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Intermolecular dearomative [4 + 2] cycloaddition of naphthalenes *via* visible-light energy-transfer-catalysis†

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The dearomative cycloaddition reaction serves as a blueprint for creating sp³-rich three-dimensional molecular topology from flat-aromatic compounds. However, severe reactivity and selectivity issues make this process arduous. Herein, we describe visible-light energy-transfer catalysis for the intermolecular dearomative [4 + 2] cycloaddition reaction of feedstock naphthalene molecules with vinyl benzenes. Tolerating a wide range of functional groups, structurally diverse 2-acyl naphthalenes and styrenes could easily be converted to a diverse range of bicyclo[2.2.2]octa-2,5-diene scaffolds in high yields and moderate *endo*-selectivities. The late-stage modification of the derivatives of pharmaceutical agents further demonstrated the broad potentiality of this methodology. The efficacy of the introduced methods was further highlighted by the post-synthetic diversification of the products. Furthermore, photoluminescence, electrochemical, kinetic, control experiments, and density-functional theory calculations support energy-transfer catalysis.

Introduction

Constructing sp³-rich three-dimensional (3D) scaffolds from two-dimensional (2D) molecules is highly challenging yet significantly impacts organic synthesis and drug discovery programs.[1] The [4 + 2] cycloaddition reaction in which two new σ-bonds, and one π-bond are formed in a 3D six-membered ring topology from two simple unsaturated reaction components, diene and dienophile, has been recognized as a powerful tool for this purpose (Fig. 1a).[2,3] In fact, this thermally allowed process has been a fundamental reaction type demonstrating its molecular complexity generating power for many years.[4] In this context, polycyclic aromatic hydrocarbons such as naphthalenes also contain alternating double bonds. Besides, they are abundant and inexpensive feedstock chemicals.[5] However, these 2D molecules displayed limited application in 3D complexity generating cycloaddition reactions due to severe challenges associated with breaking the increased stabilization conferred by aromaticity (resonance energy = 80.3 kcal mol⁻¹) and selectivity (Fig. 1b and c).[6] A typical thermal [4 + 2] cycloaddition with naphthalenes required harsh reaction conditions (high temperature up to 210 °C, pressure up to 10³ atm),[7]

specially designed reaction conditions,[8] or reactive dienophile[9] to overcome the high kinetic barrier (Fig. 1c). However, since the free energy is often positive, the reverse reaction is preferred resulting in lower product yields (Fig. 1d, blue curve).[7–9] Photochemistry provides alternative strategies for achieving challenging chemical processes in this context.[10] However, since most organic molecules are incapable of absorbing visible light efficiently, direct high-energy ultraviolet (UV) light irradiation is required. Indeed, the UV-light mediated [4 + 2] cycloaddition of naphthalene is known.[9b,11] However, their utility in organic synthesis is minimal due to the requirement of specific arenophiles, meager product yields, and unpredictable side reactions conferred by UV light (Fig. 1c). Eliminating UV irradiation should ideally broaden the synthetic applicability of this process with enriched structural diversity. The recent renaissance of visible-light photocatalysis provides a new space for dearomative [4 + 2] cycloaddition reaction *via* sensitization induced energy transfer (EnT) catalysis[12] or direct visible-light excitation of the dienophile in some cases.[13] Conceptually, a EnT process can selectively excite a ground state of a polycyclic hydrocarbon by using a photosensitizer to a higher triplet state (naphthalenes exhibit E_Ts of 54–60 kcal mol⁻¹),[12d] lowering the kinetic barriers significantly compared to thermal processes (Fig. 1d, black curve). Furthermore, milder reaction conditions and substantially higher E_T of the dearomatized product prevent the reverse reaction resulting in higher product yields.

Recently, Glorius and coworkers disclosed the sole report on intermolecular dearomative [4 + 2] cycloaddition of bicyclic azaarenes (Fig. 1e) *via* visible-light EnT catalysis.[12c] A stoichiometric Brønsted acid additive was shown to play a vital role in

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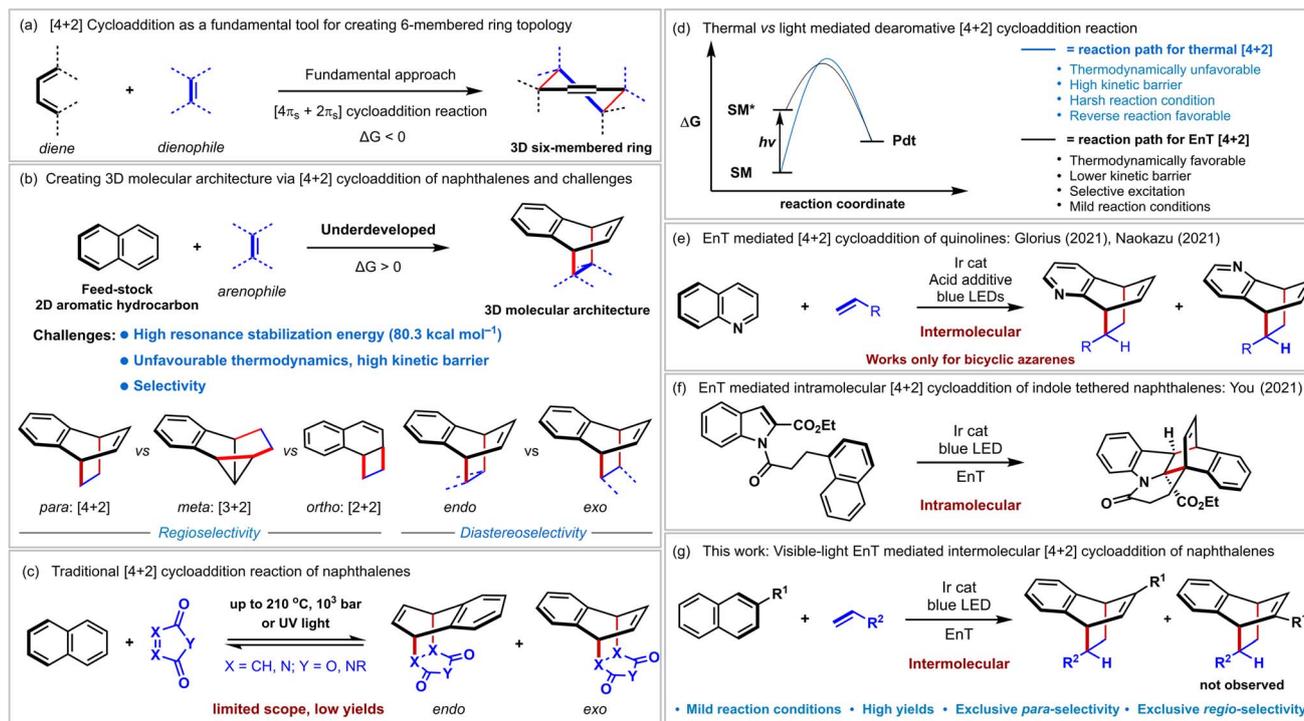
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Fig. 1 (a and b) Creating molecular complexity *via* [4 + 2] cycloaddition reaction and their challenges. (c) Traditional [4 + 2] cycloaddition reaction with naphthalenes. (d) Thermal *vs.* light-mediated cycloaddition reaction. (e and f) EnT Mediated [4 + 2] cycloaddition reaction of bicyclic azaarenes and indole tethered naphthalenes. (g) This work: visible-light EnT mediated intermolecular [4 + 2] cycloaddition reaction of naphthalenes. SM = starting material. Pdt = product.

increasing the reactivity of quinolines' triplet state toward olefins.[12b] You reported intramolecular cycloaddition of indole tethered naphthalenes (Fig. 1f).[14] The intramolecular [2 + 2] cycloaddition of 1-naphthol derivatives and [4 + 2] cycloaddition of pyridines *via* visible-light EnT catalysis were recently developed by Glorius.[12a,15] The intramolecularity prepaid the crucial entropic requirements for the last three reactions.

Besides, various groups demonstrated the application of the EnT process in diverse chemical transformations.[16] However, to the best of our knowledge, visible-light-induced intermolecular dearomative [4 + 2] cycloaddition reactions of aromatic hydrocarbons with simple alkenes have not been documented yet. Herein, we report our initial results on EnT mediated dearomative [4 + 2] cycloaddition of naphthalenes with styrenes to access bicyclo[2.2.2]octa-2,5-diene scaffolds (Fig. 1g).

Results and discussion

We commenced the visible-light mediated dearomative [4 + 2] cycloaddition reaction using 2-acetyl naphthalene **1** and 1-fluoro-4-vinyl benzene **2** as the model substrates (Table 1 and S1–S6†). Pleasingly, the irradiation of blue light-emitting diodes (λ_{max} = 427 nm) in the presence of commercially available photosensitizer Ir[(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$ (**PC1**, 1 mol%) in acetonitrile solution of **1** and **2** (in stoichiometric ratio) at room temperature resulted in the formation of the desired [4 + 2] cycloadduct **3** in 98% yield in 2 : 1 ratio, favoring *endo* (entry 1). Notably, the regioisomeric product **4** resulting from the *syn*

attack of the alkene to the 6-membered aromatic ring was not observed by the ^{1}H nuclear magnetic resonance analysis of the crude reaction mixture. The *ortho* and *meta* cycloaddition products (Fig. 1b) were also undetected in a measurable amount. We then followed the kinetics of the reaction *via* ^{1}H NMR spectroscopy (Fig. S18†).

The rate of formation of **3** was found to be almost equal to the disappearance of **1** (Fig. S19†). This supports the direct formation of [4 + 2] cycloadduct **3** without the intermediacy of an [2 + 2] adduct, as previously observed for the intramolecular reaction.[14]

Product **3** was computed to be thermodynamically uphill (Fig. S24†). However, it can be purified by flash chromatography on silica gel and was found to be stable when heated at 60 °C for 24 h. The structure of *endo*-**3** was confirmed by single-crystal X-ray crystallography.[17] Control experiments confirm that the light source and photosensitizer were necessary for this [4 + 2] cycloaddition reaction, and their absence led to no product formation (entries 2–3). As anticipated, the reaction does not provide any product when heated at 150 °C for 24 h (entry 4).

We then stride forward to gain more insights into the EnT mediated [4 + 2] cycloaddition reaction (Fig. 2). The cyclic voltammetry analysis suggested that an electron transfer from the excited **PC1** ($E_{1/2}$Ir(III)*/Ir(IV) = −0.89 V *vs.* SCE) to either **1** or **2** (reduction potentials $E_{1/2}$ = −1.81 V and −1.42 V *vs.* SCE, respectively) is not thermodynamically feasible (Fig. 2a). Similarly, an oxidative quenching of the excited **PC1** ($E_{1/2}$Ir(III)*/Ir(II) = 1.21 V *vs.* SCE) can also be ruled out. However, the Stern–

Table 1 Key reaction optimization[a]

Entry	Photosensitizer (PC)	E_T (kcal mol^{-1}), $h\nu_{max}$ (LED)	Yield of[b] 3 %	endo : exo[b]
1	Ir[(dFCF$_3$ppy)$_2$dtbbpy]PF$_6$ (**PC1**)	61.8, 427	98 (90)	2 : 1
2	—	61.8, 427	<5	—
3[c]	**PC1**	—	<5	—
4[d]	**PC1**	—	<5	—
5[e]	Xanthone (**PC2**)	74, 370	51	1.3 : 1
6	Ir(ppy)$_3$ (**PC3**)	58.1, 427	25	2 : 1
7	Ir[(ppy)$_2$bpy]PF$_6$ (**PC4**)	53.1, 427	30	2 : 1
8[e]	4CzIPN (**PC5**)	53, 427	50	1.5 : 1
9	Ir[(ppy)$_2$dtbbpy]PF$_6$ (**PC6**)	49.2, 427	45	2 : 1

[a] Reaction condition: **1** (0.1 mmol), **2** (0.12 mmol), sensitizer (1 mol%), CH$_3$CN (1 mL), blue LED irradiation under N$_2$ at rt, 24 h. [b] Yield and endo : exo ratio of **3** were determined by ^{1}H NMR analysis by using trimethoxy benzene as an internal standard. Isolated yield in the parenthesis. Triplet energy E_T from ref. [16d]. [c] In the dark. [d] In the dark at 150 °C. [e] 5 mol% sensitizer is used.

Volmer analysis shows that 2-acetyl naphthalene **1** efficiently quenches the luminescence emission of the excited photosensitizer (Stern–Volmer quenching constant $k_q = 1.6 \times 10^4$ M^{-1} s^{-1}) (Fig. 2b and c). Vinyl benzene **2** quenched the excited **PC1** at a lower rate (Fig. 2c). We then computed the S$_0$–T$_1$ gap for **1** and **2** using B3LYP/6-311+G(2d,p) level of density functional theory (Fig. S20†). The calculated triplet energies $E_T = 55.1$ kcal mol^{-1} for **1** and 57.9 kcal mol^{-1} for **2** are in good agreement with the previously reported values.[16w] Accordingly, the triplet energy transfer EnT from the photoexcited **PC1** ($E_T = 61.8$ kcal mol^{-1})[18] to substrate **1** is exergonic and more likely.

The reaction was also found to be amenable to some triplet-energy sensitizers, albeit at lesser efficiencies (Table 1, entries 5–9). However, a direct correlation between the E_Ts of the catalysts and product yields could not be drawn.[16h,19] To gain more insight into the interaction of other photosensitizers with substrates **1** and **2** and their efficiencies in catalyzing the EnT mediated cycloaddition reaction, we have performed the luminescence quenching experiments with **PC3** and **PC5**, which gave a moderate to low yield of **3**. We have found both **1** and **2** do not interact with the excited **PC3** at an appreciable rate (Fig. 2d). The luminescence intensity of excited **PC5** is moderately quenched by increasing the concentration of **1** ($k_q = 0.30 \times 10^4$ M^{-1} s^{-1}) (Fig. 2e). However, **2** does not communicate with the excited **PC5**. Further quenching studies are incorporated in ESI.† In addition, it was confirmed that an electron donor–acceptor complex between **1** and **2** does not occur, as evidenced by the lack of a change in the UV/vis spectrum (Fig. 2f). The absorption spectrum of **2** possesses small residual absorption at 370 nm (molar absorptivity $\varepsilon = 48.1$ M^{-1} cm^{-1} at 370 nm). However, direct irradiation using 370 nm Kessil LEDs (emission spectral window of ~360 to 410 nm) only gave a 35% yield of **3** (endo : exo = 1.7 : 1) (Fig. 2g). A similar observation was made in

the acetone solvent. These results additionally suggest that the photochemical dearomative cycloaddition reaction of **1** is more efficiently triggered upon energy transfer from the excited **PC1**. Additionally, complete inhibition of the dearomative [4 + 2] cycloaddition reaction under well-known E_T quenchers, including oxygen and 2,5-dimethylhexa-2,4-diene, further supported the EnT process (Fig. 2h).

Based on the observations outlined above and the literature report, it is proposed that the photosensitizer, upon visible-light excitation produces its long-lived triplet excited state (Fig. 2i). The naphthalene **1** is then activated via EnT to afford triplet intermediate **1** (T$_1$). The latter is then engaged in [4 + 2] cycloaddition with styrene **2** to yield the cycloadduct **3** via radical capture, intersystem crossing (ISC), and bond formation.

The orbital coefficients of the relevant frontier molecular orbitals were examined to understand the origin of regioselectivity (see Page S74†). The preferential formation of **3** can approximately be conceptualized considering the maximum interaction between the largest orbital components in the triplet intermediate **1** (T$_1$) and the lowest unoccupied molecular orbital of **2**. However, a detailed computational elaboration is necessary.

Finally, we explored the generality and synthetic utility of the EnT mediated dearomative [4 + 2] cycloaddition reaction (Fig. 3). First, the scalability of our protocol was tested for a 1.0 mmol scale reaction between **1** and **2** that provided 0.25 g (84% yield) of **3** with the same endo selectivity. Then, the scope of the arenophile was investigated. Halogenated (F, Cl, Br) styrenes were excellent coupling partners, yielding bicyclo[2.2.2] octa-2,5-diene scaffolds **3–8** in high yields and selectivities. The electronic nature of the substituents does not perturb the reaction. Vinyl benzenes with both electron-withdrawing (CF$_3$) and electron-donating substituents (OMe, OAc, Me, SMe) at
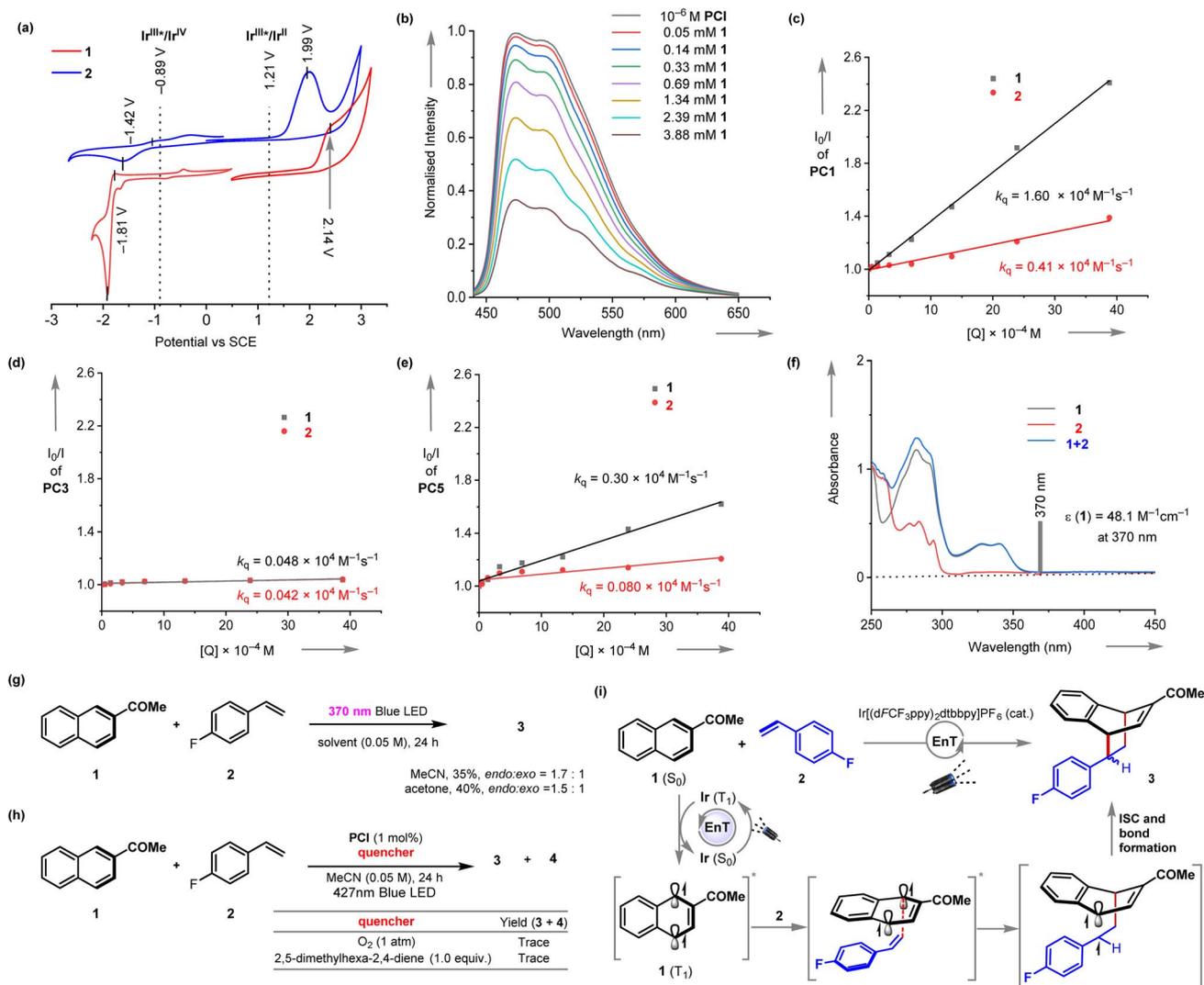
Fig. 2 Mechanistic studies and proposed mechanism. (a) Cyclic voltammetry studies. (b) Decrease in luminescence intensity of **PC1** upon addition of **1**. The Stern–Volmer plot of the luminescence quenching for (c) **PC1**, (d) **PC3**, (e) **PC5**. (f) UV-vis studies. (g) Direct excitation of **1** in the absence of photosensitizer. (h) Reaction inhibition by external E_T quencher. (i) Proposed mechanism.

different positions of the aryl ring participated in this reaction in equal efficiencies. The adducts **9–16** were obtained in 25–80% yields with a similar *endo/exo* ratio. Interestingly, vinyl naphthalene could also be utilized as an arenophile, and the adduct **17** was isolated in 39% yield. It indicated selective energy transfer to **1**. Notably, vinyl biphenyls containing diverse electronic substituents, heteroarenes, and 4-vinyl pyridines were compatible with this reaction, and the dearomative cycloadducts **18–20** were obtained in moderate to good yields. However, α- and β-methyl styrene fails to deliver the product in synthetically useful yields under these conditions. Pleasingly, the reaction was compatible with styrene derivatives of complex molecules, including gemfibrozil, clofibric acid, fenbufen, ketoprofen, and oleic acid. The adducts **21–25** were isolated in 64–80% yields and moderate *endo* selectivities. It highlighted the functional group compatibility and synthetic utility of the process for late-stage diversification of these molecules.

The scope of naphthalene derivatives was then tested. Acyl naphthalenes with diverse alkyl chains participate in this EnT mediated [4 + 2] cycloaddition reaction, delivering the adducts **26–28** in high yields and selectivities. Naphthalenes containing cyclic alkyl groups, including cyclobutane **29** and cyclopropane **30**, were also viable reaction partners. A CC-bond cleavage in a strained cyclopropane ring was not observed. In comparison, Brown recently discovered EnT mediated CC-bond cleavage in bicyclo[1.1.0]butyl naphthyl ketone for [2π + 2σ] cycloaddition reactions with styrenes.[19a] Severe ring strain in the caged molecule can be reasoned responsible. *N*-Methyl imidazole bearing keto naphthalene performed well in this reaction **31**. The structures of both the *endo*- and *exo*-diastereomers were assigned by single-crystal X-ray crystallography.[17] Interestingly, 2-carboxyalkyl naphthalenes also smoothly undergo visible-light mediated dearomative cycloaddition reaction providing high 80–85% yields of the cycloadducts **32–34**, albeit in
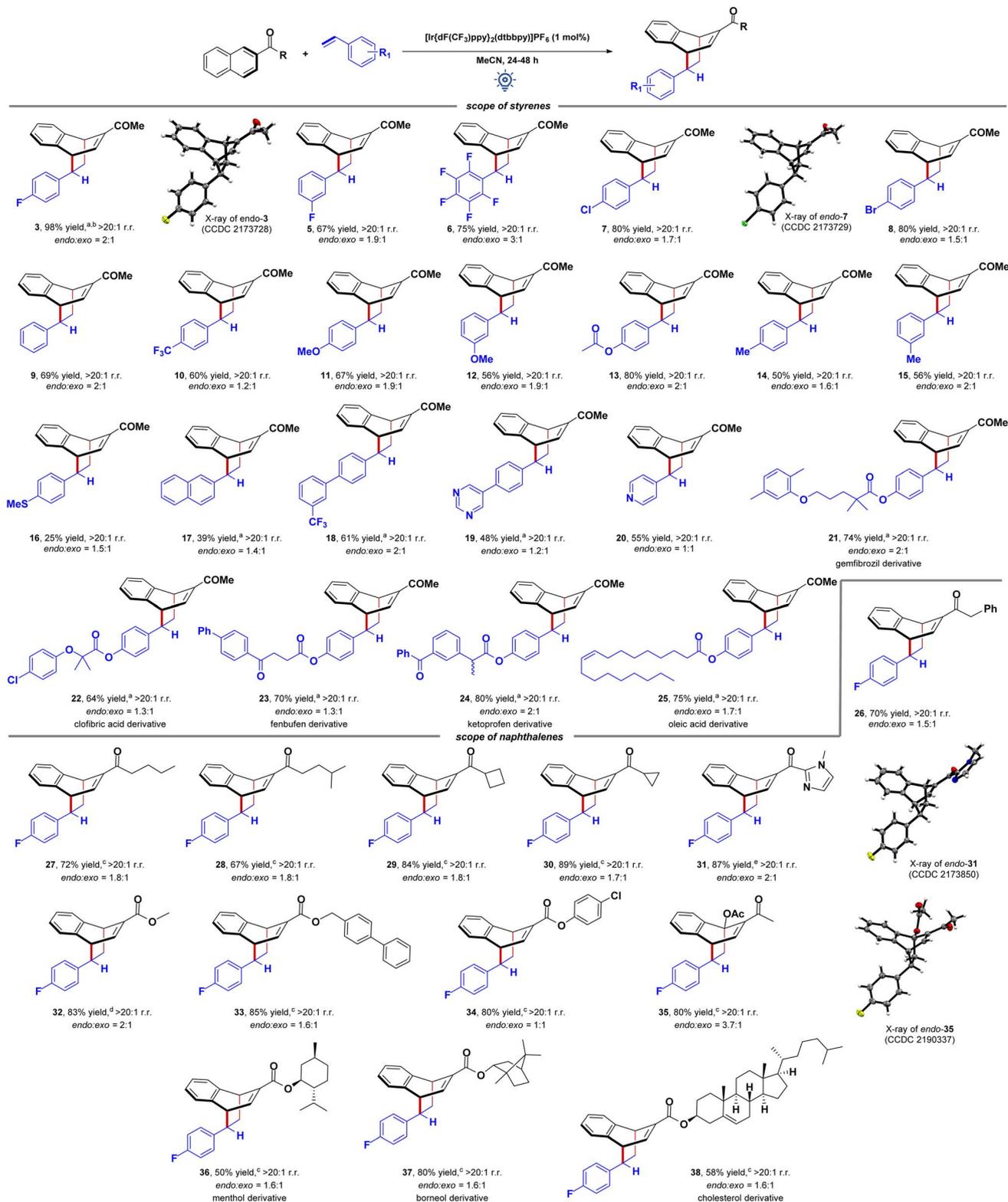
Fig. 3 Synthetic utility of the EnT mediated [4 + 2] cycloaddition reaction. Reaction conditions: Table 1, entry 1. Reaction performed in 2 mL MeCN. *Endo/exo* ratio of products was determined by ^{1}H NMR analysis using 1,3,5-trimethoxy benzene as an internal standard. Combined yields are given. Isolated yields of each isomer are provided in the ESI.† CCDC information ref. 17 [a] reaction performed in 1 mL MeCN. [b] 0.246 g, 84% yield, >20 : 1 rr., *endo* : *exo* = 1.6 : 1, when performed in 1 mmol scale. [c] Reaction carried out for 48 h. [d] Reaction carried out in MeOH solvent. [e] Reaction carried out for 48 h. rr. = regioisomeric ratio.
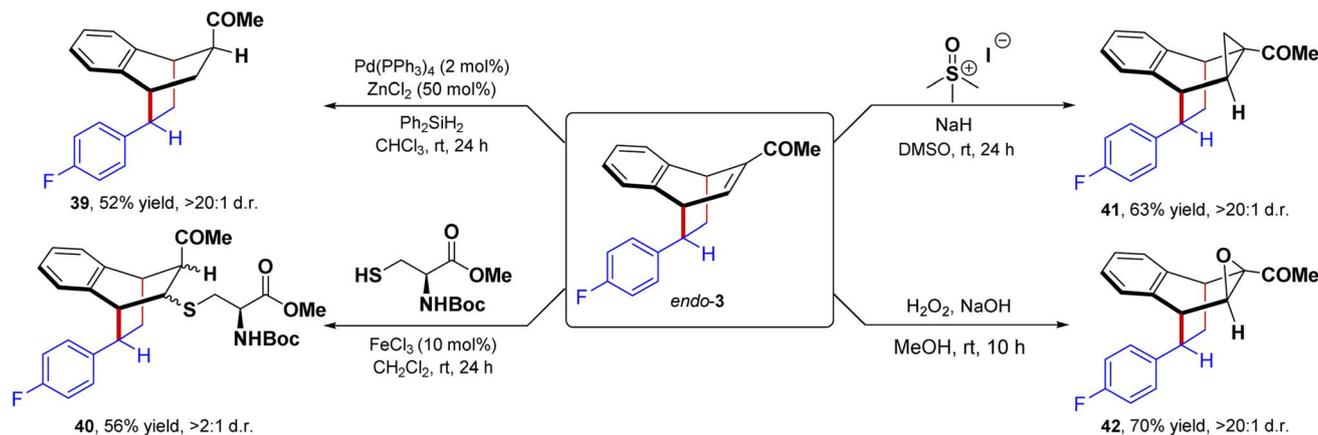
Fig. 4 Post-synthetic application of [4 + 2] cycloaddition products, dr. = diastereoselective ratio.

a moderate *endo/exo* ratio. Interestingly, 1,2-disubstituted naphthalene derivative also undergoes the dearomative cycloaddition providing the desired product **35** in high yield, and the structure of the *endo*-diastereomer was assigned by single-crystal X-ray crystallography.[17] The reaction was also compatible with the naphthalene derivatives of (−)-menthol **36**, (−)-borneol **37**, and cholesterol **38**. It again highlights the utility of the visible-light-driven dearomatization reaction.

To further demonstrate the synthetic application of the [4 + 2] dearomative cycloaddition reaction, we have performed the derivatization of the cycloadduct *endo*-**3** to obtain complex 3D molecular architecture (Fig. 4). The palladium-catalyzed reduction of the α,β-unsaturated double bond of *endo*-**3** in the presence of diphenyl silane gave the saturated product **39** in 52% yield in >20 : 1 dr. NOE spectroscopy confirmed the stereochemical assignment. Furthermore, a Michael addition of *N*-Boc-L-cysteine methyl ester delivered the adduct **40** in 56% yield and 2 : 1 dr. Notably, the Corey–Chaykovsky cyclopropanation of *endo*-**3** offered the cyclopropane **41** in 63% yield and >99 : 1 dr. Similarly, the epoxidation of *endo*-**3** in the presence of H_2O_2/NaOH delivered the epoxide **42** in 70% isolated yield as a single diastereomer.

Conclusions

In conclusion, a new strategy for intermolecular dearomative [4 + 2] cycloaddition reaction of abundant aromatic hydrocarbon naphthalene was developed. The reaction operates *via* visible-light energy transfer utilizing a commercially available sensitizer. Diverse bicyclo[2.2.2]octa-2,5-diene scaffolds were synthesized in high yields. The reaction can be scaled-up and is amicable for late-stage modification of various complex molecules. The ease of post-synthetic diversifications adds to the utility of the introduced method. Photoluminescence, electrochemical, kinetic, and control experiments helped understand the features of this visible-energy transfer catalysis. We anticipate that the protocol will further illuminate the EnT catalysis for designing complex molecular scaffolds. Further research

exploring the reaction scope and mechanisms is currently underway in this laboratory.

Data availability

The ESI† includes all experimental details, including optimization of the synthetic method, synthesis and characterization of all starting materials and products reported in this study, and mechanistic studies. NMR spectra of all products, crystallography, and computation details are included as well.

Author contributions

P. R., K. M., S. K. J. and B. M. conceived and designed the project. P. R., K. M., S. K. J. performed the experiment and contributed equally to this work. P. R., K. M., S. K. J. and B. M. wrote the manuscript. B. M. acquired the funding and directed the research.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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