



# Electrophilic Activation of [1.1.1]Propellane for the Synthesis of Nitrogen-Substituted Bicyclo[1.1.1]pentanes

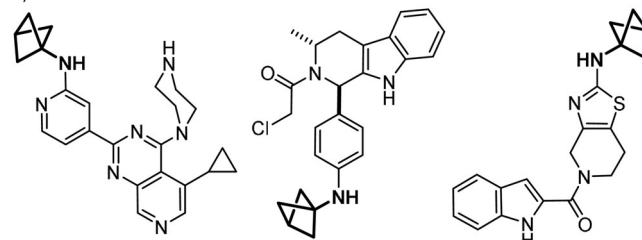
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**Abstract:** Strategies commonly used for the synthesis of functionalised bicyclo[1.1.1]pentanes (BCP) rely on the reaction of [1.1.1]propellane with anionic or radical intermediates. In contrast, electrophilic activation has remained a considerable challenge due to the facile decomposition of BCP cations, which has severely limited the applications of this strategy. Herein, we report the electrophilic activation of [1.1.1]propellane in a halogen bond complex, which enables its reaction with electron-neutral nucleophiles such as anilines and azoles to give nitrogen-substituted BCPs that are prominent motifs in drug discovery. A detailed computational analysis indicates that the key halogen bonding interaction promotes nucleophilic attack without sacrificing cage stabilisation. Overall, our work rehabilitates electrophilic activation of [1.1.1]propellane as a valuable strategy for accessing functionalised BCPs.

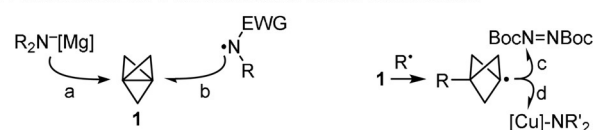
## Introduction

The bicyclo[1.1.1]pentane (BCP) fragment is recognised as a beneficial isosteric replacement of phenyl, *tert*-butyl and alkyne groups in biological<sup>[1]</sup> and material science applications.<sup>[2]</sup> Specifically, nitrogen-substituted BCPs (Figure 1A) have been reported in more than half of the patents that feature bioactive BCPs.<sup>[3]</sup> However, these bioactive compounds have been prepared from a limited set of BCP-amine

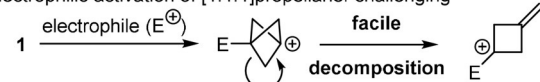
### A) Bioactive *N*-substituted BCPs



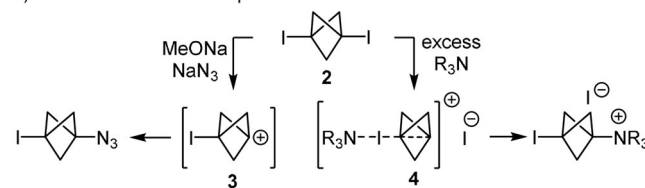
### B) *N*-substituted BCPs via anionic and radical intermediates



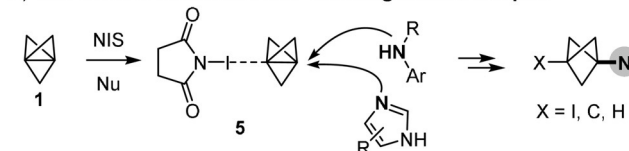
### C) Electrophilic activation of [1.1.1]propellane: challenging



### D) *N*-substituted BCPs via postulated cationic intermediates



### E) This work: *N*-substituted BCP via halogen bond complex



**Figure 1.** A) Examples of bioactive nitrogen-substituted BCPs in patents. B) Synthesis of *N*-substituted BCPs from [1.1.1]Propellane **1** with anionic and radical reagents. C) Facile decomposition of BCP carbocations. D) Synthesis of *N*-substituted BCPs from 1,3-bis-iodo-BCP **2**. E) Synthesis of *N*-substituted BCPs by electrophilic activation of **1** in halogen bond complex **5**. NIS: *N*-iodosuccinimide.

building blocks that are either commercially available, but expensive, or made in several steps from other BCP derivatives.<sup>[4]</sup> Therefore, there is an urgent need to develop synthetic methods to access a wider range of nitrogen-substituted BCPs.

In this context, [1.1.1]propellane **1** is considered the most valuable precursor of nitrogen-substituted BCPs through addition of anions and radicals to its interbridgehead bond. Thus, **1** can be attacked either by an excess of secondary bis-alkyl amines once they have been deprotonated with a strong

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base into organometallic amides (Figure 1 B, path a).<sup>[5]</sup> Moreover, electrophilic nitrogen-centred radicals that are stabilised with at least one electron-withdrawing group (EWG) can also add to **1** (path b).<sup>[6]</sup> Alternatively, nitrogen-substituted BCPs can be formed by trapping a bicyclo[1.1.1]pentyl radical intermediate either with an azodicarboxylate to give BCP-hydrazines (path c),<sup>[7]</sup> or with a Cu<sup>III</sup> complex as a carrier of nitrogen-centred nucleophiles (path d).<sup>[8]</sup>

In stark contrast to these strategies, the synthesis of nitrogen-substituted BCP derivatives by electrophilic activation of **1** in a cationic pathway appears far more challenging because of the facile decomposition of the tertiary bicyclo[1.1.1]pent-1-yl carbocation (Figure 1 C).<sup>[9]</sup> Nevertheless, Wißberg and co-workers proposed that the intermediate carbocation **3** could be formed and then trapped by an azide anion in the reaction of 1,3-bis-iodo-BCP **2** with NaN<sub>3</sub> under basic conditions (Figure 1 D).<sup>[10,11]</sup> Independently, Adcock and co-workers postulated that the reaction of a large excess of pyridine or tertiary amines with **2** led to the formation of the cationic intermediate **4** that would be then attacked by the nucleophile present in excess.<sup>[12]</sup> Unfortunately, other nucleophiles examined in that study, such as *i*-Pr<sub>2</sub>NH, pyrazine and thiazole, did not deliver the expected BCP adducts but instead partially regenerated propellane **1**, whereas the reaction of **1** with pyridine and molecular iodine gave a mixture of the expected nitrogen-substituted BCP and **2**. More recently, Zarate and co-workers have modified this procedure for the alkylation of 4-iodo-pyrazole with either **1** or **2**.<sup>[13]</sup> Thus, the electrophilic activation of propellane **1** and subsequent trapping by nucleophiles remains limited to a small set of nucleophiles, and lags behind the numerous strategies reported for the addition of anions and radicals to **1**.<sup>[14,15]</sup>

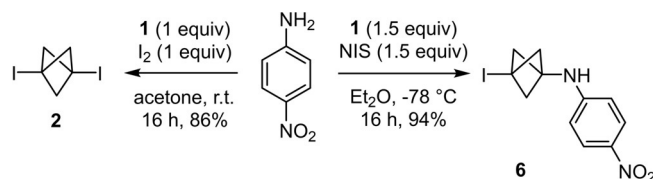
Herein, we report that the synthesis of nitrogen-substituted BCPs is enabled by electrophilic activation of propellane **1** in a halogen bond complex, which facilitates the attack of primary anilines, *N*-alkyl and *N*-aryl secondary anilines, as well as azoles (Figure 1 E). Significantly, DFT calculations suggest that halogen bond complex **5** is a minimum on the energy profile of the reaction and is electrophilic in nature, which enables nucleophilic attack, whereas the decomposition of the cage is disfavoured. Conversely, a cationic pathway involving carbocation **3** can only lead to exomethylenecyclobutane derivatives and is not a viable intermediate in the reactions leading to nitrogen-substituted BCPs. Hence, the electrophilic activation of propellane **1** in a halogen bond complex enables its attack by electron-neutral *N*-centred nucleophiles that are fundamentally distinct from the nucleophilic organometallic amides<sup>[5]</sup> and electrophilic *N*-centred radicals<sup>[6]</sup> described previously.

## Results and Discussion

### Optimisation and initial observations

We were eager to first verify whether anilines could be alkylated by propellane **1** in the presence of simple molecular iodine. However, we found that the reaction led only to the formation of 1,3-bis-iodo-BCP **2** without any trace of the

desired product (Scheme 1). Conversely, using *N*-iodosuccinimide (NIS) and keeping the temperature at  $-78^{\circ}\text{C}$  enabled the isolation of the desired product **6** in 94% yield. Applying higher temperatures was detrimental to the yield (Table 1,



**Scheme 1.** Contrasting reactivity of I<sub>2</sub> and NIS in their activation of propellane **1** for the alkylation of a model aniline substrate. NIS: *N*-iodosuccinimide.

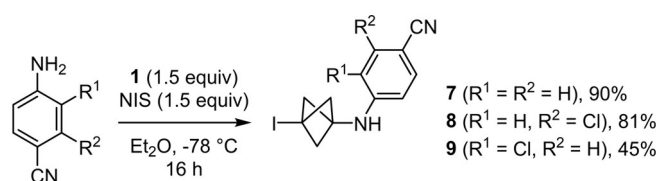
**Table 1:** Control reactions.<sup>[a,b]</sup>

Entry	Activator	Solvent	<i>T</i>	Product (Yield) <sup>[c]</sup>
1	NIS	Et <sub>2</sub> O	21 °C	<b>6</b> (8%)
2	NIS	Et <sub>2</sub> O	0 °C	<b>6</b> (27%)
3	I <sub>2</sub>	Et <sub>2</sub> O	$-78^{\circ}\text{C}$	<b>2</b> (63%) <sup>[d,e]</sup>
4	I <sub>2</sub>	MeCN	21 °C	<b>2</b> (12%) <sup>[e,f]</sup>
5	NBS	Et <sub>2</sub> O	$-78^{\circ}\text{C}$	n.a. <sup>[g]</sup>
6	NCS	Et <sub>2</sub> O	$-78^{\circ}\text{C}$	n.a. <sup>[g]</sup>

[a] For entries 1, 2, 5, and 6, aniline/**1**/activator = 1:1.5:1.5 [b] For entries 3 and 4, aniline/**1**/activator = 1:1.2:1.5 and Cs<sub>2</sub>CO<sub>3</sub> (2 equiv) was added. [c] Yields determined by <sup>1</sup>H NMR. [d] 92% of remaining aniline. [e] **6** was not formed. [f] 53% of remaining aniline. [g] Not applicable, no BCP products. NBS: *N*-bromosuccinimide. NCS: *N*-chlorosuccinimide.

entries 1 and 2), and using or slightly modifying the conditions described recently by Zarate and co-workers for the alkylation of 4-iodo-pyrazole with **1** did not lead to the formation of **6** but of 1,3-bisiodo-BCP **2** instead (entries 3 and 4).<sup>[13]</sup> Moreover, using NBS or NCS instead of NIS did not lead to the formation of the corresponding BCP analogues of **6** (entries 5 and 6). Significantly, compound **2** was left intact when treated with *para*-nitroaniline at room temperature, even for several days and independently of the solvent (acetone, Et<sub>2</sub>O or THF). This result confirmed that **2** is neither an intermediate nor a suitable starting material in the reaction leading to the desired product **6**.

Using the optimised reaction conditions, the initial exploration of the scope of anilines quickly revealed that only electron-poor anilines could lead to high yields of isolated products. Thus, compounds **7–9** could be obtained in 45–90% yield (Scheme 2). Strikingly, compounds **6–9** were not stable at room temperature for more than an hour when neat, but they were stable in solution for several days. The



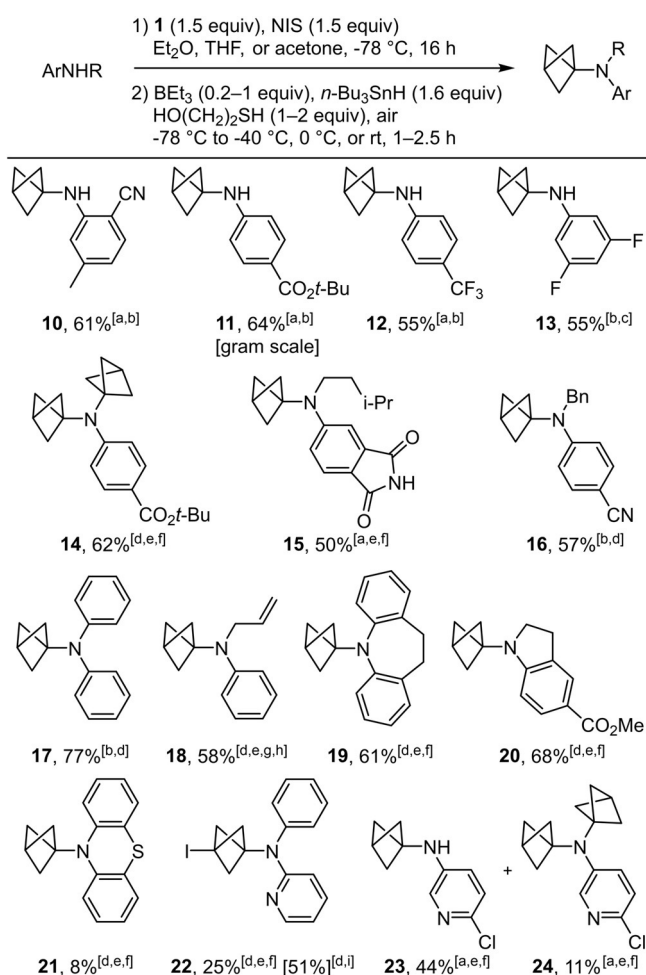
**Scheme 2.** Initial scope of 3-iodo-BCP-anilines.

lack of stability observed for **6–9** was exacerbated in the case of less electron-poor primary anilines and of secondary anilines, regardless of their electronic properties. Hence, rapid darkening of the crude mixture was observed either when removing the reaction vessel from the  $-78^{\circ}\text{C}$  bath, or even in the capillary when we monitored the formation of the most sensitive products by thin layer chromatography.

### Scope of alkylation of anilines

Despite this decomposition, it was clear that the alkylation of electronically-diverse anilines with **1** occurred satisfactorily. Only the stability of the BCP adducts was an issue, and we reasoned that removing the carbon-iodine bond would give more stable products. We therefore decided to attempt a one-pot reaction that combined the alkylation protocol described above with a reduction under the mildest conditions possible to initiate the C–I bond cleavage below room temperature with  $\text{Et}_3\text{B}$  and air in MeOH. During the optimisation of this one-pot sequence, we obtained much better results by i) not evaporating the solvent used for the alkylation ( $\text{Et}_2\text{O}$ , THF, or acetone), ii) using 2-mercaptoethanol in addition to  $n\text{-Bu}_3\text{SnH}$  to accelerate the reduction of the bicyclo[1.1.1]pentyl radical,<sup>[16]</sup> and iii) adding the reagents of the reduction at  $-78^{\circ}\text{C}$  before letting the mixture warm to room temperature or below, depending on the substrate. The choice of solvent for the alkylation of anilines with **1** was dictated by their reactivity and solubility, which both increased in the order  $\text{Et}_2\text{O} < \text{THF} < \text{acetone}$ , whereas the stability of the iodinated BCP cage during the reduction of the C–I bond decreased in that order. After concentration of the crude mixture, the tin residues were carefully removed by treatment of the crude mixture with KF and purification by chromatography on silica gel loaded with  $\text{K}_2\text{CO}_3$ .<sup>[17]</sup> Using this one-pot sequence, we were delighted to isolate a wide array of BCP-anilines **10–24** that were hitherto beyond reach (Scheme 3).

Thus, besides resonance-stabilised derivatives **10** and **11**, primary anilines substituted with groups that have only negative inductive effects gave BCPs **12** and **13** in good yields. It is noteworthy that the reaction could be conducted on the gram scale to obtain **11** in 64% yield. In that experiment, we also obtained the product of bis-alkylation **14** in low yield, which encouraged us to explore the scope of secondary anilines. Gratifyingly, using **11** as substrate of the one-pot sequence, **14** could be obtained in 62% yield. Similarly, we could obtain **15** without any evidence of C–N bond formation at the imide nitrogen atom. When working with secondary anilines as precursors of BCP-anilines, it was essential to use acetone as a solvent in several cases. In addition, it was also critical to maintain a low temperature after the addition of the reducing agents in the second stage of this one-pot protocol to avoid unwanted decomposition of the most sensitive BCP-anilines. Hence, the optimal protocol required to either allow a slow warming from  $-78^{\circ}\text{C}$  to  $0^{\circ}\text{C}$  over 2.5 hours (**14**, **15**, **19**, and **20**) or keep the reaction at  $-40^{\circ}\text{C}$  for 2 hours (**18**). With this tailored control of the temperature, we could isolate the desired compounds in



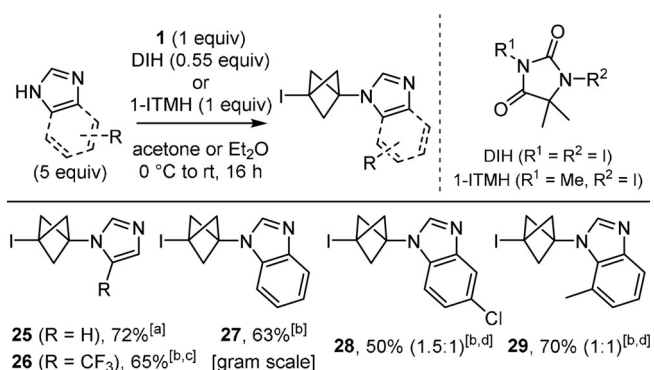
**Scheme 3.** Scope of the BCP-anilines obtained by the N-alkylation/C-I reduction one-pot sequence. All reactions were conducted on 0.2 mmol of aniline in 1 mL of solvent except otherwise noted; yields of pure isolated products. [a] In THF. [b]  $\text{BEt}_3$  (0.2 equiv),  $\text{HS}(\text{CH}_2)_2\text{OH}$  (1 equiv); reduction reaction rapidly warmed to r.t and stirred for 1 h. [c] In  $\text{Et}_2\text{O}$ . [d] In acetone. [e]  $\text{BEt}_3$  (1 equiv),  $\text{HS}(\text{CH}_2)_2\text{OH}$  (2 equiv). [f] Reduction reaction warmed to  $0^{\circ}\text{C}$  slowly over 2.5 h. [g] Reduction reaction kept at  $-40^{\circ}\text{C}$  for 2 h. [h]  $^1\text{H}$  NMR yield, volatile compound. [i] Reduction not attempted.

excellent yields, whereby BCP-anilines **17–19** were notably not stabilised by any electron-withdrawing groups. In contrast, compound **21** was obtained in only 8% yield despite a complete and clean alkylation of phenothiazine in the first stage of this one-pot reaction. Indeed, we observed the regeneration of phenothiazine in large amounts when attempting the reduction of the C–I bond under radical conditions (Figure SI-1, see supporting information).

Finally, the one-pot sequence was applied to aminopyridines and delivered **22–24**. However, the C–I bond of BCP **22** resisted the reduction conditions of the second stage of the one-pot sequence. It is also noteworthy that **22** was far more stable once isolated than **6–9** or the 3-iodo-BCPs precursors of **10–21**, and **22** could be obtained in 51% when the C–I bond reduction step was omitted. Conversely, the C–I bond reduction was possible on a 3-amino pyridine derivative and mono-BCP **23** was isolated after separation from bis-BCP **24**.

## Scope of other nitrogen-centred nucleophiles

When examining the reaction of other nitrogen-centred nucleophiles, we found that indoles and amides were unreactive, whereas the reaction of secondary alkyl amines gave complex mixtures, and those of pyrazole, carbamates and sulfonamides were both sluggish and unselective (Figure SI-2, see supporting information). Conversely, the reaction of azoles led to BCP-azoles **25–29** in good yields under slightly modified conditions (Scheme 4). Hence, an excess of nucleophile was necessary to compensate for an otherwise incomplete conversion, and replacing NIS with either commercially available 1,3-diiodo-5,5-dimethylhydantoin (DIH) or easily prepared 1-iodo-3,5,5-trimethylhydantoin (1-ITMH)

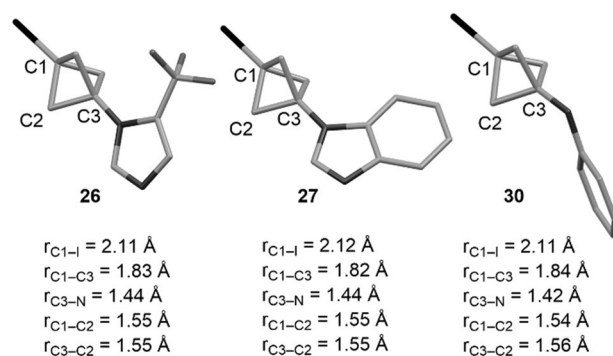


**Scheme 4.** Scope of 3-iodo-BCP-azoles. [a] In Et<sub>2</sub>O, 1-ITMH. [b] In acetone, DIH. [c] Single regioisomer. [d] Ratio of regioisomers. DIH: 1,3-diiodo-5,5-dimethylhydantoin. 1-ITMH: 1-iodo-3,5,5-trimethylhydantoin.

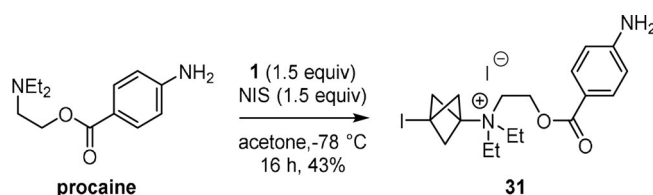
made the purification of **25–29** easier. Furthermore, using I<sub>2</sub> as electrophilic activator of **1** instead of NIS, DIH or 1-ITMH for the alkylation of imidazole led to 1,3-bis-iodo BCP **2** as major product (41%) besides **25** in lower yield (18%). It is also noteworthy that the conditions recently described by Zarate and co-workers for the alkylation of 4-iodo-pyrazole with **1**<sup>[13]</sup> did not give any trace of **25** when using imidazole as test substrate.

In addition, it is noteworthy that these BCP-azoles were more stable in neat form than the BCP-anilines **6–9**. Comparison of the X-ray crystal structures<sup>[18]</sup> of BCP-azoles **26** and **27** with the optimised geometry of model BCP-aniline **30** showed a shorter distance between the two bridgehead atoms C1 and C3 in **26** and **27** than in **30** (Figure 2). On the opposite, the C3–N bond is shorter in **30** than in **26** and **27**, and the C2–C3 bonds are in average longer than the C1–C2 bonds in **30**, a feature that is not seen in **26** and **27**. Hence, the greater distortion of the BCP cage in 1-iodo-BCP-anilines, likely due to enhanced donation of the nitrogen lone pair into the C2–C3 bond,<sup>[19]</sup> might contribute to their lack of stability.

Finally, we examined the reaction of procaine, a widely-used local anesthetic drug, under the conditions optimised for anilines. We found that C–N bond formation occurred only at the tertiary alkyl amine and not at all at the aniline, and compound **31** was isolated in 43% yield in a mixture with succinimide (Scheme 5). Overall, among the nitrogen-centred



**Figure 2.** Bond distances from X-ray crystal structures of **26** and **27** and the optimised geometry of **30** calculated at the SMD(Et<sub>2</sub>O)-B2GPP-PLYP-D3BJ/def2-TZVP level of theory. Average values for r<sub>C1-C2</sub> and r<sub>C3-C2</sub>.



**Scheme 5.** Reaction of procaine.

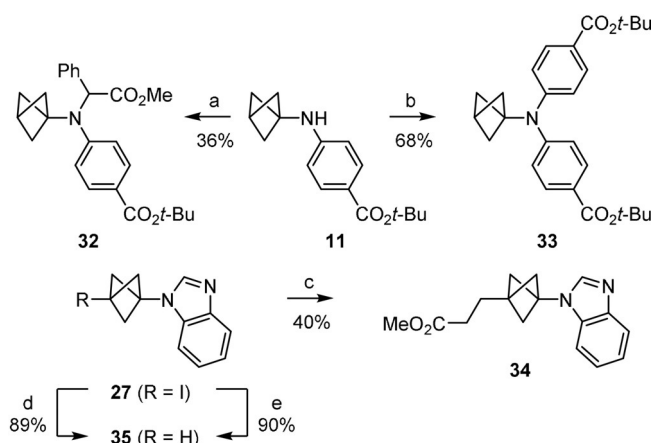
nucleophiles that gave BCP adducts with the protocol described here, the following reactivity trend is obtained: azoles < anilines < tertiary alkyl amines, in good agreement with Mayr's nucleophilicity scale.<sup>[20]</sup>

## Further functionalisation

The BCPs obtained in the reactions described above are amenable to further functionalisation. For example, under unoptimised reaction conditions compounds **32** and **33** could be obtained from BCP-aniline **10** by rhodium-catalysed N-H insertion and Buchwald-Hartwig cross-coupling, respectively (Scheme 6). It is noteworthy that both reaction classes are unprecedented for BCP-anilines. The C–I bond of the BCP-azole **27** could also be exploited for further functionalisation in a Giese reaction with methyl acrylate to give **34**, and the reduction of the C–I bond could be completed to give **35** by using either (Me<sub>3</sub>Si)<sub>3</sub>SiH and AIBN,<sup>[21]</sup> or catalytic Pd(PPh<sub>3</sub>)<sub>4</sub> under blue light irradiation.<sup>[22]</sup>

## Mechanism

Tertiary bicyclo[1.1.1]pent-1-yl carbocations are known to undergo rapid decomposition.<sup>[9]</sup> Wiberg and co-workers have computationally studied several 3-substituted bicyclo[1.1.1]pent-1-yl carbocations. However, carbocation **3** was not included in their studies, and **3** was postulated to be an intermediate species that could be trapped by nucleophiles such as azide and methoxide.<sup>[10]</sup> This is at odds with our computational study on the reactivity of [1.1.1]propellane,<sup>[23]</sup>



**Scheme 6.** Further functionalisation of the BCP-anilines and BCP-azoles. a) 1 mol%  $[\text{Rh}_2(\text{OAc})_4]$ ,  $\text{PhC}(\text{=N}_2)\text{CO}_2\text{Me}$  (2 equiv),  $\text{CH}_2\text{Cl}_2$ ,  $30^\circ\text{C}$ , 3 hours slow addition of diazo compound, then 20 h. b) 5 mol%  $[\text{Pd}(\text{Pt-Bu}_3)_2]$ ,  $t\text{-BuONa}$  (1.5 equiv),  $p\text{-BrC}_6\text{H}_4\text{CO}_2t\text{-Bu}$  (1.2 equiv), toluene,  $110^\circ\text{C}$ , 24 h. c)  $n\text{-Bu}_3\text{SnH}$  (1.1 equiv), AIBN (0.3 equiv), methyl acrylate (8 equiv), benzene,  $80^\circ\text{C}$ , 3.5 h. d)  $(\text{Me}_3\text{Si})_3\text{SiH}$  (1.8 equiv), AIBN (0.2 equiv), water,  $75^\circ\text{C}$ , 5 h. e) 3 mol%  $\text{Pd}(\text{PPh}_3)_4$ ,  $t\text{-BuOK}$  (2 equiv), isopropanol, blue light, r.t., 22 h. AIBN: azobisisobutyronitrile.

which indicates that  $\sigma\text{-}\pi$ -delocalisation is key to maintain structural integrity. Therefore, upon formation of the cation, one would expect this delocalisation to be lost, leading to the collapse of **3** (Figure SI-3, see supporting information). Indeed, our geometry optimisation of **3** in implicit ether solvent revealed that this structure is not a minimum but a transition state (TS) that features the cleavage of a C–C bond adjacent to the C–I bond (Figure 3A). This TS collapses to a bent bicyclo[1.1.0]butane-like cation **36** in which the primary cation experiences pseudo-allylic stabilisation with the interbridgehead C–C bond. Subsequently, planarisation of this cation via TS **37** is almost barrierless, leading to the formation of cyclobutyl cation **38**, which is accompanied by a modest driving force of  $3.4\text{ kcal mol}^{-1}$ . These results provide counter-evidence for the involvement of the carbocation **3** in reactions where an intact bicyclo[1.1.1]pentyl cage is present in the product.

We hypothesised that an alternative mechanism was in place, which involved halogen bond-mediated nucleophilic addition to **1**. We evaluated the nature of this interaction by computing the electrostatic potential isosurface of **1**. It reveals a pair of minima ( $-24.4\text{ kcal mol}^{-1}$ ) at either end of the propellane's interbridgehead bond (C1–C3) (Figure SI-4, see supporting information) indicating that this bond may act as a lone pair interacting with the sigma hole of a halogen bond donor.<sup>[24]</sup> We thus found that **1** binds to NIS to give halogen bond complex **5** (Figure 3B) with an estimated binding enthalpy of  $-4.5\text{ kcal mol}^{-1}$ . The propellane's cage is far less distorted in **5** than in **3**, which is indicative of greater resistance to fragmentation. Significantly, complex **5** is a true minimum with a free energy barrier to fragmentation ( $20.0\text{ kcal mol}^{-1}$ ) via TS **39** to form exomethylenecyclobutyl cation **40** (Figure 3C).

Jemmis and co-workers have studied symmetrical bis-halogen bonded complexes of [1.1.1]propellane **1**, demon-

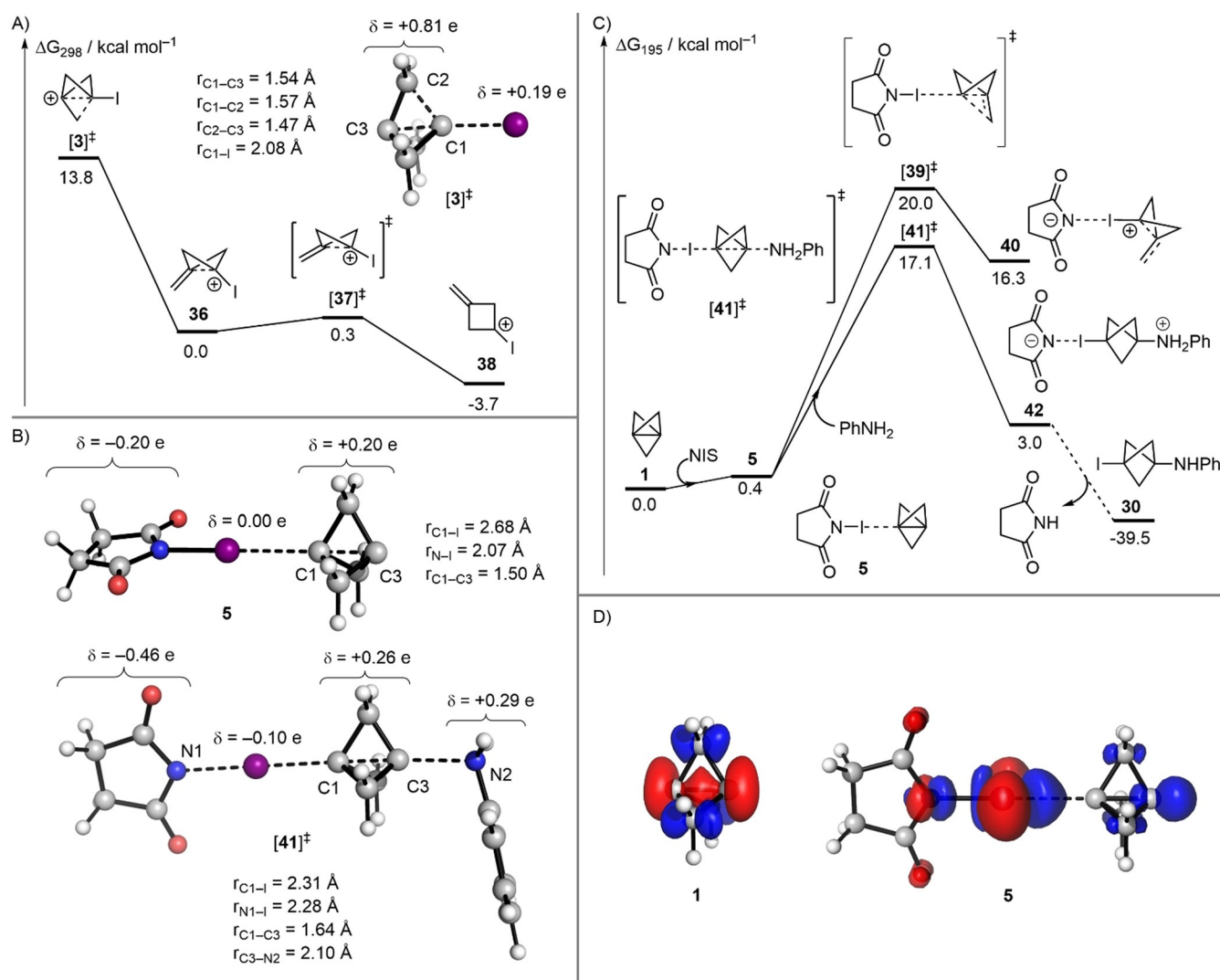
strating that the interbridgehead bond is shortened and strengthened upon formation of the complex.<sup>[24]</sup> This could indicate that **1** would become *less* reactive upon complexation with NIS. To elucidate the effect of halogen complexation on the reactivity of **1** further, we computed the dual descriptor derived from conceptual DFT, which enables the visualisation of regions that are net electrophilic or nucleophilic in a molecule.<sup>[25]</sup> Our calculations on **1** in isolation indicate that the interbridgehead bond is nucleophilic (red region, Figure 3D). However, a marked change is observed upon formation of the halogen bond complex **5**, where the interbridgehead region becomes net *electrophilic* (blue region, Figure 3D). This analysis provides a mechanism for the activation of [1.1.1]propellane: the stabilisation of the HOMO through interaction with the halogen bond donor activates the interbridgehead bond of **1** towards nucleophilic attack. Importantly, the attack of **5** by aniline via TS **41** to give intermediate **42** is favoured over the fragmentation of **5** ( $\Delta\Delta G^\ddagger = 2.9\text{ kcal mol}^{-1}$ ) (Figure 3C), suggesting that halogen bonding enables sufficient charge transfer to activate the interbridgehead C–C bond without sacrificing cage stability, which would otherwise result in fragmentation towards an exomethylene cyclobutane. As previously found for the reaction of **1** with anionic and radical intermediates,<sup>[23]</sup> our calculations suggest that the reaction of complex **5** with neutral anilines does not rely on a strain-promoted cleavage of the interbridgehead bond C1–C3. Moreover, the conversion of **5** into **42** is slightly endergonic, but it is driven toward **30** by a proton exchange that is thermodynamically favoured (Figure 3C).

Furthermore, we have also considered a scenario where *N*-iodoaniline, formed in a reaction between aniline and NIS, would be the halogen bond donor in a complex with propellane **1** prior to attack by another molecule of aniline. However, this pathway was ruled out due to its high activation barrier ( $26.9\text{ kcal mol}^{-1}$ , see supporting information). Finally, control reactions in the presence of radical TEMPO (2,2,6,6-Tetramethylpiperidinyloxy) or conducted in the dark led to expected products **6**, **25**, and **27**, which rules out a radical pathway (see supporting information).

Overall, the electrophilic activation of **1** in a halogen bond complex offers a more viable pathway towards the observed BCP products than carbocation **3** originally postulated by Wiberg,<sup>[10]</sup> which can only lead to exomethylenecyclobutane derivatives.

## Conclusion

In conclusion, we have demonstrated that electrophilic activation of [1.1.1]propellane in a halogen bond complex is a viable strategy for the synthesis of *N*-substituted BCPs. This approach enables the attack of the interbridgehead bond by neutral anilines and azoles that are electronically distinct from the nucleophilic organometallic amides and electrophilic *N*-centred radicals described in previous strategies,<sup>[5,6]</sup> and deliver *N*-substituted BCPs that were hitherto inaccessible. Moreover, DFT calculations indicate that the halogen bonding interaction enables an umpolung of the central bond



**Figure 3.** A) Optimised geometry and Hirschfeld charges ( $\delta$ ) of carbocation **3**, and the energy profile of its fragmentation calculated at the SMD(Et<sub>2</sub>O)-DLPNO-CCSD(T)/def2-TZVPP//SMD(Et<sub>2</sub>O)-B2GP-PLYP-D3BJ/def2-TZVPP level of theory. B) Optimised geometries and Hirschfeld charges ( $\delta$ ) of halogen bond complex **5** and transition state **41**. C) Energy profile of the reaction of propellane **1** with aniline and NIS. Parts B and C were calculated at the [SMD(Et<sub>2</sub>O)-DLPNO-CCSD(T)/def2-TZVPP, ma-def2-TZVPP on I//SMD(Et<sub>2</sub>O)-B2GP-PLYP-D3BJ/def2-TZVPP, ma-def2-TZVPP on I] level of theory. D) Fukui dual descriptors ( $f^{(2)}(r)$ ) for [1.1.1]propellane **1** and halogen-bond complex **5**, calculated at the B2GP-PLYP-D3BJ/def2-TZVPP level;  $f^{(2)}(r) < 0$  (red) and  $f^{(2)}(r) > 0$  (blue); isovalue = 0.005 au.

of [1.1.1]propellane to make it electrophilic without sacrificing cage stabilisation. We anticipate that this approach will pave the way for an expansion of the potential applications of the electrophilic activation of [1.1.1]propellane, a strategy that had so far remained limited in scope and therefore neglected.<sup>[9-13]</sup>

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## Conflict of Interest

The authors declare no conflict of interest.

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