Controlled Oxygenation of Multiple Contiguous C–H Bonds via Electrophotocatalysis

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Physical Sciences - Article

Keywords:

Posted Date: December 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1103950/v1

Version of Record: A version of this preprint was published at Nature on December 6th, 2022. See the published version at https://doi.org/10.1038/s41586-022-05608-x.

Abstract

Chemical reactions that directly convert carbon-hydrogen (C–H) bonds to carbon-oxygen (C–O) bonds provide a powerful means to rapidly synthesize valuable organic compounds. However, achieving multiple C–H bond oxygenation reactions at the same time is challenging, particularly because of the risk of overoxidation. Here, we report the selective oxygenation of two or three contiguous C–H bonds, enabling the conversion of simple alkylarenes to diols, triols, or their corresponding acetates. The reactions are achieved using electrophotocatalysis—a process that utilizes both light and electricity to activate a single catalyst—to promote the oxidation reactions. The rapid increase in molecular complexity achieved by these multiple oxygenations enables the synthesis of some compounds of pharmaceutical interest by dramatically shorter sequences than previously achieved.

Main Text

Most complex molecules incorporate functional groups comprised of carbon-oxygen (C–O) bonds. In particular, alcohols, ethers, and carboxylic esters are essential structural components for the majority of compounds of importance to humanity (Fig. 1A). A particularly attractive strategy to synthesize such molecules is to convert relatively inert carbon-hydrogen (C–H) bonds that are ubiquitous in simple precursor molecules into C–O bonds directly, 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 cancer therapeutic paclitaxel (Taxol), the antimalarial drug artemsinin, or the plant hormone brassinolide, by using enzymes to achieve selectivity between what can otherwise be difficult to distinguish C–H bonds (Fig. 1B).[7-9] Chemists find it more difficult to recapitulate this type of strategy, both because of the issue of site selectivity and the risk of overoxidation, which can lead to undesired carbonyl products, carbon-carbon (C–C) bond cleavages, and in the extreme, full combustion (Fig. 1C). Nevertheless, tremendous progress has been made in achieving controlled, site-selective C–H oxygenation reactions in complex settings.[1-6,10-14] However, it remains very difficult to achieve the oxygenation of multiple C–H bonds simultaneously, particularly if those bonds are adjacent to one another, where the risk of overoxidation is severe. The challenge then is to develop a chemical strategy that is strongly oxidizing enough to effect multiple C–H oxygenations yet selective enough to not result in destructive overoxidation of the substrate.

Recently, a number of challenging oxidative reactions have been achieved in a selective fashion using electrophotocatalysis,[15-31] a process that utilizes both electrochemical[32-36] and photochemical energy, often by the same catalyst. We have shown that a trisaminocyclopropenium ion (TAC^+) can serve as a potent oxidative electrophotocatalyst, enabling a range of C–H bond functionalizations and other reactions.[18-23] In one case, we showed that TAC electrophotocatalysis could achieve the diamination of vicinal C–H bonds to furnish dihydroimidazole products.[21] This reaction occurred under Ritter-type conditions, meaning that the acetonitrile solvent served as the aminating agent. Developing a similar reaction for C–H bond oxygenation would require either the use of an oxygen-based nucleophile that

could outcompete the nitrile solvent, or the use of a different solvent altogether; however, the feasibility of such a process was not at all obvious. Here, we report that TAC electrophotocatalysis can in fact achieve the controlled oxygenation of multiple contiguous C–H bonds using simply a mixture of acetic acid and acetic anhydride as the oxygen source (Fig. 1D).

A mechanistic rationale for this process is shown in Fig. 1E. The TAC cation (TAC^+) can be oxidized in an electrochemical cell at a relatively low anodic potential (1.26 V vs. Standard Calomel Electrode, SCE) to produce the deep red TAC radical dication ($TAC^{\cdot 2+}$). While this species is not itself strong enough to react with the substrate, when photoexcited it becomes a powerful oxidant ($TAC^{\cdot 2+*}$, 3.33 V vs. SCE).[18] Thus, irradiation of an electrochemical cell containing TAC^+ can oxidize an alkylarene substrate **1** via single electron transfer (SET) to generate radical cation **2**, which under the conditions leads to loss of a proton and further oxidation to produce benzylic carbocation **3**. Capture of **3** with a nucleophile such as acetic acid (AcOH) then furnishes the mono C–H-oxygenated intermediate **4**. In the presence of a Brønsted acid, **4** can undergo a reversible E_1-type elimination to generate the styrene **5** (**5** could also be formed directly from **3**). The styrene **5** is susceptible to further EPC-oxidation by $TAC^{\cdot 2+*}$, leading to radical cation **6** that can be again captured by acetic acid,[20] this time at the non-benzylic carbon. Subsequent oxidation of the resulting radical **7** with anchimeric trapping by the acetate group leads to cation **8**, which is highly susceptible to destructive opening by acetic acid to produce **9**. (For detailed mechanistic discussion, see supplementary materials).

With this mechanistic blueprint, we found that alkylated arenes could be dioxygenated under electrophotocatalytic conditions by $TAC^+ClO_4^-$ (8 mol% catalyst loading) in the presence of acetic acid (AcOH), acetic anhydride (Ac_2O), and a strong acid (trifluoroacetic acid [TFA] for branched substrates, trifluoromethanesulfonic acid [TfOH] for unbranched substrates) in methylene chloride (CH_2Cl_2) with tetraethylammonium tetrafluoroborate (Et_4NBF_4) as electrolyte. 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]. Traditional oxidants such as $Pb(OAc)_4$, oxone, tert-butyl hydroperoxide (TBHP), 2,2,6,6-tetramethylpiperidinooxy (TEMPO), MnO_2, 1,2-dichloro-4,5-dicyanobenzoquinone (DDQ), (diacetoxyiodo)benzene (PIDA), *N*-fluorobenzenesulfonimide (NFSI), $NaIO_4$ or O_2 were did not effect this transformation (see supplementary materials).

These conditions effected the vicinal C–H dioxygenation of substrates bearing a range of functionality (Fig. 2). For example, ethylbenzene was converted to diacetate **10** in 58% yield. For some substrates, a higher yield was obtained with a hydrolytic workup to furnish a 1,2-diol product such as **11**. As with most substrates, the diastereomeric ratio (dr) favored the anti isomer, but in this case only by a 2.9:1 ratio. Similarly, the dihydroxylation of *n*-pentylbenzene furnished a 1,2-diol **12**, a product that is a known precursor to a BACE2 inhibitor.[37] Interestingly, product **13** bearing a longer alkyl chain was generated in higher yield. Diol products **14** and **15** bearing bromo or chloro substituents on the arene were generated with good efficiency, with the former being isolated in higher yield but the latter with higher

diastereoselectivity. Meanwhile, a trifluoroacetamide substituent was accommodated in the formation of **16** in good yield, but with a nearly completely eroded dr. When 4-ethyltoluene was subjected to the reaction conditions, adduct **17**, in which the ethyl group was vicinally dioxygenated and the methyl group was geminally dioxygenated, was isolated in 44% yield. Products **18**-**24** demonstrate some of the breadth of functional group compatibility of this reaction, including alkyl halide (**18**), acetoxy (**19**), carbomethoxy (**20**), imide (**21**), alcohol (**22**), carboxylic acid (**23**), and amino (**24**) substituents. The carbomethoxy group resulted in the preferential formation of the syn diastereomer **20**, whereas the presence of a free carboxylic acid resulted in lactone product **23**. The dimethylamino group apparently slows the reaction rate considerably, since the diacetate **24** was isolated in only 22% yield while the monoacetate product, which we presume is a precursor to **24**, was formed in 45% yield. The amino group would certainly be protonated under the reaction conditions, and it is likely that the strongly electron-withdrawing ammonium group destabilizes the putative cationic intermediates of the dioxygenation mechanism. Substrates in which both of the vicinal C–H bonds were benzylic also proved viable, including 1,2-diphenylethane and dibenzosuberone which were converted to diol **25** and diacetate **26** respectively in modest yields. On the other hand, adducts **27** and **28** were generated in which only one of the two benzylic positions reacted. Although the biphenyl moiety can sometimes be problematic under strongly oxidizing conditions, diacetate **29** was generated in modest yield. In addition to substituted benzenes, we found that alkylated thiophenes were also viable substrates. As well as undergoing the vicinal dioxygenation reaction, under the standard conditions the 5-position of the thiophene was also acylated, leading to products **30** and **31**.

Although acetic acid and acetic anhydride are the most readily available and convenient oxygen donors for this reaction, we found that alternative ester products **32** and **33** could also be generated through the use of propionic or formic acid/anhydride respectively. Interestingly, for **33** the major isomer was *syn*.

In addition to unbranched substrates, benzylic-branched substrates also worked well, often in high yields. These substrates required the use of a less potent acid, TFA, than the unbranched substrates. Thus, the product **34** derived from cumene and the halogenated analogue **35** were generated in 72% and 92% yields respectively. The heterocyclic product **36** bearing a thiazole ring was isolated in 44% yield. The presence of benzylic trifluoroacetamide or alcohol functionality, which might have been oxidatively sensitive, nevertheless proved compatible with the formation of adducts **37** and **38** in good yields (the alcohol group was acylated under the reaction conditions). When *p*-cymene, with its competing isopropyl and methyl benzylic sites, was subjected to the reaction conditions, a nearly equal mixture of **40** and **41** were produced, with no product resulting from oxygenation of both sites identified. Furthermore, a substrate with two inequivalent sites for the non-benzylic C–H functionalization led to both **42** and **43** in nearly equal quantities. On the other hand, a b-branched substrate led to **39** exclusively, likely due to conformational considerations. A 1,1-diarylethane was dioxygenated in good yield to furnish **44**. Finally, a cycloalkane substrate, cyclohexylbenzene, led to the formation of products **45** and **46** in 36% combined yield; the modest yield in this case may be due to the competing formation of biphenyl.

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 unbranched substrates, might be prone to further oxidation after the initial dioxygenation reaction. In fact, we found that using the stronger TfOH acid with this class of substrates enabled a third C–H oxygenation, thus leading to a trioxygenation of three contiguous C–H bonds (Fig. 3). For example, cumene was converted to triacetate **47** in 61% yield under the modified conditions. As noted above, some reactions benefited from a hydrolytic workup, such as for the production of *m*-bromocumene-derived triol **48**, which was produced in 76% yield. Both *p*-iodo- and *p*-bromocumene also participated in this reaction to furnish triacetates **49** and **50** respectively. The latter was also amenable to a preparative scale reaction (1.86 g). Products with electron-donating acetoxy (**51**) or trifluoroacetamido (**52**) substituents or an electron-withdrawing acyl group (**53**) could also be accessed in modest yields. Interestingly, *p*-cymene, which led to a mixture of products (**40** and **41**) with TFA as the acid, produced a good yield of triacetate **54** (51%) with TfOH. Similarly, product **55** with electron-donating tert-butyl substituent was isolated in 37% yield. 1,1-Diphenylethane led to the formation of triacetate **56** 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- (**57**), 3-pentyl- (**58**), and 4-heptylbenzene (**59**) were produced in modest to good yields, as was the *p*-bromophenyl product **60**. The presence of tethered carbomethoxy, alkyl bromide, and acetoxy groups leading to products **61**-**63** proved feasible. Finally, a cyclic substrate, phenylcycloheptane, was converted to adduct **64** in 44% yield. Interestingly, for alkyl groups larger than isopropyl, the benzylic position was substituted with hydroxy group instead of OAc group, perhaps due to steric hindrance.

To further demonstrate the utility of this chemistry, we investigated its application to some more complicated structures (Fig. 4). For example, this procedure was employed to dioxygenate the flavor and fragrance agent celestolide, furnishing analogue **65** in 82% yield on small scale or 69% yield on a larger scale (2.5 g, 10 mmol) with inexpensive Ni plate as cathode. Analogues of a s-receptor agonist **66**[38] and a fluorobiphenyl structure related to the nonsteroidal anti-inflammatory drug flurbiprofen **67** were generated with this procedure. In addition, analogues of a retinoic acid receptor agonist[39] using either the dioxygenation (**68**) or the trioxygenation (**69**) procedures were generated in 58% and 41% yields respectively. When a modified version **70** of the antidepressant drug sertraline was subjected to these conditions, a 12-electron oxidation occurred, giving rise to the diacetate ketone **71** in 47% yield. Additionally, another 12-electron oxidation was realized with the hexaoxygenation of 1,4-diisopropylbenzene (**72**) to furnish **73** in 45% yield.

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 (**76**) was previously synthesized from **75**, which was prepared from difluoroacetophenone **74** in 8 steps and 8% overall yield (Fig. 4B)[40]. We have used the trioxygenation procedure to prepare **75** in only three steps from **74** in 44% overall yield. Similarly, an intermediate **78** on the way to vanilloid receptor ligands, which was previously prepared over 5 steps in 11% yield from *p*-nitrophenylacetic acid (**77**) [41], has been synthesized from 4-isopropylaniline (**79**) in only three steps and 42% overall yield using the trioxygenation procedure.

Additionally, cytosporanone and intermediate for inhibitors of HIV-1 protease were also efficiently produced using the current method (see supplementary materials). These sequences underscore the notion that installing several functional groups by the concurrent functionalization of multiple C–H bonds can lead to dramatic improvements in synthetic efficiency.

Oxygen-containing functional groups are nearly ubiquitous in complex small molecules. The direct installation of C–O bond functionality by the oxygenation of C–H bonds offers a powerful means to install these moieties, and it is no coincidence that this is a strategy employed by both Nature and chemists alike. Nevertheless, the installation of multiple C–O bonds at the same time in a selective fashion has been largely the purview of biosynthesis. The current method achieves such transformations by the repeated operation of a potent oxidative catalyst, but under conditions that are selective enough to avoid destructive overoxidation. This method thus further expands the power of direct C–H functionalization strategies for complex molecule synthesis.

Declarations

Acknowledgments: Funding for this work was provided by the National Institutes of Health (T.H.L., R35 GM127135) and the National Natural Science Foundation of China (K.-Y.Y., 22171046).

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 the experiments. T.S., Y.-L.L. and L.-C.L. performed the experiments.

Competing interests: The authors declare no conflicts of interest.

Supplementary Information is available for this paper.

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Figures

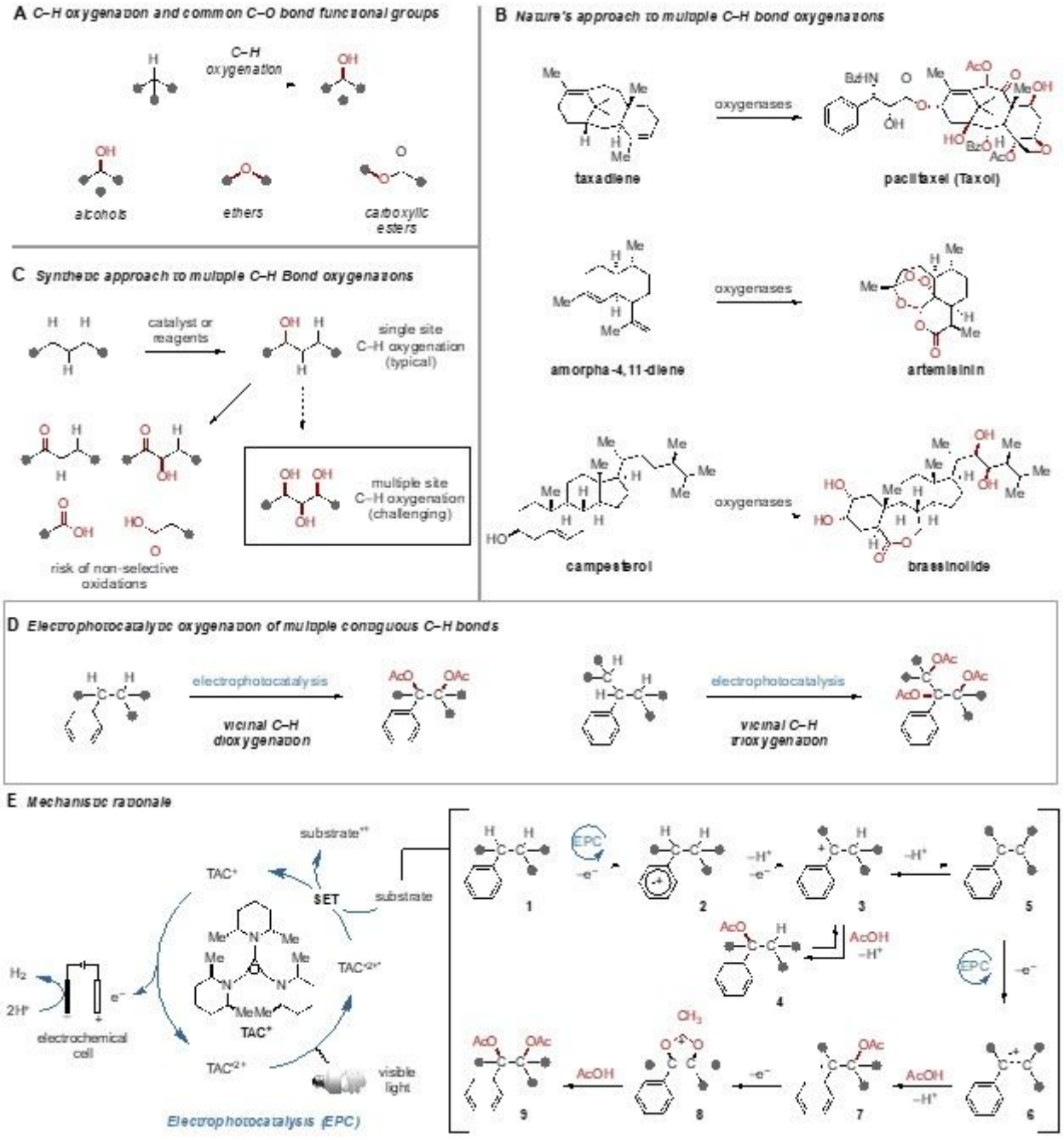

Figure 1

Oxygenation of Multiple C–H Bonds: (A) C–H oxygenation and common C–O bond functional groups. (B) Nature's approach to multiple C–H bond oxygenations. (C) Synthetic approach to multiple C–H bond oxygenations. (D) Electrophotocatalytic dioxygenation and trioxygenation of C–H bonds reported in this article. (E) Proposed mechanism of electrophotocatalytic cycle with TAC for oxygenation of multiple C–H bonds. Grey circles represent generic substituents. Ac, acetyl; Me, methyl; SET, single electron transfer; TAC, trisaminocyclopropenium.

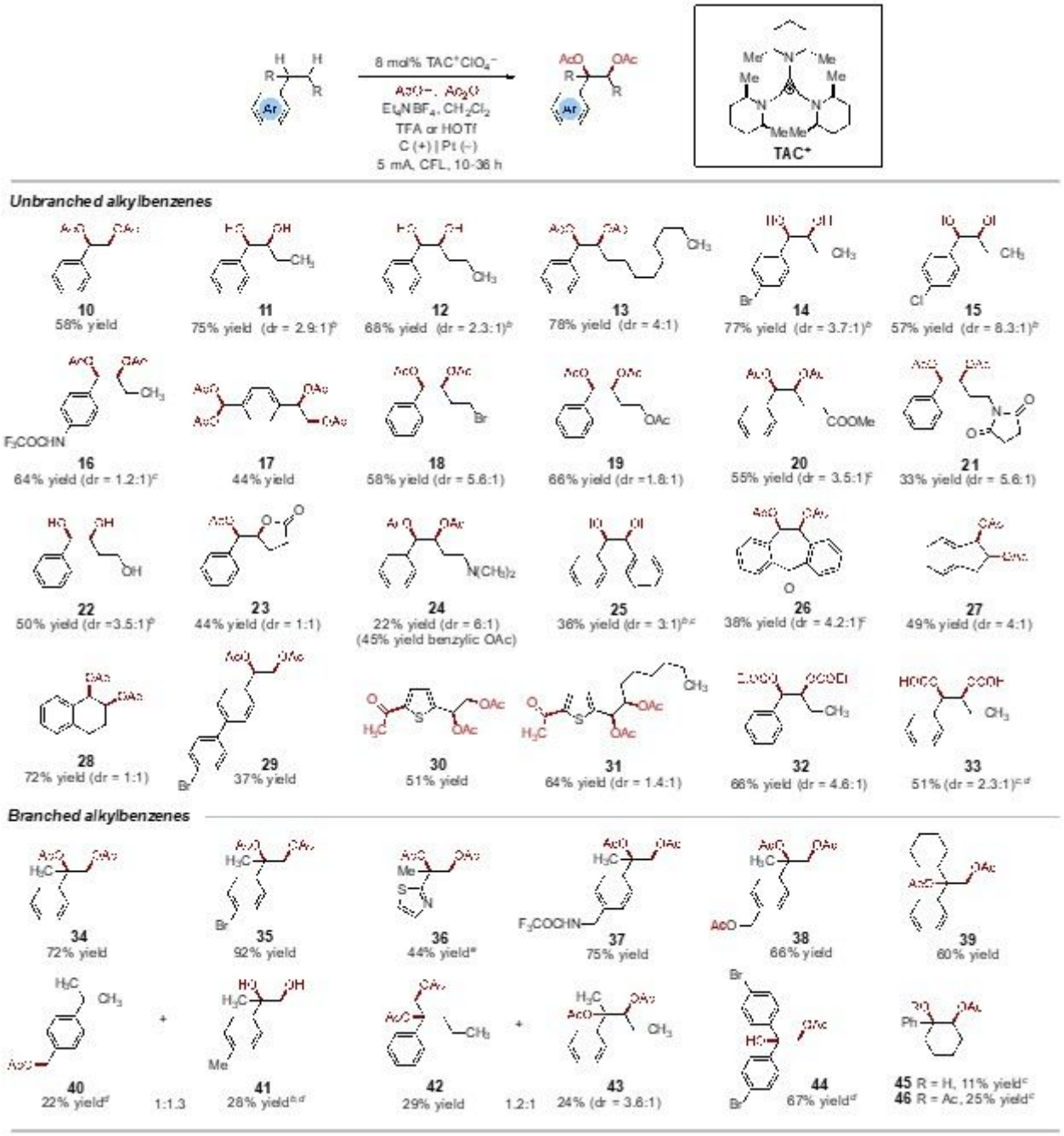

Figure 2

Substrate scope of electrophotocatalytic vicinal C–H dioxygenation. a All yields are of isolated products. See supplementary materials for experimental details. For unbranched substrates, HOTf was used, while for branched substrates, TFA was used. Unless otherwise specified, the major isomer is anti. b worked up with Na2CO3 (aq.)/MeOH; c syn product is major; d without acid anhydride. e HOTf was used instead of TFA.

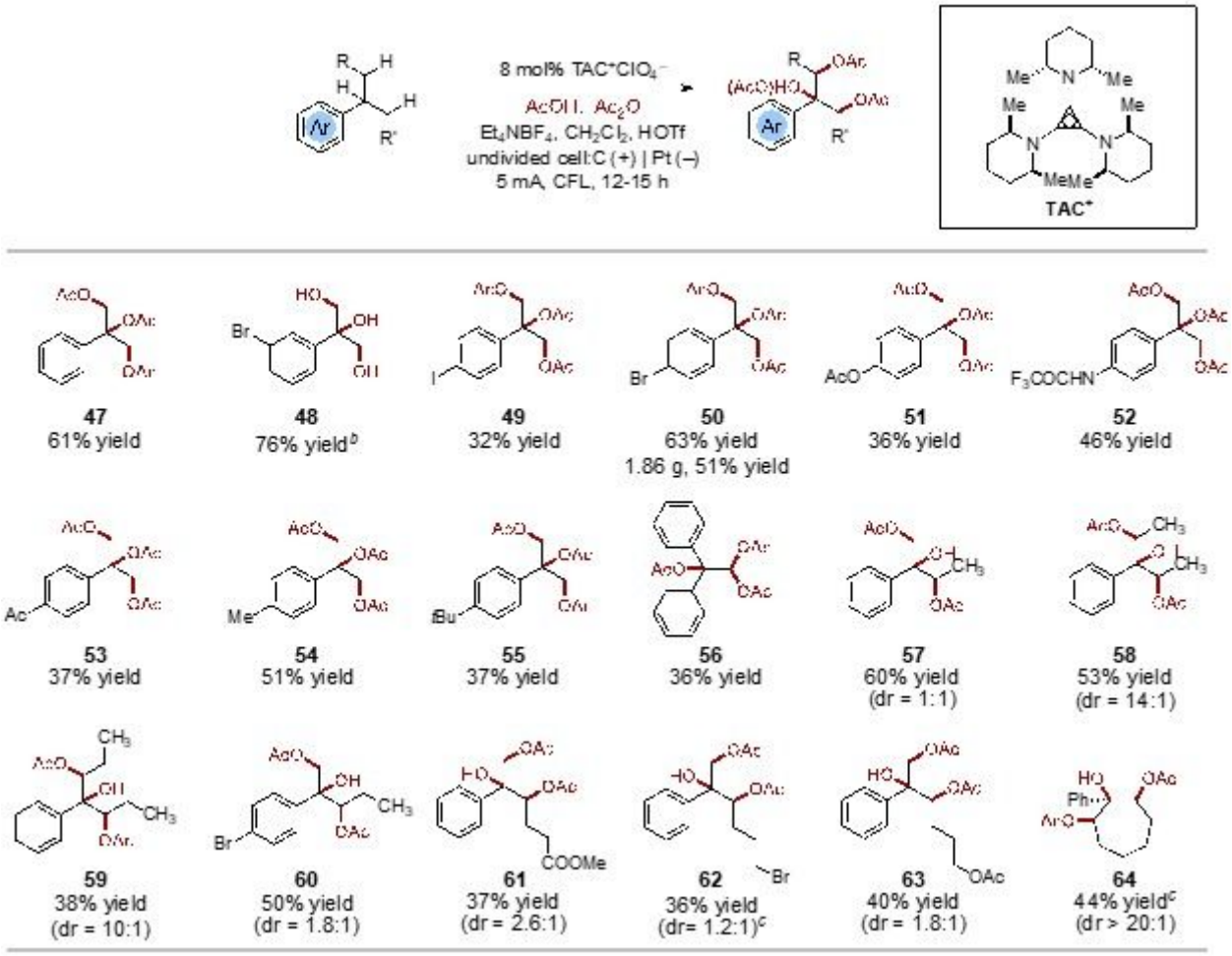

Figure 3

Electrophotocatalytic vicinal C–H trioxygenation. a See the supplementary materials for detailed reaction conditions for each substrate. Unless otherwise specified, the major isomer is anti. b worked up with Na2CO3 (aq.)/MeOH; c syn product is major.

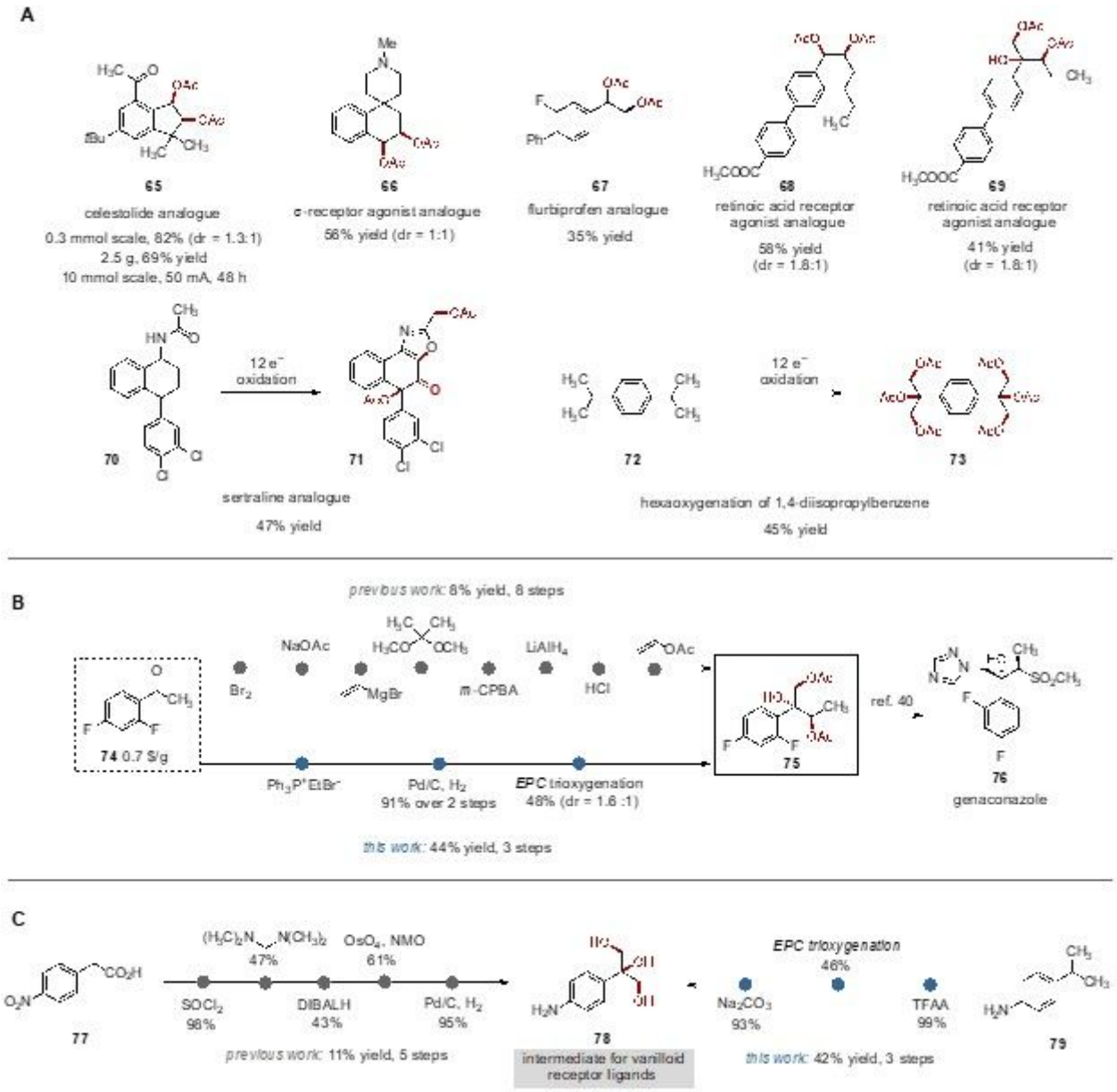

Figure 4

Synthetic applications of electrophotocatalytic multiple contiguous C–H oxygenations. (A) Late-stage dioxygenation and trioxygenation of bioactive compounds. (B) Electrophotocatalytic multiple contiguous C–H oxygenations facilitate rapid access to intermediate of genaconazole. (C) Rapid access to intermediate for vanilloid receptor ligands. See the supplementary materials for detailed reaction conditions. For more examples, see supplementary materials. m-CPBA, meta-chloroperbenzoic acid; Ph, phenyl; Et, ethyl; DIBAL-H, diisobutylaluminium hydride; NMO, N-methylmorpholine-N-oxide; TFAA, trifluoroacetic anhydride.

Supplementary Files

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- dioxygenationNatureSI.pdf