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Recent Advances in the Selective Oxidation of Alkyl C–H Bonds Catalyzed by Iron Coordination Complexes

Mercè Canta, Mònica Rodríguez, and Miquel Costas

Abstract Selective and stereoretentive oxidation of alkyl C–H bonds has been described over the last decade by employing biologically inspired iron coordination complexes as catalysts and hydrogen peroxide as oxidant. Examples of catalyst dependent C–H site selectivity have started to appear. The current paper describes an account of these findings.

Keywords Alkyl C–H oxidation · Aminopyridine ligands · Bioinspired catalysis · Hydrogen peroxide · Iron coordination complexes · Nonheme oxygenases · Selectivity

Contents

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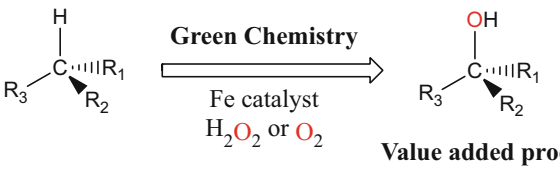
1 Importance and Scope of Alkyl C–H Oxidation Reactions

The functionalization of nonactivated alkyl C–H groups is a reaction of general interest and significance which remains as a challenge for modern chemistry [1–5]. Alkanes are convenient feedstocks because they are abundant and can be extracted from crude oil and natural gas. The catalytic oxidation of alkyl C–H groups is also highly important in organic synthesis because oxidized alkane frameworks are ubiquitous in organic molecules of industrial and biological relevance. Therefore the construction of such structures is of fundamental interest in modern organic synthesis. However, selective oxidation of alkyl C–H bonds in an environmentally sustainable manner remains as one of the main current challenges in organic synthetic chemistry (Scheme 1).

Although the oxidation of C–H groups is thermodynamically favorable, it also has large activation barriers that translate into their characteristic inert nature against most reagents. This lack of reactivity is because C–H bonds are strong, non-polarized, and localized, with a highly stabilized HOMO and a high lying LUMO. Therefore highly reactive oxidizing reagents are required to overcome these barriers, and this most commonly compromises selectivity [6, 7]. The main difficulties are (1) to control chemoselectivity, i.e., to direct the oxidation toward C–H groups in the presence of other functionalities in the molecule, usually more reactive, (2) to stop the functionalization at the desired oxidation state, thus avoiding undesired over-oxidized products, and (3) to discriminate among the various C–H groups present in a substrate, because most organic molecules contain multiple C–H sites with only slight electronic and structural differences. Given these difficulties, even though oxygenated alkyl frameworks are basic constituents of the majority of organic molecules, selective C–H oxidation is very rarely considered in synthetic planning. Instead, already oxygenated small molecules are employed in the building up of more complex structures, relying on protecting and deprotecting sequences [6–9]. On top of that, it is becoming increasingly necessary for chemical transformations to be carried out in a sustainable manner, using non-toxic and available reagents that could generate minimum waste (Scheme 1). In this regard, selective C–H oxidation is envisioned as a very powerful tool in organic synthesis because it converts ubiquitous alkyl moieties into functional groups. This translates into the rapid built-up of molecular complexity from



Scheme 1 Selective Oxidation of alkane hydrocarbons into value added product through Fe-catalyzed reactions as example of a challenging and environmentally sustainable transformation

inert functionalities, limiting the use of protecting groups, and enabling new and shorter synthetic strategies [10–13].

The development of catalysts for C–H oxidation is regarded as a highly appealing approach. These catalysts are expected to enable mild reaction conditions and introduce distinct chemo- and regioselectivities based on their electronic and steric properties, as well as their ability to engage in weak and reversible noncovalent interactions with the substrate [14]. Toward this endeavor, nature constitutes an excellent inspirational source. A number of metalloenzymes exist that perform selective C–H oxidation with high levels of chemo-, regio-, and stereoselectivity, and iron constitutes the most common metal source found in these metalloenzymes. This prominent role of iron in biological C–H oxidative transformations in combination with the availability and lack of toxicity of this element, has made this metal very attractive in synthetic catalyst development [15, 16]. Iron porphyrins have been traditionally regarded as powerful oxidation catalysts but most recently iron coordination complexes have emerged as promising and convenient alternatives with improved catalytic performance in terms of product yields and selectivities [14]. Major findings and challenges of the topic are discussed below.

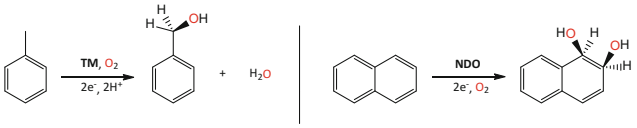
2 Precedents for Selective C–H Hydroxylations at Non-Heme Iron-Dependent Enzymes

2.1 Biological Precedents

Iron is the metal ion of choice for many biological oxidations because of its natural abundance in the geosphere, its inherent electronic properties, and its accessible redox potentials [17]. It is a ubiquitous element in living systems and its versatility is unique. The high availability of this metal and its various attainable oxidation states has led to the evolutionary selection of iron in many life processes. Iron-containing biological molecules play important roles in biologically essential transformations, such as biological oxidations and oxygen transport [18]. There is a myriad of remarkable transition-metal-dependent oxidative enzymes capable of activating dioxygen and catalyzing the selective oxidation of C–H bonds (alkane hydroxylation) or C=C groups (olefin epoxidation or *cis*-dihydroxylation) [19–24].

2.1.1 Rieske Oxygenases

In the past 15–20 years, several studies have been performed on mononuclear non-heme iron(II) enzymes. Among them, Rieske oxygenases constitute a relevant and paradigmatic example of mononuclear non-heme iron(II) proteins involved in O_2 activation reactions. Their efficiency and versatility are even greater than those of the related heme-containing Cyt P450, being able to catalyze stereoselective



Scheme 2 Benzylic hydroxylation and aromatic *cis*-dihydroxylation reactions catalyzed by Rieske oxygenases (toluene monooxygenase and naphthalene-1,2-dioxygenase, respectively)

benzylic hydroxylation and *cis*-dihydroxylation reactions (Scheme 2), among other reactions. They are also the only enzymes among both heme and non-heme iron enzymes capable of stereospecific and enantioselective *cis*-dihydroxylation of arene and olefin double bonds, which are reactions of high biotechnological interest as they initiate the biodegradation of aromatics in the soil [24–31].

Rieske oxygenases are part of a superfamily of enzymes that share a characteristic structure consisting of an oxygenase component (a mononuclear non-heme iron(II) high spin center containing a 2-His-1-carboxylate facial triad motif in the active site) [31–33]. Besides, the active site contains a reductase component (an Fe_2-S_2 Rieske center) that delivers electrons from NAD(P)H to the oxygenase center [34].

Naphthalene-1,2-dioxygenase (NDO) is one of the best studied examples of the Rieske dioxygenases family, and a catalytic cycle has been proposed [26, 34]. Studies on crystals of NDO exposed to O_2 indicate that a side-on-bound peroxo (or -hydroperoxo)-iron(III) species is the last detectable intermediate before substrate oxidation occurs [35]. In this reaction, both O_2 atoms are incorporated in the *syn*-diol product. Interestingly, labeling studies also show $H_2{}^{18}O$ incorporation into the *syn*-diol product, suggesting that the O–O bond heterolytic cleavage can generate a putative $Fe^{V}=O$ species before substrate attack, although direct evidence for this high-valent oxo species has yet to be obtained [26, 34, 36]. Moreover, phthalate dioxygenase, an enzyme of the Rieske oxygenase family, can elicit catalytic chemistry when H_2O_2 is used as oxidant thus resembling the peroxide shunt of Cyt P450 [37].

Rieske oxygenases can be naïvely taken as a precedent that simple non-heme iron sites, bound to nitrogen and oxygen based ligands, can form oxidizing species that attack oxidatively robust functionalities via mechanisms that depart from Fenton transformations, and, because of that, this family of enzymes serves to inspire development of oxidation catalysts based on simple iron coordination complexes associated with nitrogen and oxygen ligands.

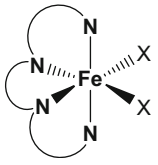
Convincing evidence for a metal-based mechanism in non-heme catalyzed C–H oxidation reactions with a synthetic catalyst appeared in 1997 in work by Que and co-workers [38] where a family of tpa-based (tpa = tris-(2-pyridylmethyl)amine) iron(II) complexes were investigated as stereospecific C–H oxidation catalysts using H_2O_2 as oxidant. Beyond their mechanistic significance, these findings were key for the future development of this chemistry with a synthetic aim, because a metal-based mechanism bears implicitly the possibility of modulating the

reactivity and thus the selectivity of the iron-based species that attack the C–H bond by means of ligand design. Instead, C–H breaking reactions initiated by hydroxyl or alkoxyl radicals are devoid of this control. Therefore, the bona fide settling on an iron-based C–H functionalization mechanism is the basis of the following past and present efforts to develop non-heme iron complexes as selective C–H oxidation catalysts [14, 17, 39].

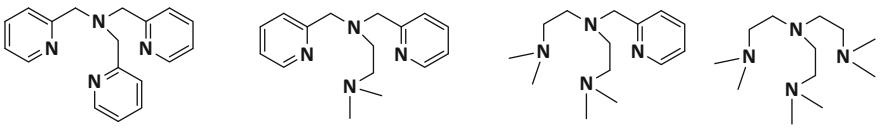
3 Iron Coordination Complexes as Catalysts for Selective C–H Bond Oxidation

Mononuclear non-heme iron(II) complexes containing *N*-based ligands, especially those containing pyridine heterocycles, have been extensively explored in metal-catalyzed transformations over the last decade [14, 17, 39, 40]. A particularly relevant aspect of the use of *N*-based ligands is that they led to the discovery of very selective C–H and C=C oxidation iron catalysts, and synthetically useful methodologies have also emerged from the use of these complexes. A very challenging aspect of this chemistry is that the catalytic activity of a complex is dramatically dependent on its ligand structure; therefore accurate design of the ligand is necessary yet not obvious [41]. The vast majority of iron complexes that can mediate stereospecific hydroxylation of alkanes contain an Fe^{II} center and tetradentate *N*-based ligands that leave two coordination positions vacant in a *cis* relative position that are occupied by weakly bound ligands (Scheme 3). The lability of these positions is a key aspect to ensure a fast reaction with the oxidant. Tripodal and linear families of complexes bearing tetradentate ligands have mostly been studied in the oxidation of alkanes employing H_2O_2 as oxidant.

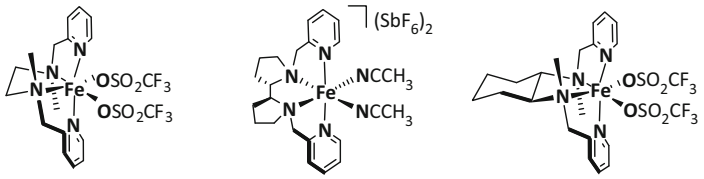
An illustrative example of tripodal ligand is tpa. As mentioned above, the combination of $[Fe(tpa)(CH_3CN)_2](ClO_4)_2$ with H_2O_2 proved to oxidize alkanes effectively. The oxidation is highly stereospecific (>99% retention of configuration for the oxidation of *cis*- and *trans*-1,2-dimethylcyclohexane (DMCH)), this being the first example of non-heme iron catalysts capable of stereospecific alkane oxidation [42, 43]. Studies with $[Fe(OTf)_2(tpa)]$ (OTf = trifluoromethylsulfonate anion) and derivatives where pyridine heterocycles were later systematically replaced by aliphatic amines (Scheme 4) were performed by Britovsek and coworkers [44]. These studies showed that at least two pyridine donors were needed



Scheme 3 Representation of N_4-tetradentate iron complexes with two *cis* coordination positions occupied by labile ligands (X)



Scheme 4 Tpa-based ligands introducing aliphatic amines used for the preparation of Fe^{II} complexes



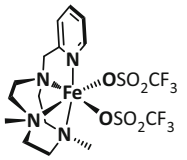
Scheme 5 Structure of $[Fe(OTf)_2(mep)]$, $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$, and $[Fe(OTf)_2(mcp)]$ catalysts

in the ligand to show reactivity distinct from Fenton-type chemistry, and are essential for high catalytic activity and selectivity in these systems.

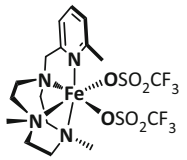
An arguably more interesting catalyst is $[Fe(OTf)_2(mep)]$ (mep = *N*,*N*′-dimethyl-*N*,*N*′-bis(2-pyridylmethyl)-ethane-1,2-diamine, Scheme 5) [43, 45, 46], which proved to be more efficient in stereospecific alkane hydroxylation than its tpa analogue but still worked under conditions of large excess of substrate [42–44, 47, 48]. Interestingly, Bermejo and coworkers recently reported the selective oxidation of steroids and terpenoids using $[Fe(OTf_2)(mep)]$ [49, 50]. In this case, substrate limiting conditions were employed, and synthetically useful yields (up to 70%) were achieved.

Another interesting ligand platform which has been extensively studied is the Pytacn (Pytacn = *N*-methyl-2-pyridyl *N*′,*N*″-dialkylsubstituted triazacyclononane) family (Scheme 6) [51]. $[Fe(OTf)_2(^{Me,H}Pytacn)]$ proved to be capable of mediating the hydroxylation of alkanes with retention of configuration [51–53]. Substitution on the N atoms of the triazamacrocycle and on the pyridine 6th position were studied in order to explore steric effects in catalytic oxidations. The 6-methyl pyridine substituted $[Fe(OTf)_2(^{Me,Me}Pytacn)]$ showed unusually high efficiency in the stereospecific oxidation of alkanes and alkenes with H_2O_2. This catalyst was also described to mediate the oxidation of alkyl C–H bonds with product yields that may be amenable for synthetic purposes [54]. Besides its high activity, this catalyst also exhibits enhanced selectivity toward methylene sites.

A major breakthrough in the field was introduced by White and Chen [55] in 2007, reporting the predictably selective oxidation of C–H bonds for the synthesis of complex molecules employing H_2O_2 as oxidant and a non-heme iron catalyst. In this case the catalyst employed was $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ (pdp = *N*,*N*'-bis (2-pyridylmethyl)-2,2′-bipyrrolidine), a coordination complex that bears a relatively bulky tetradentate ligand framework (Scheme 5). The C–H site of oxidation with this system could be predicted in complex organic molecules on the basis of

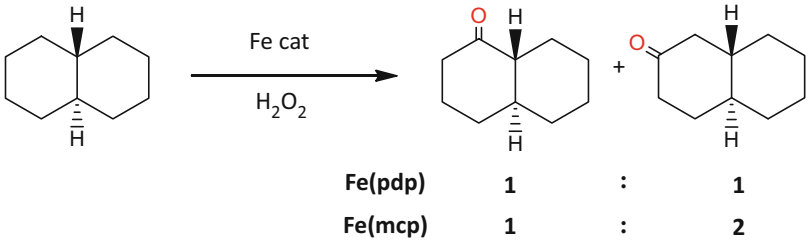


[Fe(OTf)$_2$(^{Me,H}Pytacn)]



[Fe(OTf)$_2$(^{Me,Me}Pytacn)]

Scheme 6 Structure of relevant Pytacn-based complexes for C–H oxidation reactions

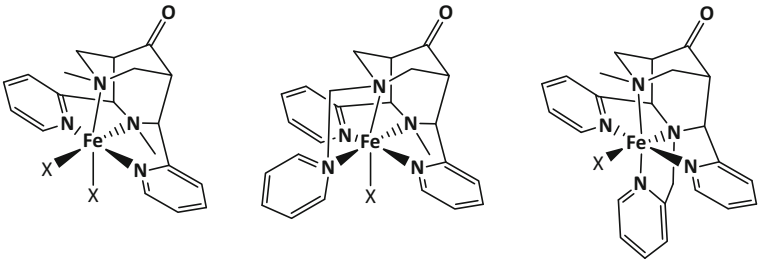


Scheme 7 Selectivity for methylenic sites of [Fe(OTf)$_2$(pdp)] and [Fe(OTf)$_2$(mcp)] in the oxidation of *trans*-decaline

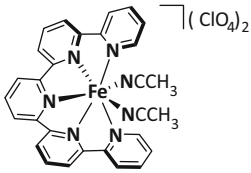
the electronic and steric environment of the C–H bonds. Additionally, when a carboxylic acid functionality was present, this group could direct oxidations toward five-membered ring lactone formation. Three years later, these authors used the same catalyst to study the effect of the combination of different effects on dictating selectivity in methylene oxidations [56]. The authors reported the site-selective oxidation of nonactivated secondary C–H bonds to afford monooxygenated products in preparative useful yields without the use of directing or activating groups. For natural products, useful levels of chemo-, site-, and diastereoselective methylene oxidations were obtained.

More recent work showed that [Fe(OTf)$_2$(mcp)] (Scheme 5), based on the cyclohexyldiamine backbone is a convenient catalyst for preparative C–H oxidation reactions [57]. Use of the cyclohexyldiamine instead of the bipyrrolidine makes the iron catalyst more easily obtained in large amounts. C–H site selectivity with this catalyst responds to electronic and stereoelectronic effects as [Fe(pdp)(CH$_3$CN)$_2$](SbF$_6$)$_2$, but the former appears to be more selective for discriminating among multiple methylenic sites. For example, [Fe(OTf)$_2$(mep)] and [Fe(pdp)(CH$_3$CN)$_2$](SbF$_6$)$_2$ oxidize the two distinct methylenic sites of *trans*-decaline, the second complex yields a roughly 1:1 ratio, whereas [Fe(OTf)$_2$(mcp)] yields a 2:1 ratio in favor of the sterically less demanding methylene site (Scheme 7).

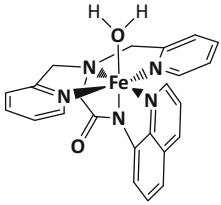
Comba and coworkers [58] described a set of rigid pentadentate iron complexes based on bispidine derivatives (Scheme 8) for the catalytic oxidation of cyclohexane, obtaining reasonably good turnover numbers (TON) (up to 34 TON).



Scheme 8 Bispidine-based catalysts, where X is solvent molecule or oxo group



Scheme 9 Structure of $[Fe(qpy)](ClO_4)_2$ catalyst reported for the oxidation of cyclohexane



Scheme 10 Structure of $[Fe^{III}(dpaq)(H_2O)]^{2+}$ catalyst

A different approach was proposed by Che and coworkers [59], who used $[Fe(qpy)](ClO_4)_2$ (qpy = 2, 2′ : 6′, 2″ : 6″, 2‴ : 6‴, 2⁗-quinquepyridine, Scheme 9) in combination with Oxone for the oxidation of cyclohexane, obtaining modest TON of products. Activated substrates were tested affording up to 85% yield for the oxidation of xanthene.

Finally, Hitomi et al. recently presented a catalytic system based on the pentadentate H-dpaq ligand (dpaq = 2-[bis-(pyridine)-2-ylmethyl)]amino-*N*-quinolin-8-yl-acetamidate, Scheme 10) [60]. The complex $[Fe^{III}(dpaq)(H_2O)]^{2+}$ was used in combination with various oxidants to show a metal-based oxidation mechanism suggested by the high alcohol/ketone (A/K) ratios obtained in the oxidation of cyclohexane, regardless of the oxidant employed. This catalyst presented a performance virtually identical to that of $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ in the oxidation of *cis*-4-methylcyclohexyl-1-pivalate and 1-substituted 3,7-dimethyl-octane without the addition of acetic acid.

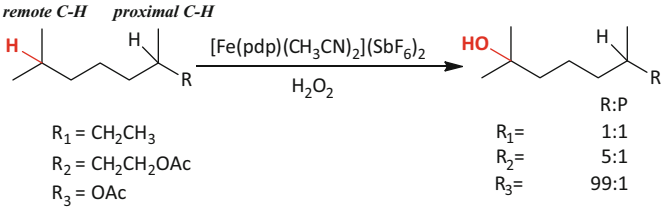
4 Tuning the Selectivity in Alkane Oxidation Reactions

One of the major subjects of interest over the last decade in metal-catalyzed alkane oxidation reactions has been the understanding of the factors determining the C–H site selectivity of such processes [61]. This knowledge is necessary to face the challenge of devising chemical tools for overcoming the innate reactivity of C–H bonds, introducing novel selectivities in these reactions.

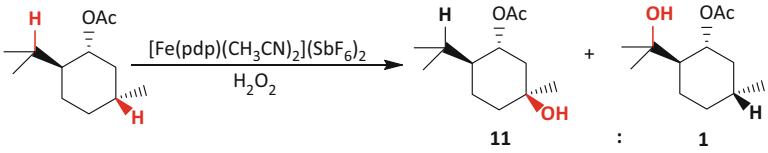
4.1 Predictably Selective Oxidations and Selectivity Patterns

A major breakthrough in predictable selectivity on aliphatic C–H oxidation reactions was introduced by White and Chen in 2007 [55]. In this landmark work, predictable selectivity when using the $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ catalyst was achieved on the basis of the electronic and steric properties of the C–H bonds, without the need for directing groups. The iron catalyst $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ (15 mol%), together with H_2O_2 as oxidant and acetic acid as additive, was capable of performing selective oxidations of nonactivated C–H bonds for a broad range of substrates. Very interestingly, this predictability could also be used to oxidize selectively complex natural products at specific C–H bonds in preparative useful yields. Selectivity can be achieved by introducing directing groups (see below), or can be predicted by considering the steric and electronic properties of the different C–H bonds of the substrate. Hydroxylation occurred preferentially at the most electron-rich tertiary C–H bond, with complete retention of stereochemistry (provided that the tertiary site was part of a stereogenic center). To test the site selectivity among different tertiary C–H bonds, small molecules with two tertiary sites were oxidized, always obtaining preferential oxidation at the tertiary C–H bond more remote from electron-withdrawing groups (EWGs). The selectivity between the two tertiary sites ranges from 5:1 (remote:proximal, R:P) to 99:1 (R:P), depending on the substrate. However, when no EWGs were present in the molecule, no selectivity was obtained, affording ratios of 1:1 (R:P) (Scheme 11).

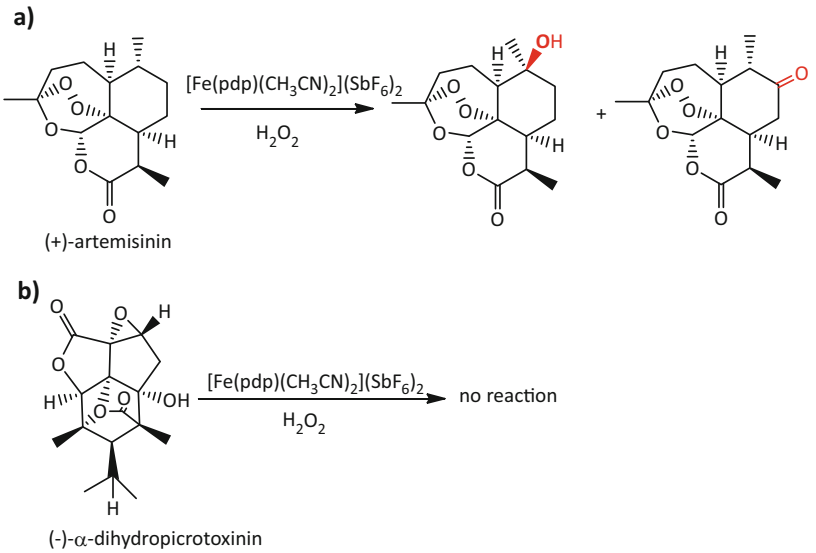
Regarding the steric effects, (−)-menthyl acetate was chosen as substrate, in which two of the three tertiary sites are virtually equivalent in terms of electronics.



Scheme 11 Oxidation of substrates with electronically different groups by $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$



Scheme 12 Selective oxidation of (−)-menthyl acetate with $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ as catalyst



Scheme 13 Oxidation of complex molecules by $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$

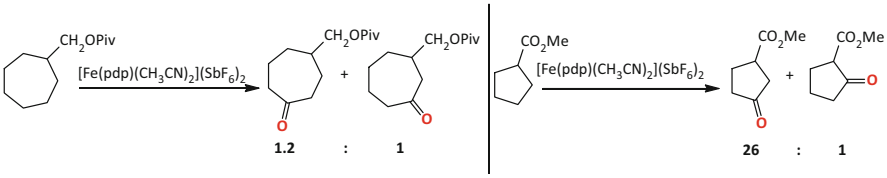
Oxidation occurred preferentially at the less hindered tertiary C–H bond, with 11:1 (accessible:hindered) selectivity and 55% combined yield (Scheme 12).

When steric and electronic effects were interplaying in a single substrate, experiments showed that the steric effects could override the electronic ones in site selectivities. The oxidation of the complex molecule (+)-artemisinin took place preferentially at the more electron-rich and less encumbered tertiary site with moderate yield (34%) which could be increased to 54% by recycling the starting material twice (Scheme 13a). More recent work showed that this oxidation also produced 22% of product arising from oxidation at a methylenic site [62]. On the other hand, in the highly hindered environment of (−)-α-dihydropicrotoxinin, no oxidation was attained, and 92% of the starting material was recovered after the oxidation process (Scheme 13b).

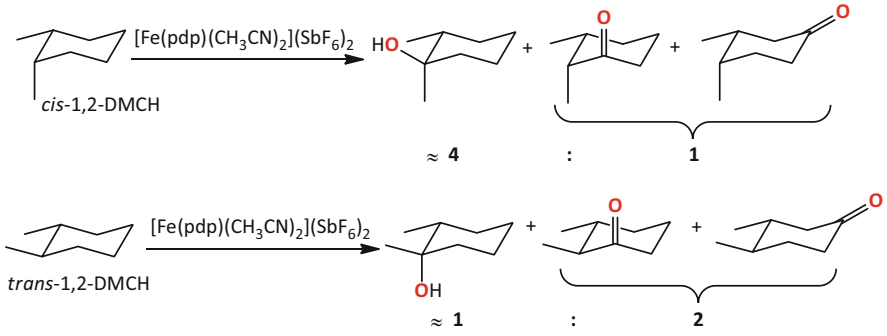
A study on methylene oxidation was presented by the same authors in 2010, using the $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ catalyst again [56]. Secondary C–H bonds have intermediate electronic and steric properties between tertiary and primary sites. Primary C–H bonds are stronger but sterically more accessible. On the other

hand, tertiary C–H bonds are weaker but sterically more encumbered. Nonactivated secondary C–H bonds could be site-selectively oxidized to afford monooxygenated products in preparative useful yields. In substrates with no electronic biasing elements, such as *n*-hexane, no site selectivity was attained. However, when EWGs were present in the substrate (inductive effects), the oxidation is biased towards the more remote site of the EWG, with selectivities ranging from 1.2:1 (R:P) to 26:1 (R:P), depending on the substrate (Scheme 14). Substrates where all protons are close to the EWG, such as cyclopentanone, showed almost no conversion.

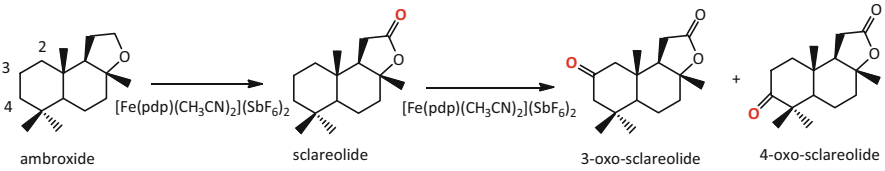
Interestingly, it was pointed out that stereoelectronic parameters based on conformational effects are also strong contributing factors to the product distribution in six-membered ring oxidations. Methylene sites adjacent to bulky groups were disfavored. However, the catalyst allows for subtle steric influence to have significant effects on the chemoselectivity of secondary vs tertiary C–H bonds. In the oxidation of *cis*-1,2-DMCH, the tertiary:secondary (3 ary:2 ary) ratio of products is 4:1, although for *trans*-1,2-DMCH the 3 ary:2 ary ratio is reversed to 1:2, favoring the oxidation at secondary sites (Scheme 15). The latter case might be explained because of the axial disposition of the tertiary C–H bonds, which are sterically more encumbered, and stronger than equatorial C–H sites. The reason is that breakage of the latter liberates strain and minimize 1,3-diaxial interactions of the methyl groups. As a result, predominantly secondary site oxidation was attained in the oxidation of *trans*-1,2-DMCH.



Scheme 14 Electronic effects on secondary C–H group oxidation by $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$



Scheme 15 Chemoselectivity of secondary vs tertiary C–H bonds in *cis*- and *trans*-1,2-DMCH oxidation by $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$



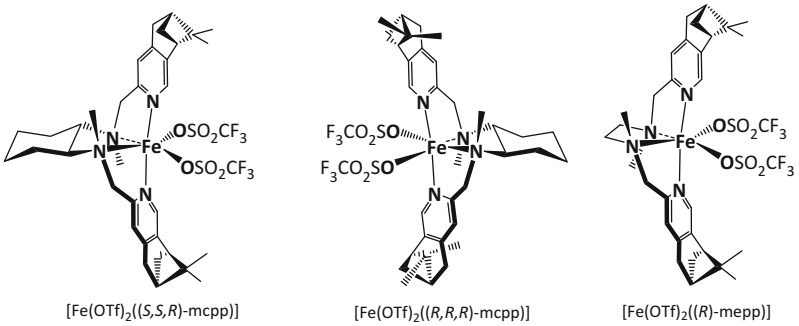
Scheme 16 Combination of stereoelectronic factors in the oxidation of terpenes by [Fe(pdp)$(CH_3CN)_2](SbF_6)_2$ [56]

On the other hand, electronic activating groups (EAGs) were used to achieve orthogonal site selectivity to inductive or steric effects by means of hyperconjugation. For example, when a cyclopropane ring was fused to a cyclohexane ring, oxidation occurred preferentially at the position more proximal to the cyclopropane ring (1:5.2 R:P). Moreover, steric, electronic, and stereoelectronic factors can be synergistically combined in the oxidation of complex natural products, resulting in useful levels of chemo-, site-, and even diastereoselective methylene oxidations. For the oxidation of complex natural products, terpenoids were chosen as appropriate substrate platforms to study the predictability of the oxidations. An interesting example of hyperconjugative effects was the oxidation of (−)-ambroxide, which selectively afforded (+)-sclareolide in high yield (80%). (+)-Sclareolide contains a lactone deactivating group, and further oxidation of this molecule yielded a mixture of (+)-3-oxo-sclareolide and (+)-4-oxo-sclareolide (1.4:1), thus oxidizing the more distal secondary sites from the EWG (Scheme 16). More recent work questions this selectivity, showing that oxidation of this substrate with [Fe$(OTf)_2$(pdp)] also produces (+)-4-oxo-sclareolide in amounts comparable to the (+)-2-oxo and (+)-3-oxo-sclareolide isomers [63].

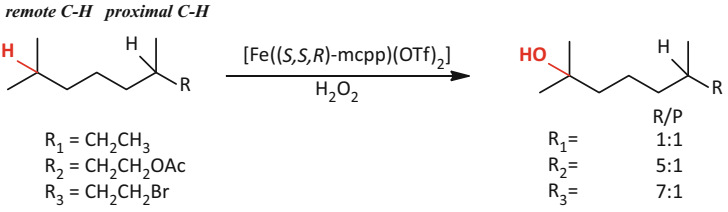
Inspired by the well-established principles in oxidation catalysis with heme complexes, Gómez et al. designed a new catalyst platform based on modifications at the well-known mep and mcp ligands (mcp = *N*,*N*′-dimethyl-*N*,*N*′-bis (2-pyridylmethyl)-cyclohexane-1,2-diamine) by introducing bulky pinene groups at positions 4 and 5 of the pyridine rings [64]. By doing so, [Fe$(OTf)_2$((*S*,*S*,*R*)-mcpp)], [Fe$(OTf)_2$((*R*,*R*,*R*)-mcpp)], and [Fe$(OTf)_2$((*R*)-mepp)] complexes were synthesized (Scheme 17).

The catalyst [Fe$(OTf)_2$((*S*,*S*,*R*)-mcpp)] stood as the most efficient of the series using very low catalyst loadings (1 mol%), even more efficient than [Fe(pdp)$(CH_3CN)_2](SbF_6)_2$ under these catalytic conditions, for the oxidation of *cis*-1,2-DMCH. Using a low loading of this catalyst (2 mol%), cyclohexane oxidation yields the corresponding ketone in 70% yield. Under these conditions, electronic effects were studied with 2,7-dimethyl-octane derivatives (Scheme 18), affording yields and selectivities very similar to those previously reported by White and coworkers (compare with Scheme 11) [55].

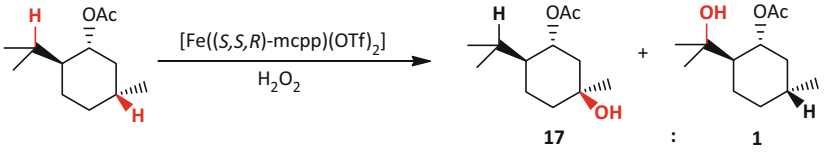
Furthermore, (−)-menthyl acetate was also tested using 3 mol% catalyst, obtaining 62% combined yield of oxidation at the tertiary sites with 17:1 selectivity (accessible:hindered) (Scheme 19). This efficiency selectivity was even more remarkable than that obtained with 15 mol% [Fe(pdp)$(CH_3CN)_2](SbF_6)_2$ [55] (compare with Scheme 12), most likely because of the well-defined chiral cavity



Scheme 17 Structure of pinene-based iron catalysts reported by Gómez et al.



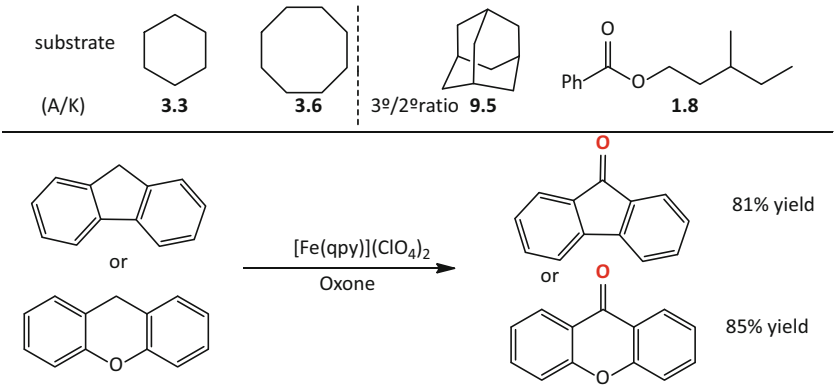
Scheme 18 Oxidation of substrates with electronically different groups by [Fe(OTf)$_2$((*S*,*S*,*R*)-mcpp)



Scheme 19 Selective oxidation of (−)-menthyl acetate with [Fe(OTf)$_2$((*S*,*S*,*R*)-mcpp)] as catalyst

around the metal center in [Fe(OTf)$_2$((*S*,*S*,*R*)-mcpp)], which provides robustness by protecting the iron site against catalyst deactivation, and enhances the selectivity of the catalyst. The effect of the pinene ring in terms of catalyst efficiency and stability was demonstrated by performing a time-profile analysis of the oxidation of (−)-menthyl acetate catalyzed by [Fe(OTf)$_2$((*S*,*S*,*R*)-mcpp)] and [Fe(OTf)$_2$((*S*,*S*)-mcp)]. These results indicated that H_2O_2 was more rapidly and efficiently consumed by the pinene-containing catalyst, which was not substantially deactivated during the course of the reaction. After a second addition of oxidant and substrate, [Fe(OTf)$_2$((*S*,*S*,*R*)-mcpp)] was the only catalyst still active and still capable of efficiently oxidizing the substrate into the desired alcohol product.

A different approach was presented by Che and coworkers using [Fe(qpy)](ClO$_4$)$_2$ (5 mol%) with Oxone [59]. High temperatures (80 °C) were required in this methodology. First of all, simple cyclic alkanes with no electronic effects



Scheme 20 Chemoselectivity of secondary vs tertiary C–H bond oxidation by $[Fe(qpy)](ClO_4)_2$

interplaying were tested. Oxidation of cyclohexane yielded 15.6 TON and 3.3 A/K ratio (A/K = [alcohol]/[ketone], [cyclohexanol]/[cyclohexanone]), whereas cyclooctane afforded 50% combined yield and 3.6 A/K ratio (Scheme 20). On the other hand, in the oxidation of adamantane, 42% yield was obtained with a 3°/2° ratio of 9.5. Hyperconjugation effects were used to direct the oxidation to the most proximal position to the EAGs. Interestingly, this catalyst supports aromatic groups on the substrate, and fluorene and xanthene were the most effectively and selectively oxidized, obtaining up to 85% yield of the ketone product (the sole product observed for these two substrates). Ester moieties were also employed as EAGs, as in the case of 3-methylpentyl benzoate, where the tertiary alcohol was obtained in 33% yield, and 18% of oxidation at the secondary most remote site (3°/2° = 1.8).

Oxidations proved to be stereospecific, as shown in the oxidation of *cis*- and *trans*-4-methylcyclohexyl benzoate, which occurred with retention of the configuration. In terms of yields, the former was more efficiently oxidized to the corresponding tertiary alcohol (45% yield) than the latter (19% yield). Finally, millimole scale oxidations of xanthene and tetrahydronaphthalene were performed, showing the practicability of this methodology. Xanthone was obtained as sole product in 83% yield in the oxidation of xanthene, whereas the products of tetrahydronaphthalene oxidation were a mixture of ketone (49%), secondary alcohol (12%), and overoxidized product (26%).

4.2 Novel Selectivity for Alkane Oxidation Reactions

It is now currently accepted that the factors governing selectivity in C–H oxidation reactions by traditional organic reagents are determined by the innate nature of the C–H bonds of the substrates [61]. Oxidations with iron catalysts such as $[Fe(OTf)_2(mep)]$ or $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ mainly appear to obey the same

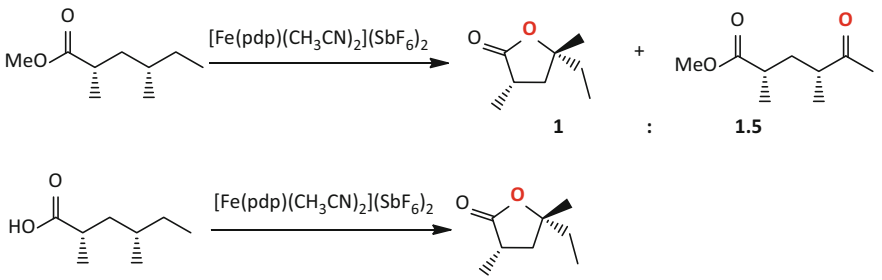
rules. Reagents that could override the intrinsic bias imposed by the general reactivity of the substrate are particularly valuable because they complement current methodologies and open novel synthetic pathways. To this end, two different approaches can be taken: the introduction of directing groups on the substrate and modifications on the catalyst architecture introducing structural aspects that condition substrate access to the catalyst active site, achieving novel selectivities differing from those dictated by the innate properties of the C–H bonds in the substrate. Both strategies are described in the following.

4.2.1 Novel Selectivity Induced by Directing Groups on the Substrate

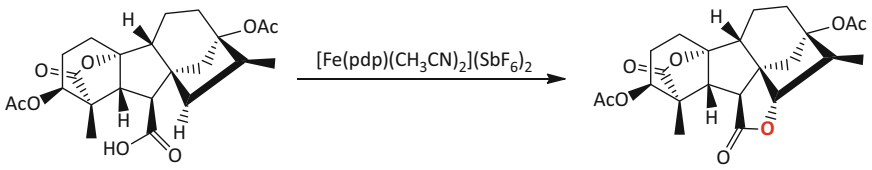
The use of directing groups on the substrate has been the most successful strategy to divert C–H regioselectivity in alkane oxidations [65–69]. In the particular case of non-heme iron-catalyzed oxidations, White and Chen presented the directed oxidation of carboxylic acid-containing substrates [55]. The authors postulated that a carboxylate group on the substrate could be used to direct the site of C–H oxidation, based on the role of carboxylates as ligands for non-heme iron complexes and the beneficial role of acetic acid on the catalytic activity of $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$. Diastereoselective lactonizations at secondary C–H sites were achieved with this methodology. For example, (+)-2,4-dimethyl-hexanoic acid was oxidized using $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ (15 mol%) and H_2O_2, furnishing a five-membered ring lactone in 70% yield, whereas the oxidation of the analogous methyl ester gave a methyl ketone as the major product (Scheme 21).

On the other hand, this methodology was evaluated with a tetrahydrogibberellic acid analog, which yielded the corresponding five-membered ring lactone as a single diastereoisomer in 52% yield (recycling the substrate once) (Scheme 22). In contrast, oxidation of the corresponding methyl ester resulted in mostly recovered starting material and mixtures of undefined oxidation products.

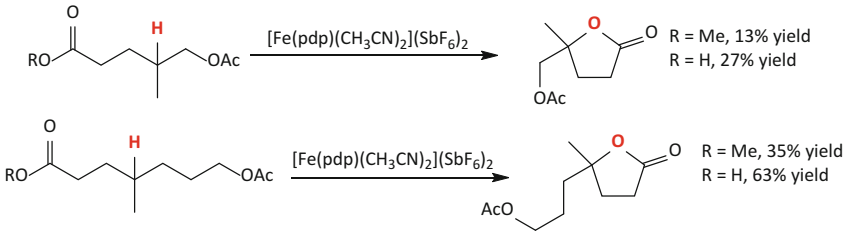
The same authors presented a more thorough study on the evaluation of the selectivity rules governing C–H oxidation of carboxylic acid-containing substrates in 2012 [70]. In this work it was shown that carboxylic acids not only controlled the



Scheme 21 Directed oxidation of a carboxylic acid-containing substrate with $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$



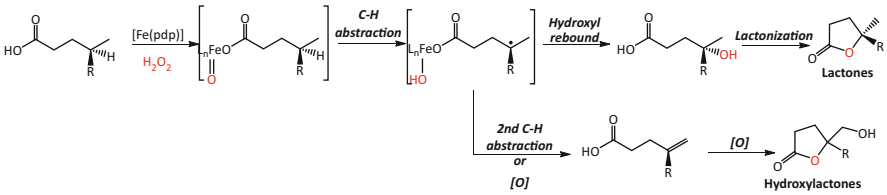
Scheme 22 Oxidation of a tetrahydrogibberellic acid analog with $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$



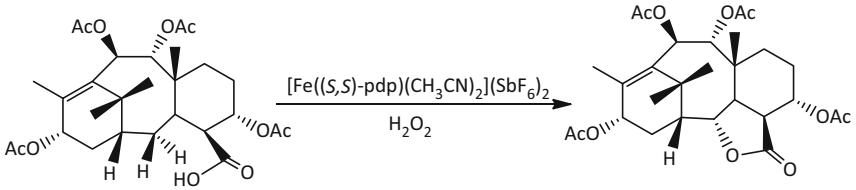
Scheme 23 Lactonization reactions of ester- and carboxylic acid-based substrates with $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$

site selectivity but they were also capable of overcoming unfavorable electronic, steric, and stereoelectronic effects within the substrate by rendering the oxidation reaction intramolecular. Linear methyl esters with EWGs were tested, showing that the substrate became more reactive as the EWGs were shifted away from the tertiary center, but poor yields were obtained. However, analogous carboxylic acid substrates were significantly more reactive, affording moderate yields of the corresponding lactones (Scheme 23).

Moreover, matched/mismatched behavior with the chiral $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ catalyst was detected when a chiral carboxylic acid was employed, although this behavior was not detected with analogous chiral methyl esters. This observation supported the proposal of carboxylic acid acting as ligand for the metal center. Enantiomeric enrichment of racemic carboxylic acid and lactone product was possible upon reaction with the chiral catalyst. In terms of steric effects, it was shown that yields of lactone products arising from oxidation of cyclohexane-derivatized carboxylic acids were virtually unaffected by the axial or equatorial disposition of the C–H bond to be oxidized, but instead methyl ester substrates were sensitive. From a mechanistic point of view, it is proposed that, analogous to C–H hydroxylation, the iron catalyst reacts with H_2O_2 and carboxylic acid substrate to generate an iron-oxo carboxylate as the active oxidant species, capable of intramolecular hydrogen atom abstraction to afford a short-lived carbon-centered substrate radical. This radical can proceed via two different rebound pathways to furnish the lactone product: (1) carboxylate rebound to form lactone directly or (2) hydroxyl rebound followed by lactonization (Scheme 24). The latter pathway is favored according to labeling studies, which showed that doubly ^{18}O-labeled carboxylic acid led to predominantly singly labeled lactone. Alternatively, the carbon-centered



Scheme 24 Proposed mechanism for $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$-catalyzed C–H lactonization reactions



Scheme 25 Directed oxidation of a taxane-based substrate to its lactone product with $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$

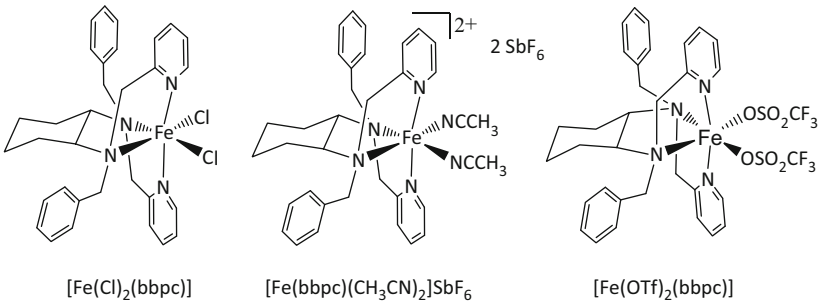
radical can undergo a second hydrogen abstraction to furnish an olefin intermediate, and further oxidation to yield hydroxylactones. Very interestingly, this strategy was employed in the site-directed oxidation of a taxane, obtaining moderate yield (49%) of the desired lactone (Scheme 25).

4.2.2 Novel Selectivity Induced by Steric Modifications on the Catalyst Architecture

A more subtle and elaborated approach exploited by enzymes relies on employing highly spatially structured oxidizing sites that could regulate selectivity by controlling access and orientation of the substrate in its approach toward the oxidizing unit. Pursuing this strategy, new bioinspired iron catalysts have been designed introducing steric modifications on the catalyst architecture to overcome the innate reactivity of C–H bonds and achieve novel selectivities in C–H bond oxidations.

In an attempt to alter the regioselectivity of non-heme iron catalysis, Goldsmith and coworkers [71] described a new mcp-modified ligand framework, where they replaced the methyl groups on the amine nitrogens with benzyl groups. Three iron complexes were synthesized – $[FeCl_2(bbpc)]$, $[Fe(OTf)_2(bbpc)_2]$, and $[Fe(bbpc)(CH_3CN)_2](SbF_6)_2$ (bbpc = *N*,*N*′-di(phenylmethyl)-*N*,*N*′-bis(2-pyridinylmethyl)-1,2-cyclohexanediamine) (Scheme 26) – and appeared to catalyze the oxidation of alkanes by H_2O_2, being the hexafluoroantimoniate complex the most active and selective for alkane hydroxylation.

Interestingly, the bulk installed on the ligand architecture directs the oxidation toward the less sterically hindered positions of substrates. Reaction of [Fe(bbpc)



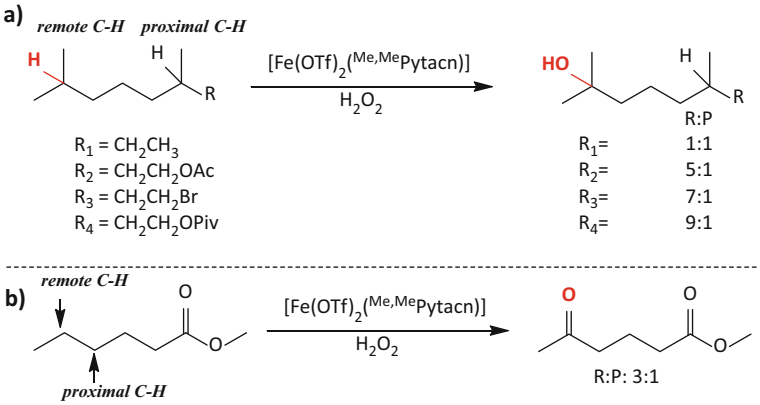
Scheme 26 Benzyl-modified mcp iron catalysts for efficient alkane oxidation reactions

$(CH_3CN)_2](SbF_6)_2$ (15 mol%) with *cis*- and *trans*-1,2-DMCH showed preferential oxidation for tertiary and secondary sites, respectively. As previously mentioned, this can be explained in terms of strain release of 1,3-diaxial interactions. Interestingly, when comparing these results with previously described catalysts under the same catalytic conditions, a clear preference for oxidation at the secondary position was observed for both substrates when the [Fe(bbpc)] catalysts were employed. Despite the high catalyst loading employed, yields obtained are modest (~30%). This effect might be attributed to the steric hindrance offered by the *N*-benzyl group.

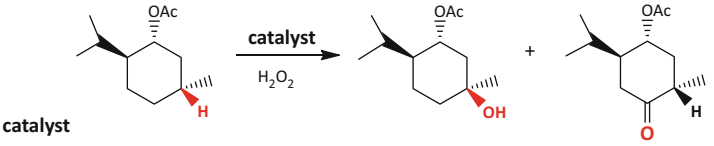
In recent work by Prat et al. [54], [Fe(OTf)$_2$(^{Me,Me}Pytacn)] (^{Me,Me}Pytacn = 1-(6-methyl-2-pyridylmethyl)-4,7-dimethyl-1,4,7-triazacylononane) was described as an efficient catalyst with enhanced preference for oxidizing methylenic sites. Interestingly, low catalyst loadings (3 mol%) were used in this protocol, and the addition of acetic acid appeared not to be strictly required for efficient catalysis, indicating the remarkably facile O–O lysis for this catalyst.

Following the same trend as the previously mentioned catalysts, oxidation with [Fe(OTf)$_2$(^{Me,Me}Pytacn)] occurred preferentially at the tertiary position more remote from EWGs, indicating its electrophilic nature (Scheme 27a). The remote/proximal ratios obtained were virtually the same as those attained with catalysts [Fe(pdp)$(CH_3CN)_2](SbF_6)_2$ and [Fe(OTf)$_2$((*S*,*S*,*R*)-mcpp)] (for comparison see Schemes 11 and 18, respectively). However, using [Fe(OTf)$_2$(^{Me,Me}Pytacn)], a significant amount of secondary site oxidation (ketone formation) was observed. Moreover, methylene oxidation was also sensitive to the electronic properties of the C–H bonds, as shown in the oxidation of methyl hexanoate (Scheme 27b).

Steric effects on the substrate also appeared to play a role in the oxidation reactions. An interesting example is 1,1-DMCH, where oxidation at adjacent position to the methyl groups was disfavored because of steric encumbrance, and the other two methylenic sites were thus favored. The enhanced selectivity for secondary sites was best illustrated in the oxidation of (−)-menthyl acetate, which furnished a ~2:1 mixture of tertiary alcohol:ketone after selective oxidation at the methylenic site. This behavior was in stark contrast with that offered by [Fe(pdp)



Scheme 27 Oxidation of substrates with electronically different groups by [Fe(OTf)$_2$(^{Me,Me}Pytacn)]. a) Hydroxylation of tertiary C-H bonds, b) oxidation of methylenic sites.

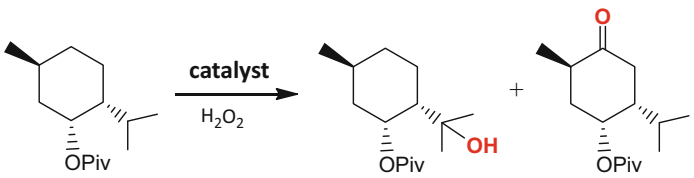


catalyst			
[Fe(OTf)$_2$(^{Me,Me}Pytacn)]	**2**	:	**1**
[Fe(pdp)(CH$_3$CN)$_2$](SbF$_6$)$_2$	**5**	:	**1**
[Fe(OTf)$_2$((*S,S,R*)-mcpp)]	**19**	:	**1**

Scheme 28 Oxidation of (−)-menthyl acetate with various catalysts described in the literature

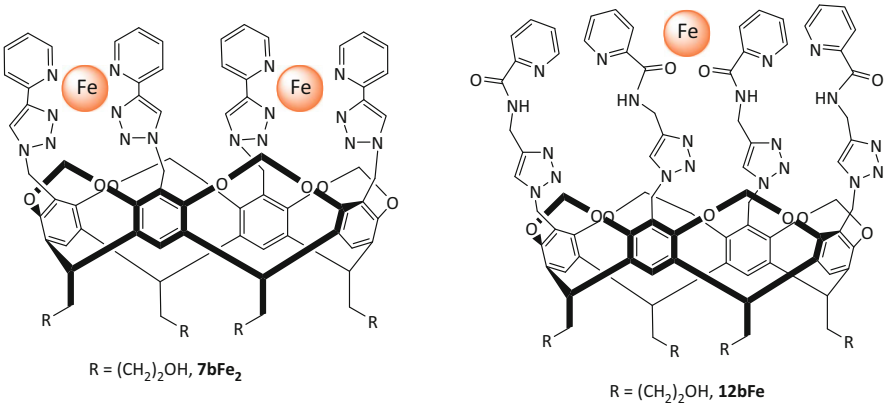
(CH$_3$CN)$_2$](SbF$_6$)$_2$ [55, 56] and [Fe(*S,S,R*)-mcpp)(OTf)$_2$] [64] under analogous conditions, which fairly selectively hydroxylate the most sterically exposed tertiary C–H bond (5:1 A/K and 19:1 A/K, respectively, Scheme 28).

On the other hand, in the oxidation of *trans*-cyclohexane-based substrates, oxidation at methylenic positions was found to be in competition with that of tertiary C–H bonds. *trans*-1,2-DMCH yielded a normalized 24:76 3°/2° ratio, and this trend was even more significant in the oxidation of *trans*-decaline (4:96), indicating that products arising from methylene oxidation are largely dominant. The rationale for this behavior lies on the steric demand exerted by the methyl group in the α-position of the pyridine, which remains in close proximity to the iron site. This fact favors preferential oxidation at the spatially more accessible methylenic sites in contrast to the more embedded tertiary C–H bonds. More importantly, this could be applied to divert regioselectivity in the C–H oxidation of (+)-neomenthyl esters (Scheme 29). Whereas [Fe(OTf)$_2$(pdp)] offered poor discrimination between secondary and tertiary C–H bonds, [Fe(OTf)$_2$((*S,S,R*)-mcpp)] and [Fe(OTf)$_2$(^{Me,Me}Pytacn)] were found to be complementary, the former



catalyst			
[Fe(OTf)$_2$(^{Me,Me}Pytacn)]	**27**	:	**73**
[Fe(OTf)$_2$(pdp)]	**39**	:	**61**
[Fe(OTf)$_2$((*S,S,R*)-mcpp)]	**80**	:	**20**

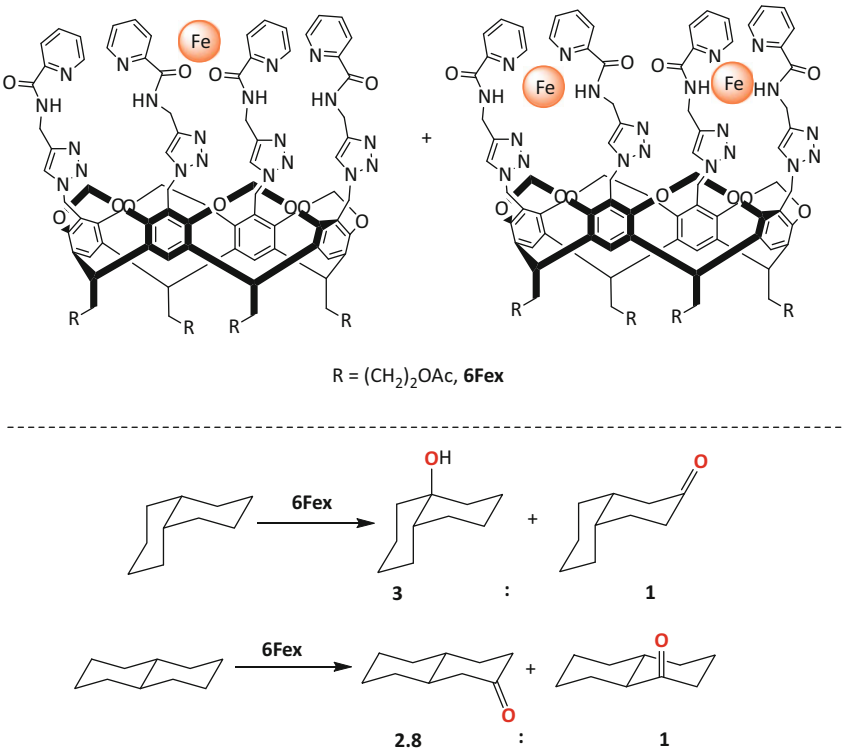
Scheme 29 Oxidation of (+)-neomenthyl pivalate with various catalysts described in the literature



Scheme 30 Resorcinarene-based cavitands used as catalysts for fluorene oxidation

yielding the tertiary alcohol as the major product (up to 80:20 normalized 3°/2° ratio) and the latter affording preferential oxidation at the methylenic site (up to 27:73 normalized 3°/2° ratio).

A different approach was proposed by Hooley and coworkers [72]. In this study resorcinarene-based cavitands were used as catalysts, which allow for binding of iron(II) by bidentate ligands, leaving empty sites for further reactivity at the metal sites. The iron-coordinated cavitands 7bFe$_2$ and 12bFe (Scheme 30) bore free coordination sites, and thus they were envisioned to perform C–H oxidation reactions under mild conditions, inspired by the mode of action of the Rieske oxygenases. However, these catalysts proved inactive towards cyclohexane and methylcyclohexane oxidations. In contrast, they were able to convert fluorene smoothly to fluorenone using TBHP as oxidant.

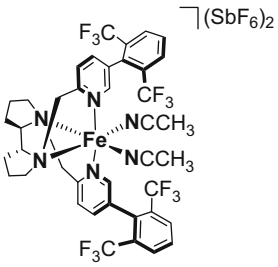


Scheme 31 Regioselectivity in the oxidation of *cis*- and *trans*-decaline by 6Fex and structure of the catalyst

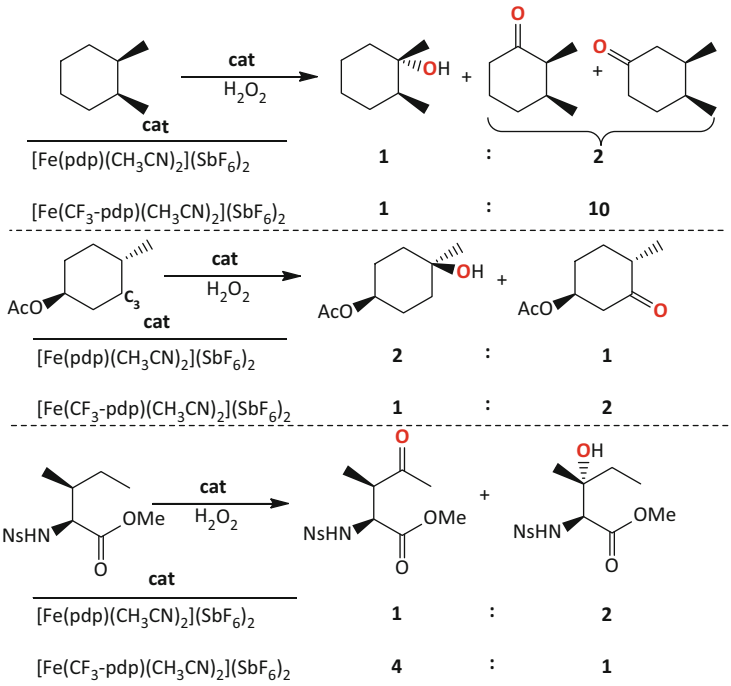
In a later study [73], the authors showed that 6Fex (Scheme 31) was capable of efficiently oxidizing *cis*-decaline to the tertiary alcohol (*cis*-2-decalol) and the ketone product (*cis*-2-decalone) (up to 69% yield) using TBHP. Interestingly, the addition of acetic acid was not strictly required for the outcome of the reaction, although long reaction times (24 h) and high temperatures (60 °C) were needed. Good selectivity for the tertiary alcohol was obtained (up to 75% normalized regioselectivity). On the other hand, *trans*-decaline afforded *trans*-2-decalone and *trans*-3-decalone as oxidized products in a 2.8:1 ratio with an overall yield of 46%. Interestingly, these catalysts were also able to oxidize benzylic methylenic sites very efficiently (up to 88% yield for the oxidation of 1-ethyl-4-methyl benzene).

Very recently White and coworkers [62] designed a new catalyst [Fe(CF_3-pdp)(CH_3CN)$_2$](SbF_6)$_2$ (CF_3-pdp = *N*,*N*′-bis(5-(2,6-di-(trifluoro)-methyl-phenyl)-2-pyridylmethyl)-2,2′-bipyrrolidine) that used a trajectory restriction strategy to achieve predictable, catalyst-controlled site-selectivity (Scheme 32).

In the oxidation of *trans*-1,2-DMCH, this catalyst exhibited enhanced selectivity towards secondary sites (10:1 2°/3° ratio), whereas the structurally related [Fe(pdp)(CH_3CN)$_2$](SbF_6)$_2$ catalyst provided a 2:1 2°/3° ratio (Scheme 33). On the other

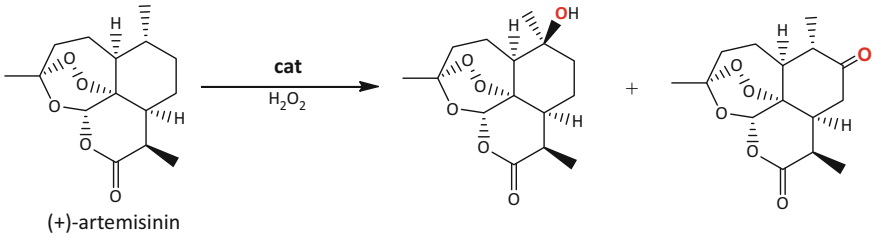


Scheme 32 Structure of trajectory restrictive catalyst $[Fe(CF_3\text{-pdp})(CH_3CN)_2](SbF_6)_2$ for catalyst-controlled site-selectivity



Scheme 33 Difference in regioselectivity attained with catalysts $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ and $[Fe(CF_3\text{-pdp})(CH_3CN)_2](SbF_6)_2$

hand, this catalyst was able to overturn the inherent reactivity of the substrates. This was the case of *trans*-4-methylcyclohexyl acetate, which gave the tertiary alcohol as major product when $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ was used (1:2 2°/3° ratio) but the C_3-ketone was the major product when $[Fe(CF_3\text{-pdp})(CH_3CN)_2](SbF_6)_2$ was employed (2:1 2°/3° ratio). The protected (+)-isoleucine changed from 1:2 to 4:1 2°/3° ratio when the sterically encumbered catalyst was used to oxidize this substrate.

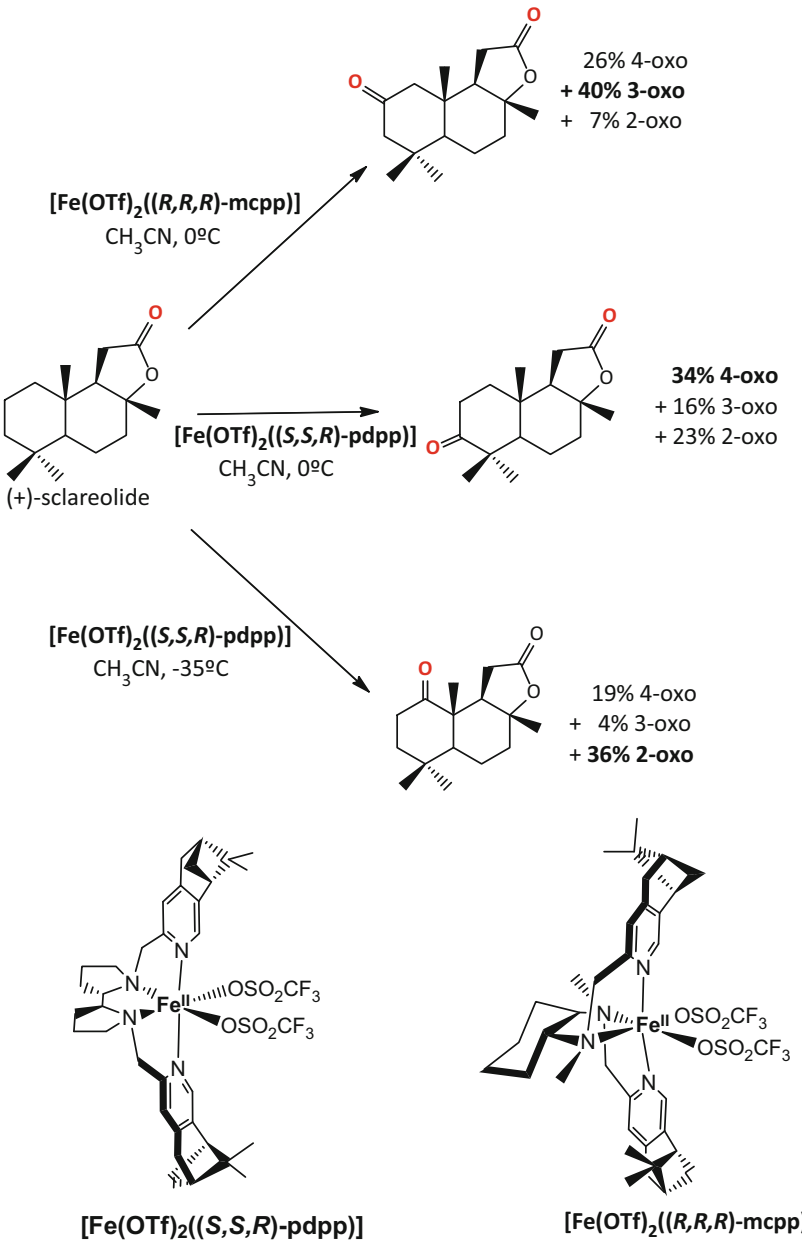


cat			
$[Fe(pdp)(CH_3CN)_2](SbF_6)_2$	1.3	:	1
$[Fe(CF_3\text{-}pdp)(CH_3CN)_2](SbF_6)_2$	1	:	11

Scheme 34 Oxidation of artemisinin with $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ and $[Fe(CF_3\text{-}pdp)(CH_3CN)_2](SbF_6)_2$

This strategy was further investigated in the oxidation of complex molecules such as (+)-artemisinin, where two products result: (+)-10β-hydroxy-artemisinin (3° site) and (+)-9-oxo-artemisinin (2° site). Whereas $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ catalyst afforded 2:1 2°/3° ratio, $[Fe(CF_3\text{-}pdp)(CH_3CN)_2](SbF_6)_2$ yielded 10:1 2°/3° ratio, the latter able to override strong electronic substrate bias (Scheme 34).

Modulation of selectivity among multiple methylene sites has been rarely observed and constitutes a major challenge. Nevertheless, changes in site selectivity in the functionalization of structurally rich natural product substrates using iron catalysts have been documented. For example, site selectivity in the oxidation of (+)-sclareolide was achieved by using highly structured non-heme iron catalysts containing pinene rings attached to pyridine moieties (Scheme 35). Hence, (+)-1-oxo-sclareolide, (+)-2-oxo-sclareolide, and (+)-3-oxo-sclareolide can be obtained as the main product in 36% (61% selectivity), 40% (55% selectivity), and 34% (47% selectivity) yield, respectively, by choosing the appropriate experimental conditions and catalyst. Although those yields may seem modest, they are competitive with enzymatic oxidations. For example, (+)-2-oxo-sclareolide is obtained enzymatically with reduced yields and longer reaction times.



Scheme 35 Regioselective oxidation among multiple methylene sites with [Fe(OTf)$_2$((*R*,*R*,*R*)-mcpp)], [Fe(OTf)$_2$((*S*,*S*,*R*)-pdpp)], and [Fe(OTf)$_2$((*S*,*S*,*R*)-pdpp)]

5 Novel Reactivity on C–H Oxidation

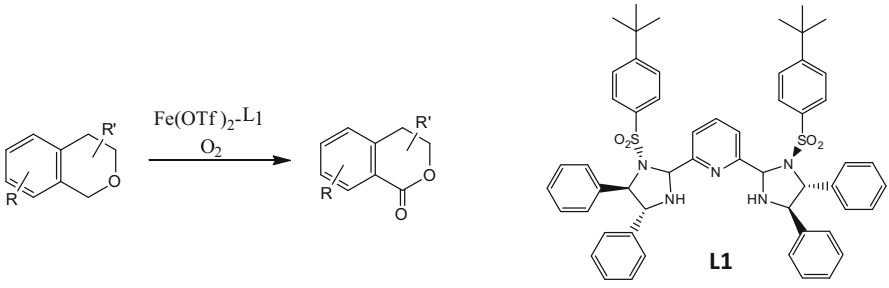
In addition to the most common C–H oxygenation reactions of alkanes employing peroxides as oxidants, novel reactivity for these substrates has emerged in the past few years. Remarkable examples of this emerging reactivity involves the α-oxygenation of electron-rich substrates employing O_2 as terminal oxidant, and desaturation of alkane C–H bonds.

5.1 α-Oxygenation

An original work in the field of C–H oxidation was reported by Xiao and coworkers [74] in 2014, when they developed novel iron catalysts with tridentate pyridine bissulfonylimidazolidine ligands for the α-oxidation of ethers under 1 atm of O_2 and additive-free conditions. This system relies on environmentally friendly conditions to oxidize electron-rich substrates selectively using O_2 as oxidant, with excellent mass balance and high turnover numbers. Most remarkably, H_2 is formed as the only side-product. The conditions mentioned provide the oxidation of important motifs for natural products as isochromans and phthalans. In case of isochromans (Scheme 36), the reaction proceeds with high chemoselectivity, with no alcohol byproduct formation and with good mass balance, with no degradation of the substrate. The presence of substituents in the alkyl ring does not affect the reaction yield. However, substituents in the aromatic ring show electronic effects because the electron-withdrawing groups induce higher TONs, whereas electron-donating substituents give the opposite effect. Moreover, very electron-rich isochromans can also be oxidized, but with lower TONs. This is the first reported iron system able to oxidize such electron-rich substrates.

5.2 Desaturation

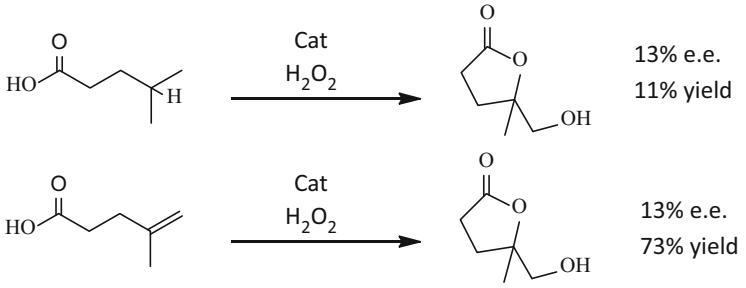
Nature has developed enzymes that have the ability to catalyze different type of reactions. An example is those enzymes that can perform hydroxylation or



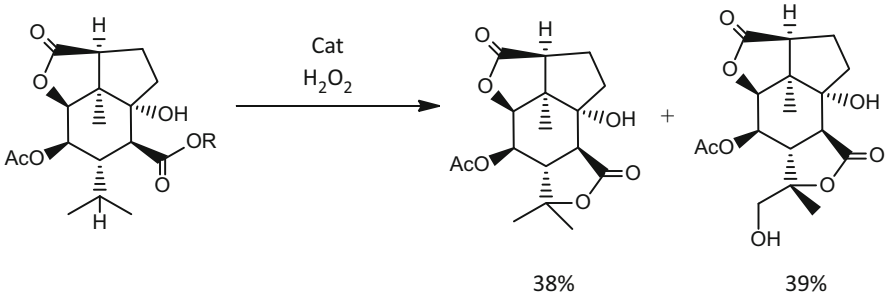
Scheme 36 Oxidation of electron-rich isochromans using iron catalyst

desaturation activity depending on the substrate. Hydroxylation reactions have been described for a good number of iron oxidation catalysts, but it was in 2011 when White and coworkers [75] described that $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ is able to disclose substrate-dependent hydroxylase/desaturase activity in aliphatic C–H bonds in substrates containing carboxylic acids. This ability was demonstrated when the 4-methylpentanoic acid was exposed to oxidizing conditions in the presence of $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ catalyst (Scheme 37). The product is proposed to result from a desaturation reaction that rapidly oxidizes to an epoxide and finally an intramolecular lactonization takes place to give the final product. This proposal was demonstrated by exposing the supposed alkene product from the desaturation reaction to the same reaction conditions that finally give the same product. Moreover, with the use of the chiral $[Fe(pdp)(CH_3CN)_2](SbF_6)_2$ catalyst, both reactions gave the same enantioenriched hydroxylactone product and also favored the same enantiomer.

This enzyme-like reactivity enables the synthesis of highly complex molecules from substrates containing carboxylic acids, such as picrotoxinin derivatives which, when exposed to the same oxidizing conditions, yield lactone and hydroxylactone products (Scheme 38).



Scheme 37 Desaturation/hydroxylation reaction of 4-methylpentanoic acid using $[Fe((R,R)\text{-pdp})(CH_3CN)_2](SbF_6)_2$ as catalyst



Scheme 38 Synthesis of highly complex lactone molecules using $[Fe((S,S)\text{-pdp})(CH_3CN)_2](SbF_6)_2$

References

1. Sheldon RA, Kochi JA (1981) Metal-catalyzed oxidation of organic compounds. Academic, New York
2. Shilov AE, Shul′pin GB (2000) Activation and catalytic reaction of saturated hydrocarbons in the presence of metal complexes. Kluwer Academic, Boston
3. Dyker G (2005) Handbook of C–H transformation, vol 1–2. Wiley-VCH, Weinheim
4. Pérez PJ (2013) Alkane C–H activation by single-site metal catalysis, vol 38. Springer, The Netherlands
5. Bordeaux M, Galarneau A, Drone J (2012) Angew Chem Int Ed 51:10712
6. Gutekunst WR, Baran PS (2011) Chem Soc Rev 40:1976
7. McMurray L, O'Hara F, Gaunt M (2011) Chem Soc Rev 40:1885
8. Che C-M, Lo VK-Y, Zhou C-Y, Huang J-S (2011) Chem Soc Rev 40:1950
9. Yamaguchi J, Yamaguchi AD, Itami K (2012) Angew Chemie Int Ed 51:8960
10. Labinger JA, Bercaw JE (2002) Nature 417:507
11. Godula K, Sames D (2006) Science 312:67
12. Chen K, Baran PS (2009) Nature 459:824
13. White MC (2012) Science 335:807
14. Lloret J, Company A, Gómez L, Costas M (2013) Alkane C–H activation by single-site metal catalysis, vol 38. Springer, The Netherlands
15. Enthaler S, Junge K, Beller M (2008) Angew Chemie Int Ed 47:3317
16. Schröder K, Junge K, Bitterlich B, Beller M (2010) Top Organomet Chem 33:83
17. Que L Jr, Tolman WB (2008) Nature 455:333
18. Cotton FA, Wilkinson G, Murillo CA, Bochmann M (1999) Advanced inorganic chemistry. Wiley, New York
19. Meunier B, Bernadou J (2000) Struct Bond 97:1
20. Schlichting I, Berendzen J, Chu K, Stock AM, Maves SA, Benson DE, Sweet RM, Ringe D, Petsko GA, Sligar SG (2000) Science 287:1615
21. Meunier B, de Visser SP, Shaik S (2004) Chem Rev 104:3947
22. Montellano POD (2004) Cytochrome P450: structure, mechanism and biochemistry, 3rd edn. Springer, New York
23. Kovaleva EG, Lipscomb JD (2008) Nat Chem Biol 4:186
24. Barry SM, Challis GL (2013) ACS Catal 3:2362
25. Gibson DT, Subramanian V (1984) Microbial degradation of aromatic hydrocarbons. Marcel Dekker, New York
26. Gibson DT, Resnick SM, Lee K, Brand JM, Torok DS, Wackett LP, Schocken MJ, Haigler BE (1995) J Bacteriol 177:2615
27. Hudlicky T, Gonzalez D, Gibson DT (1999) Aldrichimica Acta 32:35
28. Gibson DT, Parales RE (2000) Curr Opin Biotechnol 11:236
29. Wolfe MD, Parales JV, Gibson DT, Lipscomb JD (2001) J Biol Chem 276:1945
30. Costas M, Mehn MP, Jensen MP, Que L Jr (2004) Chem Rev 104:939
31. Bruijnincx PCA, van Koten G, Klein Gebbink RJM (2008) Chem Soc Rev 37:2581
32. Hegg EL, Que L Jr (1997) Eur J Biochem 250:625
33. Koehntop KD, Emerson JP, Que LJ (2005) J Biol Inorg Chem 10:87
34. Kauppi B, Lee K, Carredano E, Parales RE, Gibson DT, Eklund H, Ramaswamy S (1998) Structure 6:571
35. Karlsson A, Parales JV, Parales RE, Gibson DT, Eklund H, Ramaswamy S (2003) Science 299:1039
36. Wolfe MD, Altier DJ, Stubna A, Popescu CV, Münck E, Lipscomb JD (2002) Biochemistry 41:9611
37. Wolfe MD, Lipscomb JD (2003) J Biol Chem 278:829
38. Chen K, Que L (2001) J Am Chem Soc 123:6327
39. Costas M, Chen K, Que L Jr (2000) Coord Chem Rev 200–202:517

40. Talsi EP, Bryliakov KP (2012) Coord Chem Rev 256:1418
41. Codola Z, Lloret J, Costas M (2014) *Progress in Inorganic Chemistry*: Vol. 59. Wiley, p 447
42. Kim C, Chen K, Kim J, Que L Jr (1997) J Am Chem Soc 119:5964
43. Chen K, Que L Jr (1999) Chem Commun 1375
44. Britovsek GJP, England J, White AJP (2005) Inorg Chem 44:8125
45. Toftlund H, Pedersen E, Yde-Adersen S (1984) Acta Chem Scand Ser A 38:693
46. Okuno T, Ito S, Ohba S, Nishida Y (1997) J Chem Soc Dalton Trans 3547
47. England J, Davies CR, Banaru M, White AJP, Britovsek GJP (2008) Adv Synth Catal 350:883
48. England J, Gondhia R, Bigorra-Lopez L, Petersen AR, White AJP, Britovsek GJP (2009) Dalton Trans 27:5319
49. Clemente-Tejeda D, López-Moreno A, Bermejo FA (2012) Tetrahedron 68:9249
50. Clemente-Tejada D, López-Moreno A, Bermejo FA (2013) Tetrahedron 69:2977
51. Company A, Gómez L, Güell M, Ribas X, Luis JM, Que L Jr, Costas M (2007) J Am Chem Soc 129:15766
52. Company A, Gómez L, Fontrodona X, Ribas X, Costas M (2008) Chem Eur J 14:5727
53. Prat I, Company A, Postils V, Ribas X, Que L Jr, Luis JM, Costas M (2013) Chem Eur J 19:6724
54. Prat I, Gómez L, Canta M, Ribas X, Costas M (2013) Chem Eur J 19:1908
55. Chen MS, White MC (2007) Science 318:783
56. Chen MS, White MC (2010) Science 327:566
57. Canta M, Font D, Gómez L, Ribas X, Costas M (2014) Adv Synth Catal 356:818
58. Comba P, Maurer M, Vadivelu P (2009) Inorg Chem 48:10389
59. Liu P, Liu Y, Wong E, Xiang S, Che C-M (2011) Chem Sci 2:2187
60. Hitomi Y, Arakawa K, Funabiki T, Kodera M (2012) Angew Chemie Int Ed 51:3448
61. Newhouse T, Baran PS (2011) Angew Chemie Int Ed 50:3362
62. Gormisky PE, White MC (2013) J Am Chem Soc 135:14052
63. Gómez L, Canta M, Font D, Prat I, Ribas X, Costas M (2013) J Org Chem 78:1421
64. Gómez L, Garcia-Bosch I, Company A, Benet-Buchholz J, Polo A, Sala X, Ribas X, Costas M (2009) Angew Chemie Int Ed 48:5720
65. Chen K, Richter JM, Baran PS (2008) J Am Chem Soc 130:7247
66. Kasuya S, Kamijo S, Inoue M (2009) Org Lett 11:3630
67. Simmons EM, Hartwig JF (2012) Nature 483:70
68. Wang Y-F, Chen H, Zhu X, Chiba S (2012) J Am Chem Soc 2012:11980
69. Zhang S-Y, He G, Zhao Y, Wright K, Nack WA, Chen G (2012) J Am Chem Soc 134:7313
70. Bigi MA, Reed SA, White MC (2012) J Am Chem Soc 134:9721
71. He Y, Gorden JD, Goldsmith CR (2011) Inorg Chem 50:12651
72. Djernes KE, Moshe O, Mettry M, Richards DD, Hooley RJ (2012) Org Lett 14:788
73. Djernes KE, Padilla M, Mettry M, Young MC, Hooley RJ (2012) Chem Commun 48:11576
74. Gonzalez-de-Castro A, Robertson CM, Xiao J (2014) J Am Chem Soc 136:8350
75. Bigi MA, Reed SA, White MC (2011) Nat Chem 3:216