Photoexcited Nitroarenes as Ozone Surrogates for the Oxidative Cleavage of Olefins

Daniele Leonori (daniele.leonori@rwth-aachen.de)
RWTH Aachen University https://orcid.org/0000-0002-7692-4504
Alessandro Ruffoni
RWTH Aachen University
Charlotte Hampton
University of Manchester
Marco Simonetti
University of Manchester

Physical Sciences - Article

Keywords:

Posted Date: May 4th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1590024/v1

Version of Record: A version of this preprint was published at Nature on August 23rd, 2022. See the published version at https://doi.org/10.1038/s41586-022-05211-0.

Photoexcited Nitroarenes as Ozone Surrogates for the Oxidative Cleavage of Olefins

Alessandro Ruffoni[1,2], Charlotte Hampton[1,2], Marco Simonetti[1,*] and Daniele Leonori[1,3,*]

[1]*Department of Chemistry, University of Manchester, Manchester M13 9PL, UK*

[2]*These authors contributed equally*

[3]*Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, Aachen, 52056, Germany*

The oxidative cleavage of olefins is an integral process that converts feedstocks into high-value synthetic intermediates[1,2,3]. The most viable method to oxidatively cleave C–Cπ bonds in one chemical step is with ozone[4,5,6,7], which however poses technical and safety challenges owing to the explosive nature of ozonolysis products[8,9]. Herein, we present a distinct approach to achieve oxidative cleavage of olefins using nitroarenes and purple light irradiation. We demonstrate that photoexcited nitroarenes are effective ozone surrogates that undergo facile radical [3+2] cycloaddition with olefins. The resulting "*N*-doped" ozonide cycloadducts are safe to handle and lead to the corresponding carbonyl products under mild hydrolytic conditions. These features have enabled the controlled cleavage of all types of olefins in the presence of a broad array of commonly used organic functionalities. Furthermore, by harnessing electronic, steric, and mediated polar effects, the structural and functional diversity of nitroarenes has provided a modular platform to obtain site-selectivity in substrates containing more than one olefin.

Olefins are feedstock materials harvested on ton-scale from petroleum and vegetable biomass routinely exploited by the bulk chemical industry to access oxygen-enriched synthetic intermediates[1,2,3]. Ozonolysis is a widely adopted method to achieve this and requires a specialised apparatus for the conversion of molecular oxygen (O_2) into highly reactive ozone (O_3)[6,7]. This species undergoes a [1,3] dipolar cycloaddition with the olefin converting a stable chemical into a high-energy 1,2,3-ozonide **A** from which cycloreversion is immediate. The consequent C–C σ-bond cleavage event generates carbonyl oxide **B** and carbonyl compound **C** which recombine to give 1,2,4-ozonide **D**. Depending on reaction solvent and work-up procedure, **B** or **D** can lead to aldehydes/ketones as well as carboxylic acids or alcohols[4,5] (Fig. 1a).

Despite its attractive synthetic versatility, ozone toxicity (lethal at 5 ppm), explosivity, and extreme oxidising power (E_0 = 2.07 V) raise critical safety, technical, and chemical concerns[8,9]. As a result, ozonolytic strategies are often challenging to translate into the fine chemical industry[10,11,12], particularly in the discovery sector which heavily relies on parallel and high-throughput screening platforms[13]. Consequently, alternative strategies for olefin oxidation based on high-valent heavy-metal oxides have been devised. However, these approaches can yield mixtures of products of various oxidation degrees, and cause trace metal contaminations

that are problematic with the stringent pharmaceutical sector regulations[14,15]. Oxidative cleavages using O_2 and a suitable (photo)catalyst have also been developed, but they are limited to activated olefins[16,17].

Overall, there is no other type of reactivity able to mirror the unique ability of ozone to cleave olefins. Herein, we introduce nitroarenes, a class of abundant feedstocks, as photoexcitable and easy-to-dose ozone surrogates. Upon simple purple light absorption, these species react with olefins enabling access to "*N*-doped" ozonides, which can be accumulated until a controlled C–C bond cleavage step takes place. This reactivity engages a large class of olefins, is tolerant of the most used organic functionalities, and allows the targeting of specific double bonds in molecules possessing multiple C–Cπ sites.

In approaching the design of an alternative method to oxidatively cleave olefins, we were intrigued by the possibility of using nitroarenes **N** as ozone surrogates and access 1,3,2-dioxazolidines **E** (Fig. 1b). Despite the nitro group being isoelectronic with ozone, nitroarenes do not engage in thermal [1,3] dipolar cycloadditions with olefins due to high kinetic barriers[18,19]. Pioneering works from Büchi[20] and De Mayo[21] indicated an opportunity to by-pass these challenging pericyclic processes through direct nitroarene photoexcitation. As such, intersystem crossing (ISC) from the singlet excited nitroarene delivers the long-lived triplet state (T_1) ***N**. In analogy to T_1-carbonyls, ***N** have n,π* configuration which translates into O-radical-type reactivity. ***N** can intercept olefins and, via the formation of biradical **F**, deliver "*N*-doped" ozonides **E**. However, this chemistry necessitated high-energy irradiation, utilised the olefin as the solvent, and the mechanism by which **E** evolves into the C–C cleavage products and defines their subsequent fate was unsolved[20,21,22,23]. These rather unpractical reactivity requirements and limited understanding have resulted in no synthetic application.

We envisaged that by tailoring the nature of the nitroarene we would have been able to translate this reactivity over the broad spectrum of olefins, including challenging terminal substrates, and run it in a stoichiometric manner, which is crucial for synthetic purposes. Furthermore, understanding and thereby controlling the decomposition of **E** would be pivotal to channel its reactivity toward olefin cleavage.

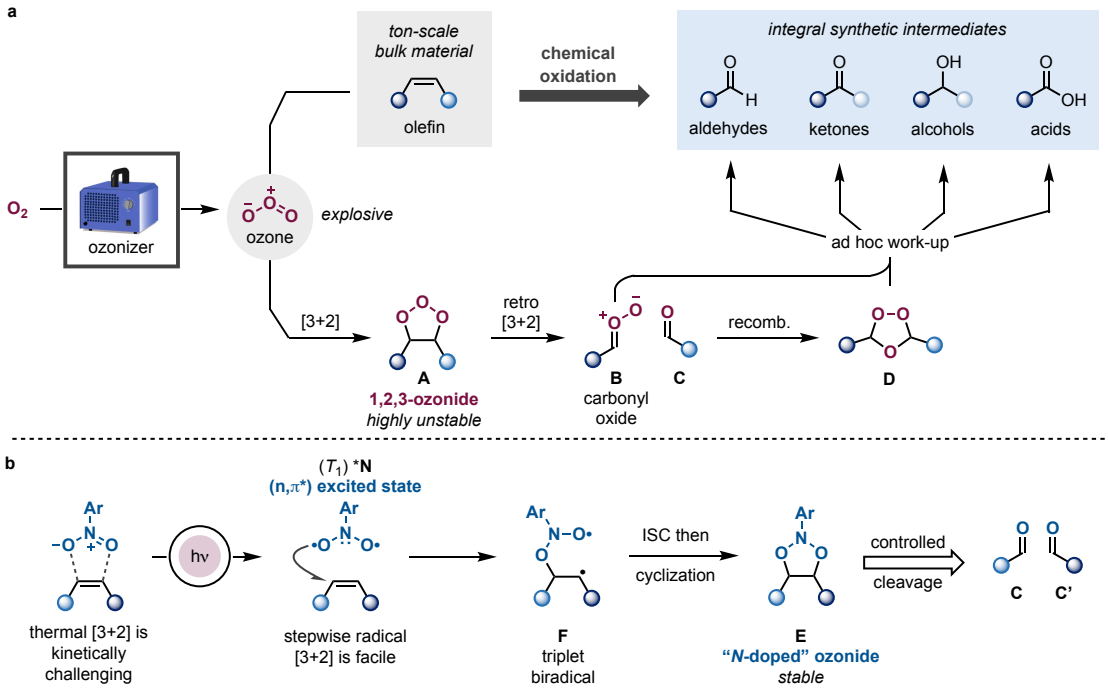

Fig. 1. Excited nitroarenes as ozone surrogates. a, Ozonolysis for the oxidative cleavage of olefins. **b**, Mechanism for the formation of **E**. Ar = aryl.

We started our investigation evaluating the initial rates of disappearance of **1** (k_{obs}) in photocycloaddition reactions (purple LEDs irradiation, λ = 390 nm[24,25]) with a variety of electronically diverse *meta* and/or *para* (di)substituted nitroarenes **N** to give stable bisadamantene-containing[22] **E** (Fig. 2a). The resulting Hammett plot[26] showed a strong linear free-energy relationship between the electronic character of the nitroarene and k_{obs} (ρ = 0.82). This means the reactivity profile of nitroarenes as photo-responsive oxidants can be easily tuned by correct placement of electron-withdrawing groups on their aromatic core that amplify the electrophilic character of their excited states. *ortho*-Substituted **N** were less effective suggesting that steric hindrance can also influences their reactivity (see Supplementary Information).

We then evaluated the reaction of unactivated **2**, which is a challenging type of olefin in this chemistry. Pleasingly, irradiation of **2** with commercial **N1** resulted in the high-yielding formation of **E1** (Fig. 2b). In contrast to the explosive nature of **A**, "*N*-doped"-ozonides could be accumulated in solution at –30 ºC and are stable in the solid state (see Supplementary Information).

Subsequently, we set out to understand how to convert **E** into the corresponding carbonyl compounds **C** and **C'** (Fig. 2c). We speculated that two pathways might be operating: an ozonolysis-type cycloreversion would deliver **C** and carbonyl imine **G** (*path a*) or a different cycloreversion-mode could directly lead to **C**/**C'** and nitrene **I** (*path b*). To shed light on this, we prepared **E2** which features an *ortho* 3,5-dimethylpyrazole group as a probe for nitrene formation[27,28]. Simple exposure of **E2** to CH_3CN–H_2O led to the almost quantitative formation

of ketone **3** and *N*-arylhydroxylamine **H1**. Conversely, in anhydrous CH_3CN **E2** yielded **3** in 98% and **4** in 97%, whose structure was confirmed by X-ray analysis. As **4** is indicative of a [1,3] dipolar cycloaddition between **G1** and CH_3CN, these experiments rule out the intermediacy of nitrenes and demonstrate that **E** undergoes an ozonolysis-type cycloreversion generating **C** and **G** which, with H_2O, is hydrolysed to **C'** and **H**. Although the generation of **G** was postulated by Büchi[20], its existence has not been demonstrated before. Related dipoles have been engaged in 1,3-dipolar cycloadditions only two times since Husgein's initial prediction[29,30], but never with nitrile dipolarophiles.

Next, we studied the decomposition of **E1** in $CH_3CN–H_2{}^{18}O$ (Fig. 2d) which gave **5** in 93% yield and 92% ^{18}O-incorporation, along with **H2** (20%), azoxy derivative **K1** (3%), and nitrone **J1** (condensation of **H2** with formalin **6**, 61%). **K1** stems from disproportionation of **H2** (see Supplementary Information). This experiment demonstrates that the cycloreversion of **E1** generates **6** and the more stabilised dipole **G**, which is then hydrolysed. However, when decomposition of **E3** was evaluated in $CH_3CN–H_2O$, **7** was obtained in a decreased 71% yield, likely via the in-situ formation of nitrone **J**. Indeed, when decomposition of **E3** was run with external formalin, **7** was obtained in 95% yield (see Supplementary Information). Despite the decomposition step being very effective, the equilibrium in the condensation between **H** and **C**/**C**', and subsequent side reactions[31], rendered the purification of the aldehydes products challenging. Thus, we developed two simple one-pot work-up procedures to remove **H** by addition of either K_2HPO_4 and urea (conversion of **H** into **K**) or *N*-phenylmaleimide (conversion of nitrones like **J1** into **L**), which eased the purification of the aldehydes (Fig. 4e, see Supplementary Information).

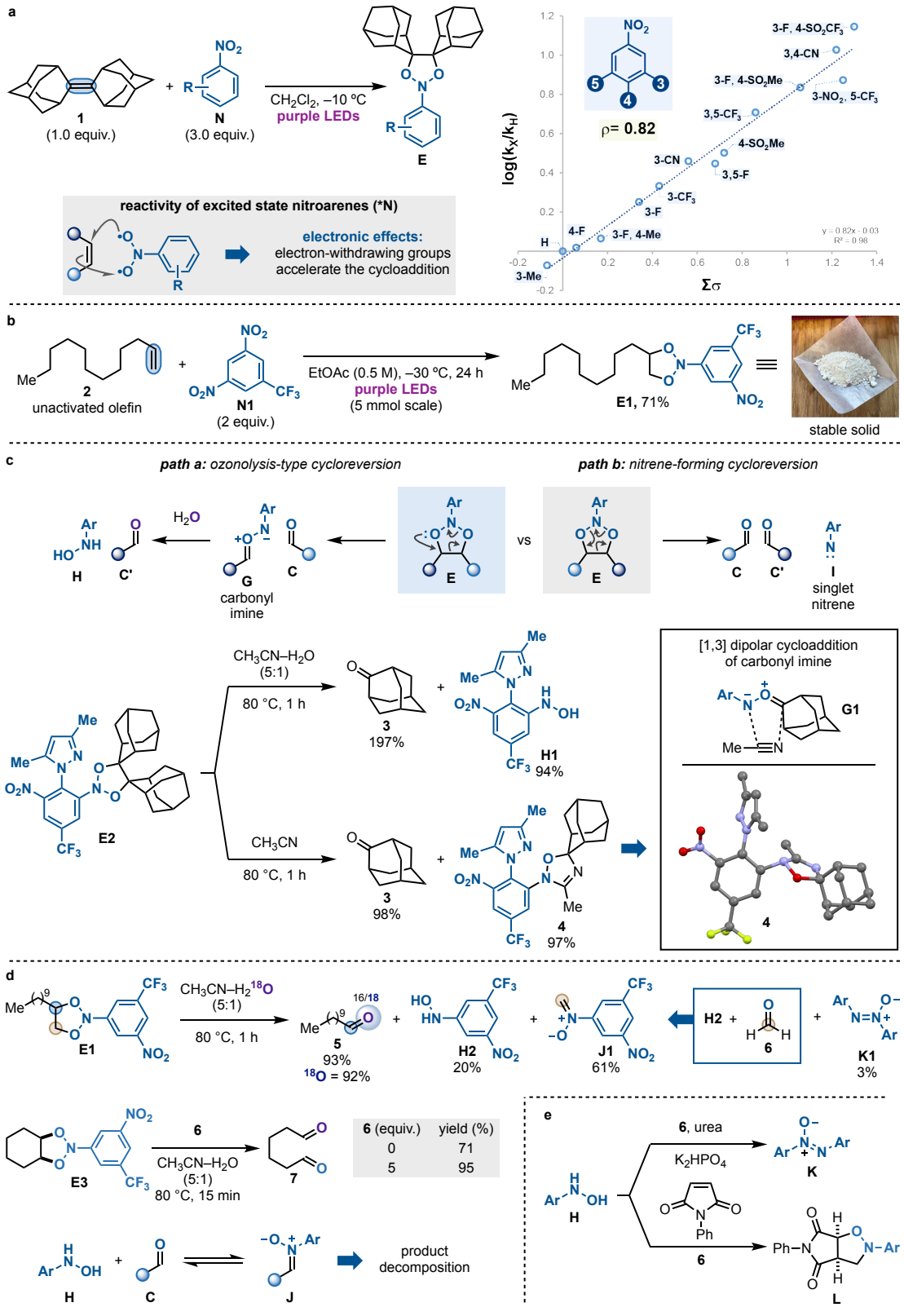

Fig. 2. Mechanistic experiments. **a**, Hammett plot analysis. **b**, Preparation of **E1**. **c**, Mechanism for the decomposition of **E** and the role of H_2O. **d**, ^{18}O-labelling experiments and the role of **6**. **e**, Methods for the removal of **H**.

Having devised conditions to accumulate and decompose "*N*-doped" ozonides, we decided to benchmark the synthetic utility of the process. While **N1** was able to engage all substrates present in Fig. 3, other nitroarenes (**N2–7**) were evaluated to improve the yield depending on the olefin. We believe this is a powerful aspect of this reactivity as functionalised nitroarenes are readily available and dosable reagents that can be evaluated in screening platforms. Exploration began with linear terminal olefins **2**, **8**–**32** equipped with a distal functionality R. Pleasingly, several commonly encountered organic functionalities like nitrile (**8**), aldehyde (**9**), ketone (**10**), carboxylic acid (**11**), halogens (**12**–**15**), free (**16**) and protected amines (**17**–**20**), azide (**21**), nitro group (**22**), free (**23** also on 5 mmol scale, **27**) and protected alcohols (**24**, **25**), epoxide (**26**), thiocyanate (**28**), thioethers (**29**, **30**), phosphonate (**31**), and boronic ester (**32**) proved compatible giving the corresponding aldehydes in high yields. In some cases, we found the use of CH_2Cl_2 solvent with hexafluoroisopropanol (HFIP) as the additive to be crucial to ensure good reactivity. Since ***N** can abstract hydridic α-N/O/S C(sp^3)–H bonds[32,33], the inclusion of HFIP suppressed this unwanted process by H-bonding to the heteroatom[34] (see Supplementary Information). In the case of amines, simple protonation was required to insulate the substrate from detrimental side-oxidations. Disubstituted substrates reacted well as demonstrated by the cleavage of several industrially relevant oleic acid derivatives **33**–**38** (*Z*), as well as ether *E*-**39** and cyclic systems of different size (**40**, **41**). Furthermore, both *gem*-disubstituted **42** and trisubstituted **43** were compatible. Electron-rich and -poor styrenes (**44**–**46**), (*E* and *Z*)-β-Me and α-Me-styrenes (**47**, **48** and **49**), as well as (*E* and *Z*)-stilbenes reacted smoothly (**50**, **51**). Next, we explored the cleavage of structurally complex and densely functionalised derivatives (**52**–**62**). Unactivated terminal olefins of isophytol (**52**), sclareol (**53**) and alibendol (**54**), which also features an electron rich aromatic core, could all be oxidised. The disubstituted olefins of caryophyllene oxide (**55**) and montelukast (**56**), the trisubstituted alkenes of phytol (**57**), (–)-α-cedrene (**58**), triprolidine (**59**), chlorprothixene (**60**), and lumefantrine (**61**), as well as the tetrasubstituted (*Z*)-tamoxifen **62**, were successfully engaged. Another feature of ***N** is their aptitude to act as triplet sensitisers[35] which can isomerise the olefins during photocycloaddition. Indeed, unreacted **62** was recovered as *Z*/*E* mixture.

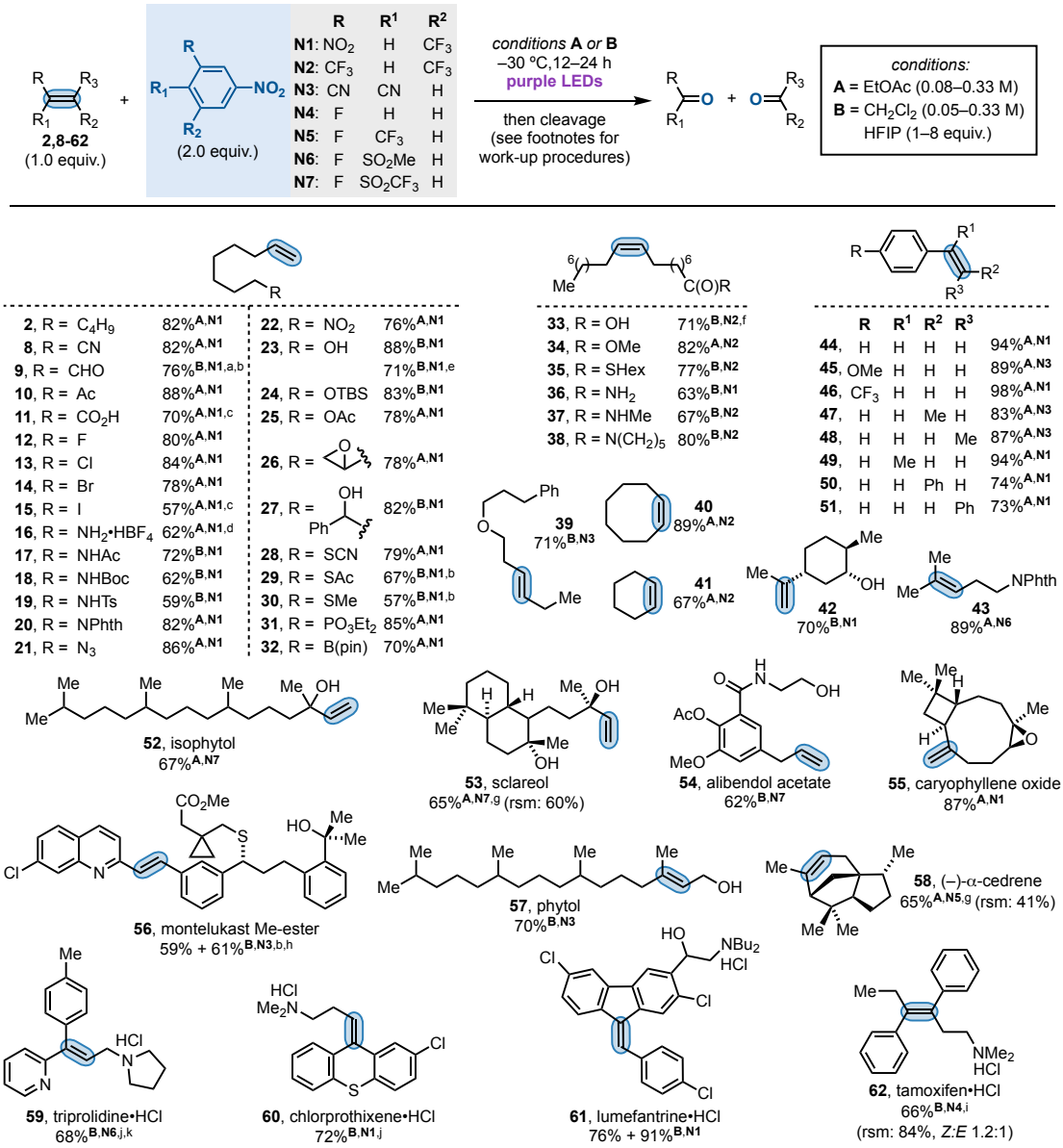

Fig. 3. Scope of the process. Bold-font footnotes A and B, and N1–N7 refer to reaction conditions and nitroarenes, respectively. If the yield of two cleaved fragments deriving from the same olefin differs, the first yield refers to the carbonyl compound with higher molecular weight. Cleavage: CH_2O (0–6 equiv.) in CH_3CN/THF:H_2O (3.1:1); work-up: K_2HPO_4 and urea or *N*-phenylmaleimide. See Supplementary Information for details. [a]Olefin with 10C linear chain. [b]Perfluoro-*tert*-butanol (PFTB) used in place of HFIP. [c]Olefin with 6C linear chain. [d]60 h. [e]5.0 mmol scale; **N1** (1.5 equiv.); 48 h. [f]2,6-Lutidine in place of HFIP. [g]Olefin (2 equiv.). [h]Another product of S oxidation to sulfoxide = 6% yield. [i]Olefin (5 equiv.). [j]Aminoaldehyde derivative not detected. [k]40 h. rsm = remaining starting material.

An often-encountered challenge in oxidative cleavage chemistry is achieving olefin selectivity in substrates containing more than one C–Cπ site. We speculated that the inherent modularity of our approach would enable chemoselective differentiation through the interplay of electronic

effects. To test this hypothesis, we prepared substrates **63**–**68** that contain two different olefins linked by an identical alkyl spacer and evaluated them in stoichiometric reactions with **N1**, **N2**, **N4**, and **N8** providing the heat-map shown in Fig. 4a. These results show that site-selectivity is a function of the electronic nature of the nitroarene and that of the two olefins. Specifically, the selectivity increases when using less electrophilic nitroarenes, and when the two olefins have substituents that make one C–Cπ bond increasingly more electron-rich than the other. This means that the reactivity of ***N**[21] parallels that of ozone and Huisgen type-III dipolar cycloadditions in general[36]. Consequently, modulation of the nitroarene electronics can be used to amplify narrow reactivity differences when substrate control is difficult to implement. Indeed, the use of **N8** and **N4** enabled the fully selective cleavage of trisubstituted alkene (**63**) and styrene (**64**) in the presence of monosubstituted olefins. Furthermore, striking discrimination was achieved between internal and terminal double bonds (**65**, 97%), tri- vs di-alkyl substituted C–Cπ sites (**66**, 87%), styrene vs an internal olefin (**67**, 85%), as well as the two highly activated alkenes of **68** (69%). Moreover, a complete selectivity for the terminal alkene of **69** was obtained even with **N1**, yielding the corresponding alkyne-containing product in 82% yield.

To demonstrate reactivity control through electronic, steric, and mediated polar effects, we evaluated several complex and bio-active molecules containing two C–Cπ sites (Fig. 4b, see Supplementary Information). (–)-Carvone **70** and fusidic acid **71** demonstrated complete regiocontrol based on electronics as olefin conjugation with carbonyl functionalities directed the reactivity toward the other alkenes. In the case of polyunsaturated steroids exemestane **72** and megestrol acetate **73** oxidative cleavage occurred at the distal, hence less deactivated, C–Cπ sites. Lynestrol **74** showcased olefin oxidation in the presence of alkynes, while allylestrenol acetate **75**, linalool **76**, and *trans*-caryophyllene **77** demonstrated the selective cleavage of trisubstituted olefins over terminal and *gem*-disubstituted ones. Geranyl acetate **78** and perillyl acetate **79** contain trisubstituted olefins with an allylic OAc group that provides weak inductive deactivation. While this enables the preferential cleavage of the other C–Cπ sites, higher selectivity was obtained adding HFIP (H-bonding with the OAc group). Analogously, the presence of the electron-withdrawing ammonium group in cyclobenzaprine **80** allowed the disubstituted stilbene-type olefin to react over the trisubstituted one. Steric control over olefin regioselectivity is likely the main factor determining the selectivity in the oxidative cleavage of bisabolol acetate **81** and valencene **82** where the least hindered acyclic olefins were oxidised despite their degree of substitution.

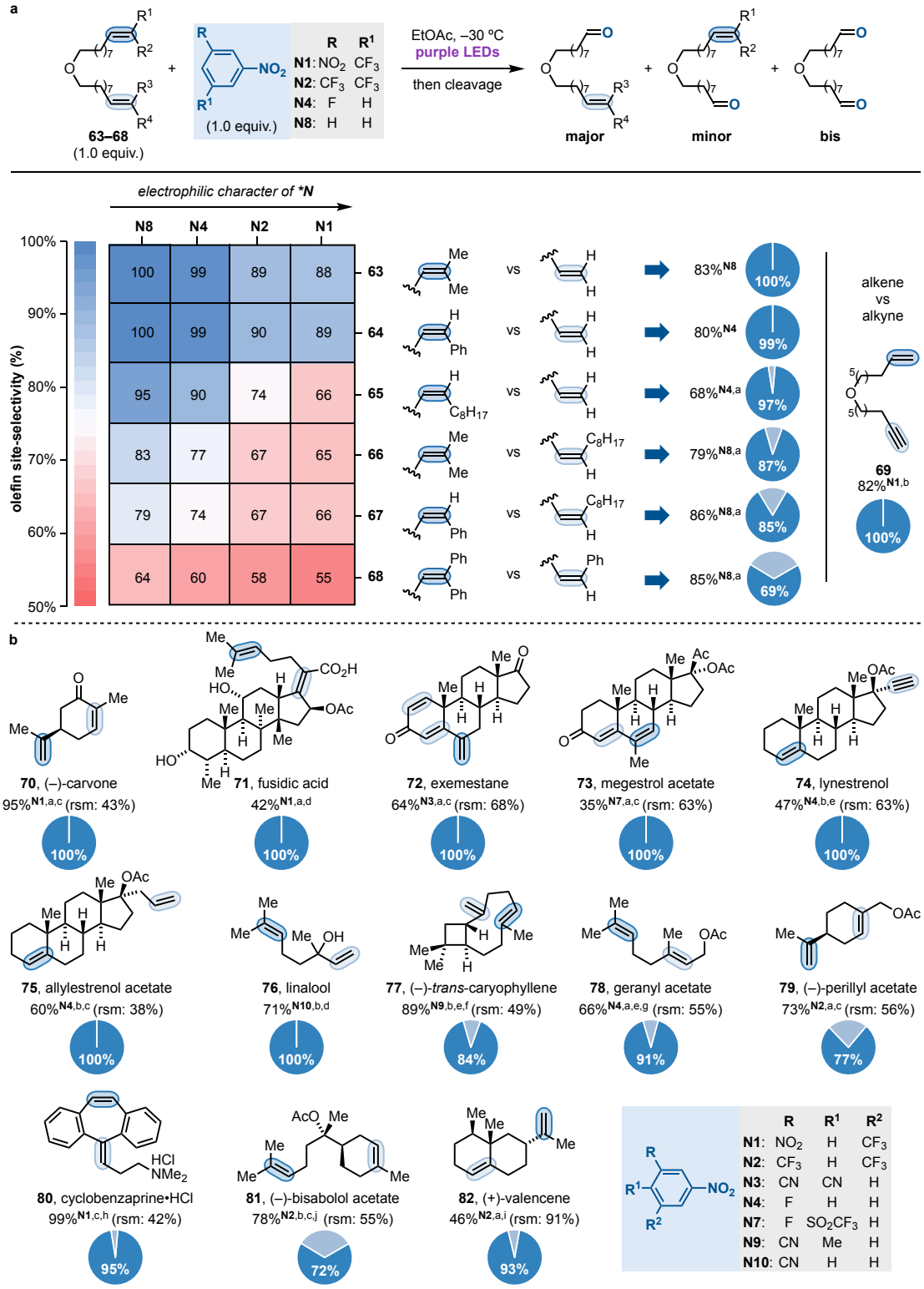

Figure 4. Achieving olefin selectivity. a, Competition experiments. Bold-font footnotes N1, N2, N4, N8 refer to nitroarenes used. Cleavage: CH_2O (0–6 equiv.) in CH_3CN/THF:H_2O (3.1:1). Selectivity determined considering **bis**. See Supplementary Information for details. [a]Olefin (2.5 equiv.). [b]**N1** (2 equiv.); CH_2Cl_2 with HFIP (1 equiv.). **b**, Complex examples. Bold-font footnotes N1–N4, N7, N9, N10 refer to nitroarenes used. [a]CH_2Cl_2 with HFIP (0.5–6 equiv.). [b]EtOAc. [c]Olefin (2 equiv.). [d]**N** (2 equiv.). [e]Olefin (3 equiv.). [f]Bis-cleaved product = 3%

yield. [g]Bis-cleaved product = 2% yield. [h]CH_2Cl_2 without HFIP. [i]Olefin (5 equiv.). [j]Bis-cleaved product = 6% yield. rsm = remaining starting material.

Owing to the striking functional group compatibility and levels of site-selectivity achievable, our findings demonstrate that nitroarenes are tuneable and easy-to-dose photo-responsive ozone surrogates, which have the premise to become a powerful and reliable tool to oxidatively cleave olefins.

Acknowledgments: D. L. thanks EPSRC for a Fellowship (EP/P004997/1) and a grant (EP/V046799/1), the European Research Council for a research grant (758427), the Leverhulme Trust for additional support (Philip Leverhulme Prize to D. L.). Dr I. J. Vitorica-Yrezabal (University of Manchester) is kindly acknowledged for solving the X-ray crystal structure of **4**.

Author contributions: M. S. and D. L. designed the project; M. S. directed the work; M. S., A. R. and C. H. performed all synthetic and mechanistic experiments. M. S. and D. L. wrote the manuscript.

Competing interests: Authors declare no competing interests.

Material & Correspondence: Dr Marco Simonetti, marco.simonetti@manchester.ac.uk and Prof Daniele Leonori, daniele.leonori@rwth-aachen.de

References.

[1] Baumann, H. et al. Natural fats and oils—renewable raw materials for the chemical industry. *Angew. Chem. Int. Ed.* **27**, 41–62 (1988).

[2] Corma, A., Iborra, S. & Velty, A. Chemical routes for the transformation of biomass into chemicals. *Chem. Rev.* **107**, 2411–2502 (2007).

[3] Köckritz, A. & Martin, A. Oxidation of unsaturated fatty acid derivatives and vegetable oils. *Eur. J. Lipid Sci. Technol.* **110**, 812–824 (2008).

[4] Bailey P. S. *Ozonization in Organic Chemistry* (Academic Press, 1978) Vol. 1.

[5] Fisher, T. J. & Dussault, P. H. Alkene ozonolysis. *Tetrahedron* **73**, 4233–4258 (2017).

[6] Surburg, H. & Panten, J. *Common Fragrance and Flavor Materials* (Wiley-VHC, 2006).

[7] Caron, S., Dugger, R. W., Ruggeri, S. G., Ragan, J. A. & Ripin, D. H. B. Large-scale oxidations in the pharmaceutical industry. *Chem. Rev.* **106**, 2943–2989 (2006).

[8] Allian, A. A New Paradigm in Oxidative Cleavage Reaction: The Use of Continuous Reactors To Enable Safe Scale Up of Ozonolysis. in *Managing Hazardous Reactions and Compounds in Process Chemistry* (eds. Pesti, J. A. & Abdel-Magid, A. F.) 353–382 (ACS, 2014).

[9] Kula, J. Safer ozonolysis reactions: a compilation of laboratory experience. *Chem. Health Saf.* **6**, 21–22 (1999).

[10] Van Ornum, S. G., Champeau, R. M. & Pariza, R. Ozonolysis applications in drug synthesis. *Chem. Rev.* **106**, 2990–3001 (2006).

[11] Gabric, A., Hodnik, Z. & Pajk, S. Oxidation of drugs during drug product development: problems and solutions. *Pharamaceutics* **14**, 325 (2000).

[12] Hoelderich, W. F. & Kollmer, F. Oxidation reactions in the synthesis of fine and intermediate chemicals using environmentally benign oxidants and the right reactor system. *Pure Appl.Chem.* **72**, 1273–1287 (2000).

[13] *High-Throughput Screening in Drug Discovery* (Wiley-VCH, 2006).

[14] Spannring, P., Bruijnincx, P. C. A., Weckhuysen, B. M. & Klein Gebbink, R. J. M. Transition metal-catalyzed oxidative double bond cleavage of simple and bio-derived alkenes and unsaturated fatty acids. *Catal. Sci. Technol.* **4**, 2182–2209 (2014).

[15] Maithani, M., Raturi, R., Sharma, P., Gupta, V. & Bansal, P. Elemental impurities in pharmaceutical products adding fuel to the fire. *Regul. Toxicol. Pharmacol.* **108**, 104435 (2019).

[16] Urgoitia, G., SanMartin, R., Herrero, M. T. & Domínguez, E. Aerobic cleavage of alkenes and alkynes into carbonyl and carboxyl compounds. *ACS Catal.* **7**, 3050–3060 (2017).

[17] Huang, Z. *et al.* Oxidative cleavage of alkenes by O_2 with a non-heme manganese catalyst. *J. Am. Chem. Soc.* **143**, 10005–10013 (2021).

[18] Ranganathan, S., Ranganathan, D., Ramachandran, P. V., Mahanty, M. K. & Bamezai, S. A chemical and thermochemical study of non-observed symmetry allowed reactions. *Tetrahedron* **37**, 4171–4184 (1981).

[19] Leitich, J. 1,3,2-Dioxazolidines by thermal 1,3-cycloaddition of nitro groups to strained olefins. *Angew. Chem. Int. Ed.* **15**, 372–373 (1976).

[20] Buchi, G. & Ayer, D. E. Light catalyzed organic reactions. IV. The oxidation of olefins with nitrobenzene. *J. Am.Chem. Soc.* **78**, 689–690 (1956).

[21] De Mayo, P., Charlton, J. L. & Liao, C. C. Photochemical synthesis. XXXV. Addition of aromatic nitro compounds to alkenes. *J. Am. Chem. Soc.* **93**, 2463–2471 (1971).

[22] Okada, K., Saito, Y. & Oda, M. Photochemical reaction of polynitrobenzenes with adamantylideneadamantane: the X-ray structure analysis and chemical properties of the dispiro *N*-(2,4,6-trinitrophenyl)-1,3,2-dioxazolidine product. *J. Chem. Soc. Chem. Commun.* 1731–1732 (1992).

[23] D'Auria, M., Esposito, V. & Mauriello G. Photochemical reactivity of aromatic and heteroaromatic nitroderivatives in the presence of arylalkenes. *Tetrahedron* **52**, 14253–14272 (1996).

[24] Lu, C. et al. Intramolecular reductive cyclization of *o*-nitroarenes via biradical recombination. *Org. Lett.* **21**, 1438–1443 (2019).

[25] Gang, L. et al. Light-promoted C–N coupling of aryl halides with nitroarenes. *Angew. Chem. Int. Ed.* **133**, 5290–5294 (2021).

[26] Hansch, C., Leo, A. & Taft, R. W. A survey of Hammett substituent constants and resonance and field parameters. C*hem. Rev.* **91**, 165–195 (1991).

[27] Albini, A., Bettinetti, G. & Minola, G. Photodecomposition of some para-substituted 2-pyrazolylphenyl azides. substituents affect the phenylnitrene S-T gap more than the barrier to ring expansion. *J. Am. Chem. Soc.* **121**, 3104–3113 (1999).

[28] Carra, C., Bally, T. & Albini, A. Role of conformation and electronic structure in the chemistry of ground and excited state o-pyrazolylphenylnitrenes. *J. Am. Chem. Soc.* **127**, 5552–5562 (2005).

[29] Partridge, K. M., Guzei, I. A. & Yoon, T. P. Carbonyl imines from oxaziridines: generation and cycloaddition of N–O=C dipoles. *Angew. Chem. Int. Ed.* **49**, 930–934 (2010).

[30] Zhao, E., Zhou, F. & Zhao, Y. Lewis acids promoted 3 + 2 cycloaddition of oxaziridines and cyclic allylic alcohols through carbonyl imine intermediates. *J. Org. Chem.* **84**, 4282–4293 (2019).

[31] Synthesis and transformations of nitrones for organic synthesis. *Chem. Rev.* **119**, 4684–4716 (2019).

[32] Hurley, R. & Testa, A. C. Photochemical n → π* excitation of nitrobenzene. *J. Am. Chem. Soc.* **88**, 4330–4332 (1966).

[33] R. Hurley, R. & Testa, A. C. Nitrobenzene photochemistry. II. Protonation in the excited state. *J. Am. Chem. Soc.* **89**, 6917–6919 (1967).

[34] Bietti, M. Activation and deactivation strategies promoted by medium effects for selective aliphatic C–H bond functionalization. *Angew. Chem. Int. Ed.* **57**, 16618–16637 (2018).

[35] Strieth-Kalthoff, F. & Glorius, F. Triplet energy transfer photocatalysis: unlocking the next level. *Chem* **6**, 1888–1903 (2020).

[36] Huisgen, R. 1,3-Dipolar cycloadditions. 76. Concerted nature of 1,3-dipolar cycloadditions and the question of diradical intermediates. *J. Org. Chem.* **41**, 403–419 (1976).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryInformation.pdf