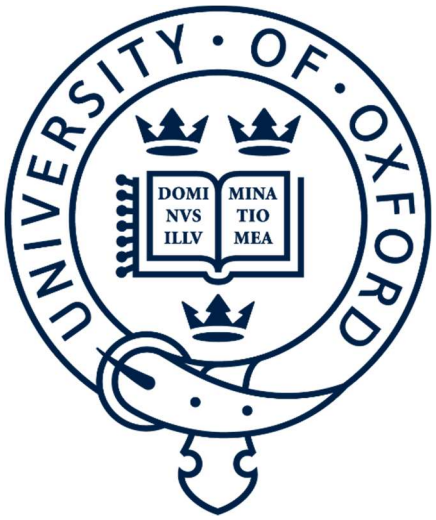
Hetero[3.1.1]propellanes:

Synthesis and Reactivity



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Hetero[3.1.1]propellanes: Synthesis and Reactivity

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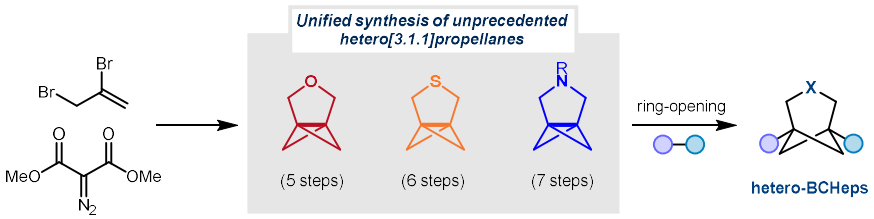
[*n*.1.1]Propellanes are compounds containing three rings fused to a central C–C bond, two of which are cyclopropanes. These compounds have become popular because of their diverse ring opening reactions which provide access to bicyclo[*n*.1.1]alkanes, valuable tools in medicinal chemistry due to their ability to act as bioisosteres for arenes. Arenes are highly abundant motifs in drugs and replacing them with saturated bioisosteres can improve the pharmacokinetic properties of a drug, such as metabolic stability, solubility and lipophilicity. Incorporating heteroatoms into bicyclo[*n*.1.1]alkanes should further improve the pharmacokinetic properties, however current approaches to such scaffolds have limitations in their scope, practicality and applicability. An ideal approach to access these scaffolds would be via ring-opening reactions of hetero[*n*.1.1]propellanes as this would allow the late-stage introduction of diverse bridgehead substituents. However, despite decades of research into propellanes made entirely from carbon atoms, heteroatom-containing small-ring propellanes are to date unknown.

This thesis presents the first synthesis of a family of hetero[3.1.1]propellanes and demonstrates a range of ring-opening reactions that allow access to diverse hetero-bicyclo[3.1.1]heptanes (hetero-BCHeps).



Declaration

The work presented in this thesis was conducted in the Department of Chemistry at the University of Oxford. This thesis is the result of my own work and contains no results obtained by others or through collaboration except where explicitly stated in the text. The work presented has not been submitted, either partially or in full, for any qualification at this or any other institution.

Rebecca Revie

September 2025

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Abbreviations

Å	Angstrom
Ac	Acyl
aq	Aqueous
Ar	Aryl
ATRA	Atom transfer radical addition
ATRC	Atom transfer radical cyclisation
BCB	Bicyclo[1.1.0]butane
BCHep	Bicyclo[3.1.1]heptane
BCHex	Bicyclo[2.1.1]heptane
BCO	Bicyclo[4.1.1]octane
BCP	Bicyclo[1.1.1]pentane
Bn	Benzyl
Boc	*tert*-Butyloxycarbonyl
bpy	2,2′-Bipyridine, 2,2′-Dipyridine, 2,2′-Dipyridyl
Bu	Butyl
°C	Degrees Celsius
cat.	Catalyst
COSY	Correlated Spectroscopy
DBH	1,3-Dibromo-5,5-dimethylhydantoin
DBU	1,8-Diazabicyclo(5.4.0)undec-7-ene
DCE	1,2-Dichloroethane
Decomp.	Decomposition
DIBALH	Diisobutylaluminium hydride
DIH	1,3-Diiodo-5,5-dimethylhydantoin
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
E	Electrophile
EDG	Electron donating group
Eq.	Equivalents
ESI	Electrospray ionization
Et	Ethyl
EWG	Electron withdrawing group

fac	Facial
h	Hour
HAT	Halogen atom transfer
HMBC	Heteronuclear Multiple Bond Correlation
HOBt	1-Hydroxybenzotriazole
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum coherence spectroscopy
Hz	Hertz
IPA	2-Propanol
IR	Infrared Spectroscopy
J	Coupling constant
LDA	Lithium diisopropylamide
M	Molar
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
min	Minute
mol	Mole
MOM	Methoxymethyl
m.p.	Melting point
Ms	Mesyl
MTBE	Methyl *tert*-butyl ether
n-	Normal
NBS	*N*-Bromosuccinimide
NCS	*N*-Chlorosuccinimide
NMR	Nuclear magnetic resonance spectroscopy
NOE	Nuclear Overhauser effect
NOESY	Nuclear Overhauser effect spectroscopy
Nu	Nucleophile
THF	Tetrahydrofuran
Ph	Phenyl
pin	Pinacol
piv	Pivaloyl
*p*Ka	Acid dissociation constant
PMDETA	*N,N,N′,N′′,N′′*-Pentamethyldiethylenetriamine
ppm	Parts per million

ppy	2-Phenylpyridine
PTH	Phenyl phenothiazine
R_f	Retention factor
rt	Room temperature
s-	Secondary
sat.	Saturated
SAR	Structure-activity-relationship
SET	Single electron transfer
t-	Tertiary
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxy
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	Tosyl
v/v	Volume/volume
w/w	Weight/weight

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1. Introduction

1.1. Introduction to propellanes

Propellanes are compounds which contain three rings fused to a central bond (Figure 1.1a). The term "propellane" was coined in 1966 by Altman and coworkers[1], who prepared some of the first synthetic compounds of this type[2,3], and noted that their structures were reminiscent of a propellor. The earliest examples of propellanes contained mainly 4- to 6-membered rings[4,5,6] fused to a central carbon-carbon bond (Figure 1.1b) and were explored for their academic interest and unusual fragmentation patterns.

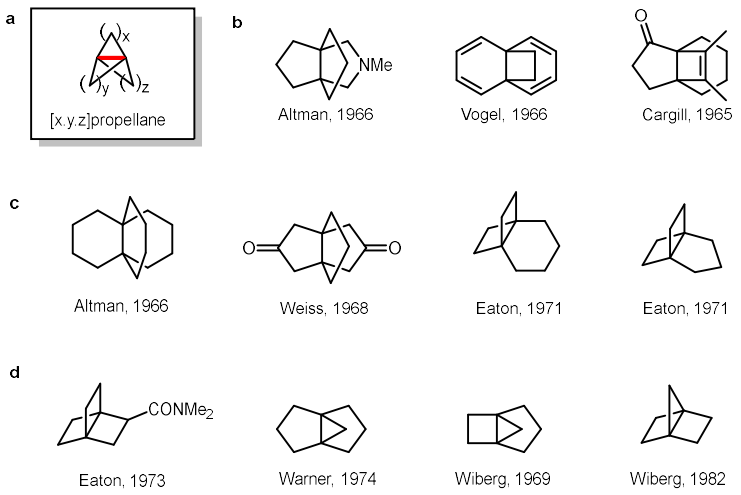


Figure 1.1 a Generic structure of a propellane. **b** Early literature examples of propellanes. **c** Further development of "large-ring" propellanes. **d** Examples of "small-ring" propellanes.

The interest in synthesising novel propellane structures continued throughout the 1960s and 70s and various elegant routes to carbocyclic "large ring" propellanes were developed[7,8,9] (Figure 1.1c). As increasing numbers of propellane structures were explored and synthetic routes became more elegant, the focus began to move towards the more challenging "small-ring" propellanes (Figure 1.1d). Synthetic routes for

propellanes containing 3- to 5-membered rings were developed[10,11,12,13,14] and there was a continued interest in investigating their reactions[15] and calculating their properties[16].

During this wave of interest in synthesising small-ring propellanes, two structures emerged which would go on to become the most famous members of the propellane family: [1.1.1]propellane and [3.1.1]propellane. These will be discussed in more detail in the following sections.

1.1.1. [1.1.1]Propellane

The synthesis of the smallest of the small-ring propellanes, [1.1.1]propellane, was achieved in 1982 by Wiberg and coworkers[17] (Figure 1.2a), following previous theoretical analysis of the compound[18]. The synthesis proceeded by bromination of bicyclo[1.1.1]pentane-1,3-dicarboxylic acid **1** to form **2**, then treatment with *t*BuLi to form the propellane **3**. An alternative synthesis was later developed using 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane **5** as a precursor (assembled from **4**) where treatment with MeLi afforded the propellane[19,20]. The latter method has since been improved[21,22] and adopted as the main (and currently best) way to synthesise [1.1.1]propellane.

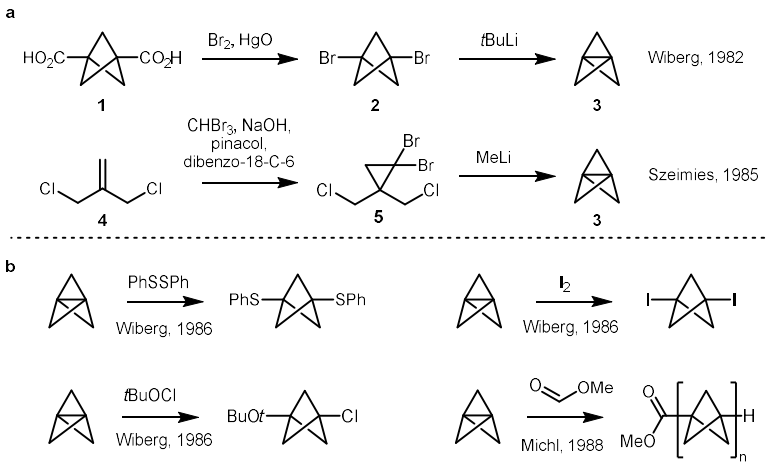


Figure 1.2 a Synthesis of [1.1.1]propellane. **b** Early examples of propellane ring-opening reactions.

It was soon realised that [1.1.1]propellane could react with radicals to form bicyclo[1.1.1]pentanes (BCPs)[23,24]; some early examples of these reactions are shown in Figure 1.2b. It was also noted that in some cases, polymers of various lengths could be formed under radical conditions, which were named "staffanes" due to their rod-like structures[25]. Following these initial reports on propellane ring-opening reactions[26], a large number of new methods emerged over the next 40 years and [1.1.1]propellane became a popular and versatile reagent for the synthesis of BCPs.

A selection of some of the most prominent radical-based ring-opening reactions of [1.1.1]propellane[27] is shown in Figure 1.3. Alkyl or aryl iodides can be added across the central propellane bond as shown by Anderson and coworkers (Figure 1.3a), either with BEt_3 as a radical initiator[28] or under $Ir(ppy)_3$ photocatalysis[29]. Molander and coworkers report a decarboxylative borylation under photochemical conditions to generate a range of alkyl-substituted BCPs[30]. Anderson and coworkers have also developed methods for the synthesis of α-quaternary BCPs[31] and α-chiral BCPs[32] via organophotocatalysis. The addition of α-amino radicals to [1.1.1]propellane can also be carried out using an organophotocatalyst[33].

It is also possible to synthesise heteroatom-substituted BCPs via radical-based methods (Figure 1.3b). Bräse and coworkers have demonstrated the addition of thiols and selenols to [1.1.1]propellane[34]. Zhu and coworkers have prepared thioether/sulfone disubstituted BCPs by the addition of a thiosulfonate[35]. Furthermore, Anderson and coworkers have reported the addition of sulfonyl halides to produce BCP sulfones[36]. Uchiyama and coworkers have demonstrated the additions of silylboranes to [1.1.1]propellane[37]. Nitrogen-substituted BCPs can be prepared by the photocatalysed fragmentation of iodomethyl aziridines as shown by Anderson and coworkers[38], or by a Cu-catalysed 3-component coupling, as shown by MacMillan and coworkers[39].

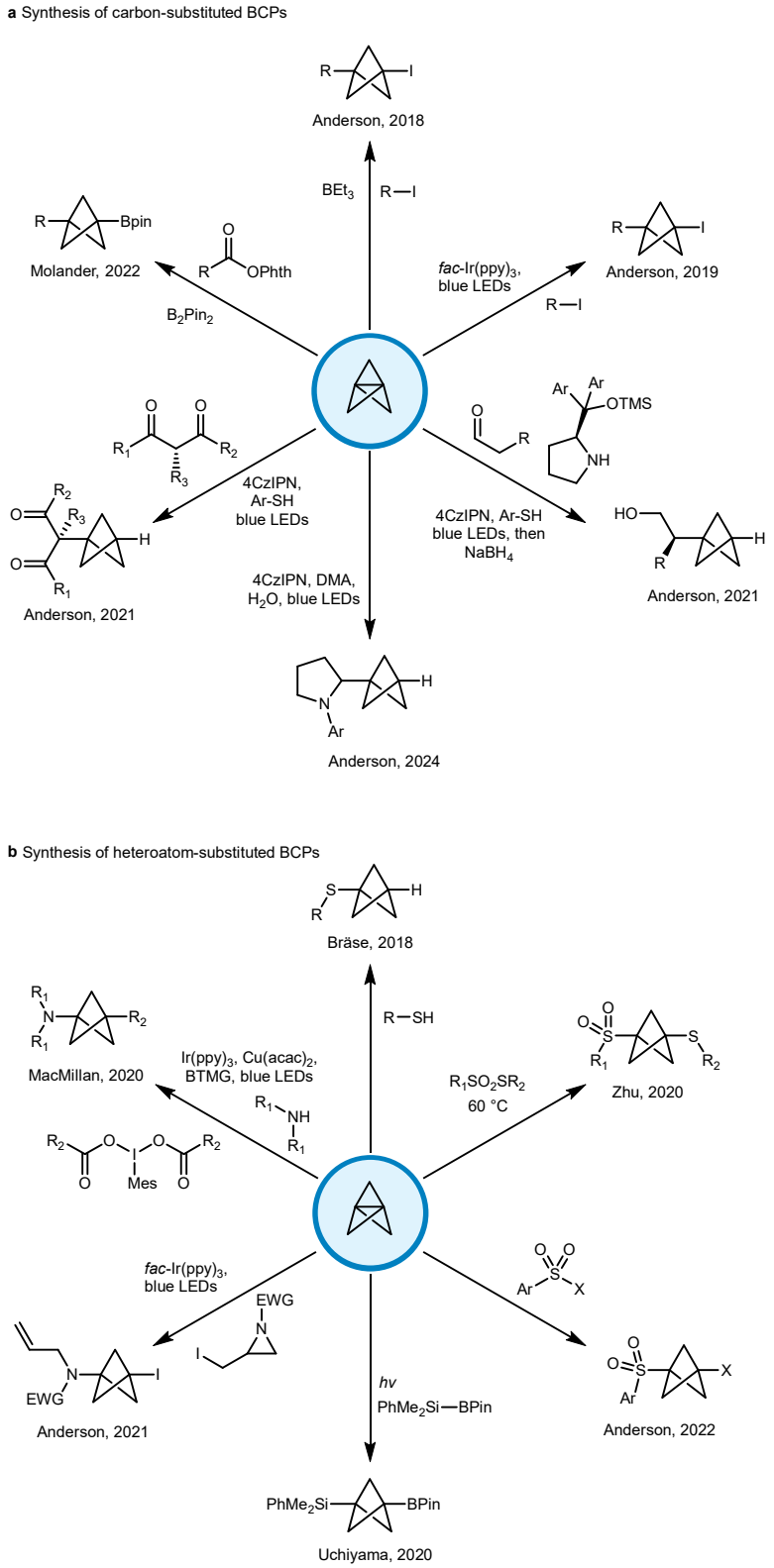


Figure 1.3 Selection of radical-based methods for the synthesis of **a** carbon-substituted and **b** heteroatom-substituted BCPs.

A variety of anionic additions to [1.1.1]propellane have also been developed (Figure 1.4). It is possible to add an aryl Grignard across the central bond under high temperature, which results in a BCP-Grignard that can be trapped with various electrophiles, as shown by de Meijere[40], Knochel[41], and Aggarwal[42]. Baran and coworkers have demonstrated the addition of turboamides to generate amine-substituted BCPs[22]. Benzylamine-substituted BCPs can be prepared via the additions of 2-azaallyl anions, as shown by Walsh and coworkers[43], who also demonstrated that BCP ketones can be accessed by the addition of 2-aryl-1,3-dithianes to [1.1.1]propellane[44]. Finally, Knochel and coworkers have shown that the addition of allylzinc reagents or zinc enolates can be used to access a range of disubstituted BCPs[45].

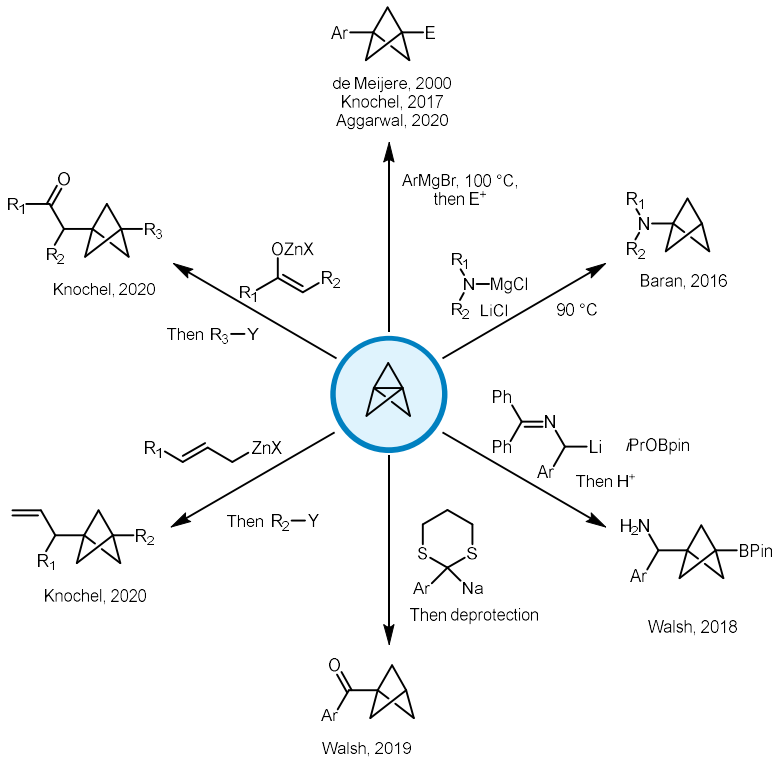


Figure 1.4 Selection of anionic ring-opening reactions of [1.1.1]propellane.

The range of synthetically accessible BCPs can be further diversified by reactions of functional handles which are installed during propellane ring-opening, and a small selection of such reactions is shown in Figure 1.5. Bridgehead C-I bonds can be further

functionalised via iron-catalysed Kumada coupling[46] or photocatalysed Giese-type coupling[38]. Alternatively, simple deiodination[38] may be performed under photoredox conditions, or by lithiation and electrophile trapping[47]. Other functional groups may also be used as handles for further reactions, for example the Minisci reaction demonstrated by Mousseau and coworkers[48] uses a carboxylic acid-derived redox-active ester-containing BCP.

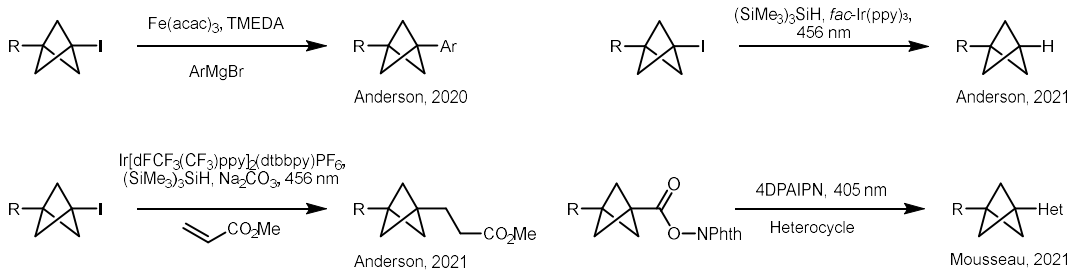


Figure 1.5 Further reactions of BCPs including Kumada coupling, Giese reaction, deiodination and Minisci reaction.

As the interest in BCPs has grown, the synthetic toolkit for their synthesis from [1.1.1]propellane has become very well-developed[49]. In fact, since the discovery of [1.1.1]propellane in 1982, tens of thousands of BCPs have been reported in the literature, almost all of which initially originate from [1.1.1]propellane (Figure 1.6a). This highlights the importance of the propellane as the compound which has enabled the synthesis of a vast number of pharmaceutically relevant intermediates.

The recent keen interest in this area has been driven by the realisation that BCPs could act as bioisosteres for *para*-disubstituted arenes. This was first suggested by Pellicciari and coworkers in 1996 with their BCP analogue of (*S*)-(4-carboxyphenyl)glycine[50] (Figure 1.6b) and later popularised by Stepan and coworkers at Pfizer in 2012 with their BCP analogue of avagacestat[51]. The concept of bioisosterism will be covered in Section 1.2.

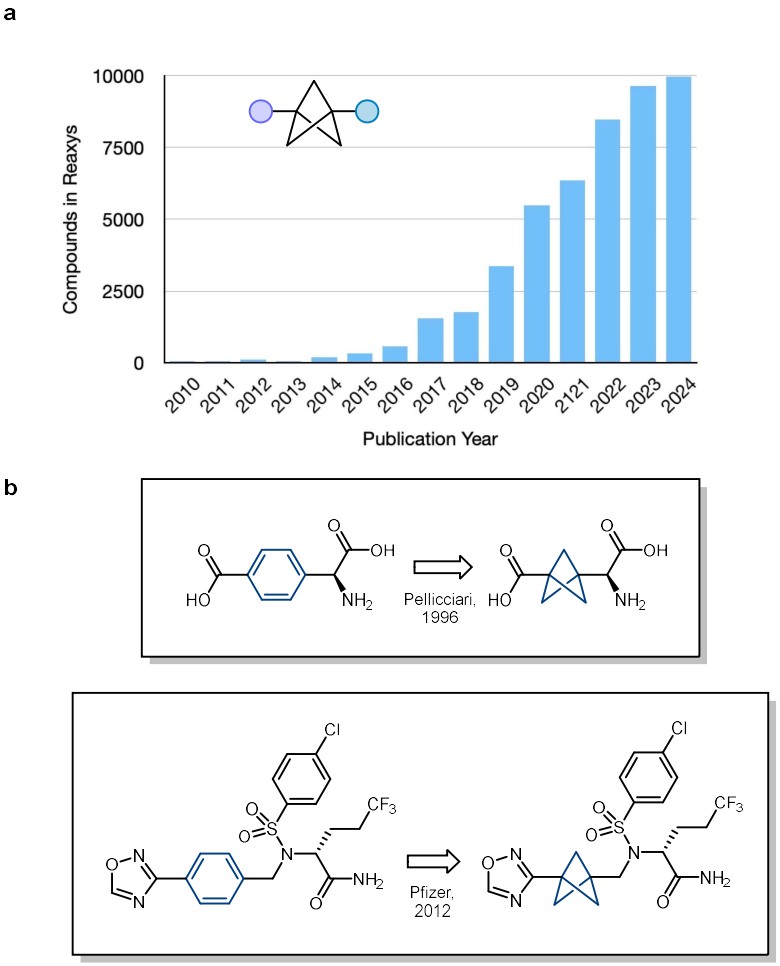


Figure 1.6 a Explosion of BCPs made from [1.1.1]propellane in recent years. **b** BCP bioisosteres in drug analogues have fuelled the popularity of these structures.

1.1.2. [3.1.1]Propellane

There was one other notable propellane which emerged during the initial wave of interest in the synthesis of small-ring propellanes in the 1980s, namely [3.1.1]propellane. The first synthesis of [3.1.1]propellane was achieved in 1980 by Gassman and coworkers[52] (Figure 1.7a). Dimethyl-1,3-cyclohexane dicarboxylate **8** was prepared from benzene-3,1-dicarboxylate **6** in two steps, then the bicyclo[3.1.1]heptane (BCHep) structure **10** was assembled via a double alkylation. This BCHep diester was converted to dibromo-BCHep **12** in two steps and the dibromo-BCHep was converted to [3.1.1]propellane **13** using elemental sodium. In 1992, an alternative synthesis was proposed by Szeimies and

coworkers[53] (Figure 1.7b), which involved a similar strategy to their [1.1.1]propellane route (Figure 1.2). Diol **15** was prepared via lithiation of **14** and trapping with ethylene oxide. This was then chlorinated to give **16**, and dibromocyclopropanation gave the propellane precursor **17**. Treatment with MeLi afforded the propellane.

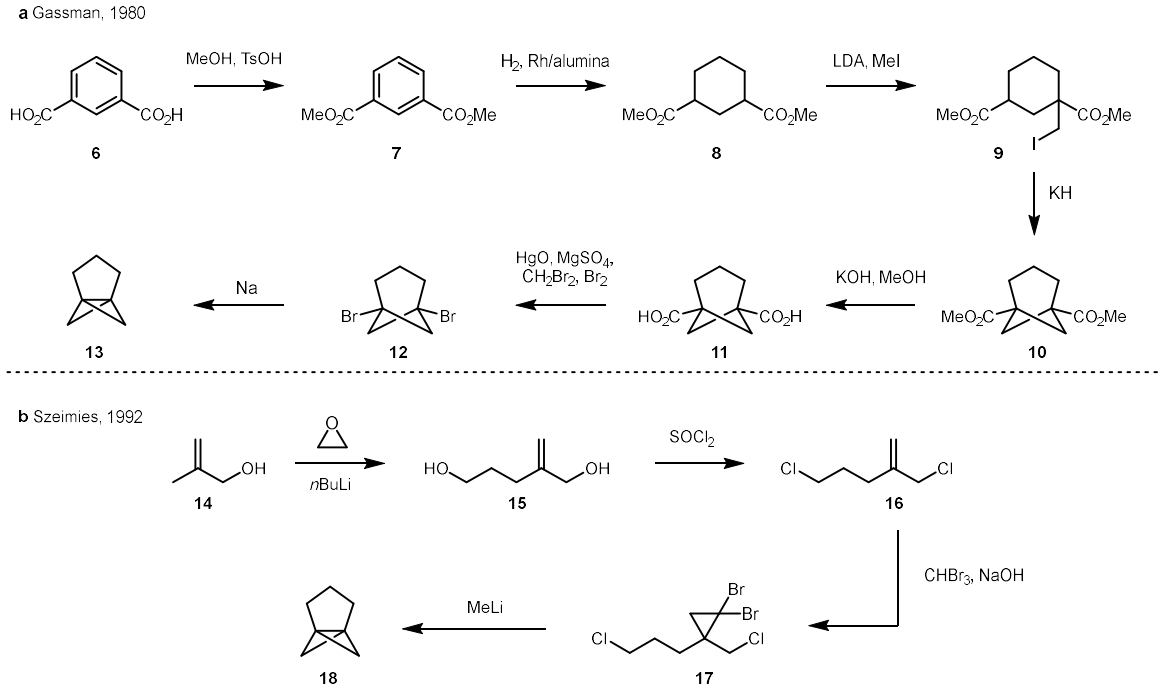


Figure 1.7 a First synthesis of [3.1.1]propellane by Gassman. **b** Alternative synthesis of [3.1.1]propellane by Szeimies.

After these initial reports on the synthesis of [3.1.1]propellane, it received very little interest for the next 30 years. However in 2022, its potential was realised as a versatile precursor for synthesising BCHeps, which were proposed as bioisosteres for *meta*-disubstituted arenes. Anderson and coworkers described an improved route to [3.1.1]propellane[47] (Figure 1.8a), based on interception of an intermediate in Szeimies' route. This started with a Kulinkovich cyclopropanation to convert **19** to **20**, followed by mesylation to give **21** and Ti-mediated rearrangement to give **16**. Dibromocyclopropanation gave **17**, then ring-closure with PhLi afforded [3.1.1]propellane in good overall yield. The original report by Gassman gave a 4.2%

overall yield, the alternative route by Szeimies gave 3.3% overall yield, and the improved route by Anderson gave 25-36% overall yield[54].

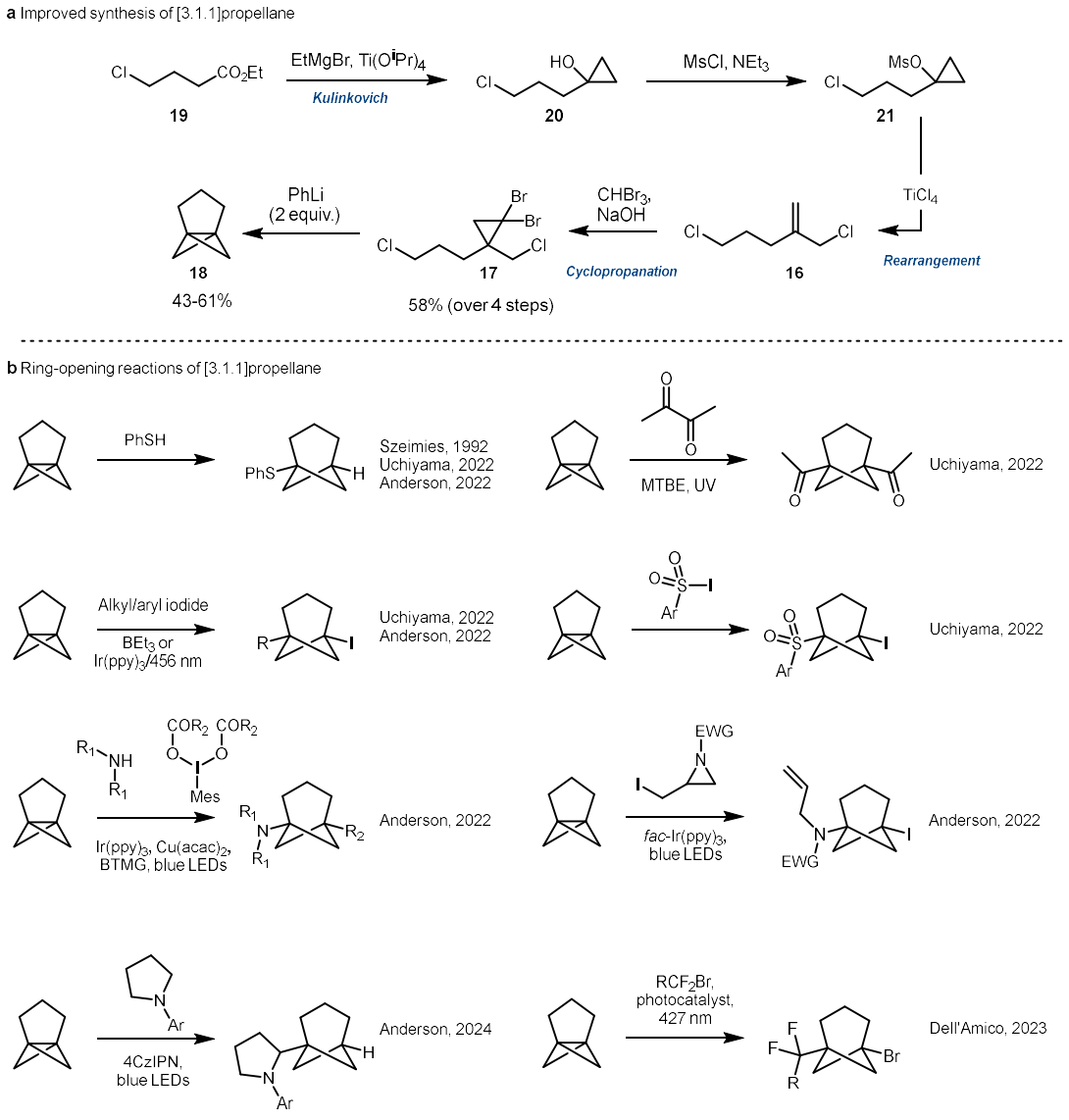


Figure 1.8 a Improved synthesis of [3.1.1]propellane. **b** Ring-opening reactions of [3.1.1]propellane.

Shortly afterwards, Uchiyama and coworkers also reported a synthesis of [3.1.1]propellane[55] based on an adaptation of Gassman's route in 23% overall yield. In both of these 2022 reports, the reactivity of [3.1.1]propellane was explored and ring-opening reactions which had been previously demonstrated for [1.1.1]propellane were attempted on [3.1.1]propellane. A selection of these reactions is shown in Figure 1.8b.

Some of the simplest ring-opening reactions included the addition of thiophenol[53,47,55] and diacetyl[55]. A range of alkyl and aryl iodides could also be added under various conditions[47,55]. The addition of a sulfonyl iodide was also possible[55]. MacMillan's copper catalysed 3-component coupling translated well to [3.1.1]propellane[39,47], as did Anderson's iodomethyl aziridine fragmentation[38,47]. Since the disclosure of the improved [3.1.1]propellane route, new propellane ring-opening reactions have been developed that have included reactions of [3.1.1]propellane in their substrate scope, for example the α-amino radical addition by Anderson and coworkers[33] and the synthesis of difluoroalkyl BCHeps by Dell'Amico and coworkers[56].

While various radical-based methods translated well from [1.1.1]propellane to [3.1.1]propellane, it was found that anionic additions were unsuccessful on [3.1.1]propellane. This can be rationalised by the fact that while [1.1.1]propellane has three cyclopropane rings onto which the incoming negative charge can be delocalised, [3.1.1]propellane has only two cyclopropane rings and is less able to stabilise an increase in electron density[47,57,58].

Finally, ring-opening reactions of [3.1.1]propellane have been used in the synthesis of BCHep analogues of anti-cancer drug sonidegib and anti-seizure drug URB597 (Figure 1.9), illustrating the utility of [3.1.1]propellane in the synthesis of medicinally-relevant compounds.

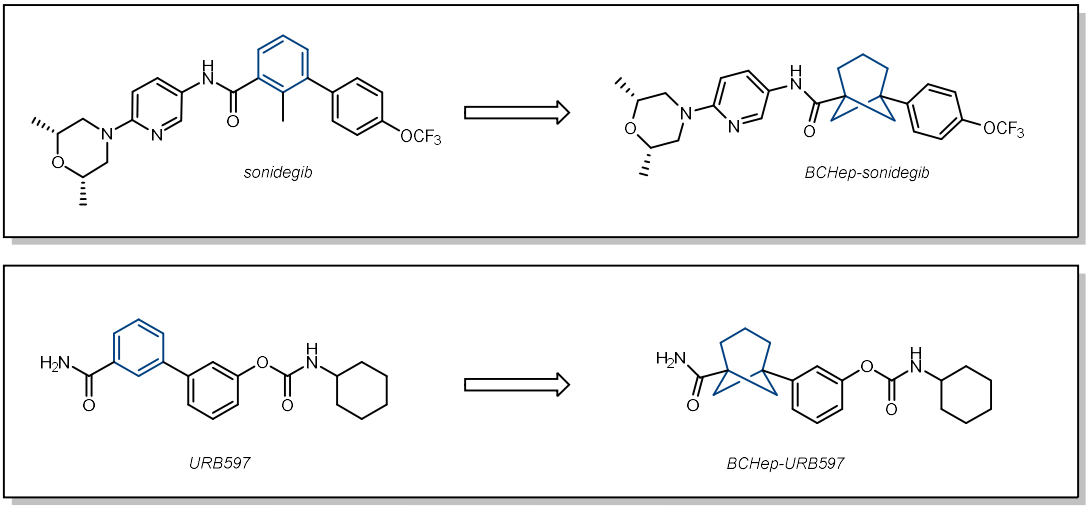


Figure 1.9 BCHep drug analogues.

1.2. Arene bioisosteres

1.2.1. Introduction to bioisosteres

A bioisostere is a motif which can replace a chemical group within the structure of a drug, maintaining its physical and chemical properties while imparting improved pharmacokinetic properties[59,60] such as metabolic stability, solubility and lipophilicity. Classical bioisosteres involve replacements with groups that have direct structural similarities, for example the replacement of H with F or D to improve metabolic stability[61], or the replacement of OH with SH[62]. Non-classical bioisosteres have greater structural differences while maintaining similar biological properties, for example the replacement of a carboxylic acid with a tetrazole[62] or a carbonyl with an oxetane[63].

Recently, there has been increasing interest in developing bioisosteres for phenyl rings, and various sp^3-rich structures have been proposed as bioisosteres for arenes with different substitution patterns[64,65]. The motivation for replacing arenes with sp^3-rich structures and a discussion of the various arene bioisosteres which have been reported will be covered in the following sections.

1.2.2. Escape from flatland

Benzene is the most common ring system in FDA approved drugs[66]. The methods for synthesising scaffolds based on arenes are historically well-established[67,68], making it easy to generate compound libraries and conduct structure activity relationship (SAR) studies. Arenes also have the benefit of providing well-defined substituent exit vectors and introducing favourable π-stacking and hydrogen bonding interactions with their biological targets[69,70]. However, there are also several disadvantages to relying on aromatic scaffolds in drug discovery. Small-molecule drugs usually act by interacting with large 3D biological macromolecules, so compound libraries which are biased towards flat aromatic structures are missing out on opportunities to explore 3D chemical space and find the most potent and specific interactions with their biological targets[71,72]. Phenyl rings can also be responsible for introducing poor pharmacokinetic properties. The π-stacking interactions between aromatic systems can limit the aqueous solubility of a drug[73] and the aromatic system can be susceptible to oxidation by cytochrome P450 enzymes, leading to overly fast metabolic clearance[74,75].

The concept of "Escape from Flatland" was introduced by Lovering and coworkers[76] in 2009. They found that the fraction of sp^3 hybridised carbons (Fsp^3) correlated with improved chances of clinical success. The reasons given for this correlation were the improved interactions between the drug and its target, the more efficient exploration of chemical space, and the improved physicochemical properties. Since this point, there has been a drive to develop methods for the synthesis of sp^3-rich building blocks, both as bioisosteres for the problematic benzene rings and as novel scaffolds for drug discovery in their own right[64,65,77,78].

1.2.3. Three-dimensional sp^3-rich benzene replacements

The surge of interest into escaping from flatland has resulted in an ever-increasing selection of sp^3-rich compounds which have been proposed as bioisosteres for arenes.

The majority of these are based on carbocyclic scaffolds, and different structures have been developed with different exit vectors that allow them to act as bioisosteres for either *para, meta*, or *ortho* disubstituted benzene.

Figure 1.10 shows a selection of scaffolds which have been proposed as potential bioisosteres for *para-, meta-*, and *ortho*-benzenes. For *para*-benzenes, the most common replacement is a 1,3-BCP[27], due to its ease of access from [1.1.1]propellane. The angle between exit vectors matches that of *para*-disubstituted benzene, but the distance between exit vectors is slightly shorter. Other proposed *para*-arene bioisosteres include 1,4-cubane[79], 1,4-bicyclo[2.2.2]octane (BCO)[80] and 2-oxa-1,4-BCO[81], which all have very similar distances and angles between substituents as the original benzene, however methods for their synthesis are more cumbersome and less well-established than 1,3-BCP. 2,6-Spiro[3.3]heptane[82] has also been proposed as a replacement for *para*-benzene, however the angles and distance between substituents map less closely onto benzene.

Several structures have been proposed as bioisosteres for *meta*-disubstituted benzene and those with the closest match of distances and bond angles are 1,5-BCHep[47] and 3-oxa-1,5-BCHep[83]. The 1,3-cubane[79] structure is also a relatively good match in terms of geometry. Other structures that have been proposed include 1,6-spiro[3.3]heptane[82], 1,3-cuneane[84], 3,5-nortricyclane[85] and 2,6-[2]-ladderane[86]. The 1,2-BCP[87] structure has a substituent distance and angle between that which would be required for *meta*- and *ortho*- benzene, and has been proposed as a bioisostere for both. Several variations of the bicyclo[2.1.1]hexane (BCHex) structure have been proposed as bioisosteres for *meta*-benzene, including 1,3-BCHex[88], 1,4-BCHex[88] and 2-oxa-1,4-BCHex[89].

Variations on the BCHex structure have also been proposed as replacements for *ortho*-disubstituted benzene, including 1,2-BCHex[88], 1,5-BCHex[90] and 2-oxa-4,5-BCHex[91]. Other proposed bioisosteric replacements for *ortho*-benzene include 1,2-stellane[92], 1,2-BCHep[93] and 1,2-cubane[79].

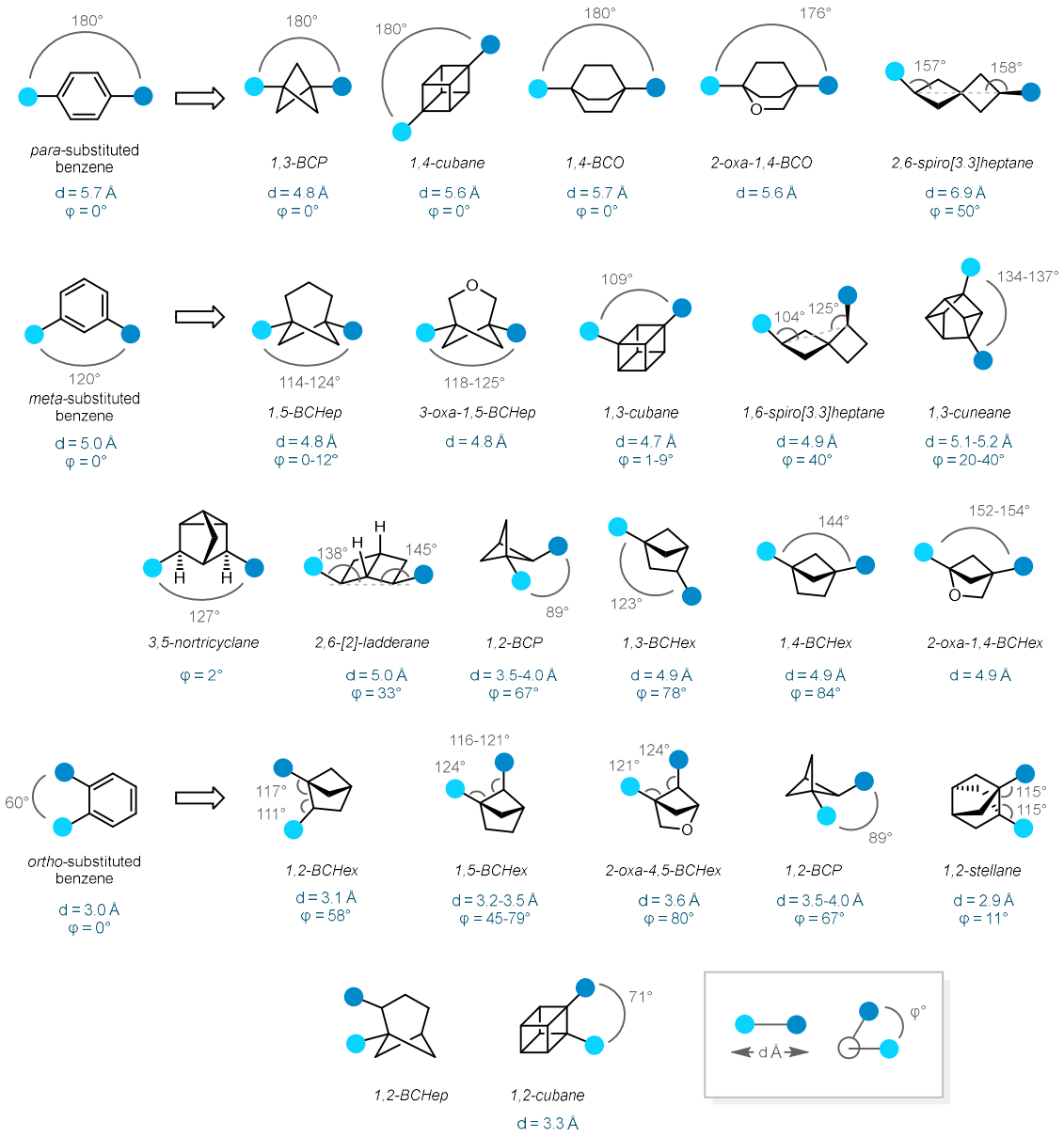


Figure 1.10 Potential bioisosteres for *para*, *meta* and *ortho* disubstituted benzene. Distances and angles are taken from references [47], 64, [94], 85 and [95].

1.2.4. Carbocyclic arene bioisosteres

Some of the structures shown in Figure 1.10 have been incorporated into drug analogues to investigate their activity and pharmacokinetic properties, and to determine their suitability as bioisosteres. A selection of drug analogues with such bioisosteric replacements is shown in Figure 1.11.

As introduced in Section 1.1.1, the first BCP drug analogues were the glutamate receptor agonist by Pellicciari and coworkers[50], which showed similar potency to its parent arene analogue, and the γ-secretase inhibitor by Stepan and coworkers[51], which showed improved potency over its parent arene analogue. The BCP γ-secretase inhibitor analogue was also investigated for its pharmacokinetic properties and it was found to have improved solubility and metabolic stability over the parent arene.

These findings by Stepan on the pharmacokinetic properties prompted the investigation of a range of different BCP drug analogues by many different research groups, including those shown in Figure 1.11. Stepan and coworkers later synthesised a BCP analogue of the anti-cancer drug imatinib[96], which showed improved solubility and comparable metabolic stability to the parent arene, however the potency was reduced in this case. Hirst and coworkers[97] prepared a BCP analogue of the lipoprotein-associated phospholipid A2 inhibitor darapladib, which showed improved solubility and similar potency to the original drug. Another example of a BCP replacement is demonstrated by Adsool and coworkers[98], where the BCP analogue of resveratrol showed improved solubility and metabolic stability, as well as similar potency to the parent arene compound.

Williams and coworkers have investigated the replacement of the *para* disubstituted benzene in the agrochemical diflubenzuron with a cubane[99,100] and found that this resulted in improved potency. Another less common *para* benzene replacement is the

BCO, and Wang and coworkers have demonstrated this to be effective in the MDM2 inhibitor, resulting in improved metabolic stability and potency[80].

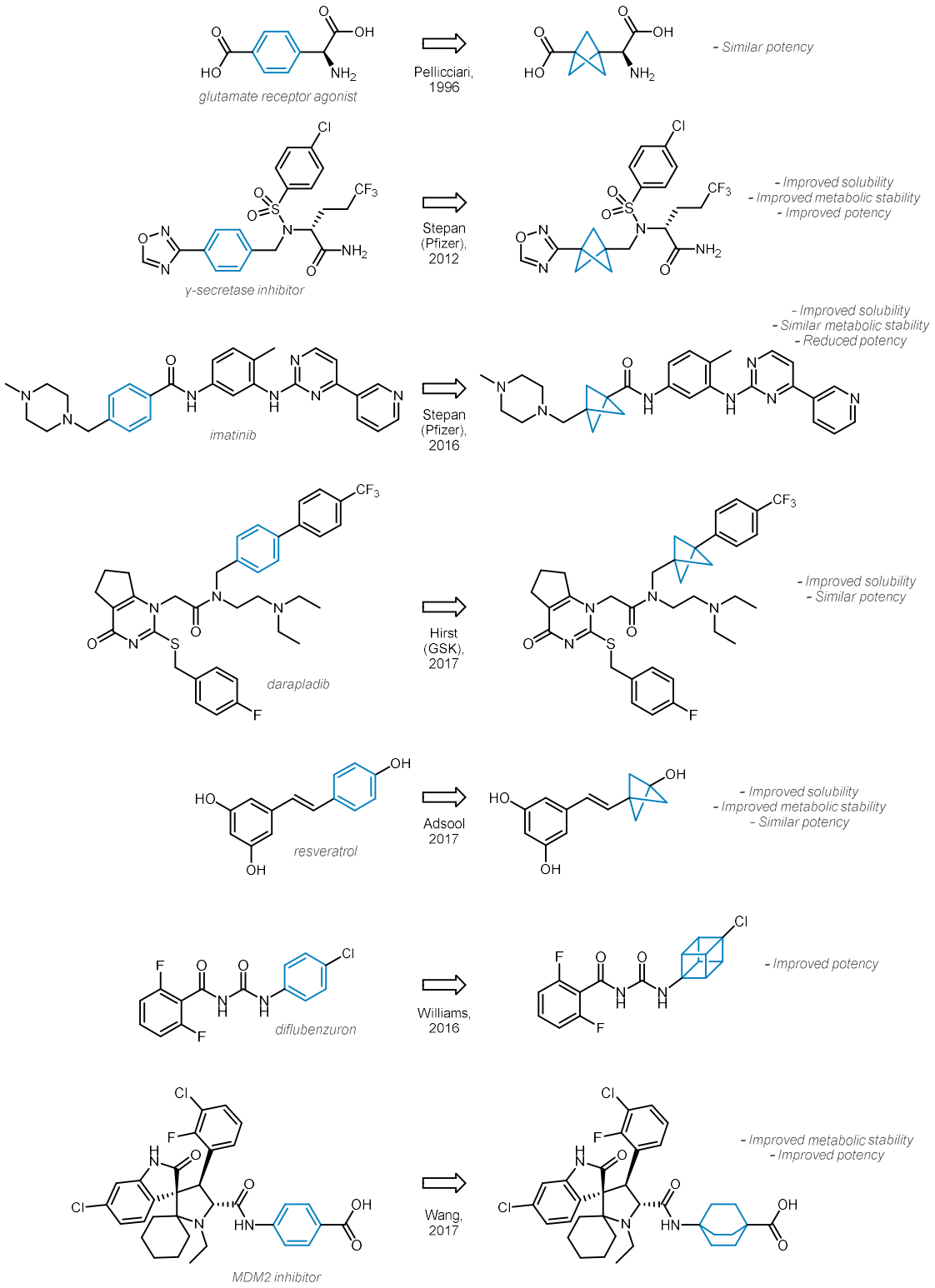


Figure 1.11 Bioisosteric replacements for *para*-disubstituted benzene.

In recent years, the search for *meta*-disubstituted benzene bioisosteres has received increasing amounts of interest, and a variety of structures have been tested as bioisosteres in drug analogues (Figure 1.12). As noted above, perhaps the most prominent example of a *meta*-benzene replacement is the BCHep, which can be accessed from [3.1.1]propellane, as introduced in Section 1.1.2. The BCHep replacement in the anti-cancer drug sonidegib results in improved metabolic stability and similar potency and solubility, while the BCHep replacement in the fatty acid amide hydrolase inhibitor URB597 showed improved metabolic stability and similar solubility but slightly reduced potency[47]. Mykhailiuk and coworkers have replaced the same *meta*-benzene in sonidegib with a spiro[3.3]heptane[82]. This spirocycle has both *cis* and *trans* isomers available, however both isomers showed reduced metabolic stability and potency, as well as similar solubility. The replacement of the *meta*-disubstituted benzene in the anti-inflammatory drug ketoprofen with a cuneane motif was investigated by Iwabuchi and coworkers[84], who found that it had similar ligand efficiency to its parent arene compound.

The nortricyclane scaffold was investigated by Morken and coworkers[85] and used to replace the *meta*-benzene in sonidegib and URB597. In sonidegib this resulted in improved solubility, but slightly reduced metabolic stability and potency, whereas in URB597 it resulted in improved solubility and metabolic stability, as well as slightly reduced potency. It is worth noting that in all examples with slightly reduced potency, the potency is still within a workable range, meaning that the drug may simply require some re-optimisation to regain its original potency. MacMillan and coworkers[79] have reported the replacement of the *meta*-disubstituted benzene in the cystic fibrosis drug lumacaftor with a 1,3 disubstituted cubane, resulting in improved metabolic stability and solubility, as well as similar potency. Finally, Baran and coworkers[101] showed that replacement of the *meta*-benzene in sonidegib with a 1,2 disubstituted BCP resulted in improved metabolic stability and solubility.

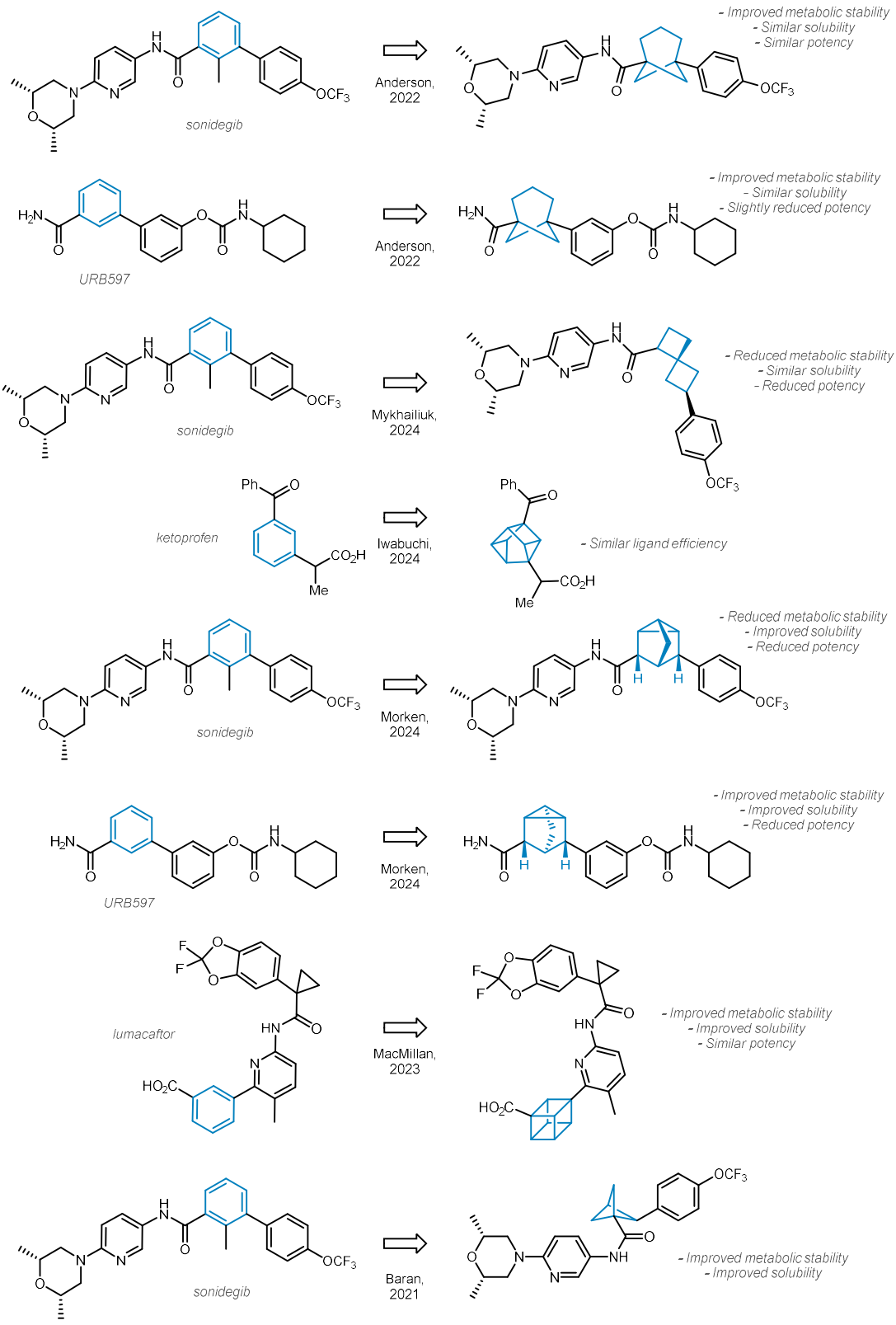


Figure 1.12 Bioisosteric replacements for *meta*-disubstituted benzene.

There are also several scaffolds which have been tested as bioisosteres for *ortho*-disubstituted benzene (Figure 1.13). The 1,5-disubstituted bicyclo[2.1.1]hexane (BCHex) has been investigated by Mykhailiuk and coworkers[90] as a bioisostere for the *ortho* benzene in the agrochemical boscalid, and it showed similar potency to the parent arene. The 1,5-BCHex has also been investigated by Tortosa and coworkers[102] as a bioisostere in the high blood pressure drug telmisartan, and it demonstrated similar ligand efficiency.

Alternatively, a 1,2-BCHex could be used to replace an *ortho* benzene, and this was reported by Mykhailiuk and coworkers[103]. The 1,2-BCHex analogue of the lipid-lowering drug lomitapide showed improved solubility but reduced metabolic stability, whereas the 1,2-BCHex analogue of the hyponatremia drug conivaptan showed improved solubility and metabolic stability. MacMillan and coworkers[87] investigated 1,2 disubstituted BCPs as bioisosteres for *ortho* benzenes and they found that the 1,2-BCP analogue of telmisartan showed increased solubility and similar potency, while the 1,2-BCP analogue of the D^3-dopamine agonist showed similar solubility but reduced metabolic stability.

There are now a large number of carbocyclic scaffolds available to choose from for use as bioisosteres with established methods for their synthesis[65,95], however there are limitations to relying entirely on these carbocyclic compounds. For example, some of the larger structures like BCHep, BCO and spiro[3.3]heptane introduce more hydrophobic character into the drug, leading to poor solubility. This issue could be solved by incorporating heteroatoms such as oxygen into the ring system. It can also be difficult to diversify substituents on the bridge positions as these substituents often have to be introduced at an early stage in the synthesis. However, if a heteroatom such as nitrogen were present in the ring, it would be relatively easy to vary the substituent on this heteroatom at a late stage.

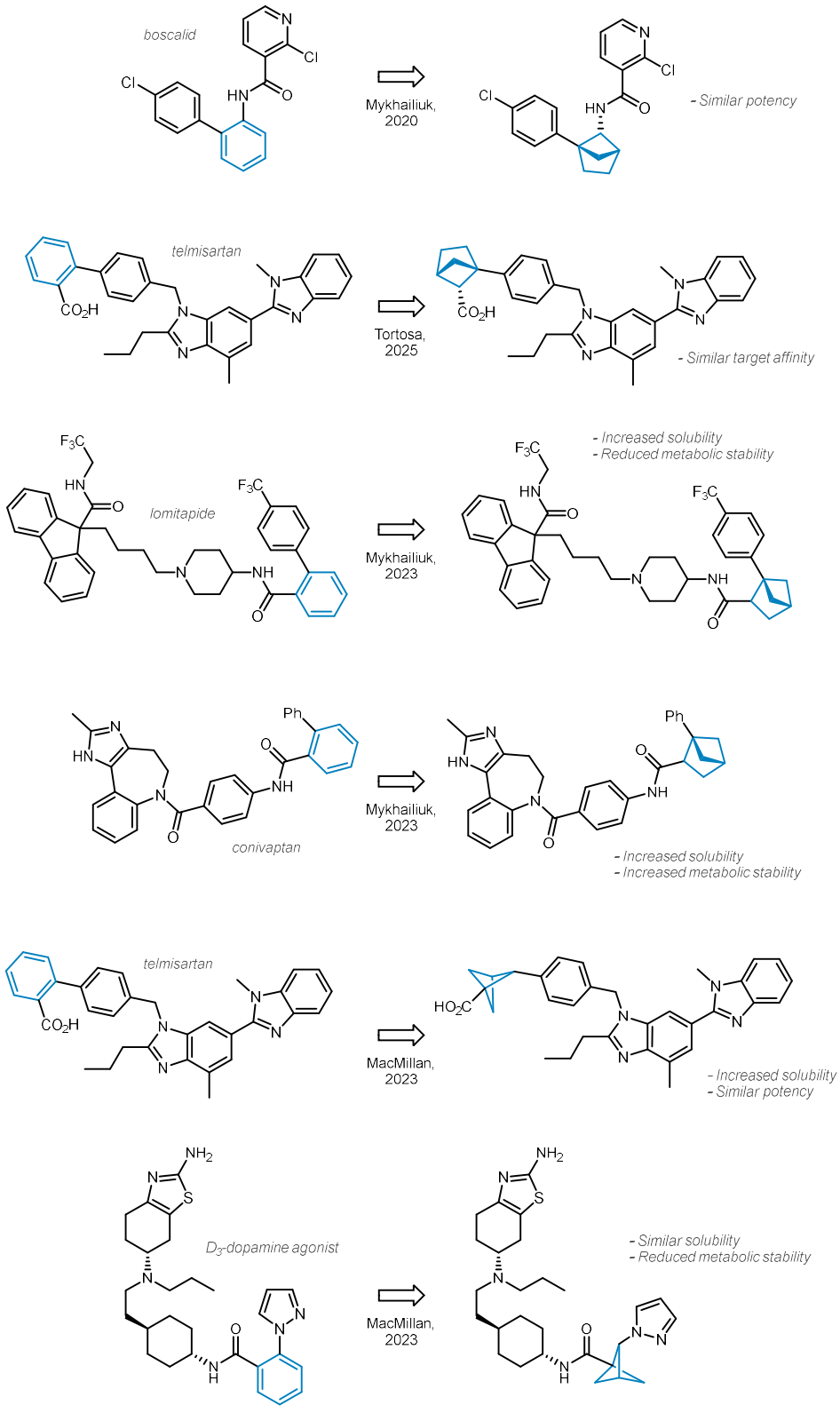


Figure 1.13 Bioisosteric replacements for *ortho*-disubstituted benzene.

Incorporating heteroatoms also opens up the possibility of developing bioisosteres for heteroarenes, such as pyridine, which would not be possible with carbocyclic structures. Exploring heterocyclic structures would also allow for the generation of more diversity within the scaffold itself, since various different heteroatoms could be introduced in various positions in the ring. The increased diversity within the scaffold and the ease of introducing bridge substituents would allow for greater efficiency in the exploration of chemical space in drug discovery. Heterocyclic sp^3-rich structures would therefore be of interest both as improved next generation bioisosteres for various arenes and heteroarenes, but also as novel 3D scaffolds for drug discovery.

1.2.5. Heterocyclic arene bioisosteres

The idea of incorporating heteroatoms into arene bioisosteres has recently gained momentum and there are now a few examples of such bioisosteric replacements in the literature (Figure 1.14).

Mykhailiuk and coworkers replaced the *meta*-disubstituted pyridine in the antihistamine rupadatine with a 3-aza-BCHep and this resulted in improved solubility and metabolic stability[104]. Similarly, they replaced the *meta*-benzene in sonidegib with a 3-oxa-BCHep and this resulted in dramatically improved solubility over both the parent arene compound and the carbocyclic BCHep analogue, however the metabolic stability was slightly reduced[83]. The same authors investigated the incorporation of oxygen into other sizes of rings, including the 2-oxa-BCHex scaffold[91]. When the *ortho* benzene in lomitapide was replaced with a 2-oxa-BCHex, this resulted in similar solubility and slightly reduced metabolic stability, and in the 2-oxa-BCHex analogue of boscalid, the solubility and metabolic stability were both improved, but the potency was slightly reduced. They also investigated the 2-oxa-BCO scaffold as a *para* disubstituted benzene replacement, and the 2-oxa-BCO analogue of imatinib showed improved solubility and improved metabolic stability[94]. Aggarwal and coworkers employed a 3,6-diaza-BCHep as

a rigid 3D analogue of piperazine and found that the 3,6-diaza-BCHep analogue of DB04232 showed similar metabolic stability to the parent compound[105].

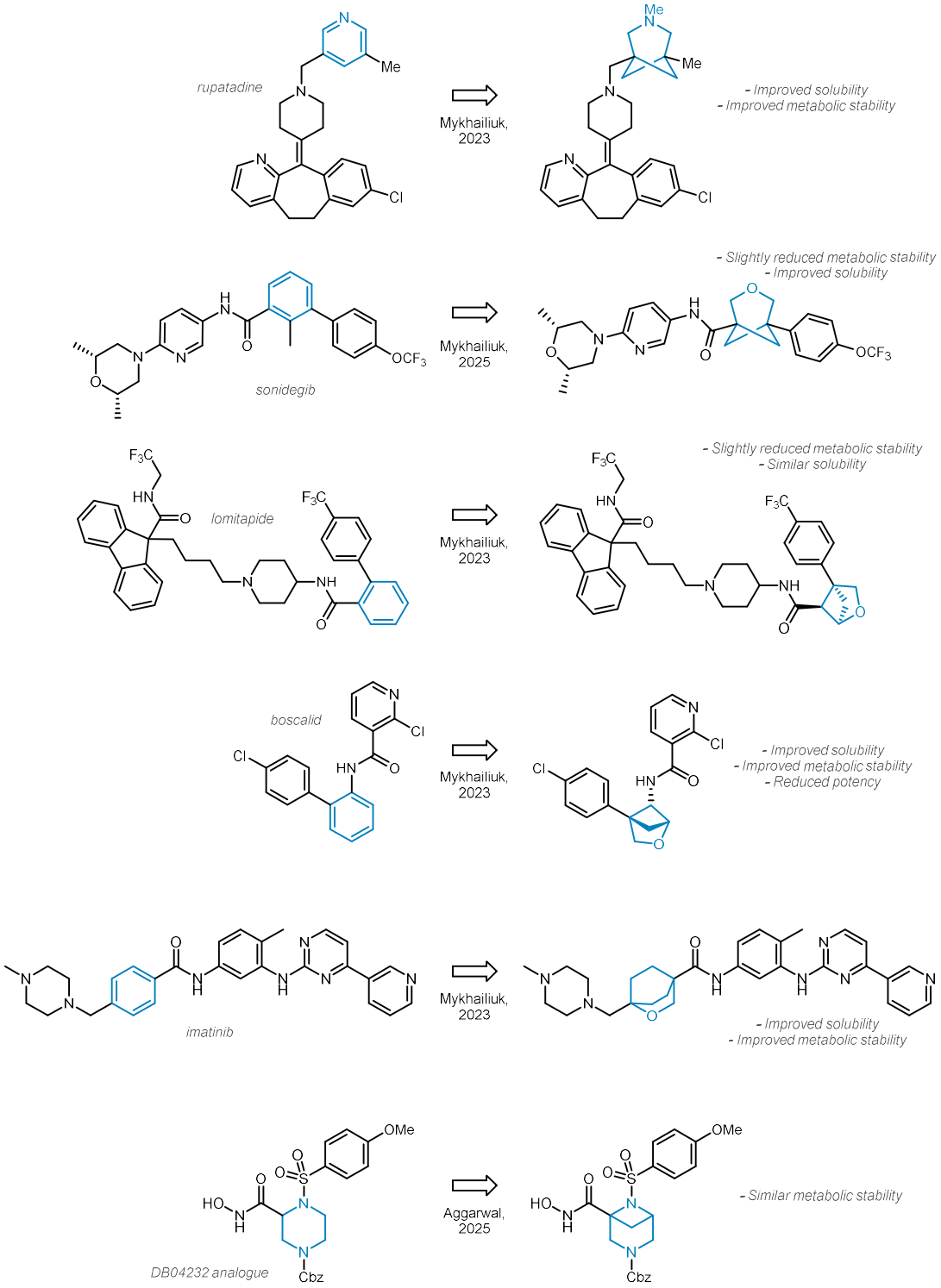


Figure 1.14 Heterocyclic bioisosteric replacements.

1.3. Synthesis of hetero-BCHeps

While the field of heterocyclic bioisosteres is still in its early stages and only a few examples have been tested in drug analogues, there has been an increasing interest in the synthesis of these compounds. The development of novel synthetic approaches to a diversity of heterocyclic structures will enable the synthesis of more drug candidates and bioisosteric analogues in the future. One scaffold which has been the focus of much synthetic effort is the hetero-BCHep. This is because hetero-BCHeps have the potential to act as bioisosteres for various disubstituted or polysubstituted arenes and heteroarenes. The methods that have been developed allow for the incorporation of different heteroatoms in various positions on the ring and the introduction of both bridgehead and bridge substituents. The current literature methods for the synthesis of hetero-BCHeps can be grouped into the categories of intermolecular cycloadditions (with either radical or polar mechanisms), intramolecular cycloadditions, and cyclisations.

1.3.1. Intermolecular cycloadditions (radical)

Intermolecular cycloadditions involving bicyclo[1.1.0]butanes (BCBs) have emerged as one of the most popular ways to access a diverse range of hetero-BCHeps with bridge and bridgehead substituents. Several distinct methods have been developed involving either radical or two-electron mechanisms, all of which use a catalyst to activate one or other of the cycloaddition components.

Within the group of cycloadditions that proceed by radical mechanisms, the reaction can be enabled by either generating a radical from the BCB component, or the non-BCB component. Figure 1.15 shows examples of the latter strategy, examples of which typically proceed by similar mechanisms. A photocatalyst (PC) is employed to firstly generate a radical from the non-BCB component by single electron transfer (SET), which then reacts with the strained central bond of the BCB to generate a cyclobutyl radical.

This radical is then oxidised (and in doing so reduces the photocatalyst), followed by ring closure by nucleophilic capture of the carbocation. This tactic provides access to a range of 2-hetero-BCHeps, always with the heteroatom positioned on the side of the BCHep furthest from the bridgehead carbonyl that originated in the BCB.

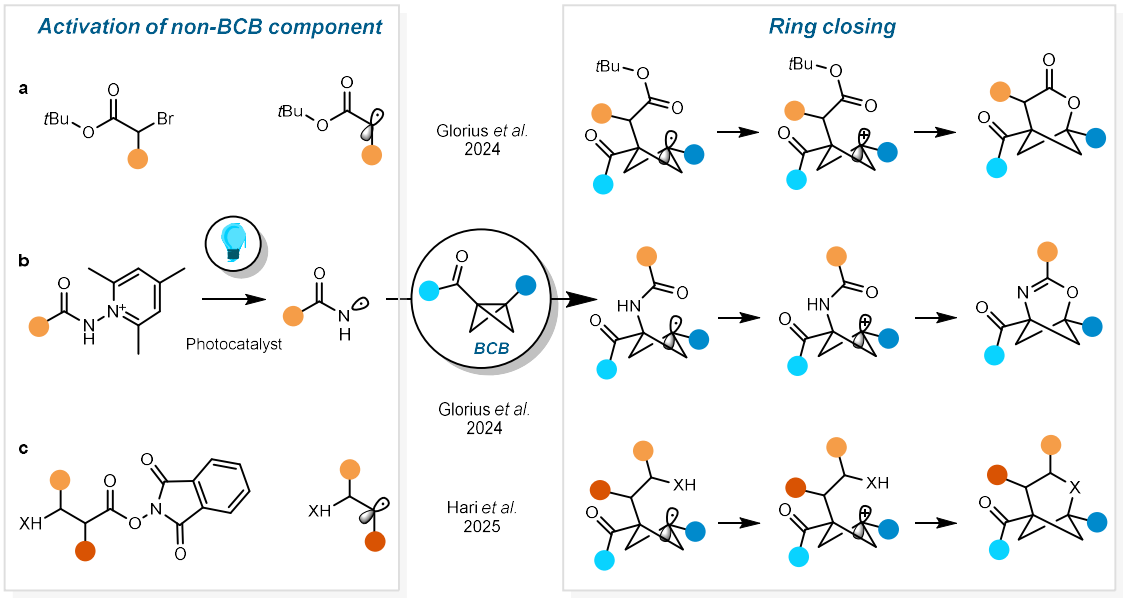


Figure 1.15. Radical-based intermolecular cycloadditions involving activation of non-BCB component.

Using this approach, Glorius *et al.*[106] accessed 2-oxa-BCHeps from *tert*-butyl α-bromoesters (Figure 1.15a) with an aromatic group on one of the bridgehead positions and an ester or amide on the other, where release of the *tert*-butyl cation facilitates ring closure. The bridge position can feature an alkyl or benzyl substituent, or no substituent. The same group (Figure 1.15b) also demonstrated the synthesis of 2-oxa-4-aza-BCHeps via the addition of *N*-centred radicals generated from pyridinium hydrazides,[107] which similarly feature an aromatic group on one of the bridgehead positions and an ester or amide on the other; various aryl groups could be installed on the bridge position. Hari *et al.*[108] reported an elegant method to access both 2-oxa- and 2-aza-BCHeps (Figure 1.15c, again with an aromatic group on one of the bridgehead positions and an ester on the other). Here, use of a redox-active ester enabled decarboxylative generation of an alkyl

radical, with a separate β-heteroatom nucleophile undergoing cyclisation. Various alkyl and aryl groups can be installed on either of the bridge positions, including spirocyclic and fused rings. Enantiopure hetero-BCHeps could also be achieved using chiral precursors, since the stereochemistry at the nucleophile-bearing carbon atom on the backbone is maintained throughout the transformation.

An alternative strategy to achieve a formal (3+2) cycloaddition firstly generates a radical from the BCB, as demonstrated by Zheng *et al.* (Figure 1.16).[109] Here, a Ti^{III} catalyst triggers reductive ring-opening of the BCB via a ketyl radical anion, leading to an enolate-cyclobutyl radical. The radical is then trapped by addition to a vinyl azide with loss of N_2, and the resulting iminyl radical undergoes cyclisation by addition to the Ti^{IV} enolate, a process that ejects and regenerates the Ti^{III} catalyst. As before, this method accommodates a range of aromatic bridge substituents, and the bridgehead substituents are again an aromatic ring and a carbonyl. However, in contrast to the above methods, the heteroatom is introduced on the side of the BCHep closest to the carbonyl substituent.

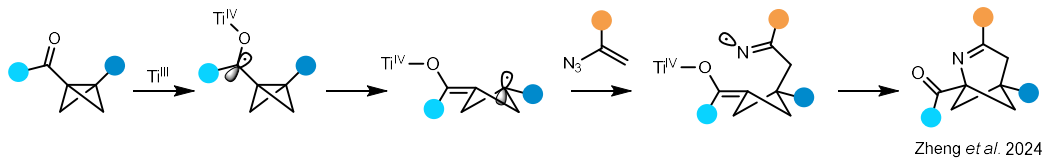


Figure 1.16 Radical-based intermolecular cycloaddition involving activation of BCB component.

1.3.2. Intermolecular cycloadditions (polar)

In a similar manner to radical-mediated formal cycloadditions, the polar equivalents can be enabled either by activating the BCB with a Lewis acid, or by activating the non-BCB component. Examples of reactions which proceed by activating the non-BCB component are shown in Figure 1.17. In most of these cases, the activated component acts as a

nucleophile and attacks the BCB, causing it to open and form an enolate. The enolate then reacts to close the ring.

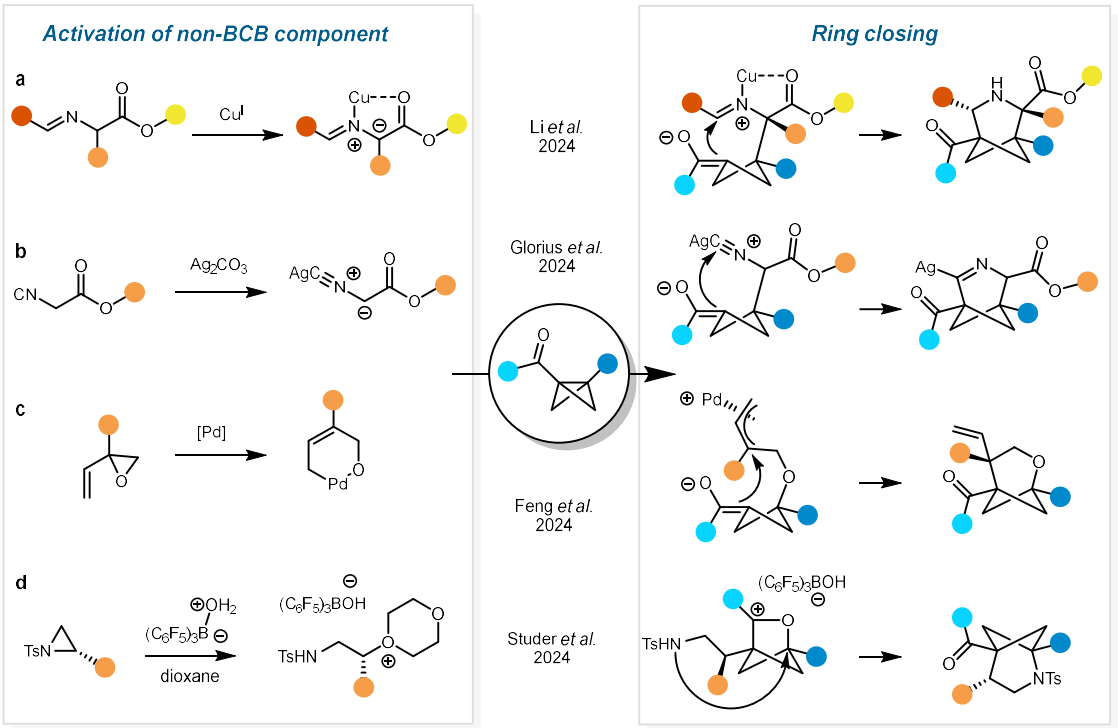


Figure 1.17 Polar intermolecular cycloadditions involving activation of the non-BCB component.

In a method reported by Li *et al.*[110], an aldimine ester is activated by a Cu^{I} catalyst to produce a Cu-ylide intermediate (Figure 1.17a). This proceeds to attack the BCB, leading to a 3-aza-BCHep structure. This method tolerates bridgehead substituents of aryl or hydrogen on one side and ketone on the other. The bridge substituents are most commonly aryl, ester and alkyl. If chiral ligands are used with the Cu catalyst, then chiral products may be obtained. The Glorius group also report a silver-enabled cycloaddition[111] which uses Ag_2CO_3 to generate a silver-isocyanide complex (Figure 1.17b). This complex acts as a nucleophile and attacks the BCB in the same way. However, after ring closure, the product undergoes a further cycloaddition reaction with another isocyanide complex to produce a 3-aza-BCHep with an ester and an alkene as

the bridge substituents. As before, the bridgehead substituents are mainly a combination of aryl and carbonyl.

In an alternative method by Feng *et al.*[112], a Pd catalyst facilitates an epoxide ring-opening by forming a π-allyl group, leaving the alkoxy group free to attack the BCB (Figure 1.17c). The resulting enolate can close onto either side of the π-allyl system and the regioselectivity is controlled by the ligand chosen for the Pd catalyst. The bridge substituents are always a vinyl and aryl in the 4-position and the bridgehead substituents are always a ketone on one side and an aryl or hydrogen on the other side. The use of chiral phosphine ligands enables the synthesis of enantioenriched 2-oxa-BCHeps.

Finally, Studer *et al.*[113] reported a method involving the activation of an aziridine with $B(C_6F_5)_3$, which results in stereospecific ring opening of the aziridine by dioxane (Figure 1.17d). Then, in contrast to previous methods, the BCB acts as the nucleophile and attacks the non-BCB component, causing the dioxane to leave and forming an oxa-BCHex intermediate. The nitrogen then reacts across the ring, resulting in a 2-aza-BCHep structure. The bridgehead substituents are a hydrogen on the same side as the nitrogen and an aryl ketone on the other side. Various sulfonamides can be tolerated on the nitrogen and various substituents can be introduced onto the 4-position of the bridge, including aryl, alkyl and allyl groups. The stereochemistry of the aziridine is conserved throughout the reaction, as the mechanism involved two S_N2 reactions at the same site.

An alternative way to carry out a polar cycloaddition, shown in Figure 1.18, is to activate the BCB with a Lewis acid, which promotes BCB fragmentation to an enolate-cyclobutyl cation. The nucleophilic part of an ambiphilic reaction partner captures the cation, and finally the enolate reacts with the electrophilic centre of the partner to close the 3-atom bridge. As these reactions rely on BCB activation, they inevitably feature a carbonyl group on one of the BCB bridgehead positions (which can coordinate to a Lewis acid) and an

aryl group on the other bridgehead position (which can stabilise the intermediate carbocation).

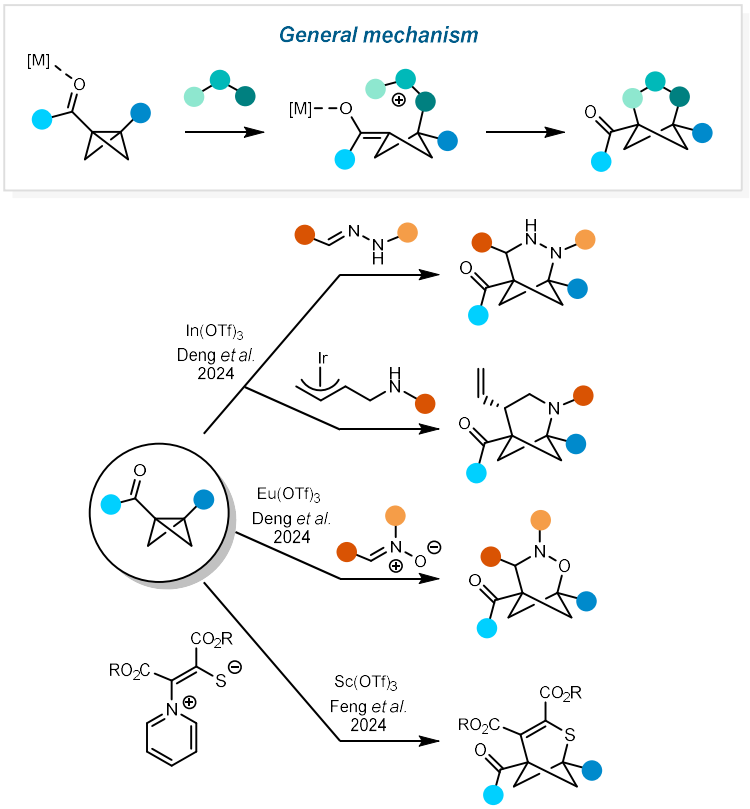


Figure 1.18 Polar intermolecular cycloadditions involving activation of BCB component.

Examples include the method by Deng *et al.*[114] which uses $Eu(OTf)_3$ to facilitate reaction of a nitrone with the BCB, providing access to 2-oxa-3-aza-BCHeps. In another method by the same group[115], $In(OTf)_3$ catalyses the formal cycloaddition of hydrazones, leading to 2,3-diaza-BCHeps, or the stepwise addition of amine-substituted π-allylindium species, leading to 2-aza-BCHeps. The 2-aza-BCHeps have the potential to be enantiopure when a chiral iridium catalyst is also used. As before, these methods feature mainly aryl and carbonyl bridgehead substituents on the hetero-BCHep product, while a range of mainly aryl substituents are available for the bridge positions. The Feng group reported a related method[116] using $Sc(OTf)_3$ as a catalyst to effect the addition of 1,4-zwitterionic pyridinium thiolates, affording thia-bicyclo[3.1.1]heptenes. This method

produces compounds with similar aryl and carbonyl substituents on the bridgehead positions, but this time the bridge substituents are esters.

To summarise this section, it is possible to synthesise a wide variety of hetero-BCHeps by intermolecular cycloadditions, with heteroatoms in various positions in the ring, via a wide selection of different radical and polar catalytic methods. However, all methods share the common feature of a strain-release reaction involving the BCB central bond, followed by ring closure to from the BCHep; this arguably limits the diversity of bridgehead substituents, which must be amenable to the activation process, and are therefore most commonly an aryl group on one side and a carbonyl on the other. These methods offer wider variation in the pattern of bridge substitution, however most of them are limited by the requirement to have at least one bridge substituent of a certain type at a particular site on the ring. These methods could become more broadly applicable if it were possible to precisely introduce any desired substituent at any position on the ring, including with control of absolute stereochemistry, or indeed to prepare BCHeps with no bridge substituents if so desired.

1.3.3. Intramolecular cycloadditions

Despite a longer history, intramolecular cycloadditions are relatively underexplored compared to the intermolecular variant as an approach to hetero-BCHeps. (2+2) Cycloadditions of 1,5 dienes usually favour the "cross product" bicyclo[2.1.1]hexane over the "straight product" bicyclo[2.2.0]hexane (Figure 1.19). However, cycloadditions of 1,6 dienes usually favour the "straight product" bicyclo[5.1.0]heptane over the "cross product" bicyclo[3.1.1]heptane[117]. There are however a small number of reports where this has been achieved.

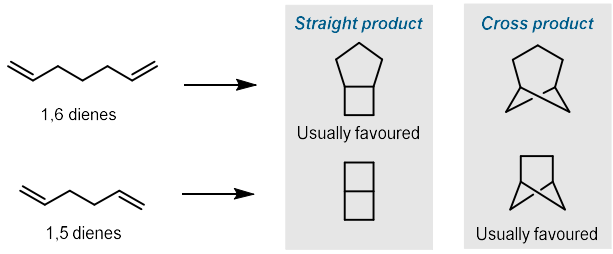


Figure 1.19 Straight product vs. cross product in intramolecular cycloadditions.

In one of the earliest syntheses of aza-BCHeps, Schieweck *et al.* reported a thermal (2+2) cycloaddition of *N*-acryloyl acrylimides, decorated with various substituents, to generate 3-aza-BCHep diones (Figure 1.20a).[118] In this reaction, one of the bridgehead substituents is an aryl group, but the other can be aryl, alkyl or a hydrogen atom. Additionally, the nitrogen substituent can be aryl, alkyl or H. This method could therefore potentially provide access to a wide range of medicinally-relevant BCHeps with varying substitution patterns, albeit with the limitation that carbonyls must be included on the bridge, which introduces potential issues with downstream imide stability.

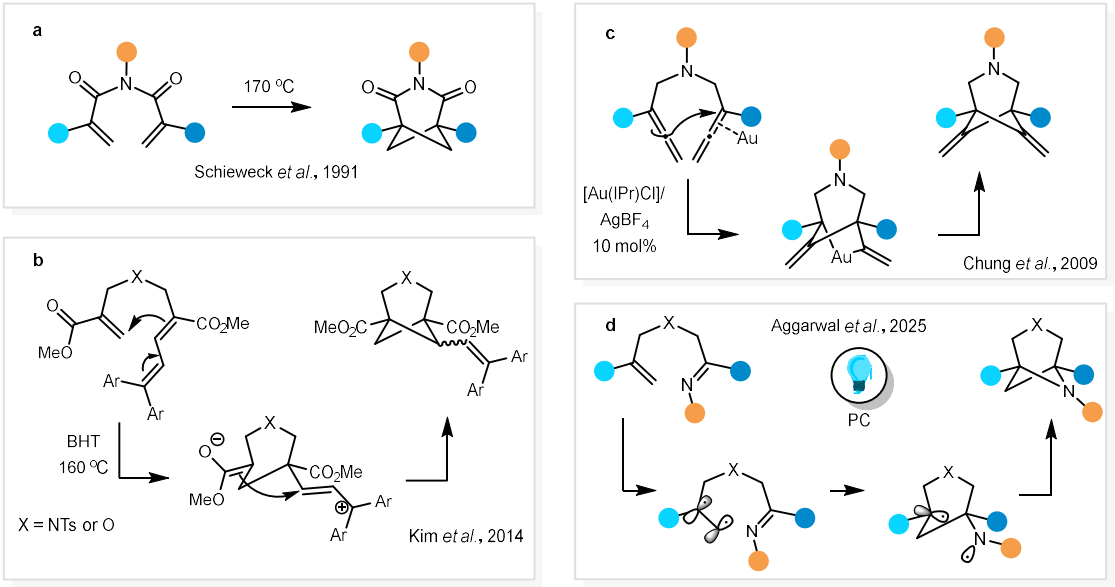


Figure 1.20 Intramolecular cycloadditions. **a** Thermal cycloaddition of *N*-acryloylacrylimides. **b** Stepwise thermal cycloaddition. **c** Gold-catalysed cycloaddition. **d** Photocatalysed cycloaddition.

A complementary method described by Kim *et al.*[119] (Figure 1.20b) circumvents the need for carbonyls on the three-atom bridge by including a sidechain on the smaller bridge that can stabilise a positive charge, allowing the reaction to proceed in a stepwise manner via Prins-type cyclisation. This produces BCHeps with no substituents on the larger bridge and with esters on the bridgehead positions, which would be useful for further functionalisation. However the diaryl vinyl group, which is necessary for reactivity, is retained on the cyclobutane bridge. This method could certainly become more applicable should the diaryl part prove amenable to further functionalisation, or if other, more medicinally relevant groups could be installed at this position.

An alternative method developed by Chung *et al.* (Figure 1.20c) uses an *N*-heterocyclic carbene/Au(I) catalyst system to mediate a formal cycloaddition between two allenes[120]. This reaction is proposed to begin with nucleophilic attack of one allene component onto the Au-bound allene. This gives a gold-bridged intermediate which then undergoes reductive elimination to form the product. A limited selection of aryl and alkyl groups may be installed at the bridgehead positions, and the substituent on the nitrogen atom can be either an aryl or sulfonyl group. An advantage of this method is that it does not introduce unnecessary substituents on the larger bridge, however it does result in alkenes on both of the smaller bridges. The utility of this method could be expanded by further functionalisation of these alkenes, and by extending the scope of the bridgehead substituents.

While the previous three examples were from over 10 years ago, the intramolecular cycloaddition has recently made its way back into current literature with a report from the Aggarwal group[105] (Figure 1.20d). This method proceeds by a radical mechanism, which is typically challenging because the “straight product” is favoured over the “cross product” due to the kinetic preference of a 5-exo-trig over a 6-exo-trig cyclisation. The authors overcome this issue by including a radical-stabilising group at the C1 position to

disfavour the 5-exo-trig, leading to the desired “cross product”. The group X in the larger bridge may be oxygen, carbon or nitrogen with various protecting groups. The bridgehead substituent can be a range of aryl, allyl or carbonyl groups. Additional carbonyls may also be introduced on the bridge positions but these are not necessary.

These examples of intramolecular cycloadditions were mostly reported before the current trends in using (hetero)bicycloalkanes as bioisosteres in drug scaffolds. As such, they represent an underexplored area which could be profitable to revisit; if the scope of substituents could be expanded and further functionalisations developed, these methods could become useful tools for the synthesis of hetero-BCHeps.

1.3.4. Cyclisations

Aside from cycloadditions, the main way to construct hetero-BCHeps is by cyclisation reactions. There are several varieties of ring-closing strategies to choose from, which provide access to a range of hetero-BCHeps with heteroatoms in various positions on the ring.

Perhaps the most prominent cyclisation method in the recent literature is that reported by Mykhailiuk *et al.* and Ryabchuk *et al.* (Figure 1.21a), where a spirocyclic cyclobutane-oxetane is used as a starting material. Reduction of either a nitrile[104] or ester[121,122] on the cyclobutane precedes Lewis acid-promoted cyclisation onto the oxetane, resulting in 3-hetero-BCHeps with no bridge substituents. A restriction of this strategy is that one of the bridgehead substituents is inevitably a primary alcohol, while the other (cyclobutyl) substituent can be one of a wide range of aromatic, alkyl, ester or nitrile groups. Importantly, this method is scalable and provides opportunities for further facile functionalisation to access a wide range of pharmaceutically relevant compounds. Subsequent to Mykhailiuk's work, the Johnson group described a related strategy using a bromonium ion as electrophilic trigger for 2-oxa-4-aza-BCHep synthesis.[123] Possible

substituents for the bridge position in this chemistry include a wide range of aryl and alkyl groups, while the alkyl bromide on the bridgehead position offers opportunities for further functionalisation. It is also possible to have a limited number of additional substituents already installed on the cyclobutane before the ring closure.

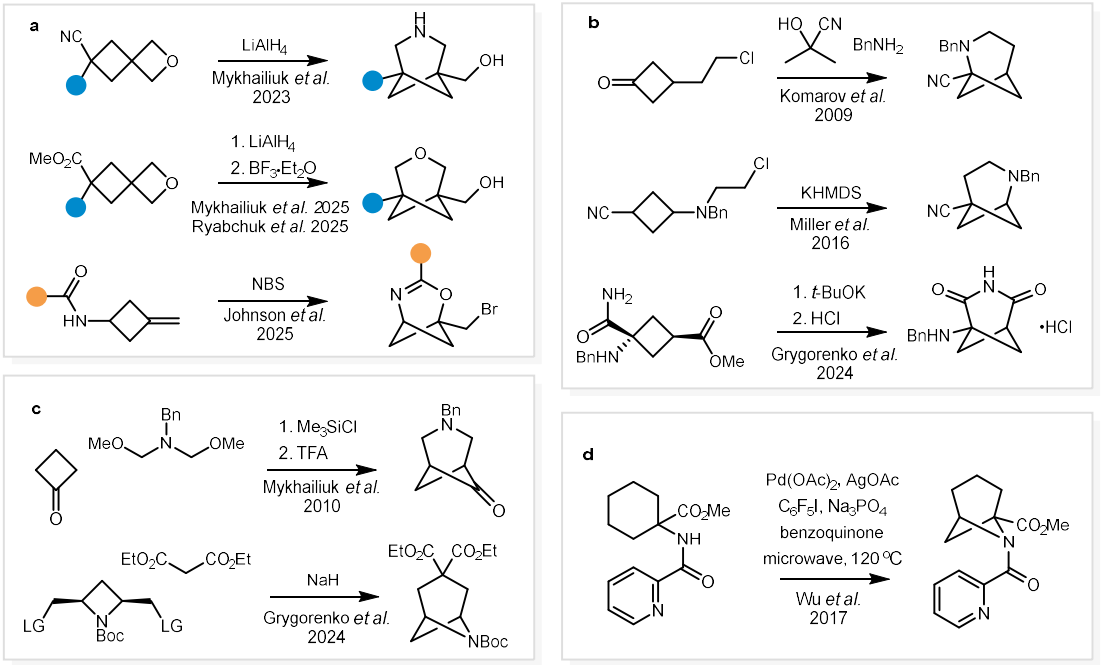


Figure 1.21 Ring-closing reactions. **a** Spirocyclic cyclobutane cyclisations**. b** Non-symmetric cyclobutane cyclisations. **c** Symmetric intermolecular reactions**. d** C-H amination reaction.

The next group of methods shown in Figure 1.21b also involves cyclobutane-containing starting materials, however these are not spirocyclic and the mode of ring-closure varies between methods. They furnish hetero-BCHeps with the heteroatom in the 2-position. Komarov *et al.*[124] report a Strecker-type cyclisation which forms a C-N bond to make 2-aza-BCHeps. The cyclisation was only attempted with the substituents shown, however there are opportunities for further functionalisation on the nitrogen or nitrile. A similar method was reported by Miller *et al.*[125], but this time a C-C bond is formed last by deprotonation adjacent to the nitrile, then attack of the aza-enolate on the pendent chloride. This results in 2-aza-BCHeps with the bridgehead nitrile group at the other side, which similarly present opportunities for further functionalisation. An arguably

more limited cyclisation by imide formation was also reported by Grygorenko and co-workers[126]. The transformation was performed with only the substitution pattern shown, however it proved scalable and both the carbonyl and benzyl groups could be further functionalised.

Another variety of cyclisation reaction, shown in Figure 1.21c, involves a one-pot tandem reaction between two symmetrical components. Mykhailiuk *et al.*[126] report a method which uses a double Mannich reaction to afford 3-aza-BCHeps, which installs a ketone in the 6-position. More recently, Grygorenko *et al.*[127] reported a double alkylation of diethyl malonate with a symmetric 1,3-disubstituted azetidine to generate 6-aza-BCHeps. Similarly, the transformation was performed with only one set of substituents, but was scalable and a variety of further functionalisations were possible. Both of these symmetrical additions furnish building blocks that can be prepared on multi-decagram scale, and can be easily modified to provide access to medicinally relevant compounds.

A final and rather unique mode of cyclisation is a C-H amination reported by Wu *et al.* (Figure 1.21d).[128] In this process, Pd-catalysed C-H activation occurs at the γ-position of the aminocyclohexane substrate, followed by formation of the 6-aza-BCHep by reductive elimination. The bridgehead substituents explored included a hydrogen atom, and a limited number of esters, while the nitrogen atom was substituted only with the pyridyl ketone shown. C–H activation at the δ-position could also be achieved, so it seems possible that through careful choice of starting materials, this method could be expanded to access aza-BCHeps with the nitrogen in alternative positions on the ring. Cyclisation by C–H activation is certainly an underdeveloped area when it comes to bridged small ring chemistry, and could merit further exploration to unearth its full potential.

1.4. Contribution of this thesis

Current methods for the synthesis of hetero-BCHeps have several limitations. The intermolecular cycloaddition reactions onto BCBs are the most prominent method in the literature, however the BCBs must be prepared with certain substituents at the bridgehead positions which are required for their stability and reactivity. This usually involves an aryl group at one side and a carbonyl at the other side. This limits the scope of bridgehead substituents that can be installed in the hetero-BCHep because these are predetermined by the BCB. Many of these cycloadditions also have requirements for certain substituents on the non-BCB component, which become bridge substituents in the hetero-BCHep. The scope for these bridge substituents is often narrow and can lead to hetero-BCHeps with unwanted bridge substituents that limit their use as bioisosteres. Indeed, there are few examples of drug analogues that have been prepared via intermolecular cycloadditions. The intramolecular cycloadditions are still underexplored and currently have similar limitations in their requirements for certain bridge and bridgehead substituents which may not be desired in the target compound. Mykhailiuk's cyclisations of spirocyclic starting materials are arguably the most precise way of constructing hetero-BCHeps without introducing unnecessary substituents, however they invariably introduce a hydroxymethyl group at one bridgehead position, and the substituent at the other bridgehead position is introduced early in the synthesis, rather than a more diversifying late stage.

There is therefore still a need for methods to achieve concise and modular syntheses of hetero-BCHeps which allow for the late-stage diversification of bridgehead substituents. This could be achieved via ring-opening reactions of hetero[3.1.1]propellanes, which would produce difunctionalised hetero-BCHeps in a single step with no unnecessary bridge substituents. This would be a complementary route to the existing methods and

would allow access to hetero-BCHeps which are difficult or impossible to prepare using other routes.

However, despite decades of research into propellanes made entirely from carbon atoms, small-ring propellanes containing heteroatoms are to date unknown. In this thesis, a novel route to a family of hetero[3.1.1]propellanes is reported, the first of the small-ring heteropropellanes to succumb to chemical synthesis. This is a significant advancement both in the field of propellane chemistry, as it opens up opportunities for the investigation of the properties and reactivity of this new type of propellane, and also in the field of heterocyclic small-ring bioisosteres, as it introduces a versatile new synthetic approach to these important pharmaceutical intermediates.

The synthesis of these hetero[3.1.1]propellanes proved to be a challenging task, since it was not possible to simply adapt the existing routes to carbocyclic propellanes, and a new synthetic route had to be developed from scratch. This was achieved on a multi-decagram scale and involved a common intermediate, which could be leveraged to access propellanes containing three different heteroatoms. A range of ring-opening reactions of these propellanes was also investigated, providing access to a diverse selection of disubstituted hetero-BCHeps. Furthermore, the incorporation of a nitrogen into the propellane scaffold provided a unique opportunity to investigate bridge-substituted propellanes with various substituents on the nitrogen. This thesis explores the synthesis and reactivity of hetero[3.1.1]propellanes and demonstrates their potential as exciting new tools for medicinal chemistry.

2. Synthesis of hetero[3.1.1]propellanes

2.1. Retrosynthesis of 3-oxa[3.1.1]propellane

The first propellane to be targeted was 3-oxa[3.1.1]propellane and several different strategies for its synthesis were investigated. Each unsuccessful attempt provided new insights which were used to improve the design of subsequent routes. The synthesis of 3-oxa[3.1.1]propellane was considered from a retrosynthetic perspective, where the strategies investigated could be grouped into four main disconnections: disconnection to a cyclopropane (Figure 2.1a), disconnection to a BCB (Figure 2.1b), disconnection to a dihalo-BCHep (Figure 2.1c), and disconnection to a tetrahydrofuran (Figure 2.1d).

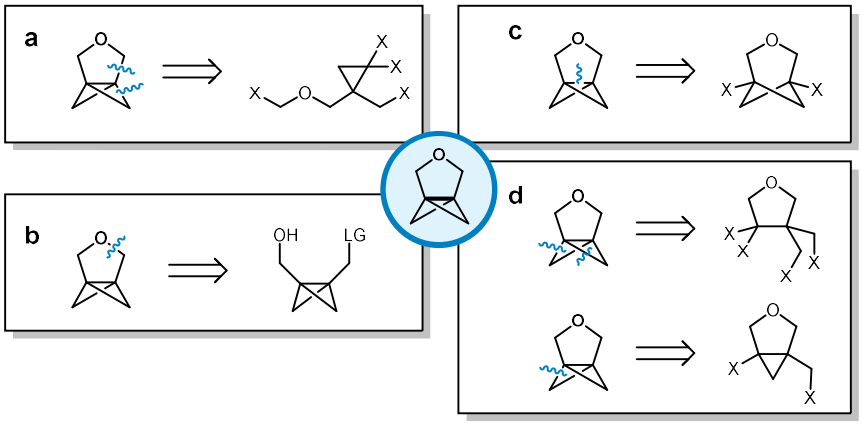


Figure 2.1 Possible retrosyntheses of 3-oxa[3.1.1]propellane.

2.1.1. Disconnection to cyclopropane

Perhaps the most obvious route to consider in the synthesis of a hetero[3.1.1]propellane is a simple adaptation of the existing route to carbocyclic [3.1.1]propellane (Figure 2.2a). If an oxygen atom could be introduced in **19** then the route could be followed through in the same way as for the carbocyclic analogue, to arrive at the oxapropellane. However,

having an oxygen in this position in **23** (Figure 2.2b) results in the introduction of a chloromethoxy group, which is rather unstable and susceptible to nucleophilic attack, and would likely be difficult to carry through the synthesis. In fact, it proved unsuccessful to introduce this group in even the first step of the synthesis.

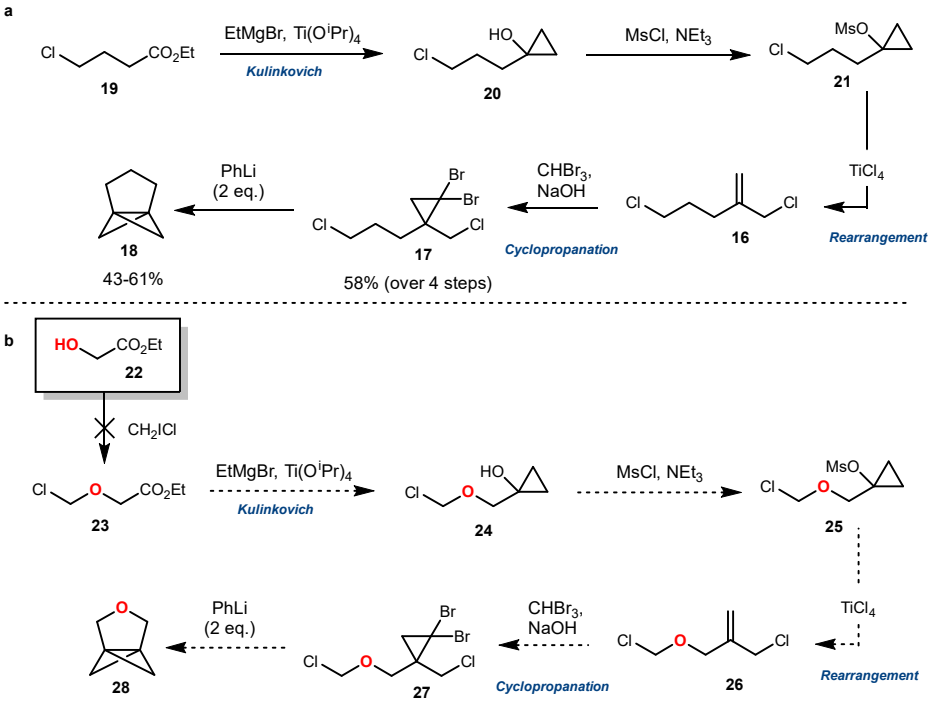


Figure 2.2. a Established route to carbocyclic [3.1.1]propellane. **b** Adapted route to 3-oxa[3.1.1]propellane.

One way to improve this strategy would be to introduce the chloromethoxy group later in the synthesis. Compound **27** was targeted because after installing the chloromethoxy group, the only step remaining is the propellane formation (Figure 2.3). The synthesis of **27** was first attempted via S_N2 substitution of **5** (Figure 2.3a), however this was unsuccessful and an unexpected product was obtained instead, which will be discussed further in Section 2.1.1.1. An alternative synthesis of **27** was proposed (Figure 2.3b), starting from alkene **30**. This involved a TBS monoprotection to give **31** (41%), then a chlorination of the remaining hydroxy group to give **32** (64%), and finally dibromocyclopropanation (55%) to access intermediate **33**. However, after TBS cleavage

to give **29**, the introduction of the chloromethoxy group was once again unsuccessful by any of the conditions attempted.

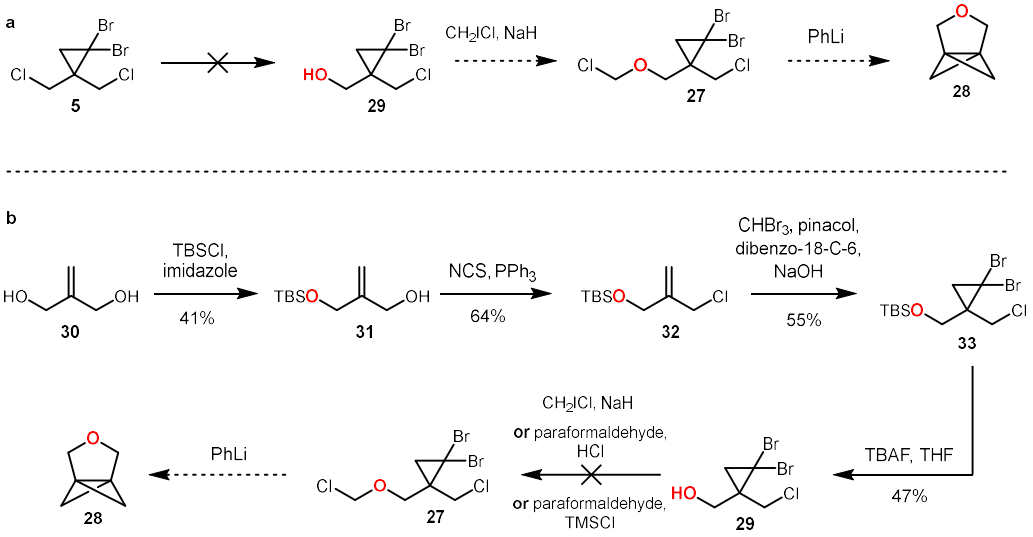


Figure 2.3. a First route to intermediate **27**. **b** Second route to intermediate **27**.

It became clear that a chloromethoxy-containing intermediate would not be suitable and a different strategy would have to be developed that was not based on the original carbocyclic strategy. It was decided to investigate an entirely different disconnection, involving a BCB intermediate.

2.1.1.1. An unexpected debromination reaction

The attempted conversion of **5** to **29** had an unexpected outcome, namely the replacement of one of the bromine atoms with a hydrogen to give **34** (Figure 2.4a). This was curious enough that it was decided to investigate this outcome further and to probe the mechanism by which this occurred. Classic methods in the literature for the monodebromination of dibromocyclopropanes involve harsh conditions or toxic reagents, such as Ti(O*i*Pr)$_4$ and EtMgBr[129], tri(*n*-butyl)tin hydride[130], or methyllithium[131] (Figure 2.4b), and there is one recent method which involves organophotocatalysis[132]

(Figure 2.4c). A simple and mild method for this transformation may therefore be of use to synthetic chemists.

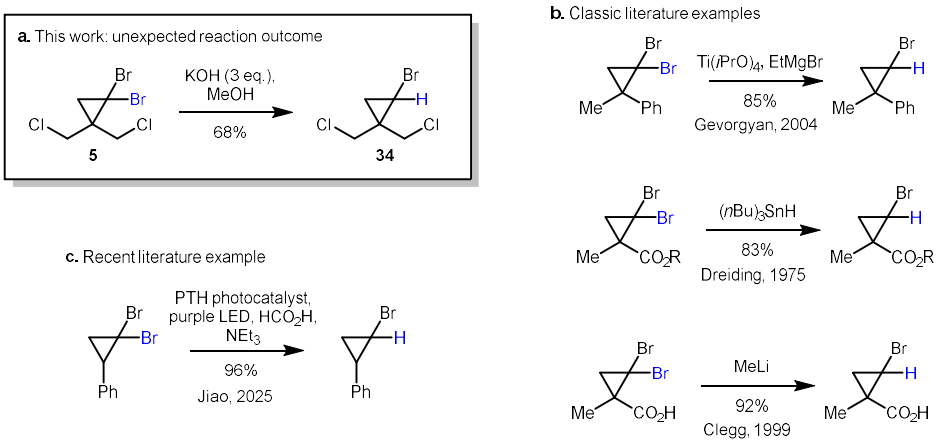
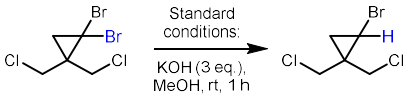


Figure 2.4. a Classic literature examples of debromination of dibromocyclopropanes. **b** Recent photocatalytic method for debromination. **c** Unexpected debromination reaction involving simple and mild conditions.

A series of mechanistic experiments was conducted to gain insights into the mechanism of this transformation (Table 2.1). Firstly, the amount of KOH was varied. The yield remained high using 2 or 3 eq. of KOH, however when this was reduced to 1 eq. KOH the yield dropped significantly, suggesting that 2 eq. KOH are required for this transformation. NaOH was also a suitable (and arguably superior) base. The addition of TEMPO to the reaction mixture completely inhibited the reaction, indicating that it likely proceeds via a radical mechanism. Interestingly, when dry, de-gassed MeOH was used, the yield dropped significantly, suggesting that O_2 may be involved in the reaction mechanism. The reaction also proved possible with EtOH, *i*PrOH, or *n*PrOH as the solvent, although the yields (after 1 h) were lower.

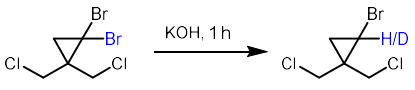
Table 2.1. Mechanistic experiments.



Deviation from standard conditions	NMR yield
3 eq. KOH (standard conditions)	68%
2 eq. KOH	74%
1 eq. KOH	45%
3 eq. NaOH	85%
TEMPO added	0%
Dry, de-gassed MeOH	37%
EtOH	56%
i-PrOH	22%
n-PrOH	10%

A series of deuterium incorporation experiments was also conducted to gain further insights into the mechanism (Table 2.2). When the solvent was CD_3OD, the reaction proceeded with almost complete deuterium incorporation, and the NMR yield also decreased significantly, suggesting the presence of a large kinetic isotope effect. Interestingly, when CD_3OH was used, almost complete deuterium incorporation was again observed, as well as a strong kinetic isotope effect. This indicates that the hydrogen in the product derives from the methyl group of the methanol solvent and that hydrogen transfer may be involved in the rate determining step. When a 1:1 mixture of CH_3OH/CD_3OD was used, the percentage of deuterium incorporation dropped by more than half, showing that the hydrogen atom in the product was preferentially taken from CH_3OH.

Table 2.2. Deuterium incorporation experiments.



Solvent	NMR yield	D incorporation
CH_3OH	68%	0%
CD_3OD	11%	97%
CD_3OH	14%	98%
1:1 CH_3OH/CD_3OD	65%	10%

A mechanism was proposed based on these results (Figure 2.5). KOH enables the formation of a methoxide ion from methanol. Then, in a single electron transfer (SET) step, an electron is transferred from the methoxide ion to oxygen, resulting in the formation of methoxyl and superoxide radicals. The former radical undergoes a 1,2-hydrogen atom shift, resulting in a radical on the primary carbon atom. This carbon-centred radical then abstracts a bromine atom from the dibromocyclopropane in a halogen atom transfer (XAT) step. The resulting cyclopropyl radical then abstracts a hydrogen (or deuterium) from the solvent in a hydrogen atom transfer (HAT) step to generate the product and a $^{\cdot}CH_2OH$ radical, which can react with a dibromocyclopropane to propagate the cycle. The XAT step also generates bromomethanol, which will immediately react with KOH to generate formaldehyde and KBr.

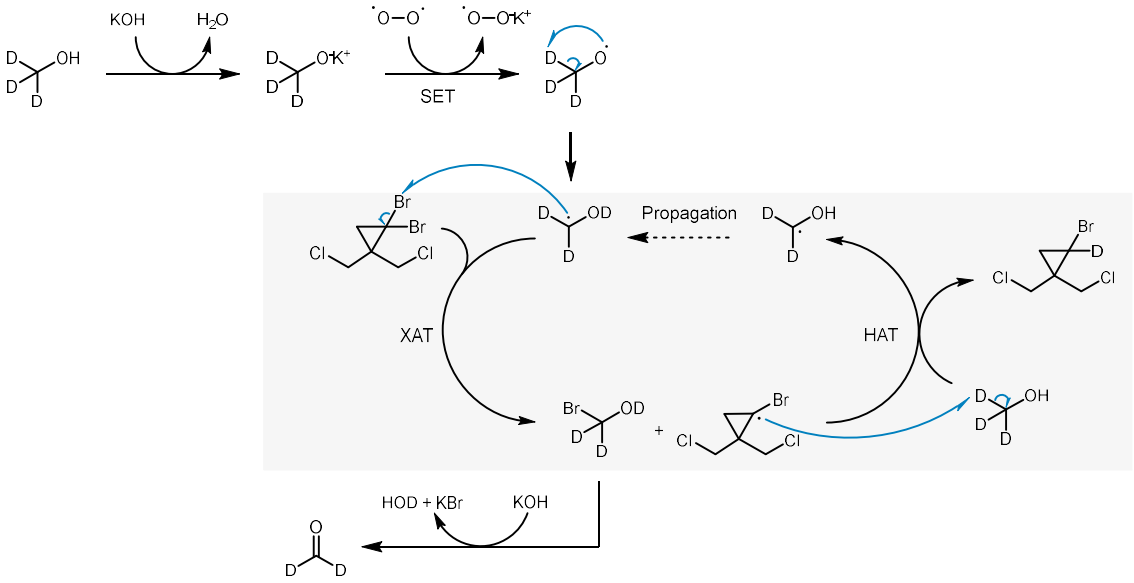


Figure 2.5. Proposed mechanism for debromination.

Further exploration of the scope of the reaction would be necessary to determine if this might be widely applicable as a mono-debromination method. Future work may also include investigation of whether the cyclopropyl radical can be trapped before it undergoes HAT, which could open up the possibility of developing a new radical coupling reaction. For example, a Giese-type addition could be envisaged, similar to the MeOH-induced XAT and Giese addition from Yang and co-workers[133].

2.1.2. Disconnection to BCB

Returning to the retrosynthesis of 3-oxa[3.1.1]propellane, one way to avoid an intermediate containing the chloromethoxy group would be to disconnect on the 5-membered ring, leading to a BCB intermediate, as shown in Figure 2.1b. The first proposed route to a BCB intermediate (Figure 2.6a) took intermediate **33** from the previous route (Figure 2.3b), which was treated with PhLi, then paraformaldehyde. This was intended to form BCB **35**, which could, after deprotection then hydroxy group activation, be used to form the propellane via an S_N2 reaction to close the tetrahydrofuran

ring. However, the BCB intermediate **35** could not be reliably isolated. Normally, BCBs benefit from electron-withdrawing groups to enhance their stability[134,135], but this BCB does not feature any such stabilising groups.

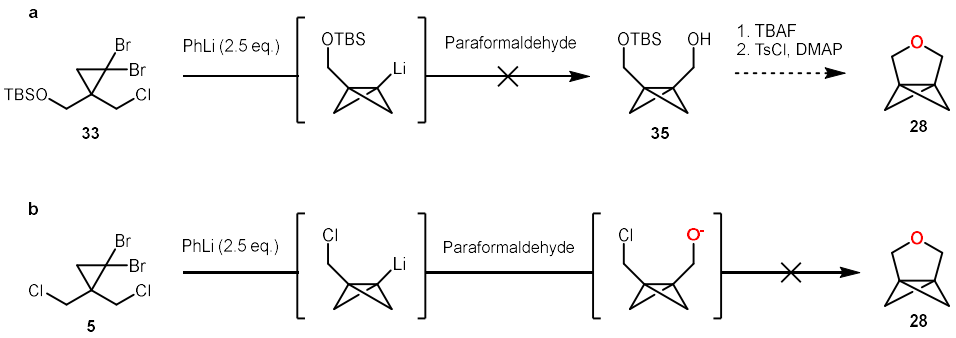


Figure 2.6. a First route to a BCB intermediate. **b** Second route to a BCB intermediate.

One way to avoid this unstable intermediate would be to engineer a concerted BCB formation from **5**, followed by ring-closure to the propellane (Figure 2.6b). However, this was also unsuccessful and produced a complex reaction profile; it was difficult to control the multiple cyclisations and electrophile trapping. Therefore, a new route was needed that would both avoid unstable intermediates and involve transformations that are robust, simple and easy to control.

2.1.3. Disconnection to dihalo-BCHep

Another disconnection of 3-oxa[3.1.1]propellane that could be considered is the central bond, leading to a dihalo-BCHep precursor such as **38**. This could theoretically be used to generate a propellane by lithium-halogen exchange of one of the halogens and then ring-closure, releasing the remaining halide, analogous to the methods of carbocyclic [3.1.1]propellane formation described by the Gassman[52] and Uchiyama[55] groups. However, unlike the carbocyclic substrates, this heterocyclic precursor would carry the

risk that after lithium-halogen exchange, elimination of the alkoxide could take place to form an alkene.

The synthesis of this dihalo-BCHep precursor appeared to be a difficult task. The synthesis of the carbocyclic analogue involves a double alkylation step with CH_2I_2, to construct the BCHep scaffold[52], however this step could be incompatible with the heterocyclic ring **36**, since as noted above it may result in elimination instead of alkylation (Figure 2.7a). One might also consider the possibility of a [2+2] cycloaddition from **39** to construct the scaffold **37** (Figure 2.7b). However, while this is well-established for the construction of bicyclo[2.1.1]hexanes[90,136,137], it is much more challenging for BCHeps because the regioselectivity is in favour of a straight rather than a crossed product[105] and there are only a few examples of the crossed product known in the literature[118,119,120,105] (Section 1.3), none of which would give the correct substitution pattern.

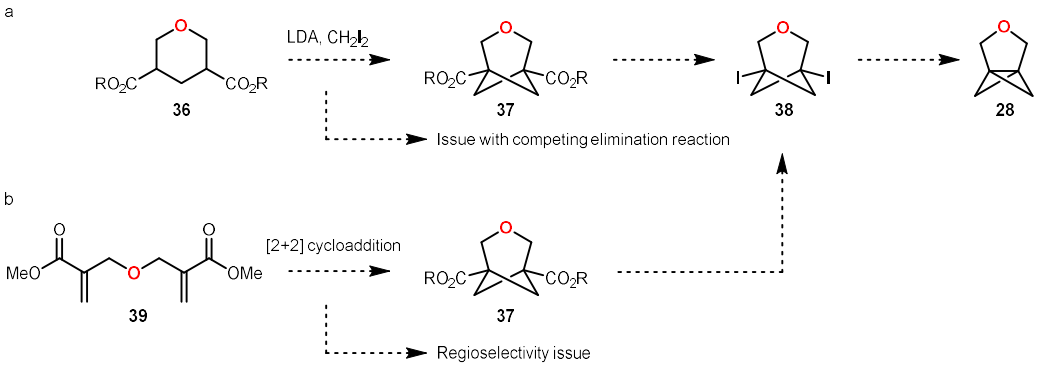


Figure 2.7 Challenges with the synthesis of diiodoBCHeps. **a** Issues with adaptation of Gassman's route. **b** Issues with cycloaddition approach.

While no viable synthetic route to this dihalo-BCHep intermediate **38** could be identified, it remained an interesting target. In Section 3.2.3, the question of whether it would make a suitable propellane precursor if a synthesis could be identified, will be discussed further.

2.1.4. Disconnection to tetrahydrofuran

An ideal stable precursor to the propellane would be a tetrahydrofuran, either with or without a fused cyclopropane (Figure 2.1d). Several routes were proposed, involving intermediate **40**.

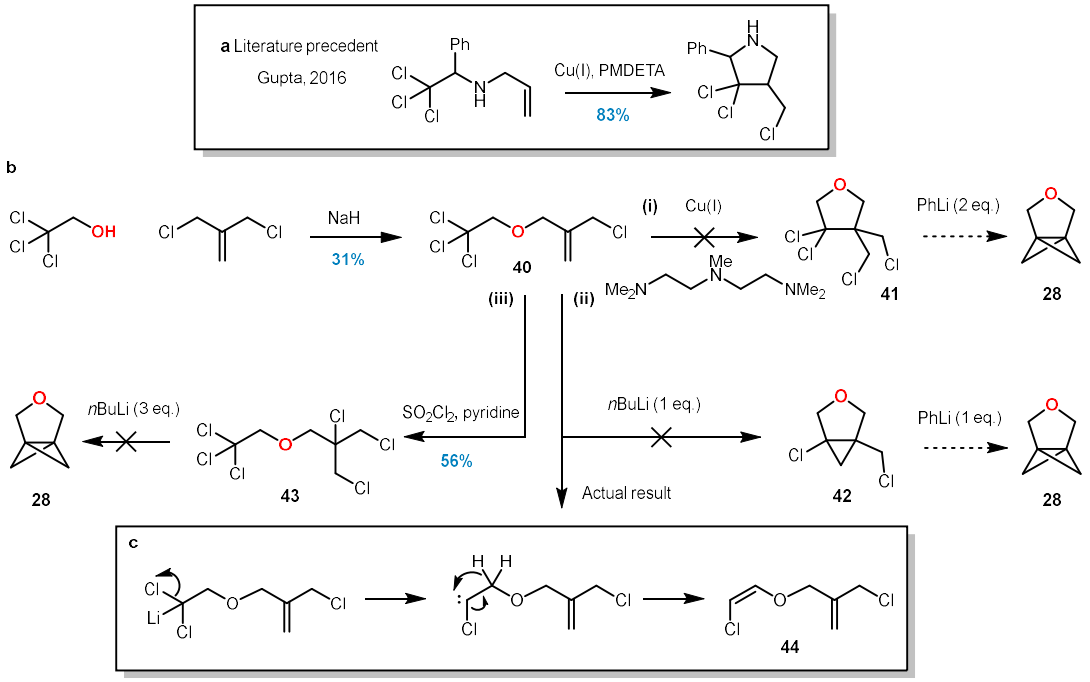


Figure 2.8. First group of proposed routes from the tetrahydrofuran disconnection.

Firstly, a Cu(I) catalysed atom transfer radical cyclisation (ATRC) was attempted for the conversion of **40** to **41** (Figure 2.8b, route (i)), based on a literature report by Gupta and coworkers for a similar system[138] (Figure 2.8a). However, the conditions did not translate well to our system, and since relatively little is known about this transformation in the literature, it was decided to investigate alternatives.

One of these alternatives was to instead generate a carbene from the trichloromethyl group in **40** using *n*BuLi, which could then react with the alkene in a cyclopropanation reaction to give **42** (Figure 2.8b, route (ii)). However, when this was attempted, a proposed side product **44** was observed amongst a complex reaction mixture instead of

the intended product. The carbene was formed successfully, but it underwent a Wolff rearrangement to chloroenol ether **44** before it could react with the alkene (Figure 2.8c).

An attempt was then made to chlorinate the double bond in **40** to give **43** and then perform the three ring closures in a concerted manner to give the propellane **28** (Figure 2.8b, route (iii)). However, this produced a complex reaction profile and it was decided that it would be too difficult to control the multiple possible outcomes in the lithiation step. A simple, stepwise process would be preferable for the design of the synthetic route.

This led to the next proposed strategy, which targeted intermediate **51** (a variation on intermediate **42**) by a different route (Figure 2.9). This route began with a Wittig reaction to generate alkene **46** from **45**, which worked very smoothly in 90% yield. This was then brominated to give **47** in 47% yield over two steps.

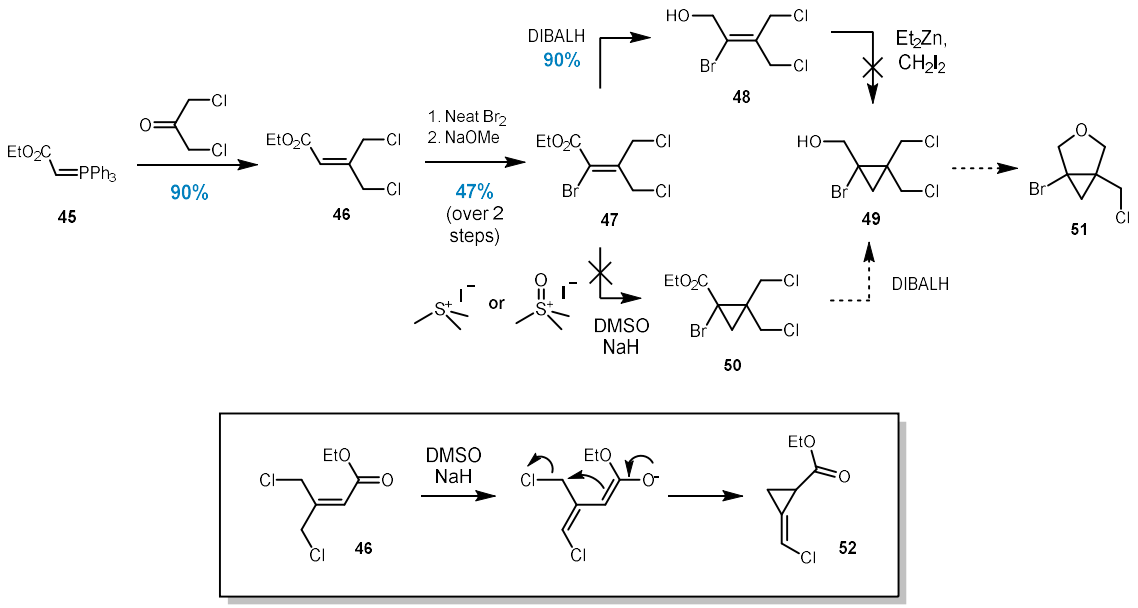


Figure 2.9 Second group of routes to tetrahydrofuran intermediate.

At this point, there are two options for the cyclopropanation. Firstly, a reduction to give **48** followed by Simmons-Smith cyclopropanation to give **49** was attempted. The reduction worked smoothly, but the Simmons-Smith reaction was unsuccessful and

generated a complex reaction profile, which could indicate that the halides in this compound are incompatible with the Et_2Zn.

A second option is a Corey-Chaykovsky cyclopropanation[139] to give **50** from **47**, however when this was attempted, only starting material remained. An attempt was made to perform this cyclopropanation on earlier intermediate **46**, to see if the bromide could be the issue here. An unexpected cyclopropylidene was formed during this reaction, which could be explained by the mechanism shown in Figure 2.9. Starting material **46** was deprotonated, forming an extended enolate. This enolate then reacted to form the cyclopropane **52**, with the chloride as the leaving group. It was concluded that an alternative strategy was needed since the chlorides were preventing the successful reaction outcome. It was therefore decided to target intermediate **51** by a different route.

An alternative method of cyclopropanation to explore would be the reaction of diazo compound **53** with an alkene to give **50** (Figure 2.10a). This transformation required an α-bromo diazo compound, which is unusual, but there is literature precedent for its reaction with alkenes[140]. The alkene is also electron deficient, which may make the cyclopropanation difficult, so it was decided to attempt the transformation with various Co(II) catalysts which are known to be effective with electron-deficient alkenes[141,142].

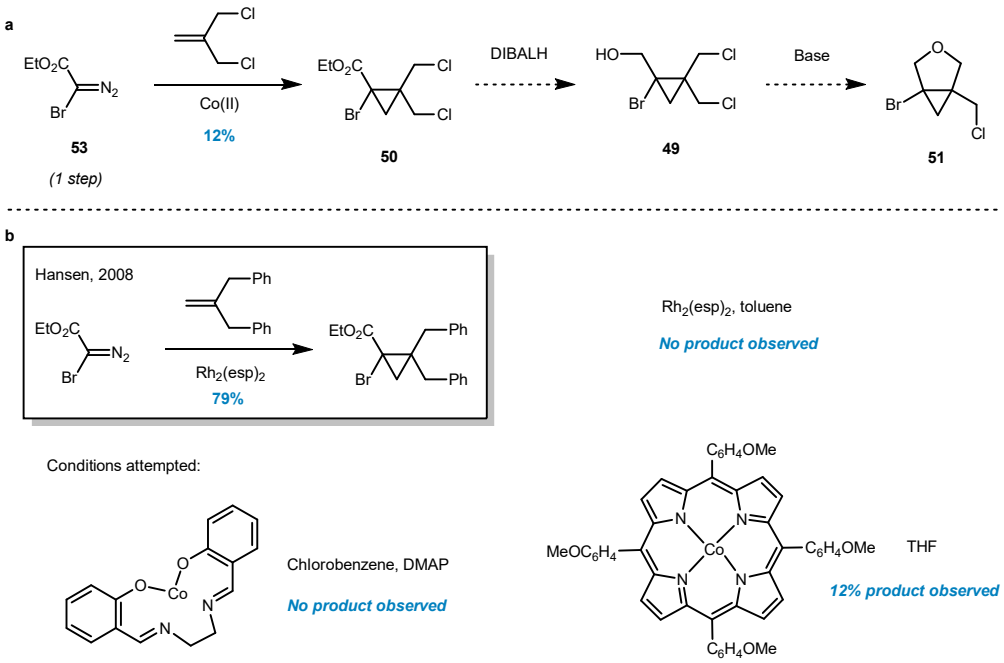


Figure 2.10 a Third route to tetrahydrofuran intermediate. **b** Attempts at cyclopropanation.

After investigating various conditions for this transformation (Figure 2.10b), trace amounts of product were detected with the porphyrin Co(II) catalyst. However, the amount of product could not be increased above 12%. This diazo compound is quite unstable and it may be the case that under the reaction conditions, it is decomposing faster than it is participating in the desired reaction. However, the trace amount of product was promising so for the next strategy to be explored, a more stable diazo compound **54** was chosen (Figure 2.11a). This required an even more electron deficient alkene than before, however there were some promising literature precedents for diazo addition onto such an alkene[143,144] (Figure 2.11b).

The same conditions attempted previously in Figure 2.10b were investigated for this cyclopropanation (Figure 2.11c). However, this time it was the $Rh_2(esp)_2$ catalyst which provided traces of cyclopropane product. Therefore, further Rh(II) catalysts were investigated and it was found that $Rh_2(TPA)_4$ was the most effective (Figure 2.11d). For further optimisation of this step, see Section 2.2.

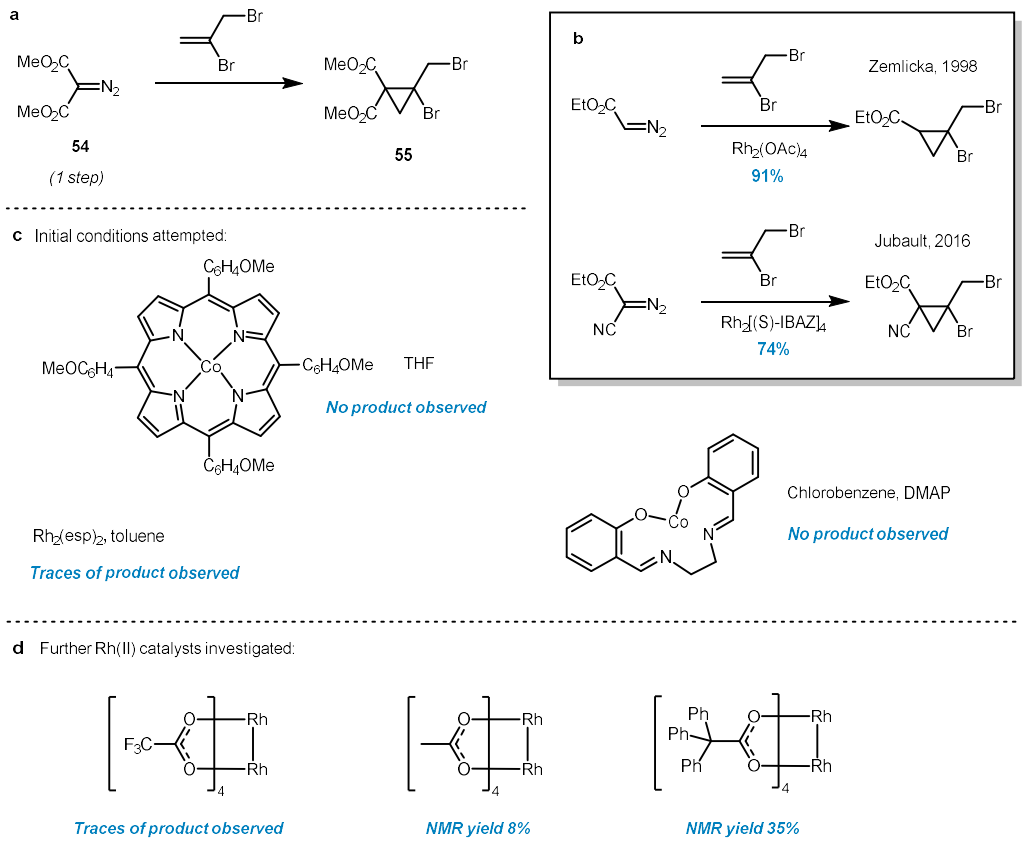


Figure 2.11. Alternative cyclopropanation.

This Rh catalysed cyclopropanation for the formation of **55** proved to be the key step in the synthesis, because it essentially positions all functional groups where they are needed, and all that is left to do is a series of functional group manipulations and S_N2 reactions. The rest of the synthetic route is shown in Figure 2.12, where the tetrahydrofuran precursor is accessed by DIBALH reduction of cyclopropane **55** to give **56**, followed by KOH-induced cyclisation to give **57**, then an Appel reaction of the hydroxy group to give **58**. The propellane formation step carries the risk of alkoxide elimination after the lithium-halogen exchange, however it was found that this transformation proceeded very smoothly with no elimination product formed. With a successful route to the target 3-oxa[3.1.1]propellane now identified, each step was examined to identify the optimal conditions.

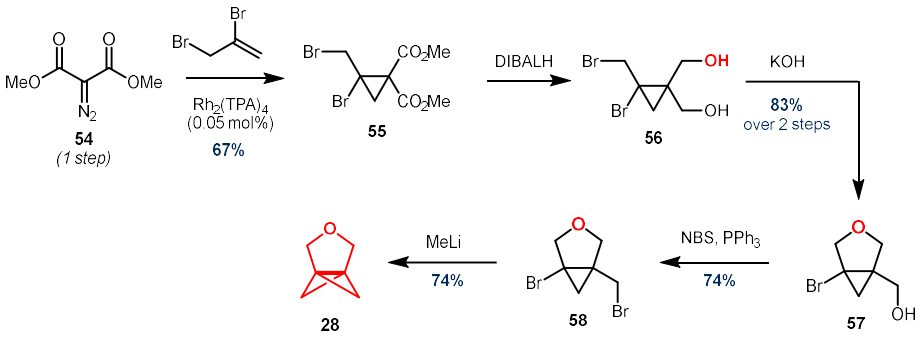


Figure 2.12. Successful route to 3-oxa[3.1.1]propellane.

2.2. Optimisation of oxa[3.1.1]propellane route

The starting diazo compound **54** was prepared according to a literature procedure[145] in 86% yield. For the cycloaddition, it is known that slow addition of the diazo compound can improve the yield by reducing the undesired dimerization of the diazo compound[143,144]. In this reaction (Figure 2.12), the yield was increased from 35% to 64% by adding the diazo compound via syringe pump over 8 hours. It was found that the catalyst loading could be decreased from the literature conditions[144] of 2 mol% down to 0.05 mol% without any decrease in yield. A side product **59** was identified in 12% yield, however it was found to be separable from the desired product and did not limit the scalability of the reaction. In fact, the reaction was successfully scaled up to 30 g with the yield maintained at 67%.

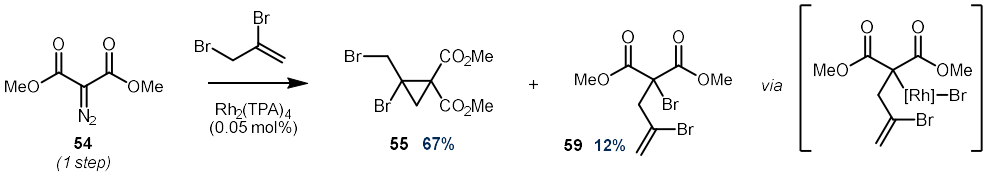
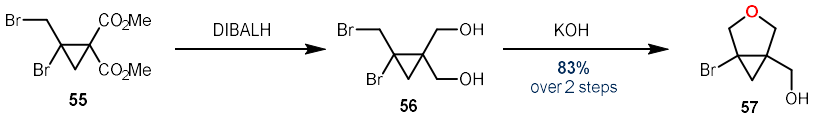


Figure 2.13 Cyclopropanation step

The next step involved the reduction of the ester groups and DIBALH was found to be the optimal reducing agent for this transformation (Table 2.3). $LiAlH_4$ produced a complex reaction profile, while $LiBH_4$ produced a small amount of product, amongst

other unwanted products. No reaction was seen using $NaBH_4$, whereas DIBALH afforded the product cleanly. Pure product could be obtained in 53% yield by column chromatography or trituration, but the best overall yield was obtained when the crude product was used directly in the next step without further purification, giving 83% overall yield. For the cyclisation step, NaH or KOH were identified as suitable bases. The reaction in KOH/MeOH gave a good yield with no column required, which is beneficial for the scalability of the process. This two-step process was successfully performed on a 15 g scale at 83% overall yield.

Table 2.3. Reduction and cyclisation steps.



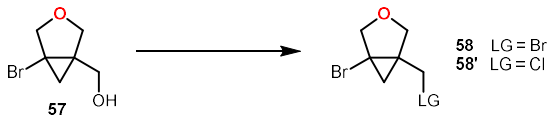
Conditions (55 to 56)	Result
DIBALH, THF	53%
$LiAlH_4$, THF	Undesired products
$LiBH_4$, THF	29% + Undesired products
$NaBH_4$, MeOH	No reaction

Conditions (56 to 57)	Result
NaH, THF, 40 °C	90%
*t*BuOK, THF, 40 °C	40%
KOH, MeOH, 40 °C	91%
K_2CO_3, THF, 40 °C	No reaction

The next step was to convert the hydroxy group in **57** into a good leaving group and there were several options for how this might be done (Table 2.4). Initially, chlorination was attempted, and while $SOCl_2$, oxalyl chloride, and $PhSO_2Cl$ were all unsuccessful, the Appel reaction with NCS and PPh_3 worked in 45% yield. This slightly low yield may be accounted for by the relatively high volatility of the chlorinated product. Mesylation also worked well (88% yield), and tosylation proceeded in 67% yield. However the mesylated product was found to be unsuccessful as a starting material for the propellane formation reaction, due to the incompatibility of the mesyl group with the organolithium reagent.

It is possible that the tosyl group could have avoided this issue, however it was decided that a halide leaving group would be optimal to give the simplest purification procedure after the propellane formation, since only a lithium halide would be formed as a by-product. Bromination was explored next and it was found that both NBS and CBr_4 were suitable reagents for an Appel reaction and the brominated product has the advantage of being slightly less volatile than the chlorinated product, although care must still be taken during its concentration. The NBS reaction was successfully performed on an 8 g scale in 74% yield.

Table 2.4 OH activation step.



Conditions	Result	Conditions	Result
$SOCl_2$	Complex reaction mixture	MsCl, NEt_3, DMAP	88%
Oxalyl chloride, pyridine, DMF	Complex reaction mixture	TsCl, NEt_3, DMAP	67%
$PhSO_2Cl$, pyridine	Complex reaction mixture	CBr_4, PPh_3	63%
NCS, PPh_3	45%	NBS, PPh_3	74%

The propellane formation step was initially attempted on the chlorinated precursor **58'**, using PhLi, by analogy to the formation of carbocyclic [3.1.1]propellane[47], and these conditions were found to be successful. The brominated precursor **58** was later found to perform just as well. In the established protocol for the synthesis of carbocyclic [3.1.1]propellane, PhLi is used as the lithiating agent, which results in the formation of PhBr as a by-product[47]. PhBr has a similar boiling point to the propellane, so the propellane is isolated a solution also containing PhBr. It was decided to attempt the oxapropellane formation using MeLi instead, so that the by-product would be MeBr,

which should be much easier to remove and, pleasingly, MeLi was indeed found to be a suitable lithiating agent. The final task was to identify a procedure for the isolation of the propellane. Carbocyclic [3.1.1]propellane can be isolated by co-distillation with nBu$_2$O, which is the solvent that the PhLi comes in. Since MeLi in Et$_2$O was being used for the oxa[3.1.1]propellane formation and the reaction solvent was also Et$_2$O, it was decided to add nBu$_2$O to the reaction mixture before distillation. The Et$_2$O with MeBr was removed first, then the propellane was collected as a 0.12 M solution in nBu$_2$O in 43% yield.

While this demonstrated that it is possible to apply the same distillation procedure to the oxa[3.1.1]propellane, it was also noted that the reaction mixture was already remarkably clean before distillation. In fact, apart from the Et$_2$O solvent, the reaction mixture only contained the propellane product and the MeBr and LiBr by-products. It was found that the process of isolation could be simplified by avoiding the distillation. Instead, NaHCO$_3$ was added to quench any residual MeLi and the reaction mixture was filtered through celite then partially concentrated under reduced pressure to remove MeBr. This gave a solution of propellane in Et$_2$O which in fact had an even cleaner NMR spectrum than the solution obtained by distillation. Traces of LiBr remained after filtration, however this was not found to affect any further reactions. It was found by reaction monitoring that 4 h was the optimal reaction time for the lithiation/cyclisation and it was also found that the MeLi could be added at room temperature rather than the previously suggested -78 °C[47]. This step was performed on a 5 g scale and the propellane solution was stored under a nitrogen atmosphere, in an amber glass bottle in the freezer. The solution was found to be stable indefinitely when stored under these conditions.

2.3. Synthesis of 3-thia[3.1.1]propellane

With a robust route to 3-oxa[3.1.1]propellane in hand, it was then questioned whether this route could be leveraged to provide access to propellanes containing other heteroatoms, and 3-thia[3.1.1]propellane was chosen as the next target. One could consider achieving this by starting with a different diazo compound that contains a sulfur atom, however perhaps a more elegant solution would be to intercept one of the later intermediates with a sulfur nucleophile, so that the routes will be divergent (Figure 2.14).

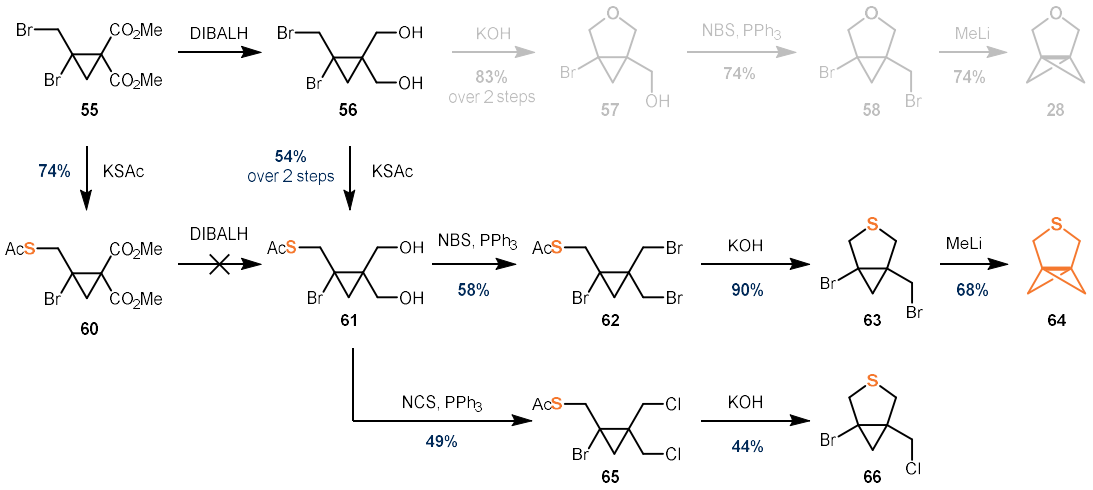


Figure 2.14 Routes to 3-thia[3.1.1]propellane.

It was found that both intermediates **55** and **56** could both be intercepted with thioacetate. The substitution reaction of KSAc with **55** gave the highest yield of 74%, however the subsequent reduction step to access **61** was then difficult to control due to the multiple similar carbonyl environments. Alternatively, reduction of **55** to **56** followed by KSAc substitution gave **61** in 54% overall yield for these two steps. The lower yield can be accounted for by the fact that **57** is formed as a side product from the cyclisation of **56** under basic conditions. At this point, there is once again a choice for how to convert the hydroxy groups into good leaving groups. Treatment with NBS and PPh_3 afforded the brominated product **62** in 57% yield, while treatment with NCS and

PPh_3 gave the chlorinated product **65** in 49% yield. In the next step, treatment with KOH results in hydrolysis of the thioester, followed by cyclisation. At this stage it is beneficial to follow the bromination route, because the cyclisation product **63** is less volatile than the equivalent product **66** in the chlorination route. The propellane formation from **63** to form **64** once again proceeded smoothly and did not require distillation. It was performed on a 1 g scale, at 68% yield and stored as a solution in the freezer.

2.4. Synthesis of 3-aza[3.1.1]propellane

The final target to complete the set of hetero[3.1.1]propellanes is an aza[3.1.1]propellane. Identifying a route to this target proved to be more involved than the thia[3.1.1]propellane and several routes were investigated before this was achieved.

One robust way to introduce a nitrogen is via a nucleophilic substitution with sodium azide. This was first attempted on the same diol intermediate **56** that was intercepted in the thia[3.1.1]propellane route (Figure 2.15). However, despite some attempts at optimisation, the yield of this step to form **67** could not be improved above 17%. This low yield may be due to the presence of the hydroxy groups, so an attempt was then made to firstly chlorinate these groups to give **69** and then introduce the azide. With the hydroxy groups removed, the sodium azide substitution was improved to give **68** 62% yield. The next step would be to reduce the azide, leading to a primary amine which would most likely cyclise onto the chloride to give **70**. Various conditions were investigated for this transformation, however none were found to be successful. Conditions attempted included PPh_3, H_2O, THF; PBu_3, H_2O, THF; PMe_3, H_2O, THF; Pd/C, H_2, MeOH; Rh on alumina, H_2, AcOH, toluene/EtOAc; PtO_2, H_2, EtOAc. When phosphine reagents were used, it appeared that the phosphines may have reacted with the chloromethyl groups, while the other conditions produced complex reaction profiles which suggested the conditions were too harsh and were also interfering with the chlorides.

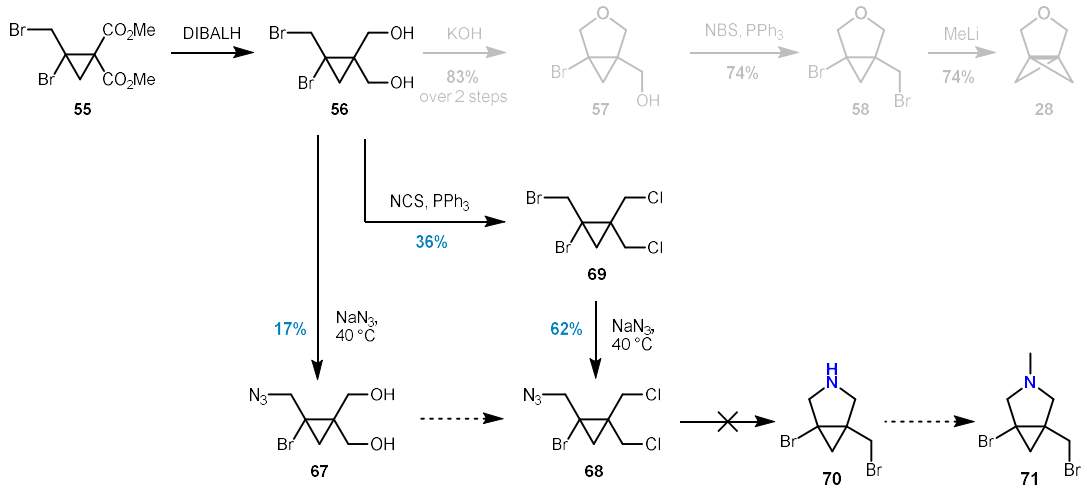


Figure 2.15. First proposed routes to 3-aza[3.1.1]propellane via azide substitution.

An attempt was then made to introduce an a $MeNH_2$ nucleophile directly to either intermediate **69** or **55**, however this was unsuccessful in both cases. In the reaction with **69**, this simply led to an E2 elimination product **72**.

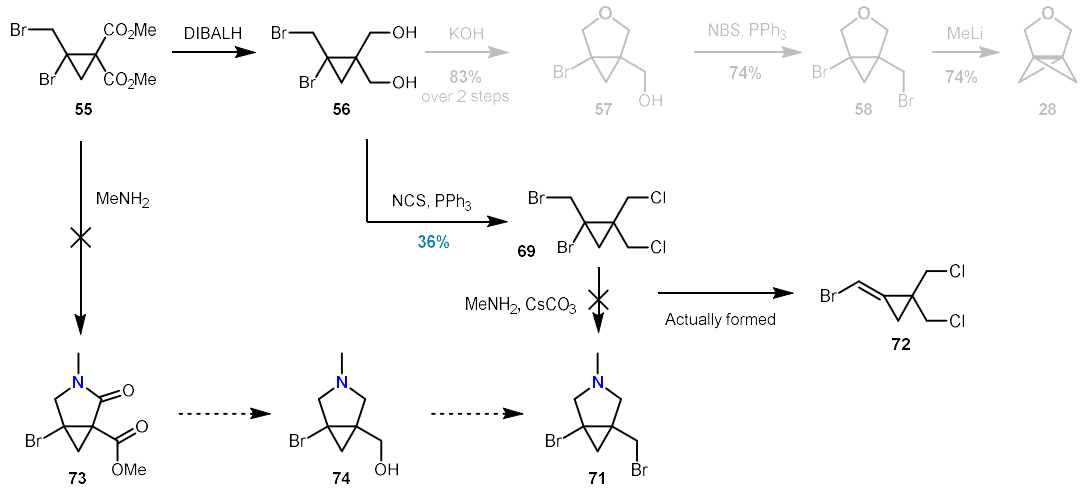


Figure 2.16 Second proposed routes to aza[3.1.1]propellane via amine substitution.

Returning to azide substitution, this was then attempted on the earlier intermediate **55** and found to be successful (Figure 2.17). This reaction afforded **75** in 96% yield with no need for column chromatography, and was easily scaled up to 14 g.

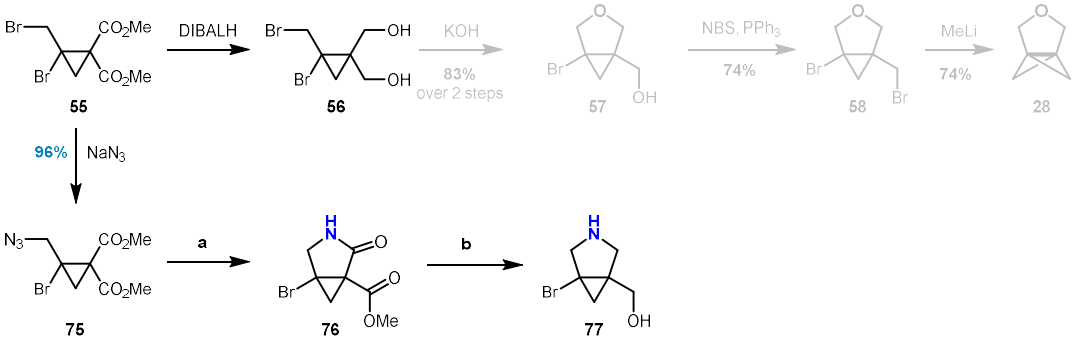


Figure 2.17 Azide substitution and reduction steps.

Table 2.5 Conditions attempted for azide reduction.

Conditions (a)	Result
PPh_3, H_2O/THF	16%
PBu_3, H_2O/THF	61%
$NaBH_4$, $NiCl_2{\cdot}6H_2O$, MeOH	25%

Table 2.6 Conditions attempted for ester/lactam reduction.

Conditions (b)	Result
DIBALH	Only reduces ester
$LiAlH_4$	Complex reaction mixture
Borane·THF complex	Complex reaction mixture
Borane·SMe_2 / THF complex	Complex reaction mixture
$LiBH_4$	Complex reaction mixture
Red-Al	40%

The next step was reduction (and then cyclisation) of the azide **75** to from **76**. Staudinger conditions PPh_3/H_2O/THF were firstly attempted, and this afforded a small amount of product in 16% yield (Table 2.5). Changing the phosphine to PBu_3 improved the yield to 61%. A Ni(II) catalysed $NaBH_4$ reduction also gave a moderate 25% yield, but the PBu_3 Staudinger reduction was chosen as the optimal solution. During scale-up of this step, it was necessary to add the azide **75** to the reaction mixture slowly at 0 °C and to monitor

the internal temperature, since this reaction was highly exothermic. The product **76** was difficult to isolate by column chromatography due to its high polarity, but it was found that it could instead be isolated directly from the reaction mixture by trituration, which is a benefit from a scalability perspective. This step was successfully scaled up to 13 g in 61% yield.

The next step requires reduction of the lactam and ester to form **77**. Various conditions were investigated (Table 2.6) and Red-Al was found to be uniquely effective for this transformation. Use of DIBALH resulted only in the reduction of the ester, while all other reducing agents produced complex reaction profiles.

It was found that an Appel reaction on this product **77** to form **70** did not work, but if the amine was firstly protected by methylation (to give **74**), then the Appel reaction was possible (Figure 2.18). With intermediate **71** in hand, the propellane formation to give **78** was attempted with the same conditions as for the other propellanes; however, surprisingly this did not work and unreacted starting material remained.

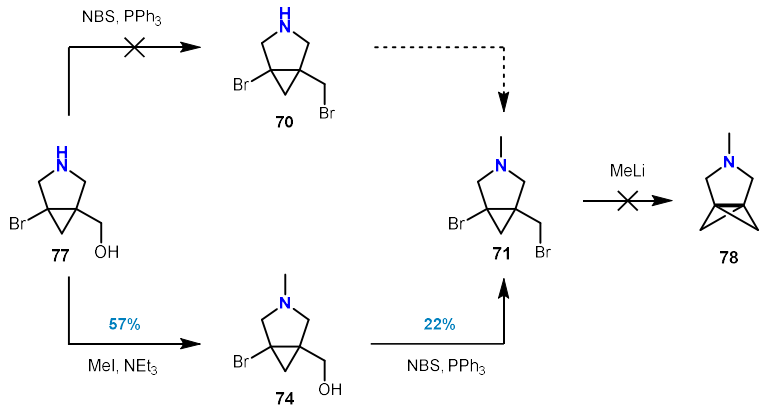


Figure 2.18 Preparation of methylated propellane precursor and attempt at propellane formation.

A possible reason for the propellane formation not proceeding could be the lack of inductive stabilisation for the carbanion formed after lithium-halogen exchange. This halogen–lithium exchange is quite different to those classically used in propellane

synthesis, which involve (more reactive) dibromocyclopropanes. To investigate this hypothesis, a series of propellane precursors with alternative protecting groups on the nitrogen were prepared (Figure 2.19). These were each prepared in good yields by protection of the nitrogen in **77** followed by bromination. For the Bn compound **79**, CBr_4 had to be used instead of NBS for the Appel reaction, because the use of NBS resulted in the formation of benzyl radicals leading to unwanted side-reactivity.

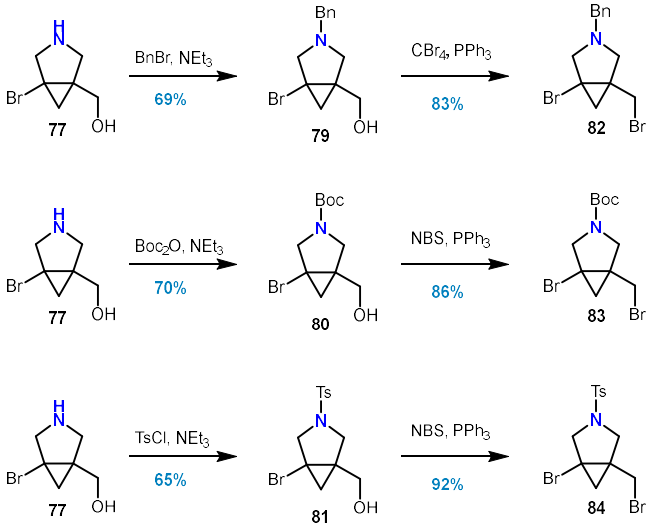
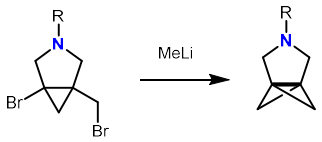


Figure 2.19 Preparation of alternative azapropellane precursors.

The propellane formation reaction with MeLi was attempted with each of these precursors (Table 2.7). With electron donating substituents Me and Bn, no reaction was observed and starting material remained. A small amount of propellane was detected with the Boc substituent, as well as side reactivity. The electron withdrawing Ts group performed best, proceeding in 98% yield, and was chosen as the standard nitrogen substituent for further studies.

Table 2.7. Propellane formation with different nitrogen substituents.



R Group	Result
Me	No reaction
Bn	No reaction
Boc	20% + side reactions
Ts	98%

With the Ts group chosen as the optimal substituent, further modifications were made to the synthetic route (Figure 2.20). The product **77** of the Red-Al reduction of **76** is very polar and difficult to isolate, so the tosylation to give **81** was performed directly without purification, giving the best overall yield of 40% at 3 g scale. In the propellane formation step, it was necessary to use THF as the solvent rather than Et_2O because both **84** and **85** had poor solubility in Et_2O. This propellane formation step was faster than the oxa- and thia-propellane formations and only took 1 h. The propellane formation was performed on a 2 g scale in 98% yield.

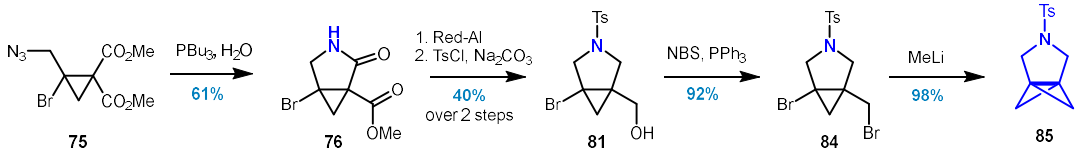


Figure 2.20. Route to 3-(Ts)-aza[3.1.1]propellane.

Remarkably, the 3-(Ts)-aza[3.1.1]propellane proved sufficiently stable that it was possible to grow a crystal at room temperature by diffusion of a pentane/Et_2O mixture into a solution of propellane in THF (Figure 2.21; the crystal structure was solved by Yasmine Biddick). As expected[57], the central C3-C4 bond is slightly elongated. This is the

first room temperature X-ray crystallography structure of any small-ring propellane (the X-ray structure of [1.1.1]propellane has previously been obtained at low temperature[146]) and gives a fascinating insight into its geometry.

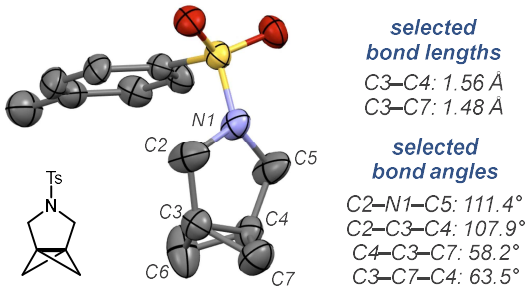


Figure 2.21 Crystal structure of 3-(Ts)-aza[3.1.1]propellane.

2.5. Overview of hetero[3.1.1]propellanes

The synthesis of a family of hetero[3.1.1]propellanes has now been achieved. The routes involve a common intermediate, assembled by a Rh-catalysed cyclopropanation, and are modular and scalable, as shown in Figure 2.22.

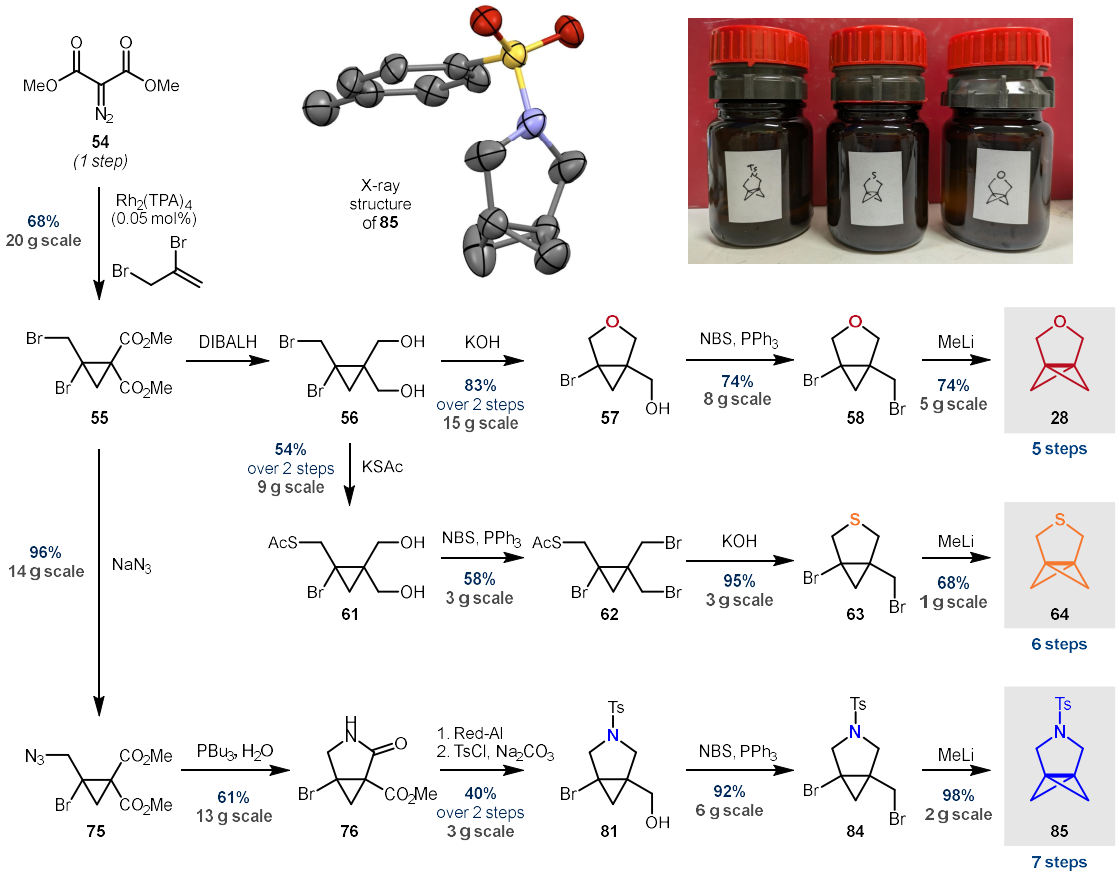


Figure 2.22 Divergent routes of a family of hetero[3.1.1]propellanes.

The stability of each propellane over time was investigated by preparing a sample of each propellane and measuring the NMR spectrum of the same sample each day (Figure 2.23) (see supporting information for full details). Between measurements, the NMR samples were left at rt under air. The oxa- and aza-propellanes showed remarkable stability under these conditions and their concentration remained essentially constant over the timeframe measured, however the thiapropellane degraded relatively quickly under

ambient conditions. However, when the propellanes were stored under nitrogen in the freezer, they were stable for several months without any degradation.

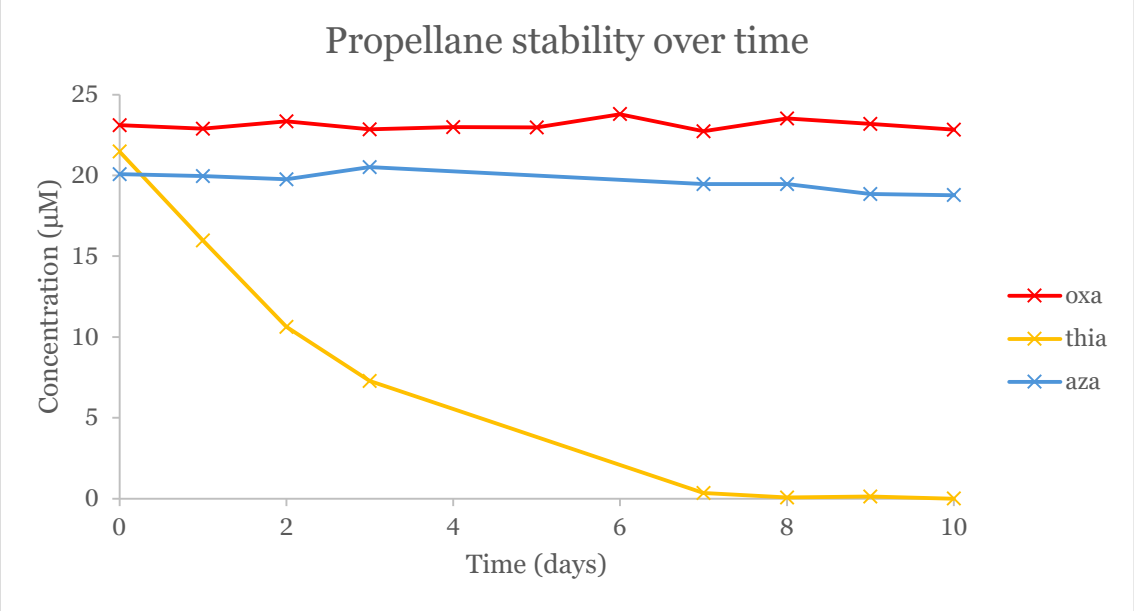


Figure 2.23. Propellane stability over time under ambient conditions.

3. Reactions of hetero[3.1.1]propellanes

3.1. Ring-opening reactions

3.1.1. Scope of radical ring-opening reactions

A variety of radical-based ring-opening reactions were investigated and the full scope of these is shown in Figure 3.1. Compounds **86a**, **86c**, **86e**, **86h**, **86i**, **86j**, **86k**, **86l**, **86o**, **86p**, **86q**, **86t**, **86u**, **86x** and **86aa** were synthesised by Ayan Dasgupta. The crystal structure of compound **86i** was solved by Kirsten Christensen. The crystal structure of **86z** was solved by Agamemnon Crumpton.

The atom transfer radical addition (ATRA) of alkyl halides across the central propellane bond is one of the most versatile and widely used reactions for the installation of a diverse range of bridgehead substituents[147,28]. This reaction can either be initiated with BEt_3[28] or photocatalysed using an $Ir(ppy)_3$ photocatalyst[29] and both methods were employed in the investigation of the scope of these ring-opening reactions. A selection of electron deficient alkyl iodides could be added, affording products **86a**-**86d** in good yields overall. An electron rich alkyl iodide gave products **86e** and **86f**, and a benzyl iodide gave **86g**. For the oxapropellane, the photocatalysed method gave slightly higher yields of **86a** and **86e** than the BEt_3 initiated method, but for the azapropellane the two methods performed equally well in the synthesis of **86b** and **86f**. The oxapropellane reacted well and gave high yields for both electron rich and electron deficient radicals, but the azapropellane gave better yields with electron deficient radicals. The addition of an aryl iodide gave **86h** in good yield, and nitrogen heterocycle-containing compounds **86i** and **86j** were also synthesised in good yields. The addition of alkyl bromides was successful in examples **86k**-**86n**.

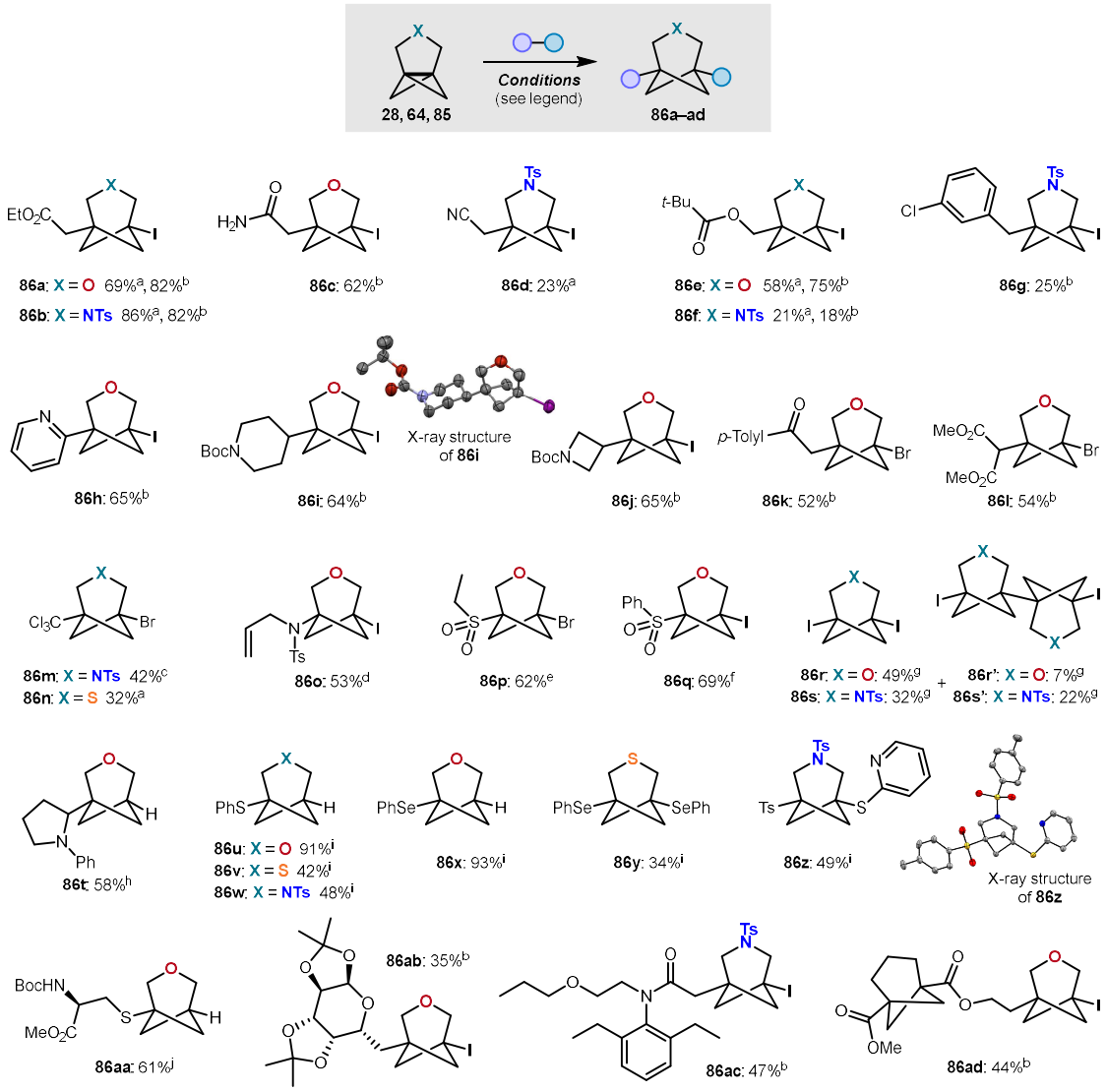


Figure 3.1 Radical ring-opening reactions of hetero[3.1.1]propellanes. Reaction conditions: **a** BEt_3 (10 mol%) in Et_2O, 25 °C. **b** $Ir(ppy)_3$ (2.5 mol%), *t*-BuCN, blue LEDs (450-456 nm), 25 °C. **c** direct reaction with organohalide without initiator. **d** α-iodoaziridine, $Ir(ppy)_3$ (2.5 mol%), *t*-BuCN, blue LEDs (450-456 nm), 25 °C. **e** RSO_2Br, Et_2O, 25 °C. **f** RSO_2I, -5 °C, 10 min. **g** I_2, 25 °C. **h** *N*-phenylpyrrolidine, 4CzIPN (2.5 mol%), blue LEDs (440 nm), dimethylacetamide, 25 °C. **i** chalcogen or dichalcogen, 25 °C. **j** cysteine derivative, BEt_3 (10 mol%). The structures of **86i** and **86z** were determined using single crystal X-ray diffraction.

The addition of heteroatom-centred radicals was also possible. Compound **86o** was prepared from the fragmentation of an iodomethyl aziridine[38]. Additionally, halosulfonylation[36] afforded products **86p** and **86q** in good yields. The addition of I_2 gave an inseparable mixture of diiodoBCHep and staffane dimer **86r/86r'** and **86s/86s'**; interestingly, the proportion of the dimer was higher for the azapropellane

reaction than the oxapropellane reaction. Addition of an α-amino radical via photoredox catalysis[33] was also successful, giving **86t**. Various chalcogen-centred radicals could be added[34,23,35], giving products **86u**-**86z**. Some biologically relevant compounds were also prepared, including cysteine derivative **86aa**, galactopyranose derivative **86ab** and pretilachlor derivative **86ac**. Finally, compound **86ad** is the first example of a compound containing both carbocyclic and heterocyclic BCHeps.

In general, the oxapropellane ring opening reactions performed best, followed by the azapropellanes, and then the thiapropellanes. The reasons for these differences in reactivity will be discussed in the following sections.

3.1.2. Reactivity of 3-(Ts)-aza[3.1.1]propellane

While many useful examples of azapropellane ring-opening reactions have been demonstrated, there are some cases where the yields were lower than the corresponding oxapropellane reactions, and some instances where a reaction which did work on the oxapropellane did not work on the azapropellane. Figure 3.2 shows examples of proposed side products formed during propellane ring-opening reactions. In Figure 3.2a, side products include a staffane dimer **86z'** and H-substituted bridgehead species **86z''**, the latter of which presumably formed through H-atom abstraction. In Figure 3.2b, there is a side product **86'** which arises from a rearrangement of the propellane, similar to a side reaction documented for carbocyclic [3.1.1]propellane by Szeimies and coworkers[53].

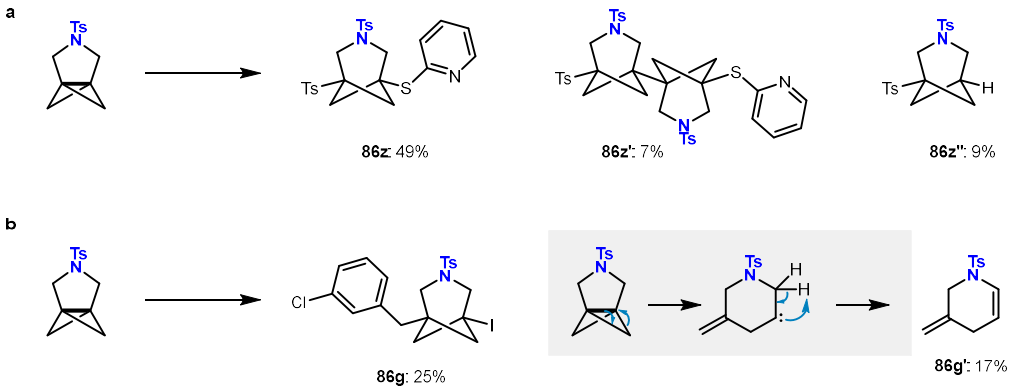


Figure 3.2 a Side products formed alongside product **86z**. **b** Side product formed alongside product **86g**.

There were some examples of reaction types which did work with the oxapropellane but not with the azapropellane, shown in Figure 3.3. The attempted addition of the azetidine radical to form **87a** (Figure 3.3a) did not proceed and unreacted propellane was recovered. Similarly, the iodomethyl aziridine reaction (Figure 3.3b) returned unreacted propellane, as well as alkene **87b'**. This shows that the radical fragmentation happened successfully, but the resulting nitrogen-centred radical preferred to engage in a hydrogen atom abstraction rather than reacting with the propellane in the desired manner. The halosulfonylation of the azapropellane was unsuccessful with any of the substrates or conditions attempted. With the conditions in Figure 3.3c, a proposed propellane protonation product **87c'** was observed amongst a complex reaction mixture. The conditions in Figure 3.3d afforded traces of product as well as an iodination staffane dimer **87d'**. In an attempt to avoid this iodination, DBH was used instead of DIH, however no product was observed with these conditions (Figure 3.3e).

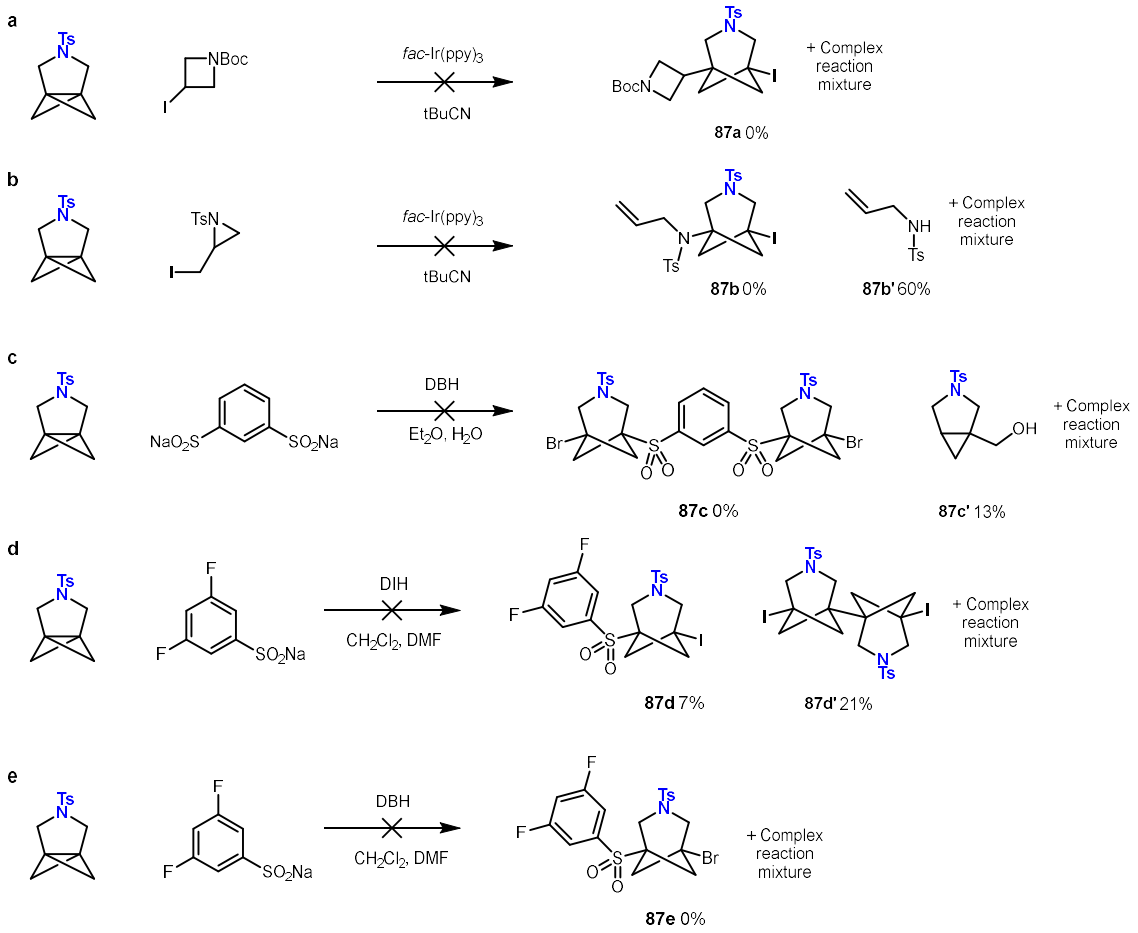


Figure 3.3 Unsuccessful reactions on 3-(Ts)-aza[3.1.1]propellane.

To summarise, these results indicate that the azapropellane is less reactive than the oxapropellane. There are some instances where unreacted azapropellane is recovered and some instances where side reactions including rearrangement or hydrogen atom abstraction compete with the desired reaction. It also seems apparent that the azapropellane is especially prone to staffane formation and this is sometimes observed as a side product.

3.1.3. Reactivity of 3-thia[3.1.1]propellane

The ring-opening scope of the thiapropellane was more limited than the other propellanes. Figure 3.4a shows a variety of thia-BCHeps which were targeted but were unsuccessful. All these attempted reactions led to complex reaction mixtures and most of these had noticeable alkene signals in the ^{1}H NMR spectrum of the reaction mixture.

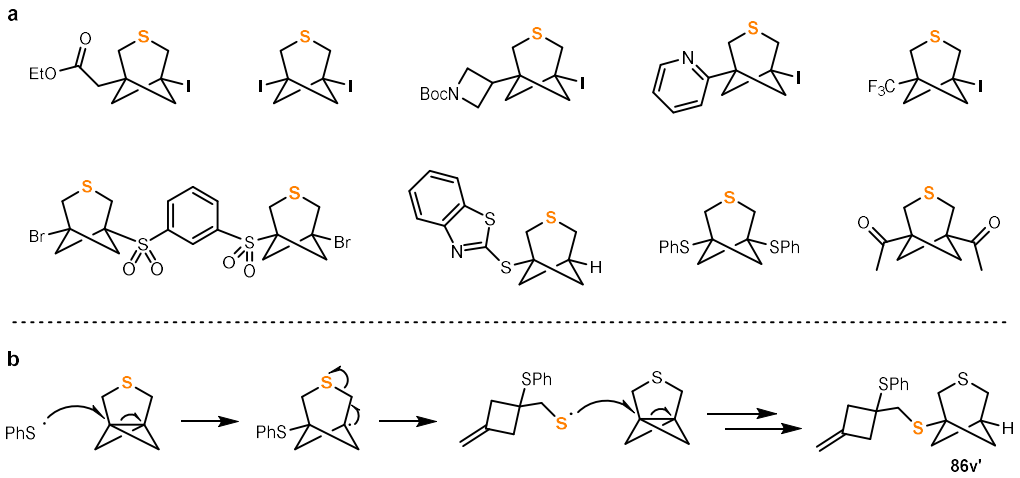


Figure 3.4 a Unsuccessful thia-BCHep targets. **b** Proposed mechanism for radical fragmentation.

Even the thiophenol reaction, which successfully afforded a thia-BCHep, also produced a mixture of side products. One of these side products was isolated and the structure confirmed as compound **86v'**. A mechanism was suggested for the formation of this side product (Figure 3.4b), in which the BCHep radical fragments via cleavage of the relatively weak C-S bond, generating an alkene and leaving a radical on the sulfur atom. At this point, there may be several options for what this radical could react with, leading to the complex reaction profiles observed. One of these options is to react with another propellane molecule, leading to **86v'**. It was found that the proportion of side product **86v'** could be decreased and the proportion of the product **86v** could be increased by increasing the amount of PhSH from 1 eq. to 10 eq. This radical fragmentation may explain the complex reaction mixtures and alkene signals observed in the unsuccessful reactions. It is therefore apparent that the only reactions to be successful were those with very efficient radical trapping steps, so that the trapping of the thia-BCHep radical was faster than the fragmentation.

An attempt was made to oxidise the thiapropellane, to see if this might influence its reactivity (Figure 3.5). When mCPBA was added to a solution of 3-thia[3.1.1]propellane, an immediate oxidation followed by cheletropic extrusion of SO_2 (or SO) occurred. When

this reaction was performed in an NMR tube, it was clear that the 1,3-dimethylenecyclobutane[148] was formed immediately. Over 20 h, another alkene signal appeared and both alkene signals decreased in size, which could indicate that first one, then both alkenes in 1,3-dimethylenecyclobutane are being further oxidised to epoxides. Attempts to carry out a single oxidation to the sulfoxide were unsuccessful.

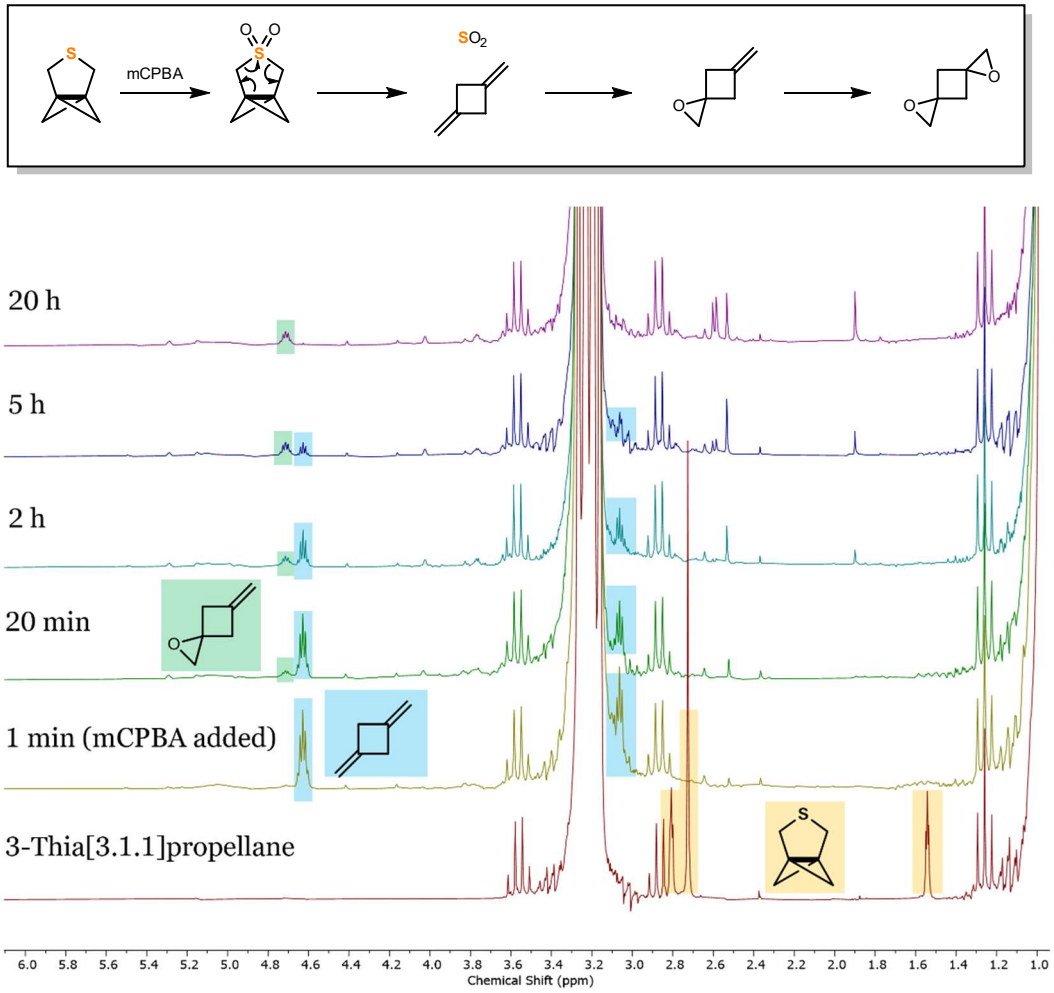


Figure 3.5 Oxidation of 3-thia[3.1.1]propellane.

3.1.4. Attempted anionic ring-opening reactions

It is known that while carbocyclic [1.1.1]propellane reacts readily with radicals and anions, carbocyclic [3.1.1]propellane only reacts with radicals[47]. Nonetheless, some anionic reactions were attempted on 3-oxa[3.1.1]propellane in case it might be more

capable of stabilising an incoming negative charge. The attempted reactions are shown in Figure 3.6. It was attempted to react the 3-oxa[3.1.1]propellane with phenylmagnesium bromide[41], a zinc enolate[45], a turbo-amide[22,149] and a 2-azaallyl anion[43], however none of these reactions were successful, indicating that this propellane behaves similarly to the carbocyclic [3.1.1]propellane with its lack of reactivity towards anions.

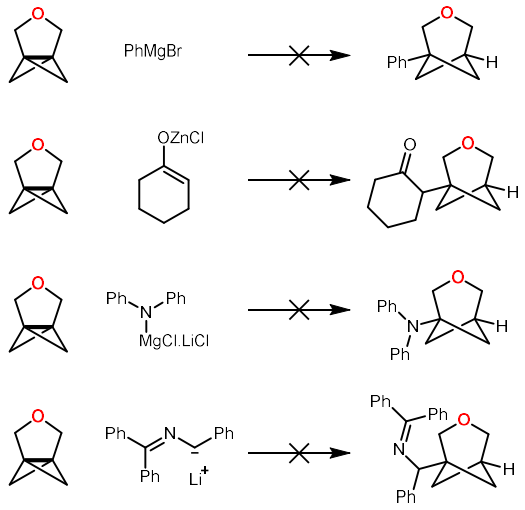


Figure 3.6 Attempted anionic ring-opening reactions.

3.2. Further reactions of hetero-BCHeps

3.2.1. C-I Functionalisations

Preliminary studies were conducted to functionalize the C-I bond which is present in many of the hetero-BCHeps that were prepared. An iron-catalysed Kumada coupling is known for the functionalisation of carbocyclic BCP[46] and BCHep[47] iodides. This method was attempted using compound **86e** and was successful, giving compound **88** in 49% yield (Figure 3.7a). It is possible to functionalise BCP iodides by a photocatalysed Giese-type coupling[38]. This methodology has not yet been achieved with carbocyclic BCHeps,

however it was attempted on oxa-BCHep **86i** and found to be moderately successful, giving the product **89** in 35% yield (Figure 3.7b). Also observed was **89'**, the result of hydrogen atom abstraction before the BCHep radical could react with the alkene coupling partner. Also possible on BCP iodides is a deiodination reaction carried out under photoredox conditions[38], and this methodology translated well to the aza-BCHep **86ac**, giving **90** in 72% yield (Figure 3.7c).

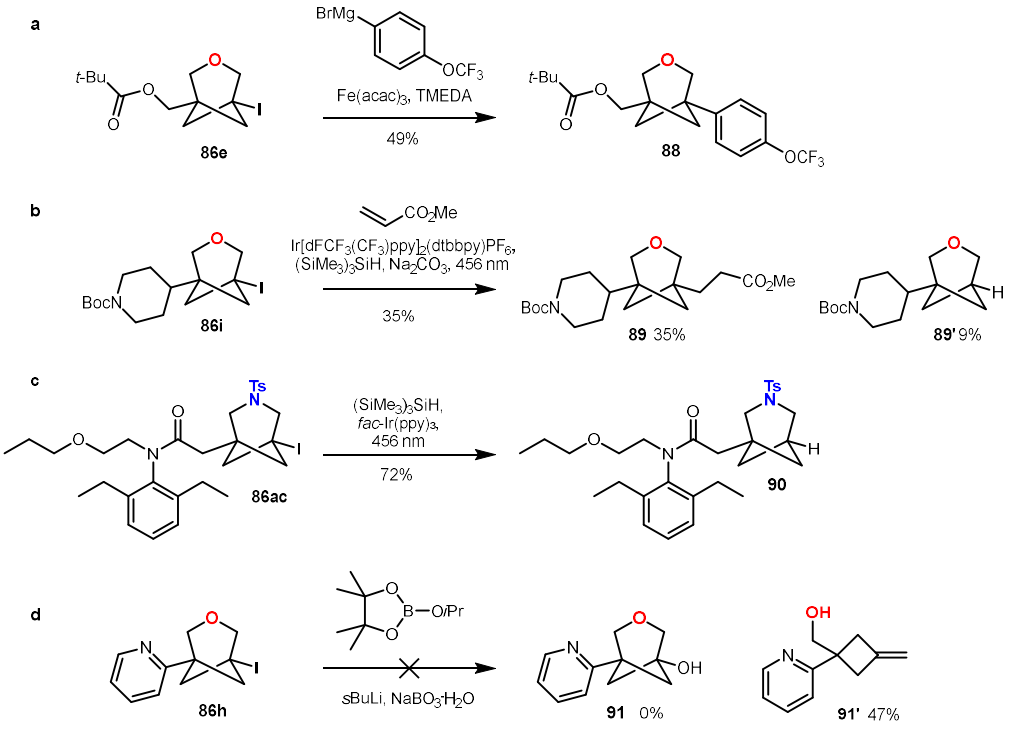


Figure 3.7 Further functionalisation of C-I bond. **a** Kumada coupling. **b** Giese coupling. **c** Deiodination. **d** Attempted lithiation and electrophile trapping.

Carbocyclic BCHeps can be lithiated and trapped with an electrophile[47], however when this was attempted on oxa-BCHep **86h**, it resulted in elimination and fragmentation of the BCHep scaffold to give **91'** (Figure 3.7d). This is understandable given the ability of the oxygen atom to stabilise the resulting negative charge upon fragmentation.

3.2.2. Synthesis of a drug analogue

To illustrate the utility of these methods, an oxa-BCHep analogue of the anti-cancer drug sonidegib was synthesised (Figure 3.8). Compound **88**, prepared via Kumada coupling, was subjected to hydrolysis and oxidation[83] in 46% overall yield to give **92**. Then, amide coupling[83] gave oxa-BCHep-sonidegib **93** in 70% yield.

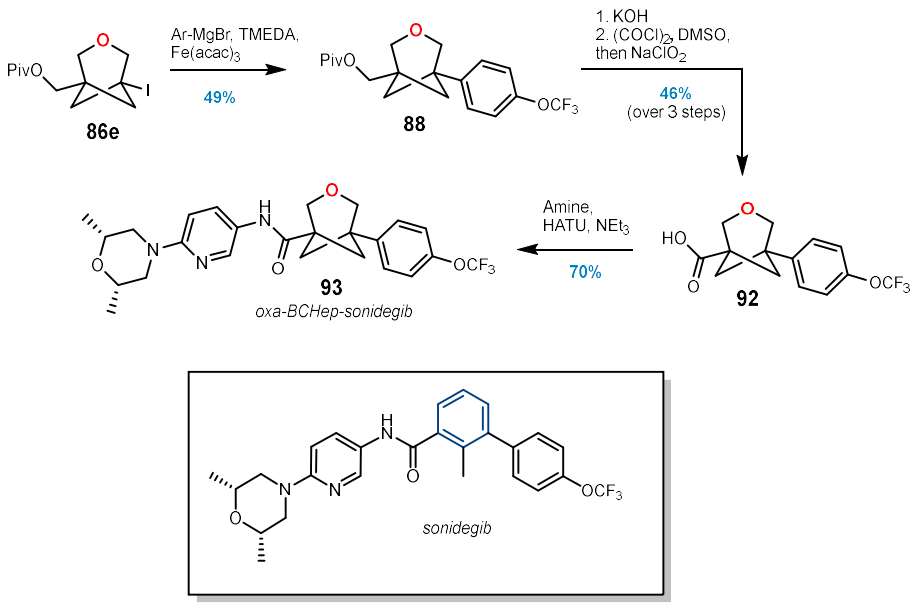


Figure 3.8 Synthesis of oxa-BCHep-sonidegib.

Mykhailiuk[83] and Ryabchuk[122] have performed analysis of the biological properties of this oxa-BCHep-sonidegib analogue (Table 3.1) and found that the water solubility was greatly improved over both the carbocyclic BCHep[47] and parent arene analogues. The metabolic stability was slightly decreased relative to the arene analogue, as was the biological activity, however the biological activity was better than the carbocyclic BCHep analogue and still within a useful range.

Table 3.1. Biological properties of oxa-BCHep-sonidegib determined by Mykhailiuk[83].

	Sonidegib	Carbocyclic BCHep-sonidegib	oxa-BCHep-sonidegib
Solubility (μmol)	6	4	34
Metabolic stability $t_{1/2}$ (min)	104	120	61
Biological activity IC_{50} (nM)	1	616	96

3.2.3. Re-formation of propellanes

With the diiodoBCHeps **86r** and **86s** in hand, the opportunity arose to test whether the disconnection in Figure 2.1c might be a viable suggestion. The inseparable mixtures of diiodoBCHep and staffane dimer **86r/86r'** and **86s/86s'** were each treated with MeLi and the propellane formation proceeded smoothly, affording the propellanes in good yields (Figure 3.9). This transformation carries the risk of alkoxide elimination after lithium-halogen exchange (see Figure 3.7d), however it was found to proceed smoothly, with no elimination product observed. Notably, in both the oxa and aza compounds, both the monomer and dimer were able to re-form the propellane, even though this involves the breaking of a C–C bond in the dimer. This validates the diiodoBCHep as an alternative hetero[3.1.1]propellane precursor, and it would be an interesting target if an alternative independent route for its synthesis could be developed in the future.

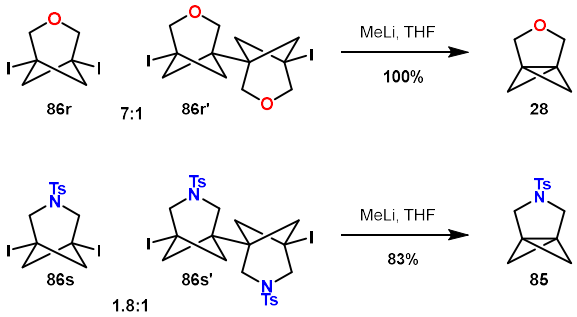


Figure 3.9 Re-formation of oxa and azapropellanes from diiodoBCHeps.

3.2.4. Deprotection of aza-BCHeps

Conditions for the Ts deprotection of the aza-BCHeps were explored, since this will allow further funtionalisation of the nitrogen after BCHep formation. It was found that this deprotection could not be carried out (under reductive conditions) in the presence of the C–I bond, but once this was deiodinated, the detosylation proceeded smoothly with Mg/MeOH and sonication to give **94** in 79% yield (Figure 3.10).

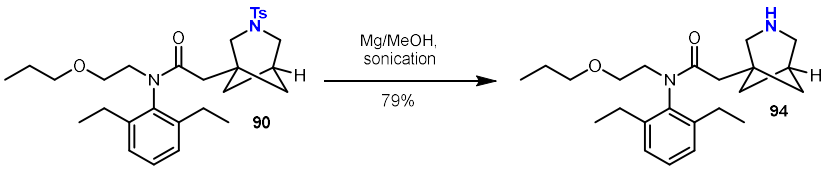


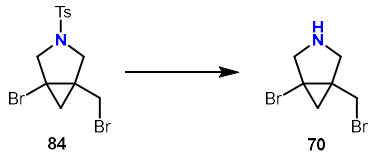
Figure 3.10 Aza-BCHep deprotection.

4. A closer look at aza[3.1.1]propellanes

4.1. First generation aza[3.1.1]propellanes

During the development of the aza[3.1.1]propellane route (Section 2.4), various azapropellane precursors were prepared by adding a protecting group to the amine in **77**, then brominating to give different propellane precursors (Figure 2.19). It was envisioned that to make the process of varying the nitrogen substituent more modular and streamlined, the propellane precursor **84** could instead be deprotected to **70** and a new substituent installed, reducing the number of steps involved. Various conditions were investigated for the deprotection of the tosyl group (Table 4.1) and HBr with phenol was chosen as optimal. Sodium naphthalenide, SmI_2/pyrrolidine[150,151] and SmI_2/DMPU[152] all resulted in decomposition, possibly due to side-reactivity with the C–Br bonds.

Table 4.1 Reaction conditions screening for tosyl deprotection of propellane precursor.



Conditions	Result
Sodium naphthalenide, THF, -78 °C	Decomposition
SmI_2, H_2O, pyrrolidine, THF, rt	Decomposition
SmI_2, THF, DMPU, 70 °C	Decomposition
HBr 30%, phenol, 70 °C	90% NMR yield (48% isolated)

The deprotected product **70** could be purified with a reduction in yield, but the best overall yields were obtained when the next step was performed on the crude product. Since it was established that electron-withdrawing groups performed best in the

propellane ring-closure step (Section 2.4), a selection of sulfonamides was chosen to investigate further for propellane formation (Figure 4.1). Various sulfonyl chlorides were reacted with the crude amine **70** to prepare the propellane precursors **95a-c**. All the synthesised precursors performed well in the propellane formation step, affording azapropellanes **96a-c** in good yields.

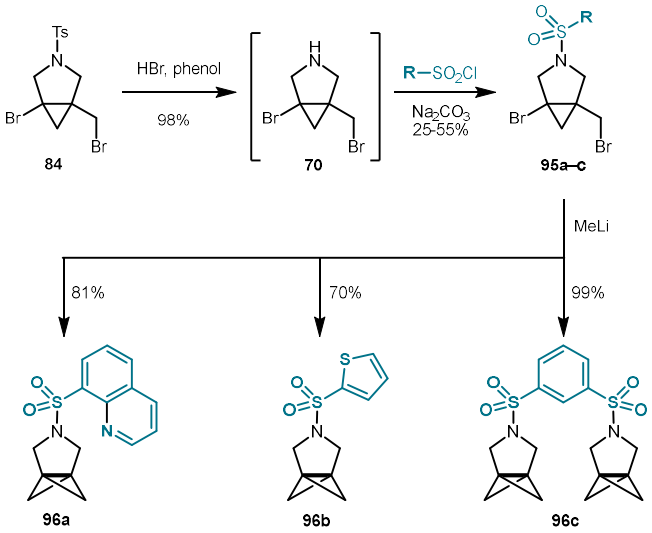


Figure 4.1 Synthesis of sulfonamide propellanes.

4.2. Next generation aza[3.1.1]propellanes

While an efficient approach to generate a range of sulfonamide propellanes has been developed, it was clear that the requirement for the nitrogen substituent to be an electron withdrawing group was a limitation that still needed to be solved. The following sections address this issue by firstly identifying a further improved and more scalable approach for diversifying the nitrogen substituent, and then investigating propellane formation for new derivatives bearing a variety of these substituents.

4.2.1. Improved route to aza[3.1.1]propellanes

While the tosyl deprotection followed by introduction of a new nitrogen substituent (Section 4.1) successfully reduced the number of steps involved in varying the substituent, its main drawbacks were the harsh conditions needed for the deprotection and the difficulty in purifying the intermediate **70**. These disadvantages were addressed by switching from a *N*-Ts to an *N*-Boc common intermediate (Figure 4.2). The Boc group was introduced after the Red-Al reduction, giving **80** in 56% yield over two steps on a 4 g scale. The Appel reaction then proceeded smoothly with 86% yield on a 5 g scale to give the propellane precursor and common intermediate **83**. This intermediate was more straightforward to deprotect than the tosyl intermediate and the deprotected amine **70** was produced in 92% yield with no need for column chromatography purification. The amine was obtained after workup as a white pure solid which could be easily handled and stored. New substituents could be introduced easily onto this amine with only simple purifications required.

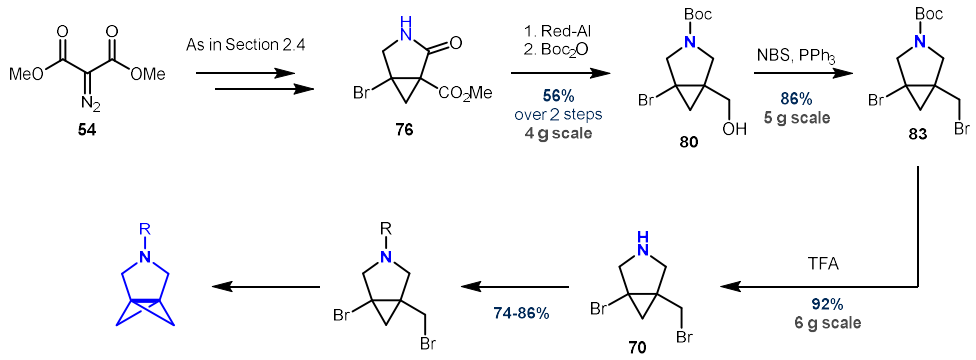


Figure 4.2. Improved route to aza[3.1.1]propellanes with *N*-Boc intermediate.

Propellane formation was investigated with Boc, Bn, allyl, pyridyl and pivaloyl substituents. The benzyl, allyl and pivaloyl substituted propellane precursors were prepared from **70** in good yields (Figure 4.3). The Buchwald-Hartwig reaction to introduce the pyridyl group was unsuccessful on intermediate **70**, but proved effective

on earlier intermediate **77**, with the following bromination step affording precursor **101** in 87% yield.

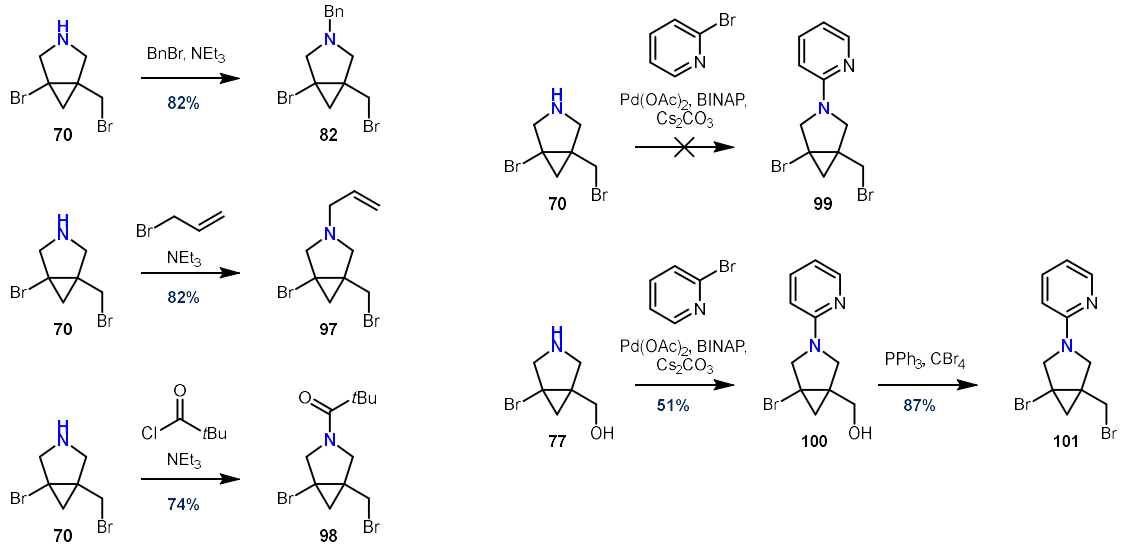


Figure 4.3 Preparation of azapropellane precursors.

4.2.2. Investigating propellane formation

With five diverse *N*-substituted propellane precursors in hand, the conditions for propellane formation were explored. It was previously proposed that the reason the propellane formation with electron rich *N*-substituents did not proceed could be the lack of stabilisation for the intermediate anion (Section 2.4). A mechanism consistent with this is proposed in Figure 4.4. The starting material may be in equilibrium with the lithiated intermediate and the position of the equilibrium is gradually pulled across by the irreversible propellane formation. The closure of the 3-membered ring to form the propellane is fast, evidenced by the fact that the lithiated intermediate is not observed in the reaction mixture NMR spectrum. Aliquots of the reaction mixture can be taken to monitor the progress of the reaction and analysed by NMR spectroscopy in C_6D_6, and these show varying mixtures of starting material and product but the lithiated

intermediate was not detected. To accelerate the reaction, various factors could be altered to shift the position of equilibrium towards the lithiated intermediate. These include stabilising the lithiated intermediate by inductive electron withdrawal, increasing the strength of the organolithium reagent, or increasing the number of equivalents of organolithium used. It was previously noted that the reaction time for the formation of oxa[3.1.1]propellane and thia[3.1.1]propellane with MeLi was 4 h, with (*N*-Ts)aza[3.1.1]propellane it was 1 h and with (*N*-Me)aza[3.1.1]propellane, it did not proceed. This indicates that the O and S are more electronegative and inductively electron withdrawing than the *N*-Me, but the *N*-Ts is more inductively withdrawing than the O or S.

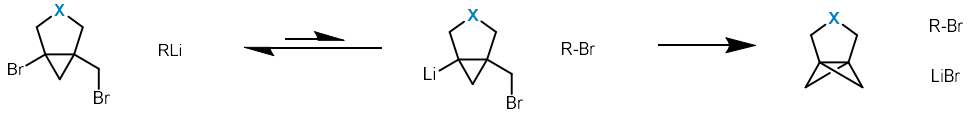


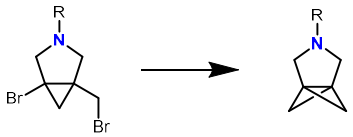
Figure 4.4 Proposed mechanism for propellane formation.

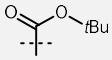
The use of increased equivalents of organolithium would suffer from notable practical limitations associated with the need to quench excess organolithium upon reaction completion. MeLi was firstly attempted for each of the substrates bearing these five substituents and the reaction was monitored over time. If the reaction was not complete after 24 h, then the reaction time was deemed too long and *n*BuLi, a stronger organolithium was used instead. The results of propellane formation with MeLi and *n*BuLi for each substituent are shown in Table 4.2.

The benzyl and allyl containing substrates showed only partial conversion after 24 h with MeLi, but complete conversion in 5 min with *n*BuLi. Since *n*BuLi is a stronger lithiating agent, it pushes the equilibrium in favour of the lithiated intermediate and allows the reaction to proceed more rapidly. The key disadvantage of these reaction conditions is the generation of *n*BuBr as the by-product instead of MeBr, with the removal of *n*BuBr

being challenging since it has a similar boiling point to the THF solvent. However, reaction times above 24 h were assessed as impractical and therefore *n*BuLi was chosen as the optimal reagent for this transformation.

Table 4.2 Investigating conditions for propellane formation.



R group	MeLi	*n*BuLi
	51% conversion in 24 h	Complete conversion in 5 min
	55% conversion in 24 h	Complete conversion in 5 min
	Complete conversion in 1 h	Complete conversion in 5 min
	20% product + side reaction in 1 h	Complete conversion in 5 min
	Complete conversion in 1 h	Complete conversion in 5 min

The *N*-pyridyl substrate showed complete conversion in 1 h with MeLi, so this was chosen as the optimal reagent. On the other hand, the *N*-Boc substrate showed only partial conversion upon treatment with MeLi, along with side reactions that led to a complex reaction mixture. However, when *n*BuLi was used instead, the reaction proceeded smoothly and full conversion was achieved in 5 minutes. Since *n*BuLi is a stronger organolithium reagent, the lithium-halogen exchange became more favourable which shifted the position of equilibrium towards the product. The dibrominated starting material was therefore not present in the reaction mixture for long enough to give the organolithium reagent a chance to react with the Boc group to generate side products. The *N*-pivaloyl substrate showed complete conversion in 1 h with MeLi. The bulky *t*Bu

group seemed to be necessary to avoid reaction of the MeLi with the amide and when a less bulky Ph group was present (i.e. benzoyl), side reactivity likely due to reaction at the carbonyl was observed in addition to propellane formation. With the optimal conditions identified for each substrate, the propellane formation reactions were performed on larger scale (Figure 4.5). The previous limitation for strongly electron withdrawing substituents has now been overcome by varying the organolithium reagent.

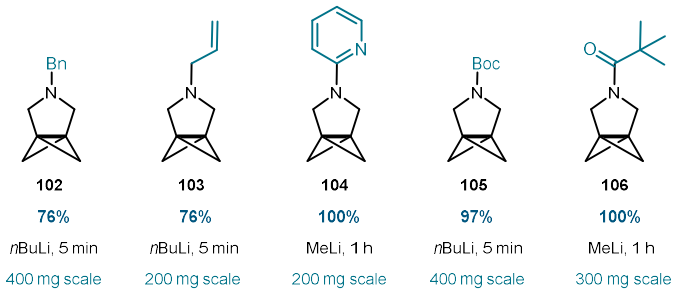


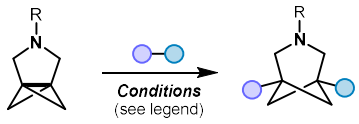
Figure 4.5 Successful propellane formation with a variety of *N*-substituted substrates.

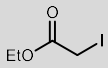
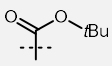
4.2.3. Ring opening reactions of azapropellanes

With five diverse azapropellanes in hand, their ring-opening reactions were investigated and compared to the original *N*-Ts propellane (Table 4.3). Ethyl iodoacetate was the best substrate overall, giving the highest yields for most propellanes. Iodomethyl pivalate had lower yields in general and 2-iodopyridine proved to be the least efficient substrate for these azapropellanes, despite its good yield for the oxapropellane (Section 3.1.1). The *N*-Bn propellane demonstrated similar performance to the *N*-Ts propellane for the iodomethyl pivalate, 2-iodopyridine and iodine substrates, although the yield for the ethyl iodoacetate was significantly lower. This could be rationalised by the potential generation of radical species involving the benzyl group, giving rise to side reactions. The *N*-allyl propellane demonstrated comparable results to the *N*-Bn propellane for the iodomethyl pivalate, but showed an improved yield for the ethyl iodoacetate, possibly due to its lower susceptibility to radical side reactions. The *N*-pyridyl propellane exhibited moderate efficacy across the various substrates and had the best yield for the

2-iodopyridine addition. The *N*-Boc propellane performed unexpectedly poorly overall, except for the iodine addition, with no product was detected for attempted addition of iodomethyl pivalate or 2-iodopyridine. The *N*-pivaloyl propellane performed similarly to the *N*-allyl and *N*-pyridyl propellanes for ethyl iodoacetate addition and similarly to the *N*-Ts propellane for iodomethyl pivalate addition. The reaction with iodine proceeded similarly across all propellanes and produced significant amounts of [2]staffane dimers in all cases.

Table 4.3. Isolated yields of propellane ring-opening reactions with different *N*-substituents. Conditions for ethyl iodoacetate, iodomethyl pivalate, and 2-iodopyridine addition were $Ir(ppy)_3$ (2.5 mol%), *t*-BuCN, blue LEDs (450-456 nm), 25 °C. Iodination was carried out by direct addition of I_2 to propellane solution.



R group	Substrate			
				I_2
Ts	82% (**86b**)	18% (**86f**)	9% (**86ae**)	76% overall monomer : dimer 1.5 (**86s**) : 1 (**86s'**)
	22% (**86af**)	30% (**86ag**)	9% (**86ah**)	57% overall monomer : dimer 1.4 (**86ai**): 1 (**86ai'**)
	58% (**86aj**)	27% (**86ak**)		
	53% (**86al**)	29% (**86am**)	20% (**86an**)	46% overall monomer : dimer 1.7 (**86ao**) : 1 (**86ao'**)
	43% (**86ap**)	0%	0%	60% overall monomer : dimer 2.0 (**86aq**) : 1 (**86aq**)
	54% (**86ar**)	16% (**86as**)		

None of these new substituents provided any significant improvements in ring-opening yields over the original Ts substituent. Future work may be directed towards identifying higher-yielding conditions for azapropellane ring-opening reactions in general.

4.3. Hammett plot

The ability to easily vary the substituent on the nitrogen opens the possibility to gain a deeper insight into propellane reactivity by construction of a Hammett plot. This is the first time such an insight into propellane reactivity has been possible, since it is difficult to introduce bridge substituents into carbocyclic propellanes[49,27,101,153]. A series of sulfonamide propellanes with various aromatic substituents were prepared with all propellane formations proceeding in good yields (Figure 4.6).

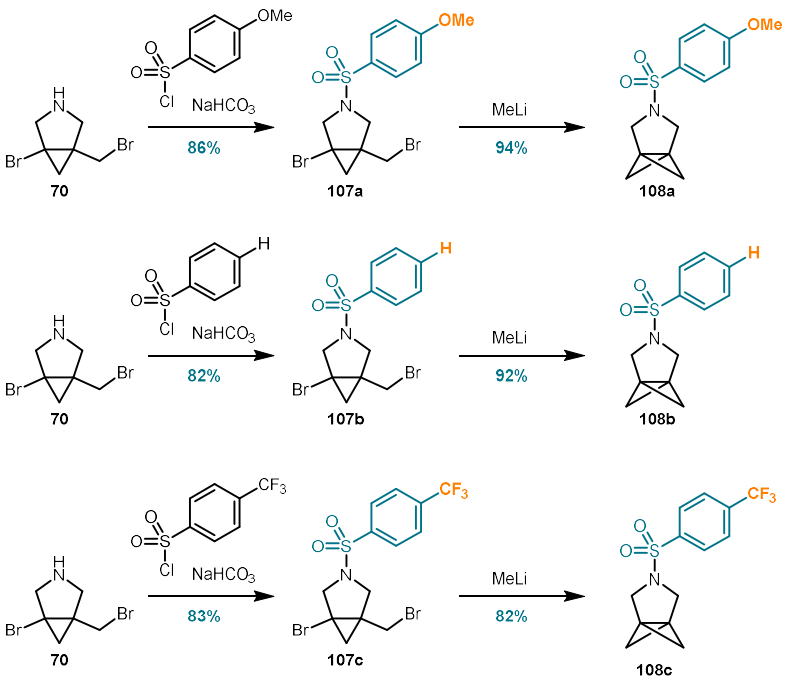
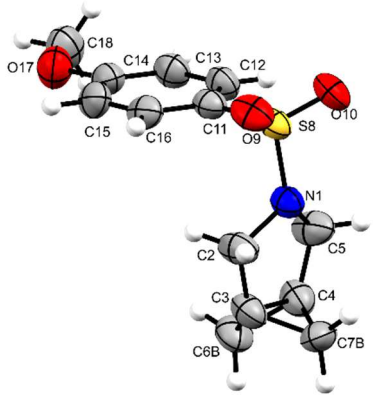


Figure 4.6 Formation of propellanes for Hammett plot.

A crystal structure of propellane **108a** was obtained (Table 4.4; this crystal structure was solved by Agamemnon Crumpton) and this was compared to the structure of the *N*-Ts propellane **85** (Section 2.4). The central propellane bond is the same length in both

propellanes, and all the other bond lengths and angles are very similar except for the angle around the nitrogen, which has more sp^2 character in *N*-Ts propellane **85** and more sp^3 character in propellane **108a**. This suggests that any differences in reactivity which might be observed between these propellanes arise from the electron density in the propellane ring system rather than any changes in geometry.

Table 4.4. Comparison of crystal structures between propellanes **85** and **108a**.



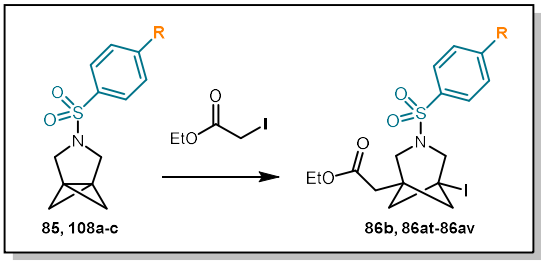
Bond lengths		
	-OMe (108a)	**-Me (85)**
C3-C4	1.56 Å	1.56 Å
C3-C7	1.45-1.52 Å	1.48 Å

Bond Angles		
	-OMe (108a)	**-Me (85)**
C2-N1-C5	109.6°	111.4°
C2-C3-C4	107.2°	107.9°
C4-C3-C7	56.0-59.3°	58.2°
C3-C7-C4	61.8-66.3°	63.5°

With a series of four sulfonamide propellanes in hand, experiments for a Hammett plot were devised. Competition experiments were set up between pairs of propellanes to

measure the ratios of reaction rates. Ethyl iodoacetate was chosen as the substrate for the competition experiments, which were performed under photoredox-catalysed conditions, as these were found to be more reproducible than the BEt_3-initiated method. It was found that the competition reactions could not be run with an excess of propellanes due to the formation of complex mixtures of (presumably) mixed staffanes. Instead, the competition experiments were set up with the standard 1.2 eq. total of propellanes (1:1 ratio), and stopped before they reached completion by the addition of excess I_2 to ensure that the concentration of propellane did not become limiting. The reactions were found to be remarkably fast and only required 10 seconds of irradiation for partial conversion. The results of the competition experiments were found to be consistent between attempts. For full details of experimental setup and calculations see the Experimental Section 6.3.

Using the results from the competition experiments, the following Hammett plot was constructed (Figure 4.7). The Hammett plot shows that propellanes with more electron rich substituents such as OMe have faster rates of reaction (higher $\log(k_X/k_H)$) than propellanes with electron withdrawing groups such as CF_3. The effect is small with a ρ value of -0.127 because the group that is being varied is far from the bond that is reacting. However, the fact that the effect is observable at all at this distance from the reaction centre is notable. This supports the idea that propellanes are nucleophilic and react more readily when there is a greater electron density within the strained inter-bridgehead bond.



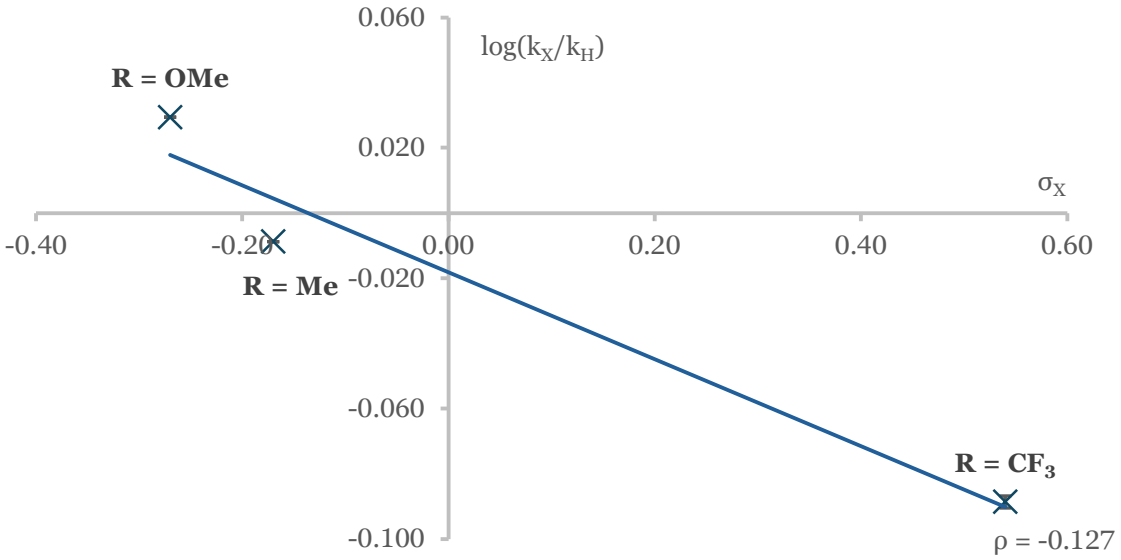


Figure 4.7 Hammet plot comparing reactivities of different propellanes with ethyl iodoacetate.

5. Conclusions and future work

5.1.1. Conclusions

The aims set out at the beginning of this thesis were to identify a synthetic route to hetero[3.1.1]propellanes and to use these propellanes to access diverse disubstituted hetero-BCHeps. This has been achieved and marks a major contribution to the field of propellane chemistry (Figure 5.1).

The route to 3-oxa[3.1.1]propellane was identified first, after a retrosynthetic consideration of the target compound and the exploration of many different synthetic pathways. It was not possible to simply adapt the existing route to carbocyclic [3.1.1]propellane, since this would result in unstable intermediates featuring a chloromethoxy group. Disconnection to a BCB was also unsuccessful due to the lack of stability in the BCB precursor. Disconnection to a precursor with the tetrahydrofuran ring already installed proved to be the best strategy. Numerous routes were investigated to reach this type of precursor, and a successful route was eventually identified, starting with a key rhodium-catalysed cyclopropanation. The rest of the synthetic route proceeded smoothly through a series of robust, scalable and high yielding transformations. The propellane formation step proceeded smoothly and proved to be more practical than the formation of carbocyclic propellanes because there was no need for a cumbersome distillation. Finally, a disconnection to a dihalo-BCHep was also considered, and this was confirmed as a valid approach by the re-formation of the oxa- and azapropellanes from dihalo-BCHep precursors.

With a successful route to 3-oxa[3.1.1]propellane in hand, propellanes containing other heteroatoms were targeted. Intermediates in this route were intercepted with sulfur and nitrogen containing nucleophiles in order to access 3-thia- and 3-aza[3.1.1]propellanes. Remarkably, it was possible to generate a crystal structure of the aza[3.1.1]propellane at

room temperature. The modular nature of these three routes that involve a common intermediate would be advantageous to the medicinal chemist looking to generate diverse compound libraries.

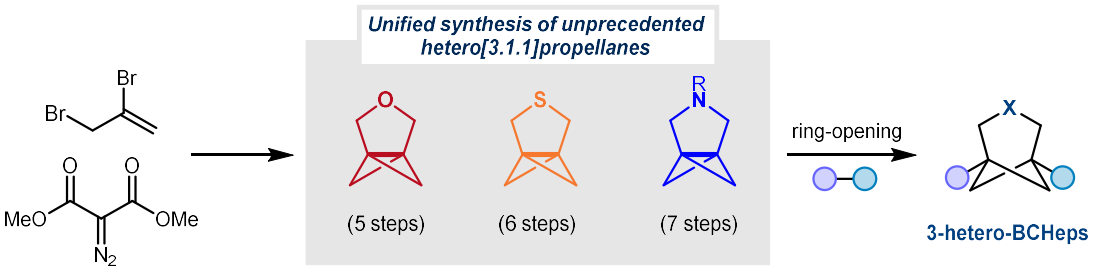


Figure 5.1 Project summary.

A range of propellane ring-opening reactions have also been demonstrated, affording a variety of bridgehead disubstituted hetero-BCHeps. This late-stage diversification of the bridgehead positions is a further advantage for drug discovery programmes. The selection of hetero-BCHep compounds that can be made from hetero[3.1.1]propellanes is highly complementary to those that can be made by other methods and includes compounds that would have been previously inaccessible. The utility of these propellane ring-opening reactions was illustrated by the synthesis of an oxa-BCHep analogue of sonidegib from one of the ring-opened products. As well as identifying a wealth of useful ring-opening reactions, some unexpected reaction pathways of propellanes were also uncovered, including the fragmentation of thia-BCHep radicals after ring opening and the staffane formation of aza[3.1.1]propellanes.

The presence of a nitrogen atom in the propellane scaffold presented an opportunity for the incorporation of a bridge substituent on the propellane. Initial attempts to diversify the substituent on the nitrogen were limited to strongly electron withdrawing groups, however by changing the organolithium reagent used for ring-closure it was possible to access a more diverse range of *N*-substituted propellanes. Ring-opening reactions of these propellane provided access to various *N*-substituted aza-BCHeps. Alternatively, the

nitrogen can be deprotected after the formation of *N*(Ts)-BCHeps from *N*(Ts)[3.1.1]propellane, allowing for the possibility of introducing a new nitrogen substituent at this stage. The ability to vary the nitrogen substituent on the propellane also opened up the possibility to investigate propellane reactivity by constructing a Hammett plot, the results of which showed that propellanes with electron donating substituents were more reactive than those with electron withdrawing substituents.

The synthesis of the family of hetero[3.1.1]propellanes presented in this thesis is the first example of a route to small-ring heteroatom-containing propellanes and it provides a solution to a problem which has remained unsolved in propellane chemistry for decades. Since carbocyclic [1.1.1]propellane and [3.1.1]propellane alone have enabled the synthesis of tens of thousands of medicinally relevant bicyclic compounds, this new family of hetero[3.1.1]propellanes could be expected to find similar widespread interest and applications in drug discovery and medicinal chemistry.

5.1.2. Future Work

The results in this thesis are the first steps into the area of small-ring heteropropellanes and therefore open up many possibilities for future work. Since the discovery of [1.1.1]propellane and [3.1.1]propellane in the 1980s, it took many decades for the full scope of their ring-opening reactions to be realised, and new methods for such ring-opening reactions are still being discovered today. These new hetero[3.1.1]propellanes will likewise require further studies to test the limits of what can be achieved with them and to unlock the full potential of their ring-opening reactions (Figure 5.2a). The aza[3.1.1]propellane in particular deserves further attention to fully understand the link between the nature of the *N*-substituent and the efficiency of ring-opening reactions.

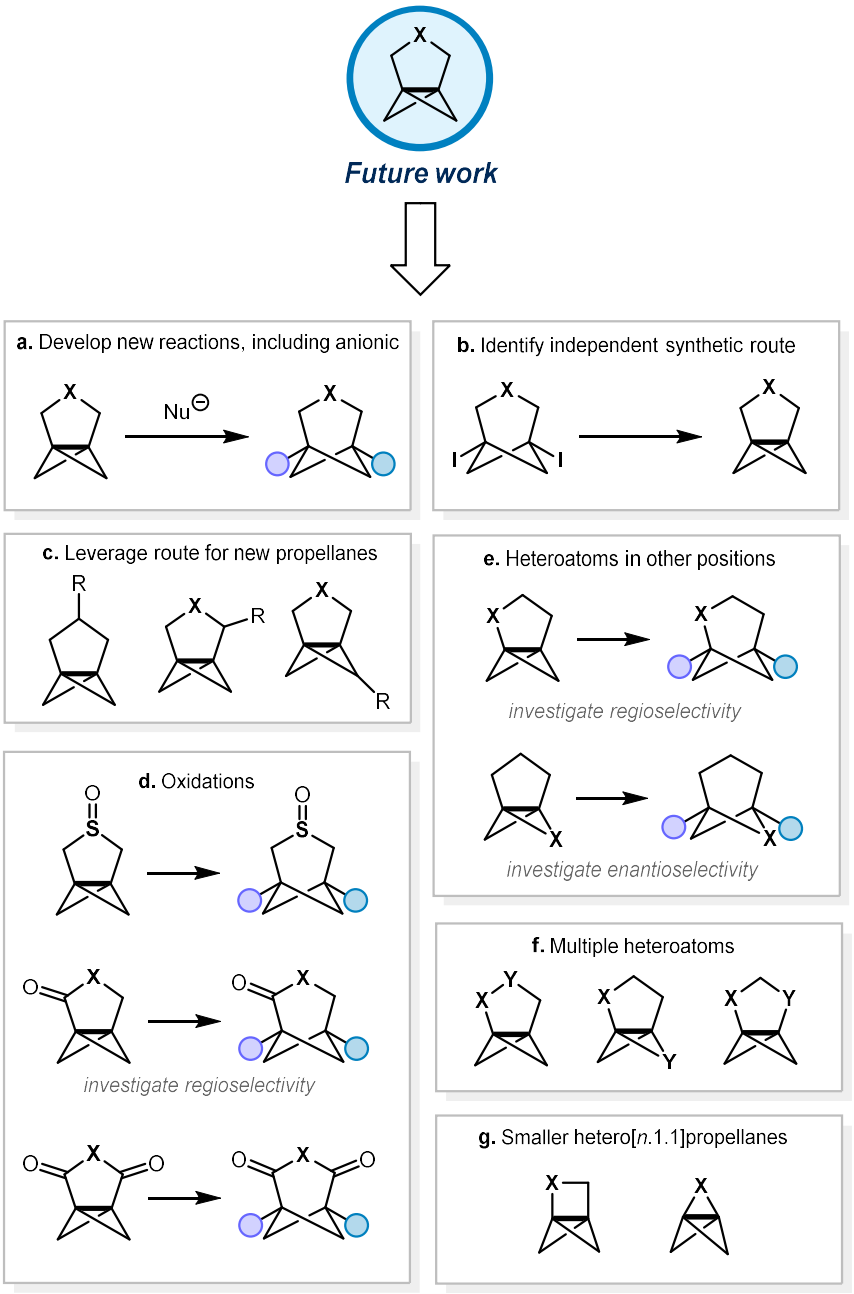


Figure 5.2 Suggestions for future work. **a** Develop new propellane ring-opening reactions, including anionic reactions. **b** Identify an independent synthetic route to the dihalo-BCHep propellane precursor. **c** Leverage existing route to introduce other nucleophiles or bridge substituents. **d** Oxidations of sulfur or bridge positions. **e** Propellanes with heteroatoms in other positions. **f** Propellanes containing multiple heteroatoms. **e** Smaller-ring hetero[*n*.1.1]propellanes.

While [1.1.1]propellane reacts readily with both radicals and anions, both carbocyclic and heterocyclic [3.1.1]propellanes have only been reported to react with radicals, due to the lack of stabilisation for incoming negative charge. Future work could include the

investigation of whether there are any hetero[3.1.1]propellanes that could in fact react with anions (Figure 5.2a).

In this thesis, the diiodo oxa- and aza-BCHeps have been validated as potential propellane precursors, however an independent route for their synthesis is yet to be identified. This could potentially be a fruitful avenue for further investigation and it would be interesting to discover if a route involving these intermediates could compete with the efficiency and modularity of the routes reported here (Figure 5.2b).

It was possible to leverage the initial route to 3-oxa[3.1.1]propellane to access propellanes containing other heteroatoms, since the intermediates in this route are easy to intercept with nucleophiles. This raises the question of whether these intermediates could be intercepted with other nucleophiles to access new heterocyclic or even carbocyclic propellanes. It may also be possible to manipulate the intermediates to introduce bridge substituents in various positions on the propellane structures (Figure 5.2c).

Propellanes containing oxidised sulfur atoms may also merit further investigation. While oxidation of the thia[3.1.1]propellane to the sulfone proved unsuccessful due to the cheletropic extrusion of SO_2, oxidation to the sulfoxide was not explored. This could potentially be attempted either on the thiapropellane or on the precursor before propellane formation. If tolerated in the propellane, it would be interesting to see what effect the sulfoxide might have on propellane reactivity and ring-opening reactions (Figure 5.2d).

Oxidations on the positions adjacent to the heteroatoms may also be interesting to consider, for example to generate lactone or lactam propellanes. These might be expected to have rather different reactivities to the standard oxa- and azapropellanes and they

would also present the interesting question of what would happen with the regioselectivity of ring-opening (Figure 5.2d).

Another interesting avenue to consider would be the synthesis of new hetero[3.1.1]propellanes with heteroatoms in other positions on the ring or with multiple heteroatoms (Figure 5.2e-f). This would most likely require a completely different synthetic approach from the 3-hetero[3.1.1]propellanes and would present an interesting synthetic challenge. Depending on the position of the heteroatom, it would also introduce the opportunity to investigate the regioselectivity or enantioselectivity of ring opening.

An even more challenging synthetic target would be smaller ring hetero[*n*.1.1]propellanes (Figure 5.2g). These have been the subject of computational studies[154] but have not yet been prepared in the lab. Perhaps our results on the synthesis of hetero[3.1.1]propellanes may inspire others to attempt the synthesis of these challenging targets.

6. Experimental procedures

6.1. General experimental information

NMR Spectroscopy: Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on Bruker AVIII HD 400, NEO 600, AVIII HD 500, and AVII 500 spectrometers (University of Oxford). ^{1}H, and ^{13} chemical shifts (δ) are quoted in parts per million (ppm). ^{1}H NMR spectra were recorded using an internal deuterium lock for the residual protons in benzene-*d* (δ = 7.16) or chloroform-*d* (δ = 7.26). ^{13}C NMR spectra were recorded using an internal deuterium lock in benzene-*d* (δ = 128), chloroform-*d* (δ = 77.16). Assignments were determined either on the basis of unambiguous chemical shift or coupling patterns, COSY, HSQC, HMBC and/or NOESY experiments. Peak multiplicities are defined as s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), m (multiplet) and br (broad). Coupling constants (*J*) are reported to the nearest 0.1 Hz.

Mass Spectroscopy: High-resolution mass spectra (HRMS) were recorded by the Departmental Mass Spectrometry Service, University of Oxford on a Thermo Scientific Exactive Mass Spectrometer (Waters Equity autosampler and pump) for electrospray ionization (ESI) and an Agilent 7200 Accurate Mass QTOF GCMS (using a SIM Direct Insertion Probe) for electron ionization (EI) and chemical ionization (CI). HRMS (ESI) data were recorded on a Waters Xevo G2-XS Q-TOF instrument (IISC India). High-resolution values are calculated to 4 decimal places from the molecular formula, and all values are within a tolerance of 5 ppm.

Infrared Spectroscopy: Infrared spectra were obtained on a Bruker Tensor 27 FT-IR spectrometer, as a thin film by evaporation of a solution onto a diamond ATR module. Wavelengths of maximum absorbance (υ_{max}) are quoted in cm^{-1}.

Chromatography: Column chromatography refers to normal phase column chromatography and was performed on silica gel (Merck Si 60, 0.040–0.063 mm) under a positive pressure of nitrogen, using the stated solvent system. Analytical thin-layer chromatography was performed on pre-coated aluminium-backed plates (Merck Kieselgel 60 F_{254} plates) with visualization by ultraviolet light (254 nm) and/or by staining with potassium permanganate or vanillin. Retention factors (R_f) are reported with the solvent system in parentheses.

Materials/procedures: All air- or moisture-sensitive reactions were carried out in anhydrous solvents under an inert atmosphere of argon or nitrogen. Light-sensitive reactions were carried out under aluminium foil protection. Heating was performed using a silicone oil bath. Dry tetrahydrofuran, CH_2Cl_2, pyridine, triethylamine and diethyl ether were collected from an mBraun SPS-800 solvent purification system, having been passed through anhydrous alumina columns. "rt" refers to room (ambient) temperature, typically 23 °C.

Photochemical setup: Photochemical reactions were carried out in an EvoluChem PhotoRedOx Box with an LED lamp (HCK1012-01-010 405 nm or HCK1012-01-002 450-455 nm or Kessil PR160, 456 nm) positioned 10 cm away from the vial, with fan cooling.

Melting points: Recorded using a Gallenkamp melting point apparatus, and are uncorrected.

Safety note: all reactions involving diazo compounds or azides were carried out behind a blast shield, although no uncontrolled decomposition has been observed.

General procedure 1: Reaction with chalcogen (RXH)[47]

Hetero[3.1.1]propellane (1.0 eq.) was added dropwise to a solution of thiol/benzeneselenol (1.1 eq.) in anhydrous diethyl ether. The reaction mixture was stirred for 1 h at ambient temperature, then diluted with diethyl ether and washed with 1 M aqueous NaOH solution (x3), followed by brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The product was purified by column chromatography on silica gel.

General procedure 2: BEt_3-initiated atom transfer radical addition[155]

An alkyl iodide (1 eq.) was added to a stirred diethyl ether solution of hetero[3.1.1]propellane (1.2-1.5 eq.) at 0 °C. Et_3B (10 mol%, 1 M in hexane) was then added. The mixture was stirred until complete consumption of the alkyl iodide, as monitored by TLC. The reaction mixture was then concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel.

General procedure 3: Photoredox-catalysed atom transfer radical addition[29]

To a 4 mL screw-capped vial equipped with a stirrer bar were added *fac*-$Ir(ppy)_3$ (2.5 mol%), an alkyl or aryl halide (1.0 eq.), and *t*-BuCN (0.13 M). Hetero[3.1.1]propellane (1.5-2.0 eq.) was added and the mixture was degassed with N_2 for 5 minutes. The vial was placed in the photobox, and the stirred reaction mixture was irradiated with blue LEDs (HCK1012-01-002 450-455 nm or Kessil PR160, 456 nm) with fan cooling for the specified time. After the consumption of the iodides as monitored by TLC, the reaction mixture was concentrated, and the product was purified by column chromatography on silica gel.

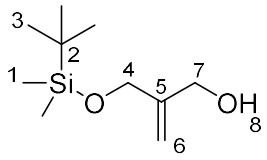
General procedure 4: Propellane formation

To a solution of propellane precursor (1.0 eq.) in THF (0.1 M) at -78 °C was added the organolithium reagent (1.0 eq.) and the mixture was stirred at -78 °C for 5 min. The mixture was then warmed to room temperature and stirred until completion. $NaHCO_3$ (1.0 eq.) was added and the mixture was stirred for another 5 min, then filtered through a celite pad and eluted with THF. The mixture was partially concentrated under reduced pressure to give the product as a solution in THF, which was stored in a glass bottle with an AcroSeal under N_2 at -20 °C.

Caution: During the partial concentration process, bromomethane will be released.

6.2. Experimental procedures and characterisation data

2-(((*tert*-Butyldimethylsilyl)oxy)methyl)prop-2-en-1-ol (31)



To a solution of 2-methylenepropane-1,3-diol (1.23 mL, 30.0 mmol, 1.00 eq) and imidazole (1.22 g, 17.9 mmol, 1.19 eq) in dry CH_2Cl_2 (50.0 mL) at 0 °C was added TBSCl (1.91 g, 12.7 mmol, 0.84 eq). The mixture was stirred at rt for 2 h then HCl (1M, 20 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic layers washed with brine (1 x 50 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane / Et_2O, 4:1) gave the product as a pale yellow oil (1.03 g, 5.08 mmol, 41%).

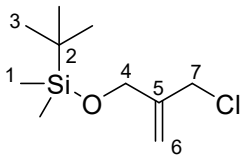
R_f 0.35 (4:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.11-5.09 (1H, m, H6), 5.09-5.07 (1H, m, H6), 4.25 (2H, s, H4), 4.17 (2H, s, H7), 1.75 (1H, br s, H8), 0.91 (9H, s, H3), 0.09 (6H, s, H1).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 147.6 (C5), 111.3 (C6), 65.3 (C7), 64.9 (C4), 26.0 (C3), 18.4 (C2), -5.3 (C1).

Analytical data matches that previously reported[13].

***tert*-Butyl((2-(chloromethyl)allyl)oxy)dimethylsilane (32)**



To a stirred solution of **31** (1.00 g, 4.94 mmol, 1.00 eq) and PPh_3 (1.56 g, 5.95 mmol, 1.20 eq) in CH_2Cl_2 (100 mL) at 0 °C was added *N*-chlorosuccinimide (792 mg, 5.93 mmol, 1.20 eq) portion wise and the mixture was stirred at rt for 30 min. MeOH (40 mL), sat. NH_4Cl solution (40 mL) and H_2O (20 mL) were added. The mixture was extracted with CH_2Cl_2 (3 x 60 mL), washed with brine (100 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane / Et_2O, 19:1) gave the product as a pale yellow oil (694 mg, 3.14 mmol, 64%).

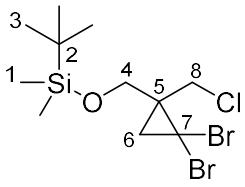
R_f 0.64 (19:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.23 (1H, q, J = 1.5 Hz, H6), 5.21-5.20 (1H, m, H6), 4.24 (2H, s, H4), 4.10 (2H, s, H7), 0.92 (9H, s, H1), 0.09 (6H, s, H3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 144.7 (C5), 114.6 (C6), 63.5 (C4), 45.2 (C7), 26.0 (C1), 18.5 (C2), -5.3 (C3).

Analytical data matches that previously reported[14].

***tert*-Butyl((2,2-dibromo-1-(chloromethyl)cyclopropyl)methoxy)dimethylsilane (33)**



To a stirred solution of dibenzo-18-crown-6 (46.0 mg, 0.128 mmol, 0.05 eq) and pinacol (12.1 mg, 0.102 mmol, 0.04 eq) in CH_2Cl_2 (1.13 mL) was added **32** (564 mg, 2.55 mmol, 1.00 eq), then $CHBr_3$ (445 μL, 5.11 mmol, 2.00 eq), then 50% aqueous NaOH solution (1.50 mL, 10 eq). The mixture was heated under reflux at 50 °C and vigorously stirred for 16 h. The mixture was diluted with H_2O (8 mL), CH_2Cl_2 (8 mL) and extracted with CH_2Cl_2 (3 x 8 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane / EtOAc, 19:1) gave the product as a pale yellow oil (554 mg, 1.41. mmol, 55%).

R_f 0.66 (19:1 pentane / EtOAc).

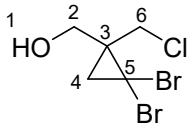
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.95-3.86 (4H, m, H4/8), 1.68 (1H, d, J = 8.1 Hz, H6), 1.66 (1H, d, J = 8.2 Hz, H6), 0.92 (9H, s, H3), 0.11 (3H, s, H1), 0.10 (3H, s, H1).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 64.8 (C4), 48.2 (C8), 32.2 (C6), 26.0 (C3), 18.4 (C2), -5.3 (C1).

IR (thin film, ν_{max} / cm^{-1}): 2955 (w, C-H), 2930 (w, C-H), 2858 (w, C-H).

HRMS (ES^+) Not found.

(2,2-Dibromo-1-(chloromethyl)cyclopropyl)methanol (29)



To a stirred solution of **33** (200 mg, 0.509 mmol, 1.00 eq) in THF (2.00 mL) at 0 °C was added TBAF (0.508 mL, 1 M in THF, 0.508 mmol, 1.00 eq) and the mixture was stirred at 0 °C for 30 min. Then sat. NH_4Cl (2 mL) was added and the mixture was extracted with Et_2O. The combined organic layers were washed with brine (4 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane / Et_2O, 4:1) gave the product as a white crystalline solid (66.3 mg, 0.238 mmol, 47%).

R_f 0.22 (4:1 pentane / EtOAc).

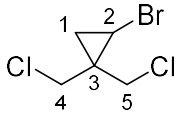
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.12 (1H, d, *J* = 12.8 Hz, H2), 4.10 (1H, dd, *J* = 11.6, 0.8 Hz, H6), 3.86 (1H, dd, *J* = 12.2, 1.0 Hz, H2), 3.84 (1H, dd, *J* = 11.6, 1.0 Hz, H6), 1.76 (1H, dd, *J* = 8.1, 0.8 Hz, H4), 1.73 (1H, d, *J* = 8.1 Hz, H4).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 65.2 (C2), 47.9 (C6), 35.8 (C5), 32.4 (C3), 32.1 (C4).

IR (thin film, ν_{max} / cm^{-1}): 3390 (br, O-H), 2954 (w, C-H), 2926 (w, C-H), 1732

HRMS (ES^+) Not found.

2-Bromo-1,1-bis(chloromethyl)cyclopropane (34)



To a solution of 1,1-dibromo-2,2-bis(chloromethyl)cyclopropane (60.0 mg, 0.202 mmol, 1.0 eq.) in MeOH (1.0 mL) was added KOH (22.7 mg, 0.404 mmol, 2.0 eq.) and the mixture was stirred at rt under air for 20 h. The solvent was removed under reduced pressure, then water (2 mL) was added and the mixture was extracted with Et_2O (3 x 2 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product (29.9 mg, 0.137 mmol, 68%) as a colourless oil. The reaction did not go all the way to completion and the isolated product contained a 10% impurity of starting material. The yield was calculated using quantitative NMR.

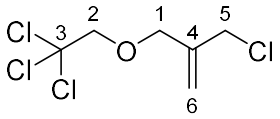
R_f 0.59 (19:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.01 (1H, d, *J* = 11.7 Hz), 3.79 (1H, d, *J* = 11.6 Hz), 3.75 (1H, d, *J* = 11.9 Hz), 3.45 (1H, d, *J* = 11.7 Hz), 3.12 (1H, dd, *J* = 7.9, 5.0 Hz), 1.47 (1H, t, *J* = 7.5 Hz), 1.12 (1H, ddd, *J* = 7.2, 5.0, 1.0 Hz)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 47.8, 47.7, 29.1, 26.6, 22.9.

Data in accordance with literature report[132].

3-Chloro-2-((2,2,2-trichloroethoxy)methyl)prop-1-ene (40)



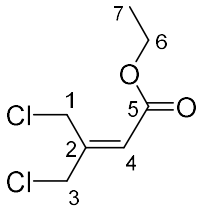
To a solution of NaH (669 mg, 16.7 mmol, 2.5 eq.) in THF (20 mL) at 0 °C was added 2,2,2-trichloroethan-1-ol (641 µL, 6.69 mmol, 1.0 eq.) and the mixture was stirred for 10 min. The mixture was added dropwise to a solution of 3-chloro-2-(chloromethyl)prop-1-ene (930 µL, 8.03 mmol, 1.2 eq.). The mixture was stirred at 90 °C for 3 h, then at 60 °C for 18 h. Water (30 mL) was added and the mizture was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with brine (60 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (pentane / Et_2O 19:1) gave the product (489 mg, 2.06 mmol, 31%) as a yellow oil.

R_f 0.42 (19:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.38 (1H, q, *J* = 0.9 Hz, H6), 5.32 (1H, q, *J* = 1.2 Hz, H6), 4.40 (2H, s, H1/5), 4.16 (2H, d, *J* = 1.0 Hz, H1/5), 4.08 (2H, s, H2).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 141.1, 118.2, 82.5, 72.7, 60.5, 45.0.

Ethyl 4-chloro-3-(chloromethyl)but-2-enoate (46)



To a solution of (Carbethoxymethylene)triphenylphosphorane (5.49 g, 15.8 mmol, 1.00 eq) in CH_2Cl_2 (40.0 mL), was added 1,3-dichloropropan-2-one (2.00 g, 15.8 mmol, 1.00 eq) slowly at rt. The mixture was stirred at rt overnight, then concentrated under reduced pressure and added directly to a column. Purification by column chromatography (SiO_2, pentane/Et_2O 10:1) gave the product as a colourless oil (2.79 g, 14.2 mmol, 90%).

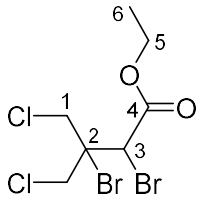
R_f 0.27 (19:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.07 (1H, s, H4), 4.81 (2H, s, H1), 4.26 (2H, d, *J* = 1.1 Hz, H3), 4.22 (2H, q, *J* = 7.2 Hz, H 6), 1.30 (3H, t, *J* = 7.2 Hz, H7).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 164.9 (C5), 149.3 (C2), 122.4 (C4), 61.0 (C6), 45.7 (C3), 38.2 (C1), 14.3 (C7).

Analytical data matches that previously reported[156].

Ethyl 2,3-dibromo-4-chloro-3-(chloromethyl)butanoate (47')



Conc. Br_2 (2.18 mL, 42.6 mmol, 5.00 eq) was added to **46** (1.68 g, 8.52 mmol, 1.00 eq) and stirred at rt for 3 h. The mixture was diluted with CH_2Cl_2 (100 mL) then quenched with sat. $Na_2S_2O_3$ (100 mL). Brine (20 mL) was added, then the mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic extracts were washed with brine (50 mL), then water (50 mL), then brine (50 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product as a yellow oil without further purification (2.63 g, 7.36 mmol, 85%).

R_f 0.53 (19:1 pentane / EtOAc).

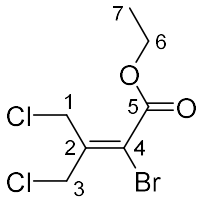
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.99 (1H, s, H3), 4.60 (1H, d, *J* = 12.7 Hz, H1), 4.29 (1H, q, *J* = 7.2 Hz, H5), 4.28 (1H, q, *J* = 7.2 Hz, H5), 4.26 (1H, d, *J* = 12.6 Hz, H1), 4.19 (1H, d, *J* = 12.7 Hz, H1), 4.02 (1H, d, *J* = 12.7 Hz, H1), 1.34 (3H, t, *J* = 7.1 Hz, H6).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 166.7 (C4), 65.6 (C2), 63.1 (C5), 49.7 (C1), 49.3 (C1), 48.5 (C3), 14.0 (C6).

IR (thin film, ν_{max} / cm^{-1}): 2986, 11745, 1372, 1236, 977.

HRMS (ES^+) Not found.

Ethyl 2-bromo-4-chloro-3-(chloromethyl)but-2-enoate (47)



To a solution of NaOMe (625mg, 11.6 mmol, 1.76 eq) in dry MeOH (20.0 mL) was added a solution of **47'** (2.34 g, 6.56 mmol, 1.00 eq) in dry MeOH (20.0 mL). The mixture was stirred at rt for 23 h, then the solvent was removed under reduced pressure. The residue was diluted with Et_2O (60 mL), washed with water (3 x 40 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product as a yellow/brown oil with no further purification (989 mg, 3.58 mmol, 55%).

R_f 0.36 (19:1 pentane / EtOAc).

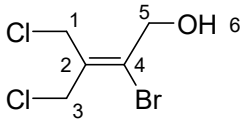
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.55 (2H, s, H1/3), 4.48 (2H, s, H1/3), 4.34 (2H, q, *J* = 7.1 Hz, H6), 1.37 (3H, t, *J* = 7.1 Hz, H7).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 162.8 (C5), 142.0 (C2), 118.5 (C4), 63.3 (C5), 44.4 (C1/3), 40.6 (C1/3), 14.1 (C7).

IR (thin film, ν_{max} / cm^{-1}): 2984, 1724, 1274, 1176, 1032.

HRMS (ES^+) Not found.

2-Bromo-4-chloro-3-(chloromethyl)but-2-en-1-ol (48)



To a stirred solution of **47** (150 mg, 0.544 mmol, 1.00 eq) in dry CH_2Cl_2 (2.50 mL)) at -78 °C was added DIBAL (1.14 mL of 1.00 M solution in hexanes, 1.14 mmol, 2.10 eq) dropwise. The mixture was stirred at -78 °C for 1 h then rt for 1 h. The mixture was cooled to 0 °C, then MeOH (0.75 mL) followed by sat. aqueous Rochelle salt (5 mL) and water (2mL) were added. The resulting gel was stirred at rt until complete phase separation. The aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the product as a colourless oil without further purification (115 mg, 0.492 mmol, 90%).

R_f 0.16 (9:1 pentane / EtOAc).

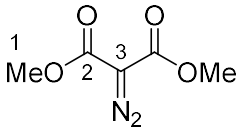
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.50 (2H, s, H5), 4.42 (2H, s, H1), 4.36 (2H, s, H3).

^{13}C NMR (125 MHz, $CDCl_3$) δ_C 134.4 (C2), 133.0 (C4), 64.8 (C5), 45.6 (C1), 39.9 (C3).

IR (thin film, ν_{max} / cm^{-1}): 3419 (br), 2952, 1636, 1442, 1076.

HRMS (ES^+) Not found.

Dimethyl 2-diazomalonate (54)



The product was prepared according to a modified literature procedure[145]. To a solution of dimethyl malonate (17.3 mL, 151 mmol, 1.0 eq.) and *p*-ABSA (40.0 g, 167 mmol, 1.1 eq.) in dry MeCN (150 mL) at 0 °C was added DBU (24.9 mL, 167 mmol, 1.1 eq.) dropwise over 30 min, keeping the internal temperature below 20 °C. The mixture was then warmed to rt and stirred for 3 h. NH_4Cl sat. (20 mL) was added, then the solvent was removed under reduced pressure. Water (400 mL) was added and the mixture was extracted with Et_2O (3 x 400 mL), then the combined organic layers were washed with brine (600 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The mixture was filtered through a silica plug and eluted with a 4:1 mixture of hexane/EtOAc until all of the yellow substance was removed from the silica. Concentration under reduced pressure gave the product (20.6 g, 130 mmol, 86%) as a yellow oil.

R_f 0.20 (4:1 pentane / EtOAc).

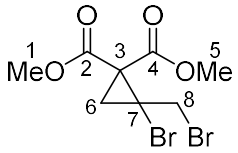
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.83 (6H, s, H1).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 161.2, 52.7.

Analytical data matches that previously recorded[145].

Note: For safety reasons, to avoid isolation of neat diazo compound, the product is not concentrated until completely free of solvent, but is taken forward to the next step with around 10% residual solvent remaining. The amount of product was determined by NMR spectroscopy.

Dimethyl 2-bromo-2-(bromomethyl)cyclopropane-1,1-dicarboxylate (55)



To a solution of rhodium(II) triphenylacetate dimer (93.8 mg, 65.1 μmol, 0.050 mol%) in dry CH_2Cl_2 (100 mL) was added 2,3-dibromoprop-1-ene (25.5 mL, 80%, 208 mmol, 1.6 eq.). A solution of dimethyl 2-diazomalonate **54** (20.6 g, 130 mmol, 1.0 eq.) in dry CH_2Cl_2 (20.0 mL) was added *via* a syringe pump over 8 h at rt then the mixture was stirred at rt for an additional 8 h. The solvent was removed under reduced pressure, then purification by column chromatography (SiO_2, pentane/Et_2O 19:1 → 8:2) gave the product (29.1 g, 88.2 mmol, 68%) as a colourless oil.

R_f 0.26 (8:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.07 (2H, s, H8), 3.84 (3H, s, H1 or 5), 3.80 (3H, s, H1 or 5), 2.29 (1H, d, J = 7.2 Hz, H6), 2.06 (1H, d, J = 7.2 Hz, H6).

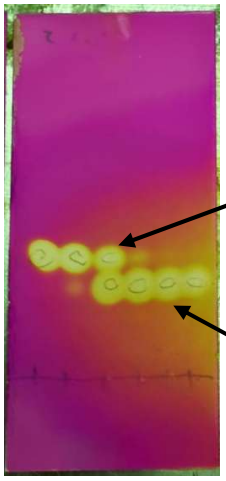
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 166.9, 165.9, 53.6, 53.5, 42.3, 41.2, 38.3, 30.8.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2955, 1743, 1438, 1345, 1258.

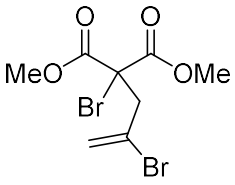
HRMS (ES^+) calc. for $C_8H_{11}Br_2O_4$ $[M+H]^+$ 328.9019, found 328.9006.

Note: some product fractions contained traces of catalyst, giving them a blue colour, but this did not impact the following steps.

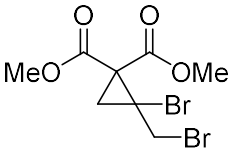
Note: the following TLC plate shows a typical result from a column for this step. The second fraction contains the product. To achieve good separation, the column should be eluted with pentane/Et_2O 19:1 until the first fraction has eluted, then the solvent mixture may be increased to pentane/Et_2O 8:2.



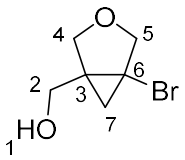
Side product



Major product



(5-Bromo-3-oxabicyclo[3.1.0]hexan-1-yl)methanol (57)



To a solution of **55** (15.0 g, 46.0 mmol, 1.0 eq.) in dry THF (150 mL) at -78 °C was added DIBALH (200 mL, 1.0 M solution in hexanes, 200 mmol, 4.3 eq.). The mixture was stirred at -78 °C for 2.5 h, allowed to warm slowly to rt and stirred for an additional 30 min. The mixture was cooled to 0 °C and Rochelle's salt (250 mL, aq. sat.) was added slowly. The cloudy mixture was stirred at rt for 5 h until it became clear. THF was removed under reduced pressure, then the aqueous layer was extracted with EtOAc (3 x 200 mL). The combined organic layers were washed with brine (300 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford (2-Bromo-2-(bromomethyl)cyclopropane-1,1-diyl)dimethanol (**56**).

The crude product **56** from the first step was dissolved in MeOH (100 mL) and added to a solution of KOH (4.50 g, 80.0 mmol, 1.8 eq.) in MeOH (150 mL). The mixture was heated to 60 °C for 1 h, then the solvent was removed under reduced pressure. Water (100 mL) was added and the mixture was extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product **57** (7.40 g, 38.0 mmol, 84%) as a yellow oil, which required no further purification.

R_f 0.45 (4:6 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.09 (1H, d, *J* = 8.2 Hz, H4 or H5), 4.00 (1H, d, *J* = 8.7 Hz, H4 or H5), 3.98 (1H, d, *J* = 12.5 Hz, H2), 3.88 (1H, d, *J* = 8.3 Hz, H4 or H5), 3.83 (1H, d, *J* = 9.1 Hz, H 4 or H5), 3.82 (1H, d, *J* = 11.8 Hz, H2), 1.69 (1H, br s, H1), 1.33 (1H, d, *J* = 6.1 Hz, H7), 1.19 (1H, d, *J* = 6.1 Hz, H7).

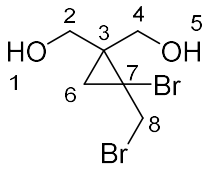
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 75.1, 70.0, 63.5, 37.2, 34.0, 20.8.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3422, 2870, 1074, 1040, 998.

HRMS (ES^+) Not found.

If desired, the product **56** of the first step can be isolated by trituration. A representative procedure is as follows:

(2-Bromo-2-(bromomethyl)cyclopropane-1,1-diyl)dimethanol (56)



To a solution of **55** (6.69 g, 20.3 mmol, 1.0 eq.) in dry THF (50.0 mL) at -78 °C was added DIBALH (83.1 mL, 1.0 M solution in hexanes). The mixture was stirred at -78 °C for 2 h, then stirred at 0 °C for a further 1 h. Rochelle's salt (100 mL, aq, sat.) was added and the cloudy mixture was stirred at rt for 3 h until it became clear. THF was removed under reduced pressure, then the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Trituration from a 7:3 mixture of pentane:Et_2O gave the product (2.59 g, 9.45 mmol, 47%) as a white amorphous solid which was collected by filtration.

R_f 0.24 (4:6 pentane / EtOAc).

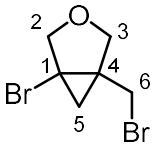
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.15 (1H, d, *J* = 11.9 Hz, H2), 4.08 (1H, d, *J* = 12.2 Hz, H4), 4.03 (1H, d, *J* = 12.0 Hz, H8), 3.93 (1H, d, *J* = 12.0 Hz, H8), 3.89 (1H, d, *J* = 12.0 Hz, H2), 3.76 (1H, d, *J* = 12.2 Hz, H4), 2.23 (2H, br s, H1/H5), 1.36 (1H, d, *J* = 7.1 Hz, H6), 1.23 (1H, d, *J* = 7.1 Hz, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 69.9, 64.1, 44.2, 42.6, 37.1, 26.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3373, 2947, 1436, 1229, 1025.

HRMS (ES^+) calc. for $C_6H_{11}Br_2O_2$ $[M+H]^+$ 272.9120, found 272.9122.

1-Bromo-5-(bromomethyl)-3-oxabicyclo[3.1.0]hexane (58)



To a solution of **57** (7.59 g, 39.3 mmol, 1.0 eq.) in dry CH_2Cl_2 (100 mL), was added NBS (8.40 g, 47.2 mmol, 1.2 eq.). PPh_3 (12.4 g, 47.2 mmol, 1.2 eq.) was then added in portions at 0 °C and the mixture was stirred at rt for 1 h. Pentane (150 mL) was added to the reaction mixture and stirred for 10 minutes at room temperature. The mixture was filtered through a celite pad, and the filtrate was concentrated. Purification by column chromatography (SiO_2, pentane/Et_2O 19:1) gave the product (7.43 g, 29.0 mmol, 74%) as a pale yellow oil.

R_f 0.33 (19:1 pentane / Et_2O).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.99 (1H, d, *J* = 8.4 Hz, H2/3), 3.81 (1H, d, *J* = 8.6 Hz, H2/3), 3.77 (1H, d, *J* = 8.6 Hz, H2/3), 3.76 (1H, dd, *J* = 8.4, 1.2 Hz, H2/3), 3.54 (1H, d, *J* = 11.0 Hz, H6), 3.51 (1H, d, *J* = 11.0 Hz, H6), 1.42 (1H, d, *J* = 6.3 Hz, H5), 1.14 (1H, d, *J* = 6.3 Hz, H5).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 75.0, 71.4, 40.1, 34.2, 33.1, 23.6.

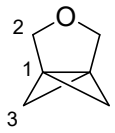
IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2939, 2869, 1442, 1358, 1177, 948.

HRMS (ES^+) Not found.

Note: the product is relatively volatile and must be concentrated carefully with pressure not lower than 250 mbar. However, we have not observed any stability issues with the storage of this propellane precursor over a period of several months.

3-Oxa[3.1.1]propellane (28)

Method 1 (filtration):



To a stirred solution of **58** (5.03 g, 15.7 mmol, 1.0 eq.) in dry Et_2O (80 mL) at rt was added MeLi (12.1 mL, 1.3 M in Et_2O, 15.7 mmol, 1.0 eq.). The mixture was stirred at rt for 4 h, then $NaHCO_3$ (1.32 g, 15.7 mmol, 1.0 eq) was added. The mixture was cooled to 0 °C, then passed through a celite pad and eluted with Et_2O (100 mL). The mixture was partially concentrated under reduced pressure to give the product as a solution in Et_2O (72.0 mL, 0.16 M, 11.7 mmol, 74%), which was stored in an amber glass bottle with an AcroSeal under N_2 at -20 °C. The concentration was determined by integrating the ^1H peak at 2.51 ppm relative to the Et_2O peaks.

^{1}H NMR (600 MHz, C_6D_6) δ_H 3.68 (4H, s, H2), 2.51 (2H, s, H3), 1.62 (2H, s, H3).

^{13}C NMR (151 MHz, C_6D_6) δ_C 73.8 (C2), 53.9 (C3), 28.6 (C1).

Note: the solution of product contains a white precipitate, presumed to be LiBr, which does not affect subsequent reactions.

Caution: During the partial concentration process, bromomethane will be released.

Storage: It is recommended to store the propellane solution in the freezer (-20 °C) at <0.5 M concentration, under which conditions it is stable for a period of (at least) several months. See Section 6.4 for further discussion on stability.

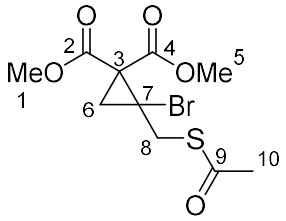
Method 2 (distillation):

To a stirred solution of **58** (1.02 g, 3.19 mmol, 1.0 eq.) in dry Et_2O (16 mL) at rt was added MeLi (2.45 mL, 1.3 M in Et_2O, 3.19 mmol, 1.0 eq.). The mixture was stirred at rt for 4 h, then $NaHCO_3$ (268 mg, 3.19 mmol, 1.0 eq) was added. *n*Bu_2O (30 mL) was added and the mixture was distilled using a rotary evaporator (30 °C water bath) with a dry ice cold finger condenser and a receiving flask immersed in an acetone/dry ice bath. The Et_2O fraction containing bromomethane was removed by slowly decreasing the pressure to 150 mbar and this fraction was discarded. The *n*Bu_2O fraction containing 3-oxa[3.1.1]propellane was then distilled by slowly decreasing the pressure to <10 mbar. This gave the product as a solution in *n*Bu_2O (27.0 mL, 0.065 M, 1.76 mmol, 55%), which was stored in an amber bottle with an AcroSeal under N_2 at -20 °C. The concentration was determined by integrating the ^1H peak at 2.42 ppm relative to the Et_2O peaks.

^{1}H NMR (400 MHz, C_6D_6) δ_H 3.51 (4H, s, H2), 2.42 (2H, t, *J* = 1.4 Hz, H3), 1.64 (2H, t, *J* = 1.4 Hz, H3)

^{13}C NMR (101 MHz, C_6D_6) δ_C 73.2 (C2), 53.9 (C3), 22.8 (C1).

Dimethyl 2-((acetylthio)methyl)-2-bromocyclopropane-1,1-dicarboxylate (60)



A solution of **55** (53.2 mg, 0.161 mmol, 1.0 equiv.) and potassium thioacetate (20.3 mg, 0.177 mmol, 1.1 equiv.) in dry DMF (1.0 mL) was heated to 50 °C for 2.5 h. Water (3 mL) and Et_2O (3 mL) were added. The organic layer was washed with water (3 x 3mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the product (38.8 mg, 0.119 mmol, 74%) as a yellow oil.

R_f 0.46 (7:3 pentane / EtOAc).

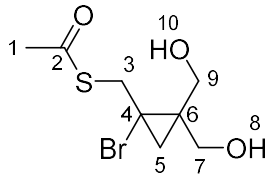
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.95 (1H, d, *J* = 14.4 Hz, H8), 3.82 (3H, s, H1 or H5), 3.79 (3H, s, H1 or H5), 3.55 (1H, d, *J* = 14.5 Hz, H8), 2.37 (3H, s, H10), 2.15 (1H, d, *J* = 7.2 Hz, H6), 1.97 (1H, d, *J* = 7.2 Hz, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 194.0 (C9), 167.0 (C2 or C4), 166.3 (C2 or C4), 53.5 (C1 or C5), 53.4 (C1 or C5), 41.4 (C3 or C7), 40.8 (C3 or C7), 37.7 (C8), 30.5 (C10), 29.0 (C6).

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 1739 (s, C=O), 1698 (s, C=O).

HRMS (ES^+) calc. for $C_{10}H_{14}BrO_5S$ $[M+H]^+$ 324.9740, found 324.9740, error +0.04 ppm.

(1-Bromo-2,2-bis(hydroxymethyl)cyclopropyl)methyl ethanethioate (61)



To a solution of **55** (8.51 g, 25.8 mmol, 1.0 eq.) in dry THF (65 mL) at -78 °C was added DIBALH (106 mL, 1.0 M solution in hexanes, 106 mmol, 4.1 eq.). The mixture was stirred at -78 °C for 2 h, then 0 °C for 1 h, then rt for 1 h. Rochelle's salt (100 mL, aq., sat.) was added and the cloudy mixture was stirred at rt for 16 h until it became clear. THF was removed under reduced pressure, then the aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude product **56**.

The crude product **56** was dissolved in MeOH (30 mL) and potassium thioacetate (2.95 g, 25.8 mmol, 1.0 eq.) was added. The mixture was stirred at rt for 3 h, then the solvent was removed under reduced pressure. Water (50 mL) was added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 4:6) gave the product **61** (3.75 g, 13.9 mmol, 54%) as a white solid.

R_f 0.30 (4:6 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.18 (1H, d, *J* = 11.9 Hz, H7/9), 4.12 (1H, d, *J* = 12.0 Hz, H7/9), 3.85 (1H, dd, *J* = 12.0, 1.6 Hz, H7/9), 3.83 (1H, d, *J* = 14.8 Hz, H3), 3.73 (1H, dd, *J* = 12.0, 1.7 Hz, H7/9), 3.54 (1H, d, *J* = 14.7 Hz, H3), 2.39 (3H, s, H1), 1.14 (1H, d, *J* = 7.0 Hz, H5), 1.12 (1H, d, *J* = 6.9 Hz, H5).

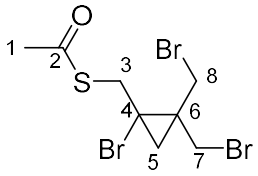
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 195.2, 71.0, 65.6, 45.0, 39.7, 35.6, 30.6, 24.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3395, 2943, 1692, 1422, 1137, 1029.

HRMS (ES^+) calc. for $C_8H_{13}BrO_3SNa$ $[M+Na]^+$ 290.9661, found 290.9664.

m.p. 54 °C

(1-Bromo-2,2-bis(bromomethyl)cyclopropyl)methyl ethanethioate (62)



To a stirred solution of **61** (3.16 g, 11.7 mmol, 1.0 eq.) and NBS (5.22 g, 29.4 mmol, 2.5 eq.) in dry CH_2Cl_2 (120 mL) at 0 °C was added PPh_3 (7.70 g, 29.4 mmol, 2.5 eq.) portionwise. The mixture was stirred at rt for 10 min, then H_2O_2 (30%, 3.6 mL) and water (100 mL) were added. The organic layer was removed and mixture was extracted with CH_2Cl_2 (2 x 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was diluted with pentane / Et_2O (9:1), filtered through a silica pad and concentrated under reduced pressure to give the product (2.70 g, 6.84 mmol, 58%) as a white solid.

R_f 0.27 (19:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) 4.01 (1H, dd, *J* = 10.9, 1.0 Hz, H7/8), 3.85 (1H, d, *J* = 10.9 Hz, H7/8), 3.85 (1H, dd, *J* = 11.3, 0.9 Hz, H7/8), 3.82 (1H, d, *J* = 13.5 Hz, H3), 3.77 (1H, dd, *J* = 11.1, 1.0 Hz, H7/8), 3.50 (1H, d, *J* = 14.9 Hz, H3), 2.42 (3H, s, H1), 1.43 (2H, s, H5).

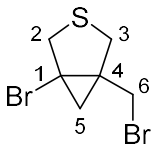
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 194.8, 48.0, 40.0, 39.0, 35.2, 34.8, 30.8, 30.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2970, 1693, 1428, 1354, 1293, 1135.

HRMS (ES^+) Not found.

m.p. 75 °C

1-Bromo-5-(bromomethyl)-3-thiabicyclo[3.1.0]hexane (63)



To a suspension of **62** (2.70 g, 6.84 mmol, 1.0 eq.) in MeOH (35 mL) was added KOH (767 mg, 13.7 mmol, 2.0 eq.) and the mixture was stirred at 50 °C for 1 h. The solvent was removed under reduced pressure, then water (60 mL) was added and the mixture was extracted with Et_2O (3 x 60 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product (1.77 g, 6.51 mmol, 95%) as a low melting point pale yellow solid. We have not observed any stability issues with the storage of this propellane precursor over a period of several months.

R_f 0.59 (19:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) 3.73 (1H, d, *J* = 10.8 Hz, H2/3), 3.63 (1H, d, *J* = 10.8 Hz, H2/3), 3.45 (1H, d, *J* = 11.2 Hz, H2/3), 3.31 (1H, d, *J* = 10.9 Hz, H2/3), 3.29 (1H, d, *J* = 11.3 Hz, H6), 2.89 (1H, d, *J* = 11.3 Hz, H6), 2.07 (1H, d, *J* = 6.6 Hz, H5), 1.13 (1H, d, *J* = 6.6 Hz, H5).

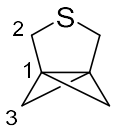
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 44.3, 41.0, 38.7, 35.9, 34.6, 22.6.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2927, 1432, 1343, 1224, 1105, 1018.

HRMS (ES^+) Not found.

m.p. 33 °C

3-Thia[3.1.1]propellane (4)



To a stirred solution of **13** (0.961 g, 3.53 mmol, 1.0 eq.) in dry Et_2O (18 mL) at rt was added MeLi (2.72 mL, 1.3 M in Et_2O, 3.53 mmol, 1.0 eq.). The mixture was stirred at rt for 4 h, then $NaHCO_3$ (297 mg, 3.53 mmol, 1.0 eq) was added. The mixture was cooled to 0 °C, then passed through a celite pad and eluted with Et_2O (50 mL). The mixture was partially concentrated under reduced pressure to give the product as a solution in Et_2O (18.5 mL, 0.13 M, 2.41 mmol, 68%), which was stored in an amber glass bottle with an AcroSeal under N_2 at -20 °C. The concentration was determined by integrating the ^1H peak at 2.79 ppm relative to the Et_2O peaks.

^{1}H NMR (400 MHz, C_6D_6) δ_H ^{1}H NMR (400 MHz, C_6D_6) δ 2.78 (2H, t, *J* = 1.4 Hz, H3), 2.70 (4H, s, H2), 1.58 (2H, t, *J* = 1.4 Hz, H3).

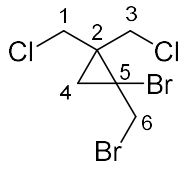
^{13}C NMR (101 MHz, C_6D_6) δ_C 52.4 (C2), 37.7 (C1), 37.7 (C3).

Note: the solution of product contains a white precipitate, presumed to be LiBr, which does not affect subsequent reactions.

Caution: During the partial concentration process, bromomethane will be released.

Storage: It is recommended to store the propellane solution in the freezer (-20 °C) at <0.5 M concentration, under which conditions it is stable for a period of (at least) several weeks–months.

1-Bromo-1-(bromomethyl)-2,2-bis(chloromethyl)cyclopropane (69)



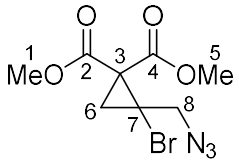
To a solution of **56** (100 mg, 0.365 mmol, 1.0 equiv.) and PPh_3 (182 mg, 0.694 mmol, 1.9 equiv.) in dry CH_2Cl_2 (3.00 mL) at 0 °C was added NCS portionwise (97.5 mg, 0.730 mmol, 2.0 equiv.). The mixture was stirred at rt for 1 h then sat. NH_4Cl solution (3 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O 19:1) gave the product (23.6 mg, 0.0759 mmol, 21%) as a pale yellow oil.

R_f 0.31 (19:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.15 (1H, d, *J* = 11.8 Hz, H1/3/6), 3.99 (1H, d, *J* = 12.2 Hz, H1/3/6), 3.96 (1H, d, *J* = 12.2 Hz, H1/3/6), 3.80 (1H, d, *J* = 12.0 Hz, H1/3/6), 3.76 (1H, d, *J* = 12.2 Hz, H1/3/6), 3.72 (1H, d, *J* = 12.2 Hz, H1/3/6), 1.54 (1H, d, *J* = 7.5 Hz, H4), 1.46 (1H, d, *J* = 7.6 Hz, H4).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 49.6, 45.2, 44.2, 40.8, 36.9, 30.6.

Dimethyl 2-(azidomethyl)-2-bromocyclopropane-1,1-dicarboxylate (75)



To a solution of **55** (14.3 g, 43.3 mmol, 1.0 eq.) in dry DMF (70 mL) was added NaN_3 (2.82 g, 43.3 mmol, 1.0 eq.) and the mixture was stirred at 40 °C for 4 h. Et_2O (500 mL) was added and the mixture was washed with water (3 x 500 mL). Each water wash was back-extracted with Et_2O (2 x 500 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product (12.2 g, 41.8 mmol, 96%) as a yellow oil.

R_f 0.40 (6:4 pentane / Et_2O).

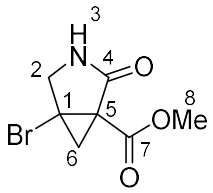
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.03 (1H, d, *J* = 13.8 Hz, H8), 3.89 (1H, d, *J* = 13.8 Hz, H8), 3.83 (3H, s, H1/5), 3.79 (3H, s, H1/5), 2.16 (1H, d, *J* = 7.2 Hz, H6), 1.93 (1H, d, *J* = 7.2 Hz, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 167.3, 166.1, 56.4, 53.7, 53.4, 39.7, 39.6, 27.8.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2956, 2109, 1731, 1436, 1250.

HRMS (ES^+) calc. for $C_8H_{10}BrN_3O_4Na$ $[M+Na]^+$ 313.9747, found 313.9747.

Methyl 5-bromo-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate (76)



To a stirred solution of PBu_3 (11.2 mL, 44.8 mmol, 1.0 eq.) and water (0.808 mL, 44.8 mmol, 1.0 eq.) in THF (110 mL) at 0 °C was added a solution of **75** (13.1 g, 44.8 mmol, 1.0 eq.) in THF (20 mL) dropwise over 45 min, keeping the internal temperature below 5 °C. The mixture was stirred at 0 °C for a further 30 min, then slowly warmed to rt over 30 min and stirred at rt for 1 h. The mixture was then concentrated under reduced pressure. Trituration from THF/pentane (1:5) gave the product (6.40 g, 27.3 mmol, 61%) as a white solid.

R_f 0.17 (3:7 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.07 (1H, s, H3), 3.85 (3H, s, H8), 3.82 (2H, d, *J* = 0.9 Hz, H2), 2.38 (1H, d, *J* = 6.2 Hz, H6), 1.66 (1H, d, *J* = 6.2 Hz, H6).

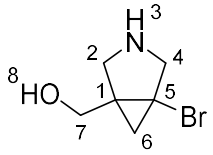
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.8, 165.4, 53.2, 51.8, 37.8, 34.4, 27.0.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3210, 1730, 1708, 1439, 1248.

HRMS (ES^+) calc. for $C_7H_9BrNO_3$ $[M+H]^+$ 233.9760, found 233.9768.

m.p. 109 °C (dec.)

(5-Bromo-3-azabicyclo[3.1.0]hexan-1-yl)methanol (77)



To a solution of methyl 5-bromo-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate **76** (783 mg, 3.35 mmol, 1.0 eq.) in THF (24 mL) at 0 °C was added Red-Al (3.26 mL, 60% wt., 10.0 mmol, 3.0 eq.) dropwise, then the mixture was stirred at rt for 6 h. Rochelle salt solution sat. (20 mL) was added and the mixture was stirred until it became clear. The layers were separated, then the aqueous layer was extracted with a 3:1 mixture of $CHCl_3$:*i*PrOH (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product as a pale yellow solid (432 mg, 3.35 mmol, 67%), which was used in the next step without further purification.

R_f 0.07 (9:1 EtOAc / MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.93 (1H, d, *J* = 12.2 Hz, H2/4), 3.82 (1H, d, *J* = 12.2 Hz, H2/4), 3.34 (1H, d, *J* = 11.5 Hz, H2/4), 3.26 – 3.15 (2H, m, H7), 2.93 (1H, d, *J* = 11.7 Hz, H2/4), 2.15 (2H, s, H3/8), 1.18 (1H, d, *J* = 6.7 Hz, H6), 1.15 (1H, d, *J* = 6.9 Hz, H6).

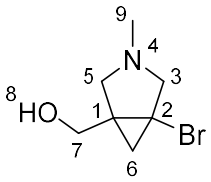
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 64.7, 57.2, 49.3, 40.0, 34.7, 19.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3306, 2874, 1686, 1442, 1083.

HRMS (ES^+) calc. for $C_6H_{11}BrNO$ $[M+H]^+$ 192.0019, found 192.0011.

m.p. 104 °C

5-Bromo-3-methyl-3-azabicyclo[3.1.0]hexan-1-yl)methanol (74)



To a solution of (5-bromo-3-azabicyclo[3.1.0]hexan-1-yl)methanol **77** (100 mg, 0.521 mmol, 1.0 eq.) and MeI (32.4 µL, 0.521 mmol, 1.0 eq.) in THF (1.0 mL) was added NEt_3 (72.6 µL, 0.521 mmol, 1.0 eq.) and the mixture was stirred at 50 °C for 2 h. The mizture was concentrated under reduced pressure, then water (1 mL) was added. The mixture was extracted with Et_2O (3 x 1 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product (60.9 mg, 0.296 mmol, 57%) as a yellow oil.

R_f 0.36 (9:1 CH_2Cl_2 / MeOH).

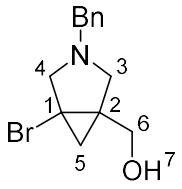
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.92 (1H, d, *J* = 12.2 Hz, H8), 3.72 (1H, d, *J* = 12.2 Hz, H7), 3.33 (1H, d, *J* = 8.6 Hz, H5/3), 2.94 (1H, d, *J* = 8.9 Hz, H5/3), 2.68 (1H, d, *J* = 8.6 Hz, H5/3), 2.63 (1H, d, *J* = 8.9 Hz, H5/3), 2.33 (3H, s, H9), 1.72 (1H, s, H8), 1.64 (1H, d, *J* = 5.8 Hz, H6), 1.00 (1H, d, *J* = 5.8 Hz, H6).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 65.1, 64.7, 57.2, 41.2, 38.2, 34.1, 21.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3355, 2789, 1451, 1040.

HRMS (ES^+) calc. for $C_7H_{13}BrNO$ $[M+H]^+$ 206.0175, found 206.0173.

(3-Benzyl-5-bromo-3-azabicyclo[3.1.0]hexan-1-yl)methanol (79)



To a solution of **77** (219 mg, 1.14 mmol, 1.0 eq.) and benzyl bromide (136 μL, 1.14 mmol, 1.0 eq.) in THF (8.0 mL) was added NEt_3 (159 μL, 1.14 mmol, 1.0 eq.) and the mixture was stirred at room temperature for 1h. The mixture was concentrated under reduced pressure and water (6 mL) was added. The mixture was extracted with Et_2O (3 x 6 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product (222 mg, 0.787 mmol, 69%) as a colourless oil.

R_f 0.29 (7:3 pentane / EtOAc).

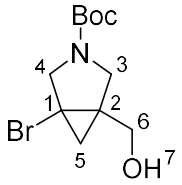
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.34 – 7.21 (5H, m, Bn), 3.90 (1H, d, *J* = 12.3 Hz, H6), 3.73 (1H, d, *J* = 12.2 Hz, H6), 3.65 (1H, d, *J* = 13.0 Hz, Bn), 3.61 (1H, d, *J* = 13.0 Hz, Bn), 3.32 (1H, d, *J* = 8.5 Hz, H3/4), 2.92 (1H, d, *J* = 8.8 Hz, H3/4), 2.74 (1H, d, *J* = 8.5 Hz, H3/4), 2.67 (1H, d, *J* = 8.8 Hz, H3/4), 1.73 (1H, d, *J* = 5.5 Hz, H5), 1.57 (1H, s, H7), 1.00 (1H, d, *J* = 5.5 Hz, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.7, 128.7, 128.4, 127.2, 65.2, 62.4, 58.8, 54.8, 38.0, 33.6, 21.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3521, 2802, 1723, 1495, 1041.

HRMS (ES^+) calc. for $C_{13}H_{17}BrNO$ $[M+H]^+$ 282.0488, found 282.0489.

***tert*-Butyl 1-bromo-5-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (80)**



To a solution of **77** (100 mg, 0.521 mmol, 1.0 eq.) and Boc_2O (114 mg, 0.521 mmol, 1.0 eq.) in THF (2.0 mL) was added NEt_3 (72.6 μL, 0.521 mmol, 1.0 eq.) and the mixture was stirred at 50 °C for 1h. The mixture was concentrated under reduced pressure and water (2 mL) was added. The mixture was extracted with Et_2O (3 x 2 mL) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product (107 mg, 0.366 mmol, 70%) as a white solid.

R_f 0.35 (6:4 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.08 – 3.89 (2H, m, H3/4/6), 3.75 (1H, app. dd, *J* = 12.4, 4.9 Hz, H3/4/6), 3.69 – 3.52 (3H, m, H3/4/6), 1.75 (1H, app. p, *J* = 5.8 Hz, H7), 1.44 (9H, s, Boc), 1.23 (1H, d, *J* = 6.5 Hz, H5), 1.14 (1H, app. t, *J* = 5.1 Hz, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 154.5, 80.3, 64.4, 64.2, 56.1, 55.7, 49.0, 48.5, 36.1, 35.7, 34.1, 33.5, 28.5, 22.9.

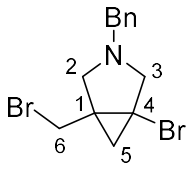
Note: extra peaks in the ^{1}H and ^{13}C spectra are due to the presence of rotamers.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3435, 2876, 1703, 1415, 1126.

HRMS (ES^+) calc. for $C_{11}H_{18}BrNO_3Na$ $[M+Na]^+$ 314.0362, found 314.0358.

m.p. 70 °C

3-Benzyl-1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane (82)



To a solution of **79** (94.9 mg, 0.336 mmol, 1.0 eq.) and CBr_4 (134 mg, 0.404 mmol, 1.2 eq.) in CH_2Cl_2 (4.0 mL) at 0 °C was added dropwise a solution of PPh_3 (106 mg, 0.404 mmol, 1.2 eq.) in CH_2Cl_2 (4 mL) and the mixture was stirred at room temperature for 2 h. Water (4 mL) was added and the mixture was extracted with Et_2O (3 x 4 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane / Et_2O 19:1) gave the product (96.4 mg, 0.279 mmol, 83%) as a colourless oil.

R_f 0.19 (98:2 pentane / EtOAc).

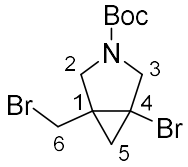
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39 – 7.24 (5H, m, Bn), 3.67 (2H, s, Bn), 3.65 (1H, d, *J* = 10.9 Hz, H6), 3.62 (1H, d, *J* = 10.9 Hz, H6), 3.35 (1H, d, *J* = 8.6 Hz, H2/3), 3.05 (1H, d, *J* = 8.8 Hz, H2/3), 2.76 (1H, d, *J* = 8.7 Hz, H2/3), 2.61 (1H, d, *J* = 8.9 Hz, H2/3), 1.96 (1H, d, *J* = 5.6 Hz, H5), 1.09 (1H, d, *J* = 5.6 Hz, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.4, 128.6, 128.4, 127.3, 62.2, 58.6, 56.4, 41.1, 37.3, 32.6, 24.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2800, 2360, 1226, 1151.

HRMS (ES^+) calc. for $C_{13}H_{16}Br_2N$ $[M+H]^+$ 343.9644, found 343.9644.

***Tert*-butyl 1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (83)**



To a solution of **80** (5.38 g, 18.4 mmol, 1.0 eq.) and NBS (3.93 g, 22.1 mmol, 1.2 eq.) in CH_2Cl_2 (120 mL) at 0 °C was added a solution of PPh_3 (5.80 g, 22.1 mmol, 1.2 eq.) in CH_2Cl_2 (10 mL) dropwise. The mixture was stirred at rt for 1 h then concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentante/EtOAc 9:1) gave the product (5.60 g, 15.8 mmol, 86%) as a white solid.

R_f 0.33 (9:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.10-3.99 (1H, m, H2/3/6), 3.79 – 3.45 (5H, m, H2/3/6), 1.43 (9H, s, Boc), 1.33 (1H, d, J = 6.6 Hz, H5), 1.29 (1H, d, J = 6.7 Hz, H5)

^{13}C NMR (101 MHz, $CDCl_3$) 154.2, 80.5, 55.8, 55.6, 50.5, 50.0, 38.9, 38.7, 35.7, 35.5, 33.2, 32.5, 28.5, 25.8.

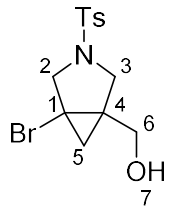
Note: the ^{1}H and ^{13}C spectra show additional signals due to the presence of rotamers.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2977, 1704, 1404, 1175, 1120.

HRMS (ES^+) calc. for $C_{11}H_{17}Br_2NO_2Na$ $[M+Na]^+$ 375.9518, found 375.9508.

m.p. 44 °C

(5-Bromo-3-tosyl-3-azabicyclo[3.1.0]hexan-1-yl)methanol (81)



To a stirred solution of **76** (3.10 g, 13.2 mmol, 1.0 eq.) in dry THF (125 mL) at 0 °C was added Red-Al (10.8 mL, 60%, 33.1 mmol, 2.5 eq.) and the mixture was stirred at rt for 5 h. Rochelle's salt (70 mL) was added slowly at 0 °C (note: vigorous quenching) and the mixture was stirred for 10 min at rt until it became clear. The mixture was diluted with water (50 mL), then Na_2CO_3 (2.10 g, 19.8 mmol, 1.5 eq.) was added. The mixture was cooled to 0 °C and TsCl (2.52 g, 13.2 mmol, 1.0 eq.) was added. The mixture was stirred at 0 °C for another 5 min, then at rt for 1 h. The THF was removed under reduced pressure and the mixture was extracted with EtOAc (3 x 120 mL). The combined organic extractes were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (6:4 pentane / EtOAc) gave the product (1.82 g, 5.26 mmol, 40%) as a white solid.

R_f 0.24 (6:4 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.3 Hz, Ts), 7.35 (2H, d, *J* = 8.0 Hz, Ts), 3.95 (1H, d, *J* = 9.2 Hz, H2/3), 3.90 (1H, dd, *J* = 12.4, 7.6 Hz, H6), 3.66 (1H, dd, *J* = 12.4, 4.6 Hz, H6), 3.56 (1H, d, *J* = 9.4 Hz, H2/3), 3.32 (1H, d, *J* = 9.4 Hz, H2/3), 3.26 (1H, dd, *J* = 9.2, 1.2 Hz, H2/3), 2.45 (3H, s, Ts), 1.52 (1H, dd, *J* = 7.8, 4.9 Hz, H7), 1.38 (1H, d, *J* = 6.6 Hz, H5), 1.12 (1H, d, *J* = 6.5 Hz, H5).

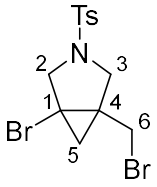
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 133.2, 130.0, 127.7, 64.0, 56.6, 49.9, 35.2, 33.7, 21.7, 21.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3535, 2924, 1346, 1167, 1030.

HRMS (ES^+) calc. for $C_{13}H_{17}BrNO_3S$ $[M+H]^+$ 346.0107, found 346.0111.

m.p. 130 °C

1-Bromo-5-(bromomethyl)-3-tosyl-3-azabicyclo[3.1.0]hexane (84)



To a stirred solution of **81** (5.80 g, 16.8 mmol, 1.0 eq.) and NBS (3.58 g, 20.1 mmol, 1.2 eq.) in dry CH_2Cl_2 (80 mL) at 0 °C was added a solution of PPh_3 (5.27 g, 20.1 mmol, 1.2 eq.) in CH_2Cl_2 (10 mL) dropwise. The mixture was stirred at rt for 1 h, then concentrated under reduced pressure. Purification by column chromatography (8:2 pentane / Et_2O) gave the product (6.32 g, 15.4 mmol, 92%) as a white solid. We have not observed any stability issues with the storage of this propellane precursor over a period of several months.

R_f 0.21 (8:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.68 (2H, d, *J* = 8.3 Hz, Ts), 7.36 (2H, d, *J* = 7.9 Hz, Ts), 3.95 (1H, d, *J* = 9.4 Hz, H2/3), 3.65 (1H, d, *J* = 9.5 Hz, H2/3), 3.52 (1H, d, *J* = 11.1 Hz, H6), 3.47 (1H, d, *J* = 11.1 Hz, H6), 3.24 (1H, d, *J* = 15.9 Hz, H2/3), 3.22 (1H, d, *J* = 16.2 Hz, H2/3), 2.45 (3H, s, Ts), 1.54 (1H, d, *J* = 6.7 Hz, H5), 1.19 (1H, d, *J* = 6.8 Hz, H5).

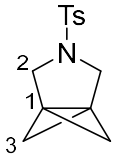
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 133.2, 130.1, 127.6, 56.5, 51.7, 38.1, 34.8, 32.8, 24.5, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2923, 1351, 1166, 1100, 1013.

HRMS (ES^+) calc. for $C_{13}H_{16}Br_2NO_2S$ $[M+H]^+$ 407.9263, found 407.9251.

m.p. 124 °C

3-(*N*-Tosyl)aza[3.1.1]propellane (85)



To a stirred solution of **84** (2.00 g, 4.89 mmol, 1.0 eq.) in dry THF (40 mL) at -78 °C was added MeLi (3.76 mL, 1.3 M in Et_2O, 4.89 mmol, 1.0 eq.). The mixture was stirred at -78 °C for 10 min then at rt for 1 h. $NaHCO_3$ (411 mg, 4.89 mmol, 1.0 eq) was added, then the mixture was cooled to 0 °C, passed through a celite pad and eluted with THF (100 mL). The mixture was partially concentrated under reduced pressure to give the product as a solution in THF (26.0 mL, 0.18 M, 4.79 mmol, 98%), which was stored in an amber glass bottle with an AcroSeal under N_2 at -20 °C. The concentration was determined by integrating the ^1H peak at 3.17 ppm relative to the THF peaks.

^{1}H NMR (500 MHz, C_6D_6) δ_H 7.62 (2H, d, *J* = 8.2 Hz, Ts), 6.99 (2H, d, *J* = 8.0 Hz, Ts), 3.17 (4H, s, H2), 2.04 (3H, s, Ts), 2.03 (2H, t, *J* = 1.7 Hz, H3), 1.31 (2H, t, *J* = 1.7 Hz, H3).

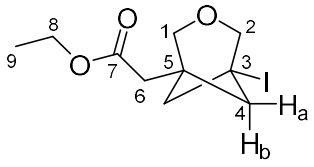
^{13}C NMR (126 MHz, C_6D_6) δ_C 143.3 (Ts), 135.0 (Ts), 129.8 (Ts), 127.9 (Ts), 53.6 (C2), 52.1 (C3), 22.4 (C1), 21.1 (Ts Me).

HRMS (ES^+) calc. for $C_{13}H_{16}NO_2S$ $[M+H]^+$ 250.0896, found 250.0900.

Caution: During the partial concentration process, bromomethane will be released.

Storage: It is recommended to store the propellane solution in the freezer (-20 °C) at <0.5 M concentration, under which conditions it is stable for a period of (at least) a year.

Ethyl 2-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)acetate (86a)



Method 1: Synthesised in accordance with *General Procedure 3* using iodomethyl propionate (43.0 mg, 0.200 mmol, 1.0 eq.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.5 eq, 0.25 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 2 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column gel (SiO_2, pentane/Et_2O 8:2) to afford the title compound **86a** (51.0 mg, 0.160 mmol, 82%) as a colourless oil.

Method 2: Synthesised in accordance with *General Procedure 2* using iodomethyl propionate (43.0 mg, 0.200 mmol, 1 eq.), oxa[3.1.1]propellane (1.2 mL, 0.300 mmol, 1.5 eq, 0.25 M in diethyl ether) and BEt_3 (20.0 µL, 1.0 M in hexane, 10 mol%). The reaction was stirred at ambient temperature for 45 min. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane / Et_2O 8:2) to afford the title compound **86a** (43.0 mg, 0.140 mmol, 69%) as a colourless oil.

$\mathbf{R_f}$ = 0.5 (8:2 pentane/Et_2O).

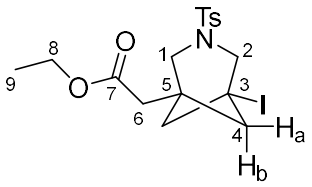
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.13-4.09 (4H, singlet from H1/H2 and quartet from H8 overlapped), 3.80 (2H, s, H1/H2), 2.60-2.58 (2H, m, $H4_b$), 2.51-2.49 (2H, m, $H4_a$), 2.36 (2H, s, H6), 1.25 (3H, t, J = 7.1 Hz, H9).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 170.2, 77.8, 72.1, 60.8, 48.7, 44.6, 41.4, 27.6, 14.4.

IR (thin film, ν_{max} / cm^{-1}): 2944, 2859, 1733, 1273, 1246, 1196, 1086.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{10}H_{16}IO_3]^+$ 311.0139, found 311.0135.

Ethyl 2-(5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetate (86b)



Method 1: Prepared according to *General Procedure 3,* using 3-(*N*-tosyl)aza[3.1.1]propellane **14** (0.630 mL, 0.20 M, 126 μmol, 1.2 eq.), ethyl 2-iodoacetate (12.4 μL, 105 μmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.7 mg, 2.6 μmol, 2.5 mol%). The mixture was stirred and irradiated for 1 h. Purification by column chromatography (SiO_2, pentane / EtOAc 8:2) gave the product (39.7 mg, 85.7 μmol, 82%) as a colourless oil.

Method 2: Prepared according to *General Procedure 2*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (1.25 mL, 0.15 M in THF, 0.288 mmol, 2.0 eq.), ethyl 2-iodoacetate (17.4 μL, 0.147 mmol, 1.0 eq.) and BEt_3 (14.7 μL, 1.0 M solution in hexanes, 14.7 μmol, 0.1 eq). The mixture was stirred for 1 h. Purification by column chromatography (SiO_2, pentane/EtOAc 8:2) gave the product (58.7 mg, 0.127 mmol, 86%) as a colourless oil.

R_f 0.29 (8:2 pentane / EtOAc).

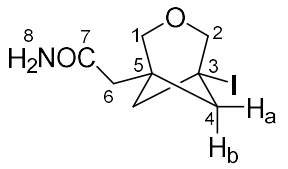
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.3 Hz, Ts), 7.33 (2H, d, *J* = 7.7 Hz, Ts), 4.09 (2H, q, *J* = 7.1 Hz, H8), 3.84 (2H, s, H1/2), 3.36 (2H, s, H1/2), 2.51-2.46 (2H, m, $H4_b$), 2.43 (3H, s, Ts), 2.40 (2H, s, H6), 2.18-2.10 (2H, m, $H4_a$), 1.22 (3H, t, *J* = 7.2 Hz, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.9, 143.9, 134.3, 130.0, 127.4, 60.9, 59.2, 52.2, 48.7, 42.0, 41.5, 22.5, 21.7, 14.3.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2943, 1731, 1345, 1160, 1094.

HRMS (ES^+) calc. for $C_{17}H_{23}INO_4S$ $[M+H]^+$ 464.0387, found 464.0395.

2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)acetamide (86c)



Synthesised in accordance with *General Procedure 3* using 2-iodoacetamide (37.0 mg, 0.200 mmol, 1 eq.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.2 eq, 0.25 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 3 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane/EtOAc 8:2) to afford the product (35.0 mg, 0.120 mmol, 62%) as a white solid.

R_f = 0.2 (8:2 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.49 (1H, s, H8), 5.34 (1H, s, H8), 4.14 (2H, s, H1/H2), 3.85 (2H, s, H1/H2), 2.62-2.61 (2H, m, $H4_b$), 2.55-2.52 (2H, m, $H4_a$), 2.28 (2H, s, H6).

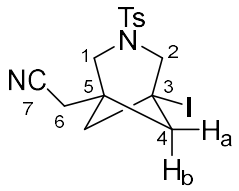
^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ_C 171.4, 77.8, 72.2, 48.7, 44.9, 42.6, 27.7.

IR (thin film, ν_{max} / cm^{-1}): 3381, 2945, 2861, 1732, 1666, 1419, 1242, 1198, 1024.

HRMS (ESI+) $[M+Na]^+$ calculated for $[C_8H_{12}INO_2Na]^+$ 303.9805, found 303.9805.

m.p. 113-115 ^oC

2-(5-Iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetonitrile (86d)



Synthesised in accordance with *General Procedure 2*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (2.13 mL, 0.15 M in THF, 0.320 mmol, 2.0 eq.), 2-iodoacetonitrile (11.6 µL, 0.160 mmol, 1.0 eq.) and BEt_3 (16.0 µL, 16.0 µmol, 10 mol%). The mixture was stirred for 1 h. Purification by column chromatography (SiO_2, pentane/EtOAc 7:3) gave the product (23.3 mg, 56.0 µmol, 35%) as a white solid.

R_f 0.27 (7:3 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.71 (2H, d, J = 8.3 Hz, Ts), 7.36 (2H, d, J = 8.1 Hz, Ts), 3.86 (2H, s, H1/2), 3.36 (2H, s, H1/2), 2.59-2.50 (2H, m, $H4_b$), 2.46 (2H, s, H6), 2.45 (3H, s, Ts), 2.18-2.09 (2H, m, $H4_a$).

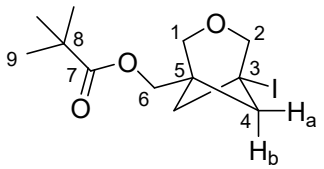
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 133.9, 130.2, 127.4, 115.8, 58.9,51.8, 47.5, 40.8, 25.5, 21.7, 19.6.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2920, 1343, 1159, 1011.

HRMS (ES^+) calc. for $C_{15}H_{18}IN_2O_2S$ $[M+H]^+$ 417.0128, found 417.0126.

m.p. 126 °C

(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)methyl pivalate (86e)



Method 1: Synthesised in accordance with *General Procedure 3* using iodomethyl pivalate (48.0 mg, 0.200 mmol, 1 eq.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.2 eq, 0.25 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 5 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product (51.0 mg, 0.150 mmol, 75%) as a colourless oil.

Method 2: Synthesised in accordance with *General Procedure 2* using iodomethyl pivalate (48.0 mg, 0.200 mmol, 1 eq.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.5 eq, 0.25 M in diethyl ether) and BEt_3 (20 μL, 1.0 M in hexane, 10 mol%). The reaction was stirred at ambient temperature for 8 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product (39.0 mg, 0.120 mmol, 58%) as a colourless oil.

R_f = 0.3 (8:2 pentane / Et_2O)

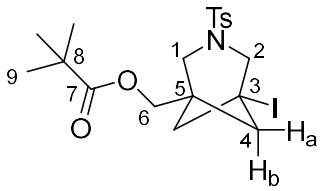
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.16 (2H, s, H1/2/6), 3.92 (2H, s, H1/2/6), 3.81 (2H, s, H1/2/6), 2.59-2.55 (2H, m, H4$_b$), 2.41-2.37 (2H, m, H4$_a$), 1.20 (9H, s, H9).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ_C 178.2, 78.2, 70.4, 66.1, 47.0, 46.2, 39.1, 27.4, 27.3.

IR (thin film, ν_{max} / cm^{-1}): 2986, 2863, 1732, 1600, 1503, 1479, 1363, 1282, 1155, 1085.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{12}H_{20}IO_3]^+$ 339.0452, found 339.0459.

(5-Iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)methyl pivalate (86f)



Method 1: Synthesised in accordance with *General Procedure 3*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (1.54 mL, 0.15 M in THF, 0.354 mmol, 2.0 eq.), iodomethyl pivalate (28.2 µL, 0.182 mmol, 1.0 eq) and *fac*-Ir(ppy)$_3$ (3.0 mg, 4.5 µmol, 2.5 mol%). The mixture was stirred and irradiated with blue LED (450-455 nm) for 4 h. Purification by column chromatography (SiO_2, pentane/EtOAc 9:1) gave the product (18.3 mg, 37.2 µmol, 21%) as a white solid.

Method 2: Prepared according to *General Procedure 2,* using 3-(*N*-tosyl)aza[3.1.1]propellane **14** (0.900 mL, 0.20 M, 180 µmol, 1.2 eq.), iodomethylpivalate (23.3 µL, 150 µmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (2.5 mg, 3.8 µmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 9:1) gave the product (13.1 mg, 26.6 µmol, 18%) as a white solid.

R_f 0.16 (9:1 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.71 (2H, d, *J* = 8.3 Hz, Ts), 7.34 (2H, d, *J* = 8.1 Hz, Ts), 3.93 (2H, s, H1/2), 3.89 (2H, s, H1/2), 3.33 (2H, s, H6), 2.50-2.45 (2H, m, $H4_b$), 2.45 (3H, s, Ts), 2.03-1.97 (2H, m, $H4_a$), 1.18 (9H, s, H9).

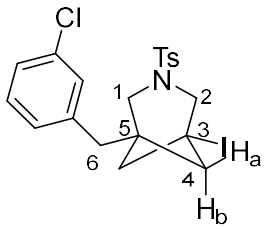
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 178.0, 144.0, 134.3, 130.0, 127.4, 66.3, 59.6, 50.3, 46.2, 44.0, 39.1, 27.3, 22.1, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2974, 1733, 1344, 1283, 1163.

HRMS (ES$^+$) calc. for $C_{19}H_{27}INO_4S$ $[M+H]^+$ 492.0700, found 492.0686.

m.p. 137 °C

1-(3-Chlorobenzyl)-5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptane (86g)



Synthesised in accordance with *General Procedure 3*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (1.60 mL, 0.15 M in THF, 0.240 mmol, 1.2 eq.), 1-chloro-3-(iodomethyl)benzene (50.5 mg, 0.200 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (3.3 mg, 5.0 μmol, 2.5 mol%). The mixture was stirred and irradiated with 450-455 nm blue light in a photobox with fan cooling for 4 h. Purification by column chromatography (SiO_2, pentane/Et_2O 8:2) gave the product (25.2 mg, 50.2 μmol, 25%) as a yellow solid.

R_f 0.17 (8:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.60 (2H, d, *J* = 8.3 Hz, Ts), 7.29 (2H, d, *J* = 8.0 Hz, Ts), 7.25-7.21 (2H, m, Ar H), 6.97 (1H, s, Ar H), 6.93-6.84 (1H, m, Ar H), 3.85 (2H, s, H1/2/6), 3.21 (2H, s, H1/2/6), 2.66 (2H, s, H1/2/6), 2.43 (3H, s, Ts), 2.42-2.37 (2H, m, $H4_b$), 2.00-1.91 (2H, m, $H4_b$).

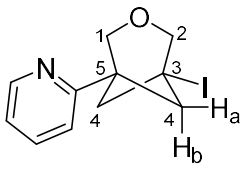
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.8, 138.4, 134.6, 134.3, 130.0, 130.0, 129.3, 127.7, 127.3, 127.2, 59.5, 52.2, 48.3, 44.7, 43.3, 23.2, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2943, 1597, 1342, 1160, 1094.

HRMS (ES^+) calc. for $C_{20}H_{22}ClINO_2S$ $[M+H]^+$ 502.0099, found 502.0087.

m.p. 156 °C

2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)pyridine (86h)



Synthesised in accordance with *General Procedure 3* using 2-iodopyridine (41.0 mg, 0.200 mmol, 1.0 eq.), oxa[3.1.1]propellane (1.30 mL, 0.240 mmol, 1.5 eq, 0.23 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 3 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product (39.0 mg, 0.130 mmol, 65%) as a yellow oil.

R_f = 0.3 (6:4 pentane / Et_2O).

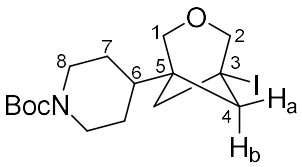
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.54 (1H, dd, *J* = 4.9, 1.9 Hz, ArH), 7.66 (1H, td, *J* = 7.7, 1.8 Hz, ArH), 7.17 (1H, ddd, *J* = 7.5, 4.9, 1.2 Hz, ArH), 7.07 (1H, dt, *J* = 7.9, 1.1 Hz, ArH), 4.26 (2H, s, H1/H2), 4.06 (2H, s, H1/H2), 3.01-2.97 (2H, m, $H4_b$), 2.84-2.80 (2H, m, $H4_a$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 161.0, 149.5, 136.9, 122.1, 120.0, 77.9, 72.8, 52.4, 48.3, 27.3.

IR (thin film, ν_{max} / cm^{-1}): 2946, 2858, 1589, 1471, 1423, 1216, 1040.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{11}H_{13}INO]^+$ 302.0036, found 302.0039.

***tert*-Butyl 4-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)piperidine-1-carboxylate (86i)**



Synthesised in accordance with *General Procedure 3* using *tert*-butyl 4-iodopiperidine-1-carboxylate (62.0 mg, 0.200 mmol, 1.0 eq.), oxa[3.1.1]propellane (1.40 mL, 0.300 mmol, 1.5 eq, 0.22 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 4 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product (52.0 mg, 0.130 mmol, 64%) as a crystalline solid.

R_f = 0.45 (8:2 pentane/ EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.15 (2H, m, H8), 4.12 (2H, s, H1/H2), 3.75 (2H, s, H1/H2), 2.59-2.54 (2H, m, H8, 2.48-2.44 (2H, m, H4$_b$), 2.38-2.35 (2H, m, H4$_a$), 1.48-1.36 (3H, m, H6/7), 1.44 (9H, s, Boc), 1.11 (1H, dd, *J* = 12.6, 4.4 Hz, H7), 1.06 (1H, dd, *J* = 12.5, 4.4 Hz, H7).

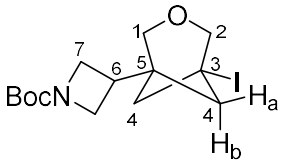
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 154.8, 79.7, 78.3, 70.9, 50.3, 46.9, 42.7, 28.8, 28.6, 26.9.

IR (thin film, ν_{max} / cm^{-1}): 2936, 2857, 1688, 1426, 1367, 1242, 1038.

HRMS (ESI+) $[M+Na]^+$ calculated for $[C_{16}H_{26}INO_3Na]^+$ 430.0850, found 430.0862.

m.p. 72-75 °C

***tert*-Butyl 3-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)azetidine-1-carboxylate (86j)**



Synthesised in accordance with *General Procedure 3* using *tert*-butyl 3-iodoazetidine-1-carboxylate (57.0 mg, 0.200 mmol, 1.0 eq.), oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 1.5 eq, 0.25 M in Et_2O) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 4 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product (49.0 mg, 0.130 mmol, 65%) as a light yellow oil.

R_f = 0.3 (8:2 pentane / Et_2O).

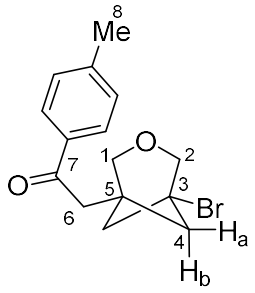
^{1}H NMR (600 MHz, $CDCl_3$) δ_H 4.16 (2H, s, H1/H2), 3.87 (2H, t, *J* = 8.2 Hz, H7), 3.68-3.65 (4H, m, H1/H2+H7), 2.58-2.55 (2H, m, $H4_b$), 2.38-2.35 (1H, m, H6), 2.35-2.31 (2H, m, $H4_a$), 1.43 (9H, s, Boc).

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 156.3, 79.9, 78.3, 71.1, 50.0, 48.3, 44.4, 31.4, 28.5, 27.4.

IR (thin film, ν_{max} / cm^{-1}): 2974, 2882, 1698, 1478, 1404, 1301, 1252, 1084.

HRMS (ESI+) $[M+Na]^+$ calculated for $[C_{14}H_{22}INO_3Na]^+$ 402.0537, found 402.0538.

2-(5-Bromo-3-oxabicyclo[3.1.1]heptan-1-yl)-1-(p-tolyl)ethan-1-one (86k)



Synthesised in accordance with *General Procedure 3* using 2-bromo-1-(*p*-tolyl)ethan-1-one (43.0 mg, 0.200 mmol, 1.0 eq.), oxa[3.1.1]propellane (1.30 mL, 0.300 mmol, 1.5 eq, 0.23 M in diethyl ether) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 5 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography (SiO_2, pentane/Et_2O 9:1) to give the product (32.0 mg, 0.100 mmol, 52%) as a crystalline solid.

R_f = 0.5 (9:1 pentane / Et_2O).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.78 (2H, d, *J* = 8.3 Hz, ArH), 7.26 (2H, d, *J* = 7.9 Hz, ArH), 4.05 (2H, s, H1/H2), 3.82 (2H, s, H1/H2), 3.06 (2H, s, H6), 2.54-2.50 (2H, m, $H4_a$), 2.45-2.42 (2H, m, $H4_b$), 2.41 (3H, s, H8).

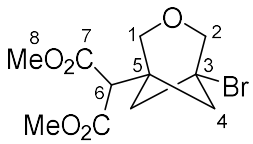
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 196.9, 144.5, 134.6, 129.6, 128.3, 75.5, 72.2, 52.2, 47.5, 44.6, 41.4, 21.8.

IR (thin film, ν_{max} / cm^{-1}): 2949, 2859, 1681, 1606, 1572, 1406, 1180, 1036.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{15}H_{18}BrO_2]^+$ 309.0485, found 309.0482.

m.p. 93-95 ^oC

Dimethyl 2-(5-bromo-3-oxabicyclo[3.1.1]heptan-1-yl)malonate (86l)



Synthesised in accordance with *General Procedure 3* using dimethyl bromomalonate (42.0 mg, 0.200 mmol, 1.0 eq.), oxa[3.1.1]propellane (1.30 mL, 0.300 mmol, 1.5 eq, 0.24 M in diethyl ether) and *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%). The mixture was irradiated with 456 nm light at ambient temperature for 4 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified via column chromatography chromatography (SiO_2, pentane/Et_2O 8:2) to give the product (33.0 mg, 0.110 mmol, 54%) as a colourless oil.

R_f = 0.5 (8:2 pentane / Et_2O)

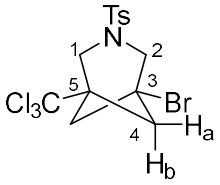
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.01 (2H, s, H1/H2), 3.85 (2H, s, H1/H2), 3.73 (6H, s, H8), 3.45 (1H, s, H6), 2.53-2.47 (4H, m, H4).

^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ_C 167.2, 75.4, 70.2, 56.9, 52.7, 50.9, 46.2, 42.4.

IR (thin film, ν_{max} / cm^{-1}): 2955, 2867, 1740, 1437, 1332, 1239, 1087.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{11}H_{16}BrO_5]^+$ 307.0176, found 307.0178.

1-Bromo-3-tosyl-5-(trichloromethyl)-3-azabicyclo[3.1.1]heptane (86m)



To a stirred solution of 3-(*N*-tosyl)-aza[3.1.1]propellane (1.33 mL, 0.15 M in THF, 0.200 mmol, 1.0 eq.) at -78 °C was added CCl_3Br (59.2 µL, 0.600 mmol, 3.0 eq.). The mixture was stirred at -78 °C for 15 min, then at rt for 1 h. The mixture was then concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O 9:1) gave the product (37.7 mg, 84.2 µmol, 42%) as a white solid.

R_f 0.31 (9:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74 (2H, d, *J* = 8.1 Hz, Ts), 7.37 (2H, d, *J* = 8.0 Hz, Ts), 3.77 (2H, s, H1/2), 3.75 (2H, s, H1/2), 2.92-2.82 (2H, m, $H4_b$), 2.46 (3H, s, Ts), 2.14-2.04 (2H, m, $H4_a$).

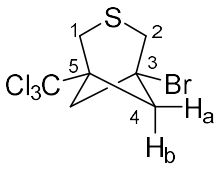
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.3, 134.1, 130.2, 127.5, 101.6, 56.4, 55.5, 49.8, 44.6, 44.3, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2872, 1344, 1162, 1035, 1014.

HRMS (ES^+) calc. for $C_{14}H_{16}BrCl_3NO_2S$ $[M+H]^+$ 445.9145, found 445.9130.

m.p. 136 °C

1-Bromo-5-(trichloromethyl)-3-thiabicyclo[3.1.1]heptane (86n)



To a solution of 3-thia[3.1.1]propellane (1.00 mL, 0.12 M, 0.12 mmol, 1.0 eq.) in Et_2O at -78 °C was added CCl_3Br (59.2 µL, 0.60 mmol, 5.0 eq.), then BEt_3 (12.0 µL, 1.0 M solution in hexanes, 12.0 µmol, 10 mol%). The mixture was stirred at -78 °C for 15 min then rt for 1 h. The mixture was concentrated under reduced pressure, then purification by column chromatography (SiO_2, pentane 100%) gave the product (11.9 mg, 38.3 µmol, 32%) as a white solid.

R_f 0.29 (100% pentane).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.43 (2H, s, H1/2), 3.27 (2H, s, H1/2), 3.12-3.03 (2H, m, $H4_b$), 2.69-2.60 (2H, m, $H4_a$).

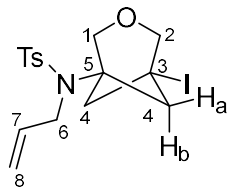
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 104.2, 57.1, 49.3, 45.1, 40.3, 31.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2934, 1272, 1137, 775.

HRMS (ES^+) Not found

m.p. 77 °C

_N_-allyl-_N_-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)-4-methylbenzene sulfonamide (86o)



Prepared according to the literature procedure[157] and in accordance with *General Procedure 3*, using 2-(iodomethyl)-1-tosylaziridine (67.0 mg, 0.200 mmol, 1.0 eq.), *fac*-Ir(ppy)$_3$ (3.0 mg, 2.5 mol%), *t*-BuCN (1.5 mL) and oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 0.25 M in Et_2O, 1.5 eq.). The mixture was irradiated with 456 nm light for 4 h. The crude reaction mixture was purified via column chromatography (SiO_2, pentane/Et_2O 8:2) to give the product (46.0 mg 0.110 mmol, 53%) as a colourless oil.

R_f = 0.3 (8:2 pentane / Et_2O).

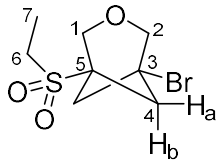
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.69 (2H, d, *J* = 8.3 Hz, ArH), 7.31 (2H, d, *J* = 7.8 Hz, ArH), 5.75 (1H, ddt, *J* = 17.2, 10.1, 6.3 Hz, H7), 5.16 (1H, dd, *J* = 11.0, 1.3 Hz, H8), 5.13 (1H, dd, *J* = 10.5, 1.2 Hz, H8), 3.98 (2H, s, H1/H2), 3.93 (2H, s, H1/H2), 3.77 (2H, dt, *J* = 6.3, 1.4 Hz, H6), 2.83-2.80 (2H, m, $H4_b$), 2.82-2.75 (2H, m, $H4_a$), 2.44 (3H, s, H9).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 143.8, 138.7, 135.3, 130.0, 127.3, 118.6, 76.8, 71.7, 62.7, 49.8, 49.3, 22.1, 21.7.

IR (thin film, ν_{max} / cm^{-1}): 2954, 2862, 1437, 1335, 1238, 1087.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{16}H_{21}INO_3S]^+$ 434.0281, found 434.0281.

1-Bromo-5-(ethylsulfonyl)-3-oxabicyclo[3.1.1]heptane (86p)



The reaction was carried out according to the literature procedure[158]. To an oven-dried vial, ethanesulfonyl bromide (35.0 mg, 0.200 mmol, 1.0 eq.) was added. The vial was sealed with a PTFE cap, and Et_2O (1.50 mL) was added. The reaction mixture was degassed for 10 min, after which oxa[3.1.1]propellane (1.20 mL, 0.300 mmol, 0.24 M in Et_2O, 1.5 eq.) was added, and degassing was continued with argon for an additional 5 min. The reaction mixture was stirred at ambient temperature overnight. The solvent was then removed under reduced pressure, and the crude reaction mixture was treated with Et_2O (5.0 mL) and cooled in an ice bath for 30 min. The resulting cloudy solution was filtered, and the solvent was removed under reduced pressure, to give the product (35.0 mg 0.120 mmol, 62%) as a thick, colourless oil.

Note: The product is not stable on silica gel.

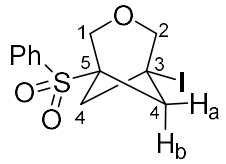
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.09 (2H, s, H1/H2), 4.06 (2H, s, H1/H2), 3.01-3.07 (2H, m, $H4_b$), 2.86 (2H, q, J = 7.5 Hz, H6), 2.53-2.49 (2H, m, $H4_a$), 1.39 (3H, t, J = 7.5 Hz, H7).

^{13}C NMR (151MHz, $CDCl_3$) δ_C 75.0, 67.0, 60.6, 48.4, 44.0, 42.8, 5.7.

IR (thin film, ν_{max} / cm^{-1}): 2953, 2866, 1599, 1436, 1312, 1237, 1040.

HRMS not found.

1-Iodo-5-(phenylsulfonyl)-3-oxabicyclo[3.1.1]heptane (86q)



The reaction was carried out according to the literature procedure[158]. A solution of sodium benzenesulfinate salt (0.50 mL, 0.500 mmol, 1.0 M in H_2O, 2.5 eq.) was added dropwise to a suspension of 1,3-diiodo-5,5-dimethylhydantoin (76.0 mg, 0.200 mmol, 1.0 eq.) in CH_2Cl_2 (1.0 mL) at -5 °C (ice/NaCl). The mixture was stirred vigorously for 15 minutes, then a solution of oxa[3.1.1]propellane (0.8 mL, 0.20 mmol, 0.25 M in Et_2O, 1.0 eq.) was added. The slurry was stirred at -5 °C for 10 minutes and then sonicated for a few seconds at ambient temperature to ensure complete mixing. The reaction was quenched at ambient temperature by addition of saturated aqueous $Na_2S_2O_3$ (0.50 mL). The biphasic mixture was poured into H_2O (2 mL) and extracted with CH_2Cl_2 (3 × 2 mL). The combined organic phases were concentrated in vacuo. The crude reaction mixture was treated with Et_2O (5 mL) and cooled in an ice bath for 30 minutes. The resulting cloudy solution was filtered, and the solvent was removed under reduced pressure, yielding the product (50.0 mg 0.140 mmol, 69%) as a thick colourless liquid.

Note: The product is not stable on silica gel.

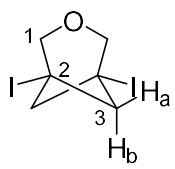
^{1}H NMR (600 MHz, C_6D_6) δ_H 7.46 (2H, dd, *J* = 8.3, 1.3 Hz, ArH), 6.94-6.86 (1H, m, ArH), 6.82 (2H, dd, *J* = 8.4, 7.2 Hz, ArH), 3.70 (2H, s, H1/H2), 3.68 (2H, s, H1/H2), 3.08-3.05 (2H, m, $H4_b$), 1.94-1.91 (2H, m $H4_a$).

^{13}C NMR (151 MHz, C_6D_6) δ_C 136.6, 133.7, 129.2, 129.1, 77.1, 66.7, 64.9, 44.3, 23.0.

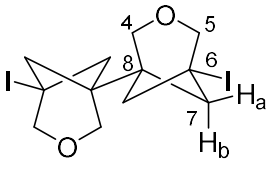
IR (thin film, ν_{max} / cm^{-1}): 2925, 2872, 1690, 1583, 1450, 1300, 1159, 1081.

HRMS (ESI+) $[M+H]^+$calculated for $[C_{12}H_{14}IO_3S]^+$ 364.9703, found 364.9685.

1,5-Diiodo-3-oxabicyclo[3.1.1]heptane (86r) and 5,5'-Diiodo-3,3'-dioxa-1,1'-bi(bicyclo[3.1.1]heptane) (86r')



86r



86r'

To a stirred solution of 3-oxa-[3.1.1]propellane (0.60 mL, 0.14 M in THF, 84.0 μmol, 1.0 eq.) was added iodine (21.3 mg, 84.0 μmol, 1.0 eq.) and the mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure, then purification by column chromatography (SiO_2, pentane/Et_2O 19:1) gave the inseparable products **86r** and **86r'** (17.3 mg) as a yellow solid in a 1.0:0.15 ratio of **86r**:**86r'** as determined from the ^1H NMR spectrum, with 64% overall yield.

R_f 0.42 (19:1 pentane / Et_2O).

^1H NMR (400 MHz, $CDCl_3$) δ_H 4.12 (4H, s, H1), 4.05 (4H, s, H4/5), 4.03 (4H, s, H4/5), 3.25-3.15 (2H, m, $H3_b$), 3.14-3.08 (4H, m, $H7_b$), 3.04-2.95 (2H, m, $H3_a$), 2.94-2.86 (4H, m, $H7_a$)

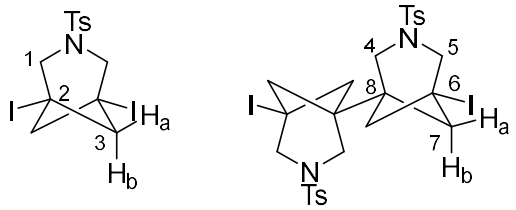
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 76.5, 55.7, 24.6.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2862, 1456, 1244, 1072, 976.

HRMS (ES^+) Not found

m.p. 43 °C

1,5-Diiodo-3-tosyl-3-azabicyclo[3.1.1]heptane (86s) and 5,5'-Diiodo-3,3'-ditosyl-3,3'-diaza-1,1'-bi(bicyclo[3.1.1]heptane) (86s')



86s **86s'**

To a stirred solution of 3-(*N*-tosyl)-aza[3.1.1]propellane (1.32 mL, 0.15 M in THF, 0.198 mmol, 1.1 eq.) was added iodine (45.7 mg, 0.180 mmol, 1.0 eq.) and the mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure, then purification by column chromatography (SiO_2, pentane/EtOAc 19:1) gave the inseparable products **86s** and **86s'** (58.1 mg) as a yellow solid in a 1.4:1.0 ratio of **86s:86s'** as determined from the ^{1}H NMR spectrum, with 75% overall yield.

R_f 0.20 (19:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (6H, d, *J* = 8.3 Hz, Ts), 7.36 (6H, d, *J* = 8.1 Hz, Ts), 3.80 (4H, s, H1), 3.76 (4H, s, H4/5), 3.69 (4H, s, H4/5), 3.18-3.05 (2H, m, $H3_b$), 3.04-2.96 (4H, m, $H7_b$), 2.70-2.59 (2H, m, $H3_a$), 2.58-2.50 (4H, m, $H7_a$), 2.45 (9H, s, Ts).

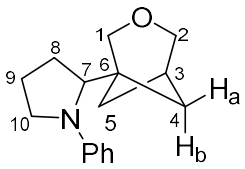
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 144.3, 144.3, 134.1, 130.2, 127.4, 127.4, 58.2, 58.0, 55.8, 55.6, 54.3, 47.2, 21.7, 19.4, 16.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2869, 1344, 1160, 1012.

HRMS (ES^+) calc. for $C_{13}H_{15}I_2NO_2SNa$ $[M(\mathbf{18s})+Na]^+$ 525.8805, found 525.8807.

m.p. 167 °C

2-(3-Oxabicyclo[3.1.1]heptan-1-yl)-1-phenylpyrrolidine (86t)



The reaction was carried out according to the literature procedure[33]. To an oven-dried vial containing 1-(4-bromophenyl)pyrrolidine (450 mg, 0.200 mmol, 10.0 eq.) and 4CzIPN (4.0 mg, 2.5 mol%) was added anhydrous DMA (0.50 mL) and H_2O (36.0 µL, 2.0 mmol, 10.0 eq.). The solution was deggased with argon for 15 minutes before adding oxa[3.1.1]propellane (0.80 mL, 0.300 mmol, 1.0 eq, 0.25 M in Et_2O). The vial was sealed and irradiated with a 440 nm Kessil PR160L LED lamp. After stirring at ambient temperature for 18 h, the solution was diluted with EtOAc (5.0 mL) and washed with 5% LiCl solution (10.0 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The crude reaction mixture was purified via column chromatography using silica gel to afford the product (44.0 mg, 0.140 mmol, 68%) as a colourless crystalline solid.

m.p. 88-90 °C

R_f = 0.5 (19:1 pentane / Et_2O).

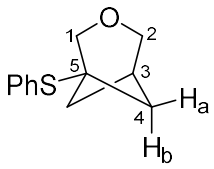
^{1}H NMR (600 MHz, $CDCl_3$) δ_H 7.22-7.20 (2H, m, ArH), 6.69 (1H, t, *J* = 7.3 Hz, ArH), 6.58 (2H, d, *J* = 8.1 Hz, ArH), 3.91–3.86 (4H, m, H1/2), 3.61 (1H, td, *J* = 8.7, 2.5 Hz, H10), 3.45 (1H, dd, *J* = 7.0, 3.5 Hz, H7), 3.18 (1H, td, *J* = 9.3, 7.4 Hz, H10), 2.18 (1H, tt, *J* = 6.5, 3.3 Hz, H3), 2.02–1.92 (4H, m, $H4_b/5_b/9$), 1.82–1.78 (2H, m, H8), 1.62 (1H, t, *J* = 8.2 Hz, $H4_a/5_a$), 1.56 (1H, t, J = 8.4 Hz, $H4_a/5_a$).

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 149.4, 129.0, 116.1, 112.8, 73.8, 70.9, 61.2, 50.3, 48.7, 34.5, 32.5, 31.4, 28.0, 24.4.

IR (thin film, ν_{max} / cm^{-1}): 2954, 2853, 1600, 1503, 1341, 1238, 1055.

HRMS (ESI-) $[M-H]^-$ calculated for $[C_{16}H_{20}NO]^-$ 242.1550, found 242.1539.

1-(Phenylthio)-3-oxabicyclo[3.1.1]heptane (86u)



Synthesised in accordance with *General Procedure 1* using thiophenol (24.0 mg, 0.220 mmol, 1.1 eq.) and oxa[3.1.1]propellane (0.80 mL, 0.200 mmol, 1.0 eq, 0.24 M in diethyl ether), stirred at ambient temperature for 1 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography chromatography (SiO_2, pentane/Et_2O 9:1) to afford the product (38.0 mg, 0.180 mmol, 91%) as a colourless solid.

R_f = 0.2 (99:1 pentane / Et_2O).

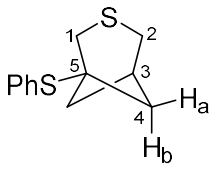
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.42–7.40 (2H, m, ArH), 7.32 –7.30 (3H, m, ArH), 3.89 (2H, s, H1), 3.85 (2H, d, *J* = 2.2 Hz, H2), 2.46 (1H, tt, *J* = 6.8, 2.2 Hz, H3), 2.22–2.19 (2H, m, $H4_b$), 1.93–1.89 (2H, m, $H4_a$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 134.9, 131.7, 129.0, 128.3, 74.6, 69.9, 50.4, 38.3, 32.9.

IR (thin film, ν_{max} / cm^{-1}): 2951, 2858, 1474, 1233, 1124, 1024.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{12}H_{15}OS]^+$ 207.0838, found 207.0835.

1-(Phenylthio)-3-thiabicyclo[3.1.1]heptane (86v)



A solution of 3-thia[3.1.1]propellane (1.67 mL, 0.12 M, 0.200 mmol, 1.0 eq.) in Et_2O was added dropwise to stirred neat PhSH (0.205 mL, 2.00 mmol, 10 eq.). The mixture was stirred at rt for 30 min then diluted with Et_2O (2 mL), washed with 1 M aq NaOH (3 mL x 3), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/Et_2O 98:2) gave the product (18.5 mg, 83.2 μmol, 42%) as a colourless oil.

R_f 0.24 (98:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.44-7.36 (2H, m, Ar H), 7.35-7.28 (3H, m, Ar H), 3.16 (2H, s, H1), 3.03 (2H, d, J = 3.3 Hz, H2), 2.77-2.70 (1H, m, H3), 2.40-2.29 (2H, m, $H4_b$), 2.18-2.08 (2H, m, $H4_a$).

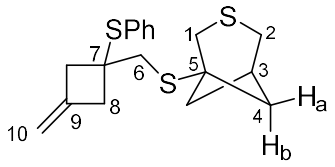
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 134.8, 132.3, 129.0, 128.3, 50.0, 38.5, 37.9, 32.8, 31.0.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2933, 1583, 1438, 1202, 1097.

HRMS (ES^+) calc. for $C_{12}H_{15}S_2$ $[M+H]^+$ 223.0610, found 223.0614.

A side product was observed in this reaction, where upon reaction with PhSH, the resulting BCHep radical fragmented, forming a new sulfur-based radical, which attacked a second molecule of propellane. The proportion of this side product in the reaction mixture decreased with increasing amounts of PhSH added. When 1 eq. PhSH was used, the ratio of **86v:86v'** was 1:0.5. When 10 eq. PhSH was used, the ratio was 1:0.1.

Fragmentation product, 1-(((3-methylene-1-(phenylthio)cyclobutyl)methyl)thio)-3-thiabicyclo[3.1.1]heptane (86v')



R_f 0.19 (98:2 pentane / Et_2O).

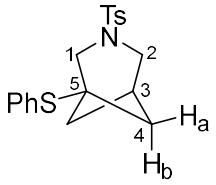
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.55-7.49 (2H, m, Ar H), 7.37-7.30 (3H, m, Ar H), 4.90 (2H, p, *J* = 2.3 Hz, H10), 3.17 (2H, s, H1), 3.04 (2H, d, *J* = 3.3 Hz, H2), 2.95-2.91 (2H, m, H8), 2.84-2.79 (2H, m, H8), 2.82 (2H, s, H6), 2.75 (1H, tt, *J* = 7.3, 3.4 Hz, H3), 2.27-2.19 (2H, m, $H4_b$), 2.12-2.05 (2H, m, $H4_a$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 141.9, 135.1, 132.7, 129.1, 128.7, 108.8, 47.8, 47.3, 44.6, 38.5, 38.4, 38.0, 32.8, 30.6, 29.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3073, 2935, 1678, 1475, 1438, 1260.

HRMS (ES^+) calc. for $C_{18}H_{22}S_3Na$ $[M+Na]^+$ 357.0776, found 357.0768.

1-(Phenylthio)-3-tosyl-3-azabicyclo[3.1.1]heptane (86w)



Synthesised in accordance with *General Procedure 1*, using 3-(*N*-tosyl)-aza[.3.1.1]propellane (1.33 mL, 0.15 M in THF, 0.200 mmol, 1.0 eq.) and PhSH (20.5 µL 0.200 mmol, 1.0 eq.). Purification by column chromatography (SiO_2, pentane/Et_2O 7:3) gave the product (35 mg, 97 µmol, 48%) as a white solid.

R_f 0.23 (7:3 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.61 (2H, d, *J* = 8.3 Hz, Ar H), 7.42–7.24 (7H, m, Ar H), 3.53 (2H, s, H1), 3.42 (2H, d, *J* = 2.6 Hz, H2), 2.49 (1H, tt, *J* = 6.5, 2.7 Hz, H3), 2.43 (3H, s, Ts), 2.16–2.05 (2H, m, $H4_b$), 1.50–1.40 (2H, m, $H4_a$).

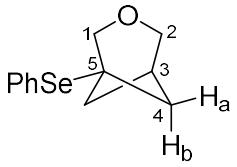
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 143.4, 135.1, 134.7, 131.2, 129.8, 129.1, 128.7, 127.3, 54.8, 49.6, 48.5, 38.0, 29.7, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2943, 1340, 1164, 1123, 1012.

HRMS (ES^+) calc. for $C_{19}H_{22}NO_2S_2$ $[M+H]^+$ 360.1087, found 360.1089.

m.p. 99 °C

1-(Phenylselenyl)-3-oxabicyclo[3.1.1]heptane (86x)



Synthesised in accordance with *General Procedure 1* using benzeneselenol (35.0 mg, 0.220 mmol, 1.1 eq.) and oxa[3.1.1]propellane (0.80 mL, 0.200 mmol, 1.0 eq, 0.24 M in Et_2O), stirred at ambient temperature for 1 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 9:1) to afford the product (47.0 mg, 0.190 mmol, 93%) as a colorless solid.

R_f = 0.2 (99:1 pentane / Et_2O)

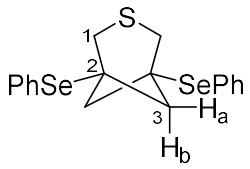
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.54–7.53 (2H, m, ArH), 7.35–7.27 (3H, m, ArH), 3.99 (2H, s, H1), 3.88 (2H, d, *J* = 2.1 Hz, H2), 2.52 (1H, tt, *J* = 6.8, 2.2 Hz, H3), 2.33–2.27 (2H, m, $H4_b$), 1.98–1.94 (2H, m, $H4_a$).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 136.6, 129.1, 128.4, 126.9, 75.5, 69.9, 46.4, 39.1, 34.7.

IR (thin film, ν_{max} / cm^{-1}): 2947, 2855, 1578, 1473, 1435, 1232, 1122, 1038.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{12}H_{15}OSe]^+$ 255.0283, found 255.0274.

1,5-Bis(phenylselanyl)-3-thiabicyclo[3.1.1]heptane (86y)



To a solution of 3-thia[3.1.1]propellane (1.15 mL, 0.13 M, 0.150 mmol, 1.0 eq.) in Et_2O was added diphenyl diselenide (46.8 mg, 0.150 mmol, 1.0 eq.) and the mixture was stirred for 3 h at rt. The mixture was concentrated under reduced pressure, and the residue purified by column chromatography (SiO_2, pentane/Et_2O 98:2) to give the product (43.4 mg, 0.102 mmol, 68% approx.) as a pale yellow oil, which contained a small unidentified impurity that co-eluted with the product. Trituration from pentane removed this impurity with some loss of yield to give the product (21.8 mg, 51.4 μmol, 34%) as a white crystalline solid.

R_f 0.12 (98:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.49 (4H, d, *J* = 6.6 Hz, Ar H), 7.39-7.32 (2H, m, Ar H), 7.32-7.27 (4H, m, Ar H), 3.21 (4H, s, H1), 2.73-2.63 (2H, m, $H3_b$), 2.61-2.52 (2H, m, $H3_a$).

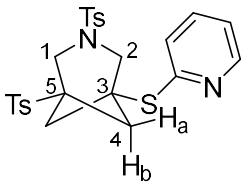
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 136.7, 129.3, 128.8, 127.2, 47.4, 43.9, 38.1.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3070, 2930, 1475, 1436, 1200, 1065.

HRMS (ES^+) calc. for $C_{18}H_{19}SSe_2$ $[M+H]^+$ 426.9532, found 426.9544.

m.p. 87 °C

1-(Pyridin-2-ylthio)-3,5-ditosyl-3-azabicyclo[3.1.1]heptane (86z)



Prepared according to the literature procedure[35]. To a solution of *S*-2-pyridyl tolylthiosulfonate (54.3 mg, 0.205 mmol, 1.0 eq.) in dry MeCN (1.5 mL) was added of 3-(*N*-tosyl)-aza[3.1.1]propellane (2.05 mL, 0.15 M in THF, 0.307 mmol, 1.5 eq.) and the mixture was stirred at 60 °C for 16 h. The mixture was then cooled to rt, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2, pentane/EtOAc 7:3) to give the product (51.9 mg, 0.101 mmol, 49%) as a white solid.

R_f 0.29 (7:3 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.29 (1H, ddd, *J* = 4.9, 1.9, 0.9 Hz, Ar H), 7.67 (2H, d, *J* = 8.3 Hz, Ts), 7.63 (2H, d, *J* = 8.3 Hz, Ts), 7.49 (1H, td, *J* = 7.7, 1.9 Hz, Ar H), 7.37 (2H, d, *J* = 8.0 Hz, Ts), 7.29 (2H, d, *J* = 8.0 Hz, Ts), 7.11 (1H, d, *J* = 8.0 Hz, Ar H), 7.02 (1H, ddd, *J* = 7.4, 4.9, 1.1 Hz, Ar H), 3.82 (2H, s, H1/2), 3.55 (2H, s, H1/2), 2.81-2.71 (2H, m, $H4_b$), 2.49 (3H, s, Ts), 2.45 (3H, s, Ts), 2.00-1.90 (2H, m, $H4_a$).

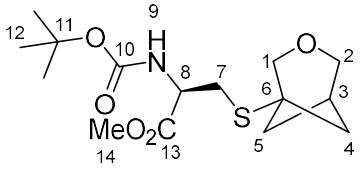
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 156.9, 149.7, 145.7, 143.9, 136.6, 134.4, 132.3, 130.3, 129.9, 129.3, 127.5, 123.7, 120.6, 60.6, 53.8, 48.0, 43.1, 39.0, 21.9, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2926, 1578, 1416, 1317, 1160.

HRMS (ES^+) calc. for $C_{25}H_{27}N_2O_4S_3$ $[M+H]^+$ 515.1128, found 515.1136.

m.p. 164 °C

Methyl *S*-(3-oxabicyclo[3.1.1]heptan-1-yl)-N-(*tert*-butoxycarbonyl) cysteinate (86aa)



Synthesised in accordance with *General Procedure 1* using *N*-(*tert*-Butoxycarbonyl)-L-cysteine methyl ester (47.0 mg, 0.200 mmol, 1 eq.), oxa[3.1.1]propellane (1.00 mL, 0.260 mmol, 1.3 eq, 0.27 M in diethyl ether) and BEt_3 (20.0 µL, 1.0 M in hexane, 10 mol%). The reaction was stirred at ambient temperature for 2.5 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to afford the product (44.0 mg, 0.130 mmol, 67%) as a colourless oil.

Scaled up synthesis:

Synthesised in accordance with *General Procedure 1* using *N*-(*tert*-Butoxycarbonyl)-L-cysteine methyl ester (240 mg, 1.00 mmol, 1 eq.), oxa[3.1.1]propellane (4.80 mL, 1.30 mmol, 1.3 eq, 0.27 M in diethyl ether) and BEt_3 (0.10 mL, 1.0 M in hexane, 10 mol%). The reaction was stirred at ambient temperature for 2.5 h. All volatiles were removed under vacuum, and the crude reaction mixture was purified by column chromatography (SiO_2, pentane/Et_2O 8:2) to afford the product (200 mg, 0.610 mmol, 61%) as a light yellow oil.

R_f = 0.3 (8:2 pentane / Et_2O)

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.28 (1H, d, *J* = 7.9 Hz, H9), 4.52 (1H, d, *J* = 5.5 Hz, H8), 3.88 (2H, s, H1), 3.87 (2H, d, *J* = 2.2 Hz, H2), 3.77 (3H, s, H14), 2.95 (1H, dd, *J* =

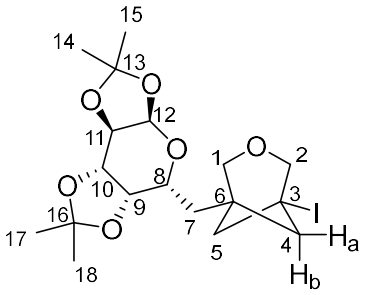
13.4, 4.9 Hz, H7), 2.90 (1H, dd, *J* = 13.2, 5.3 Hz, H7), 2.50 (1H, tt, *J* = 6.9, 2.2 Hz, H3), 2.17 (2H, m, H4/5), 1.90 (2H, m, H4/5), 1.45 (9H, s, H12).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 171.3, 155.2, 80.4, 74.8, 69.7, 53.5, 52.8, 48.0, 38.0, 37.9, 32.7, 31.2, 28.5.

IR (thin film, ν_{max} / cm^{-1}): 3352, 2975, 2861, 1748, 1714, 1508, 1439, 1362, 1314, 1167, 1044.

HRMS (ESI+) $[M+H]^+$ calculated for $[C_{15}H_{26}NO_5S]^+$ 332.1526, found 332.1520.

(3aR,5R,5aS,8aS,8bR)-5-((5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)methyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran (86ab)



Synthesised in accordance with *General Procedure 3*, using 3-oxa[3.1.1]propellane (1.61 mL, 0.14 M in Et_2O, 0.225 mmol, 1.5 eq.), (3aR,5S,5aR,8aS,8bR)-5-(iodomethyl)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran[159] (55.5 mg, 0.150 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (2.5 mg, 3.8 μmol, 2.5 mol%). The mixture was stirred and irradiated with 456 nm blue light in a photobox with fan cooling for 16 h. Purification by column chromatography (SiO_2, pentane/EtOAc 9:1) gave the product (24.5 mg, 52.5 μmol, 35%) as a white solid.

R_f 0.16 (9:1 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.48 (1H, d, *J* = 5.2 Hz, H12), 4.56 (1H, dd, *J* = 7.9, 2.4 Hz, H10), 4.27 (1H, dd, *J* = 5.1, 2.4 Hz, H11), 4.13 (2H, s, H2), 4.01 (1H, dd, *J* = 7.9, 1.9 Hz, H9), 3.84 (1H, dd, *J* = 9.7, 1.4 Hz, H1), 3.76 (1H, dd, *J* = 9.6, 1.5 Hz, H1), 3.73 (1H, dt, *J* = 10.2, 2.2 Hz, H8), 2.64 (1H, d, *J* = 8.8 Hz, $H4_b/H5_b$), 2.55 (1H, d, *J* = 8.9 Hz, $H4_b/H5_b$), 2.45 (1H, t, *J* = 8.3 Hz, $H4_a/H5_a$), 2.41 (1H, t, *J* = 8.3 Hz, $H4_a/H5_a$), 1.80 (1H, dd, *J* = 14.9, 10.2 Hz, H7), 1.55 (3H, s, H14/15), 1.49 (1H, dd, *J* = 14.9, 2.3 Hz, H7), 1.43 (3H, s, H14/15/17/18), 1.33 (3H, s, H14/15/17/18), 1.32 (3H, s, H14/15/17/18).

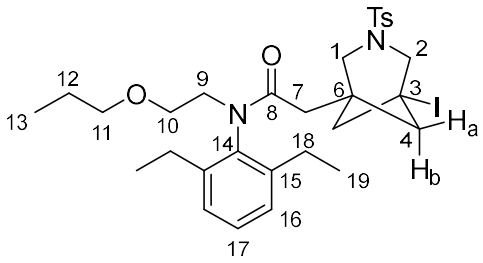
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 109.3, 108.6, 96.7, 78.1, 73.7, 73.0, 71.1, 70.3, 64.4, 49.2, 48.6, 46.3, 36.9, 29.4, 26.3, 26.1, 25.0, 24.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2986, 1383, 1212, 1169, 1071.

HRMS (ES^+) calc. for $C_{18}H_{28}IO_6$ $[M+H]^+$ 467.0925, found 467.0928.

m.p. 149 °C

***N*-(2,6-Diethylphenyl)-2-(5-iodo-3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)-*N*-(2-propoxyethyl)acetamide (86ac)**



Synthesised in accordance with *General procedure 3*, using 3-(*N*-tosyl)-aza[3.1.1]propellane (1.07 mL, 0.14 M in THF, 0.150 mmol, 1.5 eq.), N-(2,6-diethylphenyl)-2-iodo-N-(2-propoxyethyl)acetamide[29] (40.3 mg, 0.100 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.6 mg, 2.5 μmol, 2.5 mol%). The mixture was stirred and irradiated with 456 nm blue light in a photobox with fan cooling for 16 h. Purification by column chromatography (SiO_2, pentane/EtOAc 8:2) gave the product (30.9 mg, 47.3 μmol, 47%) as a colourless oil.

R_f 0.34 (8:2 pentane / EtOAc).

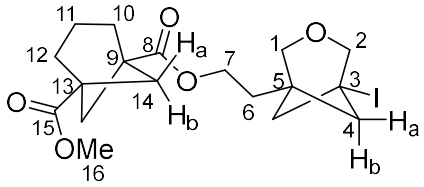
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.3 Hz, Ts Ar), 7.37-7.30 (3H, m, H17, Ts Ar), 7.20 (2H, d, *J* = 7.7 Hz, H16), 3.80 (2H, s, H1/2), 3.67 (2H, t, *J* = 6.3 Hz, H9/10), 3.53 (2H, t, *J* = 6.2 Hz, H9/10), 3.37 (2H, s, H1/2), 3.31 (2H, t, *J* = 6.7 Hz, H11), 2.56 (2H, m, H18), 2.49-2.40 (5H, m, H18/Ts Me), 2.40-2.34 (2H, m, $H4_b$), 2.21-2.14 (2H, m, $H4_a$), 1.96 (2H, s, H7), 1.51 (2H, qt, *J* = 7.2, 7.1 Hz, H12), 1.26 (6H, t, *J* = 7.5 Hz, H19), 0.86 (3H, t, *J* = 7.4 Hz, H13)

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 170.4, 143.7, 141.2, 139.0, 134.6, 130.0, 128.8, 127.4, 126.8, 72.9, 67.6, 59.2, 52.4, 49.4, 49.3, 42.1, 41.3, 24.0, 23.4, 23.0, 21.7, 14.4, 10.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2970, 1654, 1459, 1400, 1342, 1160.

HRMS (ES^+) calc. for $C_{30}H_{42}IN_2O_4S$ $[M+H]^+$ 653.1905, found 653.1895.

1-(2-(5-Iodo-3-oxabicyclo[3.1.1]heptan-1-yl)ethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate (18ad)



Synthesised in accordance with *General Procedure 3*, using 3-oxa[3.1.1]propellane (1.07 mL, 0.14 M in Et_2O, 0.150 mmol, 1.5 eq.), 1-(2-iodoethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate **S1** (35.2 mg, 0.100 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.6 mg, 2.5 μmol, 2.5 mol%). The mixture was stirred and irradiated with 456 nm blue light in a photobox with fan cooling for 16 h. Purification by column chromatography (SiO_2, pentane/EtOAc 8:2) gave the product (19.8 mg, 44.2 μmol, 44%) as a colourless oil.

R_f 0.30 (8:2 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.13 (2H, s, H1/2), 4.02 (2H, t, *J* = 6.4 Hz, H7), 3.76 (2H, s, H1/2), 3.68 (3H, s, H16), 2.55-2.50 (2H, m, $H4_b$), 2.50-2.46 (2H, m, $H14_b$), 2.46-2.41 (2H, m, $H4_a$), 2.01-1.87 (6H, m, H10/11/12), 1.85-1.77 (2H, m, $H14_a$), 1.73 (2H, t, *J* = 6.4 Hz, H6).

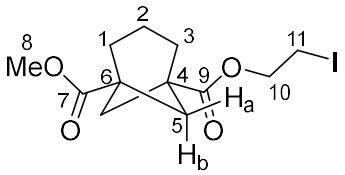
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 175.5, 175.0, 78.0, 72.5, 61.0, 52.0, 48.8, 46.0, 42.4, 38.1, 35.3, 29.6, 29.5, 28.2, 16.1.

Note: both C9 and C13 appear at 42.4 ppm.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2952, 1731, 1287, 1220, 1128.

HRMS (ES^+) calc. for $C_{18}H_{26}IO_5$ $[M+H]^+$ 449.0820, found 449.0814.

1-(2-Iodoethyl) 5-methyl bicyclo[3.1.1]heptane-1,5-dicarboxylate (S1)



To a stirred solution of 5-(methoxycarbonyl)bicyclo[3.1.1]heptane-1-carboxylic acid [160, 161] (198 mg, 1.00 mmol, 1.0 eq.) in CH_2Cl_2 (5.0 mL) at 0 °C was added 2-iodoethanol (0.156 mL, 2.00 mmol, 2.0 eq.), DMAP (183 mg, 1.50 mmol, 1.5 eq.) and EDCI.HCl (383 mg, 2.00 mmol, 2.0 eq.). The mixture was stirred at 0 °C for 2 h, then $NaHCO_3$ sat. (5 mL) was added. The mixture was extracted with CH_2Cl_2 (3 x 5 mL), then the prganic phases were combined, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 9:1) gave the product **S1** (208 mg, 0.591 mmol, 59%) as a colourless oil.

R_f 0.25 (9:1 pentane / EtOAc).

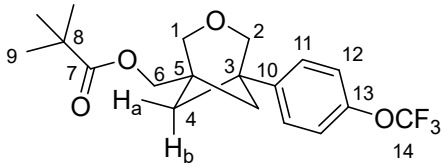
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.30 (2H, t, *J* = 6.7 Hz, H10), 3.66 (3H, s, H8), 3.28 (2H, t, *J* = 6.7 Hz, H11), 2.56-2.46 (2H, m, $H5_b$), 2.05-1.96 (4H, m, H1/3), 1.94-1.85 (2H, m, H2), 1.87-1.78 (2H, m, $H5_a$)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 175.5, 174.4, 64.4, 51.9, 42.4, 42.4, 38.1, 29.6, 29.6, 16.0, 0.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2952, 1731, 1455, 1286, 1219, 1125.

HRMS (ES^+) calc. for $C_{12}H_{18}IO_4$ $[M+H]^+$ 353.0244, found 353.0244.

(5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptan-1-yl)methyl pivalate (88)



To prepare the Grignard reagent, Mg turnings (88.0 mg, 3.62 mmol, 1.2 eq.) were added to a flask which was heated under vacuum for 1 minute. THF (2.5 mL) and I_2 (one crystal) were added, then 1-bromo-4-(trifluoromethoxy)benzene (0.448 mL, 3.02 mmol, 1.0 eq.) was added dropwise. The mixture was heated under reflux for 2 h, then cooled to room temperature. The concentration of the reagent was determined by iodometric titration.

To a solution of **86e** (134 mg, 0.396 mmol, 1.0 eq.) and $Fe(acac)_3$ (28.1 mg, 79.2 μmol, 0.2 eq.) in THF (0.2 mL) was added TMEDA (24.0 μL, 0.158 mmol, 0.4 eq.) and the mixture was stirred for 5 min. A solution of (4-(trifluoromethoxy)phenyl)magnesium bromide in THF (0.81 mL, 0.98 M, 2.0 eq.) was added slowly over 2 h. The mixture was stirred at room temperature for an additional 2 h, then quenched with NH_4Cl sat. (3 mL). The mixture was extracted with Et_2O (3 x 3 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 9:1) gave the product (71.7 mg, 0.193 mmol, 49%) as a colourless oil.

R_f 0.22 (9:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.16 (1H, d, *J* = 8.0 Hz, H11/12), 7.13-7.08 (2H, m, H11/12), 3.96 (2H, s, H6), 3.89 (2H, s, H1/2), 3.85 (2H, s, H1/2), 2.16-2.08 (2H, m, $H4_b$), 2.07-2.00 (2H, m, $H4_a$), 1.20 (9H, s, H9).

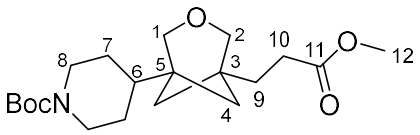
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 178.5, 148.0, 143.3, 127.0, 120.6 (q, *J* = 258.3 Hz), 121.2, 76.3, 71.8, 67.0, 43.8, 39.4, 39.1, 37.5, 27.4.

^{19}F NMR (376 MHz, $CDCl_3$) δ_F -57.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2934, 1730, 1511, 1260, 1161.

HRMS (ES^+) calc. for $C_{19}H_{24}F_3O_4$ $[M+H]^+$ 373.1621, found 373.1640.

tert-Butyl 4-(5-(3-methoxy-3-oxopropyl)-3-oxabicyclo[3.1.1]heptan-1-yl)piperidine-1-carboxylate (89)



To a solution of *tert*-Butyl 4-(5-iodo-3-oxabicyclo[3.1.1]heptan-1-yl)piperidine-1-carboxylate (20.0 mg, 49.1 μmol, 1.0 eq.), Na_2CO_3 (10.4 mg, 98.2 μmol, 2.0 eq.) and $Ir[dFCF_3(CF_3)ppy]_2(dtbbpy)PF_6$ (1.4 mg, 1.2 μmol, 2.5 mol%) in a 9:1 mixture of $MeOH/H_2O$ (0.5 mL) was added $(SiMe_3)_3SiH$ (30.3 μL, 98.2 μmol, 2.0 eq.) and methyl acrylate (26.5 μL, 295 μmol, 6.0 eq.) and the mixture was degassed with nitrogen for 5 min. The vial was placed in a photobox and stirred and irradiated with 456 nm LEDs for 24 h. The mixture was poured onto H_2O (3 mL) and extracted with CH_2Cl_2 (3 x 3 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane / EtOAc 8:2) gave the product (6.3 mg, 17 μmol, 35%) as a colourless oil.

R_f = 0.10 (8:2 pentane/ EtOAc).

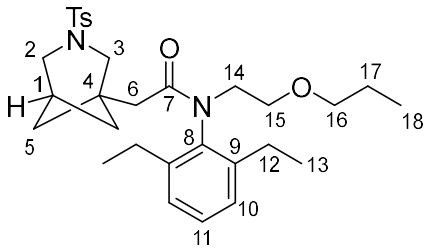
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.19 – 4.11 (2H, m, H8), 3.71 (2H, s, H1/2), 3.67 (3H, s, H12), 3.66 (2H, s, H1/2), 2.57 (2H, t, *J* = 13.0 Hz, H8), 2.25 – 2.18 (2H, m, H10), 1.68 – 1.60 (2H, m, H9), 1.60 – 1.56 (2H, m, H4), 1.50 – 1.46 (4H, m, H4/7), 1.45 (9H, s, Boc), 1.29 – 1.22 (1H, m, H6), 1.11 (1H, dd, *J* = 12.6, 4.4 Hz, H7), 1.05 (1H, dd, *J* = 12.5, 4.3 Hz, H7).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 174.1, 154.9, 79.5, 74.4, 72.8, 51.8, 44.2 (br), 42.3, 38.8, 37.0, 31.5, 29.5, 28.6, 26.7. Note: the signal from C8 is broad due to the presence of rotamers and the signals from C5 and C6 overlap.

IR (thin film, ν_{max} / cm^{-1}): 2932, 2856, 1741, 1694, 1427, 1173.

HRMS (ESI+) $[M+Na]^+$ calculated for $[C_{20}H_{33}NO_5Na]^+$ 390.2251, found 390.2254.

***N*-(2,6-diethylphenyl)-*N*-(2-propoxyethyl)-2-(3-tosyl-3-azabicyclo[3.1.1]heptan-1-yl)acetamide (90)**



Prepared according to the literature procedure[157]. To a solution of **86ac** (85.5 mg, 0.131 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (2.1 mg, 3.3 µmol, 2.5 mol%) in *t*BuCN (1.0 mL) was added Si(SiMe$_3$)H (72.7 µL, 0.236 mmol, 1.8 eq.) and the mixture was degassed with N_2 for 5 min. The vial was placed in a photobox and the stirred reaction was irradiated with blue LEDs (Kessil PR160, 456 nm) with fan cooling for 1 h. The reaction mixture was concentrated under reduced pressure and the product was purified by column chromatography (SiO_2, pentane/EtOAc 8:2) to give the product (49.7 mg, 94.4 µmol, 72%) as a pale yellow oil.

R$_f$ 0.23 (8:2 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.70 (2H, d, *J* = 8.2 Hz, Ts), 7.33 – 7.27 (3H, m, Ts/H11), 7.19 (2H, d, *J* = 7.7 Hz, H10), 3.68 (2H, t, *J* = 6.3 Hz, H14/15), 3.55 (2H, t, *J* = 6.3 Hz, H14/15), 3.40 (4H, s, H2/3), 3.31 (2H, t, *J* = 6.8 Hz, H16), 2.60-2.52 (2H, m, H12), 2.50 – 2.40 (2H, m, H12), 2.42 (3H, s, Ts), 2.34 (1H, tt, *J* = 6.1, 2.7 Hz, H1), 1.87 (2H, s, H6), 1.84 – 1.77 (2H, m, H5), 1.51 (2H, tq, *J* = 7.2, 7.2 Hz, H17), 1.41 – 1.33 (2H, m, H5), 1.25 (6H, t, *J* = 7.6 Hz, H13), 0.85 (3H, t, *J* = 7.4 Hz, H18).

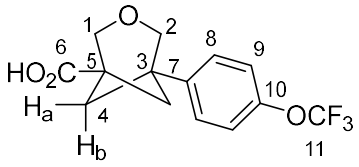
^{13}C NMR ^{13}C NMR (126 MHz, $CDCl_3$) δ_C 171.4, 143.2, 141.3, 139.4, 135.0, 129.7, 128.6, 127.5, 126.7, 72.9, 67.7, 54.6, 50.1, 49.3, 41.1, 39.4, 36.0, 29.8, 23.4, 23.0, 21.7, 14.4, 10.7.

Note: the ^{1}H and ^{13}C spectra show additional peaks due to the presence of rotamers.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2964, 1656, 1459, 1396, 1341, 1159.

HRMS (ES^{+}) calc. for $C_{30}H_{43}N_2O_4S$ $[M+H]^{+}$ 527.2938, found 527.2938.

5-(4-(Trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxylic acid (92)



To a solution of **88** (71.7 mg, 0.193 mmol, 1.0 eq.) in MeOH (2.0 mL) was added KOH (23.0 mg, 0.410 mmol, 2.1 eq.) and the mixture was heated at 50 °C for 20 h. The mixture was then concentrated under reduced pressure and water (3 mL) was added. The mixture was extracted with EtOAc (3 x 3 mL), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was used directly in the next step.

The oxidation was carried out according to the literature procedure[83]. To a solution of oxalyl chloride (21.0 µL, 0.251 mmol, 1.3 eq.) in CH_2Cl_2 (4 mL) at -78 °C was added a solution of DMSO (20.6 µL, 0.290 mmol, 1.5 eq.) in CH_2Cl_2 (0.5 mL) dropwise and the mixture was stirred at -78 °C for 1 h. The crude product from the previous step was dissolve in CH_2Cl_2 (0.5 mL) and added to the reaction mixture dropwise. The mixture was stirred at -78 °C for 4 h. NEt_3 (0.11 mL, 0.772 mmol, 4.0 eq.) was added and the mixture was stirred at rt overnight. The mixture was washed with water (2 x 2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. THF (2 mL) was added, followed by 2-methylbut-2-ene (63.4 µL, 0.598 mmol, 3.1 eq.). A solution of NaH_2PO_4 (27.8 mg, 0.232 mmol, 1.2 eq.) in water (0.5 mL) was added. The mixture was cooled to 0 °C, then a solution of $NaClO_2$ (20.9 mg, 0.232 mmol, 1.2 eq.) in water (0.5 mL) was added dropwise. The mixture was stirred at rt overnight, then concentrated under reduced pressure. The residue was diluted with water (3 mL) then acidified with conc. HCl to pH 5. The mixture was extracted with EtOAc (3 x 3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give the crude

product (26.8 mg, 88.6 μmol, 46%) as an orange oil which was used directly in the next step without further purification.

R_f 0.28 (2:1 hexane / THF).

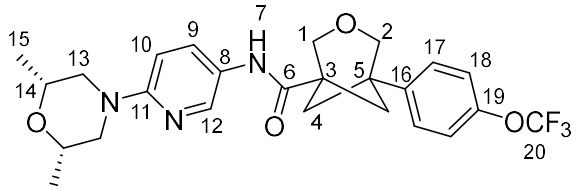
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.18-7.08 (4H, m, H8/9), 4.12 (2H, s, H1/2), 3.85 (2H, s, H1/2), 2.56-2.50 (2H, m, $H4_b$), 2.32-2.26 (2H, m, $H4_a$).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 176.9, 148.1, 142.5, 126.9, 121.2, 120.6 (q, J = 258.2 Hz), 75.5, 69.6, 43.3, 42.9, 38.5.

^{19}F NMR (376 MHz, $CDCl_3$) δ_F -58.0.

Analytical data matches that previously recorded[83].

N-(6-((2R,6S)-2,6-dimethylmorpholino)pyridin-3-yl)-5-(4-(trifluoromethoxy)phenyl)-3-oxabicyclo[3.1.1]heptane-1-carboxamide (93)



The amide coupling was carried out according to the literature procedure[83]. To a solution of **92** (26.8 mg, 88.7 µmol, 1.0 eq.), 6-((2S,6R)-2,6-dimethylmorpholino)pyridin-3-amine (18.4 mg, 88.7 µmol, 1.0 eq.) and HATU (40.5 mg, 0.106 mmol, 1.2 eq.) in DMF (0.5 mL) was added NEt_3 (49.4 µL, 0.355 mmol, 4.0 eq.) and the mixture was stirred at 50 °C for 8 h. Water (2 mL) and EtOAc (2 mL) were added. The layers were separated and the organic layer was washed with water (2 x 2 mL) and each wash was back-extracted with EtOAc. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, hexane / THF 2:1) gave the product (30.5 mg, 62.1 µmol, 70%) as a yellow solid.

R_f 0.24 (2:1 hexane / THF).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.13 (1H, d, *J* = 2.8 Hz, H12), 7.86 (1H, dd, *J* = 9.1, 2.8 Hz, H9), 7.23-7.08 (4H, m, H17/18/7), 6.61 (1H, d, *J* = 9.1 Hz, H10), 4.16 (2H, s, H1/2), 3.97 (1H, dd, *J* = 12.7, 1.8 Hz, H13), 3.88 (2H, s, H1/2), 3.71 (2H, dqd, *J* = 10.5, 6.2, 2.5 Hz, H14), 2.55-2.40 (6H, m, H4/13), 1.26 (3H, s, H15), 1.25 (3H, s, H15).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.1, 156.7, 148.2, 142.4, 140.0, 131.8, 127.0, 125.1, 121.3, 120.6 (q, *J* = 258.5 Hz), 107.1, 75.6, 71.7, 71.3, 51.3, 45.1, 42.4, 38.5, 19.1.

^{19}F NMR (376 MHz, $CDCl_3$) δ_F -57.9.

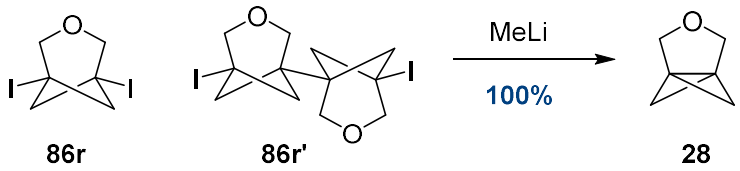
IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2867, 1651, 1511, 1493, 1256, 1224.

HRMS (ES^+) calc. for $C_{25}H_{28}F_3N_3O_4Na$ $[M+Na]^+$ 514.1924, found 514.1932.

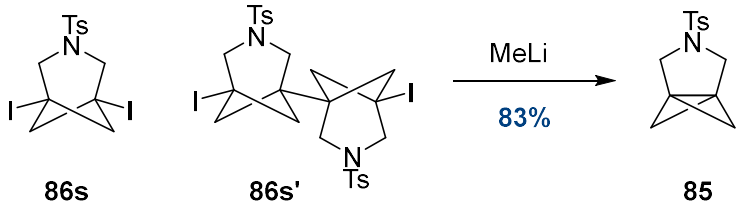
m.p. 202 °C.

Analytical data matches that previously recorded[83].

Alternative method for propellane formation:

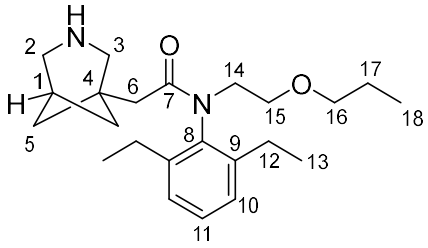


A 1.4:1.0 mixture of **86r:86r'** (10.9 mg total, including **86r** (9.14 mg, 26.1 µmol, 1.0 eq.) and **86r'** (1.75 mg, 3.92 µmol, 0.15 eq.)) was dissolved in Et_2O (0.40 mL) and cooled to -78 °C. MeLi (26.0 µL, 1.35 M solution in Et_2O, 35.1 µmol, 1.3 eq.) was added and the mixture was stirred at -78 °C for 10 min. The mixture was then stirred at rt for 1 h. The yield was determined directly from the reaction mixture by ^1H NMR spectroscopy using a CH_2Cl_2 internal standard (5.0 µL). The mixture contained 34.1 µmol product, 100% yield, and the NMR matched that reported above for compound **28**.



A 1.4:1.0 mixture of **86s:86s'** (21.0 mg total, including **86s** (10.2 mg, 20.3 µmol, 1.0 eq.) and **86s'** (10.8 mg, 14.4 µmol, 0.70 eq.)) was dissolved in THF (0.17 mL) and cooled to -78 °C. MeLi (32.1 µL, 1.3 M solution in Et_2O, 41.7 µmol, 2.1 eq.) was added and the mixture was stirred at -78 °C for 10 min. The mixture was then stirred at rt for 1 h. The yield was determined directly from the reaction mixture by ^1H NMR spectroscopy using a CH_2Cl_2 internal standard (2.5 µL). The mixture contained 40.6 µmol product, 83% yield, and the NMR matched that reported above for compound **85**.

2-(3-Azabicyclo[3.1.1]heptan-1-yl)-*N*-(2,6-diethylphenyl)-*N*-(2-propoxyethyl)acetamide (94)



To a solution of **90** (27.6 mg, 52.4 μmol, 1.0 eq.) in MeOH (1.5 mL) was added Mg powder (25.5 mg, 1.05 mmol, 20 eq.) and the mixture was sonicated for 2 h. Another portion of Mg was added and the mixture was sonicated for a further 1 h, then stirred at rt for 16 h. HCl (aq, 1M) was added until the mixture became clear and then the mixture was adjusted to pH 8 with sat. $NaHCO_3$ solution. The mixture was extracted with EtOAc (3 x 15 mL), then the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, CH_2Cl_2/NH_3 (7 M, in MeOH) 9:1) gave the product (15.3 mg, 41.2 μmol, 79%) as a yellow oil.

R_f 0.40 (9:1 CH_2Cl_2/NH_3 (7 M, in MeOH) 9:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.30 (1H, dd, *J* = 8.3, 7.0 Hz, H11), 7.19 (2H, d, *J* = 7.7 Hz, H10), 5.49 (1H, br s, N-H), 3.67 (2H, t, *J* = 6.3 Hz, H14/15), 3.52 (2H, t, *J* = 6.2 Hz, H14/15), 3.49 (2H, s, H3), 3.40 (2H, d, *J* = 2.5 Hz, H2), 3.30 (2H, t, *J* = 6.7 Hz, H16), 2.63 – 2.37 (5H, m, H1/12), 1.96-1.89 (2H, m, H5), 1.91 (2H, s, H6), 1.88 – 1.81 (2H, m, H5), 1.50 (2H, tq, *J* = 7.2, 7.2 Hz, H17), 1.25 (6H, t, *J* = 7.6 Hz, H13), 0.84 (3H, t, *J* = 7.4 Hz, H18).

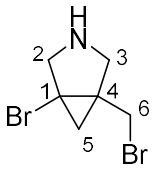
^{13}C NMR ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 171.2, 141.2, 139.0, 128.8, 126.8, 72.9, 67.6, 51.7, 49.3, 47.5, 41.5, 39.4, 35.9, 29.9, 23.4, 22.9, 14.4, 10.6.

Note: the ^{1}H and ^{13}C spectra show additional peaks due to the presence of rotamers.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3462, 2965, 1652, 1457, 1400, 1113.

HRMS (ES^{+}) calc. for $C_{23}H_{37}N_2O_2$ $[M+H]^{+}$ 373.2850, found 373.2850.

1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane (70)



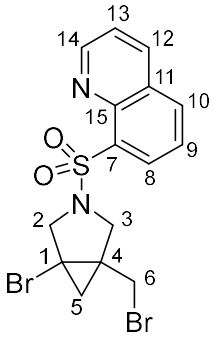
To a solution of HBr in acetic acid (33%, 12.1 mL, 73.3 mmol, 30 eq.) was added phenol (2.30 g, 24.4 mmol, 10 eq.). 1-Bromo-5-(bromomethyl)-3-tosyl-3-azabicyclo[3.1.0]hexane **84** (1.00 g, 2.44 mmol, 1.0 eq.) was added and the mixture was stirred at 70 °C for 2 h. The mixture was then made adjusted to pH 8 with 1 M aq NaOH (250 mL) and extracted with Et_2O (3 x 200 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the crude product **70** (2.45 g, 25% w/w, 2.40 mmol, 98%) as an orange oil. The yield was determined by NMR; the doublet at 3.39 ppm was integrated relative to a CH_2Cl_2 internal standard. The crude product was taken forward without further purification to all subsequent amine functionalisation steps.

R_f 0.19 (3:7 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.64 (2H, s, H6), 3.43 (1H, d, *J* = 11.8 Hz, H2/3), 3.27 (1H, d, *J* = 11.8 Hz, H2/3), 3.20 (1H, d, *J* = 11.9 Hz, H2/3), 3.10 (1H, d, *J* = 11.9 Hz, H2/3), 1.37 (1H, d, *J* = 7.1 Hz, H5), 1.27 (3H, d, *J* = 6.9 Hz, H5)

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 56.4, 50.6, 41.8, 35.9, 33.8, 22.9.

8-((1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)quinoline (95a)



To a solution of **70** (812 mg, 16% w/w, 0.500 mmol, 1.0 eq.) and Na_2CO_3 (79.5 mg, 0.750 mmol, 1.5 eq.) in THF (0.8 mL) and water (0.8 mL) was added quinoline-8-sulfonyl chloride (171 mg, 0.750 mmol, 1.5 eq.) and the mixture was stirred at rt for 1 h. The THF was removed under reduced pressure and the mixture was diltued with water (10 mL) and extracted with Et_2O (3 x 10 mL). The combined organicc extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Recrystallisation from Et_2O at -20 °C gave the product (102 mg, 0.229 mmol, 46%) as a colourless crystalline solid.

R_f 0.17 (8:2 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.08 (1H, dd, *J* = 4.2, 1.8 Hz, Ar H), 8.44 (1H, dd, *J* = 7.4, 1.5 Hz, Ar H), 8.24 (1H, dd, *J* = 8.3, 1.8 Hz, Ar H), 8.03 (1H, dd, *J* = 8.2, 1.5 Hz, Ar H), 7.60 (1H, t, *J* = 7.8 Hz, Ar H), 7.53 (1H, dd, *J* = 8.3, 4.2 Hz, Ar H), 4.34 (1H, d, *J* = 9.9 Hz, H2/3), 4.00 (1H, d, *J* = 9.9 Hz, H2/3), 3.81 (1H, d, *J* = 9.9 Hz, H2/3), 3.76 (1H, d, *J* = 10.0 Hz, H2/3), 3.55 (1H, d, *J* = 11.0 Hz, H6), 3.51 (1H, d, *J* = 11.1 Hz, H6), 1.27 (1H, d, *J* = 6.7 Hz, H5), 1.12 (1H, d, *J* = 6.9 Hz, H5).

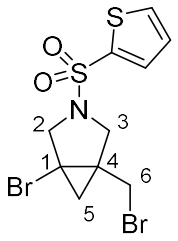
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 151.5, 144.1, 137.1, 136.7, 133.9, 133.1, 129.2, 125.7, 122.4, 56.9, 52.0, 38.7, 35.3, 32.8, 24.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2877, 1494, 1338, 1164, 1145.

HRMS (ES^+) calc. for $C_{15}H_{15}N_2O_2S$ $[M+H]^+$ 444.9216, found 444.9211.

m.p. 130 °C

1-Bromo-5-(bromomethyl)-3-(thiophen-2-ylsulfonyl)-3-azabicyclo[3.1.0]hexane (95b)



To a solution of **70** (810 mg, 16% w/w, 0.500 mmol, 1.0 eq.) and Na_2CO_3 (79.5 mg, 0.750 mmol, 1.5 eq.) in THF (0.8 mL) and water (0.8 mL) was added thiophene-2-sulfonyl chloride (137 mg, 0.750 mmol, 1.5 eq.) and the mixture was stirred at rt for 1 h. The THF was removed under reduced pressure and water (10 mL) was added. The mixture was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. Recrystallisation from Et_2O at -20 °C gave the product (111 mg, 0.277 mmol, 55%) as a white crystalline solid.

R_f 0.21 (7:3 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.66 (1H, d, *J* = 5.1 Hz, Ar H), 7.60 (1H, dd, *J* = 3.8, 1.3 Hz, Ar H), 7.18 (1H, dd, *J* = 5.0, 3.7 Hz, Ar H), 3.99 (2H, d, *J* = 9.5 Hz, H2/3), 3.67 (2H, d, *J* = 9.7 Hz, H2/3), 3.56 (2H, d, *J* = 11.1 Hz, H6), 3.49 (2H, d, *J* = 11.1 Hz, H6), 3.38 (2H, d, *J* = 9.6 Hz, H2/3), 3.36 (2H, d, *J* = 9.6 Hz, H2/3), 1.49 (2H, d, *J* = 6.8 Hz, H5), 1.23 (2H, d, *J* = 6.8 Hz, H5).

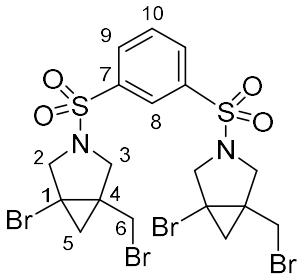
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 136.2, 132.9, 132.7, 128.0, 56.8, 52.0, 37.8, 34.7, 32.9, 24.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2861, 1722, 1358, 1228, 1165, 1045, 1018.

HRMS (ES^+) calc. for $C_{10}H_{12}NO_2S_2$ $[M+H]^+$ 399.8671, found 399.8670.

m.p. 98 °C

1,3-Bis((1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)sulfonyl)benzene (95c)



To a solution of **70** (510 mg, 25% w/w, 0.500 mmol, 2.0 eq.) and Na_2CO_3 (79.5 mg, 0.750 mmol, 3.0 eq.) in THF (0.8 mL) and water (0.8 mL) was added benzene-1,3-disulfonyl dichloride (68.8 mg, 0.250 mmol, 1.0 eq.) and the mixture was stirred at rt for 1 h. The THF was removed under reduced pressure and the mixture was diltued with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Trituration from Et_2O at gave the product (43.9 mg, 61.6 μmol, 25%) as a white solid.

R_f 0.21 (1:1 pentane / Et_2O).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.21 (1H, s, H8), 8.05 (2H, dd, J = 7.9, 1.8 Hz, H9), 7.81 (1H, t, J = 7.8 Hz, H10), 4.04 (2H, d, J = 9.5 Hz, H2/3), 3.72 (2H, d, J = 9.6 Hz, H2/3), 3.55 (2H, d, J = 11.2 Hz, H2/3), 3.49 (2H, d, J = 11.0 Hz, H2/3), 3.35-3.24 (4H, m), 1.56 (2H, d, J = 6.9 Hz, H5), 1.27 (2H, d, J = 6.9 Hz, H5)

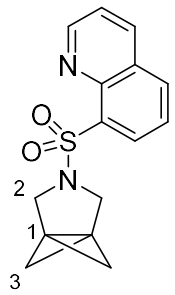
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 138.7, 138.6, 131.7, 131.7, 130.9, 126.2, 56.6, 56.6, 51.8, 37.5, 37.5, 34.5, 34.5, 32.8, 32.8, 24.6.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3060, 1438, 1358, 1184, 1120.

HRMS (ES^+) calc. for $C_{18}H_{20}Br_4N_2O_4S_2Na$ $[M+Na]^+$ 730.7490, found 730.7513.

m.p. 97 °C

3-(Quinolin-8-ylsulfonyl)-3-azatricyclo[3.1.1.0^{1,5}]heptane (96a)



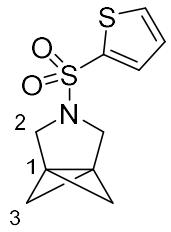
To a stirred solution of **95a** (95.5 mg, 0.214 mmol, 1.0 eq.), in dry THF (2.1 mL) at -78 °C was added MeLi (0.165 mL, 1.3 M, 0.214 mmol, 1.0 eq.). The mixture was stirred at -78 °C for 10 min, then at rt for 1 h. $MgSO_4$ (200 mg) was added to the reaction mixture and this was stirred for 10 min. Then the mixture was passed through a celite filter, eluted with THF (1.0 mL). The mixture was partially concentrated under reduced pressure (120 mbar) to remove MeBr and Et_2O, giving the product as a solution in THF (1.80 mL, 0.10 M, 0.173 mmol, 81%), which was stored under nitrogen at -20 °C. The yield was determined by integrating the singlet at 3.79 ppm relative to the THF peak.

^{1}H NMR (500 MHz, C_6D_6) δ_H 8.67 (1H, dd, *J* = 4.2, 1.8 Hz, Ar H), 8.48 (1H, dd, *J* = 7.3, 1.5 Hz, Ar H), 7.62 (1H, dd, *J* = 8.3, 1.8 Hz, Ar H), 7.45 (1H, dd, *J* = 8.2, 1.5 Hz, Ar H), 7.10 (1H, dd, *J* = 8.2, 7.3 Hz, Ar H), 6.90 (1H, dd, *J* = 8.3, 4.2 Hz, Ar H), 3.79 (4H, s, H2), 2.10 (2H, t, *J* = 1.6 Hz, H3), 1.35 (2H, t, *J* = 1.5 Hz, H3).

^{13}C NMR (126 MHz, C_6D_6) δ_C 150.9, 144.6, 139.3, 136.4, 133.1, 133.0, 129.2, 125.7, 122.0, 53.7, 52.1, 23.2.

HRMS (ES^+) calc. for $C_{15}H_{15}N_2O_2S$ $[M+H]^+$ 287.0849, found 287.0853.

3-(Thiophen-2-ylsulfonyl)-3-azatricyclo[3.1.1.0^{1,5}]heptane (96b)



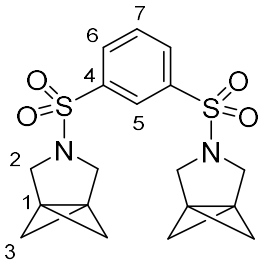
To a stirred solution of **95b** (85.5 mg, 0.213 mmol, 1.0 eq.), in dry THF (2.1 mL) at -78 °C was added MeLi (0.158 mL, 1.35 M in Et_2O, 0.213 mmol, 1.0 eq.). The mixture was stirred at -78 °C for 10 min, then at rt for 1 h. $MgSO_4$ (200 mg) was added to the reaction mixture and this was stirred for 10 min. Then the mixture was passed through a celite filter and eluted with THF (1.0 mL). The mixture was partially concentrated under reduced pressure (120 mbar) to remove MeBr and Et_2O, giving the product as a solution in THF (1.14 mL, 0.13 M, 0.150 mmol, 70%), which was stored under nitrogen at -20 °C. The yield was determined by integrating the triplet at 1.94 ppm relative to the THF peak.

^{1}H NMR (400 MHz, C_6D_6) δ_H 7.33 (1H, dd, *J* = 3.7, 1.3 Hz, Ar H), 7.01 (1H, dd, *J* = 5.0, 1.3 Hz, Ar H), 6.62 (1H, dd, *J* = 5.0, 3.7 Hz, Ar H), 3.23 (4H, s, H2), 1.94 (2H, t, *J* = 1.7 Hz, H3), 1.29 (2H, t, *J* = 1.6 Hz, H3).

^{13}C NMR (101 MHz, C_6D_6) δ_C 138.2, 132.2, 131.7, 126.2, 53.8, 52.2, 22.7.

HRMS (ES^+) calc. for $C_{10}H_{12}NO_2S_2$ $[M+H]^+$ 242.0304, found 242.0301.

1,3-Bis((3-azatricyclo[3.1.1.01,5]heptan-3-yl)sulfonyl)benzene (96c)

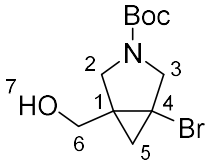


To a stirred solution of **95c** (50.8 mg, 71.3 μmol, 1.0 eq.), in dry THF (1.0 mL) at -78 °C was added MeLi (0.110 mL, 1.3 M in Et_2O, 0.143 mmol, 2.0 eq.). The mixture was stirred at -78 °C for 10 min, then at rt for 1 h. $MgSO_4$ (100 mg) was added to the reaction mixture and this was stirred for 10 min. Then the mixture was passed through a celite filter and eluted with THF (1.0 mL). The mixture was partially concentrated under reduced pressure (120 mbar) to remove MeBr and Et_2O, giving the product as a solution in THF (0.40 mL, 0.18 M, 70.9 μmol, 99%), which was stored under nitrogen at -20 °C. The yield was determined by integrating the triplet at 1.98 ppm relative to a $CHCl_3$ internal standard.

^{1}H NMR (400 MHz, C_6D_6) δ_H 8.37 (1H, t, *J* = 1.8 Hz, H5), 7.82 (2H, dd, *J* = 7.8, 1.8 Hz, H6), 7.25 (1H, t, *J* = 7.8 Hz, H7), 3.17 (8H, s, H2), 1.98 (4H, t, *J* = 1.7 Hz, H3), 1.30 (4H, t, *J* = 1.7 Hz, H3).

^{13}C NMR (101 MHz, C_6D_6) δ_C 139.6, 131.2, 130.6, 126.1, 53.8, 52.1, 22.6.

***tert*-Butyl 1-bromo-5-(hydroxymethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate (80)**



To a solution of methyl 5-bromo-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate **76** (4.00 g, 17.1 mmol, 1.0 eq.) in THF (120 mL) at 0 °C was added Red-Al (16.7 mL, 60% wt., 51.3 mmol, 3.0 eq.) dropwise, then the mixture was stirred at rt for 17 h. Rochelle salt solution sat. (60 mL) was added and the mixture was stirred until it became clear. The layers were separated, then the aqueous layer was extracted with a 3:1 mixture of $CHCl_3$:*i*PrOH (3 x 100 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The product was directly re-dissolved in a 1:1 mixture of THF:H_2O (30 mL). Boc_2O (4.48 g, 20.5 mmol, 1.2 eq.) was added and the mixture was stirred for 4 h at rt. Water (50 mL) and EtOAc (50 mL) were added and the mixture was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 6:4) gave the product (2.80 g, 9.58 mmol, 56%) as a white solid.

R_f 0.35 (6:4 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.12 – 3.89 (2H, m, H2/3/6), 3.75 (1H, dd, *J* = 12.4, 4.9 Hz, H2/3/6), 3.68 – 3.52 (3H, m, H2/3/6), 1.78-1.72 (1H, m, H7), 1.44 (9H, s, Boc), 1.23 (1H, d, *J* = 6.5 Hz, H5), 1.15-1.12 (1H, m, H5).

^{13}C NMR (101 MHz, $CDCl_3$) 154.5, 80.3, 64.4, 64.2, 56.1, 55.7, 49.0, 48.5, 36.1, 35.7, 34.1, 33.5, 28.5, 22.9.

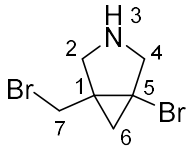
Note: the ^{1}H and ^{13}C spectra show additional signals due to the presence of rotamers.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3435, 2977, 1703, 1415, 1177.

HRMS (ES^{+}) calc. for $C_{11}H_{18}BrNO_3Na$ $[M+Na]^{+}$ 314.0362, found 314.0358.

m.p. 70 °C

1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane (70)



To a solution of tert-butyl 1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane-3-carboxylate **2** (6.18 g, 17.4 mmol, 1.0 eq.) in CH_2Cl_2 (30 mL) was added TFA (6.66 mL, 87.0 mmol, 5.0 eq.) and the mixture was stirred at rt for 8 h. $NaHCO_3$ sat. (100 mL) was added and the mixture was extracted with EtOAc (3 x 100 mL). The mixture was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product (4.10 g, 16.1 mmol, 92%) as a white solid.

R_f 0.22 (2:8 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.66 (1H, d, *J* = 10.8 Hz, H7), 3.62 (1H, d, *J* = 10.8 Hz, H7), 3.35 (1H, d, *J* = 11.7 Hz, H2/4), 3.18 (1H, d, *J* = 11.7 Hz, H2/4), 3.09 (1H, d, *J* = 11.8 Hz, H2/4), 3.02 (1H, d, *J* = 11.8 Hz, H2/4), 1.79 (1H, s, H3), 1.35 (1H, d, *J* = 6.7 Hz, H6), 1.21 (1H, d, *J* = 6.8 Hz, H6).

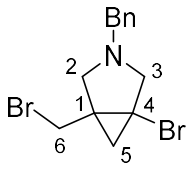
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 57.2, 51.1, 43.1, 36.7, 33.9, 22.8.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2871, 1434, 1223, 908.

HRMS (ES^+) calc. for $C_6H_{10}Br_2N$ $[M+H]^+$ 253.9174, found 253.9178.

m.p. 68 °C

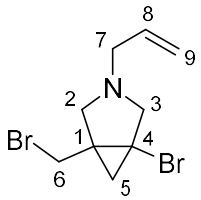
3-Benzyl-1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane (82)



To a solution of 1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **70** (500 mg, 1.96 mmol, 1.0 eq.) and NEt_3 (0.410 mL, 2.94 mmol, 1.5 eq.) in THF (8.0 mL) was added benzyl bromide (0.350 mL, 2.94 mmol, 1.5 eq.) and the mixture was stirred at 50 °C for 22 h. The mixture was concentrated under reduced pressure, then water (10 mL) was added and the mixture was extractd with Et_2O (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 98:2) gave the product (553 mg, 1.60 mmol, 82%) as a colourless oil.

Analytical data match that reported above.

3-Allyl-1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane (97)



To a solution of 1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **70** (500 mg, 1.96 mmol, 1.0 eq.) and NEt_3 (0.410 mL, 2.94 mmol, 1.5 eq.) in THF (8.0 mL) was added allyl bromide (0.255 mL, 2.94 mmol, 1.5 eq.) and the mixture was stirred at 50 °C for 22 h. The mixture was concentrated under reduced pressure, then water (10 mL) was added and the mixture was extractd with Et_2O (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 19:1) gave the product (474 mg, 1.61 mmol, 82%) as a colourless oil.

R_f 0.25 (19:1 pentane / EtOAc).

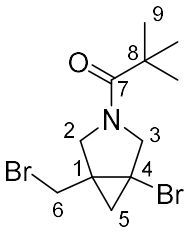
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.79 (1H, ddt, *J* = 16.7, 10.1, 6.4 Hz, H8), 5.18 (1H, dq, *J* = 17.1, 1.6 Hz, H9), 5.10 (1H, ddt, *J* = 10.2, 2.1, 1.2 Hz, H9), 3.60 (2H, s, H6), 3.34 (1H, d, *J* = 8.8 Hz, H2/3), 3.10 (2H, dq, *J* = 6.5, 1.7 Hz, H7), 3.05 (1H, d, *J* = 8.9 Hz, H2/3), 2.67 (1H, d, *J* = 8.7 Hz, H2/3), 2.53 (1H, d, *J* = 8.9 Hz, H2/3), 1.85 (1H, d, *J* = 5.7 Hz, H5), 1.05 (1H, d, *J* = 5.7 Hz, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 135.2, 117.5, 62.3, 57.5, 56.5, 41.1, 37.3, 32.7, 24.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3077, 2905, 2804, 1225, 923.

HRMS (ES^+) calc. for $C_9H_{14}Br_2N$ $[M+H]^+$ 293.9488, found 293.9488.

1-(1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexan-3-yl)-2,2-dimethylpropan-1-one (98)



To a solution of 1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **70** (500 mg, 1.96 mmol, 1.0 eq.) and NEt_3 (0.410 mL, 2.94 mmol, 1.5 eq.) in THF (8.0 mL) was added pivaloyl chloride (0.362 mL, 2.94 mmol, 1.5 eq.) and the mixture was stirred at rt for 1 h. The mixture was concentrated under reduced pressure, then water (10 mL) was added and the mixture was extractd with Et_2O (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 8:2) gave the product (491 mg, 1.45 mmol, 74%) as a white solid.

R_f 0.34 (8:2 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.38 (1H, d, *J* = 11.1 Hz, H2/3/6), 4.03 (1H, d, *J* = 11.2 Hz, H2/3/6), 3.73-3.70 (2H, m, H2/3/6), 3.65 (1H, d, *J* = 10.9 Hz, H2/3/6), 3.60 (1H, d, *J* = 11.0 Hz, H2/3/6), 1.28 (2H, s, H5), 1.23 (9H, s, H9).

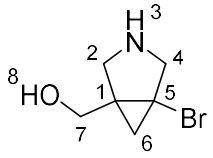
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 177.0, 56.9, 51.6, 39.1, 35.3, 30.4, 27.6, 25.7, 24.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2974, 1635, 1478, 1408, 1195.

HRMS (ES^+) calc. for $C_{11}H_{18}Br_2NO$ $[M+H]^+$ 337.9750, found 337.9749.

m.p. 35 °C

(5-Bromo-3-azabicyclo[3.1.0]hexan-1-yl)methanol (77)



To a solution of methyl 5-bromo-2-oxo-3-azabicyclo[3.1.0]hexane-1-carboxylate **76** (783 mg, 3.35 mmol, 1.0 eq.) in THF (24 mL) at 0 °C was added Red-Al (3.26 mL, 60% wt., 10.0 mmol, 3.0 eq.) dropwise, then the mixture was stirred at rt for 6 h. Rochelle salt solution sat. (20 mL) was added and the mixture was stirred until it became clear. The layers were separated, then the aqueous layer was extracted with a 3:1 mixture of $CHCl_3$:*i*PrOH (3 x 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give the product as a pale yellow solid (432 mg, 3.35 mmol, 67%), which was used in the next step without further purification.

R_f 0.07 (9:1 EtOAc / MeOH).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.93 (1H, d, *J* = 12.2 Hz, H2/4), 3.82 (1H, d, *J* = 12.2 Hz, H2/4), 3.34 (1H, d, *J* = 11.5 Hz, H2/4), 3.26 – 3.15 (2H, m, H7), 2.93 (1H, d, *J* = 11.7 Hz, H2/4), 2.15 (2H, s, H3/8), 1.18 (1H, d, *J* = 6.7 Hz, H6), 1.15 (1H, d, *J* = 6.9 Hz, H6).

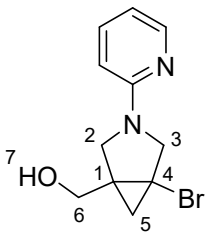
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 64.7, 57.2, 49.3, 40.0, 34.7, 19.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3306, 2874, 1686, 1442, 1083.

HRMS (ES^+) calc. for $C_6H_{11}BrNO$ $[M+H]^+$ 192.0019, found 192.0011.

m.p. 104 °C

(5-Bromo-3-(pyridin-2-yl)-3-azabicyclo[3.1.0]hexan-1-yl)methanol (100)



To a solution of (5-Bromo-3-azabicyclo[3.1.0]hexan-1-yl)methanol **77** (411 mg, 2.14 mmol, 1.0 eq.), $Pd(OAc)_2$ (24.0 mg, 0.107 mmol, 0.05 eq.), (±)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthalene (133 mg, 0.214 mmol, 0.1 eq.) and Cs_2CO_3 (1.39 g, 4.28 mmol, 2.0 eq.) in DMF (10.7 mL) was added 2-bromopyridine (0.204 mL, 2.14 mmol, 1.0 eq.) and the mixture was stirred at 80 °C for 6 h. Water (50 mL) and Et_2O (50 mL) were added and the mixture was washed with water (3 x 50 mL), with each water wash back-extracted with Et_2O (3 x 50 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane / EtOAc 6:4) gave the product (295 mg, 1.10 mmol, 51%) as a pale yellow solid.

R_f 0.14 (6:4 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.14 (1H, ddd, *J* = 5.0, 1.9, 0.9 Hz, Ar H), 7.45 (1H, ddd, *J* = 8.5, 7.2, 1.9 Hz, Ar H), 6.60 (1H, ddd, *J* = 7.2, 5.0, 0.9 Hz, Ar H), 6.36 (1H, dt, *J* = 8.5, 0.9 Hz, Ar H), 4.23 (1H, d, *J* = 10.0 Hz, H2/3), 4.05 (1H, d, *J* = 12.3 Hz, H6), 3.84 (1H, d, *J* = 12.3 Hz, H6), 3.79 – 3.67 (3H, m, H2/3), 2.02 (1H, br s, H7), 1.31 (1H, d, *J* = 6.6 Hz, H5), 1.29 (1H, d, *J* = 6.2 Hz, H5).

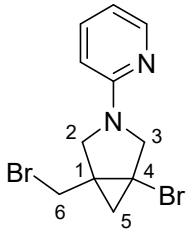
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 157.4, 148.3, 137.5, 113.0, 106.8, 64.6, 57.3, 49.9, 36.8, 34.3, 24.1.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3365, 2856, 1601, 1493, 1442.

HRMS (ES^+) calc. for $C_{11}H_{14}BrN_2O$ $[M+H]^+$ 269.0284, found 269.0277.

m.p. 89 °C

1-Bromo-5-(bromomethyl)-3-(pyridin-2-yl)-3-azabicyclo[3.1.0]hexane (101)



To a solution of **100** (296 mg, 1.10 mmol, 1.0 eq.) and CBr_4 (438 mg, 1.32 mmol, 1.2 eq.) in CH_2Cl_2 (5.0 mL) was added PPh_3 (346 mg, 1.32 mmol, 1.2 eq.). The mixture was stirred at rt for 30 min, then concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentante/EtOAc 9:1) gave the product (317 mg, 0.955 mmol, 87%) as a white solid.

R_f 0.31 (9:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.15 (1H, dd, *J* = 5.0, 1.9 Hz, Ar H), 7.47 (1H, ddd, *J* = 8.8, 7.0, 1.9 Hz, Ar H), 6.63 (1H, dd, *J* = 7.2, 5.1 Hz, Ar H), 6.38 (1H, d, *J* = 8.4 Hz, Ar H), 4.24 (1H, d, *J* = 9.9 Hz, H2/3/6), 3.87 (1H, d, *J* = 9.9 Hz, H2/3/6), 3.74 – 3.65 (3H, m, H2/3/6), 3.60 (1H, d, *J* = 9.9 Hz, H2/3/6), 1.50 (1H, d, *J* = 6.3 Hz, H5), 1.36 (1H, d, *J* = 6.3 Hz, H5).

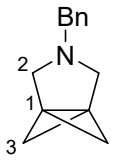
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 157.2, 148.3, 137.5, 113.3, 106.8, 57.1, 51.6, 39.8, 36.1, 33.4, 26.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2854, 1599, 1490, 1475, 1444.

HRMS (ES^+) calc. for $C_{11}H_{13}Br_2N_2$ $[M+H]^+$ 330.9440, found 330.9445.

m.p. 54 °C

3-(*N*-Benzyl)aza[3.1.1]propellane (102)

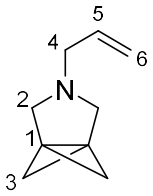


Prepared according to *General Procedure 4*, using 3-benzyl-1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **82** (399 mg, 1.16 mmol, 1.0 eq.) and *n*BuLi (1.10 mL, 1.05 M solution in hexanes, 1.16 mmol, 1.0 eq.). The mixture was stirred for 5 min. The product (7.6 mL, 0.15 M, 1.12 mmol, 97%) was obtained as a pale yellow solution. The concentration was determined using CH_2Cl_2 as an internal standard.

^{1}H NMR (400 MHz, C_6D_6) δ_H 7.25-7.12 (3H, m, Bn), 7.06 (2H, tt,, *J* = 6.9, 1.7 Hz, Bn), 3.37 (2H, s, Bn), 2.52 (2H, t, *J* = 1.4 Hz, H3), 2.46 (4H, s, H2). The other signal for the H3 protons is obscured by the THF signal.

^{13}C NMR (101 MHz, C_6D_6) δ_C 139.9, 128.6, 128.5, 127.1, 58.1, 57.8, 52.3, 21.1.

3-(*N*-Allyl)aza[3.1.1]propellane (103)

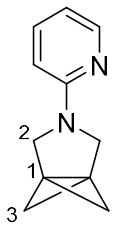


Prepared according to *General Procedure 4*, using 3-allyl-1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **97** (224 mg, 0.759 mmol, 1.0 eq.) and *n*BuLi (0.643 mL, 1.18 M solution in hexanes, 0.759 mmol, 1.0 eq.). The mixture was stirred for 5 min. The product (5.0 mL, 0.16 M, 0.780 mmol, 100%) was obtained as a colourless solution. The concentration was determined using CH_2Cl_2 as an internal standard.

^{1}H NMR (400 MHz, C_6D_6) δ_H 5.74 (1H, ddt, *J* = 17.2, 10.1, 6.3 Hz, H5), 5.02 (1H, dq, *J* = 17.1, 1.7 Hz, H6), 4.90 (1H, ddt, *J* = 10.1, 2.2, 1.3 Hz, H6), 2.85 (2H, dt, *J* = 6.3, 1.4 Hz, H4), 2.54 (2H, t, *J* = 1.3 Hz, H3), 2.48 (4H, s, H2). The other signal for the H3 protons is obscured by the THF signal.

^{13}C NMR (101 MHz, C_6D_6) δ_C 136.6, 115.8, 58.1, 56.6, 52.4, 33.4.

3-(*N*-Pyridin-2-yl)aza[3.1.1]propellane (104)

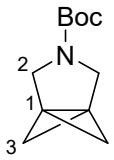


Prepared according to *General Procedure 4*, using 3-pyridin-2-yl-1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **101** (237 mg, 0.715 mmol, 1.0 eq.) and MeLi (0.581 mL, 1.23 M solution in Et_2O, 0.715 mmol, 1.0 eq.). The mixture was stirred for 1 h. The product (7.5 mL, 0.097 M, 0.727 mmol, 100%) was obtained as a pale yellow solution. The concentration was determined by integrating the ^1H signals in the product relative to the THF signals.

^{1}H NMR (400 MHz, C_6D_6) δ_H 8.15-8.11 (1H, m, Ar H), 7.13 (1H, m, Ar H), 6.35 (1H, ddd, *J* = 7.1, 5.0, 1.1 Hz, Ar H), 6.00-5.94 (1H, m, Ar H), 3.44 (4H, s, H2), 2.25-2.21 (2H, m, H3). The other signal from H3 is obscured by the THF signal.

^{13}C NMR (101 MHz, C_6D_6) δ_C 157.5, 148.3, 136.2, 111.6, 106.3, 52.3, 51.5, 21.6.

3-(*N*-Boc)aza[3.1.1]propellane (105)

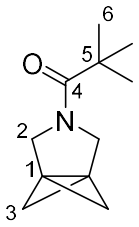


Prepared according to *General Procedure 4*, using 3-Boc-1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **83** (443 mg, 1.25 mmol, 1.0 eq.) and *n*BuLi (1.19 mL, 1.05 M solution in hexanes, 1.25 mmol, 1.0 eq.). The mixture was stirred for 5 min. The product (6.6 mL, 0.14 M, 0.945 mmol, 76%) was obtained as a yellow solution. The concentration was determined using CH_2Cl_2 as an internal standard.

^{1}H NMR (500 MHz, C_6D_6) δ_H 3.49 (2H, s, H2), 3.29 (2H, s, H2), 2.07 (2H, t, J = 1.6 Hz, H3), 1.41 (9H, s, Boc). The other signal for the H3 protons is obscured by the THF signal.

^{13}C NMR (126 MHz, C_6D_6) δ_C 153.5, 52.2, 51.4, 28.5, 22.7.

3-(*N*-Piv)aza[3.1.1]propellane (106)

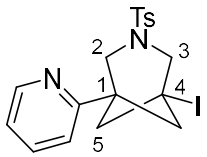


Prepared according to *General Procedure 4*, using 3-Piv-1-bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **98** (300 mg, 0.885 mmol, 1.0 eq.) and MeLi (0.719 mL, 1.23 M solution in Et_2O, 0.885 mmol, 1.0 eq.). The mixture was stirred for 1 h. The product (5.5 mL, 0.12 M, 0.672 mmol, 76%) was obtained as a colourless solution. The concentration was determined by integrating the ^1H signals in the product relative to the THF signals.

^{1}H NMR (400 MHz, C_6D_6) δ_H 2.24 (2H, t, *J* = 1.6 Hz, H3), 1.47 (2H, t, *J* = 1.5 Hz, H3), 1.06 (9H, s, H6). The signal for H2 is obscured by the THF signal.

^{13}C NMR (101 MHz, C_6D_6) δ_C 175.8, 52.4, 51.6, 38.4, 28.3, 27.0.

1-Iodo-5-(pyridin-2-yl)-3-tosyl-3-azabicyclo[3.1.1]heptane (86ae)



Prepared according to *General Procedure 3,* using 3-(*N*-tosyl)aza[3.1.1]propellane **85** (0.78 mL, 0.20 M, 156 μmol, 1.2 eq.), 2-iodopyridine (13.8 μL, 130 μmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (2.1 mg, 3.3 μmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 8:2) gave the product (5.1 mg, 11 μmol, 9%) as a yellow oil.

R_f 0.18 (8:2 pentane / EtOAc).

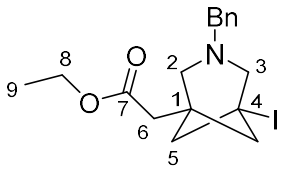
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.52 (1H, ddd, *J* = 4.9, 1.8, 0.9 Hz, Ar H), 7.77 – 7.70 (2H, m, Ts), 7.66 (1H, td, *J* = 7.7, 1.8 Hz, Ar H), 7.35 (2H, d, *J* = 7.6 Hz, Ts), 7.18 (1H, ddd, *J* = 7.6, 4.9, 1.1 Hz, Ar H), 7.06 (1H, dt, *J* = 7.9, 1.0 Hz, Ar H), 3.98 (2H, s, H2/3), 3.61 (2H, s, H2/3), 2.94 – 2.88 (2H, m, H5), 2.48 – 2.43 (2H, m, H5), 2.45 (3H, s, Ts).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 160.8, 149.6, 143.9, 137.0, 134.3, 130.1, 127.5, 122.5, 119.9, 59.3, 53.0, 49.1, 48.4, 22.4, 21.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2360, 1590, 1473, 1341, 1163.

HRMS (ES$^+$) calc. for $C_{18}H_{20}IN_2O_2S$ $[M+H]^+$ 455.0285, found 455.0287.

Ethyl 2-(3-benzyl-5-iodo-3-azabicyclo[3.1.1]heptan-1-yl)acetate (86af)



Prepared according to *General Procedure 3,* using 3-(*N*-Benzyl)aza[3.1.1]propellane **102** (1.00 mL, 0.15 M, 0.150 mmol, 1.2 eq.), ethyl 2-iodoacetate (14.8 µL, 0.125 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (2.1 mg, 3.1 µmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 19:1) gave the product (11.0 mg, 27.5 µmol, 22%) as a yellow oil.

R_f 0.22 (19:1 pentane / EtOAc).

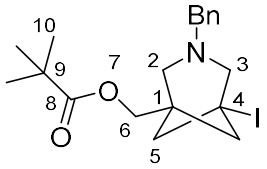
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.35 – 7.29 (5H, m, Bn), 4.09 (2H, q, *J* = 7.1 Hz, H8), 3.65 (2H, s, Bn), 3.26 (2H, s, H2/3), 2.69 (2H, s, H2/3), 2.57 – 2.52 (2H, m, H5), 2.51 – 2.45 (2H, m, H5), 2.37 (2H, s, H6), 1.22 (3H, t, *J* = 7.1 Hz, H9).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 170.7, 138.3, 128.8, 128.5, 127.2, 66.5, 60.6, 60.0, 58.1, 50.8, 42.9, 42.8, 27.7, 14.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 3027, 1738, 1494, 1336.

HRMS (ES$^+$) calc. for $C_{17}H_{23}INO_2$ $[M+H]^+$ 400.0768, found 400.0756.

(3-Benzyl-5-iodo-3-azabicyclo[3.1.1]heptan-1-yl)methyl pivalate (86ag)



Prepared according to *General Procedure 3,* using 3-(*N*-Benzyl)aza[3.1.1]propellane **102** (1.00 mL, 0.15 M, 0.150 mmol, 1.2 eq.), iodomethylpivalate (19.4 µL, 0.125 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (2.1 mg, 3.1 µmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 19:1) gave the product (16.1 mg, 37.7 µmol, 30%) as a yellow solid.

R_f 0.22 (19:1 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.34-7.29 (4H, m, Bn), 7.27-7.24 (1H, m, Bn), 3.88 (2H, s, Bn), 3.67 (2H, s, H26), 3.30 (2H, s, H3), 2.64 (2H, s, H2), 2.50 – 2.45 (2H, m, H5), 2.44 – 2.38 (2H, m, H5), 1.18 (9H, s, H10).

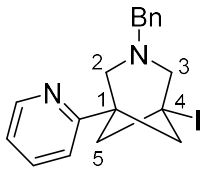
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 178.3, 138.2, 128.8, 128.5, 127.3, 67.0, 66.9, 60.0, 55.8, 48.0, 45.3, 39.1, 27.4, 27.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2801, 1732, 1282, 1154, 1029.

HRMS (ES$^+$) calc. for $C_{19}H_{27}INO_2$ $[M+H]^+$ 428.1081, found 428.1071.

m.p. 43 °C

3-Benzyl-1-iodo-5-(pyridin-2-yl)-3-azabicyclo[3.1.1]heptane (86ah)



Prepared according to *General Procedure 3,* using 3-(*N*-Benzyl)aza[3.1.1]propellane **102** (1.00 mL, 0.15 M, 0.150 mmol, 1.2 eq.), 2-iodopyridine (13.3 μL, 0.125 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (2.1 mg, 3.1 μmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 9:1) gave the product (4.4 mg, 12 μmol, 9%) as a yellow oil.

R_f 0.13 (9:1 pentane / EtOAc).

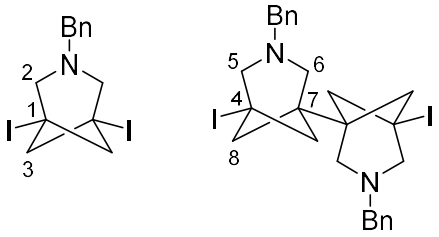
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.51 (1H, dt, *J* = 4.8, 1.4 Hz, Ar H), 7.60 (1H, td, *J* = 7.7, 1.9 Hz, Ar H), 7.37 – 7.22 (5H, m, Ar H), 7.11 (1H, ddd, *J* = 7.5, 4.9, 1.1 Hz, Ar H), 7.04 (1H, dt, *J* = 7.8, 1.1 Hz, Ar H), 3.73 (2H, s, Bn), 3.39 (2H, s, H2/3), 2.98 (2H, s, H2/3), 2.93 – 2.81 (4H, m, H5).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 149.4, 136.7, 129.2, 128.9, 128.5, 128.4, 127.3, 121.8, 119.8, 66.6, 60.1, 53.6, 50.2, 29.9, 21.6.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2799, 1589, 1493, 1431, 1211.

HRMS (ES$^+$) calc. for $C_{18}H_{20}IN_2$ $[M+H]^+$ 391.0666, found 391.0660.

3-Benzyl-1,5-diiodo-3-azabicyclo[3.1.1]heptane (86ai) and 3,3'-dibenzyl-5,5'-diiodo-3,3'-diaza-1,1'-bi(bicyclo[3.1.1]heptane) (86ai')



To a stirred solution of 3-(*N*-benzyl)aza-[3.1.1]propellane **102** (1.00 mL, 0.15 M in THF, 0.150 mmol, 1.0 eq.) was added iodine (38.1 mg, 0.150 mmol, 1.0 eq.) and the mixture was stirred at rt for 30 min. The mixture was concentrated under reduced pressure, then purification by column chromatography (SiO_2, pentane/EtOAc 98:2) gave the inseparable products **86ai** and **86ai'** (31.3 mg) as a white solid in a 1.4:1.0 ratio of **86ai:86ai'** as determined from the ^{1}H NMR spectrum, with 57% overall yield.

R_f 0.17 (98:2 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.36-7.27 (15H, m, Bn), 3.66 (4H, s, Bn), 3.64 (2H, s, Bn), 3.21 (4H, s, H2), 3.18 (4H, s, H5/6), 3.14-3.11 (2H, m, H3), 3.09 (4H, s, H5/6), 3.07-3.02 (2H, m, H3), 3.03-2.98 (4H, m, H8), 2.97-2.92 (4H, m, H8).

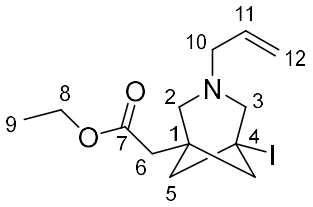
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 137.6, 128.8, 128.6, 127.5, 65.0, 64.9, 62.3, 59.6, 59.5, 57.9, 56.2, 49.8, 23.4, 20.4. Note: the aromatic Bn signals are identical in each of these two compounds.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2801, 1494, 1454, 1212, 1159.

HRMS (ES^+) calc. for $C_{13}H_{16}I_2N$ $[M+H]^+$ 439.9367, found 439.9348.

m.p. 60 °C

Ethyl 2-(3-allyl-5-iodo-3-azabicyclo[3.1.1]heptan-1-yl)acetate (86aj)



Prepared according to *General Procedure 3,* using 3-(*N*-Allyl)aza[3.1.1]propellane **103** (0.750 mL, 0.16 M, 0.120 mmol, 1.2 eq.), ethyl 2-iodoacetate (11.8 µL, 0.100 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.6 mg, 2.5 µmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 9:1) gave the product (20.4 mg, 58.4 µmol, 58%) as a colourless oil.

R_f 0.28 (9:1 pentane / EtOAc).

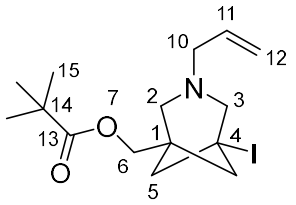
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.83 (1H, ddt, *J* = 16.7, 10.2, 6.5 Hz, H11), 5.19 (1H, dq, *J* = 17.2, 1.7 Hz, H12), 5.12 (1H, d, *J* = 10.2 Hz, H12), 4.11 (2H, q, *J* = 7.1 Hz, H8), 3.25 (2H, s, H2/3), 3.12 (2H, d, *J* = 6.5 Hz, H10), 2.68 (2H, s, H2/3), 2.48 (4H, s, H5), 2.39 (2H, s, H6), 1.24 (3H, t, *J* = 7.1 Hz, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.7, 134.9, 117.8, 66.3, 60.6, 58.8, 58.0, 50.7, 43.0, 42.7, 27.6, 14.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2788, 1733, 1369, 1236, 1191.

HRMS (ES^+) calc. for $C_{13}H_{20}INO_2Na$ $[M+Na]^+$ 372.0431, found 372.0431.

(3-Allyl-5-iodo-3-azabicyclo[3.1.1]heptan-1-yl)methyl pivalate (86ak)



Prepared according to *General Procedure 3,* using 3-(*N*-Allyl)aza[3.1.1]propellane **103** (0.750 mL, 0.16 M, 0.120 mmol, 1.2 eq.), iodomethylpivalate (15.5 µL, 0.100 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.6 mg, 2.5 µmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 9:1) gave the product (10.2 mg, 27.0 µmol, 27%) as a colourless oil.

R_f 0.39 (9:1 pentane / EtOAc).

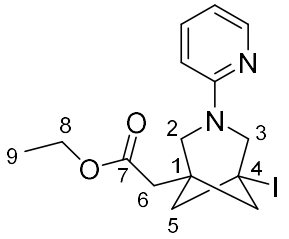
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.84 (1H, ddt, *J* = 16.8, 10.1, 6.5 Hz, H11), 5.21 (1H, dq, *J* = 17.2, 1.5 Hz, H12), 5.14 (1H, ddt, *J* = 10.1, 2.0, 1.2 Hz, H12), 3.91 (2H, s, H6), 3.28 (2H, s, H3), 3.14 (2H, dt, *J* = 6.5, 1.3 Hz, H10), 2.66 (2H, s, H2), 2.50 – 2.43 (2H, m, H5), 2.39 – 2.32 (2H, m, H5), 1.21 (9H, s, H15).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 178.3, 134.7, 117.9, 67.0, 66.8, 58.8, 55.8, 47.9, 45.2, 39.1, 27.4. Note: the signals for C4 and C15 overlap in this spectrum.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2975, 2790, 1733, 1480, 1282, 1153.

HRMS (ES$^+$) calc. for $C_{15}H_{25}INO_2$ $[M+H]^+$ 378.0925, found 378.0918.

Ethyl 2-(5-iodo-3-(pyridin-2-yl)-3-azabicyclo[3.1.1]heptan-1-yl)acetate (86al)



Prepared according to *General Procedure 3,* using 3-(*N*-pyridin-2-yl)aza[3.1.1]propellane **104** (1.01 mL, 0.097 M, 98.4 μmol, 1.2 eq.), ethyl 2-iodoacetate (9.71 μL, 82.0 μmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.3 mg, 2.1 μmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 8:2) gave the product (16.9 mg, 43.8 μmol, 53%) as a yellow oil.

R_f 0.37 (8:2 pentane / EtOAc).

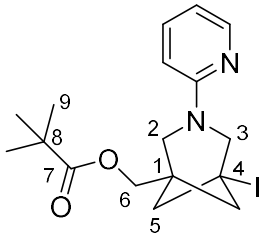
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.21 (1H, dd, *J* = 4.9, 1.9 Hz, Ar H), 6.64 (1H, dd, *J* = 7.1, 4.9 Hz, Ar H), 6.48 (1H, d, *J* = 8.6 Hz, Ar H), 4.15 (2H, q, *J* = 7.2 Hz, Ar H), 4.07 (2H, s, H2/3), 3.54 (2H, s, H2/3), 2.73-2.68 (2H, m, H5), 2.57 (2H, s, H6), 2.49 – 2.38 (2H, m, H5), 1.27 (3H, t, *J* = 7.1 Hz, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 170.4, 157.1, 148.0, 137.4, 112.7, 105.2, 60.8, 60.3, 52.8, 49.5, 42.3, 41.6, 25.1, 14.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2980, 1731, 1598, 1474, 1372.

HRMS (ES$^+$) calc. for $C_{15}H_{20}IN_2O_2$ $[M+H]^+$ 387.0564, found 387.0572.

(5-Iodo-3-(pyridin-2-yl)-3-azabicyclo[3.1.1]heptan-1-yl)methyl pivalate (86am)



Prepared according to *General Procedure 3,* using 3-(*N*-pyridin-2-yl)aza[3.1.1]propellane **104** (1.01 mL, 0.097 M, 98.4 μmol, 1.2 eq.), iodomethylpivalate (12.7 μL, 82.0 μmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.3 mg, 2.1 μmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 9:1) gave the product (9.7 mg, 23 μmol, 29%) as a white solid.

R_f 0.19 (9:1 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 8.22 (1H, dd, *J* = 5.1, 1.9 Hz, Ar H), 7.56 – 7.49 (1H, m, Ar H), 6.66 (1H, dd, *J* = 7.1, 5.0 Hz, Ar H), 6.49 (1H, d, *J* = 8.6 Hz, Ar H), 4.10 (2H, s, H2/3/6), 4.09 (2H, s, H2/3/6), 3.56 (2H, s, H2/3/6), 2.71 – 2.65 (2H, m, H5), 2.33 – 2.28 (2H, m, H5), 1.23 (9H, s, H9).

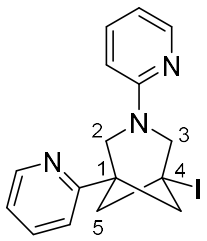
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 178.3, 157.1, 147.9, 137.6, 112.9, 105.3, 66.9, 60.7, 51.0, 46.8, 44.0, 39.2, 27.4, 24.7.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2974, 1730, 1599, 1485, 1438, 1153.

HRMS (ES$^+$) calc. for $C_{17}H_{24}IN_2O_2$ $[M+H]^+$ 415.0877, found 415.0886.

m.p. 95 °C

1-Iodo-3,5-di(pyridin-2-yl)-3-azabicyclo[3.1.1]heptane (86an)



Prepared according to *General Procedure 3,* using 3-(*N*-pyridin-2-yl)aza[3.1.1]propellane **104** (1.01 mL, 0.097 M, 98.4 μmol, 1.2 eq.), 2-iodopyridine (8.7 μL, 82 μmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.3 mg, 2.1 μmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 7:3) gave the product (6.2 mg, 16 μmol, 20%) as a yellow oil.

R_f 0.29 (7:3 pentane / EtOAc).

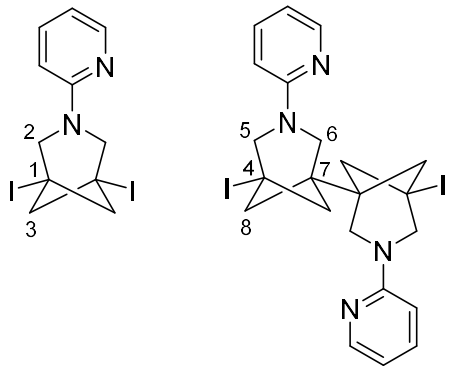
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.58 (1H, ddd, *J* = 5.0, 1.9, 0.7 Hz, Ar H), 8.21 (1H, ddd, *J* = 5.0, 2.0, 0.9 Hz, Ar H), 7.68 (1H, td, *J* = 7.7, 1.8 Hz, Ar H), 7.51 (1H, ddd, *J* = 8.8, 7.1, 2.0 Hz, Ar H), 7.19 (2H, m, Ar H), 6.69 – 6.61 (1H, m, Ar H), 6.52 (1H, d, *J* = 8.6 Hz, Ar H), 4.21 (2H, s, H2/3), 3.80 (2H, s, H2/3), 3.16 – 3.06 (2H, m, H5), 2.78 – 2.68 (2H, m, H5).

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 161.8, 157.1, 149.6, 148.0, 137.6, 136.8, 122.3, 120.1, 112.8, 105.3, 60.4, 53.7, 49.3, 49.1, 29.9.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2852, 1598, 1485, 1471, 1438,

HRMS (ES$^+$) calc. for $C_{16}H_{17}IN_3$ $[M+H]^+$ 378.0462, found 378.0477.

1,5-Diiodo-3-(pyridin-2-yl)-3-azabicyclo[3.1.1]heptane (86ao) and 5,5'-diiodo-3,3'-di(pyridin-2-yl)-3,3'-diaza-1,1'-bi(bicyclo[3.1.1]heptane) (86ao')



To a stirred solution of 3-(*N*-pyridin-2-yl)aza-[3.1.1]propellane **104** (1.00 mL, 0.097 M in THF, 97.0 μmol, 1.0 eq.) was added iodine (24.6 mg, 97.0 μmol, 1.0 eq.) and the mixture was stirred at rt for 30 min. The mixture was concentrated under reduced pressure, then purification by column chromatography (SiO_2, pentane/EtOAc 19:1) gave the inseparable products **86ao** and **86ao'** (16.0 mg) as a white solid in a 1.7:1.0 ratio of **86ao**:**86ao'** as determined from the ^{1}H NMR spectrum, with 46% overall yield.

R_f 0.31 (19:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 8.22 (3H, ddd, *J* = 6.0, 2.1, 1.1 Hz, Ar H), 7.52 (3H, ddt, *J* = 8.7, 7.2, 1.7 Hz, Ar H), 6.68 (3H, ddd, *J* = 6.8, 4.8, 1.9 Hz, Ar H), 6.46 (3H, dd, *J* = 8.6, 4.2 Hz, Ar H), 4.03 (4H, s, H2), 4.00 (4H, s, H5/6), 3.91 (4H, s, H5/6), 3.36 – 3.27 (2H, m, H3), 3.26 – 3.16 (4H, m, H8), 2.98 – 2.89 (2H, m, H3), 2.88 – 2.81 (4H, m, H8).

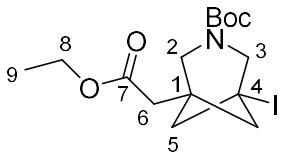
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 148.0, 137.7, 113.4, 113.3, 105.2, 105.1, 59.1, 58.9, 56.8, 56.5, 55.1, 48.6, 21.5, 18.6. Note: some of the aromatic peaks overlap between the two compounds.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2852, 1598, 1483, 1436, 1372.

HRMS (ES^+) calc. for $C_{11}H_{13}I_2N_2$ $[M+H]^+$ 426.9163, found 426.9185.

m.p. 101 °C

***tert*-Butyl 1-(2-ethoxy-2-oxoethyl)-5-iodo-3-azabicyclo[3.1.1]heptane-3-carboxylate (86ap)**



Prepared according to *General Procedure 3,* using 3-(*N*-Boc)aza[3.1.1]propellane **105** (0.900 mL, 0.14 M, 0.126 mmol, 1.2 eq.), ethyl 2-iodoacetate (12.4 μL, 0.105 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.7 mg, 2.6 μmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 9:1) gave the product (18.3 mg, 44.8 μmol, 43%) as a colourless oil.

R_f 0.23 (9:1 pentane / EtOAc).

^{1}H NMR (500 MHz, $CDCl_3$) δ_H 4.18 – 4.07 (2H, m, H8), 3.94 (s) and 3.91 (s) (2H, H2/3), 3.39 (s) and 3.38 (s) (2H, H2/3), 2.65 – 2.54 (2H, m, H5), 2.46 (s) and 2.45 (s) (2H, H6), 2.36 – 2.28 (2H, m, H5), 1.48 (s) and 1.46 (s) (9H, Boc), 1.30-1.23 (3H, m, H9)

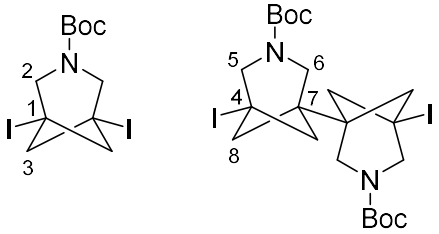
^{13}C NMR (126 MHz, $CDCl_3$) δ_C 170.3, 170.2, 154.9, 154.9, 60.8, 59.2, 58.9, 51.8, 51.6, 49.0, 48.9, 42.2, 42.1, 41.2, 41.2, 28.6, 28.6, 24.6, 23.8, 14.4.

Note: the ^{1}H and ^{13}C spectra show additional signals due to the presence of rotamers.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2978, 1734, 1694, 1385, 1167.

HRMS (ES$^+$) calc. for $C_{15}H_{24}INO_4Na$ $[M+Na]^+$ 432.0642, found 432.0638.

***tert*-Butyl 1,5-diiodo-3-azabicyclo[3.1.1]heptane-3-carboxylate (86aq) and di-*tert*-butyl 5,5'-diiodo-3,3'-diaza[1,1'-bi(bicyclo[3.1.1]heptane)]-3,3'-dicarboxylate (86aq')**



To a stirred solution of 3-(*N*-Boc)aza-[3.1.1]propellane **105** (0.900 mL, 0.14 M in THF, 0.126 mmol, 1.0 eq.) was added iodine (32.0 mg, 0.126 mmol, 1.0 eq.) and the mixture was stirred at rt for 30 min. The mixture was concentrated under reduced pressure, then purification by column chromatography (SiO_2, pentane/EtOAc 19:1) gave the inseparable products **86aq** and **86aq'** (29.6 mg) as a white solid in a 2.0:1.0 ratio of **86aq**:**86aq'** as determined from the ^{1}H NMR spectrum, with 60% overall yield.

R_f 0.32 (19:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.89 (2H, s, H2), 3.86 (4H, s, H2/5/6), 3.82 (2H, s, H5/6), 3.77 (2H, s, H5/6), 3.74 (2H, s, H5/6), 3.25 – 3.17 (2H, m, H3/8), 3.14 – 3.07 (2H, m, H3/8), 2.85 – 2.78 (2H, m, H3/8), 2.76 – 2.70 (2H, m, H3/8), 1.47 (27H, s, Boc).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 154.1, 154.1, 153.9, 80.8, 80.8, 80.8, 58.1, 57.9, 57.7, 57.5, 56.2, 55.5, 55.1, 54.6, 48.0, 47.8, 28.5, 21.1, 20.4, 18.1, 17.4.

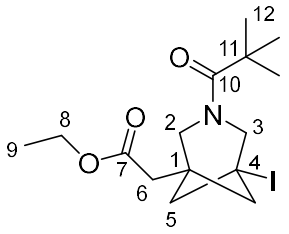
Note: extra signals in the ^{1}H and ^{13}C NMR are due to the presence of rotamers.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2976, 1682, 1391, 1356, 1183.

HRMS (ES$^+$) calc. for $C_{11}H_{17}I_2NO_2Na$ $[M+Na]^+$ 471.9241, found 471.9223.

m.p. Decomposition at 120 °C

Ethyl 2-(5-iodo-3-pivaloyl-3-azabicyclo[3.1.1]heptan-1-yl)acetate (86ar)



Prepared according to *General Procedure 3,* using 3-(*N*-Piv)aza[3.1.1]propellane **106** (1.00 mL, 0.12 M, 0.120 mmol, 1.2 eq.), ethyl 2-iodoacetate (11.8 μL, 0.100 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.6 mg, 2.5 μmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 8:2) gave the product (21.3 mg, 54.2 μmol, 54%) as a yellow oil.

R_f 0.26 (8:2 pentane / EtOAc).

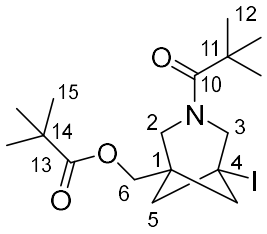
^{1}H NMR (600 MHz, $CDCl_3$) δ_H 4.18 (2H, s, H2/3), 4.13 (2H, q, *J* = 7.1 Hz, H8), 3.66 (2H, s, H2/3), 2.62 – 2.55 (2H, m, H5), 2.47 (2H, s, H6), 2.35 – 2.29 (2H, m, H5), 1.29 (9H, s, H12), 1.25 (3H, t, *J* = 7.1 Hz, H9).

^{13}C NMR (151 MHz, $CDCl_3$) δ_C 177.4, 170.2, 60.9, 60.5, 53.1, 49.0, 42.8, 42.2, 41.6, 39.6, 28.2, 14.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2977, 1731, 1627, 1358, 1188.

HRMS (ES^+) calc. for $C_{15}H_{25}INO_3$ $[M+H]^+$ 394.0874, found 394.0868.

5-Iodo-3-pivaloyl-3-azabicyclo[3.1.1]heptan-1-yl)methyl pivalate (86as)



Prepared according to *General Procedure 3,* using 3-(*N*-Piv)aza[3.1.1]propellane **106** (1.00 mL, 0.12 M, 0.120 mmol, 1.2 eq.), iodomethylpivalate (15.6 μL, 0.100 mmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (1.6 mg, 2.5 μmol, 2.5 mol%). The mixture was stirred and irradiated for 4 h. Purification by column chromatography (SiO_2, pentane / EtOAc 8:2) gave the product (6.8 mg, 16 μmol, 16%) as a white solid.

R_f 0.41 (8:2 pentane / EtOAc).

^{1}H NMR (600 MHz, $CDCl_3$) δ_H 4.22 (2H, s, H2/3), 4.01 (2H, s, H2/3), 3.64 (2H, s, H6), 2.62 – 2.54 (2H, m, H5), 2.23 – 2.17 (2H, m, H5), 1.31 (9H, s, H12), 1.21 (9H, s, H15).

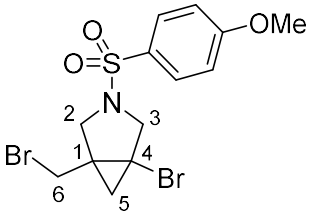
^{13}C NMR (151 MHz, $CDCl_3$) δ_C 178.2, 177.6, 66.8, 46.4, 39.7, 39.1, 28.6, 28.2, 27.4. Note: the signals for C2 and C3 are too broad to be observed. The signal for C4 overlaps with one of C12 or C15.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2973, 1732, 1630, 1479, 1402, 1359, 1152.

HRMS (ES$^+$) calc. for $C_{17}H_{29}INO_3$ $[M+H]^+$ 422.1187, found 422.1184.

m.p. 78 °C

1-Bromo-5-(bromomethyl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane (107a)



To a solution of 1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **70** (500 mg, 1.96 mmol, 1.0 eq.) in a mixture of THF (2.0 mL) and $NaHCO_3$ (aq. sat. 2.0 mL) was added 4-methoxybenzenesulfonyl chloride (608 mg, 2.94 mmol, 1.5 eq.) and the mixture was stirred at rt for 1 h. Water (10 mL) was added and the mixture was extractd with Et_2O (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 8:2) gave the product (715 mg, 1.68 mmol, 86%) as a white solid.

R_f 0.29 (8:2 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.73 (2H, d, *J* = 8.9 Hz, Ar H), 7.02 (2H, d, *J* = 8.9 Hz, Ar H), 3.94 (1H, d, *J* = 9.3 Hz, H2/3), 3.89 (3H, s, Me), 3.63 (1H, d, *J* = 9.5 Hz, H2/3), 3.52 (1H, d, *J* = 11.1 Hz, H6), 3.47 (1H, d, *J* = 11.1 Hz, H6), 3.23 (1H, d, *J* = 9.4 Hz, H2/3), 3.19 (1H, d, *J* = 9.4 Hz, H2/3), 1.57 (1H, d, *J* = 6.7 Hz, H5), 1.20 (1H, d, *J* = 6.7 Hz, H5).

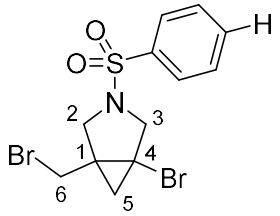
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 163.5, 129.8, 127.7, 114.6, 56.5, 55.8, 51.6, 38.1, 34.9, 32.8, 24.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 1596, 1498, 1261, 1161, 1100.

HRMS (ES^+) calc. for $C_{13}H_{15}Br_2NO_3SNa$ $[M+Na]^+$ 445.9032, found 445.9024.

m.p. 90 °C

1-Bromo-5-(bromomethyl)-3-(phenylsulfonyl)-3-azabicyclo[3.1.0]hexane (107b)



To a solution of 1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **70** (500 mg, 1.96 mmol, 1.0 eq.) in a mixture of THF (2.0 mL) and $NaHCO_3$ (aq. sat. 2.0 mL) was added benzenesulfonyl chloride (0.375 mL, 2.94 mmol, 1.5 eq.) and the mixture was stirred at rt for 1 h. Water (10 mL) was added and the mixture was extractd with Et_2O (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 9:1) gave the product (633 mg, 1.60 mmol, 82%) as a white solid.

R_f 0.20 (9:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.81 (2H, d, *J* = 7.3 Hz, Ar H), 7.65 (1H, t, *J* = 7.3 Hz, Ar H), 7.58 (2H, t, *J* = 7.5 Hz, Ar H), 3.98 (1H, d, *J* = 9.4 Hz, H2/3), 3.68 (1H, d, *J* = 9.6 Hz, H2/3), 3.53 (1H, d, *J* = 11.1 Hz, H6), 3.48 (1H, d, *J* = 11.1 Hz, H6), 3.28 (1H, d, *J* = 9.5 Hz, H2/3), 3.24 (1H, d, *J* = 9.5 Hz, H2/3), 1.53 (1H, d, *J* = 6.7 Hz, H5), 1.21 (1H, d, *J* = 6.7 Hz, H5).

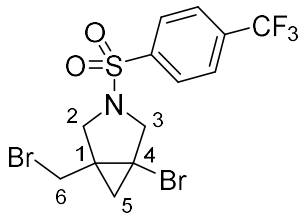
^{13}C NMR (101 MHz, $CDCl_3$) δ_C 136.4, 133.4, 129.5, 127.6, 56.6, 51.7, 38.0, 34.7, 32.8, 24.5.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2865, 1476, 1352, 1228, 1168, 1101.

HRMS (ES^+) calc. for $C_{12}H_{14}Br_2NO_2S$ $[M+H]^+$ 393.9107, found 393.9112.

m.p. 84 °C

1-Bromo-5-(bromomethyl)-3-((4-(trifluoromethyl)phenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane (107c)



To a solution of 1-Bromo-5-(bromomethyl)-3-azabicyclo[3.1.0]hexane **3** (500 mg, 1.96 mmol, 1.0 eq.) in a mixture of THF (2.0 mL) and $NaHCO_3$ (aq. sat. 2.0 mL) was added 4-(trifluoromethyl)benzenesulfonyl chloride (720 mg, 2.94 mmol, 1.5 eq.) and the mixture was stirred at rt for 1 h. Water (10 mL) was added and the mixture was extractd with Et_2O (3 x 10 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography (SiO_2, pentane/EtOAc 19:1) gave the product (753 mg, 1.63 mmol, 83%) as a white solid.

R_f 0.13 (19:1 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.94 (2H, d, *J* = 8.2 Hz, Ar H), 7.84 (2H, d, *J* = 8.2 Hz, Ar H), 4.02 (1H, d, *J* = 9.4 Hz, H2/3), 3.71 (1H, d, *J* = 9.6 Hz, H2/3), 3.53 (1H, d, *J* = 11.1 Hz, H6), 3.49 (1H, d, *J* = 11.1 Hz, H6), 3.29 (1H, d, *J* = 9.4 Hz, H2/3), 3.26 (1H, d, *J* = 9.5 Hz, H2/3), 1.56 (1H, d, *J* = 6.8 Hz, H5), 1.26 (1H, d, *J* = 6.8 Hz, H5).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 140.2, 135.0 (q, *J* = 33.1 Hz), 126.7 (q, *J* = 3.8 Hz), 123.3 (q, *J* = 273.4 Hz), 56.6, 51.8, 37.6, 34.5, 32.8, 24.5.

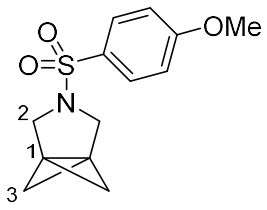
^{19}F NMR (377 MHz, $CDCl_3$) δ_F -63.1.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 1405, 1358, 1171, 1133, 1107.

HRMS (ES^+) calc. for $C_{13}H_{13}Br_2F_3NO_2S$ $[M+H]^+$ 461.8980, found 461.8994.

m.p. 96 °C

3-((4-Methoxyphenyl)sulfonyl)aza[3.1.1]propellane (108a)

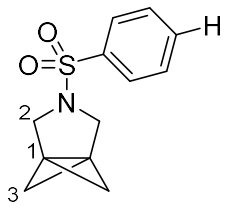


Prepared according to *General Procedure 4*, using 1-bromo-5-(bromomethyl)-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane **107a** (500 mg, 1.18 mmol, 1.0 eq.) and MeLi (0.956 mL, 1.23 M solution in Et_2O, 1.18 mmol, 1.0 eq.). The mixture was stirred for 1 h. The product (7.6 mL, 0.15 M, 1.11 mmol, 94%) was obtained as a colourless solution. The concentration was determined by integrating the ^1H signals in the product relative to the THF signals.

^{1}H NMR (500 MHz, C_6D_6) δ_H 7.67 (2H, d, *J* = 8.8 Hz, Ar H), 6.74 (2H, d, *J* = 8.9 Hz, Ar H), 3.38 (3H, s, Me), 3.18 (4H, s, H2), 2.07 (2H, t, *J* = 1.7 Hz, H3), 1.33 (2H, t, *J* = 1.7 Hz, H3).

^{13}C NMR (126 MHz, C_6D_6) δ_C 163.3, 123.0, 129.5, 114.4, 55.3, 53.6, 52.2, 22.4.

3-(Phenylsulfonyl)aza[3.1.1]propellane (108b)

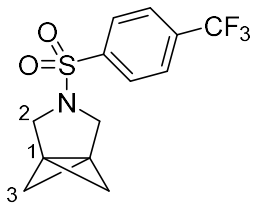


Prepared according to *General Procedure 4*, using 1-bromo-5-(bromomethyl)-3-(phenylsulfonyl)-3-azabicyclo[3.1.0]hexane **107b** (365 mg, 0.924 mmol, 1.0 eq.) and MeLi (0.751 mL, 1.23 M solution in Et_2O, 0.924 mmol, 1.0 eq.). The mixture was stirred for 1 h. The product (4.7 mL, 0.18 M, 0.845 mmol, 92%) was obtained as a pale yellow solution. The concentration was determined by integrating the ^1H signals in the product relative to the THF signals.

^{1}H NMR (400 MHz, C_6D_6) δ_H 7.72–7.67 (2H, m, Ar H), 7.27–7.17 (3H, m, Ar H), 3.16 (4H, s, H2), 2.02 (2H, t, *J* = 1.7 Hz, H3), 1.32 (2H, t, *J* = 1.7 Hz, H3).

^{13}C NMR (101 MHz, C_6D_6) δ_C 137.9, 132.7, 129.3, 127.7, 53.6, 52.1, 22.5.

3-((4-(trifluoromethyl)phenyl)sulfonyl)aza[3.1.1]propellane (108c)



Prepared according to *General Procedure 4*, using 1-bromo-5-(bromomethyl)-3-((4-(trifluoromethyl)phenyl)sulfonyl)-3-azabicyclo[3.1.0]hexane **107c** (399 mg, 0.862 mmol, 1.0 eq.) and MeLi (0.700 mL, 1.23 M solution in Et_2O, 0.862 mmol, 1.0 eq.). The mixture was stirred for 1 h. The product (5.2 mL, 0.14 M, 0.704 mmol, 82%) was obtained as a pale yellow solution. The concentration was determined by integrating the ^1H signals in the product relative to the THF signals.

^{1}H NMR (400 MHz, C_6D_6) δ_H 7.77 (2H, d, *J* = 8.1 Hz, Ar H), 7.55 (2H, d, *J* = 8.3 Hz, Ar H), 3.18 (4H, s, H2), 2.10 (2H, t, *J* = 1.7 Hz, H3), 1.37 (2H, t, *J* = 1.6 Hz, H3)

^{13}C NMR (101 MHz, C_6D_6) δ_C 141.8, 134.0 (q, *J* = 32.3 Hz), 128.4, 126.53 (q, *J* = 3.6 Hz), 124.1 (q, *J* = 273.3 Hz), 53.7, 52.1, 22.6.

^{19}F NMR (376 MHz, C_6D_6) δ_F -63.4.

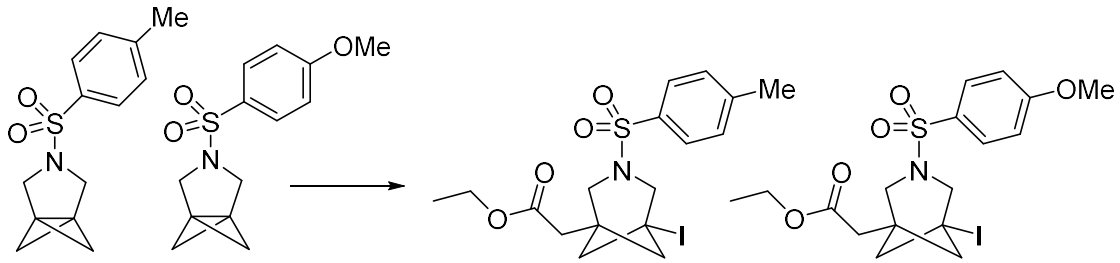
6.3. Hammett plot

The rates of reaction of different propellanes were compared *via* competition experiments. The reaction was stopped before going to completion to ensure the concentration of propellanes did not become limiting. The reaction could not be run with excess propellanes, because this led to the formation of complex mixtures of mixed staffanes.

General procedure 5 for competition experiments:

To a solution of *fac*-Ir(ppy)$_3$ (1.6 mg, 2.5 μmol, 2.5 mol%) in *t*BuCN (0.5 mL) was added propellane A solution (60 μmol, 0.60 eq.) and propellane B solution (60 μmol, 0.60 eq.), then ethyl 2-iodoacetate (11.8 μL, 100 μmol, 1.0 eq.). The mixture was stirred and irradiated with blue LEDs (Kessil PR160, 456 nm) for 10 sec, then iodine (254 mg, 1.00 mmol, 10 eq.) was immediately added (to quickly react with all leftover propellanes and generate diiodoBCHeps with higher R_f values than the products) and the mixture was stirred for a further 5 min. Thee, sat. $Na_2S_2O_3$ solution (7 mL) was added and the mixture was extracted with Et_2O (3 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Column chromatography (SiO_2) was used to separate the diiodoBCHeps from the product BCHeps. The two product BCHeps were isolated together and the relative amounts of each were determined by comparing the integration of the aromatic ^{1}H signals. A reference sample for each of the product BCHeps was obtained either by a second column to separate the two products, or by an independent synthesis. Each competition experiment was repeated and the average of the two results used for the Hammett plot.

Competition experiment 1: 3-(*N*-tosyl)aza[3.1.1]propellane (85) vs 3-((4-Methoxyphenyl)sulfonyl)aza[3.1.1]propellane (108a)



The competition experiment was performed according to *General Procedure 5*, using 3-(*N*-tosyl)aza[3.1.1]propellane **85** (0.30 mL, 0.20 M, 60 μmol) and 3-((4-methoxyphenyl)sulfonyl)aza[3.1.1]propellane **108a** (0.40 mL, 0.15 M, 60 μmol). The diiodoBCHeps were separated from the product BCHeps by column chromatography (SiO_2, pentane / EtOAc 19:1 to 8:2).

Ratio of total product BCHeps to total diiodoBCHeps (as determined by ^1H NMR before column):

Test 1 – 1.00 : 1.84

Test 2 – 1.00 : 1.14

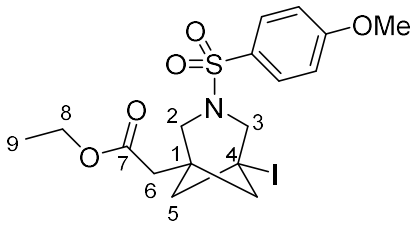
Ratio of product **86b** to product **86at**:

Test 1 – 1.00 : 1.13

Test 2 – 1.00 : 1.13

A reference sample of ethyl 2-(5-iodo-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.1]heptan-1-yl)acetate **86at** was obtained as a colourless oil by further separation of the two compounds (SiO_2, pentane / EtOAc 8:2) and the full characterisation is shown below:

Ethyl 2-(5-iodo-3-((4-methoxyphenyl)sulfonyl)-3-azabicyclo[3.1.1]heptan-1-yl)acetate (86at)



R_f 0.31 (8:2 pentane / EtOAc).

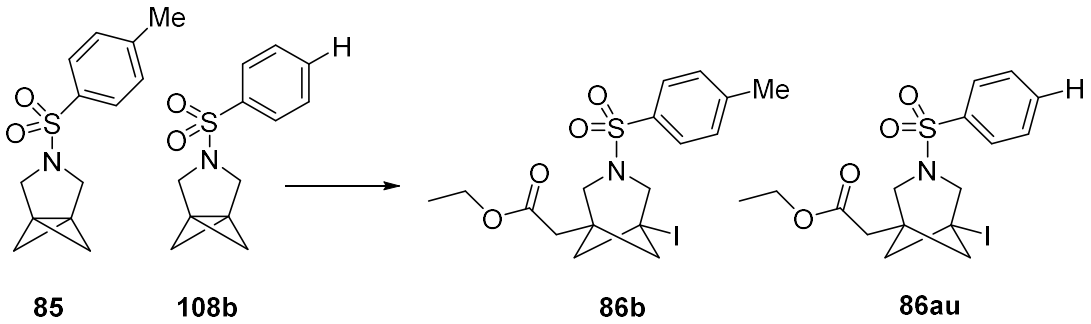
^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.76 (2H, d, *J* = 8.9 Hz, Ar H), 7.01 (2H, d, *J* = 8.9 Hz, Ar H), 4.11 (2H, q, *J* = 7.1 Hz, H8), 3.89 (3H, s, OMe), 3.84 (2H, s, H2/3), 3.37 (2H, s, H2/3), 2.53 – 2.47 (2H, m, H5), 2.42 (2H, s, H6), 2.20 – 2.12 (2H, m, H5), 1.23 (3H, t, *J* = 7.1 Hz, H9).

^{13}C NMR (126 MHz, $CDCl_3$) δ_C 169.9, 163.2, 129.5, 129.1, 114.5, 60.9, 59.2, 55.8, 52.2, 48.8, 42.0, 41.5, 22.6, 14.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2361, 1732, 1597, 1498, 1342, 1157.

HRMS (ES^+) calc. for $C_{17}H_{23}INO_5S$ $[M+H]^+$ 480.0336, found 480.0342.

Competition experiment 2: 3-(*N*-tosyl)aza[3.1.1]propellane (85) vs 3-phenylsulfonyl)aza[3.1.1]propellane (108b)



85 **108b** **86b** **86au**

The competition experiment was performed according to *General Procedure 5*, using 3-(*N*-tosyl)aza[3.1.1]propellane **85** (0.30 mL, 0.20 M, 60 μmol) and 3-(phenylsulfonyl)aza[3.1.1]propellane **108b** (0.33 mL, 0.18 M, 60 μmol). The diiodoBCHeps were separated from the product BCHeps by column chromatography (SiO_2, pentane / EtOAc 19:1 to 8:2).

Ratio of total product BCHeps to total diiodoBCHeps (as determined by ^1H NMR before column):

Test 1 – 1.00 : 0.81

Test 2 – 1.00 : 1.48

Test 3 – 1.00 : 0.70

Ratio of product **86b** to product **86au**:

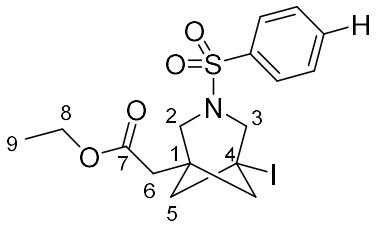
Test 1 – 1.00 : 1.02

Test 2 – 1.00 : 1.08

Test 3 – 1.00 : 1.02

After the first two tests, the ratios did not match closely enough, so a third test was done, which was a closer match to test 1. Therefore, the average of test 1 and test 3 was taken for the Hammett plot. A reference sample of ethyl 2-(5-iodo-3-(phenylsulfonyl)-3-azabicyclo[3.1.1]heptan-1-yl)acetate **86au** was obtained by independent synthesis, the method for which is shown below.

Ethyl 2-(5-iodo-3-(phenylsulfonyl)-3-azabicyclo[3.1.1]heptan-1-yl)acetate (86au)



Prepared according to *General Procedure 3,* using 3-(Phenylsulfonyl)aza[3.1.1]propellane **108b** (0.33 mL, 0.18 M, 60 μmol, 1.2 eq.), ethyl 2-iodoacetate (5.9 μL, 50 μmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (0.8 mg, 1.3 μmol, 2.5 mol%). The mixture was stirred and irradiated for 1 h. Purification by column chromatography (SiO_2, pentane / EtOAc 8:2) gave the product (18.7 mg, 41.6 μmol, 83%) as a colourless oil.

R_f 0.27 (8:2 pentane / EtOAc).

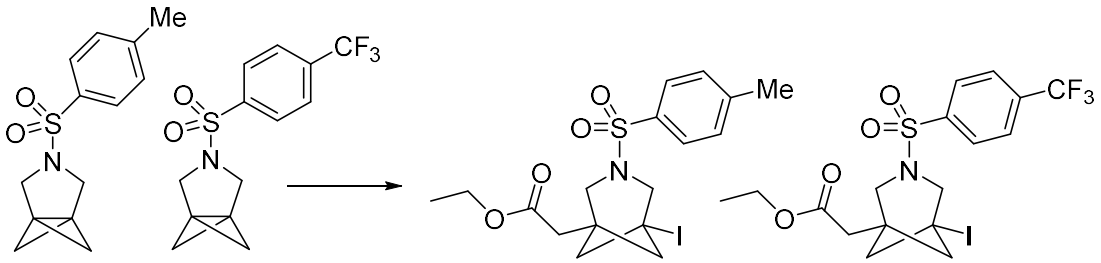
^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.87 – 7.79 (2H, m, Ar H), 7.66 – 7.60 (1H, m, Ar H), 7.59 – 7.53 (2H, m, Ar H), 4.10 (2H, q, *J* = 7.1 Hz, H8), 3.87 (2H, s, H2/3), 3.39 (2H, s, H2/3), 2.54 – 2.45 (2H, m, H5), 2.42 (2H, s, H6), 2.20 – 2.11 (2H, m, H5), 1.22 (3H, t, *J* = 7.1 Hz, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.9, 137.3, 133.1, 129.4, 127.4, 60.9, 59.2, 52.2, 48.7, 42.0, 41.5, 22.4, 14.4.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 2871, 1731, 1342, 1163, 1093.

HRMS (ES$^+$) calc. for $C_{16}H_{21}INO_4S$ $[M+H]^+$ 450.0231, found 450.0232.

Competition experiment 3: 3-(*N*-tosyl)aza[3.1.1]propellane (85) vs 3-((4-(trifluoromethyl)phenyl)sulfonyl)aza[3.1.1]propellane (108c)



85 **108c** **86b** **86av**

The competition experiment was performed according to *General Procedure 5*, using 3-(*N*-tosyl)aza[3.1.1]propellane **85** (0.30 mL, 0.20 M, 60 μmol) and 3-((4-(trifluoromethyl)phenyl)sulfonyl)aza[3.1.1]propellane **108c** (0.43 mL, 0.14 M, 60 μmol). The diiodoBCHeps were separated from the product BCHeps by column chromatography (SiO_2, pentane / EtOAc 19:1 to 8:2).

Ratio of total product BCHeps to total diiodoBCHeps (as determined by ^1H NMR before column):

Test 1 – 1.00 : 1.78

Test 2 – 1.00 : 1.93

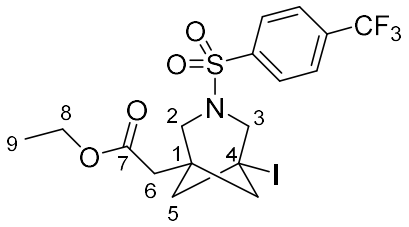
Ratio of product **86b** to product **86av**:

Test 1 – 1.16 : 1.00

Test 2 – 1.17 : 1.00

A reference sample of ethyl 2-(5-iodo-3-(phenylsulfonyl)-3-azabicyclo[3.1.1]heptan-1-yl)acetate was obtained by independent synthesis, the method for which is shown below.

Ethyl 2-(5-iodo-3-((4-(trifluoromethyl)phenyl)sulfonyl)-3-azabicyclo[3.1.1]heptan-1-yl)acetate (86av)



Prepared according to *General Procedure 3,* using 3-((4-(trifluoromethyl)phenyl)sulfonyl)aza[3.1.1]propellane **108c** (0.43 mL, 0.14 M, 60 μmol, 1.2 eq.), ethyl 2-iodoacetate (5.9 μL, 50 μmol, 1.0 eq.) and *fac*-Ir(ppy)$_3$ (0.8 mg, 1.3 μmol, 2.5 mol%). The mixture was stirred and irradiated for 1 h. Purification by column chromatography (SiO_2, pentane / EtOAc 8:2) gave the product (18.5 mg, 35.8 μmol, 72%) as a colourless oil.

R_f 0.42 (8:2 pentane / EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.96 (2H, d, *J* = 8.2 Hz, Ar H), 7.83 (2H, d, *J* = 8.3 Hz, Ar H), 4.10 (2H, q, *J* = 7.1 Hz, H8), 3.88 (2H, s, H2/3), 3.42 (2H, s, H2/3), 2.54 – 2.49 (2H, m, H5), 2.44 (2H, s, H6), 2.21 – 2.12 (2H, m, H5), 1.22 (3H, t, *J* = 7.1 Hz, H9).

^{13}C NMR (101 MHz, $CDCl_3$) δ_C 169.8, 141.0, 134.8 (q, *J* = 33.1 Hz), 127.9, 126.6 (q, *J* = 3.9 Hz), 123.4 (q, *J* = 272.3 Hz), 61.0, 59.2, 52.3, 48.7, 41.9, 41.5, 21.7, 14.3.

^{19}F NMR (376 MHz, $CDCl_3$) δ_F -63.1.

IR (thin film, ν_{max} / cm^{-1}; selected peaks): 1732, 1323, 1167, 1133, 1062.

HRMS (ES^+) calc. for $C_{17}H_{20}F_3INO_4S$ $[M+H]^+$ 518.0104, found 518.0116.

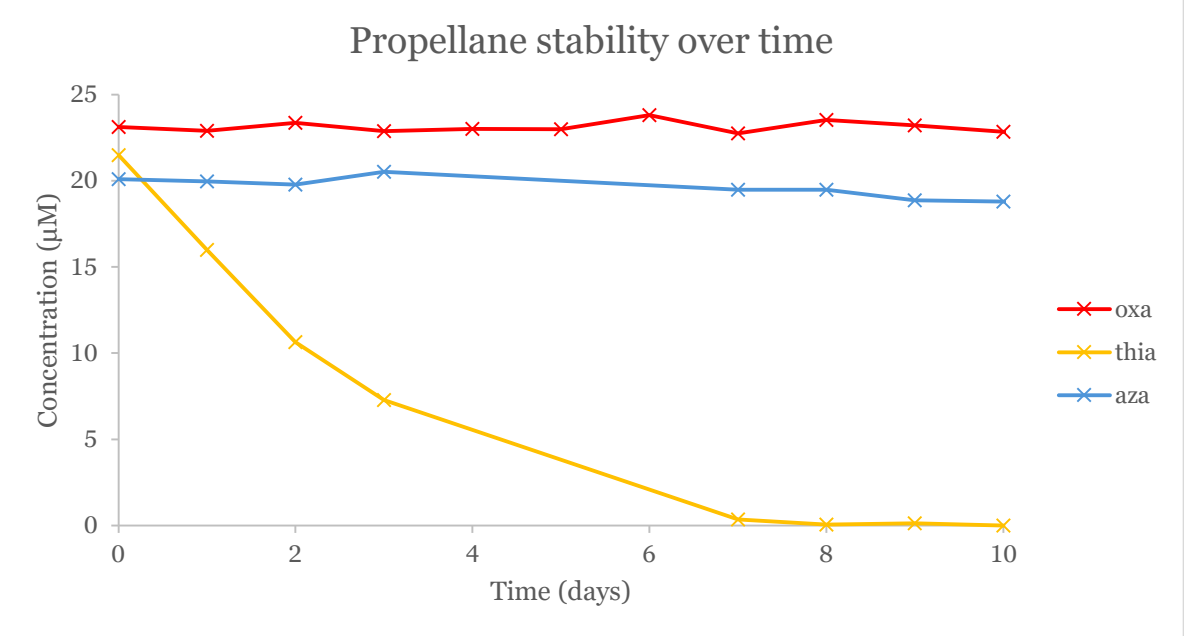
The following table was used to construct the Hammett plot:

R Group	σ_X	K_X/K_H		$\log(K_X/K_H)$			
		Test 1	Test 2	Test 1	Test 2	Average	Error
Me	-0.17	0.98	0.98	-0.009	-0.009	-0.009	0.000
OMe	-0.27	1.07	1.07	0.029	0.029	0.029	0.000
CF_3	0.54	0.82	0.81	-0.087	-0.090	-0.089	0.002

Since each competition experiment involved the 3-(*N*-tosyl)aza[3.1.1]propellane, the values for K_X/K_H were calculated using $(K_X/K_{Me})*(K_{Me}/K_H)$. The Hammett plot was contrcuted using these data.

6.4. Propellane stability

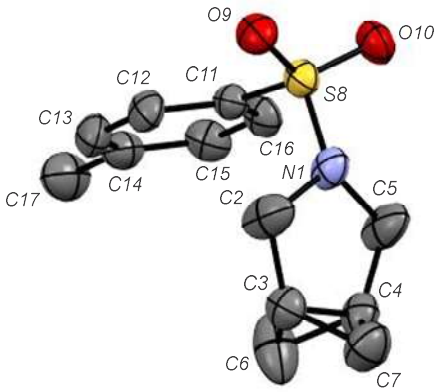
We have analysed the stability of the hetero[3.1.1]propellane solutions by preparing an NMR sample of each propellane and measuring the ^{1}H NMR spectrum of the same sample each day. The samples were prepared in C_6D_6 in air, and the concentrations were calculated by integrating the propellane peaks relative to a DCE internal standard (5 µL). The concentration of each sample was adjusted to be roughly the same by adjusting the amount of C_6D_6 added. Between measurements, the NMR samples were left at rt under air. The concentration of the oxa- and azapropellanes remained essentially constant over the timeframe measured (10 days), however the thiapropellane degraded relatively quickly under ambient conditions.



6.5. X-ray crystallographic data

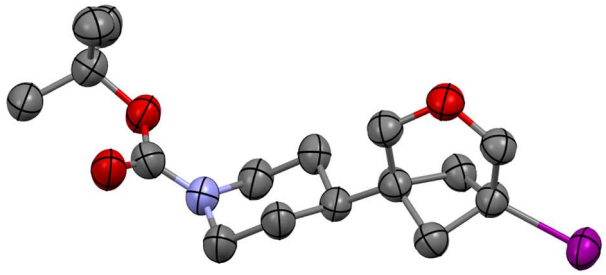
Single crystal X-ray diffraction data were collected using a Rigaku Oxford SuperNova diffractometer and a Rigaku Synergy-DW. Raw frame data was reduced using CrysAlisPro. The structures of **85**, **86i** and **86z** were solved using 'Superflip'[162] before refinement with CRYSTALS[163, 164]. The structure of **108a** was solved using *ShelXT*[165] in *Olex2*[166] before refinement with *ShelXL*[167]. Crystallographic data for **85** and **86i** has been deposited with the Cambridge Crystallographic Data Centre (CCDC 2412510-2412511) and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

Table 6.1 Crystal data and structure refinement for **85**



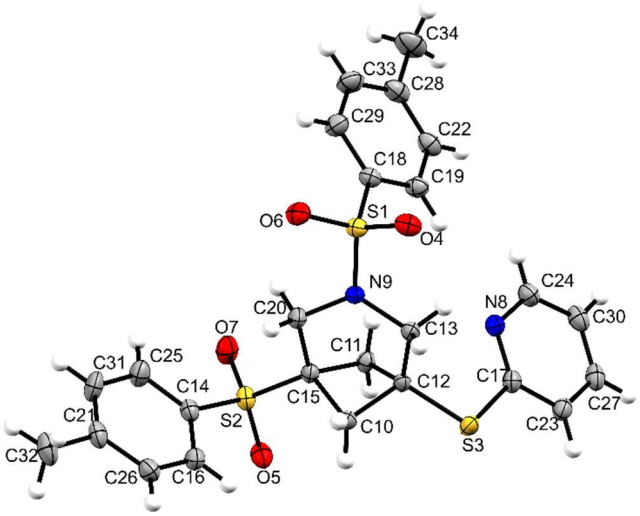
CCDC identification code	2412510	
Empirical formula	C13 H15 N1 O2 S	
Formula weight	249.33	
Temperature	210 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.5561(4)	α = 107.620(5)°
	b = 8.6377(5)	β = 94.191(4)°
	c = 8.8534(4)	γ = 101.295(5)°
Volume	605.37(6) Å³	
Z	2	
Crystal size	0.07 × 0.23 × 0.36 mm³	
Reflections collected	5628	
Independent reflections	2487 [R(int) = 0.028]	
Completeness to theta = 73.913°	99.5%	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2485 / 0 / 154	
Goodness-of-fit on F^2	0.9868	
Final R indices [I>2sigma(I)]	R1 = 0.0458, wR2 = 0.1269	
R indices (all data)	R1 = 0.0489, wR2 = 0.1333	

Table 6.2 Crystal data and structure refinement for **86i**



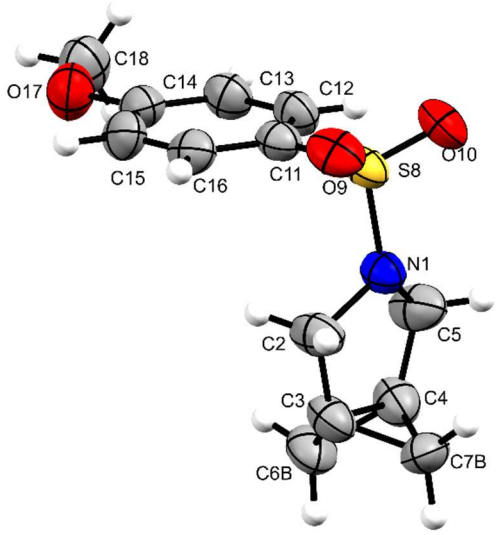
CCDC identification code	2412511	
Empirical formula	C16 H26 I N O3	
Formula weight	407.29	
Temperature	100 K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 40.8370(6) Å	α = 90°
	b = 5.9142(1) Å	β = 107.493(2)°
	c = 30.9152(5) Å	γ = 90°
Volume	7121.3(2) Å³	
Z	16	
Crystal size	0.03 × 0.06 × 0.11 mm³	
Reflections collected	155737	
Independent reflections	7350 [R(int) = 0.064]	
Completeness to theta = 73.805°	99.9%	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7350 / 0 / 379	
Goodness-of-fit on F^2	0.9920	
Final R indices [I>2sigma(I)]	R1 = 0.0684, wR2 = 0.1657	
R indices (all data)	R1 = 0.0756, wR2 = 0.1760	

Table 6.3 Crystal data and structure refinement for **86z**



Empirical formula	C25 H26 N2 O4 S3	
Formula weight	514.69	
Temperature	150 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 10.2637(4) Å	
	b = 10.5402(5) Å	α = 93.819(3)°
	c = 11.7026(5) Å	β = 94.108(3)°
Volume	1197.47(9) Å³	γ = 107.741(4)°
Z	2	
Crystal size	0.179 x 0.101 x 0.037 mm³	
Reflections collected	14915	
Independent reflections	4882 [R(int) = 0.040]	
Completeness to theta = 74.498°	99.6%	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4881 / 0 / 307	
Goodness-of-fit on F^2	0.9808	
Final R indices [I>2sigma(I)]	R1 = 0.0342, wR2 = 0.0854	
R indices (all data)	R1 = 0.0447, wR2 = 0.0928	

Table 6.4 Crystal data and structure refinement for **108a**



Empirical formula	C13 H15 N O3 S	
Formula weight	265.32	
Temperature	250 K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.4283(4) Å	
	b = 9.0260(5) Å	α = 106.459(5)°
	c = 9.2686(5) Å	β = 108.081(5)°
Volume	1197.47(9) Å³	γ = 90.863(4)°
Z	2	
Crystal size	0.63 × 0.166 × 0.11 mm³	
Reflections collected	5220	
Independent reflections	5220 [R(int) = 0.0157]	
Completeness to theta = 76.3°	99%	
Data / restraints / parameters	5220/22/184	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R_1 = 0.0471, wR_2 = 0.1356	
R indices (all data)	R_1 = 0.0540, wR_2 = 0.1410	

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