# Synthesis of *meta*-substituted arene bioisosteres from [3.1.1]propellane

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**Summary Paragraph:** Small-ring cage hydrocarbons are common bioisosteres for *para*-substituted benzene rings in drug design[1]. The popularity of these structures derives from the superior pharmacokinetic properties they exhibit compared to the parent aromatics, including improved solubility and reduced susceptibility to metabolism[2,3]. A prime example is the bicyclo[1.1.1]pentane motif, which is mainly synthesised by ring-opening of the inter-bridgehead bond of the strained hydrocarbon [1.1.1]propellane with radicals or anions[4]. In contrast, scaffolds mimicking *meta*-substituted arenes are lacking due to the challenge of synthesising saturated isosteres that accurately reproduce substituent vectors[5]. Here we show that bicyclo[3.1.1]heptanes (BCHeps), hydrocarbons whose bridgehead substituents map precisely onto the geometry of *meta*-substituted benzenes, can be conveniently accessed from [3.1.1]propellane. We found that [3.1.1]propellane can be synthesized on multigram scale, and readily undergoes a range of radical-based transformations to generate medicinally-relevant carbon- and heteroatom-substituted BCHeps, including pharmaceutical

analogues. Comparison of ADME properties of these analogues revealed enhanced metabolic stability relative to their parent arene-containing drugs, validating the potential of this *meta*-arene analogue as an $sp^3$-rich motif in drug design. Collectively, our results show that BCHeps can be prepared on useful scales using a variety of methods, offering a novel surrogate for *meta*-substituted benzene rings for implementation in drug discovery programmes.

**Main Text:** Strategies for the structural modification of lead molecules that improve physicochemical and pharmacokinetic properties such as metabolic stability are increasingly sought in drug development[6]. One example is the replacement of aromatic rings with non-classical bioisosteres such as small-ring cage hydrocarbons[1,3,5,7]. Such structures display a higher fraction of saturated carbon atoms compared to the parent arenes ($Fsp^3$, corresponding to greater three-dimensionality), a property linked to greater clinical success rates[8]. Amongst these motifs, the replacement of planar *para*-substituted arenes with bicyclo[1.1.1]pentanes (BCPs, Fig. 1a), which have similar dimensions and identical substituent vectors to the parent aromatic, has emerged as a popular strategy[2,9,10]. For instance, substitution of the fluorinated arene in the Alzheimer's treatment avagacestat with a BCP resulted in an analogue that maintained the bioactivity of the parent compound, but displayed an improved pharmacokinetic profile[2]. More generally, cage hydrocarbons expand the vector space around a molecular core, offering new opportunities in drug design.

*Meta*-substituted arenes are also commonplace in pharmaceuticals and agrochemicals[11]. However, in stark contrast to the numerous $sp^3$-rich bioisosteres for *ortho*- and *para*-substituted arenes[2,9,10,12], a geometrically-accurate bioisostere for *meta*-arenes is yet to be discovered. Recent reports on the use of (hetero)bicyclo[2.1.1]hexanes[13-17] and bridge-substituted BCPs[18-20] have contributed to this arena (Fig. 1b). However, those motifs fail to recreate the bond vectors displayed in the *meta*-substituted aromatic, and a precise and accessible mimic remains absent from the arsenal of the medicinal chemist.

Here we report a solution to this challenge in the form of the saturated carbocycle bicyclo[3.1.1]heptane (BCHep, Fig. 1c), the bridgehead substituent vectors of which precisely replicate those of the parent *meta*-arene (~119° and ~120° respectively). While BCHeps have been prepared by ring expansion of BCPs[21] and by cyclization of cyclohexane dicarboxylates[22], these approaches can be limited in substituent scope or involve lengthy synthetic sequences. We show that BCHeps can instead be conveniently and directly accessed from [3.1.1]propellane (**1**), a homologue of [1.1.1]propellane (**2**) which is widely used as the near-ubiquitous source of BCPs[4]. We found **1** to be a versatile precursor that undergoes a variety of radical-based transformations to access a wide range of functionalized BCHeps, including drug analogues. Profiling of the ADME properties of these analogues reveals that, like BCPs, BCHeps significantly improve physicochemical properties compared to their arene parents. As such, we anticipate that this novel scaffold should offer a readily accessible bioisostere for broad implementation in drug discovery programmes.

Higher [n.1.1]propellanes such as **1** have to date been of predominantly theoretical interest[23,24]; these elusive molecules have likely been overlooked in synthetic and medicinal chemistry due to the challenge of their synthesis and reported instability[25,26]. We devised a strategy to synthesise **1** on multigram scale (Fig. 1d), which began with Kulinkovich cyclopropanation of commercially available γ-chloroester **3**[27]. Mesylation of the resulting alcohol **4**, followed by $TiCl_4$-mediated cyclopropyl–allyl chlorinative rearrangement and dibromocyclopropanation, afforded cyclopropane **5** in 58% yield over four steps on >30 mmol scale with only one chromatographic purification. Reaction of **5** with two equivalents of phenyllithium generated **1** in yields of 43–61% after distillation; the resulting solution of **1** (0.25–0.50 M in dibutyl ether) can be stored at –20 °C under an inert atmosphere for several months with negligible decomposition.

Aside from solvolysis[25], previous reports on the chemistry of **1** detail only one productive reaction – the addition of thiophenol to generate BCHep phenyl thioether[26]. As a prelude to exploring the wider reactivity of **1**, we first compared the calculated reaction barriers for the addition of a prototypical radical ($CH_3^{\bullet}$) and nucleophile ($NH_2^-$) with those for **2** (Fig. 2a)[28]. These calculations

predict that **1** should be similarly susceptible to the addition of radicals to the inter-bridgehead C–C bond ($\Delta\Delta G^{\ddagger}$ = –1.1 kcal mol$^{-1}$ between **1** and **2**), but that the reaction of **1** with anions is less favourable ($\Delta\Delta G^{\ddagger}$ = +5.4 kcal mol$^{-1}$). This in part may relate to the greater increase of charge density inside the propellane cage in anionic additions, which can be better accommodated by **2** due to the presence of a third three-membered ring that enables enhanced charge delocalization[28,29]. Our calculations therefore suggest that **1** should be amenable to the same panoply of radical functionalization chemistry established in the [1.1.1]propellane/BCP arena.

This theoretical analysis correlated well with experimental findings. We first explored atom transfer radical addition (ATRA) reactions, which are a powerful method to access disubstituted BCPs from **1**. Both $Et_3B$-initiated[30] and $Ir(ppy)_3$-catalyzed[31] addition of a variety of C–I bonds to **1** proceeded efficiently to afford diverse BCHep scaffolds (Fig. 2b). The photoredox-catalyzed variant ($Ir(ppy)_3$) proved more general and higher yielding, affording iodo-BCHeps from α-iodocarbonyls (**6a**–**6d**) benzyl iodides (**6e**–**6f**), alkyl iodides (**6g**–**6k**), α-amino acids (**6l**), and heteroaryl iodides (**6m**). In contrast to ATRAs with [1.1.1]propellane[30], $Et_3B$ initiation was suitable mainly for electrophilic radicals such as α-iodocarbonyls (**6a**, **6b**) and azetidines (**6h**). Notably, the addition of iodotrifluoromethane to **1** proceeded in the absence of an external initiator to afford **6n**, which could be a valuable building block for the synthesis of bioisosteres of *meta*-$CF_3$-substituted arenes. Addition to alkyl bromides such as bromomalonate (**6o**, 57%) and bromotrichloromethane (**6p**, 68%) also proved feasible, the latter proceeding without an initiator. The chemistry could further be applied to the late-stage bicycloheptylation of various drug analogues, affording BCHep derivatives of corticosterone (**6q**), nicotinic acid (**6r**), brequinar (**6s**) and indomethacin (**6t**) which were obtained from the corresponding alkyl iodides. Notably, in contrast to equivalent ATRA reactions with [1.1.1]propellane, no ‘staffane’ byproducts arising from [3.1.1]propellane oligomerization were observed.

Bridgehead amine substituents are highly attractive as potential *meta*-substituted aniline bioisosteres. We found that the three-component metallaphotoredox catalyzed coupling of iodonium dicarboxylates, [1.1.1]propellane and *N*-heteroarenes described by the Macmillan group[32] translated smoothly to [3.1.1]propellane (Fig. 2c), affording azole- and sulfonamide-substituted BCHeps **7a**–**7g** in good yields, including pharmaceutical derivatives (gemfibrozil, **7g**). The synthesis of *N*-substituted iodo-BCHeps was achieved using other methods, such as pyrazole BCHep **7h** by reaction of **1** with pyrazole / $I_2$[33], and allyl sulfonamide BCHep **7i** from radical fragmentation of an iodomethyl aziridine[34]. As well as *C*- and *N*-centered radicals, other heteroatoms proved excellent substrates for reactions with **1** (Fig. 2d): Thioether **8a** and selenoether **8b** were formed in quantitative yields at room temperature, sulfonothioate addition (**8c**, **8d**) proceeded efficiently under heating[35,36], and reaction with a disulfide could be achieved under UV irradiation (**8e**)[37]. The successful bicycloheptylation of protected cysteine (**8f**) in diethyl ether highlights the potential for applicationsin peptide modification[38]; unexpectedly, reaction of a similar cysteine residue in a tripeptide ((L,L,D) δ-(α-aminoadipolyl)-Cys-Val, ACV) in aqueous buffer afforded the rearranged adducts **9** and **10** (Fig. 2e), which may arise from a cationic reaction pathway. While the reason for this reactivity difference is unknown, it is clear that selective *S*-alkylation of cysteine is possible under physiologically-relevant conditions.

Iodinated BCHeps offer opportunities for C–I functionalization towards medicinally-relevant difunctionalized scaffolds. Investigation of iron-catalyzed Kumada cross-coupling[39] revealed efficient reaction of iodo-BCHeps with both aryl and heteroaryl Grignard reagents to afford (hetero)aryl BCHeps in excellent yields (**11a**–**11f**, Fig. 3a). BCHep functionalization was also possible by lithiation of the iodide; reaction of the resulting bridgehead carbanion with $CO_2$ or *i*-PrOBpin gave carboxylic acid **11g** and hydroxy-BCHep **11h** (after *in situ* oxidation) respectively, the latter of which corresponds to a *meta*-phenol bioisostere.

X-Ray structural determination of several crystalline BCHeps enabled us to study the geometry of the scaffold in more detail (Fig. 3b). Two substituent vector angles were considered: the exit vector

angle α (~120° for *m*-arenes), and the out-of-plane vector angle ϕ (the dihedral angle along the BCHep inter-bridgehead axis, ~0° for *m*-arenes). Comparison of the BCHep solid state structures with computed structures of the BCHep and the equivalent *meta*-arene showed excellent agreement for both angles (Δα = 0–7°, Δϕ = 3–11°), validating our hypothesis that the replacement of *meta*-substituted arenes with a BCHep conserves the critical substituent geometry.

Kumada cross-coupling was deployed to synthesise two BCHep drug analogues (Fig. 4a). The BCHep analogue of the anticancer agent sonidegib was accessed from coupling product **11e** by pivaloate ester hydrolysis, oxidation of the resulting primary alcohol to the carboxylic acid **13**, and amide formation with aminopyridine **14** (53% yield over three steps, 19% from **1**). BCHep-URB597, the parent *meta*-arene of which was developed as a fatty acid amide hydrolase inhibitor, was synthesized from **6j** by a similar cross-coupling / hydrolysis / oxidation sequence, followed by amide formation, debenzylation, and carbamoylation with cyclohexyl isocyanate (16% over 5 steps). Computational conformer sampling once again revealed a similar global topology between BCHep-sonidegib and the parent drug for the vector angles α and ϕ (Fig. 4b). Here, an additional parameter was considered: the rotational orientation of the planes between the two substituent groups as defined by the dihedral angle ψ (Δψ = 13°). The BCHep displayed a shallow potential energy profile for rotation around the BCHep–substituent C–C bond (ΔG = 1.5 kcal $mol^{-1}$), reflecting a low conformational preference of the substituents adjacent to the quaternary carbons of the BCHep, whereas for the parent arene more defined minima exist (ΔG = 12 kcal $mol^{-1}$, see the Supplementary Information for details). This may suggest that BCHeps offer significant flexibility in substituent conformation, which could be a valuable property for drug design by facilitating a more adaptable association with protein targets.

Synthesis of these drug analogues raises the question of how the physicochemical and pharmacological properties of the BCHep compare with the parent arene (Fig. 4c). The cLogP, Topological Polar Surface Area (TPSA) and solubility of each drug / analogue pair are remarkably similar, demonstrating that BCHeps can be readily deployed in drug design as true *meta*-arene

bioisosteres. In keeping with their well-established BCP cousins, BCHeps showed reduced clearance rates in mouse and human liver microsomes compared to their arene equivalents, while membrane permeability (Caco-2) was improved. The BCHep analogues were also tested for CYP inhibition and also generally showed an improvement compared to their corresponding arenes (Fig 4c). URB597 inhibits CYP1A2 and CYP2C9 with $IC_{50}$'s below 10 μM, but BCHep-URB597 is 7- and 3-fold weaker against these two polymorphic enzymes. Collectively, these data underline the potential power of the BCHep scaffold as a beneficial motif for improving the pharmacokinetic and physicochemical properties of drug candidates.

Bridgehead-disubstituted bicyclo[3.1.1]heptanes (BCHeps) accurately replicate the geometry of *meta*-substituted arenes, and are readily accessed by radical ring opening of [3.1.1]propellane. This unusual member of the propellane family can be prepared on multigram scale, but to date has barely been explored as a BCHep precursor. A wide variety of radical-based functionalizations demonstrate the potential of this entry to novel bioisosteres; application to the synthesis of pharmaceutical analogues provides a first demonstration of BCHep installation for use in $sp^3$-rich drug design.

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**Fig. 1. Comparison of *para*- and *meta*-substituted arene bioisosteres, and synthesis of [3.1.1]propellane. a**, Bicyclo[1.1.1]pentanes (BCPs) derived from [1.1.1]propellane (**2**) are bioisosteres for *para*-substituted benzene rings. **b**, Previous mimics of *meta*-substituted arenes, which do not accurately reproduce the geometry of the aromatic. **c**, Bicyclo[3.1.1]heptanes (BCHeps) derived from [3.1.1]propellane (**1**) exactly mimic the geometry of *meta*-substituted arenes. **d**, A multigram scale synthesis of [3.1.1]propellane.

**Fig. 2. Theoretical analysis of [1.1.1] and [3.1.1]propellane reactivity and synthesis of BCHeps from [3.1.1]propellane. a**, Reactivity profile of **1** calculated at SMD(THF)-DLPNO-CCSD(T)/ma-def2-QZVPP//SMD(THF)-B2PLYP-D3BJ/def2-TZVP (ma-def2-TZVP on N) level of theory. **b**, Carbon/halogen-substituted BCHeps prepared from organohalides using a) $Ir(ppy)_3$ (2.5 mol%), blue LED irradiation, or b) $Et_3B$ (10 mol%) as initiator, or c) without an initiator. **c**, Nitrogen-substituted BCHeps prepared using d) dual photoredox / Cu-catalyzed coupling of iodonium dicarboxylates and N-heteroarenes, or e) pyrazole / $I_2$, or f) α-iodoaziridine, $Ir(ppy)_3$ (2.5 mol%), blue LEDs. **d**, g) Chalcogen-substituted BCHeps prepared by direct reaction with the chalcogen–X precursor. **e**, Cysteine-selective conjugation studies using the (L,L,D) δ-(α-aminoadipolyl)-Cys-Val (ACV) tripeptide in aqueous phosphate buffer (50 mM, pH 8.0). Reactions run on 0.1–0.2 mmol scale unless shown otherwise. See the Supplementary Information for details.

**Fig. 3. BCHep functionalization and topological analysis of crystalline derivatives. a**, Functionalization of iodo-BHeps through a) iron-catalyzed Kumada coupling, or b) lithiation / electrophilic quench. **b**, Comparison of angles between substituent vectors from single crystal X-ray structures ('X-ray'), and computed structures for BCHeps and the parent arenes ('$BCHep_{calc}$' and '*m*-$Ar_{calc}$', CPCM(THF)-B2PLYP-D3BJ/def2-TZVP level of theory). See the Supplementary Information for details.

**Fig. 4. Synthesis of BCHep pharmaceutical analogues and comparison of pharmacokinetic profile and metabolic stability. a**, Synthesis of BCH analogues of sonidegib and URB597. **b**, Computational investigation of the topology of BCHep-sonidegib. **c**, Physicochemical and metabolic profile of BCHep-sonidegib and BCHep-URB597 along with their parent compounds. See the Supplementary Information for details.

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**Author contribution**

E.A.A., N.F., J.N. and A.J.S. conceived the project. Experimental work was carried out by N.F., J.N., B.R.S., P.R., T.Z.G. and T.G.. H.D.P. collected the crystallographic data. N.F. and A.J.S. carried out

the computational analysis. The project was supervised by E.A.A., F.D., P.E.B. and C.J.S.. E.A.A., N.F., J.N. and F.D. wrote the initial manuscript which was reviewed and edited by E.A.A., N.F., J.N., R.C.S., P.E.B. and F.D..

## Competing interest declaration

The authors declare no competing interests.

## Additional information

Supplementary Information is available for this paper. Crystallographic data for **6s**, **7f**, **7h**, **8d** and **12** are deposited with the CCDC (2175923–2175926 and 2176171). The minimum datasets (physicochemical and pharmacokinetic property analysis in Fig. 4c) have been deposited in the Oxford Research Archive (https://ora.ox.ac.uk). Correspondence and requests for materials should be addressed to Edward A. Anderson. Reprints and permissions information is available at www.nature.com/reprints.

## Online-only Methods

### Synthesis of [3.1.1]propellane

***1-(3-Chloropropyl)cyclopropan-1-ol, S1.***

A solution of ethyl 4-chlorobutanoate (5.60 mL, 40.0 mmol, 1.0 equiv.), and Ti(O*i*-Pr)$_4$ (1.20 mL, 4.0 mmol, 0.10 equiv.) in anhydrous diethyl ether (60 mL) was cooled to 0 °C and a solution of EtMgBr (33.3 mL, 3.0 M in $Et_2O$, 100 mmol, 2.5 equiv.) was added dropwise over 90 minutes. The mixture was stirred for further 30 minutes at 0 °C, then the mixture was *slowly* quenched by dropwise addition of 10% aqueous $H_2SO_4$ (50 mL). The organic layer was washed sequentially with $H_2O$ (70 mL), $NaHCO_3$ (sat., aq., 70 mL), brine (70 mL), then dried ($Na_2SO_4$), filtered and

concentrated *in vacuo* to afford **S1** (4.73 g, 35.1 mmol, 88%) as a colourless oil which was used without further purification.

***1-(2-Chloroethyl)cyclopropyl methanesulfonate, 4.***

A solution of **S1** (4.73 g, 35.1 mmol, 1.00 equiv.) and triethylamine (7.05 mL, 50.7 mmol, 1.44 equiv.) in anhydrous $CH_2Cl_2$ (60 mL) was cooled to 0 °C and methanesulfonyl chloride (3.08 mL, 40.0 mmol, 1.14 equiv.) was added dropwise over 30 minutes. The mixture was stirred for a further 30 minutes at 0 °C, then quenched with water (30 mL). The layers were separated, and the organic layer was washed sequentially with $H_2O$ (60 mL), 10% $H_2SO_4$ (aq., 50 mL), $NaHCO_3$ (sat., aq., 50 mL) and brine (50 mL), then dried ($Na_2SO_4$), filtered and concentrated *in vacuo* to afford **4** (7.20 g, 33.9 mmol, 96%) as a pale-yellow oil which was used without further purification.

***5-Chloro-2-(chloromethyl)pent-1-ene, S2.***

To solution of **4** (7.20 g, 33.8 mmol, 1.0 equiv.) in anhydrous $CH_2Cl_2$ (60 mL) was slowly added $TiCl_4$ (5.72 mL, 52.4 mmol, 1.55 equiv.) at room temperature over 20 minutes. The mixture was stirred at room temperature for 3 h, then slowly quenched with $H_2O$ (60 mL) at 0 °C with vigorous stirring. The layers were separated, and the organic layer was washed sequentially with $H_2O$ (2 × 70 mL), $NaHCO_3$ (sat., aq., 70 mL), brine (70 mL), then dried ($MgSO_4$), filtered and concentrated *in vacuo* (300 mbar, 30 °C) to afford **S2** (4.46 g, 29.1 mmol, 86%) as a clear pale-yellow liquid. *Note: The product is volatile under reduced pressure (isolated with residual solvent) and was taken forward without further purification. The state yield makes allowance for residual solvent.*

***1,1-Dibromo-2-(chloromethyl)-2-(3-chloropropyl)cyclopropane, 5.***

To a vigorously stirred (1000 rpm) solution of **S2** (4.46 g, 29.1 mmol, 1.00 equiv.), $CHBr_3$ (20.4 mL, 233 mmol, 8.00 equiv.), dibenzo-18-crown-6 (524 mg, 1.47 mmol, 0.05 equiv.) and pinacol (137 mg, 1.15 mmol, 0.04 equiv.) in $CH_2Cl_2$ (37 mL) was added 50% NaOH solution (22 mL) dropwise over 20 minutes at 50 °C. The resulting mixture was stirred for 5 h at 50 °C, then cooled to room temperature and diluted with *n*-pentane (100 mL) and distilled water (100 mL). The

resulting suspension was filtered through a pad of celite and washed with additional *n*-pentane (100 mL). Additional distilled water (100 mL) was added to the filtrate. The layers were separated and the organic layer was washed with brine (150 mL), then dried ($Na_2SO_4$), filtered and concentrated *in vacuo*. The crude product was purified by column chromatography (⌀ 4 cm, 40 g $SiO_2$, gradient 100% pentane to 95:5 pentane / EtOAc) to afford **5** (7.50 g, 23.1 mmol, 79%) as a colourless oil.

***[3.1.1]Propellane, 1.***

To a cooled (–78 °C) solution of **5** (9.74 g, 30.0 mmol, 1.0 equiv.) in anhydrous $Et_2O$ (160 mL) was slowly added phenyllithium (31.8 mL, 60.4 mmol, 2.01 equiv., 1.9 M in *n*-$Bu_2O$). The resulting mixture was stirred at −78 °C for 15 minutes then warmed to room temperature and stirred for 7 h. The mixture was then distilled using a rotary evaporator (25 °C water bath temperature) equipped with a dry-ice cold finger condenser, with the receiving flask immersed in a dry ice / acetone 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 **1** in *n*-$Bu_2O$ which was stored under an inert atmosphere at −20 °C. The yield was determined by $^1$H NMR spectroscopy using 1,2-dichloroethane as an internal standard (see below). The concentration of the [3.1.1]propellane solution ranged between 0.25 M and 0.50 M, with yields of 43-61%. *Note: The resulting propellane stock solution contains bromobenzene which does not influence the reactions presented herein.*

**Reactions of [3.1.1]propellane**

***General procedure: Photoredox-catalyzed ATRA[31] (Figure 4b, conditions a)***

To a flame dried, screw-capped vial equipped with a stirrer bar was added *fac*-$Ir(ppy)_3$ (2.5 mol%), alkyl or aryl halide (1.0 equiv.), *t*-BuCN (0.1 M) and [3.1.1]propellane (1.1 to 2.0 equiv. of a solution in *n*-$Bu_2O$). The vial was placed under nitrogen, and the solution was degassed *via* a modified freeze-pump-thaw cycle (vacuum was only applied while the reaction mixture was frozen

due to TCH volatility). The stirred mixture was irradiated with blue LEDs (Kessil PR160 456 nm) with fan cooling for the indicated time. The reaction mixture was concentrated, and the residue was purified by column chromatography.

***General procedure: ATRA with $BEt_3$[30] (Figure 4b, conditions b)***

Under air, a solution of alkyl iodide (1.0 equiv.) in [3.1.1]propellane (1.1 to 1.5 equiv. of a solution in *n*-$Bu_2O$) was cooled to 0 °C and $Et_3B$ (10 mol%, 1.0 M in hexane) was added *via* syringe (needle tip in the solution). The mixture was stirred until the reaction reached completion as monitored by thin layer chromatography. The reaction mixture was then concentrated and the residue purified by column chromatography.

***General procedure: Ir/Cu catalysed additions to [3.1.1]propellane[32] (Figure 4c, conditions d)***

To a flame dried, screw-capped vial equipped with a stirrer bar was added *fac*-$Ir(ppy)_3$ (2.0 mol%), amine starting material (1.0 equiv.), iodomesitylene biscarboxylic acid (2.0 equiv.), $Cu(acac)_2$ or $Cu(TMHD)_2$ (0.60 equiv), 2-*tert*-butyl-1,1,3,3-tetramethylguanidine BTMG (3.0 equiv.) and anhydrous 1,4-dioxane (0.03 M). The solution was sparged with Ar for 10 minutes then [3.1.1]propellane (1.5 equiv. of a solution in *n*-$Bu_2O$) was added, the vial capped and sealed with parafilm. The mixture was stirred and irradiated with blue LEDs (Kessil PR160 456 nm) with fan cooling for 16 h. The reaction mixture was diluted with EtOAc and washed with 30% aqueous ammonia solution. The phases were separated, and the aqueous phase was extracted with EtOAc (3 ×). The combined organics were dried ($Na_2SO_4$), filtered and concentrated *in vacuo.* The residue was purified by column chromatography.

***General procedure: Addition of thiols (Figure 4d, conditions g)***

To a solution of thiol (1.1 equiv.) in anhydrous diethyl ether was added [3.1.1]propellane (1.0 equiv., of a solution in *n*-$Bu_2O$) dropwise. The mixture was stirred for 1 h then the mixture was diluted with diethyl ether, washed with 1 M aqueous NaOH solution (3 ×). The organic layer was

dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The obtained crude product was either purified by column chromatography or trituration.

***General procedure: Disulfide addition[37] (Figure 4d, conditions g)***

To a flame dried, screw-capped vial was added disulfide (3.0 equiv.) and [3.1.1]propellane (1.0 equiv. of a solution in *n*-$Bu_2O$). The mixture was irritated with a LED lamp (HepatoChem Evoluchem HCK1012-01-011 365 nm) with fan cooling for 20 h. The solvents were removed *in vacuo* and the resulting residue was purified by column chromatography.

***General procedure: Addition of Sulfonylthionates[35] (Figure 4d, conditions g)***

To a solution of the specific thiosulfonate (1.0 equiv.) in anhydrous MeCN was added [3.1.1]propellane solution (1.5 equiv.). The flask was sealed and heated to 60 °C for 16 h, then cooled to room temperature and concentrated *in vacuo*. The crude product was purified by column chromatography.

***General procedure: Iron-catalyzed Kumada coupling[39] (Figure 5a)***

To a flame-dried vial was added BCHep iodide (1.0 equiv.) and $Fe(acac)_3$ (20 mol%). The vial was then evacuated and refilled with $N_2$ (g) three times. To this was added anhydrous THF (0.2 mL) and TMEDA (40 mol%), and the resulting mixture was stirred for 5 minutes. The Grignard reagent (1.6 equiv.) was then added *via* syringe pump over approximately 1 h at room temperature. The reaction was stirred for a further 1 h, then quenched by addition of aqueous $NH_4Cl$ (2 mL, saturated). The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 × 1 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography.

**Author Information**

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