

# A twofold radical based synthesis of *N,C*-difunctionalized bicyclo[1.1.1]pentanes

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**ABSTRACT:** Bicyclo[1.1.1]pentylamines (BCPAs) are of growing importance to the pharmaceutical industry as *sp*<sup>3</sup>-rich bioisosteres of anilines and *N-tert*-butyl groups. Here we report a facile synthesis of 1,3-disubstituted BCPAs using a twofold radical functionalization strategy. Sulfonamidyl radicals, generated through fragmentation of  $\alpha$ -iodoaziridines, undergo initial addition to [1.1.1]propellane to afford iodo-BCPAs; the newly formed C–I bond in these products is then functionalized via a silyl-mediated Giese reaction. This chemistry also translates smoothly to 1,3-disubstituted iodo-BCPs. A wide variety of radical acceptors and iodo-BCPAs are accommodated, providing straightforward access to an array of valuable aniline-like isosteres.

Bicyclo[1.1.1]pentanes (BCPs) are of significant interest to the pharmaceutical, agrochemical and materials industries as *sp*<sup>3</sup>-rich surrogates for 1,4-disubstituted arenes, *tert*-butyl groups, and alkynes.<sup>1–9</sup> Bicyclo[1.1.1]pentylamines (BCPAs) are similarly attractive due to their potential use as non-toxic bioisosteres for aniline and *N-tert*-butyl motifs in drug candidates. BCPAs have been shown to improve properties such as metabolic tolerance and bioactivity (Figure 1a),<sup>10–11</sup> and feature as desirable derivatives in numerous patents.<sup>12–16</sup>

Early approaches to BCPAs involved multi-step routes using pre-formed BCP building blocks (derived from [1.1.1]propellane **1**, Figure 1b), such as acyl nitrene rearrangements<sup>17–20</sup> or reduction of BCP azides or hydrazines.<sup>21–22</sup> More recently, methods have been developed that prepare BCPAs directly from **1** by reaction with amide anions,<sup>23–25</sup> which can also provide access to *N,C*-disubstituted BCPAs (Figure 1b, path a). However, these processes can require elevated temperatures, restricting functional group tolerance. The amination of BCP radicals formed by addition of *C*-centered radicals to **1** (generated under Fe(II)<sup>26</sup> or metallaphotoredox<sup>27</sup> catalysis) offer alternative solutions (paths b, c). In marked contrast to the addition of *C*-centered radicals to **1**, reactions with *N*-centered radicals are under-explored as an entry to BCPAs. Following the seminal work of Wiberg on the reaction of **1** with nitric oxide,<sup>28</sup> this area lay dormant until the elegant demonstration by Leonori *et al.* of a three component construction of 1,3-disubstituted BCPAs via photoredox decarboxylative generation of amidyl radicals (path d).<sup>29</sup> However, even this chemistry is restricted to the installation of halogen or sulfur substituents at the 3-position of the BCPA. Very recently, an amidopyridylation of [1.1.1]propellane has been described by Hong and co-workers.<sup>30</sup>

In previous work we described the efficient synthesis of iodo-BCPs by atom transfer radical addition (ATRA) of alkyl and (hetero)aryl iodides to the C1–C3 bond of **1**,<sup>31–32</sup> and questioned

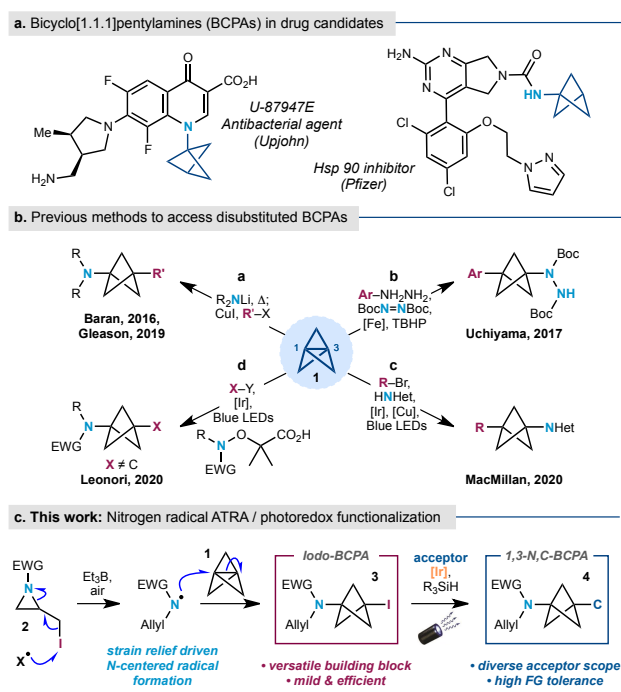


Figure 1. **a** Bicyclo[1.1.1]pentylamines (BCPAs) in pharmaceuticals. **b** Methods to access BCPAs. **c** Fragmentation / *N*-centered radical ATRA, and photocatalyzed functionalization of iodo-BCPAs.

whether this approach could be applied to the synthesis of BCPAs. We recognized that *N*-centered radicals can be conveniently accessed by fragmentation of  $\alpha$ -iodoaziridines (**2**, Figure 1c),<sup>33–34</sup> and hypothesized that **1** could serve as a suitable radical acceptor, with the resulting BCP radical then abstracting an iodine atom from the  $\alpha$ -iodoaziridine starting material. The C–I bond resident in the iodo-

**Table 1. Optimization of  $\alpha$ -iodoaziridine fragmentation / *N*-centered radical addition to **1**.**

Entry	Conditions <sup>a</sup>	<b>1</b> <sup>b</sup> (equiv.)	Co-solvent <sup>c</sup>	Temp (°C)	Yield (%) <sup>d</sup>	<b>3a</b> : <b>3a-S</b> <sup>e</sup>
1	A	2.0	—	20	67	6:1
2	A	2.0	—	0	63	11:1
3	A	1.3	—	20	71	17:1
4	A	1.3	CH <sub>2</sub> Cl <sub>2</sub>	20	72 (75) <sup>f</sup>	>20:1
5	A	1.3	CH <sub>2</sub> Cl <sub>2</sub> <sup>g</sup>	20	64	>20:1
6	A	1.0 <sup>h</sup>	CH <sub>2</sub> Cl <sub>2</sub>	20	65	>20:1
7	A	1.1	CH <sub>2</sub> Cl <sub>2</sub>	20	67	>20:1
8	B	1.3	<i>t</i> -BuCN	30	31	20:1
9	B	2.0	<i>t</i> -BuCN	30	57	14:1

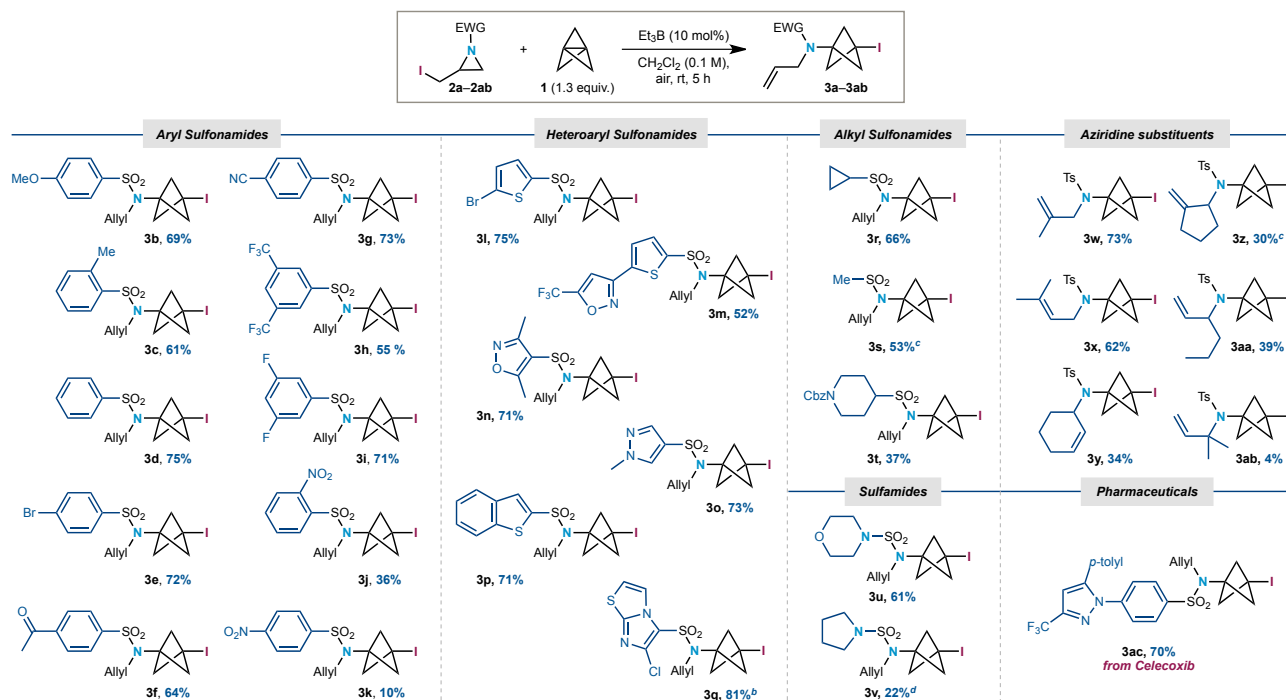
<sup>a</sup> Conditions A: Et<sub>3</sub>B (10 mol%), air, 5 h. Conditions B: *fac*-Ir(ppy)<sub>3</sub> (2.5 mol%), Blue LEDs (18 W), N<sub>2</sub>, 18 h. <sup>b</sup> **1** was used as a 0.6–0.8 M solution in Et<sub>2</sub>O unless indicated otherwise. <sup>c</sup> **2a** was prepared as a 1.0 M solution in the co-solvent, where used. <sup>d</sup> NMR yield, determined using mesitylene as internal standard. <sup>e</sup> Determined by <sup>1</sup>H NMR spectroscopic analysis of the crude reaction mixture. <sup>f</sup> Yield in parentheses is the isolated yield, including <5% **3a-S** and **3a-H** impurities. <sup>g</sup> **1** was prepared as a 1.06 M solution in CH<sub>2</sub>Cl<sub>2</sub>. <sup>h</sup> 1.5 equiv. of **2a**.

BCPA product **3** would then provide a handle further functionalization, potentially via re-formation of a BCP radical. Here we report the realization of this  $\alpha$ -iodoaziridine fragmentation/ATRA to form iodo-BCPAs, and the application of these products in photoredox-catalyzed Giese-type processes<sup>35–36</sup> to access *C*-substituted BCPAs

4.<sup>37</sup>

$\alpha$ -Iodoaziridine **2a** was selected for reaction optimization (Table 1). Based on the studies of Taguchi,<sup>33–34</sup> and our experience with the addition of *C*-centered radicals to **1**,<sup>31–32</sup> triethylborane was first tested as an initiator. Pleasingly, the desired C–N  $\sigma$  bond fragmentation/ATRA proceeded efficiently using 2.0 equiv. of **1**, giving iodo-BCP sulfonamide **3a** in 67% yield (entry 1); small amounts of staffane **3a-S**, H-atom abstraction product **3a-H**, and *N*-allylsulfonamide **5a** were also observed. The proportion of staffane (6:1) could be significantly reduced by lowering the reaction temperature (11:1, entry 2) or the equivalents of **1** (17:1, Entry 3). Suspecting that **3a-H** and **5a** might arise from H-atom abstraction from the solvent, use of CH<sub>2</sub>Cl<sub>2</sub> as co-solvent was tested and indeed reduced the levels of these byproducts (entry 4), giving a 75% yield of **3a** with <5% of **3a-S** and **3a-H**. A solution of **1** in CH<sub>2</sub>Cl<sub>2</sub> was prepared, however no further benefit in yield was observed (entry 5). Employing **1** as the limiting reagent proved equally effective (entry 6). Pleasingly, the reaction could also be performed on multigram scale with near-equivalent efficiency using just 1.1 equiv. of **1** (entry 7, 6.50 mmol (2.19 g) of **2a**, 67%). Comparable yields were achieved under photoredox catalysis,<sup>38</sup> with *fac*-Ir(ppy)<sub>3</sub> performing the best,<sup>39</sup> however a higher loading of **1** was required (entries 8–9).

Under the optimised conditions, iodo-BCPA synthesis was found to be applicable to a wide range of  $\alpha$ -iodoaziridines (Figure 2). Aryl sulfonamide aziridines bearing electron-donating (**3a–c**, 61%–75%), electron-neutral (**3d**, 75%) and electron-withdrawing (**3e–i**, 55–73%) substituents all gave high yields of the desired products, although aryl nitrosulfonamides were less successful (**3j** and **3k**, 10–36%). Notably, an aryl ketone (**3f**) was also tolerated, which would likely not be possible under anionic conditions for amide additions to **1**. Aziridines featuring heterocyclic sulfonamides including thiophenes (**3l–m**), oxazole (**3n**), pyrazole (**3o**), benzothiophene (**3p**) and imidazothiazole (**3q**) all reacted smoothly, affording the corresponding BCPA products in good to excellent yields (52–81%).



**Figure 2. Scope of  $\alpha$ -iodoaziridine fragmentation / ATRA with **1**. Reactions conducted on 0.15 mmol scale, yields are isolated yields. <sup>a</sup> 6.50 mmol **2a** (2.19 g), 1.1 equiv. of **1**. <sup>b</sup> Isolated as an inseparable 7:1 mixture with the corresponding staffane **3p-S**; yield of **3p**. <sup>c</sup> 1.6 equiv. of **1**. <sup>d</sup> 0.09 mmol scale.**

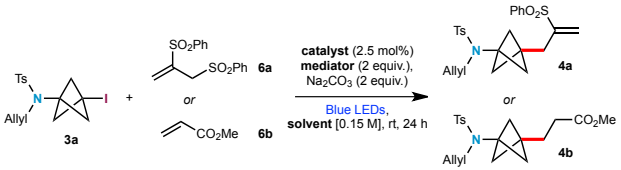
Alkyl sulfonamide (**3r–t**, 37–66%) and sulfamide substituted aziridines (**3u–3v**, 21–61%) were also accommodated.<sup>40</sup>

We next investigated substitution of the  $\alpha$ -iodoaziridine backbone. Pleasingly, aziridines featuring substituents at the 1-, 2- and 3-positions were tolerated, including fused cyclopentane and cyclohexane aziridines (**3w–aa**, 30–73%), although reaction of a trisubstituted aziridine was low yielding (**3ab**, 4%). Finally, the potential of this chemistry to operate in settings relevant to medicinal chemistry research was demonstrated via iodobicyclopentylation of the non-steroidal anti-inflammatory drug celecoxib (**3ac**, 70%).

The C–I bond in the iodo-BCPA product is an attractive handle for C–C bond formation. However, attempted lithiation / electrophilic trapping of iodo-BCPA **3a** was unsuccessful due to ejection of the sulfonamide anion, presumably accompanied by re-formation of **1**.<sup>39</sup> Precedent for radical-based BCP bridgehead C–C bond formation in *N,C*-BCPs is limited: to date only a handful of azide or triazole *N*-substituents have been studied, with reliance on organotin reagents,<sup>22</sup> or the radical acceptor as reaction solvent.<sup>41</sup> We questioned whether photoredox catalysis could offer a solution to this challenge, where the bridgehead C–I bond could be functionalized through Giese-type reactions.<sup>35–36</sup> Previous studies have demonstrated the use of silane and silanol mediators<sup>42</sup> to generate radicals from simple alkyl<sup>43–47</sup> and aryl<sup>48</sup> halides under photoredox catalysis, however use on the BCP scaffold is unprecedented.

Iodo-BCPA **3a** was selected for reaction optimization (Table 2), with allyl sulfone **6a** as an acceptor (Table 2). Initial attempts using Ir[(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> with (Me<sub>3</sub>Si)<sub>3</sub>SiH (TTMSS) as a radical mediator delivered addition product **4a** in 16% yield, along with a significant amount of the deiodination product **3a–H** (entry 1).<sup>49</sup> This competing H-atom abstraction by the presumed BCPA radical intermediate could be avoided by using (Me<sub>3</sub>Si)<sub>3</sub>SiOH,

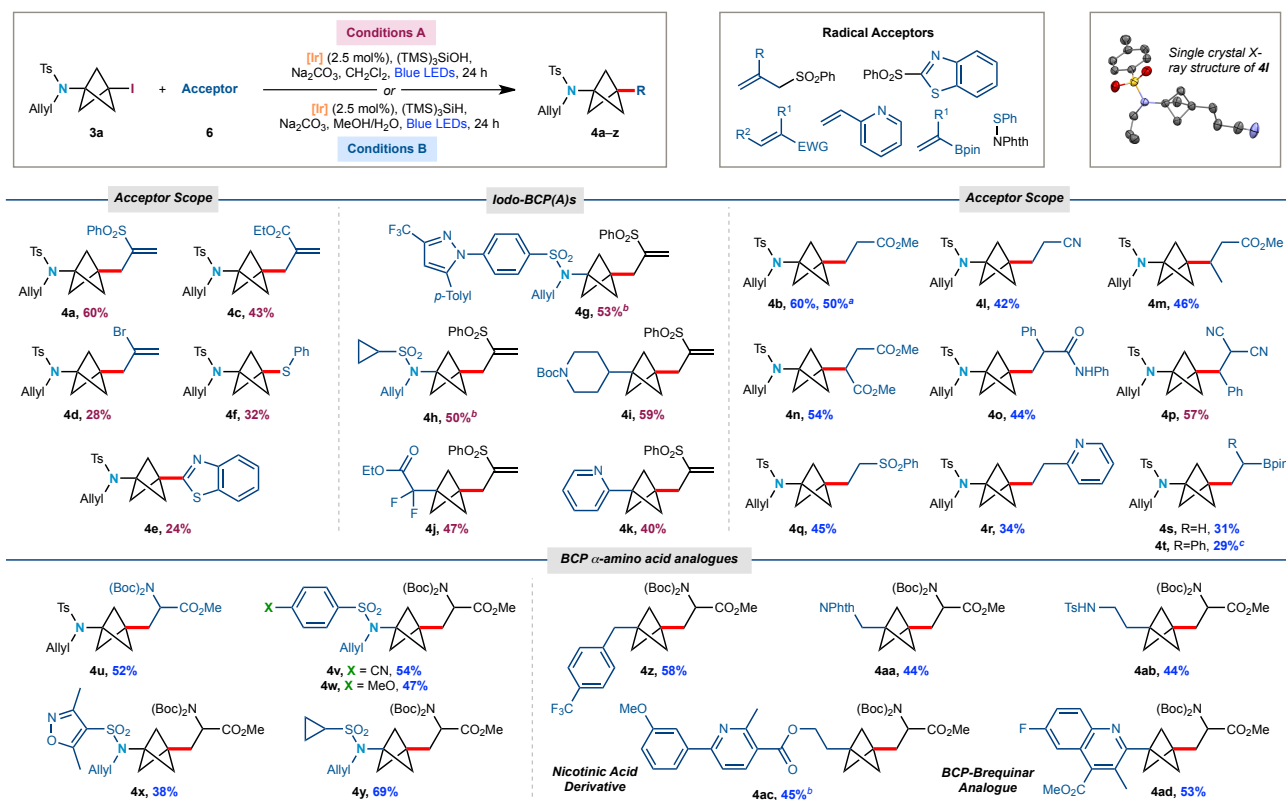
**Table 2. Giese Reaction Optimization**



Entry	Catalyst	<b>6</b> (equiv.)	Mediator	Solvent	Yield (%) <sup>a</sup>
1	Ir[(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	<b>6a</b> (3)	(Me <sub>3</sub> Si) <sub>3</sub> SiH	MeOH	16
2	Ir[(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	<b>6a</b> (3)	(Me <sub>3</sub> Si) <sub>3</sub> SiOH	MeOH	38
3	Ir[(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	<b>6a</b> (3)	(Me <sub>3</sub> Si) <sub>3</sub> SiOH	CH <sub>2</sub> Cl <sub>2</sub>	60 <sup>b</sup>
4	4-CzIPN <sup>c</sup>	<b>6a</b> (3)	(Me <sub>3</sub> Si) <sub>3</sub> SiOH	CH <sub>2</sub> Cl <sub>2</sub>	56
5	Ru(bpz) <sub>3</sub> (PF <sub>6</sub> ) <sub>2</sub>	<b>6a</b> (3)	(Me <sub>3</sub> Si) <sub>3</sub> SiOH	CH <sub>2</sub> Cl <sub>2</sub>	6
6	Ir[(dF(F)ppy) <sub>2</sub> (dCF <sub>3</sub> bpy)]PF <sub>6</sub>	<b>6a</b> (3)	(Me <sub>3</sub> Si) <sub>3</sub> SiOH	CH <sub>2</sub> Cl <sub>2</sub>	41
7	Ir[(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	<b>6b</b> (3)	(Me <sub>3</sub> Si) <sub>3</sub> SiOH	CH <sub>2</sub> Cl <sub>2</sub>	3
8	Ir[(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	<b>6b</b> (6)	(Me <sub>3</sub> Si) <sub>3</sub> SiOH	CH <sub>2</sub> Cl <sub>2</sub>	9
9	Ir[(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	<b>6b</b> (6)	(Me <sub>3</sub> Si) <sub>3</sub> SiH	CH <sub>2</sub> Cl <sub>2</sub>	48
10	Ir[(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	<b>6b</b> (6)	(Me <sub>3</sub> Si) <sub>3</sub> SiH	MeOH/H <sub>2</sub> O <sup>d</sup>	60 <sup>b</sup>
11	Ir[(dF(CF <sub>3</sub> )ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub>	<b>6b</b> (3)	(Me <sub>3</sub> Si) <sub>3</sub> SiH	MeOH/H <sub>2</sub> O <sup>d</sup>	44

<sup>a</sup> NMR yield, determined using mesitylene as internal standard. <sup>b</sup> Isolated yield. <sup>c</sup> 5 mol% catalyst. <sup>d</sup> MeOH/H<sub>2</sub>O (9:1).

which acts as a silyl radical source via silanolate oxidation / radical-Brook rearrangement.<sup>48, 50</sup> This led to a significant improvement in yield (38%, entry 2), which was further enhanced to 60% using CH<sub>2</sub>Cl<sub>2</sub> as solvent, likely due to improved solubility of **6a** (entry 3). Variation of the photocatalyst led to decreased yields of **4a**, although the organocatalyst 4-CzIPN was also well-suited to this



**Figure 3.** Scope of iodo-BCPA functionalization; reactions conducted on 0.15 mmol scale with Ir[(dF(CF<sub>3</sub>)ppy)<sub>2</sub>(dtbbpy)]PF<sub>6</sub> (2.5 mol%). Red yields indicate Conditions A; blue yields indicate Conditions B. <sup>a</sup> 1.00 mmol scale; <sup>b</sup> 0.13 mmol scale. **4l** was determined by single crystal X-ray diffraction.<sup>51 c</sup> The crude boronic ester was directly oxidized with H<sub>2</sub>O<sub>2</sub> / NaOH (aq.); the yield refers to the isolated of the corresponding alcohol.

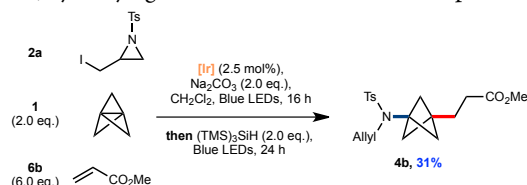
chemistry (entries 4-6). To our surprise, use of methyl acrylate (**6b**) as a radical acceptor under these conditions resulted in poor yields of product **4b**, even with increased acceptor loading (3-9%, entry 7-8). Use of TTMSS restored productive reactivity (48%, entry 9), and changing the reaction solvent to MeOH / H<sub>2</sub>O (9:1) (entry 10) delivered an optimum yield of **6b** of 60%.

With two sets of reaction conditions in hand (Conditions A – Table 2, entry 3; Conditions B – Table 2, entry 10), the Giese methodology was applied to a wide range of radical acceptors (Figure 3). Under Conditions A, various 2-substituted allylic sulfones delivered the corresponding allyl-BCPA products **4a**, **4c** and **4d** (29-60%). Reaction of a benzothiazole sulfone delivered the heteroarylated BCPA **4e** in modest yield, while sulfuration with *N*-(phenylthio)phthalimide also proved possible (**4f**, 32%). Variation of the sulfonamide group was also well tolerated (**4g** and **4h**, 50-53%), the former of which demonstrates functionalization of the anti-inflammatory agent Celecoxib. Encouraged by these results, we further tested the methodology on *C*-substituted iodo-BCPs; to our delight, these readily accessible substrates,<sup>31-32</sup> featuring ester, piperidine and pyridine functionalities, reacted well with allyl sulfone **6a** to give **4i-k** in 40-59% yield.

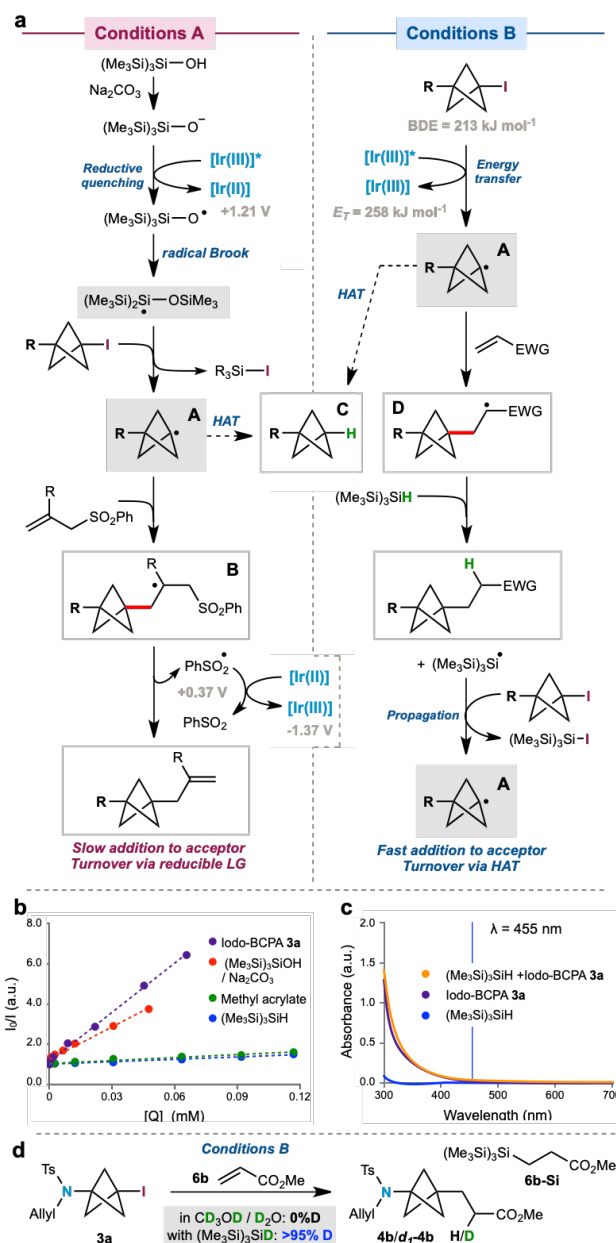
Conditions B proved suitable for acrylonitrile, acrylate, and acrylamide type acceptors (**4b**, **4l-4o**, 42-60%); reaction on 1.0 mmol scale proceeded with similar efficiency, giving a yield of 50% of **4b**. Somewhat surprisingly, the use of 2-benzylidene malononitrile proceeded poorly under these conditions, but delivered **4p** in 57% yield using Conditions A. Variation of the electron-withdrawing group to a vinyl sulfone (**4q**), and even a vinyl pyridine (**4r**) or vinylboronic esters (**4s-4t**) was also successful. In the latter cases, the boronic esters proved challenging to purify, and for **4t** an oxidative work-up instead directly provided the corresponding alcohol.

The photocatalytic iodo-BCPA functionalization also offers a powerful strategy for the mild generation of previously unobtainable, pharmaceutically-relevant BCPA  $\alpha$ -amino acid derivatives. This was demonstrated through the reaction of dehydroalanine with a range of iodo-BCPAs (under Conditions B) to give BCPA analogues of 4-amino phenylalanine (**4u-4y**, 38-69%). Once again, we were pleased to find that this chemistry translated well to *C*-substituted iodo-BCPs. This two-step approach thus provided access to diverse BCP phenylalanine derivatives **4z-4ad** (44-58%), including nicotinic acid derivative **4ac** (45%) and BCP-Brequinar analogue **4ad** (53%). Collectively, these examples illustrate the excellent functional group tolerance of this Giese chemistry, which should render it of significant utility in drug discovery programs.

With both the iodoaziridine fragmentation / ATRA and Giese addition established, we questioned whether the two processes might take place in a single reaction, such that the intermediate BCPA radical is captured directly by the radical acceptor, or that the intermediate iodo-BCPA undergoes an *in situ* Giese reaction. Attempts to realize a one-pot cascade resulted only in formation of *N*-allyl sulfonamide **4a**, where direct HAT from the silane to the *N*-centered radical outcompeted addition to [1.1.1]propellane **1** (Scheme 1). However, by delaying addition of the silane until complete



**Scheme 1.** One-pot synthesis of *C,N*-difunctionalized BCP **4b**.



**Figure 4.** a Possible mechanisms of Giese reaction of iodo-BCPAs. b Stern-Volmer quenching study using **3a**, (Me<sub>3</sub>Si)<sub>3</sub>SiH, (Me<sub>3</sub>Si)<sub>3</sub>SiOH and methyl acrylate. c UV/visible spectra of **3a**, (Me<sub>3</sub>Si)<sub>3</sub>SiH, and (Me<sub>3</sub>Si)<sub>3</sub>SiH + **3a**. d Deuterium labelling study.

consumption of the iodoaziridine **2a** (16 h, [Ir] catalysis), the entire ATRA / Giese process could be performed without isolation of the intermediate iodo-BCPA. The overall yield for this transformation (31%, 55% per step) is consistent with that for the isolated steps (57%, 60%).

The distinct nature of the two silanes used in these Giese functionalizations may suggest that different mechanisms operate in the two cases. Previous studies<sup>42-44, 48</sup> have suggested that reaction with either mediator requires initial formation of a silyl radical. In the case of (Me<sub>3</sub>Si)<sub>3</sub>SiOH (Figure 4a, Conditions A), this can be achieved by oxidation of the silanolate ion (generated on deprotonation of the silanol under basic conditions) by the redox-active excited triplet state of the iridium catalyst ( $E^{\text{red}} \text{Ir(III)}^* / \text{Ir(II)} = +1.21 \text{ V vs. SCE in MeCN}$ ),<sup>52-53</sup> followed by radical Brook rearrangement.<sup>54</sup> The resulting silyl radical then abstracts an iodine atom from the iodo-BCP(A)



to give the BCP(A) radical **A**, which then undergoes addition to the radical acceptor. For acceptors such as allyl sulfones (Conditions A, radical **B**), this addition is presumably sufficiently slow that H-atom transfer to **A** can compete when using  $(\text{Me}_3\text{Si})_3\text{SiH}$  as mediator (to give **C**), rationalizing the need for  $(\text{Me}_3\text{Si})_3\text{SiOH}$ . Catalyst turnover is then achieved via reduction of the sulfinyl radical to the sulfinate ion ( $E^{\text{red}} \text{PhSO}_2^{\cdot-} / \text{PhSO}_2^- = +0.37 \text{ V vs. SCE}$ ;<sup>55</sup>  $E^{\text{ox}} \text{Ir(II)}/\text{Ir(III)} = +1.37 \text{ V vs. SCE in MeCN}$ ).<sup>52</sup>

For Conditions B ( $(\text{Me}_3\text{Si})_3\text{SiH}$  mediator), it has been proposed that  $(\text{Me}_3\text{Si})_3\text{Si}^{\cdot}$  can be generated by direct oxidation of the silane ( $[E^{\text{ox}}(\text{Me}_3\text{Si})_3\text{SiH} / (\text{Me}_3\text{Si})_3\text{SiH}^{+\cdot} = +0.73 \text{ V vs. SCE in MeCN}]$ ),<sup>56</sup> followed by deprotonation. To explore this possibility, a Stern-Volmer quenching study was carried out (Figure 4b). To our surprise, this revealed that  $(\text{Me}_3\text{Si})_3\text{SiH}$  is a poor quencher of the excited state photocatalyst (blue line), but iodo-BCPA **3a** is an efficient quencher (purple line). In contrast,  $(\text{Me}_3\text{Si})_3\text{SiOH}$  (in the presence of  $\text{Na}_2\text{CO}_3$  to mimic basic reaction conditions) is able to quench the catalyst excited state (red line), which offers support that Conditions A can proceed according to the proposed mechanism.

Voltammetry experiments<sup>39</sup> revealed that the first (irreversible) reduction of **3a** occurs at  $-2.29 \text{ V}$ , which is in excess of the reducing power of most common photocatalysts and renders an oxidative quenching pathway unlikely. We further considered that visible light might effect homolysis of the C–I bond, however UV/visible spectroscopy (Figure 4c) revealed no absorption at  $455 \text{ nm}$  (blue LEDs). Control experiments (see the SI) further demonstrated that all reaction components were essential for the success of the reaction, and that no addition occurred in the absence of the silane. We therefore suggest that the efficient quenching of the photocatalyst excited state by iodo-BCPA may be due to Dexter energy transfer.<sup>57–58</sup> The energy of the  $T_1$  triplet state of  $\text{Ir}[(\text{dF}(\text{CF}_3)\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  is  $258 \text{ kJ mol}^{-1}$ ;<sup>52</sup> given the bond dissociation energy of C–I bonds is in the region of  $\sim 213 \text{ kJ mol}^{-1}$ , homolysis of the C–I bond by this mechanism appears feasible. The resulting BCP radical **A** can then undergo addition to the acceptor to give the EWG-stabilized radical **D** (or competing HAT to generate **C**). Radical **D** then undergoes H-atom transfer with  $(\text{Me}_3\text{Si})_3\text{SiH}$  to generate the Giese product, along with  $(\text{Me}_3\text{Si})_3\text{Si}^{\cdot}$ , which propagates the reaction by I-atom abstraction from the iodo-BCPA. Deuteration studies were carried out to gain support for this reaction pathway, or whether a possible reduction by Ir(II) operates ( $E^{\text{red}} \cdot\text{CH}(\text{CH}_3)\text{CO}_2\text{Et} / \text{CH}(\text{CH}_3)\text{CO}_2\text{Et} = +0.66 \text{ V vs. SCE in MeCN}$ ) as in Conditions A (Figure 4d).<sup>59</sup> In contrast to findings by ElMarrouni *et al.*,<sup>45</sup> no product deuteration was observed on conducting the reaction in  $\text{CD}_3\text{OD} / \text{D}_2\text{O}$ , suggesting SET from Ir(II) is not operative. However, use of  $(\text{Me}_3\text{Si})_3\text{SiD}$  led to complete deuteration at the  $\alpha$ -position ( $>95\%$ ), which strongly supports the proposed propagation pathway. The observation of the silane adduct of methyl acrylate (**6b–Si**) further supports the intermediacy of the silyl radical.

With methods to access diverse 1,3-disubstituted BCPAs established, we briefly investigated a selection of further transformations (Figure 5). Principal among these was the ability to cleave either the allyl or sulfonyl substituent from the nitrogen atom. The former was achieved on BCPA **3a** under mild conditions using  $\text{Pd}(\text{PPh}_3)_4$  and 1,3-dimethylbarbituric acid (**7**, 72%),<sup>60</sup> while smooth detosylation was effected on **4b** via sonication with  $\text{Mg}/\text{MeOH}$ , which gave amine **8** in 64% yield. Simple deiodination of **3a** was carried out under photoredox conditions (**9**, 54%), while the *N*-allyl group could be oxidized to epoxide **10** (oxone/KBr, 71%),<sup>61</sup> aldehyde **11** ( $\text{O}_3$ , 71%) or BCP glycine analogue **12** ( $\text{RuCl}_3/\text{NaIO}_4$ , 34%). Finally,

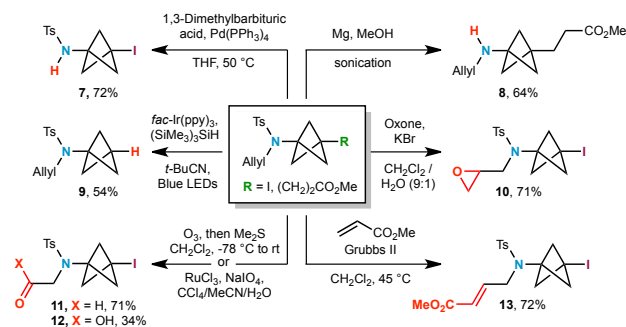


Figure 5. Further transformations.

cross metathesis with methyl acrylate gave **13** (Grubbs II, 72%).

In summary, this twofold radical functionalization of [1.1.1]propellane offers a versatile and convenient route to prepare 1,3-*N,C*-disubstituted BCPs, opening up a new route to valuable aniline isosteres. The chemistry displays high functional group tolerance, affording products that are unobtainable by previous methods. The application of this chemistry to amino acid and drug analogues highlights the potential utility of this methodology for the pharmaceutical industry.

## ASSOCIATED CONTENT

### Supporting Information

Supporting Information is available free of charge via the Internet at <http://pubs.acs.org>, including experimental details and copies of both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra.

### Accession Codes

CCDC 2078089 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif), or by emailing [data\\_request@ccdc.cam.ac.uk](mailto:data_request@ccdc.cam.ac.uk), or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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All authors have given approval to the final version of the manuscript.

### Notes

The authors declare no competing financial interest.

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## TOC graphic:

