Polysubstituted Benzene Bioisosteres and Beyond: Photochemical Access to Bicyclo[2.1.1]hexanes

Marius Reinhold,[a] Justin Steinebach,[a] Johannes C. L. Walker*[a]

[a] Marius Reinhold MSc., Justin Steinebach, Jun.-Prof. Dr. Johannes C L. Walker
Institut für Organische und Biomolekulare Chemie
Georg-August-Universität-Göttingen
Tammannstr. 2, 37077 Göttingen
E-mail: johannes.walker@chemie.uni-goettingen.de

Supporting information for this article is given via a link at the end of the document.

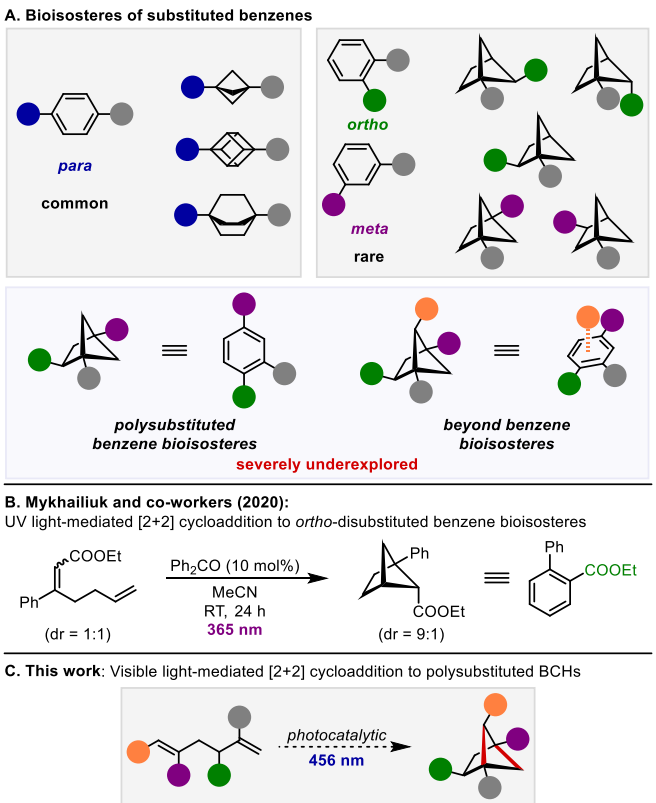
Abstract: Bicyclo[2.1.1]hexanes are a versatile platform for the exploration of chemical space, with 10 different substituent vectors available. Disubstituted bicyclo[2.1.1]hexanes have been proposed as bioisosteres of *ortho*- and *meta*-substituted benzenes, both far less investigated than their *para*-benzene counterparts, but the bicyclo[2.1.1]hexane platform also provides new exciting opportunities for molecular design. Polysubstituted benzene bioisosteres and structures bearing substituent geometries that are non-existant in aromatic chemical space can be prepared using the bicyclo[2.1.1]hexane platform. We report the development of a photocatalytic intramolecular [2+2] cycloaddition approach to polysubstituted bicyclo[2.1.1]hexanes that provides access to these high-value motifs and enables the investigation of unexplored chemical space.

The inclusion of more saturated and three-dimensional structures into drug-discovery programmes has been recognized as a critical requirement for the future of pharmaceutical drug design.[1] The incorporation of these structures has been demonstrated to improve the physiochemical and pharmacokinetic profile of drug candidates and compounds with a higher degree of saturated, sp^3 hybridized centres tend to progress further through clinical trials to commercialization.[2] However, general synthetic strategies to useful and versatile saturated structural cores remain extremely rare.[3]

One area that has received attention is the development of bioisosteres of *para*-substituted benzene rings (Scheme 1A).[4,5] Disubstituted cubanes,[6,7] and bridged bicyclic bicyclo[2.2.2]octanes and bicyclo[1.1.1]pentanes[8] (BCPs) have been proposed as saturated replacements for *para*-substituted benzene rings in drug compounds. For example, the replacement of a benzene ring in *Darapladib* with a BCP led to an almost three-fold increase in aqueous solubility.[9] However, routes to *ortho*- and *meta*-substituted benzenes bioisosteres are comparatively rare.[10,11,12] This is despite the importance of such motifs to drug design; 224 FDA approved drugs contain *ortho*-substituted benzenes, and 68 contain *meta*-substituted benzenes.[13] Recently, it was proposed that substituted bicyclo[2.1.1]hexanes (BCHs) could be used as a platform for both *ortho*- and *meta*-substituted benzene bioisosteres.[5] Extensions of this concept to bioisosteres of benzenes containing three or more substituents are rarer still,[14] although such compounds would be highly useful building blocks for drug discovery; for example, some 328 FDA approved drugs contain a 1,2,4-trisubstituted benzene.[13,15]

Beyond the development of bioisosteres, saturated and three-dimensional structures such as bridged bicyclic compounds provide exciting opportunities to move into chemical space not usually accessible to aromatic motifs, giving us new opportunities to design drug candidates that can bind ever more precisely with their biological target, improving selectivity and reducing target promiscuity.[2b] For example, some tetrasubstituted bicyclo[2.1.1]hexanes (BCHs) could be thought of as analogues of benzene systems bearing a substituent perpendicular to the π-system (see Scheme 1A).

We are interested in developing versatile synthetic methods towards high-value structurally complex motifs. We recently published an organophotocatalytic [2+2] cycloaddition of electron-deficient styrenes to cyclobutanes and of 1,6-heptadienes to bicyclo[3.2.0]heptanes.[16] Their 1,5-hexadiene homologues undergo crossed [2+2] cycloaddition to give BCHs with protocols harnessing direct irradiation of the substrate[17] and triplet sensitization with UV light both known.[18] Recently, Mykhailiuk and co-workers reported a UV light/benzophenone-mediated cycloaddition of 1,5-hexadienes to give disubstituted BCHs that could function as *ortho*-substituted benzene bioisosteres (Scheme 1B).[10a] However, this reactivity platform is potentially extremely versatile and we believed it could be used to give unified access to a whole range of *ortho*- and *meta*-substituted

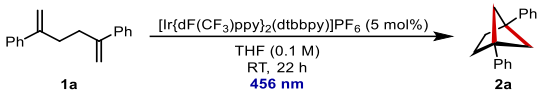


Scheme 1. Bioisosteres of Benzene and intramolecular crossed [2+2] cycloaddition as a strategy to polysubstituted bicyclo[2.1.1]hexanes.

benzene bioisosteres, polysubstituted benzene bioisosteres, and allow us to build compounds that have no direct analogue in aromatic chemical space (Scheme 1C). In addition, we wanted to develop a visible light-mediated procedure that would eliminate the need to use UV light sources and tolerate a broad range of functional groups.[19] We now report the results of our investigations.

Reaction optimization was performed with diene **1a**, and resulting in the following reactions conditions: [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ (5 mol%), THF (0.1 M), RT, 22 h, irradiation at 456 nm (for details see Supporting Information). Under these reaction conditions, diene **1a** was transformed into BCH **2a** in near quantitative yield (Table 1, Entry 1). For comparison with other commonly used photocatalysts, reaction with [Ru(bpy)$_3$]Cl$_2$ afforded none of the desired BCH **2a** (Entry 2), but the organic dye 4CzIPN allowed for moderate conversion over an extended reaction time (Entry 3). Reducing the catalyst loading of the Iridium photocatalyst led to a lower conversion (Entry 4), and control experiments in the absence of photocatalyst (Entry 5) or irradiation (Entry 6) led to no formation of BCH **2a**. Performing the reaction on more preperatively relevant scales was also successful, with BCH **2a** being isolated in 94% yield on 0.19 mmol scale (Entry 7) and 91% yield on 1.00 mmol scale (Entry 8).

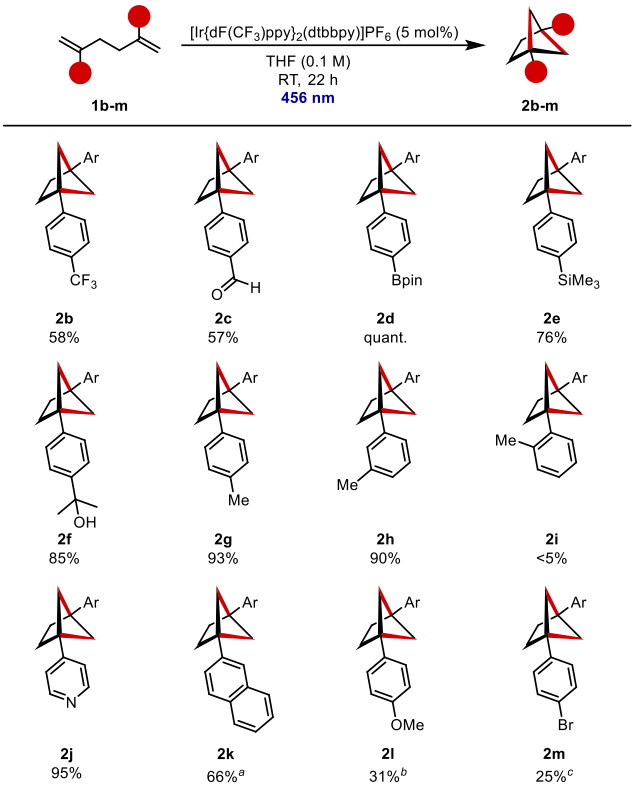
Table 1. Optimization of reaction conditions.[a]



entry	deviation from standard conditions	yield (%)[b]
1	none	96
2	[Ru(bpy)$_3$]Cl$_2$	<5
3	4CzIPN, 48 h	55
4	1 mol% [Ir]	27[c]
5	No photocatalyst	<5
6	Reaction in the dark	<5
7	44.5 mg, 0.19 mmol	94[d]
8	234 mg, 1.00 mmol, 66 h	91[d]

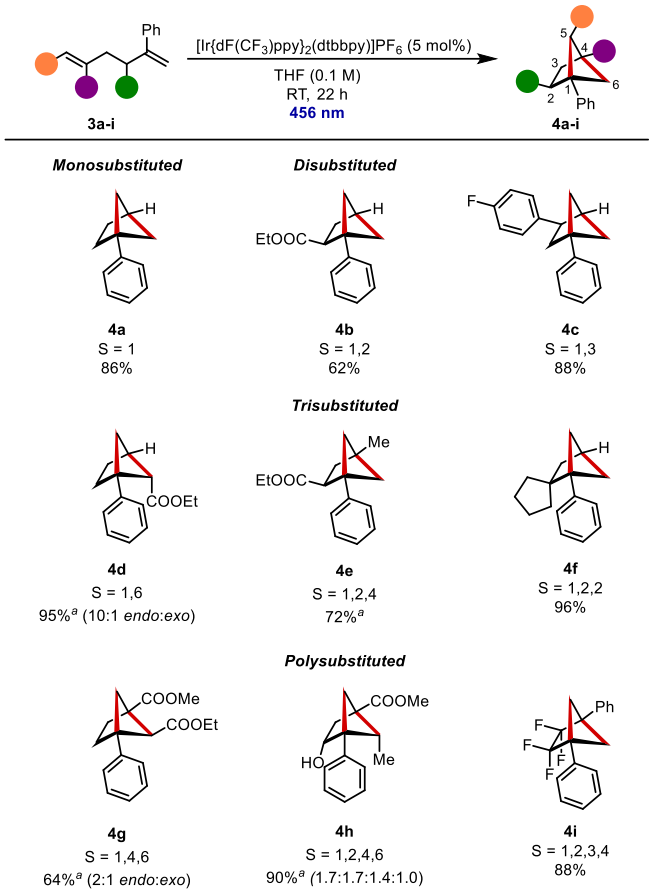
[a] The reactions were performed on 10 mg (of **1a**) scale and were degassed by three freeze-pump-thaw cycles prior to irradiation. For further details see Supporting Information. [b] Yield estimated from the ^{1}H NMR of the reaction mixture relative to 1,3,5-trimethoxybenzene as internal standard. [c] Conversion estimated by ^{1}H NMR spectroscopy relative to unreacted **1a**. [d] Isolated yield.

With optimized conditions in hand, we turned our attention to the substrate scope of the reaction, with initial investigations concentrating on functional group tolerance (Scheme 2). A range of disubstituted dienes **1b**-**m** were prepared (see Supporting Information for details) and subjected to the optimized reaction conditions. Electron-withdrawing substituents including trifluoromethyl (in **2b**), aldehydes (in **2c**) and boronate esters (in **2d**) were all well tolerated, with boronate ester **2d** a particular standout, being prepared in quantitative yield. Electron-donating substituents such as trimethylsilyl (in **2e**), unprotected tertiary alcohols (in **2f**) and alkyl groups (in **2g**-**h**) could also be incorporated. A series of differently-substituted tolyl derivatives **1g**-**i** were prepared to establish the effect of increased steric hinderance on the reaction. Both *para*-methyl- (in **2g**) and *meta*-methyl-substituted (in **2h**) BCHs could be prepared but the *ortho*-methyl substituents in **1i** prevented the desired cycloaddition. Heterocyclic substituents such as pyridines (in **2j**) as well as extended aromatic systems (in **2k**) were also tolerated. Methoxy (in **2l**) and bromide substituents (in **2m**) could both be incorporated but resulted in lower conversions to the desired products and the final BCHs **2l**-**m** could not be separated from unreacted dienes **1l**-**m**.



Scheme 2. Scope of photocatalytic crossed [2+2] cycloaddition; functional group tolerance. Reactions were performed on 0.20 mmol scale. Yields refer to isolated material after flash column chromatography unless otherwise stated. [a] 66 h reaction time. [b] Isolated together with unreacted diene **1l**. [c] Yield estimated from the ^{1}H NMR of the reaction mixture relative to 1,3,5-trimethoxybenzene as internal standard.

We then wanted to explore the variety of substitution patterns that are accessible under our developed reaction conditions (Scheme 3). To make comparison between compounds simpler, the numbered positions of the substituents are given alongside the formed structure. To begin with, monosubstituted BCH **4a**, bearing a single bridgehead aryl group, could be formed in 86% yield. Disubstituted BCHs with 1,2-substitution (as in **4b**), 1,3-substitution (as in **4c**), and 1,6-substitution (as in **4d**) were also all accessible. **4d** was formed in 10:1 *endo*:*exo* selectivity. Moving onto trisubstituted BCH frameworks, 1,2,4-trisubstituted BCH **4e** was formed in 72% yield and 1,2,2-substituted spirocycle **4f** was formed in 96% yield. 1,4,6-trisubstituted BCH **4g**, bearing two different ester functional groups, was prepared in 64% yield. BCHs containing more than three substituents could also be formed. 1,2,4,6-tetrasubstituted BCH **4h**, which contains both an unprotected alcohol and an ester functionality, was prepared in 90% yield as a mixture of diastereomers. Fluorinated bicyclo[1.1.1]pentanes are highly desirable building blocks for medicinal chemistry.[20] The corresponding tetrafluorinated BCH **4i** could be prepared in 88% yield.



Scheme 3. Scope of photocatalytic crossed [2+2] cycloaddition; accessing different vectors. Reactions were performed on 0.20 mmol scale. Yields refer to isolated material after flash column chromatography. S = substitution. [a] 66 h reaction time.

Attention then turned to investigating the reaction mechanism. Using cyclic voltammetry, the oxidation potential of diene **1a** was measured to be $E(\mathbf{1a}^{+}/\mathbf{1a})$ = +1.64 V vs SCE, outside the range of the Iridium photocatalyst [E(Ir*/Ir^{-}) = +1.21 V vs SCE] (Figure 1A).[21] The reduction potential of **1a** was measured to be $E(\mathbf{1a}/\mathbf{1a}^{-})$ = –2.72 V vs SCE, again outside the range of the Iridium photocatalyst [E(Ir*/Ir+) = –0.89 V vs SCE].[21] This suggests that a redox mechanism is unlikely. However, the reported excited state of styrenes lies at approximately 61.7 kcal mol^{-1},[22] which should be accessible to the photocatalyst (61.8 kcal mol^{-1}).[22] In line with this, addition of the known triplet quencher isoprene led to a reduced conversion of diene **1a** (Figure 1B). We therefore propose the following mechanism for the reaction (Figure 1C). The iridium photocatalyst is excited by the 456 nm LEDs and energy transfer from the photoexcited state to diene **1a** leads to photoexcited **1a***. The diradical nature of this intermediate leads to a 5-*exo*-tet cyclisation to diradical **5** and radical recombination gives BCH **2a**.

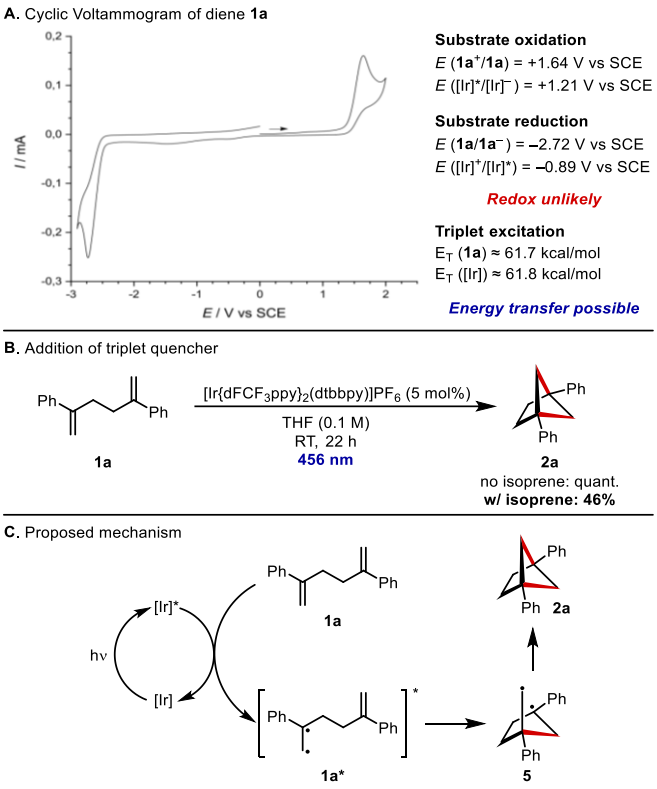


Figure 1. Mechanistic studies and proposed mechanism. A: Cyclic voltammogram of diene **1a** and comparison of redox potentials to those of the photoexcited catalyst. B: Control experiment with the addition of the triplet quencher isoprene. C: Proposed mechanism for the [2+2] cycloaddition reaction.

In conclusion, we have developed a visible light-mediated photocatalytic [2+2] cycloaddition reaction of 1,5-hexadienes that gives flexible access to differently substituted, high-value BCH scaffolds. The reaction tolerates a broad range of functional groups and provides rare and unified access to compounds that could be used as *ortho*-, *meta*-, and polysubstituted benzene bioisosteres. Beyond that, compounds with substituent geometries not found in aromatic chemical space can also be prepared, indicating the potential of both the BCH core and this method to drive the development of functional organic compounds and pharmaceuticals into new directions. The method speaks to the current desire for reactions that enable rapid complexity generation in three-dimensional space and we hope it will find use in the near future!

Acknowledgements

We wish to thank Martin Simon, University of Göttingen for his assistance with HPLC chromatography. M.R thanks the Stiftung Industrieforschung for a scholarship. J.C.L.W. thanks the Fonds der Chemischen Industrie for the award of a Material Cost Allowance. J.C.L.W and M.R thank the Georg-August-Universität Göttingen for financial support. J.C.L.W thanks Prof. Manuel Alcarazo for his continuous generous support and guidance.

Keywords: bioisosteres • photocatalysis • cycloaddition • bicyclo[2.1.1]hexanes • multi-vector

References

[1] (a) D. G. Brown, J. Boström, *J. Med. Chem*. **2016**, *59*, 4443–4458; (b) J. Boström, D. G. Brown, R. J. Young, G. M. Keserü, *Nat. Rev. Drug Discov.* **2018**, *17*, 709–727; (c) D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem*. **2018**, *10*, 383–394.

[2] (a) F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem*. **2009**, *52*, 6752–6756; (b) F. Lovering, *Med. Chem. Commun*. **2013**, *4*, 515–519.

[3] M. Golfmann, J. C. L. Walker, *Commun. Chem.* **2023**, *6*, 9.

[4] For reviews, see: (a) M. A. M. Subbaiah, N. A. Meanwell, *J. Med. Chem.* **2021**, *64*, 14046–14128; (b) E. G. Tse, S. D. Houston, C. M. Williams, G. P. Savage, L. M. Rendina, I. Hallyburton, M. Anderson, R. Sharma, G. S. Walker, R. S. Obach, M. H. Todd, *J. Med. Chem.* **2020**, *63*, 11585–11601; (c) G. M. Locke, S. S. R. Bernhard, M. O. Senge, *Chem. Eur. J.* **2019**, *25*, 4590–4647; (d) Y. P. Auberson, C. Brocklehurst, M. Furegati, T. C. Fessard, G. Koch, A. Decker, L. La Vecchia, E. Briard, *ChemMedChem* **2017**, *12*, 590–598.

[5] P. K. Mykhailiuk, *Org. Biomol. Chem.* **2019**, *17*, 2839–2849.

[6] For reviews, see: (a) T. A. Reekie, C. M. Williams, L. M. Rendina, M. Kassiou, *J. Med. Chem.* **2019**, *62*, 1078–1095; (b) K. F. Biegasiewicz, J. R. Griffiths, G. P. Savage, J. Tsanaktsidis, R. Priefer, *Chem. Rev.* **2015**, *14*, 6719–6745; (c) G. W. Griffin, A. P. Marchand, *Chem. Rev.* **1989**, *89*, 997–1010.

[7] (a) B. A. Chalmers, H. Xing, S. Houston, C. Clark, S. Ghassabian, A. Kuo, B. Cao, A. Reitsma, C.-E. P. Murray, J. E. Stok, G. M. Boyle, C. J. Pierce, S. W. Littler, D. A. Winkler, P. V. Bernhardt, C. Pasay, J. J. De Voss, J. McCarthy, P. G. Parsons, G. H. Walter, M. T. Smith, H. M. Cooper, S. K. Nilsson, J. Tsanaktsidis, G. P. Savage, C. M. Williams, *Angew. Chem. Int. Ed.* **2016**, *55*, 3580–3585; (b) S. D. Houston, T. Fahrenhorst-Jones, H. Xing, B. A. Chalmers, M. L. Sykes, J. E. Stok, C. Farfan Soto, J. M. Burns, P. V. Bernhardt, J. J. De Voss, G. M. Boyle, M. T. Smith, J. Tsanaktsidis, G. P. Savage, V. M. Avery, C. M. Williams, *Org. Biomol. Chem.* **2019**, *17*, 6790–6798.

[8] For reviews, see: (a) J. Turkowska, J. Durka, D. Gryko, *Chem. Commun*. **2020**, *56*, 5718–5734; (b) X. Ma, L. N. Pham, *Asian J. Org. Chem.* **2020**, *9*, 8–22; (c) J. Kanazawa, M. Uchiyama, *Synlett* **2019**, *30*, 1–11; (d) M. D. Levin, P. Kaszynski, J. Michl, *Chem. Rev.* **2000**, *100*, 169–234; (e) E. W. Delia, I. J. Lochert, *Org. Prep. Proced. Int.* **1996**, *28*, 411–441.

[9] N. D. Measom, K, D. Down, D, J. Hirst, C, Jamieson, E, S. Manas, V, K. Patel, D. O. Somers, *ACS Med. Chem. Lett.* **2017**, *8*, 43–48.

[10] For selected routes to *ortho*-substituted benzene bioisosteres, see: (a) A. Denisenko, P. Garbuz, S. V. Shishkina, N. M. Voloshchuk, P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2020**, *59*, 20515–20521; (b) Y. Yang, J. Tsien, J. M. E. Hughes, B. K. Peters, R. R. Merchant, T. Qin, *Nat. Chem.* **2021**, *13*, 950–955; (c) J.-X. Zhao, Y.-X. Chang, C. He, B. J. Burke, M. R. Collins, M. Del Bel, J. Elleraas, G. M. Gallego, T. P. Montgomery, J. J. Mousseau, S. K. Nair, M. A. Perry, J. E. Spangler, J. C. Vantourout, P. S. Baran, *Proc. Natl Acad. Sci. USA* **2021**, *118*, e2108881118.

[11] For selected routes to *meta*-substituted benzene bioisosteres, see: (a) V. V. Levterov, Y. Panasyuk, V. O. Pivnytska, P. K. Mykhailiuk, *Angew. Chem. Int. Ed.* **2020**, *59*, 7161–7167; (b) N. Frank, J. Nugent, B. R. Shire, H. D. Pickford, P. Rabe, A. J. Sterling, T. Zarganes-Tzitzikas, T. Grimes, A. L. Thompson, R. C. Smith, C. J. Schofield, P. E. Brennan, F. Duarte, E. A. Anderson, *Nature* **2022**, *611*, 721–726; (c) T. Iida, J. Kanazawa, T. Matsunaga, K. Miyamoto, K. Hirano, M. Uchiyama, *J. Am. Chem. Soc.* **2022**, *144*, 21848–21852; (d) R. C. Epplin, S. Paul, L. Herter, C. Salome, E. N. Hancock, J. F. Larrow, E. W. Baum, D. R. Dunstan, C. Ginsburg-Moraff, T. C. Fessard, M. K. Brown, *Nat. Commun.* **2022**, *13*, 6056.

[12] For a review of routes to bridge-functionalised bicyclo[1.1.1]pentanes, see: J. M. Anderson, N. D. Measom, J. A. Murphy, D. L. Poole, *Angew. Chem. Int. Ed.* **2021**, *60*, 24754–24769.

[13] According to a search of the database http://www.drugbank.ca on 21/02/2023.

[14] Recently, routes to trisubstituted BCH motifs that would fulfill this requirement have been reported, see: (a) R. Kleinmans, T. Pinkert, S. Dutta, T. O. Paulisch, H. Keum, C. G. Daniliuc, F. Glorius, *Nature* **2022**, *605*, 477–482; (b) R. Guo, Y.-C. Chang, L. Herter, C. Salome, S. E. Braley, T. C. Fessard, M. K. Brown, *J. Am. Chem. Soc.* **202**, *144*, 7988–7994; (c) S. Agasti, F. Beltran, E. Pye, N. Kaltsoyannis, G. E. M. Crisenza, D. J. Procter, *Nat. Chem.* **2023**, *Accepted Article*, DOI = 10.1038/s41557-023-01135-y.

[15] A. Nilova, L.-C. Campeau, E. C. Sherer, D. R. Stuart, *J. Med. Chem.* **2020**, *63*, 13389–13396.

[16] M. Golfmann, L. Glagow, A. Giakoumidakis, C. Golz, J. C. L. Walker, *Chem. Eur. J.* **2023**, *29*, e202202373.

[17] (a) K. J. Crowley, *J. Am. Chem. Soc.* **1964**, *86*, 5692–5693; (b) R. Srinivasan, K. H. Carlough, *J. Am. Chem. Soc*. **1967**, *89*, 4932–4936; (c) J. K. Crandall, C. F. Mayer, *J. Org. Chem.* **1970**, *35*, 3049–3053.

[18] (a) R. S. H. Liu, G. S. Hammond, *J. Am. Chem. Soc.* **1967**, *89*, 4936–4944; (b) C. Yamada, M. Pahk, R. Liu, *J. Chem. Soc. D* **1970**, 882–882; (c) J. J. Bloomfield, D. C. Owsley, *Tetrahedron Lett.* **1973**, *21*, 1795–1798.

[19] In the course of our investigation, the following study into photochemical [2+2] cycloadditions to BCHs were published: (a) L. Herter, I, Koutsopetras, L. Turelli, T. Fessard, C. Salomé, *Org. Biomol. Chem.* **2022**, *20*, 9108–9111; (b) T. Rigotti, T. Bach, *Org. Lett.* **2022**, *24*, 8821–8825.

[20] (a) X. Ma, D. L. Sloman, Y. Han, D. J. Bennett, *Org. Lett.* **2019**, *21*, 7199–7203; (b) R. M. Bychek, V. Hutskalova, Y. P. Bas, O. A. Zaporozhets, S. Zozulya, V. V. Levterov, P. K. Mykhailiuk, *J. Org. Chem.* **2019**, *84*, 15106–15117; (c) X. Ma, Y. Han, D. J. Bennett, *Org. Lett.* **2020**, *22*, 9133–9138.

[21] C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.

[22] F. Strieth-Kalthoff, M. J. James, M. Teders, L. Pitzer, F. Glorius, *Chem. Soc. Rev*. **2018**, *47*, 7190–7202.