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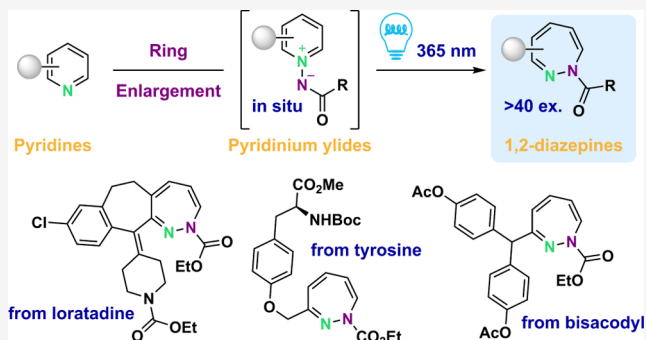


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Supporting Information

ABSTRACT: In this report, we developed a unified and standardized one-pot sequence that converts pyridine derivatives into 1,2-diazepines by inserting a nitrogen atom. This skeletal transformation capitalizes on the *in situ* generation of 1-aminopyridinium ylides, which rearrange under UV light irradiation. A thorough evaluation of the key parameters (wavelength, reaction conditions, activating agent) allowed us to elaborate on a simple, mild, and user-friendly protocol. The model reaction was extrapolated to more than 40 examples, including drug derivatives, affording unique 7-membered structures. Mechanistic evidence supports the transient presence of a diazanorcaradiene species. Finally, pertinent transformations of the products, including ring contraction reactions to form pyrazoles, were conducted and paved the way to a broad application of the developed protocol.



INTRODUCTION

Heterocyclic scaffolds are ubiquitous in bioactive molecules and particularly coveted in drug design as they confer selectivity and valuable properties to a potential drug candidate.^{1–3} Among them, pyridine-containing compounds could be found in a vast part of the FDA-approved bioactive molecules (Figure 1A).^{4–7} Indeed, this aromatic core can be prepared and modified in many efficient ways.^{8,9} On the other hand, 7-membered ring azaheterocycles, like 1,2-diazepines, are much less studied.¹⁰ The two heterocycles only differ by one nitrogen atom, yet they contrast sharply. Reported syntheses of 1,2-diazepines exclusively rely on the combination of well-designed 1,5-dielectrophiles and hydrazine, as the N–N bond formation is reputed to be challenging.¹⁰ The latter induces side reactivities such as oligomerization, polyalkylation, or even potential hydrolysis of the substrate. Therefore, it is not surprising to find this motif in only a handful of bioactive substrates.^{11–15} Among them, benzofused derivatives represent the most common motif, as the aromatic ring restricts the conformation of the 1,5-dielectrophile, thus facilitating the key annulation step with hydrazine. In contrast, the synthesis of monocyclic 1,2-diazepines can be tedious, as shown with the preparation of a progesterone receptor antagonist, which relies on laborious protocols and inefficient purification.¹² However, 1,2-diazepines could be very compelling if one wants to modulate the geometry or the properties of a target compound. According to the Hückel rule, 1,2-diazepine is nonaromatic, and its planarity is disrupted, offering benefits in terms of selectivity of a 3-dimensional architecture.

Over the past years, many elegant strategies have emerged aiming at editing aromatic skeletons^{16–18} by inserting,^{19–28} deleting,^{29,30} or swapping atoms^{31–34} in a short amount of time and steps (Figure 1B). Thus, one could rapidly evaluate the potential interest of drug analogues by interchanging the nature of one (or more) aromatic ring(s). This paradigm shift would greatly accelerate drug discovery and prevent time-consuming and in-depth retrosynthetic analysis to access complex analogues through nontraditional disconnections.³⁵ Therefore, we wondered if pyridines could be seen as an abundant feedstock for the synthesis of 1,2-diazepines by developing a methodology to incorporate a nitrogen atom into the pyridine core.

An important milestone was reached in the 70s with the photochemical rearrangement of 1-aminopyridinium ylides into 1,2-diazepines by Streith and Cassal (Figure 1C).^{36,37} Several research groups slightly extended the scope of accessible 1,2-diazepines.^{38–41} However, tedious synthesis and isolation of the starting materials remain a significant drawback. Despite the indisputable interest of 1-aminopyridinium salts in organic synthesis,⁴² this reaction remained a scientific curiosity and was never applied to any synthesis. To

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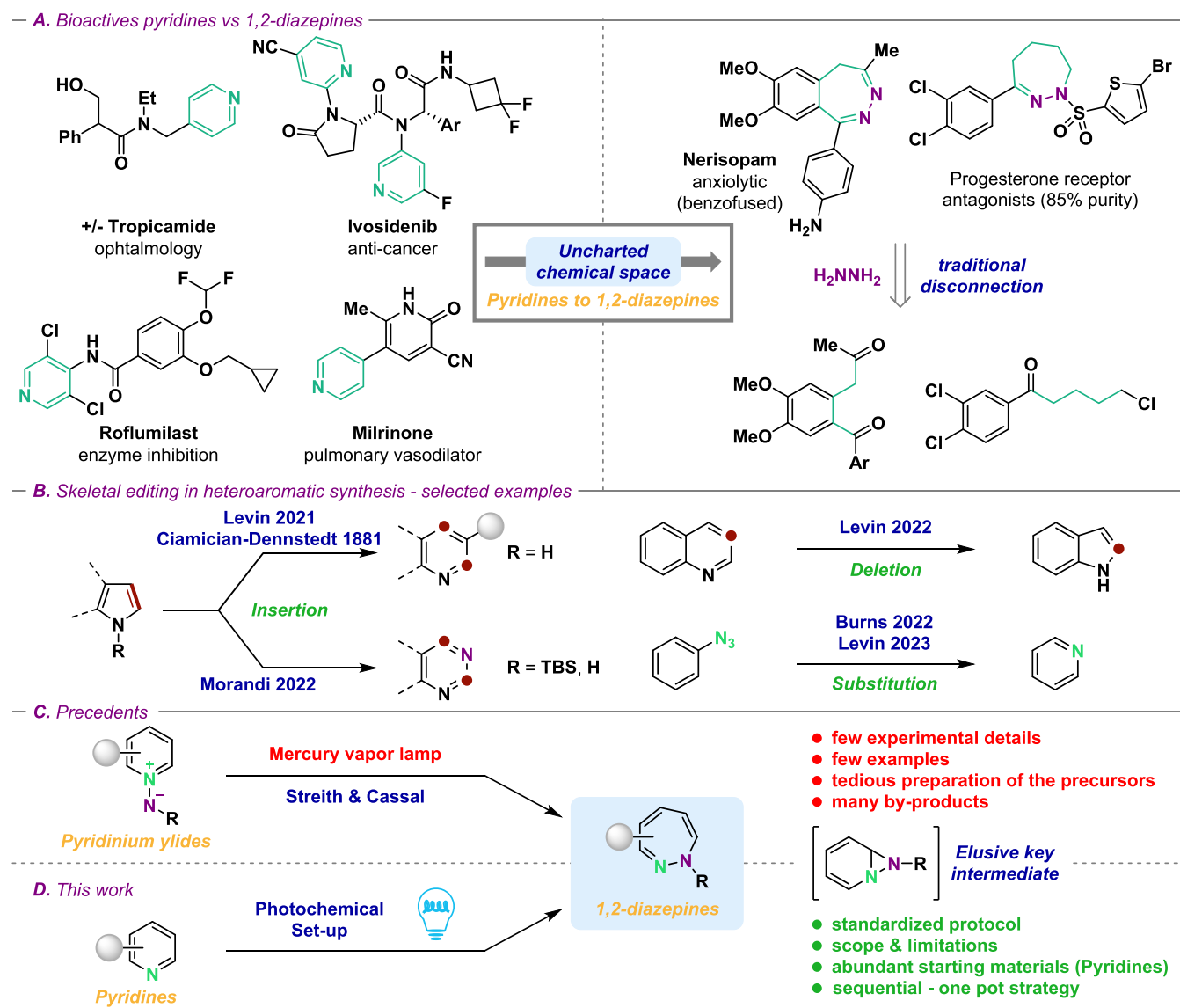


Figure 1. Context of the study.

tackle these hurdles, a unified and standardized protocol is required to facilitate access to 1,2-diazepines and ensure reproducibility. Based on this statement, we aim at developing a sequential protocol in which the photoactive 1-aminopyridinium ylide is generated *in situ* from pyridine derivatives, thus unlocking the dearomative ring enlargement for the synthesis of 1,2-diazepines from readily available building blocks (Figure 1D).²⁸ In order to provide a general and user-friendly strategy, the key parameters of this transformation will be scrutinized.

RESULTS AND DISCUSSION

Our investigations started by studying the optimal wavelength by UV-vis absorbance to trigger the photochemical rearrangement (Figure 2A).⁴³ Ylides bearing various substituents on the exocyclic nitrogen atom were prepared according to the reported procedures.^{44,45} In all cases, an absorbance band was found between 330 and 370 nm in CH₂Cl₂, whose intensity decreases over time. Therefore, we monitored the conversion of one aminopyridinium ylide by ¹H NMR in deuterated DMSO by directly irradiating the solution at 365 nm with a

coaxial optical fiber in the spectrometer. A first order decay of the starting material was clearly identified, leading to the clean formation of a dearomatized product, which turned out to be the corresponding 1,2-diazepine. In addition, several *para*-substituents were investigated in a Hammett study (Figure 2B). The moderate negative ρ value is in good agreement with a loss of a negative charge during the rate-determining step, which is not directly conjugated to the considered benzene ring (see the Supporting Information for kinetics). As a matter of fact, the more donating the substituent is, the faster is the rate. In contrast, substrates substituted with strong electron-withdrawing groups were more reluctant to form the expected products. This can be explained by a partial loss of the negative charge on the exocyclic nitrogen atom in the mesomeric form.

We next turned our attention to the photochemical rearrangement of readily available and bench stable 1-aminopyridinium ylides (Figure 2C). Several representative substrates were prepared and isolated in order to assess the influence of the substituent on the negatively charged nitrogen atom (see the Supporting Information for the synthetic procedures). After a preliminary optimization phase, we

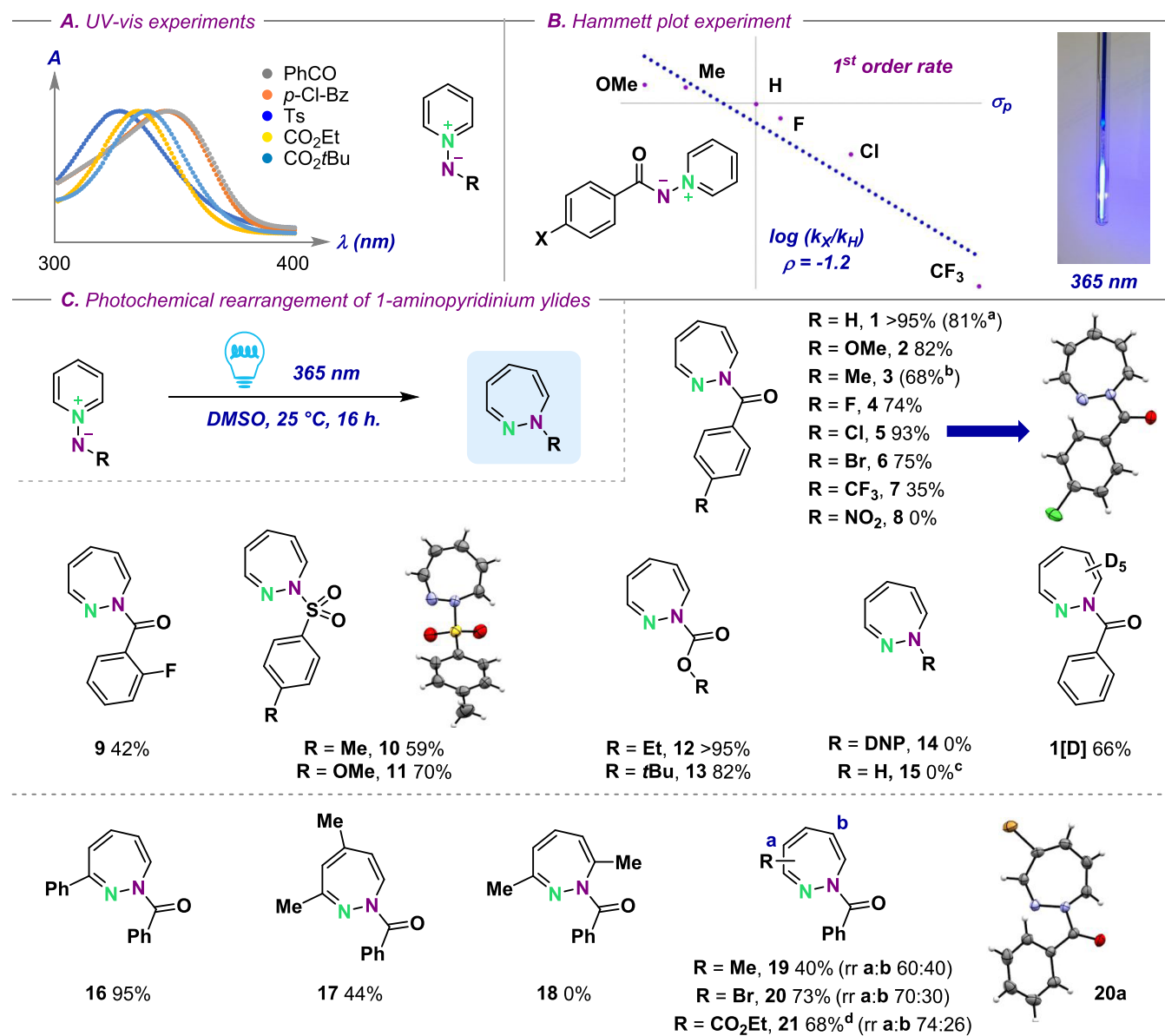


Figure 2. Optimization of the photochemical rearrangement. Isolated yields of pure products are reported. ^a2 equiv of TEMPO were added. ^bNeat compound **3** is unstable and rapidly decomposes. The yield of the pure material in solution was estimated by ¹H qNMR spectroscopy. ^cSame outcome is observed if 1 equiv of AcOH or NEt₃ is added. ^dObtained as an inseparable mixture. DNP = 2,4-dinitrophenyl.

found that irradiation of ylides at 365 nm was very effective in both CH₂Cl₂ and DMSO, with the latter ensuring better solubility. First of all, benzoyl derivatives bearing different substituents were engaged. In general, good to excellent yields were obtained after the isolation of the desired 1,2-diazepines (**1–6**). Noteworthy, **1** was still isolated in 81% yield when 2 equiv of TEMPO, a radical scavenger, were added to the reaction vessel. Moreover, the chlorinated analogue **5** afforded suitable crystals for X-ray diffraction, thus confirming the structure of the product. Nonetheless, electron-withdrawing groups attached to the *para* or *ortho* position of the benzoyl core were detrimental to the outcome (**7–9**); in the case of a nitro group, the reactivity was switched off. This trend was confirmed when sulfonylated analogues were prepared. Although the corresponding diazepine **10** could be isolated in 59% yield and crystallized,⁴⁶ one can observe the concomitant formation of both pyridine and tosylamide resulting from the N–N bond cleavage. Indeed, given the

withdrawing nature of the tosyl group, this side reactivity follows the trend observed in the benzoyl series. Thus, replacing a methyl group for a methoxy group in **11** to counterbalance the electronics improved the yield. In accordance with reports in the literature,^{36,37} we could achieve good yields of the 1,2-diazepine when carbamate derivatives were engaged in our photochemical setup (**12** and **13**). This feature is particularly interesting if one wants to functionalize the inserted nitrogen atom at will by taking advantage of the reactivity of carbamates. As expected, electron-deficient aromatic substituents like a 2,4-dinitrophenyl did not lead to the desired product **14**. In fact, the irradiation of the parent ylide gave intractable crude mixtures in which the starting material could be detected in low amounts (ca. 25%). The unsubstituted and commercially available 1-aminopyridinium iodide was engaged under the same protocol. Even in the presence of additives, the crude analyses showed no conversion or, in the presence of triethylamine, a mixture of both the

starting material and pyridine. Interestingly, the preparation of the pentadeuterated 1,2-diazepine proceeded well, thus affording **1[D]** in 66% yield.

We next turned our attention to substituted pyridines and their impact on selectivity during the photochemical rearrangement. As expected, when the C2-position is blocked either with a phenyl or a methyl group, the insertion exclusively occurs between N1 and C6, as shown with compounds **16** and **17**. The ylide prepared from 2,6-lutidine failed to give the desired product **18**, thus confirming the sensitivity of the reaction toward steric hindrance when both active sites are inaccessible. When the C3-position is substituted, two regioisomers are obtained, independently of the electronic nature of the corresponding substituent (**19–21**). In the case of **20**, the two different 1,2-diazepines were easily separated, and the major product was unambiguously confirmed by X-ray diffraction. This result indicates that the selectivity is once again in favor of the less hindered reactive site.

In order to develop a one-pot sequence to convert pyridines into 1,2-diazepines, we envisaged generating the 1-aminopyridine ylide *in situ*. Based on our previous observations, substrate **22** should remain intact under UV light irradiation. Furthermore, as some *N*-benzoyl-1,2-diazepines appear to be poorly stable (**2** and **3** especially; **1** to a lesser extent), we selected ethyl chloroformate and triethylamine as reactants to generate the corresponding ylide. To our delight, we rapidly identified CH_2Cl_2 as a good candidate to perform both the generation of the ylide and the photochemical rearrangement as **12** was detected in the crude NMR in 78% yield (Figure 3 top, inset table, entries 1–4). While DIPEA led to a slight erosion of the yield, it remained quite efficient (entry 5). However, the use of inorganic bases like Cs_2CO_3 failed to improve the yield, mainly due to their poor solubility in CH_2Cl_2 (entry 6). Similarly, analogous activating agents such as PhCOCl or Boc_2O performed very well under these conditions, giving the corresponding 1,2-diazepines **1** and **13** in excellent isolated yields (entries 7 and 8). Finally, increasing the concentration allowed us to reduce the amount of CH_2Cl_2 while preparing **12** in similar yields (entry 9).

With these optimal conditions in hand, we had to find the most suitable aminating agent in order to elaborate a fully compatible protocol to convert pyridines into 1,2-diazepines in a single-flask operation (Figure 3 bottom, inset table). After querying the literature (see details in the Supporting Information), we selected **MSH** (*O*-(mesitylsulfonyl)-hydroxylamine) for several reasons: (a) it can be easily prepared in 2 steps from cheap and commercially available reactants and collected by filtration; (b) as an hydrate, usually between 20 and 40% water, it is an air and moisture tolerant solid, which could be stored under regular atmosphere for several days without any noticeable alteration (see the Supporting Information for potential hazard).⁴⁷ Thus, we could generate the 1-aminopyridinium *in situ* from the parent pyridine **23** within 1 h at 40 °C. Noteworthy, 4 Å molecular sieves appeared to increase the yield, although it is not mandatory to achieve synthetically useful yields. Taking advantage of our previous conditions, we achieved our goal of dearomatizing pyridine **23** via an N-atom insertion, and we could isolate the desired product **12** in 84% yield.

The scope and limitations of our protocol were explored (Figure 4). First, we found that several N-activators were compatible with our one-pot procedure, including PhCOCl (**1**), Boc_2O (**13**), CbzCl (**24**), base-sensitive FmocCl (**25**),

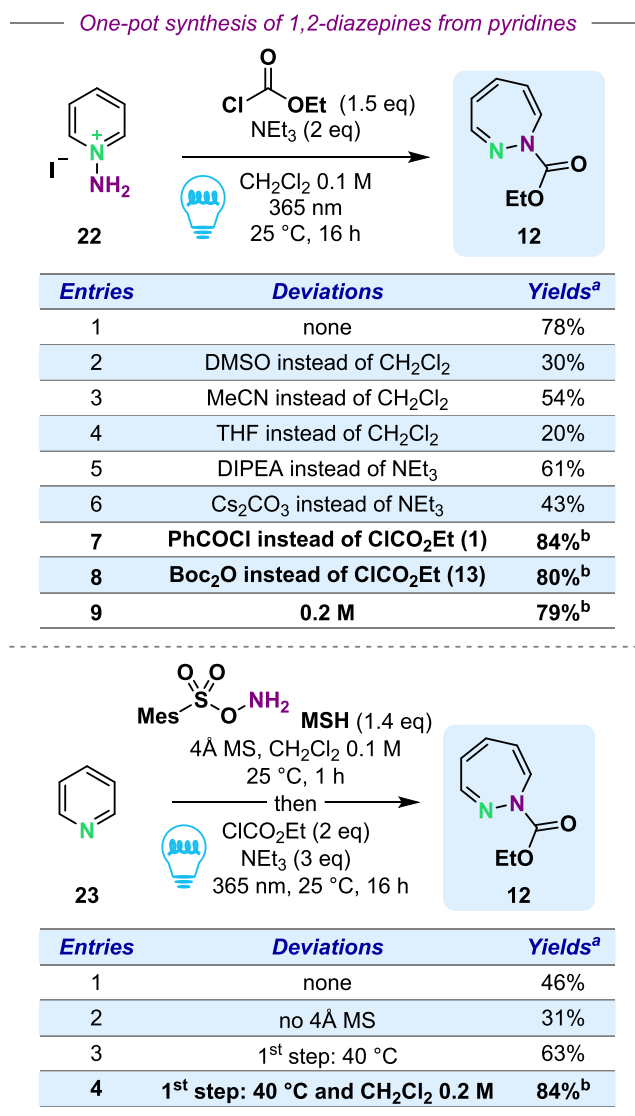


Figure 3. One-pot synthesis of 1,2-diazepines. ^aYields determined by ¹H qNMR spectroscopy with mesitylene as the internal standard. ^bIsolated yields of pure products are reported.

AllocCl (**26**), and even TrocCl (**27**), with a modest yield. Alkylpyridines gave satisfactory results affording the desired diazepines, although the yield drops when the pyridine is substituted with a benzyl group in the 4-position (**28–33**). Aromatic groups, including furan and thiophene, on the C2 carbon boded well under our conditions (**34–36**). We then questioned the functional group tolerance of our strategy. Indeed, nitrile (**37**), methoxy (**38**), ketones (**39**, **40**, and **47**), esters (**41** and **45**), amides (**46**, **50**, and **51**), or halogens (**42–44**, and **50**) were all tolerated and smoothly reacted to afford the corresponding 1,2-diazepines in modest to very good yields. Worth mentioning, these examples highlight the undeniable interest of this methodology as it permits access to previously out-of-reach molecules. As stated before, the most straightforward route to make 1,2-diazepines capitalizes on the use of hydrazine, which can be incompatible and particularly challenging with electrophilic moieties or polycarbonylated fragments. Only one 7-membered heterocycle is obtained when a 2- or 4-substituted pyridine is engaged. However, for 3-substituted substrates, both regioisomers were

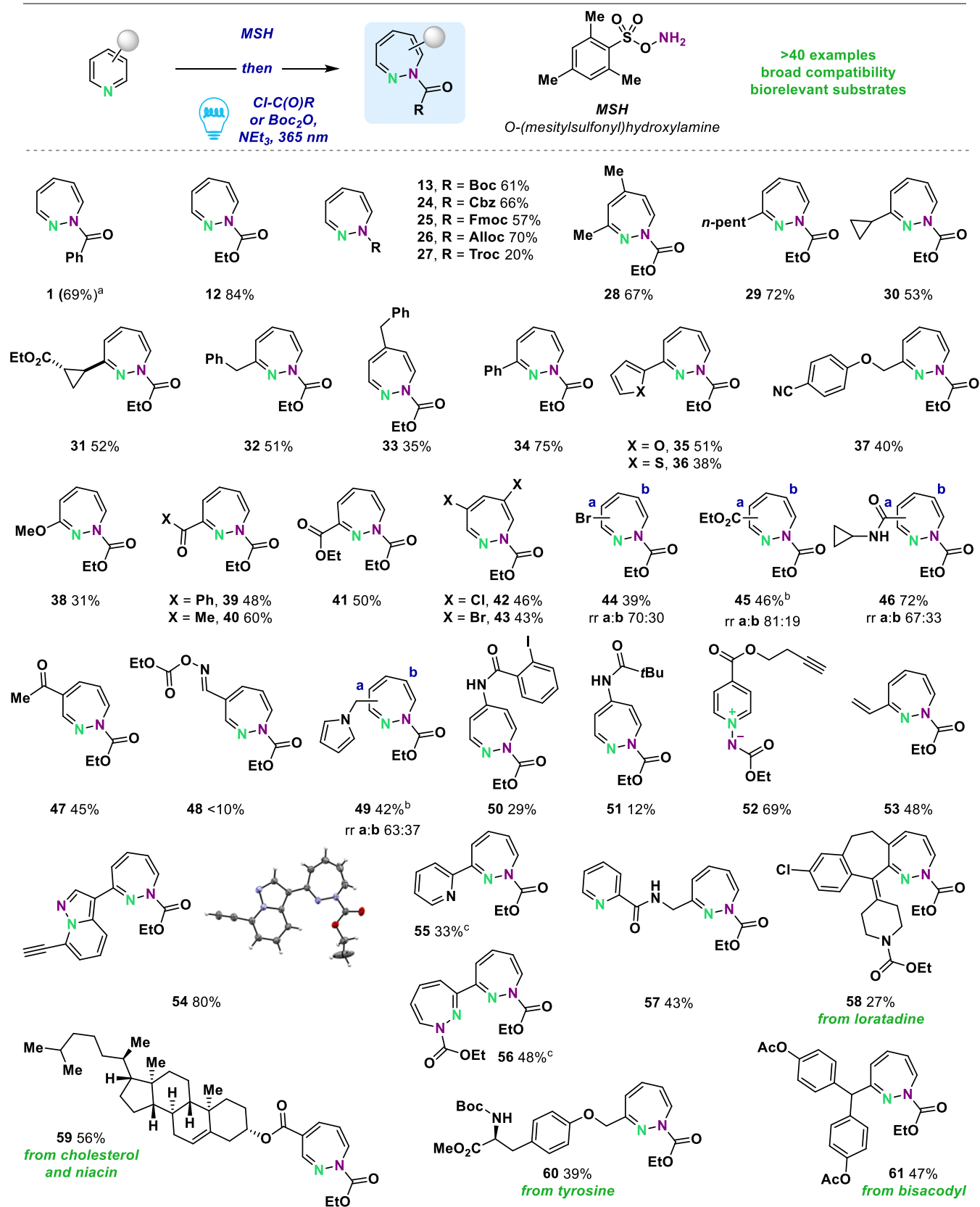


Figure 4. Substrate scope. Isolated yields of pure products are reported. ^aYield determined by ¹H qNMR spectroscopy with mesitylene as the internal standard. ^bObtained as an inseparable mixture. ^cMSH (2.8 equiv), ClCO₂Et (4 equiv), NEt₃ (6 equiv).

often obtained. In all cases, the selectivity is governed by the steric factors yielding preferentially the 4-substituted 1,2-

diazepine (**44**, **45**, **46**, and **49**). Therefore, one reaction enables the synthesis of up to 2 analogues with potentially

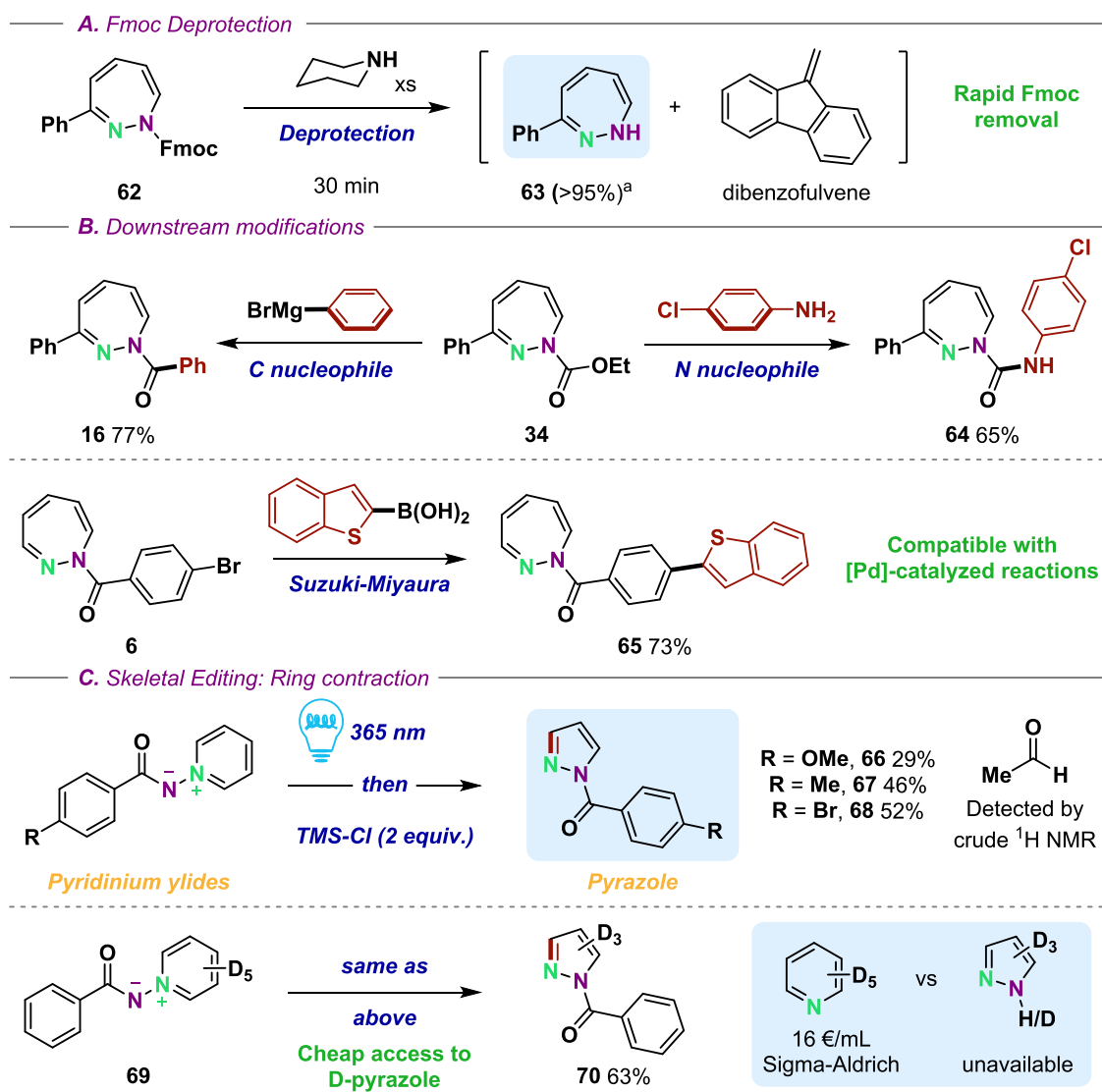


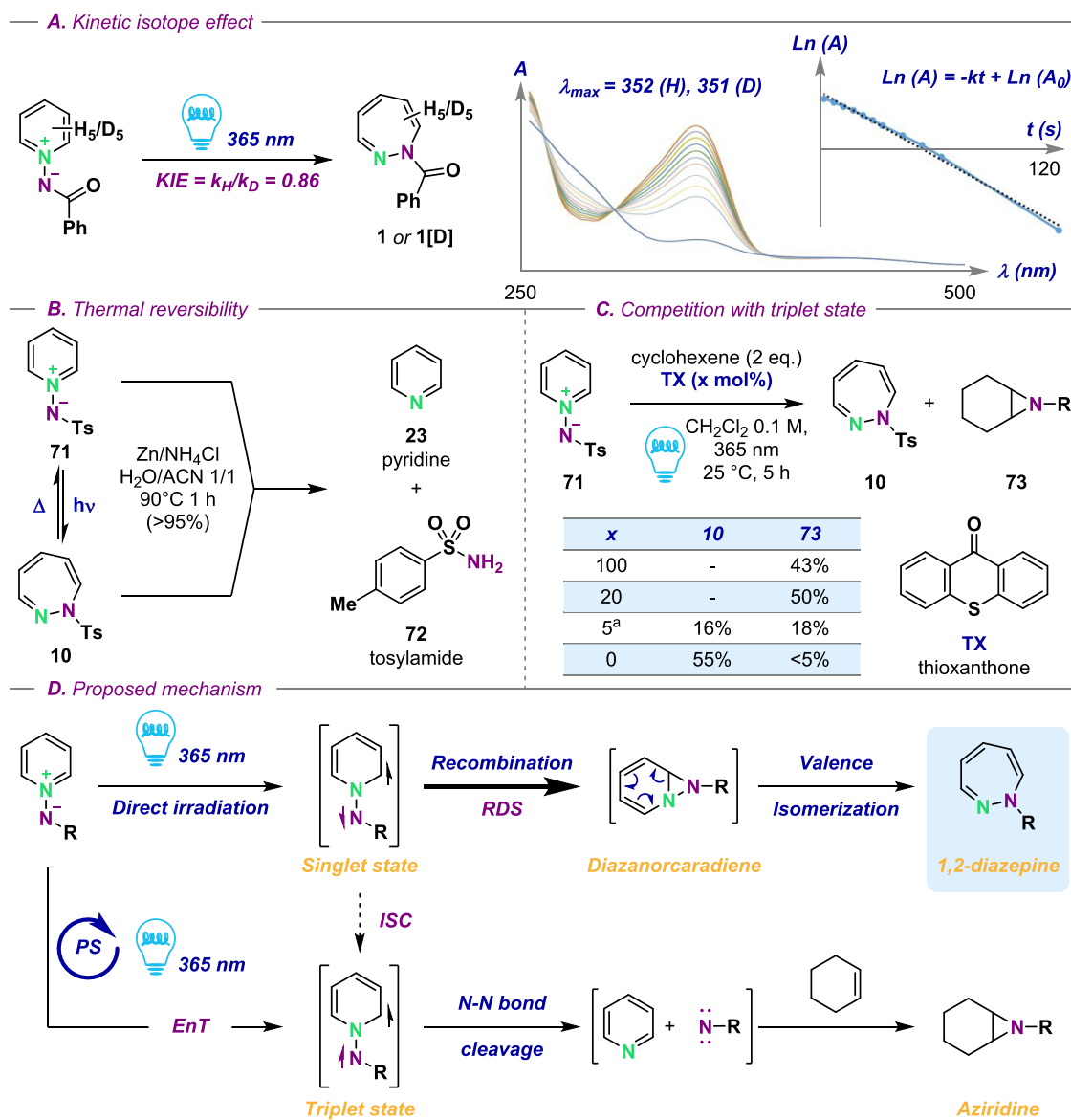
Figure 5. Functionalization and reactivity of 1,2-diazepines. See the [Supporting Information](#) for detailed procedures. ^aCharacterized in situ by NMR spectroscopy.

different properties. Interestingly, compound **47** was isolated as the sole isomer from the crude mixture. Pyridine bearing an aldoxime functional group could undergo rearrangement, furnishing **48**, although in low yield. In addition, the free OH group readily reacted with the ethyl chloroformate in excess. Electron-withdrawing groups in the C4 position inhibited the rearrangement;⁴⁸ we could nonetheless isolate the unreacted ylide **52** with a good yield. In the case of 2-vinylpyridine, the double bond was well tolerated, as we could not notice any side reactivity on the pending olefin (**53**). In contrast, the ethynyl derivative leads to the unexpected formation of a 1,2-diazepine bonded with a fused pyrazolo-[1,5-*a*]pyridine ring in 80% yield (**54**).⁴⁹ The structure of the latter was unambiguously revealed by X-ray diffraction. Then, we engaged 2,2'-bipyridine with twice the amount of MSH, ethyl chloroformate, and triethylamine. To our delight, we could easily separate the two main products, **55** and **56**, which turned out to result from one and two rearrangements, respectively. Interestingly, when 2 electronically different pyridines are present in the same molecule, only the more electron-rich reacts, as shown in compound **57**. Finally, we

could successfully prepare the 1,2-diazepine-based analogues of some relevant complex molecules like loratadine **58** (antihistamine drug), an ester of cholesterol and niacin (vitamin B₃) **59**, a tyrosine derivative **60** (neurotransmitters synthesis), and bisacodyl **61** (laxative). Even though **58** was obtained in moderate yield, the unusual structure of this tricyclic scaffold comprising two contiguous 7-membered rings makes it very challenging to prepare with another route.

These newly prepared substrates were then engaged in several postfunctionalization reactions ([Figure 5](#)). First, the rapid cleavage of the Fmoc protecting group was monitored for diazepine **62**, leading to the clean formation of **63** and dibenzofulvene ([Figure 5A](#)). Although the latter was straightforward, isolation or direct utilization of the free diazepine failed. Similar observations were made on the Boc derivative, although the cleavage of this protecting group appears to be more tedious (see the [Supporting Information](#)). We hypothesized that intermediate **63** might be too fragile and, therefore, decomposes promptly.

Rather than removing the protecting group, we decided to take advantage of the vast panel of activating groups enabling



the formation of the diazepines (Figure 5B). In fact, two representative nucleophiles readily displaced the ethoxylate, leading to the clean formation of **16** and **64** in very good yields for C and N nucleophiles, respectively. In addition, we could confirm that the seven-membered ring was fully compatible with a benchmark Suzuki–Miyaura reaction, leading to the coupled product **65** in 73% yield.

Noteworthy, we found an unprecedented serendipitous ring contraction reaction allowing the formation of pyrazoles from 1,2-diazepines upon simple treatment with an excess of TMS-Cl (Figure 5C). This Lewis acid triggers the ring-opening of the diazepine core followed by a 1,4-addition/retro-Mannich sequence affording both the pyrazole and acetaldehyde, whose presence was confirmed by crude ¹H NMR. Thus, we could capitalize on this transformation in a telescoped sequence from 1-aminopyridinium ylides affording the corresponding benzoylated pyrazoles **66**, **67**, and **68** in 29–52% yield. Although this interesting skeletal edition is very useful from a retrosynthetic point of view, we could also demonstrate an advantageous utility for a cheap preparation of deuterated pyrazoles from

deuterated pyridine as **70** was prepared one-pot in 63% from the parent ylide **69**.

Since the first report on the rearrangement of 1-amino-pyridinium ylides into 1,2-diazepines, the key intermediate remained elusive.⁵⁰ In fact, the bicyclic diazanorcaradiene was often proposed as its ring-opening can be explained due to the high ring strain. Although the latter has never been observed, it is a rather reasonable hypothesis and is in fair agreement with other processes furnishing 7-membered rings.^{31,32,51–53} Preliminary NMR experiments were conducted at $-60^\circ C$ in order to monitor the transient species. At this temperature, the rearrangement proceeds at a very slow rate, but the diazepine as well as the starting ylides only were detected (see the Supporting Information for details and additional experiments).

As the diazanorcaradiene cannot be directly observed, one can think its formation occurred during the rate-determining step (RDS) and, therefore, its opening leading to the formation of the 1,2-diazepine proceeds at a faster rate. To support this hypothesis, we measured the kinetic isotope effect (KIE) for

the formation of **1** and its deuterated analogue **1[D]** (Figure 6A).⁵⁴ To our delight, we evaluated the KIE at 0.86, which is in line with an inverse secondary KIE. In other words, during the RDS, the hybridization of a carbon atom bearing a proton or a deuterium atom changes from sp^2 to sp^3 (see the Supporting Information for more details on the KIE). Thus, the diazanorcaradiene is likely formed during the RDS, making its observation impossible by classical NMR techniques.

It has been postulated in several reports that both the ylide and the diazepine were in equilibrium.⁵⁰ Although we could not detect such an equilibrium in solution at room temperature, we could recover pyridine **23** and tosylamide **72** when the tosylated ylide **71** was engaged in reducing conditions in quantitative amounts (Figure 6B: Zn/NH₄Cl 90 °C, see details in the Supporting Information). The latter experiment suggests a reduction of the N–N bond, leading to the two aforementioned products. The same behavior was monitored when diazepine **10** was engaged under the same protocol, thus pointing to a reversible formation of the parent ylide under thermal/acidic conditions.

Upon direct irradiation, aminopyridinium ylides reach their singlet excited state, which is productive in the diazepine rearrangement, whereas the lower in energy triplet state triggers the homolytic cleavage of the N–N bond. Streith and co-workers performed an experiment in which the parent carbamate containing ylide is irradiated at 538 nm in the presence of >50 mol % of Eosin Y.⁵⁰ Indirect activation of the ylide through energy transfer generating the triplet state resulted in a complete quenching of the rearrangement and detection of pyridine in 58% yield in acetone. In order to test whether or not this behavior is generalizable, we engage the tosylated 1-aminopyridinium ylide **71** with various amounts of Eosin Y in DMSO-*d*₆ at 528 and 450 nm. Even under blue light irradiation, both pyridine **23** and tosylamide **72** were detected by ¹H NMR with a low photosensitizer loading (5 mol %). It is noteworthy that the corresponding diazepine was not observed, which is in good agreement with our optimization table (see the Supporting Information). Although this experiment is compelling, we wanted to monitor the competition between the singlet and triplet states at 365 nm (Figure 6C). To do so, we engaged thioxanthone (TX) as a photosensitizer. The latter is known to be an energy transfer (EnT) catalyst generating triplet excited states upon UV light irradiation. Cyclohexene was selected to trap transient nitrene release upon N–N bond cleavage. To our surprise, with 1 equiv of TX, only aziridine **73** was detected in 43% yield; not even traces of diazepine **10** were formed. A similar outcome is obtained for 20 mol % of photosensitizer. However, below this catalyst loading, the conversion is not complete, and the diazepine was found in the crude mixture. Finally, the blank experiment led to the formation of **10** as the major product (55%), while only traces of **73** were found. In summary, these experiments suggest that the presence of a photosensitizer can completely inhibit the formation of diazepine to promote the triplet excited state. Moreover, we also envisaged an EnT event from TX to the diazepine, resulting in undetectable decompositions. This was confirmed by engaging **10** with 20 mol % of TX under the same conditions. After 5 h, the substrate was completely consumed, and neither **71** nor **73** was recovered (see the Supporting Information).

Altogether and based on the previous reports, a mechanism was proposed (Figure 6D). Direct activation of the *in situ*-formed 1-aminopyridinium ylide generates exclusively the

singlet excited state intermediate, which rearranges to the postulated diazanorcaradiene. The latter rapidly opens affording the desired 1,2-diazepine. Upon direct activation under UV light, the intersystem crossing (ISC) leading to the triplet state remains a minor pathway, as noted in our NMR profiles. Under our reaction conditions, it becomes significant when the ylide is decorated with a tosyl group. Sulfonylated groups can indeed stabilize a radical on the neighboring nitrogen atom, thus extending its lifetime. As the rearrangement seems to be slowed down by strong withdrawing groups on the exocyclic nitrogen atom, it is not surprising to observe the formation of up to 20% of pyridine for tosylated starting materials. The competitive triplet pathway can be promoted with energy transfer (EnT) photosensitizers such as TX, leading to the formation of pyridine and the nitrene fragment.

CONCLUSIONS

In conclusion, we have established a unified protocol using commercially available resources and easily prepared reagents to dearomatize pyridine derivatives by inserting nitrogen atoms within the aromatic core. The ring expansion is triggered by the photochemical activation of 1-aminopyridinium ylides formed *in situ*. The synthesized products, even the simplest ones, were previously out of reach due to the lack of efficient methods to selectively prepare 1,2-diazepines. In fact, our protocol can be applied to pharmaceuticals to prepare the 7-membered ring analogues in a short amount of time and thus accelerate the discovery of potential drug candidates. Downstream functionalization reactions were successfully applied to the newly prepared 1,2-diazepines, thus offering many options to the practitioners. An unexpected skeletal editing ring contraction reaction was discovered that virtually allows the conversion of pyridine to pyrazole derivatives. Finally, mechanistic studies were conducted in order to support the formation of the diazanorcaradiene, elusive intermediate of the photochemical rearrangement. Further transformations involving the formed 1,2-diazepines are currently being studied in our group.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.3c14467>.

Experimental procedures, characterization data, NMR experiments, and crystallographic data (PDF)

Accession Codes

CCDC 2279846, 2279847, 2279848, 2279849, and 2279850 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, 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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Notes

The authors declare no competing financial interest.

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DEDICATION

In memory of Professor Jacques Streith.

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