OL | Organic Letters

pubs.acs.org/OrgLett Letter

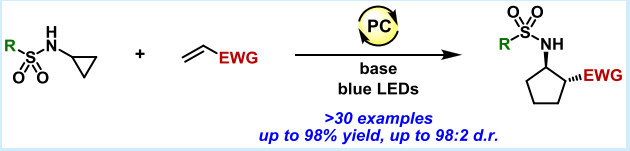
Diastereoselective Photoredox-Catalyzed [3 + 2] Cycloadditions of *N*-Sulfonyl Cyclopropylamines with Electron-Deficient Olefins

Dawn H. White, Adam Noble, Kevin I. Booker-Milburn,* and Varinder K. Aggarwal*

Cite This: *Org. Lett.* 2021, 23, 3038–3042 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A highly diastereoselective, visible-light-induced [3 + 2] cycloaddition between *N*-sulfonyl cyclopropylamines and electron-deficient olefins is reported. The reactions proceed via the oxidation of a sulfonamide aza-anion by an organic photocatalyst to generate a nitrogen-centered radical. Strain-induced ring opening and intermolecular addition to the olefin generate an intermediate carbon-centered radical that is reduced to an anion prior to 5-exo cyclization. This enables a highly diastereoselective construction of *trans*-cyclopentanes possessing synthetically useful functional groups.



Cyclopropanes possess unique reactivity due to their inherent torsional and angular strain, with the release of ring strain being utilized as a driving force for a diverse range of reactions.[1−3] Cyclopropylamines, in particular, demonstrate a variety of possible reaction pathways depending on the conditions employed, as the nitrogen serves as an important handle for activation.[4] Donor−acceptor (DA) cyclopropanes can be subjected to a variety of cycloadditions or ring-opening reactions, whereas the transition-metal-catalyzed cleavage of cyclopropylamines can access a range of small- to medium-sized heterocycles.[2−4] Cyclopropylamines can also be employed in [3 + 2] cycloadditions with alkenes to generate amino-cyclopentane motifs through a radical mechanism. Traditionally, this approach has relied on the use of strong oxidants or stoichiometric photooxidants in the presence of UV light to activate the nitrogen via radical cation formation, which initiates β-scission of the strained cyclopropane ring.[5−7] Whereas these methodologies have laid the foundations for future developments, the harsh radical-generating conditions often result in overoxidation and low product yields. Modern visible-light photoredox catalysis provides a mild approach to combat these synthetic challenges and has facilitated many developments into [3 + 2] annulations.[8−14]

In 2012, Zheng and coworkers reported the first visible-light photoredox-catalyzed [3 + 2] cycloaddition of cyclopropylamine derivatives (Scheme 1a).[9a] The use of *N*-aryl cyclopropylamines permitted direct oxidation to an amine radical cation, which triggered cyclopropane opening and subsequent trapping of the resulting carbon-centered radical with alkenes or alkynes, affording cyclopentane or cyclopentene products, respectively.[9,10] Although modest diastereoselectivity could be achieved when generating 5,5-fused ring systems, little or no diastereoselectivity was observed when using styrene derivatives or acrylonitrile in the construction of monocyclic structures. Stephenson and coworkers developed an alternative approach, where imines were employed as masked nitrogen-centered radicals (Scheme 1b).[11,12] When subjected to violet-light irradiation, a diradical was formed from the imine, which initiated the strain-driven homolysis of the cyclopropane and enabled [3 + 2] cycloadditions with styrenes. However, the construction of monocyclic cyclopentanes by intermolecular cycloaddition proceeded with no diastereoselectivity.[12] More recently, the groups of Jiang and Ooi independently published enantioselective variants of Zheng's original protocol (Scheme 1c,d).[13,14]

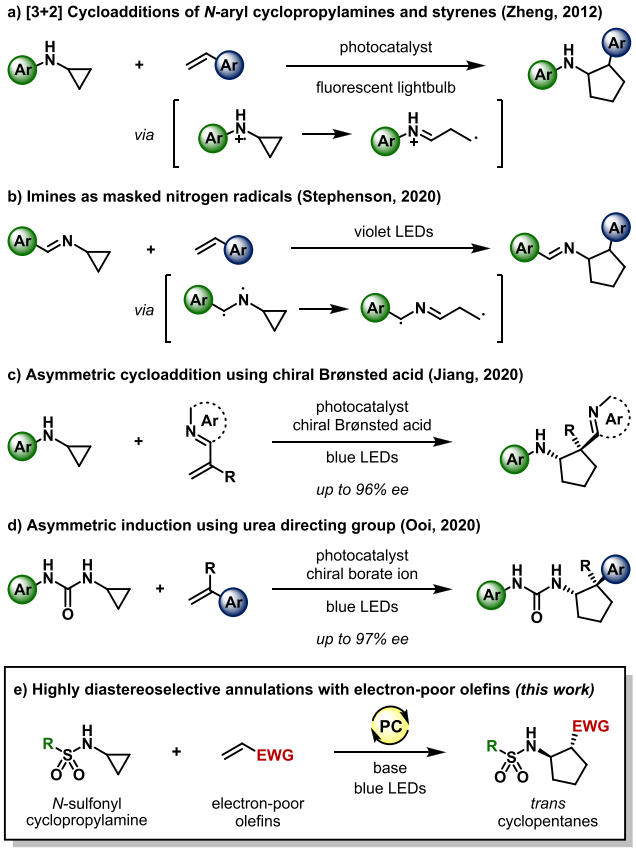
Whereas the published protocols provide approaches to access amino-cyclopentanes in both a diastereoselective and enantioselective fashion, they are predominantly reliant upon the use of styrene-based alkenes as the radical acceptor. Additionally, only Ooi and coworkers employed a protecting group strategy, where the urea directing group could be cleaved. Both factors greatly restrict the potential for downstream synthetic modification. To address these issues, it was our vision to develop a protocol that employed protected cyclopropylamines and could be applied to a broad range of non-styrene-based alkenes, therefore allowing the synthesis of cyclopentanes with functional synthetic handles. Herein we report the first [3 + 2] cycloaddition of *N*-sulfonyl cyclopropylamines with electron-poor olefins to give trans-substituted cyclopentanes with high diastereoselectivities using visible-light photoredox catalysis.

We began our investigation by considering potential protecting groups on the cyclopropylamine. One of the main drawbacks of exchanging the aryl motif on the cyclopropyl-

Received: March 1, 2021
Published: April 6, 2021

https://doi.org/10.1021/acs.orglett.1c00711
Org. Lett. 2021, 23, 3038−3042

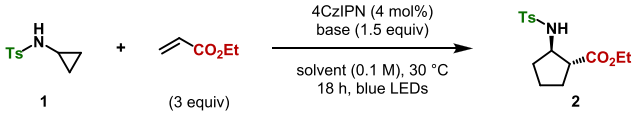
Scheme 1. Photoinduced Construction of Cyclopentanes from Cyclopropylamines



amine for a carbamate or sulfonamide is that the oxidation potential of the amino group dramatically increases (e.g., $E_{p/2}$ vs SCE in MeCN is 0.92 V for *N*-phenyl cyclopropylamine[13] and 2.24 V for *N*-tosyl cyclopropylamine **1**), making the generation of nitrogen radical cations by single-electron oxidation challenging for these substrates. However, in the case of sulfonamides, the acidity of the NH allows deprotonation followed by facile oxidation of the resulting aza-anion.[15,16] Therefore, we envisioned that *N*-sulfonyl cyclopropylamines could undergo a stepwise deprotonation and oxidation event to initiate a [3 + 2] cycloaddition with alkenes under mild photoredox conditions.

To investigate the feasibility of this proposal, we studied the reaction of *N*-tosyl cyclopropylamine **1** with ethyl acrylate (Table 1). The organic photocatalyst 2,4,5,6-tetrakis(9*H*-carbazol-9-yl) isophthalonitrile (4CzIPN) was chosen because it can be readily synthesized and proves to be more cost efficient than transition-metal counterparts.[17,18] We were pleased to observe that using sodium phosphate as the base and DCM as the solvent gave amino-cyclopentane **2** in 52% yield after irradiation with blue light-emitting diodes (LEDs) for 18 h (entry 1). The evaluation of various bases and solvents led to the identification of potassium phosphate and DCM as the optimal choices (entries 2−5). The reaction concentration proved to be a critical factor, as changing from 0.1 to 0.025 M enhanced the yield of **2** significantly to 75% (entry 6). This is likely a result of the lower local concentration of olefin minimizing deleterious polymerization pathways. A drying agent additive of sodium sulfate also enhanced the yield of **2** to an optimal 82% (entry 7). In contrast with previous reports

Table 1. Optimization Studies[a]



entry	base	solvent	concentration (M)	d.r.	% yield
1	Na_3PO_4	DCM	0.1	80:20	52[b]
2	Na_3PO_4	MeCN	0.1	67:33	20
3	Na_3PO_4	DMSO	0.1	84:16	21
4	K_2CO_3	DCM	0.1	84:16	25
5	K_3PO_4	DCM	0.1	84:16	56
6	K_3PO_4	DCM	0.025	84:16	75
7[c]	**K_3PO_4**	**DCM**	**0.025**	**84:16**	**82**[b]
8[c,d]	K_3PO_4	DCM	0.025		0
9[c,e]	K_3PO_4	DCM	0.025		0
10[c]	none	DCM	0.025		trace

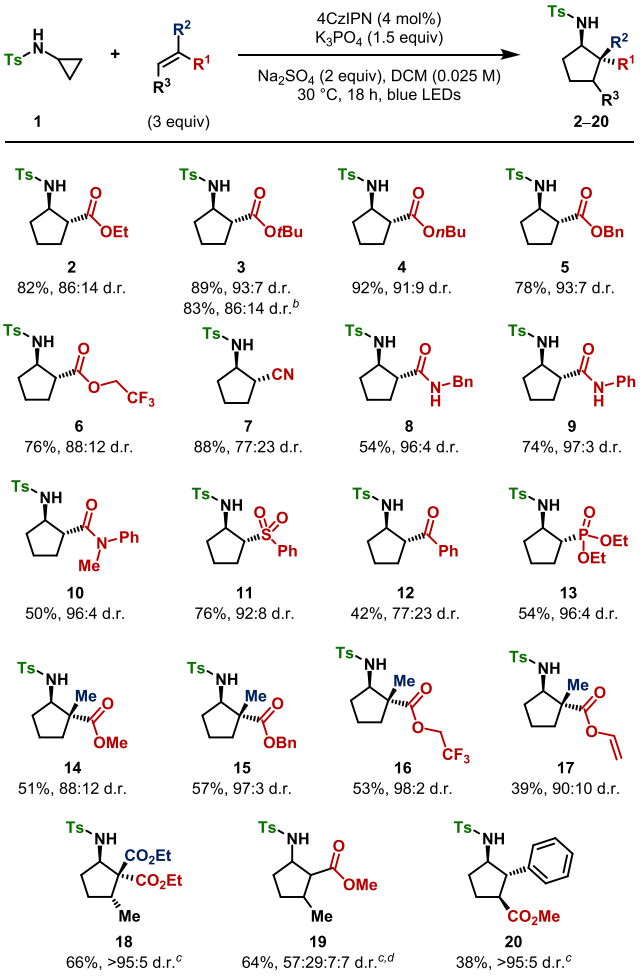
[a]Yields and d.r. were determined by ^{1}H NMR analysis using 1,4-dinitrobenzene as the internal standard. [b]Isolated yields after column chromatography. [c]With Na_2SO_4 (2 equiv). [d]Reaction performed in the dark. [e]Without 4CzIPN.

utilizing *N*-aryl cyclopropylamines and styrenes, which proceeded with low diastereoselectivity, we were delighted that **2** was formed with high trans selectivity. (See the SI for details of the analysis.) Control experiments confirmed that a photoredox mechanism is operative, as no product was observed in the absence of a light source or photocatalyst (entries 8 and 9). Additionally, only trace product was formed in the absence of a base (entry 10), highlighting the importance of generating the active radical species through oxidation of the corresponding sulfonamide anion. We also tested alternative carbamate protecting groups (Boc, Cbz) under the optimized conditions, but no reaction was observed. (See the SI for details.) This highlights the importance of having either a strong electron-withdrawing group (Ts) on nitrogen, to enable the generation of an aza-anion, or an aryl group on nitrogen, both of which facilitate subsequent single-electron oxidation.

Exploration of the scope began by examining the effect of the olefin substituents on the reaction (Scheme 2). It was found that changing the alkyl group on the acrylate had no negative effect on the yield or diastereoselectivity (**2**−**6**); however, bulkier substituents gave enhanced trans selectivity. Acrylonitrile gave high yields of product **7**, but a drop in the diastereoselective bias was observed, which can be attributed to the small size of the nitrile group (*vide infra*). Acrylamides were also tolerated, providing products **8**−**10** with excellent diastereoselectivities. Other electron-withdrawing functionalities on the olefin also proved successful, including sulfones (**11**), aryl ketones (**12**), and phosphonate esters (**13**). Whereas sulfone **11** and phosphonate **13** were formed with excellent diastereoselectivity, phenyl vinyl ketone gave **12** with lower selectivity. We subsequently explored the use of 1,1-disubstituted alkenes. Pleasingly, the cyclization of various methacrylates proceeded well, despite increased steric bulk, to afford more complex trisubstituted cyclopentanes **14**−**17**. Although modest yields were obtained, superb levels of diastereoselectivity were observed for the construction of these quaternary center-containing products. Interestingly, vinyl methacrylate chemoselectively provided product **17** in reasonable yield, despite the presence of the less hindered vinyl group, which highlights the importance of alkene electronics in

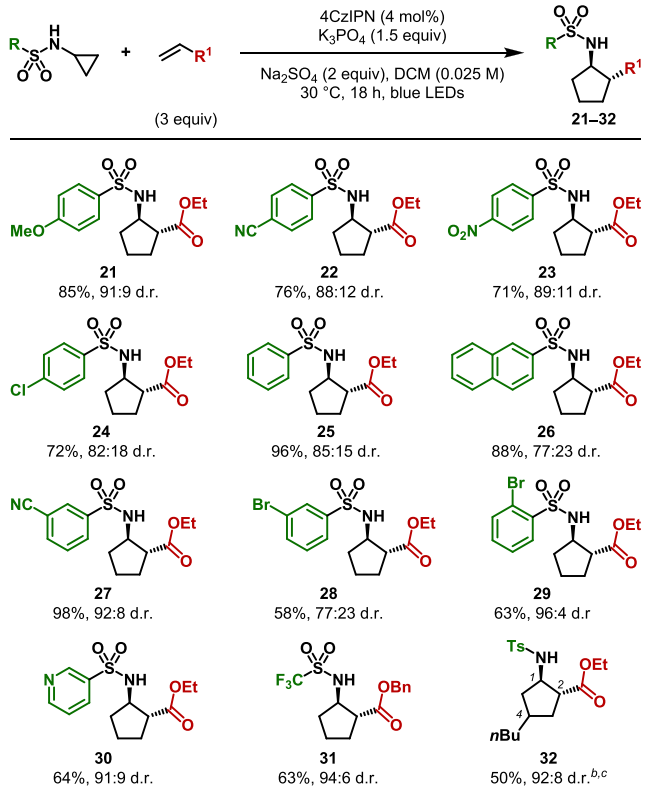
https://doi.org/10.1021/acs.orglett.1c00711
Org. Lett. 2021, 23, 3038−3042

Scheme 2. Alkene Scope[a]



[a]Performed using 0.1 mmol of **1**. Yields are of isolated products after chromatographic purification. The d.r. was determined by LCMS analysis of crude reaction mixtures. [b]Performed using 1.0 mmol of **1**, no Na_2SO_4, and a reaction concentration of 0.05 M. [c]Performed using 0.2 mmol of **1** and a reaction concentration of 0.1 M. [d]Major diastereomer not assigned.

Scheme 3. Sulfonamide Scope[a]



[a]Performed using 0.1 mmol of *N*-sulfonylcyclopropylamine. Yields are of isolated products after chromatographic purification. The d.r. was determined by LCMS analysis of crude reaction mixtures. [b]Performed using 0.1 mmol of *N*-((1*R*,2*R*)-2-butylcyclopropyl)-4-methylbenzenesulfonamide. [c]1,4-selectivity was 54:46.

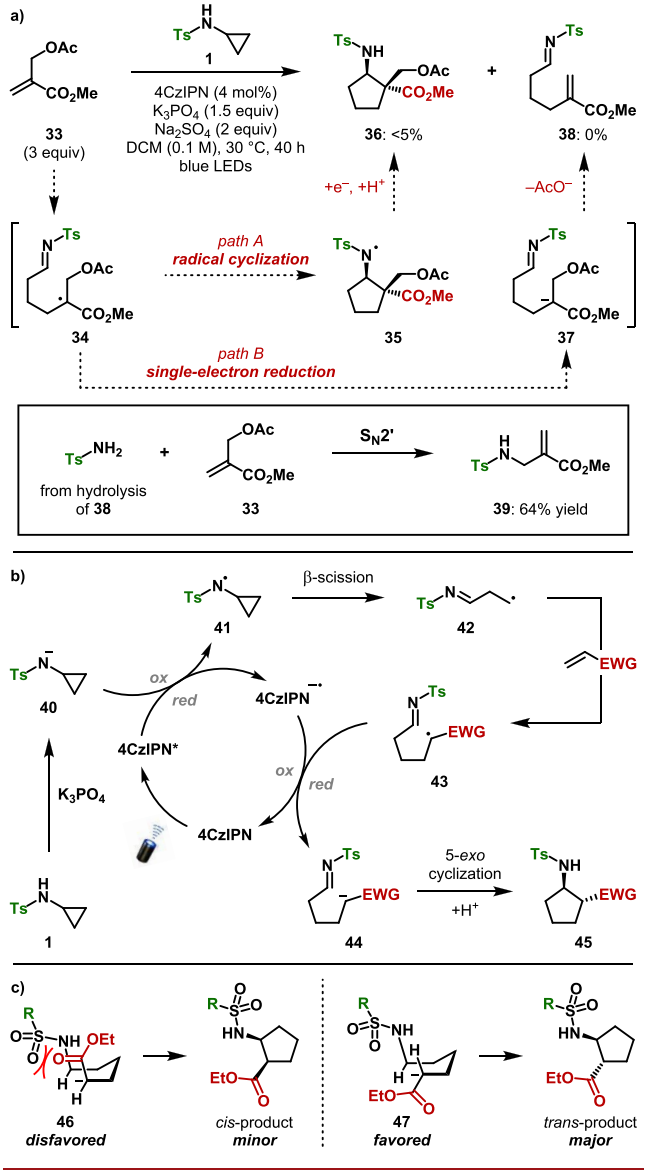
determining the rate of intermolecular radical addition of the nucleophilic alkyl radical intermediate. We next explored the reactivity of enoates bearing β-substituents. Diethyl ethylidenemalonate provided tetrasubstituted cyclopentane **18** in good yield with excellent 1,3-trans selectivity, whereas the methyl crotonate-derived cyclopentane **19** was formed with low diastereoselectivity. Interestingly, methyl cinnamate provided cyclopentane **20** with excellent diastereoselectivity and with the reverse regioselectivity,[19] albeit in low yield.

Given the importance of sulfonamides in medicinal chemistry,[20] we investigated the effect of different sulfonyl substituents on the cyclopropylamine substrate (Scheme 3). A wide array of functionalities were found to be tolerated, including ortho, meta and para substitution patterns (**21**–**29**). The transformation was insensitive to the electronics of the aryl substituent, with both electron-donating and electron-withdrawing groups providing the products in high yield with good trans diastereoselectivity. Additionally, *ortho*-, *meta*-, and *para*-halides could be implemented (**24**, **28**, and **29**), providing useful handles for further derivatizations. A pyridyl sulfonamide gave the corresponding product **30** in good yield with good selectivity, and trifluoromethyl sulfonamide derivative **31** could be accessed with excellent selectivity. Finally, the effect of substitution on the cyclopropane ring was briefly surveyed. We were pleased to observe that the reaction of a trans-disubstituted cyclopropylamine provided 1,2,4-trisubstituted cyclopentane **32** in moderate yield and with high 1,2-trans selectivity; however, no diastereoselectivity was observed at the four-position.

We next turned our attention to the mechanism of the cycloaddition reaction. All previously reported photoredox-catalyzed [3 + 2] cycloadditions of styrene derivatives were proposed to proceed through a radical cyclization of an intermediate benzylic radical onto an imine.[9−14] However, under our optimal conditions, styrenes proved unsuccessful (see the SI for details), whereas electron-deficient olefins excelled. This led us to suspect that the intermediate electrophilic radical, formed upon radical addition to the electron-deficient olefin, was first reduced to the corresponding stabilized anion prior to cyclization. This was investigated using allylic acetate **33** (Scheme 4a), which would give cyclopentane **36** if a radical cyclization of intermediate **34** occurred prior to the single-electron reduction of the nitrogen-centered radical **35** (path A) but would form imine **38** under an anionic cyclization pathway due to the rapid elimination of the acetate group from anion **37** (path B). Interestingly, cyclopentane **36** was observed in only trace amounts, whereas the major product was allylic sulfonamide **39**, formed *via* the reaction of *p*-toluenesulfonamide with **33**. This provides

https://doi.org/10.1021/acs.orglett.1c00711
Org. Lett. 2021, 23, 3038−3042

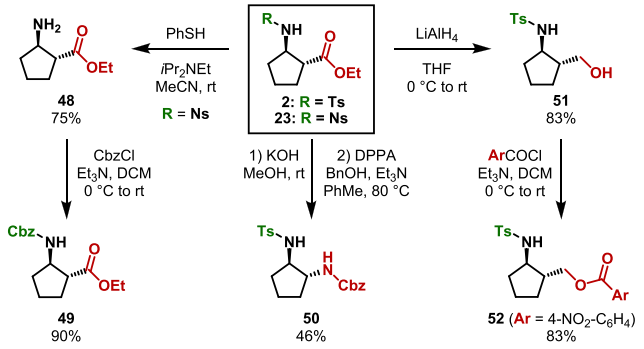
Scheme 4. Mechanistic Studies and Proposed Mechanism



indirect evidence of the formation of imine **38**, which can be hydrolyzed by adventitious water to produce *p*-toluenesulfonamide. This observation suggests the 5-exo cyclization predominantly occurs through an anionic mechanism, although the formation of trace amounts of **36** suggests that a minor radical cyclization pathway could also occur. On the basis of these results, we propose the mechanism shown in Scheme 4b. After the initial deprotonation of sulfonamide **1** by the phosphate base, the single-electron oxidation of aza-anion **40** ($E_{p/2}$ = 1.18 V vs SCE in MeCN) by photoexcited 4CzIPN ($E_{1/2}$ = 1.49 V vs SCE in MeCN)[17] generates the nitrogen-centered radical **41**.[16,21] Strain-induced ring-opening of the cyclopropane in **41** occurs through *β*-scission to form alkyl radical **42**. Intermolecular trapping with an electron-deficient olefin, followed by single-electron reduction of the resulting radical **43** by the reduced state of the photocatalyst regenerates ground-state 4CzIPN and provides the stabilized carbanion **44**. Facile 5-exo cyclization of the nucleophilic carbanion onto the electrophilic *N*-sulfonyl imine and protonation deliver the substituted cyclopentane product **45**. We hypothesized that the diastereoselective bias can be attributed to electronic and steric repulsion between the *N*-sulfonyl imine and the electron-withdrawing group (Scheme 4c), where conformer **46** suffers from unfavorable steric and dipole−dipole interactions, thus cyclization occurs preferentially through conformer **47** to provide high selectivity for the trans product.[22]

Finally, we aimed to demonstrate the synthetic utility of the cyclopentane products (Scheme 5). Reduction of the ester

Scheme 5. Product Derivatizations



functionality in cyclopentane **2** proceeded smoothly to afford alcohol **51** in 83% yield, with further esterification being performed to obtain crystalline derivative **52** used for structural determination. Saponification and Curtius rearrangement gave *trans*-diamino cyclopentane **50** with two different protecting groups for selective modification. The nosyl-protected **23** underwent sulfonyl deprotection under mild conditions to form primary amine **48** in 75% yield, allowing the installation of alternative protecting groups, such as carbamate **49**.

In summary, we have developed a protocol for visible-light photocatalytic [3 + 2] cycloadditions of *N*-sulfonyl cyclopropylamines with electron-deficient olefins to afford novel cyclopentane ring systems in high yields and with excellent trans diastereoselectivity. The scope of the alkene partner is broad and can be extended to the construction of challenging quaternary centers in a diastereoselective fashion. The robust nature of the process, coupled with mild reaction conditions, allows entry to a wide variety of cyclopentane products bearing useful synthetic handles for subsequent downstream modification.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00711.

General procedures, characterization data, and copies of NMR spectra for all novel compounds (PDF)

Accession Codes

CCDC 2065115 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or 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.

https://doi.org/10.1021/acs.orglett.1c00711
Org. Lett. 2021, 23, 3038−3042

AUTHOR INFORMATION

Corresponding Authors

Varinder K. Aggarwal − *School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom;* orcid.org/0000-0003-0344-6430; Email: v.aggarwal@bristol.ac.uk

Kevin I. Booker-Milburn − *School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom;* orcid.org/0000-0001-6789-6882; Email: k.booker-milburn@bristol.ac.uk

Authors

Dawn H. White − *School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom*

Adam Noble − *School of Chemistry, University of Bristol, Bristol BS8 1TS, United Kingdom;* orcid.org/0000-0001-9203-7828

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00711

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We acknowledge the EPSRC (DTA award) for funding. We thank Dr. Natalie Pridmore (University of Bristol) for X-ray crystallography analysis and Sayad Doobary (University of Bristol) and Mark Deeprose (University of Bristol) for assistance with conducting cyclic voltammetry experiments.

REFERENCES

(1) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. Use of Cyclopropanes and their Derivatives in Organic Synthesis. *Chem. Rev.* **1989**, *89*, 165−198.

(2) Reissig, H. U.; Zimmer, R. Donor−Acceptor-Substituted Cyclopropane Derivatives and Their Application in Organic Synthesis. *Chem. Rev.* **2003**, *103*, 1151−1196.

(3) Cavitt, M. A.; Phun, L. H.; France, S. Intramolecular Donor−Acceptor Cyclopropane Ring-Opening Cyclizations. *Chem. Soc. Rev.* **2014**, *43*, 804−818.

(4) Sokolova, O. O.; Bower, J. F. Selective Carbon−Carbon Bond Cleavage of Cyclopropylamine Derivatives. *Chem. Rev.* **2021**, *121*, 80−109. and references cited therein.

(5) Takemoto, Y.; Yamagata, S.; Furuse, S.-i.; Iwata, C. CAN-Mediated Tandem 5-*exo*-Cyclisation of Tertiary Aminocyclopropanes: Novel Accelerative Effect of an *N*-Benzyl Group for Oxidative Ring-Opening. *Chem. Commun.* **1998**, 651−652.

(6) (a) Lee, J.; U, J. S.; Blackstock, S. C.; Cha, J. K. Facile Ring Opening of Tertiary Aminocyclopropanes by Photooxidation. *J. Am. Chem. Soc.* **1997**, *119*, 10241−10242. (b) Ha, J. Du; Lee, J.; Blackstock, S. C.; Cha, J. K. Intramolecular [3 + 2] Annulation of Olefin-Tethered Cyclopropylamines. *J. Org. Chem.* **1998**, *63*, 8510−8514.

(7) For other radical-mediated ring-opening reactions of cyclopropylamines, see: (a) Madelaine, C.; Six, Y.; Buriez, O. Electrochemical Aerobic Oxidation of Aminocyclopropanes to Endoperoxides. *Angew. Chem., Int. Ed.* **2007**, *46*, 8046−8049. (b) Wang, M.-M.; Waser, J. Oxidative Fluorination of Cyclopropylamides through Organic Photoredox Catalysis. *Angew. Chem., Int. Ed.* **2020**, *59*, 16420−16424.

(8) Shaw, M. H.; Twilton, J.; MacMillan, D. W. C. Photoredox Catalysis in Organic Chemistry. *J. Org. Chem.* **2016**, *81*, 6898−6926.

(9) (a) Maity, S.; Zhu, M.; Shinabery, R. S.; Zheng, N. Intermolecular [3 + 2] Cycloaddition of Cyclopropylamines with Olefins by Visible-Light Photocatalysis. *Angew. Chem., Int. Ed.* **2012**, *51*, 222−226. (b) Nguyen, T. H.; Maity, S.; Zheng, N. Visible Light Mediated Intermolecular [3 + 2] Annulation of Cyclopropylanilines with Alkynes. *Beilstein J. Org. Chem.* **2014**, *10*, 975−980.

(10) (a) Staveness, D.; Sodano, T. M.; Li, K.; Burnham, E. A.; Jackson, K. D.; Stephenson, C. R. J. Providing a New Aniline Bioisostere through the Photochemical Production of 1-Amino-norbornanes. *Chem.* **2019**, *5*, 215−226. (b) Muriel, B.; Gagnebin, A.; Waser, J. Synthesis of Bicyclo[3.1.0]hexanes by (3 + 2) Annulation of Cyclopropenes with Aminocyclopropanes. *Chem. Sci.* **2019**, *10*, 10716−10722.

(11) Staveness, D.; Collins, J. L.; McAtee, R. C.; Stephenson, C. R. J. Exploiting Imine Photochemistry for Masked N-Centered Radical Reactivity. *Angew. Chem., Int. Ed.* **2019**, *58*, 19000−19006.

(12) Sowden, M. J.; Collins, J. L.; Staveness, D.; Stephenson, C. A One Pot Photochemical Method for the Generation of Functionalized Aminocyclopentanes. *ChemRxiv* **2020**, DOI: 10.26434/chemrxiv.13079159.v1.

(13) Yin, Y.; Li, Y.; Gonçalves, T. P.; Zhan, Q.; Wang, G.; Zhao, X.; Qiao, B.; Huang, K.-W.; Jiang, Z. All-Carbon Quaternary Stereocenters α to Azaarenes via Radical-Based Asymmetric Olefin Difunctionalization. *J. Am. Chem. Soc.* **2020**, *142*, 19451−19456.

(14) Uraguchi, D.; Kimura, Y.; Ueoka, F.; Ooi, T. Urea as a Redox-Active Directing Group under Asymmetric Photocatalysis of Iridium-Chiral Borate Ion Pairs. *J. Am. Chem. Soc.* **2020**, *142*, 19462−19467.

(15) Wang, X.; Xia, D.; Qin, W.; Zhou, R.; Zhou, X.; Zhou, Q.; Liu, W.; Dai, X.; Wang, H.; Wang, S.; Tan, L.; Zhang, D.; Song, H.; Liu, X.-Y.; Qin, Y. A Radical Cascade Enabling Collective Syntheses of Natural Products. *Chem.* **2017**, *2*, 803−816.

(16) Tanaka, H.; Sakai, K.; Kawamura, A.; Oisaki, K.; Kanai, M. Sulfonamides as New Hydrogen Atom Transfer (HAT) Catalysts for Photoredox Allylic and Benzylic C−H Arylations. *Chem. Commun.* **2018**, *54*, 3215−3218.

(17) Speckmeier, E.; Fischer, T. G.; Zeitler, K. A Toolbox Approach to Construct Broadly Applicable Metal-Free Catalysts for Photoredox Chemistry: Deliberate Tuning of Redox Potentials and Importance of Halogens in Donor−Acceptor Cyanoarenes. *J. Am. Chem. Soc.* **2018**, *140*, 15353−15365.

(18) Nicewicz, D. A.; Nguyen, T. M. Recent Applications of Organic Dyes as Photoredox Catalysts in Organic Synthesis. *ACS Catal.* **2014**, *4*, 355−360.

(19) Lovett, G. H.; Sparling, B. A. Decarboxylative Anti-Michael Addition to Olefins Mediated by Photoredox Catalysis. *Org. Lett.* **2016**, *18*, 3494−3497.

(20) Apaydın, S.; Török, M. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 2042−2050.

(21) Whereas we believe that stepwise deprotonation and oxidation is the favored reaction pathway, an alternative mechanism involving proton-coupled electron transfer (PCET) cannot be eliminated. Weaker bases such as K_2CO_3 and Cs_2CO_3 were able to deliver the desired amino-cyclopentane products, albeit in lower yield, suggesting that PCET operates in tandem to a minor extent. See: Chu, J. C. K.; Rovis, T. Amide-Directed Photoredox-Catalysed C−C Bond Formation at Unactivated sp^3 C−H Bonds. *Nature* **2016**, *539*, 272−275.

(22) The trans selectivity was found to remain constant throughout the course of the reaction and after prolonged reaction times, which suggests that the diastereoselectivity is not a result of a postcyclization epimerization.