Title

Skeletal Editing Approach to Bridge-Functionalized Bicyclo[1.1.1]pentanes from Azabicyclo[2.1.1]hexanes

Journal

Journal of the American Chemical Society, 145(20)

ISSN

0002-7863

Authors

Wright, Brandon A
Matviitsuk, Anastassia
Black, Michael J
et al.

Publication Date

2023-05-24

DOI

10.1021/jacs.3c02616

Peer reviewed

HHS Public Access

Author manuscript

J Am Chem Soc. Author manuscript; available in PMC 2023 June 20.

Published in final edited form as:

J Am Chem Soc. 2023 May 24; 145(20): 10960–10966. doi:10.1021/jacs.3c02616.

Skeletal Editing Approach to Bridge-Functionalized Bicyclo[1.1.1]pentanes from Azabicyclo[2.1.1]hexanes

Brandon A. Wright[‡],
Department of Chemistry, University of California, Berkeley, California 94720, United States

Anastassia Matviitsuk[‡],
Janssen Research and Development, San Diego, California 92121, United States

Michael J. Black[§],
Department of Chemistry, University of California, Berkeley, California 94720, United States

Pablo García-Reynaga[§],
Janssen Research and Development, San Diego, California 92121, United States

Luke E. Hanna,
Janssen Research and Development, San Diego, California 92121, United States

Aaron T. Herrmann,
Janssen Research and Development, San Diego, California 92121, United States

Michael K. Ameriks,
Janssen Research and Development, San Diego, California 92121, United States

Richmond Sarpong,
Department of Chemistry, University of California, Berkeley, California 94720, United States

Terry P. Lebold
Janssen Research and Development, San Diego, California 92121, United States

Abstract

Corresponding Authors: **Terry P. Lebold** – *Janssen Research and Development, San Diego, California 92121, United States*; terry.lebold@gmail.com; **Richmond Sarpong** – *Department of Chemistry, University of California, Berkeley, California 94720, United States*; rsarpong@berkeley.edu.

[‡]Author Contributions
B.A.W. and A.M. contributed equally.

[§]Author Contributions
M.J.B. and P.G.-R. contributed equally.

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.3c02616

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c02616.
Experimental procedures, characterization data, NMR spectra, and X-ray crystallographic data (PDF)

Accession Codes
CCDC 2247338 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

The authors declare no competing financial interest.

Azabicyclo[2.1.1]hexanes (aza-BCHs) and bicyclo[1.1.1]pentanes (BCPs) have emerged as attractive classes of sp^3-rich cores for replacing flat, aromatic groups with metabolically resistant, three-dimensional frameworks in drug scaffolds. Strategies to directly convert, or "scaffold hop", between these bioisosteric subclasses through single-atom skeletal editing would enable efficient interpolation within this valuable chemical space. Herein, we describe a strategy to "scaffold hop" between aza-BCH and BCP cores through a nitrogen-deleting skeletal edit. Photochemical [2+2] cycloadditions, used to prepare multifunctionalized aza-BCH frameworks, are coupled with a subsequent deamination step to afford bridge-functionalized BCPs, for which few synthetic solutions currently exist. The modular sequence provides access to various privileged bridged bicycles of pharmaceutical relevance.

An important aspect of pharmaceutical discovery is the ability to rapidly access pharmacophores that occupy diverse regions of chemical space.[1] The recognized merits of three-dimensionality in this regard have led to the development of methods to access saturated bioisosteric replacements of unsaturated molecular scaffolds.[2–4] Molecular frameworks containing a high fraction of sp^3-hybridized atoms exhibit improved solubility,[5–10] metabolic stability,[2,6,8,11] and target specificity,[12–14] and are positively correlated with clinical success.[15] Despite the attractive features of sphere-like,[16,17] sp^3-rich building blocks, this chemical space remains underexplored due to the paucity of methods for their synthesis (Figure 1A). This holds true in the context of azabicyclo[2.1.1]hexanes (aza-BCHs) and bicyclo[1.1.1]-pentanes (BCPs), which serve as key bicyclic cores for replacing pyrrolidine or phenyl-containing structural motifs in drug candidate scaffolds (Figure 1B).[5,18,19] Recently, single-atom skeletal editing has emerged as a new strategic paradigm for structural modification of core scaffolds and presents an attractive opportunity to explore adjacent chemical space without de novo synthetic sequences (Figure 1C).[20] Therefore, we sought to apply this paradigm through the union of [2+2] photocycloaddition and *N*-atom deletion chemistries that would "scaffold hop" between aza-BCHs and BCPs (Figure 1D).

Early synthetic strategies for aza-BCH preparation involved the use of photochemical processes to generate strained rings from flat, unstrained precursors (Figure 2A). Krow's approach centered on oxidative rearrangement of strained [2.2.0] Dewar-dihydropyridines to the aza-BCH core.[21] Analogous cycloaddition strategies have since followed: Piotrowski,[22] Booker-Milburn,[23,24] and Mykhailiuk[25] employed an intramolecular [2+2] addition from *N*-allyl enamides to assemble diverse 1-substituted aza-BCHs, while Leitch[26] developed an intermolecular formal (3+2) cycloaddition approach between imines and bicyclo[1.1.0]butanes.

Following contributions from Wiberg,[27,28] Baran,[29] Anderson,[30,31] MacMillan,[32] and others,[33–36] many syntheses of BCPs rely on strain-release of [1.1.1]propellane using one- or two-electron nucleophiles (Figure 2B). Such 1,3-functionalized "*para*-" BCPs can be further derivatized using an increasing number of methods.[37–41] Recently, 1,2-functionalized BCPs—long sought-after isosteres for *ortho*- or *meta*-substituted arenes—have also been prepared by Baran/Pfizer[42] and Ma[43] from prefunctionalized [1.1.1]propellanes. In addition, MacMillan[44] reported that 2-brominated BCPs enable cross-coupling to access 1,2,3-

substituted variants. In a distinct strategy, Qin and Merck showcased a Barluenga/Valdes-type intramolecular cydization with pinacol boronates to furnish functionalized BCPs.[45]

Considering these approaches, we sought to develop a complementary route that leveraged recent advances in both photoredox cycloadditions and skeletal editing to access both aza-BCH and BCP scaffolds. We also recognized that, given differences in solubility[25,46] and available growth vectors, a direct “scaffold hop” between aza-BCH and BCP frameworks would be appealing for probing sp^3-rich chemical space.

Central to our plan was the progressive introduction of strain starting from readily available ketone- and allyl amine-containing building blocks (Figure 2C). Building on work from Pietrowski,[22] Booker-Milburn,[23,24] and others,[25] we were drawn to a modular approach to aza-BCHs wherein initial condensation/*N*-acylation to generate enamides would set the stage for an intramolecular [2+2] cycloaddition to afford [2.1.1] scaffolds (strain energy: ~6.3 kcal/mol per atom).[47] Following aza-BCH deprotection, nitrogen deletion through isodiazene formation, dinitrogen extrusion, and radical recombination[48] would yield the BCP framework (strain energy: 13.6 kcal/mol per carbon).[47] In this way, the nitrogen atom would serve as both a linchpin to template the [2+2] cycloaddition and a traceless handle for the final deamination step.

We envisioned isodiazene formation could be achieved using recently popularized methods, induding anomeric amides,[49] iodonitrenes,[50] and sulfamoyl azides.[51] Given the steric and strain considerations of the aza-BCH, potential concerns for this sequence included 1) lack of aza-BCH reactivity toward deaminating reagents and 2) nonproductive diradical termination, such as β-fragmentation, which would render the BCP-forming step unfeasible.[49,52,53] While nitrogen deletion has been successfully applied to azetidine-[49,51] and pyrrolidine-containing[50] structures, this transformation would, to the best of our knowledge, represent the most strained ring system formed using this approach to date.

We began by surveying several reagents to achieve nitrogen deletion of aza-BCH **1** to yield BCP **2**. While hydroxy-(tosyloxy)iodobenzene (HTIB, **4**)[50] and NH_3/MeOH in TFE at 80 °C gave trace product (Table 1, entry 1), the formation of sulfamoyl azides[51] with sulfuryl azide transfer reagent **5**,[54] followed by treatment with LiO*t*-Bu at 120 °C, was more efficient. This produced desired BCP **2** in an improved 25% yield, along with 11% of ring-opened diene **3** (Table 1, entry 2). Conditions from Levin,[49] employing *N*-(benzyloxy)-*N*-(pivaloyloxy)-4-(trifluoromethyl)benzamide (**6**)[55,56] in THF at 45 °C, gave the desired BCP **2** in 41% yield and diene **3**[49] in 7% yield (Table 1, entry 3). Although modest in efficiency, this reactivity is remarkable given the steric hindrance around the amine, as well as the substantial ring strain inherent to the BCF core (68 kcal/mol; 13.6 kcal/mol per carbon)[47,57] in comparison to the more thermodynamically stable 1,4-diene.

Anomeric amides bearing a smaller methoxy substituent or a chloride leaving group led to low yields of BCP **2** (Table 1, entries 4 and 5). Attempts to further optimize conditions with Levin’s reagent (**6**),[49] through variations in temperature and concentration, were met with diminished success (Table 1, entries 6–9). Finally, addition of metal salts intended to

stabilize the diradical intermediate resulted in either decomposition or reduced yields (Table 1, entries 10 and 11).

Next, we prepared a panel of monosubstituted aza-BCHs (Scheme 1A) to probe the role of aryl electronics in the deamination. To this end, condensation of allyl amines with aryl ketones followed by treatment with trifluoroacetic anhydride (TFAA) smoothly afforded the corresponding trifluoroacetyl (TFA)-protected enamides. While irradiation of *N*-allyl enamide **2a** with a Hanovia medium-pressure Hg-lamp (200–400 nm) gave initial success (95%), the recent development of visible light photosensitizers[58,59] suggested that the [2+2] cycloaddition could proceed under milder conditions. Irradiation of **2a** with a blue LED light source (450 nm) and catalytic $Ir(ppy)_3$ (1 mol%) facilitated the intramolecular [2+2] cycloaddition in 56% yield.[60] Switching to $[Ir(dF(CF_3)ppy)_2dtbbpy]PF_6$ (1 mol%)[58,60,61] yielded the targeted aza-BCH in >99% isolated yield.[62] This cycloaddition, followed by TFA cleavage, afforded an array of aza-BCHs which were subjected to the optimized deamination conditions (Scheme 1B).

Benzylic substitution has been previously observed to facilitate nitrogen deletion through isodiazene decomposition.[49,63] Thus, we expected yields of the BCP products to improve with electron-donating substituents at the bridgehead carbon. However, no clear discernible trend in aryl ring electronics with respect to levels of BCP formation (16–51% yield) was observed for these substrates (**2, 7–15**). In each of these cases, isolation was challenging due to the volatility of the monosubstituted BCP,[37] and yields were determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. Other radical stabilizing groups, such as benzyl ester **15**, afforded an 8% NMR yield of the BCP product, albeit with significant amounts of diene.

Following these initial observations, we next targeted the formation of 1,2-functionalized BCPs. As a first example, we anticipated that incorporating a methylene-amino substituent would probe the reaction's tolerance to bridge substitution and provide a functional handle for further derivatization. Synthesis of 1,2-substituted aza-BCHs commenced with the [2+2] cycloaddition of enamide **16a-(*Z*)** containing an internal (*Z*)-configured alkene. Subsequent [2+2] cycloaddition afforded the aza-BCH system (**16b** and *epi*-**16b**) in 70% yield and 6:1 d.r. (Scheme 2). Given that the (*Z*)-alkene (**16a-(*Z*)**, >20:1 (*Z*)/(*E*)) was exclusively employed in the reaction, the erosion of stereospecificity to a 6:1 d.r. suggested that a stepwise mechanism is likely operative. To probe this hypothesis, enamide **16a-(*E*)** was subjected to the photo-cycloaddition, resulting in formation of **16b** and *epi*-**16b** in an identical diastereomeric ratio, further supporting a stepwise mechanism for the observed diastereoconvergence.[64,65]

With the substituted aza-BCH scaffold in hand, **16b** was deprotected with NaOH in MeOH to give free amine **17**, which was then subjected to the deamination. Gratifyingly, the desired BCP (**18**) was obtained in a serviceable 32% isolated yield, enabling access to this important class of bridge-functionalized BCPs.

Having established a method for synthesizing 1,2-substituted BCPs, we explored the scope with respect to the bridgehead substituent. Phenyl derivatives with various electronics

were tolerated, furnishing the corresponding BCPs (**18–20**, Scheme 3) in similar yields (26–32%). Heteroarenes bearing a nitrogen at the 2-position gave improved yields in most cases. Electron-poor heteroarenes such as pyrimidines (**21**), pyrazines (**22**), and 2-, 3-, and 4-substituted pyridyl systems (**23–25**) participated faithfully in this chemistry to give the functionalized BCPs (28–52%). Pyridyl derivative **25**, isolated as the TFA salt, enabled unambiguous characterization by X-ray crystallography. Notably, halogenated heterocycles such as **26** and **27**, which contain vectors for further functionalization, were also compatible. Although aryl bromides have previously thwarted photocycloaddition approaches due to the heavy atom effect,[59] bromo-pyrimidine **27** could nevertheless be accessed (35%). Fused bicyclic heterocycles, such as quinolones (**28**) and azaindoles (**29**), performed well to give the 1,2-BCPs in isolated yields of 60% and 29%, respectively. Substrates possessing electron-rich heteroaromatics such as pyrazoles (**30**), thiophenes (**31**), isoxazoles (**32**), and furans (**33**) also smoothly furnished the desired products (26–41%).

We next sought to investigate additional substitution patterns using this approach. Variations in the allyl amine fragment, such as the use of a crotyl amine, were well tolerated, giving the corresponding methyl-decorated BCP **34** in 35% yield. However, generation of *gem*-disubstituted BCP **35** from prenylamine-derived aza-BCH proved difficult, representing an apparent upper steric limit to this type of diradical C–C bond formation (**35**, Scheme 4A). Allyl amine containing a methylene benzyloxy group, however, performed smoothly and yielded the desired BCP (**36**) in 45% yield.

1,2,4-Trisubstituted BCPs were also pursued with this strategy. Photocycloaddition of trisubstituted *N*-allyl enamide **37** afforded the corresponding aza-BCH in 63% yield (5:1 d.r.). Deprotection yielded free amine **38** which, following nitrogen deletion, afforded the unique 1,2,4-carbon-substituted BCP **39** in 25% yield (Scheme 4B). This substitution pattern stands as a complement to existing methods for preparing 1,2,3- and 1,2,3,4-decorated BCP scaffolds.[2,44]

The cycloaddition/scaffold-hop sequence reported here can also be performed on a gram scale (Scheme 4C). Accordingly, [2+2] photocycloaddition of *N*-allyl enamide **22a** was readily adapted to >5 g scale and proceeded smoothly (79%) using a Vapourtec UV-150 flow reactor,[25] affording both diastereomers (**22c** and *epi*-**22c**) of the aza-BCH after deprotection. Major diastereomer **22c** could be subjected to nitrogen deletion on a gram scale with no loss in efficiency (52%). Notably, minor diastereomer *epi*-**22c** also proved competent in the deamination (37%),[66] demonstrating that either diastereomer could be used in a convergent manner.

Discovery-stage pharmaceutical research hinges on the ability to rapidly access diverse regions of chemical space, particularly those with sphere-like, sp^3-rich cores. To address this need, we developed a strategy for navigating between strained-bicyclic scaffolds through a nitrogen-deleting “scaffold hop”. This approach takes advantage of readily available starting materials and a complexity-building [2+2] cycloaddition followed by a skeletal edit. The enamide nitrogen serves as a linchpin for templating the cycloaddition as well as a traceless handle for the subsequent nitrogen deletion step. In this way, a panel of substituted aza-BCHs and BCPs can be accessed, simplifying the preparation of these bioisosteric

motifs. More broadly, this strategy demonstrates how skeletal editing can directly switch between classes of pharmaceutically relevant bicyclic scaffolds and enable rapid exploration of adjacent chemical space.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank Dr. Hasan Celik at UC Berkeley's NMR facility College of Chemistry, supported in part by NIH (S10OD024998), for spectroscopic assistance and Drs. Ulla Andersen and Zongrui Zhou at the UC Berkeley QB3 Mass Spectrometry Facility for mass spectrometry analysis. Special thanks to Dr. Guoyun Bai, Deszra Shariff, Heather Mcallister, and Dr. Mona Sharar at Janssen Research and Development for NMR analysis/acquisition of HRMS. We also thank Dr. John Basca at Emory University for assistance with X-ray crystallographic analysis.

Funding

R.S. is grateful to Janssen Research and Development for support (Agreement No. 1501907). Partial support of the work conducted at Berkeley was received from the NIGMS (R35 GM130345). B.A.W. is grateful to the National Science Foundation for a graduate fellowship (DGE-1752814) and UC Cancer Research Coordinating Committee for additional funding.

REFERENCES

(1). Campos KR; Coleman PJ; Alvarez JC; Dreher SD; Garbaccio RM; Terrett NK; Tillyer RD; Truppo MD; Parmee ER The Importance of Synthetic Chemistry in the Pharmaceutical Industry. Science 2019, 363 (6424), No. eaat0805. [PubMed: 30655413]

(2). Anderson JM; Measom ND; Murphy JA; Poole DL Bridge Functionalisation of Bicyclo[1.1.1]Pentane Derivatives. Angew. Chem., Int. Ed 2021, 60 (47), 24754–24769.

(3). Mykhailiuk PK Saturated Bioisosteres of Benzene: Where to Go Next? Org. Biomol. Chem 2019, 17 (11), 2839–2849. [PubMed: 30672560]

(4). Subbaiah MAM; Meanwell NA Bioisosteres of the Phenyl Ring: Recent Strategic Applications in Lead Optimization and Drug Design. J. Med. Chem 2021, 64 (19), 14046–14128. [PubMed: 34591488]

(5). Stepan AF; Subramanyam C; Efremov IV; Dutra JK; O'Sullivan TJ; DiRico KJ; McDonald WS; Won A; Dorff PH; Nolan CE; Becker SL; Pustilnik LR; Riddell DR; Kauffman GW; Kormos BL; Zhang L; Lu Y; Capetta SH; Green ME; Karki K; Sibley E; Atchison KP; Hallgren AJ; Oborski CE; Robshaw AE; Sneed B; O'Donnell CJ 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 (7), 3414–3424. [PubMed: 22420884]

(6). Nicolaou KC; Vourloumis D; Totokotsopoulos S; Papakyriakou A; Karsunky H; Fernando H; Gavrilyuk J; Webb D; Stepan AF Synthesis and Biopharmaceutical Evaluation of Imatinib Analogues Featuring Unusual Structural Motifs. ChemMed-Chem 2016, 11 (1), 31–37.

(7). Pu Q; Zhang H; Guo L; Cheng M; Doty AC; Ferguson H; Fradera X; Lesburg CA; McGowan MA; Miller JR; Geda P; Song X; Otte K; Sciammetta N; Solban N; Yu W; Sloman DL; Zhou H; Lammens A; Neumann L; Bennett DJ; Pasternak A; Han Y. Discovery of Potent and Orally Available Bicyclo[1.1.1]-Pentane-Derived Indoleamine-2,3-Dioxygenase 1 (iDO1) Inhibitors. ACS Med. Chem. Lett 2020, 11 (8), 1548–1554. [PubMed: 32832022]

(8). Measom ND; Down KD; Hirst DJ; Jamieson C; Manas ES; Patel VK; Somers DO. Investigation of a Bicyclo[1.1.1]-Pentane as a Phenyl Replacement within an LpPLA2 Inhibitor. ACS Med. Chem. Lett. 2017, 8 (1), 43–48. [PubMed: 28105273]

(9). Tse EG; Houston SD; Williams CM; Savage GP; Rendina LM; Hallyburton I; Anderson M; Sharma R; Walker GS; Obach RS; Todd MH. Nonclassical Phenyl Bioisosteres as Effective

Replacements in a Series of Novel Open-Source Antimalarials. J. Med. Chem 2020, 63 (20), 11585–11601. [PubMed: 32678591]

(10). Auberson YP; Brocklehurst C; Furegati M; Fessard TC; Koch G; Decker A; La Vecchia L; Briard E Improving Nonspecific Binding and Solubility: Bicycloalkyl Groups and Cubanes as Para-Phenyl Bioisosteres. ChemMedChem. 2017, 12 (8), 590–598. [PubMed: 28319646]

(11). Goh YL; Cui YT; Pendharkar V; Adsool VA Toward Resolving the Resveratrol Conundrum: Synthesis and in Vivo Pharmacokinetic Evaluation of BCP-Resveratrol. ACS Med. Chem. Lett 2017, 8 (5), 516–520. [PubMed: 28523103]

(12). Clemons PA; Bodycombe NE; Carrinski HA; Wilson JA; Shamji AF; Wagner BK; Koehler AN; Schreiber SL Small Molecules of Different Origins Have Distinct Distributions of Structural Complexity That Correlate with Protein-Binding Profiles. Proc. Natl. Acad. Sci. U. S. A 2010, 107 (44), 18787–18792. [PubMed: 20956335]

(13). Lovering F Escape from Flatland 2: Complexity and Promiscuity. MedChemComm 2013, 4 (3), 515–519.

(14). Monteleone S; Fuchs JE; Liedl KR Molecular Connectivity Predefines Polypharmacology: Aliphatic Rings, Chirality, and Sp^3 Centers Enhance Target Selectivity. Front. Pharmacol 2017, 8, 552. [PubMed: 28894419]

(15). Lovering F; Bikker J; Humblet C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. J. Med. Chem 2009, 52 (21), 6752–6756. [PubMed: 19827778]

(16). Sauer WHB; Schwarz MK Molecular Shape Diversity of Combinatorial Libraries: A Prerequisite for Broad Bioactivity. J. Chem. Inf. Comput. Sci 2003, 43 (3), 987–1003. [PubMed: 12767158]

(17). Cox B; Zdorichenko V; Cox PB; Booker-Milburn KI; Paumier R; Elliott LD; Robertson-Ralph M; Bloomfield G. Escaping from Flatland: Substituted Bridged Pyrrolidine Fragments with Inherent Three-Dimensional Character. ACS Med. Chem. Lett 2020, 11 (6), 1185–1190. [PubMed: 32550999]

(18). Mingzhe J; Martin TAT; Desai MC; Jin H; Pyun H-J Polycyclic-Carbamoylpyridone Compounds and Their Use for the Treatment of HIV Infections. WO2015006733A1, 2015.

(19). Dargazanli G; Estenne-Bouhtou G; Mafroud A-K N-[(2-Azabicyclo [2.1.1]Hex-1-Yl]-Aryl-Methyl]-Benzamide Derivatives, Preparation Thereof, and Therapeutic Use Thereof. WO2010092286A, 2010.

(20). Jurczyk J; Woo J; Kim SF; Dherange BD; Sarpong R; Levin MD Single-Atom Logic for Heterocycle Editing. Nat. Synth 2022, 1 (5), 352–364. [PubMed: 35935106]

(21). Krow GR; Lee YB; Lester WS; Christian H; Shaw DA; Yuan JA Novel Synthesis of 2-Azabicyclo[2.1.1]Hexane from Pyridine. J. Org. Chem 1998, 63 (23), 8558–8560.

(22). Piotrowski DW A Concise Route to Novel 1-Aryl and 1-Pyridyl-2-Azabicyclo[2.1.1]Hexanes. Synlett 1999, 1999 (07), 1091–1093.

(23). Elliott LD; Berry M; Harji B; Klauber D; Leonard J; Booker-Milburn KI A Small-Footprint, High-Capacity Flow Reactor for UV Photochemical Synthesis on the Kilogram Scale. Org. Process Res. Dev 2016, 20 (10), 1806–1811.

(24). Elliott LD; Booker-Milburn KI Photochemically Produced Aminocyclobutanes as Masked Dienes in Thermal Electrocyclic Cascade Reactions. Org. Lett 2019, 21 (5), 1463–1466. [PubMed: 30763101]

(25). Levterov VV; Michurin O; Borysko PO; Zozulya S; Sadkova IV; Tolmachev AA; Mykhailiuk PK Photochemical In-Flow Synthesis of 2,4-Methanopyrrolidines: Pyrrolidine Analogues with Improved Water Solubility and Reduced Lipophilicity. J. Org. Chem 2018, 83 (23), 14350–14361. [PubMed: 30358395]

(26). Dhake K; Woelk KJ; Becica J; Un A; Jenny SE; Leitch DC Beyond Bioisosteres: Divergent Synthesis of Azabicyclohexanes and Cyclobutenyl Amines from Bicyclobutanes. Angew. Chem., Int. Ed 2022, 61 (27), No. e202204719.

(27). Wiberg KB; Walker FH [1.1.1] Propellane. J. Am. Chem. Soc 1982, 104 (19), 5239–5240.

(28). Wiberg KB; Waddell ST; Laidig K [1.1.1]Propellane: Reaction with Free Radicals. Tetrahedron Lett. 1986, 27 (14), 1553–1556.

(29). Gianatassio R; Lopchuk JM; Wang J; Pan C-M; Malins LR; Prieto L; Brandt TA; Collins MR; Gallego GM; Sach NW; et al. Strain-Release Amination. Science 2016, 351 (6270), 241–246. [PubMed: 26816372]

(30). Nugent J; Arroniz C; Shire BR; Sterling AJ; Pickford HD; Wong ML; Mansfield SJ; Caputo DF; Owen B; Mousseau JJ; et al. A General Route to Bicyclo[1.1.1]Pentanes through Photoredox Catalysis. ACS Catal. 2019, 9 (10), 9568–9574.

(31). Wong ML; Mousseau JJ; Mansfield SJ; Anderson EA Synthesis of Enantioenriched α-Chiral Bicyclo[1.1.1]Pentanes. Org. Lett 2019, 21 (7), 2408–2411. [PubMed: 30869907]

(32). Zhang X; Smith RT; Le C; McCarver SJ; Shireman BT; Carruthers NI; MacMillan DWC Copper-Mediated Synthesis of Drug-like Bicyclopentanes. Nature 2020, 580 (7802), 220–226. [PubMed: 32066140]

(33). Dilmaç AM; Spuling E; de Meijere A; Bräse S Propellanes—From a Chemical Curiosity to "Explosive" Materials and Natural Products. Angew. Chem., Int. Ed 2017, 56 (21), 5684–5718.

(34). Makarov IS; Brocklehurst CE; Karaghiosoff K; Koch G; Knochel P Synthesis of Bicyclo[1.1.1]Pentane Bioisosteres of Internal Alkynes and Para-Disubstituted Benzenes from [1.1.1]-Propellane. Angew. Chem., Int. Ed 2017, 56 (41), 12774–12777.

(35). Della EW; Taylor DK Synthesis of Some Bridgehead-Bridgehead-Disubstituted Bicyclo[1.1.1]Pentanes.J. Org. Chem 1994, 59 (11), 2986–2996.

(36). Kanazawa J; Maeda K; Uchiyama M Radical Multicomponent Carboamination of [1.1.1] Propellane. J. Am. Chem. Soc 2017, 139 (49), 17791–17794. [PubMed: 29131599]

(37). Messner M; Kozhushkov SI; de Meijere A Nickel-and Palladium-Catalyzed Cross-Coupling Reactions at the Bridgehead of Bicyclo[1.1. 1]Pentane Derivatives-A Convenient Access to Liquid Crystalline Compounds Containing Bicyclo[1.1.1]Pentane Moieties. Eur. J. Org. Chem 2000, 2000 (7), 1137–1155.

(38). Yu IF; Manske JL; Diéguez-Vázquez A; Misale A; Pashenko AE; Mykhailiuk PK; Ryabukhin SV; Volochnyuk DM; Hartwig JF Catalytic Undirected Borylation of Tertiary C-H Bonds in Bicyclo[1.1.1]Pentanes and Bicyclo[2.1.1]Hexanes. Nat. Chem 2023, DOI: 10.1038/s41557-023-01159-4.

(39). VanHeyst MD; Qi J; Roecker AJ; Hughes JM; Cheng L; Zhao Z; Yin J Continuous Flow-Enabled Synthesis of Bench-Stable Bicyclo [1.1. 1] Pentane Trifluoroborate Salts and Their Utilization in Metallaphotoredox Cross-Couplings. Org. Lett 2020, 22 (4), 1648–1654. [PubMed: 31990565]

(40). Polites VC; Badir SO; Keess S; Jolit A; Molander GA Nickel-Catalyzed Decarboxylative Cross-Coupling of Bicyclo [1.1. 1] Pentyl Radicals Enabled by Electron Donor-Acceptor Complex Photoactivation. Org. Lett 2021, 23 (12), 4828–4833. [PubMed: 34100624]

(41). Salgueiro DC; Chi BK; Guzei IA; García-Reynaga P; Weix DJ Control of Redox-Active Ester Reactivity Enables a General Cross-Electrophile Approach to Access Arylated Strained Rings. Angew. Chem., Int. Ed 2022, 61 (33), No. e202205673.

(42). Zhao J-X; Chang Y-X; He C; Burke BJ; Collins MR; Del Bel M; Elleraas J; Gallego GM; Montgomery TP; Mousseau JJ, Nair SK; Perry MA; Spangler JE; Vantourout JC; Baran PS 1,2-Difunctionalized Bicyclo[1.1.1]Pentanes: Long-Sought-after Mimetics for Ortho/Meta-Substituted Arenes. Proc. Natl. Acad. Sci. U. S. A 2021, 118 (28), No. e2108881118. [PubMed: 34244445]

(43). Ma X; Han Y; Bennett DJ Selective Synthesis of 1-Dialkylamino-2-Alkylbicyclo-[1.1.1]Pentanes. Org. Lett 2020, 22 (22), 9133–9138. [PubMed: 33170018]

(44). Garry OL; Heilmann M; Chen J; Liang Y; Zhang X; Ma X; Yeung CS; Bennett DJ; MacMillan DWC Rapid Access to 2-Substituted Bicyclo[1.1.1]Pentanes. J. Am. Chem. Soc 2023, 145 (5), 3092–3100. [PubMed: 36696089]

(45). Yang Y; Tsien J; Hughes JME; Peters BK; Merchant RR; Qin T. An Intramolecular Coupling Approach to Alkyl Bioisosteres for the Synthesis of Multisubstituted Bicycloalkyl Boronates. Nat. Chem 2021, 13 (10), 950–955. [PubMed: 34584254]

(46). Denisenko A, Garbuz P; Voloshchuk N; Holota Y; Mykhailiuk P Water-Soluble Bioisosteres of the Ortho-Substituted Phenyl Ring. ChemRxiv June 30, 2022 DOI: 10.26434/chemrxiv-2022-tln0p-v2 (Accessed on 2022-07-06).

(47). Wiberg KB The Concept of Strain in Organic Chemistry. Angew. Chem., Int. Ed. Engl 1986, 25 (4), 312–322.

(48). Dannenberg JJ; Rocklin D A Theoretical Study of the Mechanism of the Thermal Decomposition of Azoalkanes and 1,1-Diazenes. J. Org. Chem 1982, 47 (23), 4529–4534.

(49). Kennedy SH; Dherange BD; Berger KJ; Levin MD Skeletal Editing through Direct Nitrogen Deletion of Secondary Amines. Nature 2021, 593 (7858), 223–227. [PubMed: 33981048]

(50). Hui C; Brieger L; Strohmann C; Antonchick AP Stereoselective Synthesis of Cyclobutanes by Contraction of Pyrrolidines. J. Am. Chem. Soc 2021, 143 (45), 18864–18870. [PubMed: 34748319]

(51). Qin H; Cai W; Wang S; Guo T; Li G; Lu H N-Atom Deletion in Nitrogen Heterocycles. Angew. Chem., Int. Ed 2021, 60 (38), 20678–20683.

(52). Lee M-S; Hrovat DA; Borden WT Ab Initio Calculations on the.Beta.-Cleavage Reactions of Polycyclic Radicals. Why Does Cubylcarbinyl React Much Faster than Either Homocubyl or 1-Bicyclo[1.1.1]Pentyl? J. Am. Chem. Soc 1995, 117 (41), 10353–10357.

(53). Meinwald J; Szkrybalo W; Dimmel DR Bicyclo[1.1.1]Pentane horn Mercury Sensitized and Unsensitized Gas Phase Photolyses of Bicyclo[2.1.1]Hexan-2-One. Tetrahedron Lett. 1967, 8 (8), 731–733.

(54). Culhane JC; Fokin VV Synthesis and Reactivity of Sulfamoyl Azides and 1-Sulfamoyl-1,2,3-Triazoles. Org. Lett 2011, 13 (17), 4578–4580. [PubMed: 21812453]

(55). Kennedy SH; Dherange BD; Berger KJ; Levin MD Author Correction: Skeletal Editing through Direct Nitrogen Deletion of Secondary Amines. Nature 2022, 608 (7921), No. E11.

(56). It has recently been reported that anomeric amides such as **6** are potentially genotoxic and therefore should be handled with caution.

(57). Levin MD; Kaszynski P; Michl J Bicyclo[1.1.1]Pentanes,[*n*]Staffanes, [1.1.1]Propellanes, and Tricyclo[2.1.0.$0^{2,5}$]Pentanes. Chem. Rev 2000, 100 (1), 169–234. [PubMed: 11749237]

(58). Elliott LD; Kayal S; George MW; Booker-Milburn K. Rational Design of Triplet Sensitizers for the Transfer of Excited State Photochemistry from UV to Visible. J. Am. Chem. Soc 2020, 142 (35), 14947–14956. [PubMed: 32786778]

(59). Druzhenko T; Skalenko Y; Samoilenko M; Denisenko A; Zozulya S; Borysko PO; Sokolenko MI; Tarasov A; Mykhailiuk PK Photochemical Synthesis of 2-Azabicyclo[3.2.0]Heptanes: Advanced Building Blocks for Drug Discovery. Synthesis of 2,3-Ethanoproline. J. Org. Chem 2018, 83 (3), 1394–1401. [PubMed: 29297689]

(60). Lorthioir O; Demanze S; Nassoy A-C Blue Light Enabled Access to Novel (Hetero)Aromatic Bridged Pyrrolidine Alcohols. Tetrahedron Lett. 2022, 108, 154129.

(61). Rigotti T; Bach T Bicyclo[2.1.1]Hexanes by Visible Light-Driven Intramolecular Crossed [2+2] Photocycloadditions. Org. Lett 2022, 24 (48), 8821–8825. [PubMed: 36414533]

(62). Reports by Lorthioir[60] and Rigotti[61] were disclosed during the preparation of this manuscript.

(63). Hinman R; Hamm K The Oxidation of 1, 1-Dibenzylhy-drazines1. J. Am. Chem. Soc 1959, 81 (13), 3294–3297.

(64). Ragains JR; Winkler JD Pseudosymmetry in Azabicyclo[2.1.1]Hexanes. A Stereoselective Construction of the Bicyclic Core of Peduncularine. Org. Lett 2006, 8 (20), 4437–4440. [PubMed: 16986919]

(65). Tamura Y; Ishibashi H; Hirai M; Kita Y; Ikeda M Photochemical Syntheses of 2-Aza-and 2-Oxabicyclo [2.1.1] Hexane Ring Systems. J. Org. Chem 1975, 40 (19), 2702–2710.

(66). BCP yield difference can be attributed to increased quantities of ring-opened diene from *epi*-**22c** compared to **22c**, suggesting that the minor diastereomer is more prone to β-fragmentation pathways.

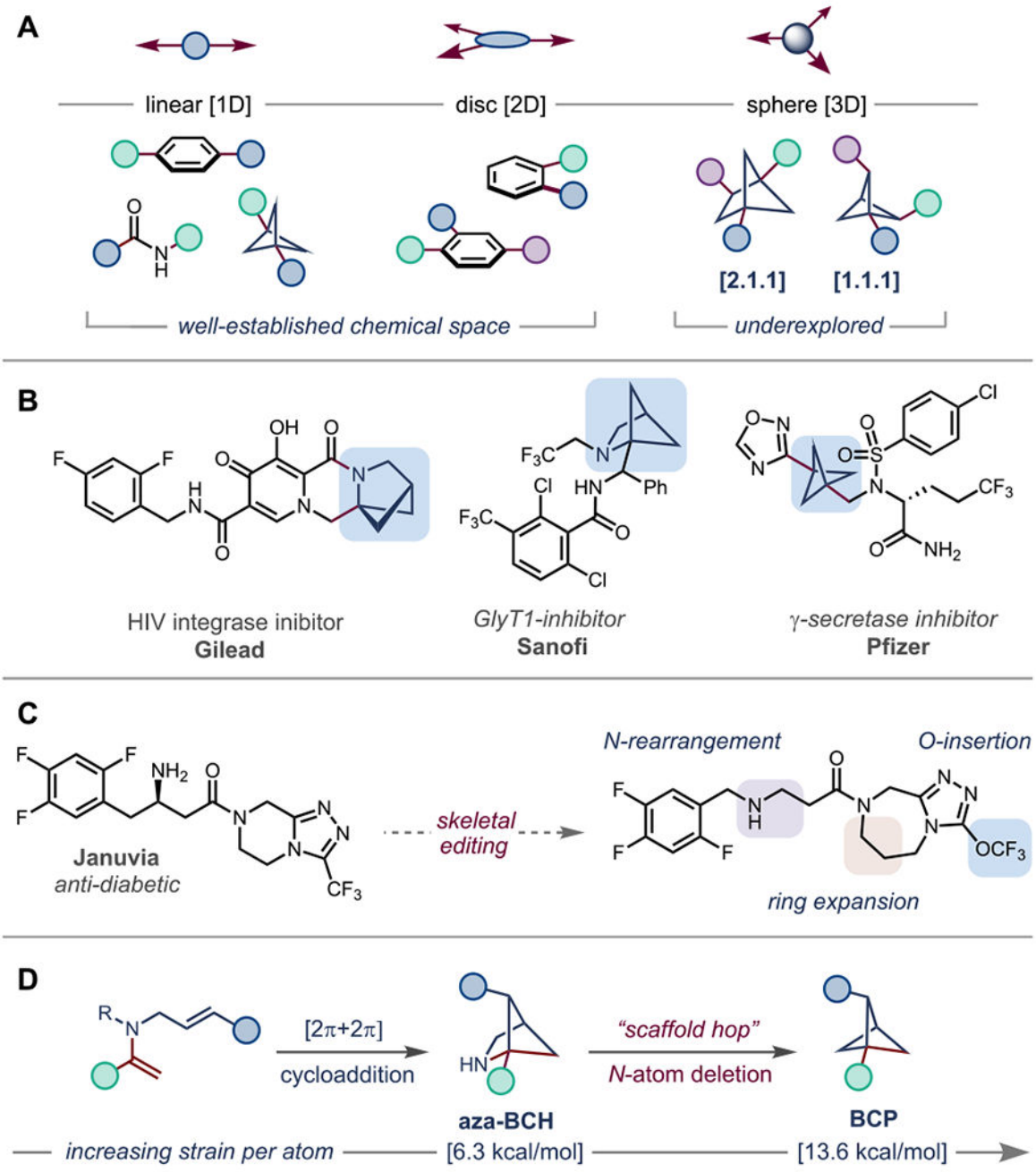


Figure 1.

A) Chemical space according to substituent display. B) Preclinical candidates including aza-BCH or BCP motifs. C) Skeletal editing as a strategy for late-stage core modification. D) *N*-atom deletion as a strategy for scaffold hopping between aza-BCH and BCP cores.

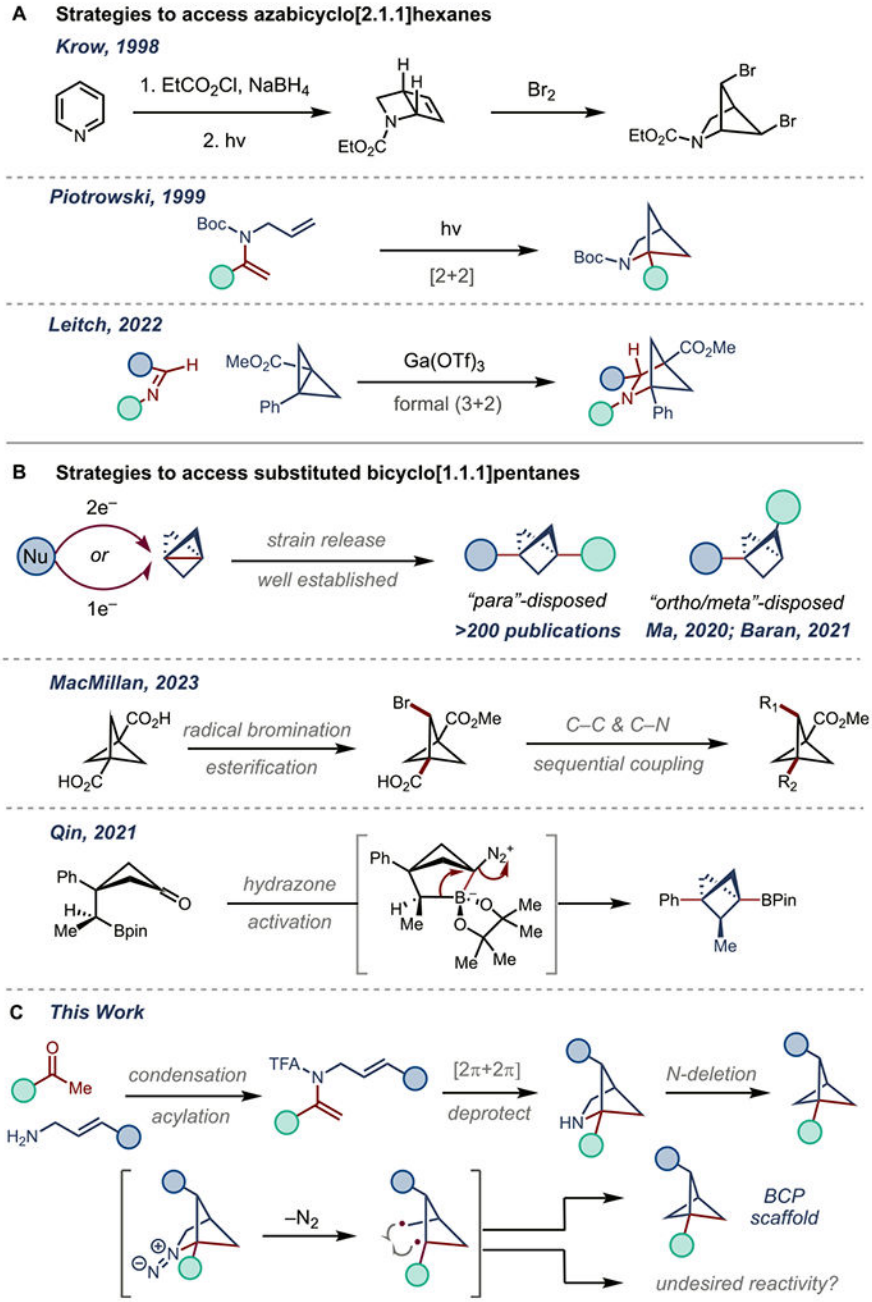
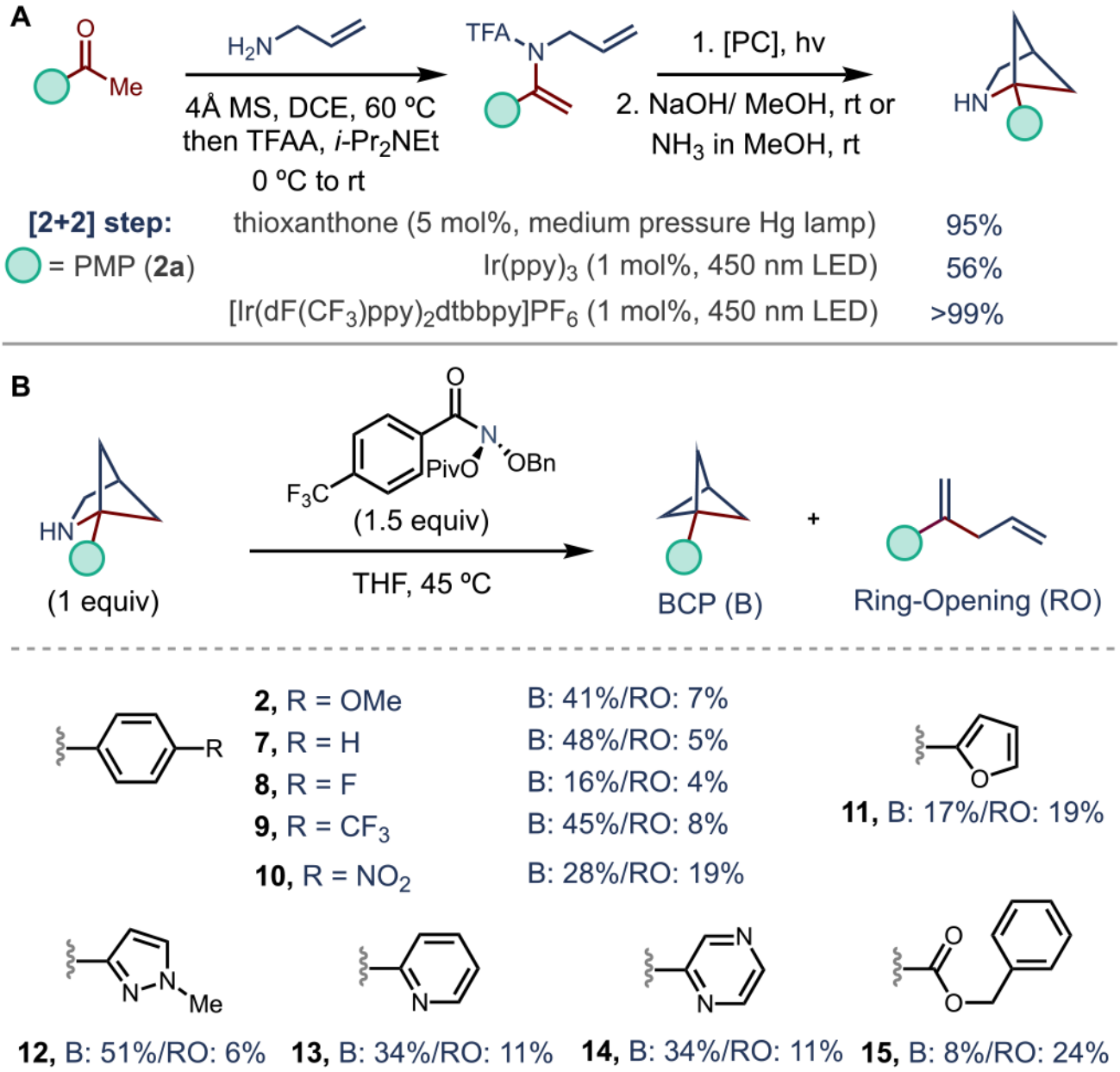


Figure 2.

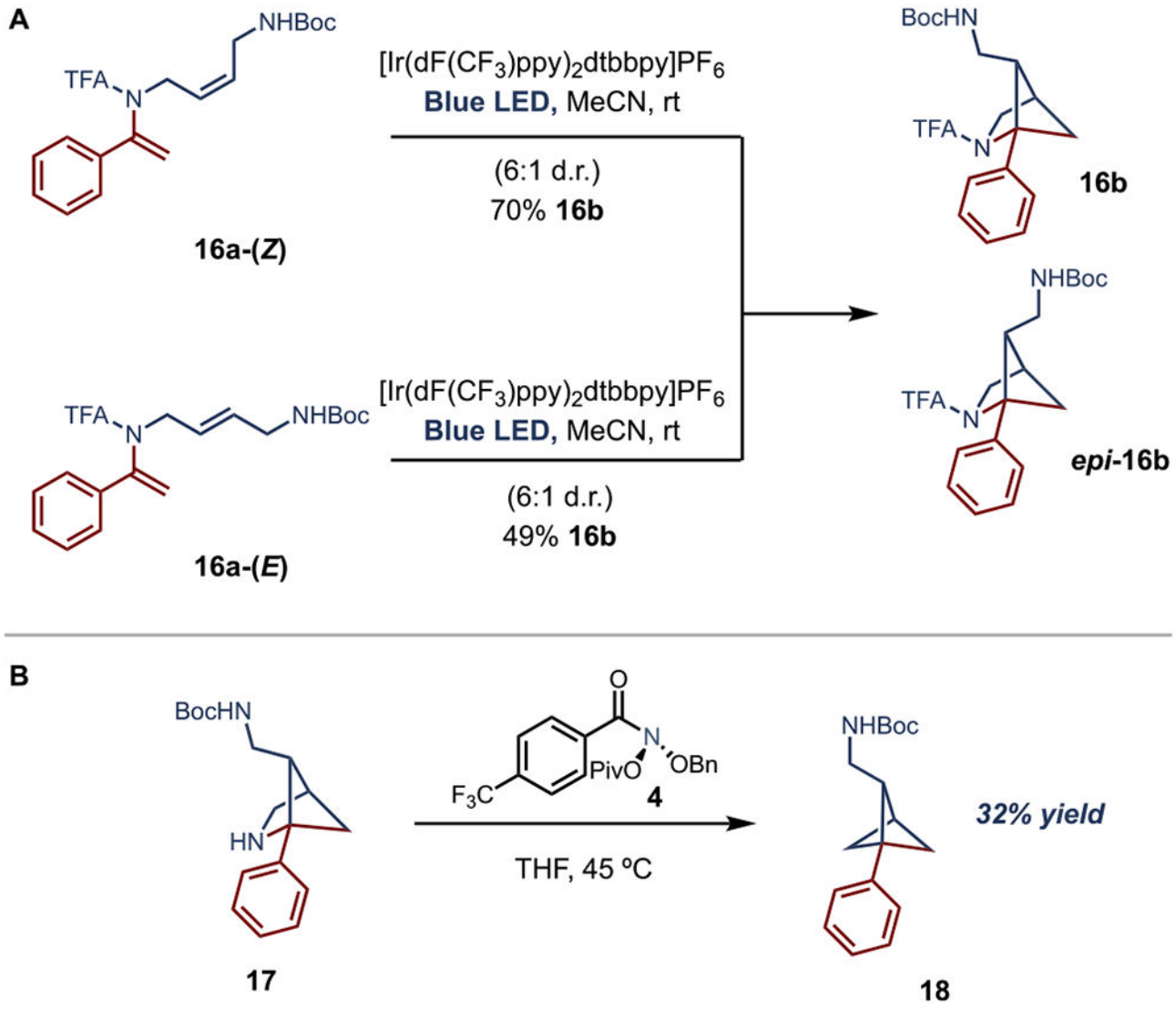
A) Previous approaches for aza-BCH synthesis. B) Known strategies for 1,2-BCP preparation. C) Nitrogen deletion to form BCPs through progressive formation of ring strain.



Scheme 1.

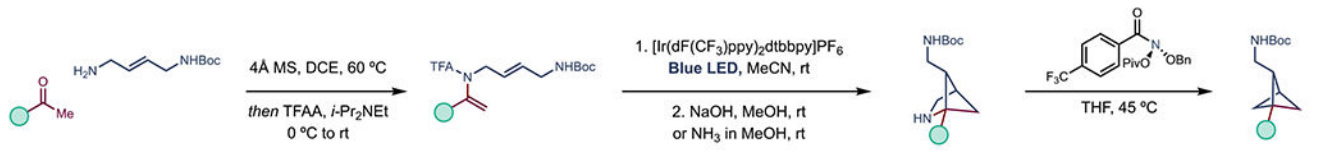
A) Synthetic Sequence to Access Aza-BCH Cores and B) Synthesis of Monosubstituted BCPs through Nitrogen Deletion[a,b]

[a]Yields are based on NMR comparison to internal standard. [b]PMP = p-methoxyphenyl.

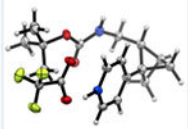


Scheme 2.

A) Diastereoconvergent [2+2] Photocycloaddition to Access 1,2-Substituted Aza-BCH Scaffolds and B) Synthesis of 1,2-Substituted BCPs through Nitrogen Deletion



Phenyl				6-Membered Heterocycles				
Entry	18	19	20	21	22	23	24	25
A: Enamide yield (%)	48	45	63	71	66	55	83	44
B: [2+2] yield (%, d.r.)	49 (6:1 d.r.)	75 (5:1 d.r.)	87[a] (5:1 d.r.)	52[a] (6:1 d.r.)	80 (7:1 d.r.)	76[a] (6:1 d.r.)	68 (7:1 d.r.)	65[a] (10:1 d.r.)
C: Deprotection yield (%)	79	91	86	82	97	76[a]	96	70
D: BCP yield (%)	32	28	26	47	52	28[b]	44	30

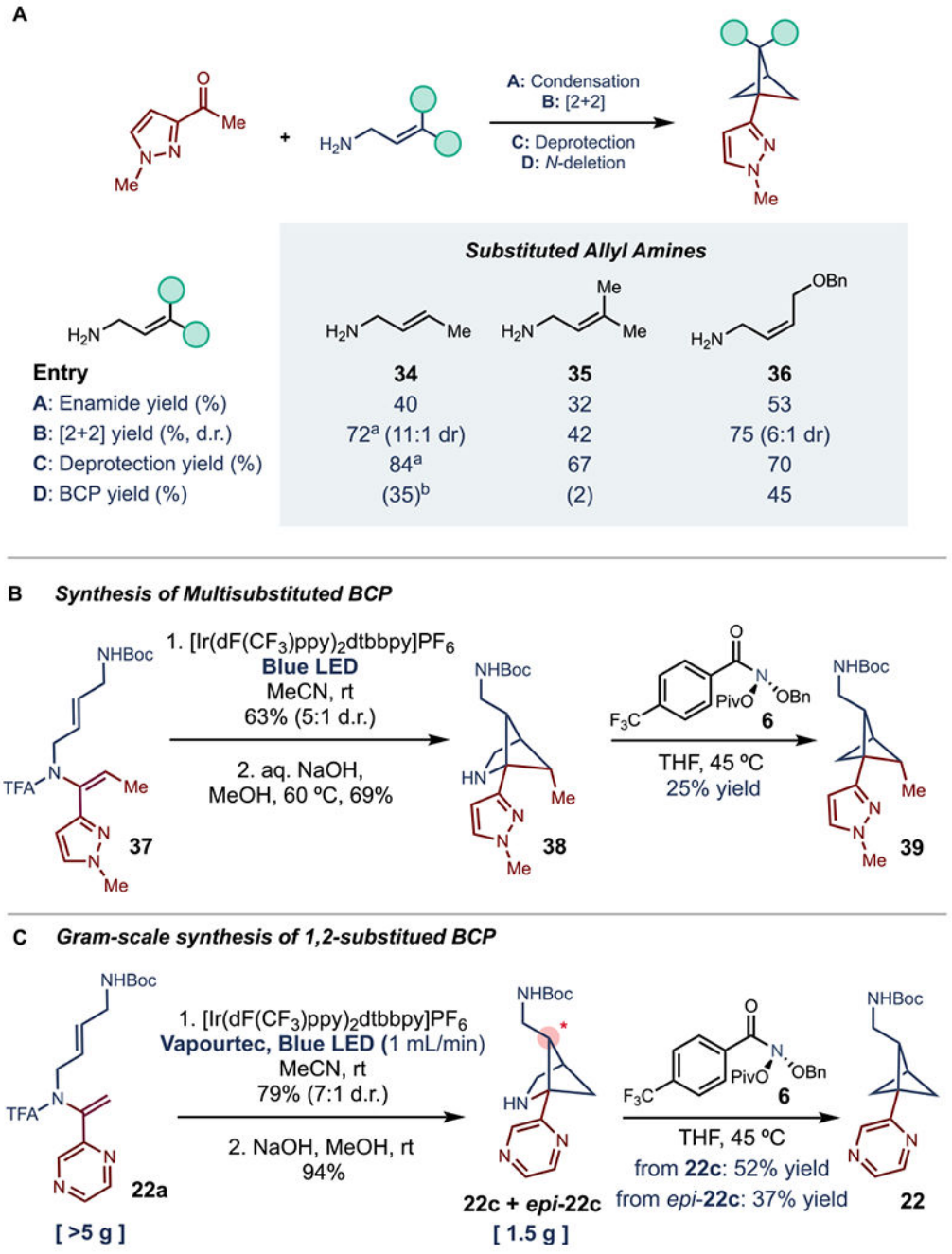


25•TFA [x-ray]

Halogenated Heterocycles		Fused Heterocycles		5-Membered Heterocycles			
Entry	26	27	28	29	30	31	32	33
A: Enamide yield (%)	37	72	47	40	56	57	50	22
B: [2+2] yield (%, d.r.)	79[a] (5:1 d.r.)	35[a] (10:1 d.r.)	57[a] (10:1 d.r.)	80[a] (10:1 d.r.)	77 (5:1 d.r.)	72 (7:1 d.r.)	53 (7:1 d.r.)	51[c]
C: Deprotection yield (%)	86[a]	60	82	52	98	99	93	95
D: BCP yield (%)	61[b]	35	60	29	41	39	(35)	26

Scheme 3. Aryl Scope of 1,2-Substituted BCPs through Nitrogen Deletion

[a]Mixture of diastereomers. [b]Nitrogen deletion carried out on mixture of diastereomers. [c]Diastereomeric ratio not determined due to the instability of the intermediate. NMR yields indicated in parentheses.

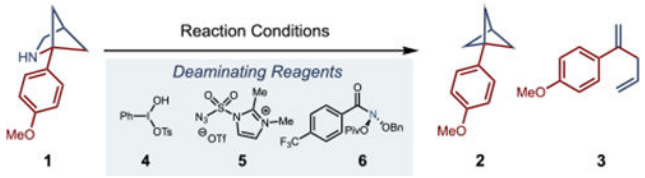


Scheme 4. A) Scope of Substituted Allyl Amines in Nitrogen Deletion, B) Synthesis of 1,2,4-Substituted BCPs, and C) Gram-Scale Preparation of Aza-BCH and BCP Cores

[a]Mixture of diastereomers. [b]Nitrogen deletion carried out on mixture of diastereomers. NMR yields indicated in parentheses.

Table 1.

Optimization Studies



		Yield (%)	
Entry	**Reaction Conditions**	**2**	**3**
1	HTIB (**4**), NH_3 in MeOH, TFE, 80 °C[a]	<5	n.d.
2	**5**, MeCN, LiO*t*-Bu, dioxane, 120 °C[b] (2 steps)	25	11
3	Levin's reagent (**6**), THF, 45 °C[c]	41	7
4	Modified Levin's reagent: *N*-OMe	8	4
5	Modified Levin's reagent: *N*-Cl	0	0
6	23 °C	20	3
7	45–120 °C	41	7
8	0.05 M THF	22	4
9	0.8 M THF	28	2
10	$Cu(OTf)_2$, $Ni(OTf)_2$, $Fe(OTf)_3$[d]	dec.	n.d.
11	$Co(OAc)_2$[d]	21	4

[a]"Reaction conditions: NH_3 in MeOH (8 equiv), HTIB (2.5 equiv), TFE, 80 °C.

[b]Step 1: **5** (1 equiv), MeCN, Step 2: LiO*t*Bu (1 equiv), 1,4-dioxane, 120 °C.

[c]**1** (1 equiv), **4** (1.5 equiv), THF, 45 °C.

[d]**1** (1 equiv), **6** (1.5 equiv), THF, metal salt (0.1 equiv), 45 °C.

See the Supporting Information for full experimental details.

n.d. = not determined; dec. = decomposition.