Rapid and scalable halosulfonylation of strain-release reagents

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ABSTRACT: Sulfonylated aromatics are commonplace motifs in drugs and agrochemicals. However, methods for the direct synthesis of sulfonylated non-classical arene bioisosteres, which could improve the physicochemical properties of drug and agrochemical candidates, are limited. Here we report a solution to this challenge: a one-pot halosulfonylation of [1.1.1]propellane, [3.1.1]propellane and bicyclo[1.1.0]butanes that proceeds under practical, scalable and mild conditions. The sulfonyl halides used in this chemistry feature aryl, heteroaryl and alkyl substituents, and are conveniently generated *in situ* from readily available sulfinate salts and halogen atom sources. This methodology enables the synthesis of an array of pharmaceutically and agrochemically relevant sulfonyl BCP, BCHep and cyclobutyl halides, on milligram to decagram scales.

Main Text: Aryl sulfones are prevalent motifs in pharmaceutical and agrochemical compounds, such as the basal carcinoma treatment vismodegib and the rice herbicide cafenstrol (Figure 1a),[1] and methods for their synthesis are in high demand.[2] The development of sulfonylated bioisosteres of aromatic rings, which could improve physicochemical and pharmacokinetic properties, is therefore an important goal in drug and agrochemical discovery.[3] Methodologies to access such compounds are hence of significant interest, as demonstrated by the emergence of sulfonyl bicyclo[1.1.1]pentanes (BCPs) and cyclobutanes in medicinal chemistry patents.[4] While monosubstituted BCP sulfones can be efficiently prepared through oxidation of BCP thioethers (Figure 1b, left),[4a, 5] preparation of the disubstituted sulfonyl BCPs reported to date has required lengthy syntheses involving manipulation of BCP 1,4-dicarboxylic acid.[4a-d] In short, concise and convenient methods to synthesize disubstituted BCP sulfones (and similar structures) remain elusive.

The direct addition of sulfonyl groups to [1.1.1]propellane **1** offers an attractive method to achieve these sought-after compounds (Figure 1b, right). This approach has been explored in the addition of certain sulfonyl chlorides (R = Me, Ph) to **1**, but required harsh UV irradiation, and suffered from poor to average yields and/or uncontrolled reactivity that generated (n=2) staffanes.[6] Thioether- and selenoether-substituted BCP sulfones have been prepared in a similar manner through mild heating or irradiation of dichalcogenides.[7] *S,C*-disubstituted BCP sulfones bearing β-carbonyl, allyl or alkynyl substituents are accessible using photocatalysis; however, this method utilizes non-commercial, tailored substrates such as enol sulfonate esters or alkynyl sulfones.[8]

We recently demonstrated the suitability of [1.1.1]propellane **1** and [3.1.1]propellane (**4**, Figure 1c) to engage in atom transfer radical addition (ATRA) reactions with carbon and nitrogen-centred radicals to afford halide-functionalized *para- and meta*-arene bioisosteres.[9] However, equivalent methodologies to access

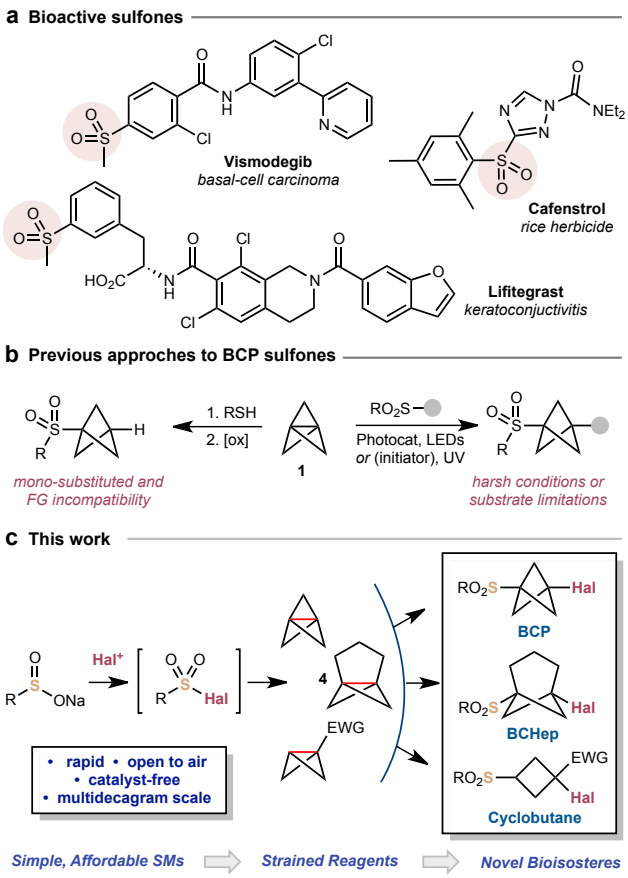


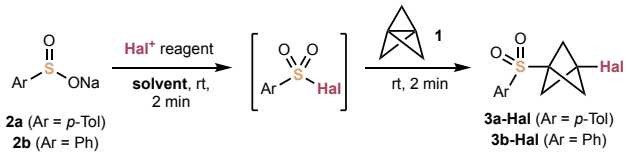
Figure 1. a Bioactive aryl sulfones. **b** Existing syntheses of sulfonyl BCPs. **c** This work: A scalable *in situ* formation of sulfonyl halides for addition reactions across strained hydrocarbons.

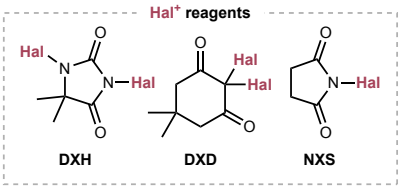
sulfonyl BCP and bicyclo[3.1.1]heptane (BCHep) iodides and bromides are so far unknown. Here, we exploit sulfonyl halides, which can be easily generated *in situ* from readily available sulfinate salts, to rapidly construct difunctionalized sulfonyl arene bioisosteres *via* direct radical addition to strained hydrocarbon reagents. This chemistry proceeds in high yields in as little as a few minutes and is scalable to multidecagram quantities. We further disclose that the resultant halide and sulfone provide convenient handles for product diversification through radical and anionic C–C bond formation.[9b, 10]

Our initial goal was to achieve an efficient radical addition of sulfonyl halides with [1.1.1]propellane **1**. Several challenges were anticipated, such as desulfonylation or elimination of the sulfonyl halide, background reaction of **1** with halogenating reagents to form di-halo BCPs, and oligomerization to form staffane byproducts. With these issues in mind, we designed a protocol to generate sulfonyl halides *in situ* from readily available sulfinate salts with electrophilic halogen sources, prior to the addition of **1** (Table 1). Using sodium toluenesulfinate **2a**, reaction with *N*-iodosuccinimide (NIS) or ICl and **1** gave encouraging yields of sulfone BCP iodide **3a-I** (41% and 49% respectively, entries 1 and 2), which increased to 78% using 1,3-diiodo-5,5-dimethylhydantoin (DIH, entry 3). Other iodinating reagents such as 2,2-diiododimedone (DID) or I_2 offered no improvement (entries 4-5), also affording rearranged *exo*-cyclobutene products or, in the latter case, di-iodinated BCP.

Proceeding with DIH as the iodine source, we found that the reaction solvent significantly influenced the yield of **3a-I**: THF was surpassed by solvents such as Et_2O, CH_2Cl_2 and H_2O, all of which gave the desired **3a-I** in near quantitative yield with only trace staffane formation (entries 6–8). No reaction was observed in the

Table 1. Optimization of halosulfonylation of **1**.[a]





Entry	Substrate	Hal$^+$	Solvent	Yield **3a** or **3b** (%)[b]
1	**2a**	NIS	THF	41
2	**2a**	ICl	THF	49
3	**2a**	DIH	THF	78
4	**2a**	DID	THF	31
5	**2a**	I_2	THF	7[c]
6	**2a**	DIH	Et_2O	100
7	**2a**	DIH	H_2O	99
8	**2a**	DIH	CH_2Cl_2	100[d]
9[e]	**2a**	DIH	Et_2O	nr
10	**2a**	DBH	Et_2O	9
11	**2a**	DBH	Et_2O	100[d,f]
12	**2a**	NBS	Et_2O	50
13	**2b**	I_2	Et_2O	91[g]
14	**2b**	Br_2	Et_2O	97[g]

[a] Optimization carried out on 0.15 mmol scale, with 2.5 equiv. sulfinate (1.0 M in H_2O), 1.0 equiv. of halogenating agent and 1.0 equiv. of **1** (0.75 M in Et_2O). [b] ^{1}H NMR yields calculated with mesitylene as internal standard. [c] 18% di-iodo BCP observed. [d] Isolated yield. [e] Reaction run in the dark. [f] 18 h reaction time after addition of **1**. [g] 1.0 equiv. of isolated sulfonyl halide (prepared in MeCN) and 1.3 equiv. of **1** were reacted in Et_2O for 15 h at rt.

absence of light, supporting a radical-based mechanism (entry 9). Lower reaction temperatures (-5 °C) were equally efficient, and proved important in the subsequent substrate evaluation.[11] We were pleased to find that on switching the halogenating reagent to 1,3-dibromo-5,5-dimethylhydantoin (DBH), these conditions could also be applied to the formation of sulfonyl BCP bromide **3a-Br**. Interestingly, the intermediate sulfonyl bromide was formed within 2 min, but an extended reaction time of 18 h was required for complete reaction with **1** (entries 10 and 11), the latter affording **3a-Br** in quantitative yield. NBS also proved a suitable brominating agent for the sulfinate salt (entry 12). The chemistry could be applied on multidecagram scale, highlighting the robust nature of the addition; for example, phenylsulfonyl BCP iodide **3b-I** could be obtained in 91% yield on a 34 g scale (entry 13), while the BCP bromide **3b-Br** was isolated in 97% yield on 96 g scale (entry 14). In these cases, the sulfonyl halide intermediate was pre-isolated using I_2 and Br_2 as halogen sources before reaction with **1**.

With conditions in hand for iodo- and bromosulfonylation of **1**, the scope of the reaction was studied (Figure 2). Aryl sulfinates bearing neutral or electron-donating substituents(**2a**–**2c**) gave the corresponding sulfone BCP iodides and bromides **3a**–**3c** in near quantitative yields (96–100%, up to ~2 g scale). Halogenated arenes

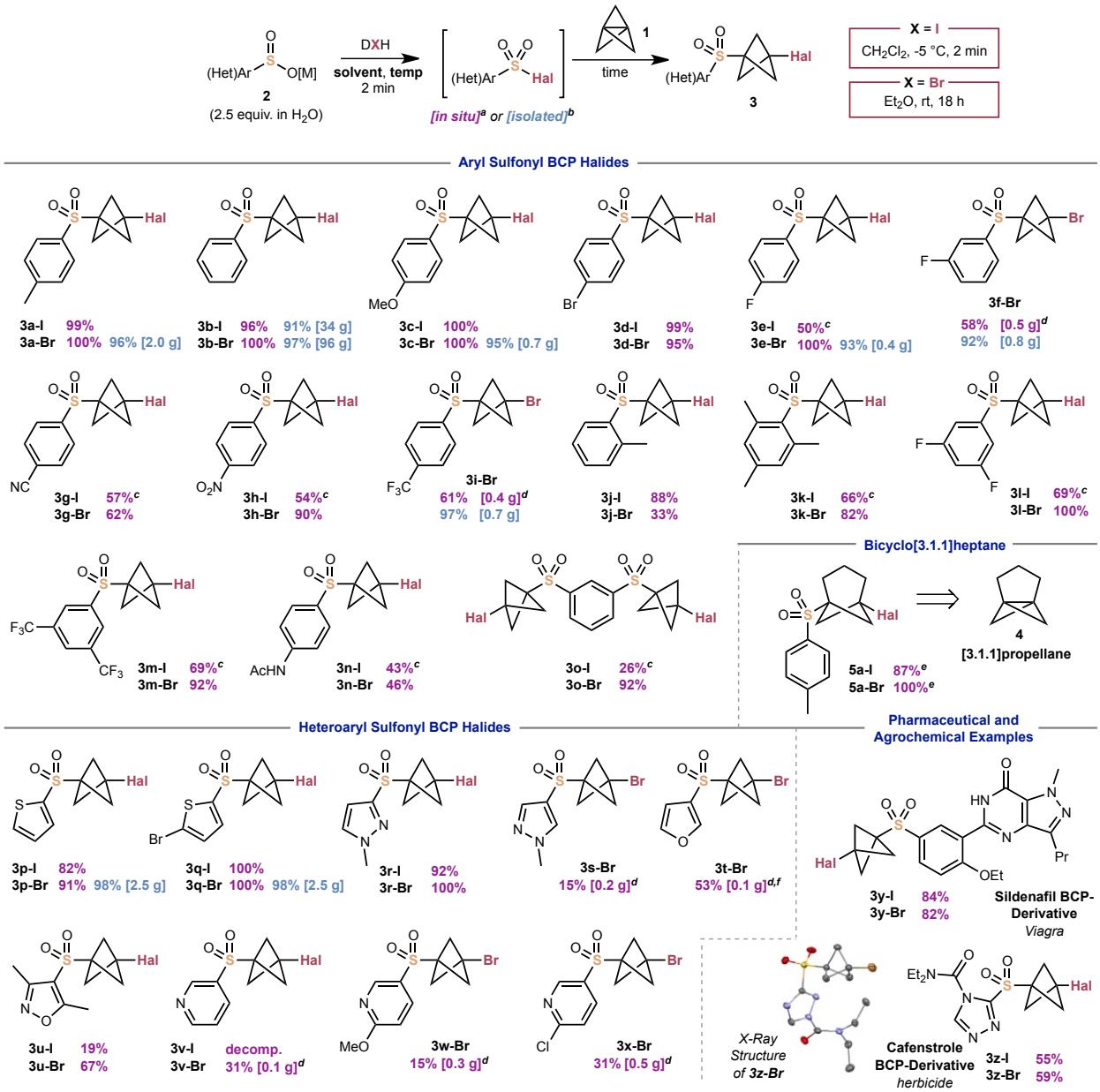


Figure 2. Scope of halosulfonylation of [1.1.1] and [3.1.1]propellane with aryl and heteroaryl sulfinates. [a] Yields in purple represent sulfonyl halides prepared *in situ* from **2**; reactions carried out on 0.2 mmol scale using 1.0 equiv. of **1** (0.70–0.75 M in Et_2O), 1.0 equiv. of DIH or DBH, and 2.5 equiv. of Na or Li sulfinate (1.0 M in H_2O) under the conditions in the title scheme. [b] Yields in blue represent use of isolated sulfonyl halides; 1.0 equiv. of sulfonyl halide and 1.3 equiv. of **1** stirred in Et_2O at rt for 15 h. [c] **2** (1.0 M in DMF) was iodinated at -40 °C; after addition of **1**, stirred at -40 °C for 20 min, then rt for 10 min. [d] 1.0 equiv. of **2** was brominated using 1.0 equiv. of NBS in Et_2O at rt for 30 min; then 1.5 equiv. of **1**, 15 h, rt. [e] 1.0 equiv. of [3.1.1]propellane **4** (0.23 M in Et_2O) instead of **1**. [f] 0.95 equiv. of $PPh_3{\cdot}Br_2$ instead of NBS, 1.0 equiv. of **2** and 1.5 equiv. of **1** in MeCN for 15 h at rt.

were well-tolerated, particularly for BCP bromide synthesis (**3d**–**3f**, 50–100%). Good to excellent yields were also observed for electron-deficient aryl sulfonyl bromides **3g-Br**–**3i-Br** (for example, the *p*-CF_3 aryl sulfone **3i-Br** was obtained in 97% yield from the isolated sulfonyl bromide intermediate on 0.7 g scale, or in 61% yield using a one-pot procedure); however the corresponding iodides performed less well, and typically benefited from cooling to -40 °C to limit competing desulfonylation. Sterically-encumbered *o*-tolyl and mesityl sulfinates proceeded smoothly, giving BCP iodide **3j-I** in 88% yield, and mesityl adducts **3k-I** and **3k-**

Br in 66% and 82% yield respectively. A lower yield of **3j-Br** was observed (33%) due to competing benzylic bromination of the methyl group. Additional *m*-electron-withdrawing substituents were also accommodated, with 3,5-di-F and 3,5-di-CF_3 arenes affording sulfonyl BCP halides **3l** and **3m** in 58–100% yield. The inferior reactivity observed with acetamide **2n** was surprising, even on cooling to -40 °C, possibly due to competing reaction at the amide. A bis-arylsulfinate could even be used successfully to deliver bis-sulfonyl BCP iodide **3o-I** and bromide **3o-Br** in 26% and 92% yield respectively. [3.1.1]Propellane **4** is emerging as a convenient reagent to access novel *m*-substituted arene bioisosteres;[12] pleasingly, the addition of sulfonyl halides translated smoothly to this propellane, giving sulfonyl BCHep halide products in excellent yields (**5a-I**, 87% and **5a-Br**, 100%).

Many heteroaryl sulfonyl halides excelled under these protocols. Electron-rich 5-membered heterocyclic sulfinates performed best, such as thiophene **2p** and 2-bromothiophene **2q**, with yields ranging from 82–99% for both the iodide and bromide products. The thiophene sulfonyl BCP bromides could be prepared on 2.5 g scale from the isolated sulfonyl bromides with equally impressive 98% yields for both substrates. 3-Pyrazole sulfinate **2r** was similarly successful, giving the BCP iodide and bromide **3r-I**/**Br** in 92% and 100% yields, respectively, whereas 2-pyrazole sulfinate gave a poor yield of the bromide **3s-Br** (15%). 3-Furyl sulfonyl BCP bromide **3t-Br** was achieved in 53% yield using $PPh_3{\cdot}Br_2$ complex to prepare the sulfonyl bromide *in situ*. Substrates containing *N*-nucleophilic sites proved challenging, presumably due to competing reactivity with the sulfonyl halide:[13] oxazole **2u** gave a low yield of the BCP iodide **3u-I** (19%) but a 67% yield of the bromide **3u-Br**. Iodosulfonylation of pyridylsulfinate **2v** was unsuccessful, while the pyridyl sulfonyl bromide adducts **3v-Br**–**3x-Br** were isolated in reduced yields of 15–31%, on up to 0.5 g scale. Pleasingly, we found that the methodology could be readily applied in pharmaceutical and agrochemical settings, successfully achieving BCP derivatives of vasodilating drug sildenafil (**3y-I**, 84% and **3y-Br**, 82%) and the rice herbicide cafenstrole (**3z-I**, 55% and **3z-Br**, 59%).

In contrast to arylsulfonyl halides, the generation of alkylsulfonyl iodides and bromides is challenging due to their tendency to undergo rapid elimination to form HI/HBr and SO_2.[14] We were encouraged to find that our standard conditions using dihalohydantions as the halogen source enabled the formation of alkyl sulfonyl halides *in situ*; however, rather than the desired addition reaction, only *N*-sulfonylation of the hydantoin byproduct was observed on addition of [1.1.1]propellane **1**. Further evaluation of suitable halogenating agents identified $BnMe_3N^+ICl_2^-$ and Br_2 as convenient alternatives which enabled the smooth halo-sulfonylation of **1** (Figure 3). Typically, alkylsulfonyl iodides added rapidly to **1** (within 2 min), whereas alkylsulfonyl bromides benefited from addition of Et_3B (10 mol%) to obtain optimal yields in just 2 hours on small scales; the latter adducts could also be synthesised on decagram scale over a 15 h period without an initiator. Primary alkyl sulfinates gave good to excellent yields of sulfonyl BCP bromides (**7a-Br**–**7c-Br** 64–98%), where the methyl and ethyl sulfonyl products were also synthesized in near quantitative yields on >30 g scale from the isolated sulfonyl bromides. Equivalent sulfonyl BCP iodides **7a-I** and **7c-I** were also generated in high yields (99% and 64% respectively). These compounds provide valuable opportunities for further sulfone-based reactivity; for example, deprotonation / CO_2 quench of BCP bromide **7a-Br** delivered carboxylic acid **8** in 72% yield on 25 g scale, which could be a useful building block in drug discovery by analogy to its bioisosteric phenyl counterpart.[15] The reaction of phenylethyl sulfinate gave the BCP iodide **7d-I** in an excellent 98% yield; unfortunately, attempted bromosulfonylation resulted in decomposition. An oxetane-containing sulfinate successfully gave BCP iodide **7e-I** and bromide **7e-Br** in 99% and 100% yield respectively. Methyl propanoate BCP sulfone **7f** was synthesised as both the iodide (**7f-I**, 39%) and the bromide (**7f-Br**, 73%). The latter underwent smooth E1cB elimination to the halide-substituted BCP sulfinate **9**,[16] which could be used to access other derivatives (e.g. BCP sulfonamides via halogenation / amination).

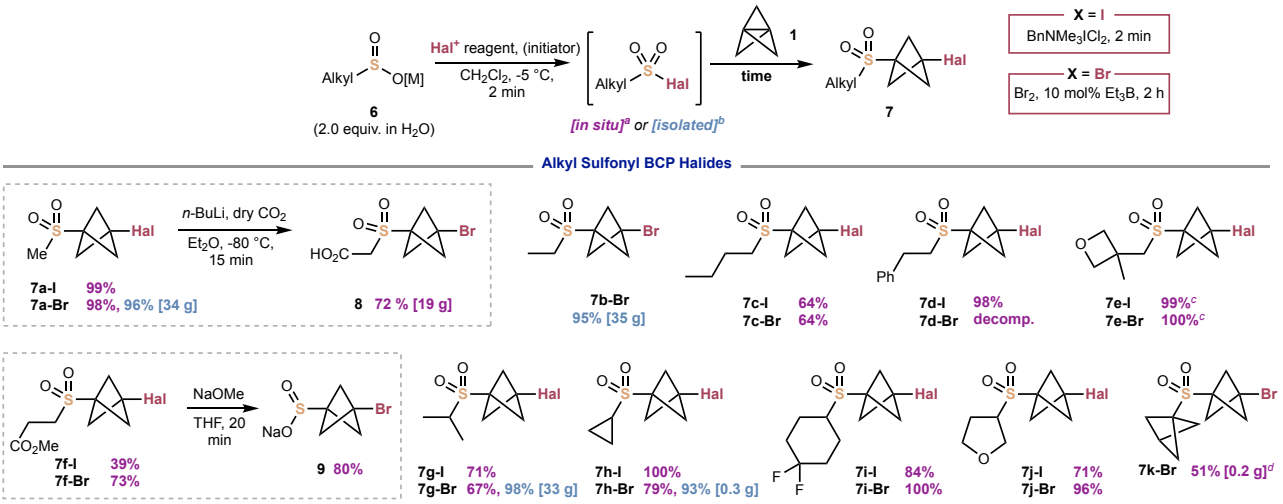


Figure 3. Scope of alkyl sulfonyl BCP halides. [a] Yields in purple represent sulfonyl halides prepared *in situ* from **6**. Reactions carried out on 0.1 mmol scale using 1.0 equiv. of **1** (0.70–0.75 M in Et_2O) and 2.0 equiv. of Na or Li sulfinate (1.0 M in H_2O) under the conditions in the title scheme. BCP iodides: 1.4 equiv. of $BnNMe_3ICl_2$ was used. BCP bromides: 1.8 equiv. of Br_2 with 10 mol% of Et_3B was used. [b] Yields in blue represent use of isolated sulfonyl halides. Reactions used 1.0 equiv. of sulfonyl bromide and 1.3 equiv. of **1**, stirred in Et_2O for 15 h at rt, without initiator. [c] 0.5 µmol scale. [d] 0.95 equiv. of $PPh_3{\cdot}Br_2$ complex instead of Br_2, 1.0 equiv. of **6** and 1.5 equiv. of **1** in MeCN at rt for 15 h.

Secondary alkyl sulfinates performed admirably, such as isopropyl, cyclopropyl, and difluorocyclohexyl motifs (**7g**–**7i**, 67–100%); notably, the isopropyl sulfone BCP bromide **7g-Br** was afforded in an excellent 96% yield on 33 g scale. Tetrahydrofuran-substituted sulfone **7j** was prepared as the BCP iodide and bromide in 71% and 96% yields, respectively. Finally, the bis-BCP sulfone bromide **7k-Br** was achieved in 51% yield with $PPh_3.Br_2$ as the brominating agent.

With successful additions to [1.1.1] and [3.1.1]propellane established, we questioned whether other strained hydrocarbons might undergo successful halosulfonylation. To our delight, bicyclo[1.1.0]butanes (BCBs) **10** proved highly suitable reagents for this chemistry, in the presence of 10 mol% Et_3B initiator (Figure 4a). Although BCBs have been subject to the addition of alkyl radicals, α-amino radicals, and thiols, previous work has exclusively involved monosubstituted BCBs;[17] to our knowledge, the addition of sulfonyl radicals has not been reported. Tosyl iodide, generated *in situ* from sulfinate salt **2a**, underwent smooth addition to monosubstituted BCBs **10a**–**c** to afford iodocyclobutyl sulfones substituted with amide (**11a-I**, 80%, 2.5:1 *dr*), aryl sulfone (**11b-I**, 66%, 2.1:1 *dr*), and alkyl sulfone (**11c-I**, 28%, 10:1 *dr*) groups. Tosyl bromide engaged in an analogous addition to BCB **10a** to give the sulfonylated bromocyclobutane **11a-Br** in 72% yield (2.3:1 *dr*). Most pleasingly, sulfonyl addition to disubstituted BCB **10d** returned an exceptional yield of 94% of the iodo-sulfonylated cyclobutane **11d-I** (3.3:1 *dr*), in what represents the first addition of any radical to a disubstituted BCB.

The halide resident in the BCP product offers many opportunities for further chemistry. As such, we were excited to observe the successful photocatalyzed Giese addition of tosyl BCP iodide **3a-I** to a dehydroalanine derivative, giving the α-amino acid analogue **12** in an excellent 76% yield (Figure 4b).

Finally, we studied the potential of this chemistry to extend beyond sulfur-centered radicals, and identified phosphonate functionalities, which are prevalent within drug discovery as (for example) antivirals, pro-nucleotides, and farnesyl pyrophosphate synthase inhibitors, as potential targets (Figure 4c).[18] In the event,

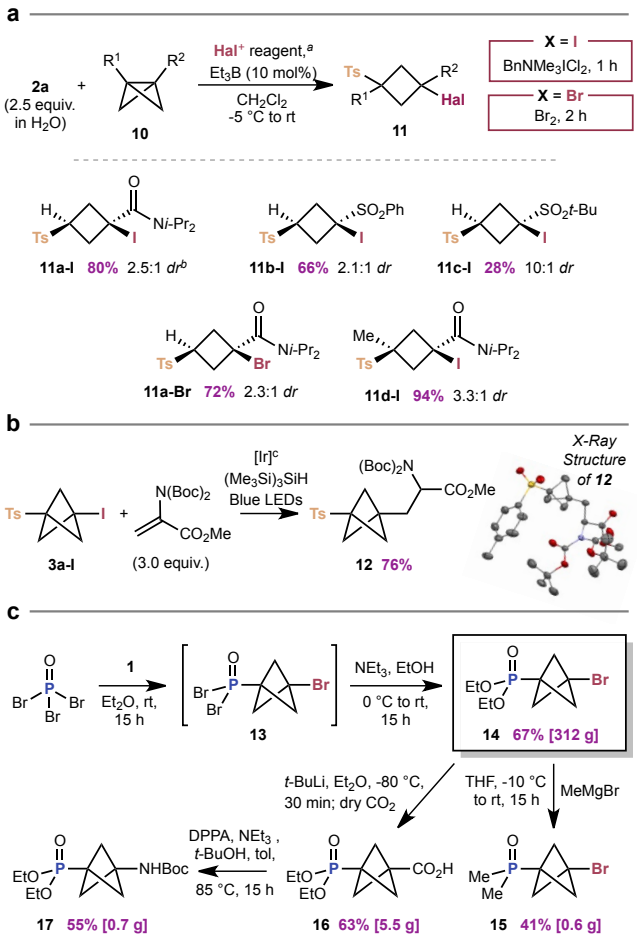


Figure 4. a Addition of sulfonyl halides to BCBs. **b** Giese reaction of a sulfonyl BCP iodide. **c** Synthesis and functionalisation of phosphonate BCP bromides. [a] Reactions carried out on a 0.1 mmol scale, using 2.5 equiv. of **2a** (1.0 M in H_2O) and either 1.4 equiv. of $BnNMe_3ICl_2$ or 1.8 equiv. of Br_2, stirred for 2 min before addition of 1.0 equiv. of BCB **10** (0.1 M in CH_2Cl_2) and 10 mol% Et_3B. [b] The major diastereoisomer of **11a-I** was assigned by NOESY correlations; other adducts were assigned by comparison of ^1H NMR spectra. [c] 2.5 mol% $Ir[(dF(CF_3)ppy)_2(dtbbpy)]PF_6$, 2.0 equiv. of Na_2CO_3, 2.0 equiv. of $(Me_3Si)_3SiH$, MeOH/H_2O (1:1), blue LEDs, rt, 24 h.

the direct addition of phosphoryl tribromide with **1**, followed by reaction of the intermediate dibromide **13** with ethanol, enabled the synthesis of 312 g of phosphonate BCP bromide **14** (67% yield). This versatile BCP building block could be converted to the phosphine oxide **15** on treatment with MeMgBr (41%), or to the phosphoryl BCP carboxylic acid **16** via lithium-halogen exchange and trapping of the resultant bridgehead carbanion with CO_2 (63% on 5.5 g scale). Accessed in just three steps from **1**, it is worth noting that the methyl ester of **15** has previously required seven steps for its preparation and use as a glutamate receptor ligand.[19] Finally, Curtius rearrangement enabled the synthesis of phosphoryl carbamate BCP **17**.

In conclusion, we have developed a practical, efficient, and flexible methodology to directly construct sulfonyl and phosphonate BCP, BCHep and cyclobutyl halides from simple sulfinate salts and convenient electrophilic halogen sources. A wide range of substituents were tolerated, enabling the preparation of pharmaceutical and agrochemical analogues. The collection of heteroaryl and alkyl sulfone products represents a particularly significant advance in the functionality of sulfonyl halide reagents accessible to date. The reaction protocols are rapid and straightforward to execute, forgoing the need for anhydrous solvents, inert reaction conditions, or metal catalysts, and translate exceptionally to decagram and even hundred-

gram scales. Selected further manipulations of the products highlight their potential utility in the synthesis of novel medicinally-relevant bioisosteres, which cannot be easily accessed by other means.

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