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Photochemistry

Bicyclo[2.1.1]hexanes via Intramolecular Formal (3+2)-Cycloaddition

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Abstract: We report a synthesis of bicyclo[2.1.1]hexanes via an intramolecular formal (3+2) cycloaddition of allylated cyclopropanes bearing a 4-nitrobenzimine substituent. Both activated and unactivated alkenes are tolerated in the transformation. The bicyclic imine products are prone to photo-induced ring opening, allowing for the epimerization of C5-stereogenic compounds.

Introduction

Bicyclo[2.1.1]hexanes (BCHs) and related bridged bicyclic systems have attracted renewed synthetic interest due to their potential as sp^3-rich arene bioisosteres and more generally as rigid scaffolds for drug and/or agrochemical discovery (Figure 1A–B).[1] Introduction of multiple substituents to the BCH skeleton leads to diverse derivatives varying in their symmetry and exit vector geometries.[1h] As functionally useful BCH building blocks cannot be sourced from nature, de novo synthesis of the ring system is required. BCHs have been made through various methods including ring contraction of norbornanes,[2] intramolecular alkylation of cyclopentanes,[3] intramolecular Barluenga-Valdés coupling of cyclobutanone hydrazones,[4] (2+2)-cycloaddition of 1,5-dienes,[5] and the formal (3+2)-cycloaddition of bicyclobutanes and alkenes (Figure 1C).[1d,e,6] Recent developments in the latter two approaches have been enabled by the field's growing adoption of visible-light absorbing photosensitizers in reaction design. Herein, we report a new approach to BCHs, namely, the formal (3+2) cycloaddition of allylic cyclopropanes.

The underlying formal (3+2)-cycloaddition chemistry of cyclopropanes with alkenes is well-developed.[7] In one such study, we reported the intramolecular reaction of arene-linked cyclopropylimines with alkenes to generate arene-fused norbornanes. (Figure 1D).[8] In this approach to cyclopropane activation, excitation of the imine triggers homolytic opening of the cyclopropane to a biradical, **Int-I**. This species may either undergo 6-exo-trig cyclization and a final ring closure step to give the bicyclic product **XVI**, or may close to give a 1-pyrroline **XVII**.[8a,9] The bicyclic imines can be hydrolyzed and functionalized to give bioactive derivatives.[10] We originally sought to expand this methodology to prepare the unfused norbornane system **XVIb**. However, removing the rigid arene linker from the system led to an inversion of selectivity towards the undesired 1-pyrroline formation. We hypothesized that allylic cyclopropanes would selectively undergo formal (3+2) cycloaddition since a kinetically favored 5-exo-trig cyclization would be the first step of the desired cyclization cascade, and because we anticipated linker length would have little impact on the pyrroline formation pathway (Figure 1D).[11] A SciFinder search conducted on April 25th, 2024 returned no compounds containing the 5-aryl-1-amino BCH substructure, indicating the products of this reaction occupy a unique area of chemical space.

Results and Discussion

We began our study with allylic cyclopropane substrates containing activated alkenes that could accelerate radical cyclization and provide C5-substituted BCH arylethylamine products. Irradiation of cinnamylated cyclopropyl imine **1a** for 30 minutes led to complete conversion, providing **2a** and **2a'** in high isolated yield as a separable mixture of diastereomers (Figure 2A). The expected pyrroline side product **3a** was not detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The reaction mixture became increasingly yellow during the course of irradiation, and the strongly colored impurity was identified as 2-azadiene **4a'**. The formation of **4a'** was taken as strong evidence of BCH decomposition, as the alkene-derived

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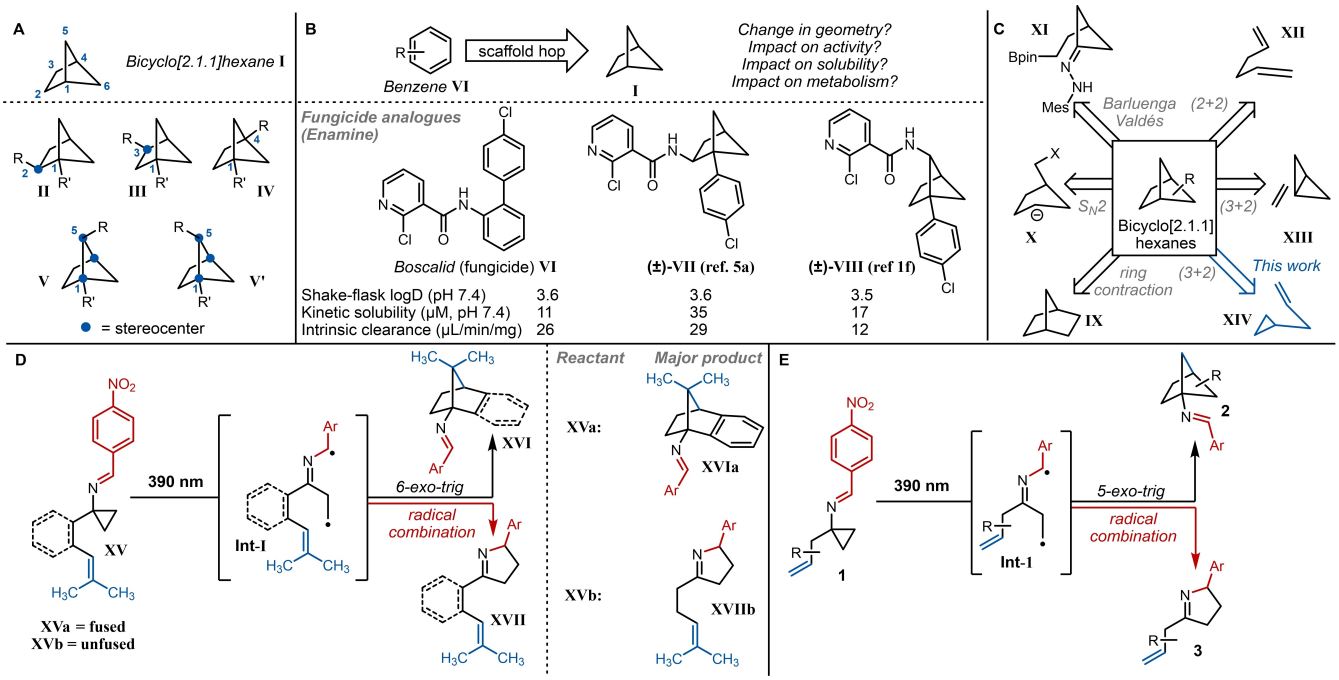

Figure 1. (A) Bicyclo[2.1.1.)hexane structure and patterns of disubstitution. (B) Comparison of bicyclo[2.1.1]hexane and benzene as scaffold for bioactive molecules. (C) Synthetic approaches to bicyclo[2.1.1]hexanes. (D) Linker impact in synthesis of bicyclo[2.2.1]heptanes using imine photochemistry. (E) This work.

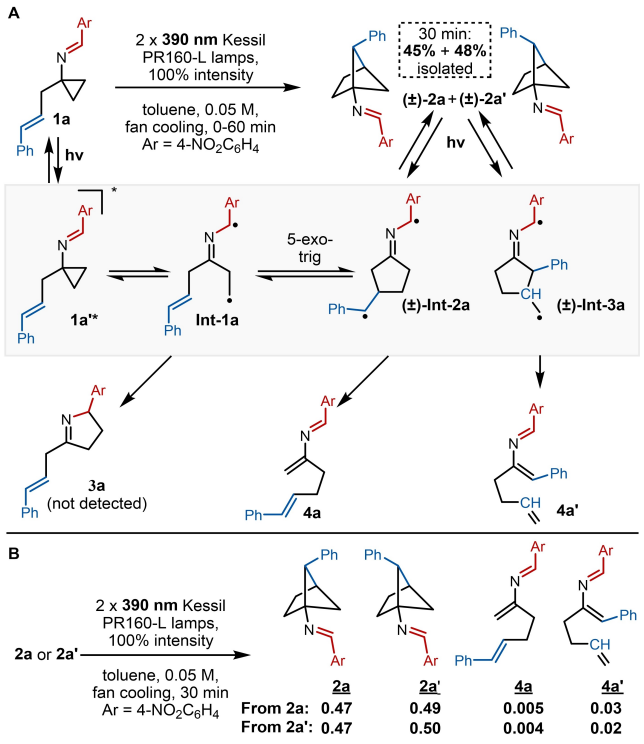

Figure 2. (A) Initial hit and simplified mechanistic proposal (B) Resubbjecting isolated bicyclic products leads to epimerization. The product distribution was determined by quantitative proton nuclear magnetic resonance spectroscopy (Q^1H NMR).

carbons from **1a** are no longer bonded in **4a'**. Decreasing the reaction time to 10 minutes allowed for complete conversion of **1a** while minimizing azadiene formation. From reaction time optimization data, we found that the ratio of **2a** and **2a'** varies as a function of time before stabilizing, suggesting product interconversion and supporting the formation of **Int-2a** from the BCH products. Resubjecting **2a** or **2a'** to the reaction conditions gave nearly identical distributions of **2a**, **2a'**, **4a**, and **4a'**, further supporting the formation of **Int-2** from **2a** and **2a'** and allowing for recycling of **2a** or **2a'** if only the epimer was desired (Figure 2B).

We next explored the scope of this transformation with respect to substituents on the styrene moiety. All substituted styrene systems we studied efficiently converted to the corresponding BCHs as evident from quantitative ^{1}H NMR spectroscopic assay yields in excess of 80 % (Q^1H NMR, Table 1, combined assay yields bolded, isolated yields in parentheses). Epimers **2** and **2'** and the trace amounts of azadiene products were generally separable by normal phase silica gel column chromatography. *Para*- and *meta*-substituted styrene substrates (Table 1, **1b**–**1f** and **1g**–**1i**, respectively) showed negligible diastereoselectivity. *Ortho*-substituted systems showed higher diastereoselectivity on the order of 2:1, suggesting modest discrimination between the sterically similar methylene and ethylene bridges (Table 1, **1j**–**1m**).

Incorporation of additional substituents onto the nitroarene chromophore had minor impacts on reaction performance (Table 1, **1n** and **1o**). Introduction of a methyl group to the alkene of model substrate **1a** gave **1p**, which underwent

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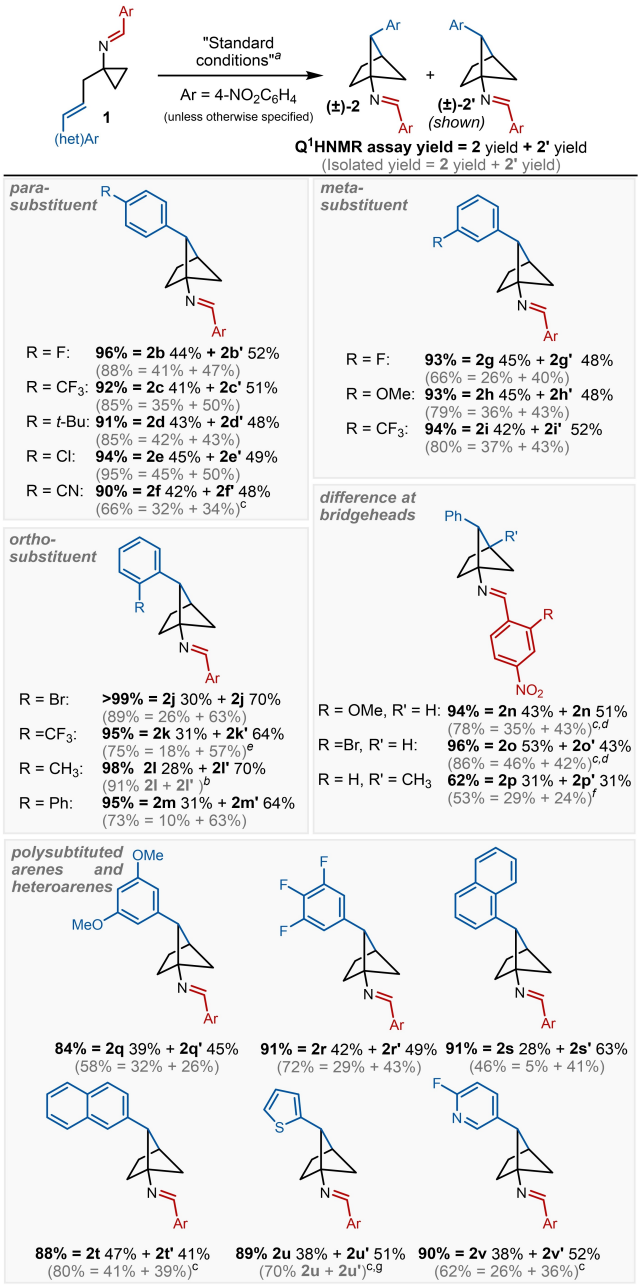
Table 1: Substrate scope for vinyl (hetero)aromatic systems.



[a] Standard conditions: 0.2 mmol scale, 2-dram vial, 2×390 nm Kessil PR160-L lamps at 100% intensity, toluene, 0.05 M, fan cooling, 10 minute reaction. Unless otherwise specified, each diastereomer was isolated and separately characterized. All chiral compounds were generated as racemates. [b] Isolated material d.r. = 1:3. [c] 0.1 mmol scale. [d] 15 minute reaction time. [e] substrate was 1:0.08 mixture of E:Z alkene isomers. [f] 3 hour reaction time. [g] Isolated material d.r. = 0.39:1.

significantly slower photoreaction than disubstituted alkenes and gave only moderate assay yield (Q^1H NMR) even at full conversion (62% combined **2p**+**2p'**, versus approximately 90% for other substrates). This result is consistent with a reversible cyclopropane ring opening and a slowing of the 5-exo-trig cyclization step, allowing for competitive side reactivity as supported by peaks consistent with 1-pyrroline formation in the crude ^1H NMR spectrum. The methyl group difference between **1a** and **1p** did not have an appreciable impact on the diastereomeric ratio of the resulting BCHs.

More highly substituted arenes were likewise tolerated in the photoreaction and showed diastereoselectivity consistent with the aforementioned trends of disubstituted arenes. For example, the 1-naphthyl substitution of **1r** led to similar diastereoselectivity as an *ortho* substituent, which contrasts the lack of selectivity observed for 2-naphthyl substrate **1s**. Vinyl heteroaromatic substrates **1t** and **1u**

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were also tolerated, giving thiophene and pyridine-substituted BCHs, respectively.

Inspired by our previous efforts in the separation of azadienes from imines, we also explored a telescoped hydrolytic approach to BCH primary amines (Table 2).[12] Hydrolysis of the crude reaction mixtures allowed non-basic 4-nitrobenzaldehyde and azadiene-derived ketones to be purged via liquid/liquid extraction.

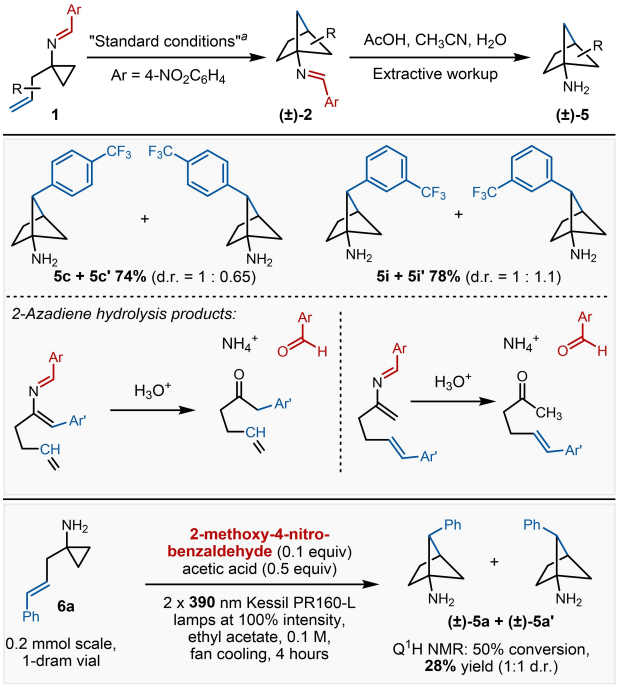
Given the efficiency of the photochemical transformation, the ease and reversibility of imine condensation, and the tendency of the 2-azadiene products to hydrolyze to regenerate the chromophore-related aldehyde, we hypothesized this system would be amenable to an organocatalytic modification. Indeed, irradiating **6a** in the presence of 0.1 equivalents of 2-methoxy-4-nitrobenzaldehyde and acetic acid additive led to a combined yield of **5a** and **5a'** of 28%, showing turnover and establishing a proof of concept for aldehyde catalysis in imine photochemistry.[13]

Unactivated alkenes were also tolerated in the formal cycloaddition, including the parent allylic system **1w**, which formed the achiral BCH **2w** (Table 3). Whereas the 1,2-disubstituted styrene systems (vide supra) showed high cyclization selectivity at room temperature, heating of compound **1w** during irradiation was critical to achieving high selectivity for **2w** versus the competitive pyrroline formation.[14] The yield of **2w** isolated from a >1 mmol scale batch reaction was comparable to the 0.2 mmol trials. The reaction of **1w** to **2w** is also amenable to continuous flow processing, which would facilitate further scale-up (see Supporting Information for details).

The introduction of a methyl substituent to the alkene of the substrate improved room-temperature selectivity, forming **2x** and **2x'**, consistent with accelerated 5-exo-trig cyclization to give a secondary radical intermediate. Prenylated substrate **1y** was also tolerated, but it formed **2y** inefficiently due to significant mass balance shifting towards a 2-azadiene side product, suggesting a steric penalty in the final ring closure to form the C5–C1 bond of the BCH system. Cyclohexene-containing substrate **1z** gave the achiral caged product **2z** in moderate yield. The core of **2z** is a close analogue of 1-adamantylamine, which is used to treat influenza and Parkinson's disease.[15] Hydrophobic tricyclic systems accessible by our approach may fill a similar niche to adamantane in pharmaceutical research.[16] The parent tricyclic hydrocarbon of **2z** has not been reported in the literature to date.

Spiro piperidine substrate **1aa** gave a mixture of regioisomeric achiral BCHs. While **1aa** may open to give a biradical containing either a primary or tertiary radical fragment, the major product is consistent with reaction of the less-stabilized primary biradical intermediate **Int-4**. The biradicals **Int-4** and **Int-5** likely interconvert. One would expect the cyclization of **Int-4** to be accelerated by the Thorpe–Ingold effect, which may also explain the superior BCH selectivity as compared to parent allylated system **1w** under ambient temperature "fan cooling" conditions, as less pyrroline formation was observed from photoreaction of **1aa** than **1w**. The products **2aa** and **2aa'** are differentially protected diamines, a class of building blocks frequently

Table 2: Telescoped hydrolysis approach to access primary amines.



[a] Standard conditions: 0.2 mmol scale, 2-dram vial, 2×390 nm Kessil PR160-L lamps at 100% intensity, toluene, 0.05 M, fan cooling, 30 minutes; then, concentration in vacuo, addition of acetonitrile (3 mL), water (1 mL), and acetic acid (2 mL), room temperature, 12 hours. All chiral compounds were generated as racemates.

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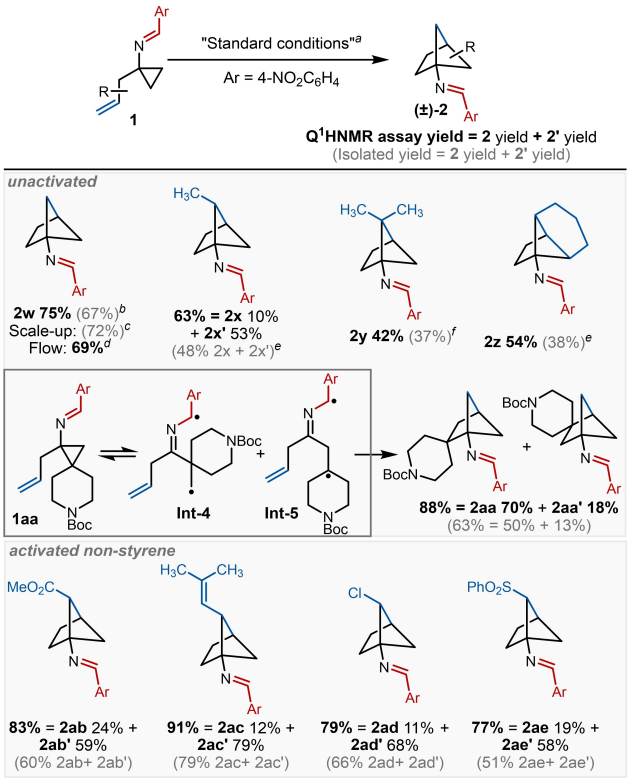
Table 3: Substrate scope for alkenes lacking (hetero)arene conjugation.



[a] Standard conditions: 0.2 mmol scale, 2-dram vial, 2×390 nm Kessil PR160-L lamps at 100% intensity, toluene, 0.05 M, fan cooling, 10 minutes. All chiral compounds were generated as racemates. [b] Reaction conducted at 110 °C [c] Scale-up conditions: 1.72 mmol scale, 4-dram vial, 2×390 nm Kessil PR160-L lamps at 100% intensity, toluene, 110 °C, 2 h. [d] Flow conditions: 5 mL PFA reactor, 385 nm LEDs at 100% intensity, toluene, 0.2 M, 100 °C, 8 minute residence time [e] 60 minute reaction time [f] 30 minute reaction time.

used as cores for small molecule drug development and as linkers in the synthesis of bifunctional degraders.[17]

Activated alkenes lacking aromatic substituents were also competent substrates for the formal cycloaddition. Substrates containing unsaturated ester, diene, vinyl chloride, and vinyl sulfone functional groups were all efficiently transformed to the desired BCHs in moderate diastereoselectivity under the standard reaction conditions (Table 3, **2ab**–**2ae**, crude d.r. ranging from 2.5:1 to 6.8:1). Whereas the arylated and alkylated BCHs prepared in this study were bench-stable in the absence of light, the systems with a C5 electron-withdrawing group were not, which may be a consequence of polar donor-acceptor reactivity of the embedded cyclobutane.

We next explored the functionalization of the BCHs prepared via the photochemical methodology described herein. Hydrolysis of the parent system **2w** with *para*-toluene sulfonic acid monohydrate led to the direct precipitation of **5w•TsOH** (Scheme 1A). The reported routes to **5w** and its hydrochloride salt proceed through bicyclo-[1.1.1]pentane-1-carboxylic acid, which has been prepared in low yield from several commodity chemicals. The route to **5w•TsOH** described herein compares favorably with these reported routes in terms of yield, step count, and operational simplicity (see Supporting Information for full comparison of routes and references). The direct precipitative hydrolysis conditions used for **2w** were also compatible with several other BCH imines.

Since this particular substitution pattern of 5-aryl-1-amino BCH had not been previously described, we hoped to demonstrate that this class of alpha-tertiary amine is readily N-functionalized. BCH imines **2e** and **2e'** were individually subjected to a hydrolysis / acylation sequence to give **7e** and **7e'**, a diastereomeric set of analogues of the fungicide Boscalid (Scheme 1B). **7e** and **7e'** complement the previously synthesized BCH Boscalid analogues **VII** and **VIII** described in Figure 1, demonstrating how the methodology reported herein could be employed in a structure activity relationship study and showing how the high yields of both diastereomers could facilitate the independent evaluation of derivatives thereof.[1f,5a]

Sulfonylation of the ammonium salt **5a'•TsOH** to give **8a'** was also straightforward (Scheme 1C). We envisioned sulfonamides like **8a'** could potentially also be made by a formal (3+2)-cycloaddition of an N-sulfonyl cyclopropylamine and an alkene, as had been described intermolecularly in the literature for electron-deficient alkenes (styrenes were notably outside the reported scope).[18] However, subjecting **9a** to the reported conditions led only to alkene isomerization, likely reflective of quenching of the excited photocatalyst by the alkene rather than the sulfonamide. While we anticipate the allylated cyclopropane retrosyn-

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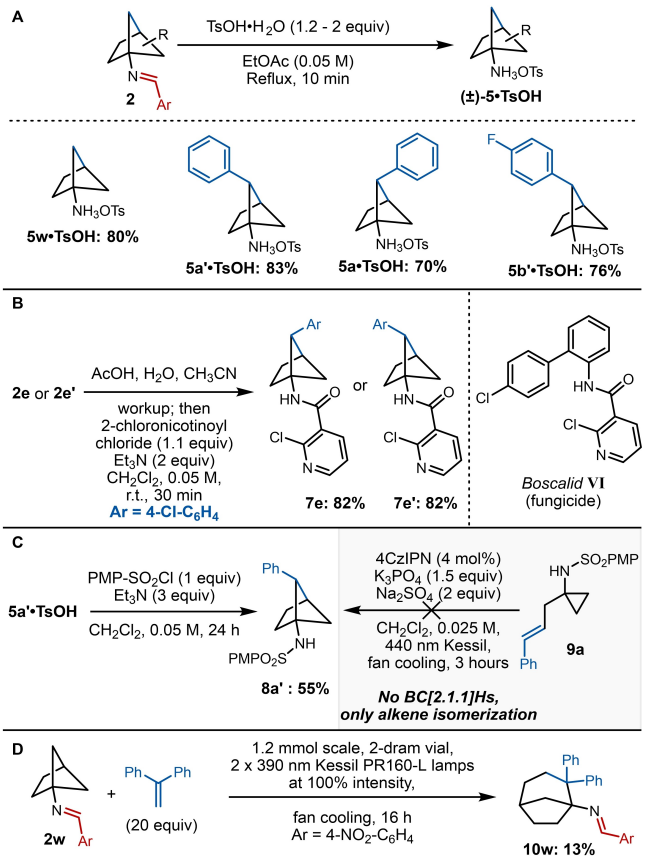

Scheme 1. (A) Functional group manipulations of BCHs (B) BCH imine hydrolysis and acylation. (C) Formal cycloaddition of BCH and 1,1-diphenylethylene to give a bicyclo[3.2.1]octane. See Supporting Information for experimental details. PMP = *para*-methoxyphenyl.

thetic disconnection of arylated BCHs could be accomplished with optimization, this result highlights a benefit of the 4-nitrobenzimine direct excitation approach; the selective activation of the imine avoids complications that can be introduced by electron transfer and/or energy transfer processes of typical photosensitizers.

The functionalization of BCHs by ring opening has not been studied extensively, and we were curious to follow up on mechanistic insights from our optimization study. The photo-induced epimerization of C5-stereogenic BCH imines provided clear evidence that these species undergo ring opening and subsequently close at a rate significantly faster than decomposition. However, we were unsure of the extent to which the parent system **2w** underwent this ring-opening process. By irradiating **2w** in the presence of 1,1-diphenylethylene as the radical trap, we observed formal cycloaddition, with **10w** being isolated in modest yield, confirming the excited state ring opening reactivity of **1w**, and providing a first proof of concept for the formal (4+2)-cycloaddition of BCHs with alkenes (Scheme 1D).

Conclusions

In conclusion, we have developed a photochemical method for the synthesis of bicyclo[2.1.1]hexanes using imine photochemistry to generate reactive biradical intermediates. Owing to its mild and redox-neutral conditions, the reaction shows high functional group tolerance. Using this methodology, BCHs with substitution at any of the positions on the bicyclic system may be prepared. The resulting imines are easily hydrolyzed to give primary amine building blocks of a previously unknown class. We expect this (3+2) approach to the BCH ring system will generalize to other classes of allylated cyclopropanes via alternative methods of ring activation, further simplifying the routes towards derivatives of this ring system.

Supporting Information

The authors have cited additional references within the Supporting Information.[19–23]

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: imine · photochemistry · cycloaddition · bicyclo[2.1.1]hexane · bicyclo[3.2.1]octane

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