ORGANIC CHEMISTRY

Scaffold hopping by net photochemical carbon deletion of azaarenes

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Discovery chemists routinely identify purpose-tailored molecules through an iterative structural optimization approach, but the preparation of each successive candidate in a compound series can rarely be conducted in a manner matching their thought process. This is because many of the necessary chemical transformations required to modify compound cores in a straightforward fashion are not applicable in complex contexts. We report a method that addresses one facet of this problem by allowing chemists to hop directly between chemically distinct heteroaromatic scaffolds. Specifically, we show that selective photolysis of quinoline *N*-oxides with 390-nanometer light followed by acid-promoted rearrangement affords *N*-acylindoles while showing broad compatibility with medicinally relevant functionality. Applications to late-stage skeletal modification of compounds of pharmaceutical interest and more complex transformations involving serial single-atom changes are demonstrated.

The maturation of chemical synthesis has given rise to an era in which molecules can be exhaustively optimized to serve specific purposes under exceptional multidimensional constraints, enabling increasingly precise applications of these compounds. The intensity of this enterprise manifests most visibly in medicinal chemistry, where the simultaneous management of efficacy, specificity, absorption, and lifetime is accomplished through meticulous tailoring of promising candidate molecules (*1*, *2*). While these molecular optimizations establish structure-activity relationships by iterative modification of a series of parent compounds, the synthetic practice underlying these campaigns is rarely in line with its philosophical roots. Rather than converting a lead compound to the next candidate in a manner matching their underlying thought process, these campaigns instead largely rely on iterative resynthesis, because the reactions necessary to perform the envisioned direct conversion are often not applicable in complex settings (Fig. 1A) (*3*, *4*). This shortcoming is particularly conspicuous when conducting a "scaffold hop"—a common strategy that leverages computational estimates of three-dimensional molecular similarity (or in silico binding affinity to the target) to predict isofunctional structures with distinct cores (*5*, *6*). The logic of this strategy can be immediately appreciated by comparing members of a given class of pharmaceuticals, for example, the cholesterol-lowering therapeutics pitavastatin and fluvastatin or the anti-inflammatory drugs etoricoxib and celecoxib; this same logic is also clear when comparing compounds in a given development series, such as the dideazafolic acid antecedent to the chemotherapy agent pemetrexed (Fig. 1B) (*7*–*9*). Unfortunately, the execution of a predicted scaffold hop is among the most difficult of possible lead optimization strategies to perform directly. Unlike diversification strategies relying on robust, late-stage coupling reactions that can target some peripheral substructures of a lead molecule for rapid interrogation, molecular cores are far more challenging to examine in a similar fashion because of the often-distinct preparative methods for the relevant (hetero)cyclic frameworks. As such, chemists interested in examining a scaffold hop are typically required to resort instead to an effective reset of their synthetic campaign, beginning from scratch to traverse laterally in chemical space.

Accordingly, a pressing challenge and increasing recent area of focus for modern organic synthesis is the development of transformations that can address the molecular skeleton with precision and enable direct scaffold hops between distinct core substructures within a given class of compounds. Ideally, such transformations would enable control at the level of single-atom precision (Fig. 1C), with more sophisticated changes possible through iterative elementary skeletal modifications (*10*). Notable recent contributions from several groups have been reported in the context of saturated aliphatic heterocycles (*11*–*13*). Although the centrality of aromatic and heteroaromatic scaffolds in medicinal chemistry suggests a clear priority for similar azaarene interconversion strategies, the stability of aromatic systems poses a substantial challenge: The reactive species typically required to breach the core are often not compatible with densely functionalized druglike compounds and rarely promote precise, selective downstream chemistry (*14*–*16*). We report here a transformation that confronts this challenge, enabling a broadly applicable ring contraction of quinoline *N*-oxides and related azaarenes. Subsequent deacylation of the product *N*-acylindole allows this transformation to serve as a net carbon deletion (Fig. 1D).

This advance is built on the classical photochemistry of quinoline *N*-oxides (**1**), whose diverse rearrangement products were meticulously cataloged by Buchardt, Streith, Kaneko, and Albini (Fig. 2A) (*17*–*19*). Although *N*-acylindoles (**2**) and related hydration products have been observed arising from a limited set of substrates, more complex rearrangement products often predominate, including quinolones, 2- and 3-acylindoles (bearing noncleavable acyl groups), and 3-hydroxyquinolines. Product mixtures of these compounds are typically observed, and in many cases, seemingly minute perturbations to the substrate structure result in drastic changes to the product distribution (see figs. S20 to S28 and the associated discussion for a brief summary). Beyond this, the classical mercury (Hg) lamp irradiation conditions are incompatible with many complex quinolines of relevance to medicinal chemistry (an observation we have reproduced—see below). On the basis of prior mechanistic work on these and related photochemical transformations, we suspected that the undesired products were the result of secondary photoprocesses of the intermediate, formally antiaromatic 2,1- and/or 3,1-benzoxazepines (**3**) (*20*, *21*). We hypothesized that these two-photon by-products could be avoided using a milder, narrow-spectrum light source.

Indeed, we have found that the use of 390-nm light-emitting diodes (LEDs) in place of traditional mercury lamps substantially improves this classical photoreaction, turning an academic curiosity into a potential workhorse transformation with broad utility (*22*–*27*). This selective irradiation of quinoline *N*-oxides produces high yields of the corresponding 3,1-benzoxazepine in the photolysate, with subsequent in situ treatment with an acid catalyst promoting isomerization to the *N*-acylindoles in similarly high yield. As detailed below, this enables challenging indole and azaindole syntheses; facilitates late-stage, direct scaffold hopping of medicinal compounds; and serves as a productive springboard for further skeletal modification strategies.

We began our investigation with 2-methylquinoline *N*-oxide (**1a**) (Fig. 2B). Irradiation with a 390-nm LED in toluene at ambient temperature for 5 hours resulted in complete consumption of the quinoline *N*-oxide, affording the corresponding benzoxazepine **3a** in 91% nuclear magnetic resonance (NMR) yield, along with a minor quantity of the deoxygenation product **4a** (15:1 selectivity). Although **3a** was not isolable without substantial decomposition, its conversion could be monitored by LED-NMR, allowing measurement of a quantum

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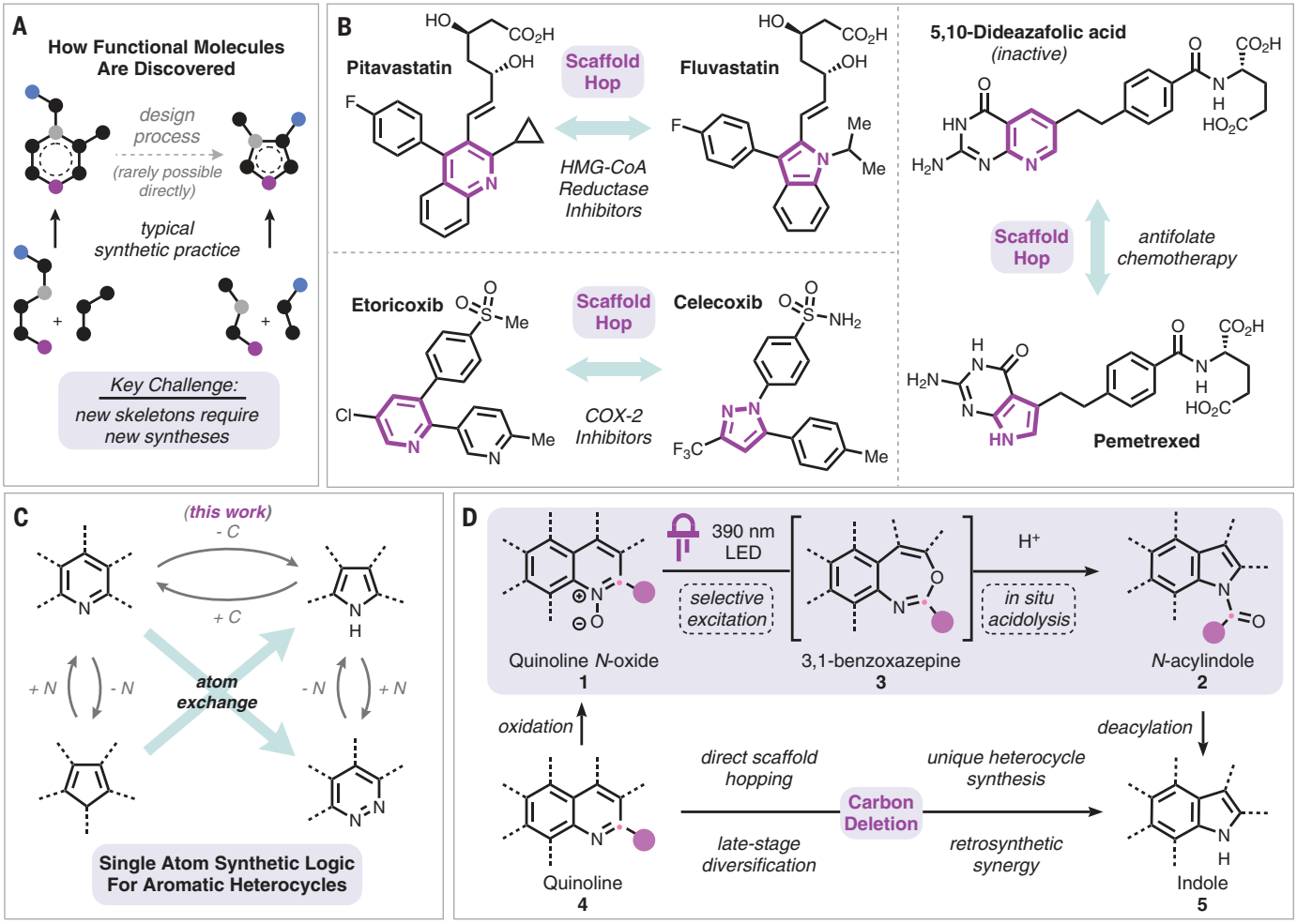

Fig. 1. Introduction to scaffold hopping and single-atom skeletal editing. (**A**) Schematic representation of the disconnect between design and synthesis in molecular optimization. (**B**) Selected examples of scaffold hopping in medicinal chemistry. HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; Me, methyl group; COX-2, cyclooxygenase-2. (**C**) Single-atom skeletal editing for heterocycle interconversion. (**D**) Carbon deletion of azaarenes delineated in this work.

yield, Φ, of 0.096 for conversion of the quinoline *N*-oxide (*28*). In contrast to **3a**, cyano-substituted benzoxazepine **3b** was found to be readily isolable and could similarly be prepared by irradiation with a 390-nm LED in 83% isolated yield. The increased stability of **3b** offered an opportunity to probe our light source hypothesis. As predicted, **3b** was found to be substantially more stable upon further irradiation by the LED than under mercury lamp irradiation (Fig. 2C). The benzoxazepine was returned in near-quantitative recovery after 6 hours in the former case, whereas nearly half of the material degraded to a mixture of products in the same period under the latter conditions. Examination of the absorption spectra of **1b** and **3b** reveals the origin of this drastic light source effect (Fig. 2D). Whereas the quinoline *N*-oxide has a relative absorption maximum, λ_{max}, at 386 nm, the benzoxazepine shows a substantial hypsochromic shift to a λ_{max} of 323 nm, such that the LED accomplishes selective irradiation of the starting material while the mercury lamp promotes photodegradation of the benzoxazepine.

Our interest in the photochemical behavior of quinoline *N*-oxides stemmed not from the benzoxazepine intermediates themselves but rather from the indole products presumed to arise from them. Classical studies had suggested that these indole products were the result of adventitious (or added) water generating acid, which in turn acted on the 3,1-benzoxazepine (*29*). This prompted us to examine the effect of exogenous acid additives. The crude photolysate consisting predominantly of methyl-substituted benzoxazepine **3a** reacted smoothly under the action of trifluoroacetic acid to afford acylindole **2a** in 78% yield relative to **1a**. To determine the mechanism by which the protonated benzoxazepine evolves to product, we conducted an ^{18}O labeling study, which showed substantial but incomplete maintenance of the isotopic label in the hydrolysis process. This result is most consistent with two concurrent pathways for benzoxazepine hydrolysis, although the potential for ^{18}O-water liberated in the *N*-protonation pathway to react further precludes a quantitative analysis of the partitioning between these pathways (Fig. 2E) (*30*).

Although direct photochemistry can often vary as a function of substrate structure, the efficacy and advantage of the 390-nm LED was found to be surprisingly general, both with respect to the substituent on the excised carbon and the residual indole substituents (Fig. 3). A wide range of quinoline *N*-oxides with varying substitution patterns were found to undergo facile photorearrangement to afford the corresponding benzoxazepine, and the subsequent acid-promoted rearrangement was likewise found to be generally applicable. For most substrates, trifluoroacetic acid was effective for this latter operation, although in cases bearing 3-substituents (**1m**, **1ac**, **1x**, and **1ag**) or electron-withdrawing groups (**1b** and **1s**) on the quinoline, the more acidic *para*-toluenesulfonic acid afforded higher yields. This protocol

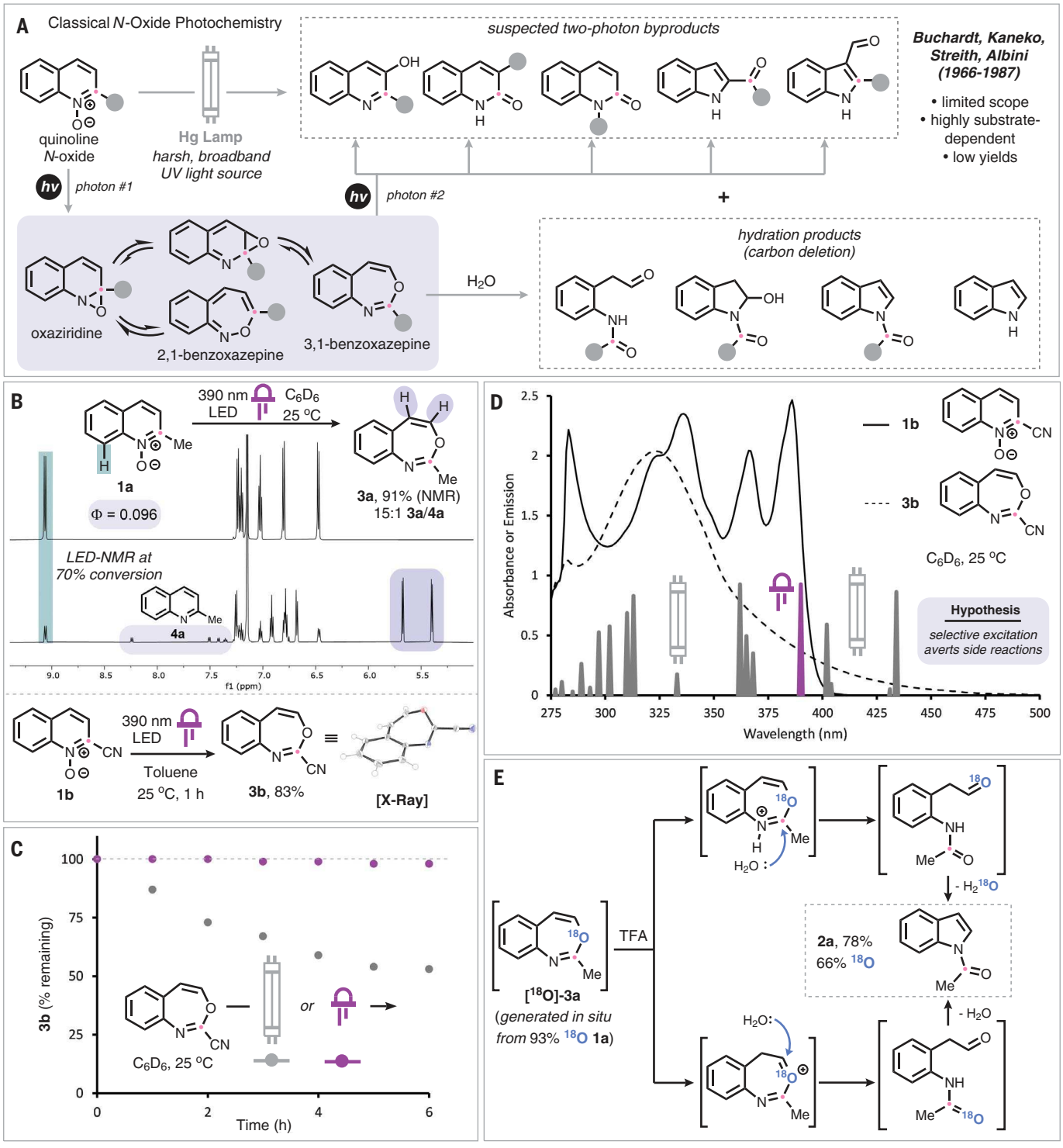

Fig. 2. Mechanistic basis for light source effects in quinoline *N*-oxide photochemistry and mechanism of acid-promoted benzoxazepine rearrangement to indole. (**A**) Summary of classical photochemical rearrangements promoted by broadband mercury lamp irradiation. (**B**) LED-NMR study of 390-nm LED photolysis of **1a** and isolation of 2-cyano-3,1-benzoxazepine (**3b**) from LED photolysate of quinoline *N*-oxide **1b**. ppm, parts per million. (**C**) Photostability study of **3b** under LED and Hg lamp irradiation. (**D**) Ultraviolet–visible absorption spectra of **1b** and **3b** with overlaid relative emission spectra of 390-nm Kessil lamp and 200-W medium-pressure Hg lamp (normalized to an emission intensity of 1 for λ_{max}). (**E**) Labeling study of trifluoroacetic acid (TFA)–promoted rearrangement of **3a**.

was also found to be amenable to a one-pot process, with initial formation of the *N*-oxide induced by hydrogen peroxide in dichloromethane followed by dilution of the crude reaction mixture with toluene (95:5) before irradiation affording the *N*-acylindole in only slightly diminished yields (69%) relative to the two-pot procedure with purified *N*-oxide (78%). As noted above, this transformation was found to be robust to a wide variety of functionality commonly encountered in medicinal chemistry, including other heterocycles (**2d**, **2e**, **2f**,

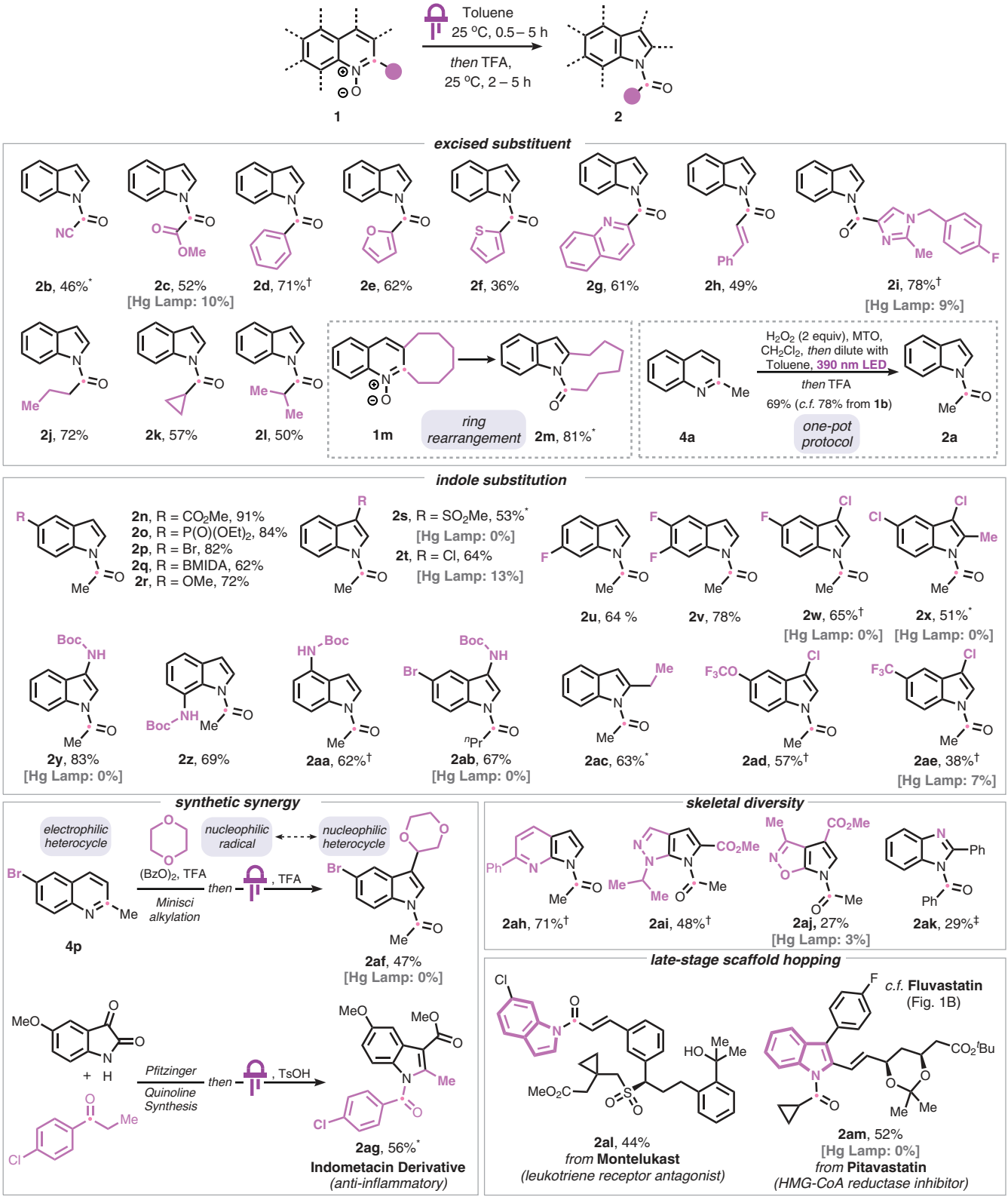

Fig. 3. Scope of the photochemical conversion of azaarene *N*-oxides into acylazoles. Conditions: **1** (0.3 mmol), toluene (0.06 M), 390-nm LED, 0.5 to 5 hours at 25°C, then TFA (0.3 mmol) for 2 to 5 hours at 25°C. Isolated yields are given. The asterisk symbol indicates where acidolysis was conducted with TsOH•H_2O instead of TFA. The single-dagger symbol indicates where acidolysis was conducted at 60°C. The double-dagger symbol indicates where, instead of acidolysis, photolysate was concentrated and refluxed in H_2O/MeOH (1:1). Hg lamp yields measured by proton nuclear magnetic resonance versus an internal standard. Ph, phenyl group; OMe, methoxy group; MTO, methyltrioxorhenium; BMIDA, *N*-methyliminodiacetyl boronate; Boc, butoxycarbonyl; ^{n}Pr, *n*-propyl; TsOH, *para*-toluenesulfonic acid; $(BzO)_2$, benzoyl peroxide; ^{t}Bu, *tert*-butyl.

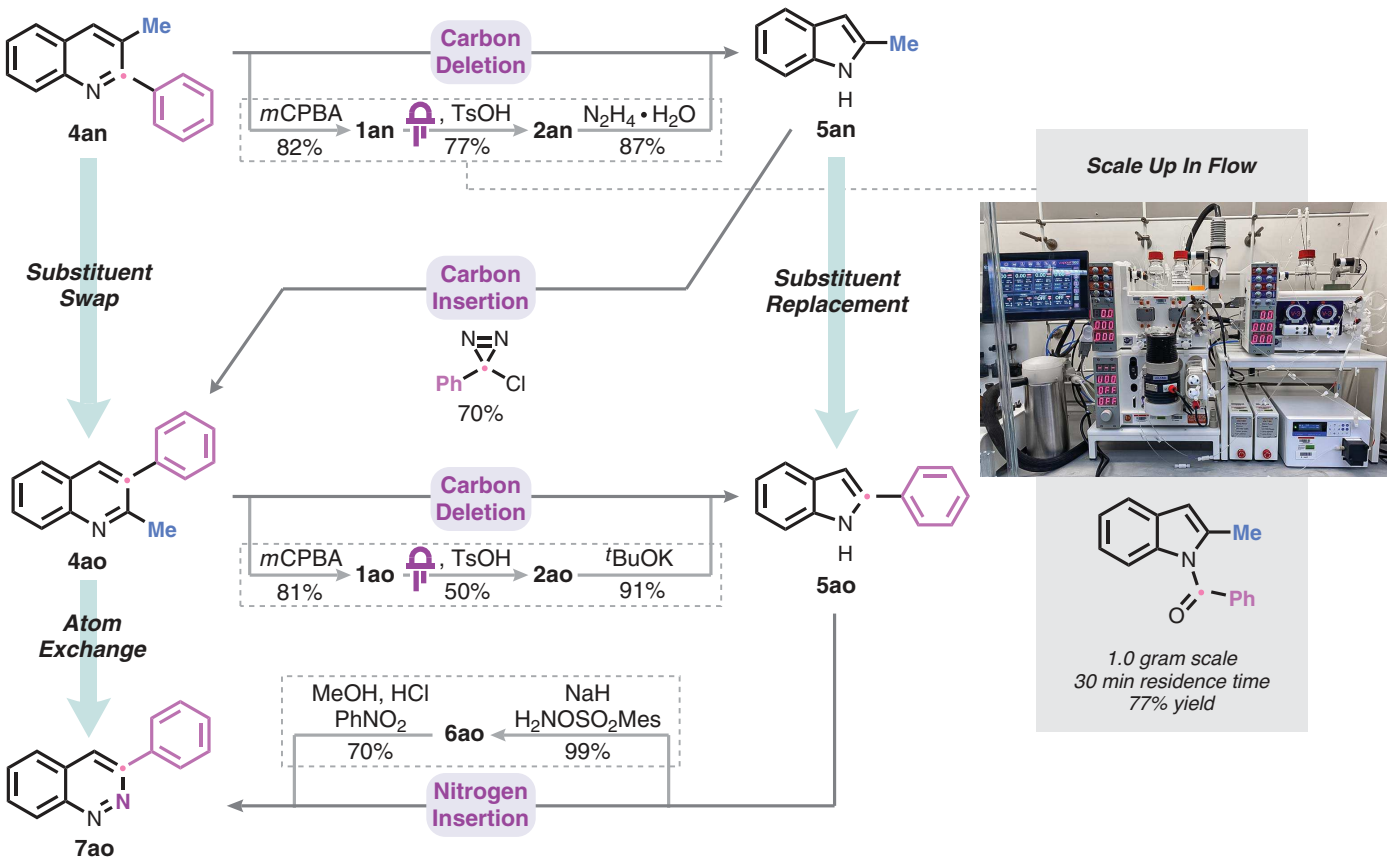

Fig. 4. Carbon deletion as a springboard for more complex scaffold hopping strategies and flow scale-up of photochemical rearrangement. Net substituent swaps of quinolines, substituent replacements of indoles, and C-to-N exchange of quinolines into cinnolines. See supplementary materials for detailed conditions. *m*CPBA, *meta*-chloroperoxybenzoic acid; tBuOK, potassium *tert*-butoxide; MeOH, methanol; HCl, hydrochloric acid; $PhNO_2$, nitrobenzene; NaH, sodium hydride; H_2NOSO_2Mes, *O*-mesitylsulfonyl hydroxylamine.

2g, and **2i**), polyhalogenation (**2v**, **2w**, and **2x**), carbamates (**2y**, **2z**, **2aa**, and **2ab**), phosphonates (**2o**), sulfones (**2s**), and boronic esters (**2q**). Notably, the scope demonstrated here was found to be a direct consequence of the milder light source. Of 12 quinolines examined, five gave detectable indole products at substantially diminished yield (3 to 13%) when a mercury lamp was used for the initial photolysis, with the remaining seven giving completely intractable mixtures. Additionally, complete solubility in toluene was not a requirement, with dissolution over the course of irradiation observed for a number of substrates (e.g., **1s**, **1q**, **1y**, **1af**, and **1aj**). In all cases, full conversion of the starting material was achieved with sufficient irradiation time. The most common by-product observed was deoxygenation of the *N*-oxide to afford the parent azaarene. Limitations of the photolysis were principally related to the 2-substituent (hydrogen, tertiary alkyls, and heteroatom substitution were not tolerated; see supplementary materials for further details). We also note that oxidatively sensitive functionality is not maintained in the initial *N*-oxidation (e.g., sulfides are converted to sulfones).

An interesting consequence of the switch between electron-poor quinoline and electron-rich indole heterocycles is the ability to interface their distinct reactivities and syntheses through carbon deletion. This is exemplified in the first instance by the preparation of indole **2af** through Minisci alkylation of the parent quinoline at the 4-position, resulting in the net 3-alkylation of the final, nucleophilic indole product with an nucleophilic radical—a challenging retrosynthetic strategy to realize via known methods (*31*–*33*). Quinoline **4ag** demonstrates the latter interplay of the two heterocyclic scaffolds, allowing the Pfitzinger quinoline synthesis to serve additionally as an indole synthesis (*34*). The product **2ag** is related to the anti-inflammatory medicine indomethacin (*35*).

Higher polyazaarenes were also found to be productive substrates, enabling the preparation of 7-azaindole, pyrrolopyrazole, pyrroloisoxazole, and benzimidazole scaffolds through net carbon deletion of the parent fused-ring azine. The 5,5-fused systems are highly challenging to prepare by traditional heterocycle syntheses and thus showcase a distinctive advantage of our approach. To further highlight the utility of this method, we demonstrated its capacity to modify complex medicinal compounds. Starting from montelukast (Singulair), a widely prescribed leukotriene inhibitor, the pendant chloroquinoline could be transformed into the corresponding acylindole **2al** (*36*). Finally, the direct scaffold hop from pitavastatin to its indole congener **2am** could be accomplished, creating a link in chemical space to fluvastatin via carbon deletion (*37*).

As noted above, linear combinations of distinct single-atom insertions and deletions offer exciting opportunities to devise more complex skeletal editing transformations. Figure 4 showcases the ways in which carbon deletion can be leveraged as a foundation for such strategies using a simple model system. Starting with quinoline **4an**, carbon deletion affords the indole **5an**, with the photorearrangement scalable up to 1 g in flow. Subsequent application of our previously reported C3-selective carbon insertion reaction gives the isomeric quinoline **4ao**, which has formally had its C2 and C3 substituents swapped relative to the starting **4an** (*38*). This quinoline can again be subjected to carbon deletion to afford indole **5ao**. Here, comparison to its predecessor **5an** reveals the effective replacement of the methyl

substituent with a phenyl. Finally, if indole **5ao** is subjected to nitrogen insertion through a precedented *N*-amination and oxidative aromatization sequence, cinnoline **7ao** can be accessed, now the formal C-to-N exchange product of starting quinoline **4ao** (*39*–*41*).

This work offers a broadly applicable, C2-selective, net carbon deletion of quinolines and related azaarenes through a ring contraction of the corresponding *N*-oxides. Avoiding deleterious overreaction through selective photoexcitation renders classical *N*-oxide photochemistry applicable to medicinal chemistry applications. This work further showcases the potential for direct scaffold hopping enabled by the carbon deletion transform, especially when used in combination with the growing library of single-atom skeletal edits.

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ACKNOWLEDGMENTS

We thank D. Nagib (Ohio State University) and C. Hong (Merck & Co., Inc., Kenilworth, NJ, USA) for helpful discussions. We thank J. Andrews (Hanovia/Colight) for providing spectral output data for the mercury lamp. We also thank A. Filatov, S. Whitmeyer, P. Kelly, and Y.-S. Chen for assistance with SXRD acquisition at beamline 15-ID-B,C,D. **Funding:** M.D.L. thanks the Packard Foundation and National Institutes of Health (R35 GM142768) for funding. X-ray diffraction data reported here were collected at ChemMatCARS Sector 15, which is supported by the NSF under grant NSF/CHE-1834750, and used resources of the Advanced Photon Source, a US DOE Office of Science User Facility operated for the DOE Office of Science by Argonne National Laboratory under contract DE-AC02-06CH11357. **Author contributions:** J.W. and M.D.L. conceived of the work. J.W. conducted synthetic experiments including purification and characterization. J.W., M.D.L., S.A.B., and A.H.C. designed the experiments reported in this work. S.A.B. conducted LED-NMR and quantum yield measurements. J.W., A.H.C., and Y.J. conducted the ^{18}O labeling experiment. A.H.C. and U.F.M. conducted the flow experiments. All authors prepared the manuscript. A.H.C. and M.D.L. directed the research. **Competing interests:** The authors declare no competing interests. **Data and materials availability:** X-ray dataset for compound **3b** is freely available at the Cambridge Crystallographic Data Centre under deposition number 2159035.

SUPPLEMENTARY MATERIALS

science.org/doi/10.1126/science.abo4282
Materials and Methods
Figs. S1 to S49
Tables S1 to S4
NMR Spectra
References (*42*–*99*)

3 February 2022; accepted 25 March 2022
10.1126/science.abo4282

Science

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Science, 376 (6592), • DOI: 10.1126/science.abo4282

Carbon excision

Quinolines and indoles are both very common core motifs in drug molecules. Because they differ by just a single carbon in their ring frameworks, it would be useful to interconvert them during structure-activity relationship studies. However, aromatic stabilization in these compounds makes that process difficult. Woo *et al*. now report that narrow-wavelength irradiation of quinoline *N*-oxides in the near-ultraviolet range followed by acid treatment cleanly excises a ring carbon to produce an indole, avoiding secondary photoproducts that were previously observed using broadband light. —JSY