Article

Photoexcited nitroarenes for the oxidative cleavage of alkenes

https://doi.org/10.1038/s41586-022-05211-0

Received: 24 April 2022

Accepted: 9 August 2022

Published online: 23 August 2022

Check for updates

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The oxidative cleavage of alkenes is an integral process that converts feedstock materials into high-value synthetic intermediates[1–3]. The most viable method to achieve this in one chemical step is with ozone[4–7]; however, this poses technical and safety challenges owing to the explosive nature of ozonolysis products[8,9]. Here we report an alternative approach to achieve oxidative cleavage of alkenes using nitroarenes and purple-light irradiation. We demonstrate that photoexcited nitroarenes are effective ozone surrogates that undergo facile radical [3+2] cycloaddition with alkenes. The resulting '*N*-doped' ozonides are safe to handle and lead to the corresponding carbonyl products under mild hydrolytic conditions. These features enable the controlled cleavage of all types of alkenes 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 alkene.

Alkenes are feedstock materials that are obtained on the ton scale from petroleum and vegetable biomass and are exploited by the bulk chemical industry to access oxygen-enriched synthetic intermediates[1–3]. Ozonolysis is a widely adopted method to achieve this and requires specialized 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 alkene, 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 the reaction solvent and the work-up procedure, **B** or **D** can lead to aldehydes or 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 oxidizing power (standard reduction potential 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[10–12], particularly in the discovery sector, which heavily relies on parallel and high-throughput screening platforms[13]. Consequently, alternative strategies for alkene oxidation based on high-valent heavy-metal oxides (MO_4, where M is a metal) have been devised[14–16]. 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[17]. Oxidative cleavages using O_2 and a suitable (photo)catalyst have also been developed, but they are limited to activated alkenes[18,19].

Overall, there is no other type of reactivity able to mirror the unique ability of ozone to cleave alkenes. Here 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 alkenes enabling access to '*N*-doped' ozonides, which can be accumulated until a devised controlled C–C bond cleavage step takes place. This reactivity engages a large class of alkenes, is tolerant of the most used organic functionalities and allows the targeting of specific double bonds in molecules with multiple C–Cπ sites.

In approaching the design of an alternative method to oxidatively cleave alkenes, we considered the possibility of using nitroarenes **N** as ozone surrogates to 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 alkenes owing to high kinetic barriers[20,21]. The pioneering works of refs. [22,23] demonstrated an opportunity to by-pass these challenging pericyclic processes through direct nitroarene photoexcitation. As such, intersystem crossing from the singlet excited nitroarene delivers the long-lived triplet state (T_1) *__N__. In analogy to T_1 carbonyls, *__N__ have a (n,π^*) configuration, which translates into O-radical-type reactivity. *__N__ can intercept alkenes in radical [3+2]-like fashion and, via the formation of biradical **F**, deliver *N*-doped ozonides **E**. However, this chemistry necessitated high-energy irradiation, utilized the alkene as the solvent, and the mechanism by which **E** evolves into the C–C cleavage products and defines their subsequent fate was unsolved[22–25]. 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 alkenes, 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 towards alkene cleavage.

We started our investigation evaluating the initial rates of disappearance of **1** (k_{obs}) in photocycloaddition reactions (purple light-emitting

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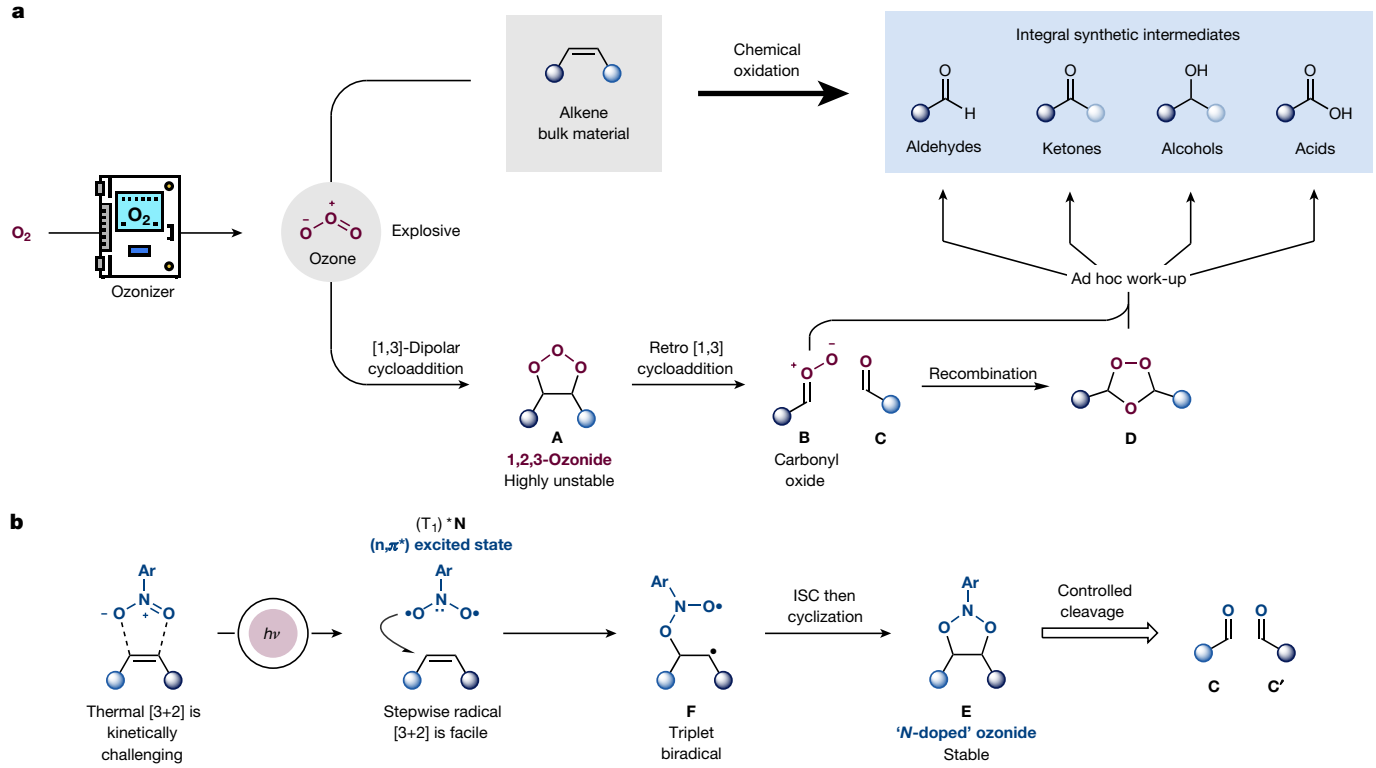

Fig. 1 | Excited nitroarenes as ozone surrogates. a, Ozonolysis for the oxidative cleavage of alkenes. **b**, Mechanism for the formation of **E**. Ar, aryl; ISC, intersystem crossing.

diode irradiation, wavelength $\lambda = 390$ nm (refs. [26,27])) with a variety of electronically diverse *meta*- and/or *para*-(di)substituted nitroarenes **N** to give stable bisadamantene-containing[24] **E** (Fig. 2a). The resulting Hammett plot[28] showed a strong linear free-energy relationship between the electronic character of the nitroarene and k_{obs} (sensitivity constant $\rho = 0.82$). This means that the reactivity profile of nitroarenes as photo-responsive oxidants can be easily tuned by correct placement of electron-withdrawing groups on their aromatic core to amplify the electrophilic character of their excited states. *Ortho*-substituted **N** were less effective, which suggests that steric hindrance can also influence their reactivity (Supplementary Information).

We then evaluated the reaction of unactivated **2**, which is a challenging type of alkene in this chemistry. 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 can be accumulated in solution at −30 °C and are stable in the solid state (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[29,30]. Simple exposure of **E2** to CH_3CN–H_2O led to the almost quantitative formation of ketone **3** and *N*-arylhydroxylamine **H1**. Conversely, in acetonitrile (CH_3CN), **E2** yielded **3** in 98% yield and **4** in 97% yield, 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 water (H_2O), is hydrolysed to **C′** and **H**. Although the generation of **G** was postulated by Huisgen[22], its existence has not been demonstrated before. Related dipoles have been engaged in 1,3-dipolar cycloadditions only twice since Huisgen's initial prediction[31,32], 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** (Supplementary Information). This experiment demonstrates that the cycloreversion of **E1** generates **6** and the more stabilized 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, probably via the in situ formation of nitrone **J**. Indeed, when decomposition of **E3** was run with external formalin, **7** was obtained in 95% yield (Supplementary Information). Despite the decomposition step being very effective, the equilibrium in the condensation between **H** and **C**/**C′**, and subsequent side reactions[33], 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 dipotassium phosphate (K_2HPO_4) and urea (conversion of **H** into **K**) or *N*-phenylmaleimide (conversion of nitrones such as **J1** into **L**), which eased the purification of the aldehydes (Fig. 4e and Supplementary Information).

Having devised conditions to accumulate and decompose *N*-doped ozonides, we decided to benchmark the synthetic utility of the process. Although **N1** was able to engage all substrates present in Fig. 3, other nitroarenes (**N2**–**N7**) were evaluated to improve the yield depending on the alkene. We believe that this is a powerful aspect of this reactivity as functionalized nitroarenes are readily available and dosable reagents that can be evaluated in screening platforms. Exploration began with linear terminal alkenes **2** and **8**–**32** equipped with a distal functionality R. Several commonly encountered organic functional groups, such as nitrile (**8**), aldehyde (**9**), ketone (**10**), carboxylic acid (**11**), halogens (**12**–**15**), free (**16**) and protected (**17**–**20**) amines, azide (**21**), nitro group (**22**), free (**23** also on 5-mmol scale, **27**) and protected (**24** and **25**) alcohols, epoxide (**26**), thiocyanate (**28**), thioethers (**29** and **30**), phosphonate (**31**) and boronic ester (**32**), proved compatible, giving the corresponding aldehydes in high yields. In some cases, we found that the use of dichloromethane (CH_2Cl_2) solvent with hexafluoroisopropanol

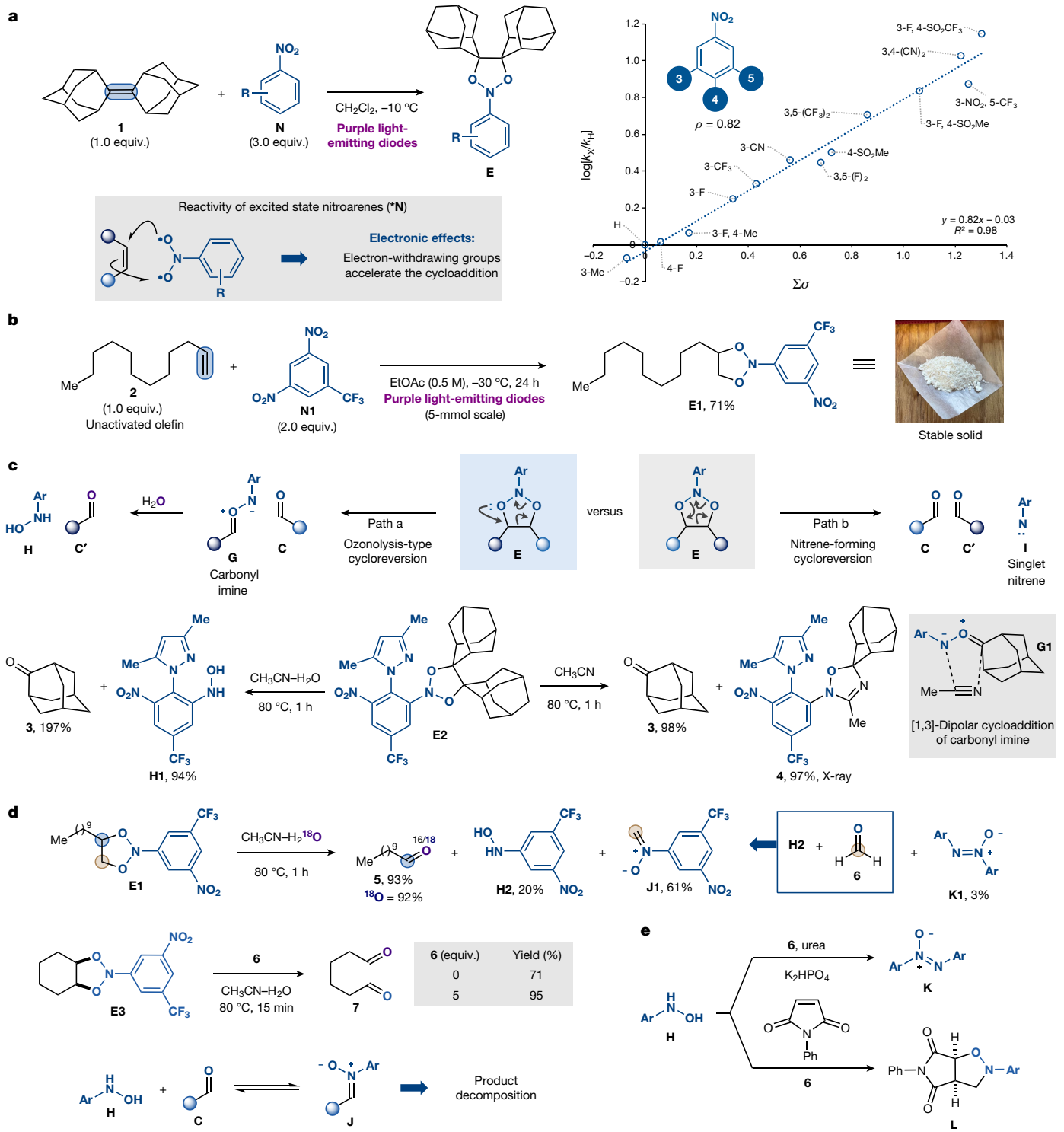

Fig. 2 | Mechanistic experiments. a, Hammett plot analysis. k_X refers to k_{obs} with 3-, 4-, 3,5- or 3,4-(di)substituted nitroarenes, k_H refers to the parent unsubstituted nitrobenzene and σ is the Hammett constant. **b**, Preparation of **E1**. **c**, Mechanism for the decomposition of **E** and the role of H_2O. **d**, ^{18}O-labelling experiments and the role of **6**. **e**, Methods for the removal of **H**.

(HFIP) as the additive to be crucial to ensure good reactivity. As *N can abstract hydridic α-N/O/S C(sp^3)–H bonds[34,35], the inclusion of HFIP suppressed this unwanted process by hydrogen bonding to the heteroatom[36] (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** and **41**). Furthermore, both *gem*-disubstituted (–)-dihydrocarveol **42** and trisubstituted **43** were compatible, as well as diene **44**. Electron-rich and -poor styrenes (**45**–**47**), (*E* and *Z*)-β-Me and α-Me-styrenes (**48**, **49** and **50**), as well as (*E* and *Z*)-stilbenes reacted smoothly (**51** and **52**). Next, we explored the cleavage of structurally complex and densely functionalized derivatives (**53**–**63**). Unactivated terminal alkenes of isophytol (**53**), sclareol (**54**) and alibendol (**55**), which also features an electron-rich aromatic core,

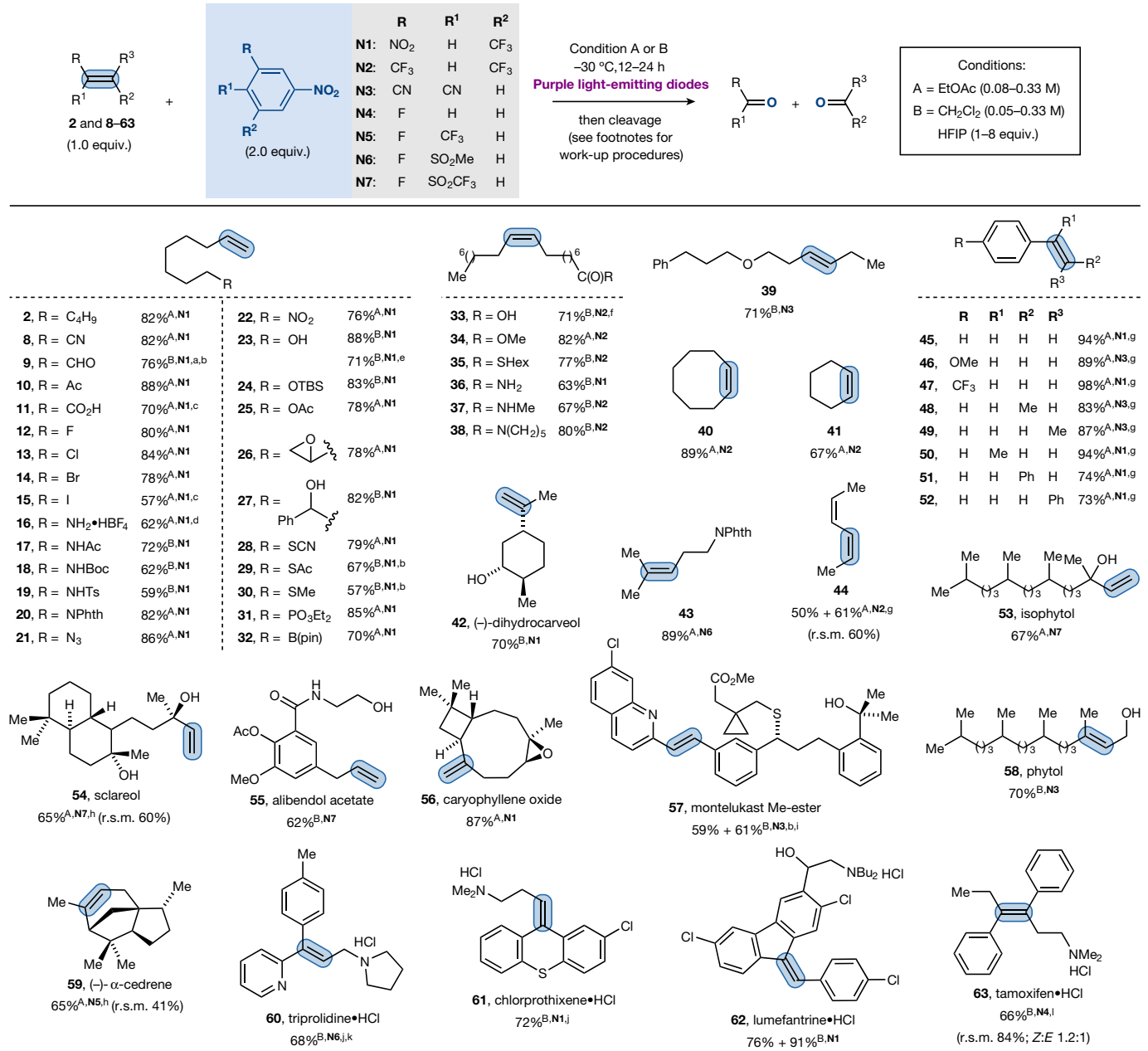

Fig. 3 | Scope of the process. 'A' and 'B' refer to the reaction conditions and **N1**–**N7** refer to the nitroarenes. If the yield of two cleaved fragments deriving from the same alkene differs, the first yield refers to the carbonyl compound with the higher molecular weight. Cleavage: CH_2O (0–6 equiv.) 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]Alkene with a 10C linear chain. [b]Perfluoro-*tert*-butanol (PFTB) used in place of HFIP. [c]Alkene with a 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]NMR yield. [h]Alkene (2 equiv.). [i]Another product of S oxidation to sulfoxide, 6% yield. [j]Aminoaldehyde derivative not detected. [k]40 h. [l]Alkene (5 equiv.). r.s.m., remaining starting material.

could all be oxidized. The disubstituted alkenes of caryophyllene oxide (**56**) and montelukast (**57**), the trisubstituted alkenes of phytol (**58**), (−)-α-cedrene (**59**), triprolidine (**60**), chlorprothixene (**61**) and lumefantrine (**62**), as well as the tetrasubstituted (*Z*)-tamoxifen **63**, were successfully engaged. Another feature of *__N__ is their aptitude to act as triplet sensitizers[37], which can isomerize the alkenes during photocycloaddition. Indeed, unreacted **63** was recovered as *Z*/*E* mixture.

An often-encountered challenge in oxidative cleavage chemistry is achieving regiocontrol 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 **64**–**69** that contain two different alkenes 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 depends on the electronic nature of the nitroarene and that of the two alkenes. Specifically, the selectivity increases when using less electrophilic nitroarenes, and when the two alkenes have substituents that make one C−Cπ bond increasingly more electron-rich than the other. This means that the reactivity of *__N__ (ref. [23]) parallels that of ozone and Huisgen type-III dipolar cycloadditions in general[38]. Consequently, modulation of the nitroarene electronics can be used to amplify narrow reactivity differences when substrate control is difficult to implement. Indeed,

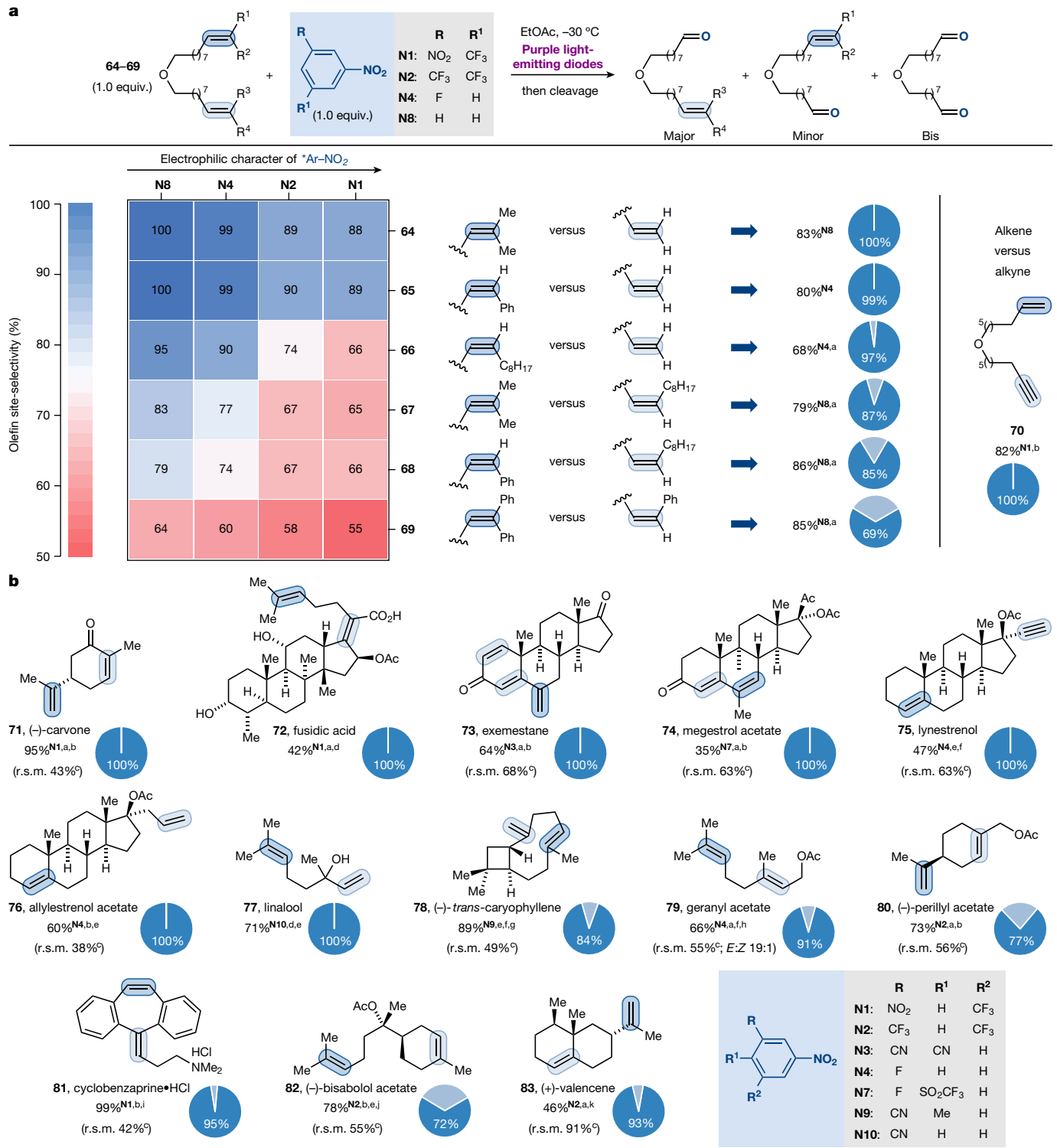

Fig. 4 | Achieving alkene selectivity. a, Competition experiments. **N1**, **N2**, **N4** and **N8** refer to the nitroarenes used. Cleavage: CH_2O (0–6 equiv.) in CH_3CN/THF:H_2O (3.1:1). Selectivity determined considering bis gas chromatography-flame ionization detection (GC-FID) yield. See Supplementary Information for details. [a]Alkene (2.5 equiv.). [b]**N1** (2 equiv.); CH_2Cl_2 with HFIP (1 equiv.). **b**, Complex examples. **N1**–**N4**, **N7**, **N9** and **N10** refer to the nitroarenes used. [a]CH_2Cl_2 with HFIP (0.5–6 equiv.). [b]Alkene (2 equiv.). [c]NMR yield. [d]N (2 equiv.). [e]EtOAc. [f]Alkene (3 equiv.). [g]Bis-cleaved product 3% yield. [h]Bis-cleaved product 2% yield. [i]CH_2Cl_2 without HFIP. [j]Bis-cleaved product 6% yield. [k]Alkene (5 equiv.).

the use of **N8** and **N4** enabled the fully selective cleavage of trisubstituted alkene (**64**) and styrene (**65**) in the presence of monosubstituted alkenes. Furthermore, striking discrimination was achieved between internal and terminal double bonds (**66**, 97%), tri-alkyl versus di-alkyl substituted C–Cπ sites (**67**, 87%), styrene versus an internal alkene (**68**, 85%), as well as the two highly activated alkenes of **69** (69%). Moreover, a complete selectivity for the terminal alkene of **70** 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 multiple C–Cπ sites (Fig. 4b and Supplementary Information). (−)-Carvone **71** and fusidic acid **72** showed regiocontrol based on electronics as alkene conjugation with carbonyl functionalities directed the reactivity towards the other alkenes. In the case of polyunsaturated steroids exemestane **73** and megestrol acetate **74**, oxidative cleavage occurred at the distal, hence less deactivated, C–Cπ sites. Lynestrol **75** showcased alkene oxidation in the presence of alkynes, whereas allylestrenol acetate **76**, linalool **77** and *trans*-caryophyllene **78** showed the selective cleavage of trisubstituted alkenes over terminal and *gem*-disubstituted ones. Geranyl acetate **79** and perillyl acetate **80** contain trisubstituted alkenes with an allylic OAc group that provides weak inductive deactivation. Although this enables the preferential cleavage of the other C–Cπ sites, higher selectivity was obtained adding HFIP (hydrogen bonding with the OAc group). Analogously, the presence of the electron-withdrawing ammonium group in cyclobenzaprine **81** allowed the disubstituted stilbene-type alkene to react over the trisubstituted one. We propose that steric control might be the main factor determining the selectivity in the oxidative cleavage of bisabolol acetate **82** and valencene **83** where the least hindered acyclic alkenes were oxidized despite their degree of substitution.

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

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-022-05211-0.

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Data availability

The data that support the findings of this study are available from the corresponding author (D.L.) upon reasonable request.

Acknowledgements 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.). We acknowledge I. J. Vitorica-Yrezabal (University of Manchester) for solving the X-ray crystal structure of **4**, and N. S. Sheikh for discussions.

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 The authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41586-022-05211-0.

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Peer review information *Nature* thanks Martins Oderinde and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.