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Article

Double Strain-Release [2π+2σ]-Photocycloaddition

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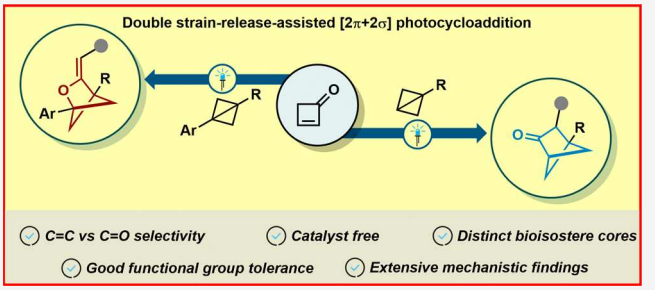
ABSTRACT: In pursuit of potent pharmaceutical candidates and to further improve their chemical traits, small ring systems can serve as a potential starting point. Small ring units have the additional merit of loaded strain at their core, making them suitable reactants as they can capitalize on this intrinsic driving force. With the introduction of cyclobutenone as a strained precursor to ketene, the photocycloaddition with another strained unit, bicyclo[1.1.0]butane (BCB), enables the reactivity of both π-units in the transient ketene. This double strain-release driven [2π+2σ]-photocycloaddition promotes the synthesis of diverse heterobicyclo[2.1.1]hexane units, a pharmaceutically relevant bioisostere. The effective reactivity under catalyst-free conditions with a high functional group tolerance defines its synthetic utility. Experimental mechanistic studies and density functional theory (DFT) calculations suggest that the [2π+2σ]-photocycloaddition takes place via a triplet mechanism.



INTRODUCTION

With the conceptual development of strain release,[1] researchers have leveraged the inherent reactivity originating from the thermodynamic push and destabilization. These "spring-loaded" molecules provide a great platform for accessing complex molecular entities under mild and sustainable conditions by factoring out the requirement for additional sources of energy (Scheme 1A). In 2016, Baran and co-workers reported a strain-release-driven amination, which fueled the interest in merging it with the rising concept of bioisosterism.[2] Ring systems, especially small and strained ring systems with a double bond or with a bridged bond, hold high-profile importance in transformations that generate bioisosteric systems. Recent works from Brown[3] and our group[4,5] demonstrated that a high energy-containing molecule, bicyclo[1.1.0]butane (ΔE = 66.3 kcal/mol),[6] could be efficiently engaged in [2π+2σ]-photocycloadditions giving rise to highly sought-after, yet complex sp^3-rich units. Given the influence of saturated isosteres as target molecules in rational drug design, the demand for expanding its chemical space[7] promises to unravel new exit vectors, potency, pharmacological properties, and physiological assessments (Scheme 1B).[8] The spatially rigid distribution of substituents and incorporation of heteroatoms in thereby generated 3D chemical moieties dictate the degree and efficiency of metabolic activity, thus bringing in a prospective replacement for the closely resembling parent aromatic core in drug motifs. For instance, Mykhailiuk and co-workers showed that 2-oxabicyclo[2.1.1]hexanes (oxa-BCHs), a potential bioisostere for *meta*-substituted arene rings, proved to be more hydrophilic and less lipophilic than proclaimed bicyclo[1.1.1]pentanes.[9,36] The oxa-BCH unit is further claimed to be 30 times more hydrophilic, less lipophilic, and more stable than the corresponding parent *meta*-substituted benzene ring. Since the conceptual advancement of "escape from flatland", many reports from Brown,[3] Studer,[10] Procter,[11] Molander,[12] Leitch,[13] Aggarwal,[14] Li,[15] Wang,[16] Waser,[17] Shi,[18] Bach,[19] and our group[5,20] displayed BCBs as potential precursors for 3D-chemical space exploration.

Cyclobutenone—another strained system—is well regarded as a precursor for reactive vinyl ketene intermediates under photochemical conditions.[21] Ketene represents one of the keystone reactive intermediates[22] that has offered myriads of unique reactions over the last century.[23] Staudinger and Wilsmore independently landed on the serendipitous discovery of this highly reactive species which plays a remarkable role in the origin of numerous drug candidates, industrial manufacture of acetic acid, acetic anhydride, and paper industry.[24] In line with being a reactive intermediate, ketenes offer an incredibly rich reactivity continuum out of which the [2π+2π]-cycloaddition[25] shares undivided attention.[26,27] Having two orthogonal π-systems in a reactive intermediate grants an extra edge of introducing divergence in a cycloaddition

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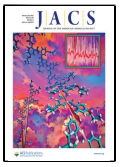

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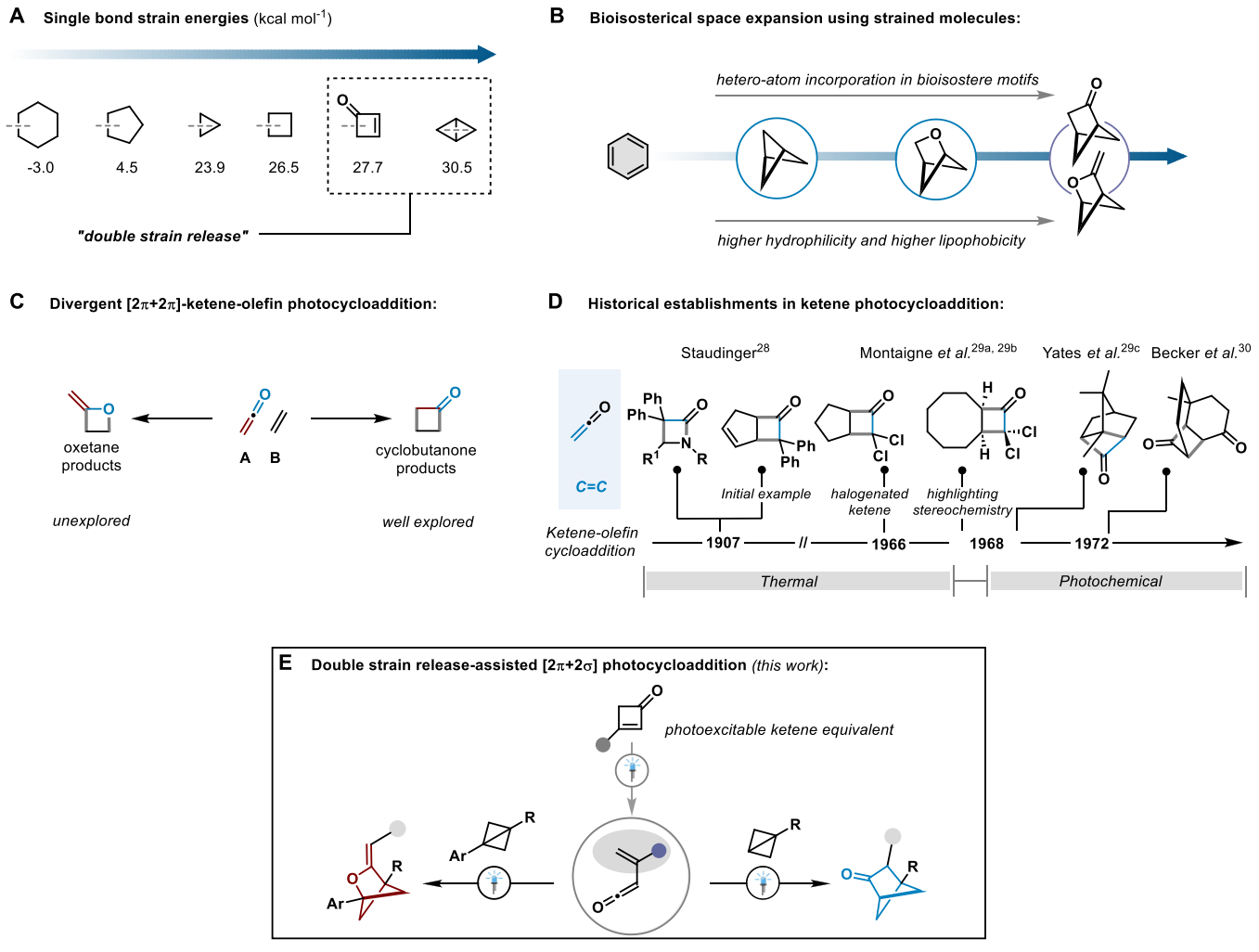
Scheme 1. Aim and Motivation: (A) Ring Systems with Increasing Strained Σ-Bond Energy; Bond Strain Energies Are Estimated Using Homodesmotic Reactions (See the SI for Details), (B) Expansion of sp^3-Rich Chemical Space and Comparison on Physiological Parameters, (C) Two Distinct Π-Units in Ketene for Cycloaddition, (D) Historical Findings on Ketene [2π+2π]-Cycloaddition, and (E) Double Strain-Release-Assisted Divergent Photocycloaddition of Ketenes with Bicyclo[1.1.0]butanes



process, producing structurally diverse chemical entities (Scheme 1C).

After the first report on the cycloaddition of ketenes with imines and the olefins in 1907,[28] several follow-ups started emerging (Scheme 1D).[29,30] After decades of extensive research, cycloaddition methodologies involving ketenes were limited to the alkenyl part of the ketene reacting with an olefin partner to produce cyclobutanones. Besides the dimerization of ketenes,[26,31] limited examples are reported for the ketene carbonyl acting as a 2π component.[32]

Incorporating these two strained units from the higher end of the ring strain spectrum would enhance the thermodynamic feasibility of the system, allowing them to operate under mild conditions (Scheme 1E). In this work, we went on to explore the concept of double strain-release, which eventually unveils the orthogonal reactivity of two π-units of ketene for practical and straightforward access to new sp^3-enriched species of heterobicyclo[2.1.1]hexanes under catalyst-free conditions.

RESULTS AND DISCUSSION

Reaction Optimization. Based on a report stating the comparatively high reactivity of haloketenes,[33] we commenced with reacting a bench-stable halogen-based cyclobutenone—4,4-dichloro-3-(4-methoxyphenyl)cyclo-but-2-en-1-one—**1a** (3.0 equiv) with BCB **2a** (1.0 equiv) in toluene under visible light irradiation with blue LEDs (10 W per vial). This setup without photocatalyst accounts for the process to be benign and simple.[34] To our delight, cycloadduct **3a** was observed as an exclusive product after overnight stirring with a 71% ^{1}H NMR yield. Intrigued by the findings, we began to probe the reaction conditions which offered an incremented yield of 82% under diluted conditions (0.05 M). Notably, the addition of a catalytic amount of triplet sensitizers did not bring any significant improvement (^{1}H NMR yield = 71%) (see the SI for the full optimization table). This imposed the utilization of direct, visible-light-induced excitation to achieve the excited states of cyclobutenone **1a**. No product formation took place in the absence of irradiation at room temperature or even at 60 °C in control experiments which speaks against a thermal background activity. Captivated by the outputs, a phenyl-attached disubstituted BCB was employed using the optimized parameters. Surprisingly, a cycloadduct with the carbonyl part of the ketene was observed to be the major product with a

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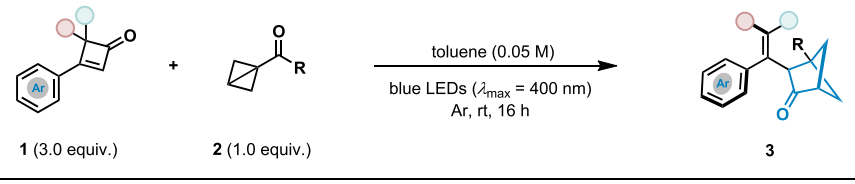
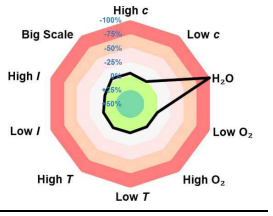
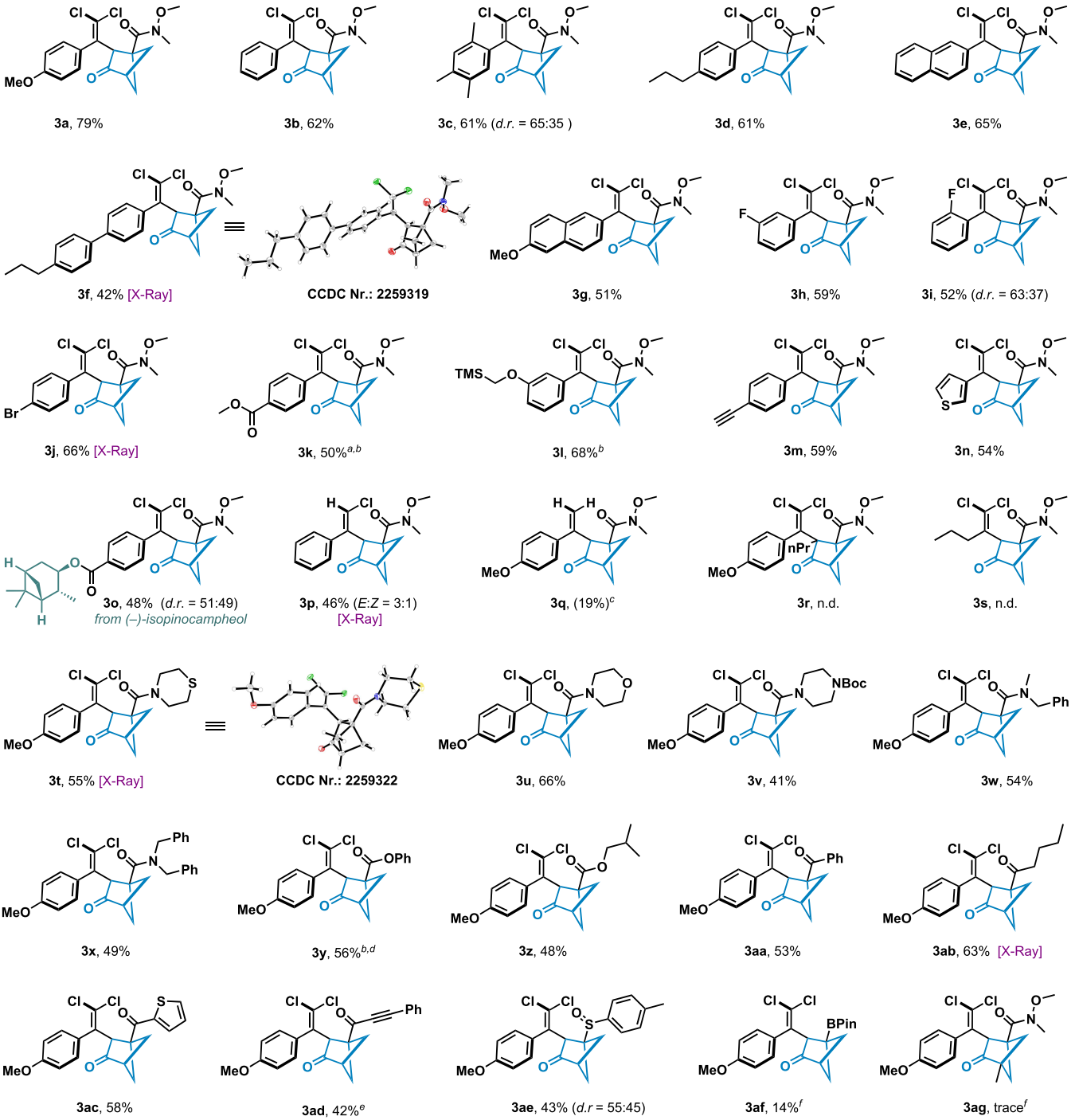
Scheme 2. Substrate Scope for C═C Cycloaddition and Sensitivity Assessment: Standard Reaction Conditions: 1 (3.0 equiv), BCB 2 (0.20 mmol, 1.0 equiv) in Toluene (0.05 M) at 27−30 °C under Irradiation with Blue LEDs (λ_{max} = 400 nm, 10 W Per Vial) for 16 h; Atropdiastereomeric, Diastereomeric, and *E*:*Z* Ratios Are Obtained from Crude ^{1}H NMR Analysis







[a] λ_{max} = 365 nm, [b] 5.0 equiv of **1**, [c] ^{1}H NMR yield is reported, [d] reaction irradiated for 48 h, [e] performed on 0.15 mmol scale. [f] 5.0 equiv of **1a** and 0.1 M toluene, [X-Ray] = crystal structure, n.d. = not detected.

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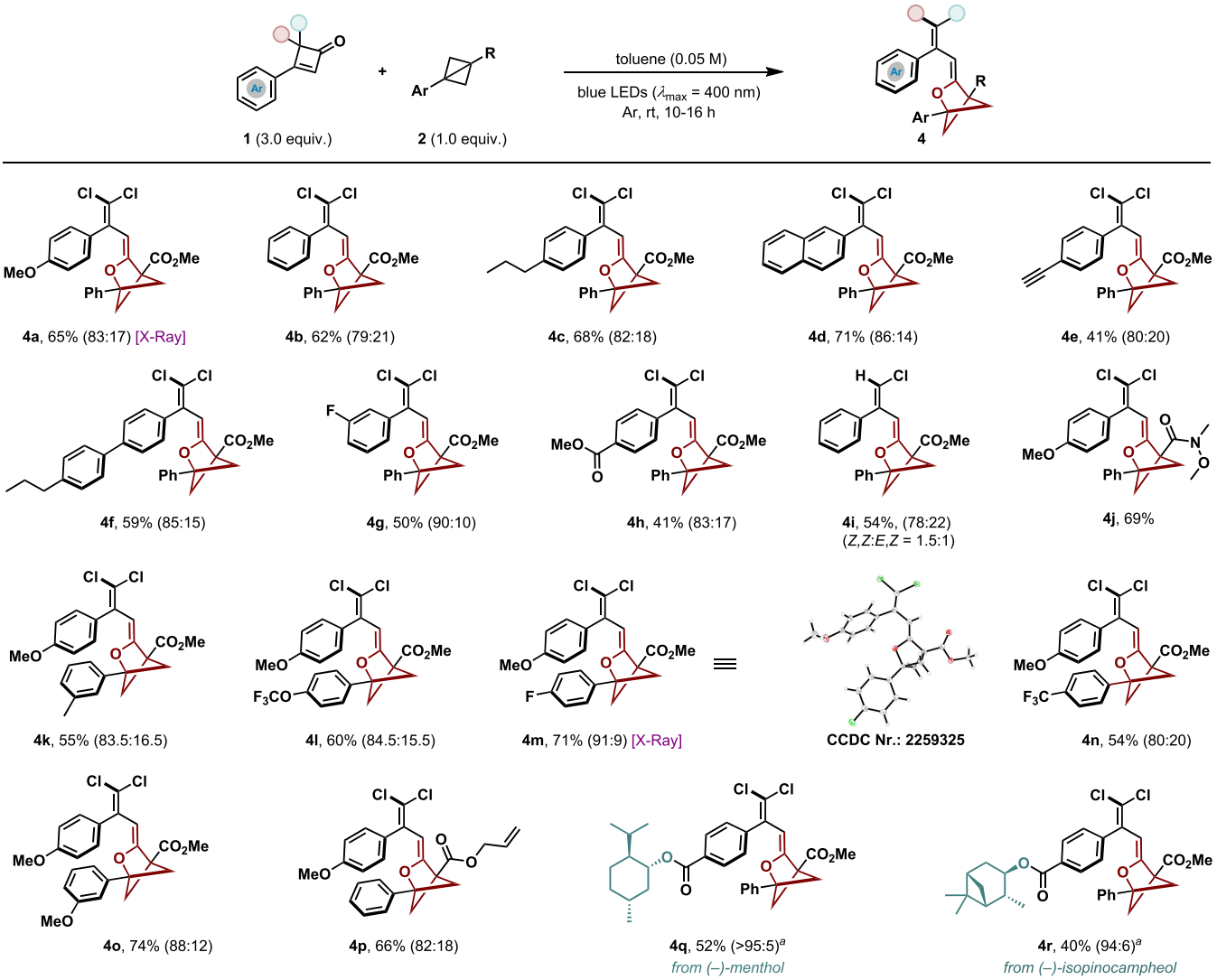
Scheme 3. Substrate Scope for C═O Cycloaddition: Standard Reaction Conditions: 1 (3.0 equiv), BCB 2 (0.20 mmol, 1.0 equiv) in Toluene (0.05 M) at 27−30 °C under Irradiation with Blue LEDs (λ_{max} = 400 nm, 10 W per Vial)



Reaction times are mentioned in the Supporting Information. All the ratios mentioned in parentheses demonstrate C═O/C═C product ratios (unless otherwise mentioned) obtained from crude ^{1}H NMR analysis. [X-Ray] = crystal structure. [a]5.0 equiv of **1**.

good selectivity of 83:17, thereby offering a divergent synthesis of bioisostere cores (see SI for additional details).

Reaction Scope. Under the optimized set of conditions, we began to systematically investigate the generality of this protocol (Scheme 2). First, a wide range of substituted aromatic cyclobutenones were tested with BCB **2a** under the optimal settings. A series of arenes bearing mono- and multialiphatic substitution were well transformed to substituted bicyclo[2.1.1]hexan-2-one units (**3b**−**3d**). The steric clash between the *ortho*-substituted methyl and alkenyl chlorine fostered the formation of atropodiastereomers in **3c**. Extension of conjugated π-units to naphthalene and biaryl (**3e**−**3g**) proved to be fruitful, furnishing the desired cycloadducts in good yields. Fluorine incorporation at both the *meta*-(**3h**) and *ortho*-positions (**3i**) was successfully tested, offering generous yields of 52% and 59%, respectively. Aryl bromide (**3j**) also survived under the present protocol with a 66% isolated yield, thereby highlighting a potential reactive site for further downstream modification. Both ester (**3k**) and silyl group (**3l**) also displayed the desired reactivity with **2a**. The reaction of a cyclobutenone bearing a pendant alkynyl moiety (**3m**), believably a suitable unit for click chemistry, participated well under the optimized condition. In addition, a thiophene-derived strained ketene precursor (**3n**) offered a decent yield of 54%. A bicyclic monoterpene unit—(−)-isopinocampheol—embedded in a cyclobutenone (**3o**), underwent smooth conversion with a moderate yield. Examples with monochloro alkenyl (**3p**) and *gem*-dihydroalkenyl group (**3q**) discard the mandate of having a *gem*-dichloro unit in the ketene backbone. Nonetheless, disubstituted ketene (**3r**) poses a limitation in the current protocol.

Along the line of our hypothesis, the aliphatic ketene synthon (**3s**) did not provide any cycloaddition product, thus asserting the need for a light-absorbing unit in the molecule

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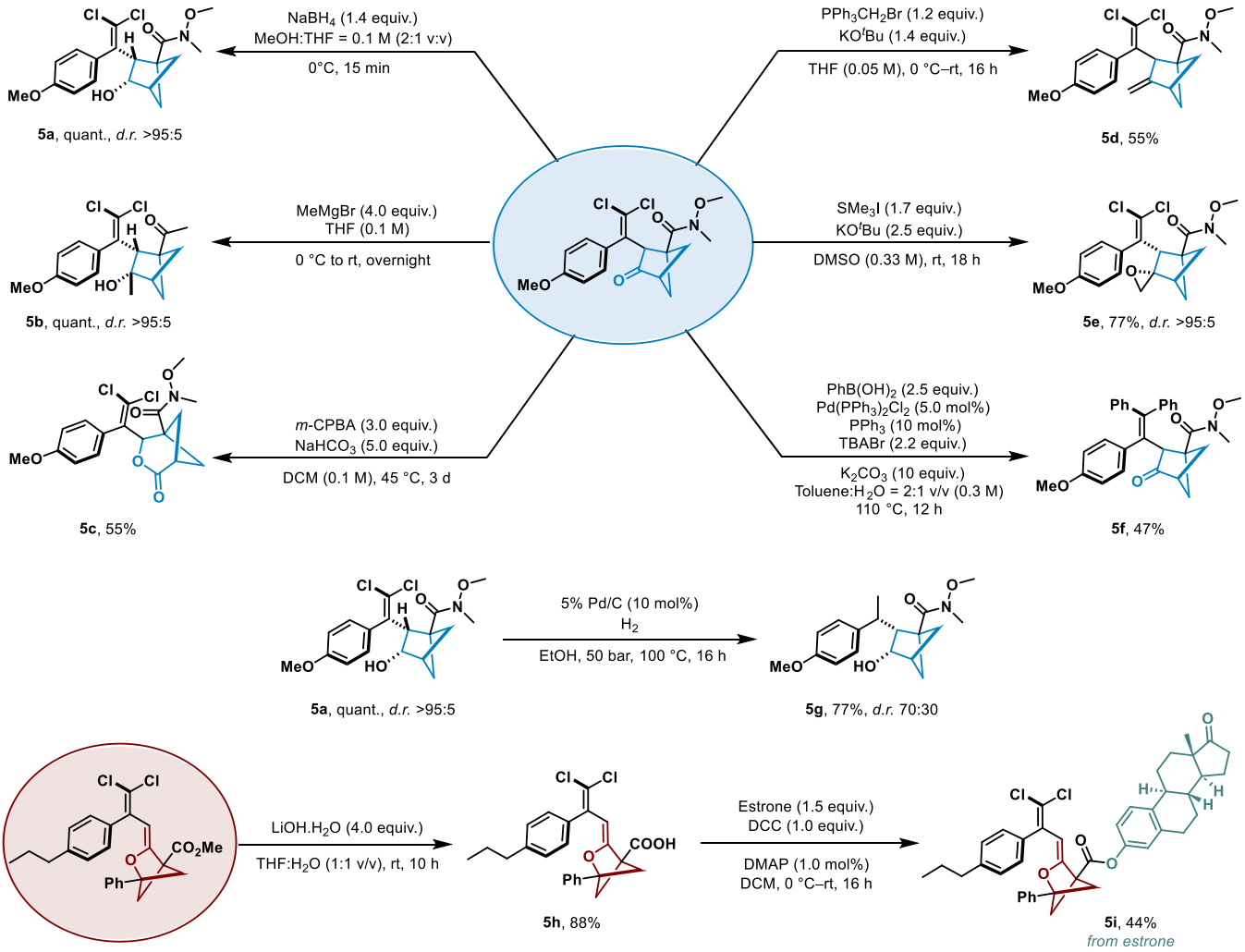
Scheme 4. Post Modification of Catalytically Obtained Products



(see SI for more unsuccessful entries). The projection of substituents across the strained BCB determines the behavior of corresponding isosteres in the physiological platform, for example, engaging in drug-target interactivity, exposed polarity, and solvation. In this regard, we set out to investigate the effect of substitution patterns on BCBs. Subjecting various amides constituting thiomorpholine (**3t**), morpholine (**3u**), Boc-protected piperazine (**3v**), and disubstituted alkyl group (**3w**–**3x**) substantiates the tolerance of amide—in general—under the present scheme. Both aromatic (**3y**) and aliphatic ester (**3z**) coupled successfully, albeit consuming the standard ketene precursor **1a** in excess (5.0 equiv) for the former case. Similar performance was observed when aromatic (**3aa**), aliphatic (**3ab**), and heteroaromatic ketone (**3ac**) containing BCBs were submitted to the reaction conditions. The cycloadduct formation across the strained bond despite the presence of a competitively reactive alkynyl moiety (**3ad**) emphasizes the chemoselectivity of the underlined strategy. Next, a sulfoxide-based BCB was tested, delivering the anticipated ring closure product **3ae** in a modest diastereomeric ratio. Further, a BPin-substituted BCB delivered the photocycloadduct **3af** in a diminished yield, whereas for the disubstituted BCB (**3ag**), no product was detected.

Moving on, we set out to explore the underrepresented divergent aspect in the arsenal of ketene chemistry (Scheme 3). Selected cyclobutenones were applied for testing the generality of the divergent protocol with BCB **2q**. Diverse aromatic backbones were applied including phenyl (**4b**), *n*-propyl (**4c**), naphthalene (**4d**), alkynyl (**4e**), and biaryl system (**4f**) to provide the desired [2π+2σ]-cycloaddition products in good yields. Extending the scope to fluoro- (**4g**) and ester-substituted (**4h**) cyclobutenones exhibited good tolerance, as well. It is pertinent to note that monohalo-bearing cyclobutenone (**4i**) provided satisfactory yields with good C═O/C═C selectivity, whereas changing the BCB's ester unit to Weinreb amide gave an exclusive C═O cycloaddition product **4j**. Pleasingly, several electronically neutral (**4k**–**4l**), electron-withdrawing (**4m**–**4n**), and electron-donating substituents on disubstituted BCBs (**4o**) could be engaged in the ongoing methodology conveniently with attractive selectivity. Tempted by the competitive reactivity of BCBs over alkenes, we questioned whether a similar behavior could be realized under this divergent photocycloaddition approach. Indeed, a BCB with a tethered alkene reacted in a chemoselective fashion, affording the sought-after product (**4p**) in a good yield. Finally, installing menthol (**4q**) and isopinocampheol (**4r**) also provided access to the diverse BCH motifs in synthetically useful yields.

Product Modifications. The [2π+2σ]-coupled products generated by our method provide multiple synthetic linchpins

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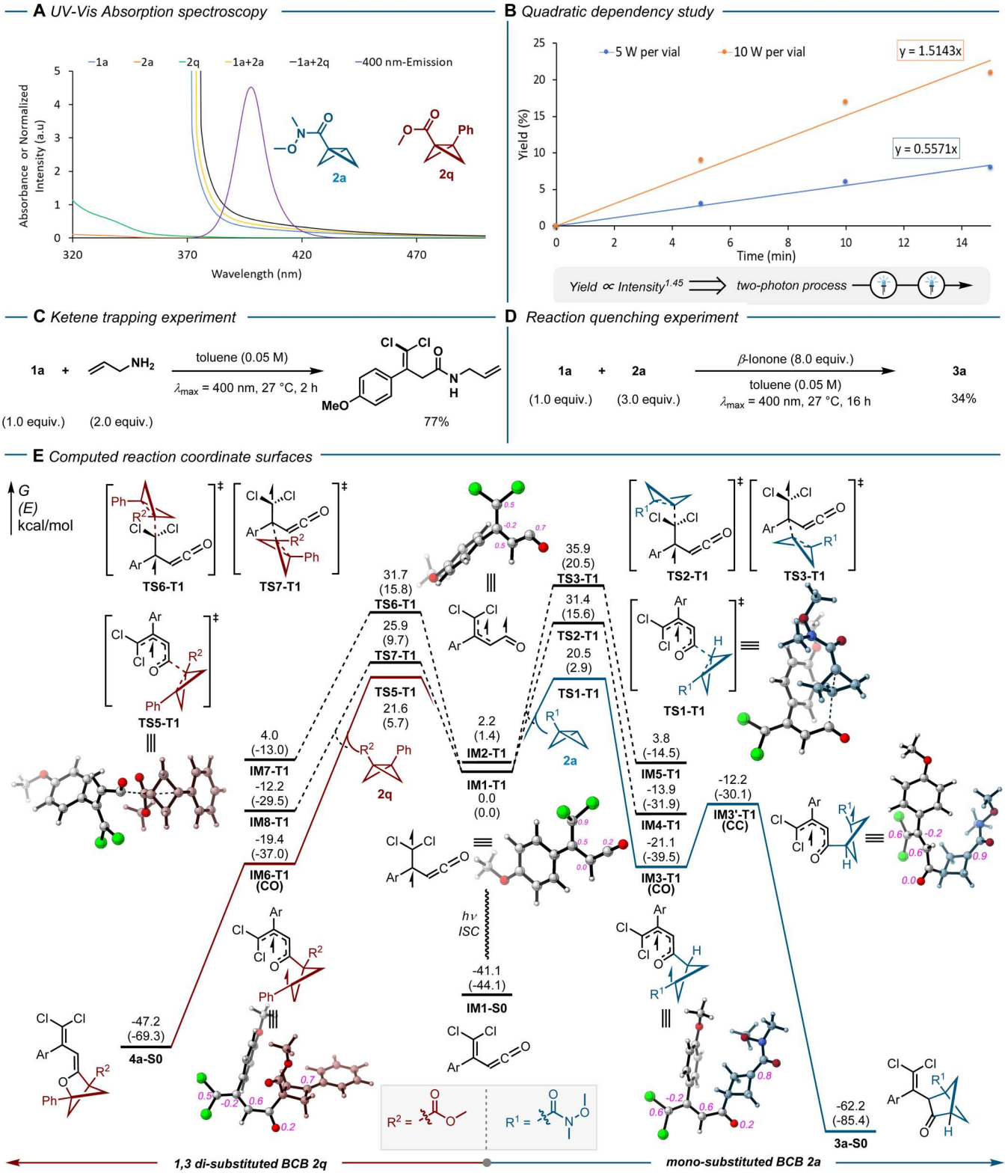
Scheme 5. Experimental and Computational Mechanistic Highlights: (A) UV−Vis Absorption Spectrum Showing 1a as Exclusive Absorbing Species at 400 nm, (B) Quadratic Dependency Study as a Proof for a Two-Photon Process, (C) Proof of Formation of Ketene after Excitation, (D) Triplet Quenching Studies with β-Ionone, and (E) Computed Reaction Coordinate Surface with Monosubstituted BCB 2a and Disubstituted BCB 2q



DFT calculations were conducted at the UM062X/def2TZVP/SMD (solvent = toluene)//UM06-2X/def2SVP/SMD (solvent = toluene) level of theory.[35] Ar = 4-OMe benzene.

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for further post-diversification (Scheme 4). Subjecting **3a** to classical nucleophilic addition reactions furnished a quantitative amount of synthetically important secondary alcohol **5a** and tertiary alcohol **5b** with excellent diastereoselectivity. The cyclic ketone moiety of **3a** could be smoothly converted into another popular class of biosiostere **5c**,[36] closely mimicking the *meta*-substituted benzenes via Baeyer−Villiger oxidation. Next, Wittig conditions were applied to access cyclic external alkene **5d** from the ketone group. Fortunately, by treating **3a** with trimethylsulfonium iodide under a basic medium, we managed to obtain the epoxide-embedded spiro compound **5e** in excellent yield. Noteworthy, the coupling of phenylboronic acid with **3a** gives smooth entry into tetracarbon-substituted alkene unit **5f**, thus extending the scope of substituents at the alkenyl position. We could successfully administer compound **5a** under hydrogenation conditions which resulted in dechlorination and thereby formed a hydrocarbon unit containing bicyclic unit **5g**. Finally, basic hydrolysis of **4c** converted the ester group to carboxylic acid **5h**, followed by installation of an estrone molecule, delivering another drug unit containing the entity **5i**.

Mechanistic Highlights. We performed several mechanistic experiments to probe the reaction mechanism. The UV−visible spectrum revealed that only cyclobutenone **1a** absorbs in the visible region of the spectrum, suggesting that direct excitation of cyclobutanone **1a** forms the ketene intermediate via a retro 4π-electrocyclic ring opening reaction. We also performed density functional theory (DFT) calculations to support the ketene formation mechanism (see SI for details; Scheme 5A). Considering the earlier reports on photolysis of cyclobutenone,[37] we postulate that a consecutive two-photon process[30,38] would be operating under the standard reaction conditions. Indeed, the quadratic dependency study displayed a 2.75 times increase in the reaction yield with the doubling of light intensity (Scheme 5B). This showed a deviation from linearity, demonstrating a possible consumption of two photons. The first photon initiates the photoelectrocyclization ring opening of cyclobutenone to form a ketene intermediate. The second photon excites the in situ generated ketene intermediate and initiates the subsequent [2π+2σ] cycloaddition with BCB. In addition, using allyl amine, we successfully captured the reactive ketene intermediate from **1a** with complete conversion (Scheme 5C). The addition of β-Ionone, a known triplet quencher,[39] to the standard reaction condition resulted in a decreased yield of **3a** from 79 to 34% (Scheme 5D). Because the rapid ketene formation from **1a** follows an open-shell singlet profile, an efficient quenching of the next step by a triplet quencher could suggest a viable triple pathway after the second excitation. The quantum yield of the reaction was determined to be Φ = 0.07, which eliminates the possibility of the chain process being operative. Trapping experiments with TEMPO yielded no product (**3a**), which is in agreement with Tidwell's trapping studies on related systems.[40]

We conducted DFT studies to further probe the origin of regioselectivity in the [2π+2σ] photocycloaddition of mono- and 1,3-disubstituted BCBs (**2a** and **2q**) into the ketene intermediate **IM1** (Scheme 5E). Based on the triplet quenching experiments, photoexcitation followed by intersystem crossing (ISC) of the ketene intermediate **IM1** forms the diradical intermediate **IM1-T1**, in which the spin densities are located on the dichloro-substituted alkene (π to π^* excitation). Isomerization of **IM1-T1** forms **IM2-T1** which consists of an allyl radical and a carbonyl radical. Both monosubstituted BCB **2a** and 1,3-disubstituted BCB **2q** favor insertion into the carbonyl radical in **IM2-T1** via **TS1-T1** ($\Delta G_{TS1}^{\ddagger}$ = 20.5 kcal/mol) and **TS5-T1** ($\Delta G_{TS5}^{\ddagger}$ = 21.6 kcal/mol), correspondingly. Consistent with our previous studies, for both **TS1-T1** and **TS5-T1**, the strained BCB σ-bond is cleaved simultaneously with the C−C bond formation at the carbonyl of the ketene triplet. The competing regioisomeric BCB insertion transition states (**TS2-T1** & **TS3-T1**, **TS6-T1** & **TS7-T1**) are kinetically and thermodynamically disfavored. Competing BCB insertions to the allyl group also have higher free energy barriers (see the SI for additional details). The origin of C═C/C═O selectivity is decided in the radical−radical recombination step from **IM3** and **IM6**. The origin of BCB substitution on product selectivity is the subject of further investigation and is beyond the synthetic aspect of this current study.

CONCLUSIONS

The displayed strategy allowed the straightforward formation of two distinct heteroatom-containing isosteres in synthetically rewarding yields. Here, with cyclobutenones being a source of in situ ketene equivalents and BCBs providing the conformational rigidity, this work also highlights the ongoing double strain-release event making the [2π+2σ]-photocycloaddition thermodynamically feasible. The broad functional group tolerance and the bicyclic core modification demonstrate the high synthetic utility of this methodology. The stagewise mechanism and selectivity queries are well-supported by experimental evidence and extensive DFT calculations. Overall, we believe our findings have far-reaching potential in the field of ketene-photocycloaddition and could eventually spur interest in harnessing potential energies from reaction partners in a sustainable way.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c11563.

All the experimental procedures, characterization, and crystallographic data (PDF)

Accession Codes

CCDC 2259319−2259325 contain 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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Notes

The authors declare no competing financial interest.

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