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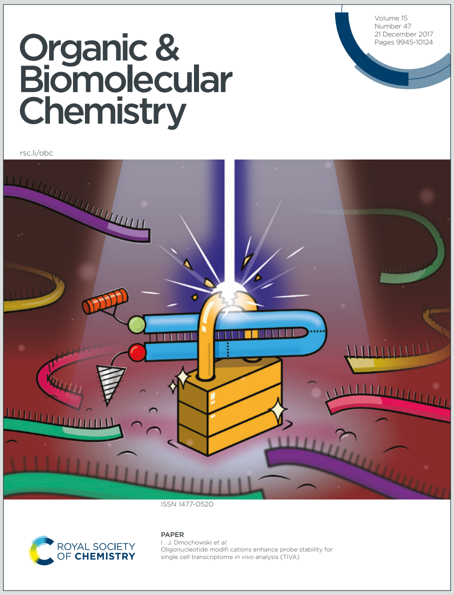

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ARTICLE

A Scalable Continuous Photochemical Process for the Generation of Aminopropylsulfones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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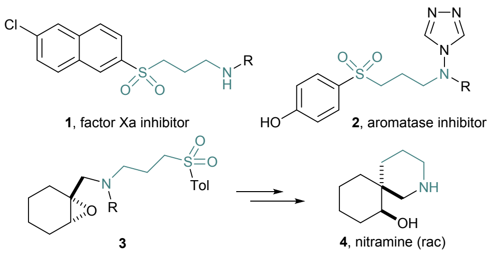
An efficient continuous photochemical process is presented that delivers a series of novel γ-aminopropylsulfones via a tetrabutylammonium decatungstate (TBADT) catalysed HAT-process. Crucial to this success is the exploitation of a new high-power LED emitting at 365 nm that was found to be superior to an alternative medium-pressure Hg lamp. The resulting flow process enabled the scale-up of this transformation reaching throughputs of 20 mmol/h at substrate concentrations up to 500 mM. Additionaly, the substrate scope of this transformation was evaluated demonstrating the straightforward incorporation of different amine substituents as well as alkyl appendages next to the sulfone moiety. It is anticipated that this methodology will allow for further exploitations of these underepresented γ-aminopropylsulfone scaffolds in the future.

Introduction

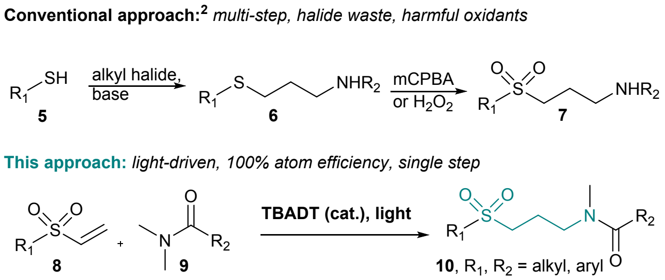
Aminoalkylsulfones are versatile, yet underexplored structural motifs that constitute of an amine group along with a sulfone moiety separated by an alkyl chain. In contrast to their more prevalent alkyl sulfonamide isomers[1], that are common motifs in many drug molecules, synthetic routes to such aminoalkylsulfones are scarce and typically require labour-intensive multistep syntheses. These commonly include functional group interconversions such as C-S bond formation to yield thioethers and their subsequent oxidation to render the sulfone moiety.[2] Despite this several recent reports emphasise the value of these structures. Specifically, γ-aminopropylsulfones stand out as they play a key role for instance in the synthesis of factor Xa inhibitors (**1**),[2] aromatase inhibitors (**2**)[3] as well as synthetic precursors towards natural products such as the spirocyclic alkaloid nitramine[4] (**4**, Scheme 1).



Scheme 1: Examples and use of γ-aminopropylsulfones.

To address this lack of efficient entries into these important motifs we set out to develop a robust process that would expedite their construction in a highly step- and atom-efficient manner. Specifically, we wished to devise a modular route based on creating a new C-C bond from simple and readily available building blocks. Although this strategic disconnection is desirable, the formation of C-C bonds conventionally requires suitably pre-functionalised substrates. To circumvent this prerequisite, we wished to exploit an alternative approach that is based on simple functionalised alkene and *N*-alkyl amide precursors that upon C-H bond activation would allow forging the key C-C bond (Scheme 2).

Scheme 2: Conventional synthesis versus HAT process towards γ-aminopropylsulfones.



To enable this transformation, we opted to use tetrabutylammonium decatungstate (TBADT) as a simple yet effective photocatalyst that would activate the C-H bond[5] of an alkylamide derivative, creating a carbon-centred radical species that would couple with an electron-deficient alkene. This attractive approach would thus use readily available alkylamide species together with vinyl sulfones aided by TBADT as a well-known photocatalyst that would render the desired γ-aminopropylsulfone products via a hydrogen atom transfer (HAT) process.

The use of TBADT as a readily available photocatalyst in HAT transformations has garnered a significant amount of interest in recent years.[6] As evident from many applications, and highlighted in recent review articles,[7] the union of continuous

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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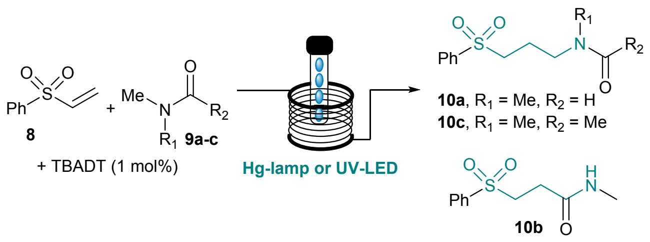
flow processing and photochemistry can provide significant improvements compared to conventional batch operations due to uniform irradiation profiles, short pathlengths of light along with higher reaction control based on excellent heat and mass transfer. This not only accounts for the popularity of developing valuable continuous photochemical transformations in general,[8] but also provides a means for effective and seamless reaction scale-up, which we were particularly interested in. In addition, we were encouraged by recent reports by Fagnoni, Noël and others[9] who have presented important studies based on continuous photochemical approaches utilising TBADT-mediated HAT processes.

Results and discussion

To commence our studies, we wished to evaluate the most suitable parameters for conducting this C-C bond forming process in continuous flow mode. We therefore opted to exploit a Vapourtec E-series flow reactor system in combination with peristaltic pumps that can handle light suspensions better than alternative piston pumps.[10] This was complemented by a FEP coil reactor (10 mL) and two light sources; firstly the established UV150 module, which is based on a tuneable medium-pressure mercury lamp (adjustable 75-150 W power) that can be combined with different filters and suitable temperature regulation.[11] In addition, we wished to study a new high-power LED (adjustable 50-100 W power) that is available for this reactor platform and emits at 365 nm thus potentially representing a milder and more selective light source.[9c,12]

Next, we selected phenyl vinyl sulfone (**8**, PVS) along with *N*,*N*-dimethylformamide (DMF), *N*-monomethylformamide (NMF) and *N*,*N*-dimethylacetamide (DMA) as reaction partners that would generate the respective γ-aminopropylsulfones (**10a**-**10c**) in the presence of freshly prepared TBADT[13] (1 mol% in MeCN) and the chosen light source (Scheme 3).



Scheme 3: Photochemical reaction set-up.

In accordance with literature reports we expected for DMF and DMA reaction at the *N*-methyl group, whereas NMF would react via the formyl C-H bond.[14] At this point the input power for the high-power LED was set to 75 W, whereas the input power of the Hg-lamp was set about 50% higher to 110 W in order to counterbalance the reduced efficiency of the latter due to emitting light in the visible and IR region that was blocked by using a low-pass filter (see SI for UV spectra).

A mixture of phenyl vinyl sulfone (**8**, PVS, 1 equiv.), coupling partner (**9a**-**9c**, 4 equiv.) and TBADT (1 mol%) were dissolved in MeCN (100-500 mM wrt PVS) and pumped through the irradiated flow reactor (Table 1). The reactor temperature was maintained at 25-30° using a stream of compressed air for effective cooling. The crude reaction mixture, which displayed a blue colour upon exiting the reactor, was filtered over a pad of celite (ca. 2 cm, to remove TBADT), concentrated under reduced pressure and analysed by HPLC (at 250 nm).

Table 1: Comparative flow study using different substrates.

	substrate	residence time [min]	concentration (PVS) [mM]	yield[a] UV150 [b]	yield[a] LED [c]
1	DMF	30	100	88	94
2	DMF	15	100	80	81
3	DMF	30	300	90	99 (88)
4	DMF	15	300	77	94
5	DMF	30	500	71	99
6	DMF	15	500	54	95
7	NMF	15	300	100	100
8	NMF	7.5	300	87	100
9	NMF	15	500	99	100 (96)
10	NMF	7.5	500	74	99
11	DMA	15	300	87	84
12	DMA	15	500	87	88 (79)

[a] based on calibrated HPLC; [b] operated at 110 W; [c] operated at 75W, numbers in brackets refer to isolated yields, typical scale 1 mmol, 4 equiv. of substrate used.

Initially, this study indicated that for DMF both light sources perform well at a PVS concentration of 100 mM with residence times of 30 and 15 minutes, respectively (entries 1 and 2). However, upon increasing the concentration to 300 and 500 mM, it became apparent that the LED lamp gave rise to higher HPLC yields even at the shorter residence time of 15 minutes (entries 3-6). We surmise that this is testament to the higher photon flux of the high-power LED at the favourable wavelength of 365 nm.

Similarly, NMF displayed the same trend where at longer residence times of 15 minutes (entries 7 and 9) both lamps perform equally well, whereas only the high-power LED retained this efficiency when increasing the throughput (residence time 7.5 minutes, entries 8 and 10).

Interestingly, when moving from formamides to acetamides both lamps show similar performance at different concentrations (entries 11 and 12), yet a preference for the LED lamp is given due to its higher energy efficiency. Crucially, these observations were verified by isolated yields that closely matched the HPLC results thus demonstrating the ready scalability of this approach towards different γ-aminopropylsulfones (**10a**-**10c**).

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Therefore, this study indicates that the high-power UV-LED is generally performing better in these applications than the medium-pressure Hg lamp even at lower input power (75 W for LED vs. 110 W for Hg lamp). It is believed that this can be ascribed to the LED's near monochromatic light (365 nm) whereas the filtered Hg-lamp suffers from energy loss due to dissipation effects as well as additional side-products along with discoloration of the crude reaction product (pale yellow for LED lamp vs. brown for Hg-lamp).

Based on these findings we next applied the UV-LED reactor set-up to a selection of additional substrates and were able to realise the effective formation of all desired γ-aminopropylsulfone derivatives (**10a**-**10i**) that were isolated in good to excellent yields. A general trend seen in most amide reaction partners was that slightly extended residence times (up to 60 min) and 2 mol% of TBADT were required to achieve full conversion of PVS. In all cases except for product **10b** the observed product coupled via the alkyl group adjacent to the amide nitrogen as anticipated. Furthermore, this study established that substrates bearing aryl chromophores are tolerated thus extending the scope towards making a variety of alkyl and aryl substituted systems. A key feature of this continuous photochemical approach remains its high productivity allowing substrate concentrations ranging from 300 to 500 mM.

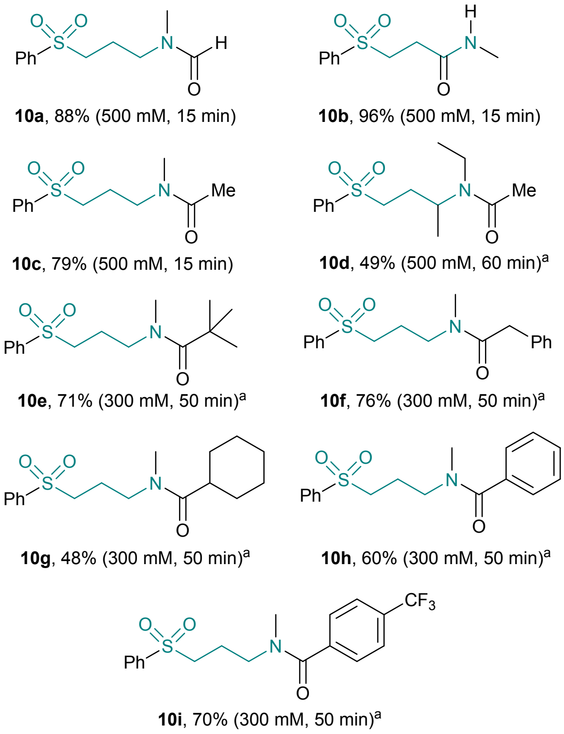

10a, 88% (500 mM, 15 min)
10b, 96% (500 mM, 15 min)
10c, 79% (500 mM, 15 min)
10d, 49% (500 mM, 60 min)[a]
10e, 71% (300 mM, 50 min)[a]
10f, 76% (300 mM, 50 min)[a]
10g, 48% (300 mM, 50 min)[a]
10h, 60% (300 mM, 50 min)[a]
10i, 70% (300 mM, 50 min)[a]

Figure 1: Substrate scope using the LED module with PVS ([a] 2 mol% TBADT, 100 W LED), typical scale 1 mmol, 4 equiv. of substrate used.

As NMR analysis of all structures indicated the presence of rotamers that would not fully coalesce at elevated temperature, we employed single crystal X-ray diffraction on product **10i** which confirmed the anticipated connectivity (Figure 2).

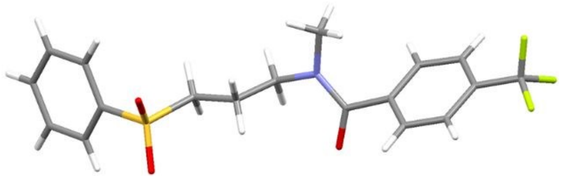


Figure 2: Crystal structure of γ-aminopropylsulfone **10i**.[15]

A further aspect of this study targeted the variation of the phenyl group introduced from phenyl vinyl sulfone in the interest of incorporating alternative alkyl moieties. We thus subjected commercially available ethyl vinyl sulfone to our continuous LED set-up and adjusted reaction time based on substrate reactivity. Gratifyingly, these substrate modifications were well tolerated allowing for delivering a small selection of novel γ-aminopropylsulfones (**10j**-**m**) in high isolated yield and throughput as depicted in Figure 3.

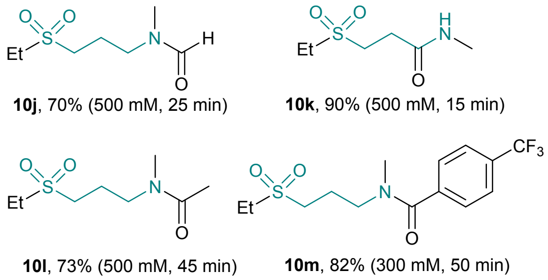
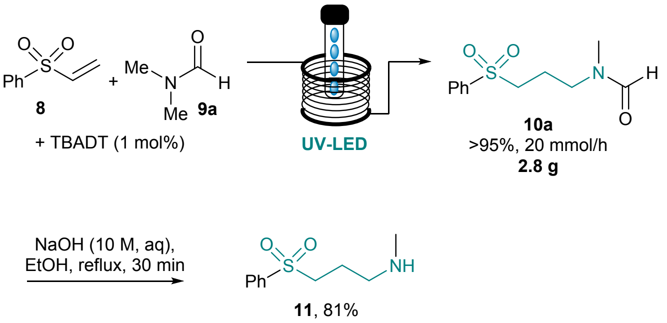

10j, 70% (500 mM, 25 min)
10k, 90% (500 mM, 15 min)
10l, 73% (500 mM, 45 min)
10m, 82% (300 mM, 50 min)

Figure 3: Extended substrate scope using the LED set-up.

To assess the value of our flow process for creating these products in multi-gram amounts we wished to scale this transformation and additionally demonstrate the feasibility of cleaving the amide group to render free the γ-amino-propylsulfone (e.g. **11**). Based on the previous optimisation studies using DMF as coupling partner, we exploited this system (e.g. **10a**) based on conditions expected to provide the highest throughput (e.g. entry 6, table 1).



Scheme 4: Reaction scale-up and batch formamide cleavage.

The photochemical reaction performed well as before (500 mM, 15 minutes) allowing to process 2 g of PVS substrate over a

DOI: 10.1039/D0OB01801E

period of 35 minutes which is equivalent to a throughput of 20 mmol/h. As HPLC analysis on the crude mixture indicated quantitative conversion of PVS the residual catalyst was removed by filtration over celite followed by evaporation of the volatiles under reduced pressure. The resulting oil was dissolved in EtOH (5 M) and treated with NaOH (10 M, aq.) before refluxing for 30 minutes. Pleasingly, the desired free γ-aminopropylsulfone **11** was isolated after acid-base extraction in high yield allowing for further elaboration of this building block.

Conclusions

In summary, we report the effective flow-based synthesis of a series of γ-aminopropylsulfones exploiting a photochemical HAT process catalysed by TBADT. The use of a new high-power LED lamp in conjunction with continuous processing provides an effective means to generate a series of these underexploited scaffolds. The robustness of this flow process was demonstrated through the scaled synthesis of one target compound at a concentration of 500 mM achieving a throughput of 20 mmol/h. The facile removal of the pendent formyl group was achieved by standard hydrolysis under basic conditions which enables further derivatisation on the free amino group of the γ-aminopropylsulfone.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the School of Chemistry at UCD for providing a PhD-scholarship (MDF) and University College Dublin for seed funding (SF1606 and SF1609 to MB). We furthermore thank the Erasmus council for support through an internship (SB). Dr Helge Müller-Bunz is thanked for solving the X-ray structure reported. We are furthermore grateful to Duncan Guthrie (Vapourtec) for support and helpful discussions. We acknowledge generous support of our research through Science Foundation Ireland (Infrastructure Call 2018 18/RI/5702 and European Regional Development Fund 12/RC2275_P2).

Notes and references

‡ These authors contributed equally.

1 (a) S. S. A. Shah, G. Rivera, M. Ashfaq, *Mini Rev. Med. Chem.*, **2013**, *13*, 70-86. (b) M. Feng, B. Tang, S. H. Liang, X. Jiang, *Curr. Top. Med. Chem.*, **2016**, *16*, 1200-1216.
2 Y. Imaeda, T. Miyawaki, H. Sakamoto, F. Itoh, N. Konishi, K. Hiroe, M. Kawamura, T. Tanaka, K. Kubo, *Bioorg. Med. Chem.*, **2008**, *16*, 2243.
3 C. Bubert, L. W. Lawrence Woo, O. B. Sutcliffe, M. F. Mahon, S. K. Chander, A. Purohit, M. J. Reed, B. V. L. Potter, *ChemMedChem*, **2008**, *3*, 1708.
4 D. Tanner, H. H. Ming, M. Bergdahl, *Tetrahedron Lett.*, **1988**, *29*, 6493.
5 For selected recent reviews, please see: (a) X. Tang, X. Jia, Z. Huang, *Chem. Sci.*, **2018**, *9*, 288. (b) K. I. Goldberg, A. S. Goldman, *Acc. Chem. Res.*, **2017**, *50*, 620. (c) D. Munz, T. Strassner, *Inorg. Chem.*, **2015**, *54*, 5043. (d) S. Santoro, F. Ferlin, L. Ackermann, L. Vaccaro, *Chem. Soc. Rev.*, **2019**, *48*, 2767. (e) S. Govaerts, A. Nyuchev, T. Noël, *J. Flow Chem.* **2020**, *10*, 13-71.
6 (a) D. Ravelli, M. Fagnoni, T. Fukuyama, T. Nishikawa, I. Ryu, *ACS Catal.*, **2018**, *8*, 701. (b) D. Dondi, M. Fagnoni, A. Albini, *Chem. Eur. J.*, **2006**, *12*, 4153. (c) D. Ravelli, S. Protti, M. Fagnoni, *Acc. Chem. Res.* **2016**, *49*, 2232. (d) M. D. Tzirakis, I. N. Lykakis, M. Orfanopoulos, *Chem. Soc. Rev.* **2009**, *38*, 2609.
7 (a) C. Sambiago, T. Noël, *Trends Chem.*, **2020**, *2*, 92. (b) M. Di Filippo, C. Bracken, M. Baumann, *Molecules*, **2020**, *25*, 356. (c) T. H. Rehm, *ChemPhotoChem* **2020**, *4*, 235-254. (d) M. Berton, J. M. de Souza, I. Abdiaj, D. T. McQuade, D. R. Snead, *J. Flow Chem.* **2020**, *10*, 73-92. (e) D. Cambie, C. Bottecchia, N. J. W. Straathof, V. Hessel, T. Noël, *Chem. Rev.*, **2016**, *116*, 10276. (f) L. D. Elliott, J. P. Knowles, P. J. Koovits, K. G. Maskil, M. J. Ralph, G. Lejeune, L. J. Edwards, R. I. Robinson, I. R. Clemens, B. Cox, D. D. Pascoe, G. Koch, M. Eberle, M. B. Berry, K. I. Booker-Milburn, *Chem. Eur. J.*, **2014**, *20*, 15226. (g) J. W. Tucker, Y. Zhang, T. F. Jamison, C. R. J. Stephenson, *Angew. Chem. Int. Ed.*, **2012**, *51*, 4144.
8 For recent examples, please see: (a) C. Bracken, M. Baumann, *J. Org. Chem.*, **2020**, *85*, 2607. (b) J. D. Williams, M. Nakano, R. Gerardy, J. A. Rincon, O. de Frutos, C. Mateos, J.-C. M. Monbaliu, C. O. Kappe, *Org. Process Res. Dev.*, **2019**, *23*, 78. (c) E. B. Corcoran, F. Lévesque, J. P. McMullen, J. R. Naber, *ChemPhotoChem*, **2018**, *2*, 931. (d) M. Ruggeri, A. W. Dombrowski, S. W. Djuric, I. R. Baxendale, *ChemPhotoChem*, **2019**, *3*, 1212. (e) Y. Chen., M. Leonardi, P. Dingwall, R. Labes, P. Pasau, D. C. Blakemore, S. V. Ley, *J. Org. Chem.*, **2018**, *83*, 15558. (f) L. D. Elliott, J. P. Knowles, C. S. Stacey, D. J. Klauber, K. I. Booker-Milburn, *React. Chem. Eng.*, **2018**, *3*, 86. (g) L. D. Elliott, M. Berry, B. Harji, D. Klauber, J. Leonard, K. I. Booker-Milburn, *Org. Process Res. Dev.*, **2016**, *20*, 1806.
9 (a) F. Bonassi, D. Ravelli, S. Protti, M. Fagnoni, *Adv. Synth. Catal.*, **2015**, *357*, 3687. (b) G. Laudadio, S. Govaerts, Y. Wang, D. Ravelli, H. F. Koolman, M. Fagnoni, S. W. Djuric, T. Noël, *Angew. Chem. Int. Ed.* **2018**, *57*, 4078. (c) G. Laudadio, Y. Deng, K. van der Wal, D. Ravelli, M. Nuno, M. Fagnoni, D. Guthrie, Y. Sun, T. Noël, *Science*, **2020**, *369*, 92-96. (d) Z. Wen, A. Maheshwari, C. Sambiago, Y. Deng, G. Laudadio, K. Van Aken, Y. Sun, H. P. L. Gemoets, T. Noël, *Org. Process Res. Dev.*, **2020**, Doi: 10.1021/acs.oprd.0c00235.
10 For an early example, please see: M. Baumann, I. R. Baxendale, *Eur. J. Org. Chem.* **2017**, 6518-6524.
11 The UV150 module and the high-power LED are available from Vapourtec (https://www.vapourtec.com/#).
12 M. Di Filippo, M. Baumann, *Eur. J. Org. Chem.*, **2020**, Doi: 10.1002/ejoc.202000957.
13 S. Protti, D. Ravelli, M. Fagnoni, A. Albini, *Chem. Commun.* **2009**, *47*, 7351-7353.
14 S. Agnoni, D. Ravelli, D. Emma, D. Dondi, M. Fagnoni, A. Albini, *Adv. Synth. Catal.* **2008**, *350*, 2209-2214.
15 The crystal structure of **10i** was deposited with the Cambridge Crystallographic Database (https://www.ccdc.cam.ac.uk/) and is available free of charge; CCDC2018541.