Title	Pyrrolidine synthesis via ring contraction of pyridines
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Article

Pyrrolidine synthesis via ring contraction of pyridines

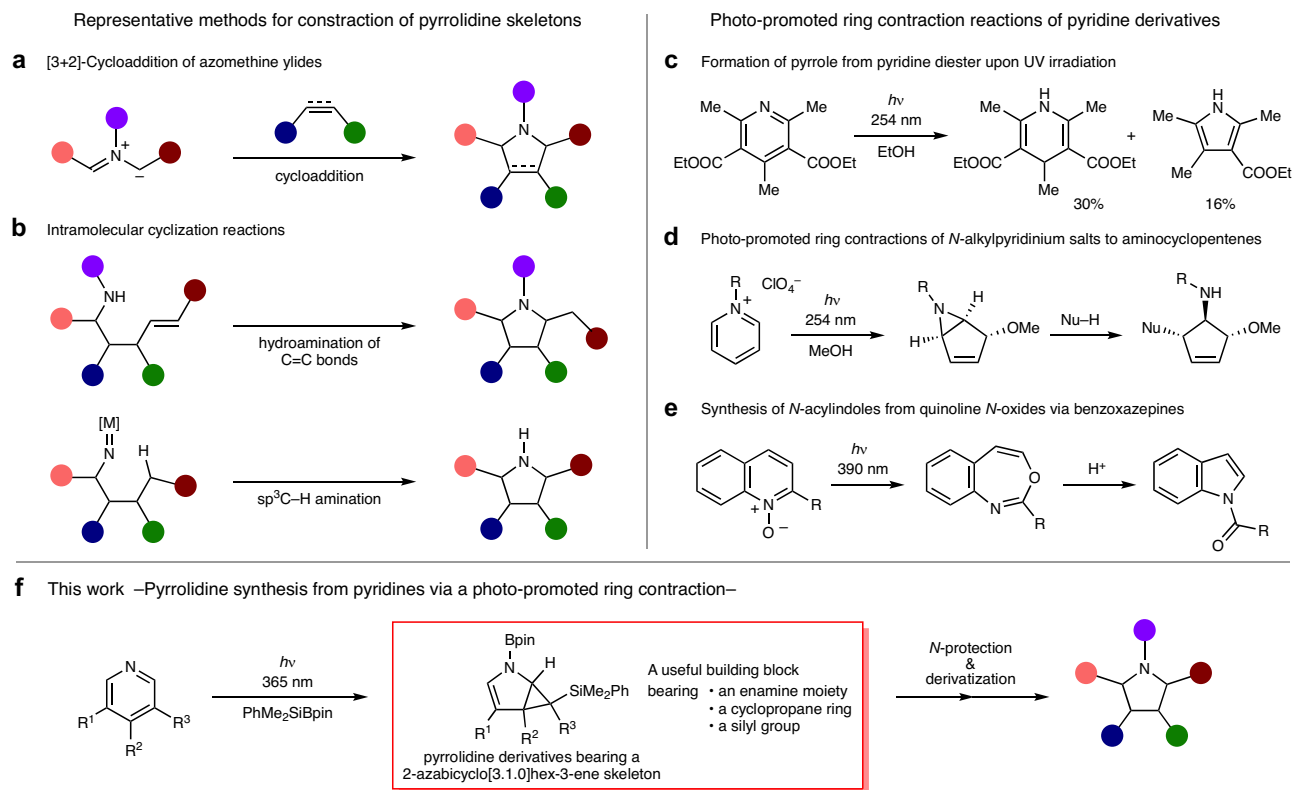Ryoga Ueno[1], Shohei Hirano[1] & Jun Takaya [2] ✉

A ring contraction of easily available cyclic compounds to smaller cycles that are valuable but difficult to synthetically access is one of important skeletal editing strategies. Pyrrolidine synthesis via a ring contraction of pyridines, which are abundant, cheap, and readily available bulk chemicals in chemical industry, is highly promising to accelerate drug discovery and development research due to the great demand of pyrrolidine skeletons in medicinal molecules. Herein we report a photo-promoted ring contraction of pyridines with silylborane to afford pyrrolidine derivatives bearing a 2-azabicyclo[3.1.0]hex-3-ene skeleton. The reaction demonstrates broad substrate scope with high functional group compatibility, realizing facile access to 6-silyl-2-azabicyclo[3.1.0]hex-3-ene derivatives that work as powerful synthons for the synthesis of functionalized pyrrolidines and nitrogen-containing compounds. The reaction mechanism is clarified to proceed via 2-silyl-1,2-dihydropyridine and vinylazomethine ylide as intermediates, which are connected via photochemical or thermal silyl migration.

Pyrrolidine is one of prevalent core structures found in biologically active natural products and medicinal molecules[1–3]. Development of synthetic methods to access pyrrolidine skeletons with broad scope and high functional group compatibility is of great importance not only to accelerate drug discovery research but also to explore chemical spaces of nitrogen-containing compounds. [3 + 2] cycloaddition reactions of azomethine ylides with alkenes and alkynes have been widely investigated, affording pyrrolidine derivatives with a wide range of substitution patterns and excellent stereoselectivity (Fig. 1a)[4,5]. Intramolecular cyclization approaches utilizing such as amination of unsaturated carbon-carbon bonds[6–9] and insertion of nitrene species into sp^3C−H bonds[10–12] have also been recognized as powerful methods for efficient construction of pyrrolidine rings (Fig. 1b). However, preparation of the appropriate starting materials is necessary in most case of these reactions, thus limiting their versatility.

Meanwhile, a ring contraction of cyclic compounds to smaller cycles that are valuable but difficult to synthetically access is a useful strategy in synthetic organic chemistry. This is regarded as skeletal editing, which has rapidly emerged as a powerful concept to expand molecular diversity[13,14]. Considering the synthesis of pyrrolidine derivatives via ring contractions, it is highly desirable to use pyridines as

starting materials, which are abundant, cheap, and readily available bulk chemicals in chemical industry. However, such ring contraction reactions have scarcely been achieved to date. There are several examples of pyrrole synthesis from *N*-alkylpyridinium salts or pyridines via sequential ring-cleavage and ring-closure under oxidative conditions[15–19]. Photoreactions are promising to realize skeletal editing although direct excitation of pyridine itself requires ultraviolet irradiation[20–23], which often causes side reactions and is not suitable for practical synthetic reactions. As an early example of a photo-promoted ring contraction of pyridines, in 1969, Kellogg reported that irradiation of 254 nm light to pyridine diester afforded dihydropyridine along with a small amount of pyrrole (Fig. 1c)[24]. In 1972, Kaplan and Wilzbach reported a photoreaction of an *N*-methylpyridinium salt in water to yield an aziridine derivative, 6-azabicyclo[3.1.0]hex-3-ene-2-ol, via 4π electrocyclization followed by hydration[25]. This reaction was further extended by Mariano into practical synthesis of aminocyclopentene derivatives by combining it with a subsequent nucleophilic ring-opening reaction of the aziridine moiety (Fig. 1d)[26,27]. The photolysis of pyridine *N*-oxides was reported to give 2-acylpyrroles in low yields[28]. Recently, optimizing this reaction, Levin realized skeletal editing of quinoline *N*-oxides to *N*-acylindoles via net one carbon deletion, in

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Representative methods for constraction of pyrrolidine skeletons

a [3+2]-Cycloaddition of azomethine ylides

b Intramolecular cyclization reactions

hydroamination of C=C bonds

sp³C–H amination

Photo-promoted ring contraction reactions of pyridine derivatives

c Formation of pyrrole from pyridine diester upon UV irradiation

d Photo-promoted ring contractions of *N*-alkylpyridinium salts to aminocyclopentenes

e Synthesis of *N*-acylindoles from quinoline *N*-oxides via benzoxazepines

f This work –Pyrrolidine synthesis from pyridines via a photo-promoted ring contraction–

pyrrolidine derivatives bearing a 2-azabicyclo[3.1.0]hex-3-ene skeleton

A useful building block bearing
- an enamine moiety
- a cyclopropane ring
- a silyl group

N-protection & derivatization

Fig. 1 | Synthetic approaches to pyrrolidines and ring contraction reactions of pyridines. a [3 + 2]-Cycloaddition of azomethine ylides with alkenes and alkynes as a representative synthetic approach to pyrrolidine derivatives. **b** Examples for intramolecular cyclization reactions to access pyrrolidine skeletons via hydroamination and sp³C–H amination. **c** An early example of a photo-promoted direct ring contraction of pyridine to pyrrole upon UV light irradiation. **d** A ring contraction of pyridinium salts to cyclopentene derivatives under UV irradiation. **e** Synthesis of *N*-acylindoles via photo-promoted skeletal rearrangement of quinoline *N*-oxides to benzoxazepines followed by acidolysis. **f** This work: A photo-promoted ring contraction of pyridines to pyrrolidine derivatives bearing a 2-azabicyclo[3.1.0]hex-3-ene skeleton.

which quinoline *N*-oxides were photochemically converted to benzoxazepines upon 390 nm irradiation followed by ring-opening and closure under acidic conditions (Fig. 1e)[29]. These precedents evidenced high feasibility of the ring contraction strategy using pyridines as starting materials leading to 5-membered ring scaffolds, although most cases necessitate the preparation of *N*-alkylpyridinium salts or *N*-oxides as pre-activation steps. Several related studies on skeletal editing, not limited to ring contraction, of pyridine derivatives such as pyridinium ylides have also been reported[30–34]. The development of a ring contraction reaction of pyridines to give pyrrolidine skeletons without pre-activation remains a desirable but challenging task.

Herein we report a photo-promoted ring contraction of pyridines with silylborane to afford pyrrolidine derivatives bearing a 2-azabicyclo[3.1.0]hex-3-ene skeleton (Fig. 1f). Derivatization of the products to variously substituted and functionalized pyrrolidine derivatives and other nitrogen-containing compounds is demonstrated, disclosing their high synthetic utility as building blocks in organic synthesis.

Results
Reaction development
Considering the photochemical reactivity of pyridine derivatives, we expected that a Lewis acid–base adduct derived from pyridine and a certain boron reagent could be photochemically activated upon irradiation with practical wavelengths, possibly undergoing ring contractions as seen in the cases of pyridinium salts. After examining various boron reagents and reaction conditions, it was found that photo-irradiation of a benzene-d_6 solution of pyridine and silylborane (2-(dimethylphenylsilyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, PhMe₂SiBpin) using a 365 nm LED at 25 °C in a J Young NMR tube

afforded a pyrrolidine derivative, *N*-boryl-6-silyl-2-azabicyclo[3.1.0] hex-3-ene **2a**, in excellent yield (Fig. 2a). **2a** was unstable in air and not isolable. The structure of **2a** was fully characterized by NMR analyses (Fig. 2b) and also confirmed by XRD analyses after derivatizing to solid compounds (vide infra). Three hydrogen atoms on the cyclopropane ring appear at $\delta = 3.91$ (H$_e$), 2.10 (H$_c$), and −0.59 (H$_d$), which is significantly shifted upfield due to the shielding effect of both a cyclopropane ring and a silyl group. The diastereomer locating the silyl group *trans* to the nitrogen atom on the cyclopropane ring was formed selectively. The reaction using bis(pinacolato)diboron (B₂pin₂) or 1,1,2,2-tetramethyl-1,2-diphenyldisilane ((PhMe₂Si)₂) instead of PhMe₂SiBpin did not proceed at all (Entries 1 and 2, Fig. 2c). Importantly, visible light irradiation using 430 nm LEDs also promoted the reaction to give **2a** in 85% yield although the reaction time was extended to 11 h for sufficient conversion (Entry 3). Moreover, reducing the amount of silylborane to 1.0 equiv. did not cause any problems, yielding **2a** in 91% yield after 5 h (Entry 4).

With the optimal reaction conditions in hand, derivatization of **2a** to an air-stable and isolable compound by protecting the nitrogen atom was examined. Screening of various *N*-protecting groups and reaction conditions disclosed that addition of 1.0 equiv. each of benzoyl chloride and pyridine to the solution of **2a** obtained after the photoreaction afforded *N*-benzoyl enamide **3a** as a single diastereomer in 83% (based on pyridine), which was successfully purified and isolated by basic alumina column chromatography in air (Fig. 3). This one-pot procedure enabled facile preparation of *N*-benzoyl-2-azabicyclo[3.1.0]hex-3-ene derivatives **3** from various pyridines as starting materials. The reaction of 4-substituted pyridines with R² = Me, Bn, *n*-Pr, and Ph proceeded smoothly to give **3b-e**, having the alkyl or aryl

a Reaction of pyridine with silylborane under 365 nm photoirradiation
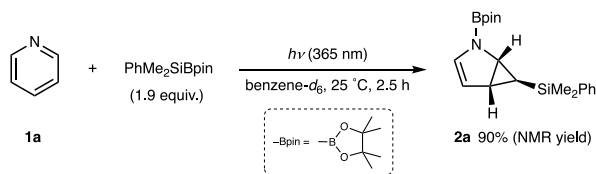
b ¹H NMR spectrum of 2a
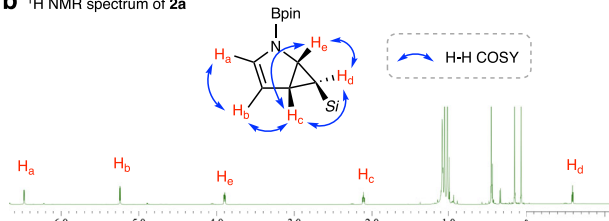
c Examination of reaction conditions

Entry	Variation from the standard conditions	Yield of 2a[a]
1	B₂pin₂ instead of PhMe₂SiBpin[b]	no reaction
2	(PhMe₂Si)₂ instead of PhMe₂SiBpin[b]	no reaction
3	430 nm instead of 365 nm	48% (85%)[c]
4	1.0 equiv. of PhMe₂SiBpin, 5 h	91%

[a] Determined by ¹H NMR. [b] 3.0 equiv. pyridine to diboron or disilane, 2 h. [c] 11 h.

Fig. 2 | The photo-promoted ring contraction of pyridine with silylborane to form a pyrrolidine derivative, N-boryl-6-silyl-2-azabicyclo[3.1.0]hex-3-ene 2a. a The optimized ring contraction reaction of pyridine with silylborane to give the pyrrolidine derivative **2a** in 90% yield. **b** The ¹H NMR spectrum of **2a** with connectivities observed by the H-H COSY measurement. **c** Selected data obtained in the screening of reaction conditions.

substituents at the 5-position of the 2-azabicyclo[3.1.0]hex-3-ene skeleton. The relative stereochemistry of the major isomer is *trans/trans* (defined as the relationship of R²/Si to the nitrogen atom on the cyclopropane ring), although the stereoselectivity is affected by the size of R². Interestingly, the selectivity was completely reversed when employing 4-*tert*-butylpyridine as a substrate, giving a *trans/cis* isomer of **3f** selectively due to the large steric repulsion between the ʹBu and the Si groups. *tert*-Butyldimethylsilyl ether and acetate as protected alcohols were tolerant to the reaction conditions, affording the corresponding products **3g-i** bearing the functionalized alkyl chains in good yields. Importantly, pyridines bearing various carbonyl groups, such as ethyl ester and Weinreb's amide, were successfully used to give the corresponding pyrrolidine derivatives **3j-l** in moderate to good yields. Various protecting groups were employable under the reaction conditions as demonstrated in the facile formation of enamide **3m**, **3n**, **3o**, which bear a cyclic acetal moiety as masked aldehyde or a *tert*-butyl carbamate (Boc) moiety as protected amine. The reaction of 4-trifluoromethylpyridine proceeded to generate a CF₃-containing product **2p** in 54% yield, enabling easy access to fluorinated pyrrolidine building blocks. Importantly, pyridines containing alkyl chloride, alkene, and internal/terminal alkyne underwent the ring contraction reaction to afford **3q-t** without any problems. This reaction realizes facile synthesis of pyrrolidine derivatives **3** equipped with an enamide moiety and a functionalized alkyl chain, which would work as promising building blocks for polycyclic alkaloid synthesis via further C–C bond formation. Furthermore, this protocol was successfully applied to 3,5-dimethylpyridine to give *N*-benzoyl-4,6-dimethyl-6-silyl-2-aza-bicyclo[3.1.0]hex-3-ene **3u** stereoselectively in good yield, thus demonstrating generality with substituents at 3,5-positions. 3-Methyl and 3-ethylpyridines afforded two regioisomers that possess the substituent at the enamine moiety or the cyclopropane carbon adjacent to

the silyl group (**3v:3v′** = 37%:42%, **3w:3w′** = 36%:24%). 3,4-Dimethyl-pyridine were also employable to give **3x** and **3x′** stereoselectively (**3x:3x′** = 26%:39%). 2-Substituted pyridines such as 2-picoline and 2-fluropyridine and other aromatic heterocycles such as pyrimidine did not react at all, probably due to the difficulty of forming pyridine-silylborane adducts. Synthetic utilization of a particular *N*-Boc-2-aza-bicyclo[3.1.0]hex-3-ene derivative, which is prepared by mono-cyclopropanation of *N*-Boc pyrrole with diazoacetate, has been extensively studied by Reiser and other research groups. However, the preparation method suffers from low yield and limited substrate scope due to selectivity issues in the cyclopropanation step[35–41]. This reaction demonstrates wide substrate generality and excellent functional group compatibility, thus establishing a practical method to access pyrrolidine derivatives bearing a 2-azabicyclo[3.1.0]hex-3-ene skeleton from easily available pyridines.

Transformation to functionalized pyrrolidine derivatives and other nitrogen-containing compounds

The ring contraction product **3** furnishes an enamine, a cyclopropane, and a silyl moieties as reactive functional groups usable for further C–C bond formation and functionalization[36–42]. To demonstrate its synthetic utility as a synthon for various functionalized pyrrolidines, reactivity of **2a** and **3a** was investigated. The photo-promoted ring contraction reaction was scalable with the same setup for photo-irradiation, enabling preparation of ca. 3 g of **3a** from 10 mmol of pyridine at one time (Fig. 4a). Treatment of *N*-borylenamine **2a** with phenyl thioglycolate afforded tricyclic lactam **4a** having an *N,S*-acetal moiety in 75% yield, which is expected to work as a precursor to an iminium ion by acidic activation for further C–C bond formation (Fig. 4b). Hydrogenation of **3a** with Pd/C gave a saturated pyrrolidine derivative **5a** in 72% yield (Fig. 4c) along with 2-(silylmethyl)pyrrolidine **6a** via regioselective reductive C–C bond cleavage of the cyclopropane ring (Fig. 4d)[43]. The silyl group of **5a** was converted to a hydroxy group by the Tamao-Fleming oxidation (HF/KF/H₂O₂)[44], providing cyclopropanol-fused pyrrolidine **7a** in 41% yield (Fig. 4e). The reaction of **5a** with 2 equiv. of TBAF afforded a desilylation product **8a** in 47% yield (Fig. 4f). The enamide moiety of **3a** underwent an inverse electron demand Diels-Alder reaction with a 2-pyrone derivative **9** to give **10a** in good yield[45], realizing rapid construction of the complex tetracyclic pyrrolidine skeleton from pyridine in three steps (Fig. 4g). Furthermore, it was also revealed that acidic methanolysis of **3a** afforded a cyclopropylamine derivative **11a** equipped with a silyl group and an acetal moiety stereoselectively (Fig. 4h). This is a highly useful and practical method to rapidly access to the functionalized cyclopropane derivatives starting from readily available pyridines. The structures of **4a**, **10a**, and **11a** were clarified by XRD analyses. These results demonstrate high versatility of the 6-silyl-2-azabicyclo[3.1.0]hex-3-ene skeleton as a building block for the synthesis of various pyrrolidines and nitrogen-containing compounds.

Mechanistic study

We carried out several UV-Vis measurements and NMR experiments to gain insights into the reaction mechanism. Firstly, in the UV-Vis absorption spectra, neither pyridine or silylborane showed any absorptions above 350 nm, while a mixture of both reagents displayed an absorption at 350 nm (Fig. 5a). These observations indicate that the pyridine-silylborane adduct generated in situ is photochemically excited upon 365 nm LED irradiation to undergo the reaction as initially expected. Secondly, time course analysis of the reaction by ¹H NMR disclosed that small amounts of *N*-boryl-2-silyl-1,2-dihydropyridine **12a** and *N*-boryl-4-silyl-1,4-dihydropyridine **13a** were generated along with **2a** in the beginning of the reaction using 430 nm LEDs although the reaction upon 365 nm irradiation did not show any detectable intermediates (Fig. 5b). The 2-silyl isomer **12a** disappeared after a long period of irradiation while the 4-sily isomer **13a** remained and
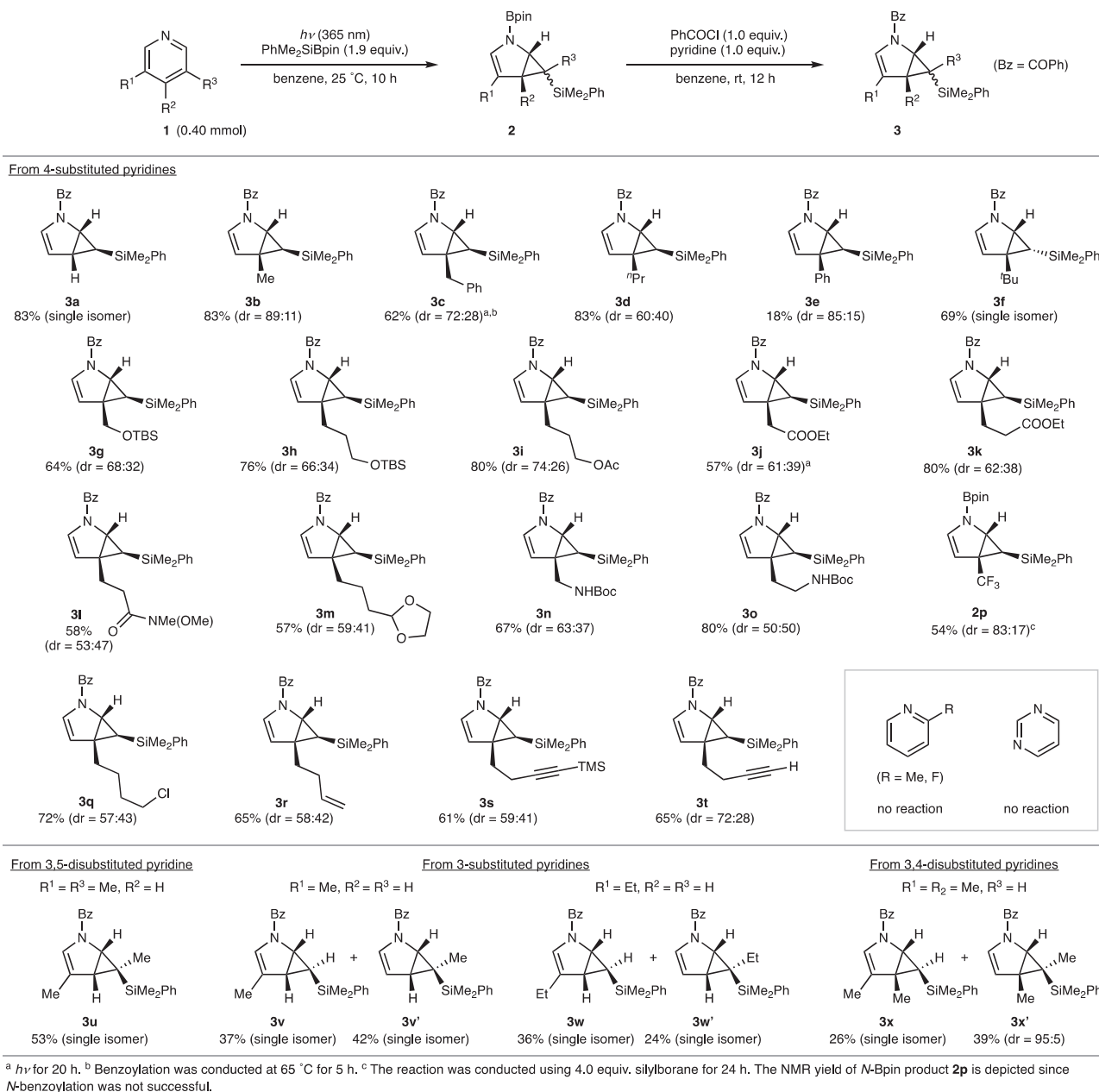
Fig. 3 | Substrate scope of the photo-promoted ring contraction of pyridines. Wide generality of pyridine substrates and excellent compatibility with various functional groups are demonstrated, enabling facile access to pyrrolidine derivatives bearing a 2-azabicyclo[3.1.0]hex-3-ene skeleton from easily available pyridines. TBS *tert*-butyldimethylsilyl, Ac acetyl, Boc *tert*-butoxycarbonyl, TMS trimethylsilyl.

accumulated (up to 3%, 11 h), which was finally consumed after additional irradiation at 365 nm for 2 h. These data are highly indicative of the intermediacy of dihydropyridines **12a** and **13a** in the reaction. Thirdly, we found that the product **2a** underwent skeletal rearrangement by heating at 140 °C for 2 h to give 1,2-dihydropyridine **12a** quantitatively (Fig. 5c). Then, the formed **12a** was confirmed to be fully converted to **2a** upon photoirradiation at 365 nm for 1 h, thus proving the photoreactivity of **12a** leading to **2a**. No formation of the 4-silyl isomer **13a** was observed during the thermolysis of **2a**. Furthermore, it was revealed that the product **2u** derived from 3,5-dimethylpyridine also exhibited the same interconvertible reactivity with heat and light, affording 3,5-dimethyl-2-silyl-1,2-dihydropyridine **12u** as a single product bearing a silyl group at the 2-position and Me-substituents at the 3- and 5-positions. These experimental data clarify that the photoreaction of pyridines with silylborane initially generates 2-silyl-1,2-dihydropyridines **12** as a major intermediate via the pyridine-

silylborane adduct, which is then converted to the products **2** under the influence of photoenergy through the migration of the silyl group from the 2-position to the 3-position. Regarding the photochemical skeletal rearrangement reaction of 1,2-dihydropyridine derivatives, in 1971, Biellmann reported a photoreaction of a particular Hantzsch ester derivative to form a 2-azabicyclo[3.1.0]hex-3-ene derivative in low yield[46], which was proposed to proceed via electrocyclization to generate a 1-azatriene intermediate (Fig. 5d)[47–49]. This is a very specific example and has not been developed as a synthetic reaction to date. Moreover, the mechanism via the 1-azatriene intermediate is not consistent with our system, as shown in Fig. 5c (R = Me), which demonstrates that the silyl group is migrating between the carbon atoms at the 2- and 3-positions of the dihydropyridine ring.

According to the experimental results, a plausible reaction mechanism involving 2-silyl-1,2-dihydropyridine as an intermediate was investigated by DFT calculations (ωB97XD/def2-TZVPP/

a Large scale reaction
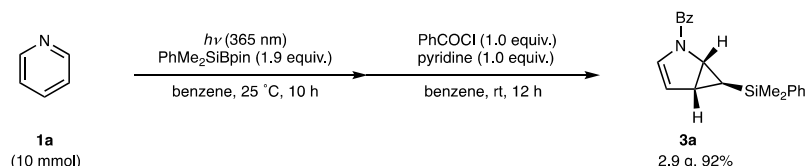
b Formation of lactam with *N,S*-acetal
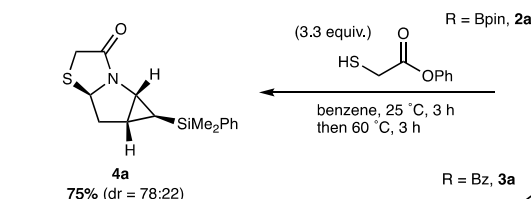
h Cyclopropane synthesis
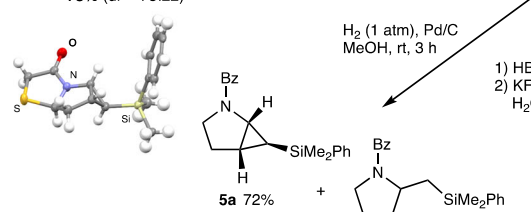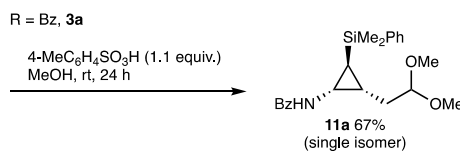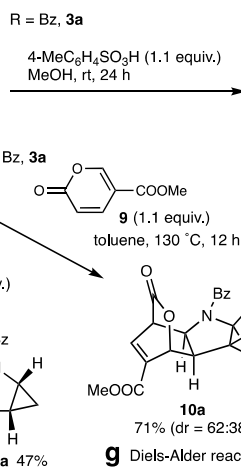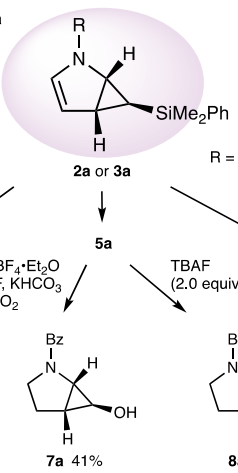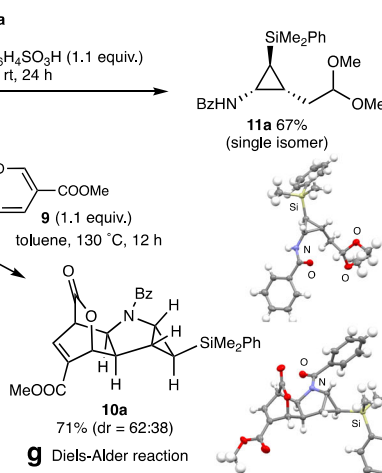
Fig. 4 | Large-scale synthesis and transformation of 2 and 3 to various pyrrolidine derivatives and other nitrogen-containing compounds. a A large scale reaction using 10 mmol pyridine. **b** The formation of tricyclic lactam **4a** having an *N,S*-acetal moiety by the reaction of **2a** with phenyl thioglycolate. **c** Hydrogenation of the enamide moiety of **3a** to give a saturated derivative **5a**. **d** Reductive ring-opening of the cyclopropane moiety to give 2-(silylmethyl)pyrrolidine **6a**. **e** The Tamao-Fleming oxidation of the silyl group of **5a** to afford cyclopropanol **7a**. **f** Desilylation of **5a** with TBAF to afford **8a**. **g** The Diels-Alder reaction of **3a** with a 2-pyrone derivative **9** to afford a tetracyclic compound **10a**. **h** Acidic alcoholysis to afford a functionalized cyclopropane **11a**.

SMD(benzene)) (Fig. 5e). Gibbs free energies and Cartesian coordinates of the optimized structures are provided in Supplementary Dataset. The pyridine-silylborane adduct **A** is less stable than starting compounds and generated reversibly. The TD-DFT calculation supports that the adduct **A** exhibits an absorption maximum at 349 nm, which is almost identical to that observed in the UV-Vis spectrum (Fig. 5a). We propose that photoexcited states of **A**, either or both a singlet state ^{1}**A*** and a triplet state ^{3}**A***, induce migration of the silyl group from the boron atom to the C2-position of the pyridine ring to form 2-silyl-1,2-dihydropyridine **D** (Fig. S10)[50,51]. As a photochemical reaction pathway from the 2-silyl-1,2-dihydropyridine intermediate **D** to the product, we found that a singlet excited state ^{1}**D*** undergoes 1,2-silyl migration via a ^{1}**TS1*** ($\Delta E = 6.4$ kcal/mol) to generate vinylazomethine ylide **E** bearing the silyl group at the 3-position. Finally, a thermally-promoted, disrotatory electrocyclic ring-closing reaction of **E** proceeds almost barrierlessly according to the Woodward-Hoffmann (W–H) rules, furnishing the 6-silyl-2-azabicyclo[3.1.0]hex-3-ene skeleton of **F**[52]. The ring-closing and -opening electrocyclic reactions are reversible at room temperature, thus suggesting that the ratio of diastereomers of **F** is thermodynamically controlled. Regarding the thermally-promoted reaction from **F** to **D**, the reverse 1,2-silyl migration from **E** to **D** is not plausible under thermal conditions due to the mismatched orbital symmetry. Instead of that, 1,4-silyl migration of the silyl group from the 3-position to the 6-position in **E**, which is regarded as a thermally-allowed 1,4-sigmatoropic rearrangement reaction, proceeds via **TS2** to afford 2-silyl-1,2-dihydropyridine **D**. This is the rate-determining step of the thermally promoted reverse reaction requiring an activation energy of 32.8 kcal/mol from *trans* **F**, which can be overcome by heating at 140 °C. Moreover, the electrocyclic ring-opening reaction of **F** to generate a 1-azatriene intermediate **G**

needs an activation energy of 44.9 kcal/mol via **TS3** and is ruled out. Consequently, we have elucidated that the ring contraction proceeds via the *N*-boryl-2-silyl-1,2-dihydropyridine intermediate **12** that is photochemically generated from pyridines and silylboranes. The 2-silyl-1,2-dihydropyridine undergoes unprecedented photo-induced 1,2-silyl migration to form 3-silylazomethine ylide, which furnishes the pyrrolidine skeleton via a thermally-allowed disrotatory ring-closing reaction. The details of the theoretical calculations are descried in the supplementary information (Fig. S9–S14).

In conclusion, we have developed a photo-promoted ring contraction reaction of pyridines with silylborane to give pyrrolidine derivatives bearing a 2-azabicyclo[3.1.0]hex-3-ene skeleton. The reaction demonstrates broad substrate scope with high functional group compatibility, and the obtained products work as a powerful synthon for the synthesis of functionalized pyrrolidines and other nitrogen-containing compounds. The reaction proceeds via 2-silyl-1,2-dihydropyridine and vinylazomethine ylide as intermediates, which are connected by unprecedented photochemical or thermal silyl migration. This reaction provides a synthetic strategy to rapidly access pyrrolidine skeletons from readily available pyridines, leading to acceleration of drug development research and exploration of chemical spaces of nitrogen-containing compounds.

Methods

General procedure for one-pot synthesis of 3 via ring contraction followed by *N*-benzoylation

A solution of pyridine derivatives **1** (0.40 mmol) and PhMe$_2$SiBpin (200 μL, 0.87 mmol) in benzene (2.0 mL) was placed in a sealed glass tube. The solution was photo-irradiated at 365 nm with stirring at 25 °C for 10 h. To the solution of the generated
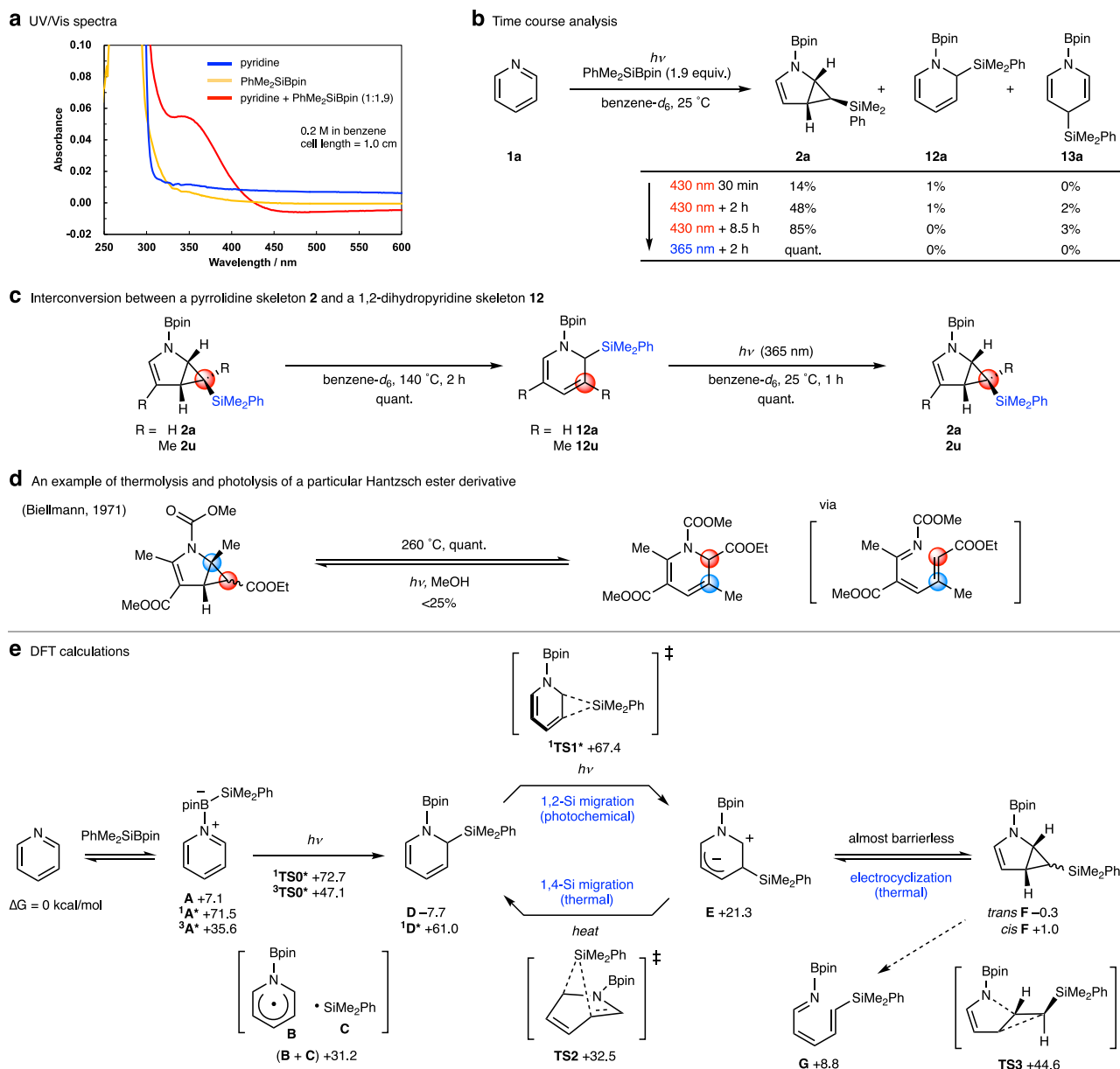
Fig. 5 | Investigations on the reaction mechanism. a UV-Vis spectra of benzene solutions of pyridine (a blue line), silylborane (a yellow line), and a mixture of pyridine and silylborane (a red line). **b** Time course analysis of the ring contraction reaction of pyridine with silylborane. **c** Interconversion between the products **2** and 1,2-dihydropyridines **12**. **d** An example of thermolysis and photolysis of a particular Hantzsch ester derivative reported by Biellmann. **e** DFT calculations (ωB97XD/def2-TZVPP/SMD(benzene)). G$_{rel}$ refer to Gibbs' free energies relative to that of pyridine and PhMe$_2$SiBpin in kcal/mol.

N-boryl-6-silyl-2-azabicyclo[3.1.0]hex-3-ene **2** were added pyridine (32.0 μL, 0.397 mmol) and benzoyl chloride (48.0 μL, 0.413 mmol) at room temperature for *N*-benzoylation. After stirring for 12 h, the mixture was filtered through a short pad of Celite®. The solvent was removed under reduced pressure to give a crude mixture, which was purified by alumina chromatography to give **3**.

Data availability

The experimental data generated in this study are provided in Supplementary Information file. The Gibbs free energies and Cartesian coordinates of the optimized structures in theoretical calculations are provided in the Supplementary Data 1 file. The crystallographic data CCDC 2414193 (**4a**), 2414194 (**10a**), and 2414195 (**11a**) have been deposited in The Cambridge Crystallographic Data Centre. The data can be obtained free of charge via

www.ccdc.cam.ac.uk/structures. Data supporting the findings of this manuscript are also available from the corresponding author upon request.

References

1. Petri, G. L. et al. Pyrrolidine in drug discovery: a versatile scaffold for novel biologically active compounds. *Top. Curr. Chem.* **379**, 34 (2021).
2. Speck, K. & Magauer, T. The chemistry of isoindole natural products. *Beilstein J. Org. Chem.* **9**, 2048–2078 (2013).
3. Holladay, M. W., Dart, M. J. & Lynch, J. K. Neuronal nicotinic acetylcholine receptors as targets for drug discovery. *J. Med. Chem.* **40**, 4169–4194 (1997).
4. Dubey, S. et al. Recent advances in the (3+2) cycloaddition of azomethine ylide. *N. J. Chem.* **47**, 8997–9034 (2023).

5. Padwa, A. & Pearson, W. H. (eds.) Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products. Nashville, TN (John Wiley & Sons, 2002).

6. Ye, Y. et al. Using enzymes to tame nitrogen-centred radicals for enantioselective hydroamination. *Nat. Chem.* **15**, 206–212 (2023).

7. Wang, P., Zhao, Q., Xiao, W. & Chen, J. Recent advances in visible-light photoredox-catalyzed nitrogen radical cyclization. *Green Synth. Catal.* **1**, 42–51 (2020).

8. Rocard, L. et al. Earth-abundant 3d Transition metal catalysts for hydroalkoxylation and hydroamination of unactivated alkenes. *Catalysts* **11**, 674 (2021).

9. Bernoud, E., Lepori, C., Mellah, M., Schulz, E. & Hannedouche, J. Recent advances in metal free- and late transition metal-catalysed hydroamination of unactivated alkenes. *Catal. Sci. Technol.* **5**, 2017–2037 (2015).

10. Qin, J., Zhou, Z., Cui, T., Hemming, M. & Meggers, E. Enantioselective intramolecular C–H amination of aliphatic azides by dual ruthenium and phosphine catalysis. *Chem. Sci.* **10**, 3202–3207 (2019).

11. Munnuri, S. et al. Catalyst-controlled diastereoselective synthesis of cyclic amines via C–H functionalization. *J. Am. Chem. Soc.* **139**, 18288–18294 (2017).

12. Meng, D., Tang, Y., Wei, J., Shi, X. & Yang, M. Copper-catalyzed remote (δ) C(sp³)–H bond amination: a practical strategy to construct pyrrolidine derivatives. *Chem. Commun.* **53**, 5744–5747 (2017).

13. Peplow, M. Almost magical': chemists can now move single atoms in and out of a molecule's core. *Nature* **618**, 21–24 (2023).

14. Joynson, B. W. & Ball, L. T. Skeletal editing: interconversion of arenes and heteroarenes. *Helvetica Chim. Acta* **106**, (2023).

15. Tang, J. et al. Tandem ring-contraction/regioselective C–H iodination reaction of pyridinium salts. *J. Org. Chem.* **88**, 2809–2821 (2023).

16. Peng, X.-J. et al. Photocatalyst-controlled and visible light-enabled selective oxidation of pyridinium salts. *Sci. China Chem.* **64**, 753–760 (2021).

17. Liu, X., Liu, C. & Cheng, X. Ring-contraction of Hantzsch esters and their derivatives to pyrroles via electrochemical extrusion of ethyl acetate out of aromatic rings. *Green Chem.* **23**, 3468–3473 (2021).

18. Xu, K. et al. Synthesis of 2-formylpyrroles from pyridinium iodide salts. *Org. Lett.* **22**, 6107–6111 (2020).

19. Pathirana, C. et al. A rare pyridine to pyrrole conversion leading to a side product in epoxide ring opening. *Tetrahedron Lett.* **50**, 1586–1587 (2009).

20. Linnell, R. H. & Noyes, W. A. Photochemical studies. XLIV. Pyridine and mixtures of acetone and pyridine 1. *J. Am. Chem. Soc.* **73**, 3986–3988 (1951).

21. Caplain, S., Catteau, J. P. & Lablache-Combier, A. Liquid-phase photochemistry of pyridine and 2- and 4-picoline. *J. Chem. Soc. D Chem. Commun.* **0**, 1475–1476 (1970).

22. Wilzbach, K. E. & Rausch, D. J. Photochemistry of nitrogen heterocycles. Dewar pyridine and its intermediacy in photoreduction and photohydration of pyridine. *J. Am. Chem. Soc.* **92**, 2178–2179 (1970).

23. Roebke, W. Gas-phase photolysis of 2-picoline. *J. Phys. Chem.* **74**, 4198–4203 (1970).

24. Kellogg, R. M., Bergen, T. Jvan & Wynberg, H. Photochemical ring contraction, reduction, and solvent addition in pyridines. *Tetrahedron Lett.* **10**, 5211–5214 (1969).

25. Kaplan, L., Pavlik, J. W. & Wilzbach, K. E. Photohydration of pyridinium ions. *J. Am. Chem. Soc.* **94**, 3283–3284 (1972).

26. Ling, R., Yoshida, M. & Mariano, P. S. Exploratory investigations probing a preparatively versatile, pyridinium salt photoelectrocyclization–solvolytic aziridine ring opening sequence. *J. Org. Chem.* **61**, 4439–4449 (1996).

27. Zou, J. & Mariano, P. S. The synthetic potential of pyridinium salt photochemistry. *Photochem. Photobiol. Sci.* **7**, 393–404 (2008).

28. Serra-Errante, G. & Sammes, P. G. An improved method for aromatic hydroxylation with heteroaromatic oxides. *J. Chem. Soc. Chem. Commun.* **0**, 573–574 (1975).

29. Woo, J. et al. Scaffold hopping by net photochemical carbon deletion of azaarenes. *Science* **376**, 527–532 (2022).

30. Jurczyk, J. et al. Single-atom logic for heterocycle editing. *Nat. Synth.* **1**, 352–364 (2022).

31. Woo, J., Stein, C., Christian, A. H. & Levin, M. D. Carbon-to-nitrogen single-atom transmutation of azaarenes. *Nature* **623**, 77–82 (2023).

32. Cheng, Q. et al. Skeletal editing of pyridines through atom-pair swap from CN to CC. *Nat. Chem.* **16**, 741–748 (2024).

33. 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).

34. Luo, J., Zhou, Q., 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).

35. Bubert, C., Voigt, J., Biasetton, S. & Reiser, O. A new approach to β- and γ-amino esters and amino aldehydes by regioselective ozonolysis of 2,3-dihydropyrroles and 1,2,3,4-tetrahydropyridines. *Synlett* **1994**, 675–677 (1994).

36. Gheorghe, A., Schulte, M. & Reiser, O. Synthesis of functionalized pyrrolidin-2-ones and (S)-vigabatrin from pyrrole. *J. Org. Chem.* **71**, 2173–2176 (2006).

37. Pilsl, L. K. A., Ertl, T. & Reiser, O. Enantioselective three-step synthesis of homo-β-proline: a donor–acceptor cyclopropane as key intermediate. *Org. Lett.* **19**, 2754–2757 (2017).

38. Fu, J., Wurzer, N., Lehner, V., Reiser, O. & Davies, H. M. L. Rh(II)-catalyzed monocyclopropanation of pyrroles and its application to the synthesis pharmaceutically relevant compounds. *Org. Lett.* **21**, 6102–6106 (2019).

39. Yedoyan, J., Wurzer, N., Klimczak, U., Ertl, T. & Reiser, O. Regio- and Stereoselective synthesis of functionalized dihydropyridines, pyridines, and 2H-Pyrans: heck coupling of monocyclopropanated heterocycles. *Angew. Chem. Int. Ed.* **58**, 3594–3598 (2019).

40. Sonnleitner, C. M., Park, S., Eckl, R., Ertl, T. & Reiser, O. Stereoselective synthesis of tropanes via a 6π-electrocyclic ring-opening/huisgen [3+2]-cycloaddition cascade of monocyclopropanated heterocycles. *Angew. Chem. Int. Ed.* **59**, 18110–18115 (2020).

41. Wurzer, N. et al. Heck-type coupling of fused bicyclic vinylcyclopropanes: synthesis of 1,2-dihydropyridines, 2,3-dihydro-1H-azepines, 1,4-cyclohexadienes, and 2H-pyrans. *ACS Catal.* **11**, 12019–12028 (2021).

42. Yang, Y. et al. Controllable skeletal and peripheral editing of pyrroles with vinylcarbenes. *Angew. Chem. Int. Ed.* **63**, e202401359 (2024).

43. Barrett, A. G. M. & Tam, W. Regioselective ring opening of vinylcyclopropanes by hydrogenation with palladium on activated carbon. *J. Org. Chem.* **62**, 7673–7678 (1997).

44. Shintani, R., Fujie, R., Takeda, M. & Nozaki, K. Silylative cyclopropanation of allyl phosphates with silylboronates. *Angew. Chem. Int. Ed.* **53**, 6546–6549 (2014).

45. Spieß, P., Berger, M., Kaiser, D. & Maulide, N. Direct synthesis of enamides via electrophilic activation of amides. *J. Am. Chem. Soc.* **143**, 10524–10529 (2021).

46. Biellmann, J. F. & Goeldner, M. P. Synthèse et propriétés d'homopyrroles substitués. *Tetrahedron* **27**, 2957–2965 (1971).

47. George, M. V., Mitra, A. & Sukumaran, K. B. Thermal and photochemical transformations of hetero-1,3,5-hexatrienes into five-membered rings—possible pericyclic reactions. *Angew. Chem. Int. Ed. Engl.* **19**, 973–983 (1980).

48. Fowler, F. W. Synthesis and Thermolysis of N-Methoxycarbonyl-2,3-homopyrrole. *Angew. Chem. Int. Ed. Engl.* **10**, 135–135 (1971).

49. Tanny, S. R., Grossman, J. & Fowler, F. W. Synthesis and thermal rearrangement of the 2-azabicyclo[3.1.0]hex-3-ene ring system. *J. Am. Chem. Soc.* **94**, 6495–6501 (1972).

50. Morimasa, Y., Kabasawa, K., Ohmura, T. & Suginome, M. Pyridine-based organocatalysts for regioselective syn-1,2-silaboration of terminal alkynes and allenes. *Asian J. Org. Chem.* **8**, 1092–1096 (2019).
51. Takemura, N., Sumida, Y. & Ohmiya, H. Organic photoredox-catalyzed silyl radical generation from silylboronate. *ACS Catal.* **12**, 7804–7810 (2022).
52. Ischay, M. A., Takase, M. K., Bergman, R. G. & Ellman, J. A. Unstabilized azomethine ylides for the stereoselective synthesis of substituted piperidines, tropanes, and azabicyclo[3.1.0] systems. *J. Am. Chem. Soc.* **135**, 2478–2481 (2013).

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J.T. conceived the work. R.U. and S.H. performed all experiments and collected experimental data with the help of J.T. J.T. supervised the project and wrote manuscript. All authors contributed to editing of the manuscript.

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