

Synthesis and Functionalization of α -Chiral Bicyclo[1.1.1]pentanes



Marie L. J. Wong

Jesus College
University of Oxford

A thesis submitted to the Board of the Faculty of Physical Sciences
in partial fulfilment of the requirements for the degree of

Doctor of Philosophy

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This thesis is dedicated to my parents,

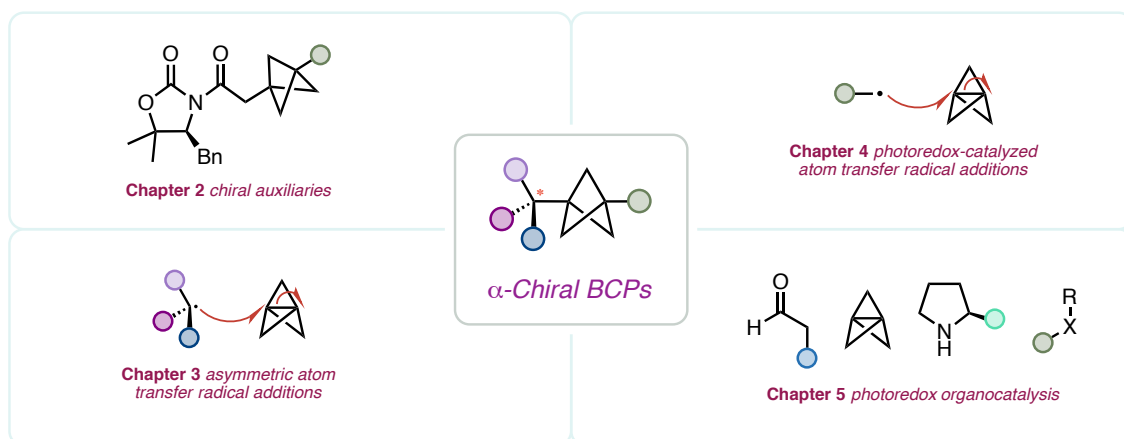
Toon Ngee and Pooi Yin.

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Recent years have seen many developments in bicyclo[1.1.1]pentane (BCP) chemistry, providing insights into their synthesis, reactivity and applications. This thesis describes the development of novel methodologies to synthesize α -chiral BCPs, an underexplored area with great potential due to the importance of stereocontrolled molecular design. The first general methodology for the synthesis of α -chiral BCPs was achieved, utilizing BCP substrates with chiral auxiliaries in a range of highly diastereoselective enolate reactions (**Chapter 2**). An asymmetric atom transfer radical addition was then investigated, involving the formation of a radical species in a chiral environment prior to reaction with [1.1.1]propellane (**Chapter 3**). Studies into alternative modes of radical formation resulted in a highly general photoredox-catalyzed atom transfer radical addition with [1.1.1]propellane to access 1,3-disubstituted BCPs, establishing the first use of photoredox catalysis for C–C σ -bond functionalization (**Chapter 4**). A multicatalytic strategy was then developed for a direct, enantioselective reaction between simple aldehydes and [1.1.1]propellane, representing the first report of the radical ring-opening of [1.1.1]propellane and construction of the stereocenter occurring in a single step (**Chapter 5**).



Declaration

The work presented in this thesis was conducted at the Department of Chemistry, University of Oxford. This thesis is a product of my own work and includes no results obtained through collaboration, except where specifically indicated in the text. The work presented has not been submitted, either partially or in full, for any qualification at this or at any other institution.

Marie L. J. Wong

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None of this would have been possible without the generous support and funding from the SBM, Jesus College and Wastech Multigreen. I would like to thank Prof. Darren Dixon, Prof. Martin Smith, Lara, Laura and Maitane for giving me a place here.

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help never ceases to amaze me. The group would not be complete without the many Part IIs and visiting students we have had over the years, thank you for making my time here so enjoyable. Zhong Hui, it was a pleasure working with you during your Part II. And last but not least, I am honored to have been a part of Team BCP. Dimitri, you have been a great friend and never fail to brighten the darkest days with some singing and dancing in the lab. Carlos, thank you so much for your patience and kindness – you have been an inspiration to me. Thank you to both of you for welcoming me into this project and for setting the bar so high! Ali, Beth, Helena and Jeremy, the best chemistry pals, I could not have asked for a better team to work with – thank you for all the good times. Ali and Steve, thank you for all your contributions to my projects.

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Finally, to the most important people in my life, my parents and my brother, thank you for *everything*. I know that this is your dream as much as it is mine and I would have never made it this far without you. I hope I can make it up to you one day.

Terima kasih.

Abbreviations

$[\alpha]_D$	Specific optical rotation
δ	Chemical shift
Δ	Heat (reflux)
$\Delta\Delta E^\ddagger$	Energy difference between competing transition states
$\Delta\Delta E^{\text{dist}}$	Energy difference between competing transition state geometries
μ	Micro-
λ_{max}	Wavelength of maximum absorbance
Φ	Quantum yield
$^\circ\text{C}$	Degrees Celsius
($\pm$)	Racemic mixture
[cat]	Generic catalyst
[M]	Generic metal species
$\text{\AA}$	Ångström(s)
Ac	Acetyl
acac	Acetylacetonate
Ad	Adamantyl
AIBN	Azobisisobutyronitrile
APCI	Atmospheric-pressure chemical ionization
app	Apparent
aq.	Aqueous
Ar	Aryl
ATRA	Atom transfer radical addition
ATRC	Atom transfer radical cyclization
ATRP	Atom transfer radical polymerization
BAIB	Bis(acetoxy)iodobenzene
BCO	Bicyclo[2.2.2]octane
BCP	Bicyclo[1.1.1]pentane
BDE	Bond dissociation energy
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
Boc	<i>tert</i> -Butyloxycarbonyl
BOMCl	Benzyl chloromethyl ether
BOX	Bis(oxazoline)
Bpin	Pinacolboryl
bpy	2,2'-Bipyridine
br	Broad
Bu	Butyl
ⁱ Bu	<i>iso</i> -Butyl
ⁿ Bu	<i>n</i> -Butyl
^s Bu	<i>sec</i> -Butyl
^t Bu	<i>tert</i> -Butyl
Bz	Benzoyl
<i>c</i>	Concentration (specific optical rotation)

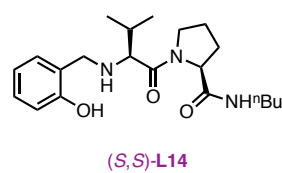
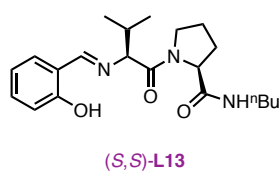
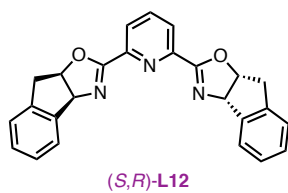
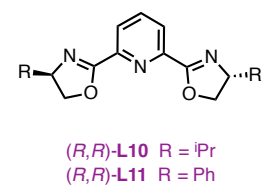
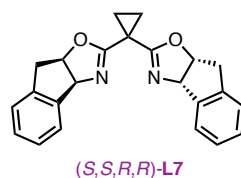
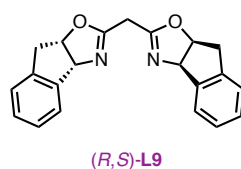
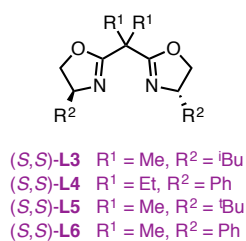
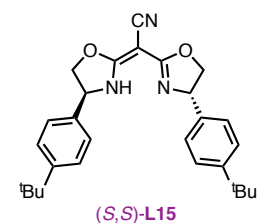
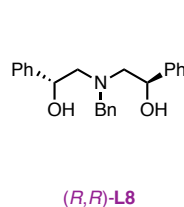
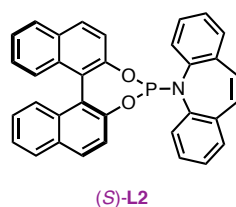
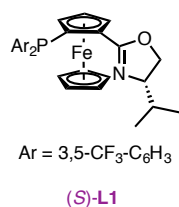
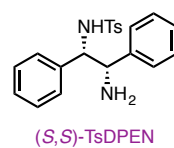
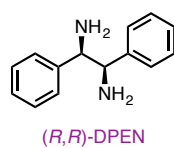
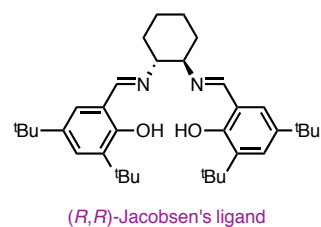
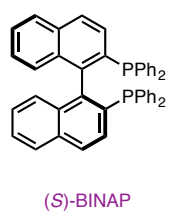
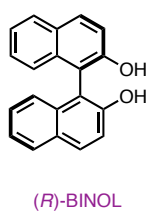
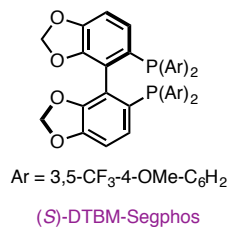
<i>c</i> -	Cyclo-
cat.	Catalyst
Cbz	Benzyloxycarbonyl
CFL	Compact fluorescent lamp
CI	Chemical ionization
cm	Centimeter(s)
cod	1,5-Cyclooctadiene
conc.	Concentrated
COSY	Homonuclear correlation spectroscopy
Cy	Cyclohexyl
4CzIPN	1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene
d	Doublet
dap	2,9-Bis(<i>p</i> -anisyl)-1,10-phenanthroline
DBAD	Di- <i>tert</i> -butyl azodicarboxylate
DCE	1,2-Dichloroethane
dCF ₃ bpy	5,5'-Bis(trifluoromethyl)-2,2'-bipyridine
DCM	Dichloromethane
deg	Degree(s)
dFppy	2-(4,6-Difluorophenyl)pyridine
dF(CF ₃)ppy	3,5-Difluoro-2-[5-(trifluoromethyl)-2-pyridine]phenyl
DIPA	Diisopropylamine
DIPEA	<i>N,N</i> -Diisopropylethylamine
dm	Decimeter(s)
DMA	<i>N,N</i> -Dimethylacetamide
DMAP	4-(Dimethylamino)pyridine
DME	1,2-Dimethoxyethane
DMF	<i>N,N</i> -Dimethylformamide
DMP	Dess–Martin periodinane
dmpy	2-(4-Methylphenyl)-5-(methylpyridine)
DMSO	Dimethyl sulfoxide
DPEN	1,2-Diphenylethylenediamine
dpm	Dipivaloylmethanato
dppf	1,1'-Bis(diphenylphosphino)ferrocene
dppp	1,3-Bis(diphenylphosphino)propane
<i>dr</i>	Diastereomeric ratio
dtbbpy	4,4'-Di- <i>tert</i> -butyl-2,2'-bipyridine
(<i>S</i>)-DTBM-Segphos	(<i>S</i>)-(+)-5,5'-Bis[di(3,5-di- <i>tert</i> -butyl-4-methoxyphenyl)phosphino]-4,4'-bi-1,3-benzodioxole
E	Generic electrophile
E°	Standard reduction potential
EA	Electron acceptor
ED	Electron donor
EDA	Electron donor-acceptor
EDCI	<i>N</i> -Ethyl- <i>N'</i> -(3-dimethylaminopropyl)carbodiimide hydrochloride
<i>ee</i>	Enantiomeric excess
<i>e.g.</i>	<i>exempli gratia</i> (for example)
EI	Electron ionization
<i>ent</i> -	Enantiomer
Equiv.	Equivalent
ESI	Electrospray ionization

Et	Ethyl
EWG	Electron withdrawing group
<i>fac</i>	Facial
FG	Functional group
Fmoc	Fluorenylmethyloxycarbonyl
Fmppy	2-(4-Fluorophenyl)-5-(methylpyridine)
4'-Fppy	2-(4-Fluorophenyl)pyridine
g	Gram(s)
h	Hour(s)
<i>hν</i>	Photon(s)
HAT	Hydrogen atom transfer
Het	Hetero-
Hex	Hexyl
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazane
HOBT	Hydroxybenzotriazole
HPLC	High performance liquid chromatography
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
Hz	Hertz
<i>i.e.</i>	<i>id est</i> (that is)
IR	Infrared
<i>J</i>	Coupling constant
kcal	Kilocalorie(s)
kJ	Kilojoule(s)
L	Liter(s)
L*	Generic chiral ligand
LDA	Lithium diisopropylamide
LED	Light-emitting diode
LG	Generic leaving group
LiDBB	Lithium 4,4'-di- <i>tert</i> -butylbiphenylide
m	Multiplet
M	Molar concentration (mol dm ⁻³)
Me	Methyl
Mes	Mesityl or 2,4,6-trimethylphenyl
Mes-Acr-Me ⁺	9-Mesityl-10-methylacridinium
mg	Milligram(s)
MHz	Megahertz
min	Minute(s)
mL	Milliliter(s)
mm	Millimeter(s)
mmol	Millimole(s)
Moc	Methoxycarbonyl
mol	Mole(s)
m.p.	Melting point
MS	Molecular sieves
<i>n</i> -	Normal
N	Normality
N719	Di-tetrabutylammonium <i>cis</i> -bis(isothiocyanato)bis(2,2'-bipyridyl-4,4'-dicarboxylato)ruthenium

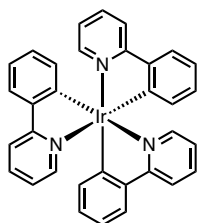
naph	Naphthyl
NaTCA	Sodium trichloroacetate
NBS	<i>N</i> -Bromosuccinimide
NCI	Non-covalent interaction
n.d.	Not determined
NFSI	<i>N</i> -Fluorobenzenesulfonimide
nm	Nanometer(s)
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOESY	Nuclear Overhauser effect spectroscopy
n.r.	No reaction
ns	Nanosecond(s)
Nuc	Generic nucleophile
Organocat.	Organocatalyst
<i>p</i> -	<i>para</i> -
Pent	Pentyl
PG	Protecting group
Ph	Phenyl
Photocat.	Photocatalyst
$\text{p}K_{\text{a}}$	$-\log_{10}K_{\text{a}}$, where K_{a} is the acid dissociation constant
PMB	<i>p</i> -Methoxybenzyl
PMP	<i>p</i> -Methoxyphenyl
ppm	Parts per million
ppy	2,2'-Phenylpyridine
^iPr	<i>iso</i> -Propyl
^nPr	<i>n</i> -Propyl
PyBOX	Pyridine-2,6-bis(oxazoline)
q	Quartet
quin	Quintet
R	Generic group/substituent
R_{f}	Retention factor
R_{F}	Generic (per)fluorinated alkyl group
<i>rac</i> -	Racemic
rt	Room temperature (21 °C)
s	Second(s)
s	Singlet
sat.	Saturated
SCE	Saturated calomel electrode
<i>sec</i> -	Secondary
sept	Septet
SET	Single electron transfer
SFC	Supercritical fluid chromatography
SIMes	1,3-Bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene
SOMO	Singly occupied molecular orbital
t	Triplet
t_{R}	Retention time
TBAI	Tetrabutylammonium iodide
TBS	<i>tert</i> -Butyldimethylsilyl
TCP	Tricyclo[1.1.1.0 ^{1,3}]pentane or [1.1.1]propellane
TEBAC	Benzyltriethylammonium chloride

TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
<i>tert</i> -	Tertiary
TES	Triethylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
TFDA	Trimethylsilyl 2,2-difluoro-2-(fluorosulfonyl)acetate
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	<i>N,N,N',N'</i> -Tetramethylethylenediamine
TMP	2,2,6,6-Tetramethylpiperidine
TMS	Trimethylsilyl
TPP	2,4,6-Triphenylpyrylium
Ts	<i>para</i> -Toluenesulfonyl
TTMSS	Tris(trimethylsilyl)silane
UV	Ultraviolet
V	Volt(s)
vs.	Versus
<i>v/v</i>	Volume by volume
W	Watt(s)
wt.	Weight
X	Generic group/substituent
Y	Generic group/substituent

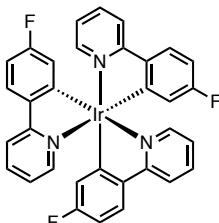
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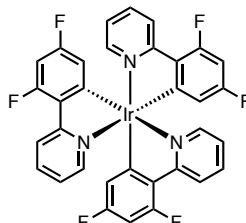
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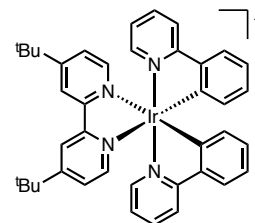
fac-Ir(ppy)₃



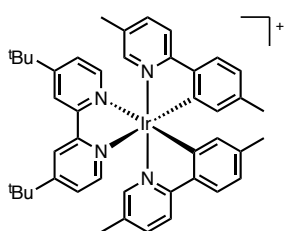
Ir(4'-Fppy)₃



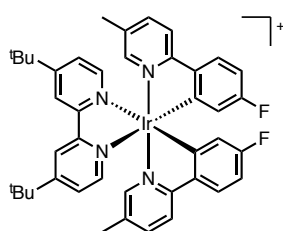
Ir(dFppy)₃



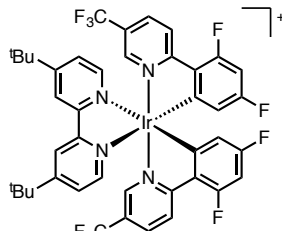
[Ir(ppy)₂(dtbbpy)]⁺



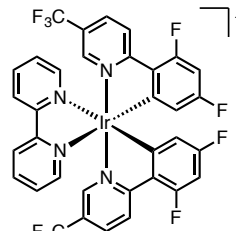
[Ir(dmppy)₂(dtbbpy)]⁺



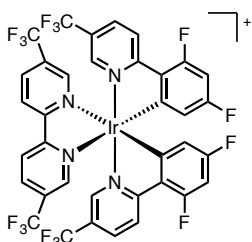
[Ir(Fmppy)₂(dtbbpy)]⁺



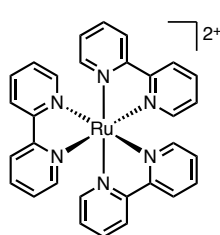
[Ir(dF(CF₃)ppy)₂(dtbbpy)]⁺



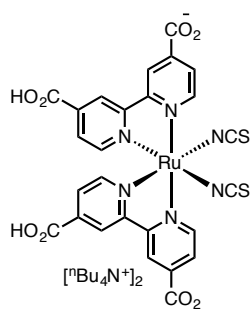
[Ir(dF(CF₃)ppy)₂(bpy)]⁺



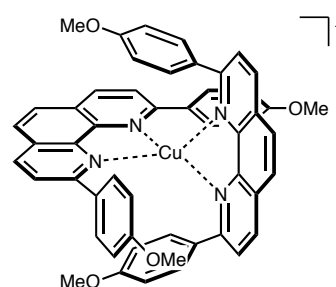
[Ir(dF(CF₃)ppy)₂(dCF₃bpy)]⁺



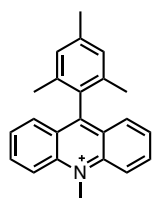
[Ru(bpy)₃]²⁺



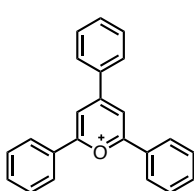
N719



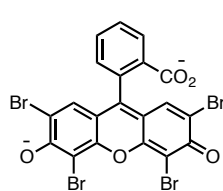
[Cu(dap)₂]⁺



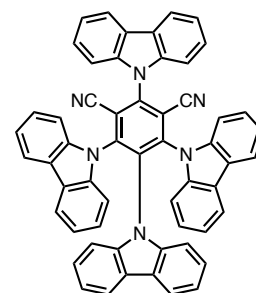
Mes-Acr-Me⁺
(Fukuzumi catalyst)



TPP⁺



Eosin Y



4CzIPN

Table of Contents

Abstract	i
Declaration	iii
Acknowledgements	v
Abbreviations	ix
Chiral ligands	xiv
Photocatalysts	xv
1 Introduction	1
1.1 Bicyclo[1.1.1]pentanes	1
1.1.1 Properties of bicyclo[1.1.1]pentanes	2
1.1.2 Early syntheses of bicyclo[1.1.1]pentanes	5
1.2 [1.1.1]Propellane	6
1.2.1 Synthesis of [1.1.1]propellane	8
1.2.2 Reactivity of [1.1.1]propellane	9
1.3 Synthesis of bicyclo[1.1.1]pentanes	11
1.3.1 Reactions of [1.1.1]propellane with radicals	12
1.3.2 Reactions of [1.1.1]propellane with nucleophiles	14
1.3.3 Reactions of [1.1.1]propellane with electrophiles	16
1.3.4 Cyclizations, ring contractions and ring expansions	17
1.3.5 Reactions of bicyclo[1.1.1]pentane derivatives	19
1.4 Applications of bicyclo[1.1.1]pentanes	23
1.4.1 Bioisosterism and drug design	23
1.4.2 Materials and supramolecular chemistry	26
1.5 Asymmetric synthesis of bicyclo[1.1.1]pentanes	27
1.5.1 α -Chiral bicyclo[1.1.1]pentanes	28
1.5.2 Project overview	31
2 Diastereoselective enolate reactions with chiral auxiliaries	34
2.1 Introduction	34
2.2 Preliminary studies and reaction optimization	37
2.3 Reaction scope	39

2.4	Derivatization of α -chiral BCP products	45
2.5	Synthesis of BCP analogues of bioactive molecules	46
2.6	Conclusions	48
3	Asymmetric atom transfer radical additions	51
3.1	Introduction	51
3.1.1	Atom transfer radical additions	52
3.1.2	Asymmetric radical reactions	54
3.1.3	Asymmetric atom transfer radical additions	58
3.2	Diastereoselective atom transfer radical additions with [1.1.1]propellane	59
3.3	Enantioselective atom transfer radical additions with [1.1.1]propellane	64
3.4	Conclusions	71
4	Photoredox-catalyzed atom transfer radical additions	73
4.1	Introduction	73
4.2	Photoredox-catalyzed atom transfer radical additions	77
4.3	Atom transfer radical additions with [1.1.1]propellane	80
4.3.1	Reaction optimization	81
4.3.2	Substrate synthesis	82
4.3.3	Reaction scope	85
4.3.4	Mechanistic studies	88
4.4	Conclusions	89
5	Enantioselective photoredox organocatalysis	92
5.1	Introduction	92
5.1.1	Single-catalyst strategies	93
5.2	Multi-catalytic strategies	95
5.2.1	Photoredox organocatalysis	96
5.2.2	Hydrogen atom transfer catalysis	99
5.3	Asymmetric ring-opening of [1.1.1]propellane	101
5.3.1	Reaction optimization	105
5.3.2	Reaction scope	113
5.3.3	Derivatization of α -chiral BCP products	116
5.3.4	Computational analysis	117
5.4	Conclusions	119
6	Conclusions and future work	122
7	References	127

8	Appendices	151
8.1	Chapter 2	151
8.1.1	Attempted synthesis of Sibi oxazolidinone auxiliary	151
8.1.2	Optimization: Enolate reaction	152
8.1.3	Optimization: Diastereoselective aldol reaction	152
8.1.4	Optimization: Diastereoselective hydroxymethylation reaction	153
8.2	Chapter 3	154
8.2.1	ATRA with α -bromocarbonyls	154
8.2.2	ATRA with lanthanide Lewis acids and PyBOX ligands	155
8.2.3	Other asymmetric radical-based strategies	156
8.3	Chapter 5	157
8.3.1	Attempted synthesis of HAT catalysts	157
8.3.2	Optimization: Photocatalysts	158
8.3.3	Optimization: Reaction concentrations and solvent ratios	159
8.3.4	Optimization: Reaction stoichiometries and time	160
8.3.5	Control experiments	161
9	Supplementary Information	162

1

Introduction

1.1 Bicyclo[1.1.1]pentanes

Bicyclo[1.1.1]pentane (BCP) **1** is a caged structure consisting of three rings of four carbon atoms each and is the simplest bicyclic bridged compound (**Figure 1.1**). Similar caged structures with the BCP framework include tricyclo[1.1.1.0^{1,3}]pentane ([1.1.1]propellane or TCP, **2**) and [*n*]staffanes [*n*]**3**, which are oligomers bearing repeating BCP units. Related structures such as tricyclo[2.1.0.0^{2,5}]pentane **4**^[1-3] and hexafluorobicyclo[1.1.1]pentane **5**^[4] have also been successfully synthesized, but other highly cyclized structures bearing the BCP skeleton such as tetracyclo[2.1.0.0^{1,3}.0^{2,4}]pentane **6** remain unknown.

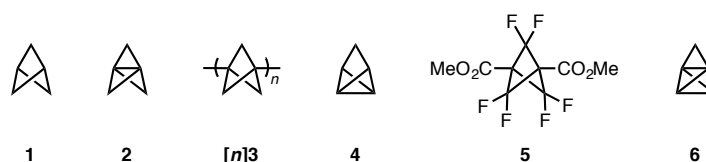


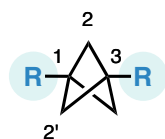
Figure 1.1. Bicyclo[1.1.1]pentane **1** and related compounds.

1.1.1 Properties of bicyclo[1.1.1]pentanes

Most known BCPs and $[n]$ staffanes are solids at ambient temperature and atmospheric pressure, while most known [1.1.1]propellanes are liquids.^[5] The parent bicyclo[1.1.1]pentane **1** boils at the same temperature as *n*-pentane (36 °C) but has a melting point that is almost 100 °C higher.^[5] Likewise, $[n]$ staffanes **[*n*]**3**** also have much higher melting points than *n*-alkanes with the same number of carbons and similar functional groups, which is attributed to a highly efficient crystal packing and a low change in entropy of melting of the rigid rod structure compared to the flexible *n*-alkane chains.^[6] Bicyclo[1.1.1]pentane **1** and $[n]$ staffanes **[*n*]**3**** are generally stable up to around 300 °C.^[6-7]

The structural properties of BCP and $[n]$ staffane derivatives have been studied by X-ray diffraction, electron diffraction and microwave spectroscopy, and a summary of bond lengths and angles is given in **Table 1.1**.^[5] The parent bicyclo[1.1.1]pentane **1** has a symmetrical shape (D_{3h})^[8] and an interbridgehead (C1–C3) distance that has been reported as 1.845 Å^[9] and 1.874 Å^[10] (**Figure 1.2**). For BCPs without bridge substitution (**1**, **7** – **9**), the C1–C3 distance generally varies between 1.80 and 1.91 Å, depending on the bridgehead substituent. It decreases when there are electron-withdrawing groups at the bridgehead position (**7** and **8**), due to a reduction in 1,3-nonbonding repulsion, and increases with electron-donating substituents (**9**).^[11] Notably, the quaternary BCP salt **8** bearing an electron-withdrawing pyridinium substituent has a C1–C3 distance of 1.80 Å, the shortest known distance between non-bonded carbon atoms.^[12] On the other hand, perfluorination of the bridge carbons **5**^[4] results in a large increase of the C1–C3 distance to 1.979 Å, due to the larger C–CF₂–C valence angle (Bent's rule).^[13] The intracage interbridgehead distances of $[n]$ staffane

derivatives are around 1.88 Å^[14] and also depend on the bridgehead substituents (**10** and **11**), as well as the number of BCP units in the chain (**12** and **13**).



Distance (Å)		Angle (°)	
Cl – C3	1.80 – 1.91	Cl – C2 – C3	71.2 – 75.2
Cl/3 – C2	1.51 – 1.56	C2 – Cl – C2'	86.0 – 90.2
R – Cl	1.10 – 2.12	R – Cl – C2	125.2 – 128.0

Table 1.1. Summary of bond lengths and angles in BCP derivatives.

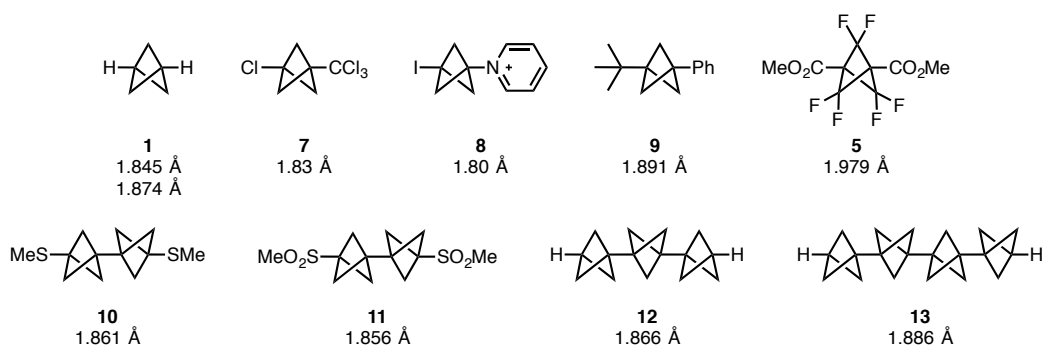


Figure 1.2. Intracage interbridgehead distances of several BCP derivatives.

The bridgehead geometries and hybridizations of BCP derivatives are important for electronic communication between functional groups attached to the BCP unit, and affect the reactivity of the compound as a whole.^[8] The formal s-character of a C–H bond can be estimated from the one-bond coupling constant using Muller and Pritchard’s empirical relationship: % s = $^1J_{C-H} / 5$ (**Figure 1.3**).^[15] Unstrained hydrocarbons such as acetylene **14**, benzene **15** and cyclohexane **16** display s-characters in line with their expected hybridizations (50%: sp, 33%: sp², 25%: sp³). Exocyclic C–H bonds in relatively unstrained cyclic molecules such as triptycene **19** and bicyclo[2.2.2]octane (BCO) **18** display a higher degree of s-character compared to

cyclohexane **16**, but the more highly strained bicyclo[1.1.1]pentane **1** and cubane **17** have formal bond characters that are much closer to that of benzene **15** (*i.e.*, sp^2).

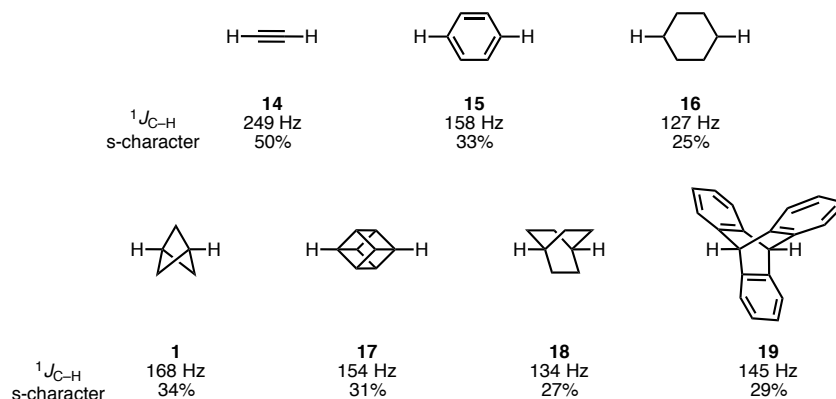


Figure 1.3. Comparison of NMR and hybridization data between BCP **1** and other hydrocarbons.

The short interatomic bridgehead distances and large s-character of bridgehead C–H bonds in BCP derivatives result in highly efficient electronic communication both within the carbon scaffold (‘through-bond’) and between the bridgehead carbons (‘through-space’), as can be seen when considering the acidity of bridgehead-substituted carboxylic acids (**Figure 1.4**).^[8,16] BCP **20a** is much more acidic than the corresponding BCO acid **21a** as a result of the increased s-character, and therefore electronegativity, of the exocyclic carbon bonding orbitals. Electron-withdrawing substituents at the other bridgehead position also exert a greater influence on the pK_a for BCP derivatives (**20a** and **20b**: $\Delta(pK_a) = 0.94$; **20a** and **20c**: $\Delta(pK_a) = 0.88$) than for the corresponding BCO derivatives (**21a** and **21b**: $\Delta(pK_a) = 0.82$; **21a** and **21c**: $\Delta(pK_a) = 0.75$).

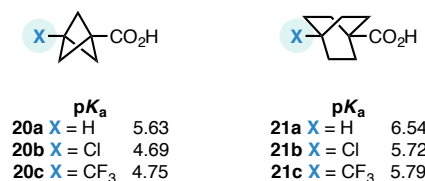


Figure 1.4. Comparison of acidities of BCP and BCO acids.

Values determined in EtOH:H₂O (1:1, v/v).

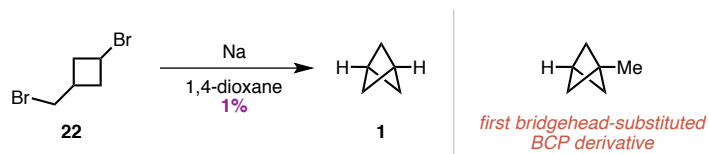
The unusual characteristics of BCPs are further exemplified by their strain energy. The overall ring strain of a system comprises angle strain, torsional strain and transannular strain, with angle strain being the dominant factor for small cyclic molecules. The bridgehead carbons of the parent BCP **1** have a high strain energy (68 kcal mol⁻¹) compared to other small cycloalkanes (**Figure 1.5**).^[8,17] It should be noted that the thermodynamic instability of strained molecules has little bearing on their kinetic stabilities, which in the case of BCP **1** is considerable,^[7,18] allowing BCP-containing molecules to be synthesized and stored for extended periods of time.

					
Strain energy (kcal mol ⁻¹)	27.7	26.3	16 0.4	1 68.0	18 7.4
Strain energy per C–C bond (kcal mol ⁻¹)	9.1	6.6	0.1	11.3	0.8

Figure 1.5. Strain energies of BCP **1** and other cycloalkanes.

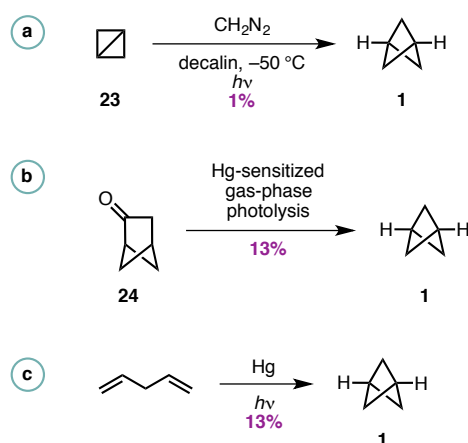
1.1.2 Early syntheses of bicyclo[1.1.1]pentanes

Bicyclo[1.1.1]pentane **1** was first synthesized by Wiberg in 1964 by a Wurtz-type cyclization of 1-bromo-3-(bromomethyl)cyclobutane **22** to give 1% of the desired cycloalkane (**Scheme 1.1**).^[19] Several different metals and solvents,^[20] and an electrochemical cyclization^[21-22] were also studied, but failed to produce yields greater than 8%. The Wurtz coupling was also used to synthesize the first bridgehead-substituted BCP derivatives.^[20]



Scheme 1.1. First synthesis of BCP **1** via a Wurtz-type cyclization.

A year later, Wiberg also demonstrated the first example of a ring expansion to synthesize **1** *via* a carbene addition to bicyclo[1.1.0]butane **23** (Scheme 1.2a).^[23] Shortly after these early reports, several other methods to synthesize **1** were published including a mercury-sensitized gas-phase photolysis of ketone **24** to induce a ring contraction^[24] (Scheme 1.2b) and a mercury-photosensitized internal cycloaddition of 1,4-pentadiene^[25] (Scheme 1.2c).



Scheme 1.2. Early syntheses of BCP **1**.

Numerous synthetic protocols to BCPs and their derivatives have been developed over the years, but the most commonly used precursor to date is [1.1.1]propellane **2** through reactions across the interbridgehead C–C bond.

1.2 [1.1.1]Propellane

Propellanes (tricyclo[$m.n.p.0^{x,y}$]alkanes), a term coined by Ginsburg in 1966,^[26] are a class of polycyclic compounds with a central single bond and three carbon or heteroatom bridges between the two bridgehead atoms (Figure 1.6a).^[27] The bridgehead carbons of small ring propellanes have an inverted tetrahedral geometry, and much of the interest in this class of compounds stems from their unique structural features and reactivities, which make them invaluable model compounds for the study

of ring strain. The first synthesis of a propellane-containing compound was reported in 1934, involving Diels-Alder reactions between maleic anhydride **25** and various 1,3-dienes to give products such as **26** (Figure 1.6b).^[28] The propellane framework is also commonly found in natural products, generally with a core structure of at least two n -membered rings with $n \geq 5$ (Figure 1.6c).^[27,29-30] A variety of inorganic metalla[1.1.1]propellanes have been prepared including tin,^[31] germanium^[32] and silicon^[33] analogues as well as silicon-bridged tin and germanium species^[34] (Figure 1.6d).

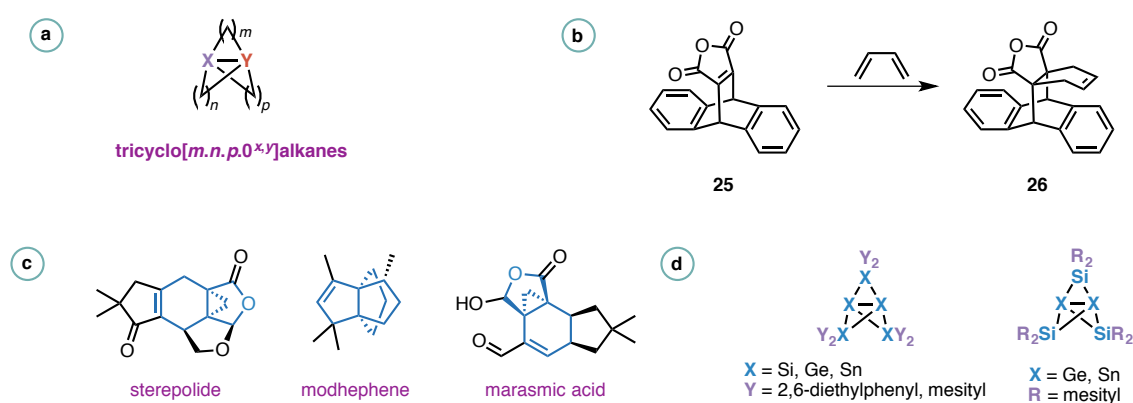
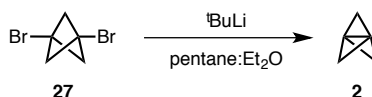
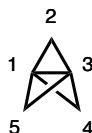


Figure 1.6. Propellanes: synthesis, natural products and inorganic analogues.

The simplest member of this class of compounds, [1.1.1]propellane **2**, was initially predicted to be incapable of existence due to its instability with respect to rearrangement.^[35] Despite this, it was successfully prepared for the first time by Wiberg in 1982 *via* a lithium–halogen exchange/cyclization of **27** (Scheme 1.3).^[36] Neat [1.1.1]propellane **2** is stable only for several minutes in the gas phase at 110 °C^[36] and polymerizes spontaneously in the liquid phase at temperatures above 0 °C, but can be stored as a solid in liquid nitrogen.^[5] On the other hand, dilute ethereal solutions of **2** (usually around 0.4 – 1.0 M) can be stored at –20 °C for several months. A summary of structural data of [1.1.1]propellane **2** obtained from gas-phase electron diffraction and X-ray crystallographic studies is given in Table 1.2.^[27]



Scheme 1.3. First synthesis of [1.1.1]propellane **2**.

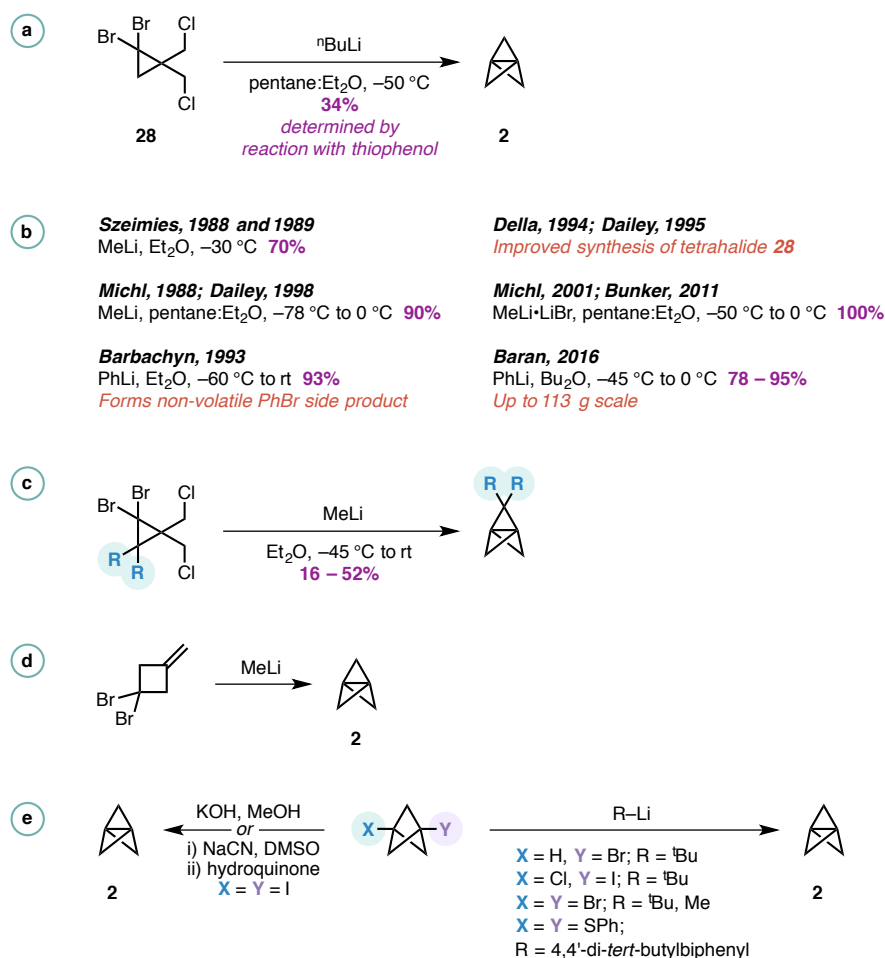


Distance (Å)		Angle (°)	
C – H	1.09	H – C – H	116.0
C1 – C2	1.52	C1 – C2 – C3	63.8
C1 – C3	1.58	C1 – C3 – C2	58.8
		C2 – C1 – C4	92.9

Table 1.2. Summary of bond lengths and angles in [1.1.1]propellane **2**.

1.2.1 Synthesis of [1.1.1]propellane

A seminal discovery by Szeimies in 1985 of a highly efficient route to [1.1.1]propellane **2** paved the way for its widespread use as a synthetic intermediate to BCPs (**Scheme 1.4a**).^[37] Cyclization of tetrahalide **28**, which is now commercially available, results in the formation of [1.1.1]propellane **2**, a process that has subsequently been optimized^[38-47] (as detailed in **Scheme 1.4b**) and is now amenable for large-scale synthesis (>100 g of **2**)^[47] as well as the synthesis of bridge-substituted derivatives^[48-49] (**Scheme 1.4c**) and solvent-free [1.1.1]propellane **2** as a solid.^[40,50] Other synthetic routes involve carbene pathways^[51] (**Scheme 1.4d**) and the regeneration of [1.1.1]propellane **2** from 1,3-disubstituted BCPs^[42,52-55] (**Scheme 1.4e**).



Scheme 1.4. Synthesis of [1.1.1]propellane 2.

1.2.2 Reactivity of [1.1.1]propellane

[1.1.1]Propellane **2** generally reacts across its central C–C bond in the presence of radical and nucleophilic species to yield intermediates bearing a bicyclo[1.1.1]pent-1-yl moiety, which can be trapped to afford 1,3-disubstituted BCPs (**Figure 1.7**). Under certain reaction conditions, such as in the presence of electrophiles, a bridging bond can be broken in addition to the interbridgehead bond to give three- or four-membered cyclic derivatives.

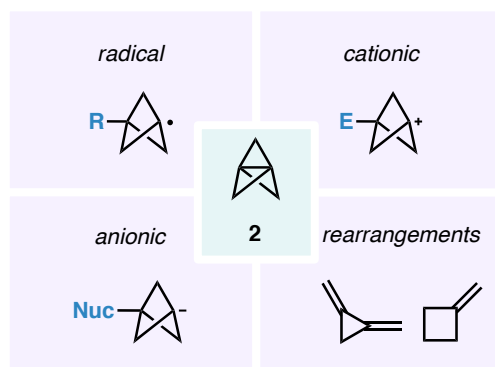
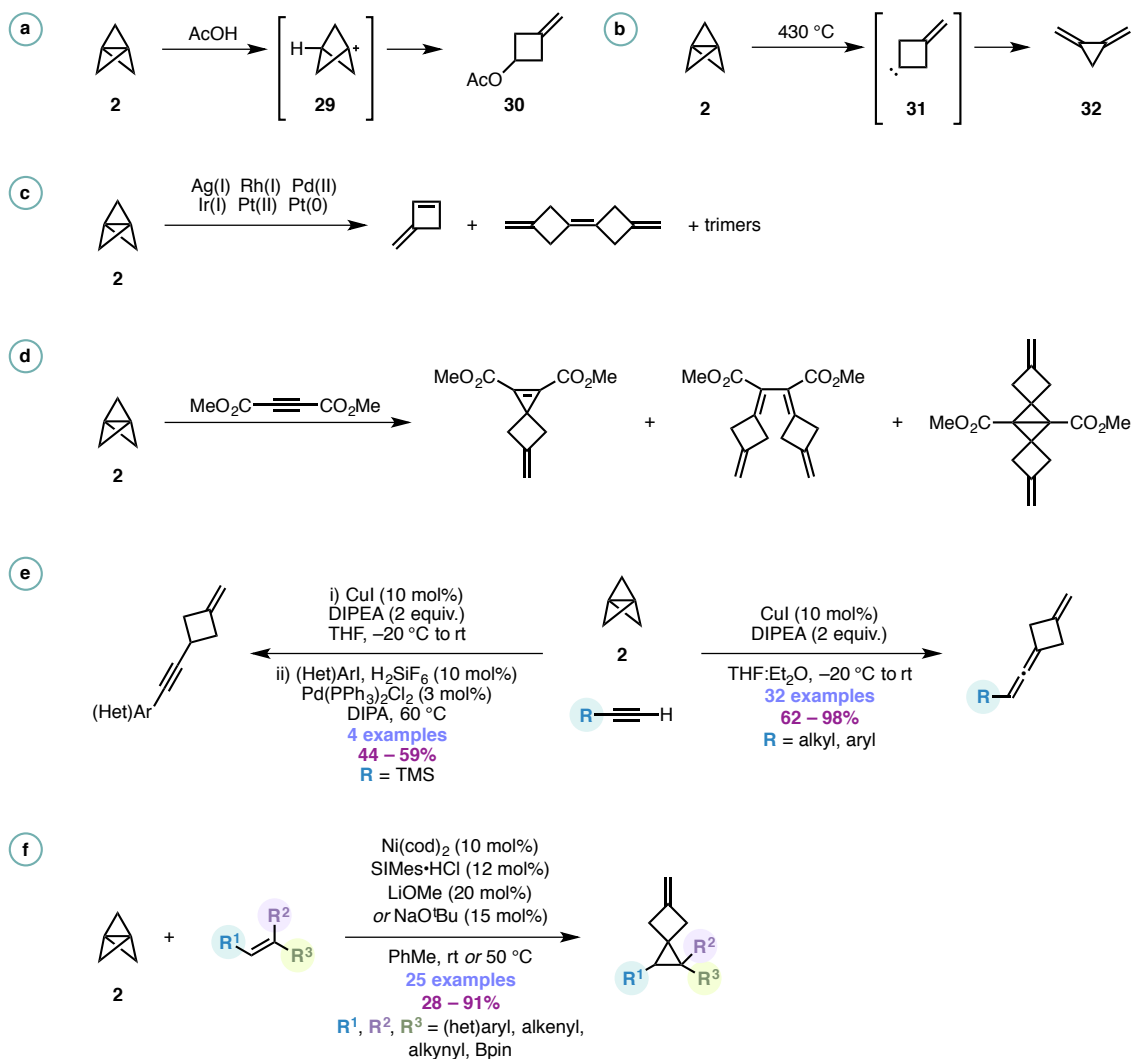


Figure 1.7. Reactions of [1.1.1]propellane **2**.

The first studied reaction of [1.1.1]propellane **2** was a rearrangement to form methylenecyclobutane **30**, triggered by protonation with acetic acid and fragmentation of the resulting bicyclopentyl cation **29** (Scheme 1.5a).^[36] Rearrangements can also be thermally induced, producing 1,2-dimethylenecyclopropane **32** via a methylenecyclobutylidene intermediate **31** (Scheme 1.5b),^[56-57] or catalyzed by transition metals, in which case a mixture of four-membered ring products and various other trimers are formed (Scheme 1.5c).^[35] Reactions of **2** with electron-deficient alkenes and alkynes also lead to rearrangement products through the formation of a biradical (Scheme 1.5d).^[35] The tendency for [1.1.1]propellane **2** to rearrange has been exploited in several synthetic methodologies developed recently, including a copper-catalyzed ring opening^[58] (Scheme 1.5e) and a nickel-catalyzed cyclopropanation^[59] (Scheme 1.5f).



Scheme 1.5. Rearrangement products from reactions of [1.1.1]propellane **2**.

1.3 Synthesis of bicyclo[1.1.1]pentanes

The other classes of reactions involving [1.1.1]propellane **2**, especially those with radicals and nucleophiles, are widely used to access BCP derivatives. There also exist alternative synthetic routes to access the BCP framework from precursors that do not possess this framework, involving cyclizations, ring expansions or ring contractions (**Figure 1.8**).^[5]

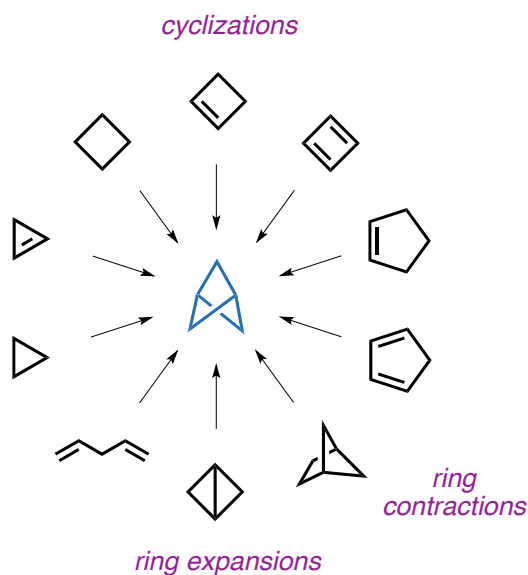


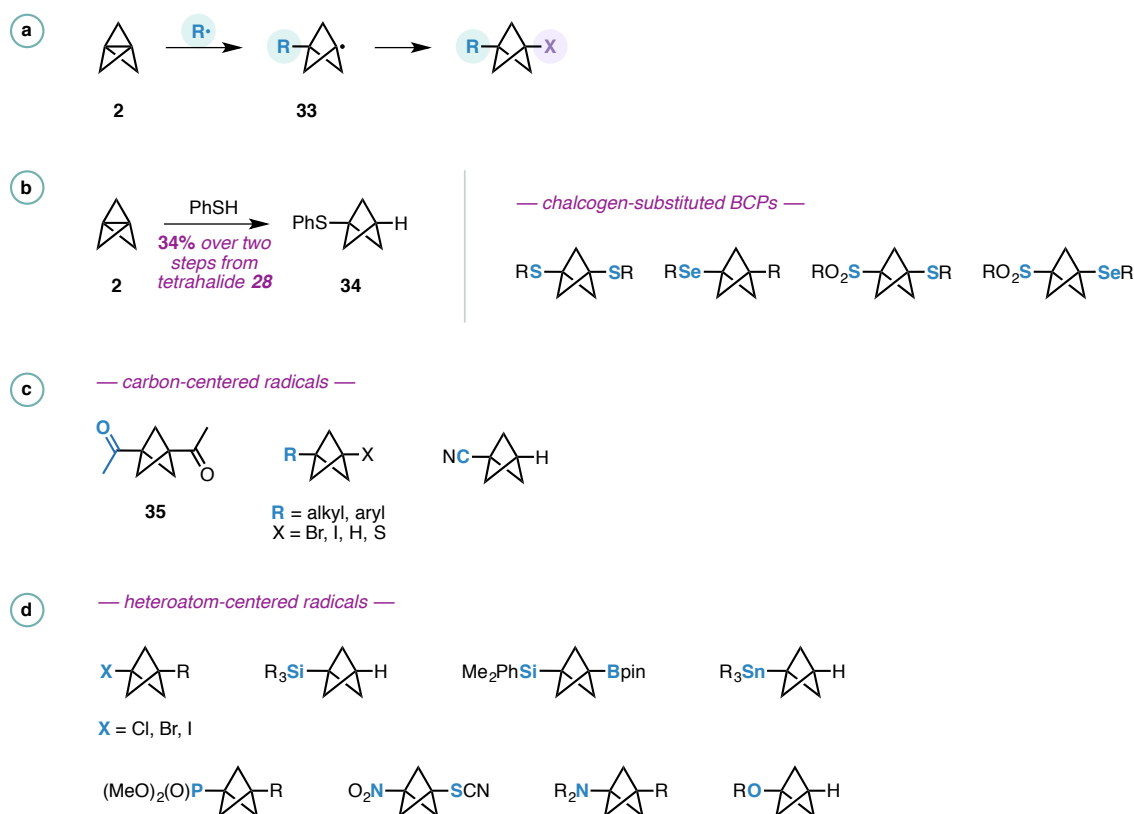
Figure 1.8. Synthetic routes to access the bicyclo[1.1.1]pentane framework.

1.3.1 Reactions of [1.1.1]propellane with radicals

Radical addition across the central C–C bond of [1.1.1]propellane **2** is one of the most utilized reactions to access a variety of bicyclo[1.1.1]pentane and $[n]$ staffane derivatives (**Scheme 1.6a**).^[60-61] The high s-character and unhindered, pyramidal nature of the bridgehead carbon results in a much higher reactivity of the bicyclopentyl radical **33** compared to other tertiary alkyl radicals.^[5,62] At the same time, there is also a substantial barrier of 26 kcal mol⁻¹ towards ring opening of the bicyclopentyl radical,^[63] which inhibits the potential rearrangements observed elsewhere (for example, with cationic intermediates). Although early reports of radical reactions with [1.1.1]propellane **2** relied on the use of toxic reagents (*e.g.*, tributyltin hydride), high temperatures and/or high-energy light irradiation, significant developments in the field of radical chemistry have enabled the highly efficient generation of radicals under milder reaction conditions for the synthesis of BCP derivatives. The first reported radical addition to [1.1.1]propellane **2** was the ring opening with thiophenol to give sulfur-substituted BCP **34** (**Scheme 1.6b**).^[37] Similar processes have since been

developed to obtain chalcogen-substituted BCPs through alkyl and aryl thiol,^[64-65] disulfide,^[38,66-68] or organoselenium^[64,66,69] addition, as well as fluoroalkylthio- and fluoroalkylseleno-functionalization^[70] (**Scheme 1.6b**). [1.1.1]Propellane **2** is also known to react rapidly with other carbon- and heteroatom-centered radicals without significant levels of oligomerization (**Scheme 1.6c and 1.6d**).^[5,35,39,41,46,60,66,71-78] One of the most important precursors to a range of BCP derivatives is diketone **35**, first reported in 1988 by Michl from the reaction between [1.1.1]propellane **2** and diacetyl under mercury lamp irradiation.^[39] A scaled-up synthesis of **35** in a flow reactor has also been reported recently, yielding 51.8 g of the desired product after 70 minutes (58% yield; in comparison with 26.5 g, 58% yield, 8 hours in batch).^[79] Diketone **35** can be isolated as a crystalline solid and the versatility of the carbonyl functionalities allows it to be used as a convenient, storable precursor to BCP derivatives, in particular for asymmetric 1,3-disubstitution. However, in cases where the chain transfer constant¹ of free-radical addition is low, oligomerization can occur to form a mixture of [*n*]staffanes [***n***]**3** ($1 \leq n \leq 6$),^[6,80] a process that is also favored under certain reaction conditions, such as a high concentration of [1.1.1]propellane **2**.

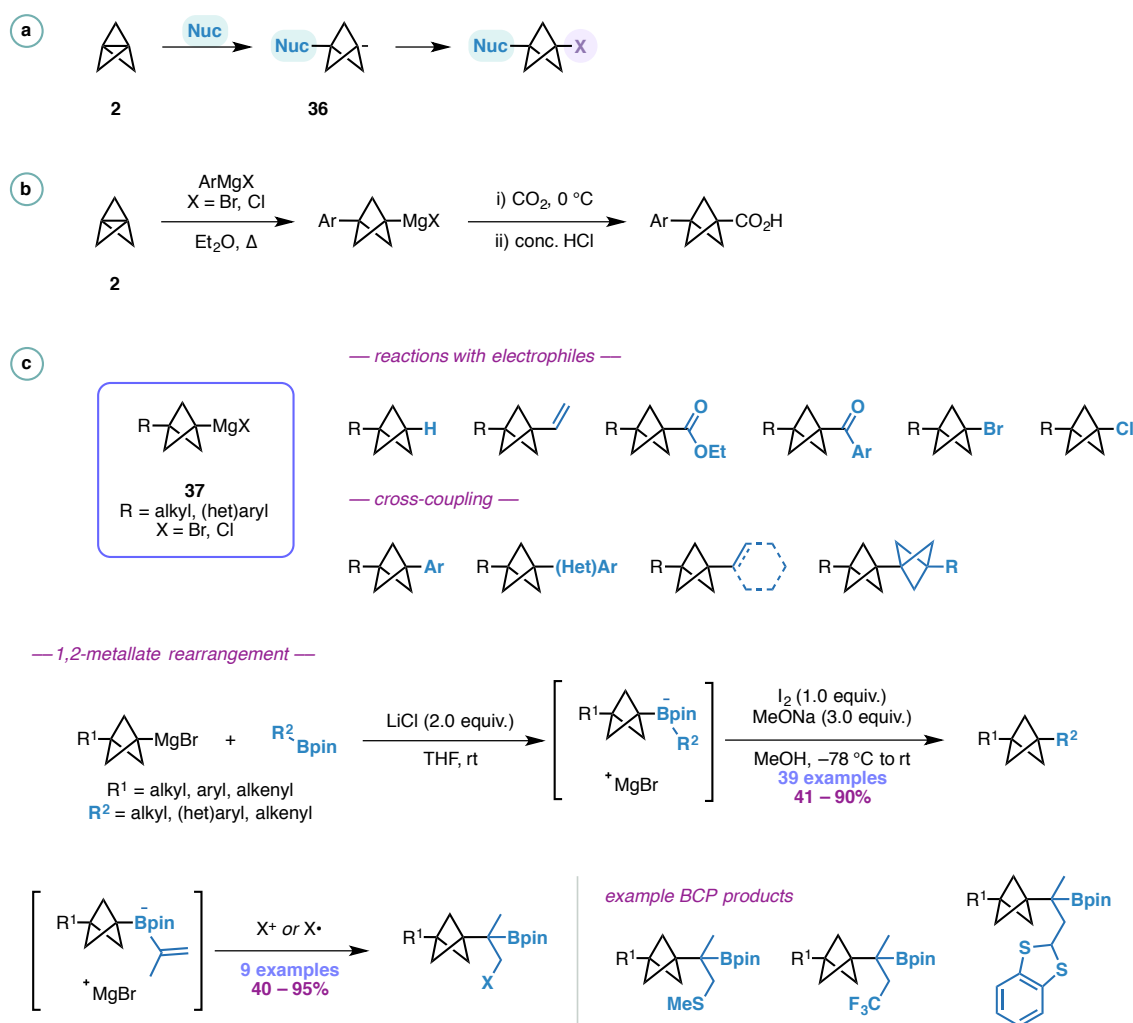
¹ The chain transfer constant quantifies the relative reactivity of chain transfer to propagation.



Scheme 1.6. Reactions of [1.1.1]propellane **2** with radicals.

1.3.2 Reactions of [1.1.1]propellane with nucleophiles

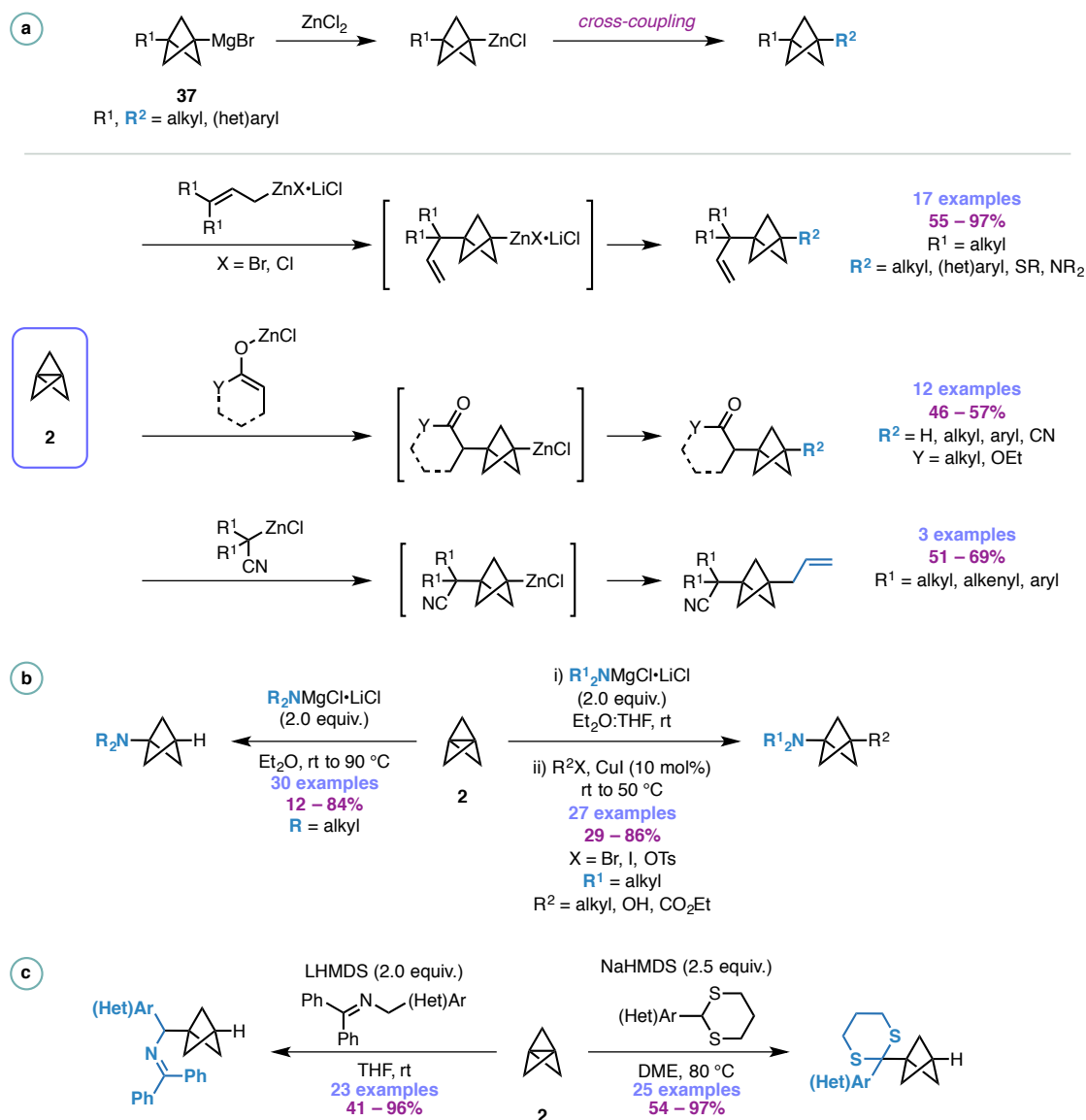
An alternative way to synthesize BCP derivatives is *via* the addition of nucleophiles to [1.1.1]propellane **2** and subsequent reaction of the resulting BCP intermediate **36** (**Scheme 1.7a**). However, a major drawback for this class of reactions is that they typically require elevated temperatures. The earliest report of such a transformation is the addition of aryl Grignard reagents to **2** followed by trapping with carbon dioxide to form BCP carboxylic acids (**Scheme 1.7b**).^[55] The scope of this process has been significantly expanded over the years to prepare a range of alkyl, aryl and heteroaryl BCP-Grignards **37**, which are versatile intermediates that can undergo transformations such as reactions with electrophiles,^[71,81] cross-coupling processes^[71,81-84] and 1,2-metallate rearrangements^[85] (**Scheme 1.7c**).



Scheme 1.7. Reactions of [1.1.1]propellane **2** with Grignard reagents.

Transmetallation of the BCP-Grignard intermediates **37** to form zinc halides has also been successfully applied in cross-coupling reactions,^[71,81] and a related transformation involving the addition of zinc halides and enolates to **2** was recently reported (**Scheme 1.8a**).^[86] Magnesium amides can also undergo addition to [1.1.1]propellane **2**, yielding terminal bridgehead amines^[47,87] or 1,3-disubstituted BCPs via a copper-catalyzed coupling of the metallated intermediate^[88] (**Scheme 1.8b**). The Walsh group have also reported the addition of α -heterosubstituted carbanions to [1.1.1]propellane **2** to synthesize BCP-containing benzylamines and 1,3-dithianes (**Scheme 1.8c**).^[89-90] By analogy to the radical oligomerizations described

earlier, [1.1.1]propellane **2** can also undergo anionic polymerization in the presence of organolithium species.^[80,91]



Scheme 1.8. Reactions of [1.1.1]propellane **2** with zinc species and α -heterosubstituted carbanions.

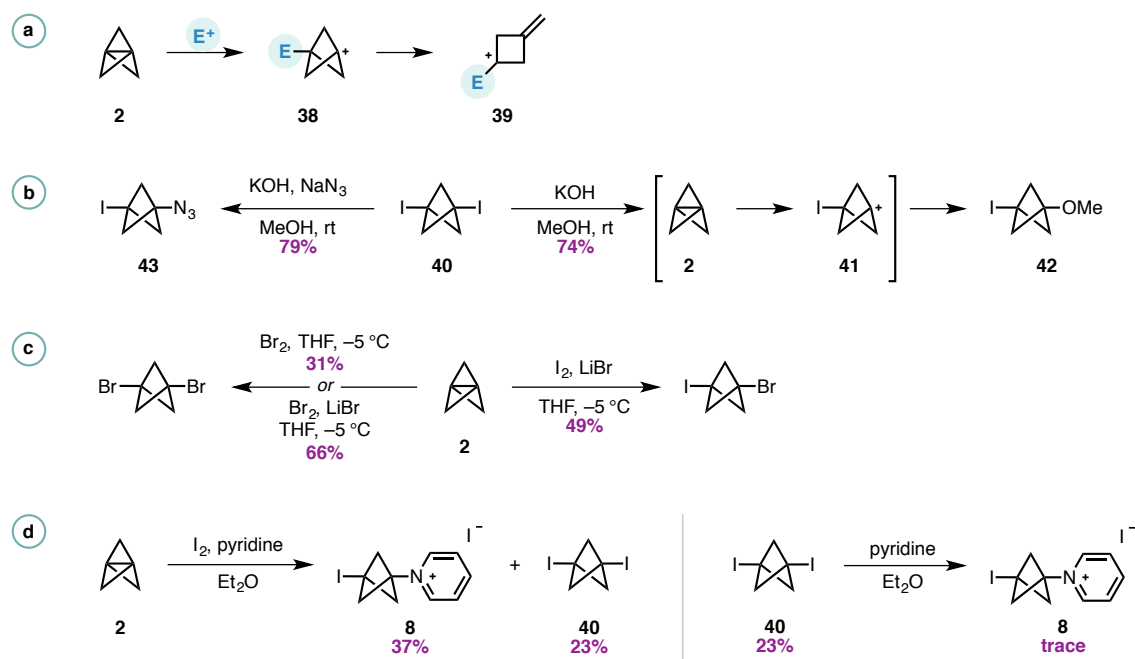
1.3.3 Reactions of [1.1.1]propellane with electrophiles

[1.1.1]Propellane **2** reacts rapidly with electrophiles and, generally, gives ring-opened rearrangement products (discussed in **Section 1.2.2**) as the rearrangement of the bicyclopentyl cation **38** to the 3-methylenecyclobutyl cation **39** occurs without a significant activation barrier (**Scheme 1.9a**).^[92-93] For the parent BCP **1**, rearrangement

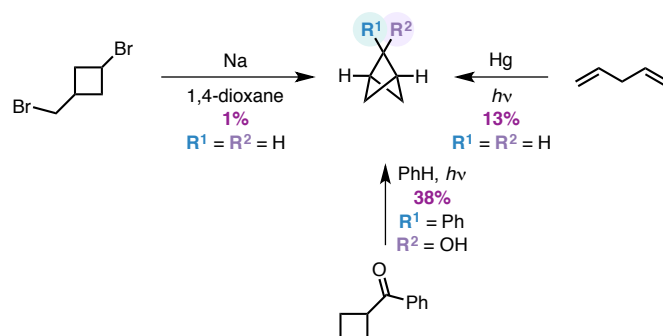
of the corresponding bicyclopentyl cation **29** occurs faster than nucleophilic addition at the bridgehead, but its 3-iodo and 3-bromo analogues are less susceptible to rearrangement and have been successfully intercepted.^[60] The treatment of 1,3-diiodobicyclo[1.1.1]pentane **40** with base in methanol resulted in the formation of 1-iodo-3-methoxybicyclo[1.1.1]pentane **42** *via* the formation of [1.1.1]propellane **2** and then the 3-iodobicyclopentyl cation **41** (**Scheme 1.9b**).^[55,94] The same reaction carried out in the presence of an azide anion, a good carbocation trapping agent, resulted in the formation of 1-azido-3-iodobicyclo[1.1.1]pentane **43** (**Scheme 1.9b**).^[55,94] The reactions of both iodine and bromine with [1.1.1]propellane **2** are also postulated to proceed *via* a 3-halobicyclopentyl cation that can be intercepted by external nucleophiles such as lithium bromide to yield mixed dihalides (**Scheme 1.9c**).^[95] A nucleophile-stabilized bicyclopentyl cation has also been suggested as the intermediate in the reaction between **2** with iodine and pyridine, giving the pyridinium salt **8** and 1,3-diiodobicyclo[1.1.1]pentane **40** (**Scheme 1.9d**).^[96-97] The formation of quaternary salt **8** does not proceed *via* the 1,3-diiodide **40** as the direct reaction between **40** and pyridine only gives trace amounts of **8**.

1.3.4 Cyclizations, ring contractions and ring expansions

Other methods to access BCP compounds have also been reported where the precursor does not have the BCP framework, although these generally lack the versatility and efficiency of the [1.1.1]propellane-based reactions previously discussed. Several early BCP syntheses relied on a cyclization strategy including a Wurtz cyclization,^[19-22] a photocycloaddition of 1,4-pentadiene^[25] and a photocyclization of substituted cyclobutane derivatives^[98-99] (**Scheme 1.10**).

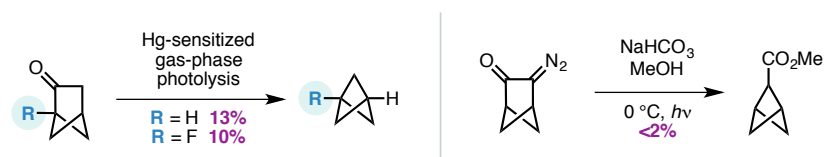


Scheme 1.9. Reactions of [1.1.1]propellane **2** with electrophiles.



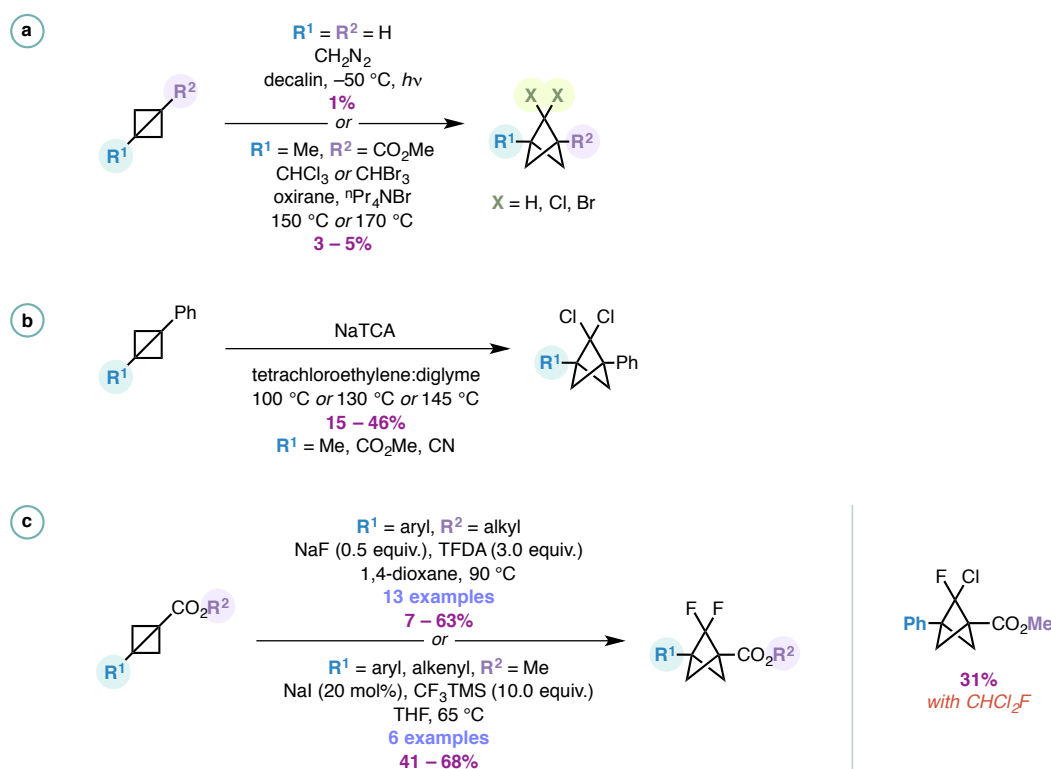
Scheme 1.10. Cyclizations to access the BCP framework.

Although the bicyclo[2.1.1]hexane framework can undergo ring contractions to yield BCP derivatives, either by a mercury-sensitized gas-phase photolysis^[24,100-101] or a Wolff rearrangement,^[102] this strategy has not been widely used due to the low yields and/or the requirement to conduct these reactions in the gas phase (**Scheme 1.11**).^[103]



Scheme 1.11. Ring contractions to access the BCP framework.

A more successful approach to BCP synthesis is the ring expansion of bicyclo[1.1.0]butanes. Initial reports of this transformation with carbenes were low yielding (1 – 5%) (**Scheme 1.12a**),^[23,104] but an optimization of reaction conditions reported by Applequist resulted in this method becoming a popular route to 2,2-dichlorobicyclo[1.1.1]pentane derivatives (**Scheme 1.12b**).^[105-106] Very recently, this methodology was extended to synthesize 2,2-difluorobicyclo[1.1.1]pentane derivatives by difluorocarbene insertion and one example of a 2-chloro-2-fluorobicyclo[1.1.1]pentane was reported (**Scheme 1.12c**).^[107-109]



Scheme 1.12. Ring expansions to access the BCP framework.

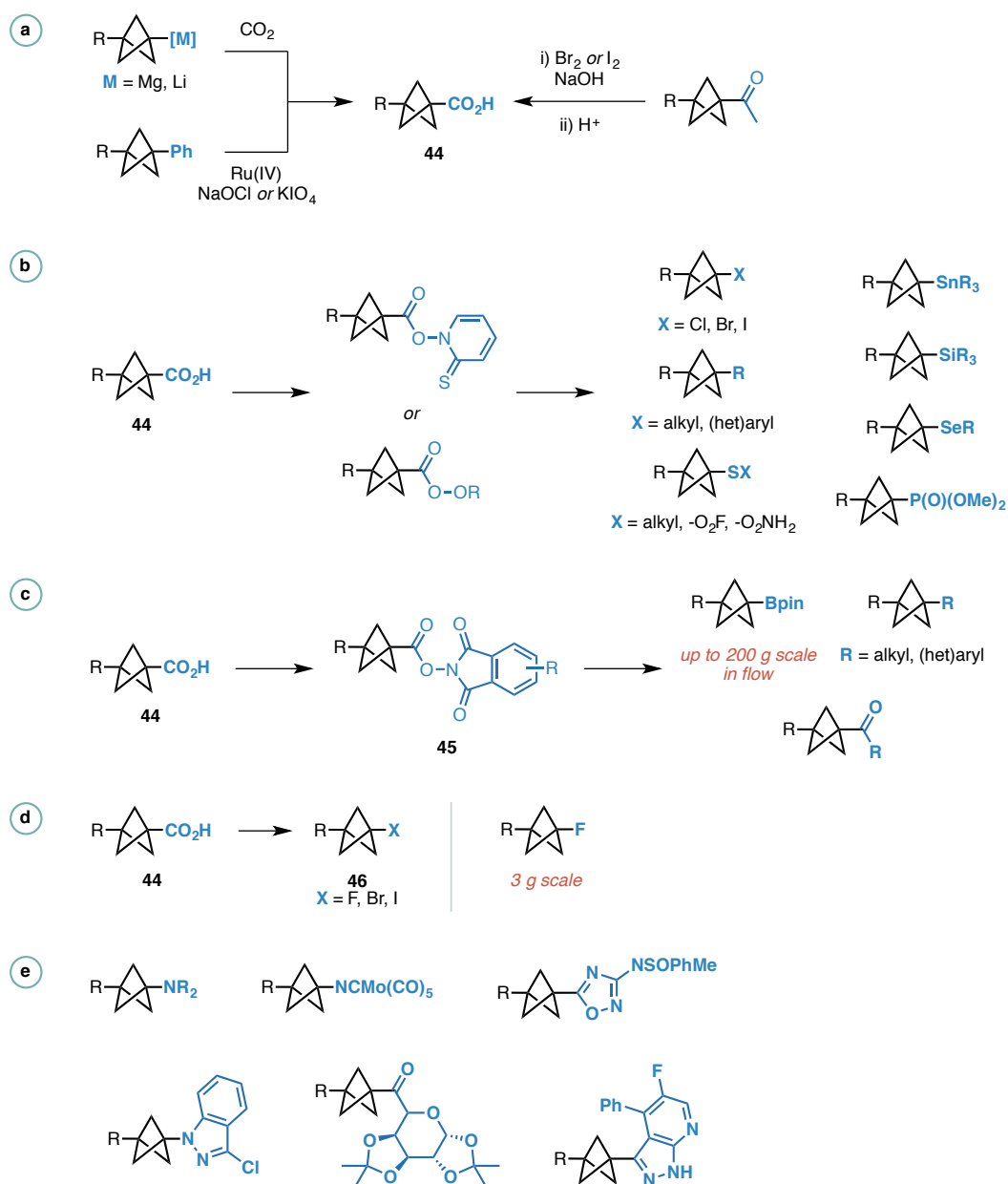
1.3.5 Reactions of bicyclo[1.1.1]pentane derivatives

Bicyclopentane derivatives can themselves be used as precursors to an even larger set of BCP compounds through further manipulations of the synthetic handles attached to the caged structure. In particular, carboxylic acids and halogens have proven to be highly

successful in this regard, and the vast majority of reactions of BCP derivatives involve precursors bearing one of these two groups at the bridgehead positions.^[60,110]

BCP carboxylic acids **44** are generally synthesized by carbonation of metallated BCPs,^[55,71,81] oxidation of phenyl-BCPs^[106] or oxidation of acetyl-BCPs^[39] (**Scheme 1.13a**). Early applications of BCP carboxylic acids **44** generally relied on the conversion of the acid motif into a Barton ester or peroxide, which could then be further functionalized to obtain heteroatom-, alkyl- and (hetero)aryl-substituted BCPs (**Scheme 1.13b**).^[42,60,111-113] More recently, an increasingly popular method for activating the carboxylic acid is its conversion to a redox-active ester **45** bearing a phthalimide moiety that can undergo single electron transfer (SET) processes. Decarboxylative fragmentation of **45** forms a bridgehead bicyclopentyl radical that has been shown to undergo cross-coupling,^[114] borylation^[115-120] and alkylation^[121] (**Scheme 1.13c**). Another common transformation of BCP acids **44** is to BCP halides **46** *via* halodecarboxylation reactions (**Scheme 1.13d**).^[122-124] Although other more efficient methods to synthesize bromo- and iodo-BCPs are now available, the fluorodecarboxylation process is still the only scalable route to fluoro-BCPs.^[124] The carboxylic acid motif has also been exploited in the synthesis of amino-substituted BCPs^[125-129] as well as alkyl-^[130] and heteroaryl-BCPs,^[131-132] and some examples of the BCP products that can be obtained from the corresponding acids are shown in **Scheme 1.13e**.

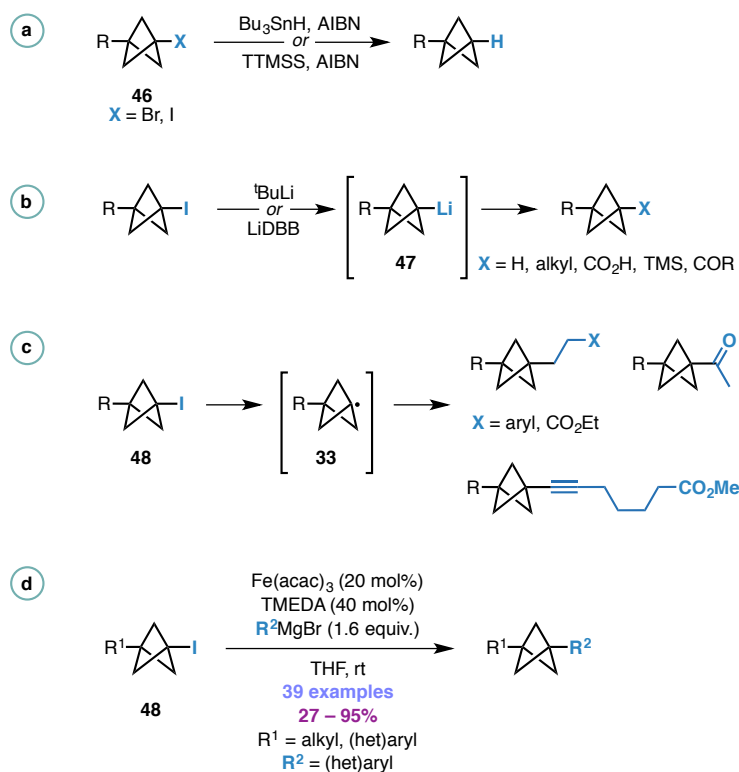
Bridgehead-substituted BCP halides **46** display great potential as a starting point for further functionalization and can be obtained from the halodecarboxylation reactions detailed above or, more efficiently, by radical additions to [1.1.1]propellane **2**.^[35,71,111,133] Reduction of the carbon–halogen bond has been widely used to access terminal BCPs (**Scheme 1.14a**),^[111,134] and lithium–halogen exchange^[135]



Scheme 1.13. Synthesis and reactions of BCP carboxylic acids **44**.

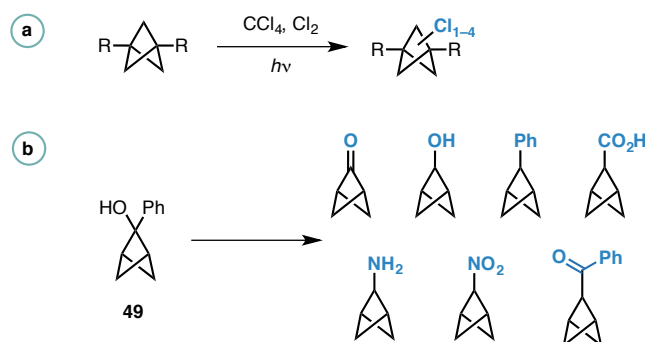
to form a bicyclopentyllithium species **47** has been employed in cross-couplings^[71,136] and trapping reactions with electrophiles^[71] (**Scheme 1.14b**). BCP iodides **48**, in particular, can undergo halogen atom abstraction to regenerate the bridgehead radical **33**, which can then be subjected to reactions such as additions to unsaturated systems,^[111,137] carbonylations^[111] and alkynylation^[138] (**Scheme 1.14c**). Recently, in work developed in the Anderson group, iodo-BCP compounds **48** were shown to

perform well in cross-coupling reactions to afford 1,3-dicarbon-substituted BCPs (Scheme 1.14d).^[139]



Scheme 1.14. Reactions of BCP halides **46**.

Reactions of bridge-substituted BCP derivatives, on the other hand, are relatively scarce and generally involve BCPs bearing halogens or hydroxyl groups on the bridge. Both BCP acids **44** and BCP halides **46** have been used in radical chlorinations to form bridge-chlorinated derivatives with up to four chlorine atoms (Scheme 1.15a).^[140-141] 2-Phenylbicyclo[1.1.1]pentan-2-ol **49**, which can be obtained from a photocyclization (Section 1.3.4),^[98-99] can be used as a precursor to several different 2-substituted BCPs through various manipulations of the bridge substituent (Scheme 1.15b).^[142-143]



Scheme 1.15. Bridge-substituted BCP derivatives.

1.4 Applications of bicyclo[1.1.1]pentanes

Much of the initial interest in bicyclo[1.1.1]pentanes and [1.1.1]propellanes lies in their use as models for theoretical and experimental studies on small polycyclic systems, especially relating to ring strain and other geometric properties. More recently, the focus has shifted to their applications as a unique class of non-conjugated rigid hydrocarbons in fields such as materials, supramolecular and medicinal chemistry. The rapid development of new synthetic routes towards BCPs in recent years, as discussed in the previous section, has largely been driven by this renewed interest.

1.4.1 Bioisosterism and drug design

The concept of isosterism was introduced by Langmuir in 1919, who observed that atoms, groups and molecules with the same number and arrangement of valence electrons possess similar physical properties.^[144] This definition was reformulated several times, notably by Grimm in 1925^[145-146] and Erlenmeyer in 1932,^[147] but early characterizations of isosterism predominantly focused on similarities in electronic configurations, which are not sufficient to relate the physical and chemical properties of atoms, groups and molecules to their biological properties. To alleviate the restrictions of these definitions when applied in a medicinal chemistry context, the term

‘bioisostere’ was conceived by Friedman in 1951 for compounds that “*fit the broadest definition for isosteres and have the same type of biological activity*”.^[148] This definition considers the macromolecular recognition of such compounds in biological systems, which is an important aspect of this concept, but fails to account for other physicochemical properties that are critical to the optimization process in medicinal chemistry.^[149] This was expanded upon by Burger in 1991 to form what is now the widely accepted definition, stating that “*bioisosteres are compounds or groups that possess near-equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties such as hydrophobicity. Bioisosteric compounds affect the same biochemically associated systems as agonists or antagonists and thereby produce biological properties that are related to each other.*”^[150]

Bioisosteric relationships are centered around the replication of functional biological properties and molecular recognition systems that are often unique to a specific environment.^[151] Hence, the effectiveness of a bioisostere in one setting may not necessarily be translatable to another with equal levels of success.^[152] Parameters that can be considered in a bioisosteric replacement include size, shape (bond angles, hybridization), electronic distribution (polarizability, inductive effects, charge, dipoles), lipid/water solubility, pK_a , chemical reactivity (and selectivity), potency and hydrogen bonding capacity. Bioisosteric replacement can also be used as a strategy to generate novel intellectual property.^[153]

Bioisosteres can be classified into two groups: classical and non-classical.^[146,152-153] Classical bioisosteres arose from an early appreciation of the concept of bioisosterism and comprise structurally simple mono-, di- and trivalent atoms or groups, tetrasubstituted atoms and ring equivalents, some examples of which are given in

Figure 1.9a. Non-classical bioisosteres resulted from an extension of such a concept to more sophisticated approaches using functionalities that differ in electronic, physicochemical and spatial features to mimic the biological properties of a parent functionality. These compounds can either be cyclic and non-cyclic isosteres (*i.e.*, cyclic group used to emulate a non-cyclic group and *vice versa*), or exchangeable group isosteres (where properties of discrete functional elements are imitated) (**Figure 1.9b**).

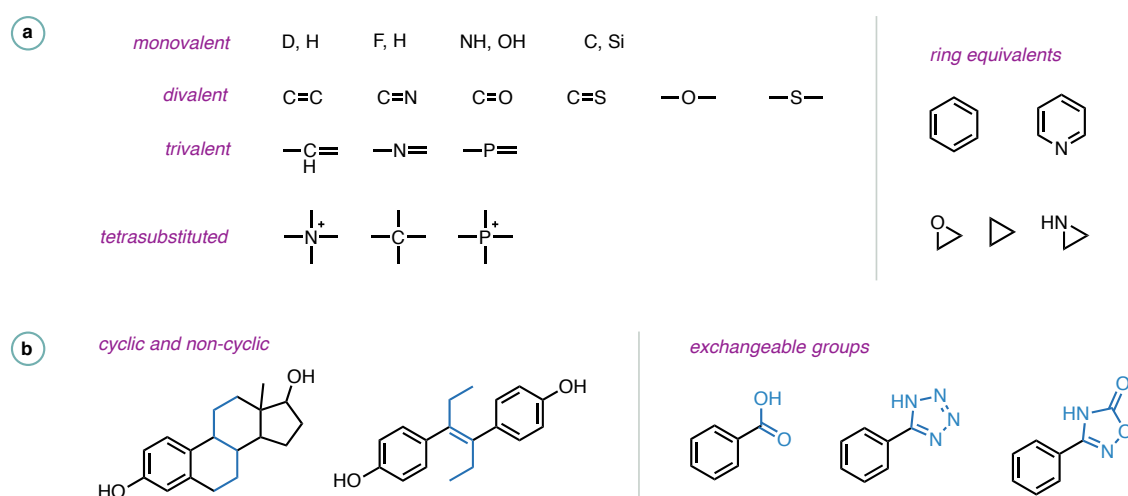


Figure 1.9. Classical and non-classical bioisosteres.

The bicyclo[1.1.1]pentane unit has emerged as a non-classical bioisostere for phenyl,^[112,154-158] *tert*-butyl^[159-160] and alkynyl^[81] groups, exploiting its rigid carbon framework to replace moieties that bear similar geometric features.^[8,27,161] The first example of bioisosteric replacement with a BCP unit was reported in 1993 by Barbachyn, where a *tert*-butyl group was replaced to give a compound with enhanced antibacterial activity (**Figure 1.10**).^[159] One of the most successful applications of a BCP bioisostere was reported by Stepan and coworkers, where a fluorophenyl group of a γ -secretase inhibitor was replaced, leading to an equipotent compound that displayed significant improvements in passive permeability, aqueous solubility, oral absorption characteristics and *in vitro* metabolic stability (**Figure 1.10**).^[154] In this study, the bicyclopentane unit performed better than other phenyl ring substitutes studied.

— Barbachyn, 1993 —

— Stepan, 2012 —

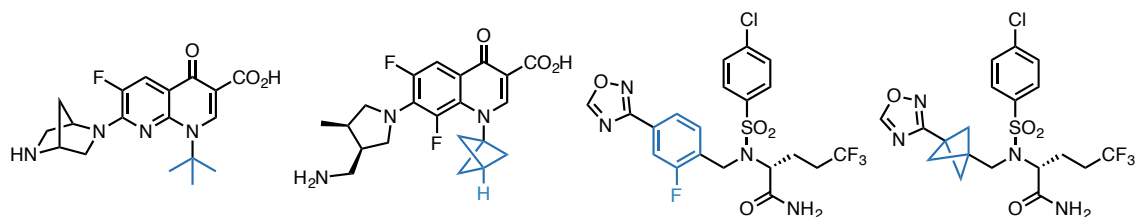


Figure 1.10. Bioisosteric replacement with the BCP motif.

More generally, it has also been found that increased carbon–carbon bond saturation, and therefore complexity, in a molecule correlates with increased success in a drug discovery setting, suggesting that saturated, three-dimensional systems like the BCP unit should be preferred over flat, unsaturated motifs.^[162-164] To this end, the use of rigid, three-dimensional scaffolds such as the BCP moiety has become an attractive strategy to access a larger chemical space, even when they are not specifically intended as bioisosteres for a different functional group (**Figure 1.11**).^[155,157,165-167]

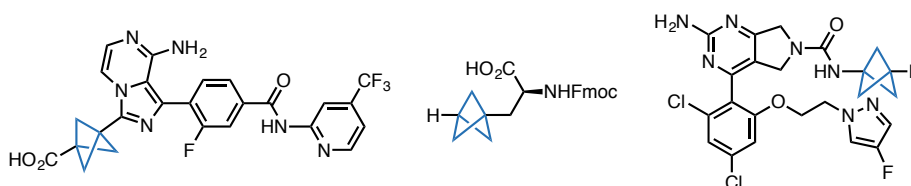


Figure 1.11. Non-bioisosteric applications of the BCP motif in drug development.

1.4.2 Materials and supramolecular chemistry

The bicyclopentane framework possesses numerous favorable characteristics that make it amenable for applications in materials and supramolecular chemistry;^[5,168] for example, it is optically transparent, chemically inert and has numerous sites for lateral functionalization. Incorporation of this non-conjugated scaffold as simple rigid rods has been shown to increase thermal stability, enhance electronic communication and improve the mechanical properties of the resulting compounds. The ability of [1.1.1]propellane **2** to undergo facile polymerization (**Section 1.3**) has also resulted in

the synthesis and study of a large variety of polybicyclo[1.1.1]pentyl derivatives. A selection of relevant BCP-containing structures is shown in **Figure 1.12**, including liquid crystalline materials,^[8] surfactants,^[169] dendrimers,^[170] self-assembled monolayers,^[171] supramolecular metal–organic frameworks,^[172] molecular rotors^[173-174] and multi-porphyrin arrays.^[175]

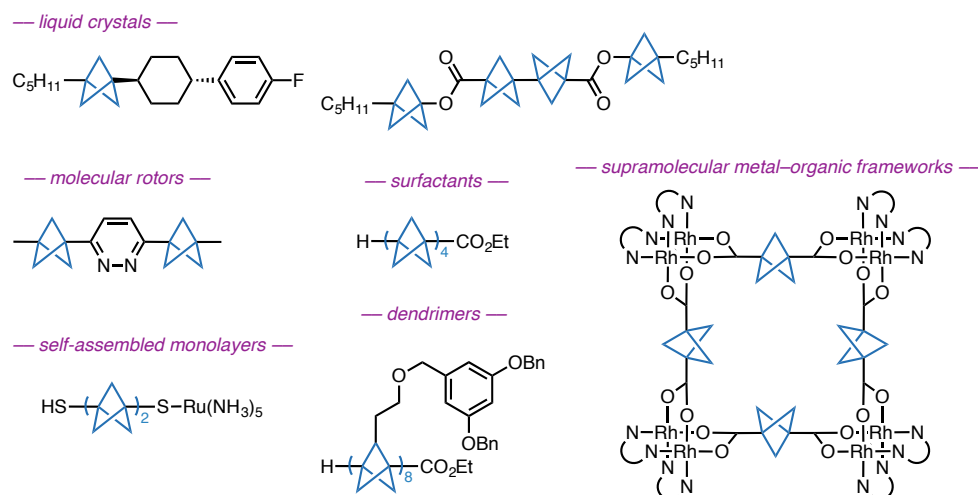


Figure 1.12. BCP-containing compounds in materials and supramolecular chemistry.

1.5 Asymmetric synthesis of bicyclo[1.1.1]pentanes

Bicyclo[1.1.1]pentanes are becoming increasingly popular motifs in a diverse range of applications, and numerous new synthetic methodologies centering on these unique structures have been developed.^[8,27,176-180] However, a class of BCP compounds that bear one of the most important features in organic synthesis yet remain scarce in the literature is those with stereocenters adjacent to the BCP unit (**Figure 1.13**). Asymmetric synthesis is one of the key processes in synthetic chemistry that still poses major challenges to discovery and development in the field, and is highly relevant to areas beyond organic synthesis, where the ability to selectively control spatial elements in the design of molecules is desirable. Considering the demonstrable potential of the BCP motif in fields ranging from materials to medicinal chemistry, the development of

methodologies to efficiently access α -chiral BCP compounds would be of great importance, as it would vastly expand the possibilities for controlled diversification of a three-dimensional chemical space.^[181]

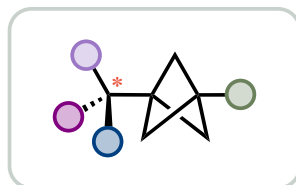
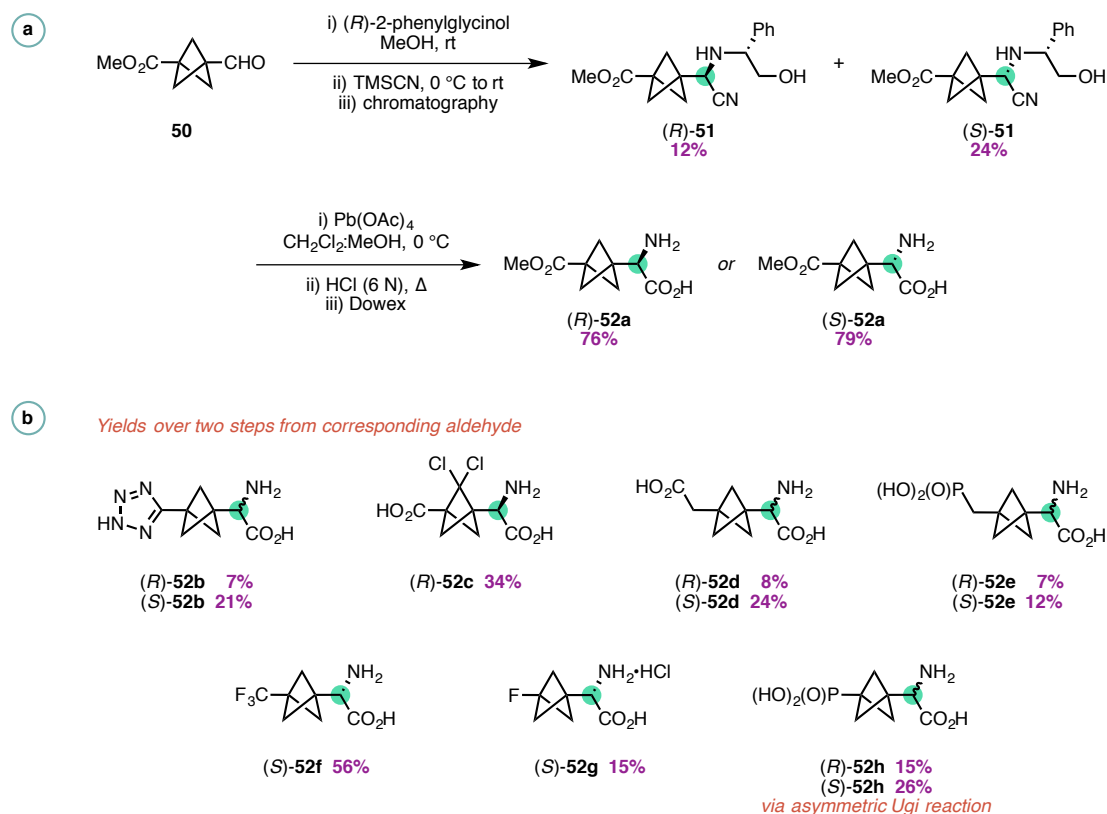


Figure 1.13. α -Chiral bicyclo[1.1.1]pentane.

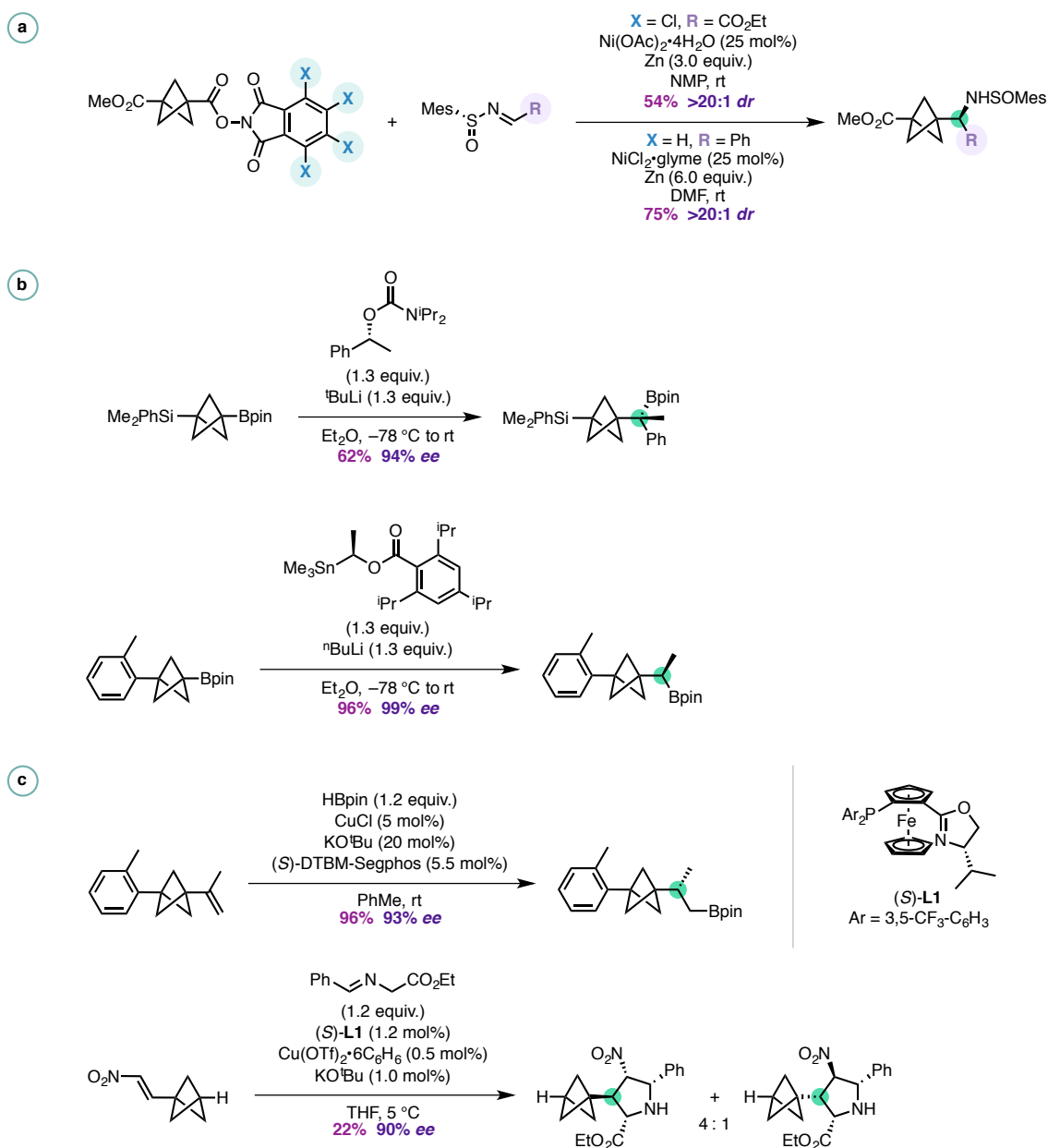
1.5.1 α -Chiral bicyclo[1.1.1]pentanes

The first bicyclo[1.1.1]pentane with an adjacent stereocenter, featuring an amino acid moiety, was disclosed by Pellicciari in 1996 (**Scheme 1.16a**).^[182] An asymmetric Strecker reaction between BCP aldehyde **50** and (*R*)-2-phenylglycinol afforded diastereomers (*R*)-**51** and (*S*)-**51**, which were separated by chromatography. Oxidative cleavage, acid hydrolysis and ion exchange chromatography of each diastereomer gave the enantiopure amino acids (*R*)-**52a** and (*S*)-**52a**. This strategy was applied to the synthesis of several other chiral BCP amino acids as shown in **Scheme 1.16b**.^[183-189] A similar approach involving an asymmetric Ugi reaction and subsequent separation of diastereomers was also reported.^[190]

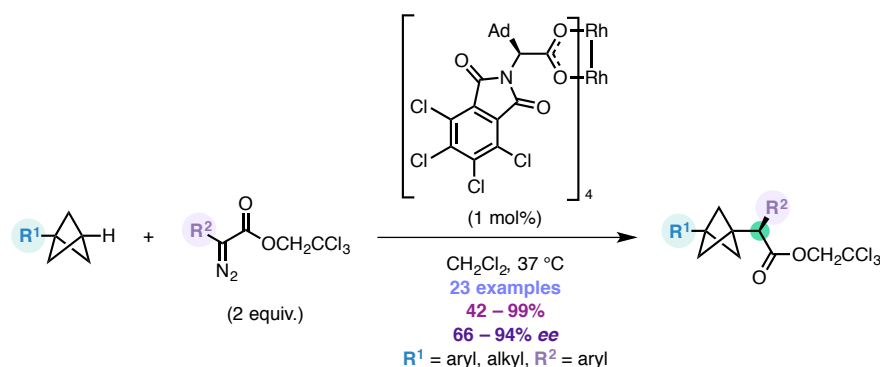


Scheme 1.16. Synthesis of α -chiral BCP amino acid derivatives.

In the last two years, new approaches to α -chiral BCPs have emerged, involving BCP redox active esters and chiral sulfinamide auxiliaries^[191-192] (**Scheme 1.17a**) as well as asymmetric homologations of BCP boronic esters^[77,85] (**Scheme 1.17b**). Two examples of catalytic processes have also been reported: an asymmetric hydroboration^[85] and an *endo*-selective [3+2] cycloaddition^[193] (**Scheme 1.17c**). However, these approaches only delivered isolated examples of α -chiral BCPs, lacking the true generality needed for the diversification of this class of compounds.

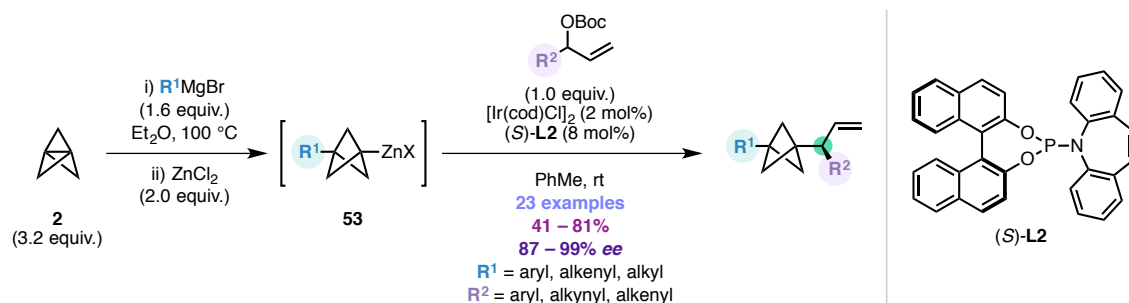
Scheme 1.17. Other syntheses of α -chiral BCPs.

Of these very recent reports, only two were shown to be of general applicability. In the first example, the Davies group developed a Rh-catalyzed C–H activation strategy involving the bridgehead C–H bond of terminal BCPs (Scheme 1.18).^[194] Intermolecular $\text{C}(\text{sp}^3)\text{--H}$ insertion of a donor/acceptor diazo compound at the bridgehead position is catalyzed by a chiral dirhodium complex without disruption of the carbocyclic framework, yielding a range of aryl- and alkyl-substituted BCPs with high levels of enantioselectivity.



Scheme 1.18. Rh-catalyzed C–H insertion of terminal BCPs.

The Aggarwal group have also disclosed a 1,3-difunctionalization of [1.1.1]propellane **2**, in which a zinc species **53**, formed from Grignard addition and transmetallation, undergoes an enantioselective Ir-catalyzed allylic substitution (**Scheme 1.19**).^[195] An array of enantioenriched allyl-substituted BCPs can be synthesized, with the terminal alkene enabling the subsequent introduction of various other functionalities.



Scheme 1.19. Ir-catalyzed allylic substitution of BCP-Grignards.

1.5.2 Project overview

At the commencement of this research project, examples of α -chiral BCPs were few and far between, with only 8 examples of chiral BCP amino acid derivatives known in the literature (**Scheme 1.16**, **Section 1.5.1**). Despite the potential value of these compounds, a general and efficient approach to access them had not yet been realized. Pre-existing examples typically featured low-yielding and lengthy routes that required toxic

reagents, stoichiometric chiral reagents and resolution processes to separate diastereomers.

This thesis describes the efforts to investigate this underexplored area in bicyclopentane chemistry. We opted to focus on BCPs bearing an α -carbonyl stereocenter, as the carbonyl group is one of the most common reactive components in organic structures and would serve as a highly versatile synthetic handle for further functionalization of the chiral BCP products. α -Carbonyl stereocenters are also commonly found in bioactive molecules and, considering the potential applications of BCP compounds in drug design, the synthesis of BCP compounds with α -carbonyl stereocenters is attractive. A selection of biomolecules bearing benzylic stereocenters and the corresponding BCP analogues are shown in **Figure 1.14**.

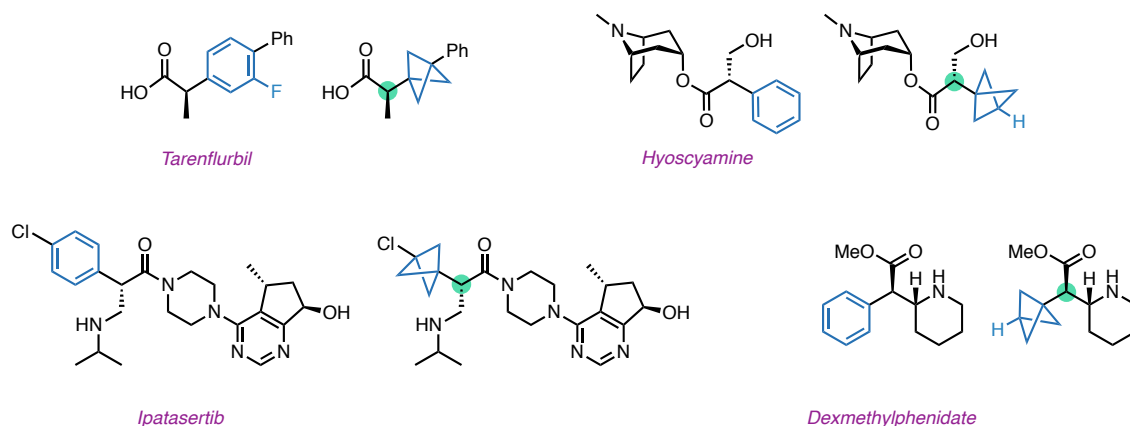
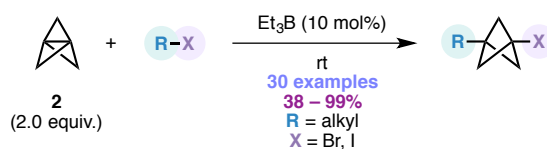


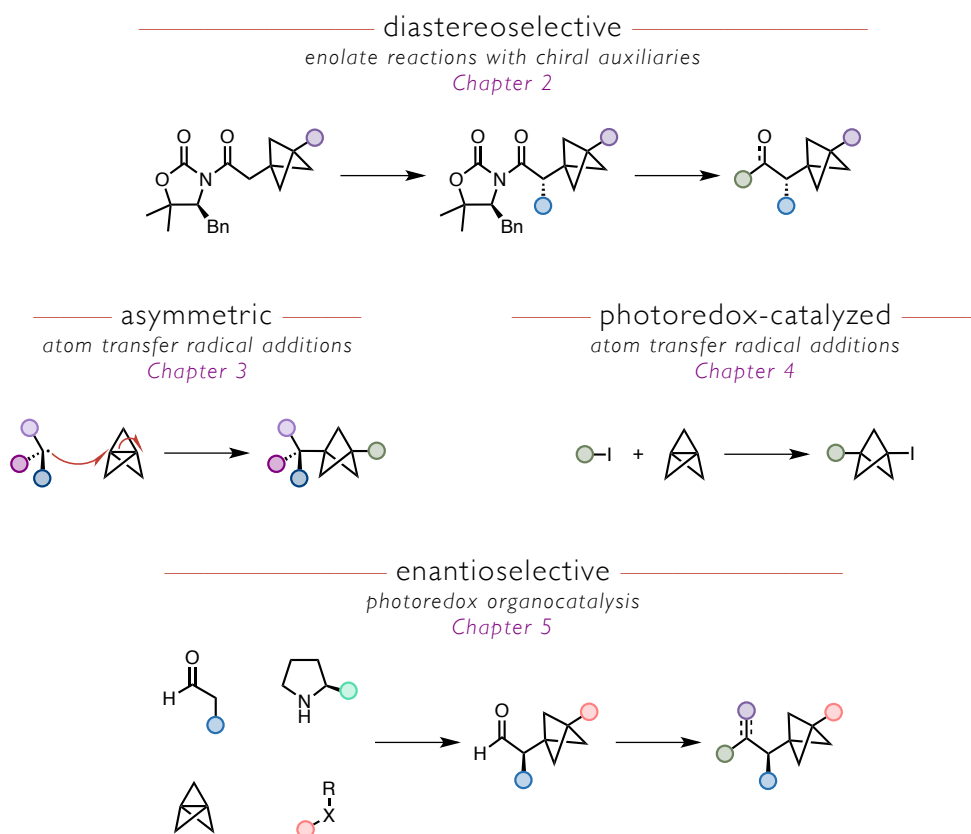
Figure 1.14. Biomolecules bearing benzylic stereocenters and the corresponding BCP analogues.

This work builds on expertise in the Anderson group on bicyclopentane chemistry, utilizing and extending the atom transfer radical addition (ATRA) developed to prepare 1-halo-3-substituted BCPs (**Scheme 1.20**).^[133] This methodology is highly efficient for radical reactions with [1.1.1]propellane **2** under mild reaction conditions and tolerates a wide range of functional groups, giving bridgehead-substituted BCP halides that can readily undergo further functionalization.



Scheme 1.20. Bicyclopentane chemistry developed in the Anderson group.

Throughout our investigation, we have utilized several proven strategies from asymmetric synthesis to access α -chiral BCPs (**Scheme 1.21**). These include the use of chiral auxiliaries (**Chapter 2**) as well as asymmetric radical reactions (**Chapters 3** and **5**), exploiting the known propensity of [1.1.1]propellane **2** to react with open-shell species (**Chapter 4**).



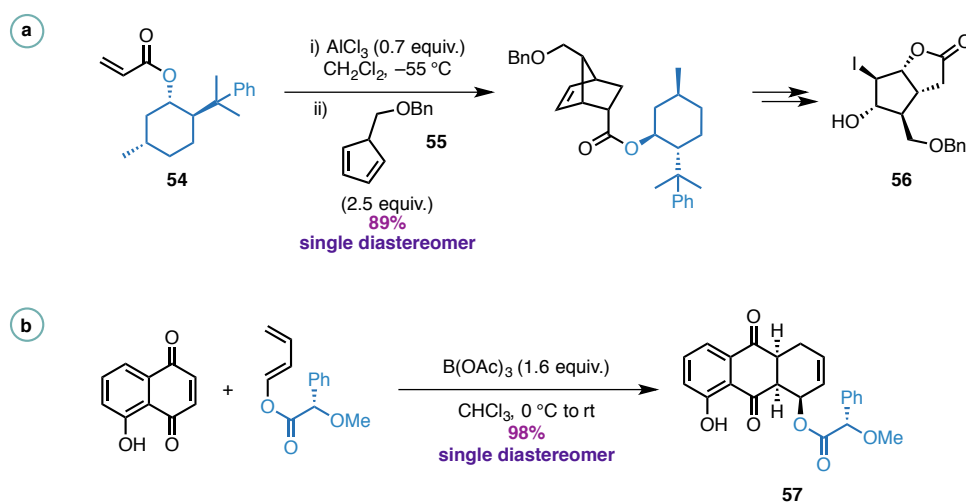
Scheme 1.21. Project overview.

Diastereoselective enolate reactions with chiral auxiliaries

2.1 Introduction

Enantio- or diastereomerically pure compounds can be obtained by chiral resolution processes, which involve a substrate, reagent, solvent or catalyst with a chiral element that can influence the stereochemical outcome of the reaction.^[196] One of the earliest and most successful strategies employed in asymmetric reactions is the use of chiral auxiliaries, which are enantiomerically pure compounds that are appended onto a substrate and exert an influence on the stereochemical outcome of the reaction, usually by sterically differentiating the diastereotopic faces of a molecule.^[197] Although other methods such as asymmetric catalysis and biocatalysis offer increasingly efficient ways of accessing chiral molecules, the use of chiral auxiliaries remains one of the most reliable processes to achieve high stereoselectivity and still features in many synthetic endeavors.

Chiral auxiliaries were first introduced in 1975 by Corey to access an optically pure intermediate **56** used in the synthesis of prostaglandins *via* an asymmetric Diels–Alder reaction between acrylate ester **54** and cyclopentadiene **55** (Scheme 2.1a).^[198] Several years later, Trost conducted another asymmetric Diels–Alder reaction with a chiral mandelic acid auxiliary, obtaining the adduct **57** in 98% yield as a single diastereomer (Scheme 2.1b).^[199]



Scheme 2.1. First reports of the use of chiral auxiliaries in asymmetric synthesis.

The use of chiral auxiliaries has since been well-established in a range of transformations with numerous compounds being successfully applied as auxiliaries (Figure 2.1a).^[200] One of the most notable examples is the *N*-acyloxazolidinone auxiliary, developed by Evans in 1981 for asymmetric aldol condensations, and a diverse array of structural variants have subsequently been reported (Figure 2.2b).^[201] The success of this class of auxiliaries can largely be attributed to their ease of preparation and diversification, commercial availability, ready installation and cleavage, and ability to provide high levels of asymmetric induction. Both enantiomeric forms are readily obtained as they are usually derived from the corresponding amino acids and, in some cases, it is possible to prepare all diastereomers

of a product from a single isomer of the auxiliary by modifying the reaction conditions.^[200]

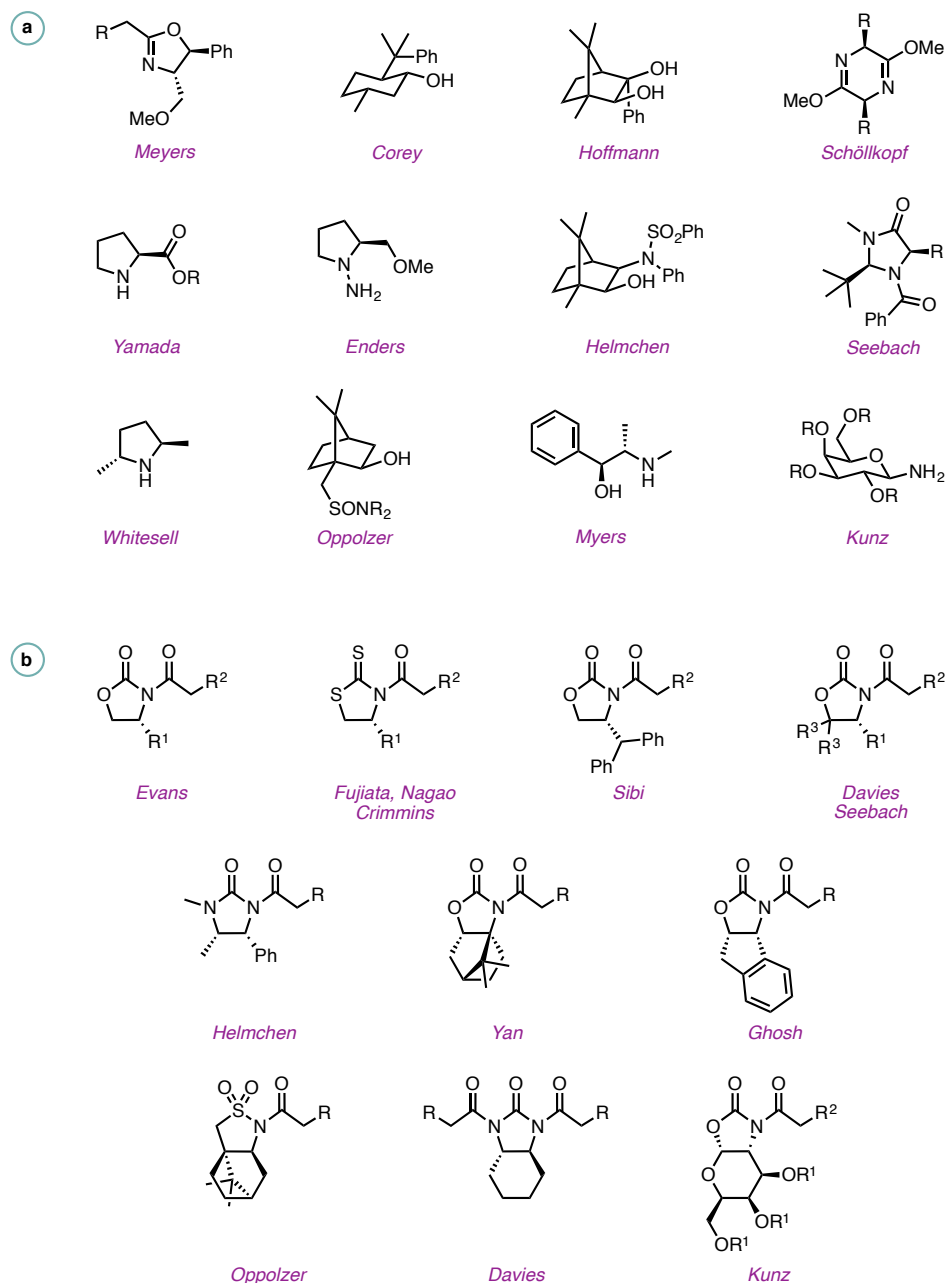
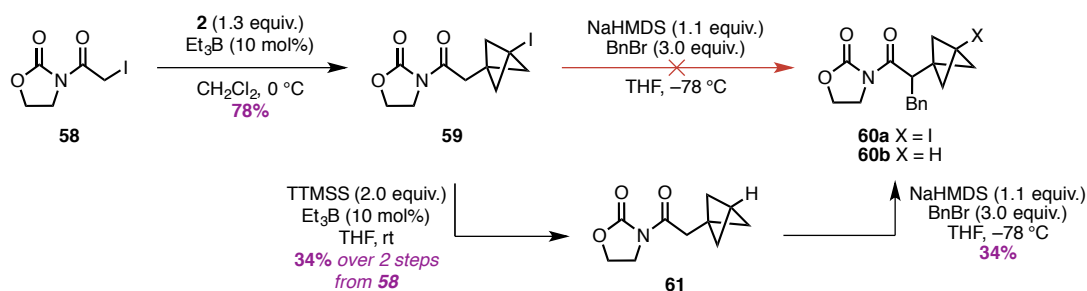


Figure 2.1. Chiral auxiliaries in synthesis.

2.2 Preliminary studies and reaction optimization

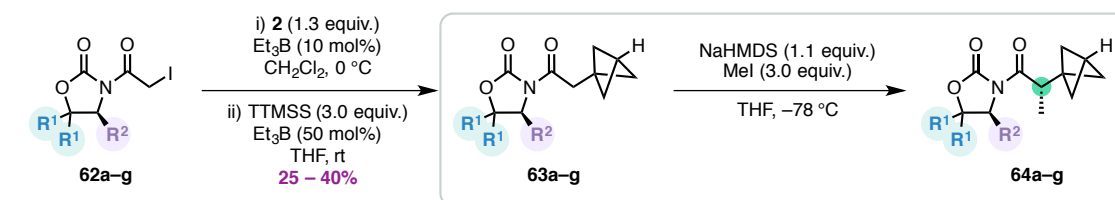
N-Acyloxazolidinones have enjoyed great success as chiral auxiliaries for the construction of α -carbonyl stereocenters *via* diastereoselective alkylations, and we anticipated that this would be a successful strategy for the synthesis of BCP compounds bearing such stereocenters. Investigations into this approach were initiated with the synthesis of a substrate bearing an *N*-acyloxazolidinone and a BCP unit, utilizing the ATRA methodology developed in the Anderson group.^[133] Achiral substrate **58** was subjected to an ATRA with [1.1.1]propellane **2**, yielding 78% of the desired product **59** (Scheme 2.2). Direct enolate alkylation of the iodo-BCP **59** only resulted in decomposition products, but alkylation of the terminal BCP **61** (formed by reduction of iodide **59**) was successful, giving the benzylated product **60b** in 34% yield.



Scheme 2.2. Preliminary studies for the diastereoselective alkylation.

Several substrates bearing different chiral oxazolidinones were then synthesized utilizing the above ATRA–reduction sequence to investigate the effects of the auxiliary substituents on the diastereoselective alkylation (Table 2.1). Substrates **63a** – **63c** featuring commercially available oxazolidinones as popularized by Evans were first considered, but these gave generally modest yields and/or diastereoselectivities in the alkylation reaction (entries 1 – 3, 29 – 85%, 3:1 – >20:1 *dr*). Notably, substrate **63c**, featuring a benzyl substituent on the auxiliary, gave the desired product in good yield and diastereoselectivity (entry 3, 85%, 14:1 *dr*). Substrate *ent*-**63d**, containing a

benzhydryl-functionalized auxiliary developed by Sibi,^[202] was also considered but multiple attempts to synthesize this oxazolidinone were unsuccessful (entry 4, **Appendix 8.1.1**). The study was then extended to SuperQuat auxiliaries, developed by Davies, which are known for excellent levels of stereoinduction as well as high yielding auxiliary removal and recycling.^[203-205] These indeed proved to be superior, as the alkylation of substrates **63e** – **63g** led to single diastereomers of the desired products **64e** – **64g** (entries 5 – 7, 22 – 84%, >20:1 *dr*). The auxiliary on substrate **63g**, again featuring a benzyl substituent, was identified as being optimal for this reaction, affording **64g** in good yield and excellent selectivity (entry 7, 84%, >20:1 *dr*).



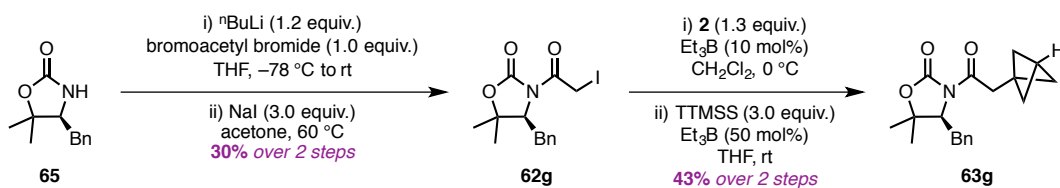
Entry	Substrate	R ¹	R ²	Yield (64a-g) ^a	<i>dr</i> ^b
1	63a	H	ⁱ Pr	36%	>20:1
2	63b	H	Ph	29%	3:1
3	63c	H	Bn	85%	14:1
4	<i>ent</i> - 63d	H	$\text{CH}(\text{Ph})_2$	—	—
5	63e	Me	Ph	50%	>20:1
6	63f	Ph	Bn	22%	>20:1
7	63g	Me	Bn	84%	>20:1

^aYields of isolated products. ^bDetermined by ^1H NMR analysis of the crude reaction mixture.

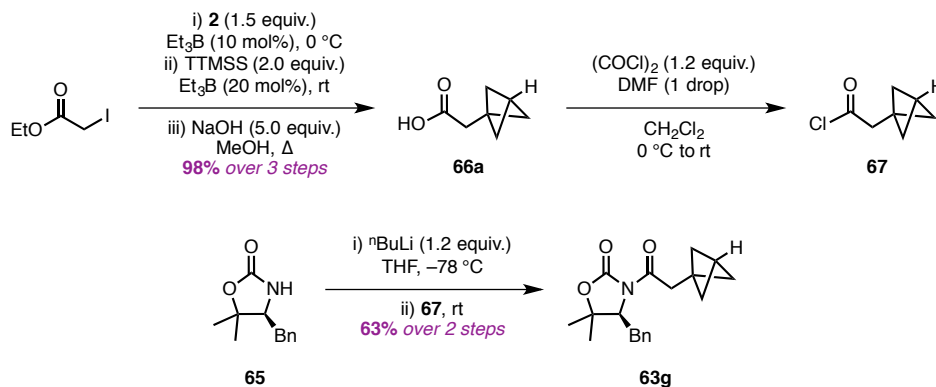
Table 2.1. Optimization of chiral auxiliaries for the diastereoselective alkylation.

An improved synthesis of substrate **63g** was then developed, involving an ATRA to access acid **66a**, followed by conversion to the acyl chloride **67** and coupling with the auxiliary, facilitating a multigram synthesis of **63g** (1.81 g of **63g** obtained from 1.33 g of **66a**, 63%) (**Scheme 2.3**).

— Initial synthetic route —

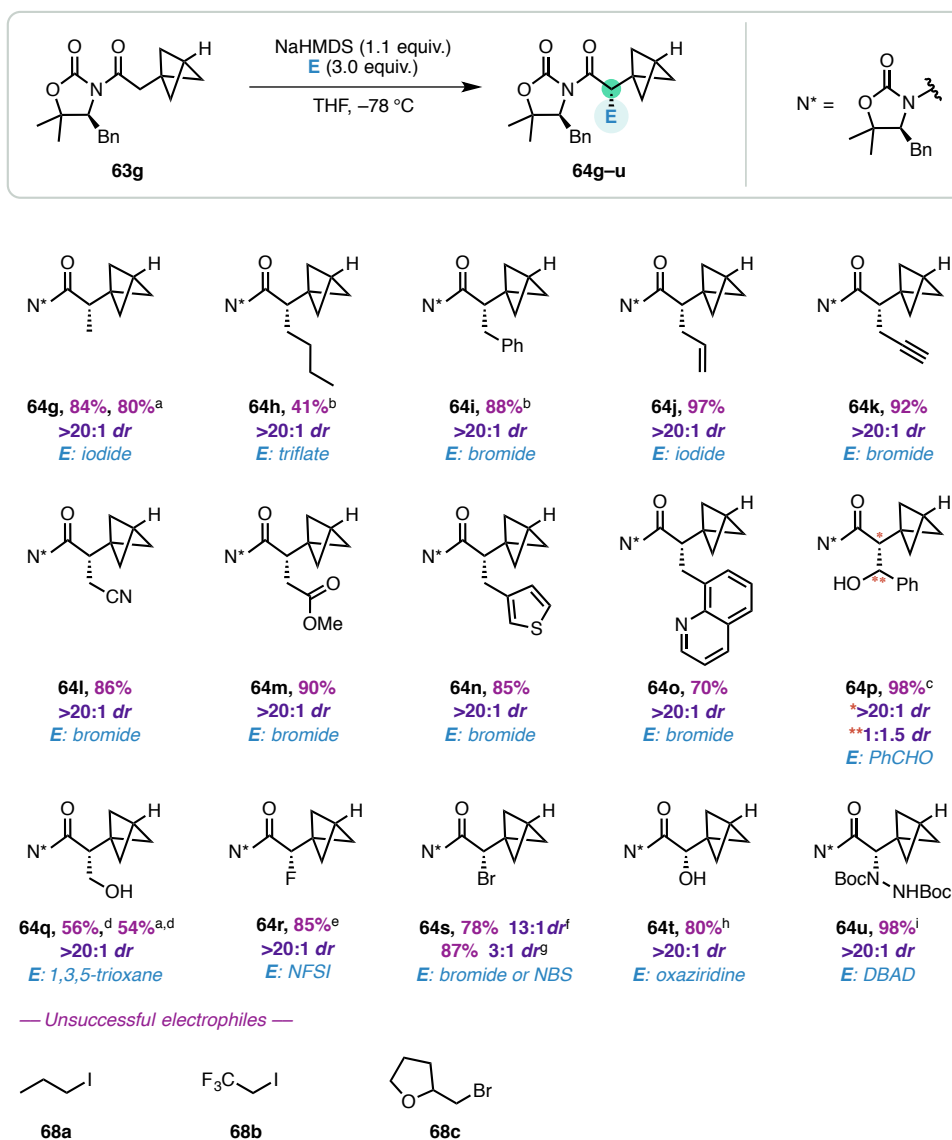


— Improved synthetic route —

Scheme 2.3. Improved synthetic route to **63g**.

2.3 Reaction scope

A brief optimization of reaction conditions was carried out (**Appendix 8.1.2**), with sodium enolates found to be superior to the corresponding lithium enolates, as has been observed for other similar diastereoselective alkylations with oxazolidinone auxiliaries.^[206] Therefore, we opted to use NaHMDS (1.1 equiv.) and an electrophile (3.0 equiv.) in THF at $-78\text{ }^{\circ}\text{C}$ as a general procedure for preparation of the α -chiral BCP products. With these optimized reaction conditions, the scope of the reaction was explored with substrate **63g** (**Figure 2.2**).



Reaction conditions unless stated otherwise:

- i) **63g** (0.15 mmol, 1.0 equiv.), NaHMDS (1.1 equiv.), THF, -78 °C, 30 min; ii) electrophile **E** (3.0 equiv.).
Reaction times varied with the electrophile; see **Chapter 9, Section 9.3.3** for details.

^a 1.33 mmol scale. ^b -78 °C to 0 °C. ^c ⁿBu₂BOTf (1.1 equiv.), DIPEA (1.2 equiv.), CH₂Cl₂, 0 °C; ii) PhCHO (1.1 equiv.), -78 °C. ^d TiCl₄ (1.0 equiv.), CH₂Cl₂, 0 °C; ii) DIPEA (1.1 equiv.); iii) 1,3,5-trioxane (1.2 equiv.), TiCl₄ (1.0 equiv.), rt. ^e **E** = NFSI (1.3 equiv.). ^f **E** = 2-(bromomethyl)-5-nitrofuran. ^g **E** = NBS. ^h NaHMDS (1.2 equiv.); 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine (1.5 equiv.). ⁱ **E** = di-*tert*-butyl azodicarboxylate (1.3 equiv.).

Figure 2.2. Scope of the diastereoselective enolate reaction.

A diverse range of electrophiles reacted successfully under these reaction conditions, affording the desired products in good to excellent yields and as a single diastereomer in almost all cases. Alkyl halide electrophiles were generally well tolerated, affording BCP products containing saturated (**64g** and **64i**, 84 – 88%, >20:1 *dr*) and unsaturated alkyl

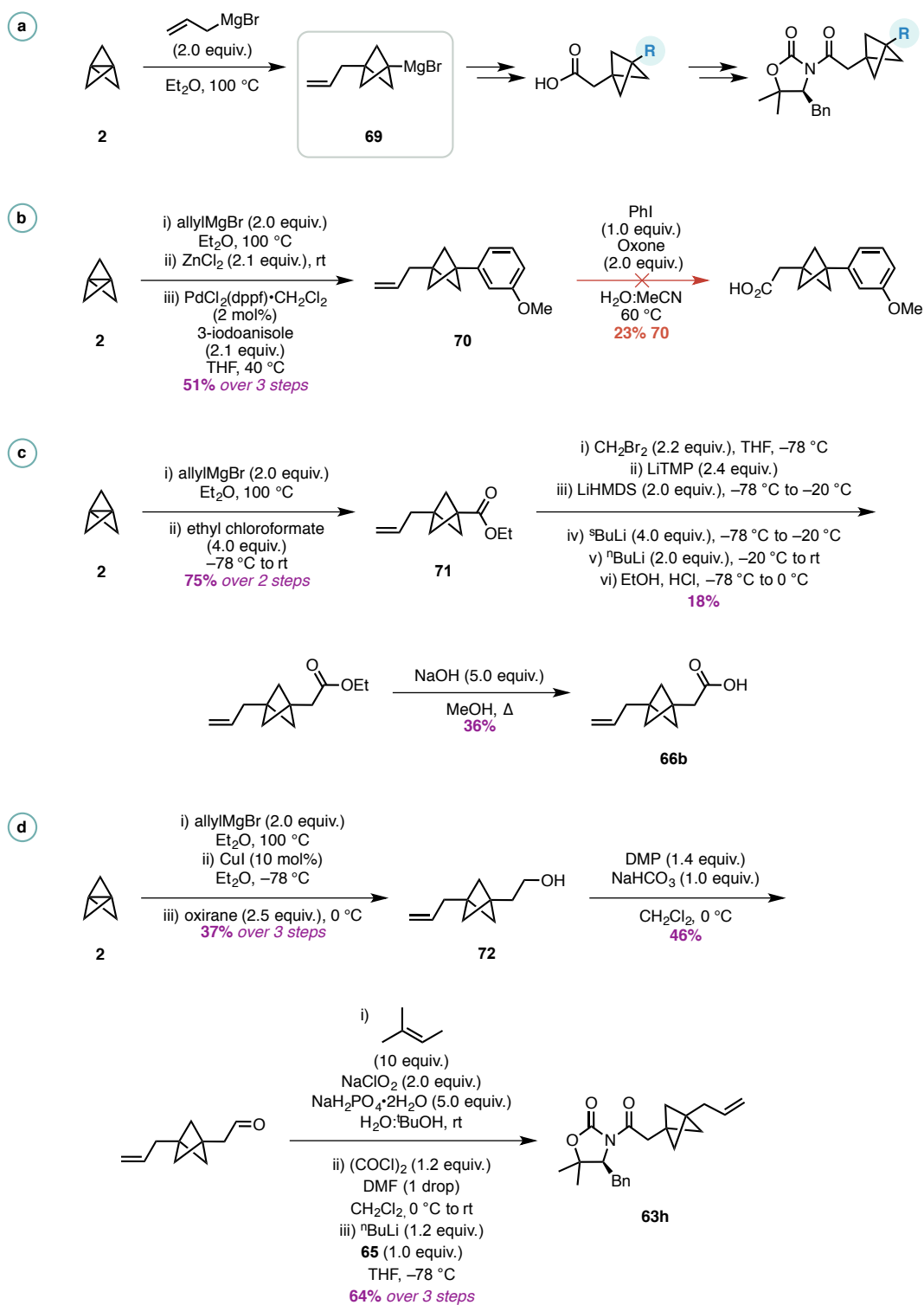
chains (**64j** and **64k**, 92 – 97%, >20:1 *dr*), heteroatoms (**64l** and **64m**, 86 – 90%, >20:1 *dr*), and heterocycles (**64n** and **64o**, 70 – 85%, >20:1 *dr*). Most of these reactions proceeded at –78 °C, but less reactive electrophiles required either warming to 0 °C (**64h**, **64i**) or use of the corresponding alkyl trifluoromethanesulfonate (**64h**).^[207-208] **63g** also underwent a diastereoselective aldol reaction *via* the dibutylboron enolate to afford **64p** in excellent yield and selectivity at the α -carbonyl stereocenter (98%, >20:1 *dr*), but modest selectivity at the benzylic position (1:1.5 *dr*) (see **Appendix 8.1.3** for optimization of reaction conditions). A diastereoselective hydroxymethylation protocol was also developed with 1,3,5-trioxane as a formaldehyde equivalent,^[209] allowing the formation of **64q** in 56% yield and >20:1 *dr*. Extensive optimization of the hydroxymethylation conditions revealed that an excess of 1,3,5-trioxane was required to ensure complete reaction conversion and the presence of a Lewis acid was crucial to activate both the substrate and 1,3,5-trioxane (see **Appendix 8.1.4** for further details). When less activated electrophiles such as *p*-formaldehyde and *N*-(hydroxymethyl)phthalimide were used, fragmentation of the enolate and extrusion of the oxazolidinone auxiliary was observed, potentially due to ketene formation, as has been noted in the literature.^[204,206,210]

The direct installation of heteroatoms at the α -carbonyl position was considered next, with fluorination (**64r**, 85%) and bromination (**64s**, 78%) both occurring with high diastereoselectivity (13:1 *dr*). Interestingly, the reaction with 2-(bromomethyl)-5-nitrofuran resulted in bromination instead of the expected installation of the heterocycle, with the product **64s** formed with much higher diastereoselectivity (13:1 *dr*) than the analogous reaction with *N*-bromosuccinimide (87%, 3:1 *dr*). Using the Davis oxaziridine^[211] and di-*tert*-butyl azodicarboxylate as electrophiles resulted in successful

α -hydroxylation and α -hydrazinylation respectively, affording the products **64t** (80%) and **64u** (98%) in high yields as single diastereomers.

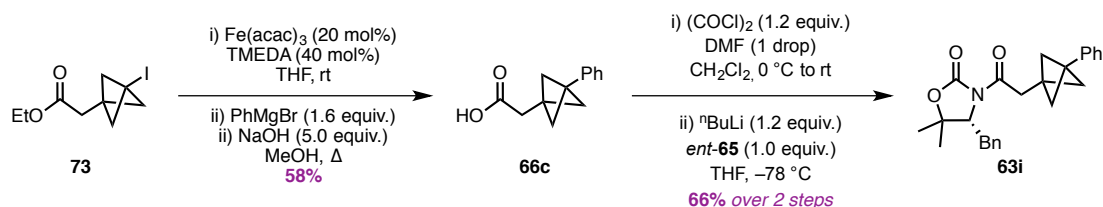
The yields and selectivities were also maintained when conducting the diastereoselective reactions on a larger scale (1.33 mmol) (**64g** and **64q**). However, a small number of electrophiles were not successful in the reaction (**68a** – **68c**), and only the cleaved auxiliary **65** was recovered, presumably *via* a ketene fragmentation pathway of the enolate.^[204,206,210]

The application of this chemistry to the synthesis of α -chiral 1,3-disubstituted BCPs was then pursued to broaden the scope of the enolate reaction. Initial attempts to achieve this involved the formation of the BCP-Grignard **69**; both bridgehead positions could then be functionalized, leading ultimately to a carboxylic acid on one end that can be coupled to the chiral auxiliary (**Scheme 2.4a**). Transmetallation of BCP-Grignard **69** with zinc chloride followed by a Pd-catalyzed cross-coupling afforded aryl BCP **70**, but oxidative cleavage of the alkene was unsuccessful (**Scheme 2.4b**). Alternatively, the BCP-Grignard **69** could be reacted with ethyl chloroformate, giving the ester **71** in 75% yield over two steps. However, subsequent multi-step homologation and hydrolysis were low-yielding and inefficient for the synthesis of significant quantities of the acid **66b** (**Scheme 2.4c**). The most successful route eventually involved reaction of the BCP-Grignard **69** with copper(I) iodide and oxirane to form the alcohol **72**, which could then be oxidized and coupled with the chiral auxiliary **65** to give allyl-BCP substrate **63h** (**Scheme 2.4d**).



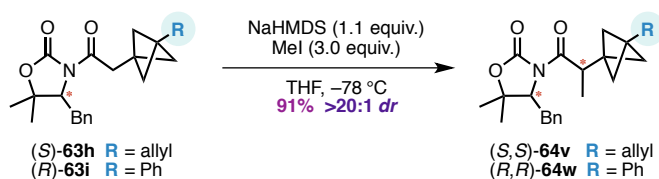
Scheme 2.4. Synthesis of 1,3-disubstituted BCP substrates.

A similar approach was attempted with phenylmagnesium bromide to access a phenyl substituted BCP, but proved to be unsuccessful. Instead, cross-coupling of the BCP iodide **73** was used to obtain the phenyl-substituted BCP **66c**, which was then converted to substrate **63i** (Scheme 2.5).



Scheme 2.5. Synthesis of phenyl-substituted BCP substrate **63i**.

The diastereoselective alkylation was evaluated with the two 1,3-disubstituted substrates **63h** and **63i**, and the corresponding products (**64v** and **64w**) were obtained in excellent yields and selectivities in both cases (91%, >20:1 *dr*) (Scheme 2.6).



Scheme 2.6. Diastereoselective alkylation of 1,3-disubstituted BCP substrates.

The configuration of the newly formed stereocenter in the BCP products was confirmed by X-ray crystallographic analysis of three compounds **64k**, **64m** and **64t** (carried out by Steven Mansfield) (Figure 2.3) and the stereochemistry of the remaining compounds was assigned by analogy.

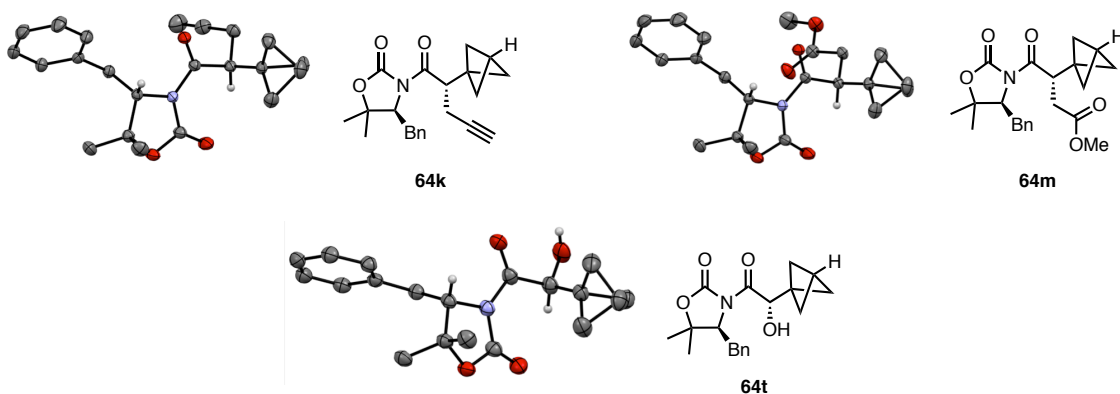
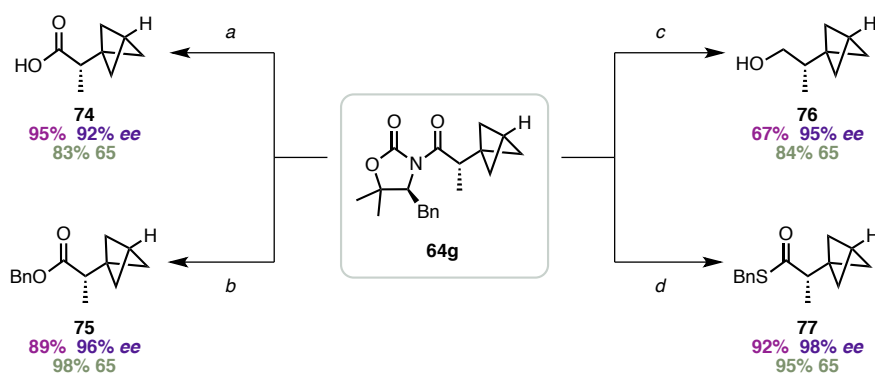


Figure 2.3. Solid-state structures of **64k**, **64m** and **64t**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms (except at the stereocenters and the hydroxyl) have been omitted for clarity.

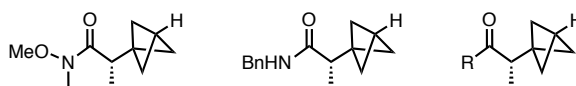
X-ray crystallographic analysis was carried out by Steven Mansfield.

2.4 Derivatization of α -chiral BCP products

Having successfully used the SuperQuat auxiliary for the introduction of an α -carbonyl stereocenter, removal of the auxiliary would enable derivatization of the carbonyl functional group, paving the way to a wide array of α -chiral BCP building blocks. This was readily accomplished by hydrolysis, esterification, reduction and thioesterification processes to provide enantioenriched BCPs **74** – **77** in good to excellent yields (67 – 95%; note: volatility of product **76** likely resulted in diminished yields) while maintaining high levels of enantiopurity (92 – 98% *ee*) (**Scheme 2.7**). The SuperQuat auxiliary **65** could be recovered in good yield (83 – 98%) and recycled in the substrate synthesis. Attempts to convert **64g** to a Weinreb amide, an amide and a ketone were also carried out but were not successful.



— Unsuccessful derivatizations —



Reaction conditions:

- a:** LiOH (3.05 equiv.), H₂O₂:THF:H₂O, 0 °C to rt. **b:** BnOH (2.0 equiv.), ⁿBuLi (1.5 equiv.), THF, 0 °C.
c: LiAlH₄ (1.8 equiv.), THF, -78 °C. **d:** BnSH (1.1 equiv.), ⁿBuLi (1.0 equiv.), THF, -78 °C to rt.

Scheme 2.7. Removal of the SuperQuat auxiliary and carbonyl functionalization.

2.5 Synthesis of BCP analogues of bioactive molecules

Finally, the optimized methodology for accessing BCPs bearing adjacent stereocenters was applied to the synthesis of molecules of biological relevance. Three target molecules bearing benzylic stereocenters were selected, where the phenyl ring could be substituted by a BCP unit (**Figure 2.4**).

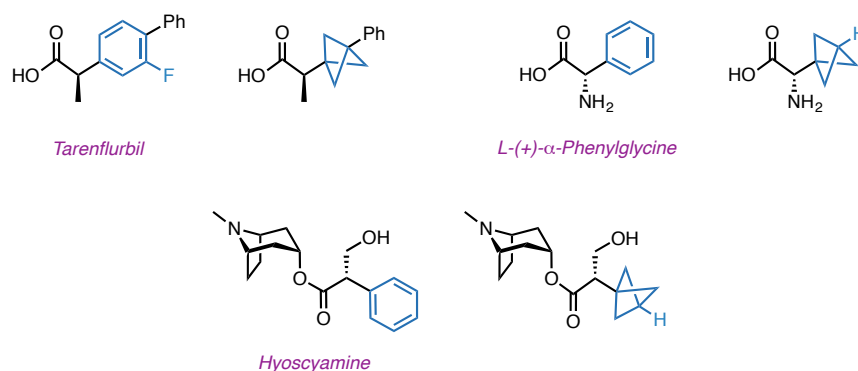
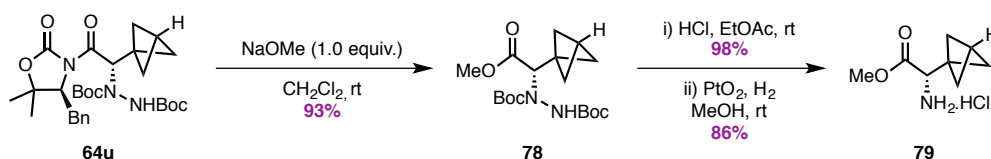


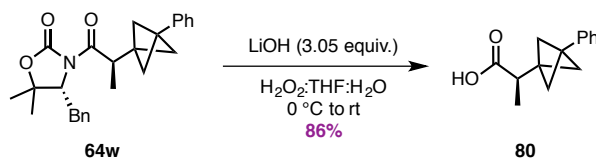
Figure 2.4. Bioactive molecules and the corresponding BCP analogues.

First, the asymmetric methodology was used in the synthesis of a BCP analogue of the amino acid, L-(+)- α -phenylglycine (**Scheme 2.8**). Methanolysis of **64u**, obtained from the diastereoselective α -carbonyl hydrazinylation, afforded methyl ester **78** (93%), which underwent Boc deprotection under acidic conditions followed by Pt-catalyzed hydrogenolysis of the N–N bond to form the BCP analogue of L-(+)- α -phenylglycine methyl ester hydrochloride **79** in 78% yield over three steps from **64u**.



Scheme 2.8. Synthesis of BCP-phenylglycine **79**.

Next, the asymmetric synthesis of a BCP analogue of tarenflurbil, a nonsteroidal anti-inflammatory drug studied for its potential as a treatment for Alzheimer's disease, was carried out. This was achieved by hydrolysis of the 1,3-disubstituted BCP **64w**, giving an 86% yield of BCP-tarenflurbil **80** (**Scheme 2.9**).



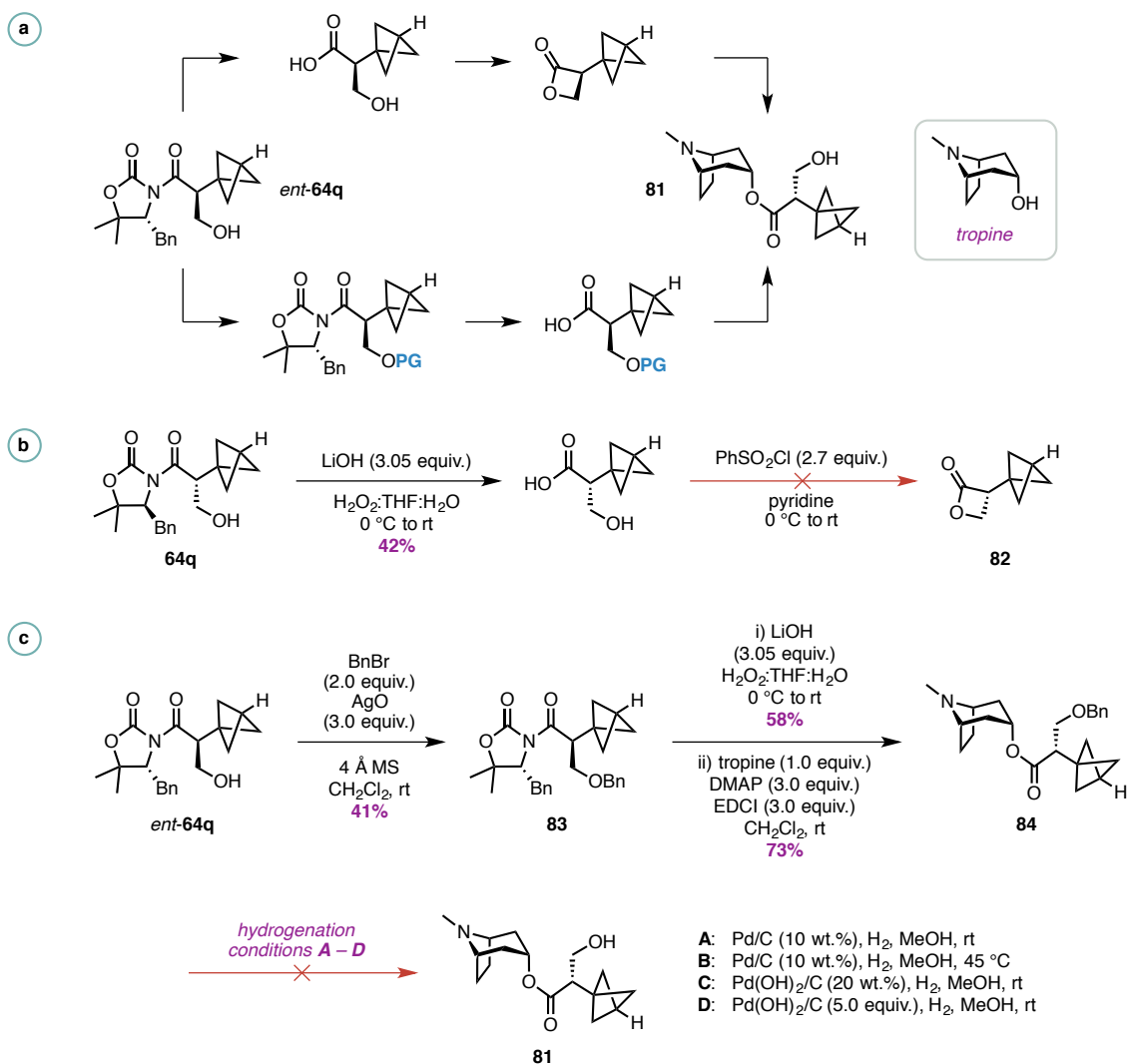
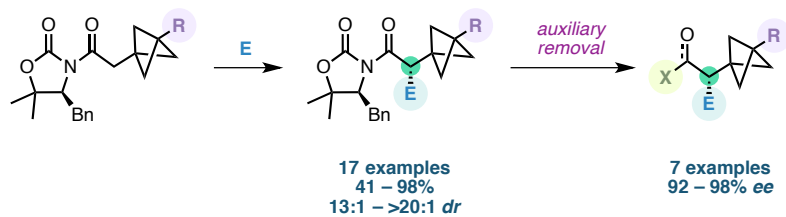
Scheme 2.9. Synthesis of BCP-tarenflurbil **80**.

We then sought to synthesize the BCP analogue of the tropane alkaloid hyoscyamine, which has been used to treat stomach/intestinal disorders and heart problems, and control the symptoms of Parkinson's disease. Several synthetic routes were evaluated, including the formation of a lactone from the hydroxymethylated BCP compound **64q** and the use of various alcohol protecting groups prior to cleavage of the auxiliary and esterification with tropine (**Scheme 2.10a**). An attempt to synthesize lactone **82** was unsuccessful, giving predominantly decomposition products (**Scheme 2.10b**). Several

different alcohol protecting groups were then evaluated with substrate *ent*-**64q**. Using a *tert*-butyldimethylsilyl (TBS) or *p*-methoxybenzyl (PMB) protecting group, the corresponding esterification products could not be obtained reliably, due to undesired deprotection at various stages of the synthetic route, incompatibility with the esterification conditions and/or the formation of numerous side products that could not be separated from the desired compound. However, the benzyl-protected BCP **83** could undergo successful auxiliary cleavage and coupling with tropine to afford the desired ester **84** (Scheme 2.10c). Unfortunately, several attempts at deprotection invariably resulted in a complex mixture of products. With hydrogenation conditions **D**, the desired debenzylated BCP product **81** was detected by high-resolution mass spectrometry but multiple attempts to purify the compound were not successful. Due to time constraints and the successful applications of the diastereoselective methodology to the synthesis of two other target molecules, further efforts to obtain BCP-hyoscyamine **81** were suspended in favor of other research directions.

2.6 Conclusions

In summary, the work developed in this chapter represents the first general method to synthesize BCP compounds bearing an adjacent stereocenter. It capitalizes on expertise developed in the Anderson group to access BCP derivatives *via* ATRA chemistry,^[133] the products of which can then be linked to a chiral auxiliary, enabling the diastereoselective introduction of an adjacent substituent (Scheme 2.11). In contrast to the existing examples in the literature at the time, this methodology offers a more convergent and efficient route to these enantioenriched BCP compounds, and circumvents the need for toxic reagents and/or resolution processes to obtain the desired

Scheme 2.10. Attempted synthesis of BCP-hyoscyamine **81**.Scheme 2.11. Synthesis of α -chiral BCPs via diastereoselective enolate reactions.

products as single diastereomers. It remains one of the most general and readily scaled processes for accessing these potentially valuable compounds.

BCP compounds bearing chiral oxazolidinone auxiliaries can undergo enolate reactions to access α -chiral BCPs with a wide range of functionalities on the stereocenter in high yields and often as a single diastereomer. Modified synthetic routes also enabled the use of 1,3-disubstituted BCP derivatives in the diastereoselective reaction. This methodology proved to be highly versatile in delivering novel BCP products, with an array of alkyl, aryl, heteroaryl and heteroatom functional groups being successfully introduced at the α -carbonyl stereocenter. Facile removal of the SuperQuat auxiliary allowed further diversification of the BCP products without erosion of enantiopurity. These features make this protocol amenable towards the synthesis of enantioenriched biomolecules bearing a BCP unit, as demonstrated by the synthesis of BCP-phenylglycine, BCP-tarenflurbil and benzyl-protected BCP-hyoscyamine. Part of the work presented in this chapter was published in *Organic Letters* in 2019.^[212]

Asymmetric atom transfer radical additions

3.1 Introduction

Organic free radicals were first reported in 1900 by Gomberg upon his discovery of the triphenylmethyl radical.^[213] Several early examples of radical processes had in fact preceded this discovery, such as the Kolbe electrochemical decarboxylation in 1848^[214] and the pinacol coupling in 1859,^[215] although they were only later understood to proceed *via* radical intermediates. Despite this long history, radical reactions were, for many years, regarded as inferior to ionic processes due to their highly unpredictable and unselective nature.^[216-218] These perceptions, however, have been steadily countered by the emergence of numerous innovative strategies that harness the reactivity of radicals in productive synthetic processes, expedited by significant advances in the understanding of the inherent stability and lifetime of these species.

Far from their initial perception as a mere ‘chemical curiosity’,^[217] radical reactions are now known to offer many advantages over ionic processes. Radicals are generally inert

to reactive functionalities, less sensitive to sterics than their ionic counterparts, can facilitate rapid increases in molecular complexity, and enable the most direct means of reactivity umpolung.^[216] This is especially evident in the widespread applications of radical reactions in the synthesis of complex natural products, as well as their use in various industrial settings; some examples are shown in **Figure 3.1**.^[216,219]

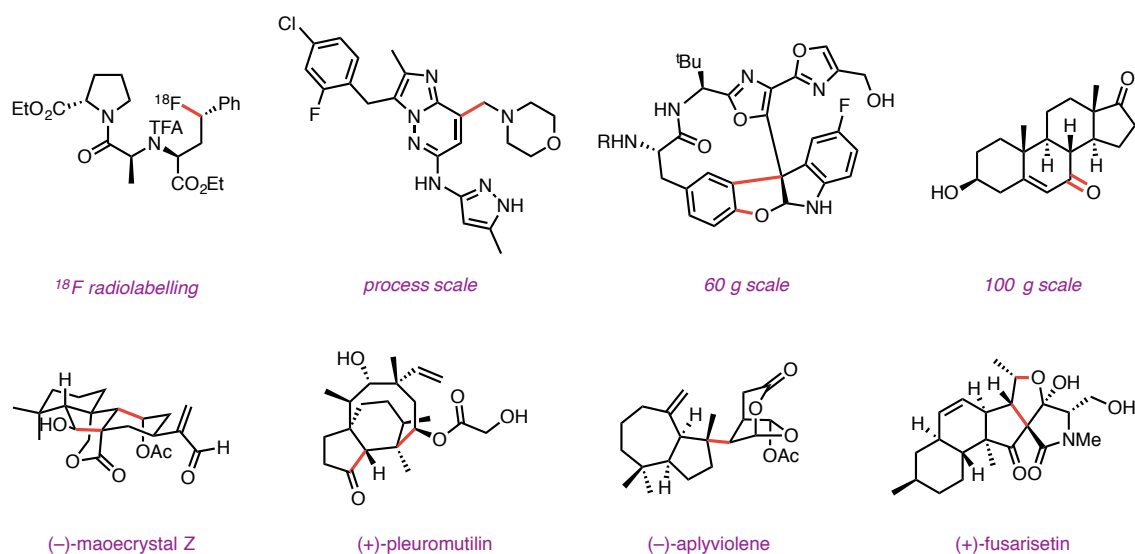


Figure 3.1. Applications of radical reactions in industrial settings and natural product synthesis (bonds formed through radical processes are highlighted).

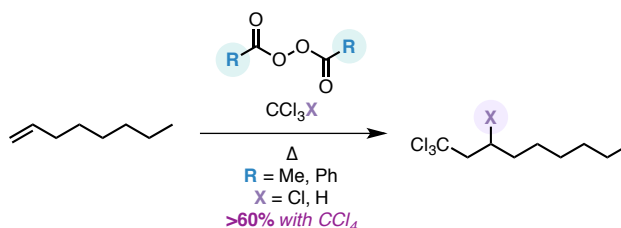
3.1.1 Atom transfer radical additions

One of the most influential discoveries in radical chemistry is the atom transfer radical addition (ATRA) reaction, encompassing a wide variety of radical addition processes in which a carbon–heteroatom or heteroatom–heteroatom bond is homolytically cleaved and added across another bond, usually an alkene, alkyne or other multiply bonded functionality (**Scheme 3.1**).^[220] An ATRA begins with an initiation step to form the radical species, which is then followed by chain-propagating steps.



Scheme 3.1. General mechanism of an atom transfer radical addition.

In 1933, Kharasch proposed the ‘peroxide effect’, where a free radical chain reaction accounts for the anti-Markovnikov addition of hydrogen bromide to unsymmetrical alkenes in the presence of peroxide initiators.^[221] This prompted further studies of free radical reactions, culminating in the first example of an ATRA reported by Kharasch in 1945.^[222] This seminal work was concerned with the addition of polyhalogenated alkanes to olefins in the presence of peroxide initiators and heat (**Scheme 3.2**). Good yields of the monoadducts were obtained for additions to simple olefins such as 1-octene, but the formation of higher-order polymers was observed for more reactive olefins such as styrene.



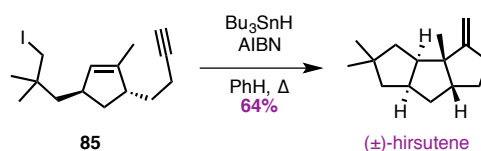
Scheme 3.2. First reported ATRA by Kharasch.

Atom transfer processes are now widely used in organic synthesis, with other notable extensions of this process including atom transfer radical cyclizations (ATRCs)^[223] and polymerizations (ATRP).^[224-227] One of the benefits of ATRA-type processes is that they are inherently non-reductive and therefore yield products that are more highly functionalized than the corresponding starting materials.^[220]

3.1.2 Asymmetric radical reactions

Another major discovery that countered the misconception of radical chemistry as being unselective and uncontrollable was the development of asymmetric radical reactions.^[228-234] This was pioneered by Curran, Giese, Porter, Sibi and Renaud in the 1980s and 1990s, who successfully employed radicals in a range of stereoselective reactions.

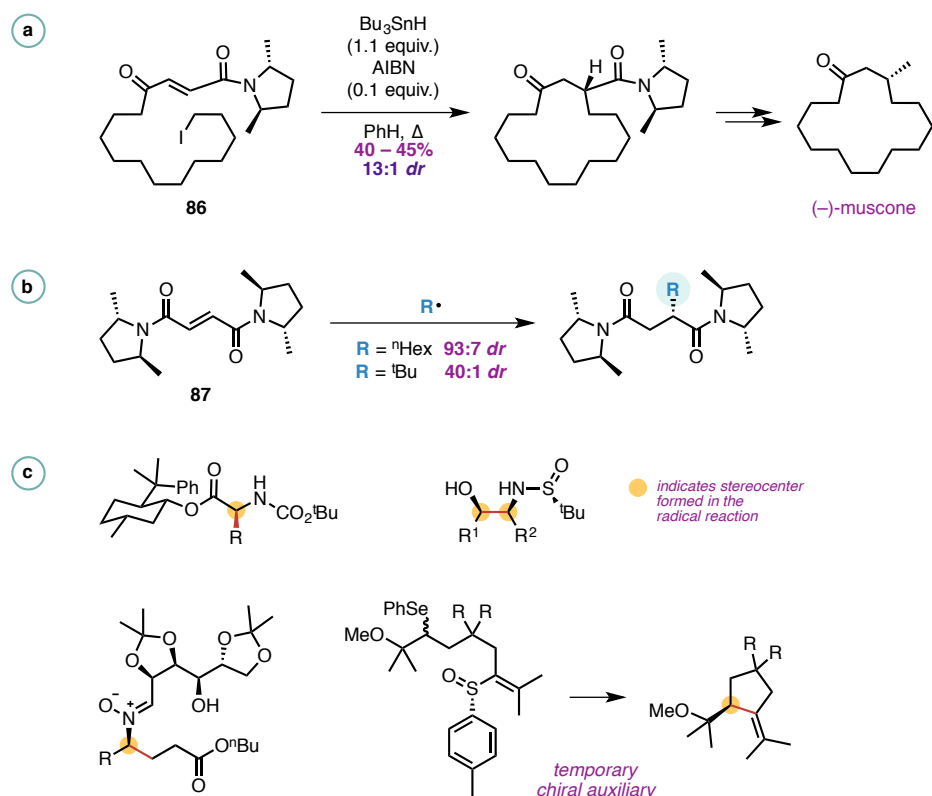
Early asymmetric radical transformations relied on strategies that have been successful in other non-radical reactions, typically involving substrate- or reagent-controlled asymmetric induction. Initial examples of stereoselective radical reactions were substrate-controlled, where an existing chiral center on the substrate influences the stereochemical outcome of the reaction, usually through the formation of a new stereocenter. One of the landmark reports of this strategy is the 1985 synthesis of (±)-hirsutene by Curran, which is also one of the most influential examples of radical cascades in natural product synthesis (**Scheme 3.3**).^[235] The carbon-centered radical formed from iodine abstraction of **85** undergoes two successive cyclizations to afford the tricyclic natural product after hydrogen atom transfer (HAT) from tributyltin hydride, which also serves to propagate the radical cycle.



Scheme 3.3. Substrate-controlled asymmetric radical reactions in the synthesis of (±)-hirsutene.

Much like their success in ionic reactions (as described in **Chapter 2**), chiral auxiliaries have also found widespread application in substrate-controlled asymmetric radical reactions. In one of the earliest examples by Porter in 1989, a C_2 -symmetric amide auxiliary was appended onto substrates **86** and **87** for use in an intramolecular radical

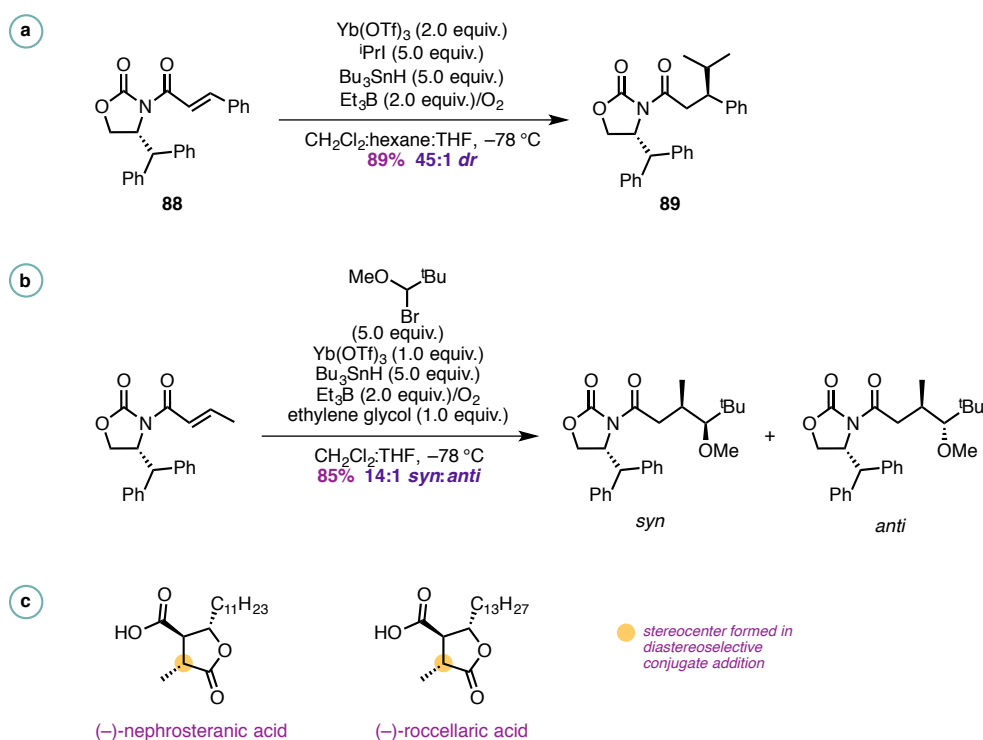
macrocyclization^[236] (**Scheme 3.4a**) and an intermolecular conjugate addition^[237] respectively (**Scheme 3.4b**). A selection of products formed from radical processes that involve the use of other chiral auxiliaries is shown in **Scheme 3.4c**, including chiral alcohols,^[238-239] *tert*-butanesulfinamides,^[240] sulfoxides^[241] and carbohydrate-based auxiliaries.^[242]



Scheme 3.4. Chiral auxiliaries in asymmetric radical reactions.

Many of the major developments that established the ability of radicals to undergo highly stereoselective processes featured the use of chiral oxazolidinone auxiliaries. Pioneering work by the groups of Sibi and Porter relied heavily on the use of these auxiliaries in combination with Lewis acids,^[243-244] which were predominantly used to enhance the reactivity of α -carbonyl radicals in reactions such as conjugate additions and allylations.^[244-245] In an early example of such a transformation, substrate **88** underwent a diastereoselective conjugate addition in the presence of a lanthanide Lewis acid, forming the product **89** in 89% yield and 45:1 *dr* (**Scheme 3.5a**).^[246] This

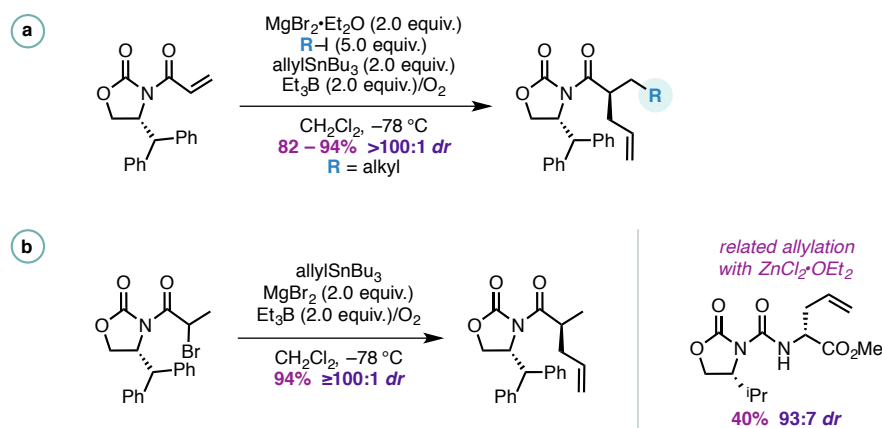
methodology was then extended to the synthesis of products bearing β - and γ -stereocenters^[247] (**Scheme 3.5b**) and has since found applications in the synthesis of natural products^[248] (**Scheme 3.5c**).



Scheme 3.5. Chiral oxazolidinone auxiliaries in asymmetric radical conjugate additions.

α,β -Unsaturated substrates can also be subjected to a tandem conjugate addition/allylation sequence to form α -carbonyl stereocenters with excellent diastereoselectivity (**Scheme 3.6a**).^[249] In a related transformation, α -carbonyl radicals generated from the corresponding α -bromocarbonyls can undergo a highly stereoselective allylation (**Scheme 3.6b**).^[250-252]

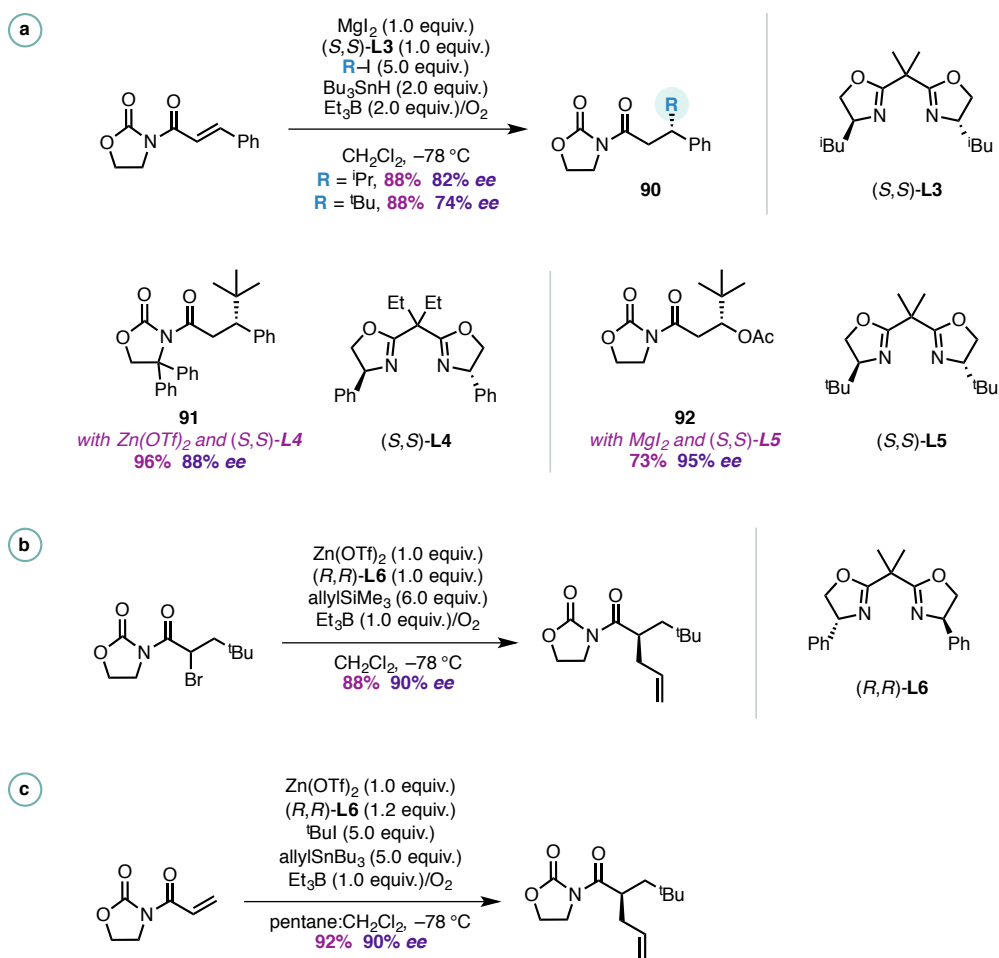
The success of these Lewis acid-catalyzed reactions with substrates bearing chiral oxazolidinone auxiliaries paved the way for further developments of enantioselective processes with achiral substrates. The use of Lewis acids with chiral ligands, in particular bis(oxazoline) (BOX) ligands, was highly successful in enantioselective



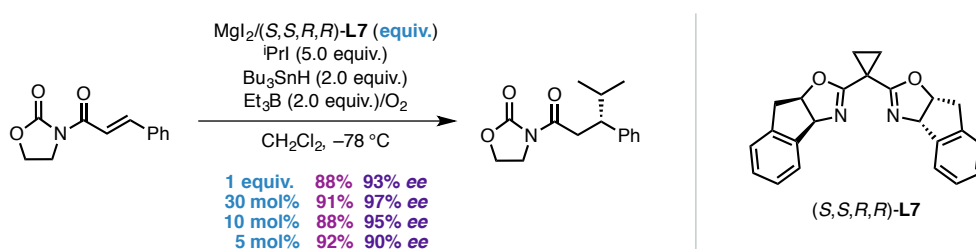
Scheme 3.6. Chiral oxazolidinone auxiliaries in asymmetric radical allylations.

conjugate additions, forming products such as **90**, **91** and **92** with excellent levels of enantioselectivity (**Scheme 3.7a**).^[253-255] Highly enantioselective variants of direct allylation^[256] (**Scheme 3.7b**) and conjugate addition/allylation^[257-258] (**Scheme 3.7c**) processes with achiral oxazolidinone substrates were also disclosed, again utilizing Lewis acid–BOX ligand complexes to induce asymmetry.

These transformations were initially thought to require stoichiometric amounts of the chiral Lewis acid–ligand complex for complete complexation of the substrate, in order to avoid any unselective background reaction. However, it was later found that catalytic amounts of the chiral complex were still able to catalyze reactions while maintaining high levels of efficiency and selectivity, as the non-Lewis acid-mediated reaction is negligible at -78 °C and complexation is needed to generate the reactive species (**Scheme 3.8**).^[259-263]



Scheme 3.7. Oxazolidinone substrates in enantioselective radical reactions.



Scheme 3.8. Oxazolidinone substrates in catalytic enantioselective radical reactions.

3.1.3 Asymmetric atom transfer radical additions

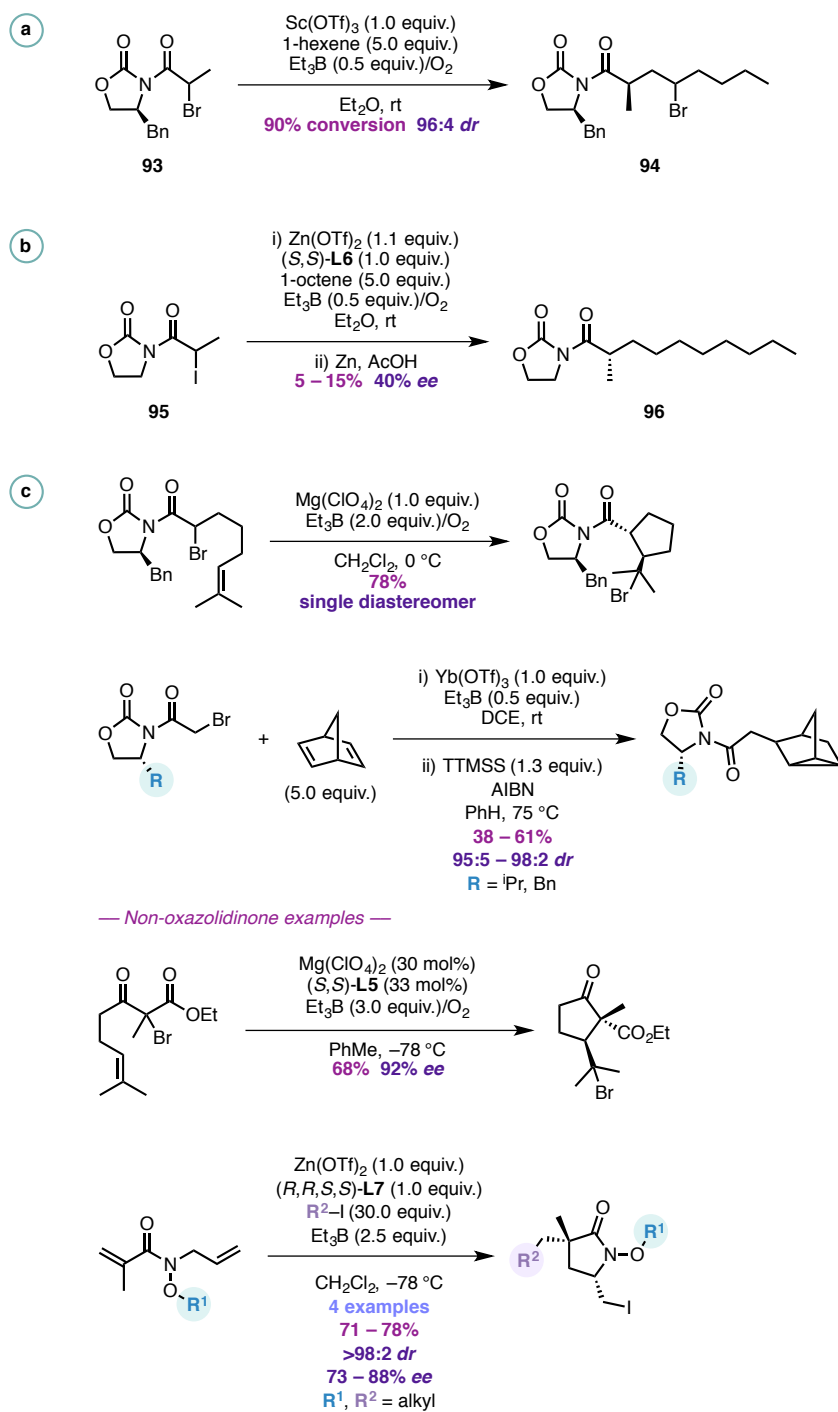
Having established the effectiveness of the oxazolidinone template in Lewis acid-catalyzed reactions, similar strategies were utilized to develop asymmetric atom transfer reactions. Chiral substrate **93** was shown to undergo a highly diastereoselective

ATRA with 1-hexene to afford **94** with 96:4 *dr* (>90% conversion) (**Scheme 3.9a**).^[245] In the same study, achiral iodide **95** was subjected to an enantioselective ATRA with a chiral Lewis acid–BOX ligand complex, forming **96** in low yields (5 – 15%) but with promising levels of enantioselectivity (40% *ee*) (**Scheme 3.9b**). Several highly stereoselective examples of atom and group transfer processes have since been disclosed with chiral^[264-266] and achiral^[267-270] substrates, with only substoichiometric amounts of the Lewis acid–ligand complex required in some cases (**Scheme 3.9c**). However, these reactions typically involve the use of superstoichiometric amounts of radical acceptor, triethylborane initiator or radical precursor.

3.2 Diastereoselective atom transfer radical additions with

[1.1.1]propellane

Oxazolidinone templates have been shown to be extremely promising motifs for inducing asymmetry in radical reactions, either through the influence of a stereocenter on the auxiliary, or by coordination of the 1,3-dicarbonyl framework to a chiral Lewis acid–ligand complex. Building upon the success of both the ATRA of alkyl halides with [1.1.1]propellane **2**^[133] and the diastereoselective methodology using chiral oxazolidinones (**Chapter 2**), we sought to develop a direct asymmetric ATRA to synthesize α -chiral BCPs, where the formation of the stereocenter and installation of the BCP would occur in a single step (**Figure 3.2**). Coordination of the substrate to a Lewis acid through the 1,3-dicarbonyl framework was expected to direct the facial selectivity of the addition to [1.1.1]propellane **2** by blocking one face of the α -carbonyl radical towards addition, thus creating a chiral environment. Substrate complexation to a Lewis acid also renders the resulting α -carbonyl radical more electrophilic,^[245] which is



Scheme 3.9. Asymmetric atom transfer radical additions.

expected to be favorable as, when developing the ATRA chemistry in the group,^[133] it was found that [1.1.1]propellane **2** reacts more rapidly with electron-deficient alkyl halides than electron-neutral ones.

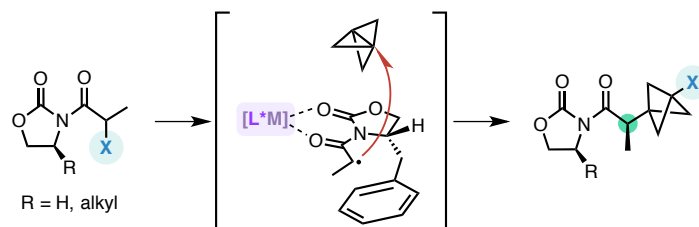
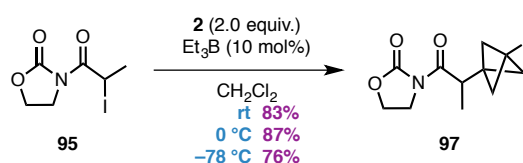


Figure 3.2. Direct asymmetric ATRA with [1.1.1]propellane **2**.

Substrate **95** was first synthesized and subjected to the ATRA at low temperatures, which were expected to be advantageous for controlling the selectivity in asymmetric reactions (**Scheme 3.10**). The reaction proceeded smoothly at $-78\text{ }^{\circ}\text{C}$, with only a slight decrease in yield observed when compared to the reaction at room temperature (76% vs. 83%). Complete reaction conversion was achieved after 2 h at all three temperatures.



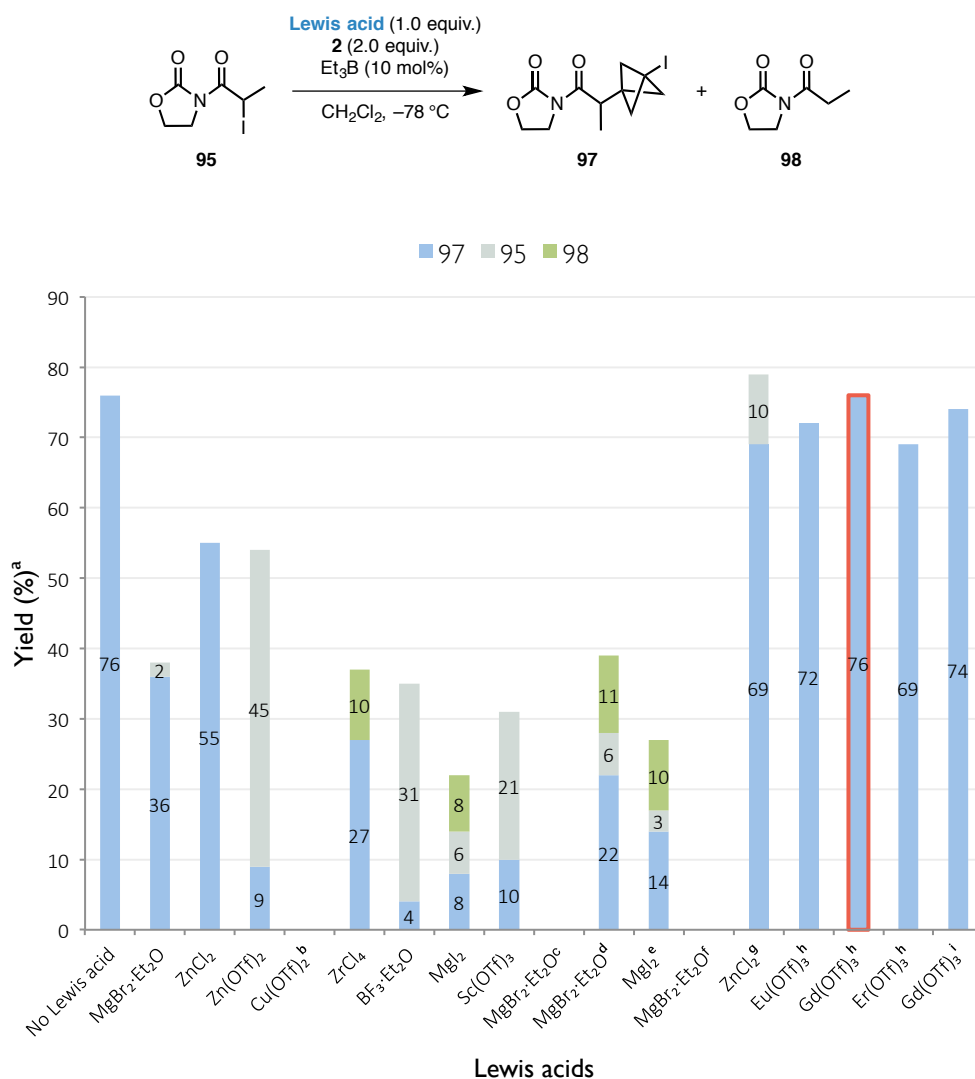
Scheme 3.10. Effect of temperature on the ATRA with [1.1.1]propellane **2**.

A range of Lewis acids were then evaluated, with one equivalent initially used to maximize substrate complexation throughout the course of the reaction (**Figure 3.3**). Preforming the substrate-Lewis acid complex before addition of the other reagents ([1.1.1]propellane **2** and triethylborane) was found to give more consistent results than single addition of all reagents, and this procedure was used throughout the investigation. After extensive screening, it was unexpectedly found that the presence of Lewis acids inhibited the radical reaction, in contrast to the literature reports on similar

Lewis acid-catalyzed radical reactions. Reaction rates with main group and transition metal Lewis acids were sluggish, with mixtures of the desired product **97**, unreacted starting material **95** and dehalogenated product **98** being obtained. Variation of the other reaction parameters such as solvent, temperature, concentration and reagent stoichiometry offered no improvement to the reaction outcome. We then turned to lanthanide triflates, which have been found to perform well in similar asymmetric radical reactions,^[248,261,263,271-272] and found that these delivered better results in the ATRA with [1.1.1]propellane **2**. Lower levels of reaction inhibition were observed, and the desired product **97** was formed exclusively, with Gd(OTf)₃ in particular affording the product in 76% yield.

As alkyl iodides are known to react more efficiently with [1.1.1]propellane **2** than other alkyl halides,^[133] the bromide analogue of **95** was considered in the ATRA, in hope that the Lewis acids would be better able to activate a substrate that is less reactive. Unfortunately, the reactions with the bromide were inefficient, lower yielding and produced more undesired side products (**Appendix 8.2.1**).

We then proceeded to investigate the effect of lanthanide Lewis acids in a diastereoselective ATRA with chiral substrates (**Scheme 3.11**). Substrate **99**, bearing a benzyl motif that was found to be advantageous in the diastereoselective enolate reactions discussed in **Chapter 2**, was subjected to the ATRA with [1.1.1]propellane **2**. In the absence of Lewis acids, the desired BCP product **100** was obtained in 71% yield and, as might be expected, no inherent diastereoselectivity was observed (1:1 *dr*). Unfortunately, only low levels of diastereoselectivity were attained in the presence of Gd(OTf)₃ (51%, 1.9:1 *dr*). The reaction was then carried out with substrate **101** containing a SuperQuat auxiliary, having noted its superior performance in the

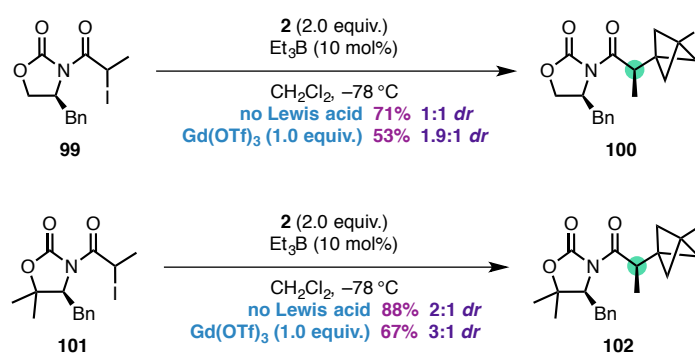


Reactions conducted on 0.5 mmol scale, 1.0 mL of CH₂Cl₂ (0.5 M), 3 h reaction time if complete reaction conversion achieved or 24 h otherwise.

^aYields of isolated products. ^bDecomposition products only. ^cCH₂Cl₂ (6.7 mL, 0.07 M); decomposition products only. ^dTHF (1.0 mL) instead of CH₂Cl₂. ^eMgI₂ (2.0 equiv.). ^fEt₃B (1.0 equiv.); decomposition products only. ^g-40 °C. ^hTHF (1.0 mL) as co-solvent. ⁱTHF (2.0 mL) instead of CH₂Cl₂.

Figure 3.3. Effect of Lewis acids on the ATRA with [1.1.1]propellane **2**.

diastereoselective enolate reactions (**Chapter 2**). In the absence of a Lewis acid, a modest preference for one of the diastereomeric products **102** was observed (2:1 *dr*) but only a slight enhancement of diastereoselectivity was achieved when conducting the reaction with a Lewis acid (3:1 *dr*). Given the success of the enolate alkylation reactions using a relatively weak sodium counterion as the complexation agent, this was somewhat surprising and suggested that a chiral ligand may be required to achieve meaningful levels of selectivity.

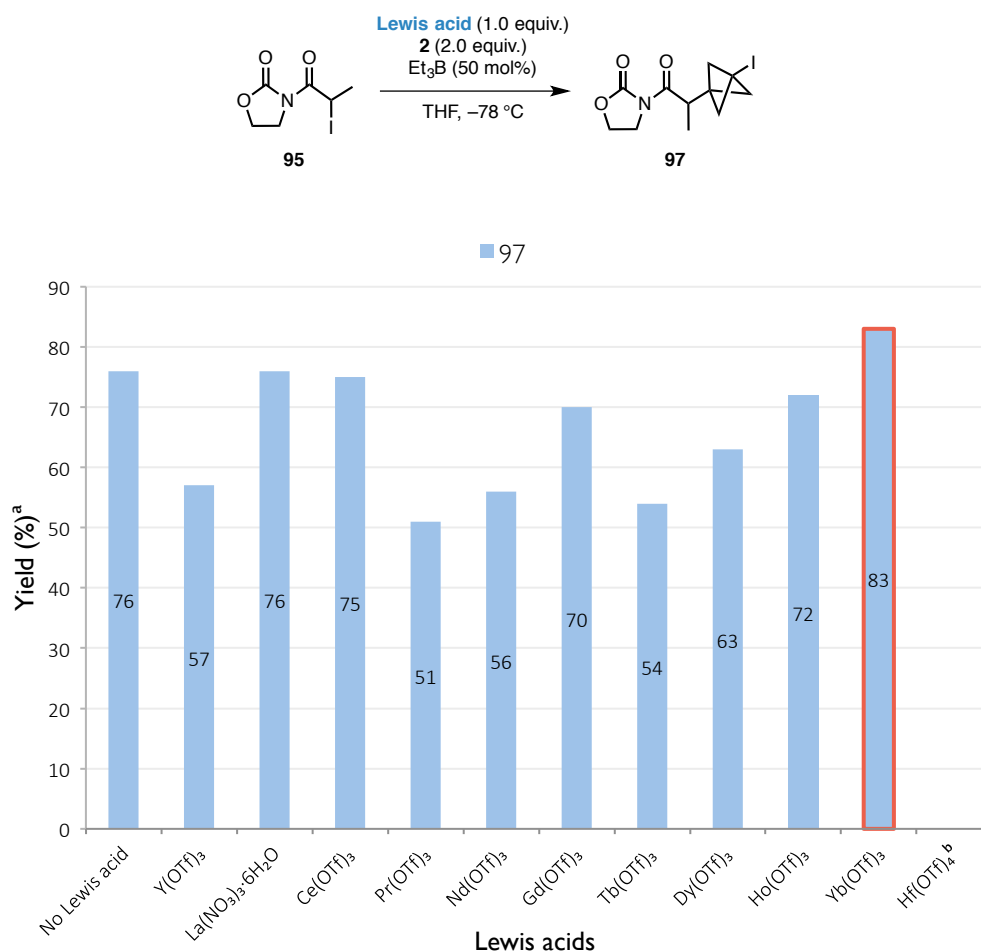


Scheme 3.11. Effect of Lewis acids on the diastereoselective ATRA with [1.1.1]propellane **2**.

3.3 Enantioselective atom transfer radical additions with [1.1.1]propellane

Studies towards an enantioselective variant of the ATRA with [1.1.1]propellane **2** were therefore carried out with the aim of employing an achiral substrate in the reaction, with the source of chirality being a chiral Lewis acid–ligand complex. Taking into account the findings from the Lewis acid screen conducted for the diastereoselective reaction with chiral substrates (**Section 3.2**), a more extensive screen of lanthanide Lewis acids was carried out after a brief reoptimization of reaction conditions (reagent stoichiometry and solvent) to counter the inefficient reaction rates observed earlier, ensuring that the reactions reach complete conversion after about 2 h (**Figure 3.4**). Using 50 mol% of triethylborane and THF as the solvent, the reaction was found to proceed optimally in the presence of Yb(OTf)₃, affording 83% of the desired product.

Several classes of ligands were examined in combination with Yb(OTf)₃ but only pyridine-2,6-bis(oxazoline) (PyBOX) ligands^[273] were found to induce low levels of enantioselectivity (**Figure 3.5**; note: the absolute stereochemistry of the BCP products was not determined in this study).

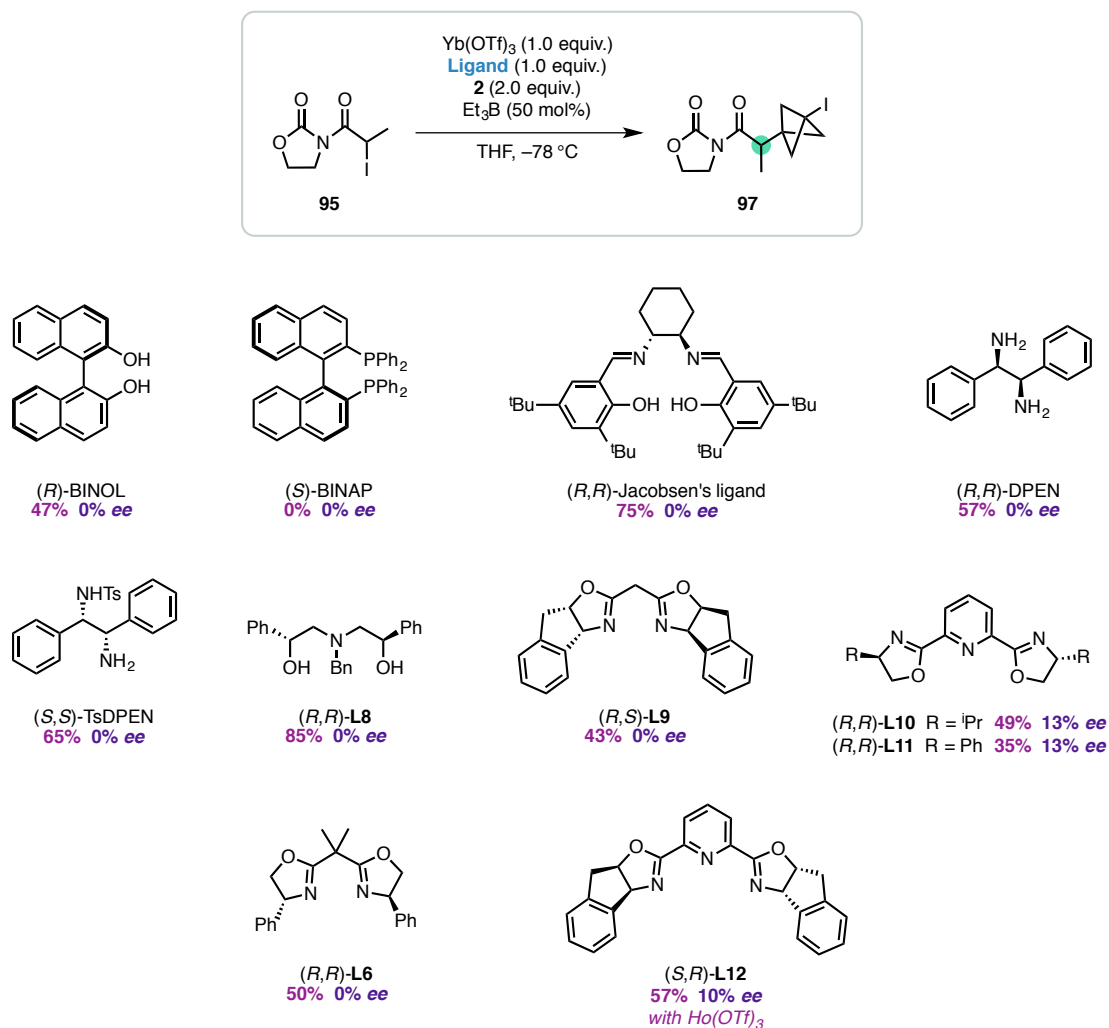


Reactions conducted on 0.2 mmol scale, 0.8 mL of THF (0.25 M).

^aYields of isolated products. ^bDecomposition products only.

Figure 3.4. Effect of lanthanide Lewis acids on the ATRA with [1.1.1]propellane 2.

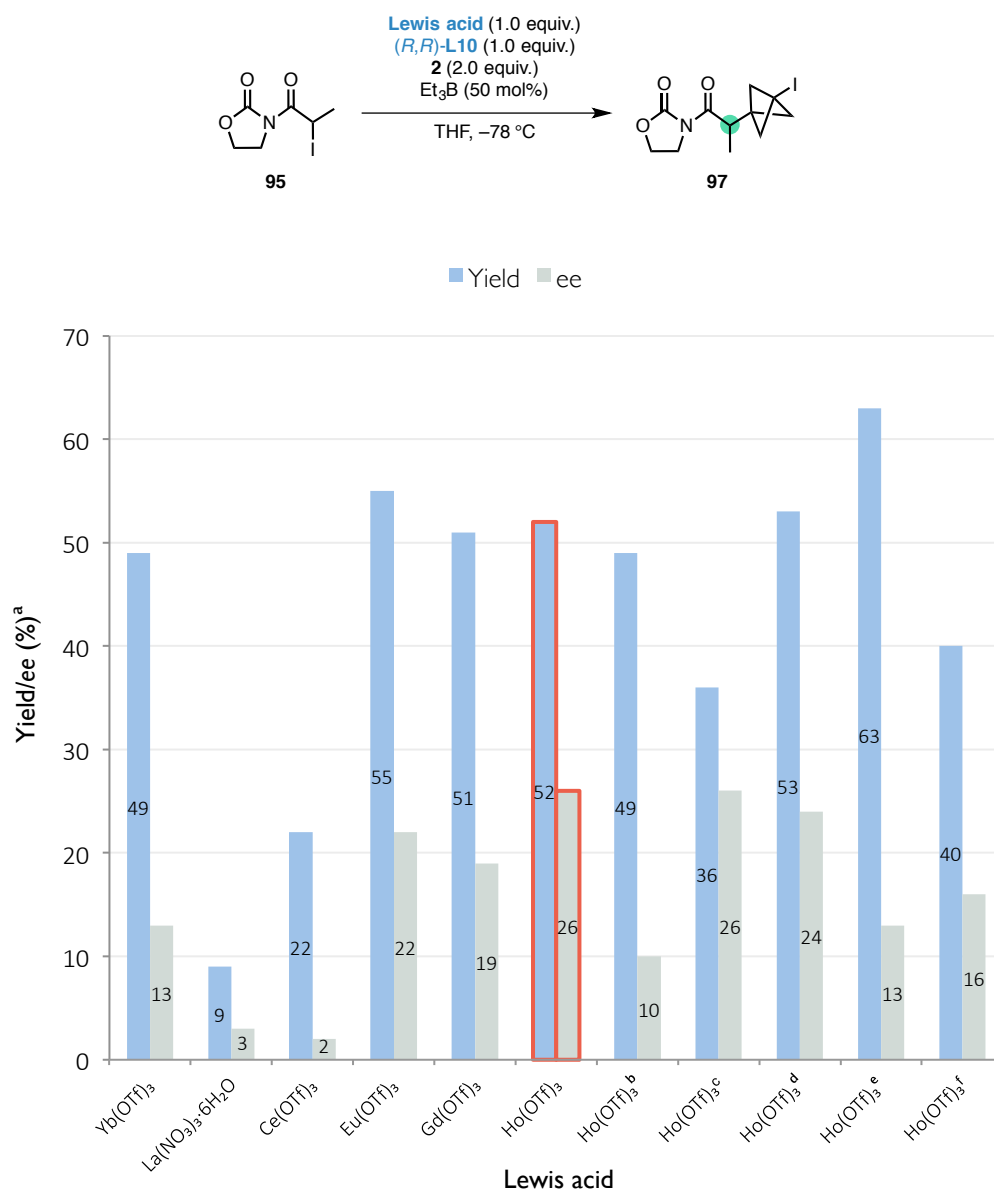
A re-examination of the lanthanide Lewis acids in combination with PyBOX ligand (*R,R*)-**L10** resulted in a more promising 26% *ee*, obtained in the reaction with Ho(OTf)₃ (**Figure 3.6**). Unfortunately, further attempts to improve reaction efficiency and selectivity by varying the amounts of triethylborane initiator, and ratios of Ho(OTf)₃ and (*R,R*)-**L10** in the reaction were not successful. The desired product was consistently obtained in lower yields and/or enantioselectivities when various combinations of super- and substoichiometric amounts of both the Lewis acid and ligand were used (see **Appendix 8.2.2** for further details).



Reactions conducted on 0.2 mmol scale, 0.8 mL of THF (0.25 M); yields of isolated products.

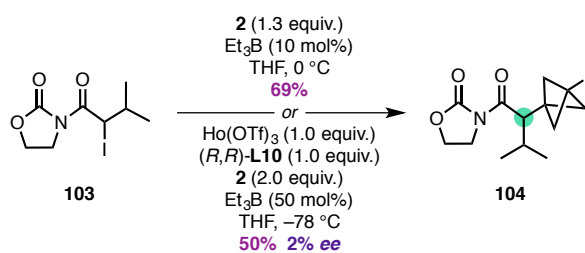
Figure 3.5. Effect of chiral ligands on the ATRA with [1.1.1]propellane **2**.

Nevertheless, having identified reaction conditions that were able to induce some asymmetry in the ATRA, other substrates bearing different substituents on the α -carbonyl position were considered. α -Carbonyl substituents that are more sterically demanding than a methyl group were expected to enhance adoption of the desired radical conformation in the chiral complex. Although we were not able to access the ethyl analogue, the isopropyl analogue **103** could be synthesized. Subjecting this substrate to the asymmetric ATRA conditions resulted in a 50% yield of the desired product **104** but a disappointing 2% ee (Scheme 3.12).



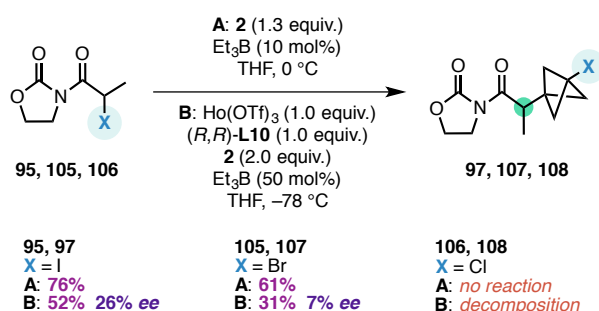
Reactions conducted on 0.2 mmol scale, 0.8 mL of CH₂Cl₂ (0.25 M).
^aYields of isolated products. ^bHo(OTf)₃ (0.5 equiv.), (*R,R*)-**L10** (0.5 equiv.). ^cHo(OTf)₃ (1.5 equiv.), (*R,R*)-**L10** (1.5 equiv.). ^dHo(OTf)₃ (1.2 equiv.), (*R,R*)-**L10** (0.5 equiv.). ^eEt₃B (70 mol%).
^fEt₃B (10 mol%) added after every hour (three additions).

Figure 3.6. Effect of lanthanide Lewis acids and (*R,R*)-**L10** on the ATRA with [1.1.1]propellane **2**.



Scheme 3.12. ATRA of substrate **103** with [1.1.1]propellane **2**.

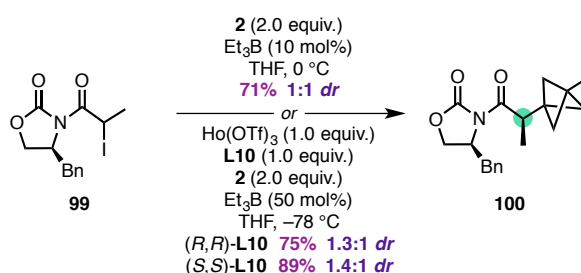
α -Iodocarbonyls were used throughout this study as they were found to perform better in ATRA reactions with [1.1.1]propellane **2**, having a greater reaction efficiency and affording the desired products in higher yields. However, their high reactivity could be detrimental in an asymmetric setting as non-stereoselective and more rapid background reactions of uncomplexed substrates could potentially be significant. Therefore, we also evaluated α -bromo- **105** and α -chlorocarbonyl substrates **106** to investigate the ability of Lewis acids to catalyze the ATRA with a less reactive substrate, with the intention of suppressing any background reactions of the uncomplexed substrate (**Scheme 3.13**). Unfortunately, the reactions were found to be less efficient with these two substrates and no catalytic effect of the Lewis acid was observed.



Scheme 3.13. Effect of α -halocarbonyls on the ATRA with [1.1.1]propellane **2**.

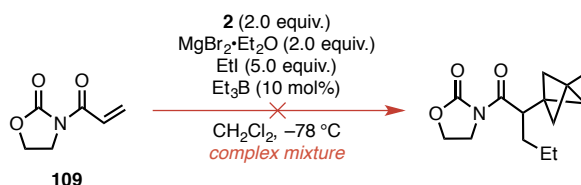
Given the modest levels of asymmetric induction in both the diastereoselective and enantioselective reactions, the asymmetric ATRA conditions were further examined in the reaction of a substrate bearing a chiral auxiliary with a chiral Lewis acid to determine whether any matched or mismatched relationships existed between the substrate and ligand enantiomers (**Scheme 3.14**). As noted above, substrate **99** displayed no inherent stereochemical preference in the reaction without external complexing agents (**Scheme 3.11**); disappointingly, it also reacted with near equivalent and poor diastereoselectivity in the presence of either enantiomer of the ligand **L10**. The chiral Lewis acid–ligand complex appears to have a limited influence

on stereoinduction in this ATRA process, consistent with the low levels of asymmetric induction in the above studies with an achiral oxazolidinone substrate. This could be due to poor conformational control in the radical intermediate formed in the reaction, or poor facial selectivity in the reaction with [1.1.1]propellane **2** as the chiral environment of the Lewis acid–ligand complex may be too remote from the α -carbonyl reaction center.



Scheme 3.14. ATRA of chiral substrate **99** in the presence of a chiral Lewis acid–ligand complex.

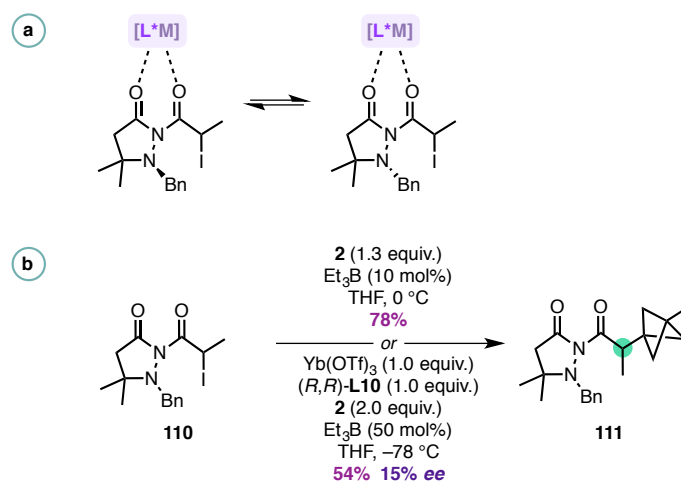
Considering the success of tandem radical conjugate addition/trapping processes to form α -carbonyl stereocenters (Section 3.1.2), we examined a similar approach with oxazolidinone substrate **109**, involving an initial conjugate addition with a carbon-centered radical and trapping of the resulting α -carbonyl radical with [1.1.1]propellane **2** (Scheme 3.15). Unfortunately, this strategy was unsuccessful and a complex mixture of products was obtained. One of the main complications with this strategy is the undesired direct addition of ethyl radicals to [1.1.1]propellane **2**.



Scheme 3.15. Conjugate addition/ATRA with [1.1.1]propellane **2**.

As the parent oxazolidinone template appeared to be unsuitable for developing an asymmetric Lewis acid-catalyzed ATRA with [1.1.1]propellane **2** to form α -chiral

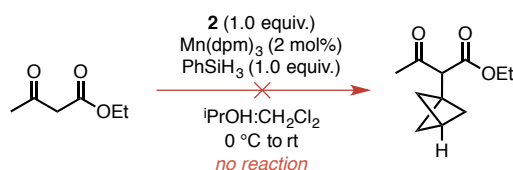
BCPs, other templates that can coordinate to a Lewis acid complex were explored. We considered a chiral relay auxiliary strategy, where an achiral template bearing a stereochemically fluxional group is used to amplify the influence of a chiral Lewis acid complex, as it would inherently adopt a matched ‘temporary’ configuration.^[274] Pyrazolidinone templates have been successful in such applications: although they have no static chirality, the fluxional nitrogen is able to relay asymmetric information from the chiral complex to the α - or β -carbonyl reaction site (**Scheme 3.16a**). Pyrazolidinone substrate **110** was subjected to the asymmetric ATRA conditions with Yb(OTf)₃ and (*R,R*)-**L10** but unfortunately, the product **111** was again obtained with poor enantioselectivity (15% *ee*) (**Scheme 3.16b**).



Scheme 3.16. ATRA with chiral relay auxiliary in the presence of a chiral Lewis acid–ligand complex.

The low levels of selectivity obtained in the reactions investigated could be due to the α -carbonyl reaction site being too remote from the chiral environment of the Lewis acid. Hence, we decided to investigate the formation of an α -carbonyl radical at the central carbon of a 1,3-dicarbonyl framework for a reaction with [1.1.1]propellane **2**, expecting that the closer proximity of the complexing agent and the reaction site to be advantageous in inducing asymmetry. To this end, ethyl acetoacetate was subjected to a radical alkylation but failed to react under the conditions stated below (**Scheme 3.17**).

Several other templates and strategies were also considered to achieve an asymmetric reaction but failed to provide any promising preliminary results (**Appendix 8.2.3**).



Scheme 3.17. Radical alkylation with [1.1.1]propellane **2**.

3.4 Conclusions

The asymmetric ATRA of α -iodocarbonyls with [1.1.1]propellane **2** was thoroughly investigated in an attempt to develop a general protocol for the synthesis of α -chiral BCPs. We evaluated a diastereoselective process where a substrate with a chiral auxiliary could be coordinated to a Lewis acid to create a chiral environment around the α -carbonyl radical that is formed in the reaction. Concurrently, we studied an enantioselective process where an achiral substrate can be coordinated to a chiral Lewis acid–ligand complex to induce asymmetry. It was unexpectedly found that many commonly used Lewis acids inhibited the ATRA, but the use of lanthanide triflates in general was less detrimental to the reaction outcome.

In the diastereoselective reaction, the inherent preference of the substrate was found to dictate the stereochemical outcome of the reaction, but only low levels of stereoinduction could be attained, either in the presence of a lanthanide Lewis acid alone or in combination with a chiral ligand. Promising levels of enantioselectivities were obtained in the reaction with achiral substrates and a chiral complex with PyBOX ligands, but despite extensive optimization of reaction conditions, the reaction outcomes could not be improved.

Other strategies, including installation of a chiral relay auxiliary, were also unable to provide any satisfactory results. Although these investigations have identified the potential for an asymmetric ATRA to be used to access α -chiral BCPs, we did not pursue this approach further and instead moved on to other strategies to achieve an asymmetric radical reaction.

Photoredox-catalyzed atom transfer radical additions

4.1 Introduction

The renewed interest in radical chemistry over the last few years has largely been driven by the development of transformations that exploit their unique chemical reactivity, which is often complementary to that of two-electron manifolds. One of the most rapidly evolving and expanding areas of radical chemistry is the use of photocatalytic processes for the generation of open-shell species.^[275-294] While this strategy is well-established in areas such as carbon dioxide reduction, solar cell materials, water splitting, photovoltaic cells and energy storage,^[277,281] applications in organic synthesis were sporadic until the late 2000s.

Early photochemical methodologies suffered from limitations as most organic molecules do not absorb visible light,^[276] but this lack of absorbance has now become one of the crucial factors for the success of photocatalytic reactions. Key to many recent discoveries in the field is the recognition that certain classes of compounds can be

selectively excited by visible light, with the resulting excited-state species engaging in single electron or energy transfer processes with non-light absorbing organic molecules. This minimizes the likelihood of undesired side reactions arising from direct excitation of the organic substrate. This conversion of visible light into chemical energy can be carried out under mild reaction conditions, which is particularly desirable in the development of environmentally benign synthetic methodologies.^[295] This is especially relevant to radical chemistry, a field that has traditionally relied on toxic and hazardous reagents (*e.g.*, tributyltin hydride, azobisisobutyronitrile, triethylborane, peroxides), high temperatures and/or high-energy UV light irradiation.^[296]

The term *photocatalysis* describes processes that require light as the energy source, as well as a light-absorbing *photocatalyst*.^[290] *Photoredox catalysis* is one of the main areas of photocatalysis and involves electron transfer between a substrate and a species that is in an excited state due to light irradiation. Another mode of activation involves *photosensitization*, where energy is transferred from an excited-state photocatalyst to a substrate, which is itself not able to absorb visible light.^[293] In a related process, the photoexcitation of *electron donor-acceptor (EDA) complexes*, formed by association of an electron-rich and an electron-poor component, does not rely on an external photocatalyst. Instead, absorption of light by the complex itself can induce electron transfer events to generate radical species.^[297]

Photoredox-catalyzed processes generally follow one of two mechanistic pathways characterized by the primary direction of electron transfer with respect to the excited-state catalyst **[cat]*** (**Figure 4.1**).^[283,285] In a reductive quenching cycle, the excited-state catalyst **[cat]*** is quenched by an electron-donating species, which can be a substrate or a reductant present in the reaction. Conversely, in an oxidative quenching cycle, **[cat]*** is oxidized by an oxidant. The catalyst turnover step then involves

returning the catalyst, $[\text{cat}]^-$ or $[\text{cat}]^+$, to its original oxidation state by a substrate or an external redox-active reagent in the reaction. The substrate can play the role of an electron donor (ED) or electron acceptor (EA), and these reactions can be net oxidative, net reductive or net redox-neutral. Net oxidative and reductive reactions require an external oxidant or reductant respectively, while net redox-neutral reactions generally involve more complex systems that are often mediated by an external redox-active co-catalyst.

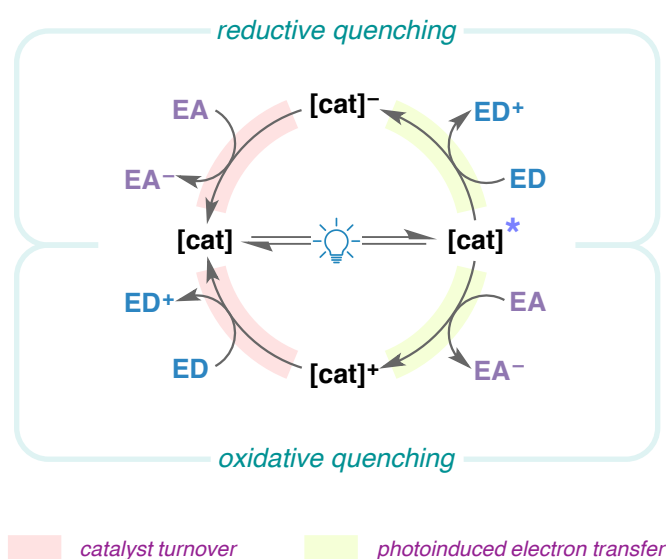


Figure 4.1. Oxidative and reductive quenching cycles in photoredox catalysis.

As the excited-state catalyst $[\text{cat}]^*$ can act as either an oxidant and a reductant, this creates a unique redox framework where new modes of organic molecule activation through the formation of open-shell species can be uncovered.^[281] Some commonly used photoredox catalysts are shown in **Figure 4.2**, including ruthenium and iridium polypyridyl complexes, as well as organic dyes.^[290,298] These catalysts have been extremely successful in photocatalytic processes due to their desirable photophysical properties, and ease of synthesis and handling. Furthermore, their modular framework enables catalyst tuning for predictive modification of ground- and excited-state properties. The ability of these photocatalysts to absorb higher-energy visible

light (generally in the range of 400 – 475 nm) is advantageous as it maximizes the potential energy gain while avoiding undesired reactivity arising from direct excitation of organic molecules.^[277] Ideal photocatalysts should be stable in solution, have a relatively long excited state lifetime (>1 ns) and the quantum yield² of formation of the excited state should be as high as possible.^[288,299]

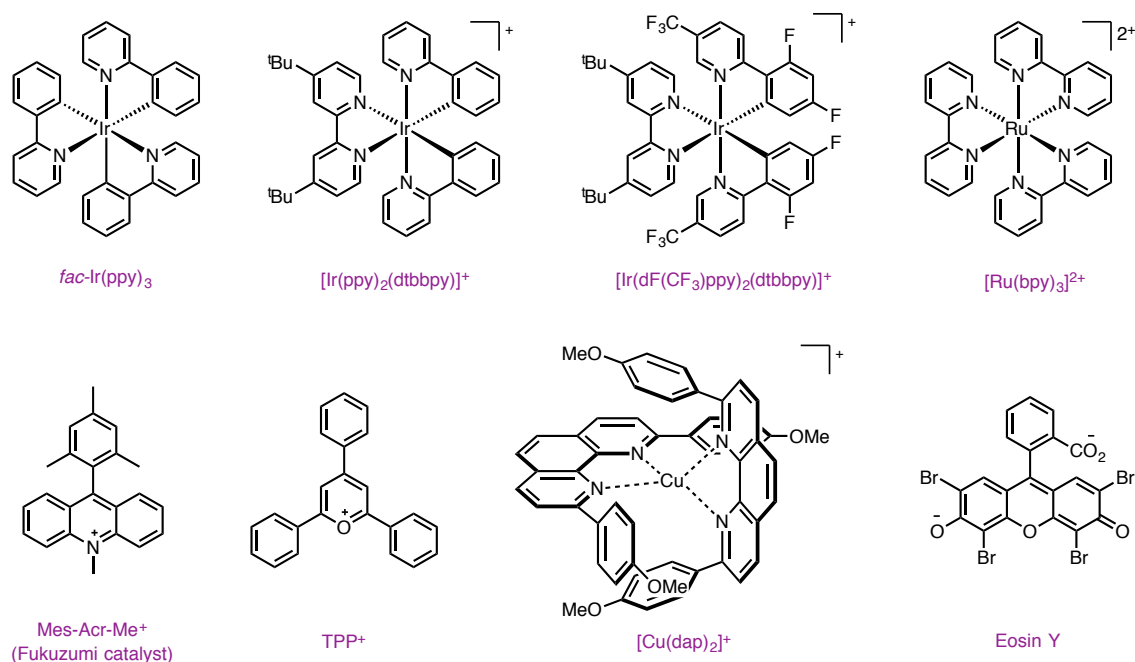


Figure 4.2. A selection of common photoredox catalysts.

Photocatalytic transformations are now widely used in the synthesis of complex molecular frameworks and in industrial settings.^[282,287,300] The desire to increase reaction efficiency and scalability, standardize operating protocols, and improve reproducibility has resulted in significant developments in the operating procedures of these reactions, such as the development of high power light sources, integrated photoreactors and continuous flow processes.^[296,301-302] Notably, higher reaction efficiencies have been observed in continuous flow setups compared to batch processes, circumventing the issues associated with dimension-enlarging scale-up of photocatalytic

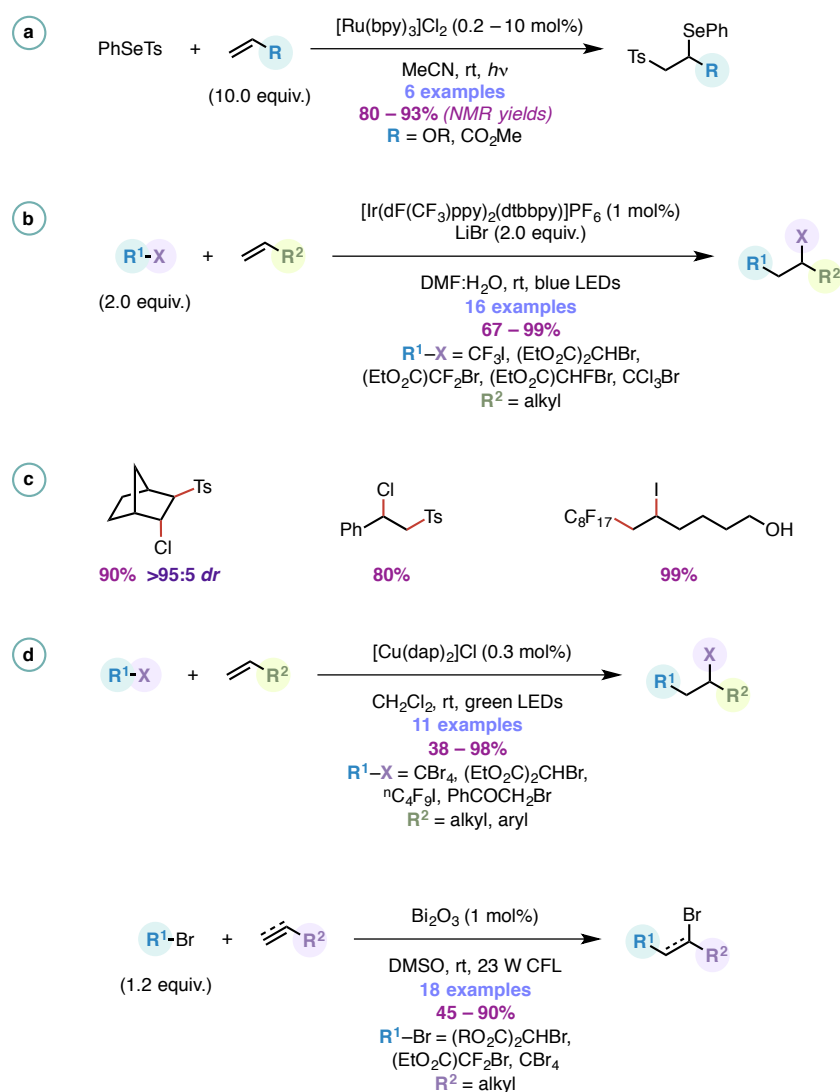
² The quantum yield of a photochemical reaction is defined as the ratio of the moles of product formed to the einsteins of photons absorbed.

reactions such as the attenuation of photon transport, overirradiation and non-uniform light penetration.^[79,281,302]

4.2 Photoredox-catalyzed atom transfer radical additions

Atom transfer reactions have featured regularly among the radical reactions that have been investigated in a photochemical context. One of the earliest reports of a photoredox-catalyzed group transfer process was disclosed in 1994 by Barton, leading to the functionalization of electron-rich olefins in high yields (**Scheme 4.1a**).^[303] Nearly 20 years later, the first general methodology for the photoredox-catalyzed ATRA of activated bromo- and iodoalkanes to olefins was reported by Stephenson, with the aim of developing a mild protocol that avoided the use of toxic and hazardous initiators (**Scheme 4.1b**).^[304] The scope of this reaction has now been extended to include activated alkyl chlorides and perfluoroalkyl iodides as radical precursors, and 1,2-disubstituted alkenes and styrene derivatives as acceptors; some examples of products are shown in **Scheme 4.1c**.^[305] Adaptations to polymerization^[306] and continuous flow processes^[301] have also been successful. Furthermore, inexpensive and non-toxic photocatalysts such as copper complexes^[225,307-310] and semiconductors^[311] can be utilized in place of metal complexes in visible light-driven ATRA reactions (**Scheme 4.1d**).

The vast majority of photoredox-catalyzed ATRA reactions have focused on intermolecular 1,2-difunctionalization of double bonds with activated radical precursors, giving access to compounds such as those shown in **Figure 4.3a**.^[312-315] Alternatively, these radical addition processes can also be incorporated into multicomponent reactions, usually proceeding by oxidation of the radical intermediate



Scheme 4.1. Early reports of photoredox-catalyzed ATRA reactions.

resulting from addition to the olefin and subsequent trapping of the cation by a nucleophilic species (**Figure 4.3b**).^[313] These reactions enable the synthesis of a wide array of highly functionalized compounds, some examples of which are shown in **Figure 4.3c**.

Recently, Nagib and coworkers reported an innovative atom transfer approach to the synthesis of vinyl iodides, involving polarity-reversed reactivity of carbonyl functionalities by single-electron reduction to form an α -acetoxy carbon-centered radical (**Scheme 4.2**).^[316] Visible-light homolysis of the $\text{Mn}_2(\text{CO})_{10}$ precatalyst and *in*

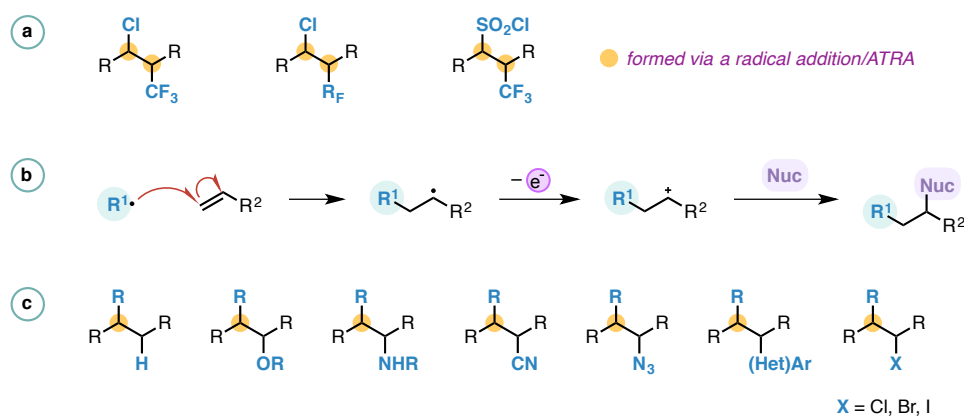
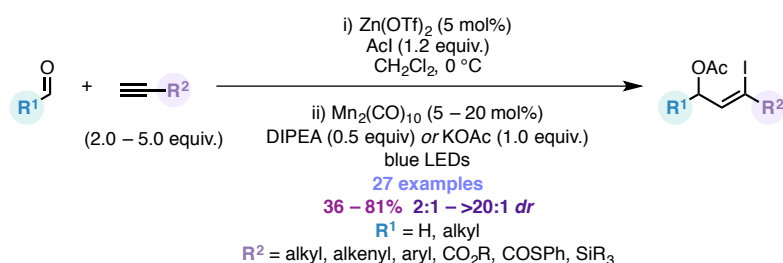


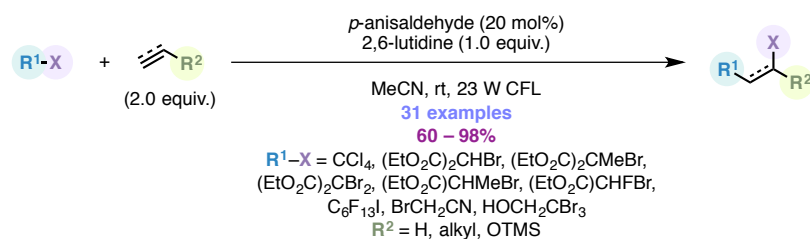
Figure 4.3. Vicinal difunctionalization of double bonds by photoredox-catalyzed ATRA reactions.



Scheme 4.2. α -Acetoxy radical reactivity via atom transfer catalysis in the synthesis of vinyl iodides.

situ conversion of the carbonyl group to an α -acetoxy iodide with a weak C–I bond facilitates reduction to the α -acetoxy carbon-centered radical without the use of strong, stoichiometric reductants. The resulting radical can engage in an ATRA with various alkynes, affording a range of vinyl iodides in a Z-selective process.

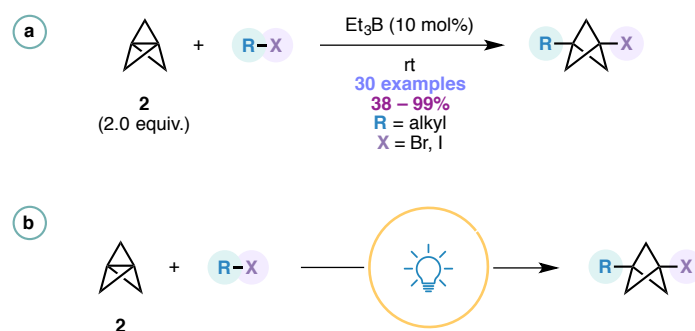
In a separate protocol developed by the Melchiorre group, ATRA reactions of activated haloalkanes across alkenes and alkynes can also be carried out under exceptionally mild conditions by photosensitization with simple organic molecules (**Scheme 4.3**).^[317] *p*-Anisaldehyde, in its excited state, can undergo energy transfer to an alkyl halide, resulting in homolytic cleavage to form alkyl radicals that can engage in ATRA processes with unsaturated moieties.



Scheme 4.3. ATRA of activated haloalkanes to unsaturated moieties by photosensitization.

4.3 Atom transfer radical additions with [1.1.1]propellane

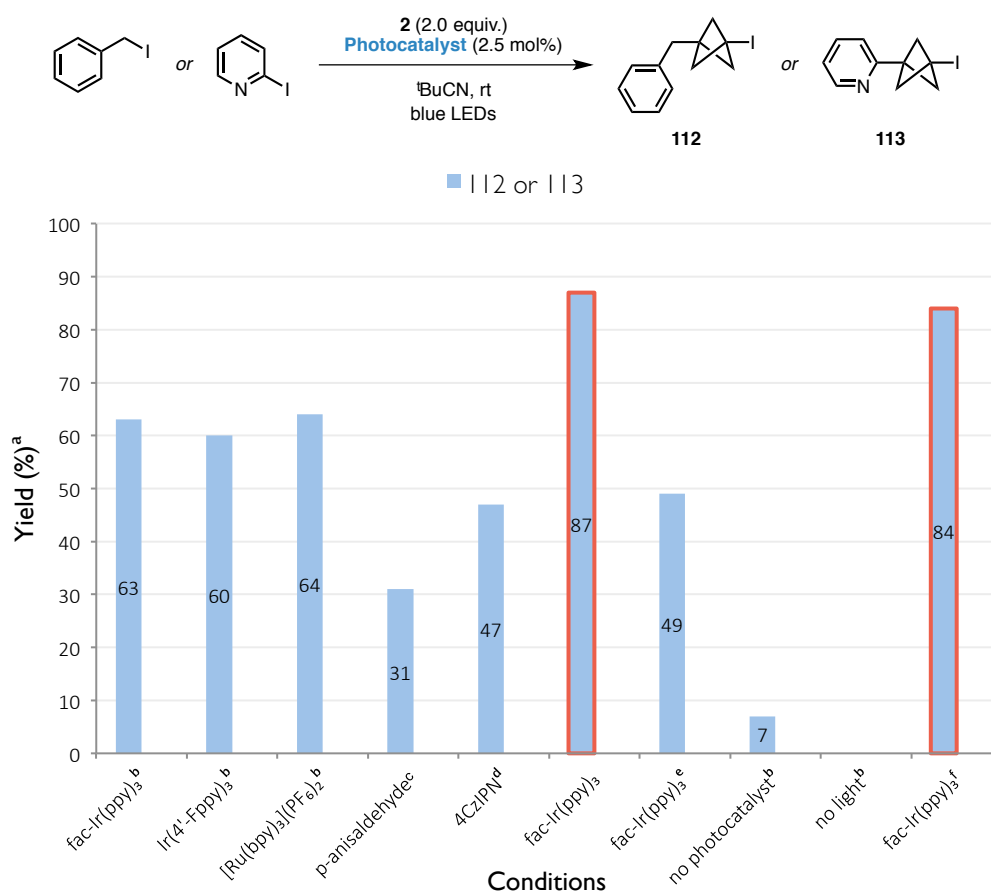
The ATRA of alkyl halides with [1.1.1]propellane **2** developed in the Anderson group is a highly efficient approach to accessing 1,3-disubstituted BCPs (**Scheme 4.4a**).^[133] However, this methodology employs the pyrophoric initiator triethylborane, and displays some limitations in functional group tolerance. Classes of compounds not suitable for this chemistry include halides with free amine moieties and (hetero)aryl halides. Other substrates such as benzyl iodide were also inefficient. Having noted the success of photoredox catalysis in atom transfer reactions, we sought to utilize this strategy in reactions with [1.1.1]propellane **2** in order to overcome the aforementioned limitations (**Scheme 4.4b**). Although the addition of photoredox-generated radicals to unsaturated functionalities is well-established, analogous reactions to functionalize carbon–carbon σ -bonds were unknown when this investigation was initiated. However, this process was expected to be feasible due to the high propensity of [1.1.1]propellane **2** to react with radicals.^[318]



Scheme 4.4. ATRA reactions with [1.1.1]propellane **2**.

4.3.1 Reaction optimization

Optimization of the reaction conditions was carried out by Dr. Carlos Arroniz, Helena Pickford and Bethany Shire and is discussed briefly for the sake of completeness. Benzyl iodide, a substrate which as noted was poorly reactive in the triethylborane-initiated ATRA methodology, was utilized in the optimization studies. Several different photocatalysts were found to be effective, with *fac*-Ir(ppy)₃ (2.5 mol%) delivering the desired product **112** in an optimal 87% yield (**Figure 4.4**). Two equivalents of [1.1.1]propellane **2** was required to ensure complete conversion, while avoiding the formation of [*n*]staffanes. Pivalonitrile was identified as the best solvent for the reaction, and control experiments confirmed that both the photocatalyst and irradiation with blue LEDs was required. The optimized reaction conditions were also applied to aryl and heteroaryl iodides, which are unreactive in standard radical chain reactions. This proved to be successful: for example, the BCP product **113** was obtained in high yield (84%) under the same reaction conditions.



^aYields of isolated products unless stated otherwise. ^bMeCN instead of ^tBuCN. ^cMeCN instead of ^tBuCN, photocatalyst (20 mol%), white LEDs; yield determined by ¹H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. ^dMeCN instead of ^tBuCN, photocatalyst (5 mol%). ^eDMF instead of ^tBuCN; yield determined by ¹H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. ^fWith 2-iodopyridine.

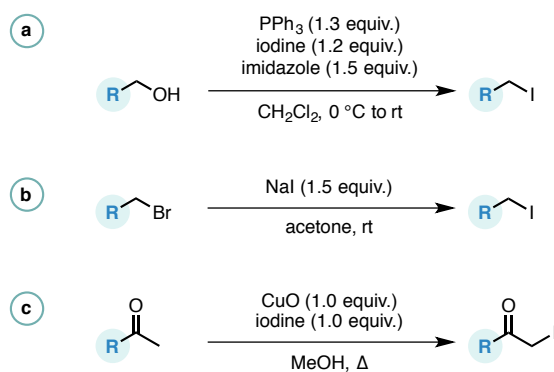
Figure 4.4. Optimization of reaction conditions for the ATRA with [1.1.1]propellane **2** carried out by

Dr. Carlos Arroniz, Helena Pickford and Bethany Shire.

4.3.2 Substrate synthesis

The work presented in this chapter explores the scope of the photoredox-catalyzed ATRA with [1.1.1]propellane **2** using the optimized reaction conditions above. This study focused on the use of alkyl iodides with heterocyclic and (hetero)benzylic motifs, and α -iodocarbonyl substrates in the reaction. Other substrate classes were also considered and were the focus of work carried out by coworkers on the project. A selection of these results is detailed at the end of **Section 4.3.3**.

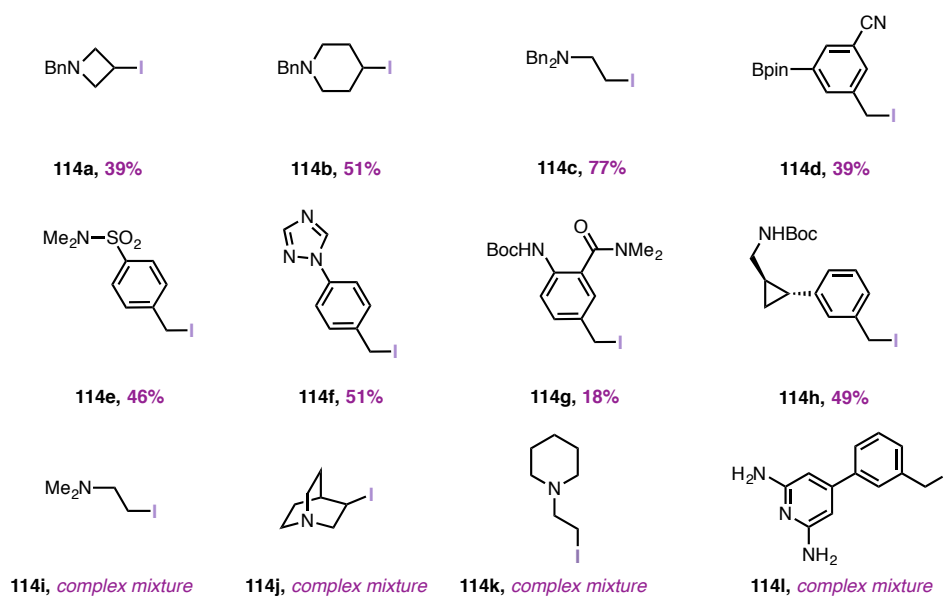
To initiate these investigations, various alkyl iodide substrates were synthesized *via* Appel reactions (**Scheme 4.5a**), Finkelstein reactions (**Scheme 4.5b**) or copper oxide-mediated α -carbonyl iodinations (**Scheme 4.5c**).



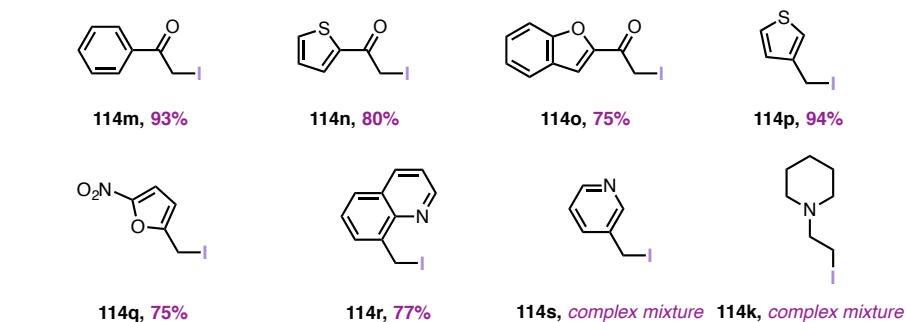
Scheme 4.5. Synthetic routes to alkyl iodide substrates.

A number of substrates bearing different functionalities were successfully obtained, as shown in **Figure 4.5**. Unfortunately, several substrates were not compatible with the reaction conditions and the corresponding alkyl iodides could not be accessed, with complex mixtures of undesired products obtained instead.

Appel reaction



Finkelstein reaction



Copper oxide-mediated iodination

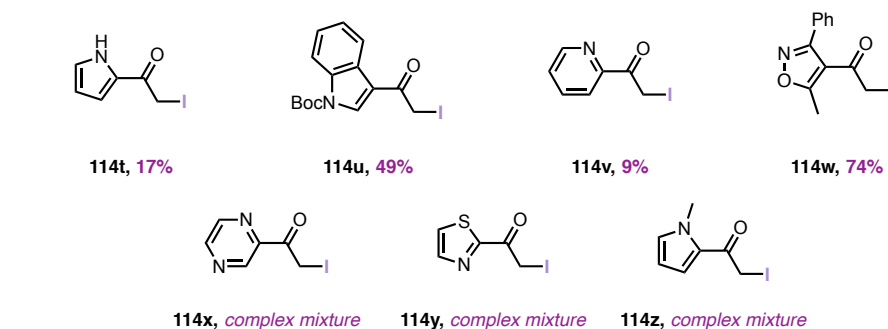
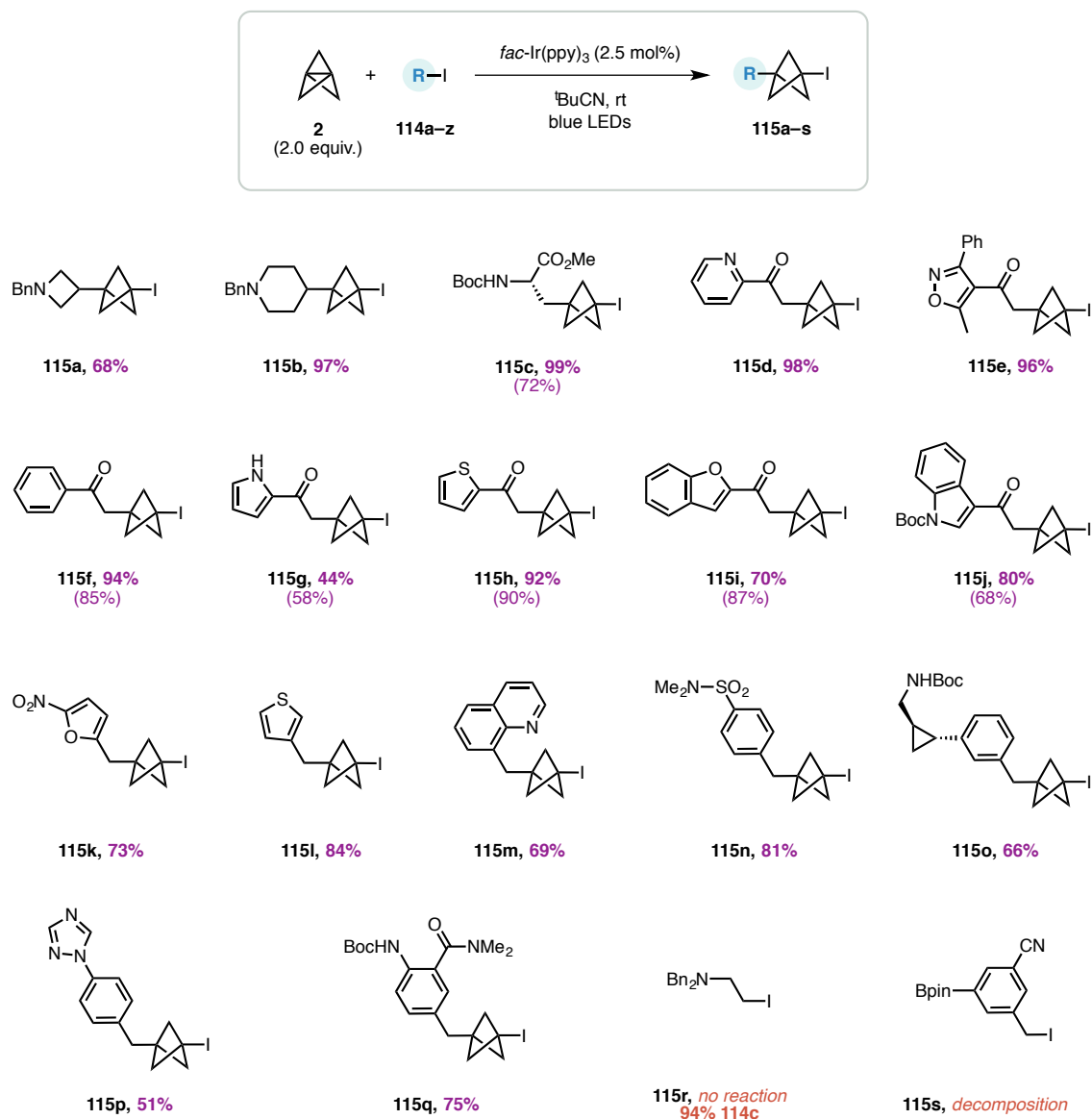


Figure 4.5. Alkyl iodide substrates.

4.3.3 Reaction scope

With the optimized reaction conditions in hand, the scope of the reaction was investigated with the alkyl iodide substrates (**Figure 4.6**).



Yields in parentheses were obtained for the same substrate with the triethylborane-initiated methodology.

Figure 4.6. Scope of the photoredox-catalyzed ATRA with [1.1.1]propellane **2**.

The majority of alkyl iodide substrates surveyed performed very well in the photoredox-catalyzed ATRA. Unactivated alkyl iodides were highly efficient in the reaction, providing products **115a** – **115c** in high yields (68 – 99%). In particular, the synthesis of the iodo-BCP analogue of phenylalanine **115c** was achieved with a

near-quantitative yield (99%). α -Iodocarbonyl substrates bearing different aryl and heteroaryl substituents reacted cleanly to afford the corresponding BCP products **115d** – **115j** in high yields (70 – 98%) with the exception of **115g**, where a moderate 44% yield was obtained. The installation of a BCP adjacent to a (hetero)benzylic motif was also possible, giving the desired products in good yields (**115k** – **115q**, 51 – 84%). Unfortunately, tertiary amine substrate **114c** was unreactive under the reaction conditions and only decomposition products were observed with benzylic substrate **114d**.

Further investigations into the scope of the reaction were also carried out by Dr. Carlos Arroniz, Dr. Jeremy Nugent, Helena Pickford and Bethany Shire with the help of Dimitri Caputo and Benjamin Owen for the synthesis of several substrates and obtaining preliminary results. A selection of the results obtained from these studies is discussed below.

The photoredox-catalyzed ATRA with [1.1.1]propellane **2** proved to be an extremely general and efficient method for accessing BCP derivatives, generally affording the BCP products in higher yields than the triethylborane-initiated methodology and allowing the synthesis of previously inaccessible BCP compounds (**Figure 4.7a**). However, limitations of this methodology include longer reaction times and difficulties associated with conducting photocatalytic reactions on a larger scale. Several other BCP products obtained through further explorations of the reaction scope is shown in **Figure 4.7**. The reaction was particularly suitable for the synthesis of aryl and heteroaryl BCP iodides (**Figure 4.7b**), as well as numerous other 1-halo-3-substituted BCPs (**Figure 4.7c**). This methodology could also be used to access highly complex polycyclic frameworks by incorporating [1.1.1]propellane **2** as an intermolecular trap in radical cyclizations (**Figure 4.7d**). The potential of this methodology was further

demonstrated through the late-stage diversification of biomolecules, with several examples shown in **Figure 4.7e**. The BCP derivatives synthesized possess a highly versatile halogen functionality, which can be used as a handle for further derivatizations (see discussion in **Chapter 1, Section 1.3.5**).

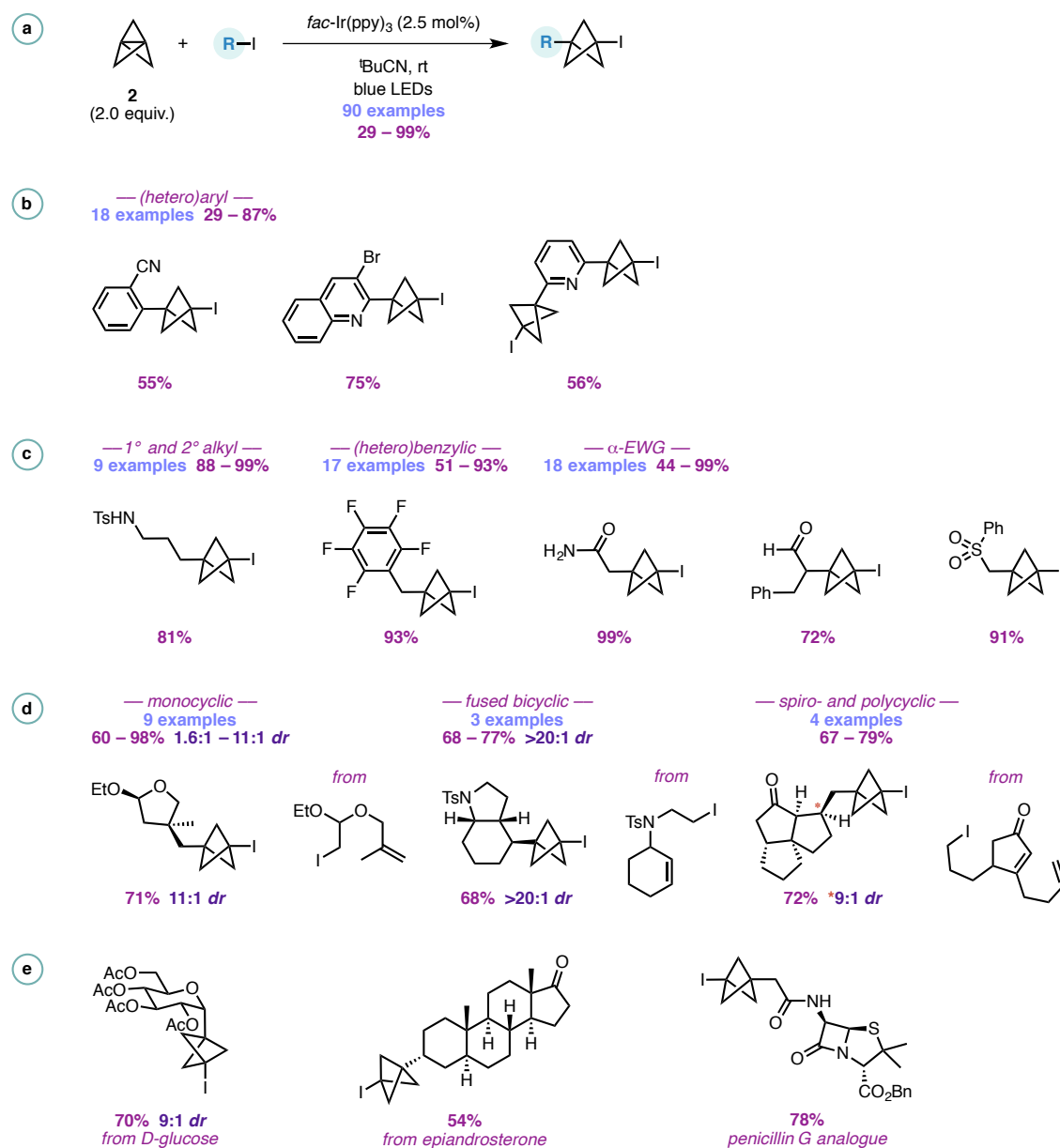


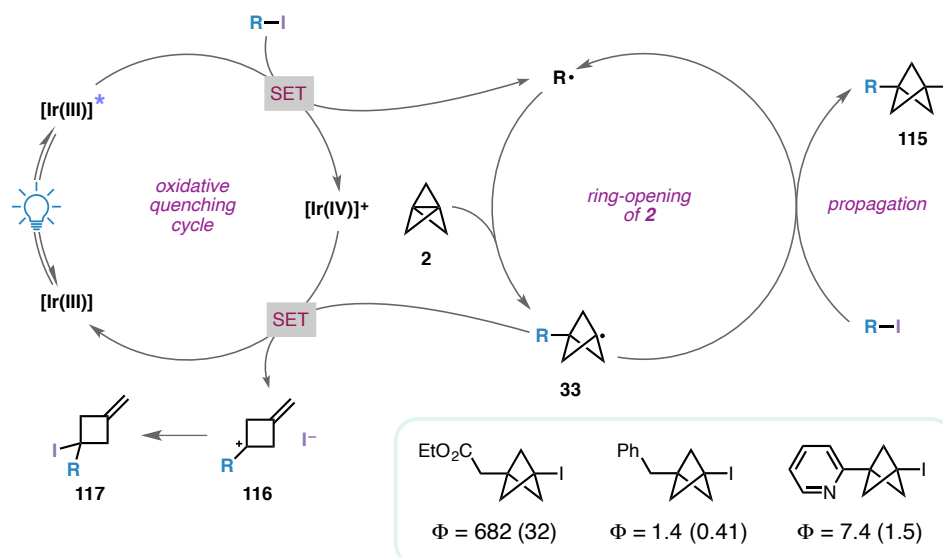
Figure 4.7. Selected examples from the scope of the photoredox-catalyzed ATRA with [1.1.1]propellane **2**. Further investigations into the reaction scope were carried out by

Dr. Carlos Arroniz, Dr. Jeremy Nugent, Helena Pickford and Bethany Shire

with the help of Dimitri Caputo and Benjamin Owen.

4.3.4 Mechanistic studies

Studies into the mechanism of the photoredox-catalyzed ATRA by density functional theory calculations and quantum yield experiments were carried out by Dr. Jeremy Nugent, Alistair Sterling and Prof. Fernanda Duarte, and are included here for completeness. The proposed mechanism begins with a single electron transfer (SET) from the excited-state photocatalyst $[\text{Ir(III)}]^*$ to the halide substrate (**Figure 4.8a**). This induces mesolytic cleavage of the carbon–halogen bond to form a carbon-centered radical, which can effect ring-opening of [1.1.1]propellane **2**. The resulting bicyclopentyl radical **33** can engage in propagation steps to form the desired halogenated product **115** and regenerate the chain carrier, or it can reduce the photocatalyst $[\text{Ir(IV)}]^+$ and form a bridgehead bicyclopentyl cation, which would be expected to rearrange rapidly to form a methylenecyclobutane cation **116**, and therefore products such as **117**. Quantum yields (Φ) of the reaction with several substrates were determined (**Figure 4.8b**), which revealed that the reaction with ethyl iodoacetate proceeds predominantly by a chain process ($\Phi = 682$). However, lower quantum yields were obtained for benzyl iodide ($\Phi = 1.4$) and 2-iodopyridine ($\Phi = 7.4$), consistent with their inability to undergo efficient ATRA under these or the triethylborane-initiated reaction conditions and indicating that photoredox catalysis is essential for these substrates.



Standard deviations for quantum yield measurements are shown in parentheses.

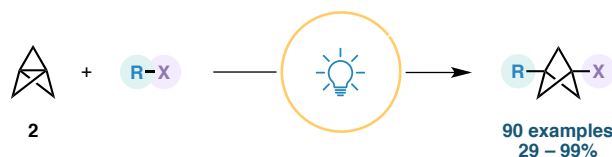
Figure 4.8. Proposed reaction mechanism for the photoredox-catalyzed ATRA with [1.1.1]propellane **2**.

Mechanistic studies were carried out by Dr. Jeremy Nugent, Alistair Sterling and Prof. Fernanda Duarte.

4.4 Conclusions

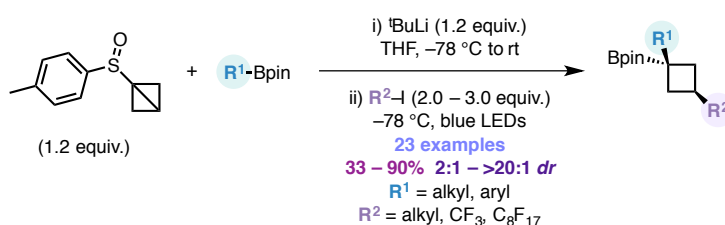
A highly general and efficient route to 1,3-disubstituted BCP derivatives was developed by capitalizing on the unique reactivity of [1.1.1]propellane **2** towards radical species and the ease of radical generation through photoredox catalysis. This work represents the first examples of the use of photoredox catalysis to functionalize carbon–carbon σ -bonds (**Scheme 4.6**). The work in this chapter focused on alkyl iodide substrates with heterocyclic, (hetero)benzylic and carbonyl functionalities, the majority of which performed well in the ATRA reaction with [1.1.1]propellane **2**. In collaboration with other coworkers on the project, it was found that the ATRA reaction proceeds under mild reaction conditions and displays excellent functional group tolerance, circumventing the limitations of the triethylborane-initiated methodology and making it suitable for late-stage functionalization applications. The ability to intercept radical intermediates from intramolecular cyclization reactions with the capture of

[1.1.1]propellane **2** constitutes a novel and highly effective method to construct complex polycyclic frameworks. The work presented in this chapter was published in *ACS Catalysis* in 2019.^[319]



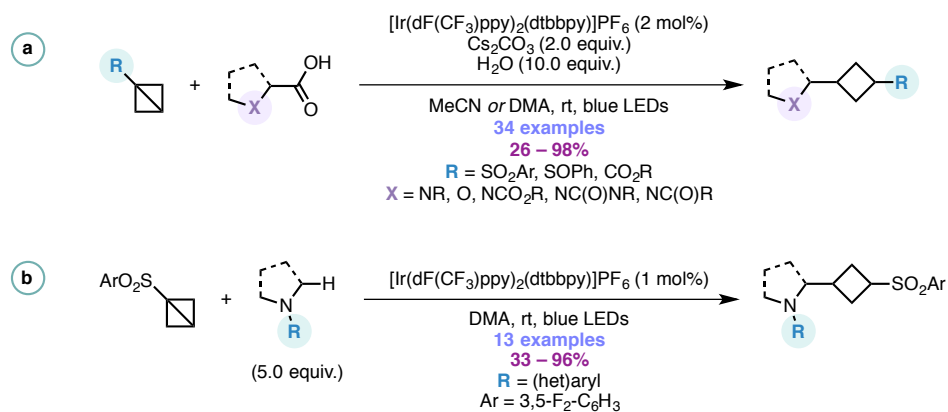
Scheme 4.6. Photoredox-catalyzed ATRA with [1.1.1]propellane **2**.

Since the completion of this investigation, three reports utilizing photocatalytic methods for carbon–carbon σ -bond functionalization have been disclosed. The Aggarwal group have developed a radical addition across the central C–C bond of bicyclobutane derivatives to synthesize cyclobutyl boronic esters (**Scheme 4.7**).^[320] This reaction proceeds in the absence of a photocatalyst through visible light-induced homolysis of a C–I bond.



Scheme 4.7. Stereocontrolled synthesis of cyclobutyl boronic esters.

Ernouf, Cintrat and coworkers have also utilized bicyclobutane derivatives in a photoredox-catalyzed decarboxylative radical addition to prepare difunctionalized cyclobutanes (**Scheme 4.8a**).^[321] A similar approach was undertaken by Jui and coworkers, where α -amino radicals formed from aniline derivatives can undergo addition reactions to substituted bicyclobutanes (**Scheme 4.8b**).^[322]



Scheme 4.8. α -Amino radical addition for the synthesis of cyclobutane derivatives.

These initial reports on the use of light-driven chemistry in small polycyclic systems have provided a good foundation for further developments of photocatalytic processes for the functionalization of carbon–carbon σ -bonds.

Enantioselective photoredox organocatalysis

5.1 Introduction

Asymmetric catalysis has provided vast opportunities to access enantiomerically pure compounds and has been an area of intense research within organic chemistry. Despite growing attention towards photochemical synthetic methods in recent years, the ability to control absolute stereochemistry in these reactions generally remains an unsolved problem, as evidenced by the scarcity of asymmetric variants.^[323-331] The excited-state intermediates inherent to photochemical processes are characterized by short lifetimes, high reactivity and weak inter-/intramolecular interactions, resulting in less efficient transfer of chiral information between reacting species as compared to the corresponding ground-state approaches.^[323,331] Furthermore, the fundamental concept behind catalytic asymmetric reactions — to decrease the activation barrier by addition of a catalyst and to favor a reaction pathway that involves some form of asymmetric induction, often by the catalyst itself — cannot generally be applied to photochemical

reactions. The absorption of a 400 nm photon corresponds to an energy uptake of approximately 300 kJ mol^{-1} ,^[327] meaning that molecules gain sufficient energy upon irradiation to undergo rapid reactions without the need for further catalysis. Hence, differentiating between diastereomeric transition states becomes a challenge. For a successful asymmetric photochemical reaction, the substrate must already exist in a chiral environment upon excitation.

Early attempts to achieve stereoselective photochemical transformations relied on absolute asymmetric synthesis^[332] with circularly polarized light, which generally resulted in poor selectivities ($<1\% ee$) that decreased as reaction conversion increased.^[323,331] Solid-state asymmetric photochemistry also received some attention, where strategies such as the crystallization of achiral compounds into chiral point groups,^[323] ionic chiral auxiliaries^[333] and host–guest frameworks with a chiral inductor^[230] were developed, but these methods are not amenable for widespread use in organic synthesis.

5.1.1 Single-catalyst strategies

The recent resurgence of interest in photocatalytic processes has resulted in several breakthroughs in conducting these reactions in an asymmetric setting, with initial efforts focusing on single-catalyst strategies. Small molecules^[323,334] and larger supramolecular frameworks^[335-336] have been used as photochemically inert, chiral templates for light-driven processes, but more innovative approaches have focused on chiral catalysts that allow substrate excitation only upon association. These chiral photocatalysts generally operate by carrying out photosensitization processes, altering/enhancing light absorption or deactivating decay pathways of the excited state upon formation of the

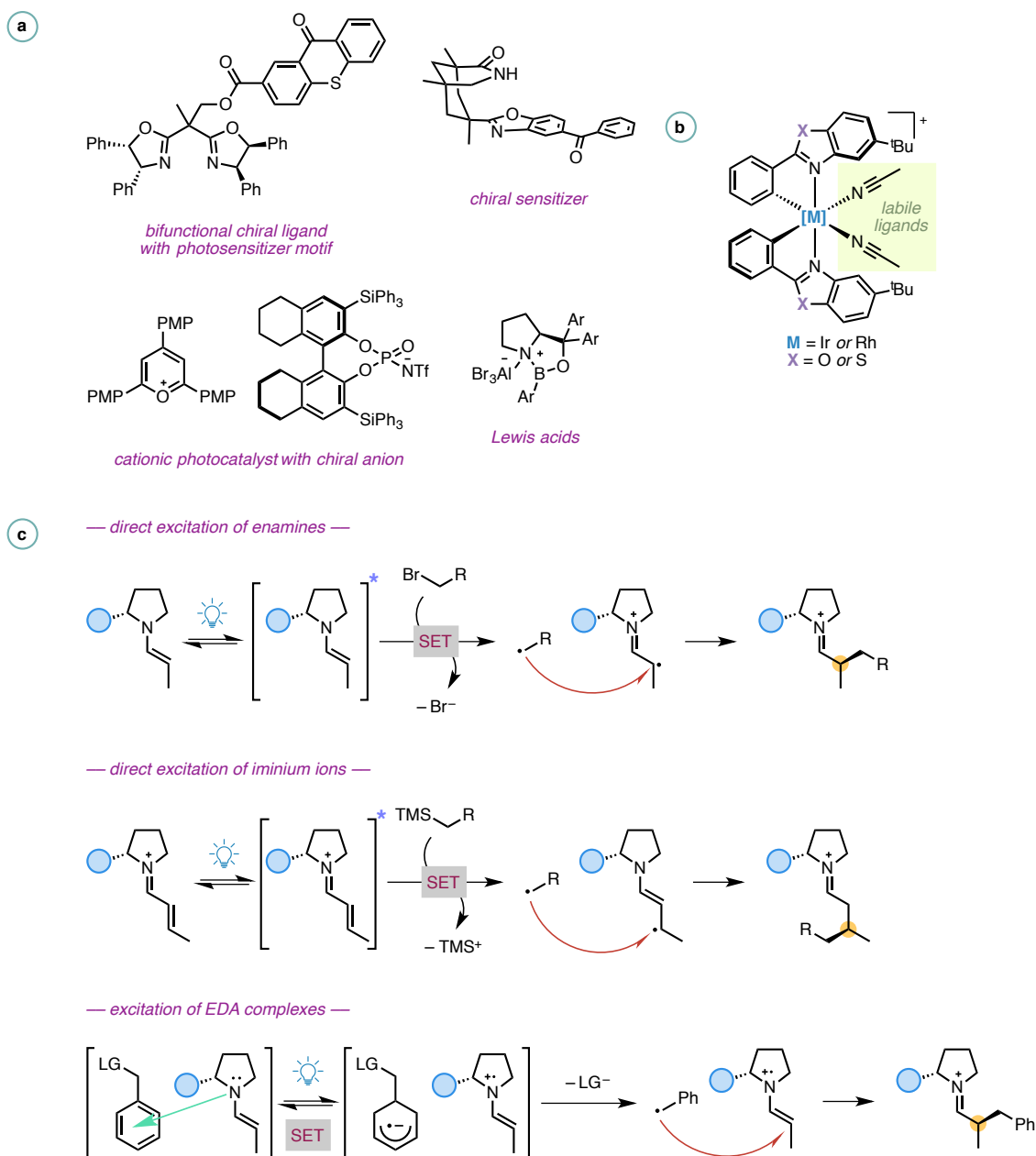


Figure 5.1. A selection of photocatalysts and their modes of action in asymmetric photocatalytic reactions.

catalyst–substrate complex.^[327] Several photocatalysts that utilize different modes of activation are shown in **Figure 5.1a**, including chiral photosensitizers,^[337] Lewis acids,^[338–341] chiral ligands for transition metals^[342–343] and cationic photocatalysts with chiral anions.^[344] Configurationally stable chiral-at-metal complexes have also been shown to serve as both chiral Lewis acids and photosensitizers for a variety of asymmetric photocatalytic reactions (**Figure 5.1b**).^[345–348] Another notable

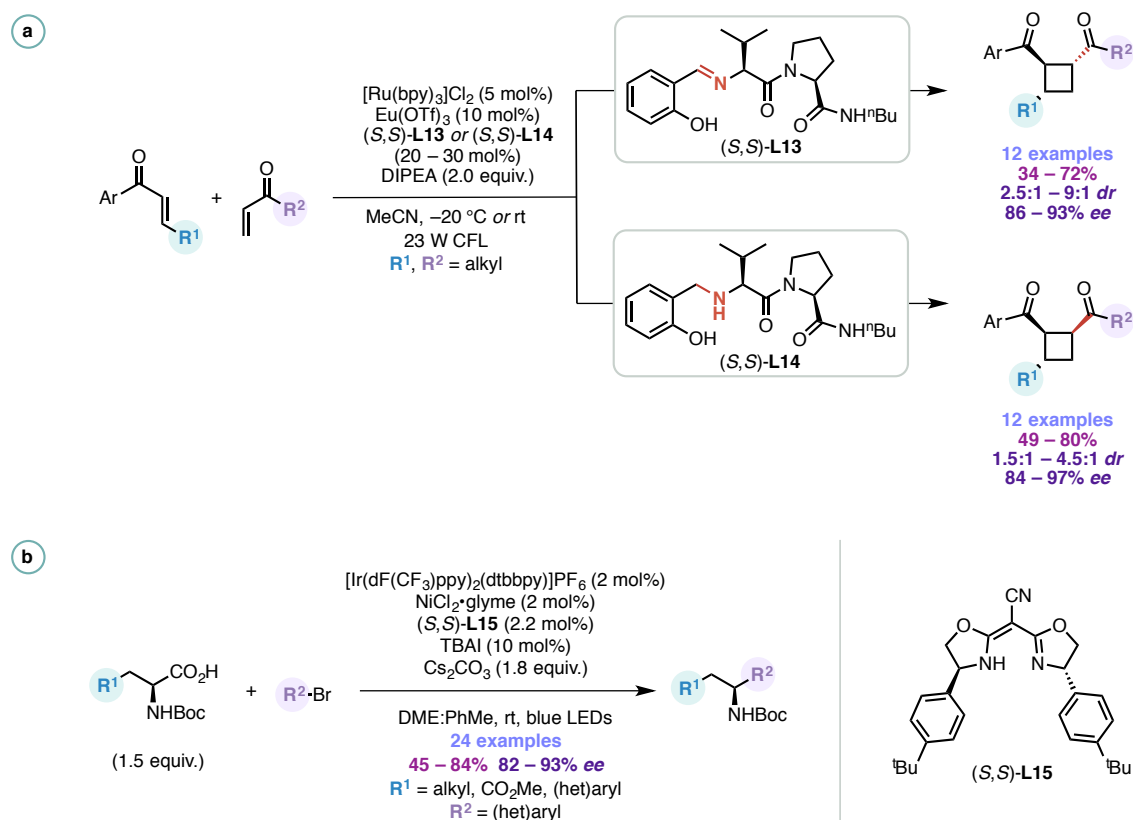
single-catalyst strategy, pioneered by the Melchiorre group, involves the use of chiral organocatalysts to form enamines^[349] and iminium ions^[350] that can generate reactive radical intermediates, either through direct excitation or the formation of chiral electron donor–acceptor (EDA) complexes (**Figure 5.1c**).^[351–352] The use of enzymes in biocatalytic photochemical processes is also an emerging field, with several recent publications highlighting the potential of this strategy in asymmetric catalysis.^[353–354]

5.2 Multi-catalytic strategies

A powerful strategy emerges when photocatalysis is combined with non-photochemical catalysis to access novel reaction pathways.^[355–361] Decoupling of the photochemical and stereodifferentiating processes allows complementary activation methods to be harnessed simultaneously in transformations that would otherwise be difficult or impossible to achieve, for example by activation of functionalities that are typically inert under photocatalytic conditions by a co-catalyst. Photocatalytic methods offer a highly efficient approach to generating reactive radical intermediates, which can be intercepted by a separate catalyst that can modulate the reactivity or selectivity of the overall transformation.^[361]

One of the earliest realizations of the potential of this approach was the merger of photoredox catalysis and Lewis acid catalysis in enantioselective [2+2] photocycloadditions with chiral lanthanide complexes by Yoon and coworkers (**Scheme 5.1a**).^[362] This dual catalytic strategy has now been extended to other photocycloadditions^[363–366] and conjugate additions.^[367] The development of stereoselective metallaphotoredox catalysis has also proven to be highly successful, where SET events resulting from visible light activation generate radical intermediates that can participate in transition metal-mediated catalytic cycles (**Scheme 5.1b**).^[368–370]

More recently, highly selective cooperative photoredox and enzymatic catalytic processes have also been reported, which bodes well for further development of this class of reactions.^[371-375]



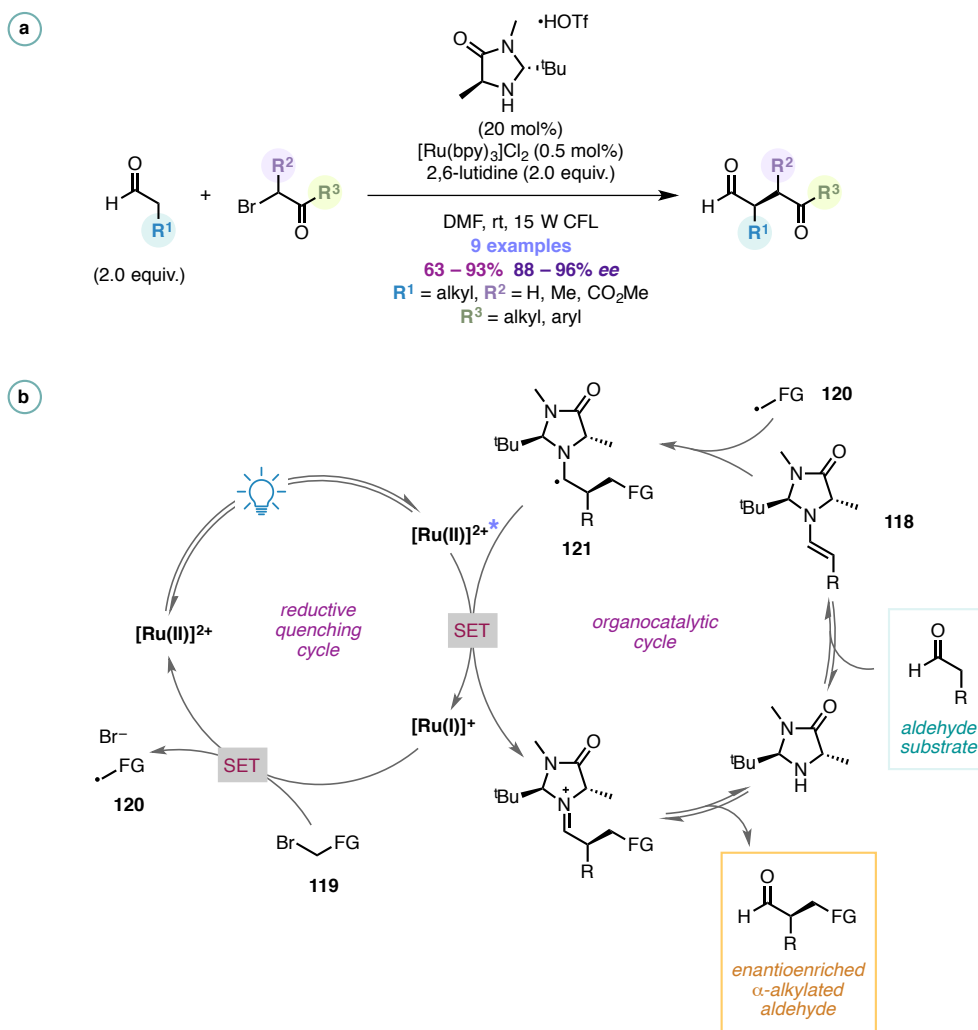
Scheme 5.1. Dual catalytic strategies in asymmetric photoredox reactions.

5.2.1 Photoredox organocatalysis

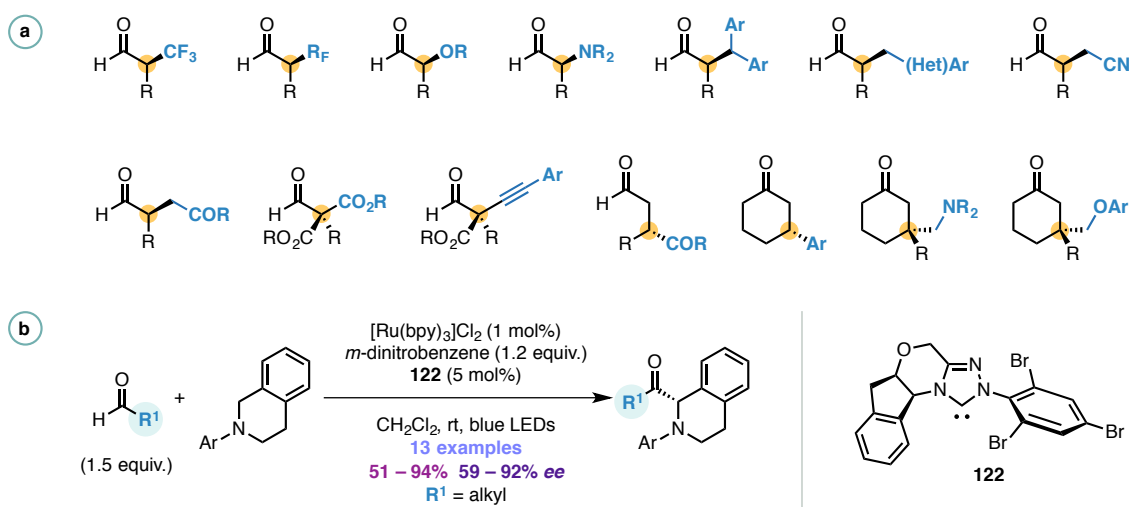
Organocatalysis has established itself as one of the main branches of asymmetric catalysis, having seen great success in the two-electron reactivity domain.^[376-379] Organocatalyzed reactions are highly reliable due to the identification of generic modes of substrate activation, and the catalysts are easily prepared and modified, typically non-toxic, and generally insensitive to oxygen and moisture.^[376-377] Both enantiomers of various organic molecules are also easily available from biological sources (*e.g.*, amino acids), making them highly suitable for use as catalysts in asymmetric settings.

Seminal work from the MacMillan group in 2008 opened the field of photoredox catalysis to the organic synthesis community, featuring the first example of photoredox organocatalysis for the enantioselective alkylation of aldehydes (**Scheme 5.2a**).^[380-381] The reaction is postulated to proceed *via* reduction of the excited state photocatalyst $[\text{Ru(II)}]^{2+*}$ by a sacrificial quantity of the enamine **118** formed from condensation of an amine organocatalyst with an aldehyde substrate (**Scheme 5.2b**). The resulting metal complex $[\text{Ru(I)}]^+$ is a strong reductant that can undergo SET to the α -bromocarbonyl **119**, forming an electron-deficient radical **120** and regenerating the photocatalyst in the process. In the enantiodetermining step, the radical intermediate **120** adds to the enamine **118** formed in the organocatalytic cycle, producing electron-rich radical **121** which effects reductive quenching of the excited-state photocatalyst $[\text{Ru(II)}]^{2+*}$, closing both catalytic cycles after hydrolysis to reform the organocatalyst. Further investigations into this transformation have culminated in the successful use of other photocatalysts including organic dyes,^[382-383] inorganic semiconductors,^[384-386] chiral metal–organic frameworks,^[387] earth-abundant metals^[388] and bifunctional scaffolds.^[389]

Numerous other strategies combining photoredox and organocatalytic cycles have since been developed, relying on covalent or non-covalent modes of substrate activation.^[390-391] Covalent activation typically involves the formation of enamines^[392] or iminium ions in the stereoselective functionalization of carbonyl-bearing substrates to access a range of enantioenriched compounds; some examples of products that can be obtained using this approach are shown in **Scheme 5.3a**.^[393-408] *N*-Heterocyclic carbenes have also been used to reverse the reactivity of electron-deficient substrates (**Scheme 5.3b**).^[409-410]

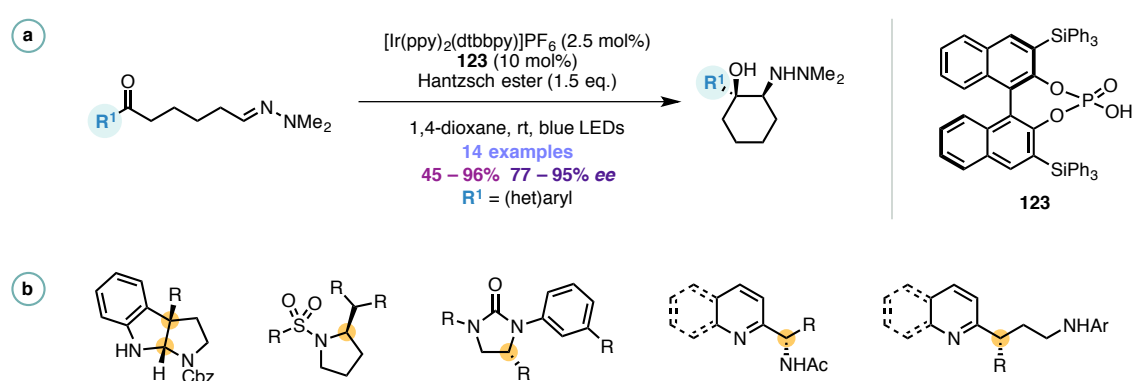


Scheme 5.2. First report of the merger of organo- and photoredox catalysis for the enantioselective alkylation of aldehydes.



Scheme 5.3. Covalent substrate activation in photoredox organocatalysis.

The first report of non-covalent organocatalysis in light-mediated radical chemistry was an aza-pinacol cyclization mediated by a proton-coupled electron transfer with chiral phosphoric acids (**Scheme 5.4a**).^[411-412] Non-covalent activation methods have generally focused on the use of hydrogen-bonding interactions between chiral Brønsted acids and substrates,^[413-416] and chiral phosphoric acids, in particular, have been successfully employed in several different asymmetric transformations; some examples of enantioenriched products that can be obtained using this strategy are shown in **Scheme 5.4b**.^[417-422]



Scheme 5.4. Non-covalent substrate activation in photoredox organocatalysis.

5.2.2 Hydrogen atom transfer catalysis

The formation of closed-shell species *via* radical termination events of the intermediates generated from photoinduced electron transfer is often challenging, and one of the fundamental radical-based processes that achieves this is hydrogen atom transfer (HAT), which can be defined as the concerted movement of a proton and an electron ($H^\bullet$) in a single kinetic step.^[423] HAT catalysis has proven to be highly versatile for the direct or indirect activation of aliphatic R–H bonds in photocatalyzed reactions.^[424] Only a limited number of photocatalysts in the excited state have the intrinsic ability to abstract H-atoms directly from substrates: typical examples are

aromatic ketones and polyoxometalates. A more broadly successful alternative is indirect substrate activation through cooperative photo- and HAT catalysis, which proceeds through the formation of a thermal H-abtractor, usually a radical species that can undergo HAT with a co-catalyst.^[424-425]

This multicatalytic strategy has been exploited extensively in the anti-Markovnikov functionalization of olefins^[426-427] using simple HAT catalysts such as 2-phenylmalononitrile, substituted thiophenols and aryl disulfides; **Figure 5.2a** contains several examples of products that have been obtained using this approach and the bonds formed after olefin functionalization are highlighted. ^[428-438] Sulfur-based HAT catalysts, in particular, have been extremely effective in various multicatalytic photoredox reactions^[439-443] due to their high redox activity in SET processes, suitable bond dissociation energies and ease of modification of the substituent attached to the sulfur atom (**Figure 5.2b**).^[444-446]

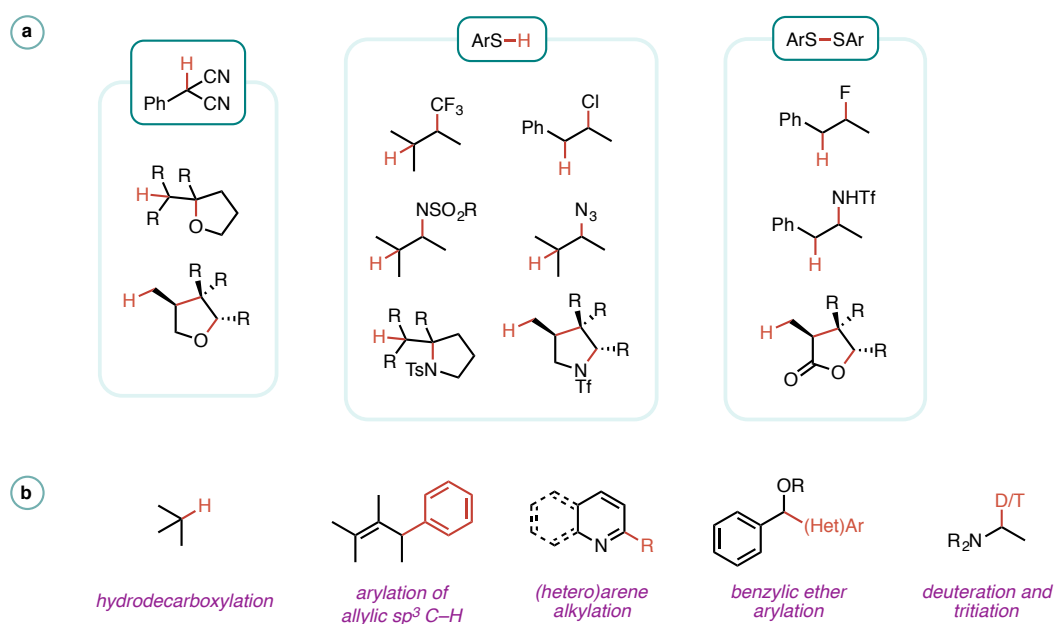
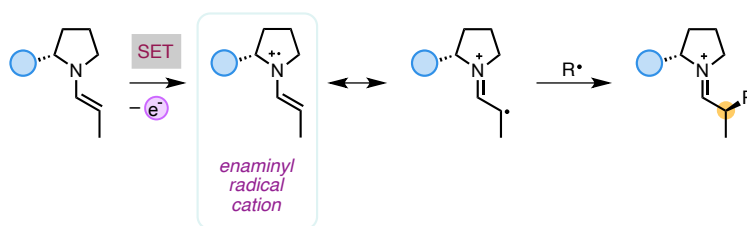


Figure 5.2. Merger of photoredox and HAT catalysis.

5.3 Asymmetric ring-opening of [1.1.1]propellane

To further our investigations towards developing general synthetic methodologies to access α -chiral BCPs, we turned to asymmetric photoredox-catalyzed strategies, especially considering the successful development of the photoredox-catalyzed ATRA with [1.1.1]propellane **2** (**Chapter 4**). Photoredox catalysis offers exceptional control of reactivity and selectivity in radical-based processes under mild reaction conditions, especially in combination with non-photochemical catalytic modes of activation.

Carbonyl compounds, such as simple aldehydes, are usually activated with chiral secondary amine organocatalysts through enamine formation. This intermediate can be intercepted by single electron oxidation to form an enaminy radical cation (**Scheme 5.5**). This mode of activation, termed singly occupied molecular orbital (SOMO) catalysis, has been widely used for the enantioselective functionalization of α -carbonyl centers by capture of these radical cations with SOMO-philic reagents such as alkenes and arenes.^[447-448]

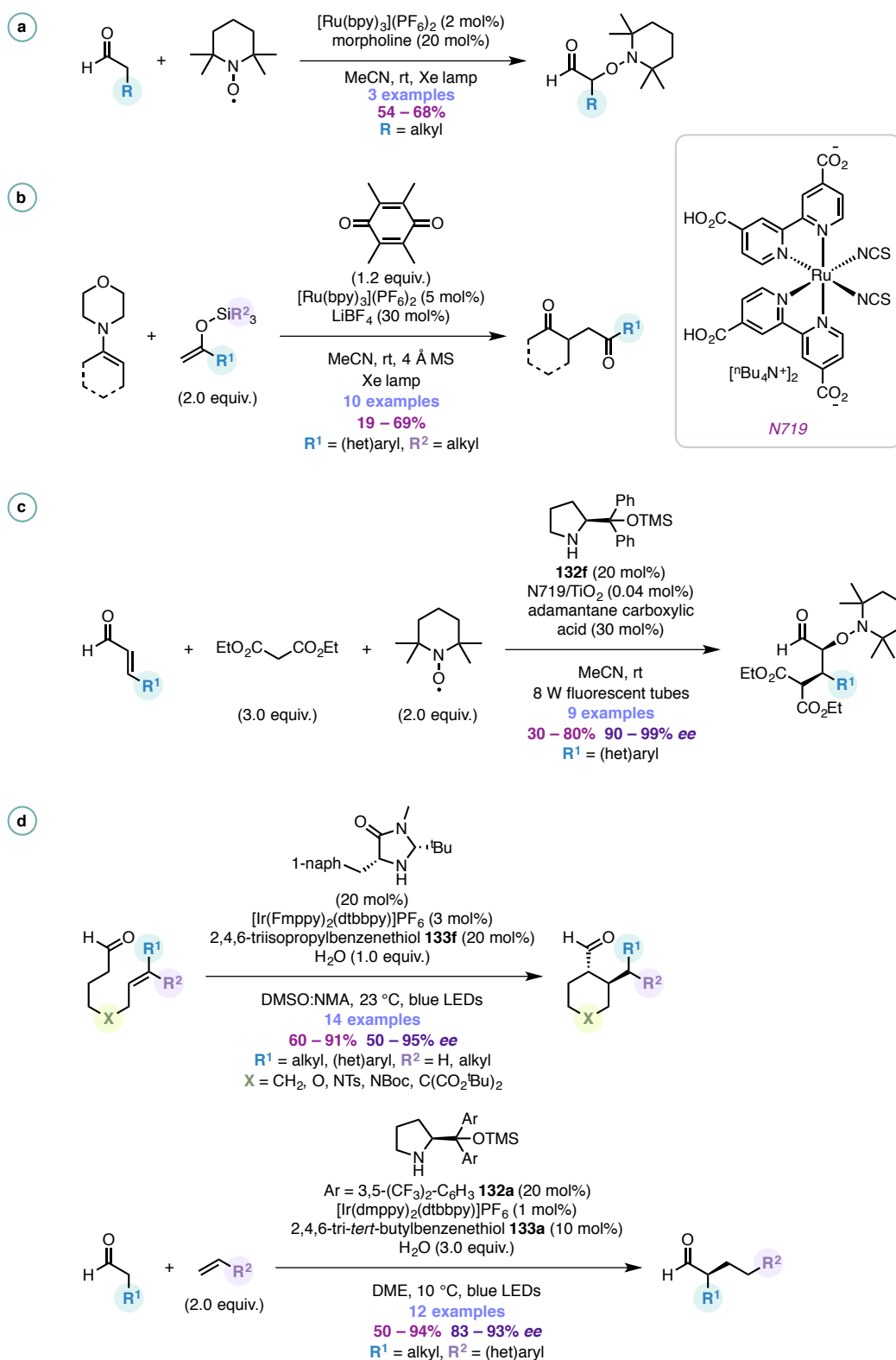


Scheme 5.5. SOMO activation of enamines formed from simple aldehydes and amine organocatalysts.

Toxic and expensive oxidizing agents are often used for these processes and superstoichiometric amounts are generally required.^[448] However, these drawbacks can be avoided by the use of a photocatalyst to mediate the electron transfer process in which the enaminy radical cation is generated. The potential of this multicyclic system has been explored in several isolated reports, with the first being a non-asymmetric oxyamination of aldehydes reported by Koike and Akita in 2009 that

uses morpholine as the organocatalyst and TEMPO as the radical trap (**Scheme 5.6a**).^[449] The same group then reported a similar approach for the synthesis of γ -diketones with silyl enol ethers using duroquinone as the terminal oxidant (**Scheme 5.6b**).^[450] The first asymmetric transformation utilizing this strategy was reported in 2012 by Jang and coworkers, where aldehydes with α - and β -stereocenters were obtained from a tandem conjugate addition/oxyamination process (**Scheme 5.6c**).^[451] In 2017, MacMillan and coworkers disclosed a highly enantioselective inter- and intramolecular α -alkylation of aldehydes, exploiting a ternary catalytic system involving organo-, photoredox and HAT catalysis (**Scheme 5.6d**).^[452]

We envisioned that a similar strategy could be used for an asymmetric reaction with [1.1.1]propellane **2** as the enaminyll radical trap, giving access to chiral BCP products bearing an α -carbonyl stereocenter. This approach would constitute a direct, asymmetric ring-opening of [1.1.1]propellane **2** to construct both the BCP motif and the stereocenter simultaneously. The design of this multicyclic process involves the single-electron oxidation of an electron-rich enamine **124** by reductive quenching of the excited-state photocatalyst **[cat]***, giving the key enaminyll radical cation intermediate **125** (**Figure 5.3**). Addition of this radical cation **125** to [1.1.1]propellane **2** would install the BCP motif and construct the α -carbonyl stereocenter in a single step. The ability of [1.1.1]propellane **2** to act as an efficient radical trap is crucial to the feasibility of this enantiodetermining step: only activated olefins (styrenes)^[452] and stable radicals (TEMPO)^[451] have been shown to react with enaminyll radical cations under similar conditions. Finally, the incorporation of a HAT catalytic cycle to intercept the resulting bicyclopentyl radical **126** would form the enantioenriched aldehyde



Scheme 5.6. SOMO activation of enamines by photoredox organocatalysis.

product after hydrolysis of the iminium ion **127**. Reduction of the resulting HAT catalyst radical **129** regenerates the ground-state photocatalyst **[cat]**, and subsequent protonation reforms the HAT catalyst **128**.

The synergistic merger of three catalytic cycles with high selectivity and efficiency is critical for the success of this transformation, as several undesirable reaction pathways are possible. The different catalysts can be deactivated by reactions with [1.1.1]propellane **2** itself; in particular, the radical **129**, formed after HAT, can undergo addition to [1.1.1]propellane **2**. Efficient reductive HAT of the bicyclopentyl radical **126** is also required to avoid the formation of $[n]$ staffane derivatives that result from further reactions with [1.1.1]propellane **2**.

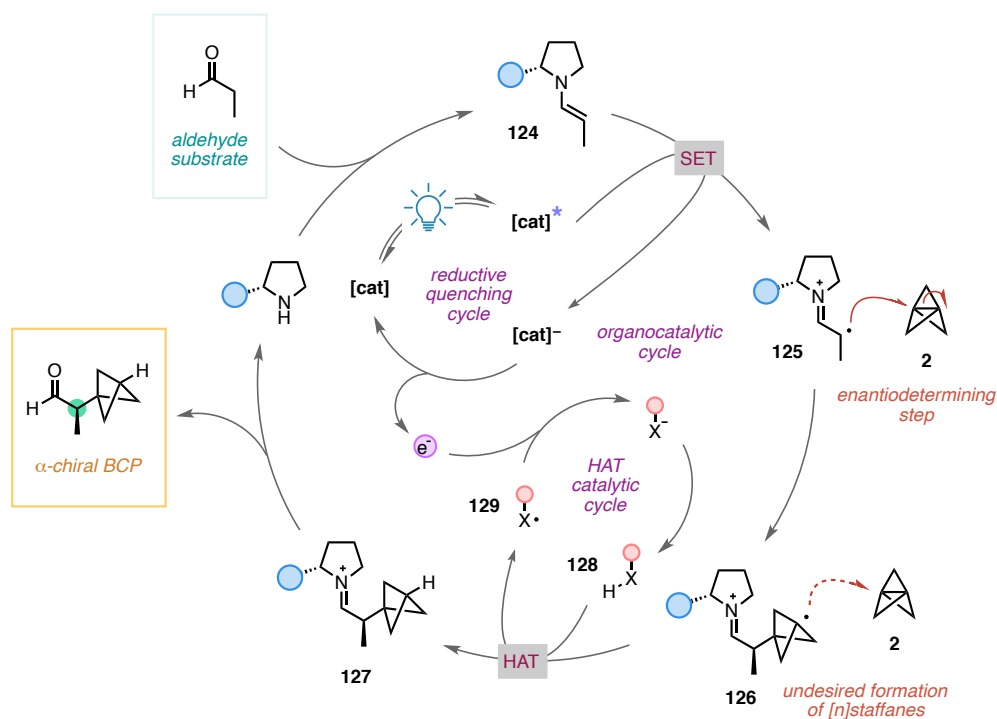
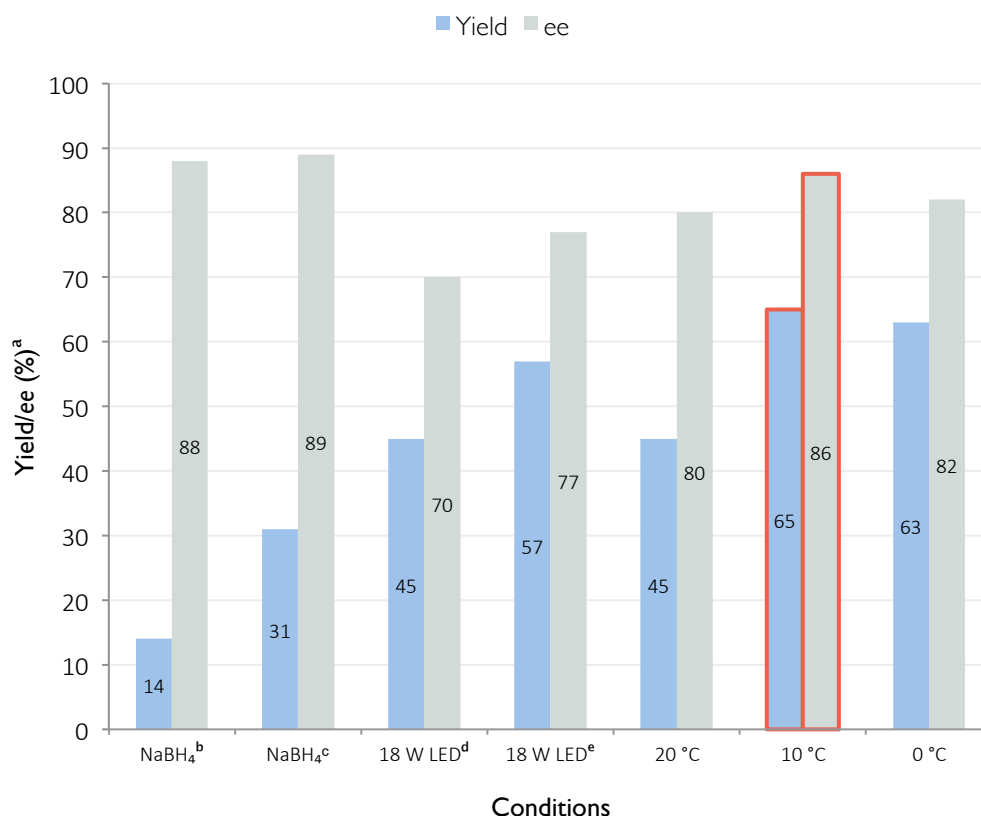
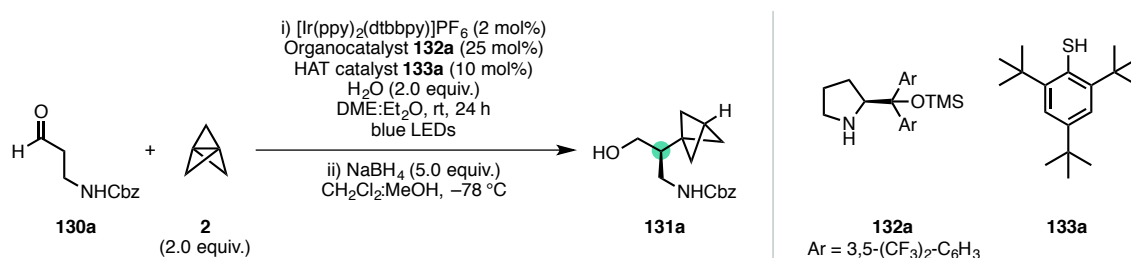


Figure 5.3. Design of a multicatalytic system for the direct asymmetric ring-opening of [1.1.1]propellane **2**.

5.3.1 Reaction optimization

Initial investigations into the feasibility of this multicatalytic approach for the synthesis of α -chiral BCPs were carried out with aldehyde substrate **130a** (Figure 5.4). Substrate **130a** was selected for the optimization studies as it possesses a UV-active chromophore to facilitate high performance liquid chromatography (HPLC) analysis for *ee* determination. The reaction was first attempted with aldehyde **130a** (1.0 equiv.), [1.1.1]propellane **2** (2.0 equiv.), iridium photocatalyst [Ir(ppy)₂(dtbbpy)]PF₆ (2 mol%), organocatalyst **132a** (25 mol%) and HAT catalyst **133a** (10 mol%) in DME with blue LED irradiation. The desired BCP product **131a** was obtained with high enantioselectivity (88% *ee*) but low yield (14%), with a reduction to the corresponding alcohol carried out before product isolation to avoid epimerization of the α -carbonyl stereocenter and to facilitate purification. Modification of the reduction conditions by increasing the amount of sodium borohydride (5.0 equiv.) resulted in a slightly improved yield (31%) while maintaining the enantioselectivity (89% *ee*). The reaction proceeded more efficiently when a more powerful light source was used, affording the product in 57% yield (18 W blue LEDs instead of blue LED strips fixed to the inside of a crystallization dish; see Chapter 9, Section 9.1 for more information). The reduction in enantioselectivity (77% *ee*) in this reaction was likely due to the increased reaction temperatures when a more powerful LED is used, and it was found that cooling the reaction to 10 °C led to a further increase in yield (65%) while restoring the high levels of enantioselectivity (86% *ee*) (see Chapter 9, Section 9.1 for details of the experimental setup for conducting photocatalytic reactions at reduced temperatures).



Reactions conducted on a 0.25 mmol scale.

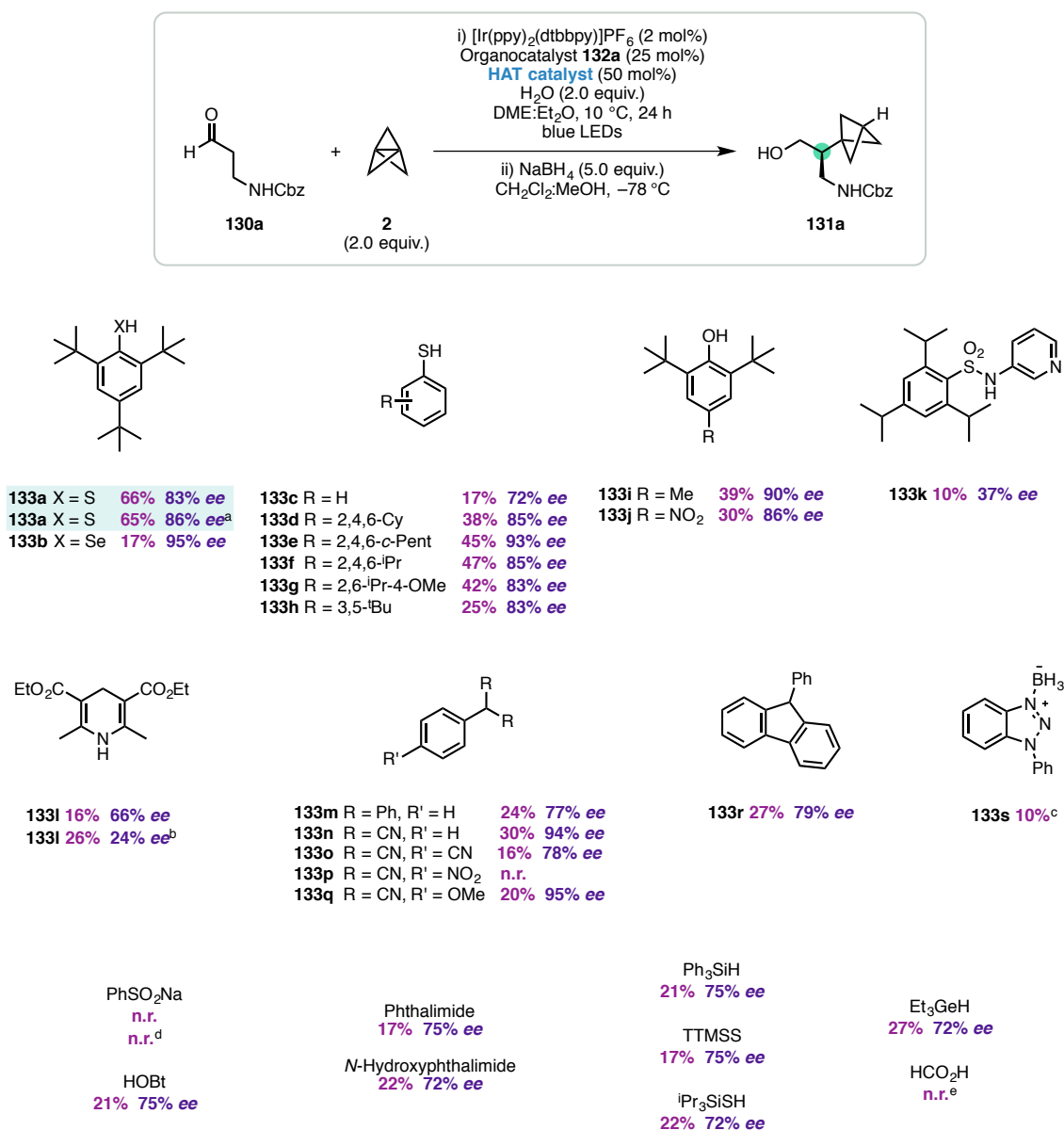
^aYields of isolated products. ^b NaBH_4 (2.0 equiv.), blue LED strips in a crystallization dish. ^cBlue LED strips in a crystallization dish. ^d405 nm. ^e450 – 455 nm.

Figure 5.4. Optimization of reaction conditions for the asymmetric ring-opening of [1.1.1]propellane **2**.

An extensive examination of HAT catalysts was then performed, involving a range of compounds that are known to act as HAT agents, such as silanes and 2-arylmalononitriles (**Figure 5.5**). Thiophenols were found to be superior to other classes of catalysts, affording the desired product in high enantioselectivity. HAT processes with thiol catalysts are known to be highly effective due to a polarity match with the electron-rich substrate radical as well as the small S–H bond dissociation

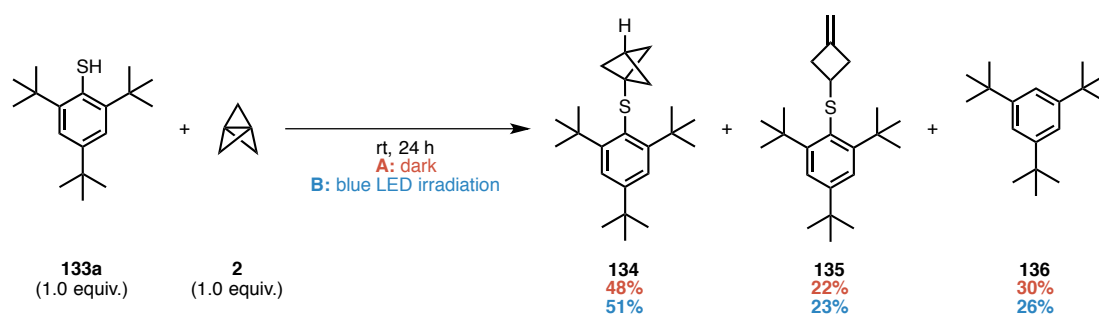
energy (BDE) (thiophenol: $\text{BDE}_{\text{S-H}} = 79 \text{ kcal mol}^{-1}$).^[444-446] The thiyl radical ($E^\circ[\text{PhS}^\bullet/\text{PhS}^-] = +0.16 \text{ V vs. SCE}$)^[453] formed in the reaction can also undergo facile reduction by the Ir(II) complex ($E^\circ[\text{Ir(III)/Ir(II)}] = -1.51 \text{ V vs. SCE}$).^[454] The reaction with sterically hindered thiophenol **133a**, in particular, was able to provide the desired BCP product **131a** in 66% yield and 83% *ee*, with this level of reaction efficiency and selectivity maintained when the catalyst loading was reduced from 50 mol% to 10 mol% (65%, 86% *ee*). The synthesis of several other thiophenols with different substituents on the aryl ring was attempted, but was unsuccessful (**Appendix 8.3.1**).

As thiols are known to react efficiently with [1.1.1]propellane **2**,^[64] the reaction between thiol catalyst **133a** and [1.1.1]propellane **2** itself was studied (**Scheme 5.7**). The formation of thiyl radicals in the asymmetric reaction could lead to undesired side reactions that consume the HAT catalyst. The reaction conducted in the dark (with aluminium foil protection) and under blue LED irradiation produced similar results, with the thiol-BCP adduct **134** being obtained in 48 – 51% yield, along with the rearrangement product **135** and 1,3,5-tri-*tert*-butylbenzene **136**. However, none of these products were observed in the asymmetric reaction, demonstrating the efficiency of thiol **133a** as a HAT catalyst.



Reactions conducted on 0.25 mmol scale; yields of isolated products.
^a**133a** (10 mol%). ^bBu₃N (50 mol%). ^cee not determined. ^dNaOAc (50 mol%). ^eHCO₂H (2.0 equiv.), Bu₃N (2.0 equiv.).
 n.r.: no reaction.

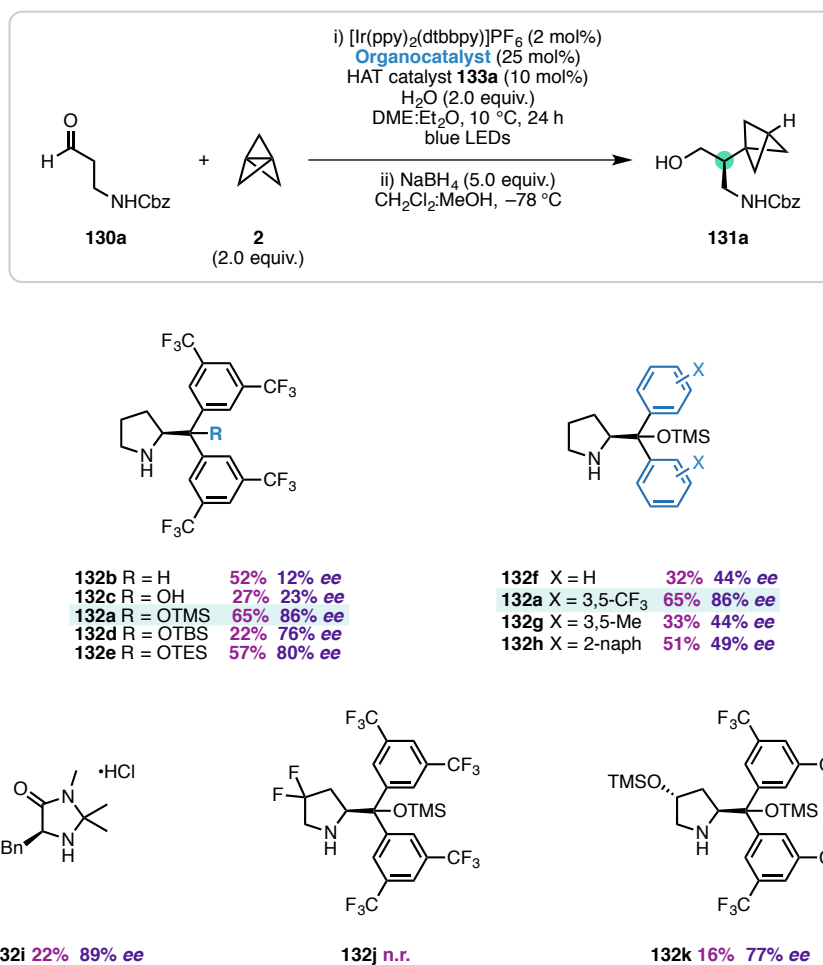
Figure 5.5. Optimization of HAT catalysts for the asymmetric ring-opening of [1.1.1]propellane **2**.



Scheme 5.7. Reaction between thiol catalyst **133a** and [1.1.1]propellane **2**.

Next, the effects of the organocatalyst on the efficiency and selectivity of the asymmetric reaction were examined (**Figure 5.6**). Diarylprolinol silyl ethers have been successful in other similar reactions^[451-452] and it was found that the nature of the substituents on both the silicon atom and the arene rings were highly influential on the reaction outcome. The silyl ether motif on the organocatalyst was crucial for high reactivity and selectivity, with a trimethylsilyl (TMS) group being optimal. Substituents on the arene rings of the organocatalyst were equally important, with the 3,5-bis(trifluoromethyl)phenyl group proving to be ideal for high yield and enantioselectivity in the asymmetric reaction (see **Section 5.3.4** for further discussions on the effects of arene substitution on enantioinduction). The commercially available organocatalyst **132a** outperformed the other catalysts surveyed, providing the desired BCP product **131a** in 65% yield and 86% *ee*.

A screen of various photocatalysts was then carried out (**Figure 5.7**; see **Appendix 8.3.2** for further details). We found that iridium complexes with a bipyridine (bpy) ligand were more effective, and [Ir(ppy)₂(dtbbpy)]PF₆ was identified as the optimal photocatalyst.



Reactions conducted on a 0.25 mmol scale; yields of isolated products.

Figure 5.6. Optimization of organocatalysts for the asymmetric ring-opening of [1.1.1]propellane **2**.

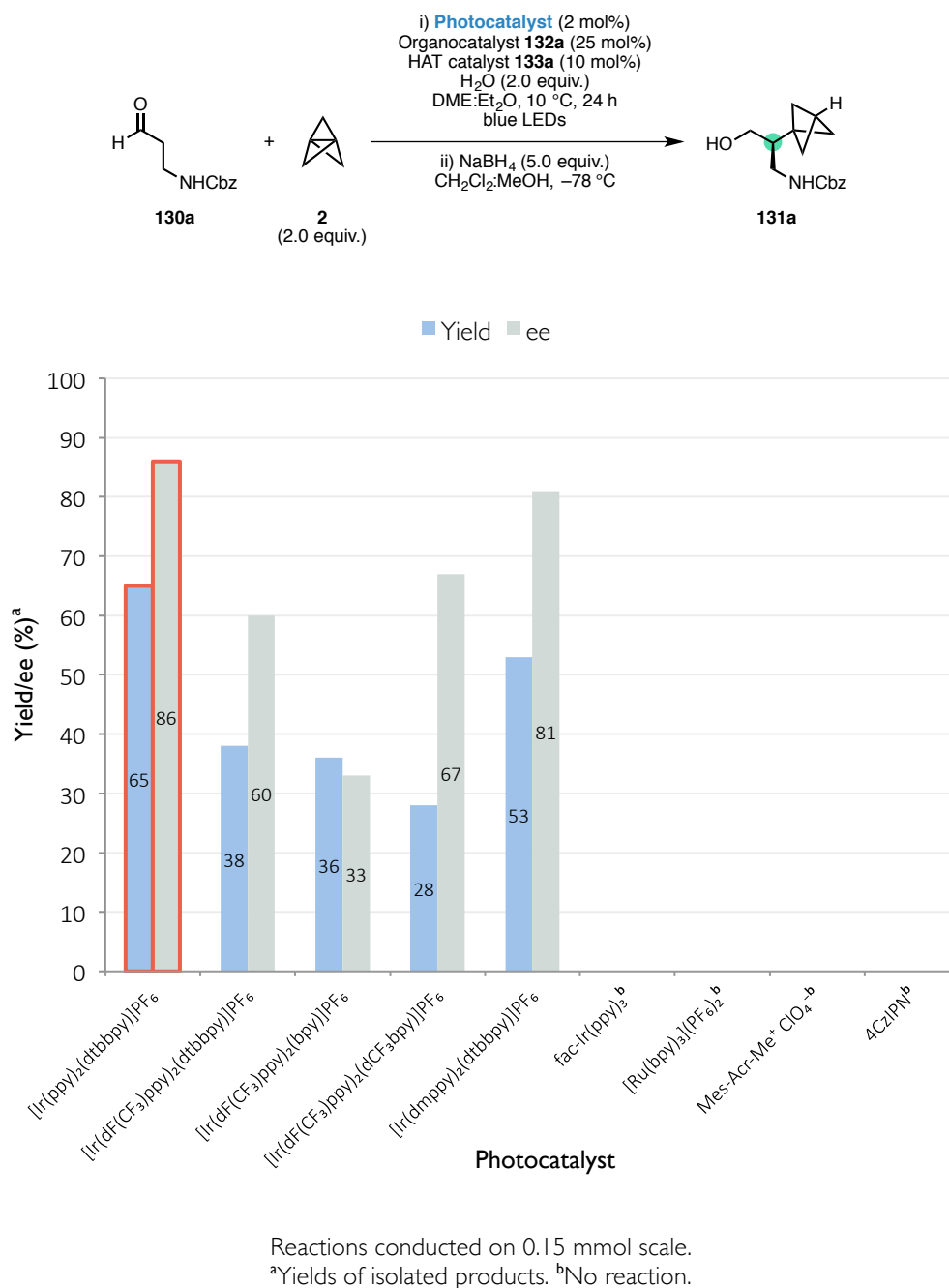
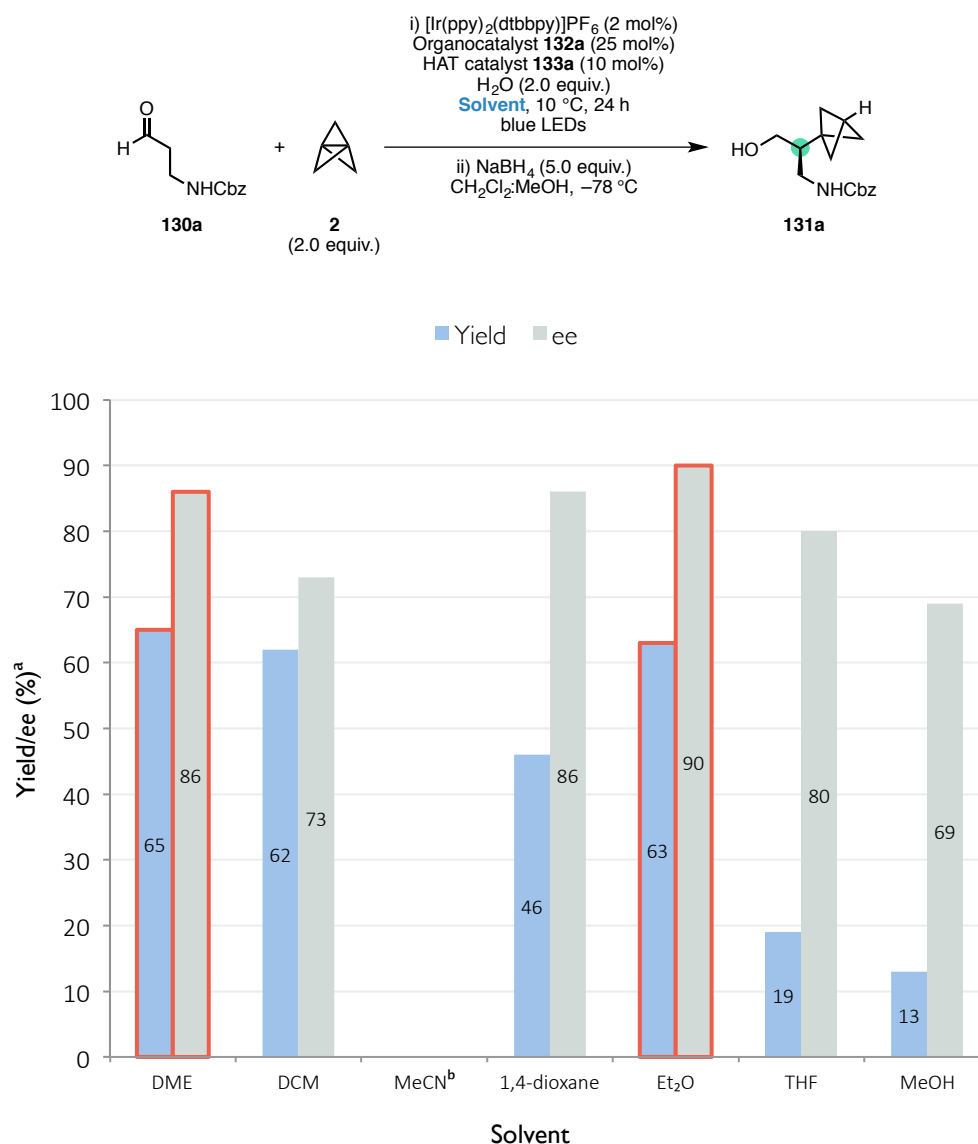


Figure 5.7. Optimization of photocatalysts for the asymmetric ring-opening of [1.1.1]propellane **2**.

A survey of solvents found that several ethereal solvents were compatible in the reaction (**Figure 5.8**). After further optimization of reaction concentrations and solvent ratios, a 1:1 mixture of DME and Et₂O was found to be ideal for the reaction (**Appendix 8.3.3**), which was advantageous as [1.1.1]propellane **2** is typically synthesized as a solution in Et₂O that can be stored for up to six months at -20 °C.



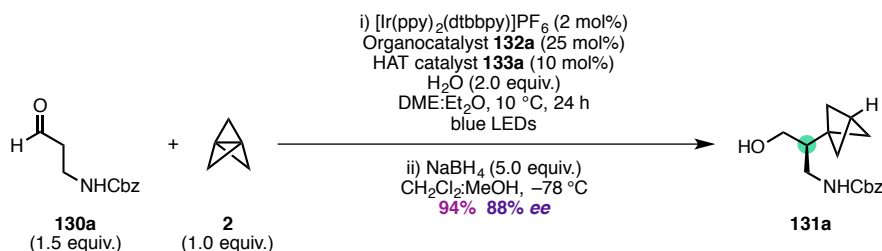
Reactions conducted on a 0.15 mmol scale.

^aYields of isolated products. ^bNo reaction.

Figure 5.8. Optimization of solvents for the asymmetric ring-opening of [1.1.1]propellane **2**.

Further fine-tuning of the reaction conditions was undertaken, involving optimization of the reaction time and stoichiometry of reactants/reagents (**Appendix 8.3.4**). An important finding was that using [1.1.1]propellane **2** as the limiting reagent and the aldehyde substrate in excess (1.5 equiv.) enabled the synthesis of BCP product **131a** in 94% yield and 88% *ee* (**Scheme 5.8**). This is beneficial as [1.1.1]propellane **2** is the most valuable component of the reaction system. Control experiments were also carried out to confirm that all three catalysts were required in the reaction, with no reaction

observed in the absence of blue LED irradiation, the photocatalyst and the organocatalyst, and only trace amounts of the desired product was observed in the reaction without the HAT catalyst (**Appendix 8.3.5**). Under the optimized reaction conditions, α -chiral BCP product **131** could be obtained in 94% yield and 88% *ee* from commercially available or easily accessible reagents.

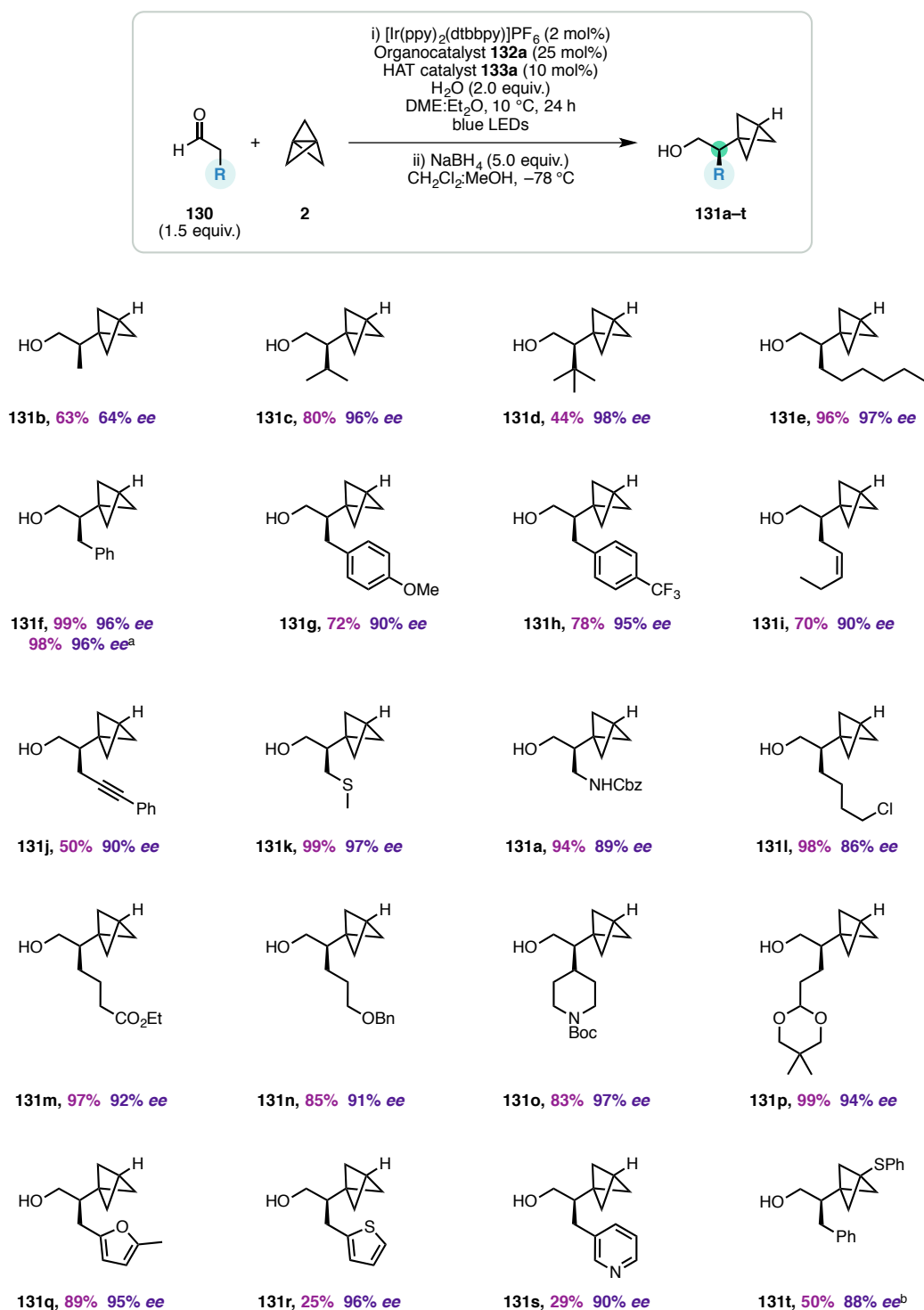


Scheme 5.8. Optimized reaction conditions for the asymmetric ring-opening of [1.1.1]propellane **2**.

5.3.2 Reaction scope

With the optimized reaction conditions in hand, we sought to evaluate this methodology with a range of aldehyde substrates (**Figure 5.9**).

The triple catalytic system was found to perform well with aldehydes bearing a wide range of substituents, affording the desired products in high yields and excellent enantioselectivities in most cases. Simple alkyl aldehydes were well-tolerated under the reaction conditions (**131b – 131e**, 44 – 96%, 64 – 98% *ee*), including substrates bearing more sterically demanding α -carbonyl substituents (**131c** and **131d**). However, only modest enantioselectivity was achieved in the reaction with propionaldehyde (**131a**, 64% *ee*); this outcome was subsequently rationalized through computational studies (**Section 5.3.4**). Chiral BCP products bearing aryl (**131f – 131h**), alkenyl (**131i**) and alkynyl (**131j**) motifs were also obtained with excellent enantioselectivities (90 – 96% *ee*) and good yields (50 – 99%). An array of substrates



Reactions conducted on a 0.20 mmol scale.

^a1.00 mmol scale. ^bN-(Phenylthio)phthalimide (4.0 equiv.) instead of HAT catalyst **133a**.

Figure 5.9. Scope of the asymmetric ring-opening of [1.1.1]propellane **2**.

bearing heteroatom-containing functional groups were also successful in the reaction, affording the desired products (**131a**, **131k** – **131p**) with high efficiency and selectivity (85 – 99%, 86 – 97% ee). In particular, BCP **131o** featuring a piperidine

moiety, which is a heterocyclic motif that is of interest in the pharmaceutical industry,^[455-456] could be formed in 83% yield and 97% *ee*. α -Chiral BCPs with heteroaromatic motifs (**131q** – **131s**) could also be synthesized, although these substrates proved to be more challenging under the reaction conditions. Furanyl-BCP **131q** could be accessed in 89% yield and 95% *ee*, and while thiophenyl-BCP **131r** and pyridinyl-BCP **131s** were obtained with excellent levels of enantiopurity (90 – 96% *ee*), the yields were significantly diminished (25 – 29%), potentially due to instability of the corresponding aldehyde substrates and/or products under the reaction conditions, as evidenced by the increased formation of undesired side products in the reaction. The asymmetric reaction can also be conducted on a larger scale, and BCP product **131f** was prepared on a 1 mmol scale with no reduction in yield or selectivity (98%, 96% *ee*). For further diversification, we considered the use of other reagents to trap the bicyclopentyl radical, and sulfur-substituted BCP product **131t** was obtained in 50% yield and 88% *ee* when *N*-(phenylthio)phthalimide (4.0 equiv.) was used in place of the HAT catalyst. The absolute stereochemistry of BCP product **131b** was determined by comparison of supercritical fluid chromatography (SFC) traces (after derivatization) to the same compound with known absolute stereochemistry; the stereochemistry of the remaining BCP products were assigned by analogy (see **Chapter 9, Section 9.6.5** for further details).

Several other classes of substrates were also evaluated in the asymmetric reaction but failed to provide the desired products (**Figure 5.10**). Poor reaction conversion and low levels of enantioselectivity at the α -carbonyl stereocenter was observed for phenylacetaldehyde derivatives. Aldehydes with heteroatom substituents at the α -carbonyl position were unreactive and complex mixtures of products were obtained in

the reactions with several other substrates, in which the desired products could not be detected.

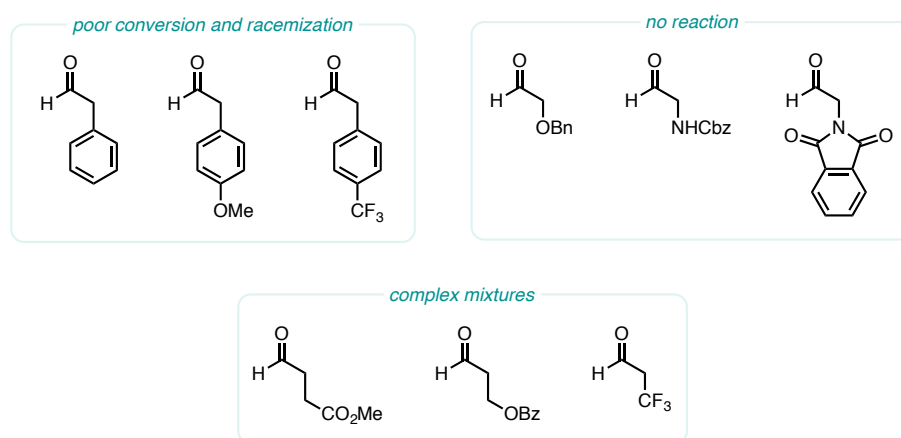
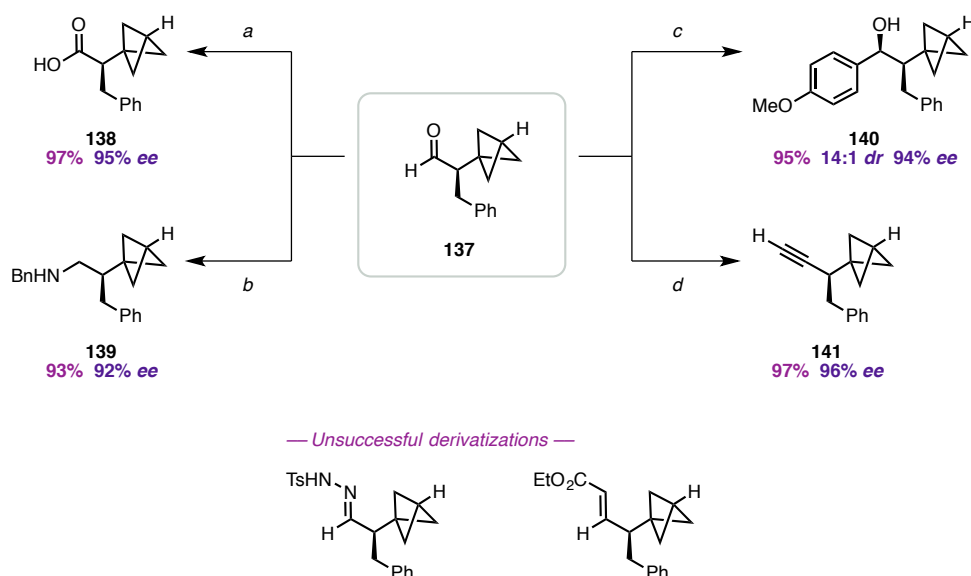


Figure 5.10. Unsuccessful substrates.

5.3.3 Derivatization of α -chiral BCP products

The multicyclic approach to accessing α -chiral BCPs proved to be extremely versatile, affording a range of BCP derivatives with high levels of efficiency and selectivity. The formation of α -carbonyl stereocenters was targeted because of the potential of the carbonyl functionality to undergo various derivatizations. Thus, aside from the reduction to the corresponding alcohol, we also explored other transformations of the aldehyde **137** obtained directly from the asymmetric reaction (**Scheme 5.9**). Oxidation to the carboxylic acid **138** proceeded smoothly, affording the desired product in 97% yield with no erosion of enantiopurity (95% *ee*). The aldehyde **137** could also be subjected to a reductive amination to obtain secondary amine **139** with minimal epimerization of the stereocenter (93%, 92% *ee*). Excellent levels of diastereoselectivity were achieved in the reaction between aldehyde **137** and an aryl Grignard reagent under Felkin–Anh control, giving a BCP product **140** with both α - and β -stereocenters (95%, 14:1 *dr*, 94% *ee*). Finally, homologation of the enantioenriched aldehyde **137** was

carried out, giving access to alkyne **141** in 97% yield and 96% *ee*. Conversion of aldehyde **137** to a tosylhydrazone and an olefin was attempted, but only unreacted starting material was recovered. Due to time constraints, these derivatization conditions were not repeated or further optimized.



Reaction conditions:

a: BAIB (2.0 equiv.), TEMPO (0.2 equiv.), CH₂Cl₂:H₂O, rt. **b:** i) BnNH₂ (1.3 equiv.), AcOH (1.3 equiv.), Et₃N (1.4 equiv.), DCE, rt; ii) NaBH(OAc)₃ (2.5 equiv.). **c:** 4-MeO-PhMgBr (3.2 equiv.), THF, -78 °C to rt. **d:** AcC(N₂)P(O)(OMe)₂ (2.0 equiv.), K₂CO₃ (2.0 equiv.), MeOH, rt.

Scheme 5.9. Derivatization of the aldehyde products obtained directly from the asymmetric ring-opening of [1.1.1]propellane **2**.

5.3.4 Computational analysis

Computational analysis of the reaction was performed by Alistair Sterling and Prof. Fernanda Duarte to elucidate the origin of enantioinduction, especially considering the observed dependence of enantioselectivity on the substituents on the organocatalyst arene and the substrate α -carbonyl position. The radical cation formed in the reaction is expected to exist as an equilibrium mixture of the *s-cis* and *s-trans* forms, and the reaction with [1.1.1]propellane **2** can proceed from either the ‘open’ or ‘closed’ face of the radical cation, relative to the position of the substituent on the 2-position of the

pyrrolidine ring (**Figure 5.11a**). The four possible reaction pathways result in the formation of two diastereomers of the radical addition product before hydrolysis of the organocatalyst (following the definitions used by Jørgensen^[457]). Substrate **130a'**, bearing a methoxycarbonyl (Moc) group, was selected as a simplified version of substrate **130a**, with a benzyloxycarbonyl (Cbz) group, which was used in the reaction optimization and afforded the corresponding BCP product **131a** in 94% yield and 89% *ee*.

The *Si-s-trans* and *Si-s-cis* pathways lead to formation of the major diastereomer, with the former being sterically favored; on the other hand, the *Re-s-trans* and *Re-s-cis* pathways both result in the formation of the minor diastereomer. Substrate **130a'** displays a marked preference for addition to the 'open' face of the *s-trans* conformer (**TS-130a'**, $\Delta\Delta E_{Re/Si}^{\ddagger} = 4.9 \text{ kcal mol}^{-1}$), consistent with the high enantioselectivity in the experimental results obtained. This preference can be attributed to the absence of unfavorable steric effects in this conformer as well as the presence of stabilizing non-covalent interactions (NCIs) between the sidechain of the aldehyde substrate (the Moc group) and the pyrrolidine substituents in the transition state, specifically the C–H $\cdots$ F and C–H $\cdots$ O interactions (**Figure 5.11b**). Replacing the 3,5-bis(trifluoromethyl)phenyl groups of the organocatalyst with unsubstituted phenyl groups weakens these NCIs (**TS-130a'-H**, $\Delta\Delta E_{Re/Si}^{\ddagger} = 0.4 \text{ kcal mol}^{-1}$) and results in poorer enantioselectivity, as is observed experimentally (44% *ee* with organocatalyst **132f** compared to 89% *ee* with organocatalyst **132a**). This is further exemplified in the reduced selectivity observed in the reaction with propionaldehyde (experimental *ee* of 64%), which only has a methyl sidechain and therefore, reduced NCIs (**TS-130b**, $\Delta\Delta E_{Re/Si}^{\ddagger} = 2.2 \text{ kcal mol}^{-1}$). Increasing the length of the alkyl chain on the aldehyde substrate, as is the case in the reaction with octanal,

restores the high selectivity (97% *ee*), due to an increase in dispersion and C–H...F interactions (**TS-130e**, $\Delta\Delta E_{Re/Si}^{\ddagger} = 3.4 \text{ kcal mol}^{-1}$).

The *Re-s-trans* and *Re-s-cis* transition states are less favored compared to the *Si-s-trans* transition state ($\Delta\Delta E_{Re-s-trans/Si-s-trans}^{\text{dist}} = 6.0 \text{ kcal mol}^{-1}$ and $\Delta\Delta E_{Re-s-cis/Si-s-trans}^{\text{dist}} = 7.2 \text{ kcal mol}^{-1}$) due to the significant structural distortions required, which can also be attributed to the increased steric repulsion and absence of stabilizing NCIs in these conformations. Interestingly, formation of the minor diastereomer *via* the *Re-s-trans* pathway (*i.e.*, addition of [1.1.1]propellane **2** to the ‘closed’ face) was found to be more favorable than isomerization to the *Re-s-cis* conformer, followed by addition to the ‘open’ face ($\Delta\Delta E_{Re-s-cis/Re-s-trans}^{\ddagger} = 0.9 \text{ kcal mol}^{-1}$). These findings outline the importance of NCIs between the pyrrolidine substituents and the sidechain of the aldehyde substrate, as well as the influence of steric effects in the transition state, favoring the reaction of the *s-trans* conformer with [1.1.1]propellane **2** from the ‘open’ face.

5.4 Conclusions

The exploration of a multicatalytic strategy for enantioselective radical-based reactions has culminated in the development of the first asymmetric ring-opening of [1.1.1]propellane **2** for the synthesis of α -chiral BCPs (**Scheme 5.10**). The synergistic merger of organo-, photoredox and HAT catalysis enables a highly efficient and enantioselective reaction between simple aldehyde substrates and [1.1.1]propellane **2**, allowing the installation of the BCP unit and construction of the α -carbonyl stereocenter to occur in a single step. Enantioenriched BCP derivatives bearing a diverse array of

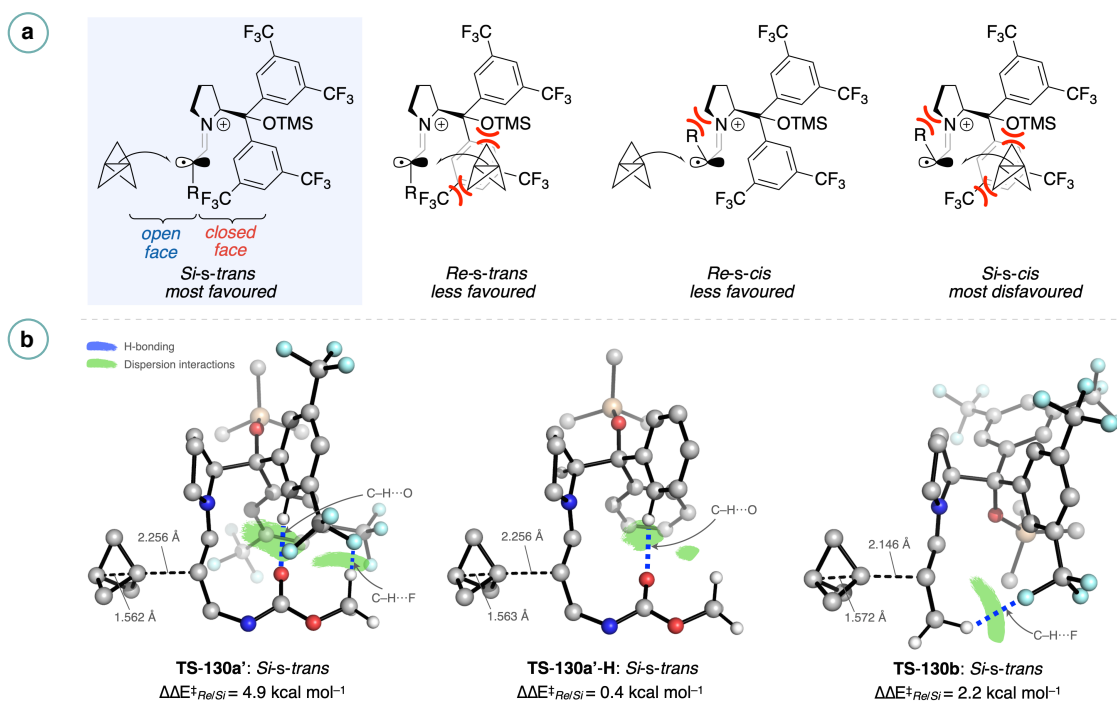
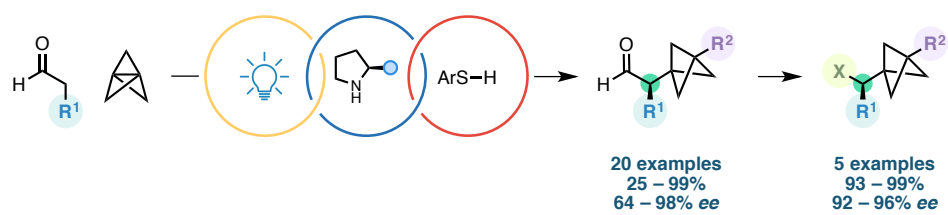


Figure 5.11. Computational analysis of the addition of the radical cation intermediate to

[1.1.1]propellane **2** performed by Alistair Sterling and Prof. Fernanda Duarte.

functional groups can be obtained directly from [1.1.1]propellane **2** and this methodology represents the only route to α -chiral BCPs that does not involve synthetic manipulations of a pre-formed BCP derivative. Multicomponent radical reactions with [1.1.1]propellane **2** are challenging, with only a handful of examples reported in the literature,^[46,73,76,78] and this methodology successfully utilizes this approach to synthesize both terminal and 1,3-disubstituted BCP derivatives. The versatility of the carbonyl motif as a synthetic handle for further derivatization was also demonstrated, providing access to α -chiral BCP derivatives that are otherwise difficult or impossible to obtain. Computational studies of the reaction uncovered interactions between components of the substrate and the organocatalyst that are crucial for the success of the transformation. This methodology is expected to be a valuable contribution to the fields of asymmetric photoredox catalysis and bicyclopentane chemistry. The work presented in this chapter was published in *Nature Communications* in 2021.^[458]



Scheme 5.10. The direct, asymmetric synthesis of α -chiral BCPs from [1.1.1]propellane 2.

Conclusions and future work

Interest in bicyclopentane chemistry has surged in recent years, largely driven by developments that have focused on the synthesis and reactivity of [1.1.1]propellane **2**, the most commonly used precursor to BCP derivatives. The diverse reactivity of [1.1.1]propellane **2** with radicals, nucleophiles and electrophiles has led to the development of numerous methodologies to access a range of BCP derivatives and other (poly)cyclic molecules. The growing attention towards bicyclopentane chemistry also stems from successful applications of these caged structures as bioisosteres and unsaturated, three-dimensional motifs in drug design, as well as in other materials and supramolecular chemistry settings.

An underexplored area of bicyclopentane chemistry that possesses great potential is the synthesis of α -chiral BCP derivatives, a highly valuable class of compounds due to the fundamental importance of stereocontrolled diversification in a three-dimensional chemical space in molecular design. Prior to the efforts detailed in this thesis, only several isolated examples of α -chiral BCP amino acid derivatives were known, relying on low-yielding and lengthy synthetic routes that involved toxic reagents,

stoichiometric chiral reagents and resolution processes for the separation of diastereomers.

The work in this thesis sought to address the lack of general and efficient methods to synthesize α -chiral BCP derivatives by exploiting the reactivity of [1.1.1]propellane **2** with radicals (**Scheme 6.1**). The synthesis of BCP derivatives bearing an α -carbonyl stereocenter was targeted, as the carbonyl group would provide a highly versatile synthetic handle to facilitate further derivatizations of the enantioenriched BCP compounds obtained.

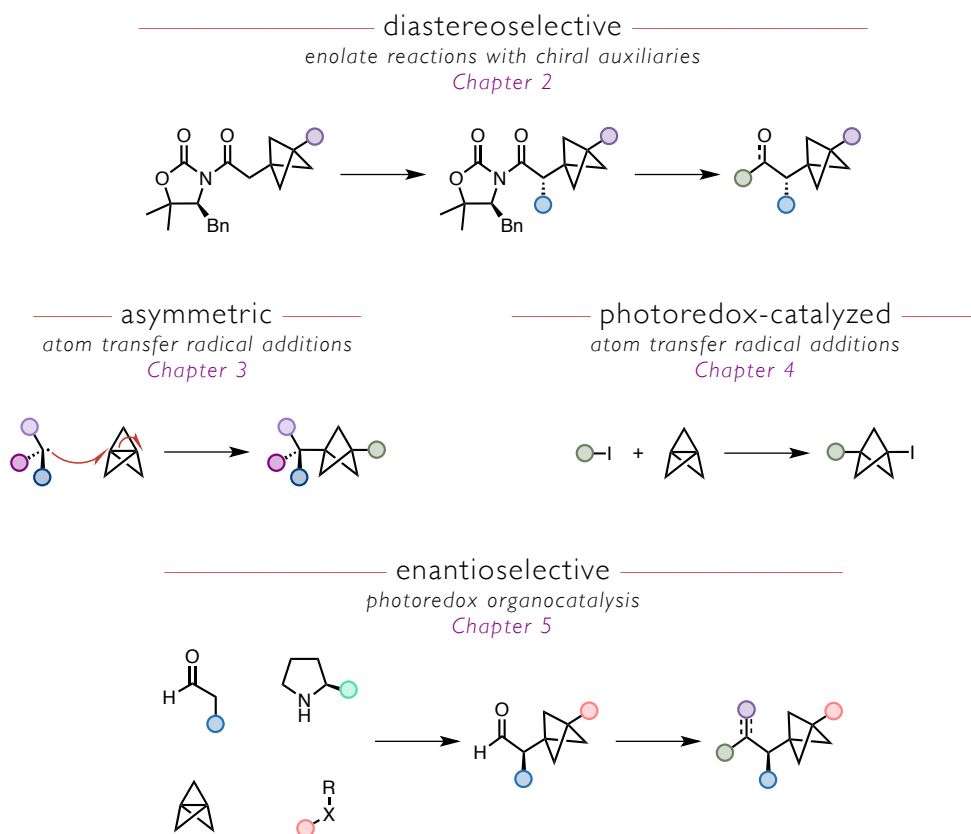
A highly diastereoselective methodology involving BCP substrates bearing chiral oxazolidinone auxiliaries was first developed, in which the substrates undergo a variety of enolate reactions to form α -chiral BCPs in good yields with excellent levels of diastereoselectivity (**Chapter 2**).^[212] The synthesis of 1,3-disubstituted α -chiral BCPs was also achieved, as well as the removal of the auxiliary and subsequent diversification of the BCP products without erosion of enantiopurity, including in applications towards the synthesis of several BCP analogues of biomolecules. This approach enabled access to novel BCP derivatives and represents the first general methodology to synthesize these enantioenriched compounds.

To expand on the atom transfer radical addition with [1.1.1]propellane **2** developed in the Anderson group, an asymmetric variant of the reaction was next investigated, involving the formation of a radical in a chiral environment for an asymmetric reaction with [1.1.1]propellane **2** (**Chapter 3**). Extensive studies were carried out towards this goal, focusing on the complexation of a chiral substrate to a Lewis acid complex for a diastereoselective radical reaction, as well as the complexation of an achiral substrate to a chiral Lewis acid–ligand complex for an enantioselective radical reaction. Ultimately,

only moderate levels of stereoselectivity were achieved, demonstrating the potential of this strategy for accessing α -chiral BCPs, but thorough investigation of the reaction parameters did not result in an improvement of the reaction outcomes.

Alternative modes of substrate activation to generate radical species were then considered, culminating in the development of an exceptionally general photoredox-catalyzed atom transfer radical addition with [1.1.1]propellane **2** to form 1,3-disubstituted BCP derivatives (**Chapter 4**).^[319] The work in this thesis focused on examining the scope of the reaction with alkyl iodides bearing heterocyclic and (hetero)benzylic motifs, as well as α -iodocarbonyl substrates. This methodology exhibited a broad functional group tolerance and constitutes the first use of photoredox catalysis for carbon–carbon σ -bond functionalization.

The synergistic merger of photoredox catalysis with other catalytic modes of activation has been highly successful for accessing novel reaction pathways, and a multicyclic strategy was investigated for the synthesis of α -chiral BCPs. This resulted in the development of a combined photoredox, organo- and HAT catalysis approach for the direct reaction of simple aldehyde substrates with [1.1.1]propellane **2**, in which the installation of the BCP unit and formation of the stereocenter occurs in a single step (**Chapter 5**). A range of aldehyde substrates successfully underwent the asymmetric reaction to form products with excellent yields and enantioselectivities, and the carbonyl functionality can be readily manipulated to obtain an array of novel α -chiral BCP compounds. Notably, radical multicomponent reactions with [1.1.1]propellane **2** are rare and the construction of a stereocenter upon radical ring-opening of [1.1.1]propellane **2** is unprecedented.



Scheme 6.1. Project overview.

To further explore the asymmetric synthesis and functionalization of BCP compounds, a wide variety of other strategies in asymmetric radical chemistry can also be studied in the context of α -chiral bicyclopentane synthesis, capitalizing on the tendency of [1.1.1]propellane **2** to react with radical species. The stereoselective trapping of a bridgehead bicyclopentane radical resulting from radical addition to [1.1.1]propellane **2** can also be investigated as an alternative approach to form the adjacent stereocenter. In a conceptually-related strategy, the formation of an anionic species in a chiral environment can be used to effect ring-opening of [1.1.1]propellane **2**. A general route to BCPs with an adjacent quaternary stereocenter would also be attractive as only one example of such a compound has been reported to date.^[77]

Bridge-substituted BCP derivatives remain scarce and an efficient route to accessing these compounds would be highly desirable. Furthermore, the ability to introduce a

stereocenter at the bridge positions is currently unprecedented and would be an extremely advantageous development for use in three-dimensional molecular design. Several strategies can be investigated to achieve this, including a stereoselective C–H activation at the bridge positions of a BCP derivative, a stereoselective C–H activation at the bridge positions of a BCB derivative followed by ring expansion to form a BCP, and a stereoselective insertion of a methylene unit across the central C–C bond of a BCB derivative to form the BCP unit.

Caged polycyclic structures such as bicyclo[1.1.1]pentanes and [1.1.1]propellane **2** have fascinated chemists for many years and the revival of interest in these molecules will certainly uncover many novel aspects of their synthesis and reactivity. Further developments in the field will also result in the ability to improve and increase their applications in a variety of different settings beyond organic synthesis.

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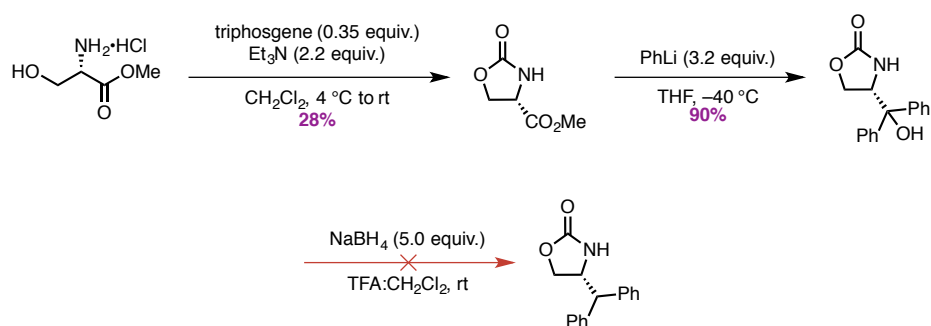
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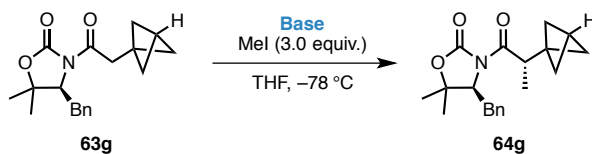
8.1 Chapter 2

8.1.1 Attempted synthesis of Sibi oxazolidinone auxiliary



Scheme 8.1. Attempted synthesis of Sibi oxazolidinone auxiliary.

8.1.2 Optimization: Enolate reaction

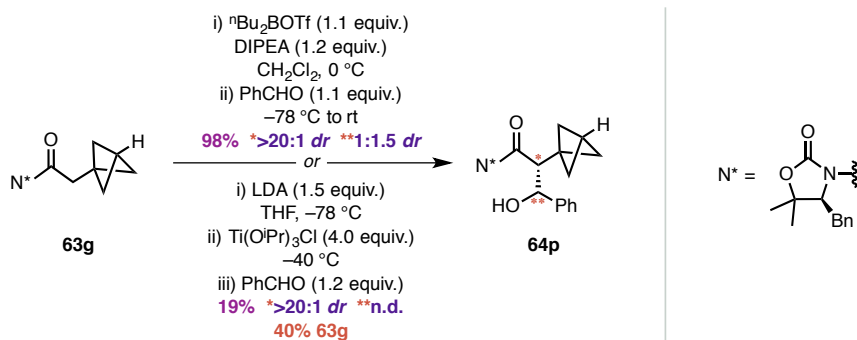


Entry	Base (equiv.)	Yield (64g) ^a	Yield (63g) ^a
1	NaHMDS (1.1)	84%	—
2	LiHMDS (1.2)	—	76%
3	LDA (1.1)	—	67%

Reactions conducted on a 0.20 mmol scale. ^aYields of isolated products.

Table 8.1. Optimization of enolate reaction conditions.

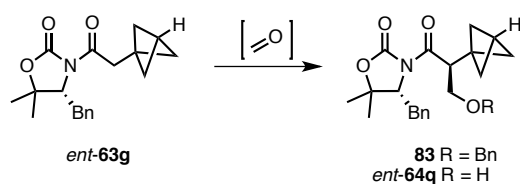
8.1.3 Optimization: Diastereoselective aldol reaction



n.d. = not determined.

Scheme 8.2. Optimization of diastereoselective aldol reaction conditions.

8.1.4 Optimization: Diastereoselective hydroxymethylation reaction



Entry	Conditions	$[\text{O}]$	Yield (83/ ent-64q) ^a	Yield (ent-64q) ^a	Yield (ent-65) ^a
1 ^b	NaHMDS (1.1 equiv.) THF, -78 °C	BOMCl (3.0 equiv.)	21%	21%	—
2 ^c		<i>p</i> -formaldehyde (10.0 equiv.)	—	22%	—
3 ^d		<i>p</i> -formaldehyde (10.0 equiv.)	—	33%	45%
4 ^e		<i>p</i> -formaldehyde (9.0 equiv.)	complex mixture		
5 ^f		1,3,5-trioxane (1.2 equiv.) TiCl ₄ (1.0 equiv.)	—	8%	—
6		<i>N</i> -(hydroxymethyl) phthalimide (2.0 equiv.)	—	—	36%
7 ^f	i) TiCl ₄ (1.0 equiv.) ii) DIPEA (1.1 equiv.) CH ₂ Cl ₂ , 0 °C	1,3,5-trioxane (1.2 equiv.) TiCl ₄ (1.0 equiv.)	32%	25%	—
8 ^f	i) TiCl ₄ (1.1 equiv.) ii) DIPEA (1.2 equiv.) CH ₂ Cl ₂ , 0 °C	1,3,5-trioxane (1.2 equiv.) TiCl ₄ (1.1 equiv.)	26%	28%	—
9 ^g		1,3,5-trioxane (10.0 equiv.) TiCl ₄ (1.1 equiv.)	24%	21%	—
10 ^g		1,3,5-trioxane (10.0 equiv.) TiCl ₄ (10.0 equiv.)	34%	24%	—
11 ^g		1,3,5-trioxane (5.0 equiv.) TiCl ₄ (1.1 equiv.)	56%	—	—
12 ^g		1,3,5-trioxane (6.0 equiv.) TiCl ₄ (1.1 equiv.)	41%	—	—
13 ^g		1,3,5-trioxane (7.0 equiv.) TiCl ₄ (1.1 equiv.)	53%	—	—
14 ^{g,h}		1,3,5-trioxane (5.0 equiv.) TiCl ₄ (1.1 equiv.)	54%	—	—

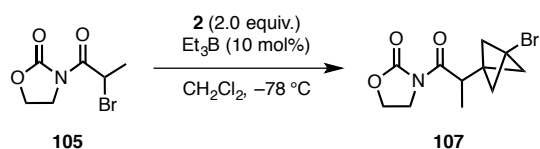
^aYields of isolated products. ^bWith **63g**, R = Bn. ^c*p*-Formaldehyde cracked into THF. ^d*p*-Formaldehyde cracked directly into reaction mixture. ^eSolid *p*-formaldehyde added directly into reaction mixture.

^fTiCl₄ (1 M in CH₂Cl₂). ^gTiCl₄ (neat). ^hAnhydrous DIPEA.

Table 8.2. Optimization of diastereoselective hydroxymethylation reaction conditions.

8.2 Chapter 3

8.2.1 ATRA with α -bromocarbonyls



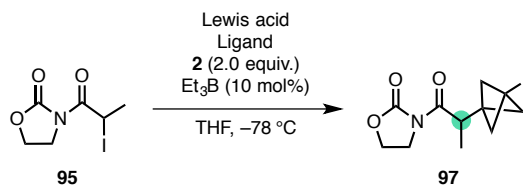
Entry	Lewis Acid (equiv.)	Yield (107) ^a	Yield (105) ^a
1 ^b	—	61%	—
2	$\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ (2.0)	49%	—
3 ^c	$\text{MgBr}_2 \cdot \text{Et}_2\text{O}$ (2.0)	10%	—
4	ZnCl_2 (1.0)	23%	29%
5	$\text{Gd}(\text{OTf})_3$ (1.0)	49%	—

Reactions conducted on a 0.50 mmol scale, 1.0 mL of CH_2Cl_2 (0.5 M). ^aYields of isolated products.

^b CH_2Cl_2 (0.5 mL, 1.0 M). ^c Et_3B (10 mol%).

Table 8.3. ATRA of α -bromocarbonyl substrate **105** with [1.1.1]propellane **2**.

8.2.2 ATRA with lanthanide Lewis acids and PyBOX ligands



Entry	Lewis Acid (equiv.)	Ligand (equiv.)	Yield (97) ^a	ee
1	Yb(OTf) ₃ (1.0)	(R,R)- L10 (1.0)	49%	13%
2 ^b	Yb(OTf) ₃ (1.0)	(R,R)- L10 (1.0)	19%	7%
3	Yb(OTf) ₃ (1.0)	(R,R)- L10 (1.1)	52%	16%
4	Yb(OTf) ₃ (1.0)	(R,R)- L10 (2.0)	63%	3%
5	Gd(OTf) ₃ (1.0)	(R,R)- L10 (1.0)	51%	19%
6	La(NO ₃) ₃ •6H ₂ O (1.0)	(R,R)- L10 (1.0)	9%	3%
7	Ce(OTf) ₃ (1.0)	(R,R)- L10 (1.0)	22%	2%
8	Eu(OTf) ₃ (1.0)	(R,R)- L10 (1.0)	55%	22%
9	Zn(OTf) ₂ (1.0)	(R,R)- L6 (1.0)	58%	2%
10	Ho(OTf) ₃ (1.0)	(R,R)- L10 (1.0)	52%	26%
11	Ho(OTf) ₃ (0.1)	(R,R)- L10 (0.1)	59%	5%
12	Ho(OTf) ₃ (0.1)	(R,R)- L10 (1.5)	69%	3%
13	Ho(OTf) ₃ (0.5)	(R,R)- L10 (0.5)	49%	10%
14	Ho(OTf) ₃ (0.5)	(R,R)- L10 (1.0)	59%	4%
15	Ho(OTf) ₃ (1.0)	(R,R)- L10 (1.2)	70%	9%
16	Ho(OTf) ₃ (1.0)	(R,R)- L10 (2.0)	66%	3%
17	Ho(OTf) ₃ (1.2)	(R,R)- L10 (0.1)	59%	2%
18	Ho(OTf) ₃ (1.2)	(R,R)- L10 (1.5)	53%	24%
19	Ho(OTf) ₃ (1.5)	(R,R)- L10 (1.5)	36%	26%
20 ^c	Ho(OTf) ₃ (1.0)	(R,R)- L10 (1.0)	63%	13%
21 ^d	Ho(OTf) ₃ (1.0)	(R,R)- L10 (1.0)	40%	16%
22 ^e	Ho(OTf) ₃ (1.0)	(R,R)- L10 (1.0)	31%	7%

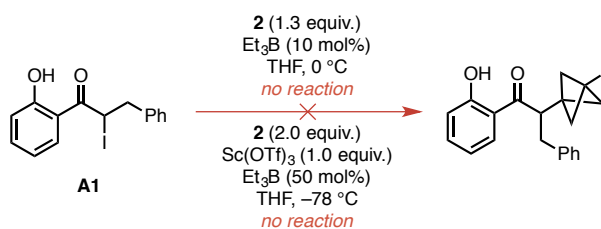
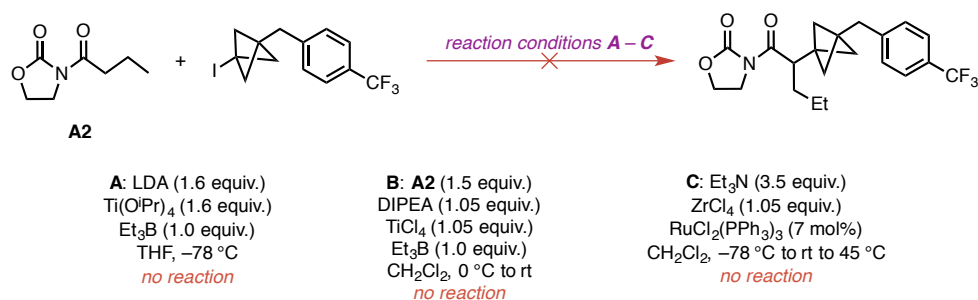
Reactions conducted on a 0.20 mmol scale, 0.8 mL of THF (0.25 M). ^aYields of isolated products.

^bEt₃B (30 mol%). ^cEt₃B (70 mol%). ^dEt₃B (10 mol%) added after every hour (three additions).

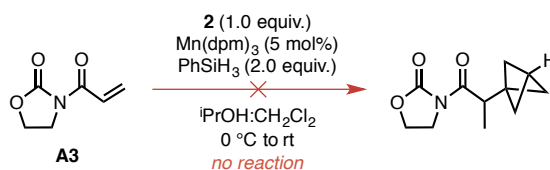
^eWith α -bromocarbonyl **105** (1.0 equiv.).

Table 8.4. ATRA of α -bromocarbonyl substrate **95** with [1.1.1]propellane **2**.

8.2.3 Other asymmetric radical-based strategies

Scheme 8.3. ATRA with **A1** and [1.1.1]propellane **2**.

Scheme 8.4. Radical alkylation of enolates.

Scheme 8.5. Radical alkylation with [1.1.1]propellane **2**.

8.3 Chapter 5

8.3.1 Attempted synthesis of HAT catalysts

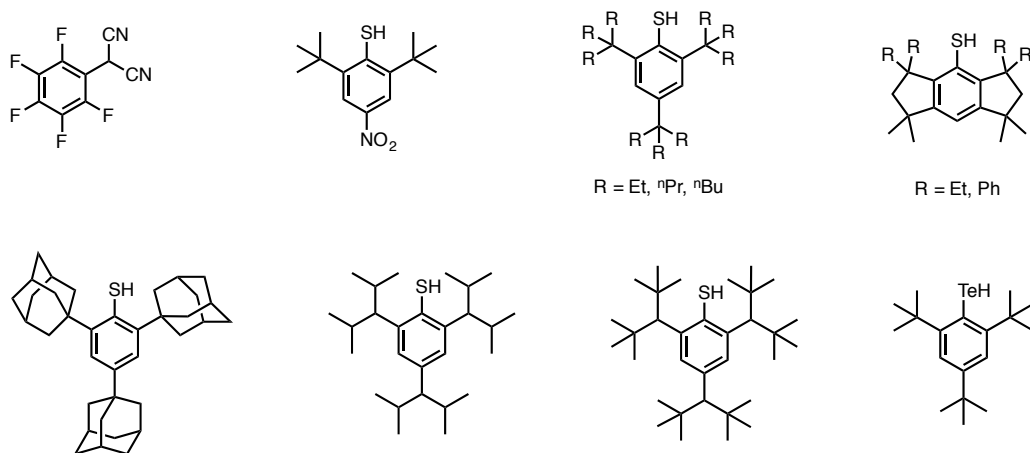
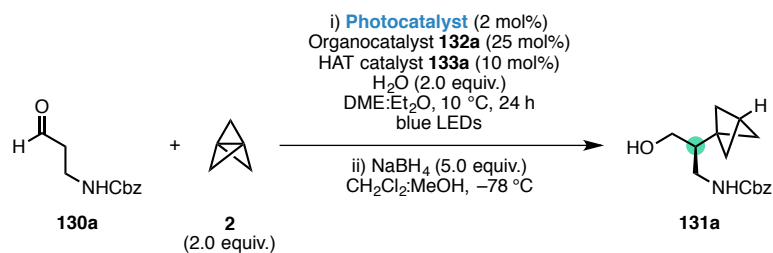


Figure 8.1. Unsuccessful synthesis of other HAT catalysts.

8.3.2 Optimization: Photocatalysts



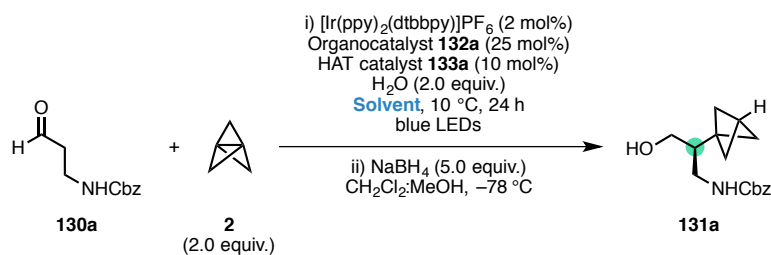
Entry	Photocatalyst	Yield (131a) ^a	ee
1	[Ir(ppy) ₂ (dtbbpy)]PF ₆	65%	86%
2	[Ir(dF(CF ₃)ppy) ₂ (dtbbpy)]PF ₆	38%	60%
3	[Ir(dF(CF ₃)ppy) ₂ (bpy)]PF ₆	36%	33%
4	[Ir(dF(CF ₃)ppy) ₂ (dCF ₃ bpy)]PF ₆	28%	67%
5	[Ir(dmppy) ₂ (dtbbpy)]PF ₆	53%	81%
6	<i>fac</i> -Ir(ppy) ₃	n.r.	—
7	Ir(dFppy) ₃	n.r.	—
8	Ir(4'-Fppy) ₃	n.r.	—
9	[Ru(bpy) ₃](PF ₆) ₂	n.r.	—
10	Mes-Acr-Me ⁺ ClO ₄ ⁻	n.r.	—
11	4CzIPN	n.r.	—
12 ^b	[Ir(ppy) ₂ (dtbbpy)]PF ₆	61%	92%
13 ^b	[Ir(dmppy) ₂ (dtbbpy)]PF ₆	56%	94%

Reactions conducted on a 0.15 mmol scale; DME:Et₂O (2:1). ^aYields of isolated products.

^bOctanal (1.0 equiv.) instead of **130a**; 0.20 mmol scale.

Table 8.5. Optimization of photocatalysts for the asymmetric ring-opening of [1.1.1]propellane **2**.

8.3.3 Optimization: Reaction concentrations and solvent ratios

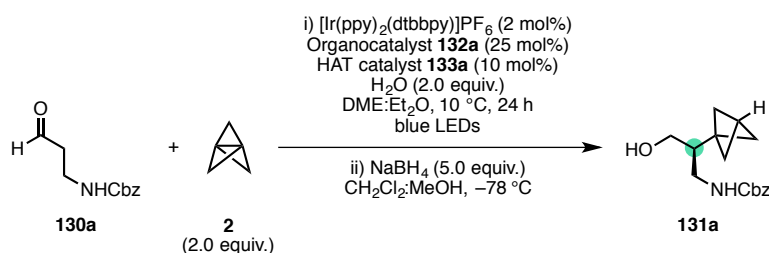


	Entry	Variation of conditions	Yield (131a) ^a	ee
co-solvent ^b	1	DME	65%	86%
	2	DCM	62%	73%
	3	MeCN	n.r.	—
	4	1,4-dioxane	46%	86%
	5	Et ₂ O	63%	90%
	6	THF	19%	80%
	7	MeOH	13%	69%
concentration ^c	8	DME : Et ₂ O (0.12 M)	40%	89%
	9	DME : Et ₂ O (0.20 M)	65%	86%
	10	DME : Et ₂ O (0.25 M)	38%	78%
solvent ratio ^d	11	DME : Et ₂ O (0.5 : 1.0)	59%	88%
	12	DME : Et ₂ O (1.0 : 1.0)	65%	86%
	13	DME : Et ₂ O (1.6 : 1.0)	66%	85%

Reactions conducted on a 0.15 mmol scale. ^aYields of isolated products. ^bRatio of co-solvent to Et₂O from [1.1.1]propellane **2** solution: 2:1; overall concentration: 0.20 M. ^cDME : Et₂O (2:1). ^dConcentration: 0.20 M.

Table 8.6. Optimization of solvents for the asymmetric ring-opening of [1.1.1]propellane **2**.

8.3.4 Optimization: Reaction stoichiometries and time



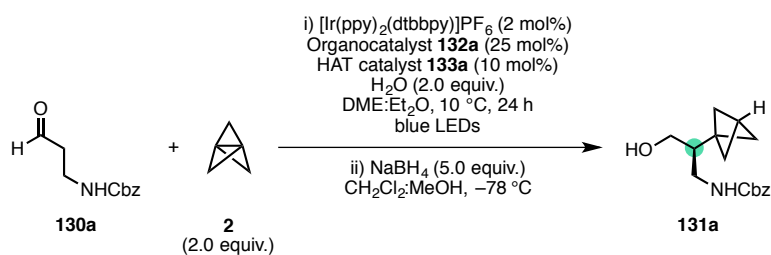
	Entry	Variation of conditions	Yield (131a) ^a	ee
HAT cat.	1	133a (10 mol%)	65%	86%
	2	133a (30 mol%)	70%	82%
	3 ^b	133a (50 mol%)	66%	83%
organocat	4	132a (20 mol%)	50%	85%
	5	132a (25 mol%)	65%	86%
	6	132a (30 mol%)	57%	89%
photocat.	7	$[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (1.0 mol%)	50%	82%
	8	$[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (2.0 mol%)	65%	86%
	9	$[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (2.5 mol%)	65%	85%
H_2O	10	H_2O (1.0 equiv.)	62%	88%
	11	H_2O (2.0 equiv.)	65%	86%
	12	H_2O (3.0 equiv.)	62%	83%
[1.1.1]propellane 2	13	2 (2.0 equiv.)	65%	86%
	14	2 (1.5 equiv.)	69%	87%
	15	2 (1.3 equiv.)	71%	86%
	16	2 (1.1 equiv.)	71%	87%
	17 ^c	2 (1.3 equiv.)	67%	89%
	18 ^c	2 (1.1 equiv.)	68%	90%
reaction time	19 ^c	17 h	61%	92%
	20 ^c	24 h	68%	90%
	21 ^c	46 h	68%	90%
aldehyde	22 ^d	octanal (1.3 equiv.)	88%	95%
	23 ^d	octanal (1.5 equiv.)	96%	95%
	24 ^d	130a (1.5 equiv.)	94%	88%

Reactions conducted on a 0.15 mmol scale; DME:Et₂O (1:1). ^aYields of isolated products. ^b0.25 mmol scale.

^cOctanal (1.0 equiv.) instead of **130a**; 0.20 mmol scale. ^d[1.1.1]Propellane **2** (1.0 equiv.); 0.20 mmol scale.

Table 8.7. Optimization of reagent/reactant stoichiometries and reaction time for the asymmetric ring-opening of [1.1.1]propellane **2**.

8.3.5 Control experiments



Entry	Variation of conditions	Yield (131a) ^a	ee
1	no photocatalyst	n.r.	—
2	no organocatalyst	n.r.	—
3	no HAT catalyst	trace	—
4	no light irradiation	n.r.	—

Reactions conducted on a 0.15 mmol scale; $\text{DME}:\text{Et}_2\text{O}$ (1:1). ^aYields of isolated products.

Table 8.8. Control experiments.

Supplementary information

Table of contents

9.1	General experimental considerations	164
9.2	Synthesis of [1.1.1]propellane	168
9.3	Chapter 2: Diastereoselective enolate reactions with chiral auxiliaries	169
9.3.1	General experimental procedures	169
9.3.2	Preliminary studies and reaction optimization	171
9.3.3	Reaction scope: BCP products	199
9.3.4	Reaction scope: 1,3-disubstituted BCP substrates and products	219
9.3.5	Auxiliary removal and derivatization of α -chiral BCP products	232
9.3.6	Synthesis of BCP analogues of bioactive molecules	247
9.3.7	Appendix	255
9.4	Chapter 3: Asymmetric atom transfer radical additions	258
9.4.1	General experimental procedures	258
9.4.2	Diastereoselective ATRA with [1.1.1]propellane	260
9.4.3	Enantioselective ATRA with [1.1.1]propellane	269
9.4.4	Chiral ligands	283
9.4.5	Appendix	284

9.5	Chapter 4: Photoredox-catalyzed atom transfer radical additions	286
9.5.1	General experimental procedures	286
9.5.2	Alkyl iodide substrates	288
9.5.3	Reaction scope: BCP products	302
9.6	Chapter 5: Asymmetric photoredox organocatalysis	316
9.6.1	General experimental procedures	316
9.6.2	HAT catalysts	320
9.6.3	Organocatalysts	341
9.6.4	Aldehyde substrates	362
9.6.5	Reaction scope: BCP products	378
9.6.6	Derivatization of α -chiral BCP products	426
9.7	X-ray crystallography	433
9.8	References	442

9.1 General experimental considerations

NMR Spectroscopy: Proton (^1H), carbon (^{13}C) and fluorine (^{19}F) NMR spectra were recorded on a Bruker AVIII HD 400, NEO 400, AVIII HD 500, AVII 500 or AVIII HD 600 spectrometer. Proton, carbon and fluorine chemical shifts (δ) are quoted in parts per million (ppm) to the nearest 0.01 ppm for ^1H and ^{19}F NMR spectra, and 0.1 ppm for ^{13}C spectra. ^1H NMR spectra were recorded using an internal deuterium lock for the residual protons in CDCl_3 ($\delta = 7.26$), toluene- d_8 ($\delta = 2.08$), methanol- d_4 ($\delta = 3.31$), dimethyl sulfoxide- d_6 (DMSO- d_6) ($\delta = 2.50$) or benzene- d_6 ($\delta = 7.16$). ^{13}C NMR spectra were recorded using an internal deuterium lock in CDCl_3 ($\delta = 77.16$), toluene- d_8 ($\delta = 20.43$), methanol- d_4 ($\delta = 49.00$), DMSO- d_6 ($\delta = 39.52$) or benzene- d_6 ($\delta = 128.06$). ^{19}F NMR spectra were not externally referenced. Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HSQC, HMBC and/or NOESY experiments. Peak multiplicities are defined as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sept (septet), m (multiplet), br (broad) and app (apparent). Coupling constants (J) are reported to the nearest 0.1 Hz. We would like to thank the University of Oxford Departmental NMR Service, Jos Kamps and Jonathan Yong for assistance in acquiring NMR spectra.

Mass Spectrometry: Low-resolution mass spectra were recorded on a Micromass LCT Premier Open Access using electrospray ionization (ESI). High-resolution mass spectra (HRMS) were recorded by the Departmental Mass Spectrometry Service, University of Oxford on a Thermo Scientific Exactive Mass Spectrometer (using a Waters Equity autosampler and pump) for ESI and an Agilent 7200 Accurate Mass QTOF GCMS (using a SIM Direct Insertion Probe) for electron ionization (EI) and

atmospheric-pressure chemical ionization (APCI). High-resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

Infrared Spectroscopy: Infrared spectra were obtained in CHCl_3 as solvent on a Bruker Tensor 27 FT-IR spectrometer. The sample was prepared as a thin film on a diamond ATR module. Wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1} . Only selected, characteristic IR absorption data are provided for each compound.

Melting Points: Melting points were obtained using a Griffin melting point apparatus and are uncorrected.

Polarimetry: Optical rotations were recorded on a Perkin Elmer 241 or 341 polarimeter with a path length of 1 dm (using the sodium D line, 589 nm). $[\alpha]_{\text{D}}$ are reported in units of $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. Concentrations are reported in g/100 mL. Temperatures are reported in $^{\circ}\text{C}$.

X-ray crystallography: Details of instrumentation and techniques are reported in Section 9.7.

Chromatography: Column chromatography refers to normal phase column chromatography and was performed on silica gel obtained from Merck (Silica gel Si 60, 0.040-0.063 mm) under a positive pressure of nitrogen, using the stated solvent system. Analytical thin-layer chromatography (TLC) was used to monitor reaction progress and performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F₂₅₄ plates)

with visualization by ultraviolet light (254 nm) and/or by staining with vanillin, ninhydrin, phosphomolybdic acid and potassium permanganate. Retention factors (R_f) are reported with the solvent system in parentheses. High performance liquid chromatography (HPLC) for enantiomeric excess (ee) determination was carried out using a Phenomenex Lux i-Amylose-1 (250 mm $\times$ 4.6 mm ID) or DAICEL CHIRALPAK IA, IB or IC (250 $\times$ 4.6 mm) column (wavelength: 210 nm or 250 nm) with purified material. Chiral supercritical fluid chromatography (SFC) separations were conducted on a Waters Acquity UPC system using the Empower software with a CHIRALPAK ID (250 $\times$ 4.6 mm) column.

Materials/procedures: All air- or moisture-sensitive reactions were carried out with anhydrous solvents in flame-dried glassware under an inert atmosphere of argon. Light-sensitive reactions were carried out under aluminium foil protection. Heating was performed using an oil or sand bath. Anhydrous tetrahydrofuran (THF), dichloromethane, diethyl ether, dimethoxyethane (DME), triethylamine, chloroform, pyridine, toluene, *N,N*-dimethylformamide (DMF), acetonitrile and 1,4-dioxane were collected fresh from an mBraun SPS-800 solvent purification system, having been passed through anhydrous alumina columns. All other commercially available reagents and solvents, where appropriate, were dried and purified before use using standard procedures. Petroleum ether refers to the fraction of light petroleum ether boiling at 40 – 60 °C.

Photochemical equipment and setup:

Three LED lamps were used:

- Tingkam[®] Waterproof 5M 5050 SMD RGB LED Strips fixed to the inside of a crystallization dish.
- Evoluchem[™] 18 W LED (405 nm). The vial was positioned on a stir plate approximately 5 cm away from the LED and under a strong flow of nitrogen to dissipate the heat generated from the LED.
- Evoluchem[™] 18 W LED (450 – 455 nm). For reactions run at room temperature, the vial was positioned on a stir plate approximately 5 cm away from the LED and under a strong flow of nitrogen to dissipate the heat generated by the LED. For reactions run at lower temperatures (0 °C, 10 °C and 20 °C), the vial was positioned on a stir plate approximately 5 cm away from the LED and submerged in a cooling bath (isopropanol) in a large crystallization dish with a Huber TC50E immersion cooler.

9.2 Synthesis of [1.1.1]propellane



According to the procedure of Baran *et al.*^[1] To a solution of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane **28** (28.2 g, 95.0 mmol, 1.0 equiv.) in Et₂O (60 mL) at –40 °C under an inert atmosphere was added phenyllithium (1.9 M in dibutyl ether, 100 mL, 190 mmol, 2.0 equiv.) *via* cannula over 30 min. The resulting mixture was then stirred at 0 °C for 2 h and distilled in a rotary evaporator at room temperature, having both the condenser and collection flask of the rotary evaporator cooled to –78 °C. The title compound was collected as a clear, colorless solution (0.62 M in Et₂O, 85.0 mL, 52.7 mmol, 56%) and used in subsequent reactions as a solution in Et₂O. The yield and approximate concentration of the solution was calculated using quantitative NMR with DCE as an internal standard. 0.2 mL of the solution of [1.1.1]propellane **2** in Et₂O was diluted with DCE (50 μL) and CDCl₃ (0.5 mL). The ratio of DCE (4H) to [1.1.1]propellane **2** (6H) was determined and used to calculate the approximate concentration of the solution. Two runs were carried out and the average used as the final approximated concentration.

¹H NMR (200 MHz, CDCl₃) δ 1.94 (6H, s).

Spectroscopic data in agreement with that reported previously.^[2]

9.3 Chapter 2: Diastereoselective enolate reactions with chiral auxiliaries

9.3.1 General experimental procedures

General procedure A: Oxazolidinone acylation

Adapted from the procedure of Sibi et al.^[3] To a solution of the oxazolidinone (1.0 equiv.) in THF (2 mL/mmol of oxazolidinone) at the stated temperature under an inert atmosphere was added *n*-butyllithium (1.6 M or 2.5 M in hexane, 1.2 equiv.) dropwise. After stirring for the stated time at the same temperature, the acyl bromide or acyl chloride (1.0 equiv.) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to room temperature and, after stirring for the stated time, the reaction was quenched with NH₄Cl (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (× 2). The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was either used in a subsequent reaction without further purification or purified by column chromatography.

General procedure B: Finkelstein reaction

Adapted from the procedure of Porter et al.^[4] To a solution of the alkyl bromide (1.0 equiv.) in acetone (10 mL/mmol of alkyl bromide) was added sodium iodide (3.0 equiv.). The reaction was stirred under reflux (70 °C) for the stated time, after which the reaction mixture was washed with water and the aqueous phase extracted with CH₂Cl₂ (× 3). The combined organic extracts were washed with

Na₂S₂O₃ (aq., sat.), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by column chromatography.

General procedure C: ATRA of organohalide with [1.1.1]propellane 2

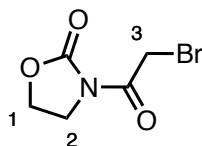
A capped vial was charged with the organohalide (1.0 equiv.) and solvent, and was cooled to the stated temperature. [1.1.1]Propellane **2** (solution in Et₂O, 1.3 equiv.) was added and the mixture was stirred for 2 – 3 min at the stated temperature. Et₃B (1 M in hexane, 0.1 equiv.) was syringed into the mixture and the reaction mixture was left to stir at the stated temperature. The reaction was monitored by TLC and upon completion, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography or recrystallization.

General procedure D: Diastereoselective enolate reaction

Adapted from the procedure of Evans et al.^[5] To a solution of the oxazolidinone substrate (1.0 equiv.) in THF (7 mL/mmol of oxazolidinone) at –78 °C under an inert atmosphere was added sodium bis(trimethylsilyl)amide (2.0 M in THF, 1.1 equiv.) dropwise and the reaction mixture left to stir for 30 min at –78 °C. The electrophile (3.0 equiv.) was then added dropwise and the reaction mixture left to stir for the stated time at the stated temperature. Upon completion, NH₄Cl (aq., sat.) was then added and the aqueous phase extracted with CH₂Cl₂ (× 3). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography.

9.3.2 Preliminary studies and reaction optimization

3-(2-Bromoacetyl)oxazolidin-2-one, S1



2-Oxazolidinone (1.74 g, 20.0 mmol, 1.0 equiv.) and *n*-butyllithium (2.5 M in hexanes, 9.60 mL, 24.0 mmol, 1.2 equiv.) in THF (35 mL) were submitted to **General Procedure A** for 1 h at 0 °C. Bromoacetyl bromide (1.74 mL, 20.0 mmol, 1.0 equiv.) was then added at 0 °C and the reaction mixture was allowed to warm to room temperature over 3 h. The title compound was obtained as a yellow oil, which was used without further purification (3.26 g, 15.6 mmol, 78%).

R_f 0.64 (EtOAc), [UV, vanillin]

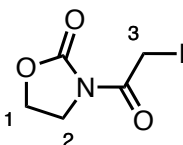
m.p. 72 – 74 °C

^1H NMR (400 MHz, CDCl_3) δ 4.52 (s, 2H, H3), 4.49 (t, J = 8.1 Hz, 2H, H1), 4.09 (t, J = 8.1 Hz, 2H, H2).

^{13}C NMR (101 MHz, CDCl_3) δ 166.2, 153.2, 62.6, 42.9, 27.7.

Spectroscopic data in agreement with that reported previously.^[6]

3-(2-Iodoacetyl)oxazolidin-2-one, 58



3-(2-Bromoacetyl)oxazolidin-2-one **S1** (3.25 g, 15.6 mmol, 1.0 equiv.) and sodium iodide (7.04 g, 46.9 mmol, 3.0 equiv.) in acetone (160 mL) were submitted to **General**

Procedure B for 16 h. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a pale yellow solid (2.20 g, 8.61 mmol, 55%).

R_f 0.14 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 50 – 54 °C

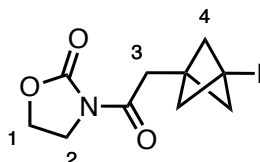
¹H NMR (400 MHz, CDCl₃) δ 4.47 (t, *J* = 8.1 Hz, 2H, H1), 4.41 (s, 2H, H3), 4.06 (t, *J* = 8.1 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 168.1, 153.0, 62.3, 43.0, –3.8.

HRMS (APCI) Found [M+H]⁺ = 255.9467; C₅H₇O₃N¹²⁷I requires 255.9465.

IR (film) ν_{max} /cm^{–1} 3068, 2984, 2919, 1765, 1682, 1472, 1389, 1369, 1325, 1217, 1151, 1084, 1045, 1025, 966, 853, 756, 739, 610.

3-(2-(3-Iodobicyclo[1.1.1]pentan-1-yl)acetyl)oxazolidin-2-one, **59**



3-(2-Iodoacetyl)oxazolidin-2-one **58** (0.13 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.68 M in Et₂O, 0.96 mL, 0.65 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 50 μL, 50 μmol, 0.1 equiv.) in CH₂Cl₂ (0.3 mL) were submitted to **General Procedure C** for 1.5 h at 0 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a yellow solid (0.12 g, 0.39 mmol, 78%).

R_f 0.24 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 72 – 74 °C

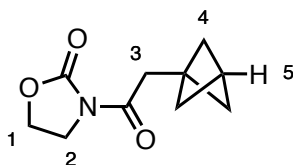
¹H NMR (500 MHz, CDCl₃) δ 4.41 (t, *J* = 8.1 Hz, 2H, H1), 4.00 (t, *J* = 8.1 Hz, 2H, H2), 3.21 (s, 2H, H3), 2.35 (s, 6H, H4).

¹³C NMR (126 MHz, CDCl₃) δ 170.2, 153.5, 62.2 (3C), 61.2, 42.5, 37.4, 29.9, 6.4.

HRMS (APCI) Found [M+H]⁺ = 321.9933; C₁₀H₁₃O₃N¹²⁷I requires 321.9935.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2982, 2916, 1769, 1700, 1474, 1386, 1297, 1221, 1169, 1044, 1015, 956, 831, 756, 712, 648.

3-(2-(Bicyclo[1.1.1]pentan-1-yl)acetyl)oxazolidin-2-one, **61**



3-(2-Iodoacetyl)oxazolidin-2-one **58** (0.13 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.68 M in Et₂O, 0.96 mL, 0.65 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 50 μL, 50 μmol, 0.1 equiv.) in CH₂Cl₂ (0.3 mL) were submitted to **General Procedure C** at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo*. The capped vial containing 3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetyl)oxazolidin-2-one **59** was charged with TTMSS (0.31 mL, 1.0 mmol, 2.0 equiv.) and THF (0.5 mL). After stirring for 2 – 3 min at room temperature, Et₃B (1 M in hexane, 50 μL, 50 μmol, 0.1 equiv.) was syringed into the reaction mixture. The reaction mixture was left to stir at room temperature for 18 h and was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a yellow oil (33 mg, 0.17 mmol, 34% over two steps).

R_f 0.26 (petroleum ether/EtOAc, 7:3), [UV, phosphomolybdic acid]

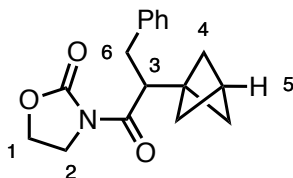
¹H NMR (400 MHz, CDCl₃) δ 4.38 (t, *J* = 8.1 Hz, 2H, H1), 4.00 (t, *J* = 8.1 Hz, 2H, H2), 3.12 (s, 2H, H3), 2.47 (s, 1H, H5), 1.79 (s, 6H, H4).

¹³C NMR (101 MHz, CDCl₃) δ 171.4, 153.5, 62.0, 51.5 (3C), 42.5, 41.1, 38.1, 28.5.

HRMS (ESI⁺) Found [M+Na]⁺ = 218.0788; C₁₀H₁₃O₃NNa requires 218.0788.

IR (film) ν_{max} /cm⁻¹ 2967, 2909, 2873, 1776, 1698, 1387, 1338, 1221, 1201, 1142, 1040, 839, 760.

3-(2-(Bicyclo[1.1.1]pentan-1-yl)-3-phenylpropanoyl)oxazolidin-2-one, 60b



3-(2-(Bicyclo[1.1.1]pentan-1-yl)acetyl)oxazolidin-2-one **61** (33 mg, 0.17 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 95 μ L, 0.19 mmol, 1.1 equiv.) and benzyl bromide (61 μ L, 0.51 mmol, 3.0 equiv.) in THF (0.6 mL) were submitted to **General Procedure D** at -78 °C. After the addition of benzyl bromide, the reaction mixture was left to stir for 3 h at -78 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a white solid (16 mg, 57 μ mol, 34%).

R_f 0.31 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 224 – 228 °C

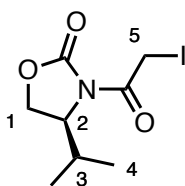
¹H NMR (400 MHz, CDCl₃) δ 7.31 – 7.10 (m, 5H, ArH), 4.51 (dd, *J* = 10.7, 4.8 Hz, 1H, H3), 4.35 – 4.16 (m, 2H, H1), 3.97 – 3.79 (m, 2H, H2), 3.00 (dd, *J* = 13.8, 10.7 Hz, 1H, H6), 2.78 (dd, *J* = 13.8, 4.8 Hz, 1H, H6), 2.51 (s, 1H, H5), 1.76 (dd, *J* = 9.9, 9.1 Hz, 6H, H4).

^{13}C NMR (101 MHz, CDCl_3) δ 173.3, 153.2, 139.6, 129.0 (2C), 128.4 (2C), 126.3, 61.8, 49.8 (3C), 46.0, 45.3, 42.6, 34.9, 27.3.

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 308.1257$; $\text{C}_{17}\text{H}_{19}\text{O}_3\text{NNa}$ requires 308.1257.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2980, 1758, 1696, 1478, 1382, 1270, 1225, 1196, 1182, 1104, 1043, 939, 758, 744, 697.

(S)-3-(2-Iodoacetyl)-4-isopropylloxazolidin-2-one, 62a



(S)-4-Isopropylloxazolidin-2-one (2.58 g, 20.0 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 15.0 mL, 24.0 mmol, 1.2 equiv.) in THF (40 mL) were submitted to **General Procedure A** for 1 h at 0 °C. Bromoacetyl bromide (1.74 mL, 20.0 mmol, 1.0 equiv.) was then added at 0 °C and the reaction mixture was allowed to warm to room temperature over 4.5 h. (S)-3-(2-Bromoacetyl)-4-isopropylloxazolidin-2-one was obtained as a yellow oil and used without further purification.

(S)-3-(2-Bromoacetyl)-4-isopropylloxazolidin-2-one (4.68 g, 18.7 mmol, 1.0 equiv.) and sodium iodide (8.41 g, 56.1 mmol, 3.0 equiv.) in acetone (190 mL) were submitted to **General Procedure B** for 15 h. Purification by column chromatography (SiO_2 , petroleum ether/EtOAc, 9:1) afforded the title compound as an off-white solid (1.11 g, 3.73 mmol, 19% over two steps).

R_f 0.43 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 35 – 40 °C

¹H NMR (400 MHz, CDCl₃) δ 4.58 (d, *J* = 9.3 Hz, 1H, H5), 4.48 – 4.43 (m, 1H, H2), 4.33 (t, *J* = 8.7 Hz, 1H, H1), 4.28 – 4.21 (m, 2H, H1 and H5), 2.41 (septd, *J* = 7.0, 3.6 Hz, 1H, H3), 0.93 (d, *J* = 7.0 Hz, 6H, H4).

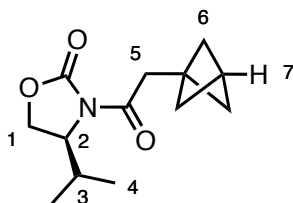
¹³C NMR (101 MHz, CDCl₃) δ 168.1, 153.4, 63.6, 58.7, 28.2, 18.1, 14.9, –2.9.

HRMS (APCI) Found [M+H]⁺ = 297.9931; C₈H₁₃O₃N¹²⁷I requires 297.9935.

IR (film) ν_{max}/cm^{–1} 2964, 1775, 1691, 1388, 1366, 1317, 1207, 1159, 1083, 1023, 973.

[α]_D²⁵ +69.9 (*c* = 1.0, CHCl₃)

(*S*)-3-(2-(Bicyclo[1.1.1]pentan-1-yl)acetyl)-4-isopropylloxazolidin-2-one, 63a



(*S*)-3-(2-Iodoacetyl)-4-isopropylloxazolidin-2-one **62a** (0.15 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (1.07 M in Et₂O, 0.61 mL, 0.65 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 50 μL, 50 μmol, 0.1 equiv.) in CH₂Cl₂ (0.3 mL) were submitted to **General Procedure C** at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo*. The capped vial containing (*S*)-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetyl)-4-isopropylloxazolidin-2-one was charged with TTMS (0.46 mL, 1.5 mmol, 3.0 equiv.) and THF (0.5 mL). After stirring for 2 – 3 min at room temperature, Et₃B (1 M in hexane, 0.25 mL, 0.25 mmol, 0.5 equiv.) was syringed into the reaction mixture. The reaction mixture was left to stir at room temperature for 4.5 h and was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as a light yellow solid (61 mg, 0.26 mmol, 51% over two steps).

R_f 0.52 (petroleum ether/EtOAc, 7:3), [UV, phosphomolybdic acid]

m.p. 28 – 30 °C

¹H NMR (500 MHz, CDCl₃) δ 4.43 (dt, *J* = 8.1, 3.4 Hz, 1H, H2), 4.24 (dd, *J* = 9.1, 8.1 Hz, 1H, H1), 4.20 (dd, *J* = 9.1, 3.0 Hz, 1H, H1), 3.24 (d, *J* = 14.8 Hz, 1H, H5), 3.04 (d, *J* = 14.8 Hz, 1H, H5), 2.49 (s, 1H, H7), 2.41 – 2.32 (m, 1H, H3), 1.82 (s, 6H, H6), 0.91 (dd, *J* = 16.2, 7.0 Hz, 6H, H4).

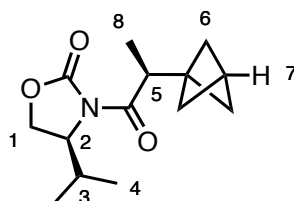
¹³C NMR (126 MHz, CDCl₃) δ 171.2, 154.1, 63.3, 58.6, 51.6 (3C), 41.3, 38.5, 28.6, 28.6, 18.2, 14.8.

HRMS (ESI⁺) Found [M+Na]⁺ = 260.1257; C₁₃H₁₉O₃NNa requires 260.1257.

IR (film) ν_{max} /cm⁻¹ 2966, 2909, 2873, 1781, 1700, 1388, 1373, 1232, 1203, 1023.

[α]_D²⁵ +70.8 (*c* = 0.5, CHCl₃)

(*S*)-3-((*S*)-2-(Bicyclo[1.1.1]pentan-1-yl)propanoyl)-4-isopropylloxazolidin-2-one, 64a



(*S*)-3-(2-(Bicyclo[1.1.1]pentan-1-yl)acetyl)-4-isopropylloxazolidin-2-one **63a** (42 mg, 0.17 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 0.10 mL, 0.19 mmol, 1.1 equiv.) and iodomethane (32 μ L, 0.52 mmol, 3.0 equiv.) in THF (0.6 mL) were submitted to **General Procedure D** at –78 °C. After the addition of iodomethane, the reaction mixture was left to stir for 6 h at –78 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as a yellow oil (15 mg, 61 μ mol, 36%).

R_f 0.50 (petroleum ether/EtOAc, 7:3), [UV, phosphomolybdic acid]

m.p. 209 – 211 °C

¹H NMR (500 MHz, CDCl₃) δ 4.41 (dt, *J* = 7.7, 4.0 Hz, 1H, H2), 4.26 – 4.17 (m, 2H, H1), 4.03 (q, *J* = 6.9 Hz, 1H, H5), 2.48 (s, 1H, H7), 2.37 (septd, *J* = 7.0, 4.0 Hz, 1H, H3), 1.72 (dd, *J* = 9.5, 1.4 Hz, 3H, H6), 1.70 (dd, *J* = 9.5, 1.4 Hz, 3H, H6), 1.13 (d, *J* = 6.9 Hz, 3H, H8), 0.91 (d, *J* = 7.0 Hz, 3H, H4), 0.87 (d, *J* = 7.0 Hz, 3H, H4).

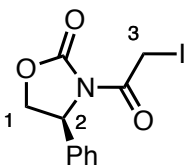
¹³C NMR (126 MHz, CDCl₃) δ 174.8, 154.0, 63.4, 58.9, 49.4 (3C), 45.9, 38.8, 28.8, 27.1, 18.2, 14.8, 13.8.

HRMS (ESI⁺) Found [M+H]⁺ = 252.1596; C₁₄H₂₂O₃N requires 252.1594.

IR (film) ν_{max}/cm⁻¹ 2964, 2925, 2872, 1784, 1703, 1375, 1220, 773.

[α]_D²⁵ +37.8 (*c* = 0.2, CHCl₃)

(S)-3-(2-Iodoacetyl)-4-phenyloxazolidin-2-one, 62b



(*S*)-4-Phenyloxazolidin-2-one (3.26 g, 20.0 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 15.0 mL, 24.0 mmol, 1.2 equiv.) in THF (40 mL) were submitted to **General Procedure A** for 1 h at 0 °C. Bromoacetyl bromide (1.74 mL, 20.0 mmol, 1.0 equiv.) was then added at 0 °C and the reaction mixture was allowed to warm to room temperature over 5 h. (*S*)-3-(2-Bromoacetyl)-4-phenyloxazolidin-2-one was obtained as a yellow oil and used without further purification.

(*S*)-3-(2-Bromoacetyl)-4-phenyloxazolidin-2-one (5.32 g, 18.7 mmol, 1.0 equiv.) and sodium iodide (8.42 g, 56.2 mmol, 3.0 equiv.) in acetone (190 mL) were submitted to **General Procedure B** for 15 h. Purification by column chromatography (SiO₂,

petroleum ether/EtOAc, 19:1) afforded the title compound as a light yellow solid (1.29 g, 3.91 mmol, 20% over two steps).

R_f 0.33 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 120 – 122 °C

¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.28 (m, 5H, ArH), 5.43 (dd, *J* = 8.9, 4.0 Hz, 1H, H2), 4.74 (t, *J* = 8.9 Hz, 1H, H1), 4.51 (d, *J* = 9.5 Hz, 1H, H3), 4.32 (dd, *J* = 8.9, 4.0 Hz, 1H, H1), 4.28 (d, *J* = 9.5 Hz, 1H, H3).

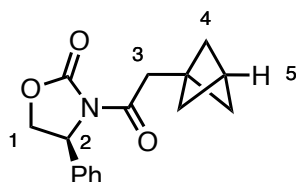
¹³C NMR (126 MHz, CDCl₃) δ 167.3, 153.1, 138.2, 129.4 (2C), 129.2, 126.1 (2C), 70.2, 58.0, –2.9.

HRMS (APCI) Found [M+H]⁺ = 331.9774; C₁₁H₁₁O₃N¹²⁷I requires 331.9778.

IR (film) ν_{max}/cm^{–1} 1778, 1698, 1386, 1329, 1203, 1153, 1082, 762, 699.

[α]_D²⁵ +59.9 (*c* = 1.0, CHCl₃)

(S)-3-(2-(Bicyclo[1.1.1]pentan-1-yl)acetyl)-4-phenyloxazolidin-2-one, 63b



(S)-3-(2-Iodoacetyl)-4-phenyloxazolidin-2-one **62b** (0.17 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (1.07 M in Et₂O, 0.61 mL, 0.65 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 50 μL, 50 μmol, 0.1 equiv.) in CH₂Cl₂ (0.3 mL) were submitted to **General Procedure C** at 0 °C. After 1.5 h, the reaction mixture was concentrated *in vacuo*. The capped vial containing (S)-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetyl)-4-phenyloxazolidin-2-one was charged with TTMSS (0.46 mL, 1.5 mmol, 3.0 equiv.) and THF (0.5 mL). After stirring for 2 – 3 min at room temperature, Et₃B (1 M in hexane,

0.25 mL, 0.25 mmol, 0.5 equiv.) was syringed into the reaction mixture. The reaction mixture was left to stir at room temperature for 4.5 h and was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as a white solid (52 mg, 0.19 mmol, 38% over two steps).

R_f 0.48 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 102 – 106 °C

¹H NMR (500 MHz, CDCl₃) δ 7.42 – 7.28 (m, 5H, ArH), 5.43 (dd, *J* = 8.8, 3.6 Hz, 1H, H2), 4.67 (t, *J* = 8.8 Hz, 1H, H1), 4.29 (dd, *J* = 8.8, 3.6 Hz, 1H, H1), 3.23 (d, *J* = 14.8 Hz, 1H, H3), 3.05 (d, *J* = 14.8 Hz, 1H, H3), 2.43 (s, 1H, H5), 1.74 (dd, *J* = 9.4, 1.6 Hz, 3H, H4), 1.71 (dd, *J* = 9.4, 1.6 Hz, 3H, H4).

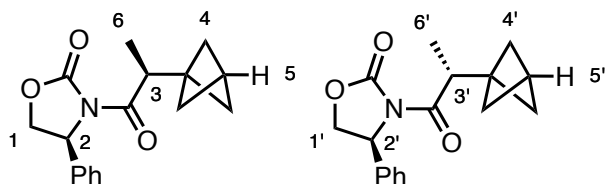
¹³C NMR (126 MHz, CDCl₃) δ 170.6, 153.7, 139.3, 129.3 (2C), 128.9, 126.3 (2C), 69.9, 57.7, 51.6 (3C), 41.2, 38.5, 28.5.

HRMS (ESI⁺) Found [M+Na]⁺ = 294.1101; C₁₆H₁₇O₃NNa requires 294.1101.

IR (film) ν_{max} /cm⁻¹ 2967, 2909, 2872, 1781, 1704, 1384, 1330, 1199, 1138.

[α]_D²⁵ +78.5 (*c* = 0.1, CHCl₃)

(4*S*)-3-(2-(Bicyclo[1.1.1]pentan-1-yl)propanoyl)-4-phenyloxazolidin-2-one, 64b



(*S*)-3-(2-(Bicyclo[1.1.1]pentan-1-yl)acetyl)-4-phenyloxazolidin-2-one **63b** (88 mg, 0.32 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 0.18 mL, 0.36 mmol, 1.1 equiv.) and iodomethane (60 μL, 0.96 mmol, 3.0 equiv.) in THF (1.2 mL) were submitted to **General Procedure D** at –78 °C. After the addition of

iodomethane, the reaction mixture was left to stir for 6 h at $-78\text{ }^{\circ}\text{C}$. Purification by column chromatography (SiO_2 , petroleum ether/EtOAc, 9:1) afforded the title compound as a white solid (27 mg, 94 μmol , 29%, 3:1 *dr*).

R_f 0.45, 0.55 (petroleum ether/EtOAc, 7:3), [UV, phosphomolybdic acid]

m.p. 84 – 88 $^{\circ}\text{C}$

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 286.1436$; $\text{C}_{17}\text{H}_{20}\text{O}_3\text{N}$ requires 286.1438.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2970, 2909, 2873, 1780, 1703, 1382, 1232, 1198, 703.

$[\alpha]_{\text{D}}^{25} +136.5$ ($c = 0.1$, CHCl_3)

Diastereomer 1 (*S*)-64b

^1H NMR (500 MHz, CDCl_3) δ 7.41 – 7.27 (m, 5H, Ar*H*), 5.41 (dd, $J = 8.7, 3.3$ Hz, 1H, H2), 4.66 (t, $J = 8.7$ Hz, 1H, H1), 4.26 (dd, $J = 8.7, 3.3$ Hz, 1H, H1), 4.03 (q, $J = 6.9$ Hz, 1H, H3), 2.49 (s, 1H, H5), 1.74 (dd, $J = 9.5, 1.6$ Hz, 3H, H4), 1.70 (dd, $J = 9.5, 1.6$ Hz, 3H, H4), 1.04 (d, $J = 6.9$ Hz, 3H, H6).

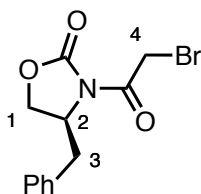
^{13}C NMR (126 MHz, CDCl_3) δ 174.2, 153.7, 139.5, 129.4 (2C), 128.8, 125.8 (2C), 69.9, 57.9, 49.4 (3C), 45.8, 39.0, 27.1, 13.5.

Diastereomer 2 (*R*)-64b

^1H NMR (500 MHz, CDCl_3) δ 7.43 – 7.29 (m, 5H, Ar*H'*), 5.44 (dd, $J = 9.0, 4.1$ Hz, 1H, H2'), 4.67 (t, $J = 9.0$ Hz, 1H, H1'), 4.35 (dd, $J = 9.0, 4.1$ Hz, 1H, H1'), 4.04 (q, $J = 6.8$ Hz, 1H, H3'), 2.35 (s, 1H, H5'), 1.54 (dd, $J = 9.6, 1.4$ Hz, 3H, H4'), 1.50 (dd, $J = 9.6, 1.4$ Hz, 3H, H4'), 1.04 (d, $J = 6.8$ Hz, 3H, H6').

^{13}C NMR (126 MHz, CDCl_3) δ 174.2, 153.7, 139.5, 129.4 (2C), 128.8, 125.8 (2C), 69.9, 57.9, 49.4 (3C), 45.8, 39.0, 27.1, 13.5.

(S)-4-Benzyl-3-(2-bromoacetyl)oxazolidin-2-one, S2



Adapted from the procedure of Falck et al.^[7] To a solution of (S)-4-benzyl-2-oxazolidinone (2.66 g, 15.0 mmol, 1.0 equiv.) in THF (28 mL) at -78°C under an inert atmosphere was added *n*-butyllithium (2.5 M in hexanes, 6.60 mL, 16.5 mmol, 1.1 equiv.) dropwise. After stirring at -78°C for 1 h, bromoacetyl bromide (1.57 mL, 18.0 mmol, 1.2 equiv.) was added dropwise to the reaction mixture and the mixture was allowed to warm to room temperature. After 4 h, the reaction was quenched with NH_4Cl (aq., sat., 20 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , petroleum ether/EtOAc, 7:3) afforded the title compound as a light yellow solid (3.42 g, 11.5 mmol, 77%).

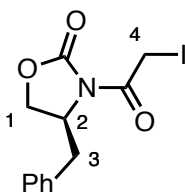
R_f 0.43 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.41 – 7.18 (m, 5H, ArH), 4.70 (ddt, $J = 9.6, 7.5, 3.4$ Hz, 1H, H2), 4.55 (d, $J = 2.9$ Hz, 2H, H4), 4.29 – 4.21 (m, 2H, H1), 3.33 (dd, $J = 13.4, 3.4$ Hz, 1H, H3), 2.81 (dd, $J = 13.4, 9.6$ Hz, 1H, H3).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 166.1, 153.1, 134.9, 129.6 (2C), 129.2 (2C), 127.7, 66.8, 55.6, 37.7, 28.4.

Spectroscopic data in agreement with that reported previously.^[7]

(S)-4-Benzyl-3-(2-iodoacetyl)oxazolidin-2-one, 62c



(S)-4-Benzyl-3-(2-bromoacetyl)oxazolidin-2-one **S2** (0.89 g, 3.0 mmol, 1.0 equiv.) and sodium iodide (1.3 g, 9.0 mmol, 3.0 equiv.) in acetone (38 mL) were submitted to **General Procedure B** for 20 h. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a white solid (0.57 g, 1.6 mmol, 55%).

R_f 0.43 (petroleum ether/EtOAc, 7:3), [UV]

m.p. 82 – 84 °C

¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.19 (m, 5H, ArH), 4.70 (ddt, *J* = 9.7, 7.5, 3.4 Hz, 1H, H2), 4.49 (d, *J* = 9.8 Hz, 1H, H4), 4.40 (d, *J* = 9.8 Hz, 1H, H4), 4.30 – 4.18 (m, 2H, H1), 3.32 (dd, *J* = 13.4, 3.4 Hz, 1H, H3), 2.79 (dd, *J* = 13.4, 9.7 Hz, 1H, H3).

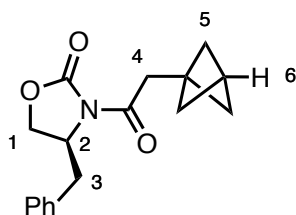
¹³C NMR (101 MHz, CDCl₃) δ 168.0, 152.9, 134.9, 129.6 (2C), 129.2 (2C), 127.6, 66.4, 55.5, 37.4, –2.8.

HRMS (APCI) Found [M+H]⁺ = 345.9934; C₁₂H₁₃O₃N¹²⁷I requires 345.9935.

IR (film) *v*_{max}/cm^{–1} 1777, 1690, 1388, 1355, 1313, 1200, 1149, 1088, 995, 740, 703, 616.

[*α*]_D²⁵ +52.9 (*c* = 1.0, CHCl₃)

(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)oxazolidin-2-one, 63c



(S)-4-Benzyl-3-(2-iodoacetyl)oxazolidin-2-one **62c** (0.17 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (1.07 M in Et₂O, 0.61 mL, 0.65 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 50 μL, 50 μmol, 0.1 equiv.) in CH₂Cl₂ (0.3 mL) were submitted to **General Procedure C** at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo*. The capped vial containing (S)-4-benzyl-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetyl)oxazolidin-2-one was charged with TTMSS (0.46 mL, 1.5 mmol, 3.0 equiv.) and THF (0.5 mL). After stirring for 2 – 3 min at room temperature, Et₃B (1 M in hexane, 0.25 mL, 0.25 mmol, 0.5 equiv.) was syringed into the reaction mixture. The reaction mixture was left to stir at room temperature for 6.5 h and was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 17:3) afforded the title compound as a white solid (56 mg, 0.20 mmol, 40% over two steps).

R_f 0.45 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 80 – 84 °C

¹H NMR (400 MHz, CDCl₃) δ 7.37 – 7.20 (m, 5H, ArH), 4.67 (ddt, *J* = 10.1, 6.7, 3.6 Hz, 1H, H2), 4.21 – 4.12 (m, 2H, H1), 3.35 (dd, *J* = 13.3, 3.6 Hz, 1H, H3), 3.22 (d, *J* = 15.1 Hz, 1H, H4), 3.11 (d, *J* = 15.1 Hz, 1H, H4), 2.70 (dd, *J* = 13.3, 10.1 Hz, 1H, H3), 2.51 (s, 1H, H6), 1.84 (s, 6H, H5).

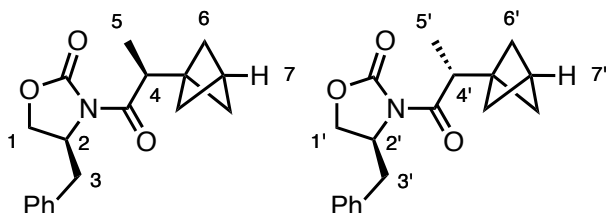
¹³C NMR (101 MHz, CDCl₃) δ 171.2, 153.5, 135.5, 129.6 (2C), 129.1 (2C), 127.5, 66.2, 55.4, 51.6 (3C), 41.2, 38.5, 38.2, 28.6.

HRMS (ESI⁺) Found [M+Na]⁺ = 308.1257; C₁₇H₁₉O₃NNa requires 308.1257.

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2980, 2908, 1782, 1699, 1384, 1238, 1076, 956, 772.

$[\alpha]_{\text{D}}^{25} +42.0$ ($c = 0.1$, CHCl_3)

(4*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one, 64c



(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)oxazolidin-2-one **63c** (45 mg, 0.16 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 87 μL , 0.17 mmol, 1.1 equiv.) and iodomethane (30 μL , 0.48 mmol, 3.0 equiv.) in THF (0.6 mL) were submitted to **General Procedure D** at -78°C . After the addition of iodomethane, the reaction mixture was left to stir for 5.5 h at -78°C . Purification by column chromatography (SiO_2 , petroleum ether/EtOAc, 7:3) afforded the title compound as a yellow solid (41 mg, 0.14 mmol, 85%, 14:1 *dr*).

R_f 0.71 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 46 – 50 $^\circ\text{C}$

^1H NMR (400 MHz, CDCl_3) δ 7.37 – 7.19 (m, 10H, Ar*H* and Ar*H'*), 4.71 – 4.56 (m, 2H, H2 and H2'), 4.16 (d, $J = 5.0$ Hz, 4H, H1 and H1'), 4.04 (q, $J = 6.9$ Hz, 2H, H4 and H4'), 3.40 (dd, $J = 13.3, 3.3$ Hz, 1H, H3'), 3.30 (dd, $J = 13.4, 3.2$ Hz, 1H, H3), 2.74 (dd, $J = 13.4, 9.8$ Hz, 1H, H3), 2.60 (dd, $J = 13.3, 10.9$ Hz, 1H, H3'), 2.49 (s, 2H, H7 and H7'), 1.73 (d, $J = 9.5$ Hz, 6H, H6 and H6'), 1.70 (d, $J = 9.5$ Hz, 6H, H6 and H6'), 1.15 (d, $J = 6.9$ Hz, 6H, H5 and H5').

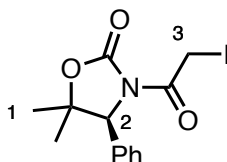
^{13}C NMR (101 MHz, CDCl_3) δ 174.7, 153.4, 135.5, 129.6 (2C), 129.1 (2C), 127.5, 66.1, 55.8, 49.4 (3C), 45.9, 39.0, 38.1, 27.0, 13.4.

HRMS (ESI⁺) Found [M+Na]⁺ = 322.1414; C₁₈H₂₁O₃NNa requires 322.1414.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2971, 2910, 2873, 1780, 1698, 1454, 1375, 1236, 1197, 702.

$[\alpha]_{\text{D}}^{25} +33.5$ ($c = 0.2$, CHCl₃)

(S)-3-(2-Iodoacetyl)-5,5-dimethyl-4-phenyloxazolidin-2-one, 62e



(S)-5,5-Dimethyl-4-phenyloxazolidin-2-one (3.83 g, 20.0 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 15.0 mL, 24.0 mmol, 1.2 equiv.) in THF (40 mL) were submitted to **General Procedure A** for 1 h at 0 °C. Bromoacetyl bromide (1.74 mL, 20.0 mmol, 1.0 equiv.) was then added at 0 °C and the reaction mixture was allowed to warm to room temperature over 4.5 h. (S)-3-(2-Bromoacetyl)-5,5-dimethyl-4-phenyloxazolidin-2-one was obtained as a yellow oil and used without further purification.

(S)-3-(2-Bromoacetyl)-5,5-dimethyl-4-phenyloxazolidin-2-one (6.24 g, 20.0 mmol, 1.0 equiv.) and sodium iodide (8.99 g, 60.0 mmol, 3.0 equiv.) in acetone (200 mL) were submitted to **General Procedure B** for 16 h. Purification by column chromatography (SiO₂, petroleum ether/CH₂Cl₂, 4:1) afforded the title compound as a yellow oil (0.566 g, 1.58 mmol, 8% over two steps).

R_f 0.48 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.42 – 7.31 (m, 3H, ArH), 7.22 – 7.15 (m, 2H, ArH), 5.05 (s, 1H, H2), 4.47 (d, $J = 9.3$ Hz, 1H, H3), 4.41 (d, $J = 9.3$ Hz, 1H, H3), 1.63 (s, 3H, H1), 1.02 (s, 3H, H1).

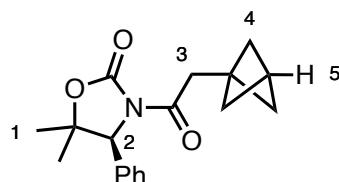
^{13}C NMR (126 MHz, CDCl_3) δ 167.7, 152.7, 135.6, 129.1 (4C), 129.0, 83.3, 67.3, 29.4, 23.8, -2.7.

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 381.9911$; $\text{C}_{13}\text{H}_{14}\text{O}_3\text{N}^{127}\text{INa}$ requires 381.9911.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2981, 1773, 1698, 1335, 1267, 1220, 1163, 1139, 1080, 773.

$[\alpha]_{\text{D}}^{25} +31.4$ ($c = 0.1$, CHCl_3)

(S)-3-(2-(Bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyl-4-phenyloxazolidin-2-one, 63e



(S)-3-(2-Iodoacetyl)-5,5-dimethyl-4-phenyloxazolidin-2-one **62e** (0.18 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.80 M in Et_2O , 0.81 mL, 0.65 mmol, 1.3 equiv.) and Et_3B (1 M in hexane, 50 μL , 50 μmol , 0.1 equiv.) in THF (0.5 mL) were submitted to **General Procedure C** at 0 $^\circ\text{C}$. After 40 min, the reaction mixture was concentrated *in vacuo*. The capped vial containing (S)-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyl-4-phenyloxazolidin-2-one was charged with TTMSS (0.46 mL, 1.5 mmol, 3.0 equiv.) and THF (0.5 mL). After stirring for 2 – 3 min at room temperature, Et_3B (1 M in hexane, 0.25 mL, 0.25 mmol, 0.5 equiv.) was syringed into the reaction mixture. The reaction mixture was left to stir at room temperature for 5.5 h and was then concentrated *in vacuo*. Purification by column chromatography (SiO_2 , petroleum ether/ EtOAc , 9:1) afforded the title compound as a white solid (60 mg, 0.20 mmol, 40% over two steps).

R_f 0.45 (petroleum ether/ EtOAc , 7:3), [UV, vanillin]

m.p. 68 – 70 °C

¹H NMR (500 MHz, CDCl₃) δ 7.40 – 7.30 (m, 3H, ArH), 7.17 – 7.11 (m, 2H, ArH), 5.05 (s, 1H, H2), 3.23 (d, *J* = 14.7 Hz, 1H, H3), 3.14 (d, *J* = 14.7 Hz, 1H, H3), 2.46 (s, 1H, H5), 1.79 (dd, *J* = 9.5, 1.7 Hz, 3H, H4), 1.76 (dd, *J* = 9.5, 1.7 Hz, 3H, H4), 1.60 (s, 3H, H1), 0.99 (s, 3H, H1).

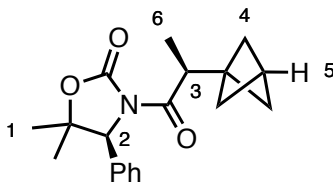
¹³C NMR (126 MHz, CDCl₃) δ 170.9, 153.3, 136.5, 129.0 (4C), 128.8, 82.3, 67.1, 51.7 (3C), 41.3, 38.7, 29.2, 28.6, 23.8.

HRMS (ESI⁺) Found [M+H]⁺ = 300.1596; C₁₈H₂₂O₃N requires 300.1594.

IR (film) ν_{max} /cm⁻¹ 2966, 2872, 1776, 1705, 1368, 1335, 1266, 1222, 1162, 1134, 1020, 772, 700.

$[\alpha]_{\text{D}}^{25} +37.9$ (*c* = 0.1, CHCl₃)

(S)-3-((S)-2-(Bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyl-4-phenyl-oxazolidin-2-one, 64e



(S)-3-(2-(Bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyl-4-phenyloxazolidin-2-one **63e** (45 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μL, 0.17 mmol, 1.1 equiv.) and iodomethane (28 μL, 0.45 mmol, 3.0 equiv.) in THF (0.6 mL) were submitted to **General Procedure D** at –78 °C. After the addition of iodomethane, the reaction mixture was left to stir for 2.5 h at –78 °C. Purification by column chromatography (SiO₂, pentane/EtOAc, 9:1) afforded the title compound as a white solid (24 mg, 76 μmol, 50%).

R_f 0.55 (pentane/EtOAc, 7:3), [UV, vanillin]

m.p. 153 – 154 °C

¹H NMR (500 MHz, CDCl₃) δ 7.41 – 7.29 (m, 3H, ArH), 7.21 – 7.08 (m, 2H, ArH), 5.05 (s, 1H, H2), 4.13 (q, *J* = 6.9 Hz, 1H, H3), 2.50 (s, 1H, H5), 1.75 (dd, *J* = 9.5, 1.6 Hz, 3H, H4), 1.72 (dd, *J* = 9.5, 1.6 Hz, 3H, H4), 1.61 (s, 3H, H1), 1.04 (d, *J* = 6.9 Hz, 3H, H6), 0.98 (s, 3H, H1).

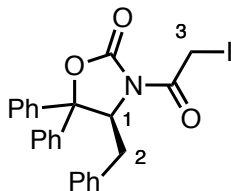
¹³C NMR (126 MHz, CDCl₃) δ 174.4, 153.2, 136.8, 129.0 (4C), 128.7, 82.0, 67.4, 49.5 (3C), 46.1, 39.1, 29.1, 27.1, 23.7, 13.4.

HRMS (ESI⁺) Found [M+Na]⁺ = 336.1570; C₁₉H₂₃O₃NNa requires 336.1570.

IR (film) ν_{max} /cm⁻¹ 2965, 2937, 2906, 2870, 1758, 1703, 1369, 1325, 1226, 1163, 1105, 715.

[α]_D²⁵ +77.1 (*c* = 0.1, CHCl₃)

(S)-4-Benzyl-3-(2-iodoacetyl)-5,5-diphenyloxazolidin-2-one, 62f



(S)-4-Benzyl-5,5-diphenyloxazolidin-2-one (2.0 g, 6.0 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 4.5 mL, 7.2 mmol, 1.2 equiv.) in THF (40 mL) were submitted to **General Procedure A** for 1 h at –78 °C. Bromoacetyl bromide (0.52 mL, 6.0 mmol, 1.0 equiv.) was then added at –78 °C and the reaction mixture was allowed to warm to room temperature over 5 h. (S)-4-Benzyl-3-(2-bromoacetyl)-5,5-diphenyloxazolidin-2-one was obtained as a yellow oil and used without further purification.

(*S*)-4-Benzyl-3-(2-bromoacetyl)-5,5-diphenyloxazolidin-2-one (2.7 g, 6.0 mmol, 1.0 equiv.) and sodium iodide (2.7 g, 18 mmol, 3.0 equiv.) in acetone (60 mL) were submitted to **General Procedure B** for 16 h. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 19:1) afforded the title compound as a pale yellow oil (1.1 g, 2.3 mmol, 39% over two steps).

R_f 0.52 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.47 – 7.40 (m, 2H, ArH), 7.39 – 7.30 (m, 3H, ArH), 7.25 – 7.14 (m, 5H, ArH), 7.13 – 7.05 (m, 3H, ArH), 6.76 – 6.69 (m, 2H, ArH), 5.60 (dd, *J* = 8.1, 4.7 Hz, 1H, H1), 4.28 (s, 2H, H3), 2.89 (dd, *J* = 14.2, 4.7 Hz, 1H, H2), 2.77 (dd, *J* = 14.2, 8.1 Hz, 1H, H2).

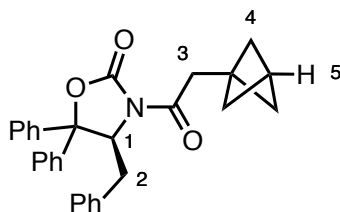
¹³C NMR (101 MHz, CDCl₃) δ 167.2, 151.7, 141.2, 137.2, 136.0, 129.1, 129.1 (4C), 128.5, 128.4 (2C), 128.4 (2C), 126.7, 126.6 (2C), 126.2 (2C), 89.2, 62.6, 36.3, –3.0.

HRMS (APCI) Found [M+H]⁺ = 498.0553; C₂₄H₂₁O₃N¹²⁷I requires 498.0561.

IR (film) ν_{max} /cm^{–1} 3062, 3030, 1785, 1694, 1494, 1450, 1409, 1355, 1311, 1219, 1170, 997, 758, 699.

[α]_D²⁵ –125.8 (*c* = 0.2, CHCl₃)

(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-diphenyloxazolidin-2-one, **63f**



(*S*)-4-Benzyl-3-(2-iodoacetyl)-5,5-diphenyloxazolidin-2-one **62f** (0.25 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.80 M in Et₂O, 0.81 mL, 0.65 mmol, 1.3 equiv.) and

Et₃B (1 M in hexane, 50 μ L, 50 μ mol, 0.1 equiv.) in THF (0.5 mL) were submitted to **General Procedure C** at 0 °C. After 3 h, the reaction mixture was concentrated *in vacuo*. The capped vial containing (S)-4-benzyl-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-diphenyloxazolidin-2-one was charged with TTMSS (0.46 mL, 1.5 mmol, 3.0 equiv.) and THF (0.5 mL). After stirring for 2 – 3 min at room temperature, Et₃B (1 M in hexane, 0.25 mL, 0.25 mmol, 0.5 equiv.) was syringed into the reaction mixture. The reaction mixture was left to stir at room temperature for 21 h and was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 19:1) afforded the title compound as a white solid (55 mg, 0.13 mmol, 25% over two steps).

R_f 0.52 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 100 – 102 °C

¹H NMR (500 MHz, CDCl₃) δ 7.51 – 7.44 (m, 2H, ArH), 7.38 – 7.28 (m, 3H, ArH), 7.25 – 7.14 (m, 5H, ArH), 7.12 – 7.04 (m, 3H, ArH), 6.78 – 6.71 (m, 2H, ArH), 5.61 (dd, *J* = 8.1, 4.8 Hz, 1H, H1), 3.25 (d, *J* = 14.1 Hz, 1H, H3), 2.87 (dd, *J* = 14.1, 4.8 Hz, 1H, H2), 2.82 – 2.70 (m, 2H, H2 and H3), 2.32 (s, 1H, H5), 1.57 (dd, *J* = 9.5, 1.9 Hz, 3H, H4), 1.50 (dd, *J* = 9.5, 1.9 Hz, 3H, H4).

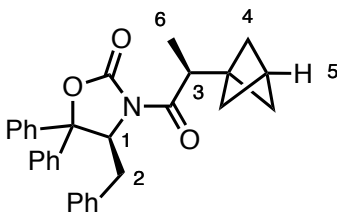
¹³C NMR (101 MHz, CDCl₃) δ 170.3, 152.1, 141.5, 137.5, 136.4, 129.1 (2C), 129.0 (3C), 128.4 (2C), 128.3 (2C), 128.3, 126.5 (3C), 126.1 (2C), 88.4, 62.2, 51.4 (3C), 41.1, 38.5, 36.8, 28.2.

HRMS (ESI⁺) Found [M+Na]⁺ = 460.1884; C₂₉H₂₇O₃NNa requires 460.1883.

IR (film) ν_{max} /cm⁻¹ 3063, 3030, 2964, 2908, 2872, 1788, 1700, 1495, 1451, 1354, 1221, 1192, 1167, 998, 759, 699.

[α]_D²⁵ -265.8 (*c* = 0.1, CHCl₃)

(S)-4-Benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-diphenyl-oxazolidin-2-one, 64f



(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-diphenyloxazolidin-2-one **63f** (35 mg, 80 μ mol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 44 μ L, 88 μ mol, 1.1 equiv.) and iodomethane (15 μ L, 0.24 mmol, 3.0 equiv.) in THF (0.6 mL) were submitted to **General Procedure D** at -78 $^{\circ}$ C. After the addition of iodomethane, the reaction mixture was left to stir for 5 h at -78 $^{\circ}$ C. Purification by column chromatography (SiO_2 , pentane/EtOAc, 9:1) afforded the title compound as a colorless oil (7.8 mg, 17 μ mol, 22%).

R_f 0.48 (pentane/EtOAc, 7:3), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 7.55 – 7.45 (m, 2H, ArH), 7.39 – 7.20 (m, 8H, ArH), 7.12 – 7.06 (m, 3H, ArH), 6.80 – 6.70 (m, 2H, ArH), 5.61 (dd, J = 7.8, 5.3 Hz, 1H, H1), 3.92 (q, J = 6.9 Hz, 1H, H3), 2.84 (dd, J = 14.1, 5.3 Hz, 1H, H2), 2.74 (dd, J = 14.1, 7.8 Hz, 1H, H2), 2.19 (s, 1H, H5), 1.33 (dd, J = 9.5, 1.8 Hz, 3H, H4), 1.18 (dd, J = 9.5, 1.8 Hz, 3H, H4), 0.94 (d, J = 6.9 Hz, 3H, H6).

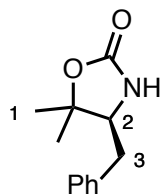
^{13}C NMR (126 MHz, CDCl_3) δ 173.7, 152.1, 141.6, 137.5, 136.5, 129.2 (2C), 128.9, 128.9 (2C), 128.4 (2C), 128.3 (2C), 128.2, 126.5, 126.4 (2C), 126.1 (2C), 88.3, 62.4, 48.9 (3C), 45.6, 38.8, 36.7, 26.5, 13.0.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 452.2221$; $\text{C}_{30}\text{H}_{30}\text{O}_4\text{N}$ requires 452.2220.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2968, 2872, 1787, 1699, 1495, 1451, 1366, 1232, 700.

$[\alpha]_{\text{D}}^{25}$ -151.0 (c = 0.1, CHCl_3)

(S)-4-Benzyl-5,5-dimethyloxazolidin-2-one, 65



Adapted from the procedure of Sadow et al.^[8] To a solution of methylmagnesium bromide (3 M in Et₂O, 100 mL, 300 mmol, 6.0 equiv.) in Et₂O (280 mL) at 0 °C under an inert atmosphere was added L-phenylalanine methyl ester hydrochloride (10.8 g, 50.0 mmol, 1.0 equiv.) in portions over 1 h. The mixture was allowed to stir at room temperature for 24 h. Upon completion, NH₄Cl (aq., sat., 300 mL) was added dropwise to quench the reaction. A white solid formed and was separated from the Et₂O solution. The solid was dissolved in NH₄Cl (aq., sat., 160 mL) and water (160 mL), the phases were separated and the aqueous phase was extracted with Et₂O (4 × 120 mL). The organic extracts were combined, dried (Na₂SO₄), filtered and concentrated *in vacuo*. (S)-3-Amino-2-methyl-4-phenylbutan-2-ol was obtained as a colorless oil, which was used without further purification (7.11 g, 39.7 mmol, 79%).

According to the procedure of Davies et al.^[9] To a solution of (S)-3-amino-2-methyl-4-phenylbutan-2-ol (6.50 g, 36.3 mmol, 1.0 equiv.) in CH₂Cl₂ (380 mL) was added carbonyl diimidazole (7.06 g, 43.5 mmol, 1.2 equiv.) and the resulting mixture was heated at reflux (45 °C) for 20 h. Upon completion, HCl (aq., 1 M, 300 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (2 × 150 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 4:1) afforded the title compound as a pale yellow oil (6.03 g, 29.4 mmol, 81%).

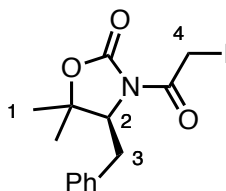
R_f 0.14 (pentane/EtOAc, 7:3), [UV, phosphomolybdic acid]

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.16 (m, 5H, ArH), 4.78 (s, 1H, NH), 3.69 (dd, *J* = 10.9, 3.7 Hz, 1H, H2), 2.84 (dd, *J* = 13.4, 3.7 Hz, 1H, H3), 2.68 (dd, *J* = 13.4, 10.9 Hz, 1H, H3), 1.49 (s, 3H, H1), 1.46 (s, 3H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 157.9, 137.0, 129.3 (2C), 129.0 (2C), 127.4, 83.3, 63.2, 37.3, 27.7, 22.1.

Spectroscopic data in agreement with that reported previously.^[10]

(*S*)-4-Benzyl-3-(2-iodoacetyl)-5,5-dimethyloxazolidin-2-one, 62g



(*S*)-4-Benzyl-5,5-dimethyloxazolidin-2-one **65** (0.54 g, 2.6 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 2.0 mL, 3.1 mmol, 1.2 equiv.) in THF (5.2 mL) were submitted to **General Procedure A** for 30 min at –78 °C. Bromoacetyl bromide (0.23 mL, 2.6 mmol, 1.0 equiv.) was then added at –78 °C and the reaction mixture was allowed to warm to room temperature over 4.5 h. (*S*)-4-Benzyl-3-(2-bromoacetyl)-5,5-dimethyloxazolidin-2-one was obtained as a yellow oil and used without further purification.

(*S*)-4-Benzyl-3-(2-bromoacetyl)-5,5-dimethyloxazolidin-2-one (0.86 g, 2.6 mmol, 1.0 equiv.) and sodium iodide (1.2 g, 7.9 mmol, 3.0 equiv.) in acetone (26 mL) were submitted to **General Procedure B** for 19 h. Purification by column chromatography (SiO₂, pentane/EtOAc, 17:3) afforded the title compound as a yellow oil (0.30 g, 0.79 mmol, 30% over two steps).

R_f 0.52 (pentane/EtOAc, 7:3), [UV, phosphomolybdic acid]

¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.20 (m, 5H, ArH), 4.50 (dd, *J* = 9.9, 3.7 Hz, 1H, H2), 4.46 (d, *J* = 9.5 Hz, 1H, H4), 4.36 (d, *J* = 9.5 Hz, 1H, H4), 3.16 (dd, *J* = 14.5, 3.7 Hz, 1H, H3), 2.90 (dd, *J* = 14.5, 9.9 Hz, 1H, H3), 1.40 (s, 3H), 1.38 (s, 3H).

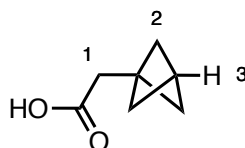
¹³C NMR (126 MHz, CDCl₃) δ 168.3, 152.1, 136.7, 129.2 (2C), 128.9 (2C), 127.1, 83.1, 64.0, 34.9, 29.0, 22.5, –2.5.

HRMS (ESI⁺) Found [M+Na]⁺ = 396.0068; C₁₄H₁₆O₃N¹²⁷INa requires 396.0067.

IR (film) ν_{max} /cm^{–1} 2980, 1776, 1692, 1358, 1320, 1277, 1085, 734, 621.

$[\alpha]_{\text{D}}^{25}$ –10.0 (*c* = 0.1, CHCl₃)

2-(Bicyclo[1.1.1]pentan-1-yl)acetic acid, 66a



Adapted from the procedure of Anderson et al.^[11] To a solution of ethyl 2-iodoacetate (0.59 mL, 5.0 mmol, 1.0 equiv.) and [1.1.1]propellane **2** (0.89 M in Et₂O, 8.4 mL, 7.5 mmol, 1.5 equiv.) at 0 °C was added Et₃B (1 M in hexane, 0.50 mL, 0.50 mmol, 0.1 equiv.) and the resulting mixture stirred for 30 min. TTMSS (3.1 mL, 10 mmol, 2.0 equiv.) and Et₃B (1 M in hexane, 1.0 mL, 1.0 mmol, 0.2 equiv.) were then added and the reaction mixture stirred at room temperature. After 30 min, sodium hydroxide (1.0 g, 25 mmol, 5.0 equiv.) in MeOH (10 mL) was added and the reaction mixture was stirred at 80 °C for 1 h. The reaction mixture was then concentrated *in vacuo* and water (20 mL) was added. The phases were separated and the aqueous phase was extracted with Et₂O (3 × 10 mL). The aqueous phase was acidified to pH 1 with HCl (conc.) and extracted with Et₂O (3 × 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column

chromatography (SiO₂, CH₂Cl₂/MeOH, 19:1) afforded the title compound as a colorless oil (0.44 g, 3.5 mmol, 70%).

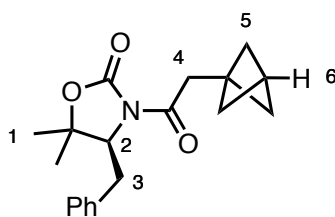
R_f 0.36 (CH₂Cl₂/MeOH, 9:1), [potassium permanganate]

¹H NMR (400 MHz, CDCl₃) δ 2.51 (s, 2H, H1), 2.50 (s, 1H, H3), 1.82 (s, 6H, H2).

¹³C NMR (101 MHz, CDCl₃) δ 178.1, 51.4 (3C), 40.7, 38.3, 28.2.

Spectroscopic data in agreement with that reported previously.^[11]

(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one,
63g



Procedure 1

(S)-4-Benzyl-3-(2-iodoacetyl)-5,5-dimethyloxazolidin-2-one **62g** (0.19 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.80 M in Et₂O, 0.81 mL, 0.65 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 50 μL, 50 μmol, 0.1 equiv.) in THF (0.5 mL) were submitted to **General Procedure C** at 0 °C. After 1 h, the reaction mixture was concentrated *in vacuo*. The capped vial containing (S)-4-benzyl-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one was charged with TTMSS (0.46 mL, 1.5 mmol, 3.0 equiv.) and THF (0.5 mL). After stirring for 2 – 3 min at room temperature, Et₃B (1 M in hexane, 0.25 mL, 0.25 mmol, 0.5 equiv.) was syringed into the reaction mixture. The reaction mixture was left to stir at room temperature for 2 h and was then concentrated *in vacuo*. Purification by column chromatography (SiO₂,

pentane/EtOAc, 9:1) afforded the title compound as a yellow oil (68 mg, 0.22 mmol, 43% over two steps).

Procedure 2

According to the procedure of Palomo et al.^[12] To a solution of 2-(bicyclo[1.1.1]pentan-1-yl)acetic acid **66a** (1.16 g, 9.20 mmol, 1.0 equiv.) in CH₂Cl₂ (4.5 mL) at 0 °C under an inert atmosphere was added oxalyl chloride (0.934 mL, 11.0 mmol, 1.2 equiv.) in CH₂Cl₂ (4.5 mL). One drop of DMF was added and the reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to afford 2-(bicyclo[1.1.1]pentan-1-yl)acetyl chloride **67** as an orange oil, which was used immediately without further purification.

In a separate flask, (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one **65** (1.89 g, 9.20 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 6.90 mL, 11.0 mmol, 1.2 equiv.) in THF (27 mL) were submitted to **General Procedure A** for 2.5 h at –78 °C. 2-(Bicyclo[1.1.1]pentan-1-yl)acetyl chloride **67** (1.33 g, 9.20 mmol, 1.0 equiv.) was then added dropwise at –78 °C and the reaction mixture was allowed to warm to room temperature over 18 h. Purification by column chromatography (SiO₂, pentane/EtOAc, 19:1) afforded the title compound as a yellow oil (1.81 g, 5.77 mmol, 63% over two steps).

R_f 0.40 (pentane/EtOAc, 9:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.32 – 7.16 (m, 5H, ArH), 4.49 (dd, *J* = 9.9, 3.6 Hz, 1H, H2), 3.19 – 3.05 (m, 3H, H3 and H4), 2.83 (dd, *J* = 14.4, 9.9 Hz, 1H, H3), 2.46 (s, 1H, H6), 1.77 (s, 6H, H5), 1.32 (s, 3H, H1), 1.32 (s, 3H, H1).

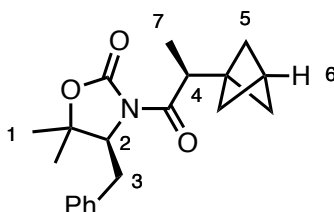
^{13}C NMR (126 MHz, CDCl_3) δ 171.4, 152.6, 137.1, 129.2 (2C), 128.8 (2C), 126.9, 82.0, 63.6, 51.6 (3C), 41.4, 38.8, 35.6, 28.7, 28.5, 22.5.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 314.1751$; $\text{C}_{19}\text{H}_{24}\text{O}_3\text{N}$ requires 314.1751.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2969, 2872, 1778, 1698, 1356, 1235, 733.

$[\alpha]_{\text{D}}^{25} -11.3$ ($c = 0.2$, CHCl_3)

(S)-4-Benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one, 64g



(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (63 mg, 0.20 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 0.11 mL, 0.22 mmol, 1.1 equiv.) and iodomethane (37 μL , 0.60 mmol, 3.0 equiv.) in THF (1.3 mL) were submitted to **General Procedure D** at -78°C . After the addition of iodomethane, the reaction mixture was left to stir for 1 h at -78°C . Purification by column chromatography (SiO_2 , petroleum ether/EtOAc, 9:1) afforded the title compound as a white solid (55 mg, 0.17 mmol, 84%).

Scaled-up procedure

(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (0.416 g, 1.33 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 0.730 mL, 1.46 mmol, 1.1 equiv.) and iodomethane (0.248 mL, 3.98 mmol, 3.0 equiv.) in THF (8 mL) were submitted to **General Procedure D** at -78°C . After the addition of iodomethane, the reaction mixture was left to stir for 1 h at -78°C .

Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as a white solid (0.349 g, 1.07 mmol, 80%).

R_f 0.48 (petroleum ether/EtOAc, 9:1), [UV, phosphomolybdic acid]

m.p. 95 – 97 °C

¹H NMR (400 MHz, CDCl₃) δ 7.35 – 7.18 (m, 5H, ArH), 4.51 (dd, *J* = 9.5, 4.0 Hz, 1H, H2), 4.07 (q, *J* = 6.8 Hz, 1H, H4), 3.09 (dd, *J* = 14.3, 4.0 Hz, 1H, H3), 2.88 (dd, *J* = 14.3, 9.5 Hz, 1H, H3), 2.48 (s, 1H, H6), 1.71 (dd, *J* = 9.4, 2.2 Hz, 6H, H5), 1.39 (s, 3H, H1), 1.37 (s, 3H, H1), 1.05 (d, *J* = 6.8 Hz, 3H, H7).

¹³C NMR (126 MHz, CDCl₃) δ 174.7, 152.6, 137.2, 129.3 (2C), 128.8 (2C), 126.9, 81.8, 63.8, 49.5 (3C), 46.1, 39.0, 35.7, 28.6, 27.0, 22.4, 13.5.

HRMS (ESI⁺) Found [M+H]⁺ = 328.1908; C₂₀H₂₆O₃N requires 328.1907.

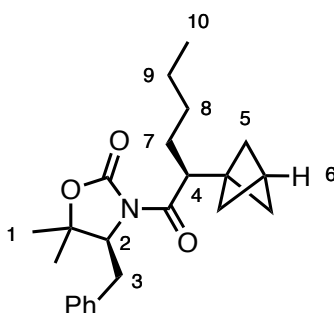
IR (film) ν_{max} /cm⁻¹ 2969, 2872, 1778, 1698, 1356, 1235, 733.

[α]_D²⁵ +2.6 (*c* = 0.2, CHCl₃)

9.3.3 Reaction scope: BCP products

The synthesis of substrate (*S*)-4-benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** and BCP product (*S*)-4-benzyl-3-((*S*)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one **64g** is detailed in Section 9.3.2.

(S)-4-Benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)hexanoyl)-5,5-dimethyloxazolidin-2-one, 64h



Adapted from the procedure of Trost et al.^[13] To a solution of 1-butanol (0.46 mL, 5.0 mmol, 1.0 equiv.) in CH₂Cl₂ (18 mL) at –78 °C under an inert atmosphere was added pyridine (0.48 mL, 5.9 mmol, 1.2 equiv.) followed by triflic anhydride (0.86 mL, 5.1 mmol, 1.02 equiv.) over 30 min. The reaction mixture was left to stir for 2 h. Upon completion, brine (20 mL) was added. The reaction mixture was diluted with Et₂O (10 mL). The phases were separated and the organic phase was washed with water (30 mL), aqueous CuSO₄ (30 mL) and brine (30 mL), dried (MgSO₄), filtered and concentrated *in vacuo*. Butyl trifluoromethanesulfonate was obtained as a colorless oil, which was used without further purification (0.89 g, 4.3 mmol, 87%).

(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 µL, 0.17 mmol, 1.1 equiv.) and butyl trifluoromethanesulfonate (93 mL, 0.45 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at –78 °C. After the addition of butyl trifluoromethanesulfonate, the reaction mixture was left to stir for 30 min at –78 °C and then warmed to 0 °C over 23 h. Purification by column chromatography (SiO₂, pentane/EtOAc, 9:1) afforded the title compound as a colorless oil (22 mg, 61 µmol, 41%).

R_f 0.50 (pentane/EtOAc, 9:1), [UV, phosphomolybdic acid]

¹H NMR (500 MHz, CDCl₃) δ 7.33 – 7.20 (m, 5H, ArH), 4.55 (dd, *J* = 9.7, 3.6 Hz, 1H, H2), 4.09 (dd, *J* = 10.2, 4.2 Hz, 1H, H4), 3.10 (dd, *J* = 14.4, 3.6 Hz, 1H, H3), 2.90 (dd, *J* = 14.4, 9.7 Hz, 1H, H3), 2.48 (s, 1H, H6), 1.74 (dd, *J* = 9.6, 1.7 Hz, 3H, H5), 1.70 (dd, *J* = 9.6, 1.7 Hz, 3H, H5), 1.38 (s, 3H, H1), 1.35 (s, 3H, H1), 1.45 – 1.11 (m, 6H, H7, H8 and H9), 0.86 (t, *J* = 7.3 Hz, 3H, H10).

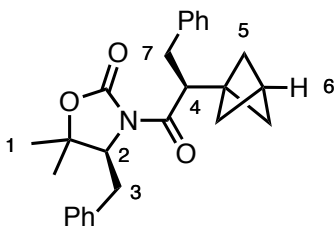
¹³C NMR (126 MHz, CDCl₃) δ 174.3, 152.6, 137.2, 129.2 (2C), 128.8 (2C), 126.9, 81.7, 63.9, 49.9 (3C), 45.7, 44.7, 35.8, 30.0, 28.9, 28.6, 27.3, 22.9, 22.4, 14.1.

HRMS (ESI⁺) Found [M+Na]⁺ = 392.2196; C₂₃H₃₁O₃N²³Na requires 392.2196.

IR (film) ν_{max} /cm⁻¹ 2966, 2872, 1778, 1695, 1375, 1352, 1237, 1094, 732.

[α]_D²⁵ -5.6 (*c* = 0.2, CHCl₃)

(*S*)-4-Benzyl-3-((*S*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-phenylpropanoyl)-5,5-dimethyloxazolidin-2-one, 64i



(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-

2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μ L, 0.17 mmol, 1.1 equiv.) and benzyl bromide (54 μ L, 0.45 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at -78 °C. After the addition of benzyl bromide, the reaction mixture was left to stir for 30 min at -78 °C and then for 1 h at 0 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as a white solid (53 mg, 0.13 mmol, 88%).

R_f 0.48 (petroleum ether/EtOAc, 9:1), [UV, phosphomolybdic acid]

m.p. 150 – 152 °C

¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.11 (m, 10H, ArH), 4.62 (dd, *J* = 10.9, 4.8 Hz, 1H, H4), 4.43 (dd, *J* = 10.1, 2.8 Hz, 1H, H2), 3.02 (dd, *J* = 13.8, 10.9 Hz, 1H, H7), 2.81 (dd, *J* = 13.8, 4.8 Hz, 1H, H7), 2.70 (dd, *J* = 14.7, 2.8 Hz, 1H, H3), 2.52 (s, 1H, H6), 2.51 (dd, *J* = 14.7, 10.1 Hz, 2H, H3), 1.78 (s, 6H, H5), 1.31 (s, 3H, H1), 1.24 (s, 3H, H1).

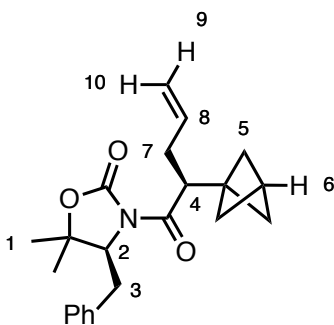
¹³C NMR (126 MHz, CDCl₃) δ 173.6, 152.4, 139.5, 137.3, 129.1 (4C), 128.7 (2C), 128.4 (2C), 126.8, 126.3, 81.6, 63.8, 49.9 (3C), 46.2, 45.4, 35.3, 35.0, 28.7, 27.5, 22.3.

HRMS (ESI⁺) Found [M+H]⁺ = 404.2221; C₂₆H₃₀O₄N requires 404.2220.

IR (film) ν_{max}/cm⁻¹ 2959, 2867, 1761, 1686, 1373, 1241, 1099, 703.

[α]_D²⁵ -15.7 (*c* = 0.1, CHCl₃)

(S)-4-Benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)pent-4-enoyl)-5,5-dimethyloxazolidin-2-one, 64j



(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-

2-one 63g (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μL, 0.17 mmol, 1.1 equiv.) and allyl iodide (41 μL, 0.45 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at -78 °C. After the addition of allyl iodide, the reaction mixture was left to stir for 3 h at -78 °C. Purification by

column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as a pale yellow oil (51 mg, 0.14 mmol, 97%).

R_f 0.45 (petroleum ether/EtOAc, 9:1), [UV, phosphomolybdic acid]

¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.20 (m, 5H, ArH), 5.80 – 5.67 (m, 1H, H8), 5.04 (dq, *J* = 17.1, 1.7 Hz, 1H, H10), 4.96 (dq, *J* = 10.3, 1.7 Hz, 1H, H9), 4.53 (dd, *J* = 10.0, 3.2 Hz, 1H, H2), 4.25 (dd, *J* = 10.2, 4.6 Hz, 1H, H4), 3.08 (dd, *J* = 14.5, 3.2 Hz, 1H, H3), 2.86 (dd, *J* = 14.5, 10.0 Hz, 1H, H3), 2.50 (s, 1H, H6), 2.49 – 2.42 (m, 1H, H7), 2.25 – 2.18 (m, 1H, H7), 1.77 (dd, *J* = 9.6, 1.7 Hz, 3H, H5), 1.74 (dd, *J* = 9.6, 1.7 Hz, 3H, H5), 1.37 (s, 3H, H1), 1.34 (s, 3H, H1).

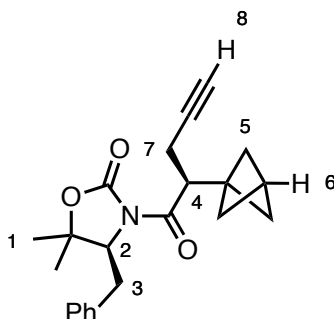
¹³C NMR (126 MHz, CDCl₃) δ 173.6, 152.6, 137.3, 136.0, 129.2 (2C), 128.8 (2C), 126.9, 116.5, 81.7, 64.0, 49.9 (3C), 45.4, 44.2, 35.7, 33.3, 28.7, 27.4, 22.4.

HRMS (ESI⁺) Found [M+Na]⁺ = 376.1883; C₂₂H₂₇O₃NNa requires 376.1883.

IR (film) ν_{max}/cm⁻¹ 2971, 2910, 2872, 1776, 1695, 1374, 1353, 1241, 1096, 701.

[α]_D²⁵ -4.2 (*c* = 0.2, CHCl₃)

(S)-4-Benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)pent-4-ynoyl)-5,5-dimethyloxazolidin-2-one, 64k



(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one 63g (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in

THF, 83 μ L, 0.17 mmol, 1.1 equiv.) and propargyl bromide (80% wt. in PhMe, 50 μ L, 0.45 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at -78 $^{\circ}$ C. After the addition of propargyl bromide, the reaction mixture was left to stir for 5 h at -78 $^{\circ}$ C. Purification by column chromatography (SiO₂, pentane/EtOAc, 9:1) afforded the title compound as a white solid (48 mg, 0.14 mmol, 92%).

R_f 0.36 (pentane/EtOAc, 9:1), [UV, vanillin]

m.p. 90 – 92 $^{\circ}$ C

¹H NMR (500 MHz, CDCl₃) δ 7.33 – 7.28 (m, 4H, ArH), 7.25 – 7.20 (m, 1H, ArH), 4.54 (dd, J = 9.9, 3.2 Hz, 1H, H2), 4.38 (dd, J = 9.1, 5.8 Hz, 1H, H4), 3.16 (dd, J = 14.6, 3.2 Hz, 1H, H3), 2.91 (dd, J = 14.6, 9.9 Hz, 1H, H3), 2.54 (ddd, J = 16.7, 9.1, 2.7 Hz, 1H, H7), 2.50 (s, 1H, H6), 2.33 (ddd, J = 16.7, 5.8, 2.7 Hz, 1H, H7), 1.91 (t, J = 2.7 Hz, 1H, H8), 1.79 (dd, J = 9.5, 1.7 Hz, 3H, H5), 1.75 (dd, J = 9.5, 1.7 Hz, 3H, H5), 1.38 (s, 3H, H1), 1.36 (s, 3H, H1).

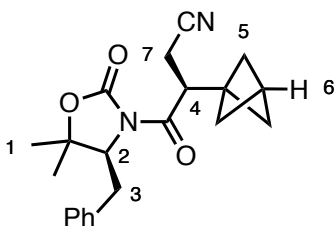
¹³C NMR (126 MHz, CDCl₃) δ 172.6, 152.4, 137.2, 129.3 (2C), 128.8 (2C), 126.9, 82.2, 81.9, 69.5, 64.0, 50.0 (3C), 44.9, 44.3, 35.6, 28.8, 27.3, 22.4, 18.6.

HRMS (ESI⁺) Found $[M+Na]^+ = 374.1728$; C₂₂H₂₅O₃NNa requires 374.1723.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3290, 2972, 2911, 2873, 1776, 1694, 1374, 1242, 1101, 701.

$[\alpha]_{\text{D}}^{25}$ -3.8 (c = 0.8, CHCl₃)

(*S*)-4-((*S*)-4-Benzyl-5,5-dimethyl-2-oxooxazolidin-3-yl)-3-(bicyclo[1.1.1]pentan-1-yl)-4-oxobutanenitrile, **64l**



(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μ L, 0.17 mmol, 1.1 equiv.) and bromoacetonitrile (31 μ L, 0.45 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at -78 $^{\circ}$ C. After the addition of bromoacetonitrile, the reaction mixture was left to stir for 3 h at -78 $^{\circ}$ C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as a white solid (45 mg, 0.13 mmol, 86%).

R_f 0.14 (petroleum ether/EtOAc, 9:1), [UV, phosphomolybdic acid]

m.p. 130 – 132 $^{\circ}$ C

¹H NMR (500 MHz, CDCl₃) δ 7.34 – 7.20 (m, 5H, ArH), 4.56 – 4.44 (m, 2H, H2 and H4), 3.13 (dd, J = 14.5, 4.0 Hz, 1H, H3), 2.93 (dd, J = 14.5, 9.4 Hz, 1H, H3), 2.58 (dd, J = 16.7, 8.0 Hz, 1H, H7), 2.54 (s, 1H, H6), 2.45 (dd, J = 16.7, 6.5 Hz, 1H, H7), 1.82 (dd, J = 9.6, 1.8 Hz, 3H, H5), 1.79 (dd, J = 9.6, 1.8 Hz, 3H, H5), 1.40 (s, 3H, H1), 1.39 (s, 3H, H1).

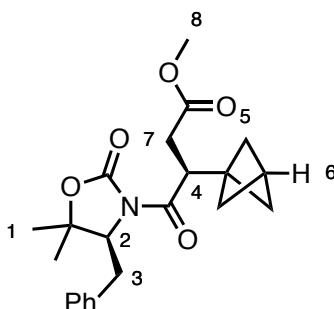
¹³C NMR (126 MHz, CDCl₃) δ 170.9, 152.3, 136.8, 129.2 (2C), 128.9 (2C), 127.1, 118.4, 82.4, 64.0, 50.0 (3C), 44.3, 41.8, 35.6, 28.7, 27.2, 22.4, 17.0.

HRMS (ESI⁺) Found $[M+Na]^+ = 375.1680$; C₂₁H₂₄O₃N₂Na requires 375.1679.

IR (film) ν_{max} /cm⁻¹ 2973, 2875, 1777, 1693, 1377, 1244, 1102, 701.

$[\alpha]_{\text{D}}^{25}$ -2.6 (c = 0.2, CHCl₃)

Methyl (S)-4-((S)-4-benzyl-5,5-dimethyl-2-oxooxazolidin-3-yl)-3-(bicyclo[1.1.1]pentan-1-yl)-4-oxobutanoate, 64m



(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μ L, 0.17 mmol, 1.1 equiv.) and methyl bromoacetate (43 μ L, 0.45 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at -78 $^{\circ}$ C. After the addition of methyl bromoacetate, the reaction mixture was left to stir for 7.5 h at -78 $^{\circ}$ C. Purification by column chromatography (SiO_2 , pentane/EtOAc, 9:1) afforded the title compound as a white solid (52 mg, 0.13 mmol, 90%).

R_f 0.24 (pentane/EtOAc, 9:1), [UV, vanillin]

m.p. 96 – 98 $^{\circ}$ C

^1H NMR (500 MHz, CDCl_3) δ 7.34 – 7.18 (m, 5H, ArH), 4.57 (dd, J = 11.4, 3.9 Hz, 1H, H4), 4.53 (dd, J = 10.5, 2.5 Hz, 1H, H2), 3.63 (s, 3H, H8), 3.18 (dd, J = 14.8, 2.5 Hz, 1H, H3), 2.95 – 2.87 (m, 2H, H3 and H7), 2.51 (s, 1H, H6), 2.45 (dd, J = 17.3, 3.9 Hz, 1H, H7), 1.76 (dd, J = 9.5, 1.7 Hz, 3H, H5), 1.72 (dd, J = 9.5, 1.7 Hz, 3H, H5), 1.38 (s, 3H, H1), 1.33 (s, 3H, H1).

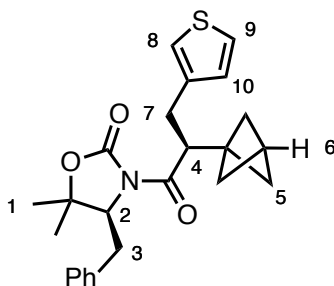
^{13}C NMR (126 MHz, CDCl_3) δ 173.3, 172.6, 152.4, 137.7, 129.2 (2C), 128.8 (2C), 126.8, 81.8, 64.1, 51.9, 49.8 (3C), 44.3, 41.0, 35.1, 33.6, 28.8, 27.4, 22.5.

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 408.1779$; $\text{C}_{22}\text{H}_{27}\text{O}_3\text{NNa}$ requires 408.1781.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2970, 2873, 1779, 1738, 1694, 1384, 1354, 1278, 1244, 1176.

$[\alpha]_{\text{D}}^{25} -5.0$ ($c = 0.3$, CHCl_3)

(*S*)-4-Benzyl-3-((*S*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-(thiophen-3-yl)propanoyl)-5,5-dimethyloxazolidin-2-one, 64n



(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μL , 0.17 mmol, 1.1 equiv.) and 3-(bromomethyl)thiophene (49 μL , 0.45 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at $-78\text{ }^{\circ}\text{C}$. After the addition of 3-(bromomethyl)thiophene, the reaction mixture was left to stir for 7.5 h at $-78\text{ }^{\circ}\text{C}$. Purification by column chromatography (SiO_2 , pentane/ CH_2Cl_2 , 7:3) afforded the title compound as a white solid (52 mg, 0.13 mmol, 86%).

R_f 0.57 (pentane/EtOAc, 17:3), [UV, vanillin]

m.p. 135 – 136 $^{\circ}\text{C}$

^1H NMR (500 MHz, CDCl_3) δ 7.30 – 7.17 (m, 6H, ArH and H9), 6.99 – 6.95 (m, 2H, H8 and H10), 4.61 (dd, $J = 11.1, 4.7$ Hz, 1H, H4), 4.45 (dd, $J = 10.1, 2.8$ Hz, 1H, H2), 3.08 (dd, $J = 14.2, 11.1$ Hz, 1H, H7), 2.76 (dd, $J = 14.5, 4.7$ Hz, 2H, H7 and H3), 2.60 (dd, $J = 14.5, 10.1$ Hz, 1H, H3), 2.52 (s, 1H, H6), 1.78 (dd, $J = 9.1, 1.6$ Hz, 3H, H5), 1.77 (dd, $J = 9.1, 1.6$ Hz, 3H, H5), 1.33 (s, 3H, H1), 1.27 (s, 3H, H1).

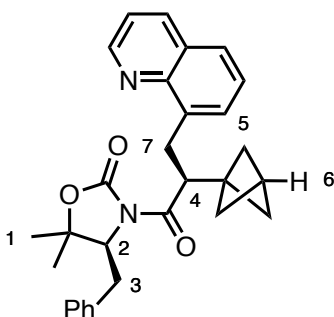
^{13}C NMR (126 MHz, CDCl_3) δ 173.7, 152.5, 139.9, 137.3, 129.1 (2C), 128.8 (2C), 128.7, 126.8, 125.5, 121.5, 81.7, 63.8, 49.9 (3C), 45.8, 45.3, 35.0, 29.8, 28.7, 27.4, 22.4.

HRMS (ESI⁺) Found [M+Na]⁺ = 432.1606; C₂₄H₂₇O₃NNa³²S requires 432.1604.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2969, 2909, 2872, 1775, 1694, 1497, 1454, 1374, 1353, 1276, 1235, 1201, 1100, 972.

$[\alpha]_{\text{D}}^{25}$ -29.3 (c = 0.3, CHCl₃)

(S)-4-Benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)-3-(quinolin-8-yl)propanoyl)-5,5-dimethyloxazolidin-2-one, 64o



(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **53g** (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μ L, 0.17 mmol, 1.1 equiv.) and 8-(bromomethyl)quinoline (0.10 g, 0.45 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at -78 °C. After the addition of 8-(bromomethyl)quinoline, the reaction mixture was stirred for 7.5 h at -78 °C. Purification by column chromatography (SiO₂, pentane/EtOAc, 19:1) afforded the title compound as a colorless oil (48 mg, 0.11 mmol, 70%).

R_f 0.17 (pentane/EtOAc, 9:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 8.95 (dd, J = 4.2, 1.8 Hz, 1H, ArH), 8.10 (dd, J = 8.2, 1.8 Hz, 1H, ArH), 7.63 (dd, J = 8.2, 1.4 Hz, 1H, ArH), 7.58 (dd, J = 7.1, 1.4 Hz, 1H, ArH), 7.40 – 7.34 (m, 2H, ArH), 7.24 – 7.12 (m, 5H, ArH), 4.92 (dd, J = 8.2, 6.6 Hz, 1H, H4), 4.44 (dd, J = 10.3, 2.7 Hz, 1H, H2), 3.62 (d, J = 7.8 Hz, 2H, H7), 2.76 (dd,

$J = 14.4, 2.7$ Hz, 1H, H3), 2.55 (s, 1H, H6), 2.48 (dd, $J = 14.4, 10.3$ Hz, 1H, H3), 1.86 (s, 6H, H5), 1.30 (s, 3H, H1), 1.19 (s, 3H, H1).

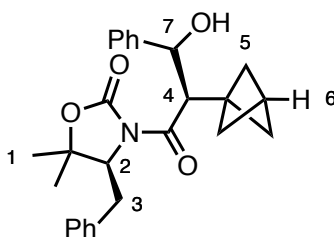
^{13}C NMR (126 MHz, CDCl_3) δ 174.2, 152.3, 149.6, 147.2, 138.6, 137.4, 136.2, 129.3, 129.1 (2C), 128.7 (2C), 128.5, 126.7, 126.5, 126.1, 121.1, 81.4, 63.9, 50.0 (3C), 45.8, 45.3, 35.1, 30.8, 28.7, 27.5, 22.3.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 455.2326$; $\text{C}_{29}\text{H}_{31}\text{O}_3\text{N}_2$ requires 455.2329.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2969, 2872, 1776, 1693, 1371, 1353, 1237, 1100, 795, 733, 700.

$[\alpha]_{\text{D}}^{25} -72.1$ ($c = 0.07$, CHCl_3)

(S)-4-Benzyl-3-((2R,3R)-2-(bicyclo[1.1.1]pentan-1-yl)-3-hydroxy-3-phenylpropanoyl)-5,5-dimethyloxazolidin-2-one, 64p



Adapted from the procedure of Evans et al.^[14] To a solution of (S)-4-benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.) in CH_2Cl_2 (0.5 mL) at 0 °C under an inert atmosphere was added dibutylboryl trifluoromethanesulfonate (1 M in Et_2O , 0.17 mL, 0.17 mmol, 1.1 equiv.) followed by DIPEA (31 μL , 0.18 mmol, 1.2 equiv.). After 30 min, the reaction mixture was cooled to -78 °C and benzaldehyde (17 μL , 0.17 mmol, 1.1 equiv.) was added. The reaction mixture was left to stir at -78 °C for 3.5 h. The reaction was warmed to 0 °C, quenched with pH 7 phosphate buffer (0.5 mL), H_2O_2 :MeOH (1:1, 30%, 0.5 mL) was added and the reaction mixture was left to stir for 1 h. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×0.5 mL). The combined organic

extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 19:1) afforded the title compound as a pale yellow oil (61 mg, 0.15 mmol, 98%, 1:1.5 *dr*).

R_f 0.29 (pentane/EtOAc, 9:1), [UV, phosphomolybdic acid]

¹H NMR (500 MHz, CDCl₃) δ 7.49 – 7.10 (m, 20H, ArH and ArH'), 5.02 (dd, *J* = 8.0, 3.4 Hz, 1H, H7), 5.00 (dd, *J* = 7.1, 3.3 Hz, 1H, H7'), 4.73 (d, *J* = 7.1 Hz, 1H, H4'), 4.67 (d, *J* = 8.0 Hz, 1H, H4), 4.38 (dd, *J* = 9.8, 3.5 Hz, 1H, H2'), 4.23 (dd, *J* = 10.2, 3.3 Hz, 1H, H2), 3.07 (dd, *J* = 14.6, 3.3 Hz, 1H, H3), 2.80 (dd, *J* = 14.6, 10.2 Hz, 1H, H3), 2.58 (d, *J* = 3.3 Hz, 1H, OH'), 2.50 (dd, *J* = 14.6, 3.5 Hz, 1H, H3'), 2.48 (s, 1H, H6), 2.47 (s, 1H, H6'), 2.43 (dd, *J* = 14.6, 9.8 Hz, 1H, H3'), 2.41 (d, *J* = 3.4 Hz, 1H, OH), 1.90 – 1.83 (m, 6H, H5), 1.86 – 1.80 (m, 6H, H5'), 1.31 (s, 3H, H1'), 1.25 (s, 6H, H1 and H1'), 1.22 (s, 3H, H1).

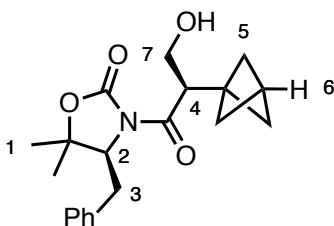
¹³C NMR (126 MHz, CDCl₃) δ 173.0, 172.5, 152.3 (2C), 142.2, 141.9, 137.1, 137.0, 132.3, 132.2, 129.1 (2C), 129.0 (2C), 128.8 (2C), 128.8 (2C), 128.6 (2C), 128.4 (2C), 128.0, 127.9, 127.0, 126.9 (2C), 126.9, 82.1, 81.8, 74.8, 74.6, 63.5, 63.4, 51.5 (3C), 51.5 (3C), 51.3, 51.0, 43.7, 43.6, 35.6, 34.8, 28.7, 28.6, 27.9 (2C), 22.4, 22.3.

HRMS (ESI⁺) Found [M+Na]⁺ = 442.1988; C₂₆H₂₉O₄NNa requires 442.1989.

IR (film) ν_{max} /cm⁻¹ 2968, 2914, 2873, 1777, 1692, 1455, 1373, 1277, 1237, 1207, 1179, 1100, 1057.

[α]_D²⁵ -3.2 (*c* = 0.2, CHCl₃)

(S)-4-Benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)-3-hydroxypropanoyl)-5,5-dimethyloxazolidin-2-one, 64q



Adapted from the procedure of Miller *et al.*^[15] To a solution of (S)-4-benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (31 mg, 0.10 mmol, 1.0 equiv.) in CH₂Cl₂ (0.5 mL) at 0 °C under an inert atmosphere was added titanium tetrachloride (12 μL, 0.11 mmol, 1.1 equiv.) dropwise and the reaction mixture left to stir for 10 min. DIPEA (11 μL, 0.12 mmol, 1.2 equiv.) was then added dropwise and the reaction mixture left to stir for 40 min. 1,3,5-Trioxane (45 mg, 0.50 mmol, 5.0 equiv.) was then added followed by titanium tetrachloride (12 μL, 0.11 mmol, 1.1 equiv.) dropwise. The reaction mixture was left to stir for 3 h. Upon completion, NH₄Cl (aq., sat., 0.5 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 0.5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 7:3) afforded the title compound as a white solid (19 mg, 56 μmol, 56%).

Scaled-up procedure

(S)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (0.422 g, 1.34 mmol, 1.0 equiv.), titanium tetrachloride (0.162 mL, 1.48 mmol, 1.1 equiv.), DIPEA (0.281 mL, 1.61 mmol, 1.2 equiv.) and 1,3,5-trioxane (0.606 g, 6.72 mmol, 5.0 equiv.) in CH₂Cl₂ (6 mL) were submitted to the

above procedure. Purification by column chromatography (SiO₂, pentane/EtOAc, 7:3) afforded the title compound as a white solid (0.248 g, 0.722 mmol, 54%).

R_f 0.33 (pentane/EtOAc, 7:3), [UV, phosphomolybdic acid]

m.p. 109 – 110 °C

¹H NMR (500 MHz, CDCl₃) δ 7.33 – 7.21 (m, 5H, ArH), 4.55 (dd, *J* = 8.7, 4.9 Hz, 1H, H2), 4.25 (dd, *J* = 8.4, 4.2 Hz, 1H, H4), 3.84 (ddd, *J* = 11.1, 8.4, 7.0 Hz, 1H, H7), 3.70 (ddd, *J* = 11.1, 6.1, 4.2 Hz, 1H, H7), 3.07 (dd, *J* = 14.3, 4.9 Hz, 1H, H3), 2.94 (dd, *J* = 14.3, 8.7 Hz, 1H, H3), 2.48 (s, 1H, H6), 1.79 (dd, *J* = 9.6, 1.8 Hz, 3H, H5), 1.76 (dd, *J* = 9.6, 1.8 Hz, 3H, H5), 1.41 (s, 3H, H1), 1.40 (s, 3H, H1).

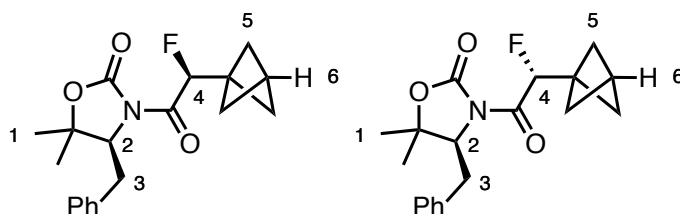
¹³C NMR (126 MHz, CDCl₃) δ 173.5, 152.5, 137.0, 129.3 (2C), 128.8 (2C), 127.0, 82.1, 63.7, 62.1, 50.7 (3C), 47.1, 43.2, 35.9, 28.5, 28.0, 22.2.

HRMS (ESI⁺) Found [M+H]⁺ = 344.1859; C₂₀H₂₆O₄N requires 344.1856.

IR (film) ν_{max}/cm⁻¹ 2975, 2913, 2871, 1777, 1697, 1376, 1356, 1277, 1241, 1207, 1182, 1102.

[α]_D²⁵ -13.1 (*c* = 0.2, CHCl₃)

(4*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)-2-fluoroacetyl)-5,5-dimethyloxazolidin-2-one, 64r



(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-

2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μL, 0.17 mmol, 1.1 equiv.) and *N*-fluorobenzenesulfonimide (62 mg,

0.20 mmol, 1.3 equiv.) in THF (1 mL) were submitted to **General Procedure D** at $-78\text{ }^{\circ}\text{C}$. After the addition of *N*-fluorobenzenesulfonimide, the reaction mixture was left to stir for 3 h at $-78\text{ }^{\circ}\text{C}$. Purification by column chromatography (SiO_2 , pentane/EtOAc, 19:1) afforded the title compound as a colorless oil (42 mg, 0.13 mmol, 85%, 13:1 *dr*).

R_f 0.14 (pentane/EtOAc, 17:3), [UV, phosphomolybdic acid]

¹H NMR (500 MHz, CDCl_3) δ 7.34 – 7.22 (m, 10H, ArH and ArH'), 6.08 (d, $J_{\text{HF}} = 50.4\text{ Hz}$, 1H, H4), 6.05 (d, $J_{\text{HF}} = 50.4\text{ Hz}$, 1H, H4'), 4.61 (dd, $J = 10.6, 3.7\text{ Hz}$, 1H, H2'), 4.49 (dd, $J = 10.0, 3.2\text{ Hz}$, 1H, H2), 3.24 (dd, $J = 14.6, 3.2\text{ Hz}$, 1H, H3), 3.17 (dd, $J = 14.5, 3.7\text{ Hz}$, 1H, H3'), 2.92 (dd, $J = 14.6, 10.0\text{ Hz}$, 1H, H3), 2.83 (dd, $J = 14.5, 10.6\text{ Hz}$, 1H, H3'), 2.55 (s, 1H, H6), 2.54 (s, 1H, H6'), 1.90 (dd, $J = 9.4, 1.5\text{ Hz}$, 6H, H5 and H5'), 1.88 (dd, $J = 9.4, 1.5\text{ Hz}$, 6H, H5 and H5'), 1.40 (s, 6H, H1 and H1'), 1.39 (s, 6H, H1 and H1').

¹³C NMR (126 MHz, CDCl_3) δ 168.2 (d, $J_{\text{CF}} = 23.5\text{ Hz}$), 152.2, 136.8, 129.2 (2C), 128.9 (2C), 127.1, 87.2 (d, $J_{\text{CF}} = 178.6\text{ Hz}$), 83.5, 64.0, 49.8 (d, $J_{\text{CF}} = 4.7\text{ Hz}$) (3C), 43.3 (d, $J_{\text{CF}} = 26.8\text{ Hz}$), 35.3, 28.7, 28.1 (d, $J_{\text{CF}} = 1.9\text{ Hz}$), 22.4.

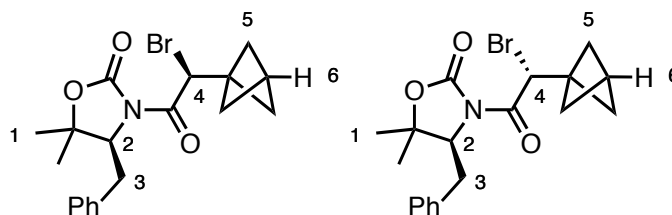
¹⁹F NMR (377 MHz, CDCl_3) δ -194.7 (d, $J = 50.5\text{ Hz}$), -195.3 (d, $J = 50.6\text{ Hz}$, F').

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 354.1474$; $\text{C}_{19}\text{H}_{22}\text{O}_3\text{NFNa}$ requires 354.1476.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2969, 2909, 2873, 1691, 1681, 1658, 1650, 1502, 1494, 1461, 1453, 1258, 1199, 1011, 956, 926, 771, 734, 700.

$[\alpha]_{\text{D}}^{25} -23.5$ ($c = 0.2$, CHCl_3)

(4*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)-2-bromoacetyl)-5,5-dimethyl-oxazolidin-2-one, 64s



Procedure 1

(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (25 mg, 80 μ mol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 44 μ L, 88 μ mol, 1.1 equiv.) and *N*-bromosuccinimide (43 mg, 0.24 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at -78 $^{\circ}$ C. After the addition of *N*-bromosuccinimide, the reaction mixture was stirred for 4 h at -78 $^{\circ}$ C. Purification by column chromatography (SiO₂, pentane/EtOAc, 9:1) afforded the title compound as a pale yellow oil (27 mg, 70 μ mol, 87%, 3:1 *dr*).

Procedure 2

(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μ L, 0.17 mmol, 1.1 equiv.) and 2-(bromomethyl)-5-nitrofurane (93 mg, 0.45 mmol, 3.0 equiv.) in THF (1 mL) were submitted to **General Procedure D** at -78 $^{\circ}$ C. After the addition of 2-(bromomethyl)-5-nitrofurane, the reaction mixture was stirred for 2 h at -78 $^{\circ}$ C. Purification by column chromatography (SiO₂, pentane/EtOAc, 19:1) afforded the title compound as a pale yellow oil (46 mg, 0.12 mmol, 78%, 13:1 *dr*).

R_f 0.36 (pentane/EtOAc, 9:1), [UV, phosphomolybdic acid]

¹H NMR (500 MHz, CDCl₃) δ 7.34 – 7.20 (m, 10H, ArH and ArH'), 5.85 (s, 1H, H4), 5.78 (s, 1H, H4'), 4.53 (dd, *J* = 10.0, 3.4 Hz, 2H, H2 and H2'), 3.18 (dd, *J* = 14.5, 3.4 Hz, 1H, H3), 3.13 (dd, *J* = 10.7, 3.6 Hz, 1H, H3'), 2.88 (dd, *J* = 14.5, 10.0 Hz, 2H, H3 and H3'), 2.55 (s, 1H, H6), 2.53 (s, 1H, H6'), 1.91 (dd, *J* = 9.5, 1.8 Hz, 6H, H5 and H5'), 1.87 (dd, *J* = 9.5, 1.8 Hz, 6H, H5 and H5'), 1.38 (s, 6H, H1 and H1'), 1.36 (s, 6H, H1 and H1').

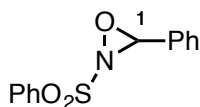
¹³C NMR (126 MHz, CDCl₃) δ 167.9, 152.1, 136.7, 129.2 (2C), 128.9 (2C), 127.0, 82.6, 64.1, 49.9 (3C), 45.2, 44.3, 34.7, 28.8, 27.8, 22.5.

HRMS (ESI⁺) Found [M+Na]⁺ = 414.0674; C₁₉H₂₂O₃N⁷⁹BrNa requires 414.0675.

IR (film) ν_{max} /cm⁻¹ 2975, 2913, 2877, 1777, 1705, 1497, 1454, 1359, 1278, 1244, 1203, 1176, 1097, 962.

$[\alpha]_{\text{D}}^{25}$ -16.6 (*c* = 0.5, CHCl₃) (13:1 *dr*)

3-Phenyl-2-(phenylsulfonyl)-1,2-oxaziridine, S3



Adapted from the procedure of Cid et al.^[16] To a solution of benzenesulfonamide (1.57 g, 10.0 mmol, 1.0 equiv.) and 4 Å molecular sieves (10 g) in CH₂Cl₂ (31 mL) under an inert atmosphere were added benzaldehyde (1.22 mL, 12.0 mmol, 1.2 equiv.) and pyrrolidine (83.5 μL, 1.00 mmol, 0.1 equiv.). The reaction mixture was stirred in a sealed flask at 60 °C for 20 h. The reaction mixture was then filtered through a short pad of Celite and concentrated *in vacuo*. (*E*)-*N*-Benzylidenebenzenesulfonamide was obtained as a white solid, which was used without further purification (1.71 g, 6.98 mmol, 70%).

Adapted from the procedure of Banerjee et al.^[17] To a solution of (*E*)-*N*-benzylidenebenzenesulfonamide (1.71 g, 6.98 mmol, 1.0 equiv.) in PhMe (68 mL) at room temperature was added K₂CO₃ (8.08 g, 58.5 mmol, 8.4 equiv.) in water (43 mL). The reaction mixture was stirred vigorously and a solution of Oxone® (5.13 g, 16.7 mmol, 2.4 equiv.) in water (43 mL) was added. If, after 1 h, the reaction had not reached completion, the aqueous phase was removed from the reaction mixture and a fresh solution of K₂CO₃ (8.08 g, 58.5 mmol, 8.4 equiv.) in water (43 mL) was added, followed by a solution of Oxone® (5.13 g, 16.7 mmol, 2.4 equiv.) in water (43 mL). This process was repeated a further three times and, upon completion, the phases were separated and the aqueous phase was extracted with PhMe (3 × 50 mL). The combined organic extracts were washed with Na₂SO₃ (aq., 10%, 150 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The resulting yellow oil was triturated with pentane to afford a light yellow solid. Purification by recrystallization (EtOAc/hexane) afforded the title compound as white crystals (1.49 g, 5.69 mmol, 82%).

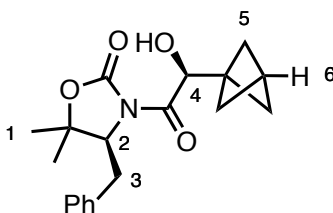
R_f 0.24 (pentane/EtOAc, 9:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 8.0 Hz, 2H, SO₂Ph*H*), 7.80 – 7.73 (m, 1H, SO₂Ph*H*), 7.68 – 7.61 (m, 2H, SO₂Ph*H*), 7.51 – 7.37 (m, 5H, Ph*H*), 5.50 (s, 1H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 135.2, 134.8, 131.6, 130.6, 129.5 (2C), 129.5 (2C), 128.9 (2C), 128.4 (2C), 76.4.

Spectroscopic data in agreement with that reported previously.^[17-18]

(S)-4-Benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)-2-hydroxyacetyl)-5,5-dimethyloxazolidin-2-one, 64t



Adapted from the procedure of Fürstner *et al.*^[19] To a solution of the (S)-4-benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.) in THF (1 mL) at $-78\text{ }^{\circ}\text{C}$ under an inert atmosphere was added sodium bis(trimethylsilyl)amide (2.0 M in THF, 90 μL , 0.18 mmol, 1.2 equiv.) dropwise and the reaction mixture left to stir for 30 min at $-78\text{ }^{\circ}\text{C}$. A solution of 3-phenyl-2-(phenylsulfonyl)-1,2-oxaziridine **S3** (59 mg, 0.23 mmol, 1.5 equiv.) in THF (0.5 mL) was then added dropwise and the reaction mixture left to stir at $-78\text{ }^{\circ}\text{C}$ for 20 min. A solution of camphorsulfonic acid (0.17 g, 0.75 mmol, 5.0 equiv.) in THF (1.5 mL) was then added to quench the reaction at $-78\text{ }^{\circ}\text{C}$ and the cooling bath removed to allow the reaction mixture to warm to room temperature. Water (1.5 mL) was then added and the reaction mixture was concentrated *in vacuo*. The remaining aqueous phase was extracted with EtOAc ($3 \times 1\text{ mL}$). The combined organic extracts were washed with NaHCO_3 (aq., sat., 3 mL) and brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , CH_2Cl_2) afforded the title compound as a white solid (40 mg, 0.12 mmol, 80%).

R_f 0.19 (pentane/EtOAc, 7:3), [UV, vanillin]

m.p. 112 – 114 $^{\circ}\text{C}$

¹H NMR (500 MHz, CDCl_3) δ 7.35 – 7.20 (m, 5H, ArH), 5.33 (d, $J = 9.9\text{ Hz}$, 1H, H4), 4.48 (dd, $J = 9.9, 3.4\text{ Hz}$, 1H, H2), 3.21 (dd, $J = 14.5, 3.4\text{ Hz}$, 1H, H3), 3.06 (d,

$J = 9.9$ Hz, 1H, *OH*), 2.91 (dd, $J = 14.5, 9.9$ Hz, 1H, H3), 2.52 (s, 1H, H6), 1.81 (dd, $J = 9.3, 1.3$ Hz, 3H, H5), 1.78 (dd, $J = 9.3, 1.3$ Hz, 3H, H5), 1.42 (s, 3H, H1), 1.38 (s, 3H, H1).

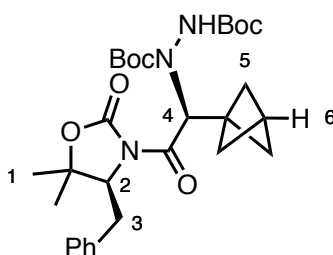
^{13}C NMR (126 MHz, CDCl_3) δ 173.8, 152.1, 136.9, 129.1 (2C), 128.9 (2C), 127.1, 83.2, 70.3, 64.2, 49.2 (3C), 45.8, 35.3, 28.7, 27.5, 22.5.

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 352.1519$; $\text{C}_{19}\text{H}_{23}\text{O}_4\text{NNa}$ requires 352.1519.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3407, 2973, 2912, 2875, 1782, 1693, 1356, 1102, 727.

$[\alpha]_{\text{D}}^{25} -6.2$ ($c = 0.18$, CHCl_3)

Di-*tert*-butyl 1-((*S*)-2-((*S*)-4-benzyl-5,5-dimethyl-2-oxooxazolidin-3-yl)-1-(bicyclo[1.1.1]pentan-1-yl)-2-oxoethyl)hydrazine-1,2-dicarboxylate, 64u



(*S*)-4-Benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)acetyl)-5,5-dimethyloxazolidin-2-one **63g** (47 mg, 0.15 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 83 μL , 0.17 mmol, 1.1 equiv.) and di-*tert*-butyl azodicarboxylate (45 mg, 0.20 mmol, 1.3 equiv.) in THF (1 mL) were submitted to **General Procedure D** at -78 $^{\circ}\text{C}$. After the addition of di-*tert*-butyl azodicarboxylate, the reaction mixture was stirred for 5 min at -78 $^{\circ}\text{C}$ and quenched by addition of NH_4Cl (aq., sat., 2 mL) at -78 $^{\circ}\text{C}$. Purification by column chromatography (SiO_2 , pentane/EtOAc, 9:1) afforded the title compound as a pale yellow oil (80 mg, 0.15 mmol, 98%).

R_f 0.29 (pentane/EtOAc, 17:3), [UV, vanillin]

¹H NMR (500 MHz, toluene-*d*₈, 363 K) δ 6.68 (br s, 1H, NH), 6.38 (s, 1H, H4), 4.27 (dd, *J* = 10.1, 2.7 Hz, 1H, H2), 3.18 (dd, *J* = 14.6, 2.7 Hz, 1H, H3), 2.58 (dd, *J* = 14.6, 10.1 Hz, 1H, H3), 2.38 (s, 1H, H6), 1.96 (dd, *J* = 9.6, 2.0 Hz, 3H, H5), 1.43 (s, 8H, C(CH₃)₃), 1.39 (s, 10H, C(CH₃)₃), 0.97 (s, 3H, H1), 0.96 (s, 3H, H1).

¹³C NMR (126 MHz, toluene-*d*₈, 298 K) δ 172.9, 151.7, 81.6, 77.7 (2C), 64.4, 59.9, 51.8 (3C), 43.4, 34.8, 28.7, 28.4 (3C), 28.2, 28.1 (3C), 22.0.

Note: Proton signals corresponding to ArH and the three remaining H5 protons are obscured by solvent signals. Carbon signals corresponding to the phenyl group are obscured by solvent signals. Broad carbon signal corresponding to carbonyls of the Boc groups at 155 ppm observed.

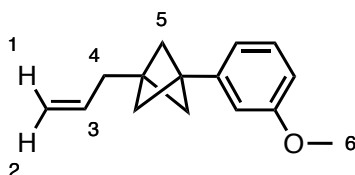
HRMS (ESI⁺) Found [M+Na]⁺ = 566.2837; C₂₉H₄₁O₇N₃Na requires 566.2837.

IR (film) ν_{max}/cm⁻¹ 2977, 1783, 1734, 1717, 1653, 1559, 1507, 1473, 1457, 1394, 1368, 1302, 1242, 1159, 1101, 1026.

[α]_D²⁵ +5.8 (*c* = 0.3, CHCl₃)

9.3.4 Reaction scope: 1,3-disubstituted BCP substrates and products

1-Allyl-3-(3-methoxyphenyl)bicyclo[1.1.1]pentane, 70



Adapted from the procedure of Knochel et al.^[20] To a solution of allylmagnesium bromide (1 M in Et₂O, 2.0 mL, 2.0 mmol, 2.0 equiv.) in an Ace pressure vial (20 mL) sealed with a septum at room temperature under an inert atmosphere was added [1.1.1]propellane **2** (0.81 M in Et₂O, 1.2 mL, 1.0 mmol, 1.0 equiv.). The septum was

replaced with a screw cap and the vial was placed in an oil bath at 100 °C behind a blast shield. After stirring for 3.5 h, the vial was removed from the oil bath and cooled to 0 °C in an ice bath. Zinc chloride (1.9 M in 2-methyltetrahydrofuran, 1.1 mL, 2.1 mmol, 2.1 equiv.) was added and the reaction mixture was stirred at room temperature for 10 min. PdCl₂(dppf)·CH₂Cl₂ (16 mg, 20 μmol, 0.02 equiv.), 3-iodoanisole (0.25 mL, 2.1 mmol, 2.1 equiv.) and THF (0.5 mL) were added to the reaction mixture and the vial was placed into an oil bath at 40 °C. After 4.5 h, NH₄Cl (aq., sat., 5 mL) was added followed by Et₂O (2 mL). The phases were separated and the aqueous phase was extracted with Et₂O (3 × 3 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/CH₂Cl₂, 19:1) afforded the title compound as a pale yellow oil (0.11 g, 0.51 mmol, 51%).

R_f 0.40 (pentane/CH₂Cl₂, 7:3), [UV, vanillin]

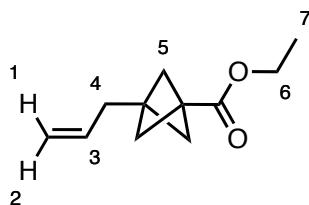
¹H NMR (500 MHz, CDCl₃) δ 7.23 – 7.19 (m, 1H, ArH), 6.81 (dt, *J* = 7.6, 1.3 Hz, 1H, ArH), 6.76 – 6.73 (m, 2H, ArH), 5.83 – 5.73 (m, 1H, H3), 5.06 – 5.00 (m, 2H, H1 and H2), 3.80 (s, 3H, H6), 2.30 (dt, *J* = 7.2, 1.3 Hz, 2H, H4), 1.89 (s, 6H, H5).

¹³C NMR (126 MHz, CDCl₃) δ 159.7, 143.3, 135.7, 129.3, 118.6, 116.0, 111.9, 111.7, 55.3, 52.2 (3C), 42.4, 37.9, 36.8.

HRMS (APCI) Found [M+H]⁺ = 215.1432; C₁₅H₁₉O requires 215.1430.

IR (film) ν_{max}/cm⁻¹ 2960, 2904, 2866, 2834, 1641, 1603, 1583, 1433, 1266.

Ethyl 3-allylbicyclo[1.1.1]pentane-1-carboxylate, **71**



Adapted from the procedure of Knochel et al.^[20] To a solution of allylmagnesium bromide (1 M in Et₂O, 4.0 mL, 4.0 mmol, 2.0 equiv.) in an Ace pressure vial (20 mL) sealed with a septum at room temperature under an inert atmosphere was added [1.1.1]propellane **2** (0.81 M in Et₂O, 2.5 mL, 2.0 mmol, 1.0 equiv.). The septum was replaced with a screw cap and the vial was placed in an oil bath at 100 °C behind a blast shield. After stirring for 4 h, the vial was removed from the oil bath and cooled to –78 °C in an acetone/dry ice bath for 30 min. Ethyl chloroformate (0.77 mL, 8.0 mmol, 4.0 equiv.) was then added in one portion and the vial was removed from the cooling bath. The reaction mixture was left to warm to room temperature. After 17 h, NH₄Cl (aq., sat., 8 mL) was then added followed by Et₂O (2 mL). The phases were separated and the aqueous phase was extracted with Et₂O (3 × 4 mL). The combined organic extracts were washed with brine (15 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 49:1) afforded the title compound as a pale yellow oil (0.27 g, 1.5 mmol, 75%).

R_f 0.52 (pentane/EtOAc, 9:1), [vanillin]

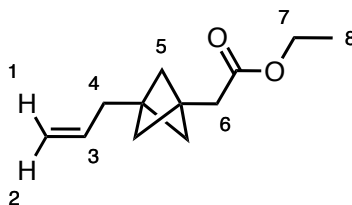
¹H NMR (500 MHz, CDCl₃) δ 5.76 – 5.63 (m, 1H, H3), 5.05 – 4.97 (m, 2H, H1 and H2), 4.11 (q, *J* = 7.1 Hz, 2H, H6), 2.23 (d, *J* = 7.2 Hz, 2H, H4), 1.90 (s, 6H, H5), 1.25 (t, *J* = 7.1 Hz, 3H, H7).

¹³C NMR (126 MHz, CDCl₃) δ 170.5, 134.8, 116.6, 60.5, 51.5 (3C), 39.1, 38.6, 36.4, 14.3.

HRMS (APCI) Found $[M+H]^+ = 181.1224$; $C_{11}H_{17}O_2$ requires 181.1223.

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 3025, 2921, 2845, 1733, 1262, 1193.

Ethyl 2-(3-allylbicyclo[1.1.1]pentan-1-yl)acetate, S4



Adapted from the procedure of Kowalski et al.^[21] To a solution of 2,2,6,6-tetramethylpiperidine (0.23 mL, 1.4 mmol, 2.4 equiv.) in THF (1.4 mL) at 0 °C under an inert atmosphere was added *n*-butyllithium (2.5 M in hexane, 0.50 mL, 1.3 mmol, 2.2 equiv.). In a separate vial, *n*-butyllithium (2.5 M in hexane, 0.46 mL, 1.1 mmol, 2.0 equiv.) was added to a solution of hexamethyldisilazane (0.24 mL, 1.1 mmol, 2.0 equiv.) in THF (0.9 mL) at 0 °C under an inert atmosphere. In a third vial, a stirred mixture of ethyl 3-allylbicyclo[1.1.1]pentane-1-carboxylate **71** (0.10 g, 0.57 mmol, 1.0 equiv.) and dibromomethane (88 μL , 1.3 mmol, 2.2 equiv.) in THF (0.9 mL) under an inert atmosphere was cooled to -78 °C. After stirring for 30 min, the lithium 2,2,6,6-tetramethylpiperidide solution was cooled to -78 °C and added to the solution containing ethyl 3-allylbicyclo[1.1.1]pentane-1-carboxylate **71**. After 5 min, the solution of lithium bis(trimethylsilyl)amide was cooled to -78 °C and added dropwise to the reaction mixture and the resulting mixture was left to stir for 15 min at -78 °C. The reaction mixture was then allowed to warm to -20 °C over 5 min and then cooled to -78 °C. A solution of *sec*-butyllithium (1.4 M in cyclohexane, 1.6 mL, 2.3 mmol, 4.0 equiv.) was then added dropwise and the reaction mixture left to stir for 15 min. The reaction mixture was then warmed to -20 °C and *n*-butyllithium (2.5 M in hexane, 0.46 mL, 1.1 mmol, 2.0 equiv.) was added. The

reaction mixture was allowed to warm to room temperature and left to stir for 2 h. The reaction mixture was then cooled to $-78\text{ }^{\circ}\text{C}$ and quenched by dropwise addition into a solution of acidic ethanol (3.4 mL) at $0\text{ }^{\circ}\text{C}$. The mixture was diluted with ether (23 mL) and HCl (aq., 1 M, 4 mL) was added. The phases were separated and the aqueous phase was extracted with Et_2O ($3 \times 5\text{ mL}$). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2 , pentane/ CH_2Cl_2 , 7:3) afforded the title compound as a pale yellow oil (20 mg, 0.10 mmol, 18%).

Note: Acidic ethanol was prepared by adding acetyl chloride slowly to ice-cooled absolute ethanol (1:5 v/v) at $0\text{ }^{\circ}\text{C}$ and stirring for 30 min at room temperature prior to use.

R_f 0.57 (pentane/EtOAc, 9:1), [vanillin]

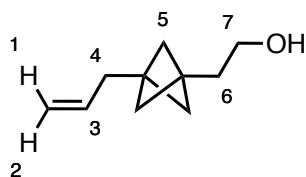
^1H NMR (500 MHz, CDCl_3) δ 5.75 – 5.67 (m, 1H, H3), 5.02 – 4.95 (m, 2H, H1 and H2), 4.12 (q, $J = 7.2\text{ Hz}$, 2H, H7), 2.47 (s, 2H, H6), 2.21 (d, $J = 7.2\text{ Hz}$, 2H, H4), 1.61 (s, 6H, H5), 1.25 (t, $J = 7.2\text{ Hz}$, 3H, H8).

^{13}C NMR (126 MHz, CDCl_3) δ 171.8, 135.7, 115.9, 60.3, 51.2 (3C), 39.2, 38.1, 36.8, 36.5, 14.5.

HRMS (APCI) Found $[\text{M}+\text{H}]^+ = 195.1382$; $\text{C}_{12}\text{H}_{19}\text{O}_2$ requires 195.1380.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3053, 1723, 1575, 1471, 1440, 1223.

2-(3-Allylbicyclo[1.1.1]pentan-1-yl)ethan-1-ol, **72**



Adapted from the procedure of Knochel *et al.*^[20] To a solution of allylmagnesium bromide (1 M in Et₂O, 4.0 mL, 4.0 mmol, 2.0 equiv.) in an Ace pressure vial (20 mL) sealed with a septum at room temperature under an inert atmosphere was added [1.1.1]propellane **2** (0.88 M in Et₂O, 2.3 mL, 2.0 mmol, 1.0 equiv.). The septum was replaced with a screw cap and the vial was placed in an oil bath at 100 °C behind a blast shield. After stirring for 3.5 h, the vial was removed from the oil bath and cooled to –78 °C. Copper(I) iodide (38 mg, 0.20 mmol, 0.1 equiv.) was added and the reaction mixture left to stir for 5 min. The reaction mixture was warmed to 0 °C and ethylene oxide (2.5 – 3.3 M in THF, 2.0 mL, 5.0 mmol, 2.5 equiv.) was added. After stirring for 21 h, NH₄Cl (aq., sat., 8 mL) was then added followed by Et₂O (2 mL). The mixture was left to stir for 15 min. The phases were separated and the aqueous phase was extracted with Et₂O (3 × 3 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 17:3) afforded the title compound as a pale yellow oil (0.11 g, 0.75 mmol, 37%).

R_f 0.19 (pentane/EtOAc, 17:3), [vanillin]

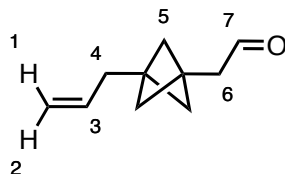
¹H NMR (400 MHz, CDCl₃) δ 5.79 – 5.61 (m, 1H, H3), 5.09 – 4.90 (m, 2H, H1 and H2), 3.65 (t, *J* = 6.8 Hz, 2H, H7), 2.19 (d, *J* = 7.2 Hz, 3H, H4), 1.72 (t, *J* = 6.8 Hz, 2H, H6), 1.53 (s, 6H, H5).

¹³C NMR (101 MHz, CDCl₃) δ 135.8, 115.7, 61.6, 50.8 (3C), 39.3, 38.1, 37.0, 35.0.

HRMS Molecular or pseudo molecular ions could not be found using ESI, APCI, EI.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2951, 2934, 2866, 2146, 1640, 1433, 1259, 1052, 995.

2-(3-Allylbicyclo[1.1.1]pentan-1-yl)acetaldehyde, S5



Adapted from the procedure of Anderson et al.^[22] To a solution of 2-(3-allylbicyclo[1.1.1]pentan-1-yl)ethan-1-ol **72** (61 mg, 0.40 mmol, 1.0 equiv.) in CH_2Cl_2 (3.2 mL) at 0 °C under an inert atmosphere was added Dess-Martin periodinane (0.24 g, 0.56 mmol, 1.4 equiv.) and NaHCO_3 (34 mg, 0.40 mmol, 1.0 equiv.). The reaction mixture was allowed to warm to room temperature. After 27 h, NaHCO_3 (aq., sat., 2 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (aq., 10%, 2 mL) were added. The mixture was stirred for 30 min. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 2 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane/EtOAc, 9:1) afforded the title compound as a pale yellow oil (28 mg, 0.18 mmol, 46%).

R_f 0.76 (pentane/EtOAc, 7:3), [vanillin]

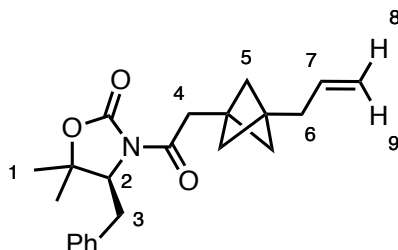
¹H NMR (400 MHz, CDCl_3) δ 9.71 (t, J = 2.8 Hz, 1H, H7), 5.76 – 5.63 (m, 1H, H3), 5.03 – 4.95 (m, 2H, H1 and H2), 2.55 (d, J = 2.8 Hz, 2H, H6), 2.21 (d, J = 7.2 Hz, 2H, H4), 1.67 (s, 6H, H5).

¹³C NMR (126 MHz, CDCl_3) δ 201.6, 135.4, 116.1, 51.5 (3C), 46.2, 41.1, 36.8, 35.2.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 151.1118$; $\text{C}_{10}\text{H}_{15}\text{O}$ requires 151.1117.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3076, 2956, 2919, 2866, 1727, 1640, 1432, 1258, 1125, 995, 913.

(S)-3-(2-(3-Allylbicyclo[1.1.1]pentan-1-yl)acetyl)-4-benzyl-5,5-dimethyloxazolidin-2-one, 63h



To a solution of 2-(3-allylbicyclo[1.1.1]pentan-1-yl)acetaldehyde **S5** (27 mg, 0.18 mmol, 1.0 equiv.) in *tert*-butanol (2.5 mL) at room temperature was added 2-methyl-2-butene (0.19 mL, 1.8 mmol, 10 equiv.). To the reaction mixture was added a solution of sodium chlorite (80%, 60 mg, 0.53 mmol, 2.0 equiv.) and sodium phosphate monobasic dihydrate (0.14 g, 0.89 mmol, 5.0 equiv.) in water (2.5 mL). The reaction mixture was left to stir for 20 h, after which brine (5 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (4 × 2 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to afford 2-(3-allylbicyclo[1.1.1]pentan-1-yl)acetic acid, which was used without further purification.

Adapted from the procedure of Palomo et al.^[12] To a solution of 2-(3-allylbicyclo[1.1.1]pentan-1-yl)acetic acid (29 mg, 0.18 mmol, 1.0 equiv.) in CH_2Cl_2 (0.3 mL) at 0 °C under an inert atmosphere was added oxalyl chloride (18 μL , 0.21 mmol, 1.2 equiv.). One drop of DMF was added and the reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to afford 2-(3-allylbicyclo[1.1.1]pentan-1-yl)acetyl chloride as an orange oil, which was used immediately without further purification.

In a separate flask, (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one **65** (37 mg, 0.18 mmol, 1.0 equiv.) and *n*-butyllithium (2.5 M in hexanes, 85 μ L, 0.21 mmol, 1.2 equiv.) in THF (0.5 mL) were submitted to **General Procedure A** for 50 min at -78°C . 2-(3-Allylbicyclo[1.1.1]pentan-1-yl)acetyl chloride (33 mg, 0.18 mmol, 1.0 equiv.) was then added dropwise at -78°C and the reaction mixture was allowed to warm to room temperature over 17 h. Purification by column chromatography (SiO_2 , pentane/EtOAc, 17:3) afforded the title compound as a yellow oil (40 mg, 0.11 mmol, 64% over three steps).

R_f 0.67 (pentane/EtOAc, 7:3), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 7.34 – 7.21 (m, 5H, ArH), 5.76 – 5.63 (m, 1H, H7), 5.05 – 4.90 (m, 2H, H8 and H9), 4.51 (dd, $J = 9.9, 3.7$ Hz, 1H, H2), 3.22 – 3.13 (m, 3H, H3 and H4), 2.85 (dd, $J = 14.4, 9.9$ Hz, 1H, H3), 2.20 (d, $J = 7.2$ Hz, 2H, H6), 1.63 (s, 6H, H5), 1.35 (s, 6H, H1).

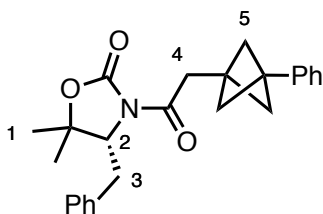
^{13}C NMR (126 MHz, CDCl_3) δ 171.5, 152.6, 137.2, 135.6, 129.2 (2C), 128.8 (2C), 126.9, 115.9, 82.0, 63.6, 51.4 (3C), 39.7, 38.2, 36.7, 36.7, 35.6, 28.7, 22.5.

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 376.1882$; $\text{C}_{22}\text{H}_{27}\text{O}_3\text{NNa}$ requires 376.1883.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2968, 2868, 1779, 1698, 1356, 1330, 1277, 1236, 1184, 1159, 1091, 913.

$[\alpha]_{\text{D}}^{25} -7.7$ ($c = 0.2$, CHCl_3)

(R)-4-Benzyl-5,5-dimethyl-3-(2-(3-phenylbicyclo[1.1.1]pentan-1-yl)acetyl)-oxazolidin-2-one, 63i



Adapted from the procedure of Caputo^[23] To a flame-dried vial was added Fe(acac)₃ (35 mg, 0.10 mmol, 0.2 equiv.), TMEDA (30 μ L, 0.20 mmol, 0.4 equiv.) and ethyl 2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetate **73** (0.14 g, 0.50 mmol, 1.0 equiv.) under an inert atmosphere. THF (0.5 mL) was added and the resulting mixture was stirred at room temperature for 5 min. Phenylmagnesium bromide (1 M in THF, 0.80 mL, 0.80 mmol, 1.6 equiv.) was added at 1.8 mL/h *via* syringe pump at room temperature and, upon completion of addition, water (0.5 mL) was added. The phases were separated and the aqueous phase was extracted with Et₂O (3 $\times$ 0.5 mL). The combined organic extracts were placed in a separate vial and sodium hydroxide (0.10 g, 2.5 mmol, 5.0 equiv.) in MeOH (1 mL) was added slowly. The resulting mixture was stirred at 80 $^{\circ}$ C for 2 h. The reaction mixture was then concentrated *in vacuo*, diluted with water (2 mL) and HCl (conc.) was added until pH $\sim$ 1. The aqueous phase was extracted with Et₂O (3 $\times$ 2 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to afford 2-(3-phenylbicyclo[1.1.1]pentan-1-yl)acetic acid **66c** as a colorless oil (59 mg, 0.29 mmol, 58%).

According to the procedure of Palomo *et al.*^[12] To a solution of 2-(3-phenylbicyclo[1.1.1]pentan-1-yl)acetic acid **66c** (59 mg, 0.29 mmol, 1.0 equiv.) in CH₂Cl₂ (0.6 mL) at 0 $^{\circ}$ C under an inert atmosphere was added oxalyl chloride (29 μ L, 0.35 mmol, 1.2 equiv.). One drop of DMF was added and the reaction mixture was

allowed to stir at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* to afford 2-(3-phenylbicyclo[1.1.1]pentan-1-yl)acetyl chloride as an orange oil, which was used immediately without further purification.

In a separate flask, (*R*)-4-benzyl-5,5-dimethyloxazolidin-2-one *ent*-**65** (60 mg, 0.29 mmol, 1.0 equiv.) and *n*-butyllithium (2.5 M in hexanes, 0.14 mL, 0.35 mmol, 1.2 equiv.) in THF (0.9 mL) were submitted to **General Procedure A** for 2.5 h at -78°C . 2-(3-Phenylbicyclo[1.1.1]pentan-1-yl)acetyl chloride (64 mg, 0.29 mmol, 1.0 equiv.) was then added dropwise at -78°C and the reaction mixture was allowed to warm to room temperature over 20 h. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 17:3) afforded the title compound as a yellow oil (75 mg, 0.19 mmol, 66% over two steps).

R_f 0.52 (petroleum ether/ Et_2O , 3:2), [UV, phosphomolybdic acid]

^1H NMR (400 MHz, CDCl_3) δ 7.34 – 7.27 (m, 6H, ArH), 7.25 – 7.17 (m, 4H, ArH), 4.55 (dd, $J = 9.8, 3.9$ Hz, 1H, H2), 3.27 (d, $J = 2.3$ Hz, 2H, H4), 3.19 (dd, $J = 14.3, 3.9$ Hz, 1H, H3), 2.88 (dd, $J = 14.3, 9.8$ Hz, 1H, H3), 2.05 (s, 6H, H5), 1.37 (s, 3H, H1), 1.36 (s, 3H, H1).

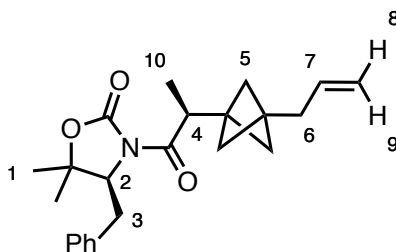
^{13}C NMR (126 MHz, CDCl_3) δ 171.4, 152.7, 140.8, 137.1, 129.2 (2C), 128.8 (2C), 128.3 (2C), 127.0, 126.5, 126.2 (2C), 82.2, 63.6, 53.4 (3C), 42.8, 37.9, 35.6, 35.4, 28.7, 22.5.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 390.2065$; $\text{C}_{25}\text{H}_{28}\text{O}_3\text{N}$ requires 390.2064.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2967, 2910, 2869, 1777, 1697, 1392, 1357, 1277, 1258, 1237, 1184, 1159, 1130, 1089.

$[\alpha]_{\text{D}}^{25} +10.8$ ($c = 0.2$, CHCl_3)

(*S*)-3-((*S*)-2-(3-Allylbicyclo[1.1.1]pentan-1-yl)propanoyl)-4-benzyl-5,5-dimethyl-oxazolidin-2-one, 64v



(*S*)-3-(2-(3-Allylbicyclo[1.1.1]pentan-1-yl)acetyl)-4-benzyl-5,5-dimethyloxazolidin-2-one **63h** (34 mg, 96 μ mol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 52 μ L, 0.11 mmol, 1.1 equiv.) and iodomethane (18 μ L, 0.29 mmol, 3.0 equiv.) in THF (0.6 mL) were submitted to **General Procedure D** at -78 $^{\circ}$ C. After the addition of iodomethane, the reaction mixture was left to stir for 3 h at -78 $^{\circ}$ C. Purification by column chromatography (SiO_2 , pentane/EtOAc, 19:1) afforded the title compound as a pale yellow oil (32 mg, 87 μ mol, 91%).

R_f 0.43 (pentane/EtOAc, 9:1), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 7.32 – 7.19 (m, 5H, ArH), 5.74 – 5.63 (m, 1H, H7), 5.03 – 4.92 (m, 2H, H8 and H9), 4.50 (dd, J = 9.5, 3.9 Hz, 1H, H2), 4.09 (q, J = 6.8 Hz, 1H, H4), 3.08 (dd, J = 14.3, 3.9 Hz, 1H, H3), 2.88 (dd, J = 14.3, 9.5 Hz, 1H, H3), 2.20 (d, J = 7.1 Hz, 2H, H6), 1.55 (dd, J = 9.4, 1.3 Hz, 3H, H5), 1.53 (dd, J = 9.4, 1.3 Hz, 3H, H5), 1.38 (s, 3H, H1), 1.37 (s, 3H, H1), 1.05 (d, J = 6.8 Hz, 3H, H10).

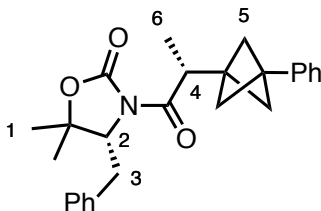
^{13}C NMR (126 MHz, CDCl_3) δ 174.9, 152.6, 137.2, 135.5, 129.3 (2C), 128.8 (2C), 126.9, 116.0, 81.8, 63.8, 49.3 (3C), 41.5, 38.3, 38.3, 36.7, 35.7, 28.6, 22.4, 13.6.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 368.2224$; $\text{C}_{23}\text{H}_{30}\text{O}_3\text{N}$ requires 368.2220.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2968, 2907, 2869, 1778, 1697, 1497, 1457, 1374, 1277, 1235, 1182, 1158, 1090, 913.

$[\alpha]_{\text{D}}^{25} -1.2$ ($c = 0.3$, CHCl_3)

(*R*)-4-Benzyl-5,5-dimethyl-3-((*R*)-2-(3-phenylbicyclo[1.1.1]pentan-1-yl)propanoyl)-oxazolidin-2-one, **64w**



(*R*)-4-Benzyl-5,5-dimethyl-3-(2-(3-phenylbicyclo[1.1.1]pentan-1-yl)acetyl)oxazolidin-2-one **63i** (39 mg, 0.10 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 55 μL , 0.11 mmol, 1.1 equiv.) and iodomethane (19 μL , 0.30 mmol, 3.0 equiv.) in THF (0.7 mL) were submitted to **General Procedure D** at -78°C . After the addition of iodomethane, the reaction mixture was left to stir for 3 h at -78°C . Purification by column chromatography (SiO_2 , petroleum ether/ Et_2O , 9:1) afforded the title compound as a pale yellow oil (37 mg, 91 μmol , 91%).

R_f 0.38 (petroleum ether/ Et_2O , 4:1), [UV, phosphomolybdic acid]

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.33 – 7.17 (m, 10H, ArH), 4.54 (dd, $J = 9.4, 4.0$ Hz, 1H, H2), 4.20 (q, $J = 6.8$ Hz, 1H, H4), 3.11 (dd, $J = 14.3, 4.0$ Hz, 1H, H3), 2.91 (dd, $J = 14.3, 9.4$ Hz, 1H, H3), 1.98 (dd, $J = 9.5, 1.6$ Hz, 3H, H5), 1.95 (dd, $J = 9.5, 1.6$ Hz, 3H, H5), 1.40 (s, 3H, H1), 1.38 (s, 3H, H1), 1.13 (d, $J = 6.8$ Hz, 3H, H6).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 174.8, 152.6, 140.8, 137.1, 129.3 (2C), 128.8 (2C), 128.3 (2C), 126.9, 126.6, 126.2 (2C), 81.9, 63.8, 51.3 (3C), 41.3, 40.1, 38.2, 35.7, 28.6, 22.4, 13.7.

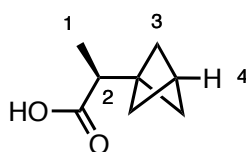
HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 426.2040$; $\text{C}_{26}\text{H}_{29}\text{O}_3\text{NNa}$ requires 426.2040.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2970, 2908, 2870, 1776, 1697, 1497, 1455, 1373, 1277, 1237, 1182, 1160, 1102.

$[\alpha]_{\text{D}}^{25} +2.6$ ($c = 0.3$, CHCl_3)

9.3.5 Auxiliary removal and derivatization of α -chiral BCP products

(*S*)-2-(Bicyclo[1.1.1]pentan-1-yl)propanoic acid, **74**



Adapted from the procedure of Zakarian *et al.*^[24] To a solution of (*S*)-4-benzyl-3-((*S*)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one **64g** (82 mg, 0.25 mmol, 1.0 equiv.), H_2O_2 (30%, 0.24 mL) and water (0.24 mL) in THF (1 mL) at 0 °C was added lithium hydroxide (18 mg, 0.76 mmol, 3.05 equiv.). The reaction mixture was allowed to warm to room temperature and stirred for 3 h, after which water (0.15 mL), H_2O_2 (30%, 0.15 mL) and lithium hydroxide (18 mg, 0.76 mmol, 3.05 equiv.) were added at room temperature and stirred for a further 3 h. The reaction was quenched by the addition of Na_2SO_3 (aq., 1.5 M, 1 mL) and HCl (aq., 1 M, 1 mL) and allowed to stir until two transparent phases were visible (pH ~4). The phases were separated and the aqueous phase extracted with EtOAc (3 $\times$ 2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was dissolved in EtOAc (1 mL) and the organic phase was extracted with NaOH (aq., 3 M, 3 $\times$ 1 mL) and water (2 $\times$ 1 mL). The aqueous extracts were combined and set aside. The organic phase was washed with HCl (aq., 1 M, 1 mL) and brine (1 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford (*S*)-4-benzyl-5,5-

dimethyloxazolidin-2-one **65** as a colorless oil (43 mg, 0.21 mmol, 83%). The aqueous phase that was set aside previously was acidified with HCl (aq., 1 M) to pH 1 and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford the title compound as a colorless oil (33 mg, 0.24 mmol, 95%).

R_f 0.57 (CH₂Cl₂/MeOH, 19:1), [phosphomolybdic acid]

¹H NMR (500 MHz, CDCl₃) δ 2.59 (q, *J* = 7.0 Hz, 1H, H2), 2.50 (s, 1H, H4), 1.74 (s, 6H, H3), 1.10 (d, *J* = 7.0 Hz, 3H, H1).

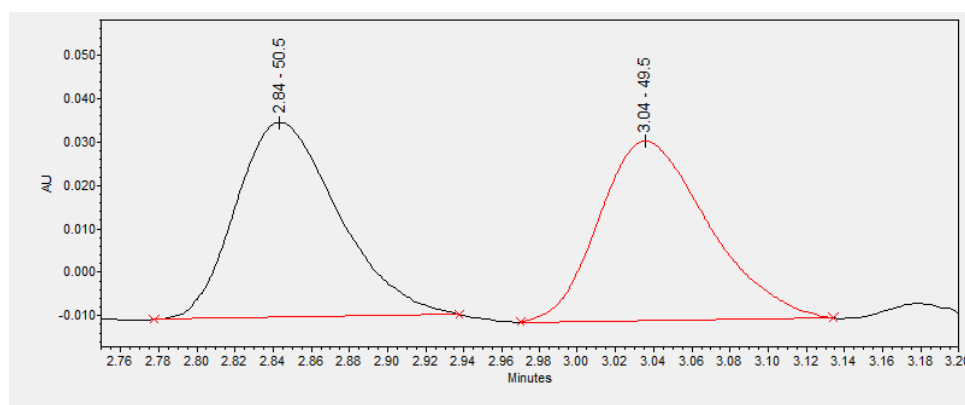
¹³C NMR (126 MHz, CDCl₃) δ 178.8, 49.3 (3C), 45.4, 41.4, 26.7, 13.4.

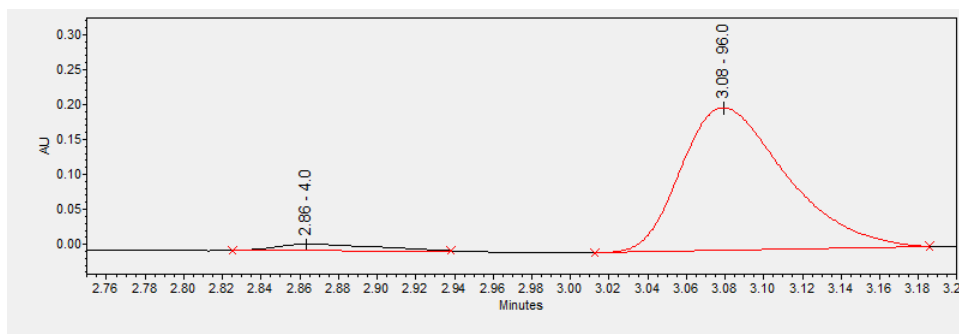
HRMS (ESI⁺) Found [M+H]⁺ = 139.0762; C₈H₁₁O₂ requires 139.0765.

IR (film) ν_{max}/cm⁻¹ 2969, 2909, 2873, 1732, 1708, 1262, 1219, 772.

[α]_D²⁵ +22.6 (*c* = 0.1, CHCl₃)

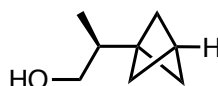
SFC 92% *ee* (CHIRALPAK ID, 1 – 30% MeOH/CO₂ gradient over 5 min, 1.5 mL/min, *t_R* major – 3.0 min, minor – 2.8 min) after derivatization to (*S*)-2-(bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate (*S*)-**S6**.





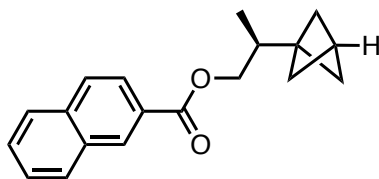
Derivatization for *ee* determination

(*S*)-2-(Bicyclo[1.1.1]pentan-1-yl)propan-1-ol, (*S*)-**76**



Adapted from the procedure of Zakarian *et al.*^[24] To a solution of lithium aluminium hydride (1 M in THF, 0.09 mL, 0.09 mmol, 1.8 equiv.) in THF (0.25 mL) at $-78\text{ }^{\circ}\text{C}$ under an inert atmosphere was added (*S*)-2-(bicyclo[1.1.1]pentan-1-yl)propanoic acid **74** (7 mg, 0.05 mmol, 1.0 equiv.) in THF (0.25 mL). The reaction was stirred for 3 h at $-78\text{ }^{\circ}\text{C}$. Upon completion, water (20 μL) was added at $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was stirred for 5 min. NaOH (aq., 3 M, 20 μL) was then added and the reaction mixture was left to stir for 5 min at $-78\text{ }^{\circ}\text{C}$ and then warmed to room temperature. Water (70 μL) was added and the reaction mixture was stirred for a further 2 h at room temperature. The reaction mixture was then filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane/EtOAc, 17:3) afforded the title compound as a colorless oil (2 mg, 0.01 mmol, 8%). The spectroscopic data of 2-(bicyclo[1.1.1]pentan-1-yl)propan-1-ol **76** is detailed below.

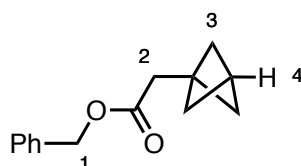
(S)-2-(Bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate, (S)-S6



Adapted from the procedure of Zakarian et al.^[24] To a solution of (S)-2-(bicyclo[1.1.1]pentan-1-yl)propan-1-ol **76** (2 mg, 0.01 mmol, 1.0 equiv.), Et₃N (3 μ L, 0.02 mmol, 2.0 equiv.) and DMAP (0.1 mg, 1 μ mol, 0.1 equiv.) in CH₂Cl₂ (0.06 mL) at 0 °C under an inert atmosphere was added 2-naphthoyl chloride (4 mg, 0.01 mmol, 2.0 equiv.). After 10 min, the reaction mixture was warmed to room temperature and left to stir for 17 h. Upon completion, NH₄Cl (aq., sat., 0.1 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 $\times$ 0.1 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 9:1) afforded the title compound as a pale yellow oil (0.8 mg, 3 μ mol, 24%). The spectroscopic data of 2-(bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate **S6** is detailed below.

Synthesis of racemic 2-(bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate, *rac*-S6

Benzyl 2-(bicyclo[1.1.1]pentan-1-yl)acetate, S7



Adapted from the procedure of Anderson et al.^[11] To a solution of benzyl 2-bromoacetate (0.48 mL, 3.0 mmol, 1.0 equiv.) in CH₂Cl₂ (6.0 mL) at room

temperature was added tetrabutylammonium iodide (1.7 g, 4.5 mmol, 1.5 equiv.). The reaction mixture was stirred for 10 min and [1.1.1]propellane **2** (0.69 M in Et₂O, 8.7 mL, 6.0 mmol, 2.0 equiv.) was added. Et₃B (1 M in hexane, 0.30 mL, 0.30 mmol, 0.1 equiv.) was then syringed into the reaction mixture. After 1 h, the reaction mixture was concentrated *in vacuo*. The residue was then dissolved in CH₂Cl₂ (6.0 mL) and TTMS (1.9 mL, 6.0 mmol, 2.0 equiv.) was then added. After stirring for 2 – 3 min at room temperature, Et₃B (1 M in hexane, 1.5 mL, 1.5 mmol, 0.5 equiv.) was syringed into the reaction mixture. The reaction mixture was left to stir at room temperature for 3 h, after which it was concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/CH₂Cl₂, 1:1) afforded the title compound as a pale yellow oil (0.43 g, 2.0 mmol, 66%).

R_f 0.57 (CH₂Cl₂), [UV, vanillin]

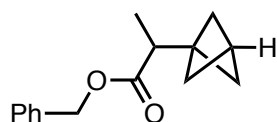
¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.29 (m, 5H, ArH), 5.11 (s, 2H, H1), 2.51 (s, 2H, H2), 2.46 (s, 1H, H4), 1.77 (s, 6H, H3).

¹³C NMR (126 MHz, CDCl₃) δ 171.5, 136.2, 128.7 (2C), 128.5 (2C), 128.3, 66.3, 51.4 (3C), 41.1, 38.6, 28.1.

HRMS (APCI) Found [M+H]⁺ = 217.1224; C₁₄H₁₇O₂ requires 217.1223.

IR (film) ν_{max}/cm⁻¹ 3054, 2966, 2873, 1736, 1575, 1471, 1439, 1222.

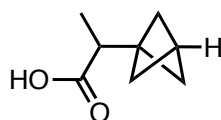
Benzyl 2-(bicyclo[1.1.1]pentan-1-yl)propanoate, *rac*-75



Benzyl 2-(bicyclo[1.1.1]pentan-1-yl)acetate **S7** (0.43 g, 2.0 mmol, 1.0 equiv.), sodium bis(trimethylsilyl)amide (2.0 M in THF, 1.1 mL, 2.2 mmol, 1.1 equiv.) and

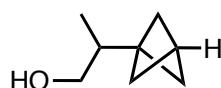
iodomethane (0.37 mL, 6.0 mmol, 3.0 equiv.) in THF (12 mL) were submitted to **General Procedure D** at 0 °C. After the addition of iodomethane, the reaction mixture was left to stir for 3 h at 0 °C. Purification by column chromatography (SiO₂, pentane/CH₂Cl₂, 1:1) afforded the title compound as a pale yellow oil (0.15 g, 0.65 mmol, 32%). The spectroscopic data of benzyl 2-(bicyclo[1.1.1]pentan-1-yl)propanoate **75** is detailed below.

2-(Bicyclo[1.1.1]pentan-1-yl)propanoic acid, *rac*-74



Adapted from the procedure of Shioiri et al.^[25] To a solution of benzyl 2-(bicyclo[1.1.1]pentan-1-yl)propanoate *rac*-**75** (37 mg, 0.16 mmol, 1.0 equiv.) in MeOH (3.2 mL) at room temperature under an inert atmosphere was added Pd/C (10% wt., 3.7 mg, 16 μmol, 0.1 equiv.). The reaction mixture was stirred at room temperature under a H₂ atmosphere. After 6 h, the reaction mixture was filtered through a pad of Celite® and concentrated *in vacuo* to afford the title compound as a colorless oil (22 mg, 0.16 mmol, 97%). The spectroscopic data of 2-(bicyclo[1.1.1]pentan-1-yl)propanoic acid **74** is detailed above.

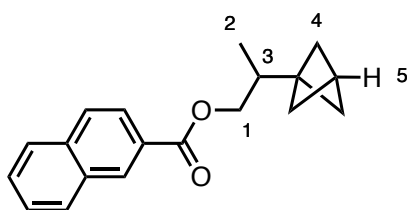
2-(Bicyclo[1.1.1]pentan-1-yl)propan-1-ol, *rac*-76



Adapted from the procedure of Zakarian et al.^[24] To a solution of lithium aluminium hydride (1 M in THF, 0.28 mL, 0.28 mmol, 1.8 equiv.) in THF (0.25 mL) at 0 °C under an inert atmosphere was added 2-(bicyclo[1.1.1]pentan-1-yl)propanoic

acid *rac*-**74** (22 mg, 0.16 mmol, 1.0 equiv.) in THF (0.25 mL). The reaction was stirred for 5 h at 0 °C. Upon completion, the reaction mixture was cooled to –78 °C, water (40 µL) was added and the reaction mixture was stirred for 5 min. NaOH (aq., 3 M, 40 µL) was then added and the reaction mixture was left to stir 5 min at –78 °C and then warmed to room temperature. Water (0.14 mL) was added and the reaction mixture was stirred for a further 2 h at room temperature. The reaction mixture was then filtered and concentrated *in vacuo* to afford the title compound, which was used without further purification (19 mg, 0.15 mmol, 95%). The spectroscopic data of 2-(bicyclo[1.1.1]pentan-1-yl)propan-1-ol **76** is detailed below.

2-(Bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate, *rac*-S6



Adapted from the procedure of Zakarian et al.^[24] To a solution of 2-(bicyclo[1.1.1]pentan-1-yl)propan-1-ol *rac*-**76** (19 mg, 0.15 mmol, 1.0 equiv.), Et₃N (42 µL, 0.30 mmol, 2.0 equiv.) and DMAP (1.8 mg, 15 µmol, 0.1 equiv.) in CH₂Cl₂ (0.8 mL) at 0 °C under an inert atmosphere was added 2-naphthoyl chloride (58 mg, 0.30 mmol, 2.0 equiv.). After 10 min, the reaction mixture was warmed to room temperature and left to stir for 17 h. Upon completion, NH₄Cl (aq., sat., 0.8 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 0.5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 9:1) afforded the title compound as a pale yellow oil (18 mg, 65 µmol, 43%).

R_f 0.71 (pentane/EtOAc, 17:3), [UV, vanillin]

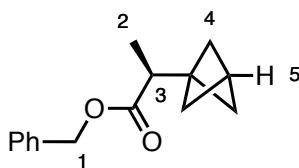
¹H NMR (500 MHz, CDCl₃) δ 8.60 (s, 1H, ArH), 8.06 (dd, *J* = 8.6, 1.7 Hz, 1H, ArH), 7.96 (d, *J* = 8.1 Hz, 1H, ArH), 7.89 (d, *J* = 8.9 Hz, 2H, ArH), 7.60 – 7.54 (m, 2H, ArH), 4.28 (dd, *J* = 10.7, 6.6 Hz, 1H, H1), 4.17 (dd, *J* = 10.7, 6.6 Hz, 1H, H1), 2.51 (s, 1H, H5), 2.07 (h, *J* = 6.8 Hz, 1H, H3), 1.75 (s, 6H, H4), 0.99 (d, *J* = 6.8 Hz, 3H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 167.0, 135.6, 132.7, 131.1, 129.5, 128.3, 128.3, 127.9, 127.9, 126.8, 125.4, 68.2, 49.0 (3C), 47.4, 34.2, 27.3, 13.9.

HRMS (ESI⁺) Found [M+H]⁺ = 281.1536; C₁₉H₂₀O₂ requires 281.1536.

IR (film) ν_{max}/cm⁻¹ 2962, 2907, 2870, 1717, 1467, 1282, 1227, 1196.

Benzyl (*S*)-2-(bicyclo[1.1.1]pentan-1-yl)propanoate, 75



Adapted from the procedure of Trost et al.^[26] To a solution of benzyl alcohol (41 μL, 0.40 mmol, 2.0 equiv.) in THF (1 mL) at room temperature under an inert atmosphere was added *n*-butyllithium (2.5 M in hexane, 0.12 mL, 0.30 mmol, 1.5 equiv.). The reaction mixture was added to a separate vial containing (*S*)-4-benzyl-3-((*S*)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one **64g** (65 mg, 0.20 mmol, 1.0 equiv.) in THF (1 mL) at 0 °C under an inert atmosphere. The reaction mixture was stirred at 0 °C for 5 h. Upon completion, the reaction mixture was warmed to room temperature and NH₄Cl (aq., sat., 2 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 2 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column

chromatography (SiO₂, pentane/EtOAc, 9:1) afforded the title compound as a pale yellow oil (41 mg, 0.18 mmol, 89%).

R_f 0.74 (pentane/EtOAc, 17:3), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.39 – 7.29 (m, 5H, ArH), 5.13 (d, *J* = 12.3 Hz, 1H, H1), 5.09 (d, *J* = 12.3 Hz, 1H, H1), 2.60 (q, *J* = 7.0 Hz, 1H, H3), 2.45 (s, 1H, H5), 1.69 (d, *J* = 9.6 Hz, 3H, H4), 1.65 (d, *J* = 9.6 Hz, 3H, H4), 1.09 (d, *J* = 7.0 Hz, 3H, H2).

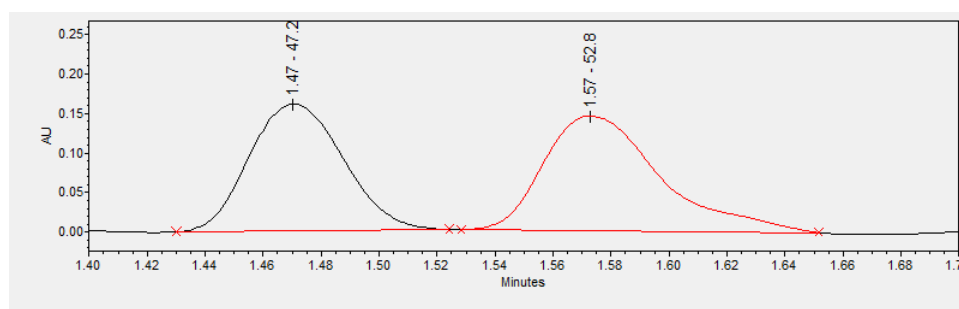
¹³C NMR (126 MHz, CDCl₃) δ 174.3, 136.3, 128.6 (2C), 128.5 (2C), 128.3, 66.2, 49.4 (3C), 45.8, 41.7, 26.8, 13.5.

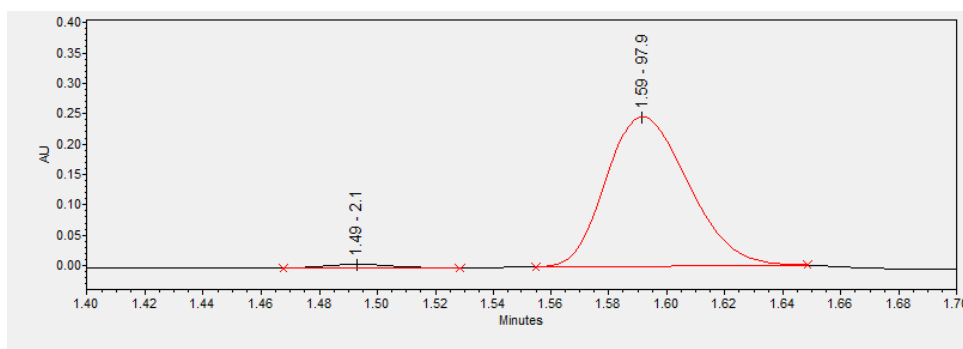
HRMS (ESI⁺) Found [M+Na]⁺ = 253.1200; C₁₅H₁₈O₂Na requires 253.1199.

IR (film) ν_{max} /cm⁻¹ 2969, 2910, 2873, 1736, 1456, 1261, 1198, 1173, 1146, 1128, 751, 698.

[α]_D²⁵ +9.8 (*c* = 0.2, CHCl₃)

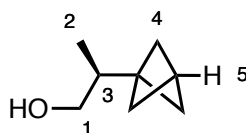
SFC 96% *ee* (CHIRALPAK ID, 1 – 30% MeOH/CO₂ gradient over 5 min, 1.5 mL/min, *t_R* major – 1.6 min, minor – 1.5 min)





The synthesis of racemic benzyl 2-(bicyclo[1.1.1]pentan-1-yl)propanoate *rac-75* is detailed above.

(S)-2-(Bicyclo[1.1.1]pentan-1-yl)propan-1-ol, (S)-76



Adapted from the procedure of Zakarian et al.^[24] To a solution of lithium aluminium hydride (1 M in THF, 0.27 mL, 0.27 mmol, 1.8 equiv.) in THF (0.25 mL) at $-78\text{ }^{\circ}\text{C}$ under an inert atmosphere was added (S)-4-benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one **64g** (49 mg, 0.15 mmol, 1.0 equiv.) in THF (0.25 mL). The reaction was stirred for 4 h at $-78\text{ }^{\circ}\text{C}$. Upon completion, water (20 μL) was added at $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was stirred for 5 min. NaOH (aq., 3 M, 20 μL) was then added and the reaction mixture was left to stir for 5 min at $-78\text{ }^{\circ}\text{C}$ and then warmed to room temperature. Water (70 μL) was added and the reaction mixture was stirred for a further 2 h at room temperature. The reaction mixture was then filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane/EtOAc, 17:3) afforded the title compound as a colorless oil (13 mg, 0.10 mmol, 67%).

R_f 0.31 (pentane/EtOAc, 7:3), [vanillin]

¹H NMR (400 MHz, CDCl₃) δ 3.64 – 3.52 (m, 1H, H1), 3.43 – 3.32 (m, 1H, H1), 2.48 (s, 1H, H5), 1.68 (s, 6H, H4), 1.16 (t, *J* = 5.7 Hz, 1H, H3), 0.85 (d, *J* = 7.0 Hz, 3H, H2).

Note: the *OH* resonance was not observed.

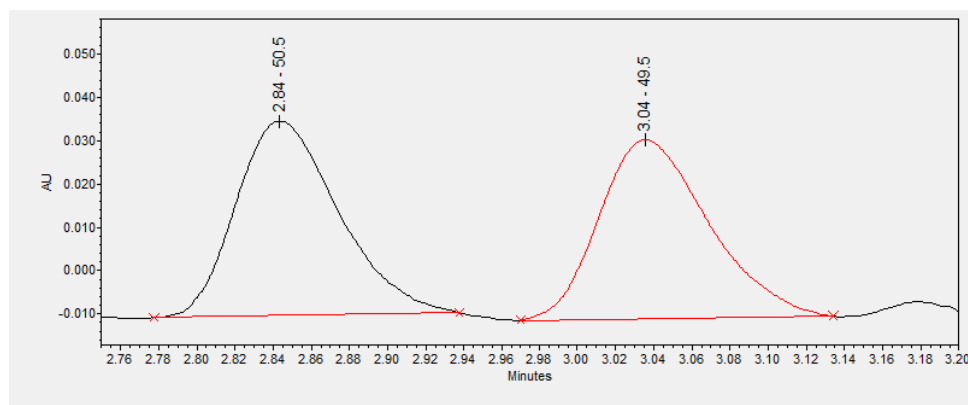
¹³C NMR (126 MHz, CDCl₃) δ 66.6, 49.0 (3C), 47.5, 37.2, 27.4, 13.5.

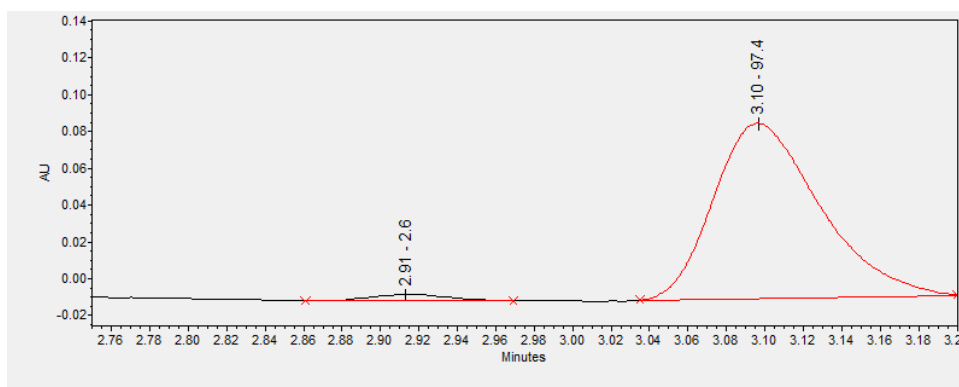
HRMS Molecular or pseudo molecular ions could not be found using ESI, Ammonia CI and Methane CI.

IR (film) ν_{max} /cm⁻¹ 2960, 2923, 2911, 2870, 1205, 773.

[α]_D²⁵ +2.9 (*c* = 0.17, CHCl₃)

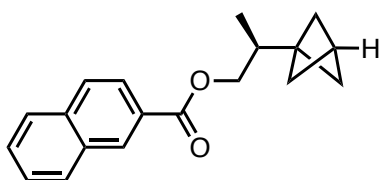
SFC 95% *ee* (CHIRALPAK ID, 1 – 30% MeOH/CO₂ gradient over 5 min, 1.5 mL/min, *t_R* major – 3.0 min, minor – 2.8 min) after derivatization to (*S*)-2-(bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate (*S*)-**S6**.





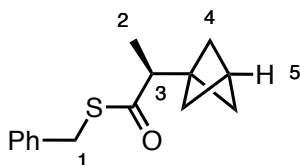
Derivatization for *ee* determination

(*S*)-2-(Bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate, (*S*)-**S6**



Adapted from the procedure of Zakarian *et al.*^[24] To a solution of (*S*)-2-(bicyclo[1.1.1]pentan-1-yl)propan-1-ol **76** (13 mg, 0.10 mmol, 1.0 equiv.), Et₃N (30 μ L, 0.20 mmol, 2.0 equiv.) and DMAP (1.2 mg, 10 μ mol, 0.1 equiv.) in CH₂Cl₂ (0.5 mL) at 0 °C under an inert atmosphere was added 2-naphthoyl chloride (38 mg, 0.20 mmol, 2.0 equiv.). After 10 min, the reaction mixture was warmed to room temperature and left to stir for 17 h. Upon completion, NH₄Cl (aq., sat., 0.6 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 $\times$ 0.5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 9:1) afforded the title compound as a pale yellow oil (3.9 mg, 14 μ mol, 14%). The spectroscopic data of 2-(bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate **S6** is detailed above. The synthesis of racemic 2-(bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate *rac*-**S6** is detailed above.

S-Benzyl (S)-2-(bicyclo[1.1.1]pentan-1-yl)propanethioate, 77



Adapted from the procedure of Trost *et al.*^[26] To a solution of benzyl mercaptan (26 μ L, 0.22 mmol, 1.1 equiv.) in THF (0.5 mL) at 0 °C under an inert atmosphere was added *n*-butyllithium (2.5 M in hexane, 80 μ L, 0.20 mmol, 1.0 equiv.) and the reaction mixture was stirred for 30 min. The reaction mixture was then cooled to –78 °C and added dropwise to a separate vial containing (S)-4-benzyl-3-((S)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one **64g** (66 mg, 0.20 mmol, 1.0 equiv.) in THF (0.6 mL) at –78 °C under an inert atmosphere. The reaction mixture was stirred at –78 °C for 6 h and left to warm to room temperature over 15 h. The reaction mixture was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/CH₂Cl₂, 9:1) afforded the title compound as a pale yellow oil (45 mg, 0.18 mmol, 92%).

R_f 0.05 (pentane/CH₂Cl₂, 9:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.21 (m, 5H, ArH), 4.13 (d, *J* = 13.8 Hz, 1H, H1), 4.08 (d, *J* = 13.8 Hz, 1H, H1), 2.76 (q, *J* = 6.9 Hz, 1H, H3), 2.47 (s, 1H, H5), 1.69 (s, 6H, H4), 1.12 (d, *J* = 6.9 Hz, 3H, H2).

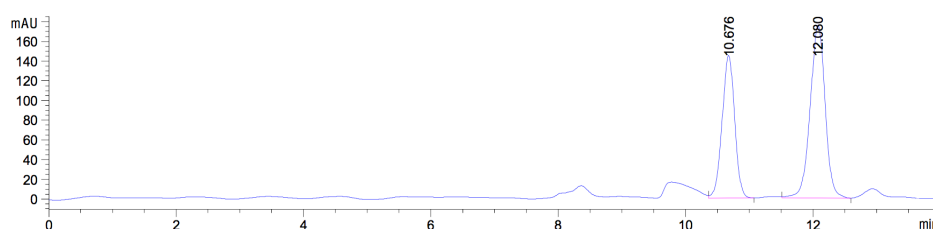
¹³C NMR (126 MHz, CDCl₃) δ 200.0, 138.0, 129.0 (2C), 128.7 (2C), 127.3, 50.3, 49.4 (3C), 45.6, 33.1, 27.0, 13.7.

HRMS (ESI⁺) Found [M+Na]⁺ = 269.0971; C₁₅H₁₈ONa³²S requires 269.0971.

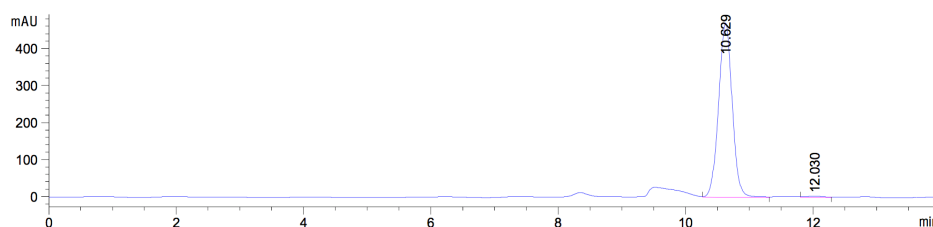
IR (film) ν_{max} /cm^{–1} 2978, 2915, 2879, 1779, 1719, 1454, 1377, 1277, 1249, 1205, 1103, 993.

$[\alpha]_{\text{D}}^{25} +11.3$ ($c = 0.2$, CHCl_3)

HPLC 98% *ee* (CHIRALPAK IA, 2% IPA/hexane, 1.3 mL/min, t_{R} major – 10.6 min, minor – 12.0 min)



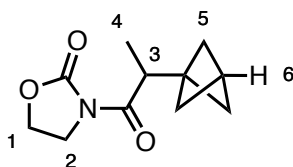
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.676	VB	0.2120	1984.19385	144.69740	40.7822
2	12.080	VB	0.2512	2881.15259	175.78648	59.2178



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.629	VV	0.2272	6991.32813	470.96484	98.8375
2	12.030	VV	0.3083	82.23152	3.92634	1.1625

Synthesis of racemic *S*-benzyl 2-(bicyclo[1.1.1]pentan-1-yl)propanethioate, *rac*-77

3-(2-(Bicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one, S8



To a solution of 3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one **97** (0.10 g, 0.30 mmol, 1.0 equiv.) in CH_2Cl_2 (0.3 mL) was added TTMSS (0.28 mL, 0.90 mmol, 3.0 equiv.). After stirring for 2 – 3 min at room

temperature, Et₃B (1 M in hexane, 0.15 mL, 0.15 mmol, 0.5 equiv.) was syringed into the reaction mixture. The reaction mixture was left to stir at room temperature for 4.5 h, after which the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 7:3) afforded the title compound as a pale yellow oil (13 mg, 62 μmol, 21%).

R_f 0.33 (pentane/EtOAc, 7:3), [UV, vanillin]

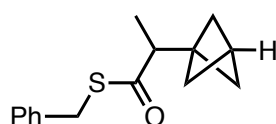
¹H NMR (400 MHz, CDCl₃) δ 4.45 – 4.33 (m, 2H, H1), 4.04 – 4.00 (m, 2H, H2), 2.49 (s, 1H, H6), 1.73 (dd, *J* = 9.4, 1.8 Hz, 3H, H5), 1.69 (dd, *J* = 9.4, 1.8 Hz, 3H, H5), 1.10 (d, *J* = 6.8 Hz, 3H, H4).

¹³C NMR (126 MHz, CDCl₃) δ 174.9, 153.4, 61.9, 49.4 (3C), 45.9, 42.8, 38.8, 27.0, 13.3.

HRMS (ESI⁺) Found [M+Na]⁺ = 232.0946; C₁₁H₁₅O₃N²³Na requires 232.0944.

IR (film) ν_{max}/cm⁻¹ 2968, 2910, 2874, 1777, 1698, 1385, 1249.

***S*-Benzyl 2-(bicyclo[1.1.1]pentan-1-yl)propanethioate, *rac*-77**

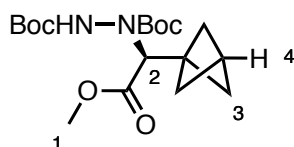


Adapted from the procedure of Trost et al.^[26] To a solution of benzyl mercaptan (8.0 μL, 68 μmol, 1.1 equiv.) in THF (0.2 mL) at 0 °C under an inert atmosphere was added *n*-butyllithium (2.5 M in hexane, 25 μL, 62 μmol, 1.0 equiv.) and the reaction mixture was stirred for 30 min. The reaction mixture was then cooled to –78 °C and added dropwise to a separate vial containing 3-(2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one **S8** (13 mg, 62 μmol, 1.0 equiv.) in THF (0.2 mL) at –78 °C under an inert atmosphere. The reaction mixture was stirred at –78 °C for 6 h

and left to warm to room temperature over 18.5 h. The reaction mixture was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/CH₂Cl₂, 9:1) afforded the title compound as a pale yellow oil (15 mg, 59 μmol, 96%). The spectroscopic data of *S*-benzyl 2-(bicyclo[1.1.1]pentan-1-yl)propanethioate **77** is detailed above.

9.3.6 Synthesis of BCP analogues of bioactive molecules

Di-*tert*-butyl (S)-1-(1-(bicyclo[1.1.1]pentan-1-yl)-2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate, **78**



Adapted from the procedure of Bull et al.^[27] To a solution of di-*tert*-butyl 1-((*S*)-2-((*S*)-4-benzyl-5,5-dimethyl-2-oxooxazolidin-3-yl)-1-(bicyclo[1.1.1]pentan-1-yl)-2-oxoethyl)hydrazine-1,2-dicarboxylate **64u** (0.13 g, 0.24 mmol, 1.0 equiv.) in CH₂Cl₂ (5 mL) at room temperature under an inert atmosphere was added sodium methoxide (25% wt. in MeOH, 56 μL, 0.24 mmol, 1.0 equiv.). After 5 min, NH₄Cl (aq., sat., 5 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/EtOAc, 17:3) afforded the title compound as a pale yellow oil (84 mg, 0.23 mmol, 93%).

R_f 0.36 (pentane/EtOAc, 17:3), [vanillin]

¹H NMR (500 MHz, CDCl₃) δ 4.90 – 4.70 (m, 1H, H2), 3.73 (s, 3H, H1), 2.51 – 2.40 (m, 1H, H4), 1.94 – 1.82 (m, 6H, H3), 1.52 – 1.42 (m, 18H, C(CH₃)₃).

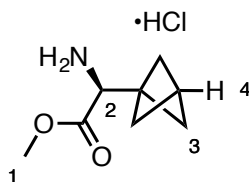
¹³C NMR (126 MHz, CDCl₃) δ 171.5, 155.9, 154.7, 82.1, 81.4, 60.4, 52.1, 51.0 (3C), 42.4, 28.4 (3C), 28.2 (3C), 28.1.

HRMS (ESI⁺) Found [M+Na]⁺ = 393.1995; C₁₈H₃₀O₆N₂Na requires 393.1996.

IR (film) ν_{max}/cm⁻¹ 2978, 2879, 1740, 1712, 1479, 1392, 1368, 1319, 1243, 1158.

[α]_D²⁵ +2.7 (c = 0.3, CHCl₃)

Methyl (S)-2-amino-2-(bicyclo[1.1.1]pentan-1-yl)acetate hydrochloride, 79



Adapted from the procedure of Uchiyama *et al.*^[28] To a solution of di-*tert*-butyl (S)-1-(1-(bicyclo[1.1.1]pentan-1-yl)-2-methoxy-2-oxoethyl)hydrazine-1,2-dicarboxylate **78** (0.12 g, 0.33 mmol, 1.0 equiv.) in EtOAc (0.6 mL) at room temperature was added HCl (4.0 M in dioxane, 0.83 mL, 3.3 mmol, 10.0 equiv.). The reaction mixture was stirred at room temperature for 26 h. The reaction mixture was concentrated *in vacuo* to afford methyl (S)-2-(bicyclo[1.1.1]pentan-1-yl)-2-hydrazinylacetate hydrochloride (68 mg, 0.33 mmol, 98%).

To a solution of methyl (S)-2-(bicyclo[1.1.1]pentan-1-yl)-2-hydrazinylacetate hydrochloride (68 mg, 0.33 mmol, 1.0 equiv.) in MeOH (0.6 mL) at room temperature under an inert atmosphere was added platinum(IV) oxide (7.4 mg, 33 μmol, 0.1 equiv.). The reaction mixture was stirred at room temperature for 24 h under a H₂ atmosphere. The reaction mixture was then filtered and the filtrate was concentrated *in vacuo* to afford the title compound as a white solid (54 mg, 0.28 mmol, 86%).

R_f 0.38 (CH₂Cl₂/MeOH, 19:1), [ninhydrin]

m.p. 174 – 175 °C

¹H NMR (500 MHz, methanol-*d*₄) δ 4.03 (s, 1H, H2), 3.84 (s, 3H, H1), 2.57 (s, 1H, H4), 1.92 (dd, *J* = 9.6, 1.9 Hz, 3H, H3), 1.89 (dd, *J* = 9.6, 1.9 Hz, 3H, H3).

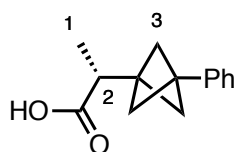
¹³C NMR (126 MHz, methanol-*d*₄) δ 169.5, 55.0, 53.4, 50.5 (3C), 43.0, 28.1.

HRMS (ESI⁺) Found [M+H]⁺ = 156.1020; C₈H₁₄O₂N requires 156.1019.

IR (film) ν_{max}/cm⁻¹ 3395, 2975, 2917, 2880, 1745, 1622, 1525, 1442, 1379, 1321, 1274, 1235, 1213, 1171, 1083, 1051.

[α]_D²⁵ +2.9 (*c* = 0.3, CHCl₃)

(*R*)-2-(3-Phenylbicyclo[1.1.1]pentan-1-yl)propanoic acid, 80



Adapted from the procedure of Zakarian et al.^[24] To a solution of (*R*)-4-benzyl-5,5-dimethyl-3-((*R*)-2-(3-phenylbicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one **64w** (29 mg, 71 μmol, 1.0 equiv.), H₂O₂ (30%, 80 μL) and water (80 μL) in THF (0.3 mL) at 0 °C was added lithium hydroxide (5.1 mg, 0.21 mmol, 3.05 equiv.). The reaction mixture was allowed to warm to room temperature and stirred for 2 h, after which water (30 μL), H₂O₂ (30%, 30 μL) and lithium hydroxide (5.1 mg, 0.21 mmol, 3.05 equiv.) were added at room temperature and stirred for a further 2 h. The reaction was quenched by the addition of Na₂SO₃ (aq., 1.5 M, 0.5 mL) and HCl (aq., 1 M, 0.5 mL) and allowed to stir until two transparent phases were visible (pH ~4). The phases were separated and the aqueous phase extracted with EtOAc (3 × 1 mL). The combined organic extracts were washed with brine (5 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The crude material was dissolved in EtOAc (1 mL) and the

organic phase was extracted with NaOH (aq., 3 M, 3×1 mL) and water (2×1 mL). The aqueous extracts were combined and set aside. The organic phase was washed with HCl (aq., 1 M, 1 mL) and brine (1 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford (*R*)-4-benzyl-5,5-dimethyloxazolidin-2-one *ent*-**65** as a colorless oil (12 mg, 59 μmol , 83%). The aqueous phase that was set aside previously was acidified with HCl (aq., 1 M) to pH 1 and extracted with EtOAc (3×3 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a colorless oil (13 mg, 61 μmol , 86%).

R_f 0.30 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 49:1), [phosphomolybdic acid]

^1H NMR (400 MHz, CDCl_3) δ 7.33 – 7.27 (m, 2H, ArH), 7.25 – 7.18 (m, 3H, ArH), 2.73 (q, $J = 7.0$ Hz, 1H, H2), 2.01 (s, 6H, H3), 1.20 (d, $J = 7.0$ Hz, 3H, H1).

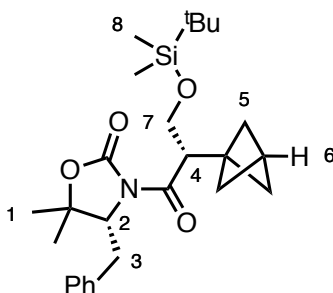
^{13}C NMR (101 MHz, CDCl_3) δ 180.2, 140.8, 128.3 (2C), 126.6, 126.2 (2C), 51.2 (3C), 41.1, 40.8, 39.5, 13.5.

HRMS (ESI $^-$) Found $[\text{M}-\text{H}]^- = 215.1078$; $\text{C}_{14}\text{H}_{15}\text{O}_2$ requires 215.1078.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2968, 2909, 2871, 1706, 1459, 1417, 1260, 1230, 1168.

$[\alpha]_{\text{D}}^{25} -15.4$ ($c = 0.1$, CHCl_3)

(*R*)-4-Benzyl-3-((*S*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-((*tert*-butyldimethylsilyl)-oxy)propanoyl)-5,5-dimethyloxazolidin-2-one, S9



Adapted from the procedure of Sugawara *et al.*^[29] To a solution of (*R*)-4-benzyl-3-((*S*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-hydroxypropanoyl)-5,5-dimethyloxazolidin-2-one *ent*-**64q** (0.19 g, 0.54 mmol, 1.0 equiv.) in CH₂Cl₂ (5 mL) at –78 °C under an inert atmosphere was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.25 mL, 1.1 mmol, 2.0 equiv.) and 2,6-lutidine (0.19 mL, 1.6 mmol, 3.0 equiv.). The reaction mixture was left to stir at 0 °C for 2 h and then quenched by addition of Na₂CO₃ (aq., sat., 5 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 3 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a colorless oil (0.21 g, 0.47 mmol, 86%).

R_f 0.74 (pentane/EtOAc, 7:3), [UV, phosphomolybdic acid]

¹H NMR (500 MHz, CDCl₃) δ 7.30 (d, *J* = 4.4 Hz, 4H, Ar*H*), 7.24 – 7.21 (m, 1H, Ar*H*), 4.53 (dd, *J* = 10.2, 2.8 Hz, 1H, H₂), 4.38 (dd, *J* = 8.9, 5.3 Hz, 1H, H₄), 3.93 (t, *J* = 9.4 Hz, 1H, H₇), 3.68 (dd, *J* = 9.4, 5.3 Hz, 1H, H₇), 3.16 (dd, *J* = 14.5, 2.8 Hz, 1H, H₃), 2.85 (dd, *J* = 14.5, 10.2 Hz, 1H, H₃), 2.47 (s, 1H, H₆), 1.78 (dd, *J* = 9.6, 1.7 Hz, 3H, H₅), 1.74 (dd, *J* = 9.6, 1.7 Hz, 3H, H₅), 1.35 (s, 3H, H₁), 1.34 (s, 3H, H₁), 0.85 (s, 9H, C(CH₃)₃), 0.05 (s, 3H, H₈), 0.02 (s, 3H, H₈).

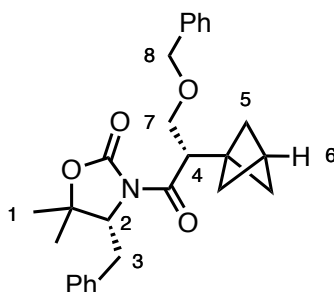
^{13}C NMR (126 MHz, CDCl_3) δ 173.0, 152.4, 137.4, 129.2 (2C), 128.8 (2C), 126.8, 81.6, 63.9, 62.4, 50.5 (3C), 47.8, 43.1, 35.5, 28.8, 28.0, 26.0 (3C), 22.4, 18.3, -5.3 (2C).

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 458.2720$; $\text{C}_{26}\text{H}_{40}\text{O}_4\text{NSi}$ requires 458.2721.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2962, 2929, 2874, 1780, 1699, 1354, 1097.

$[\alpha]_{\text{D}}^{25} +5.2$ ($c = 0.2$, CHCl_3)

(*R*)-4-Benzyl-3-((*S*)-3-(benzyloxy)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one, 83



Adapted from the procedure of Williams *et al.*^[30] To a solution of (*R*)-4-benzyl-3-((*S*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-hydroxypropanoyl)-5,5-dimethyloxazolidin-2-one *ent*-**64q** (0.19 g, 0.57 mmol, 1.0 equiv.) in CH_2Cl_2 (3.0 mL) at room temperature under an inert atmosphere was added 4 Å molecular sieves (0.20 g) followed by silver(I) oxide (0.40 g, 1.7 mmol, 3.0 equiv.). After stirring for 10 min at room temperature, benzyl bromide (0.14 mL, 1.1 mmol, 2.0 equiv.) was added. The reaction flask was wrapped in aluminium foil and stirred for 4 days. The reaction mixture was then filtered over Celite® and the solid residue rinsed with CH_2Cl_2 (3×2 mL) and the filtrate was concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 9:1) afforded the title compound as a pale yellow oil (0.11 g, 0.23 mmol, 41%).

R_f 0.60 (pentane/ Et_2O , 7:3), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.18 (m, 10H, ArH), 4.56 – 4.51 (m, 2H, H2 and H4), 4.49 (s, 2H, H8), 3.82 (t, *J* = 9.2 Hz, 1H, H7), 3.56 (dd, *J* = 9.2, 5.0 Hz, 1H, H7), 3.12 (dd, *J* = 14.6, 3.1 Hz, 1H, H3), 2.84 (dd, *J* = 14.6, 9.9 Hz, 1H, H3), 2.47 (s, 1H, H6), 1.77 (dd, *J* = 9.5, 1.8 Hz, 3H, H5), 1.74 (dd, *J* = 9.5, 1.8 Hz, 3H, H5), 1.36 (s, 3H, H1), 1.34 (s, 3H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 172.8, 152.5, 138.4, 137.3, 129.2 (2C), 128.8 (2C), 128.4 (2C), 127.7 (2C), 127.6, 126.8, 81.7, 73.2, 69.4, 63.9, 50.4 (3C), 45.3, 43.1, 35.4, 28.8, 27.9, 22.4.

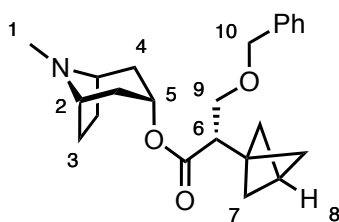
HRMS (ESI⁺) Found [M+H]⁺ = 434.2331; C₂₇H₃₂O₄N requires 434.2326.

IR (film) *v*_{max}/cm⁻¹ 2969, 2911, 2872, 1777, 1697, 1497, 1454, 1374, 1355, 1277, 1236, 1158, 1099.

[α]_D²⁵ +16.9 (*c* = 0.3, CHCl₃)

**(1*R*,3*r*,5*S*)-8-Methyl-8-azabicyclo[3.2.1]octan-3-yl
(bicyclo[1.1.1]pentan-1-yl)propanoate, 84**

(*S*)-3-(benzyloxy)-2-



Adapted from the procedure of Zakarian et al.^[24] To a solution of (*R*)-4-benzyl-3-((*S*)-3-(benzyloxy)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one **83** (43 mg, 0.10 mmol, 1.0 equiv.), H₂O₂ (30%, 96 μL) and water (96 μL) in THF (0.4 mL) at 0 °C was added lithium hydroxide (7.3 mg, 0.31 mmol, 3.05 equiv.). The reaction mixture was allowed to warm to room temperature and stirred for 4 h. The reaction was quenched by the addition of Na₂SO₃ (aq., 1.5 M, 1 mL) and HCl (aq., 1 M, 1 mL) and allowed to stir until two transparent phases were visible (pH ~4). The phases

were separated and the aqueous phase extracted with EtOAc (3×2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was dissolved in EtOAc (1 mL) and the organic phase was extracted with NaOH (aq., 3 M, 3×1 mL) and water (2×1 mL). The aqueous extracts were combined and set aside. The organic phase was washed with HCl (aq., 1 M, 1 mL) and brine (1 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford (*R*)-4-benzyl-5,5-dimethyloxazolidin-2-one *ent*-**65** as a colorless oil (9.8 mg, 48 μmol , 48%). The aqueous phase that was set aside previously was acidified with HCl (aq., 1 M) to pH 1 and extracted with EtOAc (3×2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford (*S*)-3-(benzyloxy)-2-(bicyclo[1.1.1]pentan-1-yl)propanoic acid as a colorless oil (14 mg, 58 μmol , 58%).

Adapted from the procedure of Fürstner et al.^[31] To a solution of (*S*)-3-(benzyloxy)-2-(bicyclo[1.1.1]pentan-1-yl)propanoic acid (14 mg, 58 μmol , 1.0 equiv.) and tropine (8.2 mg, 58 μmol , 1.0 equiv.) in CH_2Cl_2 (0.5 mL) at room temperature under an inert atmosphere was added DMAP (21 mg, 0.17 mmol, 3.0 equiv.) and EDCI (34 mg, 0.17 mmol, 3.0 equiv.). The reaction mixture was stirred at room temperature for 47 h. Upon completion, water (1.0 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×1 mL). The combined organic extracts were washed with brine (2 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , $\text{Et}_2\text{O}/\text{EtOH}$, 2:3) afforded the title compound as a pale yellow oil (16 mg, 42 μmol , 73%).

R_f 0.10 ($\text{CHCl}_3/\text{EtOH}$, 2:3), [phosphomolybdic acid]

$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.36 – 7.27 (m, 5H, ArH), 5.07 (t, $J = 5.5$ Hz, 1H, H5), 4.49 (dd, $J = 12.3, 4.1$ Hz, 2H, H10), 3.72 (t, $J = 9.3$ Hz, 1H, H9), 3.53 (dd, $J = 9.3,$

5.1 Hz, 1H, H9), 3.14 – 3.06 (m, 2H, H2), 2.82 (dd, $J = 9.3, 5.1$ Hz, 1H, H6), 2.48 (s, 1H, H8), 2.29 (s, 3H, H1), 2.20 – 2.13 (m, 2H, H4), 1.99 – 1.93 (m, 4H, H3), 1.76 (dd, $J = 9.6, 1.7$ Hz, 3H, H7), 1.74 (dd, $J = 9.6, 1.7$ Hz, 3H, H7), 1.71 – 1.65 (m, 2H, H4).

^{13}C NMR (126 MHz, CDCl_3) δ 171.5, 138.3, 128.5 (2C), 127.7 (3C), 73.4, 69.4, 67.2, 60.1 (2C), 50.4 (3C), 48.8, 42.9, 40.5, 36.8, 36.8, 27.7, 25.6, 25.5.

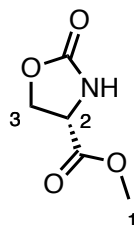
HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 370.2374$; $\text{C}_{23}\text{H}_{32}\text{O}_3\text{N}$ requires 370.2377.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2964, 2930, 2872, 1728, 1636, 1624, 1617, 1489, 1456, 1449, 1363, 1238, 1199, 1180, 1114, 1065, 1035.

$[\alpha]_{\text{D}}^{25} +0.7$ ($c = 0.6$, CHCl_3)

9.3.7 Appendix

Methyl (*S*)-2-oxooxazolidine-4-carboxylate, S10



Adapted from the procedure of Motherwell et al.^[32] To a solution of L-serine methyl ester hydrochloride (0.93 g, 6.0 mmol, 1.0 equiv.) and Et_3N (1.8 mL, 13 mmol, 2.2 equiv.) in CH_2Cl_2 (28 mL) at 4 °C under an inert atmosphere was added triphosgene (0.62 g, 2.1 mmol, 0.35 equiv.) in CH_2Cl_2 (4 mL) dropwise over 45 min. The reaction mixture was stirred for 15 min at 4 °C and then warmed to room temperature and stirred for 1 h. Upon completion, NH_4Cl (aq., sat., 10 mL) and CH_2Cl_2 (20 mL) were added and the mixture was left to stir for 20 min. The phases were then separated and the organic phase was washed with water (10 mL). The

combined aqueous phases were extracted with CH₂Cl₂ (20 mL). The combined organic extracts were dried (MgSO₄) and concentrated *in vacuo*. The title compound was obtained as a white solid, which was used without further purification (0.25 g, 1.7 mmol, 28%).

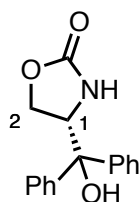
R_f 0.35 (EtOAc), [ninhydrin]

¹H NMR (400 MHz, CDCl₃) δ 6.22 (s, 1H, NH), 4.61 (t, *J* = 9.1 Hz, 1H, H2), 4.53 (dd, *J* = 9.1, 4.5 Hz, 1H, H3), 4.43 (dd, *J* = 9.1, 4.5 Hz, 1H, H3), 3.82 (s, 3H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 170.6, 158.9, 66.8, 53.8, 53.2.

Spectroscopic data in agreement with that reported previously.^[33]

(*S*)-4-(Hydroxydiphenylmethyl)oxazolidin-2-one, S11



Adapted from the procedure of Martin et al.^[34] To a solution of phenyllithium (1.9 M in dibutyl ether, 4.97 mL, 9.44 mmol, 3.2 equiv.) in THF (7 mL) at –40 °C under an inert atmosphere was added methyl (*S*)-2-oxooxazolidine-4-carboxylate **S10** (0.428 g, 2.95 mmol, 1.0 equiv.) in THF (3 mL) dropwise. The reaction mixture was stirred for 1 h at –40 °C, after which, NH₄Cl (aq., sat., 20 mL) was added and the cooling bath removed. The mixture was poured into brine (30 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. The title compound was obtained as a white solid, which was used without further purification (0.713 g, 2.65 mmol, 90%).

R_f 0.36 (petroleum ether/EtOAc, 1:1), [UV, vanillin]

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.54 (s, 1H, *OH*), 7.49 – 7.41 (m, 4H, *ArH*), 7.32 – 7.25 (m, 4H, *ArH*), 7.22 – 7.16 (m, 2H, *ArH*), 6.01 (s, 1H, *NH*), 5.06 (dd, *J* = 9.1, 5.1 Hz, 1H, H1), 4.18 (t, *J* = 8.8 Hz, 1H, H2), 4.03 (dd, *J* = 8.4, 5.1 Hz, 1H, H2).

Spectroscopic data in agreement with that reported previously for the enantiomer of the title compound.^[35]

9.4 Chapter 3: Asymmetric atom transfer radical additions

9.4.1 General experimental procedures

General procedure A: Oxazolidinone acylation

Adapted from the procedure of Sibi et al.^[3] To a solution of the oxazolidinone (1.0 equiv.) in THF (2 mL/mmol of oxazolidinone) at the stated temperature under an inert atmosphere was added *n*-butyllithium (1.6 M or 2.5 M in hexane, 1.2 equiv.) dropwise. After stirring for the stated time at the same temperature, the acyl bromide or acyl chloride (1.0 equiv.) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm to room temperature and, after stirring for the stated time, the reaction was quenched with NH₄Cl (aq., sat.). The phases were separated and the aqueous phase was extracted with EtOAc (× 2). The combined organic extracts were washed with water and brine, dried (Na₂SO₄) and concentrated *in vacuo*. The residue was either used in a subsequent reaction without further purification or purified by column chromatography.

General procedure B: Finkelstein reaction

Adapted from the procedure of Porter et al.^[4] To a solution of the alkyl bromide (1.0 equiv.) in acetone (10 mL/mmol of alkyl bromide) was added sodium iodide (3.0 equiv.). The reaction was stirred under reflux (70 °C) for the stated time, after which the reaction mixture was washed with water and the aqueous phase extracted with CH₂Cl₂ (× 3). The combined organic extracts were washed with Na₂S₂O₃ (aq., sat.), dried (Na₂SO₄), filtered and concentrated *in vacuo*. The residue was purified by column chromatography.

General procedure C: ATRA of organohalide with [1.1.1]propellane 2

A capped vial was charged with the organohalide (1.0 equiv.) and solvent, and was cooled to the stated temperature. [1.1.1]Propellane **2** (solution in Et₂O, 1.3 equiv.) was added and the mixture was stirred for 2 – 3 min at the stated temperature. Et₃B (1 M in hexane, 0.1 equiv.) was syringed into the mixture and the reaction mixture was left to stir at the stated temperature. The reaction was monitored by TLC and upon completion, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography or recrystallization.

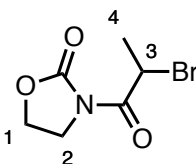
General procedure D: Asymmetric ATRA of organohalide with [1.1.1]propellane 2

A capped vial was charged with the organohalide (1.0 equiv.), Lewis acid, ligand and solvent, and was stirred at room temperature for 30 min. The reaction mixture was then cooled to the stated temperature, [1.1.1]propellane **2** (solution in Et₂O) was added and the mixture was stirred for 2 – 3 min at the stated temperature. Et₃B (1 M in hexane) was syringed into the mixture and the reaction mixture left to stir at the stated temperature. The reaction was monitored by TLC and upon completion, NH₄Cl (aq., sat.) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (× 3). The combined organic extract were dried (Na₂SO₄) and concentrated *in vacuo*. The residue was purified by column chromatography.

9.4.2 Diastereoselective ATRA with [1.1.1]propellane

The synthesis of (*S*)-4-benzyl-5,5-dimethyloxazolidin-2-one **65** is detailed in **Section 9.3.2**.

3-(2-Bromopropanoyl)oxazolidin-2-one, **105**



2-Oxazolidinone (2.61 g, 30.0 mmol, 1.0 equiv.) and *n*-butyllithium (2.5 M in hexanes, 14.4 mL, 36.0 mmol, 1.2 equiv.) in THF (55 mL) were submitted to **General Procedure A** for 1 h at 0 °C. 2-Bromopropionyl bromide (3.14 mL, 30.0 mmol, 1.0 equiv.) was then added at 0 °C and the reaction mixture was allowed to warm to room temperature over 2.5 h. The title compound was obtained as a yellow solid, which was used without further purification (6.20 g, 27.9 mmol, 93%).

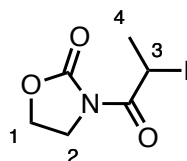
R_f 0.57 (EtOAc), [UV, vanillin]

$^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.70 (q, $J = 6.9$ Hz, 1H, H3), 4.47 (t, $J = 8.2$ Hz, 2H, H1), 4.07 (t, $J = 8.2$ Hz, 2H, H2), 1.84 (d, $J = 6.9$ Hz, 3H, H4).

$^{13}\text{C NMR}$ (101 MHz, CDCl_3) δ 169.9, 152.7, 62.3, 43.0, 38.1, 20.7.

Spectroscopic data in agreement with that reported previously.^[3]

3-(2-Iodopropanoyl)oxazolidin-2-one, **95**



3-(2-Bromopropanoyl)oxazolidin-2-one **105** (6.20 g, 27.9 mmol, 1.0 equiv.) and sodium iodide (12.6 g, 83.7 mmol, 3.0 equiv.) in acetone (300 mL) were submitted to **General Procedure B** for 15 h. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 4:1) afforded the title compound as a light yellow solid (6.46 g, 24.0 mmol, 86%).

R_f 0.26 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

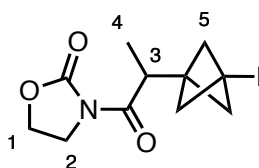
m.p. 209 – 211 °C

¹H NMR (400 MHz, CDCl₃) δ 5.84 (q, *J* = 6.9 Hz, 1H, H3), 4.53 – 4.40 (m, 2H, H1), 4.13 – 3.98 (m, 2H, H2), 1.99 (d, *J* = 6.9 Hz, 3H, H4).

¹³C NMR (101 MHz, CDCl₃) δ 172.8, 152.7, 62.2, 43.1, 22.5, 12.7.

Spectroscopic data in agreement with that reported previously.^[4]

3-(2-(3-Iodobicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one, **97**



3-(2-Iodopropanoyl)oxazolidin-2-one **95** (0.13 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.82 mL, 0.65 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 50 μL, 50 μmol, 0.1 equiv.) in CH₂Cl₂ (0.3 mL) were submitted to **General Procedure C** for 1.5 h at –78 °C. Purification by column chromatography (SiO₂,

petroleum ether/EtOAc, 4:1) afforded the title compound as a white solid (0.15 g, 0.44 mmol, 89%).

R_f 0.29 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 82 – 86 °C

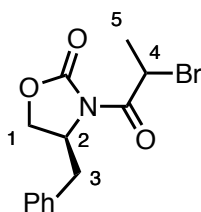
¹H NMR (400 MHz, CDCl₃) δ 4.41 (t, *J* = 8.0 Hz, 2H, H1), 4.09 (q, *J* = 6.9 Hz, 1H, H3), 4.00 (t, *J* = 8.0 Hz, 2H, H2), 2.27 (dd, *J* = 9.1, 1.4 Hz, 3H, H5), 2.23 (dd, *J* = 9.1, 1.4 Hz, 3H, H5), 1.12 (d, *J* = 6.9 Hz, 3H, H4).

¹³C NMR (101 MHz, CDCl₃) δ 173.8, 153.3, 62.0, 59.4 (3C), 48.5, 42.8, 38.9, 14.1, 6.3.

HRMS (APCI) Found [M+H]⁺ = 336.0090; C₁₁H₁₅O₃N¹²⁷I requires 336.0091.

IR (film) ν_{max} /cm⁻¹ 2978, 2914, 1771, 1698, 1357, 1248, 1178, 1073, 1028, 989, 957, 934, 844, 757, 693.

(4*S*)-4-Benzyl-3-(2-bromopropanoyl)oxazolidin-2-one, S12



(*S*)-4-Benzyl-2-oxazolidinone (2.09 g, 11.8 mmol, 1.0 equiv.) and *n*-butyllithium (2.5 M in hexanes, 5.70 mL, 14.2 mmol, 1.2 equiv.) in THF (30 mL) were submitted to **General Procedure A** for 45 min at 0 °C. 2-Bromopropionyl bromide (1.24 mL, 11.8 mmol, 1.0 equiv.) was then added at 0 °C and the reaction mixture was allowed to warm to room temperature over 3 h. The title compound was obtained as a yellow oil, which was used without further purification (3.47 g, 11.1 mmol, 94%).

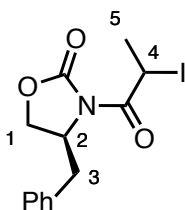
R_f 0.45 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

¹H NMR (200 MHz, CDCl₃) δ 7.37 – 7.25 (m, 5H, ArH), 5.73 (q, *J* = 6.8 Hz, 1H, H4), 4.76 – 4.70 (m, 1H, H2), 4.26 – 4.20 (m, 2H, H1), 3.31 (dd, *J* = 13.5, 3.4 Hz, 1H, H3), 2.80 (dd, *J* = 13.5, 9.6 Hz, 1H, H3), 1.87 (d, *J* = 6.8 Hz, 3H, H5).

¹³C NMR (101 MHz, CDCl₃) δ 169.8, 152.6, 134.9, 129.6 (2C), 129.2 (2C), 127.6, 66.4, 55.3, 38.7, 37.2, 20.6.

Spectroscopic data in agreement with that reported previously.^[36]

(4*S*)-4-Benzyl-3-(2-iodopropanoyl)oxazolidin-2-one, 99



(4*S*)-4-Benzyl-3-(2-bromopropanoyl)oxazolidin-2-one (3.47 g, 11.1 mmol, 1.0 equiv.) and sodium iodide (5.00 g, 33.3 mmol, 3.0 equiv.) in acetone (110 mL) were submitted to **General Procedure B** for 16 h. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as a yellow solid (1.85 g, 5.14 mmol, 46%).

R_f 0.33 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 142 – 144 °C

¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.24 (m, 5H, ArH), 5.88 (q, *J* = 6.8 Hz, 1H, H4), 4.77 – 4.71 (m, 1H, H2), 4.24 – 4.18 (m, 2H, H1), 3.34 (dd, *J* = 13.5, 3.4 Hz, 1H, H3), 2.77 (dd, *J* = 13.5, 10.0 Hz, 1H, H3), 2.03 (d, *J* = 6.8 Hz, 3H, H5).

¹³C NMR (126 MHz, CDCl₃) δ 171.6, 152.6, 135.0, 129.6 (2C), 129.2 (2C), 127.6, 66.3, 55.3, 36.6, 22.4, 13.9.

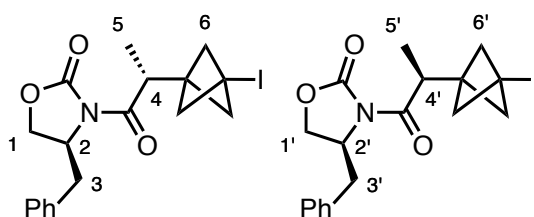
HRMS (APCI) Found $[M+H]^+ = 360.0086$; $C_{13}H_{15}O_3N^{127}I$ requires 360.0091.

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2921, 1781, 1696, 1383, 1365, 1241, 1209, 1111, 743, 702.

$[\alpha]_D^{25} +75.9$ ($c = 0.1$, CHCl_3)

(4S)-4-Benzyl-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one,

100



(4S)-4-Benzyl-3-(2-iodopropanoyl)oxazolidin-2-one **99** (0.18 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.68 M in Et_2O , 0.96 mL, 0.65 mmol, 1.3 equiv.) and Et_3B (1 M in hexane, 50 μL , 50 μmol , 0.1 equiv.) in CH_2Cl_2 (0.5 mL) were submitted to **General Procedure C** for 1 h at -78°C . Purification by column chromatography (SiO_2 , petroleum ether/ EtOAc , 19:1) afforded the title compound as a white solid (0.15 g, 0.35 mmol, 71%, 1:1 *dr*). Stereochemistry of the products were confirmed by reduction of the iodide with TTMSS and comparison to (4S)-4-benzyl-3-(2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one **64c** with known stereochemistry.

Diastereomer 1 (*R*)-100

R_f 0.45 (petroleum ether/ EtOAc , 7:3), [UV, vanillin]

m.p. 78 – 80 $^\circ\text{C}$

^1H NMR (500 MHz, CDCl_3) δ 7.39 – 7.20 (m, 5H, *ArH*), 4.67 (ddt, $J = 10.5, 6.9, 3.5$ Hz, 1H, H2), 4.20 – 4.15 (m, 2H, H1), 4.12 (q, $J = 6.8$ Hz, 1H, H4), 3.36 (dd, $J = 13.1, 3.5$ Hz, 1H, H3), 2.64 (dd, $J = 13.1, 10.5$ Hz, 1H, H3), 2.30 (dd, $J = 9.4, 1.5$ Hz, 3H, H6), 2.27 (dd, $J = 9.4, 1.5$ Hz, 3H, H6), 1.14 (d, $J = 6.8$ Hz, 3H, H5).

¹³C NMR (126 MHz, CDCl₃) δ 173.5, 153.3, 135.3, 129.5 (2C), 129.2 (2C), 127.6, 66.3, 59.5 (3C), 55.6, 48.7, 39.0, 38.5, 13.8, 6.1.

HRMS (APCI) Found [M+H]⁺ = 426.0541; C₁₈H₂₁O₃N¹²⁷I requires 426.0561.

IR (film) ν_{max}/cm⁻¹ 2980, 1779, 1698, 1380, 1212, 1179, 968, 844, 701.

[α]_D²⁵ +8.2 (*c* = 0.5, CHCl₃)

Diastereomer 2 (*S*)-100

R_f 0.57 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 94 – 96 °C

¹H NMR (500 MHz, CDCl₃) δ 7.36 – 7.27 (m, 3H, ArH'), 7.22 – 7.18 (m, 2H, ArH'), 4.65 (ddt, *J* = 9.7, 6.2, 3.5 Hz, 1H, H2'), 4.23 – 4.15 (m, 2H, H1'), 4.08 (q, *J* = 6.9 Hz, 1H, H4'), 3.26 (dd, *J* = 13.4, 3.5 Hz, 1H, H3'), 2.75 (dd, *J* = 13.4, 9.7 Hz, 1H, H3'), 2.29 (dd, *J* = 9.3, 1.7 Hz, 3H, H6'), 2.25 (dd, *J* = 9.3, 1.7 Hz, 3H, H6'), 1.18 (d, *J* = 6.9 Hz, 3H, H5').

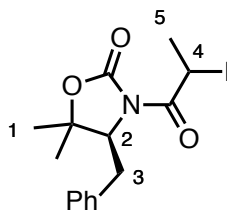
¹³C NMR (126 MHz, CDCl₃) δ 173.7, 153.2, 135.2, 129.6 (2C), 129.1 (2C), 127.6, 66.3, 59.4 (3C), 55.5, 48.5, 39.1, 38.0, 14.3, 6.2.

HRMS (APCI) Found [M+H]⁺ = 426.0561; C₁₈H₂₁O₃N¹²⁷I requires 426.0561.

IR (film) ν_{max}/cm⁻¹ 2980, 1779, 1698, 1380, 1212, 1179, 968, 844, 701.

[α]_D²⁵ +58.4 (*c* = 0.1, CHCl₃)

(4*S*)-4-Benzyl-3-(2-iodopropanoyl)-5,5-dimethyloxazolidin-2-one, 101



(*S*)-4-Benzyl-5,5-dimethyloxazolidin-2-one **65** (0.25 g, 1.2 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 0.92 mL, 1.5 mmol, 1.2 equiv.) in THF (3 mL) were submitted to **General Procedure A** for 30 min at -78°C . 2-Bromopropionyl bromide (0.13 mL, 1.2 mmol, 1.0 equiv.) was then added at -78°C and the reaction mixture was allowed to warm to room temperature over 3.5 h. (*S*)-4-Benzyl-3-(2-bromopropanoyl)-5,5-dimethyloxazolidin-2-one was obtained as a yellow oil and used without further purification.

(*S*)-4-Benzyl-3-(2-bromopropanoyl)-5,5-dimethyloxazolidin-2-one (0.42 g, 1.2 mmol, 1.0 equiv.) and sodium iodide (0.55 g, 3.7 mmol, 3.0 equiv.) in acetone (12 mL) were submitted to **General Procedure B** for 18 h. Purification by column chromatography (SiO_2 , pentane/EtOAc, 19:1) afforded the title compound as a yellow solid (0.23 g, 0.60 mmol, 49% over two steps, 2:1 *dr*).

R_f 0.24, 0.31 (pentane/EtOAc, 9:1), [UV, vanillin]

m.p. 101 – 102 $^{\circ}\text{C}$

^1H NMR (500 MHz, CDCl_3) δ 7.36 – 7.20 (m, 10H, Ar*H* and Ar*H'*), 5.93 (q, $J = 6.8$ Hz, 1H, H4'), 5.88 (q, $J = 6.9$ Hz, 1H, H4), 4.57 (dd, $J = 10.4, 3.0$ Hz, 1H, H2'), 4.46 (dd, $J = 9.4, 4.1$ Hz, 1H, H2), 3.21 (dd, $J = 14.7, 3.0$ Hz, 1H, H3'), 3.12 (dd, $J = 14.4, 4.1$ Hz, 1H, H3), 2.92 (dd, $J = 14.4, 9.4$ Hz, 1H, H3), 2.88 (dd, $J = 14.7, 10.4$ Hz, 1H, H3'), 2.01 (d, $J = 6.8$ Hz, 3H, H5'), 1.93 (d, $J = 6.9$ Hz, 3H, H5), 1.45 (s, 3H, H1), 1.38 (s, 3H, H1), 1.37 (s, 3H, H1'), 1.33 (s, 3H, H1').

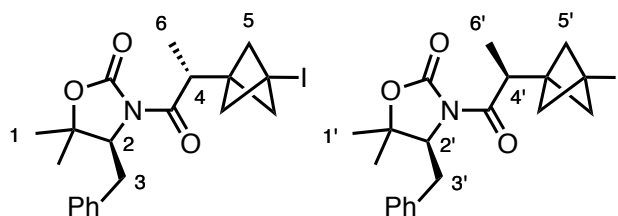
^{13}C NMR (126 MHz, CDCl_3) δ 172.0, 171.7, 152.2, 151.8, 136.9, 136.8, 129.2 (2C), 129.2 (2C), 128.9 (2C), 128.8 (2C), 127.1, 127.0, 83.3, 82.5, 64.3, 63.9, 35.8, 33.4, 29.1, 28.9, 22.7, 22.4, 22.3, 22.2, 14.8, 13.8.

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 410.0224$; $\text{C}_{15}\text{H}_{18}\text{O}_3\text{N}^{127}\text{INa}$ requires 410.0224.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2928, 1775, 1693, 1278, 1249, 1106, 699.

$[\alpha]_{\text{D}}^{25} -17.2$ ($c = 0.09$, CHCl_3)

(4*S*)-4-Benzyl-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one, 102



(4*S*)-4-Benzyl-3-(2-iodopropanoyl)-5,5-dimethyloxazolidin-2-one **101** (77 mg, 0.20 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.62 M in Et_2O , 0.42 mL, 0.26 mmol, 1.3 equiv.) and Et_3B (1 M in hexane, 20 μL , 20 μmol , 0.1 equiv.) in THF (0.2 mL) were submitted to **General Procedure C** for 3.5 h at -78°C . Purification by column chromatography (SiO_2 , pentane/ EtOAc , 9:1) afforded the title compound as a yellow solid (80 mg, 0.18 mmol, 88%, 2:1 *dr*). Stereochemistry of the products were confirmed by reduction of the iodide with TTMSS and comparison to (*S*)-4-benzyl-3-((*S*)-2-(bicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethyloxazolidin-2-one **64g** with known stereochemistry.

R_f 0.17, 0.24 (pentane/ EtOAc , 9:1), [UV, vanillin]

m.p. 88 – 89 $^\circ\text{C}$

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 476.0690$; $\text{C}_{20}\text{H}_{24}\text{O}_3\text{N}^{127}\text{INa}$ requires 476.0693.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2980, 2925, 2883, 1776, 1697, 1376, 1238, 1179, 846, 772.

$[\alpha]_{\text{D}}^{25}$ -17.2 ($c = 0.09$, CHCl_3)

Diastereomer 1 (*R*)-102

^1H NMR (500 MHz, CDCl_3) δ 7.34 – 7.19 (m, 5H, ArH), 4.50 (dd, $J = 9.2, 4.4$ Hz, 1H, H2), 4.12 (q, $J = 7.0$ Hz, 1H, H4), 3.04 (dd, $J = 14.4, 4.4$ Hz, 1H, H3), 2.88 (dd, $J = 14.4, 9.2$ Hz, 1H, H3), 2.26 (dd, $J = 9.3, 1.7$ Hz, 3H, H5), 2.22 (dd, $J = 9.3, 1.7$ Hz, 3H, H5), 1.39 (s, 3H, H1), 1.38 (s, 3H, H1), 1.06 (d, $J = 7.0$ Hz, 3H, H6).

^{13}C NMR (126 MHz, CDCl_3) δ 173.6, 152.5, 136.8, 129.2 (2C), 128.8 (2C), 127.0, 82.1, 63.6, 59.5 (3C), 48.7, 39.1, 35.6, 28.7, 22.3, 14.2, 6.3.

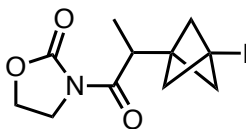
Diastereomer 2 (*S*)-102

^1H NMR (500 MHz, CDCl_3) δ 7.35 – 7.20 (m, 5H, ArH'), 4.53 (dd, $J = 10.2, 3.5$ Hz, 1H, H2'), 4.12 (q, $J = 6.9$ Hz, 1H, H4'), 3.15 (dd, $J = 14.3, 3.5$ Hz, 1H, H3'), 2.84 (dd, $J = 14.3, 10.2$ Hz, 1H, H3'), 2.24 (dd, $J = 9.2, 1.6$ Hz, 3H, H5'), 2.22 (dd, $J = 9.2, 1.6$ Hz, 3H, H5'), 1.35 (s, 3H, H1'), 1.32 (s, 3H, H1'), 1.12 (d, $J = 6.9$ Hz, 3H, H6').

^{13}C NMR (126 MHz, CDCl_3) δ 173.9, 152.4, 136.8, 129.1 (2C), 128.9 (2C), 127.1, 82.3, 63.9, 59.5 (3C), 48.7, 39.2, 35.6, 28.8, 22.6, 13.8, 6.3.

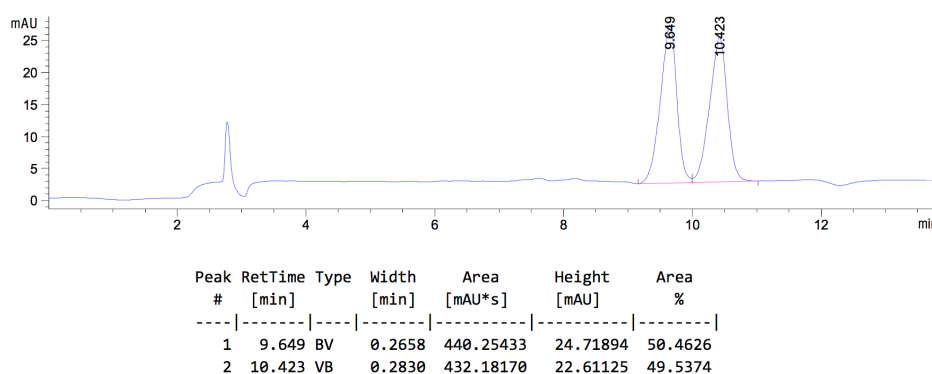
9.4.3 Enantioselective ATRA with [1.1.1]propellane

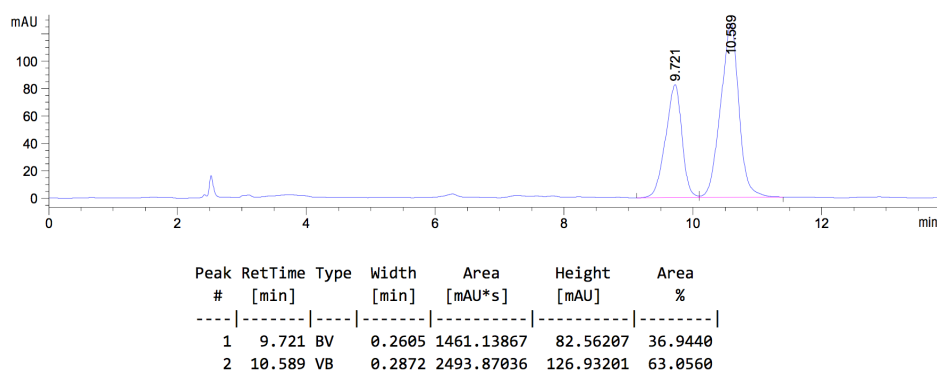
3-(2-(3-Iodobicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one, **97**



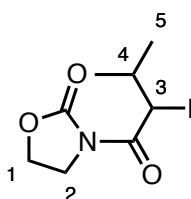
3-(2-Iodopropanoyl)oxazolidin-2-one **95** (54 mg, 0.20 mmol, 1.0 equiv.), holmium trifluoromethanesulfonate (0.12 g, 0.20 mmol, 1.0 equiv.), (*R,R*)-**L10** (60 mg, 0.20 mmol, 1.0 equiv.), [1.1.1]propellane **2** (1.07 M in Et₂O, 0.37 mL, 0.40 mmol, 2.0 equiv.) and Et₃B (1 M in hexane, 0.10 mL, 0.10 mmol, 0.5 equiv.) in THF (0.8 mL) were submitted to **General Procedure D** for 1 h at −78 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a white solid (35 mg, 0.10 mmol, 52%). The spectroscopic data of 3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one **97** is detailed in **Section 9.4.2**.

HPLC 26% *ee* (CHIRALPAK IA, 6% IPA/hexane, 1.3 mL/min, *t_R* major – 10.6 min, minor – 9.7 min)





3-(2-Iodo-3-methylbutanoyl)oxazolidin-2-one, 103



2-Oxazolidinone (2.61 g, 30.0 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 22.5 mL, 36.0 mmol, 1.2 equiv.) in THF (92 mL) were submitted to **General Procedure A** for 1 h at 0 °C. Isovaleryl chloride (3.66 mL, 30.0 mmol, 1.0 equiv.) was then added at 0 °C and the reaction mixture was allowed to warm to room temperature over 4 h. 3-(3-Methylbutanoyl)oxazolidin-2-one was obtained as a orange solid, which was used without further purification (4.55 g, 26.6 mmol, 89%).

Adapted from the procedure of Stephenson et al.^[37] To a solution of 3-(3-methylbutanoyl)oxazolidin-2-one (0.86 g, 5.0 mmol, 1.0 equiv.) in THF (50 mL) at –78 °C under an inert atmosphere was added sodium bis(trimethylsilyl)amide (2 M in THF, 5.0 mL, 10 mmol, 2.0 equiv.) and the reaction mixture allowed to stir for 45 min. *N*-Iodosuccinimide (1.2 g, 5.5 mmol, 1.1 equiv.) was then added and the mixture allowed to stir for 3.5 h. Upon completion, water (50 mL) and EtOAc (50 mL) was added. The phases were separated and the organic phase was washed with water (50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo*.

Purification by column chromatography (SiO₂, pentane/EtOAc, 17:3) afforded the title compound as a light yellow solid (0.11 g, 0.37 mmol, 7%).

R_f 0.34 (petroleum ether/EtOAc, 7:3), [UV, phosphomolybdic acid]

m.p. 71 – 73 °C

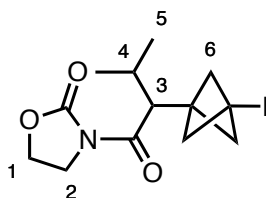
¹H NMR (500 MHz, CDCl₃) δ 5.63 (d, *J* = 9.0 Hz, 1H, H3), 4.51 – 4.39 (m, 2H, H1), 4.13 – 4.00 (m, 2H, H2), 2.24 – 2.07 (m, 1H, H4), 1.19 (d, *J* = 6.6 Hz, 3H, H5), 1.02 (d, *J* = 6.6 Hz, 3H, H5).

¹³C NMR (126 MHz, CDCl₃) δ 171.0, 152.9, 62.1, 43.1, 32.0, 31.1, 23.3, 20.1.

HRMS (ESI⁺) Found [M+Na]⁺ = 319.9754; C₈H₁₂O₃N¹²⁷I²³Na requires 319.9754.

IR (film) ν_{max}/cm⁻¹ 2976, 2959, 2918, 2872, 1772, 1680, 1469, 1370, 1311, 1246, 1200, 1119, 1099, 1082, 1037, 1024, 924, 700, 628.

3-(2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-3-methylbutanoyl)oxazolidin-2-one, **104**



Procedure 1

3-(2-Iodo-3-methylbutanoyl)oxazolidin-2-one **103** (71 mg, 0.24 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.80 M in Et₂O, 0.39 mL, 0.31 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 24 μL, 24 μmol, 0.1 equiv.) in THF (0.24 mL) were submitted to **General Procedure C** for 1 h at 0 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as white crystals (60 mg, 0.17 mmol, 69%).

Procedure 2

3-(2-Iodo-3-methylbutanoyl)oxazolidin-2-one **103** (59 mg, 0.20 mmol, 1.0 equiv.), holmium trifluoromethanesulfonate (0.12 g, 0.20 mmol, 1.0 equiv.), (*R,R*)-**L10** (60 mg, 0.20 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.80 M in Et₂O, 0.50 mL, 0.40 mmol, 2.0 equiv.) and Et₃B (1 M in hexane, 0.10 mL, 0.10 mmol, 0.5 equiv.) in THF (0.8 mL) were submitted to **General Procedure D** for 18 h at −78 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a white solid (37 mg, 0.10 mmol, 50%).

R_f 0.38 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 108 – 109 °C

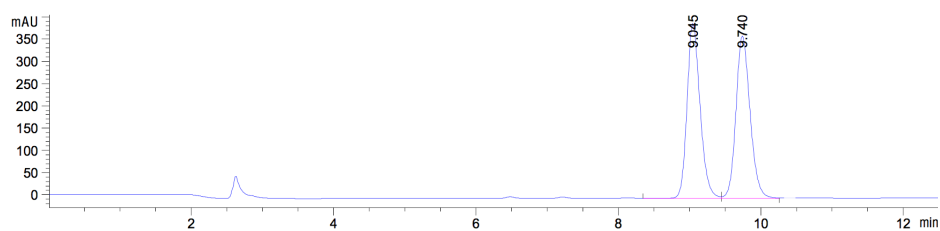
¹H NMR (500 MHz, CDCl₃) δ 4.44 – 4.35 (m, 2H, H1), 4.06 – 3.94 (m, 3H, H2 and H3), 2.34 (dd, *J* = 9.3, 1.7 Hz, 3H, H6), 2.30 (dd, *J* = 9.3, 1.7 Hz, 3H, H6), 2.08 – 1.96 (m, 1H, H4), 1.01 (d, *J* = 6.7 Hz, 3H, H5), 0.89 (d, *J* = 6.7 Hz, 3H, H5).

¹³C NMR (126 MHz, CDCl₃) δ 173.3, 153.4, 61.8, 61.0 (3C), 50.5, 47.7, 42.7, 30.1, 21.5, 20.9, 6.5.

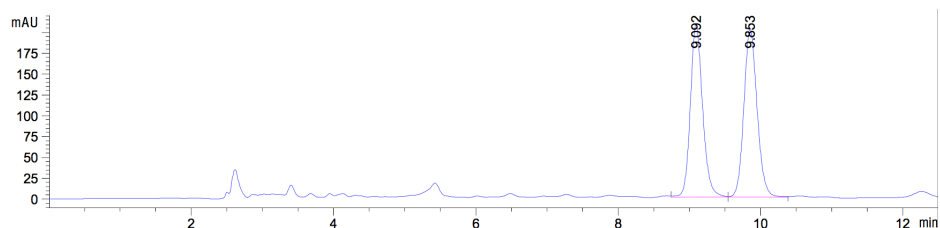
HRMS (ESI⁺) Found [M+Na]⁺ = 386.0224; C₁₃H₁₈O₃N¹²⁷I²³Na requires 386.0224.

IR (film) *v*_{max}/cm^{−1} 2966, 2972, 2918, 2874, 1766, 1687, 1479, 1393, 1363, 1213, 1180, 1125, 1100, 1042, 1019, 931, 858, 838, 762, 703.

HPLC 2% *ee* (CHIRALPAK IB, 5% IPA/hexane, 1.3 mL/min, *t_R* major – 9.9 min, minor – 9.1 min)

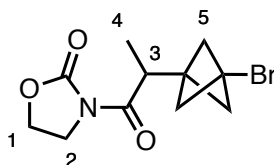


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.045	BV	0.1945	5003.13330	392.99377	49.8684
2	9.740	VV	0.2129	5029.54590	364.67911	50.1316



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.092	VB	0.1836	2486.61963	207.75023	48.8818
2	9.853	BV	0.1980	2600.38770	202.25391	51.1182

3-(2-(3-Bromobicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one, **107**



Procedure 1

3-(2-Bromopropanoyl)oxazolidin-2-one **105** (0.11 g, 0.50 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.68 M in Et₂O, 0.96 mL, 0.65 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 50 μL, 50 μmol, 0.1 equiv.) in CH₂Cl₂ (0.5 mL) were submitted to **General Procedure C** for 2 h at 0 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a yellow solid (87 mg, 0.30 mmol, 61%).

Procedure 2

3-(2-Bromopropanoyl)oxazolidin-2-one **105** (44 mg, 0.20 mmol, 1.0 equiv.), holmium trifluoromethanesulfonate (0.12 g, 0.20 mmol, 1.0 equiv.), (*R,R*)-**L10** (60 mg, 0.20 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.80 M in Et₂O, 0.50 mL, 0.40 mmol, 2.0 equiv.) and Et₃B (1 M in hexane, 0.10 mL, 0.10 mmol, 0.5 equiv.) in THF (0.8 mL) were submitted to **General Procedure D** for 24 h at −78 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a yellow solid (18 mg, 63 μmol, 31%).

R_f 0.31 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 76 – 80 °C

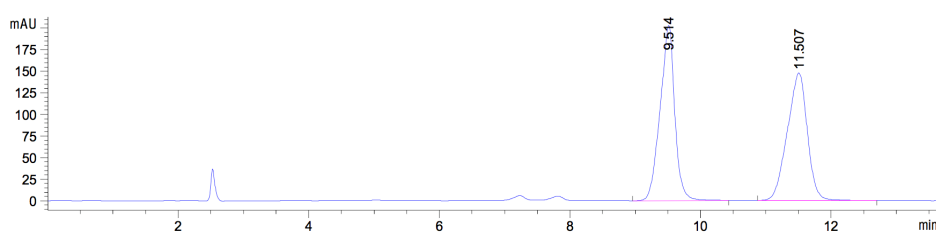
¹H NMR (500 MHz, CDCl₃) δ 4.41 (t, *J* = 8.2 Hz, 2H, H1), 4.12 (q, *J* = 6.9 Hz, 1H, H3), 4.01 (t, *J* = 8.2 Hz, 2H, H2), 2.19 (dd, *J* = 9.3, 1.4 Hz, 3H, H5), 2.16 (dd, *J* = 9.3, 1.4 Hz, 3H, H5), 1.15 (d, *J* = 6.9 Hz, 3H, H4).

¹³C NMR (126 MHz, CDCl₃) δ 173.9, 153.3, 62.0, 57.6 (3C), 42.8, 42.2, 37.8, 36.5, 14.3.

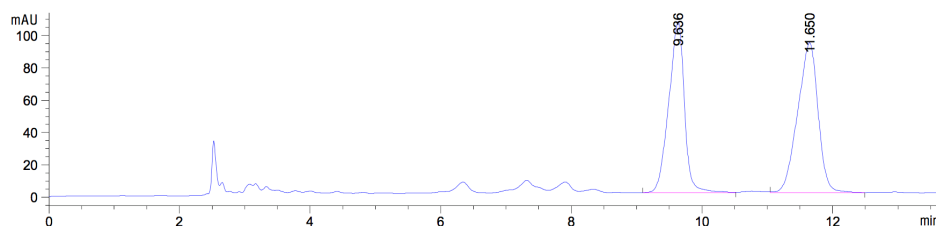
HRMS (ESI⁺) Found [M+Na]⁺ = 310.0050; C₁₁H₁₄O₃N⁷⁹BrNa requires 310.0049.

IR (film) *v*_{max}/cm^{−1} 2973, 2922, 1760, 1693, 1476, 1398, 1369, 1228, 1186, 1139, 1041, 994, 960, 932, 848, 759, 696.

HPLC 7% *ee* (CHIRALPAK IA, 6% IPA/hexane, 1.3 mL/min, *t_R* major – 11.7 min, minor – 9.6 min)

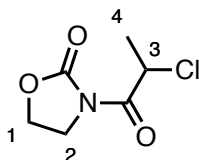


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.514	BB	0.2219	3160.77686	202.77145	50.1191
2	11.507	VB	0.3124	3145.75049	147.71982	49.8809



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.636	BV	0.2418	1758.41064	105.85239	46.6030
2	11.650	VV	0.3193	2014.75610	92.78606	53.3970

3-(2-Chloropropanoyl)oxazolidin-2-one, 106



2-Oxazolidinone (1.74 g, 20.0 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 15.0 mL, 24.0 mmol, 1.2 equiv.) in THF (60 mL) were submitted to **General Procedure A** for 1 h at 0 °C. 2-Chloropropanoyl chloride (1.94 mL, 20.0 mmol, 1.0 equiv.) was then added at 0 °C and the reaction mixture was allowed to warm to room temperature over 2.5 h. The title compound was obtained as an orange oil, which was used without further purification (3.26 g, 18.4 mmol, 92%).

R_f 0.64 (EtOAc), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 5.67 (q, *J* = 7.2, 6.8 Hz, 1H, H3), 4.48 (t, *J* = 7.8 Hz, 2H, H1), 4.12 – 4.04 (m, 2H, H2), 1.71 (d, *J* = 6.8 Hz, 3H, H4).

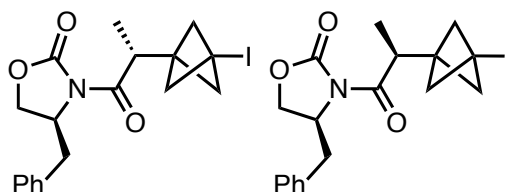
^{13}C NMR (101 MHz, CDCl_3) δ 169.7, 152.8, 62.5, 50.4, 43.0, 20.7.

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 200.0087$; $\text{C}_6\text{H}_8\text{O}_3\text{N}^{35}\text{ClNa}$ requires 200.0085.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2933, 1775, 1709, 1390, 1221, 1126, 1101, 1069, 1039, 1003.

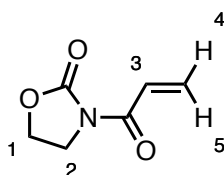
(4*S*)-4-Benzyl-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one,

100



(4*S*)-4-Benzyl-3-(2-iodopropanoyl)oxazolidin-2-one **99** (72 mg, 0.20 mmol, 1.0 equiv.), holmium trifluoromethanesulfonate (0.12 g, 0.20 mmol, 1.0 equiv.), (*R,R*)- or (*S,S*)-**L10** (60 mg, 0.20 mmol, 1.0 equiv.), [1.1.1]propellane **2** (0.80 M in Et_2O , 0.50 mL, 0.40 mmol, 2.0 equiv.) and Et_3B (1 M in hexane, 0.10 mL, 0.10 mmol, 0.5 equiv.) in THF (0.8 mL) were submitted to **General Procedure D** for 1 h at -78°C . Purification by column chromatography (SiO_2 , petroleum ether/ EtOAc , 9:1) afforded the title compound as a white solid (with (*R,R*)-**L10**: 64 mg, 0.15 mmol, 75%, 1.3:1 *dr*; with (*S,S*)-**L10**: 75 mg, 0.18 mmol, 89%, 1.4:1 *dr*). The spectroscopic data of (4*S*)-4-benzyl-3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoyl)oxazolidin-2-one **100** is detailed in **Section 9.4.2**.

3-Acryloyloxazolidin-2-one, 109



Adapted from the procedure of Sibi et al.^[38] To a solution of 2-oxazolidinone (1.74 g, 20.0 mmol, 1.0 equiv.) in THF (80 mL) at $-78\text{ }^{\circ}\text{C}$ under an inert atmosphere was added methylmagnesium bromide (3 M in Et_2O , 6.67 mL, 20.0 mmol, 1.0 equiv.) dropwise. The reaction mixture was stirred for 30 min at $-78\text{ }^{\circ}\text{C}$. Acryloyl chloride (1.95 mL, 24.0 mmol, 1.2 equiv.) was then added dropwise and the reaction mixture stirred for 1 h at $-78\text{ }^{\circ}\text{C}$. Upon completion, NH_4Cl (aq., sat., 80 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc ($3 \times 50\text{ mL}$). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , petroleum ether/EtOAc, 1:1) afforded the title compound as an off-white solid (1.33 g, 9.44 mmol, 47%).

R_f 0.67 (EtOAc), [UV, vanillin]

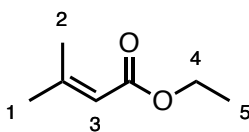
m.p. 209 – 211 $^{\circ}\text{C}$

^1H NMR (400 MHz, CDCl_3) δ 7.50 (dd, $J = 17.0, 10.5\text{ Hz}$, 1H, H3), 6.56 (dd, $J = 17.0, 1.7\text{ Hz}$, 1H, H5), 5.91 (dd, $J = 10.4, 1.7\text{ Hz}$, 1H, H4), 4.45 (t, $J = 8.0\text{ Hz}$, 2H, H1), 4.09 (t, $J = 8.0\text{ Hz}$, 2H, H2).

^{13}C NMR (101 MHz, CDCl_3) δ 165.2, 153.5, 132.0, 127.1, 62.3, 42.8.

Spectroscopic data in agreement with that reported previously.^[39]

Ethyl 3-methylbut-2-enoate, S13



According to the procedure of Tambar *et al.*^[40] To a suspension of sodium hydride (60% dispersion in mineral oil, 2.0 g, 50 mmol, 1.0 equiv.) in THF (250 mL) at room temperature under an inert atmosphere was added triethyl phosphonoacetate (9.9 mL, 50 mmol, 1.0 equiv.) dropwise. After 1 h, acetone (3.7 mL, 50 mmol, 1.0 equiv.) was added and the resulting mixture was stirred for 23 h. The reaction was quenched by the addition of water (250 mL). The phases were separated and the aqueous phase extracted with Et₂O (3 × 100 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as a clear oil (0.99 g, 7.7 mmol, 16%).

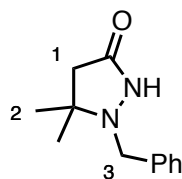
R_f 0.43 (petroleum ether/EtOAc, 9:1), [UV, phosphomolybdic acid]

¹H NMR (400 MHz, CDCl₃) δ 5.69 – 5.64 (m, 1H, H3), 4.14 (q, *J* = 7.2 Hz, 2H, H4), 2.16 (d, *J* = 1.4 Hz, 3H, H2), 1.89 (d, *J* = 1.4 Hz, 3H, H1), 1.27 (t, *J* = 7.2 Hz, 3H, H5).

¹³C NMR (101 MHz, CDCl₃) δ 166.9, 156.6, 116.3, 59.6, 27.5, 20.3, 14.5.

Spectroscopic data in agreement with that reported previously.^[41]

1-Benzyl-5,5-dimethylpyrazolidin-3-one, S14



According to the procedure of Chen *et al.*^[42] To a solution of ethyl 3-methylbut-2-enoate **S13** (0.99 g, 7.7 mmol, 1.0 equiv.) in ethanol (2 mL) was added hydrazine monohydrate (0.45 mL, 9.3 mmol, 1.2 equiv.) and the reaction mixture was heated to reflux (85 °C). After 2 h, the mixture was concentrated *in vacuo* to afford 5,5-dimethylpyrazolidin-3-one, which was used without further purification.

According to the procedure of Sibi *et al.*^[43] To a solution of 5,5-dimethylpyrazolidin-3-one (0.88 g, 7.7 mmol, 1.0 equiv.) in acetonitrile (8 mL) was added benzyl bromide (0.92 mL, 7.7 mmol, 1.0 equiv.), K₂CO₃ (1.1 g, 7.7 mmol, 1.0 equiv.) and sodium iodide (0.12 g, 0.77 mmol, 1.0 equiv.). The reaction mixture was heated to reflux (90 °C) for 16 h. The reaction was quenched with water (10 mL), the phases were separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 7:3) afforded the title compound as a light yellow solid (0.70 g, 3.4 mmol, 44% over two steps).

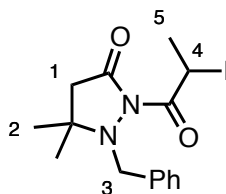
R_f 0.19 (petroleum ether/EtOAc, 1:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.27 (m, 5H, ArH), 6.39 (s, 1H, NH), 3.79 (s, 2H, H3), 2.43 (s, 2H, H1), 1.38 (s, 6H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 174.2, 137.1, 129.3 (2C), 128.9 (2C), 128.0, 62.5, 57.1, 43.1, 25.4 (2C).

Spectroscopic data in agreement with that reported previously.^[43]

1-Benzyl-2-(2-iodopropanoyl)-5,5-dimethylpyrazolidin-3-one, 110



1-Benzyl-5,5-dimethylpyrazolidin-3-one **S14** (0.70 g, 3.4 mmol, 1.0 equiv.) and *n*-butyllithium (1.6 M in hexanes, 2.6 mL, 4.1 mmol, 1.2 equiv.) in THF (6 mL) were submitted to **General Procedure A** for 30 min at $-78\text{ }^{\circ}\text{C}$. 2-Bromopropionyl bromide (0.36 mL, 3.4 mmol, 1.0 equiv.) was then added at $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was allowed to warm to room temperature over 3 h. 1-Benzyl-2-(2-bromopropanoyl)-5,5-dimethylpyrazolidin-3-one was obtained as a light yellow solid and used without further purification.

1-Benzyl-2-(2-bromopropanoyl)-5,5-dimethylpyrazolidin-3-one (1.2 g, 3.4 mmol, 1.0 equiv.) and sodium iodide (1.5 g, 10 mmol, 3.0 equiv.) in acetone (30 mL) were submitted to **General Procedure B** for 15 h. Purification by column chromatography (SiO_2 , petroleum ether/EtOAc, 17:3) afforded the title compound as an off-white solid (0.51 g, 1.3 mmol, 39% over two steps).

R_f 0.43 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 120 – 124 $^{\circ}\text{C}$

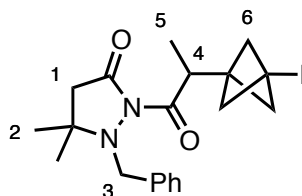
^1H NMR (400 MHz, toluene- d_8 , 80 $^{\circ}\text{C}$) δ 7.43 – 7.38 (m, 2H, ArH), 7.13 – 6.93 (m, 3H, ArH), 5.73 (q, $J = 6.8\text{ Hz}$, 1H, H4), 3.74 (s, 2H, H3), 2.07 (s, 2H, H1), 1.73 (d, $J = 6.8\text{ Hz}$, 3H, H5), 0.89 (s, 3H, H2), 0.78 (s, 3H, H2).

^{13}C NMR (101 MHz, toluene- d_8 , 80 $^{\circ}\text{C}$) δ 173.4, 168.0, 137.6, 129.2, 128.6 (2C), 127.6 (2C), 60.9, 56.6, 43.6, 26.9, 26.1, 22.6, 16.5.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 387.0564$; $\text{C}_{15}\text{H}_{20}\text{O}_2\text{N}_2^{127}\text{I}$ requires 387.0564.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3023, 2970, 2932, 1747, 1680, 1493, 1351, 1226, 940, 777, 724.

1-Benzyl-2-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoyl)-5,5-dimethylpyrazolidin-3-one, 111



Procedure 1

1-Benzyl-2-(2-iodopropanoyl)-5,5-dimethylpyrazolidin-3-one **110** (77 mg, 0.20 mmol, 1.0 equiv.), [1.1.1]propellane **2** (1.07 M in Et₂O, 0.24 mL, 0.25 mmol, 1.3 equiv.) and Et₃B (1 M in hexane, 20 μ L, 20 μ mol, 0.1 equiv.) in THF (0.3 mL) were submitted to **General Procedure C** for 2.5 h at 0 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 9:1) afforded the title compound as white crystals (70 mg, 0.16 mmol, 78%).

Procedure 2

1-Benzyl-2-(2-iodopropanoyl)-5,5-dimethylpyrazolidin-3-one **110** (77 mg, 0.20 mmol, 1.0 equiv.), ytterbium trifluoromethanesulfonate (0.12 g, 0.20 mmol, 1.0 equiv.), (*R,R*)-**L10** (60 mg, 0.20 mmol, 1.0 equiv.), [1.1.1]propellane **2** (1.07 M in Et₂O, 0.37 mL, 0.40 mmol, 2.0 equiv.) and Et₃B (1 M in hexane, 0.10 mL, 0.10 mmol, 0.5 equiv.) in THF (0.8 mL) were submitted to **General Procedure D** for 4 h at –78 °C. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 8:2) afforded the title compound as a white solid (48 mg, 0.11 mmol, 54%).

R_f 0.43 (petroleum ether/EtOAc, 7:3), [UV, vanillin]

m.p. 98 – 100 °C

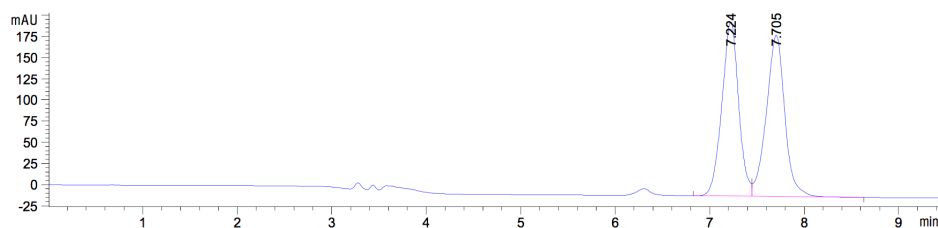
¹H NMR (400 MHz, CDCl₃) δ 7.48 – 7.27 (m, 5H, ArH), 3.90 (q, *J* = 7.0 Hz, 1H, H4), 2.59 (s, 2H, H3), 2.21 (s, 6H, H6), 1.54 (s, 2H, H1), 1.24 (s, 3H, H2), 1.21 (s, 3H, H2), 1.03 (d, *J* = 7.0 Hz, 3H, H5).

¹³C NMR (126 MHz, CDCl₃) δ 174.5, 169.2, 137.7, 129.1 (2C), 128.5 (2C), 127.7, 60.5, 59.6 (3C), 57.1, 48.7, 44.0, 40.1, 26.6, 26.1, 14.4, 6.9.

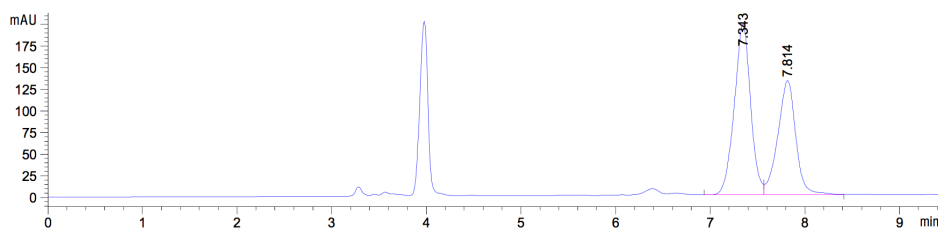
HRMS (ESI⁺) Found [M+H]⁺ = 453.1028; C₂₀H₂₆O₂N₂¹²⁷I requires 453.1034.

IR (film) ν_{max} /cm⁻¹ 2978, 2960, 2935, 2912, 2874, 2837, 1738, 1702, 1452, 1345, 1176, 833, 772, 694.

HPLC 15% *ee* (CHIRALPAK IA, 3% IPA/hexane, 1.0 mL/min, *t*_R major – 7.3 min, minor – 7.8 min)



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.224	BV	0.1858	2536.23022	205.78270	49.4658
2	7.705	VB	0.2048	2591.00903	190.35574	50.5342

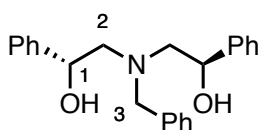


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.343	BV	0.1779	2367.41626	197.35751	57.6251
2	7.814	VV	0.1980	1740.89307	131.89000	42.3749

9.4.4 Chiral ligands

The following ligands are commercially available and used directly as supplied: (*R*)-BINOL, (*S*)-BINAP, (*R,R*)-Jacobsen, (*R,R*)-DPEN, (*S,S*)-TsDPEN, (*R,R*)-**L6**, (*R,R*)-**L9**, (*R,R*)-**L10**, (*R,R*)-**L11** and (*S,R*)-**L12**.

(1*R*,1'*R*)-2,2'-(Benzylazanediyl)bis(1-phenylethan-1-ol), (*R,R*)-**L8**



According to the procedure of Procter *et al.*^[44] To a solution of (*R*)-styrene oxide (1.3 mL, 11 mmol, 2.2 equiv.) in MeOH (10 mL) was added benzylamine (0.55 mL, 5.0 mmol, 1.0 equiv.). The reaction mixture was heated to 75 °C for 23 h, after which the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 8:2) afforded the title compound as a light yellow oil (0.89 g, 2.6 mmol, 51%).

R_f 0.57 (petroleum ether/EtOAc, 1:1), [UV, vanillin]

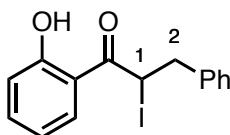
¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.23 (m, 15H, ArH), 4.76 (dd, *J* = 9.6, 3.7 Hz, 2H, H1), 3.99 (d, *J* = 13.5 Hz, 1H, H3), 3.69 (d, *J* = 13.5 Hz, 1H, H3), 3.30 (br s, 2H, OH), 2.80 (dd, *J* = 13.4, 9.6 Hz, 2H, H2), 2.76 (dd, *J* = 13.4, 3.7 Hz, 2H, H2).

¹³C NMR (101 MHz, CDCl₃) δ 142.3, 138.3, 129.3, 128.7, 128.6 (6C), 127.8, 127.6, 126.0 (6C), 71.0 (2C), 62.8 (2C), 60.0.

Spectroscopic data in agreement with that reported previously.^[44]

9.4.5 Appendix

1-(2-Hydroxyphenyl)-2-iodo-3-phenylpropan-1-one, A1



Adapted from the procedure of King et al.^[45] To a solution of copper(II) bromide (11.2 g, 50.0 mmol, 1.7 equiv.) in EtOAc (25 mL) was added a solution of 2'-hydroxy-3-phenylpropiophenone (6.79 g, 20.0 mmol, 1.0 equiv.) in CH₂Cl₂ (25 mL). The reaction mixture was stirred vigorously and heated at reflux (45 °C). After 28 h, the reaction mixture was cooled to room temperature and water (50 mL) was added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. 2-Bromo-1-(2-hydroxyphenyl)-3-phenylpropan-1-one was obtained as a yellow solid, which was used without further purification.

2-Bromo-1-(2-hydroxyphenyl)-3-phenylpropan-1-one (3.05 g, 10.0 mmol, 1.0 equiv.) and sodium iodide (4.50 g, 30.0 mmol, 3.0 equiv.) in acetone (100 mL) were submitted to **General Procedure B** for 27 h. Purification by column chromatography (SiO₂, petroleum ether/EtOAc, 19:1) afforded the title compound as a yellow solid (0.250 g, 0.710 mmol, 7%).

R_f 0.40 (petroleum ether/EtOAc, 9:1), [UV, vanillin]

m.p. 40 – 45 °C

¹H NMR (500 MHz, CDCl₃) δ 7.63 (ddd, *J* = 7.6, 1.5, 0.6 Hz, 1H, Ar*H*), 7.58 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H, Ar*H*), 7.33 – 7.20 (m, 5H, Ar*H*), 7.09 (dt, *J* = 8.5, 0.8 Hz, 1H,

ArH), 7.04 (ddd, $J = 7.9, 7.2, 0.8$ Hz, 1H, ArH), 4.78 (dd, $J = 8.7, 3.6$ Hz, 1H, H1), 3.37 (dd, $J = 14.7, 3.6$ Hz, 1H, H2), 2.99 (dd, $J = 14.7, 8.7$ Hz, 1H, H2).

^{13}C NMR (101 MHz, CDCl_3) δ 201.2, 172.8, 138.2, 136.2, 129.5 (2C), 128.6 (2C), 127.1, 124.4, 122.0, 121.1, 113.7, 85.9, 37.6.

HRMS (APCI) Found $[\text{M}-\text{I}]^+ = 225.0907$; $\text{C}_{15}\text{H}_{13}\text{O}_2$ requires 225.1910.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3022, 1703, 1613, 1598, 1460, 1298, 1212, 1194, 1143, 1068, 1029, 878, 754, 733, 696.

9.5 Chapter 4: Photoredox-catalyzed atom transfer radical additions

9.5.1 General experimental procedures

General procedure A: Appel reaction

According to the procedure of Cossy et al.^[46] To a solution of the alcohol (1.0 equiv.) in CH_2Cl_2 (4 mL/mmol of alcohol) at room temperature under an inert atmosphere were added triphenylphosphine (1.3 equiv.) and imidazole (1.5 equiv.). The resulting mixture was cooled to 0 °C and iodine (1.2 equiv.) was added portionwise. The reaction mixture was then left to stir overnight (~16 h) at room temperature, after which, it was poured into water (5 mL/mmol of alcohol). The phases were separated and the aqueous phase was extracted with Et_2O ($\times 3$). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by column chromatography.

General procedure B: Finkelstein reaction

Adapted from the procedure described by Lee et al.^[47] To a solution of the alkyl bromide (1.0 equiv.) in acetone (1 mL/mmol of alkyl bromide) was added sodium iodide (1.5 equiv.). The resulting mixture was stirred in the dark and the reaction was monitored by TLC. Upon completion, the mixture was diluted with water and Et_2O , and the phases were separated. The aqueous phase was extracted with Et_2O ($\times 2$). The combined organic phases were washed with $\text{Na}_2\text{S}_2\text{O}_3$ (aq., 10 %) and brine, dried (MgSO_4) and concentrated *in vacuo*. The product obtained was used in a subsequent reaction without further purification.

General procedure C: Copper(I) oxide mediated iodination

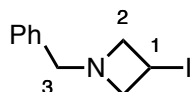
According to the procedure of Wu *et al.*^[48] To a solution of the methylketone (1.0 equiv.) in MeOH were added copper(I) oxide (1.0 equiv.) and iodine (1.0 equiv.). The reaction mixture was stirred for 5 min, heated to 75 °C for 2–3 h and then concentrated *in vacuo*. The residue was taken up in EtOAc and filtered, and the organic filtrate was washed with Na₂S₂O₃ (aq., 10%), dried (MgSO₄) and concentrated *in vacuo*. The residue was purified by column chromatography.

General procedure D: Photoredox-catalyzed ATRA with [1.1.1]propellane 2

To a screw-capped vial equipped were added *fac*-Ir(ppy)₃ (0.025 equiv.), alkyl halide (1.0 equiv.), [1.1.1]propellane **2** (solution in Et₂O, 2.0 equiv.) and pivalonitrile (10 mL/mmol of alkyl halide). The vial was sealed and the reaction mixture was placed under an atmosphere of argon, and the solution was degassed *via* three freeze-pump-thaw cycles (vacuum was only applied while the reaction mixture was frozen due to volatility of [1.1.1]propellane **2**). The reaction mixture was irradiated with blue LEDs for the stated time (see **Section 9.1** for experimental setup). The reaction mixture was then concentrated *in vacuo* and the residue was purified by column chromatography.

9.5.2 Alkyl iodide substrates

1-Benzyl-3-iodoazetidine, 114a



1-Benzylazetidin-3-ol (0.25 g, 1.5 mmol, 1.0 equiv.), triphenylphosphine (0.51 g, 2.0 mmol, 1.3 equiv.), imidazole (0.15 g, 2.3 mmol, 1.5 equiv.) and iodine (0.46 g, 1.8 mmol, 1.2 equiv.) in CH₂Cl₂ (6 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a pale yellow oil (0.16 g, 0.58 mmol, 39%).

R_f 0.17 (pentane/Et₂O, 4:1), [UV, potassium permanganate]

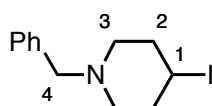
¹H NMR (500 MHz, CDCl₃) δ 7.34 – 7.22 (m, 5H, ArH), 4.44 (quin, *J* = 6.8 Hz, 1H, H1), 3.95 (td, *J* = 6.8, 2.0 Hz, 2H, H2), 3.71 (s, 2H, H3), 3.57 (td, *J* = 6.8, 2.0 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 137.6, 128.6 (2C), 128.6 (2C), 127.4, 66.4 (2C), 63.6, 5.3.

HRMS (ESI⁺) Found [M+H]⁺ = 274.0089; C₁₀H₁₃N¹²⁷I requires 274.0087.

IR (film) ν_{max} /cm⁻¹ 3027, 2951, 2829, 1494, 1453, 1362, 1214.

1-Benzyl-4-iodopiperidine, 114b



1-Benzyl-4-hydroxypiperidine (0.38 g, 2.0 mmol, 1.0 equiv.), triphenylphosphine (0.68 g, 2.6 mmol, 1.3 equiv.), imidazole (0.20 g, 3.0 mmol, 1.5 equiv.) and

iodine (0.61 g, 2.4 mmol, 1.2 equiv.) in CH₂Cl₂ (9 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a pale yellow oil (0.31 g, 1.0 mmol, 51%).

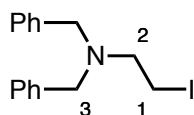
R_f 0.29 (pentane/Et₂O, 4:1), [UV, potassium permanganate]

¹H NMR (400 MHz, CDCl₃) δ 7.33 – 7.27 (m, 4H, ArH), 7.28 – 7.23 (m, 1H, ArH), 4.29 (s, 1H, H1), 3.48 (s, 2H, H4), 2.69 – 2.55 (m, 2H, H3), 2.32 – 2.03 (m, 6H, H2 and H3).

¹³C NMR (101 MHz, CDCl₃) δ 138.4, 129.2 (2C), 128.4 (2C), 127.2, 63.3, 53.8 (2C), 38.4 (2C), 28.6.

Spectroscopic data in agreement with that reported previously.^[46]

***N*-Benzyl-2-iodoethan-1-amine, 114c**



2-(Benzylamino)ethan-1-ol (0.36 g, 1.5 mmol, 1.0 equiv.), triphenylphosphine (0.51 g, 2.0 mmol, 1.3 equiv.), imidazole (0.15 g, 2.3 mmol, 1.5 equiv.) and iodine (0.46 g, 1.8 mmol, 1.2 equiv.) in CH₂Cl₂ (6 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a pale yellow oil (0.40 g, 1.1 mmol, 77%).

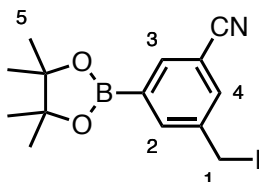
R_f 0.67 (pentane/Et₂O, 4:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.22 (m, 10H, ArH), 3.63 (s, 4H, H3), 3.16 (dd, *J* = 8.1, 6.9 Hz, 2H, H1), 2.83 (dd, *J* = 8.1, 6.9 Hz, 2H, H2).

^{13}C NMR (101 MHz, CDCl_3) δ 139.1 (2C), 129.0 (4C), 128.4 (4C), 127.3 (2C), 58.2 (2C), 56.2, 4.2.

Spectroscopic data in agreement with that reported previously.^[49]

3-(Iodomethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile, 114d



3-(Hydroxymethyl)-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (0.26 g, 1.0 mmol, 1.0 equiv.), triphenylphosphine (0.34 g, 1.3 mmol, 1.3 equiv.), imidazole (0.10 g, 1.5 mmol, 1.5 equiv.) and iodine (0.31 g, 1.2 mmol, 1.2 equiv.) in CH_2Cl_2 (4 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 4:1) afforded the title compound as a pale yellow oil (0.14 g, 0.39 mmol, 39%).

R_f 0.69 (pentane/ Et_2O , 3:2), [UV, vanillin]

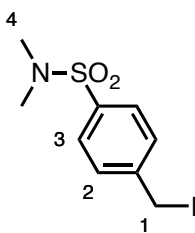
^1H NMR (500 MHz, CDCl_3) δ 7.98 (dd, $J = 1.9, 1.1$ Hz, 1H, H2), 7.95 (t, $J = 1.3$ Hz, 1H, H3), 7.73 (t, $J = 1.9$ Hz, 1H, H4), 4.42 (s, 2H, H1), 1.35 (s, 12H, H5).

^{13}C NMR (126 MHz, CDCl_3) δ 140.3, 138.9 (2C), 137.7, 134.6, 118.4, 112.9, 84.8 (2C), 25.0 (4C), 2.5

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 391.0327$; $\text{C}_{14}\text{H}_{17}\text{O}_2\text{N}^{10}\text{B}^{127}\text{INa}$ requires 391.0326.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2979, 2927, 2851, 1710, 1598, 1372, 1235, 1143.

4-(Iodomethyl)-*N,N*-dimethylbenzenesulfonamide, 114e



4-(Hydroxymethyl)-*N,N*-dimethylbenzenesulfonamide (0.22 g, 1.0 mmol, 1.0 equiv.), triphenylphosphine (0.34 g, 1.3 mmol, 1.3 equiv.), imidazole (0.10 g, 1.5 mmol, 1.5 equiv.) and iodine (0.31 g, 1.2 mmol, 1.2 equiv.) in CH₂Cl₂ (4 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane/Et₂O, 3:2) afforded the title compound as a white solid (0.15 g, 0.46 mmol, 46%).

R_f 0.26 (pentane/Et₂O, 3:2), [UV, vanillin]

m.p. 100 – 101 °C

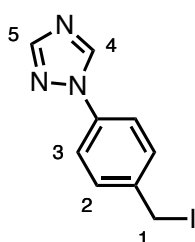
¹H NMR (500 MHz, CDCl₃) δ 7.73 – 7.68 (m, 2H, H3), 7.55 – 7.51 (m, 2H, H2), 4.47 (s, 2H, H1), 2.72 (s, 6H, H4).

¹³C NMR (126 MHz, CDCl₃) δ 144.5, 135.1, 129.5 (2C), 128.4 (2C), 38.1 (2C), 3.0.

HRMS (ESI⁺) Found [M+Na]⁺ = 347.9526; C₉H₁₂O₂N¹²⁷INaS requires 347.9526.

IR (film) ν_{max}/cm⁻¹ 2920, 2848, 1340, 1160.

1-(4-(Iodomethyl)phenyl)-1*H*-1,2,4-triazole, 114f



(4-(1*H*-1,2,4-Triazol-1-yl)phenyl)methanol (0.18 g, 1.0 mmol, 1.0 equiv.), triphenylphosphine (0.34 g, 1.3 mmol, 1.3 equiv.), imidazole (0.10 g, 1.5 mmol,

1.5 equiv.) and iodine (0.31 g, 1.2 mmol, 1.2 equiv.) in CH₂Cl₂ (4 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane/Et₂O, 2:3) afforded the title compound as a pale yellow solid (57 mg, 0.20 mmol, 20%).

R_f 0.10 (pentane/Et₂O, 2:3), [UV, vanillin]

m.p. 210 – 212 °C

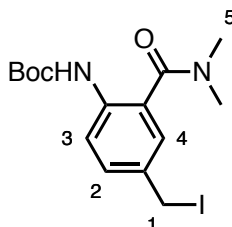
¹H NMR (500 MHz, CDCl₃) δ 8.55 (s, 1H, H5), 8.11 (s, 1H, H4), 7.65 – 7.59 (m, 2H, H3), 7.54 – 7.51 (m, 2H, H2), 4.49 (s, 2H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 152.9, 140.9, 139.8, 136.4, 130.3 (2C), 120.5 (2C), 3.9.

HRMS (ESI⁺) Found [M+H]⁺ = 285.9836; C₉H₉N₃¹²⁷I requires 285.9836.

IR (film) ν_{max}/cm⁻¹ 2922, 2851, 1524, 1276, 1153.

***tert*-Butyl (2-(dimethylcarbamoyl)-4-(iodomethyl)phenyl)carbamate, 114g**



tert-Butyl (2-(dimethylcarbamoyl)-4-(hydroxymethyl)phenyl)carbamate (0.29 g, 1.0 mmol, 1.0 equiv.), triphenylphosphine (0.34 g, 1.3 mmol, 1.3 equiv.), imidazole (0.10 g, 1.5 mmol, 1.5 equiv.) and iodine (0.31 g, 1.2 mmol, 1.2 equiv.) in CH₂Cl₂ (4 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane/Et₂O, 3:2) afforded the title compound as a yellow oil (72 mg, 0.18 mmol, 18%).

R_f 0.17 (pentane/Et₂O, 3:2), [UV, vanillin]

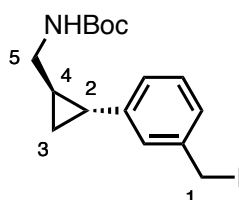
¹H NMR (500 MHz, CDCl₃) δ 8.16 – 8.04 (m, 2H, H3 and NH), 7.36 (dd, *J* = 8.6, 2.2 Hz, 1H, H2), 7.23 (d, *J* = 2.2 Hz, 1H, H4), 4.42 (s, 2H, H1), 3.08 (br d, *J* = 42.9 Hz, 6H, H5), 1.50 (s, 9H, C(CH₃)₃).

¹³C NMR (126 MHz, CDCl₃) δ 169.9, 152.9, 137.3, 132.6, 131.0, 128.5, 123.6, 121.0, 80.9, 40.1, 35.6, 28.4 (3C), 5.3.

HRMS (ESI⁺) Found [M+Na]⁺ = 427.0488; C₁₅H₂₁O₃N₂¹²⁷INa requires 427.0489.

IR (film) ν_{max}/cm⁻¹ 2925, 1727, 1630, 1518, 1392, 1240, 1155.

***tert*-Butyl ((2-(3-(iodomethyl)phenyl)cyclopropyl)methyl)carbamate, 114h**



tert-Butyl (((1*S*,2*S*)-2-(4-(hydroxymethyl)phenyl)cyclopropyl)methyl)-carbamate (0.28 g, 1.0 mmol, 1.0 equiv.), triphenylphosphine (0.34 g, 1.3 mmol, 1.3 equiv.), imidazole (0.10 g, 1.5 mmol, 1.5 equiv.) and iodine (0.31 g, 1.2 mmol, 1.2 equiv.) in CH₂Cl₂ (4 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow oil (0.19 g, 0.49 mmol, 49%).

R_f 0.57 (pentane/Et₂O, 3:2), [UV, vanillin]

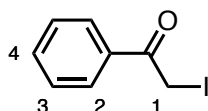
¹H NMR (400 MHz, CDCl₃) δ 7.20 – 7.15 (m, 2H, Ar*H*), 7.07 – 7.04 (m, 1H, Ar*H*), 6.93 – 6.88 (m, 1H, Ar*H*), 4.68 (br s, 1H, NH), 4.41 (s, 2H, H1), 3.28 – 3.05 (m, 2H, H5), 1.82 – 1.74 (m, 1H, H4), 1.45 (s, 9H, C(CH₃)₃), 1.33 – 1.27 (m, 1H, H2), 0.97 – 0.86 (m, 2H, H3).

^{13}C NMR (126 MHz, CDCl_3) δ 156.0, 143.4, 139.4, 128.9, 126.4, 126.2, 125.5, 79.5, 44.8, 28.6 (3C), 23.3, 21.9, 14.5, 5.9.

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 410.0588$; $\text{C}_{16}\text{H}_{22}\text{O}_2\text{N}^{127}\text{INa}$ requires 410.0587.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3354, 2976, 2929, 1697, 1509, 1167.

2-Iodo-1-phenylethan-1-one, 114m



2-Bromo-1-phenylethan-1-one (0.20 g, 1.0 mmol, 1.0 equiv.) and sodium iodide (0.23 g, 1.5 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General Procedure B** for 17 h to afford the title compound as a yellow oil (0.23 g, 0.93 mmol, 93%).

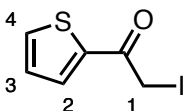
R_f 0.21 (pentane/ Et_2O , 97:3), [UV, vanillin]

^1H NMR (400 MHz, CDCl_3) δ 8.02 – 7.97 (m, 2H, H2), 7.64 – 7.57 (m, 1H, H4), 7.52 – 7.46 (m, 2H, H3), 4.37 (s, 2H, H1).

^{13}C NMR (101 MHz, CDCl_3) δ 193.0, 134.0, 133.6, 129.2 (2C), 129.0 (2C), 1.8.

Spectroscopic data in agreement with that reported previously.^[11]

2-Iodo-1-(thiophen-2-yl)ethan-1-one, 114n



2-Bromo-1-(thiophen-2-yl)ethan-1-one (0.21 g, 1.0 mmol, 1.0 equiv.) and sodium iodide (0.23 g, 1.5 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General**

Procedure B for 17 h to afford the title compound as an orange oil (0.20 g, 0.80 mmol, 80%).

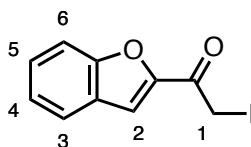
R_f 0.36 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.80 (dd, *J* = 3.8, 1.1 Hz, 1H, H4), 7.69 (dd, *J* = 4.9, 1.1 Hz, 1H, H2), 7.16 (dd, *J* = 4.9, 3.8 Hz, 1H, H3), 4.30 (s, 2H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 186.2, 140.5, 135.2, 133.6, 128.5, 1.4.

Spectroscopic data in agreement with that reported previously.^[11]

1-(Benzofuran-2-yl)-2-iodoethan-1-one, 114o



1-(Benzofuran-2-yl)-2-bromoethan-1-one (0.24 g, 1.0 mmol, 1.0 equiv.) and sodium iodide (0.23 g, 1.5 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General Procedure B** for 17 h to afford the title compound as a yellow solid (0.19 g, 0.75 mmol, 75%).

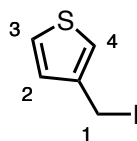
R_f 0.36 (pentane/EtOAc, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.74 (dt, *J* = 7.9, 1.0 Hz, 1H, H3), 7.65 (d, *J* = 1.0 Hz, 1H, H2), 7.60 (dq, *J* = 8.4, 1.0 Hz, 1H, H6), 7.53 – 7.50 (m, 1H, H5), 7.35 – 7.31 (m, 1H, H4), 4.37 (s, 2H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 184.1, 155.9, 149.9, 129.0, 127.2, 124.3, 123.6, 114.7, 112.7, 0.8.

Spectroscopic data in agreement with that reported previously.^[11]

3-(Iodomethyl)thiophene, 114p



3-(Bromomethyl)thiophene (0.11 g, 1.0 mmol, 1.0 equiv.) and sodium iodide (0.23 g, 1.5 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General Procedure B** for 20 h to afford the title compound as a pale yellow oil (0.21 g, 0.94 mmol, 94%).

R_f 0.74 (pentane/Et₂O, 7:3), [UV, vanillin]

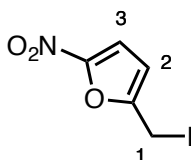
¹H NMR (500 MHz, CDCl₃) δ 7.29 (dd, *J* = 5.0, 3.0 Hz, 1H, H3), 7.27 – 7.25 (m, 1H, H4), 7.11 (dd, *J* = 5.0, 1.4 Hz, 1H, H2), 4.47 (s, 2H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 139.3, 128.6, 126.7, 123.3, –1.1.

HRMS (EI) Found [*M*–I]⁺ = 97.0103; C₅H₅S requires 97.0106.

IR (film) *v*_{max}/cm^{–1} 3098, 2905, 1683, 1565, 1428, 1153, 1080.

2-(Iodomethyl)-5-nitrofuran, 114q



3-(Bromomethyl)-5-nitrofuran (0.21 g, 1.0 mmol, 1.0 equiv.) and sodium iodide (0.23 g, 1.5 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General Procedure B** for 20 h to afford the title compound as a dark orange oil (0.19 g, 0.75 mmol, 75%).

R_f 0.10 (pentane/Et₂O, 4:1), [UV, vanillin]

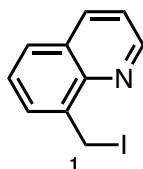
¹H NMR (500 MHz, CDCl₃) δ 7.24 (d, *J* = 3.7 Hz, 1H, H3), 6.58 (d, *J* = 3.7 Hz, 1H, H2), 4.42 (s, 2H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 155.4, 151.6, 113.0, 111.4, −10.2.

HRMS Molecular or pseudo molecular ions could not be found using ESI, APCI and EI.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3137, 1692, 1536, 1495, 1350, 1245.

8-(Iodomethyl)quinoline, 114r



3-(Bromomethyl)quinoline (0.22 g, 1.0 mmol, 1.0 equiv.) and sodium iodide (0.23 g, 1.5 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General Procedure B** for 20 h to afford the title compound as a pale yellow solid (0.21 g, 0.77 mmol, 77%).

R_f 0.14 (pentane/Et₂O, 4:1), [UV, vanillin]

m.p. 84 – 85 °C

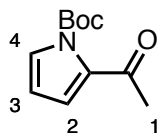
¹H NMR (500 MHz, CDCl₃) δ 9.03 (dd, *J* = 4.2, 1.8 Hz, 1H, Ar*H*), 8.16 (dd, *J* = 8.3, 1.8 Hz, 1H, Ar*H*), 7.84 (dd, *J* = 7.1, 1.4 Hz, 1H, Ar*H*), 7.77 (dd, *J* = 8.3, 1.4 Hz, 1H, Ar*H*), 7.48 – 7.42 (m, 2H, Ar*H*), 5.19 (s, 2H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 149.9, 145.7, 137.9, 136.4, 129.9, 128.9, 128.3, 126.6, 121.8, 1.9.

HRMS (APCI) Found [M+H]⁺ = 269.9775; C₁₀H₉N¹²⁷I requires 269.9774.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1685, 1573, 1499, 1404, 1320, 1249.

***tert*-Butyl 2-acetyl-1*H*-pyrrole-1-carboxylate, S15**



To a solution of 2-acetylpyrrole (0.22 g, 2.0 mmol, 1.0 equiv.) and di-*tert*-butyl dicarbonate (0.48 g, 2.2 mmol, 1.1 equiv.) in THF (26 mL) at room temperature under an inert atmosphere was added sodium hydride (60% dispersion in mineral oil, 0.15 g, 3.8 mmol, 1.9 equiv.) as a suspension in THF (18 mL) dropwise. After stirring for 25 h, the suspension was diluted with EtOAc (50 mL) and the reaction was quenched with NH₄Cl (aq., sat., 30 mL). The organic phase was washed with NH₄Cl (aq., sat., 3 × 30 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as a yellow solid (73 mg, 0.35 mmol, 18%).

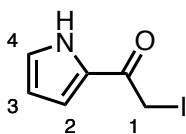
R_f 0.52 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.32 (dd, *J* = 3.1, 1.6 Hz, 1H, H4), 6.85 (dd, *J* = 3.6, 1.6 Hz, 1H, H2), 6.17 (dd, *J* = 3.6, 3.1 Hz, 1H, H3), 2.45 (s, 3H, H1), 1.58 (s, 9H, C(CH₃)₃).

¹³C NMR (101 MHz, CDCl₃) δ 188.6, 149.1, 134.3, 128.1, 121.3, 110.1, 85.0, 28.1, 27.7 (3C).

Spectroscopic data in agreement with that reported previously.^[11]

2-Iodo-1-(1*H*-pyrrol-2-yl)ethan-1-one, 114t



tert-Butyl 2-acetyl-1*H*-pyrrole-1-carboxylate **S15** (73 mg, 0.35 mmol, 1.0 equiv.), copper(I) oxide (28 mg, 0.35 mmol, 1.0 equiv.) and iodine (89 mg, 0.35 mmol, 1.0 equiv.) in MeOH (1.4 mL) were submitted to **General Procedure C**. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as a yellow solid (14 mg, 60 μmol, 17%).

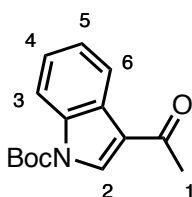
R_f 0.19 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 9.27 (br s, 1H, NH), 7.06 (td, *J* = 2.6, 1.3 Hz, 1H, H4), 7.01 (ddd, *J* = 4.0, 2.6, 1.3 Hz, 1H, H2), 6.33 (dt, *J* = 4.0, 2.6 Hz, 1H, H3), 4.20 (s, 2H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 183.5, 128.6, 126.6, 118.0, 111.4, 1.0.

Spectroscopic data in agreement with that reported previously.^[11]

tert-Butyl 3-acetyl-1*H*-indole-1-carboxylate, S16



To a solution of 3-acetylindole (0.32 g, 2.0 mmol, 1.0 equiv.) and di-*tert*-butyl dicarbonate (0.48 g, 2.2 mmol, 1.1 equiv.) in THF (26 mL) at room temperature under an inert atmosphere was added sodium hydride (60% dispersion in mineral oil, 0.15 g, 3.8 mmol, 1.9 equiv.) as a suspension in THF (18 mL) dropwise. After stirring for 25 h, the suspension was diluted with EtOAc (50 mL) and the reaction was quenched with

NH₄Cl (aq., sat., 30 mL). The organic phase was washed with NH₄Cl (aq., sat., 3 × 30 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a white solid (0.44 g, 1.7 mmol, 86%).

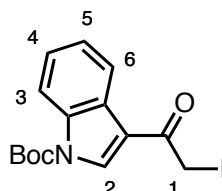
R_f 0.43 (pentane/EtOAc, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 8.40 – 8.34 (m, 1H, H3), 8.23 (s, 1H, H2), 8.14 – 8.08 (m, 1H, H6), 7.42 – 7.32 (m, 2H, H4 and H5), 2.57 (s, 3H, H1), 1.72 (s, 9H, C(CH₃)₃).

¹³C NMR (101 MHz, CDCl₃) δ 194.1, 149.3, 135.7, 132.5, 127.5, 125.6, 124.5, 122.9, 120.8, 115.1, 85.6, 28.3 (3C), 27.9.

Spectroscopic data in agreement with that reported previously.^[11]

***tert*-Butyl 3-(2-iodoacetyl)-1*H*-indole-1-carboxylate, 114u**



tert-Butyl 3-acetyl-1*H*-indole-1-carboxylate **S16** (0.44 g, 1.7 mmol, 1.0 equiv.), copper(I) oxide (0.14 g, 1.7 mmol, 1.0 equiv.) and iodine (0.43 g, 1.7 mmol, 1.0 equiv.) in MeOH (7 mL) were submitted to **General Procedure C**. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a pale yellow solid (0.32 g, 0.83 mmol, 49%).

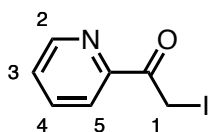
R_f 0.43 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 8.35 – 8.31 (m, 2H, H2 and H3), 8.15 – 8.08 (m, 1H, H6), 7.44 – 7.34 (m, 2H, H4 and H5), 4.31 (s, 2H, H1), 1.72 (s, 9H, C(CH₃)₃).

¹³C NMR (101 MHz, CDCl₃) δ 188.9, 149.1, 135.7, 132.9, 127.6, 126.0, 124.8, 122.9, 116.9, 115.2, 86.0, 28.3 (3C), 3.1.

Spectroscopic data in agreement with that reported previously.^[11]

2-Iodo-1-(pyridin-2-yl)ethan-1-one, 114v



1-(Pyridin-2-yl)ethan-1-one (0.11 mL, 1.0 mmol, 1.0 equiv.), copper(I) oxide (80 mg, 1.0 mmol, 1.0 equiv.) and iodine (0.25 g, 1.0 mmol, 1.0 equiv.) in MeOH (4 mL) were submitted to **General Procedure C**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a yellow oil (21 mg, 85 μmol, 9%).

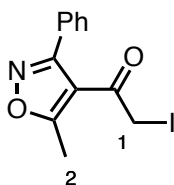
R_f 0.43 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 8.69 (ddd, *J* = 4.7, 1.8, 1.1 Hz, 1H, H2), 8.10 (dt, *J* = 7.7, 1.1 Hz, 1H, H5), 7.87 (td, *J* = 7.7, 1.8 Hz, 1H, H4), 7.51 (ddd, *J* = 7.7, 4.7, 1.1 Hz, 1H, H3), 4.69 (s, 2H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 194.6, 150.9, 149.2, 137.3, 127.8, 123.1, 1.9.

Spectroscopic data in agreement with that reported previously.^[50]

2-Iodo-1-(5-methyl-3-phenylisoxazol-4-yl)ethan-1-one, 114w



1-(5-Methyl-3-phenylisoxazol-4-yl)ethan-1-one (0.20 g, 1.0 mmol, 1.0 equiv.), copper(I) oxide (80 mg, 1.0 mmol, 1.0 equiv.) and iodine (0.25 g, 1.0 mmol, 1.0 equiv.) in MeOH (4 mL) were submitted to **General Procedure C**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a yellow oil (0.24 g, 0.74 mmol, 74%).

R_f 0.40 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.57 – 7.49 (m, 5H, ArH), 3.75 (s, 2H, H1), 2.71 (s, 3H, H2).

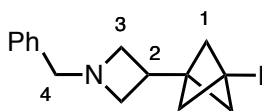
¹³C NMR (126 MHz, CDCl₃) δ 188.8, 176.5, 161.4, 130.6, 129.1 (2C), 129.1 (2C), 128.5, 114.1, 13.7, 6.1.

HRMS (ESI⁺) Found [M+H]⁺ = 327.9829; C₁₂H₁₁O₂N¹²⁷I requires 327.9829.

IR (film) ν_{max} /cm⁻¹ 1672, 1568, 1413, 1307, 699.

9.5.3 Reaction scope: BCP products

1-Benzyl-3-(3-iodobicyclo[1.1.1]pentan-1-yl)azetidine, 115a



1-Benzyl-3-iodoazetidine **114a** (41 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.65 M in Et₂O, 0.47 mL, 0.30 mmol,

2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 1:1) afforded the title compound as a yellow oil (35 mg, 0.10 mmol, 68%).

R_f 0.14 (pentane/Et₂O, 1:1), [UV, vanillin]

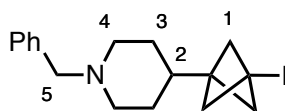
¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.21 (m, 5H, ArH), 3.53 (s, 2H, H4), 3.31 (t, *J* = 7.6 Hz, 2H, H3), 2.81 (td, *J* = 6.7, 1.4 Hz, 2H, H3), 2.62 (quin, *J* = 7.2 Hz, 1H, H2), 2.21 (s, 6H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 138.0, 128.6 (2C), 128.5 (2C), 127.2, 63.6, 59.2 (3C), 57.1 (2C), 49.3, 32.2, 8.0.

HRMS (ESI⁺) Found [M+H]⁺ = 340.0556; C₁₅H₁₉N¹²⁷I requires 340.0557.

IR (film) ν_{max} /cm⁻¹ 2919, 2877, 2851, 2820, 1181.

1-Benzyl-4-(3-iodobicyclo[1.1.1]pentan-1-yl)piperidine, **115b**



1-Benzyl-4-iodopiperidine **114b** (45 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.65 M in Et₂O, 0.47 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a yellow oil (53 mg, 0.15 mmol, 97%).

R_f 0.24 (pentane/Et₂O, 4:1), [UV, vanillin]

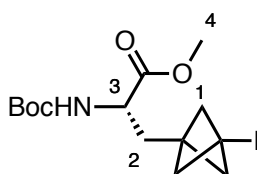
¹H NMR (500 MHz, CDCl₃) δ 7.33 – 7.22 (m, 5H, ArH), 3.47 (s, 2H, H5), 2.88 (dt, *J* = 11.9, 3.3 Hz, 2H, H4), 2.16 (s, 6H, H1), 1.87 (td, *J* = 11.9, 2.5 Hz, 2H, H4), 1.54 – 1.49 (m, 2H, H3), 1.44 – 1.40 (m, 1H, H2), 1.25 – 1.21 (m, 2H, H3).

¹³C NMR (126 MHz, CDCl₃) δ 138.5, 129.3 (2C), 128.3 (2C), 127.1, 63.6, 58.8 (3C), 53.5 (2C), 51.8, 37.7, 29.1 (2C), 8.6.

HRMS (ESI⁺) Found [M+H]⁺ = 368.0867; C₁₇H₂₃N¹²⁷I requires 368.0870.

IR (film) ν_{max}/cm⁻¹ 2914, 2799, 2759, 1175, 975.

Methyl (S)-2-((tert-butoxycarbonyl)amino)-3-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoate, 115c



Methyl (*R*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate (49 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.38 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow solid (58 mg, 0.15 mmol, 99%).

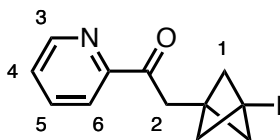
R_f 0.17 (pentane/Et₂O, 4:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 4.97 (d, *J* = 8.3 Hz, 1H, NH), 4.34 – 4.25 (m, 1H, H3), 3.74 (s, 3H, H4), 2.29 – 2.20 (m, 6H, H1), 2.13 (dd, *J* = 14.6, 4.1 Hz, 1H, H2), 1.87 (dd, *J* = 14.6, 7.6 Hz, 1H, H2), 1.45 (s, 9H, C(CH₃)₃).

¹³C NMR (101 MHz, CDCl₃) δ 172.8, 155.1, 80.3, 61.0 (3C), 52.6, 52.0, 45.5, 34.5, 28.5 (3C), 6.4.

Spectroscopic data in agreement with that reported previously.^[11]

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-(pyridin-2-yl)ethan-1-one, 115d



2-Iodo-1-(pyridin-2-yl)ethan-1-one **114v** (14 mg, 57 μ mol, 1.0 equiv.), *fac*-Ir(ppy)₃ (0.93 mg, 1.4 μ mol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.14 mL, 0.11 mmol, 2.0 equiv.) and pivalonitrile (0.6 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow oil (18 mg, 56 μ mol, 98%).

R_f 0.36 (pentane/Et₂O, 7:3), [UV, vanillin]

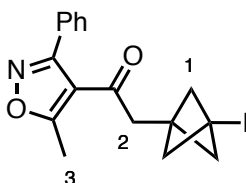
¹H NMR (500 MHz, CDCl₃) δ 8.65 (ddd, J = 4.8, 1.8, 1.1 Hz, 1H, H3), 8.01 (dt, J = 7.7, 1.1 Hz, 1H, H6), 7.84 (td, J = 7.7, 1.8 Hz, 1H, H5), 7.47 (ddd, J = 7.7, 4.8, 1.1 Hz, 1H, H4), 3.47 (s, 2H, H2), 2.34 (s, 6H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 199.1, 153.2, 149.1, 137.2, 127.5, 121.9, 61.5 (3C), 44.2, 39.7, 7.1.

HRMS (ESI⁺) Found $[M+H]^+ = 314.0036$; C₁₂H₁₃ON¹²⁷I requires 314.0036.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2972, 2915, 2877, 1698, 1176.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-(5-methyl-3-phenylisoxazol-4-yl)ethan-1-one, 115e



2-Iodo-1-(5-methyl-3-phenylisoxazol-4-yl)ethan-1-one **114w** (49 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.38 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a pale yellow oil (57 mg, 0.14 mmol, 96%).

R_f 0.45 (pentane/Et₂O, 7:3), [UV, vanillin]

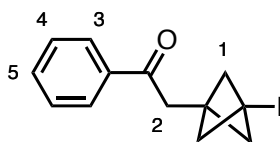
¹H NMR (500 MHz, CDCl₃) δ 7.54 – 7.44 (m, 5H, ArH), 2.67 (s, 3H, H3), 2.55 (s, 2H, H2), 2.17 (s, 6H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 193.4, 174.9, 161.6, 130.5, 129.2 (2C), 129.1 (2C), 128.8, 117.2, 61.2 (3C), 44.1, 43.6, 13.6, 6.2.

HRMS (ESI⁺) Found [M+H]⁺ = 394.0299; C₁₇H₁₇O₂N¹²⁷I requires 394.0299.

IR (film) ν_{max}/cm⁻¹ 1672, 1568, 1413, 1307, 699.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-phenylethan-1-one, 115f



2-Iodo-1-phenylethan-1-one **114m** (37 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.38 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General**

Procedure D. Purification by column chromatography (SiO₂, pentane/Et₂O, 19:1) afforded the title compound as a pale yellow solid (44 mg, 0.14 mmol, 94%).

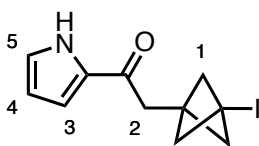
R_f 0.29 (pentane/Et₂O, 97:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.91 – 7.84 (m, 2H, H3), 7.61 – 7.54 (m, 1H, H5), 7.49 – 7.43 (m, 2H, H4), 3.20 (s, 2H, H2), 2.34 (s, 6H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 197.3, 136.8, 133.5, 128.8 (2C), 128.3 (2C), 61.4 (3C), 44.1, 40.8, 6.6.

Spectroscopic data in agreement with that reported previously.^[11]

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-(1*H*-pyrrol-2-yl)ethan-1-one, 115g



2-Iodo-1-(1*H*-pyrrol-2-yl)ethan-1-one **114t** (14 mg, 60 μmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (0.98 mg, 1.5 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.15 mL, 0.12 mmol, 2.0 equiv.) and pivalonitrile (0.6 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow solid (7.9 mg, 26 μmol, 44%).

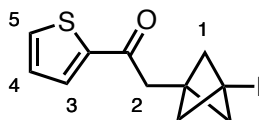
R_f 0.17 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 9.53 (br s, 1H, NH), 7.11 – 7.01 (m, 1H, H5), 6.87 – 6.78 (m, 1H, H3), 6.28 (dt, *J* = 3.8, 2.5 Hz, 1H, H4), 2.97 (s, 2H, H2), 2.31 (s, 6H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 187.1, 131.9, 125.5, 117.2, 111.0, 61.4 (3C), 44.5, 40.7, 6.5.

Spectroscopic data in agreement with that reported previously.^[11]

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-(thiophen-2-yl)ethan-1-one, 115h



2-Iodo-1-(thiophen-2-yl)ethan-1-one **114n** (38 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.38 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a pale yellow solid (44 mg, 0.14 mmol, 92%).

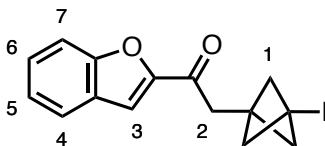
R_f 0.45 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.66 (dd, *J* = 4.9, 1.1 Hz, 1H, H5), 7.62 (dd, *J* = 3.8, 1.1 Hz, 1H, H3), 7.13 (dd, *J* = 4.9, 3.8 Hz, 1H, H4), 3.12 (s, 2H, H2), 2.34 (s, 6H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 189.9, 144.2, 134.4, 132.4, 128.4, 61.3 (3C), 44.1, 41.9, 6.2.

Spectroscopic data in agreement with that reported previously.^[11]

1-(Benzofuran-2-yl)-2-(3-iodobicyclo[1.1.1]pentan-1-yl)ethan-1-one, 115i



1-(Benzofuran-2-yl)-2-iodoethan-1-one **114o** (43 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.38 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General**

Procedure D. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a pale yellow solid (37 mg, 0.11 mmol, 70%).

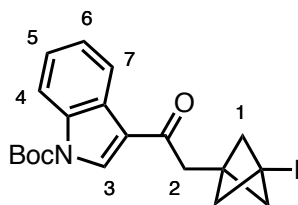
R_f 0.55 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.72 (dt, *J* = 8.0, 1.0 Hz, 1H, H4), 7.57 (dd, *J* = 8.4, 1.0 Hz, 1H, H7), 7.52 – 7.45 (m, 2H, H3 and H6), 7.33 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, H5), 3.19 (s, 2H, H2), 2.37 (s, 6H, H1).

¹³C NMR (101 MHz, CDCl₃) δ 188.1, 155.8, 152.4, 128.7, 127.1, 124.2, 123.5, 113.3, 112.6, 61.3 (3C), 43.9, 41.4, 6.2.

Spectroscopic data in agreement with that reported previously.^[11]

***tert*-Butyl 3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetyl)-1*H*-indole-1-carboxylate, 115j**



tert-Butyl 3-(2-iodoacetyl)-1*H*-indole-1-carboxylate **114u** (58 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.38 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a white solid (54 mg, 0.12 mmol, 80%).

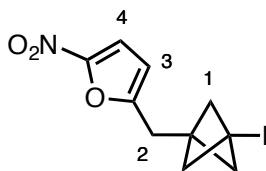
R_f 0.55 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 8.38 – 8.33 (m, 1H, H7), 8.15 (s, 1H, H3), 8.12 – 8.07 (m, 1H, H4), 7.42 – 7.32 (m, 2H, H5 and H6), 3.10 (s, 2H, H2), 2.37 (s, 6H, H1), 1.72 (s, 9H, C(CH₃)₃).

¹³C NMR (101 MHz, CDCl₃) δ 193.1, 149.2, 135.7, 132.3, 127.5, 125.8, 124.7, 122.8, 120.3, 115.1, 85.8, 61.4 (3C), 44.4, 42.4, 28.3 (3C), 6.5.

Spectroscopic data in agreement with that reported previously.^[11]

2-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)-5-nitrofuran, **115k**



2-(Iodomethyl)-5-nitrofuran **114q** (38 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.38 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as an orange oil (35 mg, 0.11 mmol, 73%).

R_f 0.21 (pentane/Et₂O, 4:1), [UV, vanillin]

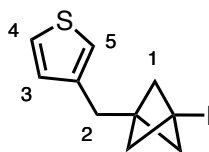
¹H NMR (500 MHz, CDCl₃) δ 7.25 (d, *J* = 3.6 Hz, 1H, H4), 6.28 (dt, *J* = 3.6, 0.7 Hz, 1H, H3), 2.98 (s, 2H, H2), 2.29 (s, 6H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 156.6, 151.8, 112.8, 110.3, 60.7 (3C), 45.1, 31.8, 5.6.

HRMS (EI) Found [M-I]⁺ = 192.0652; C₁₀H₁₀O₃N requires 192.0655.

IR (film) ν_{max}/cm⁻¹ 2993, 1528, 1494, 1390, 1354, 1236, 1176.

3-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)thiophene, **115l**



3-(Iodomethyl)thiophene **114p** (34 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.38 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a pale yellow oil (37 mg, 0.13 mmol, 84%).

R_f 0.21 (pentane), [UV, vanillin]

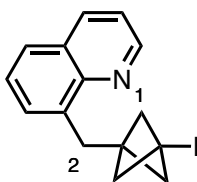
¹H NMR (500 MHz, CDCl₃) δ 7.25 (dd, *J* = 4.9, 2.9 Hz, 1H, H), 6.91 (ddd, *J* = 3.0, 1.3, 0.7 Hz, 1H), 6.83 (dd, *J* = 4.9, 1.3 Hz, 1H, H3), 2.86 (s, 2H, H2), 2.18 (s, 6H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 138.6, 128.4, 125.7, 121.4, 60.6 (3C), 48.0, 33.6, 8.1.

HRMS (EI) Found [*M*–I]⁺ = 163.0580; C₁₀H₁₁S requires 163.0576.

IR (film) *v*_{max}/cm^{–1} 2915, 2875, 2849, 1171, 981, 841.

8-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)quinoline, **115m**



8-(Iodomethyl)quinoline **114r** (40 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.79 M in Et₂O, 0.38 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow oil (35 mg, 0.10 mmol, 69%).

R_f 0.45 (pentane/Et₂O, 4:1), [UV, vanillin]

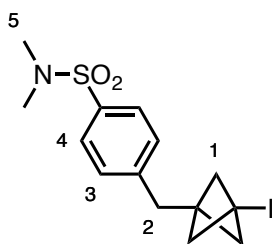
¹H NMR (500 MHz, CDCl₃) δ 8.89 (dd, *J* = 4.1, 1.8 Hz, 1H, Ar*H*), 8.13 (dd, *J* = 8.3, 1.8 Hz, 1H, Ar*H*), 7.70 (dd, *J* = 7.5, 2.1 Hz, 1H, Ar*H*), 7.48 – 7.42 (m, 2H, Ar*H*), 7.39 (dd, *J* = 8.3, 4.1 Hz, 1H, Ar*H*), 3.54 (s, 2H, H₂), 2.13 (s, 6H, H₁).

¹³C NMR (126 MHz, CDCl₃) δ 149.5, 146.9, 137.5, 136.4, 129.8, 128.6, 126.7, 126.4, 121.1, 61.1 (3C), 48.5, 34.1, 8.5.

HRMS (ESI⁺) Found [M+H]⁺ = 336.0244; C₁₅H₁₅N¹²⁷I requires 336.0244.

IR (film) ν_{max}/cm⁻¹ 2990, 2912, 2875, 1499, 1171, 839, 799.

4-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)-*N,N*-dimethylbenzenesulfonamide,
115n



4-(Iodomethyl)-*N,N*-dimethylbenzenesulfonamide **114e** (49 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.65 M in Et₂O, 0.47 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 3:2) afforded the title compound as a yellow solid (48 mg, 0.12 mmol, 81%).

R_f 0.40 (pentane/Et₂O, 1:1), [UV, vanillin]

m.p. 118 – 119 °C

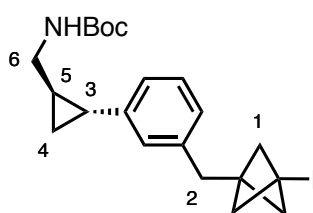
¹H NMR (500 MHz, CDCl₃) δ 7.75 – 7.68 (m, 2H, H₄), 7.25 – 7.21 (m, 2H, H₃), 2.89 (s, 2H, H₂), 2.71 (s, 6H, H₅), 2.16 (s, 6H, H₁).

^{13}C NMR (126 MHz, CDCl_3) δ 143.6, 133.8, 129.5 (2C), 128.2 (2C), 60.3 (3C), 47.7, 39.2, 38.1 (2C), 7.3.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 392.0176$; $\text{C}_{14}\text{H}_{19}\text{O}_2\text{N}^{127}\text{I}$ requires 392.0176.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2913, 1342, 1163, 953, 840.

***tert*-Butyl ((2-(3-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)phenyl)cyclopropyl)methyl)carbamate, 115o**



tert-Butyl ((2-(3-(iodomethyl)phenyl)cyclopropyl)methyl)carbamate **114h** (58 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol , 0.025 equiv.), [1.1.1]propellane **2** (0.65 M in Et_2O , 0.47 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 4:1) afforded the title compound as an orange oil (45 mg, 99 μmol , 66%).

R_f 0.24 (pentane/ Et_2O , 4:1), [UV, vanillin]

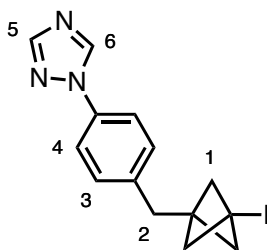
^1H NMR (500 MHz, CDCl_3) δ 7.16 (t, $J = 7.6$ Hz, 1H, ArH), 6.88 (dt, $J = 7.7$, 1.5 Hz, 1H, ArH), 6.84 (dt, $J = 7.4$, 1.4 Hz, 1H, ArH), 6.72 (t, $J = 1.9$ Hz, 1H, ArH), 4.67 (s, 1H, NH), 3.24 – 3.06 (m, 2H, H6), 2.75 (s, 2H, H2), 2.15 (s, 6H, H1), 1.77 (q, $J = 6.4$ Hz, 1H, H5), 1.45 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.27 – 1.24 (m, 1H, H3), 0.91 – 0.87 (m, 2H, H4).

^{13}C NMR (126 MHz, CDCl_3) δ 156.0, 142.9, 138.4, 128.5, 126.4, 126.2, 123.8, 79.4, 60.5 (3C), 48.3, 44.9, 39.2, 28.6 (3C), 23.3, 22.0, 14.6, 8.4.

HRMS (ESI⁺) Found [M+Na]⁺ = 476.1058; C₂₁H₂₈O₂N¹²⁷INa requires 476.1057.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2975, 1713, 1171, 839.

1-(4-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)phenyl)-1H-1,2,4-triazole, 115p



1-(4-(Iodomethyl)phenyl)-1H-1,2,4-triazole **114f** (43 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol , 0.025 equiv.), [1.1.1]propellane **2** (0.65 M in Et₂O, 0.47 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 2:3) afforded the title compound as a pale yellow solid (27 mg, 76 μmol , 51%).

R_f 0.10 (pentane/Et₂O, 1:1), [UV, vanillin]

m.p. 142 – 144 °C

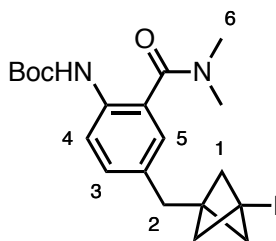
¹H NMR (500 MHz, CDCl₃) δ 8.53 (s, 1H, H6), 8.10 (s, 1H, H5), 7.63 – 7.57 (m, 2H, H4), 7.22 – 7.18 (m, 2H, H3), 2.87 (s, 2H, H2), 2.17 (s, 6H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 152.8, 140.9, 138.7, 135.6, 130.2 (2C), 120.4 (2C), 60.3 (3C), 48.1, 38.8, 7.7.

HRMS (ESI⁺) Found [M+H]⁺ = 352.0306; C₁₄H₁₅N₃I requires 352.0305.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2917, 2874, 2849, 1521, 1276, 1173.

***tert*-Butyl (2-(dimethylcarbamoyl)-4-((3-iodobicyclo[1.1.1]pentan-1-yl)methyl)-phenyl)carbamate, 115q**



tert-Butyl (2-(dimethylcarbamoyl)-4-(iodomethyl)phenyl)carbamate **114g** (61 mg, 0.15 mmol, 1.0 equiv.), *fac*-Ir(ppy)₃ (2.5 mg, 3.8 μmol, 0.025 equiv.), [1.1.1]propellane **2** (0.65 M in Et₂O, 0.47 mL, 0.30 mmol, 2.0 equiv.) and pivalonitrile (1.5 mL) were submitted to **General Procedure D**. Purification by column chromatography (SiO₂, pentane/Et₂O, 1:1) afforded the title compound as a yellow solid (54 mg, 0.11 mmol, 75%).

R_f 0.24 (pentane/Et₂O, 1:1), [UV, vanillin]

m.p. 144 – 145 °C

¹H NMR (500 MHz, CDCl₃) δ 8.06 (d, *J* = 8.5 Hz, 1H), 7.91 (br s, 1H, *NH*), 7.06 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.87 (d, *J* = 2.1 Hz, 1H), 3.06 (br d, *J* = 58.6 Hz, 6H, H6), 2.75 (s, 2H, H2), 2.13 (s, 6H, H1), 1.50 (s, 9H, C(CH₃)₃).

¹³C NMR (126 MHz, CDCl₃) δ 170.4, 153.1, 135.9, 131.8, 131.1, 127.8, 123.9, 121.2, 80.6, 60.3 (3C), 48.3, 40.1, 38.5, 35.5, 28.5 (3C), 8.1.

HRMS (ESI⁺) Found [M+H]⁺ = 471.1141; C₂₀H₂₈O₃N₂¹²⁷I requires 471.1139.

IR (film) ν_{max}/cm⁻¹ 2914, 1727, 1631, 1519, 1391, 1169.

9.6 Chapter 5: Asymmetric photoredox organocatalysis

9.6.1 General experimental procedures

General procedure A: Benzenethiol and benzeneselenol synthesis

Adapted from the procedure of Ephritikhine et al.^[51] To a suspension of magnesium turnings (2.0 equiv.) in THF (2 mL/mmol of aryl bromide) at room temperature under an inert atmosphere was added aryl bromide (1.0 equiv.). A crystal of iodine was then added and the reaction mixture heated to 80 °C in a sealed flask. After 15 h, the reaction mixture was cooled to room temperature and sulfur or selenium (1.05 equiv.) was added. The reaction mixture was then heated to 80 °C. After 1.5 h, the reaction mixture was cooled to room temperature and lithium aluminium hydride (1 M in THF, 0.5 equiv.) was added dropwise. The reaction mixture was heated to 80 °C for 30 min and then cooled to 0 °C in an ice bath. The reaction was quenched at 0 °C by addition of water (2 mL/mmol of aryl bromide) dropwise. HCl (1 N, ~2 mL/mmol of aryl bromide) was then added until good phase separation was observed. The phases were separated and the aqueous phase was extracted with Et₂O (× 3). The combined organic extracts were washed with brine, dried (Na₂SO₄) and concentrated *in vacuo*.

General procedure B: 2-Arylmalononitrile synthesis

Adapted from the procedure of Hayashi et al.^[52] To a solution of sodium hydride (60% dispersion in mineral oil, 3.0 equiv.) in THF (1 mL/mmol of aryl halide) at 0 °C under an inert atmosphere was added a solution of malononitrile (2.0 equiv.) in THF (1 mL/mmol of aryl halide) dropwise. After completion of addition, the reaction mixture was allowed to warm to room temperature and, after the evolution of gas

ceased, Pd(PPh₃)Cl₂ (0.03 equiv.) and aryl halide (1.0 equiv.) were added. The resulting mixture was stirred at 70 °C for 24 h. The reaction mixture was then cooled to room temperature, quenched by the addition of HCl (aq., 2 M, 2 mL/mmol of aryl halide). The phases were separated and the aqueous phase was extracted with Et₂O (× 3). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*.

General procedure C: Borane dimethyl sulfide complex reduction

Adapted from the procedure of Anderson et al.^[53] To a solution of carboxylic acid (1.0 equiv.) in THF (5 mL/mmol of acid) at 0 °C under an inert atmosphere was added borane dimethyl sulfide complex (2 M in THF, 1.1 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature and left to stir for the stated time. Upon completion, MeOH (0.5 mL/mmol of acid) was added and the resulting mixture was concentrated *in vacuo*. CH₂Cl₂ (10 mL/mmol of acid) was added and the organic phase was washed with NaHCO₃ (aq., sat., 5 mL/mmol of acid), HCl (aq., 2 M, 5 mL/mmol of acid) and brine (5 mL/mmol of acid). The organic phase was dried (Na₂SO₄) and concentrated *in vacuo* to afford the corresponding alcohol, which was used without further purification.

General procedure D: TEMPO/BAIB oxidation

To a solution of alcohol (1.0 equiv.) in CH₂Cl₂ (5 mL/mmol of alcohol) at room temperature was added TEMPO (0.2 equiv.) and BAIB (1.8 equiv. or 2.5 equiv.). The reaction mixture was stirred at room temperature for the stated time. Upon completion, water (3 mL/mmol of alcohol), Na₂S₂O₃ (aq., sat., 3 mL/mmol of alcohol) and NaHCO₃ (aq., sat., 3 mL/mmol of alcohol) were added. The phases were separated and

the aqueous phase was extracted with Et₂O ($\times$ 3). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*.

General procedure E: Asymmetric ring opening of [1.1.1]propellane 2

To a flame-dried vial was added [Ir(ppy)₂(dtbbpy)]PF₆ (0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (0.25 equiv.) and aldehyde (1.5 equiv., if solid). The vial was sealed with a rubber septum and Et₂O, DME and distilled water (2.0 equiv.) were then added (taking into account Et₂O from the [1.1.1]propellane **2** solution, final reaction concentration = 0.2 M with a 1:1 ratio of Et₂O to DME). The vial was then cooled in an ice bath (0 °C) and the solution was degassed by sparging with argon for 15 minutes. The vent needle was removed and [1.1.1]propellane **2** (1.0 equiv.) and aldehyde (1.5 equiv., if liquid) were then added. The vial was then capped and double-sealed with parafilm. The reaction mixture was then placed in a cooling bath at 10 °C and irradiated with blue LEDs for 24 h (see **Section 9.1** for experimental setup). The reaction mixture was then concentrated *in vacuo*. MeOH (5 mL/mmol of [1.1.1]propellane **2**) and CH₂Cl₂ (5 mL/mmol of [1.1.1]propellane **2**) were added to the vial and the reaction mixture cooled to -78 °C. Sodium borohydride (5.0 equiv.) was added and the reaction mixture was left to stir for 30 min to 1 h at -78 °C. The reaction mixture was quenched by addition of NH₄Cl (aq., sat., 5 mL/mmol of [1.1.1]propellane **2**) and water (5 mL/mmol of [1.1.1]propellane **2**). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ ($\times$ 3). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*.

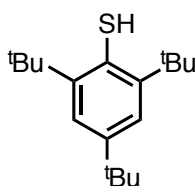
General procedure F: DMAP/EDCI coupling (for HPLC analysis of BCP products)

To a solution of alcohol (1.0 equiv.) and carboxylic acid (1.0 equiv.) in CH_2Cl_2 (10 mL/mmol of alcohol) at room temperature under an inert atmosphere was added DMAP (3.0 equiv.) and EDCI (3.0 equiv.). The reaction mixture was left to stir for the stated time. Upon completion, water (20 mL/mmol of alcohol) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 ($\times 3$). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*.

9.6.2 HAT catalysts

HAT catalysts **133c**, **133i**, **133l** and **133m** are commercially available and used directly as supplied.

2,4,6-Tri-*tert*-butylbenzenethiol, **133a**



Magnesium turnings (73 mg, 3.0 mmol, 2.0 equiv.), 2-bromo-1,3,5-tri-*tert*-butylbenzene (0.49 g, 1.5 mmol, 1.0 equiv.), sulfur (51 mg, 1.6 mmol, 1.05 equiv.) and lithium aluminium hydride (1 M in THF, 0.75 mL, 0.75 mmol, 0.5 equiv.) in THF (3 mL) were submitted to **General Procedure A**. Purification by recrystallization (pentane at $-20\text{ }^{\circ}\text{C}$) afforded the title compound as an off-white solid (0.26 g, 0.92 mmol, 61%).

R_f 0.74 (pentane/ CH_2Cl_2 , 4:1), [UV, vanillin]

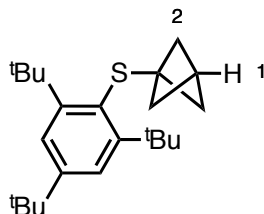
^1H NMR (400 MHz, C_6D_6) δ 7.56 (s, 2H, ArH), 3.43 (s, 1H, SH), 1.61 (s, 18H, *o*- $\text{C}(\text{CH}_3)_3$), 1.30 (s, 9H, *p*- $\text{C}(\text{CH}_3)_3$).

^{13}C NMR (101 MHz, C_6D_6) δ 151.2 (2C), 150.4, 122.8 (2C), 119.7, 37.7, 32.8 (2C), 31.8 (3C), 31.6 (6C).

Spectroscopic data in agreement with that reported previously.^[51]

Reaction of 2,4,6-tri-*tert*-butylbenzenethiol **133a** with [1.1.1]propellane **2**

Bicyclo[1.1.1]pentan-1-yl(2,4,6-tri-*tert*-butylphenyl)sulfane, **134**



A capped vial was charged with 2,4,6-tri-*tert*-butylbenzenethiol **133a** (17 mg, 60 μmol , 1.0 equiv.) and [1.1.1]propellane **2** (0.63 M in Et₂O, 9.5 μL , 60 μmol , 1.0 equiv.) and the mixture was stirred for 24 h at room temperature either in the dark with aluminium foil protection or with blue LED irradiation. The reaction mixture was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane) afforded the title compound as a colorless oil (dark: 9.9 mg, 29 μmol , 48%; blue LED irradiation: 11 mg, 31 μmol , 51%).

R_f 0.67 (pentane), [UV, vanillin]

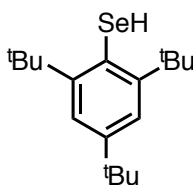
¹H NMR (500 MHz, CDCl₃) δ 7.29 (s, 2H, ArH), 2.45 (s, 1H, H1), 1.68 (s, 6H, H2), 1.53 (s, 18H, *o*-C(CH₃)₃), 1.30 (s, 9H, *p*-C(CH₃)₃).

¹³C NMR (126 MHz, CDCl₃) δ 155.3 (2C), 149.1, 130.7, 121.8 (2C), 54.1 (3C), 49.7, 38.4 (2C), 35.0, 33.6 (6C), 31.5 (3C), 27.2.

HRMS (ESI⁺) Found [M+H]⁺ = 345.2610; C₂₃H₃₇S requires 345.2611.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2961, 2910, 2875, 1587, 1481, 1390, 1359, 1240, 1206.

2,4,6-Tri-*tert*-butylbenzeneselenol, 133b



Magnesium turnings (49 mg, 2.0 mmol, 2.0 equiv.), 2-bromo-1,3,5-tri-*tert*-butylbenzene (0.33 g, 1.0 mmol, 1.0 equiv.), selenium (83 mg, 1.1 mmol, 1.05 equiv.) and lithium aluminium hydride (1 M in THF, 0.50 mL, 0.50 mmol, 0.5 equiv.) in THF (2 mL) were submitted to **General Procedure A**. The resulting residue was filtered through a short pad of silica (eluting with pentane) and the filtrate was concentrated *in vacuo*. Purification by recrystallization (hexane) afforded the title compound as a yellow solid (0.11 g, 0.33 mmol, 33%). The recrystallized sample also contained 1,3,5-tri-*tert*-butylbenzene as an impurity that could not be separated from the title compound (13%).

R_f 0.64 (pentane), [UV, vanillin]

m.p. 200 – 201 °C

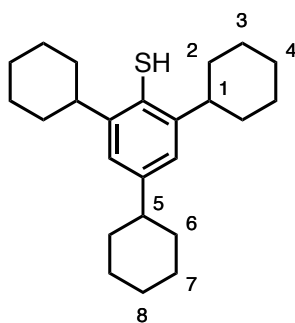
¹H NMR (500 MHz, CDCl₃) δ 7.44 (s, 2H, ArH), 1.88 (s, 1H, SeH), 1.63 (s, 18H, *o*-C(CH₃)₃), 1.31 (s, 9H, *p*-C(CH₃)₃).

¹³C NMR (126 MHz, CDCl₃) δ 152.1 (2C), 148.7, 123.0 (2C), 120.9, 38.5 (2C), 35.1, 32.1 (6C), 31.5 (3C).

HRMS (EI) Found [M]⁺ = 326.1507; C₁₈H₃₀Se requires 326.1507.

IR (film) ν_{max}/cm⁻¹ 3026, 2953, 1361, 1214, 1022.

2,4,6-Tricyclohexylbenzenethiol, 133d



According to the procedure of Buchwald *et al.*^[54] To a solution of benzene (0.45 mL, 5.0 mmol, 1.0 equiv.) and aluminium trichloride (2.1 g, 16 mmol, 3.2 equiv.) in CH₂Cl₂ (3.4 mL) at 0 °C under an inert atmosphere was added cyclohexyl bromide (2.0 mL, 16 mmol, 3.2 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Upon completion, the reaction mixture was carefully quenched with ice water (3 mL) and diluted with Et₂O (11 mL). The phases were separated and the organic phase was washed with water (3 mL) and brine (3 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The resulting residue was filtered through a short pad of silica (eluting with pentane) and the filtrate was concentrated *in vacuo* to afford 1,3,5-tricyclohexylbenzene as an orange oil (1.3 g, 4.0 mmol, 79%).

According to the procedure of Buchwald *et al.*^[54] To a solution of 1,3,5-tricyclohexylbenzene (1.3 g, 4.0 mmol, 1.0 equiv.) in CHCl₃ (3 mL) at 0 °C under an inert atmosphere was added bromine (0.20 mL, 4.0 mmol, 1.0 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature and left to stir for 20 h. The reaction mixture was then diluted with CH₂Cl₂ (7 mL) and the resulting solution was washed with water (10 mL). The aqueous phase was extracted with CH₂Cl₂ (2 × 5 mL). The combined organic extracts were washed with NaOH (aq., 10%, 7 mL) and brine (10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. The resulting residue was

filtered through a short pad of silica (eluting with pentane) and the filtrate was concentrated *in vacuo*. The resulting residue was triturated with EtOAc to afford (2-bromobenzene-1,3,5-triyl)tricyclohexane as a white solid (0.48 g, 1.2 mmol, 30%).

Magnesium turnings (49 mg, 2.0 mmol, 2.0 equiv.), (2-bromobenzene-1,3,5-triyl)tricyclohexane (0.40 g, 1.0 mmol, 1.0 equiv.), sulfur (34 mg, 1.1 mmol, 1.05 equiv.) and lithium aluminium hydride (1 M in THF, 0.50 mL, 0.50 mmol, 0.5 equiv.) in THF (2 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane) afforded the title compound as a white solid (0.23 g, 0.65 mmol, 65%).

R_f 0.48 (pentane), [UV, vanillin]

m.p. 154 – 155 °C

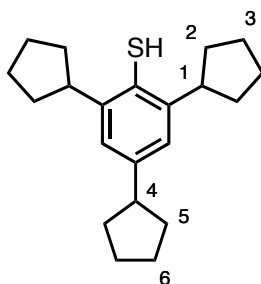
¹H NMR (500 MHz, CDCl₃) δ 6.95 (s, 2H, *ArH*), 3.10 – 3.03 (m, 2H, H1), 3.04 (s, 1H, *SH*), 2.48 – 2.40 (m, 1H, H5), 1.91 – 1.20 (m, 30H, H2, H3, H4, H6, H7 and H8).

¹³C NMR (126 MHz, CDCl₃) δ 147.1 (2C), 146.2, 124.7, 122.6 (2C), 44.8, 42.8 (2C), 34.6 (2C), 33.8 (4C), 27.3 (4C), 27.1 (2C), 26.5 (2C), 26.3.

HRMS (ESI[−]) Found [M−H][−] = 355.2466; C₂₄H₃₅S requires 355.2465.

IR (film) ν_{max} /cm^{−1} 2923, 2850, 1599, 1447.

2,4,6-Tricyclopentylbenzenethiol, 133e



According to the procedure of Buchwald *et al.*^[54] To a solution of benzene (0.45 mL, 5.0 mmol, 1.0 equiv.) and aluminium trichloride (2.1 g, 16 mmol, 3.2 equiv.) in CH_2Cl_2 (3.4 mL) at 0 °C under an inert atmosphere was added cyclopentyl bromide (1.7 mL, 16 mmol, 3.2 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 4 h. Upon completion, the reaction mixture was carefully quenched with ice water (3 mL) and diluted with Et_2O (11 mL). The phases were separated and the organic phase was washed with water (3 mL) and brine (3 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was filtered through a short pad of silica (eluting with pentane) and the filtrate was concentrated *in vacuo* to afford 1,3,5-tricyclopentylbenzene as an orange oil (1.2 g, 4.2 mmol, 84%).

According to the procedure of Buchwald *et al.*^[54] To a solution of 1,3,5-tricyclopentylbenzene (1.2 g, 4.2 mmol, 1.0 equiv.) in CHCl_3 (3 mL) at 0 °C under an inert atmosphere was added bromine (0.21 mL, 4.2 mmol, 1.0 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature and left to stir for 20 h. The reaction mixture was then diluted with CH_2Cl_2 (7 mL) and the resulting solution was washed with water (10 mL). The aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic extracts were washed with NaOH (aq., 10%, 7 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The resulting residue was filtered through a short pad of silica (eluting with hexane) and the

filtrate was concentrated *in vacuo* to afford 2-bromo-1,3,5-tricyclopentylbenzene as a colorless oil (0.76 g, 2.1 mmol, 51%).

Magnesium turnings (49 mg, 2.0 mmol, 2.0 equiv.), 2-bromo-1,3,5-tricyclopentylbenzene (0.36 g, 1.0 mmol, 1.0 equiv.), sulfur (34 mg, 1.1 mmol, 1.05 equiv.) and lithium aluminium hydride (1 M in THF, 0.50 mL, 0.50 mmol, 0.5 equiv.) in THF (2 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane) afforded the title compound as a pale yellow oil (0.29 g, 0.93 mmol, 93%).

R_f 0.60 (pentane), [UV, vanillin]

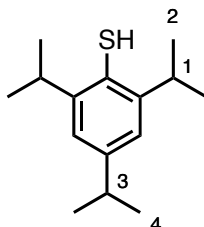
¹H NMR (400 MHz, CDCl₃) δ 7.02 (s, 2H, ArH), 3.54 (tt, *J* = 9.2, 7.4 Hz, 2H, H1), 3.13 (s, 1H, SH), 2.98 – 2.87 (m, 1H, H4), 2.15 – 1.99 (m, 6H, H2 and H5), 1.86 – 1.64 (m, 12H, H3 and H6), 1.64 – 1.54 (m, 6H, H2 and H5).

¹³C NMR (126 MHz, CDCl₃) δ 145.9 (2C), 144.5, 126.1, 122.6 (2C), 46.2, 44.3 (2C), 34.9 (2C), 33.8 (4C), 25.6 (2C), 25.6 (4C).

HRMS (EI) Found [M]⁺ = 314.2068; C₂₁H₃₀S requires 314.2063.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2950, 2867, 1599, 1563, 1452.

2,4,6-Triisopropylbenzenethiol, 133f



According to the procedure of Knowles *et al.*^[55] To a solution of lithium aluminium hydride (4 M in Et₂O, 0.75 mL, 3.0 mmol, 2.0 equiv.) in Et₂O (0.23 mL) at 0 °C under

an inert atmosphere was added a solution of 2,4,6-triisopropylbenzenesulfonyl chloride (0.45 g, 1.5 mmol, 1.0 equiv.) in Et₂O (1.1 mL) dropwise. After completion of addition, lithium aluminium hydride (4 M in Et₂O, 0.38 mL, 1.5 mmol, 1.0 equiv.) was added. The reaction mixture was allowed to warm to room temperature and was left to stir for 19.5 h. Upon completion, the reaction mixture was cooled to 0 °C and diluted with Et₂O (3 mL). The reaction was quenched with water (0.2 mL, 1 mL per gram of lithium aluminium hydride), NaOH (aq., 15% w/w, 0.2 mL, 1 mL per gram of lithium aluminium hydride) and water (0.5 mL, 3 mL per gram of lithium aluminium hydride). The reaction mixture was stirred for 10 min at 0 °C before MgSO₄ was added. The resulting slurry was stirred for 30 min at room temperature. The white solids were then removed by filtration (rinsed with Et₂O). The solution was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane) afforded the title compound as a pale yellow oil (0.24 g, 1.0 mmol, 68%).

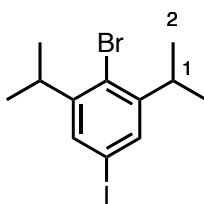
R_f 0.43 (pentane), [UV, vanillin]

¹H NMR (600 MHz, CDCl₃) δ 7.01 (s, 2H, ArH), 3.51 (sept, *J* = 6.8 Hz, 2H, H1), 3.07 (s, 1H, SH), 2.87 (sept, *J* = 6.9 Hz, 1H, H3), 1.27 (d, *J* = 6.8 Hz, 12H, H2), 1.25 (d, *J* = 6.9 Hz, 6H, H4).

¹³C NMR (151 MHz, CDCl₃) δ 148.2 (2C), 147.2, 124.4, 121.5 (2C), 34.3, 32.0 (2C), 24.2 (2C), 23.4 (4C).

Spectroscopic data in agreement with that reported previously.^[55-56]

2-Bromo-5-iodo-1,3-diisopropylbenzene, S17



According to the procedure of Nitschke *et al.*^[57] To a solution of 2,6-diisopropylaniline (1.89 mL, 10.0 mmol, 1.0 equiv.) in Et₂O (10 mL) at room temperature were added iodine (2.79 g, 11.0 mmol, 1.1 equiv.) and NaHCO₃ (aq., sat., 30 mL). The reaction mixture was left to stir at room temperature for 1.5 h, after which, Na₂S₂O₃ (500 mg) was added. The phases were separated and the aqueous phase was extracted with Et₂O (3 × 5 mL). The combined organic extracts were washed with water (20 mL), dried (Na₂SO₄) and concentrated *in vacuo* to afford 4-iodo-2,6-diisopropylaniline as a dark red/brown oil (2.91 g, 9.61 mmol, 96%).

According to the procedure of Yoshifuji *et al.*^[58] To a solution of 4-iodo-2,6-diisopropylaniline (2.91 g, 9.61 mmol, 1.0 equiv.) in acetic acid (25 mL) and sulfuric acid (conc., 10 mL) at 0 °C was added isopentyl nitrite (2.45 mL, 18.3 mmol, 1.9 equiv.) dropwise. The reaction mixture was stirred at 0 °C for 30 min. The resulting solution was then added dropwise to a separate solution of copper(I) bromide (1.93 g, 13.5 mmol, 1.4 equiv.) in hydrobromic acid (47 – 49%, 35.6 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and left to stir for 19 h. The reaction mixture was then heated to 80 °C for 30 min. Upon completion, the reaction mixture was poured onto ice water (70 mL). The phases were separated and the aqueous phase was extracted with hexane (3 × 20 mL). The combined organic extracts were washed with NaHSO₃ (aq., sat., 50 mL) and brine (50 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane) afforded the title compound as an orange oil (2.39 g, 6.50 mmol, 68%).

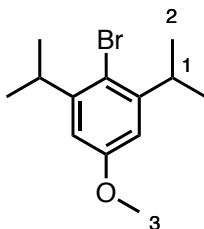
R_f 0.71 (pentane), [UV, vanillin]

¹H NMR (600 MHz, CDCl₃) δ 7.39 (s, 2H, ArH), 3.42 (sept, *J* = 6.9 Hz, 2H, H1), 1.22 (d, *J* = 6.9 Hz, 12H, H2).

¹³C NMR (151 MHz, CDCl₃) δ 150.3 (2C), 133.5, 126.7 (2C), 93.7, 33.6 (2C), 23.0 (4C).

Spectroscopic data in agreement with that reported previously.^[58]

2-Bromo-1,3-diisopropyl-5-methoxybenzene, S18



Adapted from the procedure of Buchwald et al.^[59] To a solution of 2-bromo-5-iodo-1,3-diisopropylbenzene **S17** (0.37 g, 1.0 mmol, 1.0 equiv.) in MeOH (1.0 mL) at room temperature under an inert atmosphere were added copper(I) iodide (19 mg, 0.10 mmol, 0.1 equiv.), 1,10-phenanthroline (36 mg, 0.20 mmol, 0.2 equiv.) and caesium carbonate (0.46 g, 1.4 mmol, 1.4 equiv.) (in a 21 mL screw-capped vial). The vial was sealed and the reaction mixture was heated to 110 °C and stirred for 21 h. The reaction mixture was cooled to room temperature, MeOH (1.0 mL) was added and the mixture was then heated to 120 °C for 44 h. The resulting mixture was cooled to room temperature, filtered through a short pad of silica (eluting with Et₂O) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane) afforded the title compound as a pale yellow oil (0.12 g, 0.45 mmol, 45%).

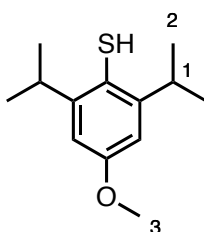
R_f 0.21 (pentane), [UV, phosphomolybdic acid]

¹H NMR (400 MHz, CDCl₃) δ 6.70 (s, 2H, ArH), 3.81 (s, 3H, H₃), 3.48 (sept, *J* = 6.8 Hz, 2H, H₁), 1.23 (d, *J* = 6.8 Hz, 12H, H₂).

¹³C NMR (126 MHz, CDCl₃) δ 159.1, 149.0 (2C), 117.2, 110.0 (2C), 55.4, 33.7 (2C), 23.1 (4C).

Spectroscopic data in agreement with that reported previously.^[60]

2,6-Diisopropyl-4-methoxybenzenethiol, 133g



Magnesium turnings (41 mg, 1.7 mmol, 2.0 equiv.), 2-bromo-1,3-diisopropyl-5-methoxybenzene **S18** (0.23 g, 0.85 mmol, 1.0 equiv.), sulfur (29 mg, 0.89 mmol, 1.05 equiv.) and lithium aluminium hydride (4 M in Et₂O, 0.11 mL, 0.42 mmol, 0.5 equiv.) in THF (1.7 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane/Et₂O, 49:1) afforded the title compound as a colorless oil (0.15 g, 0.67 mmol, 79%).

R_f 0.14 (pentane), [UV, vanillin]

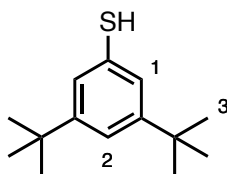
¹H NMR (400 MHz, CDCl₃) δ 6.71 (s, 2H, ArH), 3.81 (s, 3H, H₃), 3.61 (sept, *J* = 6.8 Hz, 2H, H₁), 2.87 (s, 1H, SH), 1.24 (d, *J* = 6.8 Hz, 12H, H₂).

¹³C NMR (126 MHz, CDCl₃) δ 159.2, 151.2 (2C), 117.5, 109.3 (2C), 55.3, 32.0 (2C), 23.3 (4C).

HRMS (ESI⁺) Found [M+H]⁺ = 225.1308; C₁₃H₂₁OS requires 225.1308.

IR (film) ν_{max}/cm⁻¹ 2961, 2869, 1595, 1460, 1431, 1332, 1279, 1197.

3,5-Di-*tert*-butylbenzenethiol, 133h



Magnesium turnings (0.11 g, 4.0 mmol, 2.0 equiv.), 1-bromo-3,5-di-*tert*-butylbenzene (0.54 g, 2.0 mmol, 1.0 equiv.), sulfur (67 mg, 2.1 mmol, 1.05 equiv.) and lithium aluminium hydride (1 M in THF, 1.0 mL, 1.0 mmol, 0.5 equiv.) in THF (4 mL) were submitted to **General Procedure A**. Purification by column chromatography (SiO₂, pentane) afforded the title compound as a colorless oil (0.32 g, 1.4 mmol, 71%).

R_f 0.29 (pentane), [UV, vanillin]

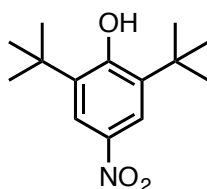
¹H NMR (500 MHz, CDCl₃) δ 7.22 (t, *J* = 1.8 Hz, 1H, H2), 7.13 (d, *J* = 1.8 Hz, 2H, H1), 3.43 (s, 1H, SH), 1.30 (s, 18H, H3).

¹³C NMR (126 MHz, CDCl₃) δ 151.9 (2C), 129.3, 124.1 (2C), 120.3, 35.0 (2C), 31.5 (6C).

HRMS (ESI[−]) Found [M−H][−] = 221.1368; C₁₄H₂₁S requires 221.1369.

IR (film) ν_{max}/cm^{−1} 2963, 2905, 2868, 1591, 1575, 1477, 1431, 1363, 1286, 1248.

2,6-Di-*tert*-butyl-4-nitrophenol, 133j



According to the procedure of Savinov *et al.*^[61] To a solution of 2,6-di-*tert*-butylphenol (0.41 g, 2.0 mmol, 1.0 equiv.) in THF (10 mL) at room temperature was added

tert-butyl nitrite (0.71 mL, 6.0 mmol, 3.0 equiv.). The reaction mixture was left to stir at room temperature for 23 h. Upon completion, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/PhMe, 4:1) afforded the title compound as a pale yellow solid (0.18 g, 0.73 mmol, 37%).

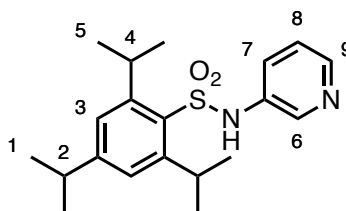
R_f 0.21 (pentane/PhMe, 7:3), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 8.12 (s, 2H, ArH), 5.93 (s, 1H, OH), 1.48 (s, 18H, *o*-C(CH₃)₃).

¹³C NMR (126 MHz, CDCl₃) δ 159.7, 140.9, 136.8 (2C), 121.6 (2C), 34.7 (2C), 30.1 (6C).

Spectroscopic data in agreement with that reported previously.^[62]

2,4,6-Triisopropyl-*N*-(pyridin-3-yl)benzenesulfonamide, 133k



Adapted from the procedure of Kanai et al.^[63] To a solution of 2,4,6-triisopropylbenzenesulfonyl chloride (0.30 g, 1.0 mmol, 1.0 equiv.) and pyridine (0.24 mL, 3.0 mmol, 3.0 equiv.) in THF (5 mL) at room temperature under an inert atmosphere was added 3-aminopyridine (0.14 g, 1.5 mmol, 1.5 equiv.). The reaction mixture was left to stir at room temperature for 24 h and then heated to 70 °C for 21 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 1:4) afforded the title compound as a white solid (0.27 g, 0.74 mmol, 74%).

R_f 0.45 (Et₂O), [UV, vanillin]

m.p. 174 – 175 °C

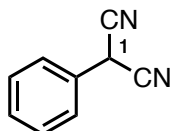
¹H NMR (500 MHz, CDCl₃) δ 8.39 (dd, *J* = 4.8, 1.5 Hz, 1H, H6), 8.17 (dd, *J* = 2.7, 0.8 Hz, 1H, H9), 7.52 (ddd, *J* = 8.3, 2.7, 1.5 Hz, 1H, H8), 7.24 (ddd, *J* = 8.3, 4.8, 0.8 Hz, 1H, H7), 7.13 (s, 2H, H3), 6.59 (s, 1H, *NH*), 3.97 (sept, *J* = 6.8 Hz, 2H, H4), 2.88 (sept, *J* = 7.0 Hz, 1H, H2), 1.23 (d, *J* = 7.0 Hz, 6H, H1), 1.17 (d, *J* = 6.8 Hz, 12H, H5).

¹³C NMR (126 MHz, CDCl₃) δ 153.7, 150.6 (2C), 147.2, 144.6, 133.3, 131.7, 131.0, 124.3 (2C), 124.0, 34.3, 30.1 (2C), 24.9 (4C), 23.7 (2C).

HRMS (ESI⁺) Found [M+H]⁺ = 361.1946; C₂₀H₂₉O₂N₂S requires 361.1944.

IR (film) ν_{max}/cm⁻¹ 2960, 2869, 1599, 1463, 1425, 1385, 1364, 1314, 1153.

2-Phenylmalononitrile, 133n



According to the procedure of Mayr *et al.*^[64] To a solution of copper(I) iodide (38 mg, 0.20 mmol, 0.2 equiv.), L-proline (23 mg, 0.20 mmol, 0.2 equiv.), K₂CO₃ (0.55 g, 4.0 mmol, 4.0 equiv.) and malononitrile (0.20 g, 3.0 mmol, 3.0 equiv.) in DMSO (5 mL) at room temperature under an inert atmosphere was added iodobenzene (0.11 mL, 1.0 mmol, 1.0 equiv.). The reaction mixture was heated to 90 °C and left to stir for 41.5 h. The reaction mixture was then cooled to 0 °C and acidified to pH 3 – 4 with HCl (aq., 2 M). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 4 mL). The combined organic extracts were washed with brine (10 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by

column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a white solid (91 mg, 0.64 mmol, 64%).

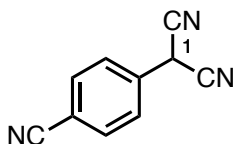
R_f 0.29 (pentane/Et₂O, 7:3), [UV, potassium permanganate]

¹H NMR (400 MHz, CDCl₃) δ 7.53 – 7.49 (m, 5H, ArH), 5.06 (s, 1H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 130.6, 130.2 (2C), 127.4 (2C), 126.3, 111.8 (2C), 28.3.

Spectroscopic data in agreement with that reported previously.^[52]

2-(4-Cyanophenyl)malononitrile, 133o



Sodium hydride (60% dispersion in mineral oil, 0.12 g, 3.0 mmol, 3.0 equiv.), malononitrile (0.13 g, 2.0 mmol, 2.0 equiv.), Pd(PPh₃)Cl₂ (21 mg, 30 μmol, 0.03 equiv.) and 4-iodobenzonitrile (0.23 g, 1.0 mmol, 1.0 equiv.) in THF (2 mL) were submitted to **General Procedure B**. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as an orange solid (19 mg, 0.11 mmol, 11%).

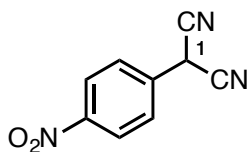
R_f 0.05 (Et₂O), [UV, potassium permanganate]

¹H NMR (500 MHz, CDCl₃) δ 7.84 (d, *J* = 8.4 Hz, 2H, ArH), 7.69 (d, *J* = 8.4 Hz, 2H, ArH), 5.16 (s, 1H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 133.9 (2C), 131.0, 128.3 (2C), 117.3, 115.1, 110.7 (2C), 28.2.

Spectroscopic data in agreement with that reported previously.^[65]

2-(4-Nitrophenyl)malononitrile, 133p



Sodium hydride (60% dispersion in mineral oil, 0.12 g, 3.0 mmol, 3.0 equiv.), malononitrile (0.13 g, 2.0 mmol, 2.0 equiv.), Pd(PPh₃)Cl₂ (21 mg, 30 μmol, 0.03 equiv.) and 1-iodo-4-nitrobenzene (0.25 g, 1.0 mmol, 1.0 equiv.) in THF (2 mL) were submitted to **General Procedure B**. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3 → EtOAc) afforded the title compound as a red solid (0.18 g, 0.96 mmol, 96%).

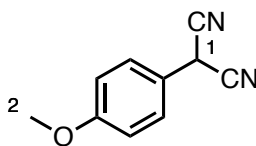
R_f 0.10 (EtOAc), [UV, potassium permanganate]

¹H NMR (500 MHz, CDCl₃) δ 8.40 (d, *J* = 8.8 Hz, 2H, *ArH*), 7.76 (d, *J* = 8.8 Hz, 2H, *ArH*), 5.21 (s, 1H, H1).

¹³C NMR (126 MHz, CDCl₃) δ 153.7, 132.3, 128.7 (2C), 125.4 (2C), 110.7 (2C), 28.0.

Spectroscopic data in agreement with that reported previously.^[66]

2-(4-Methoxyphenyl)malononitrile, 133q



Sodium hydride (60% dispersion in mineral oil, 0.12 g, 3.0 mmol, 3.0 equiv.), malononitrile (0.13 g, 2.0 mmol, 2.0 equiv.), Pd(PPh₃)Cl₂ (21 mg, 30 μmol, 0.03 equiv.) and 1-iodoanisole (0.23 g, 1.0 mmol, 1.0 equiv.) in THF (2 mL) were submitted to **General Procedure B**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as an orange solid (0.14 g, 0.82 mmol, 82%).

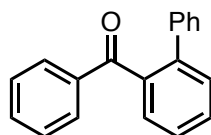
R_f 0.31 (pentane/Et₂O, 3:2), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.41 (d, *J* = 8.9 Hz, 2H, Ar*H*), 6.99 (d, *J* = 8.9 Hz, 2H), 4.99 (s, 1H, H1), 3.85 (s, 3H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 161.2, 128.7 (2C), 118.0, 115.5 (2C), 112.1 (2C), 55.7, 27.6.

Spectroscopic data in agreement with that reported previously.^[67]

[1,1'-Biphenyl]-2-yl(phenyl)methanone, S19



Adapted from the procedure of Itoi et al.^[68] To a solution of 2-bromobenzophenone (0.18 mL, 1.0 mmol, 1.0 equiv.) in THF (6.4 mL) and water (1.6 mL) at room temperature under an inert atmosphere was added phenylboronic acid (0.15 g, 1.2 mmol, 1.2 equiv.), Pd(PPh₃)₄ (0.12 g, 0.10 mmol, 0.1 equiv.) and K₂CO₃ (0.42 g, 3.0 mmol, 3.0 equiv.). The reaction mixture was heated to 80 °C and left to stir for 15 h. After cooling to room temperature, the phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 2 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 19:1) afforded the title compound as a pale yellow oil (0.15 g, 0.57 mmol, 57%).

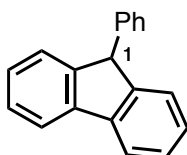
R_f 0.24 (pentane/CH₂Cl₂, 1:1), [UV, phosphomolybdic acid]

¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.62 (m, 2H, Ar*H*), 7.61 – 7.55 (m, 1H, Ar*H*), 7.54 – 7.38 (m, 4H, Ar*H*), 7.29 – 7.24 (m, 4H, Ar*H*), 7.22 – 7.12 (m, 3H, Ar*H*).

¹³C NMR (101 MHz, CDCl₃) δ 198.9, 141.3, 140.3, 139.1, 137.6, 132.9, 130.5, 130.2, 130.0 (2C), 129.1 (2C), 128.9, 128.4 (2C), 128.2 (2C), 127.5, 127.2.

Spectroscopic data in agreement with that reported previously.^[69]

9-Phenyl-9*H*-fluorene, 133r



To a rapidly stirred suspension of *p*-toluenesulfonyl hydrazide (88 mg, 0.47 mmol, 1.0 equiv.) in MeOH (0.5 mL) at 60 °C under an inert atmosphere was added [1,1'-biphenyl]-2-yl(phenyl)methanone **S19** (0.12 g, 0.47 mmol, 1.0 equiv.) as a solution in MeOH (0.5 mL) dropwise. The reaction mixture was heated to 60 °C and left to stir for 22.5 h. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (1 mL) and filtered through a short pad of silica (eluting with pentane/Et₂O, 19:1 to 7:3) to afford (*E*)-*N'*-([1,1'-biphenyl]-2-yl(phenyl)methylene)-4-methylbenzenesulfonylhydrazide as a pale pink foam (46 mg, 0.11 mmol, 23%; 71% based on recovered starting material).

According to the procedure of Wang *et al.*^[70] To a solution of (*E*)-*N'*-([1,1'-biphenyl]-2-yl(phenyl)methylene)-4-methylbenzenesulfonylhydrazide (46 mg, 0.11 mmol, 1.0 equiv.) in PhMe (1 mL) at room temperature under an inert atmosphere was added sodium hydride (60% dispersion in mineral oil, 5.2 mg, 0.13 mmol, 1.2 equiv.). The reaction mixture was then heated to 110 °C and left to stir for 5 h. Upon completion, the reaction was concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 19:1) afforded the title compound as a white solid (23 mg, 95 μmol, 88%).

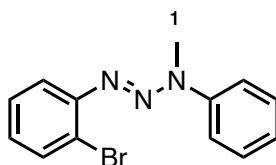
R_f 0.71 (pentane/Et₂O, 4:1), [UV, vanillin]

¹H NMR (600 MHz, CDCl₃) δ 7.80 (d, *J* = 7.6 Hz, 2H, Ar*H*), 7.38 (t, *J* = 7.4 Hz, 2H, Ar*H*), 7.32 (dd, *J* = 7.6, 1.2 Hz, 2H, Ar*H*), 7.29 – 7.20 (m, 5H, Ar*H*), 7.09 (d, *J* = 6.9 Hz, 2H, Ar*H*), 5.05 (s, 1H, H1).

¹³C NMR (151 MHz, CDCl₃) δ 148.0 (2C), 141.7, 141.2 (2C), 128.8 (2C), 128.5 (2C), 127.4 (4C), 127.0, 125.5 (2C), 120.0 (2C), 54.6.

Spectroscopic data in agreement with that reported previously.^[70]

(*E*)-1-(2-Bromophenyl)-3-methyl-3-phenyltriaz-1-ene, S20



According to the procedure of Ren *et al.*^[71] To a solution of 2-bromoaniline (0.23 mL, 2.0 mmol, 1.0 equiv.) in MeCN (2 mL) at room temperature was added HCl (conc., 0.80 mL, 10 mmol, 5.0 equiv.). The reaction mixture was cooled to –10 °C and stirred for 15 min. A solution of sodium nitrite (0.15 g, 2.1 mmol, 1.05 equiv.) in cold water (2 mL) was then added to the reaction mixture dropwise. The resulting solution was stirred at –10 °C for 30 min and then added to a solution of *N*-methylaniline (0.24 mL, 2.2 mmol, 1.1 equiv.) and K₂CO₃ (0.69 g, 5.0 mmol, 2.5 equiv.) in MeCN (2 mL) and water (4 mL), which was previously cooled to –10 °C. The resulting solution was allowed to warm to room temperature over 2 h. Upon completion, the phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 19:1) afforded the title compound as a bright orange oil (0.56 g, 1.9 mmol, 97%).

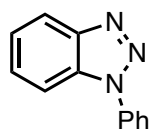
R_f 0.71 (pentane/Et₂O, 4:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.64 (dd, *J* = 8.0, 1.4 Hz, 1H, Ar*H*), 7.56 (dd, *J* = 8.1, 1.6 Hz, 1H, Ar*H*), 7.51 – 7.46 (m, 2H, Ar*H*), 7.44 – 7.37 (m, 2H, Ar*H*), 7.31 (ddd, *J* = 8.0, 7.2, 1.4 Hz, 1H, Ar*H*), 7.16 (t, *J* = 7.3 Hz, 1H, Ar*H*), 7.08 (td, *J* = 8.0, 7.2, 1.6 Hz, 1H, Ar*H*), 3.73 (s, 3H, H₁).

¹³C NMR (126 MHz, CDCl₃) δ 147.9, 145.1, 133.4, 129.4 (2C), 128.0, 127.6, 124.2, 120.9, 119.3, 117.5 (2C), 33.3.

Spectroscopic data in agreement with that reported previously.^[71]

1-Phenyl-1*H*-benzo[*d*][1,2,3]triazole, S21



Adapted from the procedure of Ren et al.^[71] To a solution of (*E*)-1-(2-bromophenyl)-3-methyl-3-phenyltriaz-1-ene **S20** (0.56 g, 1.9 mmol, 1.0 equiv.) in DMF (8 mL) at room temperature under an inert atmosphere were added Pd(OAc)₂ (22 mg, 97 μmol, 0.05 equiv.), dppp (80 mg, 0.19 mmol, 0.1 equiv.) and potassium acetate (0.23 g, 2.3 mmol, 1.2 equiv.). The reaction mixture was heated to 110 °C and left to stir for 23 h. The reaction mixture was then heated to 120 °C and left to stir for 17.5 h. The reaction mixture was then cooled to room temperature and water (5 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a pale yellow solid (0.24 g, 1.2 mmol, 63%).

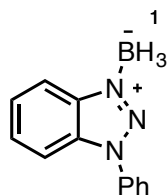
R_f 0.14 (pentane/Et₂O, 19:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 8.16 (dt, *J* = 8.2, 1.0 Hz, 1H, Ar*H*), 7.83 – 7.74 (m, 3H, Ar*H*), 7.66 – 7.60 (m, 2H, Ar*H*), 7.59 – 7.49 (m, 2H, Ar*H*), 7.45 (ddd, *J* = 8.2, 7.0, 1.0 Hz, 1H, Ar*H*).

¹³C NMR (126 MHz, CDCl₃) δ 146.7, 137.2, 132.5, 130.0 (2C), 128.8, 128.4, 124.5, 123.1 (2C), 120.5, 110.5.

Spectroscopic data in agreement with that reported previously.^[71]

1,2,3-Triazole-borane, 133s



Adapted from the procedure of Shi et al.^[72] To a solution of 1-phenyl-1*H*-benzo[*d*][1,2,3]triazole **S21** (0.24 g, 1.2 mmol, 1.0 equiv.) in THF (1.2 mL) at room temperature under an inert atmosphere was added borane-tetrahydrofuran (1 M in THF, 1.3 mL, 1.3 mmol, 1.1 equiv.) dropwise. The reaction mixture was left to stir at room temperature for 28 h, after which borane-tetrahydrofuran (1 M in THF, 1.2 mL, 1.2 mmol, 1.0 equiv.) was added and the resulting mixture left to stir at room temperature for 19.5 h. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in CH₂Cl₂ (0.5 mL) and filtered through a short pad of silica (eluting with pentane/Et₂O, 3:2) to afford the title compound as a white solid (32 mg, 0.15 mmol, 13%).

R_f 0.17 (pentane/Et₂O, 3:2), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 8.33 (dt, *J* = 8.1, 1.1 Hz, 1H, *ArH*), 7.82 – 7.77 (m, 3H, *ArH*), 7.75 – 7.71 (m, 1H, *ArH*), 7.71 – 7.66 (m, 3H, *ArH*), 7.66 – 7.62 (m, 1H, *ArH*), 3.14 – 2.59 (br m, 3H, H1).

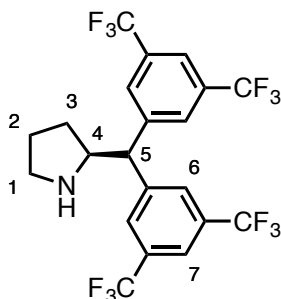
¹³C NMR (126 MHz, CDCl₃) δ 140.4, 135.5, 133.3, 130.7, 130.4 (2C), 130.2, 127.8, 123.8 (2C), 118.7, 111.5.

Spectroscopic data in agreement with that reported previously.^[72]

9.6.3 Organocatalysts

Organocatalysts **132a** and **132i** are commercially available and used directly as supplied.

(*S*)-2-(Bis(3,5-bis(trifluoromethyl)phenyl)methyl)pyrrolidine, **132b**



According to the procedure of Lin *et al.*^[73] To a solution of L-proline (2.3 g, 20 mmol, 1.0 equiv.) and K₂CO₃ (5.5 g, 40 mmol, 2.0 equiv.) in MeOH (40 mL) at 0 °C under an inert atmosphere was added ethyl chloroformate (4.6 mL, 48 mmol, 2.4 equiv.). The reaction mixture was allowed to warm to room temperature and left to stir for 22 h. The reaction mixture was then concentrated *in vacuo*. Water (10 mL) and NaHCO₃ (aq., sat., 10 mL) were added to the resulting residue and the aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na₂SO₄) and

concentrated *in vacuo* to afford 1-ethyl 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylate **S22** as a pale yellow oil (2.8 g, 14 mmol, 70%).

According to the procedure of Matsubara et al.^[74] To a solution of 1,3-bis(trifluoromethyl)-5-bromobenzene (0.52 mL, 3.0 mmol, 3.0 equiv.) in THF (2.5 mL) at 0 °C under an inert atmosphere was added isopropylmagnesium chloride (2 M in THF, 1.6 mL, 3.2 mmol, 3.15 equiv.) dropwise. The resulting mixture was stirred for 1 h at 0 °C. A solution of 1-ethyl 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylate **S22** (0.20 g, 1.0 mmol, 1.0 equiv.) in THF (4.5 mL) was then added dropwise at 0 °C. The reaction mixture was then heated to 65 °C and stirred at this temperature for 3 h. The reaction mixture was then cooled to room temperature and NH₄Cl (aq., sat., 7 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo* to afford (*S*)-1,1-bis(3,5-bis(trifluoromethyl)phenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one **S23** as a pale yellow oil (0.52 g, 0.94 mmol, 94%).

According to the procedure of Dixon et al.^[75] To a solution of (*S*)-1,1-bis(3,5-bis(trifluoromethyl)phenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one **S23** (0.49 g, 0.89 mmol, 1.0 equiv.) in ethanol (16.9 mL) containing 5% Et₃N (0.9 mL) at room temperature under an inert atmosphere was added Pd/C (10% wt., 89 mg, 100 mg/mmol of **S23**) portionwise. The reaction vial was put under vacuum and back-filled with hydrogen three times and the reaction mixture was left to stir at 40 °C under a hydrogen atmosphere for 20 h. The reaction mixture was then filtered through a pad of Celite® and the Celite® was washed with ethanol. The filtrate was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a pale yellow oil (0.23 g, 0.45 mmol, 50%).

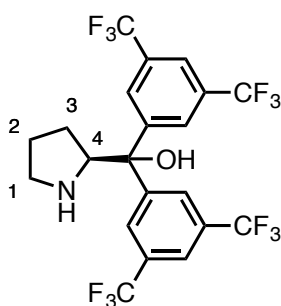
R_f 0.31 (pentane/Et₂O, 4:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.81 (s, 2H, H6), 7.78 (s, 2H, H7), 7.73 (s, 2H, H6), 4.04 (d, *J* = 9.3 Hz, 1H, H5), 3.91 (ddd, *J* = 9.3, 7.7, 6.5 Hz, 1H, H4), 3.03 – 2.91 (m, 2H, H1), 1.88 – 1.71 (m, 4H, H2, H3 and *NH*), 1.41 – 1.30 (m, 1H, H3).

¹³C NMR (126 MHz, CDCl₃) δ 144.5 (2C), 132.4 (q, *J* = 33.3 Hz, 2C), 132.3 (q, *J* = 33.3 Hz, 2C), 128.6 (d, *J* = 3.8 Hz, 2C), 128.3 (d, *J* = 3.8 Hz, 2C), 123.3 (q, *J* = 273.0 Hz, 2C), 123.2 (q, *J* = 273.0 Hz, 2C), 121.6 – 121.3 (m, 2C), 61.9, 57.9, 46.8, 31.0, 25.5.

Spectroscopic data in agreement with that reported previously.^[75]

(*S*)-Bis(3,5-bis(trifluoromethyl)phenyl)(pyrrolidin-2-yl)methanol, 132c



Adapted from the procedure of Matsubara et al.^[74] To a solution of (*S*)-1,1-bis(3,5-bis(trifluoromethyl)phenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one **S23** (0.52 g, 0.94 mmol, 1.0 equiv.) in MeOH (4 mL) at room temperature was added potassium hydroxide (0.16 g, 2.8 mmol, 3.0 equiv.). The resulting mixture was heated to 65 °C and left to stir for 18 h. The reaction mixture was then heated to 75 °C for 6 h. Potassium hydroxide (0.37 g, 6.6 mmol, 7.0 equiv.) was then added and the reaction mixture left to stir at 75 °C for 17 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting residue was diluted with water (4 mL) and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by

column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a pale yellow oil (0.31 g, 0.58 mmol, 62%).

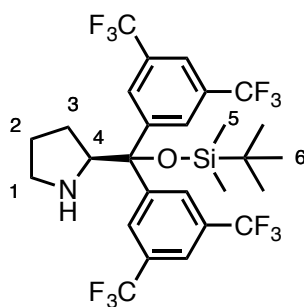
R_f 0.24 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 8.04 (s, 2H, ArH), 7.96 (s, 2H, ArH), 7.76 (d, *J* = 5.2 Hz, 2H, ArH), 5.06 (br s, 1H, OH), 4.34 (t, *J* = 7.7 Hz, 1H, H4), 3.14 – 3.00 (m, 2H, H1), 1.85 – 1.46 (m, 5H, H2, H3 and NH).

¹³C NMR (126 MHz, CDCl₃) δ 149.5, 146.6, 132.2 (q, *J* = 33.4 Hz, 2C), 131.8 (q, *J* = 32.9 Hz, 2C), 126.2 (d, *J* = 3.9 Hz, 2C), 125.8 (d, *J* = 4.1 Hz, 2C), 123.3 (q, *J* = 272.6 Hz, 2C), 123.3 (q, *J* = 273.1 Hz, 2C), 121.7 (t, *J* = 3.9 Hz), 121.5 (t, *J* = 3.9 Hz), 76.8, 64.4, 47.1, 26.9, 25.7.

Spectroscopic data in agreement with that reported previously.^[76]

(*S*)-2-(Bis(3,5-bis(trifluoromethyl)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-pyrrolidine, **132d**



According to the procedure of Lin et al.^[73] To a solution of (*S*)-bis(3,5-bis(trifluoromethyl)phenyl)(pyrrolidin-2-yl)methanol **132c** (79 mg, 0.15 mmol, 1.0 equiv.) and Et₃N (0.13 mL, 0.90 mmol, 6.0 equiv.) in CH₂Cl₂ (0.4 mL) at 0 °C under an inert atmosphere was added *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.10 mL, 0.45 mmol, 3.0 equiv.). The reaction mixture was then heated to 100 °C and left to stir for 4 h. The reaction mixture was then cooled to room

temperature and water (1 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3×1 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 19:1) afforded the title compound as a pale yellow oil (51 mg, 80 μmol , 53%).

R_f 0.64 (pentane/ Et_2O , 9:1), [UV, vanillin]

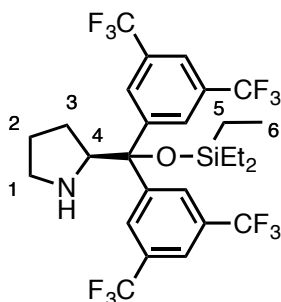
^1H NMR (500 MHz, CDCl_3) δ 8.09 (s, 2H, ArH), 7.85 (s, 2H, ArH), 7.73 (s, 2H, ArH), 4.23 (dd, $J = 8.0, 5.9$ Hz, 1H, H4), 2.89 (dt, $J = 10.2, 7.0$ Hz, 1H, H1), 2.53 (ddd, $J = 10.2, 7.0, 5.2$ Hz, 1H, H1), 1.87 – 1.71 (m, 2H, H3 and NH), 1.51 – 1.41 (m, 2H, H2 and H3), 0.94 (s, 9H, H6), 0.92 – 0.88 (m, 1H, H2), –0.21 (s, 3H, H5), –0.47 (s, 3H, H5).

^{13}C NMR (126 MHz, CDCl_3) δ 147.9, 146.2, 131.7 (q, $J = 33.4$ Hz, 2C), 130.7 (q, $J = 33.3$ Hz, 2C), 129.2 (2C), 128.9 (2C), 123.5 (q, $J = 272.7$ Hz, 2C), 123.3 (q, $J = 273.0$ Hz, 2C), 122.0 – 121.8 (m), 121.6 (t, $J = 3.6$ Hz), 82.5, 64.1, 47.4, 28.0, 26.0 (3C), 25.4, 19.0, –2.6, –3.2.

Spectroscopic data in agreement with that reported previously.^[73]

(S)-2-(Bis(3,5-bis(trifluoromethyl)phenyl)((triethylsilyl)oxy)methyl)pyrrolidine,

132e



According to the procedure of Lin et al.^[73] To a solution of (S)-bis(3,5-bis(trifluoromethyl)phenyl)(pyrrolidin-2-yl)methanol **132c** (79 mg, 0.15 mmol, 1.0 equiv.) and 2,6-lutidine (90 μ L, 0.75 mmol, 5.0 equiv.) in CH_2Cl_2 (0.3 mL) at 0 $^\circ\text{C}$ under an inert atmosphere was added triethylsilyl trifluoromethanesulfonate (0.10 mL, 0.45 mmol, 3.0 equiv.). The reaction mixture was allowed to warm to room temperature and left to stir for 28 h. Upon completion, NaHCO_3 (aq., sat., 1 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3×1 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane $\rightarrow$ pentane/ Et_2O , 9:1) afforded the title compound as a colorless oil (39 mg, 61 μ mol, 40%).

R_f 0.55 (pentane/ Et_2O , 9:1), [UV, vanillin]

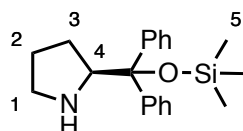
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 8.06 (s, 2H, ArH), 7.85 (s, 2H, ArH), 7.75 (s, 2H, ArH), 4.22 (dd, $J = 8.0, 6.3$ Hz, 1H, H4), 2.90 (dt, $J = 10.2, 6.8$ Hz, 1H, H1), 2.52 (ddd, $J = 10.2, 6.8, 5.6$ Hz, 1H, H1), 1.81 – 1.69 (m, 2H, H3 and NH), 1.53 – 1.38 (m, 2H, H2 and H3), 1.01 – 0.92 (m, 1H, H2), 0.84 (t, $J = 7.9$ Hz, 9H, H6), 0.39 – 0.25 (m, 6H, H5).

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 148.1, 146.3, 131.6 (q, $J = 33.4$ Hz, 2C), 130.7 (q, $J = 33.3$ Hz, 2C), 129.1 (d, $J = 3.8$ Hz, 2C), 128.6 (d, $J = 4.0$ Hz, 2C), 123.5 (q,

$J = 272.8$ Hz, 2C), 123.3 (q, $J = 272.9$ Hz, 2C), 121.9 (quin, $J = 3.9$ Hz), 121.6 (quin, $J = 3.9$ Hz), 82.3, 64.5, 47.5, 27.9, 25.6, 7.0 (3C), 6.4 (3C).

Spectroscopic data in agreement with that reported previously.^[77]

(S)-2-(Diphenyl((trimethylsilyl)oxy)methyl)pyrrolidine, 132f



According to the procedure of Bode *et al.*^[78] To a solution of (S)-diphenylprolinol (0.51 g, 2.0 mmol, 1.0 equiv.) in CH_2Cl_2 (7.6 mL) at 0 °C under an inert atmosphere was added imidazole (0.41 g, 6.0 mmol, 3.0 equiv.). Trimethylsilyl chloride (0.63 mL, 5.0 mmol, 2.5 equiv.) was then added dropwise and the reaction mixture was allowed to warm to room temperature. The reaction mixture was left to stir for 21 h. Methyl *tert*-butyl ether (13 mL) was then added and the reaction mixture was filtered. The organic phase was washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford the title compound as a colorless oil (0.53 g, 1.6 mmol, 81%).

R_f 0.17 (pentane/EtOAc, 1:1), [UV, vanillin]

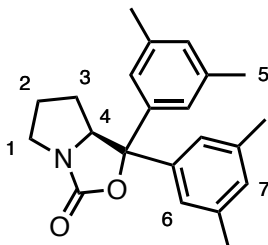
$^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.47 – 7.43 (m, 2H, ArH), 7.37 – 7.33 (m, 2H, ArH), 7.31 – 7.19 (m, 6H, ArH), 4.16 – 4.07 (m, 1H, H4), 2.95 – 2.86 (m, 1H, H1), 2.80 – 2.72 (m, 1H, H1), 1.67 – 1.57 (m, 3H, H2 and H3), 1.44 – 1.34 (m, 1H, H2), –0.09 (s, 9H, H5).

Note: the NH resonance was not observed.

$^{13}\text{C NMR}$ (126 MHz, CDCl_3) δ 146.4, 145.5, 128.6 (2C), 127.9 (2C), 127.8 (2C), 127.7 (2C), 127.3, 127.1, 83.2, 65.6, 47.2, 27.6, 25.1, 2.3 (3C).

Spectroscopic data in agreement with that reported previously.^[78]

(S)-1,1-Bis(3,5-dimethylphenyl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one, S24



Adapted from the procedure of Matsubara et al.^[74] To a solution of 1-iodo-3,5-dimethylbenzene (0.43 mL, 3.0 mmol, 3.0 equiv.) in THF (2.5 mL) at 0 °C under an inert atmosphere was added isopropylmagnesium chloride (2 M in THF, 1.6 mL, 3.2 mmol, 3.15 equiv.) dropwise. The resulting mixture was stirred for 1 h at 0 °C. A solution of 1-ethyl 2-methyl (*S*)-pyrrolidine-1,2-dicarboxylate **S22** (0.20 g, 1.0 mmol, 1.0 equiv.) in THF (4.5 mL) was then added dropwise at 0 °C. The reaction mixture was then heated to 65 °C and stirred at this temperature for 26 h. The reaction mixture was then cooled to room temperature and NH₄Cl (aq., sat., 7 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a red oil (0.33 g, 0.99 mmol, 99%).

R_f 0.38 (pentane/Et₂O, 3:2), [UV, phosphomolybdic acid]

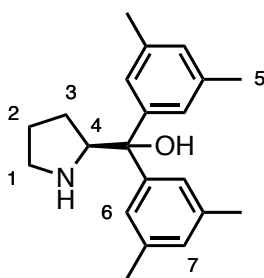
¹H NMR (400 MHz, CDCl₃) δ 7.13 (s, 2H, H6), 6.98 (s, 2H, H6), 6.93 (dt, *J* = 1.5, 0.8 Hz, 1H, H7), 6.89 (dt, *J* = 1.7, 0.8 Hz, 1H, H7), 4.50 (dd, *J* = 10.7, 5.4 Hz, 1H, H4), 3.72 (dt, *J* = 11.5, 8.1 Hz, 1H, H1), 3.23 (ddd, *J* = 11.5, 9.5, 3.7 Hz, 1H, H1), 2.30 (d, *J* = 0.8 Hz, 6H, H5), 2.29 (d, *J* = 0.8 Hz, 6H, H5), 2.03 – 1.92 (m, 1H, H2),

1.90 – 1.80 (m, 1H, H2), 1.75 – 1.66 (m, 1H, H3), 1.12 (dtd, $J = 12.5, 10.7, 8.7$ Hz, 1H, H3).

^{13}C NMR (126 MHz, CDCl_3) δ 160.9, 143.5, 140.6, 138.2 (2C), 137.9 (2C), 130.0, 129.3, 123.7 (2C), 123.3 (2C), 86.0, 69.3, 46.2, 29.1, 25.0, 21.6 (2C), 21.6 (2C).

Spectroscopic data in agreement with that reported previously.^[75]

(S)-Bis(3,5-dimethylphenyl)(pyrrolidin-2-yl)methanol, S25



Adapted from the procedure of Matsubara et al.^[74] To a solution of (S)-1,1-bis(3,5-dimethylphenyl)tetrahydro-1H,3H-pyrrolo[1,2-c]oxazol-3-one **S24** (0.33 g, 0.99 mmol, 1.0 equiv.) in MeOH (4 mL) at room temperature was added potassium hydroxide (0.56 g, 9.9 mmol, 10.0 equiv.). The resulting mixture was heated to 65 °C and left to stir for 19 h. The reaction mixture was then heated to 80 °C for 48 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting residue was diluted with water (4 mL) and extracted with EtOAc (3 × 3 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 3:2 → Et_2O) afforded the title compound as a pale yellow oil (0.13 g, 0.42 mmol, 42%).

R_f 0.14 (pentane/ Et_2O , 1:4), [UV, phosphomolybdic acid]

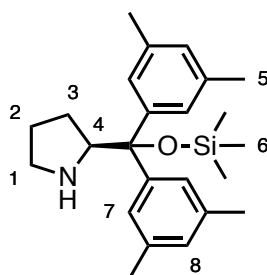
¹H NMR (500 MHz, CDCl₃) δ 7.17 (s, 2H, H₆), 7.10 (s, 2H, H₆), 6.79 (s, 2H, H₇), 4.21 (t, *J* = 7.7 Hz, 1H, H₄), 3.01 (ddd, *J* = 9.3, 6.5, 5.0 Hz, 1H, H₁), 2.94 (dt, *J* = 9.3, 7.5 Hz, 1H, H₁), 2.28 (s, 6H, H₅), 2.27 (s, 6H, H₅), 1.76 – 1.68 (m, 2H, H₂), 1.63 – 1.56 (m, 3H, H₃ and NH).

Note: the *OH* resonance was not observed.

¹³C NMR (126 MHz, CDCl₃) δ 148.3, 145.5, 137.7 (2C), 137.4 (2C), 128.3, 128.1, 123.7 (2C), 123.4 (2C), 77.4, 64.7, 46.9, 26.4, 25.7, 21.7 (2C), 21.7 (2C).

Spectroscopic data in agreement with that reported previously.^[79]

(*S*)-2-(Bis(3,5-dimethylphenyl)((trimethylsilyl)oxy)methyl)pyrrolidine, 132g



Adapted from the procedure of Pihko et al.^[80] To a solution of (*S*)-bis(3,5-dimethylphenyl)(pyrrolidin-2-yl)methanol **S25** (0.13 g, 0.42 mmol, 1.0 equiv.) and Et₃N (0.12 mL, 0.83 mmol, 2.0 equiv.) in CH₂Cl₂ (2 mL) at 0 °C under an inert atmosphere was added trimethylsilyl trifluoromethanesulfonate (0.11 mL, 0.62 mmol, 1.5 equiv.). The reaction mixture was allowed to warm to room temperature and left to stir for 25 h. Water (2 mL) was then added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 2 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 2:3) afforded the title compound as a yellow oil (70 mg, 0.18 mmol, 44%).

¹H NMR (500 MHz, CDCl₃) δ 7.03 (s, 2H, H7), 6.95 (s, 2H, H7), 6.85 (s, 1H, H8), 6.83 (s, 1H, H8), 3.96 (t, *J* = 7.3 Hz, 1H, H4), 2.87 – 2.74 (m, 2H, H1), 2.27 (s, 6H, H5), 2.26 (s, 6H, H5), 1.62 – 1.50 (m, 4H, H2, H3 and NH), 1.43 – 1.37 (m, 1H, H3), –0.10 (s, 9H, H6).

Spectroscopic data in agreement with that reported previously.^[81]

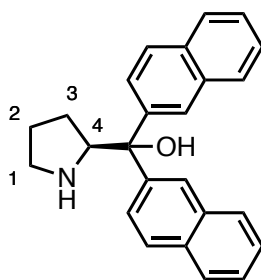
R_f 0.12 (pentane/CH₂Cl₂, 1:1), [UV, phosphomolybdic acid]

¹H NMR (400 MHz, CDCl₃) δ 8.11 (d, *J* = 1.8 Hz, 1H, Ar*H*), 8.03 (d, *J* = 2.0 Hz, 1H, Ar*H*), 7.91 – 7.76 (m, 6H, Ar*H*), 7.64 (dd, *J* = 8.7, 2.0 Hz, 1H, Ar*H*), 7.54 – 7.47 (m, 4H, Ar*H*), 7.33 (dd, *J* = 8.6, 1.9 Hz, 1H, Ar*H*), 4.80 (dd, *J* = 10.6, 5.5 Hz, 1H, H₄), 3.79 (dt, *J* = 11.5, 8.1 Hz, 1H, H₁), 3.33 (ddd, *J* = 11.5, 9.4, 3.7 Hz, 1H, H₁), 2.07 – 1.88 (m, 2H, H₂), 1.83 – 1.74 (m, 1H, H₃), 1.27 – 1.14 (m, 1H, H₃).

¹³C NMR (126 MHz, CDCl₃) δ 160.6, 140.3, 137.6, 133.2, 133.0, 132.9, 132.7, 128.8, 128.6, 128.6, 128.3, 127.7, 127.7, 126.9, 126.8, 126.7, 126.7, 125.0, 124.7, 124.4, 123.9, 86.3, 68.9, 46.3, 29.3, 25.2.

Spectroscopic data in agreement with that reported previously.^[75]

(*S*)-Di(naphthalen-2-yl)(pyrrolidin-2-yl)methanol, S27



Adapted from the procedure of Matsubara et al.^[74] To a solution of (*S*)-1,1-di(naphthalen-2-yl)tetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one **S26** (0.14 g, 0.33 mmol, 1.0 equiv.) in MeOH (1.3 mL) at room temperature was added potassium hydroxide (0.19 g, 3.3 mmol, 10.0 equiv.). The resulting mixture was heated to 100 °C and left to stir for 47 h. The reaction mixture was then cooled to room temperature and concentrated *in vacuo*. The resulting residue was diluted with water (2 mL) and extracted with EtOAc (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 2:3) afforded the title compound as a white solid (77 mg, 0.22 mmol, 66%).

R_f 0.10 (Et₂O), [UV, phosphomolybdic acid]

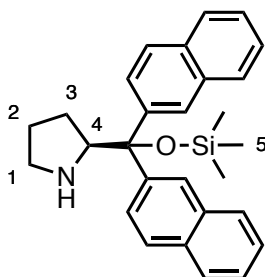
¹H NMR (400 MHz, CDCl₃) δ 8.13 – 8.07 (m, 2H, ArH), 7.85 (t, *J* = 8.1 Hz, 2H, ArH), 7.79 – 7.56 (m, 5H, ArH), 7.55 – 7.37 (m, 5H, ArH), 4.52 (t, *J* = 7.3 Hz, 1H, H4), 3.13 – 2.96 (m, 2H, H1), 1.84 – 1.58 (m, 5H, H2, H3 and NH).

Note: the OH resonance was not observed.

¹³C NMR (126 MHz, CDCl₃) δ 145.4, 142.7, 133.3, 133.2, 132.4, 132.4, 128.4, 128.3, 128.2, 127.8, 127.6, 126.3, 126.2, 126.0, 125.9, 125.8, 125.4, 124.5, 124.2, 123.9, 77.7, 64.2, 47.0, 26.6, 25.7.

Spectroscopic data in agreement with that reported previously.^[82]

(*S*)-2-(Di(naphthalen-2-yl)((trimethylsilyl)oxy)methyl)pyrrolidine, 132h



According to the procedure of Pihko *et al.*^[83] To a solution of (*S*)-di(naphthalen-2-yl)(pyrrolidin-2-yl)methanol **S27** (77 mg, 0.22 mmol, 1.0 equiv.) and Et₃N (61 μL, 0.44 mmol, 2.0 equiv.) in CH₂Cl₂ (1.8 mL) at room temperature was added trimethylsilyl chloride (33 μL, 0.26 mmol, 1.2 equiv.) and DMAP (5.3 mg, 44 μmol, 0.2 equiv.). The reaction mixture was left to stir at room temperature for 22 h. Upon completion, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 1:4) afforded the title compound as a pale yellow oil (85 mg, 0.20 mmol, 92%).

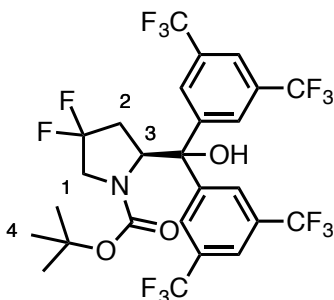
R_f 0.29 (Et₂O), [UV, vanillin/phosphomolybdic acid]

¹H NMR (500 MHz, CDCl₃) δ 8.09 (s, 1H, ArH), 8.03 (s, 1H, ArH), 7.89 – 7.76 (m, 4H, ArH), 7.68 (t, *J* = 8.5 Hz, 2H, ArH), 7.51 – 7.43 (m, 5H, ArH), 7.31 (dd, *J* = 8.7, 1.8 Hz, 1H, ArH), 4.28 (t, *J* = 7.4 Hz, 1H, H4), 2.97 – 2.88 (m, 1H, H1), 2.87 – 2.79 (m, 1H, H1), 1.78 – 1.52 (m, 4H, H2, H3 and NH), 1.47 – 1.38 (m, 1H, H2), –0.05 (s, 9H, H5).

¹³C NMR (126 MHz, CDCl₃) δ 144.2, 143.3, 133.0, 132.9, 132.6, 132.5, 128.6 (2C), 127.6 (2C), 127.6, 127.6, 127.4, 127.3, 126.7, 126.6, 126.0 (2C), 126.0, 125.7, 83.7, 65.5, 47.4, 27.8, 25.3, 2.5 (3C).

Spectroscopic data in agreement with that reported previously.^[83]

***tert*-Butyl (S)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4,4-difluoropyrrolidine-1-carboxylate, S28**



According to the procedure of Burnett et al.^[84] To a solution of *N*-Boc-4,4-difluoro-L-proline (0.50 g, 2.0 mmol, 1.0 equiv.) in acetone (5 mL) at room temperature under an inert atmosphere was added K₂CO₃ (0.42 g, 3.0 mmol, 1.5 equiv.) and iodomethane (0.19 mL, 3.0 mmol, 1.5 equiv.). The reaction mixture was stirred for 20 h at room temperature. The reaction mixture was then filtered and washed with EtOAc. The filtrate was concentrated *in vacuo* to afford 1-(*tert*-butyl) 2-methyl (S)-4,4-difluoropyrrolidine-1,2-dicarboxylate as a yellow oil (0.46 g, 1.7 mmol, 86%).

Adapted from the procedure of Matsubara et al.^[74] To a solution of 1,3-bis(trifluoromethyl)-5-bromobenzene (0.89 mL, 5.2 mmol, 3.0 equiv.) in THF (2.5 mL) at 0 °C under an inert atmosphere was added isopropylmagnesium chloride (1.5 M in THF, 3.6 mL, 5.4 mmol, 3.15 equiv.) dropwise. The resulting mixture was stirred for 1 h at 0 °C. A solution of 1-(*tert*-butyl) 2-methyl (*S*)-4,4-difluoropyrrolidine-1,2-dicarboxylate (0.46 g, 1.7 mmol, 1.0 equiv.) in THF (4.5 mL) was then added dropwise at 0 °C. The reaction mixture was then allowed to warm to room temperature and stirred at this temperature for 17 h. NH₄Cl (aq., sat., 7 mL) was then added to the reaction mixture. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a dark yellow oil (0.57 g, 0.86 mmol, 50%).

R_f 0.71 (pentane/Et₂O, 4:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.93 (s, 3H, ArH), 7.85 (s, 1H, ArH), 7.81 (s, 2H, ArH), 5.94 (br s, 1H, OH), 5.16 (dd, *J* = 9.4, 7.0 Hz, 1H, H3), 4.03 – 3.90 (m, 1H, H1), 3.14 (ddd, *J* = 23.0, 13.0, 7.5 Hz, 1H, H1), 2.64 – 2.46 (m, 1H, H2), 2.31 – 2.13 (m, 1H, H2), 1.33 (s, 9H, H4).

¹³C NMR (126 MHz, CDCl₃) δ 156.2, 145.3, 144.3, 132.2 (q, *J* = 33.6 Hz, 2C), 132.1 (d, *J* = 33.9 Hz, 2C), 127.4 (d, *J* = 4.0 Hz, 4C), 125.9 (t, *J* = 247.6 Hz), 123.2 (q, *J* = 273.0 Hz, 4C), 122.5 (dt, *J* = 6.9, 3.4 Hz, 2C), 83.2, 81.0, 64.6 (d, *J* = 4.4 Hz), 55.0 (dd, *J* = 33.4, 30.9 Hz), 38.7 (dd, *J* = 27.1, 23.8 Hz), 28.0 (3C).

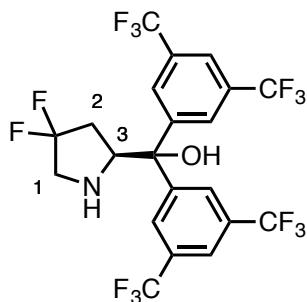
¹⁹F NMR (471 MHz, CDCl₃) δ –62.9, –62.9, –93.8 – –94.4 (m), –102.3 – –103.6 (m).

HRMS (ESI[–]) Found [M–H][–] = 660.1224; C₂₆H₂₀O₃NF₁₄ requires 660.1225.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3021, 2923, 2845, 1673, 1415, 1370, 1279, 1176, 1136.

$[\alpha]_{\text{D}}^{25} -32.1$ ($c = 0.3$, CHCl_3)

(S)-Bis(3,5-bis(trifluoromethyl)phenyl)(4,4-difluoropyrrolidin-2-yl)methanol, S29



Adapted from the procedure of Corey et al.^[85] To a solution of *tert*-butyl (S)-2-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)-4,4-difluoropyrrolidine-1-carboxylate **S28** (0.57 g, 0.86 mmol, 1.0 equiv.) in ethanol (5.0 mL) at room temperature was added sodium hydroxide (0.17 g, 4.3 mmol, 5.0 equiv.). The reaction mixture was heated to reflux (100 °C) for 40.5 h and then concentrated *in vacuo*. The reaction mixture was diluted with water (2.0 mL), neutralized with HCl (aq., 1 M) and the aqueous phase was extracted with Et₂O (3 × 2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1 and subsequently pentane/CH₂Cl₂, 4:1) afforded the title compound as an orange oil (0.15 g, 0.27 mmol, 32%).

R_f 0.24 (pentane/CH₂Cl₂, 4:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 2H, ArH), 7.94 (s, 2H, ArH), 7.81 (d, $J = 10.4$ Hz, 2H, ArH), 4.67 (s, 1H, OH), 4.64 (dd, $J = 9.5, 7.1$ Hz, 1H, H3), 3.50 – 3.32 (m, 2H, H1), 2.26 – 2.07 (m, 1H, H2), 2.03 – 1.89 (m, 1H, H2), 1.77 (br s, 1H, NH).

^{13}C NMR (126 MHz, CDCl_3) δ 147.6, 145.1, 132.7 (q, $J = 33.4$ Hz, 2C), 132.4 (q, $J = 33.6$ Hz, 2C), 128.4 (t, $J = 254.3$ Hz), 126.0 (d, $J = 3.9$ Hz, 2C), 125.4 (d, $J = 4.0$ Hz, 2C), 123.2 (q, $J = 273.0$ Hz, 4C), 122.3 (quin, $J = 3.8$ Hz), 122.1 (quin, $J = 4.0$ Hz), 76.2, 62.6 (dd, $J = 5.3, 2.1$ Hz), 54.0 (t, $J = 29.5$ Hz), 35.7 (t, $J = 24.8$ Hz).

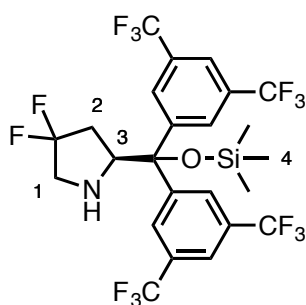
^{19}F NMR (471 MHz, CDCl_3) δ -62.8, -62.9, -95.8 – -96.8 (m), -99.5 – -100.8 (m).

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 562.0844$; $\text{C}_{21}\text{H}_{14}\text{ONF}_{14}$ requires 562.0846.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3016, 2926, 1371, 1279, 1165, 1132.

$[\alpha]_{\text{D}}^{25} -32.9$ ($c = 0.2$, CHCl_3)

(*S*)-2-(Bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-4,4-difluoropyrrolidine, 132j



According to the procedure of Pihko et al.^[83] To a solution of (*S*)-bis(3,5-bis(trifluoromethyl)phenyl)(4,4-difluoropyrrolidin-2-yl)methanol **S29** (0.15 g, 0.27 mmol, 1.0 equiv.) and Et_3N (77 μL , 0.55 mmol, 2.0 equiv.) in CH_2Cl_2 (2.2 mL) at room temperature was added trimethylsilyl chloride (42 μL , 0.33 mmol, 1.2 equiv.) and DMAP (6.7 mg, 55 μmol , 0.2 equiv.). The reaction mixture was left to stir at room temperature for 17.5 h. Upon completion, the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 99:1) afforded the title compound as a yellow oil (73 mg, 0.12 mmol, 42%).

R_f 0.60 (pentane/ Et_2O , 9:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 8.00 (s, 2H, ArH), 7.89 (d, *J* = 8.1 Hz, 2H, ArH), 7.72 (s, 2H, ArH), 4.40 (td, *J* = 9.2, 7.4 Hz, 1H, H3), 3.27 – 3.14 (m, 1H, H1), 2.90 – 2.75 (m, 1H, H1), 2.15 – 1.99 (m, 2H, H2 and NH), 1.98 – 1.81 (m, 1H, H2), –0.06 (s, 9H, H4).

¹³C NMR (126 MHz, CDCl₃) δ 147.0, 145.3, 132.2 (q, *J* = 33.6 Hz, 2C), 131.7 (q, *J* = 33.5 Hz, 2C), 129.6 (t, *J* = 253.8 Hz), 128.7 (d, *J* = 3.8 Hz, 2C), 127.6 (d, *J* = 3.7 Hz, 2C), 123.3 (q, *J* = 272.9, 270.9 Hz, 2C), 123.1 (q, *J* = 272.9 Hz, 2C), 122.4 (q, *J* = 3.8 Hz, 2C), 81.6, 63.1 (d, *J* = 6.5 Hz), 54.2 (t, *J* = 28.9 Hz), 37.4 (t, *J* = 25.0 Hz), 2.0 (3C).

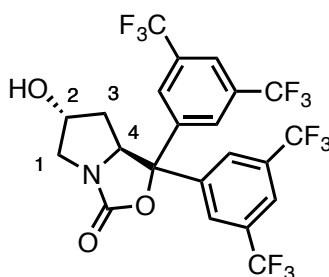
¹⁹F NMR (471 MHz, CDCl₃) δ –62.9, –62.9, –96.9, –97.4.

HRMS (ESI⁺) Found [M+H]⁺ = 634.1239; C₂₄H₂₂ONF₁₄Si requires 634.1242.

IR (film) ν_{max}/cm^{–1} 1371, 1279, 1133, 913, 843.

[α]_D²⁵ –26.6 (*c* = 0.2, CHCl₃)

(6*R*,7*aS*)-1,1-Bis(3,5-bis(trifluoromethyl)phenyl)-6-hydroxytetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one, S30



According to the procedure of Vicario *et al.*^[86] To a solution of *trans*-4-hydroxy-L-proline (1.31 g, 10.0 mmol, 1.0 equiv.) and K₂CO₃ (1.38 g, 10.0 mmol, 1.0 equiv.) in MeOH (5 mL) at 0 °C under an inert atmosphere was added methyl chloroformate (1.62 mL, 21.0 mmol, 2.1 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature and left to stir for 16.5 h. The reaction mixture

was then concentrated *in vacuo*. The resulting residue was dissolved in CH₂Cl₂ (5 mL) and water (5 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford dimethyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate as a pale yellow oil (0.95 g, 4.7 mmol, 47%).

Adapted from the procedure of Matsubara et al.^[74] To a solution of isopropylmagnesium chloride (1.5 M in THF, 9.8 mL, 15 mmol, 3.15 equiv.) at 0 °C under an inert atmosphere was added 1,3-bis(trifluoromethyl)-5-bromobenzene (2.4 mL, 14 mmol, 3.0 equiv.) in THF (10 mL) dropwise. The resulting mixture was stirred for 1 h at 0 °C. A solution of dimethyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (0.95 g, 4.7 mmol, 1.0 equiv.) in THF (18 mL) was then added dropwise at 0 °C. The reaction mixture was then heated to 65 °C and stirred at this temperature for 18.5 h. The reaction mixture was then cooled to room temperature and NH₄Cl (aq., sat., 15 mL) was added. The phases were separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 1:1) afforded the title compound as a yellow oil (1.0 g, 1.8 mmol, 39%).

R_f 0.24 (Et₂O), [UV, vanillin]

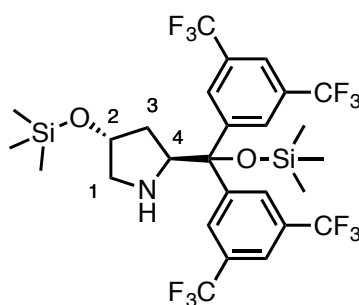
¹H NMR (400 MHz, CDCl₃) δ 7.99 (s, 2H, Ar*H*), 7.93 (s, 1H, Ar*H*), 7.90 (s, 1H, Ar*H*), 7.86 (s, 2H, Ar*H*), 4.94 (dd, *J* = 11.4, 4.8 Hz, 1H, H₄), 4.64 (q, *J* = 4.9 Hz, 1H, H₂), 4.12 (dd, *J* = 12.9, 5.6 Hz, 1H, H₁), 3.27 (d, *J* = 12.9 Hz, 1H, H₁), 1.88 (d, *J* = 3.2 Hz, 1H, OH), 1.80 (dd, *J* = 13.1, 4.9 Hz, 1H, H₃), 1.23 – 1.17 (m, 1H, H₃).

¹³C NMR (126 MHz, CDCl₃) δ 158.8, 144.4, 141.5, 133.0 (q, *J* = 33.9 Hz, 2C), 132.9 (q, *J* = 34.0 Hz, 2C), 126.0 (d, *J* = 3.8 Hz, 2C), 125.5 (d, *J* = 3.8 Hz, 2C),

123.6 (quin, $J = 3.7$ Hz), 123.0 (quin, $J = 3.6$ Hz), 122.9 (q, $J = 273.2$ Hz, 2C), 122.8 (q, $J = 273.1$ Hz, 2C), 83.6, 71.2, 67.2, 56.9, 39.4.

Spectroscopic data in agreement with that reported previously.^[86]

(2*S*,4*R*)-2-(Bis(3,5-bis(trifluoromethyl)phenyl)((trimethylsilyl)oxy)methyl)-4-((trimethylsilyl)oxy)pyrrolidine, 132k



According to the procedure of Cozzi *et al.*^[87] To a solution of (6*R*,7*aS*)-1,1-bis(3,5-bis(trifluoromethyl)phenyl)-6-hydroxytetrahydro-1*H*,3*H*-pyrrolo[1,2-*c*]oxazol-3-one **S30** (0.28 g, 0.5 mmol, 1.0 equiv.) in ethanol (1.4 mL) at room temperature was added potassium hydroxide (0.15 g, 2.6 mmol, 5.2 equiv.) and water (0.33 mL). The reaction mixture was heated to 80 °C for 17 h before being cooled to room temperature. The reaction mixture was then concentrated *in vacuo* and diluted with water (2 mL). The aqueous phase was extracted with EtOAc (3 × 2 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo* to afford (3*R*,5*S*)-5-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)pyrrolidin-3-ol as an orange oil (0.20 g, 0.37 mmol, 75%).

According to the procedure of Pihko *et al.*^[83] To a solution of (3*R*,5*S*)-5-(bis(3,5-bis(trifluoromethyl)phenyl)(hydroxy)methyl)pyrrolidin-3-ol (0.20 g, 0.37 mmol, 1.0 equiv.) and Et₃N (0.31 mL, 2.2 mmol, 6.0 equiv.) in CH₂Cl₂ (4 mL) at room temperature was added trimethylsilyl chloride (0.17 mL, 1.3 mmol, 3.5 equiv.) and

DMAP (11 mg, 93 μ mol, 0.25 equiv.). The reaction mixture was left to stir at room temperature for 22 h. Upon completion, the reaction mixture was diluted with water (4 mL). The aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane/ CH_2Cl_2 , 19:1 $\rightarrow$ pentane/ Et_2O , 9:1) afforded the title compound as a yellow oil (0.11 g, 0.16 mmol, 43%).

R_f 0.67 (pentane/ CH_2Cl_2 , 4:1), [UV, vanillin]

^1H NMR (400 MHz, CDCl_3) δ 8.01 (s, 2H, ArH), 7.84 (d, $J = 4.9$ Hz, 2H, ArH), 7.77 (s, 2H, ArH), 4.49 (t, $J = 7.9$ Hz, 1H, H4), 3.86 (br s, 1H, H2), 2.74 (d, $J = 11.6$ Hz, 1H, H1), 2.22 (dd, $J = 11.6, 3.8$ Hz, 1H, H1), 2.14 (br s, 1H, NH), 1.73 (dd, $J = 13.5, 7.6$ Hz, 1H, H3), 1.43 (ddd, $J = 13.5, 8.2, 5.1$ Hz, 1H, H3), 0.06 (s, 9H, $\text{Si}(\text{CH}_3)_3$), -0.10 (s, 9H, $\text{Si}(\text{CH}_3)_3$).

^{13}C NMR (126 MHz, CDCl_3) δ 148.2, 146.2, 131.7 (q, $J = 33.3$ Hz, 2C), 130.9 (q, $J = 33.2$ Hz, 2C), 128.8 (d, $J = 4.0$ Hz, 2C), 128.5 (d, $J = 3.9$ Hz, 2C), 123.5 (q, $J = 272.6$ Hz, 2C), 123.3 (q, $J = 272.9$ Hz, 2C), 121.9 (quin, $J = 3.9$ Hz), 121.6 (quin, $J = 3.4$ Hz), 82.3, 72.4, 62.9, 56.0, 37.8, 2.0 (3C), 0.1 (3C).

^{19}F NMR (471 MHz, CDCl_3) δ -62.8, -62.8.

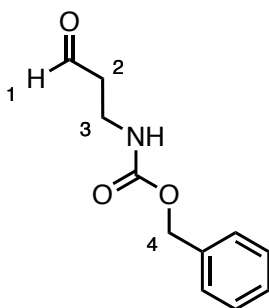
HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 686.1771$; $\text{C}_{27}\text{H}_{32}\text{O}_2\text{NF}_{12}\text{Si}_2$ requires 686.1775.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 1374, 1279, 1255, 1174, 1134, 906, 877, 842.

$[\alpha]_{\text{D}}^{25}$ -23.1 ($c = 0.3$, CHCl_3)

9.6.4 Aldehyde substrates

Benzyl (3-oxopropyl)carbamate, 130a



According to the procedure of MacMillan *et al.*^[88] To a solution of 3,3-diethoxypropan-1-amine (6.47 mL, 40.0 mmol, 1.0 equiv.) in EtOAc (80 mL) at room temperature was added NaHCO₃ (16.8 g, 200 mmol, 5.0 equiv.) and water (80 mL). Benzyl chloroformate (8.46 mL, 60.0 mmol, 1.5 equiv.) was then added and the reaction mixture was stirred at room temperature for 15 h. The phases were then separated and the aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*.

The residue was dissolved in THF (14 mL) and cooled to 0 °C. HCl (aq., 1 M, 7 mL) was then added. The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The reaction mixture was then diluted with Et₂O (50 mL) and NaHCO₃ (aq., sat., 50 mL). The phases were separated and the aqueous phase was extracted with Et₂O (3 × 30 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 2:3) afforded the title compound as a white solid (3.55 g, 17.2 mmol, 43%).

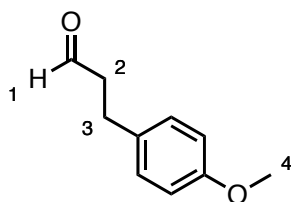
R_f 0.40 (Et₂O), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 9.81 (s, 1H, H1), 7.39 – 7.29 (m, 5H, ArH), 5.14 (br s, 1H, NH), 5.08 (s, 2H, H4), 3.49 (app q, *J* = 5.9 Hz, 2H, H3), 2.75 (t, *J* = 5.9 Hz, 2H, H2).

¹³C NMR (101 MHz, CDCl₃) δ 201.3, 156.4, 136.5, 128.7 (2C), 128.3, 128.2 (2C), 66.9, 44.2, 34.6.

Spectroscopic data in agreement with that reported previously.^[88]

3-(4-Methoxyphenyl)propanal, 130g



3-(4-Methoxyphenyl)propionic acid (0.90 g, 5.0 mmol, 1.0 equiv.) and borane dimethyl sulfide complex (2 M in THF, 2.8 mL, 5.5 mmol, 1.1 equiv.) in THF (25 mL) were submitted to **General Procedure C** for 17 h to afford 3-(4-methoxyphenyl)propan-1-ol as a clear oil (0.78 g, 4.7 mmol, 94%).

3-(4-Methoxyphenyl)propan-1-ol (0.78 g, 4.7 mmol, 1.0 equiv.), TEMPO (0.15 g, 0.94 mmol, 0.2 equiv.) and BAIB (2.7 g, 8.5 mmol, 1.8 equiv.) in CH₂Cl₂ (25 mL) were submitted to **General Procedure D** for 14 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as an orange oil (0.57 g, 3.5 mmol, 73%).

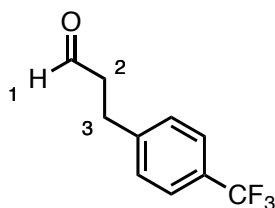
R_f 0.29 (pentane/Et₂O, 4:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 9.82 (t, *J* = 1.5 Hz, 1H, H1), 7.11 (d, *J* = 8.7 Hz, 2H, ArH), 6.84 (d, *J* = 8.7 Hz, 2H, ArH), 3.79 (s, 3H, H4), 2.91 (t, *J* = 7.6 Hz, 2H, H3), 2.75 (td, *J* = 7.6, 1.5 Hz, 2H, H2).

^{13}C NMR (126 MHz, CDCl_3) δ 201.9, 158.2, 132.4, 129.3 (2C), 114.1 (2C), 55.4, 45.7, 27.4.

Spectroscopic data in agreement with that reported previously.^[89]

3-(4-(Trifluoromethyl)phenyl)propanal, 130h



4-(Trifluoromethyl)hydrocinnamic acid (0.55 g, 2.5 mmol, 1.0 equiv.) and borane dimethyl sulfide complex (2 M in THF, 1.4 mL, 2.8 mmol, 1.1 equiv.) in THF (15 mL) were submitted to **General Procedure C** for 20 h to afford 3-(4-(trifluoromethyl)phenyl)propan-1-ol as a clear oil (0.49 g, 2.4 mmol, 96%).

3-(4-(Trifluoromethyl)phenyl)propan-1-ol (0.49 g, 2.4 mmol, 1.0 equiv.), TEMPO (75 mg, 0.48 mmol, 0.2 equiv.) and BAIB (1.4 g, 4.3 mmol, 1.8 equiv.) in CH_2Cl_2 (12 mL) were submitted to **General Procedure D** for 18 h. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 4:1) afforded the title compound as a pale yellow oil (0.26 g, 1.3 mmol, 54%).

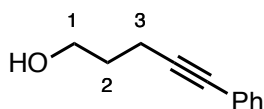
R_f 0.52 (pentane/ Et_2O , 1:1), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 9.83 (t, J = 1.1 Hz, 1H, H1), 7.55 (d, J = 8.0 Hz, 2H, ArH), 7.31 (d, J = 7.9 Hz, 2H, ArH), 3.01 (t, J = 7.5 Hz, 2H, H3), 2.82 (td, J = 7.5, 1.1 Hz, 2H, H2).

^{13}C NMR (126 MHz, CDCl_3) δ 200.8, 144.6, 128.9 (q, J = 32.4 Hz), 128.8 (2C), 125.7 (q, J = 3.8 Hz, 2C), 124.3 (q, J = 271.9 Hz), 45.0, 28.0.

Spectroscopic data in agreement with that reported previously.^[90]

5-Phenylpent-4-yn-1-ol, S31



According to the procedure of Ferreira *et al.*^[91] To a solution of iodobenzene (0.56 mL, 5.0 mmol, 1.0 equiv.) in Et₃N (15 mL) at room temperature under an inert atmosphere was added 4-pentyn-1-ol (0.51 mL, 5.5 mmol, 1.1 equiv.) and then degassed by sparging with argon for 15 min. Copper(I) iodide (38 mg, 0.20 mmol, 0.04 equiv.) and PdCl₂(PPh₃)₂ (70 mg, 0.10 mmol, 0.02 equiv.) were then added and the reaction mixture was left to stir at room temperature for 24.5 h. Upon completion, the reaction mixture was filtered through a short pad of silica (eluting with EtOAc). The filtrate was then concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 3:2) afforded the title compound as a dark orange oil (0.80 g, 5.0 mmol, 99%).

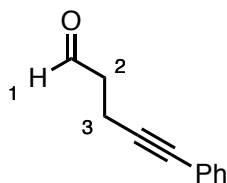
R_f 0.26 (pentane/Et₂O, 1:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.36 (m, 2H, ArH), 7.30 – 7.26 (m, 3H, ArH), 3.83 (td, *J* = 6.1, 5.5 Hz, 2H, H1), 2.55 (t, *J* = 6.9 Hz, 2H, H3), 1.87 (tt, *J* = 6.9, 6.1 Hz, 2H, H2), 1.48 (t, *J* = 5.5 Hz, 1H, OH).

¹³C NMR (126 MHz, CDCl₃) δ 131.7 (2C), 128.4 (2C), 127.8, 123.8, 89.4, 81.3, 62.0, 31.5, 16.2.

Spectroscopic data in agreement with that reported previously.^[92]

5-Phenylpent-4-ynal, 130j



5-Phenylpent-4-yn-1-ol **S31** (0.80 g, 5.0 mmol, 1.0 equiv.), TEMPO (0.16 g, 0.99 mmol, 0.2 equiv.) and BAIB (2.9 g, 8.9 mmol, 1.8 equiv.) in CH₂Cl₂ (25 mL) were submitted to **General Procedure D** for 21 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as an orange oil (0.30 g, 1.9 mmol, 39%).

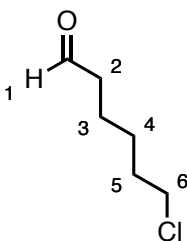
R_f 0.55 (pentane/Et₂O, 1:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 9.86 (s, 1H, H1), 7.40 – 7.36 (m, 2H, ArH), 7.30 – 7.27 (m, 3H, ArH), 2.80 – 2.72 (m, 4H, H2 and H3).

¹³C NMR (126 MHz, CDCl₃) δ 200.5, 131.6 (2C), 128.3 (2C), 127.9, 123.4, 87.7, 81.5, 42.7, 12.8.

Spectroscopic data in agreement with that reported previously.^[93]

6-Chlorohexanal, 130l



6-Chlorohexanol (0.67 mL, 5.0 mmol, 1.0 equiv.), TEMPO (0.16 g, 1.0 mmol, 0.2 equiv.) and BAIB (2.9 g, 9.0 mmol, 1.8 equiv.) in CH₂Cl₂ (25 mL) were submitted to **General Procedure D** for 18 h. Purification by column chromatography (SiO₂,

pentane/Et₂O, 17:3) afforded the title compound as an orange oil (0.58 g, 4.3 mmol, 86%).

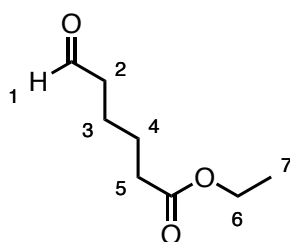
R_f 0.33 (pentane/Et₂O, 4:1), [vanillin]

¹H NMR (500 MHz, CDCl₃) δ 9.78 (t, *J* = 1.6 Hz, 1H, H1), 3.55 (t, *J* = 6.6 Hz, 2H, H6), 2.47 (td, *J* = 7.3, 1.6 Hz, 2H, H2), 1.85 – 1.76 (m, 2H, H5), 1.72 – 1.62 (m, 2H, H3), 1.55 – 1.44 (m, 2H, H4).

¹³C NMR (126 MHz, CDCl₃) δ 202.3, 44.8, 43.7, 32.3, 26.4, 21.4.

Spectroscopic data in agreement with that reported previously.^[94]

Ethyl 6-oxohexanoate, 130m



Ethyl 6-hydroxyhexanoate (0.81 mL, 5.0 mmol, 1.0 equiv.), TEMPO (0.16 g, 1.0 mmol, 0.2 equiv.) and BAIB (2.9 g, 9.0 mmol, 1.8 equiv.) in CH₂Cl₂ (25 mL) were submitted to **General Procedure D** for 18 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a light orange oil (0.73 g, 4.6 mmol, 93%).

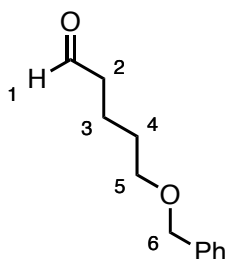
R_f 0.17 (pentane/Et₂O, 4:1), [vanillin]

¹H NMR (500 MHz, CDCl₃) δ 9.77 (t, *J* = 1.6 Hz, 1H, H1), 4.13 (q, *J* = 7.1 Hz, 2H, H6), 2.50 – 2.43 (m, 2H, H2), 2.36 – 2.29 (m, 2H, H5), 1.69 – 1.64 (m, 4H, H3 and H4), 1.25 (t, *J* = 7.1 Hz, 3H, H7).

^{13}C NMR (126 MHz, CDCl_3) δ 202.2, 173.4, 60.5, 43.7, 34.1, 24.5, 21.6, 14.4.

Spectroscopic data in agreement with that reported previously.^[95]

5-(Benzyloxy)pentanal, 130n



According to the procedure of Zhu *et al.*^[96] To a solution of sodium hydride (60% dispersion in mineral oil, 0.66 g, 17 mmol, 3.3 equiv.) in THF (7.5 mL) at 0 °C under an inert atmosphere was added a solution of 1,5-pentanediol (3.7 mL, 35 mmol, 7.0 equiv.) in THF (15 mL) dropwise. The reaction mixture was left to stir at 0 °C for 30 min. A solution of benzyl bromide (0.59 mL, 5.0 mmol, 1.0 equiv.) in THF (7.5 mL) was then added dropwise. The reaction mixture was allowed to warm to room temperature and was left to stir for 21 h. Water (5 mL) was then added and the reaction mixture was concentrated *in vacuo*. The residue was taken up in water (5 mL) and EtOAc (5 mL). The phases were separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo* to afford 5-(benzyloxy)pentan-1-ol as a pale yellow oil, which was used without further purification.

The crude residue containing 5-(benzyloxy)pentan-1-ol obtained directly from the above procedure, TEMPO (0.16 g, 1.0 mmol, 0.2 equiv.) and BAIB (2.9 g, 9.0 mmol, 1.8 equiv.) in CH_2Cl_2 (25 mL) were submitted to **General Procedure D** for 24 h.

Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a pale orange oil (0.16 g, 0.83 mmol, 17%).

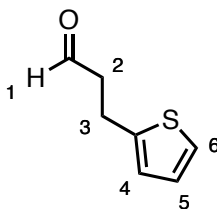
R_f 0.52 (pentane/Et₂O, 1:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 9.76 (t, *J* = 1.7 Hz, 1H, H1), 7.38 – 7.27 (m, 5H, ArH), 4.50 (s, 2H, H6), 3.49 (t, *J* = 6.1 Hz, 2H, H5), 2.46 (td, *J* = 7.2, 1.7 Hz, 2H, H2), 1.78 – 1.63 (m, 4H, H3 and H4).

¹³C NMR (126 MHz, CDCl₃) δ 202.6, 138.6, 128.5 (2C), 127.8 (2C), 127.7, 73.1, 69.9, 43.7, 29.3, 19.1.

Spectroscopic data in agreement with that reported previously.^[97]

3-(Thiophen-2-yl)propanal, 130r



According to the procedure of Su et al.^[98] To a flame-dried vial containing 2-iodothiophene (0.33 mL, 3.0 mmol, 1.0 equiv.) at room temperature was added Pd(OAc)₂ (6.7 mg, 30 μmol, 0.01 equiv.), TEBAC (0.68 g, 3.0 mmol, 1.0 equiv.) and NaHCO₃ (0.63 g, 7.5 mmol, 2.5 equiv.). Allyl alcohol (0.31 mL, 4.5 mmol, 1.5 equiv.) and DMF (12 mL) were then added. The reaction mixture was heated to 50 °C and left to stir for 5 h. The reaction mixture was then cooled to room temperature and filtered through a short pad of silica (eluting with EtOAc). The filtrate was washed with water (2 × 10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a yellow oil (0.22 g, 1.6 mmol, 53%).

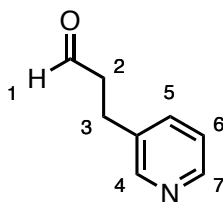
R_f 0.24 (pentane/Et₂O, 9:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 9.83 (t, *J* = 1.3 Hz, 1H, H1), 7.14 (dd, *J* = 5.2, 1.0 Hz, 1H, H6), 6.92 (dd, *J* = 5.1, 3.4 Hz, 1H, H5), 6.82 (dt, *J* = 3.4, 1.0 Hz, 1H, H4), 3.18 (td, *J* = 7.3, 1.0 Hz, 2H, H3), 2.85 (td, *J* = 7.3, 1.3 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 201.0, 143.0, 127.1, 124.9, 123.8, 45.5, 22.5.

Spectroscopic data in agreement with that reported previously.^[98]

3-(Pyridin-3-yl)propanal, 130s



According to the procedure of Su et al.^[98] To a flame-dried vial containing 3-iodopyridine (0.62 g, 3.0 mmol, 1.0 equiv.) at room temperature was added Pd(OAc)₂ (6.7 mg, 30 μmol, 0.01 equiv.), TEBAC (0.68 g, 3.0 mmol, 1.0 equiv.) and NaHCO₃ (0.63 g, 7.5 mmol, 2.5 equiv.). Allyl alcohol (0.31 mL, 4.5 mmol, 1.5 equiv.) and DMF (12 mL) were then added. The reaction mixture was heated to 50 °C and left to stir for 5 h. The reaction mixture was then heated to 60 °C and stirred for a further 23 h. Upon completion, the reaction mixture was cooled to room temperature and filtered through a short pad of silica (eluting with EtOAc). The filtrate was washed with water (2 × 10 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 1:1 → Et₂O) afforded the title compound as a yellow oil (0.18 g, 1.3 mmol, 45%).

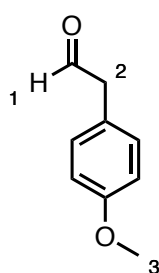
R_f 0.07 (pentane/Et₂O, 3:2), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 9.83 (t, *J* = 1.1 Hz, 1H, H1), 8.50 – 8.44 (m, 2H, H4 and H7), 7.52 (ddd, *J* = 7.7, 2.4, 1.7 Hz, 1H, H5), 7.22 (dd, *J* = 7.7, 4.8 Hz, 1H, H6), 2.96 (t, *J* = 7.4 Hz, 2H, H3), 2.82 (t, *J* = 7.4 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 200.6, 150.0, 148.0, 136.0, 135.9, 123.6, 45.0, 25.3.

Spectroscopic data in agreement with that reported previously.^[98]

2-(4-Methoxyphenyl)acetaldehyde, S32



4-Methoxyphenethyl alcohol (0.76 g, 5.0 mmol, 1.0 equiv.), TEMPO (0.16 g, 1.0 mmol, 0.2 equiv.) and BAIB (2.9 g, 9.0 mmol, 1.8 equiv.) in CH₂Cl₂ (25 mL) were submitted to **General Procedure D** for 22 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow oil (0.27 g, 1.8 mmol, 36%).

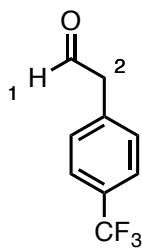
R_f 0.55 (pentane/Et₂O, 1:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 9.72 (t, *J* = 2.4 Hz, 1H, H1), 7.13 (d, *J* = 8.8 Hz, 2H, ArH), 6.91 (d, *J* = 8.8 Hz, 2H, ArH), 3.81 (s, 3H, H3), 3.63 (d, *J* = 2.4 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 199.8, 159.1, 130.8 (2C), 123.8, 114.6 (2C), 55.4, 49.9.

Spectroscopic data in agreement with that reported previously.^[99]

2-(4-(Trifluoromethyl)phenyl)acetaldehyde, S33



4-(Trifluoromethyl)phenylacetic acid (1.0 g, 5.0 mmol, 1.0 equiv.) and borane dimethyl sulfide complex (2 M in THF, 2.8 mL, 5.5 mmol, 1.1 equiv.) in THF (25 mL) were submitted to **General Procedure C** for 29 h to afford 2-(4-(trifluoromethyl)phenyl)ethan-1-ol as a clear oil (0.93 g, 4.9 mmol, 98%).

2-(4-(Trifluoromethyl)phenyl)ethan-1-ol (0.93 g, 4.9 mmol, 1.0 equiv.), TEMPO (0.15 g, 0.98 mmol, 0.2 equiv.) and BAIB (2.8 g, 8.8 mmol, 1.8 equiv.) in CH₂Cl₂ (25 mL) were submitted to **General Procedure D** for 20 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a yellow oil (0.24 g, 1.3 mmol, 26%).

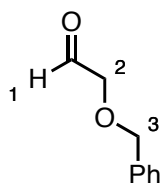
R_f 0.33 (pentane/Et₂O, 3:2), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 9.79 (t, *J* = 2.0 Hz, 1H, H1), 7.63 (d, *J* = 8.0 Hz, 2H, ArH), 7.35 (d, *J* = 8.0 Hz, 2H, ArH), 3.79 (d, *J* = 2.0 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 198.2, 136.0, 130.1 (2C), 130.0 (q, *J* = 35.9 Hz), 126.0 (q, *J* = 3.8 Hz, 2C), 124.2 (q, *J* = 272.1 Hz), 50.3.

Spectroscopic data in agreement with that reported previously.^[100]

2-(Benzyloxy)acetaldehyde, S34



According to the procedure of Vasse *et al.*^[101] To a solution of benzyloxyacetaldehyde diethyl acetal (1.1 mL, 5.0 mmol, 1.0 equiv.) in THF (13 mL) at room temperature was added HCl (aq., 1 M, 11 mL). The reaction mixture was then heated to 80 °C and left to stir for 27 h. The reaction mixture was then cooled to room temperature and water (15 mL) was added. The phases were separated and the aqueous phase was extracted with Et₂O (3 × 10 mL). The combined organic extracts were dried (Na₂SO₄), filtered and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a clear oil (0.64 g, 4.2 mmol, 85%).

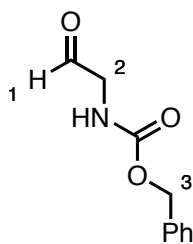
R_f 0.12 (pentane/Et₂O, 4:1), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 9.74 (t, *J* = 0.9 Hz, 1H, H1), 7.39 – 7.33 (m, 5H, ArH), 4.64 (s, 2H, H3), 4.11 (d, *J* = 0.9 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 200.6, 137.0, 128.8 (2C), 128.4, 128.2 (2C), 75.4, 73.8.

Spectroscopic data in agreement with that reported previously.^[102]

Benzyl (2-oxoethyl)carbamate, S35



Adapted from the procedure of Willis et al.^[103] To a solution of 2,2-diethoxyethylamine (0.73 mL, 5.0 mmol, 1.0 equiv.) in Et₂O (25 mL) at room temperature was added K₂CO₃ (2.1 g, 15 mmol, 3.0 equiv.) and water (25 mL). The reaction mixture was then cooled to 0 °C and benzyl chloroformate (0.70 mL, 5.0 mmol, 1.0 equiv.) was added. The reaction mixture was allowed to warm to room temperature and left to stir for 18 h. The phases were then separated and the aqueous phase was extracted with Et₂O (3 × 15 mL). The combined organic extracts were washed with citric acid (aq., 5%, 20 mL) and brine (20 mL), dried (Na₂SO₄), filtered and concentrated *in vacuo*.

The residue was dissolved in acetone (50 mL) and HCl (aq., 1 M, 50 mL) was added. The reaction mixture was left to stir at room temperature for 24 h. The phases were then separated and the aqueous phase was extracted with Et₂O (2 × 50 mL). The combined organic extracts were washed with NaHCO₃ (aq., sat., 100 mL) and brine (100 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 1:4) afforded the title compound as a pale yellow oil (0.30 g, 1.6 mmol, 31%).

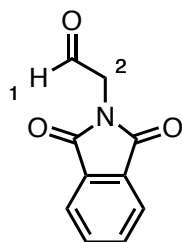
R_f 0.24 (pentane/Et₂O, 1:4), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 9.67 (s, 1H, H1), 7.40 – 7.30 (m, 5H, ArH), 5.41 (br s, 1H, NH), 5.14 (s, 2H, H3), 4.16 (d, *J* = 5.1 Hz, 2H, H2).

^{13}C NMR (126 MHz, CDCl_3) δ 196.4, 156.3, 136.2, 128.7 (2C), 128.4, 128.3 (2C), 67.4, 51.9.

Spectroscopic data in agreement with that reported previously.^[103]

2-(1,3-Dioxoisindolin-2-yl)acetaldehyde, S36



According to the procedure of Falck et al.^[7] To a solution of *N*-(2-hydroxyethyl)phthalimide (0.96 g, 5.0 mmol, 1.0 equiv.) in EtOAc (10 mL) at room temperature was added 2-iodoxybenzoic acid (3.5 g, 13 mmol, 2.5 equiv.). The reaction mixture was heated to 90 °C and left to stir for 17.5 h. The reaction mixture was then cooled to room temperature, filtered through a short pad of Celite® and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (10 mL) and filtered. The filtrate was concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 1:1) afforded the title compound as a white solid (0.78 g, 4.1 mmol, 83%).

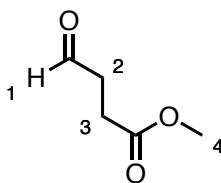
R_f 0.33 (pentane/ Et_2O , 1:4), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 9.66 (s, 1H, H1), 7.90 (dd, J = 5.5, 3.1 Hz, 2H, ArH), 7.77 (dd, J = 5.5, 3.1 Hz, 2H, ArH), 4.56 (s, 2H, H2).

^{13}C NMR (126 MHz, CDCl_3) δ 193.6, 167.6 (2C), 134.5 (2C), 132.1 (2C), 123.8 (2C), 47.5.

Spectroscopic data in agreement with that reported previously.^[7]

Methyl 4-oxobutanoate, S37



According to the procedure of Hong *et al.*^[104] To a solution of sodium methoxide (54 mg, 1.0 mmol, 0.1 equiv.) in methanol (10 mL) at room temperature under an inert atmosphere was added γ -butyrolactone (0.77 mL, 10 mmol, 1.0 equiv.). The reaction mixture was then heated to 70 °C and left to stir for 20 h. The reaction mixture was then cooled to room temperature, diluted with Et₂O (25 mL) and filtered through a short pad of silica and Celite® (eluting with Et₂O). The filtrate was concentrated *in vacuo* to afford methyl 4-hydroxybutanoate as a clear oil (0.84 g, 7.1 mmol, 71%).

Methyl 4-hydroxybutanoate (0.84 g, 7.1 mmol, 1.0 equiv.), TEMPO (0.22 g, 1.4 mmol, 0.2 equiv.) and BAIB (4.1 g, 13 mmol, 1.8 equiv.) in CH₂Cl₂ (37 mL) were submitted to **General Procedure D** for 24 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a yellow oil (0.49 g, 4.2 mmol, 59%).

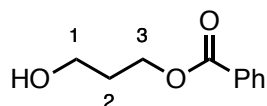
R_f 0.43 (pentane/Et₂O, 2:3), [UV, potassium permanganate]

¹H NMR (500 MHz, CDCl₃) δ 9.82 (s, 1H, H1), 3.70 (s, 3H, H4), 2.81 (t, J = 6.6 Hz, 2H, H3), 2.64 (t, J = 6.6 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 200.1, 172.8, 52.1, 38.6, 26.4.

Spectroscopic data in agreement with that reported previously.^[105]

3-Hydroxypropyl benzoate, S38



According to the procedure of Iwabuchi *et al.*^[106] To a solution of 1,3-propanediol (1.1 mL, 15 mmol, 3.0 equiv.) and triethylamine (1.4 mL, 10 mmol, 2.0 equiv.) in CH₂Cl₂ (25 mL) at 0 °C under an inert atmosphere was added benzoyl chloride (0.58 mL, 5.0 mmol, 1.0 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature and was left to stir for 25 h. The reaction mixture was then diluted with water (25 mL). The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 3:2) afforded the title compound as a clear oil (0.87 g, 4.8 mmol, 96%).

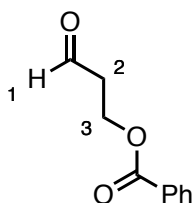
R_f 0.26 (pentane/Et₂O, 1:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 8.07 – 8.01 (m, 2H, ArH), 7.59 – 7.54 (m, 1H, ArH), 7.45 (t, *J* = 7.8 Hz, 2H, ArH), 4.50 (t, *J* = 6.1 Hz, 2H, H3), 3.78 (t, *J* = 6.1 Hz, 2H, H1), 2.01 (quin, *J* = 6.1 Hz, 2H, H2), 1.87 (br s, 1H, OH).

¹³C NMR (126 MHz, CDCl₃) δ 167.2, 133.2, 130.2, 129.7 (2C), 128.5 (2C), 61.9, 59.3, 32.1.

Spectroscopic data in agreement with that reported previously.^[106]

3-Oxopropyl benzoate, S39



3-Hydroxypropyl benzoate **S38** (0.87 g, 4.8 mmol, 1.0 equiv.), TEMPO (0.15 g, 0.97 mmol, 0.2 equiv.) and BAIB (2.8 g, 8.7 mmol, 1.8 equiv.) in CH₂Cl₂ (25 mL) were submitted to **General Procedure D** for 21 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 3:2) afforded the title compound as a yellow oil (0.34 g, 1.9 mmol, 40%).

R_f 0.40 (pentane/Et₂O, 1:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 9.87 (t, *J* = 1.5 Hz, 1H, H1), 8.01 (dd, *J* = 8.4, 1.4 Hz, 2H, ArH), 7.59 – 7.54 (m, 1H, ArH), 7.46 – 7.41 (m, 2H, ArH), 4.67 (t, *J* = 6.1 Hz, 2H, H3), 2.92 (td, *J* = 6.1, 1.5 Hz, 2H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 199.5, 166.5, 133.3, 130.3, 129.8 (2C), 128.5 (2C), 58.6, 43.0.

Spectroscopic data in agreement with that reported previously.^[107]

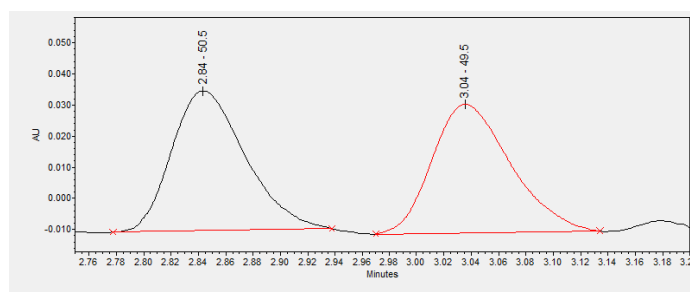
9.6.5 Reaction scope: BCP products

The following aldehydes are commercially available and used directly as supplied: propionaldehyde, isovaleraldehyde, 3,3-dimethylbutyraldehyde, octanal, hydrocinnamaldehyde, (*Z*)-4-hepten-1-al, methional, *N*-Boc-4-piperidineacetaldehyde, 5,5-dimethyl-1,3-dioxane-2-butanal, 3-(5-methyl-2-furyl)propionaldehyde.

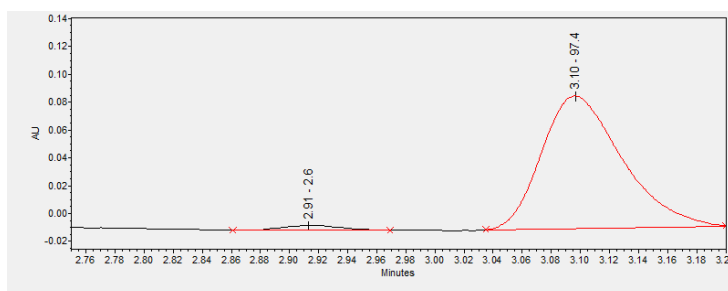
Absolute stereochemistry of the BCP product (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)propan-1-ol (*R*)-**131b** was determined by comparison of SFC traces (after derivatization to (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate (*R*)-**S6**) to that of its enantiomer (*S*)-**S6** synthesized above (**Section 9.3.5**). Absolute stereochemistry of the remaining BCP compounds were assigned by analogy. Racemic BCP products for *ee* determination were synthesized following **General Procedure E** using racemic organocatalyst *rac*-**132a**. Compounds that lacked UV-active chromophores were further derivatized to enable HPLC analysis.

SFC Conditions CHIRALPAK ID, 1 – 30% MeOH/CO₂ gradient over 5 min, 1.5 mL/min.

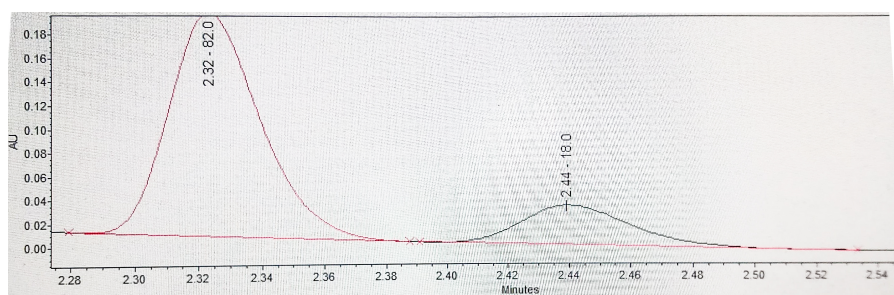
2-(Bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate *rac*-S6



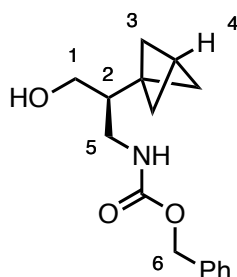
(*S*)-2-(Bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate (*S*)-S6 (95% *ee*)



(*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)propyl 2-naphthoate (*R*)-S6 (64% *ee*)



Benzyl (*S*)-(2-(bicyclo[1.1.1]pentan-1-yl)-3-hydroxypropyl)carbamate, **131a**



Benzyl (3-oxopropyl)carbamate **130a** (62 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 13:7) afforded the title compound as a pale yellow oil (52 mg, 0.19 mmol, 94%).

R_f 0.40 (pentane/Et₂O, 1:4), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.40 – 7.29 (m, 5H, ArH), 5.11 (dd, *J* = 12.3, 2.4 Hz, 2H, H6), 5.04 (br s, 1H, NH), 3.63 (ddd, *J* = 11.4, 6.7, 4.2 Hz, 1H, H1), 3.49 (dt,

$J = 11.4, 6.7$ Hz, 1H, H1), 3.40 (ddd, $J = 14.2, 7.1, 4.3$ Hz, 1H, H5), 3.19 (ddd, $J = 14.2, 7.1, 5.9$ Hz, 1H, H5), 2.74 (t, $J = 6.7$ Hz, 1H, OH), 2.48 (s, 1H, H4), 1.72 (s, 6H, H3), 1.74 – 1.67 (m, 1H, H2).

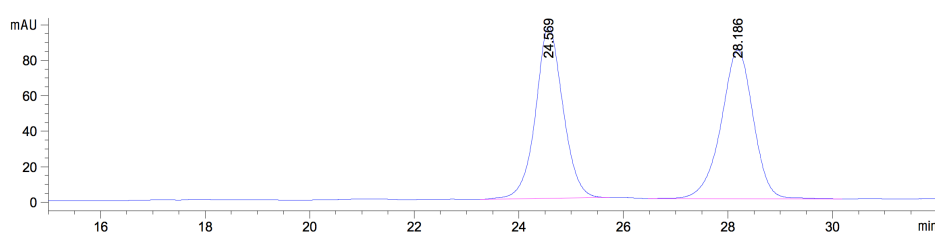
^{13}C NMR (126 MHz, CDCl_3) δ 157.6, 136.5, 128.7 (2C), 128.4, 128.3 (2C), 67.1, 61.8, 50.0 (3C), 45.3, 42.5, 40.3, 27.9.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 276.1596$; $\text{C}_{16}\text{H}_{22}\text{O}_3\text{N}$ requires 276.1594.

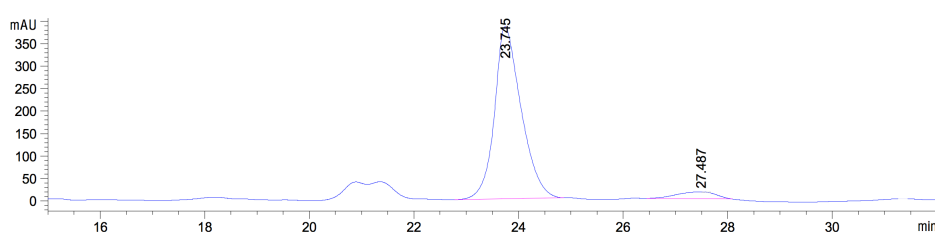
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3352, 2961, 2908, 2870, 1698, 1525, 1454, 1257.

$[\alpha]_{\text{D}}^{25} -58.1$ ($c = 0.1$, CHCl_3)

HPLC 89% *ee* (CHIRALPAK IB, 4% IPA/hexane, 1.0 mL/min, t_{R} major – 23.7 min, minor – 27.5 min).

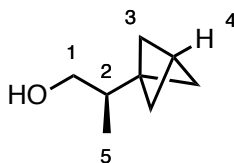


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	24.569	BB	0.5466	3524.77490	96.85780	49.5178
2	28.186	BB	0.6477	3593.42212	83.90495	50.4822



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.745	BB	0.5227	1.35612e4	383.38873	94.4829
2	27.487	MM	0.8549	791.86609	15.43752	5.5171

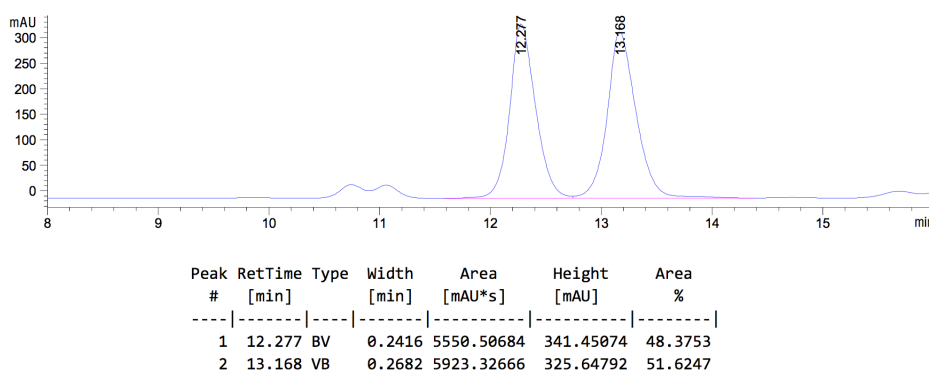
(*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)propan-1-ol, (*R*)-131b

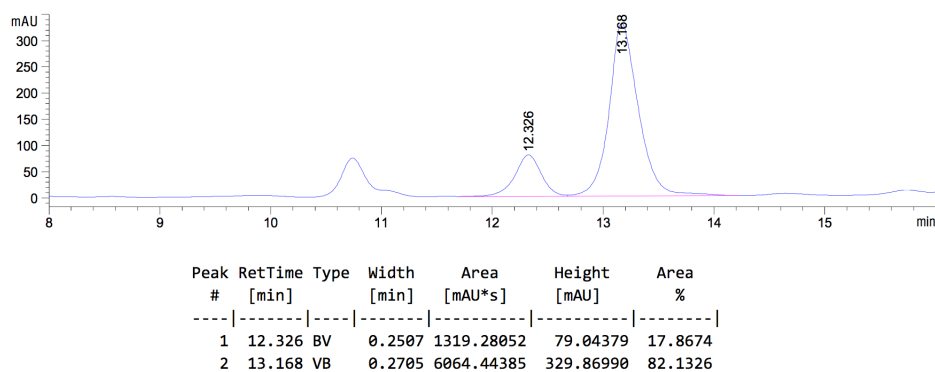


Propionaldehyde (22 μ L, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μ mol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μ mol, 0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μ mol, 0.25 equiv.), water (7.2 μ L, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 3:2) afforded the title compound as a pale yellow oil (16 mg, 0.13 mmol, 63%). The spectroscopic data of its enantiomer (*S*)-**76** is detailed above (**Section 9.3.5**).

$[\alpha]_D^{25}$ -8.6 (c = 1.1, CHCl₃)

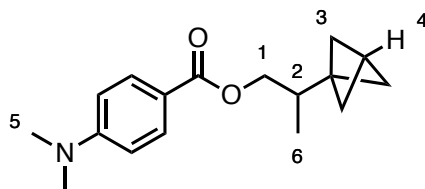
HPLC 64% *ee* (CHIRALPAK IB, 1% IPA/hexane, 0.8 mL/min, t_R major – 13.2 min, minor – 12.3 min) after derivatization to (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)propyl 4-(dimethylamino)benzoate (*R*)-**S40**.





Derivatization for *ee* determination

2-(Bicyclo[1.1.1]pentan-1-yl)propyl 4-(dimethylamino)benzoate, S40



2-(Bicyclo[1.1.1]pentan-1-yl)propan-1-ol *rac*-**131b** (6.3 mg, 50 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (8.3 mg, 50 μ mol, 1.0 equiv.), DMAP (18 mg, 0.15 mmol, 3.0 equiv.) and EDCI (29 mg, 0.15 mmol, 3.0 equiv.) in CH_2Cl_2 (0.5 mL) were submitted to **General Procedure F** for 17 h. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 4:1) afforded the title compound as a pale yellow oil (10 mg, 38 μ mol, 76%).

R_f 0.43 (pentane/ Et_2O , 4:1), [UV, vanillin]

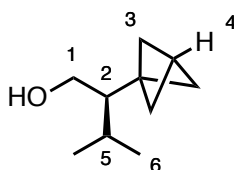
^1H NMR (400 MHz, CDCl_3) δ 7.91 (d, $J = 9.1$ Hz, 2H, ArH), 6.65 (d, $J = 9.1$ Hz, 2H, ArH), 4.15 (dd, $J = 10.7, 6.7$ Hz, 1H, H1), 4.05 (dd, $J = 10.7, 6.7$ Hz, 1H, H1), 3.04 (s, 6H, H5), 2.48 (s, 1H, H4), 1.98 (sept, $J = 6.7$ Hz, 1H, H2), 1.71 (s, 6H, H3), 0.93 (d, $J = 6.9$ Hz, 3H, H6).

^{13}C NMR (151 MHz, CDCl_3) δ 167.2, 153.4, 131.4 (2C), 117.5, 110.9 (2C), 67.3, 49.0 (3C), 47.5, 40.2 (2C), 34.2, 27.3, 13.9.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 274.1803$; $\text{C}_{17}\text{H}_{24}\text{O}_2\text{N}$ requires 274.1802.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2962, 2870, 1703, 1609, 1527, 1368, 1316, 1279, 1184, 1107.

(*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)-3-methylbutan-1-ol, 131c



Isovaleraldehyde (32 μL , 0.30 mmol, 1.5 equiv.), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (3.7 mg, 4.0 μmol , 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol , 0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol , 0.25 equiv.), water (7.2 μL , 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et_2O , 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et_2O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH_2Cl_2 (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 7:3) afforded the title compound as a pale yellow oil (25 mg, 0.16 mmol, 80%).

R_f 0.40 (pentane/ Et_2O , 7:3), [vanillin]

^1H NMR (400 MHz, CDCl_3) δ 3.64 (td, $J = 6.0, 2.1$ Hz, 2H, H1), 2.47 (s, 1H, H4), 1.88 – 1.81 (m, 1H, H5), 1.79 (d, $J = 1.3$ Hz, 6H, H3), 1.45 – 1.42 (m, 1H, H2), 0.97 (d, $J = 7.0$ Hz, 3H, H6), 0.91 (d, $J = 7.0$ Hz, 3H, H6).

Note: the OH resonance was not observed.

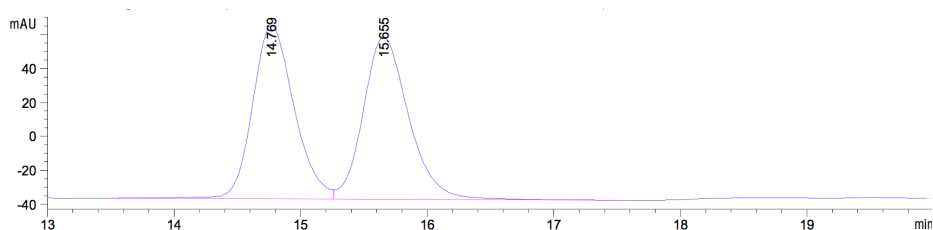
^{13}C NMR (126 MHz, CDCl_3) δ 63.0, 51.3 (3C), 48.0, 47.4, 28.2, 28.1, 21.3, 19.8.

HRMS (ESI⁺) Found [M+H]⁺ = 155.1428; C₁₀H₁₉O requires 155.1430.

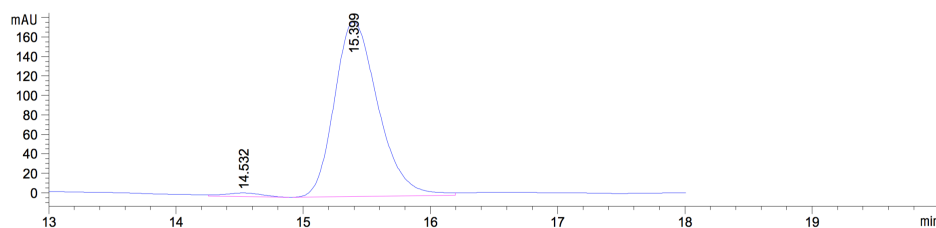
IR (film) ν_{max} /cm⁻¹ 3441, 3360, 2959, 2870, 1607, 1518, 1460, 1360, 1280.

[α]_D²⁵ -74.8 (*c* = 0.1, CHCl₃)

HPLC 96% *ee* (Lux i-Amylose-1, 3% IPA/hexane, 0.7 mL/min, *t*_R major – 15.4 min, minor – 14.5 min) after derivatization to (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-methylbutyl 4-(dimethylamino)benzoate (*R*)-**S41**.



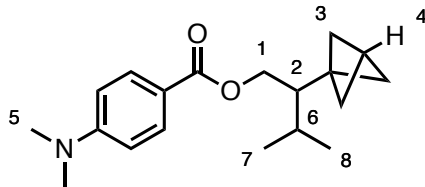
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.769	BV	0.3510	2337.20679	102.14143	49.5028
2	15.655	VB	0.3806	2384.15771	95.71879	50.4972



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.532	VB	0.3060	77.74979	3.77922	1.7877
2	15.399	BV	0.3652	4271.45654	179.79712	98.2123

Derivatization for *ee* determination

2-(Bicyclo[1.1.1]pentan-1-yl)-3-methylbutyl 4-(dimethylamino)benzoate, S41



2-(Bicyclo[1.1.1]pentan-1-yl)-3-methylbutan-1-ol *rac*-**131c** (6.1 mg, 40 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (6.5 mg, 40 μ mol, 1.0 equiv.), DMAP (15 mg, 0.12 mmol, 3.0 equiv.) and EDCI (23 mg, 0.12 mmol, 3.0 equiv.) in CH_2Cl_2 (0.4 mL) were submitted to **General Procedure F** for 15 h. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 19:1) afforded the title compound as a pale yellow oil (9.5 mg, 32 μ mol, 80%).

R_f 0.31 (pentane/ Et_2O , 9:1), [UV, vanillin]

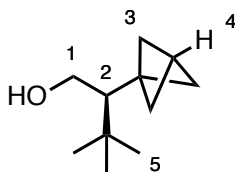
^1H NMR (500 MHz, CDCl_3) δ 7.90 (d, $J = 9.1$ Hz, 2H, ArH), 6.66 (d, $J = 9.1$ Hz, 2H, ArH), 4.26 (dd, $J = 11.0, 5.4$ Hz, 1H, H1), 4.22 (dd, $J = 11.0, 6.6$ Hz, 1H, H1), 3.04 (s, 6H, H5), 2.45 (s, 1H, H4), 1.95 – 1.87 (m, 1H, H6), 1.81 (d, $J = 1.9$ Hz, 6H, H3), 1.75 – 1.70 (m, 1H, H2), 1.02 (d, $J = 6.9$ Hz, 3H, H7), 0.94 (d, $J = 7.1$ Hz, 3H, H8).

^{13}C NMR (126 MHz, CDCl_3) δ 167.3, 153.4, 131.4 (2C), 117.5, 110.9 (2C), 64.2, 51.1 (3C), 47.4, 44.6, 40.2 (2C), 28.5, 27.9, 21.7, 19.5.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 302.2115$; $\text{C}_{19}\text{H}_{28}\text{O}_2\text{N}$ requires 302.2115.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2960, 2919, 2870, 1702, 1608, 1527, 1465, 1446, 1366, 1317, 1278, 1232, 1183, 1107.

(R)-2-(Bicyclo[1.1.1]pentan-1-yl)-3,3-dimethylbutan-1-ol, 131d



3,3-Dimethylbutyraldehyde (38 μ L, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μ mol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μ mol, 0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μ mol, 0.25 equiv.), water (7.2 μ L, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a pale yellow oil (15 mg, 87 μ mol, 44%).

R_f 0.24 (pentane/Et₂O, 9:1), [vanillin]

¹H NMR (400 MHz, CDCl₃) δ 3.74 (ddd, *J* = 11.0, 5.8, 3.3 Hz, 1H, H1), 3.65 (dt, *J* = 11.0, 6.0 Hz, 1H, H1), 2.46 (s, 1H, H4), 1.90 (s, 6H, H3), 1.31 (dd, *J* = 6.5, 3.3 Hz, 1H, H2), 0.95 (s, 9H, H5).

Note: the OH resonance was not observed.

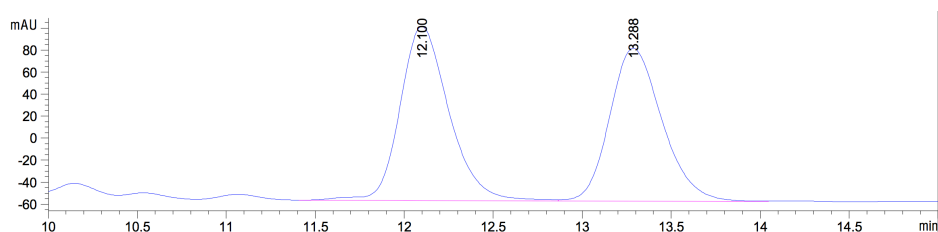
¹³C NMR (126 MHz, CDCl₃) δ 63.4, 52.6, 52.5 (3C), 47.6, 33.9, 29.1 (3C), 28.9.

HRMS (ESI⁺) Found [M+H]⁺ = 169.1589; C₁₁H₂₁O requires 169.1587.

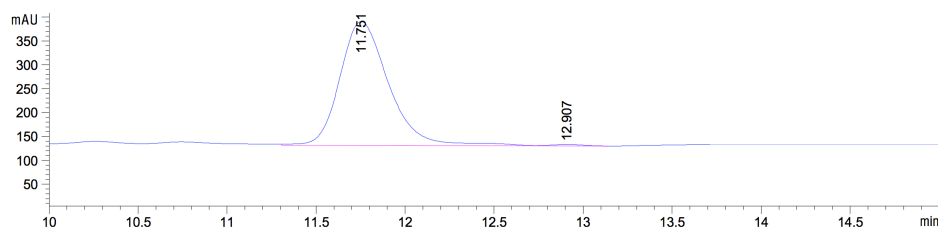
IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2958, 2923, 2871, 1463, 1365, 1325, 1245, 1199.

$$[\alpha]_{\text{D}}^{25} -29.5 \ (c = 0.1, \text{CHCl}_3)$$

HPLC 98% *ee* (Lux i-Amylose-1, 6% IPA/hexane, 0.7 mL/min, t_R major – 11.8 min, minor – 12.9 min) after derivatization to (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-3,3-dimethylbutyl 4-(dimethylamino)benzoate (*R*)-**S42**.



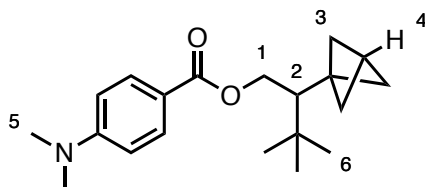
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.100	BV	0.2913	3025.22168	158.02417	51.5715
2	13.288	VV	0.3165	2840.85010	138.98952	48.4285



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.751	VV	0.2913	4967.98535	259.54993	99.2130
2	12.907	VB	0.2020	39.40602	2.98594	0.7870

Derivatization for *ee* determination

2-(Bicyclo[1.1.1]pentan-1-yl)-3,3-dimethylbutyl 4-(dimethylamino)benzoate, **S42**



2-(Bicyclo[1.1.1]pentan-1-yl)-3,3-dimethylbutan-1-ol *rac*-**131d** (9.4 mg, 56 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (9.2 mg, 56 μ mol, 1.0 equiv.), DMAP (21 mg, 0.17 mmol, 3.0 equiv.) and EDCI (32 mg, 0.17 mmol, 3.0 equiv.) in

CH₂Cl₂ (0.6 mL) were submitted to **General Procedure F** for 16 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 19:1) afforded the title compound as a pale yellow oil (16 mg, 50 μmol, 89%).

R_f 0.29 (pentane/Et₂O, 9:1), [UV, vanillin]

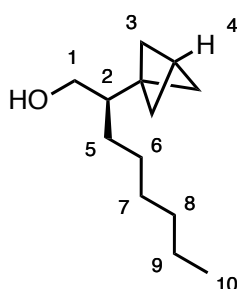
¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, *J* = 9.1 Hz, 2H, Ar*H*), 6.67 (d, *J* = 9.0 Hz, 2H, Ar*H*), 4.37 (dd, *J* = 11.3, 3.7 Hz, 1H, H1), 4.24 (dd, *J* = 11.3, 6.4 Hz, 1H, H1), 3.04 (s, 6H, H5), 2.42 (s, 1H, H4), 1.91 (s, 6H, H3), 1.63 (dd, *J* = 6.4, 3.7 Hz, 1H, H2), 1.02 (s, 9H, H6).

¹³C NMR (126 MHz, CDCl₃) δ 167.3, 153.3, 131.4 (2C), 117.7, 111.0 (2C), 64.7, 52.7 (3C), 48.8, 47.4, 40.3 (2C), 34.0, 29.1 (3C), 28.6.

HRMS (ESI⁺) Found [M+H]⁺ = 316.2271; C₂₀H₃₀O₂N requires 316.2271.

IR (film) *v*_{max}/cm⁻¹ 2961, 2908, 2870, 1702, 1609, 1527, 1477, 1446, 1365, 1280, 1183, 1108.

(*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)octan-1-ol, 131e



Octanal (47 μL, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL)

and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as a pale yellow oil (38 mg, 0.19 mmol, 96%).

R_f 0.24 (pentane/Et₂O, 4:1), [vanillin]

¹H NMR (500 MHz, CDCl₃) δ 3.57 (dd, *J* = 10.7, 6.0 Hz, 1H, H1), 3.53 (dd, *J* = 10.7, 5.2 Hz, 1H, H1), 2.48 (s, 1H, H4), 1.71 (s, 6H, H3), 1.52 – 1.48 (m, 1H, H2), 1.31 – 1.24 (m, 10H, H5, H6, H7, H8 and H9), 0.88 (t, *J* = 6.8 Hz, 3H, H10).

Note: the *OH* resonance was not observed.

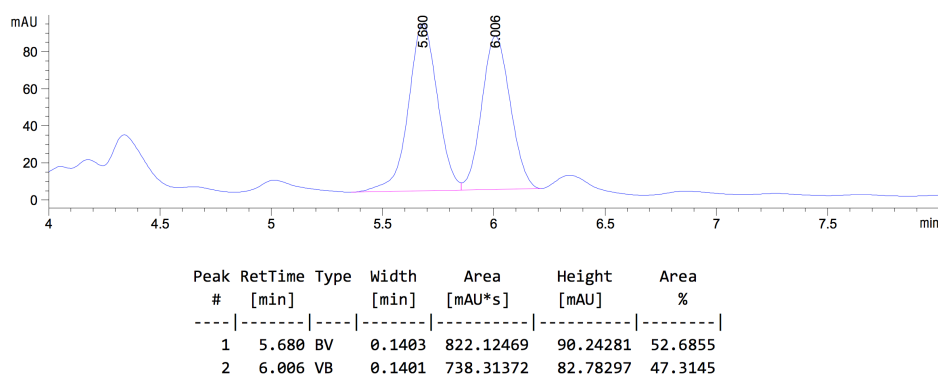
¹³C NMR (126 MHz, CDCl₃) δ 64.7, 49.8 (3C), 47.6, 42.2, 32.0, 29.9, 28.6, 27.8, 27.7, 22.8, 14.2.

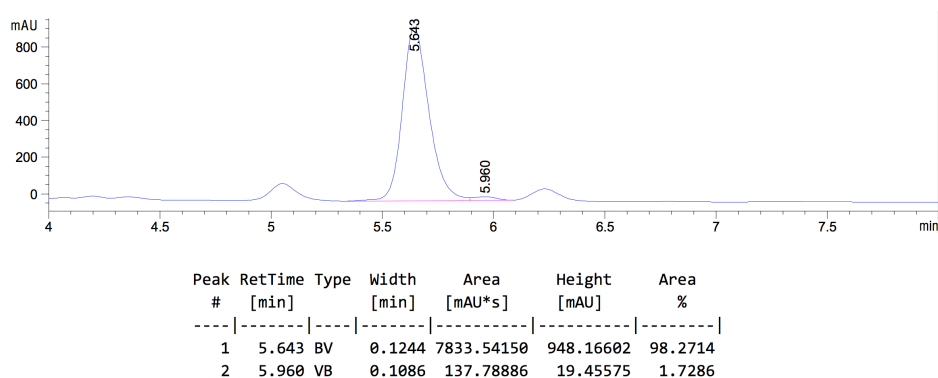
HRMS (APCI) Found [*M*+*H*]⁺ = 197.1901; C₁₃H₂₅O requires 197.1900.

IR (film) ν_{max}/cm⁻¹ 3351, 2959, 2925, 2868, 1747, 1465.

[α]_D²⁵ –51.9 (*c* = 0.1, CHCl₃)

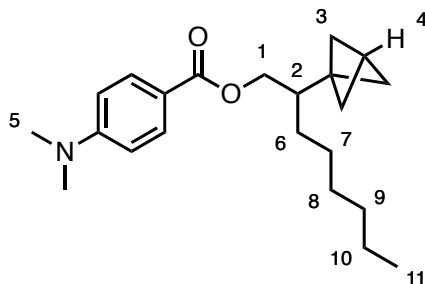
HPLC 97% *ee* (CHIRALPAK IB, 3% IPA/hexane, 1.0 mL/min, *t_R* major – 5.6 min, minor – 6.0 min) after derivatization to (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)octyl 4-(dimethylamino)benzoate (*R*)-**S43**.





Derivatization for *ee* determination

2-(Bicyclo[1.1.1]pentan-1-yl)octyl 4-(dimethylamino)benzoate, S43



2-(Bicyclo[1.1.1]pentan-1-yl)octan-1-ol *rac*-**131e** (13 mg, 64 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (11 mg, 64 μ mol, 1.0 equiv.), DMAP (24 mg, 0.19 mmol, 3.0 equiv.) and EDCI (37 mg, 0.19 mmol, 3.0 equiv.) in CH_2Cl_2 (0.6 mL) were submitted to **General Procedure F** for 25.5 h. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 9:1) afforded the title compound as a pale yellow oil (20 mg, 59 μ mol, 93%).

R_f 0.76 (pentane/ Et_2O , 3:2), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 7.90 (d, $J = 9.1$ Hz, 2H, *ArH*), 6.65 (d, $J = 9.1$ Hz, 2H, *ArH*), 4.18 (dd, $J = 10.8, 5.1$ Hz, 1H, H1), 4.14 (dd, $J = 10.9, 6.3$ Hz, 1H, H1), 3.04 (s,

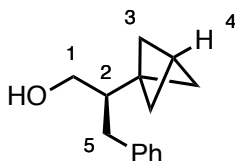
6H, H5), 2.46 (s, 1H, H4), 1.82 – 1.75 (m, 1H, H2), 1.74 (s, 6H, H3), 1.40 – 1.26 (m, 10H, H6, H7, H8, H9 and H10), 0.87 (t, $J = 6.9$ Hz, 3H, H11).

^{13}C NMR (126 MHz, CDCl_3) δ 167.2, 153.4, 131.4 (2C), 117.6, 110.9 (2C), 65.7, 49.8 (3C), 47.6, 40.2 (2C), 39.1, 31.9, 29.8, 28.9, 27.7, 27.5, 22.8, 14.3.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 344.2584$; $\text{C}_{22}\text{H}_{34}\text{O}_2\text{N}$ requires 344.2584.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2959, 2926, 2869, 1704, 1609, 1528, 1446, 1366, 1317, 1279, 1183, 1108.

(*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)-3-phenylpropan-1-ol, **131f**



Hydrocinnamaldehyde (40 μL , 0.30 mmol, 1.5 equiv.), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (3.7 mg, 4.0 μmol , 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol , 0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol , 0.25 equiv.), water (7.2 μL , 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et_2O , 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et_2O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH_2Cl_2 (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 17:3) afforded the title compound as a pale yellow oil (40 mg, 0.20 mmol, 99%).

Scaled-up procedure

Hydrocinnamaldehyde (0.20 mL, 1.5 mmol, 1.5 equiv.), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (9.1 mg, 10 μmol , 0.01 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (28 mg, 0.10 mmol, 0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol

trimethylsilyl ether **132a** (0.12 g, 0.20 mmol, 0.20 equiv.), water (36 μ L, 2.0 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (0.71 M in Et₂O, 1.4 mL, 1.0 mmol, 1.0 equiv.) in Et₂O (1.1 mL) and DME (2.5 mL), and sodium borohydride (0.19 g, 5.0 mmol, 5.0 equiv.) in MeOH (5 mL) and CH₂Cl₂ (5 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as a pale yellow oil (0.20 g, 0.98 mmol, 98%).

R_f 0.33 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.27 (m, 2H, ArH), 7.22 – 7.16 (m, 3H, ArH), 3.58 – 3.48 (m, 2H, H1), 2.66 (dd, *J* = 13.9, 5.6 Hz, 1H, H5), 2.53 (dd, *J* = 13.9, 9.5 Hz, 1H, H5), 2.49 (s, 1H, H4), 1.92 (dq, *J* = 9.5, 5.6 Hz, 1H, H2), 1.74 (dd, *J* = 9.6, 1.6 Hz, 3H, H3), 1.71 (dd, *J* = 9.6, 1.6 Hz, 3H, H3).

Note: the OH resonance was not observed.

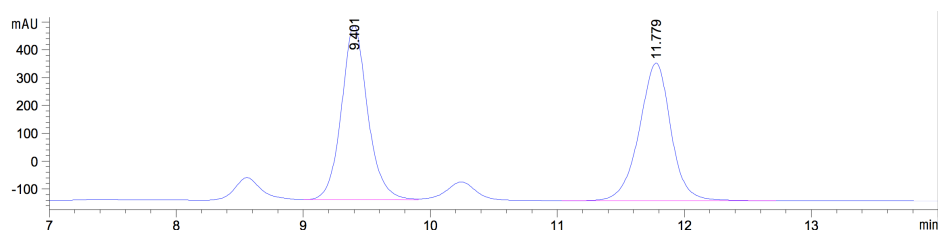
¹³C NMR (126 MHz, CDCl₃) δ 141.0, 129.1 (2C), 128.5 (2C), 126.0, 64.0, 49.8 (3C), 47.5, 44.0, 35.1, 27.7.

HRMS (ESI⁺) Found [M+Na]⁺ = 225.1251; C₁₄H₁₈ONa requires 225.1250.

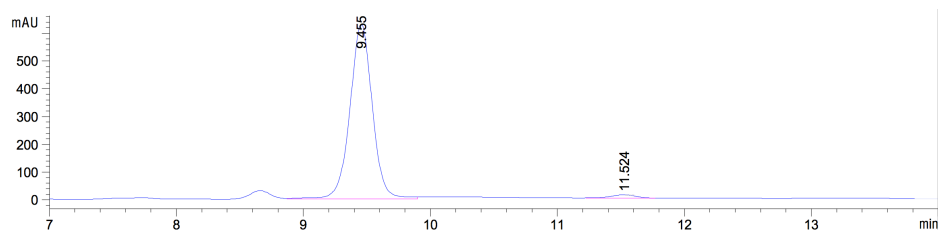
IR (film) ν_{max} /cm⁻¹ 3331, 3027, 2961, 2907, 2869, 1495, 1453, 1279, 1196.

$[\alpha]_{\text{D}}^{25}$ –13.1 (*c* = 0.2, CHCl₃)

HPLC 96% *ee* (CHIRALPAK IB, 2% IPA/hexane, 1.0 mL/min, *t_R* major – 9.5 min, minor – 11.5 min).

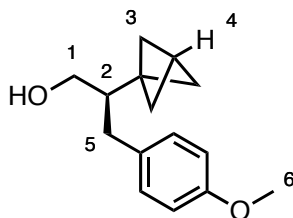


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.401	BV	0.2160	9006.82031	625.47729	51.2595
2	11.779	BB	0.2643	8564.19629	493.98157	48.7405



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.455	VV	0.1877	7746.19580	629.00031	97.9177
2	11.524	MM	0.2275	164.73134	12.06894	2.0823

(R)-2-(Bicyclo[1.1.1]pentan-1-yl)-3-(4-methoxyphenyl)propan-1-ol, 131g



3-(4-Methoxyphenyl)propanal **130g** (49 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂,

pentane/Et₂O, 7:3) afforded the title compound as a pale yellow oil (33 mg, 0.14 mmol, 72%).

R_f 0.29 (pentane/Et₂O, 3:2), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.10 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.82 (d, *J* = 8.6 Hz, 2H, Ar*H*), 3.79 (s, 3H, H₆), 3.54 (dd, *J* = 10.7, 5.0 Hz, 1H, H₁), 3.51 (dd, *J* = 10.7, 5.4 Hz, 1H, H₁), 2.61 (dd, *J* = 14.1, 5.7 Hz, 1H, H₅), 2.49 (s, 1H, H₄), 2.46 (dd, *J* = 14.1, 9.6 Hz, 1H, H₅), 1.86 (dq, *J* = 10.7, 5.4 Hz, 1H, H₂), 1.73 (dd, *J* = 9.6, 1.6 Hz, 3H, H₃), 1.71 (dd, *J* = 9.6, 1.6 Hz, 3H, H₃).

Note: the *OH* resonance was not observed.

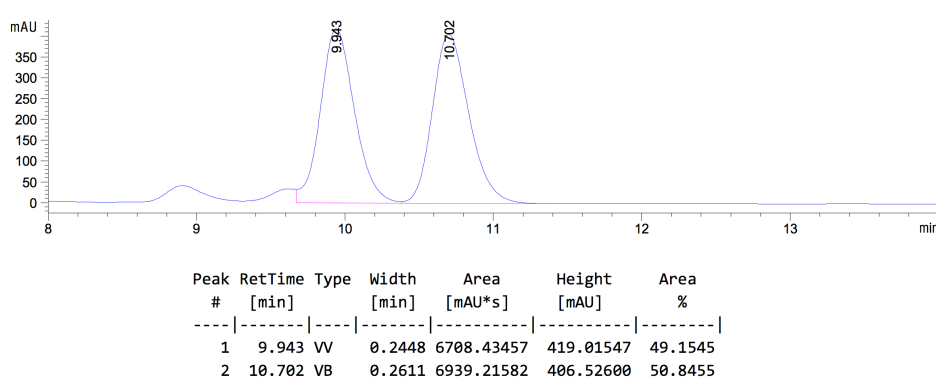
¹³C NMR (126 MHz, CDCl₃) δ 158.0, 132.9, 130.0 (2C), 113.9 (2C), 64.1, 55.4, 49.8 (3C), 47.5, 44.1, 34.2, 27.7.

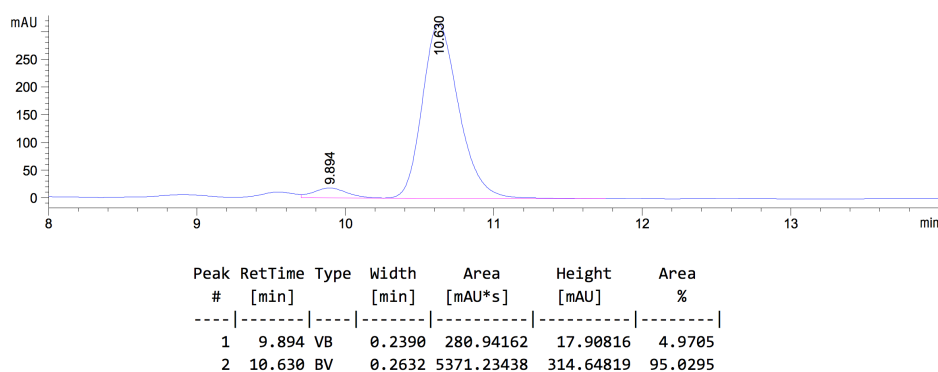
HRMS (ESI⁺) Found [M+H]⁺ = 233.1537; C₁₅H₂₁O₂ requires 233.1536.

IR (film) ν_{max}/cm⁻¹ 3406, 2961, 2907, 2869, 2835, 1612, 1512, 1246.

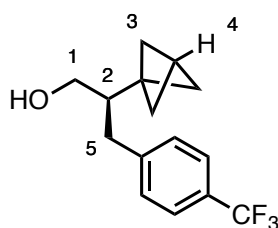
[α]_D²⁵ -15.3 (*c* = 0.3, CHCl₃)

HPLC 90% *ee* (Lux i-Amylose-1, 6% IPA/hexane, 1.0 mL/min, *t_R* major – 10.6 min, minor – 9.9 min).





(R)-2-(Bicyclo[1.1.1]pentan-1-yl)-3-(4-(trifluoromethyl)phenyl)propan-1-ol, 131h



3-(4-(Trifluoromethyl)phenyl)propanal **130h** (61 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a pale yellow oil (42 mg, 0.16 mmol, 78%).

R_f 0.36 (pentane/Et₂O, 3:2), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.52 (d, *J* = 8.0 Hz, 2H, *ArH*), 7.31 (d, *J* = 8.0 Hz, 2H, *ArH*), 3.54 (dd, *J* = 10.9, 4.8 Hz, 1H, H1), 3.51 (dd, *J* = 10.9, 5.3 Hz, 1H, H1),

2.71 – 2.62 (m, 2H, H5), 2.50 (s, 1H, H4), 1.95 – 1.89 (m, 1H, H2), 1.74 (dd, $J = 9.6$, 1.7 Hz, 3H, H3), 1.70 (dd, $J = 9.6$, 1.7 Hz, 3H, H3).

Note: the *OH* resonance was not observed.

^{13}C NMR (126 MHz, CDCl_3) δ 145.3, 129.4 (2C), 128.4 (q, $J = 32.3$ Hz), 125.3 (q, $J = 3.8$ Hz, 2C), 124.8 (q, $J = 271.9$ Hz), 63.6, 49.8 (3C), 47.2, 43.8, 34.8, 27.8.

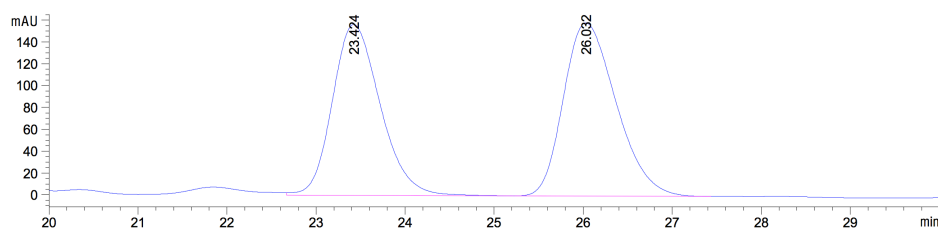
^{19}F NMR (471 MHz, CDCl_3) δ –62.3.

HRMS (ESI $^-$) Found $[\text{M}-\text{H}]^- = 269.1160$; $\text{C}_{15}\text{H}_{16}\text{OF}_3$ requires 269.1159.

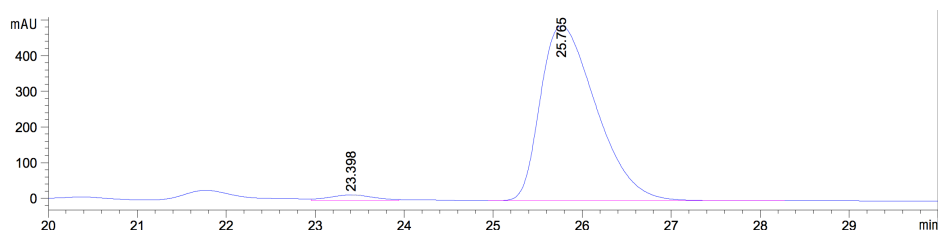
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3343, 2965, 2909, 2872, 1325, 1280, 1163, 1123, 1067, 1019.

$[\alpha]_{\text{D}}^{25} -10.6$ ($c = 0.4$, CHCl_3)

HPLC 95% *ee* (Lux i-Amylose-1, 1% IPA/hexane, 1.0 mL/min, t_{R} major – 25.8 min, minor – 23.4 min).

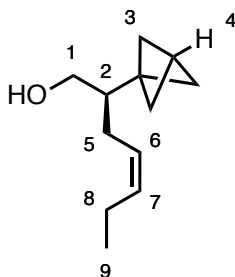


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.424	VB	0.5797	5844.25537	156.48665	47.3000
2	26.032	BB	0.6411	6511.46191	158.57822	52.7000



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.398	MM	0.5850	554.15491	15.78741	2.5339
2	25.765	BB	0.6789	2.13154e4	490.59280	97.4661

(*R,Z*)-2-(Bicyclo[1.1.1]pentan-1-yl)hept-4-en-1-ol, 131i



(*Z*)-4-Hepten-1-ol (40 μ L, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μ mol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μ mol, 0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μ mol, 0.25 equiv.), water (7.2 μ L, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as a pale yellow oil (25 mg, 0.14 mmol, 70%).

R_f 0.43 (pentane/Et₂O, 7:3), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 5.45 – 5.33 (m, 2H, H6 and H7), 3.58 (dd, *J* = 10.8, 5.8 Hz, 1H, H1), 3.53 (dd, *J* = 10.8, 5.8 Hz, 1H, H1), 2.48 (s, 1H, H4), 2.10 – 2.01 (m, 4H, H5 and H8), 1.72 (s, 6H, H3), 1.67 – 1.62 (m, 1H, H2), 0.97 (t, *J* = 7.5 Hz, 3H, H9).

Note: the *OH* resonance was not observed.

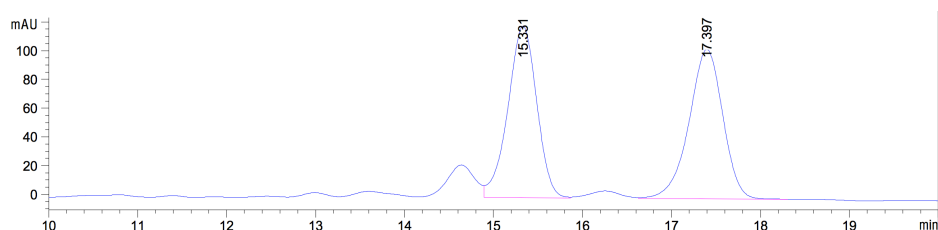
¹³C NMR (126 MHz, CDCl₃) δ 133.0, 127.7, 64.9, 49.8 (3C), 47.3, 42.7, 27.7, 26.8, 20.7, 14.3.

HRMS (ESI⁺) Found [M+H]⁺ = 181.1587; C₁₂H₂₁O requires 181.1587.

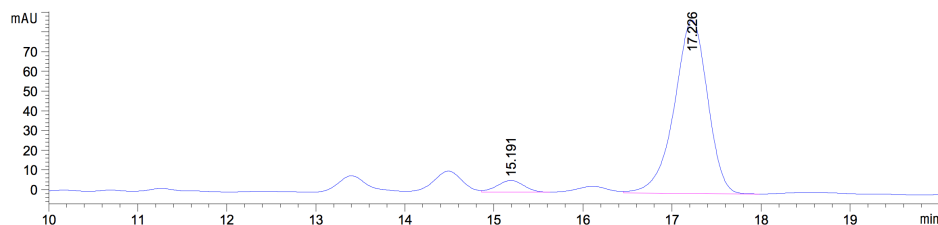
IR (film) ν_{max} /cm⁻¹ 3317, 2962, 2907, 2870, 1462, 1374, 1279, 1196, 1143, 1067, 1025.

[α]_D²⁵ -24.1 (*c* = 0.2, CHCl₃)

HPLC 90% *ee* (CHIRALPAK IC, 2% IPA/hexane, 1.0 mL/min, t_R major – 17.2 min, minor – 15.2 min) after derivatization to (*R,Z*)-2-(bicyclo[1.1.1]pentan-1-yl)hept-4-en-1-yl 4-(dimethylamino)benzoate (*R*)-**S44**.



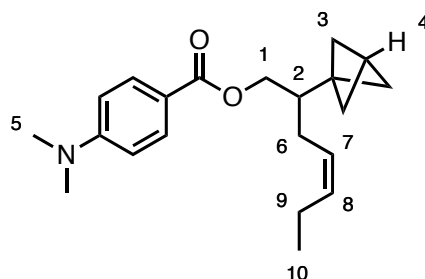
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.331	VV	0.3468	2688.97925	119.38303	49.5241
2	17.397	VB	0.4037	2740.65942	103.89968	50.4759



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.191	VB	0.3159	123.43719	5.90328	5.1538
2	17.226	VB	0.3935	2271.64990	87.91320	94.8462

Derivatization for *ee* determination

(*Z*)-2-(Bicyclo[1.1.1]pentan-1-yl)hept-4-en-1-yl 4-(dimethylamino)benzoate, **S44**



(*Z*)-2-(Bicyclo[1.1.1]pentan-1-yl)hept-4-en-1-ol *rac*-**131i** (9.0 mg, 50 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (8.3 mg, 50 μ mol, 1.0 equiv.), DMAP (18 mg,

0.15 mmol, 3.0 equiv.) and EDCI (29 mg, 0.15 mmol, 3.0 equiv.) in CH₂Cl₂ (0.5 mL) were submitted to **General Procedure F** for 23 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as a clear oil (16 mg, 48 μmol, 95%).

R_f 0.52 (pentane/Et₂O, 4:1), [UV, vanillin]

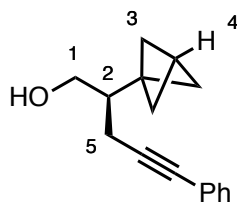
¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, *J* = 9.1 Hz, 2H, Ar*H*), 6.68 (d, *J* = 9.1 Hz, 2H, Ar*H*), 5.46 – 5.31 (m, 2H, H7 and H8), 4.18 (dd, *J* = 10.9, 5.2 Hz, 1H, H1), 4.14 (dd, *J* = 10.9, 6.3 Hz, 1H, H1), 3.04 (s, 6H, H5), 2.47 (s, 1H, H4), 2.12 (dd, *J* = 7.5, 6.3 Hz, 2H, H6), 2.08 – 1.99 (m, 2H, H9), 1.88 (quin, *J* = 6.3 Hz, 1H, H2), 1.75 (s, 6H, H3), 0.93 (t, *J* = 7.5 Hz, 3H, H10).

¹³C NMR (126 MHz, CDCl₃) δ 167.1, 153.2, 133.0, 131.4 (2C), 127.1, 117.8, 111.1 (2C), 65.3, 49.8 (3C), 47.3, 40.4 (2C), 39.8, 27.5, 26.7, 20.7, 14.3.

HRMS (ESI⁺) Found [M+H]⁺ = 328.2269; C₂₁H₃₀O₂N requires 328.2271.

IR (film) ν_{max}/cm⁻¹ 2962, 2907, 2870, 1703, 1609, 1527, 1367, 1317, 1275, 1183, 1109.

(*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)-5-phenylpent-4-yn-1-ol, 131j



5-Phenylpent-4-ynal **130j** (48 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O,

0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as a yellow oil (23 mg, 0.10 mmol, 50%).

R_f 0.38 (pentane/Et₂O, 3:2), [UV, vanillin]

¹H NMR (400 MHz, CDCl₃) δ 7.41 – 7.34 (m, 2H, ArH), 7.32 – 7.26 (m, 3H, ArH), 3.82 – 3.66 (m, 2H, H1), 2.56 – 2.38 (m, 3H, H4 and H5), 1.91 (quin, *J* = 6.3 Hz, 1H, H2), 1.80 (s, 6H, H3).

Note: the OH resonance was not observed.

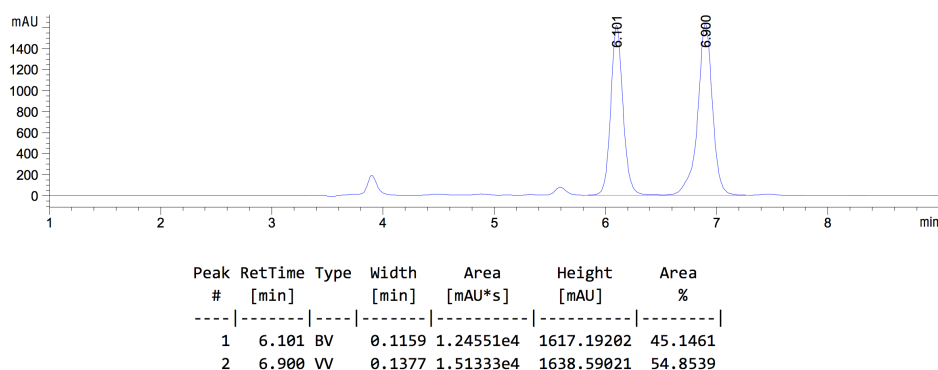
¹³C NMR (126 MHz, CDCl₃) δ 131.6 (2C), 128.4 (2C), 127.8, 123.9, 88.7, 82.1, 64.1, 49.9 (3C), 46.5, 41.6, 27.7, 19.2.

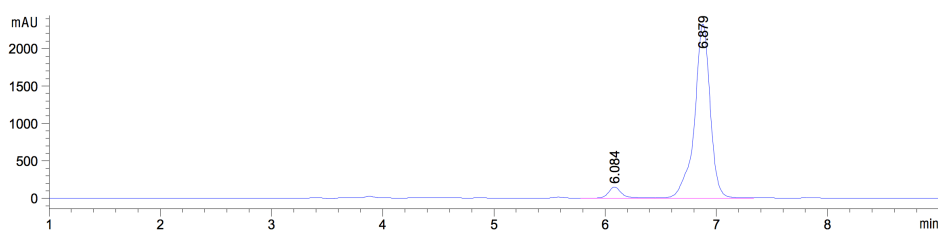
HRMS (ESI⁺) Found [M+H]⁺ = 227.1432; C₁₆H₁₉O requires 227.1430.

IR (film) ν_{max}/cm⁻¹ 3342, 2963, 2907, 2870, 1490, 1442, 1373, 1279, 1196, 1178, 1140.

[α]_D²⁵ -23.6 (*c* = 0.2, CHCl₃)

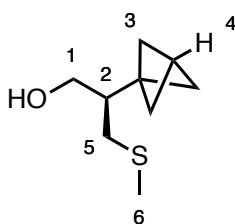
HPLC 90% *ee* (CHIRALPAK IB, 6% IPA/hexane, 1.0 mL/min, *t_R* major – 6.9 min, minor – 6.1 min).





Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.084	BV	0.1229	1210.75781	148.86757	5.0571
2	6.879	VV	0.1480	2.27310e4	2325.56519	94.9429

(R)-2-(Bicyclo[1.1.1]pentan-1-yl)-3-(methylthio)propan-1-ol, 131k



Methional (30 μ L, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μ mol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μ mol, 0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μ mol, 0.25 equiv.), water (7.2 μ L, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow oil (34 mg, 0.20 mmol, 99%).

R_f 0.43 (pentane/Et₂O, 3:2), [vanillin]

¹H NMR (400 MHz, CDCl₃) δ 3.73 (dd, *J* = 11.1, 4.7 Hz, 1H, H1), 3.65 (dd, *J* = 11.1, 6.3 Hz, 1H, H1), 2.60 (dd, *J* = 13.0, 4.7 Hz, 1H, H5), 2.49 (s, 1H, H4), 2.45 (dd,

$J = 13.0, 9.4$ Hz, 1H, H5), 2.12 (s, 3H, H6), 1.86 (ddt, $J = 9.4, 6.3, 4.7$ Hz, 1H, H2), 1.73 (s, 6H, H3).

Note: the *OH* resonance was not observed.

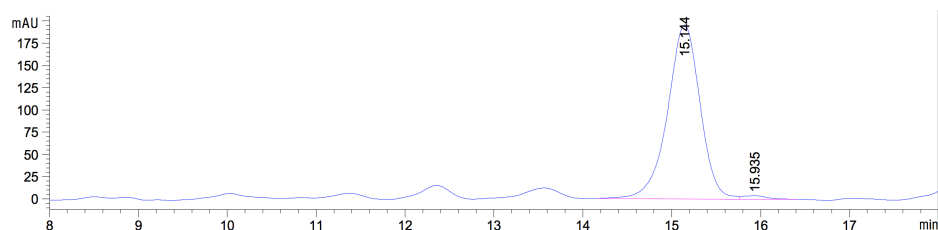
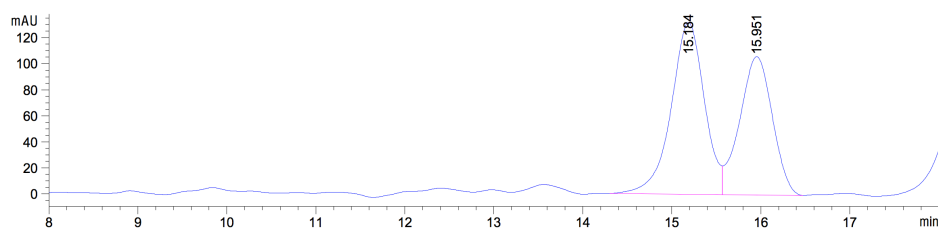
^{13}C NMR (126 MHz, CDCl_3) δ 64.5, 49.7 (3C), 46.5, 41.0, 34.6, 27.7, 16.3.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 173.0997$; $\text{C}_9\text{H}_{17}\text{OS}$ requires 173.0995.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3404, 2962, 2909, 2869, 1426, 1279, 1213, 1197, 1139, 1110, 1063, 1018.

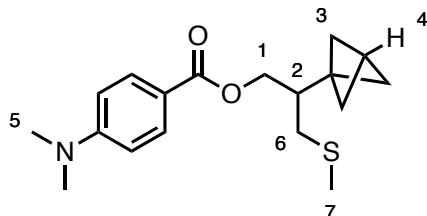
$[\alpha]_{\text{D}}^{25} -10.1$ ($c = 0.2$, CHCl_3)

HPLC 97% *ee* (CHIRALPAK IC, 8% IPA/hexane, 1.3 mL/min, t_{R} major – 15.1 min, minor – 15.9 min) after derivatization to (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-(methylthio)propyl 4-(dimethylamino)benzoate (*R*)-**S45**.



Derivatization for *ee* determination

2-(Bicyclo[1.1.1]pentan-1-yl)-3-(methylthio)propyl 4-(dimethylamino)benzoate, S45



2-(Bicyclo[1.1.1]pentan-1-yl)-3-(methylthio)propan-1-ol *rac*-**131k** (8.6 mg, 50 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (8.3 mg, 50 μ mol, 1.0 equiv.), DMAP (18 mg, 0.15 mmol, 3.0 equiv.) and EDCI (29 mg, 0.15 mmol, 3.0 equiv.) in CH_2Cl_2 (0.5 mL) were submitted to **General Procedure F** for 22 h. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 4:1) afforded the title compound as a pale yellow oil (15 mg, 48 μ mol, 96%).

R_f 0.43 (pentane/ Et_2O , 4:1), [UV, vanillin]

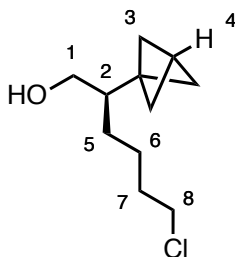
^1H NMR (500 MHz, CDCl_3) δ 7.93 (d, J = 8.9 Hz, 2H, ArH), 6.78 (d, J = 8.9 Hz, 2H, ArH), 4.33 (dd, J = 11.0, 5.1 Hz, 1H, H1), 4.31 (dd, J = 11.0, 5.7 Hz, 1H, H1), 3.06 (s, 6H, H5), 2.61 (dd, J = 13.1, 5.5 Hz, 1H, H6), 2.52 (dd, J = 13.1, 8.4 Hz, 1H, H6), 2.48 (s, 1H, H4), 2.10 (s, 3H, H7), 2.10 – 2.05 (m, 1H, H2), 1.78 (s, 6H, H3).

^{13}C NMR (126 MHz, CDCl_3) δ 166.8, 152.7, 131.5 (2C), 122.4, 111.9 (2C), 64.6, 49.9 (3C), 46.5, 40.9 (2C), 39.1, 34.0, 27.7, 16.6.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 320.1679$; $\text{C}_{18}\text{H}_{26}\text{O}_2\text{NS}$ requires 320.1679.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2962, 2910, 2869, 1701, 1608, 1527, 1445, 1368, 1317, 1279, 1233, 1183, 1107.

(R)-2-(Bicyclo[1.1.1]pentan-1-yl)-6-chlorohexan-1-ol, 1311



6-Chlorohexanal **1301** (40 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow oil (40 mg, 0.20 mmol, 98%).

R_f 0.24 (pentane/Et₂O, 4:1), [vanillin]

¹H NMR (500 MHz, CDCl₃) δ 3.63 – 3.49 (m, 4H, H1 and H8), 2.49 (s, 1H, H4), 1.81 – 1.75 (m, 2H, H7), 1.72 (d, *J* = 1.6 Hz, 6H, H3), 1.53 – 1.45 (m, 3H, H2 and H6), 1.34 – 1.27 (m, 2H, H5).

Note: the *OH* resonance was not observed.

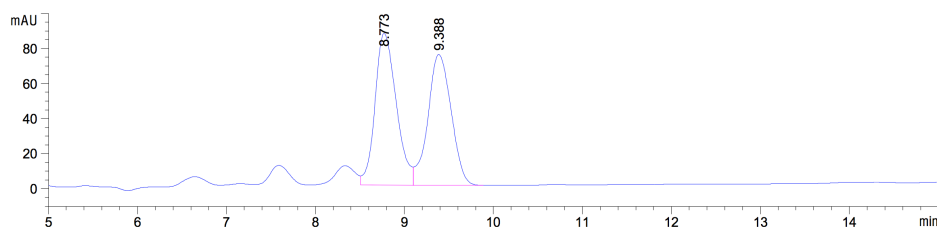
¹³C NMR (126 MHz, CDCl₃) δ 64.5, 49.8 (3C), 47.4, 45.1, 42.0, 33.1, 27.9, 27.7, 25.1.

HRMS (ESI⁺) Found [M+H]⁺ = 203.1198; C₁₁H₂₀O³⁵Cl requires 203.1197.

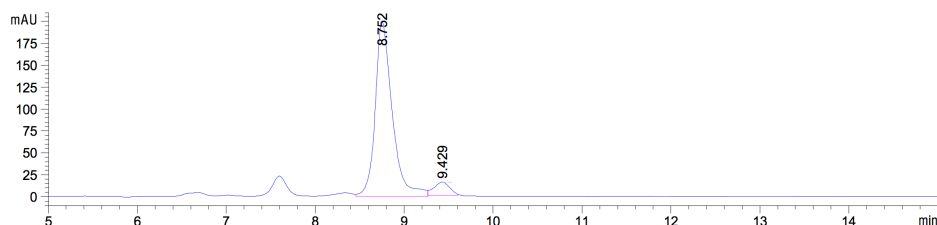
IR (film) ν_{max} /cm⁻¹ 3337, 2960, 2869, 1447, 1279, 1198, 1140.

[α]_D²⁵ -25.8 (*c* = 0.2, CHCl₃)

HPLC 86% *ee* (CHIRALPAK IB, 3% IPA/hexane, 1.0 mL/min, t_R major – 8.8 min, minor – 9.4 min) after derivatization to (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-6-chlorohexyl 4-(dimethylamino)benzoate (*R*)-**S46**.



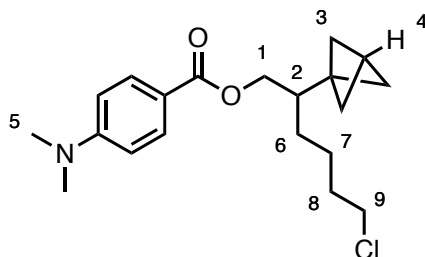
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.773	VV	0.2582	1440.46741	86.54997	51.4686
2	9.388	VB	0.2844	1358.26331	74.60453	48.5314



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.752	VV	0.1946	2647.57764	199.79578	93.1442
2	9.429	MM	0.2083	194.87386	15.59131	6.8558

Derivatization for *ee* determination

2-(Bicyclo[1.1.1]pentan-1-yl)-6-chlorohexyl 4-(dimethylamino)benzoate, **S46**



2-(Bicyclo[1.1.1]pentan-1-yl)-6-chlorohexan-1-ol *rac*-**131I** (10 mg, 50 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (8.3 mg, 50 μ mol, 1.0 equiv.),

DMAP (18 mg, 0.15 mmol, 3.0 equiv.) and EDCI (29 mg, 0.15 mmol, 3.0 equiv.) in CH₂Cl₂ (0.5 mL) were submitted to **General Procedure F** for 25 h. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a clear oil (16 mg, 47 μmol, 93%).

R_f 0.38 (pentane/Et₂O, 4:1), [UV, vanillin]

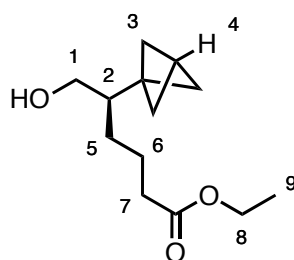
¹H NMR (500 MHz, CDCl₃) δ 7.90 (d, *J* = 9.1 Hz, 2H, Ar*H*), 6.68 (d, *J* = 9.1 Hz, 2H, Ar*H*), 4.22 – 4.13 (m, 2H, H1), 3.53 (t, *J* = 6.7 Hz, 2H, H9), 3.04 (s, 6H, H5), 2.47 (s, 1H, H4), 1.86 – 1.77 (m, 3H, H2 and H8), 1.75 (s, 6H, H3), 1.53 – 1.47 (m, 2H, H7), 1.41 – 1.33 (m, 2H, H6).

¹³C NMR (126 MHz, CDCl₃) δ 167.1, 153.3, 131.4 (2C), 117.7, 111.1 (2C), 65.5, 49.8 (3C), 47.3, 45.1, 40.4 (2C), 39.1, 33.0, 28.3, 27.5, 25.0.

HRMS (ESI⁺) Found [M+H]⁺ = 350.1882; C₂₀H₂₉O₂N³⁵Cl requires 350.1881.

IR (film) ν_{max}/cm⁻¹ 2961, 2868, 1702, 1608, 1527, 1446, 1367, 1317, 1279, 1183, 1109.

Ethyl (*R*)-5-(bicyclo[1.1.1]pentan-1-yl)-6-hydroxyhexanoate, **131m**



Ethyl 6-oxohexanoate **130m** (48 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O,

0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 3:2) afforded the title compound as a pale yellow oil (44 mg, 0.19 mmol, 97%).

R_f 0.07 (pentane/Et₂O, 4:1), [vanillin]

¹H NMR (500 MHz, CDCl₃) δ 4.13 (q, *J* = 7.1 Hz, 2H, H8), 3.60 (dd, *J* = 10.8, 5.7 Hz, 1H, H1), 3.53 (dd, *J* = 10.8, 5.7 Hz, 1H, H1), 2.48 (s, 1H, H4), 2.30 (t, *J* = 7.3 Hz, 2H, H7), 1.71 (s, 6H, H3), 1.68 – 1.63 (m, 2H, H6), 1.55 – 1.50 (m, 1H, H2), 1.34 – 1.28 (m, 2H, H5), 1.26 (t, *J* = 7.1 Hz, 3H, H9).

Note: the *OH* resonance was not observed.

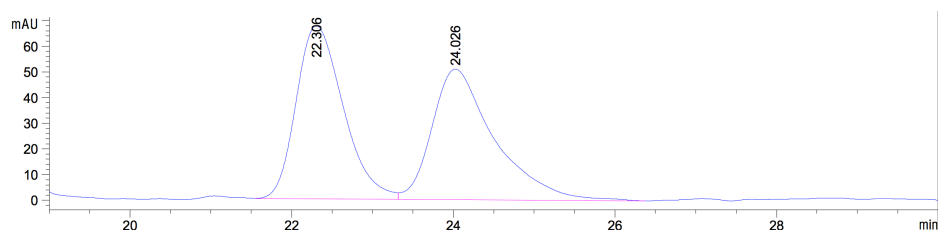
¹³C NMR (126 MHz, CDCl₃) δ 173.9, 64.3, 60.4, 49.8 (3C), 47.3, 41.9, 34.7, 28.0, 27.7, 23.0, 14.4.

HRMS (ESI⁺) Found [M+Na]⁺ = 249.1463; C₁₃H₂₂O₃Na requires 249.1461.

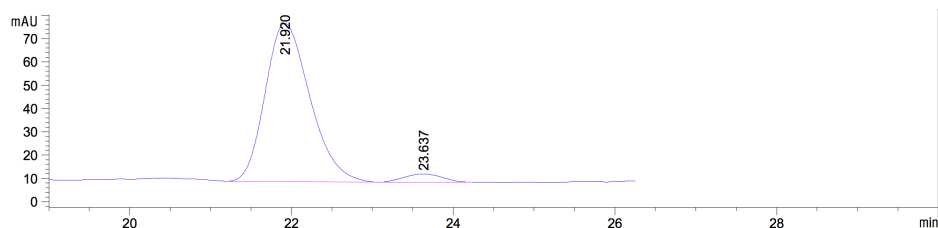
IR (film) ν_{max} /cm⁻¹ 2962, 2908, 2869, 1736, 1449, 1374, 1279.

[α]_D²⁵ -26.1 (*c* = 0.2, CHCl₃)

HPLC 92% *ee* (Lux i-Amylose-1, 3% IPA/hexane, 1.0 mL/min, *t_R* major – 21.9 min, minor – 23.6 min) after derivatization to (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-6-ethoxy-6-oxohexyl 4-(dimethylamino)benzoate (*R*)-**S47**.



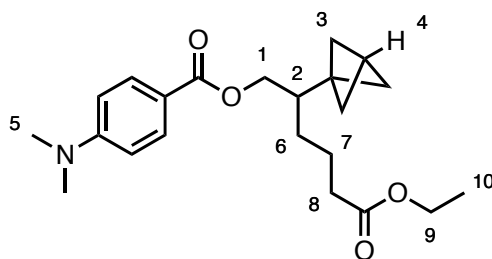
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	22.306	BV	0.6241	2726.98193	67.38924	50.0242
2	24.026	VB	0.7814	2724.33911	50.82434	49.9758



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	21.920	BB	0.5914	2607.46069	67.98797	95.7974
2	23.637	BB	0.4122	114.38885	3.54702	4.2026

Derivatization for *ee* determination

2-(Bicyclo[1.1.1]pentan-1-yl)-6-ethoxy-6-oxohexyl 4-(dimethylamino)benzoate, S47



Ethyl 5-(bicyclo[1.1.1]pentan-1-yl)-6-hydroxyhexanoate *rac*-**131m** (11 mg, 50 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (8.3 mg, 50 μ mol, 1.0 equiv.), DMAP (18 mg, 0.15 mmol, 3.0 equiv.) and EDCI (29 mg, 0.15 mmol, 3.0 equiv.) in CH_2Cl_2 (0.5 mL) were submitted to **General Procedure F** for 25 h. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 3:2) afforded the title compound as a pale yellow oil (17 mg, 45 μ mol, 89%).

R_f 0.17 (pentane/Et₂O, 4:1), [UV, vanillin]

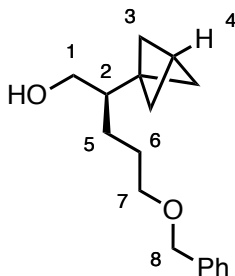
¹H NMR (500 MHz, CDCl₃) δ 7.90 (d, *J* = 9.0 Hz, 2H, Ar*H*), 6.69 (d, *J* = 9.0 Hz, 2H, Ar*H*), 4.20 – 4.15 (m, 2H, H1), 4.12 (q, *J* = 7.1 Hz, 2H, H9), 3.04 (s, 6H, H5), 2.47 (s, 1H, H4), 2.30 (t, *J* = 7.4 Hz, 2H, H8), 1.85 – 1.79 (m, 1H, H2), 1.74 (s, 6H, H3), 1.73 – 1.66 (m, 2H, H7), 1.43 – 1.31 (m, 2H, H6), 1.24 (t, *J* = 7.1 Hz, 3H, H10).

¹³C NMR (126 MHz, CDCl₃) δ 173.7, 167.1, 153.2, 131.4 (2C), 117.9, 111.2 (2C), 65.5, 60.4, 49.8 (3C), 47.3, 40.4 (2C), 39.0, 34.8, 28.6, 27.5, 23.2, 14.4.

HRMS (ESI⁺) Found [M+H]⁺ = 374.2323; C₂₂H₃₂O₄N requires 374.2326.

IR (film) ν_{max}/cm⁻¹ 2962, 2909, 2869, 1734, 1702, 1608, 1528, 1368, 1317, 1278, 1233, 1183, 1109.

(*R*)-5-(Benzyloxy)-2-(bicyclo[1.1.1]pentan-1-yl)pentan-1-ol, 131n



5-(Benzyloxy)pentanal **131n** (58 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂,

pentane/Et₂O, 3:2) afforded the title compound as a pale yellow oil (44 mg, 0.17 mmol, 85%).

R_f 0.17 (pentane/Et₂O, 3:2), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.37 – 7.27 (m, 5H, ArH), 4.50 (s, 2H, H8), 3.63 – 3.49 (m, 2H, H1), 3.46 (t, *J* = 6.5 Hz, 2H, H7), 2.48 (s, 1H, H4), 1.71 (s, 6H, H3), 1.69 – 1.63 (m, 2H, H6), 1.56 – 1.51 (m, 1H, H2), 1.44 – 1.34 (m, 2H, H5).

Note: the OH resonance was not observed.

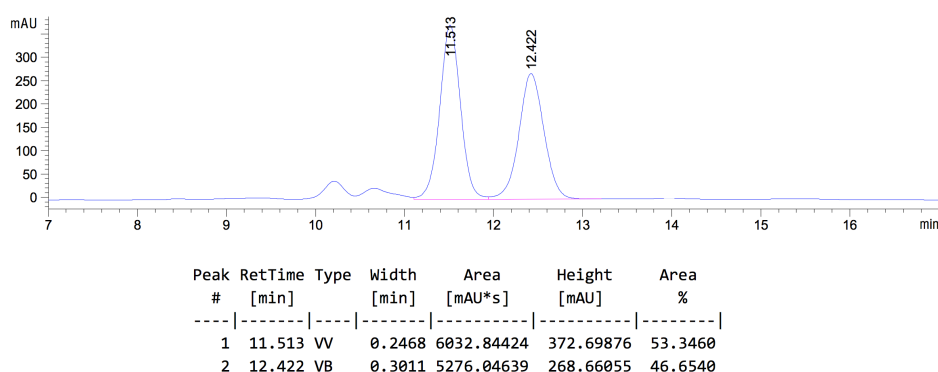
¹³C NMR (126 MHz, CDCl₃) δ 138.7, 128.5 (2C), 127.8 (2C), 127.7, 73.1, 70.8, 64.5, 49.8 (3C), 47.5, 41.9, 27.8, 27.7, 25.1.

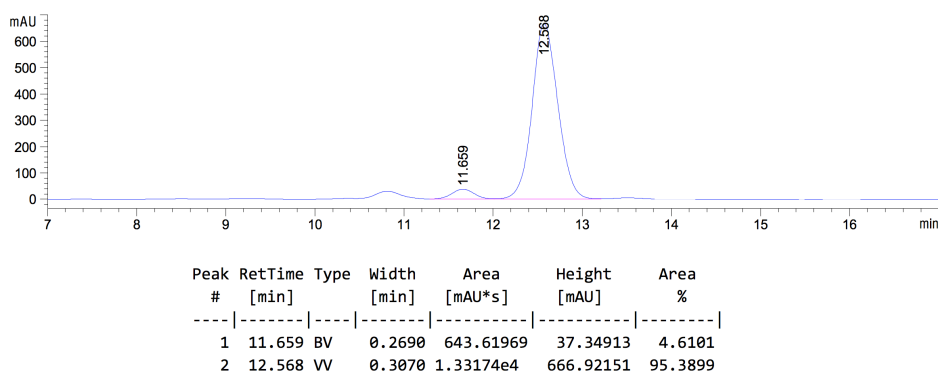
HRMS (ESI⁺) Found [M+Na]⁺ = 283.1668; C₁₇H₂₄O₂Na requires 283.1669.

IR (film) ν_{max}/cm⁻¹ 3397, 2959, 2907, 2867, 1454, 1363, 1278, 1197, 1099.

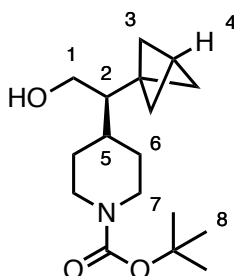
[α]_D²⁵ –14.5 (*c* = 0.4, CHCl₃)

HPLC 91% *ee* (CHIRALPAK IB, 2% IPA/hexane, 1.0 mL/min, *t*_R major – 12.6 min, minor – 11.7 min).





tert*-Butyl (*R*)-4-(1-(bicyclo[1.1.1]pentan-1-yl)-2-hydroxyethyl)piperidine-1-carboxylate, **131o*



N-Boc-4-piperidineacetaldehyde (68 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:11) afforded the title compound as a pale yellow oil (49 mg, 0.17 mmol, 83%).

R_f 0.26 (pentane/Et₂O, 2:3), [vanillin]

^1H NMR (500 MHz, CDCl_3) δ 4.19 – 4.07 (br m, 2H, H7), 3.67 (dd, $J = 10.8, 5.8$ Hz, 1H, H1), 3.62 (dd, $J = 10.8, 5.6$ Hz, 1H, H1), 2.69 – 2.58 (br m, 2H, H7), 2.48 (s, 1H, H4), 1.79 (s, 6H, H3), 1.65 – 1.60 (m, 3H, H5 and H6), 1.45 (s, 10H, H2 and H8), 1.38 (dd, $J = 12.6, 4.4$ Hz, 1H, H6), 1.28 (dd, $J = 12.6, 4.4$ Hz, 1H, H6).

Note: the OH resonance was not observed.

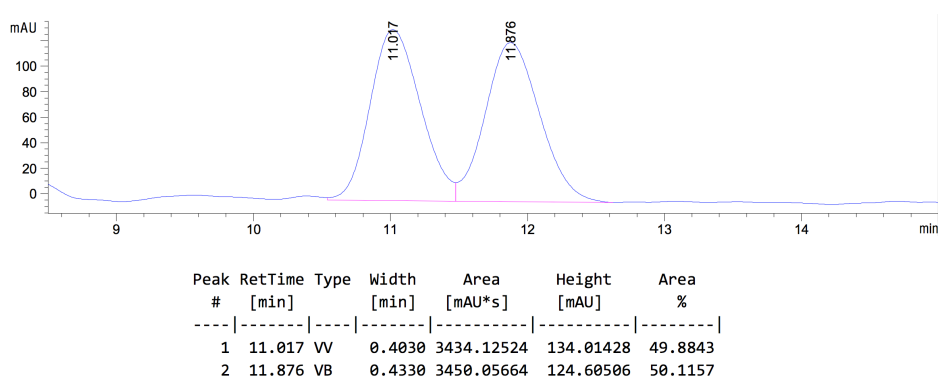
^{13}C NMR (126 MHz, CDCl_3) δ 155.0, 79.4, 62.6, 51.3 (3C), 47.1, 46.8, 44.6 (br, 2C), 36.9, 30.6 (br), 29.4 (br), 28.6 (3C), 28.2.

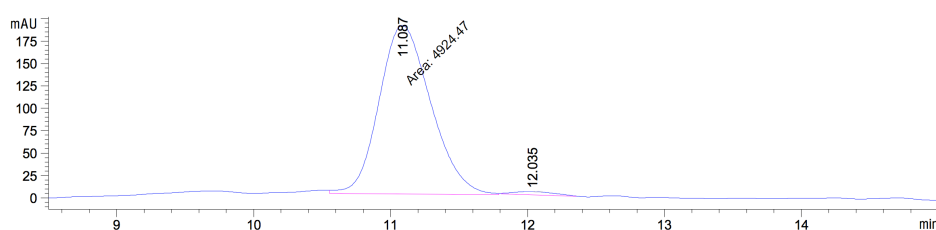
HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 318.2040$; $\text{C}_{17}\text{H}_{29}\text{O}_3\text{NNa}$ requires 318.2040.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3437, 2962, 2925, 2868, 1694, 1672, 1477, 1426, 1366, 1279, 1241, 1171.

$[\alpha]_{\text{D}}^{25} -21.4$ ($c = 0.2$, CHCl_3)

HPLC 97% ee (Lux i-Amylose-1, 10% IPA/hexane, 1.3 mL/min, t_{R} major – 11.1 min, minor – 12.0 min) after derivatization to *tert*-butyl (*R*)-4-(1-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(dimethylamino)benzoyl)oxy)ethyl)piperidine-1-carboxylate (*R*)-**S48**.

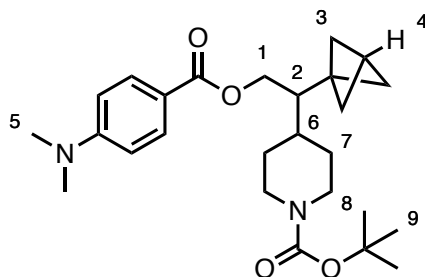




Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.087	MM	0.4367	4924.47266	187.93063	98.4584
2	12.035	MM	0.3392	77.10249	3.78795	1.5416

Derivatization for *ee* determination

tert-Butyl 4-(1-(bicyclo[1.1.1]pentan-1-yl)-2-((4-(dimethylamino)benzoyl)oxy)-ethyl)piperidine-1-carboxylate, S48



tert-Butyl 4-(1-(bicyclo[1.1.1]pentan-1-yl)-2-hydroxyethyl)piperidine-1-carboxylate *rac*-**131o** (15 mg, 50 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (8.3 mg, 50 μ mol, 1.0 equiv.), DMAP (18 mg, 0.15 mmol, 3.0 equiv.) and EDCI (29 mg, 0.15 mmol, 3.0 equiv.) in CH_2Cl_2 (0.5 mL) were submitted to **General Procedure F** for 19 h. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 1:1) afforded the title compound as a clear oil (17 mg, 39 μ mol, 77%).

R_f 0.36 (pentane/ Et_2O , 1:1), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 7.89 (d, $J = 9.0$ Hz, 2H, ArH), 6.67 (d, $J = 9.0$ Hz, 2H, ArH), 4.23 (d, $J = 5.7$ Hz, 2H, H1), 4.12 (br s, 2H, H8), 3.04 (s, 6H, H5), 2.65 (br s, 2H,

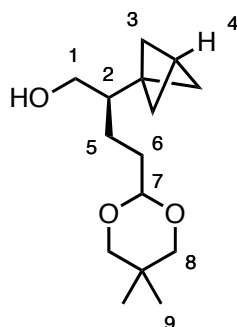
H8), 2.46 (s, 1H, H4), 1.82 (s, 6H, H3), 1.76 – 1.72 (m, 1H, H2), 1.69 – 1.65 (m, 1H, H6), 1.59 – 1.51 (m, 2H, H7), 1.45 (s, 9H, H9), 1.39 – 1.27 (m, 2H, H7).

¹³C NMR (126 MHz, CDCl₃) δ 167.1, 155.0, 153.4, 131.4 (2C), 117.4, 111.0 (2C), 79.4, 63.9, 51.2 (3C), 47.0, 45.1 (br), 45.0 (br), 43.7, 40.3 (2C), 37.4, 30.9 (br), 29.1 (br), 28.6 (3C), 28.0.

HRMS (ESI⁺) Found [M+Na]⁺ = 465.2723; C₂₆H₃₈O₄N₂Na requires 465.2724.

IR (film) ν_{max}/cm⁻¹ 2963, 2908, 2868, 1693, 1607, 1528, 1423, 1391, 1276, 1181.

(*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)-4-(5,5-dimethyl-1,3-dioxan-2-yl)butan-1-ol, 131p



5,5-Dimethyl-1,3-dioxane-2-butanol (56 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. The reduction was quenched by addition of water (2 mL) instead of NH₄Cl. Purification by column chromatography (SiO₂, pentane/Et₂O, 11:9) afforded the title compound as a pale yellow oil (50 mg, 0.20 mmol, 99%).

R_f 0.36 (pentane/Et₂O, 1:1), [vanillin]

¹H NMR (400 MHz, CDCl₃) δ 4.41 (t, *J* = 4.9 Hz, 1H, H7), 3.63 – 3.57 (m, 3H, H1 and H8), 3.53 (dd, *J* = 10.9, 5.6 Hz, 1H, H1), 3.42 (d, *J* = 10.9 Hz, 2H, H8), 2.47 (s, 1H, H4), 1.71 (s, 6H, H3), 1.71 – 1.66 (m, 2H, H6), 1.58 – 1.52 (m, 1H, H2), 1.47 – 1.35 (m, 2H, H5), 1.19 (s, 3H, H9), 0.72 (s, 3H, H9).

Note: the *OH* resonance was not observed.

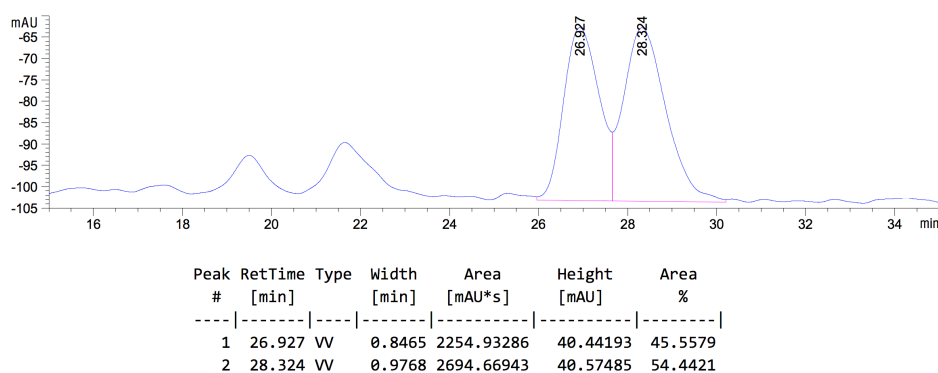
¹³C NMR (126 MHz, CDCl₃) δ 102.6, 77.4 (2C; obscured by solvent signal), 64.3, 49.8 (3C), 47.4, 42.0, 32.6, 30.3, 27.7, 23.1, 22.6, 22.0.

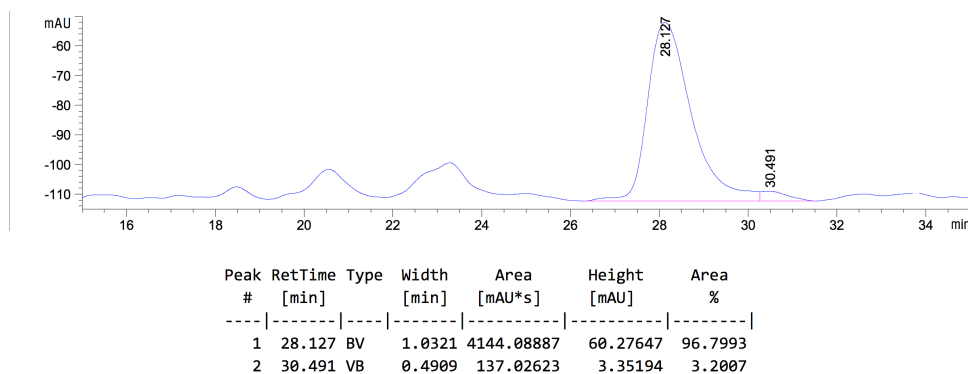
HRMS (ESI⁺) Found [M+Na]⁺ = 277.1775; C₁₅H₂₆O₃Na requires 277.1774.

IR (film) ν_{max}/cm⁻¹ 3426, 2957, 2907, 2868, 1471, 1394, 1196, 1136.

[α]_D²⁵ –32.9 (*c* = 0.2, CHCl₃)

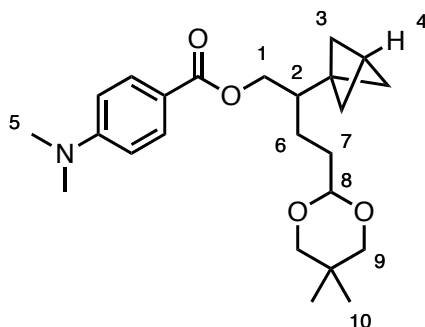
HPLC 94% *ee* (Lux i-Amylose-1, 1% IPA/hexane, 1.3 mL/min, *t_R* major – 28.1 min, minor – 30.5 min) after derivatization to (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-4-(5,5-dimethyl-1,3-dioxan-2-yl)butyl 4-(dimethylamino)benzoate (*R*)-**S49**.





Derivatization for *ee* determination

2-(Bicyclo[1.1.1]pentan-1-yl)-4-(5,5-dimethyl-1,3-dioxan-2-yl)butyl 4-(dimethyl-amino)benzoate, **S49**



2-(Bicyclo[1.1.1]pentan-1-yl)-4-(5,5-dimethyl-1,3-dioxan-2-yl)-butan-1-ol *rac*-**131p** (13 mg, 50 μ mol, 1.0 equiv.), 4-(dimethylamino)benzoic acid (8.3 mg, 50 μ mol, 1.0 equiv.), DMAP (18 mg, 0.15 mmol, 3.0 equiv.) and EDCI (29 mg, 0.15 mmol, 3.0 equiv.) in CH_2Cl_2 (0.5 mL) were submitted to **General Procedure F** for 15 h. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 3:2) afforded the title compound as a pale yellow oil (20 mg, 50 μ mol, 99%).

R_f 0.31 (pentane/ Et_2O , 3:2), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 7.91 (d, J = 8.7 Hz, 2H, ArH), 6.69 (d, J = 8.7 Hz, 2H, ArH), 4.40 (t, J = 5.0 Hz, 1H, H8), 4.17 (d, J = 5.6 Hz, 2H, H1), 3.59 (d, J = 11.1 Hz,

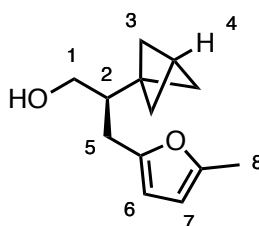
2H, H9), 3.40 (d, J = 11.1 Hz, 2H, H9), 3.04 (s, 6H, H5), 2.45 (s, 1H, H4), 1.85 – 1.78 (m, 1H, H2), 1.75 (s, 6H, H3), 1.74 – 1.69 (m, 2H, H7), 1.59 – 1.56 (m, 1H, H6), 1.48 – 1.43 (m, 1H, H6), 1.18 (s, 3H, H10), 0.71 (s, 3H, H10).

^{13}C NMR (126 MHz, CDCl_3) δ 167.1, 153.1, 131.4 (2C), 118.0, 111.2 (2C), 102.5, 77.4 (2C; signal partially obscured by solvent signal), 65.6, 49.8 (3C), 47.4, 40.4 (2C), 39.1, 33.0, 30.3, 27.5, 23.4, 23.2, 22.0.

HRMS (ESI $^+$) Found $[\text{M}+\text{H}]^+ = 402.2636$; $\text{C}_{24}\text{H}_{36}\text{O}_4\text{N}$ requires 402.2639.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 2956, 2868, 1702, 1608, 1527, 1469, 1366, 1279, 1183, 1109.

(*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)-3-(5-methylfuran-2-yl)propan-1-ol, 131q



3-(5-Methyl-2-furyl)propionaldehyde (40 μL , 0.30 mmol, 1.5 equiv.), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (3.7 mg, 4.0 μmol , 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol , 0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol , 0.25 equiv.), water (7.2 μL , 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et_2O , 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et_2O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH_2Cl_2 (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO_2 , pentane/ Et_2O , 17:3) afforded the title compound as a pale yellow oil (37 mg, 0.18 mmol, 89%).

R_f 0.07 (pentane/ Et_2O , 9:1), [UV, vanillin]

^1H NMR (400 MHz, CDCl_3) δ 5.88 (d, $J = 3.0$ Hz, 1H, H6), 5.85 – 5.82 (m, 1H, H7), 3.62 – 3.53 (m, 2H, H1), 2.62 (dd, $J = 15.2, 5.9$ Hz, 1H, H5), 2.53 (dd, $J = 15.2, 8.6$ Hz, 1H, H5), 2.48 (s, 1H, H4), 2.24 (s, 3H, H8), 2.01 – 1.92 (m, 1H, H2), 1.72 (dd, $J = 9.4, 1.1$ Hz, 3H, H3), 1.70 (dd, $J = 9.4, 1.1$ Hz, 3H, H3).

Note: the OH resonance was not observed.

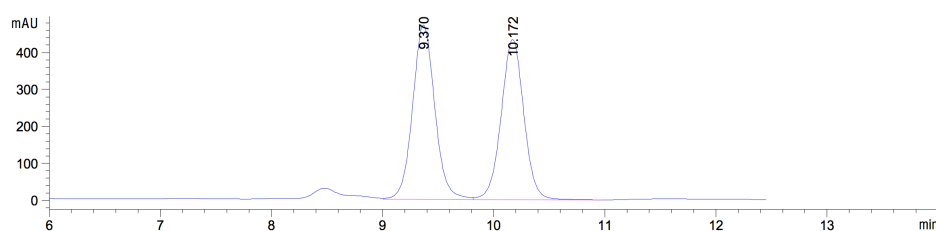
^{13}C NMR (126 MHz, CDCl_3) δ 152.8, 150.6, 106.8, 106.1, 64.4, 49.6 (3C), 47.0, 41.6, 27.6, 27.4, 13.7.

HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 207.1382$; $\text{C}_{13}\text{H}_{19}\text{O}_2$ requires 207.1380.

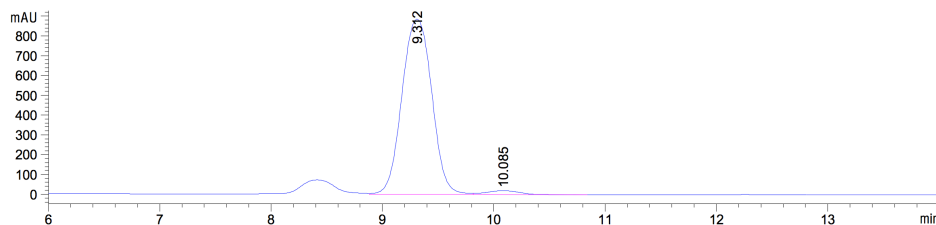
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3385, 2963, 2908, 2870, 1709, 1570, 1433, 1369, 1280, 1198, 1142, 1065, 1020.

$[\alpha]_{\text{D}}^{25} -15.4$ ($c = 0.3$, CHCl_3)

HPLC 95% *ee* (CHIRALPAK IB, 2% IPA/hexane, 0.8 mL/min, t_{R} major – 9.3 min, minor – 10.1 min).

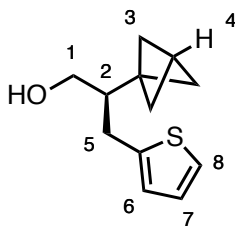


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.370	VV	0.2145	6572.25195	471.81628	51.6279
2	10.172	VB	0.2178	6157.79199	433.20355	48.3721



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.312	VV	0.3012	1.64879e4	885.58411	97.5369
2	10.085	VB	0.3247	416.37497	20.01858	2.4631

(R)-2-(Bicyclo[1.1.1]pentan-1-yl)-3-(thiophen-2-yl)propan-1-ol, 131r



3-(Thiophen-2-yl)propanal **130r** (42 mg, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol, 0.1 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow oil (10 mg, 50 μmol, 25%).

R_f 0.14 (pentane/Et₂O, 4:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.12 (dd, *J* = 5.2, 1.2 Hz, 1H, H8), 6.91 (dd, *J* = 5.2, 3.4 Hz, 1H, H7), 6.82 – 6.79 (m, 1H, H6), 3.59 (d, *J* = 5.2 Hz, 2H, H1), 2.89 – 2.77 (m, 2H, H5), 2.49 (s, 1H, H4), 1.96 – 1.90 (m, 1H, H2), 1.75 (dd, *J* = 9.6, 1.7 Hz, 3H, H3), 1.71 (dd, *J* = 9.6, 1.7 Hz, 3H, H3).

Note: the *OH* resonance was not observed.

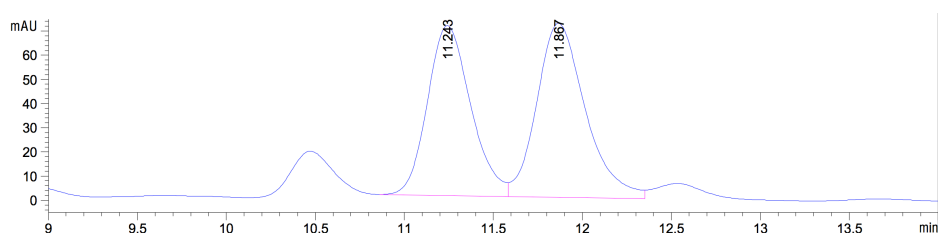
¹³C NMR (126 MHz, CDCl₃) δ 143.8, 126.9, 125.2, 123.5, 63.9, 49.8 (3C), 47.1, 44.5, 29.1, 27.7.

HRMS (ESI⁺) Found [M+H]⁺ = 209.0997; C₁₂H₁₇OS requires 209.0995.

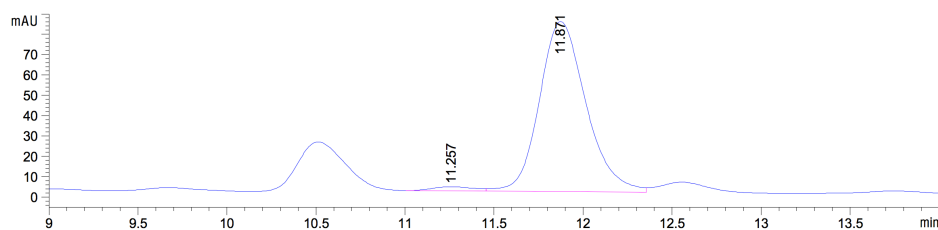
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3381, 2962, 2907, 2869, 1586, 1438, 1409, 1373, 1279, 1198, 1176, 1140.

$[\alpha]_{\text{D}}^{25} -92.8$ ($c = 0.1$, CHCl_3)

HPLC 96% *ee* (Lux i-Amylose-1, 3% IPA/hexane, 1.0 mL/min, t_{R} major – 11.9 min, minor – 11.3 min).

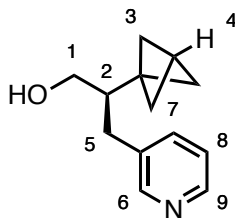


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.243	BV	0.2589	1187.49854	70.34469	46.4800
2	11.867	VV	0.2895	1367.36218	72.03519	53.5200



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.257	BV	0.2452	33.58194	2.04859	2.1539
2	11.871	VV	0.2785	1525.51978	83.74531	97.8461

(R)-2-(Bicyclo[1.1.1]pentan-1-yl)-3-(pyridin-3-yl)propan-1-ol, 131s



3-(Pyridin-3-yl)propanal **130s** (41 mg, 0.30 mmol, 1.5 equiv.), $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (3.7 mg, 4.0 μmol , 0.02 equiv.), 2,4,6-tri-*tert*-butylbenzenethiol **133a** (5.6 mg, 20 μmol , 0.1 equiv.), (*S*)- α,α -bis[3,5-bis(trifluoromethyl)phenyl]-2-

pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μ mol, 0.25 equiv.), water (7.2 μ L, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, EtOAc) afforded the title compound as a pale yellow oil (12 mg, 58 μ mol, 29%).

R_f 0.19 (EtOAc), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 8.51 – 8.43 (m, 2H, H6 and H9), 7.61 – 7.56 (m, 1H, H7), 7.25 – 7.23 (m, 1H, H8), 3.56 – 3.52 (m, 2H, H1), 2.68 – 2.59 (m, 2H, H5), 2.50 (s, 1H, H4), 1.94 – 1.88 (m, 1H, H2), 1.73 (dd, J = 9.6, 1.8 Hz, 3H, H3), 1.69 (dd, J = 9.6, 1.8 Hz, 3H, H3).

Note: the *OH* resonance was not observed.

¹³C NMR (126 MHz, CDCl₃) δ 149.9, 146.8, 137.3, 136.9, 123.6, 63.4, 49.9 (3C), 47.1, 43.6, 32.0, 27.8.

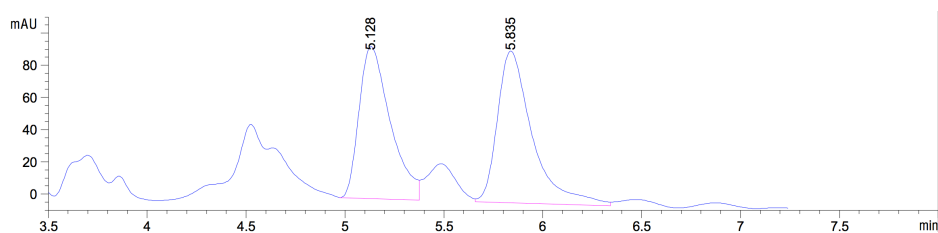
HRMS (ESI⁺) Found $[M+H]^+ = 204.1385$; C₁₃H₁₈ON requires 204.1383.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3219, 2962, 2917, 2867, 1479, 1279, 1140.

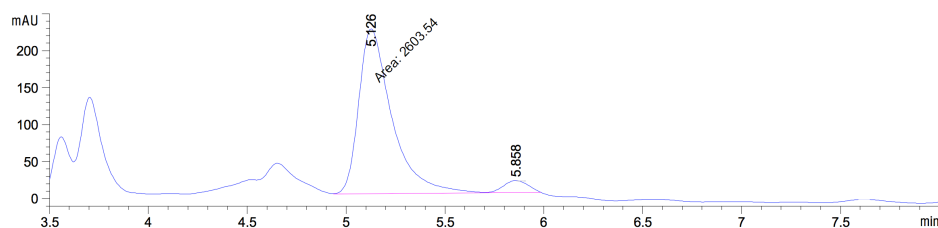
$[\alpha]_{\text{D}}^{25}$ –31.3 (c = 0.2, CHCl₃)

HPLC 90% *ee* (CHIRALPAK IB, 20% IPA/hexane, 1.3 mL/min, t_{R} major – 5.1 min, minor – 5.9 min).

Note: BCP product **131s** is slightly unstable to column chromatography and HPLC (under the specified conditions).

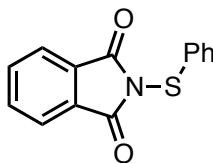


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.128	BV	0.1643	1039.00916	94.46390	47.2769
2	5.835	VV	0.1832	1158.70203	94.39435	52.7231



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.126	MM	0.1945	2603.54468	223.09227	94.8317
2	5.858	MM	0.1436	141.89253	16.47056	5.1683

***N*-(Phenylthio)phthalimide, S50**



According to the procedure of Zhao *et al.*^[108] To a solution of thiophenol (1.0 mL, 10 mmol, 1.0 equiv.) and Et₃N (0.14 mL, 1.0 mmol, 0.1 equiv.) in CH₂Cl₂ (10 mL) at 0 °C under an inert atmosphere was added a solution of sulfonyl chloride (0.81 mL, 10 mmol, 1.0 equiv.) in CH₂Cl₂ (2 mL). The reaction mixture was left to stir for 15 min at 0 °C and then allowed to warm to room temperature and stirred for a further 30 min. The reaction mixture was then cooled to 0 °C and the resulting solution was added dropwise to a solution of phthalimide (1.5 g, 10 mmol, 1.0 equiv.) and Et₃N (1.5 mL, 11 mmol, 1.1 equiv.) in CH₂Cl₂ (10 mL) at 0 °C. The resulting mixture was allowed to warm to room temperature and left to stir for 3 h. Water (20 mL) was then added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL).

The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by recrystallization (CH₂Cl₂/hexanes) afforded the title compound as white crystals (1.5 g, 5.8 mmol, 58%).

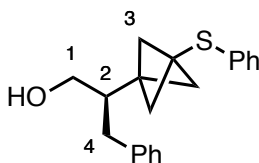
R_f 0.36 (pentane/Et₂O, 3:2), [UV, potassium permanganate]

¹H NMR (500 MHz, CDCl₃) δ 7.96 – 7.90 (m, 2H, ArH), 7.81 – 7.75 (m, 2H, ArH), 7.63 – 7.57 (m, 2H, ArH), 7.36 – 7.30 (m, 3H, ArH).

¹³C NMR (126 MHz, CDCl₃) δ 167.9 (2C), 135.2, 134.8 (2C), 132.2 (2C), 131.1 (2C), 129.5 (3C), 124.2 (2C).

Spectroscopic data in agreement with that reported previously.^[109]

(R)-3-Phenyl-2-(3-(phenylthio)bicyclo[1.1.1]pentan-1-yl)propan-1-ol, 131t



Hydrocinnamaldehyde (40 μL, 0.30 mmol, 1.5 equiv.), [Ir(ppy)₂(dtbbpy)]PF₆ (3.7 mg, 4.0 μmol, 0.02 equiv.), *N*-(phenylthio)phthalimide **S50** (0.20 g, 0.80 mmol, 4.0 equiv.), (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether **132a** (30 mg, 50 μmol, 0.25 equiv.), water (7.2 μL, 0.40 mmol, 2.0 equiv.) and [1.1.1]propellane **2** (1.02 M in Et₂O, 0.20 mL, 0.20 mmol, 1.0 equiv.) in Et₂O (0.3 mL) and DME (0.5 mL), and sodium borohydride (38 mg, 1.0 mmol, 5.0 equiv.) in MeOH (1 mL) and CH₂Cl₂ (1 mL) were submitted to **General Procedure E**. Purification by column chromatography (SiO₂, pentane/Et₂O, 17:3) afforded the title compound as a pale yellow oil (31 mg, 0.10 mmol, 50%).

R_f 0.45 (pentane/Et₂O, 1:1), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 7.45 – 7.41 (m, 2H, ArH), 7.32 – 7.23 (m, 5H, ArH), 7.20 – 7.13 (m, 3H, ArH), 3.52 (dd, $J = 10.8, 4.8$ Hz, 1H, H1), 3.48 (dd, $J = 10.8, 5.6$ Hz, 1H, H1), 2.60 (dd, $J = 13.9, 6.1$ Hz, 1H, H4), 2.54 (dd, $J = 13.9, 9.1$ Hz, 1H, H4), 2.00 (dq, $J = 9.1, 5.6$ Hz, 1H, H2), 1.86 (dd, $J = 9.5, 1.6$ Hz, 3H, H3), 1.82 (dd, $J = 9.5, 1.6$ Hz, 3H, H3).

Note: the OH resonance was not observed.

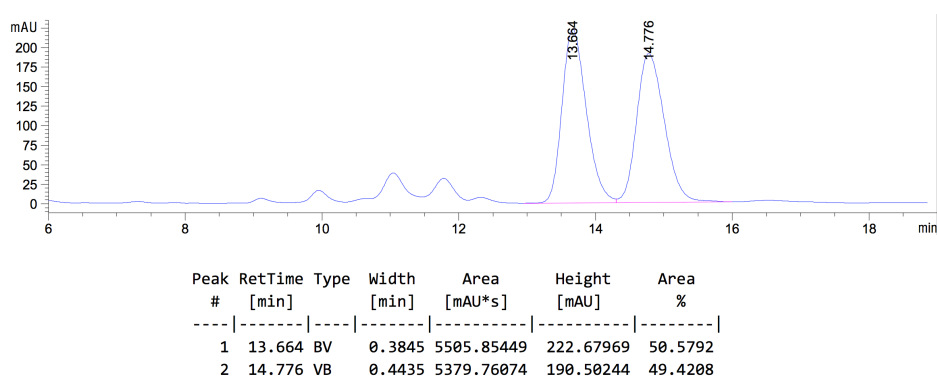
^{13}C NMR (126 MHz, CDCl_3) δ 140.4, 134.1, 133.8 (2C), 129.0 (2C), 128.9 (2C), 128.6 (2C), 127.7, 126.2, 63.7, 53.6 (3C), 51.9, 43.2, 41.9, 35.2.

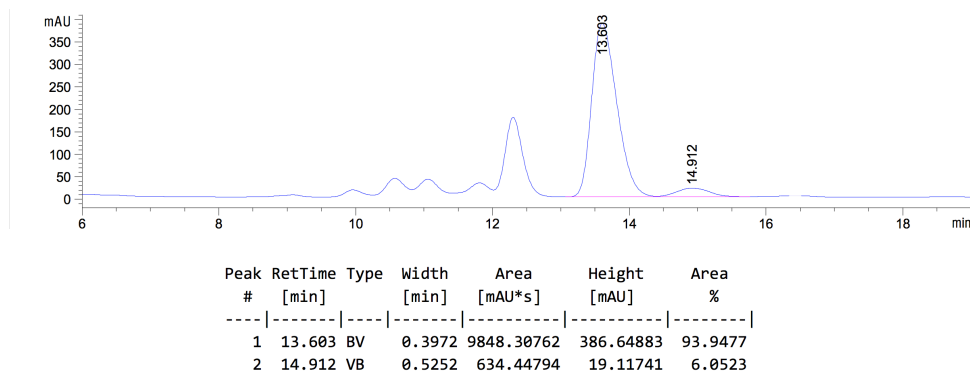
HRMS (ESI^+) Found $[\text{M}+\text{H}]^+ = 311.1465$; $\text{C}_{20}\text{H}_{23}\text{OS}$ requires 311.1464.

IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3381, 3027, 2966, 2911, 2872, 1583, 1496, 1474, 1454, 1439, 1280, 1192.

$[\alpha]_{\text{D}}^{25} -17.0$ ($c = 0.3$, CHCl_3)

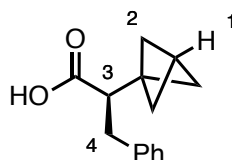
HPLC 88% ee (Lux i-Amylose-1, 5% IPA/hexane, 1.0 mL/min, t_{R} major – 13.6 min, minor – 14.9 min).





9.6.6 Derivatization of α -chiral BCP products

(*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)-3-phenylpropanoic acid, **138**



To a solution of (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-phenylpropanal **137** (obtained directly from the photoredox-catalyzed asymmetric reaction) (40 mg, 0.20 mmol, 1.0 equiv.) in CH₂Cl₂ (0.7 mL) and water (0.3 mL) at room temperature was added TEMPO (6.3 mg, 40 μ mol, 0.2 equiv.) and BAIB (0.13 g, 0.40 mmol, 2.0 equiv.). The reaction mixture was left to stir for 24 h. Upon completion, water (0.6 mL), Na₂S₂O₃ (aq., sat., 0.6 mL) and NaHCO₃ (aq., sat., 0.6 mL) were added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 $\times$ 1 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 4:1) afforded the title compound as a pale yellow (42 mg, 0.19 mmol, 97%).

R_f 0.31 (pentane/Et₂O, 7:3), [UV, vanillin]

^1H NMR (500 MHz, CDCl_3) δ 10.0 (br s, 1H, CO_2H), 7.30 – 7.16 (m, 5H, ArH), 2.94 – 2.82 (m, 2H, H4 and H3), 2.74 (dd, $J = 13.2, 4.0$ Hz, 1H, H4), 2.52 (s, 1H, H1), 1.77 (s, 6H, H2).

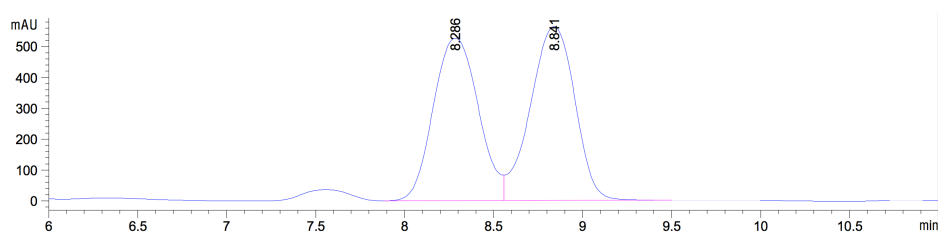
^{13}C NMR (126 MHz, CDCl_3) δ 177.5, 139.5, 128.8 (2C), 128.5 (2C), 126.4, 49.8 (3C), 49.6, 44.9, 34.9, 26.9.

HRMS (ESI^+) Found $[\text{M}+\text{Na}]^+ = 239.1043$; $\text{C}_{14}\text{H}_{16}\text{O}_2\text{Na}$ requires 239.1043.

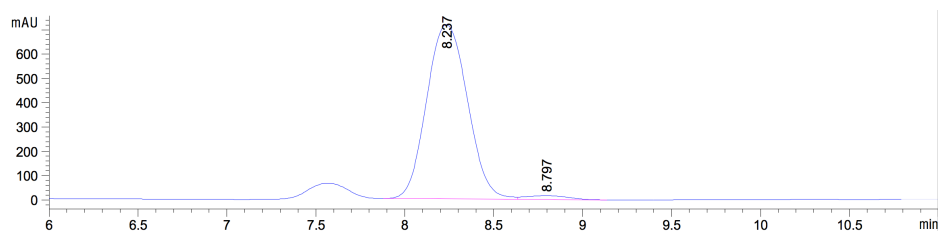
IR (film) $\nu_{\text{max}}/\text{cm}^{-1}$ 3029, 2968, 2909, 2873, 1705, 1496, 1455.

$[\alpha]_{\text{D}}^{25} -78.0$ ($c = 0.1$, CHCl_3)

HPLC 95% *ee* (CHIRALPAK IC, 2% IPA/hexane, 0.7 mL/min, t_{R} major – 8.2 min, minor – 8.8 min).

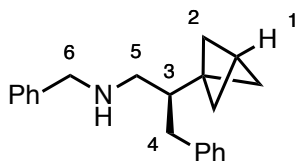


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.286	BV	0.2810	9254.02637	526.57086	48.5519
2	8.841	VB	0.2770	9806.04980	563.61884	51.4481



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.237	BV	0.2559	1.14472e4	718.57477	97.7289
2	8.797	VB	0.2592	266.02200	16.06785	2.2711

(R)-N-Benzyl-2-(bicyclo[1.1.1]pentan-1-yl)-3-phenylpropan-1-amine, 139



To a solution of (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-phenylpropanal **137** (obtained directly from the photoredox-catalyzed asymmetric reaction) (40 mg, 0.20 mmol, 1.0 equiv.) in DCE (3 mL) at room temperature under an inert atmosphere was added benzylamine (28 μ L, 0.26 mmol, 1.3 equiv.), acetic acid (15 μ L, 0.26 mmol, 1.3 equiv.) and Et₃N (39 μ L, 0.28 mmol, 1.4 equiv.). The reaction mixture was stirred vigorously for 15 min. Sodium triacetoxyborohydride (0.11 g, 0.50 mmol, 2.5 equiv.) was then added and the reaction mixture was stirred vigorously for 19.5 h. Upon completion, NaHCO₃ (aq., sat., 1.5 mL) and water (1 mL) were added. The phases were separated and the aqueous phase was extracted with CH₂Cl₂ (3 $\times$ 2 mL). The combined organic extracts were dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 7:3) afforded the title compound as a pale yellow oil (54 mg, 0.19 mmol, 93%).

R_f 0.64 (Et₂O), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.14 (m, 10H, ArH), 3.67 (d, *J* = 3.4 Hz, 2H, H6), 2.65 (dd, *J* = 13.9, 6.1 Hz, 1H, H4), 2.59 (dd, *J* = 11.8, 6.1 Hz, 1H, H5), 2.54 – 2.46 (m, 2H, H4 and H5), 2.45 (s, 1H, H1), 2.00 (dq, *J* = 8.9, 6.1 Hz, 1H, H3), 1.66 (dd, *J* = 9.5, 1.6 Hz, 3H, H2), 1.65 (dd, *J* = 9.5, 1.6 Hz, 3H, H2).

Note: the NH resonance was not observed.

¹³C NMR (126 MHz, CDCl₃) δ 141.4, 140.2, 129.1 (2C), 128.5 (2C), 128.4 (2C), 128.3 (2C), 127.0, 125.9, 54.1, 51.1, 49.6 (3C), 48.4, 41.3, 37.0, 27.4.

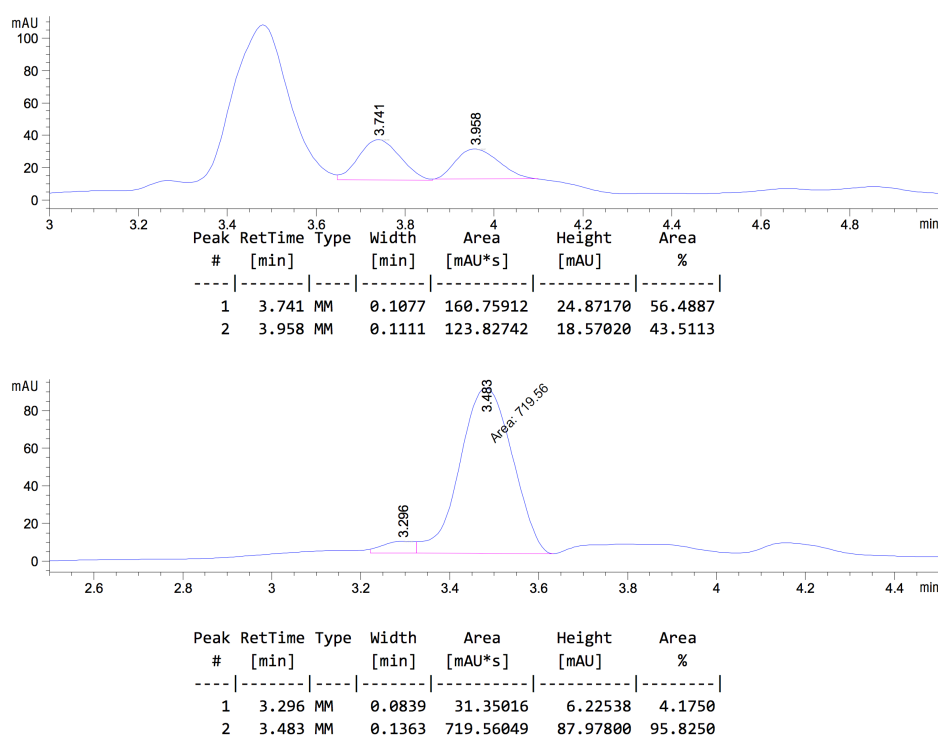
HRMS Molecular or pseudo molecular ions could not be found using ESI and APCI.

IR (film) $\nu_{\max}/\text{cm}^{-1}$ 2961, 2906, 2867, 1603, 1495, 1453, 1265, 1196.

$[\alpha]_{\text{D}}^{25} -85.9$ ($c = 0.1$, CHCl_3)

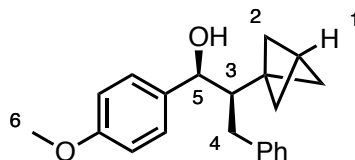
HPLC 92% *ee* (CHIRALPAK IB, 5% IPA/hexane, 1.0 mL/min, t_{R} major – 3.5 min, minor – 3.3 min).

Note: BCP product **139** is slightly unstable to HPLC (under the specified conditions).



(1*S*,2*R*)-2-(Bicyclo[1.1.1]pentan-1-yl)-1-(4-methoxyphenyl)-3-phenylpropan-1-ol,

140



To a solution of (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-phenylpropanal **137** (obtained directly from the photoredox-catalyzed asymmetric reaction) (40 mg, 0.20 mmol, 1.0 equiv.) in THF (1 mL) at $-78\text{ }^{\circ}\text{C}$ under an inert atmosphere was added

4-methoxyphenylmagnesium bromide (0.75 M in THF, 0.85 mL, 0.64 mmol, 3.2 equiv.) dropwise. The reaction mixture was allowed to warm to room temperature slowly and left to stir for 14 h. Upon completion, HCl (aq., 1 M, 1 mL) was added. The phases were separated and the aqueous phase was extracted with Et₂O (3 × 1 mL). The combined organic extracts were washed with water (2 mL) and brine (2 mL), dried (Na₂SO₄) and concentrated *in vacuo*. Purification by column chromatography (SiO₂, pentane/Et₂O, 9:1) afforded the title compound as a pale yellow (59 mg, 0.19 mmol, 95%, 14:1 *dr*).

R_f 0.12 (pentane/Et₂O, 9:1), [UV, vanillin]

¹H NMR (500 MHz, CDCl₃) δ 7.29 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.23 – 7.06 (m, 5H, Ar*H*), 6.88 (d, *J* = 8.7 Hz, 2H, Ar*H*), 4.80 (dd, *J* = 5.2, 2.2 Hz, 1H, H5), 3.81 (s, 3H, H6), 2.86 (dd, *J* = 14.3, 3.7 Hz, 1H, H4), 2.60 (dd, *J* = 14.3, 9.3 Hz, 1H, H4), 2.33 (s, 1H, H1), 2.22 (dt, *J* = 8.9, 4.2 Hz, 1H, H3), 1.56 (dd, *J* = 9.7, 1.8 Hz, 3H, H2), 1.52 (dd, *J* = 9.7, 1.8 Hz, 3H, H2).

Note: the OH resonance was not observed.

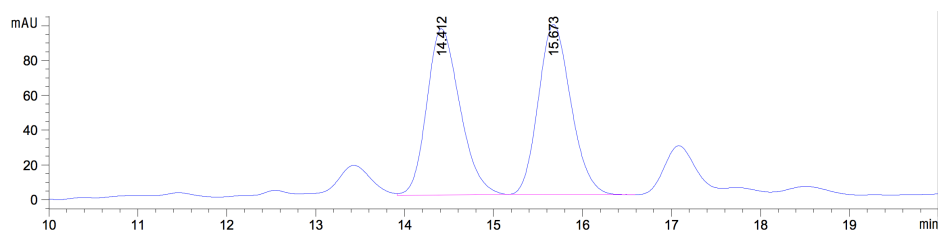
¹³C NMR (126 MHz, CDCl₃) δ 158.9, 142.1, 136.1, 129.1 (2C), 128.2 (2C), 127.5 (2C), 125.6, 113.8 (2C), 75.5, 55.4, 50.5 (3C), 48.4, 47.8, 32.6, 28.1.

HRMS Molecular or pseudo molecular ions could not be found using ESI, APCI.

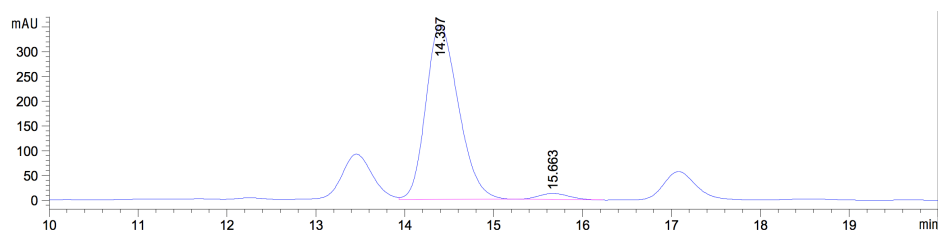
IR (film) ν_{max} /cm⁻¹ 3482, 3423, 2961, 2907, 2870, 1612, 1511, 1454, 1303, 1248, 1176.

[α]_D²⁵ –39.3 (*c* = 0.1, CHCl₃)

HPLC 94% *ee* (Lux i-Amylose-1, 5% IPA/hexane, 1.0 mL/min, *t_R* major – 14.4 min, minor – 15.7 min).

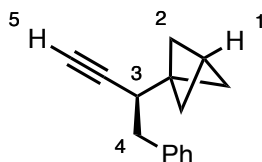


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.412	VB	0.3955	2467.87769	95.50046	49.7693
2	15.673	BB	0.3938	2490.75415	97.56338	50.2307



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.397	VB	0.3930	8950.46387	351.54779	96.7758
2	15.663	BB	0.3699	298.19360	12.42777	3.2242

(R)-1-(1-Phenylbut-3-yn-2-yl)bicyclo[1.1.1]pentane, 141



To a solution of (*R*)-2-(bicyclo[1.1.1]pentan-1-yl)-3-phenylpropanal **137** (obtained directly from the photoredox-catalyzed asymmetric reaction) (40 mg, 0.20 mmol, 1.0 equiv.) in MeOH (2 mL) at room temperature under an inert atmosphere was added dimethyl (1-diazo-2-oxopropyl)phosphonate (96 μ L, 0.40 mmol, 2.0 equiv.) and K_2CO_3 (55 mg, 0.40 mmol, 2.0 equiv.). The reaction mixture was left to stir for 19 h. Upon completion, water (4 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3×2 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2 , pentane) afforded the title compound as a clear oil (38 mg, 0.19 mmol, 97%).

R_f 0.10 (pentane), [UV, vanillin]

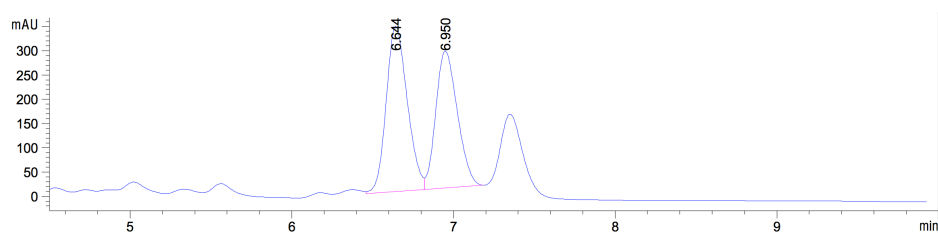
¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.18 (m, 5H, ArH), 2.79 (dd, *J* = 13.1, 4.8 Hz, 1H, H4), 2.71 (ddd, *J* = 10.2, 4.8, 2.4 Hz, 1H, H3), 2.60 (dd, *J* = 13.1, 10.2 Hz, 1H, H4), 2.53 (s, 1H, H1), 2.04 (d, *J* = 2.4 Hz, 1H, H5), 1.74 (s, 6H, H2).

¹³C NMR (126 MHz, CDCl₃) δ 139.8, 129.1 (2C), 128.3 (2C), 126.4, 84.6, 70.7, 48.9 (3C), 46.1, 38.2, 36.3, 27.0.

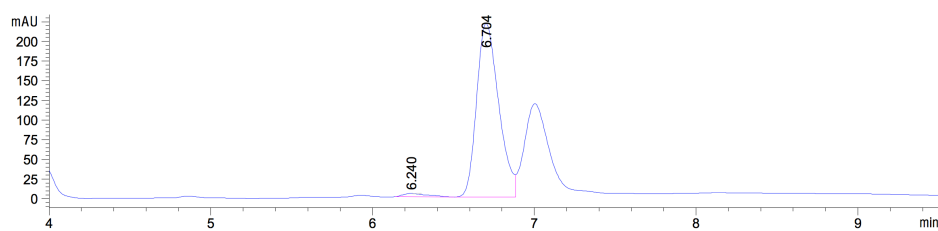
IR (film) ν_{max} /cm⁻¹ 3307, 2967, 2908, 2872, 1496, 1454, 1280, 1198.

[α]_D²⁵ –82.3 (*c* = 0.1, CHCl₃)

HPLC 96% *ee* (Lux i-Amylose-1, hexane, 0.8 mL/min, *t_R* major – 6.7 min, minor – 6.2 min).



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.644	VV	0.1416	3082.24292	340.47083	54.0212
2	6.950	VB	0.1445	2623.37793	282.16434	45.9788



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.240	MM	0.1769	45.59887	4.29621	2.1412
2	6.704	BV	0.1460	2083.96094	220.96255	97.8588

9.7 X-ray crystallography

X-ray crystallographic studies were carried out by Steven Mansfield.

Low temperature single crystal X-ray diffraction data were collected for **64k**, **64m** and **64t** with a (Rigaku) Oxford Diffraction SuperNova A diffractometer at 150 K. All data were reduced using CrysAlisPro, solved using SuperFlip^[110] and the structures were refined using CRYSTALS.^[111-112]

The Flack x parameter^[113-114] was refined in all cases. Bayesian analysis of the Bijvoet pairs was also carried out using all the data used in the refinement.^[115] This gave the Hooft y parameter, the P2 probability (the likelihood that the hand is correct given the crystal was enantiopure), and the P3 probability (the likelihood that the hand is correct given the crystal was enantiopure or racemic).

Further details about the refinements, including disorder modelling and restraints, are documented in the CIF.^[116]

Table S1. *Crystal data and structure refinement for 64k.*

Identification code	095eaa18	
Empirical formula	C ₂₂ H ₂₅ N ₁ O ₃	
Formula weight	351.45	
Temperature	150 K	
Wavelength	1.54180 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 9.75433(7) Å	$\alpha = 90^\circ$.
	b = 9.89360(7) Å	$\beta = 90^\circ$.
	c = 19.73792(18) Å	$\gamma = 90^\circ$.
Volume	1904.82(3) Å ³	
Z	4	
Density (calculated)	1.225 Mg/m ³	
Absorption coefficient	0.647 mm ⁻¹	
F(000)	752	
Crystal size	0.43 x 0.20 x 0.19 mm ³	
Theta range for data collection	4.480 to 76.531°	
Index ranges	-12 ≤ h ≤ 12, -12 ≤ k ≤ 12, -23 ≤ l ≤ 24	
Reflections collected	34166	
Independent reflections	4000 [R(int) = 0.0368]	
Completeness to theta = 76.531°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.88 and 0.56	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3986 / 0 / 236
Goodness-of-fit on F^2	1.0199
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0277$, $wR_2 = 0.0710$
R indices (all data)	$R_1 = 0.0279$, $wR_2 = 0.0712$
Largest diff. peak and hole	0.14 and -0.19 e.Å ⁻³
Absolute structure parameter (Flack)	0.01(12) for 1680 Friedel pairs
Absolute structure parameter (Hooft)	-0.07(4) for 1353 Friedel pairs
Hooft probability analysis	$P_2(\text{correct}) > 99.9999\%$, $P_3(\text{correct}) > 99.9999\%$

Table S2. *Crystal data and structure refinement for 64m.*

Identification code	094eaa18	
Empirical formula	C ₂₂ H ₂₇ N ₁ O ₅	
Formula weight	385.46	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 9.67686(10) Å	$\alpha = 90^\circ$.
	b = 10.71988(12) Å	$\beta = 90^\circ$.
	c = 19.62514(19) Å	$\gamma = 90^\circ$.
Volume	2035.81(4) Å ³	
Z	4	
Density (calculated)	1.258 Mg/m ³	
Absorption coefficient	0.725 mm ⁻¹	
F(000)	824.00	
Crystal size	0.46 x 0.12 x 0.07 mm ³	
Theta range for data collection	4.506 to 76.550°	
Index ranges	-12 ≤ h ≤ 12, -13 ≤ k ≤ 13, -24 ≤ l ≤ 24	
Reflections collected	35993	
Independent reflections	4280 [R(int) = 0.0470]	
Completeness to theta = 76.550°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.95 and 0.37	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4266 / 0 / 254
Goodness-of-fit on F^2	1.0130
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0287$, $wR2 = 0.0739$
R indices (all data)	$R1 = 0.0289$, $wR2 = 0.0742$
Largest diff. peak and hole	0.19 and -0.17 e.Å ⁻³
Absolute structure parameter (Flack)	0.00(11) for 1775 Friedel pairs
Absolute structure parameter (Hooft)	-0.01(4) for 1494 Friedel pairs
Hooft probability analysis	$P2(\text{correct}) > 99.9999\%$, $P3(\text{correct}) > 99.9999\%$

Table S3. *Crystal data and structure refinement for 64t.*

Identification code	096eaa18	
Empirical formula	C19 H23 N1 O4	
Formula weight	329.40	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21	
Unit cell dimensions	a = 11.4906(5) Å	$\alpha = 90^\circ$.
	b = 5.7102(3) Å	$\beta = 96.797(4)^\circ$.
	c = 12.8377(5) Å	$\gamma = 90^\circ$.
Volume	836.41(6) Å ³	
Z	2	
Density (calculated)	1.308 Mg/m ³	
Absorption coefficient	0.744 mm ⁻¹	
F(000)	352	
Crystal size	0.28 x 0.06 x 0.02 mm ³	
Theta range for data collection	3.467 to 76.740°.	
Index ranges	-14 ≤ h ≤ 14, -7 ≤ k ≤ 6, -16 ≤ l ≤ 16	
Reflections collected	14054	
Independent reflections	3378 [R(int) = 0.0401]	
Completeness to theta = 76.740°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.99 and 0.70	

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3364 / 1 / 218
Goodness-of-fit on F^2	1.0012
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0323$, $wR2 = 0.0823$
R indices (all data)	$R1 = 0.0354$, $wR2 = 0.0854$
Largest diff. peak and hole	0.19 and -0.14 e.Å ⁻³
Absolute structure parameter (Flack)	0.09(17) for 1365 Friedel pairs
Absolute structure parameter (Hooft)	0.02(11) for 1124 Friedel pairs
Hooft probability analysis	$P2(\text{correct}) > 99.9999\%$, $P3(\text{correct})$ 99.8552%

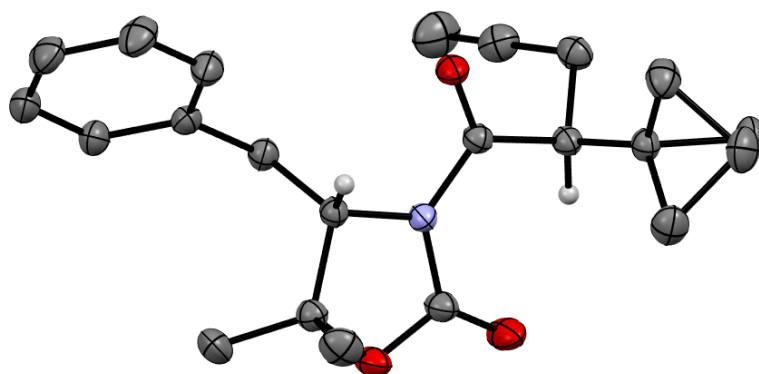


Figure S1. Solid state structure of **64k**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms (except at the stereocentres) have been omitted for clarity.

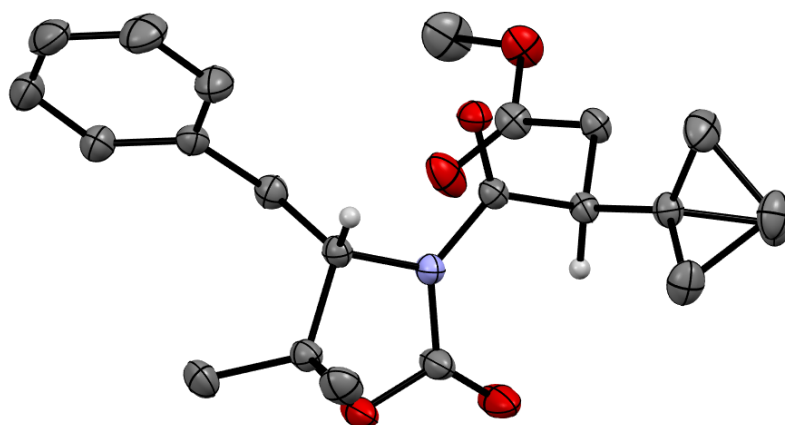


Figure S2. Solid state structure of **64m**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms (except at the stereocentres) have been omitted for clarity.

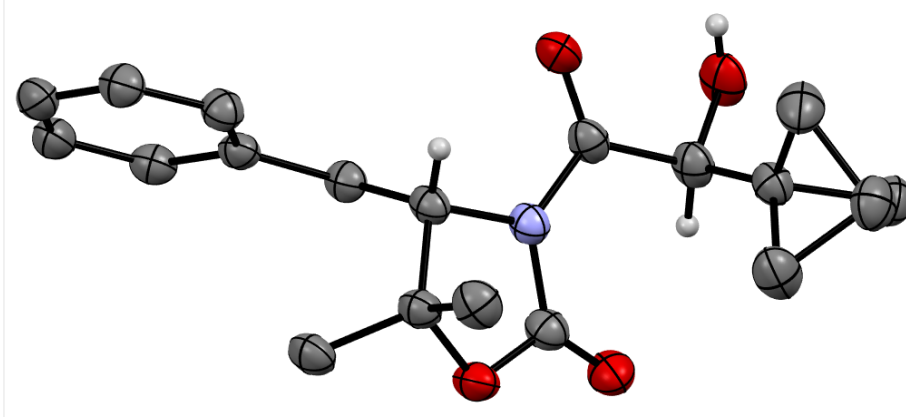


Figure S3. Solid state structure of **64t**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms (except at the stereocentres and the hydroxyl) have been omitted for clarity.

9.8 References

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