

# Advances in homogeneous and heterogeneous catalytic aerobic oxidation of isophorone to ketoisophorone

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## Abstract

Homogeneous and heterogeneous systems for the catalytic aerobic allylic oxidation of  $\alpha$ - and  $\beta$ -isophorone ( $\alpha$ - and  $\beta$ -IP) to ketoisophorone (KIP) have been investigated. A detailed study has been conducted on the influence of several parameters for the phosphomolybdic acid (PMA)/DMSO/potassium *tert*-butoxide combination which provides KIP in high yield (68% isolated) from  $\alpha$ -IP. Metal(bis-salicylaldehyde)s ( $M(\text{sal})_2$ ) are new homogeneous catalysts for  $\alpha$ - and  $\beta$ -IP oxidation.  $M(\text{sal})_2$  immobilized on aminopropyl-modified silica gel and metal(salen) incorporated in silica aerogels, prepared in our laboratory, have also been investigated for isophorone oxidation. The combined study suggests that the base/solvent plays a pivotal role in directing selectivity in the allylic oxidation of highly substituted cyclic olefins in homogeneous catalysis. In addition, the solvent/additive combination can also dictate the stability of heterogeneous catalysts under conditions necessary for facile dioxygen activation for allylic oxidation. Differences in the activities of the homogeneous and immobilized systems may be associated with the phenomenon of site isolation leading to different reaction pathways. © 2002 Elsevier Science B.V. All rights reserved.

**Keywords:** Isophorone; Oxidation; Homogeneous; Heterogeneous; Oxygen

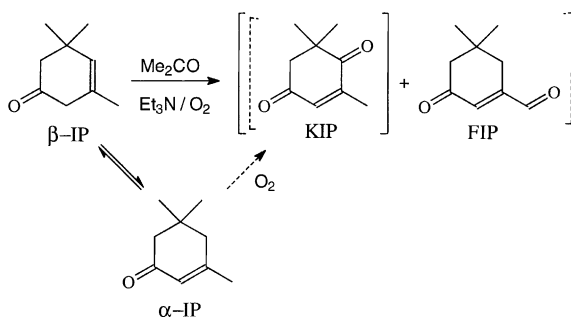
## 1. Introduction

Selective aerobic allylic oxidation of cyclic olefins, including methylcyclohexenones such as isophorone, is a chemically demanding reaction [1]. Interest in the conversion of  $\alpha$ -isophorone ( $\alpha$ -IP) to ketoisophorone (KIP) (Scheme 1) stems from its ready availability and the utility of KIP as an intermediate for the preparation of various flavoring and fragrance fine chemicals [2,3]. At present, homogeneous liquid phase oxidation of  $\beta$ -isophorone ( $\beta$ -IP) to KIP with

manganese Schiff base and tetraphenylporphyrin catalysts provides KIP in yields exceeding 90% [4,5]. In contrast, catalytic oxidation of  $\alpha$ -IP to KIP using known allylic oxidation catalysts gives KIP in poor yields only [6–11]. Given the synthetic value of KIP an effective direct catalytic oxidation of  $\alpha$ -IP to this product either homogeneous or more preferably heterogeneous, eliminating the intermediate isomerization of  $\alpha$ - to  $\beta$ -IP [12] (Scheme 1), is intrinsically very attractive. Similarly, a heterogeneous system for  $\beta$ -IP oxidation would constitute a useful development.

The environment-friendly character and associated technical advantages of heterogeneous systems for catalytic oxidation have prompted considerable efforts in

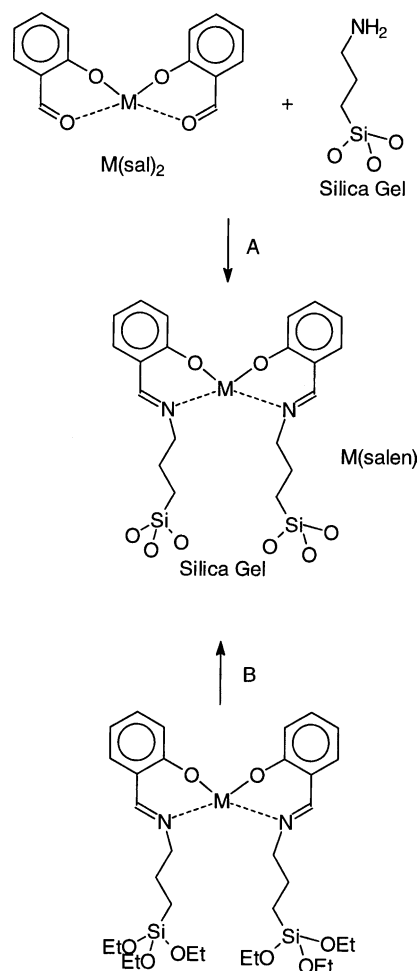
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Scheme 1. Oxidation of  $\beta$ -IP to KIP and  $\alpha$ -IP to mixtures of KIP and FIP. The isomerization of  $\beta$ - to  $\alpha$ -IP involves a 1,3-hydrogen shift.

the area of heterogenization of known homogeneous catalysts [13–15]. For example, encapsulation of  $N,N'$ -ethylenebis(salicylideneamino) complexes in porous materials, typified by zeolites, has been extensively studied in an attempt to prepare isolated catalytically active metal centers [16,17]. In this case, the catalyst is retained via pore size restrictions providing the so-called “ship-in-a-bottle” materials [18]. This approach, however, places restrictions on the support pore size which can lead to poor diffusion of reactants to and product away from the catalytically active sites. In the case of modified salen-based systems our approach has been to chemically anchor the catalyst via suitable modification of the salen ligand using two procedures shown in Scheme 2. In the first approach (A), metal(bis-salicylaldehyde) ( $M(\text{sal})_2$ ) precursors are immobilized on an aminopropyl-modified silica gel surface via Schiff base condensation [19]. Alternatively (Route B, Scheme 2), suitably modified metal(salen) precursors are immobilized via the sol-gel method in a silica matrix or immobilization on silica [20]. In the two-step acid-base catalyzed sol-gel process silyl ethoxy-modified metal(salen) precursors and tetraethoxysilane (TEOS) are hydrolyzed and co-condensed stepwise forming a silica network with bound isolated active sites. In both methods (Routes A and B, Scheme 2), the active species is covalently bound to the support thereby removing any pore size limitations [21].

Using the above strategy our group has demonstrated the utility of site isolation in hybrid based aerogels prepared via the sol-gel method for alkyl aromatic oxidation, epoxidation and DMF synthesis



Scheme 2. Immobilization of metal(salen): (A) using soluble ( $M(\text{sal})_2$ ) precursors on aminopropyl-modified silica and (B) using a soluble precursor and immobilization on silica gel or via the sol-gel method.

[20,22]. In particular for metal(salen) oxidation catalysts, the presence of isolated active sites in a silica matrix can be important in order to avoid deactivation which may occur by irreversible dimerization and/or oxidative degradation, as for the homogeneous ethylenebis(salicylideneamino) complexes [23]. The cobalt(salen) silica aerogel proved to be active for ethylbenzene oxidation. Although the catalyst exhibited low activity it did not deactivate, as was previously observed for a related immobilized chromium catalyst [24]. The combined thermal

and chemical stability of the material under catalytic conditions enabled quantitative conversion of ethylbenzene to acetophenone with good selectivity [20].

In the present contribution, we describe homogeneous and heterogeneous systems for the catalytic activation of dioxygen for the oxidation of isophorone to KIP. Firstly, we elaborate on the homogeneous phosphomolybdic acid (PMA/DMSO/KOBu<sup>t</sup>) system for  $\alpha$ -IP oxidation which we have shown provides KIP in good yield [25]. As a continuation of our search for and development of heterogeneous catalysts for fine chemicals synthesis we have investigated (M(sal)<sub>2</sub>) precursors and the silica immobilized metal(salen) catalysts for  $\alpha$ - and  $\beta$ -IP [19,20]. The results are discussed in terms of recent findings using H/D-exchange experiments to explain differences in reactivity of the two isophorone isomers and the relevant patent and scientific literature [26].

## 2. Experimental

### 2.1. Reagents

Analytical grade solvents,  $\alpha$ -,  $\beta$ -IP, KIP and all chemicals were used as supplied by Fluka. The preparation and characterization of (M(sal)<sub>2</sub>), immobilized metal(salen) catalysts on silica gel and using the

sol–gel method for silica aerogel preparations (Routes A and B, Scheme 2), have been described in detail elsewhere [19,20].

### 2.2. Catalytic oxidation of isophorone to ketoisophorone

All catalytic reactions were conducted in a 100 ml conical flask fitted with condenser and magnetic stirring, and under an oxygen atmosphere (1 bar). Typically,  $\alpha$ -IP (167 mmol) and  $\beta$ -IP (16.7 mmol) oxidations were run at 22 and 115 °C, respectively. PMA (Table 1), allylic oxidation catalysts (Table 2), (M(sal)<sub>2</sub>) (Table 3) and immobilized systems (Table 5) with isophorone, base additive/solvent (mmol/ml), catalyst (mol%) were mixed and stirred using the ratios and at the temperatures described in the respective table. Following reaction the mixture was allowed to cool under nitrogen and then analyzed by GC–MS.  $\beta$ -IP oxidation using (M(sal)<sub>2</sub>) (Table 4) and heterogenized systems (Table 5) were conducted at 22 °C. Quantitative analysis of the reaction product mixtures was carried out as described previously [25]. The multicomponent catalyst mcPMA (Entry 3, Table 1) comprised PMA/MoO<sub>3</sub>/CuSO<sub>4</sub>·5H<sub>2</sub>O in the molar ratio 0.07/0.20/0.46 mmol. In all cases, subsequent work-up of the reactions gave yields 2–6% lower than those determined by GC–MS analysis [25].

Table 1  
Allylic oxidation of  $\alpha$ -IP to KIP using PMA under various conditions<sup>a</sup>

Entry	System	Catalyst (mol%)	Temperature (°C)	Time (h)	X <sub><math>\alpha</math>-IP</sub> (%)	S <sub>KIP</sub> (%)	S <sub>FIP</sub> (%)
1	$\alpha$ -IP/DMSO/KOBu <sup>t</sup> /PMA	0.43	115	24	99.1	70.3	0
2	$\alpha$ -IP/DMSO/KOBu <sup>t</sup> /PMA	0.43	115	8	62.1	88.4	1.9
3	$\alpha$ -IP/DMSO/KOBu <sup>t</sup> /mcPMA	–	115	8	93.1	35.3	15.1
4	$\alpha$ -IP/DMSO/KOBu <sup>t</sup>	0	115	24	19.8	89.4	5.5
5	$\alpha$ -IP/DMSO	0	115	24	21.4	60.5	2.6
6	$\alpha$ -IP	0	115	24	22.2	80.3	3.4
7	$\alpha$ -IP/PMA	0.43	115	24	41.2	44.4	0
8	$\alpha$ -IP/DMSO/PMA	0.43	115	24	97.5	61.5	0
9	$\alpha$ -IP/KOBu <sup>t</sup> /PMA	0.43	115	24	59.3	50.3	1.0
10	$\alpha$ -IP/PhCN/KOBu <sup>t</sup> /PMA	0.43	115	24	52.4	30.0	1.9
11	$\alpha$ -IP/DMSO/NaOBu <sup>t</sup> /PMA	0.43	115	24	98.0	63.5	0
12	$\alpha$ -IP/DMSO/KOBu <sup>t</sup> /PMA	0.43	135	12	75.0	64.1	1.3
13	$\alpha$ -IP/DMSO/KOBu <sup>t</sup> /PMA	0.43	85	24	39.0	44.9	4.5

<sup>a</sup> Conversion (X) of  $\alpha$ -IP and selectivity (S) to KIP/FIP as determined by GC–MS analysis; mcPMA—multicomponent PMA described in experimental, DMSO (20 ml), potassium *tert*-butoxide (1 mmol).

Table 2

Various catalysts investigated for  $\alpha$ -IP oxidation with DMSO/KOBu<sup>t</sup> at 115 °C for 24 h<sup>a</sup>

Entry	System	Catalyst (mol%)	$X_{\alpha\text{-IP}}$ (%)	$S_{\text{KIP}}$ (%)	$S_{\text{FIP}}$ (%)
1	$\alpha$ -IP/DMSO/KOBu <sup>t</sup> /VO(acac) <sub>2</sub>	8.68	88.0	31.0	0.6
2	$\alpha$ -IP/DMSO/KOBu <sup>t</sup> /Na <sub>2</sub> V <sub>2</sub> O <sub>5</sub>	8.68	71.9	22.0	0.7
3	$\alpha$ -IP/DMSO/KOBu <sup>t</sup> /Cr(acac) <sub>3</sub>	8.68	17.8	45.2	2.1
4	$\alpha$ -IP/DMSO/KOBu <sup>t</sup> /TPPMnCl <sup>b</sup>	0.43	47.6	26.3	0.4

<sup>a</sup> Conversion ( $X$ ) of  $\alpha$ -IP and selectivity ( $S$ ) to KIP/FIP as determined by GC–MS analysis.<sup>b</sup> TPPMnCl: tetraphenylporphyrinmanganese chloride, DMSO (20 ml), potassium *tert*-butoxide (1 mmol).

Table 3

Results of homogeneous (M(sal)<sub>2</sub>-catalyzed (M: Cu, Mn, Co)  $\alpha$ -IP oxidation<sup>a</sup>

Entry	Time (h)	$X_{\alpha\text{-IP}}$ (%)	$S_{\text{KIP}}$ (%)	$S_{\text{FIP}}$ (%)	Additive (ml)	Temperature (°C)	Catalyst
1	20	48.5	62.3	23.5	–	115	Cu(sal) <sub>2</sub> (0.4)
2	20	23.0	4.4	–	Pyridine (5)	65	Cu(sal) <sub>2</sub> (0.4)
3	16	49.4	19.2	29.4	Pyridine (5)	115	Cu(sal) <sub>2</sub> (0.4)
4	16	87.6	29.2	10.3	DMSO (20)	115	Cu(sal) <sub>2</sub> (0.4)
5	24	98.8	8.1	–	DMSO (20)	115	Cu(sal) <sub>2</sub> (0.4)
6	20	36.0	36.4	3.94	–	115	Co(sal) <sub>2</sub> (0.4)
7	20	53.8	5.27	3.09	–	115	Mn(sal) <sub>2</sub> (0.4)

<sup>a</sup> For general conditions see experimental. Conversion ( $X$ ) of  $\alpha$ -IP and selectivity ( $S$ ) to KIP/FIP as determined by GC–MS analysis.

Table 4

A comparison of related homogeneous (M(sal)<sub>2</sub> (M: Mn, Co and Cu) catalysts for the allylic oxidation of  $\beta$ -IP to KIP<sup>a</sup>

Entry	Catalyst (mol%)	Time (h)	$X_{\beta\text{-IP}}$ (%)	$S_{\text{KIP}}$ (%)	$S_{\alpha\text{-IP}}$ (%)
1	Mn(sal) <sub>2</sub> (1.2)	19	98.8	67.2	3.8
2	Co(sal) <sub>2</sub> (1.2)	23	29.6	29.1	33.5
3	Cu(sal) <sub>2</sub> (1.2)	4	100	67.5	0.6
4	Cu(sal) <sub>2</sub> (1.2)	2	97.5	69.7	1.9
5	Cu(sal) <sub>2</sub> (1.2)	0.5	72.2	68.2	1.7
6	Cu(sal) <sub>2</sub> (1.2)	1	93.2	67.5	1.8
7	Cu(sal) <sub>2</sub> (1.2)	2	97.5	69.7	2.0
8	Cu(sal) <sub>2</sub> (1.2)	4	100.0	67.5	0.6

<sup>a</sup> For conditions see experimental; acetone (20 ml), triethylamine (6.5 mmol) and  $\beta$ -IP (16.7 mmol). Conversion of  $\alpha$ -IP ( $X$ ) and selectivity ( $S$ ) to KIP/FIP as determined by GC–MS analysis.

Table 5

Immobilized systems for  $\beta$ - and  $\alpha$ -IP oxidation to KIP for 24 h reaction

Entry	Isophorone	$X_{\text{IP}}$ (%)	$S_{\text{KIP}}$ (%)	$S_{\text{FIP}}$ (%)	Additive (ml)	Temperature (°C)	Catalyst (100 mg)
1	$\beta$ -IP	5.0	47.0	– <sup>a</sup>	Acetone (20)	22	Mn(salen)
2	$\beta$ -IP	1.9	90.0	– <sup>a</sup>	Acetone (20)	22	Cu(salen)
3	$\beta$ -IP	17.2	39.0	– <sup>a</sup>	Acetone (20)	50	Mn(salen)
4	$\beta$ -IP	10.0	30.1	– <sup>a</sup>	Neat	22	Mn(salen)
5	$\alpha$ -IP	52.2	10.9	6.0	DMSO (20)	115	Cu(salen)
6	$\alpha$ -IP	0	–	–	DMSO (20)	115	Mn(salen)
7	$\alpha$ -IP	43.1	24.6	2.5	Neat	115	Cu(salen)

<sup>a</sup>  $\beta$ -IP oxidation is not complicated by competitive allylic oxidation leading to formation of FIP, catalysts with 1.51 wt.% Mn in Mn(salen) and 1.29 wt.% Cu in Cu(salen).

### 3. Results and discussion

#### 3.1. Phosphomolybdic acid/DMSO/potassium *tert*-butoxide catalyzed $\alpha$ -isophorone oxidation

Recently, we showed that PMA efficiently catalyzed the aerobic allylic oxidation of  $\alpha$ -IP to KIP in DMSO [25]. The results of a more detailed study of the PMA/DMSO/KOBu<sup>t</sup> catalyzed oxidation are summarized in Table 1 and Fig. 1. The combination PMA/DMSO/KOBu<sup>t</sup> has several advantages over previously published methods [6–11]. Firstly, almost quantitative conversion of  $\alpha$ -IP is achieved in comparatively short reaction times (24 h versus 95 h). Secondly, under these conditions KIP is obtained in ca. 70% yield (Entry 1) as compared to 45% in the solvent-free system [6]. As expected, at low  $\alpha$ -IP conversions the selectivity to KIP is high (ca. 90%) and decreases to 70% as the reaction proceeds (Fig. 1). Small amounts of formylisophorone (FIP) (Entry 2), formed by competitive allylic oxidation at the  $\alpha$ -methyl group, were detected at short reaction times. This product appeared to further react, probably via a pinacol cross-coupling of the aldehyde, on extending the reaction time beyond 8 h (Entry 1) [27]. Ishii and co-workers have shown that for a molybdovanadophosphate catalyst regioselectivity could be reversed so that FIP was the main product [9]. In contrast to the homogeneous analog that provided KIP in very low yield (7%), molybdovanadophosphate supported on carbon gave FIP in almost 70% yield. The unusual selectivity in the latter case was

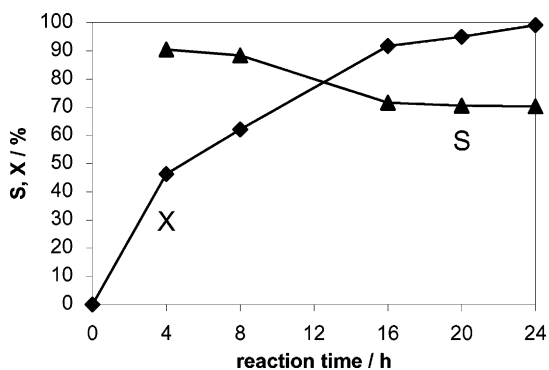


Fig. 1. Catalytic behavior of PMA (0.43 mol%) in DMSO/KOBu<sup>t</sup> under O<sub>2</sub> (1 bar) for  $\alpha$ -IP (167 mmol) conversion (X) and selectivity to KIP (S) vs. reaction time.

attributed to control exerted by the pore size of the support.

The oxidation displays a strong dependence on the choice of solvent/base (Entries 4–11, Table 1), highlighting the unique role of DMSO and KOBu<sup>t</sup>. Interestingly, in the catalyst-free autoxidation of  $\alpha$ -IP the addition of DMSO does not influence conversion but results in reduced selectivity to KIP (Entries 5, 6). In autoxidation, the introduction of a solvent is expected to have a dilution effect leading to decreased conversion, with greater selectivity to KIP [28]. The observed reduction in selectivity is compensated for by addition of KOBu<sup>t</sup> to the  $\alpha$ -IP/DMSO autoxidation (Entry 4). Notably, addition of DMSO to catalytic oxidations with  $\alpha$ -IP/PMA more than doubles conversion accompanied by a significant increase in selectivity to KIP (Entries 7, 8). An extensive study of alternative solvents showed that no reaction was observed with low boiling point (<90 °C) solvents and in benzonitrile, for example, conversion and selectivity were reduced significantly (Entry 10). In previous reports for the oxidation of  $\alpha$ -IP reaction temperatures in the range 100–150 °C with reaction times up to 6 days were typical [6–11]. PMA in combination with DMSO/KOBu<sup>t</sup> provides almost quantitative conversion of  $\alpha$ -IP at 115 °C in just 24 h. It was found that higher reaction temperatures lead only to lower selectivity to KIP while lower reaction temperatures gave poor conversion (Entries 12, 13, Table 1).

A description of the role of DMSO here simply as a polar aprotic solvent may not be complete given that DMSO is a known oxidant. Oxidation of  $\alpha$ -IP was not detected in a test reaction with vanadyl acetylacetonate as catalyst and DMSO/KOBu<sup>t</sup> in the absence of molecular oxygen. The proton solvating power of DMSO is also expected to play a significant part in the oxidation since proton abstraction is an important first step in the allylic oxidation [29]. Replacing potassium *tert*-butoxide by sodium *tert*-butoxide led to a considerable decrease in selectivity to KIP (Entry 11).

#### 3.2. Other oxidation catalysts/DMSO/potassium *tert*-butoxide for $\alpha$ -isophorone oxidation

In order to determine the range of application of the solvent/base additive, several known allylic oxidation catalysts have been investigated for the oxidation of isophorone in combination with DMSO/KOBu<sup>t</sup>

(Table 2). In all cases shown in Table 2 and also the mcPMA system (Entry 3, Table 1) the addition of DMSO gave enhanced conversion over the solvent-free oxidations [6–11]. This increase in activity was, however, accompanied by poor selectivity to KIP. Interestingly,  $\alpha$ -IP was previously described as unreactive to allylic oxidation under conditions employed for  $\beta$ -IP oxidation with tetraphenylphosphorylmanganese chloride (TPPMnCl) [5]. The same catalyst, with DMSO/KOBu<sup>t</sup>, leads to relatively high conversion of  $\alpha$ -IP although the selectivity to KIP is low (Entry 4, Table 2).

### 3.3. Metal(bis-salicylaldehyde) catalyzed $\alpha$ -IP oxidation

A summary of the homogeneous catalytic oxidation of  $\alpha$ -IP with M(sal)<sub>2</sub> (M: Cu, Co, Mn) is collected in Table 3. Of the series investigated copper(bis-salicylaldehyde) provided the best results and at reasonable  $\alpha$ -IP conversion (50% after 20 h) one can argue that high combined selectivities to KIP and FIP (85.8%) are achieved (Entry 1, Table 3). However, separation of the reactant/product mixture poses major technical problems. For copper(bis-salicylaldehyde), additives such as pyridine, KOBu<sup>t</sup>, and DMSO do not provide an improvement over Entry 1. Interestingly, the addition of pyridine to the reaction serves only to reduce selectivity to KIP (Entry 3). Again, the addition of DMSO leads to almost quantitative conversion in just 24 h, accompanied by poor selectivity to KIP (Entries 4, 5). The related manganese and cobalt(bis-salicylaldehyde)s (M(sal)<sub>2</sub>; M: Mn, Co) are relatively poor catalysts for  $\alpha$ -IP oxidation under similar conditions, exhibiting lower activity and selectivity in the oxidation of  $\alpha$ -IP (Entries 6, 7, Table 3).

### 3.4. Metal(bis-salicylaldehyde)s for $\beta$ -isophorone oxidation

The catalytic activity of copper(bis-salicylaldehyde) for the aerobic oxidation of  $\beta$ -IP is comparable to that of the homogeneous cobalt and manganese *N,N'*-ethylenebis(salicylidenaminato) catalysts described previously by Constantini et al. [4] (Table 4). Copper(bis-salicylaldehyde) provides 72% conversion in just 0.5 h and almost quantitative conversion is achieved after 2 h with good selec-

tivity to KIP (Entries 5–7). Selectivity is somewhat lower than for the manganese and cobalt *N,N'*-ethylenebis(salicylidenaminato) oxidation but might be improved by using air in place of dioxygen as oxidant and slowing down the reaction. It is noteworthy that the M(sal)<sub>2</sub> show a complete inversion of activity to that of the corresponding metal *N,N'*-ethylenebis(salicylidenaminato) catalysts [4]. Previously, only manganese and cobalt *N,N'*-ethylenebis(salicylidenaminato) were found active for  $\beta$ -IP oxidation to KIP [4]. On the other hand, manganese and cobalt(bis-salicylaldehyde)s are much less reactive than the copper analog (Entries 1–3, Table 4). Although manganese(bis-salicylaldehyde) provides almost quantitative conversion after 19 h with comparable selectivity to KIP (Entry 1) cobalt(bis-salicylaldehyde) is a relatively poor catalyst (Entry 2).

The activity of the copper(bis-salicylaldehyde) for  $\beta$ -IP oxidation depends significantly on the solvent and base additive. On reducing the base concentration, by doubling the acetone reaction volume from 20 to 40 ml,  $\beta$ -IP conversion drops from 72 to 20% accompanied by a drop of 13% in selectivity to KIP from 68.2% (0.5 h reaction). In comparison with Entry 6 in Table 4, increasing and decreasing (by  $\pm 1.4$  mmol) the amount of base gives 95.7% conversion with 63.6% selectivity, and 78.4% conversion with 66.7% selectivity (1 h reaction), respectively. Only the reduction of base amount leads to a significant change, i.e. reduction in conversion. In addition, the rate of  $\beta$ -IP oxidation depends heavily on the choice of base. For example, trihexylamine afforded 39.5% conversion (a drop of 53.5% over triethylamine) with high selectivity (81.3%) to KIP after just 1 h. On the other hand, no reaction was observed with pyridine as additive. <sup>1</sup>H and <sup>13</sup>C NMR H/D-exchange studies confirmed that under similar conditions the rate of proton abstraction from  $\beta$ -IP depends heavily in an analogous way on the choice of base [26]. Employing air as oxidant reduces the rate of reaction considerably. Extended reaction times (24 h) are required to achieve 100% conversion, with surprisingly low selectivity (44.8%) to KIP.

### 3.5. Immobilized metal(salen) for $\alpha$ - and $\beta$ -IP oxidation

As described above the copper(bis-salicylaldehyde) catalyzed oxidation of  $\beta$ -IP depends heavily on the

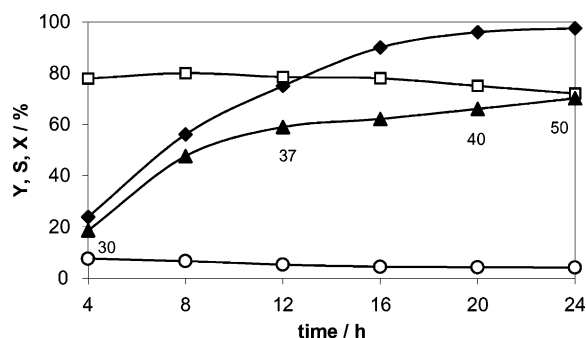


Fig. 2. Immobilized Cu(salen) (200 mg, 1.29 wt.% Cu) catalyzed oxidation of  $\beta$ -IP (16.7 mmol) in acetone (20 ml)/triethylamine (6.5 mmol) under  $O_2$  (1 bar) at 22 °C: ( $\blacktriangle$ ) KIP yield (Y), ( $\square$ ) selectivity to KIP, ( $\circ$ ) selectivity to  $\alpha$ -IP and ( $\blacklozenge$ )  $\beta$ -IP conversion. The numbers included in the figure refer to the Si/Cu ratios measured by XPS. The increase from 30 to 50 as the reaction proceeds is a clear indicator of copper leaching from the silica matrix.

choice of organic N-base. With silica supported copper(salen) (Scheme 2), and in the presence of triethylamine/acetone, oxidation of  $\beta$ -IP appeared fast in the first 8 h and gradually slowed as the conversion reached 80% (Fig. 2). Over-oxidation to a product with  $m/z$  168 is observed but selectivity to KIP is still close to 80%. XPS examination of the recovered catalyst after reaction, however, reveals that metal leaching occurred and that homogeneous oxidation is in fact being observed. Si/Cu ratios for the catalysts recovered at the given time intervals are included in Fig. 2. The elemental ratios confirm firstly that the metal leaches from the silica matrix during oxidation and secondly that the salen ligand is stable against oxidation under the reaction conditions. The copper(salen) silica aerogel catalyst displayed similar leaching trends indicating that in this case the sol-gel method does not provide a more stable immobilized catalyst.

Under conditions where the immobilized metal (salen) catalysts are stable (i.e. no metal leaching) a drastic reduction in activity for isophorone oxidation is observed with low selectivity to KIP (Table 5). At higher reaction temperature for manganese(salen) mediated  $\beta$ -IP oxidation, higher conversion with mediocre selectivity to KIP is found (Entry 3, Table 5). Following removal of the solid manganese(salen) catalyst by filtration, oxidation was not observed on stirring the reaction solution under dioxygen for a

further 24 h [30]. The inertness of dioxygen toward the enolate anion of  $\beta$ -IP is attributed to the slow rate of reaction of oxygen with carbanions [4]. Therefore, the oxidation observed here can be attributed to the immobilized catalyst. In contrast,  $\alpha$ -IP autoxidation is observed under reaction conditions (115 °C,  $O_2$ ) even in the absence of a catalyst and XPS analysis of the recovered catalyst is necessary to confirm stability against leaching.

Back-isomerization of  $\beta$ - to  $\alpha$ -IP is a considerable problem in the manganese(salen)-catalyzed oxidation of neat  $\beta$ -IP (Entry 4, Table 5). Relatively low activity with reasonable combined selectivities to KIP and  $\alpha$ -IP (30.1 and 54.2%) might be considered useful if the  $\alpha$ -IP could be recycled. Copper(salen) oxidation of neat  $\alpha$ -IP shows relatively high activity with poor selectivity to KIP (Entry 7, Table 5). In general, silica supported manganese(salen) catalysts appear more applicable for  $\beta$ -IP oxidation and copper(salen) work best for  $\alpha$ -IP oxidation. This indicates that the immobilized metal(salen)-catalyzed oxidations also proceed by somewhat different mechanisms.

Combined experimental and NMR studies confirm the importance of the tertiary N-base (triethylamine) in generating the reactive enolate intermediate which is common in both the back-isomerization and allylic oxidation of  $\beta$ -IP [26]. Unfortunately, it appears that the leaching of the metal observed with immobilized metal(salen)/triethylamine during oxidation may be associated with complexation of the metal center by triethylamine. In an attempt to obviate this problem an investigation of the immobilization of N-bases on silica for isophorone enolate generation has been pursued (Fig. 3). In methanol, and without any catalyst, the degree of back-isomerization is negligible over 14 days.  $\beta$ -IP isomerization is catalyzed by silica, most likely hydroxy groups on the surface are responsible for the activity of silica alone (Fig. 3). The higher activity of the two amine-modified silicas is attributed to the presence of the base modifier on the surface. Given the lower modifier loading of dimethylaminopropyl on silica it appears more efficient than the aminopropyl-modified silica for catalysis of this 1,3-hydrogen migration (Fig. 3). The dimethylaminopropyl group was also chosen as a base modifier since it does not interfere with the Schiff base reaction involved in the immobilization of the metal(salen) precursors [19]. Using dimethylaminopropyl-modified

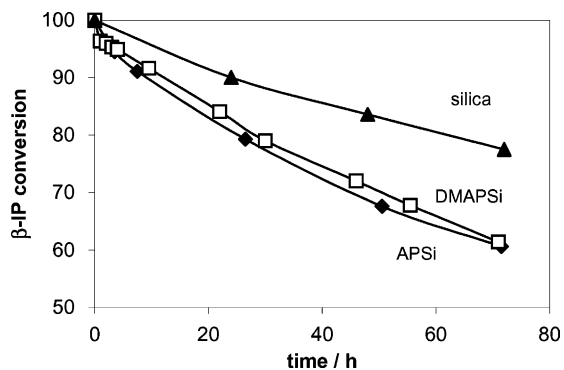


Fig. 3. Back-isomerization of  $\beta$ -IP (16.7 mmol) to  $\alpha$ -IP in methanol (20 ml) at 22 °C over various catalysts (200 mg) including: ( $\blacktriangle$ ) silica, ( $\square$ ) dimethylaminopropyl-modified silica ( $0.2 \text{ mmol g}^{-1}$ ) and ( $\blacklozenge$ ) aminopropyl-modified silica ( $1 \text{ mmol g}^{-1}$ ). In the absence of any catalyst after 2 weeks, conversion of 7.5%  $\beta$ -IP to  $\alpha$ -IP and KIP (combined selectivity of 66%) was observed.

silica as support for manganese(salen) 21.6%  $\beta$ -IP conversion with 31% selectivity to KIP is found after 24 h at 22 °C in acetone. The dimethylaminopropyl modifier appears to increase conversion significantly while selectivity is reduced (see Entry 1, Table 5 for comparison). In an alternative approach, copper(salen) supported on magnesia was investigated for heterogeneous  $\beta$ -IP oxidation in acetone. Interestingly, in this case zero conversion and no isomerization was observed even after 24 h.

### 3.6. Mechanistic considerations

In  $\beta$ - and  $\alpha$ -IP oxidation the rate-determining step is enolate formation [4]. This is confirmed by the strong dependence on the type of base found in catalysis and confirmed by NMR studies [4,26]. Although it does not rule out a free radical initiated autoxidation mechanism, the absence of any induction period (autoxidations are typically characterized by long induction periods) suggests that the oxidation of  $\beta$ -IP with copper(bis-salicylaldehyde) proceeds via a mechanism other than autoxidation [31]. Similarly, the PMA catalyzed oxidation of  $\alpha$ -IP does not display an induction period. Therefore, following proton abstraction, the reactions most likely proceed via a mechanism similar to that proposed by Constantini et al. [4].

Although not a rule, reactions of supported catalysts are generally slower than in the presence of their

homogeneous analogues. The exceptions found in the literature usually involve reactions where catalyst deactivation involved dimerization and site isolation is, therefore, invaluable [32]. The mechanism proposed by Constantini et al. for  $\beta$ -IP oxidation with manganese or cobalt  $N,N'$ -ethylenebis(salicylideneaminato) catalysts involved the participation of two metal centers in two separate one-electron processes [4]. For the silica immobilized metal(salen), with isolated active sites, it is unlikely that a comparable mechanism is possible. Therefore, for the immobilized catalysts the mechanism probably involves electron transfer between the metal (always first row transition metal ion) and the enolate anion followed by coupling of the formed radical with molecular oxygen [33]. Such a mechanism might explain the low activity and poor selectivity to KIP under conditions where the heterogeneous systems were stable.

## 4. Conclusion

$M(\text{sal})_2$ , in particular copper, are new catalysts for the oxidation of  $\alpha$ - and  $\beta$ -IP to KIP. In the latter case, these compounds activate dioxygen under very mild conditions. The combination of DMSO/ $\text{KO}^t\text{Bu}$  with PMA provides an attractive one-pot route to KIP via allylic oxidation of the more accessible  $\alpha$ -IP isomer. The aforementioned bis-salicylaldehydes compete well with literature reports for  $\beta$ -IP oxidation and the PMA system is much improved for  $\alpha$ -IP oxidation. In all cases, the generation of the isophorone enolate intermediate, which depends on the base co-catalyst, is the rate-determining step. Previously our investigations showed that the basic characteristics of the support material in the gas phase oxidation of isophorone to KIP over metal oxide catalysts were also crucial in achieving high selectivity to KIP [34].

Under the same conditions heterogenized  $M(\text{sal})_2$  and metal(salen) compounds were not stable against leaching of the metal from the solid silica matrix. An investigation of stable conditions revealed that the stable system showed very low activity and poor selectivity probably due to different reaction pathways imposed by the isolated immobilized catalytic sites. Further studies in progress involve immobilization of the PMA system for  $\alpha$ -IP oxidation. Investigations of bulky tertiary amines which catalyze proton



abstraction but cannot coordinate the metal center may provide a solution to metal leaching for the immobilized metal(salen) catalysts. Higher reaction oxygen pressure may also help obviate the low activity found for the metal(salen) systems.

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