Taming non-classical carbocations to control small ring reactivity

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Abstract: The positional selectivity of ring opening of small, strained organic rings is often considered to be governed by the maximal release of ring strain. However, reactions under cationic conditions can lead to multiple products due to the intermediacy of non-classical carbocations (carbonium ions – cations featuring a formally pentavalent carbon atom). A famous example is the solvolysis of cyclobutyl or cyclopropylmethyl derivatives, which proceed via two equilibrating non-classical carbocations – the cyclopropylcarbinyl ion (CC), and the bicyclobutonium ion (BB) – generating up to three products on nucleophilic capture. The utility of such reactions is therefore often limited, despite the value of the small ring products. Using bicyclo[1.1.0]butanes (BCBs) as a template, we show that the regiochemical outcome of small ring opening can be controlled by subtle changes to the structure of non-classical carbocation intermediates, in turn enabling the rational prediction of regioselectivity. We find that the regio- and stereochemistry of ring opening depends not only on the degree of substitution, but also the nature of the substituents, of the BCB ring system and its resulting cationic intermediate. We show that these outcomes can be rationalised by computational models, where bond lengths in the non-classical carbocation inform on the site of reaction. As BCBs are finding increasing use as tools in chemical synthesis and bioconjugation, understanding the factors that control their ring opening offers new opportunities for applications of these molecules. These findings also have consequences for the design of other chemical transformations that proceed through such non-classical intermediates.

Introduction: Small organic rings are valuable building blocks in organic synthesis, as their inherent strain can facilitate reactions that would not otherwise be possible. Control over the site-selectivity of reaction on small rings is typically explained by the release of ring strain or by steric effects, but this predictability can break down under cationic reaction conditions where the reaction pathway involves the formation of non-classical carbocation intermediates.[1] Nonclassical carbocations (Fig. 1a) have long fascinated the chemical community, as their characterisation is highly challenging, and they have the ability to form multiple products. Among the most notable of these species are the cyclopropylcarbinyl (CC) and bicyclobutonium (BB) cations (Fig. 1a) – two closely related structures of formula $[C_4H_7]^+$ – which form upon solvolysis of cyclobutyl and cylopropylmethyl derivatives. The CC-BB system is also the smallest of the nonclassical carbocations, but has been described as 'the most complex with respect to its molecular weight'.[2] Roberts *et al.* provided the first experimental insight into its dynamic nature in 1951,[3,4] and in later years Olah and Roberts characterised its structure by low temperature NMR under "stable ion conditions" (Fig. 1a).[4-6] Subsequent studies and computation have refined and confirmed the existence of the CC and BB species as equilibrating nonclassical ions, with the equilibrium favouring the latter by 1.9 kcal/mol at the MP2/6-311G*.[7] The CC-BB system has found applications in glycosidase inhibition by aiding the generation of an aspartate trapping agent through neighbouring group participation.[8-10] CC-BB has also been proposed as an intermediate in fatty acid, steroid, and terpene biosynthesis (Fig. 1b).[11-13] In contrast, its use in chemical synthesis has been relatively limited due to poor selectivity (and predictability) in product formation by nucleophilic capture, leading to one or more homoallyl, cyclopropane, cyclobutane, or cyclobutene products.[3]

In recent years bicyclo[1.1.0]butanes (BCBs) have gained popularity for their potential as bioconjugation agents[14,15] and ability to access polysubstituted four-membered rings systems,[16] including bicyclo-[1.1.1]pentanes[17-19] [2.1.1]hexanes[20-22] and [3.1.1]heptanes,[23,24] which are valuable bioisosteres in drug discovery.[25,26] The heightened strain of the central C1–C3 bond facilitates additions with nucleophiles,[15,27-32] radicals[33-35] and electrophiles,[36-39] making them valuable reagents in 'strain release' chemistry.[40] Despite these applications, their potential as an alternative entry point to the CC-BB cation has been overlooked.

Here we describe the facile generation of these non-classical carbocations by protonation of the BCB framework with a wide variety of Brønsted acids (Fig. 1c). We show how rational modification of the BCB structure defines product outcome, most notably enabling the stereoselective formation of stereochemically-rich cyclopropane adducts. Computational investigation of cation structure provides insight into this selectivity, and contributes to the delineation of factors affecting reaction outcome for small ring formation. The result is that the typically unpredictable nature of the non-classical CC-BB ion can be tamed and tuned.

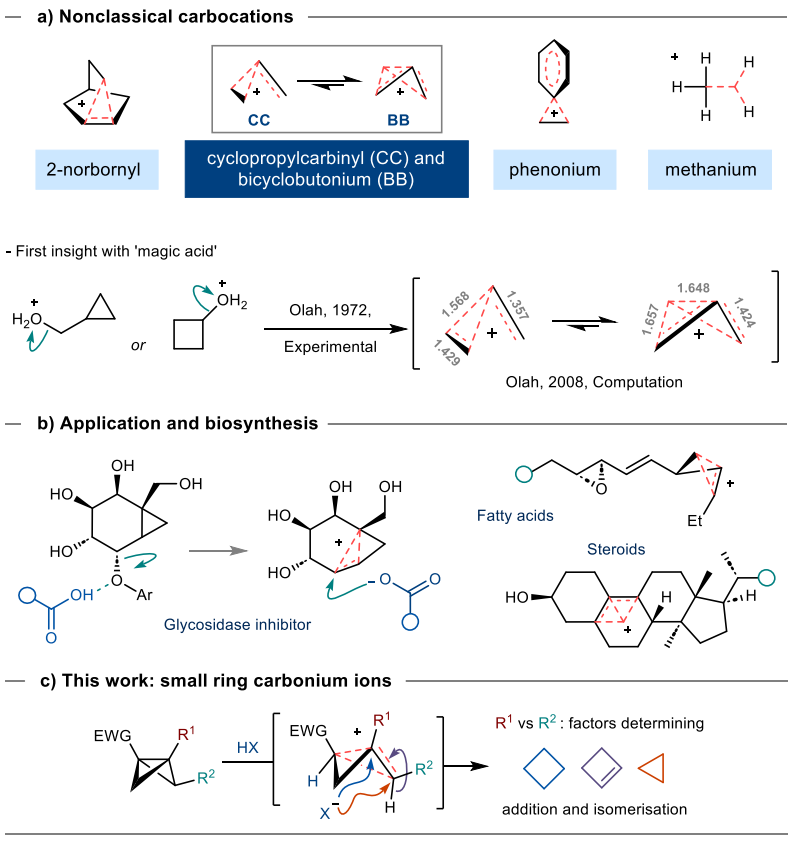

Figure 1. Non-classical carbocations. a Examples of non-classical carbocations and early insight. **b** Applications and biosynthetic nonclassical intermediates. **c** This work: formation of non-classical carbocations from bicyclo[1.1.0]butanes, and rational prediction of the reaction outcome.

In preliminary work, we had observed that trisubstituted BCB **1a**, possessing an aryl group at the bridgehead and a methyl group on of its cyclopropane bridges, underwent isomerization in near quantitative yield to cyclobutene **2a** on treatment with anhydrous hydrochloric acid (Fig. 2).[41] However reaction of BCB **1b**, bearing methyl groups at both the bridge and bridgehead positions, instead

exclusively afforded cyclopropane **2b** in high yield.[42]

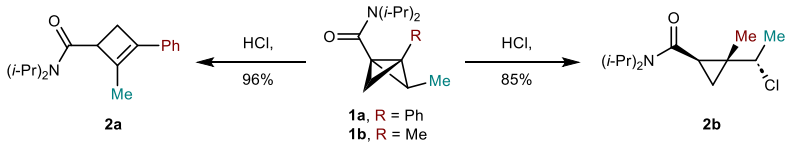

Figure 2. Preliminary results on BCB protonation.

We questioned whether general and predictable control over product selection might therefore be achieved. To our delight, treatment of **1b** with a selection of halogen, oxygen, nitrogen and sulfur-based Brønsted acids in dichloromethane at room temperature indeed led to highly product-selective reactions (Fig. 3). A variety of aliphatic and aromatic carboxylic acids exclusively delivered cyclopropane products (**2c**-**2l**, 76-88%), with diastereoselectivies ranging from 3:1 to >20:1. Here, we noted a clear relationship between pK_a and diastereomeric excess (see inset graph in Fig. 3); interestingly, the diastereoselectivity of the reaction proved insensitive to factors such as solvent, temperature, concentration, equivalents of acid and conjugate base (see Supplementary information, Section 1.3). Reaction with hydrofluoric acid provided cyclopropane **2m** in good yield (63%, 5:1 *dr*). Pleasingly, nitrogen-based acids were also effective (**2n**-**2p**), providing the pK_a of the acid (in water) was less than ~5. Other acidic hydroxyl groups were also suitable, such as an electron-deficient phenol (adduct **2q**, 65%). In the case of ambident nucleophiles such as thioacetic acid, saccharin and thiotetrazole, mixtures of *O/S*-, *N/O*- and *N/S*-substituted cyclopropane adducts were observed (**2r**-**2w**), with all isomers being formed with high diastereoselectivity. X-ray single crystal analysis of **2i**, **2o**, **2p**, **2q**, **2t**, **2u**, **2v** and **2w** showed that the major diastereomer was consistent across all acids (see Supplementary information, Section 3.0).

We next explored how the substitution pattern of the BCB, and the presumed resulting non-classical carbocation, might affect the generality and outcome of this ring opening chemistry. A series of BCBs **1c**–**1n**, bearing a variety of substituents at the bridge and bridgehead positions, were treated with trifluoroacetic acid under the standard conditions (Fig. 4). We found that cyclopropane-forming selectivity

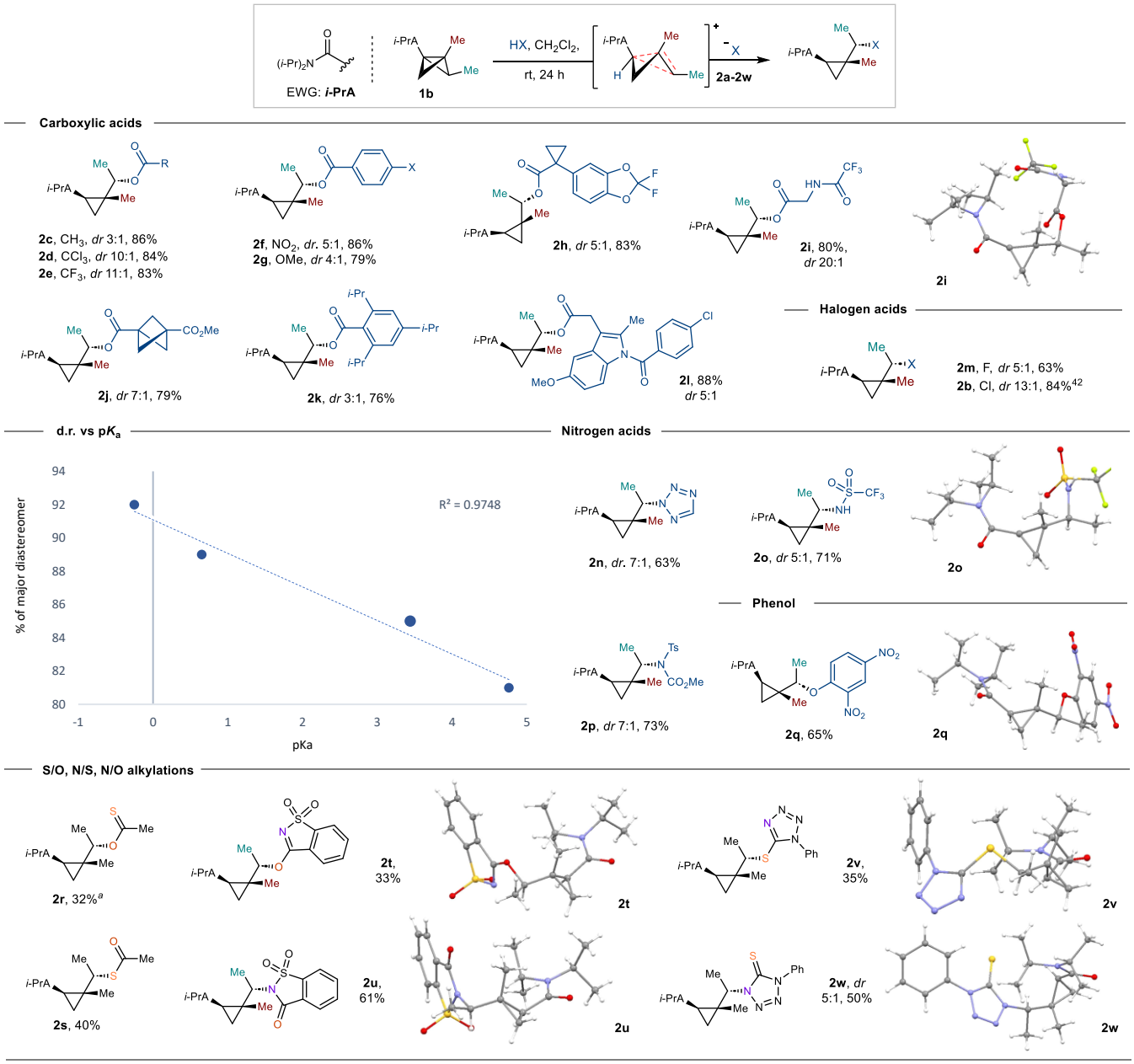

Figure 3. Chemo- and stereoselective formation of cyclopropanes from BCB **1b**. Reactions run on 0.2 mmol scale with 1.2 equiv. of acid. Structures of **2i**, **2o**, **2p**, **2q**, **2t**, **2u**, **2v** and **2w** were obtained from single crystal X-ray diffraction studies (displacement ellipsoids drawn at 50% probability). See the Supplementary Information for details. [a] Trace amounts of (*S*)-cyclobutane were obtained.

was maintained for all BCBs featuring hydrogen or alkyl substituents at the bridgehead, and alkyl or aryl substituents on the bridge (**2x**–**2z**, **2ai**, 66-98%, up to 6:1 *dr*). A switch to cyclobutane formation was observed for a disubstituted BCB featuring an alkyl substituent at the bridgehead only (**2aa**), and to cyclobutene formation with either an aryl group at the bridgehead (**2b**),[42] or an electron-withdrawing group

at the bridge (**2ab**). Given the ability of silicon groups to stabilise β-carbocations, we also prepared a range of silylated BCBs (**1g**, **1j**, **1k** and **1l**). We found that bridge silylation (**1g**) afforded a mixture of silylated and non-silylated cyclobutenes **2ae** and **2af**, which is suggestive of a localised Si-stabilised cyclobutyl cation, while bridgehead silylation alone (**1l**) delivered a cyclobutane product **2ah**, which is consistent with the ring-openings of other disubstituted systems. Intriguingly, a doubly-silylated BCB **1k** afforded the cyclopropane product (**2ag**), potentially reflecting complementary stabilising effects from the silicon atoms on a non-classical carbocation intermediate.

To further probe the mechanism of this ring-opening chemistry, we conducted a series of experimental and theoretical investigations. We found that use of deutero-trifluoroacetic acid with BCB **1b** afforded the corresponding bridgehead-deuterated cyclopropane **2aj** with 86% deuterium incorporation, supporting the formation of a specific cationic intermediate by C1 protonation. To further investigate the chemoselectivity of cation capture, a competition reaction was run between propanoic acid and *n*-propane thiol, which afforded solely the propanoic acid adduct **2al**, to the exclusion of the alternative cyclobutyl sulfide **2am**. This selectivity is extraordinary, given the typical use of BCBs as thiol-selective bioconjugation agents.[14] An additional competition experiment was carried out using **1b** between acetic acid and tetrabutylammonium chloride, which delivered a 3:1 mixture of the chloro- and acetoxy-cyclopropanes **2b** and **2c** respectively. Product **2b** could not be converted to **2c** on treatment with tetrabutylammonium acetate, suggesting both arise from competitive trapping of a common intermediate. Interestingly similar diastereomeric ratios were observed when compared to the independent treatment of **1b** with respective acids (see Supplementary, Section 1.9). This result prompted us to test the trapping of **1b** with an external nucleophile (methanol) using a catalytic amount of a non-nucleophilic acid (fluoroboric acid). To our delight, this afforded methanol adduct **2ak** in 81% yield and 2:1 *dr*.

To rationalise the product-selective outcomes of these reactions, calculations were performed at the CPCM(DCM)-DLPNO-CCSD(T)/cc-pVQZ//CPCM(DCM)-SCS-MP2/cc-pVTZ level of theory at

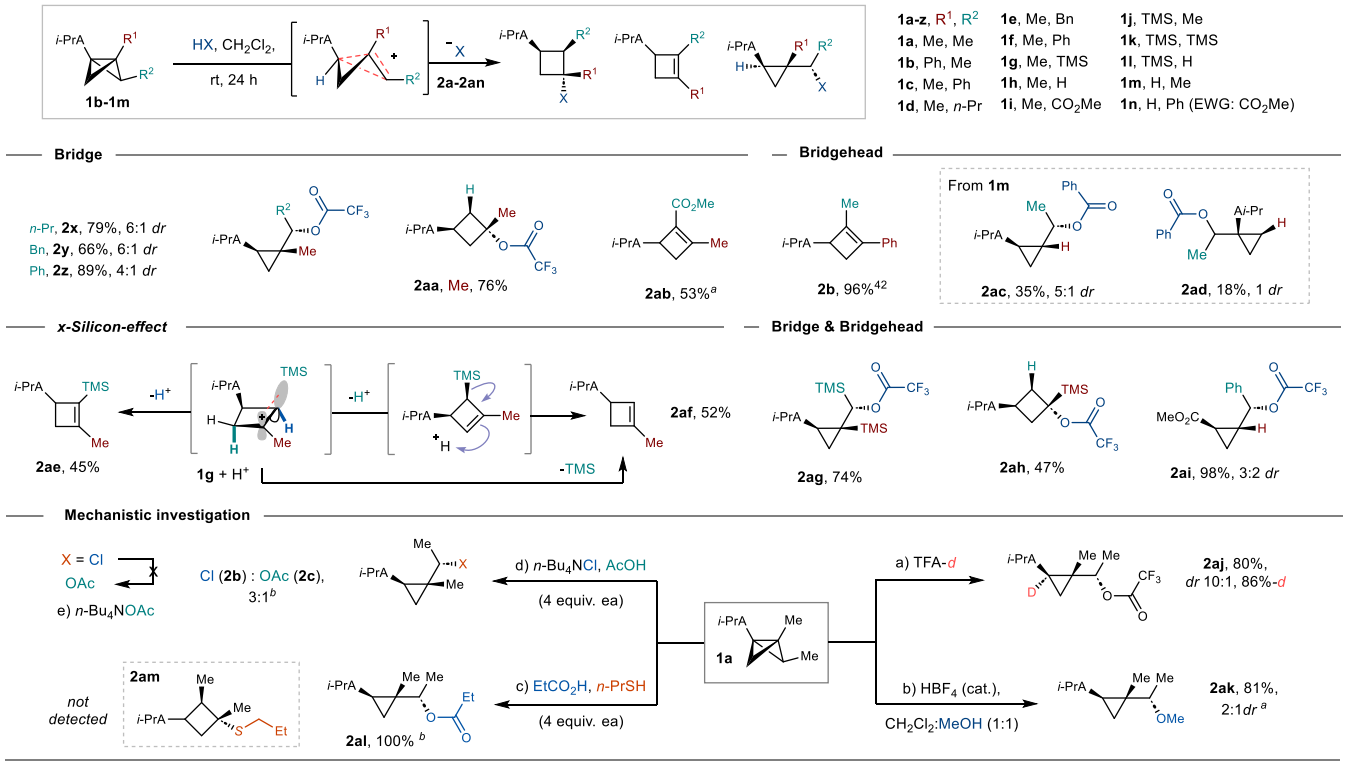

Figure 4. BCB structure-dependence of product formation, and mechanistic investigations. Reactions run on 0.2 mmol scale with 1.2 equiv. of acid. [a] Trace amounts of (*S*)-cyclobutane were obtained. [b] Conversion and ratio were determined based on ^{1}H NMR spectroscopic analysis of the crude reaction mixture.

298.15 K/1 M to gain insight into the nature of the carbocation derived from **1b** (Fig. 5a), using the simplified dimethylamide BCB **1o**. *In silico* protonation of **1o** afforded cation **3a**, which was found to exist in a shallow energy minimum corresponding to a structure intermediate between discrete non-classical BB and CC carbocations. This finding is in contrast to the BB and CC minima calculated for the parent (unsubstituted) bicyclobutonium cation, and bridgehead-methylated BBs, by Olah and co-workers, suggesting a spectrum of cation structures might explain the different reaction outcomes. The non-classical nature of **3a** is evidenced by the Mayer bond orders (BOs) and extended bond lengths of C1–C2 (BO 0.41, 1.99 Å) and C1–C3 (BO 0.57, 1.70 Å) and partial double bond character of C3–C2 (BO 1.25, 1.40 Å) compared to the equivalent bond lengths in the BCB itself (where all C–C bond lengths are ~1.50 Å). Hirshfeld atomic charges indicate distribution of the positive charge over all three atoms, which is also consistent with this three centre–two electron bond (see Supplementary Information).

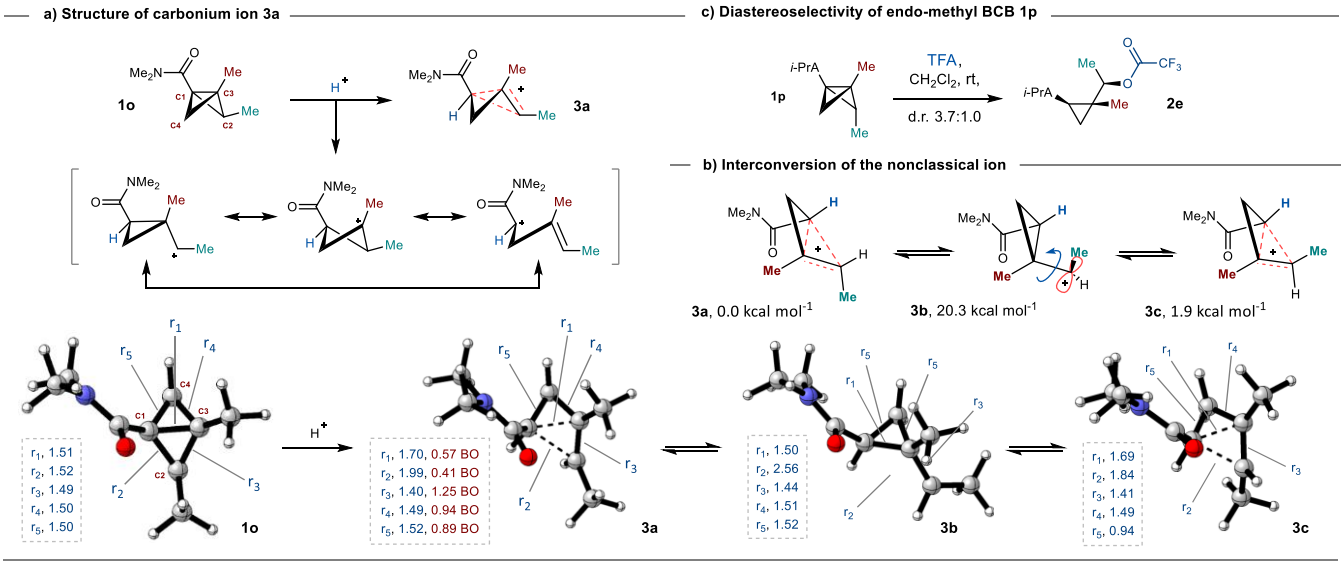

Figure 5. a Computed structures (CPCM(DCM)-DLPNO-CCSD(T)/cc-pVQZ//CPCM(DCM)-SCS-MP2/cc-pVTZ) of the BCB **1o**, and resulting non-classical cation **3a**. **b** A potential pathway for interconversion of and associated Gibbs free Energis Δ of non-classical carbocation intermediates is unlikely based on the high energy of localised cation **3b**. **c** Stereoselectivity of reaction of BCB **1p**. Units for r_n are in Angstroms. BO = Mayer bond order.

X-ray crystallographic structures also revealed an intriguing observation: The identity of the major diastereomer from cyclopropane-forming BCB ring opening in all cases appears to arise from attack on the non-classical carbocation from the same 'face' as protonation, which contrasts with the 'inversion' often observed for non-classical norbornyl cations and related structures.[43] We hypothesize that such an outcome could derive from the formation of a tight ion pair upon BCB protonation, such that the counterion is necessarily located in proximity to the cation, and on the same 'face'. Further calculations revealed that attack (by chloride) on either face of intermediate **3a** is barrierless, offering support to this theory (see Supplementary Information, Section 2.6). The dependence of the diastereoselectivity of cyclopropane-forming ring-opening on the pK_a of the conjugate acid of the nucleophile is also an intriguing aspect of this reaction, and is challenging to explain. We considered the possibility of localisation of the cation as a cyclopropylcarbinyl species **3b** (Fig. 5b), which could then allow rotation to the diastereomeric non-classical carbocation **3c**, capture of which would give the minor product

diastereomer (from attack proximal to the site of protonation). However, **3b** was found to be significantly higher in energy (by 20.3 kcal mol^{-1}) than **3a**, which appears to prohibit this pathway. We further found that reaction of the bridge-substituted *endo*-methyl diastereomer **1p** afforded product **2e** with 1:3.7 *dr* (Fig. 5c), supporting the formation of a single diastereomeric non-classical carbocation from each diastereomer of BCB, each of which reacts with discrete stereoselectivity. In the case of **1p**, non-classical cation **3c** was found to be 1.9 kcal mol^{-1} higher in energy than **3a**, and interestingly displays a shorter C1–C2 bond distance (1.84 Å in **3a** vs 1.99 Å in **3c**), which may relate to reduced selectivity for cyclopropane formation (see Supporting Information, Section 1.7). The theoretical influence of a non-coordinating tetrafluoroborate counterion on the structure of CC and BB cations has been discussed by Champagne *et al*;[44] the effect of other counterions could therefore influence the stereoselectivity of nucleophilic additions, as observed in the acetic acid/tetrabutylammonium chloride competition experiment.

We next explored structural modification of the non-classical intermediate by introducing an additional methyl substituent on the other BCB bridge (Fig. 6). Experimentally, tetrasubstituted BCB **1q** gave two products: cyclobutane **2an** (47%, as a single diastereomer) and cyclopropane **2ao** (32%, 7:1 *dr*). While this outcome was initially surprising, computational analysis again offered insight in the form of intermediate **3d**, which retains a similar structure to **3a** but with a shorter C1–C2 bond length (1.91 Å in **3d** vs 1.99 Å in **3a**). The consequence of this structural change is reduced positive charge build-up on C2 and, accordingly, a lower preference for cyclopropane formation. Interestingly, the stereocentre adjacent to the amide (C1) in **2an** has the opposite configuration to that observed in all previous reactions. This may be due to unavoidable 1,3-diaxial interactions in either of the cyclobutane conformations where the amide is *syn* to the C3-methyl group, which is absent in less substituted derivatives. Acid-catalysed epimerisation of the amide stereocentre relieves this transannular strain.

The subtle effects of the BCB substituents should also manifest in relative reaction rates, due to different extents and stabilisation of charge build up on the BCB scaffold during the protonation step. A competition

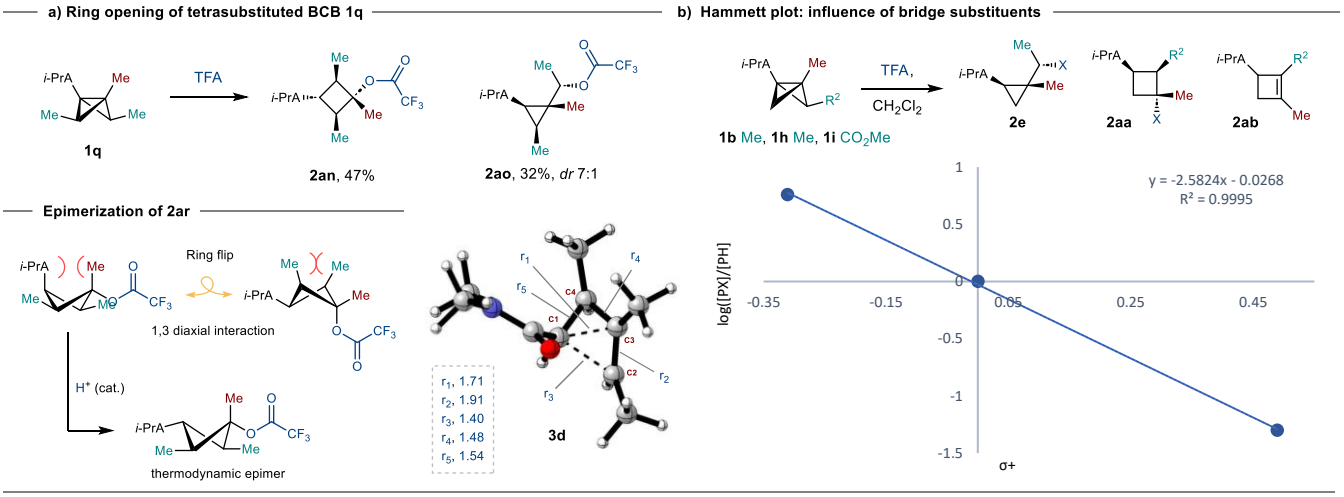

Figure 6. a Reaction of a tetrasubstituted BCB **1q**. **b** Hammett plot obtained from competition experiments in the reaction of aryl bridge-substituted BCBs. Units for r_n are in Angstroms.

study was carried out between BCB **1h** (Fig. 6b, R^2 = H) and BCBs bearing electron-donating (**1b**, R^2 = Me) and electron-withdrawing groups (**1i**, R^2 = CO_2Me), with trifluoroacetic acid under the standard reaction conditions. **1b** was found to react more rapidly than **1h**, which in turn outcompeted **1i**. Using σ^+ substituent parameters, a Hammett plot was constructed which gave a linear relationship with a ρ^+ value of -2.6, which is reflective of significant positive charge build-up on the BCB bridge atom. Compared to the ρ^+ value of -12.3 measured by Tidwell and co-workers for formation of a localised cyclopropylcarbinyl cation by vinylcyclopropane protonation,[45] and a value of -7.1 observed by Hoz and co-workers for acid-catalysed hydration of bridgehead-disubstituted BCBs,[46] our findings support a greater delocalisation of positive charge in the developing cation.

Our experimental findings, and those from previous studies,[46-51] now enable the rational prediction of reaction outcome for the acid-promoted formation and capture of the non-classical bicyclobutonium / cyclopropylcarbinyl systems, which can be depicted in the form of a flowchart of structure vs. product outcome (Fig. 7). Specifically, different extents of cation delocalisation are expected based on the degree and nature of substitution around the cationic intermediate. For mono-substituted BCBs, cyclopropane products are exclusively observed, reflecting a cyclopropylcarbinyl (CC) intermediate. Disubstituted

intermediates give complementary outcomes depending on the disposition of substituents: For bridgehead substitution, cyclobutenes are observed for aryl substituents, but cyclobutanes arise from alkyl substitution, while for bridge-functionalized BCBs, cyclopropanes arise irrespective of the nature of the substituent. The outcome for trisubstituted ions is also substituent dependent: bridgehead aryl groups once again direct the reaction towards cyclobutene products, but all other alkyl/aryl combinations afford cyclopropanes. Collectively, these observations offer a long-awaited opportunity to tame and tune the reactivity of these elusive but fascinating cationic intermediates.

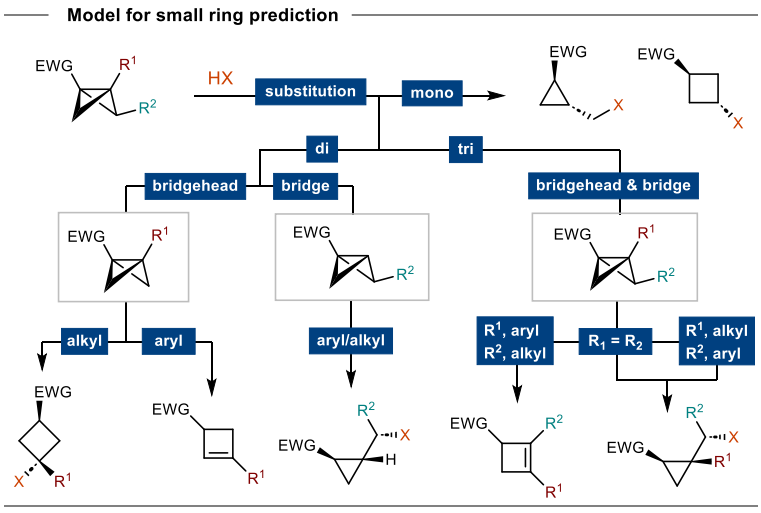

Figure 7. A flowchart for product outcome in the reaction of BCBs with acids, dependent on substitution pattern.

Conflicts of Interest statement

The authors declare no conflict of interest.

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Supplementary material statement

Experimental procedures and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra; X-ray crystallographic data (.cif); Computational data and coordinates. Crystallographic data have been deposited with the CCDC as entries CCDC 2240514-21.

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