absorption coefficient	3.566 mm^{-1}	
F(000)	504	
Crystal size	0.30 x 0.25 x 0.10 mm^3	
Theta range for data collection	3.933 to 76.352°.	
Index ranges	-12<=h<=12, -13<=k<=13, -14<=l<=14	
Reflections collected	20935	
Independent reflections	4625 [R(int) = 0.034]	
Completeness to theta = 74.061°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.70 and 0.41	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4625 / 0 / 262	
Goodness-of-fit on F^2	1.0093	
Final R indices [I>2sigma(I)]	R1 = 0.0268, wR2 = 0.0690	
R indices (all data)	R1 = 0.0276, wR2 = 0.0699	
Largest diff. peak and hole	0.30 and -0.41 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 7284. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Br(1)	5060(1)	9024(1)	2955(1)	30
C(2)	4907(2)	7155(2)	3172(1)	21
C(3)	6119(2)	6236(2)	3399(1)	26
C(4)	6068(2)	4871(2)	3590(1)	25
C(5)	4787(2)	4439(2)	3550(1)	21
C(6)	3581(2)	5377(2)	3292(1)	19
C(7)	3609(2)	6766(2)	3099(1)	18
C(8)	2336(2)	7844(1)	2822(1)	19
C(9)	886(2)	7433(1)	2728(1)	18
C(10)	891(2)	6549(1)	1887(1)	19
S(11)	146(1)	5099(1)	2398(1)	30
N(12)	1420(1)	6993(1)	756(1)	22
C(13)	2051(2)	8255(2)	149(1)	25
C(14)	3607(2)	7920(2)	-194(2)	33
C(15)	3780(2)	7036(2)	-1016(2)	42
C(16)	3011(2)	5796(2)	-465(2)	41
C(17)	1483(2)	6189(2)	-76(2)	32
O(18)	4812(1)	3066(1)	3781(1)	27
C(19)	3516(2)	2579(2)	3777(2)	32
C(20)	343(2)	6710(2)	4009(1)	23
C(21)	-222(2)	8718(1)	2244(1)	19
C(22)	-343(2)	9827(1)	2828(1)	20
C(23)	-1434(2)	10010(2)	3588(1)	25
C(24)	-1766(2)	11093(2)	4191(2)	34
C(25)	739(2)	10784(2)	2489(1)	22
O(26)	1151(1)	11299(1)	3138(1)	33
O(27)	1219(1)	11030(1)	1336(1)	24
C(28)	2286(2)	11954(2)	944(2)	28
C(29)	2643(2)	12149(2)	-352(2)	36

Table 3. Bond lengths [Å] and angles [°] for 7284.

Br(1)-C(2)	1.9129(15)	C(17)-H(171)	0.968
C(2)-C(3)	1.384(2)	C(17)-H(172)	0.961
C(2)-C(7)	1.398(2)	O(18)-C(19)	1.426(2)
C(3)-C(4)	1.378(2)	C(19)-H(191)	0.972
C(3)-H(31)	0.937	C(19)-H(193)	0.950
C(4)-C(5)	1.393(2)	C(19)-H(192)	0.955
C(4)-H(41)	0.931	C(20)-H(202)	0.955
C(5)-C(6)	1.392(2)	C(20)-H(201)	0.960
C(5)-O(18)	1.3679(18)	C(20)-H(203)	0.968
C(6)-C(7)	1.399(2)	C(21)-C(22)	1.5137(19)
C(6)-H(61)	0.939	C(21)-H(211)	0.975
C(7)-C(8)	1.5173(19)	C(21)-H(212)	0.976
C(8)-C(9)	1.5545(19)	C(22)-C(23)	1.334(2)
C(8)-H(82)	0.962	C(22)-C(25)	1.493(2)
C(8)-H(81)	0.960	C(23)-C(24)	1.498(2)
C(9)-C(10)	1.5612(19)	C(23)-H(231)	0.941
C(9)-C(20)	1.5382(19)	C(24)-H(242)	0.942
C(9)-C(21)	1.5719(19)	C(24)-H(241)	0.952
C(10)-S(11)	1.6837(15)	C(24)-H(243)	0.946
C(10)-N(12)	1.341(2)	C(25)-O(26)	1.2048(19)
N(12)-C(13)	1.475(2)	C(25)-O(27)	1.3492(19)
N(12)-C(17)	1.4787(19)	O(27)-C(28)	1.4584(18)
C(13)-C(14)	1.523(2)	C(28)-C(29)	1.494(3)
C(13)-H(131)	0.965	C(28)-H(281)	0.992
C(13)-H(132)	0.983	C(28)-H(282)	0.977
C(14)-C(15)	1.525(3)	C(29)-H(291)	0.966
C(14)-H(141)	0.970	C(29)-H(293)	0.964
C(14)-H(142)	0.980	C(29)-H(292)	0.953
C(15)-C(16)	1.519(3)		
C(15)-H(151)	0.981	Br(1)-C(2)-C(3)	117.20(11)
C(15)-H(152)	0.978	Br(1)-C(2)-C(7)	120.07(11)
C(16)-C(17)	1.524(3)	C(3)-C(2)-C(7)	122.73(14)
C(16)-H(161)	0.971	C(2)-C(3)-C(4)	119.86(14)
C(16)-H(162)	0.971	C(2)-C(3)-H(31)	120.6

C(4)-C(3)-H(31)	119.6	H(131)-C(13)-H(132)	108.1
C(3)-C(4)-C(5)	119.12(14)	C(13)-C(14)-C(15)	109.82(15)
C(3)-C(4)-H(41)	120.1	C(13)-C(14)-H(141)	109.1
C(5)-C(4)-H(41)	120.7	C(15)-C(14)-H(141)	110.8
C(4)-C(5)-C(6)	120.51(14)	C(13)-C(14)-H(142)	108.6
C(4)-C(5)-O(18)	115.73(13)	C(15)-C(14)-H(142)	111.4
C(6)-C(5)-O(18)	123.77(14)	H(141)-C(14)-H(142)	107.1
C(5)-C(6)-C(7)	121.29(13)	C(14)-C(15)-C(16)	110.61(15)
C(5)-C(6)-H(61)	119.3	C(14)-C(15)-H(151)	108.7
C(7)-C(6)-H(61)	119.4	C(16)-C(15)-H(151)	109.3
C(6)-C(7)-C(2)	116.46(13)	C(14)-C(15)-H(152)	109.4
C(6)-C(7)-C(8)	124.16(13)	C(16)-C(15)-H(152)	108.4
C(2)-C(7)-C(8)	119.39(13)	H(151)-C(15)-H(152)	110.5
C(7)-C(8)-C(9)	120.14(12)	C(15)-C(16)-C(17)	111.89(15)
C(7)-C(8)-H(82)	107.2	C(15)-C(16)-H(161)	109.3
C(9)-C(8)-H(82)	105.8	C(17)-C(16)-H(161)	108.2
C(7)-C(8)-H(81)	107.2	C(15)-C(16)-H(162)	110.8
C(9)-C(8)-H(81)	109.5	C(17)-C(16)-H(162)	108.5
H(82)-C(8)-H(81)	106.1	H(161)-C(16)-H(162)	108.0
C(8)-C(9)-C(10)	115.48(11)	C(16)-C(17)-N(12)	109.85(15)
C(8)-C(9)-C(20)	106.09(11)	C(16)-C(17)-H(171)	109.5
C(10)-C(9)-C(20)	111.91(12)	N(12)-C(17)-H(171)	108.2
C(8)-C(9)-C(21)	111.65(11)	C(16)-C(17)-H(172)	111.3
C(10)-C(9)-C(21)	105.08(11)	N(12)-C(17)-H(172)	108.8
C(20)-C(9)-C(21)	106.35(11)	H(171)-C(17)-H(172)	109.2
C(9)-C(10)-S(11)	119.18(10)	C(5)-O(18)-C(19)	117.47(12)
C(9)-C(10)-N(12)	119.52(12)	O(18)-C(19)-H(191)	106.7
S(11)-C(10)-N(12)	121.20(11)	O(18)-C(19)-H(193)	110.1
C(10)-N(12)-C(13)	128.50(12)	H(191)-C(19)-H(193)	109.7
C(10)-N(12)-C(17)	122.11(13)	O(18)-C(19)-H(192)	110.4
C(13)-N(12)-C(17)	109.36(13)	H(191)-C(19)-H(192)	110.6
N(12)-C(13)-C(14)	110.37(13)	H(193)-C(19)-H(192)	109.3
N(12)-C(13)-H(131)	111.5	C(9)-C(20)-H(202)	111.1
C(14)-C(13)-H(131)	111.3	C(9)-C(20)-H(201)	108.0
N(12)-C(13)-H(132)	106.0	H(202)-C(20)-H(201)	109.1
C(14)-C(13)-H(132)	109.3	C(9)-C(20)-H(203)	111.3

H(202)-C(20)-H(203)	108.3	H(242)-C(24)-H(243)	107.5
H(201)-C(20)-H(203)	108.9	H(241)-C(24)-H(243)	107.7
C(9)-C(21)-C(22)	116.43(11)	C(22)-C(25)-O(26)	125.69(14)
C(9)-C(21)-H(211)	109.8	C(22)-C(25)-O(27)	111.73(12)
C(22)-C(21)-H(211)	109.0	O(26)-C(25)-O(27)	122.59(14)
C(9)-C(21)-H(212)	106.6	C(25)-O(27)-C(28)	114.71(12)
C(22)-C(21)-H(212)	106.6	O(27)-C(28)-C(29)	107.19(13)
H(211)-C(21)-H(212)	108.1	O(27)-C(28)-H(281)	108.0
C(21)-C(22)-C(23)	121.29(14)	C(29)-C(28)-H(281)	111.6
C(21)-C(22)-C(25)	119.00(13)	O(27)-C(28)-H(282)	108.1
C(23)-C(22)-C(25)	119.61(14)	C(29)-C(28)-H(282)	112.9
C(22)-C(23)-C(24)	128.53(16)	H(281)-C(28)-H(282)	108.8
C(22)-C(23)-H(231)	115.3	C(28)-C(29)-H(291)	110.1
C(24)-C(23)-H(231)	116.1	C(28)-C(29)-H(293)	111.7
C(23)-C(24)-H(242)	109.2	H(291)-C(29)-H(293)	108.4
C(23)-C(24)-H(241)	113.2	C(28)-C(29)-H(292)	108.7
H(242)-C(24)-H(241)	110.2	H(291)-C(29)-H(292)	106.7
C(23)-C(24)-H(243)	108.9	H(293)-C(29)-H(292)	111.1

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7284. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Br(1)	25(1)	22(1)	42(1)	-7(1)	-9(1)	-8(1)
C(2)	20(1)	20(1)	22(1)	-5(1)	-3(1)	-4(1)
C(3)	17(1)	32(1)	29(1)	-8(1)	-4(1)	-4(1)
C(4)	19(1)	28(1)	28(1)	-9(1)	-5(1)	4(1)
C(5)	23(1)	19(1)	20(1)	-8(1)	-2(1)	1(1)
C(6)	18(1)	20(1)	21(1)	-8(1)	-4(1)	-2(1)
C(7)	18(1)	20(1)	16(1)	-6(1)	-3(1)	-2(1)
C(8)	18(1)	17(1)	23(1)	-7(1)	-4(1)	-2(1)
C(9)	17(1)	15(1)	22(1)	-6(1)	-2(1)	-2(1)
C(10)	16(1)	18(1)	26(1)	-8(1)	-6(1)	1(1)
S(11)	33(1)	21(1)	38(1)	-9(1)	-7(1)	-11(1)
N(12)	23(1)	22(1)	26(1)	-12(1)	-4(1)	-2(1)
C(13)	27(1)	23(1)	22(1)	-6(1)	-2(1)	-1(1)
C(14)	28(1)	35(1)	29(1)	-4(1)	3(1)	-3(1)
C(15)	39(1)	48(1)	30(1)	-11(1)	5(1)	11(1)
C(16)	52(1)	35(1)	34(1)	-17(1)	-2(1)	13(1)
C(17)	41(1)	32(1)	31(1)	-20(1)	-7(1)	0(1)
O(18)	27(1)	19(1)	37(1)	-11(1)	-6(1)	3(1)
C(19)	33(1)	21(1)	45(1)	-12(1)	-4(1)	-4(1)
C(20)	23(1)	21(1)	24(1)	-5(1)	-1(1)	-3(1)
C(21)	15(1)	18(1)	24(1)	-7(1)	-4(1)	-1(1)
C(22)	20(1)	17(1)	22(1)	-6(1)	-6(1)	0(1)
C(23)	24(1)	25(1)	24(1)	-8(1)	-5(1)	2(1)
C(24)	36(1)	36(1)	33(1)	-18(1)	-5(1)	10(1)
C(25)	23(1)	17(1)	27(1)	-8(1)	-6(1)	1(1)
O(26)	42(1)	32(1)	33(1)	-15(1)	-5(1)	-15(1)
O(27)	25(1)	21(1)	27(1)	-8(1)	-2(1)	-8(1)
C(28)	27(1)	24(1)	34(1)	-6(1)	-4(1)	-8(1)
C(29)	34(1)	40(1)	34(1)	-9(1)	0(1)	-14(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 7284.

	x	y	z	U(eq)
H(31)	6976	6533	3427	32
H(41)	6882	4249	3742	30
H(61)	2730	5069	3258	23
H(131)	1911	8862	629	29
H(132)	1551	8705	-576	30
H(141)	4005	8762	-581	40
H(142)	4092	7457	534	39
H(151)	4786	6736	-1147	49
H(152)	3383	7565	-1772	50
H(161)	3475	5199	230	48
H(162)	3028	5287	-1023	50
H(171)	990	6749	-765	39
H(172)	1019	5397	310	38
H(191)	3715	1593	3977	47
H(193)	2848	2816	4356	48
H(192)	3151	2961	3011	47
H(202)	-558	6432	4027	34
H(201)	261	7338	4459	35
H(203)	985	5911	4377	35
H(211)	-34	9113	1388	23
H(212)	-1139	8392	2384	21
H(231)	-2088	9383	3751	30
H(242)	-2738	11400	4187	53
H(241)	-1244	11842	3840	52
H(243)	-1549	10710	4995	53
H(281)	1884	12824	1096	35
H(282)	3092	11549	1421	34
H(291)	3374	12732	-646	53
H(293)	1838	12556	-810	54
H(292)	3017	11289	-456	53

H(82)	2191	8271	3441	23
H(81)	2586	8534	2103	24

Table 6. Hydrogen bonds for 7284 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(6)-H(61)...C(10)	0.94	2.53	3.123(2)	121
C(21)-H(211)...C(13)	0.98	2.57	3.221(2)	125
C(24)-H(243)...O(26)#1	0.95	2.54	3.404(2)	152

Single crystal X-ray diffraction for 369

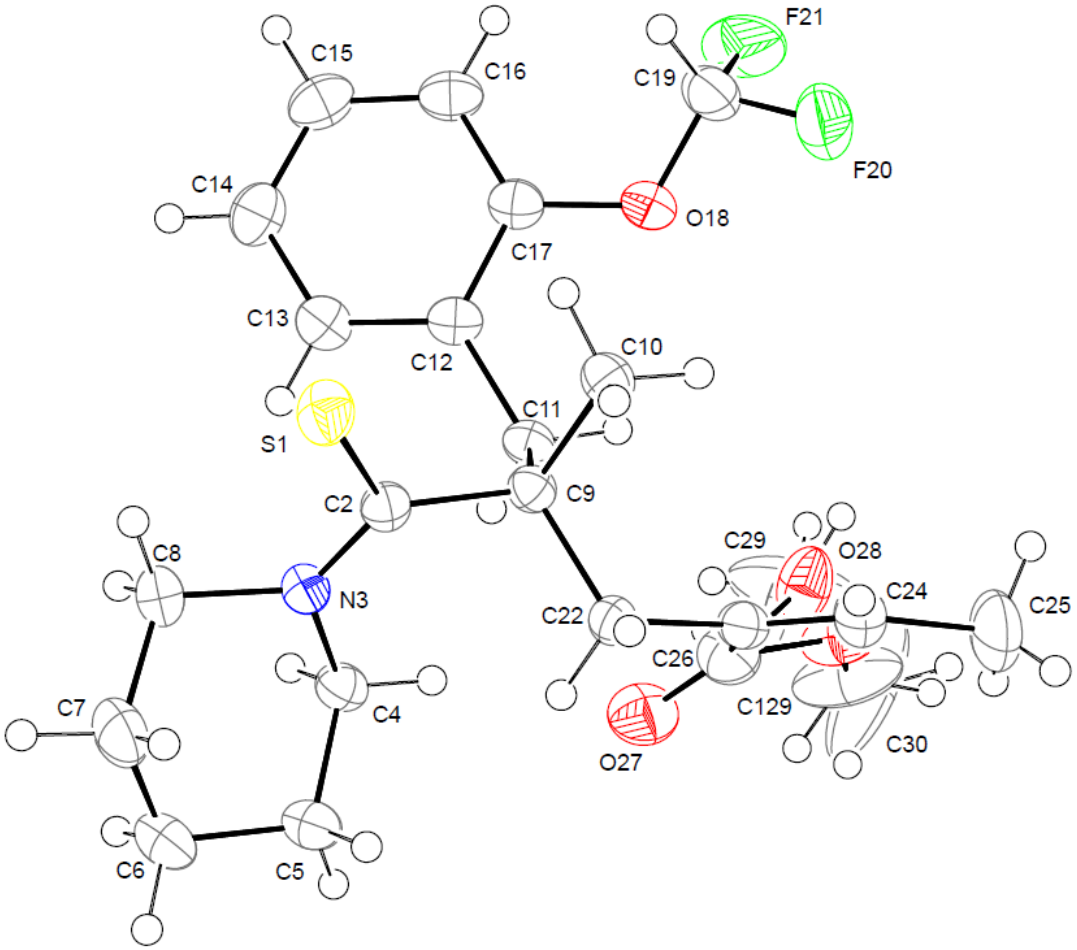


Table 1. Crystal data and structure refinement for 7312.

Identification code	7312	
Empirical formula	C23 H31 F2 N O3 S	
Formula weight	439.57	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 12.0273(3) Å	α= 90°.
	b = 17.2815(3) Å	β= 118.262(3)°.
	c = 12.3604(3) Å	γ = 90°.
Volume	2262.85(11) $Å^3$	
Z	4	
Density (calculated)	1.290 Mg/m^3	
Absorption coefficient	1.615 mm^{-1}	
F(000)	936	
Crystal size	0.32 x 0.04 x 0.02 mm^3	
Theta range for data collection	4.226 to 76.241°.	
Index ranges	-15<=h<=15, -21<=k<=21, -14<=l<=15	
Reflections collected	27871	
Independent reflections	4707 [R(int) = 0.033]	
Completeness to theta = 74.717°	99.8 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.97 and 0.85	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4706 / 129 / 299	
Goodness-of-fit on F^2	0.9919	
Final R indices [I>2sigma(I)]	R1 = 0.0443, wR2 = 0.1088	
R indices (all data)	R1 = 0.0501, wR2 = 0.1141	
Largest diff. peak and hole	0.77 and -0.51 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 7312. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	5000(1)	3048(1)	12092(1)	36
C(2)	4658(2)	2461(1)	10891(1)	26
N(3)	3659(1)	1987(1)	10470(1)	28
C(4)	3318(2)	1347(1)	9574(2)	30
C(5)	3419(2)	577(1)	10220(2)	38
C(6)	2578(2)	567(1)	10836(2)	49
C(7)	2840(2)	1270(1)	11662(2)	48
C(8)	2756(2)	2009(1)	10965(2)	37
C(9)	5467(2)	2498(1)	10218(1)	25
C(10)	6494(2)	3122(1)	10772(2)	30
C(11)	4611(2)	2730(1)	8844(1)	26
C(12)	3907(2)	3489(1)	8656(1)	28
C(13)	2759(2)	3521(1)	8675(2)	32
C(14)	2079(2)	4207(1)	8451(2)	38
C(15)	2532(2)	4875(1)	8183(2)	40
C(16)	3661(2)	4862(1)	8139(2)	37
C(17)	4338(2)	4176(1)	8386(2)	31
O(18)	5465(1)	4119(1)	8329(1)	37
C(19)	6135(2)	4773(1)	8450(2)	44
F(20)	7347(1)	4553(1)	8902(2)	68
F(21)	5806(2)	5074(1)	7338(2)	75
C(22)	6186(2)	1715(1)	10386(2)	27
C(23)	6806(2)	1608(1)	9580(2)	31
C(24)	8051(2)	1653(1)	10032(2)	42
C(25)	8839(3)	1497(2)	9406(3)	69
C(26)	5930(2)	1356(1)	8308(2)	43
O(27)	4981(2)	999(1)	8031(1)	50
O(28)	6117(3)	1717(2)	7405(3)	50
C(29)	5232(3)	1546(3)	6115(3)	72
C(30)	5652(5)	931(5)	5643(5)	141
O(128)	6523(5)	1392(2)	7604(4)	53

C(129)	5894(7)	1070(3)	6402(5)	84
C(130)	4978(9)	1590(4)	5528(6)	130

Table 3. Bond lengths [Å] and angles [°] for 7312.

S(1)-C(2)	1.6806(16)	C(15)-C(16)	1.385(3)
C(2)-N(3)	1.339(2)	C(15)-H(151)	0.946
C(2)-C(9)	1.553(2)	C(16)-C(17)	1.388(3)
N(3)-C(4)	1.479(2)	C(16)-H(161)	0.941
N(3)-C(8)	1.477(2)	C(17)-O(18)	1.394(2)
C(4)-C(5)	1.528(2)	O(18)-C(19)	1.354(2)
C(4)-H(41)	0.968	C(19)-F(20)	1.346(3)
C(4)-H(42)	0.982	C(19)-F(21)	1.342(3)
C(5)-C(6)	1.527(3)	C(19)-H(191)	0.972
C(5)-H(51)	0.978	C(22)-C(23)	1.512(2)
C(5)-H(52)	0.973	C(22)-H(221)	0.977
C(6)-C(7)	1.520(3)	C(22)-H(222)	0.957
C(6)-H(61)	0.978	C(23)-C(24)	1.330(3)
C(6)-H(62)	0.969	C(23)-C(26)	1.485(3)
C(7)-C(8)	1.518(3)	C(24)-C(25)	1.504(3)
C(7)-H(71)	0.987	C(24)-H(241)	0.952
C(7)-H(72)	0.972	C(25)-H(253)	0.945
C(8)-H(81)	0.982	C(25)-H(252)	0.976
C(8)-H(82)	0.999	C(25)-H(251)	0.954
C(9)-C(10)	1.535(2)	C(26)-O(27)	1.196(3)
C(9)-C(11)	1.564(2)	C(26)-O(28)	1.387(3)
C(9)-C(22)	1.566(2)	C(26)-O(27)	1.196(3)
C(10)-H(103)	0.975	C(26)-O(128)	1.362(4)
C(10)-H(102)	0.974	O(28)-C(29)	1.468(4)
C(10)-H(101)	0.970	C(29)-C(30)	1.417(5)
C(11)-C(12)	1.518(2)	C(29)-H(291)	0.993
C(11)-H(111)	0.980	C(29)-H(292)	0.979
C(11)-H(112)	0.979	C(30)-H(303)	0.953
C(12)-C(13)	1.393(3)	C(30)-H(302)	0.952
C(12)-C(17)	1.398(2)	C(30)-H(301)	0.950
C(13)-C(14)	1.391(3)	O(128)-C(129)	1.423(5)
C(13)-H(131)	0.939	C(129)-C(130)	1.436(6)
C(14)-C(15)	1.381(3)	C(129)-H(1291)	0.982
C(14)-H(141)	0.947	C(129)-H(1292)	0.966

C(130)-H(1301)	0.973	N(3)-C(8)-H(81)	108.5
C(130)-H(1302)	0.974	C(7)-C(8)-H(82)	108.9
C(130)-H(1303)	0.972	N(3)-C(8)-H(82)	106.8
		H(81)-C(8)-H(82)	110.3
S(1)-C(2)-N(3)	120.76(13)	C(2)-C(9)-C(10)	111.50(13)
S(1)-C(2)-C(9)	119.68(11)	C(2)-C(9)-C(11)	109.56(12)
N(3)-C(2)-C(9)	119.48(14)	C(10)-C(9)-C(11)	106.36(13)
C(2)-N(3)-C(4)	128.84(14)	C(2)-C(9)-C(22)	109.86(12)
C(2)-N(3)-C(8)	121.54(15)	C(10)-C(9)-C(22)	105.71(13)
C(4)-N(3)-C(8)	109.45(14)	C(11)-C(9)-C(22)	113.78(13)
N(3)-C(4)-C(5)	109.53(14)	C(9)-C(10)-H(103)	108.9
N(3)-C(4)-H(41)	111.4	C(9)-C(10)-H(102)	110.8
C(5)-C(4)-H(41)	109.7	H(103)-C(10)-H(102)	108.8
N(3)-C(4)-H(42)	107.3	C(9)-C(10)-H(101)	111.2
C(5)-C(4)-H(42)	110.4	H(103)-C(10)-H(101)	108.6
H(41)-C(4)-H(42)	108.6	H(102)-C(10)-H(101)	108.4
C(4)-C(5)-C(6)	111.27(16)	C(9)-C(11)-C(12)	114.85(13)
C(4)-C(5)-H(51)	109.9	C(9)-C(11)-H(111)	107.5
C(6)-C(5)-H(51)	108.7	C(12)-C(11)-H(111)	108.3
C(4)-C(5)-H(52)	108.4	C(9)-C(11)-H(112)	110.2
C(6)-C(5)-H(52)	109.9	C(12)-C(11)-H(112)	107.5
H(51)-C(5)-H(52)	108.6	H(111)-C(11)-H(112)	108.3
C(5)-C(6)-C(7)	110.52(17)	C(11)-C(12)-C(13)	121.14(15)
C(5)-C(6)-H(61)	110.8	C(11)-C(12)-C(17)	121.86(16)
C(7)-C(6)-H(61)	109.0	C(13)-C(12)-C(17)	116.90(16)
C(5)-C(6)-H(62)	108.0	C(12)-C(13)-C(14)	121.64(17)
C(7)-C(6)-H(62)	109.0	C(12)-C(13)-H(131)	118.8
H(61)-C(6)-H(62)	109.4	C(14)-C(13)-H(131)	119.5
C(6)-C(7)-C(8)	110.75(17)	C(13)-C(14)-C(15)	119.87(18)
C(6)-C(7)-H(71)	110.8	C(13)-C(14)-H(141)	120.0
C(8)-C(7)-H(71)	107.6	C(15)-C(14)-H(141)	120.1
C(6)-C(7)-H(72)	110.7	C(14)-C(15)-C(16)	120.08(17)
C(8)-C(7)-H(72)	108.2	C(14)-C(15)-H(151)	119.7
H(71)-C(7)-H(72)	108.7	C(16)-C(15)-H(151)	120.2
C(7)-C(8)-N(3)	110.37(16)	C(15)-C(16)-C(17)	119.27(17)
C(7)-C(8)-H(81)	111.8	C(15)-C(16)-H(161)	120.3

C(17)-C(16)-H(161)	120.4	O(27)-C(26)-O(28)	119.9(2)
C(12)-C(17)-C(16)	122.21(17)	C(23)-C(26)-O(27)	123.77(18)
C(12)-C(17)-O(18)	115.60(15)	C(23)-C(26)-O(128)	109.9(2)
C(16)-C(17)-O(18)	122.13(16)	O(27)-C(26)-O(128)	124.0(2)
C(17)-O(18)-C(19)	118.57(15)	C(26)-O(28)-C(29)	118.21(10)
O(18)-C(19)-F(20)	106.34(17)	O(28)-C(29)-C(30)	112.38(10)
O(18)-C(19)-F(21)	109.79(18)	O(28)-C(29)-H(291)	108.6
F(20)-C(19)-F(21)	105.73(18)	C(30)-C(29)-H(291)	106.9
O(18)-C(19)-H(191)	113.4	O(28)-C(29)-H(292)	107.8
F(20)-C(19)-H(191)	110.9	C(30)-C(29)-H(292)	107.3
F(21)-C(19)-H(191)	110.3	H(291)-C(29)-H(292)	113.9
C(9)-C(22)-C(23)	115.62(13)	C(29)-C(30)-H(303)	108.8
C(9)-C(22)-H(221)	106.2	C(29)-C(30)-H(302)	108.6
C(23)-C(22)-H(221)	108.6	H(303)-C(30)-H(302)	110.0
C(9)-C(22)-H(222)	110.7	C(29)-C(30)-H(301)	106.0
C(23)-C(22)-H(222)	108.1	H(303)-C(30)-H(301)	111.2
H(221)-C(22)-H(222)	107.4	H(302)-C(30)-H(301)	112.1
C(22)-C(23)-C(24)	121.65(17)	C(26)-O(128)-C(129)	117.94(10)
C(22)-C(23)-C(26)	114.19(15)	O(128)-C(129)-C(130)	112.32(10)
C(24)-C(23)-C(26)	123.74(17)	O(128)-C(129)-H(1291)	112.7
C(23)-C(24)-C(25)	129.2(2)	C(130)-C(129)-H(1291)	107.4
C(23)-C(24)-H(241)	115.9	O(128)-C(129)-H(1292)	108.2
C(25)-C(24)-H(241)	114.9	C(130)-C(129)-H(1292)	104.9
C(24)-C(25)-H(253)	108.6	H(1291)-C(129)-H(1292)	111.2
C(24)-C(25)-H(252)	113.0	C(129)-C(130)-H(1301)	106.8
H(253)-C(25)-H(252)	109.9	C(129)-C(130)-H(1302)	107.9
C(24)-C(25)-H(251)	109.7	H(1301)-C(130)-H(1302)	110.3
H(253)-C(25)-H(251)	106.8	C(129)-C(130)-H(1303)	107.1
H(252)-C(25)-H(251)	108.6	H(1301)-C(130)-H(1303)	112.1
C(23)-C(26)-O(27)	123.77(18)	H(1302)-C(130)-H(1303)	112.3
C(23)-C(26)-O(28)	114.61(18)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 7312. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	38(1)	43(1)	31(1)	-9(1)	19(1)	-5(1)
C(2)	24(1)	27(1)	25(1)	4(1)	10(1)	3(1)
N(3)	27(1)	28(1)	32(1)	2(1)	16(1)	0(1)
C(4)	28(1)	27(1)	31(1)	0(1)	12(1)	-3(1)
C(5)	41(1)	29(1)	46(1)	5(1)	22(1)	-2(1)
C(6)	53(1)	39(1)	67(1)	13(1)	38(1)	-3(1)
C(7)	51(1)	54(1)	54(1)	11(1)	37(1)	0(1)
C(8)	34(1)	40(1)	47(1)	1(1)	27(1)	-2(1)
C(9)	25(1)	25(1)	24(1)	1(1)	11(1)	0(1)
C(10)	27(1)	31(1)	29(1)	-2(1)	12(1)	-5(1)
C(11)	29(1)	25(1)	24(1)	0(1)	11(1)	-2(1)
C(12)	30(1)	27(1)	21(1)	2(1)	8(1)	0(1)
C(13)	29(1)	35(1)	27(1)	4(1)	9(1)	-1(1)
C(14)	30(1)	46(1)	33(1)	1(1)	10(1)	7(1)
C(15)	41(1)	35(1)	35(1)	4(1)	10(1)	11(1)
C(16)	44(1)	28(1)	34(1)	6(1)	15(1)	3(1)
C(17)	35(1)	29(1)	26(1)	2(1)	13(1)	0(1)
O(18)	43(1)	27(1)	48(1)	5(1)	27(1)	-1(1)
C(19)	56(1)	36(1)	54(1)	-6(1)	38(1)	-11(1)
F(20)	53(1)	67(1)	102(1)	-26(1)	51(1)	-17(1)
F(21)	136(2)	45(1)	84(1)	17(1)	85(1)	4(1)
C(22)	26(1)	27(1)	28(1)	3(1)	14(1)	2(1)
C(23)	38(1)	25(1)	37(1)	-1(1)	23(1)	-1(1)
C(24)	41(1)	40(1)	56(1)	-5(1)	32(1)	-3(1)
C(25)	65(2)	71(2)	106(2)	-16(2)	69(2)	-8(1)
C(26)	56(1)	38(1)	41(1)	-11(1)	28(1)	-7(1)
O(27)	53(1)	43(1)	47(1)	-14(1)	18(1)	-10(1)
O(28)	47(2)	73(2)	35(1)	7(1)	24(1)	16(1)
C(29)	41(2)	133(5)	42(2)	-11(2)	20(2)	32(3)
C(30)	65(4)	239(10)	88(4)	-95(6)	10(3)	48(5)
O(128)	101(3)	37(2)	41(2)	5(2)	49(2)	14(2)

C(129)	165(7)	46(3)	44(2)	-1(2)	51(3)	24(4)
C(130)	136(8)	74(5)	87(5)	33(5)	-25(5)	-40(5)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 7312.

	x	y	z	U(eq)
H(41)	3860	1339	9193	34
H(42)	2447	1437	8933	36
H(51)	4292	488	10845	45
H(52)	3168	164	9613	46
H(61)	2720	98	11326	59
H(62)	1706	583	10197	59
H(71)	3697	1243	12368	56
H(72)	2232	1302	11969	56
H(81)	2938	2469	11489	45
H(82)	1893	2048	10244	45
H(103)	6986	3123	10331	43
H(102)	7058	3018	11637	43
H(101)	6127	3631	10702	43
H(111)	5154	2771	8456	31
H(112)	3982	2326	8419	31
H(131)	2428	3063	8819	39
H(141)	1305	4215	8477	45
H(151)	2063	5339	8023	48
H(161)	3963	5313	7939	45
H(191)	6046	5158	8976	52
H(221)	6838	1698	11244	31
H(222)	5634	1285	10253	31
H(241)	8517	1792	10876	51
H(253)	9617	1282	9986	105
H(252)	8426	1153	8700	105
H(251)	9028	1973	9138	104
H(291)	5163	2011	5615	86
H(292)	4430	1386	6071	85
H(303)	5057	857	4800	212
H(302)	6455	1064	5721	212

H(301)	5695	488	6118	212
H(1291)	6478	926	6087	101
H(1292)	5410	629	6421	101
H(1301)	4608	1330	4736	195
H(1302)	5419	2057	5502	195
H(1303)	4359	1693	5803	195

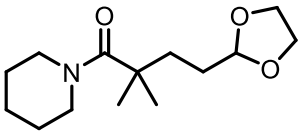
Table 6. Hydrogen bonds for 7312 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
C(4)-H(41)...C(22)	0.97	2.55	3.167(4)	121
C(4)-H(41)...O(27)	0.97	2.46	3.406(4)	165
C(11)-H(112)...C(4)	0.98	2.57	3.204(4)	122
C(15)-H(151)...O(27)#1	0.95	2.45	3.296(4)	149
C(22)-H(222)...C(4)	0.96	2.50	3.167(4)	127
C(130)-H(292)...O(27)	1.20	2.29	3.257(4)	136

5.3 Experimental Details for Chapter 3

5.3.1 Synthesis of starting materials – amides

4-(1,3-Dioxolan-2-yl)-2,2-dimethyl-1-(piperidin-1-yl)butan-1-one (453)



Prepared according to **general procedure F**, using diisopropylamine (367 μL, 2.6 mmol), *n*BuLi in hexane (0.98 mL, 2.5 mmol), 1-isobutyrylpiperidine (397 μL, 2.5 mmol) and 2-(2-bromoethyl)-1,3-dioxolane (431 μL, 3.7 mmol). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) to afford **453** as a light brown oil (533 mg, 85%).

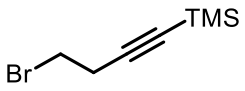
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (t, *J* = 4.1 Hz, 1H, O-C<u>H</u>-O), 3.99 – 3.78 (m, 4H, N-C<u>H$_2$</u>), 3.61 – 3.50 (m, 4H, O-C<u>H$_2$</u>-C<u>H$_2$</u>-O), 1.74 – 1.59 (m, 6H, N-CH$_2$-C<u>H$_2$</u>-C<u>H$_2$</u>), 1.54 (td, *J* = 6.0, 5.2, 3.1 Hz, 4H, NC(O)-C-C<u>H$_2$</u>-C<u>H$_2$</u>), 1.25 (s, 6H, 2 C<u>H$_3$</u>).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.9 (<u>C</u>=O), 104.6 (O-<u>C</u>H-O), 65.0 (2C, O-<u>C</u>H$_2$-<u>C</u>H$_2$-O), 46.3 (brs, 2C, N-<u>C</u>H$_2$), 42.2, 34.6 (NC(O)-C-<u>C</u>H$_2$), 29.7 (O-CH-C<u>H$_2$</u>), 27.1 (2C, 2 <u>C</u>H$_3$), 26.3 (N-CH$_2$-<u>C</u>H$_2$, 2C), 24.9 (N-CH$_2$-CH$_2$-<u>C</u>H$_2$).

HRMS (ESI) $[C_{14}H_{26}O_3N]^+$ requires m/z 256.1907, found m/z 256.1907.

IR (film) ν_{max}/cm^{-1}: 2935, 2360, 1625, 1417, 1209, 1129, 1017.

(4-bromobut-1-yn-1-yl)trimethylsilane (457)



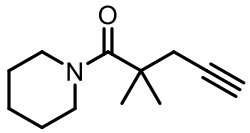
According to literature,[189] to the solution of 4-bromobut-1-yne (1.41 mL, 15.1 mmol, 1.00 eq.) in Et_2O (60 mL, 0.25 M) was added *n*BuLi in hexane (7.22 mL, 18.1 mmol, 1.20 eq.) dropwise at -78 °C under N_2 atmosphere and stirred for 1 h. TMSCl (3.82 mL, 30.1 mmol, 2.00 eq.) was then added and the solution was warmed to room temperature and stirred overnight. The reaction mixture was poured into 120 mL 2 M HCl and extracted 3 times with 50 mL Et_2O. The combined organic phases were dried over MgSO4 and concentrated *in vacuo* to afford the product 457 (1.757 g, 57%) as colourless oil.

Analytical data is consistent with literature.[189]

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (t, *J* = 7.5 Hz, 2H), 2.77 (t, *J* = 7.5 Hz, 2H), 0.16 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 103.3, 87.2, 29.9, 29.3, 24.4 .

2,2-Dimethyl-1-(piperidin-1-yl)pent-4-yn-1-one (460)



Prepared according to **general procedure F**, using diisopropylamine (367 μL, 2.6 mmol), *n*BuLi in hexane (0.98 mL, 2.5 mmol), 1-isobutyrylpiperidine (397 μL, 2.5 mmol) and 3-bromoprop-1-yne (278 μL, 3.7 mmol). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) to afford **460** as a light yellow solid (270 mg, 57%).

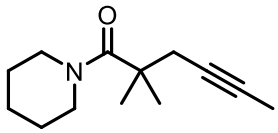
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 – 3.53 (m, 4H, N-C$\underline{H}_2$), 2.53 (d, *J* = 2.7 Hz, 2H, NC(O)-C-C$\underline{H}_2$), 2.01 (t, *J* = 2.7 Hz, 1H, C-C$\underline{H}$), 1.65 (tp, *J* = 7.6, 2.2 Hz, 2H, N-CH_2-CH_2-C$\underline{H}_2$), 1.56 (dq, *J* = 7.9, 5.5 Hz, 4H, N-CH_2-C$\underline{H}_2$-CH_2), 1.38 (s, 6H, 2 C$\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5 (C=O), 82.4 (C≡CH), 70.4 (HC≡C), 46.5 (2C, N-$\underline{C}H_2$), 41.9 (NC(O)-$\underline{C}$), 31.6 (NC(O)-C-$\underline{C}H_2$), 26.3 (N-CH_2-$\underline{C}H_2$, 2C), 25.0 (2C, 2 $\underline{C}H_3$), 24.9 (N-CH_2-CH_2-$\underline{C}H_2$).

HRMS (ESI) $[C_{12}H_{20}ON]^+$ requires m/z 194.1539, found m/z 194.1541.

IR (film) ν_{max}/cm^{-1}: 3311, 2937, 2360, 2341, 1624, 1419, 1252, 1119, 1016, 669.

2,2-Dimethyl-1-(piperidin-1-yl)hex-4-yn-1-one (461)



Prepared according to **general procedure F**, using diisopropylamine (367 μL, 2.6 mmol), *n*BuLi in hexane (0.98 mL, 2.5 mmol), 1-isobutyrylpiperidine (397 μL, 2.5 mmol) and 1-bromobut-2-yne (321 μL, 3.7 mmol). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) to afford **461** as a light brown solid (359 mg, 71%).

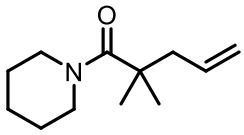
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 – 3.49 (m, 4H, N-C$\underline{H}_2$), 2.46 (q, *J* = 2.6 Hz, 2H, NC(O)-C-C$\underline{H}_2$), 1.79 (t, *J* = 2.6 Hz, 3H, C-C$\underline{H}_3$), 1.70 – 1.61 (m, 2H, N-CH_2-CH_2-C$\underline{H}_2$), 1.61 – 1.52 (m, 4H, N-CH_2-C$\underline{H}_2$-CH_2), 1.33 (s, 6H, 2 C$\underline{H}_3$).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.7 (<u>C</u>=O), 77.7 (<u>C</u>≡C), 76.7 (C≡<u>C</u>), 46.4 (2C, N-<u>C</u>H_2), 42.2 (NC(O)-<u>C</u>), 31.5 (NC(O)-C-<u>C</u>H_2), 26.3 (N-CH_2-<u>C</u>H_2, 2C), 25.4 (2C, 2 <u>C</u>H_3), 24.9 (N-CH_2-CH_2-<u>C</u>H_2).

HRMS (ESI) $[C_{13}H_{22}ON]^+$ requires m/z 208.1696, found m/z 208.1696.

IR (film) ν_{max}/cm^{-1}: 2981, 2360, 2341, 1627, 1418, 1252, 1117, 1011.

2,2-Dimethyl-1-(piperidin-1-yl)pent-4-en-1-one (465)



Prepared according to **general procedure F**, using diisopropylamine (367 μL, 2.6 mmol), *n*BuLi in hexane (0.98 mL, 2.5 mmol), 1-isobutyrylpiperidine (397 μL, 2.5 mmol) and 3-bromoprop-1-ene (317 μL, 3.7 mmol). The crude reaction mixture was purified by flash column chromatography (1/9 Et_2O/pentane) to afford **465** as a light brown solid (329 mg, 69%).

Analytical data is consistent with literature.[190]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 – 5.71 (m, 1H), 5.09 – 5.00 (m, 2H), 3.61 – 3.54 (m, 4H), 2.36 (dt, *J* = 7.2, 1.3 Hz, 2H), 1.70 – 1.60 (m, 2H), 1.56 (qd, *J* = 6.1, 3.1 Hz, 4H), 1.25 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.1, 135.1, 117.6, 46.3, 45.3, 42.3, 26.5, 26.3, 24.9.

HRMS (ESI) $[C_{12}H_{22}ON]^+$ requires m/z 196.1767, found m/z 196.1766.

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