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A new method for the selective oxidation of allylic and benzylic alcohols

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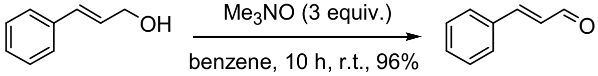
Abstract—A new method is described for the selective oxidation of allylic or benzylic alcohols, in the presence of saturated alcohols, using trimethylamine-*N*-oxide in the presence of an iron carbonyl.

The oxidation of alcohols to the corresponding carbonyls is one of the most fundamental reactions in organic synthesis.[1] The selective oxidation of allylic and benzylic alcohols is an important transformation because of the complexities in natural product structures, and many methods have been developed to accomplish this particular reaction.[2] Among them, manganese dioxide has been most widely used for the selective oxidation of allylic and benzylic alcohols in natural product synthesis.[3] Although the various methods have some synthetic advantages individually, they still suffer from one or more drawbacks, such as low yield, harsh or delicate reaction conditions, the need for large excess of oxidant, and side reactions. Therefore, it is still important to develop a selective, mild, and efficient method with easy handling.

Here, we report an efficient and practical method for the oxidation of allylic and benzylic alcohols under mild conditions using Me_3NO in the presence of CHDFe-$(CO)_3$.[4] Various conditions using different oxidants, and iron complexes were examined to optimize the reaction using cinnamyl alcohol as the substrate (Eq. 1, CHD = 1,3-cyclohexadiene).



(1)

Both the iron complex and the oxidant are essential in this transformation, and no oxidation was observed in the absence of either. Longer reaction time with less iron complex afforded lower conversion rates. And of course, the oxidation could be completed in 5 h with a larger amount of the iron complex (0.4 equiv) and Me_3NO (4 equiv). While the use of *t*-BuOOH instead of Me_3NO generated the desired product in 34% conversion in acetone, all starting material was recovered when pyridine-*N*-oxide was used as the oxidant. Another iron carbonyl complex, $Fe(CO)_4PPh_3$,[5] showed similar catalytic activity with various alcohols for this transformation. However, the use of $Fe(CO)_4PPh_3$ with Me_3NO resulted in slightly lower conversion, and caused partial double bond isomerization (10–25%) during the oxidation of geraniol and nerol. While the oxidation can be performed in a variety of solvents such as acetone or toluene, the reaction in acetonitrile, THF, or methylene chloride gave poor yields.

The oxidation of various alcohols was carried out under the optimized conditions, and the results are shown in Table 1. Primary and secondary allylic alcohols were converted to the corresponding aldehydes and ketones in good yields. No significant side reactions, such as an overoxidation to carboxylic acid or double bond isomerization were observed. In the study of substituent effects on the various *p*-substituted benzyl alcohols, *p*-chlorobenzyl alcohol gave the corresponding aldehyde with slightly better yield compared to *p*-methyl and *p*-methoxybenzyl alcohols (entries 2–4).[6] The oxidation

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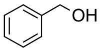
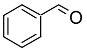
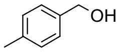
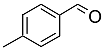
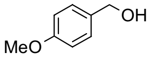
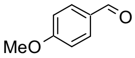
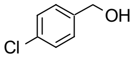
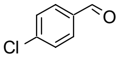
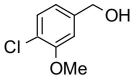
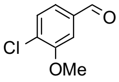
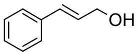
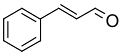
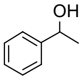
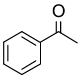
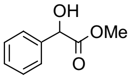
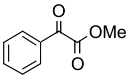
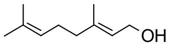
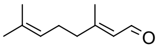
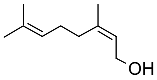
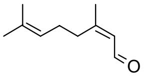
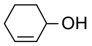
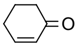
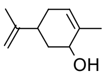
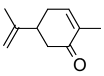
Table 1. The oxidation of various allylic and benzylic alcohols using 30% $CHDFe(CO)_3$ and 3 equiv Me_3NO

Entry	Substrate	Product	Yield[a] (%)
1			92
2			95
3			93
4			98
5			87[b]
6			93[b]
7			88
8			98
9			94[c]
10			93[c]
11			98
12			88

[a] Yield was determined by ^{1}H NMR. The only other material present is unreacted alcohol.

[b] Isolated yield and unreacted starting material was recovered (7% and 4%, respectively).

[c] Reaction time: 6 h.

of 4-chloro-3-methoxybenzyl alcohol and cinnamyl alcohol afforded 93% and 87% isolated yield together with a small amount of unreacted starting material (entries 5 and 6).[7]

The main concern during the oxidation of geraniol and nerol is double bond isomerization, since it has been described as a side reaction in various articles.[2b,g] The oxidation of geraniol and nerol should be stopped after 6 h under the given conditions, since longer reaction time resulted in partial isomerization (6–10%) with only slightly higher yield (entries 9 and 10 give isolated yields with *no* rearrangement observed).[8] This isomerization might occur via Michael–retro-Michael reaction of the aldehyde product with amine or phosphine nucleophiles that are generated during the oxidation reaction. The oxidation of a diastereomeric mixture of (−)-carveol indicates that there is no significant rate difference between axial and equatorial hydroxy groups (entry 12).[9]

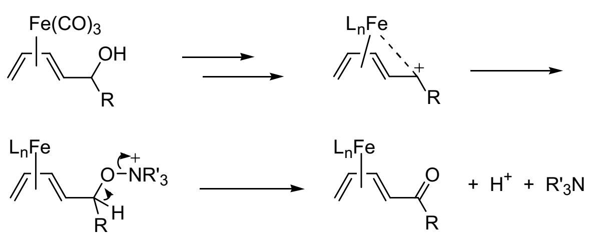
Dasgupta and Donaldson[10] have reported that iron carbonyl complexes of butadienol derivatives undergo oxidation of the pseudo-allylic alcohol on treatment with *N*-methylmorpholine *N*-oxide. A mechanism for this reaction was suggested to involve iron-assisted ionization of the alcohol, followed by addition of the *N*-oxide to the dienyl complex and then fragmentation to afford the carbonyl compound as adumbrated here in Scheme 1.

Based on this proposition, one could suggest a mechanism for the oxidation reported here that involves formation of a π-allyl–iron complex (Scheme 2). That this is unlikely is suggested by the observation that the oxidation of (−)-carveol affords (−)-carvone (Table 1, entry 12) with no loss of optical purity, and also by the fact that treatment of 1-methyl-2-cyclohexenol with our reagent gave no oxidation product, and unreacted starting material was recovered quantitatively. Formation of a π-allyl–iron intermediate would lead to racemic carvone from (−)-carveol, and also oxidation of 1-methyl-2-cyclohexenol to 3-methyl cyclohexenone. At this point in time, we do not know the mechanism for this oxidation.

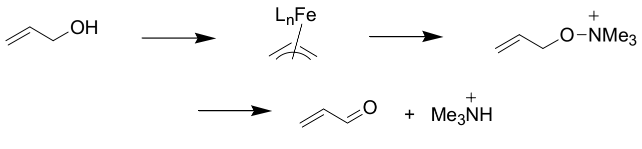
Recently, we reported the synthesis of oxazolidines using the same oxidizing system, 20% $CHDFe(CO)_3$ and 6 equiv Me_3NO.[11] In fact, Me_3NO is a common reagent for the demetalation of iron carbonyl complexes,[12] however the mechanism for this process is still uncertain.[13] The transformation of alkyl halides to the corresponding carbonyls using Me_3NO in $CHCl_3$ has also been reported.[14]

In order to determine the chemoselectivities of this reaction, the oxidation was carried out with a mixture of allylic (or benzylic) and saturated alcohol under the given conditions, and the results are shown in Table 2.

The oxidation is highly chemoselective, only cinnamyl and benzyl alcohol were oxidized to the corresponding aldehyde, and no trace of oxidation of the saturated alcohol was observed. And it appears that the presence of saturated alcohol somewhat retards the oxidation of allylic and benzylic alcohols, presumably by competitive

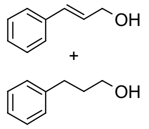
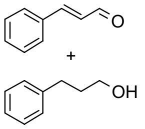
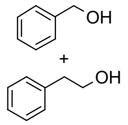
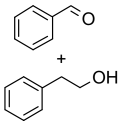


Scheme 1.



Scheme 2.

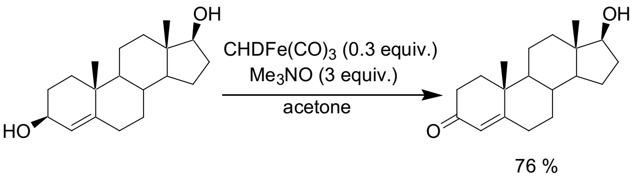
Table 2. The chemoselective oxidation of allylic and benzylic alcohols

Entry	Substrates	Product(s)	Selectivity[a]
1			82% versus 0%
2			75% versus 0%

[a] Selectivity was determined by ^{1}H NMR.

coordination of the hydroxy group to an iron catalyst intermediate (conversions are lower for the same reaction time compared with Table 1).

Androst-4-ene-3,17-diol is a useful substrate to test the chemoselectivity, because it contains both allylic and saturated alcohol moieties in the same molecule. This compound was oxidized selectively under the given conditions to afford testosterone in 76% yield after 10 h (Eq. 2).[15] Unreacted starting material was also recovered (20%), but extended reaction time did not improve the conversion.



(2)

In conclusion, we have discovered a novel and efficient method for the selective oxidation of allylic and benzylic alcohols under mild conditions, which offers an alternative to the use of MnO_2. Further studies, including catalyst development, optimization of the reaction conditions, and mechanistic experiments are in progress.

General procedure for the oxidation of allylic and benzylic alcohols: A solution of allylic alcohol (1.0 mmol), $CHDFe(CO)_3$ (0.3 mmol), and Me_3NO (3.0 mmol) in 5 mL benzene was stirred for 10 h at room temperature. Then, the reaction mixture was filtered through silica gel and evaporated under reduced pressure to afford the corresponding carbonyls. No additional purification is necessary in most cases.

Acknowledgement

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6. The oxidation using $Fe(CO)_4PPh_3$ with Me_3NO showed moderate substituent effects, and *p*-chlorobenzyl alcohol gave better conversion (*p*-Cl; 95%, *p*-H; 92%, *p*-MeO; 81%, *p*-CH_3; 71%).
7. The oxidation of these substrates using PCC in 5 mmol scale gave 88% and 75% isolated yield with no unreacted starting material.
8. The oxidation of nerol using PCC (3 equiv) at room temperature furnished 87% yield with 27% isomerization.
9. A rate difference between axial and equatorial alcohols during the oxidation of allylic alcohols has been reported: (a) Ishihara, K.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1997**, *62*, 5664–5665; (b) Fales, H. M.; Wildman, W. C. *J. Org. Chem.* **1961**, *26*, 881–886.
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15. The same transformation using other oxidants is described in Refs. 2a and 3a.