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Unified Synthesis of Azepines by Visible-Light-Mediated Dearomative Ring Expansion of Aromatic *N*-Ylides

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Cite This: *Org. Lett.* 2021, 23, 525−529 Read Online

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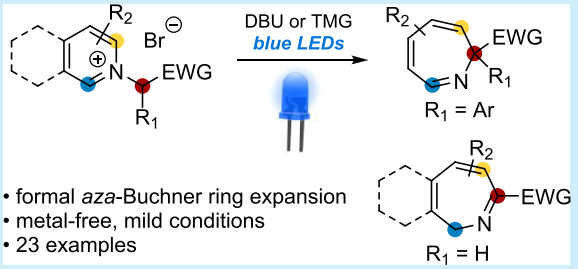
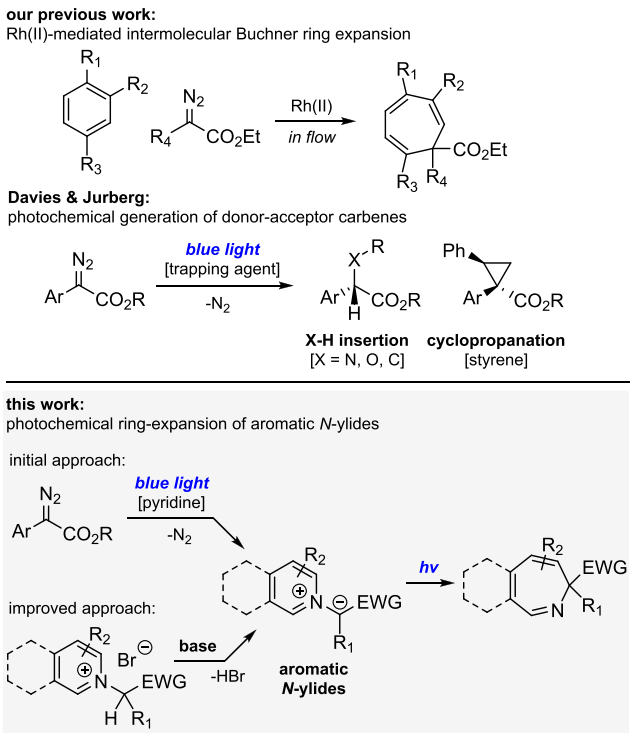
ABSTRACT: Herein, we report a unified approach to azepines by dearomative photochemical rearrangement of aromatic *N*-ylides. Deprotonation of quaternary aromatic salts with 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) or *N,N,N′,N′*-tetramethylquanidine (TMG) under visible light irradiation provides mono- and polycyclic azepines in yields up to 98%. This ring-expansion presents a new mode of access to functionalized azepines from N-heteroarenes using two straightforward steps and simple starting materials.



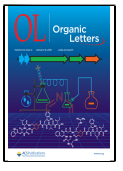
Azepines are seven-membered nitrogen heterocycles found broadly in both pharmaceuticals[1] and natural products[2] as core skeletal components and as functional appendages. They are among the top 100 most common heterocycles employed in drug discovery.[1] Current methods of synthesizing monocyclic azepines include *aza*-Prins cyclizations,[3] ring closing metathesis,[4] [4 + 3][5] and [5 + 2][6] cycloadditions, and condensation/reduction sequences.[7] These methods can have limitations in scope and utility, require multistep syntheses of precursors, or use expensive transition metal catalysts. Our interest in the synthesis of cycloheptatrienes[8] via the Buchner ring expansion led to the pursuit of an *aza* variant to access azepines directly from pyridines, which we believed would be a valued addition to the field of dearomatization.[9−11] We identified a report in which *N*-acylated isoquinolines and quinolines were ring expanded to benzazepines using copper(II) triflate and ethyl diazoacetate;[12] in another example, dihydroquinoline *N*-methylcarboxylates were ring expanded to benzazepines using TMS-diazomethane and an oxidant.[13] However, to the best of our knowledge, there is no reported method for the general dearomative ring expansion of pyridine derivatives. There are many methods to synthesize densely functionalized pyridine derivatives by both traditional ring-forming methods[14] and emergent C−H functionalization strategies;[15] a general method of pyridine ring expansion would enable modification of pre-existing libraries and facilitate modular *de novo* synthesis of azepines. Furthermore, access to the fully unsaturated azepine ring would also permit downstream manipulation of the imine and olefins.

Previously, we used flow chemistry to develop an improved protocol for the rhodium(II)-mediated intermolecular Buchner ring expansion (Scheme 1).[8] At the outset of this investigation, we were aware that dimeric rhodium(II) tetracarboxylate catalysts form stable complexes with pyridine,[16] so a different reaction paradigm was necessary. Thus, our initial approach to

Scheme 1. Previous Applications of α-Diazoacetate Decomposition, and Our Approaches to an *aza*-Buchner Ring Expansion



Received: December 7, 2020
Published: January 4, 2021

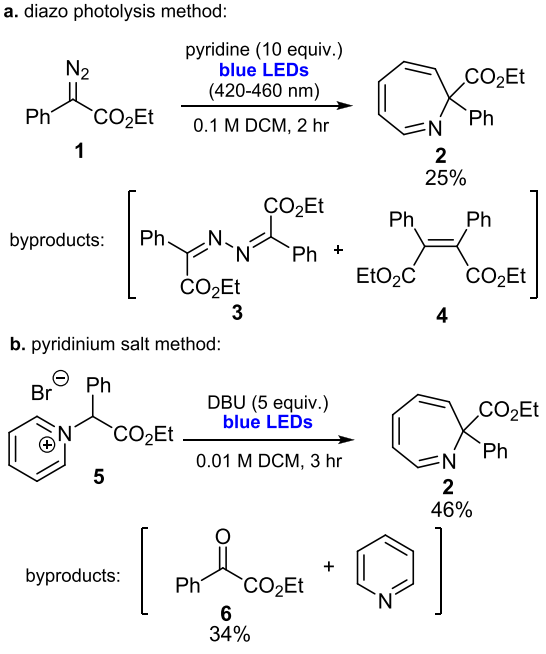


https://dx.doi.org/10.1021/acs.orglett.0c04050
Org. Lett. 2021, 23, 525−529

an *aza*-Buchner ring expansion focused on the photolysis of aryl diazoacetates (Scheme 1). In recent work, the Davies lab described the blue light photolysis of aryl diazoacetates in O−H, N−H, and C−H insertions and cyclopropanations, all of which proceed through a donor−acceptor carbene intermediate.[17] The Koenigs lab followed with cyclopropanation of alkyl-substituted arenes[18a] and cyclooctatetraenes[18b] by a similar method. Aryl diazoacetate photolysis offered access to carbenes without the use of transition metal catalysts. Trapping carbenes with pyridine would produce pyridinium ylides,[19] which have seen significant use in [3 + 2] cycloadditions along with isoquinolinium and quinolinium ylides.[20] Inspired by work from Streith et al. involving *N*-iminopyridinium ylides,[21] we reasoned that pyridinium methylides could rearrange to provide azepines via a bicyclic *aza*-norcaradiene (*aza*-NCD). Streith et al. postulated that *N*-iminopyridinium ylides are photochemically excited by UV light to give singlet diradicals by an n to π^* transition.[22] The excited species then undergoes α-recombination to form a bicyclic intermediate, and 6π electrocyclic ring opening to give the 1,2-diazepine product. Following this principle, we set out to generate pyridinium methylides via photolysis of aryl diazoacetates and identify conditions for their ring expansion to give azepines.

In our initial experiments we were pleased to find that blue-light photolysis of ethyl phenyldiazoacetate **1** in the presence of excess pyridine afforded the desired product **2** in low yields as a single regioisomer (Scheme 2a).

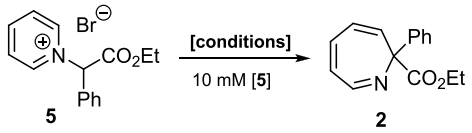
Scheme 2. Generation of Azepine (2) by Diazo Photolysis (a) and Pyridinium Salt Deprotonation (b)



However, this method required a large (10 equiv) excess of pyridine and was burdened by known carbene byproducts diazine[23] **3** and 2,3-diphenylmaleate[24] **4**. To avoid competitive side reactions and determine the photochemical dependency of the ylide rearrangement, we synthesized pyridinium bromide salt **5** (Scheme 2b) and irradiated it with blue light in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Gratifyingly, we observed improved yields of **2** compared to the diazo photolysis method; furthermore, we did not observe the carbene byproducts. However, we did observe ethyl phenylglyoxylate **6** which we presume could arise from benzylic aerobic oxidation of **5**. We reasoned that conducting the reaction in a flow photoreactor would improve photon flux and minimize aerobic oxidation,[25] so we investigated the ring expansion of pyridinium salt **5** using a flow photoreactor constructed in-house. Conducting the reaction in flow increased the yield of **2** to 91%.

With promising results from our initial experiments, we optimized the reaction conditions in flow (Table 1). The ring

Table 1. Optimization of Reaction Conditions for Ring Expansion of 5[a]



variable	entry	solvent	base (equiv)	yield (2)
solvent	1	MeOH	DBU (5)	0
	2	$CHCl_3$	DBU (5)	81
	3	MeCN	DBU (5)	81, 79[b]
	4	1,2-DCE	DBU (5)	87
	5	DCM	DBU (5)	91
base	6	DCM	2,6-lutidine (5)	n.r.
	7	DCM	TEA (5)	0
	8	DCM	DIPEA (5)	0
	9	DCM	TMP (5)	<5
	10	DCM	TMG (5)	56
	11	DCM	TBD (2.5)	93
	12	DCM	DBU (1)	43
		DCM		
concentration	13	DCM	DBU (5)	28[c]
temperature	14	DCM	DBU (5)	89[d]
	15	1,2-DCE	DBU (5)	11[e]
no light	16	DCM	DBU (5)	0[f]
no base	17	DCM	DBU (5)	n.r.
residence time	18	DCM	DBU (5)	80[g]
O_2	19	DCM	DBU (5)	19[h]

[a]Experiments carried out on 35−50 μmol scale. Yields were determined by quantitative NMR using an internal standard. Abbreviations: TMP = 2,2,6,6-tetramethylpiperidine, n.r. = no reaction. [b]MeCN (0.5% water). [c]0.10 M with respect to **5**. [d]0 °C. [e]50 °C. [f]24 h in the dark. [g]4 h residence time. [h]Batch trial under O_2 (1 atm).

expansion proceeded smoothly in polar aprotic solvents including dichloromethane, 1,2-dichloroethane (1,2-DCE), chloroform, and acetonitrile. We observed the best results with 5 equiv of strong, non-nucleophilic guanidine and amidine bases including *N,N,N′,N′*-tetramethylguanidine (TMG), DBU, and 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD). Weaker bases provided either little or no conversion to the desired product. A trial at 0.1 M pyridinium bromide **5** decreased the yield, presumably by accelerating intermolecular interactions leading to polymerization. The reaction yield was unchanged when cooled to 0 °C, but decreased significantly at 50 °C. When **5** was treated with excess DBU for 24 h in the dark, we observed no formation of azepine **2**. With blue light irradiation in the absence of base for 24 h, the starting material was recovered quantitatively. Lastly, under an oxygen atmosphere in batch, **6** and **2** were obtained in yields of 57% and 19%, respectively. We arrived at optimized reaction

https://dx.doi.org/10.1021/acs.orglett.0c04050
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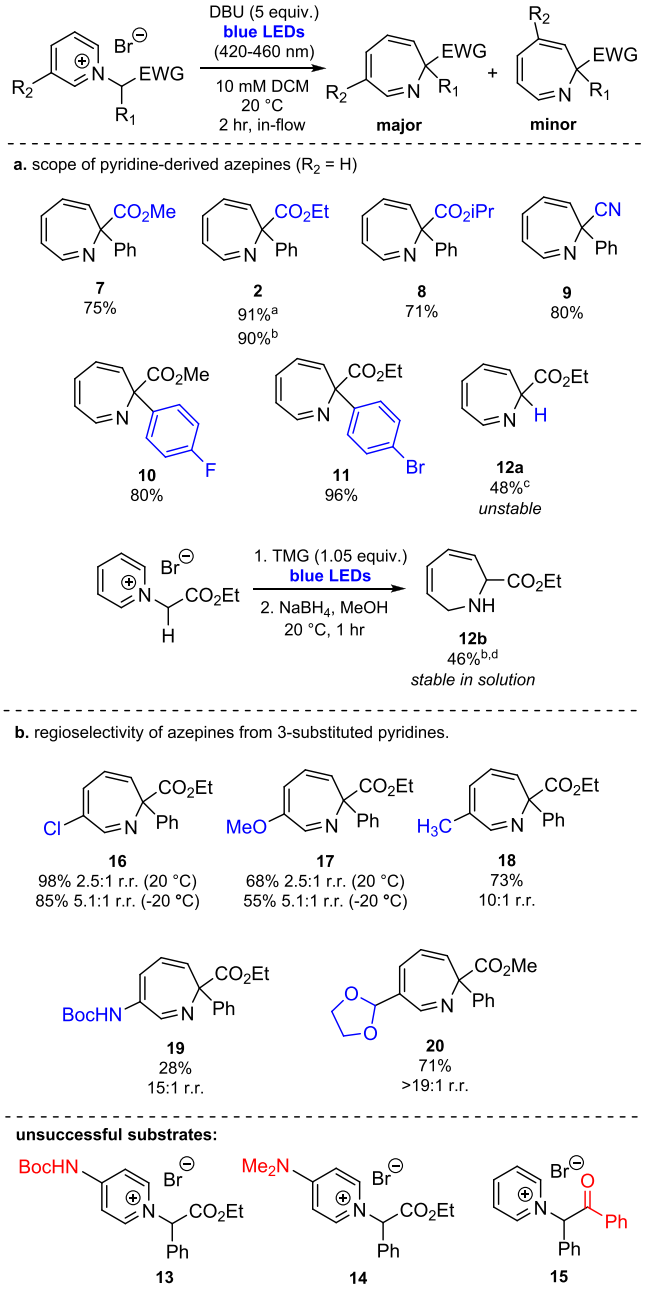
conditions which utilize 5.0 equiv of DBU in DCM, 1,2-DCE, or MeCN with a residence time of 2 h in a 440 nm flow photoreactor.

With optimized conditions for **5**, we investigated the scope of the reaction with a variety of pyridinium salts (Scheme 3a), which we synthesized by S_N2 displacement. In substrates **7**, **2**, **8**, and **9**, ester/nitrile substitution had little impact on the yield of the azepine. The addition of halogens on the phenyl ring also had no significant effect (**10**, **11**). Monosubstituted azepine **12a** was synthesized using 1.05 equiv of TMG at −20 °C. With careful workup, we were able to characterize **12a** by ^{1}H NMR. However, the product was not stable to silica gel chromatography and quickly decomposed. The instability and ^{1}H NMR spectrum of **12a** paralleled observations from Steglich's synthesis of unsubstituted 2*H*-azepine.[26] Under modified conditions, we submitted **12a** directly to $NaBH_4$ reduction in methanol giving **12b** quantitatively, which was stable in solution. Curiously, the addition of electron-donating groups at the 4-position (**13**, **14**) provided no observable azepine product; in both cases, the pyridine fragment was obtained with high recovery (>85%). We hypothesize that the 4-amino groups significantly destabilize the ylide intermediate by electron donation, promoting its decomposition. Lastly, a substrate with a phenyl ketone (**15**) gave no observable azepine. Next, we investigated the regioselectivity of the ring expansion using 3-substituted pyridinium salts (Scheme 3b). With 3-chloro and 3-methoxy derivatives (**16**, **17**), we observed poor regioselectivity (2:1 r.r.) at 20 °C; the regioselectivity was improved to 5:1 by cooling the reaction to −20 °C. With 3-methyl and 3-*N*-Boc amino substrates (**18**, **19**) we saw improved regioselectivity (10:1, 15:1, respectively). Similarly, a salt bearing an acetal (**20**) provided the highest regioselectivity, with no minor regioisomer detectable by ^{1}H NMR (>19:1 r.r.). Based on these observations, we hypothesize that the regioselectivity is guided mostly by steric constraint imparted by the R group, since groups with varied electronic contributions provided the same major regioisomer.

Scheme 3. Scope and Regioselectivity of Pyridinium Salts Yielding Monocyclic Azepines (Reported Yields Are after Isolation)



[a]100 μmol scale. [b]1 mmol scale. [c]1.05 equiv of TMG was used at −20 °C. [d]1.05 equiv of TMG at −20 °C, then $NaBH_4$ in MeOH. Regioselectivity was determined by analysis of the crude ^{1}H NMR spectrum. For clarity, the major regioisomer is shown.

With good substrate tolerance for monocyclic azepines, we sought to ring expand isoquinolines, quinolines, and phenanthridines to provide polycyclic azepines (Scheme 4a). Using an isoquinolinium salt (**21**), we optimized the reaction conditions for the formation of **31**. By adding **21** dropwise to 5 equiv of DBU, we isolated α-imino ester **31** as the sole azepine product in moderate yields (34%). We hypothesize **41** is the initial product, which isomerizes to **31** via proton transfer or 1,5-hydride shift (Scheme 4b). Other isoquinolinium salts (**22**−**25**) gave analogous 1*H*-benzo[*c*]azepines (**32**−**35**) in good yields, and the reaction operated smoothly despite modification at each major region of the molecule. Similarly, quinolinium salts **26** and **27** gave 3*H*-benzo[*c*]azepines **36** and **37**. Lastly, phenanthridinium salts **28**−**30** gave 5*H*-dibenzo-[*c*,*e*]azepines **38**−**40** in improved yields compared to the isoquinolines and quinolines. We found that employing a *tert*-butyl ester (**32**, **37**, **39**) as the electron-withdrawing group provided slightly improved yields in all three substrate types. We suspect that the added steric constraint of the large ester slows intermolecular interactions leading to decomposition.

After establishing generality of our ring expansion method, we carried out experiments to inform a plausible mechanism (Scheme 5). To determine whether an electron-withdrawing group was necessary, we synthesized 1,1-diphenylpyridinium salt **42** and subjected it to the previously optimized conditions and observed pyridine and benzophenone (**44**) as the sole products. After failing to observe **43**, we conducted a batch experiment with thoroughly degassed solvent, a range of LED wavelengths, and with gradual increase of temperature from −40 to 20 °C. Despite our efforts to achieve an oxygen-free environment, we obtained only pyridine and **44**.

We reasoned that reaction intermediates leading to azepine **43** could decompose by extrusion of pyridine affording a triplet diphenylcarbene,[27] or by oxidation of the ylide intermediate. Oxygen quenching experiments in batch showed diminished

https://dx.doi.org/10.1021/acs.orglett.0c04050
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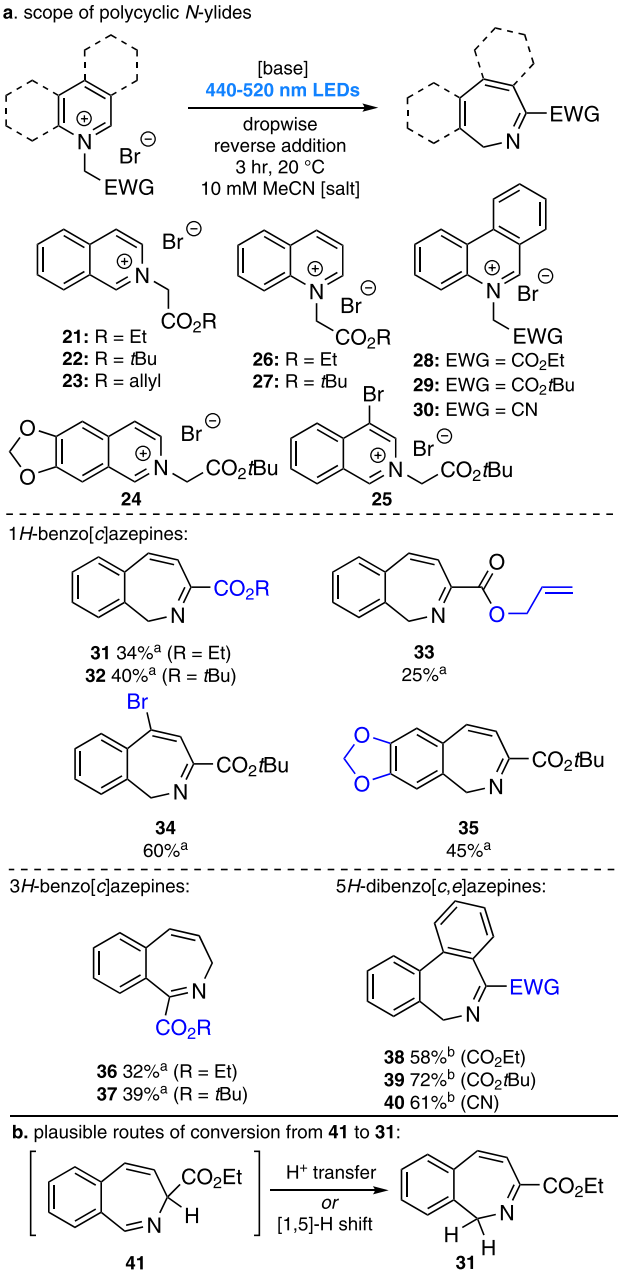
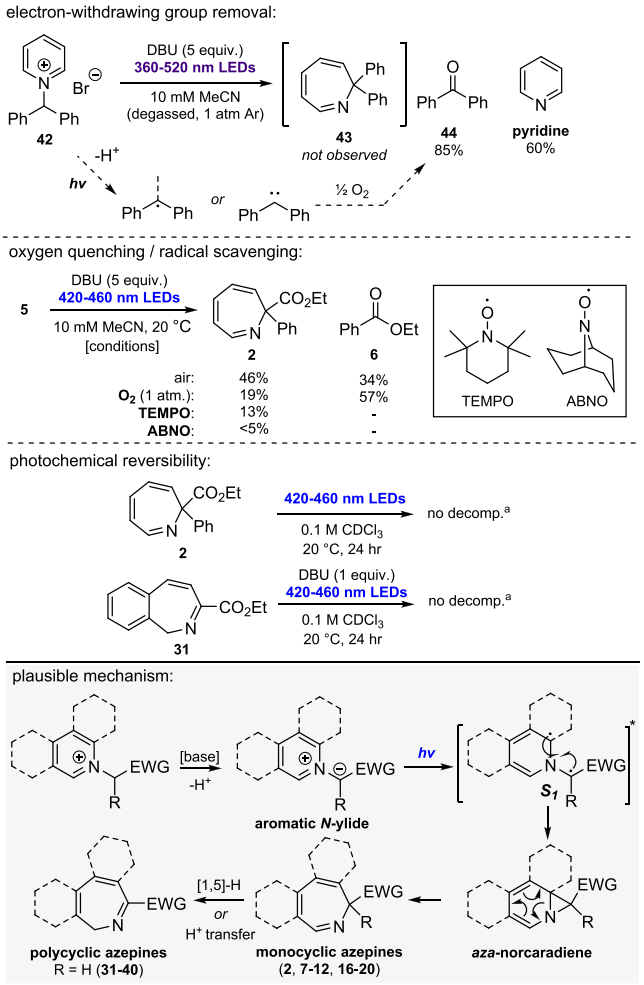
Scheme 4. Scope of Polycyclic Salts Yielding Benzo[*c*]azepines and Dibenzo[*c,e*]azepines (Reported Yields Are after Isolation)



[a]5 equiv of DBU. [b]1.05 equiv of TMG.

Scheme 5. Mechanistic Experiments and Plausible Mechanism of the Ring Expansion of Pyridinium Ylides



[a]^{1}H NMR spectra were recorded at 1, 6, 12, and 24 h.

yields of azepine **2** and increased yields of glyoxylate **6**, suggesting the presence of a radical intermediate. Similarly, two trials run with radical scavengers[28] (2,2,6,6-tetramethylpiperin-1-yl)oxyl (TEMPO) and 9-azabicyclo[3.3.1]nonane *N*-oxyl (ABNO) gave greatly diminished yields of the azepine, with ABNO nearly stopping product formation altogether. To determine reversibility, we irradiated azepines **2** and **31** with blue LEDs and monitored them by ^{1}H NMR and observed no decomposition within 24 h. Based on these observations, the electrocyclic opening of the postulated *aza*-NCD is irreversible under the reaction conditions. We propose that analogously to pyridine *N*-oxides[29] and *N*-iminopyridinium ylides,[30] pyridinium methylides undergo radical recombination from the singlet excited state giving *aza*-NCD intermediates that rapidly undergo 6π-electrocyclic ring opening, affording azepine products (Scheme 5). Further rearrangement of polycyclic products **31**−**40** gives α-imino ester/nitrile isomers, which are useful functional groups themselves.[31] In contrast to the regioisomers seen in **16**−**20**, the single regioisomers obtained in substrates **31**−**40** suggest that polycyclic *N*-ylides undergo regiospecific aziridine formation which is likely due to radical stabilization from the fused benzene ring.

In summary, we have developed a simple method for the dearomative ring expansion of aromatic *N*-heterocycles to azepines. So far, we have demonstrated generality for pyridines, isoquinolines, quinoline, and phenanthridine and have provided preliminary mechanistic studies that strongly suggest photochemical excitation of the ylide followed by diradical recombination 6π-electrocyclic ring opening. This mild demaromative ring expansion will enable the synthesis of diverse azepines from readily available starting materials.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04050.

https://dx.doi.org/10.1021/acs.orglett.0c04050
Org. Lett. 2021, 23, 525−529

General information, experimental procedures, and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Dr. Norman Lee (Boston University) for high-resoluation mass spectrometry data and colleagues of the Beeler Research Group (Boston University) for insightful discussion. NMR (CHE-0619339) and MS (CHE-0443618) facilities at Boston University are supported by the NSF.

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