Article

Electrophotocatalytic oxygenation of multiple adjacent C–H bonds

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Oxygen-containing functional groups are nearly ubiquitous in complex small molecules. The installation of multiple C–O bonds by the concurrent oxygenation of contiguous C–H bonds in a selective fashion would be highly desirable but has largely been the purview of biosynthesis. Multiple, concurrent C–H bond oxygenation reactions by synthetic means presents a challenge[1–6], particularly because of the risk of overoxidation. Here we report the selective oxygenation of two or three contiguous C–H bonds by dehydrogenation and oxygenation, enabling the conversion of simple alkylarenes or trifluoroacetamides to their corresponding di- or triacetoxylates. The method achieves such transformations by the repeated operation of a potent oxidative catalyst, but under conditions that are sufficiently selective to avoid destructive overoxidation. These reactions are achieved using electrophotocatalysis[7], a process that harnesses the energy of both light and electricity to promote chemical reactions. Notably, the judicious choice of acid allows for the selective synthesis of either di- or trioxygenated products.

Most complex molecules incorporate functional groups consisting of carbon–oxygen (C–O) bonds. A particularly attractive strategy for the synthesis of such molecules is to convert relatively inert carbon–hydrogen (C–H) bonds, which are ubiquitous in simple precursor molecules, to C–O bonds by a process known as C–H oxygenation[1–6]. Nature follows this type of strategy for the synthesis of a plethora of secondary metabolites, such as the antimalarial drug artemisinin (Fig. 1a)[8], using enzymes to achieve selectivity between what can otherwise be difficult-to-distinguish C–H bonds. Chemists find it difficult to recapitulate this type of strategy because of the challenge of site selectivity and the risk of overoxidation, which can lead to undesired carbonyl products or carbon–carbon (C–C) bond cleavage (Fig. 1b). Nevertheless, although tremendous progress has been made in achieving controlled, site-selective C–H oxygenation reactions in complex settings[1–6,9–13], it remains very difficult to oxygenate multiple C–H bonds simultaneously, particularly if those bonds are adjacent to one another, in which case the risk of overoxidation is severe. The challenge then is to develop a chemical strategy in which oxidization is sufficiently strong to effect multiple C–H oxygenations yet sufficiently selective to avoid overoxidation of the substrate.

Recently, a number of challenging oxidative reactions have been achieved in a selective fashion using electrophotocatalysis (EPC)[14–30], a process that utilizes both electrochemical[31–35] and photochemical energy to promote reactions. We have shown that a trisaminocyclopropenium ion[18] (TAC^+) can serve as a potent oxidative electrophotocatalyst (Fig. 1c), enabling a range of C–H bond functionalizations and other transformations[7,17–21]. In these reactions the TAC cation (TAC^+) is oxidized in an electrochemical cell at a relatively low anodic potential (1.26 V versus standard calomel electrode (SCE)) to produce the deep red TAC radical dication ($TAC^{\bullet 2+}$). Whereas this species is not, by itself, sufficiently strong to oxidize the substrate, when photoexcited it becomes a powerful oxidant ($TAC^{\bullet 2+*}$, 3.33 V versus SCE)[18]. Thus, irradiation of an electrochemical cell containing TAC^+ can oxidize even poorly reactive substrates via single electron transfer (SET) to generate the corresponding radical cations, which are highly reactive intermediates that can lead to a number of advantageous reaction outcomes. Previously we showed that TAC EPC could achieve the diamination of vicinal C–H bonds of alkylarenes to furnish dihydroimidazole products[20]. Given the ubiquity of polyoxygenated molecules, both in nature and in pharmaceutically active compounds, a method that achieves two or even three contiguous C–H oxygenations in one step would be of great interest.

We suggested that TAC EPC could offer a unique strategy to realize such challenging transformations using inexpensive acetic acid (AcOH) as the oxygen source. Specifically we reasoned that, under appropriate EPC conditions in the presence of AcOH, a substrate **1** bearing a redox-active substituent, such as an arene or amine derivative, could be converted to the monoxygenated intermediate **2**. Under acidic EPC conditions, **2** could undergo slow, reversible elimination to generate olefin **3**. By virtue of its conjugation to the redox-active substituent, this olefin would be prone to a second round of EPC oxidation to form the dioxygenated adduct **4**. Moreover, we reasoned that iteration of these elimination/oxidation steps with another adjacent C–H bond could lead to elusive trioxygenation products, such as **6**. Here we report the realization of this proposal for the controlled oxygenation of two or three contiguous C–H bonds of alkylarenes and trifluoroacetamides.

Under our optimized conditions, alkylated arenes were electrophotocatalytically dioxygenated using catalytic $TAC^+ClO_4^-$ (8 mol%) in the presence of AcOH, acetic anhydride (Ac_2O) and a strong acid (trifluoroacetic acid (TFA) for branched substrates or trifluoromethanesulfonic

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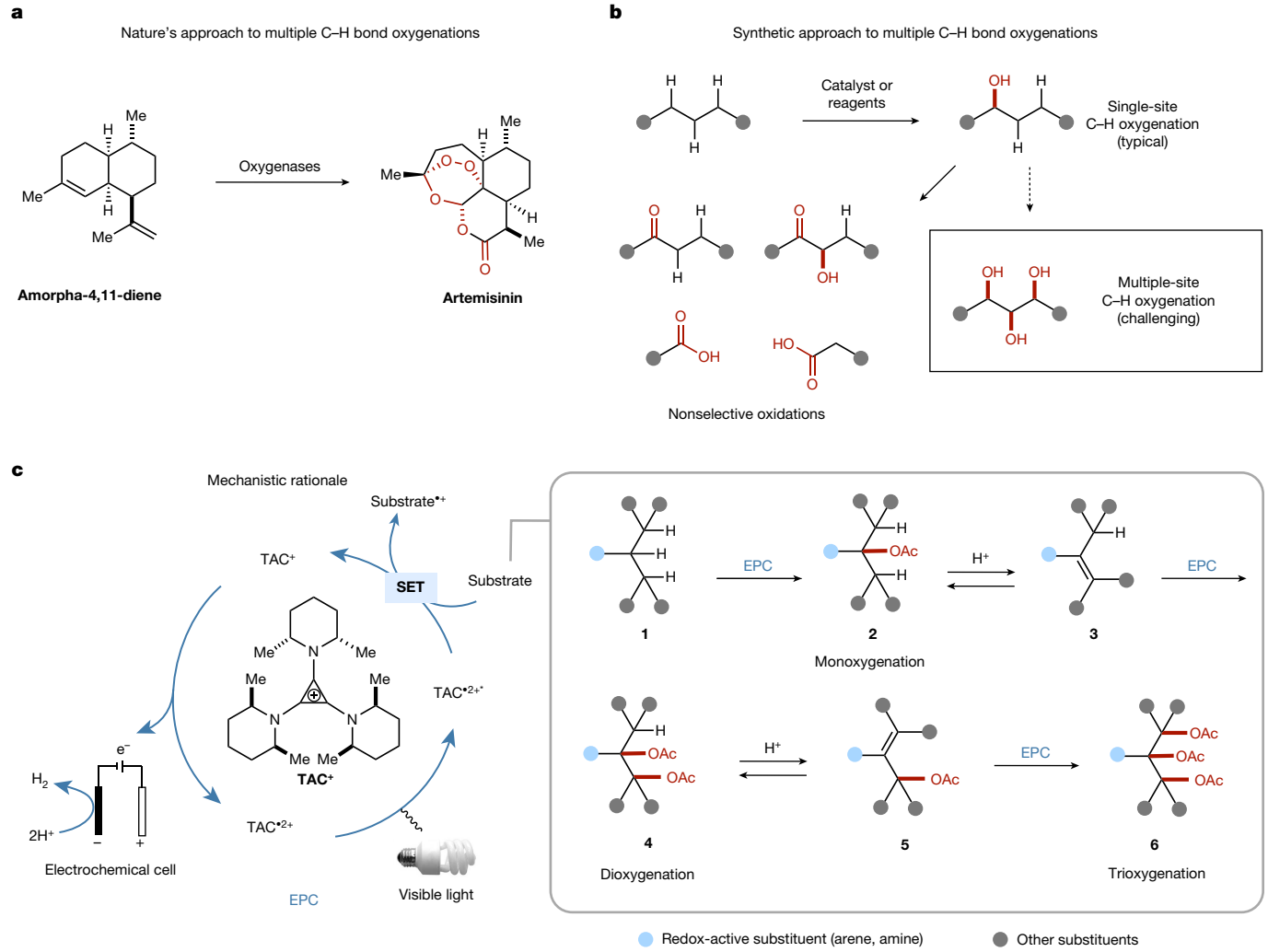

Fig. 1 | Oxygenation of multiple C–H bonds. a, Nature's approach to multiple C–H bond oxygenations. **b**, Synthetic approach to multiple C–H bond oxygenations. **c**, Mechanistic rationale of electrophotocatalytic oxygenation of multiple C–H bonds. Ac, acetyl; Me, methyl.

acid (HOTf) for unbranched substrates) in methylene chloride (CH_2Cl_2), with tetraethylammonium tetrafluoroborate (Et_4NBF_4) as electrolyte (Fig. 2). The reaction was conducted in an undivided electrolytic cell (carbon cloth anode, platinum plate cathode) under constant current (5 mA) irradiated by two compact fluorescent lights (CFLs).

These conditions effected the vicinal C–H dioxygenation of a diverse menu of branched and unbranched alkylarenes bearing a range of functionality (Fig. 2). In the simplest case, ethylbenzene was converted to diacetate **7** in 58% yield. For some substrates, a higher yield was obtained with a hydrolytic work-up to furnish a 1,2-diol product, such as **8**. The diastereomeric ratio (d.r.) typically favoured the anti isomer, to varying degrees. Dihydroxylation of *n*-pentylbenzene furnished 1,2-diol **9**, a known precursor to a beta-secretase 2 (BACE2) inhibitor, in 68% yield and 2.3:1 d.r.[36]. Interestingly, product **10**, bearing a longer alkyl chain, was generated in higher yield (78%) and diastereoselectivity (4:1). Diol **11**, bearing a bromo substituent on the arene, was generated with good efficiency. Meanwhile, a trifluoroacetamide substituent was accommodated in the formation of **12** in good yield, although with a nearly completely eroded d.r. Interestingly, under the reaction conditions 4-ethyltoluene was oxidized to form adduct **13**, in which the ethyl group was vicinally dioxygenated and the methyl group was geminally dioxygenated. Products **14**–**20** demonstrate the breadth of functional group compatibility of this reaction, which readily accommodates alkyl halide (**14**), acetoxy (**15**), carbomethoxy (**16**), imide (**17**), alcohol (**18**), carboxylic acid (**19**) and amino (**20**) substituents. The carbomethoxy group resulted in the preferential formation of the syn diastereomer **16**, whereas the presence of a free carboxylic acid resulted in lactone product **19**. The dimethylamino group apparently slows the reaction rate considerably, because diacetate **20** was isolated in only 22% yield whereas the monoacetate product, which we presume is a precursor to **20**, was formed in 45% yield. Products **21** and **22**, in which both vicinal C–H bonds are benzylic, were also accessible. On the other hand, cyclic adducts **23** and **24** were generated in which only one of the two benzylic positions reacted. Biphenyl diacetate **25** and several heteroaromatic products **26**–**28** could also be furnished. Although acetic acid is the most convenient oxygen donor, alternative esters **29** and **30** could also be accessed using formic or propionic acid and anhydride. Interestingly, for product **29**, the major isomer was syn.

In addition to unbranched substrates, benzylic-branched substrates readily participated in the transformation with the use of a weaker acid (TFA). Thus product **31**, derived from cumene—and its halogenated analogue, **32**—were generated in 72 and 92% yield, respectively. The presence of oxidatively sensitive benzylic trifluoroacetamide or alcohol functionality proved compatible, leading to adducts **33** and **34** in good yield. Diarylethane substrates also reacted efficiently to furnish products **35** and **36**. Interestingly, the reaction does not appear to favour tertiary over primary benzylic C–H bonds. When *p*-cymene was subjected to the reaction conditions, almost equal quantities of **37**

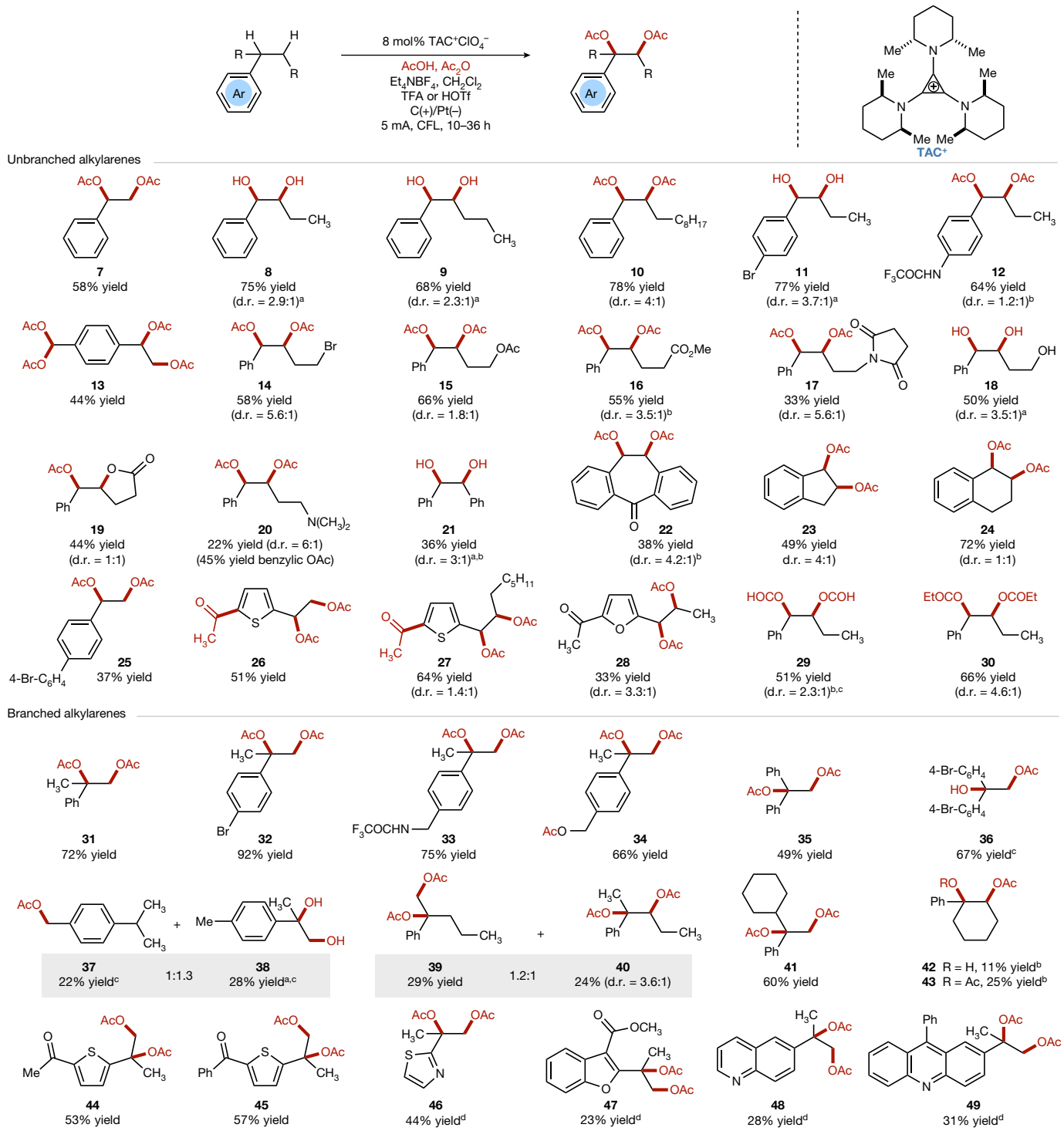

Fig. 2 | Substrate scope of electrophotocatalytic vicinal C–H dioxygenation. All yields are of isolated products. See Supplementary Information for experimental details. For unbranched and branched substrates, HOTf and TFA, respectively, were used. Unless otherwise specified, the major isomer is anti. [a]Certain products were found to be more readily isolated and purified as free diols or triols rather than as diacetates or triacetates. In these instances, hydrolytic work-up with Na_2CO_3 (aq.)/CH_3OH furnished the free alcohols, which were then isolated and purified. [b]The syn product is major. [c]Without acid anhydride. [d]HOTf was used rather than TFA.

and **38** were produced. Furthermore, a substrate with two inequivalent sites for β-C–H oxygenation led to both **39** and **40** in nearly equal quantity. On the other hand, a β-branched substrate led to **41** exclusively. Meanwhile, a cycloalkane substrate led to the formation of products **42** and **43** in 36% combined yield. We also observed that certain heteroaromatic substrates could also be generated by these reactions (**44**–**49**).

To our knowledge, there is no report of a contiguous C–H trioxygenation within a single reaction flask. Along these lines, we suggested that our proposed mechanism could be extended to provide the first example of this elusive transformation. Thus, because an E_1-type elimination is believed to be a key step in this chemistry, we speculated that branched substrates, which are more capable of ionization than

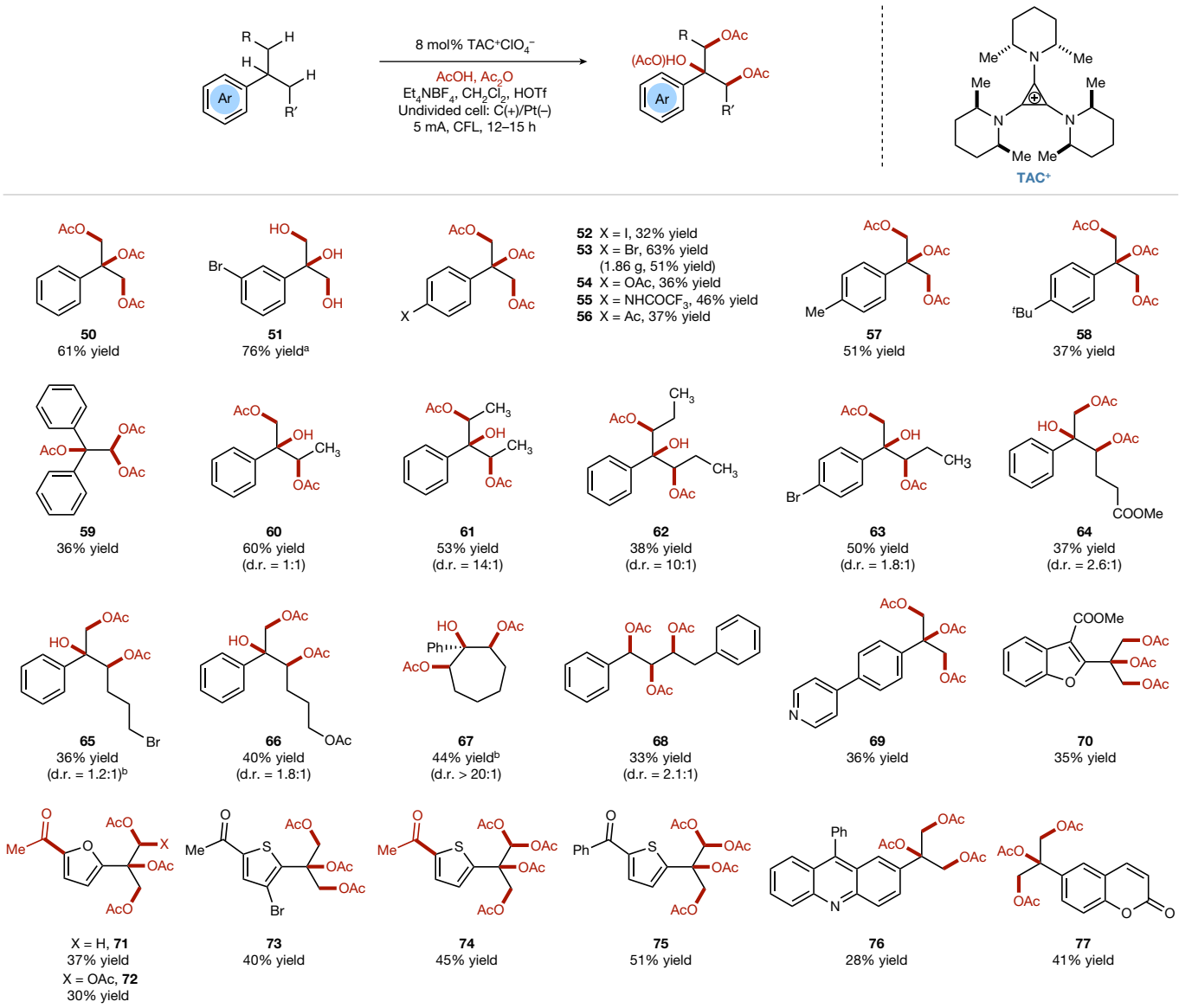

Fig. 3 | Electrophotocatalytic vicinal C–H trioxygenation. See Supplementary Information for detailed reaction conditions for each substrate. Unless otherwise specified, the major isomer was anti. [a]Worked up with Na_2CO_3 (aq.)/CH_3OH. [b]The syn product was major.

unbranched substrates, might be prone to further oxidation after the initial dioxygenation reaction. In practice we found that, by using the stronger HOTf acid with this class of substrate, we were able to achieve a third C–H oxygenation thereby leading to a new trioxygenation of three contiguous C–H bonds (Fig. 3).

A range of substrates proved amenable to this transformation. For example, cumene was converted to triacetate **50** in 61% yield and halogenated cumenes furnished triacetates **51**–**53**. The latter proved amenable to a preparative scale reaction (1.86 g). Products with electron-donating (**54**–**55**) or electron-withdrawing (**56**) substituents could be accessed in modest yield. Interestingly, *p*-cymene, which led to a mixture of products with TFA as the acid (Fig. 2), produced a good yield of triacetate **57** (51%) in the presence of HOTf. Similarly, product **58** bearing a potentially acid-labile *tert*-butyl substituent was isolated in 37% yield. Oxidation of 1,1-diphenylethane led to the formation of triacetate **59** resulting from double oxygenation of the methyl group. We also explored the reaction of alkyl groups beyond isopropyl. For example, trioxygenated products derived from 2-butyl- (**60**), 3-pentyl- (**61**) and 4-heptylbenzene (**62**) were produced in modest to good yields, as was *p*-bromophenyl product **63**. The presence of tethered carbomethoxy, alkyl bromide and acetoxy groups leading to products **64**–**66** proved feasible. In addition, a cyclic substrate was converted to adduct **67** in 44% yield. Meanwhile, we found that 1,4-diphenylbutane underwent a 1,2,3-triacetoxylation reaction to furnish **68** in 33% yield. We also examined reactions of heteroaromatic compounds, including pyridine (**69**), benzofuran (**70**), furan (**71** and **72**), thiophene (**73**–**75**), acridine (**76**) and coumarin (**77**). Such compounds could be trioxygenated—and, in some cases, even tetraoxygenated (**72**, **74** and **75**).

Although arene rings are commonplace in organic molecules and thus provide a useful handle to initiate this oxygenation chemistry, we sought to expand the utility of this strategy by exploring alternative redox-active substituents. Toward this end, we found that trifluoroacetamides could also undergo multiple vicinal C–H oxygenation (Fig. 4a)[37]. For example, piperidine trifluoroacetamide **78** was converted to triacetate **79** in 56% yield as a 10:1:0.6 mixture of diastereomers. The major stereoisomer was *cis*, *trans* as confirmed by single-crystal X-ray analysis. Moreover, 4-alkylated piperidine derivatives **80**–**83** could be generated with good diastereoselectivity, preferentially as *trans*, *trans*

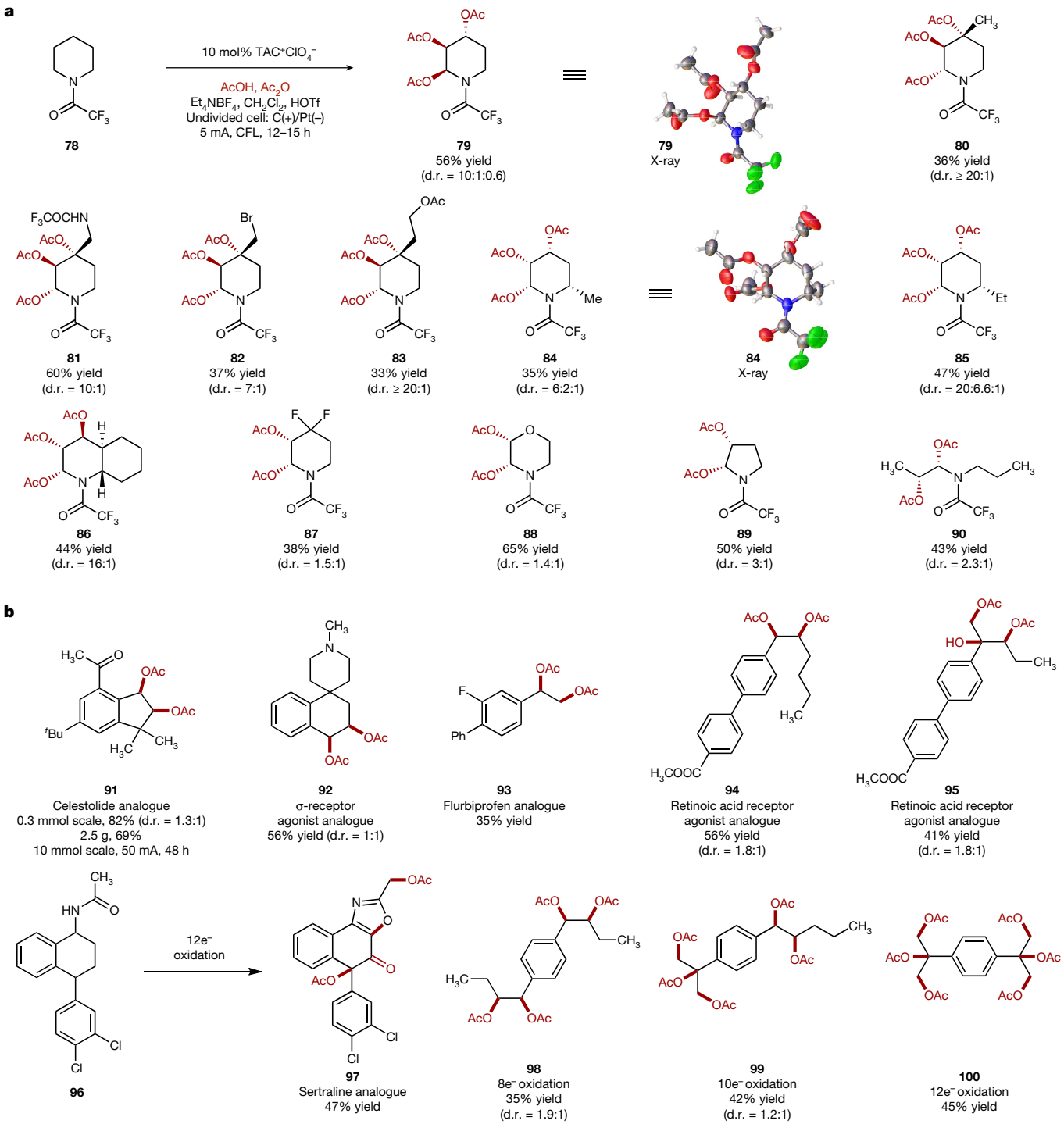

Fig. 4 | Vicinal C–H di- and trioxygenation of trifluoroacetamides and synthetic applications of electrophotocatalytic multiple adjacent C–H oxygenations. a, Di- and trioxygenation of trifluoroacetamides. **b**, Di- and trioxygenation of bioactive compound analogues. See Supplementary Information for detailed reaction conditions. ^{t}Bu, *tert*-butyl.

isomers. Meanwhile, triacetates **84** and **85** were formed in which the more frequently substituted α-carbon remained untouched. Remarkably, X-ray analysis showed an all-*cis* stereochemistry for the major isomer of **84**. These compounds are examples of azasugars, analogues of monosaccharides in which the ring oxygen has been replaced by a nitrogen atom. Many azasugars occur naturally and are of therapeutic interest, in part because they operate as glycosidase inhibitors[38]. A bicyclic trifluoroacetamide was trioxygenated on the less-substituted positions of the nitrogen ring, leading to adduct **86** in 44% yield and 16:1 diastereoselectivity. Substrates without a γ-C–H bond led to the formation of diacetates **87** and **88**, with little stereochemical preference. On the other hand, pyrrolidine trifluoroacetamide, which has γ-C–H bonds, led only to diacetate **89**. Finally, reaction of an acyclic substrate furnished diacetate **90** in 43% yield.

To further demonstrate the utility of this new peroxygenation chemistry, we applied it to the derivatization of a series of more complicated and biologically relevant structures (Fig. 4b). Under our standard conditions we achieved facile dioxygenation of the flavour and fragrance

agent celestolide, furnishing analogue **91** in 82% yield on a small scale, or at 69% yield on a larger scale (2.5 g, 10 mmol). Moreover, analogues of the sigma (σ)-receptor agonist **92** (ref. [39]) and a fluorobiphenyl structure related to the nonsteroidal anti-inflammatory drug flurbiprofen **93** were generated with this procedure. In addition, compounds **94** and **95**, representing di- and trioxygenated analogues, respectively, of a retinoic acid receptor agonist[40], were obtained in synthetically useful 58% and 41% yield, respectively. Interestingly, when substrate **96**, a modified version of the antidepressant drug sertraline, underwent 12-electron oxidation, it gave rise to diacetate ketone **97** in 47% yield. Additionally, eight-, ten- and 12-electron oxidations were realized, with the formation of tetra-, penta- and hexa-acetate products **98**–**100**, respectively.

Achieving multiple contiguous C–H oxygenations in a single operation can help to streamline the synthesis of complex molecules. For example, the antifungal agent genaconazole **103** is known to be accessible from **102**, which was itself prepared from difluoroacetophenone **101** in eight steps in 8% overall yield (Supplementary Information)[41]. Under our trioxygenation procedure we were able to prepare **102** from **101** in just three steps in 44% overall yield. In addition, we have demonstrated that the azasugar derivative **105**, a late-stage intermediate en route to glycosidase inhibitor **106**, can be synthesized in a single electrophotocatalytic step from piperidine **104** (R=$COCF_3$). The previous route from **104** to **105** (R=CO_2Me) required five separate steps[37]. Similarly, an intermediate in the synthesis of vanilloid receptor ligands, which was previously prepared over five steps in 11% yield from *p*-nitrophenylacetic acid[42], has been synthesized from 4-isopropylaniline in only three steps and 42% overall yield using the trioxygenation procedure. Further examples and mechanistic studies are included in the Supplementary Information. These sequences highlight the marked improvements in synthetic efficiency that can be realized through installation of several functional groups via concurrent functionalization of multiple C–H bonds.

Online content

Any methods, additional references, Nature Portfolio 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/s41586-022-05608-x.

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Data availability

The data supporting the findings of this study are available within the paper and its Supplementary Information.

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Author contributions T.H.L. conceived of and directed the project and prepared the manuscript. T.H.L., T.S. and K.-Y.Y. designed experiments. T.S. and Y.-L.L. performed experiments. Y.-L.L. synthesized key substrates. T.S. performed all reactions and collected and analysed data.

Competing interests The authors declare no competing interests.

Additional information

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