Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Cite this: *Chem. Sci.*, 2022, **13**, 8626

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 21st March 2022
Accepted 24th June 2022

DOI: 10.1039/d2sc01626e

rsc.li/chemical-science

Functionalisation of ethereal-based saturated heterocycles with concomitant aerobic C–H activation and C–C bond formation†

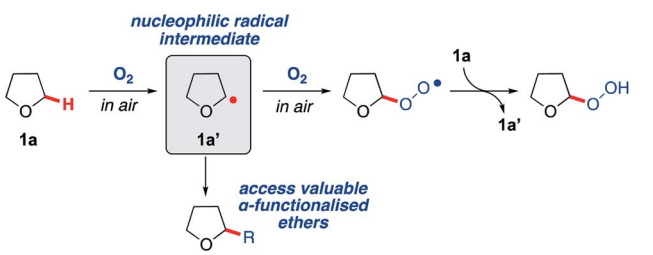
Nehaal Ahmed, Richard J. Spears, Tom D. Sheppard * and Vijay Chudasama *

With an ever-growing emphasis on sustainable synthesis, aerobic C–H activation (the use of oxygen in air to activate C–H bonds) represents a highly attractive conduit for the development of novel synthetic methodologies. Herein, we report the air mediated functionalisation of various saturated heterocycles and ethers *via* aerobically generated radical intermediates to form new C–C bonds using acetylenic and vinyl triflones as radical acceptors. This enables access to a variety of acetylenic and vinyl substituted saturated heterocycles that are rich in synthetic value. Mechanistic studies and control reactions support an aerobic radical-based C–H activation mechanism.

Introduction

Saturated heterocycles represent important motifs that are present in numerous pharmaceuticals and natural products.[1–5] In particular, there is a growing interest in the use of sp^3-rich heterocyclic scaffolds for pharmaceutical applications where they are considered likely to reduce attrition in the drug discovery pipeline.[6–8] Their widespread use is still held back by difficulties in the synthesis of these molecules from readily available precursors. The direct sp^3 C–H functionalisation of saturated heterocycles is a potentially valuable strategy that could enable a plethora of compounds to be accessed effectively from simple precursors, with C–C bond formation arguably being the most valuable transformation. However, currently available methods for direct C–H activation of saturated heterocycles require: (i) complicated directing group scaffolds/protecting groups, which necessitate additional installation and removal steps;[9,10] (ii) the presence of precious and/or toxic transition metal catalysts;[11,12] (iii) external additives or initiators, occasionally in stoichiometric quantities, that must then be separated from the product;[13,14] or (iv) high energy materials such as diazo compounds, which can be difficult to handle.[15,16] To overcome these limitations and improve sustainability, new methodologies that enable simple and sustainable C–H functionalisation of sp^3-rich heterocycles are required.[17]

Radical-based C–H bond activation is a potentially powerful and versatile strategy for the functionalisation of saturated heterocycles.[18–21] However, existing approaches, whilst effective, typically employ specialised initiators and/or careful management of reaction conditions to achieve this in a controlled fashion.[22–26] Aerobic C–H activation, utilising oxygen in air to promote radical-based C–H bond cleavage, represents a potentially ideal approach,[26–30] but to date has not been exploited for the formation of C–C bonds on saturated heterocycles. To explore this idea, we initially examined tetrahydrofuran (THF, **1a**) as a candidate for aerobic C–H activation as THF derivatives are highly sought after.[31] Moreover, the interaction of molecular oxygen with the α-C(sp^3)–H in THF (as well as many other ethers) is known to result in the generation of a nucleophilic radical intermediate **1a′** (Scheme 1), which then reacts with a second equivalent of oxygen to form a peroxy radical and completes the chain reaction by C–H activation of THF to from a peroxide species, re-generating the radical intermediate **1a′** (Scheme 1).[32–35] With this as a starting point, we wanted to consider if intermediate **1a′** could instead be trapped with suitable reaction partners in a manner that would establish an alternative chain reaction to afford THF derivatives with a new C–C bond. This could potentially form a general strategy for the preparation of α-functionalised ethers, which are very important moieties in drug discovery, representing



Scheme 1 Aerobic oxidation of THF **1a** to form a peroxide species *via* reactive nucleophilic radical intermediate **1a′**.

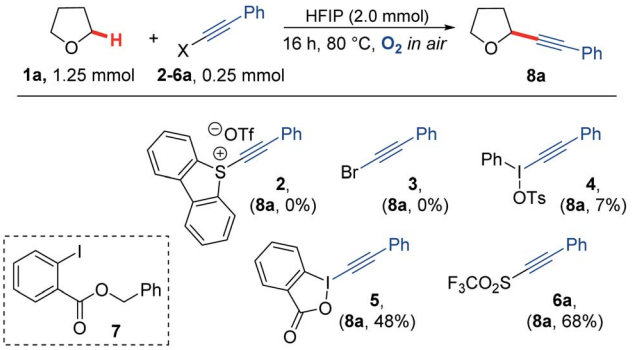
Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ, UK. E-mail: v.chudasama@ucl.ac.uk

† Electronic supplementary information (ESI) available. See https://doi.org/10.1039/d2sc01626e

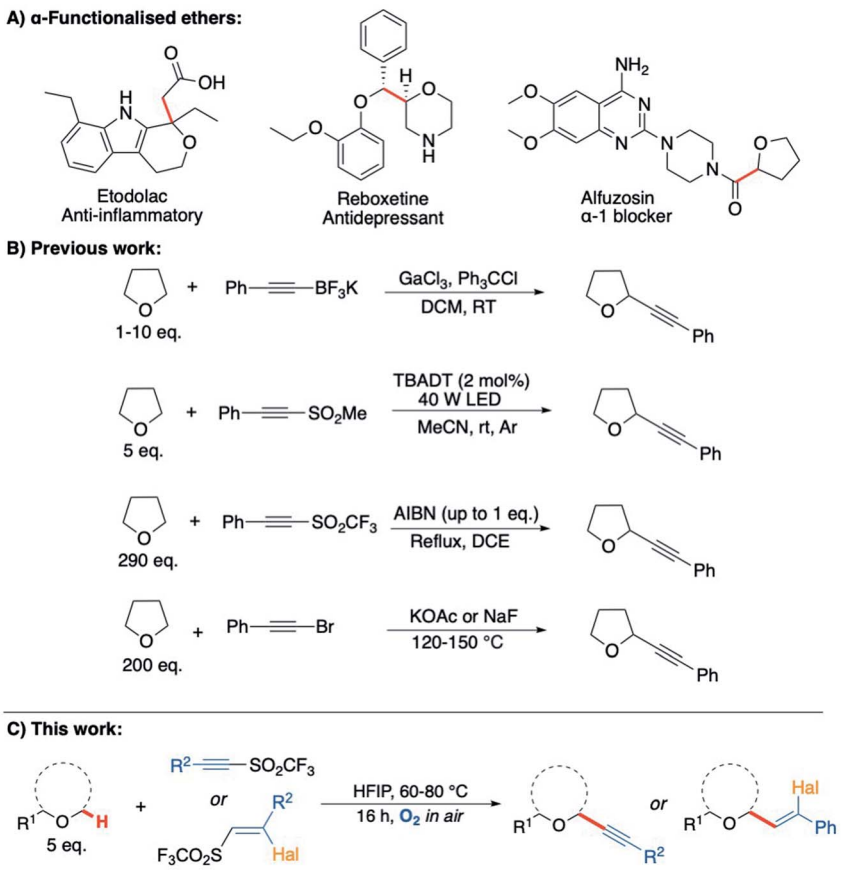
more than 20% of the top 200 small molecule drugs in the pharmaceutical industry (selected examples provided in Scheme 2A).[36]

As electron poor alkynes were expected to be highly reactive towards nucleophilic radical **1a′**, a range of alkyne reaction partners bearing leavings groups that could propagate a chain reaction cycle were tested.[37,38] The expected alkynyl-THF products would also provide a synthetically versatile scaffold, which could be readily manipulated to achieve further molecular complexity *via* transformations of the triple bond.[39–42] We envisaged that the aerobically induced formation of α-functionalised propargylic ethers would proceed *via* a radical addition/elimination reaction exploiting the nucleophilic intermediate **1a′** (Scheme 1). Previous examples of this type of radical reaction between ethers and acetylenic radical acceptors (Scheme 2) have involved the use of stoichiometric amounts of peroxides/initiators, transition metals, specialised photocatalysts or high temperatures (up to 150 °C).[43–47] By utilising the aerobic oxidation of the ether scaffolds, these additives would be unnecessary. Importantly, we also aimed to avoid the need for a vast excess of the ether traditionally required in this type of reaction,[48,49] treating ethers more as substrates as opposed to the reaction solvent.

Our study began by screening a range of acetylenic acceptors (Scheme 3) for trapping the aerobically generated THF radical **1a′** using hexafluoroisopropanol (HFIP) as a co-solvent/additive. These acceptors were selected as they have previously been reported to react with nucleophilic radicals,[53–56] and the reaction conditions selected were based on our previous work.[29] Dibenzothiophenium salt **2** had poor solubility in the THF : HFIP mixture, which led to no formation of the desired THF acetylene product under the reaction conditions; this was also the case for bromophenylacetylene **3**. Iodonium tosylate **4** was more soluble in the reaction conditions and underwent



Scheme 3 A variety of electron deficient alkenes and alkynes were trialled as radical acceptors for reaction with THF under aerobic conditions.



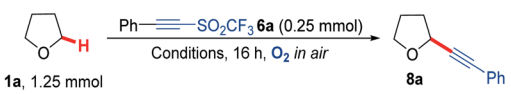
Scheme 2 (A) Bioactive α-functionalised ether scaffolds present in pharmaceuticals;[50–52] (B) previous methods for the alkynylation of THF;[41–47] (C) this work: C–H alkynylation of ethers *via* aerobic C–H activation.

some reaction, forming the acetylenic THF adduct **8a** as the only product, but in only 7% yield due to the low conversion of alkyne. Using Ph-EBX (ethynylbenziodoxolone) **5** as the radical acceptor resulted in an improved yield of the α-C–H functionalised THF product (48%), but a major side product **7**, formed *via* the rearrangement of **5**, was also isolated.[57] The most promising results were obtained using acetylenic triflone **6a**, which gave a 68% yield of the desired THF adduct **8a**. Full conversion of the triflone **6a** was observed *via* TLC and crude NMR, and the side-products did not appear to be derived from THF, suggesting some degradation of the triflone under the reaction conditions.

As the reaction of **6a** and **1a** to form the acetylenic THF product **8a** gave the most promising results, this reaction was optimised further (Table 1).[58] Initially, as we suspected degradation of alkyne **6a** under the reaction conditions, triflone **6a** was incubated in HFIP (2.0 mmol) over 16 h at 80 °C. This study revealed approximately ~20% degradation of triflone **6a** by NMR (measured using an internal standard). When employing less HFIP (1.0 or 0.4 mmol), degradation was reduced to <10% and <5% (respectively). In view of these results, a smaller amount of HFIP (1.0 and 0.40 mmol) was trialled in the C–H functionalisation reaction (entries 2 and 3), and this afforded increasing amounts of the desired product with a 93% yield of THF-alkyne **8a** being obtained with 0.4 mmol of HFIP. In the absence of HFIP, **8a** was obtained in only 41% yield (entry 4), demonstrating that the presence of HFIP was beneficial for the formation of THF-alkyne species **8a.** We believe that the unique H-bonding abilities of HFIP, which allows THF to form a higher boiling point azeotrope, enables auto-oxidation to take place at a faster rate.[59–62] Other fluorinated alcohols such as 2,2,2-trifluoroethanol and perfluoro-*tert*-butanol as substitutes for HFIP were also trialled but were found to be less effective (entries 5 and 6). Notably, the mixture of THF and HFIP used under the optimal conditions boiled at a higher temperature (*ca.* 80 °C) than THF alone and, as mentioned, this may be important in increasing the rate of radical formation. Repeating the optimised reaction conditions for the reaction of THF **1a** and acetylenic triflone **6a** in HFIP (entry 3) under an argon atmosphere whilst bubbling a constant stream of argon through the solution led to no formation of **8a** (entry 7) with most of the starting materials being recovered (only 5% consumption of triflone), confirming that the presence of molecular oxygen in air is vital for the formation of the desired product. Attempting the reaction at lower temperatures led to a reduction in the yield of **8a** (see ESI Table S1† for details). This was to be expected as the rate of formation of THF radicals is thought to be a function of temperature.[63] It was also hypothesised that the leaving group $^{\bullet}SO_2CF_3$ aids the radical chain process, as decomposition of this radical releases SO_2 and $^{\bullet}CF_3$.[64] The trifluoromethyl radical is highly reactive and polarity matched for efficient H-abstraction from THF leading to an efficient radical chain process.[65]

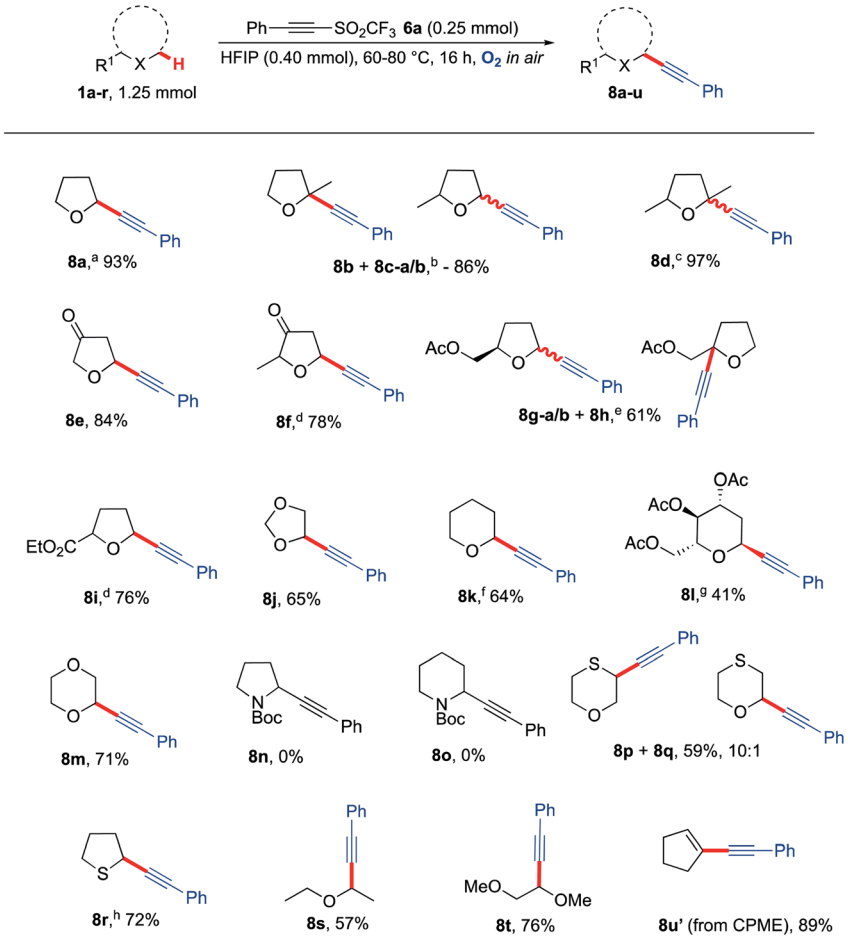
With optimised conditions in hand, the generality of the procedure to α-alkynlate various ethers was then explored (Scheme 4). Ethers were selected based on their likely susceptibility to aerobic activation based on the bond dissociation energy of their α-C–H bond(s).[66–68] Gratifyingly, many 5-membered THF derivatives provided good to excellent yields of the desired α-alkynlated ethers **8b–8j**. Interestingly, no mixture of products was obtained when functionalising 2-methyltetrahydro-3-furanone **1f** as compared to 2-methyl THF **1b**. The reaction was also compatible with the presence of ketones (**8e**, **8f**) and esters (**8g**, **8i**). Although simple alkyl-substituted ethers do not show much regioselectivity in the reactions, substrates bearing a carbonyl group (either within the THF ring or adjacent to it) typically undergo alkynylation with high regioselectivity with alkynylation not taking place adjacent to the carbonyl group (*i.e.* **8e**, **8f** and **8i**). Tetrahydropyran (THP) was readily functionalised to afford **8k** in 64% yield and 1,4-dioxane was monofunctionalised in 71% yield to give **8m**, thus showcasing compatibility with 6-membered ring systems. A longer reaction time was required for an optimal yield of **8k** when using THP as the ether (30 h); this is presumably due to the slower rate of formation of THP α-C(sp^3)–H radicals.[69] Applying the methodology to the more

Table 1 Selected optimisation experiments for the reaction of THF **1a** and phenyl acetylenic triflone **6a**[a]



Entry	*T* (°C)	Solvent/additive	Yield **8a** (%)	Conversion of Triflone **6a** (%)
1	80	HFIP (2.0 mmol)	68	100
2	80	HFIP (1.0 mmol)	78	100
3	**80**	**HFIP (0.40 mmol)**	**93**	**100**
4	66	No HFIP	41	80
5	80	CF_3CH_2OH (0.40 mmol)	49	90
6	80	*tert*-C_4F_9OH (0.40 mmol)	32	100
7	80	HFIP (0.40 mmol)[b]	0	5

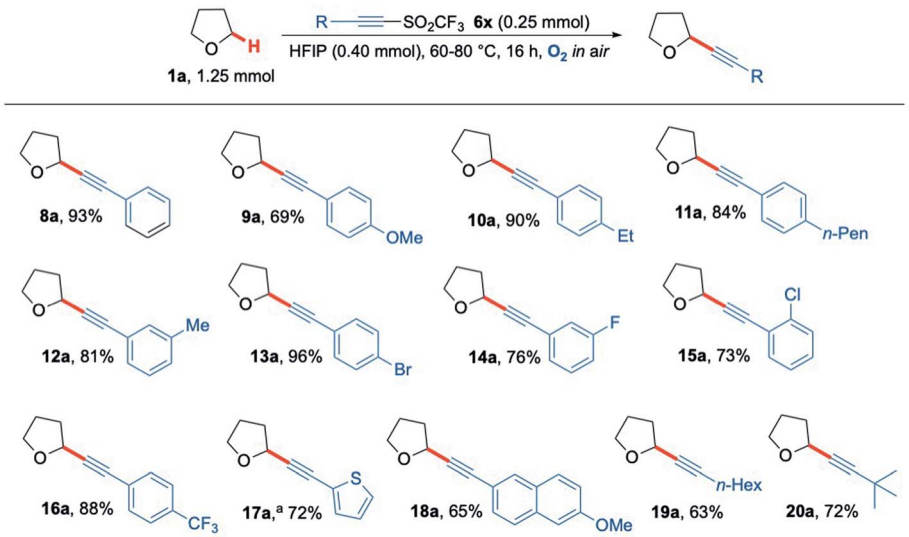
[a] See ESI for full optimisation table (Table S1). [b] Under argon.



Scheme 4 Substrate scope for the reaction of a range of heterocyclic and straight chain ether moieties with alkyne **6a**, using the optimised conditions developed in Table 1 [a] 89% yield on a gram scale. [b] 1.7 : 1:0.5 **8b** : **8c–a** : **8c–b**. [c] 3 : 1 mixture of isomers. [d] Single stereoisomer obtained. [e] 1 : 0.35 : 0.85 **8g–a** : **8g–b** : **8h**. [f] 30 h, 10 eq. THP. [g] Major diastereomer isolated, 99 : 1 dr, 48 h. [h] No HFIP, 60 °C. CPME = cyclopentyl methyl ether.

challenging 6-membered tri-acylated sugar derivative afforded product **8l** as a separable single diastereomer. Unfortunately, no reactivity was observed with *N*-Boc pyrrolidine and *N*-Boc piperidine. Although a similar BDE range is reported for these nitrogen heterocycles (377–385 kJ mol^{-1})[70] there was no evidence that they are prone to aerobic auto-oxidation under these conditions. Consistent with this observation, *N*-Ph, *N*-Ts and *N*-Bn pyrrolidines and piperidines, did not undergo reaction with triflone **6a** under the optimised reaction conditions to form any of the respective alkynylated adducts. Interestingly, the use of thioxane led to a major product where functionalisation had taken place at the sulfur α-C–H position (**8p**) whilst also giving the corresponding oxygen α-C–H functionalised regioisomer **8q**. Tetrahydrothiophene was readily converted to the acetylenic product **8r** even in the absence of HFIP; in this particular case the presence of HFIP was in fact undesirable as it was observed to promote an undesired ring-opening reaction.[19] Straight chain ethers such as diethyl ether and dimethoxyethane also proved to be compatible with the reaction conditions to afford alkynes **8s** and **8t** (respectively) in good yields. A lower temperature was required for diethyl ether due to its low boiling point; this also demonstrates that lower temperatures can still lead to efficient C–H functionalisation. Finally, using readily available CPME (cyclopentyl methyl ether) led unexpectedly to the formation of enyne **8u′**, presumably *via* elimination of methanol from the initial C–H alkynylated product.

Given the success in functionalising a range of ethereal-based species using aerobic C–H activation conditions, we next turned our attention to altering the functional groups on the acetylenic triflone. A diverse portfolio of acetylenic triflones **6b–m** were synthesised,[71] and reacted with THF under the optimised C–H functionalisation conditions (Scheme 5). A range of electron-rich aryl alkynes furnished the desired adducts **9a**, **10a**, **11a** and **12a** in excellent yields (Scheme 5). Aromatic halogen functionalities, which could serve as useful handles for further reactivity,[72] were well tolerated, yielding the THF adducts **13a**, **14a** and **15a** in 96%, 76% and 73% yield (respectively). Likewise, the medicinally relevant trifluoromethyl functional group **16a** was compatible, providing the alkynyl THF scaffold in 88% yield. Other aromatic rings such as an electron-rich thiophene and a naphthalene ring



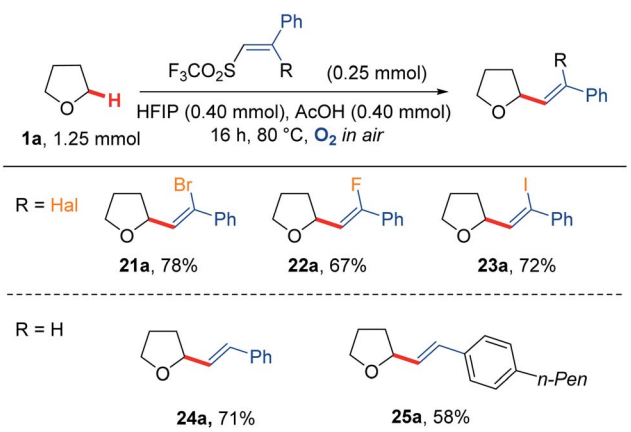
Scheme 5 Substrate scope showing a range of acetylenic THF products **8a–20a** formed *via* the aerobically generated THF radical from **1a**. [a] No HFIP and 24 h reaction time.

system were also examined, successfully affording the corresponding acetylenic products **17a** and **18a** in 72% and 65% yields respectively. Aliphatic substituents on the alkyne also proved to be compatible with the radical chain process, including both straight-chain and branched groups, giving products **19a** and **20a** in good yield (Scheme 5). Overall, the methodology proved to be wide-ranging, giving access to privileged heterocyclic and acyclic alkyne scaffolds in a simple and efficient manner.

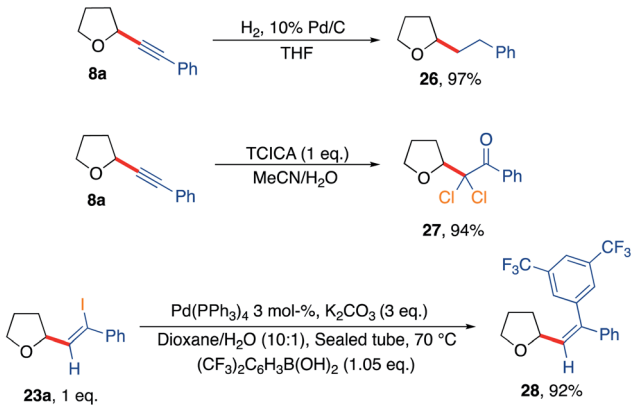
We were also able to extend the reaction scope to vinyl triflone radical acceptors (Scheme 6).[73] Using a mixture of AcOH/HFIP, which was found to improve the conversion for these reactions, good yields were observed for the formation of THF-alkene adducts **21a–25a**.[74] Use of a vinyl bromide led to a 78% isolated yield of adduct **21a**. These conditions were applied to an analogous vinyl fluoride to afford THF-alkene **22a** in 67% yield and a vinyl iodide analogue to give **23a** in 72% yield. These reactions proceeded with retention of alkene geometry. The stereochemistry was assigned based on the three-bond J_{HCCF} coupling constants for the fluoro-olefin **22a** (37 Hz), with the stereochemistry of the bromo-olefin **21a** and iodo-olefin **23a** assigned based on NOEs (see ESI† for further details). Application to simple 1,2-disubstituted vinyl triflones also yielded the respective products **24a** and **25a**, also proceeding *via* retention of vinyl triflone geometry to give the corresponding (*E*) isomers.

Further reactions of some of the alkynlated products were also explored to demonstrate their utility as versatile building blocks (Scheme 7). For example, hydrogenation of product **8a** afforded the corresponding straight chain alkane **26**. Reaction of the acetylenic THF **8a** with trichloroisocyanuric acid generated dichlorinated ketone **27** outlining the formation of a novel halogenated building block in a high yielding reaction (94%).[75] Finally, a Suzuki coupling of THF-iodoalkene derivative **23a** using 3,5-bis(trifluoromethyl)phenylboronic acid gave the corresponding coupled vinyl THF product **28** in an excellent yield of 92%.

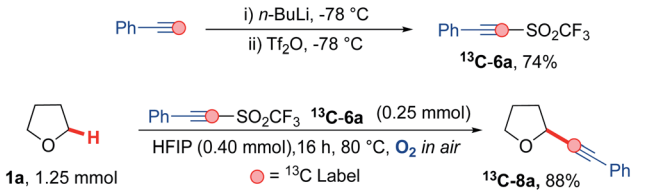
To better understand the reaction of THF with acetylenic triflone **6a**, mechanistic studies were conducted. A proposed mechanism showing two possible routes for the formation of the alkynyl THF **8a** is shown below (Scheme 8); it was hypothesised there would likely be two routes to form **8a**. Pathway A proceeds by α-addition of the THF radical **1a′** to alkyne **6a** to afford vinyl radical **29**, followed by β-elimination to generate desired product **8a**. This also leads to fragmentation of the trifluoromethylsulfonyl radical **30** to sulfur dioxide and the highly reactive trifluoromethyl radical, which can further propagate the chain reaction by abstracting an α-C–H proton of another molecule of THF **1a**. Pathway B (Scheme 8) involves initial β-addition of the THF radical **1a′** to form α-trifluoromethylsulfonyl vinyl radical **31**, which can then fragment to a vinylidene carbene species **32** and the trifluoromethylsulfonyl radical **30**. Vinylidene carbene **32** can



Scheme 6 Reactivity of vinyl triflones under aerobic conditions to give the corresponding vinyl THF scaffolds **21a–25a**.



Scheme 7 Further diversification of the synthesised products highlighting further utility of the developed aerobic C–H activation protocol.



Scheme 9 Mechanistic study involving ^{13}C labelled phenyl acetylenic triflone ^{13}C-**6a** under the optimised reaction conditions.

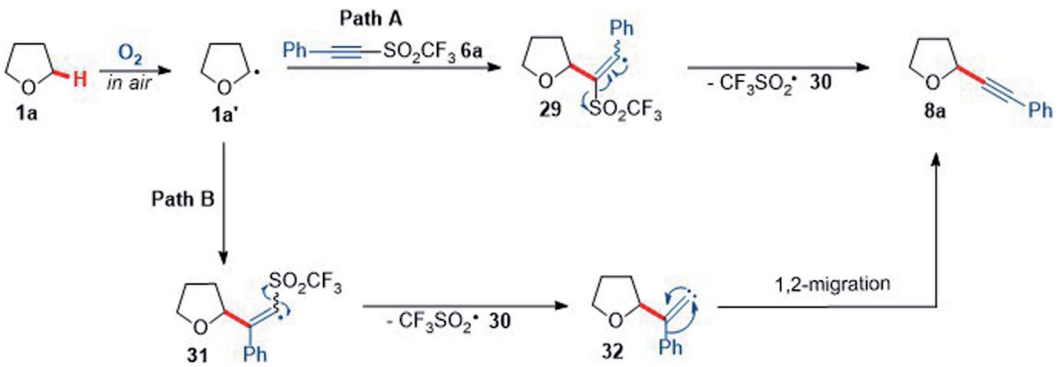
then undergo a Fritch-Buttenberg-Weichell type 1,2-rearrangement to give the acetylenic product **8a**.[76]

Carbon-13 labelling studies were used to distinguish between these two pathways *via* reaction of triflone ^{13}C-**6a** with THF **1a** (Scheme 9). Triflone ^{13}C-**6a** was prepared from phenylacetylene-2-^{13}C using the standard conditions used to form the triflone analogues. Selectively ^{13}C labelled triflone ^{13}C-**6a** was reacted with THF **1a** under the reaction conditions to afford ^{13}C-**8a**. The presence of the ^{13}C label at the alpha position on the acetylenic product ^{13}C-**8a** (highlighted in red) indicated that the reaction is highly likely to proceed *via* pathway A, where alpha addition of the THF radical **1a**′ onto phenyl acetylenic triflone **6a** affords the corresponding vinyl triflone radical **29**. The presence of the ^{13}C label was confirmed *via* an intense ^{13}C peak in the acetylenic position (89.2 ppm, see ESI†) and the corresponding ^{13}C couplings.

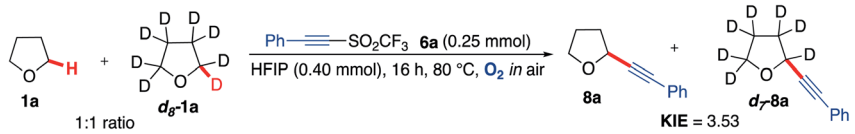
To gain further insight into the mechanism, a kinetic isotope effect (KIE) experiment was also performed. Treatment of phenyl acetylenic triflone with a mixture of THF and THF-d_8 provided both products **8a** and d_7-**8a** (Scheme 10). A K_H/K_D value of 3.53 was determined *via* liquid chromatography-mass spectrometry (LCMS) analysis (see ESI† for further details). This indicates that breakage of the initial α-C–H proton of THF is likely involved in the turnover limiting step, with a much faster reaction possible with the C–H bond than with a C–D bond.

The radical nature of the reaction was confirmed with the use of the radical trap TEMPO (2,2,6,6-(tetramethylpiperidin-1-yl)oxyl). THF **1a** was reacted with acetylenic triflone **6a** in the presence of an equivalent amount of TEMPO (0.25 mmol) at 80 °C. No product **8a** was formed under these conditions (Scheme 11) and the presence of THF-TEMPO adduct **33** was detected *via* LCMS analysis (see ESI† for further details).

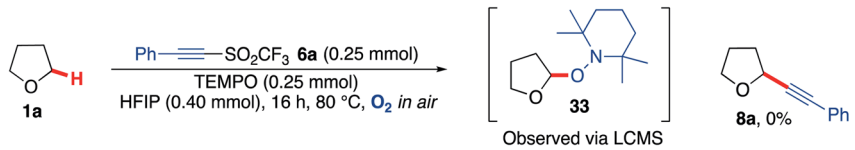
In conclusion, we have developed a method for direct aerobic C–H activation of a variety of heterocycles and ethers with subsequent C–C bond formation, by using alkenyl and alkynyl triflones as radical acceptors. This methodology represents one of the first examples of controlled metal/initiator free aerobic C–C bond formation from saturated heterocycles, and provides a breakthrough in aerobic C(sp^3)–H activation methods for the formation of privileged C(sp^3)–C(sp) and C(sp^3)–C(sp^2) bonds. A broad range of ethers, as well as some thioethers, were functionalised with a diverse range of alkynyl and alkenyl triflones with good functional group tolerance being observed. We provide mechanistic evidence for the aerobic radical pathway, involving regioselective addition of the radical to the α-position of the acetylenic triflone. Overall, we believe that the protocols we disclose in the manuscript provide a fundamental advancement in the C–H activation field, where the use of air represents a green, sustainable and freely accessible C–H bond oxidant to be utilised in synthesis.



Scheme 8 Two proposed mechanistic pathways for the reaction of THF **1a** and phenyl acetylenic triflone **6a**.



Scheme 10 Calculation of a KIE *via* reaction of THF and THF-d_8 with triflone **6a**.



Scheme 11 Radical trapping of THF **1a** by TEMPO in the presence of triflone **6a**, forming **33** *in situ*, which was detected *via* LCMS.

Data availability

All experimental and characterisation data in this article are available in the ESI.†

Author contributions

N. A., T. D. S. and V. C. conceived and designed the project; N. A. performed the synthesis experiments and R. J. S. performed the LCMS experiments. All authors analysed the data; N. A., T. D. S. and V. C. co-wrote the paper.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

The authors gratefully acknowledge the UCL Graduate School for funding N. A., and we also gratefully acknowledge the Leverhulme Trust for funding R. J. S. (RPG-2020-010). The authors also acknowledge the UCL NMR facility (Dr A. Aliev) and EPSRC funding for a 700 MHz NMR spectrometer (EP/P020410/1) and the UCL Chemistry Mass Spectrometry Facility (Dr K. Karu).

References

1 C. M. Marson, *Adv. Heterocycl. Chem.*, 2017, **121**, 13–33.
2 E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274.
3 R. D. Taylor, M. MacCoss and A. D. G. Lawson, *J. Med. Chem.*, 2014, **57**, 5845–5859.
4 L. Qili, H. Dipesh, C. Yongseok and L. Kyeong, *Molecules*, 2019, **24**, 3778–3800.
5 M. Saleem, H. J. Kim, M. Ali and Y. S. Lee, *Nat. Prod. Rep.*, 2005, **22**, 696–716.
6 M. J. Waring, J. Arrowsmith, A. R. Leach, P. D. Leeson, S. Mandrell, R. M. Owen, G. Pairaudeau, W. D. Pennie, S. D. Pickett, J. Wang, O. Wallace and A. Weir, *Nat. Rev. Drug Discov.*, 2015, **14**, 475–486.
7 F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.
8 K. Hirata, M. Kotoku, N. Seki, T. Maeba, K. Maeda, S. Hirashima, T. Sakai, S. Obika, A. Hori, Y. Hase, T. Yamaguchi, Y. Katsuda, T. Hata, N. Miyagawa, K. Arita, Y. Nomura, K. Asahina, Y. Aratsu, M. Kamada, T. Adachi, M. Noguchi, S. Doi, P. Crowe, E. Bradley, R. Steensma, H. Tao, M. Fenn, R. Babine, X. Li, S. Thacher, H. Hashimoto and M. Shiozaki, *ACS Med. Chem. Lett.*, 2016, **7**, 23–27.
9 C. Sambiagio, D. Schönbauer, R. Blieck, T. Dao-Huy, G. Pototschnig, P. Schaaf, T. Wiesinger, M. F. Zia, J. Wencel-Delord, T. Besset, B. U. W. Maes and M. Schnürch, *Chem. Soc. Rev.*, 2018, **47**, 6603–6743.
10 M. Zhang, Y. Zhang, X. Jie, H. Zhao, G. Li and W. Su, *Org. Chem. Front.*, 2014, **1**, 843–895.
11 R. Giri, B. F. Shi, K. M. Engle, N. Maugel and J. Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242–3272.
12 D. Basu, S. Kumar, S. Sudhir and R. Bandichhor, *Chem. Sci.*, 2018, **130**, 71–82.
13 B. C. Gilbert and A. F. Parsons, *J. Chem. Soc., Perkin Trans. 2*, 2002, 367–387.
14 M. C. Bryan, P. J. Dunn, D. Entwistle, F. Gallou, S. G. Koenig, J. D. Hayler, M. R. Hickey, S. Hughes, M. E. Kopach, G. Moine, P. Richardson, F. Roschangar, A. Steven and F. J. Weiberth, *Green Chem.*, 2018, **20**, 5082–5103.
15 Y. Xiang, C. Wang, Q. Ding and Y. Peng, *Adv. Synth. Catal.*, 2019, **361**, 919–944.
16 S. P. Green, K. M. Wheelhouse, A. D. Payne, J. P. Hallett, P. W. Miller and J. A. Bull, *Org. Process Res. Dev.*, 2020, **24**, 67–84.
17 R. Höfer and J. Bigorra, *Green Chem.*, 2007, **9**, 203–212.
18 T. Zhang, Y. H. Wu, N. X. Wang and Y. Xing, *Synthesis*, 2019, 4531–4548.
19 E. Voutyritsa, M. Garreau, M. G. Kokotou, I. Triandafillidi, J. Waer and C. G. Kokotos, *Chem.–Eur. J.*, 2020, **26**, 14453–14460.
20 G. N. Papadopoulos, M. G. Kokotou, N. Spilipoulou, N. F. Nikitas, E. Voutyritsa, D. I. Tzaras, N. Kaplaneris and C. G. Kokotos, *ChemSusChem*, 2020, **13**, 5934–5944.

21 N. Spiliopoulou, P. L. Gkizis, I. Triandafillidi, N. F. Nikitas, C. S. Batsika, A. Bisticha and C. G. Kokotos, *Chem.–Eur. J.*, 2022, **28**, e20220023.
22 D. Liu, C. Liu, H. Li and A. Lei, *Chem. Commun.*, 2014, **50**, 3623–3626.
23 A. Solvhoj, A. Ahlburg and R. Madsen, *Chem.–Eur. J.*, 2015, 16272–16279.
24 Z. Cui, X. Shang, X. F. Shao and Z. Q. Liu, *Chem. Sci.*, 2012, **3**, 2853–2858.
25 J. Zhao, H. Fang, W. Zhou, J. Han and Y. Pan, *J. Org. Chem.*, 2014, **79**, 3847–3855.
26 D. Hager and D. W. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 16986–16989.
27 A. Maruani, M. T. W. Lee, G. Watkins, A. R. Akhbar, H. Baggs, A. Shamsabadi, D. A. Richards and V. Chudasama, *RSC Adv.*, 2016, **6**, 3372–3376.
28 V. Chudasama, *RSC Adv.*, 2015, **5**, 44423–44426.
29 A. Shamsabadi, A. Maruani, N. Ahmed and V. Chudasama, *Org. Biomol. Chem.*, 2020, **18**, 6258–6264.
30 A. Shamsabadi and V. Chudasama, *Org. Biomol. Chem.*, 2019, **17**, 2865–2872.
31 A. K. Ghosh and D. D. Anderson, *Future Med. Chem.*, 2011, **3**, 1181–1197.
32 S. Di Tommaso, P. Rotureau, B. Sirjean, R. Fournet, W. Benaissa, P. Gruez and C. Adamo, *Process Saf. Prog.*, 2014, **33**, 64–69.
33 S. Di Tommaso, P. Rotureau, O. Crescenzi and C. Adamo, *Phys. Chem. Chem. Phys.*, 2011, **13**, 14636–14645.
34 H. Matsubara, S. Suzuki and S. Hirano, *Org. Biomol. Chem.*, 2015, **13**, 4686–4692.
35 A. Sagadevan, K. C. Hwang and M. Su, *Nat. Commun.*, 2017, **8**, 1812.
36 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451–3479.
37 U. Wille, *Chem. Rev.*, 2013, **113**, 813–853.
38 G. Zheng, Y. Li, J. Han, T. Xiong and Q. Zhang, *Nat. Commun.*, 2015, **6**, 7011–7019.
39 G. Fang and X. Bi, *Chem. Soc. Rev.*, 2015, **44**, 8124–8173.
40 R. Dorel and A. M. Enchavarren, *Chem. Rev.*, 2015, **17**, 9028–9072.
41 V. P. Boyarskiy, D. S. Ryabukhin, N. A. Bokach and A. V. Vasilyev, *Chem. Rev.*, 2016, **116**, 5894–5986.
42 R. Chinchilla and C. Nájera, *Chem. Rev.*, 2014, **114**, 1783–1826.
43 M. Wan, Z. Meng, H. Lou and L. Liu, *Angew. Chem., Int. Ed.*, 2014, **53**, 13845–13849.
44 J. Gong and P. L. Fuchs, *J. Am. Chem. Soc.*, 1996, **118**, 4486–4487.
45 J. Zhang, P. Li and L. Wang, *Org. Biomol. Chem.*, 2014, **12**, 2969–2978.
46 Q. Zhou, W. Guo, W. Ding, X. Wu, X. Chen, L. Q. Lu and W. J. Xiao, *Angew. Chem., Int. Ed.*, 2015, **54**, 11196–11199.
47 L. Capaldo and D. Ravelli, *Org. Lett.*, 2021, **23**, 2243–2247.
48 R. Zhang, L. Y. Xi, L. Zhang, S. Liang, S. Y. Chen and X. Q. Yu, *RSC Adv.*, 2014, **4**, 54349–54353.
49 Y. Yang, H. Huang, X. Zhang, W. Zeng and Y. Liang, *Synthesis*, 2013, 3137–3146.
50 K. Glaser, M. Sung, K. O'Neill, M. Belfast, D. Hartman, R. Carlson, A. Kreft, D. Kubrak, C. Hsiao and B. Weichman, *Eur. J. Pharmacol.*, 1995, **281**, 107–111.
51 E. H. F. Wong, M. S. Sonders, S. G. Amara, P. M. Tinholt, M. F. P. Piercey, W. P. Hoffman, D. K. Hyslop, S. Franklin, R. D. Porsolt, A. Bonsignori, N. Carfagna and R. A. McArthur, *Biol. Psychiatr.*, 2000, **47**, 818–829.
52 A. Jardin, H. Bensadoun, M. C. D. Cavallier, P. Attatli and BPH-ALF group, *Lancet*, 1991, **337**, 1457–1461.
53 K. Kafuta, C. J. Rugen, T. Heilmann, T. Liu, C. Golz and M. Alcarazo, *Eur. J. Org. Chem.*, 2021, 4038–4048.
54 X. Xie, L. Wang and M. Wang, *Eur. J. Org. Chem.*, 2020, 1534–1538.
55 E. A. Merritt and B. Olofsson, *Eur. J. Org. Chem.*, 2011, 3690–3694.
56 J. Waser, *Synlett*, 2016, 2761–2773.
57 A. Roy, M. K. Das, S. Chaudhuri and A. Bisai, *J. Org. Chem.*, 2018, **83**, 403–421.
58 Initially, the compatibility of HFIP and acetylenic triflone **6a** alone was explored by stirring and heating acceptor **6a** in HFIP at varying temperatures over 16 h. No notable degradation of the triflone was observed (maximum of 5% at 80 °C), but increasing the temperature did appear to result in more degradation.
59 I. Colomer, A. E. R. Chamberlain, M. B. Haughey and T. J. Donohoe, *Nat. Rev. Chem.*, 2017, **1**, 88.
60 W. J. Middleton and R. V. Lindsey, *J. Am. Chem. Soc.*, 1964, **86**, 4948–4952.
61 C. Qi, G. Force, V. Gandon and D. Leboeuf, *Angew. Chem., Int. Ed.*, 2021, **60**, 946–953.
62 I. Triandafillidi, N. F. Nikitas, P. L. Gkizis, N. Spiliopoulou and C. G. Kokotos, *ChemSusChem*, 2022, **15**, e202102441.
63 D. E. Clark, *Chem. Health Saf.*, 2001, **8**, 12–22.
64 H. Guyon, H. Chachignon and D. Cahard, *Beilstein J. Org. Chem.*, 2017, **13**, 2764–2799.
65 P. Gray, A. A. Herod and A. Jones, *Chem. Rev.*, 1971, **71**, 247–294.
66 X. Liu, Q. Zhang, S. Ito and Y. Wada, *Fuel*, 2016, **165**, 513–525.
67 I. Auzmendi-Murua and J. W. Bozzelli, *J. Phys. Chem. A*, 2014, **118**, 3147–3167.
68 V. E. Tumanov, E. A. Kromkin and E. T. Denisov, *Russ. Chem. Bull. Int. Ed.*, 2002, **51**, 1641–1650.
69 J. A. Howard and K. U. Ingold, *Can. J. Chem.*, 1969, **47**, 3809–3815.
70 D. D. M. Wayner, K. B. Clark, A. Rauk, D. Yu and D. A. Armstrong, *J. Am. Chem. Soc.*, 1997, **119**, 8925–8932.
71 T. O. P. Hayes, B. Slater, R. A. J. Horan, M. Radigois and J. D. Wilden, *Org. Biomol. Chem.*, 2017, **15**, 9895–9902.
72 S. E. Denmark, R. C. Smith, W. T. Chang and J. M. Muhuhi, *J. Am. Chem. Soc.*, 2009, **131**, 3104–3118.
73 J. S. Xiang, A. Mahadevan and P. L. Fuchs, *J. Am. Chem. Soc.*, 1996, **118**, 4284–4290.
74 T. Bhattacharya, A. Ghosh and D. Maiti, *Chem. Sci.*, 2021, **12**, 3857–3870.
75 J. M. D'Oyley, A. E. Aliev and T. D. Sheppard, *Angew. Chem., Int. Ed.*, 2014, **53**, 10747–10750.
76 P. Fritsch, *Justus Liebigs Ann. Chem.*, 1894, **279**, 319–323.