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Manganese Catalyzed Desaturation of N-acyl Amines and Ethers

Gang Li,† Patrick A. Kates, † Andrew K. Dilger,‡ Peter T. Cheng,‡ William R. Ewing,‡ and John T. Groves*†

†Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States
‡Bristol-Myers Squibb, P. O. Box 5400, Princeton, New Jersey 08543-5400, United States

homogenous catalysis, C-H activation, high-valent metal-oxo complexes, manganese porphyrins, desaturation

ABSTRACT: Enamines and enol ethers are versatile synthons for chemical synthesis. While several methods have been developed to access such molecules, prefunctionalized starting materials are usually required and direct desaturation methods remain rare. Herein, we report direct desaturation reactions of cyclic amines and cyclic ethers using a mild I(III) oxidant, PhI(OAc)₂, and an electron-deficient manganese pentafluorophenylporphyrin catalyst, Mn(TPFPP)Cl. This system displays high efficiency for α,β-desaturation of various cyclic amines and ethers. Mechanistic probes suggest that the desaturation reaction occurs via an initial α-C-H hydroxylation pathway, which serves to protect the product from over-oxidation.

Olefins occupy a key nexus in organic synthesis and process chemistry.¹ Among them, functionalized olefins such as enamines and enol ethers have attracted considerable attention. Enamines are widely represented in natural and synthetic compounds possessing useful biological and physiological properties.²⁻⁷ Enol ethers are used as cross-reaction partners in olefin metathesis,⁸ as well as substrates for access to a variety of functional polymers.⁹⁻¹⁰ In view of this level of utility, numerous methods have been developed to access such olefins. Typically, these methods require prefunctionalized starting materials, thus limiting their practicality.²⁻³,¹¹⁻¹⁹ Direct, catalytic dehydrogenation would be ideal for the conversion of simple aliphatic starting materials into valuable functionalized olefins, but such methods remain rare. Very recently, Gevorgyan et al. reported a palladium-catalyzed desaturation of aliphatic amines via a hydrogen atom transfer mechanism.²⁰ While efficient for a variety of substrates, the method requires N-benzoyl protecting groups, thus limiting its application due to the forcing conditions required for the removal of that protecting group. Moreover, the method has so far been limited to amines. A more general desaturation method that is applicable to both amines and ethers would be highly valuable.

Our long-standing interest in aliphatic C-H functionalization led us to examine manganese porphyrins and heteroatom rebound catalysis as an approach to amine and ether desaturation.²¹⁻²⁸ In an attempt to functionalize the α-C-H bond of a protected proline (1a) using a manganese(III) pentafluorophenyl porphyrin, Mn(TPFPP)Cl, we observed α,β-desaturation with iodosylbenzene as the oxidant (Table 1, entry 1). Although desaturations are commonly observed in aliphatic C-H bond oxidation reactions,²⁹⁻³⁰ this is usually a minor pathway and olefin oxygenation typically dominates. Thus, this unexpected observation encouraged us to explore the scope of this manganese-catalyzed, direct desaturation protocol.

We initiated this study by screening N-protecting groups using proline derivatives as model substrates. Each substrate resulted solely in desaturation products (Table 1, entries 1-5). Less electron-withdrawing protecting groups (Boc, Bz, Ac) gave better conversions, while more electron-withdrawing protecting groups (Ns, TFA) suppressed the reaction.

Table 1. Manganese-catalyzed desaturation of N-protected proline methyl esters with various oxidants.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>oxidant</th>
<th>conversion</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Boc</td>
<td>PhI(OAc)₂</td>
<td>35%</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>PhI(OAc)₂</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>3</td>
<td>Bz</td>
<td>PhI(OAc)₂</td>
<td>34%</td>
<td>32%</td>
</tr>
<tr>
<td>4</td>
<td>Ac</td>
<td>PhI(OAc)₂</td>
<td>28%</td>
<td>25%</td>
</tr>
<tr>
<td>5</td>
<td>Ns</td>
<td>PhI(OAc)₂</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>6</td>
<td>Boc</td>
<td>PhI(OAc)₂</td>
<td>&gt;95%</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>7</td>
<td>Boc</td>
<td>PhI(TFA)₂</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>8</td>
<td>Boc</td>
<td>PhI(OPiv)₂</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>9</td>
<td>Boc</td>
<td>MesI(OAc)₂</td>
<td>70%</td>
<td>67%</td>
</tr>
<tr>
<td>10</td>
<td>Boc</td>
<td>H₂O₂/AcOH</td>
<td>trace</td>
<td>trace</td>
</tr>
</tbody>
</table>
Conditions: substrate (0.1 mmol), Ph(OAc)₂ (0.2 mmol), Mn(TPFPP)Cl (0.005 mmol), MeCN (0.5 mL), 50 °C, 2 h. Conversions and yields determined by GC-MS using naphthalene as an internal standard.

Inspired by the results for proline desaturation, we further investigated the ability of Mn(TPFPP)Cl to catalyze the α,β-desaturation of other amines (Table 3).

Generally, 5- and 6-membered cyclic amines reacted efficiently, affording the desired desaturation products in moderate to excellent yields (2a-2f). Morpholine 1g was also reactive, producing the desired desaturation product 2g in good yield. It is interesting to note that when bis-N-Boc piperazine 1h was subjected to the reaction conditions, a double desaturation product 2h was observed. Similar double desaturation was observed for this substrate with palladium-catalyzed desaturation.²⁰ Notably, substrate reactivity decreased significantly with increasing ring size. Reaction of seven-membered rings (1i and 1j) resulted in moderate yields (2i and 2j), while reaction with a substrate with an eight-membered ring (1k) resulted in less than a 20% yield. A non-cyclic amine 1l was also tested, which only afforded trace desaturation product 2l. We expect that the transition state for desaturation requires a conformation wherein the incipient C=C bond is in conjugation with the amide group. Such a conformation is readily achieved in small ring substrates but would be more challenging or entropically disfavored in larger ring or acyclic substrates, leading to a lower yield of the enamide product.

Table 3. α,β-Desaturation of amines catalyzed by Mn(TPFPP)Cl.³

Considering the electronic similarities between cyclic amines and cyclic ethers, we applied this desaturation reaction to a panel of cyclic ether structures. Indeed, when tetrahydrofuran 1m was subjected to the desaturation conditions with a higher catalyst loading, the desired product 2m was observed in 55% NMR yield (eq. 3).
Similarly, the tetrahydropyran ester 1n afforded only the desaturated product 2n, which was isolated in 62% yield (eq. 4).

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Et} \\
1\text{n} & \quad \text{5% Mn(TPFP)Cl} \\
& \quad 2\text{ eq. Phl(OAc)}_2 \\
& \quad \text{MeCN, 50 °C} \\
\rightarrow & \quad \text{O} \quad \text{CO}_2\text{Et} \\
2\text{n} & \quad 62\% 
\end{align*}
\]

Owing to the fact that \(\alpha,\beta\)-unsaturated cyclic enecarbamates are versatile intermediates for the synthesis of various nitrogen-containing bioactive molecules,\(^6, 33-37\) it would be highly advantageous if the viability of the desaturation reaction was demonstrated on a larger scale. Accordingly, we then carried out a gram-scale reaction on 1a to explore reaction scalability. The reaction worked smoothly with no significant decrease in yield (Table 3, condition b for 2a).

We carried out the reaction under air-free conditions in dry solvent to gain some mechanistic insight. No conversion was observed under these conditions even after heating for 24 h. However, upon addition of 10 equiv of water, the desaturated product quickly appeared in quantitative yield (eq. 5). We attribute this water accelerating effect to slow hydrolysis of PhI(OAc)\(_2\) in wet solvent to form PhIO or PhI(OH)(OAc), which has also been observed in other metalloporphyrin-catalyzed oxidation reactions using PhI(OAc)\(_2\) as oxidant.\(^38-39\)

Examination of the reaction mixture by UV-Vis spectroscopy was also informative. The Mn(TPFP)Cl catalyst displayed a split Soret band at 359 and 470 nm and a Q band at 566 nm in acetonitrile, typical for manganese(III) porphyrin complexes. After addition of PhI(OAc)\(_2\) (10 equiv), the band at 470 nm disappeared and a new band at 418 nm was formed. At the same time, the Q band at 566 nm also faded while a new band was observed at 540 nm (Figure 1). The new peaks match previous reported values for oxo-Mn\(^{IV}\) species.\(^40-43\) Zhang et al. have reported similar spectra in a previous study on oxidation of olefins rapidly.\(^26, 44-47\) Also, PhI(OAc)\(_2\) is known to react with enamines.\(^48\) Thus, we were curious as to why the desaturated products could be isolated in such high yields. Interestingly, when a reaction mixture with the N-benzoyl substrate 1c was examined by mass spectrometry, a hydroxylated product (presumably the hemi-aminal) was observed (see Supporting Information). This result is analogous to observations by White with a non-heme iron catalyst.\(^32\) Bietti and Costas have also reported similar \(\alpha\)-hydroxylations of amines using a non-heme manganese catalyst.\(^49-52\) This unstable hemi-aminal product, or its acyloxy derivative, is presumably converted rapidly into the desired desaturated product during work-up. No hydroxylated intermediate was observed for the corresponding N-Boc protected substrate 1a, possibly due to the greater instability of the corresponding hemi-aminals. This hemi-aminal intermediate is likely converted to an \(\alpha\)-acyloxy-aminal intermediate in the presence of excess PhI(OAc)\(_2\), which could suppress further oxidation by the reactive oxo-Mn\(^{IV}\) species due to its steric hindrance and electron-deficiency. In contrast, when the desaturated product 2a was directly subjected to this Mn(TPFP)Cl/PhI(OAc)\(_2\) system, it was further oxidized and no substrate was recovered. Interestingly, when the cyclic lactam substrate 1o was subjected to these desaturation conditions, the \(\alpha\)-hydroxylated product 2o was isolated in high yield (eq. 6), which also supports the existence of a hemi-aminal intermediate in the desaturation reaction.

\[
\begin{align*}
\text{N} & \quad \text{O} \\
1\text{o} & \quad 1\% \text{ Mn(TPFP)Cl} \\
& \quad 2\text{ eq. PhI(OAc)}_2 \\
& \quad \text{MeCN, 50 °C} \\
\rightarrow & \quad \text{HO} \quad \text{N} \quad \text{O} \\
2\text{o} & \quad >95\% 
\end{align*}
\]

In the case of cyclic ether 1m, the corresponding hemiacetal is stable. When this hemiacetal was directly reacted with PhI(OAc)\(_2\) in acetonitrile (eq 7), the desaturated product was observed, indicating that hemiacetal could indeed be the intermediate of the desaturation reaction.
In accord with these results, we propose a mechanism for this manganese-catalyzed desaturation reaction (Figure 2). In the presence of oxidant, the manganese(III) porphyrin will be oxidized to an oxo-MnV species that abstracts the α-hydrogen atom from the substrate, resulting in a hydro-MnIV species and a substrate radical. Oxygen rebound of the substrate radical forms the unstable hemiaminal species, which dehydrates to yield the desired desaturated product.

Desaturation reactions of this type are commonly observed with various heme and non-heme iron oxides. It is noteworthy that assistance from the adjacent heteroatom in C-C desaturation has also been observed in a non-heme Fe/2OG system. However, a hydroxylated intermediate is not usually proposed in the mechanism. Our result suggests that a hydroxylation pathway may be taken into consideration in desaturations in biological systems.

In conclusion, we have demonstrated that an electron-deficient manganese porphyrin, Mn(TPPFP)Cl, is a highly efficient catalyst for the α,β-desaturation of various cyclic amines and cyclic ethers to afford a range of highly useful functionalized olefins. The reaction protocol is simple, and the reaction conditions are very mild and operationally simple. The homogeneous conditions and tolerance of air and moisture make this protocol amenable to automated and high-throughput procedures. We have also shown that this reaction has the potential to be applied at larger-scale. Our preliminary mechanistic studies indicate that the reaction proceeds via a C-H hydroxylation-dehydration pathway. An intermediate hemiaminal for cyclic amine substrate is resistant to further oxidation, resulting in a highly efficient desaturation. Further extensions of this reaction are currently ongoing.

**ASSOCIATED CONTENT**

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website.

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**Detailed condition optimization; experimental procedures for desaturation; and characterization data, including 1H and 13C NMR spectra (PDF)**

**AUTHOR INFORMATION**

**Corresponding Author**

*E-mail: jtgroves@princeton.edu*

**ORCID**

John T. Groves: 0000-0002-9944-5899
Gang Li: 0000-0001-6680-961X

**Notes**

The authors declare no competing financial interest.

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