Article

Directed Metal(Oxo) Aliphatic C—H Hydroxylations: Overriding Substrate Bias

Marinus A. Bigi, Sean A. Reed, and M. Christina White

J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 18 May 2012

Directed Metal(Oxo) Aliphatic C—H Hydroxylations: Overriding Substrate Bias

Marinus A. Bigi, Sean A. Reed, and M. Christina White*

Department of Chemistry, Roger Adams Laboratory, University of Illinois, Urbana, IL 61801, USA

C-H Bond Activation, Iron, Oxidation, Taxol

Supporting Information Placeholder

ABSTRACT: The first general strategy for a directing effect on metal(oxo)-promoted C—H hydroxylations is described. Carboxylic acid moieties on the substrate overcome unfavorable electronic, steric, and stereoelectronic biases in C—H hydroxylations catalyzed by the non-heme iron complex Fe(PDP). In a demonstration of the power of this directing effect, C—H oxidation is diverted away from an electronically favored C-1 H abstraction/rearrangement pathway in the Taxol framework to enable installation of C-2 oxidation in the naturally occuring oxidation state and stereoconfiguration.

Introduction

The search for general and selective C—H oxidations is at the forefront of reaction development in organic chemistry.[1,2] Due to the inertness of C—H bonds to most reaction conditions and the challenge of engendering selectivity among chemically similar entities, however, few methods are capable of targeting unactivated, aliphatic C—H bonds. To address these challenges, chemists have sought to harness the high reactivity of carbene, nitrene, and oxo intermediates using transition metal catalysts for C—C, C—N, and C—O bond-forming reactions. We recently described a non-heme iron(II) catalyst Fe(PDP) **1** that effects preparatively useful and predictably site-selective *intermolecular* aliphatic C—H oxidations of 2° and 3° sites using H_2O_2 as terminal oxidant.[3,4] In the course of these studies, we defined the electronic, steric, and stereoelectronic rules governing site-selectivity in C—H oxidations (Figure 1). In brief, the highly electrophilic, sterically encumbered Fe(PDP) oxidant selects for electron-rich, sterically accessible C—H bonds. Additionally, stereoelectronic effects (*e.g.*, hyperconjugative activation, relief of torsional strain and 1,3-diaxial interactions) can enable selective oxidations when multiple accessible sites are present within a substrate. Finally, these factors are operative under preparatively useful conditions intermolecularly with Fe(PDP) catalysis (1 equiv. of substrate) and conspire to furnish ≥50% of mono-oxidized products. We hypothesized that directed C—H oxidations[5,6] could override these substrate biasing elements, ultimately allowing for orthogonal selectivities to those observed in intermolecular oxidations.

Mechanistic studies on Fe(PDP) and related complexes indicate that C—H hydroxylation proceeds via a highly reactive terminal oxo. Despite long-standing interest in the use of high valent metal oxos for C—H hydroxylation,[7] a general approach for directed C—H hydroxylation has not been reported. In contrast, isoelectronic metal carbene and nitrene oxidations are capable of selective *intramolecular* C—H alkylations[8] and aminations.[9,10] There are two major requirements for the development of directed reactions with a metal-bound oxo that do not exist for analogous nitrene and carbene metal-bound oxidants: (1) the catalyst must be capable of binding both oxidant and substrate simultaneously at proximal coordination sites and, (2) the directed reaction must proceed faster than the background, intermolecular reaction. In contrast, metal-bound carbene or nitrenes are generated directly on the substrate, obviating issues of competing intermolecular reactivity or having multiple proximal coordination sites available on the catalyst.

Regarding the first challenge, we recognized that unlike metal heme catalysts where the two open coordination sites

Figure 1

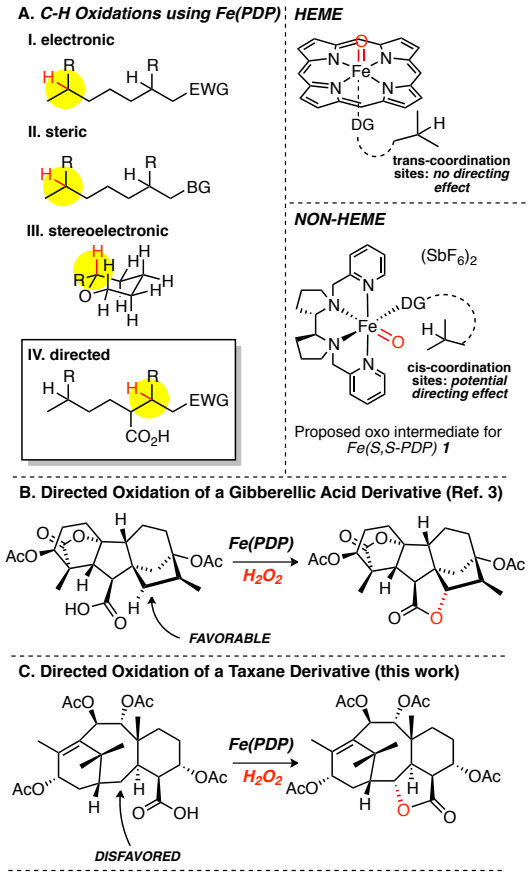
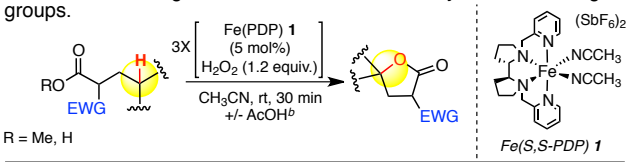


Table 1. Overriding electronic effects with carboxylic acid directing groups.

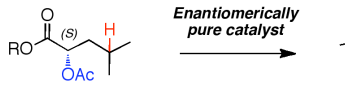


entry	R	starting material	lactone product	isolated yield[c]	rsm[d]
Electronics					
1	Me, **2**			*ester* = 13%	69%
2	H, **3**		**14**	***acid*** = 27%	53%
3	Me, **4**	*n* = 1-3		*ester* = 26%	52%
4	H, **5**		**15**	***acid*** = 50%	26%
5	Me, **6**			*ester* = 35%	42%
6	H, **7**		**16**	***acid*** = 63%	--
7	Me, **8**			*ester* = 11%[e]	67%[e]
8	H, **9**		**17**	***acid*** = 42%	22%
9	Me, **10**			*ester* = 33%[f]	51%
10	H, **11**		**18**	***acid*** = 53%[g]	--
11	Me, **12**			*ester* = 10%	43%
12	H, **13**		**19**	***acid*** = 46%	--

[a] All reactions were run using an iterative addition protocol (see ref. 3 and 4) in which 5 mol% Fe(PDP) **1** and 1.2 equiv. H_2O_2 were each added three times over the course of 30 min every 10 min for a total of 15 mol% Fe(PDP) **1** and 3.6 equiv. H_2O_2. If 15 mol% Fe(PDP) **1** and 3.6 equiv. H_2O_2 are added in one portion, then significantly lower yields and conversions are observed. [b] Reactions of methyl esters included 3 x 50 mol% AcOH. [c] Average of two runs at either 0.3 or 0.5 mmol. [d] Recovered unreacted starting material. [e] ^{1}H NMR yield. [f] The remainder of the mass balance consists of oxidized products each formed in only trace quantities. [g] Isolated ~20% yield of 'double oxidation' products arising from radical abstraction of the desired C-H bond, followed by desaturation/oxidation as outlined in Ref. 10 (see SI).

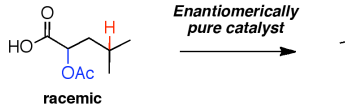
are situated *trans* to one another, non-heme iron complexes like Fe(PDP) feature two open *cis* coordination sites, potentially allowing the metal to bind both substrate and oxidant in close proximity (Figure 1A).[11,12] We chose to evaluate carboxylic acids as directing groups for Fe(PDP)-catalyzed C—H oxidations because several lines of evidence led us to hypothesize that they were acting as ligands for the Fe(PDP) oxidant. First, acetic acid (AcOH) has been shown to be a critical additive for increasing reactivity in intermolecular C—H oxidations with Fe(PDP).[3] Importantly, it has been hypothesized that carboxylic acids exert this effect with non-heme iron complexes through acceleration of oxo formation and thereby provide a theoretical (as of yet unproven) means of outcompeting the intermolecular reaction.[13] Second, we found that a carboxylic acid moiety enabled a highly site- and diastereoselective lactone-forming oxidation of a gibberellic acid derivative, albeit at an electronically and sterically favorable site (Figure 1B).[3] Finally, carboxylic acid groups have been shown to divert the usual C—H hydroxylation activity of Fe(PDP) in some cases to mixed hydroxylase/desaturase activity.[14] Herein, we describe our evaluation of the selectivity rules governing C—H oxidation of carboxylic acid-containing substrates. Our results demonstrate for the first time that carboxylic acids, in addition to simply controlling site-selectivity, are capable of overcoming unfavorable electronic, steric, and stereoelectronic effects within the substrate by way of rendering the oxidation reaction *intramolecular*. In a powerful demonstration of this effect, a carboxylic acid directing group is used to outcompete an electronically favored intermolecular taxane C—H abstraction-rearrangement reaction, allowing installation of the challenging C-2 oxidation of the taxane class of natural products (Figure 1C).[15] Significantly, the described methodology allows installation of Taxol's C-2 oxidation in the correct oxidation state and stereochemical configuration directly from the C—H bond.

Table 2a. Matched/mismatched behavior with carboxylic acid directing group.



substrate	catalyst	rsm	yield	outcome
R = H, **20**	(*R,R*)-Fe(PDP)	29%	28%	***'Mismatched'***
	(*S,S*)-Fe(PDP)	--	**51%**	***'Matched'***
R = Me, **21**	(*R,R*)-Fe(PDP)	63%	22%	*No change*
	(*S,S*)-Fe(PDP)	64%	23%	

Table 2b. Kinetic resolution with carboxylic acid directing group.



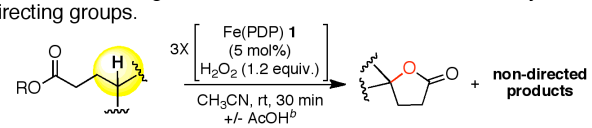
catalyst	rsm	rsm *e.e.*	yield	lactone *e.e.*
(*R,R*)-Fe(PDP)	37%	–28%	31%	+34%
(*S,S*)-Fe(PDP)	35%	+31%	33%	–35%

[a] All reactions were run as described in the footnote to Table 1.

Results and Discussion

Electronics. We first set out to probe the ability of carboxylate ligation to override electronic effects and direct oxidation to electron-deficient sites. A series of linear methyl esters equipped with an electron-withdrawing acetoxy (OAc) group

Table 3. Overriding steric and stereoelectronics with carboxylic acid directing groups.



entry	starting material	R	lactone product	isolated yield[c]	non-directed product(s)
Sterics					
1		Me, **23**		32%	**32**, 24%
2		H, **24**	**29**	54%	--
3		Me, **25**		9%[d]	**33**, 36%
4		H, **26**	**30**	50%	--
Stereoelectronics					
5		Me, **27**		2%[d,e]	**34**, 22%; **35**, 16%
6		H, **28**	**31**	58%[e]	--
Non-Directed Oxidation Products					

32 **33** **34** **35**

[a] All reactions were run as described in the footnote to Table 1. [b] Reactions of methyl esters included 3 x 50 mol% AcOH. [c] Average of two runs at either 0.3 or 0.5 mmol. [d] GC yield relative to standard curve. [e] Two cycles of Fe(PDP)/H_2O_2.

Figure 2

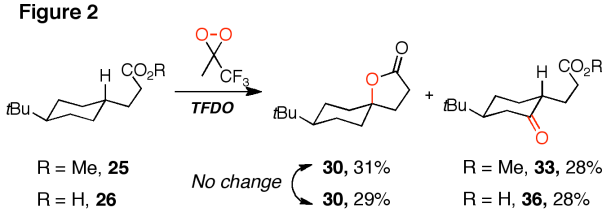
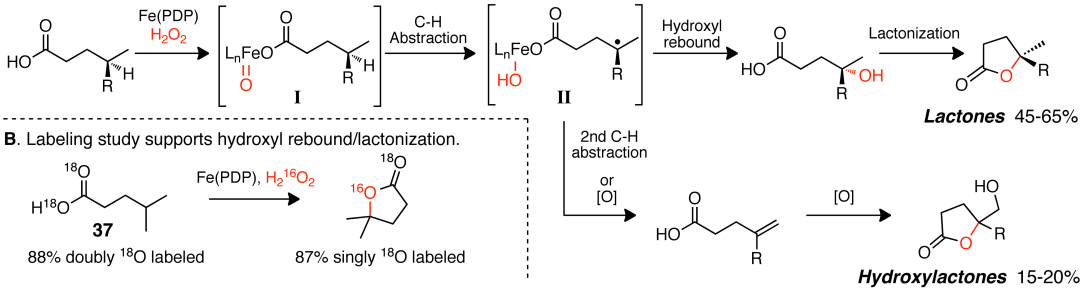


Figure 3

A. Proposed mechanism of Fe(PDP)-catalyzed C-H lactonization.



B. Labeling study supports hydroxyl rebound/lactonization.

1-3 methylene units from a 3° C—H bond was evaluated (Table 1). Consistent with our previously described selectivity rules, methyl ester **2**, with the acetoxy group nearest the site of oxidation, was the least reactive in the series (Entry 1). Notably, continuing to add oxidant after the reaction is finished fails to lead to improved yields of lactone product due to catalyst decomposition.[16] As the EWG was shifted away from the tertiary center, the substrate became progressively more reactive (Entries 3 and 5). In contrast, analogous carboxylic acid substrates (run under identical conditions, excluding only AcOH additive) were significantly more reactive in all cases examined, providing substantially higher yields of lactone products (Entries 2, 4, and 6). For example, carboxylic acid **7** furnished lactone product in 63% yield versus 35% for the analogous ester substrate **6** (Entries 5-6). The same reactivity trend was noted for linear α-chloro and protected β-amino substrates as well as for cyclohexanones **12-13** (Entries 7-12). Consistent with the carboxylic acid's proposed role as a ligand for the metal, chiral[17] carboxylic acid (*S*)-**20** exhibited matched/mismatched behavior with the chiral Fe(PDP) catalyst while oxidation of methyl ester substrate (*S*)-**21** was insensitive to a change in catalyst antipode (Table 2a). Morever, when racemic carboxylic acid (±)-**20** was exposed to the standard reaction conditions, the chiral Fe(PDP) catalyst promoted kinetic resolution of the starting material, leading to moderate levels of enantioenrichment in both recovered starting material and lactone product (Table 2b).

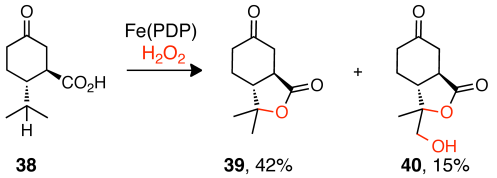
Sterics. In intermolecular C—H oxidations, sites adjacent to bulky groups are shielded from the sterically hindered Fe(PDP)-bound oxidant. To further probe the intramolecular nature of lactonization, the ability of carboxylate ligation to supersede steric effects was evaluated (Table 3). We have previously shown that axial 3° C—H sites undergo intermolecular oxidation less readily than equatorial sites with Fe(PDP), an observation we attributed to steric hindrance about the axial C—H bond. Consistent with this, we found that ester **23** (equatorial 3° C—H) afforded lactone **29** as the major product, whereas ester **25** (axial 3° C—H) afforded a low yield of lactone **30** (9%) with the major product, ketone **33,** arising from oxidation at a less sterically hindered 2° C—H site (Entries 1 and 3). In stark contrast, the analogous carboxylic acids **24** and **26** each provided lactone products in ≥ 50% yield (Entries 2 and 4). Significantly, stoichiometric organic oxidant TFDO[18] [methyl(trifluoromethyl)dioxirane] showed no directing effect; similar yields of lactone **30** and ketones **33** and **36** were furnished from both ester **25** and carboxylic acid **26** (Figure 2).

Stereoelectronics. Stereoelectronic effects can also impact site-selectivity in oxidations with Fe(PDP). Pyrans **27-28** have both 2° and 3° ethereal C—H sites stereoelectronically activated toward oxidation (Table 3, Entries 5-6). Using methyl ester **27**, approximately equal amounts of oxidation occurred at the two sites, with the 3° oxidation product **35** resulting from overoxidation of an unstable hemiketal intermediate. In contrast, carboxylic acid-directed oxidation provided the desired lactone **31** as the major product in 58% yield. Collectively, our results strongly support the role of carboxylic acids as ligands for Fe(PDP), and demonstrate that carboxylate ligation can override electronic, steric, and stereoelectronic effects operative in non-directed oxidations.

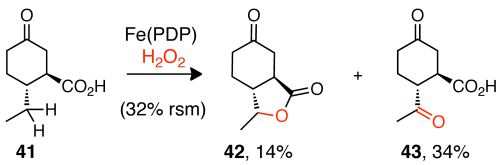
Mechanism. Aliphatic C—H lactonization under Fe(PDP catalysis likely proceeds *via* a mechanism analogous to that of C—H hydroxylation. The reaction of Fe(PDP) with H_2O_2 and a carboxylic acid substrate generates an iron oxo carboxylate (**I**) as the active oxidant (Figure 3A). Intramolecular hydrogen abstraction by **I** affords a short-lived carbon-centered substrate radical (**II**) that can furnish lactone product by two potential rebound pathways from metal-bound ligands: carboxylate rebound to form lactone directly or hydroxyl rebound followed by lactonization. Exposure of ^{18}O-labeled (88% doubly labeled) carboxylic acid **37** led to predominantly singly labeled lactone (87% singly labeled, only 8% doubly ^{18}O-labeled product, Figure 3B).[14] These results suggest that lactonization proceeds *via* hydroxyl rebound and that carboxylate rebound is, at best, a minor pathway. Interestingly, for intramolecular oxidations with Fe(PDP), the carbon-centered radical **II** can alternatively undergo desaturation to furnish olefin intermediates.[19] Further oxidation of these intermediates typically affords 10-20% yields of 'double oxidation' products (*e.g.*, hydroxylactones), which often account for much of the remaining mass balance (Figure 3A, also Table 1, Entry 10). Notably, we have never observed products of desaturation originating from 2° C—H bonds that would proceed *via* less stable 2° carbon-centered radicals. For example, although only differing in the degree of substitution at the reactive carbon, tertiary sub-

Figure 4

A. 3° C-H bonds: Mixed hydroxylase/desaturase.



B. 2° C-H bonds: Hydroxylase only.

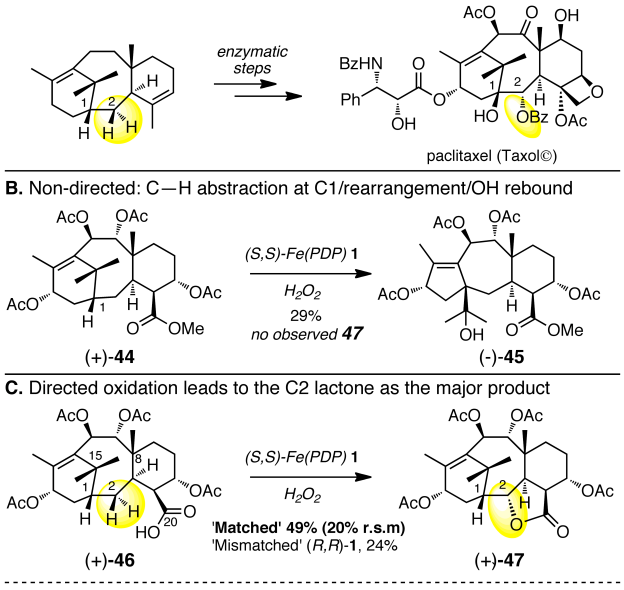


strate **38** provides both lactone **39** and 'double oxidation' product **40**,[14] while secondary substrate **41** only provides lactone **42** and ketoacid **43** (Figure 4).

Case Study: Site-selective Oxidation of Taxane. C—H activation represents a powerful tool for generating molecular diversity from hydrocarbon frameworks; for example, the anticancer drug Taxol is synthesized by Nature through the action of a series of highly selective enzymatic P450-mediated C—H oxidations (Figure 5A).[15] Pursuant to our goal of synthesizing biologically-active compounds *via* C—H oxidation and aiding the elucidation of biosynthetic pathways using catalyst **1**, we sought to explore novel site-selective oxidations of the taxane framework.

Despite its critical role in the bioactivity of Taxol,[20] installation of oxygen at C-2 via direct C—H oxidation has only been accomplished using the natural P450 taxoid hydroxylase.[20] Density functional theory (DFT) calculations on the

Figure 5



energy-minimized structure of **46** revealed that the C-1 hydrogen was the most-electron rich C—H bond and thereby the most likely to be abstracted intermolecularly by the electrophilic Fe(PDP)oxo (Figure 5). We hypothesized that an adjacent C-20 carboxylic acid directing group could redirect oxidation from C-1 to form the C—O bond at C-2. Encouragingly, our model predicted that the rigid taxane core would position the carboxylic acid in close proximity to the α-H that would lead to the desired, natural stereochemistry (see SI). Moreover, while the β-H on C-2 was shown to be sterically shielded by the methyl groups at C-8 and C-15, the α-H was relatively accessible.

Consistent with these predictions and our previous results on an analogous taxane structure,[14] intermolecular oxidation of methyl ester **44** with Fe(PDP) **1** led to C—H abstraction at C-1 followed by skeletal rearrangement and oxidation to furnish *nor*taxane **45** (Figure 5B). Notably, no desired C-2 lactone product was observed. In contrast, when carboxylic acid-containing taxane **46** was subjected to standard oxidation conditions with (*S,S*)-Fe(PDP)-**1** the major product was the lactone arising from diastereoselective hydroxylation at the α-hydrogen of C-2 (**47**, 49% yield, Figure 5C). Furthermore, the C-2 oxidation was introduced at the correct oxidation state and with the correct stereoconfiguration. Once again, the interaction of a chiral substrate with the chiral iron catalyst was observed to afford matched/mismatched selectivities in C—H oxidation: the use of the other catalyst antipode, (*R,R*)-Fe(PDP)-**1**, gave reduced yields of **47** (25%) and complex mixtures of oxidized products. For the first time a small molecule catalyst has demonstrated the capacity to directly install the C-2 hydroxyl group on a taxane. This represents a very rare example of site-selective functionalization in a complex molecule setting and our results have extraordinary potential to streamline syntheses and derivatizations of this medicinally important class of molecules.[3,4,22]

Conclusion

In summary, by acting as ligands for the metal, carboxylic acids can overcome a range of substrate biases (electronic, steric, and stereoelectronic) in C—H oxidations mediated by the non-heme iron complex Fe(PDP) **1**. Notably, while directed C—H alkylations and aminations *via* metal carbenes and nitrenes have been demonstrated to control site-selectivity, our report represents a rare example of a directing group effect that can override substrate bias.

Experimental Procedures

General Procedure for the C—H Lactonization Reaction of Carboxylic Acids: Into a 40 mL borosilicate vial was added hydrocarbon substrate (0.5 mmol, 1.0 equiv.), followed by 5 mol% Fe(PDP) catalyst **1** (23.3 mg, 0.025 mmol, 0.05 equiv.), 0.75 mL CH_3CN, and a magnetic stir bar. While the resulting deep red solution stirred, a solution of H_2O_2 (50 wt% in H_2O, 34.6 μL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH_3CN was added over a period of 1 minute (dropwise addition for 45 seconds, followed by streamwise addition for 15 seconds), generating a clear, amber brown solution. Stirring followed for 10 minutes at ambient temperature, and a solution of 5 mol% **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH_3CN was added in one burst. A second solution of H_2O_2 (50 wt% in H_2O, 34.6 μL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH_3CN was added as before and stirring followed for 10 minutes. Following this stirring period, a second solution of 5 mol% **1** (23.3 mg, 0.025 mmol, 0.05 equiv.) in 0.5 mL CH_3CN was added in one burst, followed by a third solution of H_2O_2 (50 wt% in H_2O, 34.6 μL, 0.60 mmol, 1.2 equiv.) in 4.5 mL CH_3CN. The reaction stirred a final 10 minutes and was analyzed by TLC. The crude reaction mixture was concentrated *in vacuo* and purified by flash chromatography using EtOAc/hexanes mixtures.

ASSOCIATED CONTENT

Supporting Information. Experimental procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

white@scs.uiuc.edu

ACKNOWLEDGMENT

M.C.W. is grateful to Pfizer and Bristol-Myers Squibb for financial support. M.A.B. is supported by an Illinois Distinguished Fellowship (2007-2010) and a Harold R. Snyder Fellowship (2010-2011). S.A.R.'s studies into the streamlining of natural product synthesis are supported by the NSF under the Center for Chemical Innovation in Stereoselective C–H Functionalization (CHE-0943980) and by an Ullyot Graduate Fellowship (2009-2010). J. Guerra and R. M. Williams are thanked for providing the (+)-taxusin. We thank Mr. P. Gormisky for checking the experimental procedure in Table 3, entry 6.

REFERENCES

(1) (a) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439; d) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (d) White, M.C. *Science* **2012**, *335*, 807.

(2) For discussions on the strategic use of C—H oxidation in synthesis, see: (a) Fraunhoffer, K. J; Bachovchin, D. A.; White, M. C. *Org. Lett*. **2005**, *7*, 223. (b) Covell, D. J.; Vermeulen, N. A.; Labenz, N. A., White, M. C. *Angew. Chem. Int. Ed.* **2006**, *45*, 8217. (c) Stang, E. M.; White, M. C. *Nat. Chem.* **2009**, *1*, 547. (d) Davies, H. M. L. *Nat. Chem.* **2009**, *1*, 519. (e) Newhouse, T.; Baran, P. S.; Hoffmann, R. W. *Chem. Soc. Rev*., **2009**, *38*, 3010. (f) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (g) Vermeulen, N. A.; Delcamp, J. H.; White, M.C. *J. Am. Chem. Soc.* **2010**, *132*, 11323. (h) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (i) Hoffmann, R. W. In *Elements of Synthesis Planning*; Springer: Heidelberg, 2009.

(3) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783.

(4) Chen, M. S.; White, M. C. *Science* **2010**, *327*, 566.

(5) For some examples of directed, catalytic C—H oxidations proceeding via organometallic intermediates, see: (a) Jones, W. D.; Kosar, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 5640. (b) Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529. (c) Kakiuchi, F.; Yamamoto, Y.; Chatani, N.; Murai, S. *Chem. Lett.* **1995**, 681. (d) Trost, B. M.; Imi, K.; Davies, I. W. *J. Am. Chem. Soc.* **1995**, *117*, 5371. (e) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (f) Giri, R.; Chen, X.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2005**, *44*, 2112. (g) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-H.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (h) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (i) Thalji, R. K.; Ahrendt, K. A.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2001**, *123*, 9692. (j) Campeau, L.-C.; Rousseaux, S.; Fagnou, K. *J. Am. Chem. Soc.* **2005**, *127*, 18020. (k) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (l) Wang, C.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 4194.

(6) For some examples of directed free radical C—H oxidations, see: (a) Barton, D. H. R.; Beaton, J. M.; Geller, L. E.; Pechet, M. M. *J. Am. Chem. Soc.* **1961**, *83*, 4076. (b) Barton, D. H. R.; Budhiraja, R. P.; McGhie, J. F. *J. Chem. Soc. C,* **1969**, 336. (c) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1961**, *83*, 2207. (d) Walling, C.; Padwa, A. *J. Am. Chem. Soc.* **1963**, *85*, 1597. (e) Dorta, R. L.; Francisco, C. G.; Freire, R.; Suarez, E. *Tetrahedron Lett.* **1988**, *29*, 5429. (f) Martin, A.; Perez-Martin, I.; Suarez, E. *Org. Lett.* **2005**, *7*, 2027. (g) Shenvi, R. A.; Guerrero, C. A.; Shi, J.; Li, C.-C.; Baran, P. S. *J. Am. Chem. Soc.* **2008**, *130*.

(7) (a) Ortiz de Montellano, P. R., Ed. *Cytochrome P450: Structure, Mechanism, and Biochemistry*; Plenum: New York, Ed. 3, **2005**. (b) Groves, J. T.; Nemo, T. E.; Myers, R. S. *J. Am. Chem. Soc.* **1979**, *101*, 1032. (c) Collman, J. P.; Tanaka, H.; Hembre, R. T.; Brauman, J. I. *J. Am. Chem. Soc.* **1990**, *112*, 3689. (d) Kim, C.; Chen, K.; Kim, J.; Que, L., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 5964; e) Okuno, T.; Ito, S.; Ohba, S.; Nishida, Y. *J. Chem. Soc., Dalton Trans.* **1997**, 3547. (f) Lim, M. H.; Lee, Y. J.; Goh, Y. M.; Nam, W.; Kim, C. *Bull Chem. Soc. Jpn.* **1999**, *72*, 707.

(8) Rhodium carbene C—H alkylations: (a) Doyle, M. P.; Duffy, R.; Ratnikov, M.; Zhou, L. *Chem. Rev.* **2010**, *110*, 704. (b) Davies, H. M. L.; Beckwith, R. E. J. *Chem. Rev.* **2003**, *103*, 2861. (c) Taber, D. F. In *Comprehensive Organic Synthesis*: *Selectivity Strategy and Efficiency in Modern Organic Chemistry*; Pattenden, G.; Pergamon: Oxford, **1991**; Vol. 3; p. 1045.

(9) Metal nitrene C—H aminations: (a) Espino, C. G.; Du Bois, J. Rhodium(II)-Catalyzed Oxidative Amination. In *Modern Rhodium-Catalyzed Organic Reactions;* Evans, P. A., Ed.; Wiley-VCH: Weinheim, **2005**; p. 379. (b) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (c) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (d) Huard, K.; Lebel, H. *Chem. Eur. J.* **2008**, *14*, 6222. (e) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233.

(10) For an example of a preparatively useful iron-nitrene C—H amination: Paradine, S. M.; White, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2036.

(11) The few reported approaches using metal heme complexes have relied upon appending intricate molecular recognition elements to the ligand framework and the substrate, leading to highly selective, but non-general reactions: (a) Breslow, R.; Zhang, X.; Huang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 4535. (b) Yang, J.; Gabriele, B.; Belvedere, S.; Huang, Y.; Breslow, R. *J. Org. Chem.* **2002**, *67*, 5057.

(12) For an elegant example using a carboxylic acid directing group to coordinate to the ligand of a non-heme Mn complex, see: Das, S.; Incarvito, C. D.; Crabtree, R. H.; Brudvig, G. W. *Science* **2006**, *312*, 1941.

(13) (a) White, M. C.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 7194. (b) Mas-Ballesté, R.; Que, L., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 15964. (c) For stoichiometric use of a non-heme iron complex to convert benzoic acid to salicylic acid, see: Makhlynets, O. V.; Das, P.; Taktak, S.; Flook, M.; Mas-Ballesté, R.; Rybak-Akimova, E. V.; Que, L., Jr. *Chem. Eur. J.* **2009**, *15*, 13171 and references therein.

(14) Bigi, M. A.; Reed, S. A.; White, M. C. *Nat. Chem.* **2011**, *3*, 218.

(15) Kaspera, R.; Croteau, R. *Phytochem. Rev.* **2006**, *5*, 433.

(16) Catalyst decomposition becomes prohibitive after the third 'cycle' of catalyst and oxidant have been added (see general procedure for the reaction conditions): Vermeulen, N. A.; Chen, M. S.; White, M. C. *Tetrahedron* **2009**, *65*, 3078.

(17) The word 'chiral' in this manuscript refers to chiral, non-racemic substrates and catalysts.

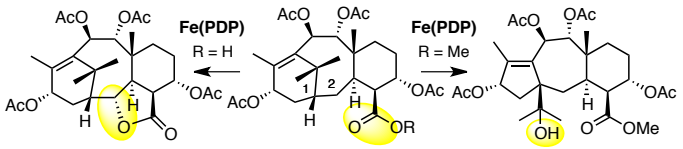
(18) Curci, R.; D'Accolti, L.; Fusco, C. *Acc. Chem. Res.* **2006**, *39*, 1.

(19) This desaturation pathway has never been observed for intermolecular C—H hydroxylation (see Ref. 12).

(20) Chen, S.-H.; Wei, J.-M.; Farina, V. *Tetrahedron Lett.* **1993**, *34*, 3205.

(21) Chau, M.; Croteau, R. *Arch. Biochem. Biophys.* **2004**, *427*, 48.

(22) (a) Lewis, C. A.; Miller, S. J. *Angew. Chem. Int. Ed.* **2006**, *45*, 5616. (b) Wender, P.A.; Hilinski, M. K.; Mayweg, A. V. W. *Org. Lett.* **2005**, *7*, 79. (c) Pathak, T. P.; Miller, S. J. *J. Am. Chem. Soc.* **2012**, *134*, 6120.


AcO
OAc
Fe(PDP)
R = H
OAc
AcO
H
H
O
O
AcO
OAc
AcO
1
2
H
H
O
OR
Fe(PDP)
R = Me
OAc
AcO
AcO
OAc
H
O
OMe
OH