A photochemical strategy towards Michael addition reactions of cyclopropenes

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Abstract:

The development of Michael addition reactions to conjugated cyclopropenes is a challenge in synthesis due to the fleeting and reactive nature of such strained Michael acceptor systems. Herein, the development of a photochemical approach towards such conjugated cyclopropenes is reported that serves as a strategic entry point to densely functionalized cyclopropanes in a diastereoselective fashion. The process involves the light-mediated generation of transient cyclopropenyl α,β-unsaturated esters from vinyl diazo esters, followed by an organic base catalyzed nucleophilic addition of N-heterocycles to directly access β-N-heterocyclic cyclopropanoic esters. With this synergistic approach, various trisubstituted cyclopropanes bearing N-heteroaryl and N-heterocyclic rings such as indole, pyrrole, benzimidazole, isatin, pyridinone and quinolinone were accessed efficiently in good yield and decent to good diastereoselectivities. Further, β-indolyl cyclopropanoic acids have been synthesized and were successfully evaluated as FABP-4 inhibitors. Theoretical calculations have been performed to elucidate the mechanism which was further supported by experimental findings.

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INTRODUCTION

The Michael reaction is of fundamental importance in organic chemistry and commonly features an electrophilic α,β-unsaturated carbonyl compound (viz. **1a**, **1b**, etc.) that reacts with a nucleophile to form a new C—C or C—heteroatom bond (**Fig. 1A**).[1-2] Michael addition reactions are today one of the most commonly used reactions in organic synthesis with broad applications across all disciplines of chemistry. Among the more advanced applications of Michael acceptors, the reversible covalent inhibition of therapeutically relevant kinases (e.g. **4**)[3] and late-stage modification of peptides (**2** to **3**)[4] for target identification and proteomics are representative examples in the area of drug discovery and bioorganic chemistry (**Fig 1B**).[5] In organic synthesis, Michael acceptors are common substrates to study organocatalysis[6-8] or transition metal catalysis[9-11] for many other applications, and significant advances have been made over the past decades to introduce a wide variety of nucleophiles onto the β-carbon atom. Despite these efforts, one of the key limitations of modern synthesis methodology still lies within cyclopropene-based Michael acceptors **1c** that are intrinsically challenging substrates themselves. Related work on the reaction of halogen-substituted cyclopropanes under highly basic conditions presumably proceeds through the intermittent formation of a cyclopropene, although a formal substitution reaction is also considered as a potential reaction pathway.[12-15] As such, the study of the reactivity of such cyclopropene-based Michael acceptors remains, even today, a significant synthetic challenge.

The development of a uniform strategy to first access cyclopropene-based Michael acceptors and engage these in a general protocol to introduce a nucleophile is, therefore, highly attractive. To achieve this goal, firstly, it is a prerequisite to access a cyclopropene-substituted carbonyl compound, which is known as fleeting intermediates from laser-flash photolysis studies of styryl-substituted diazo compounds[16-18]. Such cyclopropene intermediates recently been probed in pericyclic reactions as dienophiles.[19-21] Secondly, this transitory intermediate must be trapped by a nucleophile before undesired decomposition reactions may occur. The successful implementation of this approach should then open pathways towards a generalized method to access and engage cyclopropenes in Michael addition reactions, which – given the high reactivity of such cyclopropene-based Michael acceptors **8** and the three-dimensional nature of the reaction products – may find a broad range of applications in drug discovery and sensing applications (**Fig 1C**).[22-25]

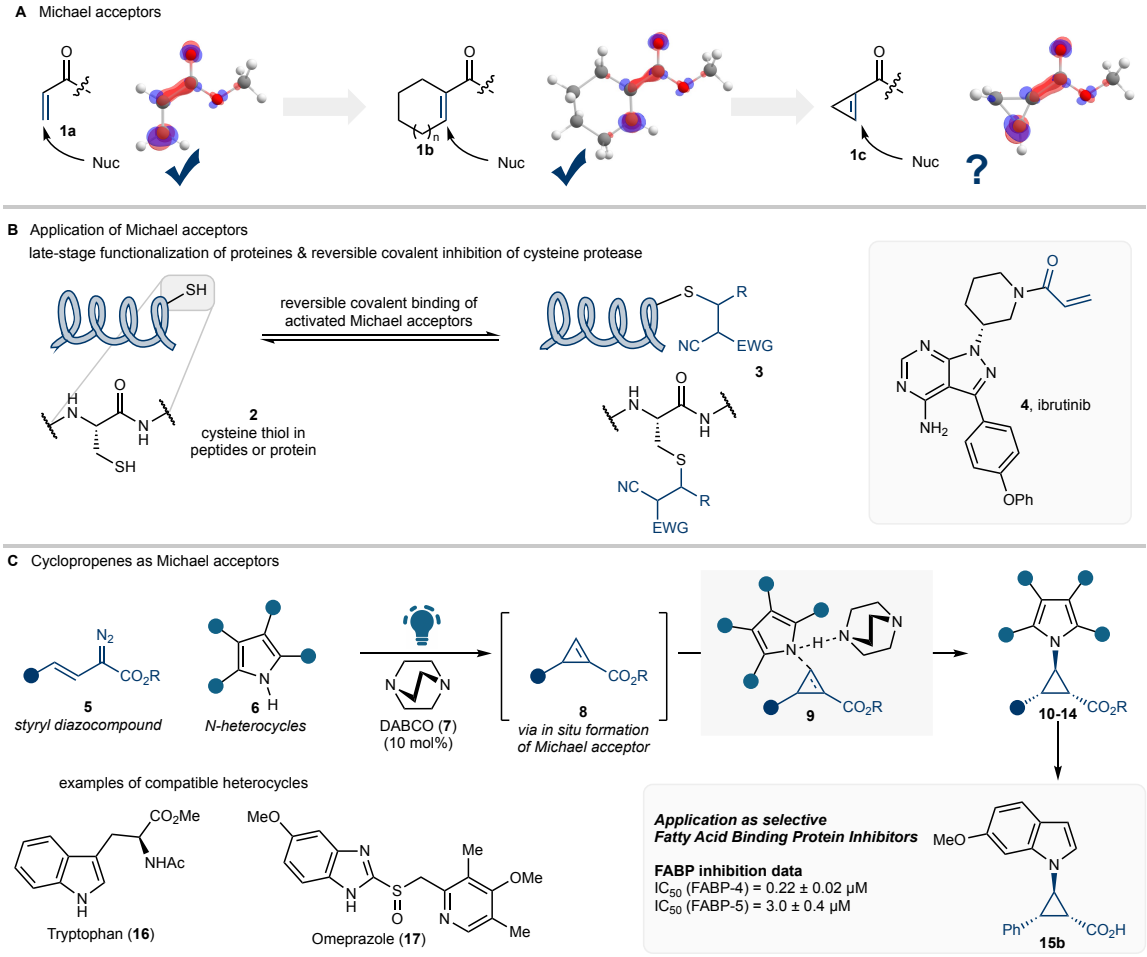

Fig. 1. A Classes of acyclic **1a** and cyclic (**1b** &**1c**) Michael acceptors. **B** reversible covalent inhibition of therapeutically relevant kinases. **C** our approach on cyclopropenes as Michael acceptors and application of addition product in mediceinal chemistry.

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REACTION DEVELOPMENT

To validate our hypothesis, we examined the reaction of mesityl-protected vinyl diazo ester **5a** with indole **6a** using Et_3N (10 mol%) as a catalyst in dichloromethane under blue LED irradiation to give cyclopropane **3** in high yield and decent diastereoselectivity (Table S1, entry 1).[26] Further optimization studies included the evaluation of different bases (Table S1, entries 1-10), substrate compositions (Table S1, entries 12-14), solvents (Table S1, entries 16-22) and ester functional groups (**Fig. 2A**, **10a-d**). Notably, the use of a mesityl-ester proved key to achieving a higher diastereomeric excess for the organocatalytic Michael addition reaction, which we assume to be related to steric reasons.

We then proceeded with the substrate scope evaluation, and a series of mesityl-/isopropyl diazo esters bearing differently substituted aryl rings were examined, including diazo esters bearing naphthyl or heteroaryl groups. In most cases, a good yield of the major diastereomeric products **10e-m** were achieved (**Fig. 2A-B**). Further, the compatibility of substituted indole heterocycles was investigated, and it was observed that the reaction is reasonably general regardless of the nature and substituent pattern at the indole ring. A series of N-cyclopropyl ester substituted indoles **10n-10y** were accessed in good yields of the major diastereoisomers (**Fig. 2C**). It is worth noting that the strong electron-withdrawing groups such as -CN, -CHO, and $-NO_2$ at different positions on the indole ring, as well as sterically demanding 2-methyl indole, were found to be tolerated under this strategy. 1*H*-Pyrrolo[2,3-*b*]pyridine, an isostere of indole, also reacts well to provide the corresponding cyclopropane **10z** in good yield. Another isostere of indole, i.e. benzimidazole, was also found to be tolerable under the standard reaction condition to afford the diastereomeric mixture (2:1) of **10aa** in 63% yield. Further, differently substituted pyrroles were also well accommodated in this transformation to provide the N-cyclopropyl pyrroles **11a-e** in acceptable yields (**Fig. 2D**). Further; we switched our investigation beyond heteroaromatic systems towards the other N-heterocycles (**Fig. 2E**). In this context, differently substituted isatins were *N*-cyclopropylated (**12a-g**) up to good yields. The substrate scope was further studied using different heterocycles such as phthalimide, 2-hydroxy pyridine, 2-hydroxy-quinolines, quinoxalin-2(1*H*)-one and dibenzoazepines. In all cases, the respective *N*-heterocycle-substituted cyclopropanes **12h-n** were obtained in good yield of major diastereoisomers. Further extension of the application included the evaluation of aniline derivatives. In this case, the use of an electron-withdrawing *N*-protecting group, such as *N*-acetyl, *N*-tosyl or *N*-Boc was required to achieve good yield and selectivity of the cyclopropanoic acid derivatives **13a-c** (**Fig. 2E**). We further examined biologically relevant N-heterocyclic substrates, the protected amino acid Tryptophane derivative (**16**) or purine alkaloids such as Theophylline and analogues thereof. In this context, we also examined the functionalization of approved drug molecules such as paracetamol, Tropisetron, Omprazole (**17**) and its precursor. Despite only little control of the relative stereochemistry between the remote stereocenter of the natural product and the cyclopropane ring, the newly formed trisubstituted cyclopropane ring in the corresponding products **14a-g** still formed in low to good diastereoselectivity for all natural products and drugs in this study (**Fig. 2F**).

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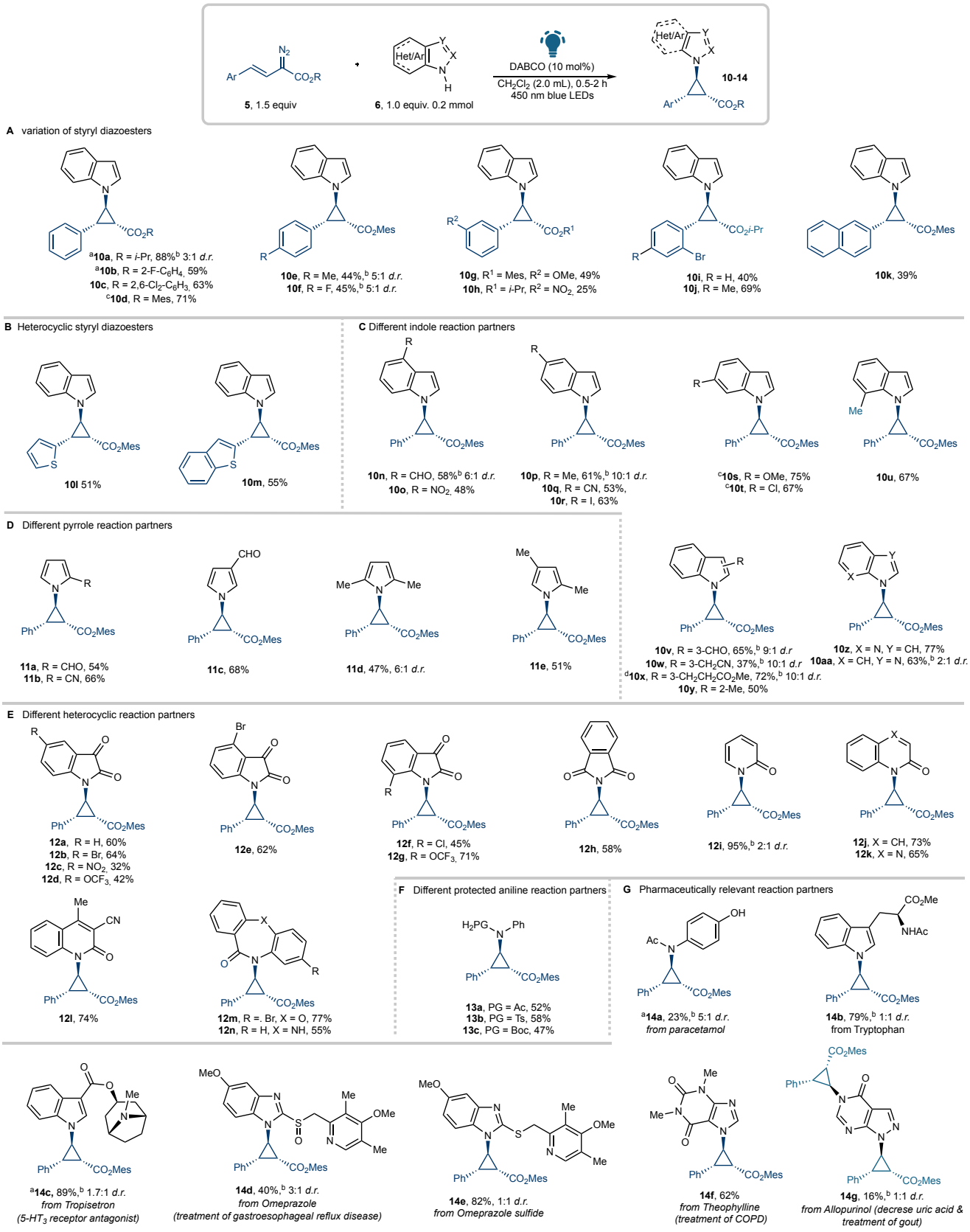

Fig. 2. Substrate scope of the cyclopropenation-Michael addition cascade reaction. **A** variation of styryl diazo compound. **B** heterocyclic styryl diazo compound. **C** variation of the indole skeleton. **D** reaction of pyrroles. **E** reaction of N-heterocycles. **F** protected anilines. **G** pharmaceutically relevant building blocks. Unless specified, the yield refers to pure diastereoisomer. [a]The reaction was performed at 0.1 mmol scale. [b]Yield of diasteromeric mixture.[c] The reaction was performed with 20 mol% of DABCO . [d]The reaction was performed at 0.15 mmol scale.

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Having a method in hand to access a wide variety of functionalized cyclopropane derivatives with high diastereoselectivity, we considered the application and scalability of this synthesis method. Using a simple flow reactor with only 1.5 mL inner volume, the reaction could be readily scaled to 1.5 g productivity per day for the cyclopropane ester 10s (Fig. 3A). Several downstream transformations of the reaction products, such as Suzuki coupling or reduction of the ester could be successfully exemplified to afford **18** and **19**, respectively (**Fig. 3B**).

Given the high relevance of three-dimensional scaffolds in modern drug discovery research, we then embarked on a one-pot synthesis protocol of cyclopropane carboxylic acid derivatives, which we sought to explore as potential inhibitors of adipocyte Fatty Acid Binding Protein (or FABP-4).[9] An increased level of free FABP-4 is found in adipose tissue, and unbound FABP-4 is used as a clinical biomarker in patients and linked to the development of diseases such as obesity, diabetes type II, atherosclerosis, or metabolic syndrome. Blocking of FABP-4 is a well-known therapeutic opportunity for obesity and related disorders; however, investigational drugs, such as BMS309403, are still lacking clinical breakthroughs (**Fig. 3D**). This may be partly related to the high occurrence of aromatic systems and an associated high lipophilicity, which in turn impacts therapeutic applications. Intrigued by this context, we therefore delved into exploring the cyclopropane carboxylic esters, accessible through the present synthesis method, in the context of drug discovery and the inhibition of FABP-4. We, therefore, conducted the facile synthesis cyclopropane carboxylic acids **15a-i** by reacting styryl diazoacetate **5a** and a diverse set of indole heterocycles in our photochemical conditions, followed by ester hydrolysis (**Fig. 3C** for details, see S31-S35). We next explored these carboxylic acid derivatives as inhibitors of fatty acid binding proteins, and to our delight, the acid **15b** gave a good initial activity with an inhibitory constant IC_{50} of 220 nM against FABP-4 and a more than 10fold selectivity over closely related target FABP-5. We further explored key physico-chemical data for **15b**, which showed a very low in vitro clearance (CL_{int} = 4.7 ± 0.6 mg μL^{-1} min^{-1}) and good solubility. This convincing data qualifies **15b** as a starting point for further lead optimization studies to further improve target affinity and selectivity and may lead to future activities in *in vivo* models.

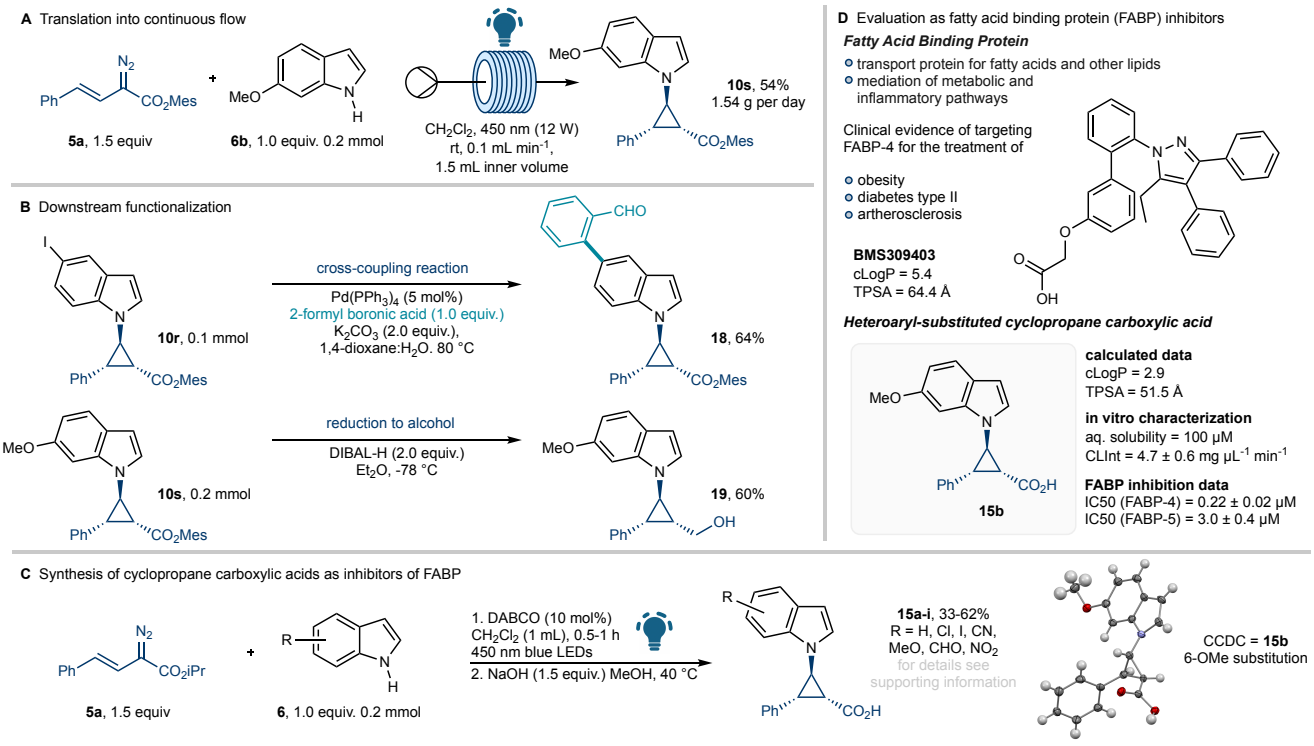

Fig. 3. Translation towards applications in synthesis and drug discovery. **A** Continuous-flow synthesis. **B** Applications in organic synthesis. **C** Applications in Drug Synthesis: One-pot synthesis of adipocyte Fatty Acid Binding Protein (FABP-4) Inhibitors. **D** Applications in Medicinal Chemistry.

We concluded our studies by examining the reaction mechanism in a combined computational and experimental study. Computations indicate the formation of a key cyclopropene intermediate **8a** from a singlet free carbene via an intramolecular cyclopropenation reaction (**Fig. 4**). In the presence of DABCO, this cyclopropene intermediate **8a** can undergo a facile reaction with unprotected indole and undergoes *N*-alkylation of the indole heterocycle, selectively. At the same time, the indole proton is transferred with the assistance of DABCO in a suprafacial fashion to the α-carbon of the ester functional group to give the cyclopropane product essentially as one diastereoisomer (for details, please see ESI, Fig. S1-S3). The intermediacy of cyclopropene **8a** was further verified by HRMS analysis of the crude mixture of the photolysis

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reaction of styryl diazoacetate **6a**. Similarly, the HRMS analysis of a reaction styryl diazoacetate **5a** and indole **6a** with butylated hydroxytoluene (BHT, **20**), as a trapping reagent revealed the formation of all possible products: cyclopropene **8a**, phenol ether **21** and indole-substituted cyclopropane **10d**. This data let us conclude that the reaction indeed proceeds through the intermittent formation of a highly reactive cyclopropene intermediate that can serve as a general precursor for highly stereoselective Michael addition reactions with various *N*-heterocycles.

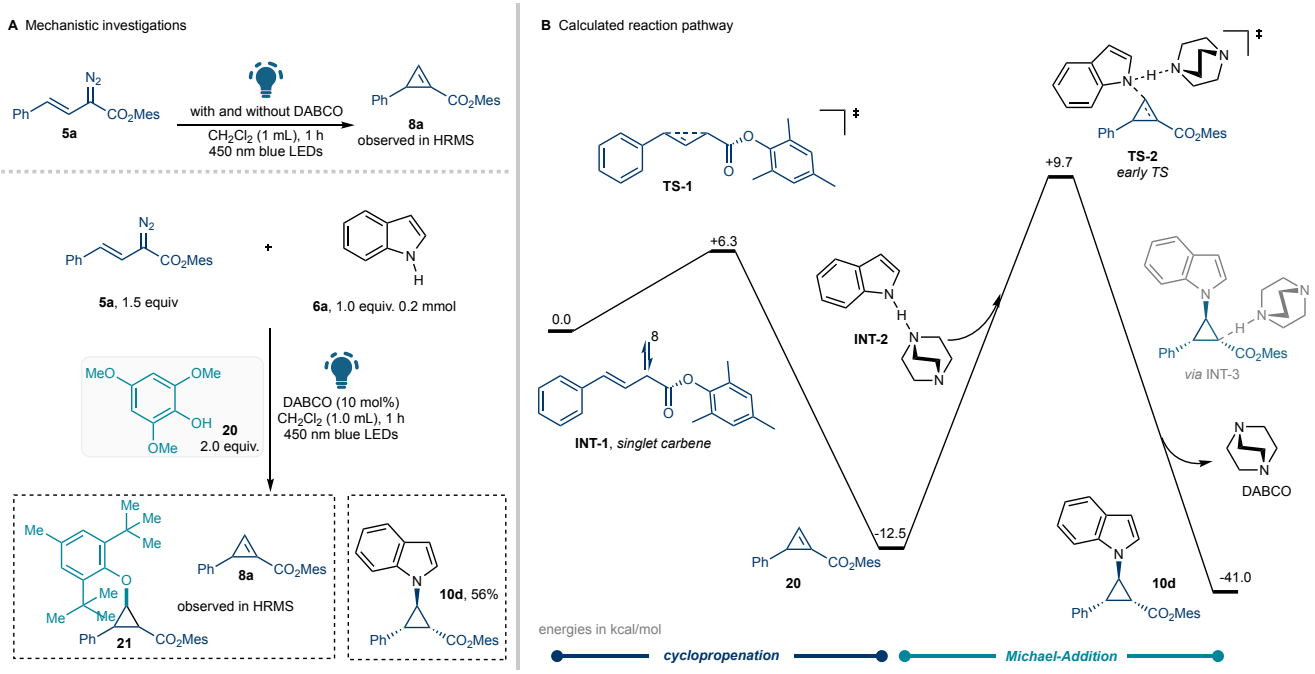

Fig. 4. Studies on the reaction mechanism. **A.** Experimental mechanistic investigations. **B.** Computational studies.

CONCLUSION

In summary, we herein present a unified strategy to access and effectively engage cyclopropene-based Michael acceptors, thus unveiling a pathway towards a broadly applicable protocol. Central to our approach is the transient photochemical synthesis of fleeting cyclopropene intermediates that were demonstrated as viable Michael acceptors in a generalized reaction with N-heterocycles, demonstrating remarkable diastereoselectivity and substrate compatibility, including intricate biologically relevant molecules. Furthermore, we explore the translational potential of our synthesis methodology, particularly in the realm of drug discovery. Leveraging the unique three-dimensional architecture conferred by cyclopropane derivatives, we pursue their utility as potential inhibitors of adipocyte Fatty Acid Binding Protein (FABP-4), a key target in metabolic disorders. Through a comprehensive investigation, we delineate a one-pot synthesis route yielding cyclopropane carboxylic acids, showcasing promising inhibitory activity against FABP-4.

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge: Experimental details and spectroscopic data for all products, full Gaussian reference, Cartesian coordinates, electronic and free energies.

Data Availability

Authors can confirm that all relevant data are included in the paper and/ or its supplementary information files

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CONFLICTS OF INTEREST

There is no conflicts of interest to declare.

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26. See supporting informtaion

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