BIOCATALYSIS

Anti-Markovnikov alkene oxidation by metal-oxo–mediated enzyme catalysis

Stephan C. Hammer, Grzegorz Kubik, Ella Watkins, Shan Huang, Hannah Minges, Frances H. Arnold*

Catalytic anti-Markovnikov oxidation of alkene feedstocks could simplify synthetic routes to many important molecules and solve a long-standing challenge in chemistry. Here we report the engineering of a cytochrome P450 enzyme by directed evolution to catalyze metal-oxo–mediated anti-Markovnikov oxidation of styrenes with high efficiency. The enzyme uses dioxygen as the terminal oxidant and achieves selectivity for anti-Markovnikov oxidation over the kinetically favored alkene epoxidation by trapping high-energy intermediates and catalyzing an oxo transfer, including an enantioselective 1,2-hydride migration. The anti-Markovnikov oxygenase can be combined with other catalysts in synthetic metabolic pathways to access a variety of challenging anti-Markovnikov functionalization reactions.

An important challenge in aerobic oxidation is the direct transformation of alkenes to the corresponding anti-Markovnikov carbonyl compounds (*1*–*3*). An efficient catalyst for this conversion could dramatically simplify synthetic routes from readily available alkenes to important commodity and fine chemicals, pharmaceuticals, and agrochemicals. Direct catalytic oxidation has proven difficult; the few reported systems mainly target reversing the Markovnikov selectivity in the palladium-catalyzed Wacker-Tsuji oxidation (*2*). Current methods depend on precious metals performing with low turnover numbers and/or stoichiometric amounts of oxidants such as iodosylbenzene (fig. S1 and table S1). Both regioselectivity and enantioselectivity remain challenging. Metal-oxo–mediated oxidation reactions are well known in chemistry and biology (*4*); however, because alkene oxidations with high-valent metal-oxo complexes follow concerted epoxidation pathways with low energy barriers, oxo transfer has not been practical for direct anti-Markovnikov oxidation (Fig. 1A, bottom) (*5*, *6*). Experiments and theory suggest that direct anti-Markovnikov oxidation pathways would be possible if a stepwise reaction path via a carbocation intermediate were favored (Fig. 1B) (*7*–*9*). However, a direct anti-Markovnikov oxo-transfer pathway has never been exploited owing to a lack of catalysts that suppress the kinetically strongly favored epoxide formation.

Enzymes can exert a high degree of control over competing reaction pathways through multiple interactions with substrates in their transition states (*10*). Enzymes control substrate conformations (*11*) and can guide high-energy intermediates such as carbocations and radicals through complex catalytic cycles (*12*, *13*). In addition to promoting a desired reaction, enzymes also actively prevent competing reactions (*14*). Given these precedents of natural catalysts, we reasoned that it should be possible for an enzyme to catalyze metal-oxo–mediated anti-Markovnikov oxidation of alkenes selectively over the kinetically favored epoxidation shown in Fig. 1B.

The cytochrome P450 monooxygenases (P450s) are a family of iron-heme–dependent enzymes that use O_2 as the terminal oxidant (*15*). P450s use their catalytic oxidant compound I for a multitude of oxidation reactions, including alkene epoxidation (*16*). In a few cases, anti-Markovnikov oxidation side products have been observed, particularly when the metabolism of synthetic molecules or the substrate scopes of new P450 variants were investigated (*17*). However, a selective alkene anti-Markovnikov oxygenase (aMOx) has never been reported. To exhibit this activity, the enzyme must trap the high-energy radical and carbocation intermediates and shift the oxo transfer from the concerted epoxidation to the stepwise anti-Markovnikov

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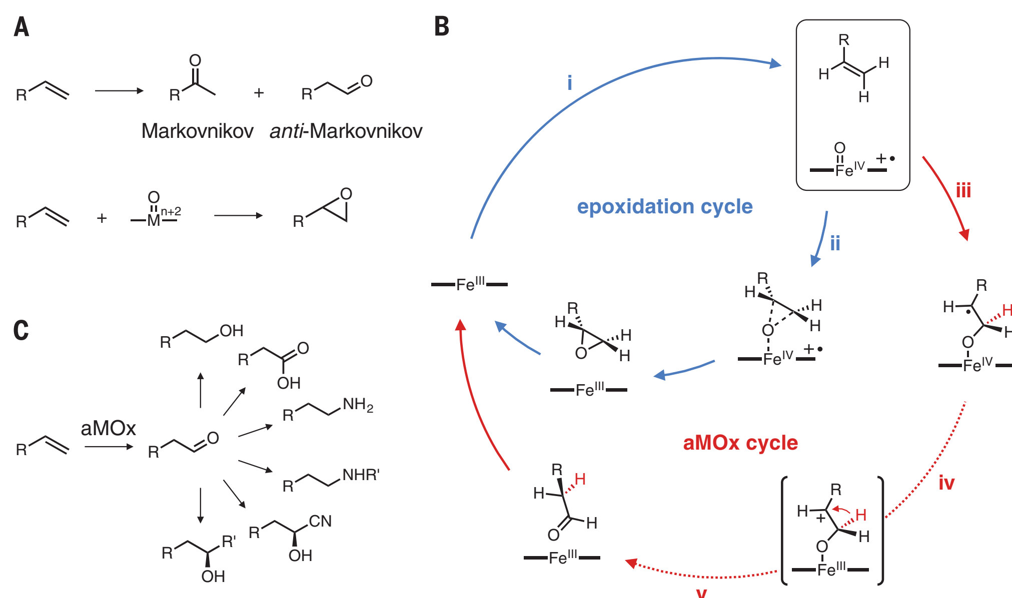

Fig. 1. Anti-Markovnikov oxidation of alkenes. (**A**) Alkene oxidation reactions. (**B**) Comparison of proposed catalytic cycles for P450-catalyzed alkene epoxidation and anti-Markovnikov oxidation. (i) Formation of metal-oxo complex, termed compound I (framed). (ii) Energetically preferred, highly concerted olefin epoxidation. (iii to v) Alternative stepwise anti-Markovnikov oxidation via an additional electron transfer (iv), yielding a high-energy carbocation intermediate. Subsequent 1,2-hydride migration (v) generates the anti-Markovnikov oxidation product. Steps iv and v might occur stepwise or in a concerted fashion. (**C**) The anti-Markovnikov oxygenase (aMOx) can be combined with various established biocatalysts in short (two-step) enzyme pathways to catalyze a variety of challenging anti-Markovnikov functionalization reactions (fig. S10). R, aryl or alkyl; M, metal.

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oxidation pathway (Fig. 1B). This could be achieved by stabilizing the reactive intermediates sufficiently to promote a 1,2-hydride migration (step v in Fig. 1B) and selectively generate the anti-Markovnikov oxidation product (fig. S2). Here we present the directed evolution of an iron-heme–dependent aMOx that oxidizes a range of styrenes to their anti-Markovnikov carbonyl compounds, using O_2 as the terminal oxidant.

To identify a suitable starting point for evolution of an aMOx, we examined a P450 from the rhodobacterium *Labrenzia aggregata* ($P450_{LA1}$). $P450_{LA1}$ has been described as a promiscuous sulfoxidation catalyst that also generates the anti-Markovnikov carbonyl compound in the epoxidation of styrene (*18*). In contrast to this report, which proposed that an epoxidation-isomerization sequence led to side-product formation, we discovered that $P450_{LA1}$ catalyzes direct anti-Markovnikov oxidation without an epoxide intermediate (fig. S3). This direct anti-Markovnikov oxidation of styrene proceeds with a total turnover number (TTN) of 100 for aldehyde product formation, which exceeds the productivity of most synthetic catalysts reported (table S1). However, performance is limited by poor selectivity, because in addition to anti-Markovnikov oxidation, the epoxide makes up more than half of the product (55%).

We sought to improve the $P450_{LA1}$ enzyme's activity and selectivity for anti-Markovnikov oxidation of styrene by directed evolution (*19*). An aldehyde-specific colorimetric reagent (fig. S4) was used to screen libraries in which the enzyme's heme domain was randomly mutated using error-prone polymerase chain reaction. Four rounds of mutagenesis and screening yielded the quintuple mutant P7 ($P450_{LA1}$ T121A-N201K-N209S-Y385H-E418G), and TTN for anti-Markovnikov oxidation increased from 100 to 1200 (Fig. 2A and tables S2 and S3). All five mutations of P7 contribute to the improved activity, but only the T121A mutation, believed to be in the active site based on a homology model of the heme domain structure (fig. S5), enhanced selectivity for the anti-Markovnikov product (from 45 to 55%). Apparently, screening libraries solely based on desired aldehyde formation increased overall enzyme activity but provided only limited control over the competing epoxidation pathway. (Single-letter abbreviations for the amino acid residues are as follows: A, Ala; E, Glu; G, Gly; H, His; I, Ile; K, Lys; L, Leu; M, Met; N, Asn; R, Arg; S, Ser; T, Thr; V, Val; Y, Tyr.)

To exert greater pressure against epoxidation, we used high-performance liquid chromatography (HPLC) to screen for increases in the ratio of anti-Markovnikov oxidation to epoxidation products. We also switched from random mutagenesis of the whole heme domain to site-saturation mutagenesis of amino acids predicted to be in the active site and heme-binding pocket (*20*, *21*). Six additional rounds of site-saturation mutagenesis and screening generated the variant that we call aMOx. It has eight additional amino acid mutations (A103L, M118L, R120H, V123I, I326V, V327M, H385V, and M391L), overall substituting 3% of the heme domain amino acids (fig. S5 and tables S2 and S3). This aMOx performs direct anti-Markovnikov oxidation of styrene with a TTN of 3800 and 81% selectivity (Fig. 2A). The enzyme's activity is improved 38-fold over the wild-type protein and is two orders of magnitude more efficient than previously reported catalysts (table S1). In contrast to small-molecule catalysts, aMOx can catalyze this aerobic oxidation using earth-abundant iron in its native heme cofactor.

In agreement with the mechanism proposed by Groves and Myers (*7*), we suggest that a 1,2-hydride migration is the central element of the aMOx catalytic cycle. We obtained support for the overall mechanism by determining that the corresponding epoxides (*R*)-**3** and (*S*)-**3** are not converted by aMOx and are therefore not intermediates in the cycle (Fig. 2B and fig. S6). The time course of the reaction also shows constant product ratios over time (fig. S7). Thus, we are confident that aMOx catalyzes a direct anti-Markovnikov oxo transfer and that directed evolution did not optimize the catalyst for an epoxidation-isomerization sequence. We also confirmed the 1,2-hydride migration by converting the isotopically labeled substrate **4** and analyzing the product by ^{1}H and ^{13}C nuclear magnetic resonance (Fig. 2C and fig. S8).

Because enzyme active sites are chiral, we reasoned that aMOx should catalyze enantioselective anti-Markovnikov oxidation of prochiral 1,1-disubstituted alkenes, such as α-methylstyrene (**6**), which are particularly challenging starting materials in asymmetric synthesis (*22*). Even though **6** was not used for screening, and the enzyme therefore did not undergo selection for enantioselectivity during directed evolution, aMOx performed the reaction with good selectivity to the corresponding (*S*)-enantiomer (enantiomeric ratio, 91:9; Fig. 2D) (*23*, *24*). We propose that the asymmetric induction occurs during the 1,2-hydride migration. Catalytic enantioselective 1,2-migrations of prochiral carbocations have been demonstrated only for the migration of alkyl groups, and often in ring-strain releasing processes (*25*, *26*). Such asymmetric 1,2-migrations are difficult because the catalyst must differentiate the prochiral faces of the highly reactive, planar carbocation intermediates. The observed enantioselectivity suggests that aMOx locks the substrate in a specific conformation that aligns one of the C–H bonds coplanar to the empty p orbital of the carbocation intermediate (Fig. 2E). These results further suggest that the mutations identified during evolution enhanced the aMOx cycle by fine-tuning the orbital alignment for the 1,2-hydride migration. A role for precise optimization is supported by the subtle steric changes introduced by many of the active-site amino acid

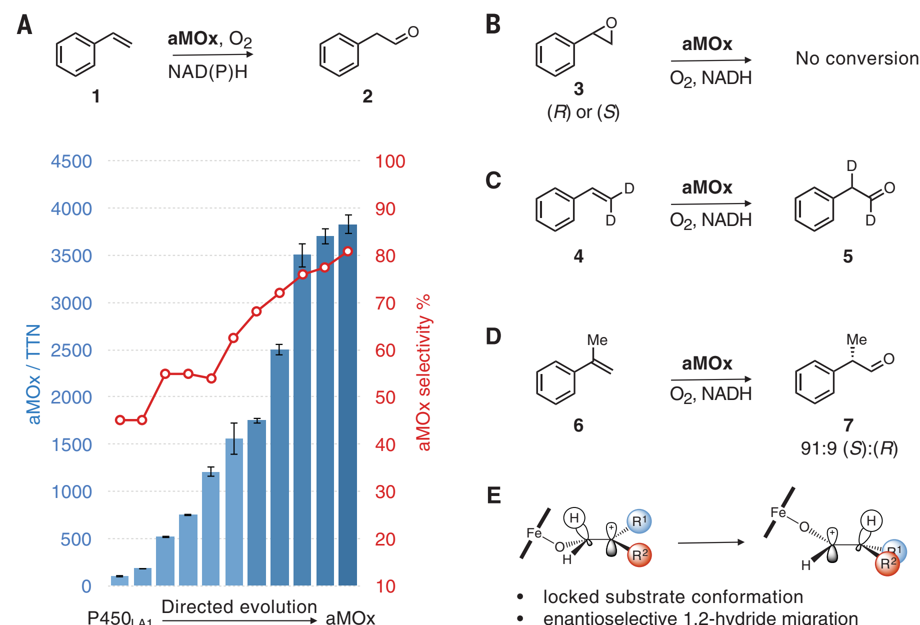

Fig. 2. Directed evolution of aMOx and mechanistic insights. (**A**) aMOx was engineered in the laboratory in 10 rounds of directed evolution using styrene **1** as a substrate (tables S2 and S3). The error bars represent the standard deviation of the total turnover number (TTN) for anti-Markovnikov oxidation in reactions run in at least two independent triplicates (minimum of six reactions). (**B**) The aMOx-catalyzed anti-Markovnikov oxidation is a direct oxidation without an epoxide intermediate (fig. S6). (**C**) Isotopic labeling experiments support a 1,2-hydride migration in the catalytic cycle (fig. S8). (**D**) aMOx-catalyzed enantioselective anti-Markovnikov oxidation (fig. S9). (**E**) Enantiocontrol of aMOx derives from the enzyme's capacity to lock the substrate in a specific conformation. Carbocation 1,2-rearrangements are best described as concerted reactions via a suprafacial 1,2-shift (*25*, *44*). NADH, reduced form of NAD^+ (nicotinamide adenine dinucleotide, oxidized form); NADPH, reduced form of $NADP^+$ (NAD^+ phosphate); D, deuterium; Me, methyl.

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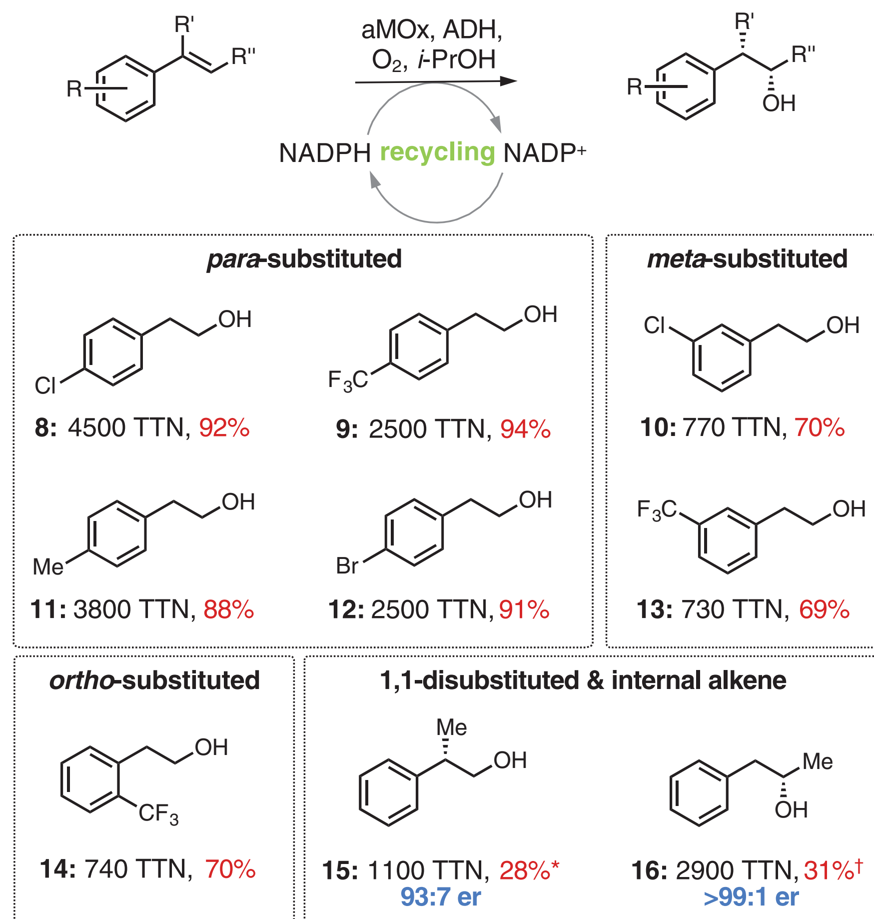

Fig. 3. Application of aMOx in anti-Markovnikov redox hydration of alkenes. The reaction conditions were 5 mM alkene, 0.25 μM aMOx, 10 units alcohol dehydrogenase (ADH), 1% *i*-PrOH, 0.1 equivalents $NADP^+$, and 2 hours reaction time at room temperature. Red, percentage of total product that is the anti-Markovnikov oxidation product. *The major product is the epoxide, with minor allylic oxidation by-product (<8%). †The major product is the epoxide, with very minor allylic oxidation by-product (<1%). *i*-PrOH, isopropanol; er, enantiomeric ratio.

substitutions (M118L, T121A, V123I, I326V, and V327M).

Laboratory evolution of non-natural enzyme function has the potential to expand biochemical synthesis by enabling new biosynthetic pathways (*27*). In this respect, aMOx can be viewed as a key enzyme in a biosynthetic platform for sophisticated anti-Markovnikov functionalization of readily available alkenes (Fig. 1C and fig. S10). As a first step toward this goal, we used aMOx in combination with an alcohol dehydrogenase (ADH) to convert alkenes to their corresponding anti-Markovnikov alcohols in a single pot. Developing catalytic strategies for this overall reaction is a long-standing challenge (*28*) with only limited solutions. Current protocols either depend on noble metals with low activity (TTN < 10) (*29*) or generate alcohol products with no enantiocontrol (*30*). An enzymatic epoxidation, isomerization, and reduction sequence was also reported very recently (*31*). Our approach is best described as an anti-Markovnikov redox hydration, because it couples aMOx-catalyzed alkene oxidation with ADH-catalyzed carbonyl reduction. In this process, ADH has a dual function: It also recycles the cofactor through isopropanol oxidation. An advantage of this approach is that anti-Markovnikov alcohol products are generated using only nontoxic O_2 and isopropanol as stoichiometric reagents. We performed in vitro experiments with various substituted styrene derivatives **8** to **14**; aMOx with ADH converted all of them with TTNs ranging from 730 to 4500 and good anti-Markovnikov selectivities (up to 94%) (Fig. 3). Conversions of the 1,1-disubstituted and internal alkenes **15** and **16** yielded valuable chiral alcohol products with high enantiomeric excess. A catalytic, enantioselective method to convert prochiral alkenes to their chiral anti-Markovnikov alcohols has not been available previously. Enantioselective protocols have depended on a hydroboration-oxidation sequence using stoichiometric amounts of boranes that are toxic, expensive, and difficult to recycle (*32*). To demonstrate that these reactions can be performed on a preparative scale (0.23 to 0.50 mmol), anti-Markovnikov alcohols **8**, **9**, and **16** were synthesized using a catalyst loading of 0.05 mol % aMOx. The products were isolated with 82, 73, and 28% yield, respectively. The aMOx performed with a TTN up to 1600, and the chiral product **16** was generated with an enantiomeric ratio of >99:1.

Control over the epoxidation and anti-Markovnikov oxo-transfer pathways did not correlate with the activating or deactivating nature of the aromatic substituents (Fig. 3). The para-substituted styrenes (**8**, **9**, **11**, and **12**) were converted with high anti-Markovnikov selectivity, whereas styrenes containing ortho and meta substituents (**10**, **13**, and **14**) showed decreased selectivity (70%). These observations further support the hypothesis that this direct anti-Markovnikov oxidation is a catalyst-controlled process that depends on precise orientation of the substrate to outcompete epoxidation. It is remarkable that substitutions directly at the carbon-carbon double bond (**15** and **16**) still allow efficient anti-Markovnikov oxidation (TTNs of 1100 and 2900), although with lower selectivity (28 and 31%). Several additional styrenes (e.g., 4-methoxy-, 2-bromo-, and 2-fluorostyrene) were converted with low to moderate selectivity for anti-Markovnikov oxidation (fig. S11). We postulate that these can be improved by the same directed evolution approach used for styrene. Although the substrate scope of any individual enzyme may be limited, it is common to engineer or obtain from natural diversity a panel of catalysts to convert a much broader set of substrates (*33*–*35*). P450 enzymes accept a very wide range of alkenes bearing a variety of functional groups (*36*), and several studies have reported aldehydes as side products in the oxidation of these substrates, including even aliphatic alkenes (*37*–*40*). We have shown here an approach that can, in principle, be used with any of these P450 catalysts to obtain highly efficient and stereoselective anti-Markovnikov oxygenases.

Various enzymes have been optimized through directed evolution for abiological chemical transformations (*41*). In many cases, these have had a chemomimetic inspiration (*42*) and implemented catalytic cycles first discovered with synthetic catalysts. A frontier in the field is to move beyond this chemomimetic approach and target new chemistry made possible by the macromolecular structure of the protein catalyst. Directed evolution of aMOx pushes the boundary by establishing a catalytic cycle that has proven impossible to exploit with previous catalysts. Enzyme engineering can explore challenging reaction pathways and fully utilize the reactions accessible to a given high-energy intermediate. With all the environmental, cost, and quality benefits that biocatalysis brings to chemical synthesis (*43*), aMOx may enable sustainable, efficient, and stereoselective anti-Markovnikov functionalization of simple alkenes to produce valuable carbonyls, alcohols, and amines.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
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Teaching an enzyme to switch sites
There has been a recent flurry of activity in modifying enzymes to conduct unnatural chemical reactions more cleanly or selectively than synthetic chemical catalysts. Hammer *et al.* now report application of a cytochrome P450 variant to an oxidation that has largely eluded efficient catalysis. They used directed evolution to mutate the enzyme so that it placed oxygen at the less substituted carbon of the C=C double bond in styrenes, forming aldehyde products. They thereby attained opposite site selectivity to that of the widely used palladium-catalyzed Wacker-Tsuji oxidation.
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