Highly Stereoselective Catalytic Synthesis of Polysubstituted Housanes: Application and Mechanistic Insights

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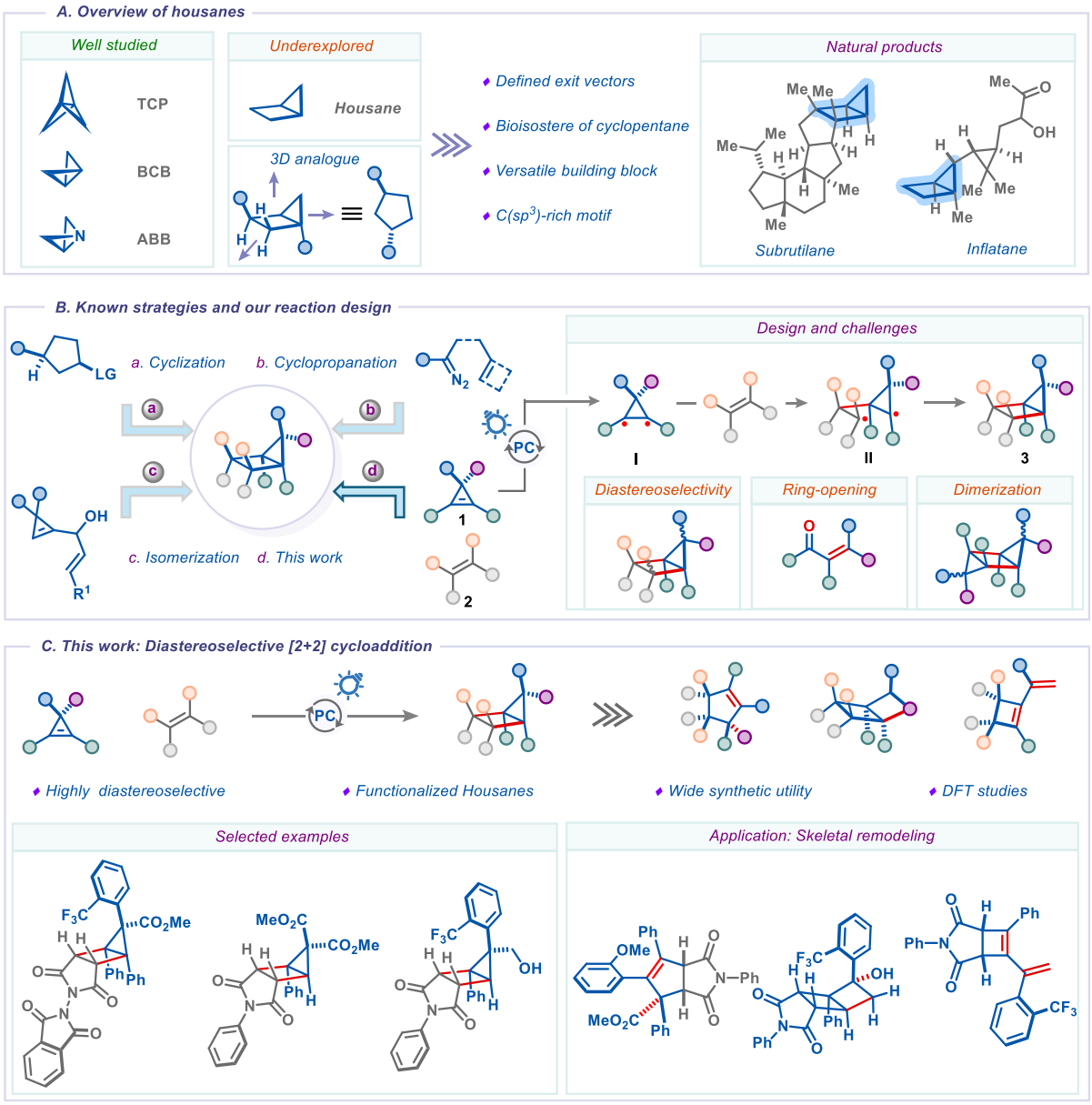
Abstract:

Ring-strain-enabled transformations have made significant progress, pushed the boundaries of unexplored chemical space, and emerged as a powerful tool for constructing complex molecules selectively and efficiently. Among the strained ring systems, [1.1.1]propellane, bicyclobutane (BCB), and azabicyclobutane (ABB) have garnered substantial attention and found numerous synthetic applications. In contrast, the chemistry of bicyclo[2.1.0]pentane, commonly known as housane, is scantly explored due to the lack of modular synthetic approaches. Herein, we describe a highly stereoselective, catalytic strategy for synthesizing polysubstituted housanes with up to three contiguous all-carbon-quaternary centers. The reaction is very efficient, works under mild conditions, requires visible light and organic dye as a photocatalyst, and exhibits a broad substrate scope. The post-synthetic diversification of the products via an unprecedented strain-release driven diastereospecific 1,2-ester migration that allows the rapid synthesis of functionalized bicyclic imides further highlighted the synthetic utility of the current protocol. Combined experimental studies and computational investigations revealed the origin of the reactivity and stereoselectivity.

Keywords: Housane • [2+2] cycloaddition • Stereoselective • 1,2-Ester migration • Bicyclic imides.

Introduction:

Constructing C(sp^3)-rich scaffolds is of great significance in synthetic chemistry as they are invaluable in pharmaceuticals and drug discovery programs, providing improved selectivity, potency, and metabolic stability of drug candidates augmented with minimizing entropic penalty when binding to biological targets.[1, 2] In this context, strained ring systems have recently attracted substantial attention since they are ideal sources of C(sp^3)-rich rings with rigid and well-defined three-dimensional (3D) spatial arrangements. Moreover, they can undergo myriads of transformations to generate diverse molecular frameworks owing to their unique bonding and the reactivity enabled by strain release.[3] As a result, considerable effort has been directed toward synthesizing and functionalizing strained ring systems. Among these,



Scheme 1: (A) Overview of housanes; **(B)** Known methods for the synthesis of housanes and our reaction design; **(C)** This work: Highly diastereoselective synthesis of polysubstituted housanes and their synthetic application.

[1.1.1]propellane, bicyclo[1.1.0]butane (BCB), and azabicyclo[1.1.0]butane (ABB) have been extensively studied and widely applied to generate highly rigid 3D architecture.[4-8] In contrast, bicyclo[2.1.0]pentane, commonly known as housane, has received scant attention. Housane is comprised of two C(sp^3)-rich rings -cyclopropane and cyclobutane with ring-strain energy of 57 kcal/mol, and it is considered as a potential bioisostere of cyclopentane (Scheme 1A).[9-12] Identifying such rigid counterparts for conformationally flexible cyclopentane is crucial to advancing drug discovery. Furthermore, housane is not only embedded in natural products but also used as a reactive intermediate in the synthesis of complex natural products (Scheme 1A).[13-19] Nevertheless, the limited synthetic accessibility of housane derivatives thwarted their application in medicinal chemistry discovery programs. Traditionally, housanes are accessed

via transannular alkylation of 1,3-functionalized cyclopentane derivatives (Scheme 1B).[11, 20, 21] However, this strategy requires multiple steps to prepare the starting material, and accessing different substitution patterns is challenging. Other alternative approaches involve metal-mediated cyclopropanation of cyclobutenes or intramolecular cyclopropanations.[22-24] Recently, the Vicente group reported an elegant strategy through Rh (II)-promoted isomerization of vinylcyclopropenyl carbinols (Scheme 1B).[25] While these strategies are highly effective, they require pre-functionalization of the starting material and expensive rhodium catalysts. Furthermore, controlling stereochemistry, especially at quaternary centers, is highly challenging as the number of substituents increases. In this context, developing efficient, sustainable, and catalytic stereoselective strategies for synthesizing polysubstituted housanes with contiguous quaternary carbon centers is highly desirable.

Over the last decade, visible light photocatalysis has evolved as a novel paradigm in chemical synthesis, harnessing photons as a traceless energy source, enabling numerous transformations under mild and sustainable conditions for constructing complex scaffolds.[26-30] In this vein, [2+2] cycloadditions under visible light have garnered significant interest, not only due to their efficiency but also their practical applicability in converting simple feedstock materials into structurally complex and unique skeletons.[31-33] We envisioned that cyclopropene **1**, a highly strained smallest carbocycle with ring-strain energy of 54.5 kcal/mol,[10] could generate a biradical intermediate **I** under energy transfer photocatalysis. Subsequent radical addition to an alkene **2** would furnish 1,4-biradical **II** that could undergo radical-radical recombination to give housane **3**. This proposal would provide a straightforward and modular approach for the construction of polysubstituted housane derivatives (Scheme 1B). The major challenges associated with this cycloaddition would be overcoming the diastereoselectivity issues[34, 35] and subduing the potential oxidative ring-opening[36] and dimerization of cyclopropene or alkene.[37] Notwithstanding these challenges, herein we report a highly diastereoselective, catalytic strategy for the synthesis of polysubstituted housanes bearing three contiguous all-carbon-quaternary centers under energy transfer photocatalysis using an organic dye (Scheme 1C). The protocol displays a broad substrate scope and excellent functional group compatibility. The applicability of this method is demonstrated by developing unprecedented strain-release driven skeletal rearrangement of the obtained housanes via an unusual 1,2-ester migration, enabling a highly stereoselective approach to densely functionalized cyclopentene derivatives. DFT calculations combined with experiment-based mechanistic studies were used to rationalize the observed reactivity and the origin of stereoselectivity.

Results and Discussion:

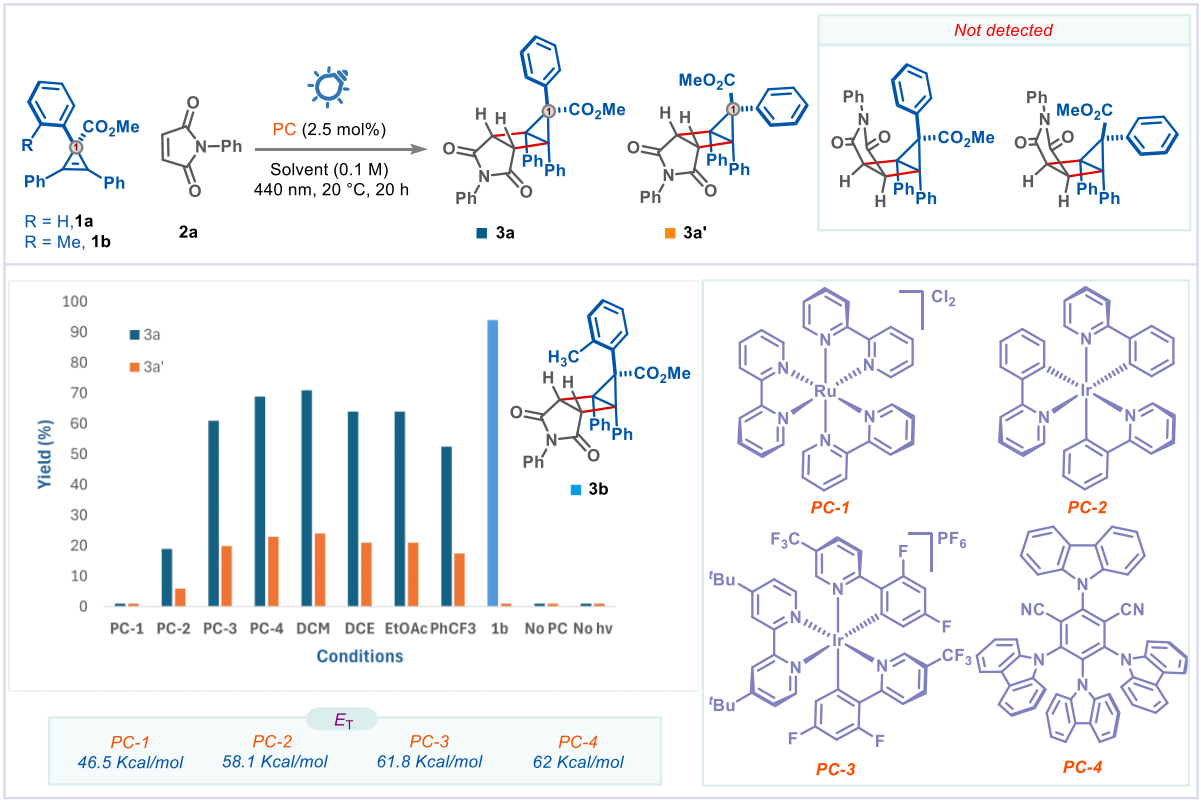
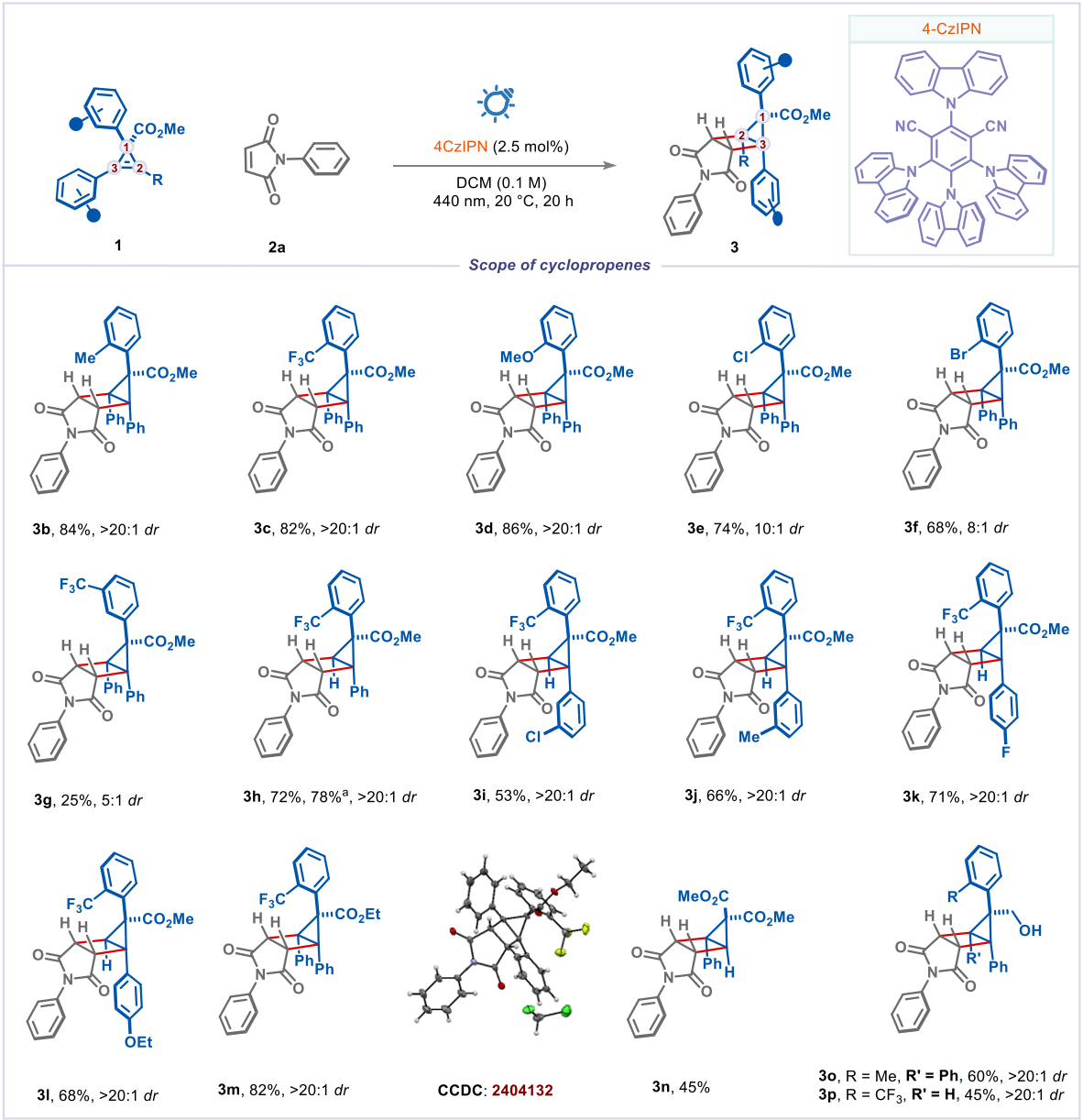


Figure 1: Optimization of the reaction conditions. From column 1 to 8, **1a** (0.10 mmol), **2a** (2 equiv), solvent (0.1 M), photocatalyst (PC) (2.5 mol%), 440 nm, 20 ˚C, 20 h. CH_3CN was used as a solvent while screening the photocatalysts. NMR yields using dibromomethane as the internal standard, and *dr* was determined by ^{1}H-NMR from the crude reaction mixture. Column 9- using **1b**. Column 10- without PC. Column 11-without light.

We commenced our investigation by studying the reaction of cyclopropene **1a** with maleimide **2a** using $[Ru(bpy)_3]Cl_2$ (PC-1) as a photocatalyst under blue light irradiation in CH_3CN at 20 °C. However, we didn't observe the formation of the desired housane **3a**, and the starting materials were simply reisolated (Figure 1, column 1). The lack of reactivity is attributed to the high triplet energy of cyclopropene **1a** (E_T = 47.2 kcal/mol) over the Ru-catalyst (E_T = 46.5 kcal/mol).[28] Next, we screened photocatalysts that have more triplet energies than cyclopropene **1a**. To our delight, $Ir(ppy)_3$ (PC-2, E_T = 58.1 kcal/mol) gave two diastereomeric products **3a** and **3a'** out of four possible products in 25% yield with complete *trans* selectivity and 3:1 *endo*/*exo* selectivity at C1 (Figure 1, column 2). The yield could be significantly improved to 82% using a higher triplet energy photocatalyst $[Ir(dF(CF_3)ppy)_2(dtbbpy)]PF_6$ (PC-3, E_T = 61.8 kcal/mol) (Figure 1, column 3). We also explored metal-free energy transfer photocatalysts and found that 4CzIPN (PC-4, E_T = 62.0 kcal/mol) is very effective and gave 92% yield (Figure 1, column 4).[38] Among the other solvents (DCM, DCE, EtOAc, and $PhCF_3$) tested, DCM was the optimal solvent for this transformation, giving 95% yield (Table 1, column 5). Controlling the *endo*/*exo* selectivity of this reaction would further enrich its

synthetic application. Thus, we next focused on improving the selectivity of the reaction. We wondered whether steric could play a role in shielding the phenyl at C1 around the *exo*-attack, ensuring the desired *endo*-selectivity. We were pleased to find that the introduction of a simple methyl group on the *ortho*-position of the phenyl in cyclopropene **1b** improved the *endo*-selectivity significantly, affording the desired product **3b** with complete stereocontrol over five contiguous chiral centers (Figure 1, column 9). Finally, control experiments confirmed that the reaction did not occur without light or a photocatalyst (Figure 1, columns 10 and 11).

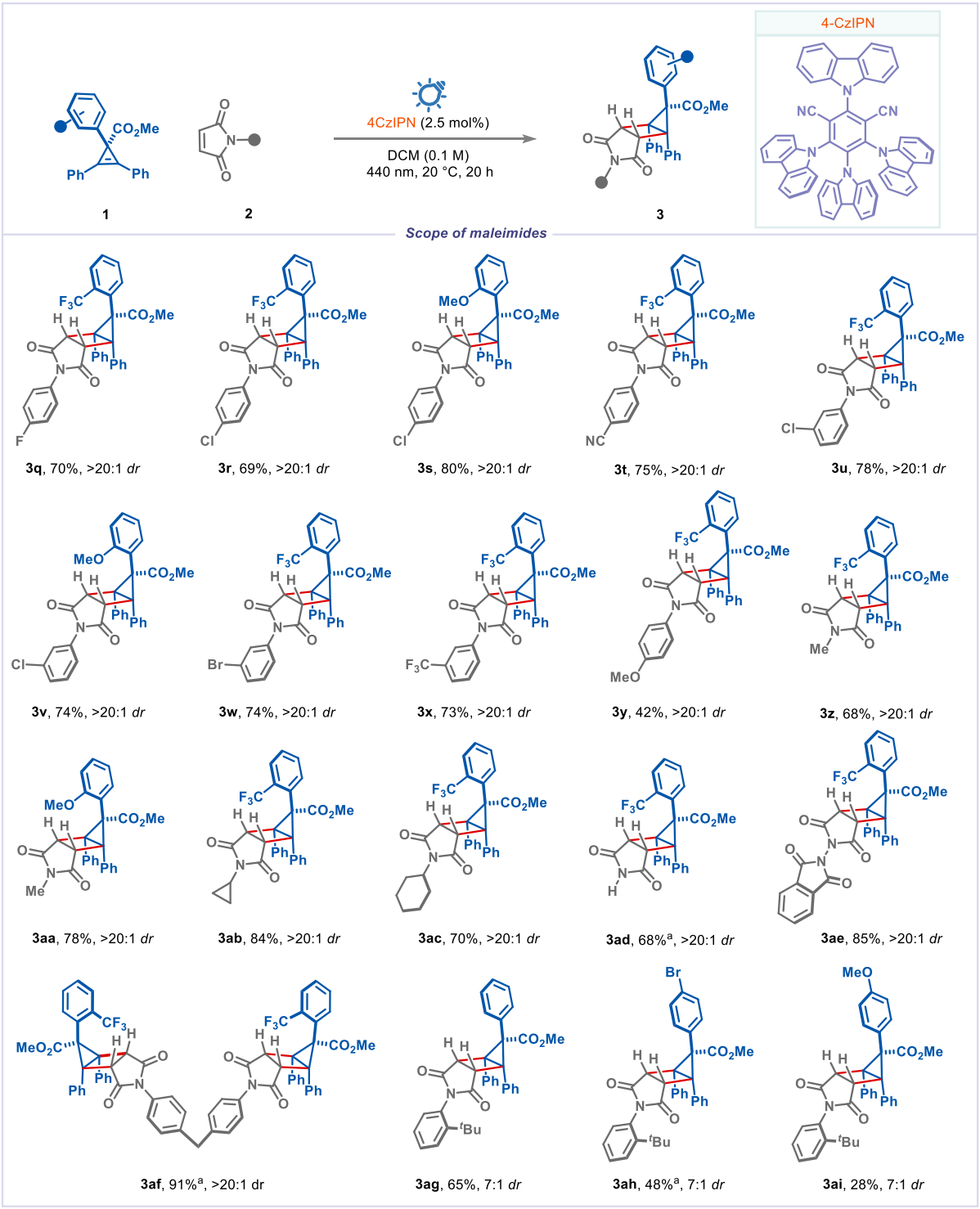


Scheme 2: Scope of housanes. Reaction conditions: 0.3 mmol of **1**, 0.6 mmol of maleimide **2a**, 3.0 mL of dry DCM, 2.5 mol% of 4CzIPN, 440 nm, 20 °C, 20 h. Yields are of isolated products, and *dr* was determined by ^{1}H-NMR and ^{19}F-NMR from the crude reaction mixture. [a]2 mmol scale.

With the optimized reaction conditions in hand, we examined the scope of the reaction with an assortment of cyclopropenes using *N*-phenylmaleimide **2a** (Scheme 2). First, we examined the

steric and electronic influences of various substitutions on the aryl group at the C1 position on cyclopropene. Electron-donating and -withdrawing substituents at the *ortho* position are well tolerated, affording the desired products (**3b**-**3d**) in excellent yields and selectivity. *ortho*-Chloro and bromo-substituted aryl groups underwent the desired transformation successfully and furnished the products **3e** and **3f** with good yields and selectivity. *meta*-CF_3-substituted aryl group also participated in this reaction, albeit in low yield and moderate selectivity. Next, we explored different substitutions at C2 and C3 positions on cyclopropene. We were pleased to find that the reaction worked well with simple H at the C2 position and gave the desired product **3h** with excellent selectivity. Additionally, the scale up of **3h** didn't hamper reaction efficiency. Various substitutions on the aryl group at the C3 position, including chloro, methyl, fluoro, and ethoxy groups, were well tolerated (**3i**-**3l**). Ethyl-ester-derived cyclopropene is also a viable substrate in this reaction, giving the product **3m** in excellent selectivity. The structure of product **3m** was unambiguously determined by X-ray analysis (CCDC 2404132). Diester containing cyclopropene yielded the housane **3n** in moderate yield. The reaction is not limited to esters at the C1 position; we could also use alkyl groups, giving the housanes **3o** and **3p**. Setting a limitation, cyclopropene containing methyl (at C2) and phenyl (at C3) was found to be inapt in this transformation (See SI for unsuccessful substrates).

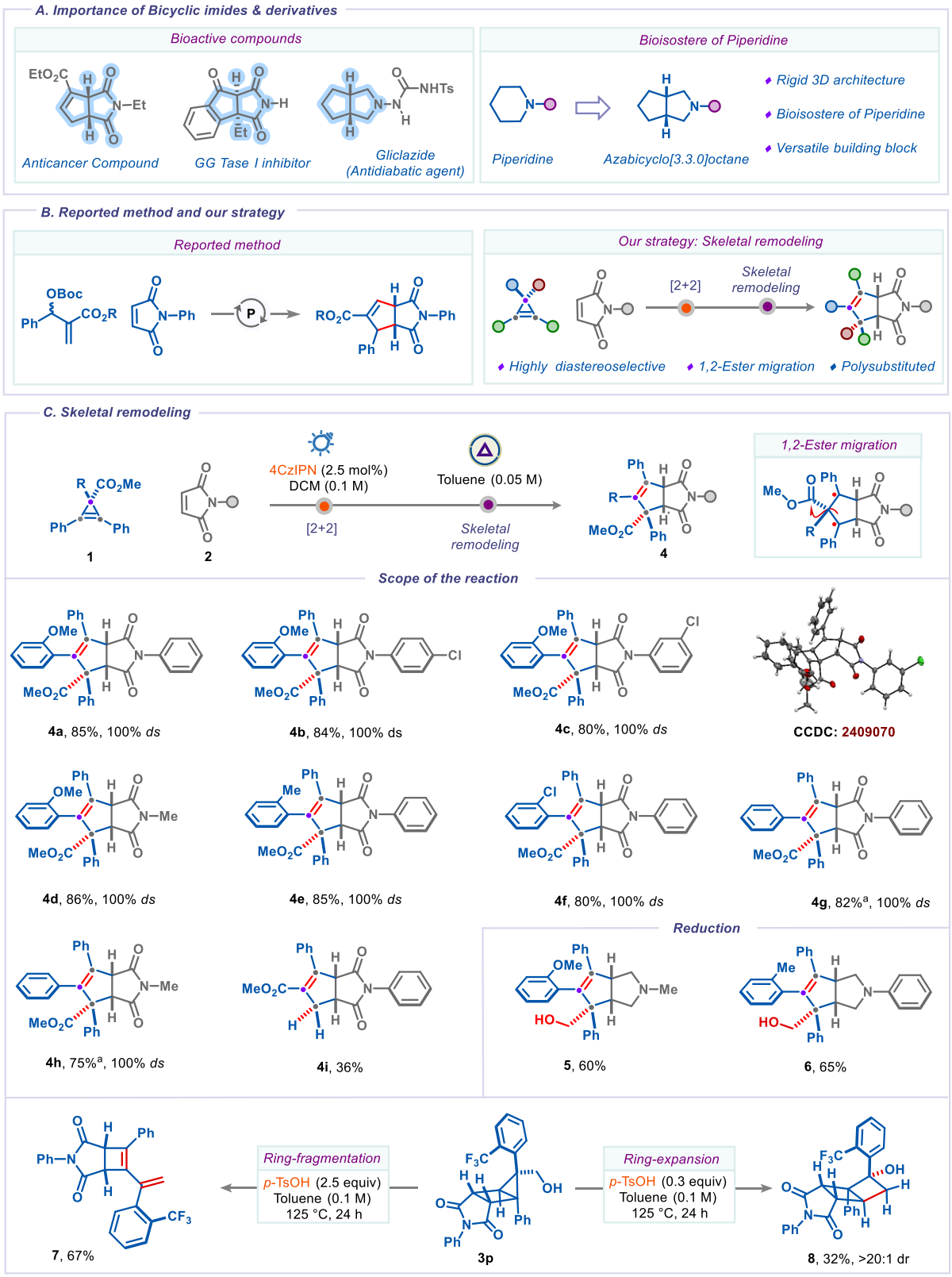
We subsequently investigated the scope of the reaction with *N*-substituted maleimides (Scheme 3). A broad range of electron-withdrawing groups on the aryl group of *N*-substituted maleimides, including fluoro, chloro, bromo, cyano, and trifluoromethyl groups, smoothly participated in the reaction to afford the corresponding housanes **3q**-**3x** in good yields with excellent selectivity. A slight drop in the reaction yield was observed when a strongly donating *para*-methoxy group was introduced (product **3y**). Next, we extended our focus to test the viability of *N*-alkylated maleimides. Various *N*-alkyl maleimides, including methyl, cyclopropyl, and cyclohexyl, were well tolerated (products **3z**-**3ac**). Notably, simple maleimide and *N*– phthalimide were well tolerated, affording the products **3ad** and **3ae** in 68% and 85% yields with excellent selectivity. To our delight, bis-maleimide participated and gave the desired bis-housane **3af**. In order to improve the selectivity with cyclopropenes having simple phenyl and *para*-substituted aryl groups at the C1 position, we employed *N*-(*ortho*-*tert*-butylphenyl)maleimide. As expected, the products **3ag**-**3ai** were obtained with improved (~2.5-fold times) selectivity. Unfortunately, maleic anhydride and other alkenes didn't participate in this reaction (See SI for unsuccessful substrates).



Scheme 3: Scope of housanes. Reaction conditions: 0.3 mmol of **1**, 0.6 mmol of maleimide **2**, 3.0 mL of dry DCM, 2.5 mol% of 4CzIPN, 440 nm, 20 °C, 20 h. Yields are of isolated products and *dr* was determined by ^{1}H-NMR and ^{19}F-NMR from the crude reaction mixture. [a]NMR yield.

Application:

In the realm of nitrogen-heterocycles, bicyclic imides and their derivatives are among the most important scaffolds serving as vital structural components within natural products, pharmaceuticals, and bioactive compounds, and, hence, lead to them spanning a wide range

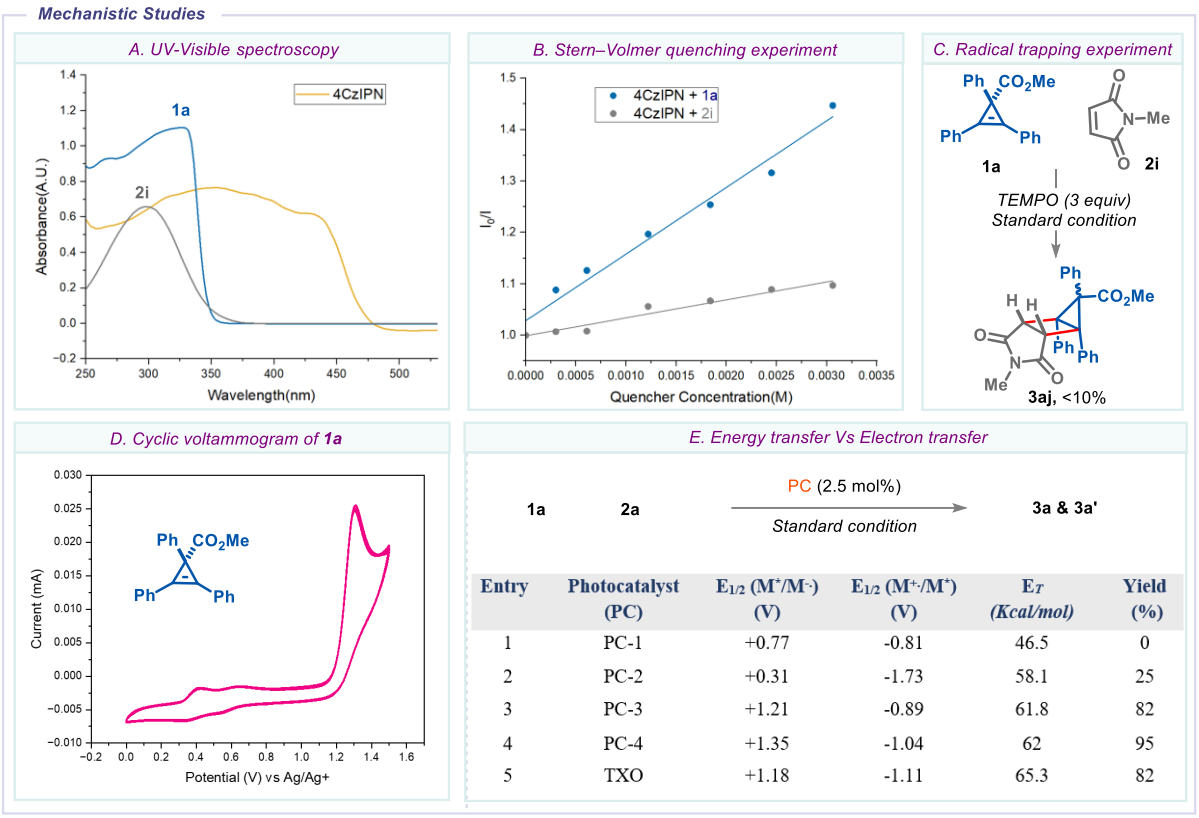


Scheme 4: (A) Importance of bicyclic imides & derivatives. (B) Reported method and our strategy: Strain-release driven 1,2-ester migration. (C) Skeletal remodeling: Reaction conditions: **Step-1** 0.3 mmol of **1**, 0.6 mmol of maleimide **2**, 3.0 mL of dry DCM, 2.5 mol% of 4CzIPN, 440 nm, 20 °C, 20 h. **Step-2** 0.3 mmol of housane crude, 6.0 mL of dry toluene, 180 °C, 60 h. [a]Using major diastereomer. For reduction, ring-fragmentation and ring-expansion reaction condition- See SI. Yields are of isolated products, and *dr* was determined by ^{1}H-NMR from the crude reaction mixture.

of drug classes, including anticancer, GG Tase-I inhibitor, antidiabetic agents (Scheme 4A).[39, 40] Moreover, owing to its restricted conformation, the bicyclic pyrrolidine motif is considered a potential bioisosteric replacement for piperidine (Scheme 4A).[41] Petrukhin and co-workers showed that replacing piperidine moiety in A1120 with bicyclic pyrrolidine significantly enhanced its binding towards RBP4 and improved pharmacokinetic and pharmacodynamic properties.[42] Nevertheless, further probing such opportunities is currently impeded by the dearth of methods that enable access to such heterobicyclic motifs. The most common method for the construction of bicyclic imides is through an intermolecular [3+2] cycloaddition (Scheme 4B).[39] Recently, "Skeletal remodeling" has garnered significant attention as a powerful tool in organic synthesis to remodel skeletal frameworks and has been widely used as a guiding strategy for assembling unique complex skeletons from simple molecular structures via deconstruction or re-editing the core ring structure through breaking and reforming carbon-carbon or carbon-heteroatom bonds.[43, 44] To demonstrate the potential synthetic utility of our strategy, we envisioned the possibility of strain release-enabled skeletal rearrangement of the obtained housane derivatives by breaking the strain C-C σ bond, followed by 1,2-aryl migration, which would directly lead to densely functionalized bicyclic imide derivatives (Scheme 4B). To our delight, the housane **3d** underwent the strain C-C σ bond scission under thermal conditions afforded a bicyclic scaffold **4a** in 20% yield with 100% diastereospecificity (*ds*). Surprisingly, the crystal structure of **4c** revealed that product **4a** emerged from an unprecedented 1,2-ester migration. To the best of our knowledge, such 1,2-ester migrations are not reported in the literature. A brief optimization of the reaction conditions by screening temperature, concentration, and reaction time improved the yield to 85%. Gratifyingly, we found that the reaction can be performed in one pot, giving similar yield and selectivity. Subsequently, we investigated the scope of this reaction (Scheme 4C). We were pleased to find that various *N*-substituted maleimides participated well, affording the corresponding substituted bicyclic scaffolds **4a**-**4d** in good yield with complete diastereospecificity. Simple phenyl and various substitutions on the aryl group at the C1 position of cyclopropene were well tolerated (products **4e**-**4h**). Interestingly, the diester-containing housane yielded the decarboxylated product **4i** (see SI for mechanism). Furthermore, the bicyclic motifs **4d** and **4e** could be reduced to give bicyclic pyrrolidine derivatives **5** and **6**. Next, the alcohol functional group in **3p** was utilized for the subsequent ring-fragmentation and ring-expansion reactions. Treating **3p** with stoichiometric *p*-TsOH gave cyclobutenyl-1,3-dienes **7.** The formation of **7** might involve carbocation generation, ring-opening, and deprotonation. The ring-expansion pathway could be induced by using a catalytic

amount of acid to give highly substituted [2]-Ladderane **8**, a class of building block that can serve as potential bioisosteres for *meta*-substituted benzene.[45]

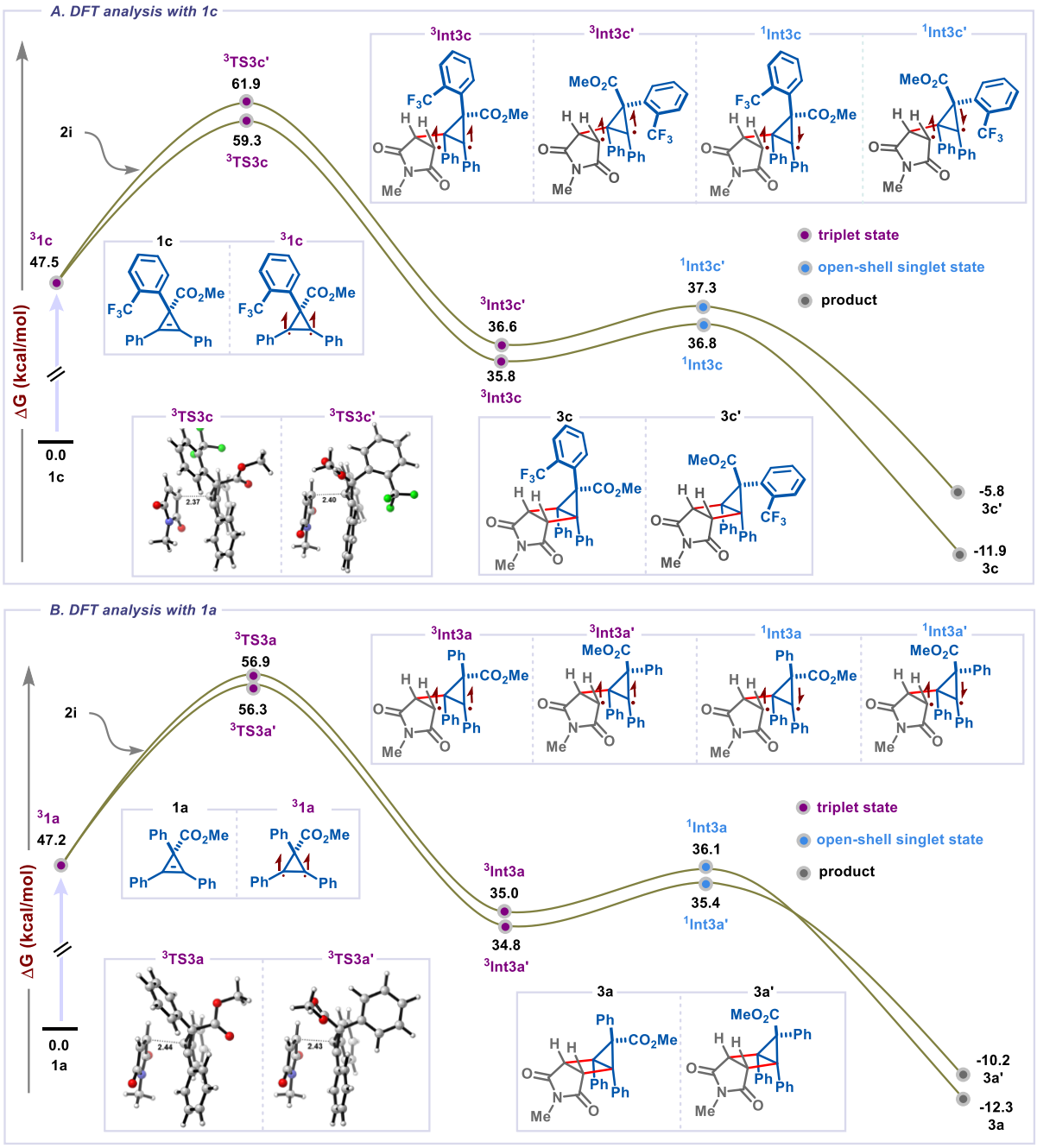
Mechanistic studies:



Entry	Photocatalyst (PC)	$E_{1/2}$ (M^{+}/M^{-}) (V)	$E_{1/2}$ ($M^{+\cdot}/M^{*}$) (V)	E_T *(Kcal/mol)*	Yield (%)
1	PC-1	+0.77	-0.81	46.5	0
2	PC-2	+0.31	-1.73	58.1	25
3	PC-3	+1.21	-0.89	61.8	82
4	PC-4	+1.35	-1.04	62	95
5	TXO	+1.18	-1.11	65.3	82

Scheme 5: Mechanistic studies (A) Ultraviolet–visible absorption spectra of the reaction components. (B) Stern–Volmer quenching studies. (C) Radical trapping experiment. (D) Cyclic voltammetry measurements versus the Ag/AgCl reference electrode (2 M LiCl in EtOH). (E) Energy transfer vs Electron transfer.

Next, a variety of mechanistic experiments were conducted to shed light on the mechanism of the reaction. First, UV/Vis spectra of the individual reaction components revealed that the photocatalyst 4-CzIPN is the only light-absorbing species around the operational wavelength (Scheme 5A). Next, Stern–Volmer quenching studies clearly demonstrated that cyclopropene **1a** is an effective quencher (vide infra) of the excited state photocatalyst compared to maleimide **2i** (Scheme 5B). The addition of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) to the reaction mixture significantly decreased the reaction yield, suggesting radical intermediacy during the reaction (Scheme 5C). To understand the nature of the quenching, we compared the triplet state energies and redox potentials of various photocatalysts and cyclopropene **1a** ($E_{1/2}$ = +1.26 V, vs. Ag/AgCl in MeCN) (Scheme 5D & 5E). This data suggests that the yields of housane (**3a** and **3a'**) correlated with the triplet state energies of photocatalysts, but no trend was observed with their redox potential. Furthermore, direct UV-light irradiation (λ_{max}= 365 nm) of the reaction mixture **1a** and **2i** furnished the housane **3aj** in 25% yield (see



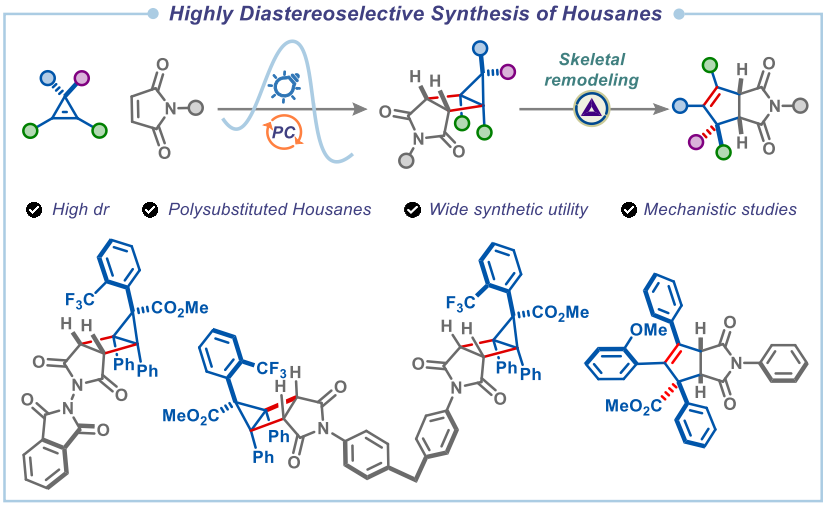
Scheme 6: Computed reaction coordinate profile of the cycloaddition reaction. (A) Using cyclopropene **1c**. (B) Using cyclopropene **1a**. We conducted the DFT study at the SMD(Dichloromethane)/(U)M06/6-311+g(d,p)//(U)M06/6-31+g(d,p) level of theory. All transition states are represented by CYL view images. The distances are in Å.

SI). These results alluded to the fact that the Dexter-type triplet-triplet EnT process is likely involved in the reaction.[46] We subsequently performed density functional theory (DFT) calculations to get insight into the reaction mechanism and the origins of diastereoselectivity. Calculations were performed at the SMD(Dichloromethane)/(U)M06/6-311+g(d,p)//(U)M06/6-31+g(d,p) level of theory (Scheme 6). The triplet state energies of cyclopropene **1c** and maleimide **2i** were computed to be 47.5 kcal/mol and 55.0 kcal/mol, respectively, and this data is aligned with our luminescence quenching experiments. The

mechanism of the reaction starts with the excitation of cyclopropene **1c** by photocatalyst to afford triplet intermediate ^{3}**1c**, which then combines with the ground state of the maleimide **2i** and forms two diastereomeric triplet intermediates ^{3}**Int3c** and ^{3}**Int3c'** via the transition states ^{3}**TS3c** and ^{3}**TS3c'** with an activation barrier of 11.8 kcal/mol and 14.4 kcal/mol, respectively. The difference in energy of these two transition states (2.6 kcal/mol) is consistent with the observed high diastereoselectivity of product **3c**. The conversion of ^{3}**Int3c** and ^{3}**Int3c'** to their corresponding open-shell singlet state counterparts ^{1}**Int3c** and ^{1}**Int3c'** can be achieved through the minimum energy crossing point (MECP). Finally, radical-radical recombination affords the two diastereomeric products **3c** and **3c'**. Next, we focused on rationalizing the low diastereoselectivity that was obtained with our model substrate **1a**. Following sensitization of the cyclopropene **1a**, initial C–C bond formation requires an activation energy of 9.7 and 9.1 kcal/mol, respectively, for the formation of two diastereomeric triplet intermediates ^{3}**Int3a** and ^{3}**Int3a'**. The small energy difference (0.6 kcal/mol) between the two diastereomeric transition states ^{3}**TS3a** and ^{3}**TS3a'** is consistent with the observed low diastereoselectivity.

Conclusion:

In conclusion, we have developed a visible-light-mediated, catalytic, highly stereoselective approach to synthesize polysubstituted housanes with up to three all-carbon-quaternary centers. This reaction operates under mild conditions, uses an organo-catalyst, and tolerates diverse functional groups on cyclopropenes and maleimides. The synthetic utility of this transformation was highlighted by developing an unprecedented strain-release driven diastereospecific 1,2-ester migration process that gives rapid access to highly functionalized bicyclic imides and their derivatives. Furthermore, subsequent diversification of housane derivatives provided access to cyclobutenyl-1,3-diene and [2]-Ladderane motifs. The observed reactivity and stereoselectivity have been rationalized by experiment-based mechanistic studies combined with DFT computation, illuminating cyclopropene's biradical nature and its interaction with maleimide. We believe that this strategy will provide a unique avenue to access and expand the chemical space of structurally intriguing housanes with high molecular complexity.



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 2404132 (for compound **3m**) and CCDC 2409070 (for compound **4c**).

Author contributions:

A. R. S. M. and D. P. H. conceived and designed the project. A. R. S. M. carried out optimization, starting materials synthesis, substrate scope, and mechanistic studies. N. A. B performed the density functional theory calculations. D. P. H. and A. R. S. M. wrote the manuscript.

Conflicts of interest:

There are no conflicts to declare.

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