UNIVERSITY OF AMSTERDAM

UvA-DARE (Digital Academic Repository)

Continuous-Flow Synthesis of Pyrylium Tetrafluoroborates

Application to Synthesis of Katritzky Salts and Photoinduced Cationic RAFT Polymerization

Sambiagio, C.; Ferrari, M.; van Beurden, K.; della Ca', N.; van Schijndel, J.; Noël, T.

DOI
10.1021/acs.orglett.1c00178

Publication date
2021

Document Version
Final published version

Published in
Organic Letters

License
CC BY-NC-ND

Link to publication

Citation for published version (APA):
Sambiagio, C., Ferrari, M., van Beurden, K., della Ca', N., van Schijndel, J., & Noël, T. (2021). Continuous-Flow Synthesis of Pyrylium Tetrafluoroborates: Application to Synthesis of Katritzky Salts and Photoinduced Cationic RAFT Polymerization. *Organic Letters*, *23*(6), 2042-2047. https://doi.org/10.1021/acs.orglett.1c00178

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, P.O. Box 19185, 1000 GD Amsterdam, The Netherlands. You will be contacted as soon as possible.

UvA-DARE is a service provided by the library of the University of Amsterdam (https://dare.uva.nl)
Download date:16 Sep 2026

OL | Organic Letters

pubs.acs.org/OrgLett

Letter

Continuous-Flow Synthesis of Pyrylium Tetrafluoroborates: Application to Synthesis of Katritzky Salts and Photoinduced Cationic RAFT Polymerization

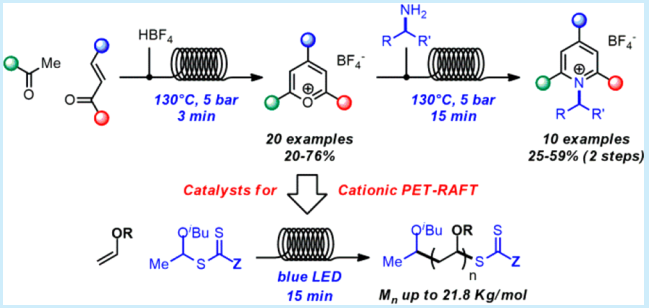
Carlo Sambiagio, Matteo Ferrari, Koen van Beurden, Nicola della Ca', Jack van Schijndel, and Timothy Noël*

Cite This: *Org. Lett.* 2021, 23, 2042–2047

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Katritzky salts have emerged as effective alkyl radical sources upon metal- or photocatalysis. These are typically prepared from the corresponding triarylpyrylium ions, in turn an important class of photocatalysts for small molecules synthesis and photopolymerization. Here, a flow method for the rapid synthesis of both pyrylium and Katrizky salts in a telescoped fashion is reported. Moreover, several pyrylium salts were tested in the photoinduced RAFT polymerization of vinyl ethers under flow and batch conditions.



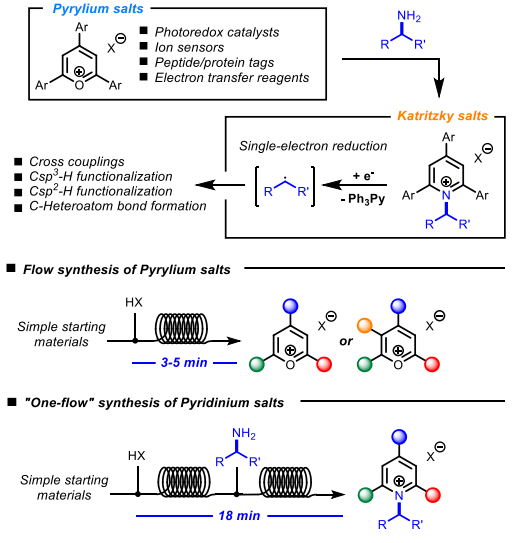
Downloaded via UNIV AMSTERDAM on June 7, 2023 at 11:13:34 (UTC).
See https://pubs.acs.org/sharingguidelines for options on how to legitimately share published articles.

2,4,6-Triarylpyrylium salts have found applications in various fields of chemistry, especially as visible-light photocatalysts for the synthesis of small molecules[1] and photoinduced polymerizations.[2] In addition to their applications as photocatalysts, pyrylium salts have been used as precursors for a variety of other heterocycles, in particular *N*-alkylpyridinium salts (Katritzky salts), via reaction with primary amines.[3] The pyridinium moiety can act in these compounds as a leaving group in nucleophilic substitution reactions[4] or can lead to fragmentation upon single-electron reduction, generating alkyl radicals. Several methods for the single electron reduction of Katritzky salts have been recently investigated. In particular, activation via metal catalysis,[5] photoredox catalysis,[6] and visible light-activated electron donor–acceptor (EDA) interactions[7] have recently found large interest in the chemistry community.

Based on our interest in flow chemistry and photochemical methodologies,[8] we developed a flow protocol for the rapid synthesis of pyrylium salts and, in a telescoped fashion, of Katritzky salts, starting from simple starting materials (Scheme 1). As the formation of both pyrylium and Katritzky salts is a thermal reaction, we reasoned that a continuous flow method in superheated conditions would promote much faster reactions than in batch.

Reversible addition–fragmentation chain transfer (RAFT) polymerization has emerged as a powerful method to generate polymeric materials with controlled properties.[9] While radical initiation has been traditionally achieved thermally, alternatives have been recently investigated. In particular, the use of photoactivated chain-transfer agents (CTAs) made possible the development of photochemical RAFT methods, which

Scheme 1. Applications of Pyrylium and Katritzky Salts in Chemistry And Outline of This Work



Received: January 17, 2021
Published: March 2, 2021

© 2021 The Authors. Published by American Chemical Society

offer milder conditions and higher degrees of control.[9b−d] Photocatalytic RAFT polymerizations are often performed in continuous flow conditions, due to the benefits of microflow chemistry in this area.[8a−c,10]

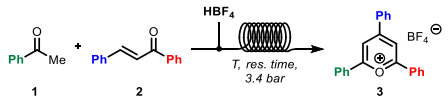
Pyrylium photocatalysts have been recently used in cationic photoinduced electron/energy transfer RAFT processes (PET-RAFT[10c,11]) for the polymerization of vinyl ethers,[2e,f] not always easy to achieve with traditional RAFT.[12] Here, we report investigations on the use of pyrylium salts for the photchemical RAFT polymerization of vinyl ethers in flow and comparison with the corresponding batch process. The use of microflow chemistry allowed for much shorter reaction time, higher molecular weight, and lower polydispersity of the polymeric materials.

Pyrylium salts are typically prepared by reaction of an acetophenone and a chalcone derivative in the presence of an acid. This protocol comprises the use of simple starting materials and allows for the synthesis of both symmetrical and unsymmetrical triarylpyryliums, and was therefore chosen for our investigations in flow. As tetrafluoroborate salts are commonly used for both pyryliums and Katritzky salts applications, we focused on these salts.

We started our investigation by performing the reaction between chalcone (**1**), acetophenone (**2**), and $HBF_4{\cdot}Et_2O$ under flow conditions for the synthesis of 2,4,6-triphenylpyrylium tetrafluoroborate (**3**) in DCE. The reaction was then optimized with respect to temperature and residence time. Reactions were performed above the boiling point of the solvent (82 °C) using a back-pressure regulator set at 3.4 bar at the end of the reactor coil. Screening of temperature showed 110 °C as the optimal temperature for the reaction, giving up to 74% yield over 5 min residence time (entry 3, Table 1). However, reactions conducted at 130 °C over 3 min residence time gave comparable results (entry 9, Table 1).

The flow protocol was tested for the synthesis of a variety of triarylpyrylium tetrafluoroborates (Scheme 2). Differently substituted chalcones could be used in the reaction, furnishing halogenated or methoxylated pyryliums **4**−**8**. Different acetophenones, including substituents such as phenyl, methoxy, methylthio, chloro, and bromo, also reacted well, giving products **9**−**15**. Heteroaromatic ketones could also be efficiently employed, and the reaction of chalcones with acetylbenzofuran and acetylbenzothiophene led to pyryliums **16**−**18**. Differently substituted pyrliums, containing alkyl moieties, were then investigated (Scheme 2). Tetrasubstituted and polycyclic pyrylium salts can be prepared by reaction of chalcones with linear or cyclic ketones. For example, indanone, cyclohexa/heptenone, and valerophenone gave pyryliums **19**−**22** in 68−76% yield.

Table 1. Selected Optimization for the Synthesis of Triphenylpyrylium Tetrafluoroborate in Flow[a]



entry	T (°C)	res time (min)	yield (%)
	Temperature Screening		
1	90	5	57
2	100	5	65−69[b]
3	110	5	69−74[b]
4	120	5	57−67[b]
5	130	5	63
	Residence Time Screening		
6	110	2	57
7	110	3	64
8	110	7	70
9	130	3	69

[a]Conditions: Feed 1: 2.5−5 mmol of acetophenone, 5−10 mmol of chalcone, diluted with DCE to 2−4 mL. Feed 2: 5−10 mmol $HBF_4{\cdot}Et_2O$, diluted with DCE to 2−4 mL. Isolated yields from direct precipitation into Et_2O at the outlet of the reactor. [b]The reported range represent the variation observed within at least two runs. Conditions in entry 3 were run several times, with results always in the reported range.

We then set out to investigate the continuous-flow synthesis of *N*-alkyl triphenylpyridinium compounds (Katritzky salts) in a "one-flow" fashion.[14] These compounds are typically prepared in batch by reaction of pyrylium salts with a primary amine in refluxing ethanol for a few hours.[5a,d,7a] A one-pot process in batch, starting from the synthesis of triphenylpyrylium **3**, followed by addition of an amine solution after 1 h of reflux, resulted in the immediate formation of smoke and deposition of amine salts on the walls of flask and condenser and resulted in a complex mixture of salts, making this process cumbersome and unpractical. A telescoped flow synthesis was therefore envisaged, starting with the initial synthesis of pyrylium, followed by immediate reaction with the desired amine.

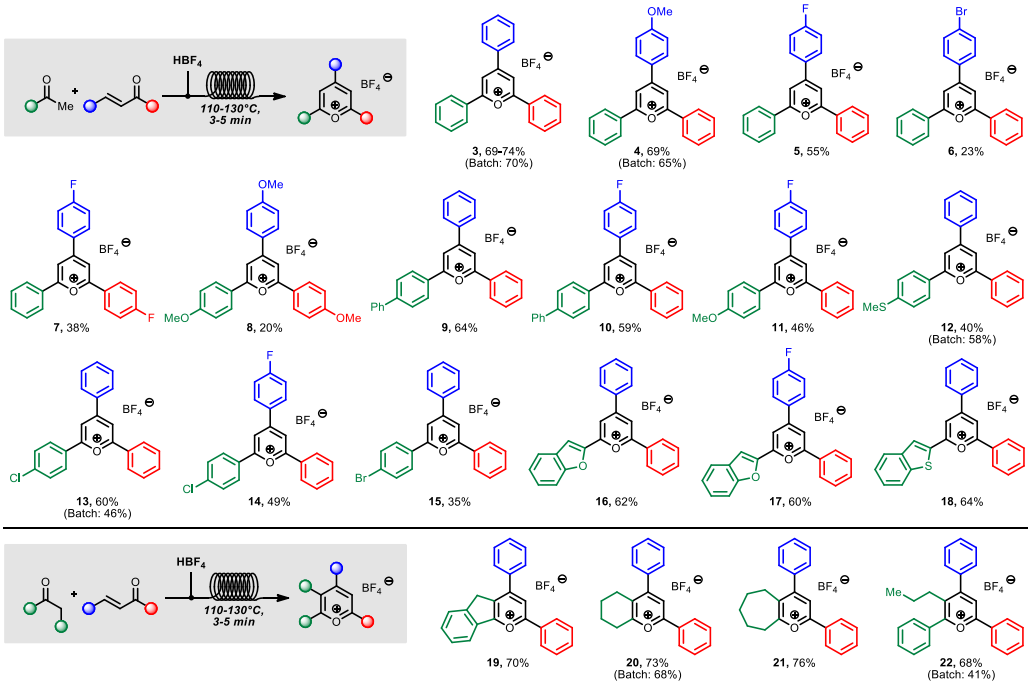
The use of DCE for both steps resulted in heavy reactor clogging. Ethanol was therefore selected as the solvent of choice for the second step, as it provides a good medium for the synthesis of pyridinium salts, good miscibility with DCE, and a comparable boiling point.[15] The temperature and residence time for the second reactor coil were set respectively at 130 °C and 15 min, making the overall residence time for the two-step process 18 min.

The telescoped protocol was applied to the synthesis of different pyridinium salts (Scheme 3). Pyridinium salts containing linear, primary alkyl chains (**23**−**25**) were obtained smoothly in 41−59% yield. Allyl- and benzylamines also reacted with comparable yields (**26**−**28**, 44−54%). The reaction with cyclopropylmethyl-, isopropyl-, cyclobutyl-, and cyclohexylamine delivered compounds **29**−**32**, albeit in lower yields (25−37%). As the yield for the triphenylpyrylium precursor **3** (first step) is in average 71%, the second step of the telescoped process results in yields of 58−83% for compounds **23**−**28**. For compounds **29**−**32**, this translates to 35−52% yield. As the reaction of secondary alkyl amines with pyrylium salts (**30**−**32**) is known to be much slower than the reaction of primary alkyl amines,[15] we suspect individual optimization might be necessary for these compounds, as well as for **29**.

Having established the efficiency of the microflow method for the fast preparation of pyrylium salts, we set out to investigate their use in the photopolymerization of vinyl ethers via cationic RAFT.[2e,f] We thus selected differently substituted

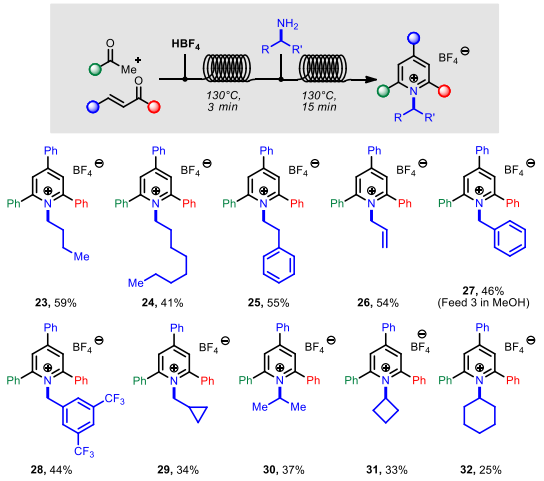
https://dx.doi.org/10.1021/acs.orglett.1c00178
Org. Lett. 2021, 23, 2042−2047

Scheme 2. Synthesis of Pyrylium Salts[a]



[a]Conditions: Feed 1: 0.5 g of chalcone (2 equiv), acetophenone (1 equiv), diluted to 2−3 mL with DCE. Feed 2: $HBF_4{\cdot}Et_2O$ (2 equiv), diluted to 2−3 mL with DCE; T = 110 or 130 °C, P = 3.4−5.2 bar, residence time = 3−5 min. Products were obtained by direct precipitation into Et_2O at the outlet of the reactor, isolated yields after filtration are reported.

Scheme 3. Synthesis of Katritzky Salts[a]



[a]Conditions: Feed 1: 0.5 g of chalcone (2 equiv), acetophenone (1 equiv), diluted to 2−3 mL with DCE. Feed 2: $HBF_4{\cdot}Et_2O$ (2 equiv), diluted to 2−3 mL with DCE. Feed 3: amine (4 equiv), diluted to 2−3 mL with EtOH; T = 130 °C, P = 3.4−5.2 bar, total residence time = 18 min. Products were obtained by direct precipitation into Et_2O at the outlet of the reactor (isolated yields after filtration and washing), or purified by chromatography.

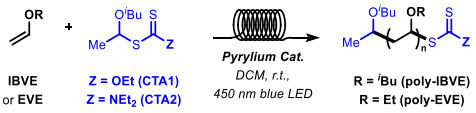
catalysts **3**, **4**, **6**, **8**, and **9** to be tested in the polymerization of benchmark monomers isobutyl vinyl ether (IBVE) and ethyl vinyl ether (EVE) under blue light irradiation. Two different CTAs, based on the xanthate and dithiocarbamate moieties, were also compared. Furthermore, a flow and a batch polymerization protocols were compared to evaluate the benefits of microflow in this process.

As shown in Table 2, the flow process resulted in generally higher molecular weight (M_n, in kg/mol) of the polymers than the batch and a slightly lower polydispersity (D). In addition, while full conversion in flow was obtained after a residence time of 15 min, the batch reaction required several hours of irradiation for completion. While the different catalysts tested generally resulted in similar properties of poly-IBVE and poly-EVE, the effect of the CTA is more remarkable. **CTA2** resulted, in general, in higher M_n, albeit with slightly higher D values than **CTA1**, indicating a somewhat lower level of control on the polymerization. The behavior of catalyst **8** in flow is noteworthy. The combination of catalysts **8** and **CTA1** resulted in very poor M_n for both polymers, while, on the contrary, its combination with **CTA2** resulted in higher M_n than all the other catalysts. This behavior was observed only under flow conditions. As in flow, the photochemical excitation of the catalyst is much enhanced with respect to batch, we suspect the unusual behaviour of catalyst **8** might be related to a faster activation of **CTA2** under these conditions. Catalyst **8** appears to have a very rapid response in the presence of both **CTA1** and **CTA2**.[16] Despite being a less strong oxidant than, for example, catalysts **3**,[2f] the extinction coefficient of **8** at 450 nm is much higher, resulting in a much faster excitation and more frequent electron transfer. This feature would be enhanced under flow conditions, thus explaining our results. We hypothesize that **CTA1** can accommodate a faster electron transfer, generating larger amounts of active CTA species, and the formation of more polymeric chains of lower M_n. **CTA2**, instead, cannot accommodate the electron transfer as efficiently, and a lower amount of radical initiator is generated, giving less, and longer polymer chains. Further investigation will, however, be needed to confirm this hypothesis.

The results obtained (in terms of M_n and D values) for the polymerization of vinyl ethers are in line with previous studies

https://dx.doi.org/10.1021/acs.orglett.1c00178
Org. Lett. 2021, 23, 2042−2047

Table 2. Photoinduced Polymerization of IBVE and EVE under Flow and Batch Conditions[a]



			flow		batch	
entry	cat.	CTA	M_n	D	M_n	D
			IBVE (R = ^{t}Bu)			
1	3	1	14.7	1.5	9.9	1.5
2	3	2	19.7	1.8	6.1	2.0
3	4	1	13.4	1.3	10.4	1.3
4	4	2	19.8	1.6	14.1	1.9
5	6	1	15.0	1.3	9.4	1.5
6	6	2	17.6	1.7	11.7	2.3
7	8	1	5.8	1.4	9.2	1.4
8	8	2	21.8	1.6	11.6	2.1
9	9	1	15.8	1.3	2.9	1.4
10	9	2	18.5	1.6	12.9	1.9
			EVE (R = Et)			
11	3	1	12.9	1.7	6.8	1.4
12	3	2	11.9	1.7	6.7	2.1
13	4	1	8.7	1.3	5.8	1.6
14	4	2	9.4	1.8	6.9	2.4
15	6	1	8.8	1.8	6.4	1.5
16	6	2	10.8	1.9	9.2	2.2
17	8	1	2.7	1.3	7.3	1.4
18	8	2	15.3	1.7	7.6	2.2
19	9	1	7.9	1.4	3.2	1.3
20	9	2	13.3	1.6	7.5	2.3

[a]Reactions performed at room temperature in DCM, with 24 W 450 nm LED irradiation. The following molecular equivalents were used: 2000:20:1 (monomer/CTA/catalyst). All experiments were run to full conversion (15 min in flow, 8 h in batch), and the properties were obtained from calibration with polystyrene standards. M_n = kg/mol.

on pyrylium catalysts. Polydispersitiy values reported in the literature range between 1.08 and 1.98 for IBVE and 1.08 and 1.89 for EVE, indicating comparable control in our experiments, with higher values observed under flow conditions.[2e,f,17] To our knowledge, no previous photochemical RAFT polymerization of vinyl ethers have been reported under flow conditions. To exclude the possibility of a catalyst-free photoiniferter polymerization, known to occur for example for acrylates and acrylamides,[18] control experiments for the polymerization of both monomers were also performed. Under otherwise identical conditions, the absence of catalysts results in essentially no polymerization, with conversions of 4−10% and M_n values about 50 times lower than with the pyrylium catalysts (see ESI).

In conclusion, we reported here the flow synthesis of a range of pyrylium tetrafluoroborate salts and a two-step flow synthesis of their derivatives *N*-alkylpyridinium salts. The use of flow technology allowed the synthesis of pyrylium salts to be completed in as short as 3 min (1+ hour in batch), while Katritzky salts can be prepared in 18 min (second step alone typically a few hours in batch). Several pyrylium salts were tested in the photochemical RAFT polymerization of vinyl ethers, under batch and flow conditions. The flow protocol resulted in a much shorter reaction time (15 min vs several hours), higher M_n, and lower D of the polymeric materials, compared to the batch procedure. The combination of photoinduced cationic RAFT polymerization and the use of microflow chemistry is in our opinion a very promising method for the fast, mild synthesis of polymeric materials with controlled properties, and although not fully explored at the moment, we believe its study will attract much interest in the near future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00178.

Experimental procedures, further optimization, product characterization, UV−vis data, and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Timothy Noël − *Department of Chemical Engineering and Chemistry, Micro Flow Chemistry and Synthetic Methodology, Eindhoven University of Technology, 5612 AZ Eindhoven, The Netherlands;* orcid.org/0000-0002-3107-6927; Email: t.noel@uva.nl

Authors

Carlo Sambiagio − *Department of Chemical Engineering and Chemistry, Micro Flow Chemistry and Synthetic Methodology, Eindhoven University of Technology, 5612 AZ Eindhoven, The Netherlands*

Matteo Ferrari − *Department of Chemical Engineering and Chemistry, Micro Flow Chemistry and Synthetic Methodology, Eindhoven University of Technology, 5612 AZ Eindhoven, The Netherlands; Department of Chemistry, Life Sciences and Environmental Sustainability (SCVSA), University of Parma, 43124 Parma, Italy*

Koen van Beurden − *Research Group Biopolymers/Green Chemistry, Avans University of Applied Science, 4818 CR Breda, The Netherlands*

Nicola della Ca' − *Department of Chemistry, Life Sciences and Environmental Sustainability (SCVSA), University of Parma, 43124 Parma, Italy;* orcid.org/0000-0002-7853-7954

Jack van Schijndel − *Research Group Biopolymers/Green Chemistry, Avans University of Applied Science, 4818 CR Breda, The Netherlands*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00178

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

C.S. acknowledges the European Union for a Marie Curie European postdoctoral fellowship (FlowAct, Grant No. 794072). M.F. acknowledges the European Union for an Erasmus+ scholarship.

■ REFERENCES

(1) (a) Alfonzo, E.; Alfonso, F. S.; Beeler, A. B. Redesign of a Pyrylium Photoredox Catalyst and Its Application to the Generation of Carbonyl Ylides. *Org. Lett.* **2017**, *19*, 2989. (b) Chandu, P.; Ghosh, K. G.; Sureshkumar, D. Metal-Free Visible-Light-Promoted Trifluoromethylation of Vinylcyclopropanes Using Pyrylium Salt as a Photoredox Catalyst. *J. Org. Chem.* **2019**, *84*, 8771. (c) Perkowski,

A. J.; Cruz, C. L.; Nicewicz, D. A. Ambient-Temperature Newman−Kwart Rearrangement Mediated by Organic Photoredox Catalysis. *J. Am. Chem. Soc.* **2015**, *137*, 15684. (d) Perkowski, A. J.; You, W.; Nicewicz, D. A. Visible Light Photoinitiated Metal-Free Living Cationic Polymerization of 4-Methoxystyrene. *J. Am. Chem. Soc.* **2015**, *137*, 7580. (e) Miranda, M. A.; Garcia, H. 2,4,6-Triphenylpyrylium Tetrafluoroborate as an Electron-Transfer Photosensitizer,. *Chem. Rev.* **1994**, *94*, 1063. (f) Reed, N. L.; Herman, M. I.; Miltchev, V. P.; Yoon, T. P. Photocatalytic Oxyamination of Alkenes: Copper(II) Salts as Terminal Oxidants in Photoredox Catalysis. *Org. Lett.* **2018**, *20*, 7345. (g) Cruz, C. L.; Nicewicz, D. A. Mechanistic Investigations into the Cation Radical Newman−Kwart Rearrangement. *ACS Catal.* **2019**, *9*, 3926. (h) Mattay, J.; Vondenhof, M.; Denig, R. Pyrylium Salts as Photosensitizers in Homogeneous and Heterogeneous Electron-Transfer Catalysis. − A Comparison with Cyano Arenes. *Chem. Ber.* **1989**, *122*, 951. (i) Morse, P. D.; Nguyen, T. M.; Cruz, C. L.; Nicewicz, D. A. Enantioselective counter-anions in photoredox catalysis: The asymmetric cation radical Diels-Alder reaction. *Tetrahedron* **2018**, *74*, 3266.

(2) (a) Goetz, A. E.; Boydston, A. J. Metal-Free Preparation of Linear and Cross-Linked Polydicyclopentadiene. *J. Am. Chem. Soc.* **2015**, *137*, 7572. (b) Ogawa, K. A.; Goetz, A. E.; Boydston, A. J. Metal-Free Ring-Opening Metathesis Polymerization. *J. Am. Chem. Soc.* **2015**, *137*, 1400. (c) Pascual, L. M. M.; Dunford, D. G.; Goetz, A. E.; Ogawa, K. A.; Boydston, A. J. Comparison of Pyrylium and Thiopyrylium Photooxidants in Metal-Free Ring-Opening Metathesis Polymerization. *Synlett* **2016**, *27*, 759. (d) Lecompère, M.; Allonas, X.; Maréchal, D.; Criqui, A. Mechanistic approach to a photochemical/thermal dual-cure initiating system based on pyrylium salt−hydroperoxide for epoxide cationic polymerization. *Polym. Chem.* **2017**, *8*, 388. (e) Kottisch, V.; Michaudel, Q.; Fors, B. P. Photocontrolled Interconversion of Cationic and Radical Polymerizations. *J. Am. Chem. Soc.* **2017**, *139*, 10665. (f) Michaudel, Q.; Chauviré, T.; Kottisch, V.; Supej, M. J.; Stawiasz, K. J.; Shen, L.; Zipfel, W. R.; Abruña, H. D.; Freed, J. H.; Fors, B. P. Mechanistic Insight into the Photocontrolled Cationic Polymerization of Vinyl Ethers. *J. Am. Chem. Soc.* **2017**, *139*, 15530. (g) Krappitz, T.; Jovic, K.; Feist, F.; Frisch, H.; Rigoglioso, V. P.; Blinco, J. P.; Boydston, A. J.; Barner-Kowollik, C. Hybrid Photo-induced Copolymerization of Ring-Strained and Vinyl Monomers Utilizing Metal-Free Ring-Opening Metathesis Polymerization Conditions. *J. Am. Chem. Soc.* **2019**, *141*, 16605.

(3) For reviews, see: (a) Kong, D.; Moon, P. J.; Lundgren, R. J. Radical coupling from alkyl amines. *Nat. Catal.* **2019**, *2*, 473. (b) Pang, Y.; Moser, D.; Cornella, J. Pyrylium Salts: Selective Reagents for the Activation of Primary Amino Groups in Organic Synthesis. *Synthesis* **2020**, *52*, 489. (c) Correia, J. T. M.; Fernandes, V. A.; Matsuo, B. T.; Delgado, J. A. C.; de Souza, W. C.; Paixao, M. W. Photoinduced Deaminative Strategies: Katritzky Salts as Alkyl Radical Precursors. *Chem. Commun.* **2020**, *56*, 503.

(4) Unsubstituted pyridinium salts can also be used for this purpose: (a) Moser, D.; Duan, Y.; Wang, F.; Ma, Y.; O'Neill, M. J.; Cornella, J. Selective Functionalization of Aminoheterocycles by a Pyrylium Salt. *Angew. Chem., Int. Ed.* **2018**, *57*, 11035. (b) Gómez-Palomino, A.; Cornella, J. Selective Late-Stage Sulfonyl Chloride Formation from Sulfonamides Enabled by Pyry-BF4. *Angew. Chem., Int. Ed.* **2019**, *58*, 18235.

(5) (a) Basch, C. H.; Liao, J.; Xu, J.; Piane, J. J.; Watson, M. P. Harnessing Alkyl Amines as Electrophiles for Nickel-Catalyzed Cross Couplings via C−N Bond Activation. *J. Am. Chem. Soc.* **2017**, *139*, 5313. (b) Guan, W.; Liao, J.; Watson, M. P. Vinylation of Benzylic Amines via C−N Bond Functionalization of Benzylic Pyridinium Salts. *Synthesis* **2018**, *50*, 3231. (c) Liao, J.; Basch, C. H.; Hoerrner, M. E.; Talley, M. R.; Boscoe, B. P.; Tucker, J. W.; Garnsey, M. R.; Watson, M. P. Deaminative Reductive Cross-Electrophile Couplings of Alkylpyridinium Salts and Aryl Bromides. *Org. Lett.* **2019**, *21*, 2941. (d) Liao, J.; Guan, W.; Boscoe, B. P.; Tucker, J. W.; Tomlin, J. W.; Garnsey, M. R.; Watson, M. P. Transforming Benzylic Amines into Diarylmethanes: Cross-Couplings of Benzylic Pyridinium Salts via C−N Bond Activation. *Org. Lett.* **2018**, *20*, 3030. (e) Plunkett, S.; Basch, C. H.; Santana, S. O.; Watson, M. P. Harnessing Alkylpyridinium Salts as Electrophiles in Deaminative Alkyl−Alkyl Cross-Couplings. *J. Am. Chem. Soc.* **2019**, *141*, 2257. (f) Yi, J.; Badir, S. O.; Kammer, L. M.; Ribagorda, M.; Molander, G. A. Deaminative Reductive Arylation Enabled by Nickel/Photoredox Dual Catalysis. *Org. Lett.* **2019**, *21*, 3346. (g) Martin-Montero, R.; Yatham, V. R.; Yin, H.; Davies, J.; Martin, R. Ni-catalyzed Reductive Deaminative Arylation at sp3 Carbon Centers. *Org. Lett.* **2019**, *21*, 2947. (h) Yu, C.-G.; Matsuo, Y. Nickel-Catalyzed Deaminative Acylation of Activated Aliphatic Amines with Aromatic Amides via C−N Bond Activation. *Org. Lett.* **2020**, *22*, 950.

(6) (a) Klauck, F. J. R.; James, M. J.; Glorius, F. Deaminative Strategy for the Visible-Light-Mediated Generation of Alkyl Radicals. *Angew. Chem., Int. Ed.* **2017**, *56*, 12336. (b) Klauck, F. J. R.; Yoon, H.; James, M. J.; Lautens, M.; Glorius, F. Visible-Light-Mediated Deaminative Three-Component Dicarbofunctionalization of Styrenes with Benzylic Radicals. *ACS Catal.* **2019**, *9*, 236. (c) Jiang, X.; Zhang, M.-M.; Xiong, W.; Lu, L.-Q.; Xiao, W.-J. Deaminative (Carbonylative) Alkyl-Heck-type Reactions Enabled by Photocatalytic C−N Bond Activation. *Angew. Chem., Int. Ed.* **2019**, *58*, 2402. (d) Ociepa, M.; Turkowska, J.; Gryko, D. Redox-Activated Amines in C(sp3)−C(sp) and C(sp3)−C(sp2) Bond Formation Enabled by Metal-Free Photoredox Catalysis. *ACS Catal.* **2018**, *8*, 11362. (e) Zhang, M.-M.; Liu, F. Visible-light-mediated allylation of alkyl radicals with allylic sulfones via a deaminative strategy. *Org. Chem. Front.* **2018**, *5*, 3443. (f) Yang, Z.-K.; Xu, N.-X.; Wang, C.; Uchiyama, M. Photoinduced C(sp3)−N Bond Cleavage Leading to the Stereoselective Syntheses of Alkenes. *Chem. - Eur. J.* **2019**, *25*, 5433. (g) Zhu, Z.-F.; Zhang, M.-M.; Liu, F. Radical alkylation of isocyanides with amino acid-/peptide-derived Katritzky salts via photoredox catalysis. *Org. Biomol. Chem.* **2019**, *17*, 1531. (h) Schönbauer, D.; Sambiagio, C.; Noël, T.; Schnürch, M. Photocatalytic deaminative benzylation and alkylation of tetrahydroisoquinolines with N-alkylpyridinium salts. *Beilstein J. Org. Chem.* **2020**, *16*, 809.

(7) (a) Wu, J.; He, L.; Noble, A.; Aggarwal, V. K. Photoinduced Deaminative Borylation of Alkylamines. *J. Am. Chem. Soc.* **2018**, *140*, 10700. (b) Wu, J.; Grant, P. S.; Li, X.; Noble, A.; Aggarwal, V. K. Catalyst-Free Deaminative Functionalizations of Primary Amines by Photoinduced Single-Electron Transfer. *Angew. Chem., Int. Ed.* **2019**, *58*, 5697. (c) Sandfort, F.; Strieth-Kalthoff, F.; Klauck, F. J. R.; James, M. J.; Glorius, F. Deaminative Borylation of Aliphatic Amines Enabled by Visible Light Excitation of an Electron Donor−Acceptor Complex. *Chem. - Eur. J.* **2018**, *24*, 17210. (d) James, M. J.; Strieth-Kalthoff, F.; Sandfort, F.; Klauck, F. J. R.; Wagener, F.; Glorius, F. Visible-Light-Mediated Charge Transfer Enables C−C Bond Formation with Traceless Acceptor Groups. *Chem. - Eur. J.* **2019**, *25*, 8240. (e) Wang, C.; Qi, R.; Xue, H.; Shen, Y.; Chang, M.; Chen, Y.; Wang, R.; Xu, Z. Visible-Light-Promoted C(sp3)-H Alkylation by Intermolecular Charge Transfer: Preparation of Unnatural α-Amino Acids and Late-stage Modification of Peptides. *Angew. Chem., Int. Ed.* **2020**, *59*, 7461.

(8) (a) Sambiagio, C.; Noël, T. Flow Photochemistry: Shine Some Light on Those Tubes! *Trends Chem.* **2020**, *2*, 92. (b) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. Applications of Continuous-Flow Photochemistry in Organic Synthesis, Material Science, and Water Treatment. *Chem. Rev.* **2016**, *116*, 10276. (c) Su, Y.; Straathof, N. J. W.; Hessel, V.; Noël, T. Photochemical Transformations Accelerated in Continuous-Flow Reactors: Basic Concepts and Applications, *Chem. Chem. - Eur. J.* **2014**, *20*, 10562. (d) Govaerts, S.; Nyuchev, A.; Noel, T. Pushing the boundaries of C−H bond functionalization chemistry using flow technology. *J. Flow Chem.* **2020**, *10*, 13.

(9) For reviews, see: (a) Moad, G.; Rizzardo, E.; Thang, S. H. RAFT Polymerization and Some of its Applications. *Chem. - Asian J.* **2013**, *8*, 1634. (b) Perrier, S. 50th Anniversary Perspective: RAFT Polymerization—A User Guide. *Macromolecules* **2017**, *50*, 7433. (c) Tian, X.; Ding, J.; Zhang, B.; Qiu, F.; Zhuang, X.; Chen, Y. Recent Advances in RAFT Polymerization: Novel Initiation Mechanisms and Optoelec-

https://dx.doi.org/10.1021/acs.orglett.1c00178
Org. Lett. 2021, 23, 2042−2047

tronic Applications. *Polymers* **2018**, *10*, 318. (d) Nothling, M. D.; Fu, Q.; Reyhani, A.; Allison-Logan, S.; Jung, K.; Zhu, J.; Kamigaito, M.; Boyer, C.; Qiao, G. G. Progress and Perspectives Beyond Traditional RAFT Polymerization. *Adv. Sci.* **2020**, *7*, 2001656.

(10) For reviews on photopolymerization in flow, see: (a) Junkers, T. Precise Macromolecular Engineering via Continuous-Flow Synthesis Techniques. *J. Flow Chem.* **2017**, *7*, 106. (b) Junkers, T.; Wenn, B. Continuous photoflow synthesis of precision polymers. *React. Chem. Eng.* **2016**, *1*, 60. (c) Zaquen, N.; Rubens, M.; Corrigan, N.; Xu, J.; Zetterlund, P. B.; Boyer, C.; Junkers, T. Polymer Synthesis in Continuous Flow Reactors. *Prog. Polym. Sci.* **2020**, *107*, 101256.

(11) Phommalysack-Lovan, J.; Chu, Y.; Boyer, C.; Xu, J. PET-RAFT polymerisation: towards green and precision polymer manufacturing. *Chem. Commun.* **2018**, *54*, 6591.

(12) Sugihara, S.; Yoshida, A.; Kono, T.-a.; Takayama, T.; Maeda, Y. Controlled Radical Homopolymerization of Representative Cationically Polymerizable Vinyl Ethers. *J. Am. Chem. Soc.* **2019**, *141*, 13954.

(13) Balaban, T. S.; Balaban, A. T. In *Science of Synthesis - Category 2, Hetarenes and Related Ring Systems*; Thomas, E. J., Ed.; Georg Thieme Verlag: Stuttgart, 2003; Vol. *14*.

(14) Bloemendal, V. R. L. J.; Janssen, M. A. C. H.; van Hest, J. C. M.; Rutjes, F. P. J. T. Continuous one-flow multi-step synthesis of active pharmaceutical ingredients. *React. Chem. Eng.* **2020**, *5*, 1186.

(15) Katritzky, A. R.; Manzo, R. H. Kinetics and mechanism of the reactions of primary amines with pyrylium cations. *J. Chem. Soc., Perkin Trans. 2* **1981**, *2*, 571.

(16) Upon addition of catalyst **8** to a mixture of monomer and CTA, the mixture immediately increased in temperature, and some solid precipitated. This seems, however, not to influence the polymerization process, and no clogging was observed when performing reactions in flow.

(17) (a) Guerre, M.; Uchiyama, M.; Folgado, E.; Semsarilar, M.; Améduri, B.; Satoh, K.; Kamigaito, M.; Ladmiral, V. Combination of Cationic and Radical RAFT Polymerizations: A Versatile Route to Well-Defined Poly(ethyl vinyl ether)-block-poly(vinylidene fluoride) Block Copolymers. *ACS Macro Lett.* **2017**, *6*, 393. (b) Uchiyama, M.; Satoh, K.; Kamigaito, M. Cationic RAFT Polymerization Using ppm Concentrations of Organic Acid. *Angew. Chem., Int. Ed.* **2015**, *54*, 1924.

(18) (a) Zaquen, N.; Yeow, J.; Junkers, T.; Boyer, C.; Zetterlund, P. B. Visible Light-Mediated Polymerization-Induced Self-Assembly Using Continuous Flow Reactors. *Macromolecules* **2018**, *51*, 5165. (b) McKenzie, T. G.; Fu, Q.; Wong, E. H. H.; Dunstan, D. E.; Qiao, G. G. Visible Light Mediated Controlled Radical Polymerization in the Absence of Exogenous Radical Sources or Catalysts. *Macromolecules* **2015**, *48*, 3864.

https://dx.doi.org/10.1021/acs.orglett.1c00178
Org. Lett. 2021, 23, 2042−2047