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Chemoselective Tertiary C—H Hydroxylation for Late-Stage Functionalization with Mn(PDP)/Chloroacetic Acid Catalysis

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This paper is dedicated to Eric N. Jacobsen on the occasion of his 60th birthday for his inspirational work on the discovery and study of practical reactions that illuminate new selectivity principles in catalysis.

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Abstract. Aromatic and heterocyclic functionality are ubiquitous in pharmaceuticals. Herein, we disclose a new Mn(PDP) catalyst system using chloroacetic acid additive capable of chemoselectively oxidizing remote tertiary C(sp^3)—H bonds in the presence of a broad range of aromatic and heterocyclic moieties. Although catalyst loadings can be lowered to 0.1 mol% under a Mn(PDP)/acetic acid system for aromatic and non-basic nitrogen heterocycle substrates, the Mn(PDP)/chloroacetic acid system generally affords 10-15% higher isolated yields on these substrates and is uniquely effective for remote C(sp^3)—H hydroxylations in substrates housing basic nitrogen heterocycles. The demonstrated ability to perform Mn(PDP)/chloroacetic acid C(sp^3)—H oxidations in pharmaceutically relevant complex molecules on multi-gram scales will facilitate drug discovery processes via late-stage functionalization.

Keywords: C—H hydroxylation; oxidation; chemoselective; site-selective; late stage functionalization

Introduction

The direct, atomistic change from C(sp^3)—H to C(sp^3)—O can have a profound impact on the physical and biological properties of pharmaceuticals and complex bioactive molecules. With medicinal chemists moving towards increasing the fraction sp^3 (Fsp^3) in small molecule therapeutics,[1] methods that enable late stage C(sp^3)—H hydroxylation are highly desirable to avoid lengthy *de novo* syntheses when accessing novel chemical space for molecule derivatization and metabolite synthesis. The discovery of Fe(PDP) catalyst **1** in 2007 demonstrated for the first time that aliphatic C—H bonds of the same bond type (3° or 2°) can be preparatively and predictably distinguished based on small differences in their steric, electronic, and stereoelectronic properties.[2,3] Ligand modifications leading to Fe(CF_3-PDP) **2** demonstrated that the site of oxidation can be altered by modifying the catalyst.[4] Using these catalysts and the principles that emerged, there has been an explosion of research in the area of late stage oxidation for diversification of drugs and natural products[3,4,5] and streamlining synthesis[6]. Despite these advances, the majority of methods are limited by chemoselectivity issues when medicinally relevant aromatic and heteroaromatic functionalities are present. The development of

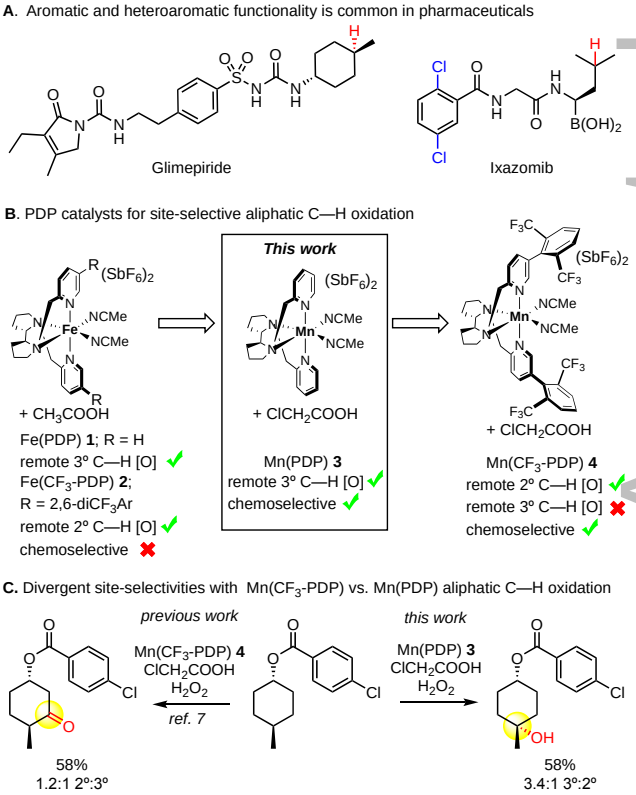

Figure 1. PDP catalysts for site-selective aliphatic C—H oxidation.

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methods that overcome this challenge stands to further increase the impact of late stage C—H functionalization in drug discovery (Figure 1.A).

We recently reported a small molecule Mn(CF_3-PDP) catalyst **4** using H_2O_2 oxidant and chloroacetic acid additive to site-selectively oxidize strong methylene bonds in the presence of more oxidatively labile halogenated aromatic and heteroaromatic functionality.[7] Non-haem Fe(PDP) **1** and Fe(CF_3-PDP) **2** catalysts were previously demonstrated to site-selectively hydroxylate strong aliphatic C—H bonds,[2,3,4] but showed no chemoselectivity for π-functionality unless deactivated with strongly electron withdrawing groups (i.e. nitro, trifluoromethyl, triflate). Alternatively, manganese has a lower redox potential[8] which disfavours undesired aromatic oxidation, while the increased basicity of the manganese oxo[9] may promote C—H abstraction. By combining manganese with the sterically bulky CF_3-PDP ligand design, which additionally may disfavor the sterically demanding π-system oxidation,[10] Mn(CF_3-PDP) **4** showed high chemoselectivity for the oxidation of strong methylene C(sp^3)—H bonds. However, the later ligand modification also limits the ability of Mn(CF_3-PDP) **4** to oxidize more sterically demanding 3° C—H bonds. Indeed, within substrates containing both 3° and 2° C—H sites available for oxidation, Mn(CF_3-PDP) **4** favors oxidation at the more accessible but less electron rich 2° C—H bonds (Figure 1.C).[7] We hypothesized investigating manganese catalyst designs with less sterically demanding ligand frameworks may allow us to access preparative oxidation of 3° C—H bonds in the presence of aromatic and heteroaromatic functionality.

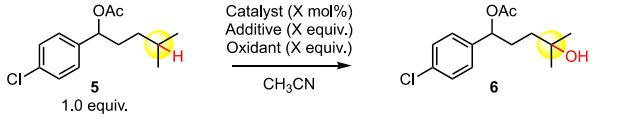
Herein we disclose a chemoselective 3° C—H hydroxylation with a Mn(PDP) **3**/chloroacetic acid catalytic system for late-stage functionalization that is tolerant of a wide variety of aromatic and heterocyclic functionality (Figure 1.B).

Results and Discussion

We began by investigating the hydroxylation of tertiary substrate **5** containing a mildly electron-deactivating *para*-chloro-substituted aromatic ring with catalysts reported to hydroxylate 3° C—H bonds in the presence of benzoate groups. Both *cis*-[Ru(dtbpy)$_2$Cl$_2$][11] and Mn(OTf)$_2$/bipy[12] catalysts afforded moderate yields and chemoselectivities under their reported conditions (Table 1.A, entry 1 – 2). Whereas Mn(CF_3-PDP) **4** gave a comparable yield and selectivity to these catalyst systems (entry 3), expectedly Fe(PDP) **1** gave no desired 3° C—H hydroxylation product **6** due to competitive aromatic oxidation (entry 4).

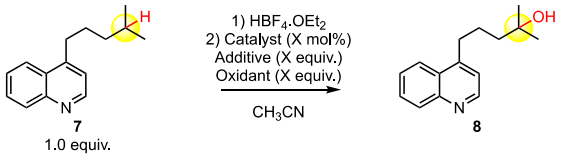
Table 1. Reaction Development.

A. *Remote 3° C(sp^3)—H hydroxylation in aromatic molecules*



Entry	Catalyst (mol%)	Additive	Oxidant	Temperature (°C)	Yield (%)	Sel. (%)[a]
1	*cis*-[Ru(dtbpy)$_2$Cl$_2$] (5%)	–	H_5IO_6 (2 equiv.)	RT	38	54
2	Mn(OTf)$_2$ (0.1%) bipy (1%)	–	AcOOH (3 equiv.)	RT	40	48
3	Mn(CF_3-PDP) **4** (10%)	$ClCH_2COOH$ (15 equiv.)	H_2O_2 (5 equiv.)	0[b]	46	51
4	Fe(PDP) **1** (3x5%)	CH_3COOH (3x0.5 equiv.)	H_2O_2 (3x1.2 equiv.)	RT[c]	0	0
5	Mn(PDP) **3** (3x5%)	CH_3COOH (3x0.5 equiv.)	H_2O_2 (3x1.2 equiv.)	RT[c]	32	81
6	Mn(PDP) **3** (10%)	CH_3COOH (15 equiv.)	H_2O_2 (5 equiv.)	RT[d]	52	87
7	Mn(PDP) **3** (10%)	CH_3COOH (15 equiv.)	H_2O_2 (5 equiv.)	0[d]	58	76
8	Mn(PDP) **3** (0.1%)	CH_3COOH (14 equiv.)	H_2O_2 (2.5 equiv.)	0[e]	60	73
	Condition A:					
9	Mn(PDP) **3** (0.1%)	CH_3COOH (14 equiv.)	H_2O_2 (2.5 equiv.)	0[f]	57	80
10	Mn(PDP) **3** (0.1%)	$ClCH_2COOH$ (14 equiv.)	H_2O_2 (2.5 equiv.)	0[f]	37	82

B. *Remote 3° C(sp^3)—H hydroxylation in basic heteroaromatic molecules*



Entry	Catalyst (mol%)	Additive	Oxidant	Temperature (°C)	Yield (%)	Sel. (%)[a]
1	Mn(PDP)(OTf)$_2$ (0.1%)	CH_3COOH (14 equiv.)	H_2O_2 (2.5 equiv.)	0[e]	0	0
2	Mn(PDP) **3** (0.1%)	CH_3COOH (14 equiv.)	H_2O_2 (2.5 equiv.)	0[f]	0	0
3	Mn(PDP) **3** (10%)	CH_3COOH (14 equiv.)	H_2O_2 (2.5 equiv.)	0[d]	33	92
4	Mn(PDP) **3** (10%)	CH_3COOH (14 equiv.)	H_2O_2 (5 equiv.)	0[d]	59	85
5	Mn(PDP) **3** (10%)	$ClCH_2COOH$ (15 equiv.)	H_2O_2 (5 equiv.)	0[b]	73	85
	Condition B:					
6	Mn(PDP) **3** (10%)	$ClCH_2COOH$ (15 equiv.)	H_2O_2 (5 equiv.)	-36[b]	70	94
7	Mn(PDP) **3** (5%)	$ClCH_2COOH$ (15 equiv.)	H_2O_2 (5 equiv.)	-36[b]	55	89
8	Mn(PDP) **3** (2.5%)	$ClCH_2COOH$ (15 equiv.)	H_2O_2 (5 equiv.)	-36[b]	41	95
9	Mn(PDP) **3** (0.1%)	$ClCH_2COOH$ (15 equiv.)	H_2O_2 (5 equiv.)	-36[b]	0	0

(*R*,*R*)-Mn(PDP) and (*S*,*S*)-Mn(PDP) used interchangeably. Isolated yields based on the average of 2-3 reactions. [a]Chemoselectivity (Sel.) = 3° C—H oxidation/total conversion. [b]Substrate, catalyst and additive with slow addition of H_2O_2 (in MeCN, 0.4 M) over 3 h. [c]Iterative addition of 5 mol% catalyst, 0.5 equiv. CH_3COOH, 1.2 equiv. H_2O_2 every 10-15 min. [d]Substrate, catalyst and additive with slow addition of H_2O_2 over 1 h. [e]Substrate, catalyst, additive with slow addition of H_2O_2 (in MeCN, 2.5 M) over 1 h and reaction mixture stirred for an additional 1 h. [f]Substrate, catalyst, additive with slow addition of H_2O_2 (in MeCN, 0.2 M) over 1 h.

Similar to our previous report, switching from iron to manganese significantly improved

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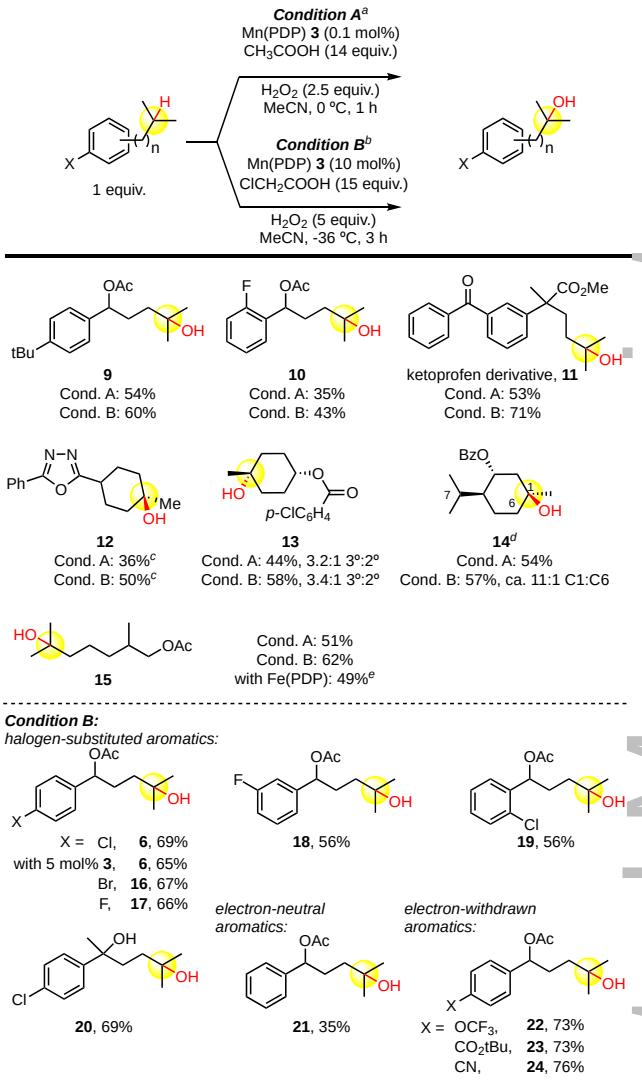
chemoselectivity. Mn(PDP) **3** under identical iterative addition conditions gave significantly higher yield (32%) of the desired 3º C—H oxidation product **6** with 81% chemoselectivity (entry 5). Switching from an iterative addition protocol to a single addition of Mn(PDP) **3** catalyst with slow addition of H_2O_2 oxidant at room temperature further increased the reactivity to a synthetically useful 52% yield of 3º alcohol **6** (entry 6). Reducing the reaction temperature from room temperature to 0 ºC further increased the yield for desired 3º oxidation, presumably by avoiding catalase-like decomposition of H_2O_2 by the manganese catalyst (entry 7).[13] We questioned whether reducing the catalyst loading would be feasible for the oxidation of weaker 3º C—H bonds. Previously reported Mn(PDP)$(OTf)_2$ catalysis for tertiary and secondary C—H oxidations at very low catalyst loadings (0.1 mol%) were known for simple aliphatic substrates, including substrates containing benzoate moieties.[12,14] Using the reported conditions with our Mn(PDP)$(SbF_6)_2$ **3** catalyst, we found that the desired product **6** was formed in comparable yield and chemoselectivity to the 10 mol% catalyst loading conditions (entry 7 versus 8). By modifying the reaction concentration, we found the chemoselectivity could be further improved to 80% (entry 9). Chloroacetic acid, a key to the high yielding conditions developed below (see Table 1.B), under these low catalyst loading conditions (0.1 mol%), afforded a substantial decrease in yield (entry 10).

We questioned if these extremely mild oxidation conditions would be effective in more complex molecular settings, particularly substrates containing basic nitrogen functionality. It has been previously demonstrated that such nitrogen functionality requires complexation with a Brønsted acid having a non-coordinating counterion (HBF_4) to enable remote aliphatic C—H oxidations with Fe or Mn(PDP) catalysis.[7,15] When a quinoline containing substrate **7** was evaluated with both Mn(PDP)$(OTf)_2$[14] and Mn(PDP)$(SbF_6)_2$ **3** catalysts, the low 0.1 mol% catalyst loading conditions established in Table 1.A were no longer competent at affording the desired remote 3º C—H oxidation product **8** (Table 1.B, entry 1 – 2). Increasing the catalyst loading from 0.1 mol% to 10 mol% restored reactivity, furnishing tertiary alcohol **8** in an encouraging 33% yield with excellent 92% chemoselectivity (entry 3). Notably, no benzylic oxidation is observed, likely due to the strong inductively withdrawing nature of the protonated quinoline. Increasing the oxidant loading from 2.5 equiv. to 5.0 equiv. provided synthetically useful 59% yield though with slightly diminished chemoselectivity (entry 4). Electron deficient chloroacetic acid additive was demonstrated to be critical for optimal 2º C—H oxidation reactivity with Mn(CF_3-PDP) catalyst **4**, possibly by increasing the electrophilicity of the postulated manganese(oxo) carboxylate intermediate.[7] Similarly, switching to chloroacetic acid and extending the oxidant addition time further increased the reactivity for Mn(PDP) **3** in 3º C—H oxidation to 73% yield (entry 5). Lowering the temperature from 0 ºC to -36 ºC gave optimal 94%

Table 2. Mn(PDP)-Catalyzed 3º C(sp^3)—H Hydroxylations in Aromatic and non-Basic Heteroaromatic Compounds.



(*R*,*R*)-MnPDP and (*S*,*S*)-Mn(PDP) used interchangeably. Isolated yields based on the average of 2-3 reactions. [a]Substrate, 0.1 mol% Mn(PDP) **3**, 14 equiv. CH_3COOH additive with slow addition of 2.5 equiv. H_2O_2 (in MeCN, 0.2 M) over 1 h at 0 ºC. [b]Substrate, 5-10 mol% Mn(PDP) **3**, 15 equiv. $ClCH_2COOH$ additive with slow addition of 5.0 equiv. H_2O_2 (in MeCN, 0.4 M) over 3 h at -36 ºC. [c]Starting material recycled once. [d](*S*,*S*)-Mn(PDP) required for optimal yield. [e]See ref. 2a.

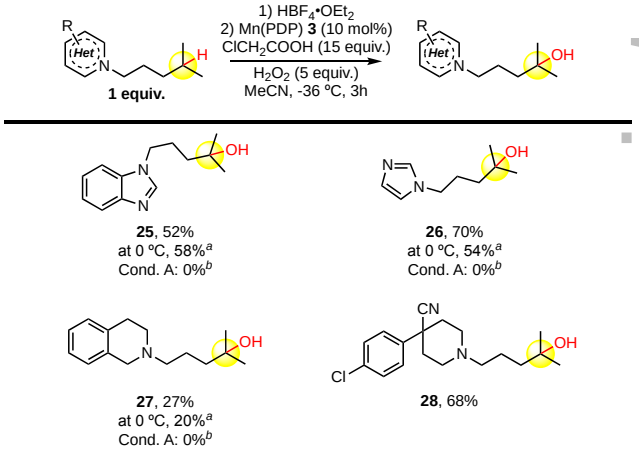
chemoselectivity while maintaining 70% yield (entry 6). In the majority of cases evaluated, the -36 ºC conditions afforded higher yields (*vide infra*). Under the optimized conditions B, we re-evaluated lowering the catalyst loading. Lowering the catalyst from 10 mol% to 5 mol% maintained the preparative utility of the reaction affording 55% yield of **8** (entry 7). Lowering the catalyst loading further to 2.5 mol% saw a significant diminishment in yield to 41% (entry 8). Re-investigation of 0.1 mol% catalyst **3** loading

under optimized conditions B furnished no product (entry 9).

After establishing the optimal conditions for Mn(PDP) **3** catalyzed 3º C—H hydroxylations, we sought to investigate their generality. We initially explored the 0.1 mol% **3** conditions (Table 1.A, entry 9, condition A) versus the 10 mol% **3** conditions (Table 1.B, entry 6, condition B) on aromatic and non-basic heteroaromatic substrates. Although condition A (0.1 mol%) gave useful yields in the majority of cases, a significant improvement was observed with condition B (10 mol%). For example, a derivative of biaryl NSAID ketoprofen afforded ca. 18% higher isolated yield of alcohol **11** under 10 mol% **3** conditions B. Interestingly, a non-basic oxadiazole heterocycle not requiring HBF_4 protection furnished alcohol **12** at the low Mn(PDP) **3** loadings of condition A, signifying that the lack of reactivity of these conditions with quinoline substrate **7** may be related to its basicity and/or the Brønsted acid complexation (*vide infra*). Highlighting the orthogonality of Mn(PDP) **3** catalysis with Mn(CF_3-PDP) **4**, a *trans*-cyclohexanol substrate housing competing tertiary and secondary sites preferentially oxidized the tertiary site under both conditions A and B (3º:2º = 3.4:1, **13**), whereas Mn(CF_3-PDP) **4** favored formation of the methylene ketone (3º:2º = 1:1.2)[7]. Similarly, benzoate-protected menthol furnished preparative yields and excellent 3º:2º selectivity (**14**), with no observed oxidation at the alternate C7 3º site. Interestingly, dioxirane[16] and oxaziridines[17] oxidants are not reported to give any selectivity on analogous menthol derived substrates whereas radical azidation methods afford C7 products, albeit in poor yields[18]. Archetypical citronellol-derived substrate afforded substantially improved yields of remote tertiary hydroxylated product **15** under Mn(PDP) **3** conditions B relative to its iron counterpart with no observed diminishment in site-selectivity.[2a] We additionally evaluated the more forcing Mn(PDP) **3** oxidation conditions B with a range of mildly electron-withdrawing halogen-substituted aromatic substrates and gratifyingly found uniformly preparative yields for tertiary C—H oxidations (**6**, **16-24**, Table 2). Consistent with previous observations, Table 1.A substrate **5** afford an *ca.* 10% increase in yield of tertiary hydroxylated product **6** under conditions B (69%) and catalyst **3** could be lowered to 5 mol% with only a small diminishment in yield (65%).

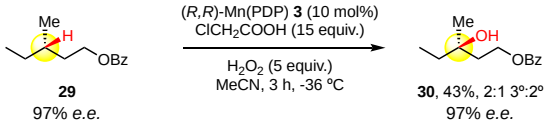
Consistent with previous observations, Mn(PDP) **3** C—H hydroxylations of substrates housing basic nitrogen moieties requiring Brønsted acid protection were uniquely effective under conditions B, with no desired product being observed under the low catalyst loading (0.1 mol%) conditions A (Table 3). The temperature influence on yield was substrate dependent: whereas a benzimidazole substrate afforded slightly higher yield of **25** under the 0 ºC conditions, the analogous imidazole substrate gave ca. 16% higher yield of **26** at -36 ºC. A challenging tetrahydroisoquinoline substrate evaluated under Mn(PDP) **3**/ chloroacetic acid catalysis at -36 ºC afforded a modest 27% yield of the desired remote 3º alcohol **27** with only a slight diminishment in yield at 0 ºC. Substrates containing electron neutral aromatic moieties have not previously been demonstrated in methylene C(sp^3)—H oxidations with Mn(CF_3-PDP) **4** catalysis due to competing aromatic oxidation. A ketobemidone analogue containing a 4-chloroarylpiperidine pharmacophore afforded remote oxidation product **28** in 68% yield under condition B.

Table 3. Mn(PDP)-Catalyzed 3º C(sp^3) —H Hydroxylations in Basic Heteroaromatic Compounds.



(*R,R*)-Mn(PDP) and (*S,S*)-Mn(PDP) used interchangeably. Isolated yields based on the average of 2-3 reactions. [a]Reactions runs at 0 ºC instead of -36 ºC. [b]Substrate, 0.1 mol% catalyst, 14 equiv. CH_3COOH additive with slow addition of 2.5 equiv. H_2O_2 (in MeCN, 0.2 M) over 1 h at 0 ºC.

We hypothesized that analogous to Fe(PDP) **1** hydroxylations, Mn(PDP) **3** oxidations proceed via a high valent metal oxidant that effects C—H hydroxylations through a mechanism that does not involve the generation of long-lived carbon centered radical species.[3] To probe this, we evaluated the oxidation of enantiomerically enriched substrate **29** under the general Mn(PDP) **3** catalysis condition B. Consistent with oxidation results with other chiral substrates (e.g. **13**, **14**), Mn(PDP) **3** oxidation of **29** proceeds with stereoretention to afford 3º alcohol **30** (eq. 1). This result is in contrast to electrochemical[19] and iron and manganese porphyrin catalyzed C—H functionalizations which proceed via long lived radicals[18,20,21] where ablation of stereochemistry at tertiary sites is observed.



Equation 1. Stereoretention Study.

The chemoselectivity and reactivity observed with Mn(PDP) **3** catalysis in the presence of

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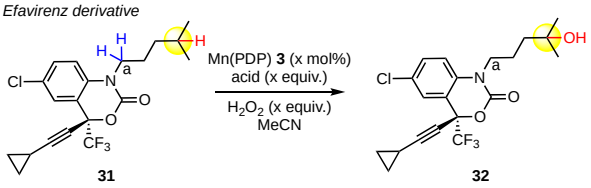
pharmaceutically relevant aromatic and heteroaromatic moieties provides an opportunity for late-stage diversification of drug scaffolds. Evaluation of an efavirenz derivative **31**, the parent compound being a WHO essential medicine for HIV, afforded tertiary hydroxylated product **32** in 53% isolated yield under condition B with no protection of the non-basic carbamate nitrogen. In addition to demonstrating high chemoselectivity for the π-systems of an aromatic and alkyne moiety, Mn(PDP) **3** tertiary oxidation also displayed preferential reactivity for tertiary C—H bond oxidation versus oxidation alpha to the heterocyclic nitrogen. Previous Mn(CF_3-PDP) **4** methylene oxidation of a hexanoyl efavirenz derivative had also shown π-system tolerance when the alpha-nitrogen site was blocked with a carbonyl moiety (*vide infra*, Fig. 3.B).[7] Warming the reaction to 0 ºC or using the low Mn(PDP) **3** catalyst loading condition A (0.1 mol%) afforded product **32** with comparable diminishments in yield to those noted in Table 2.

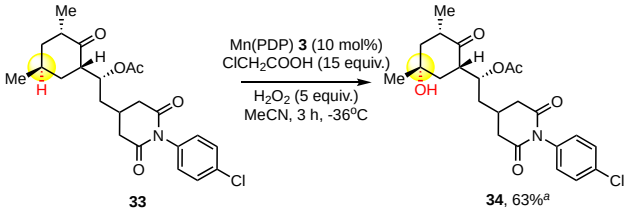
A. *Efavirenz derivative*



31 **32**

3 (mol %)	**Acid** (equiv.)	H_2O_2 (equiv.)	**Temp.** (ºC)	**Yield** (%)
10	$ClCH_2COOH$ (15)	5.0	-36	53
10	$ClCH_2COOH$ (15)	5.0	0	43
0.1	AcOH (14)	2.5	0	46

B. *Cycloheximide derivative*



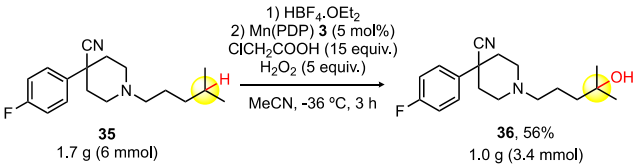
33 **34**, 63%[a]

Figure 2. Late Stage C—H Oxidation of Pharmaceutical Derivatives. [a]Starting material recycled once.

Additionally, we evaluated an aryl-substituted cycloheximide derivative **33**, the parent compound having broad antimicrobial activity, for remote tertiary oxidation on the cyclohexanone core. Consistent with previous observations, the imide functionality was tolerated with no Brønsted acid complexation.[15] Notably, Mn(PDP) **3** catalysis using general condition B was tolerant of the newly introduced aniline moiety, albeit electronically deactivated, furnishing the tertiary hydroxylated product **34** in excellent 63% yield.

Given the ability of Mn(PDP) **3** and Mn(CF_3-PDP) **4** to catalyze chemoselective tertiary and methylene C—H oxidations to access metabolites and perform late-stage functionalization on medicinally relevant candidates, we wanted to evaluate the ability to perform these oxidation reactions on scales that

A. *Mn(PDP)-catalyzed 3º hydroxylation on 1.7 g (6.0 mmol) scale*

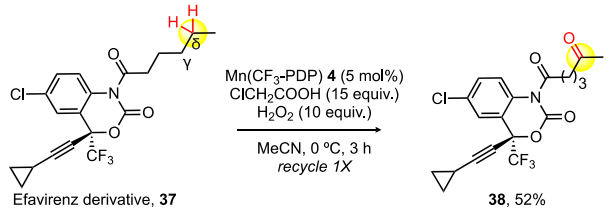


35
1.7 g (6 mmol)

36, 56%
1.0 g (3.4 mmol)

3 (mol %)	**Acid** (equiv.)	H_2O_2 (equiv.)	**Temp.** (ºC)	**Yield** (%)
10	$ClCH_2COOH$ (15)	5.0	-36	66
5	$ClCH_2COOH$ (15)	5.0	-36	60
2.5	$ClCH_2COOH$ (15)	5.0	-36	43
10	CH_3COOH (15)	5.0	0	42
0.1	CH_3COOH (14)	2.5	0	0

B. *Mn(CF_3-PDP)-catalyzed 2º oxidation on 2.5g (6.0 mmol) scale*



Efavirenz derivative, **37**
2.5 g (6 mmol)

38, 52%
4:1 δ:γ
1.3 g (3.1 mmol)

Figure 3. Scale-up C—H Oxidations of Bioactive Molecules.

facilitate drug discovery processes. We examined both Mn(PDP) **3** and Mn(CF_3-PDP) **4** catalysts for 6.0 mmol scale tertiary and methylene oxidations of pharmaceutically relevant substrates. Compound **35**, with a 4-fluoroarylpiperidine, a pharmacophore found in opioids, such as ketobemidone and haloperidol, was initially evaluated on a 0.3 mmol scale to explore lower Mn(PDP) **3** catalyst loadings under condition B that would be particularly relevant for large scale oxidations (Figure 3.A). Using Mn(PDP) **3** condition B (10 mol%), remote oxidation product **36** was isolated in an optimal 66% yield. The catalyst loading of Mn(PDP) **3** can be reduced to 5 mol% while maintaining a preparatively useful 60% yield. Underscoring the significance of the chloroacetic acid additive, a switch to acetic acid under otherwise optimal condition B furnished a comparable diminishment in yield to decreasing the catalyst loading to 2.5 mol% (42% vs 43%). Expectedly, the 0.1 mol% catalyst loading condition A afforded no product with this basic piperidine substrate. From these studies, we concluded the optimal conditions for reaction scale-up would use 5 mol% catalyst loading with chloroacetic acid additive. Following piperidine protection using the HBF_4 protection strategy,[15] a 1.7 g (6.0 mmol) C—H hydroxylation of **35** using 5 mol% Mn(PDP) **3** afforded 1.0 g (3.4 mmol) of tertiary hydroxyl product **36** in 56% yield. We additionally examined the previously reported Mn(CF_3-PDP) **4** methylene oxidation of HIV-1 drug efavirenz derivative **37**. A similar reduction in Mn(CF_3-PDP) **4** loading from 10 mol% to 5 mol% on a small scale (0.2 mmol) oxidation resulted in only minor reduction in yield (58% → 50%, see Supporting Information). On a 2.5-gram scale (6 mmol), Mn(CF_3-PDP) **4** at 5 mol% afforded ca. 41% yield of **38** with 27% recovered starting material **37**

(see Supporting Information). A simple recycle of the recovered starting material **37** afforded 1.3 grams (3.1 mmol) of remote oxidation product **38** in 52% overall yield.

Conclusion

We describe the development of the first general conditions for chemoselective Mn(PDP) **3** catalyzed tertiary C(sp^3)—H hydroxylations in substrates containing a broad range of aromatic and heteroaromatic functionality. Systematic evaluation of the previously reported[14] low loading conditions for Mn(PDP) **3** (0.1 mol%) using acetic acid additive illuminated that these conditions afford moderate to good hydroxylation yields for simple halogenated aromatics and non-basic heterocyclic substrates but prove ineffective for molecules containing basic-nitrogen heterocycles. The general oxidation conditions reported in this work using Mn(PDP) **3** catalysis at higher catalyst loadings (5-10 mol%) in combination with chloroacetic acid additive are uniquely effective in the remote C—H hydroxylation of medicinally important substrates housing basic nitrogen functionality that must be masked with Brønsted acid complexation prior to C—H oxidation. Moreover, these conditions afford 10-15% higher yields in halogenated aromatic and non-basic heteroaromatic substrates. Given the relative abundance of manganese and the ease of preparation of Mn(PDP) **3** catalyst, we believe these general conditions will find widespread use in late stage diversification of pharmaceutically relevant molecules and the rapid identification of metabolites.

Experimental Section

General Procedure for C—H Oxidation Condition A Using 0.1 mol% Mn(PDP) Catalyst

A 40 mL vial was charged with substrate (0.3 mmol, 1.0 equiv), Mn(PDP) **3** (5 mM stock solution, 60 µL, 0.3 µmol, 0.001 equiv.), CH_3COOH (0.24 mL, 4.2 mmol, 14.0 equiv.) and a stir bar. Acetonitrile (MeCN, 0.6 mL, 0.5 M) was added and the vial was sealed with a screw cap fitted with a PTFE/silicone septum. The vial was cooled to 0 ºC with an ice/water bath. A separate solution of H_2O_2 (51.0 mg, 0.75 mmol, 2.5 equiv., 50% wt. in H_2O, purchased from Sigma Aldrich) in MeCN (3.75 mL, 0.2 M) was loaded into a 10 mL syringe fitted with a 25G needle and added dropwise to the stirring reaction *via* syringe pump over 1 h (3.75 mL h^{-1} addition rate) while maintaining the reaction vial at 0 ºC. Upon completion of addition, the reaction was concentrated *in vacuo* to a minimum amount of solvent. The residue was dissolved in DCM and washed with sat. $NaHCO_3$ solution. The aqueous layer was extracted with DCM twice. The combined organic layer was dried with Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash column chromatography to afford the desired oxidation product.

General Procedure for C—H Oxidation Condition B Using 10 mol% Mn(PDP) Catalyst

A 40 ml vial was charged with substrate (0.3 mmol, 1.0 equiv.), Mn(PDP) **3** (27.9 mg, 0.03 mmol, 10 mol%), $ClCH_2CO_2H$ (425 mg, 4.5 mmol, 15.0 equiv.) and a stir bar. Acetonitrile (MeCN, 0.6 mL, 0.50 M) was added along the wall to ensure all compounds were washed beneath the solvent level and the vial was sealed with a screw cap fitted with a PTFE/silicone septum. The vial was cooled to -36 °C with a 1,2-dichloroethane/dry ice bath. A separate solution of H_2O_2 (102 mg, 1.5 mmol, 5.0 equiv., 50% wt. in H_2O, purchased from Sigma-Aldrich) in MeCN (3.75 mL, 0.4 M) was loaded into a 10 mL syringe fitted with a 25 G needle and added dropwise to the stirring reaction *via* a syringe pump over 3 h (1.25 mL h^{-1} addition rate) while maintaining the reaction vial at -36 °C. Upon completion, the reaction was concentrated *in vacuo* to a minimum amount of solvent. The residue was dissolved in DCM and washed with sat. $NaHCO_3$ solution (caution: CO_2 released) to remove $ClCH_2CO_2H$. The aqueous layer was extracted with DCM twice. The combined organic layer was dried with Na_2SO_4, filtered and concentrated. The crude mixture was purified by flash column chromatography to afford the desired oxidation product. If this method gave low conversion, an alternative addition protocol was used. See Supporting Information Methods C and D.

Detailed experimental procedures and characterization data for all new compounds are described in the supporting information.

Crystallographic data for (*S*,*S*)-Mn(PDP) **3** can be obtained free of charge from www.ccdc.cam.ac.uk/structures/ with deposit number CCDC 1869257.

Crystallographic data for (*S*,*S*)-Mn(CF_3-PDP) **4** can be obtained free of charge from www.ccdc.cam.ac.uk/structures/ with deposit number CCDC 1964541.

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Notes

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Competing Interest
The University of Illinois has filed a patent application on the Mn(CF_3-PDP) catalyst for C—H oxidation in aromatic molecules.

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FULL PAPER

Chemoselective Tertiary C—H Hydroxylation with Mn(PDP)/Chloroacetic Acid Catalysis

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