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observed H atoms to act as an energy transfer medium to the bulk, specifically for diamond surfaces in sliding contact (37).

This damping model predicts $F_{\text{vib}}^{\text{H}} / F_{\text{vib}}^{\text{D}} \approx 1.72$ for diamond and $F_{\text{vib}}^{\text{H}} / F_{\text{vib}}^{\text{D}} \approx 1.86$ for Si. Other additive, mass-independent contributions to friction beyond this phononic mechanism will reduce the measured ratios from the theoretical predictions, as observed (Table 1). The predicted ~58% difference in $F_{\text{vib}}^{\text{H}} / F_{\text{vib}}^{\text{D}}$ for diamond versus Si is within our experimental uncertainty and may also be counteracted by the increased coupling of surface vibrational modes of deuterated Si(111) to bulk phonons (13) as compared with hydrogenated Si(111) (12). On diamond, surface modes overlap much less with bulk phonons (11). Furthermore, relaxing the assumption that the adsorbates are uncoupled (that is, considering coupled delocalized vibrations) leads to a weaker predicted mass contrast (32). It is likely, however, that surface defects, which accentuate the effect of localized vibrations (9), are present and may even be the dominating contribution to dissipation.

References and Notes

A Predictably Selective Aliphatic C–H Oxidation Reaction for Complex Molecule Synthesis

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Realizing the extraordinary potential of unactivated sp³ C–H bond oxidation in organic synthesis requires the discovery of catalysts that are both highly reactive and predictably selective. We report an iron (Fe)–based small molecule catalyst that uses hydrogen peroxide (H₂O₂) to oxidize a broad range of substrates. Predictable selectivity is achieved solely on the basis of the electronic and steric properties of the C–H bonds, without the need for directing groups. Additionally, carboxylate directing groups may be used to furnish five-membered ring lactone products. We demonstrate that these three modes of selectivity enable the predictable oxidation of complex natural products and their derivatives at specific C–H bonds with preparatively useful yields. This type of general and predictable reactivity stands to enable aliphatic C–H oxidation as a method for streamlining complex molecule synthesis.

The 20th century witnessed tremendous advances in synthetic methods and strategies that have enabled small molecule targets of extraordinary complexity and biological importance to be synthesized in the laboratory (1). An important remaining challenge is to achieve syntheses with heightened levels of efficiency. Because many biologically relevant small molecules are oxidized hydrocarbons, reactions that incorporate oxidized functionality selectively into organic frameworks are of particular interest in this regard. Three general reaction classes have been developed for this purpose: functional group interconversions, C–C bond-forming reactions of preoxidized fragments, and olefin oxidations. With these reactions, modern synthetic planning often centers around the use and maintenance of preexisting oxidized functionality. A powerful new class of reactions is emerging that introduce oxidized functionality directly into aliphatic (sp³) C–H bonds. Oxidation reactions for isolated, unactivated sp³ C–H bonds capable of operating with predictable selectivities on complex substrates hold special promise for streamlining syntheses. Such reactions would provide a general way to install oxidized functionalities at a late stage, thereby reducing unproductive chemical manipulations associated with carrying them through a sequence (2, 3).

Despite important advances in the discovery of catalytic methods for aliphatic C–H bond hydroxylations, amination, and alkylations (4–6), selective reactivity with complex substrates has only been demonstrated for activated C–H bonds (i.e., adjacent to a heteroatom or π system) (7–11) or via the use of substrate directing groups (12–14). High-yielding oxidations of isolated, unactivated sp³ C–H bonds are rare, and predictable reactivity has only been shown with simple hydrocarbon substrates (10, 15–17). The paradoxical challenge in solving this problem lies in discovering a catalyst that is both highly reactive and predictably selective for oxidizing these inert and ubiquitous C–H bonds. Moreover, to be useful in complex molecule synthesis, this reactivity and selectivity must be general for a broad range of densely functionalized substrates. Nature’s design principles for creating such catalysts involve the use of elaborate protein binding pockets that inherently limit substrate generality. A different
strategy was suggested to us by seminal work on site-selective olefin oxidations using bulky, electrophilic metal catalysts (18, 19). With these reagents, mono-oxidation of polynes occurs predictably at the most electron-rich, least sterically hindered double bond. Moreover, polar functionality proximal to the olefin can direct oxidation, overriding electronic and steric effects. We hypothesized that site-selective oxidations of unactivated sp³ C–H bonds could similarly be predictably controlled if a suitably reactive metal catalyst could be discovered that is capable of discriminating the subtle electronic and steric differences between C–H bonds in complex molecules (Fig. 1). We herein report an electrophilic iron catalyst, 4, with a bulky ligand framework that uses H₂O₂, an inexpensive, environmentally friendly oxidant to effect preparations on the basis of the electronic and steric selectivities with unactivated sp³ C–H bonds in complex molecules (Fig. 1). We herein report an electrophilic iron catalyst, 4, with a bulky ligand framework that uses H₂O₂, an inexpensive, environmentally friendly oxidant to effect preparations on the basis of the electronic and steric selectivities with unactivated sp³ C–H bonds in complex molecules (Fig. 1).

We demonstrate that the site of oxidation with 4 can be predicted in complex organic substrates on the basis of the electronic and steric environment of the C–H bond. Additionally, when carboxylate functionality is present, it can direct oxidations toward five-membered ring lactone formation.

Several nonheme iron complexes have shown promising, stereospecific hydroxylation reactivities with unactivated sp³ C–H bonds in simple hydrocarbon substrates (20–23). The application of these systems to preparative C–H oxidation chemistry has been prevented by the requirement for large excesses of substrate relative to oxidant, low catalyst turnover numbers, and poor selectivities for product formation. Nevertheless, iron(mep) complexes (mep is N,N′-dimethyl-N,N′-bis(2-pyridylmethyl)-ethane, 1,2-diamine) appeared promising for preparative C–H oxidations with complex substrates because they operate via an electrophilic metal oxidant (22, 23), have a bulky ligand framework amenable to modification, and have been used for preparative epoxidations of olefins containing functionality (24).

The attempted C–H oxidation of pivalate 1 with electrophilic [Fe(II)(mep)(CH₃CN)₂] (SbF₆)₂ complex, 3, under preparative conditions (substrate as the limiting reagent) resulted in only low conversion of starting material (12%) and modest selectivity for formation of tertiary hydroxylated product, 2 (56%, Fig. 2A, entry 1). Previous studies have shown a positive correlation between flexibility of the mep ligand and the lability of its iron complexes under oxidative conditions (25). Because unselective oxidations with nonheme iron complexes are often attributed to Fenton-type chemistry upon catalyst decomposition (25), we hypothesized that increasing the rigidity of the mep ligand may lead to improved selectivities. Exchanging the ethylene bridge with a cyclohexane ring had no effect. However, incorporating the methylamines into rigidifying pyrrolidine rings, which furnishes crystallographically characterized complex 4 (26), showed a notable improvement in selectivity (92%), translating into a doubling of the yield of 2 (14% yield, entry 2). The addition of acetic acid (AcOH), previously demonstrated to have a beneficial effect on epoxidations with 3 (24), increased the catalytic activities of both 3 and 4 without substantially changing their selectivities (entries 3 and 4, respectively). This resulted in notable improvement in yields with catalyst 4 (entry 4). Whereas increasing initial catalyst loadings, equivalents of AcOH, or equivalents of H₂O₂ (alone or in combination) gave no further improvements in yield, collective addition of all three components in a portionwise manner furnished preparatively useful amounts of hydroxylated product. Specifically, we found that three consecutive additions of catalyst 4 (5 mol%), AcOH (0.5 equivalent), and H₂O₂ (1.2 equivalents) over a period of 30 min afforded diastereomERICALLY pure hydroxylated product 2 in 51% isolated yield (entry 5).

A preliminary investigation of the substrate scope highlights the selective, electrophilic nature of the oxidant generated with 4 and H₂O₂ (Fig. 3). In all cases examined, hydroxylation occurred preferentially at the most electron-rich tertiary (3°) C–H bond, despite the fact that secondary (2°) C–H bonds have a significant statistical advantage (entries 1 to 9). Although the dicatIonic iron catalyst 4 is Lewis acidic, a remarkable range of moderately Lewis basic groups were well tolerated. For example, cyclic ethers, esters, carbamates, and electron-deficient amides were compatible with this C–H oxidation reaction (Fig. 3). In all cases examined in which the 3° C–H bond is part of a stereogenic center, hydroxylation occurred with complete retention of stereochemistry (entries 6 and 7).
When coupled to asymmetric alkylation methods for constructing stereogenic 3° alkyl centers, this reaction enables a very simple approach for accessing optically pure tertiary alcohols. In substrates in which no 3° C–H bonds were available, oxidation occurred at the methylene hydrogens to afford ketone product via the intermediacy of a 2° alcohol (entry 10). The site selectivities and stereochemical outcome of oxidations with 4 are consistent with a concerted mechanism mediated by an electrophilic oxidant (27).

The mass balance of these reactions [average of circa (ca.) 51% mono-oxygenated product with ca. 29% recovered starting material (rsm)] indicates that substantial levels of indiscriminate oxidation are not incurred (Fig. 3). With a highly oxidized L-leucinol derivative, hydroxylation occurred exclusively at the 3° C–H bond (entry 8). Although greater than three iterations of 4, H2O2, and AcOH fail to increase product yields, recycling of isolated starting material provides an effective strategy for obtaining high yields with valuable substrates. For example, the L-leucinol derivative was recycled five times to obtain a 90% isolated yield of pure (−)-12 (entry 8).

Complex small molecules often contain multiple 3° C–H centers. We sought to investigate whether the site selectivity of oxidation with electrophilic catalyst 4 is sensitive to the electronic environment of the 3° C–H bond (Fig. 4A). A series of dihydrocitronellol derivatives were evaluated with electron withdrawing groups (EWGs) in α or β positions to one of the two 3° C–H centers (Fig. 4B). In substrates...
with no electronic bias, equimolar mixtures of hydroxylated products at both centers were formed (entry 1). In all other cases evaluated, hydroxylation with 4 and H₂O₂ occurred preferentially at the 3° C–H bond remote from the EWGs (entries 2 to 8). β-Acetate or halogen functionalities gave modest but useful site selectivities (entries 2 to 4), and α-electron withdrawing functionalities resulted in excellent selectivities for remote hydroxylation (entries 5 and 6). Site selectivities of >99:1 were observed when strongly electron-withdrawing carbonyls were incorporated in the α position relative to one of the 3° C–H bonds (entries 7 and 8). These results demonstrate that C–H oxidations with 4 are subject to electronic deactivation with EWGs in the α or β positions.

We next investigated whether site selectivities of oxidation with bulky catalyst 4 are sensitive to the steric environment of the 3° C–H bond. We chose to examine (−)-acetoxy-p-menthane, 23 (Fig. 4D). Energy minimization calculations were performed on (−)-23 with use of density functional theory (DFT) followed by calculation of the electrostatic atomic partial charges. In the lowest potential energy conformer of (−)-23, the two 3° C–H bonds in the γ position to the acetate group (C-1 and C-8) are the least positive and have very similar atomic charges, suggesting a high similarity in their electron densities (Fig. 4C). Thus, only on the basis of the electronic factors, equivalent levels of oxidation would be predicted at these sites. However, we observed a strong preference for oxidation at the C-1 site, most likely because this site is less sterically hindered (Fig. 4D). The gem-dimethyl group of the isopropyl unit in the energy-minimized structure is oriented away from the acetate moiety to relieve unfavorable steric interaction. This conformation places the 3° C–H bond of C-8 proximal to the acetate group, making it sterically less accessible to the oxidant than the C-1 bond (Fig. 4C). These results demonstrate that, in molecules where C–H bonds of similar electron densities are present, steric can provide a second handle for selectivity.

The interplay between electronic and steric factors in determining the selectivities of C–H oxidations with 4 was further illustrated in a study of methyl esters (Fig. 5A). Hexanoate (−)-26 was hydroxylated by 4 and H₂O₂ predominately at the 3° C–H site to afford, after an in situ lactonization, (−)-27 as the major product with methyl ketone (−)-28 as the minor product (Fig. 5A). This outcome was predicted on the basis of electronic effects. Increasing the steric bulk around this site by introducing a second methyl substituent in substrate (−)-29 reverses the selectivity and results in formation of methyl ketone (−)-31 as the major product. The 2° C–H bond oxidation by 4 also occurred at the most electron-rich, least sterically hindered site. This experiment shows that steric effects can override electronic effects in site
selectivities of oxidation with 4 and suggests that oxidation at 2° C–H sites may operate with selectivities similar to those outlined above for 3° C–H sites.

On the basis of the known role of carboxylates as ligands for nonheme iron complexes and the beneficial role of acetic acid on the catalytic activity of 4, we postulated that a carboxylate group on the substrate could be used to direct the site of C–H oxidation (28). In support of this hypothesis, hexanoic acid (+)-32 furnished only the five-membered ring lactone (+)-30 in 70% isolated yield, whereas oxidation of the analogous methyl ester (+)-29 gave methyl ketone (+)-31 as the major product (Fig. 5A). The terminal carboxylic acid moiety in (+)-32 overrides the previously noted steric effects and directs hydroxylation to the hindered 3° site. Although a unique aspect of aliphatic C–H oxidations catalyzed by 4 is that they do not require a directing group for high selectivities, the ability to use this effect provides a third and powerful handle for selectivity. Predictable reactivity in response to all three such modes of selectivity has proven elusive in prior metal-catalyzed aliphatic C–H oxidations.

The value of this aliphatic C–H oxidation reaction for late-stage synthesis rests on how predictive the electronic, steric, and carboxylatedirecting modes of selectivity are in complex molecular settings. In order to evaluate this question, we examined the C–H oxidation of several natural products and their derivatives with 4. Antimalarial compound (+)-artemisinin 34 displays five 3° C–H bonds along its tetracyclic skeleton (Fig. 5B). In addition to the site-selectivity issue posed in this substrate, a chemoselectivity challenge is present in the form of a sensitive endoperoxide moiety known to be prone to Fe(II)-mediated cleavage (29). On the basis of the selectivity rules outlined above, we predicted that the electron-rich and sterically unencumbered 3° C–H bond at C-10 would be oxidized preferentially. The remaining 3° C–H bonds are in an α and/or β position to electron-withdrawing ester and endoperoxide moieties. We were gratified to find that the selectivity rules for oxidations with 4 developed on relatively simple substrates could be extended to this complex natural product. (+)-10B-Hydroxyartemisinin, 35, was generated as the major product in 34% yield (41% rms, Fig. 5B). By recycling this valuable starting material through the reaction twice, we obtained diastereomERICally pure (+)-35 in 54% isolated yield. With the same protocol, catalyst 3 afforded (+)-35 in only 23% isolated yield. Interestingly, (+)-34 has previously been enzymatically transformed to (+)-35 in 47% yield with microbial cultures of Cunninghamamella echinulata (29). Catalyst 4 gives higher yields than the enzymatic reaction with substantially shorter reaction times (three 30-min reactions versus 4 days) and a 10-fold higher volume throughput (0.033 M versus 0.0035 M). The ability of a simple, small mole-