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Conversion of α,β-unsaturated ketones into α-hydroxy ketones using an Mn^{III} catalyst, phenylsilane and dioxygen: acceleration of conjugate hydride reduction by dioxygen

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Abstract

Treatment of a variety of α,β-unsaturated ketones with $Mn(dpm)_3$ (3 mol%)/$PhSiH_3$ (1.3 equiv.)/isopropyl alcohol/O_2, followed by reductive work-up with $P(OEt)_3$ resulted in the formation of α-hydroxyketones.

Keywords: α-hydroxyketone; manganese(III); phenylsilane; dioxygen.

Recently, we required a reaction that was capable of converting an α,β-unsaturated ester into an α-hydroxy ester, preferably in a single step.[1] In 1990 Isayama and Mukaiyama et al. reported a single step method for accomplishing the above.[2] They treated a number of simple α,β-unsaturated esters with a catalytic amount of bis(dipivaloylmethanato) manganese(II) [abbreviated to $Mn(dpm)_2$]/$PhSiH_3$/O_2 in isopropyl alcohol at 0°C, and obtained (after work-up with aqueous $Na_2S_2O_3$) the saturated α-hydroxyester in excellent yield. In this letter we report applications of this reaction to a number of α,β-unsaturated ketones, and show that the so-called manganese(II) catalyst is in fact a manganese(III) adduct. Furthermore, we have found that the hydridic character of the putative reagent $HMn(dpm)_2$ is substantially increased in the presence of dioxygen and produces a new hydridic reagent that is capable of reducing β,β-disubstituted enones.

The synthesis of acetylacetonatomanganese(II) complexes in air is known to be somewhat ligand dependent and can give rise to the tris(acetylacetonato)manganese(III) adducts.[3] Consequently, when we prepared what is described as the $Mn(dpm)_2$ complex[4] we obtained an olive green–brown solid more reminiscent of a Mn(III) complex.[5] X-Ray quality crystals of the complex were grown in isopropyl alcohol and revealed that the structure is an octahedral complex $Mn(dpm)_3$, Fig. 1, similar to $Mn(acac)_3$.[6]

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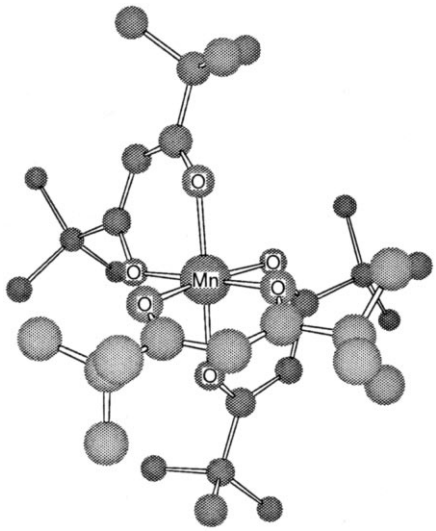


Figure 1. Chem 3D representation of $Mn(dpm)_3$ from X-ray coordinates

Treatment of the α,β-unsaturated ketones listed in Table 1 with $Mn(dpm)_3$ (3 mol%)/$PhSiH_3$/isopropyl alcohol at 0–25°C under an oxygen balloon resulted in conjugate reduction,[7] followed by oxidation at the α-position to initially produce a mixture of α-hydroperoxyketone and α-hydroxyketone. Addition of $P(OEt)_3$ at the end of the reaction reduces the intermediate α-hydroperoxide to give the α-hydroxyketone.[8]

The examples listed in Table 1 illustrate that the reaction proceeds in average (50%, entry 6) to excellent (>95%, entries 8 and 9) yields. A particularly useful transformation is the direct one-step conversion of 16-dehydroprogesterone **3** into 17α-hydroxyprogesterone **4** (85%, entry 2). This important transformation has been the subject of a number of patents[17] and papers,[18] and the method described above is superior to current methods since the non-basic conditions avoid the formation of 17-keto derivatives,[19] and the ring D-homo rearrangement.[20]

Treatment of β-ionone **9** under the standard reaction conditions surprisingly gave **10** (structure by X-ray). The bulk of the remaining mass balance was **9**, and efforts to drive the reaction to completion resulted in the formation of uncharacterized by-products. None of the 1,4-reduction product was observed.

Deuterium labeling studies in the absence of oxygen indicated that the conjugate hydride addition step is irreversible.[21] Furthermore, β,β-disubstituted enones are not reduced to their saturated derivatives in the absence of oxygen. For example, exposure of mesityl oxide **21** to $Mn(dpm)_3$/$PhSiH_3$/*i*-PrOH in the absence of oxygen did not produce any reaction, whereas the same conditions in the presence of oxygen gave **22**. Likewise **23** was inert to reduction until oxygen was introduced, and this resulted in the formation of **24** and **24a** (64%, 4:1), Scheme 1. Treatment of β-ionone **9** with $Mn(dpm)_3$/$PhSiH_3$/*i*-PrOH gave **25** (25%, large amounts of **9**), whereas, the same reaction in the presence of oxygen gave **10**.

We have also observed that the way in which the reaction flask is washed influences the product distribution. For example, treatment of **13** in a flask washed with acetone (dried) under the standard conditions gave **14** (20%) and substantial amounts of 2-nonanone (60%). Whereas, treatment of **13**, as before, but in a flask washed with Alconox® (pH 9) followed by acetone,

gave **14** (70%) and only traces of 2-nonanone (<5%). It appears that the protic surface of the flask is capable of converting **26** (Scheme 2) into the saturated derivative competitively with α-hydroperoxide **28** formation.

Table 1

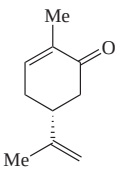
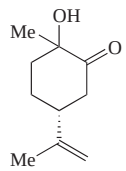
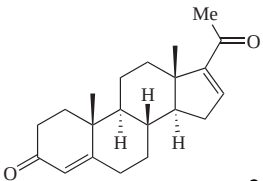
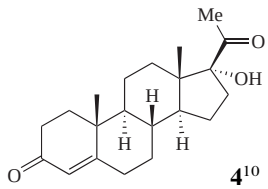
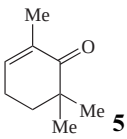
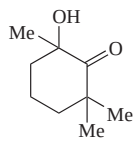
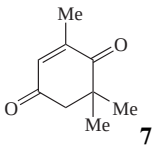
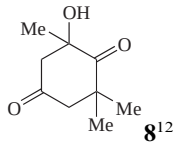
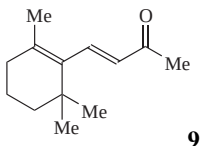
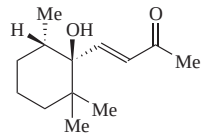
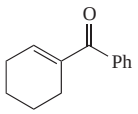
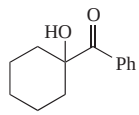
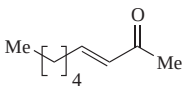
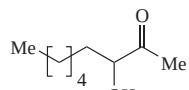
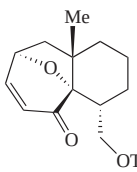
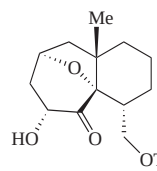
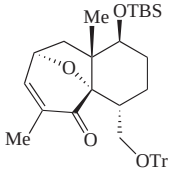
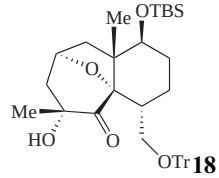
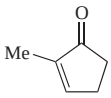
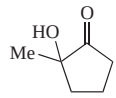
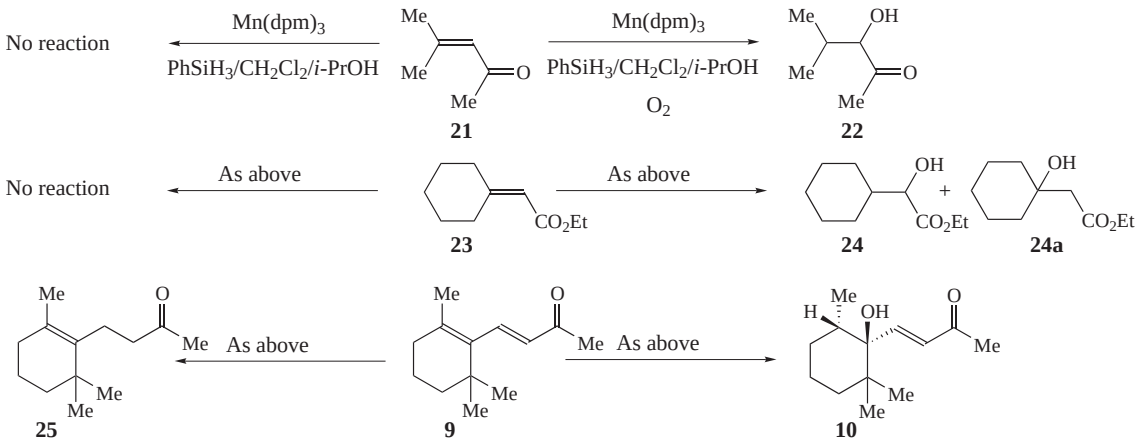
Entry	Substrate	Conditions	Product	Yield
1	 **1**	$Mn(dpm)_3$ (3 mol%), $PhSiH_3$ (2 equiv.), *i*-PrOH (0.2 M conc of **1**), O_2	 **2**[9]	78%
2	 **3**	1. $Mn(dpm)_3$ (3 mol%), $PhSiH_3$ (1.3 equiv.), *i*-PrOH/DCE, O_2. 2. $P(OEt)_3$ (1.1 equiv.)	 **4**[10]	85%
3	 **5**	As above	 **6**[11]	59%
4	 **7**	As above	 **8**[12]	87%
5	 **9**	As above	 **10**[13]	51%
6	 **11**	As above	 **12**[14]	50%
7	 **13**	As above	 **14**[15]	73%
8	 **15**	1. $Mn(dpm)_3$ (3 mol%), $PhSiH_3$ (1.3 equiv.), *i*-PrOH/DCM (1:4), O_2. 2. $P(OEt)_3$ (1.1 equiv.)	 **16**	>95%

Table 1 (Continued)

Entry	Substrate	Conditions	Product	Yield
9	 **17**	As above	 **18**	<95%
10	 **19**	As above	 **20**[16]	70%

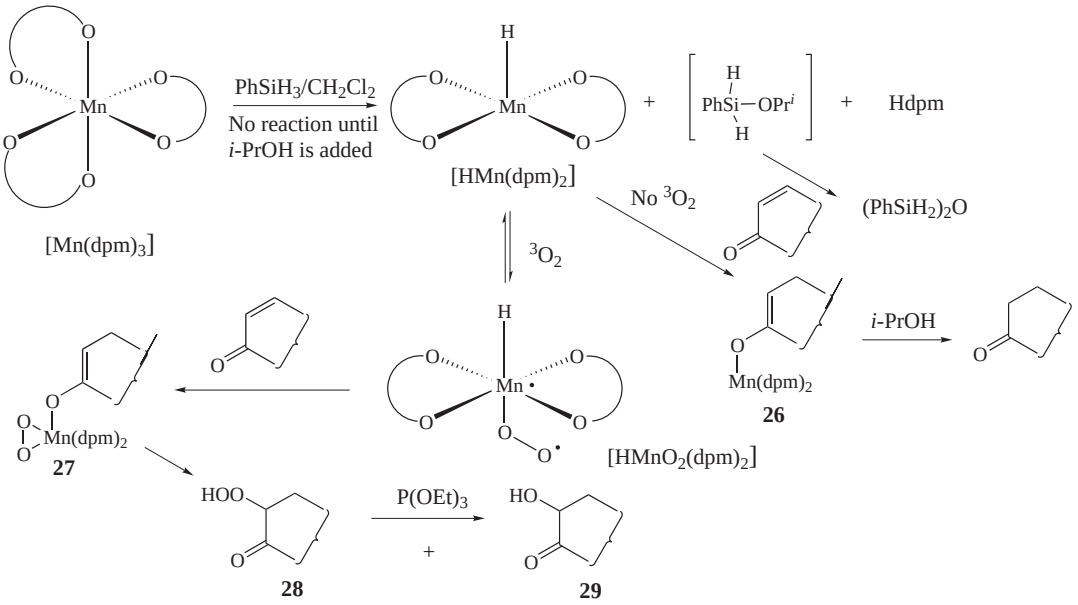


Scheme 1.

Treatment of a dark olive–green solution of $Mn(dpm)_3$ in dichloromethane with stoichiometric amounts of $PhSiH_3$ (2152 cm^{-1}) produced no change (IR), but addition of isopropyl alcohol to the solution rapidly (<1 min) produced a pale yellow solution that exhibited an IR absorption at 2168 cm^{-1}. This is consistent with the formation of $HMn(dpm)_2$.[21]

Attempts to discover the fate of phenylsilane, the hydride source, indicated that formation of phenylisopropyl(oxy)silane was inconclusive. Under the reaction conditions (and work-up) phenylisopropyl(oxy)silane would have been converted into diphenyldisiloxane,[22] which was detected (^1H NMR, authentic sample), but in relatively small amounts.

To explain these observations, especially the acceleration of conjugate reduction when oxygen is present, appears to require two distinct reducing agents. The $HMn(dpm)_2$ reagent reacts with enones to produce **26**, which is protonated to give the saturated ketone, Scheme 2. This reagent does not reduce β,β-disubstituted enones. If $HMn(dpm)_2$ (pale yellow–green) is exposed to oxygen it immediately turns dark green–brown (under vacuum the pale yellow green color



Scheme 2.

returns), and this reagent does reduce β,β-disubstituted enones (Scheme 1 and entry 5, Table 1). We suggest that the new manganese adduct formed in the presence of oxygen is $HMnO_2(dpm)_2$,[23] which reduces enones to the manganeseperoxyenolate **27**, and subsequently produces **28** and **29**.[24] Over a period of about 5 h at room temperature the peroxy-hydride $HMnO_2(dpm)_2$ loses both reducing and oxidizing capability. Efforts to characterize $HMnO_2(dpm)_2$ by X-ray crystallography are currently in progress.

It should be noted that Lippard has characterized the 'bright yellow' adduct $[Mn_4(OEt)_4(EtOH)_2(dpm)_4]$ and other similar Mn(II) adducts as alkoxide cubes with a Mn_4O_4 cubic core.[25] We have prepared $[Mn_4(OEt)_4(EtOH)_2(dpm)_4]$ according to the Lippard procedure, and when a yellow ethanol solution of the complex (cat) is treated with $PhSiH_3$ (1.3 equiv.)/O_2/4-oxoisophorone, the solution becomes olive green–brown and 4-oxoisophorone **7** (entry 4) is converted into **8** (56%).[26]

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