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Photochemical Skeletal Editing of Pyridines to Bicyclic Pyrazolines and Pyrazoles

Jiajing Luo,[§] Qingyang Zhou,[§] Zhou Xu, K. N. Houk,* and Ke Zheng*

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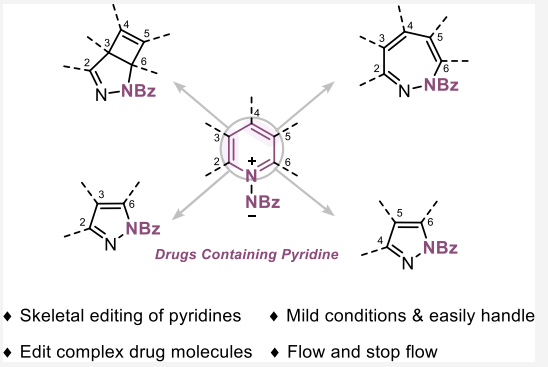
ABSTRACT: We present an efficient one-pot photochemical skeletal editing protocol for the transformation of pyridines into diverse bicyclic pyrazolines and pyrazoles under mild conditions. The method requires no metals, photocatalysts, or additives and allows for the selective removal of specific carbon atoms from pyridines, allowing for unprecedented versatility. Our approach offers a convenient and efficient means for the late-stage modification of complex drug molecules by replacing the core pyridine skeleton. Moreover, we have successfully scaled up this procedure in stop-flow and flow-chemistry systems, showcasing its applicability to intricate transformations such as the Diels−Alder reaction, hydrogenation, [3 + 2] cycloaddition, and Heck reaction. Through control experiments and DFT calculations, we provide insights into the mechanistic underpinnings of this skeletal editing protocol.



INTRODUCTION

In the realm of medicinal chemistry, ongoing advancements in synthetic methodologies are continually reshaping the landscape. One such concept, skeletal editing, facilitates the modification, addition, or removal of molecular components through mild and selective transformations. Skeletal editing involves specific site modifications to a molecule's skeleton through selective insertion, deletion, or exchange of atoms while preserving the core structure.[1−4] This approach is particularly advantageous for late-stage integration in drug discovery, as the ability to fine-tune molecular skeletons can significantly influence a drug's properties and functionality.[5−9] For instance, Avanafil, which features a pyrimidine nucleus, has demonstrated superior relaxant effects on isolated rabbit corpus cavernosum compared to its analogues with pyridine, thiazole, or triazine nuclei (Figure 1A).[7] Other notable examples include the potent covalent inhibitor of KRASG12C (AMG 510) and its analogues, as well as COX-2 inhibitors etoricoxib and celecoxib (Figure 1B,C).[8,9]

Pyridine, the second most common heterocycle found in FDA-approved drugs, plays a prevalent role in pharmaceuticals containing N-heterocycles.[10,11] Beyond its widespread presence in biologically relevant molecules, pyridine also serves essential functions in ligands and functional materials, driving the demand for innovative methods to functionalize pyridine across various disciplines.[12−15] While many approaches to pyridine editing have focused on peripheral C−H functionalization to preserve the core skeleton, direct late-stage scaffold hopping of pyridine remains underexplored.[16−18] Recent advancements by Levin and Sarpong have expanded the boundaries of this field, inspiring further progress.[1]

Pyridine skeletal editing transformations can be categorized into two strategies: ring expansion and ring contraction (Figure 1D). Typically, the nucleophilicity of the nitrogen atom of pyridines is harnessed to prepare cationic pyridinium salts.[19−23] Pyridine expansion via N-functionalized pyridinium salt (imidopyridine ylide) has been widely employed in synthetic methodologies.[24−36] Additionally, ring contractions via carbon deletion under light or electricity have been documented, yielding pyrroles or pyrazolines as exclusive products.[37−43]

Herein, we describe an efficient photochemical skeletal editing protocol for converting the pyridine ring into three distinct new skeletons, including bicyclic pyrazolines, pyrazoles, and 1,2-diazepines under mild conditions. Operating at room temperature without metal catalysts and photocatalysts, this process tolerates numerous functionalities and yields products readily convertible to corresponding high-value heterocyclic compounds in a single step. Notably, selective carbon(3,4 or 4,5) deletion via bicyclic pyrazolines or carbon(2,3 or 5,6) deletion via 1,2-diazepines of pyridine rings generates ring contraction pyrazole products. This one-pot photochemical protocol can be successfully adapted to stop-flow or flow-chemistry systems for large-scale applications. Further applications include late-stage skeletal modification of complex drug

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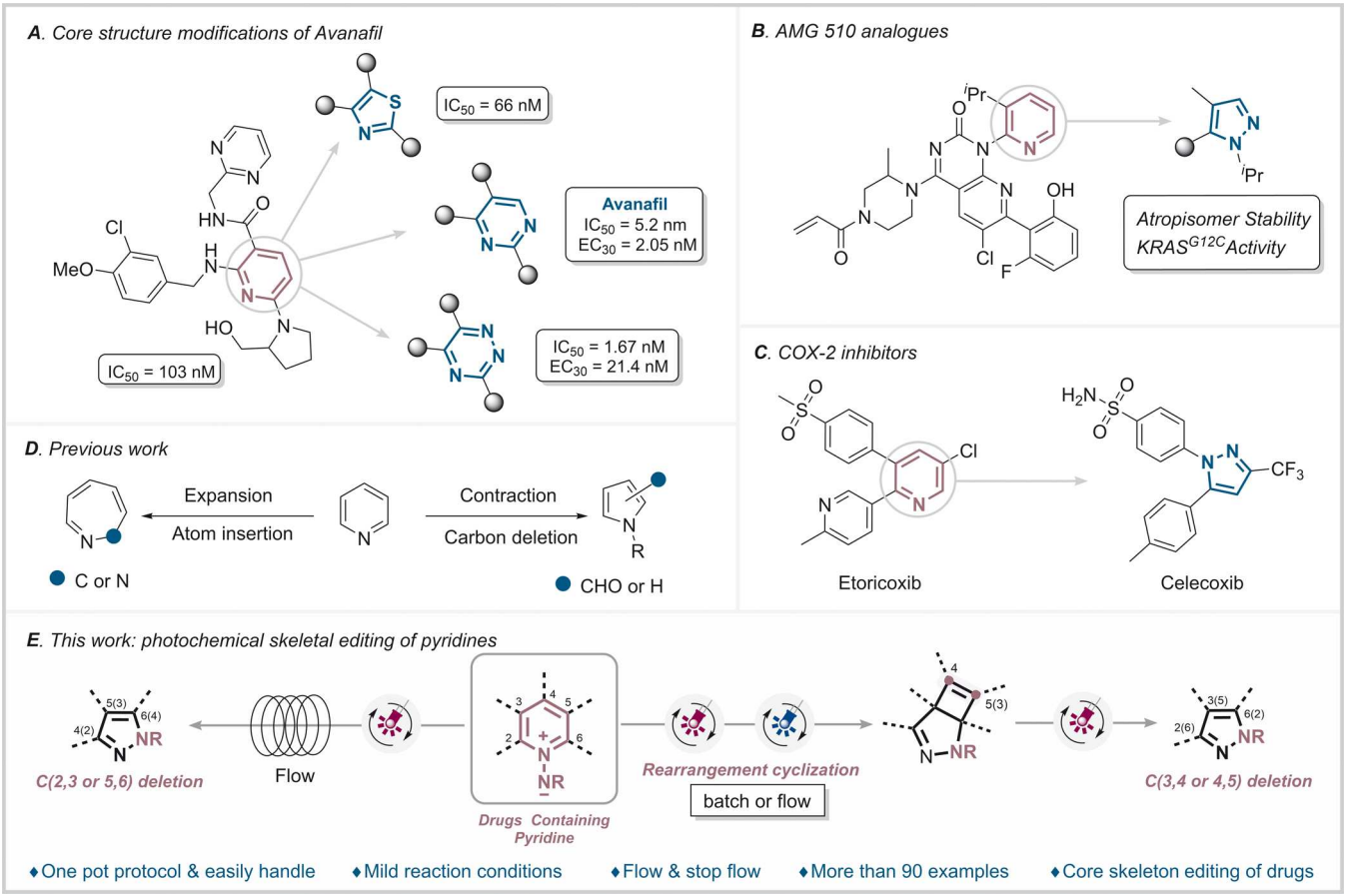


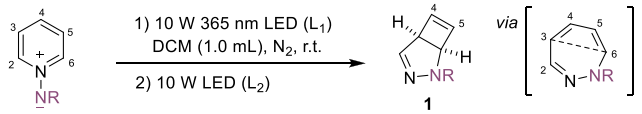
Figure 1. (A) Scaffold hopping of Avanafil. IC_{50} = half maximal effective concentration, and EC_{30} = 30% effective concentration. (B) AMG 510 analogues. (C) Etoricoxib and celecoxib. (D) Previous work. (E) This work: photochemical skeletal editing of pyridines.

compounds and more intricate transformations of skeletal editing products. This method offers a potentially convenient approach for late-stage drug molecule modification.

RESULTS AND DISCUSSION

Previous work has shown that pyridinium salts are unstable under light and will undergo a series of transformations.[24−29] We initiated an investigation into the photochemical skeletal editing protocol using pyridinium salt as a model substrate (Table 1). The cyclization product, bicyclic pyrazoline **1**, was obtained in 20% yield with 69% of the ring expansion product, 1,2-diazepine, as an intermediate when N-Bz pyridinium salt was irradiated under 365 nm light-emitting diodes (LEDs) for 24 h (entry 1). Other pyridinium salts did not yield better results: N-Ts pyridinium salt did not produce the cyclization product, and the $-CO_2$Ph-, $-CO_2{}^t$Bu-, and $-CO_2$Bn-substituted pyridinium salts resulted in lower yields (entries 2−5). After different light sources and reaction times were screened, the best outcome was achieved with 91% yield of the desired cyclization product **1** (entries 6−9). This was accomplished by irradiating with 365 nm light for 4 h, followed by 420 nm light for 72 h in dichloromethane (DCM) under a N_2 atmosphere. Control experiments confirmed that light irradiation was essential, as no cyclization product was detected in the absence of either light source (entries 10−11). Mechanistically, this approach exploits two concurrent photochemical processes. Under 365 nm LEDs, the N-functionalized pyridinium salt undergoes sequential ring expansion via nitrogen insertion, yielding 1,2-diazepines. Subsequently, under lower-energy 420 nm LEDs, excited-state

Table 1. Condition Optimization[a]



Pyridinium salt — **1** *Cyclization* — 1,2-diazepine

entry	R	light (nm) and time (h)				yield (%)[b]
		L_1	T_1	L_2	T_2	
1	Bz	365	12	365	12	20
2	Ts	365	12	365	12	ND
3	$-CO_2$Ph	365	12	365	12	18
4	$-CO_2{}^t$Bu	365	12	365	12	7
5	$-CO_2$Bn	365	12	365	12	11
6	Bz	365	4	380	72	43
7	Bz	365	4	400	72	75
8	Bz	365	4	420	72	91
9	Bz	365	4	440	72	78
10	Bz	dark	4	420	72	trace
11	Bz	365	4	dark	72	trace

[a]Pyridinium salt (0.1 mmol) in DCM (1 mL), N_2, 365 nm LEDs (L_1), at room temperature; after completely consuming the pyridinium salt, the tube was moved to the 420 nm LEDs (L_2) for the next step. [b]Isolated yields.

4π electrocyclization facilitates the folding of the compound into rigid bicyclic pyrazoline **1**, all within a single−pot reaction.

With the optimized conditions established (for more details, see the Supporting Information), the scope of rearrangement

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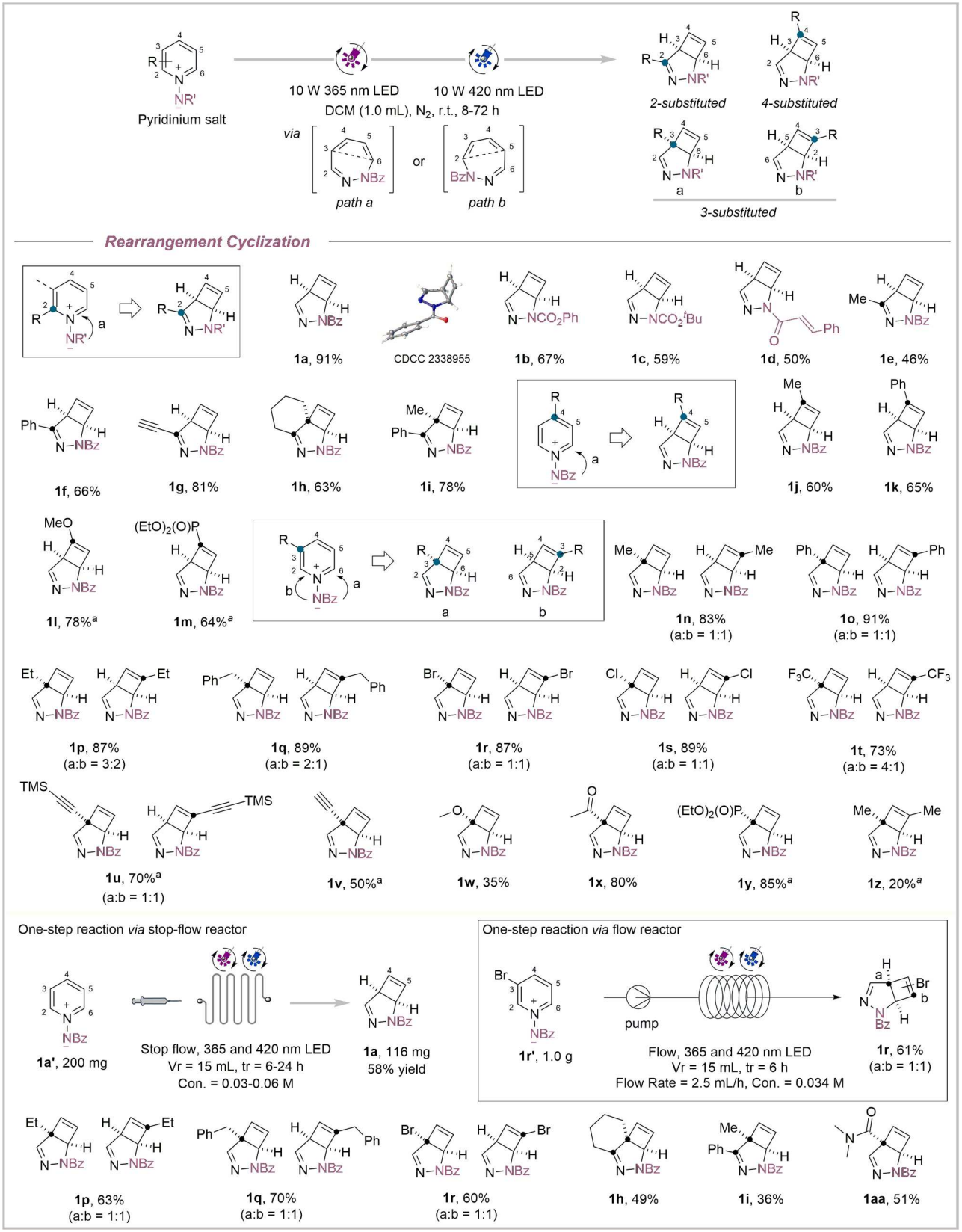

Figure 2. Scope of rearrangement cyclization. Isolated yields. The regioselectivity ratio is determined by ^{1}H NMR analysis of the isolated product mixtures. Rearrangement cyclization conditions: pyridinium salt (0.1 mmol), N_2, 365 nm LEDs, in DCM (1 mL) at room temperature; after completely consuming the pyridinium salt, the tube was moved to the 420 nm light for rearrangement (method A). [a]The intermediate 1,2-diazepine was isolated for the next step (method B).

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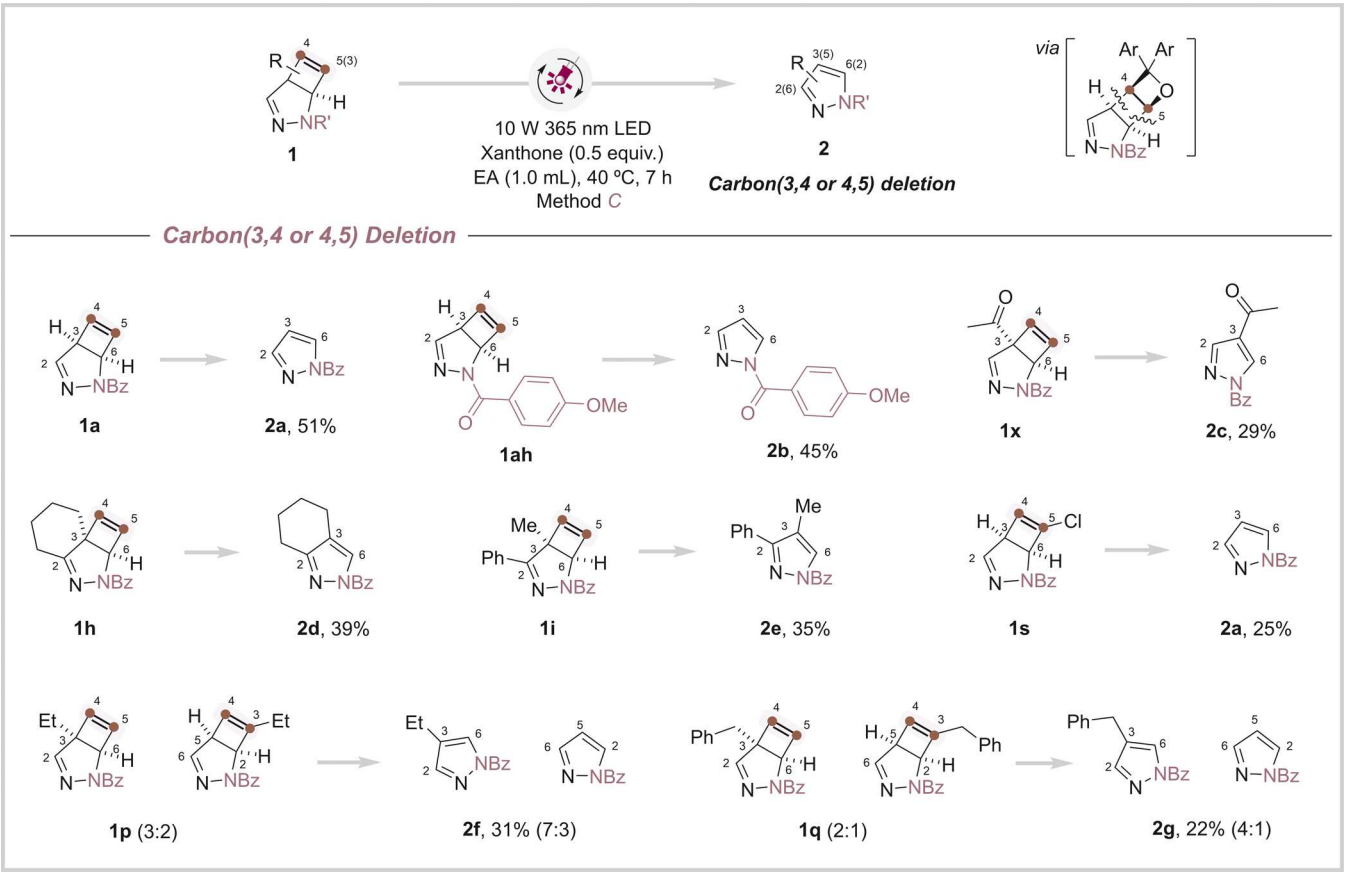

Figure 3. Scope of carbon(3,4 or 4,5) deletion. Isolated yields. The ratio is determined by ^{1}H NMR analysis of the isolated product mixtures. Carbon(3,4 or 4,5) deletion conditions: **1** (0.05 mmol), xanthone (0.5 equiv), EA (1 mL), 40 °C, N_2, 365 nm LEDs, 7 h (method C).

cyclization was summarized in Figure 2. Various pyridinium salts with different substituents were all compatible with the reaction and gave the corresponding bicyclic pyrazoline products (**1a−d**) in moderate to high yields. We further explored the scope of various pyridinium salts bearing electron-withdrawing or electron-donating groups at the 2-, 3-, or 4-positions for this rearrangement cyclization methodology. 2-substituted pyridines proved to be suitable substrates in this one-pot reaction, affording C2-functionalized bicyclic pyrazoline derivatives **1e−g** in generally good yields. Polysubstituted pyridinium salts were also investigated to leverage the translational potential of the strategy in assembling complex heterocycles. The 2,3-disubstituted substrates (**1h**, **1i**) were compatible with the reaction, delivering the corresponding products in good yield. Notably, the polycyclic product **1h** was obtained in a 63% yield from the corresponding pyridine in a one-step reaction, a challenging synthesis achievable through traditional methods. 4-substituted pyridinium salts were successfully incorporated using this one-pot protocol, yielding **1j−1m** in generally satisfactory yields. 3-substituted pyridines exhibited faster conversion to bicyclic pyrazolines compared to 2- and 4-substituted pyridines, completing the reaction in just a few hours. However, 3-substituted pyridinium salts available for nitrogen insertion in the rearrangement cyclization are nonequivalent, potentially resulting in the formation of two isomeric products ('path a' or 'path b'). The reaction rate of 'path a' predominates over 'path b', leading to the formation of products featuring synthetically challenging all-carbon quaternary ring junctions. Notably, a larger steric resistance group at the 3-position tends to favor the production of products from 'path a'. Most of the two isomeric pyrazole derivatives can be separated via column chromatography. We believe that this strategy offers significant potential for rapidly constructing compound libraries for biological exploration. Halide-containing products (**1r**, **1s**) were accessible in moderate yields, offering opportunities for further functionalization of the bicyclic pyrazoline scaffolds via cross-coupling reactions. Additionally, functional groups such as CF_3 (**1t**), ketone (**1x**), phosphonate (**1m**, **1y**), alkyne (**1g**, **1v**), and trimethylsilyl acetylene (**1u**) did not impede the reaction process, readily participating in subsequent transformations and delivering corresponding products in good yields. The one-pot photochemical protocol could be successfully adapted to stop-flow or flow-chemistry systems for rearrangement cyclization under 365 and 420 nm simultaneous irradiation, yielding corresponding products in moderate to high yields (**1p−1r**, **1h**, **1i**, **1aa**). Gram-scale synthesis was conducted using a flow reactor under 365 and 420 nm simultaneous irradiation, giving the bicyclic pyrazoline product **1r** in 61% yield.

While core skeletal editing by one-carbon deletion has been previously reported,[42,44−47] the conversion of pyridines into pyrazoles by selective two-carbon deletion has not yet been achieved. To our delight, the carbon[4,5] deletion product pyrazole **2a** was obtained in an acceptable yield when bicyclic pyrazoline **1a** was further irradiated under 365 nm light with the addition of xanthone as a catalyst (Figure 3). Previous reports have proven that the Paternò−Büchi reaction occurs between the carbonyl compound and alkene to form oxetanes.[48−51] We considered that the photosensitive xanthone can accelerate the

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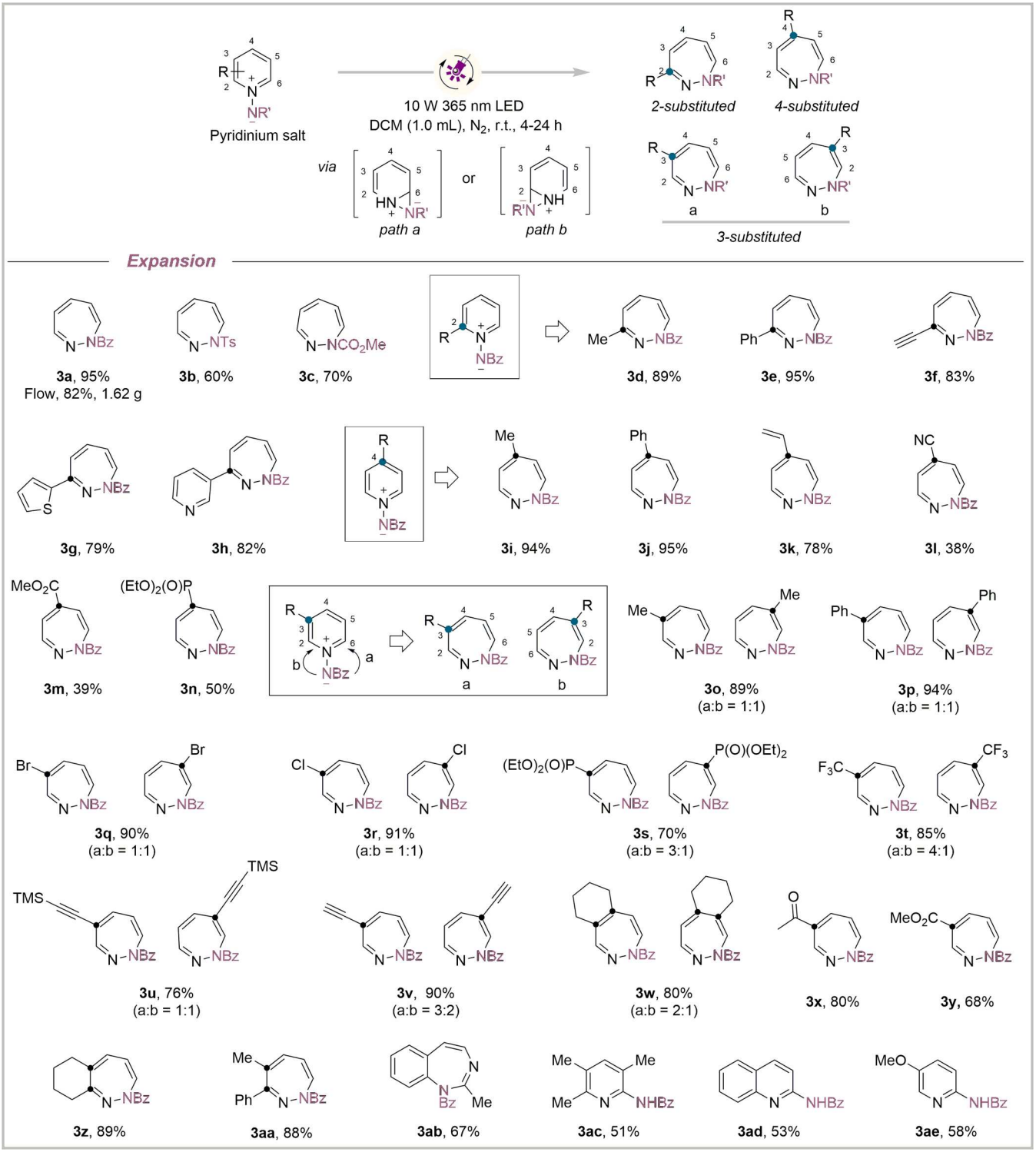

Figure 4. Scope of ring expansion. Isolated yields. The regioselectivity ratio is determined by ^{1}H NMR analysis of the isolated product mixtures. Expansion conditions: pyridinium salt (0.1 mmol), N_2, in DCM (1 mL), and 365 nm LEDs at room temperature (method D).

C−C bond breaking through energy transfer, forming a [2 + 2] transition state, producing the two-carbon deletion product pyrazole in the transformation. Other carbonyl compounds were also investigated, but no better results were obtained (for more details, see the Supporting Information, Table S4). With the optimized conditions in hand, the substrate scope of this carbon-deleting method was next examined. Methoxyl on the benzene ring (**2b**) and functional group ketone (**2c**) were well tolerated in this method. The polycyclic pyrazole **1h** can successfully transform into bicyclic pyrazoline **2d** in a moderate yield via carbon[4,5] deletion. The 2,3-disubstituted pyrazole **2e** was obtained in an acceptable yield when bicyclic pyrazoline **1i** was subjected to the reaction. When the mixture of two isomers (**1p** or **1q**) was subjected to the reaction, two different deletion products were observed via the carbon[3,4] and carbon[4,5] deletion process. The double bond bearing substituents (such as

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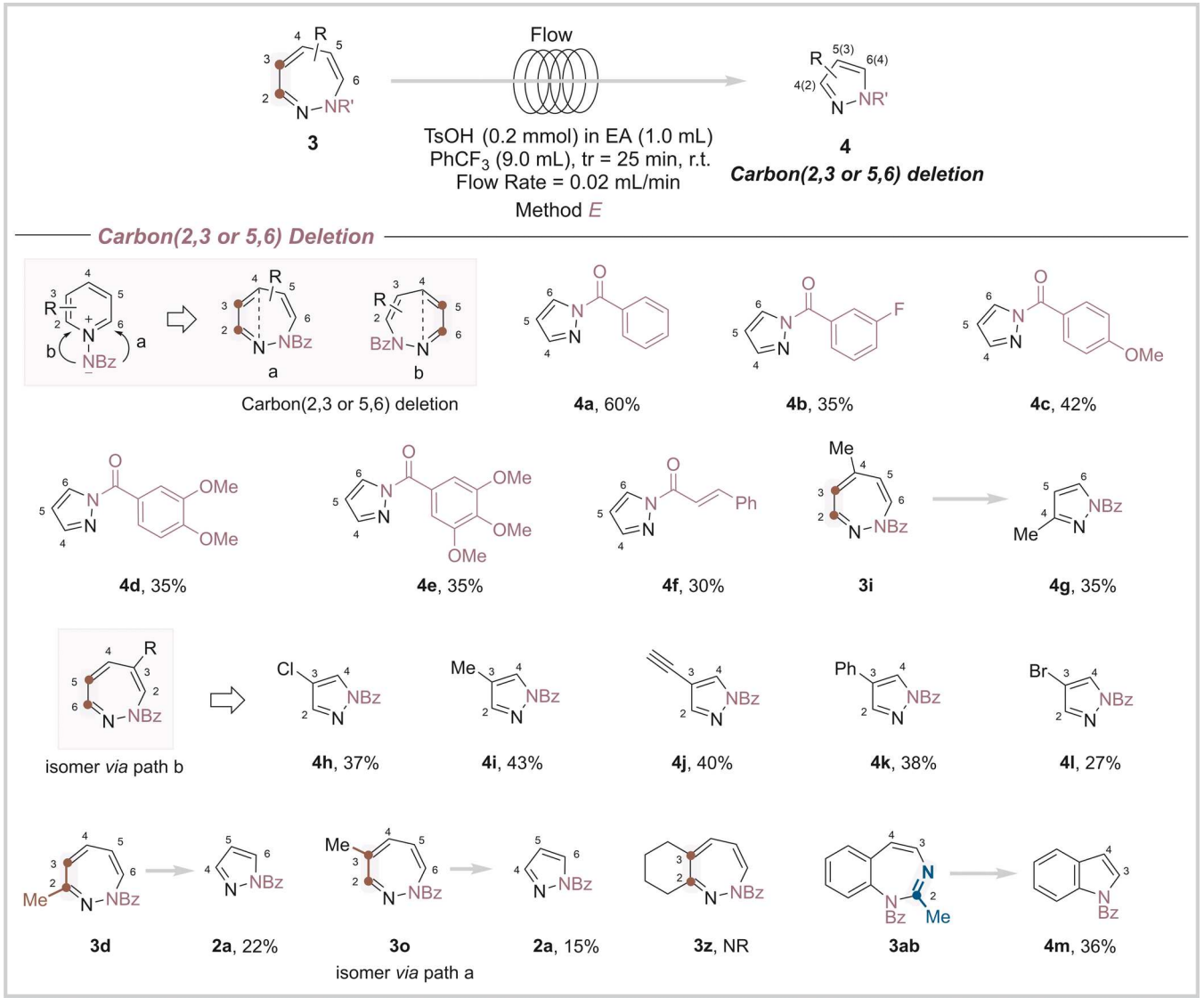

Figure 5. Scope of carbon(2,3 or 5,6) deletion. Isolated yields. Carbon deletion conditions: diazepines **3** (0.2 mmol) in 5 mL of $PhCF_3$, $TsOH{\cdot}H_2O$ (0.2 mmol) dissolved in EA (1 mL), followed by adding 4 mL of $PhCF_3$, flow reactor, rt, tr = 25 min (method E).

Et, Bn, and Cl) had no effect on the outcome of the reaction, yielding the corresponding pyrazole in reasonable yields.

The expansion products, diazepines, could be obtained as the main products via nitrogen atom insertion when the pyridinium salts were only irradiated under 365 nm LEDs. As illustrated in Figure 4, various pyridine derivatives with electron-withdrawing and -donating substituents at the 2-, 3-, and 4-positions (Cl, Br, Me, OMe, and Ph), as well as heterocyclic rings (thiophene **3g** and pyridine **3h**), were all compatible with the reaction and yielded the corresponding diazepines in moderate to high yields (39−95%). This method also tolerated various functional groups such as CF_3 (**3t**), Br (**3q**), Cl (**3r**), CN (**3l**), olefine (**3k**), alkyne (**3f**, **3v**), phosphonate (**3n**, **3s**), and ester (**3m**, **3y**), producing the corresponding products in high yields. For most 3-substituted pyridine derivatives, the expansion products were obtained in a mixture of two isomers with 1:1 regioselectivity ("path a" or "path b"). "Path a" was preferred when a large steric resistance group was present at the 3-position (phosphonate **3s**). Single products were observed when the strong electron-withdrawing group was at position 3 (acyl **3x** and ester **3y**). The disubstituted pyridines **3w**, **3z** and **3aa** also performed well in this method. Notably, our conditions allowed for the successful expansion of 1-methyl isoquinoline with a high yield (**3ab**, 67%), whereas no expansion product was observed for quinoline. For trisubstituted-pyridine, quinoline, and 3-methoxy pyridine, the α-amination products **3ac**−**3ae** were obtained in moderate yields, respectively. This expansion reaction could also be scaled up using a flow photoreactor, with product **3a** obtained in an 83% yield (1.64 g, for more details, see Supporting Information S8.1).

To our delight, unlike the carbon(3,4 or 4,5) deletion process from bicyclic pyrazolines, the 1,2-diazepine could be converted to pyrazoles by selectively deleting carbon(2,3 or 5,6) at the imine (C═N) side in the presence of acid $TsOH{\cdot}H_2O$ (Figure 5). Generally, deletion via flow chemistry yielded better outcomes compared to reactions in a batch reactor, avoiding byproducts from polymerization. A series of diazepines with different substituents on the benzene ring or *N*-protected groups (**4a**−**4f**) were well tolerated in this method, yielding carbon-[2,3] deletion products in moderate to high yields. In general, 4-substituted pyridine-derived diazepine (**4g**) gave the carbon-[2,3] deletion product. The corresponding 3-substituted

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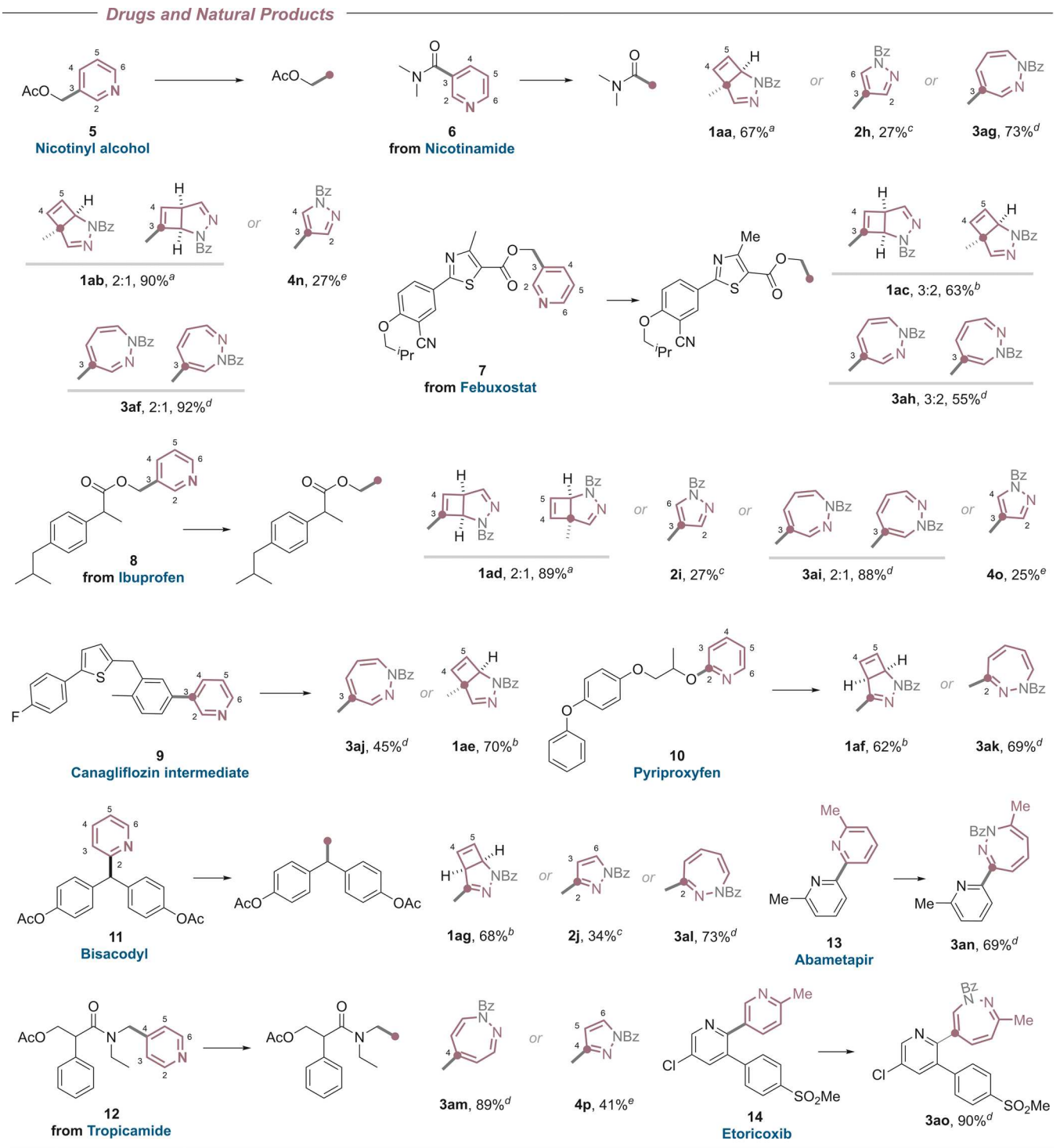

Figure 6. Skeleton editing of drugs and drug derivatives. Isolated yields. [a]Method A, [b]method B, [c]method C, [d]method D, and [e]method E.

pyrazoles were obtained via carbon[5,6] deletion in reasonable yields when the isomers ("path b") of 3-substituted pyridine-derived diazepines were subjected to the reaction, including both electron-donating and electron-withdrawing groups (**4h**–**4l**). Pleasingly, substrates with functional groups such as Cl (**4h**), Br (**4l**), benzene (**4k**), and alkyne (**4j**) were well tolerated in this method. Diazepines bearing a methyl substituent at the carbon[2,3] position (**3d** and **3o**) can undergo successful deletion to form ring contraction products, albeit with lower yields. Conversely, 2,3-disubstituted diazepine **3z** did not undergo any contraction reaction. Different from pyridine-derived diazepines, the ring expansion product **3ab** derived from 1-methylisoquinoline was contracted to the indole product **4m** through one carbon and one nitrogen atom deletion. Overall, using two different photochemical skeletal editing protocols, we can selectively delete carbon(3,4 or 4,5) via bicyclic pyrazolines or carbon(2,3 or 5,6) via 1,2-diazepines of pyridines under mild conditions to generate ring contraction pyrazole products, providing a potential convenient approach for the late-stage modification of drug molecules.

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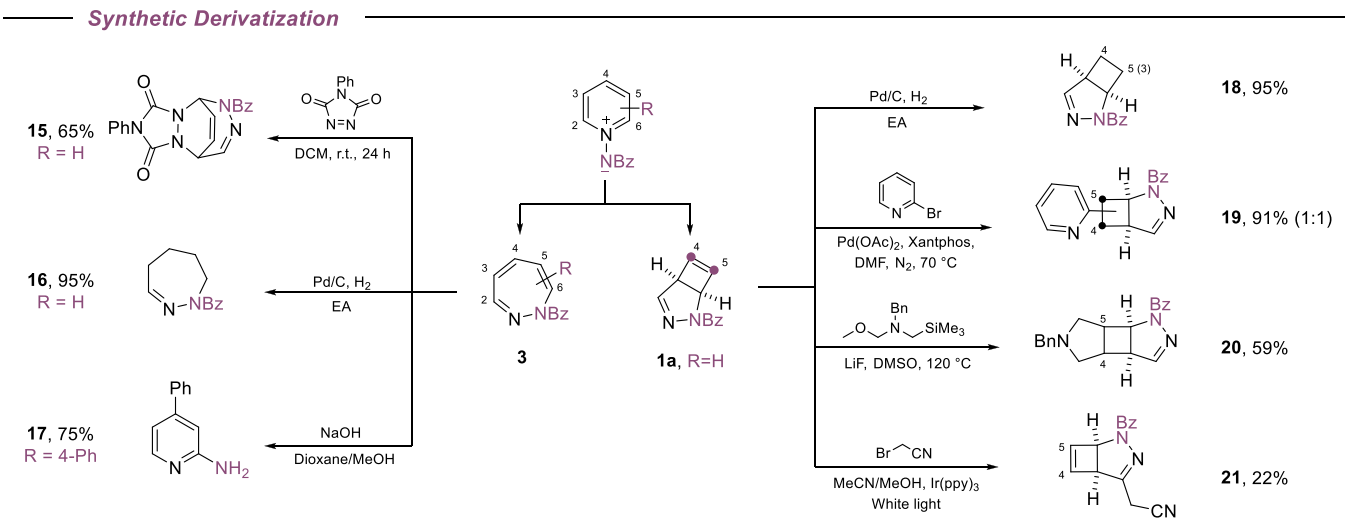

Figure 7. Synthetic derivatization. Experimental details are provided in the Supporting Information.

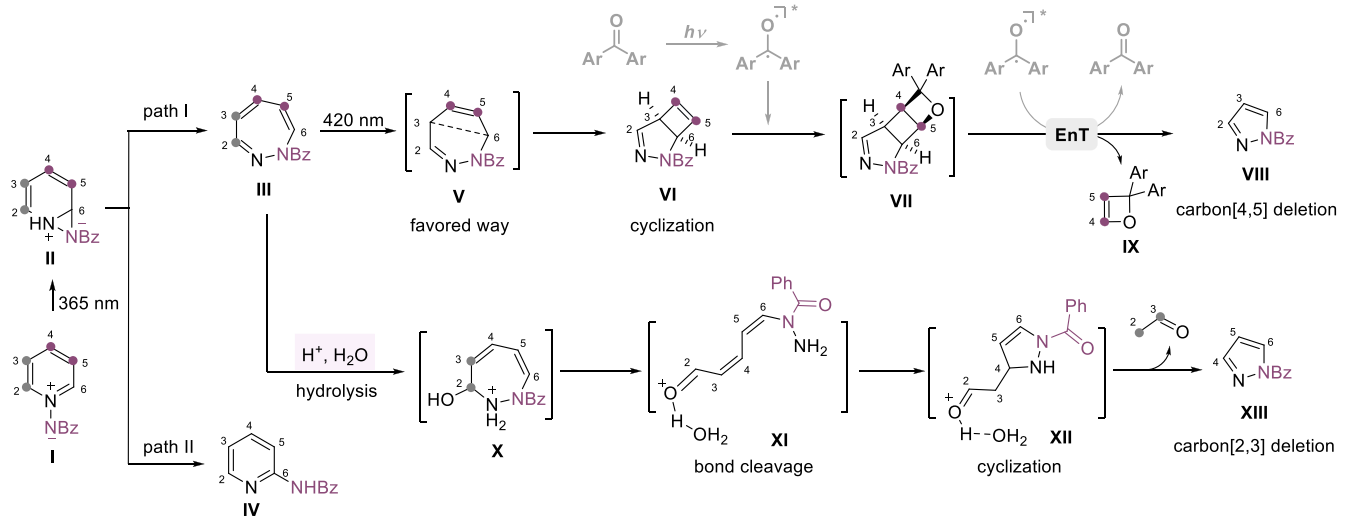

Figure 8. Proposed mechanism.

We further demonstrated the practicality of this photochemical skeleton editing strategy for the late-stage modification of complex drug molecules containing pyridine moieties (Figure 6). Our study commenced with skeleton editing of nicotinyl alcohol (**5**) and nicotinamide derivative (**6**) (3-substituted pyridines), whereby three different new skeletons (including bicyclic pyrazolines **1ab**, **1ab'**, **1aa**, carbon[4,5] deletion pyrazole **2h**, carbon[5,6] deletion pyrazole **4n**, and 2-diazepines **3ag**, **3af**) could be readily constructed under mild conditions using this photochemical skeleton editing strategy. More complex drug derivatives such as the febuxostat derivative (**7**), ibuprofen derivative (**8**), and canagliflozin intermediate (**9**) were also well tolerated in this skeleton editing strategy, yielding the corresponding products in acceptable yields. The insect growth regulator pyriproxyfen (**10**) and stimulant laxative drug bisacodyl (**11**) with 2-substituted pyridine, as well as tropicamide derivative (**12**) with 4-substituted pyridine, were also susceptible to our method, affording the corresponding skeleton editing products in reasonable yields (such as bicyclic pyrazolines **1af**, **1ag**, carbon[2,3] deletion pyrazole **4p**, carbon-[4,5] deletion pyrazole **2j**, and 1,2-diazepines **3ak**, **3al**, and **3am**). The polysubstituted bipyridine substrates abametapir (**13**) and etoricoxib (**14**) yielded expansion products **3an** and **3ao** in high yields, with only one pyridine of them being edited. However, this photochemical skeleton editing strategy has some limitations when applied to complex compounds. For instance, the carbon-deletion product pyrazole was not obtained for febuxostat (**7**), canagliflozin (**9**), and pyriproxyfen (**10**). Additionally, the bicyclic pyrazoline product was not accessible for drug molecules **12**, **13**, and **14**. These compounds constitute bicyclic and ring-contracted variants of pyridines that are in and of themselves worth pursuing in medicinal chemistry campaigns. However, it is worth noting that the inclusion of a benzoyl group is expected to significantly change the molecular architecture such that a 1:1 comparison of physicochemical properties and biological activity would be difficult to interpret.

The synthetic versatility of our protocol was further demonstrated through the diversification of the skeleton editing products (Figure 7). Diazepine, providing a 1,3-diene unit, facilitated the Diels–Alder reactions. In the presence of Cookson's reagent, diazepine **3a** underwent a Diels–Alder reaction, yielding the tricyclic compound **15** in 65% yield. Hydrogenation yielded product **16** in 95% yield in the presence of Pd/carbon (10 mol %) at room temperature. The

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Computational Studies

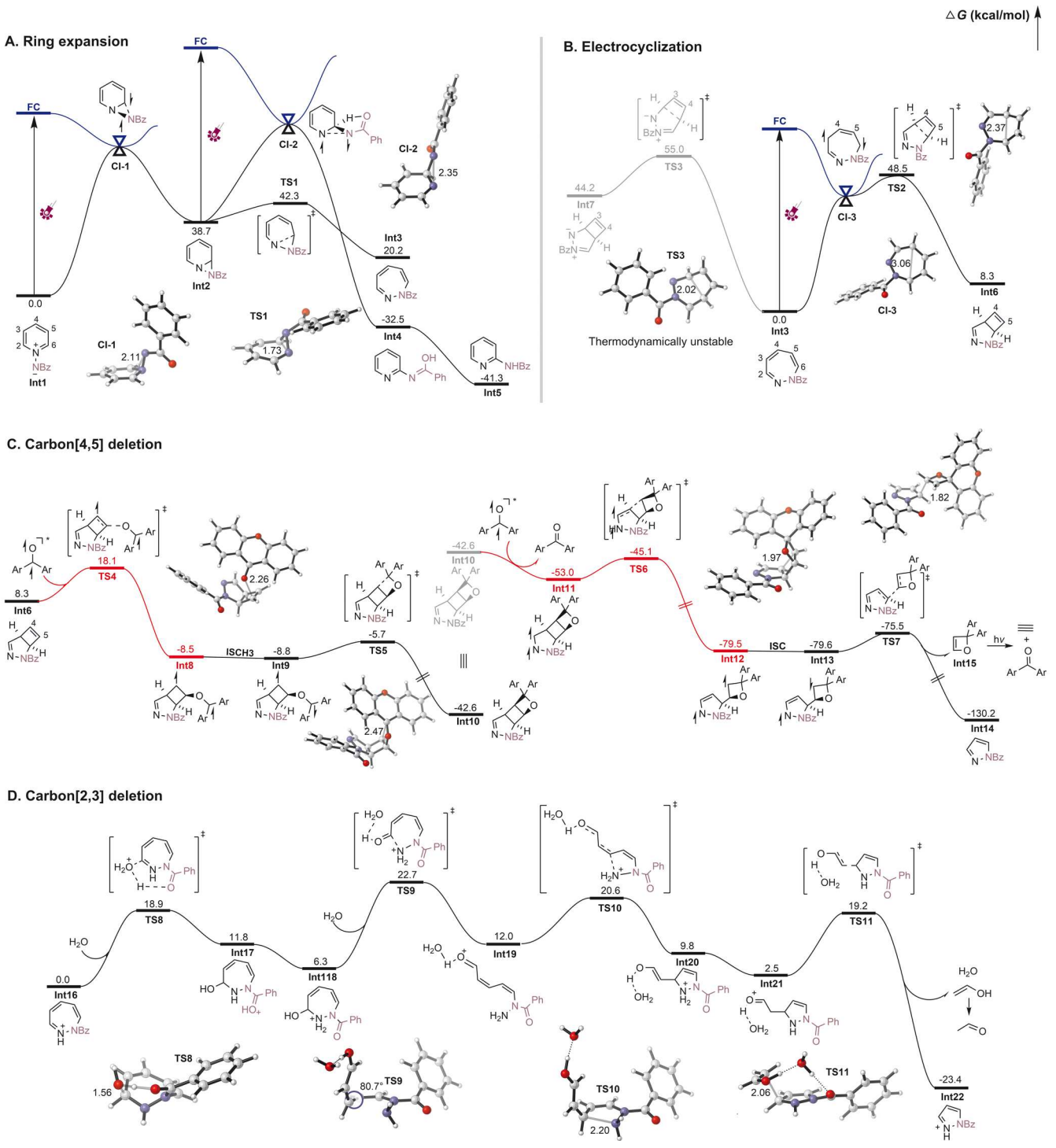

Figure 9. (A) Ring expansion of the pyridinium ylide. (B) Photochemical electrocyclization. (C) Photochemical carbon[4,5] deletion process. (D) Acid-catalyzed carbon[2,3] deletion process. Energies are in kcal/mol. Bond lengths are given in Å. Species in the T1 and S1 excited states are labeled in red and blue, respectively. Computational level: ωB97X-D/def2-TZVPP/SMD//ωB97X-D/6-31G(d)/IEEPCM.

rearrangement product 2-aminated pyridine **17** was obtained under base condition. For bicyclic pyrazoline **1a**, the C═C bond in the cyclobutene was successfully selectively reduced using the same reduction conditions, affording product **18** in excellent yield. Additionally, a reductive Heck reaction with 2-bromopyridine yielded additional product **19** in a 91% yield. A [3 + 2] cycloaddition with an azomethine ylide precursor resulted in tricyclic product **20** in 59% yield. The light-induced reaction of bicyclic pyrazoline **1a** with 2-bromoacetonitrile produced the coupling product **21** in an acceptable yield. These transformations underscore the downstream reactivity of these versatile intermediates.

To elucidate the mechanism of the photochemical skeletal editing protocol, a series of control experiments were conducted. UV−vis spectrum (Figure S4) suggests that the pyridinium salt can be activated under 365 nm LED irradiation, initiating

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sequential ring expansion via nitrogen insertion. Subsequently, the diazepine intermediate undergoes secondary excitation to form the cyclization product under lower-energy 420 nm LED irradiation. Control experiments indicate that H_2O and HCl are crucial for the carbon[2,3] deletion process, and the byproduct acetaldehyde was formed during the transformation (Supporting Information S5.2.1). For the carbon[4,5] deletion process, light and the catalyst xanthone play pivotal roles in the reaction. Examination of the reaction mixture revealed the existence of a four-membered ring intermediate, as identified through HRMS analysis (Supporting Information S5.2.2). We speculate that this deletion process proceeds through the formation of a four-membered ring transition state, followed by bond cleavage via an energy transfer process, ultimately forming the carbon[4,5] deletion product. Cleavage of the C−N bond on the pyridine leads to the ring expansion product **III**, while N−N bond cleavage yields 2-aminopyridine **IV**. Cyclization of the bicyclic compound is achieved through the rearrangement cyclization of **III** under lower-energy 420 nm LED irradiation. For the carbon[4,5] deletion process, direct excitation of xanthone to its excited state leads to rapid decay to the triplet excited state.[52−56] Energy transfer occurs between excited triplet photosensitizer xanthone and **VI** (Supporting Information Table S4). The formation of the four-membered ring transition state **VII** ([2 + 2]-like oxetane) between the carbonyl group of xanthone and the C═C double bond of alkene occurs during the reaction. The carbon[4,5] deletion product **VIII** is formed via bond cleavage of intermediate **VII** and new C═C bond formation. Imine hydrolysis in the presence of acid and water results in the cleavage of the C−N bond and double bond, yielding intermediate **X**. The carbon[2,3] deletion product **XIII** is formed alongside the byproduct acetaldehyde via bond cleavage (**XI**) and new C═N bond formation (**XII**).

DFT calculations were performed to support the proposed mechanism. For ring expansion, which is shown in Figure 9A, the reaction is initiated by the direct irradiation of pyridinium ylide reactant **Int1** which then passes through a conical intersection (CI) point **CI-1** to the ground state, generating bicyclic diazanorcaradiene **Int2** or reverting to **Int1** (see the PES scan in Figure S13). **Int2** is a highly unstable intermediate, undergoing rapid 6π electrocyclization and ring expansion to yield the stable diazepine intermediate **Int3** ($\Delta G^{\ddagger}$ = 3.6 kcal/mol).[35] **Int2** can also be excited to the first singlet excited state. This leads to another CI point (**CI-2**) with an elongated N−N bond (see the PES scan in Figure S14). De-excitation for this point leads to iminol **Int4**. **Int4** then tautomerizes to achieve side-product **Int5**, where a H atom is transferred from carbon to the carbonyl group to re-establish aromaticity. For the photochemical process (Figure 9A), diazepine **Int3** is first excited to the S1 state. After relaxation, planar **CI** point **CI-3** is reached. At that planar geometry, all eight π electrons are forced to have conjugation and thus form an antiaromatic ring.[57] DFT and CASSCF calculations (Figure S18) have shown significant diradical characteristics at **CI-3** (Figure 8B), as well as a large single electron distribution at the C3 and C6 positions. However, for the formation of the product **Int6**, extra energy is still needed for **CI-3** to overcome the distortion and reach the 4π disrotatory electrocyclization transition state **TS2** (see the PES scan in Figure S17). Only **Int6** is observed because the product **Int7** is extremely thermodynamically unstable.

The subsequent carbon[4,5] deletion is triggered by the Paternò−Büchi reaction between **Int6** and the excited triplet photosensitizer xanthone (Figure 9C). The triplet photosensitizer xanthone first attacks the C═C double bond using the single electron in oxygen (**TS4**), generating a relatively stable triplet diradical species, **Int8**.[58] The intersystem crossing (ISC) and radical recombination result in the formation of the (2 + 2) product **Int10** which can be promoted to its T1 excited state **Int11** by energy transfer (EnT) from excited xanthone. In **Int11**, the π electrons in the C═N bond are excited to two single electrons. The radical on the carbon easily drives the cleavage of the four-membered ring to release ring strain via **TS6**, giving a relatively stable triplet diradical species **Int12**. Singlet diradical **Int13** is then formed through ISC. Via rapid C−C bond cleavage (**TS7**), it decomposes into the final product **Int14** and oxetane **Int15**, as observed experimentally by HRMS.

For the acid-catalyzed carbon[2,3] deletion (Figure 9D), diazepine will first be protonated to give **Int6**. A mole of water then adds to the iminium C═N bond and intramolecular proton transfer, leading to carboxonium **Int16**. After the C−N bond breaking and ring closing, **Int17** readily undergoes a retro-aldol transition state **TS9** to generate the final product **Int20** and release acetaldehyde. The overall barrier of this process is 22.7 kcal/mol, which is spontaneous at room temperature.

CONCLUSIONS

In conclusion, our study introduces an efficient approach to skeletal editing, providing a versatile and effective strategy for the late-stage modification of complex drug molecules containing pyridine moieties. Leveraging photochemical processes, we demonstrated the ability to rapidly construct diverse scaffolds, including bicyclic pyrazolines, pyrazoles, and 1,2-diazepines, all under mild conditions. The broad substrate scope underscores the adaptability of our methodology across various pyridine derivatives. The successful application of our strategy to a range of drug derivatives underscores its potential impact on pharmaceutical research and development. Moreover, our findings offer valuable insights into the downstream reactivity of the synthesized intermediates, laying the groundwork for future exploration of their synthetic applications. Ongoing work in our laboratory focuses on further exploring the synthetic applications of skeletal editing reactions.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.4c03713.

Experimental setup, experimental procedures, preparation of starting material, optimization of reaction conditions, control experiments, computational methods, additional computational results, Cartesian coordinates of calculated structures, full spectroscopic data for all new compounds, and copies of ^{1}H and ^{13}C NMR spectra (PDF)

checkCIF/PLATON report (PDF)

Accession Codes

CCDC 2338955 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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AUTHOR INFORMATION

Corresponding Authors

K. N. Houk − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States;* orcid.org/0000-0002-8387-5261; Email: houk@chem.ucla.edu

Ke Zheng − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610065, China;* orcid.org/0000-0002-3345-7715; Email: kzheng@scu.edu.cn

Authors

Jiajing Luo − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610065, China*

Qingyang Zhou − *Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569, United States*

Zhou Xu − *Key Laboratory of Green Chemistry & Technology, Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610065, China*

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.4c03713

Author Contributions

[§]J.L. and Q.Z. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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