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Chemoselective, Metal-mediated Oxidation of (Dienol)iron Complexes with N-methylmorpholine N-oxide

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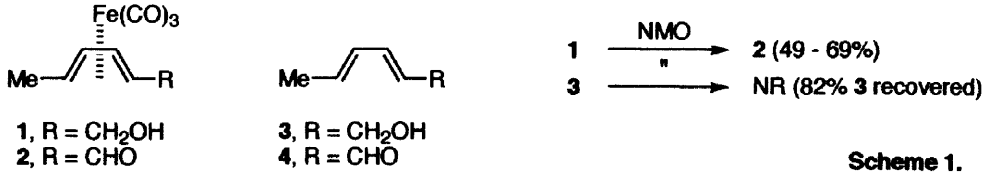
Abstract: The oxidation of (dienol)iron complexes to the corresponding (dienal)iron complexes by amine N-oxides is reported. This oxidation is selective for a hydroxyl group adjacent to the complexed diene.

Attachment of a (tricarbonyl)iron adjunct to an acyclic diene has been shown to protect the diene against reduction, oxidation, and cycloaddition reactions.[1] In addition, the steric bulk of the $Fe(CO)_3$ group serves to effect diastereoselective bond formation at unsaturated centers *adjacent* to the (diene).[1] A wide variety of natural products, including chrysanthamic acid intermediates,[2a,b] indolizidines,[2c] terpenes,[2d,e] gingerol,[2f] leukotrienes,[2g-l] oxocenes,[2m] AF toxins,[2n] polyene macrolide intermediates,[2o-q] retinoic acids,[2r] and ikarugamycin[2s] have been prepared via this methodology. Since liberation of the diene ligand is generally accomplished under oxidative conditions [$(NH_4)_2Ce(NO_2)_6$/MeOH (62-95%),[2f-n] $FeCl_3/CH_3CN$ (92%),[2d,s] Me_3NO/CH_2Cl_2/reflux (45-54%)[2b,3] or DDQ/C_6H_6 (66%)[4]] the oxidation of an alcohol functionality appended to a (diene)iron complex (eqn 1) is *notoriously variable*. Oxidation has been successfully accomplished with *i)* PDC/4Å sieves (60%),[2n] *ii)* MnO_2 (60-80%),[2l] *iii)* DMSO/$(COCl)_2$/NEt_3 (67-71%),[2m] *iv)* SO_3-pyr (54-65%),[2p] *v)* nPrMgBr/1,1'-(azodicarbonyl)dipiperidine (78-89%),[2k,o,p] and *vi)* Ag_2CO_3 (56%).[5] In the context of synthetic studies on streptenol D, we seredipitously encountered the use of amine N-oxides for the *chemoselective*, *metal-mediated*, oxidation of alcohols *adjacent* to a (diene)iron group.[6]

(1)

The reaction of (2,4-hexadien-1-ol)$Fe(CO)_3$ (**1**)[7] with N-methyl morpholine N-oxide (NMO), in a variety of solvents, gave an easily separable mixture of (2,4-hexadienal)$Fe(CO)_3$ (**2**) and recovered starting material (Scheme 1 and Table 1, entries 1-5). The standard (optimum) conditions utilize 1 equivalent NMO, ether and 4Å sieves. Attempts to force the reaction to completion with 2.1 equivalents of NMO (Table 1, entry 6) resulted in lower yields of **2**, presumably due to competitive decomplexation. Treatment of 2,4-hexadien-1-ol (**3**) under these same reaction conditions gave no evidence for a reaction and 82% starting material was recovered (Scheme 1). Treatment of a mixture of **1** and **3** (1 : 2.5) with NMO proceeded only via oxidation of **1** to give **2** (53% yield based on **1**) with no evidence for the formation of **4**. These results indicate that oxidation under these conditions is *mediated* by complexation to $Fe(CO)_3$ and is not due to the formation of a catalytically reactive iron species (ie. *not* Gif-type oxidation[8]).



1, R = CH_2OH
2, R = CHO
3, R = CH_2OH
4, R = CHO

Scheme 1.

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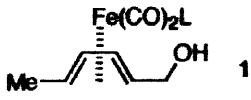
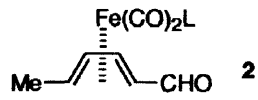
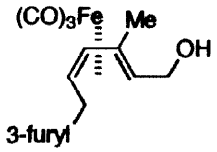
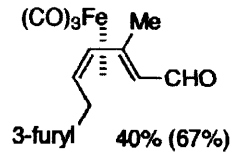
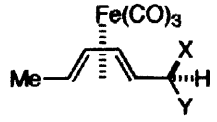
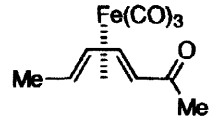
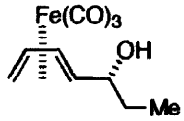
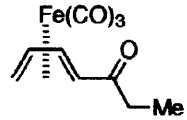
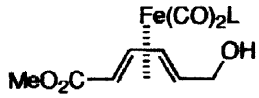
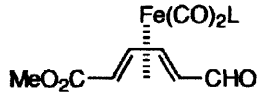
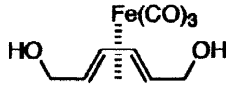
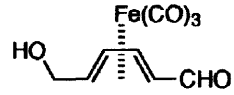
Table 1. Oxidation of (dienol)Iron Complexes with N-oxides

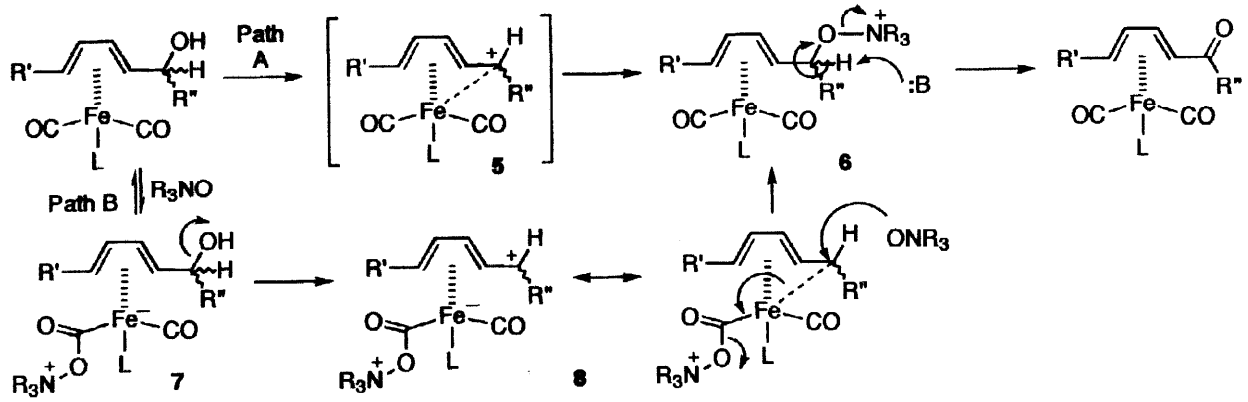
entry	(dienol)Iron complex	rxn conditions (23 °C)	oxidation product %yield (% yield based on consumed dienol)	recovered dienol
	 1		 2	
1		NMO (1.5 eq)/CH_3CN/3 h	L = CO, 49% (64%)	24%
2		NMO (1.5 eq)/C_6H_6/3 h	L = CO, 58% (70%)	17%
3		NMO (1 eq)/CH_2Cl_2/3 h	L = CO, 57% (81%)	30%
4		NMO (1 eq)/ether/3 h	L = CO, 60% (87%)	31%
5		NMO (1 eq)/ether/4A sieves/3 h	L = CO, 69% (91%)	24%
6		NMO (2.1 eq)/ether/4A sieves/3 h	L = CO, 26% (31%)	17%
7		TMANO (1 eq)/ether/4A sieves/3 h	L = CO, 45% (86%)	48%
8		NMO (1 eq)/ether/4A sieves/3 h	L = PPh_3, 70% (97%)	28%
9		NMO (1 eq)/ether/4A sieves/3 h	 40% (67%)	40%
				
10	X = OH, Y = Me	NMO (1 eq)/ether/4A sieves/3 h	52% (95%)	45%
11	X = Me, Y = OH	NMO (1 eq)/ether/4A sieves/3 h	70%	0%
12		NMO (1 eq)/ether/4A sieves/3 h	 46% (85%)	46%
				
13		NMO (1 eq)/ether/4A sieves/3 h	L = CO, 5% (16%)	70%
14		NMO (1 eq)/ether/4A sieves/3 h	L = PPh_3, 45% (80%)	45%
15		NMO (1 eq)/ether/CH_2Cl_2 4A sieves/3 h	 45% (63%) 11% dialdehyde	29%

Trimethylamine N-oxide (TMANO) may be used in place of NMO (entry 7), however no oxidation was observed when pyridine N-oxide was used. Treatment of (hexadienol)$Fe(CO)_2PPh_3$[9] with NMO gave the corresponding aldehyde complex (entry 8). The oxidation is tolerant of Z-oriented substituents (entry 9) while oxidation of ψ-exo or ψ-endo 2° dienol complexes under these conditions is also successful (entries 10-12).

In contrast, the presence of an electron withdrawing substituent on the diene led to diminished yields of the aldehyde, and decomplexation of the ligand became a competitive reaction (entry 13). The deactivating effect of an electron withdrawing substituent could be reversed by the coordination to $Fe(CO)_2PPh_3$ (entry 14). Oxidation of (2,4-

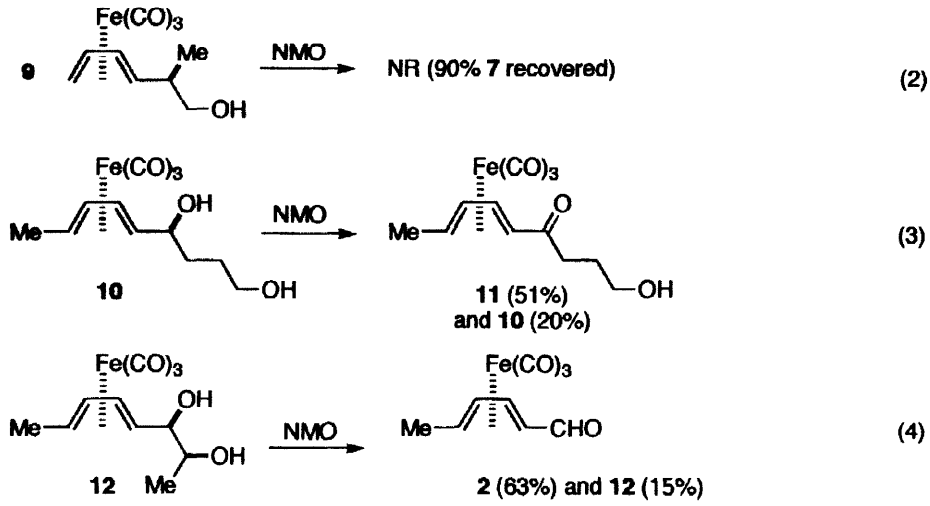
hexadien-1,6-diol)Fe(CO)$_3$[10] with one equivalent of NMO gave predominantly (6-hydroxy-2,4-hexadienal)Fe(CO)$_3$ along with (2,4-hexadiendial)Fe(CO)$_3$ (entry 15), thus indicating that oxidation of the diol to hydroxydienal occurs faster than oxidation of the resultant hydroxydienal to diendial.

We propose the following mechanism(s) to account for these results (Scheme 2). Ionization of a hydroxyl group *adjacent* to the complexed diene (Path A) results in the intermediacy of a *transoid* pentadienyl cation **5**. Addition of the amine oxide generates species **6**, which undergoes elimination of the amine. An alternative mechanism involves the zwitterionic species **7**, generated in equilibrium with the starting dienol complex via nucleophilic attack of the amine oxide on a carbon monoxide ligand (Path B). Notably, this is believed to be the first step in amine oxide mediated decarbonylation of metal carbonyls.[11] Subsequent ionization of the hydroxyl group in **7**, in the rate determining step, leads to the *transoid* pentadienyl cation **8**. Attack by a second molecule of amine oxide, and elimination of the amine and amine oxide leads to the dienal product. Consistent with either mechanism, the presence of an electron withdrawing group on the dienol ligand should destabilize the pentadienyl cation, while the presence of good σ-donor ligands on iron should stablize the pentadienyl cation intermediate.

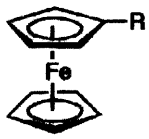


Scheme 2. Proposed mechanism(s) for Fe(CO)$_2$L mediated oxidation of dienols with amine oxides

In support of the former mechanism (Path A), it should be noted that oxidation is chemoselective for hydroxyl groups adjacent to the coordinated diene. Thus (2-methyl-3,5-hexadien-1-ol)Fe(CO)$_3$ (**9**)[1q] was recovered (90%) unreacted after treatment under the standard reaction conditions (eqn 2). Oxidation of (5,7-nonadien-1,4-diol)Fe(CO)$_3$ (**10**)[12] gave the corresponding ketone (**11**) and recovered starting material (eqn 3). Finally, oxidation of the 1,2-diol complex **12** afforded the aldehyde **2** (eqn 4); glycol cleavage proceeds due to the greater acidity of the ancillary hydroxyl proton than the methine proton.

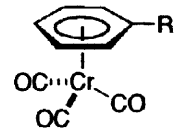


These reaction conditions are relatively specific for *iron complexed dienols*. Thus treatment of ferrocenyl methanol **13** under the standard reaction conditions gave mostly recovered starting alcohol (84%) with only minor amounts of ferrocenylcarboxaldehyde **14** (2%) and bis-ferrocenylmethyl ether (4%). Attempted oxidation of **15** gave only recovered starting material (98%). In addition, treatment of **17** under the standard reaction conditions gave only minor amounts of (benzaldehyde)$Cr(CO)_3$ **18**, (6%) along with starting material (82%) and decomplexed arene ligand.



13, R = CH_2OH $\xrightarrow{NMO}$ **14**, R = CHO (2%) and 84% **12**

15, R = CHMeOH $\xrightarrow{NMO}$ **16**, R = COMe (0%) and 98% **15**



17, R = CH_2OH $\xrightarrow{NMO}$ **18**, R = CHO (6%) and 82% **17**

In summary, we report the unprecedented, chemoselective oxidation of dienol-iron complexes with N-oxides to the corresponding dienal-iron complexes.

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(12) Complex **8** was prepared by $NaBH_4$ reduction of the lactol of (4-hydroxy-5,7-nonadienal)$Fe(CO)_3$.[13]

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