Amino-oxetanes as Amide Isosteres by an Alternative Defluoro-sulfonylative Coupling of Sulfonyl Fluorides

Nat. Chem. **2022**, *14*, 160–169

Dr. James Bull's group at Imperial College London (UK) has a long-standing interest in the preparation of four-membered rings, especially oxetanes, and has ambitions to position any functional group at any position on the ring. "We have installed various functional groups at the 2- and 3-positions, but 3-aryl-3-amino oxetanes, that can be considered as benzamide replacements, were a particular challenge," said Dr. Bull.

Recently, the group has been working with scientists at Pfizer (especially Dr. James Mousseau and Charlie Choi) on the preparation of 3,3-disubstituted oxetanes that are of interest as carbonyl replacement groups. "Work from Carreira and co-workers at Roche had previously established several favourable comparisons," said Dr. Bull. He continued: "We had developed synthetic routes to activate 3-aryl-oxetan-3-ols that react with phenols in Friedel–Crafts reactions or in thiol alkylations. However, amines were unsuccessful as nucleophiles in this way."

As part of the Bull group's broad work in this area, they prepared oxetane sulfonyl fluorides. Sulfonyl fluorides are broadly used as precursors to sulfonamides and sulfonates. In comparison to sulfonyl chlorides, these are much more hydrolytically stable and more likely to undergo sulfur fluorine exchange (SuFEx) chemistry rather than reduction. As a result, these are increasingly used in 'click' processes, including in materials chemistry and as covalent probes in medicinal chemistry.

"However, these aryl-oxetane sulfonyl fluoride species (**OSF**) did not behave at all in the usual way!" remarked Dr. Bull. "Instead, these underwent a loss of SO_2 and a fluoride ion to generate an oxetane carbocation intermediate that could react with nucleophiles, namely a defluorosulfonylative process. Specifically, we reacted these reagents with a wide range of amines to form amino oxetanes that provide an interesting mimic to the amide bond. The comparison with amides as bioisosteres is very interesting and, perhaps more importantly, the aminooxetane motif is attractive in its own right, as a small, polar and non-planar functional group that we believe provides interesting potential in medicinal chemistry. What is really attractive about this reaction is that the bond that is formed is analogous to that of a typical amide bond formation, and as a result can potentially make use of the enormous collections of amines that are available to pharmaceutical companies."

Dr. Bull pointed out that this is a very unusual generation of a carbocation under extremely mild conditions, indeed under slightly basic conditions. As a result, very high functional group tolerance was obtained, with polar functionality of various types (Figure 1). "Hindered amines, amino acid derivatives, primary and secondary amines and anilines are all successful nucleophiles," said Dr. Bull. He continued: "Phenols can either undergo the defluorosulfonylative coupling process or more typical SuFEx, depending on the conditions. We used various oxetane sulfonyl fluorides to generate a collection of 10 oxetane analogues of benzamide-containing drug compounds. We demonstrated the potential for the late-stage diversification of complex amines by reactions with amine-containing drug compounds, and also through an array with a 'diversity set' of amines run at Pfizer (by Dr. Dan Schmitt)."

The oxetane sulfonyl fluoride reacted at the same rate, with first order, independent of the nucleophile, consistent with the proposed S_N1 mechanism (Figure 2). "The structure and stability of the oxetane carbocation was itself very interesting," commented Dr. Bull. "Dr. Alistair Sterling and Prof. Fernanda Duarte, computational physical organic chemists at the University of Oxford, demonstrated that the oxetane carbocation intermediate adopts a planar conformation. This conformation places the electron-rich aromatic and the carbocation on the oxetane ring in conjugation, to enable maximum stabilisation and minimise the potential steric clashes between the *ortho* C–H bonds and the methylene groups on oxetane. Consequently, the oxygen lone pair is not involved in stabilisation. The oxetane sulfonyl fluoride reagents have good stability at and below room temperature, but readily react at slightly elevated temperatures by S_N1 ionisation through lengthening of the C–S bond."

Dr. Bull concluded: "I would like to thank all of the collaborators on this work, at Imperial College, Oxford and Pfizer, and in particular co-first authors Juan Rojas and Rosie Croft for their outstanding work in identifying, controlling and explaining this chemistry."

  • Published online: June 15, 2022 • DOI: 10.1055/s-0040-1720564

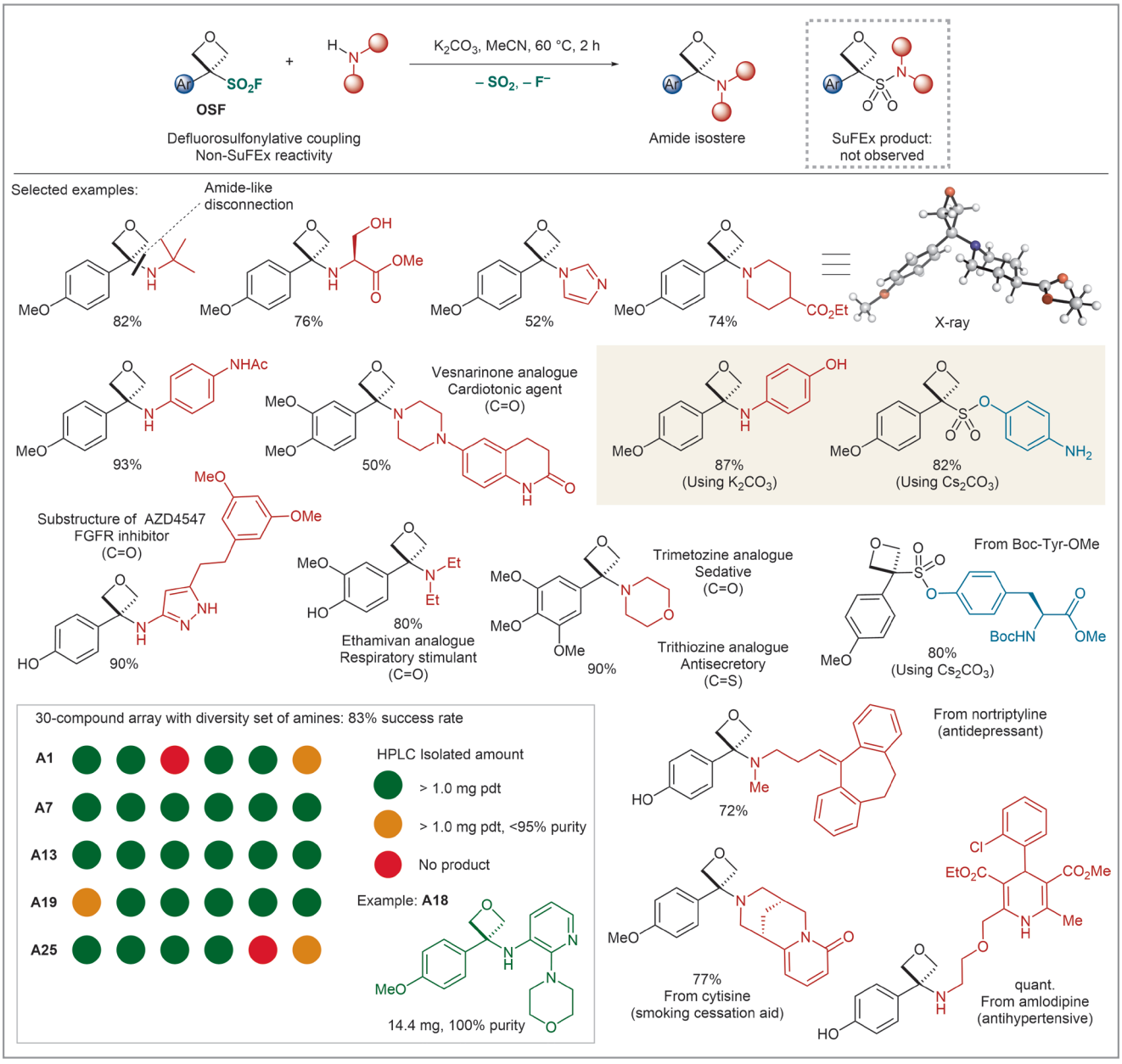

Figure 1 Reaction scope of the defluorosulfonylation of OSFs with amines and other nucleophiles; inset: thirty-compound array with an exemplary OSF (Ar = 4-MeOC$_6$H$_4$) and a diversity set of amines

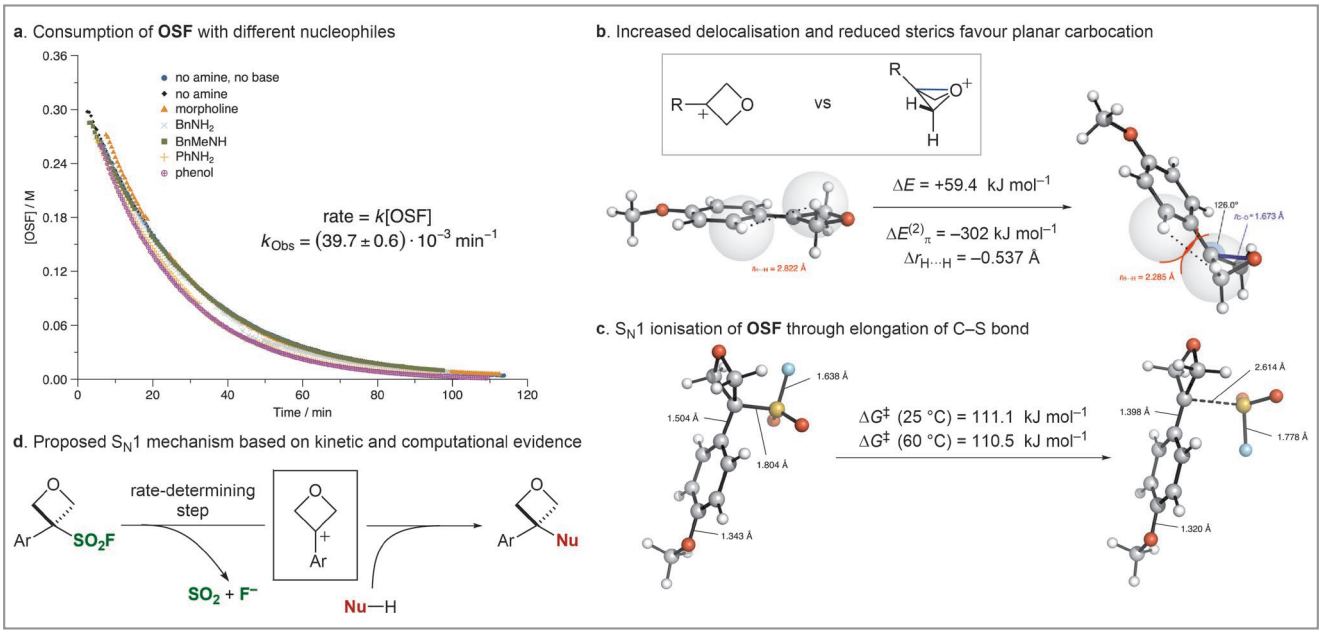

Figure 2 Kinetic and computational analysis of the defluorosulfonylative oxetane amination

About the authors

J. J. Rojas

Juan J. Rojas received his BSc degree in chemistry from the ETH Zürich (Switzerland) in 2016. After 10 months in the Swiss Armed Forces, he went to London where he obtained his MRes degree in catalysis from Imperial College London (UK), studying the activation of oxetanols using Brønsted acids in the lab of Dr. James Bull and receiving the MRes Catalysis Outstanding Performance Prize (2018). He then spent six months in the Small Molecule Division at BASF Ludwigshafen (Germany) working on organophosphorus derivatives. Currently, he is pursuing a Ph.D. with Dr. James Bull, investigating synthetic methods to access 3,3-disubstituted oxetanes through the generation of reactive oxetane intermediates.

Dr. R. Croft

Rosemary Croft obtained her MSc from Bristol University (UK) in 2014. She then went on to pursue her PhD under the supervision of Dr. James Bull at Imperial College London (UK). Her research focused on the synthesis of oxetane bioisosteres through the generation of oxetanyl carbocations. She currently works as a research chemist in weed control at Syngenta.

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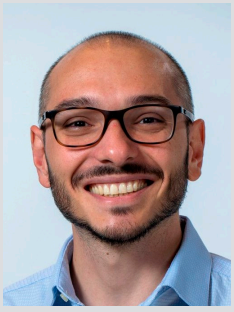
Dr. A. J. Sterling

Alistair J. Sterling received his DPhil from the University of Oxford (UK) in 2021 under the supervision of Profs. F. Duarte and E. A. Anderson, where he received an Oxford-Radcliffe Scholarship. He obtained his MChem from the same institution in 2017, spending a semester in the group of Prof. E. M. Carreira (ETH Zürich, Switzerland), before returning to Oxford to study total synthesis under the supervision of Prof. E. A. Anderson. He then transitioned from experimental to computational chemistry in 2018 while working on cyclocarbon analogues under Prof. H. L. Anderson. He is currently an EPSRC Doctoral Prize postdoctoral researcher at the University of Oxford, where his research interests include physical organic chemistry, computational chemistry and reaction development.

Dr. E. L. Briggs

Edward L. Briggs received his MChem degree (2017) from the University of Southampton (UK) which included a placement at Vertex Pharmaceuticals (Oxford, UK). He then moved to Imperial College London (UK) to undertake a PhD (2021) under the supervision of Dr. James A. Bull researching methods to synthesise medicinally relevant sulfur(VI) analogues. He is currently working as a postdoctoral training fellow at the Institute of Cancer Research (UK) under Dr. Gurdip Bhalay.



Dr. D. Antermite

Daniele Antermite graduated from the University of Bari (Italy), with an M.Sc. degree in Pharmaceutical Chemistry and Technology in 2016. During his undergraduate studies, he performed research placements in organic chemistry at the Karlsruhe Institute of Technology (Germany) and at the University of Vienna (Austria). He then joined Dr. James Bull's group at Imperial College London (UK) for his doctoral studies, focusing on Pd-catalysed C–H functionalisation of saturated heterocycles. After receiving his PhD in 2020, Daniele joined AstraZeneca Gothenburg (Sweden) as a postdoctoral fellow, where is currently working on late-stage C–H functionalisation methodologies in collaboration with Prof. Lutz Ackermann (University of Göttingen, Germany).

Dr. D. C. Schmitt

Daniel C. Schmitt received his PhD in organic chemistry from the University of North Carolina at Chapel Hill (USA) under the supervision of Prof. Jeffrey Johnson. Subsequently, he conducted postdoctoral research with Prof. Michael Krische (University of Texas at Austin, USA), focused on Ir-catalysed allylation methodology. Dan joined Pfizer in 2012 and is now a project and synthesis group leader within the Inflammation & Immunology Medicinal Chemistry department. He enjoys the development and adaption of new synthetic methodologies to parallel format for the expansion of accessible design space on drug discovery projects.

Dr. A. J. P. White

Andrew J. P. White received his PhD from Imperial College London (UK) in 1994 under the supervision of William P. Griffith. He then moved to the Chemical Crystallography Laboratory run by David J. Williams at Imperial College London in 1994, taking over the running of the laboratory upon Prof. Williams' retirement in 2003.

Prof. F. Duarte

Fernanda Duarte is an Associate Professor in the Department of Chemistry at Oxford (UK), where she leads a diverse team working at the interface of organic, supramolecular, and computational chemistry. Her main research interests centre on the prediction of chemical reactivity in the condensed phase, combining classical, quantum and machine-learning approaches. Her group has also developed a series of computational software to facilitate molecular modeling and reaction mechanism exploration. Fernanda has published 60 peer-

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 Synform **2022/07**, A103–A107 • Published online: June 15, 2022 • DOI: 10.1055/s-0040-1720564

reviewed scientific publications and received several awards, including most recently the 2020 MGMS Frank Blaney Award from the Molecular Graphics and Modelling Society, 2021 OpenEye Outstanding Junior Faculty Award from ACS COMP Division, and the 2021 Harrison-Meldola Memorial Prize from the Royal Society of Chemistry.

Dr. J. J. Mousseau

James J. Mousseau was born in Montreal, Quebec, Canada. Upon completing his BSc and MSc studies at Concordia University (Canada), he pursued his PhD studies under Professor André B. Charette at Université de Montreal (Canada) studying arene direct functionalization processes. Following an NSERC Postdoctoral Fellowship at the Massachusetts Institute of Technology (USA) under Professor Timothy F. Jamison, he began his career in 2013 at Pfizer in Groton, Connecticut (USA) working in the area of inflammation and immunology. In 2021 he moved to Halda Therapeutics (USA) investigating new modalities for the treatment of cancer. His other research interests include the development and study of strained rings and new bioisosteric motifs.

Dr. J. A. Bull

James A. Bull is a University Research Fellow and Reader in Synthetic Chemistry at Imperial College London (UK). He obtained an MSci degree and the Raphael prize from the University of Cambridge (UK), then spent a year at GlaxoSmithKline. He returned to University of Cambridge to obtain his PhD under the supervision of Professor Steven Ley. In 2007 he joined the group of Professor André Charette as a postdoctoral fellow at Université de Montréal (Canada). He joined Imperial College London in 2009 as a Ramsay Memorial Research Fellow, and in 2011 was awarded an EPSRC Career Acceleration Fellowship. In January 2016, he was awarded a Royal Society University Research Fellowship. He received a Thieme Chemistry Journal Award in 2016 and the AstraZeneca prize for synthetic chemistry in 2021. His research targets methods for the synthesis of new chemical motifs that may be practically applied in drug discovery, to provide new design elements and extend available chemical space.

 Synform **2022/07**, A103–A107 • Published online: June 15, 2022 • DOI: 10.1055/s-0040-1720564