The Total Synthesis of (+)-Waihoensene and Application of the Palladium – catalysed C-H-Activation in the Synthesis of Cyclohepta[b]indoles

Doctoral thesis for obtaining the academic degree
Doctor of Natural Science
(Dr. rer. nat.)

submitted by
Maximilian Häfner

at the

Universität Konstanz

Faculty of Sciences
Department of Chemistry

Konstanz, 2021
Date of the oral examination: 05. November 2021

1. Reviewer: Prof. Dr. Tanja Gaich
2. Reviewer: Prof. Dr. Valentin Wittmann
3. Reviewer: Prof. Dr. Rainer Winter
Meinem Großvater Hans Häfner

und meinen Eltern
„Adsuesce etiam iis, quae fieri posse desperas.“

„Übe dich auch in den Dingen, an denen du verzweifelst.“
Parts of this thesis have been presented at scientific conferences or have been published as scientific articles:

31. Irseer Naturstofftage, Kloster Irsee, 20. – 22.02.2019


Further publications not discussed in this thesis:

Abstract

I.

The total synthesis of (+)-waihoensene (III) is described in the first part of this thesis. In the initial racemic synthetic approach, the intriguing structure of waihoensene (III) was planned to be built up by an intramolecular meta-photocycloaddition. After elaboration of a versatile synthetic access towards the cycloaddition-precursor I, studies on the meta-photocycloaddition are presented.

\[
\text{hv medium pressure mercury lamp} \quad \text{meta-photocycloaddition} \quad \text{waihoensene (III)}
\]

In the second approach, the asymmetric total synthesis of the diterpene (+)-waihoensene (III) was achieved in 19 steps starting from literature-known vinylogous thioester IV. A decarboxylative asymmetric allylic alkylation enabled the construction of key intermediate VI with excellent enantioselectivity. Further elaboration allowed the stereoselective construction of cis-hydrindane VII. The unique tetracyclic carbon skeleton of waihoensene was forged by an intramolecular Pauson-Khand reaction. With the desired carbocyclic framework VIII in hands, three additional steps were needed to eventually afford (+)-waihoensene (III).
II.

The development of a general methodology towards chiral cyclohepta[b]indoles employing a palladium-catalysed cyclopropane C(sp^3)-H activation is described in the second part of this thesis. Enabled by the 8-aminoquinoline directing group, stereospecific introduction of indoles was possible. The methodology was found to be applicable to a huge variety of substituted indoles. Additionally, application of the C-H activation strategy to other aromatic heterocycles is presented.

By divergent elaboration of the C-H activation product XI, two isomeric cyclohepta[b]indole scaffolds XII and XIII can be accessed. The generality of this methodology was further proved by the synthesis of differently substituted representatives.

Furthermore, the application of this methodology towards the total synthesis of the cyclohepta[b]indole natural products exotine A (XVI) and exotine B (XVII) is presented. By altering the alcohol-to-olefin route, the synthesis of key intermediates XV was achieved.
Zusammenfassung

I.

Der erste Teil dieser Arbeit handelt von der Totalsynthese von (+)-Waihoensen (III). In einem ersten racemischen synthetischen Ansatz sollte die carbocyclische Struktur von Waihoensen mittels einer meta-Photocycloaddition aufgebaut werden. Nachdem eine effiziente Route zur Synthese der Cyclisierungsvorläufer (I) entwickelt wurde, werden weitere Versuche zur meta-Photocycloaddition vorgestellt.

II.


![Chemische Struktur und Reaktionsschema](image)

Es war möglich zwei Arten unterschiedlich substituierter Cyclohepta[b]indole XII und XIII durch gezielte Manipulation der Funktionalitäten zu erhalten. Die generelle Anwendbarkeit der Methodik wurde dabei durch die Synthese unterschiedlich substituierter Verbindungen weiter verdeutlicht.

![Syntheseschemata](image)


![Totalsynthese](image)
List of Abbreviations

[α] specific rotation
2D two dimensional
9-BBN 9-borabicyclo[3.3.1]nonane
ABSA p-acetamidobenzenesulfonyl azide
Ac acetyl
acac acetylacetonate
ADME absorption, distribution, metabolism, excretion
ADP adenosine diphosphate
AIBN 2,2′-azobis(2-methylpropionitrile)
Ar aryl
ATP adenosine triphosphate
B.C. Before Christ
b.p. boiling point
Bn Benzyl
Boc tert-butyloxy carbonyl
BOM benzyloxymethyl
BOP-Cl bis(2-oxo-3-oxazolidinyl)phosphinic chloride
brsm based on recovered starting material
calcd. calculated
cat. catalytic
Cbz benzyloxy carbonyl
CDI carbonyldiimidazole
CDP-MEP 4-diphosphocytidyl-2-C-methyl-D-erythritol 2-phosphate
CGRP calcitonin gene-related peptide
COSY correlation spectroscopy
Cp cyclopentadienyl
CuTC copper(I) thiophene-2-carboxylate
Cy cyclohexyl
DAAA decarboxylative asymmetric allylic alkylation
dba dibenzylideneacetone
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DCC dicyclohexylcarbodiimide
DCE 1,2-dichloroethane
DCM methylene chloride
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEG diethylene glycol
DFT density functional theory
DiBAL-H diisobutylaluminium hydride
DIPA diisopropylamine
DIPEA diisopropylethylamine
DMAP 4-dimethylaminopyridine
DMAPP dimethylallyl pyrophosphate
DMF N,N-dimethylformamide
DMP Dess–Martin periodinane
DMPU N,N′-dimethylpropyleneurea
DMSO dimethylsulfoxide
DMTr dimethoxytrityl
DOXP 1-deoxy-D-xylulose-5-phosphate
dppf 1,1′-Bis(diphenylphosphino)ferrocene
DVCPR divinylcyclopropane rearrangement
DXR 1-deoxy-D-xylulose-5-phosphate reductoisomerase
DXS 1-deoxy-D-xylulose-5-phosphate synthase
 e.g. *exempli gratia*
EA ethyl acetate
ED50 median effective dose
EDG electron donating group
ee enantiomeric excess
EI electron ionisation
ESI electrospray ionisation
Et ethyl
*et al.* *et alii*
EWG electron withdrawing group
FGI functional group interconversion
FGPP farnesylgeranyl pyrophosphate
FPP farnesyl pyrophosphate
GGPP geranylgeranyl pyrophosphate
GPP geranyl pyrophosphate
HG-II second generation Hoveyda–Grubbs catalyst
HMBC heteronuclear multiple bond correlation spectroscopy
HMBPP  (E)-4-hydroxy-3-methylbut-2-enyl pyrophosphate
HMG   hydroxy-3-methylglutaryl
HMPA  hexamethylphosphoramide
HPLC  high performance liquid chromatography
HR-MS high resolution mass spectrometry
HSQC  heteronuclear single quantum correlation spectroscopy
HWE-reaction  Horner-Wadsworth-Emmons reaction
hv    light irradiation
IBX   2-iodoxybenzoic acid
IC$_{50}$ half maximal inhibitory concentration
Ile   isoleucine
IPP   isopentenyl pyrophosphate
i-Pr  iso-propyl
IR    infrared spectroscopy
$J$   coupling constant
KHMDS potassium bis(trimethylsilyl)amide
LD$_{50}$ median lethal dose
LDA   lithium $N,N$-diisopropylamide
LiHMDS lithium bis(trimethylsilyl)amide
LiTMP lithium 2,2,6,6-tetramethylpiperidide
$meta$ meta
$m$-CPBA $meta$-chloroperoxybenzoic acid
Me    methyl
MeOH  methanol
MEP   2C-Methyl-$d$-erythritol-4-phosphate
MIC   minimum inhibitory concentration
MMTr  monomethoxytrityl
MOM   methoxymethyl
Ms    methylsulfonyl
MVA   mevalonate
NADPH nicotinamide adenine dinucleotide phosphate
NaHMDS sodium bis(trimethylsilyl)amide
NBS   $N$-bromosuccinimide
$n$-BuLi $n$-butyllithium
NEt$_3$ triethylamine
XIV
NHQ 8-aminoquinoline
NIS N-iodosuccinimide
NMO N-methylmorpholine N-oxide
NMR nuclear magnetic resonance
NOESY nuclear overhauser enhancement spectroscopy
Nu nucleophile
o ortho
OAc acetate
p para
p-BQ 1,4-benzoquinone
PDC pyridinium dichromate
PE petroleum ether
PG Protecting group
Ph phenyl
PhMe toluene
PIDA (diacetoxyiodo)benzene
Pin pinacolate
Piv pivaloyl
PKR Pauson-Khand reaction
PMB p-methoxybenzyl
pmdba p-methoxydibenzylideneacetone
PPTS pyridinium para-toluenesulfonate
pyr pyridine
quant. quantitative
r.t.; RT room temperature
Rf retardation factor
SIRT1 Sirtuin 1
t time
T temperature
T3P propylphosphonic anhydride
TBAF tetra(n-butyl)ammonium fluoride
TBDPS tert-butyldiphenylsilyl
TBS tert-butyldimethylsilyl
t-Bu tert-butyl
TCDI thiocarboxyldiimidazole
Teoc 2-(trimethylsilyl)ethoxycarbonyl
Tf trifluoromethylsulfonyl
TFA trifluoroacetic acid
TFE 2,2,2-trifluoroethanol
THF tetrahydrofuran
TIPS triisopropylsilyl
TLC thin layer chromatography
TMANO trimethylamine N-oxide
TMDS 1,1,3,3-tetramethyldisiloxane
TMM trimethylenemethane
TMS trimethylsilyl
TON turnover number
TPAP tetrapropylammonium perruthenate
Trt trityl; triphenylmethyl
Ts p-toluenesulfonyl
UV-Vis ultraviolet – visible (light)
Val valine
δ chemical shift
# Table of Contents

Abstract ................................................................................................................................. VIII
Zusammenfassung ................................................................................................................... X
List of Abbreviations ........................................................................................................... XII
Table of Contents ................................................................................................................ XVII

I The Total Synthesis of (+)-Waihoensene ........................................................................ 1

1. Introduction ....................................................................................................................... 2
   1.1 Natural Products and Total Synthesis ........................................................................ 2
   1.2 Terpene Natural Products ......................................................................................... 4
      1.2.1 Classification of Terpenes .................................................................................. 4
      1.2.2 Terpene Biosynthesis ......................................................................................... 5
   1.3 The Podocarp Triquinane Diterpenoid Waihoensene ............................................... 9
      1.3.1 Triquinane Natural Products .............................................................................. 9
      1.3.2 Isolation and Structural Characterisation of Waihoensene ............................... 10
      1.3.3 Previous Total Syntheses .................................................................................. 12
   1.4 The *meta*-Photocycloaddition Reaction .................................................................. 17
      1.4.1 Mechanistic Aspects .......................................................................................... 17
      1.4.2 The Application of *meta*-Photocycloaddition in Total Synthesis .................... 19
   1.5 The Decarboxylative Asymmetric Allylic Alkylation (DAAA) Reaction .................... 22
      1.5.1 Development of the DAAA reaction ................................................................... 22
      1.5.2 Mechanism of the DAAA reaction ..................................................................... 24
      1.5.3 Application of the DAAA reaction in Total Synthesis ....................................... 27
   1.6. The Pauson-Khand [2+2+1] Cycloaddition Reaction ............................................. 30
      1.6.1 Mechanistic Aspects of the Pauson-Khand Reaction ........................................ 30
      1.6.2 Application of the Pauson-Khand Reaction in Total Synthesis ......................... 33

2. Results and Discussion ..................................................................................................... 35
   2.1 First Approach – the *meta*-Photocycloaddition as Key Step ................................. 35
      2.1.1 Retrosynthetic Analysis ..................................................................................... 35
      2.1.2 Preliminary Studies ......................................................................................... 36
      2.1.3 Test System and Optimisation towards Photo-Precursors ............................... 37
2.2 Second Approach – the Asymmetric Total Synthesis of (+)-Waihoensene .......... 43
  2.2.1 Retrosynthetic Analysis .............................................................................. 43
  2.2.2 Optimisation of the DAAA reaction .......................................................... 44
    2.2.2.1 Synthesis of the DAAA precursor ......................................................... 44
    2.2.2.2 Synthesis of the ANDEN-phenyl Trost ligand ...................................... 45
    2.2.2.3 Scale-up of the DAAA reaction .............................................................. 47
  2.2.3 Synthesis of intermediate 200 ................................................................. 48
  2.2.4 Completion of the Total Synthesis ............................................................ 50

3. Summary ......................................................................................................... 52

II Application of the Palladium – catalysed C-H-Activation in the Synthesis of Cyclohepta[b]indoles ........................................................................................................ 55

1. Introduction ..................................................................................................... 56
  1.1 The Cyclohepta[b]indole Motif in Nature and Chemistry .......................... 56
    1.1.1 Natural Products containing the Cyclohepta[b]indole Motif ................. 57
    1.1.2 Non-natural Derivatives ................................................................. 59
  1.2. Construction of Cyclohepta[b]indoles .......................................................... 60
    1.2.1 Recently Developed Methodologies ...................................................... 60
      1.2.1.1 Construction of Cyclohepta[b]indoles via Cycloaddition Reactions .... 61
      1.2.1.2 Other Methodologies for the Construction of Cyclohepta[b]indoles ..... 65
    1.2.2 Total Synthesis of Cyclohepta[b]indole Natural Products .................. 67
      1.2.2.1 Total Syntheses of Actinophyllic Acid (241) ..................................... 68
      1.2.2.2 Total Synthesis of Exotine A (239) and Exotine B (240) ............... 70
      1.2.2.3 Total Syntheses of Ambigune P (247) .............................................. 72
  1.3 The Palladium – catalysed C(sp^3)-H Activation ....................................... 75
    1.3.1 Development of Palladium – catalysed C(sp^3)-H Activation ............... 76
    1.3.2 Applications of the Palladium – catalysed C(sp^3)-H Activation in Total Synthesis .... 81
      1.3.2.1 Total Syntheses utilising C-H Activation for the Formation of C-C Bonds .... 81
      1.3.2.2 Total Syntheses utilising C-H Activation for the Formation of C-Heteroatom Bonds ........................................................................................................... 86
  1.4 The Divinylcyclopropane–Cycloheptadiene Rearrangement .................... 89

2. Results and Discussion ................................................................................... 92
  2.1 Construction of Cyclohepta[b]indoles via Palladium – catalysed C(sp^3)-H Activation ........................................................................................................ 93
    2.1.1 Synthesis of the Racemic C-H Activation Precursor .............................. 94
2.1.2 Optimisation of the C-H Activation and Removal of the Directing Group ..................98
2.1.3 Asymmetric Synthesis of the C-H Activation Precursor ........................................106
2.1.4 Scope of the C-H Activation and Synthesis of Cyclohepta[b]indoles .....................110
2.2 Studies towards a Total Synthesis of Exotine A and B ...........................................115
2.3 Extension of the C-H Activation Methodology to other Heterocycles .....................123
2.3.1 Cyclohepta[b]-fused Heterocycles in Nature and Medicinal chemistry ...............123
2.3.2 Scope of the C-H Activation with Heterocycles ......................................................124

3. Summary and Outlook ...........................................................................................................127

III Experimental Part ..............................................................................................................130
1. General Details ....................................................................................................................130
2. Analytical Methods ............................................................................................................130
3. Experimental procedures ....................................................................................................132
3.1 The Total Synthesis of (+)-Waihoensene ....................................................................132
  3.1.1 The meta-Photocycloaddition Approach .................................................................132
  3.1.2 The Asymmetric Total Synthesis of (+)-Waihoensene .............................................144
  3.1.3 NMR Spectra .............................................................................................................164
  3.1.4 Chiral HPLC Chromatograms of 116 .................................................................212
  3.1.5 DFT Calculation .........................................................................................................214
3.2 Application of the Palladium – catalysed C-H-Activation in the Synthesis of
  Cyclohepta[b]indoles .............................................................................................................216
  3.2.1 Construction of Cyclohepta[b]indoles via Palladium – catalysed C(sp³)-H Activation 216
    3.2.1.1 Procedures for the Racemic Series .....................................................................216
    3.2.1.2 Procedures for the Asymmetric Series ..............................................................230
  3.2.2 Studies Towards a Total Synthesis of Exotine A and B ........................................269
  3.2.3 Extension of the C-H Activation Methodology to other Heterocycles ................278
  3.2.4 NMR Spectra .............................................................................................................288
  3.2.5 Chiral HPLC Chromatograms of 500 ....................................................................402
  3.2.6 DFT Calculation .........................................................................................................404
  3.2.7 X-ray Crystallography ...............................................................................................406

References ................................................................................................................................415

Danksagung ...............................................................................................................................428
1 The Total Synthesis of (+)-Waihoensene
1. Introduction

1.1 Natural Products and Total Synthesis

A natural product can be defined as an organic compound that is formed by a living organism. Natural products can be roughly categorised into three groups. Primary metabolites comprise all compounds which are directly involved in the growth and development of a cell, like amino acids, carbohydrates and nucleic acids. Polymeric materials that are responsible for cellular structure formation, like proteins or polysaccharides, cover the second group. Secondary metabolites, which are historically referred to as natural products, form the third and probably most structurally diverse group of compounds. They are mainly produced by bacteria, algae, corals, sponges and lower animals and are not inevitably necessary for the living cell itself. Therefore, they were regarded as biologically insignificant and believed to be waste products of the metabolism.

Meanwhile, they were found to have various functions (e.g. as weapons against other organisms, agents for symbiosis, sexual hormones or metal transporting agents), and thus being part of the producer's survival strategies. Since natural products are produced for a specific interaction with another organism, they show a broad spectrum of physiological activities. Humanity harnesses this potential for treatment of diseases and injuries since thousands of years. The use of plants or their extracts as traditional medicines was documented first already 2400 B.C. in ancient Mesopotamia. Since the discovery of the antibiotic penicillin (1) from the mould *Penicillium rubrum* natural products isolated from plants, bacteria or marine organisms have become more and more important in modern medicine (see figure 1). Prominent examples are the anticancer drugs Paclitaxel, Taxol (2), isolated from the bark of the yew tree *Taxus brevifolia*, and Trabectedin, Yondelis (3), isolated from the sea squirt *Ecteinascidia turbinata*.

![Figure 1: Terpene natural products that are used as pharmaceuticals.](image)

The importance of natural products for drug development is reflected by the number of approved drugs derived from them. In the field of cancer treatment, 64.9% of the approved drugs since 1981
are natural products or their synthetically modified relatives, thus generating billions of dollars of annual sales for the pharmaceutical industry.[9]

A main problem of these complex natural products is their availability, as they are often found in low concentrations in their natural sources. For example, it was estimated that 360 000 yew trees per year would be needed for the production of Taxol for cancer treatment solely in the US.[10] Initially, a semisynthetic route from the more readily available 10-deacetylbaccatin-III (isolated from the needles of the European yew) solved the availability issue for Paclitaxel.[11] Nowadays Taxol is produced in ton scale using plant cell fermentation technology.[12] Although not always being suitable for large scale production in pharmaceutical industry, total synthesis is often the method of choice to provide sufficient amounts of material. This is required for initial biological testing, to get insights into structure-activity relationships, to elucidate molecular structures, or to apply and improve new synthetic methodologies.[13, 14] Historically, the begin of total synthesis is marked with Wöhler’s synthesis of urea (4) in 1828 (see figure 2).[15] It is defined as synthesis of a (complex) molecule from simple starting materials. In the beginning of the 20th century, synthesis became more complex with ongoing scientific advancement, like in Robinson’s tropinone (5) synthesis (see figure 2).[16]

![Figure 2: Progress in total synthesis.](image)

With a deeper understanding of the basic principles of organic chemistry (e.g. the Woodward-Hoffmann rules) and development of new synthetic methodologies, total synthesis became a powerful tool to provide access to complex natural products.[17, 18] An outstanding role in 20th century total synthesis was taken by Woodward with his syntheses of complex natural products like steroids (e.g. cortisone (6)[19]), vitamin B12[20, 21] (together with Eschenmoser), or erythromycin A.[22-24] In 1990, Corey won the nobel prize for his development of the concept of retrosynthetic analysis, which became a fundamental tool in synthetic planning.[25] Herein, molecular simplicity is generated by breaking down the target molecule to structurally less complex building blocks, which finally leads to easier or even commercially available starting materials. Main strategies, among others,
are the removal of stereocenters under stereocontrol (e.g. through Woodward-Hoffmann controlled processes), the recognition of substructures that can undergo rearrangements to the target structure (topological strategies), and functional group interchange (FGI) resulting in different reactivity or less complexity.\textsuperscript{[26]} By applying this concept, Corey achieved the synthesis of numerous structurally complex natural products (e.g. gingkolide B (7), see figure 2).\textsuperscript{[27]}

1.2 Terpene Natural Products

Terpenes are the largest group of natural products with an estimated number of 80 000 members\textsuperscript{[28]} that possess high structural variability and complexity. They are found in almost all life forms and have a plethora of biological functions. In the cell membrane, the terpene cholesterol is incorporated to enhance its stability, retinal is responsible for vision in animal eyes, or terpenes occur in plants to attract pollinators or repel herbivores.\textsuperscript{[29]} The term terpene derives from turpentine, a distillate obtained from the resin of pine trees, which contains predominantly monoterpenes like pinene or camphene.\textsuperscript{[30]}

1.2.1 Classification of Terpenes

All terpenes have in common that they are built up from an even number of $(C_5)n$ units derived from isoprene (8). This so called “isoprene rule” or “CS rule” was formulated by Ružička in the 1950’s\textsuperscript{[31]} and accounts for the terpenes to be referred to as “isoprenoids”. Terpenes with more than eight isoprene units are termed as polyterpenes. The isopropyl moiety of the isoprene unit is defined as head, whereas the ethyl part is defined as tail. Usually the isoprene units are connected “head to tail”, except for tri- and tetraterpenes, which have a “tail to tail” connection in the centre. Biosynthetic precursors of all terpenes are isopentenyl-pyrophosphate/IPP (9) and dimethylallylpyrophosphate/DMAPP (10). In nature, isoprenoids occur not only occur as pure linear hydrocarbon chain but rather in cyclised and further functionalised form.
1.2.2 Terpene Biosynthesis

Two different pathways are known for DMAPP/IPP biosynthesis: the mevalonate (MVA) pathway (see scheme 1) and 2C-Methyl-D-erythritol-4-phosphate (MEP) or 1-deoxy-D-xylulose-5-phosphate (DOXP) pathway (see scheme 2). The MVA pathway is common to most eukaryotes, archaea, some eubacteria and also in the plant cytoplasm.\[^{32}\] It serves as feedstock for the biosynthesis of mostly higher isoprenoids, such as dolichol for glycoprotein synthesis, sterols (especially cholesterol needed for membrane structure) or steroid hormones in animals.\[^{33}\] Condensation of two units of acetyl-coenzyme A (11) leads to acetoacetylCoA (12). Another unit of 11 is transferred via the 3-hydroxy-3-methylglutaryl-CoA synthase to form HMG-CoA (13). Reduction by the HMG-CoA reductase using nicotinamide adenine dinucleotide phosphate (NADPH) as hydride source thereby leads to (R)-mevalonic acid (14). This reduction is also the rate-determining step in the MVA pathway, and the reductase is one of the most highly regulated enzymes in nature. 14 is further phosphorylated by two kinases and adenosine triphosphate (ATP) to yield mevalonate pyrophosphate (16). Decarboxylation mediated by the mevalonate pyrophosphate decarboxylase and ATP leads to the formation of IPP (9), which can be isomerised by the IPP isomerase to DMAPP (10).\[^{33-35}\] A group of important drugs targeting the MVA pathway, especially the HMG-CoA...
reductase, are the so-called “statins” (e.g. Pfizer’s atorvastatin, Lipitor\(^6\), annual sales 7 Billion $ in US, 2010), which are potent inhibitors of the reductase.\(^{[36]}\) Thus, the isoprenoid synthesis is blocked and the blood levels of cholesterol, which are associated with cardiovascular diseases, are lowered.\(^{[37]}\)

![Scheme 1: The mevalonate pathway in eukaryotes.](image)

In contrast, the MEP/DOXP pathway (scheme 2) proceeds in bacteria (prokaryotes), some eukaryotic parasites and in the plastids of plants. DMAPP/IPP synthesised by the MEP/DOXP pathway is usually converted to smaller terpenoids, like mono-, sesqui- or diterpenes.\(^{[38]}\) For decades the MVA pathway was believed to be the only source of IPP/DMAPP for isoprenoid synthesis. In the 1980’s, the groups of Rohmer and Lichtenthaler found that \(^{13}\)C labelling experiments in algae and different bacteria led to the formation of terpenoids with a labelling pattern that could not be explained by the known MVA pathway.\(^{[39–41]}\) Combined with the observation of isotope labelled 1-deoxy-\(\alpha\)-xylulose incorporation in the ubiquinone side chain by \textit{Escherichia coli},\(^{[42]}\) the MEP/DOXP pathway was discovered. DOXP (19) is formed by condensation of pyruvate (17) with glyceraldehyde-3-phosphate (18) catalysed by the DOXP synthase (DXS). Hereby, 17 is first activated by the thiamine pyrophosphatase cofactor and is condensed with 18 after decarboxylation. The same enzyme, DOXP reductoisomerase (DXR), catalyses both the isomerisation to the aldehyde erythrose and reduction to erythritol 20. Transfer of cytidyl monophosphate to 20, mediated by the corresponding synthase (CMS), gives diphosphocytidyl-erythritol 21, which is further phosphorylated by a kinase (CMK) and ATP as phosphate source to 4-diphosphocytidyl-2-C-methyl-\(\alpha\)-erythritol 2-phosphate (CDP-MEP, 22). Cyclisation is catalysed by the responsible MCS protein under release of CMP. Subsequently, the obtained cyclophosphate 23 is reduced to (\(E\))-4-hydroxy-3-methylbut-2-enyl pyrophosphate (HMBPP, 24). The isoprene building blocks IPP (9) and DMAPP (10) are formed by oxidoreductase HDR in a fixed ratio of about 5:1 in the last step.\(^{[43, 44]}\) To adjust their ratio to the requirements for further terpene biosynthesis, they can be interconverted by an isomerase in analogy to the MVA pathway.
Even though the IPP (9) and DMAPP (10) synthesis differs in distinct forms of life, the following steps of terpene biosynthesis are the same in all organisms (see scheme 3A): Starting from 9, a prenyltransferase attaches 10 in head-to-tail fashion to yield geranyl pyrophosphate (GPP, 25). This sequence is repeated several times for the higher terpene homologues (farnesyl pyrophosphate, FPP (26); geranylgeranyl pyrophosphate, GGPP (27); farnesylgeranyl pyrophosphate, FGPP (28). For tail-to-tail linked terpenoids, like triterpenes or tetraterpenes, two molecules of 26 or 27 are linked together to yield squalene (29) or phytoene (30), respectively.\(^{45}\)

Scheme 3: Terpene synthesis from IPP/DMAPP and following steps illustrated by paclitaxel.
These linear precursors now serve as starting materials for the complex terpenoids. Their biosynthesis can be separated into two parts by the sets of responsible enzymes: a cyclase phase to build up the core structure and an oxidase phase, where the functionalisation of the terpene core is accomplished (see scheme 3B). Since paclitaxel (2) is one of the best investigated natural products, it serves as an illustrative example for general terpene biosynthesis. Overall 19 enzymatic steps are needed for its biosynthesis starting from the linear diterpene precursor GGPP (27). Initially, the taxadiene synthase is responsible for the cyclisation of 27 to taxadiene (31) via several cationic cyclisation steps. To this core structure, a set of oxidases establish the oxidation pattern and transferases attach the missing parts towards 2.[46]

The physiological functions of terpenes in the human body are generally well understood, like the steroids acting as part of the cell membrane or as hormones.[47] On the contrary, the actual purpose of plant terpenes in nature is less known, merely because of their tremendous number. Volatile plant terpenes, like mono-, sesqui- and diterpenes, are primarily responsible for the interaction of the plant with the environment or for protection against abiotic stress.[48] For example, terpenes in floral scent have an effect in the mutualistic interactions of the plant with its pollinators. Pheromones are often mimicked by the plants to specifically attract one sex of the insect.[49] Yet terpenoids play not only an important role in the plant’s reproduction cycle but are also the main defence mechanism against herbivores and pathogens. On the one hand they act as scents to repel herbivores, and on the other hand terpenes attract parasitic and predatory enemies of exact these.[50] Plants accumulate terpenes in glands or trichomes, from where they are released upon damage of the tissue through herbivores.[51] The released volatiles also act as signalling molecules to neighbouring leaves and plants to induce the defence mechanism there as well.[52] Usually, it is a mixture of different terpenoid compounds synergistically working as defence. Conifer resin is comprised of a mixture of monoterpene olefins (3-carene, α-pinene) and diterpene acids. The volatile monoterpenes are believed to serve as solvent for the diterpene acids, which are toxic to herbivores and polymerise upon oxygen exposure to seal the wound.[53] In addition, monoterpenes are toxins and fungal growth inhibitors as well, but possess high volatility. The evaporation process, however, is assumed to be reduced by the less volatile diterpenes, demonstrating the interactions between different types of terpenes in plant defence.[47, 54]
1.3 The Podocarp Triquinane Diterpenoid Waihoensene

1.3.1 Triquinane Natural Products

Polyquinane natural products form a rather small group of terpenoids with more than 250 known members (see figure 4). Their special feature is that their core-structure consists of annulated 5-membered rings (lat. *quinque* = five) only. Among these, quinanes possessing three 5-membered rings are referred to as triquinanes. Triquinanes can be divided into three subgroups, depending on the mode of ring connection. There are either linear triquinanes, angular triquinanes or propellane-type triquinanes.\(^{[55]}\)

![Triquinane Natural Products](image)

*Figure 4: Classes of triquinane natural products.*

Triquinanes are not only an attractive target for synthetic chemists because of their unique architecture but also possess a broad variety of biological activities. Members of this group show, for example, cytotoxic, antimicrobial or anti-inflammatory activities.\(^{[56]}\) They have been isolated from various organisms including plants, fungi, sponges and soft corals.\(^{[56]}\)
1.3.2 Isolation and Structural Characterisation of Waihoensene

The diterpene (+)-waihoensene (38) was first isolated in 1997 by the Weaver’s group from the foliage of the podocarp tree *podocarpus totara var. waihoensis* (see figure 5). This tree is endemic to the West Coast of New Zealand’s South Island, with its main distribution around the Waiho River, which is fed by the melting water of Franz Josef Glacier. *Podocarpus totara var. waihoensis* is thought to have a hybrid origin from *podocarpus totara* and *podocarpus acutifolius*, but is considered to be an own species. Waihoensene (38) occurred in a level of about 5% of the total amount of isolated diterpenes, but was rather difficult to separate from the other diterpenes, predominantly laurenene (39), rimuene (41) and pimaradiene (42) (see figure 6). Due to its co-occurrence with 39, the only naturally appearing fenestrane, waihoensene (38) is supposed to be produced by an extended biosynthetic pathway thereof. The acid-induced rearrangement of laurenene (39) to 40 emphasises their structural relationship and the probably correlative biosynthetic origin. Despite, neither more details of the biosynthetic pathway nor any biological activity of waihoensene (38) are known.

![Figure 5: Podocarpus totara var. waihoensis. Photographer: Jeremy R. Rolfe, Licence: CC BY](59)

![Figure 6: Diterpenes isolated from podocarpus totara var. waihoensis and rearrangement product 40 of 39.](60)

The structural features of waihoensene (38) are depicted in figure 7. With its three in all-cis fashion fused five-membered rings (highlighted in blue), waihoensene (38) belongs to the group of triquinarine natural products. The relative stereochemistry could be elucidated by 2D NMR experiments and DFT calculation, exhibiting an all-cis orientation of the methyl substituents.
Nevertheless, the absolute stereochemistry could not be determined, but the sample was dextrorotatory.\textsuperscript{[57, 60]} \textbf{38} comprises a very congested tetracyclic structure combined with six contiguous stereogenic centres (black dots), whereof four are pure carbon stereocentres (orange dots). These features and the lack of functional groups, except for an exo-methylene group (highlighted in red), make waihoensene (\textbf{38}) a rather challenging target for organic chemists.\textsuperscript{[62]}
The total synthesis of waihoensene remained an unsolved challenge for about 20 years until in 2017, the group of Hee-Yoon Lee published a first total synthesis of racemic waihoensene (38).\textsuperscript{[63]} They previously established a methodology for the synthesis of polyquinane systems through a tandem [3+2] cycloaddition strategy via a trimethylenemethane (TMM) diyl intermediate, which was also applied to the synthesis of other natural products.\textsuperscript{[64-66]} As shown in scheme 4, this cycloaddition is initialised by the intramolecular cycloaddition of an allenyl diazo compound 43 leading to an diazabicycloheptene 44. Nitrogen is released upon heating, leading to the trimethylenemethane diyl intermediate 55. The radical intermediate subsequently undergoes another intramolecular [2+3] cycloaddition to afford the desired polyquinane structure 46. By altering the substitution pattern of the allene moiety, angular 46a as well as linear quinanes 46b were obtained.

![Scheme 4: Lee’s tandem TMM cycloaddition strategy.\textsuperscript{[64]}](image)

Lee’s synthesis (scheme 5)\textsuperscript{[63]} commenced with ketoester 47, which was first subjected to Takai-Lombardo olefination followed by reduction of the ester to yield alcohol 48. Oxidation and HWE-reaction led to unsaturated ester 49, which was submitted to 1,4-reduction conditions and was selectively reduced to the aldehyde using DiBAL-H. Application of the Corey-Fuchs procedure and \textit{in situ} trapping of the alkyne anion with formaldehyde furnished propargylic alcohol 51. This was further converted to the corresponding tosylate, which was treated with Grignard reagent 57 in the presence of CuCN to give the allene in a \textit{S}_2\text{N}’ reaction. After silyl deprotection, alcohol 52 was oxidised to the corresponding aldehyde using Swern’s conditions. Subsequent treatment with tosyl hydrazide gave the corresponding hydrazone, the precursor for the TMM cycloaddition. Under heating, this reacted with sodium hydride \textit{in situ} to the allenyl diazo compound, which underwent the TMM cycloaddition to the desired core-structure 53 along with some isomers in an inseparable mixture of 3.3 to 1. Oxidation of the allylic position to enone 55 showed to be difficult, resulting in low yields (<22%) using Cornforth reagent and exacerbating the purification. Therefore, a four step...
sequence exhibiting dihydroxylation, tosylation, elimination and allylic transposition/oxidation with 13% overall yield was established. With 55 in hands, the final steps were straightforward. Cuprate addition and enolate alkylation were used to attach the missing two methyl groups to 56. Final methylenation was achieved by use of the Petasis reagent in 32% yield to give (±)-waihoensene (38). Overall, Lee and co-workers needed 21 steps for the longest linear sequence from literature known ketoester 47 to waihoensene with an overall yield <1%.

Scheme 5: Total Synthesis of (±)-waihoensene (38) by Lee.[63]

Recently in spring 2020, two total syntheses of (+)-waihoensene (38) were published contemporaneously by the groups of J. Huang and Z. Yang[67] and S. Snyder.[68] They both chose a similar strategy based on a Conia-Ene/Pauson-Khand reaction sequence (scheme 6) to install the waihoensene carbon skeleton. Chirality was introduced in both cases by asymmetric conjugate addition to an enone.
Huang and Yang accomplished to synthesise (+)-waihoensene in 15 steps and with an overall yield of 3.8% starting from commercially available vinylogous ester 64 and is shown in scheme 7.\textsuperscript{67} Enone generation by addition of 65 was followed by an asymmetric conjugated addition reaction using a phosphoramidite ligand (L1).\textsuperscript{69} In situ trapping with N-(butoxymethyl)-N-ethylethanamine and oxidation with m-CPBA applying Alexakis’ conditions\textsuperscript{70} yielded enone 66 with 91% enantiomeric excess. Allylation of 66 via Sakurai reaction, ozonolysis and Ohira-Bestmann alkynylation furnished diyne 60, which underwent a Conia-ene type cyclisation to Pauson-Khand precursor 59. After testing various reaction conditions, the Pauson-Khand reaction was found to work best under an atmosphere of nitrous oxide to establish the waihoensene core framework 58. Nickel-mediated conjugated addition and acetalisation of the less hindered ketone gave 67, which was subjected to Wittig olefination followed by acetal-deprotection to yield ketone 68. The right stereochemistry of the methyl group on the six-membered ring was established by iron-catalysed hydrogen atom transfer from phenylsilane. Subsequent alkylation completed the substitution pattern in 56 and Wittig reaction finally gave (+)-waihoensene (38).
The Snyder synthesis (Scheme 8){[68]} began similarly to the Huang/Yang approach. Vinylogous ester 68 was treated with Grignard reagent 69 to generate an enone. Chirality was introduced by the aid of Hoveyda’s asymmetric conjugate addition procedure with a chiral N-heterocyclic carbene ligand (L2).[71] Deprotonation of the obtained ketone and reaction of the enolate with Mander’s reagent gave ketoester 63. Deprotection of the alkyne was followed by Toste’s gold(I)-catalysed Conia-ene reaction conditions[72] to quantitatively yield the cis-hydrindane system 62. The exo-methylene group in 62 was hydrogenated to give the β-ketoester as a 3.2 to 1 diastereomeric mixture in favour of the all-cis diastereomer. The ketone was converted to the exo-methylene group in a Wittig reaction, and the ester was reduced with DiBAL-H to give alcohol 70. Nitrile 71 was obtained by a three step sequence comprising of an oxidation, HWE reaction and 1,4-reduction. Reduction to the aldehyde with DiBAL-H and further treatment with Ohira-Bestmann reagent generated Pauson-Khand precursor 61. To build up the triquinane core-structure, enyne 61 was treated with Co₂(CO)₈ under CO – atmosphere in refluxing mesitylene. Cuprate addition gave ketone 72, which was further alkylated and subjected to Wittig conditions to eventually yield the natural product (+)-waihoense (38). Overall 17 steps were needed to complete the synthesis from commercial starting materials with a combined yield of about 1%. 
Scheme 8: Total synthesis of (+)-waihoensene (28) by Snyder.\[^{68}\]
1.4 The meta-Photocycloaddition Reaction

In 1834, the German pharmacist Hermann Trommsdorff found that colourless santonin crystals turned yellow and began to burst when irradiated with sunlight or sunlight’s purple and blue part.[73] Although he did not have the possibilities to further examine the nature of this process, he thereby described the first wavelength dependence of an organic photoreaction.[74] Photochemical transformations play a pivotal role in total synthesis, since they usually proceed with high atom efficiency and stereospecificity. Their most valuable asset is to offer fast access to complex molecular structures that is often difficult or almost impossible to achieve by other methods.[75] Among these transformations, the meta-photocycloaddition is one of the possible reaction modes in arene-alkene cycloaddition (scheme 9), which has been applied in numerous total syntheses of complex natural products.[76] It was chosen as the key transformation in a first approach towards the total synthesis of waihoensene, and therefore mechanistic aspects and selected examples of its application will be discussed in the following section.

Scheme 9: Modes of arene-alkene photocycloaddition.

1.4.1 Mechanistic Aspects

All efforts on the elucidation of the mechanism of a meta-photocycloaddition have been reviewed by Cornelisse in 1993, which lead to the postulation of the current accepted mechanism as shown in scheme 10.[77] The reaction begins with the excitation of the arene part to its first excited singlet state, for which light with a wavelength of 254 nm is required.

Scheme 10: Mechanism of the meta-photocycloaddition.
An alkene and the excited arene form a complex, a so called exciplex (see scheme 10), that could be detected by fluorescence spectroscopy. Via a polarised transition state two new σ-bonds are formed to yield a biradical intermediate in the rate-determining step. Recombination of the two radicals finally leads to the cycloaddition product.

If unsymmetrical substrates are subjected to photocycloaddition conditions, regioselectivity becomes an issue. For the use of an unsymmetrical alkene (case A in scheme 11), two products are possible, because there are two possibilities for the biradical intermediate to recombine. Indeed, irradiation of benzene (73) in the presence of isobutene (74) affords a 1:1 mixture of the cycloaddition products (75).

Regioselectivity gets even more complicated when substitution on the benzene core is considered. A 2,6-addition mode (case B) of the alkene is preferred for electron donating substituents, whereas the 2,4-addition (case C) prevails for electron withdrawing groups. Concerning the stereoselectivity, an endo orientation is favoured over an exo (case D). This can be explained in analogy to the selectivity observed for the Diels-Alder reaction: secondary orbital interactions lower the energy of the endo transition state. For example, Cornelisse et al. observed high endo selectivity in the reaction of anisole (79) with cyclopentene (81).

The first intramolecular meta-photocycloaddition was reported in 1969 when Morrison and Ferree irradiated phenyl-hex-2-ene. For intramolecular reactions, the picture changes since steric effects of the tether and the geometry of the double bond have to be considered (scheme 12). (E)-double bonds were found to react in the anticipated manner of 2,6-addition across the tether, predominantly. When the same molecule with a (Z)-double bond is irradiated, only 1,3-addition takes place. This probably arises from the steric clash between the vinylic methyl group and the tether. The result is favoured formation of the exo-exciplex and therefore the observed 1,3-addition. Nevertheless, double bond geometry is preserved in the product. The presence of an
electron donating group ortho to the tether is generally assumed to direct the regioselectivity in favour of the 1,3-addition.[76]

Scheme 12: Regioselectivity in intramolecular meta-photocycloaddition.

1.4.2 The Application of meta-Photocycloaddition in Total Synthesis

The application of the meta-photocycloaddition in total synthesis has been extensively investigated by the group of Paul Wender, starting with the total synthesis of α-cedrene (92) published in 1981.[85] Naturally, other groups also made significant contributions to this field and the results have been reviewed on several occasions.[76, 86-88]

Wender’s remarkably short synthesis of α-cedrene (92) (with solely four steps, scheme 13) began with the condensation of lithiated arene 88 and ketone 87 to yield photoprecursor 89. Upon irradiation with a medium-pressure mercury lamp, two cycloaddition products (90) were formed as an 1:1 mixture. Treatment with bromine and subsequent debromination with neat tributylstannane interconverted both photoproducts to the same product 91. Final Wolff-Kizhner reduction gave racemic α-cedrene (92).

Scheme 13: Wender’s synthesis of α-cedrene.[85]
Another complex natural product synthesised by the Wender group is the [3.3.3]propellane modhephene (37).\(^{[89]}\) Cycloaddition of vinyl acetate (94) to indan (93) gave a 10:1 mixture in favour of the desired photoisomer 96, caused by the directing effect of the alkyl substitution and the trend towards formation of 3-endo products. Saponification of the ester and oxidation to the ketone with barium manganate was followed by triple methylation to give 97. The cyclopropane in 97 was opened by cuprate 1,5-addition and the enolate was trapped as phosphordiamidate 98. Reductive removal of the phosphordiamidate and partial hydrogenation furnished (±)-modhephene (37).

Scheme 14: Wender’s synthesis of modhephene (37).\(^{[89]}\)

One of the most complex natural products synthesised by *meta*-photocycloaddition, again by the Wender group, is the pure carbon based fenestrane laurenene (39)*\(^{[90]}\), which is believed to be a biosynthetic relative of waihoensene (38).

Scheme 15: Wender’s synthesis auf laurenene (39).\(^{[90]}\)

Tricycle 100 was obtained in a 7-step sequence starting from anthranilic acid (99). Alkylation in α-position to the lactone with homoprenyl iodide and subsequent reduction gave lactol 101. Irradiation in cyclohexane gave exclusively photoproduct 102, when the light was filtered through an acidic aqueous BiCl\(_3\) solution. The occurrence of only one product can be explained by the significantly higher strain in the alternative product.\(^{[90]}\) Cyclopropane opening under Birch
conditions accompanied by lactol reduction furnished diol 103. Deoxygenation was achieved by phosphordiamidate formation and subsequent Birch reduction to yield (±)-laurenene (39).

A last example for demonstration of the enormous efficiency of this transformation is the synthesis of the dioxafenestrane penifulvin A (109) by Gaich and Mulzer.\textsuperscript{[91]} O-tolylacetic acid (104) was converted into racemic penifulvin A (109) in only 5 steps (the enantioselective route took 8 steps). Alkylation of 104 with homoprenyl bromide yielded photoprecursor 105, which furnished, upon irradiation, a 1:1 mixture of angular and linear cycloaddition products in 62% yield. The cyclopropane in 106a was opened via Birch reduction. Ozonolytic cleavage of the double bond and \textit{in situ} cyclisation of the obtained dialdehyde gave lactol 108. Final oxidation with PDC furnished penifulvin A (109) in 14% overall yield.

![Scheme 16: Synthesis of penifulvin A by Gaich and Mulzer.\textsuperscript{[91]}](image-url)
1.5 The Decarboxylative Asymmetric Allylic Alkylation (DAAA) Reaction

Quaternary carbon centres frequently occur in non-racemic biologically active compounds as part of their structural motifs. Since orbital overlap is hard to achieve for such congested stereocentres, their de novo build up is still challenging. However, several catalytic methodologies to build up these carbocentres have been developed so far.[92] One of these methods is the decarboxylative asymmetric allylic alkylation of β–ketoesters. Its main advantages are the easy access to the esters, the formation of carbon dioxide as the only stoichiometric side product and the neutral reaction conditions, which allow a broad substrate scope and provide functional group tolerance.[93] As the DAAA reaction was chosen to introduce chirality in our synthesis of waihoensene (38), its development, mechanism and selected applications in total synthesis are discussed.

1.5.1 Development of the DAAA reaction

The underlying reaction used for DAAA is the Tsuji-Trost reaction. It was first described by Jiro Tsuji et al. in 1965, when the allylation of ethyl malonate with stoichiometric amounts of π–allylpalladium chloride was observed.[94] Only five years later in 1970, the first catalytic examples were reported.[95, 96] As shown in scheme 17, the first step in the catalytic cycle is the coordination of the allyl source by the palladium centre, followed by oxidative addition under formation of a π–allylpalladium complex.

![Scheme 17: Catalytic cycle of the Tsuji-Trost reaction][97]

Soft nucleophiles tend to attack this complex on the allyl ligand, thus reducing the palladium. After decomplexation, the product and the active Pd⁰ species are released. Typical allyl sources are allylic
esters, carbonates or phosphates, whereof the carbonates are the most reactive allyl delivery reagents. A broad variety of CH-acidic compounds can serve as soft nucleophiles in the allylation, especially if they contain two neighbouring electron withdrawing groups. Less CH-acidic compounds, like ketones or esters, are usually applied as their enolates.\[^{97}\]

In the 1980s, the decarboxylative allylic alkylation of \(\beta\)-keto allylesters was reported by the groups of Tsuji and Saegusa.\[^{98,99}\] The main advantage of this transformation is that the allyl source as well as the nucleophile are incorporated into the same starting material. This allows to perform the reaction under neutral conditions, since no additional base needs to be added due to the in situ generation of the ester enolate. The first asymmetric version of the decarboxylative allylic alkylation was published in 2004 by the Tunge group.\[^{100}\] Shortly after, the groups of Stoltz\[^{101}\] and Trost\[^{102}\] published the DAAA of allyl enol carbonates towards cyclic allylated ketones (scheme 18). Stoltz used the \((S)\)-t-Bu-PHOX ligand \((S)\)-112, which was previously described by Helmchen and Pfaltz and already proved useful in Pd-catalysed allylic alkylation.\[^{103}\] In contrary to that, Trost used the previously developed \((R,R)\)-ANDEN-phenyl-Trost ligand \((R,R)\)-113\[^{104}\], which was known at this time to have higher stereoinduction. These applications allowed the first asymmetric synthesis of 2-methyl-2-allylcyclohexanone \(\text{111}\), whereas previous attempts failed due to in situ enolate scrambling.

```
Scheme 18: First DAAA reaction of enol carbonate 110 by Stoltz (left arrow)\[^{101}\] and Trost (right arrow)\[^{102}\].
```

Although enol carbonates and silyl enolethers proved to be reliable substrates in the DAAA reaction, their regioselective preparation remained unreliable and thus scope and synthetic applications were limited.\[^{105}\] This directed the attention back to the \(\beta\)-ketoesters as substrates for the DAAA reaction, since they are easily available with perfect control of regioselectivity. Following this approach, Stoltz reported several examples of DAAA with differently substituted \(\beta\)-ketoesters in high yield and good enantioselectivity (scheme 19, top panel).\[^{106}\] Trost and co-workers applied this methodology to vinylogous (thio)esters, which proved to be versatile masked 1,3-dicarbonyl building blocks. Whereas normal vinylogous esters showed low reactivity, this obstacle was circumvented by employing the corresponding thioesters.\[^{107}\] They assumed this effect to be caused by the poorer orbital overlap of sulphur and carbon, thus enhancing the reactivity of the sulphur
anallogues. Overall, they achieved high yields and excellent enantiosselectivity. Stoltz and co-workers applied their catalyst system to analogous substrates and achieved similar yields, yet slightly lower enantiosselectivity (scheme 19 lower case).

\[ \text{Scheme 19: } \text{DAAA of } \beta\text{-ketoesters by Stoltz}^{[106]} \text{ and of vinylogous thioesters by Trost (A)}^{[107]} \text{ and Stoltz (B).}^{[108, 109]} \]

1.5.2 Mechanism of the DAAA reaction

The exact mechanism of the DAAA reaction is influenced by the ligands, the substrate class, substitution patterns, additives and solvents. In general, as can be seen in scheme 20, the reaction commences with coordination of the olefinic double bond of the allyl precursor by the palladium, triggering the oxidative addition to result in an equilibrium of two allyl complexes 117 & 118.

\[ \text{Scheme 20: General catalytic cycle of the DAAA reaction.} \]
Subsequent decarboxylation is assumed to be facilitated by palladium, either by ionisation of the carboxylate or by coordination to the \( \beta \)-ketogroup.\(^{105, 110}\) Allylation can occur via two different pathways, either following the outer sphere pathway from \( 120 \) or the inner sphere pathway from \( 119 \), to yield the allylated product \( 111 \).

For enol carbonates and \( \beta \)-ketoesters subjected to conditions developed by the Stoltz group, the reaction probably proceeds via an inner sphere mechanism. The two complexes formed after the oxidative addition step, the \( \pi \)–allyl palladium carboxylate \( 117 \) and the corresponding \( \sigma \)–allyl complex \( 118 \), are believed to be in an equilibrium. Since decarboxylation presumably occurs only from the ion pair \( 117 \), the \( \sigma \)–complex \( 118 \) is believed to be a resting state and the decarboxylation is assumed to be the rate-determining step.

\[ 
\text{Scheme 21: Pericyclic transition state with the Pd/PHOX system according to Stoltz.}^{[111]} 
\]

This is supported by a zero-order dependence on substrate concentration, the isolation of a \( \sigma \)–complex and the higher reactivity of carbonates compared to esters. Association of the enolate with the palladium ion and reorganisation of the allyl ligand from a \( \eta^3 \) to \( \eta^1 \) binding mode allows the complex to minimise steric clash. Via a pericyclic transition state \( 121 \) (scheme 21), reductive elimination and C–C bond formation take place to generate the palladium-bound product \( 122 \). In addition, placing the enolate fragment away from the bulky tert-butyl group allows to predict the enantiofacial selectivity.\(^{[111]}\) These postulations have been further supported by DFT calculations by Stoltz and co-workers.\(^{[112]}\)

Studies by the Trost group for their ligand system indicated that here an outer sphere mechanism is more plausible. When they subjected racemic enol carbonate \( 123 \) to their DAAA conditions, they observed excellent kinetic resolution. Coordination of the palladium and following ionisation of the allyl carbonate should occur under inversion of the configuration. Since the product \( 124 \) shows retention of the starting configuration, the alkylation has to occur under inversion, supporting an outer-sphere \( \text{S}_{\text{N}}2 \) mechanism. They observed similar kinetic resolution for the reaction of the \( \text{trans} \)-isomer, which gave them the corresponding \( \text{trans} \)-product, and thus, supported their hypothesis.\(^{[113]}\)
To explain the stereoinduction in the alkylation step, Trost and co-workers designed a cartoon model for better visualisation (see scheme 23)\textsuperscript{[114]} In the course of the DAAA reaction of tetralone enol carbonate \textbf{126}, the formed enolate has two different modes of attacking the chiral complex (cartoon I and II). Herein, attack from the $\text{Si}$-face should be favoured to minimise steric interactions between the phenyl ring of the enolate and the ligand “wall”. For the standard enolate AAA reaction (cartoon III and IV) they suppose that a lithium enolate-LDA aggregate is formed. This would favour the attack from the $\text{Re}$-face to minimise steric interactions and would therefore yield the opposite configuration than for the DAAA reaction\textsuperscript{[113]} This hypothesis is supported by the fact that they achieved highest enantioselectivity with an excess of LDA\textsuperscript{[115]}

\textit{Scheme 22: Kinetic resolution experiment and AAA reaction by Trost}.$^{[113]}$

\textit{Scheme 23: Cartoon model for the DAAA reaction according to Trost}.$^{[113,114]}$
Due to its ability to construct quaternary carbon stereocentres, the DAAA reaction is a versatile tool in natural product total synthesis. The following examples shall illustrate its usefulness in the synthesis of different natural product classes.

The Stoltz group utilised this methodology in the total synthesis of the marine diterpene cyanthiwigin F (134) (scheme 24). Starting from diallyl succinate (128), DAAA precursor 129 was obtained from Dieckmann-condensation and subsequent methylation as a mixture of the racemic cis/trans isomers and the meso form. Treatment of the bis-β-ketoester 129 with Pd(dmba)$_2$ and the (S)-t-Bu-PHOX (112) ligand led to double decarboxylative allylation and constructed two quaternary carbon centres in one single step with over 99% enantiomeric excess. One of the ketones from diketone 130 was converted to the corresponding triflate and was further subjected to Negishi coupling with homoallyl iodide 135. Treatment with second generation Hoveyda-Grubbs catalyst formed the 7-membered ring and addition of vinylboronic acid pinacol ester followed by oxidative workup furnished aldehyde 132. Tert-butyl thiol mediated radical cyclisation constructed the five-membered ring in 133 in the desired fashion. Vinyl triflate formation and palladium mediated cuprate coupling furnished the natural product 134 in 9 steps from diallyl succinate (128).

Scheme 24: Total synthesis of cyanthiwigin F (134) by Stoltz;[116] stereocentres constructed by DAAA in red.
The Lupton group applied Stoltz’ DAAA conditions to carbazolone derivatives (see scheme 25) which allowed the formal synthesis of (+)-kopsihainanine A (139).\textsuperscript{[117]} $\beta$-Ketoester 136 was obtained in 3 steps from commercially available carbazolone 135.\textsuperscript{[118]} DAAA reaction constructed the quaternary carbon centre in high yield and with an enantioselectivity of 94%. Further treatment with formic acid led to hydrolysis of the nitrile to the amide and concomitant Boc deprotection. Subsequent $N$-benzylation afforded intermediate 138, which was a key intermediate in She’s synthesis of rac- kopsihainanine A (139).\textsuperscript{[119]}

![Scheme 25: Lupton’s formal synthesis of (+)-kopsihainanine A (139).\textsuperscript{[117]}](image)

In their total synthesis of the norhasubanan alkaloid stephadiamine (147), Trauner and co-workers\textsuperscript{[120]} initially applied a racemic decarboxylative allylic alkylation (DAA). Carboxylic acid 140 was converted to the corresponding acyl chloride, which yielded tetralone 141 after treatment with aluminium chloride under an ethylene atmosphere. $\alpha$-Alkylation with bromoacetonitrile and enol carbonate formation gave DAA precursor 142. DAA reaction and olefin metathesis with methyl acrylate delivered substrate 143 for base-mediated cyclisation in high yield. Hydrogenation of the conjugated double bond was followed by a base-mediated cyclisation cascade to give tetracycle 144. $N$-Methylation of the amide and reduction of the ester furnished aldehyde 145 as a mixture of diastereomers. Aldol reaction with formaldehyde and benzylic oxidation using DDQ were followed by cyclic ether formation to set up the stephadiamine skeleton. Further 12 steps for functional group interconversion and oxidation/reduction were needed to complete the total synthesis. In order to get access to enantioenriched material, enol carbonate 142 was subjected to DAAA conditions. After extensive screening of various ligands, Trauner and co-workers found DACH-phenyl Trost ligand \textit{(R,R)}-148 to give the best results, although delivering an only moderate enantiomeric excess of 66%. Indeed, recrystallisation of the product 149 proved useful to improve the ee up to 98%, enabling an enantioselective synthesis of stephadiamine (147).
Scheme 26: Total synthesis of stephadiamine (147) by the Trauner group.\textsuperscript{[120]}
1.6. The Pauson-Khand [2+2+1] Cycloaddition Reaction

The [2+2+1] cycloaddition reaction between an alkyne, an alkene and carbon monoxide was first described by Khand and Pauson in 1971 (scheme 27).[121] When treating the cobaltcarbonyl-complexes of acetylene (150) and phenylacetylene with norbornadiene (151) in aromatic and non-aromatic solvents, they observed the formation of new cobalt complexes concomitant with ketone byproducts. Later, they further investigated which organic products were formed in this reaction and could identify cyclopentenone 152.[122]

![Scheme 27: First described Pauson-Khand reaction][121, 122]

In contrast to the initial methodology, requiring equimolar amounts of dicobalt octacarbonyl, various catalytic methodologies were developed using cobalt complexes as well as other transition metals, like titanium, ruthenium, rhodium or iridium.[123] Due to the low regioselectivity for the intermolecular formation of cyclopentenones, the Pauson-Khand reaction is mostly used as its intramolecular version.[124] Since the Pauson-Khand reaction enables fast access to polycyclic structures, it was chosen to construct the triquinane moiety in our waihoensene synthesis. Therefore, mechanistic aspects and applications in natural product synthesis are discussed in this chapter.

1.6.1 Mechanistic Aspects of the Pauson-Khand Reaction

Magnus and co-workers suggested a mechanism based on their synthetic studies towards bicyclo[3.3.0]octenones.[125, 126] Since no intermediates beside the dicobalt – acetylene complex were detectable, Yamanaka and Nakamura conducted a density functional theory study to further determine the reaction pathway.[127] The results essentially confirmed the mechanism previously suggested by Magnus and are depicted in scheme 28. In the outset of the reaction, the alkyne 153 substitutes one carbonyl ligand at each cobalt to generate acetylene complex 155. This reaction is assumed to proceed stepwise via dissociation of a carbonyl ligand, association of the alkyne and final displacement of the second carbonyl ligand.[128, 129] Dissociation of a carbonyl ligand from 155 leads to the coordinatively unsaturated intermediate 156, which coordinates the alkene to form 157 in the next step. Insertion of the alkene is the first C-C bond forming step and is followed by CO
take-up to generate intermediate 158. The migratory insertion of CO is most likely taking place at C-4. In the next step, the acyl complex 159 is coordinatively saturated with carbon monoxide and reductive elimination yields the cobalt-bound product 161. Ligand exchange with another acetylene molecule releases the product cyclopentenone 162 and the starting dicobalt – acetylene complex 155 is re-formed.\[127\]

Scheme 28: Reaction pathway of the PKR by Yamanaka and Nakamura (lowest energy path shown).\[127\]

The regioselectivity of the Pauson-Khand reaction can be explained with alkene complex 157. The olefin tends to coordinate from the less shielded site (maximal distance to R\textsubscript{L}).\[130\] If no coordinating or large substituents are present in the alkene, no regioselectivity is observed for olefin orientation, because of the comparable steric situation at C-3 and C-4.\[131\] Thus, the PKR shows high regioselectivity with respect to the alkyne (larger substituent located α to the carbonyl in the final enone), but lacks selectivity for the alkene.\[130, 131\]

An illustrative example is the reaction of phenylacetylene and 1-octene (164) (scheme 29): the phenyl group occupies exclusively the α-position in the enone, whereas no selectivity is observed for the incorporation of the hexyl substituent.\[132\]
Dissociation of a carbonyl ligand from 155 (scheme 28) is assumed to be the rate-determining step of the reaction, since the loss of the good $\sigma$–donor and $\pi$–acceptor CO in exchange for a weaker olefin $\pi$–acceptor is energetically highly disfavoured (the alkene complex is about 15 kcal/mol higher in energy). Since this intermediate 157 is the thermodynamic maximum of the reaction, it directly reacts further to the enone product upon formation. In the course of that, it was never possible to isolate any intermediate of the PKR except for the alkyne complex.

To overcome the high activation barrier for ligand exchange, the PKR is usually performed at high temperatures. The reaction can be accelerated by the addition of Lewis-basic co-solvents (e.g. DMSO) to stabilise the unsaturated complex, or by working at relatively low carbon monoxide pressure to favour dissociation. A significant reaction rate acceleration was reported independently by Schreiber and Jeong by addition of $N$-amine oxides, like $N$-methylmorpholine oxide (NMO) or trimethylamine $N$-oxide (TMANO), to the reaction mixture. Herein, the free coordination site is formed by oxidation of a carbonyl ligand to carbon dioxide. With this methodology, inter- and intramolecular PKR could be performed at room temperature accompanied by high yields and selectivity. As demonstrated by Schreiber and co-workers (table 1), NMO addition to the PKR of 167 led to a substantial increase in selectivity due to lower reaction temperatures, whereas the overall yield remained in the same range as for the standard conditions.

Table 1: Dependence of PKR selectivity by Schreiber.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Yield (%)</th>
<th>Selectivity (168:169)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeCN, reflux</td>
<td>75</td>
<td>4:1</td>
</tr>
<tr>
<td>MeCN, ultrasound, 45 °C</td>
<td>45</td>
<td>3:1</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$, NMO (6 eq.), r.t.</td>
<td>68</td>
<td>11:1</td>
</tr>
</tbody>
</table>
1.6.2 Application of the Pauson-Khand Reaction in Total Synthesis

One of the earlier applications of the Pauson-Khand reaction in the synthesis of a complex natural product was the Schreiber synthesis of (+)-epoxydictymene (174), as shown in scheme 30.\textsuperscript{[136]} Herein, triflate 171 was obtained after an eight step sequence from commercially available (R)-pulegone (170). Lithiation of alkyne 172 and subsequent coupling with 171 furnished enyne 173 in 74% yield. Formation of the dicobalt-alkyne complex was followed by Lewis-acid mediated Nicholas reaction\textsuperscript{[137]} to yield the precursor 167 for the PKR. Heating 167 in acetonitrile constructed enone 168 in 85% yield (5:1 ratio at C-12). Unfortunately, the stereocenter at C-12 interfered with further elaboration of the enone moiety and thus, another 12 steps were necessary to invert C-12 and finish the total synthesis.

Scheme 30: Total synthesis of (+)-epoxydictymene (174) by Schreiber.\textsuperscript{[136]}

A rather unusual olefin-substrate for the Pauson-Khand reaction was used by Nomura and Mukai in their total synthesis of (±)-8α-hydroxystreptazolone (179) (scheme 31). It was the first report for the application of a 2-oxazolone derivative (an enamine equivalent) in the Pauson-Khand reaction.\textsuperscript{[138]} The synthesis commenced with substitution of the primary alkyl iodide in 175 with 2-oxazolone (180). Acetaldehyde addition to the alkyne anion gave a mixture of two diastereomers 176. Treatment with Co$_2$(CO)$_8$ furnished the precursor for the PKR. Using TMANO and molecular sieves (4 Å) as promoters\textsuperscript{[139]} enabled the reaction to proceed at -10 °C to yield the tricyclic product 177 in 51% yield. MOM-protection and 1,2-reduction of the enone yielded allylic alcohol 178. The natural product (±)-8α-hydroxystreptazolone (179) was obtained in five additional steps and 17% overall yield from iodide 175.
A catalytic variation of the Pauson-Khand reaction was employed by the Baran group in their outstanding synthesis of the diterpene ingenol (186), which is described in scheme 32. The FDA approved 186 as its mebutate (Picato®, 187) as a drug to treat actinic keratosis. The allenic Pauson-Khand precursor was obtained in a five step sequence from commercial (+)-3-carene (181).

Treatment with rhodium carbonyl chloride under an atmosphere of carbon monoxide in xylene provided gram quantities of enone 183 in 72% yield. 1,2-Grignard addition to the enone followed by dihydroxylation of the γ-double bond gave a triol which was subsequently protected as a carbonate to yield 184. Vinylogous pinacol rearrangement of the carbon skeleton occurred upon treatment with Lewis-acid to furnish the product structure in 80% yield. Further elaboration enabled access to ingenol (186) in overall 14 steps and 1.2% combined yield.
2. Results and Discussion

2.1 First Approach – the meta–Photocycloaddition as Key Step

2.1.1 Retrosynthetic Analysis

As outlined in scheme 33, in the first approach towards the total synthesis of waihoensene, a meta–photocycloaddition was chosen as key step to construct the carbocyclic framework of waihoensene (38). This reaction is extremely useful in terms of complexity constructed in one single step and is particularly suited for the construction of triquinane systems, as mentioned in chapter 1.4. Waihoensene (38), bearing an alkene as the only functional handle, was intended to be obtained by Wittig olefination from ketone 56. This ketone should be generated from pentacycle 188 by a sequence of reductive cyclopropane-opening under Birch conditions, olefin hydroboration and oxidation of the resulting alcohol. Pentacycle 188 is the angular product of an intramolecular meta–photocycloaddition of compound 189. Herein, 1,3-addition of the olefin directed by the methyl group on C-2 (marked with blue dots) should furnish the desired waihoensene core structure. The precursor for this transformation would be the product of a sp³-sp²-Suzuki coupling of vinylketone 191 and aryl iodide 190, followed by olefination of the ketone. Vinylketone 191 should be obtained by vinylation of commercially available 2,6-dimethylcyclohexanone (193). Aryl iodide 190 would be the product of a Sandmeyer reaction of 2,6-dimethylaniline (192).

Scheme 33: Retrosynthetic analysis I of waihoensene (38) (disconnections in red).
Preliminary studies towards the total synthesis of waihoensene were already conducted during my master thesis in 2016. One task therein was to establish synthetic access to the photo-precurors for the meta–photocycloaddition (scheme 34). In the course of that, vinylation of commercially available 2,6-dimethylcyclohexanone (193) was achieved using a two-step procedure. Phenylseleno acetaldehyde (195) served as masked vinyl electrophile, a methodology that was developed by Clive and co-workers. Thus, enolate formation was followed by the addition of selenoaldehyde 195 to give the aldol addition product. By further treatment of the obtained selenoalcohol with methanesulfonyl chloride and base, phenylselenyl chloride was eliminated to yield the desired vinylketone 191. Clive and co-workers stated that the formation of one diastereomer was favoured, but did not further determine which one. The cis-isomer was expected to be formed preferentially because of its lower steric interactions compared to the trans-isomer. This expectations were confirmed 1H-NOSY NMR techniques. With vinylketone 194 in hands, the next task was the sp² – sp³ – Suzuki coupling reaction. Conditions developed by Johnson and Brown, employing Pd(dppf)Cl₂ and Ph₃As seemed most promising, since no β-hydride elimination was observed. The organoborane was formed by hydroboration of vinylketone 191 with 9-BBN and could be coupled in high yields with the appropriate aryl iodides. First olefination attempts employing standard Wittig conditions led to equilibration of the tertiary methyl group under the basic reaction conditions. Hence, a mild methodology for methenylation was employed using Mg/TiCl₄-mediated dichloromethane activation developed by Yan and co-workers. However, irradiation of olefins 189 using a photoapparatus with up to 8 x 18 W 254 nm lamps or a 125 W medium pressure mercury lamp showed no formation of any products.

Scheme 34: Synthesis of photo precursors 189 during the Master thesis.
2.1.3 Test System and Optimisation towards Photo-Precursors

Based on the results of the master thesis, the lack of reactivity in the *meta*-photocycloaddition was examined first. On the one hand, the low reactivity could be an intrinsic feature of the compound itself through steric interactions disfavouring the formation of the exciplex transition state. On the other hand, a non-matching light emission of the mercury lamp could also prevent the reaction. In the course of that, a simplified test system was synthesised that should be further subjected to irradiation. *o*-Tolylactic acid (104) was converted to the corresponding methyl ester, reduced to the alcohol with DiBAL-H and re-oxidised to *o*-tolylacetaldehyde (196) with IBX.\[145\] Treatment of aldehyde 196 with allylic Grignard reagents gave low yields of homoallylic alcohols due to the high basicity of these reagents. Indeed, transmetallation to cerium trichloride\[146\] prior to aldehyde addition delivered the desired test compounds 197 in fair to good yields.

![Scheme 35: Test system for the *meta* – photocycloaddition.](image)

The photoreaction was tested (see table 2) in pentane and cyclohexane as solvents and with two different irradiation setups: a) an 18 W low pressure mercury lamp in a quartz photo reactor (about 90% 254 nm emission\[147\]); b) a 120 W medium pressure mercury lamp in a quartz photo reactor (major emission peaks in the UV range at 254, 265, 270, 302 and 313 nm\[147\]). Pentane was degassed *via* freeze-pump-thaw due to its low boiling point, whereas the cyclohexane solution was degassed by constantly passing through nitrogen. Irradiation with the low pressure lamp led to consumption of the starting material, but at a quite low rate. Irradiation times of 24 to 48 h were needed to convert the major part of the test compounds, most probably due to the relatively low power of the lamp. In contrast, the 120 W lamp afforded full consumption of the starting material after 10 to 12 h of irradiation (determined by \(^1\)H-NMR, disappearance of the aromatic signals). Separation of the photoproducts was not possible because of the formation of several isomers (the two photoisomers and additional diastereomers). Decomposition was observed with both lamps, but to a smaller extent for the 18 W lamp due to its lower power.
Table 2: Irradiation of test substrates 197 and acid 105.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Lamp</th>
<th>t [h]</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>197a, 34 mM in pentane</td>
<td>18 W LP</td>
<td>10</td>
<td>little consumption, mostly SM</td>
</tr>
<tr>
<td>2</td>
<td>197a, 26 mM in pentane</td>
<td>18 W LP</td>
<td>30</td>
<td>approx. 50% consumption</td>
</tr>
<tr>
<td>3</td>
<td>197a, 30 mM in cyclohexane</td>
<td>125 W MP</td>
<td>12</td>
<td>full consumption, several isomers</td>
</tr>
<tr>
<td>4</td>
<td>197b, 30 mM pentane</td>
<td>18 W LP</td>
<td>24</td>
<td>approx. 75% consumption</td>
</tr>
<tr>
<td>5</td>
<td>197b, 40 mM cyclohexane</td>
<td>125 W MP</td>
<td>10</td>
<td>full consumption, several isomers</td>
</tr>
<tr>
<td>6</td>
<td>105, 45 mM in pentane</td>
<td>125 W MP</td>
<td>4</td>
<td>approx. 50% consumption</td>
</tr>
<tr>
<td>7</td>
<td>105, 45 mM in pentane</td>
<td>125 W MP</td>
<td>12</td>
<td>full consumption, significant decomposition/polymerisation</td>
</tr>
</tbody>
</table>

However, the suitability of the lamp for the application in a meta-photocycloaddition was proven by the successful synthesis of penifulvin A (109), as shown in scheme 36. Irradiation of carboxylic acid 105 led after 8 to 12 h to full consumption of the starting material, but in drastically lower yield than reported in literature.\[91\] Most probably the prolonged irradiation times (in the literature 1 h with 700 W medium pressure mercury lamp)\[91\] led to decomposition. Approximately 50% (by weight) of decomposed material were obtained, that could not be further characterised. Nevertheless, 120 mg of racemic penifulvin A (109) could be synthesised according to the literature-known procedure.\[91\]


UV-VIS measurements in cyclohexane of the irradiation precursors 105 & 197 were performed to determine the required energy for the $S_0 \rightarrow S_1$ excitation process, which is responsible for the further meta–photocycloaddition. Two absorption maxima at 264 and 272 nm (figure 8) were found (1 nm bathochromic shift for the penifulvin system). This would explain the low conversion with the low pressure mercury lamp (less overlap with emission at 254 nm) and the matching with the medium pressure lamp (emission at 265 and 270 nm). Since the absorption is affected by the substitution pattern of the aromatic system, the previously synthesised system (scheme 34) for the
synthesis of waihoensene (38) should in principle overlap with the medium pressure mercury lamp. This raises the suspicion that the light source is not the reason for the lack of reactivity. A reasonable explanation could be steric interactions that disfavour the exciplex formation.

![UV-VIS spectra](image)

*Figure 8: UV-VIS spectra, only the relevant S₀ → S₁ excitation shown.*

With a new 400 W medium pressure mercury lamp we focused again on the previously developed system. To exclude the influence of the aromatic substitution pattern on the reactivity, different irradiation precursors 189 (see table 3) were synthesised (the eventually missing methyl groups could be introduced on a later stage). Problems with the reproducibility of the Suzuki coupling reaction could be solved by self-preparing the palladium catalyst. More difficulties were observed with the olefination reaction, since the dichloromethane activation method[144] gave only low yields on larger scale. Therefore, other mild methodologies for olefination were tested. Freshly prepared Petasis reagent[148,149] was unreactive in the olefination reaction, giving only traces of product (table 3, entry 1). Modified Wittig olefination (entry 2) through dropwise addition of the pre-formed ylide to the ketone led to equilibration of the tertiary methyl group. Use of fewer equivalents of ylide led to low conversion. Finally, Takai’s improved variant[150] of the very mild Lombardo olefination[151] proved to effectively convert the ketones to the corresponding olefins (entries 3 to 7). It was crucial to use a freshly prepared (or purchased) titanium (IV) chloride solution in dichloromethane, since neat addition led to drastically lower yields.
Prior to irradiation, the UV absorption for the first singlet state excitation was determined by UV-VIS spectroscopy. For the phenyl-substituted system 189c, the absorption maximum lies at ca. 262 nm with a second one at 269 nm. Additional methyl substituents increase the electron density on the aromatic core and cause a slight bathochromic shift, which results in absorption maxima at 264 and 272 nm for the tolyl substituted 189a and at 264 and 271 nm for the mesityl substituted system 189b, respectively. As expected, the anisyl system 189d shows a strong bathochromic shift due to the extension of the π – system (maxima at 272 and 279 nm). As anticipated before, meta–photocycloaddition should–in theory–be possible with these systems and a medium pressure mercury lamp.

### Table 3: Optimisation of the olefination reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cp₂TiMe₂ (1 M in PhMe, 2.2 eq.), Cp₂TiCl₂ (0.06 eq.), PhMe (R = 2-Me, 194a)</td>
<td>80</td>
<td>6</td>
<td>Traces</td>
</tr>
<tr>
<td>2</td>
<td>MePPh₃Br (2.1 eq.), n-BuLi (2.5 M in hexanes, 2.0 eq.), PhH+addition of ylide solution to ketone (R = 2-Me, 194a)</td>
<td>78 to r.t.</td>
<td>12</td>
<td>53% 1:1 d.r. 189a</td>
</tr>
<tr>
<td>3</td>
<td>Zn (9 eq.), CH₂I₂ (5 eq.), TiCl₄ (1 M in CH₂Cl₂, 2 eq.), THF, CH₂Cl₂ 3:1 (R = 2-Me, 194a)</td>
<td>0 to 40</td>
<td>16</td>
<td>75% brsm 189a</td>
</tr>
<tr>
<td>4</td>
<td>Zn (13.5 eq.), CH₂I₂ (7.5 eq.), TiCl₄ (1 M in CH₂Cl₂, 3 eq.), THF, CH₂Cl₂ 3:1 (R = 2-Me, 194a)</td>
<td>0 to r.t.</td>
<td>16</td>
<td>80% 189a</td>
</tr>
<tr>
<td>5</td>
<td>Zn (13.5 eq.), CH₂I₂ (7.5 eq.), TiCl₄ (1 M in CH₂Cl₂, 3 eq.), THF, CH₂Cl₂ 3:1 (R = 2,6-Me₂, 194b)</td>
<td>0 to r.t.</td>
<td>16</td>
<td>70% 189b</td>
</tr>
<tr>
<td>6</td>
<td>Zn (13.5 eq.), CH₂I₂ (7.5 eq.), TiCl₄ (1 M in CH₂Cl₂, 3 eq.), THF, CH₂Cl₂ 3:1 (R = H, 194c)</td>
<td>0 to r.t.</td>
<td>16</td>
<td>64% 189c</td>
</tr>
<tr>
<td>7</td>
<td>Zn (13.5 eq.), CH₂I₂ (7.5 eq.), TiCl₄ (1 M in CH₂Cl₂, 3 eq.), THF, CH₂Cl₂ 3:1 (R = 2-MeO, 194d)</td>
<td>0 to 40</td>
<td>16</td>
<td>82% 189d</td>
</tr>
</tbody>
</table>
With olefins $189$ in hand, photocycloaddition was tried again. To avoid photooxidation processes, the reactant solution was degassed prior to irradiation. The irradiation was stopped after 1, 2, 4 or 8 h. Unfortunately, all attempts for irradiation remained futile with only some degree of decomposition observed after several hours for substrates $189$. In order to exclude problems with the lamp, test substrates $197$ were irradiated. Gratifyingly, meta–photocycloaddition proceeded smoothly within 2 h of irradiation. Compound $199b$ could be isolated in 37% yield together with its photoisomer as a 1:1 mixture (scheme 37). Separation of the isomers was not possible, neither by column chromatography nor preparative TLC nor HPLC.

Scheme 37: meta–photocycloaddition of $197b$. 
However, the linear isomer 199b could be at least enriched by repeating column chromatography to be identified via 2D-NMR (COSY, HSQC and HMBC).

![Diagram of molecule 189b]

*Figure 11: Lowest-energy conformation of 189b based on DFT calculations, performed by M.Sc. Jan Herberger.*

These findings confirmed the assumption that steric reasons are responsible for the lack of reactivity. To illustrate this, the low energy conformer of 189b was calculated by density functional theory (DFT) methods. The two methyl groups are orientated in axial position on the cyclohexane ring and shield the double bond located in pseudo-equatorial position (figure 11). As a result, exciplex formation with the excited aromatic system is disfavoured, since overlap of the arene moiety with the double-bond is suppressed. Therefore, *meta*-photocycloaddition would take place – if at all – only to a small extent.
2.2 Second Approach – the Asymmetric Total Synthesis of (+)-Waihoensene

While the previous attempts towards a total synthesis of waihoensene employing a meta-photocycloaddition as the key transformation step remained fruitless, an alternative synthetic access was developed in the meantime together with M.Sc. Lisa-Catherine Rosenbaum.\textsuperscript{[152]} While she primarily focused on the synthesis of racemic waihoensene, access to a chiral intermediate was established by myself and the asymmetric total synthesis was completed according to the racemic route. The major part of these results were published in “Angewandte Chemie International Edition 2021, 60, 2939 – 2942”.\textsuperscript{[153]}

2.2.1 Retrosynthetic Analysis

The Pauson-Khand reaction is a versatile transformation for the construction of cyclopentenones (see chapter 1.6), which makes it suitable for establishing the waihoensene carbocyclic framework. This led to the following retrosynthetic analysis (scheme 38): Waihoensene (38) could be obtained from cyclopentenone 55 after methylation, organocuprate addition and olefination of the ketone moiety. 55 itself would be the product of an intramolecular Pauson-Khand reaction of enyne 61. The alkyne moiety could be obtained by Ohira-Bestmann alkylation. Construction of the cis-hydrindane should be achieved by a radical cyclisation of enone 200. The C₃ – chain bearing the benzyl ether could be introduced by Stork-Danheiser transposition. Elongation of the allyl substituent by a hydroboration/oxidation sequence followed by Ohira-Bestmann alkylation leads back to vinylogous ester 201. The quaternary stereocentre could be built up by decarboxylative asymmetric allylic alkylation, that eventually originated from commercially available 2-methylcyclohexane-1,3-dione (202).

\textit{Scheme 38: Retrosynthetic analysis II of waihoensene (38) (disconnections in red).}
2.2.2 Optimisation of the DAAA reaction

2.2.2.1 Synthesis of the DAAA precursor

The synthetic route commenced (scheme 39) with the preparation of \(\beta\)-ketoester 115 in three steps from commercially available 2-methylcyclohexane-1,3-dione (202). Conversion to the corresponding vinylogous thioester proceeded smoothly in decagram scale by \textit{in situ} activation with methanesulfonyl chloride followed by thiophenol addition.\[^{109, 154}\] Subsequent acylation with LDA and allyl chloroformate afforded \(\beta\)-ketoester 203 in 86% yield over two steps.\[^{109}\]

![Scheme 39: Synthesis of DAAA precursor 115.](image)

Final methylation by literature-known procedures afforded desired allylester 115 in varying and mediocre yields (see table 4). Treatment of 203 with cesium carbonate and methyl iodide in THF\[^{109}\] led to incomplete consumption of the starting material (entry 1). An increased amount of base and methyl iodide (entries 2 and 3) showed no significant change in yield.

\begin{table}[h]
\centering
\begin{tabular}{|c|l|c|c|c|}
\hline
\textbf{Entry} & \textbf{Conditions} & \textbf{T \[^\circ\text{C}\]} } & \textbf{t \[^\text{h}\]} & \textbf{Yield} \\
\hline
1\[^{109}\] & 203 (20 mmol), Cs\(_2\)CO\(_3\) (1.5 eq.), Mel (3 eq. + 1.75 eq. after 5 h), MeCN (0.25 M) & 80 & 7 & 58\% \\
\hline
2 & 203 (20 mmol), Cs\(_2\)CO\(_3\) (1.5 eq.), Mel (4 eq. + 2 eq. after 5 h), MeCN (0.3 M) & 80 & 8 & 61\% \\
\hline
3 & 203 (20 mmol), Cs\(_2\)CO\(_3\) (3 eq.), Mel (4 eq. + 2 eq. after 5 h), MeCN (0.35 M) & 80 & 16 & 64\% \\
\hline
4\[^{107}\] & 203 (25 mmol), NaH (1.2 eq.), Mel (1.7 eq), THF (0.25 M) & 0 to r.t. & 16 & 69\% \\
\hline
5 & 203 (25 mmol), NaH (1.2 eq.), Mel (1.7 eq. + 0.85 eq. after 6 h), THF (0.25 M) & 0 to r.t. & 24 & 82\% \\
\hline
6 & 203 (25 mmol), NaH (1.2 eq. + 0.3 eq. after 6 h), Mel (2 eq. 1 M in THF + 1 eq. neat after 6 h), THF (0.25 M) & 0 to r.t. & 24 & 88\% \\
\hline
\end{tabular}
\caption{Optimisation of the \(\beta\)-ketoester methylation.}
\end{table}
Enolate formation by deprotonation with sodium hydride and subsequent alkylation with methyl iodide, as applied to similar substrates\(^\text{[107]}\), gave better yields than the previous method (entry 4). The yield could be increased by adding an additional 0.85 eq. of methyl iodide (entry 5) after stirring overnight and running the reaction for further 6 h. Best results were achieved by adding methyl iodide as a 1 M solution in THF and an additional 0.3 eq. of sodium hydride and 1 eq. of methyl iodide (neat) after 6 h with further stirring overnight. This modified procedure led to an increase of the yield to up to 88% of the desired product. With a robust access to DAAA precursor 115, enabling the synthesis of decagram quantities, the next task was to establish the asymmetric alkylation reaction.

2.2.2.2 Synthesis of the ANDEN-phenyl Trost ligand

To introduce chirality, we chose the decarboxylative asymmetric allylic alkylation reaction because the reaction was already known for similar vinylogous thioester systems to deliver the products with high enantiomeric excesses, and it would enable fast access to the intermediate from the racemic route.\(^\text{[107]-109}\) We focused on the synthesis of the ANDEN-phenyl Trost ligand (113) because of the less facile synthesis of the (S)-t-Bu-PHOX ligand (112)\(^\text{[155]}\) and its slightly lower enantioselectivity (scheme 40). Diels-Alder reaction between anthracene (204) and dimethyl fumarate (205) proceeded slowly,\(^\text{[156]}\) but gave trans diester 206 in good yield after five days of reflux. The ester was saponified with potassium hydroxide in aqueous ethanol in quantitative yield. Chiral resolution of the diacid (rac)-207 was achieved according to the literature-known procedure\(^\text{[157]}\) with brucine (208) to form a diastereomeric salt. While the (11S,12S)-salt crystallised from the reaction mixture and could be separated by filtration, the (11R,12R)-isomer remained in solution. Optical rotation measurements in methanol confirmed a high enantiomeric excess: 

\[ [\alpha]_D^{22} = -9.1 \quad (c = 1.5, \text{ MeOH}) \]; lit.: \[ [\alpha]_D^{22} = -9.2 \quad (c = 4, \text{ MeOH}) \] \(^\text{[158]}\); \[ [\alpha]_D^{27} = -7.6 \quad (c = 1.5, \text{ MeOH}, 96\% \text{ ee}) \] \(^\text{[159]}\).

\[ \text{MeO}_2\text{C} \quad 205 \quad \text{CO}_2\text{Me} \]
\[ \begin{array}{c}
1) \text{o-xylene, reflux, 5 d} \\
2) \text{KOH, 95% EtOH, reflux, overnight quant.} \\
3) \text{brucine (3 eq.), EtOH:H}_2\text{O} 8:5, \text{reflux then crystallisation} \\
\quad 41\% \quad (11S,12S) \\
\quad 40\% \quad (11R,12R)
\end{array} \]

\[ \text{HO}_2\text{C} \quad (11S,12S)-207 \]
\[ \text{HO}_2\text{C} \quad (11R,12R)-207 \]

\[ \text{HO}_2\text{C} \quad 207 \]

Scheme 40: Chiral resolution of racemic diacid 207.
With acid (11S,12S)-207 in hand, the next task was to convert it into the corresponding (protected) diamine. Initially, a one-pot procedure for the Curtius rearrangement using diphenylphosphoryl azide (DPPA), originally developed by Yamada\cite{160}, was tested. Acid (11S,12S)-207 was treated with DPPA to in situ generate the bis-azide. This decomposed upon heating and basic hydrolysis of the intermediate isonitrile furnished diamine 209a in 40\% yield (entry 1, table 5).

**Table 5: Optimisation of the Curtius rearrangement.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>T [°C]</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DPPA (2.5 eq.), NEt₃ (2.6 eq.), PhMe (0.2 M) then aq. NaOH (4 eq., 2.5 M), THF (0.33 M)</td>
<td>r.t. to reflux</td>
<td>40% 209a</td>
</tr>
<tr>
<td>2</td>
<td>DPPA (2.5 eq.), NEt₃ (5 eq.), BnOH (10 eq.), dioxane (0.2 M)</td>
<td>r.t. to reflux</td>
<td>Traces</td>
</tr>
<tr>
<td>3</td>
<td>DPPA (2.5 eq.), NEt₃ (2.6 eq.), PhMe:t-BuOH 1:1 (0.2 M)</td>
<td>0 to reflux</td>
<td>Traces</td>
</tr>
<tr>
<td>4\cite{104}</td>
<td>a) SOCl₂ (3 eq.), DMF (cat.), PhH (0.4 M)</td>
<td>reflux</td>
<td>55% 209a</td>
</tr>
<tr>
<td></td>
<td>b) NaN₃ (2.2 eq.), DMF (0.4 M)</td>
<td>0 to r.t.</td>
<td>overall</td>
</tr>
<tr>
<td></td>
<td>c) PhMe (50 mM)</td>
<td>reflux</td>
<td></td>
</tr>
<tr>
<td></td>
<td>d) aq. NaOH (4 eq., 2.5 M), THF (0.33 M)</td>
<td>r.t.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>a) SOCl₂ (4 eq.), DMF (cat.), PhMe (0.4 M)</td>
<td>reflux</td>
<td>70% 209a</td>
</tr>
<tr>
<td></td>
<td>b) NaN₃ (2.2 eq.), DMF (0.4 M)</td>
<td>0 to r.t.</td>
<td>overall</td>
</tr>
<tr>
<td></td>
<td>c) PhMe (25 mM)</td>
<td>r.t. to reflux</td>
<td></td>
</tr>
<tr>
<td></td>
<td>d) aq. NaOH (4 eq., 2.5 M), THF (0.33 M); then HCl (4 eq., 4 M in dioxane), THF (0.33 M); then i-PrOH (0.1 M)</td>
<td>r.t.</td>
<td></td>
</tr>
</tbody>
</table>

*step 1 en detail:*

\[ \text{HO}_2\text{C} \rightarrow \text{CO}_2\text{H} \rightarrow \text{N}_3 \rightarrow \text{N}_2 \rightarrow \text{H}_2\text{O or ROH} \rightarrow \text{RNH} \rightarrow \text{Rnh} \]

\[ R = \text{H (for H}_2\text{O) 209a} \]
\[ R = \text{Cbz (for BnOH) 209b} \]
\[ R = \text{Boc (for iBuOH) 209c} \]
Neither increasing the amount of reagents nor changing the reaction time gave higher yields. To prevent the highly reactive isonitrile from side reactions, it was tried to trap it in situ as benzyl or tert-butyl carbamate (entries 2 and 3), but only trace amounts of the desired products could be isolated from a complex mixture. The original four step procedure (entry 4) by Trost and co-workers\cite{104} furnished only moderate amounts of the desired amine 209a. Slight modifications of the original procedure afforded the desired amine in good and reproducible yields on a gram scale. Especially the use of toluene during acyl chloride formation, higher dilution during the Curtius rearrangement and purification via the bishydrochloride proved crucial for the reaction (entry 5). Finally, amide formation with 2-(diphenylphosphino)benzoic\cite{104} acid afforded the desired phenyl-ANDEN Trost ligand (11S,12S)-113 in multigram quantities and quantitative yield.

2.2.2.3 Scale-up of the DAAA reaction

In order to provide enough material for the further synthesis, the DAAA reaction had to be scaled-up and optimised (table 6), since the original procedure was conducted on small scale only.\cite{107} First scale-up experiments were performed with racemic ligand and afterwards, the reaction was optimised to achieve high enantioselectivity. Degassing the solvent prior to use (three freeze-pump-thaw cycles) proved crucial for the reaction, otherwise decomposition of the catalyst occurred after short time (entry 1). With the use of 3 mol\% of commercial Pd\textsubscript{2}dba\textsubscript{3}, a yield of only 46\% was achieved (entry 2).

![Diagram](image-url)

\textbf{Table 6:} DAAA reaction scale-up.

<table>
<thead>
<tr>
<th>entry</th>
<th>scale</th>
<th>X (mmol)</th>
<th>Y (mmol)</th>
<th>t [h]</th>
<th>T [°C]</th>
<th>Yield [%]</th>
<th>ee [%]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1\textsuperscript{a}</td>
<td>1 mmol</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>r.t.</td>
<td>traces\textsuperscript{c}</td>
<td>\textsuperscript{f}</td>
</tr>
<tr>
<td>2\textsuperscript{a}</td>
<td>1 mmol</td>
<td>3</td>
<td>6</td>
<td>24</td>
<td>30</td>
<td>46\textsuperscript{d}</td>
<td>\textsuperscript{f}</td>
</tr>
<tr>
<td>3\textsuperscript{b}</td>
<td>1 mmol</td>
<td>5</td>
<td>11</td>
<td>24</td>
<td>30</td>
<td>86</td>
<td>\textsuperscript{f}</td>
</tr>
<tr>
<td>4\textsuperscript{b}</td>
<td>3.2 mmol</td>
<td>5</td>
<td>11</td>
<td>24</td>
<td>r.t.</td>
<td>80</td>
<td>\textsuperscript{f}</td>
</tr>
<tr>
<td>5\textsuperscript{b}</td>
<td>1 mmol</td>
<td>5</td>
<td>11</td>
<td>24</td>
<td>r.t.</td>
<td>86</td>
<td>94.6</td>
</tr>
<tr>
<td>6\textsuperscript{b}</td>
<td>3.2 mmol</td>
<td>3.8</td>
<td>8.3</td>
<td>24</td>
<td>r.t.</td>
<td>84</td>
<td>96.0</td>
</tr>
<tr>
<td>7\textsuperscript{b}</td>
<td>15.8 mmol</td>
<td>3.8</td>
<td>8.3</td>
<td>24</td>
<td>r.t.</td>
<td>87</td>
<td>95.6</td>
</tr>
<tr>
<td>8\textsuperscript{b}</td>
<td>15.8 mmol</td>
<td>3.8</td>
<td>8.3</td>
<td>36</td>
<td>r.t.</td>
<td>82</td>
<td>96.6</td>
</tr>
<tr>
<td>9\textsuperscript{b}</td>
<td>23.2 mmol</td>
<td>3.8</td>
<td>8.3</td>
<td>48</td>
<td>r.t.</td>
<td>80</td>
<td>96.6</td>
</tr>
</tbody>
</table>

\textsuperscript{a}commercial Pd\textsubscript{2}dba\textsubscript{3} was used; \textsuperscript{b}self-made Pd\textsubscript{2}dba\textsubscript{3} was used; \textsuperscript{c}solvent was not degassed; \textsuperscript{d}only 50% consumption; \textsuperscript{e}determined by chiral HPLC; \textsuperscript{f}racemic ligand was used.
Since it is known that \( \text{Pd}_2\text{dba}_3 \) can vary in composition and quality, especially concerning the palladium content or the amount of palladium nanoparticles\[161\], a new batch of \( \text{Pd}_2\text{dba}_3 \) chloroform adduct was synthesised according to the literature-known procedure.\[162\] Gratifyingly, with concomitant increase of the catalyst loading, full consumption of the starting material was observed to yield 86% of the desired product (S)-116 (entry 3). Compound 210, resulting from unreacted enolate according to the outer sphere mechanism (see scheme 20, chapter 1.5), was isolated in varying amounts in the subsequent attempts. Prolonged reaction times did not reduce the formation of 210. Increasing the scale of the reaction did not influence the outcome significantly (entry 4). Switching to \((11S,12S)\)-ligand 113 gave an enantiomeric excess of 94.6% on small scale (entry 5). Decreasing the catalyst loading by 25% led to slightly higher enantioselectivity (entry 6). The reaction proved to be very robust and could be scaled-up without great decrease in yield or change in selectivity (entries 7 to 9). Typically, the enantiomeric excess amounted to ca. 96%.

2.2.3 Synthesis of intermediate 200

With a robust access to optically active vinylogous thioester 116, transesterification to vinylogous methylester 201, which is more reactive in the Stork-Danheiser transposition, proceeded smoothly in excellent yields (see table 7). A methodology for the aldehyde-selective Wacker oxidation\[163\] attracted our attention to directly oxidise the allyl moiety in (S)-116 to aldehyde 212. Even after purification and drying of the solvents, only traces of desired aldehyde 212 could be isolated (entry 1, table 7). Employing a similar methodology using tert-butyl nitrite\[164\] as co-oxidant also failed (entry 2). Therefore, olefin 201 was converted to alcohol 211 via rhodium-catalysed hydroboration.\[165\] Treatment of 201 with catecholborane and Wilkinson’s catalyst followed by oxidative work-up gave alcohol 211 in very good yields. Alcohol 211 was prone to intramolecular addition-elimination reaction under slightly acidic conditions to give compound 213. This reaction was observed in CDCl₃. Despite buffering the reaction with an excess of sodium bicarbonate, the oxidation with Dess-Martin periodinane (DMP)\[166\] was slower than formation of 213 (entry 3). The neutral Ley-Griffith oxidation\[167\] catalysed by tetrapropylammonium perruthenate (TPAP) furnished aldehyde 212 in 45% yield. An increased amount of oxidant showed no effect on the yield (entry 4). Finally, good yields for the desired oxidation could be achieved via Parikh-Doering oxidation (entry 5).\[168\] Aldehyde 212 proved to be sensitive and underwent partial decomposition during chromatography. Use of crude 212 in the next reaction gave better overall yields.
Table 7: Synthesis of aldehyde 212.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>conditions</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>201</td>
<td>Pd(PhCN)$_2$Cl$_2$ (12 mol%), CuCl$_2$·2H$_2$O (12 mol%), AgNO$_2$ (6 mol%), O$_2$, t-BuOH:MeNO$_2$ (15:1, 0.05 M)</td>
<td>traces</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rh(PPh$_3$)$_2$Cl (3 mol%), catecholborane, THF; then H$_2$O$_2$, EtOH, THF, pH7 buffer</td>
<td>93%</td>
</tr>
<tr>
<td>2</td>
<td>201</td>
<td>Pd(PhCN)$_2$Cl$_2$ (7 mol%), t-BuONO (20 mol%), O$_2$, t-BuOH (0.25 M)</td>
<td>traces</td>
</tr>
<tr>
<td>3</td>
<td>211</td>
<td>DMP (3 eq.), NaHCO$_3$ (5 eq.), CH$_2$Cl$_2$ (0.1 M)</td>
<td>213</td>
</tr>
<tr>
<td>4</td>
<td>211</td>
<td>TPAP (10 mol%), NMO (1.5 eq.), MS 4Å, CH$_2$Cl$_2$ (0.1 M)</td>
<td>45%</td>
</tr>
<tr>
<td>5</td>
<td>211</td>
<td>pyr*SO$_3$ (4 eq.), NEt$_3$ (10 eq.), DMSO (0.12 M)</td>
<td>78%$^a$</td>
</tr>
</tbody>
</table>

$^a$usually aldehyde 212 was used crude in the next step.

Treatment of aldehyde 212 with Ohira-Bestmann reagent (217)$^{[269]}$ gave alkyne 214 in very good yield (scheme 41). Purification of aldehyde 212 prior to the alkynylation was not necessary to give a yield of 70% over both, the oxidation and the alkynylation steps. Iodide 216 was obtained after monobenzylation and subsequent iodination from trimethylene glycol (215) in 56% yield. Stork-Danheiser transposition of 214 with lithiated 216 eventually furnished desired enone 200 in excellent yield.

Scheme 41: Synthesis of key intermediate 200.

The route starting from commercially available 2-methylcyclohexane-1,3-dione (202) proved to be very robust and enabled access to multigram quantities of optically active enone 200 with 96% enantiomeric excess and in 32% overall yield (over 9 steps).
2.2.4 Completion of the Total Synthesis

With enone 200 in hand, the total synthesis of (+)-waihoensene could be completed in accordance with the racemic route. Since this route has already been optimised by Lisa-Catherine Rosenbaum\textsuperscript{[152, 153]}, details will not be further discussed here and it will just be shortly described in this section.

The cis-hydrindane systems were constructed with the aid of tin-mediated radical cyclisation.\textsuperscript{[170]} Thus, by treatment of enone 200 with tributyltin hydride and AIBN as radical initiator, cyclisation proceeded in very good yield, to give a diastereomeric mixture of cis-hydrindane 218. Removal of the stannane under slightly acidic conditions with pyridinium p-toluolsulfonate and subsequent equilibration of the C-7 methyl group gave the desired all cis-isomer 219 in 88% yield. The diastereomeric purity was determined to be higher than 95% by \textsuperscript{1}H-NMR. The next task was to deoxygenate the hydrindane system. Conversion of the ketone to the corresponding tosylhydrazone and reduction with catecholborane, which is a methodology developed by Kabalka and co-workers\textsuperscript{[171]}, furnished the deoxygenated bicyclic system 220 in 48% yield in two steps. Debenzylation was achieved under Birch-conditions and proceeded in good yields to give alcohol 221. Parikh-Doering oxidation\textsuperscript{[168]} of the latter and treatment with Ohira-Bestmann reagent (217)\textsuperscript{[169]} yielded the desired enyne 61 in 73% yield in two steps.

With enyne 61 in hand, the next task was to establish the waihoensene carbocyclic framework as shown in scheme 43. Reacting 61 with dicobalt octacarbonyl at room temperature followed by refluxing in xylene afforded Pauson-Khand product 55 in 43% yield. Deprotonation with lithium tetramethylpiperidine led to exclusive formation of the kinetic enolate and thus, treatment with methyl iodide yielded desired enone 222 in 61% yield together with 30% re-isolated starting material. Lewis-acid mediated methyl cuprate addition proceeded smoothly in good yield to give

\begin{itemize}
  \item 1) AIBN, n-Bu\textsubscript{3}SnH, PhH, reflux
  \item 2) PPTS, CH\textsubscript{2}Cl\textsubscript{2}, r.t.
  \item 3) NaOH\textsubscript{aq}, MeOH, 50 °C
  \item 4) TsNH\textsubscript{2}HN\textsubscript{2}, EtOH, 0 °C to r.t.
  \item 5) catecholborane, CHCl\textsubscript{3}, -10 °C; then NaOAc-H\textsubscript{2}O, reflux
  \item 6) Na, NH\textsubscript{3}, -78 °C to -69 °C
  \item 7) pyr\textsuperscript{+}SO\textsubscript{3}, NE\textsubscript{t}, DMSO, r.t.
  \item 8) Ohira-Bestmann, K\textsubscript{2}CO\textsubscript{3}, MeOH, r.t.
\end{itemize}
ketone 56. Finally, Wittig reaction afforded optically active (+)-waihoensene (38) in 82% yield as a colourless oil. The optical rotation factor was in accordance with the one reported in the isolation paper $[\alpha]_D^{23} = +42.4$ (c 0.18, CHCl$_3$); Lit.: $[\alpha]_D^{22} = +43.9$ (c 0.09, CHCl$_3$).$^{[57]}

Scheme 43: Pauson-Khand reaction of 61 and completion of the synthesis (red dot: stereocentre from DAAA).
3. Summary

In the first part of this thesis, a racemic approach towards a total synthesis of the podocarp diterpene waihoensene (38) and a completed enantioselective total synthesis are described.

As outlined in scheme 44, it was planned to synthesise the challenging triquinane core of waihoensene (38) via meta-photocycloaddition. Pursuing this strategy, a robust route for the synthesis of photoprecursor 189b was developed that also enabled the synthesis of other photoprecursors 189a,c,d. Herein, treatment of dimethyl cyclohexanone 193 with LDA and phenylseleno acetaldehyde followed by elimination with methanesulfonyl chloride led to the formation of vinylcyclohexanone 191. By reaction with 9-BBN, the precursor for a sp²-sp³ Suzuki cross coupling was formed to yield ketone 194b.

After testing various methods for methenylation of sterically hindered ketones, Takai’s modification of the Lombardo olefination was found to most effectively accomplish that transformation. Unfortunately, after several attempts, none of the irradiation conditions led to the formation of the desired waihoensene carboskeleton. To exclude problems with the lamp, a test system was irradiated to yield compounds 198b and 199b as a 1:1 mixture. Additionally, the synthesis of penifulvin A (109) could be reproduced to verify the suitability of the lamp, although in lower yields due to photopolymerisation. UV-VIS measurements of photoprecursors 189 showed that the aromatic system should undergo excitation with a medium pressure mercury lamp. The
low reactivity is most probably the result of a sterically demanding transition state, which is thus unlikely to be formed.

A second approach, which allowed completion of the total synthesis was developed together with M.Sc. Lisa-Catherine Rosenbaum. Key features were the introduction of chirality through an asymmetric allylation reaction and the construction of the carbocyclic framework by a radical cyclisation and a cobalt-catalysed intramolecular Pauson-Kand reaction. Therefore, an efficient synthetic route to optically active material 200 was developed (scheme 45). After extensive optimisation, allylester 115 was obtained after alkylation of literature known 203. Decarboxylative asymmetric allylic alkylation installed the quaternary stereocentre that determined all stereocentres introduced in later steps with 96% enantiomeric excess. Conversion to methyl vinylogous ester 201, which is more reactive in the Stork-Danheiser transposition, proceeded in excellent yields. Elongation of the allyl side chain was achieved by rhodium-catalysed hydroboration, Parikh-Doering oxidation and Ohira-Bestmann alkynylation. Reaction of alkyne 214 with lithiated 216 eventually yielded the desired enone 200 in excellent yield after acidic workup.

With enantioenriched material 200 in hands, the total synthesis of (+)-waihoensene (38) could be completed in accordance to the optimised racemic route. Radical cyclisation, stannane removal and equilibration of the α-methyl group furnished the all-cis hydrindane system 219 in high yields. Deoxygenation by conversion to the corresponding tosylhydrazone followed by reduction with catecholborane gave carbocycle 220. The benzyl ether in 220 was cleaved under Birch conditions in liquid ammonia. Oxidation to the aldehyde and alkynylation with Ohira-Bestmann reagent yielded enyne 61. Enyne underwent Pauson-Khand reaction upon treatment with dicobalt octacarbonyl and subsequent refluxing in xylene to construct the waihoensene skeleton. α-
Methylation and cuprate addition added the two missing methyl groups and eventually, Wittig olefination furnished desired (+)-waihoensene (38).

Scheme 46: Completion of the waihoensene (38) synthesis.

(+)-Waihoensene (38) was obtained in full accordance to the reported natural product. 19 steps were needed for the enantioselective total synthesis of waihoensene with an overall yield of 1.2%. Additionally, the natural product was obtained with a high enantiomeric excess and several milligrams of substance were synthesised across all runs of the sequence, which offers the opportunity for further biological testing.
II Application of the Palladium – catalysed C-H-Activation in the Synthesis of Cyclohepta[b]indoles
1. Introduction

1.1 The Cyclohepta\(b\)indole Motif in Nature and Chemistry

Alkaloids comprise a large group of around 20,000 yet isolated natural products with high structural diversity. The majority of alkaloids have been isolated from plants, but they can also be found in a variety of other organisms including fungi, marine microorganisms or animals, like puffer fish, insects or amphibians.\[^{172}\] A general definition of this heterogeneous group of natural products was proposed by Pelletier: “An alkaloid is a cyclic compound containing nitrogen in a negative oxidation state which is of limited distribution in living organisms.”\[^{173}\] Alkaloids are categorised into four different biogenetic groups, namely amino acid derived alkaloids, purine alkaloids, aminated terpenoids and polyketide alkaloids.\[^{174}\] Since alkaloids are predominantly produced as a kind of chemical defence, they show outstanding biological activities that can be directly attributed to the incorporation of nitrogen in their molecular structure and the resemblance to signalling molecules, like neurotransmitters. As a consequence, many mammals – including humans – evolved a protective mechanism to detect potentially toxic alkaloids by their bitter taste.\[^{172, 174, 175}\] One of the most potent toxins is the steroid alkaloid (figure 12) batrachotoxin (235) with a \(LD_{50}\) of about 2 \(\mu g/kg\) in mice, isolated from the Colombian arrow poison frog.\[^{176}\] A similarly toxic compound is the puffer fish poison tetrodotoxin (236), with a \(LD_{50}\) of about 230 \(\mu g/kg\) (oral in mice).\[^{177}\] However, alkaloids do not only represent strongly toxic compounds, but they are also used as therapeutics in medicine.

![Figure 12: Biologically active alkaloids.](image)

For example, the strong opioid receptor agonist morphine (237) (\(IC_{50} = 17 \text{nM for } \mu^2\)-receptor) is used as strong analgesic\[^{178}\], or the sodium channel blocker ajmaline (238) is applied in the treatment of atrial and ventricular arrhythmias.\[^{179}\] A rather large subgroup are the indole alkaloids with around 4,000 known members.\[^{172}\] Their biosynthetic precursor for the indole part is usually the amino acid tryptophan.\[^{180}\] In the last years, the indole motif was identified as “privileged motif” in medicinal chemistry, since it is an important structural subunit responsible for crucial ligand-receptor interactions and thus delivering hits for new receptor agonists and antagonists.\[^{181}\]
If a seven-membered ring is fused to the indole, the compounds are referred to as cyclohepta[b]indoles (see figure 13). This structural motif can be found in various natural products and synthetic derivatives and is associated with a plethora of biological activities. Hence, cyclohepta[b]indoles have gained the interest of the pharmaceutical industry as target structure for potential therapeutics and developing methodologies for the selective synthesis of this scaffold became more and more relevant for synthetic organic chemists. The following chapter will therefore deal with the occurrence of the cyclohepta[b]indole motif in natural products and potential pharmaceuticals as well as with recent methodologies for its construction and the synthesis of natural products.

1.1.1 Natural Products containing the Cyclohepta[b]indole Motif

A few natural products containing the cyclohepta[b]indole motif were isolated during the past years. Two recently isolated compounds (see figure 14) are exotine A (239) and exotine B (240), isolated in 2015 by Jiang and co-workers from the roots of the yasmine tree *Murraya exotica* endemic to Southeast Asia. Leaves and roots of this plant have previously been used as folk medicine and studies showed anti-oxidant, antimicrobial, antitumor, antifungal, and anti-inflammatory activities of the plant extracts. Jiang and co-workers found that the exotines act as inhibitors of lipopolysaccharide-induced nitric oxide (NO) production in BV-2 microglial cells (exotine A IC$_{50}$ = 9.2 µM; exotine B IC$_{50}$ = 39.9 µM). NO regulation plays a crucial role in cell signalling and cell-protecting events, but higher NO concentrations can lead to neurotoxicity in cells or tissues.

![Figure 13: Cyclohepta[b]indole.](image)

![Figure 14: Natural products with cyclohepta[b]indole core (highlighted in red).](image)

Actinophyllic acid (241), depicted in figure 14, was isolated 2005 by Carroll and co-workers from the leaves of *Alstonia actinophylla*. It was highly investigated by the synthetic community because of its intriguing structure and biological activity. Carroll and co-workers found that this cyclohepta[b]indole alkaloid is a potent inhibitor of carboxypeptidase U (CPU)/Hippuricase...
(IC₅₀ = 0.84 μM). CPU plays an important role in fibrinolysis, the process to remove small blood clots, and thus, actinophyllic acid (241) was further investigated as lead compound in the treatment of thrombotic diseases.[185, 193] Other members of the natural product family, aristolasene (242) and aristolasol (243) were both isolated 1988 by Husson and co-workers from Aristotelia australasica.[194] Their structure was elucidated by NMR techniques, but up to now, no biological studies have been conducted.

The above mentioned cyclohepta[b]indole alkaloids were all isolated from herbal sources, but also marine microbial sources are known. The ambiguine natural product (see figure 15) family comprises 18 members of alkaloids, including 12 cyclohepta[b]indoles isolated from different cyanobacteria[195-203], and is closely related to the hapalindole family.[202] Ambiguine D (244) was isolated together with other members from Fischerella ambigua and Westiellopsis prolifica in 1992 by Moore and co-workers.[195] The extracts of these cyanobacteria showed antifungal activity against five test fungi including Candida albicans and Penicillium notatum.[195] Ambiguine I (245) was isolated in 2007 by the Carmeli group from cultivated Fischerella sp.[197] and was found to inhibit (IC₅₀ = 30 nM) the transcription factor NF-κB, which regulates the expression of regulatory factors involved in cancer cell proliferation. Induced apoptosis was examined in colon cancer (EC₅₀ = 4.35 μM) and breast cancer cell lines (EC₅₀ = 1.7 μM).[203]

![Figure 15](image)

Orjala and co-workers isolated ambiguine K (246) together with ambiguines L – O from cultured Fischerella ambigua.[198] The crude extract thereof showed antibacterial activity against Mycobacterium tuberculosis and Bacillus anthracis.[198] One of the latest isolated members, ambiguine P (247), is the only representative without a nitrile or isonitrile functionality. In contrast to its related ambiguines, it showed only weak antibacterial activity against Candida albicans (MIC = 32.9 μM).[199]

Another large group of natural products containing the cyclohepta[b]indole motif are the monoterpenoid indole alkaloids isolated predominantly from plants of the genus Ervatamia, as depicted in figure 16.[182] This genus comprises about 120 species endemic to the (sub)tropical
regions of Asia and Australia. Their use in traditional Chinese medicine is long documented for the 
treatment of various diseases.\textsuperscript{[204]}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{ervatamine.png}
\caption{Selected Ervatamia alkaloids.}
\end{figure}

The first identified representative ervatamine \textbf{(248)} was isolated in 1971 by the Knox group from \textit{Evratamia orientalis} (see figure 16).\textsuperscript{[205]} Later, the Sauviat group found \textbf{248} to affect the cardiac membrane current and to act similar to local anesthetics and as sodium channel blocker.\textsuperscript{[206]} The decarboxylated derivatives silicine \textbf{(249)} and methuenine \textbf{(250)} (and various stereoisomers or oxo-
derivatives) have been isolated from different herbal sources including \textit{Hazunta modesta},\textsuperscript{[207]} \textit{Ervatamia malaccensis},\textsuperscript{[208]} or \textit{Ervatamia officinalis}.\textsuperscript{[209]} Methuenine \textbf{(250)} was identified as a non-
competitive antagonist against acetylcholin.\textsuperscript{[210]} Ervitisine \textbf{(251)} was found together with \textbf{250} in the 
bark of the roots of \textit{Pandaca boiteaui} and is the only bridged representative of this natural product
family.\textsuperscript{[211]}

\textit{1.1.2 Non-natural Derivatives}

As natural products containing the cyclohepta[b]indole motif show all kind of biological activity, it 
is not surprising that this product class evoked the interest of medicinal chemists as well. Several 
unnatural derivatives were synthesised and their biological functions were investigated (figure 17). 
Ethanamine substituted indole \textbf{252} was tested for its toxicity (LD\textsubscript{50} = 85 mg/kg in mice) and for its 
potential antidepressant properties. \textbf{252} was found to prevent reserpine-induced ptosis in mice 
already in low dose (ED\textsubscript{50} = 0.27 mg/kg).\textsuperscript{[212]}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{synthetic_indoles.png}
\caption{Biologically active synthetic cyclohepta[b]indoles.}
\end{figure}

When investigating structure-activity relationships for androgen receptor ligands, Zhang and co-
workers\textsuperscript{[213]} synthesised indole \textbf{253}, which showed a strong affinity to the androgen receptor
Hormone replacement therapy plays a crucial role in the treatment of various disorders in men as well as in women.\textsuperscript{[214]} Androgens do not only influence the primary or secondary sexual characteristics in humans, but their fluctuating concentration, especially in older age, is associated with various diseases, like prostate and breast cancer, cardiovascular diseases or sleep apnoea.\textsuperscript{[215]} Compound 254 (figure 17) was found to very effectively block aurora kinases A (IC\textsubscript{50} $= 0.92$ $\mu$M) and B (IC\textsubscript{50} $= 5$ nM), which have distinct functions in mitosis. Studies showed that aurora kinase inhibition as the mechanism of antiproliferative activity. Thus, these inhibitors would be attractive targets for tumour growth inhibition.\textsuperscript{[216]} SIRT1, one of seven sirtuins found in humans, influences multiple biological processes, like inflammation, aging, metabolism or oncogenesis, by acting as histone deacetylase and plays an important role in signaling pathways.\textsuperscript{[217, 218]} Chloro-substituted indole 255 (figure 17) was found to act as a potent inhibitor of SIRT1. While the (R)-enantiomer only showed mediocre inhibition (IC\textsubscript{50} $= 23$ $\mu$M), the (S)-enantiomer (IC\textsubscript{50} $= 63$ nM) showed a 500-fold inhibition potency over previously reported inhibitors. Additionally, it showed favourable ADME properties and was found to be the most potent SIRT1 inhibitor to this date.\textsuperscript{[219]} A gram-scale enantioselective synthesis for 255 has been described in 2013 by the Gaich group.\textsuperscript{[220]}

Beyond the examples depicted in figure 17, synthetic cyclohepta[b]indole derivatives show multiple further biological activities. They are also known to inhibit adipocyte fatty-acid binding protein (A-FABP)\textsuperscript{[221]} and the production of leukotriene B\textsubscript{4},\textsuperscript{[222]} or to exhibit antimicrobial properties against *Mycobacterium tuberculosis*\textsuperscript{[223]} and to act as a selective opioid $\delta$-receptor ligand.\textsuperscript{[224]}

1.2. Construction of Cyclohepta[b]indoles

Numerous methodologies for the construction of the cyclohepta[b]indole core have been developed in the past years, mostly employing pericyclic processes, but also “standard” Fischer indole synthesis has been used with certain limitations. Most methodologies up to 2016 have been extensively reviewed by the Gaich group\textsuperscript{[182]} and will therefore not be further discussed.

1.2.1 Recently Developed Methodologies

In the majority of natural products containing a cyclohepta[b]indole motif, the latter is more or less highly substituted with several stereogenic centres. Therefore, predominantly asymmetric methodologies or the construction of highly functionalised cyclohepta[b]indoles developed since 2017 will be summarised in this chapter.
1.2.1.1 Construction of Cyclohepta[b]indoles via Cycloaddition Reactions

Masson and co-workers established an asymmetric access to the cyclohepta[b]indole motif via a chiral phosphoric acid diester catalysed [4+3]-cycloaddition (see scheme 47).\textsuperscript{[225]} Reaction of indolylarylmethanols 256 with phosphoric acid derivative 258 (TRIP) \textit{in situ} generated alkylideneindoleninium ions that subsequently underwent cycloaddition with 1,3-diene-1-carbamates 257. The addition of molecular sieves proved to be crucial, since otherwise the reaction yield dropped drastically.

![Scheme 47: Chiral phosphoric acid catalysed [4+3] cycloaddition by Masson.](image)

Highest yields were achieved for $R^1 = \text{Ar}$, and electron withdrawing as well as electron donating groups were tolerated. Concerning substitution of the indole core, only unsubstituted or electron-rich indoles were tolerated, e.g. for $R^2 = 5$-Br the yield decreased to 31%. For $R^{3,5}$ alkyl groups were examined and showed no significant influence on reaction yield and asymmetric induction. Based on a model previously described by Reid and Goodman,\textsuperscript{[226]} the asymmetric induction originated from the coordination of both substrates by the phosphoric acid \textit{via} hydrogen bonding to fit in the suitable pocket of the BINOL-backbone.\textsuperscript{[225]} To summarise this methodology, 6-amino substituted tetrahydrocyclohepta[b]indoles 259 are rapidly accessible with high enantiomeric excess and bearing up to three stereogenic centres and a tetrasubstituted double bond ($R^3$, $R^4$). The major drawback is the lack of reactivity for electron-poor indoles as well as the restriction to indolylarylmethanols ($R^1 = \text{Ar}$) 256.
As depicted in scheme 48, Sun and co-workers chose a different approach towards cyclohepta[b]indoles by (formal) asymmetric rhodium catalysed [4+3]-cycloaddition of vinylinoles 260 with vinyl diazoacetates 261.\textsuperscript{[227]} For 3-vinyl substituted indoles 260a, proline-based catalyst Rh$_2$(S-DOSP)$_4$, earlier established by Davies,\textsuperscript{[228]} was found to give the best results with overall high enantioselectivity (82 to 97% ee) and fair to excellent yields. Hydrogen or methyl groups were tolerated as substituents for $R^1$ as well as alkyl or aryl groups for $R^2$, although with lower yield for $R^2 =$ alkyl. They propose the reaction to proceed via asymmetric cyclopropanation of the vinyll-substituent followed by\textit{in situ} Cope rearrangement of the divinylcyclopropane 262, in analogy to the previously reported method by Gaich and co-workers.\textsuperscript{[220]}

For 2-vinylsubstituted indoles 260b, phtalimide-based rhodium catalyst Rh$_2$(S-TCPTTL)$_4$ developed by the Hashimoto group\textsuperscript{[229]} gave the best results. High enantioselectivities (82 to 99%) were observed only for $R^1 = $ H and $R^2 = $ Ar, but electron-rich or -deficient aromatics were tolerated. For $R^1 = $ H, the authors showed that the indole moiety can be rearomatised by treatment with $p$-toluenesulfonic acid.\textsuperscript{[227]} Overall, a highly enantioselective approach towards cyclohepta[b]indoles was developed, although with limitations with respect to the substitution pattern, since predominantly aryl substituents are tolerated and the ester is required for diazo stabilisation.

A different [4+3]-cycloaddition strategy also employing 2-vinylindoles 264 (see scheme 49) was developed by Rossi and co-workers.\textsuperscript{[230]} Herein, an oxyallyl cation 265a, \textit{in situ} generated from an $\alpha$-bromoketone 265 or 266, undergoes addition to the vinyllindole 264 to form the cyclohepta[b]indole motif 267 or 268. The use of 2,2,2-trifluoroethanol (TFE) as co-solvent together with toluene inhibited reaction of the indole-3-position and led to exclusive formation of the
desired cycloaddition product. Fluorinated solvents were known for similar reactions because of
their ability to activate carbonyl compounds and to stabilise cationic intermediates.[231] Concerning
the substrate scope of the reaction, differently substituted aryl groups as well as alkyl substituents
were tolerated as R. Additionally, the electronic properties of the indole had no influence on the
reaction outcome, and thus electron withdrawing as well as electron donating groups were
tolerated.[230] Methyl-substituted cyclopentanone (R = Me) and symmetrically substituted acyclic
ketones (R = H, R = R = Me, Ph) gave satisfying yields only when TFE was employed as the sole
solvent. The reaction usually proceeded in fair to very good yield but is somehow limited to simple
alkyl or aryl substituents.

An approach utilizing a [5+2]-cycloaddition between indoles 269 as C5-donor and acetylenes 270
as C2-donor was published by the Nishida group (see scheme 50).[232] For this transformation, it was
crucial to use a Lewis-acid with σ- as well as π-electrophilic character, which is fulfilled especially
for In(III) salts.[233] Nishida and co-workers found InI to effectively catalyse the formation of
cyclohepta[b]indoles 271 for their system.[232] Alkyl, aryl or hydrogen are tolerated for R and
cyclohepta[b]indoles were obtained in fair to excellent yields. Concerning the alkyne 270 on the
other hand, the scope is limited to terminal phenylacetylenes (R = H, R = Ar), in which the
electronic properties of the aryl group do not affect the reaction outcome. In addition,
heteroaromatics, like thiophenes, indoles or benzofuranes are tolerated. For R = H and R = Bn or
R = Me and R = Ph, the yield dropped drastically. Protection of the starting indole nitrogen was
not necessary, as alkylated as well as non-protected indoles gave good yields.
Scheme 50: InI$_3$-catalysed formation of cyclohepta[b]indoles by Nishida and co-workers.$^{[232]}$

The reaction was proposed to proceed via a Friedel Crafts-like mechanism. Activation of the alkyne with InI$_3$ would generate a partial positive charge next to the stabilizing aromatic R$^1$-substituent, as previously reported,$^{[234]}$ to generate a zwitterionic intermediate 273. After electrophilic substitution and rearomatisation, 3-vinylindoles 274 are obtained, which further undergo indium-mediated cyclisation and rearomatisation to yield the desired products.$^{[232]}$

A different strategy developed by the France group (scheme 51) utilised a (formal) calcium-catalysed [5+2]-cycloaddition to construct the cyclohepta[b]indole scaffold.$^{[235]}$ Treatment of 2-indoly1 $\beta$-ketoester 275 with five equivalents of a substituted olefin 276 in the presence of Niggemann’s calcium-based catalyst$^{[236, 237]}$ afforded several substituted cyclohepta[b]indole $\beta$-ketoesters 278. The reaction is believed to proceed via activation of the $\beta$-ketoester moiety followed by Michael-type addition of the olefin to generate a cationic intermediate 277. Nucleophilic attack by the indole C-3 position followed by rearomatisation would eventually yield the product.$^{[235]}$

Scheme 51: Calcium-catalysed formal [5+2]-cycloaddition by the France group.$^{[236]}$

Concerning the substrate scope, electron withdrawing as well as donating groups on the indole core are tolerated, but other substituents than R$^2$ = H led to Nazarov-type cyclisation products. Aryl substituted alkenes with one or two donor substituents gave fair to excellent yields, but alkylated olefins were not tolerated, thus limiting the scope of the methodology.$^{[235]}$
1.2.1.2 Other Methodologies for the Construction of Cyclohepta[b]indoles

Aside from cycloaddition reactions, methodologies for cyclohepta[b]indole construction are scarce, especially for highly substitutes derivatives. An alternative approach employing a photochemical ring expansion reaction was developed by the Hiersemann group (scheme 52). \[238\] By irradiation of anilines 279, containing an alkyne functionality as well as an enamide, with 254 nm UV-light, a [2+2]-cycloaddition took place to generate tetracyclic intermediate 280. Subsequent retroelectrocyclic 4π ring enlargement furnished the desired cyclohepta[b]indoles 281. The proposed mechanism was supported by computational methods which indicated that the use of fluorinated solvents (TFE, HFIP) was crucial due to their stabilising and activating effects. \[238\]

Various electron rich or electron poor anilines (R² and R³) were tolerated in the reaction, as well as alkyl or aryl substituted alkynes (R¹). Even alcohols could be introduced on the R¹-substituent but O-protection was crucial. Additionally, the substrate scope was extended to yield cyclohepta[b]indole lactames (Z = NBoc, NAc), whereas formation of lactones (Z = O) was not possible. The methodology delivers the desired structure motif mainly in high yields (15 examples over 80% yield) and allows further manipulation of the products, since incorporation of functional groups is tolerated. \[238\]

A similar, photochemical approach was chosen by Yang and co-workers (scheme 53). \[239\] They made use of a single-electron transfer (SET) catalyst FCNIrpic (285), which allowed them to conduct the [2+2]-cycloaddition under visible light catalysis. Computational studies indicated the formation of a stabilised radical on the enaminone motif in 282, which further cyclised with the indole part to give pentacyclic intermediate 283. Ring-opening occurred via a retro-Mannich type reaction to give the desired cyclohepta[b]indole products 284.
In general, substituents \((R^1 = \text{OMe}, \text{Cl}, \text{Me}, \text{Br}, \text{CF}_3)\) are tolerated in all positions of the benzene ring without regard to their electronic properties, as well as in the 2-position of the indole \((R^2 = \text{Me}, \text{Bn})\). Cyclohepta\(b\)indoles were formed exclusively for \(Z = \text{CH}_2\), whereas incorporation of heteroatoms \((Z = \text{O}, \text{NH})\) allowed the isolation of cycloaddition products 286.\[239\]

As shown in scheme 54, a completely different approach was developed by Deng and co-workers by application of an asymmetric cyclobutanone ring-expansion strategy.\[240\] After extensive screening of several thiourea and squaramide catalysts, squaramide 289, previously described by Rawal,\[241\] showed to most effectively promote the reaction with excellent enantioselectivity. The authors propose the reaction to proceed via activation of both the cyclobutanone 288 and the 2-nitrovinylindoles 287 by hydrogen bonding (scheme 54). After Michael addition of the cyclobutanone, the fragmentation/ring enlargement of the four-membered ring is triggered by nucleophilic attack of the indole C-3 position to yield the corresponding cyclohepta\(b\)indoles 290.\[240\]

Electron donating or withdrawing substituents on the indole were tolerated, as well as pyrrole-derived starting materials. For the cyclobutanones, either \(\beta\)-ketoester or \(-\)lactams were employed \((X = \text{NHA}_\text{r}, \text{OCH}_2\text{CH}_2\text{Bn})\), while electron-donating or -withdrawing substituents on the aniline had no impact on the reaction outcome.\[240\]
Major drawback of this methodology is the inevitable formation of a cis/trans product mixture due to the enolate formation during the ring expansion step (see compound 293). Nevertheless, the authors stated the isomers to be separable by column chromatography to access the desired cyclohepta[b]indoles.\textsuperscript{[240]}

\textit{1.2.2 Total Synthesis of Cyclohepta[b]indole Natural Products}

Cyclohepta[b]indole alkaloids have received considerable interest by synthetic chemists because of their unique molecular architectures and biological activities. Hence, several total syntheses of this specific class of natural products have been published over the last years. The following chapter will give an overview about the construction of some members of this product class that gained the most interest recently.
1.2.2.1 Total Syntheses of Actinophyllic Acid (241)

Several total syntheses, formal syntheses and approaches towards a total synthesis of actinophyllic acid (241) have been published.[186, 187, 189-193, 242, 243] This natural product mainly obtained attention because of its complex structure and its antithrombotic activity.[185]

The first total synthesis of racemic 241 was published in 2008 by the Overman group,[242], followed by an analogous strategy for its asymmetric version in 2010.[187] The asymmetric synthesis (see scheme 55) started with the conversion of commercially available Boc-protected amino acid 294 to the corresponding Weinreb amide, which was further treated with dimethylvinylmagnesium bromide to yield ketone 295. Upon treatment of 295 with catalyst 306, developed by Noyori and co-workers,[244], reduction of the ketone gave allylic alcohol 296 in 91% ee. Ozonolysis furnished a half-aminal, which was further reacted with acetic anhydride to yield 73% of diacetoxy piperidine 297 in gram scale.

Scheme 55: Overman’s total synthesis of (-)-actinophyllic acid (241) hydrochloride.[187]
Scandium-catalysed iminium ion formation and trapping with indole malonate 307 was followed by treatment with DiBAL-H to remove the acetate groups and furnished indole 298 as a single diastereomer. Swern oxidation of 298 proceeded smoothly to ketone 299 in 94% yield. 299 served as the key intermediate for an oxidative bis-enolate coupling (highlighted in red in scheme 55) mediated by [Fe(DMF)₃Cl₂][FeCl₄]. This complex, which can be prepared by treatment of ferric chloride with DMF in anhydrous diethyl ether, has previously been described to mediate phenolic couplings and ketone enolate dimerization. Thus, oxidative bis-enolate coupling of 299 formed bridged ketone 300 in 59% yield without racemisation. Reaction of 300 at -78 °C with vinylmagnesium bromide led to selective 1,2-addition. Quenching at low temperatures with acetic acid and warming to -20 °C resulted in the formation of a lactone with the upper carboxylate. The lactone was further reduced to give alcohol 301. Treatment of 301 with hydrochloric acid cleaved the Boc-group to the corresponding hydrochloride that could by recrystallised to increase the ee up to 99%. The final skeletal rearrangement cascade was triggered by reacting salt 302 with formaldehyde to iminium ion 303, which underwent aza-Cope rearrangement followed by Mannich reaction. This transformation established the cyclohepta[b]indole core and eventually completed the synthesis of (−)-actinophyllic acid (241).

More recently in 2017, the Chen group published a total synthesis of racemic 241 based on a desymmetrisation strategy (see scheme 56). Symmetrical triene ketone 308, which is readily available by [6+4]-cycloaddition of tropone with either butadiene or sulfolene, served as starting material for the Chen synthesis. Acetal protection of the ketone moiety was followed by selective dihydroxylation of the isolated olefin to 309. The dihydroxy compound 309 was oxidatively cleaved with the aid of lead(IV) acetate and the intermediate dialdehyde was reductively aminated with p-methoxybenzyl amine in the presence of NaBH(OAc)₃. The resulting PMB-protected amine was further converted to the corresponding Teoc carbamate 310. As key desymmetrisation event, 310 was treated with in situ generated bromonitrile oxide (obtained from 317) to give isoxazoline 311 in 68% yield as a single stereoisomer. Subsequent methoxy substitution and oxidation formed isoxazole 312, a masked β-ketoester which already contained the required carboxylic acid substituent of actinophyllic acid. Removal of the Teoc group with TFA gave the TFA salt, which was directly subjected to aminoarylation with arylbromide 316 by a methodology previously developed by the Wolfe group. Although several reaction conditions were screened, high catalyst loading (80 mol% Pd, 160 mol% phosphine) remained necessary to effectively catalyse this transformation. Removal of the acetal group was achieved by treatment of 313 with hydrochloric acid to yield ketone 314.
Palladium-catalysed hydrogenation reduced the nitrobenzene to the corresponding aniline and cleaved the isoxazole N-O-bond to form an aldehyde intermediate, which finally underwent condensation with the aniline to afford cyclohepta\[b\]indole 315. Deprotonation with LDA and ester-enolate addition to formaldehyde ultimately furnished actinophyllic acid (241) hydrochloride after acidic workup.[190]

1.2.2.2 Total Synthesis of Exotine A (239) and Exotine B (240)

The total synthesis of exotine B (240) by the Trauner group[249] was inspired by its proposed biosynthetic formation[183] by annulation of gleinadiene (321) with an indole diene (see scheme 57). Gleinadiene (321) was synthesised by converting coumarin 318 to the corresponding iodide 319, followed by Suzuki cross-coupling with pinacol boronate 320 in 86% overall yield. In a three component reaction, indole (322), aldehyde 323 and gleinadiene (321) (slowly added via syringe pump) underwent [4+3]-cycloaddition to form cyclohepta\[b\]indole 326 in 34% yield on gram scale as a 2:1 mixture of diastereomers. The reaction conditions were described previously by Wu and co-workers, especially for the formation of cyclohepta\[b\]indoles.[250] The reaction was proposed to proceed via addition of the indole to the aldehyde and intermediate formation of cation 325 that finally cyclised with 321.[249]
Scheme 57: First total synthesis of (+)-exotine B (240) by the Trauner group.\textsuperscript{[249]}

The three component reaction with prenal was also tested, but failed to deliver any cyclohepta[b]indole product.\textsuperscript{[249]} Oxidation of sulfide 326 to the corresponding sulfoxide and thermal elimination afforded a complex product mixture, but addition of potassium carbonate led to clean formation of compound 327. Finally, olefin isomerisation was achieved with hydrogen activated Crabtree’s catalyst to yield racemic exotine B (240) in 47% yield.\textsuperscript{[249]}

An analogous synthesis of racemic exotine A (239) was published shortly after by the Martin group (scheme 58).\textsuperscript{[251]}

Scheme 58: Biomimetic synthesis of (+)-exotine A (239) by Martin and co-workers.\textsuperscript{[251]}

Herein, three component reaction between indole (322), prenal (328) and trans-dehydroosthol (329) mediated by p-TsOH furnished racemic exotine A (239) as a 17:1 mixture of diastereomers.\textsuperscript{[251]}
1.2.2.3 Total Syntheses of Ambiguine P (247)

Despite several attempts towards their total synthesis,\textsuperscript{252, 253} the cyclohepta[b]indole containing ambiguines remained an unfinished target for long. Nonetheless, total syntheses of the tetracyclic member ambiguine H have been reported by the Baran group in 2007\textsuperscript{254} and the Maji group in 2018.\textsuperscript{255} Finally, the first total synthesis of a pentacyclic representative, namely ambiguine P (247), was published by the Sarpong group in 2019 (schemes 59 and 60).\textsuperscript{256} Their synthesis started (scheme 59) with indole derivative 330, which is readily available by Cu(II)-mediated oxidative coupling of (S)-carvone with indole, as previously reported by Baran.\textsuperscript{257} 1,2-addition of 2-methyl-3-butyn-2-ol was followed by Babler-Dauben oxidative transposition\textsuperscript{258, 259} to afford 331. The next task was construction of the cyclohepta[b]indole core, which was achieved by intramolecular Nicholas reaction in 88% yield. With substitution in C-2 and C-3 already established, the subsequent Friedel-Crafts alkylation proceeded selectively at C-4 to complete the pentacyclic framework in 333.\textsuperscript{256} Conjugate addition of cyanide and reductive removal of the biscobalthexacarbonyl yielded indole 334 in 49% yield in a three step sequence. The next steps dealt with establishing the right configuration and functionalisation at C-12. Direct vinylation gave the wrong configuration in accordance with the Fürst-Plattner rule. Therefore, 334 was subjected to Rh(I)-catalysed nitrile hydration followed by treatment with methyl formate under basic conditions to establish the right configuration at C-12.\textsuperscript{256}

\begin{itemize}
  \item 1) 2-Methyl-3-butyn-2-ol, LiHMDS, THF, -78 °C to r.t.
  \item 2) PDC, CH\textsubscript{2}Cl\textsubscript{2}, r.t.; then 1 N HCl, THF, 0 °C 44% in 2 steps
  \item 3) Co\textsubscript{2}(CO)\textsubscript{8}, then BF\textsubscript{3}-Et,O, CH\textsubscript{2}Cl\textsubscript{2}, r.t. 88%
  \item 4) AlCl\textsubscript{3}, MeOH, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C to r.t.
  \item 5) Et\textsubscript{2}AlCl, TMSCl, pyr, MeCN, r.t.
  \item 6) n-Bu\textsubscript{3}SnH, PhH, 45 °C, then 2 N HCl, MeOH, r.t. 49% in 3 steps
  \item 7) Rh(PPh\textsubscript{3})\textsubscript{2}Cl, acetaldoxime, PhMe, 130 °C
  \item 8) NaHMDS, methyl formate, THF, r.t.; 54% in 2 steps
  \item 9) NaBH\textsubscript{4}, MeOH, r.t.
  \item 10) Ti\textsubscript{2}O, 2,6-di-Bu\textsubscript{2}pyr, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C 51% in 2 steps
  \item 11) TCDI, DMAP, CH\textsubscript{2}Cl\textsubscript{2}, 45 °C
  \item 12) AIBN, n-Bu\textsubscript{3}SnH, PhMe, 80 °C 44% in 2 steps
\end{itemize}
Reduction of the ketone moiety and treatment with triflic anhydride led to the formation of aldehyde 336. Removal of the alcohol functionality was achieved by thio carbamate formation and Barton-McCombie deoxygenation to afford intermediate 337.[256]

Olefination of the aldehyde in 337 and hydration of the nitrile group were achieved in the same sequence (scheme 60). Thus, addition of TMSCH₂Li afforded a secondary alcohol, which added to the nitrile upon treatment with PPTS. Finally, cleaving the TMS-group with TBAF furnished amide 338 in 52% yield over this three-step sequence.[256] PIDA-mediated Hofmann rearrangement, earlier described by Zhdankin and co-workers, [260] afforded amine 339 in 39% yield. A formylation-dehydration sequence yielded isonitrile 340 in excellent yield. Elimination of the isonitrile under basic conditions and treatment with selenium dioxide to achieve allylic oxidation completed the total synthesis.[256]

Only one month after Sarpong’s synthesis was published, the Rawal group completed a twelve step synthesis of ambiguine P (scheme 61).[261] Starting ketone 342 was obtained in a four step sequence from commercially available material as previously described by Baran and co-workers.[254] Enol triflate formation furnished the starting material 343 for a Stille cross-coupling with 350, which afforded ketone 344 in high yield upon acidic hydrolysis. Conversion to the corresponding TBS enol ether led to diene 345. Diene 345 was planned to construct the cyclohepta[b]indole moiety by a [4+3]-cycloaddition in a one-pot reaction with indole 351, as tested by the authors with model substrates.[261] However, [4+3]-cycloaddition did not occur and yielded an enone without the ring closure at C-3. After extensive screening of reaction conditions involving Lewis or Brønsted acids and bases, which led to isomerisation and side products, NaAuCl₄ was found to effectively promote the ring-closing Michael addition to form cyclohepta[b]indole 346.[261, 262]
Scheme 61: Short total synthesis of (-)-ambiguine P (247) by Rawal and co-workers.[261]

With tetracycle 346 in hands, BF₃-mediated ring closure established the desired carbon skeleton in 347 with 81% yield. Desaturation of the seven-membered ring was achieved by oxidation to the enone. Subsequent protection of the indole nitrogen yielded carbamate 348. Reduction of the ketone group and dehydration with Martin sulfurane afforded unsaturated cyclohepta[b]indole 349. Final installation of the hydroxyl group was achieved by Boc removal and treatment with NBS. The authors assumed that bromination occurred at C-23, and subsequent elimination generated a cation at C-15. Trapping the intermediate cation with water eventually yielded ambiguine P (247).[261]
1.3 The Palladium – catalysed C(sp³)-H Activation

Palladium-catalysed C-H activation is a steadily growing field in organic synthesis, as indicated by the rising number of relevant publications and their citations over the last years (see figure 18).

![Figure 18: Citations and publications covering “C-H activation total synthesis” (Source: Web of Science).](image)

Converting non-activated carbon-hydrogen bonds into carbon-oxygen, carbon-sulfur, carbon-nitrogen, carbon-halogen or carbon-carbon bonds is still a challenging task in organic chemistry. The two main problems to be solved are on the one hand the inertness of C-H bonds and on the other hand the control of site selectivity during the activation process.\(^{[263]}\) If typical bond strengths of C-H bonds are considered, functionalisation of sp\(^3\)-hybridised carbon should be the easiest to achieve, since these show the lowest bond dissociation enthalpies (figure 19).\(^{[264]}\) This fact is true for functionalisation proceeding via homolytic bond cleavage, whereas for metal-catalysed reactions the C-M bond strengths have to be considered as well (figure 19).\(^{[265, 266]}\)

![Figure 19: Bond strength for C-H and C-M bonds depending on carbon hybridisation.](image)

Catalytic C(sp\(^3\))-H activation was already proven to be effective for selective functionalisation, but C(sp\(^3\))-H activation still proves to be a challenge because of additional conformational freedom and
lacking π-orbital interactions with the metal.\textsuperscript{[267]} The activation barrier is overcome by the use of coordinative groups that direct the metal atom towards the relevant C-H bond. This solves not only the problem of the low reactivity of C-H bonds but also of the site selectivity.\textsuperscript{[263, 266]} For the addition of oxygen, nitrogen, sulphur or halogen atoms or new carbon centres to C(sp\textsuperscript{3})-H and C(sp\textsuperscript{3})-H bonds, various methodologies of catalytic C-H functionalisation have been developed in the past years, and were summarised in several reviews.\textsuperscript{[263, 266-276]} The following chapter will give a short overview about the development of Pd-mediated C(sp\textsuperscript{3})-H functionalisation and the application of Pd-catalysed C(sp\textsuperscript{3})-H activation for C-C bond formation in total synthesis.

1.3.1 Development the of Palladium – catalysed C(sp\textsuperscript{3})-H Activation

In 1965, the Cope group\textsuperscript{[277]} discovered the formation of binuclear complex 354 when treating azobenzene (352) with palladium dichloride (scheme 62). It was found that the palladium inserted into the C-H bond ortho to the azo substituent.\textsuperscript{[277]} With this discovery, the first cyclopalladation, or generally cyclometalation, was described. This built the fundament of modern C-H functionalisation reactions and was extensively researched in the past years.\textsuperscript{[278-280]}

\begin{center}
 Scheme 62: First cyclopalladation reaction of azobenzene described by the Cope group.\textsuperscript{[277]}
\end{center}

As shown in scheme 63, directing group-mediated cyclometalation usually occurs in γ-position in regard of the directing group. Coordination of the metal by the directing group activates the metal centre, which further undergoes agostic interactions with the γ-C-H bond. Due to this activation, the metal centre can finally insert into the C-H bond to generate a five-membered chelate ring complex. This reaction is influenced by the kind of coordinating group, the metal centre and the further ligands bonded to the metal. The highest impact probably has the formation of the chelate ring itself, as described in the chelate effect, which strongly favours these chelate rings in comparison to monodentate ligands.\textsuperscript{[281, 282]}

\begin{center}
 Scheme 63: General cyclometalation reaction.\textsuperscript{[281]}
\end{center}
For a couple of years, the cyclometalation reaction could not be turned into a useful application for organic synthesis because of harsh reaction conditions, low TON, low functional group tolerance and little selectivity leading to side product formation. One of the first examples for a catalytic C-C bond formation through C-H activation was reported in 1984 by Tremont and co-workers (scheme 64). They found that treatment of acetanilides with palladium acetate and methyl iodide gave ortho-methylated anilides in high yield. While first attempts needed 1.5 eq. of palladium salt, addition of excess silver acetate led to 10 turnovers/Pd in 10 min. Regarding the mechanism, a PdIV intermediate was suggested by the authors.

Several years later, the Daugulis group reported analogous arylation of anilides with high turnover rates. When the same conditions were applied to α-alkylated pyridines or quinolines, the regioselective C(sp²)-H activation of the alkyl substituents was observed. The shorter reaction times found for electron-rich aryl iodides support a mechanism via cyclopalladation followed by oxidative addition of the aryl iodide via a PdIV intermediate, as already proposed by Tremont.

Short time later, Daugulis and co-workers reported the first catalytic, directing group-mediated and regioselective C(sp³)-H arylation employing an 8-aminoquinoline amide or picolinamide as directing group (scheme 66).
Scheme 66: Regioselective C(sp$^3$)-H arylation by Daugulis and co-workers.$^{[286]}$

Initial experiments with a 2-aminomethylpyridine as directing group were not successful due to the high reactivity of its benzylic position upon the harsh reaction conditions. To circumvent this problem, they employed the 8-aminoquinoline as directing group 365 without a reactive benzylic position. This directing group proved to be very reactive, as even multiple arylation could be achieved depending on the number of equivalents of aryl iodide. Noteworthy, multiple arylation gave predominantly cis-products. Not only carboxylic acid derivatives could be C-H activated, but also amine-derived alkanes, by employing a 2-picolinamide moiety 367. This showed to be less reactive than its 8-aminoquinoline counterpart and therefore exclusively yielded the monoarylated products 368.$^{[286]}$

Despite of the 8-aminoquinoline 369 directing group being one of the most often employed chelating directing groups,$^{[287, 288]}$ several other groups have been developed in the last years to address specific requirements for the desired transformation (see figure 20).$^{[267]}$

Figure 20: Typical directing groups for the C-H functionalisation of carboxylic acids or amines.

Beside the 8-aminoquinoline 369 and 2-picolinamine 370 directing group, the 2-methylthioaniline 371 group was established by the Daugulis group as well.$^{[289]}$ It showed to effectively mediate the arylation of carboxylic acid and lactic acid derivatives without the need to add silver salts as promoter,$^{[289]}$ as well as the reaction of amino acid derivatives.$^{[290]}$ In 2014, the Sahoo group reported the bromination and chlorination of C(sp$^3$)-H bonds assisted by sulfoximine 372 as well as their subsequent acetoxylation.$^{[291]}$ The fluorinated directing groups 373-375 have been employed
by the Yu group, among other applications, for the olefination, carbonylation or asymmetric cross-coupling with organoboron reagents of C(sp\(^3\))-H bonds. Pyridylsulfonamide 376 was introduced by the Carretero group in 2013 and showed to be effective for selective \(\gamma\)-arylation of amino acids, including \(\alpha\)-quaternary amino acids and dipeptides. In 2014, the Baran group reported the arylation of cyclobutane carboxylic acid derivatives with the aid of picolinimide directing group 377. Previous attempts with aminoquinoline or thioaniline directing groups gave only poor yields and the directing groups were difficult to cleave. Triflyl protected amine 378, a rather weak coordinating group, was introduced by the Yu group and readily undergoes asymmetric C(sp\(^3\))-H arylation with arylboron reagents.

The exact mechanism for directing group-mediated Pd-catalysed C(sp\(^3\))-H arylation remained unclear for several years, although the reaction was proposed to proceed under Pd\(^{II}\) – Pd\(^{IV}\) catalysis. First evidence of Pd\(^{IV}\) complexes was published by Canty and co-workers (scheme 67). They observed oxidative addition of methyl iodide to Pd\(^{II}\) complex 379 and could verify the octahedral structure of the product 380 via X-ray structure analysis. Several years later, they described the transfer of a Ph\(^+\) from [Ph\(_2\)I]\(^+\)OTf\(^-\) to square planar palladacyclopentane 381. The resulting Pd\(^{IV}\) complex 382 was observed via NMR at low temperatures and decomposed through reductive elimination pathways, as proved by the formation of phenylbutene (70%) and phenylbutane (22%). These findings deliver further evidence on Pd\(^{IV}\) catalysis for the directing group mediated C-H arylation.

Following mechanistic studies by the Daugulis group concerning the ortho-arylation of naphtoic acid derivatives 385 (scheme 68) through C-H activation supported a Pd\(^{IV}\) mechanism as well, since Pd\(^{0}\) sources could not accomplish the desired transformation under the analogous conditions.

![Scheme 67](image1.png)

*Scheme 67: Palladium\(^{IV}\) complexes synthesised by Canty and co-workers.*

![Scheme 68](image2.png)

*Scheme 68: Benzoic acid arylation by Daugulis and co-workers.*
This was complementary to computational studies of several groups. As a result, a Pd
mechanism, together with the crucial role of silver additives, is nowadays accepted for the C-H arylation (scheme 69).

The reaction commences with coordination of the directing group towards the palladium, which is favoured by the chelate effect, to form complex 390. Subsequently, the palladium can undergo an agostic interaction with the C-H bond in \( \gamma \)-position in regard of the directing group. In consequence, this C-H bond is weakened and the palladium eventually inserts to give cyclometalated complex 392.

Scheme 69: General mechanism for the Pd-catalysed C-H arylation.

Computational and experimental studies by the groups of Yu, Houk and Wang, Dang on similar systems suggested that the role of the silver is not only regeneration of the palladium
catalyst, but also stabilisation of high-energy intermediates through the formation of Pd$^{II}$-Ag$^I$ heterodimeric complexes. The weakly bonded acetic acid is exchanged by the aryl iodide with the aid of the silver additive. Oxidative addition produces Pd$^{IV}$ complex 394, the iodide is abstracted by the silver cation. Prior to reductive elimination an octahedral Pd$^{IV}$ intermediate 395 is formed. The subsequent reductive elimination re-establishes Pd$^{II}$ and represents the crucial C-C bond forming event. Regeneration of the catalyst and release of the product occur by protonation at the amide nitrogen and ligand exchange with acetic acid.\textsuperscript{[286, 302-305]}

1.3.2 Applications of the Palladium – catalysed C(sp$^3$)-H Activation in Total Synthesis

Numerous methodologies for the directed activation of C(sp$^2$)- and C(sp$^3$)-H bonds have been described in the past years and have been compiled in several reviews.\textsuperscript{[263, 266, 267, 271, 272, 275, 276, 306]} Not surprisingly, these methodologies found their way into total synthesis and have been applied for the synthesis of various challenging natural products. The following chapter will highlight few syntheses that have been completed in the last ten years.

1.3.2.1 Total Syntheses utilising C-H Activation for the Formation of C-C Bonds

Piperarborenine B (403) was isolated from the stems of Piper arborescens together with other cyclobutane alkaloids, showing in vitro cytotoxicity against multiple cancer cell lines.\textsuperscript{[307]} In 2011, the Baran group published a total synthesis\textsuperscript{[308]} based on the C-H activation strategy previously developed by the Daugulis group utilizing amide directing groups (scheme 70).\textsuperscript{[389]} The synthesis commenced with commercial methyl coumalate (398), which underwent photochemical 4$\pi$ electrocyclisation followed by hydrogenation and amide formation to yield C-H activation precursor 399. C(sp$^3$)-H arylation with 3,4,5-trimethoxyiodobenzene (404) gave the desired product as a single diastereomomer. To introduce the other aryl substituent, the directing amide was epimerised using LiOt-Bu and the arylation was performed with 3,4-dimethoxyiodobenzene (405) in high concentration (1 M in t-BuOH). High selectivity was observed for the secondary C-H bond over the tertiary benzylic position.\textsuperscript{[308]}
Conversion of the amide to the corresponding Boc-imide followed by hydrolysis using LiOOH simultaneously removed the directing group and the methyl ester to give the free carboxylates. Treatment with oxalyl chloride gave the bis acyl chloride, which was further reacted with dihydropyridone 406 to yield the natural product 403 in a short seven step sequence.\[308\]

Applying an analogous strategy, the Baran group could also accomplish the total synthesis of pipercyclobutanamide A (411), which was previously isolated from Piper nigrum by Fujiwara and co-workers.\[310\] C-H activation precursor 407 was prepared by the same procedure as for the synthesis before (scheme 70), but 8-aminoquinoline was needed for its higher reactivity in the coupling of vinyl iodides (scheme 71).\[309\] C-H arylation proceeded smoothly in 54% yield, followed by the olefination with styryl iodide 413 in 59% yield to obtain the strained all-cis tetrasubstituted cyclobutane 409. In contrast to earlier results, protic solvents and pivalic acid as additive proved to retard the reaction. Double isomerisation of the amide and the ester moieties was achieved by treatment with sodium methoxide, followed by reductive removal of the directing group with Di/\text{BAL}-H to provide aldehyde 410. Activation of the carboxylic acid with propylphosphonic anhydride (\text{T$_3$P}) and coupling with piperidine established the amide. Finally, Ando olefination employing phosphonate 414 gave the natural product 411 in 56% yield from 410.\[309\]

*Scheme 70: Baran’s total synthesis of (±)-piperarboerenine B (403).*\[308\]
In 2014, the Maimone group published a very short synthesis of the lignin aryltetralin podophyllotoxin (419, scheme 72). This natural product serves as starting material for the type II topoisomerase targeting drugs etoposide and teniposide used for the treatment of various types of cancer.

Scheme 71: Total synthesis of (±)-piperocyclobutanamide A (411) by the Baran group.[309]

Scheme 72: Total synthesis of (±)-podophyllotoxin (419) by Maimone and co-workers.[312]
Their synthesis (scheme 72) commenced with cyclobutanol 415, which could be obtained by a two-step sequence from 6-bromopiperonal.[314] Deprotonation of 415 triggered the formation of o-quinodimethane 415a,[315] which further underwent Diels-Alder reaction with amide 416 to yield intermediate 417.[312] Subsequent reduction of the methyl ester with Super-Hydride® and acetonide formation gave C-H activation precursor 418 in 41% yield over the whole sequence. Dibenzyl phosphate proved to be an efficient additive to promote the C-H arylation. Further treatment with TFA cleaved the acetonide and lactone formation removed the methylthio aniline directing group to provide podophyllotoxin (419) in a very short five-step synthesis.[312]

In 2016, the Reisman group accomplished the asymmetric total synthesis of (+)-psiguadial (426) (scheme 73).[316] which was previously isolated from Psidium guajava, a plant used in traditional Chinese medicine.[317]

The synthesis began with the photochemical Wolff rearrangement of diazoketone 420, followed by (+)-cinchonine-mediated asymmetric ketene addition of 8-aminoquinoline (421), to furnish cyclobutanamide 422 with excellent enantioselectivity. C-H olefination with vinyliodide 423 proceeded smoothly in high yields. The directing group was cleaved to the corresponding aldehyde via reduction with Schwartz’ reagent, and the intermediate cis-aldehyde was further epimerised to the desired trans-configuration. Following Wittig olefination established the vinyl group and treatment with HCl induced deprotection of the carbonyl and shifted the double bond into conjugation to give key intermediate 425. Conversion of 425 to the natural product 426 was achieved in 10 additional steps with 8% yield.[316]
As can be seen in scheme 74, the Maulide group applied the directed C-H arylation strategy to a total synthesis of the antimalarial agent (-)-quinine (433).\textsuperscript{[318]} C-H activation precursor 427 was prepared by coupling of commercial 3-aminoquinuclidine with picolinic acid, a directing group previously introduced by Daugulis.\textsuperscript{[286]}

Coupling with p-iodoanisole proceeded in high yield to give 428 as a single isomer. Oxidative degradation\textsuperscript{[319]} of the anisole gave the corresponding carboxylic acid, which was further converted to Weinreb amide 429. Reduction with DiBAL-H and subsequent Wittig olefination established the vinyl group.\textsuperscript{[318]} Reductive cleavage of the picolinamide\textsuperscript{[320]} led to amine 430. As earlier described by the Nicolaou group,\textsuperscript{[321]} treatment of 430 with IBX furnished ketone 431. Aldol reaction with carbaldehyde 434 followed by mesylhydrazone formation to suppress epimerisation afforded hydrazone 432. Final reduction with \textit{in situ} germinated trimethoxy aluminum hydride eventually gave (-)-quinine (433).\textsuperscript{[318]}

As last example for the efficiency of C-H activation/C-C bond formation, the Baudoin synthesis of the dithiodiketopiperazine natural products (--)-epicoccin G (439) and (--)-rostrat A (440) is shown in scheme 75.\textsuperscript{[322]} Asymmetric epoxidation of cyclohexenone by application of a methodology by the List group\textsuperscript{[323]} followed by vinyl triflate formation yielded 436 in excellent enantioselectivity. Epoxide opening occurred upon treatment with alanine tert-buty1 ester in trifluoroethanol and the free alcohol was further acetylated to yield 437. Ester cleavage on silica gel and cyclisation with BOP-Cl (443) afforded diketopiperazine 438. The key double C(sp$^3$)–H activation/olefination was achieved through Pd$^{0}$/Pd$^{II}$ catalysis. These modified conditions were previously developed by the Baudoin group\textsuperscript{[324]} and afforded key intermediate 439 in excellent yield. From this intermediate, (--)-

\begin{scheme}
\textbf{Scheme 74:} Asymmetric total synthesis of (-)-quinine (433) by Maulide and co-workers.\textsuperscript{[318]}
\end{scheme}
epicoccin G (440) and (−)-rostratin A (441) were accessible over further seven and ten steps, respectively.\[322\]

Scheme 75: Total synthesis of (−)-epicoccin G (440) and (−)-rostratin A (441) by Baudoin and co-workers,\[322\]

1.3.2.2 Total Syntheses utilising C-H Activation for the Formation of C-Heteroatom Bonds

As C-H activation is not only used for the formation of new C-C bonds, the following paragraph will highlight few examples in total synthesis using C-H activation for the formation of C-heteroatom bonds. Jiadifenolide (449), isolated from Illicium jiadifengpi in 2009 by the Fukuyama group, exhibits an intriguing cage-like architecture and also possesses potent neurotrophic activity.\[325\] Five years later, the Sorensen group published a total synthesis of this sesquiterpenoid (scheme 76) starting from β-ketoester 444, which is derived from (R)-(+)-pulegone.\[326\]

Scheme 76: Sorensen’s total synthesis of jiadifenolide (449).\[326\]
Nitrile 445 was obtained after a seven step sequence, comprising a Robinson annulation\textsuperscript{[327]} and van Leusen homologation\textsuperscript{[328]}, in overall 48% yield. Acidic hydrolysis of the nitrile triggered lactone formation and also cleaved the acetal protecting group to furnish 446. Treatment with hydroxylamine hydrochloride in pyridine gave oxime 447, the precursor for a directed C-H acetoxylation.\textsuperscript{[326]} This methodology was developed by the Sanford group and uses in situ generated O-acetyl oximes as directing group for the C-H activation event.\textsuperscript{[329]} In the course of that, the crucial oxidation could be achieved to yield a 1:1 mixture of 448 and its epimer at C-5. The authors supposed that the high reaction temperature and conformational flexibility led to lack of selectivity for the methyl groups by the palladium catalyst. However, this was the only methodology to permit the desired transformation and gave access to gram-scale quantities of 448. Further conversion of 448 eventually gave jiadifenolide (449) after eight additional steps.\textsuperscript{[326]}

In 2016, the groups of Yu and Sarpong reported the formal synthesis of cyclopenta[g]indole natural product herbindole B (458) via an amine directed C-H amination strategy.\textsuperscript{[330]} The sequence began (scheme 77) with a ruthenium-catalysed [2+2+2+1]-cyloaddition of hex-3-yne (450) and norbornene derivative 451 to furnish hydroquinone 452 according to the methodology from the Mitsudo group.\textsuperscript{[330, 331]}

![Scheme 77: Formal synthesis of (±)-herbindole B (458) by the Sarpong and Yu groups.\textsuperscript{[330]}](image)

Triflation and tosylation gave intermediate 453, which further underwent Stille cross-coupling to yield aryl tosylate 454. Optimised Buchwald-Hartwig amination\textsuperscript{[332]} conditions gave the primary aniline, which was subsequently converted to the corresponding triflamide 455. Arylation of the triflamide was enabled by conditions developed by the Yu group.\textsuperscript{[328]} The reaction did not only induce the desired C-N bond formation but also caused further oxidation to yield indole 456.\textsuperscript{[330]}
Removal of the triflyl group and N-tosyl protection gave Kerr’s intermediate [457][333] and completed the formal synthesis.[330]

A last illustrative example for the versatility of directed C-H functionalisation is the total synthesis of the marine polyketide (±)-hippolachnin A (465) by the groups of Wood and Brown (scheme 78).[334] The synthesis commenced with addition of quadricyclane (459) to acyl chloride 460 under microwave irradiation. This was followed by basic hydrolysis to give carboxylic acid 461, that already exhibits to majority of the stereochemical complexity of hippolachnin A (465). Subsequent opening of the norbornene ring was achieved by ring-opening metathesis with ethylene to give 462.[334]

The crucial C-H oxidation was achieved according to the methodology previously developed by the White group.[335] This transformation is assumed to proceed via an allyl-Pd species, trapped by chromium-mediated carboxylate addition to give lactone 463 in 70% yield.[334, 335] Condensation with tert-butyl acetate, hydrogenation and transesterification finished the short synthesis of the complex natural product hippolachnin A (465).[334]
1.4 The Divinylcyclopropane–Cycloheptadiene Rearrangement

The divinylcyclopropane–cycloheptadiene rearrangement is a [3,3]-sigmatropic rearrangement and a variation of the Cope rearrangement. Unlike the Cope rearrangement, its thermodynamic driving force is mainly the release of ring strain in the course of the cyclopropane opening.\[336\] It was first described by Vogel and co-workers in 1960,\[337, 338\] but isolation of the cis-divinylcyclopropane intermediate (470) was not possible under the reaction conditions (scheme 79). Several years later in 1973, the Brown group could isolate and characterise cis-divinylcyclopropane (470), which was obtained after a sophisticated low temperature olefination and distillation sequence.\[339\]

\[\text{Scheme 79: Divinylcyclopropane rearrangement by Vogel (A) and Brown (B).}\[337-339\]]

Considering the transition state of the “traditional” Cope rearrangement (scheme 80, left part), the chair-like transition state is favoured by roughly 11 kcal/mol over a competing boat-like alternative.\[340\]

\[\text{Scheme 80: Transition states of the Cope[341] and divinylcyclopropane rearrangements (ZPVE in kcal/mol).}\[342, 343\]
As the DVCPR can proceed only from *cis*-divinylcyclopropanes, three possible transition states for this transformation have to be considered (scheme 80, right part) as in-depth DFT calculations by Özkan and Zora revealed.[342] The three distinct conformations can be adopted by the divinylcyclopropane and are interconvertible due to small energy barriers. These conformations result in three different transition states, an endo-boatlike, chairlike and exo-boatlike, where the endo-state \( T_S_{endo} \) is favoured with an activation barrier of 19.7 kcal/mol (see scheme 80). As a consequence, this pathway eventually furnishes cycloheptadiene 471 with two (Z)-double-bonds, being the thermodynamically favoured product by -20.1 kcal/mol. The other possible products are unfavoured due to increasing ring strain in the cycloheptadiene.[342] Additional calculations by Zora[344] showed a decrease in the activation barrier through incorporation of heteroatoms in the cyclopropane tether. This especially favoured the rearrangement of divinylepoxides and −aziridines to the corresponding dihydroazepines and dihydrooxepines.[344]

Introduction of a cyclopropane to a Cope-system not only benefits the “standard” rearrangement, but can also lower the activation energy in an aromatic DVCPR. The release of ring strain lowers the energy barrier for the [3,3]-rearrangement roughly by 13 kcal/mol, whereas the loss of aromaticity increases the barrier by 10 kcal/mol (scheme 81, left part).[345–347] If these effects are combined, the aromatic DVCPR is energetically slightly favoured over the analogous Cope rearrangement.[348] Early examples of an aromatic DVCPR have been reported by Maas and co-workers on the rearrangement of pyridyl- 473 or furylvinylcyclopropanes 475 and others (scheme 81, right part).[349, 350]

\[
\text{Scheme 81: The aromatic DVCPR; thermodynamic considerations[348] and examples,[349, 350]}
\]

*Trans*-configured divinylcyclopropanes are usually the thermodynamically more stable derivatives compared to their *cis*-counterparts. Although the steric requirements to undergo the DVCPR are not fulfilled in *trans*-divinylcyclopropanes, it was observed that they are able to rearrange to the corresponding cycloheptadienes at elevated temperatures (~200 °C).[337] Different isomerisation
pathways have been described for the *trans*-divinylcyclopropanes, proceeding either *via* a biradical intermediate\textsuperscript{[351-354]} or through one-centre epimerisation.\textsuperscript{[355, 356]} The DVCPR has found numerous applications in total synthesis, which have been summarised by our group some years ago in a review.\textsuperscript{[343]}
2. Results and Discussion

As cyclohepta[b]indoles comprise a large group of natural products and pharmaceutically active compounds (see chapter 1.1), we envisioned to develop a general methodology to access this versatile motif and to apply it in the total synthesis of specific natural products. A first generation approach towards cyclohepta[b]indoles, which was also applied to the synthesis of SIRT1-inhibitor 255, was published by our group in 2013 (scheme 82). The synthetic strategy to construct the seven-membered ring is based on a [3,3]-sigmatropic divinylcyclopropane/Cope-rearrangement.\[^{[220]}\]

![Scheme 82: Earlier approach towards cyclohepta[b]indoles 482 by our group.\[^{[220]}\)](https://example.com/scheme82)

Chirality was introduced \textit{via} Charette’s asymmetric variant of the Simmons-Smith cyclopropanation.\[^{[357]}\] The sigmatropic rearrangement allowed the transfer of chirality from the cyclopropane to the newly formed quaternary centre and the benzylic position, as apparent from the transition state 480 (scheme 82). Eventually, the indole-core could be rearomatised by treatment with $p$-TsOH.\[^{[220]}\]

During his PhD, Dr. Erik Stempel expanded the previously developed method by construction of trisubstituted cyclopropanes (scheme 83) that eventually enabled the total synthesis of \textit{ervatamia} alkaloids.\[^{[358]}\]

![Scheme 83: Copper-catalysed cyclopropanation by Stempel.\[^{[358]}\)](https://example.com/scheme83)

Despite the high yields and excellent diastereoselectivity, the cyclopropanation reaction remained a bottleneck, since the enantioselectivity could not be increased above 60\%.\[^{[358]}\]
It was planned to combine the chirality transfer of the sigmatropic rearrangement with a highly enantioselective construction of a multi-substituted cyclopropane. To overcome the restrictions of intermolecular cyclopropanation, the cyclopropane should be built up in an intramolecular fashion and the indole part should be attached later by stereospecific, directed Pd-catalysed C-H arylation. Thus, in retrosynthetic direction (scheme 84) general cyclohepta[b]indole 487 should be derived from divinylcyclopropane 488 through a sigmatropic rearrangement. Substituents R¹ and R² could be introduced via stereospecific olefination that leads back to substituted cyclopropane 489 after some FGI’s.

The indole moiety is planned to be introduced through a directed Pd-catalysed C(sp³)-H activation of 490 with 3-iodoindole derivatives. C-H activation precursor 490 could be obtained from lactone 491 after installation of the directing group. Lactone 491 itself would be the product of an asymmetric intramolecular cyclopropanation reaction of allyldiazo acetate 492, which should be readily available from the corresponding allylic alcohol 493.

2.1 Construction of Cyclohepta[b]indoles via Palladium – catalysed C(sp³)-H Activation

The major part of this chapter has been published as research article “Enantioselective Synthesis of Cyclohepta[b]indoles via Pd-Catalyzed Cyclopropane C(sp³)–H Activation as a Key Step” together with M.Sc. Yevhenii Sokolenko in Organic Letters 2019, 21, 7370–7374.[359]

Initially, this project was investigated simultaneously with the studies towards a total synthesis of exotine A (239) and B (240) (details see chapter 2.2), for which reason some aspects may be discussed twice. However, for reasons of clarity and comprehensibility, these two chapters were separated.
2.1.1 Synthesis of the Racemic C-H Activation Precursor

Since it was planned to apply the methodology in the total synthesis of exotine A (239) and B (240), synthetic efforts and development began with the construction of methyl-substituted cyclopropane 495 (scheme 85). By use of this key intermediate the required methyl group on the exotine cycloheptane ring would already be established. A detailed retrosynthetic analysis of the natural products will be discussed in chapter 2.2.

![Scheme 85: Short retrosynthetic analysis of exotine A (239) and B (240).](image)

The first task was the synthesis of diazoacetate 498 (see table 1) to allow examination of the intramolecular cyclopropanation reaction. Since large amounts of the desired cyclopropane would be needed, a cheap and reliable access to allylacetoacetate 497 had to be found. Transesterification of ethyl acetoacetate with methallyl alcohol (table 1) under base catalysis\cite{360} seemed best suitable for that purpose. Constant removal of ethanol was necessary to shift the equilibrium towards the product. Reproducing the reported conditions, a fair yield of 57% was obtained\cite{360} but purification was challenging due to azeotrope formation of product and starting material (entry 1A). Therefore, the reaction was conducted at higher concentration under constant removal of the ethanol/toluene azeotrope and refilling with the same amount of toluene, to increase the yield to 78%. However, a rather large contaminated side fraction was obtained (entry 2A). Lowering the number of equivalents of ethyl acetoacetate gave a rather pure product after distillation but with concomitant decrease of yield (entry 3A). Since it was anticipated that the ethyl acetoacetate would interfere in the later cyclopropanation, because of formation of ethyl diazoacetate, an alternative access was needed. Acetoacetylation with diketene-acetone adduct\cite{361} proceeded smoothly and rapidly to yield 70% of pure product 497 (entry 4A). The yield could be increased to 85% by prior distillation of the diketene-acetone adduct and by conducting the reaction at higher concentration (entry 5A).

With access to large quantities of methallyl acetoacetate 497, the next task was to prepare the corresponding diazo compound 498.

Applying Overman’s conditions\cite{362} to impure 497 gave a 73% yield of the desired product contaminated with an ethyl diazoacetate impurity, which was not possible to remove neither by
distillation nor by column chromatography (entry 6B). Therefore, only pure 497 was used in further experiments. A slightly larger scale using the same conditions gave 65% of pure diazoacetate 498 (entry 7B). Since tosyl azide, especially in its crystalline form, is classified as explosive,[363] the safer p-acetamidobenzensulfonyl azide (ABSA)[364] was preferred in future operations. As the distillation of the diazo compound was also regarded as potential hazard, the product should be purified by column chromatography. Gratifyingly, substitution of tosyl azide by ABSA followed by chromatographic purification furnished 498 in excellent yield in decagram scale (entry 8B).

Table 8: Preparation of methallyl diazoacetate 498.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>scale</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>ethyl acetoacetate (2 eq.), NEt₃ (2 eq.), PhMe (0.66 M), Dean-Stark, rflx., 6 h[360]</td>
<td>0.1 mol</td>
<td>57% after distillation, but ethyl acetoacetate impurity</td>
</tr>
<tr>
<td>2A</td>
<td>ethyl acetoacetate (2 eq.), NEt₃ (2 eq.), PhMe (1.33 M), Dean-Stark, rflx., 10 h</td>
<td>0.2 mol</td>
<td>78% after double distillation over long Vigreux column</td>
</tr>
<tr>
<td>3A</td>
<td>ethyl acetoacetate (1.3 eq.), NEt₃ (1.3 eq.), PhMe (1.33 M), Dean-Stark, rflx., 6 h</td>
<td>0.3 mol</td>
<td>46% after single distillation, pure</td>
</tr>
<tr>
<td>4A</td>
<td>Diketene-acetone adduct (1 eq.), o-xylene (1 M), rflx.</td>
<td>0.3 mol</td>
<td>70% after distillation</td>
</tr>
<tr>
<td>5A</td>
<td>Diketene-acetone adduct (1 eq.; distilled prior to use), o-xylene (2 M), rflx.</td>
<td>0.3 mol</td>
<td>85% after distillation</td>
</tr>
<tr>
<td>6B</td>
<td>TsN₃ (1.1 eq.), NEt₃ (1.2 eq.), MeCN (0.8 M), r.t.; then 16% KOHₐq, overnight[362]</td>
<td>0.1 mol</td>
<td>73% after distillation; ethyl diazoacetate impurity</td>
</tr>
<tr>
<td>7B</td>
<td>TsN₃ (1.1 eq.), NEt₃ (1.2 eq.), MeCN (0.8 M), r.t.; then 16% KOHₐq, overnight[362]</td>
<td>0.15 mol</td>
<td>65% after distillation; pure</td>
</tr>
<tr>
<td>8B</td>
<td>ABSA (1.1 eq.), NEt₃ (1.2 eq.), MeCN (0.8 M), r.t.; then 16% KOHₐq, overnight</td>
<td>0.15 mol</td>
<td>94% after column</td>
</tr>
</tbody>
</table>

With access to diazoacetate 498 established, the next target was cyclopropane 495. Initially, it was planned to examine if the C-H activation would give the desired product in the later step. Hence, racemic cyclopropanation conditions were tested without the need of an asymmetric ligand. A large variety of metal catalysts are known to decompose diazo reagents to metal carbenes that further undergo cyclopropanation with olefins. For electron-rich olefins, catalysts based on Rh, Ru, Co or Cu are usually used.[365] As potential catalysts Rh₂(OAc)₄,[366, 367] Cu(MeCN)₄PF₆,[368] Cu(OTf)₂ and Cu(OTf) as benzene or toluene adduct[369, 370] were screened, which represent typical catalysts for cyclopropanation reactions.

In general, the solvents were dried and degassed prior to the reaction. In a first experiment, diazoacetate 498 was subjected to conditions comparable to the asymmetric cyclopropanation
reaction with dirhodium carboxamide catalysts (entry 1, table 9). Herein, the chiral Rh catalyst was replaced by Rh$_2$(OAc)$_4$. Only trace amounts of product could be identified from a complex mixture, probably caused by too rapid addition of the diazo compound or the limited solubility of dirhodium tetraacetate in chlorinated solvents. Therefore, the better soluble copper complexes were investigated next. Indeed, rapid consumption of the starting material was observed with Cu(MeCN)$_4$PF$_6$ in CH$_2$Cl$_2$, but led to a complex product mixture and only dimer could be identified (entry 2).

Table 9: Catalyst screening for cyclopropanation of 498.

<table>
<thead>
<tr>
<th>#</th>
<th>catalyst</th>
<th>solvent</th>
<th>c (XY)</th>
<th>c (cat)</th>
<th>add. rate</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh$_2$(OAc)$_4$ (1 mol%)$^a$</td>
<td>CH$_2$Cl$_2$</td>
<td>0.5 M</td>
<td>1 mM</td>
<td>3 mL/min</td>
<td>traces 495</td>
</tr>
<tr>
<td>2</td>
<td>Cu(MeCN)$_4$PF$_6$ (2 mol%)$^a$</td>
<td>CH$_2$Cl$_2$</td>
<td>0.1 M</td>
<td>0.1 M</td>
<td>5 mL/min</td>
<td>499</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OTf)$_2$ (5 mol%)$^a$</td>
<td>CH$_2$Cl$_2$</td>
<td>0.2 M</td>
<td>20 mM</td>
<td>2 mL/min</td>
<td>&lt;5% 495 + 499</td>
</tr>
<tr>
<td>4</td>
<td>[Cu(OTf)$_2$]•PhH (1.5 mol%)$^a$</td>
<td>CH$_2$Cl$_2$</td>
<td>0.1 M</td>
<td>40 mM</td>
<td>2 mL/min</td>
<td>15% 495 + 499</td>
</tr>
<tr>
<td>5</td>
<td>[Cu(OTf)$_2$]•PhH (1.5 mol%)$^a$</td>
<td>CHCl$_3$</td>
<td>0.1 M</td>
<td>6 mM</td>
<td>1 mL/min</td>
<td>1:2 499:495; 29%</td>
</tr>
<tr>
<td>6</td>
<td>[Cu(OTf)$_2$]•PhH (2x2 mol%)$^b$</td>
<td>CHCl$_3$</td>
<td>0.1 M</td>
<td>1.8 mM</td>
<td>1 mL/min</td>
<td>25% 495</td>
</tr>
<tr>
<td>7</td>
<td>[Cu(OTf)$_2$]•PhMe (2 mol%)$^b$</td>
<td>CHCl$_3$</td>
<td>1 M</td>
<td>2 mM</td>
<td>2 mL/min</td>
<td>38% 495</td>
</tr>
<tr>
<td>8</td>
<td>[Cu(OTf)$_2$]•PhMe (3 mol%)$^b$</td>
<td>CH$_2$Cl$_2$</td>
<td>1 M</td>
<td>2 mM</td>
<td>1 mL/min</td>
<td>65% 495</td>
</tr>
</tbody>
</table>

$^a$commercial catalyst; $^b$freshly prepared

Salomon and Kochi reported the high catalytic activity of copper(I) triflate for the cyclopropanation of alkenes with diazoacetates. The authors also described the use of copper(II) triflate as catalyst, which is reduced in situ by the diazo compound to Cu(I). Therefore, 498 was treated with Cu(OTf)$_2$, what led to the formation of nitrogen after some induction time. Upon further addition of 498, the mixture darkened and around 5% of product could be isolated alongside with the previously observed dimer (entry 3). As [Cu(OTf)$_2$]•PhH was reported to be comparably reactive, the reaction was tested with that complex. Indeed, cyclopropane 495 could be isolated, even though in 15% yield only (entry 4).

In the course of the preparation of scopadulcic acid A, the Overman group reported the synthesis of chiral 495 with Cu(I) triflate in chloroform. Thus, the cyclopropanation was tested in chloroform with a higher dilution of the catalyst and the isolated yield of 495 increased to 29% (entry 5). [Cu(OTf)$_2$]•PhH is described as a colourless solid in literature, however, the commercial sample was a yellowish-brown powder. Therefore, the benzene as well as the toluene complex were freshly prepared according to literature procedures. Addition of a second portion of catalyst decreased the yield due to increased decomposition (entry 6). In all reactions (entries 1-6),
catalyst decomposition was observed over time. This might be rationalised by disproportionation to elemental copper and Cu(II)-salts, as a dark solid was formed during the reaction. Consequently, to shorten the addition time, the catalyst was highly diluted and a more concentrated diazoacetate solution was added. This further increased the yield to 38%, with concomitant increased dimer formation, because of the higher concentration (entry 7). Surprisingly, switching back to dichloromethane as the solvent and slightly increasing the amount of catalyst led to an increased yield up to 65% and suppression of catalyst decomposition (entry 8). It should be mentioned, however, that the yield varied between 40% and 65% for this reaction. Nevertheless, sufficient amounts of cyclopropane 495 were obtained to further conduct C-H activation experiments, so no further optimisation of the route was conducted. The asymmetric route will be discussed at a later point.

As adequate amounts of lactone 495 were available, a directing group for the subsequent C-H activation had to be chosen. C-H arylation of cyclopropanes is reported to be mediated by 8-aminoquinoline,[375-377] 2-methylthioaniline,[378] picolinic acid,[379] or perfluorinated p-aminobenzonitrile.[294] Since in general the 8-aminoquinoline (421) directing group is known to be the most reactive,[286] it was chosen for further experiments. Treatment of lactone 495 with 8-aminoquinoline (421) and KHMDS at low temperatures, as reported for similar systems by the Shuto group,[376] afforded the desired amide 500 in 71% yield (conditions A, table 10). Applying Weinreb’s mild amide formation methodology utilising trimethylaluminum[380] gave a very good yield of 89% (conditions B). Although an excess of 8-aminoquinoline was needed to ensure full conversion, nearly quantitative recovery of the remaining reagent was possible.

Table 10: 8-aminoquinoline-amide formation.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Details</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>2 eq. 8-NH₂Q, 4 eq. KHMDS (0.7 M, PhMe), 0.5 M in THF, -78 °C to r.t.</td>
<td>71%</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>3 eq. 8-NH₂Q, 3 eq. AlMe₃ (2 M, PhMe), 0.75 M in PhMe, 0 °C to r.t.</td>
<td>89%</td>
</tr>
</tbody>
</table>
2.1.2 Optimisation of the C-H Activation and Removal of the Directing Group

The next task was to find reaction conditions for the cyclopropane C(sp³)-H arylation reaction. At first, the desired cyclohepta[b]indole motif should be accessed through a one-pot arylation and divinylcyclopropane rearrangement sequence (scheme 86). Therefore, alcohol 500 was oxidised by treatment with IBX as the oxidant. Instead of delivering the free aldehyde 502, cyclic acyl hemiaminal 501 was obtained, which was in equilibrium with the aldehyde form in solution (approx. 6% of free aldehyde in solution). Subjecting this mixture to Wittig olefination conditions furnished vinylcyclopropane 503 in 77% yield, which served as test-compound for the following arylation-rearrangement sequence.

![Scheme 86: Planned first-generation access towards cyclohepta[b]indoles.](image)

For this purpose, vinylcyclopropane 503 was subjected to typical C-H arylation conditions with or without silver additives (table 11). After 6 h at 80 °C, an inseparable mixture of unidentified products was obtained together with residual 503 (entries 1&2, table 11). Conducting the reaction at higher temperatures led to complete decomposition (entries 3&4). Neither recrystallisation of the palladium catalyst nor degassing the reaction mixture by three freeze-pump-thaw cycles did yield any detectable product (entries 5&6). Since palladium-catalysed ring-opening reactions of vinylcyclopropanes are known, decomposition by this side-reaction pathway prior to any product formation was hypothesised and no further experiments were undertaken.
Table 11: Attempts for C-H arylation of vinylcyclopropane 503.

<table>
<thead>
<tr>
<th>entry</th>
<th>ArI [eq.]</th>
<th>Pd(OAc)$_2$ [mol%]</th>
<th>additive</th>
<th>solvent [M]</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>7.5</td>
<td>Ag$_2$CO$_3$; 1.1</td>
<td>PhMe; 0.15</td>
<td>80</td>
<td>6</td>
<td>no 506</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>10</td>
<td>KOAc; 1.5</td>
<td>'AmylOH; 0.2</td>
<td>80</td>
<td>6</td>
<td>no 506</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>7.5</td>
<td>Ag$_2$CO$_3$; 1.1</td>
<td>PhMe; 0.15</td>
<td>110</td>
<td>16</td>
<td>decomp.</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>10</td>
<td>KOAc; 1.5</td>
<td>'AmylOH; 0.2</td>
<td>110</td>
<td>16</td>
<td>decomp.</td>
</tr>
<tr>
<td>5</td>
<td>3 x 1</td>
<td>7.5</td>
<td>Ag$_2$CO$_3$; 1.2</td>
<td>PhMe; 0.15$^b$</td>
<td>110</td>
<td>5</td>
<td>decomp.</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>10</td>
<td>KOAc; 1.5</td>
<td>'AmylOH; 0.2$^b$</td>
<td>110</td>
<td>18</td>
<td>decomp.</td>
</tr>
</tbody>
</table>

$^a$recrystallised from benzene; $^b$degassed by three freeze-pump-thaw cycles.

For the second approach, we planned to protect the alcohol prior to C-H activation and establish the vinyl group by oxidation and olefination at a later stage. Subsequent divinylcyclopropane rearrangement should yield the desired cyclohepta[b]indole motif. Concomitant studies by Manuel Langer during his master thesis in our group on similar systems found the methoxymethyl (MOM) protecting group to be suitable for this transformation, together with Ag$_2$CO$_3$ as an additive.$^{[383]}$ Additionally, several studies by the Shuto group on similar cyclopropane systems showed the TBDPS group to be beneficial for C-H arylation.$^{[375, 376]}$ Therefore, alcohol 500 was protected using standard conditions (entries 1A & 2A, table 12) and subjected to C-H arylation conditions. First experiments were conducted with TBDPS-protected cyclopropane 507 (entries 3B-5B). Silver-free conditions gave very poor yield for the arylation reaction (entry 3B). With silver carbonate as additive on the other hand, 34% of the desired arylation product 510 could be obtained (entry 4B). Through serendipity, the tube was not sealed tightly during one attempt and parts of the toluene evaporated. Upon continuing the reaction at roughly 1 M concentration, it was found that this higher concentration did accelerate the reaction and additionally increased the yield to 55%. This was confirmed by control experiments (entry 5B).
Table 12: Optimisation of the C-H arylation reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>( \text{MOMCl (3.5 eq.), DIPEA (4.0 eq.), CH}_2\text{Cl}_2 (0.25 \text{ M}), 0 \degree \text{C to r.t.} )</td>
<td>83% 508</td>
</tr>
<tr>
<td>2A</td>
<td>( \text{TBDPSCI (3 eq.), Imidazole (4 eq.), CH}_2\text{Cl}_2 (125 \text{ mM}), \text{r.t} )</td>
<td>91% 507</td>
</tr>
<tr>
<td>3B</td>
<td>( \text{507 (1 eq.), 504 (3 eq.), Pd(OAc)}_2 (15 \text{ mol%}), \text{KOAc (1.5 eq.),}^{\text{AmyloOH (0.15 M), 110 \degree \text{C}}} )</td>
<td>14% 510</td>
</tr>
<tr>
<td>4B</td>
<td>( \text{507 (1 eq.), 504 (3 eq.), Pd(OAc)}_2 (10 \text{ mol%}), \text{Ag}_2\text{CO}_3 (1.2 eq), \text{PhMe (0.2 M), 110 \degree \text{C}}} )</td>
<td>34% 510</td>
</tr>
<tr>
<td>5B</td>
<td>( \text{507 (1 eq.), 504 (3 eq.), Pd(OAc)}_2 (10 \text{ mol%}), \text{Ag}_2\text{CO}_3 (1.2 eq), \text{PhMe (1 M), 110 \degree \text{C}}} )</td>
<td>55% 510</td>
</tr>
<tr>
<td>6B</td>
<td>( \text{508 (1 eq.), 504 (3 eq.), Pd(OAc)}_2 (10 \text{ mol%}), \text{Ag}_2\text{CO}_3 (1.2 eq), \text{PhMe (0.15 M), 110 \degree \text{C}}} )</td>
<td>36% 511</td>
</tr>
<tr>
<td>7B</td>
<td>( \text{508 (1 eq.), 504 (3 eq.), Pd(OAc)}_2 (10 \text{ mol%}), \text{Ag}_2\text{CO}_3 (1.2 eq), \text{PhMe (1 M), 110 \degree \text{C}}} )</td>
<td>53% 511</td>
</tr>
<tr>
<td>8B</td>
<td>( \text{500 (1 eq.), 504 (3 eq.), Pd(OAc)}_2 (8 \text{ mol%}), \text{Ag}_2\text{CO}_3 (1.1 eq), \text{PhMe (1 M), 110 \degree \text{C}}} )</td>
<td>23% 512</td>
</tr>
</tbody>
</table>

Employing the same conditions to the MOM-derivative 508 gave similar results (entries 6B & 7B). In a control experiment, arylation was conducted on free alcohol 500 (entry 8B). Upon complete consumption of the starting material, 23\% of lactone 512 could be isolated from the reaction mixture, due to entropically favoured ring closure after the arylation step. The reaction was usually conducted until complete consumption of the starting material. No other products could be isolated, thus indicating that either decomposition of the starting material or the product occurs under the reaction conditions.

As suitable conditions for the C-H arylation were found (table 12, entries 5B & 7B), further studies on the influence of the protecting group to improve the yield were conducted. Therefore, three sets of typical O-protecting groups were examined (scheme 87). Each set of protecting groups consisted of a smaller variant and a larger one to determine the impact of protecting group size and
stability. Silyl protecting groups typically show high stability to a large variety of conditions and therefore, the TBS and the larger TBDPS group were chosen as representatives. An additional coordinating effect of the acetal protecting groups (MOM and BOM) was assumed to stabilise the highly energetic Pd$^{IV}$ intermediate

Scheme 87: Installation of different protecting groups to 500.

The trityl group has already been reported to deliver higher yields in cyclopropane arylation.$^{[376]}$ MMTTr and DMTr groups were introduced to possibly ease the later deprotection, since stabilisation of the trityl cation increases with additional methoxy-substitution.$^{[384]}$ Introduction of the corresponding protecting groups overall gave excellent to quantitative yields.

Further C-H arylations were conducted using the optimised conditions with iodoindole 504 (3 eq.), Pd(OAc)$_2$ (10 mol%), Ag$_2$CO$_3$ (1.2 eq) in refluxing toluene (1 M) with the three different types of protecting groups (silyl ether, methoxyalkyl ether and trityl ether). In comparison, the silyl protecting groups showed the poorest results for the arylation in regard of the isolated yield (entries 1 – 3, table 13). The TBS group was partially cleaved during the reaction and the yield with the TBDPS group did not exceed 55%. Another portion of catalyst and silver additive were added to
enhance the reaction rate. This led to shorter reaction times but did not significantly influence the yield (entry 3).

Table 13: C-H arylation with different protecting groups.

<table>
<thead>
<tr>
<th>entry</th>
<th>PG</th>
<th>scale</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBS 513</td>
<td>0.5 mmol</td>
<td>41% 518</td>
</tr>
<tr>
<td>2</td>
<td>TBDPS 507</td>
<td>0.5 mmol</td>
<td>55% 510</td>
</tr>
<tr>
<td>3</td>
<td>TBDPS 507</td>
<td>1.5 mmol</td>
<td>53% 510</td>
</tr>
<tr>
<td>4</td>
<td>MOM 508</td>
<td>0.8 mmol</td>
<td>54% 511</td>
</tr>
<tr>
<td>5</td>
<td>MOM 508</td>
<td>6.3 mmol</td>
<td>53% 511</td>
</tr>
<tr>
<td>6</td>
<td>BOM 514</td>
<td>0.8 mmol</td>
<td>61% 519</td>
</tr>
<tr>
<td>7</td>
<td>BOM 514</td>
<td>6.3 mmol</td>
<td>64% 519</td>
</tr>
<tr>
<td>8</td>
<td>Trt 515</td>
<td>1.0 mmol</td>
<td>61% 520</td>
</tr>
<tr>
<td>9</td>
<td>Trt 515</td>
<td>1.0 mmol</td>
<td>65% 520</td>
</tr>
<tr>
<td>10</td>
<td>Trt 515</td>
<td>2.0 mmol</td>
<td>71% 520</td>
</tr>
<tr>
<td>11</td>
<td>MMT 516</td>
<td>1.0 mmol</td>
<td>57% 521</td>
</tr>
<tr>
<td>12</td>
<td>DMTr 517</td>
<td>1.0 mmol</td>
<td>54% 522</td>
</tr>
</tbody>
</table>

*addition of another 5 mol% of Pd(OAc)$_2$ and 0.6 eq. Ag$_2$CO$_3$ after 2 h.

Changing the protecting group to the MOM ether 508 gave yields comparable to the TBDPS group 507 (entries 4 & 5). Installation of the larger BOM group 514 led to an increased yield of around 60% (entries 6 & 7). One explanation of this result could be the higher stability of the BOM group in 514 in comparison to the MOM group in 508 associated with less decomposition of starting material and/or product. Another explanation could be the acceleration of the reaction through stabilisation of the Pd$^{IV}$ intermediate in the C-H activation step. Studies by Yu and Houk however indicated that the rate-determining step of this type of reactions might be the C-H activation itself.$^{[303]}$ A bulkier protection group might result in suitable orientation of the directing group for the C-H insertion reaction. Experiments with the trityl ethers (entries 8 – 12) showed the best results with regard to the yield. With the trityl protecting group 515, a good yield of 71% could be obtained on a 2 mmol scale (entry 10). For the MMT 516 and DMTr 517 groups, the yields decreased, which is possibly caused by their lower stability (entries 11 & 12).
With a robust procedure for the cyclopropane arylation in hands, further elaboration of the C-H activation product was investigated. As this was pursued concomitantly with optimisation studies, MOM-derivative 511 was used in the following experiments. MOM-deprotection was achieved in 97% yield by treatment with AlCl₃ and NaI (scheme 88). Oxidation of the alcohol in 509 led to acyl hemiaminal formation, as previously observed for 501 in the first approach (scheme 86). In contrast to that, 523 showed no equilibrium with the corresponding aldehyde form and did, therefore, not undergo any olefination reaction. To find a plausible explanation for the observed stability of this hemiaminal, a molecular model of 523 was rendered using DFT calculations. As illustrated in scheme 88, the molecule features a bowl-like structure. Therein, the hemiaminal proton can undergo hydrogen bonding to the quinoline nitrogen, thus stabilising the hemiaminal form.

Scheme 88: Planned second-generation approach towards cyclohepta[b]indoles.
DFT calculation by M.Sc. Jan Herberger.

To circumvent further problems by hemiaminal formation, it was intended to remove the directing group right after the C-H activation step. Several methods for the cleavage of 8-aminoquinoline amides have been reported during the last years (scheme 89). Regarding the aminoquinoline amide-bond in general, it is highly deactivated through delocalisation of the nitrogen lone-pair into the carbonyl π*-orbital, resulting in a planar structure and a Lewis-basic carbonyl oxygen. Therefore, classic hydrolysis or solvolysis of the amide bond require harsh, strongly acidic or basic reaction conditions, which might interfere with other functionalities on the molecule or lead to epimerisation.
Scheme 89: Methodologies for 8-aminoquinoline amide cleavage. [288]

Typical methodologies to increase the amide-bond reactivity is Boc-imide formation or N-methylation, with the effect on reactivity being smaller for the latter. The bulky Boc-group twists the amide bond out of plane, which reduces conjugation and finally results in an enhanced reactivity of the amide. [288] This has been applied to hydrolysis, [387, 388] solvolysis, [389] transamidation [390] and reduction [377] of the corresponding aminoquinoline amides. Oxidative cleavage by ozonolysis affords the corresponding carboxylic acids or amides. [391]

For our approach towards cyclohepta[b]indoles, we decided to reductively cleave the aminoquinoline amide to the corresponding aldehyde, which might be directly used for further olefination reactions. The Baran group reported the direct reduction of an aminoquinoline amide to the aldehyde using DiBAL-H in THF. [309] Treatment of substrate 510 with an excess of DiBAL-H resulted only in very slow conversion of the starting material without detectable product formation (entry 1). The Schwartz reagent, Cp₂Zr(H)Cl, has been reported by the Georg group to efficiently reduce primary, secondary and tertiary amides, as well as Weinreb amides, Evan’s oxazolidinone auxiliaries and Myer’s pseudoephedrine auxiliaries to the corresponding aldehydes. [392] Additionally, the reduction of 8-aminoquinoline amides to the corresponding aldehydes has been reported for sterically encumbered cyclobutane amides [316] and cyclopropane amides. [376] In a first experiment, 37% of the corresponding aldehyde was isolated after treatment with 2 eq. of Schwartz reagent (entry 2). With fewer equivalents Cp₂Zr(H)Cl, reduction of 510 led to an approximately 1:1 mixture of aldehyde and alcohol, albeit in high yield (88% combined, entry 3). Lowering the equivalents of Schwartz reagent and changing the order of addition did unexpectedly favour alcohol
formation and led to incomplete conversion (entry 4). Georg and co-workers reported that tertiary amides gave better yields in the reduction to aldehydes. Conv[...]

Table 14: Reductive cleavage of the aminoquinoline directing group.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1d</td>
<td>Dibal-H (2.5 eq.), THF, -78 °C</td>
<td>slow conversion; traces</td>
</tr>
<tr>
<td>2ac</td>
<td>Cp2Zr(H)Cl (2 eq.), THF, r.t.</td>
<td>37% 524</td>
</tr>
<tr>
<td>3ae</td>
<td>Cp2Zr(H)Cl (1.75 eq.), THF, r.t.</td>
<td>45% 524 + 43% 525</td>
</tr>
<tr>
<td>4be</td>
<td>Cp2Zr(H)Cl (1.15 eq.), THF, r.t.</td>
<td>26% 524 + 38% 525 + SM</td>
</tr>
<tr>
<td>5a-c,d</td>
<td>a) NaH (3 eq.), EtI (6 eq.), DMF, 0 °C to r.t.</td>
<td>37% 524</td>
</tr>
<tr>
<td></td>
<td>b) Cp2Zr(H)Cl (1.8 eq.), THF, r.t.</td>
<td></td>
</tr>
<tr>
<td>6d</td>
<td>2-F-pyridine (1.1 eq.), Tf2O (1.05 eq.), CH2Cl2, -78 °C; then Et3SiH (1.1 eq.), 0 °C to r.t.; then THF, citric acid</td>
<td>decomposition</td>
</tr>
<tr>
<td>7d</td>
<td>a) NaH (3 eq.), EtI (6 eq.), DMF, 0 °C to r.t.</td>
<td>no reaction</td>
</tr>
<tr>
<td></td>
<td>b) TMDS (1 eq.), Ti(OiPr)4 (1 eq.), MeCy, r.t.</td>
<td></td>
</tr>
<tr>
<td>8f</td>
<td>a) Boc2O (3 eq.), DMAP (2 eq.), MeCN, r.t.</td>
<td>93% 525</td>
</tr>
<tr>
<td></td>
<td>b) LiBH4 (4 eq.), MeOH (3 eq.), THF, 0 °C to r.t.</td>
<td></td>
</tr>
</tbody>
</table>

*a*addition of substrate to solution of Schwartz’ reagent. *b*addition of solution of Schwartz’ reagent to substrate. *c*alcohol was not isolated in this experiment, but was observed via TLC. *d*PG = TBDPS. *e*PG = BOM. *f*PG = Trt.

The Charette group reported the reduction of secondary amides by O-triflation followed by hydrosilylation to the corresponding imine, which is further hydrolysed to the corresponding aldehyde. Applying these conditions did not induce any aldehyde formation but resulted in decomposition of the starting material (entry 6). Hydrosilylation mediated by titanium(IV) isopropoxide has been described by Lemaire and co-workers to reduce tertiary and secondary amides to the corresponding aldehydes. Nonetheless, this methodology did also not induce the desired reduction (entry 7). With the problematic selective reduction of the aminoquinoline-amide to an aldehyde, the approach was changed towards complete reduction to an alcohol. To enhance the reactivity, the amide was activated by Boc-imide formation. The subsequent reduction with
LiBH₄ gave the corresponding alcohol in excellent yield over the two-step sequence (entry 8). The enhanced reducing ability of this mixture is most probably attributed to the in situ formation of methoxy-substituted lithium borohydrides.$^{[395]}$

This new strategy would allow to access two different cyclohepta[b]indole scaffolds from the same intermediate 525 depending on the following functionalisation (scheme 90). If the former amide is reduced to the alcohol and converted into an olefin that further undergoes rearrangement (amide-to-olefin route), cyclohepta[b]indoles with a quaternary stereocentre would be formed. Alternatively, if the former amide is reduced, protected and the other alcohol transformed into the olefin, cyclohepta[b]indoles with a substituted double-bond and a tertiary stereocentre would be obtained (alcohol-to-olefin route).

\[
\text{Scheme 90: Differentiation leads to different cyclohepta[b]indoles.}
\]

With the optimised C-H arylation and conditions for the removal of the directing group, the next aim was the synthesis of enantioenriched material. Furthermore, the scope of the C-H activation with differently substituted indoles should be determined. Eventually, this would result in various cyclohepta[b]indole scaffolds after differentiation of the amide and alcohol moieties.

2.1.3 Asymmetric Synthesis of the C-H Activation Precursor

To construct the desired chiral cyclopropane 495, a methodology developed by Nakada and co-workers for the intramolecular cyclopropanation of α-diazo-α-silyl acetates was chosen.$^{[396]}$ In comparison to unsilylated diazo compounds, this methodology offers higher yields and
stereoselection caused by the bulky α-silyl substituent, as stated by the authors. The catalytic system itself consists of a typical C₂-symmetric bisoxazoline ligand with a copper(I)-source. The authors found that the counter ion played a crucial role in the performance of the catalytic system, and best results were achieved with Cu(MeCN)₄PF₆ or Cu(MeCN)₄BF₄ as the metal source. Therefore, the synthetic efforts continued with the synthesis of the required, literature-known BOX ligand 532. These ligands, originally developed by Evans[397] and Corey[398], found wide application in a plethora of asymmetric transformations.[399] The synthesis began (scheme 91) with the oxidation of diol 526 in concentrated nitric acid to give 2,2-dimethyl malonic acid (527) in good yield. Malonic acid 527 was further converted to the corresponding bis-acylchloride with oxalyl chloride as the chlorinating agent. As chiral part of the ligand serves the natural amino acid (S)-valine (529), which was reduced to (S)-valinol (531) by a procedure developed by Meyers and co-workers.[401]

Subsequent amide formation with the previously synthesised malonyl chloride 528 gave 531. Finally, double dehydration with tosyl chloride under DMAP-catalysis afforded multigram quantities of 532.[402] With ligand 532 in hands, the asymmetric cyclopropanation reaction was further pursued. Nakada and co-worker’s route[396] to diazoacetate 498 seemed more favourable than the previously established one (table 8), since it replaced hazardous azides by the bench-stable N,N'-ditosylhydrazide. After some minor modification of the original procedure, decagram quantities of bromoacetate 534 were synthesised (scheme 92) by treatment of methallyl alcohol (496) with bromoacetyl bromide (533). According to the conditions reported by the Fukuyama group,[403] 534 was converted to the corresponding allyl diazoacetate 498 in good yields.
The following α-silylation showed to be more challenging. Nakadas conditions (TMSCI, DBU)[396] did not lead to full consumption of 498, not even after drying and purification of the reagents and solvents. Additionally, the α-silyl diazoacetate 535 was sensitive to an aqueous work-up, although Nakada described it to be stable. A publication of the Regitz group dealt with the synthesis of various α-silyl diazoacetates.[404] They reported that silylation proceeded efficiently by treatment with the corresponding silyl triflate and DIPEA as the base. Although Nakada reported that this transformation failed,[396] it was found that the reaction of 498 with TMSOTf and DIPEA gave the desired α-silylation product in nearly quantitative yield. Additionally, the product was usually pure enough for the next transformation after filtration over dried Celite.

The next task was to scale up the intramolecular cyclopropanation reaction (table 15). According to the original procedure,[396] the use of Cu(MeCN)₄BF₄ and Cu(MeCN)₄PF₆ provided the desired product in good yields, in which the PF₆ salt gave better results (entries 1 & 2, table 15).

### Table 15: Scale-up of the asymmetric cyclopropanation.

<table>
<thead>
<tr>
<th>entry</th>
<th>Cu(MeCN)₄X</th>
<th>M (PhMe)</th>
<th>scale</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF₄</td>
<td>10 mM</td>
<td>0.14 mmol</td>
<td>72%</td>
</tr>
<tr>
<td>2</td>
<td>PF₆</td>
<td>10 mM</td>
<td>0.14 mmol</td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td>PF₆</td>
<td>85 mM</td>
<td>20 mmol</td>
<td>58%</td>
</tr>
<tr>
<td>4</td>
<td>BF₄</td>
<td>85 mM</td>
<td>63 mmol</td>
<td>52%</td>
</tr>
<tr>
<td>5ᵃ</td>
<td>PF₆</td>
<td>85 mM</td>
<td>42 mmol</td>
<td>70%</td>
</tr>
<tr>
<td>6ᵃ</td>
<td>PF₆</td>
<td>60 mM</td>
<td>31 mmol</td>
<td>73%</td>
</tr>
<tr>
<td>7ᵃ</td>
<td>PF₆</td>
<td>75 mM</td>
<td>38 mmol</td>
<td>67%</td>
</tr>
<tr>
<td>8ᵃ</td>
<td>PF₆</td>
<td>75 mM</td>
<td>68 mmol</td>
<td>72%</td>
</tr>
</tbody>
</table>

ᵃself-prepared Cu(MeCN)₄PF₆ was used.
Performing the reaction at higher concentration (85 Mm) on larger scale led to a decreased yield of 58% for the PF$_6$ complex (entry 3) and 52% for the BF$_4$ salt (entry 4), respectively. Since the commercial sample of Cu(MeCN)$_4$PF$_6$ contained a significant amount of Cu(II), it was freshly prepared by treatment of cuprous oxide with HPF$_6$ in acetonitrile.$^{[405]}$ Gratifyingly, with this new catalyst, the reaction gave reproducible yields of ca. 70% in a concentration range of 60 to 85 mM concentration (entries 5 to 8). The enantiomeric excess was not determined at this point, since additional enantioenrichment was possible by recrystallisation of 495 from hexanes, as reported by the Overman group for the opposite enantiomer.$^{[362]}$ Nakada and co-workers reported an enantiomeric excess of 75% for this transformation.$^{[396]}$

![Diagram](image)

_Figure 21: Model for the selectivity of the cyclopropanation according to Nakada.$^{[396]}$

The stereoselectivity can be explained by a simple model discussion (figure 21). Re-face attack is favoured over the Si-face caused by the bulky trimethylsilyl group. Steric interactions with the BOX-ligand are larger in the Si-face orientation, because the TMS-group points towards the nearby isopropyl group.$^{[396]}$ Straightforward desilylation of enantioenriched lactone 536 by treatment with TBAF and subsequent recrystallisation of the sticky solid to remove the liquid racemate afforded colourless needles of 495 (scheme 93).

![Scheme 93](image)

_Scheme 93: Synthesis of C-H activation precursor 515._
After attachment of the directing aminoquinoline moiety, the enantiopurity of 500 was determined by chiral HPLC to be 98%. Gratifyingly, after tritylation, single crystals suitable for X-ray structure determination could be obtained from 515 to unambiguously assign its structure and stereochemistry (see scheme 93). With multigram quantities of 515 in hands, the scope of the C-H activation reaction was investigated as well as the synthesis of the desired cyclohepta[b]indole scaffolds.

2.1.4 Scope of the C-H Activation and Synthesis of Cyclohepta[b]indoles

A variety of differently substituted indoles were synthesised (scheme 94) by using slightly modified conditions reported by the Müller group.\textsuperscript{[406]} The methodology was found to be general for different types of indoles to yield the corresponding 3-iodo-N-tosyl indoles in good to excellent yield.

Scheme 94: Synthesis of 3-ido-N-tosyl indoles.

The scope of the C-H arylation was determined with trityl-protected 515 and few experiments with the TBDPS derivative of 507 were also conducted (see table 16). The observed trend for the lower reactivity of the TBDPS derivative (see chapter 2.1.2) could be confirmed in every case. Overall, the yields for TBDPS derivative 507 varied between 43 and 60%. For the trityl derivative 515, increased yields of 48 to 75% could be observed. Substitution of the indole with an electron-withdrawing or electron-donating group did not show to have a significant influence on the reactivity, despite for
the very electron-poor 5-nitro derivative (entries 7 & 8). This compound only gave lower yields. The position of the substituent had a drastic impact on the reaction. No significant amounts of product were formed for the 4-substituted derivatives (entries 20 & 21). This might be caused by suppressed oxidative addition because of the steric shielding of the 3-iodo position by the adjacent 4-substituent.

*Table 16: Scope of the C-H activation.*

<table>
<thead>
<tr>
<th>entry</th>
<th>PG</th>
<th>iodoindole</th>
<th>yield</th>
<th>product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trt</td>
<td>1-H</td>
<td>71%</td>
<td>520</td>
</tr>
<tr>
<td>2</td>
<td>TBDPS</td>
<td>1-H</td>
<td>55%</td>
<td>510</td>
</tr>
<tr>
<td>3</td>
<td>Trt</td>
<td>7-aza</td>
<td>75%</td>
<td>549</td>
</tr>
<tr>
<td>4</td>
<td>TBDPS</td>
<td>7-aza</td>
<td>55%</td>
<td>561</td>
</tr>
<tr>
<td>5</td>
<td>Trt</td>
<td>5-Cl</td>
<td>70%</td>
<td>550</td>
</tr>
<tr>
<td>6</td>
<td>TBDPS</td>
<td>5-Cl</td>
<td>48%</td>
<td>562</td>
</tr>
<tr>
<td>7</td>
<td>Trt</td>
<td>5-NO₂</td>
<td>48%</td>
<td>551</td>
</tr>
<tr>
<td>8</td>
<td>TBDPS</td>
<td>5-NO₂</td>
<td>43%</td>
<td>563</td>
</tr>
<tr>
<td>9</td>
<td>Trt</td>
<td>6-F</td>
<td>69%</td>
<td>552</td>
</tr>
<tr>
<td>10</td>
<td>TBDPS</td>
<td>6-F</td>
<td>60%</td>
<td>564</td>
</tr>
<tr>
<td>11</td>
<td>Trt</td>
<td>6-CO₂Me</td>
<td>60%</td>
<td>553</td>
</tr>
<tr>
<td>12</td>
<td>TBDPS</td>
<td>6-CO₂Me</td>
<td>48%</td>
<td>565</td>
</tr>
<tr>
<td>13</td>
<td>Trt</td>
<td>7-OMe</td>
<td>68%</td>
<td>554</td>
</tr>
<tr>
<td>14</td>
<td>TBDPS</td>
<td>7-OMe</td>
<td>52%</td>
<td>566</td>
</tr>
<tr>
<td>15</td>
<td>Trt</td>
<td>7-F</td>
<td>61%</td>
<td>555</td>
</tr>
<tr>
<td>16</td>
<td>TBDPS</td>
<td>7-F</td>
<td>51%</td>
<td>567</td>
</tr>
<tr>
<td>17</td>
<td>Trt</td>
<td>5-CO₂Me</td>
<td>65%</td>
<td>556</td>
</tr>
<tr>
<td>18</td>
<td>Trt</td>
<td>5-OMe</td>
<td>66%</td>
<td>557</td>
</tr>
<tr>
<td>19</td>
<td>Trt</td>
<td>5-Br</td>
<td>66%</td>
<td>558</td>
</tr>
<tr>
<td>20</td>
<td>Trt</td>
<td>4-Me</td>
<td>traces</td>
<td>559</td>
</tr>
<tr>
<td>21</td>
<td>Trt</td>
<td>4-Br</td>
<td>traces</td>
<td>560</td>
</tr>
</tbody>
</table>
Additionally, excellent chemoselectivity was observed for the brominated indole derivative (entry 19), where coupling occurred only on the expected 3-iodo position. This would offer the possibility of a late-stage functionalisation through other cross-coupling reactions. With a broad scope of arylation partners, the synthesis of differently substituted cyclohepta[b]indoles possessing tertiary or quaternary stereocentres was continued.

The *amide-to-olefin route* was investigated first (scheme 95), as no further protecting group manipulation of the corresponding C-H activation products was needed. As mentioned in chapter 2.1.2, the directing group was removed by additional activation through Boc-protection followed by reduction with the LiBH₄-MeOH system. Ley-Griffith oxidation[^167] effectively transformed cyclopropymethanol 568 into the corresponding aldehyde, which was usually pure enough for the following step after filtration over silica. Olefination was performed by standard Wittig-conditions to obtain divinylcyclopropane 569. Since the divinylcyclopropane tends to rearrange already at temperatures slightly above r.t., 569 was heated in toluene to give cyclohepta[b]indoline 570. Treatment with p-toluenesulfonic acid and methanol induced deprotection of the trityl group and partial aromatisation to the indole. Aromatisation could be driven to completion by treatment with another 0.5 eq. of p-toluenesulfonic acid to yield the desired cyclohepta[b]indole 571.

![Scheme 95: Amide-to-olefin route for differently substituted cyclohepta[b]indoles.](image-url)
Overall, good to excellent yields were achieved for each of the transformation sequences, independent of the indole substitution (table 17). Indoles with an electron-withdrawing substituent (572-574) showed no tendency for aromatisation to the indole, but do so upon tosyl-deprotection, as earlier demonstrated by our group.\textsuperscript{[220]} Therein, deprotection was achieved by treatment with samarium(II) iodide. Since indoles are prone to undergo autoxidation in air,\textsuperscript{[407, 408]} we decided to not cleave-off the protecting group until possibly needed on a later point.

<table>
<thead>
<tr>
<th>entry</th>
<th>substituent</th>
<th>reduction</th>
<th>oxidation/olefination/[3,3] deprotection/aromatisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>93%</td>
<td>60%</td>
</tr>
<tr>
<td>2</td>
<td>7-aza</td>
<td>86%</td>
<td>76%</td>
</tr>
<tr>
<td>3</td>
<td>5-Cl</td>
<td>88%</td>
<td>82%</td>
</tr>
<tr>
<td>4</td>
<td>6-F</td>
<td>78%</td>
<td>87%</td>
</tr>
<tr>
<td>5</td>
<td>7-OMe</td>
<td>91%</td>
<td>65%</td>
</tr>
</tbody>
</table>

Gratifyingly, a single crystal of a racemic sample of rearrangement product 570 allowed to unambiguously assign its relative stereochemistry. The cis-relationship of the proton at C-1 and the alcohol-substituent on C-12 is a direct result of the stereospecific [3,3]-rearrangement.

Having demonstrated the robustness of the amide-to-olefin route and the possibility to access differently substituted cyclohepta[b]indoles, further studies on the alcohol-to-olefin route were pursued (scheme 96). Alcohol 568 was Piv-protected to ensure orthogonality towards the trityl ether. Detritylation proceeded smoothly by treatment with $p$-toluenesulfonic acid and methanol as before. The oxidation/olefination/rearrangement sequence was performed in analogy to the
amide-route and gave good overall yields. Again, aromatisation was observed only for the electron-rich indoles and proceeded smoothly under acid-catalysis. The electron poor derivatives were not further aromatised (580-582). Deprotection of the pivaloyl-ester was achieved by treatment with DiBAL-H and subsequent hydrolysis of the intermediate hemiacetal.

As in the amide-to-olefin route, no difference in reactivity was observed between electron-rich and electron-poor cyclohepta[b]indoles, except for the aromatisation step. Therefore, only the electron-rich representatives were further deprotected to the free alcohols to verify the possibility for further transformations on the alcohol handle.

Table 18: Yields for the alcohol-to-olefin route.

<table>
<thead>
<tr>
<th>entry</th>
<th>substitution</th>
<th>Piv/Trt oxidation/olefination/[3,3] aromatisation/deprotection</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>72% 72%</td>
</tr>
<tr>
<td>2</td>
<td>7-aza</td>
<td>67% 72%</td>
</tr>
<tr>
<td>3</td>
<td>5-Cl</td>
<td>77% 76%</td>
</tr>
<tr>
<td>4</td>
<td>6-F</td>
<td>74% 62%</td>
</tr>
<tr>
<td>5</td>
<td>7-OMe</td>
<td>74% 72%</td>
</tr>
</tbody>
</table>

*aaromatisation was not observed and deprotection was not conducted.

Complementary studies to the developed methodology towards cyclohepta[b]indoles were performed by Yevhenii Sokolenko and are summarised in scheme 97, which further illustrated the versatility of our approach. The methodology was extended to access all-cis cyclopropane 584 with a “hidden symmetry plane”. This σ-plane served as an “enantiomeric switch”, allowing to access both cyclohepta[b]indole enantiomers 585 from one single enantiomer of C-H activation product,
thus proving the enantiodivergency of our methodology. Additionally, the scope of the olefination was broadened to obtain differently substituted cyclohepta[b]indoles, which gives the opportunity for further functionalisation and target-oriented construction of specific substitution patterns in the cyclohepta[b]indole.  

![Scheme 97: Additional work on the enantiodivergency of our methodology and scope of the olefination by M.Sc. Yevhenii Sokolenko.][359]

2.2 Studies towards a Total Synthesis of Exotine A and B

Concomitantly with the development of the new enantioselective method towards cyclohepta[b]indoles, initial studies towards a possible total synthesis of exotine A (239) and B (240) were executed. Despite few total syntheses are reported for these alkaloids, none of them enabled an enantioselective synthesis so far.\(^{251, 409, 410}\) Pd-catalysed directed C-H activation represents a valuable synthetic asset for the stereospecific formation of new C-C bonds which would otherwise require effortful multistep sequences. Regarding the cis-arrangement of the substituents on the seven-membered exotine ring, the C-H activation seemed a promising approach for their specific introduction. This led to the following retrosynthetic analysis of the exotine natural products (scheme 98): The isobutenyl-moiety should be introduced by a directed Pd-catalysed C-H olefination, which would lead back to amide 589. Therein, the carboxyl group was planned to be removed by decarboxylation. The seven-membered ring should be formed in a sigmatropic divinylcyclopropane rearrangement from intermediate 590. The right configuration of the coumarin substituent is determined by the (Z)-configuration of olefin 590 and the transfer of chirality in the rearrangement step. Vinylcyclopropane 590 should be obtained from the corresponding alkyne 591 by selective hydrogenation. The indole moiety should be introduced by
a second C-H activation process that leads back to alkyne 592. Attachment of the coumarin was planned to be achieved by Sonogashira coupling\textsuperscript{[411-413]} of the free alkyne with the corresponding halogenated coumarin, while the alkyne itself would be introduced by an Ohira-Bestmann alkynylation.\textsuperscript{[168]} Further functional group interconversion would result in cyclopropyl alcohol 500, which could be obtained from literature-known lactone 495. This lactone is planned to be prepared by an asymmetric intramolecular cyclopropanation.\textsuperscript{[396]}

![Scheme 98: First-generation retrosynthetic analysis of exotine A (239) and B (240).](image)

The synthetic efforts commenced with the preparation of the brominated 596 and iodinated coumarin 600 from commercially available aldehyde 593 in three and five steps, respectively (scheme 99).\textsuperscript{[414]} Selective methylation of the 4-hydroxy group of 593 afforded aldehyde 594 in good yield.\textsuperscript{[415]} Treatment of 594 with aluminium trichloride and bromine introduced the bromide on the 3-position with excellent selectivity and in very good yield. Perkin condensation with acetic anhydride under basic conditions afforded bromocoumarin 596 and sufficient amounts of material could be prepared for further experiments, although in low yield.
As iodoarenes are generally more reactive in the Sonogashira reaction than bromoarenes (due to faster oxidative addition),[412] iodocoumarin 600 was prepared as well. Iodination proceeded smoothly to provide salicylaldehyde 597. Subsequent Wittig-olefination introduced the vinyl group, and treatment with acryloyl chloride afforded acrylate 599 in 64% over this two-step sequence. Ring-closing metathesis with Grubbs 2\textsuperscript{nd} generation catalyst eventually yielded iodocoumarin 600 in 71% yield.[414]

Synthesis of alkyne part 602 was pursued next (table 19). Therefore, alcohol 500 was oxidised with hypervalent iodine reagent IBX to the corresponding aldehyde (as already discussed in section 2.1.1) and was further treated with Ohira-Bestmann reagent\cite{416} to afford alkyne 601 in 74% combined yield. Subsequent Sonogashira coupling was examined next for the preparation of amide 602, which should serve as starting material for the C-H arylation. Reaction of bromo-derivative 596 in triethylamine as solvent and with Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2} did not lead to any product formation, which was assumed to be caused by the low solubility of the coumarin in the amine solvent (entry 1, table 19). Therefore, DMF was added as co-solvent to improve solubility. However, despite complete dissolution of the reactants, not even trace amounts of product could be detected (entry 2). Oxidative addition is, in general, retarded for electron rich aryl halides and additionally, aryl bromides are less reactive than the corresponding iodides.\cite{417} The slow oxidative addition of 596 was anticipated to cause the lacking reactivity and therefore, the reaction was attempted with the iodo-derivative 600.
Indeed, application of the same conditions with iodocoumarin 600 yielded 51% of the desired product 602 (entry 3). Increasing the amount of aryl iodide had no significant effect on the product yield (entry 4). The in situ reduction of the palladium catalyst to Pd⁰ was supposed to be retarded under the applied conditions, for which reason the Pd-source was changed to Pd(PPh₃)₄. Gratifyingly, this modification allowed the isolation of the desired Sonogashira coupling product 602 in 80% yield.

In analogy to the C-H arylation of vinylcyclopropane 503 (see section 2.1.2), the same conditions for C-H arylation were applied to alkyne cyclopropane 602, but unfortunately, no coupling reaction was observed (table 20). Instead, rather fast decomposition of the alkyne derivative took place (entries 1 & 2). Even with the optimised conditions for the C-H arylation of cyclopropanes the desired product was not formed (entry 3) and neither were any defined side products, due to decomposition reactions.
Table 20: Conditions for the C-H arylation of alkynyl cyclopropane 602.

<table>
<thead>
<tr>
<th>entry</th>
<th>504 [eq.]</th>
<th>Pd(OAc)$_2$ [mol%]</th>
<th>add. [eq.]</th>
<th>solvent [M]</th>
<th>T [°C]</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>8</td>
<td>Ag$_2$CO$_3$; 1.1</td>
<td>PhMe; 0.15</td>
<td>110</td>
<td>decomp.</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>10</td>
<td>KOAc; 1.5</td>
<td>1'AmilOH; 0.2</td>
<td>110</td>
<td>decomp.</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>10</td>
<td>Ag$_2$CO$_3$; 1.2</td>
<td>PhMe; 1</td>
<td>110</td>
<td>decomp.</td>
</tr>
</tbody>
</table>
After the studies on a methodology for the construction of cyclohepta[b]indoles were finished (chapter 2.1), the previous retrosynthetic analysis of exotine A (239) and B (240) was revised (scheme 100). The isobutenyl-moiety should be introduced by a new C-H activation methodology employing carboxylic acids as the directing group and vinyl pinacol boronates as coupling partner, developed by the Yu group.418 This would lead back to carboxylic acid containing cyclohepta[b]indole 604, which would be the product of the divinylcyclopropane rearrangement of compound 605.

To obtain the desired configuration of the aromatic substituent, cis-selective hydrogenation of the alkyne would be essential. As in the previous analysis (scheme 98), the coumarin motif was planned to be installed via Sonogashira cross-coupling with alkyne 606. The alkyne itself would be the product of Ohira-Bestmann alkynylation, leading back to cyclopropane 520. Introduction of the indole substituent would be performed according to the developed methodology (chapter 2.1), starting from aminoquinoline amide 515. As the aminoquinoline group was found to interfere with further manipulation, it was planned to be removed after the C-H activation step in accordance to the developed methodology (chapter 2.1).

Scheme 100: Second-generation retrosynthetic analysis of exotine A (239) and B (240).
Coumarin building block 319 was synthesised according to literature-known procedures\textsuperscript{[409, 419]} in two steps (scheme 101). Starting from 3,5-dimethoxyphenol (607), Pt-catalysed hydroarylation of propiolic acid (608) afforded coumarin 318 in very good yield. Subsequent iodination was achieved selectively in 8-position by treatment with NIS and catalytic amounts of TFA to yield the desired coumarin 319.

\textit{Scheme 101: Synthesis of coumarin 319.}

The synthesis of alkyne 606 followed the previously developed methodology towards cyclohepta[b]indoles as shown in scheme 102. C-H arylation of cyclopropane 515 afforded cyclopropyl indole 520 in 71% yield and gram-scale quantities. Reductive cleavage of the directing aminquinoline amide proceeded smoothly and in excellent yield to afford alcohol 568. According to the \textit{alcohol-to-olefin route}, the alcohol was protected as pivaloyl ester and the trityl ether was cleaved by treatment with \textit{p}-tolylenesulfonic acid and methanol in a good yield of 72% over two steps.

\textit{Scheme 102: Synthesis of key intermediate alkyne 606.}

Ley-Griffith oxidation of the free alcohol afforded the corresponding aldehyde, which was subsequently treated with Bestmann-Ohira reagent to afford the desired alkyne 606 in good overall yield. The next task was to attach the coumarin moiety via Sonogashira reaction (table 21). Heating the reaction mixture above 40 °C resulted in complete decomposition of alkyne 606 (entry 1). In contrast, the application of low temperature conditions, as reported by the Usuki group in their total synthesis of desmosine,\textsuperscript{[420]} led to product formation, although in low yield (entry 2). It was found that most of the starting material underwent Glaser-Hay coupling,\textsuperscript{[421]} a commonly known
copper-catalysed side reaction, to give diyne 610. To avoid this side reaction, freshly precipitated copper(I)iodide was added to a frozen solution of the other reagents during the freeze-pump-thaw cycles for degassing. Indeed, a 74% yield of the desired product was achieved by employing this modified protocol (entry 3). The amount of Glaser-coupling product 610 could be effectively reduced to below 10%.

Indeed, a 74% yield of the desired product was achieved by employing this modified protocol (entry 3). The amount of Glaser-coupling product 610 could be effectively reduced to below 10%.

Table 21: Sonogashira coupling of alkyne 606 with different coumarins.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>ArI (2 eq.), Pd(PPh₃)Cl₂ (17 mol%), Cul (5 mol%), NEt₃/DMF 4:6, 50 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>ArI (1.1 eq.), Pd(PPh₃)₄ (15 mol%), Cul (30 mol%), DIPEA/DMF 1:5, r.t.</td>
<td>10% 603 + 54% 610</td>
</tr>
<tr>
<td>3°</td>
<td>H</td>
<td>ArI (1.1 eq.), Pd(PPh₃)₄ (15 mol%), Cul (30 mol%), DIPEA/DMF 1:5, r.t.</td>
<td>74% 603 &lt;10% 610</td>
</tr>
<tr>
<td>4°</td>
<td>OMe</td>
<td>ArI (1.1 eq.), Pd(PPh₃)₄ (15 mol%), Cul (30 mol%), DIPEA/DMF 1:5, r.t.</td>
<td>84% 609 &lt;10% 610</td>
</tr>
</tbody>
</table>

*Cul was freshly precipitated from a potassium iodide solution and dried in vacuo.

It proved to be crucial to add the copper salt to the frozen mixture, otherwise the extent, to which 610 was formed, increased. Applying the same conditions to coumarin 319 afforded the desired product in 84% yield (entry 4).

Unfortunately, attempts to partially hydrogenate the sterically demanding alkyne 609 proved to be challenging and the desired product could not be isolated under standard Lindlar conditions. However, the hydrogenation in this approach was only conducted once using the reaction conditions depicted in scheme 103. Therefore, future studies should focus on further investigations of the partial hydrogenation of alkynes 603 and 609 to enable the following rearrangement to the cyclohepta[b]indole core.

Scheme 103: Attempt for the partial hydrogenation of 609.
2.3 Extension of the C-H Activation Methodology to other Heterocycles

To prove the versatility and universal applicability of the methodology for the construction of cyclohepta[b]indoles, its extension to other heterocycles than indoles was investigated. A short general overview concerning other cyclohepta[b]-fused heterocycles will be outlined in the following chapter, followed by the results of the methodology extension.

2.3.1 Cyclohepta[b]-fused Heterocycles in Nature and Medicinal chemistry

Aromatic heterocycles represent an abundant structural motif in the pharmaceutical industry. In fact, in 2012, all top ten selling drugs on the market contained at least one heterocyclic fragment.\(^\text{[423]}\) Out of 37 newly FDA approved chemical entities in 2020, the vast majority of 28 contained a nitrogen aromatic heterocycle,\(^\text{[424]}\) a trend that has been existing for several years.\(^\text{[425-427]}\) Cyclohepta[b]-fused heterocycles are also found in nature, in drugs or biologically active lead structures in pharmaceutical research. Especially furan-based scaffolds are a motif abundantly found in natural products (see figure 23). The cyclohepta[b]benzofuran moiety was found in the marine natural products frondosin B (612)\(^\text{[428]}\) and liphagal (613).\(^\text{[429]}\) Additionally, they exhibit astonishing biological activities, like frondosin B (612) acting as a micromolar interleukin-8 receptor and protein kinase C inhibitor.\(^\text{[430]}\) The interleukin-8 receptor and the protein kinase C represent important targets for the potential treatment of inflammatory diseases or certain types of cancer.\(^\text{[431, 432]}\)

![frondosin B (612) liphagal (613) zedoarol (614) gnididione (615)](image)

*Figure 23: Cyclohepta[b]-fused furan natural products.*

Other representatives of this group of natural products are the furanoguaianes, like the sesquiterpennoids zedoarol (614)\(^\text{[433]}\) and gnididione (615),\(^\text{[434]}\) both isolated from plants. However, not only the furan-based cyclohepta[b]-heterocycles but also the thiophene, pyridine and pyrrole derivatives show biological activity. Thiophene derivative 616 showed growth inhibition and antiproliferative activity against several cancer cell lines.\(^\text{[435]}\) Cyclohepta[b]pyrrole 618 represents a group of structurally related GABA\(_A\) brain receptor ligands, potentially useful in the treatment of Alzheimer’s dementia, depression, anxiety or sleep and seizure disorders.\(^\text{[436]}\) Recently, the cyclohepta[b]pyridine rimegepant (617), acting as calcitonin gene-related peptide (CGRP) receptor
antagonist, has been approved by the FDA for the treatment of severe migraine attacks.\textsuperscript{[424]} CGRP is implicated in the transmission of pain signals in the peripheral and central nervous system and is released during migraine attacks.\textsuperscript{[437, 438]}

Encouragingly for our methodology, the divinylcyclopropane rearrangement of various heterocyclic compounds has been reported in literature. The Maas group described the rearrangement of pyridyl, thienyl and furyl vinylcyclopropanes upon heating from 100 to 200 °C and rearomatisation by further treatment with acids, bases or electrophiles.\textsuperscript{[350]} Additionally, the divinylcyclopropane rearrangement of benzofurans has already been applied in a formal synthesis of the marine natural product frondosin B by Davies and co-workers.\textsuperscript{[439]}

2.3.2 Scope of the C-H Activation with Heterocycles

With these preliminary considerations in mind, initial experiments focused on the scope of heterocycles applicable to the cyclopropane C-H arylation. A variety of electron rich and electron poor aryl iodides (figure 25) containing nitrogen, oxygen or sulfur as heteroatoms were prepared for further testing.
Iodination of the heteroaromatics was achieved by three different general methodologies (table 22): A) electrophilic iodination with iodine or NIS; B) ortho-lithiation with tert-BuLi and treatment with iodine; C) halogen exchange from the corresponding bromide by lithiation with n-BuLi and subsequent treatment with iodine. Pyrrole 619 was prepared by a two-step sequence of TIPS-protection and subsequent iodination with NIS (entry 1). Iodination of imidazole furnished a double-iodinated product, which was selectively mono-dehalogenated and tosyl-protected according to literature known conditions (entry 2). Indazole-derivative 633 was obtained by the same procedure as applied for the synthesis of 3-iodoindoles (chapter 2.1.4). Thus, treatment of indazole with iodine followed by tosyl chloride furnished 633 (entry 3) 624, 626 and 628 were prepared by lithiation of the corresponding non-haogenated derivatives and subsequent iodine addition (entries 4-6). 3-Iodofuran (620), 3-iodothiophene (623) and 3-iodobenzothiophene (627) were prepared from the corresponding bromides. Addition of n-BuLi afforded the corresponding lithiated species, which was further treated with iodine. Quinoline 632 was synthesised via an aromatic Finkelstein reaction, previously developed by Buchwald (entry 10). Pyridine-N-oxide 630 was synthesized by a literature-known procedure from 3-iodopyridine (629) through treatment with m-CPBA.

<table>
<thead>
<tr>
<th>entry</th>
<th>aryl iodide</th>
<th>method</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>619</td>
<td>A</td>
<td>83% from pyrrole[^440]</td>
</tr>
<tr>
<td>2</td>
<td>631</td>
<td>A</td>
<td>42% from imidazole[^441]</td>
</tr>
<tr>
<td>3</td>
<td>633</td>
<td>A</td>
<td>76%</td>
</tr>
<tr>
<td>4</td>
<td>624</td>
<td>B</td>
<td>70%</td>
</tr>
<tr>
<td>5</td>
<td>626</td>
<td>B</td>
<td>92%</td>
</tr>
<tr>
<td>6</td>
<td>628</td>
<td>B</td>
<td>73%</td>
</tr>
<tr>
<td>7a</td>
<td>620</td>
<td>C</td>
<td>78%</td>
</tr>
<tr>
<td>8a</td>
<td>623</td>
<td>C</td>
<td>90%</td>
</tr>
<tr>
<td>9</td>
<td>627</td>
<td>C</td>
<td>quant.</td>
</tr>
<tr>
<td>10a</td>
<td>632</td>
<td>C</td>
<td>90%[^442]</td>
</tr>
<tr>
<td>11a</td>
<td>630</td>
<td>m-CPBA</td>
<td>97%[^443]</td>
</tr>
</tbody>
</table>

[^440]: performed by B.Sc. Thimo Schneider as part of his bachelor thesis.

The scope of the C-H arylation with respect to the heteroaryl iodides using cyclopropane 515 as the substrate was investigated next. Arylation of 515 with various electron-rich aryl iodides furnished the corresponding products in good yields, with the reaction exhibiting excellent compatibility with heteroaromatics. An exception was the reaction with 2-iodoindole 624 that did not furnish any product at all and the starting material could be reisolated. The lack of reactivity might arise from steric shielding of the 2-position by the adjacent tosyl group, which would prevent the oxidative addition. However, other 2-iodinated coupling partners (625, 626 and 628) were found to give high yields in the arylation.
Table 23: Scope and yields for the C-H activation with heteroaryl iodides.

This picture changed for electron-poor heterocycles applied in cyclopropane C-H arylation. Only pyridine derivative 629 could be isolated, albeit in very low yield. This lack of reactivity was reported in similar cases and is believed to be caused by the coordinating character of pyridines.\textsuperscript{[375, 376, 444, 445]} All other electron-poor heterocycles showed complete lack of reactivity under these reaction conditions. Nevertheless, examples for the arylation with pyridines, their corresponding N-oxides or quinolines have been reported in literature.\textsuperscript{[375, 376, 444, 445]} This provides the basis to complete the investigations of the cyclopropane C-H arylation with these electron-poor systems. Future efforts should focus on the subsequent conversion to cyclohepta[b]-fused heterocycles.
3. Summary and Outlook

A methodology that enables general access to cyclohepta[b]indoles, which is a common structural motif in natural products and potential pharmaceuticals, is described in the second part of this thesis. Application of the palladium-catalysed directing group-mediated cyclopropane C(sp³)-H activation allowed the stereospecific introduction of diversely substituted indoles in cis-fashion to the directing group (scheme 104). The corresponding arylated cyclopropanes were obtained in fair to good yields and in excellent enantioselectivity.

Further transformation of either the amide or the alcohol eventually furnished two types of constitutionally isomeric cyclohepta[b]indoles (scheme 105). Transfer of chirality could be achieved through utilisation of the divinylcyclopropane rearrangement and without any loss of optical activity. The divergent functionalisation strategy enabled the rapid synthesis of compound libraries. To demonstrate the broad applicability of this methodology, several representatives with variable substitution patterns on the indole core have been synthesised.

Scheme 104: Cyclopropane C-H arylation with substituted indoles.

Further transformation of either the amide or the alcohol eventually furnished two types of constitutionally isomeric cyclohepta[b]indoles (scheme 105). Transfer of chirality could be achieved through utilisation of the divinylcyclopropane rearrangement and without any loss of optical activity. The divergent functionalisation strategy enabled the rapid synthesis of compound libraries. To demonstrate the broad applicability of this methodology, several representatives with variable substitution patterns on the indole core have been synthesised.

Scheme 105: Product diversification by divergent functionalisation strategy.
Complementary studies by M.Sc. Yevhenii Sokolenko enabled the divergent functionalisation strategy to be used to access both enantiomers of the cyclohepta[b]indole from only one precursor. Variation of the olefination reagent extended the scope of the methodology to introduce additional substituents on the seven-membered ring with excellent stereocontrol. Eventually, the methodology has been published as research article “Enantioselective Synthesis of Cyclohepta[b]indoles via Pd-Catalyzed Cyclopropane C(sp³)−H Activation as a Key Step.”[359]

Further application of this methodology towards the total synthesis of ervatamia alkaloids are currently underway in our group (scheme 106).

With the aid of the previously established methodology, the total synthesis of both natural products exotine A (239) and exotine B (250) was envisioned. Alkyne 606 was obtained in analogy to the alcohol-to-olefin route, except for the olefination step, which was replaced by Ohira-Bestmann alkynylation. After optimisation to suppress Glaser-Hay coupling, the coumarin part could be attached in good to very good yields via Sonogashira cross-coupling to furnish key intermediates 603 and 609.

With key intermediates 603 and 609 in hands, the envisioned cis-selective hydrogenation, required to trigger the divinylcyclopropane rearrangement, proved challenging and could not be realised yet.
Nevertheless, selective partial hydrogenation of alkynes to (Z)-olefins was realised on similarly sterically encumbered systems, e.g. in Baran’s total syntheses of chartelline alkaloids with Raney nickel\(^{446}\) or palladium on charcoal.\(^{447}\) The latter was also reported by the Fukuyama group in their total synthesis of aspidophytyne.\(^{448}\) The partial reduction of alkynes is a valuable transformation in organic synthesis and industry\(^{449}\) and therefore, numerous methodologies utilising heterogeneous as well as homogenous systems have been developed.\(^{450,451}\)

To elaborate the methodology in terms of general applicability, initial investigations on the scope of other aromatic heterocycles were performed (scheme 108). Gratifyingly, several electron rich heterocycles were found to be versatile coupling partners to give high yield in the C-H arylation step.

![Scheme 108: C-H arylation with other electron rich heterocycles.](image)

Subsequent functionalisation according to the amide-to-olefin or alcohol-to-olefin route was not realised yet. The coupling with 2- or 3-iodinated heterocycles (exemplarily shown in scheme 109 for the corresponding thiophenes) would enable rapid access to diversely substituted cyclohepta[b]-fused heterocycles. By variation of the olefination reagent, additional modification of the seven-membered ring (marked position) would be possible and would allow for the construction of customised scaffolds.

![Scheme 109: Envisioned product diversification dependent on the iodination position.](image)

Further studies focusing on the elaboration of the heterocyclic scaffolds are currently under investigation in the Gaich laboratories.
III Experimental Part

1. General Details

All moisture and oxygen sensitive reactions were performed using standard inert gas Schlenk-techniques under an atmosphere of nitrogen in oven-dried glassware, unless otherwise stated. Solvents or solutions were usually transferred via syringe or cannula (stainless steel or Teflon) through a rubber septum. Reactions were magnetically stirred (unless otherwise stated) and monitored by thin-layer chromatography (TLC), using silica gel coated aluminium plates impregnated with a fluorescent indicator (254 nm; Merck 60-F254). TLC plates were visualised by exposure to 254 nm light or by staining with basic potassium permanganate solution (KMnO₄), acidic ceric ammonium molybdate solution (CAM), acidic vanillin solution, acidic 2,4-dinitrophenylhydrazine solution or by iodine vapours followed by heating with a heat-gun. Flash-column chromatography was performed on silica gel (40-63 µm, 240-400 mesh, Merck). Solvents for chromatography were distilled prior to use, the petroleum ether fraction had a boiling range of 40-60 °C. Triethylamine (NEt₃), diisopropylamine (DIPA) and diisopropylethylamine (DIPEA) were distilled under nitrogen from calcium hydride prior to use. All other dry solvents were purchased from Acros Organics as “extra dry” reagents over molecular sieves and used as received. All other reagents were purchased from chemical suppliers (Sigma-Aldrich, Merck, Acros Organics, Alfa Aesar, TCI Europe, ABCR, Carbolution) and used as received unless otherwise stated. Reagents that were self-prepared can be found in the experimental.

2. Analytical Methods

NMR spectroscopy

All NMR spectra were measured on a Bruker Avance III 400, Avance III 600 or JEOL RESONANCE ECZ 400S. Chemical shifts are given in ppm and referenced to the solvent residual peaks (Chloroform-d, δ = 7.26 ppm, ¹³C, δ = 77.0 ppm; Benzene-d₆ ¹H, δ = 7.16 ppm, ¹³C, δ = 128.1 ppm; DMSO-d₆ ¹H, δ = 2.50 ppm, ¹³C, δ = 39.5 ppm, Acetone-d₆ ¹H, δ = 2.05 ppm, ¹³C, δ = 206.7, 29.9 ppm). Data are reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, p=pentet, se=sextet, h=heptet, m=multiplet), coupling constant J, integration. In case of combined multiplicities, the multiplicity with the larger coupling constant is stated first. All raw FID files were processed and analysed using MestReNova v14.0.0-23239 from Mestrelab Research S.L.
Mass spectrometry

High resolution mass spectra were measured on a LTQ Orbitrap Velos spectrometer from Thermo Fisher Scientific (Velos Pro) with or without loop-mode injection from a Waters (RP18) HPLC system or a Micromass LCT spectrometer via loop-mode injection from a Waters (Alliance 2695) HPLC system. Ionisation was achieved by ESI, modes of ionisation, calculated and found mass are given.

IR spectroscopy

IR spectra were measured on a Perkin Elmer Spectrum 100 FT-IR spectrometer. Data are represented in frequency of absorption in wavenumber [cm\(^{-1}\)]. Samples were prepared as a neat film.

Optical rotation

Optical rotation was measured on a Jasco P-2000 polarimeter using the sodium D line (589nm). Concentration and solvent are denoted in the analytical part of the experimental description.

Chiral HPLC

Chiral HPLC analysis was performed on an Agilent 1100 series HPLC-System with a Chiral PAK AD column.

UV-VIS spectroscopy

UV-VIS absorption spectra were measured on a Thermo Scientific Genesys 10S UV-VIS spectrophotometer. The cell was a quartz glass cuvette and filled with 2 mL of sample solution. Spectroscopic grade cyclohexane was used as solvent and was not degassed prior to use.

X-ray diffraction analysis

X-ray diffraction analysis of single crystals was performed at 100 K on a STOE IPDS-II diffractometer equipped with a graphite-monochromated radiation source (\(\lambda = 0.71073\text{Å}\)) and an image plate detection system. A crystal mounted on a fine glass fiber with silicon grease was employed.

Melting points

Melting points of crystalline materials were determined in open capillaries with a Krüss Melting-Point Meter KSP1 and are uncorrected.
3. Experimental procedures

3.1 The Total Synthesis of (+)-Waihoensene

3.1.1 The meta-Photocycloaddition Approach

**methyl 2-(o-tolyl)acetate (223)**

Prepared by modified literature known procedure.\textsuperscript{[145]} o-tolylacetic acid (12.8 g, 85 mmol, 1 eq.) was dissolved in methanol (170 mL) and concentrated sulphuric acid (0.1 mL) was added. The mixture was heated to reflux overnight and was allowed to cool down to room temperature. The solvent was removed in vacuo and the residue was partitioned between sat. aq. NaHCO\textsubscript{3} solution and methylene chloride (200 mL each). The aqueous phase was extracted with methylene chloride twice (100 mL each) and the combined extracts were dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. Distillation of the residue under reduced pressure (3 mbar, b.p. 93 °C) furnished the product as a colorless oil (12.7 g, 77.5 mmol, 92%). Spectroscopic data were in accordance to those reported in literature.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 7.23 - 7.13 \text{ (m, 4H), 3.69 (s, 3H), 3.65 (s, 2H), 2.32 (s, 3H) ppm.}\)

**2-(o-tolyl)ethan-1-ol (224)**

Prepared by modified literature known procedure.\textsuperscript{[145]} Methyl 2-(o-tolyl)acetate (6.6 g, 40 mmol, 1 eq.) was dissolved in anhydrous THF (160 mL) and the solution was cooled to 0 °C in an ice-bath. DiBAL-H (1 M in hexanes, 80 mL, 80 mmol, 2 eq.) was added dropwise. The reaction was stirred for 5 h whilst it was allowed to warm up to room temperature. Concentrated hydrochloric acid was added until the pH was 1. Ether (100 mL) was added and the phases were separated. The aqueous phase was extracted with ether twice (100 mL each) and the combined organic extracts were washed with brine (250 mL). The organic phase was dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EE 4:1) to furnish the product as a colorless oil (4.2 g, 30.8 mmol, 77%). Spectroscopic data were in accordance to those reported in literature.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 7.22 - 7.12 \text{ (m, 4H), 3.85 (t, } J = 6.9 \text{ Hz, 2H), 2.91 (t, } J = 6.8 \text{ Hz, 2H), 2.35 (s, 3H), 1.47 (s, 1H) ppm.}\)
2-(o-toly)acetaldehyde (196)

Prepared by modified literature known procedure.\textsuperscript{145} 2-(o-toly)ethan-1-ol (4.2 g, 30.8 mmol, 1 eq.) and IBX (17.2 g, 61.6 mmol, 2 eq.) were suspended in acetonitrile (60 mL) and the mixture was stirred for 2.5 h at 80 °C. The reaction was allowed to cool down to room temperature, filtered and concentrated in \textit{vacuo}. The residue was purified by flash column chromatography to furnish the product as a colorless oil (3.9 g, 28.8 mmol, 93%). Spectroscopic data were in accordance to those reported in literature.

$^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta = 9.71$ (t, $J = 2.3$ Hz, 1H), 7.24 – 7.14 (m, 4H), 3.71 (d, $J = 2.3$ Hz, 2H), 2.28 (s, 3H) ppm.

1-(o-toly)pent-4-en-2-ol (197a)

Cerium(III)chloride heptahydrate (2.8 g, 7.5 mmol, 1.5 eq.) was dried in high \textit{vacuo} at 150 °C overnight to give a colorless powder. After cooling to room temperature, THF (13 mL) was added and the mixture was stirred for 2 h at room temperature. The suspension was cooled to – 25 °C and allylmagnesium bromide (1 M in Et\textsubscript{2}O, 7.5 mL, 7.5 mmol, 1.5 eq.) was added dropwise. The yellow suspension was stirred for 30 min and 2-(o-toly)acetaldehyde (670 mg, 5.0 mmol, 1 eq.) in THF (5 mL) was added dropwise within 20 min. The reaction was allowed to warm up to 0 °C and was quenched by addition of sat. aq. NH\textsubscript{4}Cl solution (5 mL). The mixture was filtered over celite and was eluted with ether (150 mL). The solvent was removed in \textit{vacuo} and the residue was purified by flash column chromatography (PE:EE 20:1) to afford the product as a colorless oil (686 mg, 3.9 mmol, 78%).

$^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta = 7.21 – 7.12$ (m, 4H), 5.88 (dddd, $J = 16.9$, 10.2, 7.6, 6.6 Hz, 1H), 5.21 – 5.14 (m, 2H), 3.89 (tt, $J = 7.9$, 4.8 Hz, 1H), 2.85 (dd, $J = 13.8$, 4.9 Hz, 1H), 2.76 (dd, $J = 13.8$, 8.1 Hz, 1H), 2.38 (dddd, $J = 12.2$, 6.8, 3.0, 1.5 Hz, 1H), 2.34 (s, 3H), 2.28 (dtt, $J = 14.0$, 7.6, 1.2 Hz, 1H) 1.70 (bs, 1H) ppm.

$^{13}$C NMR (101 MHz, CDCl\textsubscript{3}) $\delta = 136.8, 136.8, 134.9, 130.6, 130.3, 126.8, 126.2, 118.3, 70.9, 41.6, 40.7, 19.8$ ppm.

IR (film): $\nu_{\text{max}} = 3405, 2927, 1640, 1492, 1435, 1054, 1031, 996, 913, 761, 741$ cm\textsuperscript{-1}.

HRMS (ESI, $m/z$) calculated for C\textsubscript{12}H\textsubscript{15}\textsuperscript{+} [M-OH]\textsuperscript{+}: 159.1168; found: 159.1169.

$R_f = 0.25$ (20:1 PE:EA).
4-methyl-1-(o-tolyl)pent-4-en-2-ol (197b)

4-methyl-1-(o-tolyl)pent-4-en-2-ol (197b) was obtained by the same procedure as described for 197a in 60% yield (4.7 mmol) on a 8.2 mmol scale. Methallylmagnesium chloride was prepared as follows: Magnesium turnings (2.43 g, 100 mmol, 2 eq.), activated by iodine, were suspended in ether (10 mL). Methallyl chloride (4.9 mL, 50 mmol, 1 eq.) in ether (40 mL) was added dropwise to keep the reaction at reflux. Upon complete addition the mixture was heated to reflux for 1 h and allowed to cool to room temperature. The Grignard reagent was filtered through a teflon canula with a plug of glass wool to remove residual magnesium.

\[ \mathrm{H}^1 \mathrm{NMR} (400 \text{ MHz, CDCl}_3) \delta = 7.22 - 7.12 (m, 4H), 4.91 (p, J = 1.6 \text{ Hz, 1H}), 4.85 (dh, J = 2.0, 1.0 \text{ Hz, 1H}), 3.99 (tt, J = 7.8, 5.2 \text{ Hz, 1H}), 2.87 - 2.74 (m, 2H), 2.35 (s, 3H), 2.29 - 2.23 (m, 2H), 1.80 (bs, 1H), 1.77 (t, J = 1.2 \text{ Hz, 3H}) \text{ ppm.} \]

\[ \mathrm{C}^{13} \mathrm{NMR} (101 \text{ MHz, CDCl}_3) \delta = 142.8, 136.9, 136.7, 130.6, 130.3, 126.7, 126.1, 126.1, 113.6, 69.2, 45.9, 40.9, 22.6, 19.8 \text{ ppm.} \]

\[ \mathrm{IR} \text{ (film): } \nu_{\text{max}} = 3422, 2931, 1646, 1494, 1448, 1376, 1111, 1056, 890, 761, 741 \text{ cm}^{-1} \].

\[ \mathrm{HRMS} \text{ (ESI, m/z) calculated for C}_{13}\text{H}_{17}^{+} [\text{M-OH}]^{+}: 173.1325; \text{ found: } 173.1326. \]

\[ R_f = 0.25 \text{ (20:1 PE:EA).} \]

1a,4a\textsuperscript{1}-dimethyl-1a,2,3,4,4a\textsuperscript{1,4b,6a-octahydrocyclopenta[a]cyclopropa[gh]pentalen-3-ol (199b)

4-methyl-1-(o-tolyl)pent-4-en-2-ol (197b) (400 mg, 2.1 mmol) was dissolved in cyclohexane (400 mL) and filled into a photo reactor. The mixture was degassed by passing through nitrogen for 15 min whilst stirring. The solution was irradiated for 2 h with a 400 W medium pressure mercury lamp in a quartz filter. The solvent was removed in vacuo and the residue was purified by flash column chromatography to obtain enriched XY (149 mg, 783 µmol, 37%) as a colourless oil alongside with contamination of the angular photoisomer and as diastereomeric mixture. Further purification via HPLC was not successful. The angular photoisomer could not be enriched due to contamination with decomposed material. 2D-NMR spectra (\textsuperscript{1}H-\textsuperscript{1}H COSY, \textsuperscript{1}H-\textsuperscript{13}C HSQC, \textsuperscript{1}H-\textsuperscript{13}C HMBC) of enriched used for assignment of XY and \textsuperscript{1}H and \textsuperscript{13}C of the photoisomeric mixture can be found in the attachment.

\[ \textsuperscript{1}H \text{ NMR} (400 \text{ MHz, CDCl}_3) \delta = 5.69 (dd, J = 5.3, 2.2 \text{ Hz, 1H}), 5.43 (dd, J = 5.3, 2.5 \text{ Hz, 1H}), 4.43 - 4.34 (m, 1H), 2.92 (dd, J = 6.2, 2.5 \text{ Hz, 1H}), 2.24 - 2.18 (m, 1H), 1.99 - 1.91 (m, 1H), 1.85 - 1.78 (m, 1H), \]
1.72 – 1.68 (m, 1H), 1.58 – 1.54 (m, 1H), 1.65 – 1.60 (m, 1H), 1.45 (d, J = 2.1 Hz, 1H), 1.32 (s, 3H), 1.10 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 134.9, 130.2, 73.5, 58.0, 55.8, 54.4, 52.4, 50.7, 49.3, 40.3, 37.8, 27.7, 15.7 ppm.

HRMS (ESI, m/z) calculated for C$_{13}$H$_{19}$O+$[M+H]^+$: 191.1430; found: 191.1431.

R$_f$ = 0.20 (20:1 PE:EA).

$(rac)$-penifulvin A (109)

Performed according to literature known procedure.$^{[9]}$ Diisopropylamine (2.0 mL, 14 mmol, 2.1 eq.) was dissolved in THF (5.5 mL) and cooled to 0 °C. n-Butyllithium (2.5 M in hexanes, 5.6 mL, 14 mmol, 2.1 eq.) was added dropwise and the mixture was stirred for 30 min at 0 °C. The LDA solution was cooled to -78 °C and o-tolylacetic acid (1.0 g, 6.6 mmol, 1 eq.) dissolved in THF (1.5 mL) was added dropwise. The reaction was warmed to -20 °C and was stirred at that temperature for 2 h. The reaction was cooled to -78 °C and 5-bromo-2-methyl-pent-2-ene (1.3 mL, 10 mmol, 1.5 eq.) was added dropwise. The reaction was allowed to warm to room temperature overnight and was quenched with sat. aq. NaHCO$_3$ solution. The aqueous phase was extracted with ether twice (50 mL each) and the organic phase was discarded. The aqueous phase was acidified to pH = 2 and was extracted with methylene chloride (4 x 100 mL). The combined extracts were dried over MgSO$_4$, filtered and concentrated in vacuo to yield the crude product 105 as yellowish oil, which was used without further purification (1.05 g, 4.5 mmol, 68%)

Crude acid 105 (4.0 g, 17 mmol) was dissolved in n-pentane (200 mL) and the solution was degassed by passing through nitrogen for 15 min. The mixture was irradiated for 10 h with a 125 W medium pressure mercury lamp in a quartz filter. The solvent was removed in vacuo to yield the crude product as mixture of photoisomers, remaining starting material and decomposition products.

Ethylamine (15 mL) was condensed into a Schlenk flask and a solution of crude photoisomers (3.59 g, 15.5 mmol, 1 eq.) in THF (3.0 mL) was added at -78 °C. Lithium (640 mg, 92.7 mmol, 6 eq.) was added in pieces and the reaction was stirred until it became deep blue (ca. 12 h). Sat. aq. NH$_4$Cl (9 mL) was added and the reaction was allowed to warm up to room temperature overnight. Ether and water were added (100 mL each) and the aqueous phase was acidified to pH = 2 and the phases
were separated. The aqueous phase was extracted with ether twice (100 mL) each and the combined extracts were dried over MgSO₄, filtered and concentrated in vacuo to yield the crude product as beige foam. The product was used without further purification.

The crude product (0.5 g) was dissolved in methylene chloride (250 mL) and cooled to -78 °C. The solution was ozonised until it became blue and the excess ozone was driven out with oxygen. Thiourea (1.1 eq.) was added in one portion and the mixture was allowed to warm up to room temperature. The solvent was removed in vacuo and the residue was purified by column chromatography to give lactol 108. From 2.0 g (8.5 mmol theor.) of crude Birch product 150 mg lactol 108 (563 µmol, 7%) were obtained in several batches, which was not further characterised.

Lactol 108 (150 mg, 563 µmol, 1 eq.) was dissolved in methylene chloride (6 mL) and PDC (850 mg, 2.25 mmol, 4 eq.) was added in one portion. The reaction was stirred for 20 min when glacial acetic acid (644 µL, 11.3 mmol, 20 eq.) was added dropwise. After stirring for 1 h the reaction was filtered over a pad of silica and was eluted with ether. The solvent was removed in vacuo and the residue was purified by flash column chromatography to furnish penifulvin A (109) as colorless crystals (120 mg, 454 µmol, 81%, 5% from crude Birch product). Spectroscopic data were in accordance to those reported in literature.

1H NMR (400 MHz, CDCl₃) δ = 5.97 (s, 1H), 3.01 – 2.95 (m, 1H), 2.79 (d, J = 15.0 Hz, 1H), 2.47 (d, J = 15.0 Hz, 1H), 2.32 (dd, J = 9.8, 5.0 Hz, 1H), 2.27 – 2.21 (m, 1H), 1.96 – 1.81 (m, 2H), 1.79 – 1.71 (m, 3H), 1.25 (s, 3H), 1.10 (s, 3H), 1.04 (s, 3H) ppm.

13C NMR (101 MHz, CDCl₃) δ = 178.0, 168.6, 103.9, 66.8, 60.9, 55.7, 46.4, 44.1, 42.1, 40.3, 32.8, 30.1, 28.2, 27.6, 27.4 ppm.

Dimethyltitanocene, Petasis reagent (225)

Prepared by modified literature known procedure.[452] Titanocene dichloride (5.8 g, 23.3 mmol, 1 eq.) was suspended in diethyl ether (100 mL) and the mixture was cooled to 0 °C in an ice-bath. Methylolithium (1.6 M in diethyl ether, 32 mL, 51.3 mmol, 2.2 eq.) was added dropwise over 1 h. The reaction was allowed to warm up to room temperature and was stirred for further 15 min. The reaction was cooled to 0 °C again and ice-water was added to destroy residual methylolithium (100 mL). The phases were separated and the organic phase was dried over MgSO₄, filtered and concentrated at low temperature in vacuo. The residue was dissolved in pentane (100 mL) and the solution was slowly cooled to -78 °C in a dry-ice acetone
bath. The product crystallised as orange needles that were filtered off and dried in *vacuo* (4.0 g, 19.2 mmol, 82%) and was used as 1 M solution in toluene, stored in the dark.

**[1,1’-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), dichloromethane adduct (226)**

Pd(PhCN)$_2$Cl$_2$ was prepared by literature known procedure.$^{[453]}$ Palladium(II)chloride (1.0 g, 8.5 mmol, 1 eq.) was suspended in benzonitrile (30 mL) and the mixture was heated to 100 °C for 20 min and was immediately filtered off. Hexanes (160 mL) was added to the filtrate at room temperature and the product precipitated as yellow solid. It was filtered off, washed with hexanes and dried in air to yield Bis(benzonitrile)palladium(II)chloride as yellow solid (1.8 g, 4.7 mmol, 55%).

DPPF was prepared by literature known procedure.$^{[454, 455]}$ Ferrocene (10.0 g, 53.8 mmol, 1 eq.) was dissolved in hexane (100 mL) and TMEDA (freshly distilled, 19.5 mL, 129 mmol, 2.4 eq.) was added. $n$-Butyllithium (2.5 M in hexanes, 47.3 mL, 118 mmol, 2.2 eq, diluted with 100 mL hexane) was added dropwise at room temperature and the reaction was stirred at room temperature overnight. The orange suspension was allowed to settle and the hexane layer was removed via syringe. The residual solid was washed with hexane (50 mL) and dissolved in THF (100 mL). The solution was cooled to -78 °C and chlorodiphenylphosphine (27.2 mL, 148 mmol, 2.75 eq.) was added dropwise. The reaction was allowed to warm up to room temperature and was carefully quenched with water (100 mL) after 3 h. Methylene chloride (150 mL) was added and the phases were separated. The aqueous phase was extracted twice with DCM (150 mL each), dried over Na$_2$SO$_4$, filtered and concentrated in *vacuo*. The residue was suspended in methanol, filtered off and washed with methanol. Drying in *vacuo* afforded DPPF (13.8 g, 24.9 mmol, 46%) as orange powder. Spectroscopic data were in accordance to those reported in literature.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.29$ (d, $J = 6.9$ Hz, 20H), 4.25 (t, $J = 1.9$ Hz, 4H), 3.99 (q, $J = 1.9$ Hz, 4H) ppm.

$^{31}$P NMR (162 MHz, CDCl$_3$) $\delta = -17.2$ ppm.

Pd(dppf)Cl$_2$*CH$_2$Cl$_2$ was prepared by literature known procedure.$^{[456]}$ Pd(PhCN)$_2$Cl$_2$ (875 mg, 2.28 mmol, 1 eq.) and DPPF (1.26 g, 2.28 mmol, 1 eq.) were dissolved in benzene (22 mL) and the reaction was stirred at room temperature overnight. The orange-red microcrystalline solid was filtered off and washed with a small amount of benzene. The solid was dissolved in methylene chloride (100 mL) and the solvent was slowly evaporated at 900 mbar in a water bath. The product was obtained as orange-red crystals (1.47 g, 1.80 mmol, 79%).

m.p.: 283 °C decomp. (lit.: 290 °C decomp.)$^{[457]}$
(2,2-diethoxyethyl)(phenyl)selane (227)

Prepared by modified literature known procedure. Diphenyldiselenide (12.0 g, 38.5 mmol, 1 eq.) was placed in a Schlenk flask under nitrogen. Ethanol (p.a., 140 mL) was added and the solution was cooled to 0 °C in an ice-bath. Sodium borohydride (3.20 g, 84.6 mmol, 3.2 eq.) was added in portions and a colourless solution was obtained. The mixture was allowed to warm up to room temperature and bromoacetaldehyde diethylacetal (11.6 mL, 77.1 mmol, 2 eq.) was added. The mixture was stirred at 58 °C for 4 h and a colourless precipitate formed. The precipitate was filtered off and the residue was concentrated in vacuo. Water and dichloromethane were added (150 mL each) and the phases were separated. The aqueous phase was further extracted twice with dichloromethane (100 mL each). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Distillation of the residue (~1 mbar, b.p. 98 °C) furnished XY as a yellow oil (16.1 g, 58.9 mmol, 77%). Spectroscopic data were in accordance to those reported in literature.

1H NMR (400 MHz, CDCl₃) δ = 7.59 – 7.52 (m, 2H), 7.34 – 7.21 (m, 3H), 4.75 (t, J = 5.7 Hz, 1H), 3.70 (dq, J = 9.4, 7.1 Hz, 2H), 3.57 (dq, J = 9.4, 7.1 Hz, 2H), 3.14 (d, J = 5.7 Hz, 2H), 1.22 (t, J = 7.1 Hz, 6H) ppm.

2-(phenylselanyl)acetaldehyde (195)

Prepared by literature known procedure. Diethylacetal 227 (16.0 g, 58.6 mmol, 1 eq.) was suspended in water (140 mL) and hydrochloric acid (37%, 7.5 mL) was added. The mixture was stirred at 50 °C for 4.5 h. The reaction was cooled down to room temperature, was neutralised with saturated sodium bicarbonate solution and was extracted with diethyl ether twice (150 mL each). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo to yield the desired aldehyde as a yellow liquid. The product was pure enough to be used in the further transformations. Significant decomposition was observed during distillation. Spectroscopic data were in accordance to those reported in literature.

1H NMR (400 MHz, CDCl₃) δ = 9.51 (t, J = 4.0 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.31 – 7.26 (m, 3H), 3.53 (d, J = 4.0 Hz, 2H) ppm.
1-hydroxy-2-(phenylselanyl)ethyl)-2,6-dimethylcyclohexan-1-one (228)

Prepared by literature known procedure. Diisopropylamine (8.5 ml, 59.4 mmol, 1.5 eq.) was dissolved in ether (160 ml) and 10 mg of 2,2' -bipyridyl was added. The solution was cooled to – 78 °C and n-butyllithium (2.5 M in hexane, 15.9 ml, 5.0 mmol) was added dropwise to give a deep red LDA solution which was stirred for further 45 min. 2,6-Dimethylcyclohexanone (mixture of isomers, 5.4 mL, 39.6 mmol, 1 eq.) in ether (80 ml) was added dropwise and the mixture was stirred further 30 min. The reaction was warmed up to 0 °C and ZnCl₂ (1 M in ether, 19.8 ml, 19.8 mmol, 0.5 eq.) was added dropwise. The yellow solution was stirred for 45 min and 195 (8.3 g, 41.6 mmol, 1.05 eq.) in ether (60 ml) was added in one portion. After stirring for further 5 min, the reaction was quenched with saturated aq. NH₄Cl solution (150 ml) and was extracted with ether (3 x 150 ml). The combined organic extracts were dried over MgSO₄ and the solvent was removed in vacuo. Flash column chromatography (hexanes – ethyl acetate 5:1) afforded 262 as a clear pale yellow oil as a mixture of diastereomers (11.9 g, 36.6 mmol, 92%). Spectroscopic data were in accordance to those reported in literature.

1H NMR (400 MHz, CDCl₃) δ = 7.55 – 7.53 (m, 2H), 7.29 – 7.27 (m, 3H), 4.13 – 4.10 (m, 1H), 3.21 (dd, J = 12.8 Hz, 1.9 Hz, 1H), 2.79 – 2.59 (m, 4H), 2.03 – 1.85 (m, 3H), 1.53 – 1.22 (m, 4H), 1.0 – 0.98 (m, 6H) ppm.

2,6-dimethyl-2-vinylcyclohexan-1-one (191)

Prepared by literature known procedure.[142] Selenoalcohol 228 (1.3 g, 4.1 mmol, 1 eq.) was dissolved in methylene chloride (40 ml) and triethyl amine (2.9 ml, 21.1 mmol, 5.2 eq.) was added. A solution of methanesulfonyl chloride (1.0 ml, 13.0 mmol, 3.2 eq.) in methylene chloride (20 ml) was added within 1.5 h via a syringe pump. After the addition was complete the reaction mixture was poured into methylene chloride (50 ml) and was washed with ice-cold 0.1 N hydrochloric acid solution (100 mL). The phases were separated and the organic layer was washed with saturated aq. NaHCO₃ solution (100 ml) and brine (100 ml). The organic phase was dried over MgSO₄ and the solvent was removed in vacuo. Kugelrohr distillation of the crude product (20 mmHg, bp. 70 °C) afforded 191 as a colorless liquid in a diastereomeric mixture of cis/trans 7.5:1 (513 mg, 3.4 mmol, 83%). Spectroscopic data were in accordance to those reported in literature. Only the major isomer assigned.

1H NMR (400 MHz, CDCl₃) δ = 5.94 (dd, J = 17.7, 10.7 Hz, 1H), 5.10 (dd, J = 10.7, 0.6 Hz, 1H), 4.95 (dd, J = 17.7, 0.6 Hz, 1H), 2.72 – 2.63 (m, 1H), 2.06 – 1.98 (m, 3H), 1.93 – 1.75 (m, 2H), 1.66 – 1.50 (m, 2H), 1.38 – 1.31 (m, 1H), 1.10 (s, 3H), 0.97 (d, J = 6.7 Hz, 3H) ppm.

13C NMR (101 MHz, CDCl₃) δ = 214.4, 143.0, 115.3, 52.5, 42.2, 41.0, 37.0, 24.6, 22.1, 14.9 ppm.
Procedure for the sp$^2$-sp$^3$ Suzuki cross-coupling

The same procedure was applied to all substrates.

2,6-dimethyl-2-phenethylcyclohexan-1-one (194c)

Vinylcyclohexanone (191) (250 mg, 1.64 mmol, 1 eq.) was placed in a Schlenk tube, dissolved in THF (1.6 mL) and cooled to 0 °C. 9-BBN (0.5 M in THF, 3.3 mL, 1 eq.) was added to give a white suspension that was stirred overnight and allowed to warm up to room temperature.

In a separate Schlenk flask, Pd(dppf)Cl$_2$·CH$_2$Cl$_2$ (40 mg, 49.0 µmol, 0.03 eq.), triphenylarsine (50.3 mg, 164 µmol, 0.1 eq.) and Cs$_2$CO$_3$ (963 mg, 2.96 mmol, 1.8 eq.) were placed and DMF (6.6 mL) was added. The mixture was degassed by applying line vaccum for 15 min whilst vigorously stirring and purging again with nitrogen. Iodobenzene (550 µL, 4.93 mmol, 3 eq.) was added and the mixture was stirred for 15 min. The borane solution was added, followed by degassed water (355 µL, 19.7 mmol, 12 eq.) causing a color change from orange-red to brown. The reaction was stirred at room temperature until complete consumption of the starting material. Water (50 mL) was added and the aqueous phase was extracted with ether trice (75 mL each). The combined organic extracts were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo.

The residue was purified by flash column chromatography (PE:EA 70:1) to obtain the product as a colorless oil (344 mg, 1.49 mmol, 91%).

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.35 – 7.24 (m, 2H), 7.21 – 7.12 (m, 3H), 2.62 (td, $J = 12.9, 6.2$ Hz, 2H), 2.24 – 2.14 (m, 2H), 2.06 (dddt, $J = 12.5, 5.7, 3.8, 2.8$ Hz, 1H), 1.96 – 1.87 (m, 2H), 1.71 – 1.51 (m, 3H), 1.34 (qd, $J = 13.0, 4.0$ Hz, 1H), 1.12 (s, 3H), 1.00 (d, $J = 6.5$ Hz, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) δ = 216.9, 142.2, 128.6, 128.4, 126.1, 49.1, 41.5, 41.1, 40.0, 36.9, 30.6, 22.6, 21.3, 15.1 ppm.

IR (film): $\nu_{\text{max}}$ = 2929, 2866, 1702, 1497, 1454, 1376, 1125, 1005, 955, 862, 735, 698 cm$^{-1}$.

HRMS (ESI, $m/z$) calculated for C$_{16}$H$_{23}$O$^+$ [M+H]$^+$: 231.1743; found: 231.1748.

R$_f$ = 0.20 (70:1 PE:EA).

2,6-dimethyl-2-(2-methylphenethyl)cyclohexan-1-one (194a)

531 mg (2.17 mmol, 87%) were obtained on a 2.5 mmol scale as a colorless oil. The reaction was conducted at 50 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ = 7.16 – 7.05 (m, 4H), 2.69 – 2.57 (m, 2H), 2.28 (s, 3H), 2.22 – 2.03 (m, 3H), 1.98 – 1.87 (m, 2H), 1.68 – 1.52 (m, 3H), 1.35 (qd, $J = 12.9, 4.1$ Hz, 1H), 1.15 (s, 3H), 1.02 (d, $J = 6.5$ Hz, 3H) ppm.
\textbf{\(\text{\(^{13}\text{C}\) NMR} \)} \((101 \text{ MHz, CDCl}_3) \) \(\delta = 216.8, 140.4, 135.8, 130.5, 128.9, 126.3, 126.3, 49.1, 41.6, 41.0, 38.8, 36.9, 27.9, 22.5, 21.3, 19.3, 15.1 \text{ ppm.}\)

\textbf{IR} \((\text{film})\): \(\nu_{\text{max}} = 2930, 1702, 1454, 1376, 1125, 1004, 955, 862, 741, 696 \text{ cm}^{-1}.\)

\textbf{HRMS} \((\text{ESI, } m/z)\) calculated for \(\text{C}_{17}\text{H}_{25}\text{O}^+ [\text{M+H}]^+: 245.1900\); found: 245.1904.

\(R_f = 0.25 \) (70:1 PE:EA).

\textbf{2-(2,6-dimethylphenethyl)-2,6-dimethylcyclohexan-1-one (194b)}

\(332 \text{ mg (1.28 mmol, 78\%)}\) were obtained on a 1.64 mmol scale as a colorless oil. The reaction was conducted at 80 °C.

\textbf{\(^1\text{H NMR} \)} \((400 \text{ MHz, CDCl}_3) \) \(\delta = 7.02 – 7.00 \text{ (m, 3H), 2.74 – 2.60 (m, 2H), 2.29 (s, 6H), 2.27 – 2.21 (m, 1H), 2.12 – 2.04 (m, 1H), 2.00 – 1.86 (m, 3H), 1.69 – 1.47 (m, 3H), 1.37 (qd, } J = 13.0, 4.0 \text{ Hz, 1H), 1.19 (s, 3H), 1.06 (d, } J = 6.4 \text{ Hz, 3H) ppm.}\)

\textbf{\(\text{\(^{13}\text{C}\) NMR} \)} \((101 \text{ MHz, CDCl}_3) \) \(\delta = 216.8, 138.6, 135.9, 128.4, 126.0, 49.1, 41.7, 40.7, 36.8, 36.6, 24.2, 22.4, 21.4, 19.8, 15.0 \text{ ppm.}\)

\textbf{IR} \((\text{film})\): \(\nu_{\text{max}} = 2929, 1702, 1465, 1376, 1125, 1002, 861, 766 \text{ cm}^{-1}.\)

\textbf{HRMS} \((\text{ESI, } m/z)\) calculated for \(\text{C}_{18}\text{H}_{27}\text{O}^+ [\text{M+H}]^+: 259.2056\); found: 259.2057.

\(R_f = 0.45 \) (20:1 PE: EA).

\textbf{2-(2-methoxyphenethyl)-2,6-dimethylcyclohexan-1-one (194d)}

\(351 \text{ mg (1.35 mmol, 82\%)}\) were obtained on a 1.64 mmol scale as a colorless oil. The reaction was conducted at 80 °C.

\textbf{\(^1\text{H NMR} \)} \((400 \text{ MHz, CDCl}_3) \) \(\delta = 7.18 \text{ (ddd, } J = 8.1, 7.4, 1.8 \text{ Hz, 1H), 7.08 (dd, } J = 7.4, 1.8 \text{ Hz, 1H), 6.87 (td, } J = 7.4, 1.1 \text{ Hz, 1H), 6.83 (dd, } J = 8.1, 1.1 \text{ Hz, 1H), 3.81 (s, 3H), 2.74 (dqd, } J = 13.0, 6.4, 5.5 \text{ Hz, 1H), 2.57 (td, } J = 12.6, 5.1 \text{ Hz, 1H), 2.27 – 2.11 (m, 2H), 2.05 (dddq, } J = 15.6, 5.6, 3.9, 2.8 \text{ Hz, 1H), 1.95 – 1.88 (m, 2H), 1.64 – 1.49 (m, 3H), 1.33 (qd, } J = 12.9, 3.9 \text{ Hz, 1H), 1.12 (s, 3H), 1.02 (d, } J = 6.4 \text{ Hz, 3H) ppm.}\)

\textbf{\(\text{\(^{13}\text{C}\) NMR} \)} \((101 \text{ MHz, CDCl}_3) \) \(\delta = 217.3, 157.4, 130.7, 129.8, 127.4, 120.6, 110.4, 55.3, 49.3, 41.2, 41.2, 38.2, 37.1, 25.3, 22.3, 21.3, 15.1 \text{ ppm.}\)

\textbf{IR} \((\text{film})\): \(\nu_{\text{max}} = 2929, 1701, 1601, 1493, 1456, 1376, 1291, 1241, 1176, 1141, 1125, 1050, 1030, 1004, 956, 862, 750 \text{ cm}^{-1}.\)

\textbf{HRMS} \((\text{ESI, } m/z)\) calculated for \(\text{C}_{17}\text{H}_{25}\text{O}_2^+ [\text{M+H}]^+: 261.1849\); found: 261.1851.

\(R_f = 0.15 \) (70:1 PE:EA).
Procedure for the Takai-Lombardo olefination

The same procedure was applied to all substrates.

\((2\text{-}(1,3\text{-dimethyl}-2\text{-methylene cyclohexyl})\text{ethyl})\text{benzene (189c)}\)

Zinc powder (<150 μm, 1.32 g, 20.2 mmol, 13.5 eq.) was dried in a Schlenk tube in high vacuo by heating with a heat gun for 30 min. After cooling to room temperature THF (6.0 mL) was added and the suspension was cooled to 0 °C. Diiodomethane (900 µL, 11.2 mmol, 7.5 eq.) was added dropwise and the reaction was stirred for 30 min at 0 °C. TiCl\(_4\) (1 M in CH\(_2\)Cl\(_2\), 4.5 mL, 4.48 mmol, 3 eq.) was added dropwise to cause a very exothermic reaction. After stirring for 10 min at 0 °C the mixture was allowed to warm up to room temperature to give a black solution. Ketone 194c (344 mg, 1.48 mmol, 1 eq.) dissolved in methylene chloride (2.0 mL) was added dropwise and the reaction was stirred overnight. The mixture was poured into sat. aq. Rochelle’s salt solution (100 mL) in a beaker and ether (100 mL) was added. The biphasic mixture was stirred until it became colorless. The phases were separated and the aqueous phase was extracted twice with ether (100 mL each). The combined organic extracts were washed with brine, dried over MgSO\(_4\), filtered and concentrated in vacuo. The residue was purified by flash column chromatography (100% PE) to furnish the product as colorless oil (218 mg, 955 µmol, 64%).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 7.27 - 7.22\) (m, 2H), 7.16 - 7.11 (m, 3H), 4.77 (dt, \(J = 8.3, 1.4\) Hz, 2H), 2.45 (td, \(J = 13.2, 5.1\) Hz, 1H), 2.26 - 2.14 (m, 2H), 2.04 (td, \(J = 13.1, 4.5\) Hz, 1H), 1.80 - 1.64 (m, 2H), 1.61 - 1.47 (m, 2H), 1.39 (ddd, \(J = 13.6, 12.6, 5.1\) Hz, 1H), 1.26 (td, \(J = 13.3, 4.3\) Hz, 1H), 1.12 (s, 3H), 1.04 (d, \(J = 6.5\) Hz, 3H), 0.96 (qd, \(J = 12.6, 4.0\) Hz, 1H) ppm.

\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta = 158.7, 143.7, 128.5, 128.4, 125.7, 104.8, 41.4, 40.4, 39.8, 37.5, 33.7, 30.8, 26.6, 22.0, 19.5\) ppm.

\(\text{IR (film)}: \nu_{\text{max}} = 2921, 1632, 1495, 1454, 1403, 1373, 893, 749, 703\) cm\(^{-1}\).

\(R_f = 0.70\) (100% PE).

\(1\text{-}(2\text{-}(1,3\text{-dimethyl}-2\text{-methylene cyclohexyl})\text{ethyl})\text{-}2\text{-methylbenzene (189a)}\)

318 mg (1.31 mmol, 80%) were obtained on a 1.64 mmol scale as a colorless oil.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta = 7.17 - 7.04\) (m, 4H), 4.80 (dt, \(J = 6.9, 1.4\) Hz, 2H), 2.47 (td, \(J = 13.2, 4.9\) Hz, 1H), 2.28 (s, 3H), 2.28 - 2.20 (m, 2H), 1.97 (td, \(J = 13.2, 4.4\) Hz, 1H), 1.82 - 1.76 (m, 1H), 1.70 (tt, \(J = 13.4, 3.9\) Hz, 1H), 1.63 - 1.49 (m, 2H), 1.40 - 1.25 (m, 2H), 1.17 (s, 3H), 1.06 (d, \(J = 6.5\) Hz, 3H), 0.99 (qd, \(J = 12.6, 4.2\) Hz, 1H) ppm.
**13C NMR** (101 MHz, CDCl₃) δ = 158.7, 141.8, 135.8, 130.3, 129.0, 126.1, 125.8, 104.8, 41.5, 40.4, 38.5, 37.5, 33.8, 28.1, 26.5, 22.1, 19.4, 19.3.

**IR (film):** νₘₕᵦ = 2921, 1634, 1457, 1373, 893, 740, 722 cm⁻¹.

**Rₚ = 0.70** (100% PE).

2-(2-(1,3-dimethyl-2-methylene cyclohexyl)ethyl)-1,3-dimethylbenzene (189b)

143 mg (560 µmol, 70%) were obtained on an 800 µmol scale as a colorless oil.

**1H NMR** (400 MHz, CDCl₃) δ = 6.99 (s, 3H), 4.83 (dt, J = 6.2, 1.4 Hz, 2H), 2.50 (td, J = 13.3, 4.7 Hz, 1H), 2.36 – 2.27 (m, 5H), 2.30 (s, 3H), 1.88 (td, J = 13.5, 4.5 Hz, 1H), 1.80 (ddq, J = 12.4, 4.2, 2.0 Hz, 1H), 1.77 – 1.65 (m, 1H), 1.65 – 1.52 (m, 2H), 1.30 (tdd, J = 13.4, 8.6, 4.5 Hz, 2H), 1.22 (s, 3H), 0.71 (d, J = 6.5 Hz, 3H), 1.01 (qd, J = 12.6, 4.1 Hz, 1H) ppm.

**13C NMR** (101 MHz, CDCl₃) δ = 158.6, 139.8, 136.0, 128.2, 125.6, 104.8, 41.5, 40.4, 37.5, 36.3, 34.0, 26.4, 24.6, 22.29, 19.8, 19.4 ppm.

**IR (film):** νₘₕᵦ = 2958, 2921, 1634, 1465, 1373, 1095, 959, 893, 765, 701 cm⁻¹.

**HRMS (ESI, m/z) calculated for C₁₉H₂₉⁺ [M+H]⁺: 257.2264; found: 257.2266.**

Rₚ = 0.70 (100% PE).

1-(2-(1,3-dimethyl-2-methylene cyclohexyl)ethyl)-2-methoxybenzene (189d)

174 mg (673 µmol, 82%) were obtained on an 826 µmol scale as a colorless oil.

**1H NMR** (400 MHz, CDCl₃) δ = 7.15 (ddd, J = 8.1, 7.4, 1.8 Hz, 1H), 7.09 (dd, J = 7.4, 1.8 Hz, 1H), 6.87 (td, J = 7.4, 1.2 Hz, 1H), 6.83 (dd, J = 8.1, 1.1 Hz, 1H), 4.78 (dt, J = 4.5, 1.4 Hz, 2H), 3.81 (s, 3H), 2.47 (td, J = 12.9, 5.0 Hz, 1H), 2.36 – 2.21 (m, 2H), 1.99 (td, J = 13.0, 4.3 Hz, 1H), 1.84 – 1.66 (m, 2H), 1.64 – 1.45 (m, 2H), 1.44 – 1.20 (m, 2H), 1.15 (d, J = 0.6 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H), 0.98 (qd, J = 13.9, 13.3, 4.7 Hz, 1H).

**13C NMR** (101 MHz, CDCl₃) δ = 159.2, 157.6, 132.1, 129.8, 126.9, 120.5, 110.4, 104.4, 55.4, 41.5, 40.5, 37.9, 37.6, 33.5, 26.4, 25.3, 22.0, 19.5 ppm.

**IR (film):** νₘₕᵦ = 2922, 1633, 1602, 1493, 1463, 1373, 1240, 1179, 1130, 1095, 1048, 1032, 893, 827, 748, 700 cm⁻¹.

**HRMS (ESI, m/z) calculated for C₁₈H₂₇O⁺ [M+H]⁺: 259.2056; found: 259.2060.**
\[ R_f = 0.70 \text{ (100\% PE)} \].

### 3.1.2 The Asymmetric Total Synthesis of (+)-Waihoensene

**dimethyl 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylate (206)**

Anthracene (28.9 g, 200 mmol, 1 eq.) was dissolved in \( o \)-xylene and dimethyl fumarate (35.7 g, 200 mmol, 1 eq.) was added. The mixture was refluxed for 5 d, was allowed to cool up to room temperature and the solvent was removed in \( \textit{vacuo} \). Recrystallisation from methanol afforded the product as a colorless crystalline solid (48.6 g, 151 mmol, 75%). An analytical sample was purified by flash column chromatography (PE:EA 9:1). Spectroscopic data were in accordance to those reported in literature. \[459\]

**\( ^1H \)-NMR** (400 MHz, CDCl\(_3\)) \( \delta = 7.37 - 7.32 \text{ (m, 2H)}, 7.27 - 7.23 \text{ (m, 2H)}, 7.15 - 7.08 \text{ (m, 4H)}, 4.76 - 4.73 \text{ (m, 2H)}, 3.64 \text{ (s, 6H)}, 3.45 - 3.42 \text{ (m, 2H)} \text{ ppm.}

**\( ^13C \)-NMR** (101 MHz, CDCl\(_3\)) \( \delta = 172.9, 142.2, 140.5, 126.6, 126.5, 124.7, 123.9, 52.4, 48.0, 46.8 \text{ ppm.}

**9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid \( \textit{rac} \)-(207)**

Diester 206 (20.0 g, 62.0 mmol, 1 eq.) was dissolved in 95% ethanol (250 mL) and KOH (13.9 g, 248 mmol, 4 eq.) was added. The mixture was stirred at reflux overnight and was allowed to cool down to room temperature. The solvent was removed in \( \textit{vacuo} \) and water (200 mL) was added. The aqueous phase was extracted with ether twice (200 mL each) and the organic extracts were discarded. The aqueous phase was acidified to \( \text{pH} = 1 \) using conc. hydrochloric acid. A colorless precipitate was formed that was filtered off, washed with water and dried in \( \textit{vacuo} \) to furnish the product (18.0 g, 61.2 mmol, 98%). Spectroscopic data were in accordance to those reported in literature. \[460\]

**\( ^1H \) NMR** (400 MHz, DMSO-\( D_6 \)) \( \delta = 7.42 - 7.37 \text{ (m, 2H)}, 7.29 - 7.23 \text{ (m, 2H)}, 7.13 - 7.06 \text{ (m, 4H)}, 4.72 \text{ (t, } J = 1.3 \text{ Hz, 2H)}, 3.12 \text{ (t, } J = 1.2 \text{ Hz, 2H)} \text{ ppm.}

**\( ^13C \) NMR** (101 MHz, DMSO-\( D_6 \)) \( \delta = 173.4, 142.6, 140.5, 126.0, 125.9, 124.7, 123.5, 47.3, 45.9 \text{ ppm.}

**\( 11S,12S \)-9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid \( \textit{S,S} \)-(207)**

Prepared by literature known procedure. \[157\] Racemic diacid 207 (6.00 g, 20.4 mmol, 1 eq.) and brucine (24.1 g, 61.2 mmol, 3 eq.) were dissolved in a mixture of ethanol (150 mL) and water (240 mL). 2 g of activated charcoal was added and the mixture was heated to reflux for 30 min. The solution was filtered and the \( (11S,12S) \)-enantiomer-salt crystallised from the solution. The crystals were filtered off and were
recrystallised from ethanol (90 mL) and water (150 mL). The obtained crystals were filtered off and were washed with a minimal amount of ethanol. After drying in air the crystals were treated with hydrochloric acid (5 M, 50 mL) and the aqueous suspension was extracted with diethyl ether (3 x 50 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo to obtain the pure (11S,12S)-enantiomer (2.47 g, 8.39 mmol, 41%).

\[ \alpha \] D\(^{22}\) = -9.1 (c = 1.5, MeOH); lit.: \[ \alpha \] D\(^{22}\) = -9.2 (c = 4, MeOH)\(^{158}\); \[ \alpha \] D\(^{20}\) = 7.6 (c = 1.5, MeOH, 96% ee)\(^{159}\)

The (11R,12R)-enantiomer remained in the aqueous phase from the first crystallisation step. Ethanol was evaporated in vacuo and hydrochloric acid (5 M, 100 mL) was added. The suspension was extracted with diethyl ether (3 x 100 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo to yield the (11R,12R)-enantiomer (2.42 g, 8.22 mmol, 40%). The spectral data were in accordance with the racemic sample.

(11S,12S)-9,10-dihydro-9,10-ethanoanthracene-11,12-diamine (209a)

Prepared by modified literature known procedure.\(^{104}\) Diacid 207 (3.33 g, 11.3 mmol, 1 eq.) was suspended in anhydrous benzene (28.3 mL) and a drop of DMF was added. Thionyl chloride (2.46 mL, 33.9 mmol, 3 eq.) was added and the mixture was heated to reflux until no more gas evolution was observed (approx. 3.5 h, testing with pH paper). The mixture was cooled to room temperature and the solvent was removed in vacuo. Anhydrous benzene (5 mL) was added and the solvent was removed again in vacuo. This was repeated three times to yield a beige solid which was directly used in the next step.

Crude dichloride (3.75 g, 11.3 mmol, 1 eq.) was dissolved in anhydrous DMF (28.3 mL) and the solution was cooled in an ice bath. After complete dissolution (approx. 1 h) sodium azide (1.62 g, 24.9 mmol, 2.2 eq.) was added in one portion. The mixture was stirred for 3 h whilst warming up to room temperature. The reaction mixture was poured in a separation funnel containing ice cooled deionised water (100 mL). Cold toluene (50 mL) was added and the phases were separated. The aqueous phase was extracted with cold toluene (3 x 30 mL) and the organic extracts were combined, dried over Na₂SO₄ and filtered into a 500 mL round bottom flask. To the previously obtained bis-azide solution was added toluene (110 mL, combined 250 mL) and the solution was stirred for 3 h at room temperature. The temperature was raised stepwise to reflux and the reaction was refluxed until no more gas evolution was observed (approx. 2 h). The reaction was cooled down to room temperature and the solvent was removed in vacuo to yield the crude bis-isocyanate.

Crude bis-isocyanate was dissolved in THF (33.5 mL) and sodium hydroxide (2.5 M, 16.8 mL, 41.9 mmol, 3.7 eq.) was added. The mixture was stirred in the dark overnight. Conc. hydrochloric acid
was added until pH = 1 followed by ether (50 mL) was added. The phases were separated and the aqueous phase was extracted with ether (50 mL) and the organic extracts were discarded. The aqueous phase was basified with sodium hydroxide pellets until pH = 14. The solution became turbid and was extracted with ether (2 x 50 mL) and dichloromethane (2 x 50 mL). The combined extracts were dried over K₂CO₃, filtered and concentrated in vacuo to yield a beige foam. The foam was dissolved in anhydrous THF (75 mL) and hydrochloric acid in 1,4-dioxane (4 M, 11.3 mL, 45.2 mmol, 4 eq.) was added. The mixture was stirred for 4 h and the solvent was removed in vacuo to afford the bis-hydrochloride. The hydrochloride was refluxed in anhydrous iPrOH (200 mL) to remove impurities. The salt was filtered off and was dried in vacuo. Dichloromethane (50 mL) and sodium hydroxide (2 M, 50 mL) were added and the phases were separated. The basic aqueous phase was extracted with dichloromethane (3 x 50 mL), the combined extracts were dried over K₂CO₃, filtered and concentrated in vacuo to obtain the pure diamine (1.88 g, 7.96 mmol, 70.2% over 4 steps) as a colorless solid. Spectroscopic data were in accordance to those reported in literature.

¹H NMR (400 MHz, CDCl₃) δ = 7.32 – 7.24 (m, 4H), 7.15 – 7.09 (m, 4H), 4.00 (s, 2H), 2.63 (s, 2H), 1.19 (bs, 4H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 142.2, 139.0, 126.5, 126.4, 126.2, 124.1, 62.4, 53.8 ppm.

N,N’-((11S,12S)-9,10-dihydro-9,10-ethanoanthracene-11,12-diyl)bis(2-(diphenylphosphanylidene)benzamide), (11S,12S)-ANDEN-phenyl Trost ligand (S,S)-113

Prepared by modified literature known procedure. Diamine 209a (1.12 g, 4.74 mmol, 1 eq.), DMAP (29.0 mg, 237 µmol, 0.05 eq.) and o-diphenylphosphinobenzoic acid (3.05 g, 9.95 mmol, 2.1 eq.) were dissolved in anhydrous dichloromethane (23.7 mL) and DCC (2.05 g, 9.95 mmol, 2.1 eq.) was added. The mixture was stirred at room temperature overnight. The reaction mixture was filtered through a pad of celite and was eluted with dichloromethane (approx. 250 mL). The solvent was removed in vacuo and the product was purified by column chromatography (PE:EE 7:3) to yield the product as a colorless foam (3.85 g, 4.74 mmol, quant.). Spectroscopic data were in accordance to those reported in literature.

¹H NMR (400 MHz, CDCl₃) δ = 7.45 – 7.24 (m, 28H), 7.18 – 7.13 (m, 4H), 7.11 – 7.05 (m, 2H), 7.00 – 6.94 (m, 2H), 5.75 (d, J = 7.1 Hz, 2H), 4.44 (d, J = 2.3 Hz, 2H), 3.95 (dt, J = 6.9, 1.3 Hz, 2H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 169.0, 141.3, 141.2 (d, J = 26 Hz), 138.8, 137.8 (d, J = 12 Hz), 137.4 (d, J = 12 Hz), 136.5 (d, J = 22 Hz), 134.6, 134.0 (d, J = 20 Hz), 133.9 (d, J = 20 Hz), 130.4, 128.9,
128.8, 128.8, 128.8, 128.7, 128.7, 128.6, 127.2 (d, $J = 5$ Hz), 126.8 (d, $J = 12$ Hz), 126.1, 124.9, 57.8, 48.8 ppm.

$^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ = -10.1 ppm.

dimethyl (2-oxopropyl)phosphonate (229)

Prepared by literature known procedure.$^{[416]}$ Potassium iodide (107 g, 648 mmol, 1 eq.) was suspended in acetone (140 mL) and acetonitrile (170 mL) and chloroacetone (60.0 g, 648 mmol, 1 eq.) was added. After stirring for 1 h, trimethyl phosphite (76.6 mL, 648 mmol, 1 eq.) was added dropwise and the mixture was stirred at room temperature overnight. The mixture was heated to 50 °C for 5 h and was allowed to cool down to room temperature. The suspension was filtered through a pad of celite, was washed with acetone and concentrated in vacuo. Distillation (2 mbar, 90-95 °C) furnished the product as a pale yellow highly viscous oil (59.6 g, 359 mmol, 56%). Spectroscopic data were in accordance to those reported in literature.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 3.77 (d, $J = 11.2$, 6H), 3.08 (d, $J = 22.8$, 2H), 2.30 (s, 3H) ppm.

$^{31}$P NMR (162 MHz, CDCl$_3$) $\delta$ = 23.0 ppm.

4-acetamidobenzenesulfonyl azide, p-ABSA (230)

Prepared by literature known procedure.$^{[416]}$ 4-acetamidobenzenesulfonyl chloride (130 g, 560 mmol, 1 eq.) and tetrabutylammonium chloride (600 mg, 2.16 mmol, 0.04 eq.) were dissolved in methylene chloride (1 L). A solution of sodium azide (56 g, 860 mmol, 1.5 eq.) in deionised water (260 mL) was added dropwise and the biphasic system was stirred at room temperature overnight. The phases were separated and the organic layer was washed with water twice (400 mL each). The organic phase was dried over MgSO$_4$, filtered and concentrated in vacuo to yield p-ABSA as a colorless solid (118 g, 492 mmol, 88%). p-ABSA was used without further characterisation.

dimethyl (1-diazo-2-oxopropyl)phosphonate, Ohira-Bestmann reagent (217)

Prepared by literature known procedure.$^{[416]}$ Phosphonate 229 (43.0 g, 259 mmol, 1.08 eq.) was placed in a three-necked flask equipped with an overhead stirred, a dropping funnel and a nitrogen inlet. Toluene (250 mL) was added and the solution was cooled to 0 °C in an ice-bath. Sodium hydride (60% in mineral oil, 9.59 g, 240 mmol, 1 eq.) was added in portions and the mixture was vigorously stirred until no more gas evolution was observed. A solution of pABSA (57.6 g, 240 mmol, 1 eq.) in THF (80 mL) was added dropwise and the mixture was vigorously stirred overnight (note: inefficient stirring lead to significantly lower
The red slurry was diluted with hexanes (400 mL) and filtered over a pad of celite and was eluted thoroughly with ether. The yellow solution was dried over MgSO4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EA 1:1) to furnish the product as a yellow liquid (35.8 g, 186 mmol, 78%). Spectroscopic data were in accordance to those reported in literature.

\( ^1 \text{H NMR} \) (400 MHz, CDCl\(_3\)) \( \delta = 3.84 \) (d, \( J = 11.9 \) Hz, 6H), 2.26 (s, 3H) ppm.

\( ^{13} \text{C NMR} \) (101 MHz, CDCl\(_3\)) \( \delta = 190.0 \) (d, \( J = 13.2 \) Hz), 53.7 (d, \( J = 5.5 \) Hz), 27.2 ppm.

\( ^{31} \text{P NMR} \) (162 MHz, CDCl\(_3\)) \( \delta = 14.2 \) ppm.

Tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct, Pd\(_2\)(dba)\(_3\)·CHCl\(_3\) (231)

Prepared by modified literature known procedure.\(^{[162]}\)

Dibenzylideneacetone (4.59 g, 19.6 mmol, 3.31 eq.) was dissolved in degassed methanol (150 mL) and sodium acetate (3.90 g, 47.5 mmol, 8.02 eq.) was added. The mixture was warmed to 50 °C and PdCl\(_2\) (1.05 g, 5.92 mmol, 1 eq.) was added in one portion. The mixture was stirred at 40 °C and a red-purple precipitate formed. The reaction was allowed to cool down to room temperature and the solvent was removed via a filter canula. The purple solid was washed with degassed water (2 x 25 mL) and acetone (2 x 15 mL) and was dried in vacuo. The solid was dissolved in hot degassed chloroform (120 mL) and was filtered to give a dark purple solution. After cooling to room temperature, degassed ether (170 mL) was carefully added and deep purple crystals began to precipitate. The precipitate was filtered off, washed with ether and dried in vacuo to yield Pd\(_2\)(dba)\(_3\)·CHCl\(_3\) as deep purple crystals (4.67 g, 4.51 mmol, 76%). The product was used without further characterisation.

2-methyl-3-(phenylthio)cyclohex-2-en-1-one (232)

Prepared by modified literature known procedure.\(^{[109,\ 154]}\) 2-methyl-1,3-cyclohexadione (14.7 g, 117 mmol, 1.00 eq.) was dissolved in anhydrous MeCN (130 mL) and TEA (18.1 mL, 131 mmol, 1.12 eq.) was added. The mixture was stirred for 5 min and was then cooled to 0 °C in an ice-bath. Methanesulfonyl chloride (9.6 mL, 124 mmol, 1.06 eq.) was added dropwise and the reaction was allowed to warm up to room temperature overnight. The mixture was recooled to 0 °C in an ice-bath. TEA (18.1 mL, 131 mmol, 1.12 eq.) and thiophenol (12.3 mL, 120 mmol, 1.03 eq.) were subsequently added. The reaction was allowed to warm to room temperature while stirring over 12 h. Sat. aqueous Na\(_2\)CO\(_3\) solution was added (350 mL), the phases were separated and the aqueous phase was extracted with diethyl ether (2 x 250 mL) and ethyl acetate (250 mL). The combined extracts were dried over MgSO\(_4\), filtered and 148
the solvent was removed in vacuo. The residue was recrystallised from MeOH:H$_2$O 82:18 (50 mL). 
The colorless crystals were filtered off, washed with precooled recrystallisation solvent and water. 
The solid was dried in vacuo to obtain colorless crystals (22.7 g, 104 mmol, 89%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.51 – 7.48 (m, 2H), 7.44 – 7.36 (m, 3H), 2.39 – 2.36 (m, 2H), 2.17 (tq, $J$ = 6.1, 1.8 Hz, 2H), 1.97 (t, $J$ = 1.8 Hz, 3H), 1.90 – 1.83 (m, 2H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 195.5, 157.8, 135.5, 130.2, 129.5, 129.4, 37.2, 30.4, 22.8, 12.3 ppm.

IR (film): $\nu_{max}$ = 3051, 2943, 1637, 1573, 1475, 1429, 1375, 1342, 1328, 1303, 1200, 1123, 1044, 1025, 990, 909, 880, 850, 752, 706, 689 cm$^{-1}$.

HRMS (ESI, m/z) calculated for C$_{13}$H$_{15}$OS$^+$ [M+H]$^+$: 219.0838; found: 219.0835.

$R_f$ = 0.25 (3:1 PE:Et$_2$O).

**allyl 3-methyl-2-oxo-4-(phenylthio)cyclohex-3-ene-1-carboxylate (203)**

Prepared by modified literature known procedure.$^{[109]}$

Diisopropylamine (12.9 mL, 91.6 mmol, 2.00 eq.) was dissolved in anhydrous toluene (300 mL) and the solution was cooled to -78 °C in an isopropanol/dry-ice bath. n-BuLi (2.5 M in hexane, 36.6 mL, 91.6 mmol, 2.00 eq.) was added dropwise and the reaction was stirred at 0 °C for 10 min. The LDA solution was recooled to -78 °C and a solution of thioester 232 (10.0 g, 45.8 mmol, 1.00 eq.) in anhydrous toluene (100 mL) was added dropwise. After 30 min, allyl chloroformate (5.1 mL, 48.1 mmol, 1.05 eq.) was added dropwise and the mixture was stirred overnight and was allowed to warm up to room temperature. 1 N aqueous KHSO$_4$ solution (200 mL) was added and the mixture was stirred for 10 min. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 200 mL). The combined organic phases were washed with brine (200 mL), dried over Na$_2$SO$_4$, filtered and concentrated in vacuo. The product was purified by column chromatography (PE:EA 9:1) to afford a pale yellow oil (13.1 g, 43.3 mmol, 95%) that solidified upon storage in the fridge.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.52 – 7.48 (m, 2H), 7.44 – 7.37 (m, 3H), 5.91 (ddt, $J$ = 17.2, 10.4, 5.6 Hz, 1H), 5.33 (dq, $J$ = 17.2, 1.6 Hz, 1H), 5.23 (dq, $J$ = 10.5, 1.3 Hz, 1H), 4.64 (qdt, $J$ = 13.3, 5.7, 1.4 Hz, 2H), 3.40 – 3.34 (m, 1H), 2.40 – 2.12 (m, 3H), 2.12 – 2.04 (m, 1H), 1.98 (t, $J$ = 1.7 Hz, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ = 189.9, 170.2, 158.4, 135.7, 132.0, 129.8, 129.6, 129.6, 129.2, 118.5, 65.8, 52.6, 28.5, 25.7, 12.4 ppm.

IR (film): $\nu_{max}$ = 2933, 1733, 1637, 1577, 1480, 1443, 1428, 1365, 1341, 1322, 1297, 1287, 1221, 1153, 1092, 1071, 1026, 993, 950, 934, 876, 832, 758, 723, 707, 692 cm$^{-1}$.
HRMS (ESI, m/z) calculated for C_{17}H_{19}O_{3}S^{+} [M+H]^+: 303.1049; found: 303.1047.

R_{f} = 0.30 (7:3 PE:Et_{2}O).

**allyl 1,3-dimethyl-2-oxo-4-(phenylthio)cyclohex-3-ene-1-carboxylate (115)**

Prepared by modified literature known procedure. Allylester 203 (7.48 g, 24.7 mmol, 1 eq.) was dissolved in anhydrous THF (100 mL) and the mixture was cooled in an ice-bath. Sodium hydride (60% dispersion in mineral oil, 1.19 g, 29.7 mmol, 1.2 eq.) was added in portions and the mixture was stirred for 15 min after the final addition. Methyl iodide (3.1 mL, 49.5 mmol, 2 eq.) dissolved in THF (50 mL) was added and the mixture was allowed to warm up to room temperature overnight. If TLC showed remaining starting material, another portion of NaH (0.3 eq.) and methyl iodide (2 x 100 mL) were added and the mixture was stirred for further 4 h at room temperature. Diethyl ether (100 mL) was added followed by water water (100 mL). The phases were separated and the aqueous phase was washed with diethyl ether (2 x 100 mL). The combined organic extracts were washed with brine (100 mL), dried over MgSO_{4}, filtered and concentrated in vacuo. Column chromatography (PE:Et_{2}O 9:1 to 7:1) afforded a pale yellow oil (6.91 g, 21.8 mmol, 88%) that slowly solidified upon storage in the fridge.

**^{1}H NMR** (400 MHz, CDCl_{3}) δ = 7.50 – 7.46 (m, 2H), 7.45 – 7.36 (m, 3H), 5.86 (ddt, J = 17.2, 10.6, 5.4 Hz, 1H), 5.31 – 5.19 (m, 2H), 4.64 (ddt, J = 13.5, 5.5, 1.5 Hz, 1H), 4.55 (ddt, J = 13.5, 5.5, 1.5 Hz, 1H), 2.37 (ddd, J = 13.2, 5.5, 4.9 Hz, 1H), 2.32 – 2.22 (m, 1H), 2.16 – 2.06 (m, 1H), 1.99 (t, J = 1.8 Hz, 3H), 1.78 (ddd, J = 13.4, 8.6, 5.0 Hz, 1H), 1.37 (s, 3H) ppm.

**^{13}C NMR** (101 MHz, CDCl_{3}) δ = 193.0, 172.7, 156.7, 135.6, 131.9, 129.8, 129.7, 129.5, 129.1, 118.2, 65.7, 52.3, 33.1, 27.4, 20.8, 12.9 ppm.

**IR (film):** ν_{max} = 2935, 1730, 1652, 1579, 1440, 1375, 1339, 1311, 1236, 1172, 1105, 1019, 982, 932, 750, 705, 692 cm^{-1}.

HRMS (ESI, m/z) calculated for C_{18}H_{21}O_{3}S^{+} [M+H]^+: 317.1206; found: 317.1197.

R_{f} = 0.20 (9:1 PE:Et_{2}O).

**(S)-6-allyl-2,6-dimethyl-3-(phenylthio)cyclohex-2-en-1-one (S)-116**

Pd_{2}dba_{3}*CHCl_{3} (0.61 g, 0.59 mmol. 0.04 eq.) and ligand (S,S)-113 (1.06 g, 1.30 mmol, 0.08 eq.) were weighed into a schlenk tube in a glove box. Freshly degassed (3 freeze-pump-thaw cycles), anhydrous 1,4-dioxane (79 mL) was added and the mixture was stirred for 20 min. In another schlenk tube, allylester 115
(5.00 g, 15.8 mmol, 1.00 eq.) was degassed in vacuo and dissolved in freshly degassed anhydrous 1,4-dioxane (79 mL). The orange catalyst solution was added to the allylester via canula and the mixture was stirred for 30 h. The yellowish mixture was concentrated in vacuo and the residue was purified by column chromatography (PE:Et₂O 7:1) to obtain the product as a pale yellow oil (3.73 g, 13.7 mmol, 87%).

The enantiomeric excess was determined to be 96% by chiral HPLC analysis (Chiral PAK AD, 1.0 ml/min, 96:4 Hexanes/ethanol, λ = 254 nm) t_r (major) = 5.8 min, t_r (minor) = 7.6 min.

\(^1\)H NMR (400 MHz, CDCl₃) δ = 7.52 – 7.48 (m, 2H), 7.45 – 7.36 (m, 3H), 5.68 (ddt, J = 16.8, 10.3, 7.4 Hz, 1H), 5.06 – 4.97 (m, 2H), 2.32 (ddt, J = 13.7, 7.2, 1.2 Hz, 1H), 2.20 – 2.11 (m, 3H), 1.96 (t, J = 1.8 Hz, 3H), 1.81 (ddd, J = 13.6, 6.8, 5.8 Hz, 1H), 1.61 (ddd, J = 12.2, 7.2, 6.0 Hz, 1H), 1.04 (s, 3H) ppm.

\(^1^3\)C NMR (101 MHz, CDCl₃) δ = 199.5, 155.5, 135.6, 134.4, 130.3, 129.5, 128.5, 118.1, 43.0, 41.6, 33.1, 26.9, 22.2, 12.9 ppm.

IR (film): \(\nu_{\text{max}}\) = 2925, 1651, 1580, 1439, 1373, 1338, 1326, 1286, 1267, 1227, 1110, 1068, 1024, 983, 914, 748, 705, 691 cm⁻¹.

HRMS (ESI, m/z) calculated for C₁₇H₂₁OS⁺ [M+H]⁺: 273.1308 ; found: 273.1301.

\([\alpha]_D^{22}\): +51.7 (c 1.45, CHCl₃).

\(R_f\) = 0.40 (7:1 PE:Et₂O).

(S)-6-allyl-3-methoxy-2,6-dimethylcyclohex-2-en-1-one (201)

Sodium (1.35 g, 58.7 mmol, 5 eq.) was washed with hexanes and was added portion wise to anhydrous methanol (58.7 mL) while cooling with an ice-bath. Vinylogous thioester (S)-116 (3.20 g, 11.8 mmol, 1 eq.) was placed in a flask and the methanolate solution was added. The mixture was heated to reflux and progress was monitored by TLC. After approx. 3.5 h the reaction was cooled to room temperature and the solvent was removed in vacuo. Sat. aqueous NaHCO₃ solution (100 mL) and diethyl ether (100 mL) were added. The phases were separated and the aqueous phase was extracted with diethyl ether (100 mL) and ethyl acetate (100 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo. Flash column chromatography (PE:Et₂O 3:1) afforded the product as a yellow oil (2.11 g, 10.9 mmol, 93%) that solidified upon storage in the fridge to yellow crystals.

\(^1\)H NMR (400 MHz, CDCl₃) δ = 5.73 (ddt, J = 16.2, 10.9, 7.4 Hz, 1H), 5.06 – 5.00 (m, 2H), 3.80 (s, 3H), 2.63 – 2.46 (m, 2H), 2.32 (ddt, J = 13.8, 7.2, 1.2 Hz, 1H), 2.16 (ddt, J = 13.8, 7.6, 1.2 Hz, 1H), 1.91 (ddd, J = 13.6, 7.1, 5.8 Hz, 1H), 1.75 – 1.69 (m, 1H), 1.67 (t, J = 1.7 Hz, 3H), 1.05 (s, 3H) ppm.
\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta = 202.6, 169.6, 134.8, 117.8, 113.2, 55.0, 42.5, 41.9, 31.4, 22.4, 21.8, 7.9\) ppm.

IR (film): \(\nu_{\text{max}} = 2923, 1615, 1461, 1375, 1353, 1232, 1153, 1114, 997, 978, 913, 879, 761, 689\) cm\(^{-1}\).

HRMS (ESI, \(m/z\)) calculated for C\(_{12}\)H\(_{19}\)O\(_2\)\([\text{M+H}]^+\): 195.1380; found: 195.1375.

\([\alpha]\)\(^\text{D}\): +3.5 (c 1.52, CHCl\(_3\)).

\(R_f = 0.25\) (3:1 PE:Et\(_2\)O).

\((R)-6-(3\text{-hydroxypropyl})-3\text{-methoxy-2,6-dimethylcyclohex-2-en-1-one (211)}\)

Wilkinson’s catalyst (257 mg, 278 \(\mu\)mol, 0.03 eq.) and vinylogous ester 201 (1.80 g, 9.27 mmol, 1 eq.) were dissolved in anhydrous THF (5.0 mL). Catecholborane (1 M in THF, 13.0 mL, 13.0 mmol, 1.4 eq.) was added while cooling in a water bath (~10 °C) and the red solution was stirred for 30 min while the red color nearly entirely disappeared. The reaction was cooled to 0 °C in an ice-bath and a mixture of THF (10 mL), EtOH (10 mL), pH 7 phosphate buffer (1 M, 20 mL) and H\(_2\)O\(_2\) (30%, 20 mL) was added. The mixture was allowed to warm up to room temperature and was stirred overnight. While cooling in an ice-bath sat. aqueous Na\(_2\)S\(_2\)O\(_3\) solution (75 mL, exothermic) was carefully added over 30 minutes. The mixture was extracted with EtOAc (3 x 75 mL) and the combined organic extracts were washed with 1 M NaOH (75 mL) and brine (75 mL). The organic phase was dried over MgSO\(_4\), filtered and concentrated in vacuo. Flash column chromatography (Et\(_2\)O to Et\(_2\)O:EtOAc 1:1) afforded the product as a pale brown oil (1.57 g, 7.41 mmol, 80%).

\(^1\text{H NMR}\) (400 MHz, Benzene-\(d_6\)) \(\delta = 3.44 (t, J = 5.9\) Hz, 2H), 3.01 (s, 3H), 2.06 (t, \(J = 1.7\) Hz, 3H), 1.95 – 1.63 (m, 4H), 1.54 (ddd, \(J = 12.8, 7.1, 5.6\) Hz, 1H), 1.49 – 1.38 (m, 3H), 1.29 (ddd, \(J = 13.6, 7.1, 5.5\) Hz, 1H), 1.05 (s, 3H) ppm.

\(^{13}\text{C NMR}\) (101 MHz, Benzene-\(d_6\)) \(\delta = 201.8, 168.8, 113.2, 63.0, 54.1, 42.2, 33.7, 31.8, 28.0, 23.0, 21.5, 8.4\) ppm.

IR (film): \(\nu_{\text{max}} = 3415, 2940, 1607, 1461, 1375, 1356, 1239, 1156, 1114, 1055, 997, 976, 764\) cm\(^{-1}\).

HRMS (ESI, \(m/z\)) calculated for C\(_{12}\)H\(_{21}\)O\(_3\)\([\text{M+H}]^+\): 213.1485; found: 213.1481.

\([\alpha]\)\(^\text{D}\): +1.5 (c 1.17, MeCN).

\(R_f = 0.25\) (1:1 EA:Et\(_2\)O).
(S)-3-(4-methoxy-1,3-dimethyl-2-oxocyclohex-3-en-1-yl)propanal (212)

Alcohol 211 (2.59 g, 12.2 mmol, 1 eq.) was dissolved in anhydrous DMSO (48.8 mL) and TEA (16.9 mL, 122 mmol, 10.00 eq.) was added. The mixture was cooled in a cold water bath (~10 °C) while a solution of pyridine sulfur trioxide complex (7.77 g, 48.8 mmol, 4 eq.) in anhydrous DMSO (48.8 mL) was added dropwise. When the starting material was consumed, diethyl ether (200 mL) and sat. aqueous NaHCO₃ solution (200 mL) were added. The phases were separated and the aqueous phase was extracted with diethyl ether (2 x 150 mL) and the combined extracts were washed with water and brine (200 mL each). The organic phase was dried over MgSO₄ and concentrated in vacuo. The product was used crude directly in the next step. An analytical sample was obtained after column chromatography (PE:EtOAc 1:1) to afford a colorless oil.

^1^H NMR (400 MHz, Benzene-d₆) δ = 9.34 (t, J = 1.4 Hz, 1H), 2.98 (s, 3H), 2.12 – 1.96 (m, 5H), 1.85 – 1.58 (m, 4H), 1.32 (ddd, J = 13.5, 6.7, 5.6 Hz, 1H), 1.21 (ddd, J = 13.3, 7.3, 5.6 Hz, 1H), 0.92 (s, 3H) ppm.

^1^3^C NMR (101 MHz, Benzene-d₆) δ = 200.7, 200.5, 168.5, 113.2, 54.1, 41.6, 39.5, 32.3, 29.3, 22.7, 21.4, 8.3 ppm.

IR (film): ν_max = 2929, 1720, 1614, 1462, 1375, 1356, 1240, 1153, 1114, 1045, 997, 976, 763 cm⁻¹.

HRMS (ESI, m/z) calculated for C₁₂H₁₉O₃⁺ [M+H]⁺: 211.1329; found: 211.1326.

[^α]^D₂₃: +1.5 (c 1.47, CHCl₃).

R_f = 0.40 (1:1 EA:PE).

(R)-4a,8-dimethyl-2,3,4,4a,5,6-hexahydro-7H-chromen-7-one (213)

Was obtained upon acid-catalysed intramolecular addition-elimination reaction from alcohol 212.

^1^H NMR (400 MHz, CDCl₃) δ = 4.39 (ddt, J = 11.1, 5.3, 2.0 Hz, 1H), 3.84 (ddd, J = 12.3, 11.0, 3.2 Hz, 1H), 2.53 (ddd, J = 17.5, 14.2, 5.6 Hz, 1H), 2.40 (ddd, J = 17.6, 5.1, 2.3 Hz, 1H), 2.19 (dtdd, J = 13.1, 12.0, 5.1, 3.7 Hz, 1H), 1.88 – 1.76 (m, 1H), 1.75 – 1.67 (m, 2H), 1.65 (s, 3H), 1.64 – 1.53 (m, 2H), 1.30 (s, 3H) ppm.

^1^3^C NMR (101 MHz, CDCl₃) δ = 199.2, 175.3, 116.1, 70.1, 36.3, 36.2, 34.0, 33.7, 23.0, 20.9, 7.7 ppm.
(R)-6-(but-3-yn-1-yl)-3-methoxy-2,6-dimethylcyclohex-2-en-1-one (214)

Crude aldehyde 212 (2.57 g, 12.2 mmol, 1 eq.) was dissolved in anhydrous MeOH (81.5 mL) and K₂CO₃ (5.07 g, 36.7 mmol, 3 eq.) was added. Ohira-Bestmann reagent (3.52 g, 18.3 mmol, 1.5 eq.) was added and the mixture was stirred overnight to give a yellow-green suspension. The reaction mixture was concentrated in vacuo and diethyl ether (250 mL) and sat. aqueous NaHCO₃ solution (250 mL) were added and the phases were separated. The aqueous phase was extracted with diethyl ether (2 x 150 mL) and the combined extracts were washed with brine (200 mL), dried over MgSO₄, filtered and concentrated in vacuo. Flash column chromatography (PE:EtOAc 3:1) afforded the product as a colorless oil (1.76 g, 8.52 mmol, 70% o2s).

¹H NMR (400 MHz, Benzene-d₆) δ = 2.96 (s, 3H), 2.23 – 2.04 (m, 2H), 2.01 (t, J = 1.7 Hz, 3H), 1.88 – 1.64 (m, 5H), 1.41 (ddd, J = 13.4, 6.7, 5.6 Hz, 1H), 1.21 (ddd, J = 13.5, 7.2, 5.6 Hz, 1H), 0.93 (s, 3H) ppm.

¹³C NMR (101 MHz, Benzene-d₆) δ = 200.3, 168.3, 113.2, 85.0, 68.8, 54.1, 42.2, 36.6, 31.8, 22.4, 21.3, 14.2, 8.4 ppm.

IR (film): ν max = 3293, 2933, 1614, 1461, 1375, 1356, 1242, 1148, 1113, 1035, 1001, 978, 866, 764 cm⁻¹.

HRMS (ESI, m/z) calculated for C₁₃H₁₉O₂⁺ [M+H]⁺: 207.1380; found: 207.1375.

[α]D²³ = -3.7 (c 1.34, CHCl₃).

Rᶠ = 0.45 (1:3 EA:PE).

3-(benzyloxy)propan-1-ol (233)

HO-OBn NaH (60% dispersion in mineral oil, 8.70 g, 217 mmol, 1.1 eq.) was suspended in anhydrous THF (200 mL) and DMSO (50 mL) and was cooled to 0 °C. Propane-1,3-diol (14.3 mL, 197 mmol, 1 eq.) in THF (75 mL) was added dropwise, and the reaction was kept for 30 min at room temperature. Benzyl bromide (25.8 mL, 217 mol, 1.1 eq.) was added dropwise. Tetrabutylammonium iodide (18.2 g, 49.3 mmol, 0.25 eq.) was added and the reaction was stirred at 60 °C overnight. To the beige slurry water (500 mL) was added and the aqueous phase was extracted twice with ether (2 x 250 mL) and ethyl acetate (2 x 250 mL). The combined organic extracts were washed with brine, dried over MgSO₄ and the solvent was removed under reduced pressure. The crude ether was purified by distillation under reduced pressure (90 - 100 °C,
0.25 mmHg) to furnish the product as a colorless oil (21.8 g, 131 mmol, 67%). The spectroscopic data matched those reported in literature.\[^{461}\]

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.39 - 7.27\) (m, 5H), 4.53 (s, 2H), 3.79 (q, \(J = 5.5\) Hz, 2H), 3.67 (t, \(J = 5.8\) Hz, 2H), 2.25 (bs, 1H), 1.88 (p, \(J = 5.7\) Hz, 2H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 138.2, 128.6, 127.9, 127.8, 73.4, 69.6, 62.1, 32.3\) ppm.

((3-iodopropoxy)methyl)benzene (216)

Prepared by literature known procedure.\[^{461}\] 3-(Benzyloxy)propan-1-ol 233 (5.0 g, 30.1 mmol, 1 eq.) was dissolved in methylene chloride (120 mL) at room temperature. PPh\(_3\) (8.3 g, 33.1 mmol, 1.05 eq.) and imidazole (2.6 g, 37.6 mmol, 1.25 eq.) were added sequentially. Iodine (8.4 g, 33.1 mmol, 1.1 eq.) was added portionwise, and the reaction mixture was stirred for 24 h at room temperature under the exclusion of light. The reaction was quenched by the addition of sat. aq. Na\(_2\)S\(_2\)O\(_3\) solution and the phases were separated. The aqueous phase was extracted with methylene chloride and the combined organic layers were dried over MgSO\(_4\). The solvent was removed under reduced pressure, and the residue was subjected to flash chromatography (20:1 PE:EA) to furnish pure ((3-iodopropoxy)methyl)benzene as a colorless liquid (6.96 g, 25.2 mmol, 84%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.39 - 7.27\) (m, 5H), 4.53 (s, 2H), 3.55 (t, \(J = 5.8\) Hz, 2H), 3.31 (t, \(J = 6.8\) Hz, 2H), 2.10 (tt, \(J = 6.8, 5.8\) Hz, 2H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 138.4, 128.6, 127.9, 127.8, 73.3, 69.8, 33.7, 3.6\) ppm.

\(R_f = 0.35\) (20:1 PE:EA).

(R)-3-(3-(benzyloxy)propyl)-4-(but-3-yn-1-yl)-2,4-dimethylcyclohex-2-en-1-one (200)

In a flame-dried Schlenk flask, t-BuLi (1.9 M in pentane, 21.4 mL, 40.7 mmol, 6 eq.) was cooled to -78 °C and a solution of ((3-iodopropoxy)methyl)benzene (216) (5.62 g, 20.4 mmol, 3 eq.) in Et\(_2\)O (47.4 mL) was added dropwise. After 1.5 h, a solution of vinylogous ester 214 (1.40 g, 6.79 mmol, 1 eq.) in Et\(_2\)O (14.2 mL) was added. The reaction mixture was stirred for 2 h at -78 °C and was then allowed to warm to -50 °C. Consumption of the starting material was controlled via TLC (approx. 4 h at -50 °C) and the reaction was quenched by the addition of 2 M hydrochloric acid. The mixture was extracted with ether (100 mL) and twice with methylene chloride (2 x 100 mL), the combined organic phases were dried over MgSO\(_4\), filtered and
concentrated in vacuo. The crude product was purified by gradient column chromatography (20:1, then 6:1 PE:EA) to furnish a colorless oil (2.05 g, 6.34 mmol, 93%).

\[ ^1H \text{ NMR} \quad (400 \text{ MHz, CDCl}_3) \delta = 7.38 – 7.26 (m, 5H), 4.53 (s, 2H), 3.53 (t, J = 6.2 Hz, 2H), 2.45 – 2.40 (m, 2H), 2.39 – 2.23 (m, 2H), 2.22 – 2.14 (m, 1H), 2.12 – 2.03 (m, 1H), 1.96 (t, J = 2.7 Hz, 1H), 1.94 – 1.81 (m, 2H), 1.79 (s, 3H), 1.78 – 1.65 (m, 4H), 1.16 (s, 3H) ppm. \]

\[ ^{13}C \text{ NMR} \quad (101 \text{ MHz, CDCl}_3) \delta = 198.7, 163.5, 138.6, 132.5, 128.6, 127.7, 127.7, 84.2, 73.1, 70.4, 68.8, 39.4, 37.8, 34.0, 33.0, 29.3, 27.6, 24.4, 14.1, 11.9 ppm. \]

IR (film): \( \nu_{\max} = 3289, 2938, 2861, 1661, 1605, 1454, 1357, 1336, 1199, 1099, 1027, 736, 698 \text{ cm}^{-1} \).

HRMS (ESI, \( m/z \)) calculated for C_{22}H_{29}O_2 \[M+H]^+: 325.2162; \text{found: 325.2155.} \]

\[ [\alpha]_D^{23} = +29.9 \quad (c 1.43, \text{CHCl}_3). \]

\( R_f = 0.25 \quad (6:1 \text{ PE:EA}) \)

(3aS,7aR)-3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-(tributylstannyl)methylene)octahydro-5H-inden-5-one (218)

In a round-bottom flask with reflux condenser, enone 200 (2.35 g, 7.24 mmol, 1 eq.) was dissolved in anhydrous benzene (150 mL). HSnBu\_3 (3.8 mL, 14.5 mmol, 2 eq.) and AIBN (60 mg, 362 \( \mu \text{mol}, 0.05 \) eq.) were added, and the mixture was heated to reflux for 4 h. HSnBu\_3 (1.9 mL, 7.25 mmol, 1 eq.) and AIBN (60 mg, 362 \( \mu \text{mol}, 0.05 \) eq.) were added, and the reaction was heated for further 4 h. Another portion of HSnBu\_3 (1.00 eq.) and AIBN (0.05 eq.) was added. The solution was heated for 14 h as TLC indicated consumption of the starting material and formation of a less polar product. After cooling to room temperature, the solvent was removed in vacuo. The residue was purified by flash chromatography (10:1 PE:EA) to remove excess stannane, and the obtained mixture of isomers (3.63 g, 5.90 mmol, 81%) was directly used in the next step.

\( R_f = 0.48 \quad (7:1 \text{ PE:EA}) \)

(3aR,4S,7aR)-3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-5H-inden-5-one (219)

Vinyl stannane 218 (2.74 g, 4.45 mmol, 1 eq.) and PPTS (2.24 g, 8.90 mmol, 2 eq.) were dissolved in DCM (64 mL) and the reaction was stirred at room temperature overnight. Water (100 mL) was added, the phases were separated and the aqueous phase was extracted with methylene chloride (3 x
100 mL). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was directly subjected to base-catalysed epimerisation. The crude product was dissolved in MeOH (44 mL) and aqueous NaOH solution (5%, 10.1 mL, 13.3 mmol, 3 eq.) was added. The mixture was heated to 50 °C and was stirred overnight. The solvent was removed in vacuo and sat. aq. NH₄Cl solution was added. The mixture was extracted with methylene chloride (3 x 100 mL), the combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash chromatography (10:1 PE:EA) to furnish the product as a colorless oil (1.27 g, 3.89 mmol, 88%).

¹H NMR (400 MHz, CDCl₃) δ = 7.37 – 7.24 (m, 5H), 4.93 (t, J = 2.2 Hz, 1H), 4.73 (t, J = 2.2 Hz, 1H), 4.48 (s, 2H), 3.46 – 3.35 (m, 2H), 2.52 – 2.31 (m, 5H), 1.91 – 1.76 (m, 3H), 1.57 – 1.35 (m, 5H), 1.10 (s, 3H), 1.08 (d, J = 7.1 Hz, 3H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 214.4, 156.4, 138.8, 128.5, 127.7, 127.6, 108.4, 72.9, 71.0, 56.1, 46.4, 44.1, 36.1, 35.9, 34.4, 28.0, 27.0, 24.1, 23.3, 11.1 ppm.

IR (film): νmax = 2952, 2861, 1707, 1647, 1496, 1454, 1373, 1327, 1205, 1156, 1100, 1028, 1007, 946, 885, 821, 734, 697 cm⁻¹.

HRMS (ESI, m/z) calculated for C₂₂H₃₁O₂⁺ [M+H]⁺: 327.2319; found: 327.2315.

[α]D²₃: +4.0 (c 1.86, CHCl₃).

Rf = 0.29 (7:1 PE:EA)

**N’-((3αR,4S,7aR)-3a-(3-(benzyloxy)propyl)-4,7a-dimethyl-3-methyleneoctahydro-5H-inden-5-ylidene)-4-methylbenzenesulfonohydrazide (234)**

Ketone 219 (900 mg, 2.76 mmol, 1 eq.) was dissolved in anhydrous EtOH (0.7 mL) and cooled to 0 °C. p-Toluenesulfonyl hydrazide (1.08 g, 4.14 mmol, 1.5 eq.) was added in one portion, and the reaction was allowed to warm to room temperature. After stirring for 24 h, the solvent was removed and the crude hydrazone was purified by column chromatography (5:1 PE:EA). Hydrazone 234 was obtained as a colorless foam (1.06 g, 2.13 mmol, 78%) as a mixture of isomers.

¹H NMR (400 MHz, CDCl₃) δ = 8.02 (bs, NH), 7.83 (d, J = 8.3 Hz, 2H), 7.34-7.27 (m, 7H), 4.60 (m, 1H), 4.46 (s, 2H), 4.43 (m, 1H), 3.40-3.31 (m, 2H), 2.57 (q, J = 7.2 Hz, 1H), 2.40 (s, 3H), 2.32-2.14 (m, 4H), 1.56-1.46 (m, 2H), 1.41-1.34 (m, 4H), 1.23-1.18 (m, 1H), 1.07 (s, 3H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 164.4, 155.2, 145.6, 138.8, 137.5, 130.1, 128.5, 127.7, 127.7, 123.8, 116.5, 109.2, 73.0, 71.0, 54.0, 44.2, 40.5, 35.4, 35.3, 28.1, 26.9, 24.0, 22.4, 21.3, 14.9 ppm.
IR (film): $v_{\text{max}} = 3218, 2940, 2875, 1647, 1599, 1453, 1384, 1332, 1185, 1163, 1093, 997, 925, 885, 813, 735, 697, 667 \text{ cm}^{-1}$.

HRMS (ESI, $m/z$) calculated for C$_{29}$H$_{39}$N$_2$O$_3$S $[\text{M+H}]^+$: 495.2676; found: 495.2672.

$[\alpha]_{D}^{22}$: +35.6 (c 1.83, CHCl$_3$).

$R_f = 0.15$ (5:1 PE:EA)

(3aS,7R,7aR)-7a-(3-(benzyloxy)propyl)-3a,7-dimethyl-1-methyleneoctahydro-1H-indene (220)

In a flame-dried Schlenk tube, hydrazone 234 (1.05 g, 2.12 mmol, 1 eq.) was dissolved in anhydrous CHCl$_3$ (4.3 mL) and the solution was cooled to -10 °C. Catechol borane (1 M solution in THF, 4.3 mL, 4.3 mmol, 2 eq.) was added dropwise, and the reaction was stirred for 40 min at -10 °C and then warmed to room temperature. After 3 h, NaOAc∙3H$_2$O (967 mg, 7.43 mmol, 3.5 eq.) was added in one portion, and the resulting slurry was heated to reflux for 90 min. Water was added, and the mixture was extracted with methylene chloride. The combined organic phases were washed with brine, dried over MgSO$_4$ and the solvent was removed in vacuo. The residue was subjected to column chromatography (80:1 PE:EA) to furnish the product as a colorless oil in (397 mg, 1.27 mmol, 60%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta = 7.37 – 7.25$ (m, 5H), 4.92 (td, $J = 2.1, 0.9$ Hz, 1H), 4.66 (td, $J = 2.5, 0.9$ Hz, 1H), 4.50 (s, 2H), 3.43 (t, $J = 6.6$ Hz, 2H), 2.39 – 2.32 (m, 2H), 1.92 – 1.83 (m, 1H), 1.72 – 1.55 (m, 3H), 1.54 – 1.29 (m, 6H), 1.29 – 1.15 (m, 3H), 1.02 (s, 3H), 1.00 (d, $J = 7.3$ Hz, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta = 156.8, 138.9, 128.5, 127.8, 127.6, 106.3, 72.9, 71.7, 51.8, 44.5, 36.7, 35.9, 30.0, 29.7, 28.3, 27.2, 24.2, 23.0, 18.2, 15.9$ ppm.

IR (film): $v_{\text{max}} = 2934, 2863, 1646, 1496, 1454, 1360, 1204, 1099, 1028, 878, 733, 696 \text{ cm}^{-1}$.

HRMS (ESI, $m/z$) calculated for C$_{22}$H$_{33}$O$^+$ [M+H]$^+$: 313.2526; found: 313.2519.

$[\alpha]_{D}^{22}$: -9.8 (c 1.18, CHCl$_3$).

$R_f = 0.20$ (80:1 PE:EA).

3-((3aR,4R,7aS)-4,7a-dimethyl-3-methyleneoctahydro-3aH-inden-3a-yl)propan-1-ol (221)

Ammonia (~15 mL) was condensed in a Schlenk flask and sodium metal (200 mg, 8.54 mmol, 10 eq.) was added in portions. The dark blue mixture was stirred for 40 min at -78 °C. A solution of benzyl ether 220 (267 mg, 854 µmmol, 1 eq.) in THF (1 mL) was added, and the reaction was warmed to -60 °C and kept at this temperature for 18 h. The mixture was re-cooled to -78 °C and solid NH$_4$Cl (5.0 g, exc.) was added. Ammonia was evaporated by allowing the reaction to warm up to room temperature. Sat. aq. NH$_4$Cl solution and ethyl acetate (75 mL each) were added to the residue and 158
the phases were separated. The aqueous phase was extracted with ethyl acetate (3 x 50 mL) and
the combined organic phases were washed with brine, dried over MgSO$_4$, filtered and concentrated
in vacuo. The crude product was purified by column chromatography (7:1 PE:EA) to furnish the
product as a colorless liquid (147 mg, 661 µmol, 78%).

**$^1$H NMR (400 MHz, CDCl$_3$)** $\delta$ = 4.92 (td, $J = 2.1, 0.9$ Hz, 1H), 4.65 (td, $J = 2.5, 0.9$ Hz, 1H), 3.59 (t, $J =
6.4$ Hz, 2H), 2.40 – 2.33 (m, 2H), 1.91 – 1.83 (m, 1H), 1.71 – 1.61 (m, 1H), 1.59 – 1.43 (m, 5H), 1.41
– 1.29 (m, 4H), 1.28 – 1.13 (m, 3H), 1.02 (s, 3H), 1.00 (d, $J = 7.2$ Hz, 3H) ppm.

**$^{13}$C NMR (101 MHz, CDCl$_3$)** $\delta$ = 156.8, 106.3, 64.2, 51.8, 44.4, 36.8, 35.9, 29.9, 29.7, 28.3, 27.3, 26.8,
22.9, 18.5, 15.8 ppm.

**IR (film)**: $\nu_{\text{max}}$ = 3311, 2932, 2866, 1646, 1459, 1384, 1055, 1009, 981, 950, 877, 745 cm$^{-1}$.

**HRMS (ESI, $m/z$) calculated for C$_{13}$H$_{27}$O$^+$ [M+H]$^+$: 223.2056; found: 223.2054.

[α]$_D^{22}$: -7.3 (c 1.83, CHCl$_3$).

$R_f$ = 0.27 (5:1 PE:EA).

**Alcohol 221** (147 mg, 661 µmol, 1 eq.) was dissolved in DMSO (1.7 mL) and cooled in
a water bath. NEt$_3$ (730 µL, 5.29 mmol, 5 eq.) and SO$_3$∙pyr (420 mg, 2.64 mmol, 4 eq.)
in DMSO (1.7 mL) were added sequentially and the mixture was stirred for 20 h at
room temperature. Water (50 mL) was added and the mixture was extracted with
ether trice (50 mL each). The combined organic layers were washed with brine, dried
over MgSO$_4$, filtered and the solvent was removed in vacuo. The crude aldehyde was directly used
in the next step without further purification.

K$_2$CO$_3$ (273 mg, 1.97 mmol, 3 eq.) and Ohira-Bestmann reagent (210 µL, 1.15 mmol, 1.75 eq.) were
added sequentially to the crude aldehyde in MeOH (4.4 mL). The reaction mixture was stirred at
room temperature for 4 h. Sat. aq. NaHCO$_3$ (50 mL) was added and the mixture was extracted with
pentane trice (50 mL each). The combined organic phases were washed with brine, dried over
MgSO$_4$, filtered and the solvent was removed in vacuo. The residue was purified by flash
chromatography (100% pentane) to furnish the desired enyne 61 as a colorless liquid (104 mg,
481 µmol, 73% o2s).

**$^1$H NMR (400 MHz, CDCl$_3$)** $\delta$ = 4.96 (td, $J = 2.2, 0.7$ Hz, 1H), 4.64 (t, $J = 2.2$ Hz, 1H), 2.41 – 2.34 (m,
2H), 2.19 – 2.00 (m, 2H), 1.93 (t, $J = 2.7$ Hz, 1H), 1.87 – 1.77 (m, 2H), 1.70 – 1.62 (m, 1H), 1.59 – 1.48
(m, 2H), 1.44 – 1.28 (m, 4H), 1.25 – 1.17 (m, 2H), 1.05 (s, 3H), 1.03 (d, $J = 7.3$ Hz, 3H) ppm.

**$^{13}$C NMR (101 MHz, CDCl$_3$)** $\delta$ = 155.8, 106.8, 86.0, 67.8, 51.9, 44.4, 36.9, 36.0, 30.2, 29.5, 29.2, 28.2,
22.6, 18.1, 15.8, 13.2 ppm.
IR (film): $v_{\text{max}} = 3312, 2936, 2118, 1646, 1459, 1448, 1385, 1239, 1059, 979, 883, 750 \text{ cm}^{-1}$.

HRMS (ESI, $m/z$) calculated for C$_{16}$H$_{25}$+$[\text{M+H}]^+$: 217.1951; found: 217.1946.

$[\alpha]_D^{22}$: -19.2 (c 1.62, CHCl$_3$).

$R_f = 0.48$ (pentane).

$(3\text{aS},5\text{aS},9\text{R},9\text{aS})$-5a,9-dimethyl-5,5a,6,7,8,9,10,11-octahydro-4H-pentaleno[6a,1-c]inden-2(3H)-one (55)

Enyne 61 (160 mg, 740 µmol, 1 eq.) was dissolved in anhydrous xylene (21 mL) and the solution was degassed via freeze-pump-thaw (3 cycles). Co$_2$(CO)$_8$ (280 mg, 814 µmol, 1.1 eq.) was added and the reaction was stirred for 2 h at room temperature, and then heated in a sealed tube to 140 °C for 22 h. The mixture was filtered over celite and was eluted with ethyl acetate, and the solvent was removed in vacuo. The residue was purified by column chromatography (10:1 PE:EA) to furnish enone 55 as a colorless solid (77 mg, 315 µmol, 43%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 5.62 (t, $J = 1.7$ Hz, 1H), 2.72 (d, $J = 17.0$ Hz, 1H), 2.56 – 2.50 (m, 2H), 2.28 (d, $J = 17.0$ Hz, 1H), 2.20 (ddd, $J = 14.1$, 8.5, 5.6 Hz, 1H), 1.83 (dt, $J = 13.4$, 8.3 Hz, 1H), 1.74 – 1.66 (m, 2H), 1.65 – 1.51 (m, 4H), 1.46 – 1.34 (m, 5H), 1.14 (s, 3H), 0.96 (d, $J = 7.1$ Hz, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta =$ 211.7, 194.8, 120.3, 64.6, 56.8, 50.6, 45.3, 41.5, 38.8, 37.7, 33.4, 33.0, 30.4, 28.0, 24.7, 17.6, 16.9 ppm.

IR (film): $v_{\text{max}} = 2916, 2864, 1695, 1630, 1457, 1408, 1379, 1295, 1244, 1196, 1169, 988, 913, 839, 808, 746, 681 \text{ cm}^{-1}$.

HRMS (ESI, $m/z$) calculated for C$_{17}$H$_{25}$O + [M+H]$^+$: 245.1900; found: 245.1893.

$[\alpha]_D^{22}$: -42.4 (c 1.11, CHCl$_3$).

$R_f = 0.19$ (10:PE:EA).

$(3\text{S},3\text{aS},5\text{aS},9\text{R},9\text{aS})$-3,5a,9-trimethyl-5,5a,6,7,8,9,10,11-octahydro-4H-pentaleno[6a,1-c]inden-2(3H)-one (222)

In a flame-dried Schlenk tube, TMP (20 µL, 115 µmol, 1.4 eq.) was dissolved in THF (30 µL) and cooled to -20 °C. n-BuLi (2.5 M solution in hexanes, 43 µL, 106 µmol, 1.3 eq.) was added dropwise, and the resulting solution was stirred at -20 °C for 15 min and then cooled to -78 °C. Enone 55 (20 mg, 82 µmol, 1 eq.) in THF (70 µL) was added and the reaction was stirred for 30 min. The flask was removed from the cooling bath for 10 min and then re-cooled to -78 °C. DMPU (16 µL, 131 µmol, 1.6 eq.) was added and the mixture was stirred for 20 min before Mel (20 µL, 328 µmol, 4 eq.) was added. The reaction was allowed to warm to room temperature in the cooling bath overnight and quenched
by the addition of sat. aq. NH₄Cl solution. The mixture was extracted with Et₂O and the combined organic phases were washed with brine, dried over MgSO₄, filtered and the solvent was removed in vacuo. Column chromatography (10:1 PE:EA) gave the product as a colorless solid (13 mg, 50.3 µmol, 61%) along with recovered starting material (3 mg, 12.3 µmol, 15%).

**1H NMR** (400 MHz, CDCl₃) δ = 5.66 (dd, J = 1.9, 1.0 Hz, 1H), 2.56 – 2.46 (m, 3H), 2.26 (ddd, J = 14.0, 9.0, 3.7 Hz, 1H), 1.98 (ddd, J = 13.9, 9.7, 8.0 Hz, 1H), 1.67 – 1.55 (m, 5H), 1.45 – 1.36 (m, 4H), 1.33 – 1.30 (m, 1H), 1.27 (d, J = 7.2 Hz, 3H), 1.26 – 1.24 (m, 1H), 1.17 (s, 3H), 0.98 (d, J = 7.1 Hz, 3H) ppm.

**13C NMR** (101 MHz, CDCl₃) δ = 213.2, 193.4, 119.3, 67.3, 49.0, 45.0, 41.5, 37.0, 34.4, 33.7, 31.7, 30.0, 28.5, 24.9, 17.5, 16.8, 12.3 ppm.

**IR (film):** ν max = 2937, 2853, 1687, 1635, 1456, 1384, 1370, 1302, 1248, 1200, 1124, 1046, 1011, 866, 787, 744, 686, 664 cm⁻¹.

**HRMS** (ESI, m/z) calculated for C₁₈H₂₇O⁺ [M+H]⁺: 259.2058; found: 259.2048.

[α]D²²: -62.7 (c 0.52, CHCl₃).

**R_f = 0.23** (10:1 PE:EA).

**In a flame-dried Schlenk tube, CuCN (23 mg, 250 µmol, 5 eq.) was suspended in Et₂O (0.5 mL) and cooled to -78 °C. MeLi (1.6 M solution in Et₂O, 320 µL, 500 µmol, 10 eq.) was added dropwise and the mixture was stirred for 5 minutes at -78 °C and for further 5 minutes at room temperature. The colorless solution was re-cooled to -78 °C. In a separate Schlenk tube, enone **222** (13 mg, 50 µmol, 1 eq.) was dissolved in Et₂O (0.25 mL) and cooled to -78 °C. BF₃·OEt₂ (20 µL, 125 µmol, 2.5 eq.) was added dropwise followed by the cuprate solution. The reaction mixture was warmed to -55 °C and stirred for 3 hours at this temperature. Sat. aq. NH₄Cl solution was added and the mixture was warmed to room temperature. The phases were separated and the aqueous layer was extracted with Et₂O. The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The crude product was purified by column chromatography (50:1 PE:EA) to give the product as a colorless solid (10 mg, 36.4 µmol, 73%).**

**1H NMR** (400 MHz, CDCl₃) δ = 2.52 (q, J = 8.3, 7.7 Hz, 1H), 2.29 (dd, J = 19.4, 1.4 Hz, 1H), 2.21 (d, J = 19.4 Hz, 1H), 1.74 – 1.61 (m, 5H), 1.59 – 1.40 (m, 6H), 1.33 – 1.27 (m, 3H), 1.13 – 1.07 (m, 1H), 1.14 (s, 3H), 1.11 (d, J = 7.8 Hz, 3H), 1.06 (s, 3H), 0.80 (d, J = 6.7 Hz, 3H) ppm.
\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 224.1, 66.2, 60.6, 52.5, 50.1, 49.1, 45.0, 42.4, 41.5, 34.8, 33.2, 29.0, 28.6, 25.7, 24.8, 19.8, 17.8, 15.6\) ppm.

IR (film): \(\nu_{\text{max}} = 2972, 2926, 2864, 1726, 1456, 1400, 1384, 1229, 1195, 1171, 1141, 1011, 963, 858, 796, 714, 667\) cm\(^{-1}\).

HRMS (ESI, m/z) calculated for C\(_{20}\)H\(_{31}\)O\(^+\) [M+H]\(^+\): 275.2369; found: 275.2361.

\([\alpha]_D\)\(^{32}\): +5.8 (c 1.68, CHCl\(_3\)).

\(R_f = 0.25\) (20:1 PE:EA).

\((+)-\text{Waihoensene (38)}\)

A suspension of KOT-Bu (36 mg, 324 \(\mu\)mol, 9 eq.) in anhydrous toluene (1 mL) was heated to 110 °C until a clear solution formed. Methyltriphenylphosphonium bromide (129 mg, 360 \(\mu\)mol, 10 eq.) was added in one portion and the bright yellow mixture was heated to 110 °C for 60 minutes. A solution of ketone 56 (10 mg, 36 \(\mu\)mol, 1 eq.) in toluene (350 \(\mu\)L) was added and the reaction was heated for further 90 minutes when TLC indicated complete consumption of the starting material. The reaction was cooled to room temperature and water was added. The aqueous phase was extracted with Et\(_2\)O and the combined organic layers were washed with brine and dried over MgSO\(_4\). The solvent was removed under reduced pressure and the residue was purified by column chromatography (100% pentane) to give \((+)-\text{waihoensene as a colorless oil (8 mg, 29.4 \(\mu\)mol, 82%).}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 4.69\) (q, \(J = 1.9\) Hz, 2H), 2.71 (q, \(J = 7.3\) Hz, 1H), 2.24 – 2.20 (m, 2H), 1.79 (pd, \(J = 7.0, 3.5\) Hz, 1H), 1.64 (td, \(J = 13.6, 6.7\) Hz, 1H), 1.62 – 1.59 (m, 1H), 1.59 – 1.57 (m, 1H), 1.56 – 1.54 (m, 2H), 1.53 – 1.50 (m, 1H), 1.50 – 1.44 (m, 1H), 1.44 – 1.40 (m, 1H), 1.40 – 1.31 (m, 2H), 1.31 – 1.27 (m, 1H), 1.27 – 1.24 (m, 1H), 1.19 – 1.14 (m, 1H), 1.14 – 1.10 (m, 1H), 1.04 (d, \(J = 7.3\) Hz, 3H), 1.02 (s, 3H), 1.02 (s, 3H), 0.91 (d, \(J = 6.9\) Hz, 3H)

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 159.8, 103.1, 68.4, 60.5, 52.6, 48.2, 44.8, 44.0, 42.1, 41.0, 36.1, 32.0, 30.6, 30.4, 28.8, 25.5, 25.1, 20.0, 19.3, 17.7\) ppm.

IR (film): \(\nu_{\text{max}} = 2924, 2866, 1656, 1458, 1375, 1263, 975, 874\) cm\(^{-1}\).

HRMS (EI, m/z) calculated for C\(_{20}\)H\(_{32}\) [M]: 272.2504; found: 272.2501.

\([\alpha]_D\)\(^{33}\): +42.4 (c 0.18, CHCl\(_3\)); Lit.: \([\alpha]_D\)\(^{32}\) = +43.9 (c 0.09, CHCl\(_3\)).

\(R_f = 0.86\) (pentane).
Comparison of NMR data of synthetic waihoensene (38) with literature\[57\]

<table>
<thead>
<tr>
<th></th>
<th>(^1\text{H NMR})</th>
<th>(^{13}\text{C NMR})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isolated [Lit]</td>
<td>Synthetic [NMR]</td>
</tr>
<tr>
<td>0.89 (d, J = 7 Hz, 3H)</td>
<td>0.91 (d, J = 6.9 Hz, 3H)</td>
<td>17.61</td>
</tr>
<tr>
<td>0.99 (s, 3H)</td>
<td>1.02 (s, 3H)</td>
<td>19.23</td>
</tr>
<tr>
<td>1.00 (s, 3H)</td>
<td>1.02 (s, 3H)</td>
<td>19.90</td>
</tr>
<tr>
<td>1.02 (d, J = 7 Hz, 3H)</td>
<td>1.04 (d, J = 7.3 Hz, 3H)</td>
<td>25.06</td>
</tr>
<tr>
<td>1.12 (m, 1H)</td>
<td>1.14 – 1.10 (m, 1H)</td>
<td>25.42</td>
</tr>
<tr>
<td>1.15 (m, 1H)</td>
<td>1.19 – 1.14 (m, 1H)</td>
<td>28.75</td>
</tr>
<tr>
<td>1.25 (m, 1H)</td>
<td>1.27 – 1.24 (m, 1H)</td>
<td>30.35</td>
</tr>
<tr>
<td>1.27 (m, 1H)</td>
<td>1.31 – 1.27 (m, 1H)</td>
<td>30.55</td>
</tr>
<tr>
<td>1.36 (m, 2H)</td>
<td>1.40 – 1.31 (m, 2H)</td>
<td>31.93</td>
</tr>
<tr>
<td>1.42 (m, 1H)</td>
<td>1.44 – 1.40 (m, 1H)</td>
<td>36.03</td>
</tr>
<tr>
<td>1.43 (m, 1H)</td>
<td>1.50 – 1.44 (m, 1H)</td>
<td>40.98</td>
</tr>
<tr>
<td>1.50 (m, 1H)</td>
<td>1.53 – 1.50 (m, 1H)</td>
<td>42.07</td>
</tr>
<tr>
<td>1.54 (m, 2H)</td>
<td>1.56 – 1.54 (m, 2H)</td>
<td>43.92</td>
</tr>
<tr>
<td>1.55 (m, 1H)</td>
<td>1.59 – 1.57 (m, 1H)</td>
<td>44.76</td>
</tr>
<tr>
<td>1.56 (m, 1H)</td>
<td>1.62 – 1.59 (m, 1H)</td>
<td>48.12</td>
</tr>
<tr>
<td>1.64 (m, 1H)</td>
<td>1.64 (td, J = 13.6, 6.7 Hz, 1H)</td>
<td>52.58</td>
</tr>
<tr>
<td>1.79 (m, 1H)</td>
<td>1.79 (pd, J = 7.0, 3.5 Hz, 1H)</td>
<td>60.50</td>
</tr>
<tr>
<td>2.20 (br s, J = 1 Hz, 2H)</td>
<td>2.24 – 2.20 (m, 2H)</td>
<td>68.35</td>
</tr>
<tr>
<td>2.69 (q, J = 7 Hz, 1H)</td>
<td>2.71 (q, J = 7.3 Hz, 1H)</td>
<td>102.96</td>
</tr>
<tr>
<td>4.69 (q, J = 2 Hz, 2H)</td>
<td>4.69 (q, J = 1.9 Hz, 2H)</td>
<td>159.70</td>
</tr>
</tbody>
</table>
3.1.3 NMR Spectra
3.1.4 Chiral HPLC Chromatograms of 116

**Figure SI-1:** Chiral HPLC chromatogram of (rac)-116.
The enantiomeric excess was determined to be 96.0\% by chiral HPLC analysis (Chiral PAK AD, 1.0 ml/min, 96:4 Hexanes/ethanol, $\lambda = 254$ nm) $t_r$ (major) = 5.8 min, $t_r$ (minor) = 7.6 min.
3.1.5 DFT Calculation

The ground state electronic structure of the full model of compound 189b was calculated by density functional theory (DFT) methods using the Gaussian 16 program packages.\textsuperscript{[462]} Open shell systems were calculated by the unrestricted Kohn-Sham approach (UKN). Geometry optimisation followed by vibrational analysis was performed in vacuum. The 6-31G(d) polarised double-\(\zeta\) basis sets\textsuperscript{[463]} were employed together with the Becke Three-Parameter Hybrid Functionals (B3LYP).\textsuperscript{[464]} Atomic coordinates of the calculated structure are provided in Table SI-1.

![Figure SI-3: Calculated low energy conformation of 189b.](image)
Table S1-1: Atomic coordinates of structure 189b.

<table>
<thead>
<tr>
<th>atom</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>-3.15482</td>
<td>-1.15073</td>
<td>0.26095</td>
</tr>
<tr>
<td>C</td>
<td>-2.4133</td>
<td>0.04838</td>
<td>0.31882</td>
</tr>
<tr>
<td>C</td>
<td>-3.02342</td>
<td>1.25772</td>
<td>-0.07363</td>
</tr>
<tr>
<td>C</td>
<td>-4.34722</td>
<td>1.24832</td>
<td>-0.5221</td>
</tr>
<tr>
<td>C</td>
<td>-5.07401</td>
<td>0.06637</td>
<td>-0.58793</td>
</tr>
<tr>
<td>C</td>
<td>-4.47558</td>
<td>-1.1241</td>
<td>-0.19491</td>
</tr>
<tr>
<td>H</td>
<td>-4.81013</td>
<td>2.18653</td>
<td>-0.82187</td>
</tr>
<tr>
<td>H</td>
<td>-6.10286</td>
<td>0.07357</td>
<td>-0.94029</td>
</tr>
<tr>
<td>H</td>
<td>-5.0394</td>
<td>-2.05403</td>
<td>-0.23683</td>
</tr>
<tr>
<td>C</td>
<td>-2.28827</td>
<td>2.57798</td>
<td>-0.01288</td>
</tr>
<tr>
<td>H</td>
<td>-1.39185</td>
<td>2.58546</td>
<td>-0.64535</td>
</tr>
<tr>
<td>H</td>
<td>-2.93312</td>
<td>3.39517</td>
<td>-0.35247</td>
</tr>
<tr>
<td>H</td>
<td>-1.96155</td>
<td>2.82173</td>
<td>1.00679</td>
</tr>
<tr>
<td>C</td>
<td>-2.56464</td>
<td>-2.47342</td>
<td>0.69873</td>
</tr>
<tr>
<td>H</td>
<td>-1.64167</td>
<td>-2.72055</td>
<td>0.15974</td>
</tr>
<tr>
<td>H</td>
<td>-2.31754</td>
<td>-2.47807</td>
<td>1.76898</td>
</tr>
<tr>
<td>H</td>
<td>-3.27442</td>
<td>-3.28883</td>
<td>0.52485</td>
</tr>
<tr>
<td>C</td>
<td>-0.96701</td>
<td>0.02375</td>
<td>0.7832</td>
</tr>
<tr>
<td>H</td>
<td>-0.72659</td>
<td>0.94849</td>
<td>1.31631</td>
</tr>
<tr>
<td>H</td>
<td>-0.84029</td>
<td>-0.77763</td>
<td>1.51715</td>
</tr>
<tr>
<td>C</td>
<td>0.01717</td>
<td>-0.20163</td>
<td>-0.39085</td>
</tr>
<tr>
<td>H</td>
<td>-0.32414</td>
<td>-1.09871</td>
<td>-0.92657</td>
</tr>
<tr>
<td>H</td>
<td>-0.08078</td>
<td>0.61785</td>
<td>-1.11414</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>atom</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>1.52893</td>
<td>-0.42027</td>
<td>-0.07907</td>
</tr>
<tr>
<td>C</td>
<td>2.13858</td>
<td>-1.07458</td>
<td>-1.35657</td>
</tr>
<tr>
<td>C</td>
<td>2.29936</td>
<td>0.88338</td>
<td>0.19533</td>
</tr>
<tr>
<td>C</td>
<td>3.6642</td>
<td>-1.20723</td>
<td>-1.34542</td>
</tr>
<tr>
<td>H</td>
<td>1.84357</td>
<td>-0.4671</td>
<td>-2.22554</td>
</tr>
<tr>
<td>H</td>
<td>1.67459</td>
<td>-2.06077</td>
<td>-1.4995</td>
</tr>
<tr>
<td>C</td>
<td>3.83099</td>
<td>0.85336</td>
<td>0.15474</td>
</tr>
<tr>
<td>C</td>
<td>4.33031</td>
<td>0.15292</td>
<td>-1.12683</td>
</tr>
<tr>
<td>H</td>
<td>3.99906</td>
<td>-1.64026</td>
<td>-2.29751</td>
</tr>
<tr>
<td>H</td>
<td>3.981</td>
<td>-1.91651</td>
<td>-0.56891</td>
</tr>
<tr>
<td>H</td>
<td>4.14542</td>
<td>1.90354</td>
<td>0.09143</td>
</tr>
<tr>
<td>H</td>
<td>5.4238</td>
<td>0.05084</td>
<td>-1.09239</td>
</tr>
<tr>
<td>H</td>
<td>4.10339</td>
<td>0.79789</td>
<td>-1.98825</td>
</tr>
<tr>
<td>C</td>
<td>1.6572</td>
<td>-1.40921</td>
<td>1.10584</td>
</tr>
<tr>
<td>H</td>
<td>1.38836</td>
<td>-0.93807</td>
<td>2.05675</td>
</tr>
<tr>
<td>H</td>
<td>0.98969</td>
<td>-2.26277</td>
<td>0.95159</td>
</tr>
<tr>
<td>H</td>
<td>2.6687</td>
<td>-1.8064</td>
<td>1.21226</td>
</tr>
<tr>
<td>C</td>
<td>4.50591</td>
<td>0.29764</td>
<td>1.42611</td>
</tr>
<tr>
<td>H</td>
<td>5.57684</td>
<td>0.53704</td>
<td>1.40791</td>
</tr>
<tr>
<td>H</td>
<td>4.07581</td>
<td>0.74859</td>
<td>2.32757</td>
</tr>
<tr>
<td>H</td>
<td>4.42109</td>
<td>-0.78843</td>
<td>1.52455</td>
</tr>
<tr>
<td>C</td>
<td>1.70627</td>
<td>2.06327</td>
<td>0.39367</td>
</tr>
<tr>
<td>H</td>
<td>0.6325</td>
<td>2.20054</td>
<td>0.41025</td>
</tr>
<tr>
<td>H</td>
<td>2.29669</td>
<td>2.96396</td>
<td>0.55029</td>
</tr>
</tbody>
</table>
3.2 Application of the Palladium – catalysed C-H-Activation in the Synthesis of Cyclohepta[b]indoles

3.2.1 Construction of Cyclohepta[b]indoles via Palladium – catalysed C(sp³)-H Activation

3.2.1.1 Procedures for the Racemic Series

2-methylallyl 3-oxobutanoate (497)

![Chemical structure of 2-methylallyl 3-oxobutanoate](image)

**Method A:** Prepared by modified literature known procedure.\[360\] Ethyl acetoacetate (50.5 mL, 0.4 mol, 2 eq.), methallyl alcohol (17.0 mL, 0.2 mol, 1 eq.) and NEt₃ (55.0 mL, 0.4 mol, 2 eq.) were dissolved in toluene (300 mL) and the mixture was heated to reflux for 10 h while continuously removing ethanol with a Dean-Stark trap. After cooling to room temperature, the mixture was washed with water (2 x 200 mL) and brine (2 x 150 mL), was dried over MgSO₄, filtered and concentrated in vacuo. Double distillation over a Vigreux column (18 mmHg, b.p. 95 – 97 °C) furnished the product as a colourless liquid as mixture of tautomers (24.5 g, 0.16 mol, 78%).

**Method B:** Prepared by modified literature known procedure.\[361\] Freshly distilled diketene-acetone adduct (39.2 mL, 0.3 mol, 1 eq.) and methallyl alcohol (25.0 mL, 0.3 mol, 1 eq.) were dissolved in o-xylene (150 mL) and the mixture was heated to reflux for 2 h. After cooling to room temperature, the solvent was removed in vacuo. Distillation of the residue (18 mmHg, b.p. 95 – 97 °C) furnished the product as a colourless liquid as mixture of tautomers (36.2 g, 0.26 mol, 85%).

*Only the keto-form was assigned via NMR.*

\[^{1}H\text{ NMR (400 MHz, CDCl}_{3}\text{): }\delta = 5.00 – 4.89 (m, 2H), 4.55 (s, 2H), 3.48 (s, 2H), 2.27 (s, 3H), 1.75 (t, J =1.2 Hz, 3H) ppm.*

4-methylbenzenesulfonyl azide (679)

![Chemical structure of 4-methylbenzenesulfonyl azide](image)

Prepared by modified literature known procedure.\[465\] Tosyl chloride (20 g, 0.11 mol, 1 eq.) was dissolved in acetone (200 mL) and the solution was cooled to 0 °C in an ice-bath. A solution of sodium azide (10.3 g, 0.16 mol, 1.5 eq.) in water (60 mL) was added dropwise. The mixture was stirred overnight whilst warming up to room temperature. The organic solvent was removed in vacuo and the aqueous phase was extracted with ether (3 x 200 mL). The combined organic extracts were washed with water, 5%aq. NaHCO₃ and water (150 mL each), were dried over MgSO₄, filtered and concentrated in vacuo to afford the product as a colourless oil (19.1 g, 97 mmol, 88%). The product solidified upon storage in the fridge,
but it is recommended to be used as liquid due to its potential explosiveness. It was used without further characterisation.

2-methylallyl 2-diazoacetate (498)

Prepared by modified literature known procedure. Allyl ester 497 (16.3 g, 104 mmol, 1 eq.) and NEt₃ (17.3 mL, 125 mmol, 1.2 eq.) were dissolved in acetonitrile (70 mL). A solution of azide (TsN₃ or p-ABSA; 115 mmol, 1.1 eq.) was added dropwise at room temperature and the mixture was stirred for 30 min upon complete addition. Aqueous KOH solution (16 wt.-%, 75 mL) was added dropwise and the mixture was stirred overnight. The slurry was poured into water (200 mL) and was extracted with ether (3 x 150 mL). The combined organic extracts were washed with brine (150 mL), dried over MgSO₄, filtered and concentrated in vacuo. The sticky residue was stirred with pentane and decanted (2 x 200 mL) to give a yellow pentane solution. The solvent was removed and the yellow residue was purified by flash column chromatography (PE:EA 20:1) to furnish the product as a yellow liquid (10.6 g, 76 mmol, 73% with TsN₃; 16.9 g, 120 mmol, 94% on a 128 mmol scale with p-ABSA).

¹H NMR (400 MHz, CDCl₃): δ = 4.95 (d, J = 16.4 Hz, 2H), 4.78 (s, 1H), 4.58 (s, 2H), 1.75 (s, 3H) ppm.

Copper(I) trifluoromethanesulfonate benzene complex (680)

[Cu(OTf)]₂·PhH  Prepared by modified literature known procedure. Copper(I) oxide (2.0 g, 14 mmol, 1 eq.) was placed in a Schlenk flask under an atmosphere of nitrogen. Anhydrous benzene (80 mL) was added, followed by addition of triflic anhydride (3.3 mL, 19.5 mmol, 1.4 eq.). The black slurry was heated to reflux until complete dissolution of the copper(I) oxide. The mixture was filtered hot through a Teflon cannula with filter head and was allowed to cool down to room temperature. A colourless solid formed and the supernatant liquid was removed via cannula. The residue was washed with benzene (2 x 10 mL) and was dried in vacuo. The product was obtained as a colourless solid (4.4 g, 8.7 mmol, 62%), which readily decomposed upon air contact. It was used without further characterisation and was stored in a glove box.

Copper(I) trifluoromethanesulfonate toluene complex (681)

[Cu(OTf)]₂·PhMe  The toluene complex was prepared by analogous procedure to the benzene complex by replacing benzene with toluene. The product was obtained as a colourless solid (3.6 g, 7.0 mmol, 50%), which readily decomposed upon air contact. It was used without further characterisation and was stored in a glove box.
5-methyl-3-oxabicyclo[3.1.0]hexan-2-one (495)

Diazoo acetate 498 (7.1 g, 50 mmol, 1 eq.) was freshly purified by column chromatography prior to use. It was dissolved in degassed anhydrous methylene chloride (50 mL) and was added via syringe pump (1.2 mL/min) to a solution of [Cu(OTf)]_2·PhMe (780 mg, 1.51 mmol, 3 mol%) in degassed anhydrous methylene chloride (550 mL). Vigorous gas evolution was observed. Upon complete addition of the diazo compound the reaction was stirred for further 1 h at room temperature. The mixture was extracted with 0.1 M EDTA solution (disodium salt), washed with brine, dried over MgSO_4, filtered and concentrated in vacuo. The residue was purified by Kugelrohr distillation (4 mbar, 180 °C) to furnish the product as a colourless oil (3.64 g, 32.5 mmol, 65%). The analytical data were in accordance with those reported in literature.\[396\]

^1H NMR (400 MHz, CDCl_3): δ = 4.22 (d, J = 9.0 Hz, 1H), 4.08 (d, J = 10.1 Hz, 1H), 1.85 (dd, J = 9.1, 2.9 Hz, 1H), 1.39 (s, 3H), 1.18 (dd, J = 9.1, 4.7 Hz, 1H), 1.06 – 0.97 (m, 1H) ppm.

bis(2-methylallyl) fumarate (499)

Fumarate 499 was obtained in variable amount as byproduct of the intramolecular cyclopropanation reaction.

^1H NMR (400 MHz, CDCl_3): δ = 6.92 (s, 2H), 4.99 (dq, J = 17.0, 1.2 Hz, 4H), 4.63 (s, 4H), 1.78 (t, J = 1.2 Hz, 6H) ppm.

2-(hydroxymethyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (500)

8-aminoquinoline (1.15 g, 8.0 mmol, 2 eq.) was dissolved in anhydrous THF (6 mL) and the solution was cooled to 0 °C. KHMDS (0.7 M in PhMe, 22.9 mL, 16.0 mmol, 4 eq.) was added dropwise to form a red solution. After stirring for 1 h, the solution was cooled to -78 °C and a solution of lactone 495 (0.55 g, 4.0 mmol, 1 eq.) was added dropwise. The reaction was stirred overnight whilst warming up to room temperature. 1 M HCl (50 mL) was added and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine, dried over MgSO_4, filtered and concentrated in vacuo. The residue was purified to furnish the product as a colourless liquid (0.73 g, 2.8 mmol, 71%).

For the AlMe₃ method and full characterisation see the asymmetric section.
2-iodoxybenzoic acid, IBX (658)

Prepared by literature known procedure.\textsuperscript{[466]} 2-iodobenzoic acid (82.5 g, 325 mmol, 1 eq.) was added in portions to a solution of Oxone® (260 g, 423 mmol, 1.3 eq.) in water (1 L). The slurry was vigorously stirred and was heated to 71 °C within 30 min with a contact thermometer in the reaction mixture. The mixture was stirred for 3 h at 71 °C and was cooled to <5 °C while stirring for additional 1.5 h. The solid was filtered off and was thoroughly washed with water (500 mL) and acetone (200 mL). After drying in vacuo the product was obtained as a colourless crystalline solid (70.7 g, 252 mmol, 78%).

\textsuperscript{1}H NMR (400 MHz, DMSO-\textit{d}_6): \( \delta = 8.15 \) (dd, \( J = 8.0, 1.0 \) Hz, 1H), 8.06 – 7.97 (m, 2H), 7.84 (td, \( J = 7.4, 1.1 \) Hz, 1H) ppm.

4-hydroxy-5-methyl-3-(quinolin-8-yl)-3-azabicyclo[3.1.0]hexan-2-one (501)

Alcohol 500 (0.44 g, 1.72 mmol, 1 eq.) was dissolved in EtOAc (12 mL) and IBX (1.44 g, 5.15 mmol, 3 eq.) was added in one portion. The mixture was stirred at 80 °C for 4 h. After cooling to room temperature, the mixture was filtered over a pad of celite and was eluted with EtOAc. Removal of the solvent in vacuo afforded the product as a colourless solid (0.42 g, 1.65 mmol, 96%). It was usually pure enough for the following transformations.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 8.83 \) (ddd, \( J = 4.3, 1.7, 1.0 \) Hz, 1H), 8.26 (dt, \( J = 8.4, 1.3 \) Hz, 1H), 7.76 (dt, \( J = 7.9, 1.3 \) Hz, 1H), 7.68 – 7.55 (m, 2H), 7.48 (ddd, \( J = 8.3, 4.3, 1.0 \) Hz, 1H), 5.29 – 5.25 (m, 1H), 2.08 – 1.98 (m, 1H), 1.54 (s, 3H), 1.16 (ddd, \( J = 8.1, 4.6, 1.0 \) Hz, 1H), 1.04 (dd, \( J = 4.5, 3.1 \) Hz, 1H) ppm.

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): \( \delta = 177.1, 149.2, 143.3, 138.0, 135.7, 129.9, 128.5, 127.2, 127.0, 121.6, 87.6, 26.2, 25.4, 20.0, 14.8 \) ppm.

IR (film): \( \nu_{\text{max}} = 3395, 1664, 1478, 1424, 1233, 1153, 1080, 897, 827, 792, 750 \) cm\textsuperscript{-1}.

HRMS (ESI, \textit{m/z}) calculated for C\textsubscript{15}H\textsubscript{15}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+}: 255.1128, found: 255.1129.
2-methyl-N-(quinolin-8-yl)-2-vinylcyclopropane-1-carboxamide (503)

Methyltriphenylphosphonium bromide (930 mg, 2.60 mmol, 3.5 eq.), KOtBu (250 mg, 2.23 mmol, 3 eq.) and hemiaminal 501 (190 mg, 0.74 mmol, 1 eq.) were stirred in toluene (7 mL) at room temperature. Upon completion water (20 mL) was added and the aqueous phases was extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EA 5:1) to yield the product as a colorless oil that solidified upon storage in the fridge (145 mg, 0.57 mmol, 77%).

1H NMR (400 MHz, CDCl₃): δ = 9.95 (s, 1H), 8.81 (dd, J = 4.2, 1.7 Hz, 1H), 8.77 (dd, J = 7.4, 1.6 Hz, 1H), 8.15 (dd, J = 8.3, 1.7 Hz, 1H), 7.55 – 7.41 (m, 3H), 6.11 (dd, J = 17.4, 10.8 Hz, 1H), 5.22 – 5.03 (m, 2H), 2.00 (dd, J = 7.9, 5.8 Hz, 1H), 1.67 (t, J = 5.2 Hz, 1H), 1.39 (s, 3H), 1.19 (dd, J = 7.9, 4.7 Hz, 1H) ppm.

13C NMR (101 MHz, CDCl₃): δ = 169.1, 148.2, 139.4, 138.4, 136.5, 134.9, 128.1, 127.6, 121.7, 121.3, 116.4, 113.6, 32.8, 28.5, 22.4, 21.7 ppm.

IR (film): νmax = 3357, 2960, 1682, 1524, 1484, 1382, 1326, 1240, 1181, 1160, 1100, 1073, 1007, 970, 918, 828, 791, 765, 738, 699 cm⁻¹.

HRMS (ESI, m/z) calculated for C16H17N2O+: 253.1335; found: 253.1335.

Rf = 0.4 (PE:EA 5:1).

2-(((tert-butyldimethylsilyl)oxy)methyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (513)

Alcohol 500 (230 mg, 0.90 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (2.7 mL). Imidazole (245 mg, 3.59 mmol, 4 eq.) was added in one portion, followed by addition of TBSCI (406 mg, 2.69 mmol, 3 eq.). The mixture was stirred overnight at room temperature. Water (50 mL) was added and the aqueous phase was extracted with methylene chloride (3 x 30 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EA 10:1) to furnish the product as a colorless liquid (324 mg, 0.87 mmol, 97%).

1H NMR (400 MHz, CDCl₃): δ = 9.96 (s, 1H), 8.82 (dd, J = 4.2, 1.7 Hz, 1H), 8.75 (dd, J = 7.5, 1.5 Hz, 1H), 8.15 (dd, J = 8.3, 1.7 Hz, 1H), 7.55 – 7.42 (m, 3H), 3.79 (d, J = 10.3 Hz, 1H), 3.73 (d, J = 10.4 Hz,
1H), 1.76 (dd, J = 7.7, 5.4 Hz, 1H), 1.40 (t, J = 5.0 Hz, 1H), 1.32 (s, 3H), 0.91 (dd, J = 7.7, 4.6 Hz, 1H), 0.70 (s, 9H), -0.03 (s, 3H), -0.14 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): δ = 169.7, 148.1, 138.4, 136.4, 135.2, 128.1, 127.6, 121.6, 121.0, 116.4, 64.8, 29.5, 29.1, 25.8, 22.7, 18.5, 18.2, -5.4, -5.4 ppm.

IR (film): $\nu_{\text{max}}$ = 3249, 2929, 2856, 1675, 1597, 1527, 1488, 1462, 1424, 1378, 1325, 1247, 1189, 1166, 1072, 978, 937, 827, 778, 756, 670 cm$^{-1}$.

HRMS (ESI, m/z) calculated for C$_{21}$H$_{31}$N$_2$O$_2$Si$^+$ [M+H]$^+$: 371.2149, found: 371.2145.

$R_f$ = 0.33 (PE:EA 10:1).

2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (507)

Prepared in full accordance to the asymmetric sample; for details see the asymmetric section.

2-((methoxymethoxy)methyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (508)

Alcohol 500 (2.0 g, 7.80 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (30 mL) and the solution was cooled to 0 °C in an ice-bath. DIPEA (5.4 mL, 31.2 mmol, 4 eq.) was added dropwise, followed by dropwise addition of MOMCl (2.1 mL, 27.3 mmol, 3.5 eq.). The reaction was stirred overnight whilst warming up to room temperature. Water (50 mL) was added and the aqueous phase was extracted with methylene chloride (3 x 50 mL). The combined organic extracts were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EA 3:1) to furnish the product as a colorless oil (1.94 g, 6.46 mmol, 83%).

$^1$H NMR (400 MHz, CDCl$_3$): δ = 10.02 (s, 1H), 8.82 (dd, J = 4.2, 1.7 Hz, 1H), 8.75 (dd, J = 7.3, 1.7 Hz, 1H), 8.15 (dd, J = 8.3, 1.7 Hz, 1H), 7.54 – 7.42 (m, 3H), 4.55 (d, J = 1.3 Hz, 2H), 3.79 (d, J = 10.1 Hz, 1H), 3.74 (d, J = 10.0 Hz, 1H), 3.25 (s, 3H), 1.81 (dd, J = 7.8, 5.5 Hz, 1H), 1.45 (t, J = 5.0 Hz, 1H), 1.36 (s, 3H), 0.97 (dd, J = 7.8, 4.6 Hz, 1H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): δ = 169.6, 148.2, 138.4, 136.5, 135.0, 128.1, 127.6, 121.7, 121.2, 116.3, 96.6, 69.7, 55.1, 29.3, 27.0, 23.1, 19.2 ppm.
IR \textit{(film)}: \nu_{\text{max}} = 3354, 2951, 1677, 1593, 1523, 1485, 1424, 1380, 1325, 1257, 1241, 1211, 1182, 1164, 1148, 1093, 1073, 1041, 1025, 967, 948, 921, 848, 825, 792, 760, 692, 669 \text{ cm}^{-1}.

HRMS (ESI, \textit{m/z}) calculated for C_{17}H_{21}N_{2}O_{3}^{+} [M+H]^{+}: 301.1547, found: 301.1543.

R_f = 0.20 (PE:EA 3:1).

\textbf{2-(((benzyloxy)methoxy)methyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (514)}

Alcohol 500 (4.0 g, 15.6 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (100 mL) and the solution was cooled to 0 °C in an ice-bath. DIPEA (10.6 mL, 62.4 mmol, 4 eq.) and BOMCl (8.4 mL, 54.6 mmol, 3.5 eq.) were subsequently added dropwise. The reaction was stirred overnight whilst warming up to room temperature. Water (150 mL) was added and the aqueous phase was extracted with methylene chloride (3 x 100 mL) the combined organic extracts were washed with brine, dried over MgSO_{4}, filtered and concentrated in \textit{vacuo}. The residue was purified by flash column chromatography (PE:EA 3:1) to furnish the product as a colorless oil (5.86 g, 15.6 mmol, quant.).

\textbf{\textit{1H NMR}} (400 MHz, CDCl_{3}): \delta = 10.04 (s, 1H), 8.82 (dd, \textit{J} = 4.2, 1.7 Hz, 1H), 8.74 (p, \textit{J} = 4.4 Hz, 1H), 8.15 (dd, \textit{J} = 8.3, 1.7 Hz, 1H), 7.49 – 7.42 (m, 3H), 7.29 – 7.18 (m, 5H), 4.68 (s, 2H), 4.52 (d, \textit{J} = 11.8 Hz, 1H), 4.43 (d, \textit{J} = 11.8 Hz, 1H), 3.89 (d, \textit{J} = 10.0 Hz, 1H), 3.78 (d, \textit{J} = 10.0 Hz, 1H), 1.83 (dd, \textit{J} = 7.8, 5.4 Hz, 1H), 1.48 (t, \textit{J} = 5.0 Hz, 1H), 1.37 (s, 3H), 0.98 (dd, \textit{J} = 7.8, 4.7 Hz, 1H) ppm.

\textbf{\textit{13C NMR}} (101 MHz, CDCl_{3}): \delta = 169.6, 148.2, 138.4, 138.2, 136.5, 135.0, 128.4, 128.1, 128.0, 127.6, 127.6, 121.7, 121.2, 116.4, 94.8, 70.0, 69.1, 29.4, 27.0, 23.1, 19.1 ppm.

IR \textit{(film)}: \nu_{\text{max}} = 3355, 2874, 1678, 1521, 1485, 1424, 1380, 1326, 1260, 1239, 1164, 1109, 1038, 968, 849, 825, 791, 735, 697 \text{ cm}^{-1}.

HRMS (ESI, \textit{m/z}) calculated for C_{23}H_{25}N_{2}O_{3}^{+} [M+H]^{+}: 377.1860, found: 377.1859.

R_f = 0.35 (PE:EA 3:1).

\textbf{2-methyl-N-(quinolin-8-yl)-2-((trityloxy)methyl)cyclopropane-1-carboxamide (515)}

Prepared in full accordance to the asymmetric sample; for details see the asymmetric section.
2-(((4-methoxyphenyl)(diphenylmethoxy)methyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (516)

Alcohol 500 (1.03 g, 4.25 mmol, 1 eq.) was dissolved in anhydrous pyridine (28 mL). MMTrCl (3.94 g, 12.8 mmol, 3 eq.) was added and the reaction was stirred at 110 °C overnight. After cooling to room temperature methanol (30 mL) was added and the solvents were removed in vacuo. The residue was purified by flash column chromatography (PE:EA 3:1) to furnish the product as pale yellow foam (1.97 g, 3.27 mmol, 90%).

\[^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3)\]: δ = 10.13 (s, 1H), 8.88 (dd, J = 4.2, 1.7 Hz, 1H), 8.78 (dd, J = 7.6, 1.4 Hz, 1H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.57 – 7.41 (m, 3H), 7.38 – 7.29 (m, 4H), 7.23 – 7.18 (m, 2H), 7.07 (dd, J = 9.3, 5.2, 2.0 Hz, 6H), 6.65 – 6.58 (m, 2H), 3.71 (s, 3H), 3.32 (d, J = 9.5 Hz, 1H), 3.26 (d, J = 9.5 Hz, 1H), 1.87 (dd, J = 7.6, 5.4 Hz, 1H), 1.32 (t, J = 5.1 Hz, 1H), 1.29 (s, 3H), 0.85 (dd, J = 7.6, 4.7 Hz, 1H) ppm.

\[^{13}\text{C} \text{NMR} (101 \text{ MHz, CDCl}_3)\]: δ = 169.4, 158.3, 148.1, 144.9, 144.9, 136.2, 135.1, 130.4, 128.7, 128.6, 128.1, 128.0, 127.6, 127.6, 126.6, 126.6, 121.6, 121.1, 112.9, 85.9, 65.0, 55.2, 29.7, 27.4, 23.4, 18.0 ppm.

\(\text{IR (film): } \nu_{\max} = 3355, 2955, 1679, 1608, 1522, 1485, 1424, 1383, 1326, 1249, 1164, 1062, 1032, 974, 899, 825, 792, 756, 727, 700 \text{ cm}^{-1}.\)

\(\text{HRMS (ESI, } m/z) \text{ calculated for } C_{35}H_{32}N_2NaO_3^+ [M+Na]^+: 551.2305, \text{ found: 551.2310.}\)

\(R_f = 0.40 \text{ (PE:EA 3:1).}\)

2-(((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (517)

Alcohol 500 (500 mg, 1.95 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (6.0 mL). DMAP (24 mg, 195 µmol, 0.1 eq.) and DMTrCl (830 mg, 2.44 mg, 1.25 eq.) were subsequently added. Net3 (540 µL, 3.90 mmol 2 eq.) was added dropwise to give a yellow solution. The reaction was stirred at room temperature until completion. Methanol (10 mL) was added and the solvents were removed in vacuo. The residue was purified by flash column chromatography (PE:EA 3:1) to furnish the product as a colourless foam (1.09 g, 1.95 mmol, quant.).

\[^1\text{H} \text{NMR} (400 \text{ MHz, CDCl}_3)\]: δ = 10.11 (s, 1H), 8.88 (dt, J = 4.1, 1.3 Hz, 1H), 8.81 – 8.73 (m, 1H), 8.16 (dt, J = 8.3, 1.3 Hz, 1H), 7.56 – 7.43 (m, 3H), 7.36 – 7.29 (m, 2H), 7.24 – 7.16 (m, 4H), 7.09 – 7.01 (m,
\[ \text{H} \text{NMR (400 MHz, CDCl}_3\text{): } \delta = 7.97 \text{ (d, } J = 8.3 \text{ Hz, 1H)}, 7.73 - 7.67 \text{ (m, 2H)}, 7.50 \text{ (s, 1H)}, 7.48 - 7.44 \text{ (m, 1H)}, 7.33 \text{ (ddd, } J = 8.3, 7.3, 1.3 \text{ Hz, 1H}), 7.28 - 7.24 \text{ (m, 1H)}, 7.20 \text{ (d, } J = 8.1 \text{ Hz, 2H)}, 4.01 \text{ (d, } J = 9.8 \text{ Hz, 1H)}, 3.75 \text{ (d, } J = 9.7 \text{ Hz, 1H}), 2.49 - 2.42 \text{ (m, 2H)}, 2.32 \text{ (s, 3H)}, 1.61 \text{ (s, 3H) ppm.} \]

\[ \text{IR (film): } v_{\text{max}} = 2924, 1757, 1525, 1446, 1367, 1249, 1167, 1125, 1003, 813, 745, 703, 686, 667 \text{ cm}^{-1}. \]

\[ \text{HRMS (ESI, } m/z \text{) calculated for C}_{21}\text{H}_{20}\text{NO}_5^+ \text{[M+H]}^+: 382.1108, \text{found: 382.1113.} \]

\[ R_f = 0.20 \text{ (PE:EA 1:1).} \]
2-(((tert-butyldimethylsilyl)oxy)methyl)-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide (518)

Prepared from cyclopropane 513 (0.20 g, 0.54 mmol), 518 was obtained as a pale yellow oil (0.14 g, 0.22 mmol, 41%).

$^1$H NMR (400 MHz, CDCl$_3$): \( \delta = 9.86 \) (s, 1H), 8.71 (dd, \( J = 4.3, 1.7 \) Hz, 1H), 8.59 (dd, \( J = 6.0, 3.0 \) Hz, 1H), 8.12 (dd, \( J = 8.3, 1.7 \) Hz, 1H), 7.95 (dt, \( J = 8.3, 0.8 \) Hz, 1H), 7.75 – 7.68 (m, 3H), 7.53 (dt, \( J = 7.7, 1.1 \) Hz, 1H), 7.47 – 7.38 (m, 3H), 7.23 (ddd, \( J = 8.4, 7.2, 1.2 \) Hz, 1H), 7.15 – 7.04 (m, 3H), 4.06 (d, \( J = 10.7 \) Hz, 1H), 3.89 (d, \( J = 10.7 \) Hz, 1H), 2.35 (dd, \( J = 8.8, 1.6 \) Hz, 1H), 2.27 (s, 3H), 2.19 (d, \( J = 8.8 \) Hz, 1H), 1.51 (s, 3H), 0.82 (s, 9H), -0.09 (s, 3H), -0.17 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): \( \delta = 167.9, 148.2, 144.5, 138.5, 136.3, 135.6, 135.2, 134.8, 132.6, 129.8, 128.0, 127.5, 126.9, 125.8, 124.6, 123.2, 121.6, 121.3, 120.0, 116.8, 116.6, 113.8, 62.2, 33.7, 30.6, 27.2, 26.0, 24.4, 21.6, 18.3, -5.6 \) ppm.

IR (film): \( \nu_{max} = 1674, 1513, 1489, 1331, 1255, 1169, 1074, 824, 702 \) cm$^{-1}$.

HRMS (ESI, \( m/z \)) calculated for C$_{36}$H$_{42}$N$_{3}$O$_{4}$SSi$^+$ [M+H$^+$]: 640.2660, found: 640.2647.

$R_f = 0.30$ (PE:EA 4:1).

2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide (510)

Prepared in full accordance to the asymmetric sample; for details and full characterisation see the asymmetric section.
2-((methoxymethoxy)methyl)-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide (511)

Prepared from cyclopropane 508 (0.25 g, 0.87 mmol), 511 was obtained as a pale yellow foam (0.26 g, 0.46 mmol, 54%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 10.12\) (s, 1H), 8.75 (dd, \(J = 4.2, 1.7\) Hz, 1H), 8.73 (dd, \(J = 6.8, 2.2\) Hz, 1H), 8.16 (dd, \(J = 8.3, 1.7\) Hz, 1H), 7.94 (d, \(J = 8.2\) Hz, 1H), 7.70 – 7.65 (m, 2H), 7.63 (d, \(J = 1.5\) Hz, 1H), 7.55 – 7.47 (m, 3H), 7.44 (dd, \(J = 8.3, 4.2\) Hz, 1H), 7.26 – 7.21 (m, 1H), 7.16 (t, \(J = 7.6\) Hz, 1H), 7.03 (d, \(J = 8.1\) Hz, 2H), 4.49 – 4.43 (m, 2H), 3.89 (d, \(J = 10.2\) Hz, 1H), 3.69 (d, \(J = 10.2\) Hz, 1H), 3.19 (s, 3H), 2.39 (dd, \(J = 9.0, 1.6\) Hz, 1H), 2.26 (d, \(J = 9.0\) Hz, 1H), 2.23 (s, 3H), 1.57 (s, 3H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 167.8, 148.2, 144.6, 138.6, 136.5, 135.7, 135.3, 135.1, 135.0, 132.5, 129.8, 128.1, 127.6, 126.9, 125.7, 124.7, 123.3, 121.7, 121.5, 119.7, 116.8, 116.8, 113.9, 96.9, 67.6, 55.3, 33.9, 28.8, 26.8, 24.8, 21.6 ppm.

IR (film): \(\nu_{\text{max}} = 1674, 1513, 1489, 1256, 1170, 1075, 1041, 821\) cm\(^{-1}\).

HRMS (ESI, \(m/z\)) calculated for \(C_{32}H_{32}N_3O_5S^+\) [M+H]\(^+\): 570.2057, found: 570.2064.

\(R_f = 0.25\) (PE:EA 2:1).

2-(((benzyloxy)methoxy)methyl)-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide (519)

Prepared from cyclopropane 514 (2.50 g, 6.64 mmol), 519 was obtained as a pale yellow foam (2.73 g, 4.23 mmol, 64%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 10.14\) (s, 1H), 8.74 (dd, \(J = 5.8, 3.1\) Hz, 2H), 8.15 (dd, \(J = 8.3, 1.6\) Hz, 1H), 7.94 (d, \(J = 8.2\) Hz, 1H), 7.67 (d, \(J = 8.4\) Hz, 3H), 7.56 – 7.47 (m, 3H), 7.43 (dd, \(J = 8.2, 4.2\) Hz, 1H), 7.32 – 7.12 (m, 7H), 6.99 (d, \(J = 8.1\) Hz, 2H), 4.58 (q, \(J = 6.6\) Hz, 2H), 4.44 (d, \(J = 12.0\) Hz, 1H), 4.38 (d, \(J = 12.1\) Hz, 1H), 3.92 (d, \(J = 10.1\) Hz, 1H), 3.80 (d, \(J = 10.2\) Hz, 1H), 2.40 (d, \(J = 8.8\) Hz, 1H), 2.27 (d, \(J = 8.9\) Hz, 1H), 2.18 (s, 3H), 1.58 (s, 3H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 167.8, 148.2, 144.6, 138.6, 138.5, 138.2, 136.5, 135.3, 135.1, 135.0, 132.5, 129.8, 128.4, 128.1, 127.9, 127.6, 127.6, 126.9, 125.8, 124.7, 123.3, 121.7, 121.5, 119.7, 116.8, 116.7, 113.9, 95.1, 69.2, 67.9, 33.9, 28.9, 26.8, 24.8, 21.6 ppm.
**IR (film):** $\nu_{\text{max}} = 2931, 1678, 1521, 1485, 1326, 1164, 1092, 1035, 825, 791, 745, 699, 667 \text{ cm}^{-1}$.

**HRMS (ESI, m/z) calculated for C$_{38}$H$_{36}$N$_3$O$_5$S$^+$ [M+H]$^+$: 646.2370, found: 646.2375.

$R_f = 0.30$ (PE:EA 2:1).

2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)-2-(((trityloxy)methyl)-cyclopropane-1-carboxamide (520)

Prepared in full accordance to the asymmetric sample; for details and full characterisation see the asymmetric section.

2-(((4-methoxyphenyl)diphenylmethoxy)methyl)-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide (521)

Prepared from cyclopropane 516 (0.50 g, 0.95 mmol), 521 was obtained as a yellow foam (0.43 g, 0.54 mmol, 57%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.60$ (s, 1H), 8.62 (dd, $J = 7.0, 2.0$ Hz, 1H), 8.57 (dd, $J = 4.2, 1.7$ Hz, 1H), 8.09 (dd, $J = 8.3, 1.7$ Hz, 1H), 7.94 (dt, $J = 8.3, 0.9$ Hz, 1H), 7.60 – 7.56 (m, 2H), 7.54 (dt, $J = 7.8, 1.1$ Hz, 1H), 7.49 – 7.41 (m, 3H), 7.38 (dd, $J = 8.3, 4.2$ Hz, 1H), 7.31 (ddt, $J = 9.5, 6.3, 1.4$ Hz, 4H), 7.21 (dd, $J = 8.4, 7.2, 1.2$ Hz, 1H), 7.17 – 7.10 (m, 3H), 7.10 – 6.97 (m, 8H), 6.63 – 6.53 (m, 2H), 3.66 (s, 3H), 3.64 (d, $J = 9.8$ Hz, 1H), 3.44 (d, $J = 9.8$ Hz, 1H), 2.34 (dd, $J = 8.8, 1.5$ Hz, 1H), 2.27 (s, 3H), 2.23 (d, $J = 8.9$ Hz, 1H), 1.59 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 167.8, 158.4, 148.1, 144.7, 144.7, 144.5, 138.4, 136.1, 135.6, 135.1, 134.7, 132.6, 130.6, 129.8, 128.6, 128.6, 127.9, 127.6, 127.4, 126.9, 126.7, 125.2, 124.7, 123.2, 121.5, 121.2, 119.8, 116.6, 116.3, 113.6, 112.9, 86.5, 62.9, 60.5, 55.2, 34.2, 29.1, 26.7, 25.4, 21.6, 21.2, 14.3 ppm.

**IR (film):** $\nu_{\text{max}} = 2925, 1683, 1598, 1521, 1486, 1447, 1367, 1325, 1249, 1171, 1129, 1096, 1032, 978, 826, 793, 746, 702, 670 \text{ cm}^{-1}$.

**HRMS (ESI, m/z) calculated for C$_{50}$H$_{42}$N$_3$O$_5$S$^+$ [M-H]$^-$: 796.2840, found: 796.2859.

$R_f = 0.30$ (PE:EA 3:1).
(2-((bis(4-methoxyphenyl)(phenyl)methoxy)methyl)-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide (522)

Prepared from cyclopropane 517 (0.80 g, 1.43 mmol), 522 was obtained as a yellow foam (0.63 g, 0.76 mmol, 54%).

^1H NMR (400 MHz, CDCl₃): δ = 9.61 (s, 1H), 8.62 (dd, J = 7.1, 2.0 Hz, 1H), 8.57 (dd, J = 4.2, 1.7 Hz, 1H), 8.09 (dd, J = 8.3, 1.7 Hz, 1H), 7.94 (dt, J = 8.3, 0.9 Hz, 1H), 7.60 – 7.56 (m, 2H), 7.54 (dt, J = 7.7, 1.0 Hz, 1H), 7.49 (d, J = 1.4 Hz, 1H), 7.47 – 7.41 (m, 2H), 7.37 (dd, J = 8.3, 4.2 Hz, 1H), 7.33 – 7.29 (m, 2H), 7.24 – 7.01 (m, 9H), 7.00 – 6.97 (m, 2H), 6.63 – 6.56 (m, 4H), 3.67 (s, 3H), 3.66 – 3.61 (m, 1H), 3.47 (dd, J = 9.8 Hz, 1H), 2.34 (dd, J = 8.8, 1.5 Hz, 1H), 2.26 (s, 3H), 2.23 (d, J = 8.8 Hz, 1H), 1.58 (s, 3H) ppm.

^13C NMR (101 MHz, CDCl₃): δ = 167.8, 158.3, 148.0, 145.3, 144.5, 138.4, 136.2, 136.1, 135.5, 135.0, 134.7, 132.6, 130.3, 129.8, 128.4, 127.9, 127.6, 127.4, 126.9, 126.5, 125.1, 124.7, 123.2, 121.5, 121.2, 119.8, 116.6, 116.3, 113.6, 112.9, 86.2, 62.8, 55.2, 34.2, 29.1, 26.7, 25.5, 21.6 ppm.

IR (film): ν_max = 1678, 1522, 1366, 1251, 1172, 1033, 825, 750, 702, 667 cm⁻¹.


R_f = 0.35 (PE:EA 2:1).

2-(hydroxymethyl)-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide (509)

MOM ether 511 (0.50 g, 0.88 mmol, 1 eq.) was dissolved in a mixture of anhydrous acetonitrile (5.8 mL) and methylene chloride (2.9 mL) and the solution was cooled in a water bath. Sodium iodide (0.66 g, 4.4 mmol, 5 eq.) was added in one portion, followed by aluminium chloride (0.59 g, 4.4 mmol, 5 eq.). The reaction was stirred at room temperature until complete consumption of the starting material. The mixture was poured into a mixture of sat. aq. Rochelle’s salt solution and sat. aq. NaHCO₃ solution (1:1; 50 mL). The aqueous phase was extracted with EtOAc (3 x 50 mL), the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EA 1:1) to furnish the product as a colourless foam (0.45 g, 0.86 mmol, 97%).
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 10.27 (s, 1H), 8.81 (dd, $J$ = 4.3, 1.7 Hz, 1H), 8.78 (dd, $J$ = 6.4, 2.6 Hz, 1H), 8.23 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.93 (d, $J$ = 8.2 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.51 (dd, $J$ = 8.3, 4.2 Hz, 1H), 7.48 – 7.37 (m, 4H), 7.29 (dd, $J$ = 8.0, 6.7 Hz, 1H), 7.22 (td, $J$ = 7.5, 1.1 Hz, 1H), 6.94 (d, $J$ = 8.1 Hz, 2H), 3.69 – 3.54 (m, 2H), 3.26 (dd, $J$ = 9.3, 4.7 Hz, 1H), 2.41 (dd, $J$ = 9.4, 1.5 Hz, 1H), 2.34 (d, $J$ = 9.4 Hz, 1H), 2.22 (s, 3H), 1.56 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 169.3, 148.6, 144.7, 138.6, 136.7, 135.0, 134.9, 134.3, 132.2, 129.7, 128.3, 127.6, 126.8, 125.1, 124.5, 123.5, 122.3, 122.0, 119.4, 117.5, 117.3, 114.1, 63.8, 34.3, 30.4, 27.0, 24.7, 21.6 ppm.

IR (film): $\nu_{\max}$ = 3326, 1671, 1523, 1486, 1365, 1171, 1123, 1019, 791, 747, 669 cm$^{-1}$.

HRMS (ESI, $m/z$) calculated for C$_{30}$H$_{28}$N$_3$O$_4$S$^+$ [M+H]$^+$: 526.1795, found: 526.1793.

$R_f$ = 0.15 (PE:EA 1:1).

4-hydroxy-5-methyl-3-(quinolin-8-yl)-6-(1-tosyl-1H-indol-3-yl)-3-azabicyclo[3.1.0]hexan-2-one (523)

Alcohol 509 (0.10 g, 0.19 mmol, 1 eq.) was dissolved in EtOAc (10 mL) and IBX (0.16 g, 0.57 mmol, 3 eq.) was added. The mixture was stirred at 80 °C for 4 h and was filtered over a pad of celite with EtOAc as eluent. The solvent was removed in vacuo to yield the crude hemiaminal as a colourless solid (95 mg, 0.18 mmol, 95%), which showed no reactivity towards standard carbonyl olefination reactions.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 9.16 (s, 1H), 8.74 (dd, $J$ = 4.3, 1.7 Hz, 1H), 8.17 (dd, $J$ = 8.4, 1.7 Hz, 1H), 7.99 – 7.93 (m, 1H), 7.76 (d, $J$ = 7.7 Hz, 1H), 7.73 – 7.66 (m, 2H), 7.57 – 7.50 (m, 2H), 7.42 (dd, $J$ = 8.3, 4.3 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.09 (d, $J$ = 8.1 Hz, 2H), 7.00 (t, $J$ = 7.9 Hz, 1H), 6.22 (dd, $J$ = 7.7, 1.3 Hz, 1H), 5.14 (d, $J$ = 1.8 Hz, 1H), 2.59 (dd, $J$ = 8.2, 1.8 Hz, 1H), 2.49 (dd, $J$ = 8.2, 1.7 Hz, 1H), 2.31 (s, 3H), 1.78 (s, 3H) ppm.
3.2.1.2 Procedures for the Asymmetric Series

**Tetrakis(acetonitrile)copper(I) hexafluorophosphate (682)**

![Chemical structure](attachment:structure.png)

Prepared by literature known procedure.[405] Copper(I) oxide (8.0 g, 56 mmol, 1 eq.) was suspended in acetonitrile (160 mL). Hexafluorophosphoric acid (60% in water, 32 mL, 224 mmol, 4 eq.) was added in 2 mL portions under stirring to cause a very exothermic reaction. Upon complete addition of HPF₆, the major part of copper(I) oxide dissolved, leaving a black residue. The hot solution was filtered off to give a teal solution. Cooling to -20 °C caused the complex to crystallise as light blue crystalline solid. The supernatant liquid was removed via cannula and the crystalline residue was recrystallised by dissolving in acetonitrile (100 mL) and addition of ether (100 mL), followed by cooling to -20 °C. The supernatant solvent was removed via cannula and the colourless crystalline solid was dried in vacuo to furnish the product (20.7 g, 55 mmol, 50%). 682 was used without further characterisation and was stored in a glove box.

**2,2-dimethylmalonic acid (527)**

![Chemical structure](attachment:structure.png)

Prepared by literature known procedure.[400] 2,2-dimethylpropan-1,3-diol (50 g, 0.48 mol) was added in small portions to ice-cooled concentrated nitric acid (300 mL). The mixture was stirred overnight whilst warming up to room temperature. The solvent was removed with a water pump and the residue was chilled to furnish a colourless precipitate. The solid was filtered off and recrystallised from water to yield 527 as a colourless solid (42.7 g, 0.32 mol, 71%).

\[ \text{m.p.} = 191 °C, \text{Lit.}[400] 193 °C. \]

**2,2-dimethylmalonyl dichloride (528)**

![Chemical structure](attachment:structure.png)

Prepared by literature known procedure.[467] 2,2-dimethylmalonic acid (25.0 g, 190 mmol, 1 eq.) was suspended in anhydrous methylene chloride (300 mL) and the mixture was cooled to 0 °C. DMF (1.9 mL, 24 mmol, 0.13 eq.) was added, followed by dropwise addition of oxalyl chloride (48.7 mL, 568 mmol, 3 eq.). The cooling bath was removed and the reaction was stirred at room temperature overnight. Distillation afforded the dichloride 528 as a pale yellow liquid (760 mmHg, b.p. = 151 – 153 °C, 28.3 g, 167 mmol, 88%) and was used without further characterisation.
(S)-2-amino-3-methylbutan-1-ol, (S)-valinol (530)

Prepared by modified literature known procedure.\cite{401} (S)-Valine (58.6 g, 500 mmol, 1 eq.) and sodium borohydride (45.4 g, 1.2 mol, 2.4 eq.) were suspended in anhydrous THF (500 mL) and the mixture was cooled to 0 °C in an ice-bath. A solution of iodine (127 g, 500 mmol, 1 eq.) in THF (250 mL) was added dropwise causing vigorous gas formation. After the addition was complete and gas evolution has ceased, the reaction was stirred at reflux overnight. After cooling to room temperature, methanol (150 mL) was added dropwise to destroy remaining borohydride. The solvent was removed in vacuo and the residue was poured into 20% aq. KOH solution (1 L). The mixture was stirred overnight and the aqueous phase was extracted with methylene chloride (3 x 800 mL). The combined extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by Kugelrohr distillation (6 mmHg, b.p. = 76 °C) to furnish the product as a colourless viscous oil that solidified upon storage in the fridge (45.2 g, 438 mmol, 88%).

\(^1\)H NMR (400 MHz, CDCl₃): δ = 3.61 (dd, J = 10.6, 3.9 Hz, 1H), 3.27 (dd, J = 10.6, 8.7 Hz, 1H), 2.53 (ddd, J = 8.5, 6.3, 3.9 Hz, 1H), 2.00 (bs, 3H), 1.61 – 1.45 (m, 1H), 0.90 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.7 Hz, 3H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl₃): δ = 64.8, 58.6, 31.6, 19.4, 18.5 ppm.

\(N^1,N^3\)-bis((S)-1-hydroxy-3-methylbutan-2-yl)-2,2-dimethylmalonamide (531)

Prepared by literature known procedure.\cite{402} (S)-Valinol (6.78 g, 65.7 mmol, 2 eq.) was dissolved in NEt₃ (22.7 mL, 164 mmol, 5 eq.) and was cooled to 0 °C in an ice-bath. Malonyl dichloride 528 (5.52 g, 32.9 mmol, 1 eq.) dissolved in methylene chloride (41.4 mL) was added dropwise. After complete addition, the cooling bath was removed and the reaction was stirred 1 h at room temperature. Methylene chloride (60 mL) and 1 M HCl (40 mL) were added and the phases were separated. The aqueous phase was extracted with methylene chloride (3 x 100 mL) and the combined organic extracts were washed with sat. aq. NaHCO₃ solution and brine, were dried over MgSO₄, filtered and concentrated in vacuo. The colourless residue was recrystallised from EtOAc to yield the product as colourless needles (5.20 g, 17.2 mmol, 53%).

\(^1\)H NMR (400 MHz, CDCl₃): δ = 6.45 (d, J = 8.8 Hz, 2H), 3.84 – 3.67 (m, 4H), 3.52 (t, J = 8.7 Hz, 2H), 3.36 (s, 2H), 3.10 (q, J = 7.3 Hz, 2H), 1.81 (h, J = 6.8 Hz, 2H), 1.48 (s, 6H), 1.40 (t, J = 7.3 Hz, 3H), 0.94 (d, J = 6.7 Hz, 6H), 0.91 (d, J = 6.8 Hz, 6H) ppm.
(4S,4’S)-2,2’-(propane-2,2-diyl)bis(4-isopropyl-4,5-dihydrooxazole), (S,S)-iPr2BOX (532)

Prepared by literature known procedure. Amide 531 (10.0 g, 33 mmol, 1 eq.) and DMAP (400 mg, 3.3 mmol, 0.1 eq.) were dissolved in methylene chloride (200 mL) and the solution was cooled to 0 °C in an ice-bath. Net3 (18.3 mL, 132 mmol, 4 eq.) was added dropwise, followed by dropwise addition of a solution of TsCl (12.6 g, 66 mmol, 2 eq.) in methylene chloride (30 mL). After complete addition the reaction was stirred for 27 h at room temperature. Sat. aq. NH₄Cl solution (140 mL) and water (80 mL) were added and the aqueous phase was extracted with methylene chloride (3 x 150 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was extracted with hot pentane (3 x 150 mL) and the combined extracts were concentrated in vacuo. The residue was purified by Kugelrohr distillation (0.5 mmHg, 97-100 °C) to furnish the product as a colourless oil (8.48 g, 31.8 mmol 96%).

³H NMR (400 MHz, CDCl₃): δ = 4.19 (td, J = 7.7, 1.2 Hz, 2H), 4.02 – 3.92 (m, 4H), 1.88 – 1.72 (m, 2H), 1.51 (s, 6H), 0.91 (d, J = 6.8 Hz, 6H), 0.85 (d, J = 6.8 Hz, 6H) ppm.

4-methyl-N’-tosylbenzenesulfonylhydrazide (659)

Prepared by literature known procedure. Tosyl hydrazide (65.1 g, 350 mmol, 1 eq.) and tosyl chloride (100 g, 525 mmol 1.5 eq.) were suspended in methylene chloride (250 mL) and the mixture was cooled to 0°C in an ice-bath. A solution of pyridine (42.3 mL, 525 mmol, 1.5 eq.) in methylene chloride (100 mL) was added dropwise to keep the temperature below 20 °C. The mixture was stirred for 3 h and was poured in a mixture of ether (400 mL) and water (200 mL). The mixture was vigorously stirred for 1 h and was filtered off. The colourless solid was dried in air and was suspended in methanol (900 mL). The slurry was heated to reflux for 3 h and was allowed to cool to room temperature. The colourless solid was filtered off and dried in vacuo to afford the product (110 g, 324 mmol, 93%).

³H NMR (400 MHz, CDCl₃): δ = 9.57 (s, 2H), 7.69 – 7.59 (m, 4H), 7.38 (d, J = 8.0 Hz, 4H), 2.40 (s, 6H) ppm.
### 2-methylallyl 2-bromoacetate (534)

Prepared by modified literature known procedure.\(^{[396]}\) Methallyl alcohol (20.0 mL, 238 mmol, 1 eq.) was dissolved in methylene chloride (500 mL) in a Schlenk flask and potassium carbonate (98.7 g, 714 mmol, 3 eq.) was added. The mixture was cooled in an ice-bath and bromoacetyl bromide (41.5 mL, 476 mmol, 2 eq.) was added dropwise over 1 h. The reaction was allowed to warm up to room temperature and was further stirred for 30 min. Water was added until complete dissolution of all salts, the phases were separated and the aqueous phase was extracted trice with methylene chloride (250 mL each). The organic extracts were washed with water and brine and were dried over MgSO\(_4\), filtered and the solvent was removed in \textit{vacuo}. Distillation (13 mbar, 77 °C) afforded the product as a colourless oil (40.7 g, 211 mmol, 89%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 5.00\) (d, \(J = 21.7\) Hz, 2H), 4.59 (s, 2H), 3.87 (s, 2H), 1.78 (s, 3H) ppm.

### 2-methylallyl 2-diazoacetate (498)

Prepared by modified literature known procedure.\(^{[396]}\) Bromoacetate 534 (20.1 g, 104 mmol, 1 eq.) was dissolved in THF (300 mL) and cooled to 0°C in an ice-bath. N,N'-Ditosylhydrazide (47.0 g, 138 mmol, 1.33 eq.) was added and the mixture was stirred 15 min to give a cloudy colourless suspension. DBU (51.5 mL, 345 mmol, 3.33 eq.) was added dropwise and the suspension became a clear solution, changed the colour to yellow and a precipitate was formed. The reaction was stirred 1 h in the ice-bath and 1 h at room temperature until all the starting material was consumed. Sat. aq. NaHCO\(_3\) solution (350 mL) was added and the phases were separated. The aqueous phase was extracted with diethyl ether (3 x 250 ml), the combined organic extracts were washed with brine, dried over MgSO\(_4\), filtered and concentrated in \textit{vacuo}. Flash column chromatography (20:1 PE:EA) furnished the product as a yellow oil (10.6 g, 75.6 mmol, 73%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 4.95\) (d, \(J = 16.4\) Hz, 2H), 4.78 (s, 1H), 4.58 (s, 2H), 1.75 (s, 3H) ppm.

### 2-methylallyl 2-diazo-2-(trimethylsilyl)acetate (535)

Diazoacetate 498 (5.44 g, 38.8 mmol, 1 eq.) and DIPEA (7.1 mL, 40.7 mmol, 1.05 eq.) were dissolved in anhydrous diethyl ether (150 mL). The solution was cooled to -78 °C in an acetone-dry-ice-bath and a solution of TMSOTf (7.1 mL, 39.1 mmol, 1.01 eq.) in anhydrous diethyl ether (25 mL) was added dropwise. The mixture was stirred for 24 h while warming up to room temperature. The mixture was filtered over a pad of celite to remove ammonium salts and was concentrated in \textit{vacuo}. Flash column chromatography
(50:1 PE:EA) yielded the product as a yellow oil (8.1 g, 38.1 mmol, 98%). The analytical data matched those reported in literature.\(^{[396]}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 4.94 \text{ (d, } J = 19.6 \text{ Hz, 2H), 4.55 \text{ (s, 2H), 1.71 \text{ (s, 3H), 0.27 \text{ (s, 9H) ppm.}}\)

\((IS,SR)-5\text{-methyl}-1\{(trimethylsilyl)\text{-3-oxabicyclo[3.1.0]hexan-2-one (536)}\)

Prepared by modified literature known procedure.\(^{[396]}\) Tetakis(acetonitrile)copper hexafluorophosphate (1.27 g, 3.40 mmol, 0.11 eq.) and BOX-ligand 532 (1.32 g, 4.95 mmol, 0.16 mmol) were dissolved in freshly degassed toluene (450 mL). The mixture was stirred for 1 h to give a light blue solution. Diazotrimethylsilylacetate 535 (6.56 g, 30.9 mmol, 1 eq.) was dried by azeotropically removing water with toluene trice. The diazo compound was dissolved in degassed toluene (100 mL) and was added dropwise over 4 h. The reaction mixture turned to a golden colour and was heated to 60 °C until the starting material was consumed (30 – 48 h). After cooling to room temperature the reaction mixture was extracted with 0.1 M EDTA solution (disodium salt), the organic phase was dried over MgSO\(_4\), filtered and concentrated in vacuo. Flash column chromatography (15:1 PE:EA) yielded the product as a colourless oil which solidified after a few hours (4.15 g, 22.5 mmol 73%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 4.20 \text{ (d, } J = 8.9 \text{ Hz, 1H), 3.95 \text{ (d, } J = 8.8 \text{ Hz, 1H), 1.37 \text{ (s, 3H), 1.13 \text{ (d, } J = 4.0 \text{ Hz, 1H), 1.07 \text{ (s, 1H), 0.18 \text{ (s, 9H) ppm.}}\)

\((IR,SS)-5\text{-methyl-3-oxabicyclo[3.1.0]hexan-2-one (495)}\)

Prepared by modified literature known procedure.\(^{[396]}\) TMS-cyclopropane 536 (6.30 g, 34.2 mmol, 1.0 eq.) was dissolved in anhydrous THF (68.4 mL) and the solution was cooled to 0 °C in an ice-bath. TBAF (1 M in THF, 51.3 mL, 51.3 mmol, 1.5 eq.) was added dropwise and the reaction was stirred for 30 min. Sat. aq. NH\(_4\)Cl solution (150 mL) was added and the aqueous phase was extracted with diethyl ether (3 x 150 mL). The combined organic phases were dried over MgSO\(_4\), filtered and concentrated in vacuo. The crude product was purified by flash column chromatography (1:1 PE:Et\(_2\)O) to yield the product as colourless sticky crystals (2.88 g, 25.7 mmol, 75%). To obtain a higher enantiomeric excess, the product was recrystallised from PE to yield colourless needles (2.31 g, 20.5 mmol, 60%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 4.22 \text{ (d, } J = 9.0 \text{ Hz, 1H), 4.08 \text{ (d, } J = 10.1 \text{ Hz, 1H), 1.85 \text{ (dd, } J = 9.1, 2.9 \text{ Hz, 1H), 1.39 \text{ (s, 3H), 1.18 \text{ (dd, } J = 9.1, 4.7 \text{ Hz, 1H), 1.06 – 0.97 \text{ (m, 1H) ppm.}}\)

234
(1R,2S)-2-(hydroxymethyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (500)

8-Aminoquinoline (8.91 g, 61.8 mmol, 3 eq.) was placed in a Schlenk flask and was
purged with nitrogen. Anhydrous toluene (50 mL) was added and the mixture was
cooled to 0 °C in an ice-bath. Trimethylaluminium (2 M in PhMe, 30.9 mL,
61.8 mmol, 3 eq.) was added dropwise resulting in the formation of a red-orange
suspension. The reaction was warmed up to room temperature, was stirred for
30 min and was recooled to 0 °C. A solution of lactone 495 (2.31 g, 20.6 mmol, 1 eq.) in PhMe
(30 mL) was added dropwise within 30 min. The reaction was stirred at room temperature until
completion and was then transferred to a sat. aq. Rochelle’s salt solution. The aqueous phase was
extracted with EtOAc (3 x 200 ml), washed with brine and the combined extracts were dried over
MgSO₄, filtered and the solvent was removed in vacuo. Column chromatography (PE:Et₂O 1:1 to
1:2) yielded the product as a beige crystalline solid (4.69 g, 18.3 mmol, 89%).

The enantiomeric excess was determined to be 98% by chiral HPLC analysis (Chiral PAK IA,
0.3ml/min, 91:9 hexanes/ethanol, λ = 254 nm) tₘ (major) = 18.5 min, tₘ (minor) = 25.0 min.

¹H NMR (400 MHz, CDCl₃) δ = 10.06 (s, 1H), 8.82 (dd, J = 4.2, 1.7 Hz, 1H), 8.70 (dd, J = 6.5, 2.5 Hz,
1H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.55 – 7.48 (m, 2H), 7.46 (dd, J = 8.3, 4.2 Hz, 1H), 3.94 (d, J = 11.9
Hz, 1H), 3.78 (d, J = 12.0 Hz, 1H), 3.30 (s, 1H), 1.76 (dd, J = 8.4, 5.6 Hz, 1H), 1.58 – 1.53 (m, 1H), 1.30
(s, 4H), 1.04 (dd, J = 8.4, 4.7 Hz, 1H) ppm.

¹³C NMR (101 MHz, CDCl₃) δ = 171.7, 148.3, 138.4, 136.6, 134.5, 128.1, 127.5, 121.8, 116.9, 65.0,
29.7, 29.5, 23.0, 19.2 ppm.

HRMS (ESI, m/z) calculated for C₁₅H₁₇N₂O₂⁺ [M+H]⁺: 257.1285, found: 257.1277.

[α]D²³: - 30.9 (c 0.29, CHCl₃).

(1R,2S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-
carboxamide (507)

Cyclopropylalcohol 500 (2.10 g, 8.19 mmol, 1 eq.) was dissolved in dry
methylene chloride (60 mL) and imidazole (2.23 g, 32.8 mmol, 4.0 eq.) was
added. The mixture was stirred at room temperature and TBDPSCI (6.4 mL,
24.6 mmol, 3.0 eq.) was added dropwise. The reaction was stirred until
completion and water was added (100 mL). The aqueous phase was extracted
with methylene chloride (3 x 100 mL) and the combined extracts were washed with brine, dried
over MgSO₄, filtered and concentrated in vacuo. Column chromatography (PE:EA 10:1) yielded the
TBDPS ether as a colourless liquid, which solidified upon storage in the fridge (3.69 g, 7.45 mmol, 91%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 10.07 \text{ (s, 1H)}, 8.85 - 8.80 \text{ (m, 2H)}, 8.15 \text{ (dd, } J = 8.3, 1.7 \text{ Hz, 1H)}, 7.63 - 7.59 \text{ (m, 2H)}, 7.57 - 7.51 \text{ (m, 3H)}, 7.48 - 7.43 \text{ (m, 2H)}, 7.37 - 7.20 \text{ (m, 6H)}, 3.89 - 3.79 \text{ (m, 2H)}, 1.84 \text{ (dd, } J = 7.6, 5.4 \text{ Hz, 1H)}, 1.39 - 1.35 \text{ (m, 4H)}, 0.89 \text{ (dd, } J = 7.6, 4.7 \text{ Hz, 1H}), 0.83 \text{ (s, 9H) ppm.}

\(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 169.7, 148.1, 138.4, 136.4, 135.2, 135.7, 134.8, 129.5, 129.4, 128.1, 127.6, 127.5, 121.6, 116.5, 65.7, 29.5, 29.2, 26.7, 22.9, 19.3, 18.3 \text{ ppm.}

HRMS (ESI, \(m/z\)) calculated for C\(_{31}\)H\(_{35}\)N\(_2\)O\(_2\)Si\(^+\) [M+H]\(^+\): 495.2462, found: 495.2457.

\([\alpha]_D^{23}: \text{68.7}^\circ \text{ (c } 0.62, \text{ CHCl}_3).\)

\((1R,2S)-2\text{-methyl-N-}{(\text{quinolin-8-yl})-2-}((\text{trityloxy})\text{methyl})\text{cyclopropane-1-carboxamide (515)}\)

Cyclopropylalcohol 500 (4.51 g, 17.6 mmol, 1 eq.), DMAP (0.54 g, 4.39 mmol, 0.25 eq.) and TrtCl (12.2 g, 43.9 mmol, 2.5 eq.) were placed in a Schlenk tube and dissolved in anhydrous methylene chloride (44 mL). Triethylamine (9.7 mL, 70.2 mmol, 4.0 eq.) was added and the mixture was stirred at 40 °C until completion. Methanol (50 mL) was added and the mixture was concentrated in vacuo. Column chromatography (PE:EA 5:1) yielded the product as a colourless foam (8.71 g, 17.5 mmol, 99%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 10.10 \text{ (s, 1H)}, 8.88 \text{ (dd, } J = 4.2, 1.7 \text{ Hz, 1H)}, 8.76 \text{ (dd, } J = 7.6, 1.4 \text{ Hz, 1H)}, 8.16 \text{ (dd, } J = 8.3, 1.7 \text{ Hz, 1H)}, 7.55 - 7.44 \text{ (m, 3H)}, 7.36 - 7.30 \text{ (m, 6H)}, 7.22 - 7.04 \text{ (m, 9H)}, 3.29 \text{ (q, } J = 9.5 \text{ Hz, 2H)}, 1.85 \text{ (dd, } J = 7.6, 5.4 \text{ Hz, 1H)}, 1.32 - 1.27 \text{ (m, 4H)}, 0.84 \text{ (dd, } J = 7.7, 4.7 \text{ Hz, 1H}) \text{ ppm.}

\(^13\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 169.3, 148.1, 144.4, 138.4, 136.5, 135.2, 128.9, 128.1, 127.6, 126.7, 121.6, 116.4, 86.2, 65.1, 29.7, 27.3, 23.4, 18.1 \text{ ppm.}

HRMS (ESI, \(m/z\)) calculated for C\(_{34}\)H\(_{30}\)N\(_2\)NaO\(_2\) [M+Na]\(^+\): 521.2199, found: 521.2188.

\([\alpha]_D^{23}: 48.5^\circ \text{ (c } 0.40, \text{ CHCl}_3).\)

**General procedure for the preparation of N-Tosyl-3-iodoindoles**

To a solution of the corresponding indole (14.3 mmol, 1 eq.) in DMF (22 mL) was added freshly powdered KOH (35.7 mmol, 2.5 eq.). The mixture was stirred for 30 min at room temperature. A solution of iodine (15.0 mmol, 1.05 eq.) in DMF (22 mL) was added dropwise and the reaction was stirred for 1 h. Powdered KOH (35.7 mmol, 2.5 eq.) was added followed by TsCl (30.0 mmol, 236
2.1 eq.). The reaction was stirred overnight and was then poured into water (200 mL). The product was filtered off, washed with water, a small amount of isopropanol and finally with petrol ether and dried in air to yield product.

In some cases, the indoles formed a sticky mass upon being poured into water, so they were extracted with diethyl ether (3 x 250 mL). The combined extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The solid residue was recrystallised from isopropanol or ethanol to yield the product.

3-iodo-1-tosyl-1H-indole (504)

Prepared from indole (11.7 g, 100 mmol), 504 was obtained as a colourless solid after recrystallisation from ethanol (36.0 g, 90.6 mmol, 91%). The analytical data matched those reported in literature.[406]

$^{1}H$ NMR (400 MHz, CDCl₃): $\delta = 7.96 (d, J = 8.5 \text{ Hz}, 1\text{H}), 7.78 (d, J = 8.1 \text{ Hz}, 2\text{H}), 7.69 (s, 1\text{H}), 7.29 – 7.38 (m, 3\text{H}), 7.24 (d, J = 8.1 \text{ Hz}, 2\text{H}), 2.35 (s, 3\text{H})$ ppm.

3-iodo-1-tosyl-1H-pyrrolo[2,3-b]pyridine (537)

Prepared from 7-azaindole (5.00 g, 42.3 mmol), 537 was obtained as a pale beige solid after filtration (13.1 g, 32.9 mmol, 78%). The analytical data matched those reported in literature.[469]

$^{1}H$ NMR (400 MHz, CDCl₃): $\delta = 8.43 (s, 1\text{H}), 8.08 (m, 2\text{H}), 7.86 (s, 1\text{H}), 7.66 (m, 1\text{H}), 7.22 – 7.31 (m, 3\text{H}), 2.36 (s, 3\text{H})$ ppm.

5-chloro-3-iodo-1-tosyl-1H-indole (543)

Prepared from 5-chloroindole (2.50 g, 16.5 mmol), 543 was obtained as a pale pink solid after recrystallisation from isopropanol (5.87 g, 13.6 mmol, 83%). The analytical data matched those reported in literature.[406]

$^{1}H$ NMR (400 MHz, CDCl₃): $\delta = 7.88 (d, J = 8.8 \text{ Hz}, 1\text{H}), 7.75 (d, J = 8.2 \text{ Hz}, 2\text{H}), 7.70 (s, 1\text{H}), 7.35 (s, 1\text{H}), 7.30 – 7.33 (m, 1\text{H}), 7.25 (d, J = 8.2 \text{ Hz}, 2\text{H}), 2.36 (s, 3\text{H})$ ppm.

3-iodo-7-methoxy-1-tosyl-1H-indole (538)

Prepared from 7-methoxyindole (2.50 g, 17.0 mmol), 538 was obtained as a pale brown powder after recrystallisation from isopropanol (4.60 g, 10.8 mmol, 63%).
**1H NMR** (600 MHz, CDCl₃): δ 7.96 (s, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 7.20 (t, J = 7.9 Hz, 1H), 7.01 (dd, J = 7.9 Hz, 0.9 Hz, 1H), 6.75 (d, J = 7.9 Hz, 1H), 3.70 (s, 3H), 2.40 (s, 3H) ppm.

**13C NMR** (150 MHz, CDCl₃): δ = 147.2, 144.7, 137.0, 135.3, 132.2, 129.6, 127.6, 124.7, 124.4, 114.7, 107.8, 64.6, 55.8, 21.8 ppm.

**HRMS** (ESI, m/z) calculated for C₁₆H₁₅INO₃S⁺ [M+H]⁺: 427.9812, found: 427.9799.

**7-fluoro-3-iodo-1-tosyl-1H-indole (539)**

![Chemical structure of 7-fluoro-3-iodo-1-tosyl-1H-indole (539)](image)

Prepared from 7-fluoroindole (2.50 g, 18.5 mmol), 539 was obtained as a pale beige powder after recrystallisation from isopropanol (5.20 g, 12.5 mmol, 68%).

**1H NMR** (400 MHz, CDCl₃): δ = 7.89 (s, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.17 – 7.24 (m, 2H), 7.03 (dd, J = 12.2 Hz, 7.4 Hz, 1H), 2.38 (s, 3H) ppm.

**13C NMR** (101 MHz, CDCl₃): δ 149.2 (d, J CF = 251.5 Hz), 145.6, 136.6 (d, J CF = 3.4 Hz), 135.2, 132.3, 130.1, 128.0 (d, J CF = 2.6 Hz), 124.5 (d, J CF = 6.8 Hz), 121.7 (d, J CF = 11.5 Hz), 118.1 (d, J CF = 3.8 Hz), 112.2 (d, J CF = 20.0 Hz), 65.0 (d, J CF = 2.4 Hz), 21.8 ppm.

**HRMS** (ESI, m/z) calculated for C₁₅H₁₂INO₂S⁺ [M+H]⁺: 415.9612, found: 415.9598.

**6-fluoro-3-iodo-1-tosyl-1H-indole (540)**

![Chemical structure of 6-fluoro-3-iodo-1-tosyl-1H-indole (540)](image)

Prepared from 6-fluoroindole (2.50 g, 18.5 mmol), 540 was obtained as a colourless powder after recrystallisation from ethanol (6.13 g, 14.8 mmol, 80%).

**1H NMR** (400 MHz, CDCl₃): δ = 7.78 (d, J = 8.4 Hz, 2H), 7.71 (dd, J = 9.5 Hz, 2.2 Hz, 1H), 7.66 (s, 1H), 7.25 – 7.32 (m, 3H), 7.03 (td, J = 8.9 Hz, 2.2 Hz, 1H), 2.37 (s, 3H) ppm.

**13C NMR** (101 MHz, CDCl₃): δ 161.7 (d, J CF = 243.5 Hz), 145.8, 134.8, 134.4 (d, J CF = 12.7 Hz), 130.3, 130.2 (d, J CF = 4.0 Hz), 128.9 (d, J CF = 1.4 Hz), 127.1, 123.2 (d, J CF = 10.0 Hz), 112.6 (d, J CF = 24.5 Hz), 100.8 (d, J CF = 28.7 Hz), 66.3 (d, J CF = 1.0 Hz), 21.8 ppm.

**HRMS** (ESI, m/z) calculated for C₁₅H₁₂INO₂S⁺ [M+H]⁺: 415.9612, found: 415.9604.

**3-iodo-5-nitro-1-tosyl-1H-indole (542)**

![Chemical structure of 3-iodo-5-nitro-1-tosyl-1H-indole (542)](image)

Prepared from 5-nitroindole (2.50 g, 15.4 mmol), 542 was obtained as a pale yellow powder after recrystallisation from ethanol (3.20 g, 7.24 mmol, 47%).

The analytical data matched those reported in literature.¹⁴⁹

**1H NMR** (400 MHz, CDCl₃): δ = 8.32 (d, J = 1.7 Hz, 1H), 8.25 (dd, J = 9.1 Hz, 1.9 Hz, 1H), 8.08 (d, J = 9.1 Hz, 1H), 7.84 (s, 1H), 7.81 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 2.38 (s, 3H) ppm.
4-bromo-3-iodo-1-tosyl-1H-indole (548)

Prepared from 4-bromoindole (2.51 g, 12.8 mmol), 548 was obtained as a colourless powder after recrystallisation from ethanol (4.33 g, 9.09 mmol, 71%). The analytical data matched those reported in literature.[470]

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.01$ (d, $J = 8.4$ Hz, 1H), 7.81 (s, 1H), 7.76 (d, $J = 8.3$ Hz, 2H), 7.42 (d, $J = 7.8$ Hz, 1H), 7.26 (d, $J = 8.3$ Hz, 2H), 7.15 (t, $J = 8.1$ Hz, 1H), 2.36 (s, 3H) ppm.

Methyl 3-iodo-1-tosyl-1H-indole-6-carboxylate (541)

Prepared from methyl indole-6-carboxylate (2.51 g, 14.3 mmol), 541 was obtained as a colourless powder after recrystallisation from ethanol (3.80 g, 8.35 mmol, 59%). The analytical data matched those reported in literature.[471]

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.66$ (s, 1H), 7.99 (dd, $J = 8.3$ Hz, 1.2 Hz, 1H), 7.80 – 7.83 (m, 3H), 7.41 (d, $J = 8.3$ Hz, 1H), 7.27 (d, $J = 8.4$ Hz, 2H), 3.97 (s, 3H), 2.36 (s, 3H) ppm.

3-iodo-4-methyl-1-tosyl-1H-indole (547)

Prepared from 4-methylindole (2.50 g, 19.1 mmol), 547 was obtained as a brown crystalline solid after recrystallisation from isopropanol (5.70 g, 13.9 mmol, 73%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.88$ (d, $J = 8.4$ Hz, 1H), 7.75 – 7.78 (m, 2H), 7.72 (s, 1H), 7.17 – 7.25 (m, 3H), 6.98 (d, $J = 7.5$ Hz, 1H), 2.79 (s, 3H), 2.34 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 145.4$, 135.0, 134.7, 132.2, 131.0, 128.3, 127.1, 126.0, 125.4, 111.6, 62.2, 21.7, 19.4 ppm.

HRMS (ESI, m/z) calculated for C$_{16}$H$_{14}$INO$_2$S$^+$ [M]$^+$: 410.9790, found: 410.9780.

3-iodo-5-methoxy-1-tosyl-1H-indole (545)

Prepared from 5-methoxyindole (2.50 g, 17.0 mmol), 545 was obtained as a beige powder after filtration and drying in air (7.01 g, 16.4 mmol, 97%). The analytical data matched those reported in literature.[460]

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.85$ (d, $J = 9.0$ Hz, 1H), 7.74 (d, $J = 7.7$ Hz, 2H), 7.65 (s, 1H), 7.22 (d, $J = 7.7$ Hz, 2H), 6.97 (d, $J = 8.8$ Hz, 1H), 6.78 (s, 1H), 3.85 (s, 3H), 2.34 (s, 3H) ppm.
methyl 3-iodo-1-tosyl-1H-indole-5-carboxylate (546)

Prepared from methyl indole-5-carboxylate (2.51 g, 14.3 mmol), 546 was obtained as a colourless powder after filtration and drying in air (6.00 g, 13.2 mmol, 92%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.98 – 8.09$ (m, 3H), 7.79 (d, $J = 8.3$ Hz, 2H), 7.75 (s, 1H), 7.26 (d, $J = 8.3$ Hz, 2H), 3.94 (s, 3H), 2.36 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 166.9, 145.9, 137.1, 134.8, 132.6, 131.1, 130.3, 127.1, 127.0, 126.3, 124.5, 113.4, 67.1, 52.4, 21.8$ ppm.

HRMS (ESI, m/z) calculated for C$_{17}$H$_{15}$INO$_4$S$^+$ [M+H]$^+$: 455.9761, found: 455.9753.

5-bromo-3-iodo-1-tosyl-1H-indole (544)

Prepared from 5-bromoindole (3.74 g, 19.1 mmol), 544 was obtained as an off-white powder after filtration and drying in air (6.75 g, 14.2 mmol, 74%). The analytical data matched those reported in literature.$^{[406]}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.83$ (d, $J = 8.8$ Hz, 1H), 7.75 (d, $J = 8.3$ Hz, 2H), 7.68 (s, 1H), 7.51 (d, $J = 1.7$ Hz, 1H), 7.45 (dd, $J = 8.8$ Hz, 1.7 Hz, 1H), 7.25 (d, $J = 8.3$ Hz, 2H), 2.36 (s, 3H) ppm.

General procedure for the Pd(II)-catalyzed C-H activation

Corresponding cyclopropane (1 eq.), silver carbonate (1.2 eq.), N-tosyl-3-iodoindole (3 eq.) and palladium acetate (0.1 eq.) were mixed up under nitrogen atmosphere in a Schlenk flask and anhydrous toluene (1 M based on cyclopropane) was added under a nitrogen flow. The seal tube was protected from light and heated in an oil bath at 110°C for 2 – 5 h. Completion of the reaction was controlled by TLC (PE:EA 3:1) After cooling down to room temperature, the reaction mixture was filtered over a pad of celite using ethyl acetate as eluent. The filtrate was dried over MgSO$_4$ and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (PE:EA 3:1) to yield the desired product.
(1R,2S,3R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)cyclopropane-1-carboxamide (510)

Prepared from cyclopropane 507 (0.30 g, 0.61 mmol), 510 was obtained as a beige foam (0.26 g, 0.34 mmol, 55%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.85$ (s, 1H), 8.69 (dd, $J = 4.2$, 1.7 Hz, 1H), 8.61 (dd, $J = 5.9$, 3.0 Hz, 1H), 8.12 (dd, $J = 8.2$, 1.6 Hz, 1H), 7.95 (d, $J = 8.3$ Hz, 1H), 7.74 (d, $J = 1.3$ Hz, 1H), 7.67 – 7.59 (m, 4H), 7.56 (d, $J = 7.8$ Hz, 1H), 7.46 – 7.39 (m, 5H), 7.36 – 7.27 (m, 3H), 7.25 – 7.19 (m, 2H), 7.12 (m, 3H), 6.99 (d, $J = 8.1$ Hz, 2H), 4.15 (d, $J = 10.9$ Hz, 1H), 4.03 (d, $J = 10.9$ Hz, 1H), 2.40 (d, $J = 7.6$ Hz, 1H), 2.24 – 2.18 (m, 4H), 1.53 (s, 3H), 0.97 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 167.8$, 148.1, 144.4, 138.4, 136.4, 135.9, 135.7, 135.6, 135.1, 134.8, 133.7, 133.6, 132.6, 129.8, 129.6, 129.5, 128.00, 127.6, 127.6, 127.5, 125.7, 124.7, 123.3, 121.6, 121.3, 119.9, 116.6, 113.7, 63.0, 33.8, 30.9, 27.4, 27.4, 24.8, 21.6, 19.4 ppm.

HRMS (ESI, m/z) calculated for C$_{46}$H$_{46}$N$_3$O$_4$SSi$^+ [M+H]^+$: 764.2973, found: 764.2967.

$[\alpha]^D_{23}$: -23.0 (c 0.53, CHCl$_3$).

(1R,2S,3R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)cyclopropane-1-carboxamide (561)

Prepared from cyclopropane 507 (0.20 g, 0.40 mmol), 561 was obtained as a beige foam (0.17 g, 0.22 mmol, 55%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.82$ (s, 1H), 8.65 (dd, $J = 4.2$, 1.6 Hz, 1H), 8.57 – 8.51 (m, 1H), 8.33 (dd, $J = 4.8$, 1.6 Hz, 1H), 8.10 (dd, $J = 8.2$, 1.7 Hz, 1H), 7.95 (d, $J = 8.3$ Hz, 2H), 7.90 – 7.83 (m, 2H), 7.59 (d, $J = 6.5$ Hz, 2H), 7.45 – 7.42 (m, 4H), 7.40 (dd, $J = 8.2$, 4.2 Hz, 1H), 7.35 – 7.27 (m, 2H), 7.25 – 7.21 (m, 2H), 7.14 (t, $J = 7.1$ Hz, 4H), 6.98 (dd, $J = 7.8$, 4.8 Hz, 1H), 4.18 (d, $J = 11.0$ Hz, 1H), 4.00 (d, $J = 10.9$ Hz, 1H), 2.37 (d, $J = 10.3$ Hz, 1H), 2.32 (s, 3H), 2.19 (d, $J = 8.7$ Hz, 1H), 1.51 (s, 3H), 1.00 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 167.6$, 148.2, 147.6, 144.9, 144.8, 138.3, 136.3, 135.3, 135.7, 134.6, 133.6, 133.5, 129.7, 129.6, 129.5, 128.3, 128.0, 127.6, 127.6, 127.5, 126.0, 124.7, 121.6, 121.4, 118.7, 116.6, 113.1, 63.0, 33.6, 30.8, 27.2, 27.1, 24.7, 21.7, 19.4 ppm.

HRMS (ESI, m/z) calculated for C$_{45}$H$_{45}$N$_4$O$_4$SSi$^+ [M+H]^+$: 765.2925, found: 765.2914.

$[\alpha]^D_{23}$: -25.5 (c 0.54, CHCl$_3$).
(1R,2S,3R)-2-(((tert-butyl)diphenylsilyl)oxy)methyl)-3-(5-chloro-1-tosyl-1H-indol-3-yl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (562)

Prepared from cyclopropane 507 (0.20 g, 0.40 mmol), 562 was obtained as a beige foam (0.15 g, 0.19 mmol, 47%).

^1H NMR (400 MHz, CDCl₃): δ = 9.89 (s, 1H), 8.72 (dd, J = 4.3, 1.7 Hz, 1H), 8.60 (dd, J = 5.5, 3.5 Hz, 1H), 8.13 (dd, J = 8.3, 1.7 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.75 (s, 1H), 7.65 – 7.58 (m, 4H), 7.48 (dd, J = 11.6, 2.1 Hz, 2H), 7.46 – 7.41 (m, 4H), 7.38 – 7.33 (m, 1H), 7.29 (t, J = 7.3 Hz, 3H), 7.20 – 7.15 (m, 3H), 7.00 (d, J = 8.1 Hz, 2H), 4.14 (d, J = 11.0 Hz, 1H), 4.01 (d, J = 10.9 Hz, 1H), 2.33 (d, J = 8.8 Hz, 1H), 2.25 (s, 3H), 2.20 (d, J = 8.8 Hz, 1H), 1.51 (s, 3H), 0.95 (s, 9H) ppm.

^13C NMR (101 MHz, CDCl₃): δ = 167.6, 148.2, 144.7, 138.4, 136.4, 136.0, 135.7, 135.3, 134.7, 134.0, 133.7, 133.5, 133.4, 129.9, 129.6, 129.3, 128.0, 127.7, 127.6, 127.5, 127.0, 126.9, 124.9, 121.6, 121.4, 119.5, 116.6, 116.2, 114.9, 62.9, 33.8, 31.0, 27.0, 24.7, 21.7, 19.4 ppm.

HRMS (ESI, m/z) calculated for C₄₆H₄₅ClN₃O₄SSi⁺ [M+H⁺]: 798.2583, found: 798.2583.

[^α]D²³: -7.0 (c 0.51, CHCl₃).

(1R,2S,3R)-2-(((tert-butyl)diphenylsilyl)oxy)methyl)-3-(7-methoxy-1-tosyl-1H-indol-3-yl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (566)

Prepared from cyclopropane 507 (0.20 g, 0.40 mmol), 566 was obtained as a beige foam (0.17 g, 0.21 mmol, 52%).

^1H NMR (400 MHz, CDCl₃): δ = 9.88 (s, 1H), 8.68 (dd, J = 4.3, 1.7 Hz, 1H), 8.59 (dd, J = 5.7, 3.4 Hz, 1H), 8.10 (dd, J = 8.3, 1.7 Hz, 1H), 7.94 (d, J = 1.5 Hz, 1H), 7.68 (d, J = 8.2 Hz, 2H), 7.62 (d, J = 6.6 Hz, 2H), 7.46 (d, J = 6.5 Hz, 2H), 7.44 – 7.40 (m, 2H), 7.38 (dd, J = 8.3, 4.3 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.27 – 7.22 (m, 3H), 7.19 (d, J = 7.3 Hz, 1H), 7.16 – 7.11 (m, 4H), 6.97 (t, J = 7.9 Hz, 1H), 6.61 (d, J = 7.9 Hz, 1H), 4.26 (d, J = 10.9 Hz, 1H), 4.08 (d, J = 10.8 Hz, 1H), 3.70 (s, 3H), 2.43 (d, J = 7.2 Hz, 1H), 2.36 (s, 3H), 2.21 (d, J = 8.7 Hz, 1H), 1.55 (s, 3H), 0.99 (s, 9H) ppm.

^13C NMR (101 MHz, CDCl₃): δ = 167.9, 148.1, 147.5, 143.8, 138.4, 137.6, 136.3, 136.0, 135.7, 135.4, 134.8, 133.8, 133.8, 129.5, 129.4, 128.2, 128.0, 127.6, 127.6, 127.5, 127.5, 124.8, 124.0, 121.5, 121.1, 116.7, 114.2, 112.7, 107.4, 63.1, 55.7, 33.6, 31.0, 27.7, 27.1, 24.8, 21.7, 19.4 ppm.

HRMS (ESI, m/z) calculated for C₄₇H₄₈N₃O₅SSi⁺ [M+H⁺]: 794.3078, found: 794.3057.
(1R,2S,3R)-2-((tert-butyldiphenylsilyl)oxy)methyl)-3-(7-fluoro-1-tosyl-1H-indol-3-yl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (567)

Prepared from cyclopropane 507 (0.20 g, 0.40 mmol), 567 was obtained as a beige foam (0.16 g, 0.21 mmol, 51%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 9.88 (s, 1H), 8.69 (dd, $J$ = 4.3, 1.6 Hz, 1H), 8.57 (p, $J$ = 4.4 Hz, 1H), 8.12 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.89 (d, $J$ = 1.5 Hz, 1H), 7.74 (d, $J$ = 7.6 Hz, 2H), 7.63 – 7.58 (m, 2H), 7.46 – 7.39 (m, 5H), 7.36 – 7.31 (m, 2H), 7.29 – 7.23 (m, 4H), 7.17 – 7.10 (m, 4H), 6.96 (td, $J$ = 7.9, 4.2 Hz, 1H), 6.86 (ddd, $J$ = 12.1, 8.0, 1.0 Hz, 1H), 4.20 (d, $J$ = 10.9 Hz, 1H), 4.04 (d, $J$ = 10.9 Hz, 1H), 2.40 (dd, $J$ = 8.7, 1.6 Hz, 1H), 2.32 (s, 3H), 2.21 (d, $J$ = 8.7 Hz, 1H), 1.54 (s, 3H), 0.98 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 167.7, 149.9 (d, $J_{CF}$ = 250.6 Hz), 148.2, 144.6, 138.4, 136.8, 136.4, 136.0, 135.9, 135.7, 134.7, 133.7, 129.9, 129.6, 129.5, 128.3, 128.0, 127.7, 127.6, 127.5, 123.9 (d, $J_{CF}$ = 6.0 Hz), 121.5 (d, $J_{CF}$ = 30.0 Hz), 116.6, 115.7, 115.2, 111.3 (d, $J_{CF}$ = 19.3 Hz), 63.0, 33.6, 31.0, 27.3, 27.1, 24.7, 22.4, 19.4 ppm.

HRMS (ESI, m/z) calculated for C$_{46}$H$_{45}$FN$_3$O$_4$SSi$^+$/[M+H]$^+$: 782.2879, found: 782.2853.

$[\alpha]_D^{23}$: -36.2 (c 0.54, CHCl$_3$).

(1R,2S,3R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-3-(6-fluoro-1-tosyl-1H-indol-3-yl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (564)

Prepared from cyclopropane 507 (0.20 g, 0.40 mmol), 564 was obtained as a beige foam (0.19 g, 0.24 mmol, 60%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 9.85 (s, 1H), 8.70 (dd, $J$ = 4.2, 1.7 Hz, 1H), 8.58 (p, $J$ = 4.4 Hz, 1H), 8.13 (dd, $J$ = 8.3, 1.7 Hz, 1H), 7.70 (d, $J$ = 1.6 Hz, 1H), 7.67 (dd, $J$ = 9.8, 2.3 Hz, 1H), 7.64 (d, $J$ = 8.4 Hz, 2H), 7.62 – 7.58 (m, 2H), 7.48 – 7.40 (m, 6H), 7.37 – 7.32 (m, 1H), 7.31 – 7.24 (m, 3H), 7.15 (t, $J$ = 7.6 Hz, 2H), 7.03 (d, $J$ = 7.8 Hz, 2H), 6.85 – 6.79 (m, 1H), 4.14 (d, $J$ = 10.9 Hz, 1H), 4.01 (d, $J$ = 10.9 Hz, 1H), 2.36 (d, $J$ = 8.8 Hz, 1H), 2.26 (s, 3H), 2.19 (d, $J$ = 8.8 Hz, 1H), 1.51 (s, 3H), 0.97 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 167.7, 161.1 (d, $J_{CF}$ = 241.1 Hz), 148.2, 144.7, 138.4, 136.4, 135.9, 135.7, 135.3, 134.7, 133.7, 133.6, 129.9, 129.6, 129.5, 128.8, 128.0, 127.6, 127.6, 127.5, 126.9,
125.9, 121.5 (d, J_CF = 30.3 Hz), 120.7 (d, J_CF = 9.6 Hz), 116.5, 116.4, 111.6 (d, J_CF = 24.8 Hz), 101.1 (d, 

HRMS (ESI, m/z) calculated for C_{66}H_{45}FN_{3}O_{4}Si^{+} [M+H]^+: 782.2879, found: 782.2857.

[α]_D^{23} = -23.7 (c 0.52, CHCl_3).

(1R,2S,3R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-3-(5-nitro-1-tosyl-1H-indol-3-yl)-N-(quinolin-8-yl)cyclopropane-1-carboxamide (563)

Prepared from cyclopropane 507 (0.20 g, 0.40 mmol), 563 was obtained as a beige foam (0.14 g, 0.17 mmol, 43%).

^1H NMR (400 MHz, CDCl_3): δ = 9.97 (s, 1H), 8.74 (dd, J = 4.3, 1.7 Hz, 1H), 8.52 (dd, J = 6.7, 2.4 Hz, 1H), 8.42 (d, J = 2.3 Hz, 1H), 8.16 – 8.08 (m, 2H), 8.02 (d, J = 9.1 Hz, 1H), 7.92 (d, J = 1.4 Hz, 1H), 7.68 – 7.64 (m, 2H), 7.63 – 7.59 (m, 2H), 7.48 – 7.42 (m, 5H), 7.39 – 7.27 (m, 4H), 7.23 – 7.18 (m, 2H), 7.06 (d, J = 7.8 Hz, 2H), 4.20 (d, J = 10.9 Hz, 1H), 4.00 (d, J = 10.9 Hz, 1H), 2.42 (d, J = 8.7 Hz, 1H), 2.27 (m, 4H), 1.53 (s, 3H), 0.95 (s, 9H) ppm.

^13C NMR (101 MHz, CDCl_3) δ = 167.4, 148.2, 145.4, 144.2, 138.3, 137.9, 136.5, 135.9, 135.7, 135.0, 134.6, 133.6, 133.5, 132.7, 130.1, 129.7, 129.7, 128.4, 128.1, 127.7, 127.4, 127.0, 121.7, 121.5, 119.9, 117.6, 116.5, 116.2, 113.9, 62.8, 33.7, 31.2, 27.0, 24.7, 21.7, 18.9 ppm.

HRMS (ESI, m/z) calculated for C_{66}H_{44}N_{4}NaO_{6}Si^{+} [M+Na]^+: 831.2643, found: 831.2599.

[α]_D^{23} = 6.2 (c 0.52, CHCl_3).

methyl 3-((1R,2S,3R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)-2-methyl-3-(quinolin-8-yl-carbamoyl)cyclopropyl)-1-tosyl-1H-indole-6-carboxylate (565)

Prepared from cyclopropane 507 (0.20 g, 0.40 mmol), 565 was obtained as a beige foam (0.16 g, 0.17 mmol, 48%).

^1H NMR (400 MHz, CDCl_3): δ = 9.89 (s, 1H), 8.71 (d, J = 4.3 Hz, 1H), 8.64 (s, 1H), 8.56 (p, J = 4.4 Hz, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.89 (s, 1H), 7.79 (d, J = 8.3 Hz, 1H), 7.67 (d, J = 8.1 Hz, 2H), 7.60 (d, J = 7.0 Hz, 2H), 7.56 (d, J = 8.3 Hz, 1H), 7.47 – 7.40 (m, 5H), 7.35 (t, J = 7.4 Hz, 1H), 7.31 – 7.26 (m, 3H), 7.16 (t, J = 7.4 Hz, 2H), 7.03 (d, J = 8.1 Hz, 2H), 4.16 (d, J = 10.9 Hz, 1H), 4.01 (d, J = 10.9 Hz, 1H), 3.91 (s, 3H), 2.39 (d, J = 8.7 Hz, 1H), 2.25 (s, 3H), 2.21 (d, J = 8.7 Hz, 1H), 1.51 (s, 3H), 0.96 (s, 9H) ppm.
$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 167.6, 167.5, 148.1, 144.8, 136.5, 136.3, 136.0, 135.7, 135.4, 134.7, 134.6, 133.7, 133.5, 130.00, 129.6, 128.7, 127.6, 127.5, 127.0, 126.5, 124.5, 121.7, 121.4, 119.6, 116.6, 115.5, 62.9, 52.3, 33.6, 31.1, 27.2, 27.1, 24.7, 21.7, 19.4 ppm.

HRMS (ESI, $m/z$) calculated for $C_{48}H_{48}N_3O_6SSi^+$ [M+H]$^+$: 822.3028, found: 822.3005.

[$\alpha$]$_D^{23}$: -3.9 (c 0.54, CHCl$_3$).

$(1R,2S,3R)$-2-methyl-N-(quinolin-8-yl)-3-(1-tosyl-1H-indol-3-yl)-2-((trityloxy)methyl)-cyclopropane-1-carboxamide (520)

Prepared from cyclopropane 515 (1.00 g, 2.01 mmol), 520 was obtained as a beige foam (1.10 g, 1.43 mmol, 71%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.59$ (s, 1H), 8.62 (d, $J = 6.8$ Hz, 1H), 8.58 (d, $J = 4.1$ Hz, 1H), 8.10 (d, $J = 8.4$ Hz, 1H), 7.96 (d, $J = 8.4$ Hz, 1H), 7.59 (d, $J = 8.2$ Hz, 2H), 7.55 (d, $J = 7.8$ Hz, 1H), 7.51 – 7.43 (m, 3H), 7.38 (dd, $J = 8.1$ Hz, 4.3 Hz, 1H), 7.35 – 7.25 (m, 6H), 7.22 (t, 7.5 Hz, 1H), 7.14 – 6.98 (m, 12H), 3.64 (d, $J = 9.9$ Hz, 1H), 3.41 (d, $J = 9.9$ Hz, 1H), 2.34 (d, $J = 8.6$ Hz, 1H), 2.28 (s, 3H), 2.23 (d, $J = 8.6$ Hz, 1H), 1.60 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 167.8, 148.1, 144.5, 144.1, 138.4, 136.1, 135.6, 135.1, 134.7, 132.6, 129.8, 128.9, 128.1, 127.9, 127.6, 127.4, 126.9, 126.8, 125.2, 124.7, 123.2, 121.5, 121.2, 119.8, 116.6, 116.2, 113.6, 86.8, 63.0, 34.2, 29.0, 26.8, 25.4, 21.7 ppm.

HRMS (ESI, $m/z$) calculated for $C_{49}H_{42}N_3O_4S^+$ [M+H]$^+$: 768.2891, found: 768.2886.

[$\alpha$]$_D^{23}$: -50.4 (c 0.28, CHCl$_3$).

$(1R,2S,3R)$-2-methyl-N-(quinolin-8-yl)-3-(tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-((trityloxy)methyl)cyclopropane-1-carboxamide (549)

Prepared from cyclopropane 515 (0.25 g, 0.50 mmol), 549 was obtained as a salmon foam (0.29 g, 0.38 mmol, 75%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.49$ (s, 1H), 8.63 – 8.54 (m, 1H), 8.54 – 8.47 (m, 1H), 8.33 (d, $J = 3.7$ Hz, 1H), 8.07 (d, $J = 8.0$ Hz, 1H), 7.92 (d, $J = 7.9$ Hz, 2H), 7.83 (d, $J = 7.5$ Hz, 1H), 7.63 (s, 1H), 7.48 – 7.39 (m, 2H), 7.37 – 7.27 (m, 7H), 7.16 (d, $J = 7.8$ Hz, 2H), 7.07 – 6.95 (m, 10H), 3.63 (d, $J = 9.7$ Hz, 1H), 3.38 (d, $J = 9.7$ Hz, 1H), 2.34 (s, 3H), 2.32 (s, 1H), 2.22 (d, $J = 8.6$ Hz, 1H), 1.64 (s, 3H) ppm.
\(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)): \(\delta = 167.6, 148.2, 147.5, 144.9, 144.8, 143.9, 138.3, 136.1, 135.9, 134.4,\)
\(129.6, 128.8, 128.3, 128.0, 127.9, 127.3, 126.8, 125.7, 124.7, 121.6, 121.3, 118.7, 116.6,\)
\(112.6, 86.9, 63.1, 33.9, 28.9, 26.6, 25.4, 21.7\) ppm.

\(\text{HRMS}\) (ESI, \(m/z\)) calculated for C\(_{48}\)H\(_{41}\)N\(_4\)O\(_4\)S\(^+\): 769.2843, found: 769.2857.

\([\alpha]_D\)\(^{23}\): -24.0 (c 0.53, CHCl\(_3\)).

\((1R,2S,3R)\)-3-\((5\text{-chloro-1-tosyl-1H-indol-3-yl})\)-2-methyl-\(N\)-(quinolin-8-yl)-2-((trityloxy)methyl)-cyclopropane-1-carboxamide (550)

\(1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 9.75\) (s, 1H), 8.74 – 8.59 (m, 2H), 8.12 (d, \(J = 8.2\) Hz, 1H), 7.88 (d, \(J = 8.8\) Hz, 1H), 7.58 (d, \(J = 8.0\) Hz, 2H), 7.55 – 7.47 (m, 4H), 7.41 (dd, \(J = 8.1, 4.2\) Hz, 1H), 7.30 (d, \(J = 7.5\) Hz, 6H), 7.20 (d, \(J = 8.7\) Hz, 1H), 7.14 – 7.00 (m, 11H), 3.64 (d, \(J = 9.9\) Hz, 1H), 3.40 (d, \(J = 9.8\) Hz, 1H), 2.31 – 2.26 (m, 4H), 2.23 (t, \(J = 8.8\) Hz, 1H), 1.60 (s, 3H) ppm.

\(\text{HRMS}\) (ESI, \(m/z\)) calculated for C\(_{49}\)H\(_{41}\)ClN\(_3\)O\(_4\)S\(^+\): 802.2501, found: 802.2496.

\([\alpha]_D\)\(^{23}\): -12.9 (c 0.50, CHCl\(_3\)).

\((1R,2S,3R)\)-3-\((7\text{-methoxy-1-tosyl-1H-indol-3-yl})\)-2-methyl-\(N\)-(quinolin-8-yl)-2-((trityloxy)methyl)-cyclopropane-1-carboxamide (554)

\(1\text{H NMR}\) (400 MHz, CDCl\(_3\)): \(\delta = 9.63\) (s, 1H), 8.61 (dd, \(J = 6.9, 1.6\) Hz, 1H), 8.54 (d, \(J = 3.0\) Hz, 1H), 8.07 (d, \(J = 8.1\) Hz, 1H), 7.70 (s, 1H), 7.63 (d, \(J = 8.2\) Hz, 2H), 7.47 – 7.38 (m, 2H), 7.37 – 7.27 (m, 7H), 7.21 – 7.13 (m, 3H), 7.08 – 6.96 (m, 10H), 6.60 (d, \(J = 7.9\) Hz, 1H), 3.69 (s, 3H), 3.64 (d, \(J = 9.8\) Hz, 1H), 3.56 (d, \(J = 9.8\) Hz, 1H), 2.41 – 2.34 (m, 4H), 2.24 (d, \(J = 8.7\) Hz, 1H), 1.59 (s, 3H) ppm.
$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 167.8, 148.1, 147.4, 144.1, 143.8, 138.4, 137.5, 136.0, 135.3, 134.7, 129.3, 128.9, 127.9, 127.7, 127.5, 127.3, 126.7, 124.7, 123.9, 121.4, 121.1, 116.7, 113.8, 112.6, 107.2, 86.8, 63.0, 55.6, 33.9, 29.1, 27.0, 25.3, 21.7 ppm.

HRMS (ESI, m/z) calculated for C$_{50}$H$_{44}$N$_3$O$_5$S$^+ [M+H]$^+$: 798.2996, found: 798.3007.

$[\alpha]_{D}^{23}$: -55.0 (c 0.62, CHCl$_3$).

$(1R,2S,3R)$-3-(7-fluoro-1H-tosyl-1H-indol-3-yl)-2-methyl-N-(quinolin-8-yl)-2-((trityloxy)methyl)-cyclopropane-1-carboxamide (555)

Prepared from cyclopropane 515 (0.25 g, 0.50 mmol), 555 was obtained as a beige foam (0.24 g, 0.31 mmol, 61%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.67$ (s, 1H), 8.66 – 8.55 (m, 2H), 8.10 (d, $J = 8.2$ Hz, 1H), 7.70 (d, $J = 7.9$ Hz, 2H), 7.65 (s, 1H), 7.49 – 7.41 (m, 2H), 7.38 (dd, $J = 8.1$ Hz, 4.1 Hz, 1H), 7.35 – 7.21 (m, 6H), 7.13 (d, $J = 8.0$ Hz, 2H), 7.10 – 6.96 (m, 10H), 6.86 (dd, $J = 11.9$ Hz, 8.1 Hz, 1H), 3.65 (d, $J = 9.8$ Hz, 1H), 3.47 (d, $J = 9.8$ Hz, 1H), 2.34 (m, 4H), 2.25 (d, $J = 8.7$ Hz, 1H), 1.61 (s, 3H)

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 167.6, 149.8$ (d, $J_{CF} = 250.0$ Hz), 148.1, 144.7, 144.0, 138.4, 136.8 (d, $J_{CF} = 3.5$ Hz), 136.2, 135.8, 134.6, 129.8, 128.9, 127.9, 127.8, 127.7 (d, $J_{CF} = 2.0$ Hz), 127.6, 127.4, 126.8, 123.8 (d, $J_{CF} = 6.8$ Hz), 122.0 (d, $J_{CF} = 10.6$ Hz), 121.4 (d, $J_{CF} = 26.8$ Hz), 116.7, 115.8 (d, $J_{CF} = 3.6$ Hz), 114.9 (d, $J_{CF} = 1.6$ Hz), 111.3 (d $J_{CF} = 20.0$ Hz), 86.8, 62.9, 33.9, 29.2, 26.7, 25.3, 21.7 ppm.

HRMS (ESI, m/z) calculated for C$_{49}$H$_{41}$FN$_3$O$_4$S$^+ [M+H]$^+$: 786.2796, found: 786.2806.

$[\alpha]_{D}^{23}$: -33.0 (c 0.58, CHCl$_3$).

$(1R,2S,3R)$-3-(6-fluoro-1H-tosyl-1H-indol-3-yl)-2-methyl-N-(quinolin-8-yl)-2-((trityloxy)methyl)-cyclopropane-1-carboxamide (552)

Prepared from cyclopropane 515 (0.25 g, 0.50 mmol), 552 was obtained as a beige foam (0.27 g, 0.34 mmol, 69%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.62$ (s, 1H), 8.65 – 8.59 (m, 2H), 8.11 (d, $J = 8.1$ Hz, 1H), 7.68 (d, $J = 9.6$ Hz, 1H), 7.60 (d, $J = 7.9$ Hz, 2H), 7.51 – 7.43 (m, 4H), 7.40 (dd, $J = 8.0$ Hz, 4.0 Hz, 1H), 7.35 – 7.27 (m, 6H), 7.15 – 6.98 (m, 11H), 6.85 (t, $J = 8.8$ Hz, 1H), 3.65 (d, $J = 9.8$ Hz, 1H), 3.39 (d, $J = 9.8$ Hz, 1H), 2.34 – 2.27 (m, 4H), 2.22 (d, $J = 8.7$ Hz, 1H), 1.60 (s, 3H) ppm.
13C NMR (101 MHz, CDCl3): δ = 167.6, 161.1 (d, JCF = 241.3 Hz), 148.1, 144.8, 144.0, 138.4, 136.2, 135.3, 135.2 (d, JCF = 12.7 Hz), 134.6, 129.9, 128.8, 127.9, 127.6, 127.4, 126.9, 126.8, 125.4 (d, JCF = 3.9 Hz), 121.5 (d, JCF = 27.8 Hz), 120.7 (d, JCF = 9.9 Hz), 116.5, 116.1, 111.6 (d, JCF = 24.3 Hz), 101.0 (d, JCF = 28.4 Hz), 86.9, 62.9, 34.0, 29.0, 26.6, 25.3, 21.7 ppm.

HRMS (ESI, m/z) calculated for C49H41FN4O4S+ [M+H]+: 786.2796, found: 786.2803.

[α]D23: -30.5 (c 0.64, CHCl3).

(1R,2S,3R)-2-methyl-3-(5-nitro-1H-indol-3-yl)-N-(quinolin-8-yl)-2-((trityloxy)methyl)cyclopropane-1-carboxamide (551)

Prepared from cyclopropane 515 (0.25 g, 0.50 mmol), 551 was obtained as a pale yellow foam (0.19 g, 0.24 mmol, 48%).

1H NMR (400 MHz, CDCl3): δ = 9.86 (s, 1H), 8.66 (d, J = 3.2 Hz, 1H), 8.61 (dd, J = 5.8 Hz, 3.0 Hz, 1H), 8.44 (d, J = 1.9 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H), 8.09 (dd, J = 9.1 Hz, 2.0 Hz, 1H), 7.99 (d, J = 9.1 Hz, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.56 (s, 1H), 7.51 – 7.47 (m, 2H), 7.44 (dd, J = 8.2, 4.2 Hz, 1H), 7.24 – 7.18 (m, 6H), 7.10 – 7.04 (m, 11H), 3.64 (d, J = 9.8 Hz, 1H), 3.31 (d, J = 9.8 Hz, 1H), 2.36 (d, J = 8.8 Hz, 1H), 2.32 – 2.27 (m, 4H), 1.66 (s, 3H) ppm.

13C NMR (101 MHz, CDCl3): δ = 167.2, 148.2, 145.4, 144.1, 143.9, 138.3, 137.7, 136.5, 135.0, 134.5, 132.6, 130.1, 128.7, 128.0, 127.8, 127.6, 127.0, 126.9, 121.7, 121.6, 119.8, 117.3, 116.6, 116.4, 113.7, 86.8, 62.5, 34.0, 29.4, 26.2, 25.0, 21.7 ppm.

HRMS (ESI, m/z) calculated for C49H41FN4O4S+ [M+H]+: 813.2741, found: 813.2744.

[α]D23: -14.8 (c 0.54, CHCl3).

Methyl 3-((1R,2S,3R)-2-methyl-3-(quinolin-8-ylcarbamoyl)-2-((trityloxy)methyl)cyclopropyl)-1-tosyl-1H-indole-6-carboxylate (553)

Prepared from cyclopropane 515 (0.25 g, 0.50 mmol), 553 was obtained as a beige foam (0.25 g, 0.30 mmol, 60%).

1H NMR (400 MHz, CDCl3): δ = 9.67 (s, 1H), 8.63 (s, 1H), 8.62 – 8.58 (m, 2H), 8.11 (dd, J = 8.2 Hz, 1.3 Hz, 1H), 7.81 (dd, J = 8.3 Hz, 1.0 Hz 1H), 7.65 – 7.59 (m, 3H), 7.55 (d, J = 8.3 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.41 (dd, J = 8.2, 4.2 Hz, 1H), 7.30 – 7.26 (m, 6H), 7.09 – 7.00 (m, 11H), 3.92 (s, 3H), 3.63 (d, J = 9.8 Hz, 1H), 3.38 (d, J = 9.9 Hz, 1H), 2.33 (d, J = 8.8 Hz, 1H), 2.29 (s, 3H), 2.24 (d, J = 8.8 Hz, 1H), 1.59 (s, 3H) ppm.
\( ^{13}\text{C} \text{NMR} \) (101 MHz, CDCl\(_3\)): \( \delta = 167.5, 167.4, 148.1, 144.8, 144.0, 138.3, 136.3, 136.2, 135.4, 134.6, 134.5, 129.9, 128.8, 128.2, 128.0, 127.6, 127.4, 127.0, 126.9, 126.6, 124.4, 121.6, 121.4, 119.6, 116.6, 116.2, 115.4, 86.9, 62.7, 52.3, 34.0, 29.2, 26.6, 25.3, 21.7 ppm.

HRMS (ESI, \( m/z \)) calculated for C\(_{51}\)H\(_{44}\)N\(_3\)O\(_6\)S\(_2\)\( +[M+H]^+ \): 826.2945, found: 826.2953.

\([\alpha]_D^{23}\) -9.1 (c 0.50, CHCl\(_3\)).

\((1R,2S,3R)-3-(5\text{methoxy-1-tosyl-1H-indol-3-yl})-2\text{-methyl-N-(quinolin-8-yl)-2-((trityloxy)methyl)}\text{-cyclopropane-1-carboxamide (557)}

Prepared from cyclopropane 515 (0.25 g, 0.50 mmol), 557 was obtained as a pale yellow foam (0.26 g, 0.33 mmol, 66%).

\(^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\)): \( \delta = 9.61 \text{ (s, 1H), 8.63 \text{ (dd, } J = 6.9, 2.0 \text{ Hz, 1H), 8.60 \text{ (dd, } J = 4.3, 1.6 \text{ Hz, 1H), 8.10 \text{ (d, } J = 8.3 \text{ Hz, 1H), 7.84 \text{ (d, } J = 8.9 \text{ Hz, 1H), 7.57 \text{ (d, } J = 8.0 \text{ Hz, 2H), 7.49 - 7.42 \text{ (m, 3H), 7.39 \text{ (dd, } J = 8.3, 4.2 \text{ Hz, 1H), 7.31 \text{ (d, } J = 8.9 \text{ Hz, 6H), 7.11 - 6.97 \text{ (m, 11H), 6.93 \text{ (d, } J = 2.5 \text{ Hz, 1H), 6.82 \text{ (dd, } J = 8.9, 2.5 \text{ Hz, 1H), 3.68 \text{ (s, 3H), 3.65 \text{ (d, } J = 9.9 \text{ Hz, 1H), 3.41 \text{ (d, } J = 9.8 \text{ Hz, 1H), 2.32 - 2.26 \text{ (m, 4H), 2.22 \text{ (d, } J = 8.7 \text{ Hz, 1H), 1.59 \text{ (s, 3H) ppm.}}}

\(^{13}\text{C} \text{NMR} \) (101 MHz, CDCl\(_3\)): \( \delta = 167.7, 156.5, 148.1, 144.4, 144.1, 138.4, 136.1, 135.5, 134.6, 133.6, 129.8, 129.7, 128.9, 128.1, 127.9, 127.6, 127.4, 126.9, 126.8, 126.1, 121.6, 121.3, 116.6, 116.2, 114.6, 113.6, 102.2, 86.9, 62.9, 55.6, 34.1, 29.0, 26.8, 25.4, 21.7 ppm.

HRMS (ESI, \( m/z \)) calculated for C\(_{50}\)H\(_{44}\)N\(_3\)O\(_5\)S\(_2\)\( +[M+H]^+ \): 798.2996, found: 798.3006.

\([\alpha]_D^{23}\) -20.9 (c 0.54, CHCl\(_3\)).

Methyl 3-\((1R,2S,3R)-2\text{-methyl-3-(quinolin-8-yl carbamoyl)-2-((trityloxy)methyl)cyclopropyl})\text{-1-tosyl-1H-indole-5-carboxylate (556)}

Prepared from cyclopropane 515 (0.25 g, 0.50 mmol), 556 was obtained as a beige foam (0.27 g, 0.33 mmol, 65%).

\(^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\)): \( \delta = 9.65 \text{ (s, 1H), 8.64 - 8.56 \text{ (m, 2H), 8.25 \text{ (s, 1H), 8.11 \text{ (dd, } J = 8.3, 1.7 \text{ Hz, 1H), 7.97 \text{ (d, } J = 8.7 \text{ Hz, 1H), 7.92 \text{ (dd, } J = 8.7, 1.6 \text{ Hz, 1H), 7.58 \text{ (d, } J = 8.2 \text{ Hz, 2H), 7.51 - 7.49 \text{ (m, 1H), 7.48 - 7.43 \text{ (m, 2H), 7.40 \text{ (dd, } J = 8.3, 4.2 \text{ Hz, 1H), 7.30 - 7.26 \text{ (m, 6H), 7.10 - 6.98 \text{ (m, 11H), 3.84 \text{ (s, 3H), 3.64 \text{ (d, } J = 9.8 \text{ Hz, 1H), 3.38 \text{ (d, } J = 9.8 \text{ Hz, 1H), 2.38 \text{ (d, } J = 8.7 \text{ Hz, 1H), 2.29 - 2.24 \text{ (m, 4H), 1.63 \text{ (s, 3H) ppm.}}

249
$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 167.5, 167.3, 148.1, 144.9, 144.0, 138.4, 137.6, 136.2, 135.3, 134.6, 132.5, 129.9, 128.8, 128.0, 127.6, 127.5, 127.0, 126.8, 126.2, 126.0, 125.3, 122.1, 121.6, 121.3, 116.9, 116.6, 113.4, 86.8, 62.8, 52.1, 34.2, 29.2, 26.5, 25.3, 21.7 ppm.

HRMS (ESI, m/z) calculated for C$_{51}$H$_{44}$N$_3$O$_6$S $^+ [M+H]^+$: 826.2945, found: 826.2939.

$[^{[\alpha]}]_D^{23}$: -11.2 (c 0.50, CHCl$_3$).

$(1R,2S,3R)-3$-$\text{[5-bromo-1-tosyl-1H-indol-3-yl]}$-$2$-$\text{[methyl-N-quinolin-8-yl]}$-$2$-$((trityloxy)methyl)$-$cyclopropane-1$-$carboxamide (558)

Prepared from cyclopropane 515 (0.25 g, 0.50 mmol), 558 was obtained as a beige foam (0.28 g, 0.33 mmol, 66%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.71$ (s, 1H), 8.66 – 8.61 (m, 2H), 8.14 (dd, $J = 8.3$, 1.7 Hz, 1H), 7.80 (d, $J = 8.8$ Hz, 1H), 7.65 (d, $J = 1.9$ Hz, 1H), 7.55 (d, $J = 8.4$ Hz, 2H), 7.52 – 7.45 (m, 2H), 7.44 – 7.40 (m, 2H), 7.31 (dd, $J = 8.8$, 1.9 Hz, 1H), 7.28 – 7.25 (m, 6H), 7.11 – 6.99 (m, 11H), 3.60 (d, $J = 9.9$ Hz, 1H), 3.36 (d, $J = 9.8$ Hz, 1H), 2.30 – 2.55 (m, 4H), 2.22 (d, $J = 8.8$ Hz, 1H), 1.59 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 167.5, 148.1, 144.8, 144.0, 136.4, 135.3, 134.6, 134.4, 133.7, 129.9, 128.8, 128.0, 127.7, 127.6, 127.5, 126.9, 126.9, 126.3, 122.6, 121.6, 121.4, 116.9, 116.7, 115.9, 115.1, 86.8, 62.6, 34.0, 28.6, 26.5, 25.2, 21.7 ppm.


$[^{[\alpha]}]_D^{23}$: -9.5 (c 0.62, CHCl$_3$).

**General procedure for the reductive removal of the 8-aminoquinoline amide**

To a solution of corresponding cyclopropane (1 eq.) in CH$_3$CN (0.1 M) was subsequently added DMAP (2 eq.) and Boc$_2$O (3 eq) at room temperature, and the mixture was heated at 40°C for 2 h. The solvent was evaporated, and the residue was partitioned between EtOAc (100 mL) and aqueous HCl (0.1 M HCl, 100 mL). The organic layer was washed with sat. aq. NaHCO$_3$ (50 mL) and brine (50 mL), dried over anhydrous MgSO$_4$, and evaporated to give the crude product. To a solution of the crude product in THF (0.1 M based on cyclopropane) was subsequently added MeOH (3 eq.) and LiBH$_4$ (2 M in THF, 4 eq.) at 0 °C, and the mixture was stirred at room temperature for 90 min. The solvent volume was doubled with Et$_2$O and the solution was cooled to 0 °C. Sat. aq. NH$_4$Cl (30 mL) was added dropwise followed by addition of water (30 mL). The resulting mixture was extracted with Et$_2$O, and the organic layer was washed with brine, dried over anhydrous MgSO$_4$, and...
evaporated. The residue was purified by column chromatography (PE:EA 2:1) to furnish the product alcohol.

\((1R,2S,3R)-2\text{-methyl-3-}(1\text{-tosyl-1H-indol-3-yl})-2\text{-}(\text{trityloxy)methyl}i\text{cyclopropyl})\text{methanol (568)}\)

Prepared from indole-substituted cyclopropane 520 (1.12 g, 1.56 mmol), 568 was obtained as a colourless foam (0.92 g, 1.46 mmol, 93%).

\(^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3): \delta = 7.84 \ (d, J = 8.3 \text{ Hz, 1H}), 7.65 \ (d, J = 8.1 \text{ Hz, 2H}), 7.39 \ (d, J = 7.3 \text{ Hz, 6H}), 7.30 – 7.15 \ (m, 13H), 7.12 \ (t, J = 7.5 \text{ Hz, 1H}), 6.84 \ (s, 1H), 3.66 \ (td, J = 11.2, 5.4 \text{ Hz, 1H}), 3.51 \ (d, J = 10.0 \text{ Hz, 1H}), 2.84 \ (t, J = 11.2 \text{ Hz, 1H}), 2.69 \ (d, J = 10.2 \text{ Hz, 1H}), 2.53 \ (d, J = 10.0 \text{ Hz, 1H}), 2.34 \ (s, 3H), 1.85 \ (d, J = 8.9 \text{ Hz, 1H}), 1.67 – 1.57 \ (m, 4H) \text{ ppm.}\)

\(^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3): \delta 144.9, 143.5, 135.6, 134.6, 131.9, 130.0, 128.4, 128.1, 127.4, 126.9, 124.8, 123.6, 123.1, 119.7, 117.6, 113.4, 87.3, 65.5, 60.5, 31.1, 25.6, 24.1, 23.7, 21.7 \text{ ppm.}\)

\text{HRMS (ESI, } m/z \text{) calculated for C}_{40}\text{H}_{37}\text{NNaO}_{4}\text{S}^{+}[\text{M+Na}]^{+}: 650.2336, \text{found: 650.2326}.\)

\([\alpha]_D^{23}: -35.5 \ (c \ 0.51, \text{CHCl}_3).\)

\((1R,2S,3R)-2\text{-methyl-3-}(7\text{-azaindole-1H-pyrrolo[2,3-b]pyridin-3-yl})-2\text{-}(\text{trityloxy)methyl}i\text{cyclopropyl})\text{methanol (661)}\)

Prepared from 7-azaindole-substituted cyclopropane 549 (0.82 g, 1.06 mmol), 661 was obtained as a pale green foam (0.58 g, 0.91 mmol, 86%).

\(^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3): \delta = 8.35 \ (dd, J = 4.8, 1.6 \text{ Hz, 1H}), 7.99 \ (d, J = 8.4 \text{ Hz, 2H}), 7.58 \ (dd, J = 7.8, 1.6 \text{ Hz, 1H}), 7.36 \ (d, J = 7.1 \text{ Hz, 6H}), 7.28 – 7.25 \ (m, 2H), 7.23 – 7.12 \ (m, 9H), 7.06 – 6.99 \ (m, 2H), 3.65 \ (td, J = 10.9, 5.4 \text{ Hz, 1H}), 3.45 \ (d, J = 9.9 \text{ Hz, 1H}), 2.83 \ (t, J = 11.2 \text{ Hz, 1H}), 2.68 \ (d, J = 10.0 \text{ Hz, 1H}), 2.48 \ (d, J = 9.9 \text{ Hz, 1H}), 2.38 \ (s, 3H), 1.83 \ (dd, J = 8.9, 1.7 \text{ Hz, 1H}), 1.66 \ (s, 3H), 1.64 – 1.55 \ (m, 1H) \text{ ppm.}\)

\(^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3): \delta 147.0, 145.1, 145.1, 143.4, 135.8, 129.7, 128.3, 128.1, 128.1, 127.4, 124.1, 124.0, 118.7, 114.1, 87.4, 65.6, 60.4, 31.0, 25.6, 24.1, 23.6, 21.8 \text{ ppm.}\)

\text{HRMS (ESI, } m/z \text{) calculated for C}_{39}\text{H}_{37}\text{N}_{2}\text{O}_{4}\text{S}^{+}[\text{M+H}]^{+}: 629.2469, \text{found: 629.2449}.\)

\([\alpha]_D^{23}: -39.9 \ (c \ 0.30, \text{CHCl}_3).\)
(1R,2S,3R)-3-(5-chloro-1-tosyl-1H-indol-3-yl)-2-methyl-2-((trityloxy)methyl)cyclopropyl)-methanol (665)

Prepared from 5-chloroindole-substituted cyclopropane 550 (0.75 g, 0.94 mmol), 665 was obtained as a pale green foam (0.54 g, 0.82 mmol, 88%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.76 (d, $J = 8.8$ Hz, 1H), 7.62 (d, $J = 8.2$ Hz, 2H), 7.39 (d, $J = 7.3$ Hz, 6H), 7.28 – 7.16 (m, 13H), 6.87 (s, 1H), 3.64 (td, $J = 11.1$, 5.6 Hz, 1H), 3.46 (d, $J = 9.9$ Hz, 1H), 2.87 (t, $J = 10.9$ Hz, 1H), 2.64 – 2.54 (m, 2H), 2.35 (s, 3H), 1.79 (dd, $J = 8.9$, 1.5 Hz, 1H), 1.67 – 1.57 (m, 4H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 145.2, 143.5, 135.2, 133.3, 133.0, 130.1, 129.2, 128.4, 128.1, 127.4, 126.9, 125.1, 124.9, 119.4, 117.3, 114.5, 87.3, 65.2, 60.3, 31.0, 25.6, 24.3, 23.5, 21.7 ppm.

HRMS (ESI, m/z) calculated for C$_{40}$H$_{36}$ClNNaO$_4$S$^+$ [M+Na]$^+$: 684.1946, found: 684.1946.

$[\alpha]_D^{23}$: -61.4 (c 0.65, CHCl$_3$).

((1R,2S,3R)-3-(6-fluoro-1-tosyl-1H-indol-3-yl)-2-methyl-2-((trityloxy)methyl)cyclopropyl)-methanol (669)

Prepared from 6-fluorooindole-substituted cyclopropane 552 (0.60 g, 0.76 mmol), 669 was obtained as a colourless foam (0.38 g, 0.59 mmol, 78%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.65 (d, $J = 8.4$ Hz, 2H), 7.56 (dd, $J = 9.7$, 2.3 Hz, 1H), 7.41 – 7.34 (m, 6H), 7.25 – 7.14 (m, 12H), 6.86 (td, $J = 8.9$, 2.3 Hz, 1H), 6.82 (d, $J = 1.6$ Hz, 1H), 3.63 (td, $J = 10.6$, 5.3 Hz, 1H), 3.45 (d, $J = 10.0$ Hz, 1H), 2.84 (t, $J = 11.2$ Hz, 1H), 2.65 (d, $J = 9.9$ Hz, 1H), 2.48 (d, $J = 9.9$ Hz, 1H), 2.36 (s, 3H), 1.81 (dd, $J = 8.9$, 1.7 Hz, 1H), 1.64 (s, 3H), 1.59 (td, $J = 9.3$, 5.5 Hz, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 161.0 (d, $J_{CF} = 241.8$ Hz), 145.2, 143.5, 135.3, 134.7 (d, $J_{CF} = 12.8$ Hz), 130.1, 128.4, 128.2, 128.1, 127.4, 126.9, 123.9 (d, $J_{CF} = 3.8$ Hz), 120.5 (d, $J_{CF} = 9.9$ Hz), 117.5, 111.6 (d, $J_{CF} = 24.3$ Hz), 100.8 (d, $J_{CF} = 28.4$ Hz), 87.3, 65.5, 60.4, 31.0, 25.6, 24.1, 23.6, 22.2 ppm.

HRMS (ESI, m/z) calculated for C$_{40}$H$_{36}$FNNaO$_4$S$^+$ [M+Na]$^+$: 668.2241, found: 668.2242.

$[\alpha]_D^{23}$: -52.6 (c 0.63, CHCl$_3$).
((1R,2S,3R)-3-(7-methoxy-1-tosyl-1H-indol-3-yl)-2-methyl-2-((trityloxy)methyl)cyclopropyl)-methanol (673)

Prepared from 7-methoxyindole-substituted cyclopropane 554 (0.60 g, 0.75 mmol), 673 was obtained as a colourless foam (0.45 g, 0.68 mmol, 91%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.62 (d, J = 8.1 Hz, 2H), 7.47 – 7.40 (m, 6H), 7.29 – 7.24 (m, 8H), 7.08 (d, J = 1.6 Hz, 1H), 7.04 (t, J = 7.8 Hz, 1H), 6.94 (d, J = 7.7 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H), 3.75 – 3.64 (m, 2H), 3.62 (s, 3H), 2.86 – 2.75 (m, 2H), 2.67 (d, J = 9.9 Hz, 1H), 2.41 (s, 3H), 1.89 (dd, J = 8.9, 1.6 Hz, 1H), 1.70 (s, 3H), 1.68 – 1.60 (m, 1H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): δ 147.3, 144.1, 143.5, 137.8, 134.8, 129.4, 128.4, 128.1, 127.4, 127.3, 125.9, 124.4, 124.0, 115.4, 112.3, 107.2, 87.3, 65.6, 60.5, 55.6, 31.0, 25.7, 24.0, 23.9, 21.7 ppm.

HRMS (ESI, m/z) calculated for C$_{41}$H$_{39}$NNaO$_5$S $^+ [M+Na]^+$: 680.2441, found: 680.2434.

[α]$_D^{23}$: -32.2 (c 0.52, CHCl$_3$).

**General procedure for the amide-to-olefin route**

Ley – Griffith Oxidation: To a solution of corresponding cyclopropylmethanol (1 eq.) in anhydrous DCM (0.1 M) was added NMO (1.5 eq.) and powdered MS 4Å (0.5 g/mmol). To this vigorously stirred suspension was added TPAP (0.1 eq.) in one portion and progress was monitored by TLC. After complete consumption of the starting material the reaction mixture was directly filtered through a small column with silica using PE/EA 3:1 as eluent. The solvent was removed to afford the corresponding aldehyde, which was used without further characterisation.

Wittig – Olefination: MePPh$_3$Br (2.1 eq.) was suspended in anhydrous THF (0.4 M). The suspension was cooled to -78 °C in a dry ice bath and NaHMDS (1 M in THF, 2.0 eq.) was added dropwise. The mixture was stirred for 30 min at -78 °C and for 30 min at room temperature. The reaction was cooled again to -78 °C and a solution of corresponding aldehyde (1 eq.) in anhydrous THF (0.2 M) was added dropwise. After 30 min at -78 °C the reaction was allowed to room temperature and was quenched by addition of water (20 mL) after 1 h. The phases were separated and the aqueous layer was extracted with diethyl ether (3x 20 mL). The combined organic extracts were washed with brine, dried over MgSO$_4$, filtered and concentrated in vacuo to yield the crude divinylcyclopropane.

Divinylcyclopropane – rearrangement: The crude divinylcyclopropane was dissolved in toluene (0.07 M) and was heated to 130 °C in a sealed tube. Progress was monitored by TLC, after approx.
4 h the reaction was finished. The solution was concentrated in vacuo and the residue was purified by column chromatography (PE:EA 3:1).

\( (5aR,9R) \)-9-methyl-5-tosyl-9-(trityloxy)methyl-5,5a,6,9-tetrahydrocyclohepta[\(b\)]indole (570) 

From cyclopropylmethanol 568 (0.35 g, 0.56 mmol), aldehyde was obtained as a colourless foam (0.26 g, 0.41 mmol, 74%). Continuing with aldehyde (0.20 g, 0.32 mmol), cyclohepta[\(b\)]indole 570 was obtained as a colourless foam (0.16 g, 0.26 mmol, 80% o2s).

\( ^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\)): \( \delta = 7.70 \) (d, \( J = 8.1 \text{ Hz} \), 1H), 7.43 – 7.36 (m, 6H), 7.25 – 7.16 (m, 13H), 7.00 (t, \( J = 7.5 \text{ Hz} \), 1H), 6.54 (d, \( J = 8.1 \text{ Hz} \), 2H), 5.94 – 5.83 (m, 1H), 5.64 – 5.53 (m, 2H), 4.94 (dt, \( J = 11.2, 3.0 \text{ Hz} \), 1H), 3.06 (qd, \( J = 8.1, 3.2 \text{ Hz} \), 2H), 2.71 (d, \( J = 8.4 \text{ Hz} \), 1H), 2.55 (ddt, \( J = 16.2, 11.2, 2.8 \text{ Hz} \), 1H), 2.04 (s, 3H), 1.11 (s, 3H) ppm.

\( ^{13}\text{C} \text{NMR} \) (101 MHz, CDCl\(_3\)): \( \delta 144.1, 143.7, 143.0, 139.2, 136.7, 133.4, 129.9, 129.5, 129.4, 129.1, 127.9, 127.4, 127.2, 124.4, 124.4, 123.8, 120.1, 116.7, 86.3, 71.9, 64.4, 43.6, 34.9, 27.9, 21.5 \text{ ppm}. 

HRMS (ESI, \text{m/z}) \) calculated for \( \text{C}_{41}\text{H}_{37}\text{NNaO}_3\text{S}^+ \) [M+Na]^+: 646.2386, found: 646.2377.

\[ [\alpha]_{D}^{23} \] -107.8 (c 0.25, CHCl\(_3\)).

\( (6R,9aR) \)-6-methyl-10-tosyl-6-(trityloxy)methyl-6,9,9a,10-tetrahydrocyclohepta[4,5]-pyrrolo[2,3-\(b\)]pyridine (664) 

From cyclopropylmethanol 661 (0.15 g, 0.24 mmol), aldehyde was obtained as a colourless foam (0.13 g, 0.20 mmol, 84%). Continuing with aldehyde (0.13 g, 0.20 mmol), cyclohepta[\(b\)]indole 664 was obtained as a colourless foam (0.11 g, 0.18 mmol, 91% o2s).

\( ^1\text{H} \text{NMR} \) (400 MHz, Benzene-\text{d}\(_6\)): \( \delta = 8.05 – 7.98 \) (m, 3H), 7.58 – 7.51 (m, 6H), 7.13 – 7.08 (m, 6H), 7.06 – 7.00 (m, 3H), 6.79 (dd, \( J = 7.6, 1.7 \text{ Hz} \), 1H), 6.61 – 6.53 (m, 2H), 6.25 (dd, \( J = 7.6, 5.0 \text{ Hz} \), 1H), 5.69 – 5.52 (m, 3H), 5.32 – 5.26 (m, 1H), 3.35 (ddd, \( J = 15.7, 8.5, 3.1 \text{ Hz} \), 1H), 3.21 – 3.12 (m, 2H), 2.35 (ddt, \( J = 16.1, 10.9, 2.8 \text{ Hz} \), 1H), 1.74 (s, 3H), 1.03 (s, 3H) ppm.

\( ^{13}\text{C} \text{NMR} \) (101 MHz, Benzene-\text{d}\(_6\)): \( \delta = 157.3, 148.5, 144.4, 143.3, 137.6, 137.1, 136.0, 129.3, 129.3, 128.8, 128.6, 127.5, 127.4, 126.4, 125.0, 122.6, 118.2, 86.6, 71.5, 63.5, 44.0, 34.7, 28.9, 21.5 \text{ ppm}. 

HRMS (ESI, \text{m/z}) \) calculated for \( \text{C}_{41}\text{H}_{37}\text{NNaO}_3\text{S}^+ \) [M+Na]^+: 625.2519, found: 625.2503.

\[ [\alpha]_{D}^{23} \] 74.3 (c 0.27, CHCl\(_3\)).

254
(5aR,9R)-2-chloro-9-methyl-5-tosyl-9-\{(trityloxy)methyl\}-5,5a,6,9-tetrahydrocyclohepta[b]indole (668)

From cyclopropylmethanol 665 (0.20 g, 0.30 mmol), aldehyde was obtained as a colourless foam (0.17 g, 0.26 mmol, 86%). Continuing with aldehyde (0.17 g, 0.26 mmol), cyclohepta[b]indole 668 was obtained as a colourless foam (0.16 g, 0.24 mmol, 95% o2s).

\(^1\)H NMR (400 MHz, Benzene-d\(_6\)): \(\delta = 7.81\) (dd, \(J = 8.7, 0.5\) Hz, 1H), 7.52 – 7.48 (m, 6H), 7.40 – 7.37 (m, 2H), 7.11 – 7.06 (m, 6H), 7.04 – 6.99 (m, 3H), 6.97 (dd, \(J = 8.7, 2.1\) Hz, 1H), 6.91 (dd, \(J = 2.2, 0.5\) Hz, 1H), 6.26 – 6.20 (m, 2H), 3.25 (ddd, \(J = 16.3, 8.5, 2.9\) Hz, 1H), 3.15 (d, \(J = 8.3\) Hz, 1H), 2.80 (d, \(J = 8.3\) Hz, 1H), 2.45 (ddt, \(J = 16.4, 10.9, 2.8\) Hz, 1H), 1.60 (s, 3H), 0.87 (s, 3H) ppm.

\(^1\)C NMR (101 MHz, Benzene-d\(_6\)): \(\delta = 144.4, 143.7, 142.3, 138.7, 136.6, 134.0, 132.0, 130.1, 129.7, 129.3, 128.6, 127.7, 127.5, 125.3, 124.5, 120.7, 118.1, 86.8, 72.0, 65.1, 43.8, 35.1, 27.6, 21.0 ppm.

HRMS (ESI, \(m/z\)) calculated for C\(_{41}\)H\(_{36}\)ClN\(_2\)O\(_3\)S\(^+\) [M+Na]\(^+\): 680.1997, found: 680.1994.

\([\alpha]\)\(_{D}\)\(^{-23}\): -113.1 (c 0.28, CHCl\(_3\)).

(5aR,9R)-3-fluoro-9-methyl-5-tosyl-9-\{(trityloxy)methyl\}-5,5a,6,9-tetrahydrocyclohepta[b]indole (672)

From cyclopropylmethanol 669 (0.20 g, 0.31 mmol), aldehyde was obtained as a colourless foam (0.18 g, 0.28 mmol, 91%). Continuing with aldehyde (0.18 g, 0.28 mmol), cyclohepta[b]indole 672 was obtained as a colourless foam (0.17 g, 0.27 mmol, 96% o2s).

\(^1\)H NMR (400 MHz, Benzene-d\(_6\)): \(\delta = 7.88\) (dd, \(J = 9.9, 2.4\) Hz, 1H), 7.54 – 7.49 (m, 6H), 7.41 (d, \(J = 8.4\) Hz, 2H), 7.11 – 7.05 (m, 6H), 7.04 – 6.99 (m, 3H), 6.63 (dd, \(J = 8.5, 5.5\) Hz, 1H), 6.43 (td, \(J = 8.6, 2.4\) Hz, 1H), 6.20 (d, \(J = 8.1\) Hz, 2H), 5.70 (ddd, \(J = 12.4, 8.4, 2.4\) Hz, 1H), 5.48 – 5.41 (m, 1H), 5.35 – 5.27 (m, 2H), 3.27 (ddd, \(J = 15.9, 8.4, 3.2\) Hz, 1H), 3.18 (d, \(J = 8.3\) Hz, 1H), 2.84 (d, \(J = 8.3\) Hz, 1H), 2.48 (ddt, \(J = 16.1, 11.1, 2.7\) Hz, 1H), 1.59 (s, 3H), 0.94 (s, 3H) ppm.

\(^1\)C NMR (101 MHz, Benzene-d\(_6\)): \(\delta = 164.2\) (d, \(J_{CF} = 246.2\) Hz), 145.2 (d, \(J_{CF} = 11.9\) Hz), 144.5, 143.7, 138.8, 136.6, 134.2, 129.7, 129.4, 128.6, 127.7, 127.4, 126.1 (d, \(J_{CF} = 2.6\) Hz), 124.6, 123.2 (d, \(J_{CF} = 3.0\) Hz), 121.5 (d, \(J_{CF} = 10.0\) Hz), 111.4 (d, \(J_{CF} = 23.7\) Hz), 104.6 (d, \(J_{CF} = 27.7\) Hz), 86.8, 72.2, 65.5, 43.7, 35.1, 27.8, 20.6 ppm.
HRMS (ESI, m/z) calculated for C₄₁H₃₆FNNaO₃S⁺ [M+Na]⁺: 664.2292, found: 664.2293.

[α]₀²³: -129.4 (c 0.51, CHCl₃).

(5aR,9R)-4-methoxy-9-methyl-5-tosyl-9-((trityloxy)methyl)-5,5a,6,9-tetrahydro-cyclohepta[b]indole (677)

From cyclopropylmethanol 673 (0.15 g, 0.23 mmol), aldehyde was obtained as a colourless foam (0.10 g, 0.15 mmol, 67%). Continuing with aldehyde (0.10 g, 0.15 mmol), cyclohepta[b]indole 677 was obtained as a colourless foam (97 mg, 0.15 mmol, 97% o2s).

¹H NMR (400 MHz, Benzene-d₆): δ = 7.69 – 7.65 (m, 2H), 7.64 – 7.60 (m, 6H), 7.20 (t, J = 7.7 Hz, 6H), 7.10 – 7.05 (m, 3H), 6.79 – 6.74 (m, 2H), 6.63 (d, J = 7.7 Hz, 2H), 6.45 – 6.40 (m, 1H), 5.84 (dt, J = 11.2, 3.1 Hz, 1H), 5.76 (dd, J = 2.7, 1.6 Hz, 1H), 5.60 (ddd, J = 12.4, 8.2, 2.3 Hz, 1H), 5.44 (ddd, J = 12.5, 2.8, 1.6 Hz, 1H), 3.30 (d, J = 8.4 Hz, 1H), 3.24 (s, 3H), 3.20 (d, J = 8.4 Hz, 1H), 3.02 (ddd, J = 15.7, 8.2, 3.3 Hz, 1H), 2.40 (ddt, J = 15.7, 11.2, 2.7 Hz, 1H), 1.84 (s, 3H), 1.14 (s, 3H) ppm.

¹³C NMR (101 MHz, Benzene-d₆): δ = 150.6, 144.6, 142.3, 140.3, 139.0, 136.3, 133.1, 129.4, 129.1, 128.6, 127.6, 127.4, 125.7, 124.8, 124.1, 113.6, 113.0, 87.1, 71.2, 65.3, 55.4, 43.6, 34.7, 28.7, 21.1 ppm.

HRMS (ESI, m/z) calculated for C₄₂H₃₉NNaO₄S⁺ [M+Na]⁺: 676.2492, found: 676.2487.

[α]₀²³: -33.6 (c 0.15, CHCl₃).

De-protection: Trityl ether (80 µmol, 1.0 eq.) and p-TsOH (80 µmol, 1.0 eq.) were dissolved in anhydrous DCM (1 mL) and methanol (0.5 mL). The reaction was stirred at room temperature and progress was monitored by TLC. After 2 h the reaction was quenched by addition of sat. NaHCO₃ solution (25 mL). The aqueous phase was extracted with DCM (3x 25 mL). The combined organic extracts were dried over MgSO₄, filtered off and concentrated in vacuo. If no indole aromatisation was observed, the product was purified by column chromatography (PE:EA 2:1) to obtain the product as a colourless foam.

In case of indole-aromatisation the crude product was used.

Indole aromatisation: Indoline (66 µmol, 1.0 eq.) was dissolved in anhydrous DCM (1 mL) and p-TsOH (66 µmol, 1.0 eq.) was added. The reaction was stirred overnight and was quenched by addition of sat. aq. NaHCO₃ solution (25 mL). The aqueous phase was extracted with DCM (3x
The combined organic extracts were dried over MgSO$_4$, filtered off and concentrated in vacuum. Column chromatography (PE:EA 2:1) furnished the desired cyclohepta[b]indoles.

**{(S)}-{9-methyl-5-tosyl-5,6,9,10-tetrahydrocyclohepta[b]indol-9-yl}methanol (571)**

From trityl ether 570 (50 mg, 80 µmol), cyclohepta[b]indole 571 was obtained as a colourless foam (25 mg, 66 µmol, 82%). Aromatisation already occurred during detritylation.

$^1$H NMR (400 MHz, Benzene-d$_6$): $\delta$ = 8.59 (d, $J$ = 8.3 Hz, 1H), 7.51 (d, $J$ = 8.0 Hz, 2H), 7.25 (d, $J$ = 7.7 Hz, 1H), 7.21 – 7.17 (m, 1H), 7.10 (t, $J$ = 7.5 Hz, 1H), 6.44 (d, $J$ = 8.0 Hz, 2H), 5.46 (dt, $J$ = 11.9, 5.0 Hz, 1H), 5.24 (d, $J$ = 12.2 Hz, 1H), 4.01 (d, $J$ = 4.3 Hz, 2H), 3.00 (q, $J$ = 10.3 Hz, 2H), 2.80 (d, $J$ = 14.6 Hz, 1H), 2.46 (d, $J$ = 14.6 Hz, 1H), 1.63 (s, 3H), 0.82 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, Benzene-d$_6$): $\delta$ = 144.2, 137.5, 137.0, 136.6, 136.0, 132.2, 129.7, 126.5, 124.5, 124.3, 124.0, 120.7, 118.4, 116.1, 70.4, 40.2, 30.5, 27.5, 24.2, 21.0 ppm.

HRMS (ESI, m/z) calculated for $C_{22}H_{24}NO_3S^+$ [M+H]$^+$: 382.1471, found: 382.1466.

[$\alpha$]$_D^{23}$: 11.3° (c 0.6, CHCl$_3$).

**{(6R,9aR)-6-methyl-10-tosyl-6,9,9a,10-tetrahydrocyclohepta[4,5]pyrrolo[2,3-b]pyridin-6-yl}methanol (572)**

From trityl ether 664 (82 mg, 131 µmol), cyclohepta[b]indole 572 was obtained as a colourless foam (48 mg, 126 µmol, 96%). Aromatisation was not observed.

$^1$H NMR (400 MHz, Benzene-d$_6$): $\delta$ = 8.21 – 8.14 (m, 2H), 8.03 (dd, $J$ = 5.0, 1.6 Hz, 1H), 6.79 (dd, $J$ = 7.6, 1.6 Hz, 1H), 6.72 (d, $J$ = 8.1 Hz, 2H), 6.25 (dd, $J$ = 7.6, 5.0 Hz, 1H), 5.67 – 5.56 (m, 2H), 5.48 (dd, $J$ = 2.9, 1.8 Hz, 1H), 5.06 (ddd, $J$ = 12.4, 3.0, 1.8 Hz, 1H), 3.30 (ddd, $J$ = 15.6, 8.5, 3.1 Hz, 1H), 3.24 – 3.07 (m, 2H), 2.30 (ddt, $J$ = 15.6, 11.0, 2.8 Hz, 1H), 1.75 (s, 3H), 1.09 (bs, 1H), 0.91 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, Benzene-d$_6$): $\delta$ = 157.2, 148.6, 143.6, 137.8, 137.0, 135.4, 129.4, 128.7, 127.7, 126.3, 125.5, 122.6, 118.3, 71.2, 63.6, 45.4, 34.4, 26.6, 21.1 ppm.

HRMS (ESI, m/z) calculated for $C_{21}H_{23}N_2O_3S^+$ [M+H]$^+$: 383.1424, found: 383.1414.

[$\alpha$]$_D^{23}$: 120.7 (c 0.27, CHCl$_3$).
((5αR,9R)-2-chloro-9-methyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[b]indol-9-yl)methanol (573)

From trityl ether 668 (0.11 g, 161 µmol), cyclohepta[b]indole 573 was obtained as a colourless foam (60 mg, 145 µmol, 90%). Aromatisation was not observed.

$^1$H NMR (400 MHz, Benzene-$d_6$): $\delta = 7.83$ (d, $J = 8.7$ Hz, 1H), 7.66 – 7.60 (m, 2H), 6.97 (dd, $J = 8.6$, 2.2 Hz, 1H), 6.93 (d, $J = 2.1$ Hz, 1H), 6.59 (dd, $J = 8.6$, 0.8 Hz, 2H), 5.62 (ddd, $J = 12.4$, 8.4, 2.4 Hz, 1H), 5.24 (dt, $J = 13.6$, 2.9 Hz, 2H), 4.99 (ddd, $J = 12.5$, 2.7, 1.6 Hz, 1H), 3.12 (ddd, $J = 16.1$, 8.4, 3.0 Hz, 2H), 3.01 (d, $J = 10.8$ Hz, 1H), 2.44 – 2.31 (m, 1H), 1.66 (s, 3H), 0.89 (bs, 1H), 0.77 (s, 3H).

$^{13}$C NMR (101 MHz, Benzene-$d_6$): $\delta = 144.2, 142.4, 139.5, 135.3, 134.4, 131.9, 130.2, 129.8, 129.5, 128.6, 126.7, 124.2, 120.9, 118.2, 71.2, 65.3, 45.2, 34.6, 26.6, 21.0.

HRMS (ESI, $m/z$) calculated for C$_{22}$H$_{23}$ClNO$_3$S$^+$ [M+H]$^+$: 416.1082, found: 416.1082.

$[\alpha]_D^{23}$: -192.9 (c 0.33, CHCl$_3$).

((5αR,9R)-3-fluoro-9-methyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[b]indol-9-yl)methanol (574)

From trityl ether 672 (0.13 g, 198 µmol), cyclohepta[b]indole 574 was obtained as a colourless foam (68 mg, 170 µmol, 86%). Aromatisation was not observed.

$^1$H NMR (400 MHz, Benzene-$d_6$): $\delta = 7.90$ (dd, $J = 9.9$, 2.4 Hz, 1H), 7.68 – 7.62 (m, 2H), 6.63 (dd, $J = 8.5$, 5.5 Hz, 1H), 6.57 – 6.50 (m, 2H), 6.43 (td, $J = 8.6$, 2.4 Hz, 1H), 5.63 (ddd, $J = 12.4$, 8.4, 2.4 Hz, 1H), 5.33 – 5.26 (m, 2H), 5.02 (ddd, $J = 12.4$, 3.2, 1.5 Hz, 1H), 3.20 – 3.09 (m, 2H), 3.03 (d, $J = 10.7$ Hz, 1H), 2.46 – 2.35 (m, 1H), 1.63 (s, 3H), 0.90 (bs, 1H), 0.82 (s, 3H) ppm.

$^{13}$C NMR (101 MHz, Benzene-$d_6$): $\delta = 164.2$ (d, $J_{CF} = 246.7$ Hz), 145.3 (d, $J_{CF} = 11.7$ Hz), 144.2, 139.6, 135.5, 134.6, 129.8, 126.6, 126.0 (d, $J_{CF} = 2.4$ Hz), 122.1 (d, $J_{CF} = 2.7$ Hz), 121.7 (d, $J_{CF} = 9.9$ Hz), 111.5 (d, $J_{CF} = 23.4$ Hz), 104.7 (d, $J_{CF} = 28.5$ Hz), 71.3, 65.6, 45.1, 34.6, 26.8, 21.0 ppm.

HRMS (ESI, $m/z$) calculated for C$_{22}$H$_{23}$FNO$_3$S$^+$ [M+H]$^+$: 400.1377, found: 400.1376.

$[\alpha]_D^{23}$: -216.3° (c 0.33, CHCl$_3$).
(S)-(4-methoxy-9-methyl-5-tosyl-5,6,9,10-tetrahydrocyclohepta[\(b\)]indol-9-yl)methanol (575)

From trityl ether 677 (64 mg, 98 \(\mu\)mol), deprotected indoline was obtained as a colourless foam (35 mg, 85 \(\mu\)mol, 87%). Continuing with indoline (23 mg, 56 \(\mu\)mol), cyclohepta[\(b\)]indole 575 was obtained as a colourless foam (21 mg, 51 \(\mu\)mol, 91%). Aromatisation already occurred during detritylation.

\(^1\text{H NMR}\) (400 MHz, Benzene-\(d_6\)): \(\delta = 7.75 - 7.70\) (m, 2H), 7.08 – 6.98 (m, 2H), 6.66 (d, \(J = 8.5\) Hz, 2H), 6.48 (dd, \(J = 7.8, 1.2\) Hz, 1H), 5.56 (dt, \(J = 12.1, 5.1\) Hz, 1H), 5.24 (dt, \(J = 12.2, 2.0\) Hz, 1H), 4.07 (dd, \(J = 5.2, 1.1\) Hz, 2H), 3.38 (s, 3H), 3.11 (d, \(J = 10.4\) Hz, 1H), 3.11 (d, \(J = 10.4\) Hz, 1H), 3.03 (d, \(J = 10.4\) Hz, 1H), 2.90 (d, \(J = 14.5\) Hz, 1H), 2.57 (dd, \(J = 14.5, 0.9\) Hz, 1H), 1.81 (s, 3H), 0.90 (s, 3H) ppm.

\(^{13}\text{C NMR}\) (101 MHz, Benzene-\(d_6\)): \(\delta = 149.4, 143.2, 140.1, 139.1, 136.8, 135.5, 129.2, 128.6, 126.9, 125.0, 121.2, 111.4, 108.4, 70.4, 55.5, 40.0, 30.5, 28.6, 24.2, 21.1\) ppm.

HRMS (ESI, \(m/z\)) calculated for C\(_{23}\)H\(_{25}\)NNaO\(_4\)S\(^+\) [M+Na\(^+\)]: 434.1397, found: 434.1392.

\([\alpha]_D^{23}\): -21.4 (c 0.14, CHCl\(_3\)).

General procedure for the alcohol-to-olefin route

**Pivaloyl protection:** Corresponding alcohol (0.62 mmol, 1 eq.) and DMAP (0.62 mmol, 1 eq.) were dissolved in anhydrous DCM (2.5 ml), and Et\(_3\)N (3.10 mmol, 5 eq.) was added in one portion followed by the dropwise addition of PivCl (2.48 mmol, 4 eq.). The reaction mixture was stirred at room temperature overnight. The mixture was diluted with DCM (100 ml) and was washed with 0.1 M HCl (50 ml), sat. NaHCO\(_3\) and brine, dried over anhydrous MgSO\(_4\), and the solvent was removed \textit{in vacuo}. The crude product was purified by column chromatography (PE:EA 5:1) to yield the desired pivaloate ester.

**Trityl deprotection:** To a solution of trityl ether (0.21 mmol, 1 eq) in anhydrous DCM (2 ml) and methanol (1 ml) was added \(p\)-TsOH (0.5 eq.) at room temperature. The reaction mixture was stirred until completion (4 – 10 h, completion monitored by TLC) before it was diluted with DCM (50ml) and quenched by the addition of sat. aq. NaHCO\(_3\). The layers were separated and the aqueous layer was extracted twice with DCM (2x20 ml). The solvent was removed under reduced pressure and the crude oil was purified by column chromatography (PE:EA 2:1) to obtain the desired alcohol.
(1R,2S,3R)-2-methyl-3-(1-tosyl-1H-indol-3-yl)-2-((trityloxy)methyl)cyclopropyl)methyl pivalate (660)

Prepared from cyclopropylmethanol 568 (0.50 g, 0.80 mmol), pivalate 660 was obtained as a colourless foam (0.51 g, 0.71 mmol, 89%).

\[
\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 7.88 \text{ (dt, } J = 8.3, 0.9 \text{ Hz, 1H), 7.63 – 7.59 (m, 2H), 7.43 (dt, } J = 7.8, 1.1 \text{ Hz, 1H}, 7.32 – 7.28 (m, 6H), 7.25 – 7.22 (m, 2H), 7.21 – 7.12 (m, 11H), 7.07 (ddd, } J = 8.0, 7.2, 1.0 \text{ Hz, 1H}, 4.21 \text{ (dd, } J = 12.0, 6.3 \text{ Hz, 1H), 3.60 (dd, } J = 12.0, 9.6 \text{ Hz, 1H), 2.97 (d, } J = 9.8 \text{ Hz, 1H), 2.86 (d, } J = 9.8 \text{ Hz, 1H), 2.34 (s, 3H), 1.89 (dd, } J = 8.6, 1.6 \text{ Hz, 1H), 1.53 – 1.46 (m, 4H), 1.16 (s, 9H) ppm.}
\]

\[
\text{C NMR (101 MHz, CDCl}_3\text{): } \delta = 178.5, 144.7, 144.0, 135.6, 134.9, 132.2, 129.9, 128.7, 127.8, 127.0, 126.9, 124.8, 124.2, 123.1, 120.4, 117.6, 113.4, 86.7, 64.2, 62.4, 38.8, 27.3, 26.8, 25.2, 24.6, 23.6, 21.7 \text{ ppm.}
\]

HRMS (ESI, m/z) calculated for C_{45}H_{45}NNaO_5S^+ [M+Na]^+: 734.2911, found: 734.2897.

\[\alpha\]_D^{23} = -15.4 (c 0.10, CHCl_3).

(1R,2S,3R)-2-(hydroxymethyl)-2-methyl-3-(1-tosyl-1H-indol-3-yl)cyclopropyl)methyl pivalate (576)

Prepared from trityl ether 660 (0.30 g, 0.42 mmol), alcohol 576 was obtained as a colourless foam (0.16 g, 0.34 mmol, 81%).

\[
\text{H NMR (400 MHz, CDCl}_3\text{): } \delta = 7.97 \text{ (d, } J = 8.3 \text{ Hz, 1H), 7.72 (d, } J = 8.2 \text{ Hz, 2H), 7.45 (d, } J = 7.7 \text{ Hz, 1H), 7.43 (d, } J = 1.7 \text{ Hz, 1H), 7.32 (t, } J = 7.8 \text{ Hz, 1H), 7.24 – 7.19 (m, 3H), 4.31 (dd, } J = 12.0, 7.3 \text{ Hz, 1H), 4.00 (dd, } J = 12.0, 8.6 \text{ Hz, 1H), 3.61 (dd, } J = 11.9, 5.2 \text{ Hz, 1H), 3.42 (d, } J = 11.7 \text{ Hz, 1H), 2.33 (s, 3H), 1.97 (dd, } J = 8.8 \text{ Hz, 1.7 Hz, 1H), 1.64 (bs, 1H), 1.52 (q, } J = 8.2 \text{ Hz, 1H), 1.43 (s, 3H), 1.24 (s, 9H) ppm.}
\]

\[
\text{C NMR (101 MHz, CDCl}_3\text{): } \delta = 178.6, 145.1, 145.3, 135.3, 132.2, 130.0, 126.9, 125.2, 124.7, 123.6, 119.8, 117.7, 114.0, 63.9, 62.7, 38.9, 27.3, 26.7, 26.3, 24.0, 23.2, 21.7 \text{ ppm.}
\]

HRMS (ESI, m/z) calculated for C_{26}H_{31}NNaO_5S^+ [M+Na]^+: 492.1815, found: 492.1799.

\[\alpha\]_D^{23} = 7.2 (c 0.54, CHCl_3).
(1R,2S,3R)-2-methyl-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-2-((trityloxy)methyl)cyclopropyl)-methyl pivalate (662)

Prepared from cyclopropylmethanol 661 (0.54 g, 0.86 mmol), pivalate 662 was obtained as a colourless foam (0.50 g, 0.71 mmol, 82%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.34$ (d, $J = 4.2$ Hz, 1H), 7.98 (d, $J = 8.1$ Hz, 2H), 7.75 (d, $J = 7.7$ Hz, 1H), 7.38 (d, $J = 1.6$ Hz, 1H), 7.27 (s, 1H), 7.26 – 7.22 (m, 7H), 7.17 – 7.08 (m, 9H), 6.93 (dd, $J = 7.8$, 4.4 Hz, 1H), 4.27 (dd, $J = 12.0$, 6.1 Hz, 1H), 3.53 (dd, $J = 12.0$, 9.9 Hz, 1H), 2.83 (q, $J = 9.7$ Hz, 2H), 2.39 (s, 3H), 2.27 (s, 3H), 1.87 (dd, $J = 8.6$, 1.6 Hz, 1H), 1.55 (s, 3H), 1.50 (ddd, $J = 9.8$, 8.5, 6.0 Hz, 1H), 1.20 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 178.5$, 147.3, 145.0, 145.0, 143.8, 135.9, 129.7, 129.0, 128.6, 128.2, 127.8, 127.1, 124.5, 124.4, 118.5, 114.0, 86.7, 64.0, 62.1, 38.8, 27.3, 26.8, 25.0, 24.6, 23.5, 21.8 ppm.

HRMS (ESI, $m/z$) calculated for C$_{44}$H$_{45}$N$_2$O$_5$S$^+ [M+H]$^+$: 713.3044, found: 713.3023.

$[\alpha]_D^{23}$: -29.0 (c 0.27, CHCl$_3$).

(1R,2S,3R)-2-(hydroxymethyl)-2-methyl-3-(1-tosyl-1H-pyrrolo[2,3-b]pyridin-3-yl)cyclopropyl)-methyl pivalate (663)

Prepared from trityl ether 662 (0.22 g, 0.31 mmol), alcohol 663 was obtained as a colourless foam (0.12 g, 0.26 mmol, 82%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.43$ (d, $J = 4.7$ Hz, 1H), 8.04 (d, $J = 8.1$ Hz, 2H), 7.80 (d, $J = 7.8$ Hz, 1H), 7.62 (s, 1H), 7.29 – 7.25 (m, 2H), 7.17 (dd, $J = 7.9$, 4.8 Hz, 1H), 4.30 (dd, $J = 12.0$, 7.3 Hz, 1H), 4.02 (dd, $J = 12.0$, 8.5 Hz, 1H), 3.65 (d, $J = 11.6$ Hz, 1H), 3.53 (d, $J = 11.6$ Hz, 1H), 2.37 (s, 3H), 1.97 (d, $J = 8.7$ Hz, 1H), 1.68 (bs, 1H), 1.53 (q, $J = 8.2$ Hz, 1H), 1.42 (s, 3H), 1.23 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 178.6$, 147.4, 145.4, 145.3, 135.6, 129.8, 128.3, 128.3, 128.1, 124.9, 124.3, 118.9, 113.9, 63.8, 62.5, 38.9, 27.3, 26.7, 26.3, 24.0, 23.1, 21.8 ppm.

HRMS (ESI, $m/z$) calculated for C$_{25}$H$_{31}$N$_2$O$_5$S$^+ [M+H]$^+$: 471.1948, found: 471.1936.

$[\alpha]_D^{23}$: 5.0 (c 0.11, CHCl$_3$).
**((1R,2S,3R)-3-(5-chloro-1-tosyl-1H-indol-3-yl)-2-methyl-2-((trityloxy)methyl)cyclopropyl)methyl pivalate (666)**

Prepared from cyclopropylmethanol 665 (0.35 g, 0.53 mmol), pivalate 666 was obtained as a colourless foam (0.34 g, 0.46 mmol, 87%).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.86 (d, $J = 8.4$ Hz, 1H), 7.63 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 2.0$ Hz, 1H), 7.38 – 7.35 (m, 6H), 7.32 – 7.30 (m, 2H), 7.28 – 7.20 (m, 11H), 4.29 (dd, $J = 12.0$, 6.1 Hz, 1H), 3.62 (dd, $J = 12.0$, 9.7 Hz, 1H), 2.99 (s, 2H), 2.40 (s, 3H), 1.90 (dd, $J = 8.6$, 1.6 Hz, 1H), 1.57 – 1.52 (m, 4H), 1.19 (s, 9H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 178.4, 145.1, 143.9, 135.2, 133.6, 133.3, 130.0, 129.1, 128.7, 127.9, 127.1, 126.9, 125.5, 125.1, 120.0, 117.3, 114.6, 86.7, 63.9, 62.1, 38.8, 27.3, 26.9, 26.7, 25.1, 24.8, 23.4, 21.7 ppm.

HRMS (ESI, m/z) calculated for C$_{45}$H$_{44}$ClNNaO$_5$S$^+$ [M+Na$^+$]: 768.2521, found: 768.2521.

[$\alpha$]$^D_{23}$: -34.6 (c 0.56, CHCl$_3$).

$((1R,2S,3R)-3-(5-chloro-1-tosyl-1H-indol-3-yl)-2-(hydroxymethyl)-2-methylcyclopropyl)methyl pivalate (667)$

Prepared from trityl ether 666 (0.15 g, 0.20 mmol), alcohol 667 was obtained as a colourless foam (90 mg, 0.18 mmol, 89%).

$^1$H NMR (600 MHz, CDCl$_3$): $\delta$ = 7.89 (d, $J = 8.8$ Hz, 1H), 7.69 (d, $J = 8.4$ Hz, 2H), 7.48 (d, $J = 1.6$ Hz, 1H), 7.41 (d, $J = 2.0$ Hz, 1H), 7.28 – 7.26 (m, 1H), 7.23 (d, $J = 8.1$ Hz, 2H), 4.19 (dd, $J = 12.0$, 7.5 Hz, 1H), 4.00 (dd, $J = 12.0$, 8.2 Hz, 1H), 3.62 (d, $J = 11.6$ Hz, 1H), 3.44 (d, $J = 11.6$ Hz, 1H), 2.35 (s, 3H), 1.92 (dd, $J = 8.7$, 1.6 Hz, 1H), 1.67 (bs, 1H), 1.52 (q, $J = 8.2$ Hz, 1H), 1.42 (s, 3H), 1.22 (s, 9H) ppm.

$^{13}$C NMR (151 MHz, CDCl$_3$): $\delta$ = 178.6, 145.4, 134.9, 133.6, 133.3, 130.2, 129.5, 126.8, 126.2, 125.4, 119.5, 117.2, 115.0, 63.8, 62.4, 38.9, 27.3, 26.6, 26.2, 24.0, 23.0, 21.7 ppm.

HRMS (ESI, m/z) calculated for C$_{26}$H$_{30}$ClNNaO$_5$S$^+$ [M+Na$^+$]: 526.1425, found: 526.1421.

[$\alpha$]$^D_{23}$: 17.7 (c 0.26, CHCl$_3$).
((1R,2S,3R)-3-(6-fluoro-1H-indol-3-yl)-2-methyl-2-((trityloxy)methyl)cyclopropyl)methyl pivalate (670)

Prepared from cyclopropylmethanol 669 (0.34 g, 0.53 mmol), pivalate 670 was obtained as a colourless foam (0.38 g, 0.52 mmol, 97%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.61$ (dd, $J = 9.0$, 2.1 Hz, 3H), 7.32 – 7.27 (m, 7H), 7.22 – 7.18 (m, 7H), 7.18 – 7.13 (m, 5H), 6.80 (td, $J = 9.0$, 2.3 Hz, 1H), 4.22 (dd, $J = 11.9$, 6.2 Hz, 1H), 3.57 (dd, $J = 12.0$, 9.7 Hz, 1H), 2.94 – 2.84 (m, 2H), 2.36 (s, 3H), 1.86 (dd, $J = 8.6$, 1.6 Hz, 1H), 1.52 (s, 4H), 1.17 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 178.4$, 161.1 (d, $J_{CF} = 241.4$ Hz), 145.1, 143.9, 135.3, 135.0 (d, $J_{CF} = 12.6$ Hz), 130.08, 128.7, 128.1, 127.8, 127.1, 126.9, 124.4 (d, $J_{CF} = 3.8$ Hz), 121.3 (d, $J_{CF} = 9.7$ Hz), 117.4, 111.4 (d, $J_{CF} = 24.1$ Hz), 100.8 (d, $J_{CF} = 28.5$ Hz), 86.7, 64.1, 62.2, 38.8, 27.3, 26.8, 25.2, 23.5, 21.7 ppm.

HRMS (ESI, $m/z$) calculated for C$_{45}$H$_{44}$FNNaO$_5$S$^+$ [M+Na$^+$]: 752.2816, found: 752.2812.

$[\alpha]_D^{23}$: -23.4 (c 0.54, CHCl$_3$).

((1R,2S,3R)-3-(6-fluoro-1H-indol-3-yl)-2-(hydroxymethyl)-2-methylcyclopropyl)methyl pivalate (671)

Prepared from trityl ether 670 (0.30 g, 0.41 mmol), alcohol 671 was obtained as a colourless foam (0.15 g, 0.31 mmol, 76%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.73$ – 7.67 (m, 3H), 7.41 (d, $J = 1.7$ Hz, 1H), 7.38 (dd, $J = 8.6$, 5.2 Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 2H), 7.02 – 6.95 (m, 1H), 4.25 (dd, $J = 12.0$, 7.4 Hz, 1H), 3.99 (dd, $J = 12.0$, 8.5 Hz, 1H), 3.59 (d, $J = 11.7$ Hz, 1H), 3.42 (d, $J = 11.7$ Hz, 1H), 2.35 (s, 3H), 1.94 (dd, $J = 8.8$, 1.7 Hz, 1H), 1.66 (bs, 1H), 1.55 – 1.48 (m, 1H), 1.41 (s, 3H), 1.23 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 178.6$, 161.3 (d, $J_{CF} = 242.2$ Hz), 145.4, 135.4 (d, $J_{CF} = 12.7$ Hz), 135.0, 130.2, 128.4, 126.9, 125.0 (d, $J_{CF} = 3.8$ Hz), 120.6 (d, $J_{CF} = 9.7$ Hz), 117.5, 112.0 (d, $J_{CF} = 24.8$ Hz), 101.4 (d, $J_{CF} = 27.7$ Hz), 63.8, 62.5, 38.9, 27.2, 26.7, 26.3, 24.0, 23.1, 21.7 ppm.

HRMS (ESI, $m/z$) calculated for C$_{26}$H$_{30}$FNNaO$_5$S$^+$ [M+Na$^+$]: 510.1721, found: 510.1714.

$[\alpha]_D^{23}$: 7.1 (c 0.27, CHCl$_3$).
((1R,2S,3R)-3-(7-methoxy-1-tosyl-1H-indol-3-yl)-2-methyl-2-((trityloxy)methyl)cyclopropyl)methyl pivalate (674)

Prepared from cyclopropylmethanol 673 (0.37 g, 0.57 mmol), pivalate 674 was obtained as a colourless foam (0.34 g, 0.46 mmol, 80%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.64 (d, $J$ = 8.0 Hz, 2H), 7.50 (d, $J$ = 1.5 Hz, 1H), 7.35 – 7.31 (m, 6H), 7.25 (d, $J$ = 8.1 Hz, 2H), 7.22 – 7.13 (m, 9H), 7.10 (d, $J$ = 7.7 Hz, 1H), 6.99 (t, $J$ = 7.8 Hz, 1H), 6.63 (d, $J$ = 7.8 Hz, 1H), 4.28 (dd, $J$ = 11.9, 6.2 Hz, 1H), 3.69 – 3.60 (m, 4H), 3.11 (d, $J$ = 9.8 Hz, 1H), 2.84 (d, $J$ = 9.8 Hz, 1H), 2.41 (s, 3H), 1.93 (dd, $J$ = 8.6, 1.5 Hz, 1H), 1.59 – 1.49 (m, 4H), 1.19 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 178.6, 147.3, 144.0, 137.7, 135.1, 129.4, 128.8, 128.1, 127.8, 127.4, 127.0, 126.6, 124.6, 123.8, 115.2, 113.2, 107.3, 86.6, 64.1, 62.5, 55.7, 38.8, 27.3, 26.7, 25.1, 24.5, 23.7, 21.8 ppm.

HRMS (ESI, m/z) calculated for C$_{46}$H$_{47}$NNaO$_6$S$^+$ [M+Na$^+$]: 764.3016, found: 764.3009.

$[\alpha]_D^{23}$: -30.8 (c 0.33, CHCl$_3$).

((1R,2S,3R)-2-(hydroxymethyl)-3-(7-methoxy-1-tosyl-1H-indol-3-yl)-2-methylcyclopropyl)methyl pivalate (675)

Prepared from trityl ether 674 (0.25 g, 0.34 mmol), alcohol 675 was obtained as a colourless foam (0.16 g, 0.32 mmol, 93%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 7.76 – 7.65 (m, 3H), 7.26 (d, $J$ = 8.1 Hz, 2H), 7.18 – 7.06 (m, 2H), 6.70 (dd, $J$ = 7.6, 1.2 Hz, 1H), 4.45 (dd, $J$ = 11.9, 7.1 Hz, 1H), 4.11 (dd, $J$ = 11.9, 8.7 Hz, 1H), 3.72 (d, $J$ = 13.6 Hz, 1H), 3.69 (s, 3H), 3.57 (d, $J$ = 11.4 Hz, 1H), 2.39 (s, 3H), 2.05 – 1.97 (m, 1H), 1.76 (bs, 1H), 1.59 – 1.51 (m, 1H), 1.45 (s, 3H), 1.24 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ = 178.7, 147.6, 144.3, 137.4, 135.0, 129.5, 127.5, 126.9, 124.8, 124.3, 115.2, 112.3, 107.5, 64.0, 62.8, 55.7, 38.9, 27.3, 26.7, 26.3, 24.0, 23.4, 21.7 ppm.

HRMS (ESI, m/z) calculated for C$_{27}$H$_{33}$NNaO$_6$S$^+$ [M+Na$^+$]: 522.1921, found: 522.1909.

$[\alpha]_D^{23}$: -7.6 (c 0.33, CHCl$_3$).
Oxidation: Corresponding alcohol (1.0 eq.) was dissolved in anhydrous DCM (0.1 M). NMO (1.5 eq.), powdered MS 4Å (500 mg/mmol) and TPAP (0.1 eq.) were added and the mixture was stirred at room temperature until completion (2 – 4 h). The crude product was directly filtered through a small column with silica using PE:EA 3:1 as eluent to yield the aldehyde.

Wittig – olefination: Methyltriphenylphosphonium bromide (2.1 eq.) was suspended in anhydrous THF (0.4 M). The mixture was cooled to -78 °C in an acetone – dry ice bath and NaHMDS (1 M in THF, 2 eq.) was added dropwise. After 30 min at -78 °C the mixture was stirred 30 min at room temperature. The yellow ylide solution was recooled to -78 °C and a solution of corresponding aldehyde (1.0 eq.) in anhydrous THF (0.2 M) was added dropwise. After 30 min at -78 °C the reaction mixture was stirred 30 min at room temperature. Water (20 mL) was added and the aqueous phase was extracted with diethyl ether (3x 20 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered off and concentrated in vacuo. The crude divinylcyclopropane was directly used in the following step.

Divinylcyclopropane – rearrangement: Crude divinylcyclopropane was dissolved in toluene (0.07 M) and was heated to 130 °C in a sealed tube. When the reaction was finished (3 – 5 h) the solvent was removed in vacuo and the product was purified by column chromatography (PE:EA 5:1) to obtain the desired cyclohepta[b]indoles as a colourless oil.

((5aR,9R)-8-methyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[b]indol-9-yl)methyl pivalate (578)

Prepared from alcohol 576 (0.23 g, 0.49 mmol), cyclohepta[b]indole 578 was obtained as a colourless oil (0.16 g, 0.35 mmol, 72% o3s)

$^1$H NMR (600 MHz, Benzene-d$_6$): $\delta$ = 8.04 (d, $J = 8.2$ Hz, 1H), 7.71 – 7.65 (m, 2H), 7.01 – 6.95 (m, 2H), 6.74 (td, $J = 7.5$, 1.0 Hz, 1H), 6.66 (d, $J = 7.8$ Hz, 2H), 5.78 (dd, $J = 8.1$, 2.7 Hz, 1H), 5.28 – 5.21 (m, 2H), 4.18 (dd, $J = 10.7$, 8.7 Hz, 1H), 4.06 (dd, $J = 10.7$, 5.6 Hz, 1H), 3.11 (ddd, $J = 16.8$, 7.4, 3.7 Hz, 1H), 2.79 – 2.71 (m, 1H), 2.37 (ddq, $J = 16.5$, 11.8, 2.3 Hz, 1H), 1.75 (s, 3H), 1.58 (s, 3H), 1.05 (s, 9H) ppm.

$^{13}$C NMR (151 MHz, Benzene-d$_6$): $\delta$ = 177.4, 144.2, 143.8, 141.3, 135.1, 133.2, 129.9, 129.9, 129.6, 128.6, 127.6, 124.5, 124.2, 120.4, 117.2, 117.2, 66.3, 64.4, 43.6, 38.7, 35.1, 27.3, 27.2, 21.1 ppm.

HRMS (ESI, m/z) calculated for C$_{27}$H$_{31}$NNaO$_4$S$^+$ [M+Na$^+$]: 488.1866, found: 488.1860.

$[\alpha]_D^{23}$: 110.3 (c 0.28, CHCl$_3$).
(6R,9aR)-7-methyl-10-tosyl-6,9,9a,10-tetrahydrocyclohepta[4,5]pyrrolo[2,3-b]pyridin-6-yl)methyl pivalate (580)

Prepared from alcohol 663 (0.11 g, 0.23 mmol), cyclohepta[b]indole 580 was obtained as a colourless oil (68 mg, 0.15 mmol, 63% o3s).

$^1$H NMR (400 MHz, Benzene-d$_6$): δ = 8.17 (d, J = 4.3 Hz, 1H), 7.95 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 7.3 Hz, 1H), 7.27 – 7.23 (m, 2H), 6.85 (dd, J = 7.6, 4.0 Hz, 1H), 6.17 (dd, J = 8.0, 2.7 Hz, 1H), 5.62 (d, J = 7.4 Hz, 1H), 5.37 (dt, J = 11.4, 3.1 Hz, 1H), 4.35 – 4.27 (m, 1H), 4.23 (dd, J = 10.8, 4.8 Hz, 1H), 3.17 – 2.99 (m, 2H), 2.46 – 2.35 (m, 4H), 1.84 (s, 3H), 1.16 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, Benzene-d$_6$): δ = 178.5, 156.5, 148.9, 144.2, 138.2, 136.5, 133.2, 129.6, 128.1, 128.1, 123.7, 122.1, 120.0, 118.7, 66.0, 63.0, 43.8, 38.9, 34.6, 27.3, 27.0, 21.7 ppm.

HRMS (ESI, m/z) calculated for C$_{26}$H$_{31}$N$_2$O$_4$S$^+$ [M+H]$^+$: 467.1999, found: 467.1987.

$\alpha$D$_{23}$: 83.2 (c 0.28, CHCl$_3$).

((5aR,9R)-2-chloro-8-methyl-5-tosyl-5a,6,9-tetrahydrocyclohepta[b]indol-9-yl)methyl pivalate (581)

Prepared from alcohol 667 (0.15 g, 0.30 mmol), aldehyde was obtained as a colourless foam (0.14 g, 0.27 mmol, 91%). Continuing with aldehyde (0.13 g, 0.26 mmol), cyclohepta[b]indole 581 was obtained as a colourless oil (0.11 g, 0.22 mmol, 83% o2s).

$^1$H NMR (400 MHz, Benzene-d$_6$): δ = 7.79 (d, J = 8.7 Hz, 1H), 7.65 – 7.60 (m, 2H), 6.99 (d, J = 2.1 Hz, 1H), 6.94 (dd, J = 8.6, 2.2 Hz, 1H), 6.71 – 6.66 (m, 2H), 5.57 (dd, J = 8.1, 2.7 Hz, 1H), 5.24 (d, J = 7.5 Hz, 1H), 5.17 (ddd, J = 11.8, 3.8, 2.7 Hz, 1H), 4.14 (dd, J = 10.7, 8.5 Hz, 1H), 3.99 (dd, J = 10.7, 5.5 Hz, 1H), 3.05 (ddd, J = 16.7, 7.3, 3.8 Hz, 1H), 2.69 (q, J = 7.4 Hz, 1H), 2.31 (ddq, J = 16.6, 11.8, 2.4 Hz, 1H), 1.77 (s, 3H), 1.56 (s, 3H), 1.02 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, Benzene-d$_6$): δ = 177.5, 144.1, 142.6, 140.0, 134.7, 133.2, 131.3, 130.3, 130.0, 129.7, 128.6, 124.0, 120.6, 119.0, 118.2, 66.1, 64.7, 43.5, 38.7, 35.0, 27.2, 21.1 ppm.

HRMS (ESI, m/z) calculated for C$_{27}$H$_{30}$ClN$_2$O$_4$S$^+$ [M+Na]$^+$: 522.1476, found: 522.1473.

$\alpha$D$_{23}$: 108.4 (c 0.50, CHCl$_3$).
(5αR,9R)-3-fluoro-8-methyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[b]indol-9-yl)methyl pivalate (582)

Prepared from alcohol 671 (0.15 g, 0.31 mmol) cyclohepta[b]indole 582 was obtained as a colourless oil (93 mg, 0.19 mmol, 62% o3s).

$^1$H NMR (400 MHz, Benzene-d$_6$): δ = 7.84 (dd, $J = 9.9$, 2.4 Hz, 1H), 7.67 – 7.62 (m, 2H), 6.70 (dd, $J = 8.5$, 5.6 Hz, 1H), 6.66 (d, $J = 6.2$ Hz, 2H), 6.42 (td, $J = 8.6$, 2.4 Hz, 1H), 5.64 (dd, $J = 8.1$, 2.7 Hz, 1H), 5.29 – 5.20 (m, 2H), 4.19 (dd, $J = 10.7$, 8.7 Hz, 1H), 4.02 (dd, $J = 10.7$, 5.5 Hz, 1H), 3.12 – 3.02 (m, 1H), 2.76 (q, $J = 7.3$, 6.8 Hz, 1H), 2.34 (dq, $J = 16.5$, 11.8, 2.3 Hz, 1H), 1.76 (s, 3H), 1.58 (s, 3H), 1.04 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, Benzene-d$_6$): δ = 177.5, 164.3 (d, $J_{CF} = 246.4$ Hz), 145.4 (d, $J_{CF} = 12.0$ Hz), 144.1, 140.2, 134.8, 133.3, 130.1, 128.6, 127.5, 125.5 (d, $J_{CF} = 2.7$ Hz), 124.0, 121.5 (d, $J_{CF} = 10.0$ Hz), 116.7 (d, $J_{CF} = 2.6$ Hz), 111.6 (d, $J_{CF} = 23.6$ Hz), 104.6 (d, $J_{CF} = 28.7$ Hz), 66.2, 65.1, 43.5, 38.7, 35.1, 27.2, 21.1 ppm.

HRMS (ESI, m/z) calculated for C$_{27}$H$_{30}$FNNaO$_4$S$^+$ [M+Na]$^+$: 506.1772, found: 506.1769.

[α]$^23$: 162.5 (c 0.54, CHCl$_3$).

((5αR,9R)-4-methoxy-8-methyl-5-tosyl-5,5a,6,9-tetrahydrocyclohepta[b]indol-9-yl)methyl pivalate (676)

Prepared from alcohol 675 (0.24 g, 0.49 mmol), cyclohepta[b]indole 676 was obtained as a colourless oil (0.16 g, 0.35 mmol, 72% o3s).

$^1$H NMR (400 MHz, Benzene-d$_6$): δ = 7.83 – 7.77 (m, 2H), 6.85 – 6.77 (m, 4H), 6.43 (dd, $J = 7.1$, 2.0 Hz, 1H), 5.97 – 5.88 (m, 2H), 5.31 (ddt, $J = 7.6$, 2.5, 1.2 Hz, 1H), 4.23 (dd, $J = 10.9$, 7.0 Hz, 1H), 4.14 (dd, $J = 10.9$, 4.9 Hz, 1H), 3.23 (s, 3H), 2.98 – 2.87 (m, 1H), 2.76 (q, $J = 6.6$ Hz, 1H), 2.35 (dq, $J = 16.3$, 11.6, 2.4 Hz, 1H), 1.92 (s, 3H), 1.63 (s, 3H), 1.20 (s, 9H) ppm.

$^{13}$C NMR (101 MHz, Benzene-d$_6$): δ = 177.9, 150.8, 142.6, 142.1, 139.1, 133.6, 133.5, 133.0, 129.2, 128.6, 127.6, 125.9, 123.9, 117.3, 113.7, 112.9, 66.4, 65.2, 55.3, 44.2, 38.9, 34.9, 27.4, 27.0, 21.2 ppm.


[α]$^23$: 25.9 (c 0.14, CHCl$_3$).
Aromatisation: Corresponding cyclohepta[b]indole (0.21 mmol, 1.0 eq.) was dissolved in anhydrous DCM (2.1 mL). p-TsOH (0.32 mmol, 1.5 eq.) was added and the reaction was stirred overnight. Sat. aq. NaHCO₃ solution (20 mL) was added and the aqueous phase was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered off and concentrated in vacuo. The crude product was directly used in the next step.

Pivaloyl deprotection: Corresponding crude pivalate (0.21 mmol, 1.0 eq.) was dissolved in anhydrous DCM (2.1 mL) and the solution was cooled to -78 °C in an acetone – dry ice bath. DIBAL-H (1 M in toluene, 0.44 mmol, 2.2 eq.) was added dropwise and the reaction was stirred for 1 h. 1 M HCl (5 mL) was added and the reaction was warmed up to room temperature. Water (20 mL) was added and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic extracts were dried over MgSO₄, filtered off and concentrated in vacuo. Column chromatography (PE:EA 2:1) furnished the product.

(R)-(8-methyl-5-tosyl-5,6,9,10-tetrahydrocyclohepta[b]indol-9-yl) methanol (579)

Prepared from pivalate 578 (98 mg, 0.21 mmol), cyclohepta[b]indole 579 was obtained as a beige foam (48 mg, 0.13 mmol, 64% o2s).

¹H NMR (400 MHz, Benzene-d₆): δ = 8.62 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.28 – 7.18 (m, 2H), 7.12 (t, J = 7.4 Hz, 1H), 6.44 (d, J = 8.0 Hz, 2H), 5.35 (t, J = 5.7 Hz, 1H), 4.23 (dd, J = 20.8, 5.9 Hz, 1H), 3.74 (d, J = 21.0 Hz, 1H), 3.29 (dd, J = 10.4, 5.9 Hz, 1H), 3.10 – 2.97 (m, 1H), 2.73 (dd, J = 15.6, 7.1 Hz, 1H), 2.54 (d, J = 15.6 Hz, 1H), 2.45 – 2.35 (m, 1H), 1.62 (s, 3H), 1.60 (s, 3H), 0.51 (bs, 1H) ppm.

¹³C NMR (101 MHz, Benzene-d₆): δ = 144.2, 139.2, 137.3, 136.9, 134.4, 132.3, 129.7, 126.4, 124.6, 123.9, 121.2, 120.2, 118.4, 115.9, 63.0, 43.9, 27.5, 24.6, 24.3, 21.0 ppm.

HRMS (ESI, m/z) calculated for C₂₂H₂₄NO₃S⁺ [M+H]^+: 382.1471, found: 382.1461.

[α]D²³: 23.5 (c 0.28, CHCl₃).

(R)-(4-methoxy-8-methyl-5-tosyl-5,6,9,10-tetrahydrocyclohepta[b]indol-9-yl) methanol (583)

Prepared from pivalate 676 (30 mg, 60 µmol), cyclohepta[b]indole 583 was obtained as a beige foam (19 mg, 46 µmol, 77% o2s).

¹H NMR (400 MHz, Benzene-d₆): δ = 7.79 – 7.75 (m, 2H), 7.07 (t, J = 7.8 Hz, 1H), 6.99 (dd, J = 7.7, 1.1 Hz, 1H), 6.73 – 6.68 (m, 2H), 6.53 – 6.49 (m, 1H), 5.45 (ddq, J = 6.6, 4.9, 1.5 Hz, 1H), 4.13 (dd, J = 20.0, 6.5, 1.2 Hz, 1H), 3.99 – 3.87 (m, 1H), 3.41 (dd, J = 10.4, 6.0 Hz, 1H), 3.37 (s, 3H), 3.24 – 3.16 (m, 1H), 2.72 (ddt, J = 15.7,
7.8, 1.6 Hz, 1H), 2.64 (dtd, \( J = 15.7, 2.9, 1.1 \text{ Hz}, 1\text{H} \)), 2.54 (dtd, \( J = 11.0, 8.2, 7.1, 3.1 \text{ Hz}, 1\text{H} \)), 1.84 (s, 3H), 1.63 (d, \( J = 1.5 \text{ Hz}, 3\text{H} \)), 0.78 (bs, 1H) ppm.

\(^{13}\text{C NMR} \) (101 MHz, Benzene-\( \text{d}_6 \)): \( \delta = 149.2, 143.1, 139.6, 139.2, 138.2, 135.7, 129.2, 128.6, 126.9, 124.9, 122.4, 121.0, 113.3, 108.6, 62.9, 55.5, 43.3, 28.7, 24.9, 23.6, 21.1 \text{ ppm} \).

\( \text{HRMS} \) (ESI, \( m/z \)) calculated for \( \text{C}_{23}\text{H}_{25}\text{NNaO}_{4}S \text{ }^{+} \text{[M+Na]}^+ \): 434.1397, found: 434.1391.

\([\alpha]_D^{23} \): 8.7 (c 0.12, CHCl\(_3\)).

### 3.2.2 Studies Towards a Total Synthesis of Exotine A and B

**2-hydroxy-4-methoxybenzaldehyde (594)**

![2-hydroxy-4-methoxybenzaldehyde](image)

Prepared by literature known procedure.\(^{[415]}\) 2,4-dihydroxybenzaldehyde (13.8 g, 100 mmol, 1 eq.) and potassium carbonate (13.8 g, 100 mmol, 1 eq.) were suspended in acetone (200 mL). Methyl iodide (6.5 mL, 100 mmol, 1 eq.) was added and the reaction was stirred at room temperature overnight. The solvent was removed in \textit{vacuo} and the residue was purified by flash column chromatography (PE:EA 4:1) to furnish \textbf{594} as a colourless solid (11.2 g, 73.6 mmol, 74%).

\(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta = 11.48 \text{ (s, 1H)}, 9.72 \text{ (d, } J = 0.6 \text{ Hz, 1H)}, 7.43 \text{ (d, } J = 8.7 \text{ Hz, 1H)}, 6.54 \text{ (dd, } J = 8.7, 2.3 \text{ Hz, 1H)}, 6.43 \text{ (d, } J = 2.3 \text{ Hz, 1H)}, 3.86 \text{ (s, 3H)} \) ppm.

\( R_f = 0.55 \) (PE:EA 4:1).

**3-bromo-2-hydroxy-4-methoxybenzaldehyde (595)**

![3-bromo-2-hydroxy-4-methoxybenzaldehyde](image)

Prepared by literature known procedure.\(^{[414]}\) Benzaldehyde \textbf{594} (1.0 g, 7.24 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (45 mL) and the solution was cooled to -20 °C. Aluminium chloride (0.82 g, 7.24 mmol, 1 eq.) was added in three portions and the mixture was stirred for 15 min. A solution of bromine (370 \( \mu \text{L}, 7.24 \text{ mmol, 1 eq.} \) in methylene chloride (20 mL) was added dropwise to form a red solution, that was stirred overnight whilst warming to room temperature. Sat. aq. \( \text{Na}_2\text{S}_2\text{O}_3 \) solution (15 mL) was added followed by 1 M HCl (20 mL). The aqueous phase was extracted with methylene chloride (3 x 25 mL), the combined extracts were washed with brine, dried over \( \text{MgSO}_4 \), filtered and concentrated in \textit{vacuo}. The residue was purified by flash column chromatography (PE:EA 4:1) to furnish the product as a colourless solid (1.41 g, 6.10 g, 84%).
1H NMR (400 MHz, CDCl3): δ = 11.92 (s, 1H), 9.72 (s, 1H), 7.51 (d, J = 8.7 Hz, 1H), 6.62 (d, J = 8.7 Hz, 1H), 4.00 (s, 3H).

13C NMR (101 MHz, CDCl3): δ = 194.4, 162.9, 160.3, 134.7, 116.3, 103.9, 99.8, 57.0 ppm.

Rf = 0.25 (PE:EA 4:1).

8-bromo-7-methoxy-2H-chromen-2-one (596)

Prepared by literature known procedure. Aldehyde 595 (1.00 g, 4.35 mmol, 1 eq.) was dissolved in acetic anhydride (3.4 mL). Potassium acetate (0.26 g, 2.61 mmol, 0.6 eq.) was added and the mixture was heated to 160 °C for 5 h. After cooling to room temperature, the reaction was diluted with EtOAc (100 mL) and the solution was washed with brine (50 mL). The organic phase was dried over MgSO4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography to furnish the product as pale yellow solid (200 mg, 784 µmol, 18%).

1H NMR (400 MHz, CDCl3): δ = 7.62 (d, J = 9.5 Hz, 1H), 7.41 (d, J = 8.6 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 6.29 (d, J = 9.5 Hz, 1H), 4.00 (s, 3H) ppm.

2-hydroxy-3-iodo-4-methoxybenzaldehyde (597)

Prepared by literature known procedure. Benzaldehyde 594 (10.0 g, 65.7 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (400 mL) and the solution was cooled to -20 °C. Aluminium chloride (8.8 g, 65.7 mmol, 1 eq.) was added in four portions and the mixture was stirred for 15 min. NIS (16.3 g, 72.3 mmol, 1.1 eq.) was added in four portions and the reaction was stirred for 2 h at -20 °C. The cooling bath was removed and the reaction was stirred overnight at room temperature. 4 M HCl (250 mL) was added, the phases were separated and the aqueous phase was extracted with methylene chloride (3 x 100 mL). The combined organic extracts were washed with sat. aq. Na2S2O3 solution and brine, dried over MgSO4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EA 5:1) to furnish the product as a colourless solid (13.3 g, 47.8 mmol, 74%).

1H NMR (400 MHz, CDCl3): δ = 12.18 (s, 1H), 9.65 (s, 1H), 7.54 (d, J = 8.6 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 4.00 (s, 3H) ppm.

2-iodo-3-methoxy-6-vinylphenol (598)

Prepared by literature known procedure. Methyltriphenylphosphonium bromide (6.75 mmol, 2.41 g, 3.5 eq.) was dissolved in anhydrous THF (15 mL) and sodium hydride (60% dispersion in mineral oil, 6.13 mmol, 0.25 g, 3.2 eq.)
was added. The mixture was heated to reflux for 2 h and was afterwards cooled to 0 °C in an ice-bath. A solution of aldehyde 597 (0.54 g, 1.93 mmol, 1 eq.) in THF (5 mL) was added dropwise and the reaction was stirred overnight at room temperature. EtOAc (100 mL) was added and the organic phase was washed with water (100 mL). The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EE 7:1) to afford the product as a pale yellow oil that solidified upon storage in the fridge (0.51 g, 1.83 mmol, 95%).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{)}: \delta = 7.38 (dd, J = 8.6, 0.6 Hz, 1H), 7.01 – 6.88 (m, 1H), 6.42 (d, J = 8.6 Hz, 1H), 5.71 – 5.62 (m, 2H), 5.21 (dd, J = 11.2, 1.4 Hz, 1H), 3.88 (s, 3H) \text{ ppm.} \]

\[ ^13C \text{ NMR (101 MHz, CDCl}_3\text{)}: \delta = 158.3, 153.2, 131.6, 127.8, 118.7, 113.9, 103.4, 79.2, 56.7 \text{ ppm.} \]

2-iodo-3-methoxy-6-vinylphenyl acrylate (599)
Prepared by literature known procedure.\[414\] Vinylphenol 598 (1.40 g, 5.07 mmol, 1 eq.) was dissolved in anhydrous methylene chloride (40 mL) and NEt₃ (2.1 mL, 15.2 mmol, 3 eq.) was added. The solution was cooled to 0 °C and acryloyl chloride (1.2 mL, 15.2 mmol, 3 eq.) was added dropwise. The reaction was stirred overnight at room temperature and MTBE (200 mL) was added. The organic phase was washed with 0.5 M HCl (3 x 50 mL), was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EA 10:1) to furnish the product as pale yellow solid (1.11 g, 3.36 mmol, 67%).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{)}: \delta = 7.53 (d, J = 8.7 Hz, 1H), 6.78 – 6.67 (m, 2H), 6.61 (dd, J = 17.5, 11.1 Hz, 1H), 6.40 (dd, J = 17.3, 10.5 Hz, 1H), 6.11 (dd, J = 10.5, 1.2 Hz, 1H), 5.64 (dd, J = 17.6, 1.0 Hz, 1H), 5.22 (dd, J = 11.1, 1.0 Hz, 1H), 3.91 (s, 3H) \text{ ppm.} \]

8-iodo-7-methoxy-2H-chromen-2-one (600)
Prepared by literature known procedure.\[414\] Acrylate 599 (2.50 g, 7.57 mmol, 1 eq.) was dissolved in anhydrous toluene (76 mL) and the solution was degassed by freeze-pump-thaw (3 cycles). Grubbs 2nd generation catalyst (321 mg, 379 µmol, 0.05 eq.) was added and the reaction was stirred for 3 h at 80 °C. The solvent was removed and the residue was purified by flash column chromatography (PE:EA 3:2) to furnish the product as a pale grey solid (1.60 g, 5.29 mmol, 71%).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{)}: \delta = 7.57 (d, J = 9.4 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.26 (d, J = 9.4 Hz, 1H), 3.99 (s, 3H) \text{ ppm.} \]
C NMR (101 MHz, CDCl₃): δ = 161.8, 160.6, 155.2, 143.2, 129.2, 114.1, 113.9, 107.5, 76.2, 57.2 ppm.

Rᶠ = 0.15 (PE:EA 1:1).

2-ethynyl-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (601)

Hemiaminal 501 (400 mg, 1.57 mmol, 1 eq.) was dissolved in anhydrous methanol (26 mL) and potassium carbonate (1.08 g, 7.83 mmol, 5 eq.) was added. Ohira-Bestmann reagent (1.20 g, 6.27 mmol, 4 eq.) was added dropwise and the reaction was stirred at room temperature overnight. Ether (100 mL) was added and the organic phase was washed with sat. aq. NaHCO₃ solution and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EA 3:1) to furnish the product as a beige solid (291 mg, 1.16 mmol, 74%)

H NMR (400 MHz, CDCl₃): δ = 10.02 (s, 1H), 8.87 – 8.76 (m, 2H), 8.16 (dd, J = 8.3, 1.7 Hz, 1H), 7.56 – 7.42 (m, 3H), 2.07 (s, 1H), 1.98 (dd, J = 8.0, 6.1 Hz, 1H), 1.82 (dd, J = 6.1, 4.7 Hz, 1H), 1.50 (s, 3H), 1.17 (dd, J = 8.0, 4.7 Hz, 1H) ppm.

13C NMR (101 MHz, CDCl₃): δ = 167.5, 148.2, 138.4, 136.5, 134.8, 128.1, 127.7, 121.7, 121.5, 116.8, 85.0, 68.3, 32.5, 25.3, 21.8, 17.0 ppm.

IR (film): νₓₓₐₓ = 3299, 2967, 2115, 1680, 1596, 1521, 1484, 1424, 1380, 1324, 1262, 1240, 1183, 1164, 1133, 1086, 976, 922, 894, 825, 806, 790, 757, 732, 667 cm⁻¹.

HRMS (ESI, m/z) calculated for C₁₆H₁₅N₂O₊ [M+H]⁺: 251.1179, found: 251.1180.

Rᶠ = 0.45 (PE:EA 3:1).

2-((7-methoxy-2-oxo-2H-chromen-8-yl)ethynyl)-2-methyl-N-(quinolin-8-yl)cyclopropane-1-carboxamide (602)

Alkyne 601 (62 mg, 250 µmol, 1 eq.) and coumarin 600 (225 mg, 750 µmol, 3 eq.) were dissolved in anhydrous DMF (900 µL). Pd(PPh₃)₄ (72 mg, 63 µmol, 0.25 eq.) and copper(I) iodide (3 mg, 13 µmol, 0.05 eq.) were added and the mixture was degassed by freeze-pump-thaw (3 cycles). Degassed NEt₃ (600 µL) was added and the reaction was stirred at 100 °C overnight. The solvent was removed in vacuo and the residue was purified by flash column chromatography (PE:EA 1:1) to furnish the product as a colourless foam (85 mg, 200 µmol, 80%).
**1H NMR** (400 MHz, CDCl₃): δ = 10.06 (s, 1H), 8.89 (dd, J = 7.5, 1.5 Hz, 1H), 8.70 (dd, J = 4.2, 1.7 Hz, 1H), 8.12 (dd, J = 8.3, 1.7 Hz, 1H), 7.55 – 7.42 (m, 3H), 7.39 (dd, J = 4.2, 1.7 Hz, 1H), 1.99 (dd, J = 6.2, 4.8 Hz, 1H), 1.32 (dd, J = 8.0, 4.8 Hz, 1H) ppm.

**13C NMR** (101 MHz, CDCl₃): δ = 167.6, 163.5, 160.7, 156.0, 156.0, 148.1, 143.1, 138.6, 136.3, 128.0, 127.7, 127.6, 121.6, 121.2, 116.8, 113.7, 112.8, 107.2, 101.7, 97.3, 69.6, 56.3, 33.5, 25.6, 22.5, 18.3 ppm.

**IR (film):** νmax = 3335, 1725, 1682, 1598, 1486, 1328, 1293, 1252, 1211, 1166, 1118, 1092, 1049, 918, 824, 793 cm⁻¹.

**HRMS** (ESI, m/z) calculated for C₂₆H₂₁N₂O₄ [M+H]^+: 425.1496, found: 425.1497.

Rf = 0.20 (PE:EA 1:1).

**5,7-dimethoxy-2H-chromen-2-one (318)**

Prepared by modified literature known procedure.¹⁴¹³ Potassium tetrachloroplatinate (38 mg, 100 µmol, 0.01 eq.) and silver acetate (67 mg, 400 µmol, 0.04 eq.) were suspended in trifluoroacetic acid (5 mL) and the solution was stirred for 1 h at room temperature to give a red suspension. The suspension was cooled in a water bath and 3,5-dimethoxyphenol (3.10 g, 20.1 mmol, 2 eq.) and propiolic acid (620 µL, 10.1 mmol, 1 eq.) were subsequently added causing an exothermic reaction. The mixture was stirred for 48 h at room temperature and was poured into methylene chloride (200 mL). Sat. aq. NaHCO₃ solution (200 mL) was added, the phases were separated and the aqueous phase was extracted with methylene chloride (100 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was recrystallised from ethanol to furnish the product as a beige crystalline solid (1.70 g, 8.24 mmol, 82%).

**1H NMR** (400 MHz, CDCl₃): δ = 8.01 – 7.93 (m, 1H), 6.45 – 6.40 (m, 1H), 6.29 (q, J = 2.2 Hz, 1H), 6.20 – 6.12 (m, 1H), 3.89 (s, 3H), 3.85 (s, 3H) ppm.

**13C NMR** (101 MHz, CDCl₃): δ = 163.9, 161.7, 157.1, 157.0, 138.9, 111.1, 104.2, 95.4, 93.0, 56.1, 56.0 ppm.
8-iodo-5,7-dimethoxy-2H-chromen-2-one (319)

Prepared by literature known procedure.\(^\text{[409]}\) Coumarin 318 (2.0 g, 9.7 mmol, 1 eq.) and NIS (2.3 g, 10.1 mmol, 1.04 eq.) were suspended in acetonitrile (11.4 mL) and the mixture was cooled to 0 °C in an ice-bath. TFA (115 µL, 1.5 mmol, 0.15 eq.) was added dropwise and the reaction was stirred overnight whilst warming up to room temperature. The solid was filtered off and triturated with methanol. The resulting colourless solid was dried in vacuo to furnish the product (2.36 g, 7.11 mmol, 73%).

\(^1\text{H NMR}\) (400 MHz, \(\text{CDCl}_3\)): \(\delta = 7.90\) (d, \(J = 9.6\) Hz, 1H), 6.32 (s, 1H), 6.15 (d, \(J = 9.6\) Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H) ppm.

\(^{13}\text{C NMR}\) (101 MHz, \(\text{CDCl}_3\)): \(\delta = 162.3, 160.9, 158.0, 155.5, 138.5, 111.8, 104.9, 90.8, 65.0, 57.0, 56.3\) ppm.

\(((1R,2S,3R)-2-formyl-2-methyl-3-(1-tosyl-1H-indol-3-yl)cyclopropyl)methyl pivalate (678)

Alcohol 576 (400 mg, 850 µmol, 1 eq.), NMO (150 mg, 1.28 mmol, 1.5 eq.) and powdered MS 4Å (425 mg, 500 mg/mmol) were suspended in anhydrous methylene chloride. TPAP (30 mg, 85 µmol, 0.1 eq.) was added and the black mixture was stirred at room temperature until complete consumption of the starting material. The mixture was filtered over a pad of silica and was eluted with methylene chloride. The solvent was removed in vacuo to afford the product as a colourless foam and was usually used crude in the following step. An analytical sample was obtained by flash column chromatography (PE:EA 5:1).

\(^1\text{H NMR}\) (400 MHz, \(\text{CDCl}_3\)): \(\delta = 8.77\) (s, 1H), 7.91 – 7.86 (m, 1H), 7.62 (d, \(J = 8.3\) Hz, 2H), 7.39 (d, \(J = 1.7\) Hz, 1H), 7.23 (d, \(J = 7.7\) Hz, 2H), 7.18 – 7.09 (m, 3H), 4.45 (dd, \(J = 12.1, 8.7\) Hz, 1H), 4.21 (dd, \(J = 12.0, 7.9\) Hz, 1H), 2.52 (dd, \(J = 8.5, 1.7\) Hz, 1H), 2.24 (s, 3H), 2.07 (q, \(J = 8.4\) Hz, 1H), 1.36 (s, 3H), 1.15 (s, 9H) ppm.

\(^{13}\text{C NMR}\) (101 MHz, \(\text{CDCl}_3\)): \(\delta = 200.8, 178.4, 145.4, 135.3, 135.0, 131.3, 130.2, 126.9, 125.6, 125.5, 124.0, 119.6, 115.1, 114.1, 60.3, 39.0, 34.6, 32.7, 29.1, 27.3, 21.7, 19.4\) ppm.

\(\text{IR (film)}\): \(\nu_{\text{max}} = 2970, 1725, 1598, 1448, 1369, 1279, 1126, 976, 813, 746, 703, 676, 656\) cm\(^{-1}\).

\(\text{HRMS (ESI, } m/z)\) calculated for \(\text{C}_{26}\text{H}_{30}\text{NO}_5\text{S}^+\ [\text{M+H}]^+\): 468.1839, found: 468.1850.

\(R_f = 0.45\) (PE:EA 5:1).
**((1R,2S,3S)-2-ethynyl-2-methyl-3-(1-tosyl-1H-indol-3-yl)cyclopropyl)methyl pivalate (606)**

Crude aldehyde 678 (300 mg, 640 µmol, 1 eq.) was dissolved in methanol (4.3 mL). Potassium carbonate (267 mg, 1.92 mmol, 3 eq.) was added followed by dropwise addition of Ohira-Bestmann reagent (150 µL, 960 µmol, 1.5 eq.) to cause evolution of nitrogen. The reaction was stirred overnight at room temperature. It was poured into ether (200 mL) and the organic phase was washed with sat. aq. NaHCO₃ solution and brine. The organic phase was dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (PE:EA 5:1) to furnish the product as a colorless foam (218 mg, 470 µmol, 73%).

**1H NMR** (400 MHz, CDCl₃): δ = 7.96 (dt, J = 8.3, 0.9 Hz, 1H), 7.74 (d, J = 1.5 Hz, 1H), 7.71 – 7.66 (m, 2H), 7.52 (ddd, J = 7.8, 1.3, 0.8 Hz, 1H), 7.30 (ddd, J = 8.4, 7.2, 1.3 Hz, 1H), 7.22 (ddd, J = 8.3, 7.3, 1.1 Hz, 1H), 7.20 – 7.15 (m, 2H), 4.23 (dd, J = 11.9, 6.8 Hz, 1H), 3.91 (dd, J = 11.9, 8.3 Hz, 1H), 2.32 (s, 3H), 2.08 (dd, J = 8.6, 1.5 Hz, 1H), 1.92 (s, 1H), 1.65 (td, J = 8.4, 6.8 Hz, 1H), 1.55 (s, 3H), 1.12 (s, 9H) ppm.

**13C NMR** (101 MHz, CDCl₃): δ = 178.6, 144.9, 135.2, 135.1, 132.2, 129.9, 126.9, 124.9, 123.3, 119.9, 117.3, 113.9, 83.9, 70.7, 62.8, 38.8, 28.5, 27.2, 26.0, 25.0, 21.7, 17.4 ppm.

**IR (film):** νₘₐₓ = 3297, 2973, 1722, 1598, 1480, 1448, 1367, 1280, 1159, 1123, 1033, 1019, 977, 812, 747, 704, 682, 660 cm⁻¹.

**HRMS (ESI, m/z) calculated for C₂₇H₂₉N₂NaO₄S⁺ [M+Na]⁺: 486.1710, found: 486.1715.**

[α]D²¹: -7.7 (c 0.12, CHCl₃).

Rₚ = 0.35 (PE:EA 5:1).

**((1R,2S,3S)-2-((7-methoxy-2-oxo-2H-chromen-8-yl)ethynyl)-2-methyl-3-(1-tosyl-1H-indol-3-yl)cyclopropyl)methyl pivalate (603)**

Alkyne 606 (100 mg, 216 µmol, 1.05 eq.) and coumarin 600 (62 mg, 205 µmol, 1 eq.) were dissolved in anhydrous DMF (1.0 mL) and DIPEA (205 µL). The mixture was degassed by freeze-pump-thaw (3 cycles) and Pd(PPh₃)₄ (36 mg, 31 µmol, 0.15 eq.) and freshly precipitated copper(I) iodide (12 mg, 62 µmol, 0.3 eq.) were added to the frozen mixture. The mixture was left frozen under vacuum for 30 min. It was purged with nitrogen and was allowed to warm up to room temperature. The mixture changed colour to dark brown and was stirred overnight. The reaction
was poured into ether (100 mL) and sat. aq. NH₄Cl solution (100 mL) was added. The aqueous phase was extracted with ether (2 x 50 mL), the combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo. The residue was purified by gradient flash column chromatography (PE:EA 3:1 to 1:1) to furnish the product as a colourless foam (97 mg, 152 µmol, 74%).

**1H NMR** (400 MHz, CDCl₃): δ = 7.97 (d, J = 1.2 Hz, 1H), 7.93 – 7.86 (m, 1H), 7.64 – 7.53 (m, 4H), 7.34 (d, J = 8.7 Hz, 1H), 7.27 – 7.18 (m, 3H), 7.05 – 6.99 (m, 2H), 6.80 (d, J = 8.7 Hz, 1H), 6.28 (d, J = 9.5 Hz, 1H), 4.43 (dd, J = 12.0, 6.4 Hz, 1H), 4.08 (dd, J = 12.0, 8.5 Hz, 1H), 3.89 (s, 3H), 2.27 (dd, J = 8.7, 1.3 Hz, 1H), 2.24 (s, 3H), 1.81 (td, J = 8.5, 6.4 Hz, 1H), 1.70 (s, 3H), 1.03 (s, 9H) ppm.

**13C NMR** (101 MHz, CDCl₃): δ = 178.6, 163.7, 160.7, 155.9, 144.6, 143.2, 134.7, 132.4, 129.8, 128.0, 126.8, 124.7, 124.6, 123.2, 119.8, 117.3, 113.9, 113.7, 112.8, 107.3, 101.8, 101.0, 72.4, 62.8, 56.7, 38.7, 29.7, 27.1, 26.18, 25.9, 21.6, 19.2 ppm.

**IR (film):** υₘₐₓ = 2963, 1721, 1597, 1496, 1448, 1399, 1367, 1293, 1252, 1164, 1116, 1092, 1047, 979, 832, 812, 746, 703, 680, 659 cm⁻¹.

**HRMS (ESI, m/z) calculated for C₃₇H₃₆NO₇S⁺ [M+H]⁺: 638.2207, found: 638.2222.

[α]D²⁰: 17.5 (c 0.12, CHCl₃).

**Rf = 0.20** (PE:EA 2:1).

**((1R,2S,3S)-2-((5,7-dimethoxy-2-oxo-2H-chromen-8-yl)ethynyl)-2-methyl-3-(1-tosyl-1H-indol-3-yl)cyclopropyl)methyl pivalate (609)**

Prepared in analogous fashion to 603. From alkyne 606 (126 mg, 272 µmol, 1 eq.) and coumarin 319 (100 mg, 299 µmol, 1.1 eq.), 609 was obtained as a colorless foam (153 mg, 229 µmol, 84%).

**1H NMR** (400 MHz, CDCl₃): δ = 7.99 (d, J = 1.2 Hz, 1H), 7.95 (d, J = 9.7 Hz, 1H), 7.90 (ddd, J = 8.2, 1.4, 0.8 Hz, 1H), 7.60 – 7.54 (m, 3H), 7.28 – 7.18 (m, 2H), 7.05 – 7.00 (m, 2H), 6.28 (s, 1H), 6.18 (d, J = 9.7 Hz, 1H), 4.42 (dd, J = 12.0, 6.3 Hz, 1H), 4.04 (dd, J = 12.0, 8.5 Hz, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 2.27 – 2.21 (m, 1H), 2.24 (s, 3H), 1.78 (td, J = 8.6, 6.3 Hz, 1H), 1.68 (s, 3H), 1.57 (s, 3H), 1.01 (s, 9H) ppm.

**13C NMR** (101 MHz, CDCl₃): δ = 178.7, 164.8, 161.0, 156.7, 144.6, 138.4, 135.3, 134.7, 132.6, 129.8, 126.8, 124.7, 124.5, 123.2, 119.8, 117.5, 113.7, 111.7, 103.8, 98.6, 94.5, 90.2, 72.4, 62.8, 56.6, 56.2, 38.7, 29.5, 27.1, 26.3, 25.7, 21.6, 19.2 ppm.
IR (film): \( \nu_{\text{max}} = 2971, 1720, 1594, 1449, 1345, 1281, 1251, 1216, 1146, 1116, 1049, 978, 810, 745, 703, 680, 658 \text{ cm}^{-1} \).

HRMS (ESI, \( m/z \)) calculated for \( \text{C}_{38}\text{H}_{37}\text{NNaO}_8\text{S}^+ \) [M+Na]\(^+\): 690.2132, found: 690.2136.

[\( \alpha \)]\(_D\)\(^{21}\): 15.6 (c 0.25, CHCl\(_3\)).

\( R_f = 0.15 \) (PE:EA 2:1).

\((1R,2S,3S)-2\text{-methyl}-2-((1S,2R,3S)-1\text{-methyl}-2-((\text{pivaloyloxy})\text{methyl})-3-(1\text{-tosyl-1H-indol-3-yl})\text{cyclopropyl})\text{buta-1,3-diyn-1-yl})-3-(1\text{-tosyl-1H-indol-3-yl})\text{cyclopropyl})\text{methyl pivalate (610)}\)

\( \text{610} \) was obtained in variable amounts as side product from the Sonogashira cross-coupling of \( \text{606} \).

\(^1H\) NMR (400 MHz, CDCl\(_3\)): \( \delta = 7.98 \) (dt, \( J = 8.3, 0.9 \text{ Hz}, 1\text{H} \)), 7.81 (d, \( J = 1.4 \text{ Hz}, 1\text{H} \)), 7.77 – 7.73 (m, 2H), 7.52 – 7.49 (m, 1H), 7.30 (ddd, \( J = 8.4, 7.3, 1.3 \text{ Hz}, 1\text{H} \)), 7.22 (ddd, \( J = 8.3, 7.3, 1.1 \text{ Hz}, 1\text{H} \)), 7.12 – 7.07 (m, 2H), 4.11 (dd, \( J = 12.0, 6.9 \text{ Hz}, 1\text{H} \)), 3.82 (dd, \( J = 12.0, 8.2 \text{ Hz}, 1\text{H} \)), 2.19 (s, 3H), 2.16 (dd, \( J = 8.6, 1.4 \text{ Hz}, 1\text{H} \)), 1.70 (td, \( J = 8.4, 6.8 \text{ Hz}, 1\text{H} \)), 1.53 (s, 3H), 1.06 (s, 9H) ppm.

\(^{13}C\) NMR (101 MHz, CDCl\(_3\)): \( \delta = 178.4, 144.9, 135.1, 135.0, 132.1, 129.9, 127.0, 125.1, 125.0, 123.5, 119.8, 117.0, 114.0, 78.5, 67.7, 62.3, 38.7, 29.8, 27.1, 26.1, 25.7, 21.5, 18.3 \text{ ppm} \).

HRMS (ESI, \( m/z \)) calculated for \( \text{C}_{54}\text{H}_{56}\text{N}_{2}\text{NaO}_8\text{S}_2^+ \) [M+Na]\(^+\): 947.3370, found: 947.3384.
3.2.3 Extension of the C-H Activation Methodology to other Heterocycles

3-iodo-1-(triisopropylsilyl)-1H-pyrrole (619)

Prepared by literature known procedure.\(^{[440]}\) Pyrrole (6.9 mL, 100 mmol, 1 eq.) was dissolved in anhydrous THF (180 mL) and the solution was cooled to -78 °C. n-Butyllithium (2.5 M in hexanes, 44.0 mL, 110 mmol, 1.1 eq.) was added dropwise, followed by dropwise addition of TIPSCI (21.4 mL, 100 mmol, 1 eq.). The reaction was allowed to warm up to room temperature and was stirred overnight. The reaction was quenched by addition of isopropanol (5 mL) and the solvent was removed in vacuo. The residue was partitioned between ether (250 mL) and water (250 mL), the phases were separated and the aqueous layer was extracted with ether (2 x 150 mL). The combined organic extracts were washed with brine, dried over MgSO4, filtered and concentrated in vacuo to afford TIPS-pyrrole as a brownish oil (22.2 g, 99.4 mmol, 99%), which was directly used in the next step.

TIPS-pyrrole (3.00 g, 13.4 mmol, 1 eq.) and hydroquinone (0.30 g, 2.69 mmol, 0.2 eq.) were dissolved in acetone (60 mL). A solution of NIS (3.02 g, 13.4 mmol, 1 eq.) in acetone (60 mL) was added dropwise and the reaction was stirred for 2 h at room temperature. The solvent was removed in vacuo and the residue was purified by flash column chromatography (100% PE) to afford the product as a colourless oil (3.89 g, 11.1 mmol, 83%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 6.79\) (dd, \(J = 2.3, 1.3\) Hz, 1H), 6.67 (t, \(J = 2.5\) Hz, 1H), 6.37 (dd, \(J = 2.8, 1.3\) Hz, 1H), 1.42 (hept, \(J = 7.5\) Hz, 3H), 1.09 (d, \(J = 7.6\) Hz, 18H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 128.9, 125.9, 117.7, 62.3, 17.9, 11.7\) ppm.

4-iodo-1-tosyl-1H-imidazole (631)

Prepared by literature known procedure.\(^{[441]}\) Imidazole (11.1 g, 163 mmol, 1 eq.) was dissolved in 4 M NaOH (600 mL) and a solution of potassium iodide (147 g, 889 mmol, 5.45 eq.) and iodine (89 g, 350 mmol, 2.15 eq.) in water (500 mL) was added dropwise. The reaction was stirred at room temperature overnight, was cooled in an ice-bath and neutralised with acetic acid. The greyish precipitate was filtered off, washed with ice water and was dried in air to afford 4,5-diiodoimidazole (52 g, 163 mmol, quant.), which was directly used in the next step.

4,5-diiodoimidazole (52 g, 163 mmol, 1 eq.) was added to a solution of potassium sulfite (254 g, 1.61 mol) in water (385 mL) and ethanol (165 mL) and the mixture was heated to reflux. After 24 h the reaction mixture was cooled to room temperature and the inorganic salts were filtered off. The ethanol was removed under reduced pressure and NaCl was added to the resulting water phase.
until saturation. The water phase was extracted with Et₂O:THF 1:1 (3 × 300 mL). The combined organic extracts were washed with sat. aq. K₂SO₃ solution, dried over Na₂SO₄, filtered, and concentrated in vacuo to furnish 4-iodoimidazole as a colourless solid (19.8 g, 102 mmol, 63%), which was directly used in the next step.

4-iodoimidazole (19.8 g, 102 mmol, 1 eq.) was dissolved in THF (150 mL) and tosyl chloride (19.5 g, 102 mmol, 1 eq.) was added. NEt₃ (14.3 mL, 102 mmol, 1 eq.) was added dropwise and the reaction was stirred for 2 d at room temperature. The solvent was removed in vacuo and the residue was recrystallised from ethanol to furnish the product as a colourless crystalline solid (23.8 g, 68.4 mmol, 67%).

¹H NMR (400 MHz, CDCl₃): δ = 7.87 (d, J = 1.4 Hz, 1H), 7.82 (d, J = 8.1 Hz, 2H), 7.42 – 7.35 (m, 3H), 2.45 (s, 3H).

3-iodo-1-tosyl-1H-indazole (633)

Indazole (3.00 g, 25.4 mmol, 1 eq.) and powdered KOH (5.34 g, 95.3 mmol, 3.75 eq.) were dissolved in anhydrous DMF (22 mL). Iodine (12.7 g, 50.8 mmol, 2 eq.) was added in portions and the mixture was stirred for 3 h at room temperature. KOH (3.56 g, 63.5 mmol, 2.5 eq.) was added, followed by addition of tosyl chloride (10.2 g, 53.3 mmol, 2.1 eq.). The reaction was stirred overnight and was poured into aq. Na₂S₂O₃ solution (300 mL), which was vigorously stirred for 2 h. The off-white precipitate was filtered off and was washed with a small amount of isopropanol. The solid was suspended in isopropanol (100 mL), stirred for 30 min and water (200 mL) was added. The precipitate was filtered off and dried in vacuo to furnish the product as a beige solid (7.69 g, 19.3 mmol, 76%).

¹H NMR (400 MHz, CDCl₃): δ = 8.17 (dt, J = 8.5, 0.9 Hz, 1H), 7.90 – 7.84 (m, 2H), 7.61 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.46 (dt, J = 8.1, 1.1 Hz, 1H), 7.38 (ddd, J = 8.0, 7.0, 0.8 Hz, 1H), 7.28 – 7.24 (m, 2H), 2.37 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ = 145.8, 140.3, 134.5, 130.4, 130.4, 130.1, 127.9, 124.9, 122.4, 113.7, 104.3, 21.8 ppm.

IR (film): νmax = 1596, 1484, 1453, 1384, 1288, 1245, 1188, 1175, 1125, 1081, 1036, 1011, 941, 810, 755, 742, 702, 686, 658 cm⁻¹.

HRMS (ESI, m/z) calculated for C₁₄H₁₂IN₂O₂S⁺ [M+H]⁺: 398.9659; found: 398.9651.
2-iodo-1-tosyl-1H-indole (624)

Prepared by literature known procedure.\textsuperscript{[472]} N-Tosylindole (10.1 g, 37.2 mmol, 1 eq.) was dissolved in anhydrous ether (350 mL) and the solution was cooled to -78 °C. t-Butyllithium (1.9 M in pentane, 20.6 mL, 39.1 mmol, 1.05 eq.) was added dropwise to give a beige suspension. The mixture was warmed up to -40 °C and was recooled to -78 °C. Iodine (28.3 g, 112 mmol, 3 eq.) was added in portions and the mixture was allowed to warm up to room temperature. Sat. aq. NH\textsubscript{4}Cl solution was added (150 mL) and the organic phase was washed with sat. aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution, dried over MgSO\textsubscript{4}, filtered and concentrated in \textit{vacuo}. The residue was purified by flash column chromatography (PE:EA 9:1) to furnish the product as a beige solid (10.3 g, 25.9 mmol, 70%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 8.32 \text{ (d, } J = 8.4 \text{ Hz, 1H}), 7.82 \text{ (d, } J = 8.0 \text{ Hz, 2H}), 7.44 \text{ (d, } J = 7.6 \text{ Hz, 1H}), 7.34 - 7.28 \text{ (m, 1H}), 7.25 \text{ (dd, } J = 7.9, 3.2 \text{ Hz, 3H}), 7.03 \text{ (s, 1H)}, 2.39 \text{ (s, 3H) ppm.}

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): \(\delta = 145.3, 138.6, 135.5, 131.9, 129.9, 127.3, 125.0, 124.3, 123.8, 119.8, 115.6, 75.5, 21.7 \text{ ppm.}

2-iodobenzo[b]thiophene (626)

Benzothiophene (1.0 mL, 8.64 mmol, 1 eq.) was dissolved in anhydrous THF (17.4 mL) and the solution was cooled to -78 °C. t-Butyllithium (1.9 M in pentane, 5.0 mL, 9.51 mmol, 1.1 eq.) was added dropwise and the reaction was stirred for 30 min. A solution of iodine (2.41 g, 9.51 mmol, 1.1 eq.) in THF (5.8 mL) was added dropwise and the reaction was stirred for 2 h at -78 °C and 2 h at room temperature. The reaction was quenched by addition of water (50 mL). Ether (50 mL) and sat. aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution (50 mL) were added, the phases were separated and the aqueous phase was extracted with ether. The combined organic extracts were washed with brine, dried over MgSO\textsubscript{4}, filtered and concentrated in \textit{vacuo}. The residue was purified by flash column chromatography (100% PE) to furnish the product as a pale yellow solid (2.07 g, 7.96 mmol, 92%). The spectroscopic data matched those reported in literature.\textsuperscript{[473]}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 7.78 - 7.74 \text{ (m, 1H)}, 7.73 - 7.69 \text{ (m, 1H)}, 7.54 \text{ (d, } J = 0.8 \text{ Hz, 1H}), 7.32 - 7.28 \text{ (m, 2H) ppm.}

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): \(\delta = 144.6, 141.0, 134.0, 124.7, 124.5, 122.4, 121.4, 78.5 \text{ ppm.}
2-iodobenzofuran (628)

281 was prepared in analogous fashion as 2-iodobenzothiophene (626) and was obtained as a colorless oil (0.89 g, 3.65 mmol, 73%) from benzofuran (5.00 mmol). The spectroscopic data matched those reported in literature.\cite{474}

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}): δ = 7.53 – 7.50 (m, 1H), 7.50 – 7.46 (m, 1H), 7.25 – 7.18 (m, 2H), 6.96 (d, J = 0.9 Hz, 1H).

\textbf{13C NMR} (101 MHz, CDCl\textsubscript{3}): δ = 158.4, 129.4, 124.4, 123.3, 119.8, 117.4, 111.0, 96.0 ppm.

3-iodothiophene (623)

3-Bromothiophene (3.0 mL, 30.7 mmol, 1 eq.) was dissolved in anhydrous ether (200 mL) and the solution was cooled to -78 °C. n-Butyllithium (2.5 M in hexanes, 12.3 mL, 30.7 mmol, 1 eq.) was added dropwise and the reaction was stirred for 45 min. A solution of iodine (8.56 g, 33.7 mmol, 1.1 eq.) in ether (140 mL) was added dropwise and the reaction was stirred overnight whilst warming up to room temperature. Water (100 mL) and sat. aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} solution (100 mL) were added and the phases were separated. The aqueous phase was extracted with ether and the combined organic extracts were washed with brine, dried over MgSO\textsubscript{4}, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (100% PE) to furnish the product as a pale yellow liquid (6.0 g, 28.7 mmol, 94%). The spectroscopic data matched those reported in literature.\cite{475}

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}): δ = 7.41 (dd, J = 3.0, 1.2 Hz, 1H), 7.20 (dd, J = 5.1, 3.0 Hz, 1H), 7.11 (dd, J = 5.0, 1.2 Hz, 1H) ppm.

\textbf{13C NMR} (101 MHz, CDCl\textsubscript{3}): δ = 134.9, 128.8, 127.4, 77.3.

3-iodofuran (620)

620 was prepared in analogous fashion as 3-iodothiophene (623) and was obtained as a yellow liquid (1.03 g, 5.3 mmol, 78%) from 3-bromofuran (6.8 mmol). Due to its high volatility residual solvent remained after evaporation.

\textbf{1H NMR} (400 MHz, CDCl\textsubscript{3}): δ = 7.44 (dd, J = 1.6, 0.8 Hz, 1H), 7.36 (t, J = 1.7 Hz, 1H), 6.50 (dd, J = 1.9, 0.8 Hz, 1H) ppm.

3-iodoquinoline (632)

Prepared by literature known procedure.\cite{476} 3-bromoquinoline (1.00 g, 4.81 mmol, 1 eq.) cooper(I) iodide (46 mg, 0.24 mmol, 0.05 eq.), sodium iodide
(1.44 g, 9.61 mmol, 2 eq.) and N,N’-dimethyl ethylenediamine (50 µL, 0.48 mmol, 0.1 eq.) were dissolved in anhydrous 1,4-dioxane (4.8 mL). The reaction was heated to 110 °C for 60 h. After cooling to room temperature it was poured into 10% aq. NH₃ solution (100 mL) and the aqueous phase was extracted with EtOAc (3 x 50 mL). The combined extracts were washed with 10% aq. NH₃ solution and brine, dried over MgSO₄, filtered and concentrated in vacuo. The residue was co-evaporated with chloroform and toluene to furnish the product as a pale beige solid (1.11 g, 4.35 mmol, 91%).

$^{1}$H NMR (400 MHz, CDCl₃): $\delta = 9.04$ (d, $J = 2.1$ Hz, 1H), 8.54 (s, 1H), 8.07 (d, $J = 8.4$ Hz, 1H), 7.73 (dd, $J = 12.6$, 7.8 Hz, 2H), 7.57 (t, $J = 7.6$ Hz, 1H) ppm.

3-iodopyridine 1-oxide (630)

[443] Prepared by literature known procedure. 3-iodopyridine (500 mg, 2.44 mmol, 1 eq.) was dissolved in methylene chloride (1.0 mL) and m-CPBA (670 mg, 3.90 mmol, 1.6 eq.) was added while cooling in an ice-bath. The reaction was stirred overnight whilst warming up to room temperature. Sat. aq. NaHCO₃ solution and 2 M aq. NaOH were added and the aqueous phase was extracted with methylene chloride. The combined extracts were washed with brine, dried over MgSO₄, filtered and the solvent was removed in vacuo. The residue was purified by flash column chromatography (EA:MeOH 9:1) to furnish the product as a beige solid (524 mg, 2.37 mmol, 97%).

$^{1}$H NMR (400 MHz, CDCl₃): $\delta = 8.51$ (s, 1H), 8.15 (d, $J = 6.6$ Hz, 1H), 7.57 (d, $J = 8.1$ Hz, 1H), 7.01 (t, $J = 7.3$ Hz, 1H) ppm.

General procedure for the Pd(II)-catalyzed C-H activation

Corresponding cyclopropane (1 eq.), silver carbonate (1.2 eq.), N-tosyl-3-iodoindole (3 eq.) and palladium acetate (0.1 eq.) were mixed up under nitrogen atmosphere in a Schlenk flask and anhydrous toluene (1 M based on cyclopropane) was added under a nitrogen flow. The seal tube was protected from light and heated in an oil bath at 110°C for 2 – 5 h. Completion of the reaction was controlled by TLC (PE:EA 3:1) After cooling down to room temperature, the reaction mixture was filtered over a pad of celite using ethyl acetate as eluent. The filtrate was dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (PE:EA 3:1) to yield the desired product.
(1R,2S,3R)-2-methyl-N-(quinolin-8-yl)-3-(1-trisopropylsilyl)-1H-pyrrol-3-yl)-2-((trityloxy)methyl)cyclopropane-1-carboxamide (634)

Prepared from cyclopropane 515 (500 mg, 1.00 mmol), 634 was obtained as a beige foam (465 mg, 0.65 mmol, 65%).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta = 9.85$ (s, 1H), 8.64 (dd, $J = 4.2$, 1.7 Hz, 1H), 8.61 (dd, $J = 6.9$, 2.2 Hz, 1H), 8.11 (dd, $J = 8.3$, 1.7 Hz, 1H), 7.51 – 7.36 (m, 8H), 7.35 – 7.27 (m, 2H), 7.18 – 7.08 (m, 8H), 6.58 (dt, $J = 2.3$, 1.2 Hz, 1H), 6.53 (t, $J = 2.4$ Hz, 1H), 6.20 (dd, $J = 2.7$, 1.4 Hz, 1H), 3.68 (d, $J = 10.0$ Hz, 1H), 3.63 (d, $J = 10.0$ Hz, 1H), 2.34 (dd, $J = 9.3$, 1.0 Hz, 1H), 2.05 (d, $J = 9.3$ Hz, 1H), 1.32 (s, 3H), 1.21 – 1.10 (m, 3H), 0.89 (dd, $J = 7.5$, 6.5 Hz, 18H) ppm.

$^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 168.6$, 148.1, 145.4, 138.6, 136.2, 135.1, 129.2, 128.1, 127.5, 127.5, 126.6, 123.6, 123.4, 121.4, 120.9, 118.9, 116.9, 112.8, 86.7, 63.1, 34.8, 29.3, 28.4, 25.1, 17.9, 12.1 ppm.

IR (film): $\nu_{\text{max}} = 3349, 3062, 2945, 2867, 1671, 1596, 1521, 1485, 1462, 1424, 1383, 1325, 1261, 1217, 1160, 1089, 1112, 1066, 1017, 937, 884, 825, 791, 752, 703, 659$ cm$^{-1}$.

HRMS (ESI, m/z) calculated for C$_{47}$H$_{53}$N$_3$NaO$_2$Si$^+$ [M+Na$^+$]: 742.3799; found: 742.3798.

[$\alpha$]$_{D}^{23}$: -96.8 (c = 0.25 CHCl$_3$).

(1R,2S,3S)-2-methyl-N-(quinolin-8-yl)-3-(thiophen-3-yl)-2-((trityloxy)methyl)cyclopropane-1-carboxamide (635)

Prepared from cyclopropane 515 (558 mg, 1.12 mmol), 635 was obtained as a yellow foam (477 mg, 821 µmol, 73%).

$^1$H NMR (400 MHz, benzene-$d_6$): $\delta = 9.99$ (s, 1H), 9.04 (d, $J = 7.8$ Hz, 1H), 8.46 (dd, $J = 4.2$, 1.6 Hz, 1H), 7.60 – 7.46 (m, 7H), 7.13 – 6.90 (m, 13H), 6.80 – 6.75 (m, 2H), 4.01 (d, $J = 9.9$ Hz, 1H), 3.89 (d, $J = 9.8$ Hz, 1H), 2.07 – 1.99 (m, 1H), 1.49 (d, $J = 9.2$ Hz, 1H), 1.24 (s, 3H).

$^{13}$C NMR (101 MHz, benzene-$d_6$): $\delta = 167.7$, 147.9, 144.8, 138.7, 136.2, 135.7, 135.6, 130.2, 129.4, 128.6, 128.0, 127.1, 124.5, 123.3, 121.4, 120.9, 116.8, 87.1, 62.0, 34.5, 32.4, 29.8, 25.1 ppm.

IR (film): $\nu_{\text{max}} = 3352, 3021, 2924, 1683, 1596, 1521, 1485, 1448, 1424, 1381, 1323, 1261, 1216, 1184, 1153, 1133, 1061, 1031, 1003, 899, 825, 791, 747, 704, 666$ cm$^{-1}$.
HRMS (ESI, m/z) calculated for C_{38}H_{32}N_{2}NaO_{2}S^{+} [M+Na]^+: 603.2077; found: 603.2076.

[α]_{D}^{23}: -49.2 (c = 0.50 CHCl_{3}).

(1R,2S,3S)-3-(furan-3-yl)-2-methyl-N-(quinolin-8-yl)-2-((trityloxy)methyl)cyclopropane-1-carboxamide (636)

Prepared from cyclopropane 515 (296 mg, 0.59 mmol), 636 was obtained as a beige foam (158 mg, 0.28 mmol, 47%).

^{1}H NMR (400 MHz, benzene-d_{6}): δ = 9.92 (s, 1H), 9.01 (dd, J = 7.8, 1.3 Hz, 1H), 8.39 (dd, J = 4.2, 1.7 Hz, 1H), 7.51 – 7.46 (m, 6H), 7.45 (dd, J = 8.3, 1.7 Hz, 1H), 7.35 (q, J = 1.1 Hz, 1H), 7.15 – 7.10 (m, 2H), 7.04 – 6.97 (m, 7H), 6.96 – 6.88 (m, 4H), 6.73 (dd, J = 8.2, 4.2 Hz, 1H), 6.21 (dd, J = 1.9, 0.8 Hz, 1H), 3.91 – 3.81 (m, 2H), 1.77 (dd, J = 9.2, 1.2 Hz, 1H), 1.46 (d, J = 9.1 Hz, 1H), 1.17 (s, 3H) ppm.

^{13}C NMR (101 MHz, benzene-d_{6}): δ = 167.8, 147.8, 144.8, 142.1, 141.3, 138.7, 136.2, 135.7, 129.4, 127.9, 127.1, 121.4, 121.0, 119.1, 116.8, 113.1, 87.0, 62.6, 34.4, 29.3, 28.1, 24.9 ppm.

IR (film): ν_{max} = 3353, 3010, 1684, 1596, 1520, 1485, 1425, 1381, 1325, 1216, 1160, 1133, 1061, 1003, 899, 874, 826, 792, 747, 704, 667 cm^{-1}.

HRMS (ESI, m/z) calculated for C_{38}H_{32}N_{2}NaO_{3}S^{+} [M+Na]^+: 587.2305; found: 587.2301.

[α]_{D}^{23}: -44.2 (c = 0.51 CHCl_{3}).

(1R,2R,3S)-2-methyl-N-(quinolin-8-yl)-3-(thiophen-2-yl)-2-((trityloxy)methyl)cyclopropane-1-carboxamide (637)

Prepared from cyclopropane 515 (500 mg, 1.0 mmol), 637 was obtained as a pale yellow foam (386 mg, 0.67 mmol, 67%).

^{1}H NMR (400 MHz, CDCl_{3}): δ = 9.85 (s, 1H), 8.67 (dd, J = 4.2, 1.7 Hz, 1H), 8.64 (dd, J = 5.9, 3.2 Hz, 1H), 8.13 (dd, J = 8.3, 1.7 Hz, 1H), 7.50 – 7.43 (m, 2H), 7.43 – 7.40 (m, 1H), 7.38 (dt, J = 8.0, 1.9 Hz, 6H), 7.20 – 7.06 (m, 10H), 6.82 (dt, J = 3.7, 1.3 Hz, 1H), 6.78 (dd, J = 5.1, 3.5 Hz, 1H), 3.71 (s, 2H), 2.60 (dd, J = 8.9, 1.2 Hz, 1H), 2.17 (d, J = 8.9 Hz, 1H), 1.46 (s, 3H).  

^{13}C NMR (101 MHz, CDCl_{3}): δ = 167.4, 148.1, 144.2, 138.5, 137.8, 136.3, 134.8, 129.1, 128.0, 127.6, 127.5, 127.1, 126.8, 126.8, 124.5, 121.5, 121.2, 116.7, 87.4, 62.3, 35.6, 30.9, 30.6, 25.2 ppm.

HRMS (ESI, m/z) calculated for C_{38}H_{32}N_{2}NaO_{2}S^{+} [M+Na]^+: 603.2077; found: 603.2073.
\( \text{IR (film): } \nu_{\text{max}} = 3057, 1686, 1597, 1520, 1484, 1448, 1384, 1324, 1165, 1062, 900, 825, 791, 746, 699 \text{ cm}^{-1}. \)

\([\alpha]_D^{21}: -34.3 \text{ (c 0.98, CHCl}_3).\)

\((1R,2S,3R)-2\text{-methyl-3-(pyridin-3-yl)-N-(quinolin-8-yl)-2-}((\text{trityloxy})\text{methyl})\text{cyclopropane-1-carboxamide (638)}\)

Prepared from cyclopropane 515 (200 mg, 0.40 mmol), 638 was obtained as a yellow oil (17 mg, 0.03 mmol, 5%).

\(^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3): \delta = 9.96 \text{ (s, 1H), 8.76 (d, } J = 4.3 \text{ Hz, 1H), 8.57 (d, } J = 6.6 \text{ Hz, 1H), 8.42 (s, 1H), 8.37 (s, 1H), 8.15 (d, } J = 8.2 \text{ Hz, 1H), 7.52 (d, } J = 7.6 \text{ Hz, 1H), 7.44 (d, } J = 5.5 \text{ Hz, 3H), 7.36 (d, } J = 7.3 \text{ Hz, 6H), 7.14 (d, } J = 7.0 \text{ Hz, 10H), 7.01 (s, 1H), 3.64 (d, } J = 9.9 \text{ Hz, 1H), 3.54 (d, } J = 9.8 \text{ Hz, 1H), 2.52 (d, } J = 8.8 \text{ Hz, 1H), 2.16 (d, } J = 9.1 \text{ Hz, 1H), 1.52 (s, 3H ppm.}}\)

\((1R,2S,3S)-3-(\text{benzo[b]thiophen-3-yl)-2-methyl-N-(quinolin-8-yl)-2-}((\text{trityloxy})\text{methyl})\text{-cyclopropane-1-carboxamide (640)}\)

Prepared from cyclopropane 515 (500 mg, 1.0 mmol), 640 was obtained as a red foam (191 mg, 0.30 mmol, 54% brsm) alongside with starting material (220 mg, 0.44 mmol, 44%).

\(^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3): \delta = 9.60 \text{ (s, 1H), 8.57 – 8.51 (m, 2H), 8.08 (dd, } J = 8.3, 1.7 \text{ Hz, 1H), 7.90 – 7.85 (m, 1H), 7.82 – 7.77 (m, 1H), 7.42 (s, 1H), 7.40 (d, } J = 1.3 \text{ Hz, 1H), 7.37 (dd, } J = 8.3, 4.2 \text{ Hz, 1H), 7.28 – 7.22 (m, 8H), 7.11 – 7.01 (m, 10H), 3.62 (d, } J = 9.8 \text{ Hz, 1H), 3.54 (d, } J = 9.9 \text{ Hz, 1H), 2.53 (dd, } J = 8.9, 1.5 \text{ Hz, 1H), 2.26 (d, } J = 8.9 \text{ Hz, 1H), 1.67 (s, 3H ppm.}}\)

\(^{13}\text{C NMR} \ (101 \text{ MHz, CDCl}_3): \delta = 168.0, 148.0, 144.0, 140.6, 140.1, 138.4, 136.2, 134.6, 129.2, 128.9, 127.9, 127.6, 127.4, 126.8, 124.7, 124.3, 124.0, 122.6, 122.3, 121.5, 121.2, 116.6, 86.7, 62.5, 34.4, 30.6, 29.1, 25.3 \text{ ppm.}}\)

\( \text{IR (film): } \nu_{\text{max}} = 1682, 1520, 1485, 1326, 1163, 1063, 825, 747, 702 \text{ cm}^{-1}. \)

\( \text{HRMS (ESI, } m/z \text{) calculated for } C_{42}H_{34}N_{2}NaO_{2}S^+ [M+Na]^+: 653.2233; \text{ found: 653.2226.} \)

\([\alpha]_D^{20}: -35.8 \text{ (c 0.53, CHCl}_3).\)
(1R,2S,3S)-3-(benzofuran-2-yl)-2-methyl-N-(quinolin-8-yl)-2-((trityloxy)methyl)cyclopropane-1-carboxamide (642)

Prepared from cyclopropane 515 (500 mg, 1.0 mmol), 642 was obtained as a beige foam (471 mg, 0.77 mmol, 77%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 9.83\) (s, 1H), 8.61 (dd, \(J = 6.2, 2.9\) Hz, 1H), 8.28 (dd, \(J = 4.3, 1.7\) Hz, 1H), 8.09 (dd, \(J = 8.3, 1.7\) Hz, 1H), 7.50 – 7.42 (m, 2H), 7.40 – 7.29 (m, 9H), 7.16 (tt, \(J = 7.3, 5.6\) Hz, 2H), 7.11 – 7.04 (m, 9H), 6.39 (d, \(J = 1.1\) Hz, 1H), 3.71 (d, \(J = 9.9\) Hz, 1H), 3.66 (d, \(J = 9.9\) Hz, 1H), 2.56 (dd, \(J = 9.1, 1.2\) Hz, 1H), 2.28 (d, \(J = 9.0\) Hz, 1H), 1.58 (s, 3H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 166.8, 154.8, 152.7, 148.1, 144.0, 138.4, 136.2, 129.1, 128.9, 127.9, 127.6, 127.4, 126.9, 123.5, 122.3, 121.5, 121.4, 120.9, 116.8, 110.9, 105.3, 86.7, 62.5, 35.0, 29.6, 28.8, 24.8 ppm.

IR (film): \(\nu_{\text{max}} = 1686, 1597, 1521, 1485, 1453, 1383, 1325, 1256, 1165, 1064, 905, 825, 743, 702\) cm\(^{-1}\).

HRMS (ESI, m/z) calculated for C\(_{42}\)H\(_{34}\)N\(_2\)NaO\(_3\)\(^{+}\) [M+Na]\(^{+}\): 637.2462; found: 637.2455.

[\(\alpha\)]\(_D\)\(^{21}\): -64.1 (c 1.60, CHCl\(_3\)).

(1R,2R,3S)-3-(benzo[b]thiophen-2-yl)-2-methyl-N-(quinolin-8-yl)-2-((trityloxy)methyl)cyclopropane-1-carboxamide (639)

Prepared from cyclopropane 515 (500 mg, 1.0 mmol), 639 was obtained as a beige foam (481 mg, 0.76 mmol, 76%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 9.70\) (s, 1H), 8.64 (dd, \(J = 6.7, 2.3\) Hz, 1H), 8.06 (dd, \(J = 8.3, 1.7\) Hz, 1H), 7.85 (dd, \(J = 4.2, 1.7\) Hz, 1H), 7.69 (dd, \(J = 7.3, 1.8, 0.7\) Hz, 1H), 7.56 – 7.52 (m, 1H), 7.48 – 7.40 (m, 2H), 7.39 – 7.33 (m, 6H), 7.32 – 7.22 (m, 4H), 7.13 (dd, \(J = 1.5, 0.8\) Hz, 1H), 7.08 – 6.97 (m, 9H), 3.80 – 3.66 (m, 2H), 2.67 (dd, \(J = 8.9, 1.5\) Hz, 1H), 2.25 (d, \(J = 8.9\) Hz, 1H), 1.59 (s, 3H) ppm.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta = 167.4, 147.9, 144.0, 140.5, 140.3, 138.7, 138.4, 136.0, 134.7, 129.0, 129.0, 127.9, 127.6, 127.4, 126.8, 124.0, 123.9, 123.9, 123.6, 122.1, 121.4, 121.3, 116.6, 86.8, 62.6, 36.1, 31.4, 30.7, 25.3 ppm.

IR (film): \(\nu_{\text{max}} = 1598, 1485, 1375, 1084, 756, 702\) cm\(^{-1}\).
HRMS (ESI, m/z) calculated for C_{42}H_{34}N_{2}NaO_{2}S\^[M+Na]^+: 653.2233; found: 653.2231.

[\alpha]_D^{21}: -77.3 (c 1.03, CHCl_3).
3.2.4 NMR Spectra
3.2.5 Chiral HPLC Chromatograms of 500

Figure SI-4: Chiral HPLC chromatogram of (rac)-500.
Figure SI-5: Chiral HPLC chromatogram of (-)-500.

The enantiomeric excess was determined to be 98% by chiral HPLC analysis (Chiral PAK IA, 0.3ml/min, 91:9 Hexanes/ethanol, λ = 254 nm) tᵣ (major) = 18.5 min, tᵣ (minor) = 25.0 min.
3.2.6 DFT Calculation

The ground state electronic structure of the full model of compound 523 was calculated by density functional theory (DFT) methods using the Gaussian 16 program packages. Open shell systems were calculated by the unrestricted Kohn-Sham approach (UKS). Geometry optimisation followed by vibrational analysis was performed in vacuum. The 6-31G(d) polarised double-ζ basis sets were employed together with the Becke Three-Parameter Hybrid Functionals (B3LYP). Atomic coordinates of the calculated structure are provided in Table SI-2.

*Figure SI-6: Calculated structure of 523.*
Table SI-2: Atomic coordinates of structure 523.

<table>
<thead>
<tr>
<th>atom</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>-4.63328</td>
<td>-0.59121</td>
<td>-1.67803</td>
</tr>
<tr>
<td>C</td>
<td>-3.60949</td>
<td>-0.30563</td>
<td>-0.80086</td>
</tr>
<tr>
<td>C</td>
<td>-3.18364</td>
<td>-1.30043</td>
<td>0.1346</td>
</tr>
<tr>
<td>C</td>
<td>-3.83786</td>
<td>-2.57152</td>
<td>0.12748</td>
</tr>
<tr>
<td>C</td>
<td>-4.89342</td>
<td>-2.81755</td>
<td>-0.78394</td>
</tr>
<tr>
<td>C</td>
<td>-5.28134</td>
<td>-1.84411</td>
<td>-1.66991</td>
</tr>
<tr>
<td>H</td>
<td>-4.92903</td>
<td>0.16603</td>
<td>-2.3976</td>
</tr>
<tr>
<td>C</td>
<td>-3.37619</td>
<td>-3.55004</td>
<td>1.04088</td>
</tr>
<tr>
<td>H</td>
<td>-3.85716</td>
<td>-4.52627</td>
<td>1.05722</td>
</tr>
<tr>
<td>H</td>
<td>-1.94448</td>
<td>-3.99046</td>
<td>2.58355</td>
</tr>
<tr>
<td>H</td>
<td>-0.92725</td>
<td>-1.71106</td>
<td>2.47367</td>
</tr>
<tr>
<td>N</td>
<td>-2.15858</td>
<td>-1.02881</td>
<td>0.99082</td>
</tr>
<tr>
<td>N</td>
<td>-2.93689</td>
<td>0.94266</td>
<td>-0.89286</td>
</tr>
<tr>
<td>C</td>
<td>-3.07585</td>
<td>2.02461</td>
<td>0.09432</td>
</tr>
<tr>
<td>C</td>
<td>-2.23186</td>
<td>1.30812</td>
<td>-2.02898</td>
</tr>
<tr>
<td>C</td>
<td>-2.15203</td>
<td>3.13125</td>
<td>-0.43801</td>
</tr>
<tr>
<td>C</td>
<td>-1.65141</td>
<td>2.67285</td>
<td>-1.78783</td>
</tr>
<tr>
<td>H</td>
<td>-1.54008</td>
<td>3.31711</td>
<td>-2.65445</td>
</tr>
<tr>
<td>O</td>
<td>-2.8406</td>
<td>1.63268</td>
<td>1.41122</td>
</tr>
<tr>
<td>H</td>
<td>-2.24548</td>
<td>0.85368</td>
<td>1.38701</td>
</tr>
<tr>
<td>O</td>
<td>-2.11942</td>
<td>0.64247</td>
<td>-3.03722</td>
</tr>
<tr>
<td>C</td>
<td>-0.6829</td>
<td>2.79992</td>
<td>-0.62225</td>
</tr>
<tr>
<td>H</td>
<td>-0.08373</td>
<td>3.71078</td>
<td>-0.68757</td>
</tr>
<tr>
<td>C</td>
<td>-2.57094</td>
<td>4.54757</td>
<td>-0.12908</td>
</tr>
<tr>
<td>H</td>
<td>-2.60027</td>
<td>4.71286</td>
<td>0.95567</td>
</tr>
<tr>
<td>H</td>
<td>-1.87487</td>
<td>5.27473</td>
<td>-0.56264</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>atom</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>-3.57149</td>
<td>4.76271</td>
<td>-0.52628</td>
</tr>
<tr>
<td>C</td>
<td>0.06427</td>
<td>1.66497</td>
<td>-0.02378</td>
</tr>
<tr>
<td>C</td>
<td>0.54707</td>
<td>1.95949</td>
<td>1.33975</td>
</tr>
<tr>
<td>C</td>
<td>0.48427</td>
<td>0.53181</td>
<td>-0.65047</td>
</tr>
<tr>
<td>C</td>
<td>1.24927</td>
<td>0.37517</td>
<td>1.48688</td>
</tr>
<tr>
<td>C</td>
<td>0.42296</td>
<td>2.45209</td>
<td>2.43978</td>
</tr>
<tr>
<td>H</td>
<td>0.30799</td>
<td>0.18159</td>
<td>-1.65729</td>
</tr>
<tr>
<td>C</td>
<td>1.83099</td>
<td>-0.00217</td>
<td>2.69702</td>
</tr>
<tr>
<td>C</td>
<td>1.01036</td>
<td>2.08922</td>
<td>3.64358</td>
</tr>
<tr>
<td>H</td>
<td>-0.13667</td>
<td>3.37907</td>
<td>2.34924</td>
</tr>
<tr>
<td>C</td>
<td>1.70595</td>
<td>0.87641</td>
<td>3.7682</td>
</tr>
<tr>
<td>H</td>
<td>2.34168</td>
<td>-0.95201</td>
<td>2.80224</td>
</tr>
<tr>
<td>H</td>
<td>0.92151</td>
<td>2.74545</td>
<td>4.50572</td>
</tr>
<tr>
<td>H</td>
<td>2.14894</td>
<td>0.60908</td>
<td>4.72437</td>
</tr>
<tr>
<td>S</td>
<td>2.06311</td>
<td>-1.64395</td>
<td>-0.23487</td>
</tr>
<tr>
<td>O</td>
<td>1.43819</td>
<td>-2.08164</td>
<td>-1.45713</td>
</tr>
<tr>
<td>O</td>
<td>2.16845</td>
<td>-2.48527</td>
<td>0.93267</td>
</tr>
<tr>
<td>C</td>
<td>3.67642</td>
<td>-1.01101</td>
<td>-0.62269</td>
</tr>
<tr>
<td>C</td>
<td>3.92031</td>
<td>-0.50268</td>
<td>-1.89951</td>
</tr>
<tr>
<td>C</td>
<td>4.68309</td>
<td>-1.03417</td>
<td>0.34025</td>
</tr>
<tr>
<td>C</td>
<td>5.18045</td>
<td>-0.00196</td>
<td>-2.19978</td>
</tr>
<tr>
<td>H</td>
<td>3.13493</td>
<td>-0.52057</td>
<td>-2.64868</td>
</tr>
<tr>
<td>C</td>
<td>5.93928</td>
<td>-0.52887</td>
<td>0.02066</td>
</tr>
<tr>
<td>H</td>
<td>4.48769</td>
<td>-1.46178</td>
<td>1.31795</td>
</tr>
<tr>
<td>C</td>
<td>6.20698</td>
<td>-5.00E-05</td>
<td>-1.24619</td>
</tr>
<tr>
<td>H</td>
<td>5.37523</td>
<td>0.38784</td>
<td>-3.19667</td>
</tr>
<tr>
<td>H</td>
<td>6.72873</td>
<td>-0.55241</td>
<td>0.76868</td>
</tr>
<tr>
<td>C</td>
<td>7.56283</td>
<td>0.57005</td>
<td>-1.57804</td>
</tr>
<tr>
<td>H</td>
<td>8.33792</td>
<td>0.178</td>
<td>-0.91139</td>
</tr>
<tr>
<td>H</td>
<td>7.85193</td>
<td>0.34224</td>
<td>-2.61018</td>
</tr>
<tr>
<td>H</td>
<td>7.56491</td>
<td>1.66394</td>
<td>-1.476</td>
</tr>
<tr>
<td>N</td>
<td>1.18092</td>
<td>-0.28349</td>
<td>0.24855</td>
</tr>
<tr>
<td>H</td>
<td>-4.11301</td>
<td>2.39853</td>
<td>0.07515</td>
</tr>
</tbody>
</table>
3.2.7 X-ray Crystallography

Figure Si-7: ORTEP-representation of 515 with ellipsoid drawn at the 50% probability level and hydrogens omitted for clarity.
Table S1-3: Crystal data and structure refinement for 515.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identification code</td>
<td>515</td>
</tr>
<tr>
<td>Empirical formula</td>
<td>C_{34}H_{30}N_{2}O_{2}</td>
</tr>
<tr>
<td>Formula weight</td>
<td>498.60</td>
</tr>
<tr>
<td>Temperature/K</td>
<td>100</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P2$_1$</td>
</tr>
<tr>
<td>a/Å</td>
<td>10.1495(10)</td>
</tr>
<tr>
<td>b/Å</td>
<td>9.6610(5)</td>
</tr>
<tr>
<td>c/Å</td>
<td>13.7408(12)</td>
</tr>
<tr>
<td>α/°</td>
<td>90</td>
</tr>
<tr>
<td>β/°</td>
<td>103.037(7)</td>
</tr>
<tr>
<td>γ/°</td>
<td>90</td>
</tr>
<tr>
<td>Volume/Å$^3$</td>
<td>1312.62(19)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>$\rho$calc/g/cm$^3$</td>
<td>1.262</td>
</tr>
<tr>
<td>$\mu$/mm$^{-1}$</td>
<td>0.078</td>
</tr>
<tr>
<td>F(000)</td>
<td>528.0</td>
</tr>
<tr>
<td>Crystal size/mm$^3$</td>
<td>0.5 × 0.267 × 0.1</td>
</tr>
<tr>
<td>Radiation</td>
<td>MoKα ($\lambda$ = 0.71073)</td>
</tr>
<tr>
<td>2Θ range for data collection/°</td>
<td>4.536 to 58.436</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-13 ≤ h ≤ 13, -12 ≤ k ≤ 13, -18 ≤ l ≤ 18</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>16080</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>6831 [$R_{int} = 0.0192$, $R_{sigma} = 0.0233$]</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>6831/1/345</td>
</tr>
<tr>
<td>Goodness-of-fit on $F^2$</td>
<td>1.035</td>
</tr>
<tr>
<td>Final R indexes [I&gt;=2σ (I)]</td>
<td>$R_1 = 0.0351$, $wR_2 = 0.0781$</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
<td>$R_1 = 0.0432$, $wR_2 = 0.0822$</td>
</tr>
<tr>
<td>Largest diff. peak/hole/Å$^3$</td>
<td>0.22/-0.15</td>
</tr>
<tr>
<td>Flack parameter</td>
<td>0.3(5)</td>
</tr>
</tbody>
</table>
Table SI-4: Fractional Atomic Coordinates ($\times 10^4$) and Equivalent Isotropic Displacement Parameters ($\AA^2 \times 10^3$) for S15. 

$U_{eq}$ is defined as 1/3 of the trace of the orthogonalised $U_{ij}$ tensor.

<table>
<thead>
<tr>
<th>Atom</th>
<th>$x$</th>
<th>$y$</th>
<th>$z$</th>
<th>$U(eq)$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C01</td>
<td>7527.0 (18)</td>
<td>6066 (2)</td>
<td>6925.4 (14)</td>
<td>28.2 (4)</td>
</tr>
<tr>
<td>C02</td>
<td>7144.5 (18)</td>
<td>6231 (2)</td>
<td>5822.2 (14)</td>
<td>26.0 (4)</td>
</tr>
<tr>
<td>C03</td>
<td>7336.5 (19)</td>
<td>7623 (2)</td>
<td>5386.7 (15)</td>
<td>29.9 (4)</td>
</tr>
<tr>
<td>C04</td>
<td>5933.6 (17)</td>
<td>7136.9 (19)</td>
<td>5369.5 (13)</td>
<td>21.9 (3)</td>
</tr>
<tr>
<td>C05</td>
<td>5175.7 (17)</td>
<td>7801.5 (18)</td>
<td>6069.1 (13)</td>
<td>20.6 (3)</td>
</tr>
<tr>
<td>C06</td>
<td>5067 (2)</td>
<td>6657 (2)</td>
<td>4388.1 (13)</td>
<td>26.7 (4)</td>
</tr>
<tr>
<td>C07</td>
<td>7730.2 (17)</td>
<td>4245 (2)</td>
<td>8227.7 (14)</td>
<td>27.3 (4)</td>
</tr>
<tr>
<td>C08</td>
<td>7734 (2)</td>
<td>5054 (2)</td>
<td>9049.7 (15)</td>
<td>33.6 (5)</td>
</tr>
<tr>
<td>C09</td>
<td>8032 (2)</td>
<td>4454 (3)</td>
<td>10010.4 (16)</td>
<td>39.5 (5)</td>
</tr>
<tr>
<td>C10</td>
<td>8354 (2)</td>
<td>3088 (3)</td>
<td>10148.8 (16)</td>
<td>40.8 (5)</td>
</tr>
<tr>
<td>C11</td>
<td>8359 (2)</td>
<td>2227 (2)</td>
<td>9321.2 (15)</td>
<td>32.8 (4)</td>
</tr>
<tr>
<td>C12</td>
<td>8684 (2)</td>
<td>807 (3)</td>
<td>9397.6 (18)</td>
<td>39.8 (5)</td>
</tr>
<tr>
<td>C13</td>
<td>8600 (2)</td>
<td>41 (2)</td>
<td>8554.8 (18)</td>
<td>39.1 (5)</td>
</tr>
<tr>
<td>C14</td>
<td>8209 (2)</td>
<td>697 (2)</td>
<td>7622.8 (17)</td>
<td>35.8 (5)</td>
</tr>
<tr>
<td>C15</td>
<td>8013.7 (17)</td>
<td>2802 (2)</td>
<td>8346.7 (14)</td>
<td>27.1 (4)</td>
</tr>
<tr>
<td>C16</td>
<td>3438.2 (16)</td>
<td>7140.8 (18)</td>
<td>6962.3 (12)</td>
<td>18.4 (3)</td>
</tr>
<tr>
<td>C17</td>
<td>4191.2 (16)</td>
<td>7900.2 (18)</td>
<td>7912.1 (12)</td>
<td>20.0 (3)</td>
</tr>
<tr>
<td>C18</td>
<td>4720.1 (17)</td>
<td>7155.5 (19)</td>
<td>8781.5 (13)</td>
<td>23.3 (3)</td>
</tr>
<tr>
<td>C19</td>
<td>5494.8 (19)</td>
<td>7805 (2)</td>
<td>9620.1 (13)</td>
<td>27.0 (4)</td>
</tr>
<tr>
<td>C20</td>
<td>5766.7 (19)</td>
<td>9201 (2)</td>
<td>9605.1 (14)</td>
<td>27.7 (4)</td>
</tr>
<tr>
<td>C21</td>
<td>5260 (2)</td>
<td>9953 (2)</td>
<td>8742.9 (15)</td>
<td>28.3 (4)</td>
</tr>
<tr>
<td>C22</td>
<td>4481.7 (18)</td>
<td>9310.2 (18)</td>
<td>7908.5 (13)</td>
<td>23.5 (4)</td>
</tr>
<tr>
<td>C23</td>
<td>2836.6 (17)</td>
<td>5781.7 (19)</td>
<td>7231.2 (12)</td>
<td>20.5 (3)</td>
</tr>
<tr>
<td>C24</td>
<td>3511.2 (19)</td>
<td>4529 (2)</td>
<td>7220.8 (13)</td>
<td>25.4 (4)</td>
</tr>
<tr>
<td>C25</td>
<td>2980 (2)</td>
<td>3307 (2)</td>
<td>7516.3 (14)</td>
<td>31.0 (4)</td>
</tr>
<tr>
<td>C26</td>
<td>1777 (2)</td>
<td>3326 (2)</td>
<td>7831.8 (14)</td>
<td>30.4 (4)</td>
</tr>
<tr>
<td>C27</td>
<td>1099.9 (19)</td>
<td>4562 (2)</td>
<td>7842.1 (14)</td>
<td>28.7 (4)</td>
</tr>
<tr>
<td>C28</td>
<td>1617.3 (18)</td>
<td>5777 (2)</td>
<td>7538.4 (13)</td>
<td>24.1 (4)</td>
</tr>
<tr>
<td>C29</td>
<td>2312.3 (16)</td>
<td>7995.1 (18)</td>
<td>6289.4 (13)</td>
<td>20.5 (3)</td>
</tr>
<tr>
<td>C30</td>
<td>1613.6 (18)</td>
<td>9055 (2)</td>
<td>6643.5 (14)</td>
<td>24.9 (4)</td>
</tr>
<tr>
<td>C31</td>
<td>582.4 (19)</td>
<td>9768 (2)</td>
<td>5998.4 (15)</td>
<td>29.4 (4)</td>
</tr>
<tr>
<td>C32</td>
<td>207.4 (17)</td>
<td>9413 (2)</td>
<td>4999.3 (15)</td>
<td>27.2 (4)</td>
</tr>
<tr>
<td>C33</td>
<td>865.6 (18)</td>
<td>8333 (2)</td>
<td>4643.5 (13)</td>
<td>24.8 (4)</td>
</tr>
<tr>
<td>C34</td>
<td>1907.6 (17)</td>
<td>7630.4 (19)</td>
<td>5281.5 (13)</td>
<td>22.2 (3)</td>
</tr>
<tr>
<td>N1</td>
<td>7446.5 (16)</td>
<td>4731.9 (18)</td>
<td>7240.3 (12)</td>
<td>28.3 (3)</td>
</tr>
<tr>
<td>N2</td>
<td>7937.0 (16)</td>
<td>2028.3 (19)</td>
<td>7503.9 (12)</td>
<td>29.8 (4)</td>
</tr>
<tr>
<td>O1</td>
<td>7854.2 (15)</td>
<td>7034.5 (17)</td>
<td>7504.0 (11)</td>
<td>36.1 (3)</td>
</tr>
<tr>
<td>O2</td>
<td>4404.5 (12)</td>
<td>6720.7 (12)</td>
<td>6393.1 (9)</td>
<td>19.4 (2)</td>
</tr>
</tbody>
</table>
Table SI-5: Anisotropic Displacement Parameters (Å²×10³) for 515. The Anisotropic displacement factor exponent takes the form: -2π²[\(h²U_{11} + 2hkU_{12} + \ldots\)].

<table>
<thead>
<tr>
<th>Atom</th>
<th>U₁₁</th>
<th>U₂₂</th>
<th>U₃₃</th>
<th>U₁₂</th>
<th>U₁₃</th>
<th>U₂₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>C01</td>
<td>18.7(8)</td>
<td>36.2(11)</td>
<td>28.5(9)</td>
<td>-0.6(8)</td>
<td>3.0(7)</td>
<td>3.9(7)</td>
</tr>
<tr>
<td>C02</td>
<td>22.0(8)</td>
<td>29.7(10)</td>
<td>27.0(9)</td>
<td>-1.8(7)</td>
<td>7.2(7)</td>
<td>3.8(7)</td>
</tr>
<tr>
<td>C03</td>
<td>27.1(9)</td>
<td>33.6(10)</td>
<td>32.0(9)</td>
<td>-1.7(8)</td>
<td>12.9(8)</td>
<td>-4.6(8)</td>
</tr>
<tr>
<td>C04</td>
<td>23.6(8)</td>
<td>21.3(8)</td>
<td>22.1(8)</td>
<td>0.3(7)</td>
<td>8.0(6)</td>
<td>0.1(7)</td>
</tr>
<tr>
<td>C05</td>
<td>21.6(7)</td>
<td>18.4(8)</td>
<td>22.7(8)</td>
<td>-0.4(7)</td>
<td>7.1(6)</td>
<td>-0.7(6)</td>
</tr>
<tr>
<td>C06</td>
<td>30.6(9)</td>
<td>28.4(9)</td>
<td>21.7(8)</td>
<td>-1.8(7)</td>
<td>7.2(7)</td>
<td>2.0(7)</td>
</tr>
<tr>
<td>C07</td>
<td>17.4(7)</td>
<td>38.6(11)</td>
<td>25.8(9)</td>
<td>0.7(8)</td>
<td>4.6(6)</td>
<td>0.8(7)</td>
</tr>
<tr>
<td>C08</td>
<td>28.7(10)</td>
<td>42.9(12)</td>
<td>29.7(10)</td>
<td>-3.0(9)</td>
<td>7.4(8)</td>
<td>4.1(8)</td>
</tr>
<tr>
<td>C09</td>
<td>41.8(11)</td>
<td>50.5(14)</td>
<td>27.0(10)</td>
<td>-4.6(10)</td>
<td>9.7(8)</td>
<td>-4.0(11)</td>
</tr>
<tr>
<td>C10</td>
<td>41.9(12)</td>
<td>53.5(15)</td>
<td>25.1(9)</td>
<td>5.3(9)</td>
<td>3.7(8)</td>
<td>-8.8(11)</td>
</tr>
<tr>
<td>C11</td>
<td>25.2(9)</td>
<td>41.9(12)</td>
<td>30.0(10)</td>
<td>5.6(9)</td>
<td>3.5(7)</td>
<td>-7.2(8)</td>
</tr>
<tr>
<td>C12</td>
<td>34.1(10)</td>
<td>40.7(12)</td>
<td>41.6(12)</td>
<td>12.2(10)</td>
<td>1.9(9)</td>
<td>-8.2(9)</td>
</tr>
<tr>
<td>C13</td>
<td>33.4(11)</td>
<td>31.7(12)</td>
<td>50.3(13)</td>
<td>7.1(10)</td>
<td>5.5(10)</td>
<td>-5.8(9)</td>
</tr>
<tr>
<td>C14</td>
<td>32.3(10)</td>
<td>35.0(11)</td>
<td>41.0(11)</td>
<td>-2.3(9)</td>
<td>10.0(9)</td>
<td>-5.0(9)</td>
</tr>
<tr>
<td>C15</td>
<td>17.5(7)</td>
<td>36.0(10)</td>
<td>27.6(9)</td>
<td>1.2(8)</td>
<td>4.9(7)</td>
<td>-2.4(7)</td>
</tr>
<tr>
<td>C16</td>
<td>20.3(7)</td>
<td>18.4(8)</td>
<td>17.2(7)</td>
<td>-0.5(6)</td>
<td>5.6(6)</td>
<td>1.3(6)</td>
</tr>
<tr>
<td>C17</td>
<td>19.6(7)</td>
<td>22.1(8)</td>
<td>19.2(7)</td>
<td>-1.9(6)</td>
<td>6.1(6)</td>
<td>0.9(6)</td>
</tr>
<tr>
<td>C18</td>
<td>24.5(8)</td>
<td>21.9(9)</td>
<td>23.4(8)</td>
<td>1.0(7)</td>
<td>5.1(7)</td>
<td>-0.6(7)</td>
</tr>
<tr>
<td>C19</td>
<td>28.0(8)</td>
<td>32.1(10)</td>
<td>20.2(8)</td>
<td>0.2(7)</td>
<td>3.6(7)</td>
<td>0.2(8)</td>
</tr>
<tr>
<td>C20</td>
<td>26.8(8)</td>
<td>32.0(11)</td>
<td>23.2(8)</td>
<td>-7.7(7)</td>
<td>3.7(7)</td>
<td>-1.6(8)</td>
</tr>
<tr>
<td>C21</td>
<td>30.9(9)</td>
<td>22.8(9)</td>
<td>31.6(10)</td>
<td>-6.5(8)</td>
<td>7.6(8)</td>
<td>-1.2(7)</td>
</tr>
<tr>
<td>C22</td>
<td>27.9(8)</td>
<td>20.2(9)</td>
<td>22.4(8)</td>
<td>-0.1(7)</td>
<td>5.2(7)</td>
<td>2.8(7)</td>
</tr>
<tr>
<td>C23</td>
<td>22.3(8)</td>
<td>22.6(8)</td>
<td>16.0(7)</td>
<td>-0.2(6)</td>
<td>3.2(6)</td>
<td>-1.3(7)</td>
</tr>
<tr>
<td>C24</td>
<td>30.9(9)</td>
<td>21.3(9)</td>
<td>25.4(8)</td>
<td>0.7(7)</td>
<td>9.3(7)</td>
<td>-0.1(7)</td>
</tr>
<tr>
<td>C25</td>
<td>44.8(11)</td>
<td>20.1(9)</td>
<td>28.2(9)</td>
<td>0.5(7)</td>
<td>8.7(8)</td>
<td>-1.4(8)</td>
</tr>
<tr>
<td>C26</td>
<td>39.0(10)</td>
<td>28.2(10)</td>
<td>22.3(8)</td>
<td>3.0(8)</td>
<td>3.5(7)</td>
<td>-11.9(8)</td>
</tr>
<tr>
<td>C27</td>
<td>25.5(8)</td>
<td>36.7(10)</td>
<td>22.9(8)</td>
<td>2.2(8)</td>
<td>3.5(7)</td>
<td>-7.9(8)</td>
</tr>
<tr>
<td>C28</td>
<td>23.0(8)</td>
<td>28.0(9)</td>
<td>20.7(8)</td>
<td>0.9(7)</td>
<td>3.8(6)</td>
<td>-1.6(7)</td>
</tr>
<tr>
<td>C29</td>
<td>18.6(7)</td>
<td>21.0(8)</td>
<td>22.1(8)</td>
<td>1.9(6)</td>
<td>5.3(6)</td>
<td>0.2(6)</td>
</tr>
<tr>
<td>C30</td>
<td>24.2(8)</td>
<td>27.0(9)</td>
<td>24.5(8)</td>
<td>0.8(7)</td>
<td>7.5(7)</td>
<td>4.2(7)</td>
</tr>
<tr>
<td>C31</td>
<td>23.8(8)</td>
<td>30.4(10)</td>
<td>35.6(10)</td>
<td>4.7(8)</td>
<td>10.2(7)</td>
<td>7.3(8)</td>
</tr>
<tr>
<td>C32</td>
<td>18.5(8)</td>
<td>29.8(10)</td>
<td>32.6(9)</td>
<td>9.9(8)</td>
<td>4.1(7)</td>
<td>0.7(7)</td>
</tr>
<tr>
<td>C33</td>
<td>22.2(8)</td>
<td>28.1(10)</td>
<td>22.8(8)</td>
<td>3.2(7)</td>
<td>2.1(7)</td>
<td>-4.6(7)</td>
</tr>
<tr>
<td>C34</td>
<td>21.1(7)</td>
<td>22.7(8)</td>
<td>23.3(8)</td>
<td>0.3(7)</td>
<td>5.9(6)</td>
<td>-1.4(7)</td>
</tr>
<tr>
<td>N01</td>
<td>27.0(8)</td>
<td>33.6(9)</td>
<td>23.3(7)</td>
<td>-1.7(7)</td>
<td>3.2(6)</td>
<td>4.2(7)</td>
</tr>
<tr>
<td>N02</td>
<td>26.0(8)</td>
<td>33.7(9)</td>
<td>30.1(8)</td>
<td>0.0(7)</td>
<td>6.9(6)</td>
<td>-2.2(7)</td>
</tr>
<tr>
<td>O01</td>
<td>35.9(8)</td>
<td>37.3(9)</td>
<td>31.8(7)</td>
<td>-3.7(6)</td>
<td>0.7(6)</td>
<td>-1.5(6)</td>
</tr>
<tr>
<td>O02</td>
<td>20.9(6)</td>
<td>18.1(6)</td>
<td>21.0(6)</td>
<td>0.0(5)</td>
<td>8.5(4)</td>
<td>0.9(4)</td>
</tr>
<tr>
<td>Atom</td>
<td>Atom</td>
<td>Length/Å</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C02</td>
<td>C01</td>
<td>1.486(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C03</td>
<td>C02</td>
<td>1.503(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C04</td>
<td>C03</td>
<td>1.494(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C04</td>
<td>C02</td>
<td>1.523(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C04</td>
<td>C06</td>
<td>1.507(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C05</td>
<td>C04</td>
<td>1.504(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C07</td>
<td>C15</td>
<td>1.425(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C07</td>
<td>C08</td>
<td>1.373(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C08</td>
<td>C09</td>
<td>1.411(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C10</td>
<td>C11</td>
<td>1.410(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C10</td>
<td>C09</td>
<td>1.362(4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C11</td>
<td>C12</td>
<td>1.409(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C13</td>
<td>C14</td>
<td>1.403(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C13</td>
<td>C12</td>
<td>1.361(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C15</td>
<td>C11</td>
<td>1.419(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C16</td>
<td>C17</td>
<td>1.541(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C16</td>
<td>C29</td>
<td>1.528(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C17</td>
<td>C22</td>
<td>1.394(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C18</td>
<td>C17</td>
<td>1.394(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C18</td>
<td>C19</td>
<td>1.389(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C19</td>
<td>C20</td>
<td>1.378(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C21</td>
<td>C20</td>
<td>1.386(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C22</td>
<td>C21</td>
<td>1.384(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C23</td>
<td>C16</td>
<td>1.528(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C23</td>
<td>C28</td>
<td>1.395(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C23</td>
<td>C24</td>
<td>1.392(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C24</td>
<td>C25</td>
<td>1.396(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C26</td>
<td>C25</td>
<td>1.385(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C27</td>
<td>C26</td>
<td>1.379(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C28</td>
<td>C27</td>
<td>1.388(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C29</td>
<td>C30</td>
<td>1.394(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C31</td>
<td>C30</td>
<td>1.392(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C32</td>
<td>C33</td>
<td>1.386(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C32</td>
<td>C31</td>
<td>1.383(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C33</td>
<td>C34</td>
<td>1.389(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C34</td>
<td>C29</td>
<td>1.398(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N01</td>
<td>C07</td>
<td>1.403(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N01</td>
<td>C01</td>
<td>1.368(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N02</td>
<td>C15</td>
<td>1.366(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N02</td>
<td>C14</td>
<td>1.318(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O01</td>
<td>C01</td>
<td>1.224(3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O02</td>
<td>C16</td>
<td>1.4437(19)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O02</td>
<td>C05</td>
<td>1.435(2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table SI-7: Bond Angles for 515.

<table>
<thead>
<tr>
<th>Atom</th>
<th>Atom</th>
<th>Atom</th>
<th>Angle/°</th>
</tr>
</thead>
<tbody>
<tr>
<td>C01</td>
<td>N01</td>
<td>C07</td>
<td>127.45(17)</td>
</tr>
<tr>
<td>C01</td>
<td>C02</td>
<td>C04</td>
<td>118.65(15)</td>
</tr>
<tr>
<td>C01</td>
<td>C02</td>
<td>C03</td>
<td>118.33(17)</td>
</tr>
<tr>
<td>C03</td>
<td>C04</td>
<td>C05</td>
<td>118.58(16)</td>
</tr>
<tr>
<td>C03</td>
<td>C04</td>
<td>C02</td>
<td>59.75(13)</td>
</tr>
<tr>
<td>C03</td>
<td>C04</td>
<td>C06</td>
<td>118.21(15)</td>
</tr>
<tr>
<td>C03</td>
<td>C02</td>
<td>C04</td>
<td>59.19(12)</td>
</tr>
<tr>
<td>C04</td>
<td>C03</td>
<td>C02</td>
<td>61.06(12)</td>
</tr>
<tr>
<td>C05</td>
<td>O02</td>
<td>C16</td>
<td>116.64(13)</td>
</tr>
<tr>
<td>C05</td>
<td>C04</td>
<td>C02</td>
<td>117.80(15)</td>
</tr>
<tr>
<td>C05</td>
<td>C04</td>
<td>C06</td>
<td>115.07(15)</td>
</tr>
<tr>
<td>C06</td>
<td>C04</td>
<td>C02</td>
<td>116.29(15)</td>
</tr>
<tr>
<td>C07</td>
<td>C08</td>
<td>C09</td>
<td>119.7(2)</td>
</tr>
<tr>
<td>C08</td>
<td>C07</td>
<td>N01</td>
<td>124.5(2)</td>
</tr>
<tr>
<td>C08</td>
<td>C07</td>
<td>C15</td>
<td>119.97(19)</td>
</tr>
<tr>
<td>C09</td>
<td>C10</td>
<td>C11</td>
<td>120.2(2)</td>
</tr>
<tr>
<td>C10</td>
<td>C11</td>
<td>C15</td>
<td>119.0(2)</td>
</tr>
<tr>
<td>C10</td>
<td>C09</td>
<td>C08</td>
<td>121.5(2)</td>
</tr>
<tr>
<td>C11</td>
<td>C15</td>
<td>C07</td>
<td>119.47(18)</td>
</tr>
<tr>
<td>C12</td>
<td>C13</td>
<td>C14</td>
<td>118.8(2)</td>
</tr>
<tr>
<td>C12</td>
<td>C11</td>
<td>C15</td>
<td>117.1(2)</td>
</tr>
<tr>
<td>C12</td>
<td>C11</td>
<td>C10</td>
<td>123.9(2)</td>
</tr>
<tr>
<td>C13</td>
<td>C12</td>
<td>C11</td>
<td>119.8(2)</td>
</tr>
<tr>
<td>C14</td>
<td>N02</td>
<td>C15</td>
<td>117.31(19)</td>
</tr>
<tr>
<td>C18</td>
<td>C17</td>
<td>C16</td>
<td>120.09(15)</td>
</tr>
<tr>
<td>C19</td>
<td>C18</td>
<td>C17</td>
<td>120.94(17)</td>
</tr>
<tr>
<td>C19</td>
<td>C20</td>
<td>C21</td>
<td>119.29(17)</td>
</tr>
<tr>
<td>C20</td>
<td>C19</td>
<td>C18</td>
<td>120.48(18)</td>
</tr>
<tr>
<td>C21</td>
<td>C22</td>
<td>C17</td>
<td>121.15(17)</td>
</tr>
<tr>
<td>C22</td>
<td>C17</td>
<td>C16</td>
<td>121.80(15)</td>
</tr>
<tr>
<td>C22</td>
<td>C17</td>
<td>C18</td>
<td>117.81(16)</td>
</tr>
<tr>
<td>C22</td>
<td>C21</td>
<td>C20</td>
<td>120.32(18)</td>
</tr>
<tr>
<td>C23</td>
<td>C16</td>
<td>C17</td>
<td>110.68(13)</td>
</tr>
<tr>
<td>C23</td>
<td>C16</td>
<td>C29</td>
<td>108.86(13)</td>
</tr>
<tr>
<td>C23</td>
<td>C24</td>
<td>C25</td>
<td>120.60(17)</td>
</tr>
<tr>
<td>C24</td>
<td>C23</td>
<td>C16</td>
<td>121.35(15)</td>
</tr>
<tr>
<td>C24</td>
<td>C23</td>
<td>C28</td>
<td>118.20(17)</td>
</tr>
<tr>
<td>C26</td>
<td>C27</td>
<td>C28</td>
<td>120.40(17)</td>
</tr>
<tr>
<td>C26</td>
<td>C25</td>
<td>C24</td>
<td>120.36(19)</td>
</tr>
<tr>
<td>C27</td>
<td>C28</td>
<td>C23</td>
<td>121.00(18)</td>
</tr>
<tr>
<td>C27</td>
<td>C26</td>
<td>C25</td>
<td>119.43(18)</td>
</tr>
<tr>
<td>C28</td>
<td>C23</td>
<td>C16</td>
<td>120.39(16)</td>
</tr>
<tr>
<td>Bond Pair</td>
<td>Bond Angle (°)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>-----------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C29 - C16 - C17</td>
<td>114.39(14)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C30 - C29 - C16</td>
<td>123.49(15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C30 - C29 - C34</td>
<td>118.16(16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C31 - C32 - C33</td>
<td>119.37(17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C31 - C30 - C29</td>
<td>120.66(17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C32 - C31 - C30</td>
<td>120.55(18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C32 - C33 - C34</td>
<td>120.27(17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C33 - C34 - C29</td>
<td>120.93(17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C34 - C29 - C16</td>
<td>118.22(15)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N01 - C07 - C15</td>
<td>115.54(17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N01 - C01 - C02</td>
<td>113.78(17)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N02 - C15 - C07</td>
<td>117.81(18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N02 - C15 - C11</td>
<td>122.7(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N02 - C14 - C13</td>
<td>124.2(2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O01 - C01 - N01</td>
<td>122.79(18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O01 - C01 - C02</td>
<td>123.41(19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O02 - C16 - C23</td>
<td>104.29(13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O02 - C16 - C17</td>
<td>108.96(13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O02 - C16 - C29</td>
<td>109.18(13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O02 - C05 - C04</td>
<td>106.33(14)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table SI-8: Hydrogen Atom Coordinates (Å×10^4) and Isotropic Displacement Parameters (Å^2×10^3) for 515.

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>U(eq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H01</td>
<td>7192.92</td>
<td>4121.71</td>
<td>6780.49</td>
<td>34</td>
</tr>
<tr>
<td>H02</td>
<td>7292.7</td>
<td>5424.13</td>
<td>5427.69</td>
<td>31</td>
</tr>
<tr>
<td>H03A</td>
<td>7701.53</td>
<td>8362.38</td>
<td>5846.72</td>
<td>36</td>
</tr>
<tr>
<td>H03B</td>
<td>7618.78</td>
<td>7644.31</td>
<td>4757.83</td>
<td>36</td>
</tr>
<tr>
<td>H05A</td>
<td>5801.31</td>
<td>8208.08</td>
<td>6635.97</td>
<td>25</td>
</tr>
<tr>
<td>H05B</td>
<td>4581.89</td>
<td>8522.78</td>
<td>5728.17</td>
<td>25</td>
</tr>
<tr>
<td>H06A</td>
<td>4433.86</td>
<td>5976.24</td>
<td>4509.84</td>
<td>40</td>
</tr>
<tr>
<td>H06B</td>
<td>5630.75</td>
<td>6257.33</td>
<td>3987.64</td>
<td>40</td>
</tr>
<tr>
<td>H06C</td>
<td>4583.69</td>
<td>7431.58</td>
<td>4041.86</td>
<td>40</td>
</tr>
<tr>
<td>H08</td>
<td>7540.13</td>
<td>5994.13</td>
<td>8973.45</td>
<td>40</td>
</tr>
<tr>
<td>H09</td>
<td>8008.87</td>
<td>5003.05</td>
<td>10562.05</td>
<td>47</td>
</tr>
<tr>
<td>H10</td>
<td>8570.93</td>
<td>2722.13</td>
<td>10791.29</td>
<td>49</td>
</tr>
<tr>
<td>H12</td>
<td>8955.97</td>
<td>394.6</td>
<td>10022.41</td>
<td>48</td>
</tr>
<tr>
<td>H13</td>
<td>8798.2</td>
<td>-900.34</td>
<td>8595.55</td>
<td>47</td>
</tr>
<tr>
<td>H14</td>
<td>8136.81</td>
<td>157.24</td>
<td>7052.63</td>
<td>43</td>
</tr>
<tr>
<td>H18</td>
<td>4552.1</td>
<td>6210.66</td>
<td>8800.43</td>
<td>28</td>
</tr>
<tr>
<td>H19</td>
<td>5832.21</td>
<td>7293.17</td>
<td>10195.73</td>
<td>32</td>
</tr>
<tr>
<td>H20</td>
<td>6284.69</td>
<td>9633.61</td>
<td>10167.38</td>
<td>33</td>
</tr>
<tr>
<td>H21</td>
<td>5443.52</td>
<td>10894.97</td>
<td>8725.1</td>
<td>34</td>
</tr>
<tr>
<td>H22</td>
<td>4146.94</td>
<td>9827.79</td>
<td>7335.38</td>
<td>28</td>
</tr>
<tr>
<td>H24</td>
<td>4323.28</td>
<td>4506.17</td>
<td>7015.08</td>
<td>30</td>
</tr>
<tr>
<td>H25</td>
<td>3435.95</td>
<td>2475.1</td>
<td>7501.26</td>
<td>37</td>
</tr>
<tr>
<td>H26</td>
<td>1428.08</td>
<td>2512.97</td>
<td>8034.83</td>
<td>36</td>
</tr>
<tr>
<td>H27</td>
<td>292.02</td>
<td>4581.18</td>
<td>8053.85</td>
<td>34</td>
</tr>
<tr>
<td>H28</td>
<td>1143.66</td>
<td>6601.23</td>
<td>7539.86</td>
<td>29</td>
</tr>
<tr>
<td>H30</td>
<td>1838.89</td>
<td>9287.8</td>
<td>7317.39</td>
<td>30</td>
</tr>
<tr>
<td>H31</td>
<td>141.82</td>
<td>10489.82</td>
<td>6241.48</td>
<td>35</td>
</tr>
<tr>
<td>H32</td>
<td>-479.94</td>
<td>9893.85</td>
<td>4570.02</td>
<td>33</td>
</tr>
<tr>
<td>H33</td>
<td>608.42</td>
<td>8077.06</td>
<td>3974.91</td>
<td>30</td>
</tr>
<tr>
<td>H34</td>
<td>2342.18</td>
<td>6907.45</td>
<td>5034.75</td>
<td>27</td>
</tr>
</tbody>
</table>
Figure SI-8: ORTEP-representation of (rac)-570 with ellipsoid drawn at the 50% probability level and hydrogens omitted for clarity; only one stereoisomer shown. CCDC 1939947 contains the supplementary crystallographic data.
References


Danksagung

An aller erster Stelle möchte ich bei Frau Prof. Tanja Gaich ganz herzlich bedanken. Zunächst einmal für die Aufnahme in die Arbeitsgruppe und alles was ich dadurch in den letzten Jahren lernen konnte. Vielen Dank für die Freiheit und Möglichkeit eigene Ideen zu verfolgen und sich weiter zu entwickeln, aber auch für den ein oder anderen Schubs in die richtige Richtung. Sowohl fachlich als auch persönlich war die Zeit sehr bereichernd, vielen herzlichen Dank.


Meinen HiWi’s, Praktikanten und Bachelor Cedric, Chrissy, Thimo, Clarissa, Nathalie und Yevhenii danke ich für ihre Mitarbeit im Labor, die alle auch einen wichtigen Beitrag zu dieser Dissertation geleistet haben.

Mein weiterer herzlicher Dank gilt den festangestellten Mitarbeiter der AG. Danke Thomas für anregende Diskussionen, deinen unendlichen Fundus an Glasgeräten und stete Hilfsbereitschaft. Danke Malin für die unzähligen Messungen und stete Hilfe mit den Analytikgeräten.

Für die super Atmosphäre auf L8 möchte ich auch der gesamten AG Wittmann herzlich danken.

An dieser Stelle möchte ich auch dem NMR-Center bestehend aus Anke Friemel und Ulrich Haunz ganz herzlich für die unendlich vielen Messungen danken.

Vielen Dank an Jan Herberger für die schnelle Hilfe bei der DFT-Rechnung.

Ein ebenso besonderer Dank gilt meinen Freunden, von zu Hause oder aus Konstanz. Danke für die großartige Zeit und die unersetzbaren Erlebnisse. Ich bin froh, dass ich Euch habe und ihr seid die Besten.


“Carpe Diem! Seize the day, boys. Make your lives extraordinary!”

Robin Williams as John Keating in “Dead Poets Society” (1989)