Tetrahedron 65 (2009) 3078–3084

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

The Fe(PDP)-catalyzed aliphatic C–H oxidation: a slow addition protocol

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ARTICLE INFO

Article history:
Received 6 October 2008
Received in revised form 14 November 2008
Accepted 25 November 2008
Available online 30 November 2008

Dedicated to Professor Justin Du Bois in celebration of his receiving the Tetrahedron Young Investigator Award

ABSTRACT

This report describes a slow addition protocol for the Fe(PDP)-catalyzed aliphatic C–H oxidation reaction. Under this protocol, the reaction can be productively driven to higher conversions without decreasing site-selectivity or chemoselectivity. The operational advantages of this procedure are highlighted in the oxidation of two complex natural product derivatives. Hydroxylated products can be obtained in high isolated yields without the need for recycling recovered starting materials.

1. Introduction

Modern synthetic planning relies on the manipulation of oxidized functionality, often ignoring ubiquitous and inert C–H bonds in organic scaffolds. Methods that directly transform C–H bonds into C–O, C–N, or C–C bonds enable the construction of oxidized materials through an orthogonal strategy,[1] often leading to simplified synthetic routes. For example, we have developed methods that allow oxygen, nitrogen, and carbon functionalities to be installed directly from allylic C–H bonds[2] and demonstrated that strategically employing such oxidations late in synthetic sequences markedly reduces unproductive chemical manipulations (i.e., oxidation state changes, protection–deprotections, functional group transformations).[3] Importantly, for these reactions to be applied at late stages of synthetic routes, they must proceed with predictable and high selectivities. Selective C–H functionalization reactions on complex substrates have been primarily accomplished for activated C–H bonds (i.e., π-system[2–4] or adjacent to a heteroatom[5]) or via the use of substrate directing groups.[6] In contrast to this, we recently disclosed an iron (Fe)-based small molecule catalyst, Fe(PDP) **1** [[Fe(II)(PDP)$(CH_3CN)_2$]$(SbF_6)_2$][7] that catalyzes the oxidation of *isolated, unactivated sp^3 C–H bonds* in complex molecular settings with predictable and high levels of selectivity *and without the requirement for directing groups*.[8–10] Selectivity for oxidation of 3° C–H bonds with **1** can be predicted using a series of simple rules based on the electronic and steric properties of the C–H bonds (vide infra). Moreover, in all cases examined when the 3° C–H bond is part of a stereogenic center, hydroxylation occurs with complete retention of stereochemistry.[8] Although not required, carboxylic acids may serve as directing groups to furnish five-membered ring lactones.[11]

2. Results

While the Fe(PDP) aliphatic C–H oxidation reaction enables for the first time the selective oxidation of complex substrates at unactivated, isolated C–H bonds with preparatively useful isolated yields (43–57%), important challenges remain; these include improving catalyst turnovers and productive substrate conversions. Currently, three iterative additions of Fe(PDP) catalyst **1** (5 mol %), hydrogen peroxide oxidant (H_2O_2, 1.2 equiv), and acetic acid additive (AcOH, 0.5 equiv) in 10–15 min intervals are utilized to obtain maximum product yields (Table 1, entry 5, Table 2). Adding more oxidant alone does not alter product yield (Table 1, entry 2), indicating that catalyst decomposition, not inefficient use of H_2O_2, is responsible for the modest yields observed. Significantly, with a single addition, increasing the catalyst loading to 15 mol % with or without increasing the amount of oxidant affords no significant improvement in yield and diminishes the selectivity for the 3° hydroxylated product **3** (Table 1, entry 1 vs entries 3 and 4). These results suggest that increased catalyst concentrations are deleterious to catalyst productivity.

Although new catalyst and reagents (**1**/H_2O_2/AcOH) are introduced during each cycle of the iterative addition protocol, the third addition fails to significantly promote product formation due to deteriorating catalyst reactivity and selectivity in the reaction mixture (Table 1, entry 5). Notably, a fourth addition of **1**/H_2O_2/AcOH is ineffective at catalyzing desired product formation (Table 1, entry 5; Table 2, entries 2 and 4). In cases where valuable starting material remains, conversion to product can be achieved using a 'recycling protocol' that consists of physically separating (via column chromatography) the starting material from the reaction

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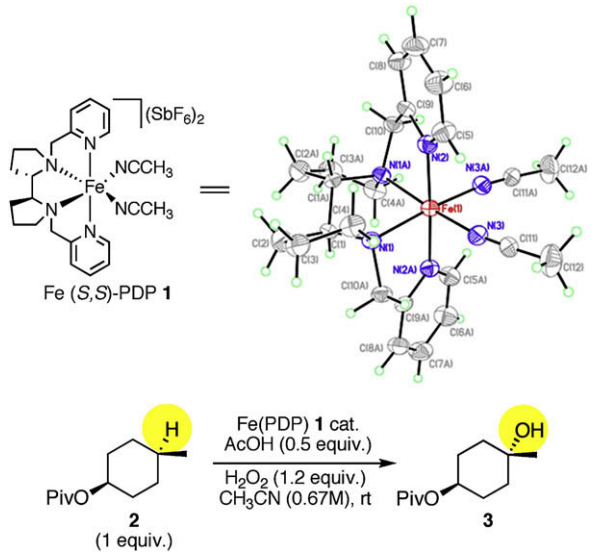
0040-4020/$ – see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.tet.2008.11.082

Table 1
Reaction optimization



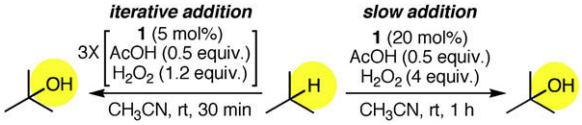
Entry	Fe(PDP) **1** (mol %)	Yield[a] (%)	Conv.[a] (%)	Select.[a] (%)
1	5	32	35	91
2	5[b]	32	42	76
3	15	28	33	85
4	15[c]	40	56	71
5	Iterative[d]			
	5	33	36	92
	10 (5)[e]	52 (19)[e]	70 (34)[e]	74 (56)[f]
	15 (5)[e]	57 (5)[e]	89 (19)[e]	64 (26)[f]
	20 (5)[e]	57 (0)[e]	96 (7)[e]	59 (0)[f]
6	15% (slow)[g]	60	95	63

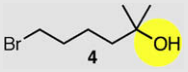
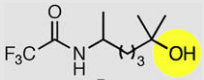
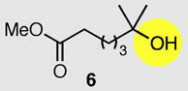
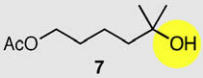
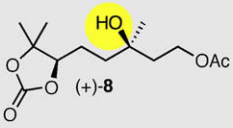
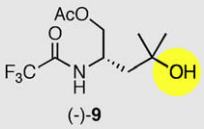
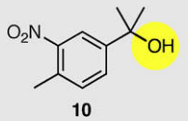
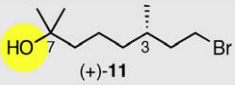
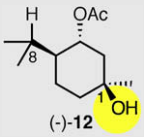
[a] Determined by GC. The stereoretentive nature of the oxidation reaction was determined by GC (average of 9 runs). Oxidation of *cis*-**2** (>98% *cis*) afforded *cis*-**3** (99.58%±0.05% *cis*).
[b] H_2O_2 (1.2 equiv) added after one iteration.
[c] H_2O_2 (3.6 equiv), 1.5 equiv AcOH, 0.67 M CH_3CN.
[d] Iterative addition of 5 mol% 1, AcOH (0.5 equiv), H_2O_2 (1.2 equiv) every 10–15 min (see Section 4).
[e] For increases in catalyst loading, yield or conversion relative to previous iteration, see values in parentheses.
[f] Selectivity for iteration is noted in parentheses.
[g] Slow addition of 15 mol% **1** (0.15 M in CH_3CN) and 3 equiv H_2O_2 (0.4 M in CH_3CN) via syringe pump over 45 min into a CH_3CN solution (0.5 M) of **2** (1 equiv) and AcOH (0.5 equiv).

mixture and re-submitting it to oxidation (Eqs. 1 and 2). These results imply that catalyst decomposition products forming during the course of the reaction are interfering with productive oxidations with **1**.

In order to investigate if catalyst decomposition proceeds via ligand oxidation, we performed the aliphatic C–H oxidation of 4-methylvaleric acid catalyzed by Fe(PDP) **1** under the standard iterative addition protocol and recovered the ligand. We obtained 48% isolated yield of the volatile lactone product and recovered 95% of the (*S,S*)-PDP ligand *unoxidized* (see Section 4). Collectively, these experimental observations suggested to us that catalyst decomposition is occurring via bi- or multimolecular reactions at the metal center to furnish species that inhibit productive oxidations. We hypothesized that slow addition of both the catalyst and oxidant over an extended period of time could disfavor these decomposition pathways and improve overall catalyst productivity. Herein we report a slow addition protocol for aliphatic C–H oxidations with **1** that generally results in higher isolated yields of hydroxylated products and, for two representative complex

Table 2
Comparison of iterative addition protocol to slow addition protocol

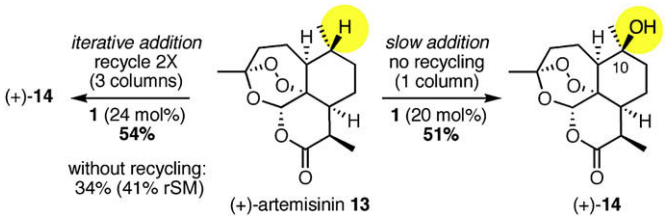


Entry	Hydroxylation product	Isolated % yield[a] (rSM[b])		
		Iterative addition[c]	Slow addition	
		5 mol %×3	15 mol %[d]	20 mol %
1 2	 **4**	46 (26) 49 (15)[e]	51 (27)	61 (0)
3 4	 **5**	43 (33) 45 (23)[e]	44 (35)	54 (23)
5	 **6**	60 (18)	61 (21)	66 (0)
6	 **7**	53 (43)	67 (30)	72 (0)
7	 (+)-**8**	43 (42)	45 (32)	50 (19)
8	 (-)-**9**	33 (67)	40 (59)	46 (50)
9	 **10**	48 (22)	56 (18)	61 (9)
10	 (+)-**11**	39 (32) 9:1 [C7:C3]	41 (22)	43 (20) 10:1 [C7:C3]
11	 (-)-**12**	50 (11) 11:1 [C1:C8]	54 (16)	55 (4) 11:1 [C1:C8]

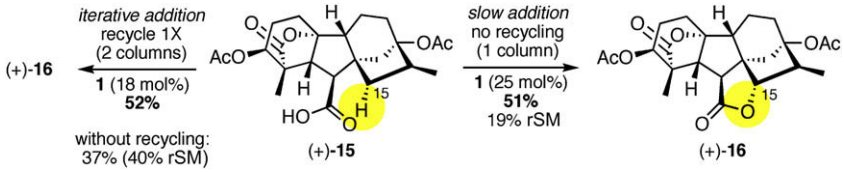
[a] Yields of isolated hydroxylated products (0.5 mmol substrate) are an average of two runs.
[b] rSM=Recovered starting material.
[c] Yields for iterative addition are from Ref. 7.
[d] Slow addition of 15 mol% 1 (0.15 M in CH_3CN) and 3 equiv H_2O_2 (0.4 M in CH_3CN) via syringe pump over 45 min into a CH_3CN solution (0.5 M) of **2** (1 equiv) and AcOH (0.5 equiv).
[e] Four iterative additions of **1** (5 mol%), AcOH (0.5 equiv), H_2O_2 (1.2 equiv).

substrates, eliminates the need for recycling starting materials to obtain high yields.

We developed a slow addition protocol in which separate solutions of catalyst **1** (15 or 20 mol%, 0.2 M CH_3CN) and H_2O_2 (50 wt% in H_2O, 3 or 4 equiv, 0.4 M CH_3CN) were simultaneously added over 45 or 60 min via syringe pump to a stirring solution of substrate (1.0 equiv, 0.5 M CH_3CN) and AcOH (0.5 equiv). The results in Table 2 are presented with comparison to those obtained using the iterative addition protocol. At comparable catalyst and



(1)



(2)

oxidant loadings (15 mol % **1**, 3 equiv H_2O_2) the slow addition protocol provides only modest improvements in yields with similar amounts of recovered starting material relative to the iterative addition protocol (Table 1, entry 6; Table 2). However, in cases where large amounts of starting material (>20%) were previously observed, the slow addition protocol, performed with slightly increased catalyst and oxidant loadings (20 mol % **1**, 4 equiv H_2O_2), afforded significant increases (11–19%) in isolated yields of hydroxylated products (Table 2, entries 1, 3, 6, 8, 9). In contrast, when the iterative addition protocol is performed with comparable increases in catalyst and oxidant loadings, as previously shown in Table 1, no significant improvement in yield is observed (Table 1, entry 5; Table 2, entries 2 and 4). Importantly, beyond the excellent yields recorded in Table 2 for these highly challenging transformations, the Fe(PDP) aliphatic C–H oxidation reaction is operationally simple to perform. Catalyst **1** exists as a purple solid that is indefinitely stable under air when refrigerated at 0 °C.[12] Moreover, with both the iterative and slow addition protocols, reactions are run open to air without excluding moisture under *a single set of experimental conditions*.

Importantly, the predictable site-selectivities and high chemoselectivities in oxidations catalyzed by **1** are not altered under the slightly more forcing conditions of increased catalyst and oxidant loadings used in the slow addition protocol (Table 2, entries 10 and 11). In molecules containing two electronically distinct 3° C–H bonds, as in (+)-**11**, electrophilic catalyst **1** maintains its selectivity for oxidation of the most electron rich C–H bond (C7). In cases where two 3° C–H bonds are electronically equivalent, as in substrate (−)-**12**, bulky catalyst **1** persists in oxidizing with high selectivity at the C–H bond that is less sterically hindered. It is important to note, however, that in cases like these where conversions are high or the substrate is robust toward oxidation under the iterative addition protocol, the slow addition protocol does not significantly improve yields. The Fe(PDP) aliphatic C–H oxidation reaction performed under the slow addition protocol remains tolerant of a wide range of functionalities such as halides, esters, carbonates, and electron-deficient amides (Table 2, entries 1–8, 10–11). Consistent with the observation that electron-deficient functionality is compatible with these oxidative conditions, we now report that aromatic functionality substituted with an electron-withdrawing nitro group is also well tolerated (Table 2, entry 9). In general, we have observed that the presence of electron-withdrawing groups on aromatic rings is crucial for deactivating them toward oxidation.

The most significant simplifying feature of the slow addition protocol is the ability to eliminate the recycling of valuable starting materials while still obtaining comparable yields of oxidized products. For example, we previously reported that the antimalarial compound (+)-artemisinin **13** could be oxidized with **1** under iterative addition conditions to afford (+)-10β-hydroxyartemisinin **14** in 34% yield with 41% recovered starting material (Eq. 1). By recycling recovered (+)-**13** through the reaction twice (three column chromatographic purifications), a total of 54% isolated yield of (+)-**14** could be obtained. Using the slow addition protocol with 20 mol % **1** and 4 equiv H_2O_2 (0.5 equiv AcOH), (+)-**14** can now be furnished in 51% isolated yield after only one chromatographic purification (Eq. 1). It is significant to note that this reaction proceeds with extraordinary site-selectivity and chemoselectivity. Specifically, (+)-artemisinin **13** is predictably oxidized preferentially at one of five 3° C–H bonds based on electronic considerations and the sensitive endoperoxide moiety is maintained with both oxidation protocols.

Consistent with our hypothesis that the AcOH additive is acting as an ancillary ligand for the active Fe catalyst, we have demonstrated that chiral carboxylic acids may direct highly diastereoselective C–H oxidations of 2° C–H bonds with **1**. For example, tetrahydrogibberellic acid analog (+)-**15** was previously oxidized with **1** under the iterative addition protocol to afford lactone (+)-**16** as a single diastereomer in 37% isolated yield with 40% recovered starting material (Eq. 2). By recycling recovered (+)-**15** through the reaction once (two chromatographic purifications), a total of 52% isolated yield of (+)-**16** could be obtained. Using the slow addition protocol with 25 mol % **1** and 5 equiv H_2O_2 (no AcOH), (+)-**16** can be now furnished directly in 51% isolated yield after only one chromatographic purification (Eq. 2). It is significant to note that with complex substrates the Fe(PDP) aliphatic C–H oxidation represents an especially powerful late stage oxidation. In considering potential alternative synthetic routes toward natural product analogs such as (+)-**14** and (+)-**16**, state-of-the-art methods would require lengthy de novo syntheses.

3. Summary and conclusions

The Fe(PDP) **1** aliphatic C–H oxidation has demonstrated for the first time that, using a highly electrophilic and sterically bulky catalyst, isolated and inert C–H bonds can be selectively oxidized in a predictable fashion based on subtle differences in their electronic and steric properties. In this report we disclose a slow addition protocol that enables increasing the catalyst and oxidant loadings to productively drive the aliphatic C–H oxidation reaction to higher conversions without sacrificing site-selectivity or chemoselectivity. The operational advantages of this new procedure are demonstrated by the ability to eliminate the recycling of recovered starting materials in the oxidation of two complex natural product

derivatives while obtaining comparable isolated yields. The increased catalyst productivity with the slow addition protocol, together with the complete recovery of PDP ligand, suggests bi- or multimolecular catalyst decomposition pathways occur at the iron center. Future studies are directed toward identifying the precise structures of these decomposition products, elucidating the mechanism by which they inhibit oxidation, and developing chemical strategies for preventing their formation.

4. Experimental

4.1. General information

The following commercially obtained reagents for the C–H oxidation reaction were used as received: H_2O_2 (50 wt % in H_2O, Sigma–Aldrich), AcOH (Mallinckrodt), CH_3CN (Sigma–Aldrich). All oxidation reactions were run under air with no precautions taken to exclude moisture. Fe(*S*,*S*-PDP) **1** catalyst was prepared as described in Ref. 8. Supplementary crystallographic data for Fe(*S*,*S*-PDP) **1** can be obtained from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif on quoting registry no. CCDC-661933. Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instruments equipped with FID detectors using a HP-5 (5%-phenyl)-methylpolysiloxane column (30 m, 0.32 mm, 0.25 μm). Chiral GC analysis was performed on an Agilent 5890 Series instruments equipped with FID detectors using a J&W cyclodex-β column (30 m, 0.25 mm, 0.25 μm). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized with UV, potassium permanganate, ceric ammonium molybdate, or vanillin staining. Slow addition protocols were performed using a New Era Pump Systems NE-300 syringe pump. Flash silica gel and reverse-phase silica gel column chromatography were performed using EM reagent silica gel 60 (230–400 mesh) and Versaflash spherical C18 bonded flash silica gel (45–75 μm, 70 Å), respectively. ^{1}H NMR spectra were recorded on a Varian Unity-400 (400 MHz) or Varian Unity-500 (500 MHz) spectrometer and are reported in parts per million using solvent as an internal standard ($CDCl_3$ at 7.26 ppm). Data reported as: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, app=apparent; coupling constant(s) in hertz; integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Varian Unity-400 (100 MHz) or Varian Unity-500 (125 MHz) spectrometer and are reported in parts per million using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). Mass spectra were obtained through the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois. Chemical ionization (CI) spectra were collected on a Waters 70-VSE spectrometer using methane as the carrier gas. Electrospray ionization (ESI) spectra were performed on a Waters Q-Tof Ultima spectrometer. IR spectra were recorded as thin films on NaCl plates on a Mattson Galaxy Series FTIR 5000 and are reported in frequency of absorption (cm^{-1}). Optical rotations were measured using a 1 mL cell with a 1 dm path length on a Perkin–Elmer 341 polarimeter or using a 1 mL cell with a 5 cm path length on a Jasco DIP-360 digital polarimeter. Optical rotations were obtained with a sodium lamp and are reported as follows: $[\alpha]_{\lambda}^{T^{\circ}C}$ (*c*=g/100 mL, solvent). UV–vis spectra were taken on a Shimadzu PharmaSpec UV-1700 UV–vis spectrophotometer with 1 cm quartz cuvettes.

4.2. General procedure for slow addition protocol

*4.2.1. Slow addition protocol (20 mol % **1**)*

A 40 mL screwtop vial was charged with the following: substrate (0.5 mmol, 1.0 equiv), CH_3CN (1.0 mL, 0.5 M), and AcOH (15.0 mg, 0.25 mmol, 0.5 equiv) and a magnetic stir bar. The vial was placed on a stir plate and stirred vigorously at room temperature while open to ambient atmosphere. A 1.0 mL glass syringe was charged with a solution of Fe(*S*,*S*-PDP) **1** catalyst (93.1 mg, 0.1 mmol, 20 mol %) in CH_3CN (0.5 mL, 0.2 M) and loaded into a syringe pump set with an addition rate of 0.5 mL/1 h (0.0083 mL/min). A 10 mL glass syringe was charged with a solution of H_2O_2 (50 wt % in H_2O, 136 μL, 2.0 mmol, 4.0 equiv) in CH_3CN (5.0 mL, 0.4 M) and loaded into a syringe pump set with an addition rate of 5 mL/1 h (0.083 mL/min). Both syringes were equipped with 26G needles and directed into the center of the uncapped vial; precautions should be taken not to touch the sides (Fig. 1). The two additions were initiated simultaneously and both Fe(*S*,*S*-PDP) **1** catalyst and H_2O_2 were added to the reaction vial over the course of 1 h. The crude mixture was concentrated via rotary evaporation to a minimal amount of CH_3CN. Et_2O was added until a brown precipitate formed. The mixture was filtered through a short plug of Celite, concentrated by rotary evaporation and purified by flash chromatography.

Figure 1. Photograph of slow addition setup.

*4.2.2. Slow addition protocol (15 mol % **1**)*

Slow addition protocol for oxidation of substrate (0.5 mmol, 1.0 equiv), AcOH (15.0 mg, 0.25 mmol, 0.5 equiv) in 1.0 mL CH_3CN with one addition of H_2O_2 (50 wt %, 102.0 μL, 1.5 mmol, 3.0 equiv, 0.4 M) in 3.75 mL CH_3CN in a 10 mL glass syringe was added at the rate of 5 mL/1 h (0.083 mL/min) over the course of 45 min. Addition of **1** (69.9 mg, 0.075 mmol, 15 mol %, 0.2 M) in 0.375 mL CH_3CN in a 1.0 mL glass syringe was added at a rate of 0.5 mL/h (0.0083 mL/min) over the course of 45 min.

4.3. General procedure for iterative addition protocol

A 40 mL screwtop vial was charged with the following: Fe(*S*,*S*-PDP) **1** catalyst (23.3 mg, 0.025 mmol, 5 mol %), substrate (0.5 mmol, 1.0 equiv), CH_3CN (0.75 mL, 0.67 M), and AcOH (15.0 mg, 0.25 mmol, 0.5 equiv) and a magnetic stir bar. The vial was placed on a stir plate and stirred vigorously at room temperature. A solution of H_2O_2 (50 wt %, 36.8 μL, 0.6 mmol, 1.2 equiv) in CH_3CN (4.5 mL, 0.13 M) was added dropwise via syringe over ca. 45–75 s. The first drop of peroxide solution instantly changed the reaction mixture from a reddish-purple color to a yellow, which quickly dissipated to an orange/purple. Subsequent drops of peroxide continued this fluctuating pattern until an amber color was reached and maintained. When no further color changes were observed, the dropwise addition rate of peroxide was increased so that the addition was completed within 45–75 s. *Significant decreases in yield were noted when the peroxide solution was added rapidly.* After

ca. 10 min, a solution of Fe(*S*,*S*-PDP) **1** catalyst (23.3 mg, 0.025 mmol, 5 mol %), AcOH (15 mg, 0.25 mmol, 0.5 equiv), in CH_3CN (0.5 mL) was added via glass pipette. This was followed by H_2O_2 (50 wt %, 36.8 μL, 0.6 mmol, 1.2 equiv) in CH_3CN (4.5 mL) added dropwise over ca. 45–75 s. A third addition was performed in the same manner for a total of 15 mol % **1**, 1.5 equiv AcOH, and 3.6 equiv H_2O_2. Each addition was allowed to stir for 10 min, for a total reaction time of 30 min.

4.4. General procedure for reaction optimization (Table 1)

Oxidation of *cis*-4-methylcyclohexyl pivalate (**2**) was performed on 0.1 mmol scale (19.8 mg, 1.0 equiv). The general procedure under 'iterative addition protocol' was followed for entries 1–5, with the vials in entries 1, 3, and 4 receiving only one (1) addition of catalyst **1**/AcOH and H_2O_2 oxidant. The vial in entry 2 received a second addition of only H_2O_2 oxidant. H_2O_2 solutions were added over a period of ca. 45 s, unless specified otherwise. An aliquot was removed from the reaction mixture 10 min after the final addition of H_2O_2 (unless otherwise specified), and diluted with Et_2O, filtered through a SiO_2 plug and analyzed by GC. All product yields reported are calibrated for response factors, rounded to the nearest whole number and reported as the average (mean) of two runs.

Table 1, entry 1. H_2O_2 (50 wt %, 7.4 μL, 0.12 mmol, 1.2 equiv) in 0.9 mL CH_3CN was added to **1** (4.7 mg, 0.005 mmol, 5 mol %), **2** (19.8 mg, 0.1 mmol, 1.0 equiv), AcOH (3.0 mg, 0.05 mmol, 0.5 equiv), in 0.15 mL CH_3CN.

Table 1, entry 2. H_2O_2 (50 wt %, 7.4 μL, 0.12 mmol, 1.2 equiv) in 0.9 mL CH_3CN was added to **1** (4.7 mg, 0.005 mmol, 5 mol %), **2** (19.8 mg, 0.1 mmol, 1.0 equiv), AcOH (3.0 mg, 0.05 mmol, 0.5 equiv), in 0.15 mL CH_3CN. After stirring for 10 min with the first addition of H_2O_2, a second addition of H_2O_2 (50 wt %, 7.4 μL, 0.12 mmol, 1.2 equiv) in CH_3CN (0.9 mL) was added to the reaction mixture.

Table 1, entry 3. H_2O_2 (50 wt %, 7.4 μL, 0.12 mmol, 1.2 equiv) in 0.9 mL CH_3CN was added to **1** (14.0 mg, 0.015 mmol, 15 mol %), **2** (19.8 mg, 0.1 mmol, 1.0 equiv), AcOH (3.0 mg, 0.05 mmol, 0.5 equiv), in 0.15 mL CH_3CN.

Table 1, entry 4. H_2O_2 (50 wt %, 22.2 μL, 0.36 mmol, 3.6 equiv) in 0.9 mL CH_3CN was added to **1** (14.0 mg, 0.015 mmol, 15 mol %), **2** (19.8 mg, 0.1 mmol, 1.0 equiv), AcOH (9.0 mg, 0.15 mmol, 1.5 equiv), in 0.15 mL CH_3CN.

Table 1, entry 5. Iterative addition protocol for oxidation of **2** (19.8 mg, 0.1 mmol, 1.0 equiv) in 0.15 mL CH_3CN. A fourth addition of **1** (4.7 mg, 0.005 mmol, 5 mol %), AcOH (3.0 mg, 0.05 mmol, 0.5 equiv), in 0.10 mL CH_3CN and H_2O_2 (50 wt %, 7.4 μL, 0.12 mmol, 1.2 equiv) in 0.9 mL CH_3CN was added. Aliquots for GC analysis were taken 10 min after each H_2O_2 addition, immediately before the next solution of **1**/AcOH was added.

Table 1, entry 6. Slow addition protocol for oxidation of **2** (99.1 mg, 0.5 mmol, 1.0 equiv), AcOH (15.0 mg, 0.25 mmol, 0.5 equiv) in 1.0 mL CH_3CN with one addition of H_2O_2 (50 wt %, 102.0 μL, 1.5 mmol, 3.0 equiv) in 3.75 mL CH_3CN was added at the rate of 5 mL/1 h (0.083 mL/min) over the course of 45 min. Addition of **1** (69.9 mg, 0.075 mmol, 15 mol %) in 0.375 mL CH_3CN was added at a rate of 0.5 mL/h (0.0083 mL/min) over the course of 45 min.

The stereoretentive nature of the Fe(PDP) **1** catalyzed oxidation of *cis*-**2** (>98% *cis*, Alfa Aesar) to *cis*-**3** was determined by GC analysis of crude reaction mixtures from two individual reactions. Authentic samples of *cis*-**3** and *trans*-**3** were used as GC standards to determine retention times. The average cis:trans ratio of **3** was found to be 242:1 (reaction 1, injection 1: cis:trans=218:1, injection 2=223:1, injection 3=197:1, injection 4=247:1; reaction 2, injection 1: cis:trans=237:1, injection 2=259:1, injection 3=258:1, injection 4=265:1, injection 5=273:1) corresponding to 99.58%±0.05% *cis*-**3**.

4.5. Comparison of iterative and slow addition protocols for C–H oxidation (Table 2, Eqs. 1 and 2)

All reactions were performed on 0.5 mmol scale and are reported as the average of two runs. Yields from iterative addition protocol, purification and full characterization of oxidation products **4**–**7**, (+)-**8**, (−)-**9**, (+)-**11**, (−)-**12** in Table 2 and (+)-**14** and (+)-**16** in Eqs. 2 and 3 are available in Ref. 8. The purification of (+)-**14** was modified from the previously reported procedure so that it was now purified by flash reverse-phase silica gel chromatography (20% CH_3CN/H_2O). All isolated products were compared with previously obtained ^1H NMR, ^{13}C NMR, ESI-MS data and were found to be identical.

*Table 2, compound **4**.* Slow addition protocol using 1-bromo-5-methylhexane (89.6 mg, 0.5 mmol, 1.0 equiv) as substrate. Purification by flash silica gel chromatography (30% EtOAc/hexanes).

20 mol % catalyst loading: run 1 (59.1 mg, 0.303 mmol, 61%), run 2 (58.2 mg, 0.298 mmol, 60%). Average: 61%. Recovered starting material (rSM): run 1 and run 2 (0 mg, 0 mmol, 0%). Average recovered starting material: 0%.

15 mol % catalyst loading: run 1 (50.7 mg, 0.259 mmol, 52%), run 2 (47.7 mg, 0.244 mmol, 49%). Average: 51%. Recovered starting material (rSM): run 1 (25.0 mg, 0.140 mmol, 28%), run 2 (22.4 mg, 0.125 mmol, 25%). Average recovered starting material: 27%.

*Table 2, compound **5**.* Slow addition protocol using 2,2,2-trifluoro-*N*-(6-methylheptan-2-yl)acetamide (112.3 mg, 0.5 mmol, 1.0 equiv) as substrate. Purification by flash silica gel chromatography (30% EtOAc/hexanes).

20 mol % catalyst loading: run 1 (63.9 mg, 0.265 mmol, 53%), run 2 (65.1 mg, 0.269 mmol, 54%). Average: 54%. Recovered starting material (rSM): run 1 (28.1 mg, 0.125 mmol, 25%), run 2 (22.5 mg, 0.100 mmol, 20%). Average recovered starting material: 23%.

15 mol % catalyst loading: run 1 (54.2 mg, 0.225 mmol, 45%), run 2 (51.7 mg, 0.210 mmol, 43%). Average: 44%. Recovered starting material (rSM): run 1 (38.2 mg, 0.170 mmol, 34%), run 2 (40.3 mg, 0.180 mmol, 36%). Average recovered starting material: 35%.

*Table 2, compound **6**.* Slow addition protocol using methyl 6-methylheptanoate (79.1 mg, 0.5 mmol, 1.0 equiv) as substrate. Purification by flash silica gel chromatography (30% EtOAc/hexanes).

20 mol % catalyst loading: run 1 (59.2 mg, 0.340 mmol, 68%), run 2 (55.7 mg, 0.320 mmol, 64%). Average: 66%. Recovered starting material (rSM): run 1 and run 2 (0 mg, 0%). Average recovered starting material: 0%.

15 mol % catalyst loading: run 1 (54.0 mg, 0.310 mmol, 62%), run 2 (52.3 mg, 0.300 mmol, 60%). Average: 61%. Recovered starting material (rSM): run 1 (15.8 mg, 0.100 mmol, 20%), run 2 (16.6 mg, 0.105 mmol, 21%). Average recovered starting material: 21%.

*Table 2, compound **7**.* Slow addition protocol using 5-methylhexyl acetate (79.1 mg, 0.5 mmol, 1.0 equiv) as substrate. Purification by flash silica gel chromatography (30% EtOAc/hexanes).

20 mol % catalyst loading: run 1 (63.2 mg, 0.363 mmol, 73%), run 2 (62.1 mg, 0.356 mmol, 71%). Average: 72%. Recovered starting material (rSM): run 1 and run 2 (0 mg, 0 mmol, 0%). Average recovered starting material: 0%.

15 mol % catalyst loading: run 1 (59.3 mg, 0.340 mmol, 68%), run 2 (57.4 mg, 0.329 mmol, 66%). Average: 67%. Recovered starting material (rSM): run 1 (25.9 mg, 0.164 mmol, 33%), run 2 (20.7 mg, 0.138 mmol, 26%). Average recovered starting material: 30%.

*Table 2, compound (+)-**8**.* Slow addition protocol using (*S*)-5-((*R*)-5,5-dimethyl-2-oxo-1,3-dioxolan-4-yl)-3-methylpentyl acetate (129.2 mg, 0.5 mmol, 1.0 equiv) as substrate. Purification by flash silica gel chromatography (40% EtOAc/hexanes).

20 mol % catalyst loading: run 1 (69.9 mg, 0.255 mmol, 51%), run 2 (67.2 mg, 0.245 mmol, 49%). Average: 50%. Recovered starting material (rSM): run 1 (25.8 mg, 0.100 mmol, 20%), run 2 (21.8 mg, 0.084 mmol, 17%). Average recovered starting material: 19%.

15 mol% catalyst loading: run 1 (61.8 mg, 0.225 mmol, 45%), run 2 (62.0 mg, 0.226 mmol, 45%). Average: 45%. Recovered starting material (rSM): run 1 (41.3 mg, 0.160 mmol, 32%), run 2 (40.8 mg, 0.158 mmol, 32%). Average recovered starting material: 32%.

*Table 2, compound (−)-**9**.* Slow addition protocol using (*S*)-4-methyl-2-(2,2,2-trifluoroacetamido)pentyl acetate (127.6 mg, 0.5 mmol, 1.0 equiv) as substrate. Purification by flash silica gel chromatography (40% EtOAc/hexanes).

20 mol% catalyst loading: run 1 (63.7 mg, 0.235 mmol, 47%), run 2 (61.0 mg, 0.225 mmol, 45%). Average: 46%. Recovered starting material (rSM): run 1 (65.1 mg, 0.255 mmol, 51%), run 2 (62.5 mg, 0.245 mmol, 49%). Average recovered starting material: 50%.

15 mol% catalyst loading: run 1 (54.2 mg, 0.200 mmol, 40%) run 2 (52.8 mg, 0.195 mmol, 39%). Average: 40%. Recovered starting material (rSM): run 1 (74.0 mg, 0.290 mmol, 58%), run 2 (75.1 mg, 0.295 mmol, 59%). Average recovered starting material: 59%.

*Table 2, compound **10**.* Slow addition protocol using 2-nitro-*p*-cymene (99.6 mg, 0.5 mmol, 90% purity) as substrate. Purification by flash silica gel chromatography (20% EtOAc/hexanes).

20 mol% catalyst loading: run 1 (59.6 mg, 0.305 mmol, 61%), run 2 (58.9 mg, 0.302 mmol, 60%). Average: 61%. Recovered starting material (rSM): run 1 (8.1 mg, 0.045 mmol, 9%), run 2 (7.2 mg, 0.040 mmol, 8%). Average recovered starting material: 9%.

15 mol% catalyst loading: run 1 (54.6 mg 0.280 mmol, 56%), run 2 (53.7 mg, 0.275 mmol, 55%). Average: 56%. Recovered starting material (rSM): run 1 (16.7 mg 0.093 mmol, 19%), run 2 (15.0 mg, 0.084 mmol, 17%). Average recovered starting material: 18%.

Iterative addition protocol: run 1 (47.6 mg, 0.244 mmol, 49%), run 2 (45.5 mg, 0.235 mmol, 47%). Average: 48%. Recovered starting material (rSM): run 1 (19.7 mg, 0.110 mmol, 22%), run 2 (18.8 mg, 0.105 mmol, 21%). Average: 22%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, J=1.5 Hz, 1H), 7.62 (dd, J=2, 8 Hz, 1H), 7.31 (d, J=8 Hz, 1H), 2.58 (s, 3H), 1.60 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 132.7, 131.8, 129.2, 120.8, 72.1, 31.7, 20.0. IR (film, cm^{-1}): (neat, cm^{-1}) 2980.4, 2934.1, 2361.1, 2344.2, 1527.4, 1345.4. HRMS (EI) m/z calcd $C_{10}H_{14}O_3N$ $[M+H]^+$: 196.09737, found: 196.09745.

*Table 2, compound (+)-**11**.* Slow addition protocol using (*S*)-1-bromo-3,7-dimethyloctane (110.6 mg, 0.5 mmol, 1.0 equiv) as substrate. Regioselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.[8] Purification by flash silica gel chromatography (10% EtOAc/hexanes).

20 mol% catalyst loading: run 1 (50.9 mg, 0.215 mmol, 43%, C7 oxidation; 4.9 mg, 0.021 mmol, 4%, C3 oxidation), run 2 (49.6 mg, 0.210 mmol, 42%, C7 oxidation). Average C7 oxidation: 43%. Recovered starting material (rSM): run 1 (22.1 mg, 0.100 mmol, 20%), run 2 (20.9 mg, 0.095 mmol, 19%). Average recovered starting material: 20%.

15 mol% catalyst loading: run 1 (47.4 mg, 0.200 mmol, 40%), run 2 (48.6 mg, 0.205 mmol, 41%). Average C7 oxidation: 41%. Recovered starting material (rSM): run 1 (24.2 mg, 0.110 mmol, 22%), run 2 (23.3 mg, 0.105 mmol, 21%). Average recovered starting material: 22%.

*Table 2, compound (−)-**12**.* Slow addition protocol using (1*R*)-menthyl acetate (99.1 mg, 0.5 mmol, 1.0 equiv) as substrate. Regioselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.[8] Purification by flash silica gel chromatography (20% EtOAc/hexanes).

20 mol% catalyst loading: run 1 (57.9 mg, 0.270 mmol, 54%), run 2 (59.8 mg, 0.280 mmol, 56%). Average: 55%. Recovered starting material (rSM): run 1 (2.0 mg, 0.010 mmol, 2%), run 2 (5.2 mg, 0.026 mmol, 5%). Average recovered starting material: 4%.

15 mol% catalyst loading: run 1 (58.7 mg, 0.274 mmol, 55%), run 2 (55.7 mg, 0.260 mmol, 52%). Average: 54%. Recovered starting material (rSM): run 1 (17.7 mg, 0.089 mmol, 18%), run 2 (12.9 mg, 0.065 mmol, 13%). Average recovered starting material: 16%.

*Eq. 1, compound (+)-**14**.* Iterative addition protocol for the oxidation of (+)-artemisinin ((+)-**13**) (0.5 mmol, 141.2 mg, 0.5 mmol, 1.0 equiv) is similar to the general procedure with the exception that only 3.0 mg AcOH (0.05 mmol, 10 mol%) was added to the reaction and the starting material was initially solvated in 2.25 mL CH_3CN (0.22 M). The subsequent two additions of **1** (5 mol%)/AcOH (10 mol%) in 0.50 mL CH_3CN and H_2O_2 (1.2 equiv) in 4.5 mL CH_3CN were added without modification from the previously described procedure. Immediately upon completion, the reaction was quenched with a solution of saturated $NaHCO_3$, extracted with Et_2O (3×30 mL), dried on $MgSO_4$, filtered, and purified by flash silica gel column chromatography (25% EtOAc/hexanes). Upon re-isolation of starting material via chromatography, the oxidation was setup again according to the iterative addition protocol described above with identical reagent stoichiometries (based on equivalents of recovered (+)-**13**). Altogether, this process of *recycling* recovered starting material was done twice.

Slow addition protocol for the oxidation of (+)-**13** (0.5 mmol, 141.2 mg, 1.0 equiv) was performed identically as described in the general procedure with a single addition of H_2O_2 (50 wt%, 136.0 μL, 2.0 mmol, 4.0 equiv) in 5.0 mL and a single addition of **1** (93.1 mg, 0.1 mmol, 20 mol%) in 0.5 mL CH_3CN was added over the course of 60 min to a solution of (+)-**13**, AcOH (15.0 mg, 0.25 mmol, 0.5 equiv) in 1.0 mL CH_3CN. The substrate was not fully soluble initially, but reached full dissolution by the end of the reaction. Upon reaction completion the crude mixture was concentrated via rotary evaporation to a brown residue and purified by flash reverse-phase silica gel column chromatography (20% CH_3CN/H_2O). Note: with slow addition protocol there is no *recycling* of starting material.

20 mol% catalyst loading: run 1 (74.4 mg, 0.249 mmol, 50%), run 2 (77.6 mg, 0.260 mmol, 52%). Average: 51%. Recovered starting material (rSM): run 1 (2.7 mg, 0.010 mmol, 2%), run 2 (5.6 mg, 0.02 mmol, 4%). Average recovered starting material: 3%.

15 mol% catalyst loading: run 1 (71.6 mg, 0.240 mmol, 48%). Recovered starting material (rSM): run 1 (20.3 mg, 0.072 mmol, 14%).

*Eq. 2, compound (+)-**16**.* Iterative addition protocol for the oxidation of 16β-tetrahydrogibberellate diacetate [(+)-**15**] (108.6 mg, 0.25 mmol, 1.0 equiv) is similar to the general procedure with the exception that 0.25 mmol of starting material was initially solvated in 1.50 mL CH_3CN (0.17 M) and no AcOH was added to the reaction. The subsequent two additions of **1** (5 mol%) in 0.50 mL CH_3CN and H_2O_2 (1.2 equiv) in 2.25 mL CH_3CN were added without modification from the previously described procedure. The crude mixture was concentrated via rotary evaporation to a brown residue and immediately purified by flash silica gel column chromatography (30:70:1 EtOAc/hexanes/AcOH). Upon re-isolation of starting material via chromatography, the oxidation was setup again according to the iterative addition protocol described above with identical reagent stoichiometries (based on equivalents of recovered (+)-**15**). This process of *recycling* recovered starting material was done once.

Slow addition protocol for the oxidation of (+)-**15** (217.2 mg, 0.5 mmol, 1.0 equiv) was performed similarly to the general procedure with the exception that AcOH was not added to the reaction mixture. A single addition of H_2O_2 (50 wt%, 170.0 μL, 2.5 mmol, 5.0 equiv) in 6.25 mL CH_3CN and a single addition of **1** (116.5 mg, 0.125 mmol, 25 mol%) in 0.625 mL CH_3CN were added over the course of 75 min to (+)-**15** in 1.0 mL CH_3CN. Upon reaction completion the crude mixture was concentrated via rotary evaporation to a brown residue and purified by flash silica gel column chromatography (30:70:1 EtOAc/hexanes/AcOH). Note: with slow addition protocol there is no *recycling* of starting material.

15 mol% catalyst loading: run 1 (86.4 mg, 0.200 mmol, 40%). Recovered starting material (rSM): run 1 (84.6 mg, 0.195 mmol, 39%).

20 mol% catalyst loading: run 1 (104.0 mg, 0.240 mmol, 48%). Recovered starting material (rSM): run 1 (54.2 mg, 0.125 mmol, 25%).

25 mol% catalyst loading: run 1 (110.3 mg, 0.255 mmol, 51%), run 2 (109.0 mg, 0.250 mmol, 50%). Average: 51%. Recovered starting material (rSM): run 1 (41.0 mg, 0.095 mmol, 19%), run 2 (39.0 mg, 0.090 mmol, 18%). Average recovered starting material: 19%.

4.6. Lactonization of 4-methylvaleric acid and recovery of free (*S,S*)-PDP ligand after oxidation

Iterative addition protocol for the oxidation of 4-methylvaleric acid (58.1 mg, 0.5 mmol, 1.0 equiv) was performed similarly to the general procedure with the exception that no AcOH was added to the reaction. The subsequent two additions of **1** (23.3 mg, 0.025 mmol, 5 mol%) in 0.50 mL CH_3CN (0.05 M) and H_2O_2 (50 wt%, 36.8 μL, 0.6 mmol, 1.2 equiv) in 4.5 mL CH_3CN (0.13 M) were added without modification from the previously described procedure. The reaction was run with two different workups; one workup was designed to isolate lactone product and a second workup was designed to isolate (*S,S*)-PDP ligand.[13]

4.6.1. Isolation of the lactone product

The reaction was quenched with a solution of saturated $NaHCO_3$. The aqueous layer was extracted with Et_2O (3×30 mL) and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated carefully by rotary evaporation at 0 °C to prevent loss of volatile product. The crude product was purified by flash silica gel column chromatography (30% EtOAc/hexanes). The product 5,5-dimethyldihydrofuran-2(3*H*)-one[14] was obtained in 27.5 mg (run 1, 0.241 mmol, 48%) and 26.9 mg (run 2, 0.236 mmol, 47%). Average: 48%.

4.6.2. Isolation of (S,S-PDP) ligand

The crude reaction was quenched with concentrated NH_4OH and concentrated via rotary evaporation at 35 °C to dryness in order to remove volatile lactone product. The brown residue was filtered through a SiO_2 plug with EtOAc as eluent to obtain free (*S,S*)-PDP ligand: run 1, 23.1 mg, 0.072 mmol, 95%; run 2, 22.8 mg, 0.071 mmol, 94%; based on 15 mol% (0.075 mmol) **1**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (dd, *J*=0.8, 4.8 Hz, 2H), 7.60 (dt, *J*=2.0, 7.8 Hz, 2H), 7.39 (d, *J*=7.6 Hz, 2H), 7.11 (dd, *J*=5.2, 6.0 Hz, 2H), 4.19 (d, *J*=14.0 Hz, 2H), 3.49 (d, *J*=14.4 Hz, 2H), 2.99 (p, *J*=4.4 Hz, 2H), 2.79 (m, 2H), 2.22 (appq, *J*=8.4 Hz, 2H), 1.77–1.64 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 148.8, 136.3, 122.7, 121.6, 65.3, 61.1, 55.3, 25.9, 23.5. IR (film, cm^{-1}): 2960, 2920, 2872, 2806, 1588, 1570, 1474, 1431, 1366, 1212, 1150, 1120, 1046, 993, 931, 897, 759. HRMS (ESI) *m/z* calcd $C_{20}H_{27}N_4$ $[M+H]^+$: 323.2236, found: 323.2239.

Acknowledgements

We are grateful to the A.P Sloan Foundation, the Camille and Henry Dreyfus Foundation, Bristol-Myers Squibb, Pfizer, Amgen, Eli Lilly, Merck Research Laboratories, Abbott Laboratories, AstraZeneca, and the University of Illinois for financial support and generous gifts. N.A.V. gratefully acknowledges Pfizer for a graduate fellowship. M.S.C. is a Harvard University graduate student completing doctoral work with M.C.W. at the University of Illinois at Urbana-Champaign. M.S.C. gratefully acknowledges Bristol-Myers Squibb for a graduate fellowship. We thank M.A. Bigi for performing the oxidative lactonization of 4-methylvaleric acid, and E.M. Stang for verifying the hydroxylation results of artemisinin. Both M.A.B. and E.M.S. are thanked for helpful discussions in the writing of this manuscript.

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