JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Synthesis of (−)-Pseudotabersonine, (−)-Pseudovincadifformine, and (+)-Coronaridine Enabled by Photoredox Catalysis in Flow

Joel W. Beatty and Corey R. J. Stephenson*

Department of Chemistry, University of Michigan, Ann Arbor, Michigan 48109, United States

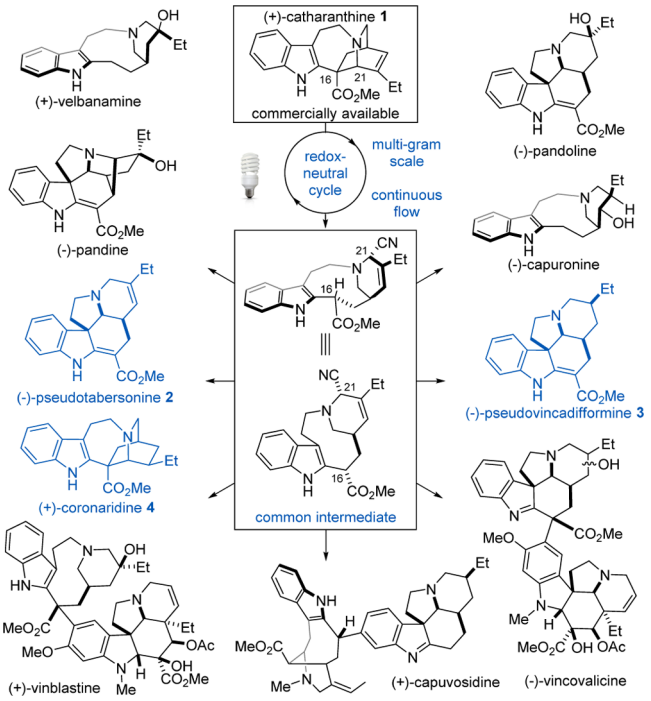
Supporting Information

ABSTRACT: Natural product modification with photoredox catalysis allows for mild, chemoselective access to a wide array of related structures in complex areas of chemical space, providing the possibility for novel structural motifs as well as useful quantities of less abundant congeners. While amine additives have been used extensively as stoichiometric electron donors for photocatalysis, the controlled modification of amine substrates through single-electron oxidation is ideal for the synthesis and modification of alkaloids. Here, we report the conversion of the amine (+)-catharanthine into the natural products (−)-pseudotabersonine, (−)-pseudovincadifformine, and (+)-coronaridine utilizing visible light photoredox catalysis.

Tunable and selective methods for the controlled redox manipulation of complex substrates are essential to successful semisynthetic efforts, and photoredox catalysis offers unique opportunities in this regard.[1] While photoredox catalysis has been utilized to great effect in a substantial body of methodology, examples of its use in natural product synthesis are comparatively limited.[2] Furthermore, the photooxidation of amine substrates has generally been limited to the functionalization of highly activated tetrahydroisoquinoline derivatives,[3,4] while the use of complex amines as a platform for synthesis has garnered minimal attention.[3] In light of the abundance of alkaloids with amine functionality, we set out to explore the synthesis of a number of structurally related natural products to further test the limits of photoredox catalysis in a complex setting.

Natural product modification for the production of biologically active compounds holds significant potential for material access, as the need for a multistep synthesis of starting material can be obviated by biological production on scale. The natural product (+)-catharanthine **1** was identified as an ideal entry point for the synthesis of a number of structurally related alkaloids through a common α-aminonitrile intermediate (Scheme 1). While catharanthine itself lacks notable bioactivity,[5] it has been the subject of much research due to its ability to undergo a unique fragmentation of its C16−C21 bond,[6] which has chiefly been exploited in the synthesis of the clinically approved chemotherapeutic agent vinblastine[7] and analogs thereof.[8] Catharanthine's abundance has contributed to the rationale behind the development of a semisynthetic strategy to vinblastine, as synthetically useful quantities are available from cell cultures.[6] A variety of oxidative,[8,9] reductive,[10] electrochemical,[11] and photolytic[12] methods for the fragmentation of **1** have been reported, and we set out to investigate the synthetic utility of catharanthine fragmentation in the synthesis of a number of related alkaloids.

Scheme 1. Catharanthine Fragmentation Provides Access to Structurally Diverse Alkaloids



Chief among our interests was the alkaloid (−)-pseudotabersonine **2** (Scheme 1), which was first generated from catharanthine by Gorman et al. by refluxing catharanthine in glacial acetic acid for 16 h.[13] Unfortunately, catharanthine's potential as a chiral pool material in such investigations was hampered by an estimated 90% racemization of the starting material and only 20% yield.[14] Kutney et al. also reported formation of pseudotabersonine from catharanthine through a two-step reduction[10]-oxidation[15] procedure, affording **2** in 18% overall yield, also with low enantiopurity.[14] Alternative examples of pseudotabersonine total syntheses are exclusively racemic.[16]

Visible light irradiation of catharanthine in the presence of polyfluorinated catalyst $Ir(dF(CF_3)ppy)_2(dtbbpy)PF_6$[17] **5** and 2 equiv of trimethylsilyl cyanide (TMSCN) provided the cyanated

Received: June 19, 2014
Published: July 8, 2014

   dx.doi.org/10.1021/ja506170g | J. Am. Chem. Soc. 2014, 136, 10270−10273

fragmentation product **6** in 93% after 3 h (Scheme 2A).[18] We further evaluated the efficiency of the transformation in a flow photochemical reactor[19] with the intention to decrease reaction time, improve scalability, and allow for the safe, controlled generation of HCN.[20] In a flow reactor with a 1.34 mL internal volume, the fragmentation reaction was complete with a residence time of only 2 min and with a slightly improved yield of 96%.

As the demonstrated photocatalytic fragmentation of catharanthine is redox neutral, we hoped that an isohypsic synthesis of pseudotabersonine could be achieved through an iminium isomerization/transannular Pictet–Spengler cascade from **6** (Scheme 2B). Acidic conditions proved effective to facilitate iminium isomerization; refluxing **6** in toluene with 4 mol % benzoic acid for 1 h provided a mixture of three compounds, including pseudotabersonine which was isolated in 13% yield (Scheme 2C). The reaction also yielded cyanated pseudotabersonine **7** and reduced starting material **8**, which is symptomatic of redox-disproportionation. Interestingly, when **7** and **8** were combined in a 1:1 ratio and subjected to the optimized rearrangement conditions at reflux (*vide infra*), pseudotabersonine was isolated in 65% as the only product from the reaction, suggesting a role for these species as possible intermediates in the transformation of **6** to pseudotabersonine. This observation supports the possibility of intermolecular hydride transfer as an operative mechanism, but does not exclude the alternative possibility of azomethine ylide isomerization.[21]

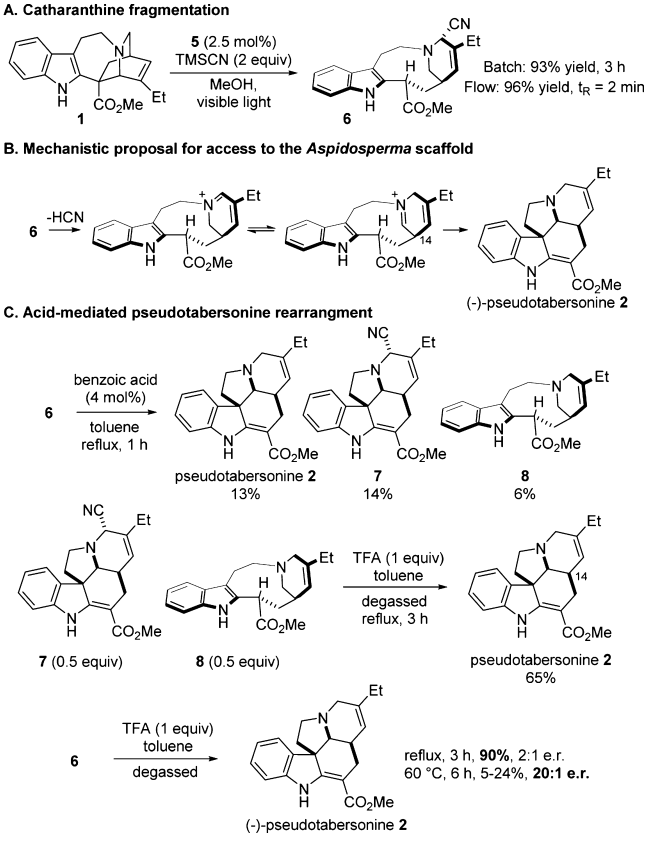
The rearrangement conditions were modified to include a full equivalent of trifluoroacetic acid with the aim of stoichiometrically forming the corresponding dihydropyridinum ion.[22] These conditions provided pseudotabersonine as the only observed product in 90% yield after 3 h (Scheme 2C). While this process provided the natural product in high yield, our sample displayed significantly lower optical rotation ($[\alpha]_D^{26} = -172$ (c 1.0 MeOH)) than that reported for the antipodal natural sample ($[\alpha]_D^{26} = +320$ (MeOH));[23] further analysis showed that the alkaloid was obtained in an enantiomeric ratio of only 2:1. While this ratio could be improved to 20:1 by performing the reaction at 60 °C, the improved enantioselectivity was accompanied by a reduction in reaction efficiency, with inconsistent yields ranging from 5 to 24%. This inconsistency in yield was also observed for the redox byproducts **7** and **8** and can likely be attributed to reduced solubility of both reactants and products as inhomogeneity was observed at these temperatures. Upon formation of the internal iminium ion, a transannular Pictet–Spengler reaction provides the natural product, and the configuration of C14 (Scheme 2B) dictates the stereochemical outcome of the transformation. The racemization mechanism is expected to involve iminium tautomerization at C14, which is possible from both proposed dihydropyridinium intermediates.

To eliminate the possibility of epimerization from the initial iminium ion intermediate, hydrogenation of the fragmentation product **6** was performed to yield **9** with high diastereoselectivity (Scheme 3), which we anticipated would provide (−)-pseudovincadifformine **3** as the rearrangement product. Interestingly, subjection of crude **9** to the aminonitrile rearrangement conditions did not provide **3** but instead yielded the natural product (+)-coronaridine **4** as the sole product in 48% yield over two steps. This is the highest yielding preparation of coronaridine from catharanthine reported to date[13] and represents a net hydrogenation of catharanthine with diastereoselectivity opposite that dictated by the substrate. The diastereomeric hydrogenation product (+)-dihydrocatharanthine was prepared in 93% yield from catharanthine as a single diastereomer through hydrogenation with Adams' catalyst.[24]

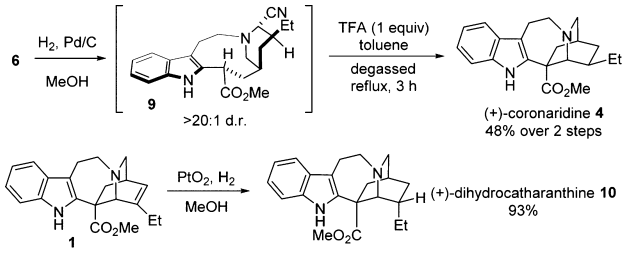
Our difficulties in producing pseudovincadifformine through iminium isomerization led us to investigate an alternative photocatalysis approach to the natural product.[15] Hydrogenation of aminonitrile **6** with heterogeneous palladium followed by workup with sodium borohydride provided the tertiary amine **11** in 98% yield with a 12:1 diastereomeric ratio in favor of the desired β-epimer (Scheme 4). Exposure of the resultant amine to oxidative photoredox conditions in flow led to the formation of (−)-pseudovincadifformine in 58% yield using diethyl 2-bromo-2-methylmalonate **12** as the terminal oxidant.[25] While the C3 and C21 methylene units are both aligned well for oxidation, the steric accessibility of C3 may provide an explanation for the selectivity observed.

A mechanistic proposal consistent with the observed reactivity proceeds with oxidation of the substrate ($E_{1/2}^{red} = +0.60$ V vs SCE)[11] by the excited state of photocatalyst **5** ($E_{1/2}^{III*/II} = +1.21$ V vs SCE) (Scheme 5).[17a] The resultant radical cation **13**

Scheme 2. Synthesis of (−)-Pseudotabersonine

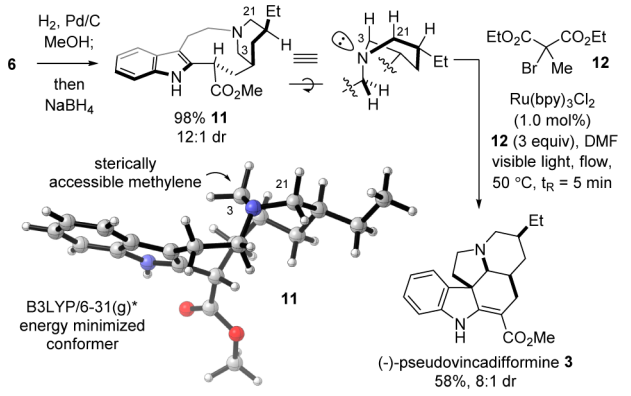


Scheme 3. Synthesis of (+)-Coronaridine

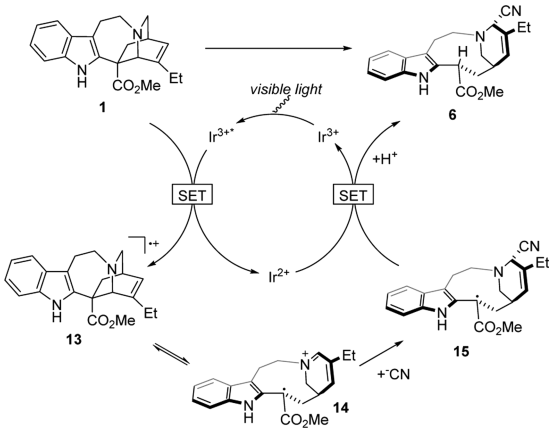


dx.doi.org/10.1021/ja506170g | J. Am. Chem. Soc. 2014, 136, 10270–10273

Scheme 4. Synthesis of (−)-Pseudovincadifformine



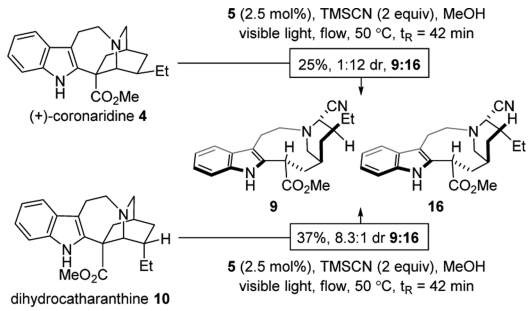
Scheme 5. Proposed Catalytic Cycle for Fragmentation



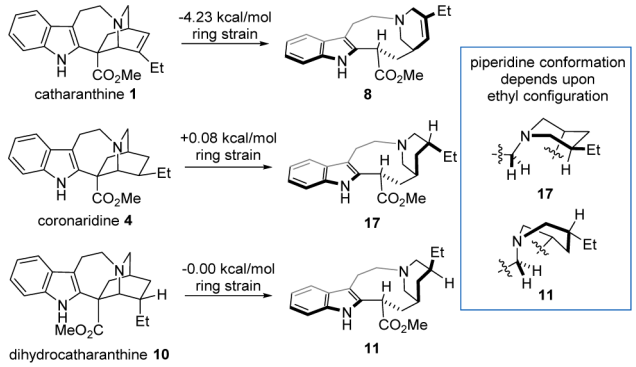
undergoes fragmentation to produce the ring opened radical cation **14** which is then trapped stereoselectively by cyanide. Reduction and protonation of **15** then affords the cyanated fragmentation product and regenerates the Ir(III) species. Interestingly, when cyanide was excluded from the reaction catharanthine was recovered unchanged, suggesting reversibility of the fragmentation event.

With both coronaridine **4** and dihydrocatharanthine **10** in hand, the generality of the light-mediated fragmentation reaction could be studied in more detail. Both **4** and **10** were subjected to the fragmentation conditions but required elevated temperature (50 °C) in addition to a residence time 21 times longer. A 25% yield of fragmented material was obtained from **4**, with slightly higher fragmentation efficiency observed for **10**. The decreased reaction efficiency observed for the hydrogenated substrates in comparison to catharanthine led us to computationally examine the role of ring-strain in fragmentation efficiency, beginning with B3LYP/6-31G* geometry optimization of relevant structures for each of the three *Iboga* alkaloids (Scheme 6).[26] Consistent with the high experimental efficiency observed, homodesmotic cleavage[27] of the C16−C21 bond of catharanthine releases 4.23 kcal/mol upon fragmentation.[18] Ring strain is clearly less of a driving force in the fragmentation of the hydrogenated alkaloids, as **4** gains 0.08 kcal/mol and **10** releases 0.00 kcal/mol (Scheme 7). Energy comparison of **4** and **10** reveals that axial orientation of the ethyl group contributes 3.15 kcal/mol of energy to the ring-closed starting material; while this energy difference is significant, it is balanced by a similar energy difference between the ring-opened diastereomers **17** and **11**. Although ring-strain release seems to contribute significantly to

Scheme 6. Photocatalytic Fragmentation of Hydrogenated *Iboga* Alkaloids



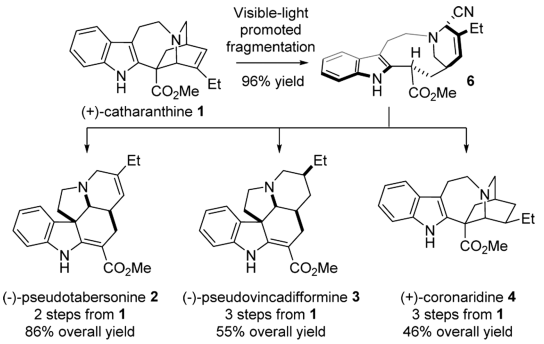
Scheme 7. Homodesmotic Strain Release Values



the thermodynamic aspects of the catharanthine fragmentation, this driving force is clearly mitigated by alkene hydrogenation.

In conclusion, the utility of photoredox catalysis as a tool for alkaloid manipulation has been demonstrated in the semisynthesis of (−)-pseudotabersonine, (−)-pseudovincadifformine, and (+)-coronaridine in 86%, 55%, and 46% overall yield from catharanthine, respectively (Scheme 8). To the best of our

Scheme 8. Synthetic summary



knowledge, for each natural product this represents the highest yielding synthetic route reported to date. Significantly, the synthesis of (−)-pseudovincadifformine relies upon visible light photoredox catalysis for two of the three total steps. The ability to efficiently generate natural products from a common advanced intermediate in this manner allows for rapid access to alternate alkaloid scaffolds, ultimately paving the way for further synthetic efforts toward structural analogs and more complex synthetic targets.

dx.doi.org/10.1021/ja506170g | J. Am. Chem. Soc. 2014, 136, 10270−10273

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, computational details, characterization data, and complete ref 26. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

crjsteph@umich.edu

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank Dr. Joseph W. Tucker for preliminary experimental contributions and Dr. James Devery, Dr. James Douglas, Mr. John Nguyen, and Professor Paul Zimmerman for their helpful discussions and suggestions. Financial support for this research from the NIH-NIGMS (R01-GM096129), the Alfred P. Sloan Foundation, the Camille Dreyfus Teacher-Scholar Award Program, Eli Lilly, Novartis, and the University of Michigan is gratefully acknowledged.

■ REFERENCES

(1) For reviews on visible-light photoredox catalysis: (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (b) Wallentin, C.-J.; Nguyen, J. D.; Stephenson, C. R. J. *Chimia* **2012**, *66*, 394. (c) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (d) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

(2) Visible light photoredox catalysis in total synthesis: (a) Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9655. (b) Lin, S.; Ischay, M. A.; Fry, C. G.; Yoon, T. P. *J. Am. Chem. Soc.* **2011**, *133*, 19350. (c) Schnermann, M. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 9576. (d) Lu, Z.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 10329. (e) Riener, M.; Nicewicz, D. A. *Chem. Sci.* **2013**, *4*, 2625. (f) Sun, Y.; Li, R.; Zhang, W.; Li, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9201. (g) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nat. Chem.* **2014**, *6*, 57.

(3) Reviews of photoredox catalysis in C−H oxidation (a) Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687. (b) Hu, J.; Wang, J.; Nguyen, T. H.; Zheng, N. *Beilstein J. Org. Chem.* **2013**, *9*, 1977.

(4) Select examples of α-amine functionalization (a) Condie, A. G.; González-Gómez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464. (b) Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 222. (c) Zhao, G.; Yang, C.; Guo, L.; Sun, H.; Chen, C.; Xia, W. *Chem. Commun.* **2012**, *48*, 2337. (d) Dai, C.; Meschini, F.; Narayanam, J. M. R.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 4425. (e) DiRocco, D. A.; Rovis, T. *J. Am. Chem. Soc.* **2012**, *134*, 8094. (f) Xuan, J.; Xia, X.-D.; Zeng, T.-T.; Feng, Z.-J.; Chen, J.-R.; Lu, Q.-L.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5653.

(5) (a) Prakash, V.; Timasheff, S. N. *Biochemistry* **1991**, *30*, 873. (b) Pereira, D. M.; Ferreres, F.; Oliveira, J. M. A.; Gaspar, L.; Faria, J.; Valentão, P.; Sottomayor, M.; Andrade, P. B. *Phytomedicine* **2010**, *17*, 646.

(6) Sundberg, R. J.; Smith, S. Q. In *The Alkaloids*; Academic Press: Waltham, MA, 2002; Vol. *59*, p 281.

(7) Neuss, N.; Neuss, M. N. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: Waltham, MA, 1990; Vol. *37*, p 229.

(8) Ishikawa, H.; Colby, D. A.; Seto, S.; Va, P.; Tam, A.; Kakei, H.; Rayl, T. J.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 4904.

(9) (a) Sundberg, R. J.; Hunt, P. J.; Desos, P.; Gadamasetti, K. G. *J. Org. Chem.* **1991**, *56*, 1689. (b) Vukovic, J.; Goodbody, A. E.; Kutney, J. P.; Misawa, M. *Tetrahedron* **1988**, *44*, 325. (c) Kutney, J. P.; Honda, T.; Joshua, A. V.; Lewis, N. G.; Worth, B. R. *Helv. Chim. Acta* **1978**, *61*, 690. (d) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017. (e) Kutney, J. P.; Hibino, T.; Jahngen, E.; Okutani, T.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Helv. Chim. Acta* **1976**, *59*, 2858. (f) Potier, P.; Langlois, N.; Langlois, Y.; Gueritte, F. *J. Chem. Soc., Chem. Comm.* **1975**, 670.

(10) Kutney, J. P.; Cretney, W. J.; Hadfield, J. R.; Hall, E. S.; Nelson, V. R. *J. Am. Chem. Soc.* **1970**, *92*, 1704.

(11) Tabakovic, I.; Gunic, E.; Gasic, M. J. *J. Chem. Soc., Perk. Trans. 2* **1996**, 2741.

(12) (a) Sundberg, R. J.; Desos, P.; Gadamasetti, K. G.; Sabat, M. *Tetrahedron Lett.* **1991**, *32*, 3035. (b) Cocquet, G.; Rool, P.; Ferroud, C. *Tetrahedron Lett.* **2001**, *42*, 839.

(13) Gorman, M.; Neuss, N.; Cone, N. J. *J. Am. Chem. Soc.* **1965**, *87*, 93.

(14) Brown, R. T.; Hill, J. S.; Smith, G. F.; Stapleford, K. S. J. *Tetrahedron* **1971**, *27*, 5217.

(15) Kutney, J. P.; Brown, R. T.; Piers, E.; Hadfield, J. R. *J. Am. Chem. Soc.* **1970**, *92*, 1708.

(16) (a) Carroll, W. A.; Grieco, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 1164. (b) Cheng, B.; Sunderhaus, J. D.; Martin, S. F. *Org. Lett.* **2010**, *12*, 3622.

(17) (a) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712. (b) This photocatalyst is commercially available from Sigma Aldrich, catalog no. L511765.

(18) See the Supporting Information for details.

(19) (a) Bou-Hamdan, F. R.; Seeberger, P. H. *Chem. Sci.* **2012**, *3*, 1612. (b) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 4140. (c) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144.

(20) For a review see: Garlets, Z. J.; Nguyen, J. D.; Stephenson, C. R. J. *Isr. J. Chem.* **2014**, *54*, 351.

(21) For a relevant discussion of these competing mechanistic pathways in a different system: Richers, M. T.; Breugst, M.; Platonova, A. Y.; Ullrich, A.; Dieckmann, A.; Houk, K. N.; Seidel, S. *J. Am. Chem. Soc.* **2014**, *136*, 6123.

(22) Treatment of **6** with 0.5 N methanolic HCl for 10 min at 0° followed by concentration of the solution provides the corresponding dihydropyridinium ion by ^{1}H NMR.

(23) Zeches, M.; Debray, M. M.; Ledouble, G.; Le Men-Olivier, L.; Le Men, J. *Phytochemistry* **1975**, *14*, 1122.

(24) Neuss, N.; Gorman, M. *Tetrahedron Lett.* **1961**, *2*, 206.

(25) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94.

(26) Frisch, M. J.; et al. *Gaussian 09*, revision D.01; Gaussian, Inc.: Wallingford CT, 2009.

(27) Wheeler, S. E.; Houk, K. N.; Schleyer, P. v. R.; Allen, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 2547.