Strain-Release Radical-Polar Crossover Annulation: A Unified Strategy to Access Spiro-, Fused-, and Enantioenriched-Aza/Oxa-Bicyclo[3.1.1]hepatanes

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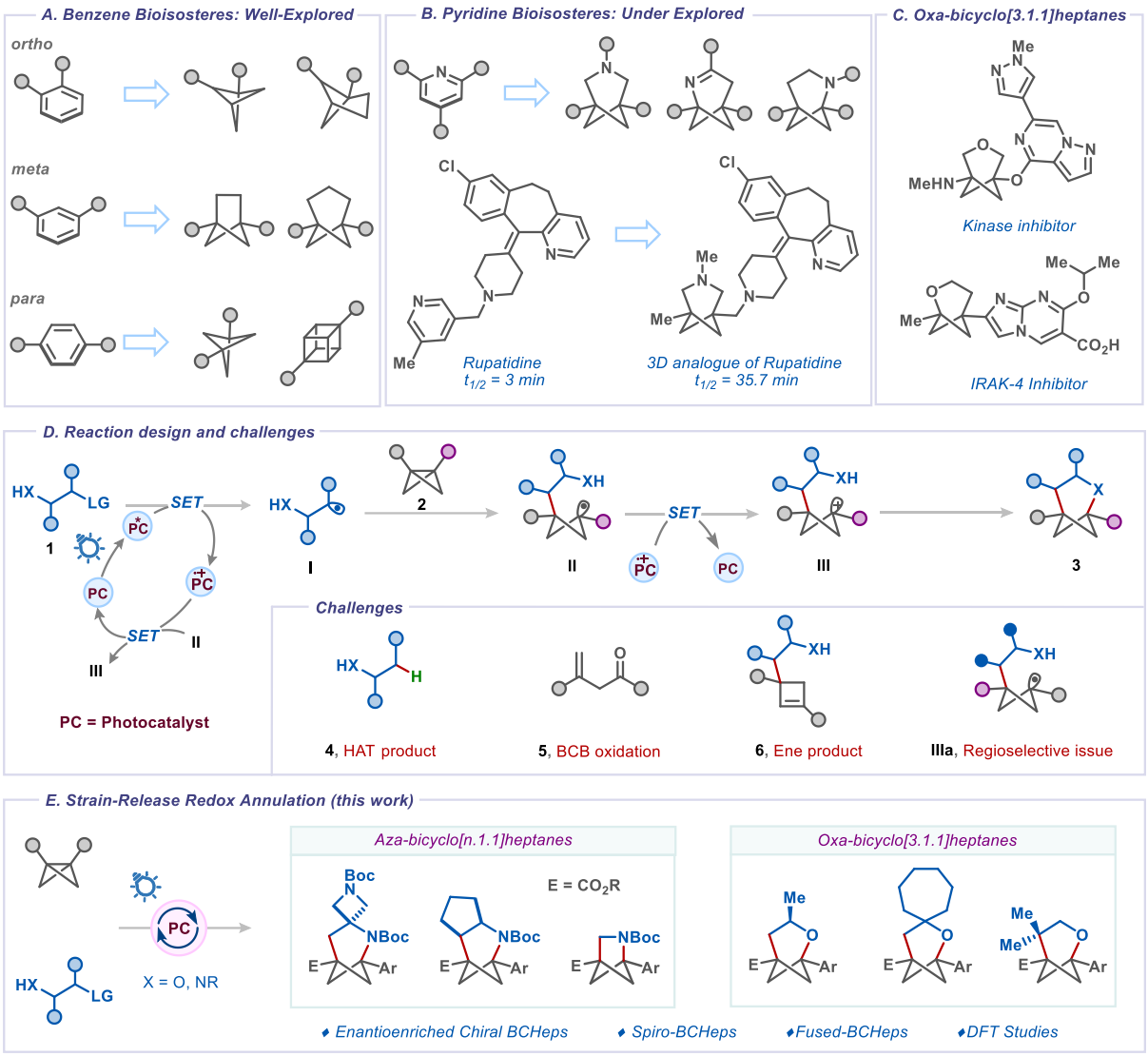
Abstract:

Conformationally rigid bridged bicyclic scaffolds have emerged as bioisosteric replacements for planar aromatic rings. However, bioisosteric mimetics of heteroaromatic rings have been investigated less due to the challenges of incorporating heteroatoms into bicycloalkanes. Herein, we report a unified strategy to access both aza- and oxa-bicyclo[3.1.1]heptanes in a single experimental protocol from readily accessible amino/hydroxy acids under photoredox catalysis. The method shows broad applicability across various redox-active esters and bicyclo[1.1.0]butanes and successfully provides previously inaccessible spiro- and fused-heterobicyclo[3.1.1]heptanes. Noteworthy, chiral amino/hydroxy acids derived redox-active esters could be used to access enantioenriched chiral heterobicyclo[3.1.1]heptanes. Furthermore, the strategy has been extended to access aza-bicyclo[2.1.1]hexanes, another important motif in medicinal chemistry. The functional groups introduced during the reaction serve as a synthetic handle for downstream manipulation, thus offering opportunities to build up molecular complexity rapidly. Density functional theory calculations and experimental studies support an oxidative radical-polar crossover mechanism and rationalize the observed regioselectivity.

Keywords: • Strain-release • Radical-Polar Crossover Annulation • Aza/oxa-bicyclo[3.1.1]heptanes • Bicyclobutane • DFT studies

Introduction:

Exploration of new chemical space by designing and preparing novel molecular entities to map biologically active space is rapidly evolving due to substantial advancements in modern organic and medicinal chemistry. Among the recent advancements, Lovering and coworkers showed that the three-dimensionality (3D) of the molecules is an important factor in determining the strength and selectivity of their protein-ligand interactions.[1] Indeed, drug candidates bearing 3D skeletons showed improved properties[2] such as solubility, lipophilicity, and metabolic stability compared to flat molecular structures, reflected in clinical trials by higher effectiveness



Scheme 1. (**A**) Benzene bioisosteres. (**B**) Pyridine bioisosteres and their importance. (**C**) Importance of oxa-bicyclo[3.1.1]heptanes. (**D**) Reaction design and challenges. (**E**) This work: Strain-release redox annulation.

and success rates. As a result, structurally rigid motifs are increasingly being used as bioisosteres of planar molecules in drug discovery and agrochemicals. Conformationally rigid cubanes and bicycloalkanes have emerged as effective bioisosteric replacements for substituted benzene rings (Scheme 1A).[3-8] Very recently, it has been shown that the introduction of heteroatom into bicyclic scaffolds not only provides new bioisosteric mimetics of heteroarenes but also confers higher water solubility and metabolic stability and reduced lipophilicity than the corresponding bicycloalkanes.[2] In 2023, the Mykhailiuk group reported that aza-bicyclo[3.1.1]heptane (3-aza-BCHep) was a potential bioisostere of pyridine and the replacement of pyridine moiety with the 3-aza-BCHep unit in Rupatidine, an anesthetic drug, showed improved physicochemical properties (Scheme 1B).[2, 9] 3-Oxa-bicyclo[3.1.1]heptane (3-Oxa-BCHep) is another important 3D scaffold present in natural products and bioactive

compounds that has gained recent attention in medicinal chemistry (Scheme 1C).[10, 11] Consequently, new catalytic and modular strategies for synthesizing heteroatom-substituted bicycloalkanes are highly desirable for enlarging the compound library accessible for drug discovery.

In recent years, Bicyclo[1.1.0]butane (BCB) has emerged as a versatile building block in organic synthesis for the efficient construction of complex cyclobutanes and bicyclo[n.1.1]alkanes.[12-24] Owing to its high ring-strain, the central carbon-carbon σ bond of BCB participates in both polar nucleophilic[25] and electrophilic addition reactions,[26] and it is also known to react with a broad range of radicals.[12, 27-31] Furthermore, the central carbon-carbon bond can undergo insertion-type reactions with carbenes and π-systems to furnish bridged bicyclic motifs.[32, 33] While these insertion strategies are very effective for the synthesis of bicyclo[n.1.1]alkanes, the methods for accessing hetero-bicyclo[n.1.1] alkanes remain less explored. In 2022, the Leitch group reported a formal (3+2) cycloaddition between arylimines and BCB to access 2-azabicyclo[2.1.1]hexanes.[34] Very recently, the groups of Glorius and Deng developed elegant strategies for synthesizing 2-oxa-4-aza- and 2-oxa-3-azabicyclo[3.1.1]heptanes.[35, 36] The reaction of BCB with vinyl azides also provides efficient access to 3-aza-BCHeps.[37] Cycloaddition reactions of BCB with ketones, *para*-quinone methides, and vinyl oxiranes afford functionalized oxa-bicyclo[n.1.1]alkanes.[38-40] Despite these advances, developing new, unified, and modular methods for inserting heteroatoms into BCBs to access highly substituted heterobicyclo[n.1.1]alkanes in a single experimental protocol is a highly appealing strategy but remains elusive.

On the other hand, it is hard to underestimate the impact of photoredox catalysis on chemical synthesis, as it enables innovative transformations to be achieved under ambient conditions with excellent functional group tolerance. Within this field, radical/polar crossover (RPC) describes a specific subset of reactions involving the splicing of radical and polar/ionic species in one pot, which creates rapid molecular complexity from simple feedstock materials. We envisioned an RPC/annulation strategy between BCB and a bifunctional reagent derived from an amino acid derivative that bearing a radical precursor and a tethered nucleophile that would enable access to a diverse set of hetero-bicyclo[n.1.1]alkanes in a modular fashion. Our reaction design involves a single-electron transfer (SET) from the excited state photocatalyst to radical precursor **1** to give radical intermediate **I** (Scheme 1D). Subsequent regioselective radical addition to BCB **2** would provide a more stable tertiary radical **II**. Next, an oxidative RPC would occur via the SET oxidation of *tertiary* radical to carbocation **III** by the oxidized photocatalyst. Finally, the tethered nucleophile was added to the carbocation intramolecularly

to furnish the desired product **3**. Notably, this strategy would benefit from using a variety of radical types and nucleophilic groups with varying tether lengths. Thus, we anticipated this redox-neutral RPC/annulation would provide a diverse range of hetero-bicyclo[n.1.1]alkanes through a unified strategy. However, this strategy involves various challenges: a) the formation of undesired HAT product **4**, BCB oxidation product **5**, and ene-type product **6**,[20] and b) addressing the regioselective issue to avoid **IIIa**. Notwithstanding these challenges, herein we report our success in realizing the strain-release RPC/annulation method to access a library of highly functionalized 3-aza-BCHeps (Scheme 1E). Our strategy allows the synthesis of spiro- and fused 3-aza-BCHeps, which are challenging to prepare using reported methods. We could also use chiral amino acids derived redox-active esters to access enantioenriched chiral 3-aza-BCHeps. Finally, we extended this strategy to synthesize 3-oxa-BCHeps and aza-bicyclo[2.1.1]hexanes, another important class of compounds in medicinal chemistry. DFT studies rationalized the observed reactivity and regioselectivity.

Results and Discussion

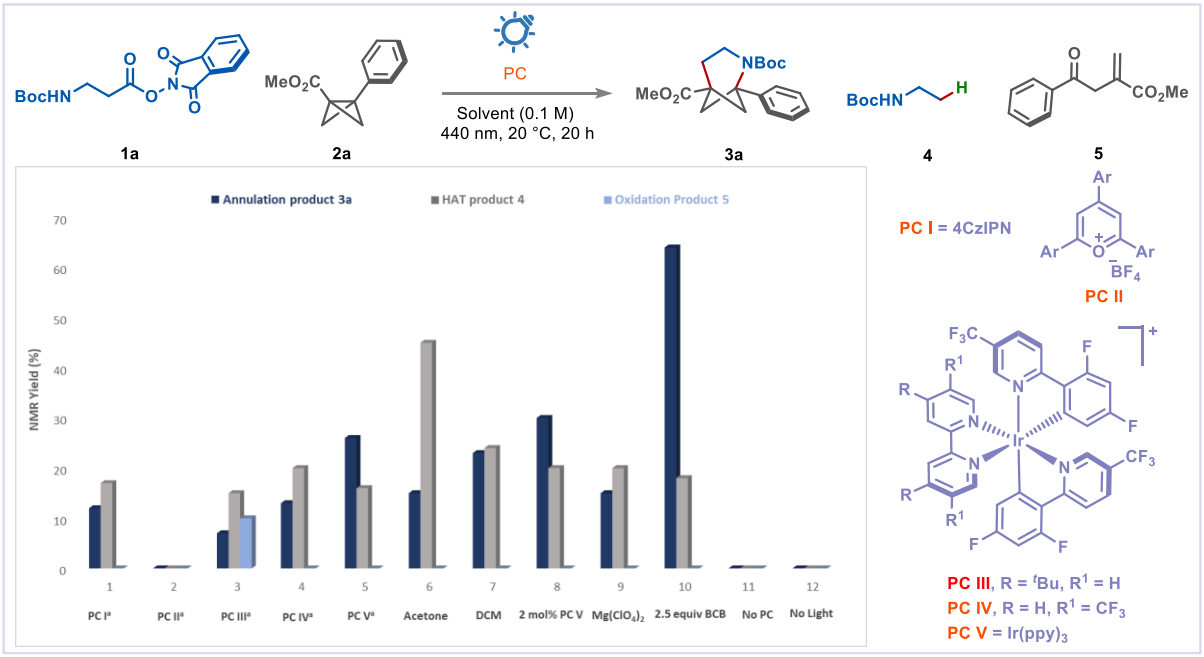
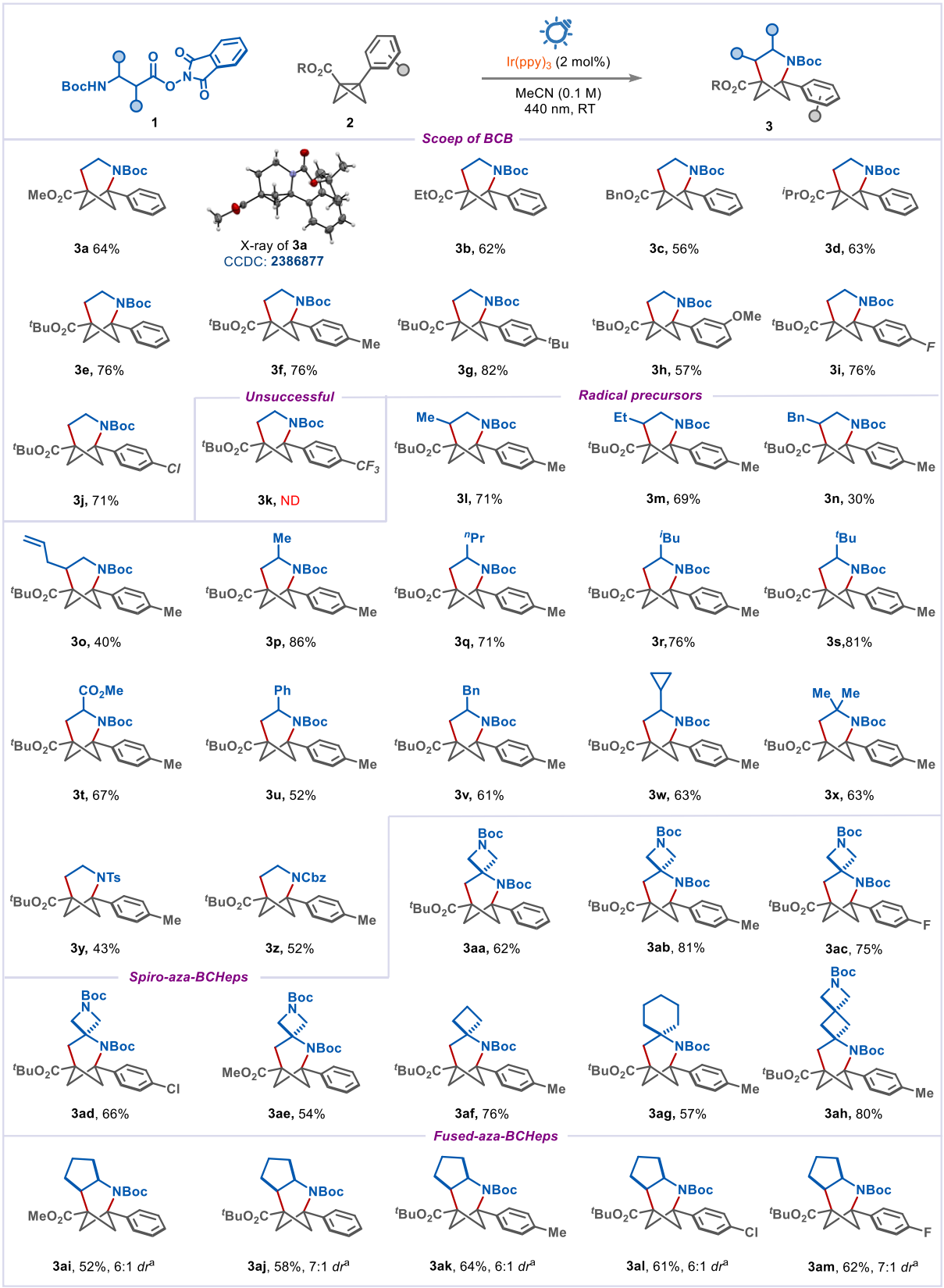


Figure 1: Optimization of the reaction conditions. RAE **1a** (0.10 mmol), BCB **2a** (1.0 equiv) PC (5 mol%), dry solvent (1.0 mL, 0.1 M), argon atmosphere, 440 nm Kessil lamp, rt, 12 h. Columns 1 to 5 and 8 to 12: MeCN (1.0 mL, 0.1 M). Columns 6 to 10 and 12: PC V. Column 10: 2.5 equiv BCB **2a**, 2 mol% PC V, 16 h. Yields were determined by ^{1}H-NMR using CH_2Br_2 as the internal standard.

We began our investigations by studying the radical redox annulation between NHPI ester **1a** and BCB **2a** using 4CzIPN (5 mol%) as a photocatalyst under blue light irradiation in MeCN. To our delight, the reaction gave the desired product **3a** in 12%, along with the HAT product **4** in 17% (Figure 1, column 1). Next, photocatalysts with different redox potentials were tested

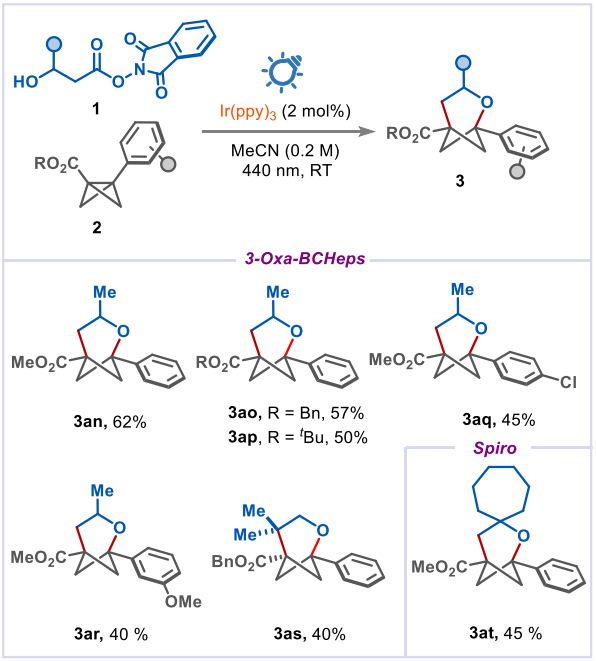
(Figure 1, columns 2-5). Pleasingly, $Ir(ppy)_3$, which has the highest reduction potential among the photocatalysts tested,[41] gave the desired product **3a** in a 26% yield (Figure 1, column 5). Other solvents were also investigated, but comparable or lower yields were obtained (Figure 1, columns 6 and 7; see SI for more optimization details). The effect of the photocatalyst loading was also tested, and a similar yield was obtained when a lower amount of photocatalyst (2 mol%) was used (Figure 1, column 8). $Mg(ClO_4)_2$, known to activate the NHPI ester,[42] didn't improve the reaction yield (Figure 1, column 9). The reaction yield is drastically improved to 67% when we used 2.5 equiv of BCB (Figure 1, column 10). Pleasingly, the synthesis of **3a** was conducted on a 2 mmol scale with similar efficiency, thus demonstrating the scalability of the reaction. Control experiments showed that the photocatalyst and light are crucial for this transformation (Figure 1, columns 11 and 12).

With the established optimal reaction conditions, we investigated the generality of the annulation reaction with various BCBs (Scheme 2). Initially, we explored the reactivity of the ester part of BCBs. Simple ethyl, benzyl, isopropyl, and *tert*-butyl esters successfully yielded the corresponding products **3a**-**3e** in good yields. The structure of **3a** was unambiguously determined through X-ray analysis (CCDC **2386877**). Next, we focused our investigations on screening various substitutions on the aryl ring of BCBs. A range of electron-donating and electron-withdrawing groups at the *para* and *meta* positions on the aromatic ring of BCB, including methyl, *tert*-butyl, methoxy, fluoro, and chloro, underwent the desired transformation successfully, yielding the desired products **3f**-**3j** in good yields. However, a trifluoromethyl group at the *para* position on the aromatic ring of BCB was found to be a non-viable substrate (product **3k**). This could be attributed to the difficulty in oxidizing the corresponding benzyl radical to benzylic carbocation. Next, we turned our attention to evaluating the scope of radical precursors using BCB **2f**. We were pleased to find that various *β*-substituents on amino acid derivatives, including methyl, ethyl, benzyl, and allyl, reacted smoothly to furnish the corresponding products **3l**-**3o** in moderate to good yields. Furthermore, a wide range of *α*-substituted amino acid derivatives bearing methyl, *n*-propyl, *iso*-butyl, *tert*-butyl, methyl carboxylate, phenyl, benzyl, and cyclopropyl were well participated, affording the desired products **3p**-**3w** in good to excellent yields. Gratifyingly, gem-dimethyl substituted radical precursor was also successfully engaged in the reaction, furnishing the product **3x** in 63% yield. Additionally, other commonly used *N*-protecting groups, such as Ts and Cbz, could also be used, providing the desired products **3y** and **3z** in synthetically useful yields.



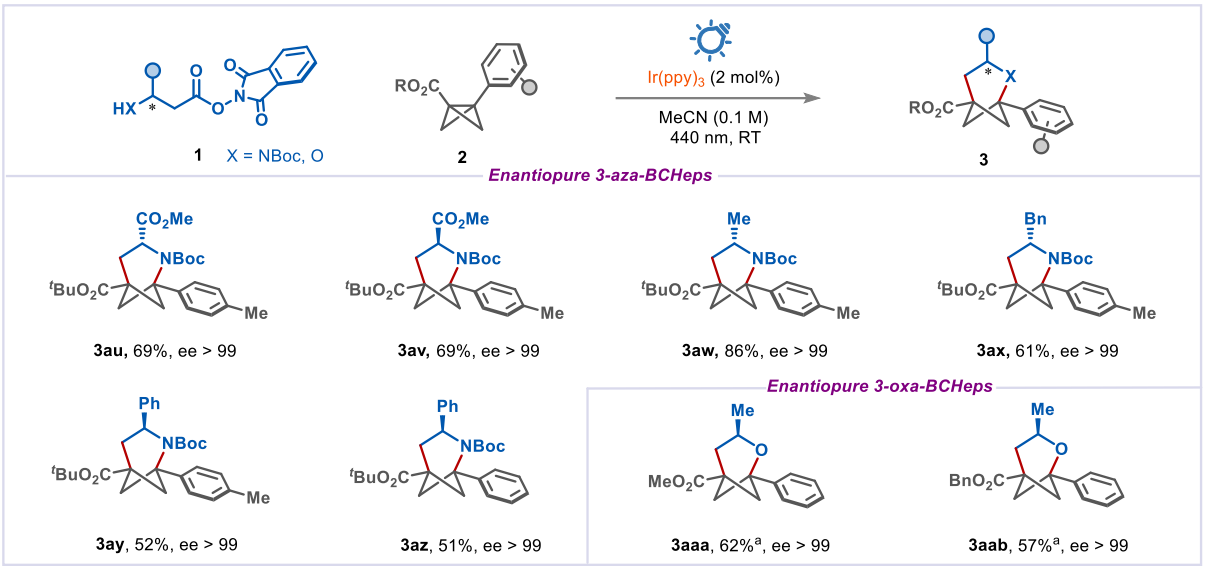
Scheme 2: Substrate scope investigation of BCBs and amino acid derived RAE. Reactions conditions: RAE **1** (0.2 mmol), BCB **2** (2.5 equiv), $Ir(ppy)_3$ (2 mol%), dry MeCN (2.0 mL, 0.1 M), 440 nm Kessil lamp, rt, 16 h. Yields are of isolated products. [a]*dr* was determined by ^{1}H-NMR from the crude reaction mixture.

Spirocyclic scaffolds are becoming increasingly important motifs in drug discovery owing to their structural novelty, which allows access to unique classes of target compounds and provides access to unexplored regions of chemical space.[43] Considering their importance, we were interested in introducing spirocyclic scaffolds into 3-aza-BCHeps to access previously inaccessible spiro-aza-BCHep derivatives (Scheme 2). To our delight, when we employed an azetidine containing amino acid derivative **1q** to our standard conditions, we obtained the desired spirocyclic compound **3aa** in 62% yield. The radical precursor 1**j** also reacted well with other BCBs, giving the desired spiro-aza-BCHeps **3ab**-**3ae** in good yields. Cyclobutyl- and cyclohexyl-substituted amino acid derivatives also provided the corresponding spiro compounds **3af** and **3ag** in 76% and 57% yield, respectively. Noteworthy, we could also access bis-spiro-aza-BCHep **3ah** when we treated the BCB **2f** with spiro-amino acid derivative **1y**. Nitrogen-based fused bicyclic compounds are ubiquitous and are constituents of many bioactive compounds.[44] Therefore, we next extended our strategy to access fused-aza-BCHeps. We were pleased to find that treatment of BCB **2a** with radical precursor **1u** gave the desired fused compound **3ai** in 52% yield with 6:1 *dr*. *tert*-Butyl ester BCB and various substituents on the arene ring of BCB, including methyl, chloro, and fluoro, were well tolerated in this reaction, affording the corresponding products **3aj**-**3am** in good yields.



Scheme 3: Substrate scope investigation of BCBs and hydroxy acid derived RAE. Reactions conditions: RAE **1** (0.2 mmol), BCB **2** (2.5 equiv), $Ir(ppy)_3$ (2 mol%), dry MeCN (1.0 mL, 0.2 M), 440 nm Kessil lamp, rt, 16 h. Yields are of isolated products.

Recent reports demonstrated that oxygen-incorporated bicyclic scaffolds exhibited not only improved water solubility, metabolic stability, and lower lipophilicity compared to all-carbon



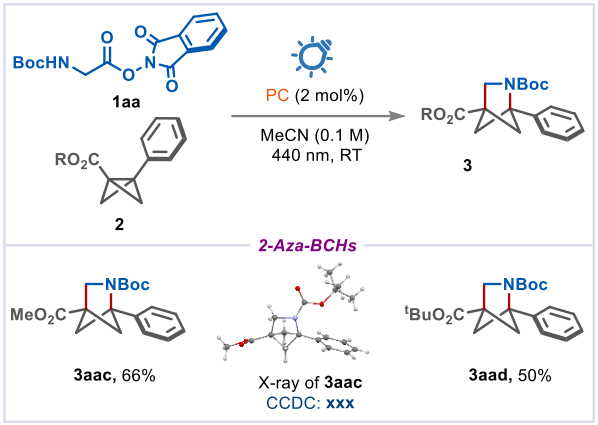
Scheme 4: Substrate scope investigation of chiral amino/hydroxy acid derived RAE. Reactions conditions: RAE **1** (0.2 mmol), BCB **2** (2.5 equiv), $Ir(ppy)_3$ (2 mol%), dry MeCN (2.0 mL, 0.1 M), [a]dry MeCN (1.0 mL, 0.2 M), 440 nm Kessil lamp, rt, 16 h. Yields are of isolated products.

bicyclic ring systems but are also present in natural products and bioactive compounds.[10] Thus, the preparation of oxygen-incorporated bicyclic scaffolds attracted much attention. We wondered whether we could adopt the strain-release annulation strategy to access 3-oxa-bicycloalkanes by changing the pendent nucleophile on the NHPI ester reagent to alcohol. We were pleased to find that treating radical precursor **1ab** with BCB **2a** under slightly modified conditions (please see SI) afforded the desired 3-oxa-BCHep **3an** in 62% yield (Scheme 3). Benzyl and *tert*-butyl ester BCBs underwent the desired transformation successfully, affording the corresponding products **3ao** and **3ap** in 57% and 50% yields, respectively. Chloro- and methoxy-substituted arenes on BCB were viable substrates in this transformation (products **3aq** and **3ar**). Dimethyl-substituted redox active ester also participated, affording a more substituted 3-oxa-BCHep **3as**. Finally, we found that our protocol also offers a straightforward route to spiro-oxa-BCHep **3at** in synthetically useful yield.

Owing to the different biological and optical properties of enantiomers, the synthesis of enantioenriched chiral compounds is an important field of research, especially in medicinal chemistry where single enantiomer drug use instead of racemate can potentially lead to more selective pharmacologic profiles and improved therapeutic indices.[45] Next, we extended our strategy using commercially available chiral amino acid derivatives to access enantioenriched chiral 3-aza-BCHeps (Scheme 4). Pleasingly, when we subjected *D*-aspartic acid derived redox active ester to standard conditions, the desired enantioenriched 3-aza-BCHep **3au** was obtained in 67% yield without any racemization. It was also possible to access the opposite enantiomer

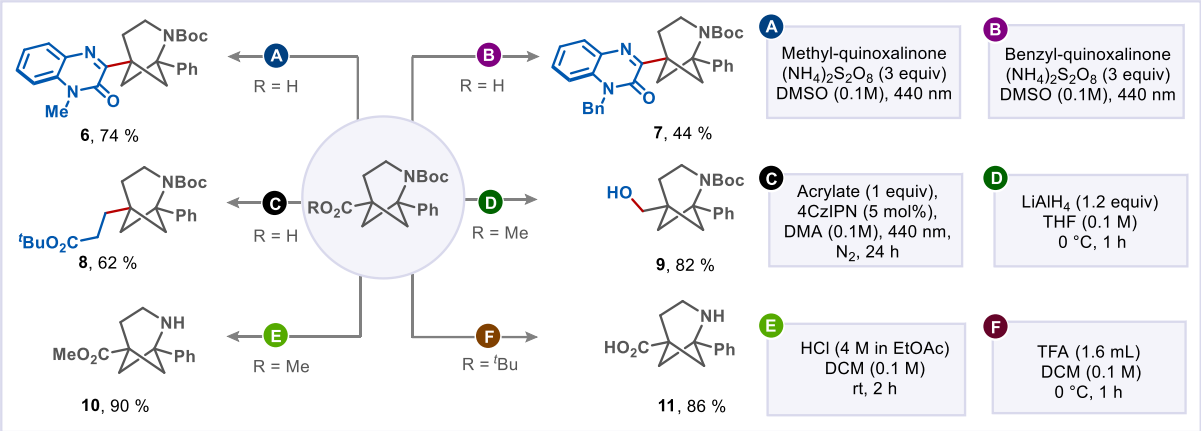
3av starting from *L*-aspartic acid. Various chiral amino acid-derived redox active esters having *α*-substituents such as methyl, benzyl, and phenyl worked well, giving the corresponding products **3aw-3az** in good yields. We could also access chiral enantioenriched 3-oxa-BCHeps **3aaa-3aab** from (*R*)-2-methyl succinic acid derivative.

2-Azabicyclo[2.1.1]hexanes (2-aza-BCHs), which are bioisosteres of *ortho*- and *meta*-substituted benzenes, and also they are considered as efficient bicyclic analogues of pyrrolidine in drug discovery.[46, 47] Therefore, we subsequently employed our annulation strategy for the synthesis of 2-aza-BCHs using redox-active ester **1aa** with one carbon unit between nucleophile and NHPI (Scheme 5). However, we didn't observe the desired product **3aac** when we subjected **1w** to the standard conditions. Switching from $Ir(ppy)_3$ to $[Ir\{dFCF3ppy\}_2(bpy)]PF_6$, this reaction successfully provided the desired product **3aac** in 66% yield. The structure of **3aac** was unambiguously determined via X-ray analysis (CCDC **2409099**). *tert*-Butyl ester-BCB also participated well in this reaction (product **3aad**). Unfortunately, the reaction couldn't be applied to access 2-oxa-BCHs (see SI for unsuccessful substrates).



Scheme 5: Access to 2-aza-BCHs. Reactions conditions: RAE **1aa** (0.2 mmol), BCB **2** (2.5 equiv), $[Ir\{dFCF_3ppy\}_2(bpy)]PF_6$ (2 mol%), dry MeCN (2.0 mL, 0.1 M), 440 nm Kessil lamp, rt, 16 h. Yields are of isolated products.

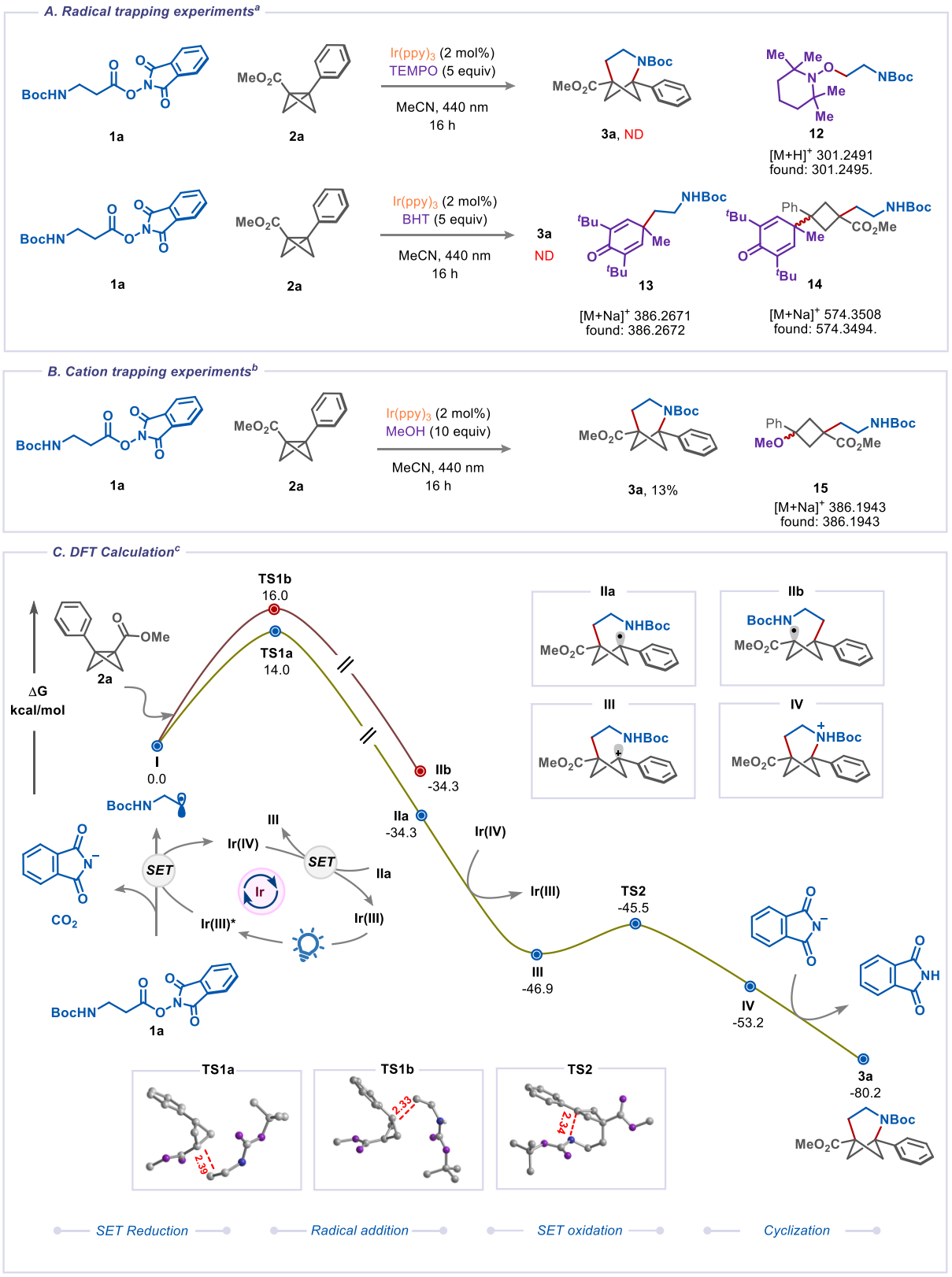
Next, we conducted a series of derivatization experiments to introduce a broader range of functional groups onto the molecular framework of aza-BCHeps, thereby enhancing its structural diversity (Scheme 6). Quinoxaline-2(1*H*)-one is an important class of heterocyclic motifs present in a wide range of biologically active natural products and pharmaceutical compounds.[48] We successfully introduced quinoxaline-2(1*H*)-one motif into the 3-aza-BCHep unit via a decarboxylative Minisci reaction by reacting the acid **3e'** with **Q1** and **Q2** using ammonium persulfate under blue light irradiation (products **6** and **7**).[49] Visible-light-mediated decarboxylative Giese reaction with acid **3e'** successfully provided the product **8** in 62% yield. The reduction of the ester group with $LiAlH_4$ yielded primary alcohol **9** in good yield.[38]



Scheme 6: Synthetic Utility.

Treatment of **3e** with HCl cleanly deprotected the Boc group to give free amine **10** in 90% yield. Notably, we could deprotect Boc and hydrolyze the ester using TFA to obtain conformationally rigid unnatural amino acid **11** in 86% yield.

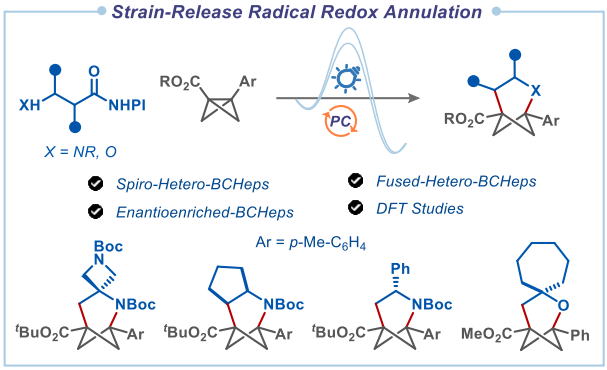
To gain insight into the mechanism of this redox annulation, we conducted several experiments to elucidate the existence of radical and carbocation intermediates. Radical trapping agents such as TEMPO and BHT completely inhibit the formation of the desired product **3a** with the detection of TEMPO adduct **12**, and BHT adducts **13** and **14**, which support the involvement of radical intermediates during the reaction (Scheme 7A). Furthermore, we detected the MeOH addition product **15** when treating the reaction mixture with MeOH, which reveals the presence of carbocation intermediated (Scheme 7B). Luminescence quenching experiments suggested that the redox-active ester quenches the excited state photocatalyst but not BCB **2a** (please see SI for details). Next, we conducted detailed DFT studies to further validate the photoredox radical/polar crossover pathway feasibility and rationalize the observed high regioselectivity. Calculations were performed at the SMD(Acetonitrile)/(U)M06/6-311+g(d,p)//(U)M06/6-31+g(d,p) level of theory (Scheme 7). First, a SET from the excited state photocatalyst Ir(III) to redox-active ester **1a** provides alkyl radical intermediate **I** and the oxidized photocatalyst Ir(IV). The radical intermediate **I** adds across the strained carbon-carbon bond to give two intermediates **IIa** and **IIb** via two regioisomeric transition states **TS1a** and **TS1b**. The reaction was highly exergonic, and the energy difference between these two transition states is 2.0 kcal/mol, which agrees with the observed high regioselectivity. Subsequent SET from the radical intermediate **IIa** to oxidized photocatalyst Ir(IV) furnishes the stable benzylic carbocation **III** while regenerating the photocatalytic cycle. Finally, intramolecular cyclization via **TS2** provides the intermediate **IV** that undergoes further deprotonation with phthalimide anion to give the desired product **3a**.



Scheme 7: Mechanistic investigation. [a]Reactions conditions: RAE **1a** (0.1 mmol), BCB **2a** (2.5 equiv), $Ir(ppy)_3$ (2 mol%), dry MeCN (2.0 mL, 0.1 M), 440 nm Kessil lamp, rt, 16 h. [b]RAE **1a** (0.1 mmol), BCB **2a** (2.5 equiv), $Ir(ppy)_3$ (2 mol%), dry MeCN (2.0 mL, 0.1 M), MeOH (10 equiv), 440 nm Kessil lamp, rt, 16 h. [c]All the geometries are optimized at the $SMD_{(MeCN)}$ /(U)B3LYP-D3/6-311++G(d,p)//(U)B3LYP-D3/6-31G(d,p) level of theory. Relative free energies (ΔG) are given in kcal/mol unit.

Conclusion

In summary, we have developed a unified strategy for the synthesis of previously inaccessible, polysubstituted hetero[3.1.1]bicycloheptanes from simple feedstocks. The method is operationally easy, proceeds under visible-light photoredox catalysis, and exhibits a broad substrate scope with both redox-active esters and BCBs. The reaction has been successfully employed to access spiro, fused, and enantioenriched hetero[3.1.1]bicycloheptanes. Moreover, the reaction could be applied to access aza-[2.1.1]-bicycohexanes. The synthetic utility of this protocol is further demonstrated by transferring the obtained products into valuable building blocks. DFT calculations and experimental studies have supported the oxidative radical polar crossover mechanism. Considering the new reactivity and demand for conformationally restricted heteroatom substituted bicyclic scaffolds in medicinal chemistry discovery programmes, we envisage that our strategy will find application in both synthetic and medicinal chemistry.



Data availability:

General information, experimental procedures, characterization data for all new compounds, NMR spectra, and coordinates of starting materials, intermediates, and transition states are in the Supplementary Information. Data for the crystal structure reported in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC) under the deposition numbers CCDC 2386877 (for compound **3a**) and CCDC 2409099 (for compound **3aac**).

Author contributions:

†B. G. and B. S. contributed equally. B. G., B. S. and D. P. H. conceived and designed the project. B. G. and B. S. carried out optimization, starting materials synthesis, substrate scope, and mechanistic studies. D. P. H. performed the density functional theory calculations. B. G., B. S. and D. P. H. wrote the manuscript.

Conflicts of interest:

There are no conflicts to declare.

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