A catalytic alkene insertion approach to bicyclo[2.1.1]hexane bioisosteres

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C(sp^3)-rich bicyclic hydrocarbon scaffolds, as exemplified by bicyclo[1.1.1]pentanes (BCPs), play an increasingly high-profile role as saturated bioisosteres of benzenoids in medicinal chemistry and crop science. Substituted bicyclo[2.1.1]hexanes (BCHs) are new emerging bicyclic hydrocarbon bioisosteres for *ortho*- and *meta*-substituted benzenes, which to date remain difficult to access. Therefore, a general synthetic route to BCHs is urgently needed, if their potential as bioisosteres is to be realized. Here, we describe a broadly applicable catalytic approach that delivers substituted BCHs by a highly atom-economical intermolecular coupling between olefins and bicyclo[1.1.0]butyl (BCB) ketones. The SmI_2–catalyzed process embraces a wide range of electron-deficient alkenes and substituted BCB ketones, operates with loadings of SmI_2 as low as 5 mol%, and is underpinned by a radical-relay mechanism that is supported by DFT calculations. The product BCH ketones have been shown to be versatile synthetic intermediates through selective downstream manipulation, and the expedient synthesis of a saturated hydrocarbon analogue of the broad spectrum antimicrobial, phthalylsulfathiazole. Our findings have provided the first general catalytic approach to the substituted BCH scaffold, and serve as a launchpad for the widespread use of this largely unexplored family of bioisosteres in medicinal chemistry.

Substituted benzene rings are a vital component of a great many approved drugs and agrochemicals. The motif is found in 45% of global marketed small molecules drugs[1-3], and in 81% of the top 200 best-selling drugs in 2020[4]; thus making it the most prevalent ring system in pharmaceuticals and one of the most attractive structural targets in drug design and development. Specific substitution patterns at the benzene ring impart a precise spatial arrangement on its substituents (in terms of interatomic distance and orientation), which is critical when small molecules have to fit in or interact with complex biological macromolecules[5]. Despite this, under physiological conditions, benzene ring systems often suffer detrimental metabolic modifications that lead to toxic metabolites, thus halting the entry of pharmaceutical candidates to the final phases of drug development. In the search for improved biological activity, pharmacological potency and physico-chemical properties – but also perhaps to side-step a patent – the replacement of the substituted benzene motif with saturated, polycyclic C(sp^3)-rich hydrocarbon scaffolds, is now a standard approach in medicinal chemistry and crop science[5-13]. Crucially, these rigid hydrocarbon bioisosteres[14-15] present a defined spatial disposition of their substituents – which effectively mimics the topological pattern of substituted benzenes – while improving the metabolic stability of the drug analogue. For example, ground-breaking studies by Pellicciari, in 1996, found that bicyclo[1.1.1]-pentyl (BCP) containing amino acid **1** was three times more active than the parent benzene analogue **2** as an antagonist of the group I metabotropic glutamate receptor mGluR1 (Figure 1A)[16]. In an industrial setting, pioneering work by Stepan replaced a fluorophenyl moiety in γ-secretase inhibitor **4** with a BCP unit to obtain patent-free **3**; boasting improved activity, solubility in water, higher metabolic stability, and lower lipophilicity than **4**[17]. A variety of C(sp^3)-rich hydrocarbon bioisosteres have since been developed for *para*-disubstituted benzene derivatives: In addition to 1,3-disubstituted BCPs **A**, bicyclo[2.2.2]octane **B** and cubane derivatives **C** are also well known (Figure 1B). In stark contrast, saturated bicyclic hydrocarbons mimicking *ortho*- and *meta*-substituted benzenoids have only recently been advanced or predicted by DFT calculations (structures **D**–**H**, Figure 1B)[8]; thus highlighting the need for efficient methods for their synthesis in order to validate their bioactivity. Within the last year, elegant synthetic routes by Baran[18] and Qin[19] have provided access to 1,2-difunctionalized BCPs **D**; while seminal work by Mykhailiuk has identified difunctionalized bicyclo[2.1.1]hexanes (BCHs)[8,20] – and related structures[21] – as attractive candidates for both *ortho*- and *meta*-substituted benzene bioisosteres, depending on their substitution pattern (**E**–**H**)[8]. In a recent study, Mykhailiuk incorporated the BCH core **E** into compounds **5** and **7** (analogues of the anti-hypertensive drug valsartan **6** and the antifungal fluxapyroxad **8**, respectively) at the expense of the corresponding *ortho*-disubstituted benzene cores[20]. Validating the postulated bioisosterism, saturated analogue **5** showed analogous level of bioactivity to the marketed agrochemical. Crucially, BCHs bearing desirable, alternative substitution patterns, such as **F**, **G** or **H** were not synthetically accessible and thus not investigated. As part of the abovementioned study focusing on the synthesis of 1,2-difunctionalized BCPs[19], Qin applied their sequence to the provision of four BCHs **H** and a single analogue of type **F**. Despite this early progress, the synthesis of sought-after 1,2- and 1,4-

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disubstituted BCHs remains a significant synthetic challenge, due to the absence of catalytic methods for their provision. A general catalytic approach is urgently needed in order to realize the potential of BCHs as bioisosteres.

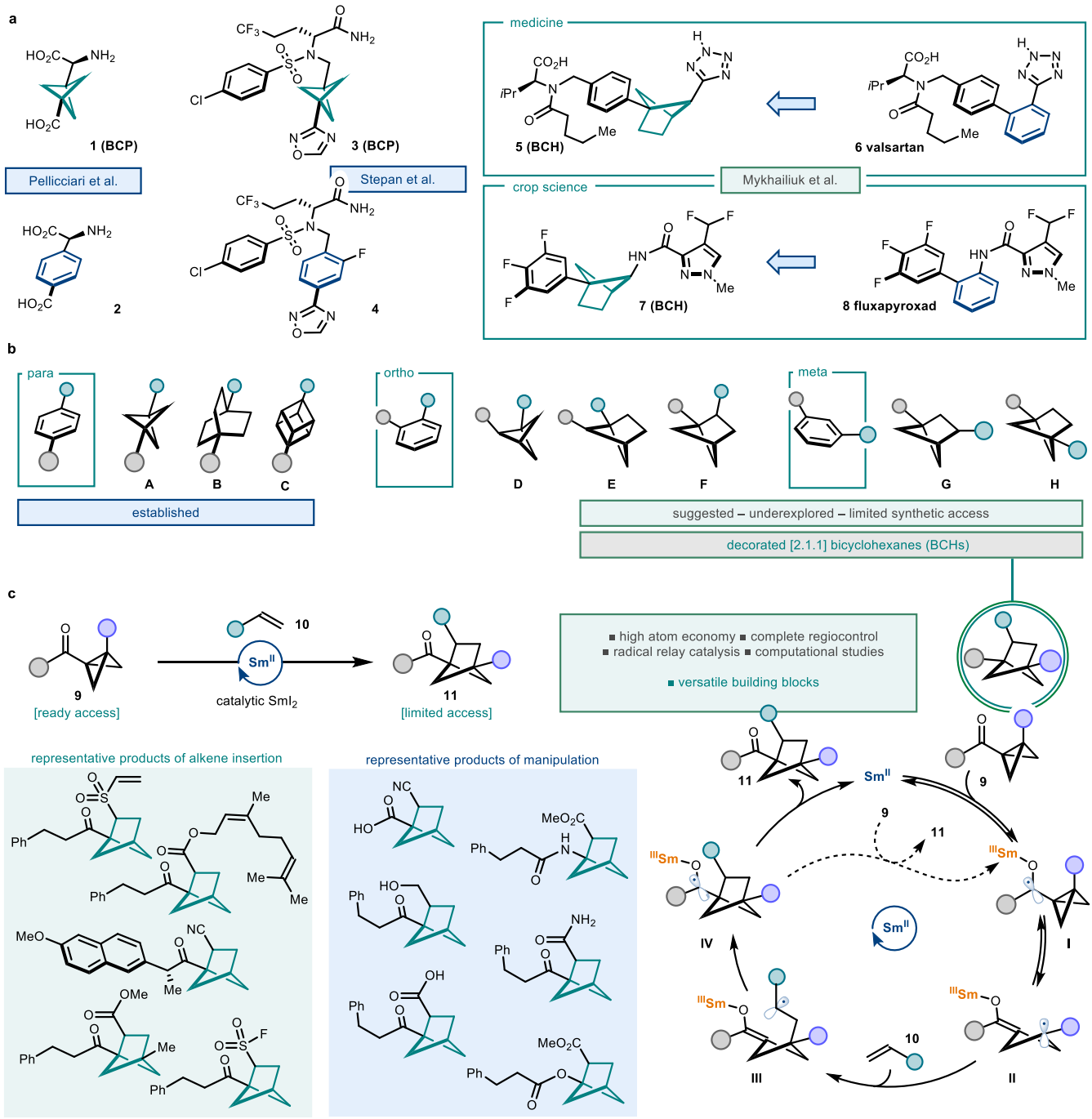


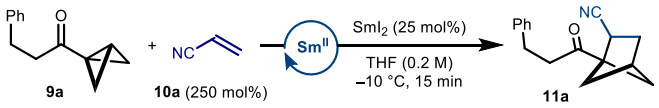
Fig 1 | Building emerging, hard-to-access BCH bioisosteres using radical relay catalysis. a, Saturated analogues of benzene-containing bioactive molecules are now commonplace in medicinal chemistry and crop science. While the use of the BCP bioisostere is well-established for *para*-disubstituted benzenes, the BCH scaffold is an emerging bioisostere for *ortho*- and *meta*-disubstituted benzenes. **b**, In contrast to *para*-disubstituted benzenes, there are few saturated, bicyclic hydrocarbon bioisosteres available for *ortho*- and *meta*-disubstituted benzenes. BCHs have emerged as the most promising candidates, however, their synthesis remains a challenge. **c**, Radical relay catalysis with SmI_2 allows the insertion of electron-deficient alkenes **10** into readily available BCB ketones **9**, delivering versatile, high-value BCH building blocks **11** with complete regiocontrol and high atom economy. Manipulation of the BCH ketone products **11** unlocks access to a range of sp^3-rich BCH bioisosteres of *ortho*- and *meta*-disubstituted benzenes for evaluation in medicinal and agrochemical settings. BCP, bicyclo[1.1.1]-pentyl, BCH, bicyclo[2.1.1]hexyl.

Herein, we demonstrate that a unique intermolecular alkene insertion into the central C–C bonds of readily accessible bicyclo[1.1.0]butyl (BCB) ketones **9**, using SmI_2 as a catalyst[22-24], constitutes the first general method to access the

BCH scaffold (Figure 1C). This highly atom economical radical approach occurs with complete regiocontrol and delivers a wide range of BCH ketones **11** (*c.f.* **F** and **H**) that are difficult to access using current synthetic methods[25-26]. Crucially, products **11** are versatile, high-value building blocks that unlock access to a range of sp^3-rich BCH bioisosteres of *ortho*- and *meta*-disubstituted benzenes for evaluation in medicinal and agrochemical settings. Computational studies suggest that the catalytic alkene insertion occurs via a radical relay mechanism[27]: The electron donated by the catalyst is relayed back, regenerating the Sm(II)-catalyst after the two desired C–C bond forming steps are complete. Reversible single electron transfer (SET) from SmI_2 to ketones **9** gives ketyl radicals **I**[28], which fragment to give enolate radicals **II**. Intermolecular coupling with electron-deficient alkenes **10** then generate radicals **III**, which rebound by addition to the Sm(III)-enolate moiety, generating new ketyl radicals **IV**. Back electron transfer to Sm(III) regenerates the SmI_2 catalyst and liberates product **11**. It is also possible that ketyl radical **IV** directly reduces starting ketone **9**[29-30], although computational calculations (vide infra) favor a radical relay process. Our radical relay catalytic strategy utilizes a commercially-available, well-known 'stoichiometric' reagent[31-32] in an unusual catalytic manifold, and enables a divergent approach to the important BCH scaffold. Crucially, our modular approach to BCHs offers advantages over the sparse literature methods to access BCH bioisosteres that rely on UV irradiation of dienes[20] or multi-step synthesis of specialized boronate ester derivatives.[19] We have shown that the BCH ketone products are versatile building blocks and have exemplified this in a short synthesis of a BCH-containing saturated hydrocarbon analogue of a broad-spectrum antimicrobial.

Results and Discussion

Method optimization. Building on our previous studies of SmI_2-catalysis[23-24], we set out to prove the viability of the proposed catalytic insertion of electron-deficient alkenes into readily available BCB ketones. The coupling of BCB ketone **9a** and acrylonitrile **10a** was selected as our prototypical system (Table 1). Pleasingly, exposure of a 1:1 mixture of **9a** and **10a**, in THF and at –10 °C, to 25 mol% of SmI_2 gave BCH ketone **11a** in 52% yield (entry 1). Increasing the amount of acrylonitrile to 2.5 equivalents was sufficient to increase the yield of **11a** to 88% (entry 3). Decreasing the temperature to –30 °C (entry 4) or increasing it to 0 °C (entry 5) or room temperature (entry 6) led to a small drop in yield. Finally, the alkene insertion proceeded well with a lower 20 mol% loading of SmI_2 (entry 7) – **11a** was obtained in 82% yield – although a lower loading of 15 mol% SmI_2 gave significantly lower yields of BCH ketone **11a** (entry 8). Alternative electron-rich alkene partners (including 1-hexene, styrene and phenylacetylene) did not participate in the SmI_2-catalyzed coupling under optimized reaction conditions, despite the complete consumption of **9a** in each case (entry 9). Crucially, replacing SmI_2 with $Sm(III)(OTf)_3$ – or alternative Lewis acids (see Tables S1 and S2 in the Supplementary Information file) – resulted in decomposition of **9a** with no formation of **11a** (entry 10); thus underscoring the role of SET in triggering the observed reactivity.



entry	deviation from above	conversion	yield **11a**
1	reaction run in the presence of 1 equiv. of **10a**	100%	52
2	reaction run in the presence of 1.5 equiv. of **10a**	100%	79
3	none	100%	88
4	reaction performed at –30 °C	100%	84
5	reaction performed at 0 °C	100%	76
6	reaction performed at ambient temperature	100%	75
7	reaction run using 20 mol% of SmI_2	100%	82
8	reaction run using 15 mol% of SmI_2	91%	55
9	1-hexene, styrene or phenylacetylene used in place of **10a**	100%	<5
10	reaction run at 25 °C, using $Sm(OTf)_3$ in place of SmI_2	100%	<5

Table 1 | Optimization of the intermolecular catalytic alkene insertion to access substituted BCH ketones. Reactions performed on a 0.1 mmol scale. Yields were determined by ^{1}H-NMR spectroscopy using nitromethane as internal standard.

Scope of the method. Adopting the conditions described in Table 1, entry 3, we evaluated the generality of the SmI_2-catalyzed insertion of alkenes **10** into BCB ketones **9**. First, a wide range of BCB ketones was prepared and coupled with acrylonitrile **10a** (Figure 2). Ketone substrates bearing primary alkyl substituents proved effective partners giving BCH ketone products **11a–h** in 67-86% yield (10-25 mol% of SmI_2). Crucially, the catalytic alkene insertion proved

compatible with the presence of carbon-bromine bonds (formation of **11g** and **11h**), as well as nitrile substituents, that are known to be reduced by SmI_2 under stoichiometric conditions[33]. More hindered ketone substrates, bearing secondary and tertiary alkyl substituents also proved to be excellent substrates, forming **11i–11t** in high yield. In particular, cyclobutyl- and cycloheptyl-BCB ketones gave **11n** and **11q** in 90% and 95% yield, respectively, in the presence of only 5 mol% of SmI_2. Interestingly, the cyclopropyl ring embedded within compound **11t** survived the SmI_2-catalyzed conditions[23-24], thus highlighting the chemoselectivity of the coupling for the BCB ring. The structure of adamantyl-containing BCH ketone **11s** was confirmed by X-ray crystallography. BCB ketones bearing additional alkyl substituents at the second bridgehead position underwent coupling with acrylonitrile to give 1,2,4-trisubstituted BCHs **11u–w**; in particular, the couplings to give **11u** and **11v** took place in near-quantitative yield. While aryl ketones of type **9** are compatible with the process, BCH products **11x** and **11y** were obtained with significantly lower efficiency. Finally, more complex ketones derived from drugs naproxen and ibuprofen, as well as naturally-occurring oleic acid, underwent smooth alkene insertion to give **11z**, **11aa** and **11ab**, respectively, in high yield and low SmI_2 loadings (Figure 2).

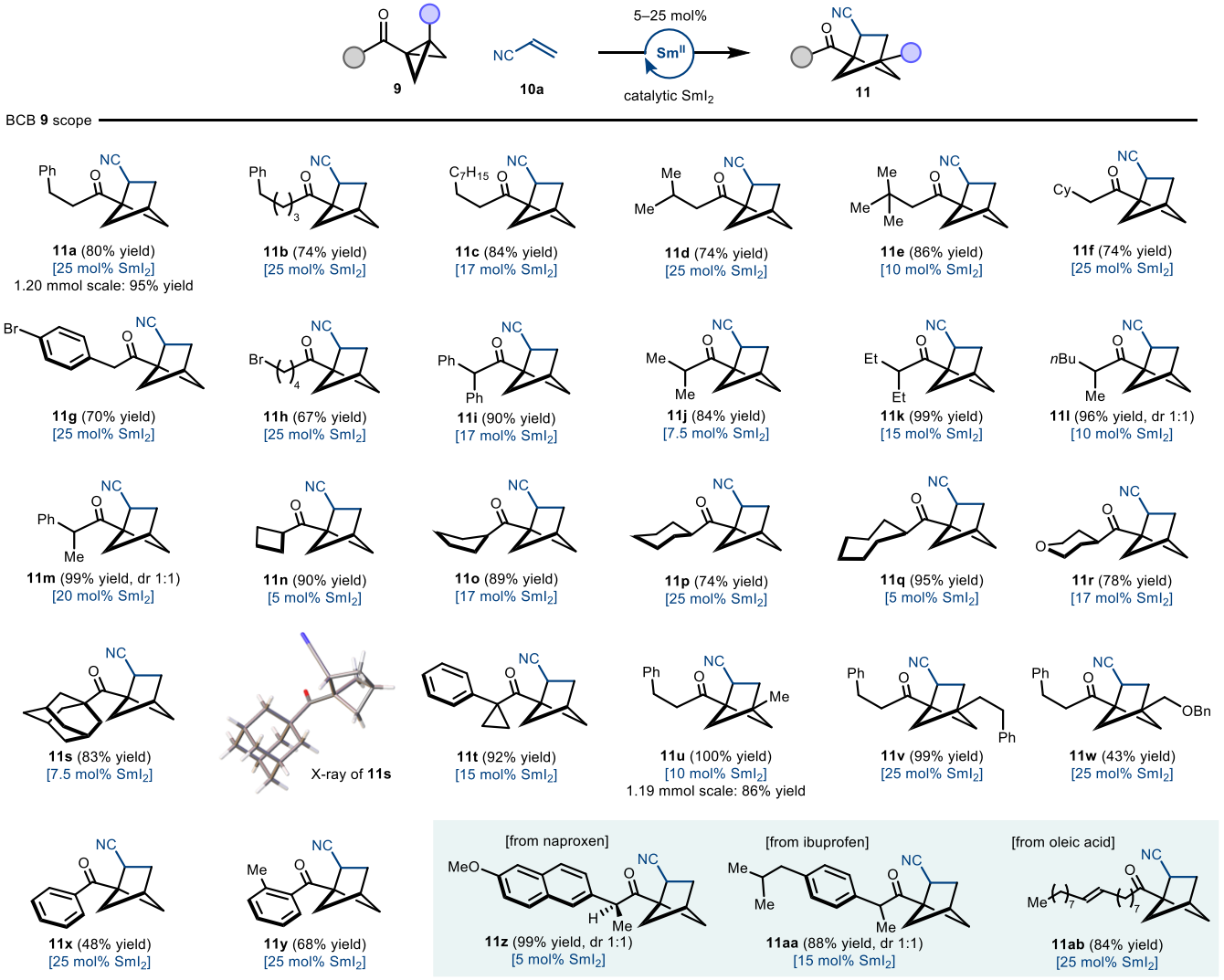


Figure 2 | Scope of the SmI_2-catalyzed alkene insertion with respect to 9. Survey of BCB ketones that can participate in the reaction. Reaction conditions: 5-25 mol% of SmI_2 was added to a solution of THF solution of BCB ketone (1 equiv.) and alkene (2.5 equiv.) in THF at –10 °C, and the reaction stirred for 15 min. Reactions performed on a 0.1 mmol scale, unless otherwise stated.

Next, a range of alkenes **10** was coupled with representative BCB ketone **9a** (Figure 3). In addition to acrylonitrile, a series of acrylates proved willing participants in the catalytic insertion process (forming BCH ketones **11ac–11aq**). The structure of *tert*-butyl ester-containing BCH ketone **11ai** was confirmed by X-ray crystallography. BCB ketones bearing an additional alkyl substituent at the second bridgehead position underwent smooth coupling with methyl acrylate to give trisubstituted BCH esters **11ad–af**; in particular, the coupling to give **11ad** took place in near-quantitative yield. The use of acrylate partners illustrated the compatibility of the process with a broad range of functionalities, including trifluoromethyl (**11ag**), alkyne (**11al**), furanyl and pyridyl (**11am**, **11an**), silicate (**11ao**), ether (**11ap**), and halide (**11aq**)

groups. Vinyl sulfones (**11ar–11at**), a vinyl sulfonate ester (**11au**), an active PFP vinyl sulfonate (**11av**), a vinyl sulfonyl fluoride (**11aw**), and a vinyl sulfonamide (**11ax**) also proved to be competent partners giving access to a range of sulfonyl-containing BCHs. The structure of sulfonyl fluoride-containing BCH ketone **11aw** was confirmed by X-ray crystallography. Finally, acrylates derived from natural products geraniol, menthol and vitamin E underwent coupling with **9a** to give complex BCHs **11ay**, **11az** and **11aaa**, respectively (Figure 3). To demonstrate the practical utility of our method, the synthesis of BCHs **11a**, **11u** and **11ac** was performed on a 1.2 mmol scale, affording the corresponding products in either comparable or even improved yield – in the case of **11a** and **11ac** (*c.f.* Figures 2-3).

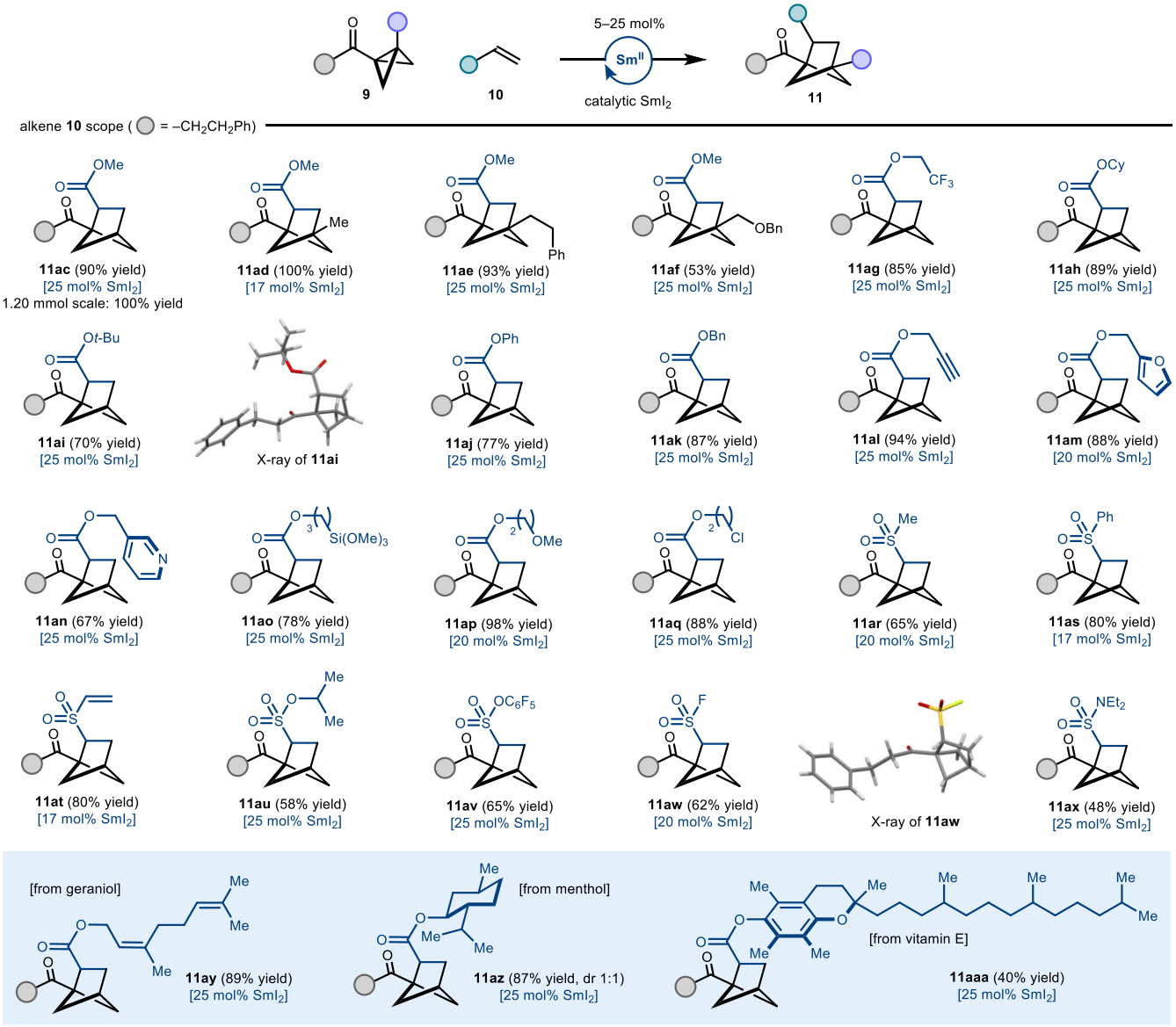


Figure 3 | Scope of the SmI_2-catalyzed alkene insertion with respect to 10. Survey of alkenes that can participate in the reaction. Reaction conditions: 5-25 mol% of SmI_2 was added to a solution of THF solution of BCB ketone (1 equiv.) and alkene (2.5 equiv.) in THF at –10 °C, and the reaction stirred for 15 min. Reactions performed on a 0.1 mmol scale, unless otherwise stated.

Mechanistic investigations. In addition to ruling out a Lewis acid-mediated process (Table 1, entry 10; see also Table S1 in the Supplementary Information), computational studies on the coupling between BCB ketone **9j** and acrylonitrile **10a** have been used to shed light on the key steps of the SmI_2-catalyzed alkene insertion. In line with our previous studies on SmI_2-catalysis[23-24], SET reduction of the ketone carbonyl in **Sm(II)–9j** generates ketyl radical **Int I** (33 kcal.mol^{-1}). Extremely facile ring opening of the BCB ring (1.9 kcal.mol^{-1}), via transition state **TS 1**, generates virtually planar cyclobutyl radical **Int II**. Radical addition to acrylonitrile (9.4 kcal.mol^{-1}), via transition state **TS 2**, gives stabilized radical **Int III**, which undergoes radical rebound on to the Sm(III)-enolate moiety in **Int III** (6.5 kcal.mol-1), via transition state **TS 3**, to give new ketyl radical **Int IV**. Finally, SET back to Sm(III) (–26.4 kcal.mol^{-1}) generates **Sm(II)–11j**. Crucially, calculations suggest that product ketyl radical **Int IV** has a similar reducing ability to the starting ketyl

radical **Int I**. Thus, rather than a case of 'reductant upconversion'[30], in which a more reducing radical is formed from a less-reducing radical and an electron-transfer chain process results, we believe it is the instability of the starting ketyl radical **I**, and the formation of a more stable product ketyl radical **IV** that is key to the catalytic process.

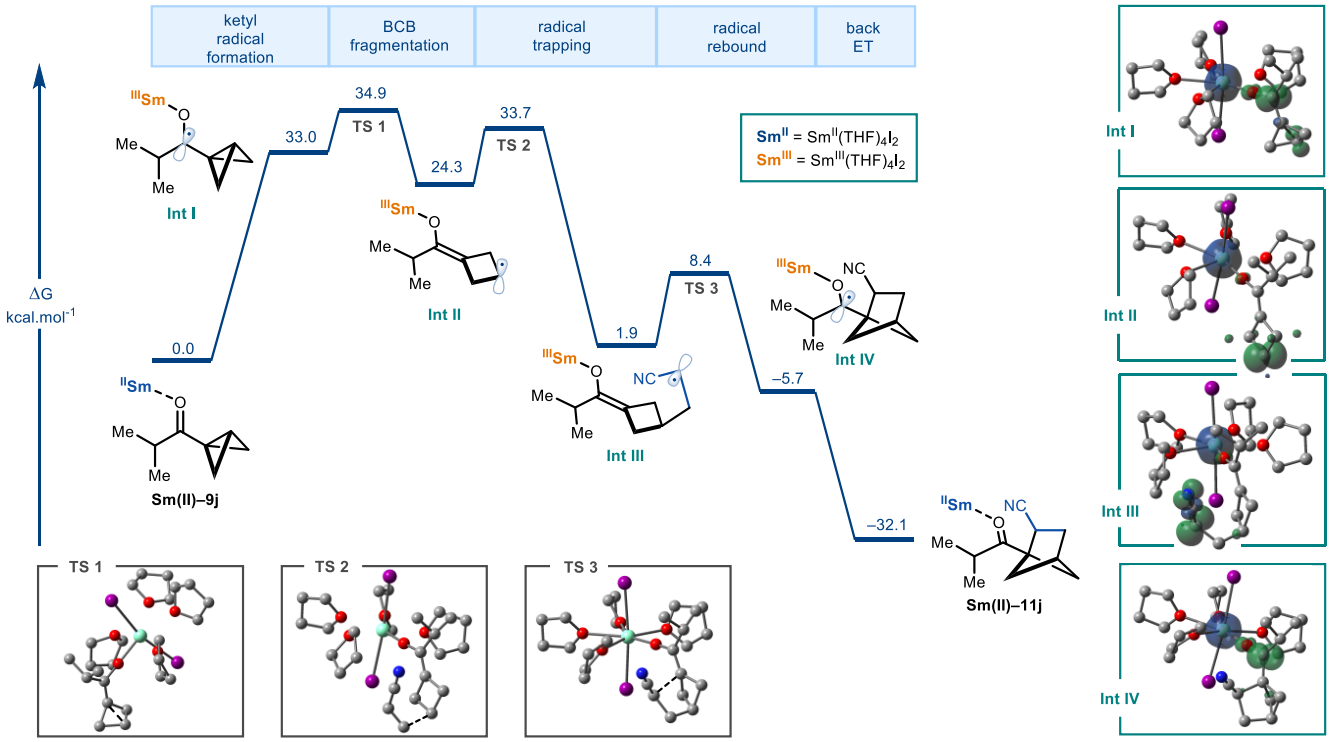


Figure 4 | Computational study of the SmI_2-catalyzed alkene insertion. Using BCB ketone **9j** and acrylonitrile **10a** as a representative pairing, computational studies have been used to study the key bond-breaking and bond-forming steps of the catalytic process: Ketyl-radical formation by SET reduction with Sm(II), BCB fragmentation, radical trapping with acrylonitrile, radical rebound on to a Sm(III)-enolate, and back electron transfer to Sm(III) with formation of BCH ketone **11j**. BCB, bicyclo[1.1.0]butyl. BCH, bicyclo[2.1.1]hexyl. ET, electron transfer.

Applications. The BCH ketone products of the SmI_2-catalyzed alkene insertion are versatile building blocks for the synthesis of decorated BCHs, as exemplified by the manipulation of **11a**. Using the material obtained from the 1.2 mmol scale SmI_2-catalyzed (20 mol%) coupling of **9a** and acrylonitrile **10a** (273 mg of **11a**, 95% yield, Figure 5a), selective reduction of the ketone or nitrile substituent delivered alcohols **12** and **13**, respectively (Figure 5b). Hydrolysis of the nitrile motif allowed access to either amide **14** or acid **15** by straightforward variation of the reaction time. Interestingly, BCH ketones **11aa** and **11a** underwent Baeyer-Villiger oxidation with complementary selectivity to give esters **16** and **17**, respectively. Finally, the oxime derived from **11aa** underwent Beckman rearrangement to give amide **18**. The structure of BCH amide **18** was confirmed by X-ray crystallography (Figure 5b).

To further showcase the value of BCH ketones **11** as intermediates for the synthesis of more elaborate BCHs of medicinal value, we prepared BCH **23**; a saturated hydrocarbon analogue of broad-spectrum antimicrobial phthalylsulfathiazole **19**, in which the BCH motif mimics the *ortho*-disubstituted benzene moiety within the drug. Ester hydrolysis in **17**, coupling with commercial aniline **21**, and hydrolysis of the nitrile in **22**, furnished **23** in expedient fashion. Comparison of the computed lowest energy conformations of analogue **23** and drug **19** suggest that the BCH analogue closely mimics the conformation of phthalylsulfathiazole; in particular, the distance between the '*ortho*' substituents is identical in the BCH analogue and in the drug (Figure 5c).

Conclusion We have demonstrated that hard-to-access, substituted bicyclo[2.1.1]hexanes (BCHs) – attractive candidates for bioisosteres of both *ortho*- and *meta*-substituted benzenes – can be readily accessed with high atom economy using a SmI_2-catalyzed insertion of electron-deficient alkenes into bicyclo[1.1.0]butyl (BCB) ketones. The catalytic process embraces a wide range of alkenes and substituted BCB ketones and operates with loadings of SmI_2 as low as 5 mol%. DFT calculations have been used to probe the radical-relay mechanism underpinning the catalysis, and the product BCH ketones have been shown to be versatile synthetic intermediates through selective manipulation procedures. These studies guided the expedient synthesis of a saturated hydrocarbon analogue of the broad

spectrum antimicrobial phthalylsulfathiazole. We expect our provision of the first general catalytic approach to substituted BCH scaffolds to prompt their use and validation in medicinal chemistry and crop science, thus ultimately allowing the potential of this largely unexplored family of bioisosteres to be realized.

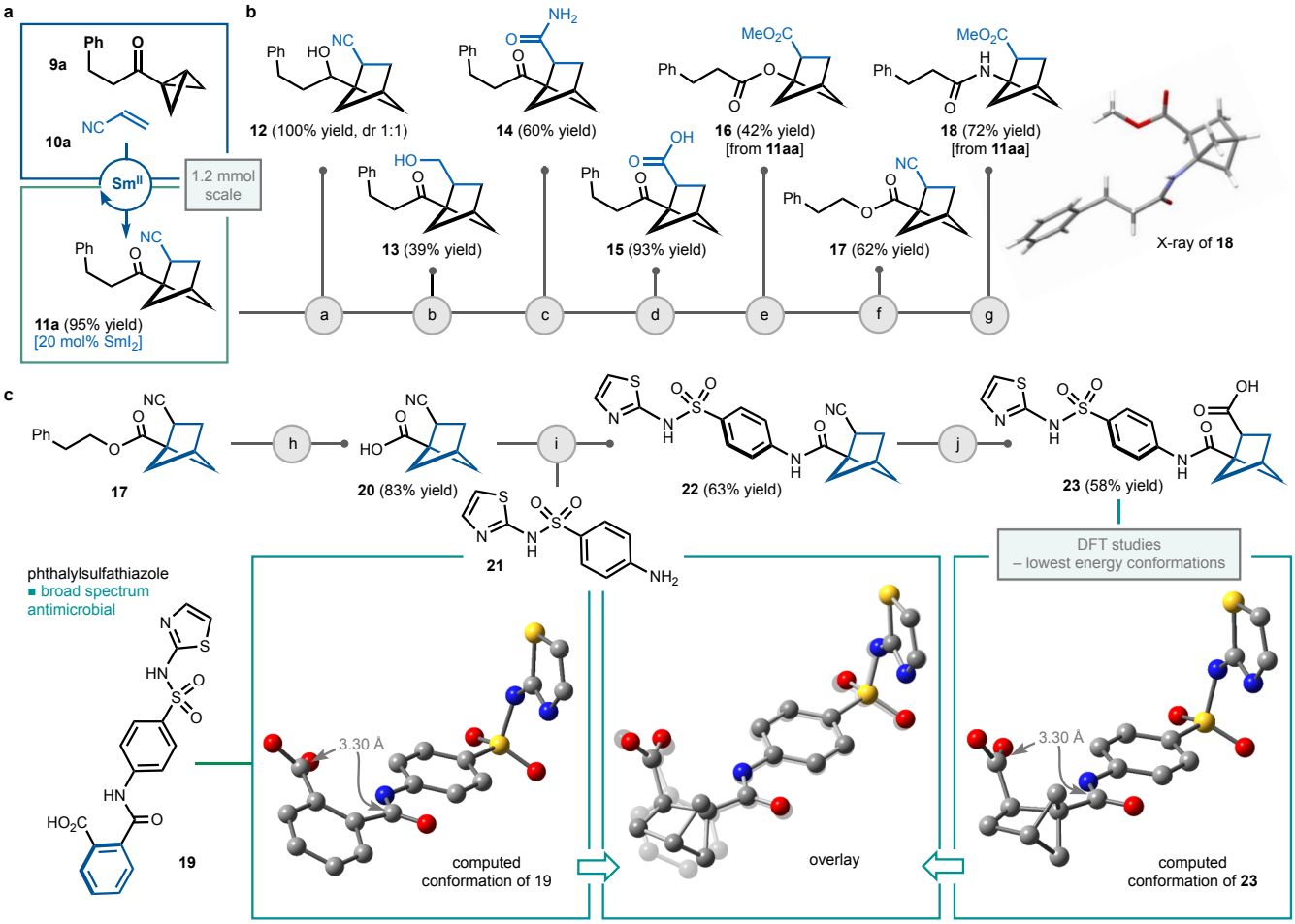


Figure 5| Applications of the SmI_2-catalyzed alkene insertion. **a**, 1.20 mmol scale preparation of BCH ketone **11a** using 20 mol% of SmI_2. **b**, selective conversion of BCH ketones **11a** and **11aa** into alcohols (by ketone or nitrile reduction), amide and acid (by alternative nitrile hydrolyses), esters (by selective Baeyer-Villiger oxidation), and protected amine (by Beckmann rearrangement of an oxime intermediate). **c,** synthesis of **23** – a BCH analogue of broad spectrum antimicrobial phthalylsulfathiazole **19**. A computational study was carried out to compare the lowest energy conformation of **19** and **23**. Reaction conditions: (a) $NaBH_4$, EtOH, RT, 100%. (b) $[RuCl_2(p\text{-cymene})]_2$, $(CH_2O)_n$, Tol–H_2O, 90 °C, 39%. (c) KOH, EtOH–H_2O, 90 °C, 4 h, 60%. (d) KOH, EtOH–H_2O, 90 °C, 36 h, 93%. (e) *m*CPBA, TFA, CH_2Cl_2, 55 °C, 42%. (f) *m*CPBA, TFA, CH_2Cl_2, 55 °C, 62% (16% of the other regioisomer). (g) (i) NaOAc, $NH_2OH{\cdot}HCl$, EtOH–H_2O, 80 °C, 100%; (ii) 50 mol% I_2, CH_3CN, 80 °C, 72% (23% of the other regioisomer). (h) LiOH, THF–H_2O, RT, 83%. (i) $SOCl_2$, 80 °C then **21**, NEt_3, THF RT, 63%. j) KOH, EtOH–H_2O, 90 °C, 58%.

Supplementary Information is linked to the online version of the paper at www.nature.com/nature.

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Author contributions S.A., G.E.M.C. and D.J.P. conceived the project. S.A. and F.B. designed and performed the experimental work. E.P. performed the computational studies. N.K. supervised the computational studies. S.A., F.B., G.E.M.C. and D.J.P. contributed to the analysis and interpretation of data. D.J.P. wrote the manuscript with input from all authors.

Data availability Materials and methods, experimental procedures, useful information, mechanistic studies, ^{1}H NMR spectra, ^{13}C NMR spectra and mass spectrometry data are available in the Supplementary Information. Raw data are available from the corresponding author on reasonable request.

Crystallographic data for compounds **11s, 11ai, 11aw** and **18** have been deposited with the Cambridge Crystallographic Data Centre, accession numbers CCDC 2129464, 2129466, 2129467, 2129468, respectively. Reprints and permissions information is available at www.nature.com/reprints. The authors declare no competing financial interests. Correspondence and requests for materials should be addressed to D.J.P. (david.j.procter@manchester.ac.uk).

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