Letter

Manganese Catalyzed Desaturation of N-acyl Amines and Ethers

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Manganese Catalyzed Desaturation of N-acyl Amines and Ethers

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

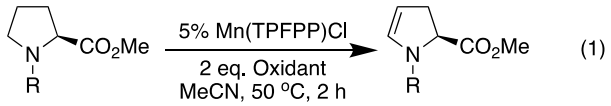
ABSTRACT: Enamines and enol ethers are versatile synthons for chemical synthesis. While several methods have been developed to access such molecules, prefunctionalized starting materials are usually required and direct desaturation methods remain rare. Herein, we report direct desaturation reactions 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.[a]



(1)

1a **2a**

entry	R	oxidant	conversion	yield
1	Boc	PhIO	35%	30%
2	TFA	PhIO	trace	trace
3	Bz	PhIO	34%	32%
4	Ac	PhIO	28%	25%
5	Ns	PhIO	trace	trace
6	Boc	$PhI(OAc)_2$	>95%	>95%
7	Boc	$PhI(TFA)_2$	trace	trace
8	Boc	$PhI(OPiv)_2$	12%	10%
9	Boc	$MesI(OAc)_2$	70%	67%
10	Boc	H_2O_2/AcOH	trace	trace

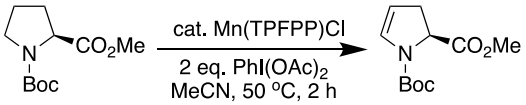
11	Boc	*m*CPBA	trace	trace
12	Cbz	$PhI(OAc)_2$	>95%	>95%

[a]Conditions: substrate (0.1 mmol), $PhI(OAc)_2$ (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. Ns = 4-nitrophenylsulfonyl, TFA = trifluoroacetate, Bz = benzoyl, Ac = acetyl, Boc = *t*Butyloxycarbonyl, Cbz = carboxybenzyl. Piv = pivaloyl, Mes = mesityl, *m*CPBA = *m*-chloroperoxybenzoic acid.

Carbamate protecting groups such as Boc or Cbz are particularly useful because they can be removed easily.[31] We then used N-Boc proline methyl ester (**1a**) as the substrate to examine the effect of oxidants in the desaturation reaction. When a milder and more soluble oxidant such as $PhI(OAc)_2$ was used, we observed quantitative conversion to the desaturated product with no side products (Table 1, entry 6, and Figure S1 in Supporting Information). Switching to a more electrophilic trifluoroacetate oxidant $PhI(O_2CCF_3)_2$ (Table 1, entry 7) severely suppressed the reaction. The bulkiness of the oxidant was also found to affect the observed reactivity. When $PhI(OPiv)_2$ was employed as the oxidant (Table 1, entry 8), the desired product was obtained in only 10% yield. A less oxidizing mesityl iodinane also resulted in a decreased yield (Table 1, entry 9). Other oxidants that have been previously used in transition-metal-catalyzed proline oxidation[32] showed no reactivity under these reaction conditions (Table 1, entries 10 and 11). Cbz-protected proline methyl ester also showed superior reactivity and a quantitative conversion was observed (Table 1, entry 12). A more electron-rich manganese catalyst, Mn(TMP)Cl, showed little catalytic activity (Table S3, entry 2, optimization reactions are presented in the Supporting Information).

We were pleased to find the desaturation reaction proceeded in good yields even with low catalyst loading (Table 2). With 1 mol% catalyst, the reaction was completed in 2 h. Decreasing the catalyst loading to 0.5% still gave a yield of 90%, although a longer reaction time was required. Further decreasing the catalyst loading to 0.1% led to a drastic decrease in yield, possibly due to catalyst-bleaching. No reaction was observed without the catalyst.

Table 2. The effect of catalyst loading on the desaturation reaction.[a]



(2)

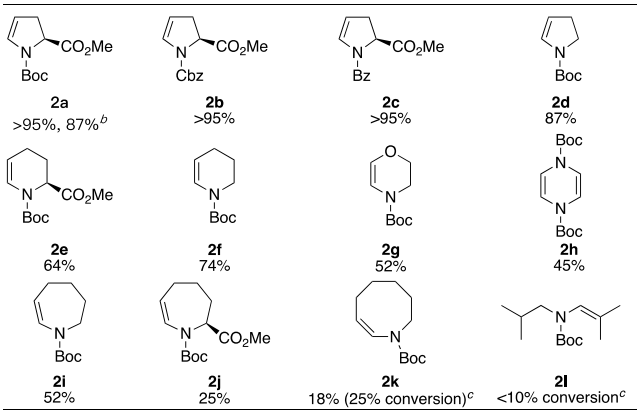
entry	catalyst loading	reaction time	conversion	yield
1	5%	2h	>95%	>95%
2	2%	2h	>95%	>95%
3	1%	2h	>95%	>95%
4	0.5%	4h	95%	90%
5	0.1%	24h	16%	12%
6	no catalyst	48h	<5%	0%

[a]Conditions: substrate (0.1 mmol), $PhI(OAc)_2$ (0.2 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).

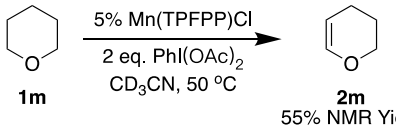
Generally, 5- and 6-membered cyclic amines reacted efficiently, affording the desired desaturation products in moderate to excellent yields (**2a**-**2f**). Morpholine **1g** was also reactive, producing the desired desaturation product **2g** in good yield. It is interesting to note that when bis-N-Boc 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.[a]



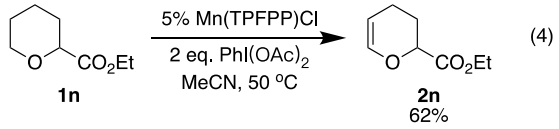
[a]Conditions: substrate (0.2 mmol), $PhI(OAc)_2$ (0.4 mmol), Mn(TPFPP)Cl (0.002 mmol), MeCN (1 mL), 50 °C, 2 h, isolated yield reported unless otherwise stated. [b]0.5 mmol scale. [c]Conversion and yield determined by GC-MS.

Considering the electronic similarities between cyclic amines and cyclic ethers, we applied this desaturation reaction to a panel of cyclic ether structures. Indeed, when tetrahydropyran **1m** was subjected to the desaturation conditions with a higher catalyst loading, the desired product **2m** was observed in 55% NMR yield (eq. 3).



(3)

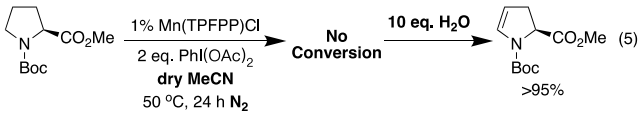
Similarly, the tetrahydropyran ester **1n** afforded only the desaturated product **2n,** which was isolated in 62% yield (eq. 4).



(4)

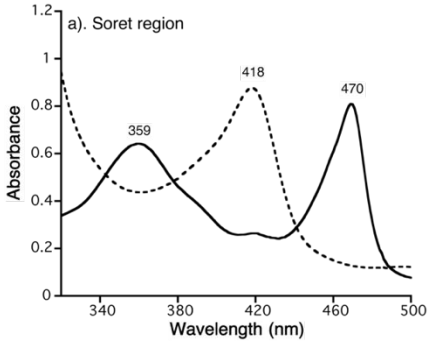
Owing to the fact that α,β-unsaturated cyclic ene-carbamates are versatile intermediates for the synthesis of various nitrogen-containing bioactive molecules,[6, 33-37] it would be highly advantageous if the viability of the desaturation reaction was demonstrated on a larger scale. Accordingly, we then 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]



(5)

Examination of the reaction mixture by UV-Vis spectroscopy was also informative. The Mn(TPFPP)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 alkenes and activated benzylic hydrocarbons.[39]



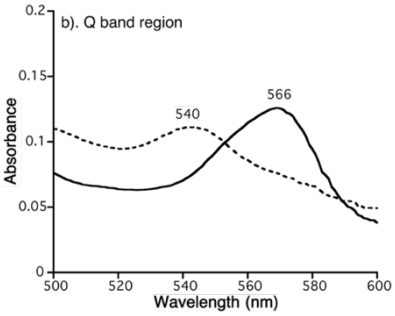
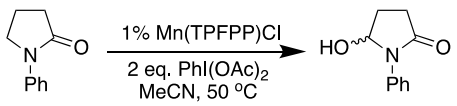


Figure 1. UV-Vis spectra observed upon addition of $PhI(OAc)_2$ to Mn(TPFPP)Cl: a) Soret region; b) Q band region. Solid line: Mn(TPFPP)Cl (10 μM) in acetonitrile; dotted line: 30 s after the addition of $PhI(OAc)_2$ (20 equiv).

The reactivity of the Mn(TPFPP)Cl/$PhI(OAc)_2$ system indicates the involvement of an oxo-Mn^{V} intermediate.[28, 39] The observed oxo-Mn^{IV} species is likely to be generated upon rapid comproportionation of oxo-Mn^{V} with a Mn^{III} species[43] and is unreactive toward these N-protected amines.

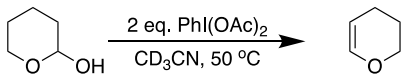
Oxo-Mn^{V} porphyrins have been shown to oxidize olefins rapidly.[26, 44-47] Also, $PhI(OAc)_2$ is known to react with enamines.[48] Thus, we were curious as to why the desaturated products could be isolated in such high yields. Interestingly, when a reaction mixture with the N-benzoyl substrate **1c** 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 α-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 acyloxy-aminal intermediate in the presence of excess PhI(OAc)2, which could suppress further oxidation by the reactive oxo-Mn^{V} species due to its steric hindrance and electron-deficiency. In contrast, when the desaturated product **2a** was directly subjected to this Mn(TPFPP)Cl/$PhI(OAc)_2$ system, it was further oxidized and no substrate was recovered. Interestingly, when the cyclic lactam substrate **1o** was subjected to this desaturation conditions, the α-hydroxylated product **2o** was isolated in high yield (eq. 6), which also supports the existence of a hemi-aminal intermediate in the desaturation reaction.



1o **2o**, >95%

(6)

In the case of cyclic ether **1m**, the corresponding hemi-acetal is stable. When this hemi-acetal was directly reacted with $PhI(OAc)_2$ in acetonitrile (eq 7), the desaturated product was observed, indicating that hemi-acetal could indeed be the intermediate of the desaturation reaction.



(7)

2m
22% NMR yield

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-Mn^{V} species that abstracts the α-hydrogen atom from the substrate, resulting in a hydro-Mn^{IV} 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[53] and non-heme iron[54] oxidases. It is noteworthy that assistance from the adjacent heteroatom in C-C desaturation has also been observed in a non-heme Fe/2OG system. [54] However, a hydroxylated intermediate is not usually proposed in the mechanism.[54] Our result suggests that a hydroxylation pathway may be taken into consideration in desaturations in biological systems.

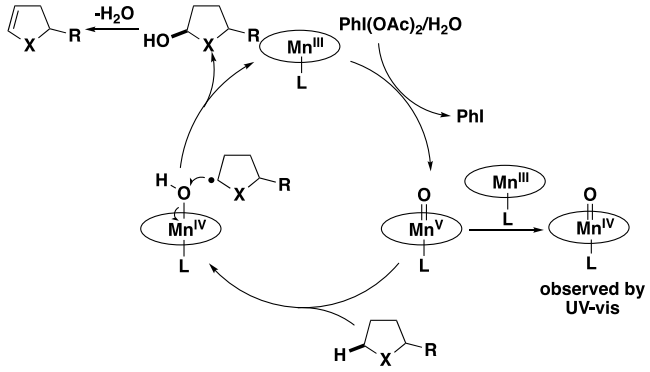


Figure 2. Proposed mechanism for manganese-catalyzed desaturation (X = N-PG or O).

In conclusion, we have demonstrated that an electron-deficient manganese porphyrin, Mn(TPFPP)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 through-put 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.

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

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Notes

The authors declare no competing financial interest.

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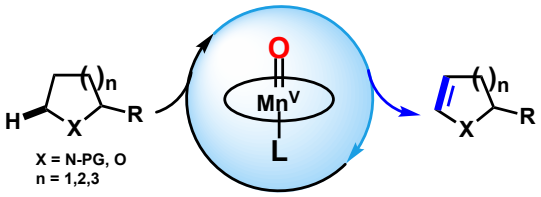
H
X
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X = N-PG, O
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