Organic LETTERS

Letter

pubs.acs.org/OrgLett

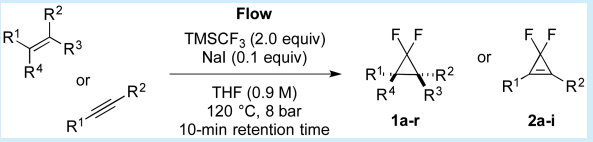
Difluorocarbene Addition to Alkenes and Alkynes in Continuous Flow

Pauline Rullière, Patrick Cyr, and André B. Charette*

Université de Montréal, Centre in Green Chemistry and Catalysis, Department of Chemistry, Faculty of Arts and Science, P.O. Box 6128, Station Downtown, Québec, Canada H3C 3J7

Supporting Information

ABSTRACT: The first *in-flow* difluorocarbene generation and addition to alkenes and alkynes is reported. The application of continuous flow technology allowed for the controlled generation of difluorocarbene from $TMSCF_3$ and a catalytic quantity of NaI. The *in situ* generated electrophilic carbene reacts smoothly with a broad range of alkenes and alkynes, allowing the synthesis of the corresponding difluorocyclopropanes and difluorocyclopropenes. The reaction is complete within a 10 min residence time at high reaction concentrations. With a production flow rate of 1 mmol/min, continuous flow chemistry enables scale up of this process in a green, atom-economic, and safe manner.



Difluorocyclopropanes have emerged as key substructures in the construction of pharmaceutically relevant compounds as well as in novel applications in material sciences (Figure 1).[1] The inclusion of fluorine atoms increases the lipophilicity, bioavailability, metabolic stability, and, in some cases, the potency of known biologically active molecules.[2,3] Consequently, developing novel methods to incorporate fluorine atoms to drug-like leads has become important to drug design and discovery (Figure 1).[1,4]

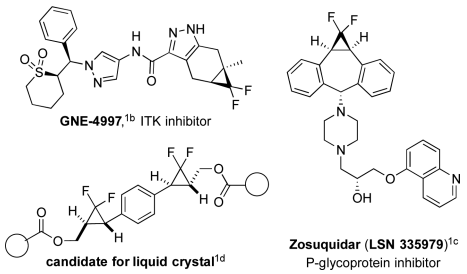


Figure 1. Integration of difluorocyclopropane scaffold into molecules of interest.

As part of our ongoing research program toward developing methods for halocyclopropane formation,[5] we aim not only to further develop methods to access these strained carbocycles but also to do so in an efficient, safe, and sustainable way, adhering to green chemistry principles.[4] Herein we report our efforts in this area, preparing *gem*-difluorocyclopropanes and *gem*-difluorocyclopropenes from simple alkenes and alkynes.

Since the seminal synthesis of the difluorocyclopropane scaffold,[6] various methods toward this attractive core have been delineated.[7] The most common syntheses of difluorocyclopropanes and -cyclopropenes have relied on the [2 + 1] cycloaddition of difluorocarbene to an alkene or alkyne.[8] Although the preparation of difluorocarbene is well precedented, it is often tedious and applies nonenvironmentally friendly conditions. Recently, greener and more facile methods applying the thermal decarboxylative elimination of sodium halodifluoroacetate have been used on a broad range of olefins.[9] While effective, this procedure suffers from the high temperatures required for carbene generation (150−180 °C) and from having a large excess of the precursor (5−10 equiv of XCF_2CO_2Na). A second similar method also employs a thermal decomposition of trimethylsilyl fluorosulfonyldifluoroacetate (TFDA).[10] This strategy has the advantage of generating carbenes that are more reactive toward electron-poor alkenes. However, the reaction conditions remain harsh, and the preparation of TFDA is tedious. To circumvent this, one of the mildest ways involves the generation of difluorocarbene from trimethylsilyl trifluoromethane ($TMSCF_3$). This reagent is safe, commercially available, and inexpensive.[11]

Given the high temperatures, pressure, and volatility of the reagents, we reasoned that a continuous flow strategy might be applied to offer access to these privileged architectures. The application of a flow chemistry setup would permit precise temperature and pressure control as well as efficient heat transfer (Figure 2). These features should allow us to scale up this transformation under safe reaction conditions while furnishing products in shorter reaction times.[12]

We began our studies by attempting traditional batch conditions in a flow reactor. The carbene was generated in the presence of the NaI activator upon heating (>60 °C). Additionally, the reagents could be safely premixed with the alkene in THF at room temperature (for solvent reoptimization, see Supporting Information). The solution was introduced into a Vapourtec system through an injection loop and passed

Received: February 29, 2016

DOI: 10.1021/acs.orglett.6b00573
Org. Lett. XXXX, XXX, XXX−XXX

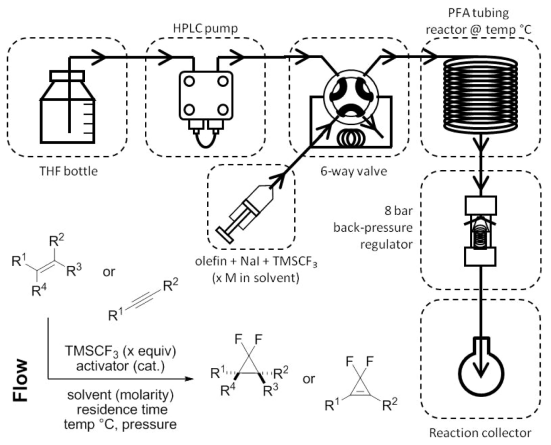
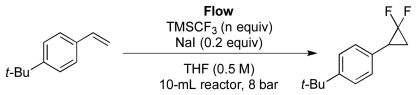


Figure 2. Flow reactor setup.

through a heated perfluoroalkoxy (PFA) reactor equipped with a back pressure regulator (BPR) to permit reaction temperatures above the boiling point of THF. At 110 °C, with 2.5 equiv of $TMSCF_3$ and a catalytic amount of NaI (0.2 equiv), the reaction proceeded within only 10 min with an 87% yield (Table 1, entry 1). This is in contrast with the 2 h reaction

Table 1. Optimization of Reaction Temperature and Residence Time[a]



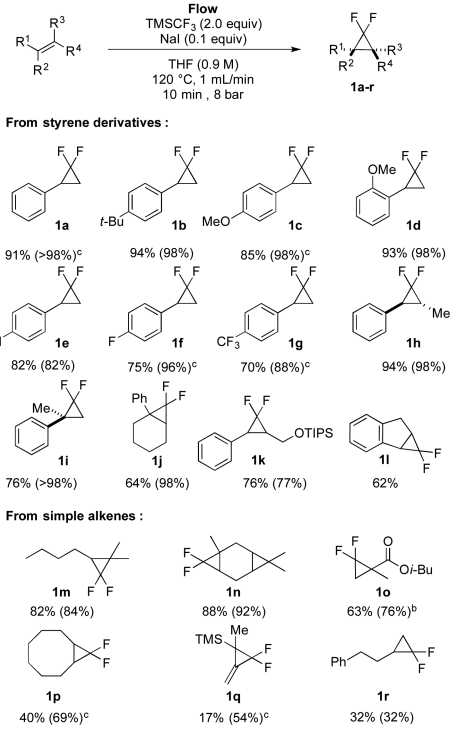
entry	residence time (min)	temp (°C)	equivalent of $TMSCF_3$	NMR yield (%)[b]
batch	120	65	2.5	100
1	10	110	2.5	87
2	10	120	2.0	98
3	15	120	1.5	92
4	20	120	1.5	91
5[c]	10	120	1.5	88
6	10	150	1.5	96
7	10	200	1.5	52
8	**10**	**120**	**2.0**[d]	**99**

[a]Reactions run on a 1 mmol scale. [b]Yields obtained by ^1H NMR spectroscopy of the crude reaction mixture using triphenylmethane as the internal standard. [c]Separated injection of a solution of $TMSCF_3$ in THF and styrene + NaI in THF in a T mixer. [d]0.9 M concentration and 0.1 equiv of NaI was used.

times required for batch processes. Such an increase in efficiency in the difluorocyclopropanation reaction can be explained by the increased reaction pressure, a better heat transfer through the high surface area of the PFA tubing, and the controlled generation of carbene. Increasing the reaction temperature to 120 °C allowed for a decrease in the amount of $TMSCF_3$ required (entry 2), affording the difluorocyclopropane in a 98% yield. Increasing the residence time to 15 and 20 min resulted in no improvement (entries 3, 4). Separate injection of a solution of the carbene precursor and of the alkene premixed with the activator did not lead to any improvement (entry 5 vs 3). A further increase of temperature to 150 and 200 °C led to the formation of byproducts, since styrene polymerization started to compete with the desired difluorocyclopropanation (entries 6, 7). The optimal reaction conditions were obtained under more concentrated conditions (from 0.5 to 0.9 mmol·L^{-1}) and using a reduced amount of catalyst NaI (0.1 equiv, entry 8). This was also consistent with the low solubility of NaI in THF at high temperatures and the fact that homogeneity is critical in continuous flow processes. We next investigated the scope of the newly developed method.

Electron-rich styrenes led to almost quantitative yields of difluorocyclopropanes (Scheme 1, products **1a–d**). Styrenes bearing electron-withdrawing substituents still provided the difluorocyclopropanes with excellent yields (entries **1e–g**).

Scheme 1. Difluorocyclopropanation of Alkenes[a,b]



[a]Reactions were run on a 3.0 mmol scale, isolated yields. [b]Yields in parentheses were obtained by ^1H NMR spectroscopy using triphenylmethane as the internal standard or ^{19}F NMR spectroscopy using fluorobenzene as the internal standard. [c]Lower isolated yield than NMR yield due to volatility of product.

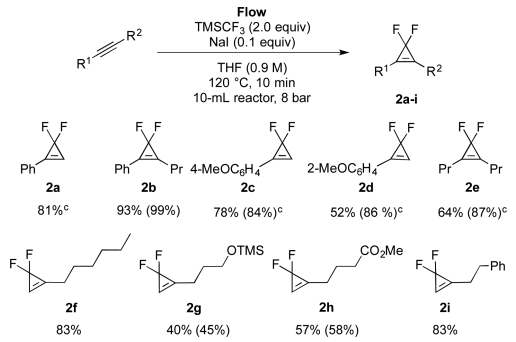
The reaction allows various substitution patterns on the alkene, affording the desired product in good to excellent yields (Scheme 1, products **1h–j**). The difluorocyclopropanation also proceeded well with indene and in the presence of functionalities, such as a silyl ether (products **1k** and **1l**).

When it comes to alkenes that are not derived from styrene, the difluorocyclopropanation yields range from modest to excellent. As expected, lower yields are observed with olefins that are less nucleophilic. The difluorocyclopropanes were obtained in good yields not only for highly substituted alkenes (products **m–n**) but also with methacrylate (product **1o**) and cyclic alkenes (product **1p**). Allenes afforded the difluorocyclopropane in moderate yield (product **1q**). The yield significantly decreased with the use of a monosubstituted aliphatic alkene (product **1r**).

This continuous flow method was also applied to difluorocyclopropenation of alkynes. The exact same conditions as those for alkenes were first used, and they were successful in the quantitative transformation of pent-1-ynylbenzene into its corresponding difluorocyclopropene (Scheme 2, product **2b**).

DOI: 10.1021/acs.orglett.6b00573
Org. Lett. XXXX, XXX, XXX–XXX

Scheme 2. Difluorocyclopropanation of Alkynes[a,b]



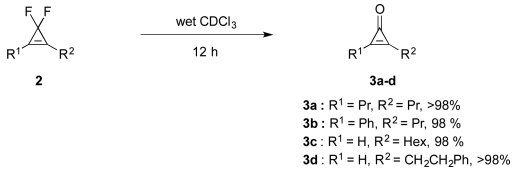
[a]Reactions were run on a 3.0 mmol scale, isolated yields. [b]Yields obtained by ^{19}F NMR spectroscopy using fluorobenzene as the internal standard are displayed in parentheses. [c]Lower isolated yield than NMR yield due to volatility of product.

Other phenylacetylene derivatives also reacted almost quantitatively (products **2a**–**d**). Under those conditions, terminal aliphatic alkynes also undergo difluorocyclopropanation with good yields (products **2e**–**i**). Functionalities, such as ester or unprotected alcohol, are tolerated, although the free alcohol gets silylated during the reaction (**2f** was prepared from pentyn-1-ol).

Difluorocyclopropenes are known for their instability[13] and, more specifically, for their ease of hydrolysis into the corresponding stable cyclopropenone.[14] Cyclopropenones have been recently established as useful building blocks in synthesis.[15]

During this work, it was shown that functionalized difluorocyclopropenes could be converted into cyclopropenones upon stirring in wet chloroform overnight (Scheme 3). For the more stable substrate **2f**, addition of silica was required to achieve the hydrolysis of the difluorocyclopropene (see Supporting Information for more details).

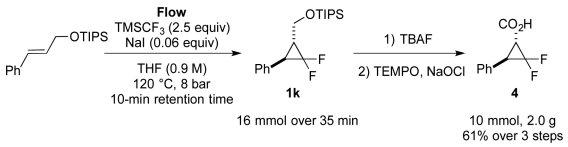
Scheme 3. Cyclopropenone Synthesis



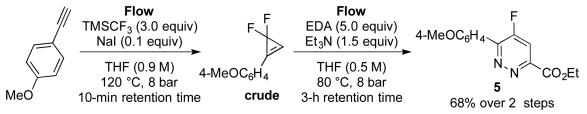
To further illustrate the versatility of the method, the synthesis of *gem*-difluorophenylcyclopropanecarboxylic acid **4** was scaled up to produce 16 mmol of the intermediate **1k** in less than 35 min (Scheme 4). The reaction would have been otherwise difficult to realize in batch under safe conditions due to the gas evolution and pressure build-up as a function of time.

To further illustrate the usefulness of this process, other applications of difluorocyclopropanes[16] and difluorocyclopropenes[17] in flow were pursued. For example, our procedure could be nicely coupled with Cossy's difluorocyclopropene cycloaddition conditions[17b] to produce 5-fluoropyridazine **5** with a good yield over two steps in an effective way with a reduced reaction time (Scheme 5).

Scheme 4. Scale-up Synthesis of Difluorocyclopropane Building Block



Scheme 5. Synthesis of 5-Fluoropyridazine in Continuous Flow



In conclusion, we have developed a protocol for the $TMSCF_3$-mediated difluorocyclopropanation of a broad range of alkenes and alkynes using flow chemistry where catalytic NaI generates the reactive carbene *in situ*. The reaction proceeded cleanly with a 1 mmol·min^{-1} production rate and a 10 min residence time, overcoming pressure and controlled carbene generation issues while reducing the amount of carbene precursor, carbene activator, and solvent. Moreover, the difluorocyclopropanes and difluorocyclopropenes can be further transformed into interesting fluorinated building blocks. Extension of the use of this in flow generated difluorocarbene for continuous flow synthesis is currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00573.

Optimization tables, experimental procedures, characterization data, and copies of NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: andre.charette@umontreal.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Science and Engineering Research Council of Canada (NSERC) under the CREATE Training Program in Continuous Flow Science and the Discovery Grant Program, the Canada Foundation for Innovation, the Canada Research Chair Program, the FRQNT Centre in Green Chemistry and Catalysis (CGCC) and Université de Montréal. The authors would like to thank Dr. Martial Bertrand and Dr. Francis Beaulieu from OmegaChem for fruitful discussions. P.C. is grateful to NSERC, FRQNT, Hydro-Québec and Université de Montréal for postgraduate scholarships. P.R. would like to thank V. Kairouz (Center for Continuous Flow Science, Université de Montréal) for her help with the flow equipment and E. Lévesque (Charette group, Université de Montréal) for the flow schemes design.

■ REFERENCES

(1) (a) Toshiyuki, I. *Current Fluoroorganic Chemistry*; ACS Symposium Series; American Chemical Society: 2007; pp 352–362, Vol. *949*. (b) Burch, J. D.; Barrett, K.; Chen, Y.; DeVoss, J.; Eigenbrot, C.; Goldsmith, R.; Ismaili, M. H. A.; Lau, K.; Lin, Z.; Ortwine, D. F.;

DOI: 10.1021/acs.orglett.6b00573
Org. Lett. XXXX, XXX, XXX–XXX

Zarrin, A. A.; McEwan, P. A.; Barker, J. J.; Ellebrandt, C.; Kordt, D.; Stein, D. B.; Wang, X.; Chen, Y.; Hu, B.; Xu, X.; Yuen, P.-W.; Zhang, Y.; Pei, Z. *J. Med. Chem.* **2015**, *58*, 3806−3816. (c) Dantzig, A. H.; Shepard, R. L.; Law, K. L.; Tabas, L.; Pratt, S.; Gillespie, J. S.; Binkley, S. N.; Kuhfeld, M. T.; Starling, J. J.; Wrighton, S. A. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 854−862. (d) Itoh, T.; Kanbara, M.; Ohashi, M.; Hayase, S.; Kawatsura, M.; Kato, T.; Miyazawa, K.; Takagi, Y.; Uno, H. *J. Fluorine Chem.* **2007**, *128*, 1112−1120.

(2) (a) Salaün, J.; Baird, M. S. *Curr. Med. Chem.* **1995**, *2*, 511−542. (b) Wipf, P.; Xiao, J. *Org. Lett.* **2005**, *7*, 103−106. (c) Nicolaou, K. C.; Sasmal, P. K.; Rassias, G.; Reddy, M. V.; Altmann, K.-H.; Wartmann, M.; O'Brate, A.; Giannakakou, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3515−3520. (d) Yang, Z. Q.; Geng, X. D.; Solit, D.; Pratilas, C. A.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2004**, *126*, 7881−7889. (e) Gaugaz, F. Z.; Redondo-Horcajo, M.; Barasoain, I.; Díaz, J. F.; Cobos-Correa, A.; Kaufmann, M.; Altmann, K.-H. *ChemMedChem* **2014**, *9*, 2227−2232. (f) Orbegozo, T.; Burel, F.; Jubault, P.; Pannecoucke, X. *Tetrahedron* **2013**, *69*, 4015. (g) David, E.; Milanole, G.; Ivashkin, P.; Couve-Bonnaire, S.; Jubault, P.; Pannecoucke, X. *Chem. - Eur. J.* **2012**, *18*, 14904.

(3) (a) Yamazaki, T.; Taguchi, T.; Ojima, I. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; John Wiley & Sons, Ltd.: 2009; pp 1−46. (b) Itoh, T. In *Fluorine in Medicinal Chemistry and Chemical Biology*; Ojima, I., Ed.; John Wiley & Sons, Ltd.: 2009; pp 313−334. (c) Shibuya, A.; Sato, A.; Taguchi, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1979−1984.

(4) (a) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L., Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411−420. (b) Watson, W. J. W. *Green Chem.* **2012**, *14*, 251−259.

(5) See for examples: (a) Navuluri, C.; Charette, A. B. *Org. Lett.* **2015**, *17*, 4288−4291. (b) Taillemaud, S.; Diercxsens, N.; Gagnon, A.; Charette, A. B. *Angew. Chem., Int. Ed.* **2015**, *54*, 14108−14112. (c) Beaulieu, L. P. B.; Schneider, J. F.; Charette, A. B. *J. Am. Chem. Soc.* **2013**, *135*, 7819−7822. (d) Beaulieu, L.-P. B.; Zimmer, L. E.; Gagnon, A.; Charette, A. B. *Chem. - Eur. J.* **2012**, *18*, 14784−14791. (e) Pons, A.; Beucher, H.; Ivashkin, P.; Lemonnier, G.; Poisson, T.; Charette, A. B.; Jubault, P.; Pannecoucke, X. *Org. Lett.* **2015**, *17*, 1790.

(6) Atkinson, B. J. *J. Chem. Soc.* **1952**, 2684−2694.

(7) For reviews on difluorocyclopropanes and -cyclopropenes synthesis, see: (a) Dolbier, W. R.; Battiste, M. A. *Chem. Rev.* **2003**, *103*, 1071−1098. (b) Fedoryński, M. *Chem. Rev.* **2003**, *103*, 1099−1132.

(8) Ni, C.; Hu, J. *Synthesis* **2014**, *46*, 842−863.

(9) X = Br: (a) Oshiro, K.; Morimoto, Y.; Amii, H. *Synthesis* **2010**, *2010*, 2080−2084. X = Cl: (b) Fujioka, Y.; Amii, H. *Org. Lett.* **2008**, *10*, 769. X = Cl: (c) Gill, D.; McLay, N.; Waring, M.; Wilkinson, C.; Sweeney, J. *Synlett* **2014**, *25*, 1756−1758. X = Cl: (d) Birchall, J. M.; Cross, G. E.; Haszeldine, R. N. *Proc. Chem. Soc.* **1960**, .81

(10) (a) Tian, F.; Kruger, V.; Bautista, O.; Duan, J.-X.; Li, A.-R.; Dolbier, W. R.; Chen, Q.-Y. *Org. Lett.* **2000**, *2*, 563−564. (b) Dolbier, W. R., Jr.; Tian, F.; Duan, J.-X.; Li, A.-R.; Ait-Mohand, S.; Bautista, O.; Buathong, S.; Marshall Baker, J.; Crawford, J.; Anselme, P.; Cai, X. H.; Modzelewska, A.; Koroniak, H.; Battiste, M. A.; Chen, Q.-Y. *J. Fluorine Chem.* **2004**, *125*, 459−469.

(11) $TMSCF_3$: (a) Wang, F.; Luo, T.; Hu, J.; Wang, Y.; Krishnan, H. S.; Jog, P. V.; Ganesh, S. K.; Prakash, G. K. S.; Olah, G. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 7153−7157. $TMSCF_2Br$: (b) Li, L.; Wang, F.; Ni, C.; Hu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 12390−12394. $TMSCF_2Cl$: (c) Wang, F.; Zhang, W.; Zhu, J.; Li, H.; Huang, K.-W.; Hu, J. *Chem. Commun.* **2011**, *47*, 2411−2413.

(12) (a) Kobayashi, S. *Chem. - Asian J.* **2016**, *11*, 425−436. (b) Adamo, A.; Beingessner, R. L.; Behnam, M.; Chen, J.; Jamison, T. F.; Jensen, K. F.; Monbaliu, J.-C. M.; Myerson, A. S.; Revalor, E. M.; Snead, D. R.; Stelzer, T.; Weeranoppanant, N.; Wong, S. Y.; Zhang, P. *Science* **2016**, *352*, 61−67. (c) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688−6729. (d) Tran, D. N.; Battilocchio, C.; Lou, S.; Hawkins, J. M.; Ley, S. V. *Chem. Sci.* **2015**, *6*, 1120−1125. (e) Plouffe, P.; Macchi, A.; Roberge, D. M. *Flow Chemistry* **2014**, 141−154.

(13) Difluorocyclopropenes decompose during purification on silica or if stored at room temperature over a few hours (or a few days depending on the substrate). Therefore, purification required the use of Et_3N pretreated silica. See Supporting Information for more details.

(14) For previous examples of difluorocyclopropene hydrolysis into cyclopropenone, see: (a) Bessard, Y.; Schlosser, M. *Tetrahedron* **1991**, *47*, 7323−7328. (b) Shih, H.-W.; Prescher, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 10036−10039. (c) Cheng, Z.-L.; Chen, Q.-Y. *Chin. J. Chem.* **2006**, *24*, 1219−1224. (d) Crabbe, P.; Carpio, H.; Velarde, E.; Fried, J. H. *J. Org. Chem.* **1973**, *38*, 1478−1483. (e) Kuzmin, A. V.; Popik, V. V. *Chem. Commun.* **2009**, 5707−5709. (f) Dehmlow, E. V.; Winterfeldt, A. *Tetrahedron* **1989**, *45*, 2925−2936.

(15) (a) Yang, Y.-L.; Zhang, Z.; Zhang, X.-N.; Wang, D.; Wei, Y.; Shi, M. *Chem. Commun.* **2014**, *50*, 115−117. (b) Hemming, K.; Khan, M. N.; Kondakal, V. V. R.; Pitard, A.; Qamar, M. I.; Rice, C. R. *Org. Lett.* **2012**, *14*, 126−129. (c) Vanos, C. M.; Lambert, T. H. *Angew. Chem., Int. Ed.* **2011**, *50*, 12222−12226.

(16) (a) Xu, J.; Ahmed, E.-A.; Xiao, B.; Lu, Q.-Q.; Wang, Y.-L.; Yu, C.-G.; Fu, Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 8231−8235. (b) Wenz, J.; Rettenmeier, C. A.; Wadepohl, H.; Gade, L. H. *Chem. Commun.* **2016**, *52*, 202−205.

(17) (a) Nihei, T.; Hoshino, T.; Konno, T. *Org. Biomol. Chem.* **2015**, *13*, 3721−3731. (b) Tran, G.; Gomez Pardo, D.; Tsuchiya, T.; Hillebrand, S.; Vors, J.-P.; Cossy, J. *Org. Lett.* **2015**, *17*, 3414−3417.

DOI: 10.1021/acs.orglett.6b00573
Org. Lett. XXXX, XXX, XXX−XXX