Organic LETTERS

Letter

pubs.acs.org/OrgLett

# Iron Complex Catalyzed Selective C−H Bond Oxidation with Broad Substrate Scope

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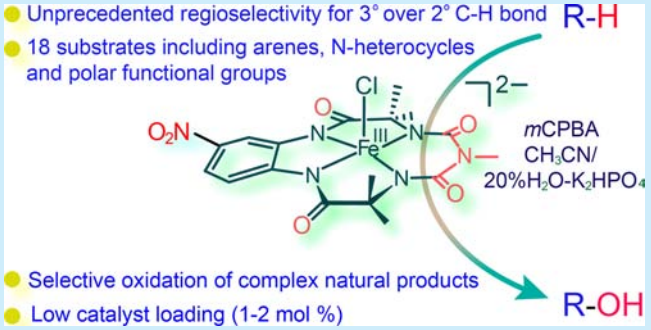
Supporting Information

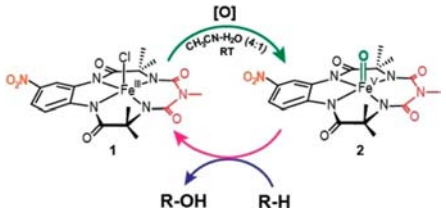
**ABSTRACT:** The use of a peroxidase-mimicking Fe complex has been reported on the basis of the biuret-modified TAML macrocyclic ligand framework (Fe−bTAML) as a catalyst to perform selective oxidation of unactivated 3° C−H bonds and activated 2° C−H bonds with low catalyst loading (1 mol %) and high product yield (excellent mass balance) under near-neutral conditions and broad substrate scope (18 substrates which includes arenes, heteroaromatics, and polar functional groups). Aliphatic C−H oxidation of 3° and 2° sites of complex substrates was achieved with predictable selectivity using steric, electronic, and stereoelectronic rules that govern site selectivity, which included oxidation of (+)-artemisinin to (+)-10$\beta$-hydroxyartemisinin. Mechanistic studies indicate $Fe^{V}(O)$ to be the active oxidant during these reactions.




Selective and predictable oxidation of alkyl C−H bonds in complex natural products under mild conditions presents a major challenge in synthetic organic chemistry.[1] Inspired by the high catalytic efficiency for the hydroxylation of alkyl C−H bonds by iron-containing enzymatic systems, chemists have developed numerous synthetic Fe-based complexes[2] including a tetradentate N-donor ligand-bound $Fe^{II}$ center with *cis* labile sites ($Fe-N_4$),[3] a mimic of the enzyme Rieske dioxygenase. Using these complexes, White[4] in 2007 and subsequently Costas[5] were able to show the oxidation of aliphatic C−H bonds using $H_2O_2$ as the oxidant on a preparative scale. In a series of reports, they demonstrated that intermolecular aliphatic C−H oxidation of 3° and 2° sites with predictable selectivity can be achieved using steric, electronic, and stereoelectronic rules that govern site selectivity.[4,5] Although significant progress has been made in the development of Fe complexes for alkyl C−H bond hydroxylation, several formidable challenges still exist. These include (i) expansion of the substrate scope to include structures derived from aryl or heteroaromatic groups ($Fe-N_4$ complexes hydroxylate aromatic rings thus rendering the catalysts inactive[3d]), (ii) expansion of the substrate scope to include structures containing single polar functional groups, particularly substrates that are sensitive to acid, (iii) selective oxidation of 3° C−H bonds in the presence of 2° C−H bonds for substrates in which the 3° C−H bonds are oriented in the axial position, and (iv) reduction of catalyst loading to 2 mol % and lower during oxidation to ensure that the reactions are economically feasible. Although ruthenium- and manganese-based complexes have also been used successfully for chemoselective C−H oxidations by Du Bois, Bryliakov, and others,[6] the development of catalytic systems based on environmentally compatible and naturally abundant metal iron remains a challenge.

We focused our attention on a functional peroxidase mimic, Fe−bTAML, a member of the broad class of catalysts called TAML activators, developed by Collins in the mid-1990s.[7−9] Upon addition of *m*-CPBA to Fe−bTAML, the peroxide-bound $Fe^{III}$ complex formed the corresponding $Fe^{V}(O)$ quantitatively at room temperature,[10] which is able to oxidize unactivated alkyl C−H bonds via C−H abstraction. We hypothesized that the lower electrophilicity of the $Fe^{V}(O)$ due to the strongly $\sigma$-donating deprotonated amide N atoms would make them more selective toward aliphatic 3° C−H bonds and unreactive toward aromatic rings. We herein report the ability of a $NO_2$[Fe−bTAML] complex (**1**) to catalyze highly stereoselective oxidation of $sp^3$ C−H bonds in the presence of the oxidant *m*-CPBA (Scheme 1).[11] We also demonstrate that **1** oxidizes a wide range of substrates predictively, including substrates derived

**Scheme 1. Schematic Diagram for Catalytic Hydroxylation of Hydrocarbons by 1**




**Received:** November 10, 2016
**Published:** January 30, 2017





DOI: 10.1021/acs.orglett.6b03359
*Org. Lett.* 2017, 19, 746−749

from benzene, containing polar functional groups as well as complex natural products with low catalyst loadings (1−2 mol %). Mechanistic studies indicate $Fe^{V}(O)$−bTAML to be the active oxidant during these reactions.

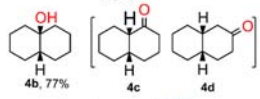
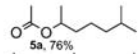
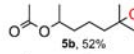
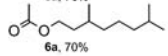
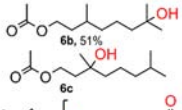
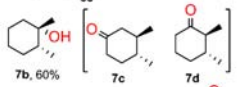
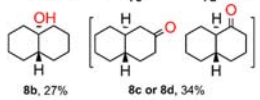
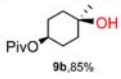
All catalytic reactions were performed under optimized conditions in which *m*-CPBA (2−5 equiv) was added using a syringe pump at a rate of 100−200 $\mu$L/h to a solution of **1** (1−2 mol %) and substrate (0.1−0.2 mmol scale) in 80% $CH_3CN$−20% $K_2HPO_4$ (aq) solvent system. The time taken for the reactions was around 2−12 h unless specifically mentioned.

Here, 3° C−H bonds are found to be preferentially oxidized in the presence of statistically more important 2° C−H bonds, with excellent mass balances and retention of configuration (RC). For *cis*-dimethylcyclohexane (**3a**), *cis*-decalin (**4a**), and pivalate (**9a**), hydroxylation predominantly occurred at 3° C−H centers (along with 98% RC) (Table 1, entries i, ii, and vii). For substrate **5a**, having an acetate group at the distal end, the selectivity toward the 3° C−H bond hydroxylation was reduced as the desired hydroxylated product **5b** yielded 57% along with 19% ketone formation (Table 1, entry iii). Electronic effects in the regioselective oxidation of 3° C−H groups (substrate **6a**) exhibited characteristic patterns of an electrophilically active species that is sensitive to inductive modulation of C−H bond reactivity by the electron-withdrawing acetate group. The yield of 3° hydroxylation was 56%, with a C7 (**6b**) to C3 (**6c**) hydroxylation ratio of 80:20 (Table 1, entry iv).

In cyclohexane derivatives, the stereochemical orientation of the 3° C−H bonds (axial or equatorial) determines the regioselective outcome of the reaction. For catalytic hydroxylation of *trans*-dimethylcyclohexane **7a**, the reaction was comparatively slower with lower GC yield (68%) of the oxidized product (Table 1, entry v) in contrast to that of **3a**. Oxidation of **7a** exhibits a significant amount of oxidation at the methylenic C−H bonds, resulting in the formation of both alcohol (**7b**, with 98% retention of configuration) and ketone (**7c** and **7d**) at a ratio of 76:24. The difference in reactivity between the *cis* (**3a** and **4a**) and *trans* isomers (**7a**, **8a**, and **9a**) can be attributed to the strain release in the transition state for the *cis* isomers (**3a** and **4a**).[4b,5a,12,13] As predicted from the analysis, for substrates **3a** and **4a**, the corresponding tertiary alcohols, **3b** and **4b**, respectively, were obtained in good yields (up to 85%), with high selectivity and high retention of configuration (98%). For oxidation of the corresponding *trans* isomers (Table 1, entries v and vi), the selectivity toward 3° C−H bonds was much lower, and the statistical advantage of the 2° C−H sites led to increased oxidation of the methylenic C−H bonds, which is especially prominent for **8a**, resulting in higher ketone formation (**8c** and **8d**) compared to **7b**. In comparison, oxidation of **7a** with the Fe−(*S,S,R*)-MCPP complex resulted in 3-fold higher yields of the ketones **7c** and **7d**.[4b,5a] The formation of ketone can also be explained by two-step oxidation of the C−H bond by a two-electron-transfer process. The second step, i.e., formation of ketone from alcohol, is ∼100 times faster than oxidation of alcohol from C−H bonds. We believe that generation of ketone in the secondary position of cyclohexane derivatives can be rationalized through this mechanism.[14]

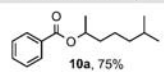
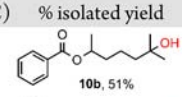
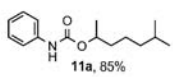
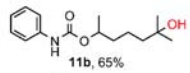
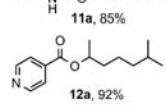
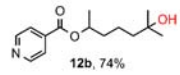
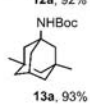
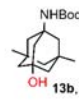
Substituted aromatic rings frequently appear in both simple and complex substrates; however, previous studies with metal-based oxidants ($Fe-N_4$ and $RuCl_3$) have known problems with deleterious arene oxidation.[4,5a,6d] With substrates **10a** and **11a**, >50% yields of their corresponding 3° alcohols, **10b** and **11b**, were observed, with <20% formation of the ketone (Table 2, entries i and ii). A bulky TBDPS group bearing substrate **15a** undergoes selective oxidation to give **15b** (Table 3, entry ii). Strikingly, substrate **12a**, which possesses an isonicotinate group, was smoothly oxidized only at the 3° C−H center to yield **12b** in 74% yield (Table 2, entry iii). The excellent mass balance observed in these reactions is indicative of exclusive arene tolerance. The ability to oxidize these sites in the presence of the basic heteroaromatic nitrogen groups without the use of Bronsted and Lewis acids to in situ protect the heteroatomic nitrogen from *N*-oxide formation is unprecedented among iron complexes.[15,16] Thus, the oxidation of substrates containing arenes (ester and carbamate) and heteroarenes addresses one of the key shortcomings of $Fe-N_4$ complexes for the chemo-

**Table 1. Regioselectivity and Diastereoselectivity for 3° C−H Bond Oxidation with 1**

| entry | substrate* % conversion (GC) | product % isolated yield | selectivity 3°:2°, RC (mol %) |
|---|---|---|---|
| (i) |  3a, 97% |  3b, 85% | 99:1, 98% |
| (ii) |  4a, 90% |  4b, 77% 4c 4d | 99:1, 98% |
| (iii) |  5a, 76% |  5b, 52% | 75:25 |
| (iv) |  6a, 70% |  6b, 51% 6c | 95:5 (6b:6c = 80:20) |
| (v) |  7a, 85% |  7b, 60% 7c 7d | 76:24, 98% |
| (vi) |  8a, 90% |  8b, 27% 8c or 8d, 34% | 38:62, 98% |
| (vii) |  9a, 91% |  9b,85% | 99:1 |

*0.2 mmol scale of **3a**, **4a**, **7a**, and **8a** was used; the rest were 0.1 mmol scale; 2 mol % catalyst was used; selectivity was determined by GC. For details and structure determination, see the SI.

**Table 2. Oxidation of 3° C−H Bonds with 1 in the Presence of Polar Functional Groups, Arenes, and N-Heterocycles**

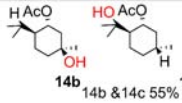
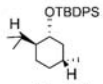
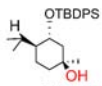
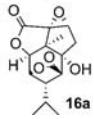
| Entry | substrate* % conversion (GC) | product % isolated yield | selectivity 3°:2° |
|---|---|---|---|
| (i) |  10a, 75% |  10b, 51% | 4:1 |
| (ii) |  11a, 85% |  11b, 65% | 6:1 |
| (iii) |  12a, 92% |  12b, 74% | 8:1 |
| (iv) |  13a, 93% |  13b, 80% | 15:1 |

*All the substrates were 0.1 mmol scale; 1 mol % catalyst; selectivity was determined by GC. For details and structure determination, see the SI.



DOI: 10.1021/acs.orglett.6b03359
*Org. Lett.* 2017, 19, 746−749

**Table 3. Use of Steric Effects To Direct 3° C−H Bond Oxidation with 1**

| entry | substrate* % conversion (GC) | product % isolated yield | selectivity 3°:2° |
|---|---|---|---|
| (i) |  **14a**, 72% |  **14b** 14b &14c 55% **14c** | 85:15 14b:14c= 3:1 |
| (ii) |  **15a**, 73% |  **15b**, 65% | >99 |
| (iii) |  **16a** | No Product, 95% RSM | |

*All of the substrateswere 0.1 mmol scale except **14a** (0.2 mmol); 2 mol % catalyst was used; selectivity was determined by GC. For details and structure determination, see the SI; RSM stands for recovered starting material.

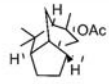
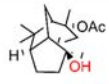
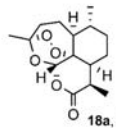
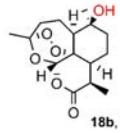
selective oxidation of C−H bonds. High product yield (80%) and mass balance were also observed for acid-sensitive NHBoc bearing substrate **13a** (Table 2, entry iv).

The role of sterics in the regioselectivity of C−H oxidation in multiple 3° C−H bonds was investigated for **14a**, **15a**, and **16a** (Table 3, entries i−iii). For menthyl acetate (**14a**), hydroxylation at both 3° C−H positions occurs, leading to the formation of products **14b** and **14c** in 55% overall yield at a ratio of 3:1 in favor of the more sterically accessible 3° C−H bond (15% ketone was also observed). This result demonstrates that the planar nature of **1** cannot efficiently distinguish between two 3° C−H bonds using sterics as was demonstrated by White for a sterically hindered Fe−$N_4$ complex that led to the formation of **14b** and **14c** in a ratio of 11:1.[4a] However, when the bulky TBDPS was used as the protecting group for the menthol −OH (substrate **15a**), **15b** was exclusively formed, demonstrating that bulky neighboring groups can be used to direct the selectivity between electronically similar 3° C−H bonds. Moreover, as previously observed by White,[4a] we were unable to oxidize the sterically inaccessible natural product picrotoxin (**16a**) (Table 3, entry iii). In this reaction, 95% of the starting material was recovered, indicating functional group tolerance of **1**.

Natural products containing unactivated methylene sites include (+)-cedryl acetate (**17a**), a derivative of cedrol. It was hydroxylated very selectively at the least sterically hindered 3° C−H bond to give **17b** (Table 4, entry i); the crystal structure is provided in the SI. The puckered structure of **17a** and release of steric strain may be responsible for its very high yield (80%), unlike using Fe−(*S*,*S*,*R*)-mcpp.[5b] Antimalarial drug (+)-artemisinin (**18a**) having five 3° C−H bonds along with the fragile endoperoxide moiety forms (+)-10$\beta$-hydroxyartemisinin (**18b**) in 38% yield (Table 4, entry ii).

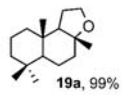
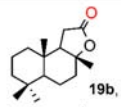
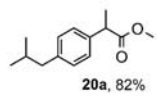
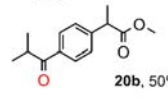
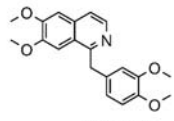
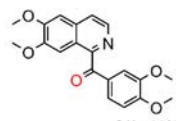
Finally, substrates bearing activated methylenic and benzylic C−H bonds were explored. Ambroxide (**19a**) was selectively oxidized among nine possible sites of oxidation to give the lactone (+)-(3*R*)-sclareolide, **19b**, in 90% yield (Table 5, entry i). Here, oxidation of the $\alpha$-ethereal C−H bond occurred exclusively without any further oxidation (even after 10 equiv of *m*-CPBA addition). This is in contrast to the oxidation by PDP complexes reported by White and Costas where formation of oxosclareolide takes place.[4b,5a,b] For ibuprofen methyl ester (**20a**) (Table 5, entry ii), the benzylic position was

**Table 4. Oxidation of 3° C−H Bonds in Complex Natural Products and Their Derivatives by 1**

| entry | substrate* % conversion | product % isolated yield |
|---|---|---|
| (i) |  **17a**, 89% |  **17b**, 80% |
| (ii) |  **18a**, 65% |  **18b**, 38% |

*For reaction with **18a**, 5 mol % of catalyst and 5 equiv of *m*-CPBA were used; time taken was 18 h; all of the substrates were 0.2 mmol scale; **17a** requires 2 mol % of catalyst.

**Table 5. Oxidation of Substrates with Activated 2° and Benzylic C−H Bonds by 1**

| entry | substrate* % conversion | product % isolated yield |
|---|---|---|
| (i) |  **19a**, 99% |  **19b**, 90% |
| (ii) |  **20a**, 82% |  **20b**, 50% |
| (iii) |  **21a**, 76% |  **21b**, 68% |

*All of the substrates were 0.1 mmol scale, 1 mol % of catalyst was used; selectivity was determined by GC. For details and structure determination, see the SI

predominantly oxidized to the ketone along with minor hydroxylation at the 3° C−H bond adjacent to the isopropyl group. Finally, papaverine (**21a**) (Table 5, entry iii), an opium alkaloid, was oxidized at the benzylic position to form the corresponding ketone **21b** in 68% yield without formation of papaverine *N*-oxide.

The very high selectivity observed indicated the involvement of a high-valent iron−oxo intermediate instead of organic radicals, as observed previously.[2d,3a,17,18] Recently, we showed the formation of an extensively characterized (HRMS, Mossbauer, EPR, resonance Raman, and EXAFS) $Fe^{V}(O)$ species at room temperature.[10] Addition of *m*-CPBA ($6 \times 10^{-5}$ M) to a solution of $5 \times 10^{-5}$ M of **1** led to the complete formation of **2**. The formation of $Fe^{V}(O)$, **2**, a violet-colored species, was well characterized by UV−vis spectroscopy (characteristic peak at 585 nm, Figure S1) and ESI-MS (mass to charge ratio: 474.0613, Figure S2). Subsequent addition of excess substrate **19a** ambroxide ($25 \times 10^{-3}$ M) led to an immediate color change, and within a few minutes, the starting $Fe^{III}$ complex **1** was completely regenerated (Figure S3-A).

To gain a better understanding on the progress of the reaction, we employed a reaction protocol in which ambroxide oxidation was initiated by the addition of *m*-CPBA ($10^{-3}$ M; 10 equiv) to a solution of **1** ($10^{-4}$ M) and substrate ($3 \times 10^{-2}$ M). After every 60 s, a further aliquot of 10 equiv of *m*-CPBA was added, which



DOI: 10.1021/acs.orglett.6b03359
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was continued until the color of the solution completely bleached out. The progress of the reaction was monitored by GC−MS (for product sclaral and sclareolide determination) and UV−vis/ESI-MS (to determine reactive intermediates). GC−MS studies at the end of this reaction showed formation of a mixture of sclaral and sclareolide (4:1) (Figure S4). The UV−vis (Figure S3-A) and GC−MS studies indicated a positive correlation between the $Fe^{III}$ recovered after each cycle and $Fe^{V}(O)$ formed initially at the start of the cycle with the gradual increase in the TON indicating that $Fe^{V}(O)$ remains the primary oxidant under aerobic conditions (Figure S3-B). In conclusion, we have reported a rationally designed iron biuret modified TAML complex (**1**) that mostly outperforms state-of-the-art Fe-based oxidation catalysts in terms of selectivity toward unactivated 3° C−H bonds, catalyst loading, product yield, and substrate scope. Specifically, this system can oxidize 3° C−H bonds in substrates bearing arene rings, N-based heterocycles, and acid-sensitive substrates, which addresses a serious drawback of Fe-based catalysts reported to date. Moreover, these reactions exhibit excellent retention of configuration while dealing with substrates like dimethylcyclohexane and decalin, irrespective of its stereochemistry (*cis* or *trans*). Apart from these, the high selectivity toward 3° C−H bonds is manifested in the selective oxidation of 3° C−H bonds in complex molecules, like natural products such as cedryl acetate and artemisinin without oxidation of methylenic C−H bonds. Thus, **1** displays great promise in the quest to develop reagents for selective oxidation of alkyl C−H bonds in complex natural products under mild conditions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03359.

General considerations and materials, characterization data of **2**, mechanistic approach for ambroxide oxidation, synthetic procedures and characterization of unreported substrates, procedure of catalytic hydroxylation reaction, characterization data and NMR spectra of products, GC and chiral GC of selected compounds, crystal structure of **17b** (ORTEP diagram), and references (PDF)

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

S.S.G. acknowledges SERB EMR/2014/0016 for funding. S.J. acknowledges UGC New Delhi for funding. We thank Miquel Costas for helpful discussions.

## ■ DEDICATION

This paper is dedicated to Professor Terrence J. Collins.

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DOI: 10.1021/acs.orglett.6b03359
*Org. Lett.* 2017, 19, 746−749