Synthesis and Applications of Polysubstituted Bicyclo[1.1.0]butanes

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ABSTRACT: Bicyclo[1.1.0]butanes (BCBs) are valuable substrates in the 'strain release' synthesis of polysubstituted four-membered ring systems, with applications including bioconjugation agents. The introduction of substituents onto the BCB bridges is challenging due to limitations in current methods for the preparation of this bicyclic scaffold, typically necessitating linear syntheses with limited functional group tolerance and/or substituent scope. Here we report the synthesis of tri- and tetrasubstituted BCBs via directed metalation of readily accessed BCB amides; this straightforward 'late stage' approach generates a wide variety of bridge-substituted BCBs that can be easily converted into other useful small ring building blocks. Access to a mono-deuterated BCB afforded unprecedented insight into the mechanism of dihalocarbene insertion into BCBs to afford bicyclo[1.1.1]pentanes (BCPs).

Bicyclo[1.1.0]butanes (BCBs, **1**, Figure 1a) are valuable tools in 'strain-release' chemistry for the synthesis of small organic ring systems.[1] BCBs that are mono- or disubstituted at the bridgehead positions have been widely exploited in this context due to their ready accessibility,[2] and range of ring-opening reactions with nucleophiles,[2c, 3] radicals[4] and electrophiles[2a, 5] to give cyclobutanes and cyclobutenes. Their utility in synthesis is highlighted by a recent total synthesis of piperarborenine B, in which the cyclobutane core was constructed through organocuprate addition to the C1–C3 bond of a disubstituted BCB.[6] Applications as tools for protein bioconjugation have also been developed due to the high chemoselectivity exhibited for alkylation of cysteine residues under mild conditions (e.g. BCB-ibrutinib).[7] 1,3-disubstituted BCBs are further employed as precursors to bicyclo[1.1.1]pentanes (BCPs), which are valuable motifs in drug design,[8] via dihalocarbene insertion into the C1–C3 bond (e.g. BCP-darapladib).[8b, 8c, 9]

In contrast to bridgehead substitution, the synthesis of bridge-substituted BCBs is challenging; the predominant chemical routes consist of 3-*exo-tet* cyclization[3e] (Path a, Figure 1b), and rhodium-catalyzed intramolecular cyclopropanation of α-diazocarbonyls (Path b).[2c, 10] Both require multistep sequences where bridge substituents are introduced early in the route, limiting product diversity. A biocatalytic approach has also been described (Path c) that can introduce two identical ester bridge substituents in trisubstituted BCBs.[11] However to the best of our knowledge, the selective synthesis of BCBs substituted at all carbon atoms on the framework is unknown.

Building on our recent work on bridgehead functionalization of BCB amides,[2a] we hypothesized that a directed bridge-metalation approach could provide a solution to this challenge, directly accessing bridge-substituted products from pre-formed BCB scaffolds (Figure 1c). Here we report the development of this late-stage strategy to stereoselectively functionalize one or both BCB bridges,[12] delivering a wide range of carbon- and heteroatom-polysubstituted BCBs in good to excellent yields. The utility of these products is illustrated through transformations to various other small ring systems, while synthesis of a monodeuterated BCB afforded unprecedented insight into the mechanism of dihalocarbene insertion to form BCPs.

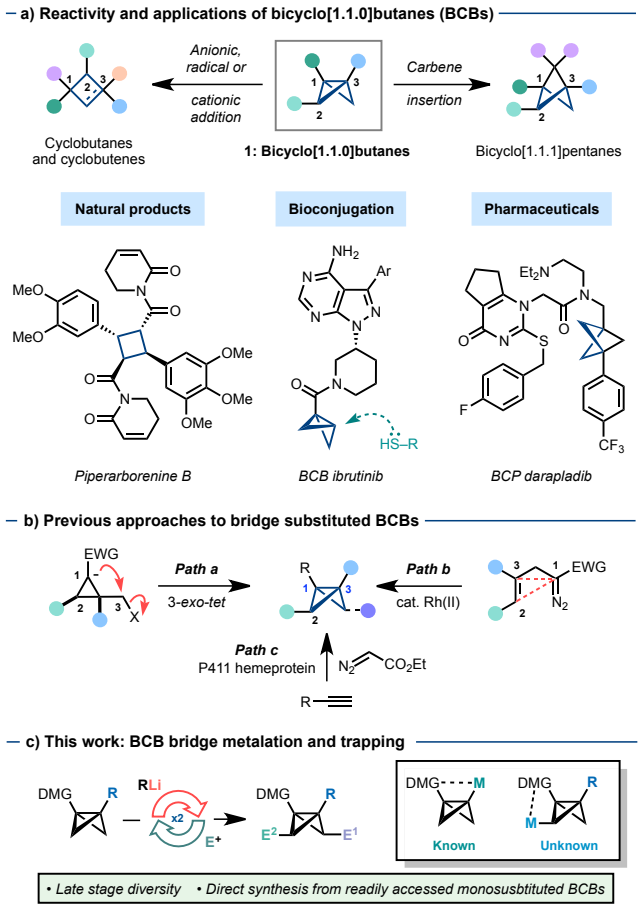
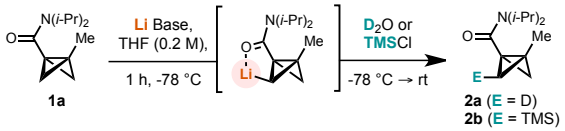


Figure 1. a Reactivity and applications of BCBs. b Existing routes to bridge substituted BCBs. c This work: BCB bridge metalation and trapping. DMG = Directed metalation group.

Investigations into the feasibility of directed bridge metalation began with BCB **1a** (Table 1). Various organolithium bases (1.1 equiv.) were able to efficiently deprotonate the bridge position, with a D_2O quench affording the *exo*-diastereomer **2a** with excellent

Table 1: Optimization of directed bridge metalation of BCB 1a.[a]



Entry	Base (1.1 eq.)	Variation of conditions	Conversion[b]
1	PhLi	D_2O	8
2	*n*-BuLi	D_2O	14
3	*s*-BuLi.TMEDA	D_2O	37
4	*t*-BuLi	D_2O	51
5	*s*-BuLi.TMEDA	-40 °C, D_2O	81
6	***s*-BuLi.TMEDA**	**0.4 M, D_2O**	**100, 99[c]**
7	*s*-BuLi.TMEDA	0.4 M, TMSCl	68[c]
8	***s*-BuLi.TMEDA[d]**	**0.4 M, TMSCl**	**82[c]**

[a] Reactions conducted on 0.1 mmol scale. Organolithium bases were used as solutions in hydrocarbon solvents; see the Supporting Information for details. [b] Conversion based on ratio of **2a**:**1a** as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yield. [d] Metalation conducted in Et_2O.

diastereoselectivity (>20:1 *dr*, Entries 1–4). Reaction conversion at –78 °C increased with base strength, with *s*-BuLi / TMEDA and *t*-BuLi giving the highest conversions after a 1 h reaction time (Entries 3 and 4). Increased conversion was achieved by conducting the reaction at –40 °C (Entry 5) and at higher concentration (0.4 M, Entry 6), the latter enabling complete metalation. Under these conditions, quenching of the reaction with chlorotrimethylsilane gave the *exo*-TMS diastereomer **2b** in 68% yield (Entry 7); conducting this reaction with Et_2O as co-solvent led to increased efficiency (82%, Entry 8).

Having identified optimal conditions for bridge metalation (Table 1, Entries 6 and 8), we assessed the scope of electrophiles that could be introduced (Scheme 1). Alkylations with iodomethane proceeded in excellent yield (**2c**, 80% / 89% on gram scale) as did reaction with allyl bromide and benzyl bromide (**2d**, 51% and **2e**, 60% respectively), while trapping with 1-iodopropane or 1-bromopropane could be optimally achieved in the presence of a catalytic amount of copper(I) iodide (**2f**, 59% and 62% respectively with 15 mol% CuI).[13] Quenching with MOMCl gave ether **2g** in high yield (81%), with epoxides also proving suitable electrophiles (**2h**, 64%). Reaction with carbonyl-based electrophiles such as benzaldehyde (**2i**) and acetone (**2j**) gave the corresponding alcohols in good yields (75% and 82%) and moderate diastereoselectivity for **2i** (2:1 *dr*); the configuration of the major diastereomer of **2i** was confirmed by single crystal X-ray diffraction studies.[14] Ketone, amide and ester groups could be readily introduced using the respective carbonyl chloride electrophiles, affording BCBs **2k**-**2m** in good to excellent yields (61–82%), again as single diastereomers.

In addition to carbon-based electrophiles, a variety of heteroatoms could also be installed: chlorotrimethylsilane (**2b**), dimethyl disulfide (**2n**), chlorodiphenylphosphine (**2o**), trimethylborate (**2p**), tributyltin chloride (**2q**) and chlorotrimethylgermane (**2r**) all afforded excellent yields of the corresponding trisubstituted BCBs (77–99%). The installation of these heteroatom substituents greatly expands the scope of BCB products over those accessible using previous approaches.

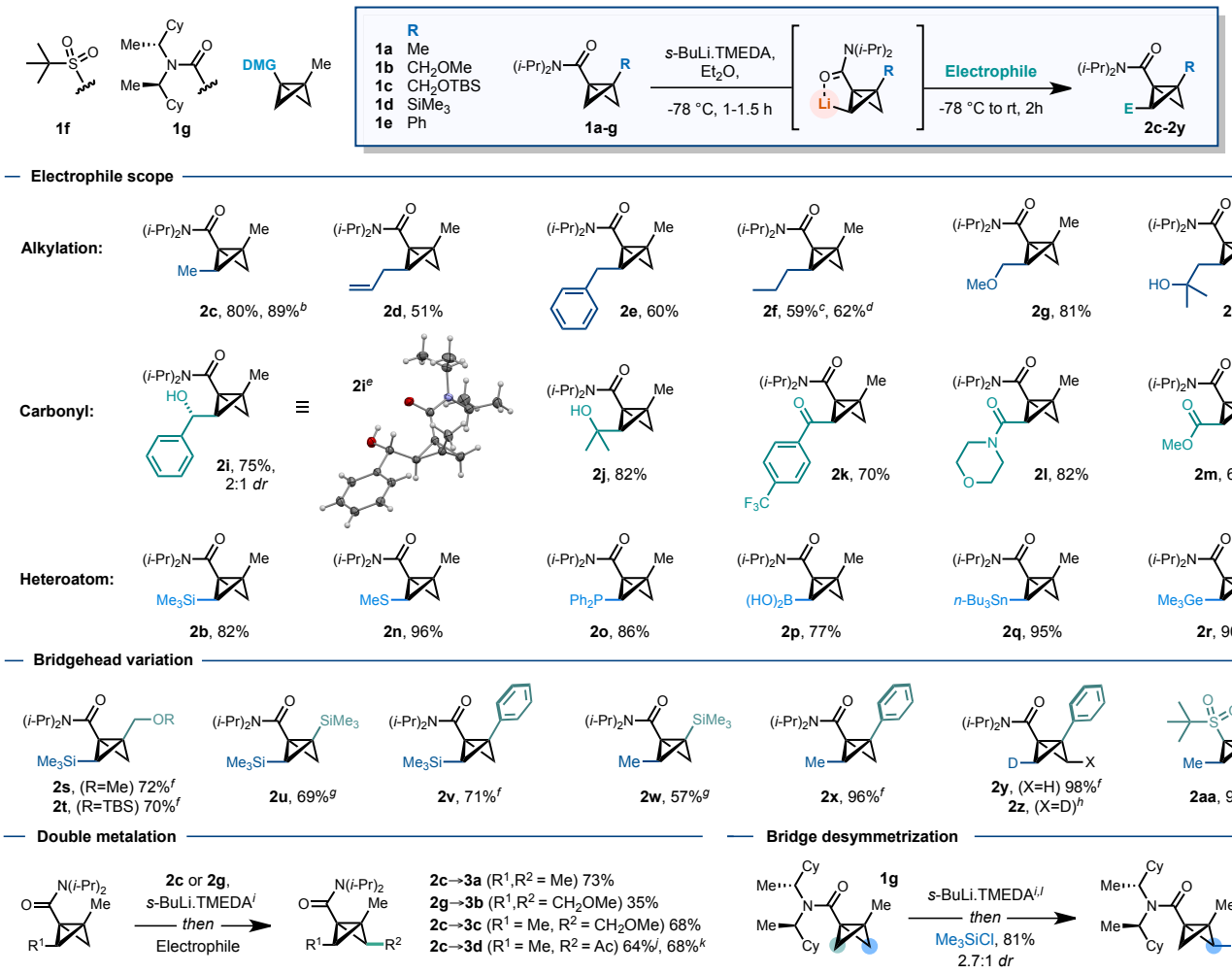
With a broad electrophile scope surveyed, we next studied the effect of variation of the bridgehead position; these substrates (**1b**–**1e**, Scheme 1) were easily prepared by directed metalation / electrophilic trapping of mono-substituted BCB amides.[15] To our delight, all four underwent smooth metalation / silylation to give trisubstituted BCBs **2s**–**2v**; a brief survey of other electrophiles (iodomethane, **2w** and **2x**; and D_2O, **2y**) also afforded the corresponding BCBs in good to excellent yields (57-98%) and diastereoselectivity (>20:1 *dr*). We were interested to observe variation in the rate of BCB metalation with different bridgehead groups; for example, the trimethylsilyl-substituted BCB **1d** required 4.0 equiv. of base and a 5 h reaction time to achieve acceptable levels of metalation (>90%), while 40% of *double* lithiation of the phenyl-substituted BCB **1e** occurred with super-stoichiometric amounts of base (2.1 equiv.) after 2 h (to give **2z**). Pleasingly, we found that the directing group itself could be varied, with *tert*-butyl sulfone **1f** enabling high-yielding methylation to trisubstituted BCB **2aa**.

The observation of double lithiation for BCB **1e** suggested that iterative bridge functionalization should be possible to give BCBs with substituents on every carbon atom. A second metalation was therefore performed on trisubstituted BCBs **2c** and **2g**. After 3 h metalation time under the optimized conditions, the lithiated BCBs were quenched to generate symmetric tetrasubstituted BCBs **3a**–**b** in 73% and 35% yields respectively. Non-symmetric BCBs were also accessible by reaction of **2c** with MOMCl (**3c**, 68%), and acetyl chloride or the equivalent Weinreb amide (**3d**, 64–68%), demonstrating the potential to access complex polyfunctionalized scaffolds. Desymmetrization strategies were also investigated; while *s*-BuLi/(+)-sparteine mediated metalation[12c] afforded minimal asymmetric induction (6% *ee*), use of the C_2-symmetric enantioenriched amide **1g** gave the silylated BCB **2ab** in 81% yield and 2.7:1 *dr*.[16] In summary, this iterative metalation / functionalization strategy offers the means to selectively substitute all carbon atoms on a BCB-amide, enabling the synthesis of compounds that are inaccessible through existing routes.[2h]

To demonstrate the utility of the polysubstituted BCB products, we examined their application in the synthesis of three additional ring systems: cyclobutanes, cyclobutenes and cyclopropanes (Scheme 2). As BCBs are useful tools for bioconjugation reactions, we first tested the ability of BCB **2c** to react with benzyl mercaptan as a representative thiol.[2b, 3b, 7] This afforded the tetrasubstituted cyclobutane **4** in 97% yield with moderate *dr* (2:1), highlighting the potential utility of polyfunctionalized BCBs in chemical biology settings. Interestingly, ring opening of BCBs under acidic conditions afforded either cyclobutene or cyclopropane products, depending on the nature of the bridgehead substituent. BCB **2x**, bearing a phenyl group at the bridgehead, underwent near quantitative isomerization to cyclobutene **5** on treatment with a catalytic amount of HCl in chloroform, with excellent regioselectivity (98%, 20:1 *rr*).[2a, 17] In contrast, reaction of methyl-bridgehead BCB **2c** led exclusively to a single diastereomer of an α-chlorocyclopropane, tentatively assigned as **6**. That no cyclobutene or other product diastereomers were observed in this reaction would support a stereospecific ring-opening pathway that proceeds via a non-classical carbocation (**7**) to give **6**, rather than stereoselective addition of chloride to a localized secondary cation.[18]

The installation of bridge halogenation would be attractive due to the potential utility of halides in further transformations. However, quenching (Li)-**2c** with halogen electrophiles such as dibromantin or iodine afforded the halogen-substituted cyclobutenes **8** and **9** respectively, instead of halo-BCBs. The halogen atom in the initially formed BCB halide intermediate **10** is likely highly activated as a

Scheme 1. Scope of BCB bridge metalation study / electrophilic trapping[a]

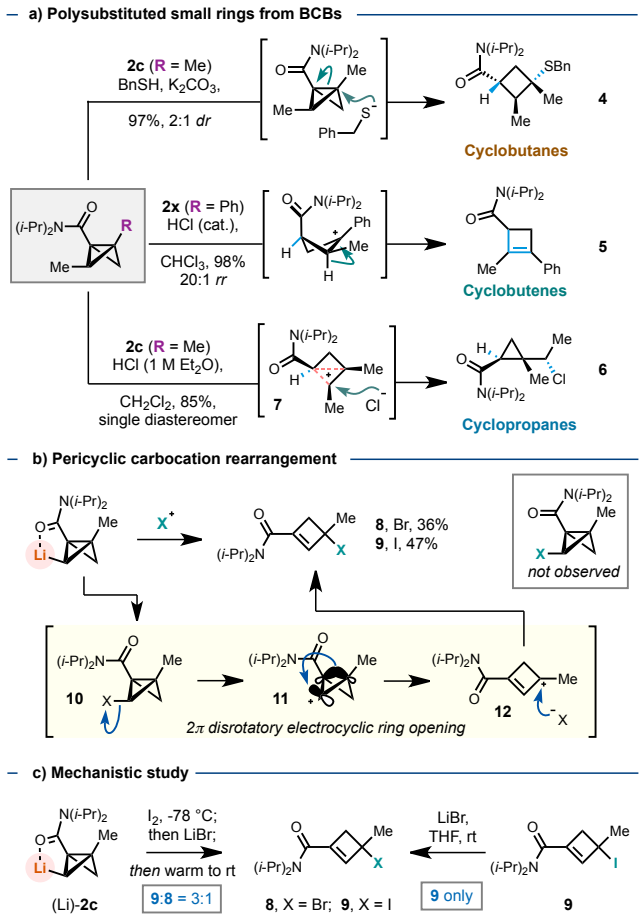


[a]Reactions run on 0.2 mmol scale using 1.1 equiv. of *s*-BuLi.TMEDA (1.2-1.4 M in cyclohexane) and 2.0 equiv. of electrophile. [b]Reaction conducted with 8.76 mmol (1.00 g) of **1a**. [c] 15 mol% of CuI and 5 equiv. of 1-iodopropane, 20 h. [d] 15 mol% of CuI and 5 equiv. of 1-bromopropane. [e] Structure of **2i** from single crystal X-ray diffraction studies (displacement ellipsoids drawn at 50% probability).[14] [f] 2 h metalation time in THF. [g] 5 h metalation time with 4.0 equiv. of *s*-BuLi.TMEDA in THF. [h] 40:60 ratio of **2z**:**2y** was isolated, as determined by ^{1}H NMR spectroscopic analysis. [i] 3 h metalation time. [j] AcCl used as electrophile. [k] *N*-methoxy-*N*-methylacetamide used as electrophile. [l] The identity of the major regioisomer could not be determined.

leaving group due to alignment of the antiperiplanar C–C bonds of the fused cyclopropane ring with the C–X σ* orbital, akin to the beta effect in cyclopropylmethyl halides.[19] Indeed, Wiberg showed that nitrobenzoate solvolysis proceeds 1000 times faster when the leaving group is adjacent (exocyclic) to a BCB compared to a cyclopropane, highlighting the heightened reactivity imparted to the leaving group by two p-rich C–C bonds.[20] Ionization of the C–X bond would lead to a (transient) carbocation **11** that could undergo a disrotatory 2π-electrocyclic ring opening to form a stabilized tertiary/allylic carbocation **12**, which is then quenched by halide ion.[21] A crossover experiment was conducted whereby the immediate product of iodine quenching (i.e., **10**, X = I) was treated at -78 °C with LiBr; a 3:1 ratio of **9**:**8** was obtained. In contrast, treatment of the isolated product **9** with LiBr led to no bromine incorporation. These results provide support for a dissociation / recombination mechanism.[15] An alternative pathway involving halide ion addition to the BCB bridgehead followed by E$_1$cb-like elimination of the bridge halide from the ensuing enolate could likely be ruled out, since no ring-opening of BCB **1a** was observed on prolonged exposure to LiBr in MeOH.

Among the most appealing applications of 1,3-disubstituted BCBs in medicinal chemistry is their conversion to bicyclo[1.1.1]pentanes (BCPs) by dihalocarbene insertion.[8b, 8c, 9] Despite the utility of this chemistry, little is known about the mechanism of this reaction, such as the facial selectivity of reaction with the dihalocarbene. Monodeuterated BCB **2y** offers a useful tool to address this question, as 'top' face addition of the difluorocarbene would afford *syn*-deuterated CF$_2$-BCP **13**, while 'bottom' face addition would lead to *anti*-deuterated BCP **14** (Scheme 3a). In the event, subjection of **2y** to our previously reported difluorocarbene insertion conditions[2a] afforded exclusively the *anti* product **14**, along with the 1,4-dienes **15** and **16**, in a 2:1:1 ratio (82% combined yield, Scheme 3a). This suggests that the singlet difluorocarbene[22] approaches the bottom face of BCB **2y** (Scheme 3b, Path A), triggering ring-opening to generate the zwitterionic intermediate **17**. This can either fragment to dienes **15** and **16** (Path B), or can undergo a ring flip to **18**, enabling cyclization of the difluoromethyl anion to **14** (Path C). The

Scheme 2. Functionalization of polysubstituted BCB Products



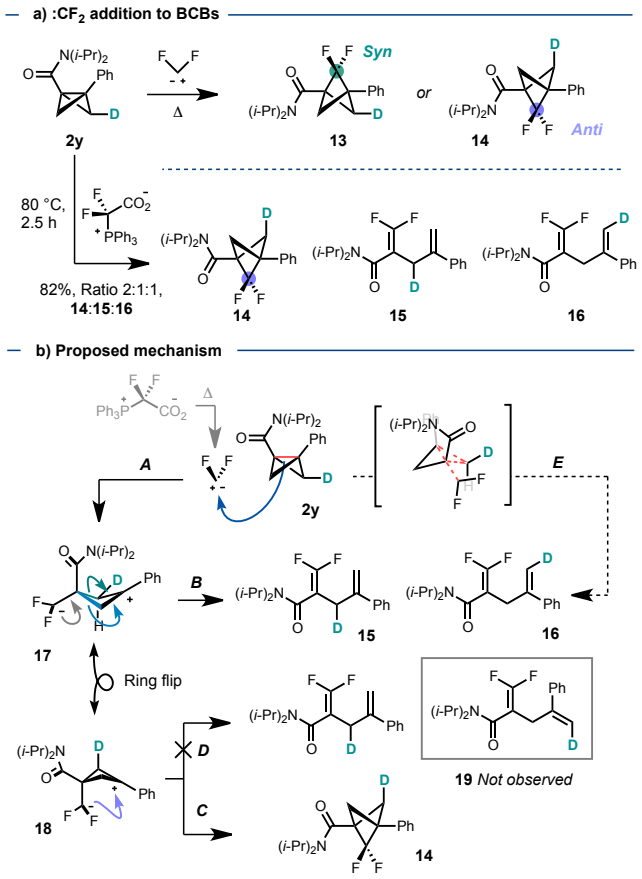
a) Synthesis of polysubstituted small ring systems from BCBs **2c** and **2x**. b) Electrocyclic rearrangement of BCB bridge halides to halocyclobutenes. c) Mechanistic evidence for proposed pathway.

stereochemistry of the deuterium atom in **16** appears to support exclusive fragmentation of **17**, as fragmentation of **18** (Path D) should generate stereoisomer **19**, and an unequal ratio of **15** and **16**, which was not observed. An alternative concerted pathway may also be possible, in which **2y** directly fragments to dienes **15** and **16** (Path E).[23] These observations provide the first experimental support for previous computational work on dichlorocarbene insertion in analogous systems,[23] which considered both stepwise and concerted routes, albeit these authors noted the distinct behaviors of dichloro- and difluorocarbene.[24]

In summary, we have developed a general iterative bridge metalation strategy to access bicyclo[1.1.0]butanes substituted at every carbon atom, using simple reagents. This approach allows the synthesis of stereodefined BCBs with a variety of substituents that cannot be easily accessed through previous routes. Further diversification of these products into other polysubstituted small ring systems highlights the utility of BCBs in strain-release reactions, along with their diverse carbocation chemistry. This method also allowed the synthesis of isotopically-labeled BCB **2y**, which enabled mechanistic elucidation of the formal (3+1) insertion and rearrangement pathways of BCBs to afford BCPs and 1,4-dienes.

ASSOCIATED CONTENT

Scheme 3. Mechanistic Investigation of Difluorocarbene Insertion into BCBs



a) Facial selectivity of difluorocarbene insertion into BCB **2y**. b) Proposed reaction mechanisms for formation of BCP **14** and 1,4-dienes **15** and **16**.

Experimental procedures, characterization data and crystallographic data for novel compounds are included in the Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest

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REFERENCES

(1) Turkowska, J.; Durka, J.; Gryko, D., Strain release – an old tool for new transformations. *Chem. Commun.* **2020**, *56*, 5718-5734.

(2) (a) McNamee, R. E.; Haugland, M. M.; Nugent, J.; Chan, R.; Christensen, K. E.; Anderson, E. A., Synthesis of 1,3-disubstituted bicyclo[1.1.0]butanes via directed bridgehead functionalization. *Chem. Sci.* **2021**, *12*, 7480-7485; (b) Schwartz, B. D.; Zhang, M. Y.; Attard, R. H.; Gardiner, M. G.; Malins, L. R., Structurally Diverse Acyl Bicyclobutanes: Valuable Strained Electrophiles. *Chem. Eur. J.* **2020**, *26*, 2808-2812; (c) Panish, R.; Chintala, S. R.; Boruta, D. T.; Fang, Y.; Taylor, M. T.; Fox, J. M., Enantioselective Synthesis of Cyclobutanes via Sequential Rh-catalyzed Bicyclobutanation/Cu-catalyzed Homoconjugate Addition. *J. Am. Chem. Soc.* **2013**, *135*, 9283-9286; (d) Wipf, P.; Stephenson, C. R. J.; Okumura, K., Transition-Metal-Mediated Cascade Reactions: C,C-Dicyclopropylmethylamines by Way of Double C,C-σ-Bond Insertion into Bicyclobutanes. *J. Am. Chem. Soc.* **2003**, *125*, 14694-14695; (e) Weber, J.; Haslinger, U.; Brinker, U. H., 1-Bromobicyclo[1.1.0]butane as an Easily Obtainable C4-Building Block: A Novel Route to Cyclobutanone. *J. Org. Chem.* **1999**, *64*, 6085-6086; (f) Gaoni, Y., New bridgehead-substituted 1-(arylsulfonyl)bicyclo[1.1.0]butanes and some novel addition reactions of the bicyclic system. *Tetrahedron* **1989**, *45*, 2819-2840; (g) Nilsen, N. O.; Skattebøl, L.; Baird, M. S.; Buxton, S. R.; Slowey, P. D., A simple route to 1-bromobicyclo[1.1.0]butanes by intramolecular trapping of 1-bromo-1-lithiocyclopropanes. *Tetrahedron Lett.* **1984**, *25*, 2887-2890; (h) Ramazanov, I. R.; Yaroslavova, A. V.; Dzhemilev, U. M., Synthesis of cyclopropane compounds: bicyclo[1.1.0]butanes, spiropentanes and bicyclopropanes. *Russ. Chem. Rev.* **2012**, *81*, 700-728.

(3) (a) Guo, L.; Noble, A.; Aggarwal, V. K., α-Selective Ring-Opening Reactions of Bicyclo[1.1.0]butyl Boronic Ester with Nucleophiles. *Angew. Chem. Int. Ed.* **2021**, *60*, 212-216; (b) Lopchuk, J. M.; Fjelbye, K.; Kawamata, Y.; Malins, L. R.; Pan, C.-M.; Gianatassio, R.; Wang, J.; Prieto, L.; Bradow, J.; Brandt, T. A.; Collins, M. R.; Elleraas, J.; Ewanicki, J.; Farrell, W.; Fadeyi, O. O.; Gallego, G. M.; Mousseau, J. J.; Oliver, R.; Sach, N. W.; Smith, J. K.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S., Strain-Release Heteroatom Functionalization: Development, Scope, and Stereospecificity. *J. Am. Chem. Soc.* **2017**, *139*, 3209-3226; (c) Gianatassio, R.; Lopchuk, J. M.; Wang, J.; Pan, C.-M.; Malins, L. R.; Prieto, L.; Brandt, T. A.; Collins, M. R.; Gallego, G. M.; Sach, N. W.; Spangler, J. E.; Zhu, H.; Zhu, J.; Baran, P. S., Strain-release amination. *Science* **2016**, *351*, 241-246; (d) Gaoni, Y.; Tomazic, A., Bridgehead reactivity, nucleophilic and radical additions, and lithium aluminum hydride reduction of 1-(arylsulfonyl)bicyclobutanes: general access to substituted, functionalized cyclobutanes. Syntheses of (.+-.)-citrilol acetate, (.+-.)-junionone, and the tricyclo[3.3.0.01,4]octane and tricyclo[4.3.0.01,7]nonane ring systems. *J. Org. Chem.* **1985**, *50*, 2948-2957; (e) Gaoni, Y.; Tomazic, A.; Potgieter, E., Stereochemistry of addition of organocopper reagents and of the hydride ion to 1-(arylsulfonyl)bicyclo[1.1.0]butanes. *J. Org. Chem.* **1985**, *50*, 2943-2947.

(4) (a) Ociepa, M.; Wierzba, A. J.; Turkowska, J.; Gryko, D., Polarity-Reversal Strategy for the Functionalization of Electrophilic Strained Molecules via Light-Driven Cobalt Catalysis. *J. Am. Chem. Soc.* **2020**, *142*, 5355-5361; (b) Ernouf, G.; Chirkin, E.; Rhyman, L.; Ramasami, P.; Cintrat, J.-C., Photochemical Strain-Release-Driven Cyclobutylation of C(sp3)-Centered Radicals. *Angew. Chem. Int. Ed.* **2020**, *59*, 2618-2622; (c) Pratt, C. J.; Aycock, R. A.; King, M. D.; Jui, N. T., Radical α-C–H Cyclobutylation of Aniline Derivatives. *Synlett* **2020**, *31*, 51-54; (d) For a visible light promoted radical addition to bicyclo[1.1.0]butanes that proceeds in the absence of a photoredox catalyst, see: Silvi, M.; Aggarwal, V. K., Radical Addition to Strained σ-Bonds Enables the Stereocontrolled Synthesis of Cyclobutyl Boronic Esters. *J. Am. Chem. Soc.* **2019**, *141*, 9511-9515; (e) Wu, X.; Hao, W.; Ye, K.-Y.; Jiang, B.; Pombar, G.; Song, Z.; Lin, S., Ti-Catalyzed Radical Alkylation of Secondary and Tertiary Alkyl Chlorides Using Michael Acceptors. *J. Am. Chem. Soc.* **2018**, *140*, 14836-14843.

(5) (a) Kerner, M. J.; Wipf, P., Semipinacol-Type Rearrangements of [3-(Arylsulfonyl)bicyclo[1.1.0]butan-1-yl]alkanols. *Org. Lett.* **2021**, *23*, 3615-3619; (b) Fawcett, A.; Biberger, T.; Aggarwal, V. K., Carbopalladation of C–C σ-bonds enabled by strained boronate complexes. *Nat. Chem.* **2019**, *11*, 117-122; (c) Walczak, M. A. A.; Krainz, T.; Wipf, P., Ring-Strain-Enabled Reaction Discovery: New Heterocycles from Bicyclo[1.1.0]butanes. *Acc. Chem. Res.* **2015**, *48*, 1149-1158.

(6) Panish, R. A.; Chintala, S. R.; Fox, J. M., A Mixed-Ligand Chiral Rhodium(II) Catalyst Enables the Enantioselective Total Synthesis of Piperarborenine B. *Angew. Chem. Int. Ed.* **2016**, *55*, 4983-4987.

(7) Tokunaga, K.; Sato, M.; Kuwata, K.; Miura, C.; Fuchida, H.; Matsunaga, N.; Koyanagi, S.; Ohdo, S.; Shindo, N.; Ojida, A., Bicyclobutane Carboxylic Amide as a Cysteine-Directed Strained Electrophile for Selective Targeting of Proteins. *J. Am. Chem. Soc.* **2020**, *142*, 18522-18531.

(8) (a) Tse, E. G.; Houston, S. D.; Williams, C. M.; Savage, G. P.; Rendina, L. M.; Hallyburton, I.; Anderson, M.; Sharma, R.; Walker, G. S.; Obach, R. S.; Todd, M. H., Nonclassical Phenyl Bioisosteres as Effective Replacements in a Series of Novel Open-Source Antimalarials. *J. Med. Chem.* **2020**, *63*, 11585-11601; (b) Bychek, R. M.; Hutskalova, V.; Bas, Y. P.; Zaporozhets, O. A.; Zozulya, S.; Levterov, V. V.; Mykhailiuk, P. K., Difluoro-Substituted Bicyclo[1.1.1]pentanes for Medicinal Chemistry: Design, Synthesis, and Characterization. *J. Org. Chem.* **2019**, *84*, 15106-15117; (c) Measom, N. D.; Down, K. D.; Hirst, D. J.; Jamieson, C.; Manas, E. S.; Patel, V. K.; Somers, D. O., Investigation of a bicyclo[1.1.1]pentane as a phenyl replacement within an LpPLA2 inhibitor. *ACS Med. Chem. Lett.* **2017**, *8*, 43-48; (d) Stepan, A. F.; Subramanyam, C.; Efremov, I. V.; Dutra, J. K.; O'Sullivan, T. J.; DiRico, K. J.; McDonald, W. S.; Won, A.; Dorff, P. H.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Riddell, D. R.; Kauffman, G. W.; Kormos, B. L.; Zhang, L.; Lu, Y.; Capetta, S. H.; Green, M. E.; Karki, K.; Sibley, E.; Atchison, K. P.; Hallgren, A. J.; Oborski, C. E.; Robshaw, A. E.; Sneed, B.; O'Donnell, C. J., Application of the bicyclo[1.1.1]pentane motif as a nonclassical phenyl ring bioisostere in the design of a potent and orally active γ-secretase inhibitor. *J. Med. Chem.* **2012**, *55*, 3414-3424; (e) Locke, G. M.; Bernhard, S. S. R.; Senge, M. O., Nonconjugated Hydrocarbons as Rigid-Linear Motifs: Isosteres for Material Sciences and Bioorganic and Medicinal Chemistry. *Chem. Eur. J.* **2019**, *25*, 4590-4647.

(9) (a) Ma, X.; Pinto, W.; Pham, L. N.; Sloman, D. L.; Han, Y., Synthetic Studies of 2,2-Difluorobicyclo[1.1.1]pentanes (BCP-F2): The Scope and Limitation of Useful Building Blocks for Medicinal Chemists. *Eur. J. Org. Chem.* **2020**, 4581-4605; (b) Ma, X.; Sloman, D. L.; Han, Y.; Bennett, D. J., A Selective Synthesis of 2,2-Difluorobicyclo[1.1.1]pentane Analogues: "BCP-F2". *Org. Lett.* **2019**, *21*, 7199-7203; (c) Applequist, D. E.; Renken, T. L.; Wheeler, J. W., Polar substituent effects in 1,3-disubstituted bicyclo[1.1.1]pentanes. *J. Org. Chem.* **1982**, *47*, 4985-4995; (d) E. Applequist, D.; W. Wheeler, J., Synthesis of 1,3-disubstituted bicyclo[1.1.1]pentanes. *Tetrahedron Lett.* **1977**, *18*, 3411-3412.

(10) Qin, C.; Davies, H. M. L., Enantioselective Synthesis of 2-Arylbicyclo[1.1.0]butane Carboxylates. *Org. Lett.* **2013**, *15*, 310-313.

(11) Chen, K.; Huang, X.; Kan, S. B. J.; Zhang Ruijie, K.; Arnold Frances, H., Enzymatic construction of highly strained carbocycles. *Science* **2018**, *360*, 71-75.

(12) (a) Ermolovich, Y.; Barysevich, M. V.; Adamson, J.; Rogova, O.; Kaabel, S.; Järving, I.; Gathergood, N.; Snieckus, V.; Kananovich, D. G., Site-Selective and Stereoselective C–H Functionalization of N-Cyclopropylamides via a Directed Remote Metalation Strategy. *Org. Lett.* **2019**, *21*, 969-973; (b) Yasui, M.; Ota, R.; Tsukano, C.; Takemoto, Y., Synthesis of cis-/All-cis-Substituted Cyclopropanes through Stereocontrolled Metalation and Pd-Catalyzed Negishi Coupling. *Org. Lett.* **2018**, *20*, 7656-7660; (c) Lauru, S.; Simpkins, N. S.; Gethin, D.; Wilson, C., Enantioselective synthesis of cyclopropylcarboxamides using s-BuLi–sparteine-mediated metallation. *Chem. Commun.* **2008**, 5390-5392; (d) Zhang, M.-X.; Eaton, P. E., BuMgNiPr2: A New Base for Stoichiometric, Position-Selective Deprotonation of Cyclopropane Carboxamides and Other Weak CH Acids. *Angew. Chem. Int. Ed.* **2002**, *41*, 2169-2171; (e) Eaton, P. E.; Daniels, R. G.; Casucci, D.; Cunkle, G. T.; Engel, P., Amide activation for cyclopropane ortho-lithiation. *J. Org. Chem.* **1987**, *52*, 2100-2102.

(13) Hughes, J. M. E.; Scarlata, D. A.; Chen, A. C. Y.; Burch, J. D.; Gleason, J. L., Aminoalkylation of [1.1.1]Propellane Enables Direct Access to High-Value 3-Alkylbicyclo[1.1.1]pentan-1-amines. *Org. Lett.* **2019**, *21*, 6800-6804.

(14) Low temperature single crystal X-ray diffraction data for **2i** were collected using a Rigaku Oxford SuperNova diffractometer at 150 K. Raw

frame data were reduced using CrysAlisPro and the structures were solved using 'Superflip' [Palatinus, L.; Chapuis, G., *J. Appl. Cryst.* **2007**, *40*, 786–790] before refinement with CRYSTALS [(a) Parois, P.; Cooper, R. I.; Thompson, A. L., *Chem. Cent. J.* **2015**, *9*:30. (b) Cooper, R. I.; Thompson, A. L.; Watkin, D. J., *J. Appl. Cryst.* **2010**, *43*, 1100–1107]. Further details about the refinements, including disorder modelling and restraints, are documented in the CIF; Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC 2117136) and can be obtained via www.ccdc.cam.ac.uk/data_request/cif.

(15) See the Supporting Information for details.

(16) An alternative route to enantioenriched polysubstituted BCBs could be envisaged by functionalization of BCBs prepared through asymmetric cyclopropanation, see Refs 2c and 10.

(17) Hoz, S.; Livneh, M.; Cohen, D., Cyclobutane-bicyclobutane system. 11. Mechanism and stereochemistry of general acid-catalyzed additions to bicyclobutane. *J. Org. Chem.* **1986**, *51*, 4537-4544.

(18) Vasin, V. A.; Petrov, P. S.; Kalyazin, V. A.; Razin, V. V., Chemo-, regio-, and stereoselectivity in acid-catalyzed hydromethoxylation of tricyclo[4.1.0.02,7]hept-1-yl and 7-methyltricyclo[4.1.0.02,7]hept-1-yl phenyl sulfones. *Russian Journal of Organic Chemistry* **2010**, *46*, 812-819.

(19) Roberts, J. D.; Mazur, R. H., Small-Ring Compounds. IV. Interconversion Reactions of Cyclobutyl, Cyclopropylcarbinyl and Allylcarbinyl Derivatives. *J. Am. Chem. Soc.* **1951**, *73*, 2509-2520.

(20) While not directly analogous to the current setting, we propose that the fused-ring nature of the BCB could exert a similar effect on an endocyclic leaving group. See: Wiberg, K. B.; Lampman, G. M.; Ciula, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J., Bicyclo[1.1.0]butane. *Tetrahedron* **1965**, *21*, 2749-2769.

(21) Merrer, D. C.; Doubleday, C., Dynamic control of dichlorocarbene addition to cyclopropene. *Journal of Physical Organic Chemistry* **2011**, *24*, 947-951.

(22) Schwartz, R. L.; Davico, G. E.; Ramond, T. M.; Lineberger, W. C., Singlet–Triplet Splittings in CX2 (X = F, Cl, Br, I) Dihalocarbenes via Negative Ion Photoelectron Spectroscopy. *The Journal of Physical Chemistry A* **1999**, *103*, 8213-8221.

(23) Rablen, P. R.; Paiz, A. A.; Thuronyi, B. W.; Jones, M., Computational Investigation of the Mechanism of Addition of Singlet Carbenes to Bicyclobutanes. *J. Org. Chem.* **2009**, *74*, 4252-4261.

(24) We note in passing that attempted BCP synthesis using the related phenyl chloro carbene afforded a product that decomposed on purification. Similar observations have been made on the stability of Ph,OH-bridge substituted BCPs: Padwa, A.; Alexander, E., Thermal and solvolytic studies with the 2-phenylbicyclo [1.1.1] pentan-2-ol system. *J. Am. Chem. Soc.* **1970**, *92*, 5674-5681.