Organic Chemistry |Hot Paper|

Intramolecular Pyridinium Oxide Cycloadditions: Systematic Study of Substitution, Diastereoselectivity, and Regioselectivity

Yi Lu, Patrick N. Dey, and Christopher M. Beaudry*[a]

Abstract: Intramolecular pyridinium oxide cycloadditions form complex polycyclic nitrogenous architectures. The diastereoselectivity and regioselectivity of pyridinium oxide cycloadditions was systematically investigated for the first time using complex substrates. Predictably high levels of diastereoselectivity and regioselectivity are observed, which can be attributed to minimization of steric (*syn*-pentane) and torsional strain in the products. The reaction is reversible under the reaction conditions, and it is stereospecific with respect to the dipolarophile geometry.

Polycyclic nitrogenous architectures are widespread in biologically active natural products. For example, the tropane alkaloids, exemplified by cocaine, are characterized by a 8-aza-bicyclo[3.2.1]octane structure, **1**.[1] Amaryllidaceae alkaloids such as siculine display a topologically distinct 1-azabicyclo[3.2.1]octane core (**2**).[2] Homopumiliotoxin 223G is a quinolizidine alkaloid (**3**) isolated from poison dart frogs.[3] Finally, the intriguing structure of the galbulimima alkaloid, himgaline, displays all of these component aza-bicyclic fragments in a 2-azatricyclo[4.4.1.0^{2,7}]undecane architecture (**4**) (Figure 1).[4,5]

Such bridged polycyclic alkaloids represent enduring challenges for synthetic chemists. A notable difficulty associated with the synthesis of the natural products shown are the stereogenic carbons bearing nitrogen.[6] In particular, all three carbons bearing the nitrogen atom in the himgaline structure are stereogenic, making this target notably complex. Many synthetic strategies have appeared to access nitrogenous bicycles, and particularly successful approaches create multiple rings in a single transformation with control of stereochemical outcomes.[7]

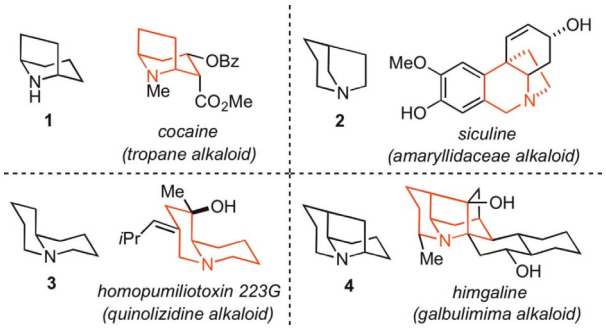
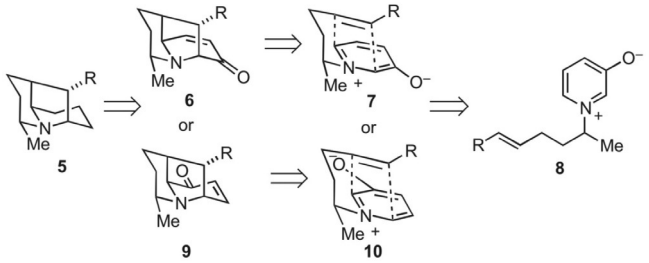


Figure 1. Polycyclic architectures featuring nitrogen atoms.

Cycloaddition reactions are particularly well suited for the challenge of preparing multiple rings with control of stereochemistry, and we wondered if such polycyclic nitrogenous frameworks could be prepared using a suitable cycloaddition. We decided to focus on the tricyclic motif found in himgaline, complete with the equatorial methyl substituent (**5**, Scheme 1). Any method capable of preparing this tricyclic architecture could, at least in principle, be used to construct any of the component bicyclic structures (**1**–**3**).



Scheme 1. Retrosynthetic analysis of azatricyclo[4.4.1.0^{2,7}]undecanes.

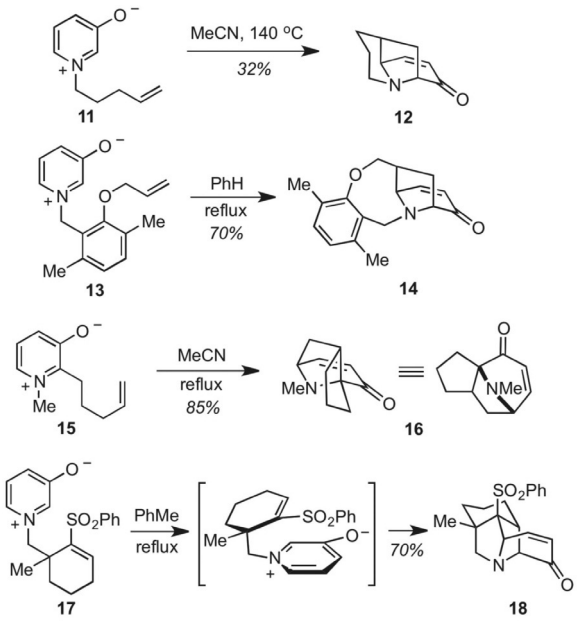
We envisioned tricyclic molecules such as **5** arising from a molecule such as enone **6**, which contains functional handles suitable for the construction of additional C–C bonds. Consideration of the topology of **6** suggested that an intramolecular dipolar cycloaddition of a pyridinium oxide with a tethered alkene dipolarophile (**7**) would give the required molecular connectivity. Moreover, it appeared that the diastereoselectivity of the cycloaddition may be controlled by a favored orientation of the molecular tether, which positions the methyl substituent in an equatorial position. The starting material for this cycloaddition would be the relatively simple pyridinium oxide **8**. One question was the regiochemistry of the cycloaddition; specifically, regioisomeric tricycle **9** would arise from cycloaddition of conformer **10**, and it was unclear to us which pathway would be favored.

Pyridinium oxide cycloadditions are well known in the literature. Since the first report by Katrizky in 1974,[8] there have been dozens of intermolecular examples.[9] Intermolecular pyri-

[a] Y. Lu, P. N. Dey, Prof. C. M. Beaudry
Department of Chemistry, Oregon State University
153 Gilbert Hall, Corvallis, OR 97333 (USA)
E-mail: christopher.beaudry@oregonstate.edu

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/chem.202100115.

dinium oxide cycloadditions require electron-poor alkene dipolarophiles (e.g. acrylonitrile, maleamide) for successful reactivity. Conversely, intramolecular pyridinium oxide cycloadditions are much fewer in number (Scheme 2). Simple *N*-pentenyl pyridinium oxide **11** reacts to form **12**.[10] Substrate **13** contained a substituted tether linking the dipole and dipolarophile, and it cyclized to give **14**.[11] In this case, the methyl substituents on the phenyl ring were carefully chosen for their buttressing effect, and less substituted congeners did not cyclize. Pyridinium oxide **15** featured a dipolarophile tethered to the pyridinium ring, rather than the nitrogen atom, and it gave the topologically distinct bicycle **16**.[12] It is notable that these intramolecular examples do not require a polarized dipolarophile, and simple terminal alkenes participate in the reaction.

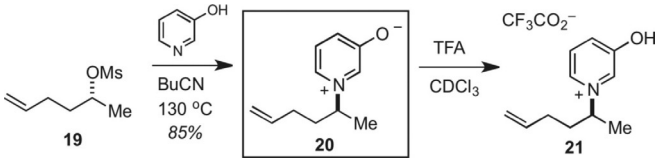


Scheme 2. Intramolecular pyridinium oxide cycloadditions.

Gin published the only example of an intramolecular cycloaddition where stereochemistry in the tether led to good diastereofacial discrimination of the dipolarophile (**17**→**18**).[13] The electronics of the dipolarophile were carefully optimized to promote the cycloaddition. The reaction was found to be reversible, which may be a result of the highly polarized dipolarophile.

Clearly, such reactions have the ability to produce complex polycyclic architectures; however, there has been no systematic investigation of substitution in such systems. Apart from these relatively isolated examples shown in Scheme 2, no study of the intramolecular pyridinium oxide cycloaddition has been reported. Specifically, the tolerance of the reaction to substitution, and the stereoselectivity of the reaction remain unstudied.

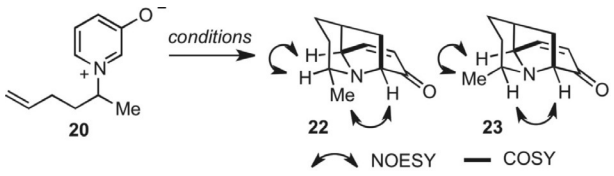
We began our investigations by preparing pyridinium oxide starting materials. There are multiple synthetic strategies for preparing pyridinium oxides; however, we found the most convenient method was the substitution of alkyl mesylates (**19**) with 3-hydroxypyridines. Characterization of the product was accomplished by NMR methods, and it appeared that the product was the zwitterionic species **20** (not the 3-hydroxyl pyridinium **21**), as protonation of **20** to give **21** was observed by NMR spectroscopy at pH < 0.[14] Pyridinium oxide **20** was prone to decomposition over a few hours, and we commonly advanced this material into the cycloaddition immediately upon isolation (Scheme 3).



Scheme 3. Preparation of pyridinium oxides.

The intramolecular cycloaddition of **20** was investigated using a variety of reaction conditions (Table 1). Simple heating of **20** did not induce the intramolecular cycloaddition (entries 1 and 2). Heating of **20** in the presence of Bronsted acid (entry 3) or Lewis acids (entry 4) were similarly ineffective at promoting the reaction. Treatment of **20** with strong base resulted in decomposition (entry 5). However, intramolecular cycloaddition of **20** did occur under mildly basic conditions (entries 6 and 7).[14] A survey of different bases identified that carbonate bases gave high yields of the cycloadduct **22** (entry 8). Sequestration of the potassium counter ion did not improve the reaction yield (entry 9). The reaction was largely insensitive to the carbonate counter-cation, and Ag_2CO_3 was similarly effective in promoting the reaction (entry 10). Polar solvents such as acetonitrile and butyronitrile gave the best reaction

Table 1. Identification of cycloaddition conditions.

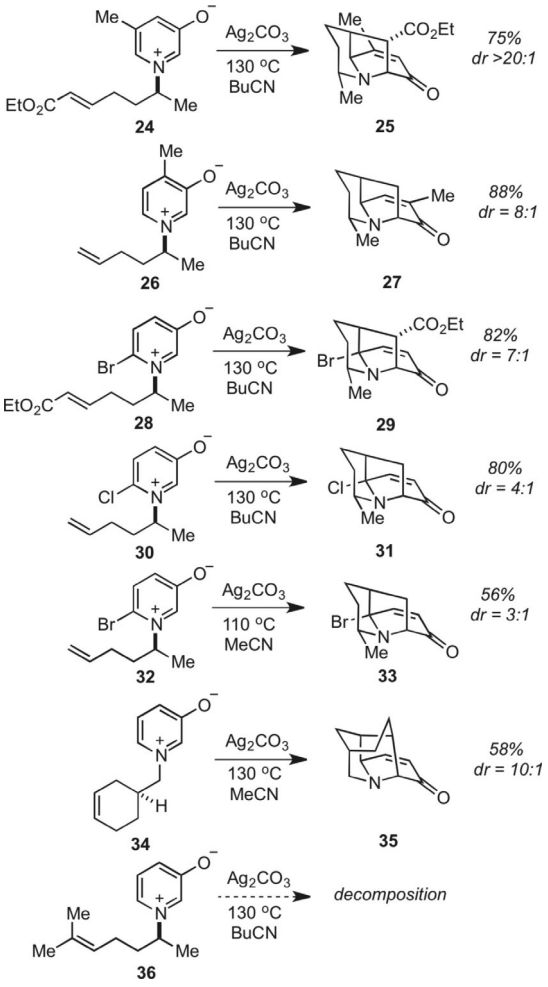


entry	conditions	yield	dr (**22**:**23**)
1	PhMe, 210 °C	0% (NR)	
2	MeCN, 210 °C	0% (NR)	
3	HCl, MeCN, 160 °C	0% (NR)	
4	$TiCl_4$, MeCN, 160 °C	0% (NR)	
5	NaOH, MeCN, 130 °C	0% (decomp)	
6	Et_3N, MeCN, 130 °C, 36 h	38%	4:1
7	K_2HPO_4, MeCN, 130 °C, 36 h	82%	5:1
8	K_2CO_3, MeCN, 130 °C, 36 h	83%	5:1
9	K_2CO_3, 18-C-6, MeCN, 130 °C, 36 h	75%	5:1
10	Ag_2CO_3, MeCN, 130 °C, 36 h	93%	6:1
11	Ag_2CO_3, BuCN, 130 °C, 36 h	87%	7:1

rates, limited the formation of unwanted by products, and gave good selectivity for the major product. The best yields were obtained in butyronitrile at 130 °C, and we settled on these as our standard conditions (entry 11).

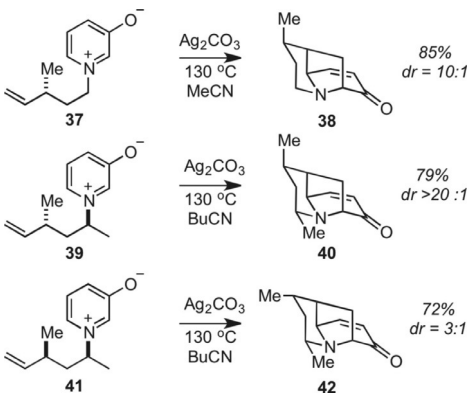
The cycloaddition reaction gave two diastereomers, which were separated and independently characterized. The structure of the major and minor diastereomers was confirmed by 2D NMR methods. Key COSY and NOESY correlations are shown in Table 1. The major product of the reaction was the anticipated diastereomer (**22**), which positions the tether methyl substituent in an equatorial orientation. The minor diastereomer (**23**) displayed the methyl substituent in an axial orientation.

We next evaluated additional substrates to investigate the ability of the intramolecular cycloaddition to create other complex bicyclic products. Substitution on the dipolarophile and the pyridinium oxide dipole was well tolerated, and in nearly all cases the yields and diastereomer ratios were synthetically useful. Substrate **24**, which contains substitution on the pyridinium ring and a more polarized dipolarophile (the type required in intermolecular dipolar cycloadditions), also reacted under our standard conditions to give **25**. Starting material **26** also contains a methyl substituent on the pyridine and an unactivated dipolarophile, and it reacted smoothly to give **27**. Interestingly, the reaction rate of **24** was not substantially different than **22** or **26**, which feature unactivated dipolarophiles. Halogen substituents are also tolerated on the pyridinium oxide. Substrate **28** contains a bromine atom on the pyridinium ring, and it reacts to form **29** in good yield. Chlorinated substrate **30** had a simple unactivated dipolarophile, and it reacted in good yield to form **31**. Brominated compound **32** also participated to give **33**. Finally, cyclic alkenes also participated as dipolarophiles, and **34** reacted to give polycyclic product **35**. Unfortunately, cyclization of trisubstituted alkene dipolarophiles such as **36** were unsuccessful (vide infra) (Scheme 4).



Scheme 4. Investigation of the cycloaddition substitution tolerance.

Additional substrates were prepared to test the hypothesis that the equatorial positioning of the tether methyl group was the stereochemical control element of the cycloaddition. When the methyl substituent was moved to different positions on the tether, the major diastereomer again featured an equatorial methyl group. Substrate **37** was prepared, and the cyclization similarly gave a major product (**38**) that displayed the equatorial methyl group. Starting material **39** has two tether methyl substituents, and the corresponding cycloaddition product **40** results from positioning of both methyl groups equatorial. The reaction was significantly more diastereoselective, and the product (**40**) was formed as a single detectable (NMR spectroscopy, TLC) diastereomer. Diastereomeric substrate **41** undergoes the cycloaddition reaction, but one methyl group must be axial in the product. In the event, product **42** was formed as a 3:1 mixture of diastereomers. Taken together, these product ratios strongly support the observation that diastereoselectivity can be controlled by the tether substituents. All major products were separated and the clean isomer was characterized by 2D NMR methods as described above (Scheme 5).



Scheme 5. Investigation of the diastereoselectivity.

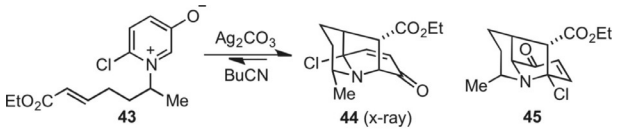
Our original hypothesis was that the stereochemical outcome of the reaction was a result of the reaction kinetics. Specifically, we anticipated that the transition state leading to the major product would be favored if the tether methyl was equatorial. This follows from Katritzky's analysis on the intermolecular reaction.[15] The reversibility in Gin's cycloaddition was attributed to the polarized vinyl sulfone dipolarophile.[12] However, we began to suspect our reactions with relatively non-polarized dipolarophiles were under thermodynamic control as well. We noticed that the product ratios were often somewhat variable, and more forcing conditions (higher tem-

peratures, longer reaction times) generally gave superior product ratios.

To investigate the reversibility of the reaction, substrate **43** was selected because in early investigations we observed stereoselectivities that seemed to vary with temperature. Moreover, the major product was a crystalline solid, which enabled us to further secure its structure and stereochemistry by X-ray crystallographic studies. In this case we also isolated and characterized the minor product isomer and found it to be a diastereomer/regioisomer. Presumably, the regiochemistry of the minor compound is a result of avoiding *syn*-pentane interactions between the chloride substituent and the axial methyl group (vide infra).

Initially, we performed the cycloaddition of **43** at lower temperatures and observed a poor product ratio (Table 2, entry 1). However, at higher temperatures the selectivity increased to 9:1 (entry 2), and longer reaction times further increased the ratio to 18:1 (entry 3). Finally, resubjection of pure **44** (entry 4) or pure **45** (entry 5) to butyronitrile at 130 °C for 36 hours led to an identical product mixture (18:1) in high yield. This is strong evidence that the cycloaddition is reversible and under thermodynamic control.

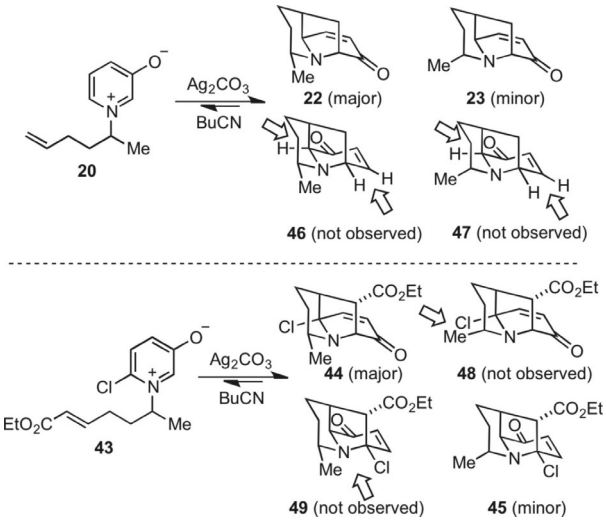
Table 2. Reversibility studies.



entry	SM	T	reaction time (hours)	yield	(**44**:**45**)
1	**43**	110 °C	4	85%	5:2
2	**43**	130 °C	4	79%	9:1
3	**43**	130 °C	36	85%	18:1
4	**44**	130 °C	36	70%	18:1
5	**45**	130 °C	36	62%	19:1

With the knowledge that the reaction is under thermodynamic control, we ruminated on the regioselectivity of the cycloaddition (Scheme 6). In the case of the relatively unsubstituted starting material **20**, the isolated products are diastereomers **22** and **23**, and regioisomeric compounds **46** and **47** were not detected. The regiochemical preference can be attributed to the minimization of torsional strain in the major product. Specifically, eclipsing of the carbonyl and the enone β-C–H bond with the adjacent methine C–H bonds is more severe in **46** than in **22**.

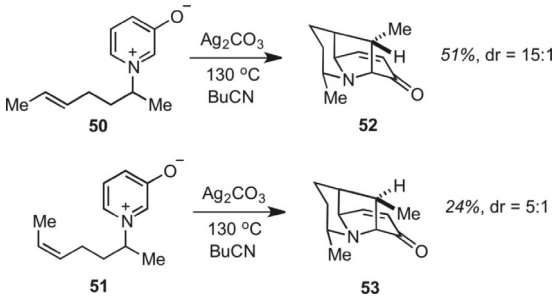
The major regioisomer often results from minimization of torsional strain, but it can be over-ridden by other factors. Chloride-containing substrate **43** undergoes cycloaddition again giving the expected major product **44**, which is the diastereomer with the equatorial methyl. The minor isolated product **45** is the diastereomer that positions the methyl group axial. However, in this case the minor product displays the opposite regiochemistry. Isomeric compounds **48** and **49** were



Scheme 6. Consideration of regioselectivity; key interactions highlighted.

not observed. In this case, the minor product regiochemistry avoids steric interaction between the chlorine atom and the axial methyl group. Both unobserved isomers (**48** and **49**) would suffer from *syn*-pentane interactions of the methyl and chloride groups.

We also wondered if the reaction was stereospecific with respect to dipolarophile substituents. We prepared geometrical isomers **50** and **51** and subjected them to our standard conditions (Scheme 7). *E*-Isomer **50** reacted to give product **52**, and *Z*-alkene isomer **51** gave **53**; the reaction is stereospecific with respect to the alkene substituents. This also suggests that although the reaction is reversible, it is likely proceeds with concerted bond formation. We observed that the cycloaddition of *E*-configured **50** was a smooth transformation that occurred under our normal conditions. However, the reaction yield with **51** was low, which results from the production of numerous byproducts. Analysis of crystal structure data for the related product **44** and models of **53** suggested that the pyrrolidine methyl substituent projects directly into the concave bicyclic structure leading to severe steric interactions. Such interactions would destabilize the transition state leading to **53**, which in turn, would explain why by products are formed competitively. Furthermore, these steric interactions would also explain the reluctance of trisubstituted alkenes such as **36** to participate in the cycloaddition reaction.



Scheme 7. Investigations of stereospecificity.

In conclusion, we have systematically studied the intramolecular cycloaddition of pyridinium oxides. A range of substitution is tolerated in the substrates, and the reaction occurs with good chemical yields. The reaction is reversible, and it is stereospecific with respect to dipolarophile stereochemistry. Diastereoselectivities can be controlled by the substituents on the intramolecular tether. Regioselectivities result from torsional or steric interactions present in the products. Efforts to apply this transformation in the synthesis of polycyclic alkaloid targets such as himgaline are underway in our laboratory and will be reported in due course.

Crystallography data

Deposition Number 2051319 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Acknowledgements

We thank Lev N. Zakharov for assistance with the X-ray crystal structure of **44**. We acknowledge funding from NSF (CHE-1956401) and Oregon State University.

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · cycloaddition · pericyclic reaction · pyridinium oxide · stereochemistry

[1] D. O'Hagan, *Nat. Prod. Rep.* **2000**, *17*, 435 – 446.
[2] Z. Jin, *Nat. Prod. Rep.* **2009**, *26*, 363 – 381.
[3] J. W. Daly, *J. Nat. Prod.* **1998**, *61*, 162 – 172.
[4] L. N. Mander, R. H. Prager, M. Rasmussen, E. Ritchie, W. C. Taylor, *Aust. J. Chem.* **1967**, *20*, 1705 – 1718.
[5] a) U. Shah, S. Chackalamannil, A. K. Ganguly, M. Chelliah, S. Kolotuchin, A. Buevich, A. McPhail, *J. Am. Chem. Soc.* **2006**, *128*, 12654 – 12655; b) D. A. Evans, D. J. Adams, *J. Am. Chem. Soc.* **2007**, *129*, 1048 – 1049.
[6] A. Hager, N. Vrielkink, D. Hager, J. Lefranc, D. Trauner, *Nat. Prod. Rep.* **2016**, *33*, 491 – 522.
[7] A. Padwa, *Russ. Chem. Bull.* **2016**, *65*, 2183 – 2194.
[8] N. Dennis, A. R. Katritzky, T. Matsuo, S. K. Parton, *J. Chem. Soc. Perkin Trans. 1* **1974**, 746 – 750.
[9] A. R. Katritzky, N. Dennis, *Chem. Rev.* **1989**, *89*, 827 – 861.
[10] a) P. G. Sammes, R. A. Watt, *J. Chem. Soc. Chem. Commun.* **1976**, 367 – 368; b) M. P. Smith, C. George, A. P. Kozikowski, *Tetrahedron Lett.* **1998**, *39*, 197 – 200.
[11] B. S. Orlek, P. G. Sammes, D. J. Weller, *J. Chem. Soc. Chem. Commun.* **1993**, 1412 – 1413.
[12] S. M. Bromidge, D. A. Archer, P. G. Sammes, *J. Chem. Soc. Perkin Trans. 1* **1990**, 353 – 359.
[13] a) K. M. Peese, D. Y. Gin, *Chem. Eur. J.* **2008**, *14*, 1654 – 1665; b) K. M. Peese, D. Y. Gin, *J. Am. Chem. Soc.* **2006**, *128*, 8734 – 8735.
[14] Acid titration of 20 suggests it is the zwitterionic pyridinium oxide not the 3-hydroxylpyridinium. See Supporting Information.
[15] N. Dennis, B. Ibrahim, A. R. Katritzky, *J. Chem. Soc. Perkin Trans. 1* **1976**, 2307 – 2334.

Manuscript received: January 12, 2021
Accepted manuscript online: January 12, 2021
Version of record online: February 10, 2021