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

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Abstract

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Experimental procedures, characterization data, NMR spectra, and X-ray crystallographic data (PDF)

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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.

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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.

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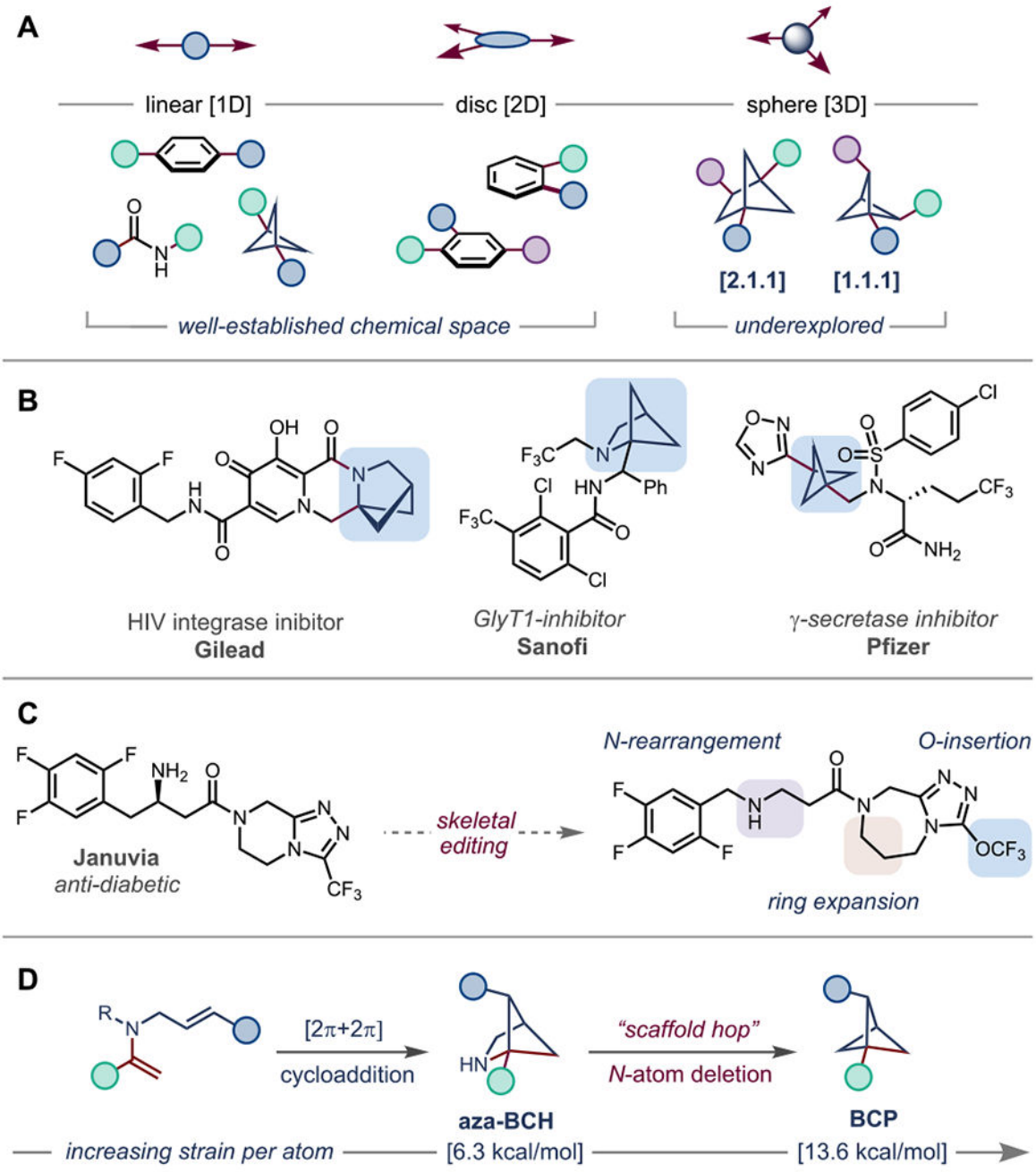


Figure 1.

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.

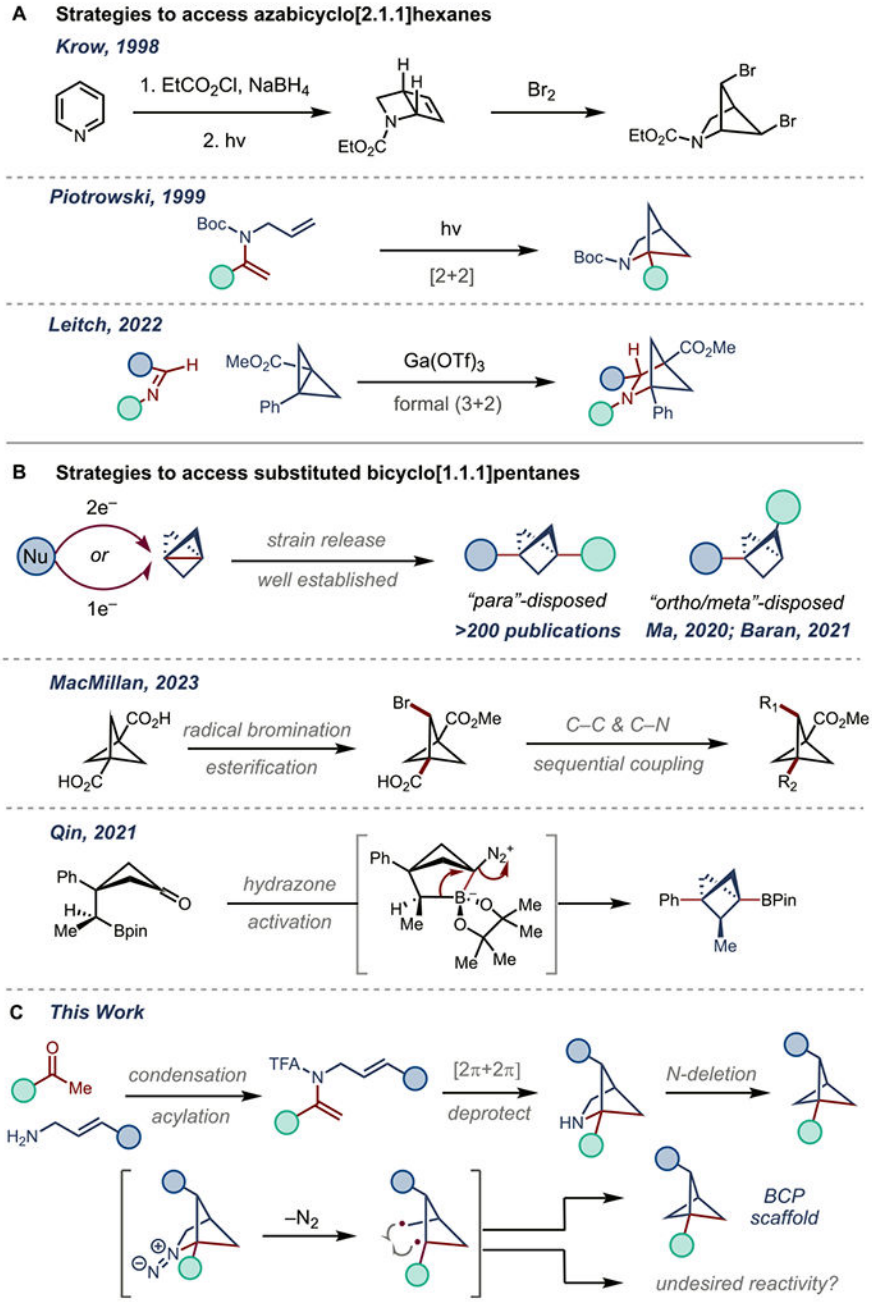
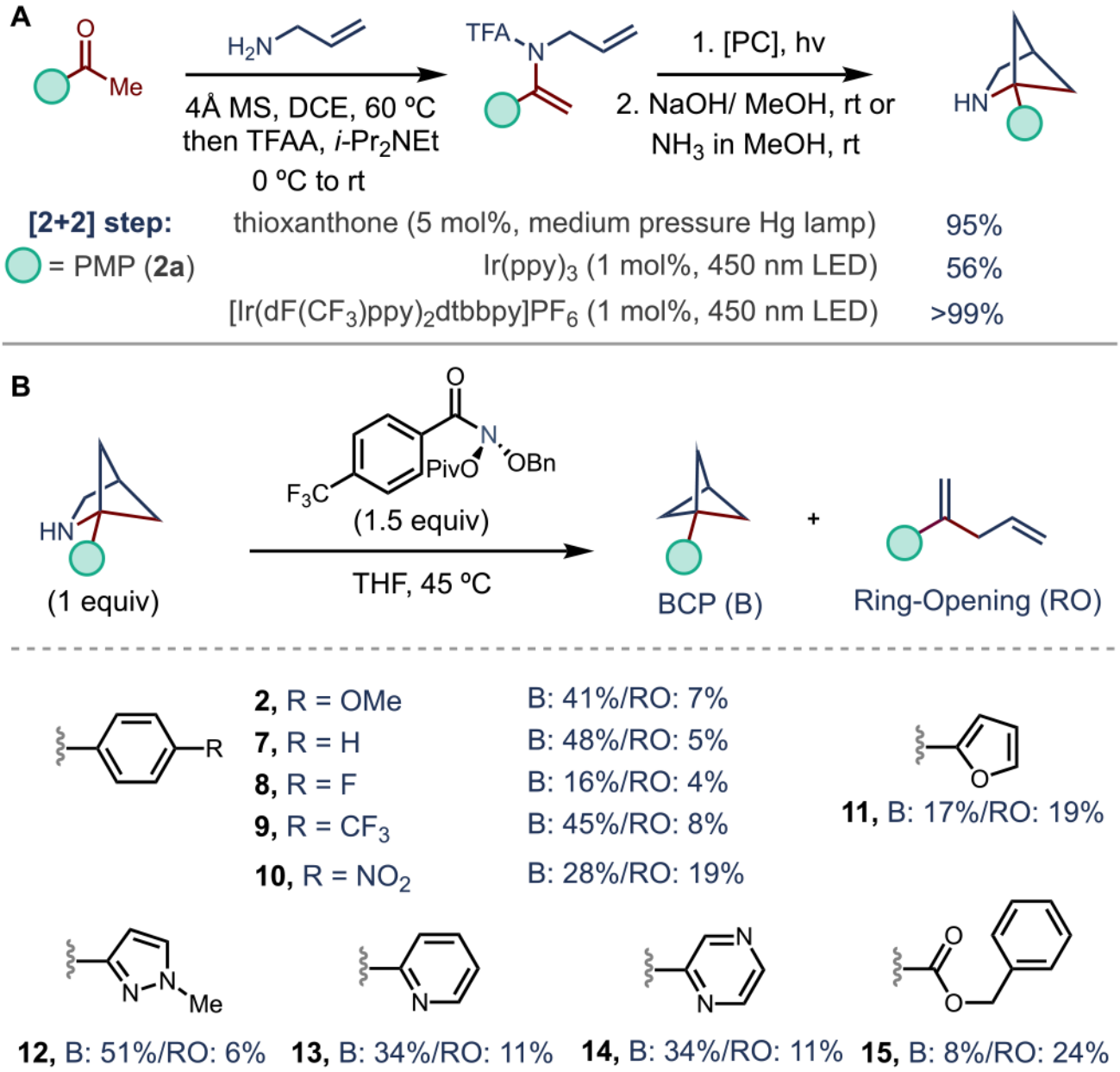


Figure 2.

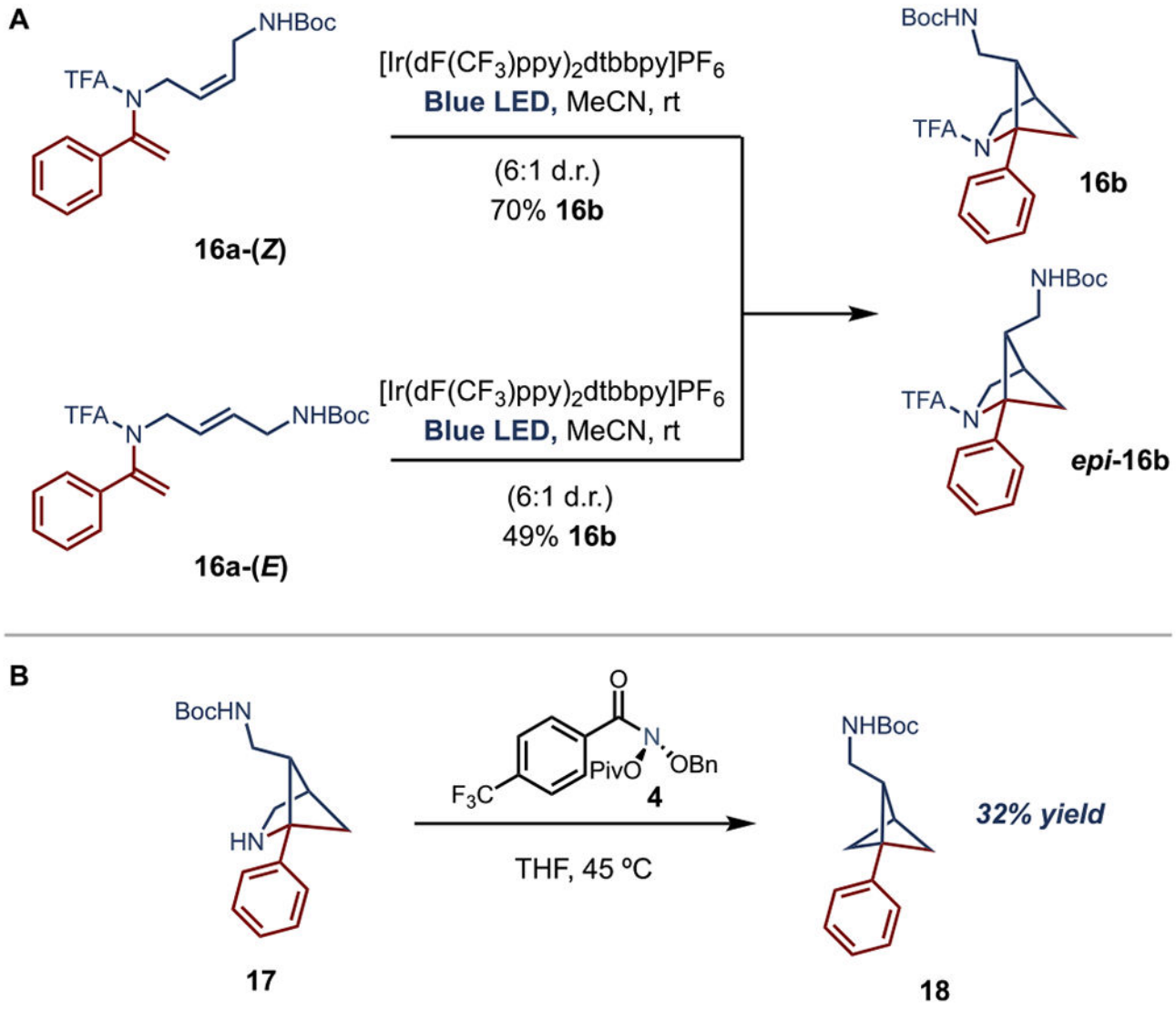
A) Previous approaches for aza-BCH synthesis. B) Known strategies for 1,2-BCP preparation. C) Nitrogen deletion to form BCPs through progressive formation of ring strain.



Scheme 1.

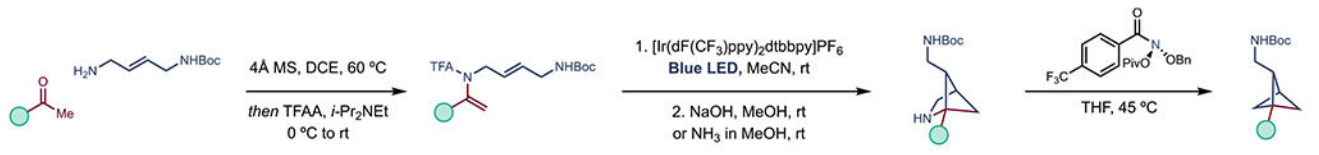
A) Synthetic Sequence to Access Aza-BCH Cores and B) Synthesis of Monosubstituted BCPs through Nitrogen Deletion[a,b]

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

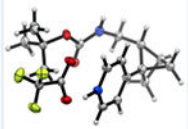


Scheme 2.

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

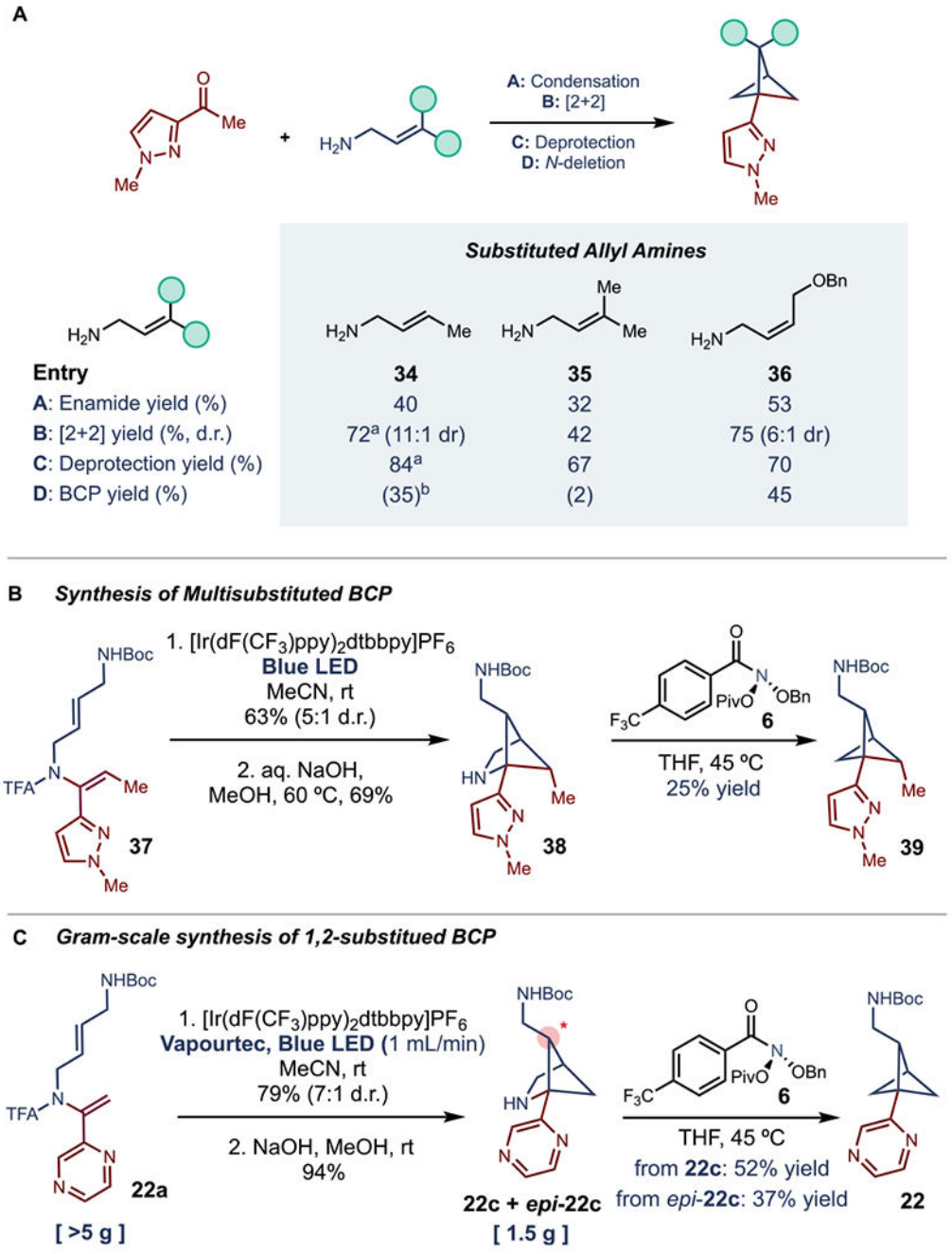


25•TFA [x-ray]

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.

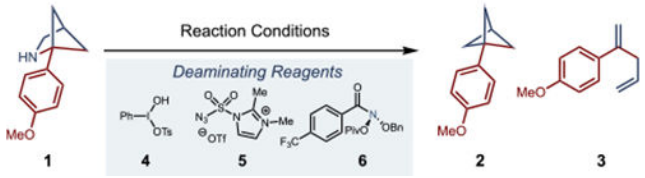


Scheme 4. A) Scope of Substituted Allyl Amines in Nitrogen Deletion, B) Synthesis of 1,2,4-Substituted BCPs, and C) Gram-Scale Preparation of Aza-BCH and BCP Cores

[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.