Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2023, **14**, 9885

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 16th June 2023
Accepted 30th August 2023

DOI: 10.1039/d3sc03083k

rsc.li/chemical-science

Synthesis of polysubstituted bicyclo[2.1.1]hexanes enabling access to new chemical space†

Marius Reinhold, Justin Steinebach, Christopher Golz and Johannes C. L. Walker *

Saturated bridged-bicyclic compounds are currently under intense investigation as building blocks for pharmaceutical drug design. However, the most common methods for their preparation only provide access to bridgehead-substituted structures. The synthesis of bridge-functionalised species is highly challenging but would open up many new opportunities for molecular design. We describe a photocatalytic cycloaddition reaction that provides unified access to bicyclo[2.1.1]hexanes with 11 distinct substitution patterns. Bridge-substituted structures that represent *ortho*-, *meta*-, and polysubstituted benzene bioisosteres, as well as those that enable the investigation of chemical space inaccessible to aromatic motifs can all be prepared using this operationally simple protocol. Proof-of-concept examples of the application of the method to the synthesis of saturated analogues of biorelevant trisubstituted benzenes are also presented.

Introduction

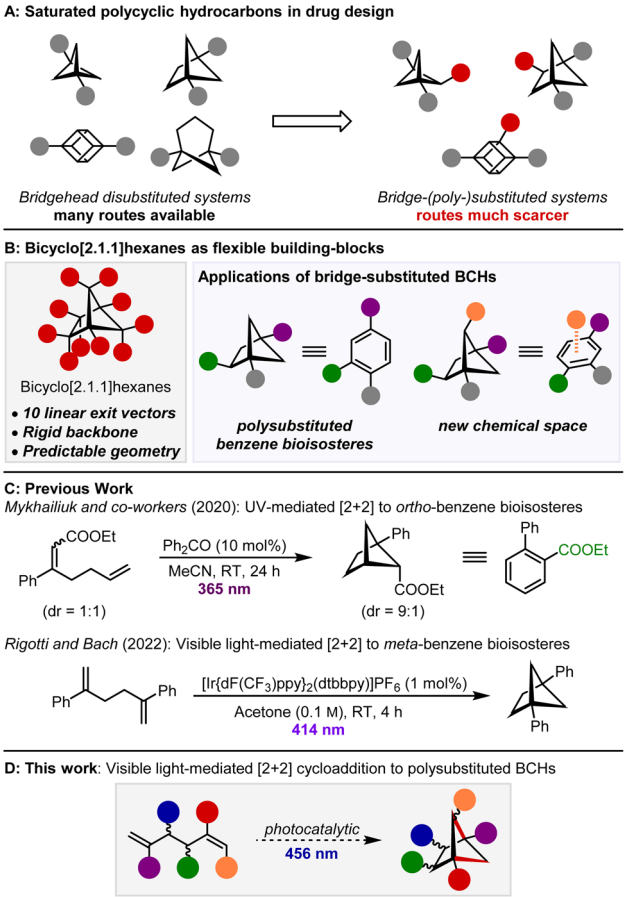
The inclusion of more saturated and three-dimensional structures in drug-discovery programmes has been identified as a key goal of future pharmaceutical research.[1,2] In this context, the use of bridgehead-disubstituted bridged bicyclic compounds has seen enormous growth in recent years (Scheme 1A). Building on early work on the preparation of *para*-disubstituted cubanes,[3,4] bridgehead disubstituted bicyclo[1.1.1]pentanes are now frequently employed as bioisosteres of *para*-substituted benzenes[5,6] and more recently, bridgehead disubstituted bicyclo[3.1.1]heptanes[7] and bicyclo[2.1.1]hexanes[8] have been prepared as bioisosteres of *meta*-substituted benzene.[9,10] However, in these examples, the bridge positions of the polycyclic scaffold remain untouched and therefore unutilised, despite the opportunities that their functionalisation would provide for drug design (Scheme 1B). For example, substitution of the bridge positions of bicyclo[2.1.1]hexanes (BCHs) could be used to extend the bioisostere concept to benzenes containing three or more substituents (328 U.S. Food and Drug Administration approved drugs contain a 1,2,4-trisubstituted benzene)[11,12] and the additional exit vectors from the bridge positions provide opportunities to explore chemical space that is inaccessible to aromatic motifs. As just one example, the apical substituent of a polysubstituted BCH would occupy the space of a hypothetical substituent above the π-system of a benzene ring.

Exploration of these opportunities is currently hampered by the scarcity of methods that enable the preparation of the required compounds. Selective functionalisation of the bridge positions *via* C–H functionalisation or cross-coupling approaches is challenging, with only a handful of examples for bicyclo[1.1.1]pentanes[13,14] and the related cubanes reported.[15] For example, MacMillan and co-workers reported a two-step bridge functionalisation of bicyclo[1.1.1]pentanes *via* bromination and subsequent metallaphotoredox amination or arylation.[13a] Examples of the functionalisation of BCHs are particularly rare.[16] *De novo* approaches which install additional substituents directly and offer a complementary approach to this challenge are emerging, but remain uncommon.[17] The recent reports of fragment insertion into bicyclo[1.1.0]butanes are powerful examples of the concept.[18,19] Cleavage of the central C–C bond enables insertion of alkenes,[18a–e,g,i,k] ketones[18h] or even ring-opened cyclopropanes[18j,f] and leads to a range of bridge-substituted structures. Despite these important advances, the above methods typically only open up one or two new substitution patterns. The ideal strategy would offer greater flexibility and provide predictable access to multiple different substitution patterns using a common disconnection. This would streamline the synthesis of these compounds and be extremely powerful for evaluating their use in drug discovery.

We recently published an organophotocatalytic [2 + 2] cycloaddition of 1,6-heptadienes to fused bicyclo[3.2.0]heptanes.[20] The 1,5-hexadiene homologues are known to instead undergo crossed [2 + 2] cycloaddition to give the bridged BCHs, either by direct irradiation of the substrate[21] or triplet sensitization with ultraviolet (UV) light.[22] Recently, Mykhailiuk and co-workers reported a UV light/benzophenone-mediated protocol to bridge-substituted 1,5-disubstituted BCHs that

Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstr. 2, 37077 Göttingen, Germany. E-mail: johannes.walker@chemie.uni-goettingen.de

† Electronic supplementary information (ESI) available. CCDC 2261999–2262001 and 2289323–2289325. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3sc03083k



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

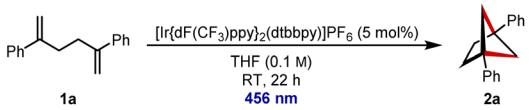
could function as *ortho*-substituted benzene bioisosteres (Scheme 1C).[17b,23,24] However, this reactivity platform is extremely versatile and we believed it could be used to give targeted access to the 10 different exit vectors of BCHs (Scheme 1D). This in turn would enable preparation of a whole range of differently-substituted BCHs, containing various combinations of bridge and bridgehead substituents, consistent with the reaction design criteria outlined above. 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.

During the course of our investigation, Fessard, Salomé and co-workers[16c] and Rigotti and Bach (Scheme 1C)[8a] reported related [2 + 2] cycloadditions of 1,5-hexadienes. While these methods are limited to 1,2- and 1,4-disubstituted BCHs respectively, we are able to prepare BCHs with in total 11 distinct substitution patterns, and provide examples of the use of the method to the preparation of saturated analogues of biorelevant trisubstituted benzenes.

Results and discussion

We began with model diene **1a**, and reaction optimization revealed that [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$ could catalyse the

Table 1 Optimization of reaction conditions



Entry[a]	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]

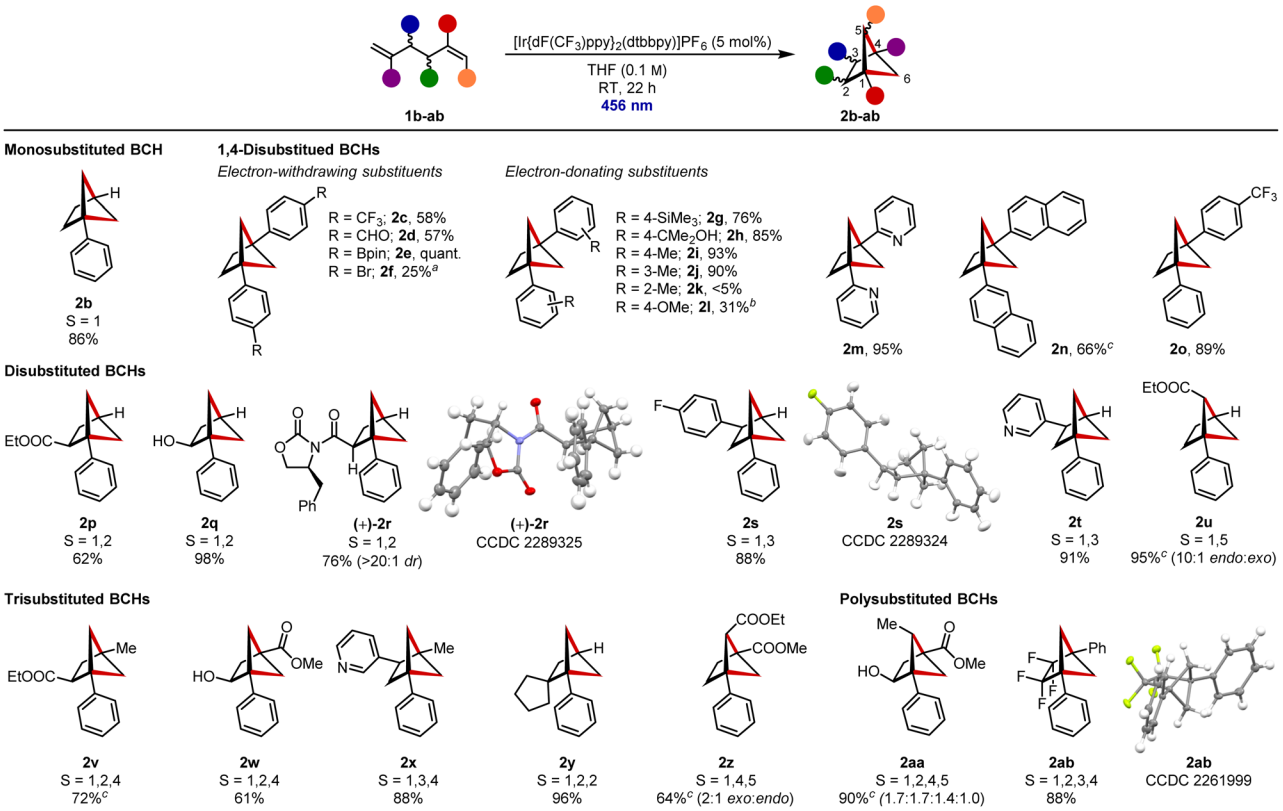
[a] The reactions were performed on 10 mg (of **1a**) scale and were degassed by three freeze–pump–thaw cycles prior to irradiation. For further details see ESI. [b] Yield estimated from the ^{1}H NMR spectrum of the reaction mixture relative to 1,3,5-trimethoxybenzene as internal standard. [c] Conversion estimated by ^{1}H NMR spectroscopy relative to unreacted **1a**. [d] Isolated yield. [Ir] = [Ir{dF(CF$_3$)ppy}$_2$(dtbbpy)]PF$_6$.

desired [2 + 2] cycloaddition with irradiation at 456 nm (for further details of the optimisation, see ESI†). Under these 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 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 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 larger 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).

With optimized conditions in hand, we turned our attention to the substrate scope of the reaction (Scheme 2). A range of disubstituted dienes **1b–1ab** were prepared (see ESI for details†) and subjected to the optimized reaction conditions. All contained at least one styrene-type motif, which is required for photoexcitation. To make comparison between differently substituted BCHs simpler, the numbered positions of the substituents are given alongside the formed structure.

To begin with, monosubstituted BCH **2b**, bearing a single bridgehead phenyl group, was formed in 86% yield.[22b] A selection of disubstituted BCHs were then prepared to enable assessment of the functional group tolerance of the reaction. Electron-withdrawing substituents including a trifluoromethyl group (in **2c**), aldehyde (in **2d**) and boronate ester (in **2e**) were well tolerated. Boronate ester **2e** was a standout, being prepared in quantitative yield. Bromide substituents could also be incorporated but resulted in lower conversion to the target BCH **2f**.

Electron-donating substituents such as a trimethylsilyl group (in **2g**) and an unprotected tertiary alcohol (in **2h**) were also tolerated. A series of tolyl derivatized dienes **1i–k** was



Scheme 2 Scope of the photocatalytic crossed [2 + 2] cycloaddition. Reactions were performed on 0.20 mmol scale. Yields refer to isolated material after flash column chromatography. S = substituent position. [a] Yield estimated from the ^{1}H NMR spectrum of the reaction mixture relative to 1,3,5-trimethoxybenzene as internal standard. [b] Isolated together with unreacted diene **1l**. [c] 66 h reaction time. Displacement ellipsoids are drawn at 50% probability level.

prepared to establish the effect of increased steric hindrance on the reaction; both *para*-tolyl- (in **2i**) and *meta*-tolyl-substituted BCHs (in **2j**) could be prepared, but the *ortho*-tolyl substituents of diene **1k** prevented the desired cycloaddition. Methoxy substituents (in **2l**) led to lower conversions. Heteroaromatic rings such as pyridines (in **2m**) as well as extended aromatic systems (in **2n**) could, however, be successfully used in place of phenyl substituents to facilitate photochemical activation. Rigotti and Bach have previously prepared a wide range of 1,4-disubstituted BCHs bearing two different substituents.[8a] We additionally prepared heterodiaryl-1,4-disubstituted BCH **2o** in 89% yield.

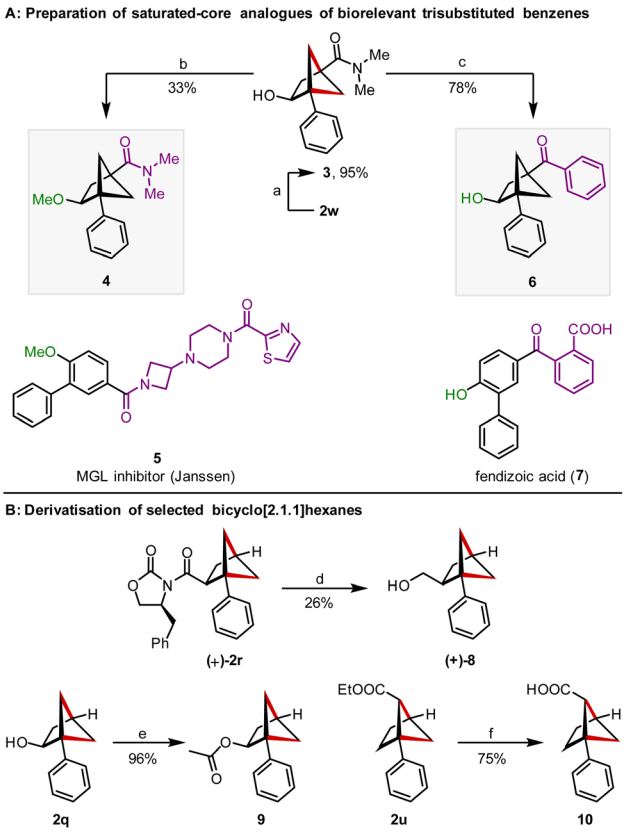
Our focus then shifted to the preparation of disubstituted BCHs that could be used as *ortho*- or *meta*-benzene bioisosteres.[9c] 1,2-Disubstituted BCH **2p**, containing a useful ester function group handle at the bridge 2-position, could be accessed in 62% yield. An alcohol functional group could also be installed in this position, with BCH **2q** then being isolated in 98% yield. Importantly, we were able to demonstrate that stereochemical information in the carbon backbone was retained through the cycloaddition. BCH (+)-**2r** was prepared in 76% yield and as a single diastereomer from the corresponding diene (also single diastereomer) and no evidence of epimerisation of the α-carbonyl stereocentre could be identified by ^{1}H NMR spectroscopy. The absolute (*S*,*S*) stereochemistry was additionally confirmed by X-ray analysis. 1,3-Disubstituted BCHs **2s** and **2t**, bearing a fluorinated aryl ring and a pyridine respectively at the bridge 3-position, were formed in 88% and 91% yield. 1,5-Disubstituted BCH **2u**, with an ester on a single-carbon bridge, was formed in high selectively (10 : 1) as the *endo* diastereomer (*endo* diastereomer has the ester substituent pointing into the larger, 5-membered ring) and was isolated in an excellent 95% yield.[17b]

Moving onto trisubstituted BCH frameworks, 1,2,4-trisubstituted BCH **2v**, which contains both aromatic and aliphatic bridgehead substituents as well as an ester at the bridge 2-position, was formed in 72% yield. 1,2,4-Trisubstituted BCH **2w**, bearing an unprotected alcohol at the bridge 2-position, was prepared in 61% yield and 1,3,4-trisubstituted BCH **2x** with a pyridine at the bridge 3-position was isolated in 88% yield. These structures could be considered as potential bioisosteres of the corresponding trisubstituted benzenes. We were also able to prepare 1,2,2-substituted BCH **2y** in 96% yield, which contains a spirocyclic centre at the bridge 2-position. 1,4,5-Trisubstituted BCH **2z**, bearing a methyl ester at the bridgehead position and ethyl ester on the single-carbon bridge, was prepared in 64% yield and 2 : 1 (*exo* : *endo*) selectivity.[25] Here, the bridge ethyl ester adopts an *ortho*-like position, but is laterally offset relative to the plane of the *meta*-like bridgehead substituents, a spatial disposition inaccessible in aromatic

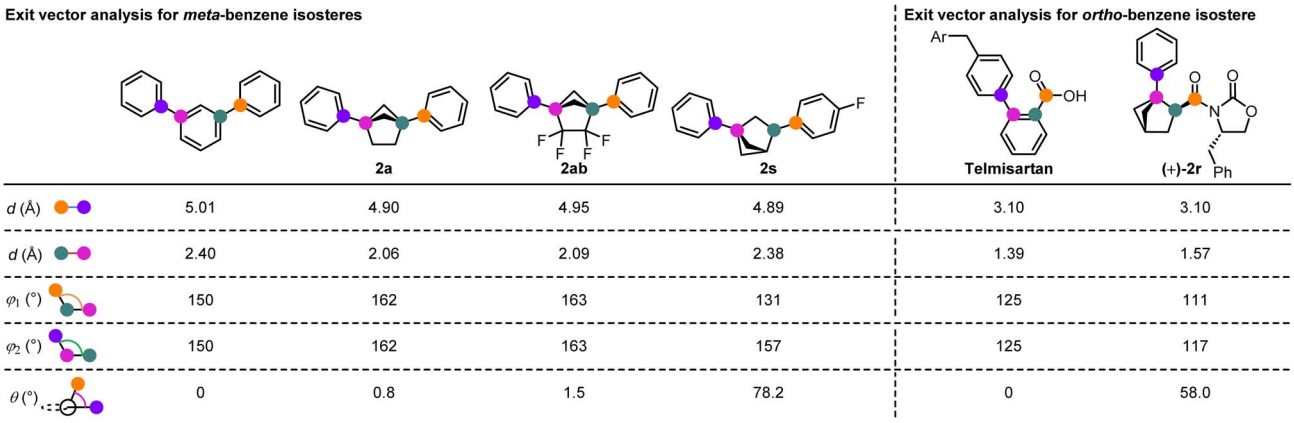
chemical space. Finally, we wanted to demonstrate that the method could be used to prepare BCHs containing more than three substituents. 1,2,4,5-Tetrasubstituted BCH **2aa**, which contains four different substituents at four different positions including an unprotected alcohol at the bridge 2-position, an ester, and an apical alkyl group at the bridge 5-position, was prepared in 90% yield as a mixture of diastereomers. This substituent pattern occupies chemical space not accessible to planar aromatic systems, and highlights the opportunities for molecular design that are available with these types of structures. Fluorinated bicyclo[1.1.1]pentanes are highly desirable building blocks in medicinal chemistry and we were able to access related 2,2,3,3-bridge-tetrafluorinated BCH **2ab** in 88% yield.[26]

We were also able to obtain crystal structures of a number of the BCH derivatives and perform a comparative exit vector analysis (Scheme 3). For the *meta*-isosteres, comparison was made to *m*-terphenyl[27] and for *ortho*-isostere (+)-**2r**, comparison was made to Telmisartan, which bears a similar *ortho*-carbonyl substitution pattern.[28] For the *meta*-isosteres, 1,4-disubstituted BCHs **2a** and **2ab**, and 1,3-disubstituted BCH **2s** could be analysed. All showed similar inter-substituent distances compared to *m*-terphenyl, but the substituent angles are arguably a better match with the 1,4-disubstituted derivatives, particularly with respect to the substituent torsion angle (near 0° for **2a** and **2ab** but 78.2° for **2s**). For *ortho*-isostere (+)-**2r**, the inter-substituent distance was an extremely good match for Telmisartan, although the angle between them in (+)-**2r** was smaller than for the parent aromatic. As expected, a torsion angle of 58° between the two substituents could be measured.

We were then able to demonstrate the viability of this method to access saturated analogues of biorelevant trisubstituted benzenes (Scheme 4A). We identified amide **5** and fendizoic acid (**7**) as model trisubstituted benzenes and BCHs **4** and **6** as simplified saturated analogues that reflected the substitution pattern of the central benzene ring. Amide **5** is a monoacylglycerol lipase (MGL) inhibitor developed by Janssen as an analgesic[29] and salts of fendizoic acid (**7**) are sold as the cough suppressant cloperastine fendizoate.[30] Starting from BCH **2w**, conversion of the methyl ester moiety into a *N*,*N*-dimethylamide led to amide **3**, which served as a shared intermediate towards BCHs **4** and **6**. Methylation of the alcohol led to methyl ether **3** and addition of phenyl lithium into the amide moiety provided aryl ketone **6**. Additionally, derivatisation of some of the compounds prepared was also possible (Scheme 4B).[31]



Scheme 4 The preparation of saturated analogues of MGL inhibitor **7** and fendizoic acid (**9**) and derivatization of selected bicyclo[2.1.1] hexanes. Reagents and conditions: (a) Me_2NH (2 equiv), *i*PrMgCl (3.5 equiv), THF, −5 °C → RT, 2 h, 95%; (b) NaH (2 equiv), MeI (2 equiv), THF, RT, 4 days, 33%; (c) PhLi (3 equiv), THF, 0 °C, 45 min, 78%; (d) $LiAlH_4$ (2.1 equiv), Et_2O, 0 °C → RT, overnight, 26%; (e) Ac_2O (5 equiv), Et_3N (5 equiv), DMAP (0.5 equiv), CH_2Cl_2, RT, overnight, 96%; (f) NaOH (3.2 equiv), EtOH : H_2O (4 : 1), RT, overnight, 75%.



Scheme 3 Exit vector analysis for selected *ortho*- and *meta*-benzene isosteres in comparison to related aromatic systems.

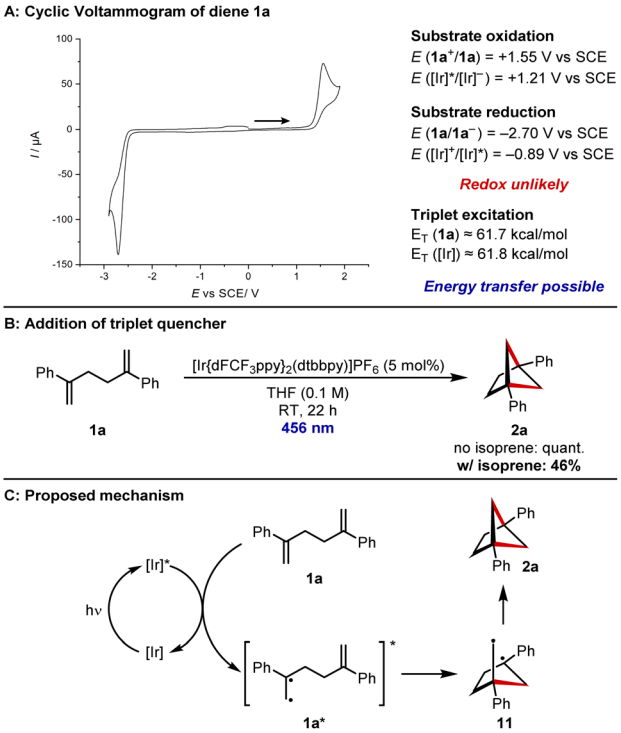


Fig. 1 Mechanistic studies and proposed mechanism. (A) Cyclic voltammogram of diene **1a** and comparison of redox potentials to those of the photoexcited catalyst (for experimental details see ESI†). (B) Control experiment with the addition of the triplet quencher isoprene. (C) Proposed mechanism for the [2 + 2] cycloaddition reaction.

Reductive cleavage of the Evans auxiliary allowed conversion of (+)-**2r** to alcohol (+)-**8** and provides an entry to enantioenriched BCHs. Acylation of the pendant alcohol of **2q** was possible in 96% yield, as was saponification of the ethyl ester in **2u**.[17b]

Finally, attention turned to investigating the reaction mechanism. Using cyclic voltammetry (for details see ESI†), the oxidation potential of diene **1a** was measured to be $E(\mathbf{1a}^{+}/\mathbf{1a}) = +1.55$ V *vs.* SCE, outside the range of the Iridium photocatalyst [$E(\mathrm{Ir}^{*}/\mathrm{Ir}^{-}) = +1.21$ V *vs.* SCE] (Fig. 1A).[32] The reduction potential of **1a** was measured to be $E(\mathbf{1a}/\mathbf{1a}^{-}) = -2.70$ V *vs.* SCE, again outside the range of the Iridium photocatalyst [$E(\mathrm{Ir}^{*}/\mathrm{Ir}^{+}) = -0.89$ V *vs.* SCE].[32] This suggests that a redox mechanism is unlikely. However, the reported excited state energy of styrenes lies at approximately 61.7 kcal mol^{-1},[33] which should be accessible to the photocatalyst (excited state energy = 61.8 kcal mol^{-1}).[33] In line with this, addition of the known triplet quencher isoprene led to a reduced conversion of diene **1a** (Fig. 1B). We therefore propose the following mechanism for the reaction (Fig. 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*-trig cyclisation to diradical **11** and lastly, radical recombination gives BCH **2a**.

Conclusions

In conclusion, we have developed a visible light-mediated photocatalytic [2 + 2] cycloaddition reaction of 1,5-hexadienes that provides unified and flexible access to BCHs containing 11 different substitution patterns. Structures that could be used as *ortho*-, *meta*-, and polysubstituted benzene bioisosteres can be prepared, along with BCHs with substituent geometries not found in aromatic chemical space. Importantly, the method allows for the predictable installation of rare bridge substituents on the BCH scaffold, and through judicious design of the starting 1,5-hexadiene, the location of the bridge substituent in the final structure can be controlled. The method speaks to the current desire for reactions that enable rapid complexity generation in three-dimensional space and we hope it will find application in the near future.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

J. C. L. W. conceptualised the project. M. R., J. S., and J. C. L. W. conceptualised and performed the experiments. C. G. performed the X-ray analyses. M. R. and J. C. L. W. wrote the original draft of the manuscript and all authors were involved in review and editing of the manuscript and have given approval to the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

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.

Notes and references

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

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

3 For reviews on the application of cubanes in medicinal chemistry, see: (*a*) T. A. Reekie, C. M. Williams, L. M. Rendina and M. Kassiou, *J. Med. Chem.*, 2019, **62**, 1078–1095; (*b*) K. F. Biegasiewicz, J. R. Griffiths,

G. P. Savage, J. Tsanaktsidis and R. Priefer, *Chem. Rev.*, 2015, **115**, 6719–6745; (*c*) G. W. Griffin and A. P. Marchand, *Chem. Rev.*, 1989, **89**, 997–1010.

4 (*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 and 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 and C. M. Williams, *Org. Biomol. Chem.*, 2019, **17**, 6790–6798.

5 For reviews on the chemistry of bicyclo[1.1.1]pentanes, see: (*a*) J. Turkowska, J. Durka and D. Gryko, *Chem. Commun.*, 2020, **56**, 5718–5734; (*b*) X. Ma and L. N. Pham, *Asian J. Org. Chem.*, 2020, **9**, 8–22; (*c*) J. Kanazawa and M. Uchiyama, *Synlett*, 2019, **30**, 1–11; (*d*) M. D. Levin, P. Kaszynski and J. Michl, *Chem. Rev.*, 2000, **100**, 169–234; (*e*) E. W. Delia and I. J. Lochert, *Org. Prep. Proced. Int.*, 1996, **28**, 411–441.

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

7 (*a*) 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 and E. A. Anderson, *Nature*, 2022, **611**, 721–726; (*b*) T. Iida, J. Kanazawa, T. Matsunaga, K. Miyamoto, K. Hirano and M. Uchiyama, *J. Am. Chem. Soc.*, 2022, **144**, 21848–21852.

8 (*a*) T. Rigotti and T. Bach, *Org. Lett.*, 2022, **24**, 8821–8825; (*b*) V. V. Levterov, Y. Panasyuk, V. O. Pivnytska and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2020, **59**, 7161–7167.

9 For general reviews on the concept of bioisosteres in medicinal chemistry, see: (*a*) M. A. M. Subbaiah and 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 and M. H. Todd, *J. Med. Chem.*, 2020, **63**, 11585–11601; (*c*) P. K. Mykhailiuk, *Org. Biomol. Chem.*, 2019, **17**, 2839–2849; (*d*) G. M. Locke, S. S. R. Bernhard and M. O. Senge, *Chem. – Eur. J.*, 2019, **25**, 4590–4647; (*e*) Y. P. Auberson, C. Brocklehurst, M. Furegati, T. C. Fessard, G. Koch, A. Decker, L. La Vecchia and E. Briard, *ChemMedChem*, 2017, **12**, 590–598.

10 A recent report also demonstrated that bicyclo[2.2.0]hexanes can be used as *meta*-benzene bioisosteres, see: 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 and M. K. Brown, *Nat. Commun.*, 2022, **13**, 6056.

11 According to a search of the database **https://www.drugbank.ca** on 21/02/2023.

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

13 (*a*) O. L. Garry, M. Heilmann, J. Chen, Y. Liang, X. Zhang, X. Ma, C. S. Yeung, D. J. Bennett and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2023, **145**, 3092–3100; (*b*) J. M. Anderson, N. D. Measom, J. A. Murphy and D. L. Poole, *Org. Lett.*, 2023, **25**, 2053–2057.

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

15 For recent examples of cubane functionalization, see: (*a*) Y. Kato, C. M. Williams, M. Uchiyama and S. Matsubara, *Org. Lett.*, 2019, **21**, 473–475; (*b*) R. Okude, G. Mori, A. Yagi and K. Itami, *Chem. Sci.*, 2020, **11**, 7672–7675; (*c*) N. Yoshino, Y. Kato, T. Mabit, Y. Nagata, C. M. Williams, M. Harada, A. Muranaka, M. Uchiyama and S. Matsubara, *Org. Lett.*, 2020, **22**, 4083–4087; (*d*) D. E. Collin, K. Kovacic, M. E. Light and B. Linclau, *Org. Lett.*, 2021, **23**, 5164–5169; (*e*) H. Takebe, N. Yoshino, Y. Shimada, C. M. Williams and S. Matsubara, *Org. Lett.*, 2023, **25**, 27–30; (*f*) M. P. Wiesenfeldt, J. A. Rossi-Ashton, I. B. Perry, J. Diesel, O. L. Garry, F. Bartels, S. C. Coote, X. Ma, C. S. Yeung, D. J. Bennett and D. W. C. MacMillan, *Nature*, 2023, **618**, 513–518.

16 (*a*) C. Yang, W. Xa, J. R. Scheffer and M. Botoshansky, *Angew. Chem., Int. Ed.*, 2005, **44**, 5087–5089; (*b*) G. Zhao, C. Yang, Q. Chen, J. Jin, X. Zhang, L. Zhao and W. Xa, *Tetrahedron*, 2009, **65**, 9952–9955; (*c*) L. Herter, I. Koutsopetras, L. Turelli, T. Fessard and C. Salomé, *Org. Biomol. Chem.*, 2022, **20**, 9108–9111.

17 For recent examples, see: (*a*) D. Staveness, T. M. Sodano, K. Li, E. A. Burnham, K. D. Jackson and C. R. J. Stephenson, *Chem*, 2019, **5**, 215–226; (*b*) A. Denisenko, P. Garbuz, S. V. Shishkina, N. M. Voloshchuk and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2020, **59**, 20515–20521; (*c*) X. Ma, Y. Han and D. J. Bennett, *Org. Lett.*, 2020, **22**, 9133–9138; (*d*) A. S. Harmata, T. E. Spiller, M. J. Sowden and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2021, **143**, 21223–21228; (*e*) Y. Yang, J. Tsien, J. M. E. Hughes, B. K. Peters, R. R. Merchant and T. Qin, *Nat. Chem.*, 2021, **13**, 950–955; (*f*) 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 and P. S. Baran, *Proc. Natl. Acad. Sci. U.S.A.*, 2021, **118**, e2108881118; (*g*) B. A. Wright, A. Matviitsuk, M. J. Black, P. García-Reynaga, L. E. Hanna, A. T. Herrmann, M. K. Ameriks, R. Sarpong and T. P. Lebold, *J. Am. Chem. Soc.*, 2023, **145**, 10960–10966.

18 (*a*) A. Cairncross and E. P. Blanchard Jr., *J. Am. Chem. Soc.*, 1966, **88**, 496–504; (*b*) A. de Meijere, H. Wenck, F. Seyed-Mahdavi, H. G. Viehe, V. Gallez and I. Erden, *Tetrahedron*, 1986, **42**, 1291–1297; (*c*) P. Wipf and M. A. A. Walczak, *Angew. Chem., Int. Ed.*, 2006, **45**, 4172–4175; (*d*) R. Kleinmans, T. Pinkert, S. Dutta, T. O. Paulisch, H. Keum, C. G. Daniliuc and F. Glorius, *Nature*, 2022, **605**,

477–482; (*e*) R. Guo, Y.-C. Chang, L. Herter, C. Salome, S. E. Braley, T. C. Fessard and M. K. Brown, *J. Am. Chem. Soc.*, 2022, **144**, 7988–7994; (*f*) Y. Zheng, W. Huang, R. K. Dhungana, A. Granados, S. Keess, M. Makvandi and G. A. Molander, *J. Am. Chem. Soc.*, 2022, **144**, 23685–23690; (*g*) M. Xu, Z. Wang, Z. Sun, Z. Ouyang, Z. Ding, T. Yu, L. Xu and P. Li, *Angew. Chem., Int. Ed.*, 2022, **61**, e202214507; (*h*) Y. Liang, R. Kleinmans, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2022, **144**, 20207–20213; (*i*) S. Agasti, F. Beltran, E. Pye, N. Kaltsoyannis, G. E. M. Crisenza and D. J. Procter, *Nat. Chem.*, 2023, **15**, 535–541; (*j*) T. V. T. Nguyen, A. Bossonnet and J. Waser, *ChemRxiv*, 2023, DOI: **10.26434/chemrxiv-2023-s8j30**; (*k*) Y. Liu, S. Lin, Y. Li, J.-H. Xue, Q. Li and H. Wang, *ACS Catal.*, 2023, **13**, 5096–5103.

19 For a review on the early examples of this type of reactivity, see: M. Golfmann and J. C. L. Walker, *Commun. Chem.*, 2023, **6**, 9.

20 M. Golfmann, L. Glagow, A. Giakoumidakis, C. Golz and J. C. L. Walker, *Chem. – Eur. J.*, 2023, **29**, e202202373.

21 (*a*) K. J. Crowley, *J. Am. Chem. Soc.*, 1964, **86**, 5692–5693; (*b*) R. Srinivasan and K. H. Carlough, *J. Am. Chem. Soc.*, 1967, **89**, 4932–4936; (*c*) J. K. Crandall and C. F. Mayer, *J. Org. Chem.*, 1970, **35**, 3049–3053; (*d*) R. A. Kleinnijenhuis, B. J. J. Timmer, G. Lutteke, J. M. M. Smits, R. de Gelder, J. H. van Maarseveen and H. Hiemstra, *Chem. – Eur. J.*, 2016, **22**, 1266–1269.

22 (*a*) R. S. H. Liu and G. S. Hammond, *J. Am. Chem. Soc.*, 1967, **89**, 4936–4944; (*b*) C. Yamada, M. Pahk and R. Liu, *J. Chem. Soc. D*, 1970, 882; (*c*) J. J. Bloomfield and D. C. Owsley, *Tetrahedron Lett.*, 1973, **21**, 1795–1798; (*d*) W. Adam, S. Grabowski, H. Platsch, K. Hannemann, J. Wirz and R. M. Wilson, *J. Am. Chem. Soc.*, 1989, **111**, 751–753; (*e*) A. Barbero, C. García and F. J. Pulido, *Synlett*, 2001, **6**, 824–826.

23 Kwon and co-workers reported a related route to benzobicyclo[3.1.1]heptanones, see: J. Zhao, J. L. Brosmer, Q. Zang, Z. Yang, K. N. Houk, P. L. Diaconescu and O. Kwon, *J. Am. Chem. Soc.*, 2017, **139**, 9807–9810.

24 Related crossed [2+2] cycloadditions to heterocyclic BCHs are also known. For selected recent examples, see: (*a*) V. V. Levterov, Y. Panasyuk, V. O. Pivnytska and P. K. Mykhailiuk, *Angew. Chem., Int. Ed.*, 2020, **59**, 7161–7167; (*b*) T. Rigotti, D. P. Schwinger, R. Graßl, C. Jandl and T. Bach, *Chem. Sci.*, 2022, **13**, 2378–2384.

25 We propose that the difference in *endo* : *exo* selectivity compared to **2u** is derived from the different geometry of the respective dienes. Diene **1u** was prepared in 98 : 2 (*Z* : *E*) selectivity and led to **2u** in 10 : 1 (*endo* : *exo*) selectivity. Diene **1z** was prepared in >99 : 1 (*E* : *Z*) selectivity and led to **2z** in 2 : 1 (*exo* : *endo*) selectivity. Mykhailiuk and co-workers (ref. 17b) also observed high 9 : 1 (*endo* : *exo*) selectivity for **2u**, but starting from a 1 : 1 mixture of isomers. Plausible transition states from the *Z*- and *E*-dienes do lead to the *endo* and *exo* products respectively (see ESI†). We believe the following explanation would be consistent with the experimental observations: (1) $E \rightarrow Z$ isomerisation is a side reaction. (2) From the 1 : 1 *E* : *Z* mixture of **1u** (ref. 17b), near complete $E \rightarrow Z$ isomerisation occurs before cyclisation and leads to high *endo* selectivity. (3) From the *E*-only isomer of **1z**, only partial isomerisation occurs before cyclisation, leading to the mixture of *exo* and *endo* products.

26 (*a*) X. Ma, D. L. Sloman, Y. Han and 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 and P. K. Mykhailiuk, *J. Org. Chem.*, 2019, **84**, 15106–15117; (*c*) X. Ma, Y. Han and D. J. Bennett, *Org. Lett.*, 2020, **22**, 9133–9138.

27 C. F. R. A. C. Lima, L. R. Gomes, L. M. N. B. F. Santos and J. N. Low, *CSD Communication*, 2012, 782202, DOI: **10.5517/ccv7ybb**.

28 (*a*) J.-R. Wang, X. Wang, L. Lu and X. Mei, *Cryst. Growth Des.*, 2013, **13**, 3261–3269; (*b*) R. Chadha, S. Bhandari, J. Haneef, S. Khullar and S. Mandal, *CrystEngComm*, 2014, **16**, 8375–8389.

29 H. Bian, K. M. Chevalier, P. J. Connolly, C. M. Flores, S.-c. Lin, L. Liu, J. Mabus, M. J. Macielag, M. E. McDonnell, P. M. Pitis, Y.-m. Zhang, S.-p. Zhang, J. Clemente and B. Zhu, *Janssen Pharmaceutica*, World Intellectual Property Organisation, WO 2010/124114 A1, 2010.

30 M. A. Catania and S. Cuzzocrea, *Ther. Clin. Risk Manage.*, 2011, **7**, 83–92.

31 During preparation of this manuscript a further report on [2 + 2] crossed cycloadditions was published. The authors also reported a range of derivatisation reactions of the BCH scaffold, see: S. Paul, D. Adelfinsky, C. Salome, T. Fessard and M. K. Brown, *Chem. Sci.*, 2023, **14**, 8070–8075.

32 C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363.

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