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4-Membered Ring Carbocations: A Positive Development in the Synthesis of 3,3-Disubstituted Oxetanes and Azetidines

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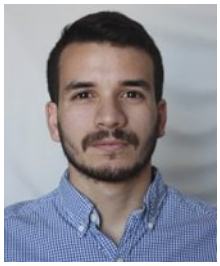
§SCS-Metrohm Award for best oral presentation in Organic Chemistry

Abstract: 4-Membered heterocycles are low molecular weight polar scaffolds with intriguing potential for drug discovery. Despite their unquestionable value, methods to access such heterocycles remain scant. Here, we describe the generation of oxetane- and azetidine-benzylic carbocations as a general strategy to access valuable 3,3-disubstituted derivatives.

Keywords: Azetidines · Bioisosteres · Carbocations · Chemical space · Oxetanes



Juan J. Rojas received his BSc degree in chemistry from the ETH Zurich in 2016 and an MRes in Catalysis from Imperial College London in 2018. After six months at BASF Ludwigshafen, he returned to Imperial College to pursue a PhD with Dr. James Bull, investigating methodologies to access 3,3-disubstituted oxetanes through the generation of reactive oxetane intermediates.

1. Introduction

1.1 *Relevance of 4-Membered Heterocycles*

The exploration of underinvestigated chemical space is paramount for the development of new medicines. Many interesting but little-studied motifs are sp^3-rich, polar and heterocyclic.[1] This type of structure is more 3-dimensional than conventional building blocks such as arenes or amides. The increased complexity and 3D nature can provide a better fit into the complex cavities of protein pockets as well as advantages in physicochemical properties. Nonetheless, limited synthetic methods continue to hamper the incorporation of saturated molecular architectures into active pharmaceutical and agrochemical ingredients.[2] An important underexplored class of motifs are 4-membered heterocycles, attractive to medicinal chemists due to their combination of high polarity with low molecular weight.[3] Whilst these structures appear increasingly in market candidate compounds, such as antiviral ziresovir (**1**),[4] antihypertensive azelnidipine (**2**)[5] or pesticide **3**,[6] methods to access them are limited (Fig. 1).

Oxetanes with a 3,3-disubstitution pattern have garnered further interest in medicinal chemistry due to their potential as replacement groups or isosteres of *gem*-dimethyl and carbonyl groups.[7] Compared to carbonyls, oxetanes show a similar dipole moment and H-bonding properties, potentially improved metabolic stability, and higher 3-dimensionality, which can benefit solubility and binding properties. Although less studied, 3,3-disubstituted azetidines can be regarded as potential surrogates of imine derivatives, with the advantage of an extra vector for functionalization on nitrogen.

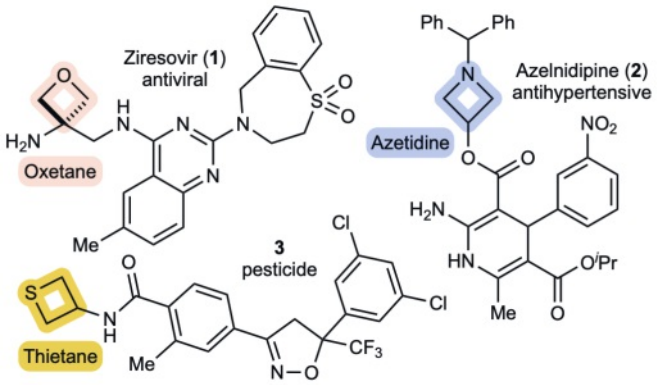


Fig. 1. Bioactive 4-membered heterocycles.

Here, we discuss recent methods for the preparation of 3,3-disubstituted oxetanes and azetidines *via* the formation of carbocations.

2. Carbocations on 4-Membered Heterocycles

A gap in methodologies to incorporate arene-substituted 4-membered heterocycles into drug-like compounds sparked a research program in our group in collaboration with Pfizer. Our goal was to develop methods to transform inexpensive heterocycle sources into valuable 3,3-disubstituted derivatives. We envisaged tertiary benzylic alcohols, available in one step from commercial oxetanone and azetidinone, would provide a good starting point for our investigation. Activation of the alcohol would generate benzylic-heterocyclic carbocation intermediates to be subsequently trapped with nucleophiles (Scheme 1). Such strained carbocations are little-studied and the influence of ring strain on reactivity was not well understood.

2.1 *Activation of Alcohols*

Our studies commenced with the activation of 3-aryl-oxetanols (**4**) with Lewis acids followed by trapping with arenes in a Friedel–Crafts reaction.[8] The key to success lay in the choice of

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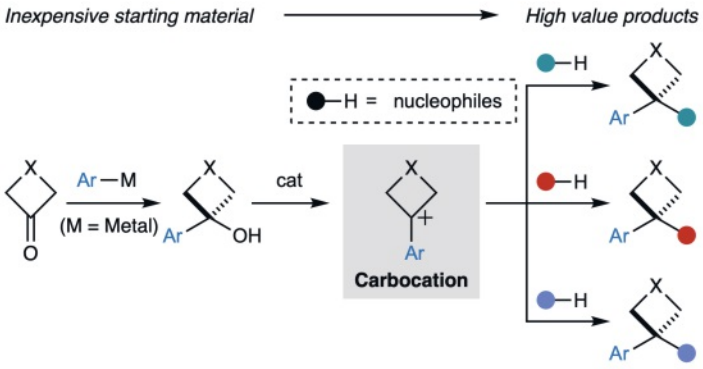
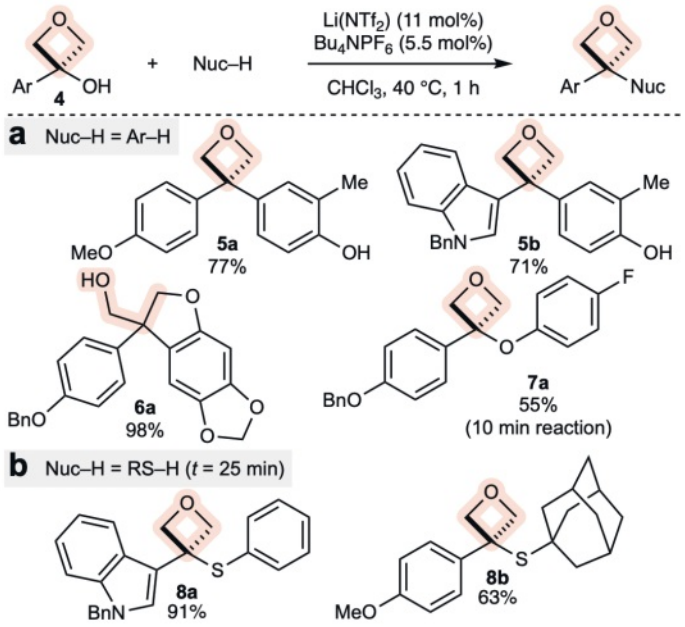


Scheme 1. Our approach: catalytic generation and functionalization of heterocyclic benzylic carbocations.

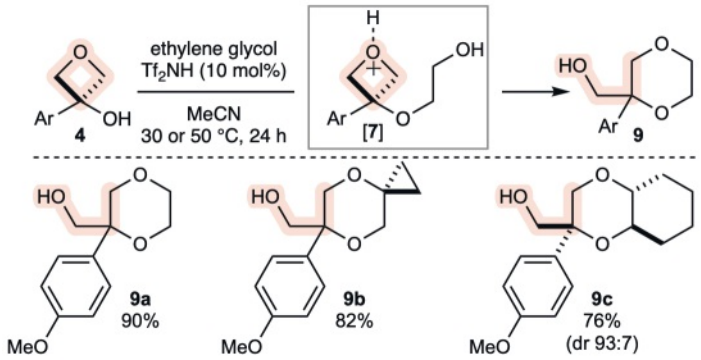
Lewis acid: too strong an acid led to ring-opening and polymerization of the oxetane, too weak an acid was not able to dehydrate the alcohol and returned starting material. The sweet spot was found with a dual catalytic system using $Li(NTf_2)$ as Lewis acid and NBu_4PF_6 as activator.[9] The reaction was successful with a range of electron-rich aromatics on the oxetanol and nucleophile sides to yield diaryl oxetanes (**5**) as isosteres of medicinally relevant diarylmethanes and benzophenones (Scheme 2a).



Scheme 2. Lewis acid-catalyzed generation of oxetane carbocations and trapping with phenols (a) and thiols (b).

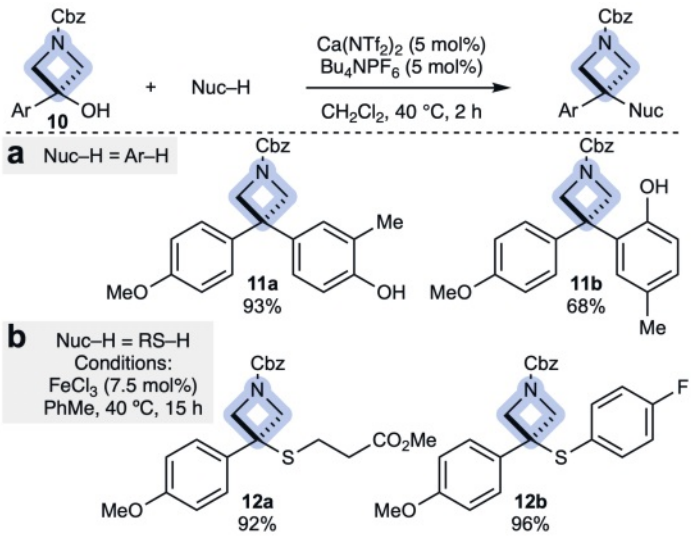
Interestingly, *para*-substituted phenol nucleophiles yielded dihydrobenzofuran products (*e.g.* **6a**), formed through an *ortho* Friedel–Crafts reaction followed by intramolecular oxetane ring-opening. Further, oxetane ethers (**7**) were shown to be intermediates of the reaction, acting as a carbocation 'reservoir', and were isolated at short reaction times.[10] The products were diversifiable through phenol handles or by oxidative cleavage of furan derivatives to generate oxetane carboxylic acid building blocks.[11] The isosterism of diaryloxetanes **5** was assessed and revealed oxetanes not to be a pharmacokinetic liability vis-à-vis ketones and generally superior to alkyl derivatives.[12] The same catalytic system was expanded to thiol nucleophiles to generate oxetane sulfides (**8**) as isosteres of thioesters (Scheme 2b).[13]

A change to a Brønsted acid catalyst made the reaction conditions compatible with bis-nucleophiles such as 1,2-diols to yield 1,4-dioxanes (**9**) in an unusual annulation reaction (Scheme 3).[14] The reaction proceeded through an oxetane ether intermediate that ring-opened *in situ* through the internal nucleophile to generate a new heterocycle. This reactivity highlights the use of oxetanes not only as medicinal motifs, but also as useful synthetic intermediates.



Scheme 3. Brønsted acid-catalyzed generation of oxetane carbocations and annulation with 1,2-diols.

Azetidinols (**10**) were found to react similarly to oxetanols and a Friedel–Crafts reaction was developed to generate diaryl azetidines (**11**) with $Ca(NTf_2)_2$ as the optimal catalyst (Scheme 4a).[15] The Cbz group on nitrogen was crucial for reactivity, proposedly by stabilizing the carbocation through a π-cation interaction. Azetidines were much less prone to ring opening than oxetanes and dihydrobenzofuran products were not observed. Thiols were compatible nucleophiles to yield azetidine sulfides **12** in high yields, which was achieved using inexpensive $FeCl_3$ as catalyst in toluene as solvent (Scheme 4b).[16]



Scheme 4. Generation and transformations of azetidine carbocations.

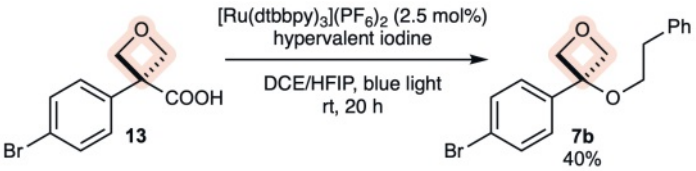
A systematic Friedel–Crafts study on different 4-ring benzylic (hetero)cyclic alcohols outlined the compatibilities of Lewis acid systems.[17] Related Friedel–Crafts conditions were developed by Trudell using excess $AlCl_3$ as Lewis acid, which tolerated less activated arylazetidinols.[18]

Amine nucleophiles however, were incompatible with the Lewis and Brønsted acid systems developed due to strong coordination to the catalytic acids. The proposed amino-oxetane

products are of high value to drug discovery as new motifs and potential isosteres of amides.[19] We were particularly interested in aryl-amino-oxetanes because they represent isosteres of benzamides, an important pharmacophore, but which often suffer from poor solubility due to their increased planarity. Existing approaches towards aryl-amino-oxetanes, which functionalize amino- or imino-oxetane precursors with an aryl fragment, cannot leverage the vast libraries of amines available to pharmaceutical companies.[20]

2.2 *Radical-polar Crossover of Oxetane Acids*

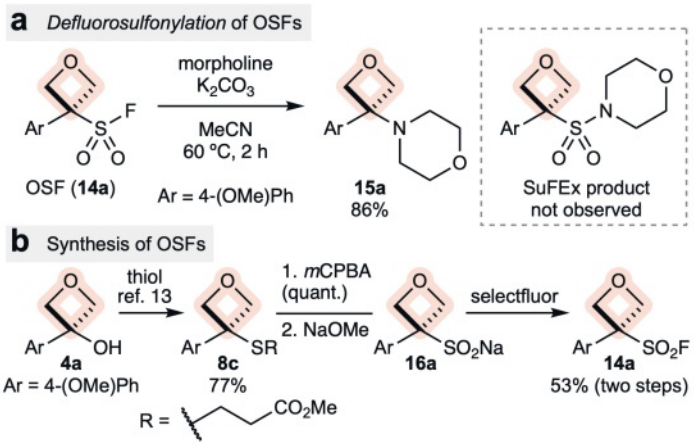
An intriguing way of generating benzylic carbocations, including an oxetane, was recently reported by Zbieg and Terrett at Genentech *via* radical-polar crossover (Scheme 5).[21] 3-Aryloxetane carboxylic acid **13** was decarboxylated under photoredox conditions, further oxidized to the benzylic carbocation and trapped with alcohols (**7b**).



Scheme 5. Generation of oxetane carbocations *via* radical-polar crossover from oxetane acid **13**.

2.3 *Defluorosulfonylation of Oxetane Sulfonyl Fluorides*

We became interested in oxetane sulfonyl fluorides (OSFs) as new oxetane building blocks, expecting them to react with nucleophiles in a Sulfur–Fluoride Exchange reaction (SuFEx) to yield oxetane-S(VI) motifs. This mode of reactivity led to sulfonyl fluorides being coined by Sharpless as click reagents.[22] To our astonishment and delight, OSFs (**14**) did not react with amines in the expected SuFEx manner. Instead, OSFs underwent *defluorosulfonylation*, meaning they lost SO_2 and F^-, and gave directly amino-oxetanes on reaction of the resulting carbocation with amines (**15**) (Scheme 6a).[23] OSF reagents such as **14a** are bench-stable and synthesized in four steps from oxetanols. The sequence involves our previously developed thiol-alkylation reaction to form sulfide **8c**,[13] followed by oxidation to the sulfone, base-mediated elimination to sulfinate **16a** and fluorination to OSF **14a** (Scheme 6b).



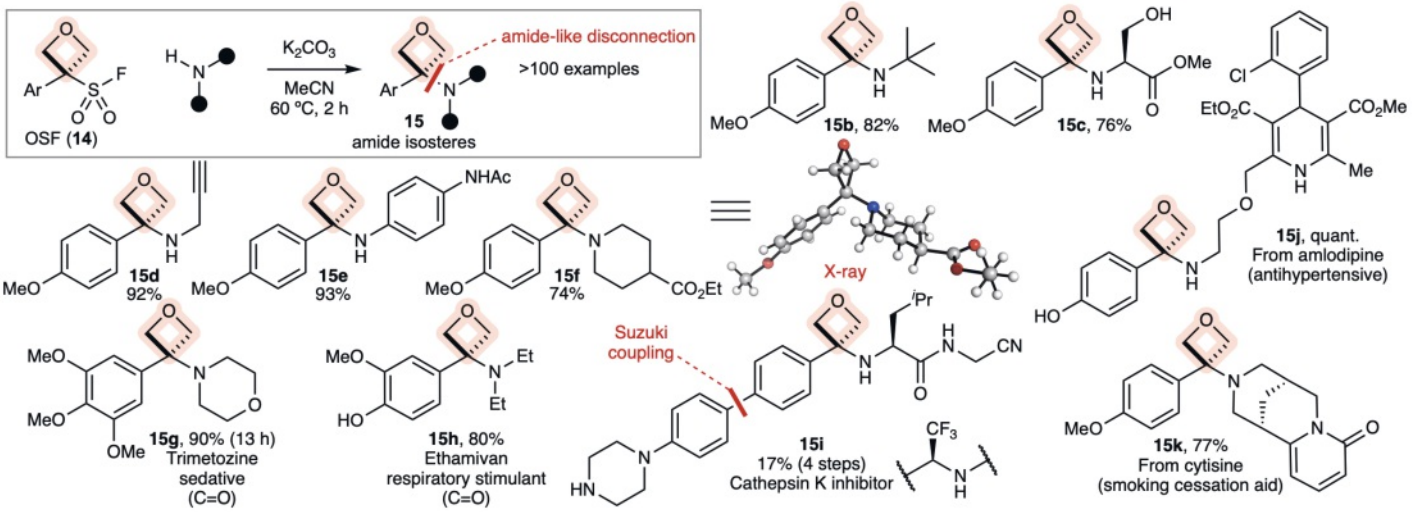
Scheme 6. Unexpected reactivity (a) and synthesis (b) of oxetane sulfonyl fluorides.

The transformation mimics the amidation reaction, the most popular reaction in medicinal chemistry, and hence allows direct use of the extensive libraries of amines available for typical amide couplings. The scope in the nucleophile component is very broad, demonstrated in over 100 diverse amino-oxetane structures and tolerating functionality such as alkynes, esters, amides, alcohols and heterocycles (**15b–f**, Scheme 7). The method was showcased through the synthesis of oxetane analogs of benzamide drugs (**15g–i**), the late-stage functionalization of complex amine-containing drugs (**15j**,**k**), and the generation of a compound library by an array screen. X-ray crystallography revealed amino-oxetanes to adopt a much more 3-dimensional conformation than the corresponding benzamides due to disruption of the conjugated π system. Other nucleophiles such as alcohols, N-heterocycles and fluoride were also compatible.[23]

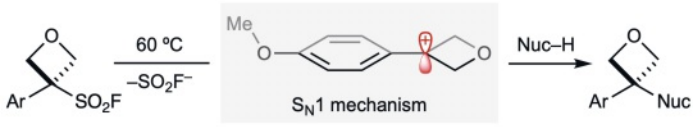
Kinetic and computational experiments supported the formation of a planar oxetane carbocation by a S_N1 mechanism with defluorosulfonylation proceeding by elongation of the C–S bond (Scheme 8). Finally, the oxetane structure was shown to be crucial to provide the right balance of carbocation stability/reactivity to favour defluorosulfonylation over the SuFEx pathway.[23]

3. Conclusions

Various methods have been developed to generate benzylic carbocations on 4-membered heterocycles. Catalytic hydroxyl



Scheme 7. Defluorosulfonylative coupling of OSFs.



Scheme 8. S_N1 defluorosulfonylation mechanism of OSFs *via* an oxetane carbocation.

activation, decarboxylation and radical-polar crossover, and an unprecedented defluorosulfonylation reaction have created a wide range of 3,3-disubstituted oxetanes and azetidines of interest for drug discovery. The defluorosulfonylative coupling of oxetane sulfonyl fluorides with amines was suitable for late-stage diversification and the study provided new insights into the nature of the oxetane carbocation. A future challenge is the adaptation of the presented methodologies to tolerate electron-poor functionality on the heterocycles, currently being insufficient to stabilize carbocations.

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[1] D. C. Blakemore, L. Castro, I. Churcher, D. C. Rees, A. W. Thomas, D. M. Wilson, A. Wood, *Nat. Chem.* **2018**, 10, 383, https://doi.org/10.1038/s41557-018-0021-z.
[2] D. G. Brown, J. Boström, *J. Med. Chem.* **2016**, *59*, 4443, https://doi.org/10.1021/acs.jmedchem.5b01409.
[3] M. Rogers-Evans, H. Knust, J.-M. Plancher, E. M. Carreira, G. Wuitschik, J. Burkhard, D. B. Li, C. Guérot, *CHIMIA* **2014**, *68*, 492, https://doi.org/10.2533/chimia.2014.492.
[4] X. Zheng, L. Gao, L. Wang, C. Liang, B. Wang, Y. Liu, S. Feng, B. Zhang, M. Zhou, X. Yu, K. Xiang, L. Chen, T. Guo, H. C. Shen, G. Zou, J. Z. Wu, H. Yun, *J. Med. Chem.* **2019**, *62*, 6003, https://doi.org/10.1021/acs.jmedchem.9b00654.
[5] K. Wellington, L. J. Scott, *Drugs* **2003**, *63*, 2613, https://doi.org/10.2165/00003495-200363230-00004.
[6] E. Q. Myriem, J. Y. Cassayre, WO Patent Appl. No. WO2014019957A2, **2014**.
[7] a) J. A. Burkhard, G. Wuitschik, M. Rogers-Evans, K. Müller, E. M. Carreira, *Angew. Chem. Int. Ed.* **2010**, *49*, 9052, https://doi.org/10.1002/anie.200907155. b) J. A. Bull, R. A. Croft, O. A. Davis, R. Doran, K. F. Morgan, *Chem. Rev.* **2016**, *116*, 12150, https://doi.org/10.1021/acs.chemrev.6b00274. c) J. J. Rojas, J. A. Bull, 'Oxetanes and Oxetenes: Monocyclic', in 'Comprehensive Heterocyclic Chemistry IV', Eds. D. S. Black, J. Cossy, C. V. Stevens, Elsevier, Oxford, **2022**, p. 212.
[8] R. A. Croft, J. J. Mousseau, C. Choi, J. A. Bull, *Chem. Eur. J.* **2016**, *22*, 16271, https://doi.org/10.1002/chem.201604031.
[9] M. Niggemann, M. J. Meel, *Angew. Chem. Int. Ed.* **2010**, *49*, 3684, https://doi.org/10.1002/anie.200907227.
[10] R. A. Croft, J. J. Mousseau, C. Choi, J. A. Bull, *Tetrahedron* **2018**, *74*, 5427, https://doi.org/10.1016/j.tet.2018.02.069.
[11] M. A. J. Dubois, M. A. Smith, A. J. P. White, A. Lee Wei Jie, J. J. Mousseau, C. Choi, J. A. Bull, *Org. Lett.* **2020**, *22*, 5279, https://doi.org/10.1021/acs.orglett.0c01214.
[12] M. A. J. Dubois, R. A. Croft, Y. Ding, C. Choi, D. R. Owen, J. A. Bull, J. J. Mousseau, *RSC Med. Chem.* **2021**, *12*, 2045, https://doi.org/10.1039/D1MD00248A.
[13] R. A. Croft, J. J. Mousseau, C. Choi, J. A. Bull, *Chem. Eur. J.* **2018**, *24*, 818, https://doi.org/10.1002/chem.201705576.
[14] J. J. Rojas, E. Torrisi, M. A. J. Dubois, R. Hossain, A. J. P. White, G. Zappia, J. J. Mousseau, C. Choi, J. A. Bull, *Org. Lett.* **2022**, *24*, 2365, https://doi.org/10.1021/acs.orglett.2c00568.
[15] C. Denis, M. A. J. Dubois, A. S. Voisin-Chiret, R. Bureau, C. Choi, J. J. Mousseau, J. A. Bull, *Org. Lett.* **2019**, *21*, 300, https://doi.org/10.1021/acs.orglett.8b03745.
[16] M. A. J. Dubois, A. Lazaridou, C. Choi, J. J. Mousseau, J. A. Bull, *J. Org. Chem.* **2019**, *84*, 5943, https://doi.org/10.1021/acs.joc.9b00613.
[17] R. A. Croft, M. A. J. Dubois, A. J. Boddy, C. Denis, A. Lazaridou, A. S. Voisin-Chiret, R. Bureau, C. Choi, J. J. Mousseau, J. A. Bull, *Eur. J. Org. Chem.* **2019**, *2019*, 5385, https://doi.org/10.1002/ejoc.201900498.
[18] M. Das, A. Weissenfluh, N. Ly, M. L. Trudell, *J. Org. Chem.* **2020**, *85*, 8209, https://doi.org/10.1021/acs.joc.0c00454.
[19] a) G. P. Möller, S. Müller, B. T. Wolfstädter, S. Wolfrum, D. Schepmann, B. Wünsch, E. M. Carreira, *Org. Lett.* **2017**, *19*, 2510, https://doi.org/10.1021/acs.orglett.7b00745. b) S. Roesner, G. J. Saunders, I. Wilkening, E. Jayawant, J. V. Geden, P. Kerby, A. M. Dixon, R. Notman, M. Shipman, *Chem. Sci.* **2019**, *10*, 2465, https://doi.org/10.1039/C8SC05474F.
[20] a) P. J. Hamzik, J. D. Brubaker, *Org. Lett.* **2010**, *12*, 1116, https://doi.org/10.1021/ol100119e. b) K. Kolahdouzan, R. Khalaf, J. M. Grandner, Y. Chen, J. A. Terrett, M. P. Huestis, *ACS Catal.* **2020**, *10*, 405, https://doi.org/10.1021/acscatal.9b03596.
[21] P. Li, J. R. Zbieg, J. A. Terrett, *ACS Catal.* **2021**, *11*, 10997, https://doi.org/10.1021/acscatal.1c03251.
[22] a) J. Dong, L. Krasnova, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2014**, *53*, 9430, https://doi.org/10.1002/anie.201309399. b) A. S. Barrow, C. J. Smedley, Q. Zheng, S. Li, J. Dong, J. E. Moses, *Chem. Soc. Rev.* **2019**, *48*, 4731, https://doi.org/10.1039/C8CS00960K.
[23] J. J. Rojas, R. A. Croft, A. J. Sterling, E. L. Briggs, D. Antermite, D. C. Schmitt, L. Blagojevic, P. Haycock, A. J. P. White, F. Duarte, C. Choi, J. J. Mousseau, J. A. Bull, *Nat. Chem.* **2022**, *14*, 160, https://doi.org/10.1038/s41557-021-00856-2.

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