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Catalyst-free, visible-light-induced [$2\pi + 2\sigma$] cycloaddition towards azabicyclohexanes

Min Yan, Zihao Ye, Ping Lu*

Research Center for Molecular Recognition and Synthesis, Department of Chemistry, Fudan University, Shanghai 200433, China

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ABSTRACT

2-Azabicyclo[2.1.1]hexanes (aza-BCHs) are constrained pyrrolidine analogues with improved physicochemical characteristics in drug design. Here, we report a direct visible light-mediated photocycloaddition of 4-aza-coumarins with mono- or disubstituted bicyclo[1.1.0]butanes for synthesizing aza-BCHs without an external catalyst. The introduction of the ester group on 4-azacoumarin is critical for direct imine excitation and versatile synthetic utility. Preliminary mechanistic studies indicated that the reaction took place primarily at the triplet hypersurface.

Rigid Csp^3-rich bicyclic hydrocarbon skeletons have been identified as valuable bioisosteres of phenyl ring in medicinal chemistry and agrochemistry since they often improve physicochemical and pharmacokinetic properties of drug candidates [1–4]. All-carbon ring systems, such as bicyclo[1.1.1]pentanes (BCPs), bicyclo[2.1.1]hexanes (BCHs), and bicyclo[3.1.1]heptanes (BCHeps), have gained rapidly growing attention as hydrocarbon bioisosteres for substituted arenes. Synthetic strategies, including the strain-release approach, have been developed to construct these highly rigid skeletons that mimic benzene derivatives with *para*-, *meta*-, and *ortho*-substituted patterns [5–26]. The heterocyclic variants, aza-BCHs as conformationally rigid pyrrolidine analogs, have shown improved water solubility, reduced lipophilicity, and retained bioactivity (Schemes 1a and b) [27–31]. The intramolecular cyclization approach was initially utilized to assemble the rigid aza-BCH scaffolds [32,33]. Further lithiation-electrophilic substitution led to functionalized aza-BCHs. However, the development of a modular approach for accessing aza-BCHs with diverse chemical space is still in demand.

We envisioned that a [$2\pi + 2\sigma$] cycloaddition of imine derivatives with bicyclo[1.1.0]butanes (BCBs) would provide substituted aza-BCHs in a straightforward and modular fashion. Although an elegant Lewis acid-catalyzed cycloaddition of *N*-aryl imine and BCBs has been disclosed [34], a metal-free approach would avoid metal residue in the active pharmaceutical ingredient [35,36]. Driven by inherent ring strain releasing, the cycloaddition of BCBs with π-bond substrates (such as C=C, N=N, N=O) has been explored in a thermal or photochemical way [37,38]. On the other hand, the photocycloaddition of imine chromophores is a long-standing challenge, attributed to radiationless decay or oxidation of the excited state of imine. Recently, several approaches have been developed to overcome these challenges in aza Paternò-Büchi reaction [39–42]. Nevertheless, the current methods mostly rely on UV irradiation or triplet sensitizer to access the excited state species (Scheme 1c) [19,43–53]. We wonder whether a rational design of imine substrate could enable a [$2\pi + 2\sigma$] photocycloaddition under visible-light irradiation in the absence of an external photocatalyst or photosensitizer.

Herein, we report our work on visible light-induced photocycloaddition of azacoumarins with mono- and disubstituted BCBs to provide aza-BCHs in a divergent regioselective manner (Scheme 1d). Furthermore, the subsequent downstream functionalization of cycloadducts enables a programmable preparation of aza-BCHs with versatile substitution patterns.

We initiated our studies with the rational design of imine substrate. In 2020, Schindler disclosed that the cyclic imine, 2-isoxazoline-3-carboxylate (**A**) [48], could be excited by visible light to its triplet state *via* an energy transfer process (Fig. 1a). Subsequently, cyclic imines, such as quinoxalinone (**B**) [49] and *N*-sulfonylimine (**C**) [50], were employed as chromophores in the photosensitized cycloaddition to deliver azetidines. We en-

* Corresponding author.
E-mail address: plu@fudan.edu.cn (P. Lu).

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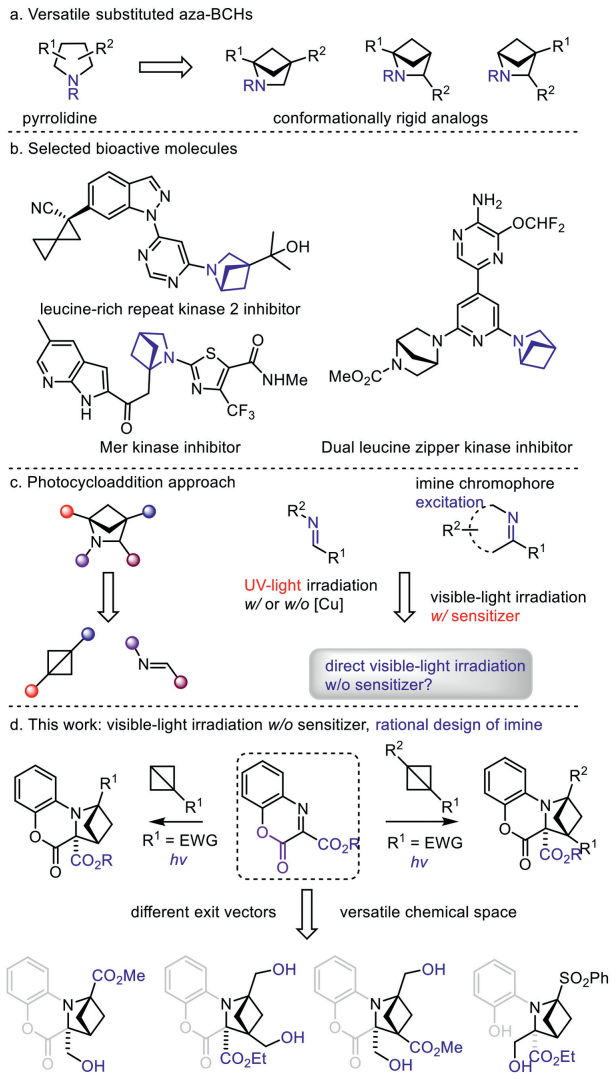


Scheme 1. Saturated bioisosteres. (a) The substituted saturated bioisosteres aza-BCHs. (b) Selected bioactive molecules containing aza-BCH motifs. (c) The retrosynthetic analysis and synthetic challenges. (d) The photocycloaddition and divergent structural elaboration.

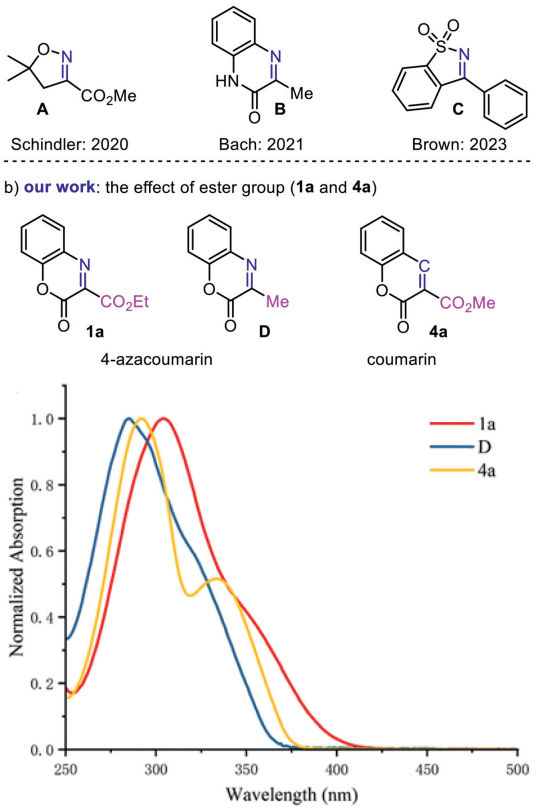


Fig. 1. (a) Studied imine chromophores. (b) Normalization absorption spectra of compounds **1a**, **D**, and **4a** ($c = 0.05$ mmol/L in CH_2Cl_2).

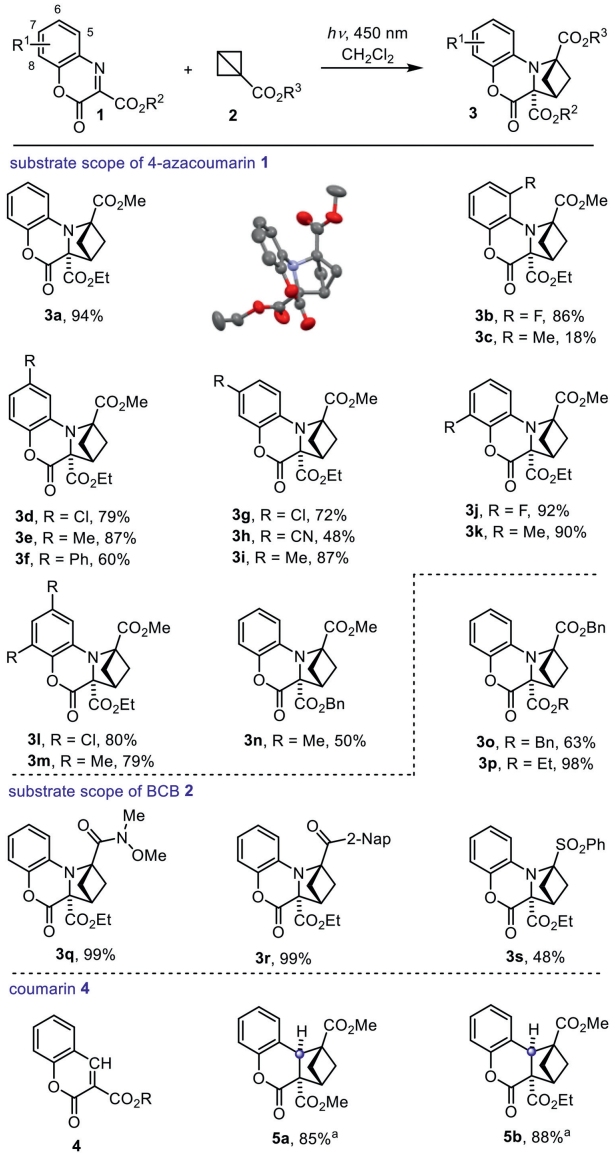
visioned that 4-azacoumarin (**1a**) would be a good candidate for direct visible light irradiation. First, the introduction of an ester group at position 3 could lower the excitation-state barrier due to lowering the energy of LUMO of imine. Second, the ester functional group could provide a useful synthetic handle, resulting in a programmable azetidine scaffold. Indeed, the UV–visible spectrum of **1a** in CH_2Cl_2 reveals a strong absorption at 304 nm ($\varepsilon = 10{,}900\ L\ mol^{-1}\ cm^{-1}$, Fig. 1b). A shoulder absorption at $\lambda \cong 360$ nm ($\varepsilon = 3700\ L\ mol^{-1}\ cm^{-1}$) is observed, and the band tails into the visible-light wavelength region. In contrast, 3-methyl-4-azacoumarin (**D**) exhibits no absorption beyond 370 nm. In addition, the spectrum of coumarin **4a** reveals two absorptions at 292 nm ($\varepsilon = 11000\ L\ mol^{-1}\ cm^{-1}$) and 333 nm ($\varepsilon = 6000\ L\ mol^{-1}\ cm^{-1}$), respectively.

Guided by the observed photophysical properties, the cycloaddition of 4-azacoumarin **1a** with methyl bicyclo[1.1.0]butane-1-carboxylate **2a** under visible-light irradiation (450 nm) was examined (For the emission spectra, see Figs. S2 and S3 in Supporting information). After optimization (Table S1 in Supporting information), the expected 2,4-methanoproline derivative **3a** could be obtained in 94% yield as a single regioisomer when using CH_2Cl_2 as solvent (Scheme 2). In comparison, no photocycloadduct was observed when the reaction of **D** and **2a** was conducted at 450 nm (Table S1).

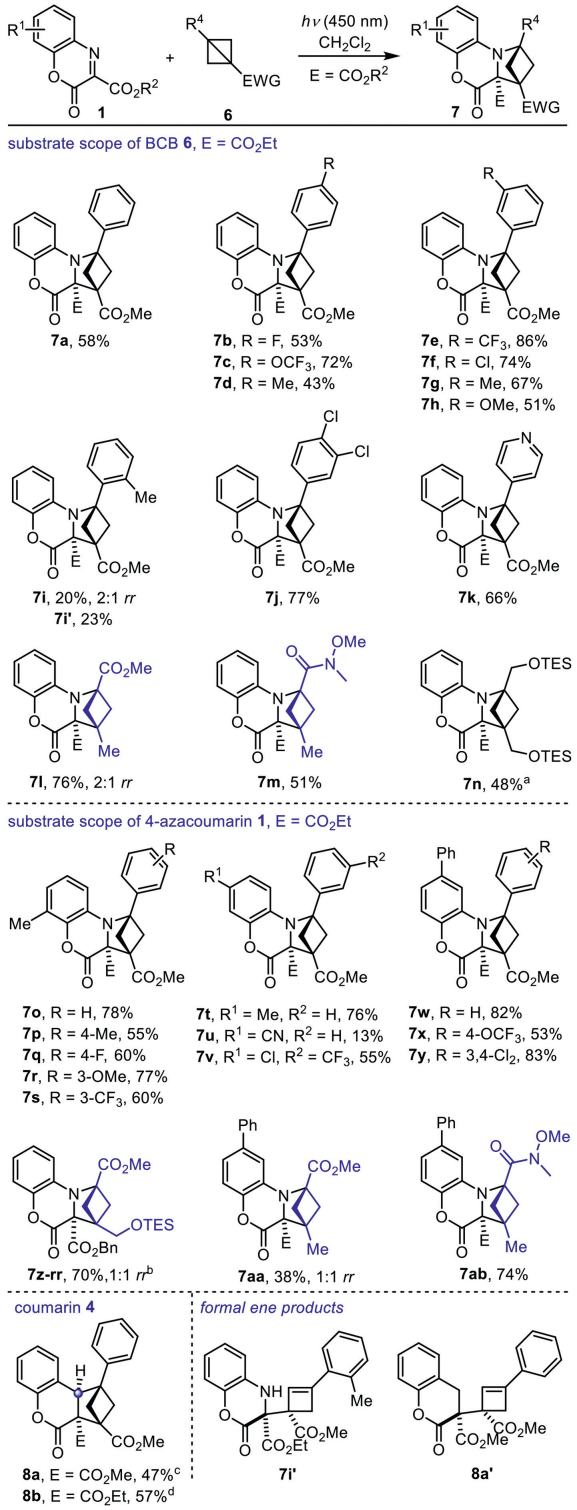
The substrate scope of 4-azacoumarin **1** was then surveyed. The 4-azacoumarin **1b** with fluoro group at position 5 provided cycloadduct **3b** in 86% yield, while the aza-BCH **3c** with methyl substituent was obtained in only 18% yield. In contrast, varying the position (6, 7, and 8) of the substituent on the phenyl ring of 4-azacoumarin **1** had little impact on yield. Both electron-rich and deficient substituents could be tolerated, giving the corresponding cycloadducts **3d**-**3k** in 48%–92% yields. In addition, disubstituted cyclic imines were applicable, giving products **3l** and **3m** in 79%–80% yields. Replacement of ethyl ester to benzyl ester afforded product **3n** in good yield as well.

The substrate scope of monosubstituted BCBs **2** was also investigated. The electron-withdrawing groups, including benzyloxycarbonyl, *N*–methoxy-*N*-methylcarbamoyl, 2-naphthoyl, and phenylsulfonyl groups, were all tolerated, giving the single regioisomers **3o**-**3s** in 48%–99% yields. Moreover, the cycloaddition of coumarins **4** was also studied. Switching the wavelength from 450 nm to 410 nm (Figs. S2 and S3), the photocycloaddition of coumarins **4** with BCB **2a** provided the corresponding BCHs **5a**-**5b** as single regioisomers in 85%–88% yields. The structures of **3a** and **5b** were determined by the single crystal X-ray diffraction analysis.

We next turned our attention to the photocycloaddition of 4-azacoumarin **1** with disubstituted BCBs **6**. After optimization (Table S2 in Supporting information), the reaction of **6a** and **1a** provided cycloadduct **7a** in 58% yield when irradiated at 450 nm in CH_2Cl_2. In contrast to cycloaddition with monosubstituted BCBs **2**, the regioselectivity was reversed. We assumed this is attributed to the stability of radical intermediate (*vide infra*). Of note, the formal ene product **7a'** (not shown, see Table S2) was also formed in 8% yield.



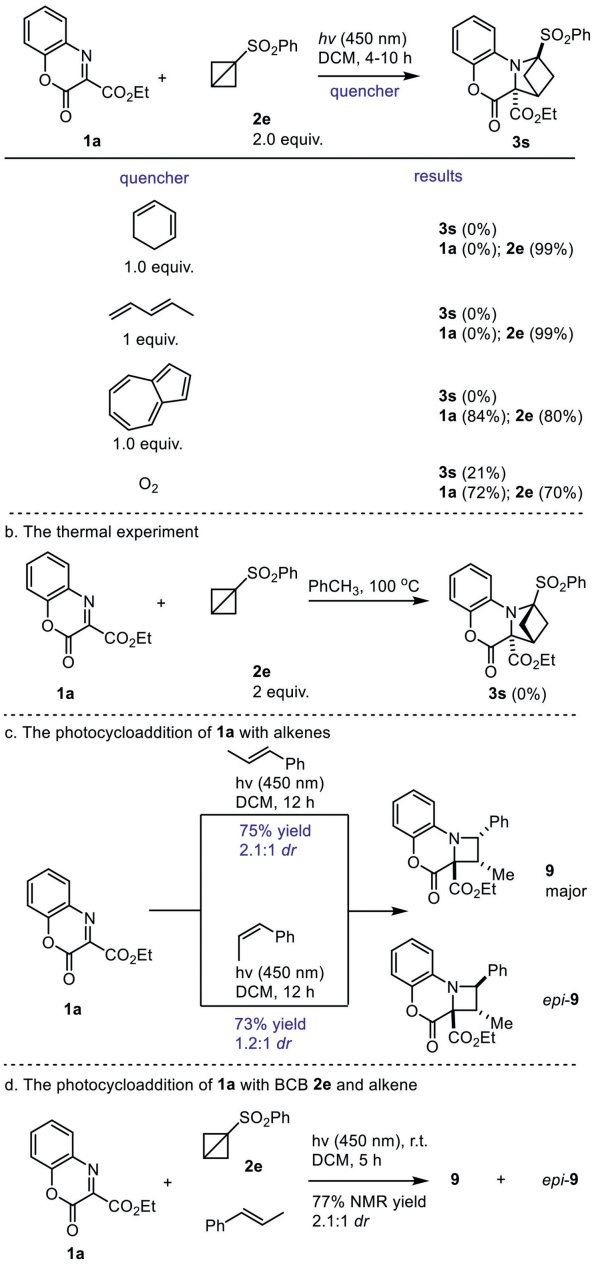
Scheme 2. The substrate scope of azacoumarin **1** and BCBs **2**. Conditions: **1** or **4** (0.1 mmol), **2** (2.0 equiv.), and CH_2Cl_2, *hν* (450 nm), r.t. [a] Irradiation at 410 nm.



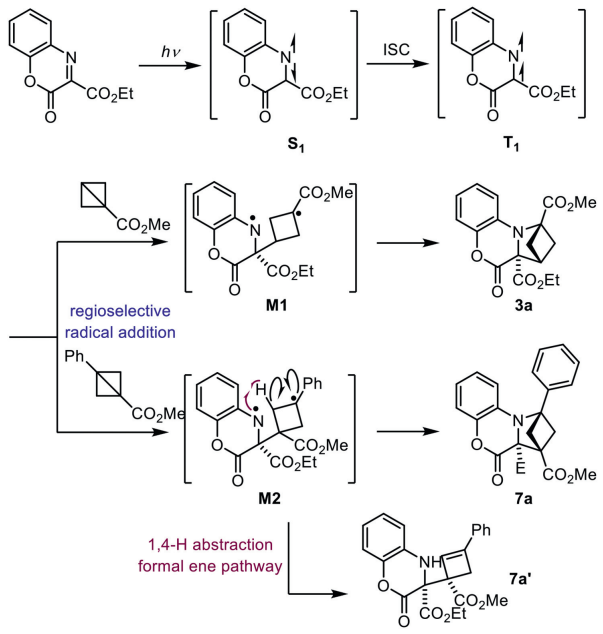
Scheme 3. The substrate scope of **1** and BCBs **6**. Conditions: **1** (0.1 mmol), **6** (2.0 equiv.), CH_2Cl_2, *hν* (450 nm), r.t. [a] **1** (0.2 mmol), **6n** (3.0 equiv.), $PhCH_3$. [b] **1m** (0.25 mmol), **6** (3.0 equiv.). [c] **4a** (0.1 mmol), CH_2Cl_2, *hν* (410 nm). [d] **4b** (0.1 mmol), MeCN, *hν* (410 nm).

The substrate scope of BCBs **6** investigated was summarized in Scheme 3. A variety of *para*- and *meta*-substituted phenyl BCBs **6** was tolerated under optimal conditions, affording the corresponding products **7b**-**7h** in 43%–86% yields as single regioisomers. Both electron-rich and deficient substituents have a minor impact on the yield. However, the regioselectivity and yield dropped significantly when *ortho*-methyl phenyl BCB was used, and the product **7i** was obtained in 20% yield and 2:1 *rr*. The formal ene product **7i'** was obtained in 23% yield. Disubstituted phenyl and heteroaromatic BCBs were also applicable, giving the cycloadducts **7j**-**7k** in 66%–77% yield. Replacing the aryl group with the alkyl group had a notable impact on the regioselectivity. When 3-methyl substituted BCB **6l** was used, the product **7l** was obtained in 76% yield and 2:1 *rr*. In sharp contrast, the reaction of Weinreb amide **6m** gave a single isomer **7m** in 51% yield. 1,3-Dialkyl BCB **6n** was also tolerated, resulting in the cycloadduct **7n** in moderate yield.

We further examined 6-, 7- and 8-substituted 4-azacoumarins **1** with an array of 3-aryl substituted BCBs **6**. Gladly, only single regioisomers were observed in all studied cases. The yields of **7o**-**7y** were in the range of 53%–83%, except for **7u**, which was isolated in 13% yield. The ene product **7u'** (not shown, see Supporting information) was formed in 33% yield. Similar regioselectivity was observed when 3-alkyl substituted BCBs were applied, affording the



Scheme 4. Preliminary mechanistic studies of photocycloaddition.



Scheme 5. Proposed reaction mechanism.

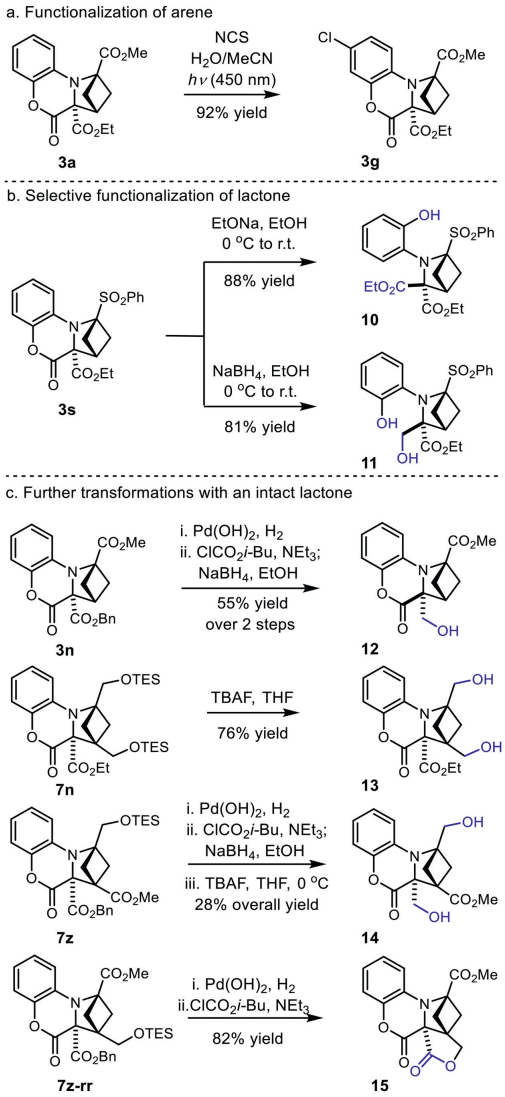
products **7z, 7aa**, and **7ab** in good yields. In addition, the cycloaddition of coumarins **4** with BCB **6a** furnished cycloadducts **8a-8b** in 47%–57% yield. Of mention, the formal ene products **8'** were also observed. The structures of **7b**, **7i'**, **7aa**, **7ab**, **8a'**, and **8b** were elucidated by X-ray diffraction studies.

The quenching experiments were first conducted to elucidate the reaction mechanism of photocycloaddition (Scheme 4). In the presence of 1 equiv. of 1,3-cyclohexadiene [54] or (*E*)−1,3-pentadiene [55] no cycloadduct **3s** was observed. Instead, the cycloaddition of **1a** with diene occurred. We assumed that the rate of reaction of **1a** with diene might be much faster than the triplet energy transfer process or the reaction might take place in the singlet manifold. As expected, the reaction was completely inhibited with a singlet and triplet quencher azulene [56]. The reaction was significantly suppressed when triplet quencher O_2 was introduced into the reaction. In addition, the thermal reaction of **1a** and **2e** gave no cycloadduct, indicating that light irradiation is critical for the success of the cycloaddition. Furthermore, the formation of a donor-acceptor complex between **1a** and **2e** could be excluded from the UV-visible absorption spectra studies (Fig. S9 in Supporting information) [57,58].

β-Methylstyrene was employed to examine the $[2\pi+2\pi]$-photocycloaddition of 4-azacoumarin. The photocyclization of **1a** with *trans*-β-methylstyrene afforded cycloadducts **9** and *epi*–**9** in 75% yield and 2.1:1 *dr*. The structure of *epi*–**9** was elucidated by X-ray diffraction studies. Meanwhile, the corresponding reaction with *cis*-β-methylstyrene afforded cycloadducts **9** and *epi*–**9** in 73% yield and 1.2:1 *dr*. In addition, the reaction of **1a** with both BCB **2e** and *trans*-β-methylstyrene afforded cycloadducts **9** and *epi*–**9** in 2.1:1 *dr*. No cycloadduct **3s** was observed. These results suggest that the photocycloaddition of 4-azacoumarin **1** likely takes place at the triplet hypersurface.

Based on control experiments and the photophysical properties of **1a**, the reaction mechanism was postulated (Scheme 5). 4-Azacoumarin **1a** was excited to the singlet state at visible-light irradiation, which then led to the formation of the triplet state *via* the intersystem crossing (ISC). The regioselectivity of radical addition was tuned by the stability of intermediates (**M1** and **M2**) [22], and the corresponding cycloadducts **3** and **7** were obtained. The 1,4-hydrogen abstraction took place in the case of 1,3-disubsituted BCB, resulting in the side product cyclobutene **7a'**.

The further synthetic utility of cycloadducts was explored to demonstrate programmable preparation of aza-BCHs with versatile substitution patterns (Scheme 6). Radical chlorination by photolysis of *N*-chlorosuccinimide (NCS) at 450 nm irradiation occurred selectively on arene moiety in **3a** [59], giving product **3g** in 92% yield. Selective opening of lactone motif was then pursued. Basic hydrolysis of **3s** using EtONa led to aza-BCH **10** in 88% yield [60], while the reduction of lactone with $NaBH_4$ provided diol **11** in 81% yield [61]. Further elaboration of cycloadducts with retaining lactone structural unit was also investigated. Reduction of the benzyloxycarbonyl group in **3n** afforded alcohol **12** *via* sequential debenzylation and reduction of mixed anhy-



Scheme 6. Further transformation of cycloadducts **3** and **7**.

dride [62]. Deprotection of silyl group in **7n** furnished diol **13** in good yield. Similarly, diol **14** with different substitution positions was obtained from **7z** through a three-step manipulation. Interestingly, lactone **15** was concurrently formed when the benzyloxycarbonyl group in **7z-rr** was transformed into mixed anhydride. The structures of **14** and **15** were elucidated by X-ray diffraction studies.

3-Dimensionality (3D) of aza-BCHs was then evaluated by the principal moment of inertia (PMI) analysis [63,64]. A survey reveals that the 3D scores ($I_1/I_3 + I_2/I_3$) of selected products range from 1.21 to 1.59, representing quite broad topological characteristics (Fig. 2). The cycloadducts **3a**, **7a,** and **7m** possess close 3D scores, in the range of 1.25–1.34. The diol derivatives **11** and **13** have much higher scores (1.50–1.59) than **14** (1.25), highlighting the importance of selective functionalization of cycloadducts.

In conclusion, we report here a visible-light-induced cycloaddition of 4-azacoumarins with BCBs, delivering a range of aza-BCHs derivatives. The reaction mechanism was proposed by combining control experiments and the photophysical properties of the imine chromophore. Selective functionalization of cycloadducts was also pursued, delivering aza-BCHs molecules with a diverse chemical space.

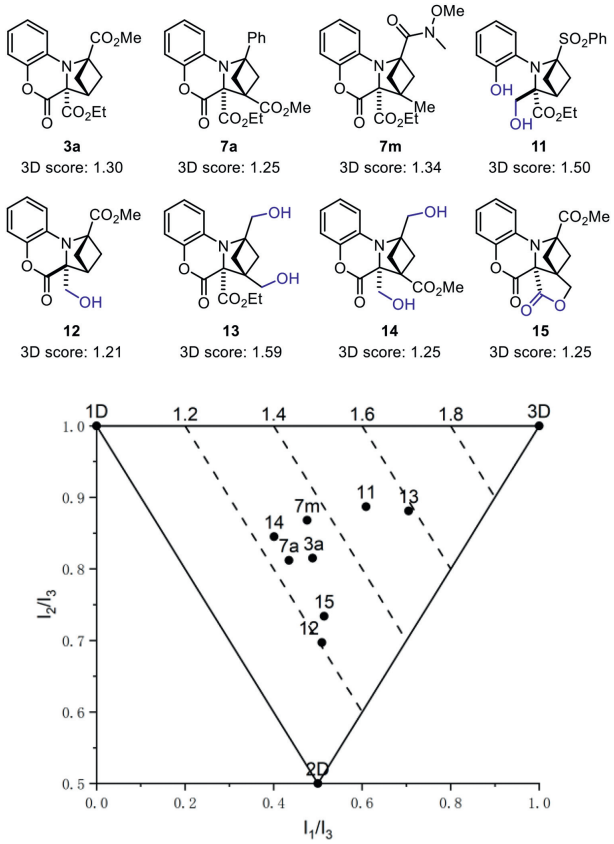


Fig. 2. PMI analysis of 3-dimensionality.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Min Yan: Methodology, Investigation. **Zihao Ye:** Investigation. **Ping Lu:** Writing – review & editing, Writing – original draft, Conceptualization.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.110540.

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