

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

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ABSTRACT: The ability to rapidly navigate a wide diversity of chemical space from simple building blocks is a cornerstone of medicinal chemistry campaigns. Aza-bicyclo[2.1.1]hexane (aza-BCH) and bicyclo[1.1.1]pentane (BCP) scaffolds have recently emerged as attractive classes of sp^3 -rich cores for replacing flat, aromatic scaffolds with metabolically resistant, three-dimensional frameworks. Over the last decade, these pharmaceutically desirable properties and increased synthetic accessibility have led to a marked increase in the adoption of aza-BCHs and BCPs into drug scaffolds. While multiple, independent methods have been developed for the preparation of these structural motifs, 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 bearing substituents that can be further derivatized.

Introduction

An important aspect of pharmaceutical discovery is the ability to rapidly access unique pharmacophores that occupy diverse regions of chemical structural 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 (i.e., two-dimensional) molecular scaffolds.² This strategy has been demonstrated as a viable path to overcome the inherent liabilities of unsaturated structural motifs.^{3,4} Molecular frameworks containing a high fraction of sp^3 -hybridized atoms (F_{sp^3}) have been shown to provide opportunities to project substituents (as growth vectors) in unique three-dimensional space with the added advantage of improving coveted pharmacological properties such as solubility^{5–10} and metabolic stability,^{2,6,8,11} as well as biological target specificity.^{12–14} These scaffolds are therefore positively correlated with clinical success.¹⁵ Despite these attractive features of sphere-like,^{16,17} sp^3 -rich building blocks, which can project substituents in a three-dimensional array, this chemical space remains largely underexplored due to the scarcity of

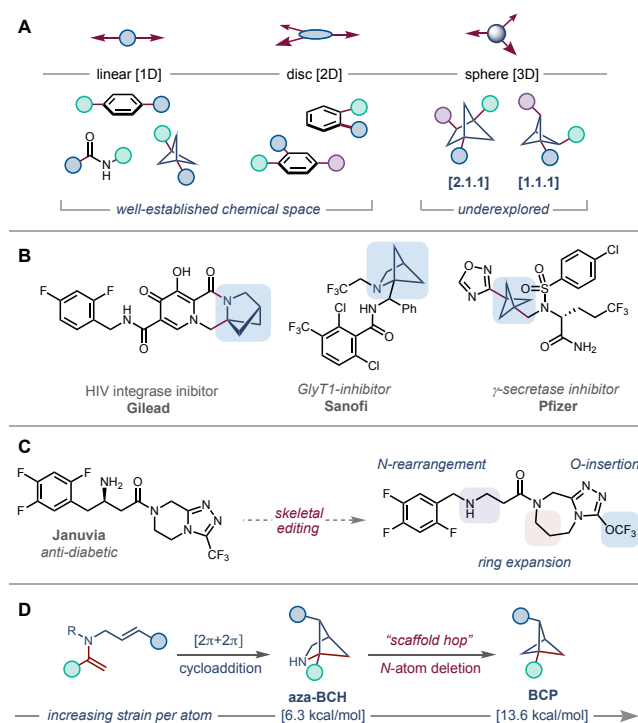


Figure 1. a) Diversity of chemical space accessed through display of substituents in a one-, two-, or three-dimensional fashion. b) Preclinical candidates including aza-BCH or BCP motifs. c) Skeletal editing as a strategy for late-stage core modification of molecular scaffolds. d) *N*-atom deletion as an enabling strategy for scaffold hopping between aza-BCH and BCP cores.

methods to access them (Figure 1A). Indeed, the development of novel and scalable strategies to rapidly access highly decorated, sp^3 -rich scaffolds would be of great value for drug discovery campaigns. This is particularly true in the context of azabicyclo[2.1.1]hexanes (aza-BCHs) and bicyclo[1.1.1]pentanes (BCPs), which have emerged as key bicyclic cores for replacing pyrrolidine or phenyl-containing structural motifs in a number of potential 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 in a late-stage fashion and pre-

sents an attractive opportunity to explore novel chemical space without the need for tailored synthetic sequences (Figure 1C).²⁰ Indeed, the ability to easily traverse the chemical landscape of saturated isosteres by directly editing their molecular topology would be highly attractive for generating new chemical matter in this uncharted territory. Therefore, we sought to apply this paradigm to access sp^3 -rich scaffolds 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 have involved the use of photochemical pericyclic processes to generate strained rings from flat, unstrained precursors (Figure 2A). For example, Krow’s approach involved the 4π -electrocyclization of dihydropyridines to strained [2.2.0] Dewar-dihydropyridines, which were then rearranged to the aza-BCH core upon treatment with oxidant.²¹ Analogous

cycloaddition strategies to directly form the requisite aza-BCH core have since followed suit: Piotrowski,²² Booker-Millburn,^{23,24} and Mykhailiuk²⁵ employed an intramolecular [2+2] from *N*-allyl enamides to rapidly assemble diverse 1-substituted aza-BCHs, while in a complementary fashion, Leitch²⁶ and co-workers developed an intermolecular formal (3+2) cycloaddition between imines and bicyclo[1.1.0]butanes to assemble multi-substituted aza-BCHs.

Following pioneering contributions from Wiberg^{27,28} and popularized by Baran,²⁹ Anderson,^{30,31} MacMillan,³² and others,^{33–36} the most commonly employed methods for the synthesis of BCPs rely on strain-release addition of groups to the central bond of

[1.1.1]propellane using one- or two-electron nucleophiles (Figure 2B). Such 1,3-functionalized BCPs are, in turn, further derivatized using an increasing number of methods.^{37–41} As a result, the vast majority of BCP derivatives prepared to date possess “*para*”-disposed substituents that reside at the bridgehead carbons exactly 180° apart. Recently, 1,2-functionalized BCPs—long sought-after isosteres for *ortho*- or *meta*-substituted arenes—have also been prepared by Baran/Pfizer⁴² and Ma⁴³ in an analogous fashion from prefunctionalized [1.1.1]-propellanes. In addition, MacMillan⁴⁴ and coworkers reported that radical 2-bromination of the BCP core and subsequent cross-coupling provides access to 1,2,3-substituted variants. In a conceptually distinct strategy, Qin and collaborators at Merck showcased the use of cyclobutyl

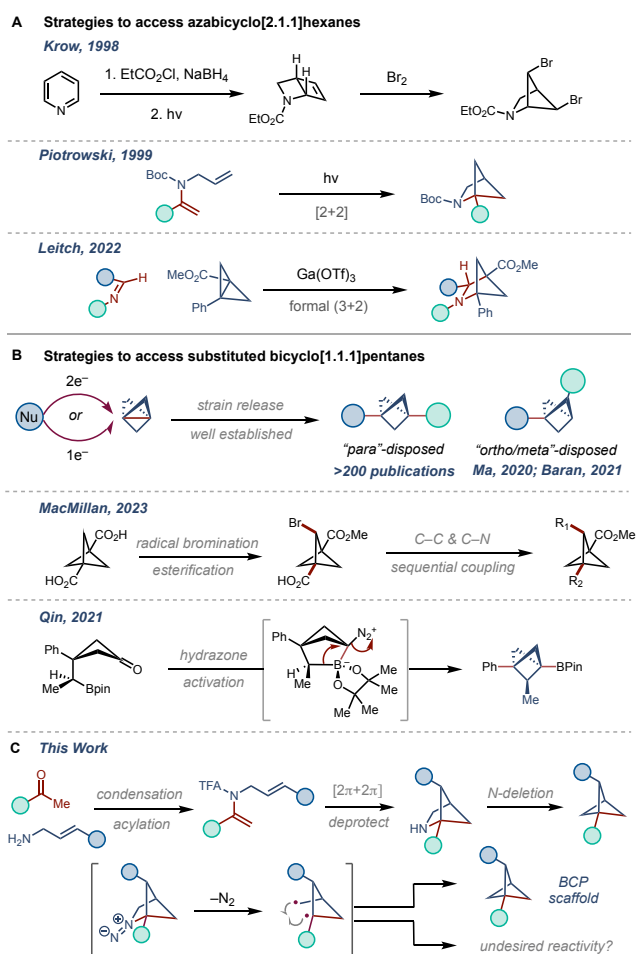


Figure 2. A) Previous approaches for aza-BCH synthesis utilizing [2+2] photocycloadditions or formal Lewis acid-mediated (3+2) B) Known strategies for 1,2-substituted BCP preparation C) Nitrogen deletion to form BCPs through progressive formation of ring strain across sequence.

sulfonylhydrazones in a Barluenga/Valdes-type intramolecular coupling with pinacol boronates to furnish functionalized BCPs.⁴⁵

In light of these approaches, we sought to develop a complementary route to rapidly generate molecular complexity that leveraged recent advances in both photoredox-catalyzed cycloadditions and skeletal editing to allow for a user-friendly, modular synthesis of both aza-BCH and BCP scaffolds starting from simple and readily available building blocks. We also recognized that, given the notable differences in solubility,^{25,46} hydrogen bond donating and accepting capabilities, as well as the available growth vectors, a direct “scaffold hop” between aza-BCH and BCP frameworks would be appealing for probing diverse chemical space among these *sp*³-rich cores.

Central to our plan for the aza-BCH to BCP “scaffold hop” 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-Millburn,^{23,24} and others,²⁵ we were drawn to a modular approach to aza-BCHs wherein initial condensation/acylation of ketone and amine reacting partners to generate enamides would set the stage for an intramolecular head-to-tail [2+2] cycloaddition to afford [2.1.1] scaffolds (strain energy of ~6.3 kcal/mol per atom).⁴⁷ Following deprotection of the aza-BCH nitrogen, skeletal editing by way of nitrogen deletion through isodiazene formation, dinitrogen extrusion, and radical recombination⁴⁸ would yield the desired BCP framework (strain energy of ~13.6 kcal/mol per carbon).⁴⁷ In this way, the nitrogen atom would serve both as a linchpin to template the [2 π +2 π] cycloaddition as well as a traceless handle for the final deamination step.

From this point, we envisioned isodiazene formation and subsequent nitrogen extrusion could be achieved using a number of recently popularized methods, including the use of anomeric amides,⁴⁹ iodonitrenes,⁵⁰ and sulfamoyl azides.⁵¹ Given the elevated steric environment imparted by the α -tertiary center, in

Table 1. Optimization studies

Entry	Reaction Conditions	Yield 2 (%)	Yield 3 (%)
1	HTIB (4), NH ₃ in MeOH, TFE, 80 °C ^a	<5	n.d.
2	5, MeCN; LiOt-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: <i>N</i> -OMe	8	4
5	Modified Levin's reagent: <i>N</i> -Cl	0	0
6	23 °C	20	3
7	45 °C to 120 °C ^d	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 ^e	decomp.	n.d.
11	Co(OAc) ₂ ^e	21	4

Reaction conditions: a) **1** (1 equiv), NH₃ in MeOH (8 equiv), HTIB (2.5 equiv), trifluoroethanol (0.1 M), 80 °C, 16 h. b) Step 1: Sulfamoyl azide (1 equiv), MeCN; Step 2: LiOt-Bu (1 equiv), 1,4-dioxane (0.1 M), 120 °C. 2 steps c) **1** (1 equiv), **4** (1.5 equiv), THF (0.2 M), 24 h, 45 °C. d) Reaction held at 45 °C for 18 h followed by 120 °C for 24 h. e) **1** (1 equiv), **4** (1.5 equiv), THF (0.2 M), metal salt (0.1 equiv) 24 h, 45 °C. See the Supplemental Information for detailed experimental procedures.

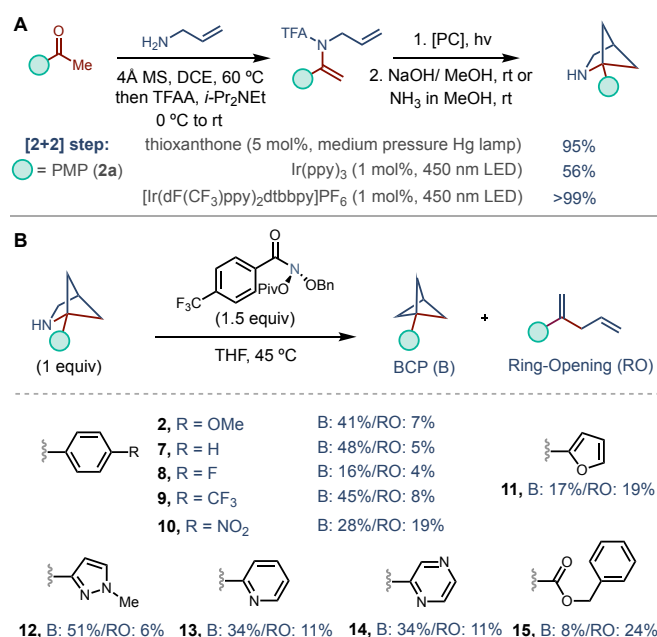
3- and 4-membered rings, respectively, this transformation would, to the best of our knowledge, represent the most strained ring system formed using this nitrogen deletion approach to date.

Results and Discussion

We began our investigations by surveying several deaminating reagents to effect the desired nitrogen deletion of azabicyclo[2.1.1]hexane **1** to arrive at desired BCP **2**. While hydroxy(tosyloxy)iodobenzene (HTIB, **4**)⁵⁰ in the presence of NH₃ in MeOH and trifluoroethanol (TFE) at 80 °C gave trace product formation (Table 1, entry 1), the use of sulfuryl azide transfer reagent **5**,⁵⁴ followed by treatment of the resulting sulfamoyl azide⁵¹ with LiOt-Bu in 1,4-dioxane at 120 °C, was more efficient (Table 1, entry 2). This produced the desired BCP in an improved 25% yield, along with 11% of the ring-opened diene (**3**, Table 1, entries 1 and 2), which ostensibly arises from strain-releasing cleavage of the cyclobutane radical intermediate. A further switch to conditions reported by Levin and coworkers,⁴⁹ employing the use of *N*-(benzyloxy)-*N*-(pivaloyloxy)-4-(trifluoromethyl)benzamide⁵⁵ (Levin's reagent, **6**) in THF under mild heating (45 °C), gave the desired BCP in 41% yield and 7% yield of the ring-opened product⁴⁹ (Table 1, Entry 3). Although modest in efficiency, this reactivity is remarkable given the inherent steric hindrance

conjunction with the significant increase in strain energy of the final ring closure, potential concerns for this sequence included 1) the possible lack of reactivity of the aza-BCH toward deaminating reagents and 2) the susceptibility of the intermediate diradical to terminate in non-productive pathways, 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-containing⁵⁰ structures to forge

around the amine handle, as well as the substantial ring strain associated with formation of the BCP core (68 kcal/mol; 13.6 kcal/mol per carbon)^{47,56} in comparison to the more thermodynamically stable skipped diene product.



Scheme 1. A) Synthetic sequence to aza-BCH cores from aryl ketone and allyl amine starting materials. B) Synthesis of monosubstituted BCPs through nitrogen deletion. Reported yields are based on NMR comparison to internal standard (1,3,5-trimethoxy benzene). For reported yields B = BCP and RO = Ring-opening.

cal intermediate arising from nitrogen extrusion resulted either in diminished yields or decomposition leading to intractable mixtures of products (Table 1, entries 10 and 11).

With optimized conditions in hand (Table 1, Entry 3), we next prepared a panel of mono-substituted aza-BCHs (Scheme 1A) to probe the role that aryl ring electronics played in the deamination sequence. In this regard, condensation of allyl amines with aryl ketones followed by treatment with TFAA smoothly afforded the corresponding TFA-protected enamides. While irradiation of *N*-allyl enamides with a Hanovia® medium pressure Hg-lamp (200–400 nm) gave initial success (95% yield), the recent development of photosensitizers^{57,58} which operate under visible light drew our attention to the possibility that the [2+2] could be conducted under milder conditions, which would render this approach more tolerant to a broader

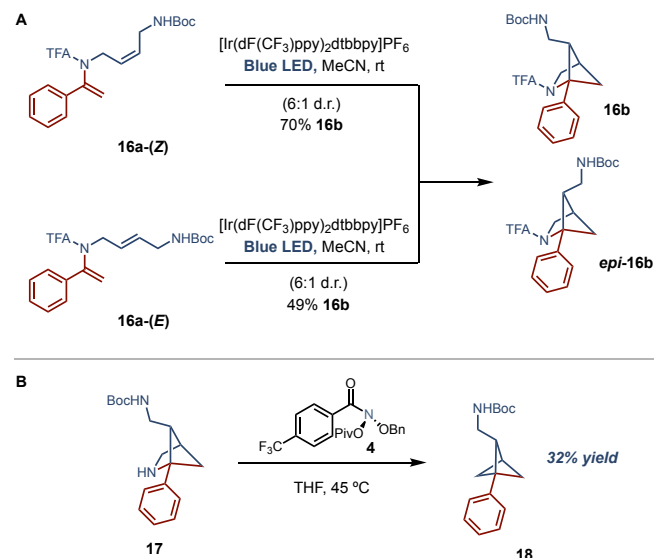
Modified versions of Levin's reagent bearing a smaller methoxy substituent or a chloride leaving group, to accelerate isodiazene formation given competing decomposition of anomeric amide **6**, led to significantly reduced or non-existent conversions and low yields of BCP **2** (Table 1, entries 4 and 5). Attempts to further optimize reaction 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 diradi-

array of functional groups. To this end, irradiation of *N*-allyl enamide **2a** with blue LED light in the presence of catalytic Ir(ppy)₃ (1 mol%) facilitated the intramolecular [2+2] cycloaddition in 56% yield.⁵⁹ Switching to [Ir(dF(CF₃)ppy)₂dtbbpy]PF₆ (1 mol%)^{57,59,60} yielded the targeted TFA-protected aza-BCH in >99% isolated yield. (The report by Lorthioir *et al.*⁵⁹ Rigotti *et al.*⁶⁰ was disclosed during the preparation of this manuscript). This cycloaddition, followed by TFA-cleavage of the protected intermediates, smoothly afforded an array of aza-BCHs which were subjected to the optimized deamination conditions (Scheme 1B).

Given that benzylic substitution has been previously observed to facilitate nitrogen deletion through isodiazene decomposition, presumably due to resonance stabilization of the diradical intermediate,^{49,61} we expected yields of the BCP products to improve with increased electron-donating ability of sp² substituents at C-1. However, no clear discernible trend in aryl ring electronics with respect to levels of BCP formation (16–51% yield) was observed for these mono-substituted substrates (**2**, **7-15**). In each of these cases, isolation of the mono-substituted BCP proved difficult given the volatility of the product, as previously reported, and yields were measured by ¹H NMR analysis using an internal standard.³⁷ Radical stabilizing groups other than arenes, such as a benzyl ester, afforded an 8% NMR yield of the BCP product, albeit with significant amounts of diene formation (Scheme 1B, **15**).

Following these initial observations, we next turned our attention to investigating the possibility of accessing 1,2-functionalized BCPs from the corresponding multi-substituted aza-BCHs. As a first example, we anticipated that incorporating a methylene-amino substituent would not only probe the reaction's tolerance to substitution at a bridging atom but also would provide a functional handle for further derivatization through standard chemistries. Synthesis of 1,2-substituted aza-BCHs commenced with the [2+2] cycloaddition of enamide **16a-(Z)** containing an internal (*Z*)-configured alkene. Subjection to the previously established conditions with [Ir(dF(CF₃)ppy)₂dtbbpy]PF₆ facilitated the [2+2] cycloaddition with

450 nm light to afford the aza-BCH system in a 6:1 diastereomeric ratio (**16b** and *epi-16b*) and a 70% isolated yield of the major diastereomer **16b** (Scheme 2, confirmed by 2D NMR, see the SI). 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 diastereomeric ratio suggested that a stepwise cycloaddition mechanism is likely operative. To probe this hypothesis, enamide **16a-(E)** bearing the (*E*)-configured alkene was subjected to the photocycloaddition, resulting in formation of **16b** and *epi-16b* in an identical diastereomeric ratio, further supporting a stepwise mechanism for the observed diastereoconvergence, in concordance with previously reported photocycloadditions of this type.^{62,63}



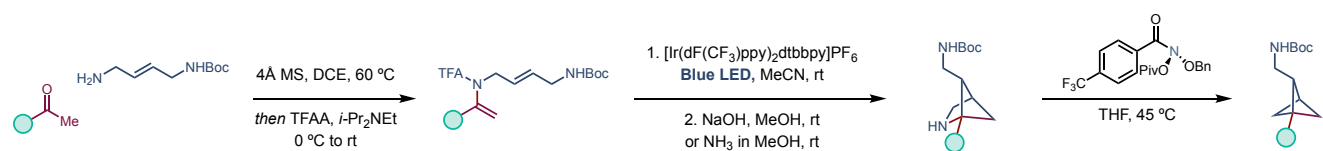
Scheme 2. A) Diastereoconvergent [2+2] photocycloaddition to access 1,2-substituted aza-BCH scaffolds. B) Synthesis of 1,2-substituted BCPs through nitrogen deletion.

With the substituted azabicyclo[2.1.1]hexane scaffold in hand, the major diastereomer **16b** was deprotected with NaOH in MeOH to give the free amine (**17**) which was then subjected to the deamination conditions. Gratifyingly, the desired BCP (**18**) was obtained in a serviceable 32% isolated yield (along with <5% yield of the ring-opened diene side product), enabling access to this important class of bridge-functionalized 1,2-substituted BCPs.

Having established a suitable method for synthesizing 1,2-substituted BCPs, we turned our attention to exploring the scope of this reaction sequence. We first investigated the effect of the aromatic group at the bridgehead carbon. Substituted phenyl rings with various electronics were tolerated in this reaction, furnishing the corresponding 1,2-substituted BCPs in similar yields (26–32% yield, see **18–20**, Scheme 3). Compared to arenes, heteroarene systems bearing a nitrogen at the 2-position gave improved isolated yields in most cases. Electron poor heteroarenes, which are ubiquitous in medicinal chemistry compound

libraries, such as pyrimidines (**21**), pyrazines (**22**) and 2-, 3-, and 4-substituted pyridyl systems (**23–25**), participated faithfully in this chemistry to give the products in isolated yields ranging from 28–52%. Pyridyl derivative **25**, isolated as the TFA salt, enabled unambiguous confirmation of the connectivity by X-ray crystallographic analysis. Notably, halogenated heterocycles such as **26** and **27**, which contain vectors for further functionalization through S_NAr or cross-coupling, were also compatible, uniquely enabled by the mildness of the [2+2] and judicious selection of deprotection conditions (NH_3 in MeOH) in the sequence. Although aryl bromides have thwarted previous UV-mediated [2+2] approaches to strained bicyclic scaffolds due to the heavy atom effect,⁵⁸ bromo-pyrimidine **27** could nevertheless be accessed under the photoredox cycloaddition conditions in 35% isolated yield. Fused bicyclic heterocycles, such as quinolines (**28**) and azaindoles (**29**), performed similarly compared to monocyclic heterocycles to give the corresponding BCP products 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 the extent to which other substitution patterns were accessible 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. 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 amines containing additional protected functionalities, such as a methylene benzyloxy group, also performed smoothly and yielded the desired BCP (**36**) in 45% yield.



Entry	Phenyl			6-Membered Heterocycles					25-TFA [x-ray]
	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	

Entry	Halogenated Heterocycles		Fused Heterocycles		5-Membered Heterocycles			
	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. Exploring the aryl scope of 1,2-substituted BCPs through nitrogen deletion. ^aYield refers to mixture of diastereomers. ^bNitrogen deletion carried out on mixture of diastereomers. ^cDiastereomeric ratio not determined due to instability of intermediate. All yields are isolated unless denoted in parentheses which indicate NMR yields based on comparison to internal standard (1,3,5-trimethoxybenzene).

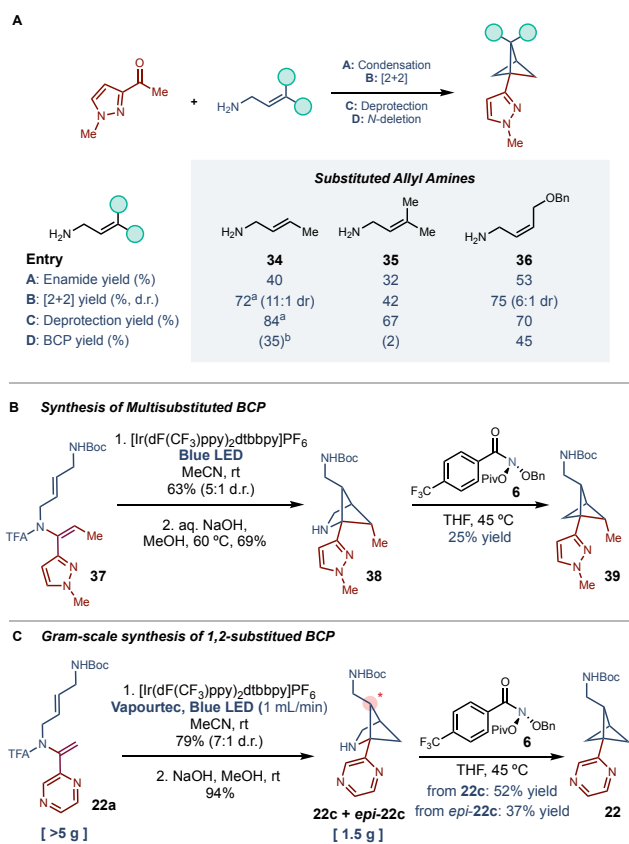
With the aim of accessing 1,2,4-trisubstituted BCPs, additional complexity could be installed via the formation of trisubstituted enamides to access multi-substituted BCP scaffolds. To this end, phenyl ethyl ketone readily formed the requisite enamide **37** from condensation with a substituted methylene-amino allyl amine followed by acylation with TFAA. Irradiation in the presence of $[\text{Ir}(\text{dF}(\text{CF}_3)\text{ppy})_2\text{dtbbpy}]\text{PF}_6$ then afforded the corresponding aza-BCH as a 5:1 diastereomeric mixture (epimeric about the methylene amino bridge) in 63% yield. Deprotection then yielded the corresponding aza-BCH **38** (confirmed by 2D NMR, see SI) which after subsequent nitrogen deletion afforded the unique 1,2,4-carbon-substituted BCP **39** in 25% yield — a scaffold that, to best of our knowledge, is reported here for the first time (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 gram scale as exemplified for BCP **22**. Accordingly, preparation of and subsequent [2+2] photocycloaddition of *N*-allyl enamide

22a was readily adapted to >5 gram scale and proceeded in good yield (79%) using a Vapourtec UV-150 flow reactor,²⁵ affording both separable diastereomers (**22c** and *epi-22c*) of the aza-BCH after subsequent TFA-cleavage. Major diastereomer **22c** could be subjected to nitrogen deletion on gram scale with no loss in efficiency (52% from **22c**), furnishing this useful BCP building block (**22**) for further discovery campaigns (Scheme 4C). Notably, minor diastereomer *epi-22c* was also competent in the *N*-deletion and proceeded in 37% yield, demonstrating that either diastereomer could be used in a convergent manner to afford the targeted BCP **22**.

Conclusions

Discovery stage pharmaceutical research hinges on the ability to rapidly access diverse regions of chemical space in which *sp*³-rich cores with high three-dimensionality are of particular interest. To address this need, we have developed a strategy for navigating strained-bicyclic chemical space through a nitrogen-deleting “scaffold hop”. Key to this approach is the marrying of recent advances in visible light photocycloadditions to rapidly generate molecular complexity from simple, flat precursors and deaminative skeletal editing to directly convert between privileged aza-BCH and BCP scaffolds. The enamide nitrogen serves as a linchpin for templating the head-to-tail [2 π +2 π] 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 quickly accessed in a modular fashion, expanding the chemical space around this sterically congested bioisosteric motif and representing the most strained ring system accessible by nitrogen deletion reported



Scheme 4. A) Scope of substituted allyl amines in nitrogen deletion to form BCPs. B) Synthesis of 1,2,4-substituted BCPs starting from substituted allyl amine and ethyl ketone fragments. C) Gram-scale preparation of aza-BCH and BCP cores. ^aYield refers to mixture of diastereomers. ^bNitrogen deletion carried out on mixture of diastereomers. All yields are isolated unless denoted in parentheses which indicate NMR yields based on comparison to internal standard (1,3,5-trimethoxybenzene).

to date. Incorporation of additional functional handles into the aza-BCH core facilitates new growth vectors for the development and optimization of host-guest interactions. More broadly, this strategy demonstrates the utility of skeletal editing for directly switching between classes of pharmaceutically relevant bicyclic scaffolds, enabling rapid exploration of two regions of chemical space. We anticipate that the ability to traverse between compact scaffolds of high three-dimensionality through skeletal editing techniques will facilitate access to additional bicyclic systems that may find use in pharmaceutical discovery and development.

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Notes

The authors declare no competing financial interest.

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