New Directions Towards the Synthesis of Bicyclo[1.1.1]pentane Derivatives

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Abstract

Bicyclo[1.1.1]pentanes have emerged as bioisosteres, used by medicinal chemists to replace 1,4-disubstituted arenes and improve the physicochemical properties of the drugs they synthesise. The existing methods to synthesise 1,3-disubstituted bicyclo-[1.1.1]pentane involve toxic reagents, hazardous chemistries and lengthy synthetic sequences. We present in this thesis a novel, modular way to access 1,3-disubstituted bicyclo[1.1.1]pentane as well as monosubstituted bicyclo[1.1.1]pentane (Figure 1). The first chapter presents a triethylborane-initiated atom transfer radical addition reaction of organohalides on tricyclo[1.1.1.$0^{1,3}$]pentane (**1**) to access in a rapid and efficient manner brominated and iodinated bicyclo[1.1.1]pentane (**2**). The reduction of the C–I bond of iodinated bicyclo[1.1.1]pentanes is presented in the second chapter. Tris(trimethylsilyl)silane was used as the reducing agent and triethylborane as the initiator, providing a less toxic alternative to tin hydride reductions and affording monosubstituted bicyclo[1.1.1]pentanes building blocks such as acids, amides, amines and amino acids (**3**). Nucleotides, peptides and drugs were successfully labelled with a bicyclo[1.1.1]pentane unit. The third chapter focusses on an iron-catalysed Kumada-Tamao-Corriu cross-coupling reaction of iodinated bicyclo[1.1.1]pentane to form arylated bicyclo[1.1.1]pentane (**4**). The reaction is particularly efficient with electron-rich organomagnesium reagents. A analogue to the drug Flurbiprofen was synthesised in excellent yield in just two steps from ethyl 2-iodopropionate and **1**.

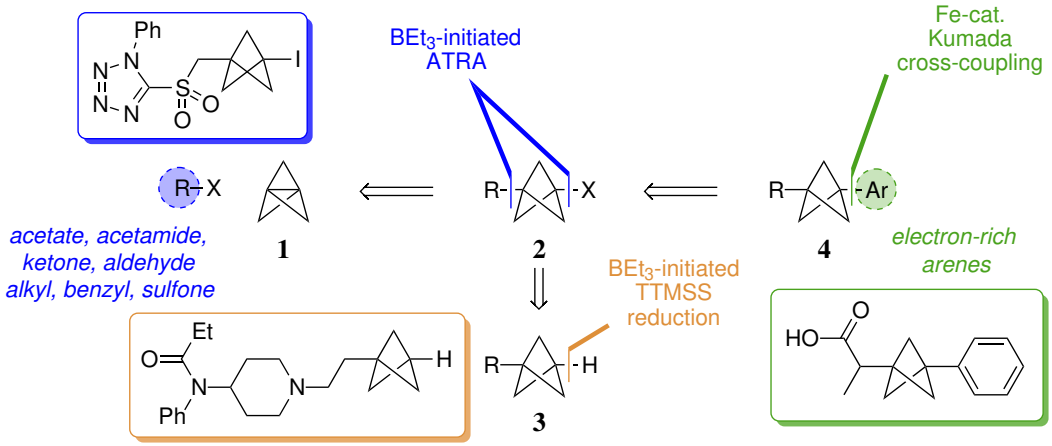

Figure 1: Synthesis of monosubstituted and disubstituted bicyclo[1.1.1]pentane derivatives

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Statement of authorship

This work was done at the Chemistry Research Laboratory, Department of Chemistry, University of Oxford between Michaelmas 2014 and Michaelmas 2018.

Dr Carlos Arroniz kindly prepared and characterised compounds **149, 150, 151, 152, 153, 158, 160, 162, 164, 165, 166, 167, 168, 181, 182, 183, 184, 185, 186, 187, 188, 189, 192, 200, 207, 238, 239 and 268**.

Ms Helen Jones kindly prepared and characterised compounds **214** and **215**.

Ms Bethany Shire kindly prepared and characterised compound **291** and performed a reaction using methylmagnesium bromide (Figure 4.11, Section 4.2.4).

Ms Helena Pickford kindly performed a reaction using tert-butylmagnesium chloride (Figure 4.11, Section 4.2.4).

Dr Alexander Dürr kindly performed and processed the computational calculation data (Section 2.8).

Mr Steven Mansfield kindly measured and processed the crystallographic data for compounds **179, 182, 197, 198, 253**.

Mr Dimitri Caputo

Contents

List of Abbreviations

Ac . . . . . Acetyl.

acac . . . . . Acetylacetonate.

AIBN . . . . . Azobisisobutyronitrile.

Ar . . . . . Aryl.

ATRA . . . . . Atom transfer radical addition.

ATRC . . . . . Atom transfer radical cyclisation.

BCP . . . . . Bicyclo[1.1.1]pentane.

BDE . . . . . Bond dissociation energy.

Bn . . . . . Benzyl.

Boc . . . . . *tert*-Butoxycarbonyl.

bpy . . . . . 2,2′-Bipyridine.

***n*Bu** . . . . . *n*-Butyl.

***t*Bu** . . . . . *tert*-Butyl.

$\mathbf{Cl_{int,app}}$ . . . . . Apparent intrinsic clearance.

CPME . . . . . Cyclopropyl methyl ether.

Cy . . . . . Cyclohexyl.

DABCO . . . . 1,4-diazabicyclo[2.2.2]octane.

dbm . . . . . Dibenzoylmethide.

DBU . . . . . 1,8-Diazabicyclo[5.4.0]undec-7-ene.

dcypt . . . . . 3,4-Bis(dicyclohexylphosphino)thiophene.

DIPEA . . . . . *N,N*-diisopropylethylamine.

DME . . . . . 1,2-dimethoxyethane.

DMEDA . . . . N,N′-Dimethylethylenediamine

DMF . . . . . *N,N*-Dimethylformamide.

DMM . . . . . 2,2-dimethoxymethane.

DMPU . . . . . 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone.

DNA . . . . . Deoxyribonucleic acid.

dpm . . . . . Dipivaloylmethide.

dppBz . . . . . 1,2-Bis(diphenylphosphino)benzene.

dppf . . . . . 1,1′-Ferrocenediyl-bis(diphenylphosphine).

dtbbpy . . . . . 4,4′-Di-tert-butyl-2,2′-dipyridyl.

e.g. . . . . . *exempli gratia* (for example).

ElogD . . . . . Experimental distribution constant.

EPR . . . . . Electron paramagnetic resonance.

Et . . . . . Ethyl.

EtOAc . . . . . Ethyl acetate.

Et_2O . . . . . Diethyl ether.

***n*Hept** . . . . . *n*-Heptane.

HLM . . . . . Human liver microsome.

HOBt . . . . . Hydroxybenzotriazole.

IC_{50} . . . . . Half maximal inhibitory concentration.

i.e. . . . . . *id est* (that is).

LiDBB . . . . . Lithium di-tert-butylbiphenylide.

logD . . . . . Distribution constant.

logP . . . . . Patition coefficient.

m . . . . . *meta*.

Me . . . . . Methyl.

MeCN . . . . . Acetonitrile.

MeOH . . . . . Methanol.

MTBE . . . . . Methyl tert-Butyl ether.

NMP . . . . . *N*-methylpyrrolidine

NMR . . . . . Nuclear Magnetic Resonance.

NOESY . . . . . Nuclear Overhauser Effect Spectroscopy.

o . . . . . *ortho*.

ots . . . . . over two steps.

p . . . . . *para*.

Pc . . . . . Phthalocyanine.

Ph . . . . . Phenyl.

pKa . . . . . Acid dissociation constant.

PMDTA . . . . *N,N,N′,N″,N″*-pentamethyldiethylenetriamine.

***i*Pr** . . . . . Isopropyl.

***n*Pr** . . . . . *n*-Propyl.

rt . . . . . Room temperature.

S_2H . . . . . Homolytic substitution.

SM / P . . . . . Ratio starting material to product.

TBAF . . . . . Tetra-*n*-butylammonium fluoride.

TBAI . . . . . Tetra-*n*-butylammonium iodide.

TBHP . . . . . *tert*-Butyl hydroperoxide.

TBS . . . . . *tert*-Butyldimethylsilyl.

1,3,5-TCH . . . 1,3,5-trimethyl-1,3,5-triazocyclohexane.

1,4,7-TCN . . . 1,4,7-trimethyl-1,4,7-triazocyclononane.

TCP . . . . . Tricyclo[1.1.1.$0^{1,3}$]pentane.

TfO . . . . . Trifluoromethanesulfonyl.

THF . . . . . Tetrahydrofuran.

THP . . . . . Tetrahydropyran.

TMCD . . . . . Tetramethylcyclohexanediamine.

TMEDA . . . . *N,N,N′,N′*-Tetramethylethylenediamine.

TMPA . . . . . tris(2-pyridylmethyl)amine.

TMS . . . . . Trimethylsilyl.

TM . . . . . Transition metal.

Ts or tosyl . . . Toluenesulfonyl.

p-TsOH . . . . para-Toluenesulfonic acid.

TTMSS . . . . . Tris(trimethylsilyl)silane.

UV . . . . . Ultraviolet.

X . . . . . Halogen.

1 Introduction

Contents

Medicinal chemists constantly battle to synthesise bioactive molecules that also possess appropriate physicochemical properties. Often, molecules may be highly active in a lab-based assay, but their solubility or permeability may be so poor that they cannot reach their biological targets once in a living organism (i.e. poor bioavailability). One solution

is the use of bioisosteres, motifs that substitute for problematic functionalities such that the physicochemical properties of the candidate are improved while the biological activity is ideally unchanged. For example, bicyclo[1.1.1]pentane (BCP) derivatives, five-membered carbon bicycles, have been used to replace a 1,4-disubstituted benzene ring in a potential drug candidate as shown in Figure 1.1.

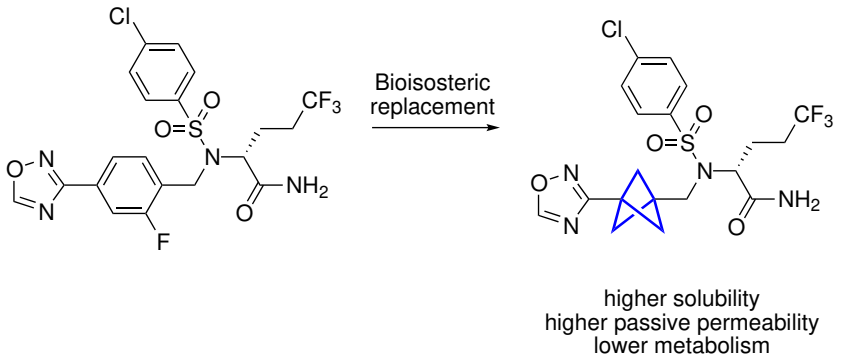


Figure 1.1: Bioisosteric replacement of a 1,4-disubstituted aryl group with bicyclo[1.1.1]pentane[1]

Before addressing BCP derivatives which will be the focus of this thesis, the concepts of isosterism and bioisosterism will to be introduced.

1.1 Isosterism

The first mention of isosterism dates back to 1919 in a paper published by Langmuir entitled "Isomorphism, Isosterism, and Covalences".[2,3] Building on the octet rule for the valence shell of main group atoms, and the fact that elements in groups of the periodic table share similarities, he hypothesised that isoelectronic molecules should share similar properties. His theory was confirmed by the comparison of the physical properties of nitrous oxide and carbon monoxide (Table 1.1).

Table 1.1: Comparison between N_2O and CO_2.

Selected properties	N_2O	CO_2
Critical pressure (atm)	75	77
Critical temperature (°C)	35.4	31.9
Viscosity at 20 °C	148×10^{-6}	148×10^{-6}
Heat conductivity at 100 °C	0.0506	0.0506
Refractive index of liquid, D line, 16 °C	1.193	1.190
Dielectric constant of liquid at 0 °C	1.598	1.582

However, Langmuir noted that the comparison is not universal: the freezing point of nitrous oxide is -102 °C while that of carbon dioxide is -56 °C. Nevertheless, he gives a definition of isosterism:

"*Compounds showing a relationship to one another like that between carbon dioxide and nitrous oxide will be called isosteric compounds, or isosteres. These terms, however, are not to be restricted to chemical compounds but are applicable to chemical radicals or to groups of atoms which hold pairs of electrons in common. A comolecule is defined as a group of atoms held together by pairs of electrons shared by adjacent atoms. Comolecules are thus isosteric if they contain the same number and arrangement of electrons. The comolecules of isosteres must, therefore, contain the same number of atoms.*"

According to that definition, he lists atoms, molecules and ions together to produce 21 groups of isosteric entities, a few of which are shown in Table 1.2.

Table 1.2: Isosteres according to Langmuir.

Type	Isosteres
1	H^-, He, Li^+
2	O^{2-}, F^-, Ne, Na^+, Mg^{2+}, Al^{3+}
3	S^{2-}, Cl^-, Ar, K^+, Ca^{2+}
4	Cu^+, Zn^{2+}
5	Br^-, Kr, Rb^+, Sr^{2+}

In 1925, Grimm's contribution extended this concept with the "Hydride displacement law":[4,5]

"*Atoms anywhere up to four places in the periodic system before an inert gas change their properties by uniting with one to four hydrogen atoms, in such manner that the resulting combinations behave like pseudoatoms, which are similar to elements in the group one to four places, respectively, to the right.*"

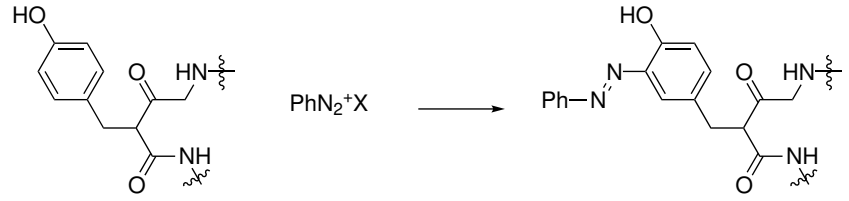
In other words, a pseudoatom is an atom linked to one or more hydrogen atoms wherein the proton is assumed to penetrate the electron shell of the larger atom enough so that the whole assembly can be approximated by the atom next in line in the pe-

riodic table. As exemplified in Table 1.3, atoms and pseudoatoms in each column are isosteric to each other.

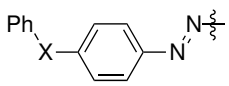
Table 1.3: Grimm's hydride replacement law.

C	N	O	F	Ne
	CH	NH	OH	HF
		CH_2	NH_2	OH_2
			CH_3	NH_3

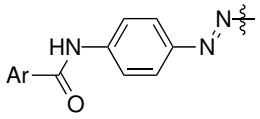
The concept of isosterism was generalised by Erlenmeyer in 1932 and for the first time applied to biological activities instead of physical properties.[6] Landsteiner showed that when antigen **5** was modified by reaction with diazonium salts **6** and injected into animals, an antibody specific to **7a** was produced (Scheme 1.1).[3,7] Building on that work, Erlenmeyer synthesised antigens **7b**, **7c** and **7d** and showed they had similar antigenic properties The same observation could be made for compounds **7e** and **7f**. This is the first example of isosteric replacement in a biological system.



5 **6** **7a**



7b X = O
7c X = NH
7d X = CH_2



7e Ar = Ph
7f Ar = 2-thiophenyl

Scheme 1.1: Modification of antigens[3,6,7]

As reported by Brown, Erlenmeyer proposed a new definition of isosteres:

[...]elements, molecules or ions in which the peripheral layers of electrons may be considered identical.[8]

Therefore, each element of the same group in the periodic table is an isostere of the other

members of the same group. Furthermore, he included pseudoatoms ("groups that appear different but that possess very similar physical properties") such as pseudohalogens (e.g. Cl $\approx$ CN $\approx$ SCN). Furthermore, as shown in the example above with compounds **7e** and **7f**, where the experiment showed that in this precise biological system $-$CH=CH$-$ $\approx$ $-$S$-$, he noted the importance of rings and their potential isosteric substitutes. With these definition and observation, isosterism translates into bioisosterism, namely the substitution of atoms, molecules or ions within a chemical entity resulting in a range of similar biological activities, rather than similar physical properties.

1.2 Bioisosterism

In 1951, Friedman defined compounds as bioisosteric "if they fit the broadest definition for isosteres and have the same type of biological activity."[9] He suggested that the molecules compared should operate *via* the same biochemical mechanism and in the same assay in order to make meaningful comparisons. Although including previous concepts of isosterism and the mentioning of biological systems, this definition overlooks the modification of physicochemical properties when operating bioisosteric replacements. Thornber, who defines bioisosteres as "groups or molecules which have chemical and physical similarities producing broadly similar biological properties", describes the properties to consider:[10]

- Size
- Shape (bond angles and hybridisation)
- Electronic distribution (polarisability, inductive effects, charge and dipoles)
- Lipid solubility
- Water solubility
- pK_a
- Chemical reactivity (in particular metabolism)
- Hydrogen bonding capacities

Depending on what properties are modified, bioisosteric replacements are categorised in terms of application:

- *Structural*. The modified group acts as a spacer, it holds substituents together in a particular configuration. Size and bond angles will be important properties.
- *Receptor interactions*. The modified group is in direct interaction with the biological system. Its size, shape, electronic distribution, pK_a, chemical reactivity and hydrogen bonding will be key parameters.

- *Pharmacokinetics*. The modified group is key in the absorption, transport and excretion of the molecule. Properties like solubilities, hydrogen bonding and pK_a will be crucial.
- *Metabolism*. The modified group prevents or facilitates metabolism. Chemical reactivity will be the critical factor.

In an attempt to include all previous definition and extensions, Burger defines bioisosteres as "*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.*"[3] This definition is the one that we will retain for being the most inclusive.

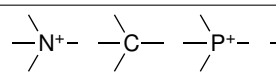
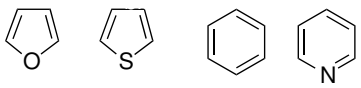
1.3 Classification of bioisosteres

Bioisosteres are usually divided into two groups: classical and non-classical bioisosteres.[8,11] Classical bioisosteres defines groups of bioisosteres that are visually similar. Non-classical bioisostere encompasses bioisosteres that do not appear similar to each other.

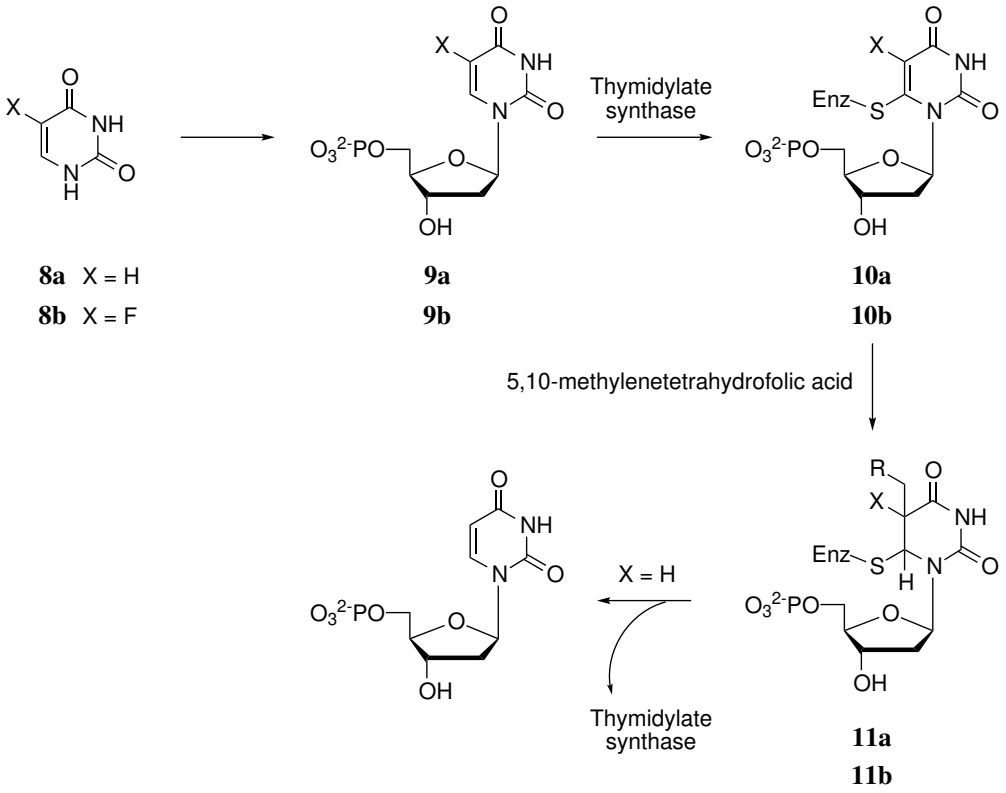
1.3.1 Classical bioisosteres

Classical bioisosteres can be classified as monovalent atoms or groups, divalent atoms or groups, trivalent atoms or groups, tetrasubstituted atoms, and ring equivalents. Examples of each class are given in Table 1.4.

Table 1.4: Categories of classical bioisosteres.

Monovalent	**Divalent**
F, H OH, NH F, OH, NH, or CH_3 for H SH, OH Cl, Br, CF_3	−C=S −C=O −C=NH −C=C−
Trivalent	**Tetrasubstituted**
	
Ring equivalents	
	

The replacement of a hydrogen atom by a fluorine atom has been used quite extensively in medicinal chemistry. One example is the analogue of uracil (**8a**), the anti-cancer agent 5-fluorouracil (**8b**, Scheme 1.2).[5] **8b** is first metabolised into 5-fluoro-2′-deoxyuridylic acid (**9b**), which inhibits thymidylate synthase (an enzyme involved in the conversion of uridylic acid to thymidylic acid, a process crucial for DNA synthesis) by reaction with thymidylate synthase to form **10b** that reacts further with 5,10-methylenetetrahydrofolic acid to yield **11b**. When the fluorine atom is not present, **11a** undergoes elimination to give the nucleotide and thymidylate synthase. However, when the fluorine is incorporated, **11b** cannot eliminate and the enzyme is inhibited. This represents a powerful example of bioisosterically induced metabolic blockage.



8a X = H
8b X = F

9a
9b

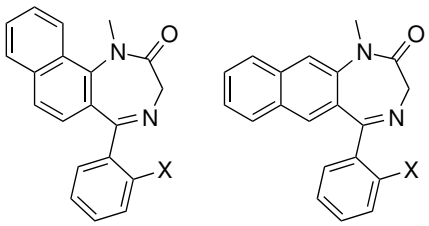
10a
10b

11a
11b

Scheme 1.2: Mode of action of uracil (**8a**) and 5-fluorouracil (**8b**).

Another H-F bioisosteric replacement is that of naphthyl-fused diazepines, which are used as an agonistic probe to the pharmacophore of benzodiazepine receptors (Table 1.5).[12] When replacing hydrogen by a fluorine atom on the phenyl ring attached to the imine in compound **12** and **13**, the binding affinity for the receptor increases drastically.

Table 1.5: Benzodiazepine receptor binding affinities for **12** and **13**.

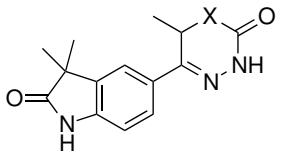


12 **13**

Compound	X	IC_{50} (nM)
12a	H	1000
12b	F	260
13a	H	1000
13b	F	55

An example of ring substitution is that of cardiac phosphodiesterase SR-PDE inhibitors **14**. When X was replaced in these indolones by different divalent isosteres, the inhibition properties were conserved (Table 1.6).[13]

Table 1.6: Inhibition of SR-PDE by indolones **14**.



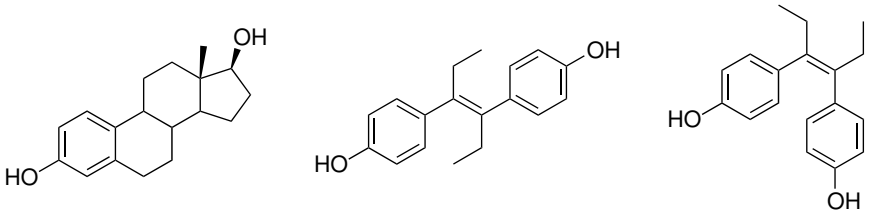
14

Compound	X	IC_{50} (μM)
14a	S	0.33
14b	CH_2	0.24
14c	NH	0.17
14d	O	0.96
14e	Se	0.54

1.3.2 Non-classical bioisosteres

Non-classical bioisosteres are bioisosteres that differ slightly from the definition of bioisosteres. Namely, they appear less similar to the group or functionality they replace. Nonetheless, they mimic electronic or steric properties that allow for the retention of biological activity. Non-classical bioisosteres are divided into two classes: Non-cyclic vs. cyclic bioisosteres and non-classical replacement of functional groups. The first class contains non-cyclic functionalities that mimic a ring, or cyclic functionalities that mimic an acyclic moiety.

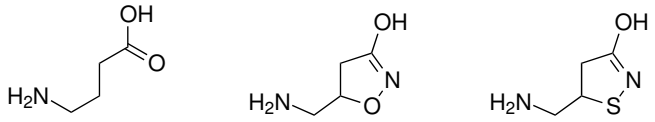
While searching for synthetic analogues of estradiol (**15**, Figure 1.2), Dodds *et al.* found that (*E*)-diethylstilbestrol (**16**) displayed high affinity for estrogen receptors.[14] The authors noted the similarity between the structure of **15** and **16** and realised that the stereochemistry of the double bond was crucial for binding, likely owing to the orientation of the phenolic hydroxyls. The other diastereomer displayed an order of magnitude reduced affinity.[15] Here, the acyclic alkene is a bioisostere for the steroidal BC rings.



15 **16** **17**

Figure 1.2: Structures of Estradiol and its analogues.

Conversely, cyclic analogues of 4-aminobutanoic acid (GABA, **18**, Figure 1.3) such as muscimol (**19**) and thiomuscimol (**20**), were developed by Krogsgaard-Larsen *et al.* and proved to be potent agonists of $GABA_A$ receptors.[16,17]



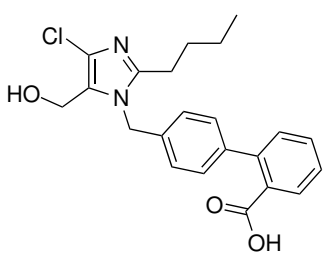
18 **19** **20**

Figure 1.3: Structures of Estradiol and its analogues.

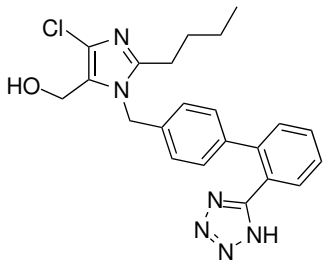
The second class of non-classical bioisosteres contains groups that replace functional groups although their structure appears somewhat different. A prime example is the replacement of carboxylic acids by heteroaromatic rings. For instance, Carini *et al.* developed a series of nonpeptidic angiotensine II receptors antagonist, antihypertensive compounds which were active when injected intravenously but displayed poor oral activity.[18] By replacing the carboxylic acid in of **21** (Table 1.7) with a tetrazole substituent in derivative **22** led to greater binding affinity to the AII receptor while maintaining the same level of acidity. Furthermore, the oral bioavailability proved much higher than that of **21**.

Another interesting bioisostere is the oxetane ring. When used in lieu of a carbonyl group, it can prevent epimerization at adjacent stereocentres and improve the metabolic stability as shown by Wuitschik *et al.* The demonstrated that spirocyclic piperidine **23** was cleared at a much slower rate than its piperidone counterpart **24** (Table 1.8) in both humans and mice. It is interesting to note that the incorporation of the oxetane moiety increases the pKa of the proximal amine, as well as the lipophilicity of the molecule. Consequently, its aqueous solubility is reduced.

Table 1.7: Non-classical bioisosteric replacement in antihypertensive agent **21**.



21

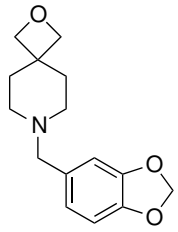


22

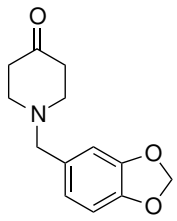
Compound	Estimated pKa	IC_{50} (μM)[a]	In vivo activity IV[b]	In vivo activity oral[b]
21	5	0.23	3	$ED_{30} = 11$
22	5−6	0.019	$ED_{30} = 0.80$	$ED_{30} = 0.59$

[a]Inhibition of specific binding of [^{3}H]angiotensin II (2 nM) to rat adrenal cortical microsomes. [b]Blood pressure lowering activity in renal hypertensive rats. The values indicate doses in mg.kg^{-1} at which statistically significant drops blood pressure were observed (>15 mmHg). ED_{30} is the effective dose in mg.kg^{-1} that lowers the blood pressure by 30 mmHg.

Table 1.8: Oxetanes as carbonyl bioisostere.



23



24

Compound	pKa[a]	log P[b]	Solubility[c]	Cl_{int} (human/mouse)[d]
23	8.3	2.0	1400	6/22
24	7.5	1.6	4000	120/88

[a]In water at 24 °C. [b]Intrinsic lipophilicity of the neutral base according to the equation log P=log D+$\log_{10}(1+10^{pK_a-pH})$ with log P being the logarithmic *n*-octanol/water distribution coefficient at pH=7.4. [c]Intrinsic solubility of the neutral base. Values obtained from the experimental thermodynamic solubility [μg.mL^{-1}] in phosphate buffer (50mM) at pH 9.9 and 22.5 ±1 °C and corrected for the pK_a value. [d]Intrinsic clearance rates [min^{-1}.mg^{-1}.μL].

The last example in this selection of non-classical bioisosteres is of prime importance to the research in this project: the bicyclo[1.1.1]pentane (BCP) unit (Figure 1.4). This five-membered carbon bicycle has been mainly used as a bioisostere for 1,4-disubstituted aryl groups (Figure 1.4a),[1] but also for *tert*-butyl (Figure 1.4b)[19] and acetylenic group (Figure 1.4c).[20]

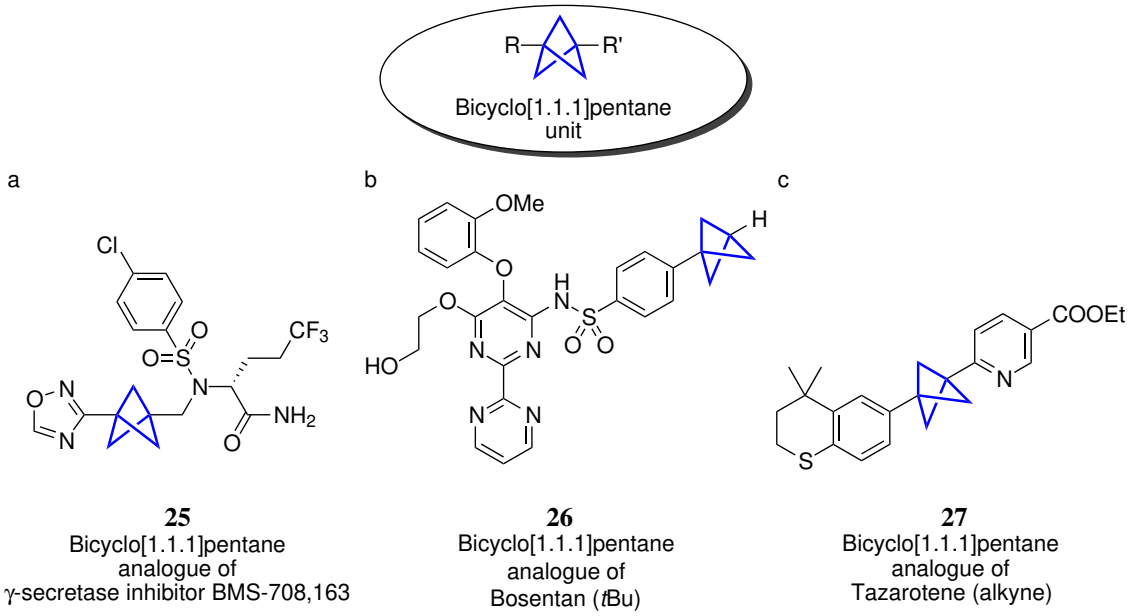


Figure 1.4: BCP structure and examples of application.

Structurally, the 1,3-disubstituted BCP group positions two substituents at 180° from each other, as would a *para*-substituted arene or a disubstituted triple bond. Generally, the unit replaced by a BCP group is not crucial to the biological activity, and consequently the surrogate molecule has roughly the same activity as the original one. Nonetheless, the BCP moiety is shorter than a benzene ring by about 0.95 Å as shown in Table 1.9 with γ-secretase inhibitor BMS-708,163 (**28**) and its bioisostere **25**.

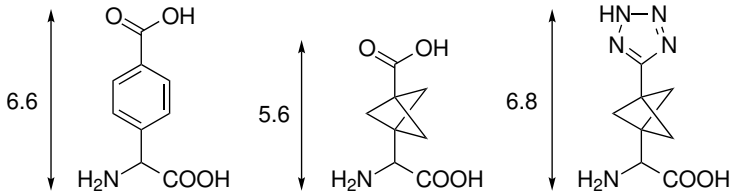
Table 1.9: Comparision of bond length values in the crystal structures[1] between **28** and **25**.

28
γ-secretase inhibitor BMS-708,163

25

Distance (in Å)	**28**	**25**
C2-C3	2.821	1.868
C1-C4	5.781	4.859

Pellicciari and co-workers showed that this shortening could be overcome by using a second bioisostere to increase the overall size of the molecule.[21] While studying the effect of the replacement of the *para*-substituted phenyl ring in **29** (Figure 1.5), a metabotropic glutamate receptors antagonist, they realised that the BCP derivative compound **30** was shorter by about 1 Å. However, by replacing the carboxylate moiety with a tetrazole, the length of **31** was similar to that of **29**.



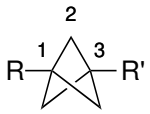
29 **30** **31**

Figure 1.5: Comparision of length values between **29**, **30** and **31** (in Å).

Levin *et al.* have compiled a comprehensive range of bond lengths and angles of BCP derivatives, measured by electron diffraction, X-ray diffraction and microwave spectroscopy.[22] Table 1.10 displays a summary, concentrating on bridge-unsubstituted BCPs.

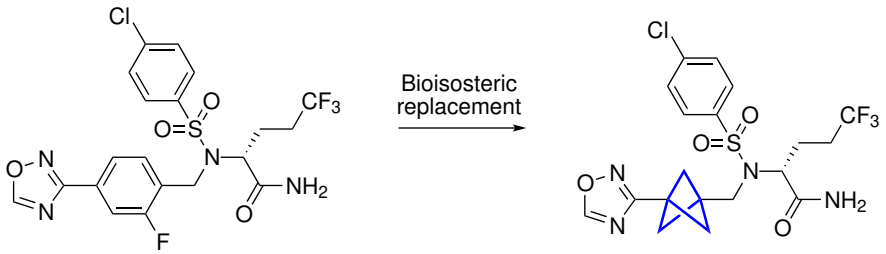
As discussed before, the use of a BCP unit results in the modification of physico-chemical properties as reported by Stepan and co-workers (Table 1.11).[1] Compounds **28** and **25** showed similar potency against the production of β-amyloid pepetide, but the

Table 1.10: Average bond distances and angles in bicyclo[1.1.1]pentane derivatives.



Geometrical feature	Range
Distance C1-C3 (in Å)	1.80−1.891
Distance C1/3-C2 (in Å)	1.51−1.561
Angle C1-C2-C3 (in deg)	71.2−75.21
Angle C2-C1-C2' (in deg)	86.0−90.2
Angle R-C1-C2/R'-C3-C2 (in deg)	126.0−128.0

Table 1.11: In vitro pharmacology, biopharmaceutical, and disposition attributes of compounds **28** and **25**.



28 **25**

Selected properties	**28**	**25**
IC_{50} ($A\beta_{42}$, nM)[a]	0.225	0.178
Human hepatocyte $Cl_{int,app}$ (μL/min/million cells)[b]	15.0	<3.80
HLM $Cl_{int,app}$ (mL/min/kg)[c]	<16.2	<8.17
RRCK P_{app} (A to B) (10^{-6}cm/s)[d]	5.52	19.3
ElogD (pH = 7.4)	4.70	3.80
Kinetic solubility (pH = 6.5, μM)	0.60	216
Thermodynamic solubility (pH = 6.5, μM)	1.70	19.7
Thermodynamic solubility (pH = 7.4, μM)	0.90	29.4

[a]IC_{50} values were obtained in a whole cell assay using hu APP_{wt} cells by measuring $A\beta_{1-42}$. [b]$Cl_{int,app}$ refers to total apparent intrinsic clearance obtained from scaling in vitro half-lives in human hepatocytes. [c]$Cl_{int,app}$ refers to total apparent intrinsic clearance obtained from scaling in vitro half-lives in human liver microsomes. [d]RRCK cells with low transporter activity were isolated from Medine-Darby canine kidney cells and were used to estimate intrinsic adsorptive permeability.

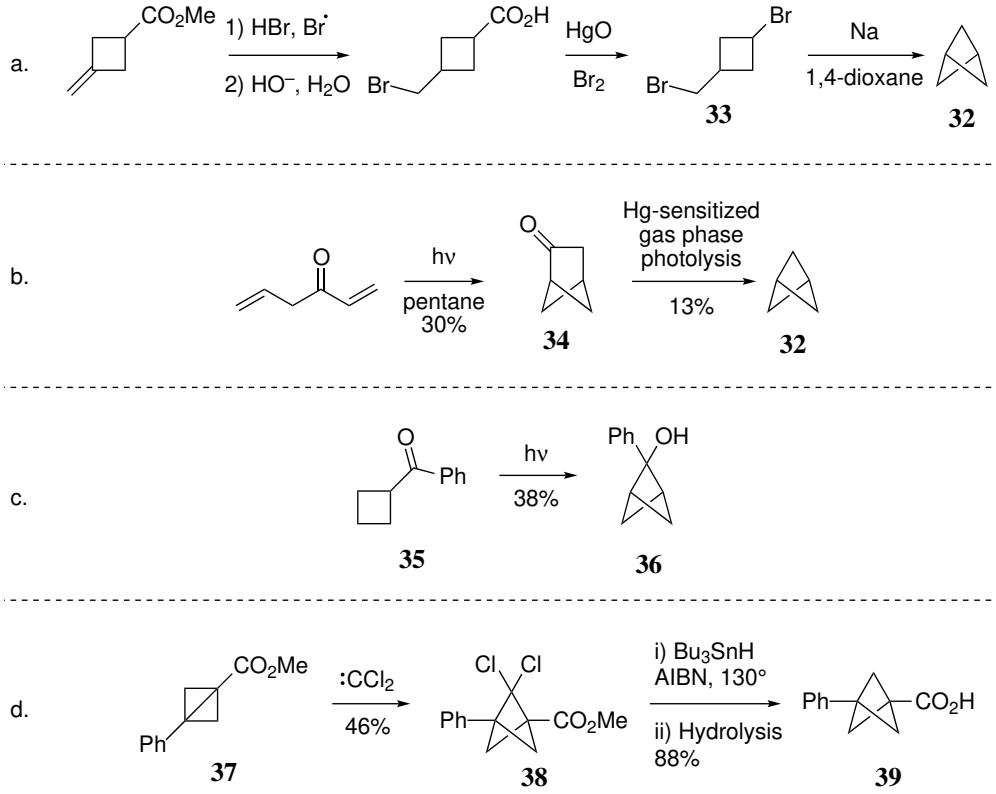
lipophilicity was reduced (ELogD(**28**) = 4.70 and ELogD(**25**) = 3.80). Furthermore, the metabolic stability increased as displayed by lower total apparent intrinsic clearance values in both human hepatocytes and human liver microsomes. The intrinsic absorptive permeability through RRCK cells was higher for **25** and, overall, its aqueous solubility increased compared to the parent compound, likely due to the disruption of π-stacking interaction and the decreased lipophilicity.

Although BCPs have been used on numerous other occasions, they have not yet reached mainstream usage among the medicinal chemistry community, which we propose is due to the lack of safe, efficient and procedurally simple methods for their synthesis.[23–26]

1.4 Synthesis of bicyclo[1.1.1]pentane derivatives

1.4.1 Early syntheses of bicyclo[1.1.1]pentane derivatives

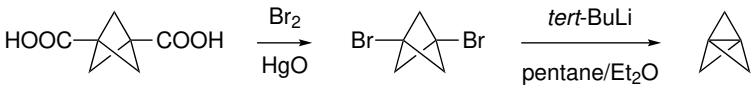
Bicyclo[1.1.1]pentane itself (**32**) was first synthesised (in very poor yield) in 1964 by Wiberg and co-workers by reaction of sodium with dibromocyclobutane **33** (Scheme 1.3a).[27] Two years later, Meinwald *et al.* achieved a Hg-sensitised gas phase photolysis of ketone **34** which afforded **32** in 13% yield (Scheme 1.3b).[28] In 1967, Padwa *et al.* used cyclobutane derivative **35** under irradiation to make substituted BCP **36** in 38% yield (Scheme 1.3c).[29] Finally, in 1977, Applequist and Wheeler achieved the addition of dichlorocarbene onto bicyclo[1.1.0]butane derivatives such as **37**, to yield dichlorinated BCP **38** in 46% yield.[30] Reduction of **38** with tin hydride and hydrolysis afforded acid **39**. Other attempts have produced only trace amounts of BCP derivatives.[31,32]



Scheme 1.3: First syntheses of BCP and BCP derivatives.

1.4.2 Synthesis of TCP

In 1982, Wiberg and Walker achieved the first synthesis of tricyclo[1.1.1.$0^{1,3}$]pentane (or [1.1.1]propellane, abbreviated TCP, **1**, Scheme 1.4), which is nowadays arguably the most common precursor to BCP derivatives.[33] The smallest member of the [n,m,o]propellane family, **1** was first synthesised in two steps from bicyclo[1.1.1]pentane-1,3-dicarboxylic acid **42** (obtained from Applequist and Wheeler's procedure after ruthenium catalysed oxidation of **39**). Hunsdiecker reaction afforded dibromide **43**, and lithium-halogen exchange/cyclisation using *tert*-butyllithium gave **1** as a solution in pentane / Et_2O.

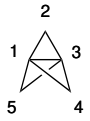


44 **45** **1**

Scheme 1.4: First synthesis of TCP, **1**.

The crystal structure and gas-phase electron diffraction of **1** provided structural data as shown in Table 1.12.[34,35]

Table 1.12: Structural data of TCP (**1**).



1

Distance (in Å)		**Angle (in °)**	
CH	1.09[a]	HCH	116.0[a]
C1−C2	1.52[b]	C1C2C3	63.8[b]
C1−C3	1.58[b]	C1C3C2	58.8[b]
		C3C1C4	92.9[b]

[a]From gas-phase electron diffraction.[35]
[b]From X-ray crystallographic analysis at 138 K.[34]

1.4.3 The central bond in TCP

The central bond of TCP has intrigued chemists since the prediction and discovery of **1**.[33,36] Wiberg and Walker performed *ab initio* calculations (basis set 6-31G*) and estimated the bond strength of **1** to be 65 kcal/mol.[33] Other calculations predicted that **1**

was not diradical bicyclo[1.1.1]penta-1,3-diyl, which lay much higher in energy.[36,37] The same calculations also predicted a negative overlap population between the bridgehead carbon, and that the bonding orbital was formed from hybrid atomic orbitals directed outwards from the ring. Experimental findings have come to the same conclusions on the electron density between the bridgehead carbons for other propellane derivatives.[38,39] A theoretical study from Polo and co-workers on the nature of that bond concluded that the bond is actually almost entirely ionic.[40] Luger *et al.* carried out high-resolution diffraction experiment onto a [1.1.1]propellane derivative and showed an absence of density accumulation along the bond axis.[41] They calculated that the Laplacian of the electronic density $\nabla^2\rho(\mathrm{r})$, a value characteristic of the variation of the electronic density along the bond, at the bond critical point (i.e. the point at which the density reaches an extremum) is positive, which is contrary to a normal C−C bond. Hiberty and co-workers recognised that a positive Laplacian along with the small electronic density at the bond critical point was indicative of a "charge-shift" bond.[42]

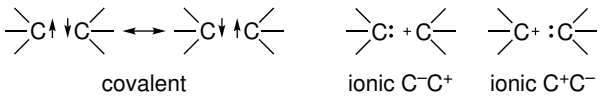


Figure 1.6: Valence bond structures.

In valence bond (VB) theory, a bond is described as a linear combination of a covalent contribution and an ionic contribution (Figure 1.6). The covalent structure is a combination of two neutral components differing by an exchange of spin and it is that exchange that causes the bonding. Either one of these two components defines a non-bonding "quasiclassical state" (QC state) that serves as a reference for the calculation of the bond strength. The energy difference between the ground state of **1** and the QC state, named "*in situ*" energy or E_{QC}, measures the stabilisation associated with the spin exchange in the covalent structure added to the resonance energy stabilisation $RE_{c\text{-}i}$, the energy associated with the mixing of covalent and ionic structures. E_{QC} does not take into account the repulsion between the adjacent bonds or lone pairs of two fragments being brought together, which weakens the bonding interaction. Thus, in most cases, it is

higher than the bond dissociation energy (BDE), which takes into account that weakening. A bond is defined as charge-shift if:[43–45]

- the covalent structure accounts for more than half the C−C bond;
- the resonance energy stabilisation $RE_{c\text{-}i}$ accounts for more than half of the overall bonding energy.

For the first point, the respective weights of each structure can be calculated. If the covalent contribution is higher than 50%, the bond can be either covalent or charge-shift. For the second point, we can compare directly $RE_{c\text{-}i}$ to the energy of the QC state (E_{QC}) given that if $RE_{c\text{-}i} > E_{QC}$ then necessarily $RE_{c\text{-}i} >$ BDE. Table 1.13 contains the information to assess the identity of the central bond. Values for ethane are added for comparison.

Table 1.13: BOVB/6-31G*-calculated energies (kcal/mol) and weights of covalent and ionic structures in [1.1.1]propellane (**1**) and ethane.

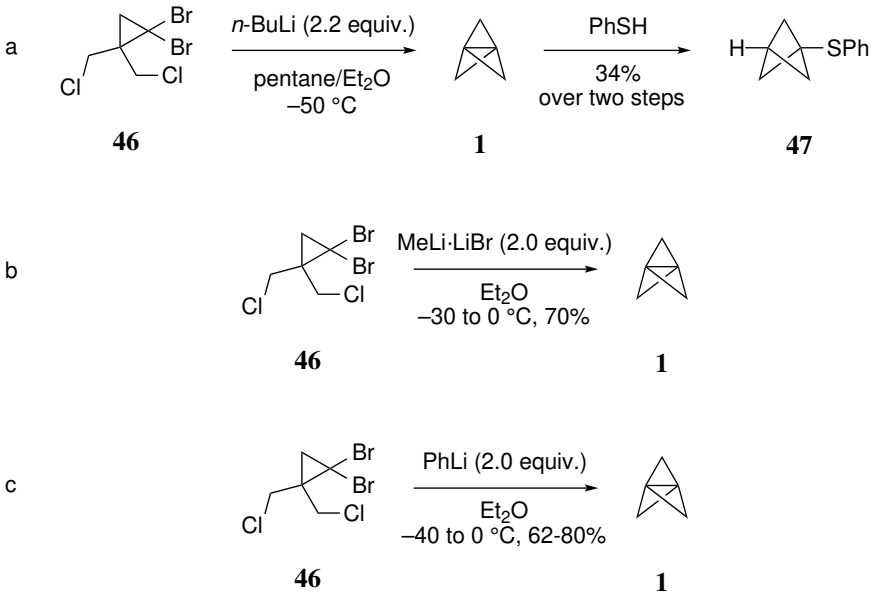
	Ground state	E_{QC}	$RE_{c\text{-}i}$	BDE	Covalent	Ionic +/−	Ionic −/+
1	0	119.1	72.2	−	62%	19%	19%
Ethane	0	138.5	36.3	96.1	55%	23%	23%

In the case of TCP, the resonance energy $RE_{c\text{-}i}$ represent more than 50% of E_{QC}. Additionally, the covalent structure contributes to more than half of the whole bond. Hiberty *et al*. thus concluded that the central bond of **1** is a charge-shift bond. For ethane, as expected, the covalent structure is the most prominent one. However, the $RE_{c\text{-}i}$ only accounts for a third of the BDE and even less for E_{QC}.

1.4.4 Synthesis of bicyclo[1.1.1]pentane from TCP

Szeimies and co-workers were the first to develop a shorter synthesis of TCP from dibromocyclopropane **46**, using *n*-BuLi in a mixture of pentane and Et_2O, albeit only citing the yield over two steps after reaction with PhSH to yield sulfide **47** (Scheme 1.5a, incidentally the first radical based reaction on TCP).[46] This was improved in 1988 by the same group[47] at the same time as Michl and co-workers, who used methyllithium (MeLi) or methyllithium-lithium bromide complex (MeLi·LiBr) instead of *n*-BuLi yielding **1** in 70% yield (Scheme 1.5b).[48] More recently, MeLi has been replaced with the less

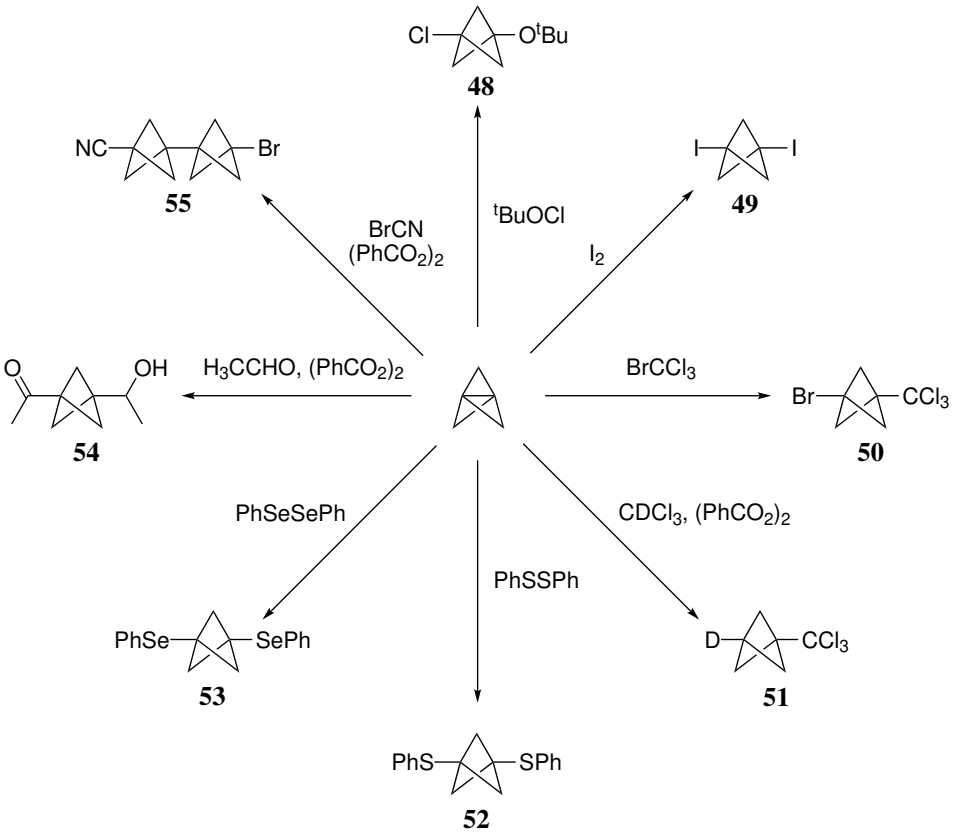
pyrophoric reagent phenyllithium (PhLi), allowing for a safer set up and yielding **1** in equivalent yield (Scheme 1.5c).[20,26,49]



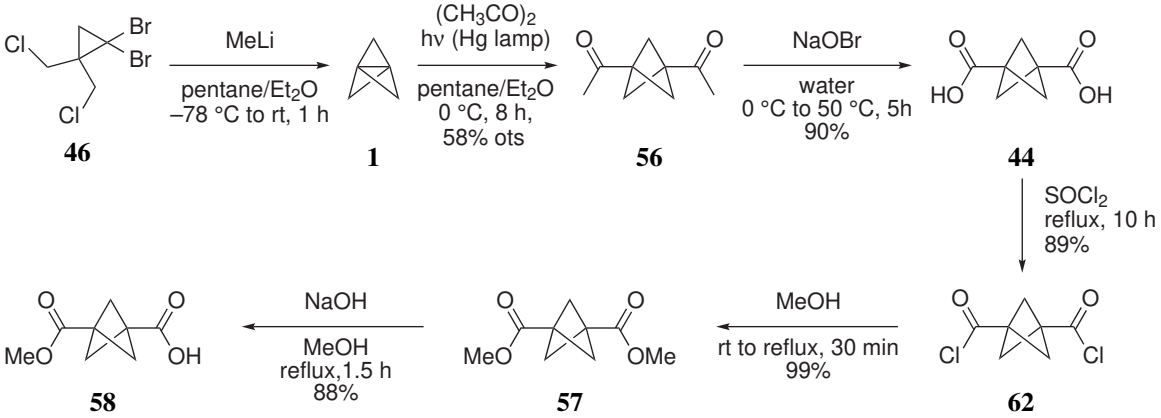
Scheme 1.5: Synthesis of **1** from **46** and organolithium reagents.

Seminal work on the use of TCP for the synthesis of BCP derivatives was published by Wiberg, Waddell and Laidig in 1986.[50] They reacted **1** with a wide variety of radical precursors as halogens, disulfides, diselenides or hypochlorite, using in certain cases a radical initiator (benzoylperoxide, $(PhCO_2)_2$), under UV light irradiation to form a range of BCP derivatives (Scheme 1.6, compounds **48**–**55**). It should be noted that oligomers of BCP, named [n]staffanes (with n the number of BCP units) can be formed when the productive radical chain propagation process is too slow, as for [2]staffane **55**. Longer oligomers can be formed but they are usually obtained in statistically smaller quantities.

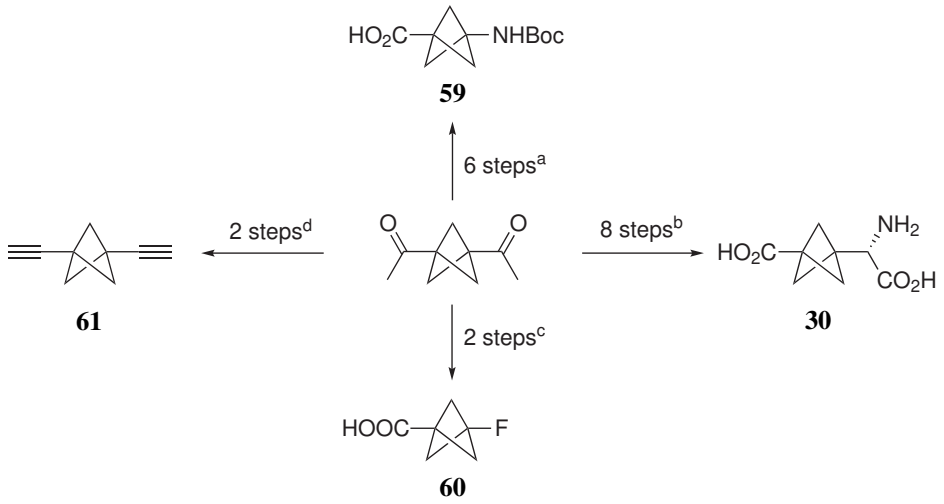
Many other radical-based openings of [1.1.1]propellane have been reported, and compiled in comprehensive reviews.[22,51] One noteworthy example is the reaction of biacetyl and **1** under light irradiation affording diketone **56** in 58% yield over two steps. (Scheme 1.7).[48] This compound can be transformed easily into the diacid **44** using sodium hypobromite, and hence diester **57** and monoacid **58**. As a result, diketone **56** is one of the most prevalent intermediates towards drug candidates or other BCP derivatives, as shown in Scheme 1.8 with amino acids **59** and **30** or building blocks **60** and **61**.[21,52–54]



Scheme 1.6: Synthesis of BCP derivatives from TCP.



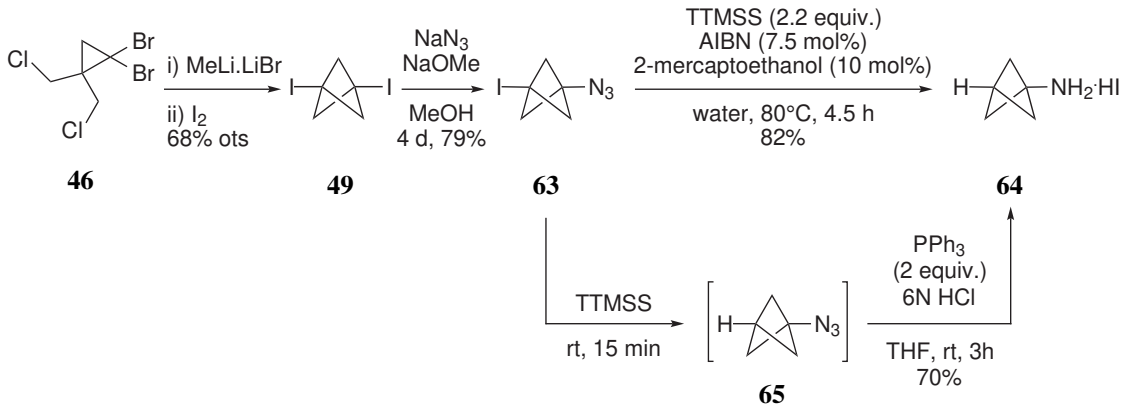
Scheme 1.7: Synthesis of 1,3-dicarbonyl BCP derivatives.



[a] Reference [52]. [b] Reference [21]. [c] Reference [53]. [d] Reference [54].

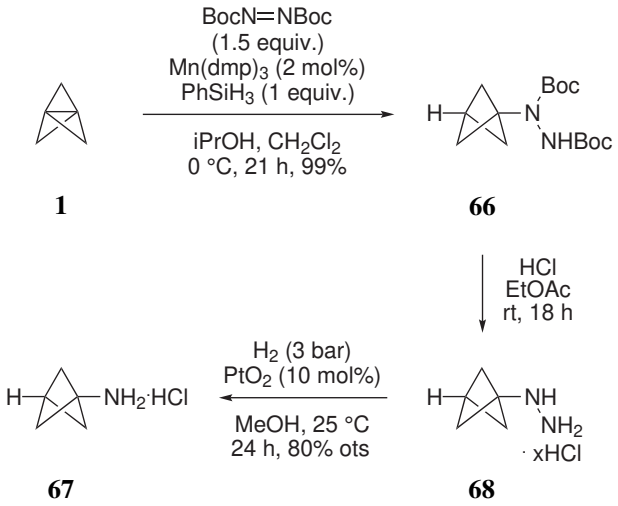
Scheme 1.8: Bioactive surrogates and building blocks from diketone **56**.

Another important BCP intermediate is dioidide **49** (Scheme 1.9). It has been used to access amine derivatives of BCPs, valuable building blocks for medicinal chemists. Although aminobicyclo[1.1.1]pentanes have been made on numerous occasions,[23,55–57] their synthesis relied on a lengthy sequence and potentially explosive Schmidt rearrangement or the use of tin derivatives. However, **49** could be reacted with sodium azide and sodium methoxide to yield iodoazide **63**. Reduction with tris(trimethylsilyl)silane (TTMSS, a bulky silane with a weaker Si−H bond than usual silanes),[58] AIBN and 2-mercaptoethanol afforded bicyclo[1.1.1]pentan-1-ammmonium iodide (**64**) in only 3 steps from TCP. Using only TTMSS, **63** was quickly reduced to azide **65** which upon Staudinger reaction then delivered **64**.



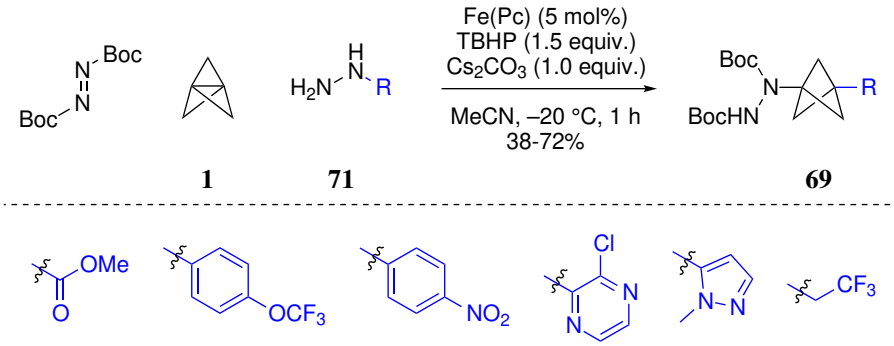
Scheme 1.9: Synthesis of bicyclo[1.1.1]pentan-1-ammonium iodide (**64**) via the reduction of 1,3-diiodobicyclo[1.1.1]pentane (**49**).

A few years earlier, building on Waser and Carreira's hydrohydrazination of double bonds,[59] Bunker *et al.* used $Mn(dpm)_3$, di-*tert*-butyl-azodicarboxylate and phenylsilane in combination with [1.1.1]propellane to produce hydrazide **66** (Scheme 1.10).[60] Boc deprotection and platinum-catalysed hydrogenation afforded bicyclo[1.1.1]pentan-1-ammonium chloride (**67**) in excellent yields.



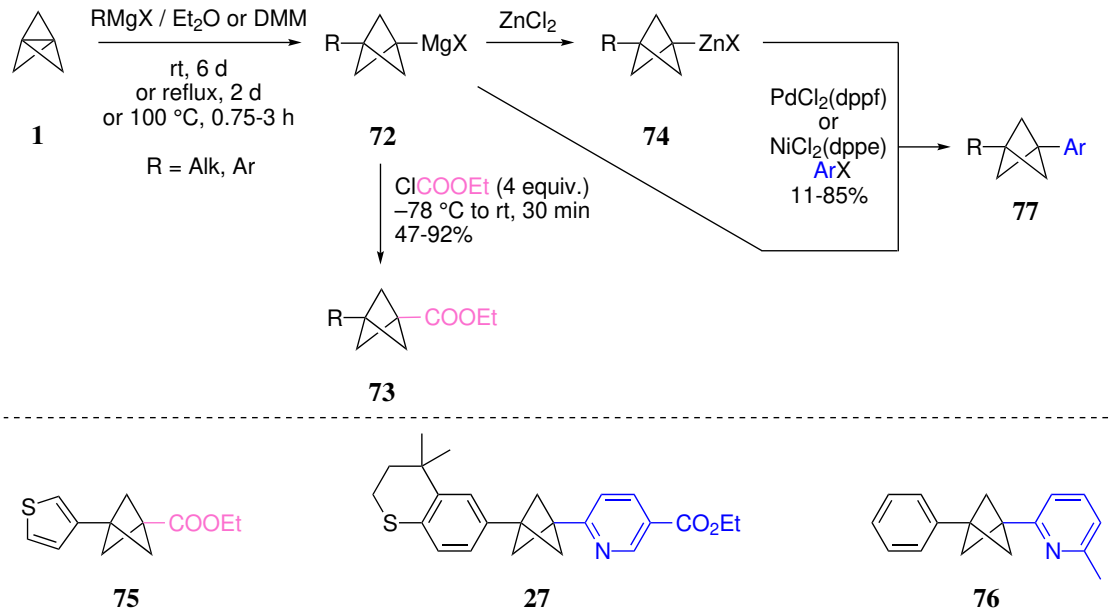
Scheme 1.10: Synthesis of bicyclo[1.1.1]pentan-1-ammonium chloride (**67**) via hydrohydrizination of TCP (**1**).

An extension of that methodology was published recently by Kanazawa *et al.*[26] Di-*tert*-butyl-azodicarboxylate, a hydrazine derivative and TCP were reacted in the presence of iron(II) phthalocyanine (Fe(Pc)), *tert*-butylhydroperoxide (TBHP) and caesium carbonate in MeCN at −20 °C for 1 h to yield *C,N*-disubstituted BCP derivative **69** (Scheme 1.11). A wide range of hydrazines can be used in this multicomponent reaction.



Scheme 1.11: Synthesis of C,N-disubstituted BCP derivatives by multicomponent carboamination of TCP.

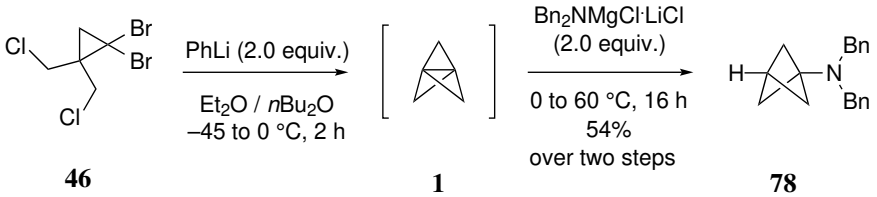
An important method to synthesise BCP derivative is the addition of Grignard reagents to **1** reported by the Szeimies group[61] and the de Meijere group (Scheme 1.12).[62] This direct addition proved to be slow (2-6 d reaction time) to yield **72**. Makarov *et al.* recently improved the method by heating **1** and the Grignard reagent in diethyl ether at 100 °C in a sealed tube allowing for a reduction of the reaction time to 45 min−3 h.[20] The corresponding BCP Grignard derivatives were quenched by electrophiles such as ethyl chloroformate (to yield esters **73**), or used in Kumada- and Neigishi-type cross-couplings (after transmetallation to **74**) to produce 1,3-disubstituted BCP derivatives. Examples include thiophene derivative **75**, BCP analogues of tazarotene **27**, and drug candidate MPEP **76**.



Scheme 1.12: Addition of Grignard reagent to TCP and reaction with electrophile or TM-catalysed cross-couplings.

Building on this work, Gianatassio *et al.* reported to access substituted aminoBCPs *via* the addition of "turbo amide" to TCP.[49] They studied the addition of substituted amides to **1** and reported an efficient "strain-release amination" procedure using special amides obtained from the reaction of amines with "turbo Grignard" (isopropylmagnesium chloride lithium chloride complex). These turbo amides were reacted with TCP (after distillation or directly from the crude reaction mixture) at high temperature (60−90 °C) in a sealed vial, yielding the corresponding substituted aminoBCP derivatives. An example

is shown in Scheme 1.13, where the turbo amide of dibenzylamine was added through **1** on a 100 g scale, affording the corresponding protected amine **78** in 54% yield over two steps. Simple hydrogenation and acidification gave **79** in excellent yield. Many more secondary amines were used and to date, it is the shortest method to access these compounds.



46 **1** **78**

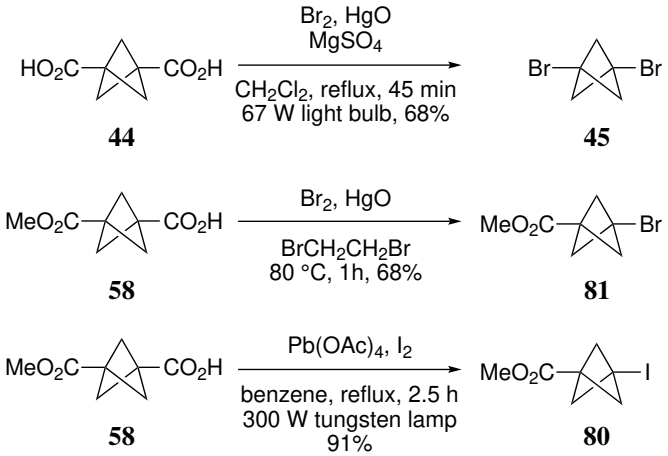
Scheme 1.13: Synthesis of N-substituted BCP derivatives by addition of "turbo amides" of [1.1.1]propellane.

1.5 Synthesis of halogenated bicyclo[1.1.1]pentanes

For the past 50 years, the preparation of BCP derivatives has revolved around the methods summarised above. The class of BCP that is of the most relevance to this project is 1-halo-3-substituted BCPs. This section will survey the synthesis of bromo- and iodoBCPs but will not cover chlorinated nor fluorinated derivatives.

1.5.1 Synthesis from carboxylic acid derivatives

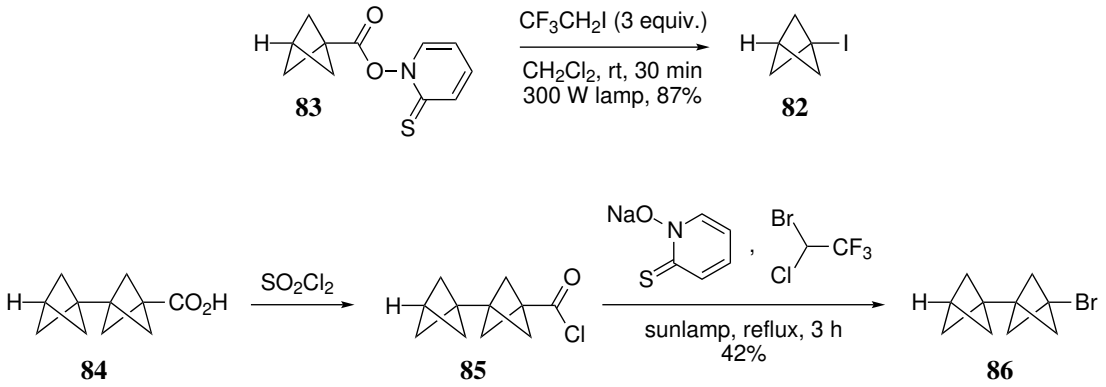
Wiberg and Walker were the first to report the synthesis of dibromide **45** from diacid **44** *via* Hunsdiecker reaction in 1982 although accurate conditions and yields were only published in 1985 (Scheme 1.14).[33,63] Applequist and co-workers conducted a similar experiment on monoacid **58** with similar yields.[64] Della and Head achieved an analogous transformation using lead acetate and iodine, to yield iodide **80** in 91% yield from **58**.[65]



Scheme 1.14: Synthesis of halogenated BCPs from carboxylic acids.

Thiohydroxamic esters, or Barton esters, have been used to access halogenated BCPs since 1988 but full reaction conditions were only published three years later when Della and Taylor achieved the synthesis of **82** from Barton ester **83** and 1,1,1-trifluoro-2-iodoethane under UV irradiation (Scheme 1.15).[66,67] In order to synthesise [n]staffanes, Michl and co-workers carried out a bromodecarboxylation starting from [2]staffane-3-carboxylic acid (**84**) using thionyl chloride to make the acid chloride derivative **85** that

was purified by distillation.[68] 2-Mercaptopyridine-1-oxide sodium salt and 1-bromo-1-chloro-2,2,2-trifluoroethane were mixed and **85** was added. Irradiation at reflux of the resulting suspension afforded bromide **86**.



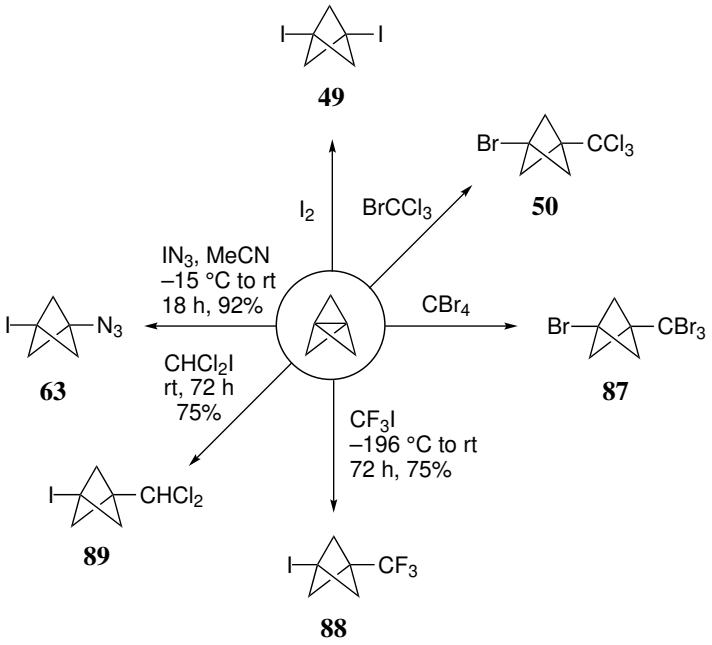
Scheme 1.15: Synthesis of halogenated BCPs from Barton esters.

1.5.2 Reaction of TCP with activated halide species

As shown earlier, activated organohalides can react with TCP without any additive. Wiberg, Waddell and Laidig reported the reaction of TCP with bromotrichloromethane, yielding 1-bromo-3-(trichloromethyl)bicyclo[1.1.1]pentane (**50**), and with iodine affording diiodide **49** (Scheme 1.16).[50] In addition, Zefirov and co-workers reported the use of carbon tetrabromide as the halide partner, yielding bromide **87**.[69] In a similar manner, iodotrifluoromethane afforded iodide **88** in 75% yield.[70] Dichloroiodomethane also proved very reactive and iodide **89** was formed in 75% yield.[71] Furthermore, pseudohalide iodine azide proved to be an excellent substrate and afforded iodide **63**.[72] These reactions all rely on the relatively low dissociation energy of the breaking bond in the starting material (Table 1.14).

1.5.3 Reaction of TCP with organohalides under light irradiation

Less activated organohalides necessitated strong light irradiation to allow for reaction with TCP. The major contributors in this area are the Zefirov,[76,77] Michl[78–80] and the Szeimies[81] groups, who showed that a large variety of organohalides could be coupled with TCP using Hg-lamp irradiation, and in some cases a radical initiator as for less activated organobromides. A selection of substrates that were reacted with TCP under



Scheme 1.16: Synthesis of halogenated BCPs from [1.1.1]propellane and activated organohalides and pseudohalides

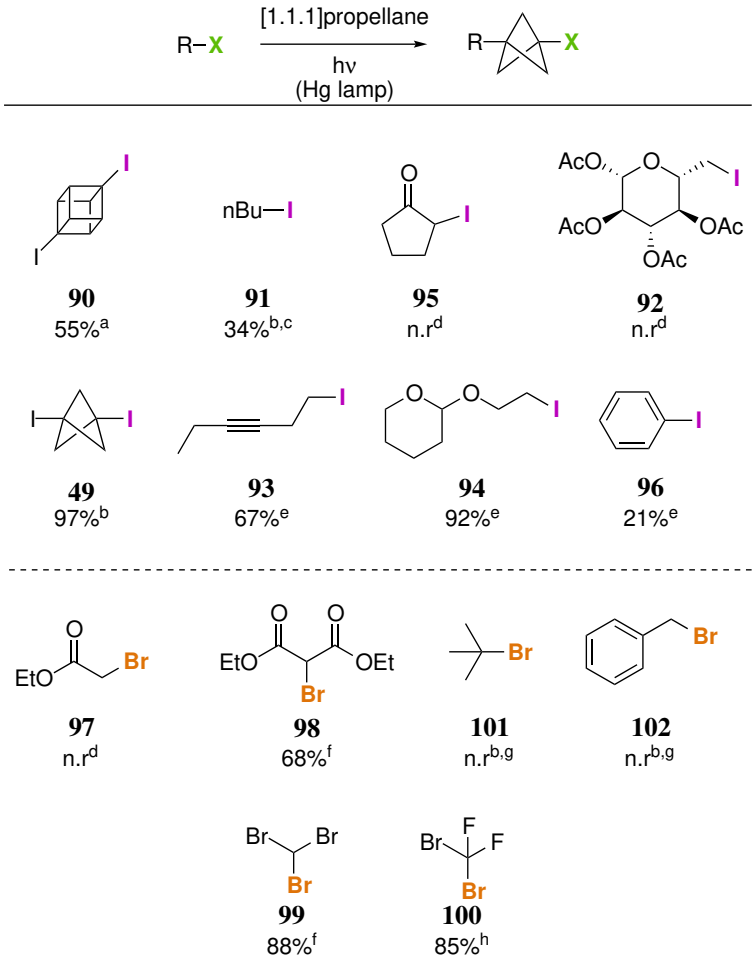
Table 1.14: Bond dissociation energies

Bond	BDE (kcal/mol)
I–I	36[a]
I–N_3	46[b]
Br–CBr_3	50[a]
Br–CCl_3	52[a]
I–CF_3	54[c]

[a]Reference [73]. [b]Reference [74]. [c]Reference [75]

UV irradiation (Table 1.15).[73–75] Where yields are not shown, the haloBCP was used directly in a subsequent reaction. Cubane **90** and BCP **49** were reactive under the reaction conditions and the corresponding BCP and [2]staffane were produced in 55% and 97% respectively. Primary alkyls **91**, **92**, **93** and **94** were reacted and gave moderate to excellent product yields. α-Iodoacetate **95** also proved reactive whereas iodobenzene (**96**) did not perform well. Activated bromide **97**, **98**, **99** and **100** produced the corresponding bromoBCP in good yield with UV light as the sole initiator, while less activated bromides **101** and **102** necessitated benzoyl peroxide to ensure reactivity.

Table 1.15: Synthesis of halogenated BCP by UV irradiation.



90 55%[a] **91** 34%[b,c] **95** n.r[d] **92** n.r[d]

49 97%[b] **93** 67%[e] **94** 92%[e] **96** 21%[e]

97 n.r[d] **98** 68%[f] **101** n.r[b,g] **102** n.r[b,g]

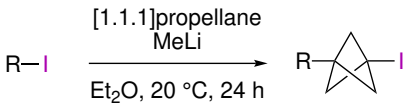
99 88%[f] **100** 85%[h]

[a]Reference [78]. [b]Reference [80]. [c]Yield calculated from tetrahalide precursor **46**. [d]Not isolated, from reference [79]. [e]Reference [81]. [f]Reference [76]. [g]Benzoyl peroxide was used as radical initiator. [h]Reference [77]. n.r. Not reported.

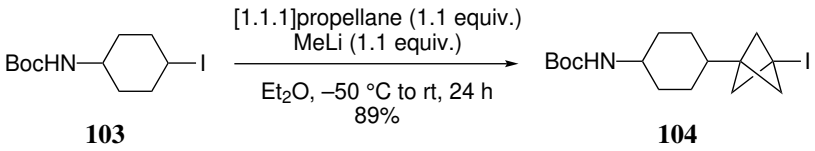
1.5.4 Reaction of TCP with organohalides and methyllithium

Szeimies and co-workers have developed a methodology using methyllithium to append organoiodides to TCP.[62] Although MeLi can be used catalytically, they reported that stoichiometric amounts were beneficial to the yield of the reaction. Despite good to excellent yields, this method suffers from low substrate tolerance due to the use of an organolithium reagent. A selection of substrates are presented in Table 1.16. Nevertheless, Bunker *et al.* used this methodology at low temperatures with substrate **103**, to avoid reaction between MeLi and the *N*-Boc group (Scheme 1.17).[82]

Table 1.16: Methyllithium-mediated addition of organoiodides to TCP.



R–I	Yield (%)
Me–I	83
*n*Pr–I	94
*n*Hept–I	81
I–$(CH_2)_3$OTHP	98
93	25
Cy–I	84



103 **104**

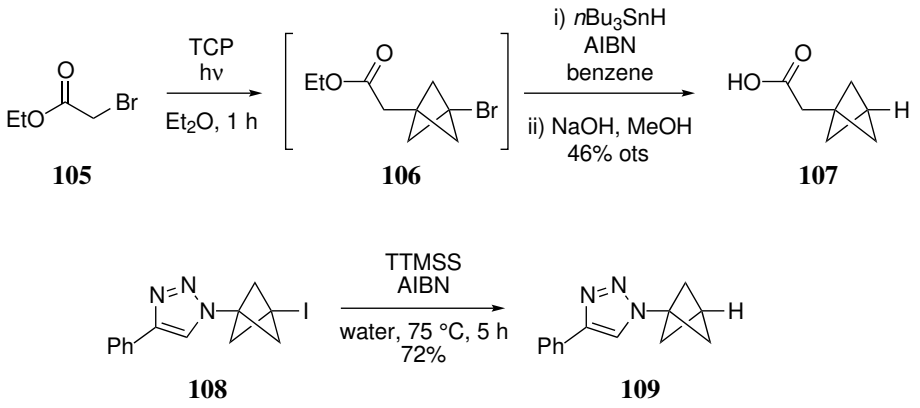
Scheme 1.17: Methyllithium-mediated addition of **103** to TCP at low temperature.

1.6 Functionalization of halogenated bicyclo[1.1.1]pentanes

1.6.1 Radical generation

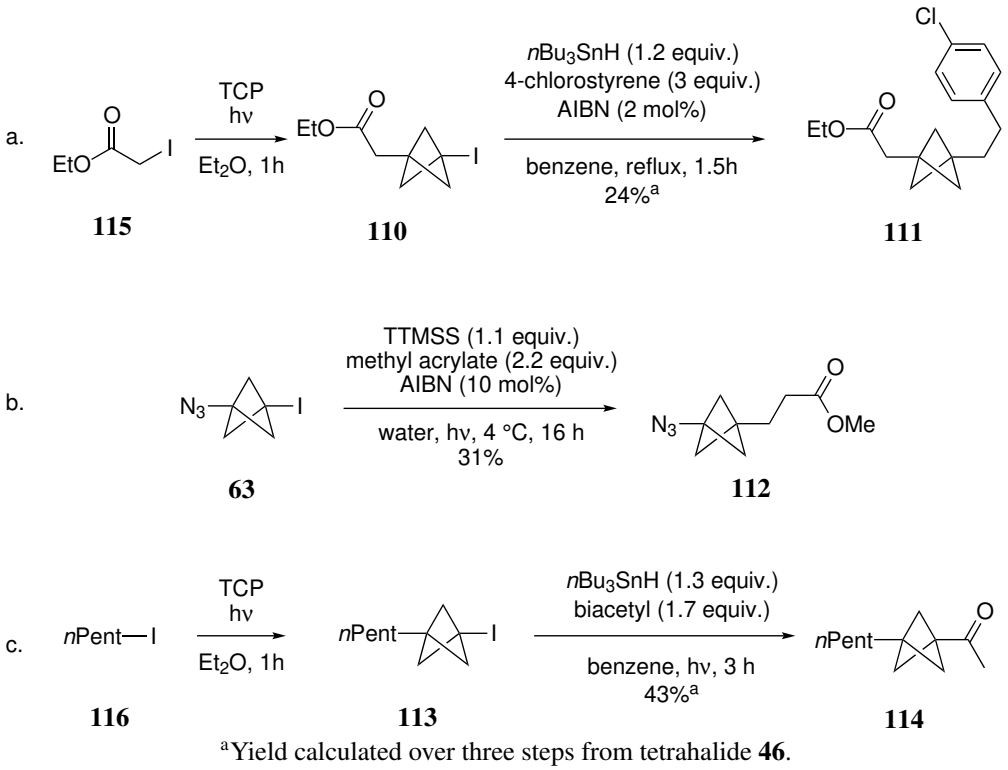
The most simple functionalisation of haloBCPs is the reduction of the C–X bond to C–H. This has been achieved on several occasions and two representative examples are presented in Scheme 1.18. In the first, ester **105** was converted to BCP **106** and reduced with tributyltin hydride and AIBN as the radical initiator.[79] Hydrolysis of the ester yielded acid **107**. A more environmentally friendly procedure was developed by Adsool and co-workers,[83] who used tris(trimethylsilyl)silane, instead of tin hydride, in combination with AIBN initiator to afford triazole **109**.

IodoBCPs have been used on many occasions in reactions to reform the radical on the bridgehead carbon, and then react it with a radical trap. Michl and co-workers have performed Giese reactions, where a free radical is quenched with an electron-deficient alkene, with a few halogenated BCPs as shown in Scheme 1.19a.[79] Ester **110** was reacted with tributyltin hydride and 4-chlorostyrene to yield BCP derivative **111**; again, the tin species could be replace with TTMSS. Azide **63** was reacted with methyl acrylate, TTMSS and AIBN to afford azidoester **112**, albeit in low yield due to difficult purification



Scheme 1.18: Tin hydride- and silicon hydride-mediated carbon-halogen bond reduction

(Scheme 1.19b).[83] Biacetyl could be used in reaction with alkyl BCP **113** and tributyltin hydride as an acyl radical trap to yield ketone **114** (Scheme 1.19c). Addition to ketones was also explored,[79] and aromatic rings proved reactive toward radical acceptors provided they were used in large excess or as the solvent of the reaction.[84]

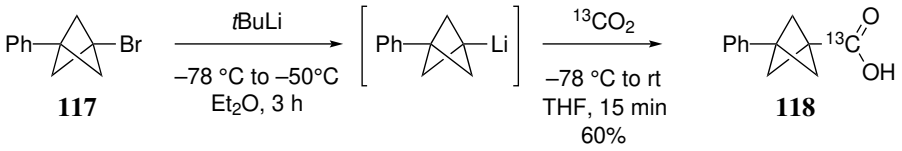


[a]Yield calculated over three steps from tetrahalide **46**.

Scheme 1.19: Tin hydride- and silicon hydride-mediated Giese reaction and ketone formation of iodinated bicyclo[1.1.1]pentanes.

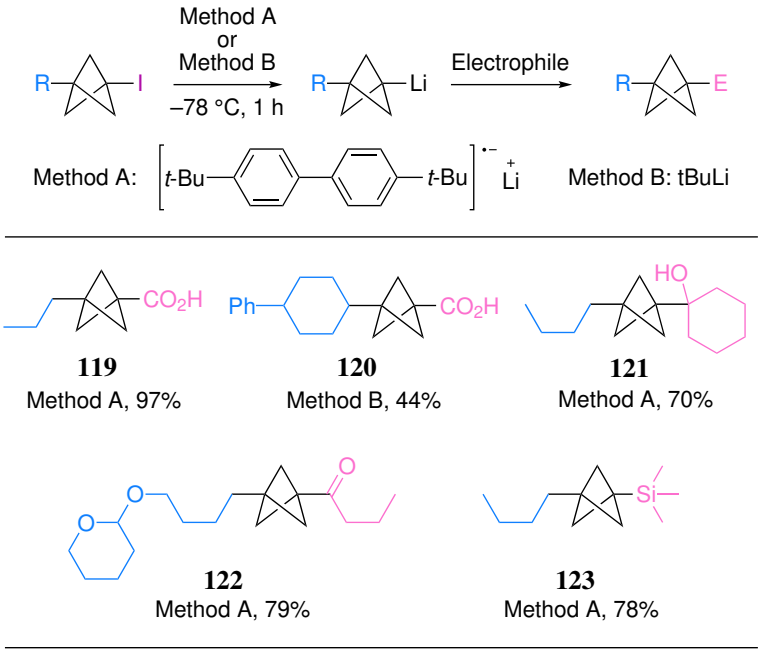
1.6.2 Metallation

Metallation reactions have emerged as potent methods to functionalise haloBCPs. Della and co-workers showed that bromide **117** could be metallated using *t*BuLi (Scheme 1.20).[66] Subsequent quenching with $^{13}CO_2$ afforded ^{13}C-labelled acid **118**.



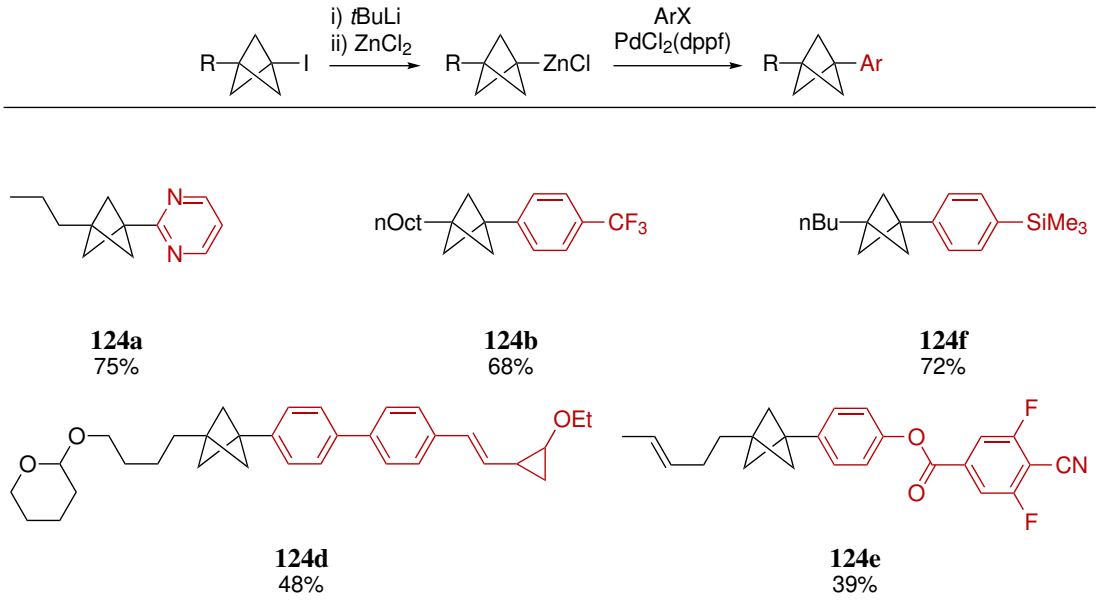
Scheme 1.20: Lithiation and carboxidation of 1-bromo-3-phenylbicyclo[1.1.1]pentane (**117**).

Messner *et al.* also showed that iodides could also be easily lithiated with either *t*BuLi or lithium 4,4'-di-*tert*-butylbiphenylide (LiDBB, Freeman's reagent) and quenched with a variety of electrophiles as shown in Scheme 1.21.[62] For example, **119** was obtained in 97% yield after treatment of the iodide with LiDBB and quenching with CO_2. **120** was obtained using *t*BuLi and CO_2, albeit in low yield. **121**, **122** and **123** were obtained after treatment with *t*BuLi and cyclohexanol, butanoic chloride, and chlorotrimethylsilane respectively in very good yields.



Scheme 1.21: Lithiation and quenching of iodinated BCP with various electrophiles.

Messner and co-workers also used lithiated BCPs in Neigishi cross-coupling reactions.[62] After transmetallation with zinc(II) chloride, the corresponding zincates were reacted with aryl halide and $PdCl_2$(dppf) at 25 °C to yield **124a–e** in very good yield for simple scaffolds, and moderate yields for more complex ones (Scheme 1.22).

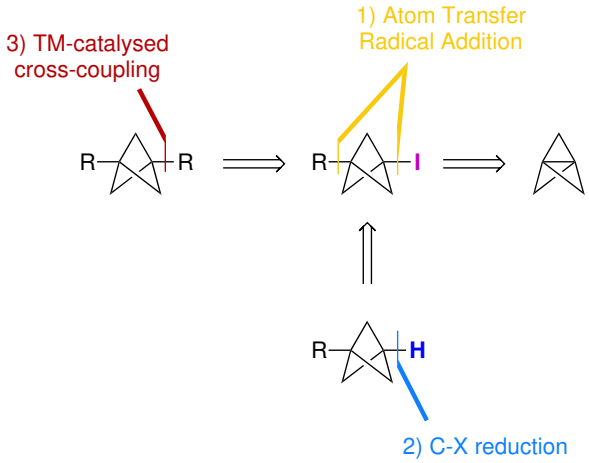


Scheme 1.22: Lithiation and cross-coupling of iodidnated BCP derivatives.

Similar cross-couplings have been reported recently and used for the synthesis of a BCP analogue of Tazarotene, although the BCP-zincates were obtained from direct addition of an organomagnesium reagent to TCP and subsequent transmetallation.[20] In those cases, the scope was very much limited to what R group could be introduced in the first place.

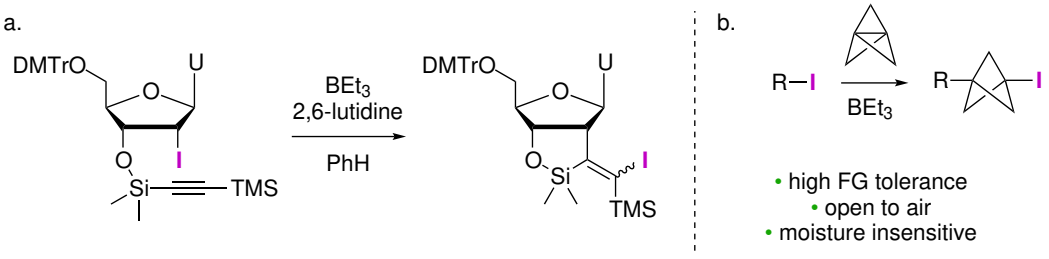
1.7 Aims of the project

It is clear that bicyclo[1.1.1]pentanes are of high interest to the medicinal chemistry community, and that despite the existence of several methods to synthesise them, their use has remained scarce. The available methods are often hazardous (*t*BuLi and MeLi) or toxic (nBu$_3$SnH), practically demanding (intense light irradiation at low temperatures), or simply too restrictive in terms of substrate tolerance. To meet the demand from the pharmaceutical industry, we proposed a modular synthesis of 1,3-disubstituted bicyclo[1.1.1]pentanes from TCP via halogenated bicyclo[1.1.1]pentane derivatives (Scheme 1.23).



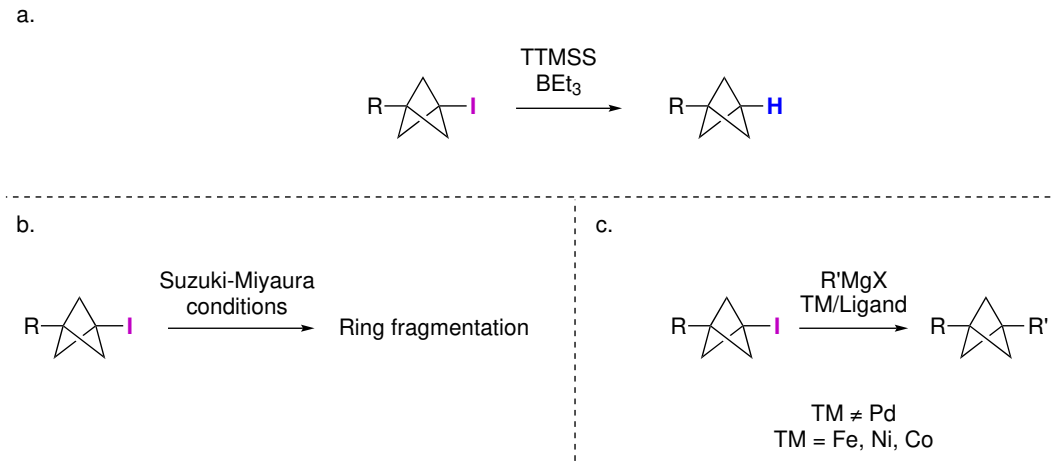
Scheme 1.23: Project outline

Based on results within our group (Scheme 1.24a),[85] we questioned whether triethylborane could be used as a radical initiator in an Atom Transfer Radical Addition (ATRA) reaction between TCP and an organohalide (Scheme 1.24b), approximating the reactivity of the central bond of TCP to that of an unsaturated bond.



Scheme 1.24: BEt_3-initiated ATRA of organohalide on [1.1.1]propellane.

We then envisaged the use of the resultant halogenated BCPs in two different ways: firstly, by reduction of the carbon-halogen bond using tris(trimethylsilyl)silane (TTMSS) as the hydride source, again with triethylborane as the radical initiator (Scheme 1.25a); and secondly to use this carbon-halogen bond in a more productive manner, by developing cross-coupling processes. Some insight was available from industrial partners that iodoBCPs would be unsuitable for Pd-catalysed couplings due to the opening of the BCP ring to yield cyclobutenes (Scheme 1.25b). It is possible that iodoBCPs are unstable towards two-electron oxidative addition or that the bycyclo[1.1.1]pentylpalladium(II) species formed in the cross-coupling reaction decomposes before the transmetallation can occur under the Suzuki-Miyaura reaction conditions. Thus, cross-couplings that proceed *via* radical species in the pathway may be more productive, as it is the case for couplings catalysed by iron or nickel species (Scheme 1.25c).



Scheme 1.25: Functionalisation of halogenated BCP

This thesis will be divided into three parts: the first chapter will concentrate on the BEt_3-initiated atom transfer radical addition of organohalides with TCP to form iodoBCPs; the second chapter will be dedicated to the BEt_3-initiated TTMSS reduction of iodoBCPs; in the final chapter, the findings on the transition metal-catalysed cross-coupling of iodoBCPs will be presented.

2

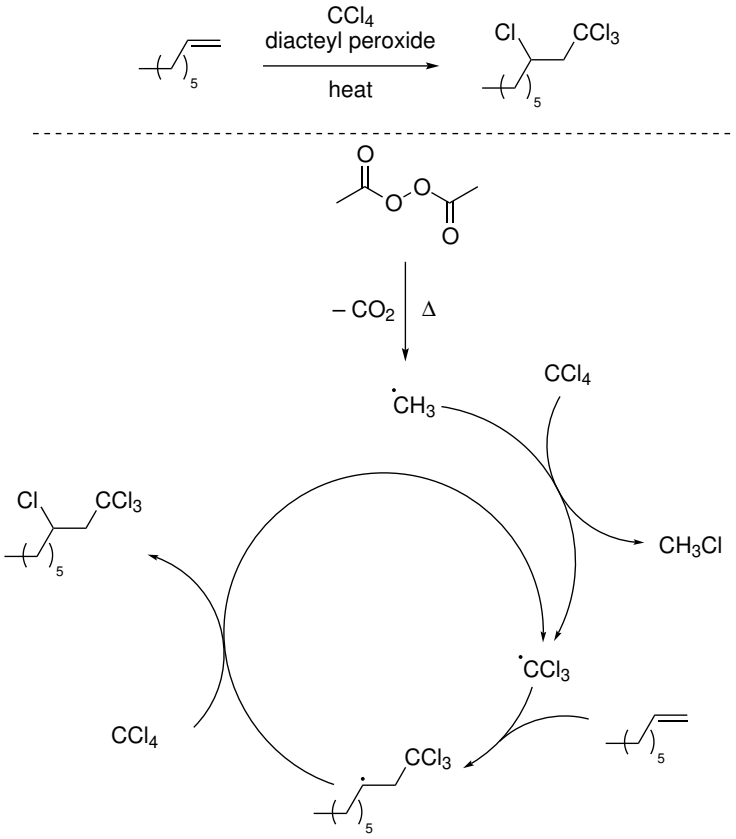
Atom-Transfer Radical Addition of organohalide on TCP

Contents

2.1 Atom Transfer Radical Addition

An Atom Transfer Radical Addition (ATRA) is a reaction during which the bond between the two components of a molecule A–B is broken homolytically, and each of the two components is added on both sides of another molecule C (often an olefin) to give A–C′–B. The first example was reported by Kharasch and co-workers in 1945, who performed an ATRA reaction of carbon tetrachloride and olefin using diacetyl or dibenzoyl peroxide as the radical initiator under heating.[86] As shown in Scheme 2.1, Kharasch *et al.* postulated

a chain reaction mechanism for the ATRA of 1-octene and carbon tetrachloride.

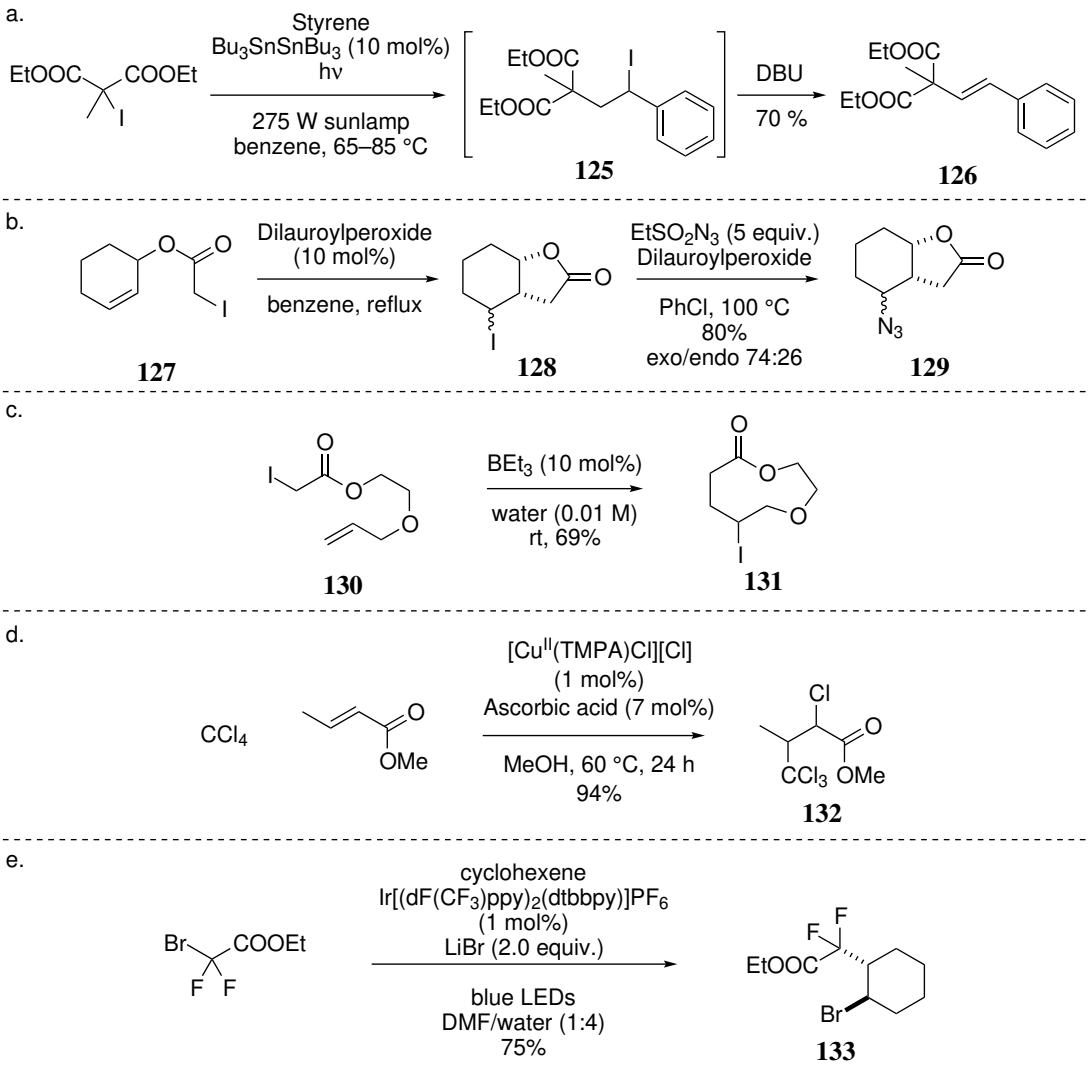


Scheme 2.1: Atom Transfer Radical Addition of carbon tetrachloride to 1-octene.

Upon heating, the peroxide bond of diacetyl peroxide breaks down into methyl radicals and CO_2. Then, the methyl radical abstracts a chlorine atom from carbon tetrachloride to yield chloromethane and a trichloromethyl radical. The trichloromethyl radical then combines with the olefin to yield a new alkyl radical, which propagates the reaction by abstracting a chlorine atom from carbon tetrachloride, forming the product and a second trichloromethyl radical.

Scheme 2.2 displays examples of ATRA reactions initiated by different methods. Curran and co-workers performed the ATRA reaction of diethyl iodomethylmalonate on styrene using hexabutyltin and light, yielding benzyl iodide **125** that was eliminated using DBU to olefin **126** (Scheme 2.2a).[87] Renaud and co-workers showed that ATRA reaction could be used to operate cyclisations; alkene-contaning α-iodoester **127** was cyclised using dilauroylperoxide at high dilution in refluxing benzene, affording compound **128** (Scheme 2.2b).[88] Subsequent radical reformation and trapping with an azide donor

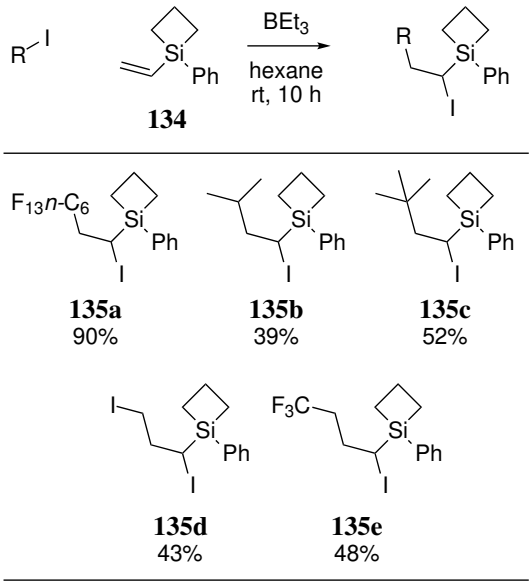
afforded compound **129**. In this case, the reaction is coined Atom Transfer Radical Cyclisation (ATRC). Oshima and co-workers showed that the synthesis of 9-membered rings was possible *via* intramolecular ATRC with the example of iodide **130**, which was reacted with triethylborane (BEt_3) in water at 0.01 M to afford medium-ring compound **131** (Scheme 2.2c).[89] Metal complexes were also used as initiators as shown in Scheme 2.2d with the copper-initiated ATRA reaction of carbon tetrachloride and methyl methacrylate yielding chloride **132**, during which ascorbic acid was used as a mild reducing agent to generate a catalytic amount of copper(I) species.[90] Photoredox processes proved to be a powerful method for initiation in the ATRA with ethyl bromodifluoroacetate and cyclohexene, affording compound **133** in 75% yield (Scheme 2.2e).



Scheme 2.2: Atom Transfer Radical Addition (a,d,e) and Cyclisation (b,c) reactions

Fewer reactions have been conducted using alkyl iodides and an example is given below. Oshima and co-workers performed the addition organoiodides on vinyl silane **134** using triethylborane as the radical initiator (Table 2.1).[91] Compounds **135a–e** were produced in moderate to excellent yields (Table 2.1).

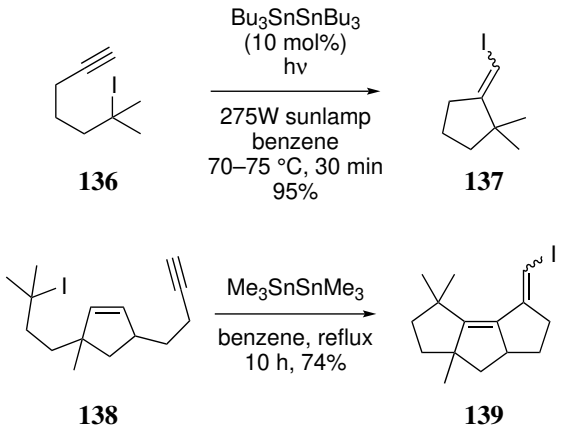
Table 2.1: ATRA of alkyl iodides on vinyl silane **134**.[91]



Interestingly, the perfluoroalkyl iodide substrate was the most efficient in the ATRA reaction, owing to the weakening of the C–I bond by inductive effect of the fluorine atoms. Consequently, there are many more reports of perfluoroalkyl iodides being used as substrate for ATRA reactions.

ATRA reactions have also been performed on alkynes and a prime example is that developed by Curran and co-workers, in which iodoalkyne **136** was cyclised using hexabutylditin and light in benzene at high temperature to vinyl iodide **137** (Scheme 2.3).[92] Similarly, they elegantly cyclised enyne **138** to tricyclic vinyl iodide **139**.

This cyclisation on alkynes inspired the Shuto group to expand their previous work on alkenes to develop a silicon-tethered radical alkyne transfer reaction (Scheme 2.4).[93–95] Compound **140** was treated with BEt_3 to form radical **141** which triggered a 5-exo-dig cyclisation to afford vinyl radical **142**, which propagated the reaction by abstracting an iodine atom from **141**, affording vinyl iodide **143** and radical **141**. Addition of tetrabutylammonium fluoride (TBAF) cleaved the cyclic siloxane to form **144** and



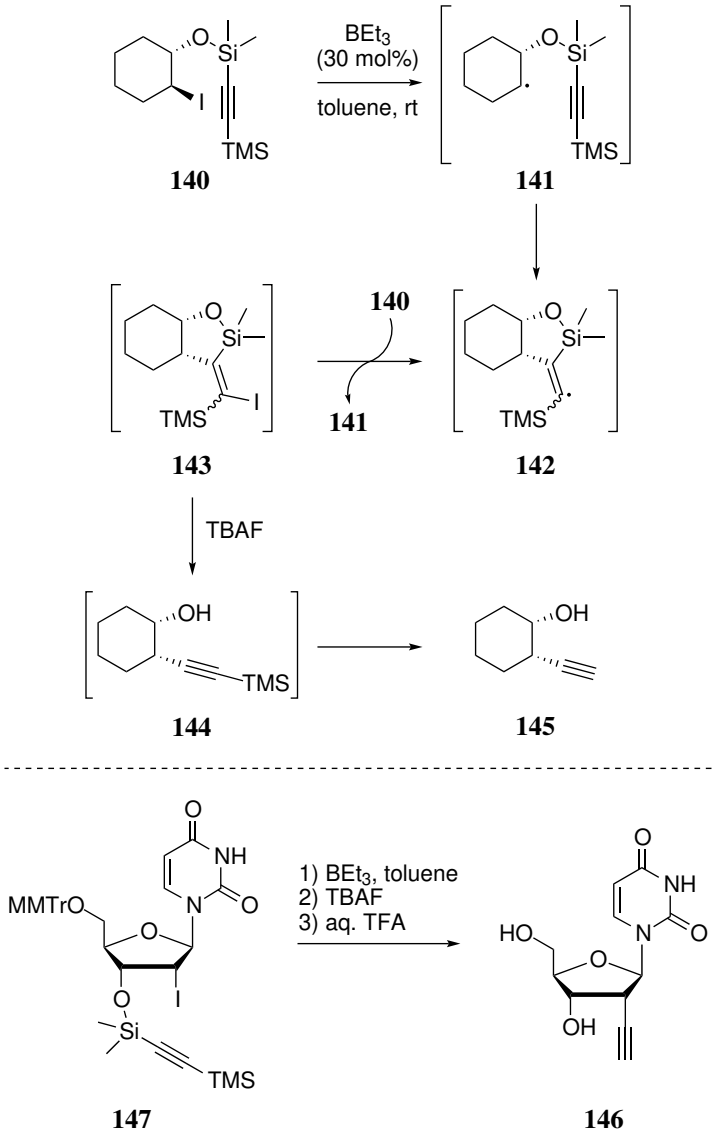
Scheme 2.3: ATRA reaction with alkynes.[92]

deprotection of the TMS group afforded **145**. They applied this methodology to the synthesis of 2'-alkynylnucleosides **146** from **147**.

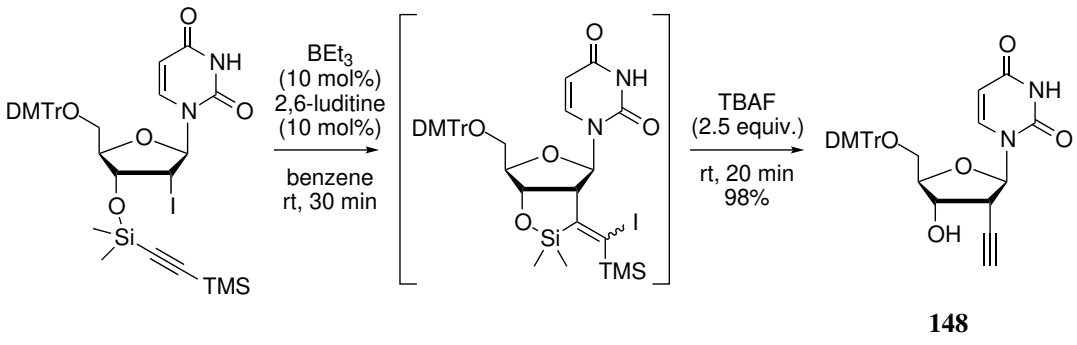
Our group utilised that same methodology for the synthesis of a similar 2′-iodo-nucleosides, compound **148** (Scheme 2.5).[85] Building on this experience, it was decided to focus our efforts on the use of triethylborane as the radical initiator.

The reaction of triethylborane and oxygen is called autooxidation and Figure 2.1 displays the elementary steps of this process.[96] In the initiation phase, triethylborane react with oxygen *via* homolytic substitution reaction (S_H2) to produce a peroxy radical and an ethyl radical (1). The peroxy radical can react with triethylborane to form a peroxy diboron species and more ethyl radicals (2). In the propagation phase, ethyl radicals react rapidly with oxygen to form ethylperoxy radicals (6). In turn, the latter reacts with triethylborane to form peroxyborinates and ethyl radicals (7). The resulting peroxyborinates decompose readily to borinate radicals and ethoxy radical (3). Both can react with triethylborane to produce more ethyl radicals (5a & 5b). Also, peroxyborinate can react directly with triethylborane, affording borinates, borinate radicals and ethyl radicals (4). Finally, at low oxygen concentration, peroxyborinates react with triethyl borane by ionic oxidation to give ethyl diethylborinate (8).

Curran and McFadden showed that the inital S_H2 step is slow compared to other steps in the process (Table 2.2).[96] They also showed that, in the case of the reduction of an organohalide with tributyltin hydride and tributylborane, high levels of oxygen inhibit the



Scheme 2.4: Silicon-tethered radical alkyne transfer reaction.[95]



Scheme 2.5: Our group synthesis of 2'-alkynylnucleoside **148**.[85]

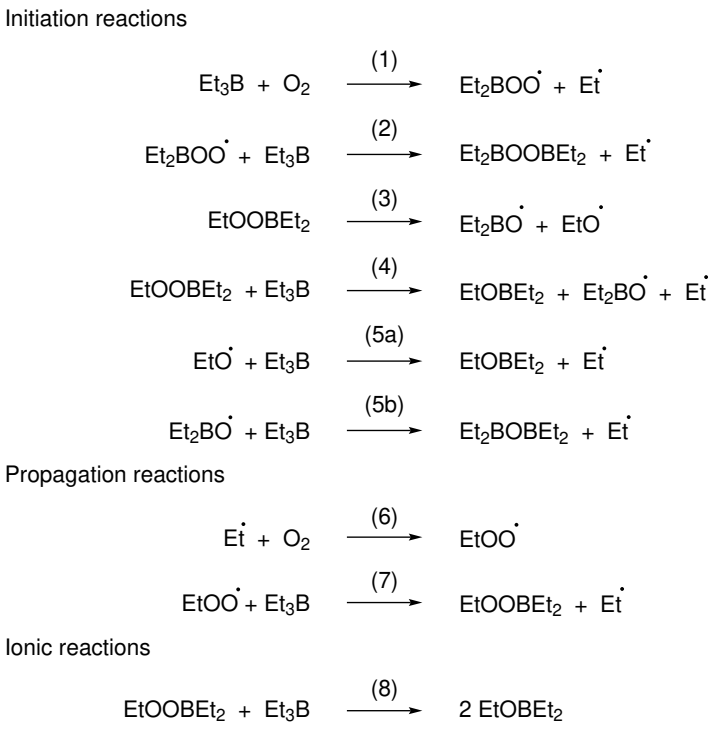


Figure 2.1: Elementary steps in the autooxidation of BEt_3.[96]

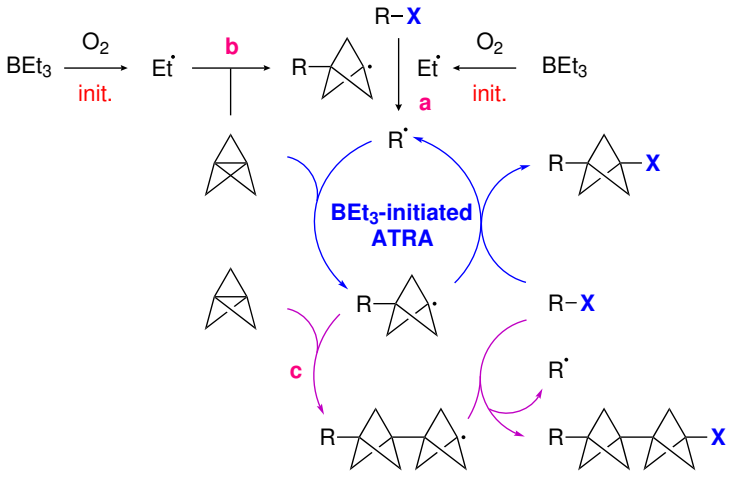
reaction by consuming butyl radical, forming peroxy radicals that react with tributylborane to form peroxyborinate and favoring the equilibrium to lie toward peroxyborinates.

Table 2.2: Rate constants for the elementary steps of the autooxidation of BEt_3.[96]

Step	Rate constant (M^{-1} s^{-1})
(1)	7×10^{-4}
(2)	$\approx 10^6$
(5a) and (5b)	$\approx 10^7$
(6)	2×10^9
(7)	2×10^6

In the context of our reaction of interest, an ethyl radical can either abstract a halogen atom from an organohalide (Scheme 2.6, path a) or attack a molecule of tricyclo[1.1.1.$0^{1,3}$]pentane (TCP, Scheme 2.6, path b). Following path a, the R$^\bullet$ can then react with TCP, yielding a substituted bicyclo[1.1.1]pentyl radical. This radical can then propagate the reaction by abstracting a halogen atom from the starting material, affording a 1-halo-3-substituted bicyclo[1.1.1]pentane (haloBCP) and reforming R$^\bullet$. According to

path b, the 3-ethylbicyclo[1.1.1]pentyl radical can abstract a halogen from the starting halide to form 1-halo-3-ethylbicyclo[1.1.1]pentane and R$^{\bullet}$. As shown previously, when the rate of propagation becomes too low, the bicyclo[1.1.1]pentyl radical start reacting with TCP to form in the end [2]staffane derivatives (path c).



Scheme 2.6: Mechanism for the ATRA of organohalides to TCP.

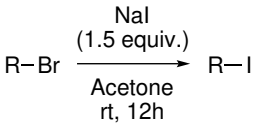
2.2 Synthesis of halogenated substrates

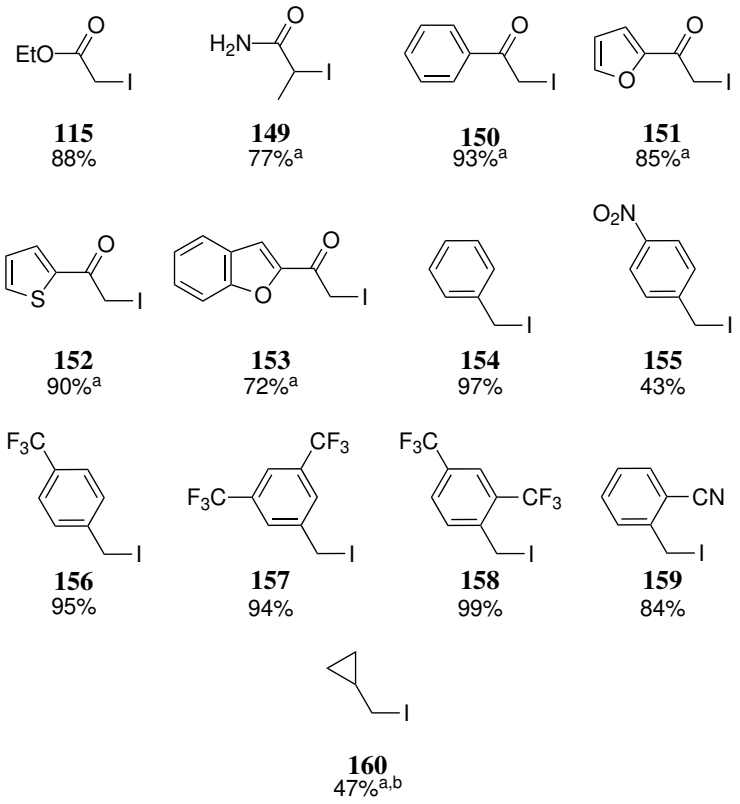
Work commenced with the synthesis of a variety of iodinated substrates via the Finkelstein reaction of alkyl bromides, using sodium iodide in acetone. α-Iodo carbonyl compounds **115**–**153**, benzyl iodides **154**–**159** and alkyl iodide **160** were synthesised accordingly as shown in Table 2.3. Alkyl iodides **161**–**163** were produced via the Appel reaction of the corresponding alcohols as shown in Table 2.4.

N-Boc protection of 2-acetylpyrrole and 2-acetylindole afforded **164** and **165** respectively, followed by copper oxide-mediated iodination to produce aromatic α-iodoketones **166** and **167** (Scheme 2.7). Unfortunately, the pyrrole derivative was deprotected during the iodination, but that was not the case for the indole derivative.

α-Iodoaldehyde **168** was synthesised from the corresponding aldehyde using L-proline and *N*-iodosuccinimide (NIS) in a reasonable yield (Scheme 2.8a). α-Iodosulfone **169** was obtained by alkylation of sodium benzenesulfinate with diiodomethane (Scheme 2.8b). α-Iodosulfone **171** was synthesised from 1-phenyl-1*H*-tetrazole-5-thiol by methylation, tungstate-mediated oxidation, deprotonation and iodination (Scheme 2.8c).

Table 2.3: Substrate synthesis via Finkelstein reaction.

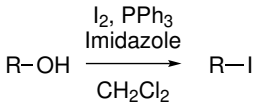


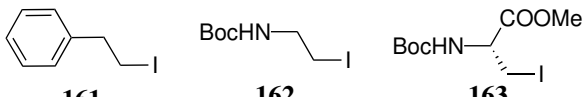


115 88%
149 77%[a]
150 93%[a]
151 85%[a]
152 90%[a]
153 72%[a]
154 97%
155 43%
156 95%
157 94%
158 99%
159 84%
160 47%[a,b]

[a]Synthesised by Dr. Carlos Arroniz. [b]NaI (5.4 equiv.).

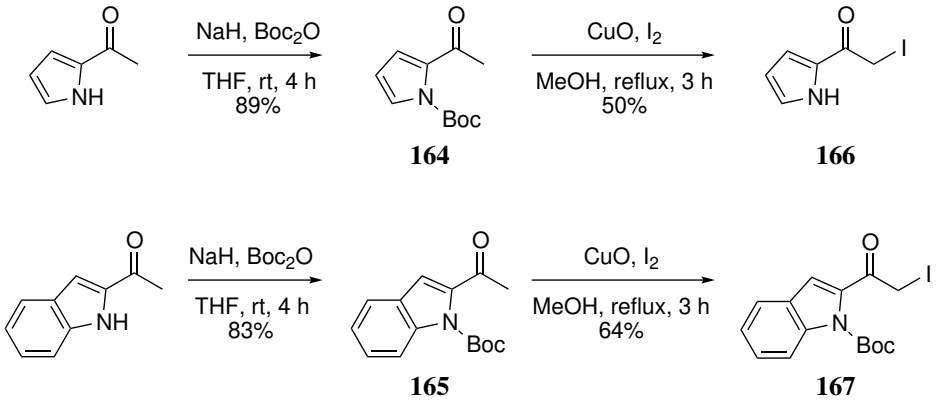
Table 2.4: Substrate synthesis via Appel reaction.





161 93%[a]
162 34%[b,c]
163 81%[d]

[a]PPh_3 (1.2 equiv.), I_2 (1.4 equiv.), imidazole (1.5 equiv.) at rt for 12 h. [b]PPh_3 (1.2 equiv.), I_2 (1.2 equiv.) at rt for 3 h. [c]Synthesised by Dr. Carlos Arroniz. [d]PPh_3 (1.5 equiv.), I_2 (1.5 equiv.), imidazole (1.5 equiv.) at 0 °C for 2 h.

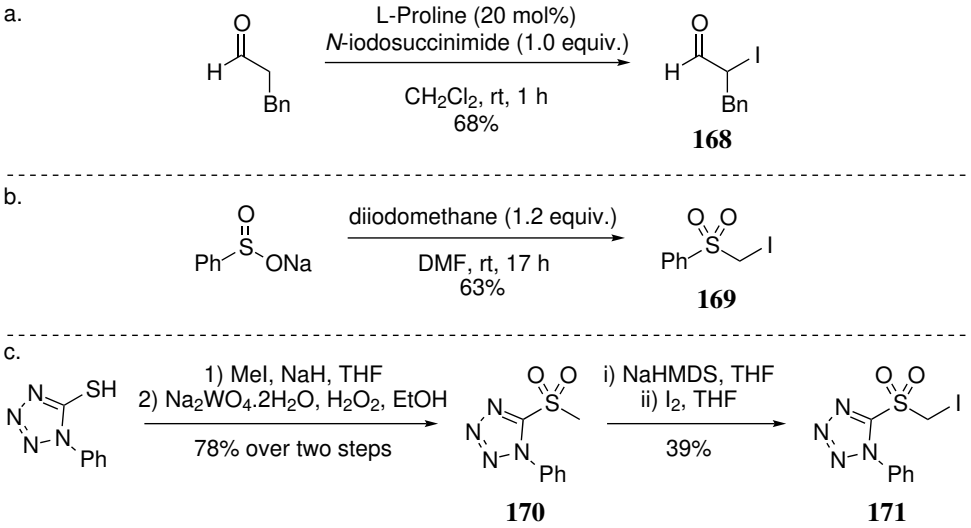


164 **166**

165 **167**

Synthesised by Dr. Carlos Arroniz.

Scheme 2.7: Substrate synthesis via copper oxide-mediated iodination.



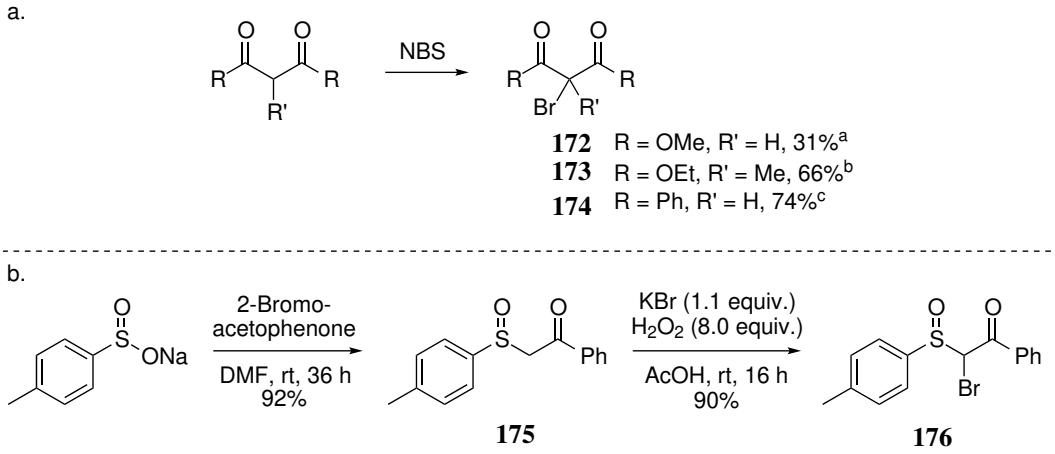
168 **169**

170 **171**

168 was synthesised by Dr. Carlos Arroniz.

Scheme 2.8: Synthesis of substrates **168**, **169** and **171**.

The brominated 1,3-dicarbonyl substrates **172**, **173** and **174** were synthesised *via* acid-catalysed bromination using *N*-bromosuccinimide (NBS) as shown in Scheme 2.9a. α-Bromo-β-ketosulfone **176** was obtained by alkylation of sodium *p*-toluenesulfinate with 2-bromoacetophenone and bromination using potassium bromide and hydrogen peroxide under acidic conditions (Scheme 2.9b). In all other cases, the substrates were purchased from available commercial sources.



[a]NBS (1.1 equiv.), *p*TsOH·H_2O (20 mol%) in $CHCl_3$ at 70 °C for 2 h. [b]NBS (1.5 equiv.) in CCl_4 at reflux for 12 h. [c]NBS (1.1 equiv.), *p*TsOH·H_2O (20 mol%) in CH_2Cl_2 at rt for 15 min.

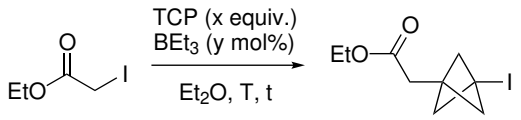
Scheme 2.9: Synthesis of brominated substrates.

2.3 Preliminary experiments and reaction optimisation

The ATRA reaction was first studied using ethyl iodoacetate (**115**), two equivalents of TCP (**1**) and 10 mol% of triethylborane (BEt_3) for 20 h at rt in the dark. Pleasingly, this reaction gave BCP derivative **110** in excellent yield (Table 2.5, entry 1). We recognised that this reaction was in fact quite rapid, reaching completion in under 15 min. It also became apparent that running the reaction in the dark was not necessary. The amount of TCP could be reduced to 1.3 equivalents, but under these conditions, the conversion was only 83% (Table 2.5, entry 3). While adding BEt_3 to the reaction mixture, an exotherm was observed, which could be prevented by cooling the reaction to 0 °C to exclude any evaporation of the volatile TCP. By doing so, completion was reached and **110** was obtained in 87% yield (Table 2.5, entry 4). The amount of BEt_3 could also be reduced to 1 mol% without affecting the yield (Table 2.5, entries 5-6). However, when using 0.5 mol%, a significant amount of starting material remained (Table 2.5, entry 7). The loading of TCP could be further reduced to 1.1 equivalents, yielding **110** in 92% yield (Table 2.5, entries 8-9). Control experiments were conducted using two equivalents of TCP and without BEt_3 in the dark showed only 39% conversion to the product over 20 h (Table 2.5, entry 10). When operating in the presence of light and in the absence of BEt_3,

the conversion was higher but the reaction failed to reach completion, confirming the need for BEt_3 to initiate a rapid reaction (Table 2.5, entry 11).

Table 2.5: Optimisation table for substrate **115**.



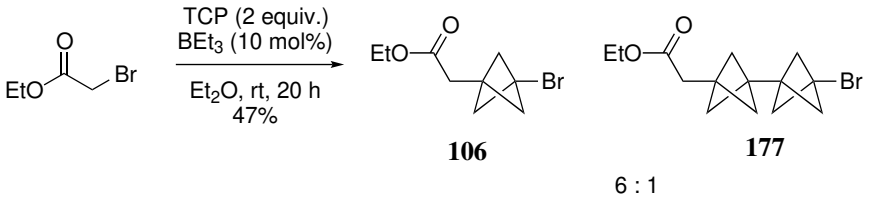
115 **110**

Entry	x (equiv.)	y (mol%)	T (°C)	t	Yield (**115/110**)
1	2.0	10	rt	20 h	90%[a]
2	2.0	10	rt	15 min	n.d. (0:100)[a]
3	1.3	10	rt	15 min	(17 : 83)
4	1.3	10	0	15 min	87%
5	1.3	5	0	15 min	89%
6	1.3	1	0	15 min	95%
7	1.3	0.5	0	15 min	(66 : 33)
8	1.2	1	0	15 min	94%
9	**1.1**	**1**	**0**	**15 min**	**92%**
10	2.0	0	rt	20 h	(61:39)[a]
11	2.0	0	rt	20 h	(36 : 64)

[a] The reaction was carried out in the dark. n.d. Not determined

We questioned whether ethyl bromoacetate could also be a suitable substrate given previous reports in the literature of its use in ATRA reactions.[97] Employing the original conditions in Table 2.5, entry 1, the product was formed in moderate yield and in a 6:1 ratio with an inseparable and common side-product found in reactions using TCP, namely the [2]staffane **177**, arising from the reaction of two TCP molecules (Scheme 2.10). Due to the carbon-bromine bond being stronger than the carbon-iodine bond, the abstraction of a bromine atom is much slower than that of an iodine atom. The attack of a bicyclo[1.1.1]pentyl radical on a molecule of TCP can thus compete with the propagation process and produce oligomers.

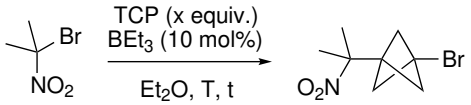
The reaction proved better using 2-bromo-2-nitropropane (**178**), to give adduct **179** (Table 2.6, entry 1). The corresponding [2]staffane was produced in a 1:10 ratio staffane / BCP but was easily separated by crystallisation, affording **179** in excellent yield. Again, the reaction proved to be extremely rapid, reaching completion within 5 min



Scheme 2.10: Synthesis of **106** and **177**.

(Table 2.6, entry 2). However, when the amount of TCP was reduced to 1.1 equivalents, completion was not reached within 5 or 15 min (Table 2.6, entry 3-4), while the use of 1.4 equivalents allowed for complete conversion (Table 2.6, entry 5-6). When using 1.3 equivalents, completion was not reached either in the dark or in the presence of light (Table 2.6, entry 7-8). A reduction of the temperature to 0 °C was beneficial and **179** was obtained in 73% yield (Table 2.6, entry 9). While reducing the amount of TCP, we observed that the amount of staffane produced went down as well. The reduction in temperature also brought that amount down. Using 1.3 equivalents of TCP at 0 °C, the NMR ratio of staffane / BCP was higher than 1:20.

Table 2.6: Optimisation table for 2-bromo-2-nitropropane.



178 **179**

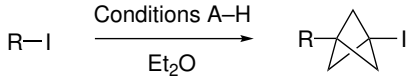
Entry	x (equiv.)	T (°C)	t	Isolated yield (**178/179**)
1	2.0	rt	20 h	68%[a]
2	2.0	rt	5 min	(0:100)[a]
3	1.1	rt	5 min	(8 : 92)[a]
4	1.1	rt	15 min	(11 : 89)[a]
5	1.5	rt	15 min	(0 : 100)[a]
6	1.4	rt	15 min	(0 : 100)[a]
7	1.3	rt	15 min	(3 : 97)[a]
8	1.3	rt	15 min	(3 : 97)
9	**1.3**	**0**	**15 min**	**73%**

[a]The reaction was carried out in the dark.

2.4 Scope of the reaction

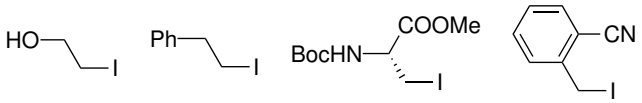
With optimised conditions in hand, the scope of the ATRA reaction was examined. A wide range of substrates was explored and a summary is depicted in Figure 2.2, presenting the synthesis of compounds **180**–**201**. It was quickly realised that although all reactions run using 2 equivalents of TCP and 10 mol% of BEt_3 at rt for 20 h reached completion, many did not when using the more economical conditions developed for ethyl iodoacetate (**115**). We therefore sought to reduce the reaction time as well as the quantities of reagents used as much as possible, while maintaining efficiency.

Table 2.7: Reoptimisation of selected substrates.



R–I	Conditions							
	A	B	C	D	E	F	G	H
202	(56%)	**80%**						
161		(66%)	(91%)	(96%) **87%**				
163			(70%)		(75%)	(80%)		**72%**
159					(75%)	(91%)	(94%)	**91%**

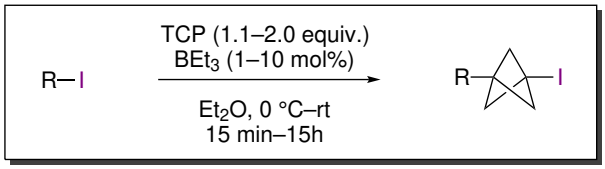
Yields in bold, conversion in parenthesis.

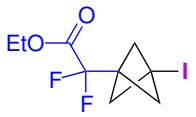


202 **161** **163** **159**

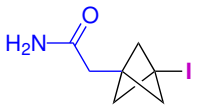
Conditions A: TCP (1.1 equiv.), BEt_3 (1 mol%), 0 °C, 15 min. **Conditions B:** TCP (1.3 equiv.), BEt_3 (10 mol%), 0 °C, 15 min. **Conditions C:** TCP (1.3 equiv.), BEt_3 (10 mol%), 0 °C, 1 h. **Conditions D:** TCP (1.3 equiv.), BEt_3 (10 mol%), 0 °C, 2 h. **Conditions E:** TCP (1.3 equiv.), BEt_3 (10 mol%), rt, 1 h. **Conditions F:** TCP (1.3 equiv.), BEt_3 (10 mol%), rt, 2 h. **Conditions G:** TCP (1.3 equiv.), BEt_3 (10 mol%), rt, 3 h. **Conditions H:** TCP (2.0 equiv.), BEt_3 (10 mol%), rt, 1 h.

Table 2.7 shows a short reoptimisation of the reaction conditions for selected substrates to account for differences in their reactivity. Compound **202** proved quite reactive, although much less so than α-iodoester **115** and needed more TCP to reach completion in a short period of time (conditions B). Although seemingly similar, iodoalkane **161** required a longer reaction time (conditions D) to reach 96% conversion. Compounds

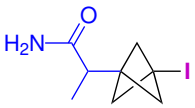




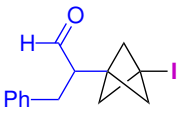
180
15 min, 98%[a]



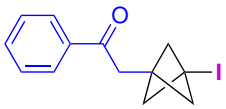
181
1.5 h, 88%[b,c,*]



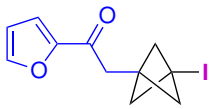
182
1.5 h, 99%[b,c,*]



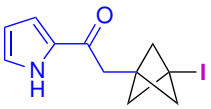
183
1 h, 38%*



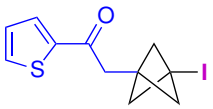
184
2 h, 85%*



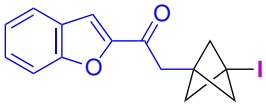
185
1 h, 79%*



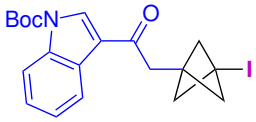
186
6 h, 58%[c,*]



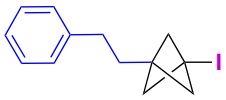
187
1 h, 90%*



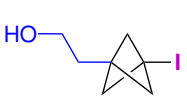
188
2 h, 87%*



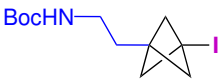
189
15 h, 68%[c,*]



190
2 h, 87%[b]

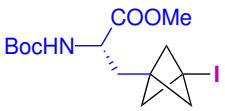


191
15 min, 86%[d]

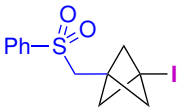


192
45 min, 86%[b,*]

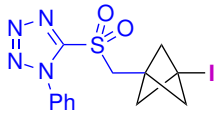
193
1h, 72%[b]



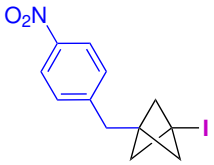
194
1 h, 72%



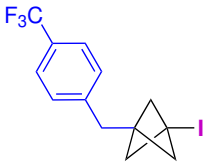
195
3 h, 61%[d]



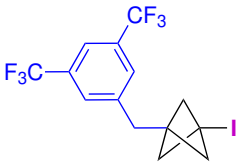
196
1 h, 93%[c,d]



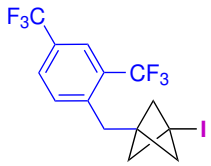
197
2 h, 90%[c]



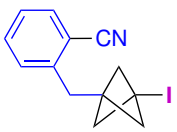
198
1 h, 76%



199
1 h, 84%



200
1 h, 91%



201
1 h, 90%

All reactions were performed using TCP (2.0 equiv.) and BEt_3 (10 mol%) at rt unless indicated otherwise. [a]TCP (1.1 equiv.), BEt_3 (1 mol%), 0 °C. [b]TCP (1.3 equiv.), rt. [c]A co-solvent was added to solubilise the substrate: MeOH for **181** and **182**; CH_2Cl_2 for **186**, **189** and **197**. [d]TCP (1.3 equiv.), 0 °C. *Synthesised by Dr Carlos Arroniz.

Figure 2.2: Scope of the BEt_3-initiated ATRA reaction of TCP and iodides.

159 and **163** proved to be much less reactive and required 2.0 equivalents of TCP and 10 mol% of BEt_3 at rt to reach completion in 1 h (conditions H).

We also synthesised the enantiomer of **163** and reacted it under the same conditions; the two BCP amino acids displayed specific rotation of opposite values, and HPLC traces showed that no epimerization occurred during the ATRA reaction (see experimentals).

In light of these results, it was decided to carry on the scope using conditions B, D and H for the rest of the substrates and vary the reaction time when necessary (Figure 2.2).

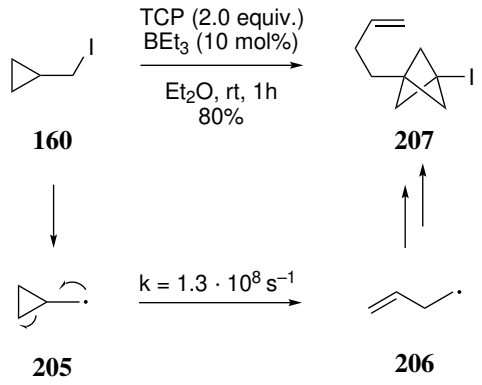
In terms of the substrate scope, difluoroester **180** was produced under the same conditions as ester **110**, while amides **181** and **182** required 1.3 equivalents of TCP at rt, possibly due to the use of MeOH to ensure complete solubility, which could result in concentration effects being responsible for the need for extra reagent. Aldehyde **183** was produced in moderate yield and was fairly unstable to light, heat and silica, as was the starting material. Aromatic ketones **184–189** required 2 equivalents of TCP and 10 mol% of BEt_3 to be obtained within 1–2 h although again, a co-solvent was needed for **186** and **189** which likely resulted in longer reaction time. Similarly to **190**, *N*-Boc amine **192** needed 1.3 equivalents of TCP at rt to reach completion within 45 min and was produced in 89% yield. Chloroalkane **193** could be prepared using less than 2 equivalents of TCP, and showed that a chlorine atom was tolerated under the reaction conditions. Sulfones **195** and **196** were produced in good yields at low temperature without degradation of the sulfone functionality. Benzyl-containing compounds **197–201** were obtained using 2 equivalents of TCP, 10 mol% of BEt_3 at rt, showing that benzyl iodides substrates were much slower to react. In the case of benzyl iodide itself, completion of the reaction could not be reached even using 2 equivalents of TCP and 10 mol% of BEt_3 for 20 h, and gave a starting material-to-product ratio of 1.4:1. When the reaction mixture was evaporated and the crude material resubmitted to the same reaction conditions, the ratio benzyl iodide/BCP increased but again, completion was not reached. Thus, the presence of an electron withdrawing group on the arene proved crucial for good reactivity.

Finally, the ATRA reaction was amenable to scale-up, with a gram scale reaction for **180** (5.00 mmol, 94%) and multi-gram scale for **198** (10.0 mmol, 71%).

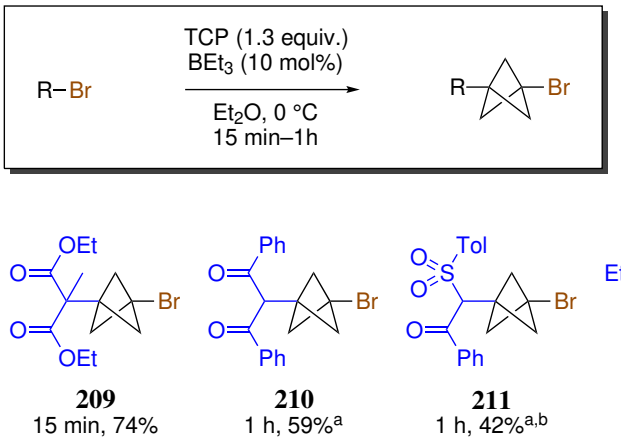
Overall, the reaction proved very tolerant of a variety of functional groups such as carbonyls, heteroaromatics, unprotected heteroatoms, chlorides, amino acids, sulfones, nitriles, trifluoromethyls and nitro groups.

During this work, it was noted that the iodoBCP products were somewhat unstable to light and heat. This instability proved to be compound dependant, with solids being significantly more stable than oils. For example, after work up of BCP ester **110**, concentration of the organic phase in the presence of light and 30 °C water bath caused a yellow to brown coloration of the oil, which was suspected to be characteristic of the presence of iodine (the colour would disappear when the oil was redissolved in an organic solvent and washed with a 10% aqueous solution of $Na_2S_2O_3$). If the oil was left on the bench at rt in the presence of light, it would also turn yellow-brown after a few hours. When concentrating the organic phase containing BCP **198** under the same conditions, no coloration of the solid was observed. Furthermore the compound could be left on the bench for 2 days before any coloration appeared. We analysed the coloured oil and solid by NMR spectroscopy and no significant amount of new material was observed, albeit the spectrum showed a less clean baseline. In both cases, the oil and the solid would decompose to a dark green oily residue within 1-2 weeks. To ensure that no decomposition would occur, the organic phases were concentrated at rt in the dark using aluminium foil to cover the rotary evaporator bath. The compounds were then stored in a freezer at –20 °C. By doing so, no significant decomposition was observed and most compounds proved indefinitely stable at this lower temperature.

To verify that the reaction was consistent with the initial radical formation from the iodide, a radical clock compound, (iodomethyl)cyclopropane (**160**), was reacted with TCP (Scheme 2.11). Only alkene **203** was observed in the crude reaction mixture, resulting from the radical ring opening of cyclopropylmethyl radical yielding homoallyl radical **204**. The rate constant for the ring opening of cyclopropylmethyl radical is estimated at $1.3 \cdot 10^8$ s^{-1}, it is thus likely that the addition of radicals to TCP is slower.[98]



Scheme 2.11: Radical-clock experiment with (iodomethyl)cyclopropane (**160**) performed by Dr Carlos Arroniz.



[a]CH_2Cl_2 was added to solubilise the substrate. [b]5% of staffane was produced alongside. [c]TCP (2 equiv.), NMR yield. [d]8% of staffane was produced alongside.

Figure 2.3: Scope of the BEt_3-initiated ATRA reaction of TCP and bromides.

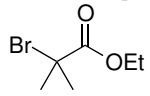
Brominated substrates were tested and proved to react fairly well using only 1.3 equivalents of TCP and 10 mol% of BEt_3 (Figure 2.3). Compounds **208** and **209** were produced within 15 min. 1,3-Diketone **210** and β-ketosulfone **211** required CH_2Cl_2 to ensure solubility and thus required a longer reaction time. Along with sulfone **211**, the corresponding [2]staffane was produced low amounts (5%) and could not be separated. Similarly, **212** was formed alongside 8% of the corresponding staffane and required further 2 equivalents of TCP to reach completion, showing that ethyl α-bromoisobutyrate (**213**) is more reactive than ethyl bromoacetate, but not as much as the 1,3-dicarbonyl substrates. We envisaged that the radical produced was more stabilised thanks to the *gem*-dimethyl group and that steric hindrance forces the bromine atom further away from the carbon it is attached to, thus weakening that bond. Deoghare and co-workers calculated

the values for the bond length and bond dissociation energy of the C–Br bond in **213** in the gas phase as shown in Table 2.8.[99] Compared to an average C–Br bond, ethyl α-bromoisobutyrate shows longer C–Br bond (2.017 Å vs. 1.94 Å) as well as a weaker bond strength (200.87 kJ/mol vs. 288 kJ/mol). Although no information about the bond length and bond dissociation energy in ethyl bromoacetate is available in the literature, the crystal structure of fluoroacetate dehalogenase RPA1163 - Asp110Asn/Bromoacetate shows that the C–Br bond length of bromoacetate is 1.957 Å.[100] When conducted at rt, the yield of the reaction decreased to 69% and NMR analysis showed 20% of staffane derivative was produced, suggesting a temperature dependance for the formation of staffane derivatives.

Table 2.8: Comparision between the BDE and bond length between the C–Br bond of α-bromoisobutyrate (**213**), bromoacetate and an average C–Br bond.

	C–Br Bond Dissociation Energy at 298 K (kJ/mol)	C–Br bond length (Å)
Average C–Br bond	288[a]	1.94[a]
Fluoroacetate dehalogenase RPA1163 - Asp110Asn/Bromoacetate	-	1.957[b]
Ethyl α-bromoisobutyrate	247.87[c]	2.017[c]

[a] Reference [101]. [b] Reference [100]. [c] Reference [99].



213

In general, we observe different types of reactivity between the radicals and TCP. Radicals bearing electron-withdrawing groups such as acetates, acetamides and sulfones reacted quickly, suggesting that TCP is the nucleophilic partner in this radical reaction. When using electron-deficient benzyl iodides, the reaction time increases significantly if the amount of TCP is not increased, but in the case of electron-neutral benzyl iodide, the reactivity was reduced to the point where completion could not be reached. Non-stabilised alkyl radicals exhibited high reactivity, despite being nucleophilic species; we hypothesised that TCP reacts rapidly with highly electrophilic radicals as well as highly nucleophilic radicals, but rather poorly with radical whose nucleophilicity is average. De Vleeschouwer and co-workers calculated the nucleophilicity of a range

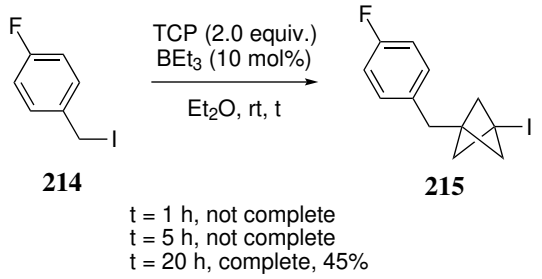
of radicals and provided a classification of these radicals from strong nucleophile to strong electrophile (Table 2.9).[102]

Table 2.9: Classification of radicals according to nucleophilicity.[102]

Character	Radicals
strong nucleophile	2-hydroxyprop-2-yl
	tert-butyl
	hydroxymethyl
moderate nucleophile	*p*-methoxybenzyl
	p-methylbenzyl
	methyl
	benzyl
	p-fluorobenzyl
weak nucleophile	2-cyanoprop-2-yl
	p-cyanobenzyl
	tert-butoxycarbonylmethyl
	cyanomethyl
moderate electrophile	tosyl
	phenylsulfonyl
strong electrophile	bromine
	chlorine
	fluorine

Interestingly, the benzyl radical, ranked as a moderate nucleophile, performed poorly under our reaction conditions. On the contrary, the phenylsulfonyl radical, ranked as a moderate electrophile, performed very well. We sought to test other radicals in that list and thus reacted *p*-fluorobenzyl iodide (**214**, made similarly to the other benzyl iodides in 80% yield) with TCP and BEt_3 as shown in Scheme 2.12. This substrate proved very slow to react compared the other benzyl iodides, requiring 20 h to reach completion (45% yield).

This showed that the *p*-fluorobenzyl radical was more reactive than the benzyl radical, but it could not outcompete more electrophilic radicals. Computational studies are underway to establish a deeper understanding of the difference in reactivity of the different radicals with TCP.



Scheme 2.12: ATRA reaction with *p*-fluorobenzyl iodide performed by Ms Helen Jones.

2.5 Unsuccessful substrates

Alongside the above results, a number of substrates proved to be unsuccessful in the ATRA reaction (Figure 2.4).

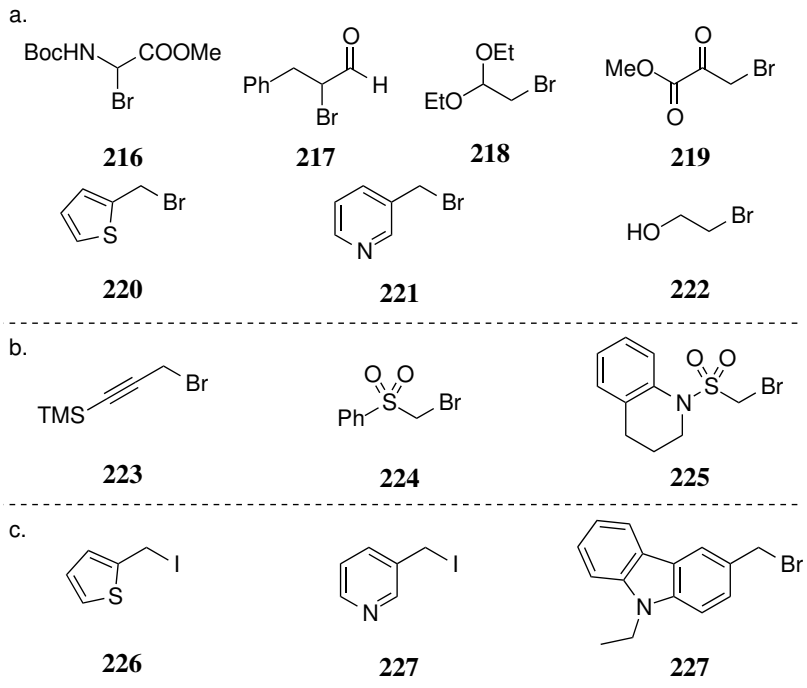


Figure 2.4: Unsuccessful substrates. a) Unreactive substrates; b) Substrates where completion was not reached; c) Substrate was unstable and could not be made or isolated.

Substrates **216–222** were all unreactive towards the reaction conditions (Figure 2.4a); it had been hoped to use **216** to synthesise a BCP derivative of phenylglycine. **217–222** were screened alongside other brominated substrates presented in Figure 2.3. This showed that the use of bromide is limited to sufficiently activated bromides or, in the case of **178** and α-bromoester **213**, to sterically hindered bromides bearing an electron-withdrawing group. Regarding substrates **223–225**, reaction completion could not be reached. After

20 h, the reaction using **223** displayed a starting material-to-product ratio of 1:3. **224** and **225** showed little conversion, although analysis of the crude reaction mixtures showed degradation and signal overlap, preventing a starting material-to-product ratio from being determined. Heteroaromatic benzylic iodides **226** and **227** and carbazole derivative **228** could not be synthesised due to their inherent instability upon isolation.

It appeared that one solution to this would be an *in situ* halogenation protocol which could additionally provide a greater range of commercially-sourced starting materials.

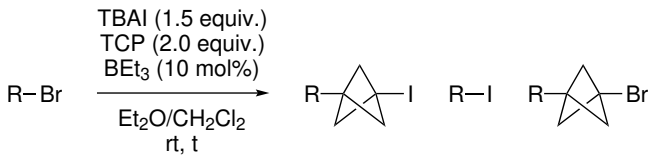
2.6 Atom Transfer Radical Addition of organoiodides made *in situ*

The *in situ* conversion of bromides to iodides and ATRA reaction was performed on a representative selection of substrates from our substrate scope. *tert*-Butylammonium iodide (TBAI) was chosen as the iodide salt, given its higher solubility in organic solvents; nonetheless, CH_2Cl_2 was used as a co-solvent to ensure complete solubility of TBAI. These reactions were conducted under the most "generous" conditions, namely 2 equivalents of TCP and 10 mol% of BEt_3 at rt. Practically, the bromide was dissolved in CH_2Cl_2 and TBAI was added. The resulting mixture was stirred for 5 min and TCP was added. After stirring for 2 min, BEt_3 was added *via* syringe and the resulting mixture stirred at rt for the corresponding amount of time.

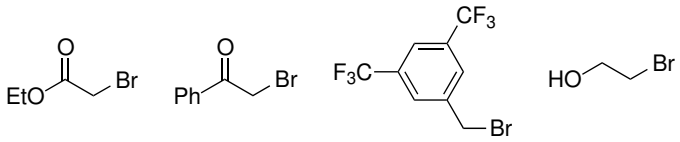
Substrate **97** performed well, it was fully converted to the iodide and reacted with TCP within 1 h. α-Bromoketone **229** proved slightly less reactive and despite a high conversion, small amounts of **229** and the corresponding α-iodoketone were found in the crude reaction mixture. Benzyl bromide **230** reacted much less rapidly and large amounts of **230** and the corresponding benzyl iodide were present after 20 h. In the case of 2-bromoethanol (**97**), no iodoBCP was detected after 20 h; large amounts of **97** and 2-iodoethanol (**202**) were present although we could not determine a ratio due to the overlap of NMR signals. The corresponding iodoBCP was not formed at all. Given that **157** and **202** proved reactive in the ATRA reaction, the rate of halide exchange seems to be an important factor. In the four cases above, no bromoBCP was detected.

Overall, the major limitation is the halide exchange. We could envisage to stir the

Table 2.10: One-pot Finkelstein and ATRA reaction.



Substrate	t (h)	R–Br / BCP–I / R–I / BCP–Br	Yield (%)	Comment
97	1	0 : 1 : 0 : 0	92	
229	20	0.02 : 1 : 0.05 : 0	n.d.	
230	20	0.69 : 1 : 0.61 : 0	n.d.	
222	20	n.d. : 0 : n.d. : 0	n.d.	X–CH_2– signal overlapping



97 **229** **230** **222**

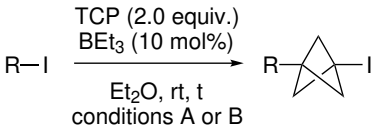
reaction mixture for a longer period of time before adding TCP to ensure full conversion of the bromide to the iodide before performing the ATRA reaction.

2.7 Study of the amount of oxygen needed for the ATRA reaction

Oxygen in the air is thought to be required in the ATRA reaction by means of activating and decomposing BEt_3 into ethyl radicals.[103] Curran and co-workers published a study on the mechanism of autooxidation of BEt_3 in air and reported that above a certain concentration of oxygen, the ethyl radicals will react with oxygen, thus inhibiting the initiation process of the radical reaction.[96] It was therefore decided to take two substrates of different reactivity, α-iodo ester **115** (very reactive) and benzyl iodide **156** (slower to react) and perform the ATRA reaction under two sets of conditions:

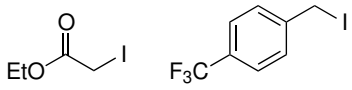
- Condition A: flame-dried vial and atmosphere of N_2
- Condition B: flame-dried vial, atmosphere of N_2 and degassed solution of TCP (by freeze-thawing under vacuum until no gaseous evolution was observed)

Table 2.11: ATRA reaction under low oxygen levels.



Substrate	Conditions	t	Yield (%)	SM / P (after 1 h)	SM / P (after 5 h)
	air	15 min	92	-	-
115	A	15 min	96	-	-
	B	15 min	87	-	-
	air	1 h	76	1 : 0	-
156	A	20 h	94	1 : 0.28	1 : 1.07
	B	20 h	73	1 : 0.28	-

Conditions A: flame-dried vial and atmosphere of N_2. **Conditions B:** flame-dried vial, atmosphere of N_2 and degassed solution of TCP.

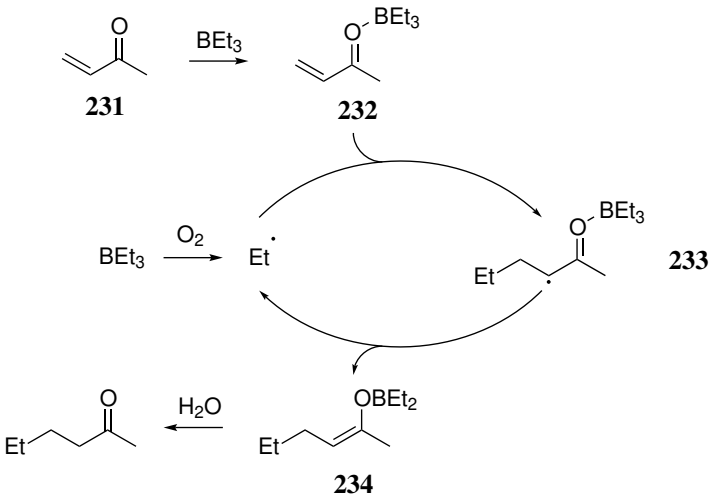


115 **156**

In the case of **115**, performing the reaction under low oxygen levels did not impair the reactivity whether under conditions A or B (Table 2.11). We hypothesised that since organoboron species can act as Lewis acids, BEt_3 could be activated and produce ethyl radicals without needing any oxygen.[103]

Maillard and co-workers showed that during the conjugate addition of triethylborane to methyl vinyl ketone (**231**), triethylborane complexes the carbonyl group to form **232** (Scheme 2.13).[104] They proposed that ethyl radicals attack complex **232**, affording radical **233** that decomposes to boron enolate **234** and ethyl radicals.

Given that ethyl iodoacetate decomposes naturally to produce iodine when exposed to light at rt, we could imagine that triethylborane accelerates this process. Alternatively, we could think the smallest amount of air added while syringing reagent in the reaction vessel was enough to initiate the radical reaction. When using **156**, the rate of the reaction was drastically reduced. Under conditions A, the starting material-to-product ratio was found to be 1:0.28 after 1 h while under air (Figure 2.2), the reaction was complete. After 5 h, the ratio had decreased to 1:1.07. The reaction mixture was then left to stir for 15 h,



Scheme 2.13: Proposed mechanism for the conjugate addition of triethylborane to methyl vinyl ketone.[104]

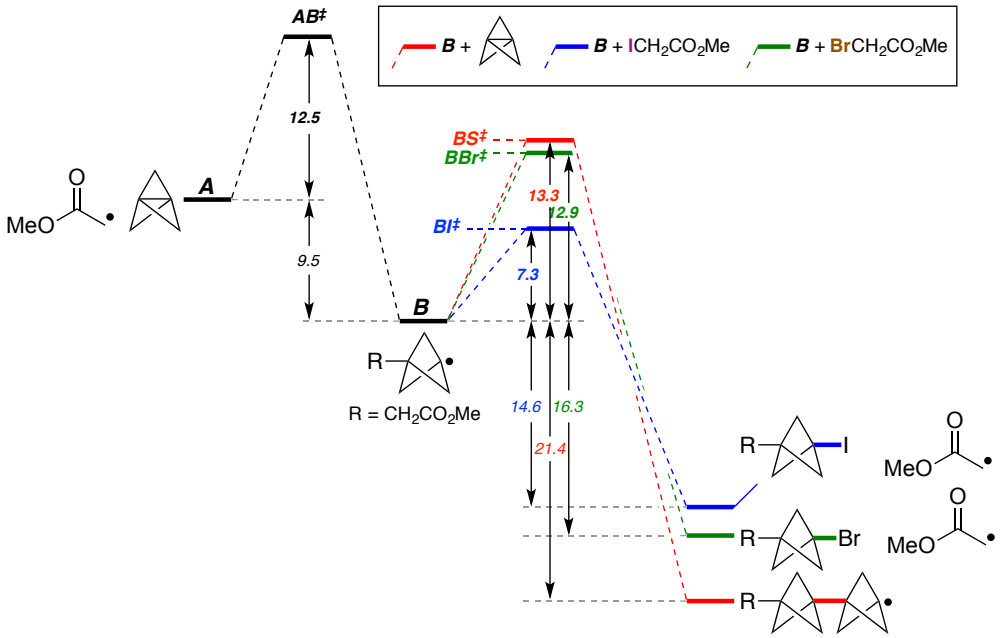
after which no starting material was found. The product, iodoBCP **198**, was obtained in 94% yield. Under conditions B, the reaction of **156** with TCP proved again to be slower, although the same ratio was observed after 1 h as with conditions A. The reaction mixture was left to stir for a further 19 h after which no starting material remained.

Overall, when oxygen was omitted from the reaction vessel as well as from the reaction mixture, it resulted in a drastic decrease of the reaction rate for the less reactive substrates.

2.8 Computational investigation on the propagation step of the ATRA reaction

While the mechanism associated with the reaction involves a radical pathway, as shown by the cyclopropane ring fragmentation observed during the formation of alkene **207**, we yet questioned why for iodides substrates the reaction propagation *via* halogen atom abstraction proceed efficiently without staffane formation, yet with bromides, staffane can be observed. We therefore decided to explore the propagation step computationally and Dr Alexander Dürr examined the reaction of methyl bromoacetate and methyl iodoacetate with TPC at the ROM062x/def2tzvp level[105] (Figure 2.5, *in vacuo*).[26] The addition of the acetyl radical to TCP (**A**) was found to be exergonic and occured *via* transition state $\boldsymbol{AB}^{\ddagger}$ ($\Delta G^{\ddagger}$ = 12.5 kcal mol^{-1}). The resultant bicyclopentyl radical ***B*** can then either abstract an iodine atom from methyl iodoacetate and proceed *via* transition

state ***BI***‡ ($\Delta G^{\ddagger}$ = 7.3 kcal mol^{-1}), or attack TCP and proceed *via* transition state ***BS***‡ ($\Delta G^{\ddagger}$ = 13.3 kcal mol^{-1}). In this case, the productive propagation step is significantly favoured over the oligomerization ($\Delta\Delta G^{\ddagger}$ = 6.1 kcal mol^{-1}). However, when the bicyclopentyl radical abstracts a bromine atom from methyl bromoacetate, the reaction proceed *via* transition state ***BBr***‡ with a barrier of 12.0 kcal mol^{-1}, which suggests that staffane formation is now competitive with the halogen abstraction propagation step ($\Delta\Delta G^{\ddagger}$ = 0.4 kcal mol^{-1}). These result are in agreement with the experimental observation (Scheme 2.10) and reflect the influence of the C–X bond strength on the propagation step of the reaction.



Calculation carried out at the ROM062x/def2tzvp level by Dr Alexander Dürr. Relative energies are in kcal.mol^{-1}

Figure 2.5: Theoretical analysis of the reaction pathway.

2.9 Conclusions

A mild, efficient, practical and substrate tolerant atom transfer radical addition to access 1-halo-3-susbtituted bicyclo[1.1.1]pentane from organohalide derivatives and TCP has been developed.

Organoiodides proved to be excellent substrates, and functional groups as acetates,

acetamides, aldehydes, ketones, alkyls, free hydroxyls, carbamates, chlorides, sulfones and benzyl moieties containing nitro, nitrile and trifluoromethyl groups were well tolerated. Regarding the reactivity of the iodide partner, electron-deficient iodides were found to react rapidly as well as electron-rich iodides. Electron-deficient benzyl iodides were reactive but slower than most of the other substrates. Moderately nucleophilic radicals, as those produced from benzyl iodide or 4-fluorobenzyl iodide reacted even slower and in the case of benzyl iodide, completion was not reached after 20 h.

Organobromides proved reactive, provided they are strongly activated by 1,3-dicarbonyl or β-ketosulfone groups, or by hindered carbonyl or nitro groups. Bromides bearing aromatic or heteroaromatic groups, as well as alkyl bromides, α-bromoketones, propargylic bromides and α-bromosulfones showed no to poor reactivity towards TCP under the studied reaction conditions.

In some cases, [2]staffanes (the association of two BCP units) were observed due to a poor propagation rate in the desired radical chain mechanism based on the carbon-bromide bond being stronger than the carbon-iodide bond. A temperature dependance was observed in the formation of staffanes in the case of 2-bromo-2-nitropropane and ethyl α-bromoisobutyrate, where the amount of staffane produced decreased with a decreasing reaction temperature.

Computational investigation showed that for iodides, the difference in free energy for the transition states associated with the abstraction of an iodine atom by a bicyclopentyl radical, and the transition state for the attack of TCP by a bicyclopentyl radical, is greater than 3 kcal mol^{-1}. This means that the formation of staffane cannot compete with the formation of iodoBCPs. In the case of bromide substrates, that free energy difference between the transition states is $\sim$ 0.4 kcal mol^{-1} and staffanes can thus form alongside bromoBCPs, which is in agreement with the experimental data collected.

IodoBCPs can be directly synthesised from organobromides using tetrabutylammonium iodide to exchange halide *in situ* provided that the exchange is rapid, or that the reaction time is long enough to allow for full conversion from bromide to iodide.

Finally, molecular oxygen in the air proved crucial to allow for complete conversion of organohalides to halogenated BCPs in the case of less reactive substrates as benzyl

iodides, but not for more reactive substrates.

The next part of this thesis will be dedicated to the functionalisation of iodoBCPs *via* lithiation reactions, and reduction of the carbon-halide bond.

3

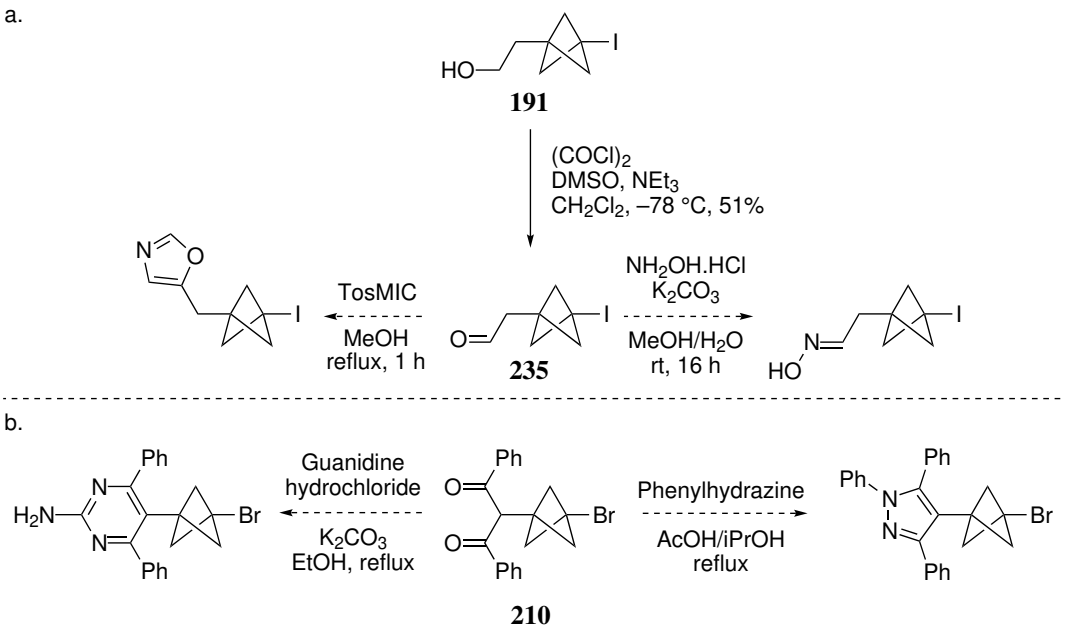
Reduction of the C–I bond of 1-iodo-3-substituted bicyclo[1.1.1]pentanes

Contents

3.1 Introduction

As mentioned in the previous chapter, iodoBCPs are somewhat unstable to light and heat, and need cryogenic storage in order to ensure that no decomposition occurs; we stored them in at –20 °C and observed no decomposition over a period of two years. Alcohol **191** proved to be particularly sensitive and showed colouration within 30 min of standing neat at room temperature under room light. Nevertheless, it could

be oxidised to the corresponding aldehyde **235** in decent yield. Aldehyde **235** proved even more unstable and upon attempted reaction with *p*-toluenesulfonylmethyl isocyanide (TosMIC) or hydroxylamine hydrochloride, **235** decomposed and no product was found (Scheme 3.1a). BromoBCP have shown greater stability and would show colouration after around 2 months of standing at room temperature. However, the same issue was encountered as with iodoBCPs; we attempted to react **210** with guanidine hydrochloride or phenylhydrazine but no product was found in either reaction mixtures. (Scheme 3.1b).

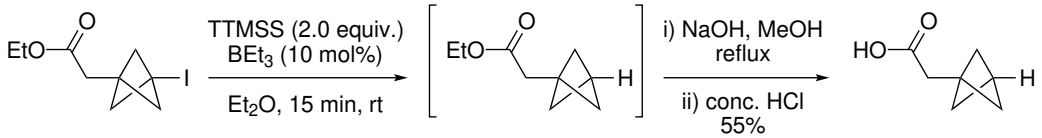


Scheme 3.1: Attempts at derivatization of iodo and bromoBCPs.

This instability was thought to be due to halogen atoms, and prompted us to find ways to transform iodoBCPs into bench stable compounds by reduction of the carbon-iodine bond, in a similar manner to the work of the Michl[79] and Adsool[83] groups (see introduction). The former used *n*-Bu_3SnH as the reducing agent and the latter $(Me_3Si)_3SiH$ (TTMSS). Both used azobisisobutyronitrile (AIBN) as the radical initiator and performed the reaction at high temperature. It was proposed that triethylborane (BEt_3) could be used in place of AIBN in the TTMSS reduction, allowing for the reaction to be carried out at room temperature.

3.2 Triethylborane-initiated tris(trimethylsilyl)silane reduction of iodinated bicyclo[1.1.1]pentanes

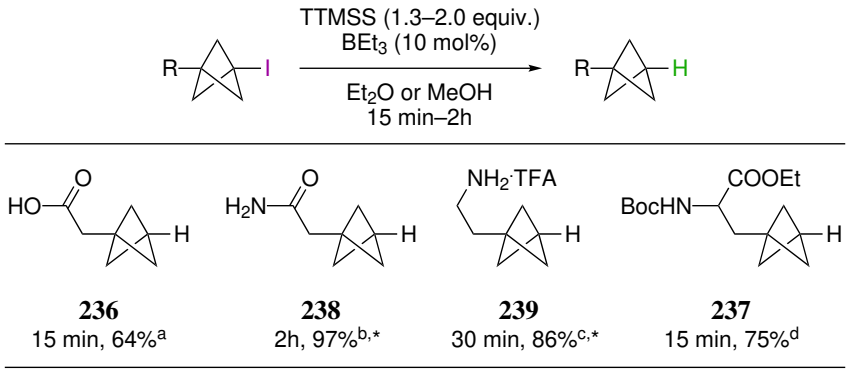
This study commenced using ester **110**, two equivalents of TTMSS and 10 mol% of BEt_3 at rt (Scheme 3.2). Within 15 min, the starting material was consumed and reduced ester **107** could be observed by ^{1}H NMR analysis of the crude reaction mixture. However, upon column chromatography, it was not possible to purify the ester from excess TTMSS and silane by-products. It was decided to hydrolyse the ester to the acid and **236** was produced in 55% yield.



110 **107** **236**

Scheme 3.2: Reduction and hydrolysis of iodide **110**.

We sought to reduced the amount of TTMSS used, and found that 1.3 equivalents also effected the reduction while retaining the same reaction time (Figure 3.1). The procedure could also be telescoped from ethyl iodoacetate into a single pot process, achieving 64% yield over the ATRA and the reduction steps. Other substrates were subjected to these reaction conditions, although for amino acid derivative **237**, the amount of TTMSS was increased to ensure rapid reaction.



236 15 min, 64%[a] **238** 2h, 97%[b,*] **239** 30 min, 86%[c,*] **237** 15 min, 75%[d]

[a]TTMSS (1.3 equiv.) in Et_2O, yield over the ATRA and reduction step from ethyl iodoacetate. [b]TTMSS (1.3 equiv.) in MeOH. [c]TTMSS (1.3 equiv.) in MeOH from Boc-protected amine **192**, the deiodination product was treated with TFA. [d]TTMSS (2.0 equiv.) in Et_2O. *Synthesised by Dr Carlos Arroniz.

Figure 3.1: Scope of the BEt_3-initiated TTMSS reduction.

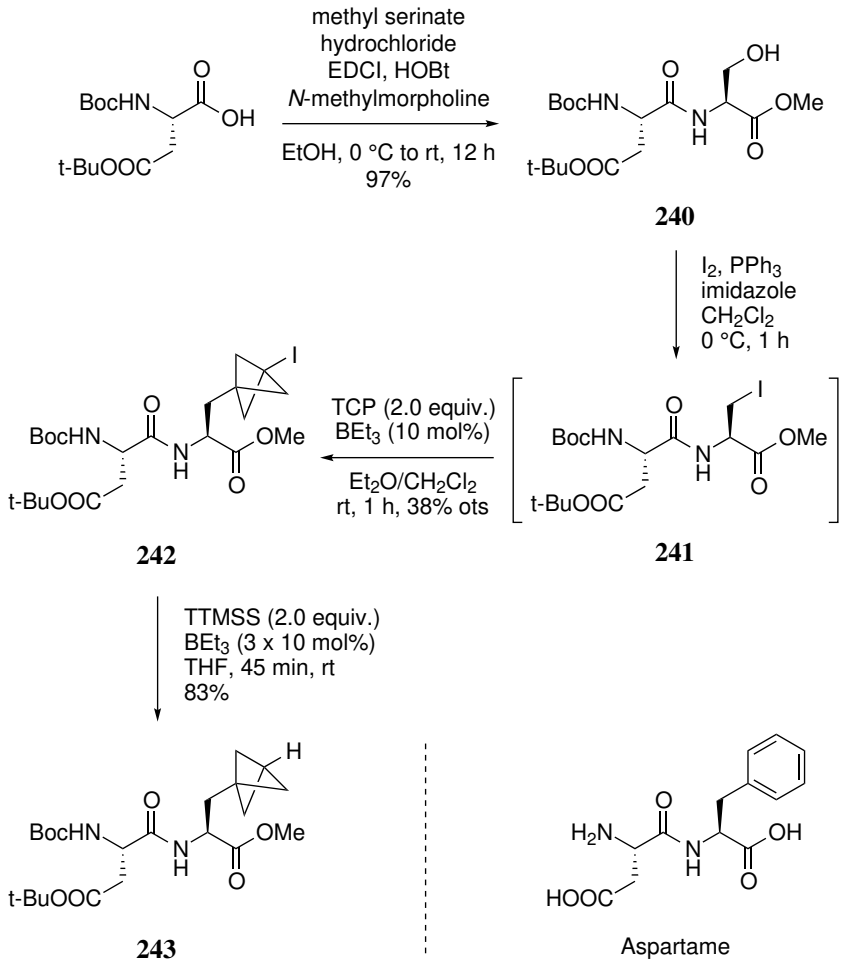
Amide **238** was produced in 97% yield using 1.3 equivalents of TTMSS after 2 h. Ammonium salt **239** was obtained from the corresponding Boc protected amine using the same amount of TTMSS, after treatment with trifluoroacetic acid (TFA) in 86% yield. Amino acid **237**, a BCP-analogue of phenylalanine, was produced in 75% yield using 2 equivalents of TTMSS within 15 min. This methodology thus allowed access to monosubstituted BCP building blocks in a mild, rapid, and less toxic fashion, compare to the use of tin hydrides and AIBN at high temperatures.

We next sought to study whether the ATRA reaction and the TTMSS-mediated reduction could be applied to more complex substrates of potential pharmaceutical interest.

3.3 Synthesis of pharmaceutically relevant monosubstituted BCP derivatives

3.3.1 Synthesis of a dipeptide surrogate

Building on the synthesis of the BCP analogue of phenylalanine (**237**, Figure 3.1), the ATRA/reduction sequence was assessed with a dipeptide. Dipeptide **240** was synthesised by coupling of methyl L-serinate hydrochloride and *N*-Boc-L-aspartic acid 4-*tert*-butyl ester using EDCI, HOBt and *N*-methylmorpholine in 97% yield (Scheme 3.3). Iodination *via* Appel reaction gave iodopeptide **241**, which could not be separated from triphenylphosphine oxide. The crude residue was therefore dissolved in CH_2Cl_2, and submitted to the ATRA reaction conditions to give BCP derivative **242** in 38% yield over two steps. The reduction of this C–I bond necessitated the use of two equivalents of TTMSS and 30 mol% of BEt_3, added in three portions every 15 min to ensure full conversion to give **243**, a protected BCP analogue of aspartame, in 83% yield. It is not obvious why three consecutive addition of BEt_3 were necessary, but failure to add extra BEt_3 resulted in incomplete reaction.

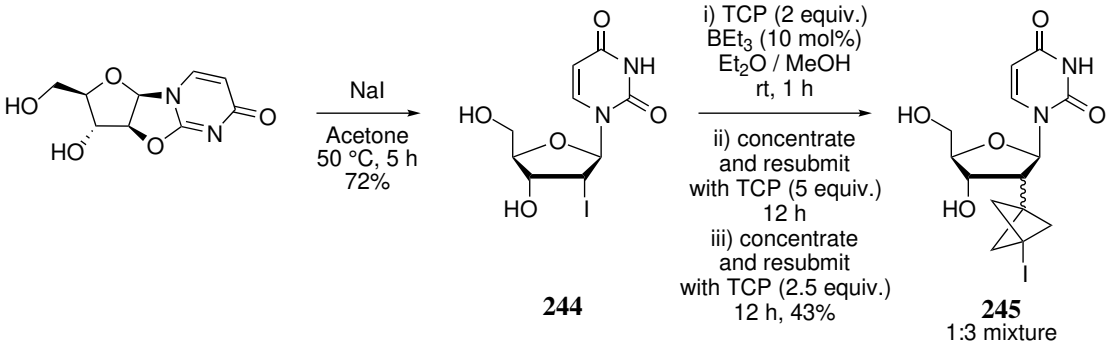


Scheme 3.3: Synthesis of the BCP analogue of aspartame.

3.3.2 Synthesis of a nucleoside surrogate

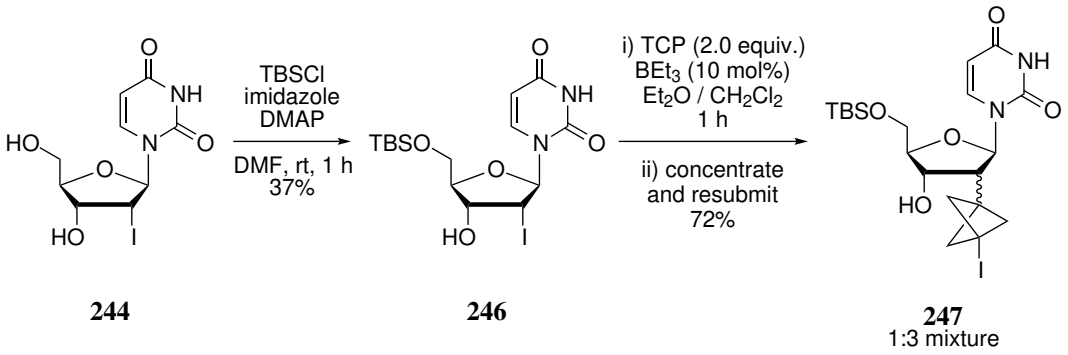
Nucleosides are important scaffolds in biology, and we wondered how these molecules would perform under the ATRA and reduction sequence. 2′-Iodonucloside **244** was synthesised from O-2,2′-cyclouridine and sodium iodide in refluxing acetone for 5 h (Scheme 3.4). When using **244** in the ATRA reaction, no product was observed after 1 h. It was thought that this might be due to the addition of methanol to ensure full solubility of **244** resulting in dilution of the reaction. The reaction mixture was concentrated and the crude residue was resubmitted to the reaction conditions using 5 equivalents of TCP, and a 1:1 mixture of starting material and product was obtained. The reaction mixture was concentrated, and resubmitted with 2.5 equivalents of TCP and stirred overnight. While full consuption of the starting material was achieved, the product could not be

easily purified by column chromatography. Two close running spots were seen by TLC, and the ^{1}H NMR spectrum revealed overlapping signals of the same multiplicity. It was hypothesised that due to the radical mechanism of this reaction, **245** was obtained as a mixture of diasteromers, in a 1:3 crude ratio.



Scheme 3.4: Synthesis of iodonucleoside **244** and attempt at the synthesis of BCP nucleoside **245**.

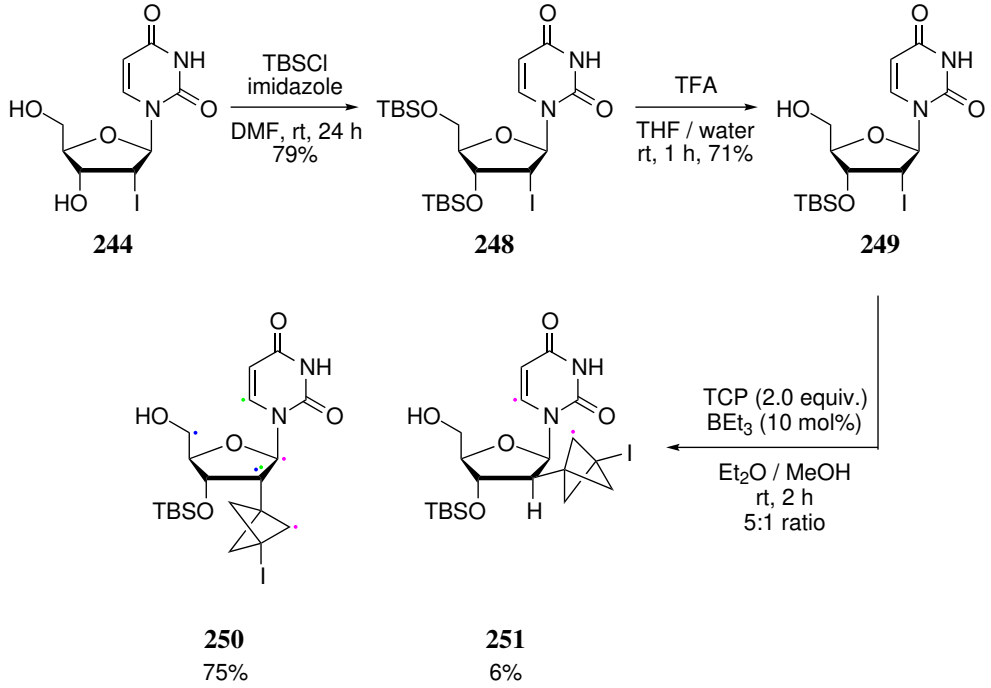
It was thought that synthesising protected derivatives of **244** might allow for chromatographic separation and/or effect the diastereomeric ratio of the BCP derivatives by constraining the ring into a particular conformation. 5′-TBS-protected nucleoside **246** was thus synthesised by monoprotection of **244** (Scheme 3.5). Reaction of **246** under the ATRA conditions using CH_2Cl_2 as a co-solvent gave after 1 h a 1:6 ratio of starting material to product. Resubmission under the same reaction condition yielded **247** as a 1:3 mixture of inseparable diastereomers.



Scheme 3.5: Synthesis of iodonucleoside **246** and attempt at the synthesis of BCP nucleoside **247**.

Finally, double silyl protection of **244** and monodeprotection of **248** using TFA gave 3′-TBS-protected nucleoside **249** (Scheme 3.6). When using **249** with MeOH as the

co-solvent (CH_2Cl_2 was not sufficient to ensure complete solubility), completion was reached within 2 h and we obtained a 1:5 mixture of diastereomers that we were able to separate. NOESY analysis allowed assignment of the structures of **250** and **251** obtained in 75% and 6% respectively after column chromatography.



Scheme 3.6: Synthesis of BCP nucleosides **250** and **251**. nOe enhancements are depicted with coloured dots.

It is not immediately obvious why the diasteromeric ratio of products changes when the TBS group is moved from the 5′ position to the 3′ position, or the basis for the stereoselectivity. The furanose ring of a nucleoside can adopt two favoured conformations, N-type or S-type, which are in a rapidly interconverting equilibrium (Figure 3.2).[106] Deoxyribonucleosides tend to favour the S-type conformation, and it is possible that the nucleoside radical, similar to a deoxyribonucleoside, also favours this conformation, resulting in a stereochemical bias when reacting with TCP. The presence of a proximal bulky group on one face of the nucleoside could shift the equilibrium one way or the other, modifying the stereochemical outcome of the reaction.

With BCP nucleoside **250** in hand, reduction of the C–I bond was performed. As shown in Scheme 3.7, **252** was accessed in good yield using 2 equivalents of TTMSS and 10 mol% of BEt_3 in a mixture of MeOH and Et_2O. It was crucial that the crude

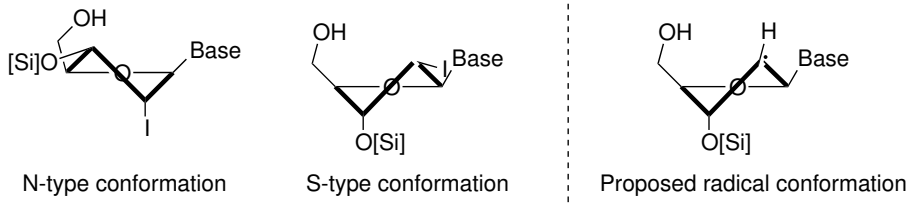
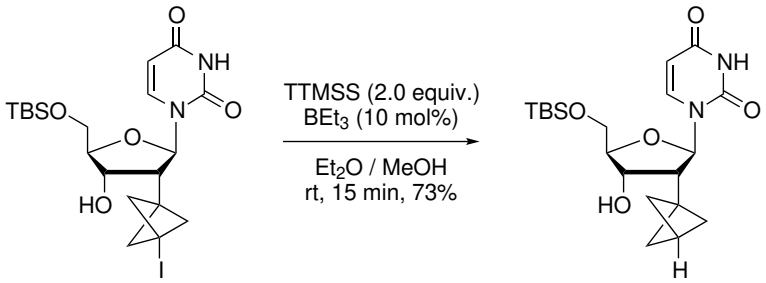


Figure 3.2: Favoured conformations for furanose ring in nucleosides and proposed confirmation for radical intermediate.

reaction mixture was washed with saturated sodium bicarbonate solution to hydrolyse the iodosilane species formed in this process to avoid formation of HI on concentration, leading to lower isolated yields.



250 **252**

Scheme 3.7: Reduction of **250** to **252**.

3.3.3 Synthesis of a drug surrogate

We were keen to demonstrate that these two methods could be used to synthesise drug surrogates bearing a BCP unit. It was decided to target a surrogate of the opioid pain medication Fentanyl, compound **253**, which seemed a good example for a proof of concept (Figure 3.3).

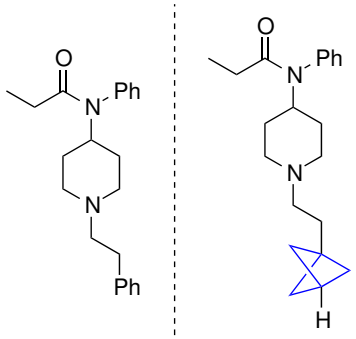


Figure 3.3: Fentanyl (left) and its BCP analogue **253** (right).

Figure 3.4 shows the retrosynthetic analysis that was devised. It was planned to access compound **253** by ATRA reaction between TCP and iodide **254**. Iodide **254** would be derived from alcohol **255** by direct Appel reaction or from chloride **256** by halide displacement. Alkylation of norfentanyl would give alcohol **255** and chloride **256**.

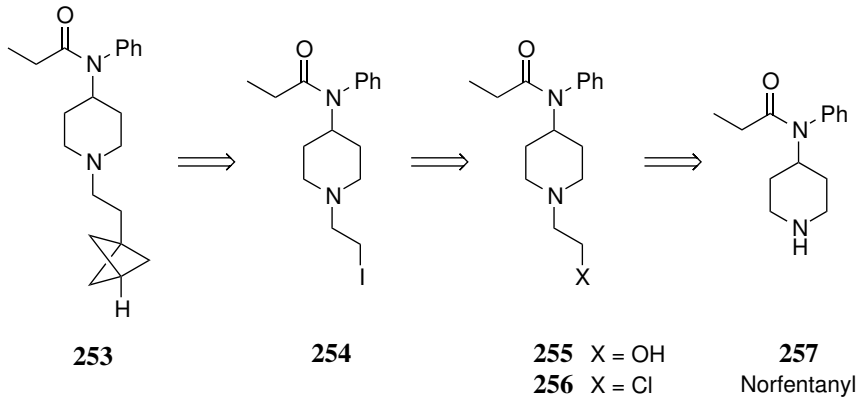
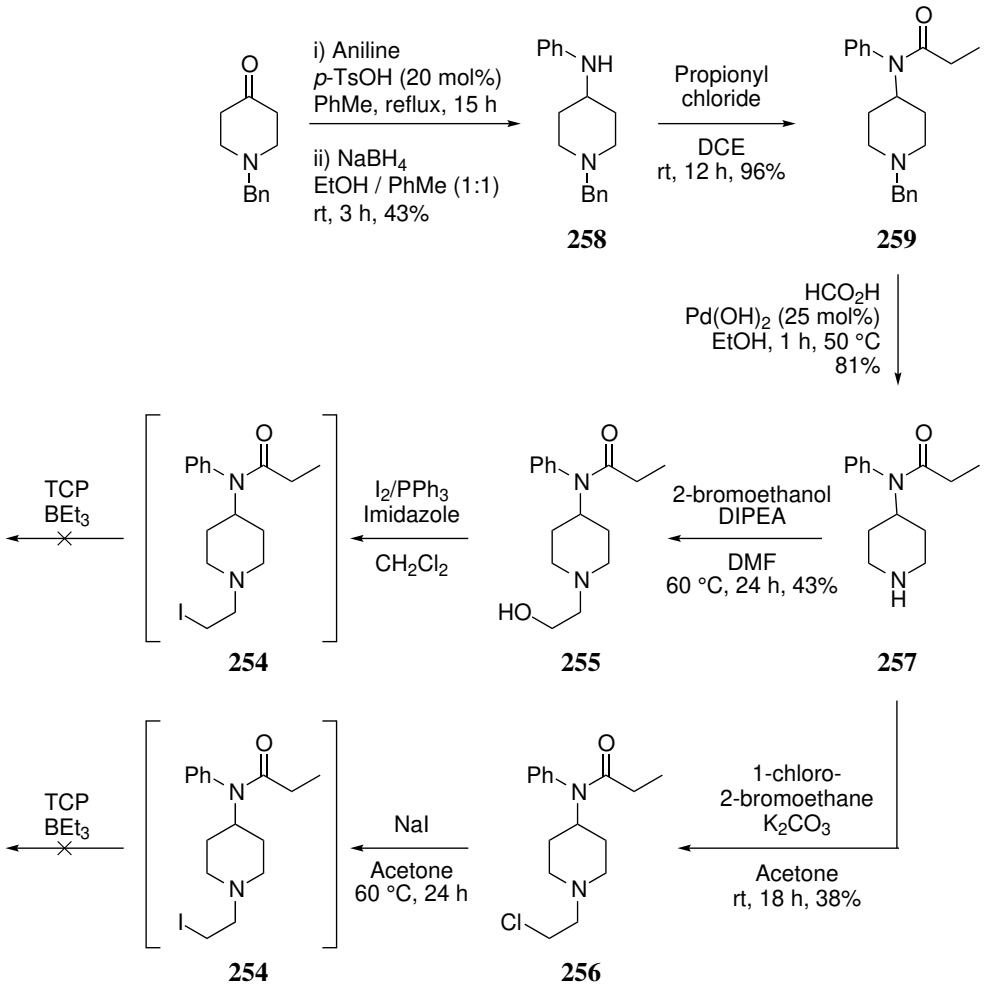


Figure 3.4: Retrosynthetic analysis for Fentanyl analogue **253**: late stage ATRA reaction and reduction.

Synthesis of norfentanyl (**257**) started with imine formation between aniline and 4-oxo-*N*-benzylpiperidine, and reduction with sodium borohydride, affording aminopiperidine **258** in 43% yield (Scheme 3.8). Amide **259** was obtained by reaction with propionyl chloride in 96% yield. Reduction using palladium on carbon and H_2 at rt failed to provide norfentanyl (**257**), however, the use of palladium hydroxide and formic acid at 50 °C for 1 h produced **257** in 81% yield. Alkylation of **257** with bromoethanol afforded **255**, and Appel reaction gave **254** as an inseparable mixture with triphenylphosphine oxide. Reaction of crude **254** with TCP and BEt_3 in CH_2Cl_2 did not yield any product.

We questioned whether the purity of the substrate was the issue, and decided to access **254** *via* Finkelstein reaction from **256**. Compound **254** in its pure form proved to be extremely unstable, and could not be isolated. Attempts were made to use it directly after the work-up as a solution in CH_2Cl_2, but again no reactivity was observed under the ATRA reaction conditions. It was hypothesised that the nitrogen atom of the piperidine might coordinate to BEt_3, inhibiting reaction initiation. We therefore attempted to access **253** using norfentanyl (**257**), and BCP building block **260** (Figure 3.5).

Attempts were initially made to access tosylate **260** *via* C–I bond reduction of alcohol **191**, followed by tosylation of alcohol **261**. Unfortunately, reaction of **191** with TTMSS



Scheme 3.8: Synthesis of Norfentanyl and attempt at synthesis and isolation of **254**.

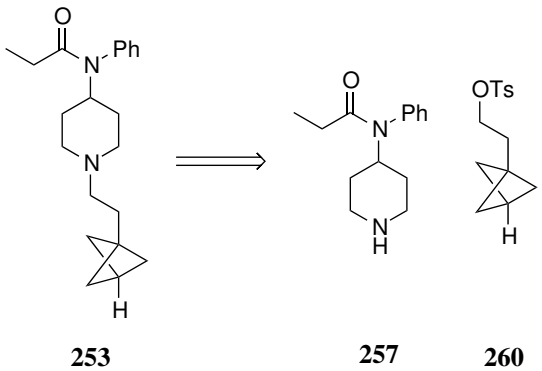
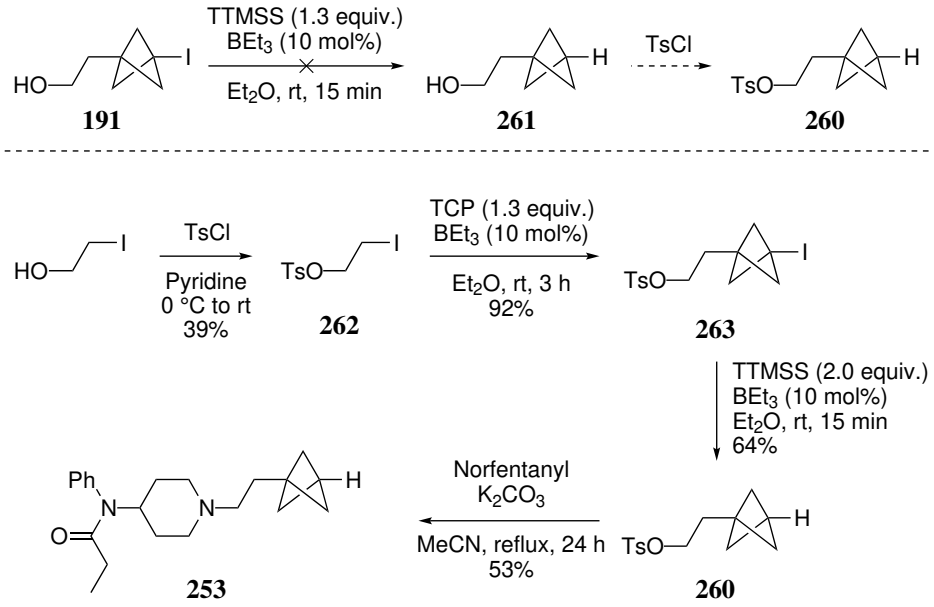


Figure 3.5: Revised retrosynthetic analysis for Fentanyl analogue **253**: building block approach.

and BEt_3 led to decomposition and no product was found. However, tosylation of 2-iodoethanol and ATRA reaction with **262** yielded BCP **263** in excellent yield. Wary that **263** might not withstand alkylation reaction conditions, the C–I bond was first reduced, which afforded tosylate **260** in 64% yield on a gram scale. Finally, alkylation of norfentanyl (**257**) with **260** afforded fentanyl analogue **253** in reasonable yield.



Scheme 3.9: Synthesis of fentanyl analogue **253**.

3.4 Conclusions

We have shown that the carbon-iodine bond of iodoBCPs can be reduced in a mild, efficient and less toxic manner compared to previous methods using tris(trimethylsilyl)silane as the hydrogen donor and BEt_3 as the radical initiator. This methodology was used to access BCP products such as acids, amides, amines and amino acids that have the potential to expand the medicinal chemist's toolbox to construct scaffolds bearing monosubstituted BCP motifs. The reduction proved quite functional group tolerant and could be used in combination with the initial ATRA reaction to synthesise more complex molecules with biological relevance, such as dipeptides, nucleosides or drug surrogates as demonstrated by the synthesis of a BCP analogue of Fentanyl. The limitation of the tolerance of free amines was discovered and represents an area for future study. The results presented in this chapter and the previous one were published earlier this year.[107]

4

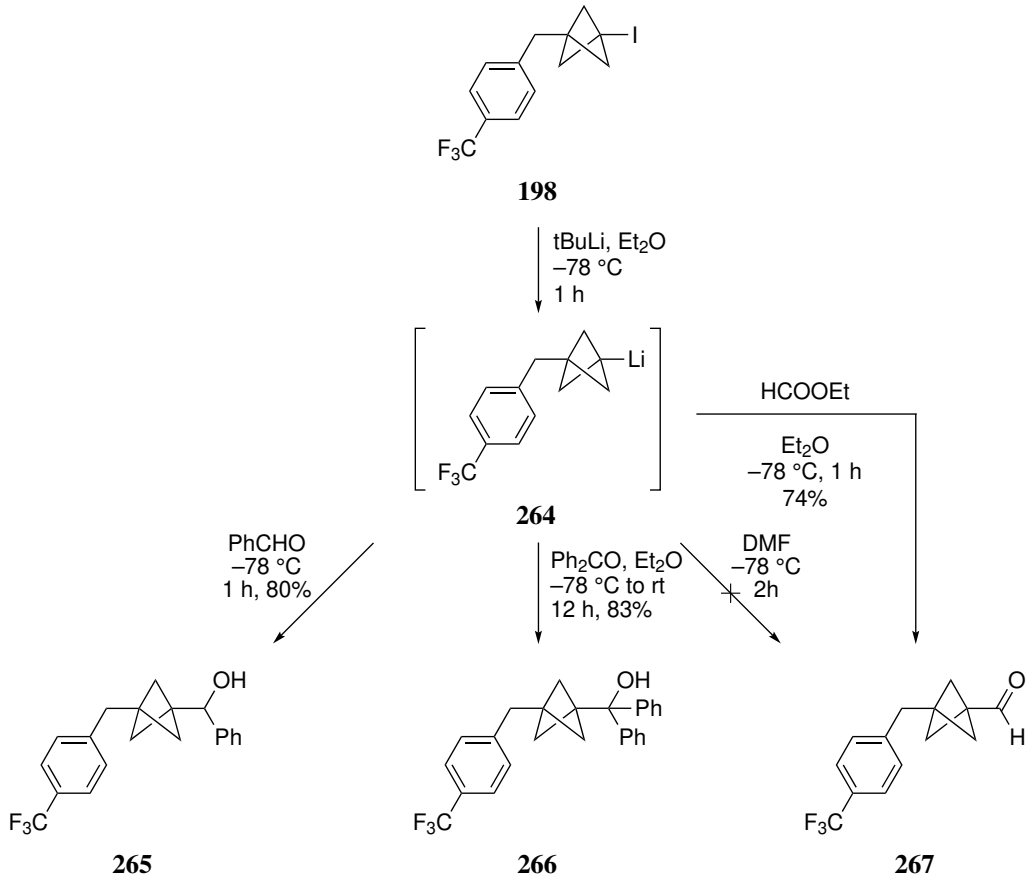
Functionalisation of 1-iodo-3-substituted bicyclo[1.1.1]pentanes

Contents

In this chapter, we will expose the different methods we have used and developed to allow for the productive functionalization of iodoBCPs.

4.1 Lithiation and electrophile quenching of iodinated bicyclo[1.1.1]pentane derivatives

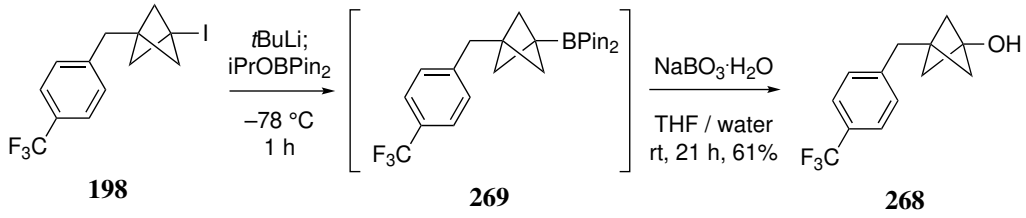
As mentioned in the introduction of this manuscript, iodinated bicyclo[1.1.1]pentanes (iodoBCPs) have been used in lithiation reactions.[20,62] Compound **198** was selected because of its limited functionality. **198** was treated with *tert*-BuLi at –78 °C and a variety of electrophiles were added (Scheme 4.1). Rapid addition of neat benzaldehyde to lithiated BCP **264** gave benzyl alcohol **265** in 80%. Addition of a solution of benzophenone in Et_2O gave tertiary alcohol **266** in 83% yield.



Scheme 4.1: Lithiation and electrophile quenching of **198**

Addition of DMF to **264** to give aldehyde **267** did not proceed well, whether the DMF was used neat or in solution, and added slowly or rapidly. Nonetheless, **267** was accessed by addition a solution of **264** to a solution of ethyl formate at –78 °C in 74% yield. Using lithiation, we were able to access phenol analogue **268**. A mixture of **198** and 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was treated at –78 °C with

*t*BuLi, affording boronic ester **269**. After extractive workup with Et_2O, the residue was dissolved in a mixture of THF and water, and treated with sodium perborate monohydrate to afford alcohol **268** (Scheme 4.2).

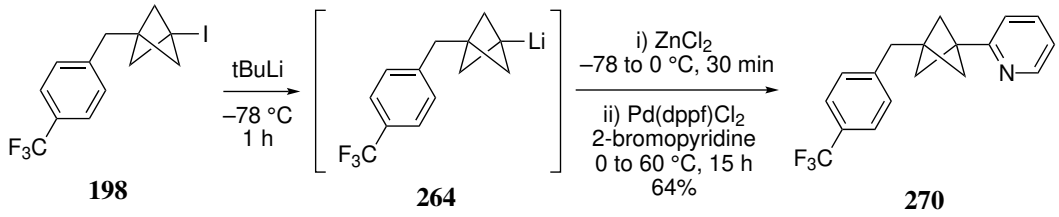


Scheme 4.2: Synthesis of phenol analogue **268** carried out by Dr Carlos Arroniz.

4.2 Cross-coupling reactions

4.2.1 Palladium-catalysed cross-coupling of bicyclo[1.1.1]pentyl nucleophiles

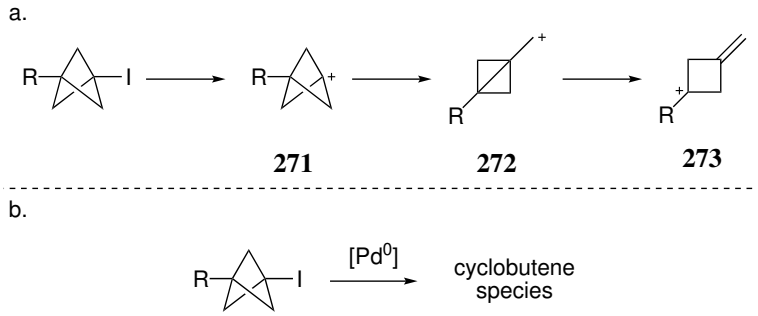
The Szeimies[62] and Knochel groups[20] showed that bicyclo[1.1.1]pentylmagnesium halide and bicylo[1.1.1]pentylzinc halides could be coupled in palladium-catalysed cross couplings. **198** was lithiated as shown previously (Scheme 4.3). The lithium species was transmetallated to the organozinc species using $ZnCl_2$. The nucleophile was added to a solution of 2-bromopyridine and Pd(dppf)Cl_2, and heated to afford BCP **270** in 64% yield.



Scheme 4.3: Lithiation, transmetallation and Neigishi cross-coupling of iodoBCP **198**.

Although being a powerful method to access 1,3-disubstituted BCPs, the lithiation of iodoBCPs poses the issue of safety due to the use of *t*BuLi. Also, there was no report in the literature of halogenated BCPs being used as the electrophile partner in a transition metal-catalysed cross-coupling reaction. Insight was given to us from industrial collaborators at Pfizer, Groton, US that iodoBCPs did not perform well in palladium-catalysed cross-coupling, generally ring opening to furnish cyclobutene species. It has been shown

and calculated that bicyclo[1.1.1]pentyl cations **271** (derived from iodoBCPs) rearrange readily into bicyclo[1.1.0]butyl cation **272** or cyclobutyl cations **273** depending on the nature of the substituent (Scheme 4.4a).[108] In both cases, reaction with a nucleophile leads to cyclobutene species.



Scheme 4.4: Rearrengment of the bicyclo[1.1.1]pentyl cation

It could be that during the oxidative addition process, the BCP opens to yield cyclobutene species (Scheme 4.4b). To circumvent this issue, it was decided to take advantage of the propensity of BCP derivatives to undergo radical transformations, and to use a transition metal that would operate via a radical mechanism. Iron,[109] nickel[110] and cobalt[111] are well know to proceed via radical mechanisms during certain cross-coupling reactions. It was decided to concentrate on the Kumada-Tamao-Corriu cross-coupling reaction because of the wide availability of Grignard reagents and literature precedent. Furthermore, iron appeared to be the best choice as it is one of the most abundant metals on Earth; it is found at about 6.3% in the Earth's crust (700 times more than nickel and 2100 times more than cobalt)[112] compared to palladium found at 3.7×10^{-9}%.[113] Iron is also much cheaper ($7.2 per 100 g)[114] than palladium ($3550 per 100 g).[115]

Iron-catalysed Kumada cross coupling have been conducted on plenty of different systems: alkyl, aryl, alkenyl and alkynyl Grignard reagents with alkyl, aryl, alkenyl and alkynyl halides or pseudohalides.[116] For the purpose of this study, couplings of alkyl halides with aryl Grignard reagents are of the highest interest. More specifically, we will concentrate on couplings involving secondary alkyl halides and higher.[116]

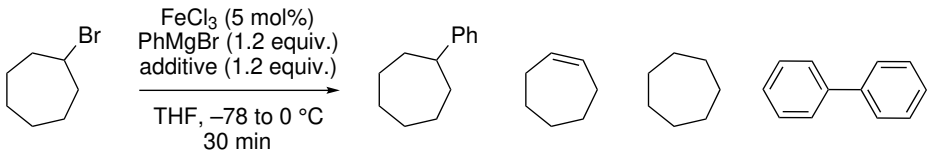
4.2.2 Iron-catalysed cross-coupling of secondary and higher alkyl halides with aryl Grignards.

In this type of couplings, the common side products are:

- the Grignard homodimer,
- the halide homodimer,
- the hydrodehalogenated compound,
- the product of β-hydride elimination from the halide partner.

Nakamura and co-workers reviewed the coupling of bromocycloheptane with phenylmagnesium bromide using $FeCl_3$ and additives.[117] They showed a different distribution of product to side products by varying the additive (Table 4.1).

Table 4.1: Additive effect on the iron-catalysed cross-coupling of bromocycloheptane with phenylmagnesium bromide.[117]



274 **275** **276** **277** **278**

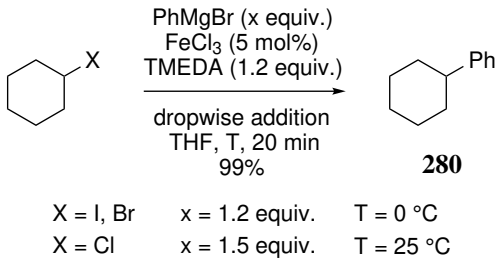
Entry	Additive	Yield (%)[a]				
		275	**276**	**277**	**274**	**279**
1	none	5	79	0	4	6
2	Et_3N	3	78	0	11	5
3	*N*-methylmorpholine	8	72	0	4	5
4	DABCO	20	2	0	75	3
5	NMP	15	3	traces	79	4
6	TMEDA	71	19	3	traces	10

[a] Determined by GC with decane as internal standard.

When no additive was used, the reaction almost reached completion and cycloheptene was the major product (entry 1, 79% yield); only 5% of the cross-coupled product was obtained. Similar results were obtained with triethylamine and *N*-methylmorpholine (entries 2–3); using 1,4-diazabicyclo[2.2.2]octane (DABCO), the yield of **275** rose to 20% and the amount of cycloheptene was negligeable (entry 4). However, large amounts of starting material remained. NMP as the additive gave similar results (entry 5). When

using TMEDA, **275** was obtained in 71% yield alongside 19% of cycloheptene, 3% of cycloheptane and traces of the starting material. They noted that the use of phosphine ligands, organozinc reagents or other iron catalysts were unsuitable for this reaction.

They applied these conditions to the coupling of cyclohexyl halides, adding a solution of Grignard reagent and additive dropwise (Scheme 4.5).



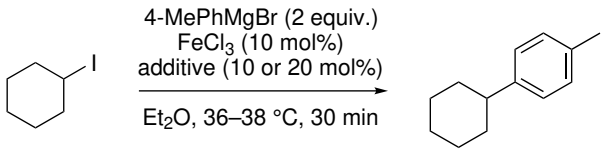
Scheme 4.5: Iron-catalysed Kumada-Tamao-Corriu cross-coupling of cyclohexyl halides with phenylmagnesium bromide.[117]

Iodocyclohexane and bromocyclohexane reacted smoothly at 0 °C using 1.2 equivalents of PhMgBr. Chlorocyclohexane proved reactive, despite needing 1.5 equivalents of Grignard reagent and the reaction to be carried at 25 °C. All three reactions produced **280** in 99% yield. They also reported the use of electron-deficient 4-(trifluoromethyl)phenylmagnesium bromide as the nucleophilic partner; in that case, the reaction necessitated 2.0 equivalents of Grignard at 25 °C to ensure completion. The yield of the reaction was also lower compared to any other entries.

Bedford and co-workers showed that simple amines could be use in catalytic amounts when the reaction was performed in refluxing Et_2O by adding the Grignard reagent rapidly to the reaction mixture; Et_3N, TMEDA and DABCO proved to be the best additives.[118] Best results were achieved when the iron-to-nitrogen ratio was 1:2. The example of iodocyclohexane is shown in Table 4.2, and as previously, bromocyclohexane and chlorocyclohexane were reactive under the reaction conditions, affording **281** in excellent yields. In all three cases, DABCO was the most effective ligand. In stark contrast with Nakamura's results, when no additive was used in the coupling of bromocyclohexane, the conversion to **281** was 39%.

Other diamines proved to be excellent ligands. Cossy and co-workers developed an iron- and cobalt-catalysed arylation of iodoazetidines, -pyrrolidines and -piperidine with

Table 4.2: Effect of simple amines and TMEDA in the cross-coupling of iodocyclohexane.[118]

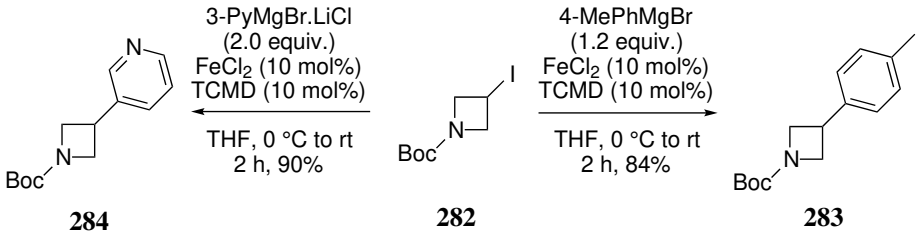


281

Conversion (%)[a]		
2 Et_3N	DABCO	TMEDA
75	100	90

[a]Determined by ^{1}H NMR spectroscopy using mesitylene as the internal standard.

arylmagnesium bromides (Scheme 4.6).[119] They used (*R,R*)-tetramethylcyclohexan-1,2-diamine (TCMD) as the ligand and iron(II) chloride as the catalyst. 3-Iodoaziridine **282** was coupled using 4-MePhMgBr to afford **283** in 84% yield. Coupling with electron-deficient 3-pyridylmagnesium bromide lithium chloride complex afforded **284** in 90% yield. When using electron-deficient Grignard reagents, 2 equivalents were needed.

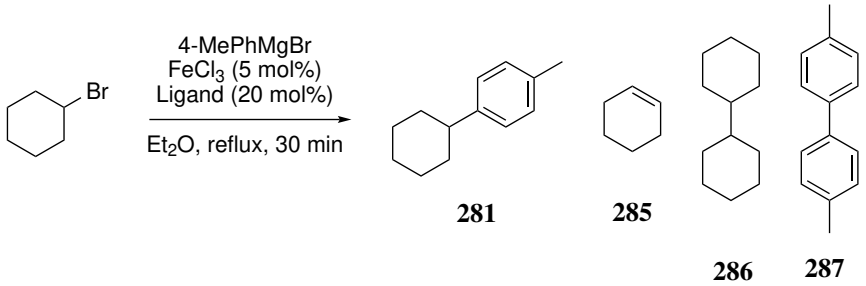


284 **282** **283**

Scheme 4.6: Iron-catalysed cross-coupling of *N*-Boc-3-iodoaziridine (**282**).[119]

Alternatively, phosphine and phosphite ligands have shown efficacy in catalysing the cross-coupling of secondary halides with aryl Grignard reagents (*via* rapid addition).[120] Bedford and co-workers reacted bromocyclohexane with 4-tolylmagnesium bromide using a variety of phosphorus-containing ligands and $FeCl_3$ in refluxing Et_2O (Table 4.3). The use of triphenylphosphine as a ligand resulted in 72% conversion to **281** (entry 1) but electron rich tricyclohexylphosphine proved more efficient (87% conversion), although more side products were found (entry 2). Trimethylphosphite was also a good ligand, affording 83% conversion (entry 3). Bisphosphines were competitive compared to monophosphines although better conversion was achieved only with longer alkyl chain between the two diphenylphosphino groups (entries 4–6).

Table 4.3: Effect of phosphorus-containing ligands on the cross-coupling of bromocyclohexane.[120]

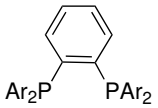


281 **285** **286** **287**

Entry	Ligand	Conversion (%)[a]			
		281	**285**	**286**	**287**
1	PPh_3	72	2	1	6
2	PCy_3	87	3	7	7
3	$P(OMe)_3$	83	0	1	13
4	$Ph_2PCH_2PPh_2$	60	2	2	4
5	$Ph_2P(CH_2)_2PPh_2$	66	1	1	5
6	$Ph_2P(CH_2)_6PPh_2$	91	2	0	8

[a]Dertermined by GC with mesitylene as internal standard.

Another bisphosphine, 1,2-bis(diphenylphosphino)benzene (dppBz, Figure 4.1), has been used in iron-catalyzed Neigishi cross-coupling by the Bedford,[121,122] and Nakamura groups.[123]



dppBz Ar = Ph

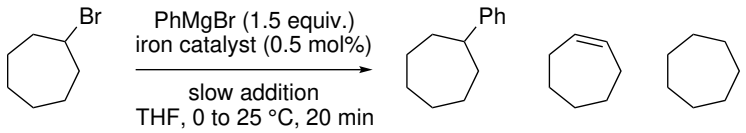
SciOPP Ar = 3,5-di(*tert*-butyl)phenyl

Figure 4.1: Structures of dppBz and SciOPP ligands.

The Nakamura group used a bulky variant of dppBz, SciOPP, that proved superior to dppBz in the cross coupling of secondary halides with aryl Grignards under slow addition conditions (Table 4.4).[124] No ligand in the reaction resulted in 21% yield for **275**, 69% for cycloheptene (**276**) and 6 % of cycloheptane (**277**) (entry 1). The complex formed by iron(II) chloride and two dppBz ligands increased the yield of **275** to 50% and decreased the amount of **276** produced (entry 2). However, the reaction was not complete and 25% of **274** was recovered. The use of complex $FeCl_2$(SciOPP) increased

the yield of the reaction to 84% and only 14% of cycloheptene was produced (entry 3). When an extra amount of ligand was added, the catalytic system performed even better, affording **275** in 91% yield (entry 4).

Table 4.4: Effect of dppBz and SciOPP ligands on the cross-coupling of bromocycloheptane.[124]



274 **275** **276** **277**

Entry	Iron catalyst	Yield (%)[a]			Recovery of **274** (%)[a]
		275	**276**	**277**	
1	$FeCl_3$	21	69	6	0
2	$[FeCl_2(dppBz)_2]$	50	20	4	25
3	$FeCl_2$(SciOPP)	84	14	0	1
4[b]	$FeCl_2$(SciOPP)	92	8	0	0

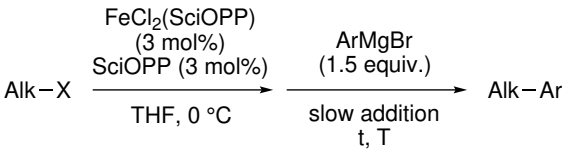
[a]Determined by GC with undecane as internal standard. [b]0.5 mol% of SciOPP was added.

Many substrates proved reactive using this catalytic system and varying time and temperature (Table 4.5). Bromocyclohexane was reacted with 4-methoxyphenylmagnesium bromide at 25 °C for 20 min to yield the product in 98% yield. Chlorocyclohexane and PhMgBr produced **280** in 82% yield at 40 °C for 3 h (entry 2). The bulky Grignard reagent 2-tolylmagnesium bromide proved reactive at 40 °C, producing the product in 95% yield (entry 3). Even a tertiary halide, 1-bromoadamantane, was reactive and the corresponding coupling product was obtained in 81% yield(entry 4).

Very few cross-couplings have been reported for tertiary halides. To the best of our knowledge, the only other Kumada cross-coupling reaction in the literature with tertiary halide is that of 1-chloroadamantane and *tert*-butylchloride with phenylmagnesium bromide catalysed by copper salts (Table 4.6).[125] The authors noted that Me-THF as the solvent for the Grignard solution was crucial to reactivity

Regarding similar couplings involving BCPs, Baran and co-workers developed a iron-catalysed decarboxylative cross-coupling of *N*-hydroxyphtalamic ester with organomagnesium and organozinc species (Scheme 4.7).[126] The authors noted that the nucleophile had to be added quickly to ensure efficiency. BCP derivative **288** was coupled with

Table 4.5: $FeCl_2$(SciOPP)-catalysed Kumada cross-coupling.[124]



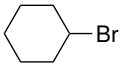
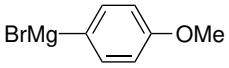
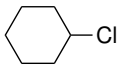
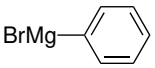
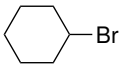
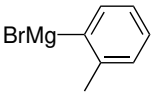
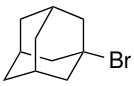
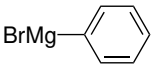
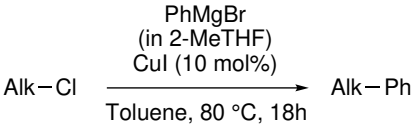
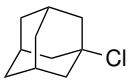
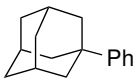
Entry	Alk−X	ArMgX	T (°C)	t	Yield (%)
1			25	20 min	98
2			40	3 h	82
3			40	20 min	95
4			40	3 h	81

Table 4.6: Copper-catalysed Kumada cross-coupling of tertiary chlorides.[125]

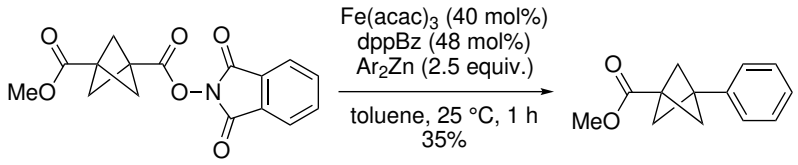


Entry	Substrate	Product	Yield (%)
1			38
2			78

diphenylzinc using iron(III) acetylacetonate and dppBz in high quantities as catalytic system in toluene to afford **289**.

4.2.3 Iron-catalysed cross-coupling of 1-iodo-3-substituted bicyclo-[1.1.1]pentanes with aryl Grignards - Rapid addition

This study commenced by a survey of a few metals. It was decided to start with a rapid addition of the Grignard in the interest of practicality, using 4-methoxyphenylmagnesium bromide (4-MeOPhMgBr, 1 M in THF). The yields were determined by ^{1}H NMR

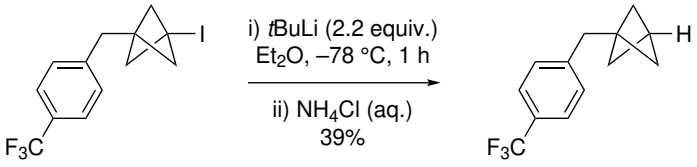


288 **289**

Scheme 4.7: Iron-catalysed decarboxylative cross-coupling of BCP derivative **288** with diphenylzinc.[126]

spectroscopy of the residue obtained after filtration of the reaction mixture over silica, elution with Et_2O and concentration, using 1,3,5-trimethoxybenzene as internal standard in $CDCl_3$, except when indicated otherwise. In all reactions, the dimer of the Grignard species was produced but not quantified. Acetylacetonate metal complexes and nickel(II) chloride glyme-dtbbpy were used as shown in Figure 4.2. Iron(III) acetylacetonate proved reactive and **290** was obtained in 42% yield; hydrodeiodinated BCP **291** was produced alongside in 23% yield. Cobalt(II) acetylacetonate was less efficient and **290** was produced in 7% yield alongside 53% of **291**. Copper(II) acetylacetonate did not produce any **290**, 71% of starting material remained and 8% of **291** was found. Similar results were obtained with chromium(III) acetylacetonate. With manganese(II) acetylacetonate, the starting material was left unreacted. Nickel(II) acetylacetonate produced **290** in very poor yield (5%) and 11% of **291** was found along with 38% of starting material. Nickel(II) chloride glyme-dtbbpy complex also proved unisuitable to catalyse the cross-coupling. Despite our best effort, we were unable to assign the rest of the material for mass balance.

A pure sample of **291** was obtained by lithiation of **292** and quenching with saturated aqueous ammonium chloride solution in 39% yield (Scheme 4.8).



198 **291**

Scheme 4.8: Synthesis of **291** by Ms Bethany Shire.

It was decided to continue this study using iron as the catalyst; several iron catalysts and complexes were tested to find the most active for the cross-coupling (Figure 4.3)

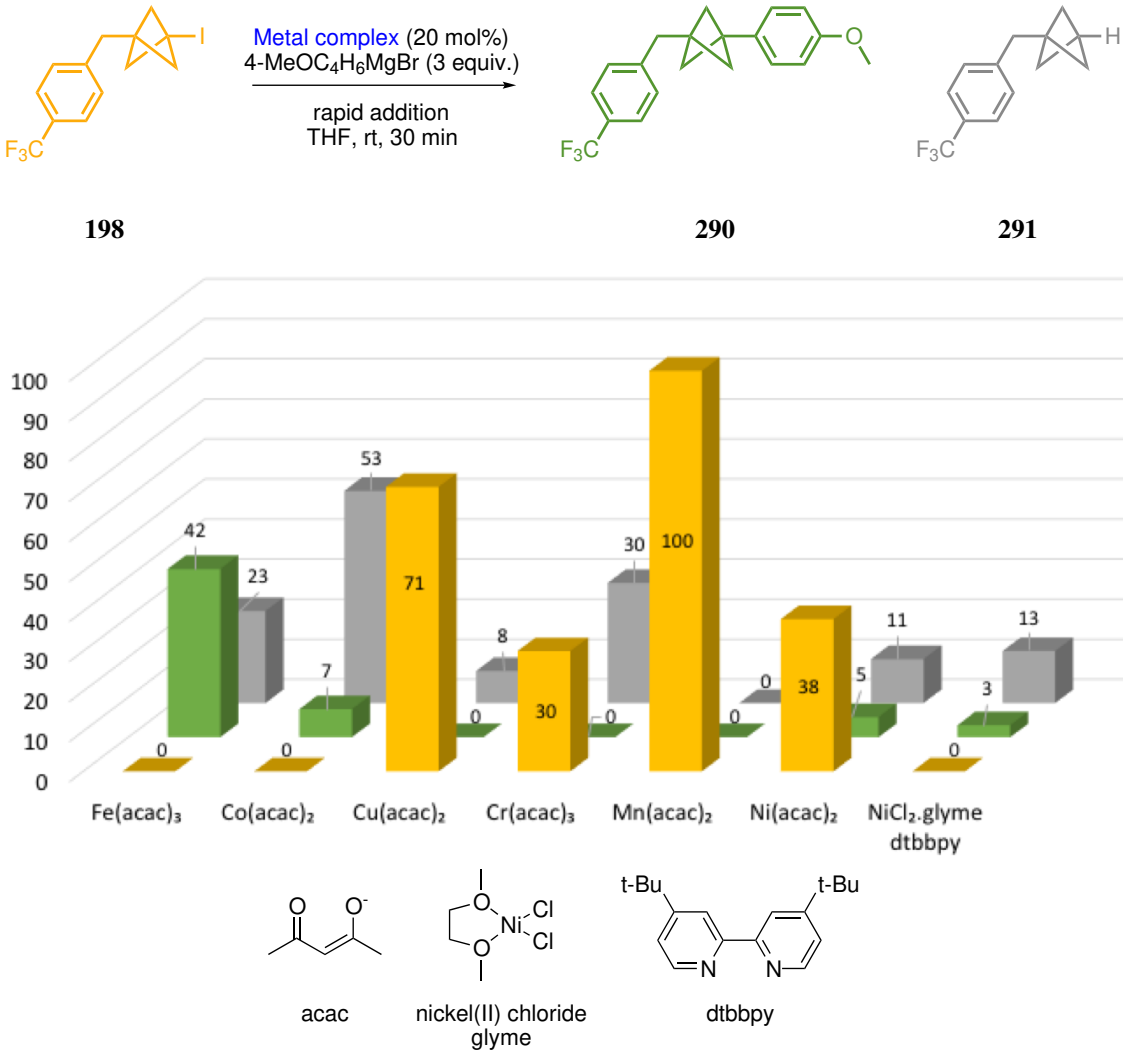
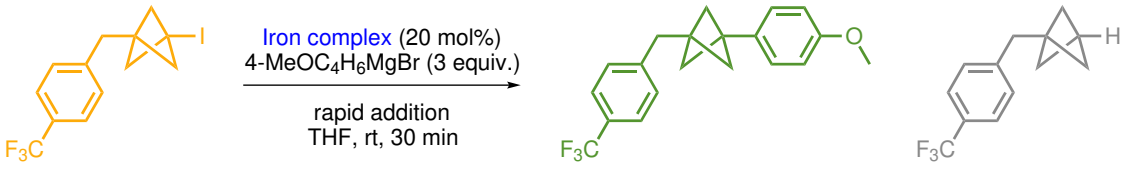


Figure 4.2: Test of metal acetylacetonate complexes and nickel(II) diglyme-dtbbpy. Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard.

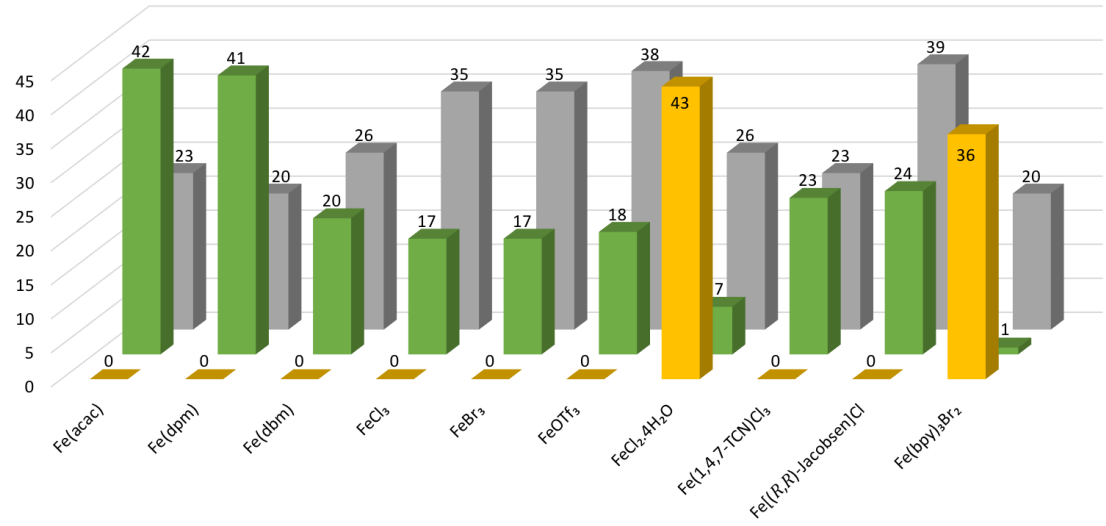
Iron(III) dipivaloylmethide ($Fe(dpm)_3$) proved as efficient as $Fe(acac)_3$ while the use of iron(III) dibenzoylmethide afforded **290** in 20% yield. Iron(III) chloride, iron(II) bromide and iron(III) trifluoromethanesulfonate afforded the product of the cross-coupling in 17%, 17% and 18% yield respectively. Upon mixing of **198** with $FeCl_3$ or $Fe(OTf)_3$ as solids, a colour change was observed (darkening). It is possible that these two complexes react with the starting material and provoke decomposition. For these three, the yield of **291** was higher than 30%. Iron(II) chloride tetrahydrate proved poor to catalyse the reaction (7% yield for **290**). It was envisaged that the coordinated water interfered with the reaction and quenched the Grignard reagent, explaining the 43% remaining starting material. The use of Fe(1,4,7-TCN)Cl_3 and Fe[(*R,R*)-Jacobsen]Cl afforded the product in

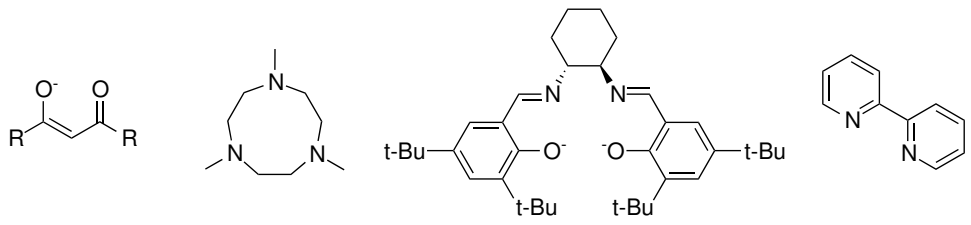
approximately the same yield, although, with the latter, more hydrodeiodination product was obtained. Finally, $Fe(bpy)_3Br_2$ was a poor catalyst, very likely due to its low solubility in THF; 36% starting material remained and 20% of **291** were produced.

Overall, iron(III) acetylacetonate proved to be the best catalyst. It is air and moisture stable, commercially available and cheap, and thus the ideal catalyst.



198 **290** **291**





acac, R = Me
dpm, R = *tert*-butyl
dbm, R = Ph

1,4,7-TCN

(*R,R*)-Jacobsen

bpy

Figure 4.3: Iron catalysts and complexes screening. Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard.

Next, this study continued with the screening of ligands. We screened a selection of ligands as depicted in Figure 4.4 and report isolated yields. The use of dppBz proved detrimental to the reaction compared to no ligand (30% yield vs 40 % yield). The SciOPP ligand did not bring a major change to the yield of the reaction, reaching 39%. Amine ligand, as TCMD, DMCD, PMDTA and DABCO showed lower yield compared to the ligandless reaction. Overall, we observed that any addition of ligand decreased the yield of the reaction.

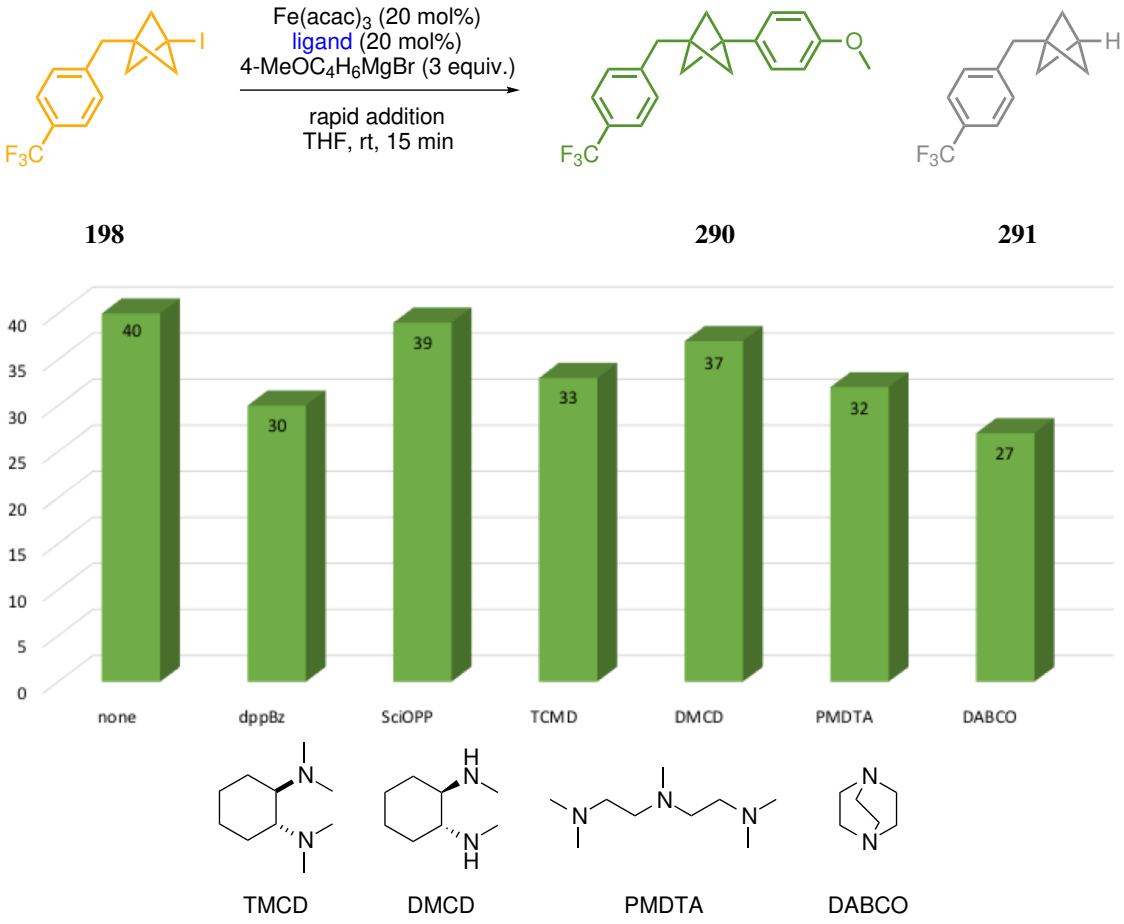


Figure 4.4: Ligand screening. Isolated yields.

The same phenomenon was observed by our industrial collaborator, Neal Sach, at Pfizer, La Jolla, who performed this cross-coupling on very small scale using a liquid handling robot inside a glovebox of N_2 atmosphere. The couplings were performed on a 1 μmol scale using 0.01 M stock solution of **198** in THF or toluene, 0.025 M stock solution of $Fe(acac)_3$ in THF and 0.5 M solution of 4-MeOPhBr in THF. The substrate and catalyst

solutions were dispensed in wells containing the neat ligand, and stirring was initiated. The Grignard solution was added at once and the resulting mixture was stirred at 25 °C for 18 h. The mixture was quenched with DMF / 1 M HCl solution (8:2, aq. HCl) and analysed directly by LC-MS. A list of the ligand classes tested is provided in Figure 4.5.

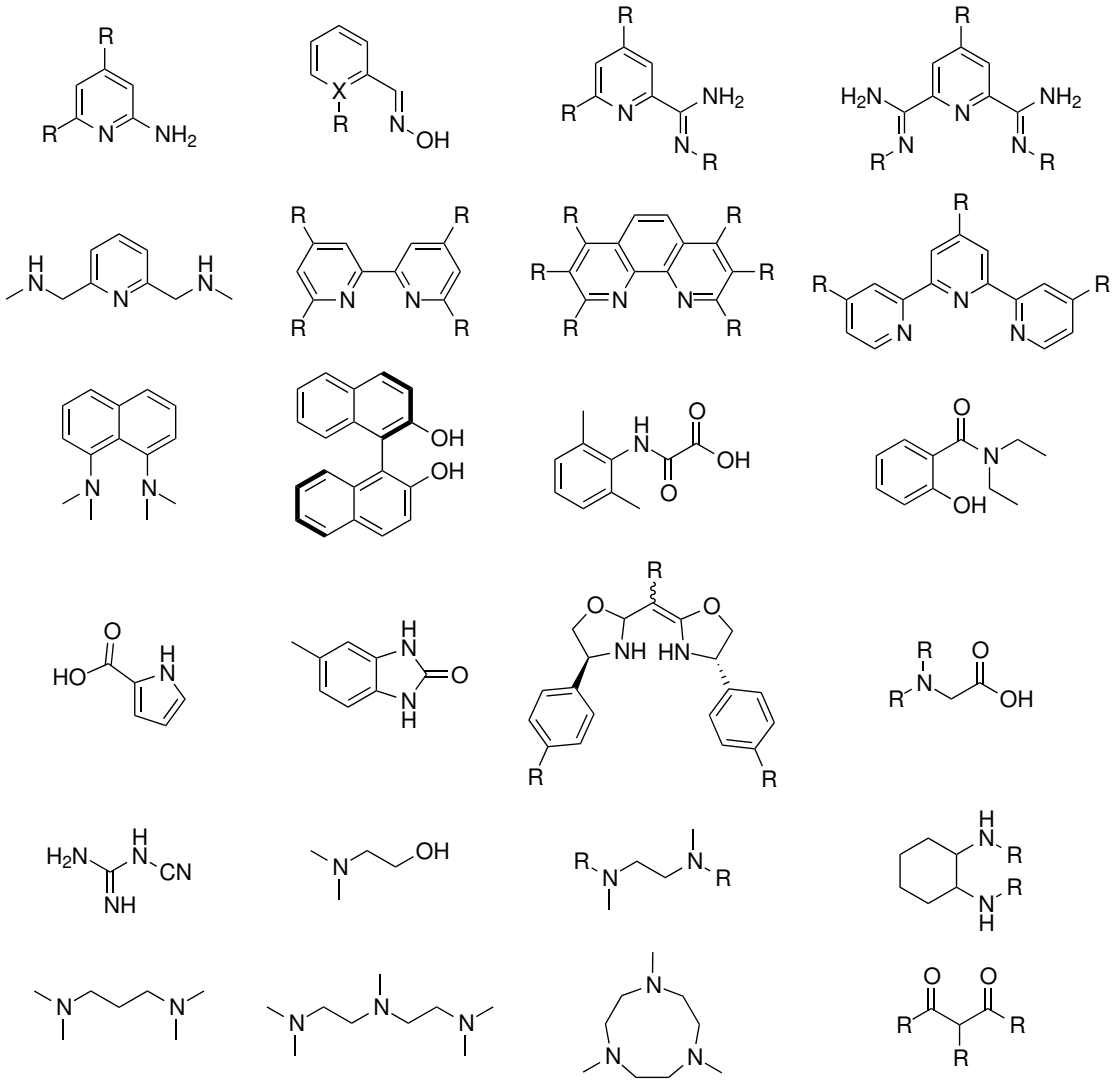


Figure 4.5: Ligand classes tested by Dr Neal Sach.

For all reaction carried out in THF, the reaction yield was under 2%. It is clear that the concentration was an important factor (0.01 M for the robot-based screening vs 0.2 M for the lab-based screening). In toluene, the highest yield achieved was 14%, using no ligands. None of the ligands presented in Figure 4.5 was able to improve the reaction, very much alike the results obtained previously (Figure 4.4).

The optimisation was continued by a solvent screen (Figure 4.6). Except for 1,2-dimethoxyethane (DME), etheral solvents (Et_2O–DMM) were not suitable for the coupling reaction. The best solvent was toluene, as observed by our collaborator, affording **290** in a slightly improved 49% yield. Benzene did not compete with toluene and **290** was produced in only 15% yield. DMPU was as efficient but gave **291** in a far greater yield than other solvents (74% yield). It is possible that the greater water content of DMPU, due to higher water solubility, played a part in the amount of **291** produced. Using deuterated THF (d_8-THF), the yield of the reaction was similar as that obtained with non-deuterated THF; however, **291** was afforded in only 9% yield. It may be an indication that **291** is produced by H-abstration of the reaction solvent from the bicyclopentyl radical intermediate. Nonetheless, given that the Grignard reagent was used as a solution in non-deuterated THF, it is not surprising to observe **291** in the reaction mixture.

Given the poor improvement achieved after screening ligands and solvents, it was decided to modify the coupling procedure by adding the Grignard slowly to the reaction mixture.

4.2.4 Iron-catalysed cross-coupling of 1-iodo-3-substituted bicyclo-[1.1.1]pentanes with aryl Grignards - Slow addition

It was decided to continue this study using $Fe(acac)_3$ as it is a cheap commercially-available catalyst stable to air and moisture. The Grignard reagent was added at 1.8 mL/min and ligands were screened, starting with phosphine ligands (Figure 4.7). Firstly, **290** was obtained in very poor yield when no ligand was used and **291** was produced in 45% yield. dppBz improved the yield of **290** to 18% but an equivalent amount starting material remained. However, the amount of **291** was reduced to 28% yield. When using dcypt, an electron-rich 1,2-bisphosphine, the yield of **290** rose to 59%. Also, **291** was only produced in 22% yield. It was thought that electron-rich phosphine were needed for a efficient reaction and simple electron-rich bisphosphine dcpe was tested; the reaction yield decreased to 28% and yield of hydrodeiodination product rose to 33%. Other electron-rich phosphines were tested; DavePhos, dcympBz, DCEPhos, ^{t}BuXantPhos, (*R,R*)-DuPhos and PNN did not improve the yield of the reaction compared to dcypt. In all cases, the

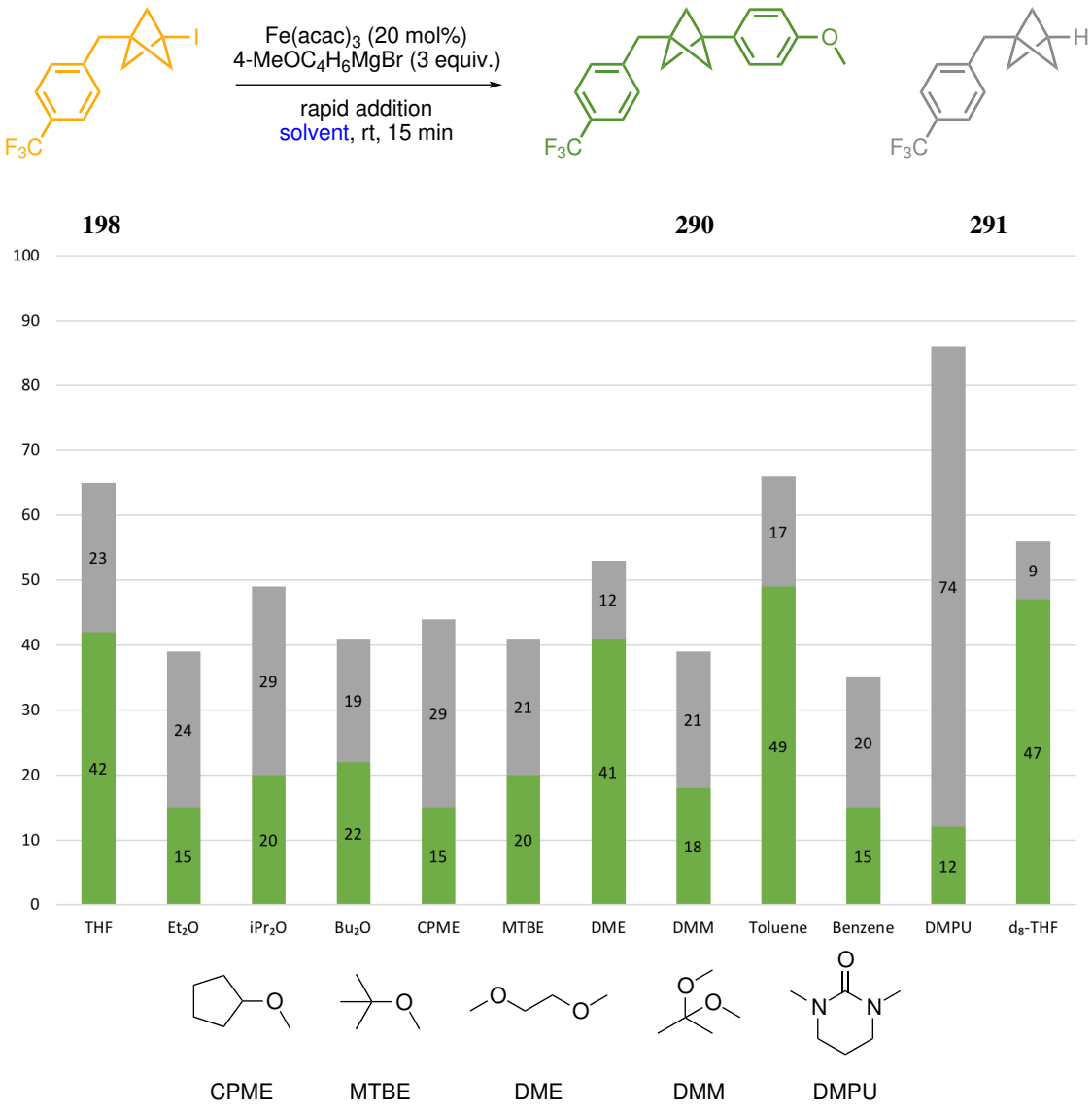


Figure 4.6: Solvent screening. Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard.

yield of **290** was under 20% and the yield of **291** above 35%. It was concluded, given the structures of the low-efficiency ligands, that the reaction necessitated an electron-rich 1,2-bisphosphine locked at a 180 ° dihedral angle. Also, as shown with (*R,R*)-DuPhos, any bulk around the phosphorus atom was detrimental to yield of the reaction.

Although dcypt catalysed the reaction efficiently, it is commercially available only from Kanto Chemical, Japan. It was synthesised according the procedure of Takise *et al.* (Scheme 4.9).[127] 3,4-Dibromothiophene was lithiated with *n*-BuLi and quenched chlorodichlohexylphosphine twice, affording **293** in 63% yield.

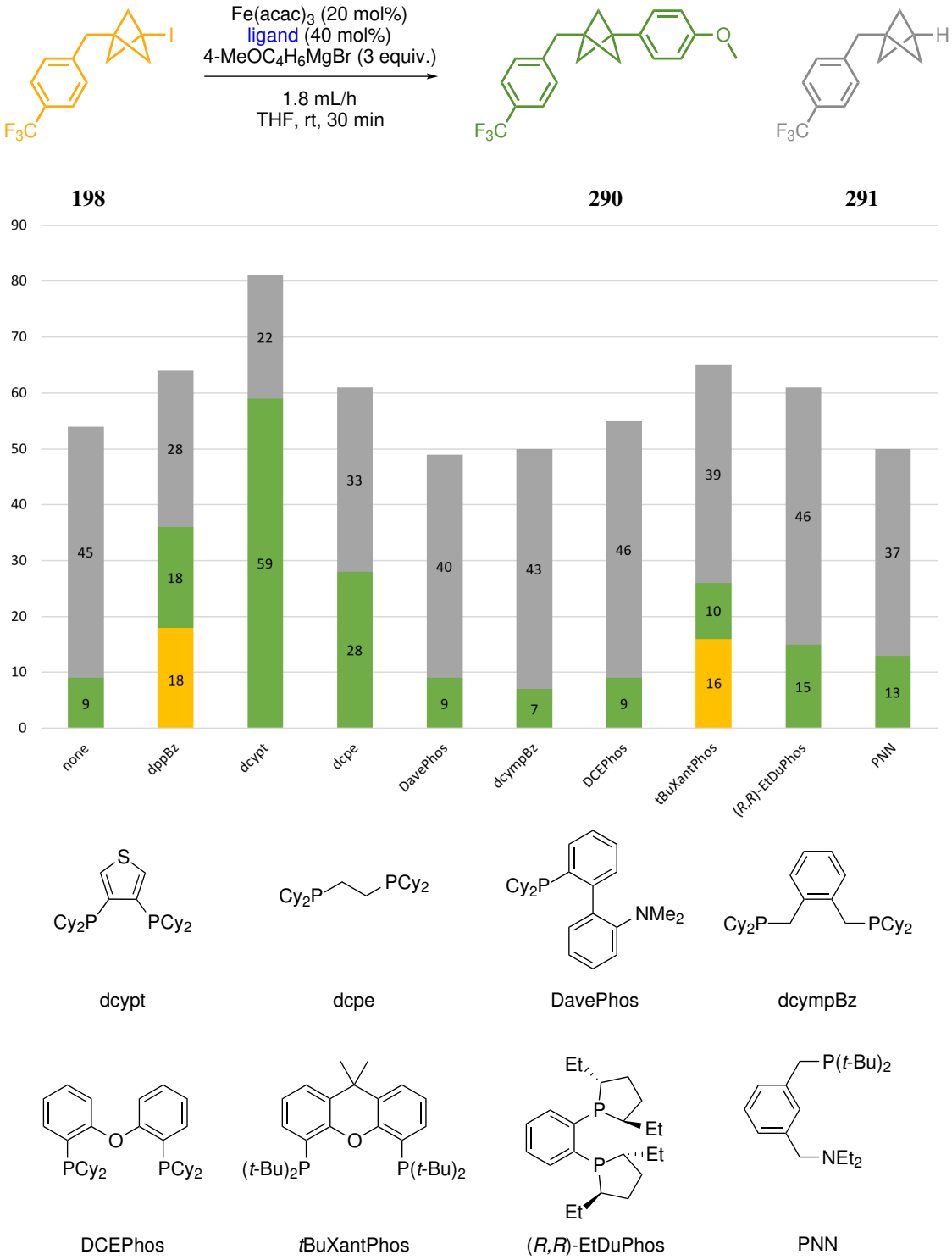
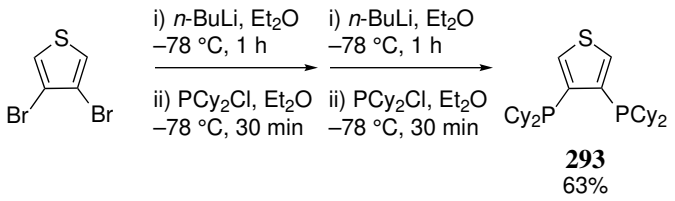


Figure 4.7: Phosphine ligand screening. Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard.



293
63%

Scheme 4.9: Synthesis of phosphine ligand dcypt (**293**).

Moreover, dcypt is a ligand of high molecular weight. It was decided to screen another class of ligands, namely nitrogen-containing ligands. Similarly to the work of Bedford and co-workers, simple amines were tested (Figure 4.8).[118] The use of triethylamine and DABCO did not allow for an efficient production of **290**, afforded in 12% yield in both cases. Also, the hydrodeiodinated BCP was produced in 46% and 58% respectively. On the other hand, using TMCD and TMEDA afforded **290** in 57% and 66% yield respectively. Furthermore, the production of **291** was limited (10% and 9 % yield respectively). The use of DMEDA allowed for only 18% yield of the cross-coupled BCP and 59% of hydrodehalogenated BCP. When the bulk was increased around the nitrogen atoms, with 1,2-dipiperidinoethane, the yield of the reaction dropped to 37% compared to TMEDA. PMDTA, a more chelating ligand, did not perform well and the product was obtained in only 17% yield. Similarly, 1,3,5-trimethyl-1,3,5-triazacyclohexane (1,3,5-TCH) and 1,4,7-trimethyl-1,4,7-triazacyclononane (1,4,7-TCN) did not improve the yield of the reaction. As noted by Bedford and co-workers, strongly chelating ligands have a deleterious effect on the yield of the reaction, likely by stabilising the iron complex to an extent that the displacement of the ligand by addition of Grignard reagent is slowed down or even inhibited.[128]

Owing to the wide availability, low price and low molecular weight of TMEDA, it was chosen as the ligand for this cross-coupling. A new solvent screen was performed (Figure 4.9). Only 1,2-dimethoxyethane (DME) and benzene proved as efficient as THF. It is interesting to note that with benzene, the amount of **291** produced was almost negligible. It is envisaged that the C-H abstraction is much more difficult on benzene due to the high energetic cost for the formation of an aryl radical. To limit volatility and toxicity, it was decided to continue the optimisation using THF.

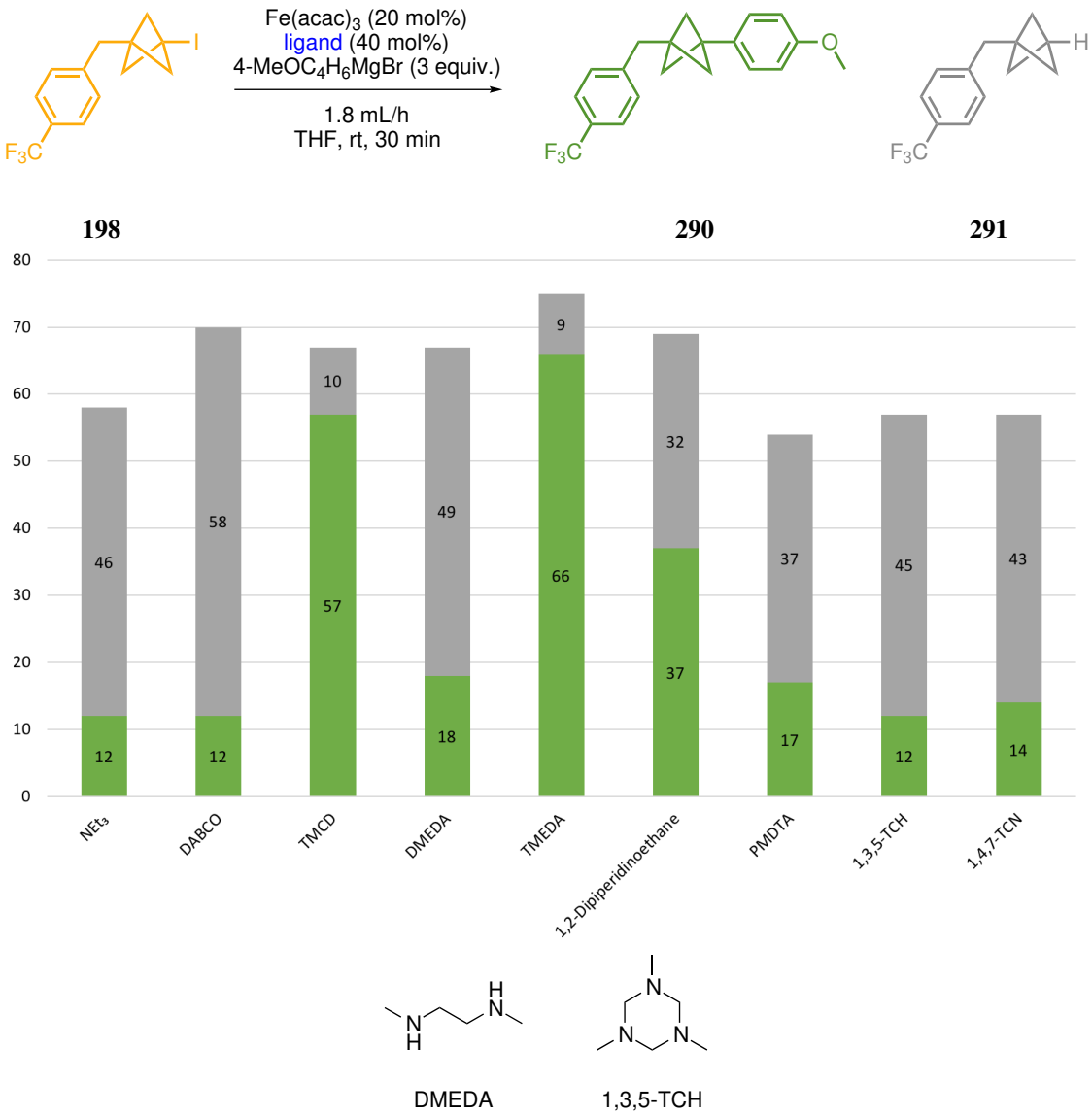


Figure 4.8: Amine-contaning ligand screening. Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard.

Next, the temperature of the reaction was investigated (Table 4.7) and yields proved inversely proportional to the temperature; at 45 °C, **290** was obtained in 67% yield (entry 1); at rt, the yield was 64% (entry 2) and at 0 °C, **290** was produced in 58% yield (entry 3). Also, at lower temperature, the amount of **291** produced was higher (8:2 ratio with **290**). It was decided to keep the reaction temperature at rt to ensure the highest functional group tolerance possible for the scope.

Then, the concentration of the reaction was surveyed (Table 4.8). As shown earlier with the work done by Dr Neal Sach (Figure 4.5), the concentration can play a major

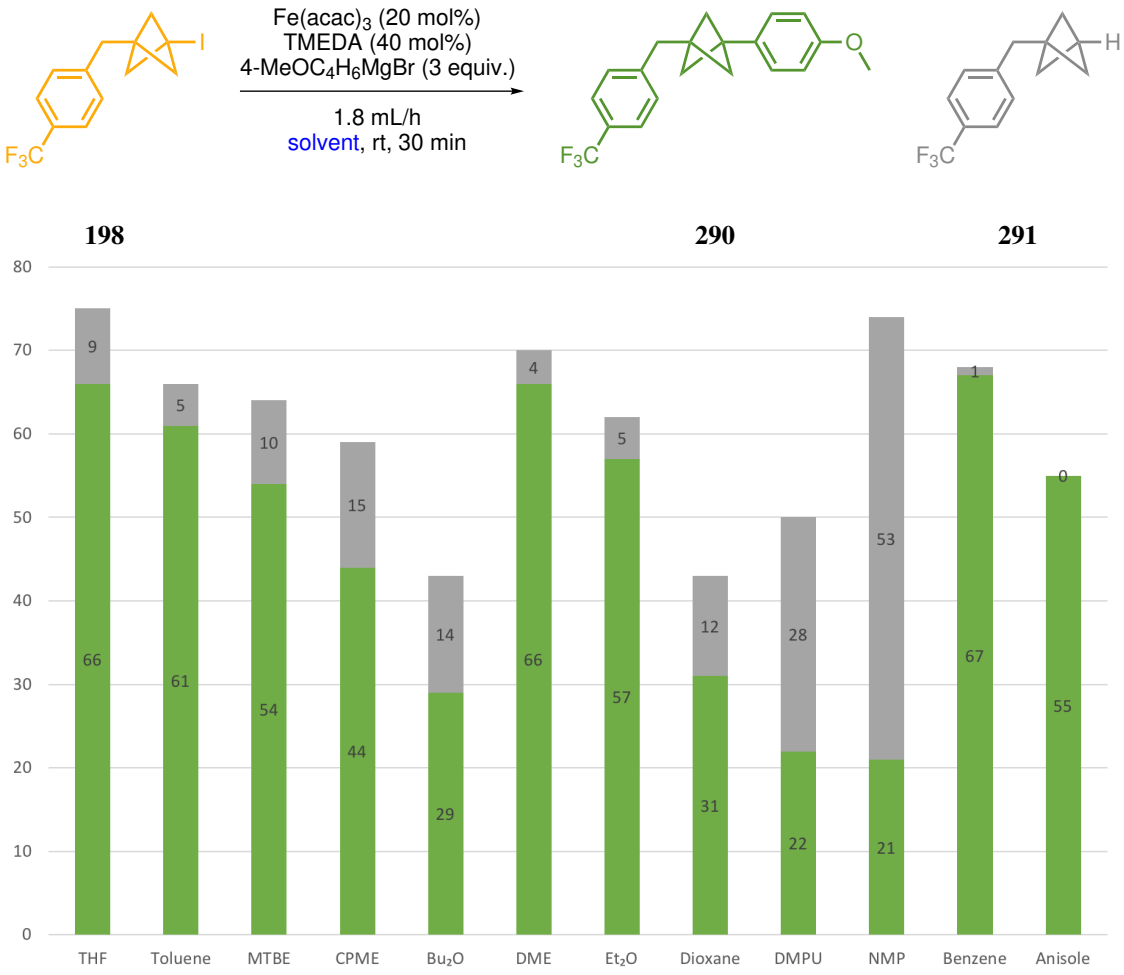
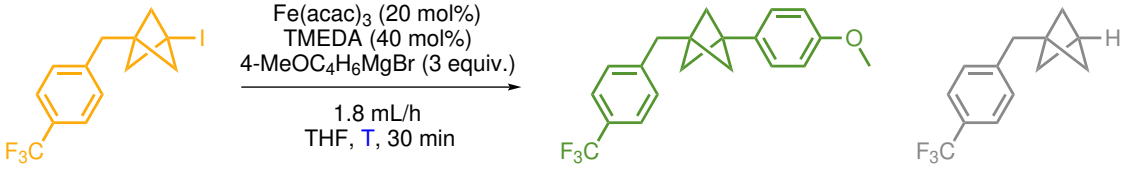


Figure 4.9: Solvent screening. Yields determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as the internal standard.

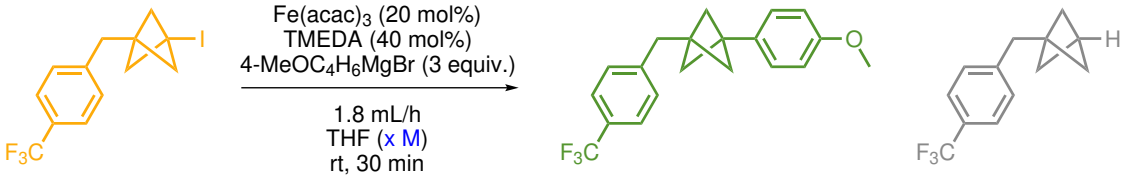
Table 4.7: Temperature screening. Isolated yields.



Entry	T	Yield (%)	Ratio **290/291** (crude NMR)
1	45 °C	67	95:5
2	rt	64	95:5
3	0 °C	58	80:20

part in this type of couplings. The starting concentration (before the addition of Grignard reagent) was varied from 0.1 M to 1.0 M, with 0.2 M the concentration at which this reaction has been operated so far. In agreement with previous results, the yield of the reaction decreased with decreasing concentration (60% at 0.1 M). Increasing the concentration from 0.2 M to 0.8 M was beneficial to the formation of **290** (64% to 73% yield) and no change was observed when operating at 1.0 M. A concentration dependance was observed for the formation of **291**; the lower the concentration, the higher the amount of hydrodehalogenated product was found. I was decided to continue using 1.0 M concentration.

Table 4.8: Concentration screening. Isolated yields.

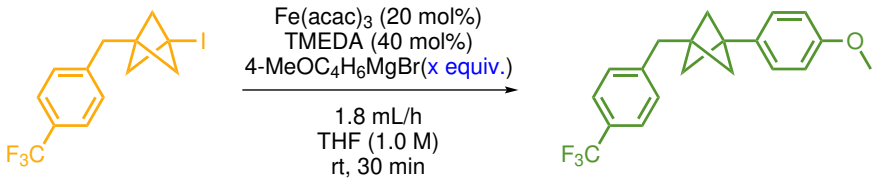


198 **290** **291**

Entry	Concentration (M)	Yield (%)	Ratio **290/291** (crude NMR)
1	0.1	60	82:18
2	0.2	64	95:5
3	0.4	66	95:5
4	0.8	73	95:5
5	1.0	73	97:3

The final optimisation step was the variation of the amount of Grignard used. The quantity of Grignard reagent was decreased to 1.6 equivalents (entries 1–4) while still reaching completion. The use of 1.4 equivalents did not allow the reaction to go to completion (entry 5). It is interesting to note that this amount accounts for the displacement of the acetylacetonate ligands of the iron catalyst (3 $\times$ 0.2 equivalents) and the coupling with one equivalent of starting material. Also, for each entry, completion was checked after the addition of the Grignard finished; apart from entry 4, the reactions were complete as soon as the slow addition ended. In the case of 1.4 equivalents (entry 4), completion was not reached after 30 min.

Table 4.9: Grignard reagent quantity screening. Isolated yield.

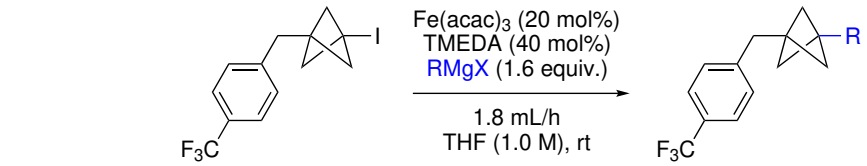


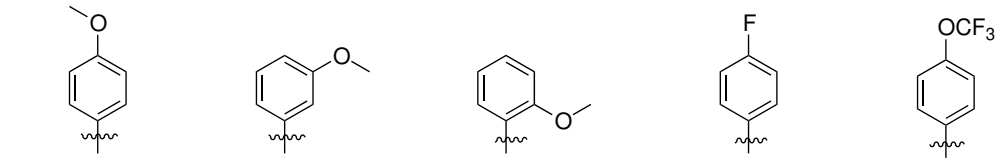
198 **290**

Entry	x equiv.	Completion
1	3.0	✓
2	2.0	✓
3	1.8	✓
4	1.6	✓
5	1.4	✘

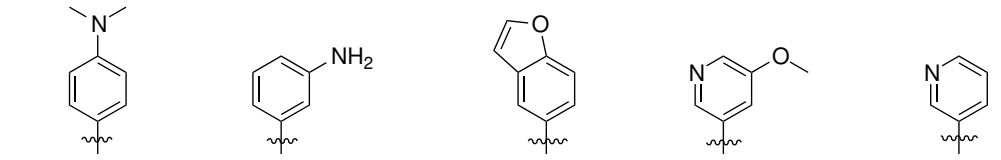
With these conditions in hand, it was decided to explore the scope of Grignard reagents (Figure 4.10). The reaction were performed on a 0.5 mmol scale of iodoBCP. Compound **290** was obtained in similar yield to prevously. *m*- and *o*-methoxy substituted compounds **294** and **295** were obtained in very good yield, 81% and 87% respectively, although **295** required the reaction to be carried out at 45 °C; reaction at rt did not yield any product. *p*-Fluorophenyl compound **296**, *p*-trifluoromethoxyphenyl compound **297** and *p*-dimethylaminophenyl **298** were produced in 71%, 72% and 68% respectively. Aniline **299** was obtained in 88% yield from the corresponding di-TMS protected Grignard reagent after acidic work-up. Benzofuran **300** was produced in moderate yield (51%) and needed 3 equivalents of Grignard for the reaction to reach completion. 3-Methoxypyridine **301** was afforded in 62% but the less electron rich pyridine **270** required higher temperature (65 °C), 3 equivalents of the corresponding Grignard and a rapid addition of the Grignard. Failure to operate under these modified conditions did not allow for reactivity and completion of the reaction.

This issue with electron-deficient organomagnesium reagents was observed with other nucleophiles. Electron-deficient organometallic reagents were unsuccessful under the developed conditions (Figure 4.11a). In all cases, the starting material was left unreacted. Electron-rich 4-(methylthio)phenylmagnesium bromide also did not yield any product. It is thought that, as can occur in palladium catalysed reactions, the sulfur atom may





290 71%
294 81%
295 87%[a]
296 71%
297 63%



298 68%
299 88%[c]
300 51%[d]
301 62%
270 44%[e]

[a]The reaction was carried out at 45 °C. [b]The reaction was performed by Ms Helena Pickford. [c]Obtained from the di-TMS protected Grignard reagent. [d]3 equivalents of the corresponding Grignard were used. [e]The reaction was carried at 65 °C using 3 equivalents of the Grignard and adding the Grignard rapidly to the reaction mixture.

Figure 4.10: Grignard reagent scope. Isolated yields

poison the metal catalyst and inhibit the reaction. Alkyl, allyl and benzyl Grignards were also unsuccessful (Figure 4.11b). No product was found after the addition ended and most of the starting material was recovered.

More Grignard reagents will be screened and it has been planned to modify the cross-coupling to allow for the reaction with electron-deficient nucleophile.

It was decided to implement this methodology along with the ATRA reaction to synthesise a BCP analogue of a known drug. Flurbiprofen (Figure 4.12a), a nonsteroidal anti-inflammatory drug, was selected and a simple retrosynthesis was devised for its analogue **302**; it should be accessed via the iron-catalysed cross-coupling of iodoBCP **303** and phenylmagnesium bromide (Figure 4.12c). **303** can be afforded from the BEt_3-initiated ATRA reaction of the corresponding α-iodoester and TCP.

Ethyl 2-iodopropionate was reacted with TCP to afford iodoBCP **305** in 80% (Scheme 4.10). Cross-coupling with phenylmagnesium bromide and hydrolysis of the

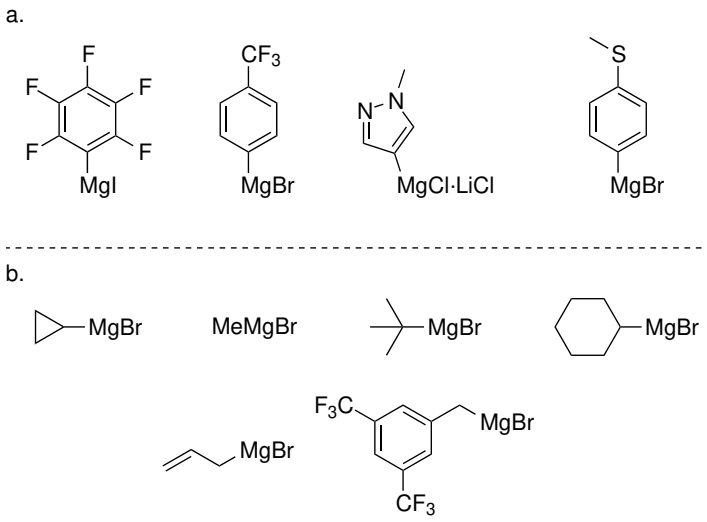


Figure 4.11: Unsuccessful aryl and heteroaryl reagents (a) and unsuccessful alkyl reagents (b). Reaction with MeMgBr was performed by Ms Bethany Shire and reaction with *tert*-butylmagnesium bromide and was performed by Ms Helena Pickford.

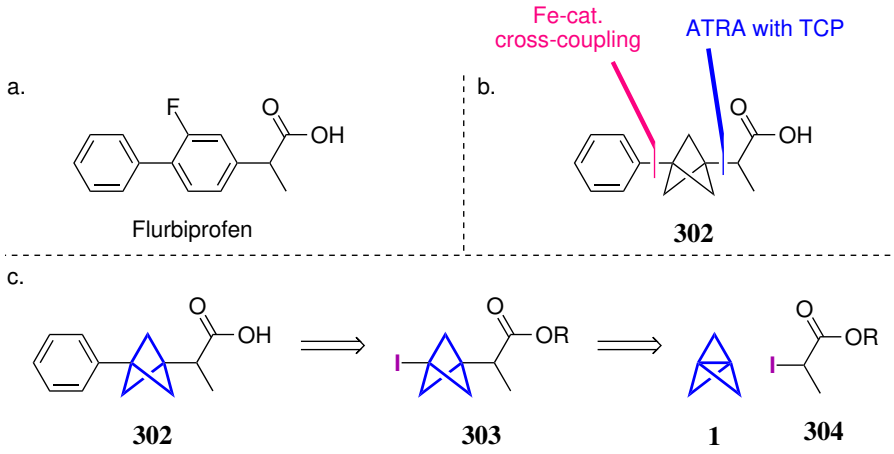
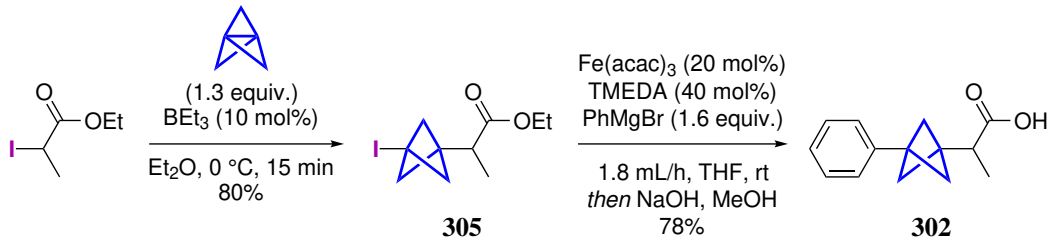


Figure 4.12: Non steroidal anti-inflamatory drug Flurbiprofen (a), Flurbiprofen BCP analogue **302** (b) and proposed retrosynthesis for **302** (c).

ester afforded acid **302** in 78% yield. The BCP analogue of Flurbiprofen was accessed in only two steps and very good yields. The compound has been sent to industrial partners for biological and physicochemical analysis and comparison with the parent drug.

This example proves that ester functionalities are compatible with the cross-coupling reaction. It is planned to extend the scope and test the performance of the various iodoBCPs synthesised in the previous chapters.

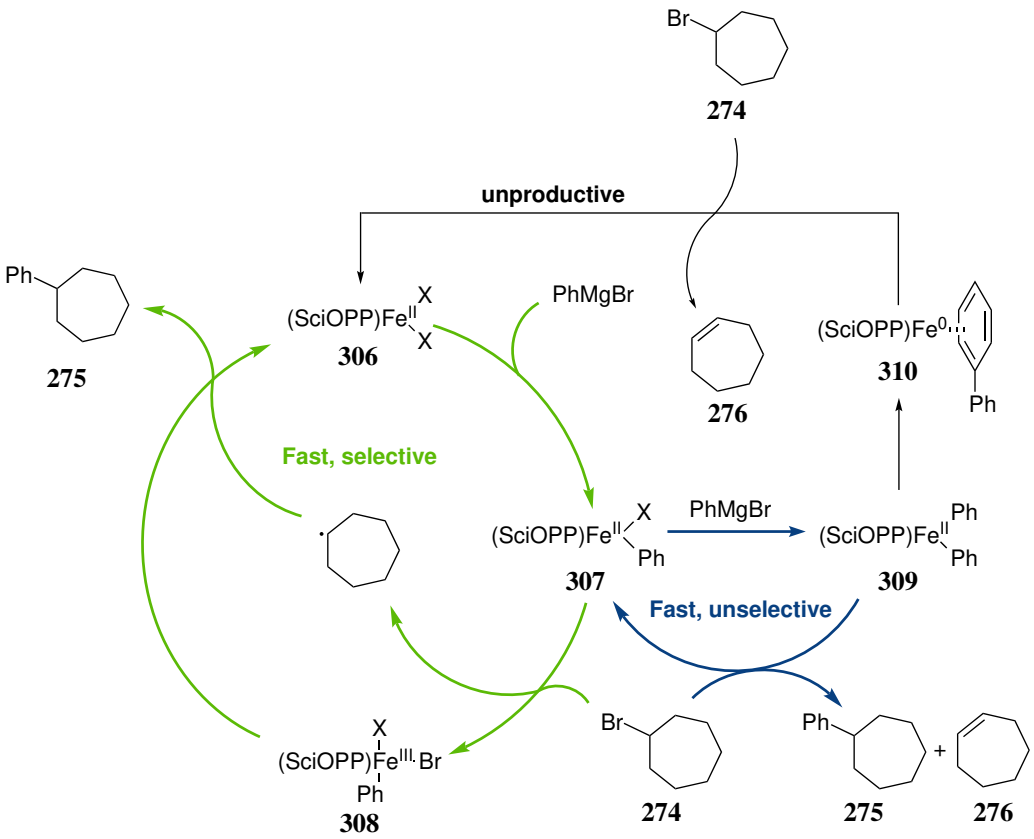


Scheme 4.10: Synthesis of the BCP analogue of Flurbiprofen, **302**

4.3 Insight in the mechanism of the reaction

Mechanisms for iron-catalysed cross couplings are still not entirely elucidated and many of the mechanistic proposal depend on the type of electrophile and nucleophile.[109] Recently, Neidig and co-workers proposed a mechanism for the cross-coupling reaction of bromocyclohexptane with phenylmagnesium bromide catalysed by iron(II) chloride-SciOPP complex.[129] Based on Nakamura's proposals,[130] Mössbauer spectroscopy analysis (indicating the oxidation state of the atom studied in the sample) of ^{57}Fe isolated complexes and reaction mixture, along with EPR spectroscopy, they proposed the mechanism given in Scheme 4.11. Reaction of complex **306** and phenylmagnesium bromide affords monoarylated complex **307** (green pathway). **307** rapidly reduces bromocyclohexane to produce iron(III) complex **308** and a cycloheptyl radical. The reaction between the radical and **308** gives the product (**275**) and and regenerates the iron complex **306** back. It was shown that **307** would also react with more phenylmagnesium bromide to produce biarylated iron complex **309** (along with the THF complex, not represented). Reaction of **309** with bromocycloheptane rapidly produces product **275** but also cycloheptene (**276**) (blue pathway). Complex **309** can also reductively eliminates to iron(0) complex **310**. Reaction with **274** produces cycloheptene (**276**) and complex **306** but no product.

As shown earlier, the coupling using $Fe(acac)_3$ and dcypt afforded **290** in 59% NMR yield. The coupling was performed using $FeCl_2(THF)_{1.5}$ as the catalyst and dcypt as the ligand, affording the product in 66% yield. It is plausible that the reaction is catalysed by an iron(II) catalyst. Nonetheless, noting that ligands have an effect on the type of iron complexes produced when reacted with Grignards (e.g. with dppbz, iron(I) species are favoured),[131] Neidig and co-workers did not exclude the possibility of iron(I) species

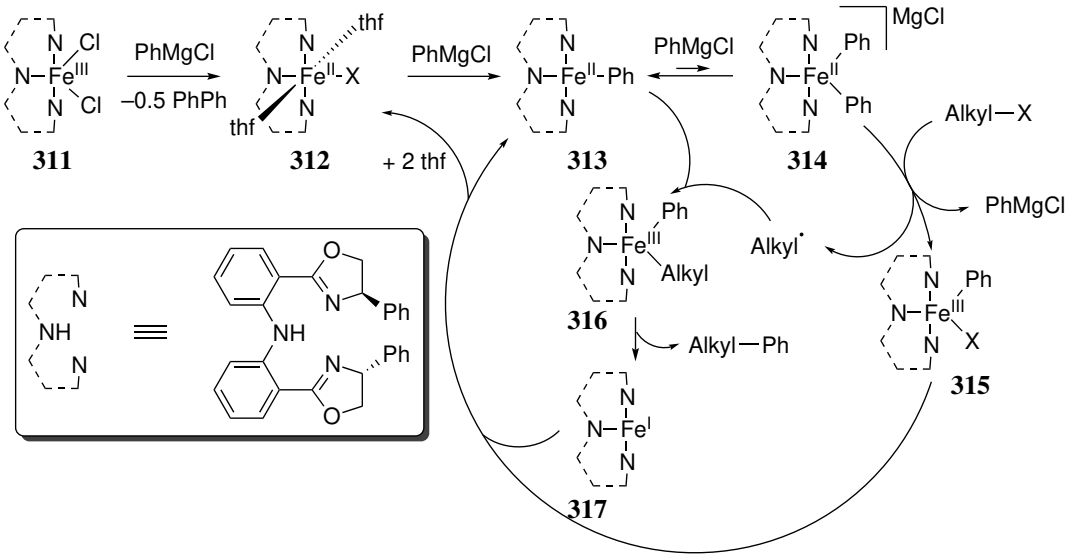


Scheme 4.11: Mechanism proposed by Neidig and co-workers.[129]

being able to catalyse the reaction.[129]

Hu and co-workers used experimental and computational data to propose a mechanism for the cross coupling of alkyl grignards with phenylmagnesium chloride (Scheme 4.12). Upon reaction with PhMgCl, complex **311** gets reduced to iron(II) complex **312**. Mono-alkylation with PhMgCl yields **313** and dialylation affords **314**. Complex **314** reduces the alkyl halide to the alkyl radical and, upon loss of PhMgCl, produces iron(III) complex **315**. The alkyl radical combines with complex **313** to afford iron(III) complex **316**. Upon reductive elimination, the product of the reaction is released alongside highly reactive iron(I) complex **317** is produced. Comproportionation of complexes **315** and **317** returns complex **312**, after coordination with THF, and complex **313**. However, the authors cannot rule out a possible recombination of the alkyl radical with **315** and reductive elimination to give the arylated alkyl compound and iron(II) complex **312**.

Overall, despite many proposed mechanisms supported by experimental evidence, the mechanism of these cross-coupling has not yet been fully elucidated.



Scheme 4.12: Mechanism proposed by Hu and co-workers.[132]

4.4 Conclusions

We have demonstrated that an iodoBCP could be lithiated and quenched with benzaldehyde, benzophenone and ethyl formate to yield the corresponding alcohol and aldehyde derivatives; it could also be transmetallated to organozinc species and cross-coupled with 2-bromopyridine in good yields. An iron-catalysed Kumada-Tamao-Corriu cross-coupling was developed to couple iodoBCPs with organomagnesium species, using iron(III) acetylacetonate as the catalyst and TMEDA as the ligand. The coupling worked well with eletron-rich aryl Grignard reagents, but poorly with electron-deficient aryl Grignards, or alkyl Grignard reagents. It was demonstrated that a drug surrogate of Flurbiprofen could be synthesised in a modular way using the ATRA and cross-coupling methodologies in only two steps from TCP (**1**) and in very good yield. This represents the first ever cross-coupling reaction of iodoBCPs with organomagnesium reagents. The scope of the reaction needs to be extended to a wider range of iodoBCPs. The mechanism of the reaction has not yet been elucidated but, according to the literature, it is likely that an iron(II) species is involved in the catalytic process.

5
Conclusion and future work

A novel, modular approach has been developed to synthesise 1,3-disubstituted BCPs to be used as bioisosteres of 1,4-disubstituted benzene rings in medicinal chemistry. A mild, efficient, and functional group tolerant BEt_3-initiated ATRA reaction of organohalides with TCP was developed, allowing for the synthesis of 1-halo-3-substituted BCPs. A wide range of iodoBCPs as well as a few bromoBCPs were obtained. The use of TTMSS and BEt_3 allowed for the reduction of the C–I bond iodoBCPs; monosubstituted BCP building blocks such as acids, amides, amines and amino acids were obtained, along with more elaborated BCP-labelled compounds such as nucleotides, peptides and a BCP analogue of Fentanyl. The first iron-catalysed Kumada-Tamao-Corriu cross-coupling of iodoBCPs was developed, which resulted in the synthesis of arylated BCPs. The coupling was particularly efficient with electron-rich aryl Grignard reagents. Combining the ATRA and the cross-coupling reactions, a BCP analogue of Flurbiprofen was synthesised. Biological and physicochemical analysis of the drug surrogates are underway. A summary is proposed in Figure 5.1.

Our group has commenced investigations in new types of initiation, namely photoredox chemistry. Exciting results have been obtained so far by Dr. Carlos Arroniz, Ms Bethany Shire, Ms Helena Pickford and Dr. Jeremy Nugent (Scheme 5.1); the scope of the reaction using BEt_3 as the initiator has been matched with overall better yields and this methodology should allow for the use of iodoarenes. Looking ahead, we intend to

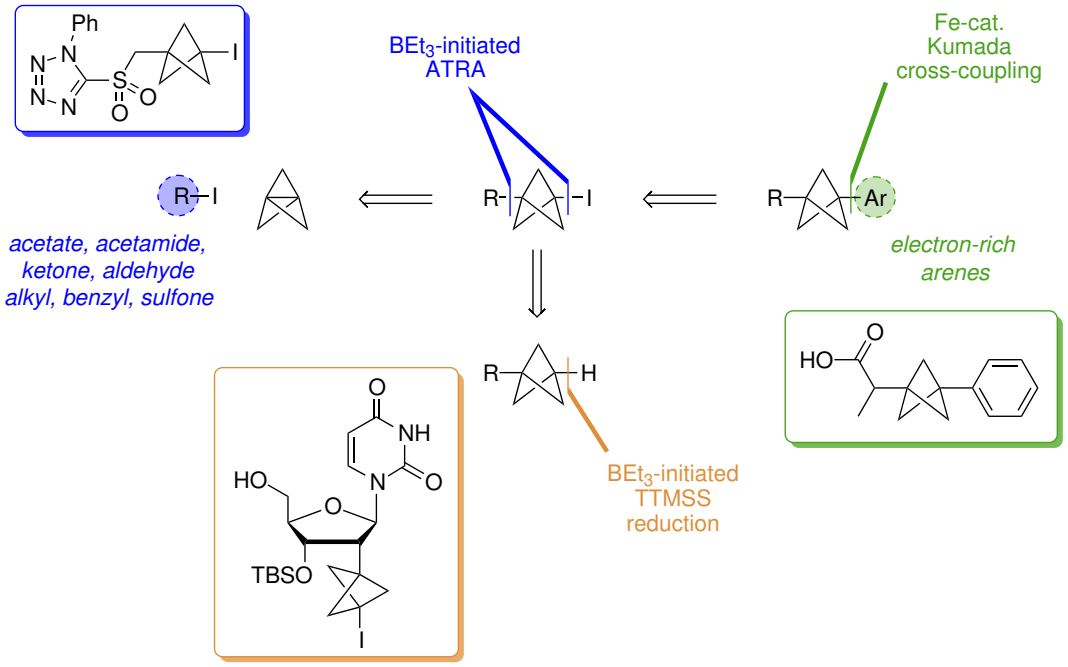
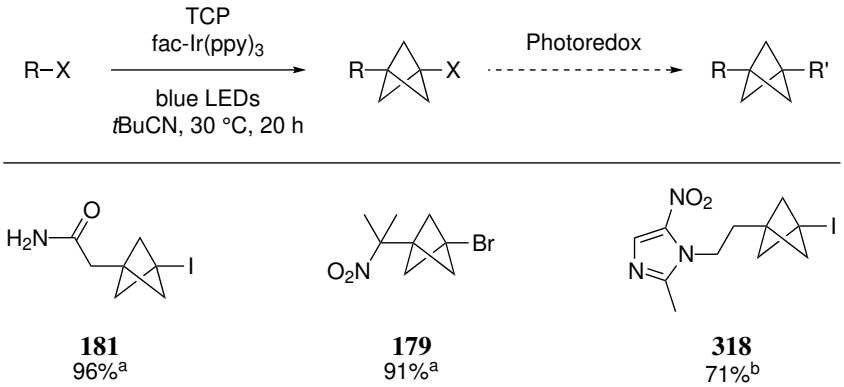


Figure 5.1: Summary of the work presented in this thesis.

explore further the functionalisation of iodoBCP using photoredox processes and to study the possibility of a one-pot ATRA and cross-coupling reaction.



181 96%[a] **179** 91%[a] **318** 71%[b]

[a]Compounds synthesised by Dr Carlos Arroniz. [b]Compound synthesised by Dr Jeremy Nugent.

Scheme 5.1: Photoredox-initiated ATRA reaction of organoiodides with TCP and potential photoredox-catalysed functionalization of iodoBCPs.

Further work has been planned to extend the scope of the cross-coupling reaction firstly towards electron-deficient aryl Grignard that have been shown to perform poorly, and secondly to alkyl Grignard, that have so far been unsuccessful. Lastly, the use of alkenyl and alkynyl Grigandrs will also be explored. The cross-coupling will be explored with a wider range of iodoBCPs that were synthesised during this study and bromoBCP

will also be considered. A survey of the type of nucleophiles will be conducted to assess their reactivity towards haloBCPs in cross-couplings (e.g. organozinc and organoborane species). It has been planned to perform the cross-coupling with different purities of iron catalyst to verify that not other metal is promoting the reaction.

Finally, the use of phenyllithium to synthesise TCP might be considered as a hindrance to its synthesis on large scale; furthermore, TCP itself is an unstable and volatile compound obtained as a solution in etheral solvents. It would be interesting to investigate a novel route for the synthesis of BCPs that avoid TCP entirely; building on the work of Applequist and Wheeler,[30] Hirst and co-workers reported the synthesis of compound **319**, a BCP analogue of a $LpLAP_2$ inhibitor using a dichlorocarbene addition on a bicyclo[1.1.0]butane derivative **320** to afford dichloroBCP compound **321**, which upon reduction of the C–Cl bonds afforded BCP derivative **322** (Figure 5.2).[133]

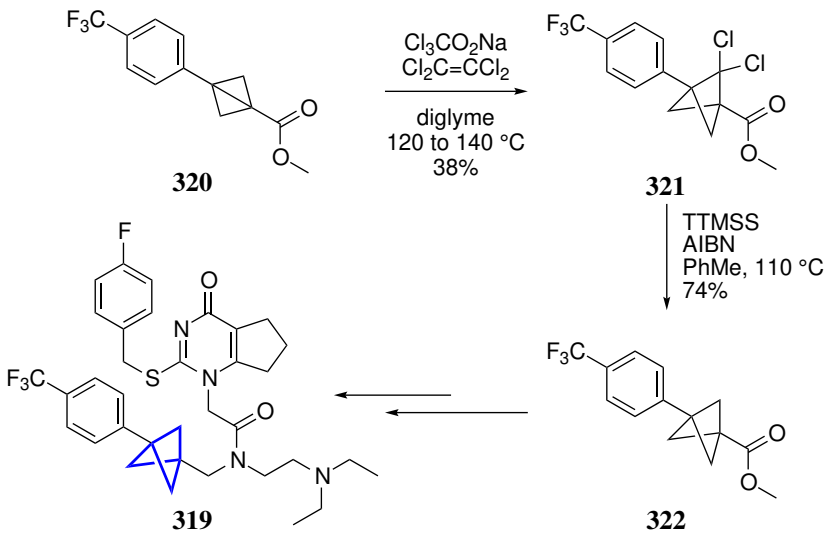


Figure 5.2: Dichlorocarbene addition to bicyclo[1.1.0]butane **320** for the synthesis of BCP derivative **319**.[133]

We are interested in expanding this chemistry to the reaction of metal carbenoids (derived from diazo compounds) with bicyclo[1.1.0]butane (Figure 5.3). This would allow for the synthesis of bridge substituted BCP, which until now have been difficult to access and far less studied.[134–138]

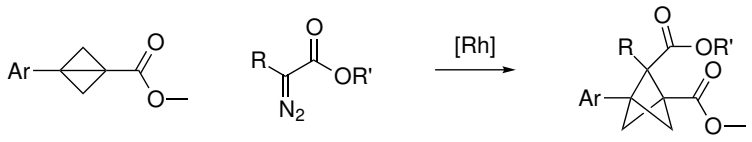


Figure 5.3: Proposed addition of rhodium carbenoid to bicyclo[1.1.0]butane for the synthesis of bridge substituted BCPs.

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Experimental

1. General Experimental Considerations

NMR Spectroscopy: Proton (^{1}H), carbon (^{13}C) and fluorine (^{19}F) NMR spectra were recorded on a Bruker AVIIIHD 400 nanobay (400 MHz) spectrometer. Proton, carbon and fluorine chemical shifts are quoted in ppm. ^{1}H NMR spectra were recorded using an internal deuterium lock for the residual protons in $CDCl_3$ (δ 7.26), CD_3OD (δ 3.31) and C_6D_6 (δ 7.16). ^{13}C NMR spectra were recorded using an internal deuterium lock in $CDCl_3$ (δ 77.0), CD_3OD (δ 49.0) and C_6D_6 (δ 128.1). Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HMBC, HSQC and/or NOESY experiments. Peak multiplicities are defined as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad; coupling constants (*J*) are reported to the nearest 0.1 Hz.

Infrared Spectroscopy: Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer with the sample being prepared as a thin film on a diamond ATR module. Absorption maxima (ν_{max}) are quoted in wavenumbers (cm^{-1}).

Mass Spectroscopy: Low resolution mass spectra were recorded on a Micromass LCT Premier Open Access using electrospray ionisation (ESI). Accurate mass (HRMS) data was determined under conditions of ESI, EI and CI on a Bruker MicroTOF. High resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

EXPERIMENTAL

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

X-ray crystallography: Details of instrumentation and techniques are reported in Section 5.

Reagents, solvents and techniques: All reagents were used directly as supplied. $Fe(dbm)_3$,[1] $Fe(1,4,7\text{-}TCN)Cl_3$,[2] $Fe(1,4,7\text{-}TCH)Cl_3$,[3] Fe[(*R,R*)-Jacobsen]Cl,[4] $Fe(bpy)_3Br_2$,[5] and TCMD[6] were prepared according to literature procedures. Solvents were either used as commercially supplied, or as purified by standard techniques. Anhydrous Et_2O was obtained from solvent dispenser units having been passed through an activated alumina column under argon. Unless otherwise stated, non-aqueous reactions were performed under air.

Reactions were monitored by thin layer chromatography on pre-coated aluminium-backed plates (Merck Kieselgel 60 with fluorescent indicator UV254). Spots were visualised by quenching of UV fluorescence or by staining with potassium permanganate or vanillin, and retention factors are reported with the solvent system in parentheses. Flash column chromatography 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.

2. General Procedures

General Procedure 1. Finkelstein reaction.

Adapted from the procedure described by Zhou et al.[7] To a solution of the specified alkyl bromide (1.0 equiv.) in acetone was added sodium iodide (1.5 equiv.). The resulting mixture was stirred in the dark until TLC showed completion. The mixture was diluted with water and Et_2O (or EtOAc) and the layers were separated. The aqueous layer was extracted twice with Et_2O (or EtOAc). The combined organics were washed with $Na_2S_2O_3$ (10 % *aq.*) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. When specified, the residue was purified by column chromatography or recrystallisation.

General Procedure 2. Appel reaction.

To a solution of the specified alcohol in CH_2Cl_2 was added triphenylphosphine and, if specified, imidazole. Iodine was added portionwise and the reaction mixture was stirred under an inert atmosphere at rt (quantities and reaction time specified in each procedure). The mixture was then diluted with water and CH_2Cl_2, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organics were washed with $Na_2S_2O_3$ (10% *aq.*) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography.

General Procedure 3. Copper oxide mediated iodination.

According to the procedure described by Yin et al.[8] To a solution of the specified methylketone (1.0 equiv.) in MeOH were added CuO (1.0 equiv.) and I_2 (1.0 equiv.). The reaction mixture was stirred for 5 min, then refluxed for 2–3 h, and then concentrated *in vacuo*. The residue was taken up in EtOAc, filtered, and the organic

filtrate washed with $Na_2S_2O_3$ (10% aq.,), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography.

General Procedure 4: Atom-transfer radical addition of halides to TCP.

To a screw-capped vial containing the specified halide (1.0 equiv.) was added tricyclo[1.1.1.0^{1,3}]propane (1.1–2.0 equiv., solution in Et_2O). The vial was capped and the mixture was stirred at the indicated temperature for 3 min. BEt_3 (1–10 mol%, 1 M in hexane) was then added to the solution via syringe (needle tip in the solution), and the mixture was stirred as specified in the individual procedure. Once complete, as judged by ^{1}H NMR spectroscopic analysis of an aliquot, the reaction mixture was concentrated and purified by column chromatography or recrystallisation.

General procedure 5: Optimisation of the TM-catalysed cross-coupling of iodoBCPs with rapid addition of the Grignard reagent.

To an oven-dried vial was added the metal complex (20 mol%), if indicated a ligand (20 mol%), and the iodoBCP (35 mg, 0.10 mmol, 1.0 equiv.). The vial was evacuated and backfilled with N_2 three times. The appropriate solvent (0.5 mL) was added and the resulting mixture was stirred at rt for 5 min. 4-(MeO)PhMgBr (0.30 mL, 1 M in THF, 0.30 mmol, 3 equiv.) was added rapidly in a single portion, and the resulting black mixture was stirred for 30 min at rt, filtered over SiO_2, and eluted with Et_2O (20 mL).

Where no ligand was used (Figures 4.2, 4.3 and 4.6), a known quantity of 1,3,5-trimethoxybenzene was added and the mixture was concentrated *in vacuo*. The yield of the reaction was determined by ^{1}H NMR spectroscopy (delay = 20 s).

Where ligands were used (Figure 4.4), the filtrate was concentrated *in vacuo* and purified by column chromatography (SiO_2, pentane / Et_2O, 98:2).

General procedure 6: Optimisation of the iron-catalysed cross-coupling of iodoBCPs with slow addition of the Grignard reagent.

To an oven-dried vial was added an iron complex (20 mol%), if indicated a ligand (40 mol%), and the iodoBCP (35 mg, 0.10 mmol, 1.0 equiv.). The vial was evacuated and backfilled with N_2 three times. The appropriate solvent (0.5 mL) was added and the resulting mixture was stirred at rt for 5 min. 4-(MeO)PhMgBr (0.16–0.30 mL, 1 M in THF, 0.16–0.30 mmol, 1.6–3 equiv.) was added at 1.8 mL/h *via* syringe pump at rt, and upon completion of the addition, the resulting black mixture was stirred for 30 min at rt, filtered over SiO_2, and eluted with Et_2O (20 mL) .

For Figures 4.7, 4.8 and 4.9, a known quantity of 1,3,5-trimethoxybenzene was added and the mixture was concentrated *in vacuo*. The yield of the reaction was determined by ^1H NMR spectroscopy (delay = 20 s).

For Tables 4.7 and 4.8, the filtrate was concentrated *in vacuo* and purified by column chromatography (SiO_2, pentane / Et_2O, 98:2).

For Table 4.9, completion of the reaction was checked immediately after the addition ended by TLC. If complete, the reaction mixture was filtered, and the filtrate was concentrated *in vacuo* and purified by column chromatography (SiO_2, pentane / Et_2O, 98:2). If not, the mixture was stirred for 30 min at rt and the same work-up procedure as Tables 4.7 and 4.8 was applied.

General procedure 7: Synthesis of Grignard reagents.

To a round-bottom flask was added magnesium turnings (3 equiv.) and, if indicated, lithium chloride (1.5 equiv.). The flask was flame-dried and, after cooling, THF was added. The resulting suspension was brought to the required temperature and the halide (1.0 equiv.) was added dropwise. After the addition was finished, the suspension was stirred as indicated. The Grignard reagent was titrated using I_2/LiCl in THF.

General procedure 8: Iron-catalysed Kumada-Tamao-Corriu cross-coupling of iodoBCPs

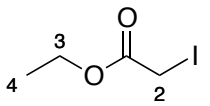
To an oven-dried vial was added $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 0.20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%), and the iodoBCP (176 mg, 0.500 mmol, 1.0 equiv.). The vial was evacuated and backfilled with N_2 three times. THF (0.5 mL) was added and the resulting mixture was stirred at rt for 5 min. Unless indicated otherwise, the appropriate Grignard reagent (solution in THF, 0.80 mmol, 1.6 equiv.) was added at 1.8 mL/h *via* syringe pump at rt, and upon completion of the addition, HCl (aq., 1 M, 2 mL) was added. The phases were separated and the aqueous was extracted with Et_2O (3 × 2 mL). The combined organics were washed with brine (5 mL), dried, and concentrated *in vacuo*. The residue was purified by column chromatography.

3. Procedures and characterisation data

Tricyclo[1.1.1.0^{1,3}]pentane (TCP), 1

According to the procedure described by Gianatassio et al.[9] To a flame-dried round-bottom flask equipped with a stirrer bar was added 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (5.0 g, 16.9 mmol, 1.0 equiv.). The reaction vessel was evacuated and back-filled with argon three times, and anhydrous Et_2O (10 mL) was added. The reaction vessel was cooled to −45 °C (dry ice / isopropanol bath). Phenyllithium (17.8 mL, 1.9 M in Bu_2O, 33.7 mmol, 2.0 equiv.) was added dropwise over 15 min at –45 °C, and the resulting mixture was stirred for 15 min at −45 °C. The cooling bath was replaced with an ice bath, and the reaction mixture was warmed to to 0 °C, and stirred at this temperature for 2 h. The mixture was then distilled at rt (10 mbar) using a rotary evaporator, the receiving flask of which was immersed in a dry ice/acetone bath. The TCP-containing distillate (10 mL, TCP concentration 0.91 M in Et_2O, 54%) was transferred in a flame-dried septum-sealed bottle under inert atmosphere, and stored at −20 °C. The yield was determined by ^{1}H NMR spectroscopy with 1,2-dichloroethane as an internal standard. The concentration of the TCP solution ranged between 0.62 M and 1.10 M, with yields of 45-61%.

Ethyl iodoacetate, 115



Ethyl bromoacetate (330 μL, 3.00 mmol, 1.0 equiv.) and sodium iodide (673 mg, 4.50 mmol, 1.5 equiv.) in acetone (10 mL) were submitted to **General Procedure 1** (12 h) to give **115** (568 mg, 2.65 mmol, 88%) as a yellow oil.

R_f = 0.46 (petroleum ether / EtOAc, 9:1), [UV].

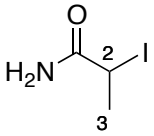
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (2H, q, *J* = 7.1 Hz, H3), 3.67 (2H, s, H2), 1.27 (3H, t, *J* = 7.1 Hz, H4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.9, 62.2, 14.0, −5.1.

HRMS (CI^+) Found $[M+NH_4]^+$ = 231.9833; $C_4H_{11}IO_2N$ requires 231.9828.

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

2-Iodopropanamide, 149



Bromopropionamide (304 mg, 2.00 mmol, 1.0 equiv.) and sodium iodide (450 mg, 3.00 mmol, 1.5 equiv.) in acetone (2 mL) were submitted to **General Procedure 1** (17 h) to give **149** (307 mg, 1.54 mmol, 77%) as a white solid.

m.p. = 150-152 °C

^{1}H NMR (400 MHz, CD_3OD) δ 4.57 (1H, q, *J* = 7.0 Hz, H2), 1.87 (3H, d, *J* = 7.0 Hz, H3).

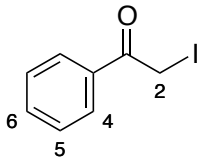
^{13}C NMR (101 MHz, CD_3OD) δ 176.8, 24.2, 16.6.

HRMS (CI^+) Found $[M+H]^+$ = 199.9567; C_3H_7INO requires 199.9567.

IR (film) ν_{max}/cm^{-1} 3335, 3165, 1686, 1410, 1060, 626.

Synthesised and characterised by Dr Carlos Arroniz.

2-Iodo-1-phenylethan-1-one, 150



2-Bromo-1-phenylethan-1-one (199 mg, 1.00 mmol, 1.0 equiv) and sodium iodide (225 mg, 1.50 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General Procedure 1** (18 h) to give **150** (227 mg, 0.930 mmol, 93%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.97 (2H, m, H4), 7.64–7.57 (1H, m, H6), 7.52–7.46 (2H, m, H5), 4.37 (2H, s, H2).

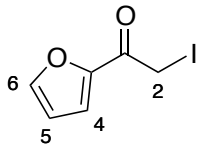
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.0, 133.9, 133.6, 129.1, 128.9, 1.9.

HRMS (EI^+) Found $[M]^+$ = 245.9541; C_8H_7IO requires 245.9536.

IR (film) ν_{max}/cm^{-1} 1670, 1269.

Synthesised and characterised by Dr Carlos Arroniz.

1-(Furan-2-yl)-2-iodoethan-1-one, 151



2-Acetylfuran (300 μL, 3.00 mmol, 1.0 equiv.), CuO (240 mg, 3.00 mmol, 1.0 equiv.) and I_2 (762 mg, 3.00 mmol, 1.0 equiv.) in MeOH (12 mL) were submitted to **General Procedure 3**. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 8:2) gave **151** (605 mg, 2.56 mmol, 85%) as a brown oil.

R_f = 0.36 (petroleum ether / Et_2O, 7:3)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, dd, *J* = 1.7, 0.8 Hz, H6), 7.31 (1H, dd, *J* = 3.6, 0.8 Hz, H4), 6.58 (1H, dd, *J* = 3.6, 1.7 Hz, H5), 4.23 (2H, s, H2).

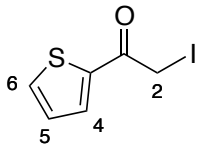
^{13}C NMR (101 MHz, $CDCl_3$) δ 182.2, 150.0, 147.1, 119.0, 113.0, 0.7.

HRMS (EI^+) Found $[M]^+$ = 235.9323; $C_6H_5IO_2$ requires 235.9329.

IR (film) ν_{max}/cm^{-1} 2980, 1660, 1461, 1292.

Synthesised and characterised by Dr Carlos Arroniz.

2-Iodo-1-(thiophen-2-yl)ethan-1-one, 152



2-Bromo-1-(thiophen-2-yl)ethan-1-one (205 mg, 1.00 mmol, 1.0 equiv.) and sodium iodide (225 mg, 1.50 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General Procedure 1** (18 h) to give **152** (0.23 g, 0.90 mmol, 90%) as a brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, dd, *J* = 3.9, 1.1 Hz, H6), 7.69 (1H, dd, *J* = 5.0, 1.1 Hz, H4), 7.16 (1H, dd, *J* = 5.0, 3.9 Hz, H5), 4.30 (3H, s, H2).

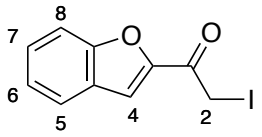
^{13}C NMR (101 MHz, $CDCl_3$) δ 186.1, 140.5, 135.2, 133.6, 128.5, 1.5.

HRMS (EI^+) Found $[M]^+$ = 251.9099; C_6H_5IOS requires 251.9100.

IR (film) ν_{max}/cm^{-1} 1645, 1409, 1278.

Synthesised and characterised by Dr Carlos Arroniz.

1-(Benzofuran-2-yl)-2-iodoethan-1-one, 153



1-(Benzofuran-2-yl)-2-bromoethan-1-one (239 mg, 1.0 mmol, 1.0 equiv.) and sodium iodide (225 mg, 1.5 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General Procedure 1** (18 h) to give **153** (0.21 g, 0.72 mmol, 72%) as a pale yellow solid.

m.p. = 103–105 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, app dt, *J* = 8.0, 1.0 Hz, H5), 7.64 (1H, d, *J* = 1.0 Hz, H4), 7.59 (1H, dq, *J* = 8.4, 1.0 Hz, H8), 7.51 (1H, ddd, *J* = 8.4, 7.1, 1.0 Hz, H7), 7.33 (1H, ddd, *J* = 8.0, 7.1, 1.0 Hz, H6), 4.36 (2H, s, H2).

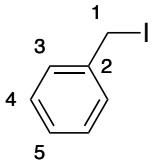
^{13}C NMR (101 MHz, $CDCl_3$) δ 184.1, 155.9, 149.9, 129.0, 127.2, 124.3, 123.6, 114.7, 112.7, 0.8.

HRMS (EI^+) Found $[M]^+$ = 285.9190; $C_{10}H_7IO_2$ requires 285.9485.

IR (film) ν_{max}/cm^{-1} 1658, 1552, 1299, 1022.

Synthesised and characterised by Dr Carlos Arroniz.

Benzyl iodide, 154



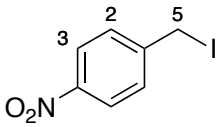
Benzyl bromide (1.39 mL, 11.7 mmol, 1.0 equiv.) and sodium iodide (2.63 g, 17.5 mmol, 1.5 equiv.) in acetone (10 mL) were submitted to **General Procedure 1** (12 h) to give the **154** (2.49 g, 11.4 mmol, 97%) as a pale yellow oil.

R_f = 0.40 (Petroleum ether), [UV]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, app d, J = 7.1 Hz, H4), 7.32 – 7.21 (3H, m, H3, H5), 4.46 (2H, s, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 128.9, 128.9, 128.0, 5.9.

1-(Iodomethyl)-4-nitrobenzene, 155



4-Nitrobenzyl bromide (664 mg, 3.07 mmol, 1.0 equiv.) and sodium iodide (691 mg, 4.61 mmol, 1.5 equiv.) in acetone (5 mL) were submitted to **General Procedure 1** (12 h). Recrystallisation from CH_2Cl_2 / pentane gave **155** (350 mg, 1.33 mmol, 43%) as pale yellow crystals.

R_f = 0.22 (petroleum ether / Et_2O, 9:1)

m.p. = 121–122 °C

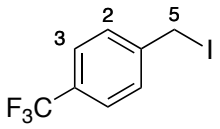
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (2H, d, *J* = 8.8 Hz, H3), 7.52 (2H, d, *J* = 8.8 Hz, H2), 4.48 (2H, s, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 146.9, 129.7, 124.2, 2.2.

HRMS (CI^+) Found $[M+NH_4]^+$ = 280.9787; $C_7H_{10}IN_2O_2$ requires 280.9781.

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

1-(Iodomethyl)-4-(trifluoromethyl)benzene, 156



4-(Trifluoromethyl)benzyl bromide (1.20 g, 5.00 mmol, 1.0 equiv.) and sodium iodide (1.12 g, 7.50 mmol, 1.5 equiv.) in acetone (10 mL) were submitted to **General Procedure 1** (12 h). Purification by column chromatography (SiO_2, pentane) gave **156** as a white solid (1.37 g, 4.79 mmol, 95%).

R_f = 0.42 (pentane)

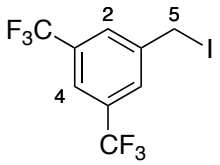
m.p. = 38–39 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 8.2 Hz, H3), 7.48 (2H, d, *J* = 8.2 Hz, H2), 4.46 (2H, s, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3 (q, *J* = 1.6 Hz), 129.9 (q, *J* = 32.6 Hz), 129.0, 125.8 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 272.1 Hz), 3.2.

Spectroscopic data in agreement with that reported previously.[12]

1-(Iodomethyl)-3,5-bis(trifluoromethyl)benzene, 157



1-(Bromomethyl)-3,5-bis(trifluoromethyl)benzene (916 μL, 5.00 mmol, 1.0 equiv.) and sodium iodide (1.12 g, 7.50 mmol, 1.5 equiv.) in acetone (5 mL) were submitted to **General Procedure 1** (12 h) to give **157** (1.68 g, 4.75 mmol, 94%) as a pale yellow solid.

R_f = 0.32 (pentane)

m.p. = 27–28 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (2H, s, H2), 7.76 (1H, s, H4), 4.49 (2H, s, H5).

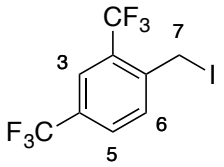
^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 132.4 (q, *J* = 33.5 Hz), 128.9 (q, *J* = 3.1 Hz), 123.1 (q, *J* = 273 Hz), 121.9 (m), 1.4.

^{19}F NMR (377 MHz, $CDCl_3$) δ −63.03.

HRMS (EI^+) Found $[M–I]^+$ = 227.0294; $C_9H_5F_6$ requires 227.0290.

IR (film) ν_{max}/cm^{-1} 1375, 1275, 1183, 1156, 1117.

1-(Iodomethyl)-2,4-bis(trifluoromethyl)benzene, 158



2,4-Bis(trifluoromethyl)benzyl bromide (188 μL, 1.00 mmol, 1.0 equiv) and sodium iodide (225 mg, 1.50 mmol, 1.5 equiv.) in acetone (1 mL) were submitted to **General Procedure 1** (12 h) to give **158** (350 mg, 0.990 mmol, 99%) as a pale orange oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (1H, s, H3), 7.76 (1H, d, *J* = 8.2 Hz, H5), 7.70 (1H, d, *J* = 8.2 Hz, H6), 4.62 (2H, s, H7).

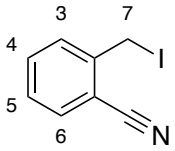
^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 133.4, 130.3 (q, *J* = 33.5 Hz), 129.2 (q, *J* = 3.8 Hz), 128.3 (q, *J* = 31.7 Hz), 123.8 – 123.4 (m), 123.4 (q, *J* = 274.4 Hz), 123.2 (q, *J* = 272.8 Hz), –2.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ –60.7, –63.0.

IR (film) ν_{max} (thin film) /cm^{-1} 1345, 1273, 1119, 1053, 671.

Synthesised and characterised by Dr Carlos Arroniz.

2-(Iodomethyl)benzonitrile, 159



2-(Bromomethyl)benzonitrile (273 mg, 1.39 mmol, 1.0 equiv.) and sodium iodide (313 mg, 2.09 mmol, 1.5 equiv.) in acetone (5 mL) were submitted to **General Procedure 1** (12 h). Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 1:0 to 1:1) gave **159** (287 mg, 1.18 mmol, 84%) as a white solid.

R_f = 0.37 (petroleum ether / Et_2O, 9:1)

m.p. = 71–72 °C (lit. 76.5–78.5 °C)[13]

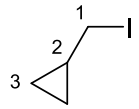
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (1H, app d, *J* = 7.6 Hz, H6), 7.57–7.50 (2H, m, H4, H5), 7.36 (1H, ddd, *J* = 7.7, 6.3, 2.5 Hz, H3). 4.60 (2H, s, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 133.4, 133.4, 130.1, 128.5, 117.0, 111.9, 0.4.

HRMS (CI^+) Found $[M+NH_4]^+$ = 260.9890; $C_8H_{10}IN_2$ requires 280.9883.

IR (film) ν_{max}/cm^{-1} 2981, 2225, 1485, 1450, 1432, 1220, 1156, 1072.

(Iodomethyl)cyclopropane, 160



(Bromomethyl)cyclopropane (1.00 g, 7.41 mmol, 1.0 equiv) and sodium iodide (6.00 g, 40.0 mmol, 5.4 equiv.) in acetone (10 mL) were submitted to **General Procedure 1** (17 h) to give **160** (629 mg, 3.46 mmol, 47%) as a colourless oil.

R_f = 0.66 (pentane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (2H, d, *J* = 7.7 Hz, H1), 1.38–1.23 (1H, m, H2), 0.87–0.77 (2H, m, H3), 0.35–0.26 (2H, m, H3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 16.1, 14.2, 11.1.

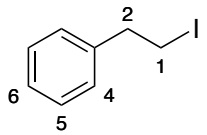
HRMS (CI^+) Found $[M+H]^+$ = 182.9666; C_4H_8I requires 182.9665.

IR (film) ν_{max}/cm^{-1} 3002, 1427, 1174, 1017.

Spectroscopic data in agreement with that reported previously.[14]

Synthesised and characterised by Dr Carlos Arroniz.

1-Iodo-2-phenylethane, 161



2-Phenylethanol (490 μL, 4.09 mmol, 1.0 equiv.), triphenylphosphine (1.40 g, 5.34 mmol, 1.3 equiv.) iodine (1.45 g, 5.71 mmol, 1.4 equiv.) and imidazole (418 mg, 6.14 mmol, 1.5 equiv.) in CH_3CN (4 mL) and Et_2O (5 mL) were submitted to **General Procedure 2** (12 h). Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 9:1) gave **161** (881 mg, 3.80 mmol, 93%) as a yellow oil.

R_f = 0.90 (petroleum ether / EtOAc, 9:1), [UV].

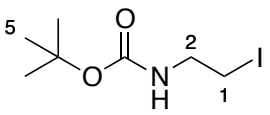
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (2H, m, H5), 7.22–7.16 (1H, m, H6), 7.14–7.10 (2H, m, H4), 3.28 (2H, t, *J* = 8.0 Hz, H2), 3.11 (2H, t, *J* = 8.0 Hz, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 128.8, 128.5, 127.0, 40.5, 5.8.

HRMS (CI^+) Found $[M+NH_4]^+$ = 250.0090; $C_8H_{13}IN$ requires 250.0087.

Spectroscopic data in agreement with that reported previously.[15]

***tert*-Butyl (2-iodoethyl)carbamate, 162**



To a solution of 2-aminoethanol (1.00 mL, 16.3 mmol, 1.0 equiv.) in CH_2Cl_2 (20 mL) at rt was added dropwise a solution of di-*tert*-butyl dicarbonate (3.90 g, 18.0 mmol, 1.1 equiv.) in CH_2Cl_2 (5 mL). After stirring for 3 h, the reaction was quenched with $NaHCO_3$ (25 mL, aq., sat.). The organic layer was separated, dried ($MgSO_4$) and concentrated. The resulting residue, triphenylphosphine (5.10 g, 19.4 mmol, 1.2 equiv.) and iodine (4.90 g, 19.4 mmol, 1.2 equiv.) in CH_2Cl_2 (25 mL) were submitted to **General Procedure 2** (3 h). Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 97:3 to 90:10) gave **162** (1.49 g, 5.50 mmol, 34%) as a pale yellow solid.

R_f = 0.62 (petroleum ether / Et_2O, 2:1)

m.p. = 38–40 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (1H, br s, NH), 3.51-3.37 (2H, m, H2), 3.22 (2H, t, *J* = 6.5 Hz, H1), 1.43 (9H, s, *t*-Bu).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.6, 79.9, 43.1, 28.5, 6.1.

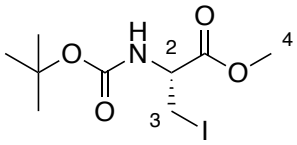
HRMS (ESI^+) Found $[M+H]^+$ = 272.0151; $C_7H_{15}INO_2$ requires 247.0147.

IR (film) ν_{max}/cm^{-1} 3340, 1687, 1506, 1249, 1160.

Spectroscopic data in agreement with that reported previously.[16]

Synthesised and characterised by Dr Carlos Arroniz.

Methyl (*R*)-2-((*tert*-butoxycarbonyl)amino)-3-iodopropanoate, 163



According to the procedure described by Koseki et al.[17] To a solution of triphenylphosphine (1.97 g, 7.50 mmol, 1.5 equiv.) and imidazole (511 mg, 7.5 mmol, 1.5 equiv.) in CH_2Cl_2 (5 mL) at 0 °C was added iodine (1.90 g, 7.50 mmol, 1.5 equiv.) portionwise. The resulting mixture was stirred for 10 min at rt and then cooled to 0 °C. Boc-Ser-OMe (1.10 g, 5.00 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) was added dropwise, and the resulting mixture was stirred at 0 °C for 2 h, and then concentrated. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 9:1) gave **163** (1.35 g, 4.10 mmol, 81%) as a white solid.

R_f = 0.10 (petroleum ether / Et_2O, 9:1)

m.p. = 41–42°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (1H, d, *J* = 7.7 Hz, NH), 4.51 (1H, dt, *J* = 7.7, 3.9 Hz, H2), 3.78 (3H, s, H4), 3.63–3.48 (2H, m, H3), 1.44 (9H, s, *t*-Bu).

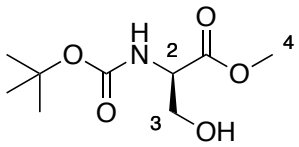
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 154.9, 80.6, 53.8, 53.1, 28.4, 8.0.

HRMS (CI^+) Found $[M+H]^+$ = 330.0201; $C_9H_{17}INO_4$ requires 330.0197.

IR (film) ν_{max}/cm^{-1} 3370, 2977, 1748, 1712, 1498, 1366, 1345, 1210, 1159.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –3.7 (c = 3.0, MeOH).

Methyl (*tert*-butoxycarbonyl)-D-serinate, Boc-D-Ser-OMe



Adapted from the procedure described by Danner et al.[18] To a solution of HCl·H-D-Ser-OMe (1.10 g, 1.0 equiv., 7.1mmol) in THF (25 mL) was added triethylamine (2.1 mL, 2.1 equiv., 15 mmol) and the resulting mixture was cooled to 0 °C. Di-*tert*-butyl-di-carbonate (1.6 mL, 0.99 equiv., 7.0 mmol) was added dropwise at 0 °C and the reaction was stirred at 60 °C for 2 h and at rt for 24 h. The reaction mixture was concentrated and diluted with Et_2O (20 mL) and water (20 mL). The phases were separated and the aqueous was extracted with Et_2O (2 × 20 mL). The combined organics were washed with HCl (aq., 1 M, 20 mL), $NaHCO_3$ (aq., sat., 20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography (pentane / ethyl acetate, 4:6) to give **Boc-D-Ser-OMe** (1.36 g, 6.20 mmol, 87%) as a colourless oil.

R_f = 0.10 (petroleum ether / Et_2O, 9:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (1H, d, *J* = 8.0 Hz, NH), 4.36 (1H, dt, *J* = 8.4, 3.9 Hz, H2), 4.00–3.89 (1H, m, H3), 3.89–3.81 (1H, m, H3), 3.75 (3Hs, H4), 2.89 (1H, br t, *J* = 5.9 Hz, OH), 1.43 (9H, s, *t*-Bu).

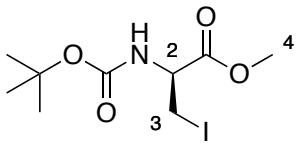
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 155.8, 80.3, 63.4, 55.7, 52.6, 28.3.

MS (ESI+) 242.0 [M+Na^+]

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ 15.7 ° (c = 3.0, MeOH)

Spectroscopic data in agreement with that reported previously.[19]

Methyl (*R*)-2-((tert-butoxycarbonyl)amino)-3-iodopropanoate, ent-163



To a solution of **Boc-D-Ser-OMe** (1.25 g, 5.70 mmol, 1.0 equiv.), triphenylphosphine (2.24 g, 8.55 mmol, 1.5 equiv.) and imidazole (582 mg, 8.55 mmol, 1.5 equiv.) in CH_2Cl_2 (20 mL) at 0 °C was added iodine (2.17 g, 8.55 mmol, 1.5 equiv.) in three portions. The resulting mixture was stirred at 0 °C for 15 min and rt for 2 h. Water (20 mL) was added, the phases were separated and the aqueous was extracted with CH_2Cl_2 (2 × 20 mL). The combined organics were washed with $Na_2S_2O_3$ (aq., 10 %, 20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (pentane / Et_2O, 9:1 to 8:2) and recrystallisation from pentane at –20 °C gave **ent-163** (1.10 g, 3.34 mmol, 58%) as white fluffy crystals.

R_f = 0.10 (petroleum ether / Et_2O, 9:1)

m.p. = 48–49 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (1H, d, *J* = 6.1 Hz, NH), 4.51 (1H, dt, *J* = 7.9, 4.0 Hz, H2), 3.79 (3H, d, *J* = 1.0 Hz, H4), 3.62–3.50 (2H, m, H3), 1.45 (9H, s, *t*-Bu).

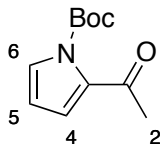
^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 155.0, 80.6, 53.8, 53.1, 28.4, 8.0.

HRMS (ESI^+) Found $[M+Na]^+$ = 352.0014; $C_9H_{16}O_4N^{127}I^{23}Na$ requires 352.0016.

IR (film) ν_{max}/cm^{-1} 3377, 2977, 2915, 2878, 1748, 1714, 1500, 1346, 1366, 1162.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ 3.8 ° (c = 3.0, MeOH)

1-(1*H*-pyrrol-2-yl)ethan-1-one, 164



To a solution of 2-acetylpyrrole (500 mg, 4.58 mmol, 1.0 equiv.) and di-*tert*-butyl dicarbonate (1.10 g, 5.04 mmol, 1.1 equiv.) in THF (60 mL) at rt, was added NaH (350 mg, 60% in mineral oil, 8.75 mmol, 1.9 equiv.) as a suspension in THF (40 mL) dropwise. After stirring for 4 h, the suspension was diluted with EtOAc (100 mL) and the reaction was quenched with NH_4Cl (aq., sat., 30 mL). The organic layer was washed with NH_4Cl (aq., sat., 3 × 30 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 7:3) gave **164** (848 mg, 4.06 mmol, 89%) as a colourless oil.

R_f = 0.49 (petroleum ether / Et_2O, 7:3)

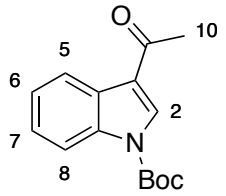
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (1H, ddd, *J* = 3.0, 1.6, 0.7 Hz, H6), 6.85 (1H, ddd, *J* = 3.6, 1.6, 0.7 Hz, H4), 6.16 (1H, ddd, *J* = 3.6, 3.0, 0.7 Hz, H5), 2.44 (3H, s, H2), 1.57 (9H, s, *t*-Bu).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.6, 149.1, 134.3, 128.1, 121.3, 110.1, 85.0, 28.1, 27.7.

Spectroscopic data in agreement with that reported previously.[20]

Synthesised and characterised by Dr Carlos Arroniz.

tert-Butyl 3-acetyl-1H-indole-1-carboxylate, 165



To a solution of 3-acetylindole (729 mg, 4.58 mmol, 1.0 equiv.) and di-*tert*-butyl dicarbonate (1.10 g, 5.04 mmol, 1.1 equiv.) in THF (60 mL) at rt was added a suspension of NaH (350 mg, 60% in mineral oil, 8.75 mmol, 1.9 equiv.) in THF (40 mL) dropwise. After stirring for 3 h, the suspension was diluted with EtOAc (100 mL) and quenched with NH_4Cl (aq., sat., 30 mL). The organic phase was washed with NH_4Cl (aq., sat., 3 × 30 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 7:3) gave **165** (982 mg, 3.58 mmol, 83%) as a white solid.

R_f = 0.44 (petroleum ether / Et_2O, 7:3)

m.p. = 142–144 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.40–8.35 (1H, m, H8), 8.23 (1H, s, H2), 8.15–8.08 (1H, m, H5), 7.42–7.32 (2H, m, H7, H6), 2.57 (3H, s, H10), 1.72 (9H, s, *t*-Bu).

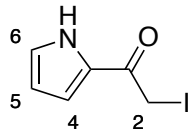
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 194.0, 149.3, 135.7, 132.5, 127.5, 125.6, 124.5, 122.8, 120.8, 115.1, 85.5, 28.3, 27.9.

HRMS (CI^+) Found $[M+H]^+$ = 260.1290; $C_{15}H_{18}NO_3$ requires 260.1281.

IR (film) ν_{max}/cm^{-1} 1656, 1169.

Synthesised and characterised by Dr Carlos Arroniz.

2-iodo-1-(1*H*-pyrrol-2-yl)ethan-1-one, 166



Compound **164** (209 mg, 1.00 mmol, 1.0 equiv.), CuO (80 mg, 1.0 mmol, 1.0 equiv.) and I_2 (254 mg, 1.00 mmol, 1.0 equiv.) in MeOH (4 mL) were submitted to **General Procedure 3**. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 9:1 to 7:3) gave **166** (118 mg, 0.500 mmol, 50%) as a yellow solid.

R_f = 0.22 (petroleum ether / Et_2O, 7:3)

m.p. = 122-124 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (1H, br s, NH), 7.10 (1H, td, *J* = 2.5, 1.3 Hz, H6), 7.02 (ddd, *J* = 3.9, 2.5, 1.3 Hz, H4), 6.32 (1H, dt, *J* = 3.9, 2.5 Hz, H5), 4.21 (2H, s, H2).

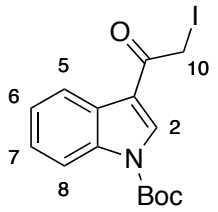
^{13}C NMR (101 MHz, $CDCl_3$) δ 183.5, 128.6, 126.6, 118.0, 111.4, 1.0.

HRMS (CI^+) Found $[M+H]^+$ = 235.9564; C_6H_7INO requires 235.9567.

IR (film) ν_{max}/cm^{-1} 3256, 1624, 1395, 1050.

Synthesised and characterised by Dr Carlos Arroniz.

***tert*-Butyl 3-(2-iodoacetyl)-1H-indole-1-carboxylate, 167**



Compound **165** (259 mg, 1.00 mmol, 1.0 equiv.), CuO (80 mg, 1.0 mmol, 1.0 equiv.) and I_2 (254 mg, 1.00 mmol, 1.0 equiv.) in MeOH (4 mL) were submitted to **General Procedure 3**. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 7:3 to 1:1) gave **167** (247 mg, 0.64 mmol, 64%) as a yellow oil.

R_f = 0.40 (petroleum ether / Et_2O, 95:5)

m.p. = 140–142 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35–8.31 (2H, m, H2, H8), 8.15–8.07 (1H, m, H5), 7.44–7.33 (2H, m, H7, H6), 4.30 (2H, s, H10), 1.72 (9H, s, *t*-Bu).

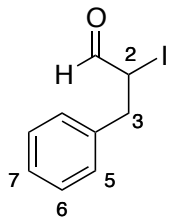
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.9, 149.1, 135.7, 132.9, 127.6, 126.0, 124.8, 122.9, 116.9, 115.2, 86.0, 28.3, 3.1.

HRMS (CI^+) Found $[M+H]^+$ = 386.0233; $C_{15}H_{17}INO_3$ requires 386.0248.

IR (film) ν_{max}/cm^{-1} 1730, 1653, 1367, 1157.

Synthesised and characterised by Dr Carlos Arroniz.

2-Iodo-3-phenylpropanal, 168



To a solution of L-proline (254 mg, 2.20 mmol, 20 mol%) and *N*-iodosuccinimide (3.22 g, 14.3 mmol, 1.3 equiv.) in dichloromethane (22 mL) was added hydrocinnamaldehyde (1.45 mL, 11.0 mmol, 1.0 equiv.). After stirring the solution for 1 h at rt, the reaction mixture was filtered through a short pad of silica (CH_2Cl_2 eluent, 150 mL) and then concentrated *in vacuo* to give **168** (1.94 g, 7.46 mmol, 68%) as a brown oil.

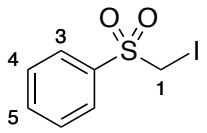
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.25 (1H, d, *J* = 2.6 Hz, CHO), 7.33–7.19 (2H, m, ArH), 7.19-7.11 (2H, m, H5), 4.66 (1H, td, *J* = 7.5, 2.6 Hz, H2), 3.45 (1H, dd, *J* = 14.6, 7.5 Hz, H3), 3.16 (1H, dd, *J* = 14.6, 7.5 Hz, H3).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 191.1, 138.2, 129.1, 128.9, 127.4, 38.7, 36.0.

Spectroscopic data in agreement with that reported previously.[9]

Synthesised and characterised by Dr Carlos Arroniz

((Iodomethyl)sulfonyl)benzene, 169



According to the procedure of Pospisil et al.[8] To a suspension of sodium benzenesulfinate (821 mg, 5.00 mmol, 1.0 equiv.) in DMF (10 mL) was added diiodomethane (484 μL, 6.00 mmol, 1.2 equiv.) dropwise. The resulting mixture was stirred at rt for 17 h. Brine (100 mL) was added and the aqueous phase was extracted with EtOAc (3 × 20 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 10:1 to 2:1) gave **169** (893 mg, 3.17 mmol, 63%) as a yellow solid.

R_f = 0.45 (petroleum ether / EtOAc, 7:3)

m.p. = 49-50°C

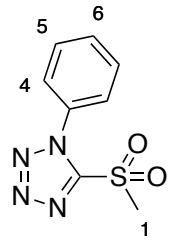
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.95 (2H, m, H3), 7.74-7.68 (1H, m, H5), 7.63-7.57 (2H, m, H4), 4.47 (2H, s, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 136.1, 134.7, 129.5, 129.1, 16.9.

HRMS (ESI^+) Found $[M+Na]^+$ = 304.9104; $C_7H_7O_2{}^{127}I^{23}Na^{32}S$ requires 304.9104.

Spectroscopic data in agreement with that reported previously.[21]

5-(Methylsulfonyl)-1-phenyl-1*H*-tetrazole, 170



To a solution of 1-phenyl-1*H*-tetrazole-5-thiol (3.56 g, 20.0 mmol, 1.0 equiv.) in THF (40 mL) at 0 °C was added sodium hydride (528 mg, 22.0 mmol, 1.1 equiv.) portionwise over 10 min. The resulting mixture was stirred at 0 °C for 30 min. Iodomethane (1.50 mL, 24.0 mmol, 1.2 equiv.) was added dropwise over 5 min. The ice water bath was removed, and the mixture was stirred at rt for 12 h. NH_4Cl (aq., sat., 40 mL) and EtOAc (20 mL) were added. The phases were separated and the aqueous was extracted with EtOAc (2 × 25 mL). The combined organics were washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in EtOH (40 mL) and the solution was cooled to 0 °C. Sodium tungstate dihydrate (587 mg, 2.00 mmol, 10 mol%) was added in one portion and the resulting mixture was stirred for 5 min at 0 °C. H_2O_2 (10.5 mL, 30% in water, 80.0 mmol, 4.0 equiv.) was added dropwise and the stirring was continued at 0 °C for 30 min and then at rt for 12 h. H_2O_2 (10.5 mL, aq., 30%, 80.0 mmol, 4.0 equiv.) was added and the stirring was resumed for a further 12 h. $Na_2S_2O_3$ (10%, aq., 40 mL) was added slowly to quench the excess peroxide. The aqueous was extracted with EtOAc (3 × 20 mL) and the combined organics were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, CH_2Cl_2 / EtOAc, 1:0 to 0:1) gave **170** (3.52 g, 15.6 mmol, 78%) as a white solid.

R_f = 0.25 (petroleum ether / EtOAc, 1:1)

m.p. = 75–76 °C

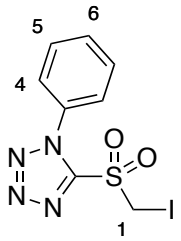
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.67 (2H, m, H4), 7.65–7.58 (3H, m, H5, H6), 3.33 (3H, s, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 133.0, 131.4, 130.1, 124.9, 39.0.

HRMS (ESI^+) Found $[M+H]^+$ = 223.0283; $C_8H_7O_2N_4{}^{32}S$ requires 223.0295, Δ 5.38 ppm

Spectroscopic data in agreement with that previously reported.[22]

5-((Iodomethyl)sulfonyl)-1-phenyl-1H-tetrazole, 171



To a solution of **170** (336 mg, 1.50 mmol, 1.0 equiv.) in THF (20 mL) at –78 °C was added NaHMDS (1.50 mL, 2.0 M in THF, 3.00 mmol, 2.0 equiv.) dropwise. The resulting mixture was stirred this temperature for 30 min and then a solution iodine (419 mg, 1.65 mmol, 1.1 equiv.) in THF (5 mL) was added dropwise. Stirring was continued at –78 °C for 30 min and the reaction mixture was quenched with NH_4Cl (aq., sat., 10 mL). The aqueous was extracted with EtOAc (3 × 20 mL) and the combined organics were washed with brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 9:1 to 8:2) and recrystallisation from CH_2Cl_2 gave **171** as a white solid (205 mg, 39%).

R_f = 0.27 (petroleum ether / EtOAc, 8:2)

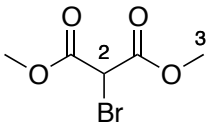
m.p. = 109–110 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.58 (5H, m, H4, H5, H6), 5.11 (2H, d, *J* = 1.4 Hz, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.6, 132.9, 131.9, 130.0, 125.3, 15.0.

Spectroscopic data in agreement with that previously reported. [23]

Dimethyl bromomalonate, 172



According to the procedure described by Wolfe et al.[24] To a solution of dimethyl malonate (3.40 mL, 30.0 mmol, 1.0 equiv.) in $CHCl_3$ (50 mL) was added *N*-bromosuccinimide (5.90 g, 33.0 mmol, 1.1 equiv.) and *p*-toluenesulfonic acid monohydrate (1.14 g, 6.00 mmol, 0.2 equiv.), and the resulting mixture was stirred for 2 h at 70 °C. The reaction was then cooled to rt, water (50 mL) was added, and the phases were separated. The aqueous was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organics were washed with $Na_2S_2O_3$ (10% aq., 50 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 9:1) gave **172** (2.00 g, 9.48 mmol, 31%) as a colourless oil.

R_f = 0.15 (petroleum ether / Et_2O, 9:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (1H, s, H2), 3.82 (6H, s, H3).

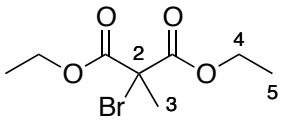
^{13}C NMR (101 MHz, $CDCl_3$) δ 165.1, 54.1, 41.7.

HRMS (ESI^+) Found $[M+H]^+$ = 210.9604; $C_5H_8O_4{}^{79}Br$ requires 210.9601.

IR (film) ν_{max}/cm^{-1} 2959, 1738, 1436, 1289, 1248, 1213, 1017.

Spectroscopic data in agreement with that reported previously.[24]

Diethyl 2-bromo-2-methylmalonate, 173



According to the procedure described by Curran et al.[25] To a solution of diethyl methylmalonate (852 μL, 5.00 mmol, 1.0 equiv.) in CCl_4 (10 mL) was added N-bromosuccinimide (1.33 g, 7.50 mmol, 1.5 equiv.). The mixture was refluxed for 12 h, then cooled to 0 °C and filtered. The filtrate was concentrated and distillation of the residue (2.0 mbar, 115 °C) gave **173** (846 mg, 3.34 mmol, 66%) as a colourless oil.

R_f = 0.36 (petroleum ether / Et_2O, 9:1)

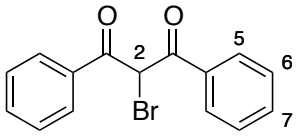
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.27 (4H, q, *J* = 7.1 Hz, H4), 2.07 (3H, s, H3), 1.29 (6H, t, *J* = 7.1 Hz, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.6, 63.2, 56.8, 26.9, 14.0.

HRMS (CI^+) Found $[M+H]^+$ = 253.0066; $C_8H_{14}{}^{79}BrO_4$ requires 253.0070.

IR (film) ν_{max}/cm^{-1} 2986, 1741, 1446, 1378, 1300, 1259, 1223, 1115, 1069, 1017.

2-Bromo-1,3-diphenylpropane-1,3-dione, 174



According to the procedure described by Izumisawa et al.[26] To a solution of 1,3-diphenylpropane-1,3-dione (2.24 g, 10.0 mmol, 1.0 equiv.) in CH_2Cl_2 (50 mL) was added *N*-bromosuccinimide (1.96 g, 11.0 mmol, 1.1 equiv.) and *p*-toluenesulfonic acid monohydrate (380 mg, 2.00 mmol, 0.2 equiv.) and the resulting mixture was stirred for 15 min at rt. Water (50 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 25 mL) and the combined organics were washed with $Na_2S_2O_3$ (aq., 10%, 25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Recrystallisation from hot cyclohexane gave **174** (2.02 g, 6.66 mmol, 74%) as white crystals.

m.p. = 86–87 °C.

R_f = 0.37 (petroleum ether / EtOAc, 7:3)

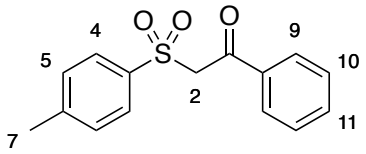
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04–7.94 (4H, m, H5), 7.65–7.55 (2H, m, H7), 7.54–7.42 (4H, m, H6), 6.57 (1H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.1, 134.4, 133.9, 129.4, 129.1, 52.8.

HRMS (ESI^+) Found $[M+H]^+$ = 303.0017; $C_{15}H_{12}{}^{79}BrO_2$ requires 303.0015.

Spectroscopic data in agreement with that reported previously.[27]

1-Phenyl-2-tosylethan-1-one, 175



According to the procedure described by Suryakiran et al.[28] To a suspension of sodium toluenesulfinate (1.00 g, 5.60 mmol, 1.0 equiv.) in DMF (10 mL) was added 2-bromoacetophenone (1.10 g, 5.60 mmol, 1.0 equiv.). The mixture was stirred at rt for 36 h. Water (150 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organics were washed with water (25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give **175** (1.42 g, 5.18 mmol, 92%) as a white powder that required no further purification.

R_f = 0.23 (Petroleum ether / EtOAc, 8:2)

m.p. = 103–104°C

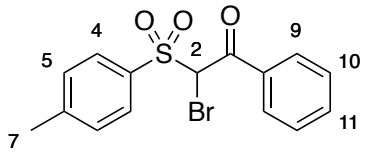
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96–7.90 (2H, m, H9), 7.76 (2H, d, *J* = 8.4 Hz, H4), 7.64–7.58 (1H, m, H11), 7.50-7.43 (2H, m, H10), 7.32 (2H, d, *J* = 8.1 Hz, H5), 4.72 (2H, s, H2), 2.43 (3H, s, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.2, 145.4, 135.8, 134.4, 129.9, 129.4, 128.9, 128.7, 77.2, 63.6, 21.8.

MS (ESI^+): 297.0 $[M + Na]^+$, 571.1 $[2M + Na]^+$.

Spectroscopic data in agreement with that reported previously.[29]

2-Bromo-1-phenyl-2-tosylethan-1-one, 176



According to the procedure described by Suryakiran et al.[30] To a suspension of **175** (400 mg, 1.46 mmol, 1.0 equiv.) and potassium bromide (191 mg, 1.60 mmol, 1.1 equiv.) in AcOH (1.5 mL) and water (0.5 mL) was added H_2O_2 (710 μL, 47 wt% aq., 11.6 mmol, 8.0 equiv.) and the resulting mixture was stirred at rt for 18 h. Water (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organics were washed with water (20 mL) and brine (20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 8:2) gave **176** (464 mg, 1.31 mmol, 90%) as a white powder.

m.p. = 154–155 °C.

R_f = 0.22 (petroleum ether / Et_2O, 8:2)

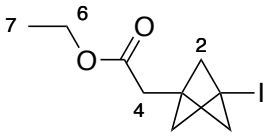
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02-7.97 (2H, m, H9), 7.87-7.82 (2H, m, H4), 7.68-7.62 (1H, m, H11), 7.54-7.48 (2H, m, H10), 7.40-7.35 (2H, m, H5), 6.23 (1H, s, H2), 2.47 (3H, s, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 186.8, 146.6, 134.9, 134.4, 131.8, 131.1, 129.7, 129.6, 129.1, 60.2, 22.0.

HRMS (ESI+) Found $[M+Na]^+$ = 374.9657; $C_{15}H_{13}O_3{}^{79}BrNaS$ requires 374.9661.

IR (film) ν_{max}/cm^{-1} 3067, 2974, 1688, 1595, 1449, 1329, 1269, 1153, 1084.

Ethyl 2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetate, 110



Ethyl iodoacetate (**115**) (59 μL, 0.50 mmol, 1.0 equiv.), TCP (0.61 mL, 0.90 M in Et_2O, 0.55 mmol, 1.1 equiv.) and BEt_3 (50 μL, 50 μmol, 10 mol%) were submitted to **General Procedure 4** at rt for 15 min at 0 °C. Purification by column chromatography (SiO_2, pentane / Et_2O, 95:5) gave **110** (129 mg, 0.460 mmol, 92%) as a yellow oil.

R_f = 0.18 (pentane / Et_2O, 95:5)

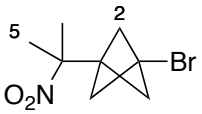
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12 (2H, q, *J* = 7.1 Hz, H6), 2.53 (2H, s, H4), 2.31 (6H, s, H2), 1.25 (3H, t, *J* = 7.1 Hz, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3, 60.9, 60.6, 43.6, 37.4, 14.3, 6.1.

HRMS (CI^+) Found $[M+H]^+$ = 281.0033; $C_9H_{14}IO_2$ requires 281.0033.

IR (film) ν_{max}/cm^{-1} 2979, 1732, 1369, 1280, 1175.

1-Bromo-3-(2-nitropropan-2-yl)bicyclo[1.1.1]pentane, 179



2-Bromo-2-nitropropane (53 μL, 0.50 mmol, 1.0 equiv.), TCP (0.70 mL, 0.93 M in Et_2O, 0.65 mmol, 1.3 equiv.) and BEt_3 (50 μL, 1 M in hexane, 50 μmol, 10 mol%) were submitted to **General Procedure 4** at 0 °C for 15 min. Recrystallisation from hot petroleum ether gave **179** (86 mg, 0.37 mmol, 73%) as white needles. These crystals were suitable for X-ray diffraction (see Section 5).

m.p. = 79–80 °C

R_f = 0.25 (petroleum ether / Et_2O, 9:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (6H, s, H2), 1.56 (6H, s, H5).

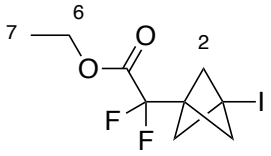
^{13}C NMR (101 MHz, $CDCl_3$) δ 86.7, 56.4, 46.0, 34.8, 23.4.

HRMS (ESI^+, CI^+, EI^+) Not found.

IR (film) ν_{max}/cm^{-1} 3005, 1549, 1371, 1356, 1200.

The structure of **182** was unambiguously confirmed by X-ray crystallography by Mr Steven Mansfield.

Ethyl 2,2-difluoro-2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetate, 180



Ethyl iododifluoroacetate (74 μL, 0.50 mmol, 1.0 equiv.), TCP (0.76 mL, 0.725 M in Et_2O, 0.55 mmol, 1.1 equiv.) and BEt_3 (5 μL, 1 M in hexane, 5 μmol, 1 mol%) were submitted to **General Procedure 4** at 0 °C for 15 min. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 95:5) gave **180** (156 mg, 0.49 mmol, 98%) as a colourless oil.

R_f = 0.38 (petroleum ether / Et_2O, 9:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.26 (2H, q, *J* = 7.1 Hz, H6), 2.37 (6H, s, H2), 1.28 (3H, t, *J* = 7.1 Hz, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 162.6 (t, *J* = 32.8 Hz), 110.7 (t, *J* = 252.2 Hz), 63.2, 57.9 (t, *J* = 2.9 Hz), 46.4 (t, *J* = 32.7 Hz), 14.2, 3.8 (t, *J* = 2.4 Hz).

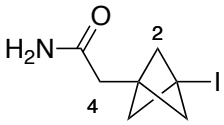
^{19}F NMR (377 MHz, $CDCl_3$) δ –109.1.

HRMS (CI^+) Found $[M+H]^+$ = 316.9843; $C_9H_{11}F_2IO_2$ requires 316.9845.

IR (film) ν_{max}/cm^{-1} 2984, 1765, 1372, 1301, 1197, 1155, 1123, 1063, 1027.

This reaction was also conducted on a 5.00 mmol scale using ethyl iododifluoroacetate (0.74 mL, 5.00 mmol, 1.0 equiv.), TCP (7.6 mL, 0.725 M in Et_2O, 5.50 mmol, 1.1 equiv.) and BEt_3 (50 µL, 1 M in hexane, 50 µmol, 1 mol%), for 15 min at 0 °C. This gave **183** in 94% yield (1.50 g).

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)acetamide, 181



2-Iodoacetamide (92 mg, 0.50 mmol, 1.0 equiv.), TCP (0.82 mL, 0.79 M in Et_2O, 0.65 mmol, 1.3 equiv.) and BEt_3 (50 µL, 1.0 M in hexane, 50 µmol, 10 mol%) in MeOH (0.3 mL) were submitted to **General Procedure 4** at rt for 1.5 h. Purification by column chromatography (SiO_2, EtOAc) gave **181** (111 mg, 0.44 mmol, 88%) as a white solid.

R_f = 0.19 (EtOAc)

m.p. = 118–120 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (1H, br s, NH), 5.34 (1H, br s, NH), 2.44 (2H, s, H4), 2.33 (6H, s, H2).

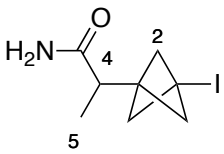
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.7, 61.0, 44.2, 39.2, 5.9.

HRMS (CI^+) Found $[M+H]^+$ = 251.9876; $C_7H_{11}INO$ requires 251.9880.

IR (film) ν_{max}/cm^{-1} 3353, 3167, 1658, 1629, 1404, 1177.

Synthesised and characterised by Dr Carlos Arroniz.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)propanamide, 182



2-Iodopropanamide (**149**) (60 mg, 0.30 mmol, 1.0 equiv.), TCP (0.50 mL, 0.79 M in Et_2O, 0.40 mmol, 1.3 equiv.) and BEt_3 (30 µL, 1.0 M in hexane, 30 µmol, 10 mol%) in MeOH (0.5 mL) were submitted to **General Procedure 4** at rt for 1.5 h. Purification by column chromatography (SiO_2, EtOAc) gave **182** (79 mg, 0.30 mmol, 99%) as a white solid. Recrystallisation by slow evaporation of a solution in $CDCl_3$ gave crystals that were suitable for X-ray diffraction (see Section 5).

R_f = 0.28 (EtOAc)

m.p. = 108–110 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29 (2H, br s, NH_2), 2.50 (1H, q, *J* = 6.9 Hz, H4), 2.26 (6H, s, H2), 1.10 (3H, d, *J* = 6.9 Hz, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.8, 59.2, 48.9, 42.7, 14.2, 6.0.

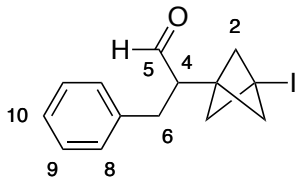
HRMS (CI^+) Found $[M+H]^+$ = 266.0035; $C_8H_{13}INO$ requires 266.0036.

IR (film) ν_{max}/cm^{-1} 3424, 3170, 1657, 1172.

Synthesised and characterised by Dr Carlos Arroniz

The structure of **185** was unambiguously confirmed by X-ray crystallography by Mr Steven Mansfield.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-3-phenylpropanal, 183



Compound **168** (78 mg, 0.30 mmol, 1.0 equiv.), TCP (0.76 mL, 0.79 M in Et_2O, 0.60 mmol, 2.0 equiv.) and BEt_3 (30 µL, 1.0 M in hexane, 30 µmol, 10 mol%) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 9:1) gave **183** (37 mg, 0.11 mmol, 38%) as a colourless oil**.**

R_f = 0.32 (petroleum ether / Et_2O, 9:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (1H, d, *J* = 2.3 Hz, H5), 7.33–7.26 (2H, m, H9), 7.26–7.20 (1H, m, H10), 7.20–7.12 (2H, m, H8), 3.04 (1H, dd, *J* = 13.9, 8.5 Hz, H6), 2.95 (1H, ddd, *J* = 8.5, 5.9, 2.3 Hz, H4), 2.73 (1H, dd, *J* = 13.9, 5.9 Hz, H6), 2.30 (3H, dd, *J* = 9.4, 1.6 Hz, H2), 2.25 (3H, dd, *J* = 9.4, 1.6 Hz, H2).

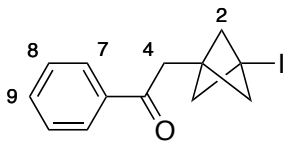
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 201.2, 138.2, 128.8, 128.8, 126.8, 59.8, 54.6, 46.5, 33.0, 6.4.

HRMS (CI^+) Found $[M+H]^+$ = 327.0242; $C_{14}H_{16}IO$ requires 327.0240.

IR (film) ν_{max}/cm^{-1} 2915, 1724, 1177.

Synthesised and characterised by Dr Carlos Arroniz.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-phenylethan-1-one, 184



Compound **150** (74 mg, 0.30 mmol, 1.0 equiv.), TCP (0.80 mL, 0.73 M in Et_2O, 0.60 mmol, 2.0 equiv.) and BEt_3 (30 µL, 1.0 M in hexane, 30 µmol, 10 mol%) were submitted to **General Procedure 4** at rt for 2 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 98:2 to 96:4) gave **184** (80 mg, 0.26 mmol, 85%) as a white solid.

R_f = 0.16 (petroleum ether / Et_2O, 97:3)

m.p. = 68–70 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91–7.84 (2H, m, H7), 7.61–7.54 (1H, m, H9), 7.49–7.43 (2H, m, H8), 3.20 (2H, s, H4), 2.34 (6H, s, H2).

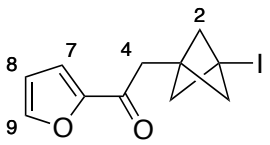
^{13}C NMR (101 MHz, $CDCl_3$) δ 197.3, 136.8, 133.5, 128.8, 128.3, 61.4, 44.1, 40.8, 6.6.

HRMS (CI^+) Found $[M+H]^+$ = 313.0081; $C_{13}H_{14}IO$ requires 313.0084.

IR (film) ν_{max}/cm^{-1} 3007, 1686, 1170, 1101.

Synthesised and characterised by Dr Carlos Arroniz.

1-(Furan-2-yl)-2-(3-iodobicyclo[1.1.1]pentan-1-yl)ethan-1-one, 185



Compound **151** (70 mg, 0.30 mmol, 1.0 equiv.), TCP (0.80 mL, 0.73 M in Et_2O, 0.60 mmol, 2.0 equiv.) and BEt_3 (30 µL, 1.0 M in hexane, 30 µmol, 10 mol%) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 95:5 to 90:10) gave **185** (72 mg, 0.24 mmol, 79%) as a white solid.

R_f = 0.32 (petroleum ether / Et_2O, 7:3)

m.p. = 51–53 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (1H, dd, *J* = 1.7, 0.8 Hz, H9), 7.16 (1H, dd, *J* = 3.6, 0.8 Hz, H7), 6.54 (1H, dd, *J* = 3.6, 1.7 Hz, H8), 3.04 (2H, s, H4), 2.32 (6H, s, H2).

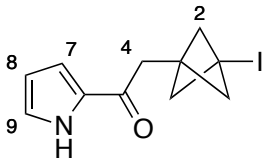
^{13}C NMR (101 MHz, $CDCl_3$) δ 186.1, 152.6, 146.8, 117.6, 112.6, 61.3, 44.0, 41.1, 6.3.

HRMS (CI^+) Found $[M+H]^+$ = 302.9873; $C_{11}H_{12}IO_2$ requires 302.9876.

IR (film) ν_{max}/cm^{-1} 2981, 1668, 1468, 1160.

Synthesised and characterised by Dr Carlos Arroniz.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-(1H-pyrrol-2-yl)ethan-1-one, 186



Compound **166** (35 mg, 0.15 mmol, 1.0 equiv.), TCP (0.37 mL, 0.82 M in Et_2O, 0.30 mmol, 2.0 equiv.) and BEt_3 (15 µL, 1.0 M in hexane, 15 µmol, 0.1 equiv.) in CH_2Cl_2 (0.3 mL) were submitted to **General Procedure 4** at rt for 6 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 8:2) gave **186** (26 mg, 0.09 mmol, 58%) as a white solid.

R_f = 0.39 (petroleum ether / Et_2O, 7:3)

m.p. = 105–107 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.83 (1H, br s, NH), 7.11–7.01 (1H, m, H9), 6.87–6.78 (1H, m, H7), 6.28 (1H, dt, *J* = 3.7, 2.5 Hz, H8), 2.98 (2H, s, H4), 2.32 (6H, s, H2).

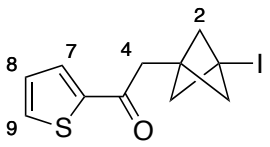
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 187.1, 131.9, 125.5, 117.2, 111.0, 61.4, 44.5, 40.7, 6.5.

HRMS (CI^+) Found $[M+H]^+$ = 302.0024; $C_{11}H_{13}INO$ requires 302.0036.

IR (film) ν_{max}/cm^{-1} 3287, 1629, 1172.

Synthesised and characterised by Dr Carlos Arroniz.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)-1-(thiophen-2-yl)ethan-1-one, 187



Compound **152** (76 mg, 0.30 mmol, 1.0 equiv.), TCP (0.80 mL, 0.73 M in Et_2O, 0.60 mmol, 2.0 equiv.) and BEt_3 (30 µL, 1.0 M in hexane, 30 µmol, 0.1 equiv.) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 95:5 to 90:10) gave **187** (86 mg, 0.27 mmol, 90%) as a white solid.

R_f = 0.37 (petroleum ether / Et_2O, 8:2)

m.p. = 70–72 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, dd, *J* = 5.0, 1.1 Hz, H9), 7.62 (1H, dd, *J* = 3.8, 1.1 Hz, H7), 7.13 (1H, dd, *J* = 5.0, 3.8 Hz, H8), 3.12 (2H, s, H4), 2.34 (6H, s, H2).

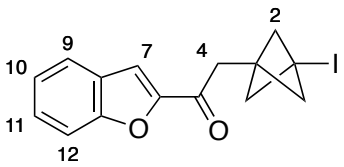
^{13}C NMR (101 MHz, $CDCl_3$) δ 189.9, 144.2, 134.4, 132.4, 128.4, 61.3, 44.1, 41.9, 6.2.

HRMS (CI^+) Found $[M+H]^+$ = 318.9647; $C_{11}H_{11}IOS$ requires 318.9648.

IR (film) ν_{max}/cm^{-1} 2910, 1660, 1421, 1221, 1170.

Synthesised and characterised by Dr Carlos Arroniz.

1-(Benzofuran-2-yl)-2-(3-iodobicyclo[1.1.1]pentan-1-yl)ethan-1-one, 188



Compound **153** (72 mg, 0.25 mmol, 1.0 equiv.), TCP (0.70 mL, 0.73 M in Et_2O, 0.50 mmol, 2.0 equiv.) and BEt_3 (25 µL, 1.0 M in hexane, 25 µmol, 10 mol%) were submitted to **General Procedure 4** at rt for 2 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 95:5) gave **188** (76 mg, 0.22 mmol, 87%) as a white solid.

R_f = 0.60 (petroleum ether / Et_2O, 7:3)

m.p. = 82–84 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (1H, dt, *J* = 8.0, 1.0 Hz, H9), 7.57 (1H, dd, *J* = 8.4, 1.0 Hz, H12), 7.52-7.46 (2H, m, H11, H7), 7.33 (1H, ddd, *J* = 8.0, 7.1, 1.0 Hz, H10), 3.19 (2H, s, H4), 2.37 (6H, s, H2).

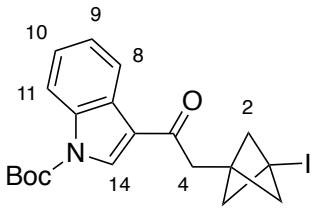
^{13}C NMR (101 MHz, $CDCl_3$) δ 188.1, 155.8, 152.4, 128.7, 127.1, 124.2, 123.5, 113.3, 112.6, 61.3, 43.9, 41.4, 6.2.

HRMS (CI^+) Found $[M+H]^+$ = 353.0041; $C_{15}H_{14}IO_2$ requires 353.0033.

IR (film) ν_{max}/cm^{-1} 1671, 1550, 1180, 1166, 759.

Synthesised and characterised by Dr Carlos Arroniz.

***tert*-Butyl 3-(2-(3-iodobicyclo[1.1.1]pentan-1-yl)acetyl)-1*H*-indole-1-carboxylate, 189**



Compound **167** (58 mg, 0.15 mmol, 1.0 equiv.), TCP (0.37 mL, 0.82 M in Et_2O, 0.30 mmol, 2.0 equiv.) and BEt_3 (15 µL, 1.0 M in hexane, 15 µmol, 10 mol%) in CH_2Cl_2 (0.3 mL) were submitted to **General Procedure 4** at rt for 15 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 95:5) gave **189** (46 mg, 0.10 mmol, 68%) as a white solid.

R_f = 0.44 (petroleum ether / Et_2O, 7:3)

m.p. = 130–132 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38–8.33 (1H, m, H8), 8.14 (1H, s, H14), 8.12]8.07 (1H, m, H11), 7.42–7.32 (2H, m, H10, H9), 3.10 (2H, s, H4), 2.37 (6H, s, H2), 1.72 (9H, s, *t*-Bu).

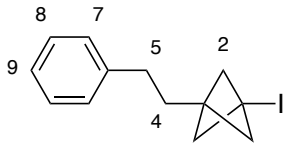
^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 149.2, 135.7, 132.3, 127.5, 125.8, 124.7, 122.8, 120.3, 115.1, 85.8, 61.4, 44.4, 42.4, 28.3, 6.5.

HRMS (CI^+) Found $[M+H]^+$ = 452.0717; $C_{20}H_{23}INO_3$ requires 452.0717.

IR (film) ν_{max}/cm^{-1} 2910, 1744, 1670, 1544, 1470, 1421, 1266, 1187.

Synthesised and characterised by Dr Carlos Arroniz.

1-Iodo-3-phenethylbicyclo[1.1.1]pentane, 190



Compound **161** (72 μL, 0.50 mmol, 1.0 equiv.), TCP (0.82 mL, 0.79 M in Et_2O, 0.65 mmol, 1.3 equiv.) and BEt_3 (50 μL, 50.0 μmol, 10 mol%) were submitted to **General Procedure 4** at 0 °C for 2 h in the dark. Purification by recrystallisation from methanol (cooled to −20 °C) gave **190** (130 mg, 0.44 mmol, 87%) as white crystals.

m.p. = 51–52°C

R_f = 0.65 (petroleum ether / Et_2O / triethylamine, 99:1:1)

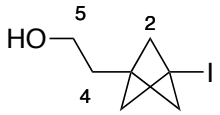
^{1}H NMR (400 MHz, C_6D_6) δ 7.15–7.09 (2H, m, H8), 7.08-7.02 (1H, m, H9), 6.91–6.85 (2H, m, H7), 2.21–2.13 (2H, m, H5), 1.87 (6H, s, H2), 1.44–1.35 (2H, m, H4).

^{13}C NMR (101 MHz, C_6D_6) δ 141.6, 128.6, 128.4, 126.3, 60.4, 48.2, 33.3, 33.1, 7.4.

HRMS (CI^+) Found $[M+H]^+$ = 299.0295, $C_{13}H_{16}I$ requires 299.0291.

IR (film) ν_{max}/cm^{-1} 3025, 2988, 2911, 2875, 1603, 1496, 1453, 1172, 1135.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)ethan-1-ol, 190



2-Iodoethanol (39 μL, 0.50 mmol, 1.0 equiv.), TCP (0.82 mL, 0.79 M in Et_2O, 0.65 mmol, 1.3 equiv.) and BEt_3 (50 μL, 50 μmol, 10 mol%) were submitted to **General Procedure 4** at 0 °C for 15 min. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 1:0 to 0:1) gave **190** (96 mg, 0.40 mmol, 80%) as a white solid.

m.p. = 44–45°C

R_f = 0.19 (petroleum ether / EtOAc, 8:2)

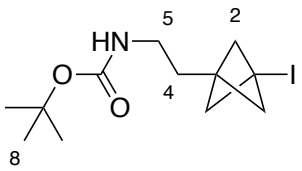
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (2H, t, *J* = 6.5 Hz, H5), 2.25 (6H, s, H2), 1.78 (2H, t, *J* = 6.5 Hz, H4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 61.1, 60.9, 46.3, 34.8, 7.3.

HRMS (EI^+) Found $[M–I]^+$ = 111.0802; $C_7H_{11}O$ requires 111.0804.

IR (film) ν_{max}/cm^{-1} 3327, 2988, 2912, 2876, 1446, 1424, 1173, 1126.

***tert*-Butyl (2-(3-iodobicyclo[1.1.1]pentan-1-yl)ethyl)carbamate, 192**



Compound **162** (271 mg, 1.00 mmol, 1.0 equiv.), TCP (1.22 mL, 1.07 M in Et_2O, 1.30 mmol, 1.3 equiv.) and BEt_3 (100 µL, 1.0 M in hexane, 100 µmol, 10 mol%) were submitted to **General Procedure 4** at rt for 45 min. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 3:1) gave **192** (303 mg, 0.90 mmol, 90%) as a white solid**.**

R_f = 0.40 (petroleum ether / Et_2O, 3:1)

m.p. = 63–65 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.44 (1H, br s, NH), 3.15–3.01 (2H, m, H5), 2.23 (6H, s, H2), 1.71 (2H, t, *J* = 7.3 Hz, H4), 1.43 (9H, s, *t*-Bu).

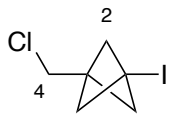
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 155.8, 79.5, 60.7, 46.5, 38.4, 32.3, 28.5, 7.1.

HRMS (ESI^+) Found $[2M+H]^+$ = 675.1154; $C_{24}H_{41}I_2N_2O_4$ requires 675.1150

IR (film) ν_{max}/cm^{-1} 3317, 1683, 1172.

Synthesised and characterised by Dr Carlos Arroniz.

1-Iodo-3-(chloromethyl)bicyclo[1.1.1]pentane, 193



Chloroiodomethane (36 μL, 0.50 mmol, 1.0 equiv.), TCP (1.1 mL, 0.79 M in Et_2O, 0.65 mmol, 31.3 equiv.) and BEt_3 (50 μL, 1 M in hexane, 50 μmol, 10 mol%) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, pentane) gave **193** (87 mg, 0.36 mmol, 72%) as a white solid.

R_f = 0.43 (pentane)

m.p. = 34–35 °C

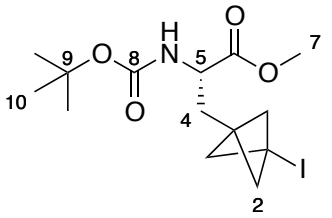
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 (2H, s, H4), 2.30 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 59.3, 47.3, 44.1, 6.1.

HRMS (CI^+) Found $[M–I]^+$ = 115.0309; C_6H_8Cl requires 115.0309.

IR (film) ν_{max}/cm^{-1} 2996, 2915, 1265, 1178.

Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(3-iodobicyclo [1.1.1]pentan-1-yl)propanoate, 194



Compound **163** (165 mg, 0.50 mmol, 1.0 equiv.), TCP (1.32 mL, 0.76 M in Et_2O, 1.00 mmol, 2.0 equiv.) and BEt_3 (50 µL, 1 M in hexane, 50 µmol, 10 mol%) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 8:2) and recrystallisation from petroleum ether gave the **194** (142 mg, 0.36 mmol, 72%) as a white solid.

R_f = 0.13 (petroleum ether / Et_2O, 9:1)

m.p. = 83–84°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (1H, d, *J* = 8.4 Hz, NH), 4.29 (1H, td, *J* = 7.9, 4.4 Hz, H5), 3.73 (3H, s, H7), 2.29–2.20 (6H, m, H2), 2.12 (1H, dd, J = 14.6, 4.0 Hz, H4), 1.86 (1H, dd, *J* = 14.6, 7.6 Hz, H4), 1.44 (9H, s, *t*-Bu).

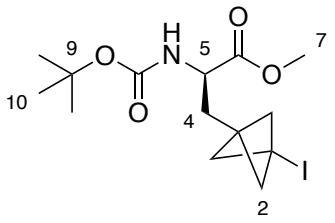
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 155.1, 80.3, 61.0, 52.6, 52.0, 45.5, 34.5, 28.5, 6.4.

HRMS (CI^+) Found $[M+H]^+$ = 396.0679; $C_7H_9O_2$ requires 396.0666.

IR (film) ν_{max}/cm^{-1} 3358, 2978, 1744, 1713, 1509, 1366, 1176.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = –0.8 (c = 3.0, MeOH)

Methyl (*R*)-2-((tert-butoxycarbonyl)amino)-3-(3-iodobicyclo [1.1.1]pentan-1-yl)propanoate, *ent*-194



Compound ***ent*-163** (165 mg, 1.0 equiv., 0.50 mmol), TCP (1.27 mL, 0.79 M in Et_2O, 2.0 equiv., 1.00 mmol) and BEt_3 (50 µL, 1 M in hexane, 10 mol%, 50 µmol) were submitted to **General Procedure 1** at rt for 1 h. Purification by column chromatography (pentane / Et_2O, 1:0 to 8:2) and recrystallisation from pentane at –20 °C gave ***ent*-194** (92 mg, 0.233 mmol, 46%) as a fluffy white solid.

R_f = 0.13 (petroleum ether / Et_2O, 9:1)

m.p. = 91–92 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (1H, d, *J* = 8.5 Hz, NH), 4.29 (1H, td, *J* = 8.0, 4.5 Hz, H5), 3.73 (3H, s, H7), 2.28–2.19 (6H, m, H2), 2.12 (1H, dd, *J* = 14.6, 4.4 Hz, H4), 1.86 (1H, dd, *J* = 14.6, 7.6 Hz, H4), 1.44 (9H, s, *t*-Bu).

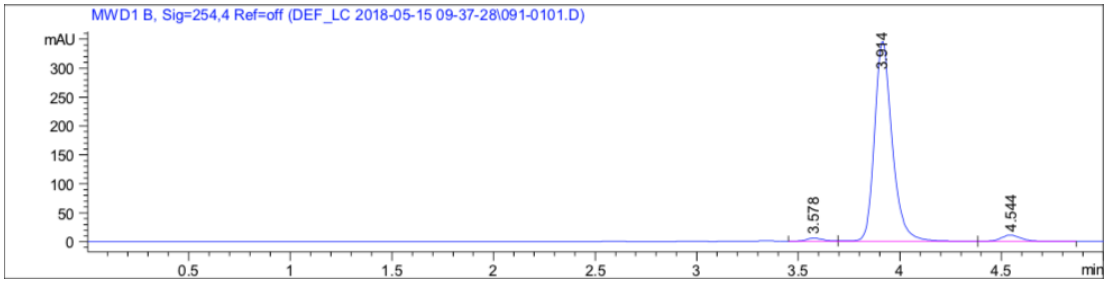
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.8, 155.1, 80.3, 61.0, 52.6, 52.0, 45.5, 34.5, 28.5, 6.4.

HRMS (ESI^+) Found $[M+Na]^+$ = 418.0480; $C_{14}H_{22}O_4N^{127}I^{23}Na$ requires 418.0486

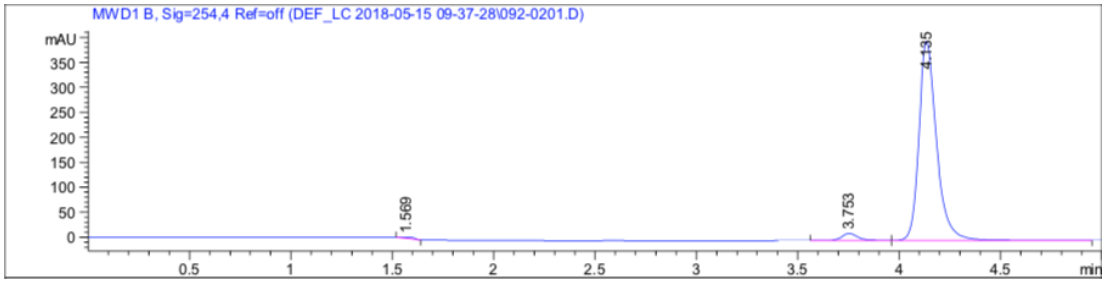
IR (film) ν_{max}/cm^{-1} 3360, 2976, 1747, 1715, 1507, 1366, 1178.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ 0.7 ° (C = 3.0, MeOH)

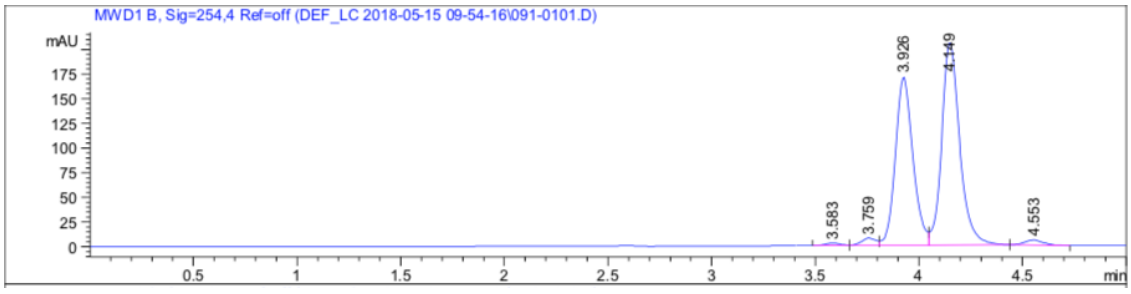
HPLC trace for **194** (Chiralpak IB, 5% IPA in hexane, flow rate = 1.3 mL/min, 254 nm)



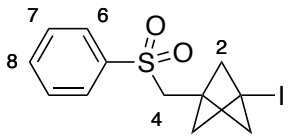
HPLC trace for ***ent*-194** (Chiralpak IB, 5% IPA in hexane, flow rate = 1.3 mL/min, 254 nm)



HPLC trace for a mixture of **194** and ***ent*-194** (Chiralpak IB, 5% IPA in hexane, flow rate = 1.3 mL/min, 254 nm)



1-Iodo-3-((phenylsulfonyl)methyl)bicyclo[1.1.1]pentane, 195



Compound **169** (142 mg, 0.50 mmol, 1.0 equiv.), TCP (0.82 mL, 0.79 M in Et_2O, 0.65 mmol, 1.3 equiv.) and BEt_3 (50 μL, 50.0 μmol, 10 mol%) were submitted to **General Procedure 4** at 0 °C for 3 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 1:0 to 0:1) gave **195** (107 mg, 0.31 mmol, 61%) as a white solid.

R_f = 0.16 (petroleum ether / Et_2O, 7:3)

m.p. = 111–112 °C

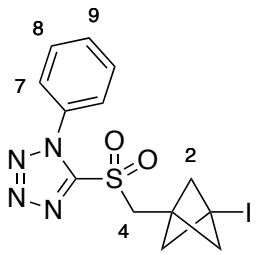
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92–7.86 (2H, m, H6), 7.71–7.64 (1H, m, H8), 7.61–7.54 (2H, m, H7), 3.34 (2H, s, H4), 2.32 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 139.8, 134.1, 129.6, 127.9, 61.2, 57.1, 40.6, 5.0.

HRMS (ESI^+) Found $[M+Na]^+$ = 370.9573; $C_{12}H_{13}O_2{}^{127}I^{23}Na^{32}S$ requires 370.9573.

IR (film) ν_{max}/cm^{-1} 2995, 2912, 1446, 1302, 1282, 1184, 1145, 1082.

5-(((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)sulfonyl)-1-phenyl-1H-tetrazole, 196



Compound **171** (110 mg, 0.314 mmol, 1.0 equiv.), TCP (0.38 mL, 1.07 M in Et_2O, 0.41 mmol, 1.3 equiv.) and BEt_3 (31 μL, 31 μmol, 10 mol%) were submitted to **General Procedure 4** at 0 °C for 1 h. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 1:0 to 8:2) gave **196** (122 mg, 0.293 mmol, 93%) as a white solid.

R_f = 0.21 (petroleum ether / EtOAc, 9 :1)

m.p. = 96–97 °C

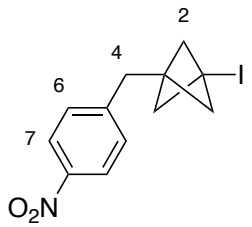
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.58 (5H, m, H6, H7, H9), 4.02 (2H, s, H4), 2.43 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.6, 133.0, 131.8, 130.0, 125.1, 61.3, 56.8, 39.6, 4.1.

HRMS (ESI^+) Found $[M+H]^+$ = 416.9877; $C_{13}H_{14}O_2{}^{127}I^{32}S$ requires 416.9877.

IR (film) ν_{max}/cm^{-1} 2995, 2912, 1446, 1302, 1282, 1184, 1145, 1082

1-Iodo-3-(4-nitrobenzyl)bicyclo[1.1.1]pentane, 197



Compound **155** (132 mg, 0.50 mmol, 1.0 equiv.), TCP (0.90 mL, 0.90 M in Et_2O, 1.00 mmol, 2.0 equiv.) and BEt_3 (50 µL, 50 µmol, 10 mol%) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, pentane / Et_2O, 95:5) gave **197** (148 mg, 0.45 mmol, 90%) as white crystals. Recrystallisation from petroleum ether / CH_2Cl_2 gave crystals that were suitable for X-ray diffraction (see Section 5).

R_f = 0.25 (pentane / Et_2O, 95:5)

m.p. = 76 °C (decomposition)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19–8.13 (2H, m, H7), 7.24–7.20 (2H, m, H6), 2.92 (2H, s, H4), 2.16 (6H, s, H2).

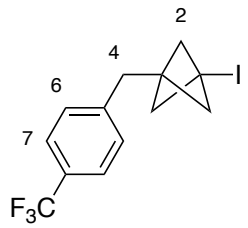
^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 145.9, 129.7, 124.0, 60.2, 47.5, 39.2, 7.0.

HRMS (CI^+) Found $[M+NH_4]^+$ = 347.0256; $C_{12}H_{16}IN_2O_2$ requires 347.0251.

IR (film) ν_{max}/cm^{-1} 2997, 1596, 1514, 1343, 1174, 1105.

The structure of **200** was unambiguously confirmed by X-ray crystallography by Mr Steven Mansfield.

1-Iodo-3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentane, 198



Compound **156** (143 mg, 0.50 mmol, 1.0 equiv.), TCP (1.27 mL, 0.79 M in Et_2O, 1.00 mmol, 2.0 equiv.) and BEt_3 (50 μL, 50 μmol, 10 mol%) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, petroleum ether) gave **198** (134 mg, 0.38 mmol, 76%) as white crystals. Recrystallisation with petroleum ether from CH_2Cl_2 gave crystals that were suitable for X-ray diffraction (see Section 5).

R_f = 0.48 (petroleum ether)

m.p. = 84–86 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (2H, d, *J* = 8.0 Hz, H7), 7.17 (2H, d, *J* = 8.0 Hz, H6), 2.87 (2H, s, H4), 2.16 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.4, 129.2, 128.9 (q, *J* = 32.4 Hz), 125.5 (q, *J* = 3.8 Hz), 124.4 (q, *J* = 271.9 Hz), 60.3, 47.9, 39.1, 7.6.

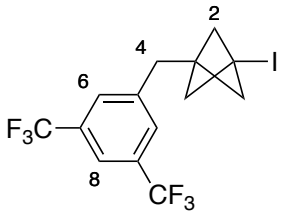
^{19}F NMR (376 MHz, $CDCl_3$) δ −62.41.

HRMS (CI^+) Found $[M+NH_4]^+$ = 370.0280; $C_{13}H_{16}F_3IN$ requires 370.0274.

IR (film) ν_{max}/cm^{-1} 2915, 1320, 1157, 1107, 1063, 1016.

The structure of **201** was unambiguously confirmed by X-ray crystallography by Mr Steven Mansfield.

1-(3,5-Bis(trifluoromethyl)benzyl)-3-iodobicyclo[1.1.1]pentane, 199



Compound **157** (177 mg, 0.50 mmol, 1.0 equiv.), TCP (1.27 mL, 0.79 M in Et_2O, 1.00 mmol, 2.0 equiv.) and BEt_3 (50 μL, 50 μmol, 10 mol%) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, petroleum ether) gave **199** (176 mg, 0.42 mmol, 84%) as a pale yellow solid.

R_f = 0.30 (petroleum ether)

m.p. = 45–46 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.64 (1H, m, H8), 7.57–7.40 (2H, m, H6), 2.96 (2H, s, H4), 2.17 (6H, s, H2).

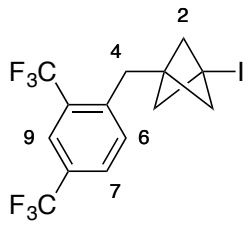
^{13}C NMR (101 MHz, $CDCl_3$) δ 140.7, 132.0 (q, *J* = 33.2 Hz), 128.9 (q, *J* = 3.0 Hz), 123.4 (d, *J* = 272.6 Hz), 120.7 (m), 60.1, 47.5, 39.0, 6.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.88.

HRMS (EI^+) Found $[M–I]^+$ = 293.0762; $C_{14}H_{11}F_6$ requires 293.0759.

IR (film) ν_{max}/cm^{-1} 2993, 2917, 1378, 1276, 1171, 1128.

1-(2,4-Bis(trifluoromethyl)benzyl)-3-iodobicyclo[1.1.1]pentane, 200



Compound **158** (106 mg, 0.3 mmol, 1.0 equiv.), TCP (0.6 mL, 0.73 M in Et_2O, 0.44 mmol, 1.5 equiv.) and BEt_3 (30 µL, 1.0 M in hexane, 30 µmol, 10 mol%) were submitted to **General Procedure 4** at rt for 21 h. Purification by column chromatography (SiO_2, petroleum ether) to give **200** (91 mg, 0.22 mmol, 72%) as a white solid.

R_f = 0.54 (petroleum ether / Et_2O, 95:5)

m.p. = 37–38 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.89 (1H, s, H9), 7.75 (1H, d, *J* = 8.1 Hz, H7), 7.32 (1H, d, *J* = 8.1 Hz, H6), 3.09 (2H, s, H4), 2.18 (6H, s, H2).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C 141.0, 132.5, 129.5 (q, *J* = 19.7 Hz), 129.1 (q, *J* = 19.7 Hz), 128.3 (app. d, *J* = 3.7 Hz), 123.4 (q, *J* = 274.7 Hz), 123.4 (q, *J* = 271.9 Hz), 123.6–123.2 (m), 60.4, 47.1, 35.4, 6.4.

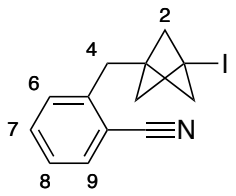
^{19}F NMR (376 MHz, $CDCl_3$) δ_F –59.3, –62.8.

HRMS (ESI^+, EI^+, CI^+) Not found

IR (film) ν_{max}/cm^{-1} 1345, 1275, 1122.

Synthesised and characterised by Dr Carlos Arroniz.

2-((3-Iodobicyclo[1.1.1]pentan-1-yl)methyl)benzonitrile, 201



Compound **159** (366 mg, 1.50 mmol, 1.0 equiv.), TCP (3.81 mL, 0.79 M in Et_2O, 4.50 mmol, 2.0 equiv.) and BEt_3 (150 μL, 150 μmol, 10 mol%) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 1:0 to 1:1) gave **201** (423 mg, 1.37 mmol, 91%) as a white solid.

R_f = 0.37 (petroleum ether / Et_2O, 9:1)

m.p. = 99–101 °C

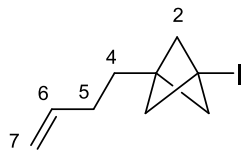
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (1H, d, *J* = 7.7 Hz, H9), 7.53 (td, *J* = 7.7, 1.3 Hz, H7), 7.33 (td, *J* = 7.7, 1.3 Hz, H8), 7.19 (1H, d, *J* = 7.7 Hz, H6), 3.07 (2H, s, H4), 2.19 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 133.1, 133.0, 130.1, 127.2, 118.0, 112.6, 60.4, 47.7, 37.7, 7.0.

HRMS (CI^+) Found $[M+NH_4]^+$ = 327.0355; $C_{13}H_{16}IN_2$ requires 327.0352.

IR (film) ν_{max}/cm^{-1} 2914, 2877, 2221, 1482, 1444, 1173.

1-(But-3-en-1-yl)-3-iodobicyclo[1.1.1]pentane, 207



Compound **160** (182 mg, 1.00 mmol, 1.0 equiv.), TCP (1.50 mL, 0.89 M in Et_2O, 1.30 mmol, 1.3 equiv.) and BEt_3 (100 µL, 1.0 M in hexane, 100 µmol, 10 mol%) were submitted to **General Procedure 4** at rt for 1 h. Purification by column chromatography (SiO_2, pentane) gave **207** (199 mg, 0.800 mmol, 80%) as a colourless liquid.

R_f = 0.62 (pentane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (1H, ddt, *J* = 16.8, 10.2, 6.5 Hz, H6), 5.03–4.91 (2H, m, H7), 2.20 (6H, s, H2), 2.07–1.96 (2H, m, H5), 1.66–1.57 (2H, m, H4).

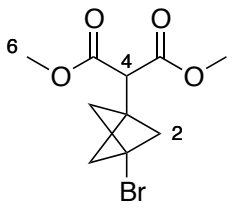
^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 115.0, 60.7, 48.4, 31.4, 31.1, 7.9.

HRMS (ESI) Found $[M+NH_4]^+$ = 266.0406; $C_9H_{17}IN$ requires 266.0400.

IR (film) ν_{max}/cm^{-1} 2987, 1172.

Synthesised and characterised by Dr Carlos Arroniz.

Dimethyl 2-(3-bromobicyclo[1.1.1]pentan-1-yl)malonate, 208



Compound **172** (132 μL, 1.00 mmol, 1.0 equiv.), TCP (1.40 mL, 0.90 M in Et_2O, 1.30 mmol, 1.3 equiv.) and BEt_3 (100 μL, 1 M in hexane, 100 μmol, 10 mol%) were submitted to **General Procedure 4** at 0 °C for 15 min. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 9:1) gave **208** (244 mg, 0.880 mmol, 88%) as a colourless oil.

R_f = 0.14 (petroleum ether / Et_2O, 9:1)

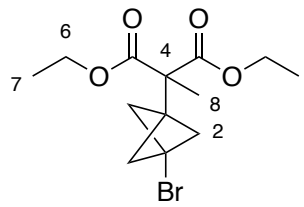
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (6H, s, H6), 3.66 (1H, s, H4), 2.33 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.4, 58.5, 52.7, 52.3, 38.1, 35.9.

HRMS (CI^+) Found $[M+H]^+$ = 210.9604; $C_{10}H_{14}{}^{79}BrO_4$ requires 277.0070 .

IR (film) ν_{max}/cm^{-1} 2955, 1735, 1219, 1052, 1022.

Diethyl 2-(3-bromobicyclo[1.1.1]pentan-1-yl)-2-methylmalonate, 209



Compound **173** (165 mg, 0.500 mmol, 1.0 equiv.), TCP (0.90 mL, 0.73 M in Et_2O, 0.50 mmol, 1.3 equiv.) and BEt_3 (50 μL, 1 M in hexane, 0.05 mmol, 10 mol%) were submitted to **General Procedure 4**. Purification by column chromatography (SiO_2, petroleum ether/Et_2O, 95:5) gave **209** (119 mg, 0.370 mmol, 74%) as a colourless oil.

R_f = 0.28 (petroleum ether / Et_2O, 9:1)

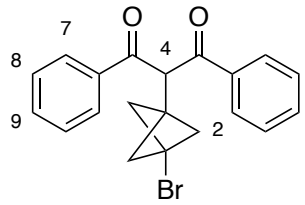
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (4H, m, H6), 2.27 (6H, s, H2), 1.38 (3H, s, H8), 1.25 (6H, t, *J* = 7.1 Hz, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.1, 61.6, 57.4, 54.2, 43.0, 36.4, 18.9, 14.3.

HRMS (CI^+) Found $[M+H]^+$ = 319.0528; $C_{13}H_{20}{}^{79}BrO_4$ requires 319.0540.

IR (film) ν_{max}/cm^{-1} 2981, 1730, 1258, 1188, 1154, 1094.

2-(3-Bromobicyclo[1.1.1]pentan-1-yl)-1,3-diphenylpropane-1,3-dione, 210



Compound **174** (152 mg, 0.500 mmol, 1.0 equiv.), TCP (0.720 mL, 0.90 M in Et_2O, 1.00 mmol, 1.3 equiv.) and BEt_3 (50 μL, 1 M in hexane, 50 μmol, 10 mol%) were submitted to **General Procedure 4** at 0 °C for 1 h. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 95:5) gave **210** (112 mg, 0.300 mmol, 59%) as an off-white solid.

R_f = 0.45 (petroleum ether / EtOAc, 8:2)

m.p. = 119–120 °C

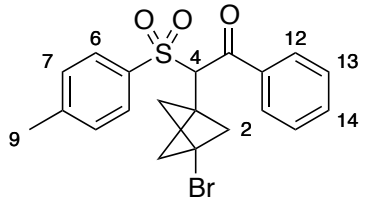
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (4H, dd, *J* = 8.4, 1.4 Hz, H7), 7.63–7.54 (2H, m, H9), 7.51–7.41 (4H, m, H8), 5.53 (1H, s, H4), 2.35 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 193.7, 136.0, 134.0, 129.1, 128.6, 59.2, 56.2, 39.1, 36.5.

HRMS (CI^+) Found $[M+H]^+$ = 369.0491; $C_{20}H_{18}{}^{79}BrO_2$ requires 369.0412.

IR (film) ν_{max}/cm^{-1} 2920, 1691, 1672, 1331, 1274, 1174.

2-(3-Bromobicyclo[1.1.1]pentan-1-yl)-1-phenyl-2-tosyl-ethan-1-one, 211



Compound **176** (177 mg, 0.500 mmol, 1.0 equiv.), TCP (0.73 mL, 0.90 M in Et_2O, 0.65 mmol, 1.3 equiv.) and BEt_3 (50 µL, 1 M in hexane, 50 µmol, 10 mol%) in CH_2Cl_2 (2 mL) were submitted to **General Procedure 4** at 0 °C for 1h. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 9:1) and recrystallisation from CH_2Cl_2 with pentane gave **211** (132 mg, 0.310 mmol, 42% yield) as determined by ^{1}H NMR spectroscopy, 95:5 mixture with the corresponding staffane derivative) as white crystals.

R_f = 0.18 (petroleum ether / EtOAc, 8:2)

m.p. = 136-–37 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78–7.74 (2H, m, H12), 7.72–7.67 (2H, m, H6), 7.61–7.55 (1H, m, H14), 7.45–7.39 (2H, m, H13), 7.28–7.23 (2H, m, H7), 5.30 (1H, s, H4), 2.39 (3H, s, H9), 2.37 (3H, dd, *J* = 9.4, 1.9 Hz, H2), 2.30 (3H, dd, *J* = 9.4, 1.9 Hz, H2).

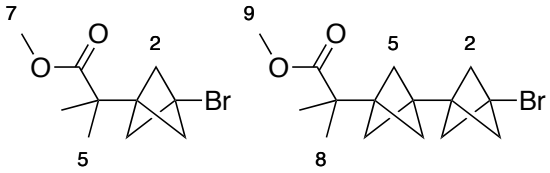
^{13}C NMR (101 MHz, $CDCl_3$) δ 190.5, 145.7, 136.5, 135.2, 134.3, 129.8, 129.7, 129.0, 128.7, 69.3, 59.4, 37.1, 35.8, 21.8.

HRMS (ESI$^+$) Found $[M+H]^+$ = 419.0298; $C_{20}H_{20}{}^{79}BrO_3S$ requires 419.0311.

IR (film) ν_{max}/cm^{-1} 3011, 2922, 1683, 1596, 1579, 1402, 1324, 1149, 1018.

Staffane derivative: **HRMS** (ESI$^+$) Found $[M+Na]^+$ = 507.0585; $C_{25}H_{25}O_3BrNaS$ requires 507.0600.

Methyl 2-(3-bromobicyclo[1.1.1]pentan-1-yl)-2-methylpropanoate (212) and 2-(3'-bromo-[1,1'-bi(bicyclo[1.1.1]pentan)]-3-yl)-2-methylpropanoate (212′).



Methyl bromodimethylacetate (64.7 µL, 0.500 mmol, 1.0 equiv.), TCP (1.10 mL, 0.90 M in Et_2O, 1.00 mmol, 2.0 equiv.) and BEt_3 (50 µL, 1 M in hexane, 50 µmol, 10 mol%) were submitted to **General Procedure 3** at rt for 15 min. Concentration and purification by column chromatography (SiO_2, petroleum ether / Et_2O, 95:5) gave **212** as a yellow oil (104 mg, 55% yield by NMR) as 80:20 mixture with **212′**.

R_f = 0.27 (petroleum ether / Et_2O, 94:6)

IR (film) ν_{max}/cm^{-1} 2974, 2918, 2880, 1731, 1469, 1448, 1434, 1387, 1366, 1271, 1190, 1158, 1120, 1009, 973, 857.

Compound **212**

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (3H, s, H7), 2.12 (6H, s, H2), 1.14 (6H, s, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 56.4, 51.9, 46.4, 43.0, 36.6, 22.5.

HRMS (CI^+) Found [M+H]+ = 247.0330; $C_{10}H_{16}{}^{79}BrO_2$ requires 247.0334.

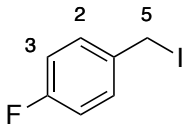
Compound **212′**

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (3H, s, H9), 2.07 (6H, s, H2), 1.49 (6H, s, H5), 1.08 (6H, s, H8).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5, 57.8, 51.6, 47.4, 44.2, 42.2, 41.2, 37.6, 36.1, 21.8.

HRMS (CI^+) Found $[M+H]^+$ = 313.0801; $C_{15}H_{22}{}^{79}BrO_2$ requires 313.0803.

1-Fluoro-4-(iodomethyl)benzene, 214



4-Fluorobenzyl bromide (498 μL, 4.00 mmol, 1.0 equiv.) and sodium iodide (900 mg, 6.00 mmol, 1.5 equiv.) in acetone (8 mL) were submitted to **General Procedure 1** to give **214** (757 mg, 3.20 mmol, 80%) as a yellow solid.

R_f = 0.33 (petroleum ether)

m.p; 25–26 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.32 (2H, m, H3), 7.04–6.92 (2H, m, H2), 4.44 (2H, s, H5)

^{13}C NMR (101 MHz, $CDCl_3$) δ 130.5, 130.4, 115.9, 115.7, 4.7.

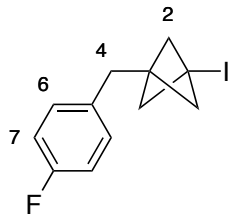
HRMS (CI^+) Found $[M]^+$ = 236.9577; C_7H_6FI requires 236.9571.

IR (film) ν_{max}/cm^{-1} 2923, 1699, 1604, 1510, 1356, 1225, 1157.

Spectroscopic data in agreement with that reported in the literature.[51]

Synthesised and characterised by Ms Helen Jones.

1-(4-Fluorobenzyl)-3-iodobicyclo[1.1.1]pentane, 215



Compound **214** (118 mg, 0.500 mmol, 1.0 equiv.), TCP (1.32 mL, 0.76 M in Et_2O, 1.00 mmol, 2.0 equiv.) and BEt_3 (50 μL, 1 M in hexane, 50 μmol, 10 mol%) were submitted to **General Procedure 4** at rt for 20 h. Purification by column chromatography (SiO_2, petroleum ether) gave **215** (66 mg, 0.22 mmol, 44%) as a colourless oil.

R_f = 0.24 (petroleum ether)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–6.92 (4H, m, H6, H7), 2.78 (2H, s, H4), 2.14 (6H, s, H2).

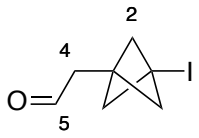
^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 160.3, 133.9, 130.2, 115.4, 60.1, 48.2, 38.3.

HRMS (CI^+) Found $[M+H]^+$ = 303.0050; $C_{12}H_{13}FI$ requires 303.0041.

IR (film) ν_{max}/cm^{-1} 2990, 2912, 2361, 1606, 1508, 1437, 1220, 1171, 1157, 1099, 1016.

Synthesised and characterised by Ms Helen Jones.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)acetaldehyde, 235



To a solution of oxalyl chloride (87 μL, 1.0 mmol, 2.0 equiv.) in CH_2Cl_2 (3 mL) at −78 °C was added DMSO (72 μL, 1.01 mmol, 2.0 equiv.). The resulting mixture was stirred at −78 °C for 10 min and alcohol **191** (120 mg, 0.504 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) was added dropwise over 2 min and the mixture was stirred for 20 min at −78 °C. Triethylamine (0.28 mL, 2.02 mmol, 4.0 equiv.) was added dropwise at the same temperature and the reaction mixture was stirred and allowed to warm up to rt over 1 h. Water (10 mL) was added and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2 and the combined organics were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo* at rt and away from light. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 8:2) gave aldehyde **235** (61mg, 0.258 mmol, 51%) as white solid.

R_f = 0.39 (petroleum ether / Et_2O, 8:2)

m.p. = 33−34°C

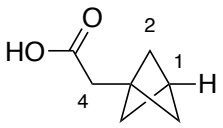
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (1H, t, *J* = 2.0 Hz, H5), 2.66 (2H, d, *J* = 2.0 Hz, H4), 2.36 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 199.1, 61.2, 45.6, 42.7, 6.3.

HRMS (CI^+) Found $[M+NH_4]^+$ = 254.0032; $C_7H_{13}ION$ requires 235.9698.

IR (film) ν_{max}/cm^{-1} 2981, 2914, 2879, 2834, 2729, 1723, 1176.

2-(Bicyclo[1.1.1]pentan-1-yl)acetic acid, 236



To a solution of **110** (296 μL, 2.50 mmol, 1.0 equiv.) and TCP (3.44 mL, 0.80 M in Et_2O, 2.75 mmol, 1.1 equiv.) at 0 °C was added BEt_3 (25 μL, 1 M in hexane, 25 μmol, 1 mol%), and the resulting mixture was stirred at 0 °C for 15 min. Tris(trimethylsilyl)silane (1.00 mL, 3.25 mmol, 1.3 equiv.) and BEt_3 (250 μL, 1 M in hexane, 250 μmol, 10 mol%) were added, and the mixture was stirred at rt for 15 min (caution: exotherm). Sodium hydroxide (500 mg, 12.5 mmol, 5.0 equiv.) in methanol (5 mL) was added (caution: exotherm) and the mixture was refluxed for 30 min, and then concentrated. Water (5 mL) was added and the mixture was extracted with Et_2O (3 × 10 mL). The aqueous phase was acidified to pH 1 with conc. HCl, extracted with Et_2O (3 × 20 mL), and the combined organics were dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, CH_2Cl_2 / methanol, 95:5) gave **236** (204 mg, 1.62 mmol, 64%) as a pungent colourless oil.

R_f = 0.25 (CH_2Cl_2 / methanol, 9:1)

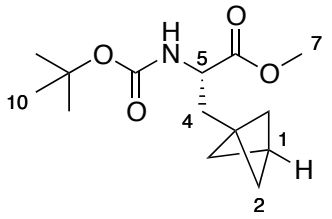
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.51 (2H, s, H4), 2.49 (1H, s, H1), 1.82 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 178.1, 51.3, 40.7, 38.3, 28.2.

HRMS (ESI^-) Found $[M-H]^-$ = 125.0608; $C_7H_9O_2$ requires 125.0608.

IR (film) ν_{max}/cm^{-1} 2968, 2909, 2874, 1706, 1509, 1407, 1300, 1258, 1229, 1201.

Methyl (*S*)-3-(bicyclo[1.1.1]pentan-1-yl)-2-((tert-butoxycarbonyl)amino)propanoate, 237



To a solution of iodide **194** (790 mg, 2.00 mmol, 1.0 equiv.) and 2,6-lutidine (0.700 mL, 6.00 mmol, 3.0 equiv.) in THF (4 mL) was added tris(trimethylsilyl)silane (1.23 mL, 4.00 mmol, 2.0 equiv.) and BEt_3 (200 μL, 1 M in hexane, 200 μmol, 10 mol%). The resulting mixture was stirred for 15 min at rt and then concentrated. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 9:1) and recrystallisation from pentane (–20 °C) gave **237** (406 mg, 1.51 mmol, 75%) as white crystals.

R_f = 0.23 (petroleum ether / Et_2O, 8:2)

m.p. = 67–68 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.93 (1H, d, *J* = 8.5 Hz, NH), 4.29 (1H, td, *J* = 8.1, 4.5 Hz, H5), 3.72 (3H, s, H7), 2.44, (1H, s, H1), 1.97 (1H, dd, *J* = 14.6, 4.5 Hz, H4), 1.76 (1H, dd, *J* = 14.6, 7.9 Hz, H4), 1.71 (6H, s, H2), 1.44 (9H, s, *t*-Bu).

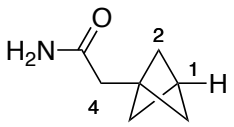
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 155.2, 79.9, 52.3, 52.3, 51.2, 42.8, 35.0, 28.5, 28.3.

HRMS (ESI^+) Found $[M+Na]^+$ = 292.1517; $C_{14}H_{23}O_4N^{23}Na$ requires 292.1519.

IR (film) ν_{max}/cm^{-1} 3352, 2979, 2952, 2905, 2870, 1736, 1677, 1536, 1246, 1156.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –15.1 (c = 3.0, MeOH)

2-(Bicyclo[1.1.1]pentan-1-yl)acetamide, 238



To a solution of **181** (178 mg, 0.710 mmol, 1.0 equiv.) in MeOH (1.8 mL) at rt were added tris(trimethylsilyl)silane (284 μL, 0.920 mmol, 1.3 equiv.) and BEt_3 (70 μL, 1.0 M in hexane, 70 μmol, 10 mol%). After stirring for 2 h, the reaction mixture was concentrated and the crude product was washed with pentane (0.5 mL). Purification by column chromatography (SiO_2, EtOAc) gave **238** (76 mg, 0.61 mmol, 86%) as a brown solid.

R_f = 0.22 (petroleum ether / Et_2O, 95:5)

m.p. = 142–144 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.66 (br s, 1H, NH), 5.41 (br s, 1H, NH), 2.51 (1H, s, H1), 2.39 (2H, s, H4), 1.81 (6H, s, H2).

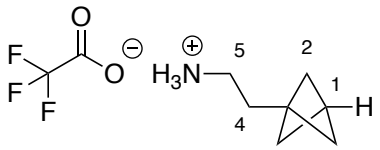
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 51.3, 41.5, 40.7, 27.9.

HRMS (CI^+) Found $[M+H]^+$ = 126.0914; $C_7H_{12}NO$ requires 126.0913.

IR (film) ν_{max}/cm^{-1} 3358, 3184, 2963, 1656, 1627, 1432, 1270.

Synthesised and characterised by Dr Carlos Arroniz.

2-(Bicyclo[1.1.1]pentan-1-yl)ethan-1-aminium 2,2,2-trifluoroacetate, 239



To a solution of **192** (242 mg, 0.720 mmol, 1.0 equiv.) in methanol (1.8 mL) at rt was added tris(trimethylsilyl)silane (288 µL, 0.940 mmol, 1.3 equiv.) and BEt_3 (70 µL, 1.0 M in hexane, 70 µmol, 10 mol%). After stirring for 30 min, the reaction mixture was concentrated. The residue dissolved with CH_2Cl_2 (1 mL) and trifluoroacetic acid (1 mL) was added dropwise at rt. After stirring for 14 h, the reaction mixture was concentrated *in vacuo* and the crude product was washed with pentane (5 x 0.25 mL). The resulting oil was dried under vacuum at 100 °C for 1 h to give **239** (158 mg, 0.700 mmol, 97%) as a thick colourless oil.

^{1}H NMR (400 MHz, CD_3OD) δ 2.89–2.84 (2H, m, H5), 2.48 (1H, s, H1), 1.81–1.78 (2H, m, H4), 1.75 (6H, s, H2).

^{13}C NMR (101 MHz, CD_3OD) δ 162.5 (q, J = 35.4 Hz), 117.9 (q, J = 291.8 Hz), 51.2, 43.4, 38.5, 31.3, 28.7.

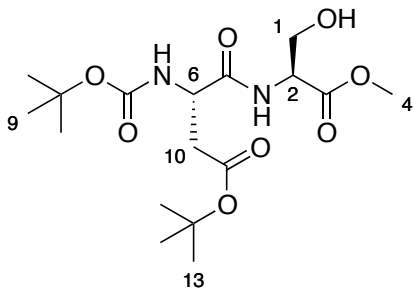
^{19}F NMR (376 MHz, $CDCl_3$) δ –77.0.

HRMS (ESI^+) Found $[M]^+$ = 112.1119; $C_7H_{14}N$ requires 112.1121.

IR (film) ν_{max}/cm^{-1} 2967, 1668, 1198, 1137.

Synthesised and characterised by Dr Carlos Arroniz.

Boc-Asp(O*t*-Bu)-Ser-OMe, 240



Adapted from the procedure described by Pu et al.[31] To a suspension of methyl serinate hydrochloride (422 mg, 4.00 mmol, 1.0 equiv.) in EtOH (10 mL) was added *N*-methylmorpholine (1.32 mL, 12.0 mmol, 3.0 equiv.), a solution of Boc-Asp(O*t*-Bu)-OH (1.19 g, 4.12 mmol, 1.03 equiv.), and HOBt (82 mg, 0.60 mmol, 30 mol%) in EtOH (10 mL). The resulting mixture was cooled to 0 °C and stirred at this temperature for 15 min. EDCI (920 mg, 4.80 mmol, 1.2 equiv.) was added in three portions at 0 °C, and the resulting mixture warmed to rt and stirred for 12 h. Water (40 mL) was added, and the aqueous phase was extracted with EtOAc (3 x 25 mL). The combined organics were washed with pH 2 buffer solution (2 × 25 mL), $NaHCO_3$ (aq., sat., 25 mL) and brine (25 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 1:1 to 7:3) gave **240** (1.53 g, 3.92 mmol, 97%) as a white foam.

R_f = 0.17 (petroleum ether / EtOAc, 1:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, d, *J* = 7.4 Hz, NH), 5.68 (1H, d, *J* = 8.6 Hz, NH), 4.57 (1H, dt, *J* = 7.2, 3.4 Hz, H2), 4.46 (1H, dt, *J* = 9.7, 5.6 Hz, H6), 4.00–3.82 (2H, m, H1), 3.74 (3H, s, H4), 3.23 (1H, t, *J* = 6.5 Hz, OH), 2.89 (1H, dd, *J* = 17.0, 5.4 Hz, H10), 2.63 (1H, dd, *J* = 17.0, 5.4 Hz, H10), 1.42 (9H, s, *t*-Bu), 1.40 (9H, s, *t*-Bu).

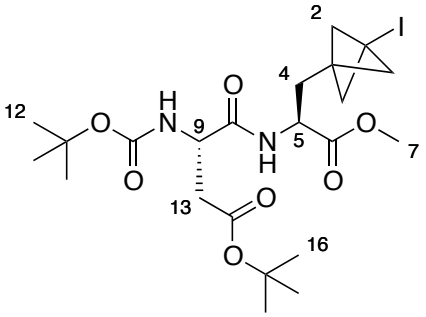
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 171.3, 170.7, 155.6, 82.1, 80.7, 62.4, 55.1, 52.8, 51.0, 37.8, 28.3, 28.1.

HRMS (ESI^+) Found $[M+Na]^+$ = 413.1899; $C_{17}H_{30}O_8N_2{}^{23}Na$ requires 413.1894.

IR (film) ν_{max}/cm^{-1} 3339, 2978, 2935, 1726, 1673, 1523, 1368, 1293, 1249, 1230, 1161.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 35.1 (c 1.1, $CHCl_3$)

Boc-Asp(OtBu)-α-(3-iodobicyclo[1.1.1]pentan-1-yl)Ala-OMe, 241



Adapted from the procedure described by Koseki et al.[17] To a solution of **240** (570 mg, 1.46 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) was added imidazole (149 mg, 2.19 mmol, 1.5 equiv.) and PPh_3 (574 mg, 2.19 mmol, 1.5 equiv.). The resulting solution was cooled to 0 °C and iodine (556 mg, 2.19 mmol, 1.5 equiv.) was added in five portions. The resulting mixture was stirred at 0 °C for 1 h, and then diluted with water (10 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organics were washed with $Na_2S_2O_3$ (aq., 10 wt%, 20 mL), dried (Na_2SO_4) and concentrated. The resulting solid was washed with pentane (2 × 10 mL) and Et_2O (2 × 10 mL), and the combined filtrates were concentrated to give a 0.41:1 mixture of Ph_3PO and **241** as an orange oil (386 mg, ~52%), which was used without further purification.

The resulting oil (386 mg, ~771 μmol, 1.0 equiv.), TCP (1.93 mL, 0.8 M in Et_2O, 1.54 mmol, 2.0 equiv.) and BEt_3 (77 μL, 1 M in hexane, 77 μmol, 10 mol%) were

submitted to **General Procedure 4** for 1 h at rt. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 1:0 to 7:3) gave **242** (312 mg, 0.55 mmol, 38% over two steps) as a white solid.

R_f = 0.19 (petroleum ether /EtOAc, 8:2)

m.p. = 105–106 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (1H, d, *J* = 7.9 Hz, NH), 5.73 (1H, d, *J* = 8.5 Hz, NH), 4.53 (td, *J* = 7.5, 4.3 Hz, H5), 4.45 (q, *J* = 5.5 Hz, H9), 3.71 (3H, s, H7), 2.88 (1H, dd, *J* = 17.1, 4.5 Hz, H13), 2.57 (1H, dd, *J* = 17.1, 6.3 Hz, H13), 2.22 (6H, s, H2), 2.12 (1H, dd, *J* = 14.8, 4.3 Hz, H4), 1.93 (1H, dd, *J* = 14.7, 7.3 Hz, H4), 1.47 (9H, s, *t*-Bu), 1.45 (9H, s, *t*-Bu).

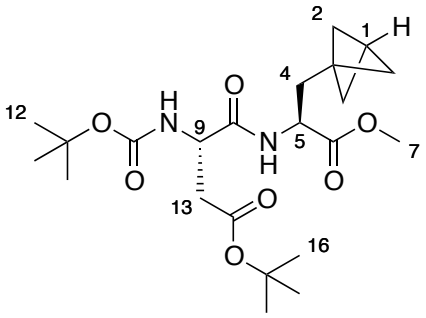
^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 171.5, 170.8, 155.7, 82.0, 80.7, 61.0, 52.6, 50.9, 50.7, 45.3, 37.0, 34.0, 28.5, 28.2, 6.3.

HRMS (ESI^+) Found $[M+H]^+$ = 567.1544; $C_{22}H_{36}O_7N_2{}^{127}I$ requires 567.1562.

IR (film) ν_{max}/cm^{-1} 3320, 2978, 2919, 1721, 1666, 1520, 1437, 1179, 1158, 1049.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 29.3 (c 1.0, $CHCl_3$).

Boc-Asp(OtBu)-α-(bicyclo[1.1.1]pentan-1-yl)Ala-OMe, 243



To a solution of **242** (56.6 mg, 100 μmol, 1.0 equiv.) in THF (0.2 mL) was added tris(trimethylsilyl)silane (62 μmol, 0.20 mmol, 2.0 equiv.). BEt_3 (10 μL, 1 M in hexane, 10 μmol, 10 mol%) was added and the resulting mixture was stirred at rt for 15 min. Further BEt_3 (2 x 10 mol%) was added at 15-minute intervals until the reaction was judged complete by TLC. The reaction mixture was then diluted with Et_2O (5 mL), and the organic phase was washed with $NaHCO_3$ (aq., sat., 5 mL). The aqueous phase was extracted with Et_2O (2 × 5 mL) and the combined organics were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 9:1 to 8:2) gave **243** (36.5 mg, 83 μmol, 83%) as a colourless oil.

R_f = 0.22 (petroleum ether / EtOAc, 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (1H, d, *J* = 6.8 Hz, NH), 5.72 (1H, d, *J* = 7.4 Hz, NH), 4.51 (2H, m, H5, H9), 3.70 (3H, s, H7), 2.85 (1H, dd, *J* = 17.0, 4.6 Hz, H13), 2.58 (1H, dd, *J* = 17.0, 6.6 Hz, H13), 2.43 (1H, s, H1), 1.97 (1H, dd, *J* = 14.7, 4.5 Hz, H4), 1.84 (1H, dd, *J* = 14.7, 7.3 Hz, H4), 1.71 (6H, s, H2), 1.45 (9H, s, *t*-Bu), 1.44 (9H, s, *t*-Bu).

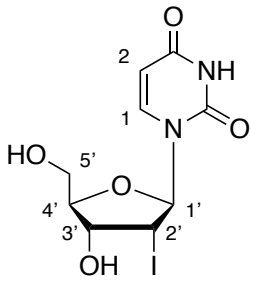
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 171.5, 170.7, 155.6, 81.8, 80.4, 52.4, 51.2, 50.7, 42.6, 37.4, 34.4, 29.8, 28.5, 28.2, 24.0.

HRMS (ESI$^+$) Found $[M+H]^+$ = 441.2593; $C_{22}H_{37}O_7N_2$ requires 441.2595.

IR (film) ν_{max}/cm^{-1} 3324, 2970, 2908, 2871, 1721, 1668, 1520, 1456, 1437, 1202, 1155.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = 12.9 (c 1.0, $CHCl_3$)

2′-Iodo-2′-deoxyuridine, 244



According to the procedure described by Haugland et al.[32] To a solution of O2,2'-cyclouridine (1.13 g, 5.00 mmol, 1.0 equiv.) in acetone (50 mL) was added sodium iodide (1.12 g, 7.50 mmol, 1.5 equiv.) and para-toluenesulfonic acid (1.43 g, 7.50 mmol, 1.5 equiv.). The resulting mixture was stirred at 50 °C for 5h, then cooled to rt and filtered. The solid was washed with acetone, and the filtrate was concentrated. The residue was diluted with acetone (7 mL) and washed with $Na_2S_2O_3$ (aq. sat., 7 mL). The aqueous phase was extracted with acetone (2 × 5 mL) and the combined organics were concentrated. Purification by column chromatography (SiO_2, CH_2Cl_2 / MeOH, 95:5 to 80:20) gave **244** (1.28 g, 3.61 mmol, 72%) as an off-white foam.

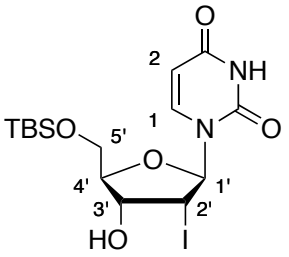
^{1}H NMR (400 MHz, MeOD) δ 7.97 (1H, d, *J* = 8.1 Hz, H1), 6.31 (1H, d, *J* = 7.4 Hz, H1'), 5.70 (1H, d, *J* = 8.1 Hz, H2), 4.49 (1H, dd, *J* = 7.4, 5.1 Hz, H2'), 4.08 (1H, q, *J* = 3.0 Hz, H4'), 3.92 (1H, dd, *J* = 5.1, 3.2 Hz, H3'), 3.79 (1H, dd, *J* = 12.2, 3.0 Hz, H5'), 3.72 (1H, dd, *J* = 12.2, 2.9 Hz, H5').

^{13}C NMR (101 MHz, MeOD) δ 165.9, 152.3, 141.8, 103.2, 91.9, 87.2, 72.2, 62.3, 32.4.

HRMS (ESI^{+}) Found $[M+Na]^{+}$ = 376.9614; $C_9H_{11}O_5N_2{}^{127}I^{23}Na$ requires 376.9505.

Spectroscopic data in accordance to that reported previously.[22]

5′-*O*-(*tert*-Butyldimethylsilyl)-2′-iodo-2′-deoxyuridine, 246



To a solution of **244** (354 mg, 1.00 mmol, 1.0 equiv.) in DMF (5 mL) was added imidazole (204 mg, 3.00 mmol, 3.0 equiv.) and 4-(N,N-dimethylamino)pyridine (12 mg, 10 mol%, 0.10 mmol), and the resulting mixture was cooled to 0 °C. *tert*-Butyldimethylsilyl chloride (158 mg, 1.05 mmol, 1.05 equiv.) was added at this temperature and the resulting mixture was stirred at rt for 1 h. NH_4Cl (sat., aq., 25 mL) was added and the aqueous was extracted with EtOAc (3 × 15 mL). The combined organics were washed with LiCl (10%, aq., 2 × 25 mL), brine (1 × 25 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, eluent load, CH_2Cl_2/EtOAc, 1:0 to 0:1) gave **246** (177 mg, 0.378 mmol, 37%) as a yellow foam.

R_f = 0.18 (CH_2Cl_2/EtOAc, 8:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.99 (1H, s, NH), 7.87 (1H, d, *J* = 8.2 Hz, H1), 6.43 (1H, d, *J* = 6.9 Hz, H1'), 5.72 (1H, d, *J* = 8.2 Hz, H2), 4.39 (1H, dd, *J* = 6.8, 4.8 Hz, H2'), 4.25 (dt, *J* = 3.8, 2.0 Hz, H4'), 3.94 (2H, m, H5', -OH) 3.84 (1H, dd, *J* = 11.7, 1.8 Hz, H5'), 2.59 (1H, d, *J* = 4.3 Hz, H3'), 0.92 (9H, s, Si*t*-Bu), 0.12 (s, 6H, SiMe), 0.12 (s, 6H, SiMe).

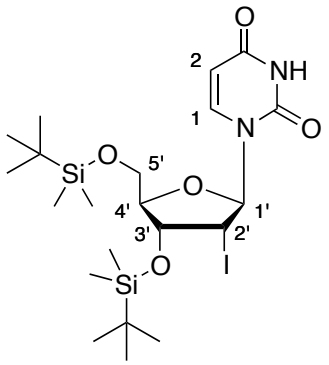
^{13}C NMR (101 MHz, $CDCl_3$) δ 163.2, 150.4, 139.5, 103.0, 90.2, 84.8, 71.7, 62.9, 33.4, 26.0, 18.5, –5.3, –5.4.

HRMS (ESI^+) Found $[M+Na]^+$ = 491.0496; $C_{15}H_{25}O_5N_2{}^{127}I^{23}Na^{28}Si$ requires 491.0470.

IR (film) ν_{max}/cm^{-1} 3200, 3061, 2953, 2929, 2857, 2361, 2341, 1680, 1463, 1209, 1103.

Spectroscopic data in agreement with that previously reported.[33]

3′,5′-Di(*O*-(*tert*-butyldimethylsilyl))-2′-iodo-2′-deoxyuridine, 248



Adapted from the procedure described by Seamon et al.[34] To a solution of **244** (1.10 g, 3.11 mmol, 1.0 equiv.) in DMF (15 mL) was added *tert*-butylchlorodimethylsilane (2.34 g, 15.6 mmol, 5.0 equiv.) and imidazole (1.06 g, 15.6 mmol, 5.0 equiv.), and the resulting mixture was stirred at rt for 24 h. Water (200 mL) was added and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organics were washed LiCl (10% aq., 2 x 50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 1:0 to 0:1) gave **248** (1.43 g, 2.45 mmol, 79%) as a white foam.

R_f = 0.23 (petroleum ether / Et_2O, 1:1)

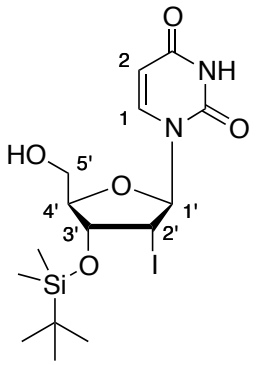
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.96 (1H, s, NH), 7.86 (1H, d, *J* = 8.2 Hz, H1), 6.38 (1H, d, *J* = 5.6 Hz, H1'), 5.71 (1H, dd, *J* = 8.2, 2.2 Hz, H2), 4.28 (1H, t, J = 5.6 Hz, H2'), 4.11 (1H, dt, *J* = 4.0, 2.0 Hz, H4'), 3.95 (1H, dd, *J* = 11.7, 2.4 Hz, H5'), 3.82 (app t, *J* = 4.5 Hz, H3'), 3.75 (1H, dd, *J* = 11.7, 1.8 Hz, H5'), 0.93 (9H, s, Si*t*-Bu), 0.92 (9H, s, Si*t*-Bu), 0.17 (3H, s, SiMe), 0.12 (3H, s, SiMe), 0.11 (3H, s, SiMe), 0.10 (3H, s, SiMe).

^{13}C NMR (101 MHz, $CDCl_3$) δ 163.1, 150.3, 139.5, 102.8, 91.2, 86.0, 71.3, 62.1, 32.4, 26.0, 25.9, 18.5, 18.3,–4.2, –4.4, –5.4, –5.4.

HRMS (CI^+) Found $[M+Na]^+$ = 605.1327; $C_{21}H_{39}O_5N_2{}^{127}I^{23}NSi_2$ requires 605.1334.

IR (film) ν_{max}/cm^{-1} 2955, 2929, 2858, 1698, 1625, 1461, 1254, 1112.

3′-*O*-(*tert*-Butyldimethylsilyl)-2′-iodo-2′-deoxyuridine, 249



Adapted from the procedure described by Sun et al.[35] To a solution of **248** (1.43 g, 2.45 mmol, 1.0 equiv.) in THF (20 mL) was added a solution of trifluoroacetic acid (5 mL) in water (5 mL) at 0 °C. The resulting mixture was allowed to stir at rt for 2 h, and then quenched cautiously with solid $NaHCO_3$. Water (50 mL) was added, and the aqueous phase was extracted with Et_2O (3 x 25 mL). The combined organics were washed with $NaHCO_3$ (aq. sat., 25 mL) and brine, dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, CH_2Cl_2 / EtOAc, 1:0 to 0:1) gave **249** (825 mg, 1.76 mmol, 71%) as a white solid.

R_f = 0.27 (CH_2Cl_2 / EtOAc, 1:1)

m.p. = 190 °C (decomposition)

^{1}H NMR (400 MHz, MeOD) δ 7.99 (1H, d, *J* = 8.1 Hz, H1), 6.35 (1H, d, *J* = 7.4 Hz, H1'), 5.75 (1H, d, *J* = 8.1 Hz, H2), 4.58 (1H, dd, *J* = 7.4, 4.5 Hz, H2'), 4.13-4.08 (2H, m, H3', H4'), 3.82 (1H, dd, *J* = 12.2, 3.1 Hz, H5'), 3.74 (1H, dd, *J* = 12.2, 2.7 Hz, H5'), 0.99 (9H, s, Si*t*-Bu), 0.24 (3H, s, SiMe), 0.19 (3H, s, SiMe).

^{13}C NMR (101 MHz, MeOD) δ 165.9, 152.4, 141.7, 103.3, 92.1, 87.9, 73.7, 62.0, 31.7, 26.4, 19.0, –4.3, –4.4.

HRMS (ESI^+) Found $[M+H]^+$ = 469.0649; $C_{15}H_{26}O_5N_2{}^{127}I^{28}Si$ requires 469.0650.

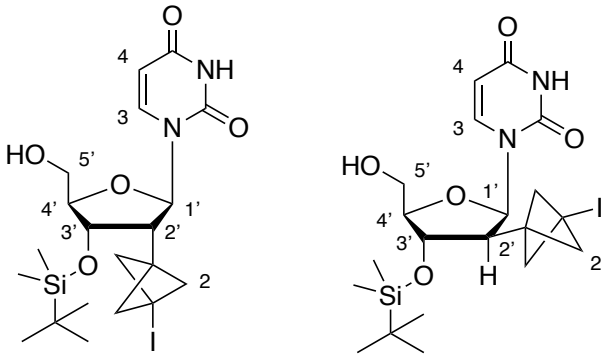
IR (film) ν_{max}/cm^{-1} 3405, 3222, 3062, 2955, 2923, 2856, 1690, 1676, 1462, 1169, 1128, 1102.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ 27.9 (c = 1.0, MeOH)

3′-*O*-(*tert*-Butyldimethylsilyl)-2′-(3-iodobicyclo[1.1.1]pentan-1-yl)-2′-deoxyuridine, 250

and

3′-*O*-(*tert*-Butyldimethylsilyl)-2′-(3-iodobicyclo[1.1.1]pentan-1-yl)-2′-deoxyarabinouridine, 251



Compound **249** (234 mg, 0.500 mmol, 1.0 equiv.), TCP (1.27 mL, 0.79 M in Et_2O, 1.00 mmol, 2.0 equiv.) and BEt_3 (50 μL, 1 M in hexane, 50 μmol, 10 mol%) in MeOH (4 mL) were submitted to **General Procedure 4** at rt for 2 h. ^{1}H NMR spectroscopic analysis of the crude material indicated a 5:1 dr of **254** : **255**. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 1:1 to 0:1) gave **250** (203 mg, 0.380 mmol, 75%) as a white foam and **251** (16 mg, 30 μmol, 6%) as a white foam.

Data for **250**:

R_f = 0.15 (petroleum ether / EtOAc, 1:1)

^{1}H NMR (400 MHz, CD_3OD) δ 7.96 (1H, d, *J* = 8.2 Hz, H3), 6.13 (1H, d, *J* = 8.6 Hz, H1'), 5.69 (1H, d, *J* = 8.2 Hz, H4), 4.45 (1H, dd, *J* = 5.0, 1.7 Hz, H3'), 3.92 (1H, td,

J = 3.3, 1.7 Hz, H4'), 3.76-3.63 (2H, m, H5'), 2.54 (1H, dd, *J* = 8.6, 4.9 Hz, H2'), 2.30 (3H, dd, *J* = 9.3, 1.5 Hz, H2), 2.24 (3H, dd, *J* = 9.3, 1.6 Hz, H2)., 0.96 (9H, s, Si*t*-Bu), 0.16 (3H, s, SiMe), 0.15 (3H, s, SiMe).

^{13}C NMR (101 MHz, CD_3OD) δ 165.8, 152.2, 142.2, 103.3, 88.9, 87.4, 75.8, 62.6, 61.9, 50.7, 45.6, 26.4, 18.7, 7.6, –3.9, –4.4.

HRMS (ESI^+) Found $[M+Na]^+$ = 557.0936; $C_{20}H_{31}O_5N_2{}^{127}I^{28}SiNa$ requires 557.0939.

IR (film) ν_{max}/cm^{-1} 2981, 2887, 1686, 1462, 1383, 1253, 1182, 1091.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ –5.6 (c = 1.0, MeOH)

The stereochemistry of C2' was determined by 2D ^{1}H NOESY data. Correlations were observed between H2' and H5', H2' and H3, H2 and H1'.

Data for **251**:

R_f = 0.18 (petroleum ether / EtOAc, 1:1)

^{1}H NMR (400 MHz, CD_3OD) δ 7.94 (1H, d, *J* = 8.1 Hz, H3), 5.99 (1H, d, *J* = 6.7 Hz, H1'), 5.75 (1H, d, *J* = 8.1 Hz, H4), 4.33 (1H, t, *J* = 5.5 Hz, H3'), 3.87 (1H, dd, *J* = 13.6, 4.1 Hz, H4'), 3.82-3.74 (2H, m, H5'), 2.78 (1H, dd, *J* = 6.7, 5.4 Hz, H2'), 2.22-2.11 (6H, m, H2), 0.91 (9H, s, Si*t*-Bu), 0.16 (6H, s, $SiMe_2$).

^{13}C NMR (101 MHz, CD_3OD) δ 166.0, 152.0, 143.3, 102.1, 87.2, 86.8, 74.2, 61.7, 61.0, 53.9, 47.0, 26.3, 18.8, 6.9, –3.7, –4.0.

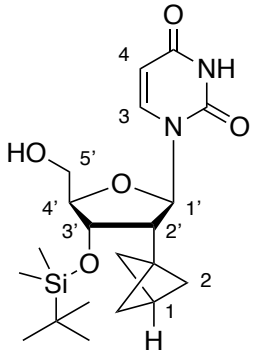
HRMS (ESI^+) Found $[M+H]^+$ = 535.1119; $C_{20}H_{32}O_5N_2{}^{127}I^{28}Si$ requires 535.1120.

IR (film) ν_{max}/cm^{-1} 3400, 3000, 2954, 2928, 2857, 1686, 1464, 1187, 1139, 1086.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ 64.2 (c = 1.0, MeOH).

The stereochemistry of C2' was determined by 2D ^{1}H NOESY data. Correlations were observed between H2 and H3.

3′-*O*-(*tert*-Butyldimethylsilyl)-2′-(bicyclo[1.1.1]pentan-1-yl)-2′-deoxyuridine, 252



To a solution of **250** (18.2 mg, 0.034 mmol, 1.0 equiv.) in MeOH/Et_2O (1:1, 1 mL) was added tris(trimethylsilyl)silane (21 μL, 68 μmol, 2.0 equiv.), then BEt_3 (3.4 μL, 3.4 μmol, 10 mol%) was added via syringe into the solution. The resulting mixture was stirred for 15 min at rt, and then concentrated. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 1:1 to 0:1) gave **252** (10.2 mg, 0.025 mmol, 73%) as an off-white solid.

R_f = 0.15 (petroleum ether / EtOAc, 1:1)

m.p. = 180 °C (decomposition)

^{1}H NMR (400 MHz, MeOD) δ 7.91 (1H, d, *J* = 8.1 Hz, H3), 6.14 (1H, d, *J* = 8.9 Hz, H1'), 5.68 (1H, d, *J* = 8.1 Hz, H4), 4.41 (1H, dd, *J* = 4.9, 1.6 Hz, H3'), 3.87 (1H, td, *J* = 3.6, 1.6 Hz, H4'), 3.64 (2H, dd, *J* = 3.6, 1.2 Hz, H5'), 2.40 (1H, s, H1), 2.34 (1H, dd, *J* = 8.9, 4.9 Hz, H2'), 1.81 (3H, dd, *J* = 9.5, 1.6 Hz, H2), 1.76 (3H, dd, *J* = 9.5, 1.6 Hz, H2), 0.92 (9H, s, Si*t*-Bu), 0.11 (3H, s, SiMe), 0.10 (3H, s, SiMe).

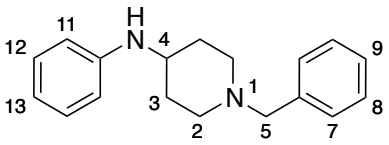
^{13}C NMR (101 MHz, MeOD) δ 165.9, 152.3, 142.5, 103.1, 89.1, 87.8, 76.1, 62.9, 52.1, 50.5, 42.5, 30.6, 26.4, 18.7, –3.9, –4.3.

HRMS (ESI^+) Found $[M+Na]^+$ = 431.1971; $C_{20}H_{32}O_5N_2{}^{23}Na^{28}Si$ requires 431.1973.

IR (film) ν_{max}/cm^{-1} 3412, 2960, 2928, 2858, 1688, 1464, 1259, 1203, 1059.

$[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ 24.3 (c = 0.86, MeOH)

1-Benzyl-*N*-phenylpiperidin-4-amine, 258



According to the procedure described by Brine et al.[36] To a solution of *N*-benzyl-4-piperidone (1.85 mL, 10.0 mmol, 1.0 equiv.) in toluene (50 mL) was added *p*-toluenesulfonic acid monohydrate (38 mg, 0.20 mmol, 0.2 equiv.) and aniline (1.00 mL, 11.0 mmol, 1.1 equiv.), and the mixture was stirred under reflux for 15 h using a Dean-Stark apparatus. The mixture was cooled to rt and EtOH (50 mL) was added. Sodium borohydride (380 mg, 10.0 mmol, 1.0 equiv.) was added portionwise and the resulting mixture was stirred at rt for 3 h. Water (20 mL) was added dropwise and the mixture was stirred for 4 h at rt, then it was acidified to pH 3 with HCl (10%, aq.) and washed with toluene (3 × 25 mL). The aqueous phase was basified with NaOH (50%, aq.), and extracted with CH_2Cl_2 (3 × 50 mL). The combined organics were dried ($MgSO_4$) and concentrated. Recrystallisation from Et_2O with petroleum ether gave **258** (1.15 g, 4.31 mmol, 43%) as yellow crystals.

R_f = 0.25 (petroleum ether / EtOAc, 1:1)

m.p. = 81–82 °C

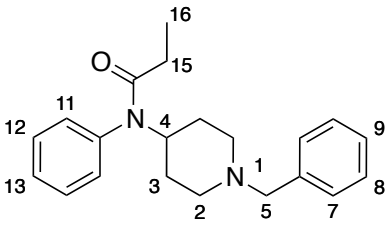
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, app. s, H7 or H8), 7.37 (2H, app. s, H7 or H8), 7.34–7.28 (1H, m, H9), 7.25-7.16 (2H, m, H12), 6.73 (1H, tt, *J* = 7.3, 1.1 Hz, H13), 6.67–6.60 (2H, m, H11), 3.58 (2H, s, H5), 3.55 (1H, br s, NH), 3.34 (1H, dq, *J* = 10.7, 5.3 Hz, H4), 2.90 (2H, dt, *J* = 11.9, 4.0 Hz, H2), 2.19 (2H, td, *J* = 11.5, 2.6 Hz, H2), 2.13-2.04 (2H, m, H3), 1.59-1.45 (2H, m, H3).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 138.5, 129.4, 129.2, 128.3, 127.1, 117.2, 113.3, 63.2, 52.5, 50.0, 32.7.

HRMS (ESI$^+$) Found $[M+H]^+$ = 267.1854; $C_{18}H_{23}N_2$ requires 267.1856.

Spectroscopic data in agreement with that reported previously.[37]

_N_-(1-Benzylpiperidin-4-yl)-_N_-phenylpropionamide, 259



According to the procedure described by Gupta et al.[37] To a solution of **258** (799 mg, 3.00 mmol, 1.0 equiv.) in 1,2-dichloroethane (5 mL) was added propionyl chloride (786 μL, 9.00 mmol, 3.0 equiv.) dropwise at rt. The resulting mixture was stirred at rt for 12 h, and then quenched with NaOH (4%, aq.). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, petroleum ether / EtOAc, 1:0 to 0:1) gave **259** (930 mg, 2.89 mmol, 96%) as a yellow oil.

R_f = 0.26 (petroleum ether / EtOAc, 1:1)

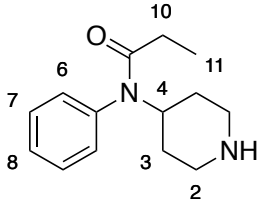
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.25 (3H, m, H12, H13), 7.25–7.08 (5H, m, H7, H8, H9), 7.03–6.94 (2H, m, H11), 4.59 (1H, tt, *J* = 12.2, 3.9 Hz, H4), 3.36 (2H, s, H5), 2.87 (2H, m, H2), 2.03 (2H, td, *J* = 12.0, 2.3 Hz, H2), 1.84 (2H, q, *J* = 7.5 Hz, H15), 1.74-1.58 (2H, m, H3), 1.31 (2H, qd, *J* = 12.3, 3.9 Hz, H3), 0.93 (3H, t, *J* = 7.5 Hz, H16).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 141.0, 139.1, 138.4, 130.5, 129.4, 129.2, 128.3, 128.3, 127.1, 63.2, 53.2, 52.4, 30.7, 28.6, 9.7.

HRMS (ESI$^+$) Found $[M+H]^+$ = 323.2110; $C_{21}H_{27}ON_2$ requires 323.2118.

Spectroscopic data in agreement with that reported previously.[37]

_N_-Phenyl-_N_-(piperidin-4-yl)propionamide (norfentanyl), 257



Adapted from the procedure described by Sudo et al.[38] To a solution of **259** (1.78 g, 5.52 mmol, 1.0 equiv.) in EtOH (20 mL) was added $Pd(OH)_2$ (969 mg, 20 wt% over carbon, 1.38 mmol, 25 mol%) and HCOOH (4.17 mL, 110 mmol, 20 equiv.). The resulting mixture was stirred at 50 °C for 1 h, filtered (celite, washed with EtOH, 3 × 20 mL). The filtrate was concentrated. Purification by column chromatography (SiO_2, CH_2Cl_2 / CH_3OH, 8:2) gave **257** (1.00 g, 4.30 mmol, 77%) as a beige foam.

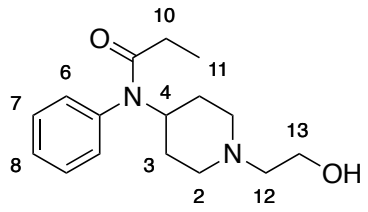
R_f = 0.28 (CH_2Cl_2 / CH_3OH, 8:2)

^{1}H NMR (400 MHz, MeOD) δ 7.54–7.43 (3H, m, H7, H8), 7.24 (2H, d, *J* = 7.3 Hz, H6), 4.77 (1H, tt, *J* = 12.2, 3.9 Hz, H4), 3.44–3.35 (2H, m, H2), 3.15–3.05 (1H, m, H2), 2.06 (2H, d, *J* = 13.7 Hz, H3), 1.96 (2H, q, *J* = 7.5 Hz, H10), 1.58 (2H, qd, *J* = 13.3, 4.1 Hz, H3), 0.97 (3H, t, *J* = 7.5 Hz, H11).

^{13}C NMR (101 MHz, MeOD) δ 176.0, 139.4, 131.4, 130.9, 130.2, 51.5, 44.9, 29.3, 28.6, 9.9.

HRMS (ESI$^+$) Found $[M+H]^+$ = 233.1649; $C_{14}H_{21}ON_2$ requires 233.1648.

_N_-(1-(2-Hydroxyethyl)piperidin-4-yl)-_N_-phenylpropionamide, 255



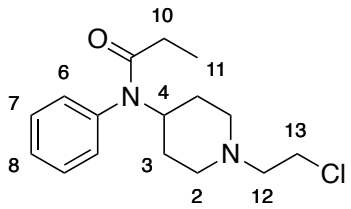
To a solution of **257** (232 mg, 1.00 mmol, 1.0 equiv.) in DMF (5 mL) was added *N,N*-diisopropyl-N-ethylamine (348 μg, 2.00 mmol, 2.0 equiv.) and 2-bromoethanol (106 μL, 1.50 mmol, 1.50 equiv.). The reaction mixture was stirred at 60 °C for 24 h and brine (50 mL) was added. The aqueous was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organics were washed with NaOH (aq., 1 M, 20 mL), water (20 mL) and brine (20 mL), dried and concentrated (Na_2SO_4). Purification by column chromatography (SiO_2, CH_2Cl_2 / MeOH, 1:0 to 9:1) gave **255** (120 mg, 0.434 mmol, 43%) as a colourless oil.

R_f = 0.23 (CH_2Cl_2 / MeOH, 9:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44–7.34 (3H, m, H7, H8), 7.11–7.02 (2H, m, H6), 4.65 (1H, tt, *J* = 12.3, 4.0 Hz, H4), 3.50 (2H, t, *J* = 5.4 Hz, H13), 2.87 (2H, dt, *J* = 12.6, 2.8 Hz, H2), 2.65 (1H, br. s, OH), 2.45 (2H, t, *J* = 5.4 Hz, H12), 2.18 (2H, td, *J* = 11.9, 2.2 Hz, H2), 1.91 (2H, q, *J* = 7.4 Hz, H10), 1.82 – 1.71 (2H, m, H3), 1.34 (2H, qd, *J* = 12.3, 3.9 Hz, H3), 1.00 (3H, t, *J* = 7.4 Hz, H11).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 139.0, 130.4, 129.4, 128.5, 59.1, 58.1, 53.0, 52.2, 30.7, 28.6, 9.7.

_N_-(1-(2-Chloroethyl)piperidin-4-yl)-_N_-phenylpropionamide, 256



To a solution of **257** (272 mg, 1.17 mmol, 1.0 equiv.) in acetone (5 mL) was added potassium carbonate (324 mg, 2.34 mmol, 2.0 equiv.) and 1-bromo-2-chloroethane (146 μL, 1.76 mmol, 1.5 equiv.). The reaction mixture was stirred at rt for 18 h and concentrated. Purification by column chromatography (SiO_2, CH_2Cl_2 / EtOAc, 1:0 to 0:1) gave **256** (112 mg, 0.380 mmol, 32%) as a colourless oil.

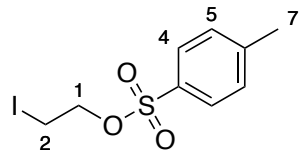
R_f = 0.33 (CH_2Cl_2 / EtOAc, 1:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.34 (3H, m, H7, H8), 7.09–7.04 (2H, m, H6),4.65 (1H, tt, *J* = 12.2, 3.9 Hz, H4), 3.50 (2H, t, *J* = 7.0 Hz, H13), 2.98–2.84 (2H, m, H2), 2.66 (2H, t, *J* = 7.0 Hz, H12), 2.21 (2H, td, *J* = 11.9, 2.3 Hz, H2), 1.91 (2H, q, *J* = 7.5 Hz, H10), 1.83–1.69 (2H, m, H3), 1.40 (2H, qd, *J* = 12.3, 3.9 Hz, H3), 1.00 (3H, t, *J* = 7.4 Hz, H11).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.7, 139.0, 130.5, 129.5, 128.4, 59.9, 53.3, 52.1, 41.2, 30.6, 28.6, 9.7.

HRMS (ESI^+) Found $[M+H]^+$ = 295.1566; $C_{16}H_{24}NO_3Cl$ requires 295.1272 .

2-Iodoethyl 4-methylbenzenesulfonate, 262



Adapted from the procedure described by Wegert et al.[39] To a round-bottomed flask charged with pyridine (2 mL) at 0 °C was added *p*-toluenesulfonyl chloride (1.91 g, 10.0 mmol, 1.0 equiv.). The resulting mixture was stirred at 0 °C for 5 min, then 2-iodoethanol (780 μL, 10.0 mmol, 1.0 equiv.) was added dropwise. The solution was allowed to warm to rt, and stirred for 2 h, then cooled to 0 °C. HCl (aq., 5 M, 10 mL) was added, and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organics were washed with $Na_2S_2O_3$ (aq., 10 wt%, 10 mL) and brine (10 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 1:0 to 0:1) gave **262** (1.28 g, 3.92 mmol, 39%) as a yellow oil.

R_f = 0.18 (petroleum / Et_2O, 9:1)

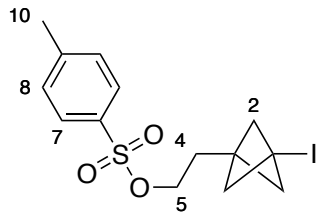
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 7.3 Hz, H4), 7.36 (2H, d, *J* = 8.0 Hz, H5), 4.23 (2H, t, *J* = 7.4 Hz, H1), 3.26 (2H, t, *J* = 7.3 Hz, H2), 2.46 (3H, s, H7).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 132.8, 130.1, 128.1, 69.7, 21.8, –1.3.

HRMS (ESI^+) Found $[M+Na]^+$ = 348.9367; $C_9H_{11}O_3{}^{127}I^{23}Na^{32}S$ requires 348.9366.

IR (film) ν_{max}/cm^{-1} 1597, 1358, 1189, 1173, 1096.

2-(3-Iodobicyclo[1.1.1]pentan-1-yl)ethyl 4-methylbenzenesulfonate, 263



Compound **262** (1.10 g, 3.37 mmol, 1.0 equiv.), TCP (5.48 mL, 0.8 M in Et_2O, 4.38 mmol, 1.3 equiv.) and BEt_3 (337 μL, 1 M in hexane, 337 μmol, 10 mol%) were submitted to **General Procedure 4** at rt for 3 h. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 1:0 to 1:1) gave **263** (1.23 g, 3.14 mmol, 92%) as a white solid.

R_f = 0.20 (petroleum ether/Et_2O, 9:1)

m.p. = 66–67 °C

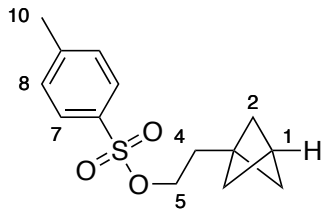
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 8.0 Hz, H7), 7.36 (2H, d, *J* = 8.0 Hz, H8), 4.00 (2H, t, *J* = 6.2 Hz, H5), 2.46 (3H, s, H10), 2.19 (6H, s, H2), 1.88 (2H, t, *J* = 6.2 Hz, H4).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1, 133.0, 130.1, 128.0, 68.0, 60.7, 45.4, 31.2, 21.8, 6.4.

HRMS (ESI^+) Found $[M+Na]^+$ = 414.9835; $C_{14}H_{17}O_3{}^{127}I^{23}Na^{32}S$ requires 414.9835.

IR (film) ν_{max}/cm^{-1} 2989, 2915, 1598, 1448, 1360, 1307, 1176, 1097, 1022.

2-(Bicyclo[1.1.1]pentan-1-yl)ethyl 4-methylbenzenesulfonate, 260



To a solution of **263** (1.23 g, 3.14 mmol, 1.0 equiv.) in THF (6 mL) were added tris(trimethylsilyl)silane (1.93 mL, 6.28 mmol, 2.0 equiv.) and then BEt_3 (314 μL, 1 M in hexane, 314 μmol, 10 mol%, syringed inside the reaction mixture). After stirring for 15 min, Et_2O (20 mL) was added, the organic phase was washed with $NaHCO_3$ (aq., sat., 15 mL) and the phases were separated. The aqueous was extracted with Et_2O (2 × 5 mL) and the combined organics were washed with brine (20 mL), dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, petroleum ether / Et_2O, 100:0 to 95:5) gave **260** (1.01 g, 3.79 mmol, 64%) as a colourless oil.

R_f = 0.36 (petroleum ether / Et_2O, 9:1)

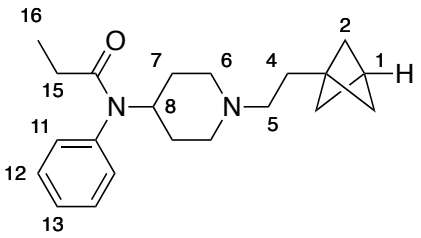
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2H, d, *J* = 7.9 Hz, H8), 7.34 (2H, d, *J* = 7.9 Hz, H7), 4.01 (2H, t, *J* = 6.7 Hz, H5), 2.44 (3H, s, H10), 2.41 (1H, s, H1), 1.76 (2H, t, *J* = 6.7 Hz, H4), 1.64 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 133.2, 129.9, 128.0, 68.9, 50.8, 42.4, 31.6, 28.1, 21.8.

HRMS (ESI^+) Found $[M+Na]^+$ = 289.0867; $C_{14}H_{18}O_3{}^{23}Na^{32}S$ requires 289.0869.

IR (film) ν_{max}/cm^{-1} 2964, 2908, 2870, 1598, 1358, 1189, 1176.

_N_-(1-(2-(Bicyclo[1.1.1]pentan-1-yl)ethyl)piperidin-4-yl)-_N_-phenylpropionamide, 253



To a vial containing **260** (93 mg, 0.35 mmol, 1.0 equiv.) was added a solution of norfentanyl (**261)** (89 mg, 0.35 mmol, 1.1 equiv.) in CH_3CN (1.5 mL). K_2CO_3 (96 mg, 0.70 mmol, 2.0 equiv.) was added and the resulting mixture was refluxed for 24 h. The mixture was cooled to rt and concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and water (5 mL), and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL) and the combined organics were dried (Na_2SO_4) and concentrated. Purification by column chromatography (SiO_2, CH_2Cl_2 / CH_3OH, 8:2) gave **253** as a pale yellow solid (64 mg, 0.20 mmol, 53%). Recrystallisation form hot petroleum ether gave pale yellow crystals that were suitable for X-ray diffraction (see Section 5).

R_f = 0.23 (CH_2Cl_2 / EtOAc, 1:1)

m.p. = 84–85 °C

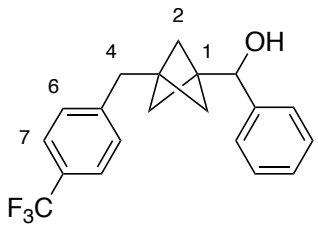
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.28 (3H, m, H13, H12), 7.05 (2H, dd, *J* = 7.8, 1.7 Hz, H11), 4.64 (1H, tt, *J* = 12.2, 4.0 Hz, H8), 2.88 (2H, dt, *J* = 12.4, 3.1 Hz, H6), 2.41 (1H, s, H1), 2.27–2.17 (2H, m, H5), 2.08-1.97 (2H, m, H6), 1.91 (2H, q, *J* = 7.4 Hz, H15), 1.81–1.70 (2H, m, H7), 1.60 (6H, s, H2), 1.55–1.46 (2H, m, H4), 1.37 (2H, qd, *J* = 12.4, 4.0 Hz, H7), 1.00 (3H, t, *J* = 7.4 Hz, H16).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 139.0, 130.5, 129.4, 128.3, 55.9, 53.2, 52.3, 50.4, 44.0, 30.7, 30.0, 28.6, 27.8, 9.7.

HRMS (ESI^+) Found $[M+H]^+$ = 327.2425; $C_{21}H_{31}ON_2$ requires 327.2431.

IR (film) ν_{max}/cm^{-1} 2959, 2867, 2766, 2360, 1659, 1596, 1495, 1194, 1093, 1056, 1018.

Phenyl(3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentan-1-yl)methanol, 265



Adapted from the procedure described by Messner et al. [40] To a solution of **198** (50 mg, 0.14 mmol, 1.0 equiv.) in Et_2O (0.5 mL) at –78 °C was added *tert*-BuLi (0.18 mL, 1.7 M in pentane, 0.31 mmol, 2.2 equiv.) dropwise. The resulting yellow solution was stirred for 1 h at –78 °C, then benzaldehyde (43 μL, 0.43 mmol, 3.0 equiv.) was added at –78 °C. The resulting solution was stirred at –78 °C for 1 h, and then quenched with HCl (1 mL, 1 M aq.,). The aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organics were washed with $NaHCO_3$ (3 mL, aq., sat.), and brine, and then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / Et_2O, 8:2) gave **265** (38 mg, 0.114 mmol, 80%) as a white solid.

R_f = 0.13 (pentane / Et_2O, 8:2)

m.p. = 62–63 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* = 8.0 Hz, H7), 7.36–7.31 (2H, m, Ar*H*), 7.30-7.26 (1H, m, H14), 7.25–7.22 (2H, m, Ar*H*), 7.18 (2H, d, *J* = 8.0 Hz, H6), 4.70 (1H, s, H10), 2.83 (2H, s, H4), 1.89 (1H, s, O*H*), 1.50 (3H, dd, *J* = 9.6, 1.6 Hz, H2), 1.45 (3H, dd, *J* = 9.6, 1.6 Hz, H2).

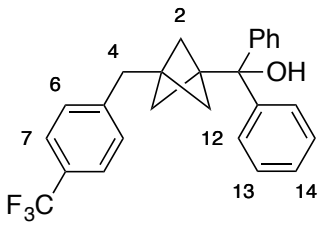
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.6, 141.7, 128.3 (q, *J* = 32.2 Hz), 128.2, 127.5, 126.0, 125.3 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.8 Hz), 73.9, 48.0, 43.9, 40.2, 39.2.

^{19}F NMR (377 MHz, $CDCl_3$) δ –62.23.

HRMS (ESI^-) Found $[M^-H]^-$ = 331.1317; $C_{20}H_{18}OF_3$ requires 331.1315.

IR (film) ν_{max}/cm^{-1} 3406, 2967, 1324, 1255, 1162, 1118, 1066, 1019.

Diphenyl(3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentan-1-yl)methanol, 266



Adapted from the procedure described by Messner et al. [40] To a solution of **198** (50 mg, 0.14 mmol, 1.0 equiv.) in Et_2O (0.5 mL) at –78 °C was added *tert*-BuLi (0.18 mL, 1.7 M in pentane, 0.31 mmol, 2.2 equiv.) dropwise. The resulting yellow solution was stirred for 1 h at –78 °C, then a solution of benzophenone (78 mg, 0.43 mmol, 3.0 equiv.) in Et_2O (0.5 mL) was added at –78 °C. The resulting solution was stirred at –78 °C for 30 min, at rt for 12 h and then quenched with NH_4Cl (2 mL, 1 M aq.,). The aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organics were washed with $NaHCO_3$ (3 mL, aq., sat.), and brine, and then dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / Et_2O, 1:0 to 1:1) gave **266** (49 mg, 0.12 mmol, 83%) as a colourless oil.

R_f = 0.21 (pentane / Et_2O, 8:2)

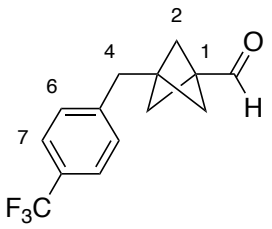
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, *J* = 8.0 Hz, 2H), 7.45–7.39 (m, 4H), 7.31–7.23 (m, 4H), 7.23–7.17 (m, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 2.80 (s, 2H), 2.12 (s, 1H), 1.65 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.0, 143.4, 129.3, 127.9, 127.0, 128.4 (q, *J* = 32.4 Hz).126.9, 125.4 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.8 Hz).49.2, 47.6, 40.4, 39.0.

HRMS (ESI^-) Found $[M^-H]^-$ = 407.1631; $C_{26}H_{22}OF_3$ requires 407.1628

IR (film) ν_{max}/cm^{-1} 3472, 3059, 2969, 2910, 2873, 1323, 1163, 1118, 1066.

3-(4-(Trifluoromethyl)benzyl)bicyclo[1.1.1]pentane-1-carbaldehyde, 267



Adapted from the procedure described by Messner et al.[40] To a solution of **198** (50 mg, 0.14 mmol, 1.0 equiv.) in Et_2O (0.5 mL) at –78 °C was added *tert*-BuLi (0.18 mL, 1.7 M in pentane, 0.31 mmol, 2.2 equiv.) dropwise. The resulting yellow solution was stirred for 1 h at –78 °C, and then added dropwise by syringe into a stirred solution of ethyl formate (34 μL, 0.43 mmol, 3.0 equiv.) in Et_2O (0.5 mL) at –78 °C. The resulting solution was stirred at –78 °C for 1 h, and then quenched with HCl (1 mL, 1 M aq.). The aqueous phase was extracted with Et_2O (3 × 3 mL). The combined organics were washed with $NaHCO_3$ (3 mL, aq., sat.) and brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / Et_2O, 8:2) gave **267** as a pale yellow oil (27 mg, 0.11 mmol, 74%).

R_f = 0.31 (pentane / Et_2O, 8:2)

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (1H, s, C*H*O), 7.55 (2H, d, *J* = 8.0 Hz, H7), 7.20 (2H, d, *J* = 8.0 Hz, H6), 2.87 (2H, s, H4), 1.86 (6H, s, H2).

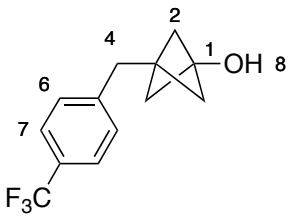
^{13}C NMR (126 MHz, CDCl3) δ 198.8, 142.7, 129.3, 128.7 (q, *J* = 32.4 Hz), 125.5 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 271.8 Hz), 50.4, 44.9, 40.9, 38.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ –62.32.

HRMS (EI^+) Found $[M+H]^+$ = 255.0995; $C_{14}H_{14}OF_3$ requires 255.0991.

IR (film) ν_{max}/cm^{-1} 2977, 1711, 1323, 1163, 1116, 1066, 1019.

3-(4-(Trifluoromethyl)benzyl)bicyclo[1.1.1]pentan-1-ol, 268



To a solution of **198** (50 mg, 0.142 mmol, 1.0 equiv.) in PhMe/THF (4:1, 1 mL) at –78°C was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (32 µL, 0.156 mmol, 1.1 equiv.) and dropwise *t*BuLi (96 µL, 1.7 M in pentane, 0.163 mmol, 1.15 equiv.). After stirring for 1 h, the reaction mixture was quenched with H_2O (1 mL), extracted three times with Et_2O, dried ($MgSO_4$) and concentrated. The residue dissolved with THF/H_2O (1:1, 2.8 mL) and sodium perborate monohydrate (43 mg, 0.426 mmol, 3 equiv.) was added at rt. After stirring for 21 h, the reaction mixture was quenched with H_2O (2 mL), extracted three times with Et_2O, dried ($MgSO_4$) and concentrated. Purification by column chromatography (SiO_2, pentane / Et_2O, 7:3) gave **268** (21 mg, 0.87 mmol, 61%) as a colourless oil.

R_f = 0.47 (pentane / Et_2O, 1:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (2H, d, *J* = 7.9 Hz, H7), 7.19 (2H, d, *J* = 7.9 Hz, H6), 2.91 (2H, s, H4), 2.41 (1H, br s, H8), 1.73 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 129.3, 128.6 (q, *J* = 32.1 Hz), 125.4 (q, *J* = 3.9 Hz), 124.5 (q, *J* = 271.7 Hz), 63.6, 53.8, 36.4, 31.3.

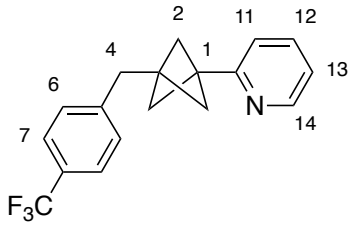
^{19}F NMR (376 MHz, $CDCl_3$) δ −62.30.

HRMS (EI^+) Found $[M]^+$ = 242.0912; $C_{13}H_{13}F_3O$ requires 242.0913.

IR (film) ν_{max}/cm^{-1} 3278, 2974, 1323, 1246, 1114, 1065.

Synthesised and characterised by Dr Carlos Arroniz.

2-(3-(4-(Trifluoromethyl)benzyl)bicyclo[1.1.1]pentan-1-yl)pyridine, 270



Adapted from the procedure described by Messner et al.[40] To a solution of **198** (106 mg, 0.300 mmol, 1.0 equiv.) in Et_2O (1 mL) at –78 °C was added *tert*-BuLi (0.45 mL, 1.7 M in pentane, 0.75 mmol, 2.5 equiv.) dropwise. The resulting yellow solution was stirred for 1 h at –78 °C, then $ZnCl_2$ (0.40 mL, 1.9 M in 2-MeTHF, 0.75 mmol, 2.5 equiv.) was added dropwise. The resulting mixture was warmed to 0 °C and stirred for 30 min. In a separate vessel was added Pd(dppf)Cl_2 (11 mg, 15 μmol, 5 mol%), 2-bromopyridine (60 μL, 0.63 mmol, 2.1 equiv.) and THF (1 mL). The resulting suspension was sonicated for 3 min and added quickly to the stirred solution of the organozinc reagent at 0 °C. The solution turned dark green instantly. The vial was heated at 60 °C for 15 h (upon heating, the solution quickly turned olive green, then yellow). After this time, the reaction mixture was cooled to rt and quenched with NH_4Cl (2 mL, aq., sat.). The aqueous phase was extracted with EtOAc (3 × 5 mL), and the combined organics were washed with NH_4Cl (5 mL, aq., sat.), and brine, then they were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane / EtOAc, 1:0 to 0:1) gave **270** as an orange waxy solid (57 mg, 0.188 mmol, 64%).

$\mathbf{R_f}$ = 0.10 (pentane / EtOAc, 9:1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (1H, ddd, *J* = 4.9, 1.8, 1.0 Hz, H14), 7.60–7.53 (3H, m, H7, H12), 7.25 (2H, d, *J* = 7.6 Hz, H6), 7.14–7.06 (2H, m, H11, H13), 2.93 (2H, s, H4), 1.97 (6H, s, H2).

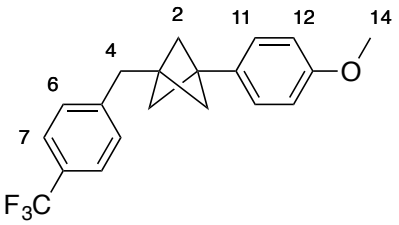
^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 149.4, 143.6, 136.3, 129.4, 128.4 (q, J = 32.3 Hz), 125.3 (q, J = 3.8 Hz), 124.5 (q, J = 271.8 Hz), 121.6, 120.7, 51.9, 43.3, 39.2, 38.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ -62.27.

HRMS (ESI^+) Found $[M+H]^+$ = 304.1306; $C_{18}H_{17}NF_3$ requires 304.1308.

IR (film) ν_{max}/cm^{-1} 2969, 1589, 1323, 1268, 1163, 1116, 1066, 1019.

1-(4-Methoxyphenyl)-3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentane, 290



Compound **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and 4-$MeOC_4H_6MgBr$ (0.92 mL, 0.87 M in THF, 0.8 mmol, 1.6 equiv.) were submitted to **General Procedure 8** at rt. Purification by column chromatography (SiO_2, pentane / Et_2O, 1:0 to 9:1) gave **290** (118 mg, 0.355 mmol, 71%) as a colourless oil.

R_f = 0.12 (pentane)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (2H, d, *J* = 7.9 Hz, H7), 7.27–7.22 (2H, m, H6), 7.11–7.06 (2H, m, H11), 6.84–6.78 (2H, m, H12), 3.78 (3H, s, H14), 2.90 (2H, s, H4), 1.84 (6H, s, H2).

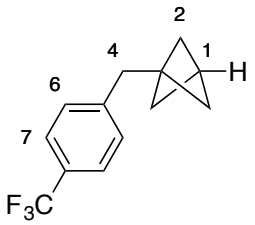
^{13}C NMR (126 MHz, $CDCl_3$) δ 158.4, 143.9, 133.5, 129.4, 128.4 (q, *J* = 32.3 Hz), 127.2, 125.3 (q, *J* = 3.8 Hz), 124.6 (q, *J* = 271.7 Hz), 113.7, 55.4, 52.3, 42.2, 39.1, 38.8.

^{19}F NMR (471 MHz, $CDCl_3$) δ –62.22.

HRMS (CI^+) Found $[M+H]^+$ = 333.1463; $C_{20}H_{20}OF_3$ requires 333.1461.

IR (film) ν_{max}/cm^{-1} 2965, 2867, 2871, 1615, 1517, 1317, 1244, 1161, 1115, 1062, 1040.

1-(4-(Trifluoromethyl)benzyl)bicyclo[1.1.1]pentane, 291



Adapted from the procedure described by Messner et al.[40] To a solution of **198** (176 mg, 0.50 mmol, 1.0 equiv.) in Et_2O (1.76 mL) at –78 °C was added *tert*-BuLi (0.65 mL, 1.7 M in pentane, 1.1 mmol, 2.2 equiv.) dropwise. The resulting yellow solution was stirred for 1 h at –78 °C, quenched with NH_4Cl (aq., sat., 1 mL) at this temperature, and was allowed to warm to rt. Water (5 mL) and Et_2O (5 mL) were added and the phases were separated. The aqueous was extracted with Et_2O (2 × 5 mL) and the combined organics were washed with $NaHCO_3$ (aq., sat., 5 mL) and brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane) gave **291** as a colourless oil (44 mg, 0.195 mmol, 39%).

R_f = 0.73 (pentane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.48 (2H, m, H7), 7.24–7.16 (2H, m, H6), 2.78 (2H, s, H4), 2.48 (1H, s, H1), 1.62 (6H, s, H2).

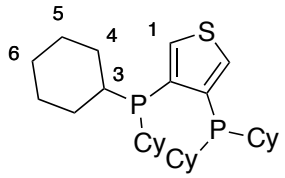
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.8, 129.2, 128.5, 128.5, 128.1 (q, J = 32.1 Hz), 125.8, 125.1 (q, J = 3.7 Hz), 124.5 (q, J = 271.8 Hz), 123.1, 120.4, 50.2, 45.0, 39.8, 28.2.

IR (film) ν_{max}/cm^{-1} 2966, 2908, 2871, 1675, 1325, 1163, 1125, 1067.

HRMS [ESI$^+$, EI$^+$, CI$^+$] Not found.

Synthesised and characterised by Ms Bethany Shire.

3,4-Bis(dicyclohexylphosphaneyl)thiophene, 293



According to the procedure of Takise et al.[41] To a solution of 3,4-dibromothiophene (0.11 mL, 1.00 mmol, 1.0 equiv.) in Et_2O (1 mL) at –78 °C was added *n*BuLi (0.4 mL, 2.5 M in hexane, 1.00 mmol, 1.0 equiv.) dropwise. The resulting mixture was stirred at this temperature for 1 h and a solution of chloro-dicyclohexylphosphine (0.23 mL, 1.05 mmol, 1.05 equiv.) in Et_2O (0.5 mL) was added dropwise. The resulting mixture was stirred for 30 min at –78 °C and *n*BuLi (0.4 mL, 2.5 M in hexane, 1.00 mmol, 1.0 equiv.) was added dropwise. After stirring for at –78 °C for 1 h, a solution of chlorodicyclohexylphosphine (0.23 mL, 1.05 mmol, 1.05 equiv.) in Et_2O (0.5 mL) was added dropwise. The mixture was stirred at –78 °C for 30 min, warmed to rt and quenched with water (5 mL). The phases were separated, the aqueous was extracted with Et_2O (3 × 5 mL), and the combined organics were washed with brine (10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue was dissolved in toluene (0.1 mL), MeOH (5 mL) was added and the resulting biphasic mixture was shaken and left to stand for 2 h, after which a white residue had solidified. The mixture was sonicated for 5 min and the suspension filtered. The white solid was dried under a steam of N_2, giving **293** (304 mg, 0.637, 63%).

R_f = 0.10 (pentane)

m.p. = 112–113 °C

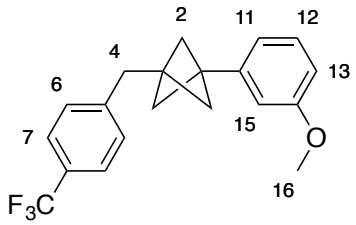
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (2H, s, H1), 1.94–1.81 (8H, m, H3, H4), 1.79–1.53 (16H, m, H4, H5), 1.35–0.97 (20H, m, H5, H6).

^{13}C NMR (126 MHz, $CDCl_3$) δ 142.0–141.3 (m), 128.6, 34.6 (t, *J* = 5.2 Hz), 30.3 (t, *J* = 8.3 Hz), 29.1 (t, *J* = 4.4 Hz), 27.7–27.1 (m), 26.6.

^{31}P NMR (162 MHz, $CDCl_3$) δ -21.0.

MS (ESI^+) 477.2 (M+H).

1-(3-Methoxyphenyl)-3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentane, 294



Compound **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and 3-$MeOC_4H_6MgBr$ (0.80 mL, 1 M in THF, 0.80 mmol, 1.6 equiv.) were submitted to **General Procedure 8** at rt. Purification by column chromatography (SiO_2, pentane / Et_2O, 98:2) gave **294** (135 mg, 0.406 mmol, 81%) as a colourless oil.

R_f = 0.14 (pentane / Et_2O, 98:2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 8.0 Hz, H7), 7.26 (2H, d, *J* = 8.1 Hz, H6), 7.20 (1H, t, *J* = 7.8 Hz, H12), 6.79–6.73 (2H, m, H11, H13), 6.73–6.70 (1H, m, H15), 3.79 (3H, s, H16), 2.92 (2H, s, H4), 1.88 (6H, s, H2).

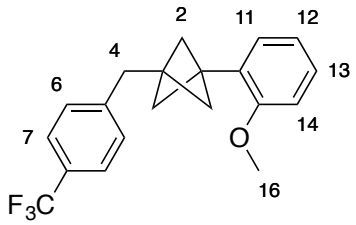
^{13}C{^{19}F} NMR (126 MHz, $CDCl_3$) δ 159.7, 143.7, 142.8, 129.4, 129.3, 128.4, 125.3, 124.6, 118.5, 111.9, 111.8, 55.3, 52.2, 42.6, 39.0, 38.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.21.

HRMS (CI^+) Found $[M+H]^+$ = 333.1462; $C_{20}H_{20}OF_3$ requires 333.1461.

IR (film) ν_{max}/cm^{-1} 2963, 2907, 2868, 1604, 1582, 1323, 1285, 1161, 1117, 1066.

1-(2-Methoxyphenyl)-3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentane, 295



Compound **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and 2-$MeOC_4H_6MgBr$ (0.80 mL, 1 M in THF, 0.80 mmol, 1.6 equiv.) were submitted to **General Procedure 8** at 45 °C. Purification by column chromatography (SiO_2, pentane / Et_2O, 98:2) gave **295** (120 mg, 0.361 mmol, 72%) as a white solid.

R_f = 0.21 (pentane / Et_2O, 98:2)

m.p. = 78–81 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 8.0 Hz, H7), 7.26 (2H, d, *J* = 7.9 Hz, H6), 7.19 (1H, *J* = 8.2, 7.4, 1.8 Hz, H13), 7.03 (1H, dd, *J* = 7.4, 1.8 Hz, H11), 6.87 (1H, td, *J* = 7.4, 1.1 Hz, H12), 6.81 (1H, dd, *J* = 8.2, 1.1 Hz, H14), 3.79 (3H, s, H16), 2.91 (2H, s, H4), 1.95 (6H, s, H2).

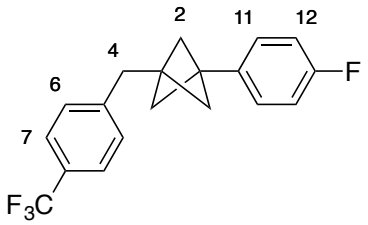
^{13}C{^{19}F} NMR (126 MHz, $CDCl_3$) δ 158.9, 144.0, 129.4, 128.8, 128.4, 128.2, 128.0, 125.3, 124.6, 120.2, 110.5, 55.2, 52.2, 41.1, 40.3, 39.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.17.

HRMS (CI^+) Found $[M+H]^+$ = 333.1463; $C_{20}H_{20}OF_3$ requires 333.1461.

IR (film) ν_{max}/cm^{-1} 2965, 2909, 2869, 1617, 1492, 1323, 1244, 1161, 1115, 1066.

1-(4-Fluorophenyl)-3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentane, 296



Compound **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and 4-FC_4H_6MgBr (0.40 mL, 2 M in THF, 0.80 mmol, 1.6 equiv.) were submitted to **General Procedure 8** at rt. Purification by column chromatography (SiO_2, pentane) gave **296** (114 mg, 0.356 mmol, 72%) as a white solid.

R_f = 0.57 (pentane)

m.p. = 67–68 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (2H, d, *J* = 7.9 Hz, H7), 7.28 (2H, *J* = 8.1 Hz, H6), 7.17–7.12 (2H, m, H11), 7.01–6.95 (2H, m, H12), 2.94 (2H, s, H4), 1.89 (6H, s, H2).

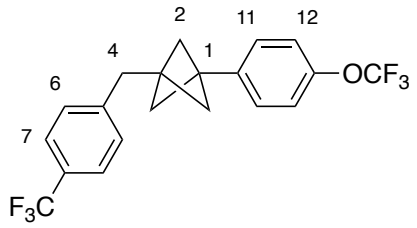
^{13}C NMR (126 MHz, $CDCl_3$) δ 161.8 (d, *J* = 244.2 Hz), 143.7, 136.9 (d, *J* = 3.0 Hz), 129.4, 128.4 (q, *J* = 32.3 Hz), 127.7 (d, *J* = 7.8 Hz), 125.3 (q, *J* = 3.7 Hz), 124.6 (q, *J* = 271.8 Hz), 115.0 (d, *J* = 21.1 Hz), 52.3, 42.0, 39.0, 38.8.

^{19}F NMR (376 MHz, $CDCl_3$) δ –62.3, –116.61 (tt, *J* = 8.9, 5.5 Hz).

HRMS (CI^+) Found $[M+H]^+$ = 321.1265; $C_{19}H_{17}F_4$ requires 321.1261.

IR (film) ν_{max}/cm^{-1} 2966, 2907, 2870, 1618, 1519, 1504, 1323, 1267, 1221, 1162, 1118, 1066.

1-(4-(Trifluoromethoxy)phenyl)-3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentane, 297



Compound **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and 4-$(F_3CO)C_4H_6MgBr$ (2.22 mL, 0.36 M in THF, 0.80 mmol, 1.6 equiv.) were submitted to **General Procedure 8** at rt. Purification by column chromatography (SiO_2, pentane / Et_2O, 98:2) gave **297** (123 mg, 0.318 mmol, 63%) as a white solid.

R_f = 0.32 (pentane / Et_2O, 98:2)

m.p. = 59–60 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (2H, d, *J* = 7.9 Hz, H7), 7.25 (2H, d, *J* = 8.0 Hz, H6), 7.19–7.14 (2H, m, H11), 7.14–7.09 (2H, m, H12), 2.92 (2H, s, H4), 1.88 (6H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.9, 143.6, 139.9, 129.4, 128.5 (q, *J* = 32.3 Hz), 127.5, 125.4 (q, *J* = 3.8 Hz), 124.6 (d, *J* = 271.7 Hz), 120.9, 120.7 (q, *J* = 256.7 Hz), 52.3, 42.0, 38.9.

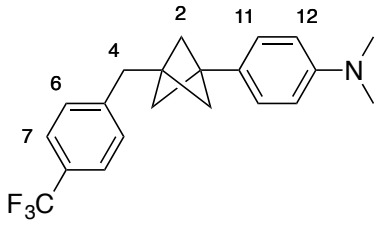
^{13}C{^{19}F} NMR (126 MHz, $CDCl_3$) δ 147.9, 143.6, 139.9, 129.4, 128.5, 127.5, 125.4, 124.6, 120.9, 120.7, 52.3, 42.0, 38.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ –57.92, –62.24.

HRMS (CI^+) Found $[M+H]^+$ = 387.1175; $C_{20}H_{17}OF_6$ requires 387.1178.

IR (film) ν_{max}/cm^{-1}2967, 2871, 1326, 1261, 1224, 1162, 1124, 1067, 1020.

_N,N_-Dimethyl-4-(3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentan-1-yl)aniline, 298



Compound **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and 4-$(Me_2N)C_4H_6MgBr$ (1.6 mL, 0.5 M in THF, 0.80 mmol, 1.6 equiv.) were submitted to **General Procedure 8** at rt. Purification by column chromatography (SiO_2, pentane / Et_2O, 1:0 to 8:2) gave **298** (116 mg, 0.336 mmol, 68%) as a white solid.

R_f = 0.47 (pentane / Et_2O, 96:4)

m.p. = 123–124 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (2H, d, *J* = 8.0 Hz, H7), 7.27 (2H, d, *J* = 7.6 Hz, H6), 7.11 – 7.05 (2H, m, H11), 6.73–6.67 (2H, m, H12), 2.92 (6H, d, *J* = 1.1 Hz, H14), 2.91 (2H, s, H4), 1.85 (6H, app d, *J* = 1.2 Hz, H2).

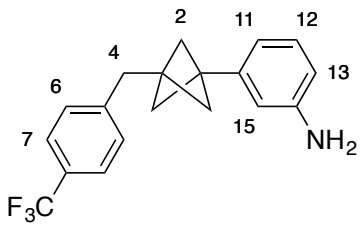
^{13}C NMR (126 MHz, $CDCl_3$) δ 149.6, 144.0, 129.5, 129.4, 128.3 (q, *J* = 32.2 Hz), 126.8, 125.3 (q, *J* = 3.9 Hz), 124.6 (q, *J* = 271.6 Hz), 52.2, 42.2, 41.0, 39.2, 38.7.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.19.

HRMS (ESI^+) Found $[M+H]^+$ = 346.1774; $C_{21}H_{23}NF_3$ requires 346.1777.

IR (film) ν_{max}/cm^{-1} 2969, 2906, 2869, 1614, 1525, 1323, 1157, 1114, 1066.

3-(3-(4-(Trifluoromethyl)benzyl)bicyclo[1.1.1]pentan-1-yl)aniline, 299



Compound **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and 3-$((Me_3Si)_2N)C_4H_6MgBr$ (0.80 mL, 1.0 M in THF, 0.80 mmol, 1.6 equiv.) were submitted to **General Procedure 8** at rt. Purification by column chromatography (SiO_2, pentane / Et_2O, 1:0 to 0:1) gave **299** (141 mg, 0.444 mmol, 88%) as a yellow solid.

R_f = 0.36 (pentane / Et_2O, 6:4)

m.p. = 86–92 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.54 (2H, m, H7), 7.30–7.23 (2H, m, H6), 7.08 (1H, t, *J* = 7.7 Hz, H12), 6.60 (1H, dt, *J* = 7.6, 1.2 Hz, H11), 6.54 (1H, ddd, *J* = 7.9, 2.4, 1.0 Hz, H13), 6.52 – 6.50 (1H, m, H15), 3.48 (2H, br. s, NH_2), 2.92 (2H, s, H4), 1.85 (6H, s, H2).

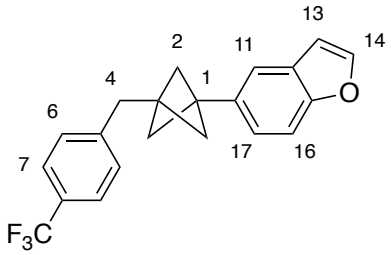
^{13}C{^{19}F} NMR (126 MHz, $CDCl_3$) δ 146.3, 143.8, 142.3, 129.3, 129.2, 128.3, 125.3, 124.6, 116.4, 113.4, 112.9, 52.1, 42.5, 39.0, 38.7.

^{19}F NMR (471 MHz, $CDCl_3$) δ –62.15.

HRMS (ESI^+) Found $[M+H]^+$ = 318.1464; $C_{19}H_{19}NF_3$ requires 318.1464.

IR (film) ν_{max}/cm^{-1} 3374, 2963, 2906, 2867, 1618, 1325, 1118, 1089, 1066.

5-(3-(4-(Trifluoromethyl)benzyl)bicyclo[1.1.1]pentan-1-yl)benzofuran, 300



Compound **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and benzofuran-5-ylmagnesium bromide (1.67 mL, 0.48 M in THF, 0.80 mmol, 1.6 equiv., [made according to **General Procedure 7** with 5-bromobenzofuran (0.313 mL, 2.50 mmol, 1.0 equiv.), and Mg (182 mg, 7.50 mmol, 3 equiv.) at reflux for 5 h]) were submitted to **General Procedure 8** at rt. Purification by column chromatography (SiO_2, pentane) gave **300** (88.7 mg, 0.259 mmol, 51%) as a white solid.

R_f = 0.26 (pentane)

m.p. = 84–85 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.55 (2H, m, H7, H14), 7.40 (1H, dt, *J* = 8.4, 0.8 Hz, H16), 7.38 (1H, d, *J* = 1.7 Hz, H11), 7.27 (2H, d, *J* = 7.9 Hz, H6), 7.12 (1H, dd, *J* = 8.4, 1.8 Hz, H17), 6.71 (1H, dd, *J* = 2.2, 0.9 Hz, H13), 2.93 (s, 2H), 1.91 (s, 7H).

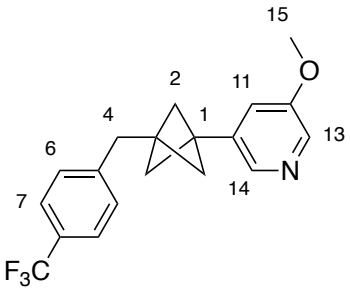
^{13}C{^{19}F} NMR (126 MHz, $CDCl_3$) δ 154.0, 145.4, 143.8, 135.9, 129.4, 128.4, 127.4, 125.3, 124.6, 122.6, 118.5, 111.0, 106.6, 52.4, 42.7, 39.0, 38.7.

^{19}F NMR (471 MHz, $CDCl_3$) δ –62.19.

HRMS (ESI^+) Found $[M+H]^+$ = 343.1300; $C_{21}H_{18}OF_3$ requires 343.1304.

IR (film) ν_{max}/cm^{-1}2962, 2902, 2866, 1329, 1273, 1146, 1122, 1067.

3-Methoxy-5-(3-(4-(trifluoromethyl)benzyl)bicyclo[1.1.1]pentan-1-yl)pyridine, 301



Compound **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and (5-methoxypyridin-3-yl)magnesium bromide lithium chloride complex (1.67 mL, 0.48 M in THF, 0.80 mmol, 1.6 equiv., [made according to **General Procedure 7** with 3-bromo-5-methoxypyridine (940 mg, 5.00 mmol, 1.0 equiv.), Mg (365 mg, 15.0 mmol, 3 equiv.) and LiCl (318 mg, 7.50 mmol, 1.5 equiv.) at 0 °C for 2 h]) were submitted to **General Procedure 8** at rt. Purification by column chromatography (SiO_2, pentane) gave **301** (103 mg, 0.309 mmol, 61%) as a colourless oil.

R_f = 0.53 (pentane / EtOAc, 1:1)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (1H, d, *J* = 2.8 Hz, H13), 8.03 (1H, d, *J* = 1.7 Hz, H14), 7.55 (2H, d, *J* = 8.0 Hz, H7), 7.23 (2H, d, *J* = 8.0 Hz, H6), 6.93 (1H, dd, *J* = 2.9, 1.7 Hz, H11), 3.81 (3H, s, H15), 2.91 (2H, s, H4), 1.90 (6H, s, H2).

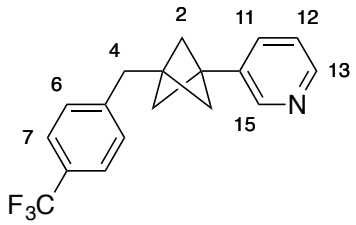
^{13}C NMR (126 MHz, $CDCl_3$) δ 155.5, 143.4, 140.3, 136.9, 135.6, 129.3, 128.5 (q, *J* = 32.3 Hz), 125.4 (q, *J* = 3.8 Hz), 124.5 (q, *J* = 271.8 Hz), 118.3, 55.6, 52.2, 40.4, 39.5, 38.9.

^{19}F NMR (377 MHz, $CDCl_3$) δ –62.24.

HRMS (ESI^+) Found $[M+H]^+$ = 334.1414; $C_{19}H_{19}ONF_3$ requires 334.1413.

IR (film) ν_{max}/cm^{-1}2966, 1590, 1418, 1324, 1275, 1163, 1118, 1066.

3-(3-(4-(Trifluoromethyl)benzyl)bicyclo[1.1.1]pentan-1-yl)pyridine, 270



To a solution of **198** (176 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), and TMEDA (30 μL, 0.200 mmol, 40 mol%) in THF (0.5 mL) at 65 °C was added rapidly pyridin-3-ylmagnesium bromide lithium chloride complex (2.42 mL, 0.33 M in THF, 0.80 mmol, 1.6 equiv., [made according to **General Procedure 7** with 3-bromopyridine (481 μL, 5.00 mmol, 1.0 equiv.), Mg (365 mg, 15.0 mmol, 3 equiv.) and LiCl (318 mg, 7.50 mmol, 1.5 equiv.) at 0 °C for 2 h]). The reaction was quenched with NH_4Cl (aq., sat., 2 mL) and the phases were separated. The aqueous was extracted with EtOAc (3 × 5 mL) and the combined organics were washed with brine (5 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (SiO_2, pentane) gave **270** (67.9 mg, 0.224 mmol, 44%) as a colourless oil.

R_f = 0.45 (pentane / EtOAc, 1:1)

m.p. = 60–63 °C

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.4 (2H, br. s, H13, H14), 7.6 (2H, d, *J* = 8.0 Hz, H7), 7.4 (1H, dt, *J* = 7.8, 2.0 Hz, H11), 7.2 (2H, d, *J* = 8.0 Hz, H6), 7.2 (1H, dd, *J* = 7.8, 4.8 Hz, H12), 2.9 (2H, s, H4), 1.9 (6H, s, H2).

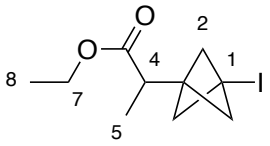
^{13}C{^{19}F} NMR (126 MHz, $CDCl_3$) δ 148.0, 147.8, 143.4, 136.1, 133.7, 129.3, 128.5, 125.4, 124.5, 123.1, 52.2, 40.5, 39.5, 38.9.

^{19}F NMR (471 MHz, $CDCl_3$) δ –62.24.

HRMS (ESI^+) Found $[M+H]^+$ = 304.1307; $C_{18}H_{17}NF_3$ requires 304.1308.

IR (film) ν_{max}/cm^{-1} 2966, 2910, 2870, 1618, 1416, 1313, 1268, 1159, 1116, 1066.

Ethyl 2-(3-iodobicyclo[1.1.1]pentan-1-yl)propanoate, 305



Ethyl 2-iodopropionate (0.340 mL, 2.50 mmol, 1.0 equiv.), TCP (4.10 mL, 0.79 M in Et_2O, 3.25 mmol, 1.3 equiv.) and BEt_3 (0.25 mL, 1 M in hexane, 0.25 mmol, 10 mol%) were submitted to **General Procedure 1** at 0 °C for 15 min. Purification by column chromatography (SiO_2, pentane / Et_2O, 95:5) gave **305** (593 mg, 2.02 mmol, 80%) as a colourless oil.

R_f = 0.12 (pentane / Et_2O, 96:4)

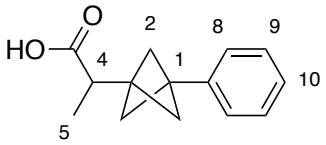
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.2–4.1 (2H, m, H7), 2.6 (1H, q, *J* = 7.1 Hz, H4), 2.2 (6H, s, H2), 1.2 (3H, t, *J* = 7.1 Hz, H8), 1.1 (3H, d, *J* = 7.1 Hz, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 60.6, 59.4, 48.6, 41.6, 14.5, 13.9, 6.3.

HRMS (EI) Found $[M–OC_2H_5]^+$ = 248.9779; $C_8H_{10}IO$ requires 248.9780.

IR (film) ν_{max}/cm^{-1} 2978, 2916, 2879, 1731, 1455, 1375, 1334, 1256, 1177, 1150.

2-(3-Phenylbicyclo[1.1.1]pentan-1-yl)propanoic acid, 302



Compound **309** (147 mg, 0.500 mmol, 1.0 equiv.), $Fe(acac)_3$ (35.3 mg, 0.100 mmol, 20 mol%), TMEDA (30 μL, 0.200 mmol, 40 mol%) and PhMgBr (0.80 mL, 1.0 M in THF, 0.80 mmol, 1.6 equiv.) were submitted to **General Procedure 8** at rt. Water (2 mL) was added and the aqueous was extracted with Et_2O (3 × 2 mL). The combined organics were placed in a RBF equipped with a stir bar and NaOH (10% in MeOH) slowly. The resulting mixture was refluxed for 30 min, concentrated *in vacuo*, diluted with water (10 mL) and conc. HCl was added until pH > 1. The aqueous was extracted with Et_2O (2 × 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*, giving **302** (84.6 mg, 0.391 mmol, 78%) as a colourless oil.

R_f = 0.30 (CH_2Cl_2 / MeOH, 98:2)

m.p. = 83–84 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3–7.3 (2H, m, Ar-H), 7.2–7.2 (3H, m, Ar-H), 2.7 (1H, q, *J* = 7.0 Hz, H4), 2.0 (6H, s, H2), 1.2 (3H, d, *J* = 7.0 Hz, H3).

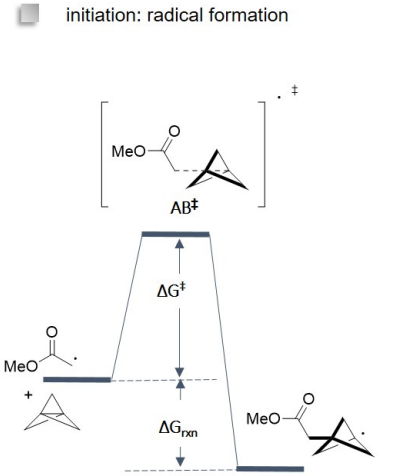
^{13}C NMR (101 MHz, $CDCl_3$) δ 180.2, 140.8, 128.3, 126.6, 126.2, 51.2, 41.1, 40.8, 39.5, 13.5.

HRMS (ESI^-) Found $[M-H]^-$ = 215.1077; $C_{14}H_{15}O_2$ requires 215.1078.

IR (film) ν_{max}/cm^{-1} 2968, 2909 (br.), 2871, 1706, 1459, 1417, 1260, 1230, 1168.

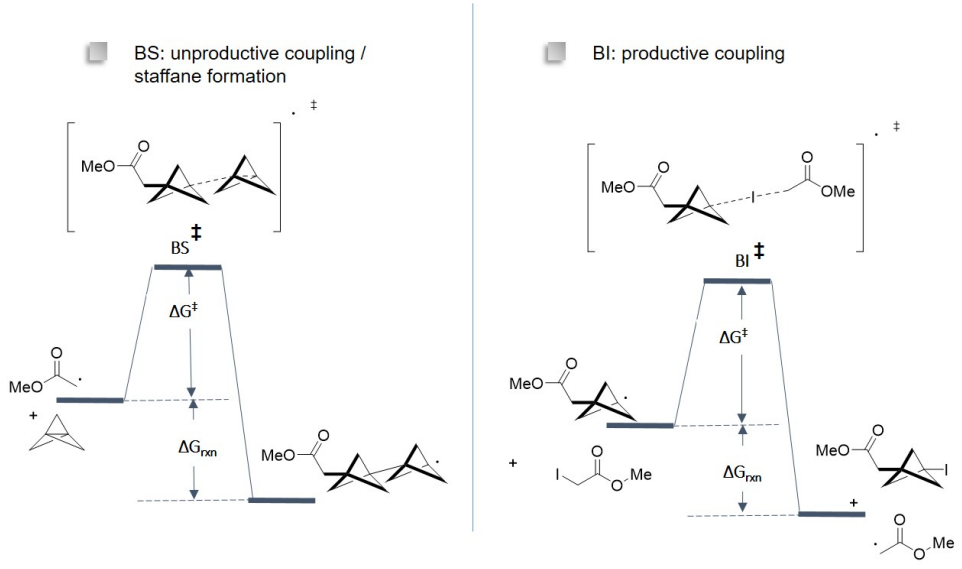
4. Computational details

All calculations were performed using Gaussian 09 software.[35] Structural optimizations and frequency calculations were performed with the (RO)B3LYP,[36] (RO)M06-2x,[37] (RO)ωB97xD[38] functional along with the def2tzvp basis set[39] *in vacuo*. Single point energies have been extracted from the same method / basis set combinations indicated above.



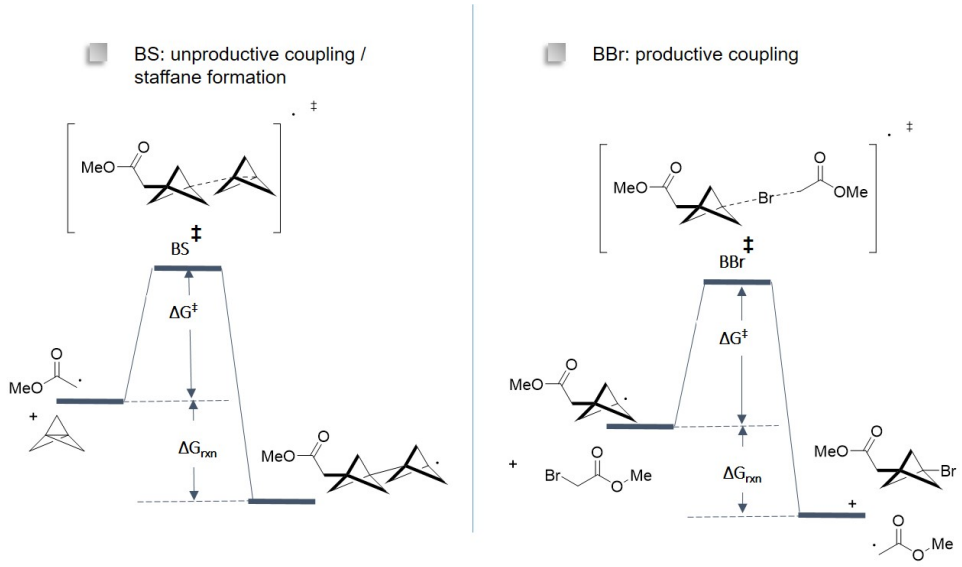
method	ΔG‡	ΔG$_{rxn}$
ROB3LYP	13.9	7.3
ROM062x	12.5	9.5
ROwb97xd	12.6	16.4

Fig S1. Comparison of computed activation barriers and exergonicities for the initiation step of the radical process depending on the method employed. All numbers in kcal/mol.



method	ΔG‡ (BS)	ΔG‡ (BI)	ΔΔG‡ (BS - BI)	ΔG$_{rxn}$ (BS)	ΔG$_{rxn}$ (BI)
ROB3LYP	14.2	7.4	6.8	-20.7	-13.8
ROM062x	13.3	7.3	6.1	-21.4	-14.6
ROwb97xd	12.3	9.0	3.3	-29.6	-16.9

Fig S2. Comparison of computed activation barriers and exergonicities for the propagation step (BI) of the radical process and the sideproduct formation (BS) depending on the method employed. All numbers in kcal/mol.



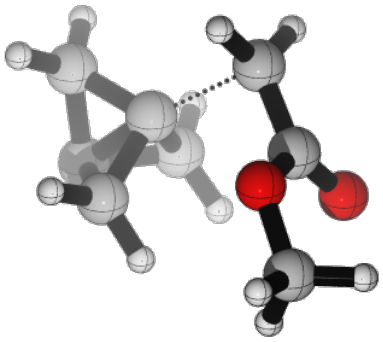
method	ΔG‡ (BS)	ΔG‡ (BBr)	ΔΔG‡ (BS - BBr)	ΔG$_{rxn}$ (BS)	ΔG$_{rxn}$ (BBr)
ROB3LYP	14.2	11.9	2.3	-20.7	-17.3
ROM062x	13.3	12.9	0.4	-21.4	-16.3
ROwb97xd	12.3	15.2	- 2.9	-29.6	-18.3

Fig S3. Comparison of computed activation barriers and exergonicities for the propagation step (BBr) of the radical process and the sideproduct formation (BS) depending on the method employed. All numbers in kcal/mol.

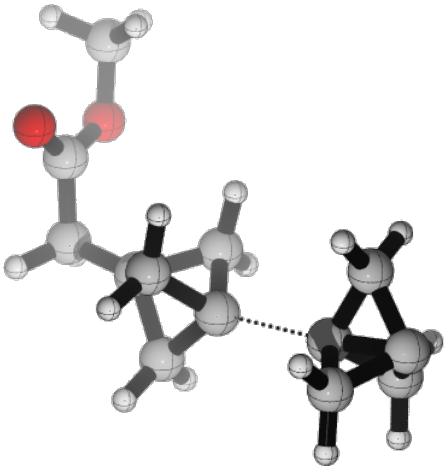
Computed structures

Representation of calculated transition states

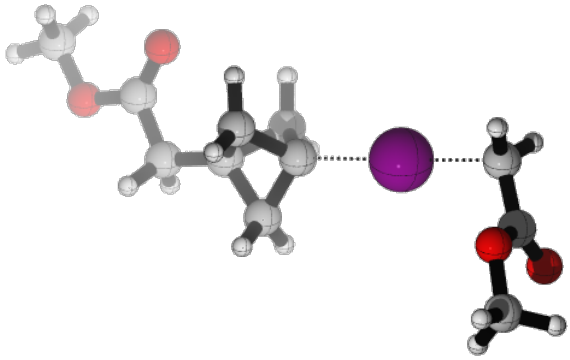
AB‡



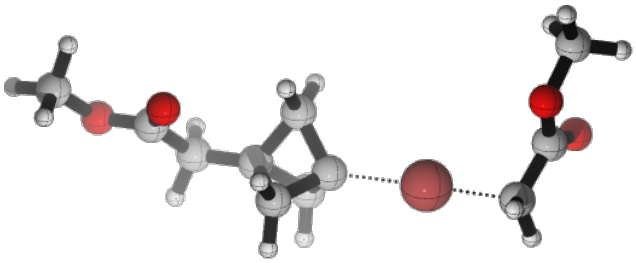
BS‡



BI‡



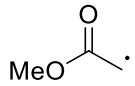
BBr‡



xyz-coordinates and energies of all computed structures

[(acetate-radical)]

i) (RO)B3LYP / def2tzvp

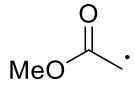


C	-1.784021000	-0.583499000	-0.000003000	O	0.533004000	-0.722805000	0.000116000
H	-2.694796000	-0.005698000	-0.000115000	C	1.824612000	-0.101265000	-0.000081000
H	-1.816427000	-1.662338000	-0.000392000	H	2.542524000	-0.917028000	-0.000479000
C	-0.525261000	0.125935000	0.000094000	H	1.950802000	0.520454000	-0.886480000
O	-0.411190000	1.335009000	-0.000017000	H	1.951406000	0.519959000	0.886614000

```
Zero-point correction=                           0.076066 (Hartree/Particle)
 Thermal correction to Energy=                    0.081850
 Thermal correction to Enthalpy=                  0.082794
 Thermal correction to Gibbs Free Energy=         0.046817
 Sum of electronic and zero-point Energies=          -267.761272
 Sum of electronic and thermal Energies=             -267.755488
 Sum of electronic and thermal Enthalpies=           -267.754544
 Sum of electronic and thermal Free Energies=        -267.790521

E[(RO)B3LYP/def2TZVP] = -267.837337601
```

ii) (RO)M06-2x / def2tzvp

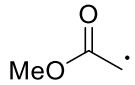


C	-1.786969000	-0.570050000	0.000001000	O	0.526442000	-0.726214000	0.000015000
H	-2.687771000	0.020613000	-0.000071000	C	1.808247000	-0.106046000	-0.000015000
H	-1.824839000	-1.646983000	-0.000002000	H	2.531575000	-0.915996000	-0.000205000
C	-0.516315000	0.126350000	0.000004000	H	1.928330000	0.517134000	-0.885758000
O	-0.389637000	1.327073000	0.000007000	H	1.928498000	0.516838000	0.885918000

```
Zero-point correction=                           0.077087 (Hartree/Particle)
 Thermal correction to Energy=                    0.082866
 Thermal correction to Enthalpy=                  0.083810
 Thermal correction to Gibbs Free Energy=         0.047694
 Sum of electronic and zero-point Energies=          -267.638577
 Sum of electronic and thermal Energies=             -267.632798
 Sum of electronic and thermal Enthalpies=           -267.631854
 Sum of electronic and thermal Free Energies=        -267.667970

E[(RO)M06-2x/def2TZVP] = -267.715663649
```

iii) (RO)ωB97xD / def2tzvp



C	-1.781130000	-0.578062000	-0.000002000	O	0.529320000	-0.719964000	0.000009000
H	-2.688672000	0.005155000	0.000015000	C	1.812001000	-0.104547000	-0.000002000
H	-1.816844000	-1.656978000	-0.000030000	H	2.532718000	-0.917955000	0.000096000
C	-0.518224000	0.125866000	0.000001000	H	1.940591000	0.516951000	-0.886561000
O	-0.402344000	1.329483000	-0.000002000	H	1.940521000	0.517135000	0.886437000

```
Zero-point correction=                           0.076495 (Hartree/Particle)
 Thermal correction to Energy=                    0.082500
 Thermal correction to Enthalpy=                  0.083445
 Thermal correction to Gibbs Free Energy=         0.046240
 Sum of electronic and zero-point Energies=          -267.665908
 Sum of electronic and thermal Energies=             -267.659903
 Sum of electronic and thermal Enthalpies=           -267.658959
 Sum of electronic and thermal Free Energies=        -267.696164

E[(RO)wB97xD/def2TZVP] = -267.742403375
```

[tcp]

i) (RO)B3LYP / def2tzvp

C	-0.854051000	-0.975927000	-0.000222000	H	1.664902000	-1.260826000	-0.000242000
C	0.000017000	-0.000052000	-0.782989000	C	-0.418366000	1.227408000	-0.000209000
H	-1.924401000	-0.811153000	-0.000193000	H	0.259239000	2.072138000	-0.000461000
H	-0.548666000	-2.014944000	-0.000201000	H	-1.471011000	1.482035000	-0.000238000
C	1.272366000	-0.251483000	-0.000208000	C	0.000134000	0.000079000	0.783927000
H	2.019345000	0.532600000	-0.000464000				

```
Zero-point correction=                           0.093075 (Hartree/Particle)
 Thermal correction to Energy=                    0.097056
 Thermal correction to Enthalpy=                  0.098000
 Thermal correction to Gibbs Free Energy=         0.066775
 Sum of electronic and zero-point Energies=           -193.986565
 Sum of electronic and thermal Energies=              -193.982584
 Sum of electronic and thermal Enthalpies=            -193.981640
 Sum of electronic and thermal Free Energies=         -194.012865

E[(RO)B3LYP/def2TZVP] = -194.059299611
```

ii) (RO)M06-2x / def2tzvp

C	0.982367000	0.841060000	-0.000210000	H	-1.457815000	1.485622000	-0.000211000
C	-0.000020000	0.000306000	-0.771841000	C	0.237405000	-1.271206000	-0.000182000
H	2.015339000	0.518157000	-0.000123000	H	-0.557930000	-2.005105000	-0.000417000
H	0.823687000	1.911601000	-0.000138000	H	1.244082000	-1.668463000	-0.000213000
C	-1.219685000	0.429944000	-0.000205000	C	-0.000164000	0.000211000	0.772681000
H	-2.066783000	-0.243703000	-0.000360000				

```
Zero-point correction=                           0.094352 (Hartree/Particle)
 Thermal correction to Energy=                    0.098244
 Thermal correction to Enthalpy=                  0.099188
 Thermal correction to Gibbs Free Energy=         0.068099
 Sum of electronic and zero-point Energies=           -193.908868
 Sum of electronic and thermal Energies=              -193.904976
 Sum of electronic and thermal Enthalpies=            -193.904032
 Sum of electronic and thermal Free Energies=         -193.935120

E[(RO)M06-2x/def2TZVP] = -194.003219431
```

iii) (RO)ωB97xD / def2tzvp

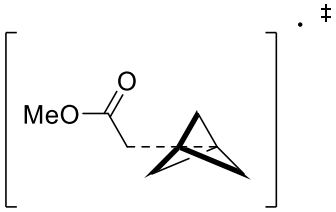
C	-1.282890000	0.179562000	-0.000290000	H	-0.144437000	-2.081325000	-0.000137000
C	-0.000246000	0.000102000	-0.777903000	C	0.797169000	1.020823000	-0.000316000
H	-1.730346000	1.166014000	-0.000053000	H	1.875168000	0.914477000	-0.000327000
H	-1.983900000	-0.646214000	-0.000069000	H	0.432654000	2.040857000	-0.000137000
C	0.485872000	-1.200435000	-0.000312000	C	-0.000015000	0.000078000	0.778992000
H	1.551524000	-1.394590000	-0.000301000				

```
Zero-point correction=                           0.093688 (Hartree/Particle)
 Thermal correction to Energy=                    0.097653
 Thermal correction to Enthalpy=                  0.098597
 Thermal correction to Gibbs Free Energy=         0.067401
 Sum of electronic and zero-point Energies=           -193.919158
 Sum of electronic and thermal Energies=              -193.915194
 Sum of electronic and thermal Enthalpies=            -193.914249
 Sum of electronic and thermal Free Energies=         -193.945445

E[(RO)wB97xD/def2TZVP] = -194.012846414
```

[AB‡]

i) (RO)B3LYP / def2tzvp

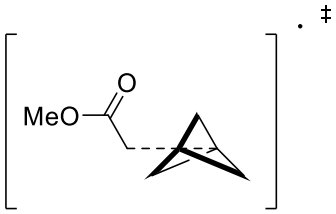


C	-2.755980000	-0.243405000	-0.770710000		C	0.456755000	-1.133583000	-1.035593000
C	-2.650210000	0.621741000	0.473956000		H	0.073840000	-2.124257000	-0.851664000
H	-3.239109000	-1.207675000	-0.664697000		H	0.362432000	-0.712655000	-2.024401000
H	-2.945601000	0.261061000	-1.710970000		C	1.499304000	-0.660756000	-0.155125000
C	-1.457388000	1.419566000	-0.027022000		O	1.814487000	-1.167542000	0.904452000
H	-0.822916000	1.884381000	0.717903000		O	2.088163000	0.475131000	-0.628297000
H	-1.589215000	1.993741000	-0.936408000		C	3.128525000	1.016987000	0.190629000
C	-1.815063000	-0.379186000	1.256224000		H	3.481965000	1.903921000	-0.329617000
H	-1.191090000	0.003609000	2.054343000		H	2.748907000	1.280947000	1.178196000
H	-2.254922000	-1.350556000	1.448503000		H	3.939859000	0.298606000	0.310600000
C	-1.370169000	-0.090003000	-0.165863000					

```
Zero-point correction=                           0.170754 (Hartree/Particle)
 Thermal correction to Energy=                    0.181244
 Thermal correction to Enthalpy=                  0.182188
 Thermal correction to Gibbs Free Energy=         0.132134
 Sum of electronic and zero-point Energies=           -461.742614
 Sum of electronic and thermal Energies=              -461.732123
 Sum of electronic and thermal Enthalpies=            -461.731179
 Sum of electronic and thermal Free Energies=         -461.781233

E[(RO)B3LYP/def2TZVP] = -461.913367074
```

ii) (RO)M06-2x / def2tzvp

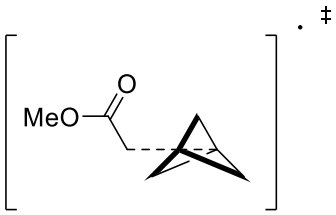


C	-2.667640000	0.095105000	-0.831862000		C	0.395433000	-1.270931000	-1.036490000
C	-2.407148000	0.716932000	0.522817000		H	0.004120000	-2.241892000	-0.779320000
H	-3.332589000	-0.759192000	-0.860725000		H	0.362051000	-0.938246000	-2.062119000
H	-2.732258000	0.767720000	-1.678222000		C	1.370938000	-0.695950000	-0.139263000
C	-1.080352000	1.331177000	0.138857000		O	1.573138000	-1.049283000	1.001459000
H	-0.376917000	1.526338000	0.939882000		O	2.002775000	0.367181000	-0.690205000
H	-1.079612000	2.047782000	-0.672914000		C	2.934469000	1.018817000	0.162328000
C	-1.809191000	-0.528466000	1.136782000		H	3.364946000	1.825890000	-0.423872000
H	-1.121216000	-0.402170000	1.963129000		H	2.435277000	1.414947000	1.047350000
H	-2.440043000	-1.407969000	1.178713000		H	3.710152000	0.324903000	0.485228000
C	-1.303376000	-0.116900000	-0.224363000					

```
Zero-point correction=                           0.172849 (Hartree/Particle)
 Thermal correction to Energy=                    0.183156
 Thermal correction to Enthalpy=                  0.184100
 Thermal correction to Gibbs Free Energy=         0.134789
 Sum of electronic and zero-point Energies=           -461.545031
 Sum of electronic and thermal Energies=              -461.534723
 Sum of electronic and thermal Enthalpies=            -461.533779
 Sum of electronic and thermal Free Energies=         -461.583090

E[(RO)M06-2x/def2TZVP] = -461.717879384
```

iii) (RO)ωB97xD / def2tzvp



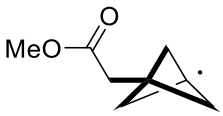
C	-1.707527000	-0.366162000	1.245967000	C	0.417958000	-1.215447000	-1.035002000
C	-2.507398000	0.687686000	0.501248000	H	0.039324000	-2.200749000	-0.814003000
H	-1.010543000	-0.029288000	2.003577000	H	0.353138000	-0.843398000	-2.046053000
H	-2.204287000	-1.303906000	1.465502000	C	1.425815000	-0.684639000	-0.146557000
C	-2.736405000	-0.172423000	-0.728877000	O	1.687828000	-1.113382000	0.955355000
H	-2.936051000	0.339758000	-1.663035000	O	2.023178000	0.414017000	-0.662462000
H	-3.278025000	-1.100970000	-0.589829000	C	2.991304000	1.031144000	0.172717000
C	-1.289072000	1.394130000	-0.064401000	H	3.388776000	1.867405000	-0.397336000
H	-1.423473000	1.971098000	-0.971799000	H	2.536032000	1.388298000	1.097832000
H	-0.582388000	1.810154000	0.644183000	H	3.788439000	0.331905000	0.426470000
C	-1.321172000	-0.113520000	-0.194871000				

```
Zero-point correction=                           0.172294 (Hartree/Particle)
 Thermal correction to Energy=                    0.182709
 Thermal correction to Enthalpy=                  0.183654
 Thermal correction to Gibbs Free Energy=         0.133907
 Sum of electronic and zero-point Energies=           -461.583156
 Sum of electronic and thermal Energies=              -461.572741
 Sum of electronic and thermal Enthalpies=            -461.571797
 Sum of electronic and thermal Free Energies=         -461.621543

E[(RO)wB97xD/def2TZVP] = -461.755449934
```

[B]

i) (RO)B3LYP / def2tzvp

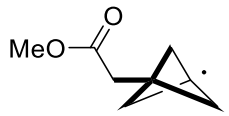


C	-2.613536000	-0.002947000	0.790519000	C	0.050151000	0.554242000	1.074538000
C	-2.590460000	-0.479962000	-0.673605000	H	-0.127924000	1.583546000	1.386894000
H	-3.103730000	0.947226000	0.994542000	H	0.154594000	-0.078232000	1.956173000
H	-2.810514000	-0.753289000	1.554279000	C	1.322630000	0.530690000	0.262920000
C	-1.341647000	-1.335304000	-0.384473000	O	1.676927000	1.402828000	-0.489139000
H	-0.701550000	-1.576552000	-1.230576000	O	2.011317000	-0.613177000	0.453150000
H	-1.458863000	-2.168697000	0.305711000	C	3.219697000	-0.752651000	-0.312077000
C	-1.695729000	0.713770000	-1.058786000	H	3.627525000	-1.722359000	-0.040416000
H	-1.074388000	0.606350000	-1.944681000	H	3.003168000	-0.712428000	-1.379020000
H	-2.128400000	1.708088000	-0.967531000	H	3.922058000	0.041982000	-0.062763000
C	-1.152428000	0.073354000	0.253515000				

```
Zero-point correction=                           0.174844 (Hartree/Particle)
 Thermal correction to Energy=                    0.184674
 Thermal correction to Enthalpy=                  0.185618
 Thermal correction to Gibbs Free Energy=         0.137500
 Sum of electronic and zero-point Energies=           -461.777615
 Sum of electronic and thermal Energies=              -461.767785
 Sum of electronic and thermal Enthalpies=            -461.766841
 Sum of electronic and thermal Free Energies=         -461.814959

E[(RO)B3LYP/def2TZVP] = -461.952458382
```

ii) (RO)M06-2x / def2tzvp

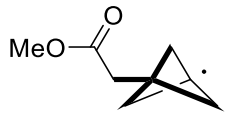


C	-2.594142000	-0.051705000	0.758421000	C	0.028760000	0.634432000	1.092021000
C	-2.492753000	-0.534778000	-0.693654000	H	-0.160190000	1.678857000	1.336937000
H	-3.136248000	0.874758000	0.932793000	H	0.132354000	0.046769000	2.003238000
H	-2.771077000	-0.808834000	1.519085000	C	1.284994000	0.554937000	0.269077000
C	-1.219221000	-1.320927000	-0.359064000	O	1.625906000	1.370301000	-0.543078000
H	-0.536350000	-1.524510000	-1.181136000	O	1.959781000	-0.579791000	0.501867000
H	-1.316442000	-2.149788000	0.338178000	C	3.119325000	-0.774561000	-0.305376000
C	-1.655104000	0.695720000	-1.061938000	H	3.539658000	-1.727351000	0.002016000
H	-0.992532000	0.609985000	-1.919317000	H	2.846543000	-0.795921000	-1.359909000
H	-2.142026000	1.665284000	-0.987564000	H	3.833846000	0.031158000	-0.142904000
C	-1.135696000	0.092800000	0.265225000				

```
Zero-point correction=                           0.177225 (Hartree/Particle)
 Thermal correction to Energy=                    0.186784
 Thermal correction to Enthalpy=                  0.187728
 Thermal correction to Gibbs Free Energy=         0.140427
 Sum of electronic and zero-point Energies=           -461.581379
 Sum of electronic and thermal Energies=              -461.571820
 Sum of electronic and thermal Enthalpies=            -461.570875
 Sum of electronic and thermal Free Energies=         -461.618177

E[(RO)M06-2x/def2TZVP] = -461.758603302
```

iii) (RO)ωB97xD / def2tzvp



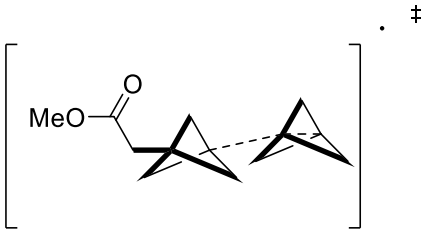
C	-2.601959000	0.037165000	0.753267000	C	0.036733000	0.675688000	1.046097000
C	-2.531277000	-0.555580000	-0.665359000	H	-0.148299000	1.730027000	1.248749000
H	-3.117558000	0.989187000	0.868105000	H	0.135411000	0.133678000	1.986424000
H	-2.804220000	-0.654863000	1.569314000	C	1.307389000	0.567856000	0.245339000
C	-1.272188000	-1.347159000	-0.269953000	O	1.692825000	1.384902000	-0.545736000
H	-0.596665000	-1.637597000	-1.072599000	O	1.943232000	-0.585897000	0.487197000
H	-1.388051000	-2.124553000	0.483328000	C	3.123363000	-0.816018000	-0.277394000
C	-1.649825000	0.623089000	-1.113214000	H	3.501396000	-1.782697000	0.044386000
H	-0.995532000	0.462053000	-1.967496000	H	2.893499000	-0.832188000	-1.342858000
H	-2.105498000	1.611503000	-1.113710000	H	3.861641000	-0.036984000	-0.088048000
C	-1.132999000	0.106691000	0.256670000				

```
Zero-point correction=                           0.177171 (Hartree/Particle)
 Thermal correction to Energy=                    0.186874
 Thermal correction to Enthalpy=                  0.187818
 Thermal correction to Gibbs Free Energy=         0.139896
 Sum of electronic and zero-point Energies=           -461.630485
 Sum of electronic and thermal Energies=              -461.620782
 Sum of electronic and thermal Enthalpies=            -461.619838
 Sum of electronic and thermal Free Energies=         -461.667759

E[(RO)wB97xD/def2TZVP] = -461.807655339
```

[BS‡]

i) (RO)B3LYP / def2tzvp

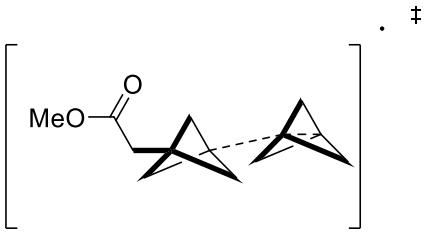


C	-0.123323000	-0.528785000	1.089402000	H	3.460941000	2.378108000	-0.531681000
C	-0.260010000	0.378246000	-0.887578000	H	3.421292000	2.074265000	1.268430000
C	0.284815000	-1.721282000	-0.687771000	H	4.385322000	-1.392833000	0.961829000
H	0.052765000	-1.359189000	1.771231000	H	3.940056000	-0.041763000	2.106339000
H	-0.400663000	0.385608000	1.609499000	H	4.435500000	-1.004162000	-1.339646000
C	-0.918152000	-0.857669000	-0.207049000	H	4.029793000	0.651360000	-1.994628000
H	-0.205604000	0.362233000	-1.975191000	C	3.190428000	0.238749000	0.027336000
H	-0.539167000	1.355733000	-0.497768000	H	-2.524228000	-2.196613000	0.283914000
H	0.374619000	-1.872480000	-1.762763000	H	-2.641370000	-1.478669000	-1.339043000
H	0.488223000	-2.627237000	-0.118389000	C	-3.307385000	-0.232624000	0.274242000
C	-2.388027000	-1.283596000	-0.296826000	O	-3.545527000	-0.087111000	1.446708000
C	0.831330000	-0.395788000	-0.116704000	O	-3.813926000	0.563886000	-0.690437000
C	3.598231000	1.671021000	0.278118000	C	-4.669342000	1.626444000	-0.240113000
C	4.730324000	0.657321000	0.131616000	H	-4.131343000	2.290979000	0.435121000
C	4.094950000	-0.355411000	1.080589000	H	-4.973559000	2.157744000	-1.137808000
C	4.142987000	0.016785000	-1.123322000	H	-5.537914000	1.222250000	0.278743000

```
Zero-point correction=                           0.268150 (Hartree/Particle)
 Thermal correction to Energy=                    0.283161
 Thermal correction to Enthalpy=                  0.284106
 Thermal correction to Gibbs Free Energy=         0.221141
 Sum of electronic and zero-point Energies=           -655.758218
 Sum of electronic and thermal Energies=              -655.743206
 Sum of electronic and thermal Enthalpies=            -655.742262
 Sum of electronic and thermal Free Energies=         -655.805227

E[(RO)B3LYP/def2TZVP] = -656.026366956
```

ii) (RO)M06-2x / def2tzvp



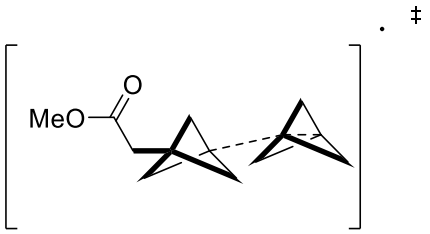
C	0.072638000	0.700412000	1.076908000	H	-2.787988000	-2.387800000	-0.285303000
C	0.224414000	-0.123736000	-0.927191000	H	-2.864689000	-1.858927000	1.467118000
C	-0.210389000	1.989921000	-0.653435000	H	-4.533203000	1.240616000	0.714124000
H	-0.079552000	1.510464000	1.787071000	H	-3.838044000	0.165339000	2.024025000
H	0.286737000	-0.253470000	1.554186000	H	-4.436572000	0.572176000	-1.503998000
C	0.912136000	1.040512000	-0.176027000	H	-3.665240000	-1.030012000	-1.943851000
H	0.208418000	-0.055070000	-2.013126000	C	-3.008052000	-0.201336000	0.003065000
H	0.441556000	-1.126607000	-0.562779000	H	2.607803000	2.187903000	0.483030000
H	-0.253724000	2.183990000	-1.723292000	H	2.714944000	1.609712000	-1.204614000
H	-0.383145000	2.876125000	-0.046196000	C	3.160950000	0.151597000	0.298680000
C	2.407110000	1.356003000	-0.190826000	O	3.375959000	-0.104193000	1.451879000
C	-0.837912000	0.674958000	-0.158991000	O	3.516603000	-0.655528000	-0.712099000
C	-3.093634000	-1.635696000	0.432031000	C	4.159803000	-1.867166000	-0.323889000
C	-4.403179000	-0.914572000	0.157173000	H	3.503192000	-2.456410000	0.315366000
C	-4.031334000	0.315388000	0.968917000	H	4.376273000	-2.399001000	-1.245455000
C	-3.938481000	-0.328010000	-1.165521000	H	5.078321000	-1.650905000	0.220093000

```
Zero-point correction=                           0.271257 (Hartree/Particle)
 Thermal correction to Energy=                    0.285966
 Thermal correction to Enthalpy=                  0.286910
 Thermal correction to Gibbs Free Energy=         0.224541
 Sum of electronic and zero-point Energies=           -655.485306
 Sum of electronic and thermal Energies=              -655.470598
 Sum of electronic and thermal Enthalpies=            -655.469654
```

```
 Sum of electronic and thermal Free Energies=         -655.532022

E[(RO)M06-2x/def2TZVP] = -655.756563332
```

iii) (RO)ωB97xD / def2tzvp



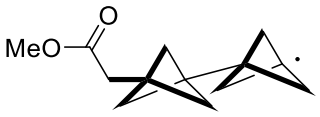
C	-0.155763000	-0.521021000	1.078746000	H	3.502597000	2.370270000	-0.516786000
C	-0.284290000	0.439139000	-0.861537000	H	3.457207000	2.070512000	1.284730000
C	0.333134000	-1.634455000	-0.716694000	H	4.217009000	-1.443097000	0.972127000
H	0.036361000	-1.364809000	1.739959000	H	3.857772000	-0.067203000	2.120546000
H	-0.481305000	0.365885000	1.619514000	H	4.273871000	-1.062304000	-1.320818000
C	-0.909725000	-0.837960000	-0.239997000	H	3.961234000	0.614337000	-1.978457000
H	-0.207345000	0.462288000	-1.947912000	C	3.124126000	0.254806000	0.048429000
H	-0.613395000	1.390539000	-0.445881000	H	-2.480648000	-2.235244000	0.172744000
H	0.452904000	-1.748416000	-1.793665000	H	-2.591909000	-1.447394000	-1.420222000
H	0.558630000	-2.550596000	-0.171713000	C	-3.282301000	-0.279295000	0.238607000
C	-2.354097000	-1.297219000	-0.367099000	O	-3.589895000	-0.234862000	1.398878000
C	0.819816000	-0.312772000	-0.094828000	O	-3.695102000	0.615904000	-0.669113000
C	3.604785000	1.657502000	0.293478000	C	-4.521310000	1.664403000	-0.171154000
C	4.677727000	0.583053000	0.141377000	H	-3.990843000	2.243506000	0.584903000
C	3.989983000	-0.390231000	1.094389000	H	-4.760228000	2.287420000	-1.028933000
C	4.044483000	-0.024725000	-1.106825000	H	-5.431339000	1.258618000	0.270389000

```
Zero-point correction=                           0.271246 (Hartree/Particle)
 Thermal correction to Energy=                    0.286012
 Thermal correction to Enthalpy=                  0.286956
 Thermal correction to Gibbs Free Energy=         0.224872
 Sum of electronic and zero-point Energies=           -655.547191
 Sum of electronic and thermal Energies=              -655.532425
 Sum of electronic and thermal Enthalpies=            -655.531481
 Sum of electronic and thermal Free Energies=         -655.593565

E[(RO)wB97xD/def2TZVP] = -655.818436833
```

[BS]

i) (RO)B3LYP / def2tzvp



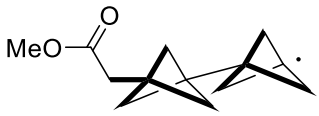
C	-0.603504000	1.654603000	-0.000021000	H	-3.613279000	-0.188225000	2.067510000
C	-0.170167000	-0.154611000	1.074570000	H	-3.978975000	1.339276000	1.161484000
C	-0.170167000	-0.154654000	-1.074541000	H	-3.613198000	-0.188517000	-2.067518000
H	-0.746468000	2.249991000	-0.903869000	H	-3.978931000	1.339112000	-1.161722000
H	-0.746471000	2.250025000	0.903804000	H	-3.145310000	-2.143444000	-0.906368000
C	0.598445000	0.667617000	-0.000002000	H	-3.145347000	-2.143318000	0.906653000
H	0.091362000	-1.208573000	1.153208000	C	-2.687482000	-0.117537000	0.000009000
H	-0.284726000	0.313992000	2.054176000	H	2.274992000	1.690891000	0.871321000
H	0.091364000	-1.208619000	-1.153138000	H	2.274970000	1.690905000	-0.871345000
H	-0.284728000	0.313910000	-2.054165000	C	3.027288000	-0.088017000	-0.000045000
C	2.049819000	1.067715000	-0.000014000	O	2.745181000	-1.258635000	-0.000068000
C	-1.229468000	0.229236000	0.000006000	O	4.297343000	0.367759000	-0.000021000
C	-3.729355000	0.281980000	1.092741000	C	5.326738000	-0.633820000	0.000079000
C	-4.443381000	-0.537268000	0.000004000	H	6.265947000	-0.087439000	0.000326000
C	-3.729313000	0.281825000	-1.092819000	H	5.249669000	-1.261972000	0.886986000
C	-3.289636000	-1.558610000	0.000099000	H	5.250023000	-1.261752000	-0.887017000

```
Zero-point correction=                           0.271414 (Hartree/Particle)
 Thermal correction to Energy=                    0.285622
```

```
 Thermal correction to Enthalpy=                  0.286566
 Thermal correction to Gibbs Free Energy=         0.227498
 Sum of electronic and zero-point Energies=           -655.816823
 Sum of electronic and thermal Energies=              -655.802615
 Sum of electronic and thermal Enthalpies=            -655.801671
 Sum of electronic and thermal Free Energies=         -655.860740

E[(RO)B3LYP/def2TZVP] = -656.088237183
```

ii) (RO)M06-2x / def2tzvp

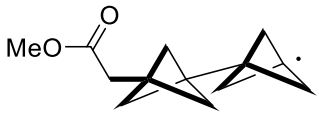


C	0.616854000	1.675401000	0.000101000	H	3.554558000	-0.217555000	-2.061797000
C	0.153187000	-0.122481000	-1.071170000	H	3.953153000	1.306934000	-1.151374000
C	0.153251000	-0.122554000	1.071279000	H	3.554701000	-0.218034000	2.061620000
H	0.770889000	2.261775000	0.907214000	H	3.953235000	1.306664000	1.151524000
H	0.770839000	2.261837000	-0.906981000	H	3.050148000	-2.147686000	0.909671000
C	-0.591385000	0.710184000	0.000104000	H	3.050087000	-2.147467000	-0.910274000
H	-0.128148000	-1.171860000	-1.139916000	C	2.652635000	-0.127218000	-0.000046000
H	0.278833000	0.347602000	-2.047902000	H	-2.273473000	1.724750000	-0.874027000
H	-0.128081000	-1.171936000	1.139975000	H	-2.273463000	1.724807000	0.874238000
H	0.278958000	0.347466000	2.048034000	C	-2.980302000	-0.067005000	0.000169000
C	-2.038554000	1.111101000	0.000124000	O	-2.659204000	-1.223461000	0.000406000
C	1.205614000	0.245691000	0.000034000	O	-4.258572000	0.338227000	-0.000208000
C	3.685084000	0.254462000	-1.090632000	C	-5.230524000	-0.704961000	-0.000255000
C	4.374372000	-0.576361000	-0.000159000	H	-6.197478000	-0.210777000	-0.001249000
C	3.685160000	0.254207000	1.090556000	H	-5.117768000	-1.329020000	-0.885993000
C	3.208653000	-1.573422000	-0.000238000	H	-5.119042000	-1.327887000	0.886445000

```
Zero-point correction=                           0.274379 (Hartree/Particle)
 Thermal correction to Energy=                    0.287592
 Thermal correction to Enthalpy=                  0.288536
 Thermal correction to Gibbs Free Energy=         0.232642
 Sum of electronic and zero-point Energies=           -655.545620
 Sum of electronic and thermal Energies=              -655.532406
 Sum of electronic and thermal Enthalpies=            -655.531462
 Sum of electronic and thermal Free Energies=         -655.587357

E[(RO)M06-2x/def2TZVP] = -655.819998096
```

iii) (RO)ωB97xD / def2tzvp



C	0.608204000	1.662390000	0.000240000	H	3.576820000	-0.202003000	-2.062639000
C	0.162307000	-0.136583000	-1.070174000	H	3.957623000	1.323364000	-1.157909000
C	0.162224000	-0.136983000	1.069945000	H	3.576438000	-0.203586000	2.062725000
H	0.757574000	2.254545000	0.905172000	H	3.957411000	1.322463000	1.159234000
H	0.757653000	2.254889000	-0.904454000	H	3.091007000	-2.143030000	0.906524000
C	-0.597948000	0.688878000	0.000009000	H	3.091177000	-2.142313000	-0.908054000
H	-0.107885000	-1.188779000	-1.147344000	C	2.662458000	-0.120363000	-0.000012000
H	0.282670000	0.331945000	-2.049168000	H	-2.272002000	1.704538000	-0.872823000
H	-0.107982000	-1.189203000	1.146713000	H	-2.271983000	1.704490000	0.872918000
H	0.282517000	0.331194000	2.049116000	C	-3.001050000	-0.080154000	0.000031000
C	-2.043983000	1.086193000	0.000028000	O	-2.699284000	-1.242190000	0.000070000
C	1.218143000	0.237633000	-0.000003000	O	-4.270335000	0.349670000	-0.000070000
C	3.702161000	0.267218000	-1.088219000	C	-5.270682000	-0.664434000	-0.000002000
C	4.413084000	-0.557709000	-0.000019000	H	-6.223235000	-0.141340000	-0.000496000
C	3.701960000	0.266372000	1.088684000	H	-5.182133000	-1.292476000	-0.886512000
C	3.245449000	-1.561255000	-0.000521000	H	-5.182679000	-1.291759000	0.887074000

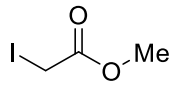
```
Zero-point correction=                           0.274507 (Hartree/Particle)
 Thermal correction to Energy=                    0.286840
 Thermal correction to Enthalpy=                  0.287784
```

```
 Thermal correction to Gibbs Free Energy=         0.234565
 Sum of electronic and zero-point Energies=           -655.620456
 Sum of electronic and thermal Energies=              -655.608123
 Sum of electronic and thermal Enthalpies=            -655.607179
 Sum of electronic and thermal Free Energies=         -655.660398

E[(RO)wB97xD/def2TZVP] = -655.894962524
```

[Iodoacetate]

i) (RO)B3LYP / def2tzvp

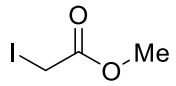


C	0.261788000	0.873644000	0.850178000	C	3.291703000	-0.964454000	-0.170615000
H	0.027020000	1.929333000	0.793573000	H	3.578179000	-1.914596000	0.270840000
H	0.286141000	0.512773000	1.872432000	H	3.110244000	-1.076006000	-1.238915000
C	1.539972000	0.587545000	0.110722000	H	4.068953000	-0.217349000	-0.015322000
O	2.022562000	1.317088000	-0.716244000	I	-1.404956000	-0.153478000	-0.088946000
O	2.081360000	-0.577116000	0.502471000				

```
Zero-point correction=                           0.080216 (Hartree/Particle)
 Thermal correction to Energy=                    0.087324
 Thermal correction to Enthalpy=                  0.088269
 Thermal correction to Gibbs Free Energy=         0.046202
 Sum of electronic and zero-point Energies=           -565.617726
 Sum of electronic and thermal Energies=              -565.610617
 Sum of electronic and thermal Enthalpies=            -565.609673
 Sum of electronic and thermal Free Energies=         -565.651740

E[(RO)B3LYP/def2TZVP] = -565.697941736
```

ii) (RO)M06-2x / def2tzvp

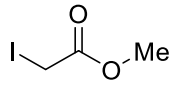


C	0.236084000	0.902007000	0.837221000	C	3.229944000	-0.965973000	-0.159871000
H	0.008632000	1.957034000	0.747974000	H	3.524338000	-1.910052000	0.287721000
H	0.264180000	0.570470000	1.869259000	H	3.031816000	-1.088509000	-1.223865000
C	1.512790000	0.589780000	0.109713000	H	4.007819000	-0.215708000	-0.026847000
O	2.000535000	1.292712000	-0.729372000	I	-1.377727000	-0.155973000	-0.088362000
O	2.038196000	-0.567904000	0.517691000				

```
Zero-point correction=                           0.081521 (Hartree/Particle)
 Thermal correction to Energy=                    0.088456
 Thermal correction to Enthalpy=                  0.089400
 Thermal correction to Gibbs Free Energy=         0.047799
 Sum of electronic and zero-point Energies=           -565.329021
 Sum of electronic and thermal Energies=              -565.322086
 Sum of electronic and thermal Enthalpies=            -565.321141
 Sum of electronic and thermal Free Energies=         -565.362743

E[(RO)M06-2x/def2TZVP] = -565.410541279
```

iii) (RO)ωB97xD / def2tzvp



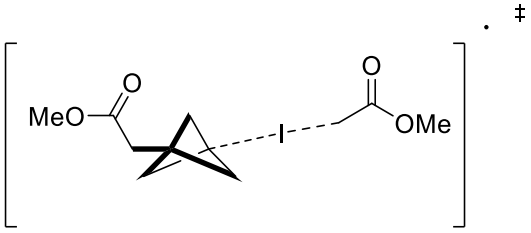
C	0.243274000	0.865308000	0.847854000	C	3.263565000	-0.955221000	-0.169496000
H	0.019407000	1.924658000	0.797810000	H	3.565183000	-1.896484000	0.281075000
H	0.279234000	0.508343000	1.872059000	H	3.074768000	-1.085412000	-1.234909000
C	1.524623000	0.583672000	0.112011000	H	4.037524000	-0.200195000	-0.034177000
O	2.001523000	1.309743000	-0.715030000	I	-1.390643000	-0.153262000	-0.089275000
O	2.065876000	-0.571064000	0.503466000				

```
Zero-point correction=                           0.081345 (Hartree/Particle)
 Thermal correction to Energy=                    0.088305
 Thermal correction to Enthalpy=                  0.089249
 Thermal correction to Gibbs Free Energy=         0.047648
 Sum of electronic and zero-point Energies=           -565.508705
 Sum of electronic and thermal Energies=              -565.501745
 Sum of electronic and thermal Enthalpies=            -565.500801
 Sum of electronic and thermal Free Energies=         -565.542402

E[(RO)wB97xD/def2TZVP] = -565.590049775
```

[BI‡]

i) (RO)B3LYP / def2tzvp

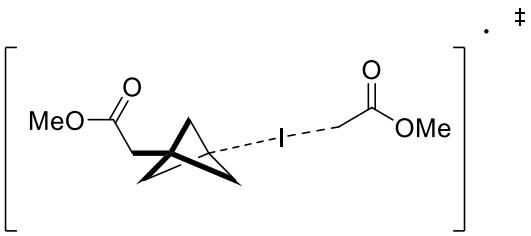


C	1.350227000	1.670812000	-0.227085000	C	-4.673786000	-0.271212000	0.388466000
C	1.793833000	-0.059341000	1.039972000	O	-5.103474000	0.690940000	-0.459860000
C	1.934343000	-0.232927000	-1.138820000	O	-4.978666000	-0.309850000	1.556760000
H	1.243819000	2.172862000	-1.186365000	C	-5.930453000	1.707407000	0.120987000
H	1.125456000	2.315651000	0.619737000	H	-6.174484000	2.386547000	-0.691734000
C	2.573874000	0.712462000	-0.071570000	H	-6.837207000	1.272123000	0.540637000
H	2.090601000	-1.090102000	1.205511000	H	-5.393291000	2.233276000	0.910214000
H	1.593136000	0.487064000	1.959180000	H	4.265398000	1.740740000	-0.919090000
H	2.238971000	-1.274004000	-1.100904000	H	4.157503000	1.867088000	0.819874000
H	1.859268000	0.160718000	-2.150452000	C	5.024701000	0.053872000	0.128370000
C	4.017702000	1.176289000	-0.016073000	O	4.770360000	-1.120000000	0.205778000
C	0.859067000	0.219824000	-0.143544000	O	6.275355000	0.550613000	0.160160000
I	-1.620738000	-0.475715000	-0.227394000	C	7.334621000	-0.413197000	0.295749000
C	-3.793672000	-1.247033000	-0.296694000	H	7.324919000	-1.109655000	-0.541731000
H	-3.740857000	-2.187384000	0.235987000	H	8.254507000	0.164543000	0.302316000
H	-3.985185000	-1.351005000	-1.357516000	H	7.225217000	-0.970931000	1.224979000

```
Zero-point correction=                           0.254579 (Hartree/Particle)
 Thermal correction to Energy=                    0.273152
 Thermal correction to Enthalpy=                  0.274097
 Thermal correction to Gibbs Free Energy=         0.200411
 Sum of electronic and zero-point Energies=          -1027.400773
 Sum of electronic and thermal Energies=             -1027.382199
 Sum of electronic and thermal Enthalpies=           -1027.381255
 Sum of electronic and thermal Free Energies=        -1027.454941

E[(RO)B3LYP/def2TZVP] = -1027.65535121
```

ii) (RO)M06-2x / def2tzvp



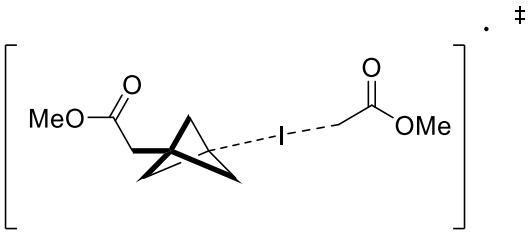
C	1.201112000	1.488620000	-0.673013000	H	1.719180000	-0.510307000	-2.059687000
C	0.778119000	0.123476000	-0.136718000	C	2.451541000	0.662003000	-0.276950000
H	1.050705000	1.662303000	-1.735703000	C	3.877833000	1.148295000	-0.408406000
H	0.970748000	2.349606000	-0.050291000	H	4.101540000	1.392289000	-1.449619000
C	1.743138000	0.244368000	1.040475000	H	4.022633000	2.066428000	0.165674000
H	2.089696000	-0.680225000	1.491077000	C	4.888128000	0.131507000	0.063889000
H	1.541505000	1.041537000	1.752109000	O	4.634302000	-0.958504000	0.495563000
C	1.837963000	-0.578551000	-0.980890000	O	6.133156000	0.604627000	-0.061429000
H	2.188411000	-1.543803000	-0.629904000	C	7.170354000	-0.281919000	0.359260000

H	8.102009000	0.247997000	0.187084000		C	-4.580384000	-0.112713000	-0.202056000
H	7.054731000	-0.524093000	1.414752000		O	-4.973061000	0.192739000	-1.297381000
H	7.138894000	-1.202710000	-0.221359000		O	-4.848018000	0.607331000	0.901616000
I	-1.561752000	-0.574282000	0.020625000		C	-5.597335000	1.796484000	0.677664000
C	-3.735871000	-1.288839000	0.103147000		H	-5.727694000	2.255613000	1.653297000
H	-3.844076000	-1.664883000	1.112748000		H	-5.055127000	2.464284000	0.008608000
H	-3.795621000	-2.044295000	-0.669319000		H	-6.563293000	1.561255000	0.232049000

```
Zero-point correction=                           0.258004 (Hartree/Particle)
 Thermal correction to Energy=                    0.276176
 Thermal correction to Enthalpy=                  0.277120
 Thermal correction to Gibbs Free Energy=         0.205009
 Sum of electronic and zero-point Energies=          -1026.916350
 Sum of electronic and thermal Energies=             -1026.898178
 Sum of electronic and thermal Enthalpies=           -1026.897234
 Sum of electronic and thermal Free Energies=        -1026.969344

E[(RO)M06-2x/def2TZVP] = -1027.17435372
```

iii) (RO)ωB97xD / def2tzvp



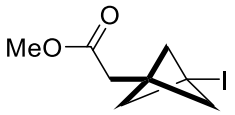
C	-1.693912000	-2.047769000	0.359729000		O	-5.046879000	1.106072000	0.808700000
C	-0.871985000	-0.801777000	0.011811000		C	-5.565727000	2.412578000	0.568510000
H	-1.671296000	-2.865149000	-0.358510000		H	-5.691397000	2.866505000	1.547573000
H	-1.655206000	-2.387689000	1.392988000		H	-4.872388000	2.996001000	-0.036951000
C	-1.774046000	0.050606000	0.913332000		H	-6.522802000	2.352740000	0.050737000
H	-1.822612000	1.115160000	0.693127000		I	1.524924000	-0.678817000	-0.074857000
H	-1.740945000	-0.158926000	1.980501000		C	3.791511000	-0.849946000	0.282429000
C	-1.795038000	-0.521807000	-1.185210000		H	4.142558000	-1.382127000	-0.594338000
H	-1.851249000	0.505101000	-1.538633000		H	3.877780000	-1.411421000	1.203989000
H	-1.781463000	-1.248145000	-1.994966000		C	4.335846000	0.520611000	0.418777000
C	-2.670817000	-0.880265000	0.048355000		O	4.493847000	1.100968000	1.461543000
C	-4.185293000	-0.960783000	0.080155000		O	4.623081000	1.057597000	-0.777990000
H	-4.520694000	-1.692498000	-0.654220000		C	5.100472000	2.397284000	-0.755698000
H	-4.509633000	-1.265930000	1.074720000		H	5.274739000	2.665428000	-1.794478000
C	-4.784092000	0.374793000	-0.280139000		H	4.359657000	3.062103000	-0.310748000
O	-4.968071000	0.759960000	-1.402345000		H	6.026620000	2.468213000	-0.184919000

```
Zero-point correction=                           0.258120 (Hartree/Particle)
 Thermal correction to Energy=                    0.276280
 Thermal correction to Enthalpy=                  0.277224
 Thermal correction to Gibbs Free Energy=         0.204406
 Sum of electronic and zero-point Energies=          -1027.142026
 Sum of electronic and thermal Energies=             -1027.123867
 Sum of electronic and thermal Enthalpies=           -1027.122923
 Sum of electronic and thermal Free Energies=        -1027.195741

E[(RO)wB97xD/def2TZVP] = -1027.40014630
```

[BI]

i) (RO)B3LYP / def2tzvp



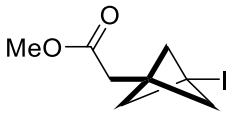
C	0.258404000	1.693043000	-0.414691000		H	0.493893000	2.502205000	0.275539000
C	0.787795000	0.293287000	-0.037303000		H	0.369446000	1.990139000	-1.457029000

C	-0.328285000	-0.329222000	-0.903724000	H	-2.674214000	1.633748000	-1.098437000
H	-0.620334000	-1.348682000	-0.655830000	C	-3.381025000	0.168324000	0.300473000
H	-0.255522000	-0.167030000	-1.978499000	O	-3.401627000	-0.360991000	1.382359000
C	-0.180718000	0.283694000	1.165201000	O	-4.212506000	-0.162454000	-0.706163000
H	-0.472235000	-0.689049000	1.553793000	C	-5.159884000	-1.206257000	-0.420685000
H	0.024158000	1.001832000	1.957979000	H	-5.734901000	-1.335673000	-1.333245000
C	-0.979078000	0.813070000	-0.063795000	H	-4.642721000	-2.128331000	-0.158349000
C	-2.423917000	1.269698000	-0.102076000	H	-5.808893000	-0.915416000	0.404417000
H	-2.556371000	2.090656000	0.607425000	I	2.853415000	-0.308692000	-0.012599000

```
Zero-point correction=                           0.177214 (Hartree/Particle)
 Thermal correction to Energy=                    0.187789
 Thermal correction to Enthalpy=                  0.188733
 Thermal correction to Gibbs Free Energy=         0.138625
 Sum of electronic and zero-point Energies=           -759.659621
 Sum of electronic and thermal Energies=              -759.649045
 Sum of electronic and thermal Enthalpies=            -759.648101
 Sum of electronic and thermal Free Energies=         -759.698209

E[(RO)B3LYP/def2TZVP] = -759.836834643
```

ii) (RO)M06-2x / def2tzvp

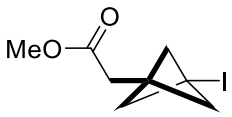


C	0.262984000	1.674192000	-0.666596000	C	-2.433309000	1.364058000	-0.309087000
C	0.728906000	0.328282000	-0.093297000	H	-2.562868000	2.266049000	0.289047000
H	0.523660000	2.558646000	-0.087793000	H	-2.692450000	1.567066000	-1.347621000
H	0.392294000	1.812565000	-1.738823000	C	-3.329199000	0.292666000	0.255779000
C	-0.392711000	-0.368610000	-0.875975000	O	-3.532310000	0.122049000	1.426154000
H	-0.726960000	-1.328867000	-0.486004000	O	-3.831420000	-0.496440000	-0.702992000
H	-0.304933000	-0.357242000	-1.961009000	C	-4.627339000	-1.586058000	-0.237894000
C	-0.239675000	0.518181000	1.082177000	H	-4.955247000	-2.116402000	-1.126676000
H	-0.570093000	-0.384815000	1.591124000	H	-4.035299000	-2.238165000	0.403109000
H	-0.013948000	1.333653000	1.766832000	H	-5.481020000	-1.215543000	0.327722000
C	-0.997258000	0.896280000	-0.214502000	I	2.745327000	-0.332373000	0.055494000

```
Zero-point correction=                           0.179593 (Hartree/Particle)
 Thermal correction to Energy=                    0.190858
 Thermal correction to Enthalpy=                  0.191802
 Thermal correction to Gibbs Free Energy=         0.139223
 Sum of electronic and zero-point Energies=           -759.295925
 Sum of electronic and thermal Energies=              -759.284659
 Sum of electronic and thermal Enthalpies=            -759.283715
 Sum of electronic and thermal Free Energies=         -759.336294

E[(RO)M06-2x/def2TZVP] = -759.475517295
```

iii) (RO)ωB97xD / def2tzvp



C	0.258705000	1.639596000	-0.712429000	C	-2.434492000	1.334626000	-0.363660000
C	0.748749000	0.314215000	-0.095604000	H	-2.561251000	2.269033000	0.183027000
H	0.508578000	2.549130000	-0.166721000	H	-2.677949000	1.494560000	-1.414194000
H	0.390965000	1.752280000	-1.788228000	C	-3.365657000	0.312702000	0.237637000
C	-0.377710000	-0.410480000	-0.857794000	O	-3.651758000	0.250089000	1.402049000
H	-0.706051000	-1.363060000	-0.443456000	O	-3.802879000	-0.557306000	-0.680797000
H	-0.289713000	-0.439743000	-1.943413000	C	-4.634212000	-1.608077000	-0.192734000
C	-0.238228000	0.537855000	1.067630000	H	-4.896921000	-2.205580000	-1.061469000
H	-0.561995000	-0.349155000	1.609768000	H	-4.096294000	-2.212535000	0.537564000
H	-0.023990000	1.373166000	1.733147000	H	-5.529922000	-1.201126000	0.275664000
C	-1.003550000	0.869708000	-0.241433000	I	2.761510000	-0.323587000	0.069031000

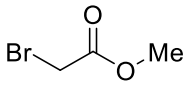
```
Zero-point correction=                           0.179656 (Hartree/Particle)
```

```
 Thermal correction to Energy=                    0.190925
 Thermal correction to Enthalpy=                  0.191869
 Thermal correction to Gibbs Free Energy=         0.139120
 Sum of electronic and zero-point Energies=           -759.500345
 Sum of electronic and thermal Energies=              -759.489077
 Sum of electronic and thermal Enthalpies=            -759.488132
 Sum of electronic and thermal Free Energies=         -759.540882

E[(RO)wB97xD/def2TZVP] = -759.680001681
```

[bromoacetate]

i) (RO)B3LYP / def2tzvp

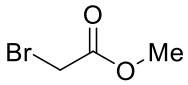


C	-0.239416000	0.764828000	0.810731000	C	2.910011000	-0.895356000	-0.166388000
H	-0.525659000	1.808834000	0.773000000	H	3.201690000	-1.868737000	0.217048000
H	-0.232650000	0.381608000	1.825712000	H	2.788982000	-0.928532000	-1.248347000
C	1.091832000	0.574950000	0.125093000	H	3.654007000	-0.141770000	0.088503000
O	1.586366000	1.378992000	-0.620791000	Br	-1.639511000	-0.234343000	-0.143867000
O	1.653878000	-0.593484000	0.466144000				

```
Zero-point correction=                           0.080665 (Hartree/Particle)
 Thermal correction to Energy=                    0.087709
 Thermal correction to Enthalpy=                  0.088653
 Thermal correction to Gibbs Free Energy=         0.047291
 Sum of electronic and zero-point Energies=          -2841.996891
 Sum of electronic and thermal Energies=             -2841.989847
 Sum of electronic and thermal Enthalpies=           -2841.988903
 Sum of electronic and thermal Free Energies=        -2842.030265

E[(RO)B3LYP/def2TZVP] = -2842.07755604
```

ii) (RO)M06-2x / def2tzvp

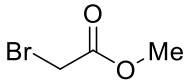


C	-0.255920000	0.790743000	0.794292000	C	2.860269000	-0.899337000	-0.156593000
H	-0.535782000	1.834867000	0.723042000	H	3.157032000	-1.868804000	0.230792000
H	-0.247921000	0.438914000	1.820555000	H	2.727673000	-0.939262000	-1.236786000
C	1.077248000	0.576948000	0.124515000	H	3.605544000	-0.142208000	0.082996000
O	1.583830000	1.359879000	-0.627313000	Br	-1.611997000	-0.237196000	-0.142703000
O	1.619139000	-0.588849000	0.477403000				

```
 Zero-point correction=                           0.081842 (Hartree/Particle)
 Thermal correction to Energy=                    0.088768
 Thermal correction to Enthalpy=                  0.089713
 Thermal correction to Gibbs Free Energy=         0.048615
 Sum of electronic and zero-point Energies=          -2841.890676
 Sum of electronic and thermal Energies=             -2841.883750
 Sum of electronic and thermal Enthalpies=           -2841.882806
 Sum of electronic and thermal Free Energies=        -2841.923903

E[(RO)M06-2x/def2TZVP] = -2841.97251788
```

iii) (RO)ωB97xD / def2tzvp



C	-0.250718000	0.747946000	0.813236000	O	1.565761000	1.371398000	-0.618324000
H	-0.529636000	1.795237000	0.790321000	O	1.649314000	-0.588637000	0.467019000
H	-0.235596000	0.358148000	1.826312000	C	2.893003000	-0.880140000	-0.169274000
C	1.081917000	0.568107000	0.128654000	H	3.212481000	-1.837144000	0.233292000

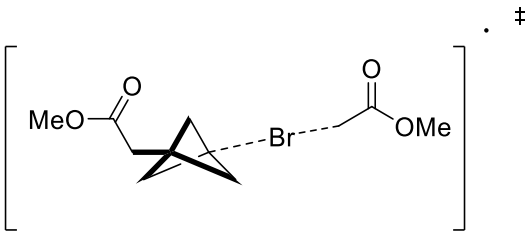
H	2.758625000	-0.945539000	-1.248688000	Br	-1.625688000	-0.232616000	-0.145148000
H	3.627409000	-0.106690000	0.053707000				

```
Zero-point correction=                           0.081656 (Hartree/Particle)
 Thermal correction to Energy=                    0.088626
 Thermal correction to Enthalpy=                  0.089570
 Thermal correction to Gibbs Free Energy=         0.048353
 Sum of electronic and zero-point Energies=          -2841.938664
 Sum of electronic and thermal Energies=             -2841.931694
 Sum of electronic and thermal Enthalpies=           -2841.930750
 Sum of electronic and thermal Free Energies=        -2841.971967

E[(RO)wB97xD/def2TZVP] = -2842.02031976
```

[BBr‡]

i) (RO)B3LYP / def2tzvp

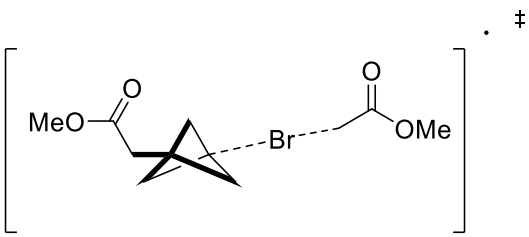


C	1.155437000	-1.321506000	1.262016000	C	-4.634513000	0.076627000	0.067035000
C	1.637147000	-1.011150000	-0.850287000	O	-4.708076000	1.351876000	-0.374985000
C	1.283267000	0.709677000	0.456264000	O	-5.110627000	-0.293783000	1.113905000
H	0.909108000	-0.978794000	2.264697000	C	-5.362009000	2.277293000	0.502914000
H	1.202157000	-2.405394000	1.180511000	H	-5.324452000	3.238170000	-0.003517000
C	2.253664000	-0.515179000	0.497726000	H	-6.395054000	1.977228000	0.677825000
H	1.828523000	-0.392071000	-1.721089000	H	-4.842421000	2.328838000	1.459610000
H	1.710718000	-2.078038000	-1.051659000	H	3.836800000	-0.155308000	1.911100000
H	1.453483000	1.428957000	-0.338637000	H	4.122986000	-1.518824000	0.858775000
H	1.042474000	1.168613000	1.413017000	C	4.590421000	0.363518000	-0.007289000
C	3.720877000	-0.502054000	0.880722000	O	5.865545000	0.341068000	0.424655000
C	0.515283000	-0.565798000	0.094052000	C	6.803912000	1.122940000	-0.334726000
Br	-1.806011000	-0.641650000	-0.404318000	H	7.763676000	0.980957000	0.153944000
C	-3.893902000	-0.785418000	-0.882903000	H	6.843464000	0.774821000	-1.366138000
H	-4.104940000	-1.836034000	-0.737587000	H	6.520165000	2.174609000	-0.323859000
H	-3.925707000	-0.457018000	-1.913694000	O	4.222143000	0.990006000	-0.966739000

```
Zero-point correction=                           0.254820 (Hartree/Particle)
 Thermal correction to Energy=                    0.273290
 Thermal correction to Enthalpy=                  0.274234
 Thermal correction to Gibbs Free Energy=         0.201810
 Sum of electronic and zero-point Energies=          -3303.773305
 Sum of electronic and thermal Energies=             -3303.754835
 Sum of electronic and thermal Enthalpies=           -3303.753891
 Sum of electronic and thermal Free Energies=        -3303.826314

E[(RO)B3LYP/def2TZVP] = -3304.02812337
```

ii) (RO)M06-2x / def2tzvp



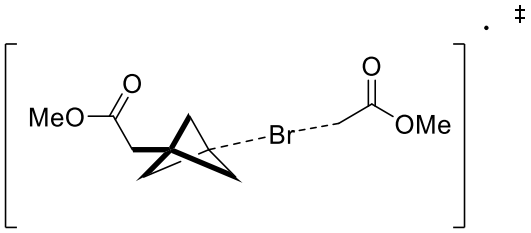
C	1.148735000	-1.615564000	1.055418000	C	2.193341000	-0.650402000	0.436096000
C	1.574326000	-0.903575000	-0.965497000	H	1.731020000	-0.122139000	-1.701977000
C	1.203019000	0.528256000	0.641333000	H	1.672403000	-1.913063000	-1.357803000
H	0.914923000	-1.465497000	2.106519000	H	1.341933000	1.382378000	-0.013839000
H	1.224564000	-2.661178000	0.766834000	H	0.970514000	0.786555000	1.671870000

C	3.666234000	-0.646730000	0.777131000	H	-6.058889000	2.213935000	0.679378000
C	0.470289000	-0.677871000	0.062515000	H	-4.447535000	2.482533000	1.365704000
Br	-1.780739000	-0.711039000	-0.386870000	H	3.809083000	-0.468656000	1.845523000
C	-3.849240000	-0.795112000	-0.806864000	H	4.110975000	-1.621209000	0.561544000
H	-4.126037000	-1.815053000	-0.575521000	C	4.441630000	0.401934000	0.018008000
H	-3.910422000	-0.533526000	-1.855616000	O	5.734648000	0.379881000	0.362687000
C	-4.491952000	0.180305000	0.104597000	C	6.561745000	1.334329000	-0.302865000
O	-4.484713000	1.420263000	-0.411573000	H	7.558493000	1.199366000	0.105602000
O	-4.946027000	-0.081685000	1.186972000	H	6.558190000	1.152805000	-1.376748000
C	-5.018272000	2.429455000	0.439126000	H	6.201291000	2.344331000	-0.113219000
H	-4.937864000	3.360603000	-0.114069000	O	3.985356000	1.163296000	-0.789053000

```
Zero-point correction=                           0.258512 (Hartree/Particle)
 Thermal correction to Energy=                    0.276525
 Thermal correction to Enthalpy=                  0.277469
 Thermal correction to Gibbs Free Energy=         0.206543
 Sum of electronic and zero-point Energies=          -3303.469478
 Sum of electronic and thermal Energies=             -3303.451466
 Sum of electronic and thermal Enthalpies=           -3303.450522
 Sum of electronic and thermal Free Energies=        -3303.521448

E[(RO)M06-2x/def2TZVP] = -3303.72799004
```

iii) (RO)ωB97xD / def2tzvp



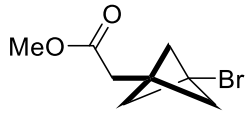
C	1.303849000	-2.047574000	0.277721000	C	-4.430319000	0.344491000	0.279146000
C	1.409547000	-0.422028000	-1.163850000	O	-4.494664000	1.321348000	-0.638666000
C	1.240462000	0.016708000	0.959837000	O	-4.734691000	0.496773000	1.433765000
H	1.221615000	-2.454003000	1.284167000	C	-4.906226000	2.593263000	-0.151961000
H	1.362945000	-2.818530000	-0.488533000	H	-4.912930000	3.254320000	-1.014732000
C	2.235510000	-0.814669000	0.096940000	H	-5.900487000	2.533519000	0.291107000
H	1.437035000	0.627445000	-1.442674000	H	-4.206754000	2.958332000	0.600597000
H	1.474408000	-1.098973000	-2.014075000	H	4.025574000	-1.220574000	1.207058000
H	1.256682000	1.091381000	0.803230000	H	4.161121000	-1.540408000	-0.506310000
H	1.152717000	-0.266290000	2.007332000	C	4.389727000	0.501019000	0.021647000
C	3.736565000	-0.845245000	0.222469000	O	5.714215000	0.408357000	0.183554000
C	0.445691000	-0.821764000	-0.043451000	C	6.445988000	1.622159000	0.024916000
Br	-1.796151000	-0.836058000	-0.194512000	H	7.488852000	1.363034000	0.185301000
C	-3.920484000	-0.918220000	-0.303254000	H	6.303491000	2.028822000	-0.976098000
H	-4.176723000	-1.780278000	0.299020000	H	6.121328000	2.361930000	0.756367000
H	-4.114018000	-1.037096000	-1.362361000	O	3.823714000	1.524842000	-0.246459000

```
Zero-point correction=                           0.258409 (Hartree/Particle)
 Thermal correction to Energy=                    0.276352
 Thermal correction to Enthalpy=                  0.277296
 Thermal correction to Gibbs Free Energy=         0.207130
 Sum of electronic and zero-point Energies=          -3303.564163
 Sum of electronic and thermal Energies=             -3303.546220
 Sum of electronic and thermal Enthalpies=           -3303.545276
 Sum of electronic and thermal Free Energies=        -3303.615442

E[(RO)wB97xD/def2TZVP] = -3303.82257154
```

[BBr]

i) (RO)B3LYP / def2tzvp

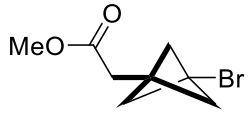


C	0.848733000	1.553473000	-0.577444000	C	-1.852116000	1.284290000	-0.232840000
C	1.309689000	0.178588000	-0.056658000	H	-1.948623000	2.178488000	0.387218000
H	1.121575000	2.417268000	0.027658000	H	-2.088689000	1.548339000	-1.263620000
H	0.973254000	1.736144000	-1.644261000	C	-2.848138000	0.267510000	0.281713000
C	0.170850000	-0.479481000	-0.859512000	O	-2.954748000	-0.064507000	1.434699000
H	-0.166354000	-1.453874000	-0.508917000	O	-3.598586000	-0.243451000	-0.713331000
H	0.251308000	-0.432629000	-1.944854000	C	-4.563459000	-1.236799000	-0.325600000
C	0.345441000	0.334867000	1.136005000	H	-5.067636000	-1.527387000	-1.242971000
H	0.010204000	-0.579792000	1.619598000	H	-4.066686000	-2.093820000	0.127583000
H	0.583225000	1.120175000	1.852132000	H	-5.273448000	-0.819460000	0.387364000
C	-0.429538000	0.771896000	-0.144666000	Br	3.148850000	-0.447881000	0.031604000

```
Zero-point correction=                           0.177700 (Hartree/Particle)
 Thermal correction to Energy=                    0.189007
 Thermal correction to Enthalpy=                  0.189952
 Thermal correction to Gibbs Free Energy=         0.137344
 Sum of electronic and zero-point Energies=          -3036.041813
 Sum of electronic and thermal Energies=             -3036.030505
 Sum of electronic and thermal Enthalpies=           -3036.029561
 Sum of electronic and thermal Free Energies=        -3036.082169

E[(RO)B3LYP/def2TZVP] = -3036.21951290
```

ii) (RO)M06-2x / def2tzvp

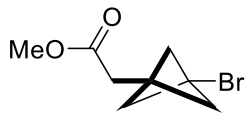


C	-0.255920000	0.790743000	0.794292000	C	2.860269000	-0.899337000	-0.156593000
H	-0.535782000	1.834867000	0.723042000	H	3.157032000	-1.868804000	0.230792000
H	-0.247921000	0.438914000	1.820555000	H	2.727673000	-0.939262000	-1.236786000
C	1.077248000	0.576948000	0.124515000	H	3.605544000	-0.142208000	0.082996000
O	1.583830000	1.359879000	-0.627313000	Br	-1.611997000	-0.237196000	-0.142703000
O	1.619139000	-0.588849000	0.477403000				

```
Zero-point correction=                           0.081842 (Hartree/Particle)
 Thermal correction to Energy=                    0.088768
 Thermal correction to Enthalpy=                  0.089713
 Thermal correction to Gibbs Free Energy=         0.048615
 Sum of electronic and zero-point Energies=          -2841.890676
 Sum of electronic and thermal Energies=             -2841.883750
 Sum of electronic and thermal Enthalpies=           -2841.882806
 Sum of electronic and thermal Free Energies=        -2841.923903

E[(RO)M06-2x/def2TZVP] = -2841.97251788
```

iii) (RO)ωB97xD / def2tzvp



C	-0.250718000	0.747946000	0.813236000
H	-0.529636000	1.795237000	0.790321000
H	-0.235596000	0.358148000	1.826312000
C	1.081917000	0.568107000	0.128654000
O	1.565761000	1.371398000	-0.618324000
O	1.649314000	-0.588637000	0.467019000
C	2.893003000	-0.880140000	-0.169274000
H	3.212481000	-1.837144000	0.233292000
H	2.758625000	-0.945539000	-1.248688000
H	3.627409000	-0.106690000	0.053707000
Br	-1.625688000	-0.232616000	-0.145148000

```
Zero-point correction=                           0.081656 (Hartree/Particle)
 Thermal correction to Energy=                    0.088626
 Thermal correction to Enthalpy=                  0.089570
 Thermal correction to Gibbs Free Energy=         0.048353
 Sum of electronic and zero-point Energies=          -2841.938664
 Sum of electronic and thermal Energies=             -2841.931694
 Sum of electronic and thermal Enthalpies=           -2841.930750
 Sum of electronic and thermal Free Energies=        -2841.971967

E[(RO)wB97xD/def2TZVP] = -2842.02031976
```

5. X-ray Crystallography

All X-ray data were collected and processed by Mr Steven Mansfield.

Low temperature[42] single crystal X-ray diffraction data were collected with a (Rigaku) Oxford Diffraction SuperNova A diffractometer at 150 or 200 K. Data were reduced using the instrument manufacturer software CrysAlisPro. All structures were solved *ab initio* using SuperFlip[43] and the structures were refined using CRYSTALS.[44,45]

Structure **5n** contained solvent accessible voids comprising of weak, diffuse electron density. The discrete Fourier transforms of the void regions were treated as contributions to the A and B parts of the calculated structure factors using PLATON/SQUEEZE[46,47] integrated within the CRYSTALS software. This enabled a comparison of models, one of which contained the disordered solvent, the other without.

Further details about the refinements, including disorder modelling and restraints, are documented in the CIF. The crystallographic data have been deposited with the CCDC as entries CCDC 1825056–1825060.

Compound Number	**182**	**197**	**198**	**179**	**253**
Moiety Formula	$C_8H_{12}NOI$, 0.5 ($CHCl_3$)	$C_{12}H_{12}NO_2I$	$C_{13}H_{12}F_3I$	$C_8H_{11}NO_2Br$	$C_{21}H_{30}N_2O$
CCDC	1825056	1825057	1825058	1825059	1825060
Space Group	C 2/c	P 2_1/c	P -1	P -1	P 2_1/n
a [Å]	25.6568(11)	12.8692(2)	5.6020(3)	7.0213(3)	14.7270(3)
b [Å]	9.9841(3)	8.45340(10)	8.9978(5)	11.7894(5)	5.77560(10)
c [Å]	9.9880(4)	11.4743(2)	13.3874(9)	12.2156(5)	21.9219(5)
α [°]	90	90	95.953(5)	72.797(4)	90
β [°]	95.639(4)	99.0055(15)	98.695(5)	86.293(4)	92.4149(18)
γ [°]	90	90	98.785(5)	89.879(3)	90
V [$Å^3$]	2546.14(17)	1232.88(3)	653.64(7)	963.76(7)	1862.96(7)
Z	8	4	2	4 (Z' = 2)	4
T [K]	150	150	200	150	150
Total Reflections	12571	26750	5134	16923	19286
R_{int}	0.0490	0.0654	0.0320	0.0503	0.0229
Reflections, Restraints, Parameters (I>-3.0/ σ (I))	2659, 347, 173	2575, 0, 145	2661, 555, 211	3998, 948, 311	3885, 462, 263
Min. and Max. Residual Density, [$eÅ^{-3}$]	-1.44, 1.34	-0.99, 0.86	-0.94, 0.76	-0.68, 0.52	-0.22, 0.22
R_1 (I>2σ(I)) wR_2	0.0399 0.1071	0.0274 0.0756	0.0358 0.0947	0.0328 0.0824	0.0377 0.0948

Table S3 Summary of X-ray crystallographic data

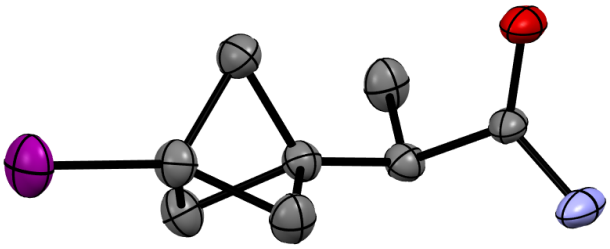


Figure S2: Solid state structure of **182**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms and disordered solvent molecules are omitted for clarity.

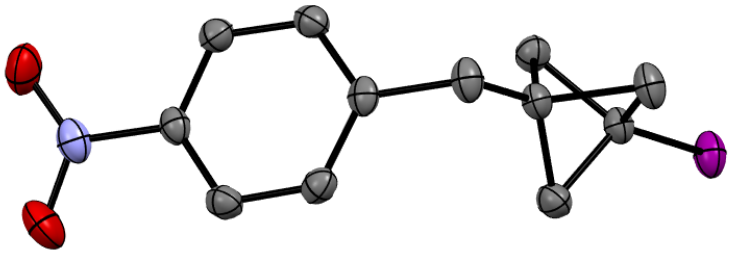


Figure S3: Solid state structure of **197**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms are omitted for clarity.

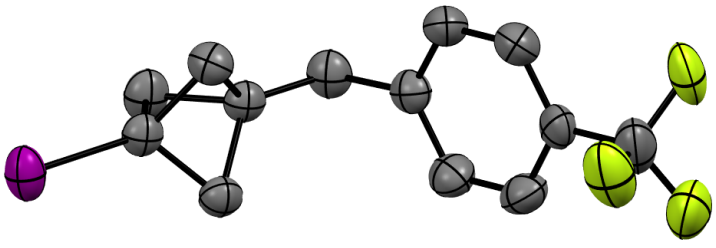


Figure S4: Solid state structure of **198**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms and disordered components are omitted for clarity.

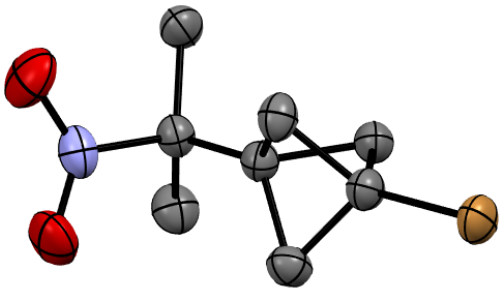


Figure S5: Solid state structure of **179**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms and disordered components are omitted for clarity.

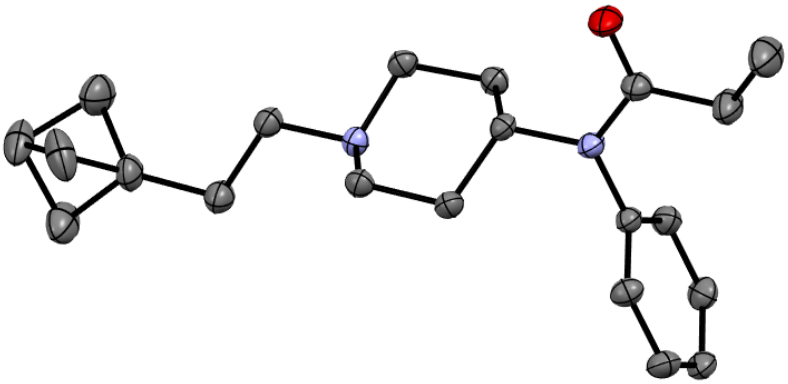


Figure S6: Solid state structure of **253**. Displacement ellipsoid plots are drawn at 50% probability. Hydrogen atoms and disordered components are omitted for clarity.

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