Synthesis of bicyclo[3.1.1]heptanes, *meta*-substituted arene isosteres, from [3.1.1]propellane

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- The bioisosteric replacement of benzene rings with saturated small ring bridged hydrocarbons is a rapidly evolving field of drug design due to e.g. improved solubility, membrane permeability, and metabolic stability.
- The bicyclo[3.1.1]heptane framework is an effective bioisostere for meta-substituted aromatic compounds. This protocol describes the synthesis of [3.1.1]propellane and its conversion to various bicyclo[3.1.1]heptane derivatives.

Key references

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2. Nugent, J. *et al. ACS Catal.* **9**, 9568-9574 (2019): https:// doi.org/10.1021/acscatal.9b03190

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Abstract

The use of saturated small ring bridged hydrocarbons as bioisosteres for aromatic rings has become a popular tactic in drug discovery. Perhaps the best known of such hydrocarbons is bicyclo[1.1.1]pentane (BCP), for which the angle between the exit vectors of the bridgehead substituents is identical to that of a *para*-substituted arene (180°). The development of *meta*-arene (bio)isosteres is much less explored, due to the challenge of identifying an accurate geometric mimic (substituent exit vector angle ~120° / dihedral angle ~0°). To address this, we recently reported

straightforward access to bicyclo[3.1.1]heptanes (BCHeps), which exactly meet these geometric properties, via radical ring-opening reactions of [3.1.1]propellane. This required the development of a scalable synthesis of [3.1.1]propellane, as well as the implementation of various ring-opening reactions and derivatizations. In this protocol, we describe methodology for a multigram scale synthesis of [3.1.1]propellane in five steps from commercially available ethyl 4-chlorobutanoate, which proceeds in an overall yield of 26-37%. We also describe the functionalization of [3.1.1]propellane to three key classes of BCHep iodides by photocatalyzed-Atom Transfer Radical Addition reactions (ATRA) using 456 nm blue light. We further report protocols for the elaboration of these products to other useful derivatives, via iron-catalysed Kumada coupling with aryl Grignard reagents, and conversion of a pivalate ester to a carboxylic acid through hydrolysis/oxidation. The total times required to synthesize [3.1.1]propellane, the BCHep iodides, and the BCHep carboxylic acid are ~53 h, 6-8 h, and 40 h respectively, requiring an average level of synthetic chemistry expertise (e.g. masters / graduate student).

[H1] Introduction

The bioisosteric replacement of benzene rings with saturated small ring bridged hydrocarbons is a rapidly evolving field of drug design in academic and industrial research (e.g. over 3000 patents have been described that feature a bicyclo[1.1.1]pentane, bicyclo[2.2.2]octane, or cubane, which can mimic *para*-substituted arenes).[1-4] Examples (Fig. 1a) include the bicyclo[1.1.1]pentane (BCP) analogue of the γ-secretase inhibitor avagacestat,[5] the 1,3-disubstituted cubane analogue of the cystic fibrosis treatment lumacaftor,[6] and the oxabicyclo[2.2.2]octane (oxa-BCO) analogue of the anticancer drug imatinib.[7] The benefits imparted on drug candidates by these substitutions include improved physicochemical and pharmacokinetic properties, such as solubility, membrane permeability, and metabolic stability.[5] The 'parent' example in this class is the bicyclo[1.1.1]pentane (BCP, Fig. 1b),[8]

where the exit vectors of its bridgehead substituents accurately mimic the 180° disposition of those of *para*-substituted aromatics. BCPs are most conveniently accessed by ring-opening of the strained central C–C bond of [1.1.1]propellane, and many methods have been described that utilize this approach.[8]

In contrast, geometrically-accurate mimics of *meta*-substituted arenes have only recently begun to emerge. Examples include [2]-ladderanes, 1,3-substituted cubanes, 1,2-disubstituted BCPs, and bicyclo[2.1.1]hexanes (and heteroatom-substituted variants);[6,9-14] however despite being useful rigid cores in their own right, such scaffolds generally fail to reproduce the specific substituent vectors of the *meta*-arene. In many cases, these saturated hydrocarbon analogues reduce the susceptibility of the molecule to metabolic degradation compared to the aromatic parent. This challenge is uniquely met by the bicyclo[3.1.1]heptane framework (BCHep, Fig. 1c), which features a ~120° exit vector angle and a near-zero dihedral angle between the bonds to its bridgehead substituents.

We recently reported the first general access to bridgehead-disubstituted BCHeps from ring opening of [3.1.1]propellane,[15] and the potential use of BCHeps as *meta*-arene isosteres due to their reduced susceptibility to metabolic degradation in two drug analogues. Crystallographic studies validated that the angles and distances between the bridgehead substituents of the BCHep molecules are indeed very similar to those of *meta*-substituted arenes. In this Protocol, we describe in detail three key processes that will enable the wider use of BCHeps by the scientific community:

1. Access to [3.1.1]propellane using a reliable, scalable five-step protocol which is conducted here on multigram scale, but could be readily conducted on larger scales if necessary;
2. Execution of photocatalyzed-atom transfer radical addition (ATRA) ring-opening reactions that offer a general entry to BCHeps functionalized with alkyl, aryl and heteroaryl substituents, and a variety of functional groups including esters, amides, carbonyls, halides, sulfides, sulfones

and sulfonamides; further scale-up of this transformation may be achieved using catalyst-free conditions in some cases (vide infra), or for sp^3-hybridized radicals conducted using Et_3B initiator, which allows larger scale protocols but can result in slightly lower yields;[16]

3. Functionalization of the BCHep products by cross-coupling, or oxidation, to introduce additional substituent diversity as might be found on typical *meta*-substituted arenes.

The experimental setup to synthesize these substituted BCHep scaffolds is simple (see below); for example, the transformation of [3.1.1]propellane to BCHep iodides requires a reaction time of 3-5 h, with an operational time of ~3 h (experimental setup: ~30 minutes; work-up and purification: ~2.5 h), and requires an average level of expertise in organic synthesis. These protocols will therefore aid researchers of a variety of levels of experience to carry out the synthesis of BCHeps in both academic and industry laboratories.

[H2] Comparison with alternative approaches.

Prior to 2022, only two routes had been developed to access [3.1.1]propellane, both of which suffered from practicality and scalability issues. In 1980, Gassman *et al.* reported an 8 step synthesis with an overall yield of 4.2% (Fig. 2).[17] They further investigated the reaction of [3.1.1]propellane with methanol at -78 °C, which gave a mixture of ring-opened products. This route suffers from the use of super-stoichiometric quantities of toxic HgO, high-pressure H_2, and hazardous sodium metal (11 equiv.) which is heated in triglyme at >215 °C. Around a decade later, Szeimies *et al.* described a second synthesis of [3.1.1]propellane, which proceeded with an overall yield of 3.3%; this route utilizes a propellane precursor in common with our own chemistry (see below), but suffers from issues such as use of the gaseous / hazardous reagent ethylene oxide, and low overall yield.[18] The group studied solely the reaction of [3.1.1]propellane with thiophenol, and its behaviour under flash vacuum pyrolysis. Subsequent to our work, Uchiyama and co-workers reported a fourth synthesis of [3.1.1]propellane involving a variation of the Gassman route, where a BCHep diiodide underwent

cyclization via metalation.[19] This route also suffers drawbacks, including the use of carcinogens such as HMPA, diiodomethane, and ICH_2CF_3; the maximum scale of propellane preparation reported is ~140 mg.

The major application of [3.1.1]propellane reported in this Protocol is its ring opening to access bicyclo[3.1.1]heptanes (BCHeps). In recent years, substituted BCHep scaffolds have been synthesized by other approaches, although wide variation of the bridgehead substituents can remain a limitation with these methods. Chief among these strategies are formal cycloaddition reactions using bicyclo[1.1.0]butanes (BCBs). In 2022, Molander *et al.* described the Ir-catalysed synthesis of trifunctionalized bicyclo[3.1.1]heptanes by the intermolecular (3σ + 2σ) cycloaddition between BCBs and cyclopropylamines.[20] In 2023, Li *et al.* demonstrated B_2pin_2-catalyzed (2σ +2σ) radical cycloaddition between BCBs and cyclopropyl ketones, where up to six substituents were successfully installed on the BCHep core.[21] In the same year, Waser and coworkers developed an Ir-catalysed (2σ+ 2σ) cycloaddition between carbonyl-substituted cyclopropanes and BCBs.[22] Recently, Glorius *et al.* described the synthesis of *poly*-substituted 3-azabicyclo[3.1.1]heptanes from the reaction of BCBs and isocyanides.[23] However, as noted above, a drawback with these approaches is the need to pre-define substituents around the BCHep framework; the propellane approach arguably provides greater diversity of functionality at the key bridghead atoms. However, one obvious drawback of the propellane approach is the difficulty to also functionalize the bridge carbon atoms, as is often achieved in the alternative methods.

[H2] Development and Overview of the Protocol.

In 2022, we reported a scalable synthesis of [3.1.1]propellane based on an improved access to the 'Szeimies precursor' (see below); this route forms the basis of the first part of this Protocol.[15]

The outline of this Protocol is illustrated in Fig. 3. Fig. 3a shows the synthetic route to [3.1.1]propellane **1** from commercially available ethyl 4-chlorobutanoate **2** which, as noted above, proceeds with an

excellent overall yield of 26-37% over five steps. This synthesis commences with a Kulinkovich cyclopropanation reaction of ethyl 4-chlorobutanoate **2** with EtMgBr (stage 1, 85%).[24] The resulting cyclopropanol **3** is then activated as a mesylate with methanesulfonyl chloride **4** (stage 2, 95%). The use of $EtSO_2Cl$ in this synthetic sequence was recently reported as a safer alternative to $MeSO_2Cl$; this gave a similar yield of the desired product.[25] Treatment of this mesylate with $TiCl_4$ effects a 2π-electrocyclic ring opening of an *in situ* generated cyclopropyl cation to give an allyl cation, which is trapped with chloride ion to form the allylic chloride **5** (stage 3, 86%). Dibromocyclopropanation employing NaOH / $CHBr_3$ with catalytic tetra-*n*-butylammonium iodide (TBAI) affords the key tetrahalide propellane precursor **6** (stage 4, 84%).[26] Importantly, only one column chromatographic purification is required over these four steps; this protocol is readily conducted on multigram scale, and the ease of purification would render it suitable for further scale-up.

Finally [3.1.1]propellane is synthesized from the tetrahalide on treatment with PhLi (2 equiv.) at low temperature (-78 °C) in di-*n*-butyl ether, then warmed to room temperature for 7 h to complete the cyclization. [3.1.1] propellane is purified by distillation using a rotary evaporator, with the collection flask immersed in a -78 °C bath. The resulting solution of [3.1.1]propellane (typically 0.25-0.50 M in *n*-Bu_2O) is stored under nitrogen in an Acro-seal amber-coloured glass bottle at -20 °C, under which conditions it is stable for several months (stage 5; 43-61%)**.** The reader should note that MeLi can also be used in place of PhLi for the synthesis of bromobenzene-free [3.1.1]propellane; treatment of **6** with 2.05 equivalents of MeLi afforded [3.1.1]propellane in 49% yield after distillation. Throughout this five step synthesis, analysis of crude reaction mixtures indicated no or only minor formation of side products, as determined by ^{1}H NMR spectra and TLC. This enabled us to conduct 4 out of 5 transformations without chromatographic purification (with only stage 4 requiring chromatography). In short, this straightforward five step sequence for the multi-gram scale synthesis of [3.1.1]propellane

offers an ideal approach for the synthesis of this key building block, proceeding in excellent overall yield (25-36%).

The second set of processes described in this Protocol cover in detail some of the most versatile uses of [3.1.1]propellane (Fig. 3b). The first of these is an iridium-catalysed (or in some cases, initiated) ATRA reaction,[27] which exhibits broad substrate scope. This chemistry was originally developed by our group for the synthesis of *C*,*I*-disubstituted BCPs from [1.1.1]propellane,[27] and translates very effectively to [3.1.1]propellane compared to the alternative use of triethylborane as a radical initiator.[15,16] While other radical additions are also effective, such as multicomponent additions of iodonium dicarboxylates and *N*-heteroarenes, as well as chalcogens and other heteroatom-based radicals,[15] the ATRA reaction arguably provides the most diverse carbon-based substituent scope on the BCHep. We describe the application of ATRA to three classes of compound: the addition of a 4-iodopiperidine derivative, 2-iodopyridine, and pivaloyloxymethyl iodide. The ATRA procedure is achieved using a simple experimental setup: a solution of the reactants (alkyl / aryl iodide, and solution of [3.1.1]propellane in *n*-Bu_2O) and catalyst (*fac*-$Ir(ppy)_3$) in pivalonitrile are sealed in a screw-cap clear glass vial, and then stirred at room temperature under blue LED irradiation (456 nm), with cooling from a clip-on fan, until the reaction reaches completion (3-5 h). We further note that a variety of other transformations are possible using [3.1.1]propellane as detailed in our original publication,[15] such as MacMillan and coworkers' iridium/copper-catalyzed *C*,*N*-difunctionalization chemistry,[28] or the direct addition of heteroatom radicals.

The iodo-BCHep products can be used in a variety of further processes, including lithiation / electrophilic quench. However, one of the most efficient, rapid and mild transformations carried out on these compounds is the Kumada coupling of the C–I bond with an aryl Grignard reagent,[29] a reaction again developed by our group in the context of iodo-BCPs. This chemistry is generally slightly higher

yielding for BCHeps compared to BCPs, proceeding in a matter of minutes and in high yields. Here this protocol is exemplified with a typical aryl Grignard reagent, whereby a solution of the BCHep substrate and $Fe(acac)_3$/TMEDA in THF are placed under nitrogen, followed by dropwise addition of the Grignard reagent over 15 min–1 h via syringe pump; the coupling is essentially complete when this addition is finished. This rate of addition corresponds to 0.32 mmol min^{-1} (15 min addition time) or 0.077 mmol min^{-1} (60 min addition time). Either rate of addition gives similar results, and would be a suitable rate of addition if further scaled up.

Another highly useful bridgehead functionality on these small ring scaffolds is a carboxylic acid, which can be used to form many other useful molecules such as amides, esters, etc., as might be found in drug molecules, as well as being a precursor to redox active esters, substrates that can be used for Minisci reactions to further functionalize the bridgehead.[30,31] In the final part of this Protocol, we show how the pivalate ester in BCHep **12** can be easily converted to a carboxylic acid by hydrolysis using 1 M NaOH solution at 50 °C, followed by oxidation of the resultant alcohol to the carboxylic acid using $NaIO_4$ / cat. $RuCl_3$.

[H2] Expertise needed to implement the protocol

Expertise in the handling of air/moisture-sensitive reagents, standard organic chemistry experimental setups, and purification techniques, are required. Overall, these protocols are relatively simple to operate, and average knowledge and training in synthetic organic chemistry (i.e. masters / graduate student level) is sufficient to implement this chemistry on small to medium preparative scales.

[H2] Limitations

Here we discuss some of the limitations of this synthesis and how these influence decision making (experimental design) and applications.

[H3] Stability of [3.1.1]Propellane

In this approach [3.1.1]Propellane is not generated as a pure product. Instead it is isolated as a solution in *n*-Bu_2O and stored at -20 °C under nitrogen. We have found that it is not advisable to concentrate the propellane solution above 0.5 M, as this leads to more rapid decomposition. At or below this concentration, the propellane solution is stable for several weeks at -20 °C and quite likely longer, although we have typically used the solution within this time period. We recommend that the propellane solution should not be stored at room temperature, as decomposition is observed within a few hours, as evidenced by the formation of a white precipitate which is presumably the 'staffane' oligomer.

However, partial degradation of the solution has not been found to be detrimental to reactivity, and the concentration of the propellane solution can simply be re-assessed using NMR spectroscopy before use (see below). We do not feel that rigorous exclusion of oxygen from the propellane solution is necessary – purge degassing is sufficient for storage as above.

It is worth noticing that the propellane precursor **6** can be stored indefinitely without any degradation, and therefore it may be more convenient to prepare the propellane 'on demand'.

[H3] Sensitivity to LED

With respect to the ATRA reactions, we have recently reported the sensitivity of [3.1.1]propellane solutions towards blue LED irradiation;[32] accelerated degradation is observed at 35 °C compared to purely thermal degradation. A slight excess (1.2-1.5 equiv.) of [3.1.1]propellane is employed for most uses (e.g. in ATRA reactions) due to gradual background degradation under the irradiation reaction conditions.

[H3] Presence of bromobenzene

During the isolation of [3.1.1]propellane, some bromobenzene (formed during bromine–lithium exchange) co-distils with the propellane, ~~which may limit some applications~~, however in our experience, the presence of bromobenzene has not limited any applications of the [3.1.1]propellane. However, use of methyllithium as an alternative lithiating agent can overcome this; if methyllithium is used, the byproduct is bromomethane which is more volatile, and therefore more easily removed.

[H3] [3.1.1]propellane does not react with anionic reagents

Unlike [1.1.1]propellane, [3.1.1]propellane has to date been found to be resistant to reactions with anionic reagents, which somewhat limits the scope of products available from this reagent. Example reactions would included addition of Grignard reagents, or dithiane anions.[7] This is due to the unfavourable build up of negative charge within the propellane framework, and the associated increase in Pauli repulsion with the C–C bonds flanking the breaking inter-bridgehead bond, in anionic addition processes.[33,34] Nonetheless, many radical reactions are successful, which generally presents a milder means to achieve additions.

[H3] Scope of the Kumada coupling

The Kumada coupling of the bridgehead BCHep iodides is generally found to be more successful when using electron-rich (hetero)aryl Grignard reagents; however, we did note that BCHep iodides seem to perform better than BCP iodides in this chemistry.

[H2] Experimental design

a) Solvents and reagents

All synthetic procedures contained in this Protocol were performed in organic solvents such as diethyl ether, pivalonitrile, dichloromethane, tetrahydrofuran, di-*n*-butyl ether, etc.. Dry solvents (such as Et_2O, THF, and CH_2Cl_2) were taken from a solvent purification system (activated alumina column) and used directly in the reactions. Chromatography solvents pentane and ethyl acetate were used as

received. Other reagents were purchased from Sigma-Aldrich, Alfa-Aesar, Thermo-Fischer, FluoroChem and BLDpharm, and used as received without further purification. Where necessary, products were purified by column chromatography using pentane or pentane/ethyl acetate as eluent.

b) Reaction scale. The reactions involved in the synthesis of [3.1.1]propellane were carried out on scales of 60-200 mmol. These procedures gave similar yields (within 2-3%) within this scale range. ATRA reactions were carried out on millimole scale (5-9 mmol). For [3.1.1]propellane synthesis, larger scales than 200 mmol would require careful control of internal reaction temperature in Stages 1–4 of the Procedure 1 of the Protocol. Stage 5 of the protocol (propellane formation) will require careful control of distillation flask temperature during propellane distillation, and may benefit from a batch approach to ensure the timeframe of the distillation process does not lead to extensive propellane decomposition. Scale up of Procedure 2 may benefit from flow chemistry setup to enable efficient irradiation. Scale up of Procedure 3 is not anticipated to provide any obstacles other than control of temperature during Grignard addition in the Kumada coupling step.

c) Storage. All intermediates and final products in this Protocol, with the exception of [3.1.1]propellane (see 'Limitations'), may be stored at -20 °C (freezer) for >3 months without any degradation, and likely for longer periods if needed.

[H1] Materials

[H2] Reagents

▲**CAUTION** Some chemicals used in this protocol are potentially harmful. A laboratory coat, gloves, and eye protection should be worn at all times during the experiment. Chemicals and solvents used in this protocol must be handled with care and stored in appropriate cabinets. The storage temperature is room temperature unless stated otherwise. Many of the organic solvents employed are highly

flammable and some cause skin/eye irritation or drowsiness; solvents should always be used in a well-ventilated fume hood. Contact with aqueous solutions of mineral acids such as hydrochloric acid and sulfuric acid can cause skin burns, eye damage, and respiratory irritation. Bases such as sodium hydroxide, triethylamine, and tetramethylethylenediamine are hygroscopic, and may cause severe skin burns and eye damage. Silica gel and celite could cause respiratory problems upon inhalation.

- Bromoform (Thermo Scientific, cat. no. A11904.0B) ▲**CAUTION** Flammable liquid, causes skin and eye irritation.
- 1-Bromo-4-(trifluoromethoxy)benzene (Sigma-Aldrich, cat. no. 339601) ▲**CAUTION** Causes skin irritation.
- Celite (Celite™ 545; Thermo Scientific, cat. no. 10461153)
- Ethyl 4-chlorobutanoate (Thermo Scientific, cat. no. A11070.22) ▲**CAUTION** Causes skin and eye irritation.
- Ethylmagnesium bromide (3 M solution in ether; Thermo Scientific, cat. no. 041675.JT) ▲**CAUTION** Flammable liquid; emits flammable gas in contact with water. Causes skin corrosion, and serious eye damage.
- Hydrochloric Acid (Fisher Scientific, cat. no. 10316380) ▲**CAUTION** Causes skin corrosion and serious eye damage.
- Iodine (Fisher Scientific, cat. no. 10439750) ▲**CAUTION** Iodine vapour is harmful to the respiratory system, and causes skin, eye, and respiratory irritation. Always open the bottle in a well-ventilated hood.
- Iodomethyl pivalate (Fluorochem, cat. no. F235580) ▲**CAUTION** Causes skin irritation, serious eye damage, and respiratory irritation.
- 2-Iodopyridine (Fluorochem, cat. no. F067334) ▲**CAUTION** Causes skin and eye irritation.

- Iron(III) acetylacetonate ($Fe(acac)_3$, Sigma-Aldrich, cat. no. F300) ▲**CAUTION** Causes skin problems and serious eye damage.
- Methanesulfonyl chloride (Sigma-Aldrich, cat. no. 471259) ▲**CAUTION** Harmful in contact with skin, causes severe skin burns, eye damage, and respiratory irritation.
- Mg turnings (Thermo Scientific, cat. no. 191085000) ▲**CAUTION** Flammable solid, emits flammable gas in contact with water.
- Phenyllithium (1.9 M solution in $^nBu_2O$; Sigma-Aldrich, cat. no. 593230) ▲**CAUTION** Flammable liquid, causes skin corrosion and serious eye damage.
- Phosphomolybdic acid hydrate (for TLC stain; Sigma-Aldrich, cat. no. 221856) ▲**CAUTION** Causes severe skin burns and eye damage.
- Potassium permanganate (for TLC stain; Sigma-Aldrich, cat. no. 223468) ▲**CAUTION** Causes severe skin burns and eye damage.
- Ruthenium(III) chloride hydrate (Sigma-Aldrich, cat. no. 206229) ▲**CAUTION** Causes skin corrosion and serious eye damage.
- Silica (for column chromatography, Sigma-Aldrich, cat. no. 1115671000)
- Sodium hydroxide, pellets (Sigma-Aldrich, cat. no. S5881) ▲**CAUTION** Causes skin corrosion and serious eye damage.
- Sodium periodate (Fisher Scientific, cat. no. 11448400) ▲**CAUTION** Causes skin corrosion and serious eye damage.
- Sulfuric acid (Sigma-Aldrich, cat. no. 30743-M) ▲**CAUTION** Causes severe skin burns and eye damage.
- *Tert*-butyl 4-iodopiperidine-1-carboxylate (Fluorochem, cat. no. F067527)
- Tetramethylethylenediamine (TMEDA, Sigma-Aldrich, cat. no. 411019) ▲**CAUTION** Highly flammable liquid and vapor, causes severe skin burns and eye damage.

• Titanium(IV) chloride (Sigma-Aldrich, cat. no. 8123820100) ▲**CAUTION** Causes skin corrosion, serious eye damage, and inhalation of vapour causes respiratory irritation.

• Titanium(IV) isopropoxide (Sigma-Aldrich, cat. no. 205273) ▲**CAUTION** Flammable liquid, causes eye irritation.

• TLC plates (TLC Silica Gel 60 F_{254}; Sigma-Aldrich, cat. no. 1055540001)

• Triethylamine (Sigma-Aldrich, cat. no. 8083521000) ▲**CAUTION** Highly flammable liquid and vapor, causes severe skin burns, eye damage, and respiratory irritation.

• Tris[2-phenylpyridine]iridium(III) (fac-Ir(ppy)$_3$, BLD pharm, cat. no. BD155809)

[H3] Solvents

▲ **CAUTION** The organic solvents below are highly flammable, and some of them cause skin/eye irritation and/ or drowsiness; all solvents should be used in a well-ventilated fume hood.

• Diethyl ether (Sigma-Aldrich, cat. no. 32203-M)

• *n*-Pentane (Sigma-Aldrich, cat. no. 34956-M)

• Ethyl acetate (Sigma-Aldrich, cat. no. 34858)

• Tetrahydrofuran (Thermo Scientific, cat. no. 348450010)

• Methanol (Sigma-Aldrich, cat. no. 34860-R)

• 1,2-Dichloroethane (Sigma-Aldrich, cat. no. 319929) ▲**CAUTION** Flamable and carcinogenic liquid, causes skin/eye irritation.

• Acetonitrile (Sigma-Aldrich, cat. no. 34851)

• Pivalonitrile (Fluorochem, cat. no. F350843)

• Benzene-d_6 (Sigma-Aldrich, cat. no. 175978) ▲**CAUTION** Flamable and carcinogenic liquid, causes skin/eye irritation.

- Dichloromethane (Sigma-Aldrich, cat. no. 34856) ▲**CAUTION** Causes skin/eye irritation and suspected of causing cancer.
- Chloroform-d (Thermo Scientific, cat. no. 166251000) ▲**CAUTION** Causes skin/eye irritation and suspected of causing cancer.

[H2] Equipment

▲**CAUTION** Glassware should never be used if scratched or otherwise damaged.

- Vials (Glass, screw neck, specimen, Fischer Scientific, cat. no. 15344779 (7 mL), 15304789 (10.5 mL), 15314789 (14 mL), 15324789 (21 mL))
- Vial (screw top, clear glass, 4mL, Sigma-Aldrich, cat. no. 27111); screw cap (with hole for 4 mL vial; Sigma-Aldrich, cat. no. 27120-U); and white silicone/TFE septa (for 4 mL screw cap; Sigma-Aldrich, cat. no. 27356)
- Teflon-coated magnetic stir bars (Fisher Scientific, stir bar box set, cat. no. 11703319 (oval); 10226853 (cylindrical)
- Round-bottomed flasks (one-neck, Scientific Glass Laboratories Ltd, cat. no. FRS25/B14, FRS50/B14, FRS50/B24, FRS100/B24, FRS250/B24, FRS500/B24, FRS1L/B24)
- Round-bottomed flasks (two-neck, Scientific Glass Laboratories Ltd, cat. no. FR1L/31A)
- Round-bottomed flasks (three-neck, Scientific Glass Laboratories Ltd, cat. no. FR1L/322P)
- Conical filter vacuum flask (Fisher Scientific, cat. no. 12343886, 12353886)
- Glass funnel filter with sintered glass disc (Fisher Scientific, cat. no. 11902148, 11942148, 11962148)
- Conical flasks (Erlenmeyer, Scientific Glass Laboratories Ltd, cat. no. FW/100, FW/250, FW/500, FW/1000)
- Beakers (Scientific Glass Laboratories Ltd, cat. no. BSF/100/H, BSF/250/H, BSF/400/H)

- Dropping funnel (250 mL, pressure-equalizing funnels, cylindrical; Scientific Glass Laboratories Ltd; EFC250/32)
- Filter funnels (Scientific Glass Laboratories Ltd; BFF 75, BFF 100, BFF 150)
- Separating Funnels with PTFE Stopcock (Fisher Scientific, cat. No. 13459966, 10426332)
- pH Indicator paper strip (e.g. Fisherbrand™, cat. no. 15930872)
- Pasteur pipette (Fischer Scientific, cat. no. 11546963)
- Adapter (cone, Scientific Glass Laboratories Ltd, cat. no. ATA/1, ATA/3)
- Condenser (Liebig, Scientific Glass Laboratories Ltd, cat. no. CL15/11)
- Chromatography columns (with stopcock and socket; I.D. 1.6 cm, 2.7 cm, 5.0 cm)
- Test tubes (Fisher Scientific, cat. no. 15862275, 15842285, 15802285)
- AcroSeal bottle (Thermo Scientific, for [3.1.1]Propellane storage)
- TLC chamber (Merck, cat. no. Z243906, Z407259)
- Filter papers (Fischer Scientific, cat. no. 11576873, 11435248, 11445248)
- Dewar (for cooling bath; Dilvac, Shallow Form; 0.5 L, 1.0 L)
- Analytical lab balances (Sartorius, cat. no. BCE224I-1S)
- Weighing boats (Fischer Scientific, Polystyrene Diamond-Shape, white)
- Suba-seal septa (red rubber, Sigma-Aldrich, cat. no. Z124559, Z124591, Z124656)
- Vacuum pump (Edwards, EM Oil Sealed Rotary Vane Pumps)
- Syringe (B. Brawn) and needle (disposable, long, B. Brawn)
- Blue LEDs (Kessil PR160 456 nm) ▲**CAUTION** Constant exposure to high intensity light is hazardous to health; could damage retina and cause vision problems.
- PhotoRedOx Box™ (HepatoChem, cat. no. HCK1006-01-016), and sample holder (HepatoChem, cat. no. HCK1006-01-019, HCK1006-01-020, HCK1006-01-021)
- Cooling fan (igenix clip-on fan, cat. no. DF6500)

- Syringe pump (Cole-Parmer)
- Glass oven (Genlab E^3 Drying Cabinet)
- Fume hood
- Schlenk line (nitrogen)
- Magnetic stirring plate with heating functionality (IKA RCT Basic; Heidolph, Hei-PLATE Mix 'n' Heat Core$^+$)

[H2] Reagent Setup

[H3] EtMgBr (3.0 M in Et_2O)

EtMgBr is used in the synthesis of 1-(3-chloropropyl)cyclopropan-1-ol (3)

Before use, determine the concentration by titration with diphenyl acetic acid if the bottle is old/used (see below). However for new and sealed bottle, the deteremination of concentration is not necessary.

[H3] Phenyllithium (1.9 M in *n*-Bu_2O)

PhLi is used in the synthesis of [3.1.1]propellane (1)

Before use, determine the concentration by titration with diphenyl acetic acid if the bottle is old/used (see below). However for new and sealed bottle, the deteremination of concentration is not necessary.

[H3] **Methyllithium** (0.75 M in Et_2O)

Methyllithium can be used instead of PhLi for the synthesis of [3.1.1]propellane (1)

Before use, determine the concentration by titration with diphenyl acetic acid if the bottle is old/used (see below). However for new and sealed bottle, the deteremination of concentration is not necessary.

[H3] **EtMgBr and PhLi**

It is recommended to establish the concentration of solutions of EtMgBr and PhLi via titration before use if the bottle is old/used. For the titration, diphenylacetic acid (106.1 mg, 0.5 mmol) is dissolved in

anhydrous THF to a volume of 1.0 mL, which provides a 0.5 M solution of diphenylacetic acid. This is titrated against the EtMgBr or PhLi solution, under a nitrogen atmosphere. The appearance of a yellow colour indicates the end point, and from the required volume of the solution, the concentration of the solution can be calculated as below.

[H2] Equipment setup

[H3] Photochemical setup (for reaction)

1. Place a photo box (PhotoRedOx Box, (HepatoChem, cat. no. HCK1006-01-016) with a sample holder and inbuilt cooling fan) on the top of a magnetic stirrer plate.
2. Install a 456 nm blue LEDs source (Kessil PR160, 456 nm) into the photo box.
3. Place the vial containing the reaction mixture into the chamber/sample holder of the photo box.
4. For the cooling of the system, install a cooling fan (clip-on) close to the photo box (as irradiation of blue light generates heat over time).
5. Start stirring the reaction mixture at room temperature (600 rpm) and switch on the cooling fan.
6. Cover the photobox with aluminum foil and/ or by a U-shape board, so that light does not come outside.

   ▲**CAUTION** Constant exposure to blue LEDs for a long time may cause eye damage. Cover the system properly to avoid direct contact with skin and eyes.
7. Finally, switch on the blue light source and stir the reaction mixture under irradiation of blue light (456 nm), for the indicated time (3-5 h) as mentioned in the relevant procedure section.
8. After the reaction, switch off the blue light, cooling fan, and stirrer plate.
9. Remove the aluminum foil and take out the reaction vial to the next step.

[H3] Cooling bath

For some reactions described in this protocol, a cooling bath is used. We used an water/ice bath for 0 °C, a NaCl/ice bath for -20 °C, and a dry ice/acetone bath for -78 °C.

[H3] Rotary evaporator (for evaporation of solvent)

1. Take the reaction mixture into a one-neck round-bottomed flask. The flask should be less than 2/3 full to avoid bumping during evaporation.
2. Connect the round-bottomed flask to a rotary evaporator with a suitable-size adaptor. Then put a (plastic) clip to the joint of the round-bottomed flask and adaptor, to avoid the flask falling into the water bath.
3. Lower the round-bottomed flask until it is slightly immersed in the water bath (water bath temperature 30 °C unless stated otherwise).
4. Start rotation of the round-bottomed flask.
5. Set a distillation pressure on the low vacuum pump attached to the rotary evaporator, depending upon the solvent. For removal of pentane use ~500 mbar, for EtOAc use ~200 mbar, for pivalonitrile use ~50 mbar or less.
6. After removal of most of the solvent, empty the collection flask, resume rotary evaporation and lower the pressure to ~10 mbar for 5-10 minutes to remove residual solvent.
7. Stop the rotation of the round-bottomed flask and then raise the flask from the water bath.
8. Release the pressure from the system, remove the (plastic) clip, disconnect the flask from the rotary evaporator. Take the residue to the next relevant step (reaction or purification).

▲**CRTICAL STEP** For a mixture of solvents, use a higher pressure first to evaporate low boiling solvents, and then use lower pressure to evaporate high boiling solvents. For example, to evaporate a mixture of pentane and ethyl acetate, use ~500 mbar first to remove pentane, and

then use ~200 mbar to remove ethyl acetate. The collection flask should be emptied to remove the collected pentane before lowering the pressure to remove the ethyl acetate.

[H3] Column chromatography (for purification)

For chromatographic separations, silica gel (230-400 mesh) is used. All separations use a gradient of ethyl acetate in pentane. A slight pressure (0.2-0.4 bar) is applied to the top of the column for faster elution. A 'slurry packing' method is described for the preparation of the chromatography column. Dry-packing methods are also possible according to the preference of the user.

1. In a well-ventilated fume hood, pour a quantity of silica gel into a glass beaker. Add pentane until a slurry is formed. ▲**CAUTION** The particle size of silica gel can cause respiratory problems upon prolonged exposure to and inhalation of the silica dust.
2. Set up a glass chromatography column on a retort stand, clamped in two places. If the column is not equipped with a glass frit above the stopcock, it will be necessary to insert a small cotton-wool plug above the stopcock. ▲**CAUTION** do not over-tighten the clamps. The column should be shrouded with plastic netting to protect against injury in the rare case of column failure under pressure.
3. Insert a glass or plastic funnel on the top of the column, and pour the silica slurry (from Step 1) into the column, to the height specified in the 'Procedure Step'.
4. Place a conical flask under the stopcock, and open the stopcock. Apply a gentle pressure to the top of the column until the silica gel settles to a constant height. It may be necessary to gently tap the side of the column to obtain a flat layer. Once the silica has settled, release the pressure and carefully add a thin layer of sand to the top of the silica column. ▲**CRITICAL STEP**The reason for adding the sand layer is to avoid the disturbing of slurry, during the addition of eluent.

5. Carefully load the compound which needs to be purified onto the column via a pipette. It may be helpful to dissolve the compound in a minimum volume of the elution solvent.
6. Allow the compound to elute onto the column under gravity, or briefly apply pressure. Do not allow the top of the column to become dry.
7. Rinse the flask with a minimum volume of eluent solvent, and load this onto the column in the same way. This step may be repeated if necessary.
8. Start the elution using the chosen eluent. For a gradient column, this should be a high pentane : EtOAc ratio.
9. After non-polar impurities have eluted (if applicable), adjust the polarity of the eluent to 1-10% EtOAc in pentane, depending upon the R_f as mentioned in the procedure section. Ideally the compound to be collected will elute in a solvent system in which it has an R_f value of 0.2-0.3. Collect the eluting fractions in test tubes or conical flasks, depending on scale.
10. During the elution of polar eluent, the desired compound elutes and is collected. Monitor the progress of the column by thin-layer chromatography (TLC) of the column fractions.
11. The exact TLC separation conditions and R_f values of the products are specified at the relevant procedure steps.
12. When the product has finished eluting, stop the chromatography, and combine the fractions containing the product. Evaporate the solvent under reduced pressure in a rotary evaporator as described above and collect it in a screw-cap vial for storing.
13. It may be desirable to flush the column with a high polarity solvent to elute more polar fractions. Or, simply apply pressure until the column is completely dry, the waste silica gel can then be carefully disposed of in a silica waste bin or equivalent manner. ▲**CAUTION** The particle size of silica gel can cause respiratory problems upon prolonged exposure to and inhalation of the silica dust.

14. Flash column chromatography can be conducted with variations of the above method. For further guidance on the process, the reader is recommended to consult the original publication from Still, Kahn and Mitra,[35] or laboratory manuals.

[H3] **Liquid/Liquid extraction using a separating funnel**

During extraction using a separating funnel, the release of inbuilt pressure (formed during the shaking of the reaction mixture) is always recommended to avoid uncontrolled release of liquids from the funnel. For the extraction, the steps are:

1. pour the reaction mixture into a separating funnel with tap closed;
2. rinse the reaction flask with extraction solvent and pour into the separating funnel;
3. stopper the funnel, then invert and immediately release pressure through the funnel tap;
4. close the tap, shake the reaction mixture well with the release of inbuilt pressure as above, repeating several times;
5. return the flask to its upright position and allow the layers to separate;
6. with the stopper removed, run off the desired layer into a conical flask through the tap;
7. repeat this process for additional extractions, collecting the desired layer in the same conical flask, and adding Na_2SO_4 or $MgSO_4$ to dry the solvent.

[H1] Procedure 1: Synthesis of [3.1.1]Propellane (1)

▲**CRITICAL** All glass apparatus used in the reaction setup is oven / flame-dried and cooled to room-temperature under a nitrogen stream. All reactions were performed under a nitrogen atmosphere and

stirred at a speed of 500-600 rpm unless stated otherwise. For the addition of solvent to the reaction mixture, the user can employ either a syringe or a cannula.

[H2] Stage 1: Synthesis of 1-(3-chloropropyl)cyclopropan-1-ol (3) ● **Timing 6 h (hands-on time 4 h)**

1. Take a 1 L three-neck round-bottomed flask equipped with a magnetic stirrer bar (length 34 mm, diameter 15 mm, oval shape) and mount it on a stirrer plate. Install a pressure-equalising dropping funnel on one side neck, and install a Suba-seal on the top of the dropping funnel. Connect the middle neck to the Schlenk line via a glass adapter or glass tap adapter. Install a Suba-seal on the other side neck of the flask (Extended Data Fig. 1).
2. Evacuate the flask by applying a vacuum through the Schlenk line. Maintain the vacuum for 5 minutes, and then refill the atmosphere inside the flask with nitrogen. Repeat this process twice more to ensure a complete, dry nitrogen atmosphere inside the flask. Leave the inlet line open to nitrogen gas.
3. Add ethyl 4-chlorobutyrate (28.0 mL, 200.0 mmol, 1.0 equiv.), $Ti(O^iPr)_4$ (6.0 mL, 20.0 mmol, 0.10 equiv.), and diethyl ether (dry, 250 mL) to the flask by a syringe through the Suba-seal on the side neck (Fig. 3a).

   ▲**CAUTION** Ti(O*i*-Pr)$_4$ causes eye irritation, use it in a well-ventilated hood and ensure the residual liquid in the syringe is quenched carefully by rinsing with ice-cold water.
4. Cool the reaction mixture to 0 °C with an ice bath under stirring.
5. Transfer a solution of EtMgBr (166.5 mL, 3.0 M in Et_2O, 500 mmol, 2.5 equiv.) to the dropping funnel through the Suba-seal. Open the stopcock of the dropping funnel cautiously, and add this solution dropwise to the reaction mixture (stirred at 0 °C) over 90-120 minutes.

   ▲**CRITICAL STEP** Overly rapid addition of EtMgBr causes a vigorous reaction. To control the reaction, it is important to add EtMgBr slowly and maintain a reaction temperature of 0 °C. Users can slowly add the solution manually via syringe if a dropping funnel is not available.

◆ **TROUBLESHOOTING**

▲**CAUTION** Ethylmagnesium bromide is dispensed as a flammable organometallic solution, always quench the syringe after each use. For this purpose, flush the syringe twice with toluene or other inert solvent, and then add 10% ammonium chloride solution cautiously, at 0 °C, to quench the Grignard.

6. Stir the reaction at 0 °C for a further 30 minutes after the addition of EtMgBr is complete.

▲**CRITICAL STEP** The majority of starting material is consumed once the Grignard addition is complete. The additional stirring of 30 minutes ensures full conversion of starting material.

7. Maintaining the reaction mixture at 0 °C, quench the reaction slowly over 20-30 minutes by dropwise addition of 10% aqueous H_2SO_4 (250 mL) through the side arm.

8. Remove the ice bath and allow the reaction mixture to warm to room temperature.

9. Transfer the reaction mixture into a separating funnel (1 L) and rinse the reaction flask with Et_2O (2 x 50 mL). Back-extract the aqueous phase another two times with Et_2O (2 x 75 mL), then discard the aqueous phase. Wash the combined organic phases sequentially with H_2O (200 mL), aq. $NaHCO_3$ (sat., 200 mL), and brine (200 mL).

10. Collect the organic phase into a conical flask (1 L) and add anhydrous $MgSO_4$ (~25 g) to dry the solution.

▲**CRITICAL STEP**Additional $MgSO_4$ may be required if the solution of the flask contains excess water. For this purpose, add $MgSO_4$ to the solution in a small proportion, and then either shake the solution manually or stir it on a stirring plate with a magnetic stirrer bar. Continue this addition, until free fine particles of $MgSO_4$ are observed at the bottom of the conical flask.

11. Filter the solution and collect the filtrate in a one-neck RB flask (1 L). Then, remove the solvent under reduced pressure using a rotary evaporator.

12. The product **3** (22.9 g, 170.0 mmol, 85%) is isolated as a colorless liquid that is used in the next stage (step 15, procedure 1) without further purification.

<PAUSE POINT> if necessary, Product **3** can be stored in a refrigerator (~5 °C) in a screw cap vial for several months under nitrogen without any degradation.

Stage 2: Synthesis of 1-(3-chloropropyl)cyclopropyl methanesulfonate (4) ● **Timing 5 h (hands-on time 4 h)**

13. Take a two-neck round-bottomed flask (1 L) equipped with a magnetic stirrer bar (length 34 mm, diameter 15 mm, oval shape) and mount it on a stirrer plate. Connect one neck to the Schlenk line through a cone adapter, and install a Suba-seal into the other neck (for the experimental setup, see Extended Data Fig. 2).

14. Repeat step 2 (Procedure 1) to fill the flask with a dry nitrogen atmosphere.

15. Add compound **3** (22.9 g, 170 mmol, 1.00 equiv.) from step 12 (Procedure 1), anhydrous CH_2Cl_2 (250 mL), and triethylamine (35.6 mL, 255.0 mmol, 1.5 equiv.) sequentially by a syringe through the Suba-seal of the side arm.

▲ **CAUTION** Triethylamine is an strong-smelling corrosive liquid; ensure it is handled in a well-ventilated fume cupboard.

◆ **TROUBLESHOOTING**

16. Cool the reaction to 0 °C using an ice bath, with stirring.

17. Once the reaction mixture is cooled to 0 °C, add methanesulfonyl chloride (15.8 mL, 104.0 mmol, 1.2 equiv.) dropwise by a syringe over 30 minutes through the side arm Suba-seal.

18. Stir the reaction mixture for another 30 minutes at 0 °C.

19. While maintaining the reaction mixture at 0 °C, quench the reaction by addition of water (150 mL) and then 10% H_2SO_4 solution (250 mL).

20. Pour the reaction mixture into a separating funnel (1 L) and rinse the reaction flask with CH_2Cl_2 (2 x 50 mL). Discard the aqueous layer after back-extracting it another two times with CH_2Cl_2 (2 x 75 mL) and wash the combined organic layers sequentially with aq. $NaHCO_3$ solution (sat., 200 mL) and then brine (200 mL).

21. Collect the organic phase into a conical flask (1 L) and add anhydrous $MgSO_4$ (~25 g) to dry the solution as described in Procedure 1, Step 10.

22. Filter the organic layer and collect the filtrate in a one-neck 1 L round-bottomed flask.

23. Remove the solvent under reduced pressure using a rotary evaporator. The product **4** (34.3 g, 161.5 mmol, 95%) is isolated as a pale-yellow oil which can be use directly in the next stage (step 25, Procedure 1) without further purification.

Stage 3: Synthesis of 5-chloro-2-(chloromethyl)pent-1-ene (5)

● **Timing 7 h (hands-on time 4 h)**

24. Take a two-neck round-bottomed flask (1 L) equipped with a magnetic stirrer bar and then repeat steps 13 and 14 of Procedure 1 to maintain a nitrogen atmosphere in the flask (see Extended Data Fig. 3).

25. Add compound **4** (34.3 g, 161.5 mmol, 1.0 equiv.) from step 23 (Procedure 1) and anhydrous CH_2Cl_2 (250 mL) through the side arm by a syringe.

26. To the stirred reaction mixture at room temperature, add $TiCl_4$ (27.4 mL, 250.3 mmol, 1.55 equiv.) dropwise by a syringe through the side arm Suba-seal, over 30-45 minutes.

▲**CAUTION** $TiCl_4$ is skin corrosive and inhalation of vapour causes respiratory irritation. Quench the residual $TiCl_4$ in the syringe by flushing with ice water.

27. Stir the reaction mixture at room temperature for 3 h.

28. Cool the stirred reaction mixture to 0 °C using an ice bath, and then quench the reaction by addition of H_2O (300 mL).

29. Transfer the reaction mixture into a separating funnel (1 L) and separate the layers. Discard the aqueous phase after back-extracting it twice with CH_2Cl_2 (2 x 75 mL). Wash the combined organic phases sequentially with H_2O (200 mL), $NaHCO_3$ (sat., aq., 200 mL), and brine (200 mL).

30. Finally, collect the organic layer into a conical flask (1 L), then add $MgSO_4$ (~25 g) to dry the layer as described in Procedure 1, Step 10.

31. Filter the organic phase and collect the filtrate into a one-neck 1 L round-bottomed flask.

32. Remove the solvent under reduced pressure using a rotary evaporator. The product **5** (21.2 g, 139 mmol, 86%) is isolated as a pale-yellow liquid which can be used in the next stage (step 34, procedure 1) without further purification.

▲**CRITICAL STEP**The product is volatile under reduced pressure. Prolonged subjection to moderate vacuum (~300-400 mbar) can lead to some loss of product along with residual solvent (~5% loss of product over 15 minutes). For the evaporation of the solvent, a pressure of 400 mbar and a rotary evaporator water bath temperature <30 °C is recommended. Once most of the solvent is evaporated, the round-bottomed flask should immediately be removed from the rotary evaporator. The product, containing some residual solvent, should be stored in a screw cap vial, or used directly in the next stage (step 34, procedure 1). The distillate may also contain some product **5**, and it is recommend to check the distillate by TLC or ^{1}H NMR spectroscopy. This fraction can be re-distilled by rotary evaporator if a significant amount of the desired olefin compound is present.

◆ **TROUBLESHOOTING**

<PAUSE POINT> If necessary, Product **5** can be stored in a refrigerator (~5 °C) in a screw cap vial for several months under nitrogen without any degradation.

Stage 4: Synthesis of 1,1-dibromo-2-(chloromethyl)-2-(3-chloropropyl)cyclopropane (6)

● **Timing 24 h (hands-on time 10-12 h)**

33. Tetra-*n*-butylammonium iodide (TBAI, 5.1 g, 13.9 mmol, 0.1 equiv.) is added to a two-neck round-bottomed flask (1 L), which is then equipped with a magnetic stirrer bar. Steps 13 and 14 of Procedure 1 are carried out (for the experimental setup, see Extended Data Fig. 4).

▲**CRITICAL STEP**Refill the nitrogen slowly to avoid TBAI being blown around the flask; it will stick to the inner wall of the flask. Any TBAI that does stick to the wall can be washed down with the bromoform used (see step 32, Procedure 1). Users can alternatively add TBAI later (in step 34, Procedure 1), after filling the flask with nitrogen. In that case, open the Suba-seal of the side arm with the flask under a slight positive pressure of nitrogen, add TBAI (e.g. from a vial), and replace the Suba-seal.

34. Add compound **5** (21.2 g, 139 mmol, 1.00 equiv.) from step 32 (Procedure 1), and then $CHBr_3$ (72.9 mL, 833 mmol, 6.0 equiv.) by syringe through the side arm.

35. Cool the reaction mixture to 0 °C and then add 50% NaOH solution (83.2 g, 2.08 mol, 15 equiv.) dropwise over 30 minutes at 0 °C, with vigorous stirring.

36. After the addition, remove the ice-bath and warm the reaction to room temperature, then stir for 12 h at 1000 rpm.

▲**CRITICAL STEP**Vigorous stirring is of critical important in this step; slow stirring leads to lower yields of product, and a stirring of at least 1000 rpm is advisable.

◆ **TROUBLESHOOTING**

37. During the reaction, a significant amount of insoluble particles are formed. After the reaction, add pentane (200 mL) and water (200 mL) to the reaction mixture and shake it well. Pass the solution through a small plug of Celite to remove the insoluble particles, washing the Celite pad with pentane (3 x 50 mL).

▲**CRITICAL STEP**Use a sintered glass funnel for this filtration. Add celite (~25 g) to the funnel and use vacuum filtration into a Buchner flask.

38. Transfer the filtrate to a separating funnel (1 L) for extraction of the product. Collect the organic layer into a conical flask (1 L) and repeat the extraction of the aqueous phase a further three times with pentane (3 x 200 mL).

39. Wash the combined organic layers with brine, collect in another conical flask (1 L), and add $MgSO_4$ (~25 g) to dry this phase as described in Procedure 1, Step 10.

40. Filter the solution into a round-bottomed flask (1 L) and remove the solvent under reduced pressure using a rotary evaporator.

▲**CRITICAL STEP**To remove unreacted bromoform, a pressure of ~0-10 mbar at 35 °C water bath is required, with prolonged rotary evaporation for ~1 h.

41. Purify the product by column chromatography. Begin the column with pentane, transitioning to 5% EtOAc in pentane, collecting the product (37.9 g, 117 mmol, 84%) as a light-yellow oil. Column details: silica (230-400 mesh), glass column length (total) 52 cm, column diameter 5 cm, silica gel height 20 cm. The product has an R_f of 0.40 in pentane (TLC stain: phosphomolybdic acid, PMA).

▲**CRITICAL STEP**If the crude product from step 40 still contains some bromoform, this can be removed during the elution with 100% pentane; bromoform will elute in the earlier fractions. By TLC, the product spot (lower spot) and an (unidentified) impurity spot (upper spot) are very very close in R_f. Therefore, after the column, some product fractions are likely to elute as pure, and some product fractions are likely to elute with the impurity. Impure fractions can be repurified by further chromatography if required.

<PAUSE POINT> If necessary, Product **6** can be stored in a refrigerator (~5 °C) in a screw cap vial for several months under nitrogen without any degradation.

[H2] Stage 5: Synthesis of [3.1.1]propellane (1) ● **Timing 11 h (hands-on time 4 h)**

<CRITICAL> This synthesis can be performed using methyl lithium instead of phenyl lithium at Step 45, procedure 1. See Box 1 for details.

42. Take a one-neck round-bottomed flask (500 mL) equipped with a magnetic stirrer bar and mount it on a stirrer plate. Install a Suba-seal on the neck and then connect the flask to the Schlenk line via a needle. Repeat step 2 (Procedure 1) to fill the flask with a nitrogen atmosphere (for the experimental setup, see Extended Data Fig. 5).

▲**CRITICAL STEP**After the reaction, the round-bottomed flask containing the reaction mixture will be connected to the rotary evaporator for distillation of [3.1.1]propellane. Use of a one-neck (NOT multi-neck) round-bottomed flask is strongly advised. If the reaction is carried out in a two-neck round-bottomed flask, transfer the solution after the reaction is complete into a nitrogen-filled one-neck round-bottomed flask by a cannula for the distillation of [3.1.1]propellane.

43. Add compound **5** (19.5 g, 60.0 mmol, 1.0 equiv.) of step 41 (procedure 1) to the flask via a syringe, and then add anhydrous Et_2O (250 mL). Start stirring.

44. Cool the flask to -78 °C using a dry-ice/acetone cooling bath (Extended Data Fig. 5d).

45. Add phenyllithium (63.6 mL, 121 mmol, 2.01 equiv., 1.9 M in *n*-Bu_2O) dropwise by a syringe at -78 °C through the Suba-seal over 30-45 minutes.

▲**CAUTION** Phenyllithium is a flammable organometallic compound, always quench the syringe after each use. For this quench, flush the syringe with a mixture of toluene/ethyl acetate and then add isopropanol slowly at 0 °C.

46. Stir the reaction mixture at −78 °C for 30 minutes, then remove the cooling bath and warm the reaction mixture to room temperature, and stir for 7 h.

[H3] ***Distillation of the [3.1.1]propellane product***

<CRITICAL> To distill the [3.1.1]propellane product from the reaction mixture, use a rotary evaporator with a water bath temperature of 30 °C (for details of distillation, see below and Extended Data Fig. 6). 47. Ideally, use a rotary evaporator with a dry-ice cold finger condenser. If this is not available, circulation of chilled fluid through a condensor spiral would be sufficient. Before starting the distillation, thoroughly clean the inside of the rotary evaporator including the adapter, collection flask, dry ice cold trap, etc with acetone.

48. Assemble the parts of the rotary evaporator and attach an empty one-neck round-bottomed flask (any size) to the rotary evaporator by an adapter.

49. Place the system under vacuum (~10 mbar) for 15-20 minutes, and then back fill with nitrogen. Repeat evacuation / N_2 fill another two times, to ensure a complete nitrogen atmosphere inside the rotary evaporator.

50. Set the water bath temperature to 30 °C and the pressure to 750 mbar. Place dry ice in the cold finger condenser of the rotavapor, and sufficient acetone to approximately half fill the finger. Now remove the Suba-seal from the neck of the reaction round-bottomed flask, remove the stirrer bar rapidly with a magnetic rod and quickly but carefully connect it to the rotary evaporator by an adapter. Secure with a plastic clip.

51. Immerse the round-bottomed flask in the water bath, and then start rotation of the flask. Place the collection flask in a -78 °C cooling bath (dry ice/acetone) and then start applying vacuum (750 mbar).

▲**CRITICAL STEP**To immerse the collection flask into the cooling bath, use a laboratory jack to raise the cooling bath (on the jack) up to the collecting flask.

52. Lower the pressure from 750 mbar to 150 mbar very slowly (over 1 hour; decrease approx. 50 mbar pressure / 5 minutes) to distill out diethyl ether.

▲**CRITICAL STEP** Sudden lowering of pressure may cause bumping of the reaction solution into the rotary evaporator. To avoid this risk, the user should lower the pressure slowly as described.

53. Once distillation of ether is complete, stop the vacuum, and refill the system with nitrogen. Stop rotation of the distilling flask.

◆ **TROUBLESHOOTING**

54. Remove the cooling bath, open the collection round-bottomed flask under a flow of nitrogen, and discard this solvent (containing Et_2O). Then, flush the round-bottomed with nitrogen, re-attach it to the rotary evaporator, and again immerse this flask into the -78 °C cooling bath.

55. Now, set the pressure to 150 mbar and restart the distillation process by rotation of the distilling flask, lowering the pressure from 150 mbar to ≤10 mbar over ~30 minutes, and holding this pressure for another 15-30 minutes to distill over most of the [3.1.1]propellane. The collection flask will now contain [3.1.1]propellane in *n*-Bu_2O (major) and Et_2O (minor).

▲**CAUTION** An amount of bromobenzene, generated from PhLi under the reaction conditions, also co-distils during this distillation. Thus, the resulting [3.1.1]propellane solution contains an amount of bromobenzene. This does not influence the atom transfer radical addition (ATRA) reactions described herein as the C–Br bond is inert to cleavage under these conditions.

56. Stop the vacuum and rotation of the distilling flask, and fill the system with nitrogen. Remove the cooling bath, detach the collection flask from the rotavapor, and syringe out the [3.1.1]propellane solution as rapidly as is safely possible, storing the solution in a nitrogen-filled Acro-seal amber-color glass bottle (store at -20 °C in a freezer, see Extended Data Fig. 6).

57. Purge the solution with nitrogen for 5 minutes, seal the bottle, and store the bottle at -20 °C in a freezer.

[H3] **Determination of the concentration of [3.1.1]propellane (^{n}Bu$_2$O/Et$_2$O solution).**

58. Add 0.2 mL of [3.1.1]propellane solution to a nitrogen-flushed NMR tube. Add 1,2-dichloroethane (30 µL, 0.38 mmol) as an internal standard, and benzene-d_6 or $CDCl_3$ (0.30 mL). Put a cap on the NMR tube, and immediately (ideally within 1 h for benzene-d_6) measure the ^{1}H NMR spectrum to determine its concentration.

<CRITICAL STEP> Chloroform-d (pre-stored over K_2CO_3) may also be used, however for this case it is recommended to record the ^{1}H NMR spectrum within 5-10 minutes to avoid acid-promoted decomposition; some decomposition can be observed after 20-30 minutes.

◆ **TROUBLESHOOTING**

59. The NMR spectrum (see Fig. 4) contains [3.1.1]propellane, ^{n}Bu$_2$O, Et$_2$O, $CDCl_3$, and 1,2-dichloroethane (0.38 mmol). Integrate the 1,2-dichloroethane peak (3.61 ppm, 4 × H) against the [3.1.1]propellane peaks (2.47 - 2.33 ppm, 4 × H):

The concentration can be calculated as follows (for the integration of the peaks, see Fig. 4):

$$c(\text{Propellane}) = \frac{n(\text{Propellane})}{V(\text{Propellane})} = \frac{\frac{\text{Integral(Propellane)}}{\text{Integral(DCE)}} \cdot n(\text{DCE})}{V(\text{Propellane})} = \frac{0.24 \cdot 0.38\ \text{mmol}}{0.2\ \text{mL}}$$

$$= 0.46\ \text{M}$$

▲ **CRITICAL STEP** For each use of this solution, remove the bottle from the refrigerator, insert a nitrogen inlet (needle). Syringe out the required volume, then remove the inlet and reseal the bottle with parafilm, and immediately put it back in the freezer (Extended Data Fig. 7). Ideally this process would be completed within 5-10 minutes to prevent any decomposition. We recommend to the user that the experimental set-up is pre-prepared, ready to add [3.1.1]propellane solution, before removing it from the freezer.

PAUSE POINT [3.1.1]propellane solution is stored at -20 °C in a freezer. No significant decomposition is observed within a month, and the concentration can be determined at any point via the above technique. We tested the storage of this solution for up to 6 months, and observed degradation of 10-30% for different batches. The concentration of the [3.1.1]propellane solution synthesized in different batches ranged between 0.25 M and 0.50 M (43-61% yield). The user may prefer to synthesize fresh [3.1.1]propellane solution "on demand".

BOX 1 Alternative Method for propellane synthesis using methyl lithium

The [3.1.1]propellane solution can also be prepared using MeLi instead of PhLi by following an equivalent procedure to that described above:

1. Add methyllithium (5.5 mL, 60.4 mmol, 2.05 equiv., 0.75 M in Et_2O) dropwise to a cooled (-78 °C), stirred solution of **6** (650 mg, 0.2 mmol mmol, 1.0 equiv.) in anhydrous Et_2O (15 mL).
2. Stir the resulting mixture at -78 °C for 15 minutes, then warm to room temperature and stir for 7 h.
3. Distill the mixture using a rotary evaporator (25 °C water bath temperature) equipped with a dry-ice cold finger condenser as describe in Stage 5, with the receiving flask immersed in a dry ice / isopropyl alcohol bath. The Et_2O fraction was removed by slowly decreasing the applied pressure to 150 mbar. This fraction was then discarded. The remaining solution was distilled by slowly reducing the applied pressure to <10 mbar to afford a solution of [3.1.1]propellane in *n*-Bu_2O, which was stored under an inert atmosphere at −20 °C.
4. Determine the yield by ^1H NMR spectroscopy using the residual ^1H peak of C_6D_6 as an internal standard. On the scale described here, [3.1.1]propellane was obtained as a 0.45 M solution in ~2.2 mL of *n*-Bu_2O, in 49% yield.

▲**CAUTION** A stoichiometric amounts of bromomethane will be genetrated during the course of reaction.

END OF BOX 1

Procedure 2: Synthesis of BCHep iodides

▲**CRITICAL** All glass apparatus used in the reaction setup is oven / flame-dried and cooled to room-temperature under a nitrogen stream. All reactions were performed under a nitrogen atmosphere and stirred at a speed of 500-600 rpm unless stated otherwise. For the addition of solvent to the reaction mixture, the user can employ either a syringe or a cannula.

▲**CRITICAL** It is recommended to establish the concentration of [3.1.1]propellane solution by ^{1}H NMR spectroscopy if stored for a prolonged period (e.g. >1 week). See procedure 1, stage 5, steps 58-59 (Fig. 4) for details.

Section 1: Synthesis of (5-iodobicyclo[3.1.1]heptan-1-yl)methyl pivalate (7) ● **Timing** 8 h (hands-on time 3 h)

<CRITICAL> Refer to the Photochemical Setup section of Equipment Setup.

Photochemical setup for ATRA reaction.

1. Take a flame-dried, one-neck round-bottomed flask (100 mL volume) equipped with a magnetic stirrer bar and secure it using a clamp. Add iodomethyl pivalate (2.18 g, 9.00 mmol, 1.0 equiv.) and *fac*-Ir(ppy)$_3$ (59 mg, 90 µmol, 1 mol%) (for the experimental setup, see Fig. 6 and Extended Data Fig. 8 , and the photochemical setup in Equipment Setup).
2. Install a Suba-seal on the top of the flask and connect it to the Schlenk line by a needle. Carefully evacuate the vial, and refil with nitrogen. Repeat this process a further two times.
3. Prepare a [3.1.1]propellane solution (**1**, 13.50 mmol) by adding PhLi solution (in n-Bu$_2$O) to a solution of compound **6** (in Et$_2$O). For details, see procedure 1, stage 5.

4. Add [3.1.1]propellane solution (**1**, 33.8 mL, 0.40 M in $^{n}Bu_2O$, 13.50 mmol, 1.50 equiv.) and ^{t}BuCN (15.0 mL) to the vial by syringe through the Suba-seal.

5. Add an exit needle to the flask, then purge the solution with nitrogen by immersing a needle with a nitrogen flow into the solution for 5 minutes. Then, remove the two needles from the Subaseal

6. Place the flask in photobox, under irradiation (456 nm) for 5 h. (Fig. 6f).

◆ **TROUBLESHOOTING**

7. Switch off the LED light, then remove the flask from the photobox. Remove the solvent under reduced pressure using a rotary evaporator (water bath temperature 30 °C).

8. Purify the residue by silica gel column chromatography. Begin the column with pentane as eluent, and then 1% EtOAc in pentane. Column details: silica (230-400 mesh), column length (total) 40 cm, column diameter 2.6 cm, silica height 18 cm, R_f 0.38 (5% EtOAc in pentane, Fig. 5). This affords the product **7** (2.12 g, 6.3 mmol, 70%) as a light yellow liquid, after removal of the chromatography solvent.

■ **PAUSE POINT** Product **7** can be stored in a screw cap vial inside a freezer at -20 °C for ≥ 6 months.

Alternative Method:

We also found that the reaction between $PivOCH_2I$ and [3.1.1]propellane can lead to the formation of **7** in the absence of photocatalyst but with blue LED irradiation; and also in the absence of photocatalyst and irradiation. These reactions proceeded with slightly lower yields of 68% and 51%, respectively. However, the reaction between 2-I-Py and [3.1.1]propellane failed to afford the desired product **9** in the absence of the photocatalyst and light.

Section 2: Synthesis of tert-butyl 4-(5-iodobicyclo[3.1.1]heptan-1-yl)piperidine-1-carboxylate (8)

● **Timing 6 h (hands-on time 3 h)**

1. Prepare a [3.1.1]propellane solution (**1**, 9.75 mmol) by adding PhLi solution (in n-Bu_2O) to a solution of compound **6** (in Et_2O). For details, see procedure 1, stage 5.
2. Follow the same procedure as Section 1, Steps 1–7, using *tert*-butyl 4-iodopiperidine-1-carboxylate (2.33 g, 7.5 mmol, 1.0 equiv.), *fac*-Ir(ppy)$_3$ (46 mg, 75 µmol, 1.0 mol%), [3.1.1]propellane solution (**1**, 24.4 mL, 0.40 M in $^{n}Bu_2O$, 9.75 mmol, 1.3 equiv.), ^{t}BuCN (12.0 mL), with irradiation for 3 h.
3. Purify the residue by silica gel column chromatography. Start the column with pentane as eluant, and then 10% EtOAc in pentane. Column details: silica (230-400 mesh), column length (total) 45 cm, column diameter 1.7 cm, silica height 15 cm, R_f 0.25 (10% EtOAc in pentane, Fig. 5). This affords the product **8** (1.85 g, 4.57 mmol, 61%) as a light yellow oil after evaporation of solvent.

■ **PAUSE POINT** Product **8** can be stored in a screw cap vial inside a freezer at -20 °C for ≥ 6 months.

Section 3: Synthesis of 2-(5-Iodobicyclo[3.1.1]heptan-1-yl)pyridine (9)

● **Timing 6 h (hands-on time 3 h)**

1. Prepare a [3.1.1]propellane solution (**1**, 7.67 mmol) by adding PhLi solution (in n-Bu_2O) to a solution of compound **6** (in Et_2O). For details, see procedure 1, stage 5.
2. Follow the same procedure as Section 1, Steps 1–7, using 2-Iodopyridine (1.03 g, 5.0 mmol, 1.0 equiv.), *fac*-Ir(ppy)$_3$ (50.0 mg, 76.0 µmol, 1.5 mol%), [3.1.1]propellane solution (**1**, 19.2 mL, 0.40 M in $^{n}Bu_2O$, 7.67 mmol, 1.5 equiv.), ^{t}BuCN (4.0 mL), with irradiation for 3 h.
3. Purify the residue by silica gel column chromatography. Begin the column with pentane as eluant, and then 10% EtOAc in pentane. Column details: silica (230-400 mesh), column length (total) 45 cm, column diameter 1.7 cm, silica height 15 cm, R_f 0.44 (20% EtOAc in pentane, Fig.

5). This affords the product **9** (1.0 g, 3.35 mmol, 67%) as a light yellow oil after evaporation of solvent.

■**PAUSE POINT** Product **9** can be stored in a screw cap vial inside a freezer at -20 °C for ≥ 6 months.

Procedure 3: synthesis of 5-(4-(trifluoromethoxy)phenyl)bicyclo[3.1.1]heptane-1-carboxylic acid (14)

▲**CRITICAL** All glass apparatus used in the reaction setup is oven / flame-dried and cooled to room-temperature under a nitrogen stream. All reactions were performed under a nitrogen atmosphere and stirred at a speed of 500-600 rpm unless stated otherwise. For the addition of solvent to the reaction mixture, the user can employ either a syringe or a cannula.

▲**CRITICAL** It is recommended to establish the concentration of [3.1.1]propellane solution by ^{1}H NMR spectroscopy if stored for a prolonged period (e.g. >1 week). See Procedure 1, Stage 5, Steps 58-59 (Fig. 4) for details.

Stage 1A: Synthesis of (4-(trifluoromethoxy)phenyl) magnesium bromide (11)

● **Timing 4 h (hands-on time 2 h)**

1. Take a flame-dried, two-neck round-bottomed flask (25 mL) equipped with a magnetic stirrer bar (length 12.7 mm, diameter 3.2 mm). Mount the flask on a stirrer plate using a clamp. Then, add Mg turnings (264 mg, 10.8 mmol, 1.2 equiv.) to the flask (Fig. 7, and Extended Data Fig. 9a-b).
2. Install a reflux condenser on the 'vertical' neck of the flask and connect the top of the condenser to the Schlenk line by a glass cone adapter or tap adaptor. Install a Suba-seal on the other neck of the flask.

3. Place the flask under vacuum and then heat the flask with a heat gun for ~2 minutes to remove moisture. Repeat step 2 (procedure 1) to place the flask under a nitrogen atmosphere.

4. Allow the the flask to cool to room temperature, and then add anhydrous THF (7.5 mL) via syringe, and I_2 (one crystal, rapid unstoppering / restoppering) through the side arm of the flask.

5. Stir the reaction mixture for 5 minutes, and then add 1-bromo-4-(trifluoromethoxy)benzene (1.35 mL, 9.00 mmol, 1.0 equiv.) dropwise via syringe through the side arm.

6. Place the flask in a sand bath and heat for 2 h at 66 °C.

7. Cool the reaction mixture to room temperature, and then titrate the resulting Grignard reagent via iodometric titration to determine the concentration of the solution.

▲**CRITICAL STEP**For the titration, take iodine (50.0 mg, 0.39 mmol) in a nitrogen-filled vial equipped with a Suba-seal. Then, add THF (0.25 mL) to dissolve the iodine. Add a solution of Grignard reagent dropwise by a syringe until the iodine colour dissipates. From the volume of Grignard reagent required to quench the iodine, calculate the concentration, by following the standard method (1 equiv. Grignard per equiv. I_2).

8. Use the resultant (4-(trifluoromethoxy)phenyl)magnesium bromide solution (**11**, determined at 0.70 M using the above procedure) in the next stage (step 13, procedure 3).

Stage 1B: Synthesis of (5-(4-(trifluoromethoxy)phenyl)bicyclo[3.1.1]heptan-1-yl)methyl pivalate (12)

● **Timing 4 h (hands-on time 3 h)**

9. Take a flame-dried one-neck round-bottomed flask (25 mL volume) equipped with a magnetic stirrer bar, and mount it on a stirrer plate using a clamp. Then add BCHep iodide **7** (1.01 g, 3. 0

mmol, 1.0 equiv.) and $Fe(acac)_3$ (210 mg, 0. 6 mmol, 0.20 equiv.) to the flask (Extended Data Fig. 9c-f).

10. Install a Suba-seal and then repeat step 2 (procedure 1) to fill the flask with a nitrogen atmosphere.

11. Now add anhydrous THF (2.0 mL) and TMEDA (180 µL, 1.2 mmol, 0.40 equiv.) to the flask via syringe through the Suba-seal.

12. Stir the resulting mixture at room temperature for 5 minutes.

13. Slowly add (4-(trifluoromethoxy)phenyl)magnesium bromide (**11**, 6.8 mL, 0.70 M in THF, 4.8 mmol, 1.60 equiv., from Step 8, Procedure 3) to the solution via a syringe. This can be carried out manually (dropwise) or via a syringe pump, over 15-60 minutes. This rate of addition corresponds to 0.32 mmol min^{-1} (15 min addition time) or 0.077 mmol min^{-1} (60 min addition time). Either rate of addition gives similar results.

◆ **TROUBLESHOOTING**

14. Stir the reaction mixture for a further 30 minutes.

15. Quench the reaction mixture by adding aq. NH_4Cl (12 mL, saturated) dropwise, and cool the stirred reaction mixture to 0 °C using an ice-bath.

16. Take the reaction mixture into a separating funnel (100 mL), and rinse the flask with diethyl ether (2 x 5.0 mL). Separate the phases, then back-extract the aqueous phase with diethyl ether (2 x 5.0 mL) and then discard the aqueous phase. Take the combined organic phases into the separating funnel and wash with brine (50 mL).

17. Collect the organic phase in a conical flask (100 mL) and dry over $MgSO_4$ (2.5 g) as described in Procedure 1, Step 10.

18. Filter the diethyl ether layer and collect it in a one-neck round-bottomed flask (100 mL) and then remove the solvent in a rotary evaporator under reduced pressure.

19. Purify the oily residue by silica gel column chromatography. Begin the column with pentane as eluent, and then 1% EtOAc in pentane. Column details: silica (230-400 mesh), column length (total) 45 cm, column diameter 1.7 cm, silica height 15 cm, and R_f 0.50 (5% EtOAc in pentane). This affords the product **12** (9.4 g, 2.52 mmol, 84%) as a light yellow liquid after removal of the chromatography solvent.

■**PAUSE POINT** Product **12** can be stored in a screw cap vial under nitrogen at -20 °C for ≥6 months.

Stage 2: Synthesis of (5-(4-(trifluoromethoxy)phenyl)bicyclo[3.1.1]heptan-1-yl)methanol (13)

● **Timing 22 h (hands-on time 2 h)**

20. Take a one-neck round-bottomed flask (50 mL volume) equipped with a magnetic stirrer bar and mount it on a stirrer plate using a clamp (for the experimental setup, see (Extended Data Fig. 10a-c)).
21. Add compound **12** (0.90 g, 2.42 mmol, 1.0 equiv.) from step 19 procedure 3, and then add MeOH (30 mL) to the vial. Dissolve the compound with stirring, and then add aq. NaOH solution (aq., 1 M, 3.41 mL, 3.3 mmol, 1.4 equiv.) to the reaction mixture.
22. Seal the flask with a Subaseal, equip with a nitrogen balloon, and place it in a preheated sand bath with stirring at 50 °C for 20 h.
23. Stop heating, remove the reaction mixture from the bath, and allow it to cool to room temperature.
24. Remove the solvent using a rotary evaporator under reduced pressure to afford a solid residue.
25. Redissolve the residue in EtOAc (20 mL), transfer it to a separating funnel (100 mL), then add H_2O (20 mL). Extract the aqueous phase using EtOAc (3 × 10 mL).

26. Collect the combineed EtOAc phases in a conical flask (100 mL) and dry over $MgSO_4$ (2.5 g) as described in Procedure 1, Step 10.

27. Filter the solution, and collect the filtrate in a one-neck round-bottomed flask (100 mL). Remove the solvent under reduced pressure using a rotary evaporator. The resulting alcohol (675 mg, ~2.35 mmol, ~97%, white solid) can be used directly in the next stage (step 29, procedure 3) without further purification.

Stage 3: Synthesis of 5-(4-(trifluoromethoxy)phenyl)bicyclo[3.1.1]heptane-1-carboxylic acid (14)

● **Timing 6 h (hands-on time 3 h)**

28. Take a one-neck round-bottomed flask (50 mL volume) equipped with a magnetic stirrer bar (length 12.7 mm, diameter 3.2 mm) and mount it on a stirrer plate using a clamp (for the experimental setup, see Extended Data Fig. 10d-f).

29. Add compound **13** (620 mg, 2.2 mmol, 1.0 equiv.), and then add a mixture of MeCN / CH_2Cl_2 / distilled water (1:1:2, v/v; total volume 10 mL). Now add $NaIO_4$ (1.9 g, 8.8 mmol, 4.0 equiv.) and $RuCl_3.xH_2O$ (24 mg, 108 µmol, 0.05 equiv.). Install a Subaseal on the flask.

30. Stir the reaction mixture vigorously at room temperature for 3 h.

31. Filter the solution through a small pad of tightly packed Celite (vacuum filtration, glass sinter funnel) to remove the fine particles. Collect the filtrate in a conical flask. Rinse the Celite pad with CH_2Cl_2 (2 x 5.0 mL) and collect the filtrate in the same conical flask.

32. Add $MgSO_4$ (5.0 g) to the conical flask to dry the solution. Filter the solution and collect the organic phase in a one-neck round-bottomed flask (100 mL).

33. Remove the solvent under reduced pressure using a rotary evaporator, and then add 1 M NaOH (20 mL) to the residue to make the sodium salt of the desired carboxylic acid.

◆ **TROUBLESHOOTING**

34. Extract the aqueous layer with Et_2O three times (3 x 10 mL); collect the aqueous layer in a conical flask (100 mL) and discard the Et_2O solution.

▲**CRITICAL STEP**Here, all unwanted (non-carboxylic acid) side products dissolve in Et_2O and only the desired sodium salt of the carboxylic acid product (-COONa) remains in the aqueous phase. It is important to use sufficient base to completely form this salt.

35. Acidify (lower pH, pH 3-4) the aqueous phase with 1 N HCl to convert the carboxylic acid sodium salt to the carboxylic acid.

◆ **TROUBLESHOOTING**

36. Extract the aqueous phase with EtOAc (3 × 15 mL) and collect it in a conical flask (100 mL).

37. Add $MgSO_4$ (5.0 g) to the flask to dry the EtOAc phase as described in Procedure 1, Step 10.

38. Filter the solution and collect the filtrate in a one-neck round-bottomed flask (100 mL). Remove the solvent under reduced pressure using a rotary evaporator and collect the desired acid **14** as a white solid (443 mg, 1.48 mmol, 68%). No further purification is required.

■**PAUSE POINT** Acid **14** can be stored without degradation in a screw-cap vial under nitrogen for ≥ 3 months at -20 °C.

Troubleshooting

Troubleshooting advice can be found in Table 1.

Table 1| Troubleshooting table.

Step	Problem	Probable reason	Possible solution
5 (Procedure 1)	The yield of the desired product was lower than expected	The temperature of the reaction mixture was not	Maintain the bath temperature at 0 °C with ice / water. For this purpose,

	with formation of more side product by the nucleophilic addition of EtMgBr to the carbonyl. (Note that this potential problem was not observed in our hands.)	maintained at 0 °C during the Grignard addition. It is possible that even if the ice bath temperature was 0 °C at the start of the reaction, the bath temperature can increase slowly during the addition of Grignard resulting in the ice slowly melting.	remove the cold water from the bath and add some ice, at regular time intervals.
15 (Procedure 1)	Lower yield	Et_3N may contain water, as it is somewhat hygroscopic, which may quench the reaction mixture before it is completed. The use of an old Et_3N bottle may be a reason for this high water content.	Either dry the Et_3N following standard procedure or use a new sealed bottle of Et_3N.
32 (Procedure 1)	Lower yield of olefinic product.	The product is volatile and may condense in the collection flask of the rotary evaporator during evaporation of solvent.	Ensure the water bath temperature is <30 °C, and the evaporation pressure is >400 mbar.

			Re-distil the collected solution at a lower temperature / higher pressure to isolate further product.
36 (Procedure 1)	Lower conversion / yield.	Insufficient mixing of the biphasic reaction mixture.	Use a good quality stirrer plate / larger stirrer bar and monitor the stirring rate (≥1000 rpm), or an overhead stirrer.
53 (Procedure 1)	The lower yield of [3.1.1]propellane.	A portion of the desired product may have distilled over with diethyl ether due to a higher water bath temperature. Alternatively, propellane in the distilling flask may start to decompose as it becomes more concentrated, if the distillation takes too long.	There may be some error with the digital reading of the water bath temperature and therefore the user should double-check the bath temperature with a thermometer too, to confirm that the bath temperature does not exceed 30 °C.
58 (Procedure 1)	Degradation of [3.1.1]propellane solution.	Moisture or oxygen taken into the [3.1.1]propellane bottle. Or decomposition of the solution happens after	Purge the solution for a few minutes with an N_2 flow. Do not keep the bottle outside of the freezer for a long

		storage of bottle for a long time at room temperature.	time, and replace immediately in the freezer after each use.
6 (Procedure 2, section 1)	Significantly lower conversion / yield.	Cooling fan / blue LEDs / stirring ceased during the reaction.	Check cooling fan or blue LEDs or stirring and monitor the reaction. Ensure the LED is a suitable distance from the sample.
13 (Procedure 3, stage 1B)	The lower yield of acid **12**.	Rapid decomposition of the iron catalyst during the reaction. This may be due to the immediate addition of the Grignard reagent before the complex formation between $Fe(acac)_3$ and TMEDA.	After the addition of $Fe(acac)_3$, TMEDA, and THF, wait at least 5 minutes for Fe/TMEDA complex formation and then add the Grignard reagent. This may slow the decomposition of the catalyst during the reaction.
33, 35 (Procedure 3, stage 3)	The lower yield of acid **14**.	Incomplete basification (step 33) or acidification (step 35) of the reaction mixture during the workup process by some human error. If the solution is not the correct pH, an amount	Check the pH of the solution carefully before performing each extraction.

		of product will stay in the organic phase (step 33) and aqueous phases (step 35), respectively.	

Timing

Procedure 1: synthesis of [3.1.1]propellane (1; stage 1-5)

Stage 1 (Steps 1-12): 6 h (4 h hands-on-time)

Stage 2 (Steps 13-23): 5 h (4 h hands-on-time)

Stage 3 (Steps 24-32): 7 h (4 h hands-on-time)

Stage 4 (Steps 33-41): 24 h (10-12 h hands-on-time)

Stage 5 (Steps 42-59): 11 h (4 h hands-on-time)

Procedure 2: synthesis of BCHep iodides (7-9; section 1-3)

Section 1 (Steps 1–8): 8 h, (3 h hands-on-time)

Section 2 (Steps 1–3): 6 h (3 h hands-on-time)

Section 3 (Steps 1–3): 6 h (3 h hands-on-time)

Procedure 3: synthesis of BCHep acid (14; stage 1-3)

Stage 1A (Steps 1-8), (optional): 4 h (2 h hands-on-time)

Stage 1B (Steps 9–19): 4 h (3 h hands-on-time)

Stage 2 (Steps 20–27): 22 h (2 h hands-on-time)

Stage 3 (Steps 28–38): 6 h (3 h hands-on-time)

Anticipated results

All intermediates in the synthesis of [3.1.1]propellane, products of propellane ATRA reactions, and subsequent derivatives described in this protocol have previously been isolated and characterized. The ATRA reactions proceed in good yields (63-72%), although a slight decrease of yield (5-10%) is noticed upon scale-up. Analytical data for the products are contained in the Supplementary Information, with copies of ^{1}H and ^{13}C NMR spectra (Fig. S1-S18).

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Author contributions

B.P., A.D., N.F., J.N. and E.A.A. contributed intellectually and practically to the development of this protocol. The manuscript was written by B.P., A.D. and E.A.A. with input from all authors.

Competing interests

The authors declare that there are no competing financial interests.

Data availability

The authors declare that additional data related to this protocol are available in the 'key references using this protocol'. Analytical data for the different compounds described here are taken directly from the primary paper (see 'Related links'), and are included in the Supplementary Information.

Additional information

Related links

Key references used in this protocol

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Supplementary Information

This section contains characterisation data, and copies of ^{1}H and ^{13}C NMR spectra of the key compounds described in this protocol.

FIGURES

Fig. 1| (a) Examples of small bridged ring bioisosteres of benzene rings in drug analogues. (b) Bicyclo[1.1.1]pentanes (BCPs) as isosteres of *para*-substituted arenes. (c) Bicyclo[3.1.1]heptanes (BCHeps) as isosteres of *meta*-substituted arenes .

Fig. 2| Other syntheses of [3.1.1]propellane, and comparison with our approach.

Fig. 3| Overview of Protocol content. (a) Preparation of compound **1** as described in Procedure 1. (b) derivatisation of compound **1** as described in Procedures 2, and 3.

Fig. 4| ^{1}H NMR spectrum of [3.1.1]propellane solution in $CDCl_3$.

Fig. 5| Overview of Procedure 2 and TLC images in the right hand side for the formation of **7**, **8** and **9**.

Fig. 6| General photochemical experimental setup for small-scale reaction in a screw-cap vial. a) Photobox, **b)** Sample holder, **c)** Blue light source, **d)** Intensity control of light (100% is used here), **e)** Photobox with a sample holder on a stirrer plate, **f)** Reaction vial in the photobox, **g)** Photobox with external cooling fan, **h)** Photobox covering with aluminium foil, **i)** Inside view of photo-reaction, and **j)** Photobox covering with aluminium foil coated U-shape board.

Fig. 7| Overview of Procedure 3.

EXTENDED DATA FIGURES

Extended Data Fig. 1 | Synthesis of compound 3. a) Initial experimental setup, **b)** Reaction flask with reagents, **c)** Dropwise addition of EtMgBr at 0 °C, **d)** At the end of EtMgBr addition (see TLC plate,

inset), **e)** Reaction mixture in a separating funnel after quenching with H_2SO_4, and **f)** After extraction, drying of solution over $MgSO_4$.

Extended Data Fig. 2| Synthesis of compound 4. a) Addition of substrate to the nitrogen filled flask (see TLC plate, inset), **b)** Transfer of solvent through cannula, **c)** During the addition of $MeSO_2Cl$, **d)** At the end of $MeSO_2Cl$ addition, **e)** At the end of rection (after 30 minutes stirring), and **f)** After quenching the reaction mixture with water.

Extended Data Fig. 3| Synthesis of compound 5. a) Reaction flask on a stirrer plate, **b)** Flask with substrate (**4**) and CH_2Cl_2, **c)** After few drops addition of $TiCl_4$, **d)** During addition of $TiCl_4$, **e)** End of reaction (after 3 h stirring), (see TLC plate, inset) and **f)** After quenching the reaction mixture with water.

Extended Data Fig. 4| Synthesis of compound 6. a) Reaction flask with substrate (**5**), TBAI, and $CHBr_3$, **b)** Addition of NaOH at the beginning, **c)** After the addition of NaOH, **d)** Reaction mixture after 12 h stirring, **e)** Reaction mixture after extraction, and **f)** Purified compound **6** in a round-bottomed flask (see TLC plate, inset).

Extended Data Fig. 5| Synthesis of [3.1.1]propellane (1). a) Nitrogen filled flask with stirrer bar, **b)** After addition of substrate (**6**), **c)** After the addition of Et_2O, **d)** Reaction mixture -78 °C in a dry ice/acetone cooling bath, **e)** Syringing out PhLi solution (1.9 M in $^nBu_2O$), and **f)** Addition of PhLi solution to the reaction mixture, **g)** Reaction mixture after the addition of PhLi solution, and **h)** Reaction mixture after 7 h stirring.

Extended Data Fig. 6| Distillation of [3.1.1]propellane (1). a) Dry-ice cold finger of rotary evaporator, **b)** Full setup of the distillation, **c)** After distillation of Et_2O, **d)** After distillation of [3.1.1]propellane in $^nBu_2O$, **e)** Syringe out of [3.1.1]propellane solution from collection flask, and **f)** Storing of [3.1.1]propellane solution (**1**) in a acro-seal bottle.

Extended Data Fig. 7| Handling of [3.1.1]propellane solution (1). a) [3.1.1]Propellane bottle held by a clamp, **b)** After removing the screw cap, **c)** Syringing out the solution with a nitrogen inlet attached, **d)** After resealing the bottle.

Extended Data Fig. 8| Experimental setup for compound 7 (section 1). a-e) Small-scale reaction in a screw cap vial. a) Screw cap vial with a magnetic stirrer bar, iodomethyl pivalate and *fac*-Ir(ppy)$_3$ catalyst, **b)** Reaction vial connected to the Schlenk line by a needle, **c)** Purging of the reaction mixture, **d)** Reaction vial on a photo reactor, and **e)** After the reaction (~5 h stirring). **f-i) Preperative-scale reaction in a one-neck round-bottomed flask. f)** Flask, magnetic stirrer bar, and Subaseal, **g**) Flask connected to the Schlenk line by a needle, **h**) After addition of [3.1.1]propellane solution and pivalonitrile, and **i**) After the photochemical reaction.

Extended Data Fig. 9| Grignard synthesis and Kumada coupling. Panels a-b show Grignard; panels c-f for Kumada coupling. **a)** Reaction mixture after addition of I_2, **b)** During heating of the reaction mixture, **c)** During addition of Grignard reagent **11** to the reaction mixture (for small-scale reaction in a screw cap vial), **d)** Flask with a stirrer bar, and Fe(acac)$_3$, **e)** Stirring of reaction mixture after the addition of substrate (**7**), TMEDA, and THF under N_2, and **f)** During addition of Grignard **11** to the reaction mixture.

Extended Data Fig. 10| Hydrolysis and oxidation reactions. Panels a-c show hydrolysis; panels d-f show oxidation. Preparative-scale synthesis (a-b, and d-e), and small-scale synthesis (c and f). **a)** Flask with a magnetic stirrer, substrate (**12**), aq. NaOH solution and methanol, **b)** During heating of the reaction mixture, **c**) Heating of the reaction mixture in a screw cap vial. **d)** Flask with a magnetic stirrer, $NaIO_4$, and solvent, **e)** After addition of $RuCl_3.xH_2O$, and **f)** Reaction mixture after 3 h stirring.