nature communications

Article

https://doi.org/10.1038/s41467-026-68969-1

Photoinduced polarity-mismatched transformations of isoquinolines into naphthalenes

Received: 11 July 2025

Accepted: 22 January 2026

Published online: 09 February 2026

Check for updates

Congcong Zhang[1], Jianing Zhang[1], Yu Lan[2,3,4] ✉, Yunlong Qin[1], Zerong Guo[1], Wenjing Zhang[2] ✉ & Qilin Wang[1] ✉

Isosteric replacement is an important strategy for lead optimization in drug-development paradigms. However, it is usually restricted to cost- and labor-intensive de novo syntheses. We here report a photochemical photosensitizer-free skeletal-editing strategy to directly transform easily accessible isoquinolines into synthetically challenging naphthalene derivatives in a single operation. Directed by density functional theory calculations, the key factor enabling the (4 + 2) cycloaddition between two polarity-mismatched species was harnessing photonic energy to overcome fundamental electronic hurdles by the combination of isoquinolinium carbonate as the electron-donor-acceptor complex. The high compatibility of this methodology was expanded to late-stage functionalization of commercial drugs, thus enriching optimization libraries. Importantly, value-adding access to valuable polycyclic aromatic hydrocarbons, numerous ligands and drug analogies is also demonstrated.

The optimization of compound libraries remains a central task in drug-development campaigns. However, this process often suffers from challenges in terms of synthetic accessibility[1,2]. Ideally, late-stage interconversion of already-existing or easy-to-make libraries to other challenging candidates provides exceptional potential to accelerate drug discovery by avoiding cost- and labor-intensive de novo syntheses through nontraditional disconnections[3]. In this domain, skeletal editing has emerged as a promising strategy to precisely modify molecular skeletons at the atomic level without altering peripheral functional groups[4–9]. Many notable atom-insertion and -deletion reactions[10–28], along with a handful of atom-swap reactions[29–37], have been reported, providing improvements to the structural diversity and complexity of existing libraries, thereby enabling access to new biological space (Fig. 1a).

During the evaluation of drug candidates, a single-atom in the core skeleton can have a dramatic influence on its drug-target interactions, physicochemical properties and metabolic stability (Fig. 1b). For instance, Liu and co-workers discovered that replacing the nitrogen atom in a pyridine core with a carbon atom bearing a cyano group can efficiently modulate its hydrogen-bonding affinity with a receptor, reporting a 65-fold potency improvement in selective, orally active p38α MAP kinase inhibitors[38]. Obviously, conducting isosteric replacement skeletal editing (such as atom-swapping), without the need for multi-step, independent syntheses, is the most straightforward approach to preparing bioisosteres with minimal changes in the molecule's topology, enabling rapid structure-activity relationship (SAR) analysis[39]. However, this is highly challenging due to the thermodynamic mismatches in atom-exchange processes, which require the precise cleavage and formation of multiple chemical bonds without disrupting peripheral substitutions.

Isoquinolines[40] and naphthalenes[41] are isosteres, both of which are of great significance in natural product chemistry, medicinal chemistry and material science. Conventional methods for their synthesis have relied on linear, iterative de novo synthesis. The

[1]College of Chemistry and Molecular Sciences, Henan University, Kaifeng, PR China. [2]College of Chemistry, and Pingyuan Laboratory, Zhengzhou University, Zhengzhou, Henan, PR China. [3]State Key Laboratory of Antiviral Drugs, and Pingyuan Laboratory, Henan Normal University, Xinxiang, Henan, PR China. [4]School of Chemistry and Chemical Engineering, Chongqing Key Laboratory of Chemical Theory and Mechanism, Chongqing University, Chongqing, PR China. ✉e-mail: lanyu@cqu.edu.cn; zhangwj@zzu.edu.cn; wangqilin@henu.edu.cn

https://doi.org/10.1038/s41467-026-68969-1

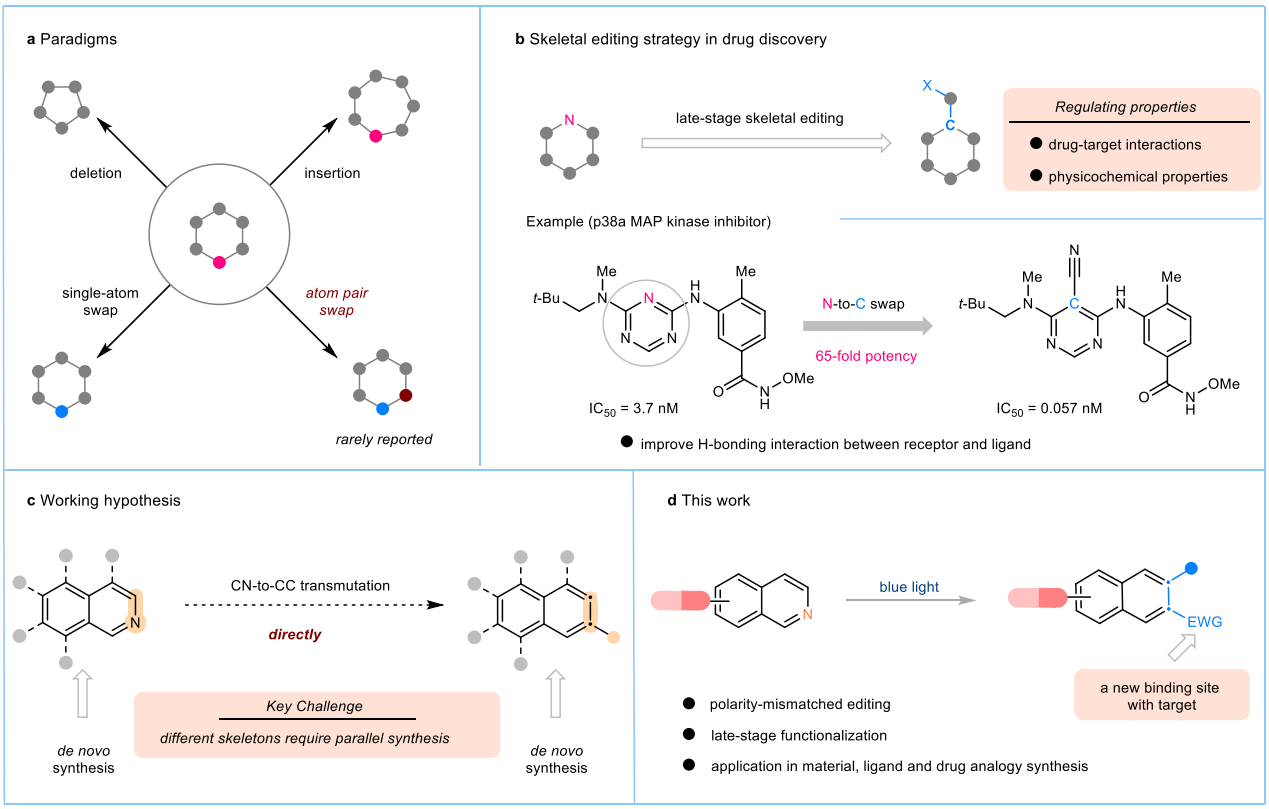


Fig. 1 | Introduction. a Common skeletal editing paradigms. **b** Skeletal editing strategy in drug discovery. **c** Our working hypothesis to directly transform isoquinolines into naphthalenes via CN-to-CC transmutation. **d** This atom pair swap methodology induced by photocatalysis.

presence of the nitrogen atom in isoquinolines endows the C-H groups around the core with different reactivities, thus making post-functionalization with precise regioselectivity control much easier. In sharp contrast, naphthalene is geometrically symmetric. Therefore, to obtain specific naphthalenes, a precursor with a correctly dispositioned functionality handle must be prepared in advance, much of which are difficult to access. Moreover, functionality sensitivity must be considered during the synthetic sequence. Accordingly, long- and/or low-yielding synthetic sequences are often required to obtain complex naphthalene derivatives.

The ubiquity and the importance of isoquinolines render them popular candidates for the development of CN-to-CC atomic-pair exchange reactions to directly prepare naphthalene derivatives (Fig. 1c). This offers the synthetic advantages that readily available precursors can be reshaped into synthetically challenging compounds for optimization libraries by obviating multi-step de novo syntheses. Accomplishment of this transformation necessitates orchestrating the sequential processes of breaking aromaticity, substituting from CN to CC, and restoring aromaticity. However, surgically performing and synchronizing these steps is a daunting task.

Herein, we report the successful implementation of such a CN-to-CC swap reaction. Upon visible-light irradiation, easily accessible isoquinolinium salts are directly transformed into the corresponding naphthalenes in the absence of any photosensitizer. Simultaneously, this strategy introduces a new target-binding site. This allows for rapid SAR analysis, providing the possibility to quickly recognize privileged compounds. The application of this highly functional group tolerable strategy is further demonstrated by late-stage functionalization of commercial drugs, thus expanding the biological space (Fig. 1d). Moreover, the desired products possess rich reactivity, allowing them to undergo various transformations to access useful polycyclic aromatic hydrocarbons (PAHs), ligands and drug analogies.

Results

Reaction development

Structurally, azaarenes have inbuilt π-conjugation systems, enabling them to serve as dienes to participate in Diels-Alder cycloadditions. However, unlike aromatics[42,43], their moderate electron-deficiency makes them poor candidates, with only few intramolecular examples reported[44]. Generally, two activation modes are often adopted to drive the Diels-Alder reaction forward: one is transforming an azaarene into a more electron-deficient azaarene-based onium by quaternization, and the other is converting it into an electron-rich semi-saturated azaarene via a N/C-difunctionalization process (Fig. 2a). For instance, Kozmin and co-workers reported an inverse-electron-demand Diels-Alder reaction between quaternized isoquinoliniums and siloxy alkynes initiated by catalytic amount of Au or stoichiometric Ag[45,46]. Quite recently, the groups of Studer and Boswell independently pioneered polarity-inversion strategies to transform pyridines into 1,2-dihydropyridines, thus allowing for a normal (4 + 2) cycloaddition with arynes or electron-deficient alkynes[47,48]. Both strategies generate bridged intermediates, which are unstable and susceptible to rearomatization through the excision of a CN fragment from the core, thus achieving the CN-to-CC swap. Nevertheless, despite being highly efficient, they are constrained to polarity-matched two-electron processes, thus resulting in scope and product diversity issues.

We reasoned that radical chemistry might overcome these electronic obstacles and facilitate thermally unattainable catalytic conversion. As shown in Fig. 2b, our synthetic design focused on initiating an electrophile-electrophile coupling through a polarity-inversion process under photoredox catalysis. Upon visible-light irradiation, isoquinolinium salts absorb photonic energy for excitation and incur charge-transfer from the anion to the isoquinolinium moiety. Then the electron-donor-acceptor (EDA) mechanism to reduce the isoquinolinium to a radical was proposed and calculated by density

https://doi.org/10.1038/s41467-026-68969-1

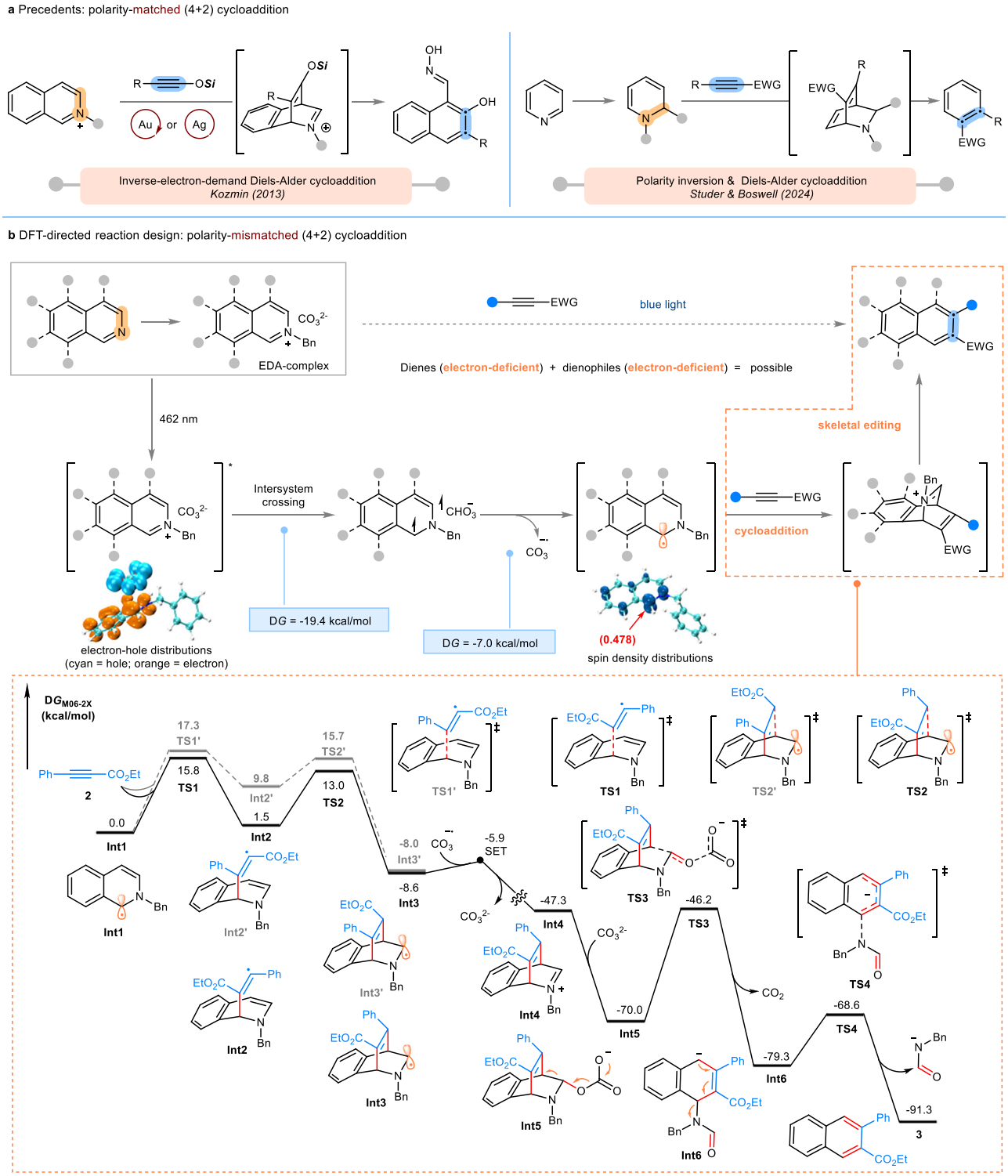
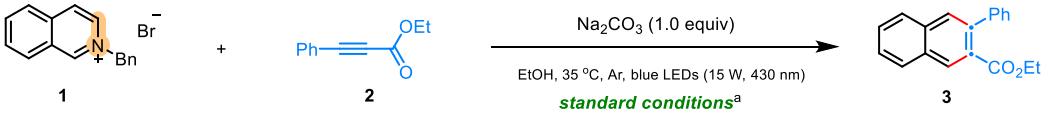


Fig. 2 | Design fundamentals and proof-of-concept studies. a Previous reports for azaarene-to-arene conversion via polarity-matched cycloaddition process. **b** Our synthetic design: DFT calculations-directed photoredox radical chemistry to solve the mismatched polarity hurdle.

functional theory (DFT) method. Based on the screening studies on a series of bases through the UV/vis absorption spectroscopy and Stern-Volmer experiments, the isoquinolinium carbonate salt is demonstrated to be the effective photoactive complex (for details, see Supplementary Figs. S7–S14 in Supplementary Information). The TD-DFT calculations reveal this complex can be excited by irradiation at 462 nm. The electron-hole distributions in the first excited state (S1) clearly indicate charge transfer from the carbonate to the isoquinolinium through π-π interactions. Then the intersystem crossing process yields a triplet structure, releasing 19.4 kcal/mol of energy. The subsequent separation of the isoquinoline radical and carbonic radical anion (CO_3·) liberates 7.0 kcal/mol of heat, mainly due to the effect of entropy increase. The spin density distributions in the isoquinoline radical show the largest population of the spin at the C(1)-atom. The reduced isoquinoline radical becomes electronically rich by the absorption of one electron, enabling cycloaddition with an

https://doi.org/10.1038/s41467-026-68969-1

Table 1 | Optimization of reaction conditions[a]



Entry	Changes from the standard conditions	Yield of 3[b]
1	None	75%
2	4.0 mmol scale	62%
3	In DMSO	64%
4	NEt_3, DABCO or DBU as the base in DMSO	47%, 38%, 38%
5	In THF, DMF, CH_3CN or DCE	6%, 57%, 45%, 30%
6	Isoquinolinium chloride was used	53%
7	Other LEDs sources (340 nm, 390 nm, 525–530 nm)	22%, 61%, 21%
8	5 Å MS (100 mg) was added	83% (82%, 83%, 84%)[c]
Control experiments		
9	No light or in air	N.D.
10	No Na_2CO_3	16%
11	With TEMPO (2.0 equiv.) or BHT (2.0 equiv.)	N.D.
12	With anthracene (5.0 equiv.)	62%
13	With phenanthrene (5.0 equiv.)	63%
14	With pyridazine (1.0 equiv.)	64%
15	With styrene (1.0 equiv.)	54%
16	With 2,5-dimethylhexa-2,4-diene (1.0 equiv.)	66%

N.D. Not Detected.
[a]Standard conditions: **1** (0.4 mmol), **2** (0.2 mmol), Na_2CO_3 (0.2 mmol), EtOH (1.5 mL), argon, blue LEDs (430 nm, 15 W), 35 °C for 36 h.
[b]Isolated yields obtained by column chromatography.
[c]Repeated experiments.

electron-deficient alkyne through successive radical additions via transition states **TS1** and **TS2**. As a result, (4 + 2) cycloaddition is accomplished, yielding the radical intermediate **Int3**. Regarding the regioselectivity, the computational results reveal higher energies for all corresponding isomers (**TS1', TS2', Int2'** and **Int3'**) involved in the cycloaddition which is initiated by the isoquinoline radical adding to C_β of the ethyl phenylpropiolate. Subsequently, the single electron transfer (SET) process occurs between intermediate **Int3** and the carbonic radical anion (CO_3·-), affording the iminium cation intermediate **Int4**. Then the given CO_3^{2-} is added back to **Int4**, yielding a much more stable intermediate **Int5**. The cascade SET and nucleophilic addition facilitates continuous energy release by totally 61.4 kcal/mol. Then the bridged structure is disrupted through the C−C bond cleavage via transition state **TS3**, with CO_2 being released concurrently. The activation energy for this step is 23.8 kcal/mol, a reasonable value for the experimental conditions. Finally, the rearomatization proceeding via **TS4** promotes release of the naphthalene product with simultaneous elimination of a N-benzylformamide anion. It is noteworthy that the N-benzylformamide was detected via GC-MS analysis (Supplementary Fig. S5 in supplementary information), offering experimental support for the rationality of the proposed mechanism. Therefore, the DFT calculations indicated that our photoredox radical strategy could be feasible. Although seemingly simple, unfavorable (4 + 2) cycloaddition between the phenyl rings in the isoquinoline core and alkynes should be avoided[49]. Moreover, all steps should be synchronized in a single reaction, genuinely enabling the direct late-stage functionalization of drugs.

To test the feasibility of our mechanistic hypothesis, we began our investigation with isoquinolinium bromide **1** and ethyl 3-phenylpropiolate **2** as model substrates (Table 1). This reaction proceeded successfully under blue-light irradiation (430 nm, 15 W) in EtOH with Na_2CO_3 as the base, and the desired editing product **3** was obtained in 75% yield after 36 h (entry 1). Scaling the reaction up to 4.0 mmol delivered the desired product **3** in 62% yield (entry 2). Performing the reaction in DMSO resulted in a slightly lower yield (64%, entry 3). Replacing Na_2CO_3 with organic bases, such as NEt_3, DABCO and DBU, gave inferior results (entry 4). An evaluation of solvents indicated that EtOH was optimal (entries 1 vs. 5). Isoquinolinium chloride was also amenable, albeit with lower efficiency (53%, entry 6). The reaction remained active under the irradiation with wavelengths ranging from 340 to 530 nm, with 430 nm emerging as optimal (entries 1 vs. 7). Addition of 5 Å molecular sieves was beneficial to yield (entry 8). The experiments were repeated three times, affording **3** in virtually identical yield each time (entry 8). Complete inhibition was observed when performing the reaction in the dark or in air (entry 9). The removal of Na_2CO_3 resulted in a dramatic decrease in yield, highlighting the crucial role of the base (entry 10). The addition of radical scavengers, such as TEMPO or BHT, to the reaction system did not afford the desired product (entry 11), and adducts between isoquinolinium and TEMPO or BHT were detected by HRMS analysis, confirming the radical nature of the reaction (for details, see supplementary information). Adding anthracene, phenanthrene, pyridazine, styrene or 2,5-dimethyl-2,4-hexadiene to the reaction system had no obvious inhibitory effect on the yields (entries 12-16), thus ruling out an energy-transfer process.

We performed a series of control experiments to further explore the mechanism of this polarity-mismatched skeletal editing strategy. UV−Vis absorption analysis showed that significant bathochromic shift was observed when mixing **1** with Cs_2CO_3 and the absorption extends into visible light region, confirming that isoquinolinium-CO_3^{2-} is the

https://doi.org/10.1038/s41467-026-68969-1

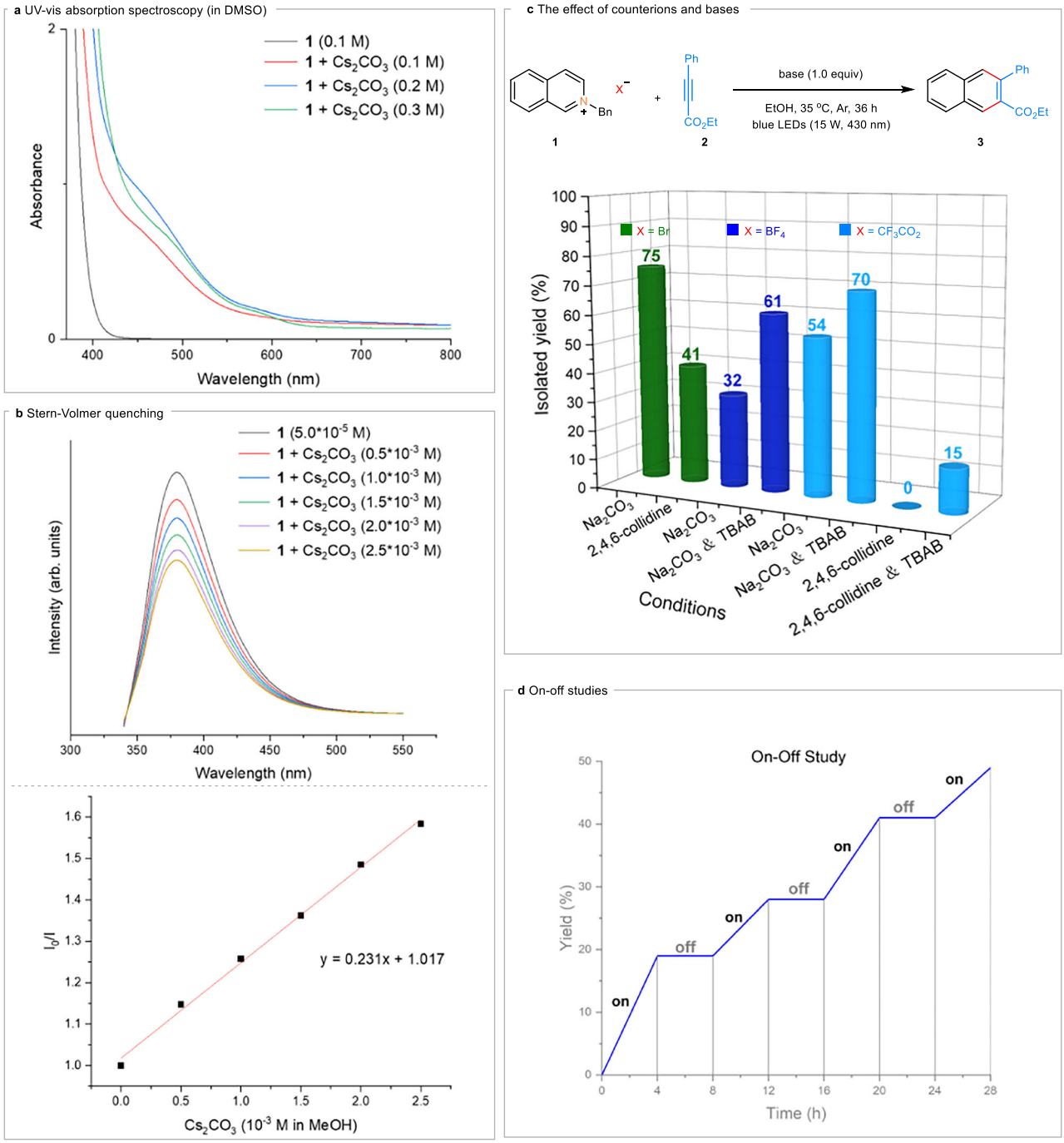


Fig. 3 | Mechanistic investigations. a UV–Vis absorption spectroscope. **b** Stern-Volmer quenching experiments to determine the interaction between **1** and CO_3^{2-}. **c** Control experiments to evaluation the effect of the counterions and the bases. **d** "Light-on/off" experiments.

light-active species (Fig. 3a). A series of Stern-Volmer quenching experiments indicated that isoquinolinium bromide **1** is efficiently quenched in a manner linearly correlated with the concentration of carbonate anion, supporting the formation of an EDA complex from isoquinolinium and carbonate anion (Fig. 3b). In the reaction system, both the bromine anion and the CO_3^{2-} can serve as the reductant to transfer one electron to the isoquinolinium core. To clarify their roles, we performed some control experiments (Fig. 3c). Replacing Na_2CO_3 with 2,4,6-collidine, a base with poor reducing capacity, resulted in a decrease in yield (41% vs. 75%). Similarly, reduced yields were observed when changing the bromine anion with a non-redox active anion, such as BF_4^- and $CF_3CO_2^-$ (32% vs. 75%, and 54% vs. 75%). However, addition of TBAB to the reaction mixture offered a substantial improvement in yield. Not surprisingly, the reaction was completely suppressed when the counterion was $CF_3CO_2^-$ and the base was 2,4,6-collidine, while a 15% yield was obtained upon adding TBAB to the reaction system. These results clearly confirm that both the bromine anion and Na_2CO_3 behave as reducing agents to synergistically promote the skeletal-editing reaction. The light-on/off experiments indicated that consecutive irradiation is a prerequisite for product formation (Fig. 3D).

Reaction scope

With the optimized conditions in hand, the substrate scope of this photoinduced polarity-mismatched skeletal-editing strategy was

https://doi.org/10.1038/s41467-026-68969-1

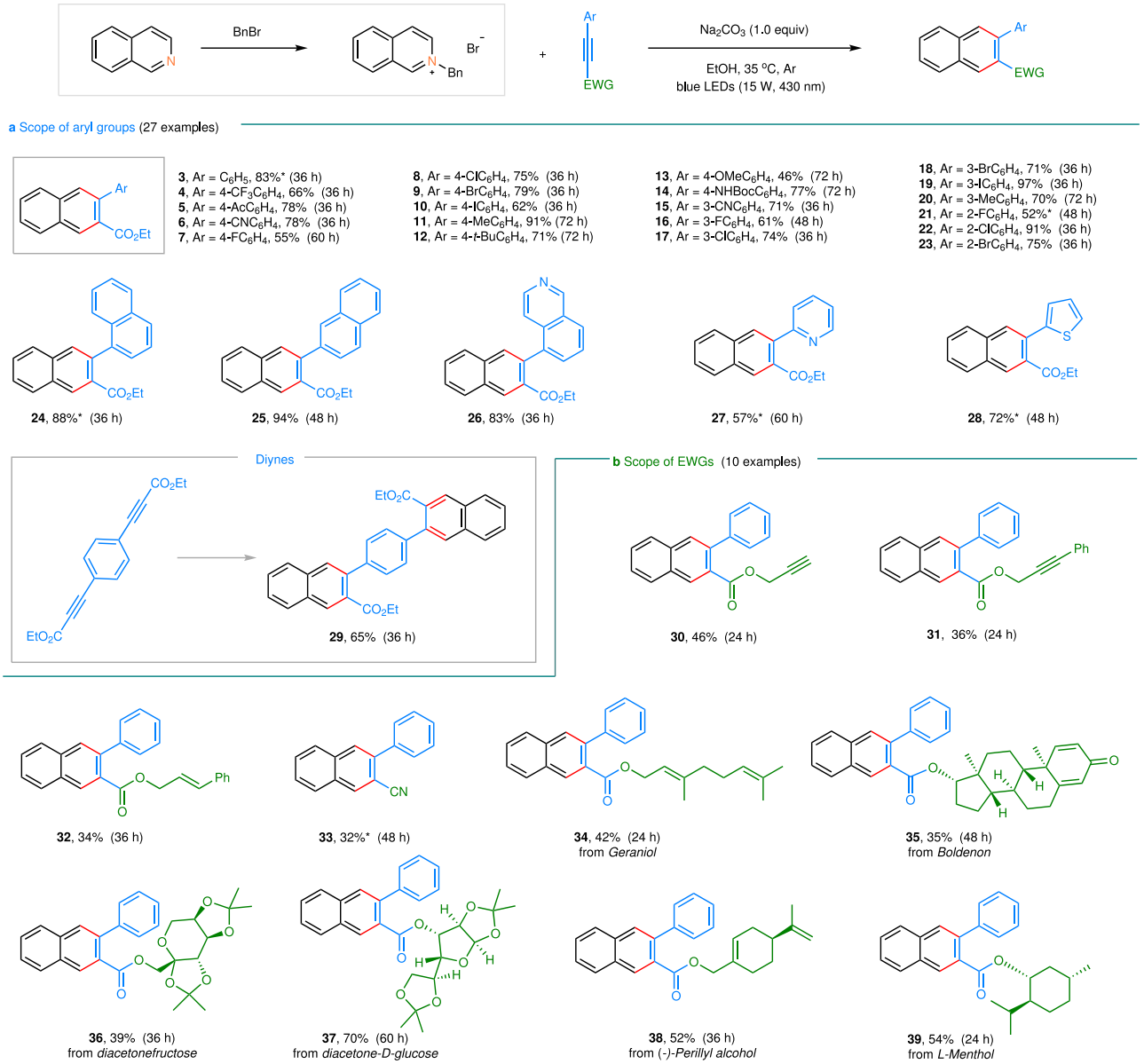


Fig. 4 | Substrate compatibility toward various alkynes. a Scope of aryl groups. **b** Sope of EWGs. Reaction conditions: **1** (0.4 mmol), alkynes (0.2 mmol), Na_2CO_3 (0.2 mmol), EtOH (1.5 mL), argon, blue LEDs (430 nm, 15 W), 35 °C. Asterisk indicates 100 mg of 5 Å molecular sieves added. Isolated yields obtained by silica gel column chromatography.

explored. Initially, we investigated the effect of substituents on the aromatic rings of alkynes. As shown in Fig. 4a, a wide range of substituents at varied positions and with different electronic characters were found to be compatible in this transformation, enabling the synthesis of **4**–**23** in 46–97% yields. Among them, the iodo substituent remained untouched under visible-light irradiation (**10** and **19**). The phenyl substituent could be extended to fused aromatic rings (**24** and **25**) and heteroaromatic rings (**26, 27**, and **28**). A di-alkynoate was also a competent substrate with the two C-C triple bonds participating in the reaction successfully to construct a more complex molecule (**29**), which have been difficult to access by conventional methods. In examining the scope of the electron-withdrawing groups on the alkynes (Fig. 4b), we found that the additional unsaturated bonds on the ester groups did not interfere with the skeletal-editing processes, leaving these reactive functional groups untouched (**30, 31, 32**, and **34**). Furthermore, a cyano group was also tolerant (**33**). The broad compatibility of this method prompted us to investigate its application to complex alkynoates with bioactive natural products and drugs, and the results indicated that they show good reactivity with excellent functional group tolerance and complete stereochemical retention (**34**–**39**).

Subsequently, synthetic tolerance toward a wide range of isoquinolinium salts was studied (Fig. 5a). In general, easily accessible isoquinolinium salts, irrespective of their substitution positions and electronic natures, displayed good reactivity and successfully participated in this reaction, providing an efficient entry to otherwise difficult-to-access multi-substituted naphthalenes (**40**–**52**). Indole substitution was also well-accommodated (**45** and **51**). For a 5-methoxy substituted isoquinolinium salt, the reaction occurred regioselectively at the azaheterocycle rather than the benzene ring, regardless of the steric repulsion between the methoxy group and the incoming phenyl group during the cycloaddition step, to produce **52** in 58% yield. A 4-cyano substituted isoquinolinium was also applicable, but with distinctly site-selective CN deletion (**53**) in which the C1 carbon atom was

https://doi.org/10.1038/s41467-026-68969-1

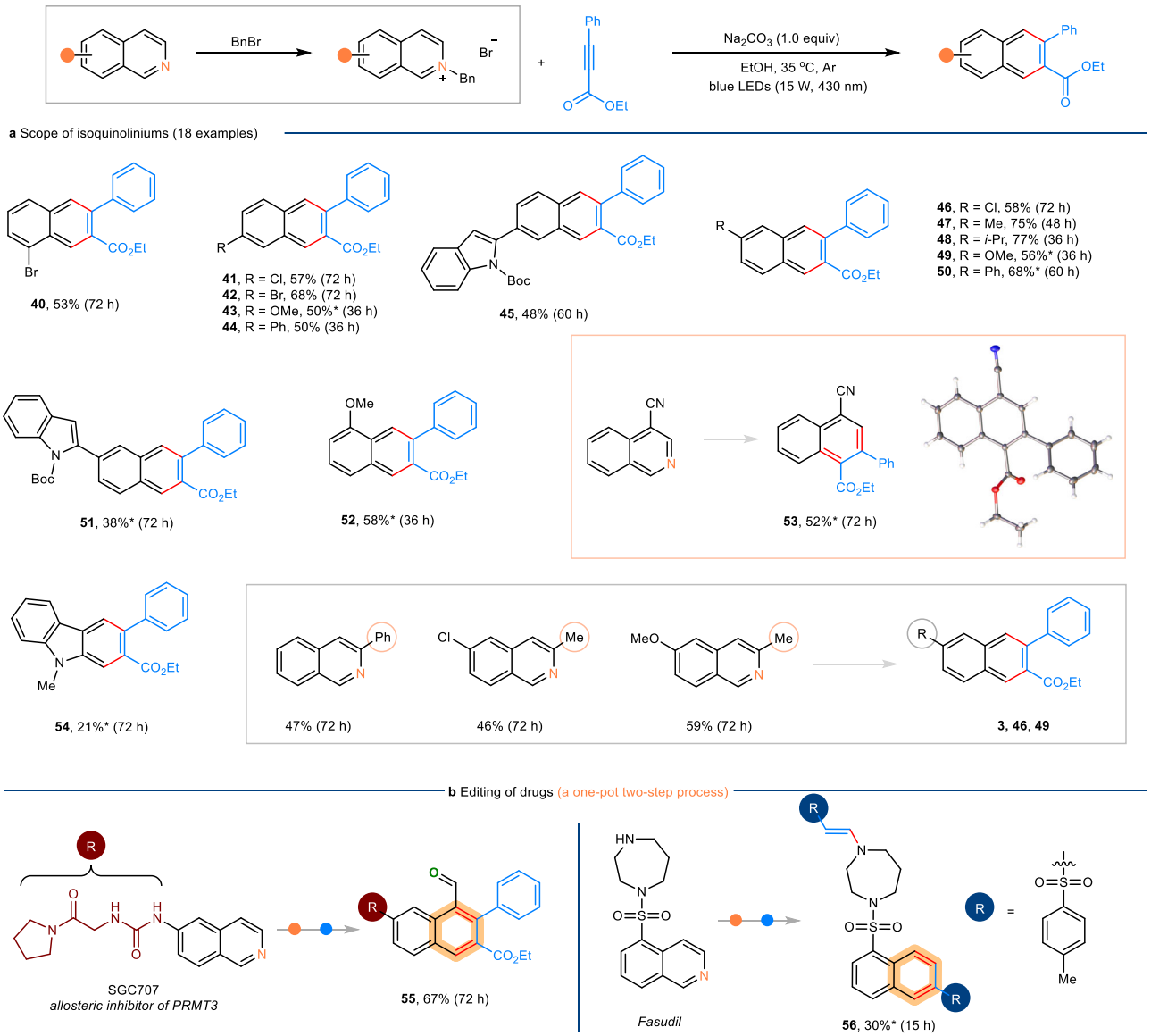


Fig. 5 | Substrate scope with respect to various isoquinoliniums. a Scope of isoquinoliniums. **b** Editing of drugs. Reaction conditions: isoquinoliniums (0.4 mmol), alkynes (0.2 mmol), Na_2CO_3 (0.2 mmol), EtOH (1.5 mL), argon, blue LEDs (430 nm, 15 W), 35 °C. Asterisk indicates 100 mg of 5 Å molecular sieves added. Isolated yields obtained by silica gel column chromatography.

cut off. Norharman, a neuroactive β-carboline alkaloid natural product[50], was directly transformed into the synthetically useful 9H-carbazole (**54**) through a simple CN-to-CC swap. A broad scope of substituents on the excised C3 carbon atom was also observed. Isoquinoliniums bearing sterically demanding phenyl and methyl groups could all be used (**3, 46**, and **49**).

To further underscore the applicability of this approach, we demonstrated its capacity for late-stage functionalization of complex medicinal molecules (Fig. 5b). SGC707 is a potent, selective and cell-active PRMT3 allosteric inhibitor[51]. Using our method facilitated rapid conversion to its naphthalene analog (**55**). Fasudil, a clinical drug for the treatment of cerebral vasospasm[52], was also a good candidate to test the capacity of our method, smoothly affording **56** in 30% yield. These investigations clearly showcase the potential application of this CN-to-CC transmutation strategy, in which a single operation from readily available materials could provide a robust entry to products that are otherwise difficult to accessible, in drug discovery and development.

Synthetic applications

The ester groups in our products not only provide a target-binding site, they also offer valuable transformable functionality, undergoing various chemical conversions. By harnessing their rich reactivity, we prepared a lot of synthetically valuable PAHs and ligands (Fig. 6a). For instance, **3** could undergo a Friedel-Crafts acylation reaction with the aid of H_2SO_4 to afford useful benzofluorenone **57** in 79% yield. Condensation of the ester in **27** with (S)−2-amino-2-phenylethan-1-ol followed by intramolecular cyclization provided an approach to chiral oxazoline ligand **58**. The ester groups could be effectively transformed into aldehydes through a sequence of DIBAL-H reduction and PCC oxidation. The fruitful reactivity of aldehydes further extended the application of this skeletal-editing strategy. For example, a sequential process comprising a Wittig reaction and photoinduced carbocyclization afforded tetraphene **59**. Moreover, its analogue benzo[j]phenanthridine **60** could be attained by replacing the ylide reagent with hydroxylamine. Condensation with (S)-N-phenylpyrrolidine-2-carboxamide yielded **61** in 98% yield. Ligand **62** could also be efficiently

https://doi.org/10.1038/s41467-026-68969-1

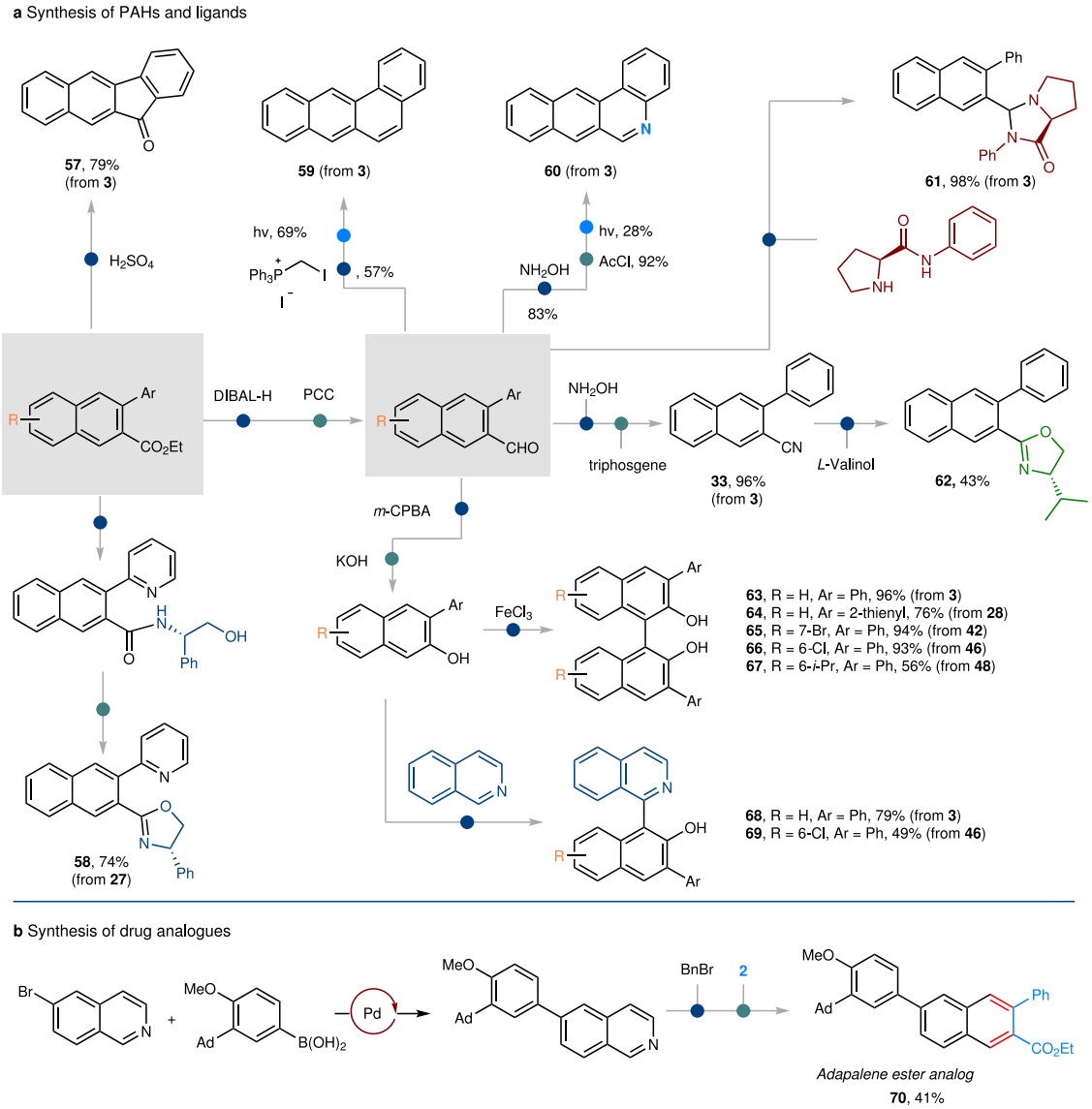


Fig. 6 | Synthetic applications. a Synthetic transformations to access various PAHs and liangd. **b** The use of our skeletal editing strategy to prepare adapalene analog. Isolated yields obtained by silica gel column chromatography.

prepared through a sequence of aldehyde-to-cyano transformation and ensuing condensation with L-valinol. Notably, the resulting 2-naphthaldehydes could undergo a classical Dakin reaction to be converted into synthetically useful 2-naphthols, which underwent self-coupling or cross-coupling with isoquinolines to prepare BINOLs (**63**–**67**) and QUINOLs (**68** and **69**), respectively. In view of the synthetic capacity of this method to construct various differently substituted naphthols, our approach can largely enrich the structures of resulting BINOLs and QUINOLs[53]. The synthetic utility of this protocol was further explored to prepare an adapalene analog. As shown in Fig. 6b, the isoquinoline precursor could be easily synthesized via a Pd-catalyzed Suzuki coupling from commercially available materials. Then, by employing our skeletal editing strategy, the desired adapalene analogue **70** was afforded.

Discussion

The common-sense paradigm that electron-deficient isoquinolines, without cumbersome activation, will not serve as efficient dienes to undergo (4 + 2) cycloaddition with electron-deficient dienophiles may have been leading chemists to ignore important reactions. We have herein developed a photoinduced photosensitizer-free skeletal-editing strategy to transform easily accessible isoquinolines into synthetically challenging naphthalene derivatives. Directed by DFT calculations, the (4 + 2) cycloaddition between the two polarity-mismatched species was accomplished successfully. The pivotal factor to this success was utilizing the isoquinolinium carbonate as an EDA complex to harness photonic energy and achieve polarity inversion for the isoquinolinium cation. This strategy featured simple conditions, wide applications in late-stage functionalization, and a robust synthetic capacity to access valuable PAHs, various ligands and drug analogues. We believe that this study will have an important impact on developing more skeletal-editing strategies to shorten drug-discovery campaigns.

Methods

General procedure for the photoinduced skeletal editing of isoquinoliniums into naphthalenes

To an oven-dried 10 mL vial sealed with rubber septa charged with a magnetic stir bar was added isoquinolinium salts (0.40 mmol, 2.0 equiv.), alkynes (0.20 mmol, 1.0 equiv.) and Na_2CO_3 (0.20 mmol, 1.0 equiv.) at room temperature. Then, EtOH (1.5 mL) was added. Then, the reaction mixture was degasified using argon for 15 min under constant purging and monitoring. The reaction mixture was stirred at 35 °C

under irradiation at 430 nm LEDs (15 W) for the specified time. After completion (monitored by TLC), the crude mixture was concentrated under reduced pressure, then purified using silica gel column chromatography (silica gel 200–300 mesh size, using petroleum ether/ethyl acetate as eluent). (Note: for the formation of products **21, 24, 27, 28, 33, 43, 49**–**54** and **56**, 100 mg of 5 Å MS were added.).

Experimental procedures

Full details on all experimental procedures can be found in the Supplementary Information.

Data availability

The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers CCDC 2330390 (**42**), CCDC 2380827 (**53**), CCDC 2491967 (**72**), CCDC 2491967 (**73'**) and CCDC 2491971 (**75**). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. The X-ray crystallographic coordinates for structures reported in this study are provided in the Supplementary Data 1 file. All other data supporting the findings of this study, including additional optimization, experimental procedures, compound characterization and mechanistic studies, are available within the paper and its Supplementary Information files. Data supporting the findings of this study are also available from the corresponding authors upon request. The coordinates of the optimized structures in this study are provided in the Source Data file. Source data are provided with this paper.

References

1. Blakemore, D. C. et al. Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.* **10**, 383–394 (2018).
2. Campos, K. R. et al. The importance of synthetic chemistry in the pharmaceutical industry. *Science* **363**, eaat0805 (2019).
3. Ma, C.-H., Lindsley, C. W., Chang, J.-B. & Yu, B. Rational molecular editing: a new paradigm in drug discovery. *J. Med. Chem.* **67**, 11459–11466 (2024).
4. Jurczyk, J. et al. Single-atom logic for heterocycle editing. *Nat. Synth.* **1**, 352–364 (2022).
5. Joynson, B. W. & Ball, L. T. Skeletal editing: interconversion of arenes and heteroarenes. *Helv. Chim. Acta* **106**, e202200182 (2023).
6. Xu, P.-W. & Studer, A. Skeletal editing through cycloaddition and subsequent cycloreversion reactions. *Acc. Chem. Res.* **58**, 647–658 (2025).
7. Liu, Z.-H., Zhang, X.-L. K., Sivaguru, P. & Bi, X.-H. Triftosylhydrazone in single-atom skeletal editing. *Acc. Chem. Res.* **58**, 130–149 (2025).
8. Lu, H., Chang, J. & Wei, H. Transition metal-catalyzed nitrogen atom insertion into carbocycles. *Acc. Chem. Res.* **58**, 933–946 (2025).
9. Ding, L.-L., Fan, Y. & Lu, H.-J. Skeletal editing based on nitrogen-atom manipulation. *Chem. Soc. Rev.* **54**, 8145–8169 (2025).
10. Wang, H.-M. et al. Dearomative ring expansion of thiophenes by bicyclobutane insertion. *Science* **381**, 75–81 (2023).
11. Reisenbauer, J. C., Green, O., Franchino, A., Finkelstein, P. & Morandi, B. Late-stage diversification of indole skeletons through nitrogen atom insertion. *Science* **377**, 1104–1109 (2022).
12. Lyu, H., Kevlishvili, I., Yu, X., Liu, P. & Dong, G.-B. Boron insertion into alkyl ether bonds via zinc/nickel tandem catalysis. *Science* **372**, 175–182 (2021).
13. Liu, S.-P. et al. Tunable molecular editing of indoles with fluoroalkyl carbenes. *Nat. Chem.* **16**, 988–997 (2024).
14. Zhang, X.-L. et al. Asymmetric dearomative single-atom skeletal editing of indoles and pyrroles. *Nat. Chem.* **17**, 215–225 (2025).
15. Wu, F.-P. et al. Ring-expansion of indene by photoredox-enabled functionalized carbon-atom insertion. *Nat. Catal.* **7**, 242–251 (2024).
16. Wu, L.-C. et al. Diversified ring expansion of saturated cyclic amines enabled by azlactone insertion. *Nat. Chem.* **16**, 1951–1959 (2024).
17. Wang, J.-J., Lu, H., He, Y., Jing, C.-X. & Wei, H. Cobalt-catalyzed nitrogen atom insertion in arylcycloalkenes. *J. Am. Chem. Soc.* **144**, 22433–22439 (2022).
18. Hyland, E. E., Kelly, P. Q., McKillop, A. M., Dherange, B. D. & Levin, M. D. Unified access to pyrimidines and quinazolines enable by N-N cleaving carbon atom inserion. *J. Am. Chem. Soc.* **144**, 19258–19264 (2022).
19. Dherange, B. D., Kelly, P. Q., Liles, J. P., Sigman, M. S. & Levin, M. D. Carbon atom insertion into pyrroles and indoles promoted by chlorodiazirines. *J. Am. Chem. Soc.* **143**, 11337–11344 (2021).
20. Schmitt, H. L. et al. Regiodivergent ring-expansion of oxindoles to quinolinones. *J. Am. Chem. Soc.* **146**, 4301–4308 (2024).
21. Joynson, B. W., Cumming, G. R. & Ball, L. T. Photochemically mediated ring expansion of indoles and pyrroles with chlorodiazirines: synthetic methodology and thermal hazard assessment. *Angew. Chem. Int. Ed.* **62**, e202305081 (2023).
22. Boudry, E., Bourdreux, F., Marrot, J., Moreau, X. & Ghiazza, C. Dearomatization of pyridines: photochemical skeletal enlargement for the synthesis of 1,2-diazepines. *J. Am. Chem. Soc.* **146**, 2845–2854 (2024).
23. Uhlenbruck, B. J. H., Josephitis, C. M., Lescure, L., Paton, R. S. & McNally, A. A deconstruction-reconstruction strategy for pyrimidine diversification. *Nature* **631**, 87–93 (2024).
24. Woo, J. et al. Scaffold hopping by net photochemical carbon deletion of azaarenes. *Science* **376**, 527–532 (2022).
25. Jurczyk, J. et al. Photomediated ring contraction of saturated heterocycles. *Science* **373**, 1004–1012 (2021).
26. Peng, Q.-P. et al. Photochemical phosphorus-enabled scaffold remodeling of carboxylic acids. *Science* **385**, 1471–1477 (2024).
27. Luo, J.-J., Zhou, Q.-Y., Xu, Z., Houk, K. N. & Zheng, K. Photochemical skeletal editing of pyridines to bicyclic pyrazolines and pyrazoles. *J. Am. Chem. Soc.* **146**, 21389–21400 (2024).
28. Bartholomew, G. L., Carpaneto, F. & Sarpong, R. Skeletal editing of pyrimidines to pyrazoles by formal carbon deletion. *J. Am. Chem. Soc.* **144**, 22309–22315 (2022).
29. Roure, B. et al. Photochemical permutation of thiazoles, isothiazoles and other azoles. *Nature* **637**, 860–868 (2025).
30. Kim, D. et al. Photocatalytic furan-to-pyrrole conversion. *Science* **386**, 99–105 (2024).
31. Pearson, T. J. et al. Aromatic nitrogen scanning by *ipso*-selective nitrene internalization. *Science* **381**, 1474–1479 (2023).
32. Woo, J., Stein, C., Christian, A. H. & Levin, M. D. Carbon-to-nitrogen single-atom transmutation of azaarenes. *Nature* **623**, 77–82 (2023).
33. Zhu, T.-T., Cui, X.-H., Ma, W.-J., Qi, X.-J. & Wei, H. Synthesis of naphthalene derivatives via nitrogen-to-carbon transmutation of isoquinolines. *Sci. Adv.* **11**, eads5928 (2025).
34. Wang, T.-Q. et al. Skeletal editing of pyridine and quinoline *N*-oxides through nitrogen to carbon single atom swap. *CCS Chem* **7**, 392–402 (2025).
35. Conboy, A. & Greaney, M. F. Synthesis of benzenes from pyridines via N to C switch. *Chem* **10**, 1940–1949 (2024).
36. Wu, F.-P. et al. Nitrogen-to-functionalized carbon atom transmutation of pyridine. *Chem. Sci.* **15**, 15205–15211 (2024).
37. Morofuji, T., Nagai, S., Watanabe, A., Inagawa, K. & Kano, N. Streptocyanine as an activation mode of amine catalysis for the conversion of pyridine rings to benzene rings. *Chem. Sci.* **14**, 485–490 (2023).
38. Liu, C.-J. et al. 5-Cyanopyrimidine derivatives as a novel class of potent, selective and orally active inhibitors of p38α MAP kinase. *J. Med. Chem.* **48**, 6261–6270 (2005).
39. Subbaiah, M. A. N. & Meanwell, N. A. Bioisosteres of the phenyl ring: recent strategic applications in lead optimization and drug design. *J. Med. Chem.* **64**, 14046–14128 (2021).

40. Marshall, C. M., Federice, J. G., Bell, C. N., Cox, P. B. & Njardarson, J. T. An update on the nitrogen heterocycle compositions and properties of U.S. FDA-approved pharmaceuticals (2013–2023). *J. Med. Chem.* **67**, 11622–11655 (2024).
41. Bhosale, S. V. et al. Naphthalene diimides: perspectives and promise. *Chem. Soc. Rev.* **50**, 9845–9998 (2021).
42. Piacentini, P., Bingham, T. W. & Sarlah, D. Dearomative ring expansion of polycyclic arenes. *Angew. Chem. Int. Ed.* **61**, e202208014 (2022).
43. Davis, C. W. et al. Copper-catalyzed dearomative 1,2-hydroamination. *Angew. Chem. Int. Ed.* **63**, e202407281 (2024).
44. Ma, J. J. et al. Direct dearomatization of pyridines via an energy-transfer-catalyzed intramolecular [4+2] cycloaddition. *Chem* **5**, 2854–2864 (2019).
45. Cabrera-Pardo, J. R., Chai, D. I., Liu, S., Mrksich, M. & Kozmin, S. A. Label-assisted mass spectrometry for the acceleration of reaction discovery and optimization. *Nat. Chem.* **5**, 423–427 (2013).
46. Cabrera-Pardo, J. R., Chai, D. I., Liu, S. & Kozmin, S. A. Silver-promoted benzannulation of siloxyalkynes with pyridinium and isoquinolinium salts. *Adv. Synth. Catal.* **355**, 2495–2498 (2013).
47. Cheng, Q. et al. Skeletal editing of pyridines through atom-pair swap form CN to CC. *Nat. Chem.* **16**, 741–748 (2024).
48. Boswell, B. R., Zhao, Z.-S., Gonciarz, R. L. & Pandya, K. M. Regioselective pyridine to benzene edit inspired by water-displacement. *J. Am. Chem. Soc.* **146**, 19660–19666 (2024).
49. Ma, J.-J. et al. Photochemical intermolecular dearomative cycloaddition of bicyclic azaarenes with alkenes. *Science* **371**, 1338–1345 (2021).
50. Allen, J. R. F. & Holmstedt, B. R. The simple β-carboline alkaloids. *Phytochemistry* **19**, 1573–1582 (1980).
51. Kaniskan, H. Ü et al. A potent, selective and cell-active allosteric inhibitor of protein arginine methyltransferase 3 (PRMT3). *Angew. Chem. Int. Ed.* **54**, 5166–5170 (2015).
52. Feng, Y.-B., LoGrasso, P. V., Defert, O. & Li, R.-S. Rho kinase (ROCK) inhibitors and their therapeutic potential. *J. Med. Chem.* **59**, 2269–2300 (2016).
53. Jiang, P.-Y., Fan, K.-F., Li, S.-Y., Xiang, S.-H. & Tan, B. Metal-free oxidative cross-coupling enabled practical synthesis of atropisomeric QUINOL and its derivatives. *Nat. Commun.* **12**, 2384–2392 (2021).

Acknowledgements

Financial support was provided by the National Natural Science Foundation of China (22471059 and 22101073 for Q.W.) and the Natural Science Foundation of Henan (242300421133 for Q.W.).

Author contributions

Y.L., W.Z. and Q.W. conceived the idea and supervised the whole project. C.Z., J.Z., Y.Q., and Z.G. performed the experiments. Y.L., W.Z. and Q.W. analyzed and interpreted the results. W.Z. and Y.L. conducted DFT calculations. W.Z. and Q.W. prepared the Supplementary Information. Y.L., W.Z. and Q.W. directed the project and wrote the manuscript. All the authors have approved the final version of the manuscript for submission.

Competing interests

The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41467-026-68969-1.

Correspondence and requests for materials should be addressed to Yu Lan, Wenjing Zhang or Qilin Wang.

Peer review information *Nature Communications* thanks the anonymous reviewers for their contribution to the peer review of this work. A peer review file is available.