Harnessing Carbene Reactivity of [1.1.1]Propellane for [2,3]-Sigmatropic Rearrangement: Application and Mechanistic Studies

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Abstract:

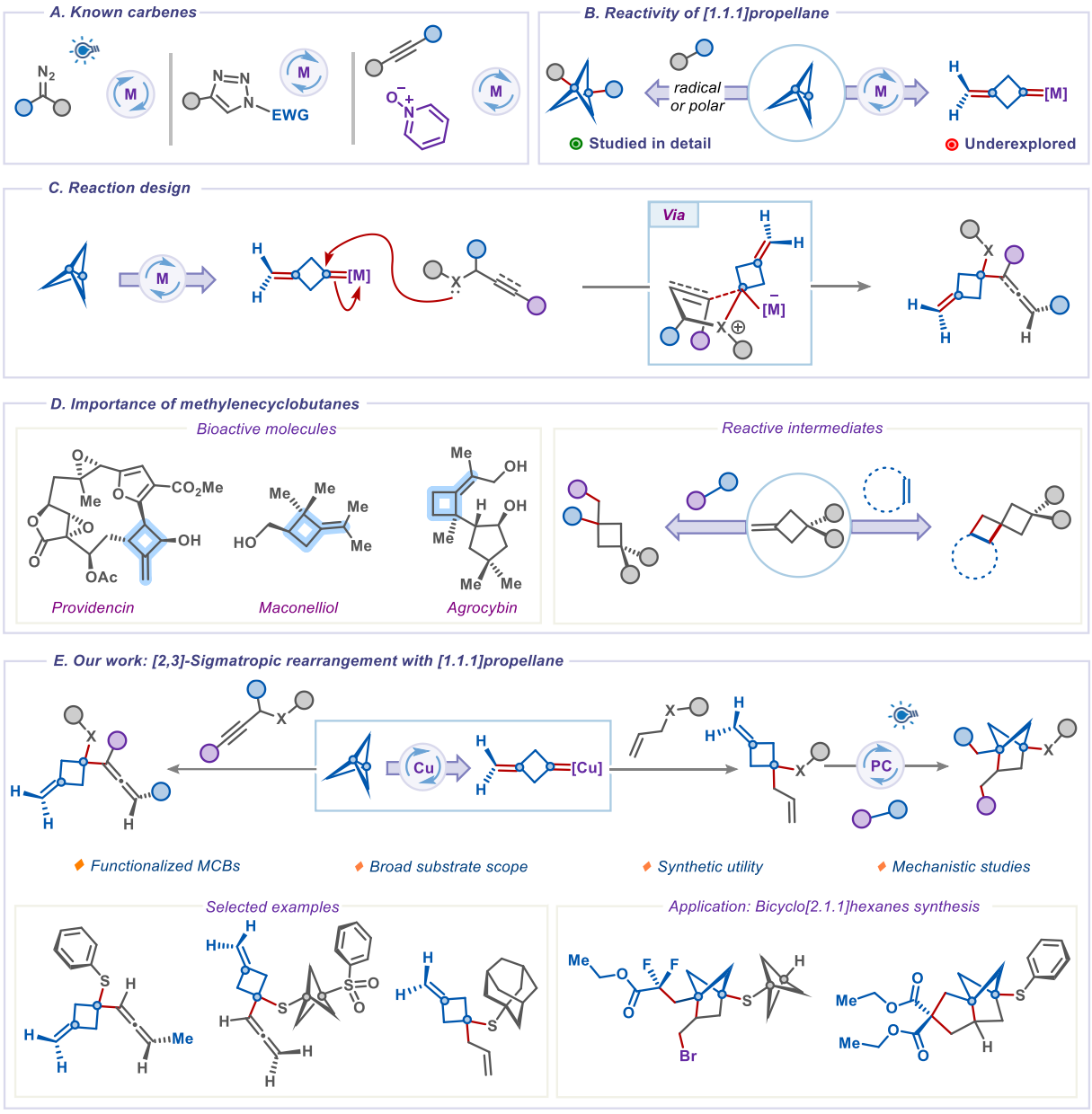
[1.1.1]Propellane is a highly strained smallest tricyclic hydrocarbon, and its reactivity is primarily engrossed by addition reactions across the strained C-C bond, leading to the formation of bicyclo[1.1.1]pentane derivatives. Herein, we present an unprecedented [2,3]-sigmatropic rearrangement that uses [1.1.1]propellane as a carbene precursor to rapidly access allenylated or allylated methylenecyclobutanes. The reaction is highly efficient and scalable, works well under mild conditions, and can tolerate remarkable functional groups on propargyl and allyl sulfides/selenides. Another significant achievement of this approach is the utility of the obtained products in synthesizing substituted bicyclo[2.1.1]hexanes, potential bioisosteres of *ortho* and *meta*-substituted benzenes, by developing a novel photocatalyzed radical cascade cyclization. Density functional theory calculations have suggested that the mechanism of this reaction proceeds via a Cu(I)-assisted five-membered envelope transition state to give the [2,3]-rearrangement product.

Keywords: [1.1.1]Propellane, Carbenes, Sigmatropic rearrangement, Methylenecyclobutanes, Bicyclo[2.1.1]hexanes

Introduction:

Carbene transfer reactions are highly effective in organic synthesis, creating molecular complexity selectively through X-H insertions, additions, or rearrangement reactions.[1-5] The most common way of generating carbenes is from highly reactive diazoalkanes using metal catalysts or photoirradiation (scheme 1A).[3-8] The other alternative precursors for carbenes include substituted triazoles or alkynes with pyridine *N*-oxides using transition metal catalysts.[9-16] Generating carbenes via the activation of C−C bonds is highly beneficial as it provides unique opportunities for constructing backbones of organic molecules. However, it is highly arduous due to the dormancy of the C−C bonds and the absence of metal-carbon bond interactions. In this context, ring-strain energy in small organic molecules has been exploited to promote the challenging C−C bond activation. Cyclopropanes and bicyclo[1.1.0]butanes are known to generate carbenes under metal catalysis by double C-C bond activation, but they are limited to only a few examples.[17-23] Consequently, systems that could facilitate the challenging double C−C bond activation to generate metal carbenes at ambient conditions for increasing molecular diversity in synthetic organic chemistry are highly desirable.

[1.1.1]Propellane is the smallest member of the propellane family, with a strain energy of ~100 kcal/mol. It exhibits unique reactivity due to the presence of an "inverted" central C-C σ-bond connecting the bridgehead carbons.[24-26] The reactivity of [1.1.1]propellane is predominantly focused on the difunctionalization of the bridgehead bond via either radical or ionic pathways owing to its omniphilic reactivity, leading to the formation of bicyclo[1.1.1]pentane derivatives (Scheme 1B).[27-30] Despite the surge in a growing number of examples of



Scheme 1: **(A)** Known carbenes; **(B)** Reactivity of [1.1.1]propellane; **(C)** Reaction design; **(D)** Importance of methylenecyclobutanes; **(E)** Our work: [2,3]-Sigmatropic rearrangement with [1.1.1]propellane and its applications.

1,3-difunctionalizations of [1.1.1]propellane, its carbene reactivity is less explored.[31-35] However, its inherent ring strain should furnish the required driving force for enabling the challenging double C−C bond activation to generate a metal carbene species via retro-cyclopropanation.

The Doyle-Kirmse reaction, a [2,3]-sigmatropic rearrangement of onium ylides rendered by reacting a metal carbene with allyl or propargyl compounds, is among the powerful methods for the concomitant formation of C–C and C-X bonds.[36-39] This reaction has found a plethora of applications in the preparation of complex natural products and pharmaceuticals.[40-46] Owing to the widely applicable chemistry of the Doyle-Kirmse reaction, developing new carbene precursors for this rearrangement, especially with versatile handles, will potentially open up substantial chemical space and could lead to new avenues in organic synthesis. We envisioned that the carbenes generated by C-C bond activation of [1.1.1]propellane under metal catalysis

could be exploited in the Doyle Kirmse reaction (Scheme 1C). The key to accomplishing this would be to subdue the undesired isomerization and oligomerization reactions of metal-carbene intermediates.[31] This proposal not only offers novel reactivity between methylenecyclobutyl carbenes and allyl or propargyl sulfides/selenides but also presents a mechanistically distinct method to access valuable functionalized methylenecyclobutanes (MCBs). In addition to their presence in several naturally occurring and biologically active compounds,[47] MCBs are versatile reactive intermediates due to the presence of both the *exo*-methylene unit and reactive four-membered ring and thus participate in a variety of cycloadditions, difunctionalizations, ring-expansions leading to highly valuable building blocks (Scheme 1D).[48-50] Herein, we report our success in the development of the first [2,3]-sigmatropic rearrangement with MCB carbenes under copper catalysis (Scheme 1E). A wide range of propargyl and allyl -sulfides and -selenides are well tolerated. The reaction exhibits broad scope and remarkable functional group tolerance. Noteworthy, the obtained products were efficiently transformed into trisubstituted bicyclo[2.1.1]hexanes through a photocatalyzed radical cascade cyclization, a strategy that has not been previously reported. Additionally, the *exo*-methylene, the allyl or allenyl groups, and the sulfide moieties of the products can serve as versatile synthetic handles for further transformations. Density functional theory calculations provide insight into the reaction mechanism and suggest a Cu(I)-bound five-membered envelope transition state to give the product.

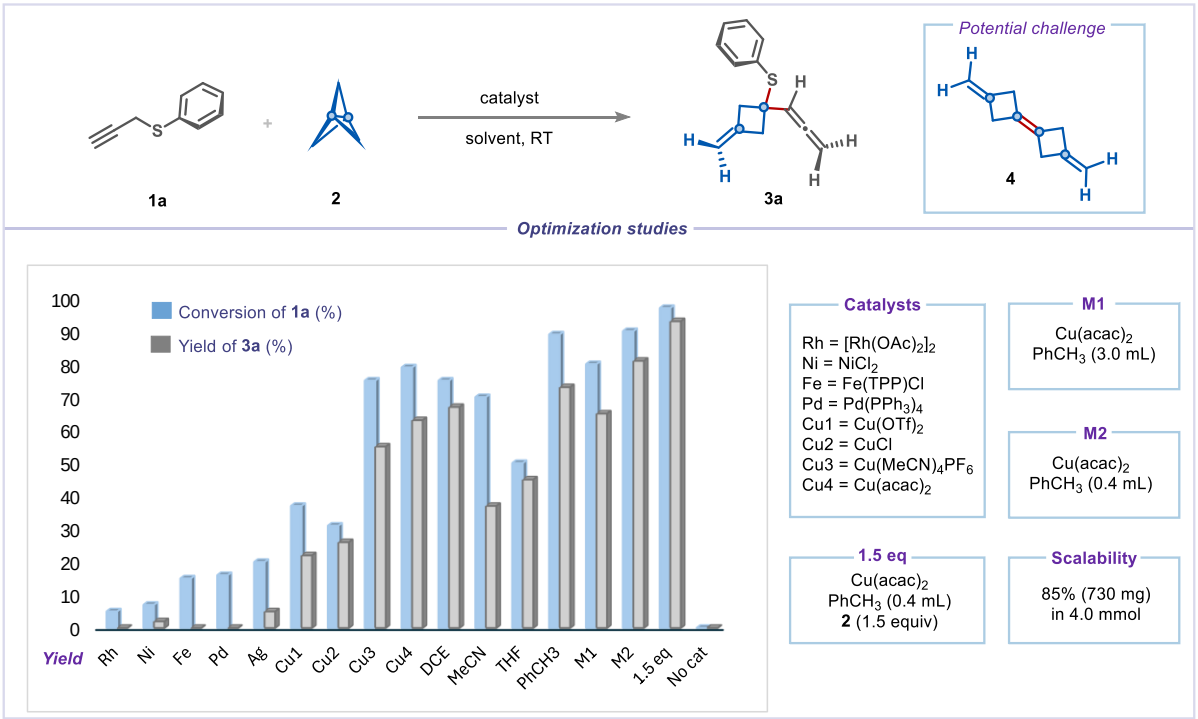
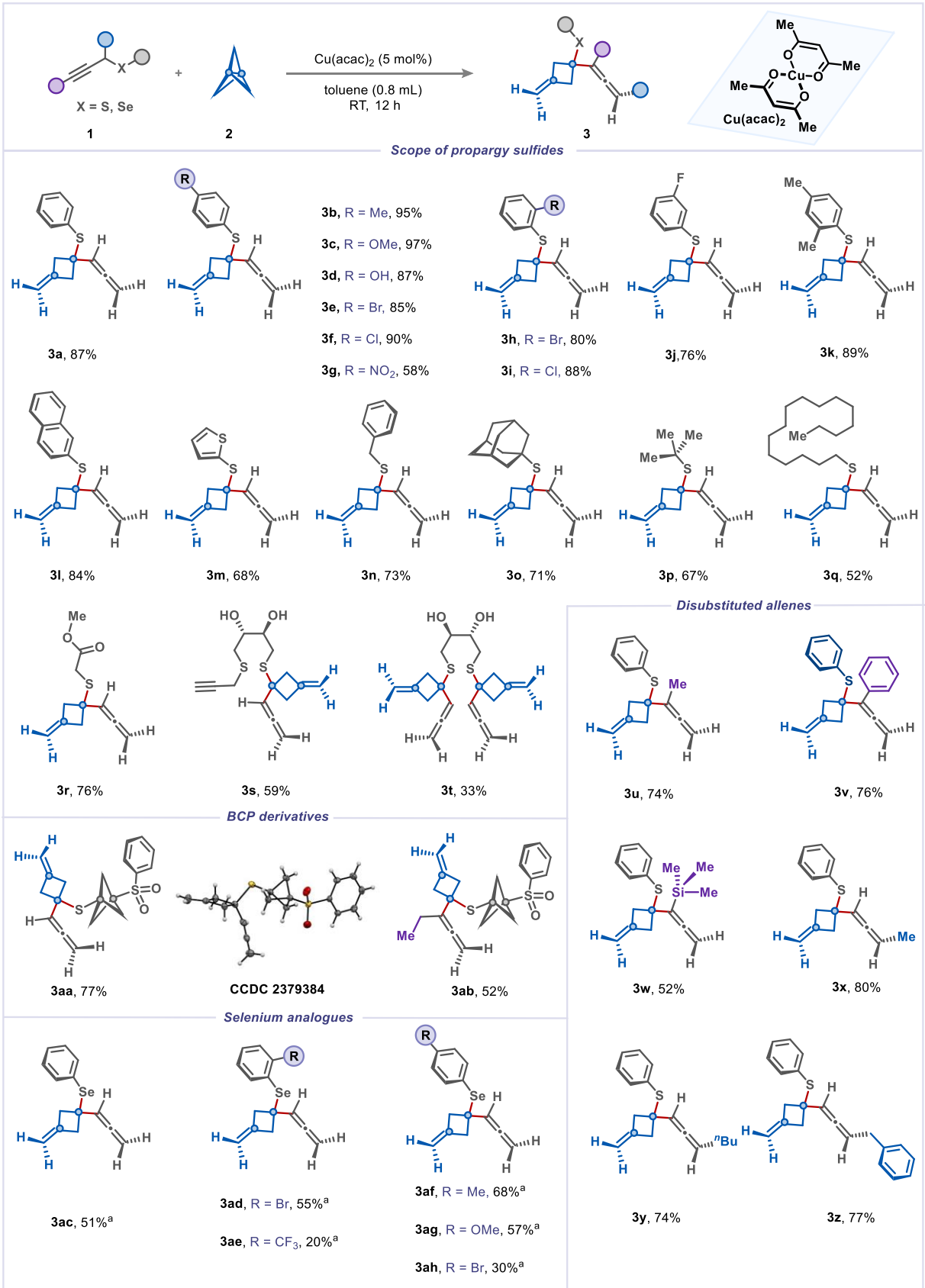


Figure 1: Optimization of reaction conditions. Reaction conditions: 0.15 mmol of **1a**, 0.15 mmol of **2**, catalysts (5 mol%), anhydrous solvent (1.5 mL), room temperature, 12 h. All catalysts were screened with anhydrous DCM solvent. Conversions and NMR yield were calculated using 1,3,5-trimethoxybenzene as an internal standard.

Results and Discussion:

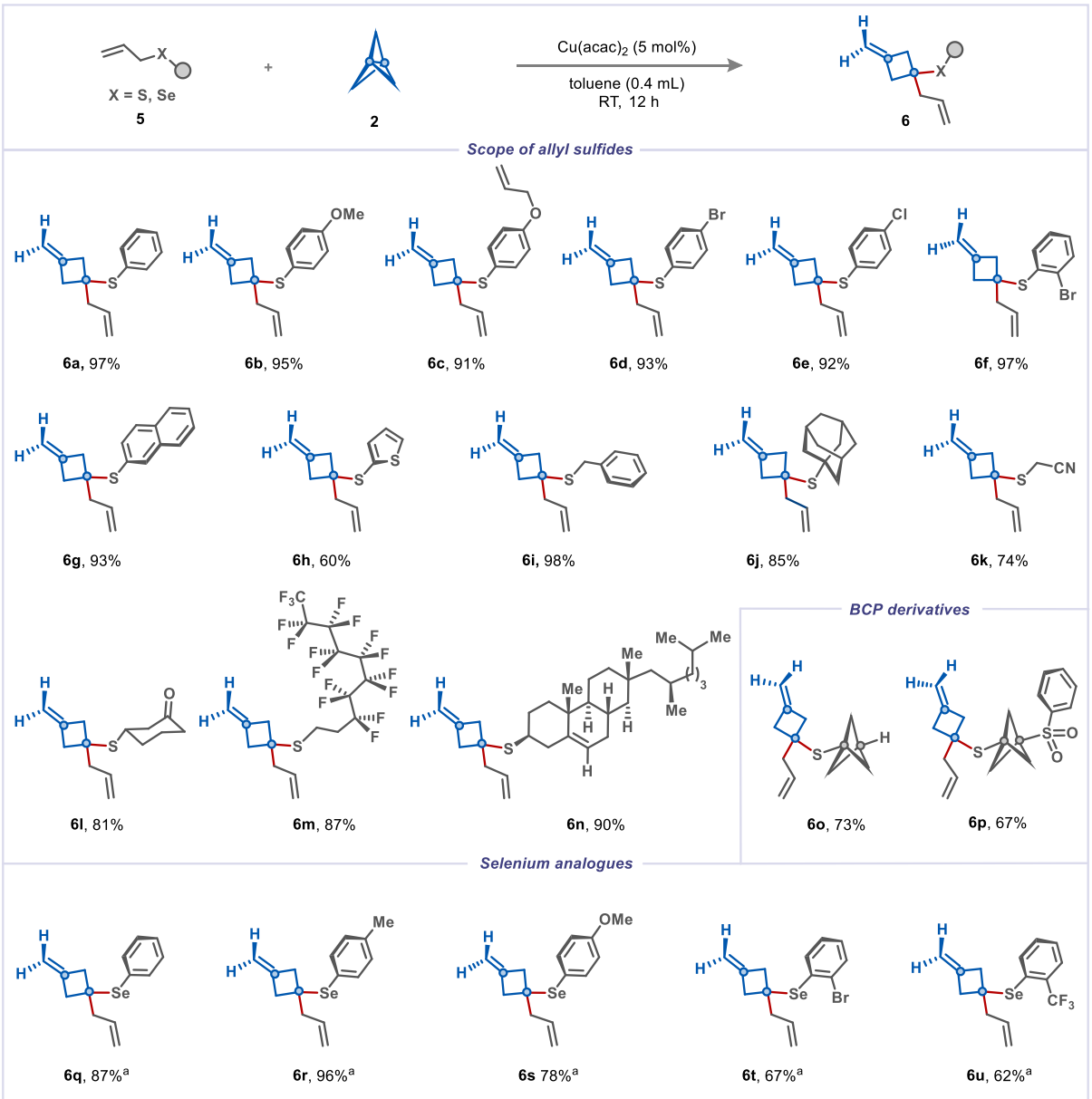
We initiated our investigations by exploring the [2,3]-sigmatropic rearrangement between [1.1.1]propellane **2** and phenyl propargyl sulfide **1a** using $Rh_2(OAc)_4$, a catalyst that Wiberg and coworkers used for the generation of MCB Rh-carbene.[31] However, only a trace amount of product **3a** was observed, along with a significant amount of dimer product **4** (Column 1, Figure 1). Next, we screened various metal catalysts to obviate the dimerization product **4** (Columns 2-9, Figure 1). Among the catalysts tested, $Cu(acac)_2$ was the best catalyst, affording the desired product in 63% yield (Column 9, Figure 1). The solvent screening revealed that toluene is the most effective, yielding the product in 73% (Column 13, Figure 1). Increasing the reaction concentration led to an improvement in the yield (Column 15, Figure 1). Further optimization identified the use of 1.5 equiv of **2** as optimal, giving the desired product in 93% yield (Column 16, Figure 1). Pleasingly, the synthesis of **3a** was performed on a 4 mmol scale with similar efficiency, thus highlighting the scalability of the reaction. No product formation occurred in the absence of $Cu(acac)_2$, indicating that the copper catalyst is essential for the reaction (Column 17, Figure 1).

With the optimized conditions established, we investigated the scope of propargyl sulfides that could be employed (Scheme 2). A wide range of electron-donating and electron-withdrawing substituents at the *para* position of arene rings reacted smoothly, providing the desired allenylated MCBs (**3b-3g**) in good to excellent yields. Notably, unprotected phenol was well tolerated, whereas such a functional group is incompatible with previously reported carbene transfer reactions.[51] *ortho*- and *meta*-Substituted arenes were also engaged in the reaction (products **3h, 3i,** and **3j**). Disubstituted-phenyl, naphthyl, and thiophenyl-derived propargyl sulfides underwent the desired transformation successfully, affording the desired products **3k**–**3m** in good yields. The reaction is not limited to aryl propargyl sulfides; benzyl and a broad range of alkyl propargyl sulfides, including adamantyl, *tert*-butyl, and long alkyl chains, were well tolerated (**3n**–**3q**). The α-ester-substituted propargyl sulfide was also found to be a suitable substrate (product **3r**). Interestingly, diol-containing bis-propargyl sulfide participated well, providing both mono- and di-allenylated MCBs **3s** and **3t** in 59% and 33% yields, respectively. Next, we explored various substitutions on internal alkynes. Methyl, phenyl, and trimethylsilyl groups were well tolerated, affording geminal disubstituted allenes bearing MCBs (products **3u**-**3w**). Pleasingly, substrates containing the substitutions on propargylic position displayed excellent reactivity to provide chiral disubstituted allenes **3x**-**3z**. Finally, pushing the limitations of this transformation, we tested bicyclo[1.1.1]pentane (BCP) bearing propargyl sulfides. To our delight, we obtained the corresponding BCP pendant MCBs **3aa** and **3ab** in good yields. The structure of product **3aa** was determined through X-ray crystallographic analysis (CCDC 2379384). As organoselenium compounds are prevalent in pharmaceuticals and are versatile reactive intermediates in organic synthesis, we were eager to explore whether phenyl propargyl selenides could be used in our reaction, thus expanding our product portfolio also to include selenium-bearing MCBs as well. Indeed, we found that under slightly modified conditions, phenyl propargyl selenides furnished the desired MCB **3ac** in 51% yield. Electron-donating and electron-withdrawing substituents on *ortho* and *para* positions were tolerated well (products **3ad**-**3ah**).



Scheme 2: Scope of propargyl sulfides **1**. Reaction Conditions: 0.30 mmol of **1**, 1.5 equiv of **2,** 5.0 mol% of $Cu(acac)_2$, 0.80 mL of anhydrous toluene, room temperature, 12 h. Yields are of isolated products. [a]Reactions were performed on a 0.15 mmol scale.

Given the versatility of the Doyle-Kirmse reaction for introducing various functionalities into carbene, we proceeded to investigate whether our reaction could be extended beyond propargyl sulfides. We were delighted to find that the treatment of phenyl allyl sulfide **5a** with **2** under standard conditions gave the desired allylated MCB **6a** in excellent yield, though with some difficulties in isolating the product from unidentified impurities (Scheme 3). However, we successfully suppressed the formation of impurities by using a slight excess of **2**. To demonstrate the robust nature of the protocol, we performed the reaction on a 2 mmol scale, and the desired product **6a** was obtained with a 95% yield. Next, we turned our attention to the scope of allyl phenyl sulfides. Functional groups such as ethers, bromo, and chloro on aromatic rings were well tolerated, providing the corresponding products **6b-6f** in excellent yields. It is worth mentioning that the reaction shows very high chemoselectivity towards allyl sulfides (product **6c**) in the presence of allyl ether. Napthyl and thiophene-substituted allyl sulfides were



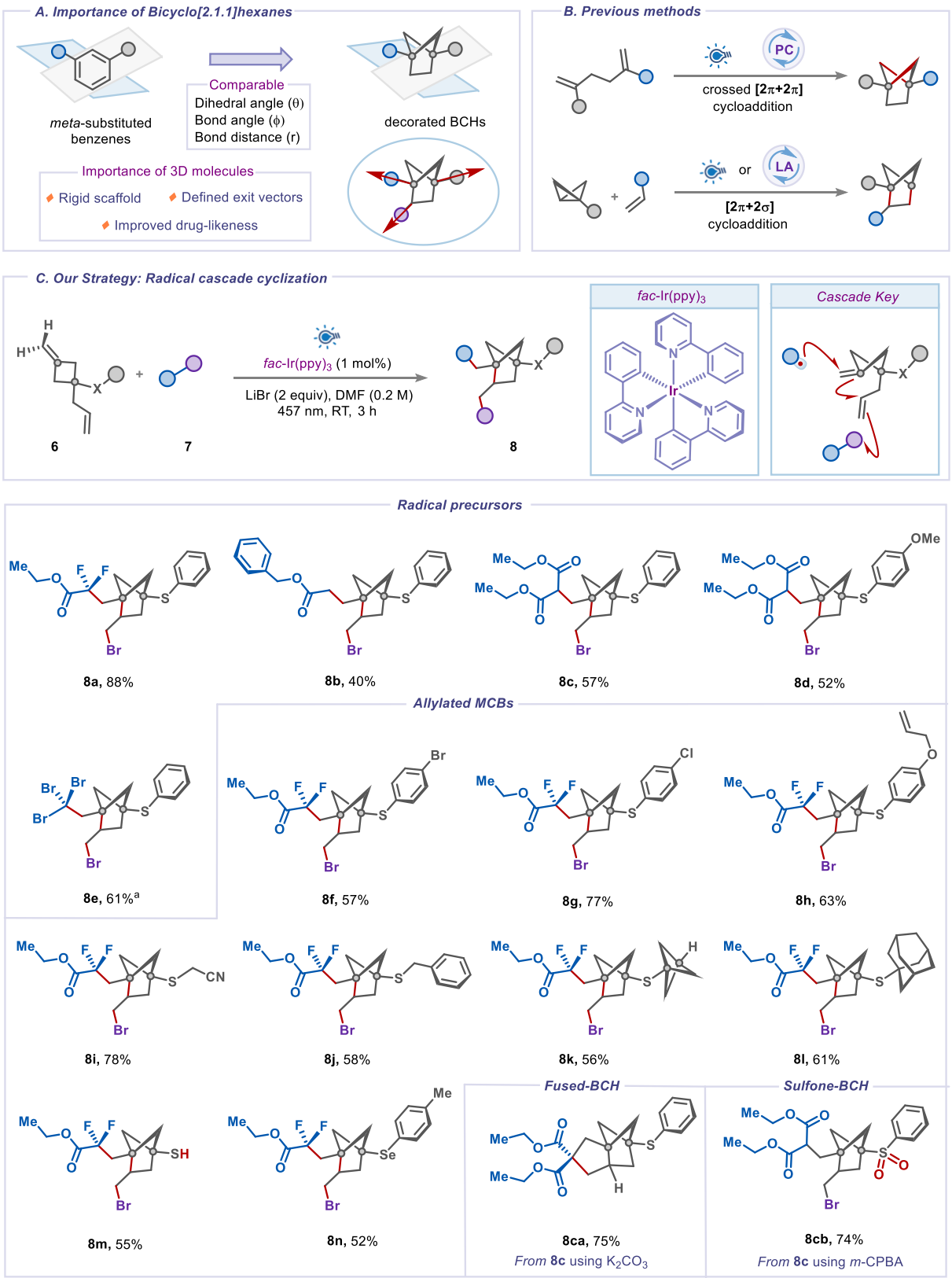
Scheme 3: Scope of allyl sulfides **4**. Reaction Conditions: 0.15 mmol of **4**, 2.0 equiv of **2**, 5.0 mol% of $Cu(acac)_2$, 0.40 mL of anhydrous toluene, room temperature, 12 h. Yields are of isolated products. *a* 0.40 mL of anhydrous DCM was used instead of toluene.

also viable substrates in this reaction (products **6g** and **6h**). Several aliphatic allyl sulfides with functional groups, including cyano, keto, fluorinated alkyl chain, and olefins, were tested and well tolerated to give the products **6i**-**6n** in excellent yields. Gratifyingly, BCP-derived allyl sulfide gave the desired BCP-bearing MCBs **6o** and **6p** in 73% and 67% yields, respectively. Lastly, we demonstrated that allyl selenides were also effective partners, with the MCB selenides **6q**-**6u** formed in good to excellent yields.

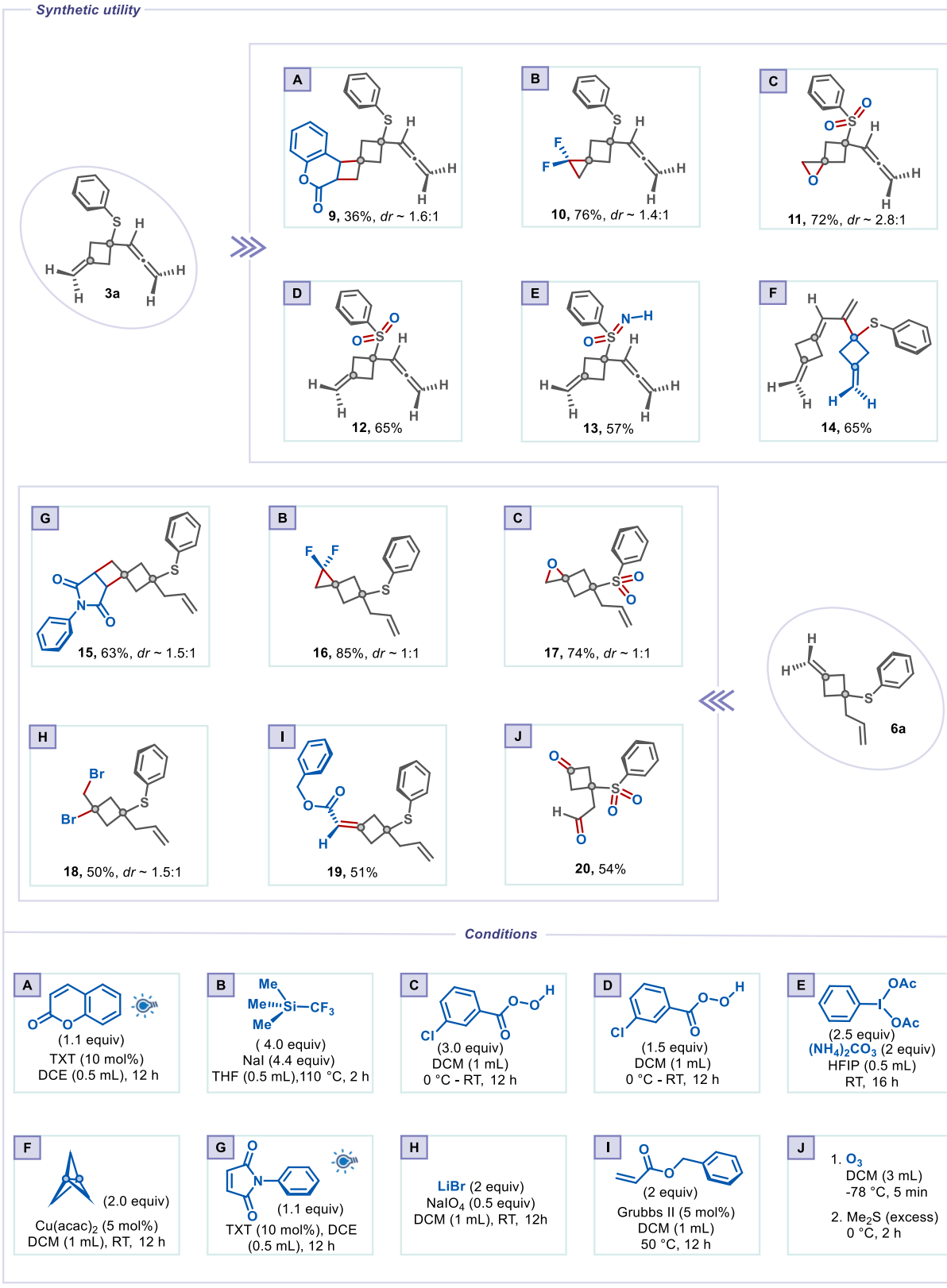
Application:

Aromatic rings are prevalent in various bioactive compounds, from naturally occurring substances to synthetic drugs. However, the propensity of π-electron-rich aromatic rings toward oxidation can lower their metabolic stability.[52] In this context, strategies that aim to modify lead compounds could enhance metabolic stability, thus reducing the drug dosage regimen. One of the strategies to increase metabolic stability is to increase the sp^3-carbon content of potential drug candidates.[53] The rigid structure of hydrocarbons provides a precise spatial orientation of substituents, mimicking the topological arrangement of aromatic rings and increasing metabolic stability. A range of C(sp^3)-rich hydrocarbon bioisosteres has since been developed for *para*-substituted benzenes.[27,28,53] In contrast, saturated sp^3-hybridized bioisosteres of *ortho*- and *meta*-substituted benzenes are less investigated. Recently, bicyclo[2.1.1]hexanes (BCHs) have attracted significant attention as bioisosteres of *ortho*- and *meta*-substituted benzenes, depending on the substitution pattern (Scheme 4A).[54,55] The most common methods for synthesizing BCHs are through an intramolecular [2+2] cycloaddition of 1,5-dienes or [2π+2σ] cycloaddition of BCBs (Scheme 4B).[56-61] In order to effectively tailor the properties of BCHs, new strategies that would give different exit-vector arrangements are highly desirable.

To demonstrate the synthetic utility of our methodology, we envisioned employing the alkylated MCBs as novel precursors for the synthesis of highly functionalized BCHs. We anticipated that radicals generated via single electron reduction of bifunctional reagent **7** under photoredox catalysis could add to a more reactive *exo*-methylene group in **6** followed by 5-*exo*-trig cyclization onto the olefin and subsequent group transfer would give tri-substituted BCHs **8** (Scheme 4C). To our delight, treatment of allylated MCB **6a** with ethyl 2-bromo-2,2-difluoroacetate (**7a**) using 4CzIPN as a photocatalyst in acetonitrile under blue light irradiation gave the desired product **8a** in 42% yield. After thoroughly investigating various photocatalysts, solvents, and additives, we found that the yield could be improved to 88% by using $Ir(ppy)_3$ as a catalyst and LiBr as an additive in DMF solvent (See SI for the complete optimization studies). This protocol is compatible with various α-bromo mono and di-esters, providing the desired BCHs with moderate to good yields (products **8b**-**8d**). Interestingly, tetrabromomethane is also a viable substrate under these conditions (product **8e**). Next, we explored the scope of allylated MCBs using **7a**. We were pleased to find that bromo, chloro, and allyl ether on the arene ring of the allylated MCBs were well tolerated (products **8f**-**8h**). Furthermore, cyano and benzyl groups were also compatible under the reaction conditions, giving products **8i** and **8j** in 78% and 58%, respectively. BCP and adamantyl substituted MCBs successfully underwent the desired radical cascade to give high C(sp^3)-rich hydrocarbon motifs **8k** and **8l**. To our surprise, treating compound **6l** under our standard reaction conditions resulted in the formation of free thiol substituted BCH **8m** that could be utilized as a synthetic handle for further installing diverse functionalities. The allylated MCB selenide **6r** also participated in this



Scheme 4: (A) Importance of bicyclo[2.1.1]hexanes (BCHs). **(B)** Previous methods on BCH synthesis. **(C)** Our strategy: Radical cascade cyclization and scope study. Reaction conditions: 0.10 mmol of **6**, 0.15 mmol of **7**, 1.0 mol% of *fac*-Ir(ppy)$_3$ catalyst, 0.20 mmol of LiBr, anhydrous DMF (0.50 mL), 457 nm in Photocube, room temperature, 3 h. [a]12 h instead of 3h. Yields are of isolated compounds.



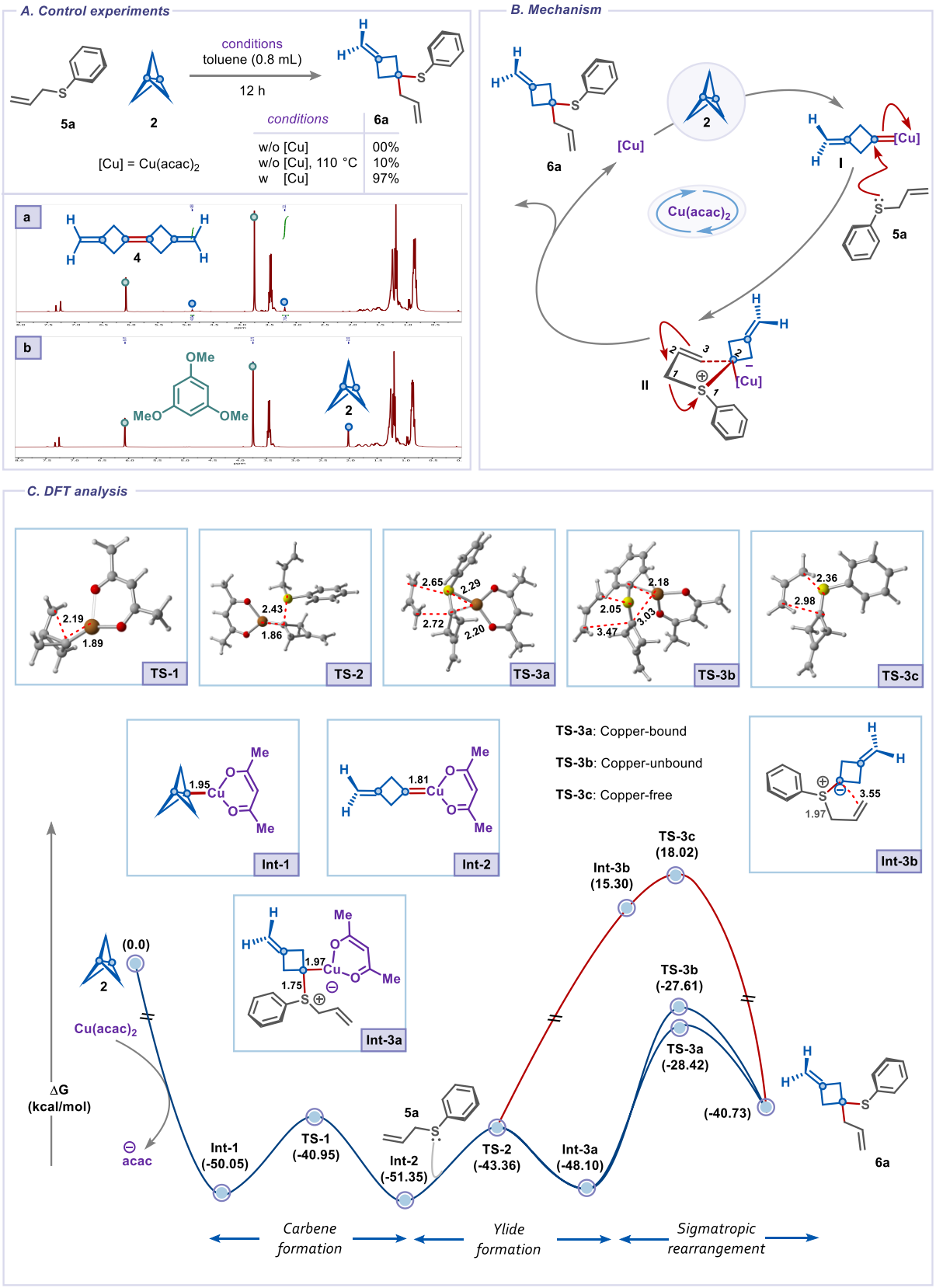
Scheme 5: Synthetic utility of MCBs. Reaction Conditions: All reactions were performed on a 0.10 mmol scale. Yields are of isolated products. The diastereomeric ratio (*dr*) was determined from the ^{1}H-NMR of the crude reaction mixture.

reaction, affording product **8n** in 52% yield. The functional groups introduced during the radical cascade could be further utilized to access a highly complex fused BCH **8ca** in 75% yield. To the best of our knowledge, this type of fused-BCH has not yet been reported in the literature. Finally, BCH-sulfone **8cb** could also be accessed by treating **8c** with *m*-CPBA.

We further demonstrated the synthetic utility of the obtained products by efficiently transforming them into valuable building blocks (Scheme 5). We obtained the spiro-fused product **9** upon photoirradiation of allenylated MCB **3a** with chromone using thioxanthone as a photosensitizer. Selective difluorocyclopropanation with $TMSCF_3$ provided difluorocyclopropyl-spirocyclobutane **10** in good yield. Spiro-epoxy sulfone **11** was obtained when treating **3a** with an excess of *m*-CPBA, whereas lowering the amount of *m*-CPBA gave the sulfone **12** selectively. Sulfoximine-MCB **13** could be synthesized by reacting **3a** with phenyliodine(III) diacetate (PIDA) and ammonium carbonate. Notably, **3a** underwent the second Doyle-Kirmse reaction with [1.1.1]propellane **2** to give highly substituted conjugated diene **14** in 65% yield. Next, we explored the synthetic utility of allylated-MCBs. A [2+2] cycloaddition between **6a** and maleimide derivative under energy transfer photocatalysis gave the desired spiro-fused product **15** in 63% yield. Spiro[2.3]hexane **16** and oxaspiro[2.3]hexane **17** were accessed by treating **6a** with $TMSCF_3$ and *m*-CPBA, respectively. Selective bromination of *exo*-methylene bond in **6a** was possible to afford the product **18**. Alkylidenecyclobutane **19** could be obtained through a metathesis reaction between MCB **6a** and benzyl acrylate. Finally, ozonolysis of **6a** yielded cyclobutanone **20** bearing aldehyde and sulfone substituents, which can serve as useful synthetic handles for further elaboration.

Mechanistic Study:

Our investigation into the reaction mechanism was centered on probing whether the reaction follows a metal-bound or free-ylide pathway. To determine whether the reaction proceeds through a free-ylide pathway, we reacted allyl phenyl sulfide **5a** and [1.1.1]propellane **2** in toluene without $Cu(acac)_2$; no product **6a** formation was observed. Even at reflux conditions in toluene, the desired product **6a** was obtained only in 10% yield, whereas 97% yield was obtained with the copper catalyst at room temperature (Scheme 6A). Moreover, treatment of [1.1.1]propellane **2** with $Cu(acac)_2$ at room temperature gave dimer **4** (Scheme 6Aa), whereas no dimer was detected without the copper catalyst (Scheme 6Ab), indicating the involvement of copper-carbene species. These control experiments support the idea that the copper not only activates [1.1.1]propellane **2** to give copper-carbene species but also participates in the [2,3]-rearrangement process (Scheme 6B). Next, we conducted DFT calculations to gain a deeper understanding of the reaction mechanism drawn from experimental observations (Scheme 6C). Geometry optimizations and frequency calculations were carried out using B3LYP/Def2TZVP, whereas the single-point energy calculations were performed at the B3LYP/Def2QZVPP using the SMD model. The copper catalytic cycle starts with a complexation between $Cu(acac)_2$ and [1.1.1]propellane **2** to give **Int-1**, which then undergoes a concerted ring-opening in which two C−C bonds are cleaved, leading to the formation of the copper-carbene intermediate **Int-2** through a transition state (**TS-1)** with an activation energy of 9 kcal/mol. Subsequent addition of allyl phenyl sulfide **5a** to the copper-carbene generates the copper-bound ylide **Int-3** with a barrier of 7 kcal/mol (**TS-2**). For the [2,3] sigmatropic rearrangement, we considered all three

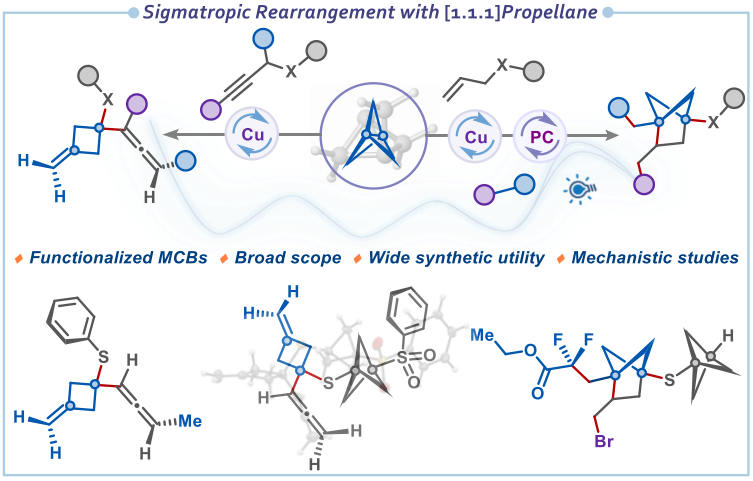


Scheme 6: (**A**) Control experiments**:** (**a**) [1.1.1]Propellane with $Cu(acac)_2$, (b) [1.1.1]Propellnae without $Cu(acac)_2$. (**B**) Proposed Reaction mechanism. (**C**) DFT studies. Geometry optimizations and frequency calculations were carried out using B3LYP/Def2TZVP, whereas the single-point energy calculations were performed at the B3LYP/Def2QZVPP using the SMD model**.** All transition states are represented by CYL view images.

pathways, i.e., copper-bound, copper-unbound, and free-ylide.[62] Our calculations suggested that the copper-bound pathway (**TS-3a**) is energetically favored over the free-ylide pathway (**TS-3c**), and it is closely competing with the copper-unbound pathway (**TS-3b**), where the copper is associated with the phenyl ring. The experimental and computational studies show that the reaction proceeds through a copper-bound five-membered transition state to furnish the [2,3]-rearrangement product.

Conclusion:

In summary, we have developed the first [2,3]-sigmatropic rearrangement with [1.1.1]propellane by harnessing its carbene reactivity to access densely functionalized allenylated or allylated MCBs. The reaction protocol is highly practical and illustrated by mild reaction conditions, high yields, and the use of an inexpensive copper catalyst. The reaction offers a broad scope across a large pool of propargyl and allyl sulfides and selenides and exhibits a remarkable functional group tolerance. The synthetic utility of the protocol was demonstrated by transforming the allylated-MCBs into substituted bicyclo[2.1.1]hexanes through a novel photocatalyzed radical cascade cyclization. The versatility of the functional groups introduced during the reaction was further highlighted by converting them into valuable building blocks for chemical synthesis. Combined experimental and computational studies suggested the metal-bound mechanism for the rearrangement step. We believe that our strategy will stimulate researchers to use the carbene reactivity of [1.1.1]propellane to develop new transformations in organic synthesis, ultimately unlocking the potential of this largely uncharted research area.



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 number CCDC 2379384.

Author contributions:
S. M. and D. P. H. conceived and designed the project. S. M. carried out optimization, substrate scope, and mechanistic studies. A. A. contributed to starting materials synthesis and studied the substrate scope of selenides. D.P.H. and S. M. performed the density functional theory calculations. D. P. H. and S. M. wrote the manuscript.

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Conflicts of interest:
There are no conflicts to declare.

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