

# Silica-supported imines as mild, efficient base catalysts

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Received (in Montpellier, France) 29th March 2000, Accepted 31st May 2000

Published on the Web 5th July 2000

Imine grafted silicas are found to be mild and effective base catalysts for Knoevenagel and Michael reactions.

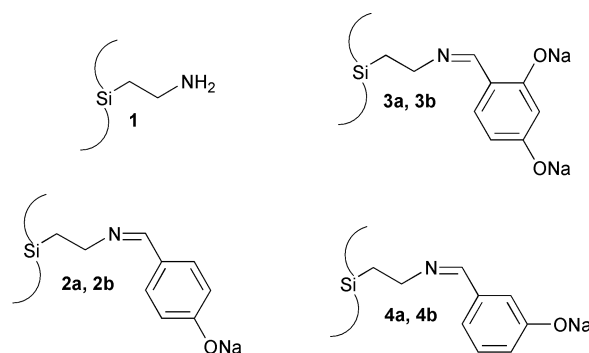
Heterogeneous base catalysis is becoming a major area of chemical research due to the wide variety of organic transformations that can be carried out under basic conditions, and the continuing drive for cleaner, more efficient processes.<sup>1,2</sup> Both amines and imines are well-known basic functions<sup>3,4</sup> and amines have been used as the active basic site in many supported base catalysts.<sup>5–7</sup> The major drawback of these catalysts is the irreversible formation of surface-bound amide groups during the Knoevenagel reaction.<sup>5</sup> In both amines and imines the lone pair is able to act as a Brønsted base by accepting a proton from a Brønsted acid. In imines the lone pair can also act as a Lewis base by donating its electrons to another compound or metal centre, aided by the electron donating ability of the C=N bond.<sup>4,8</sup> Basicity is diminished or even absent when the unshared lone pair is involved in multiple bonding in a delocalised system such as H-bonding.<sup>9–11</sup>

In this paper work has been carried out as part of a project investigating the basic character of silica-supported phenolates, which have been shown to be effective base catalysts for the Michael reaction.<sup>12</sup> The phenolate moiety is attached to a silica surface *via* an imine bond, see Scheme 1. A series of simple supported phenolate catalysts were prepared using this original method<sup>12</sup> (method a, Scheme 2). Improvements have been made to increase the surface loading and catalytic activity of these first catalysts. Characterisation of the catalysts by IR and UV methods revealed the susceptibility of the imine bond to hydrolysis, leading to a reduced loading of surface groups on these catalysts. New catalysts were prepared using a modified method of preparation and these catalysts showed an increased surface loading of both organic groups and sodium counterions. This increased loading, however, leads to lower activity in the Knoevenagel reaction than found with the original catalysts. However, after hydrolysis, it was found

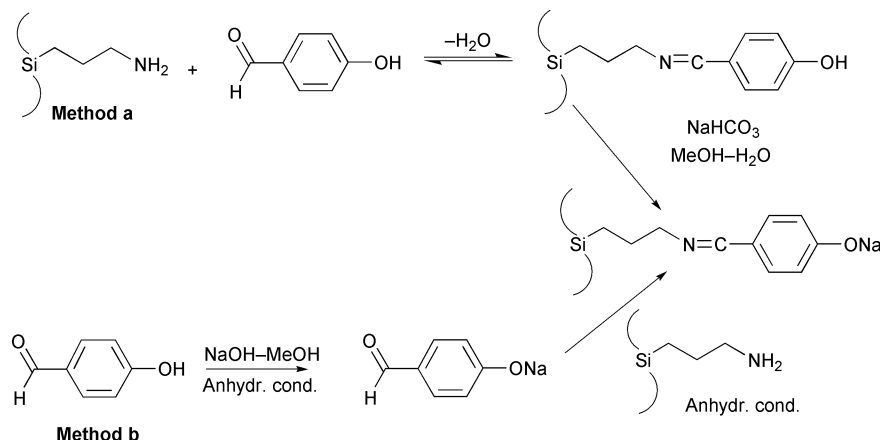
that the catalytic activity increases despite the significant reduction in catalytic sites. This implies that it is the few remaining sites that are the most catalytically active. We also present evidence that it is in fact the imine group that is the basic site of the catalyst. In this paper we report the effectiveness of the imine group to catalyse both Knoevenagel and Michael reactions. We also show that while the groups attached to the imine bond influence the catalytic activity of the catalysts, it is the imine group, and not the phenolate, which is the basic site of the catalysts.

## Experimental

All reagents were purchased from Aldrich Chemical Company, Fluorochem and Lancaster Chemicals and used as received. All solvents used were AR grade. Infrared spectroscopy was carried out using a Bruker Equinox 55 IR. Thermal



**Scheme 1** AMPS 1 and phenolate catalysts prepared *via* methods a and b.



**Scheme 2** Differences in methods of preparation of the phenolate catalysts.

analysis was carried out using a Stanton STA 625 machine and UV results were obtained using a CE 3055 3000 series UV spectrometer. Product yields were calculated by GC, using internal standards, with an HP 5890 series GC system with an HP1 column.

### Preparation of the catalysts

3-Aminopropyltrimethoxysilane (3.59 g, 20 mmol) was added to Kieselgel 100 silica (20 g) in ethanol (250 ml) and stirred at room temperature for 24 h. This was filtered and the solid washed with ethanol and diethyl ether and dried at 100 °C, to give AMPS **1**.

Following a method previously published,<sup>12</sup> a set of supported phenolate catalysts was prepared *via* method a: 4-Hydroxybenzaldehyde (1.22 g, 10 mmol) was added to AMPS (5 g) in ethanol (100 ml) and stirred at room temperature for approximately 5 min. A distinct colour change was seen from white to yellow. This mixture was filtered and the solid washed with ethanol until the washings ran colourless. In 1 : 1 water-methanol solvent mixture (50 ml : 50 ml), sodium hydrogen carbonate was dissolved (1 g), and then the solid from the previous stage was added and stirred for 1 h. This mixture was then filtered and the solid washed with water (100 ml) and methanol (100 ml) and finally dried at 100 °C to give **2a**.

Method b was developed to prepare catalysts under more anhydrous conditions: Sodium hydroxide (0.4 g, 10 mmol) was dissolved in methanol (50 ml). 4-Hydroxybenzaldehyde (1.22 g, 10 mmol) was then added to the sodium hydroxide solution and stirred at room temperature for approximately 20 min. Then AMPS (5 g) was added to the solution along with methanol (50 ml) and stirred for 24 h. This mixture was then filtered and the solid washed with methanol, until the washings ran colourless, and dried at 100 °C.

Catalysts not containing an -ONa unit were made using the aldehyde of the group to be added to the surface. Each aldehyde (10 mmol) was stirred in ethanol (100 ml) with AMPS (5 g) overnight at room temperature. Each of the catalysts was then filtered off and washed with ethanol (approx. 100 ml), and dried at 100 °C.

### Characterisation of the catalysts

The infrared spectrum of AMPS was typical, showing a broad, weak band at 1650–1560 cm<sup>-1</sup>, corresponding to OH<sub>def</sub> of bound water and silanols and NH<sub>2 def</sub>, as well as C-H<sub>str</sub> at 2800–2950 cm<sup>-1</sup>. The supported phenol and phenolate spectra showed additional bands of moderate intensity, which corresponded with imine stretches in the range of 1690–1640 cm<sup>-1</sup>.<sup>13</sup> Other bands (*e.g.*, C<sub>arom</sub>-H<sub>str</sub>) from the phenolate moiety were too weak to be assigned, due to the broad, intense O-H<sub>str</sub> of the support. Elemental analysis showed a low surface loading of phenol and phenolate groups for the catalysts prepared *via* method a. Increased surface loadings were seen for the catalysts prepared *via* method b. These analyses are given in Table 1.

### Solution stability study of catalyst 4b

For the solution stability study, 0.25 g of catalyst **4b** was stirred overnight at 20 °C in 20 ml of each solution. The solutions used were water, methanol, ethanol, dilute sodium hydrogen carbonate and dilute hydrochloric acid. Each hour a sample was taken (1 ml) and filtered. Each filtrate was then standardised to pH 12 with 0.01 M NaOH solution. A set of standards was produced to correlate and calculate the quantity of phenolate lost from each of the experiments. UV absorption at 254 nm was used to calculate the amount of phenolate present in the filtrate.

### Catalytic procedures

Knoevenagel condensations between pentan-3-one (0.86 g, 10 mmol) and ethyl cyanoacetate (1.13 g, 10 mmol) were carried out in refluxing cyclohexane (15 ml) with a Dean and Stark trap to remove water. In all cases biphenyl was employed as an internal standard (0.15 g, 1 mmol) and 0.25 g of each catalyst was used.

Michael reactions were performed at reflux temperature. Nitromethane was employed as the solvent as well as a substrate (15 ml). 2-Cyclohexen-1-one was the other reactant (0.96 g, 10 mmol), and nitrobenzene was used as an internal standard (0.1 ml, 1 mmol). In each case 0.25 g of catalyst was employed. Samples were periodically withdrawn from both reactions and analysed by GC.

## Results and discussion

### Catalysts prepared *via* method a

Elemental analysis of the catalysts prepared *via* method a (Scheme 2) showed a low surface loading of the phenolate groups with only traces of sodium; results are shown in Table 1.

AMPS has a surface loading of approximately 1 mmol g<sup>-1</sup>.<sup>6</sup> A carbon : nitrogen ratio of 3 : 1 was thus expected for AMPS, and 10 : 1 for the phenolate catalysts **2–4**. The AMPS catalyst showed the expected results. The 'extra' carbon seen in Table 1 is typical and can be attributed to non-hydrolysed methoxy groups on the silicon of the grafted unit or on the silicon dioxide surface.<sup>14</sup> Catalyst **2a** (OH form) is the 4-substituted phenol, that is before treatment with NaHCO<sub>3</sub>. Catalysts **2a**, **3a** and **4a**, however, show low C : N ratios and very small sodium loadings. This indicates that there is significantly less than 100% conversion to imine and incomplete exchange of OH to ONa. This may be due to an incomplete coupling reaction, although such reactions are typically quantitative. A more likely explanation is that the imine bonds, known to be susceptible to hydrolysis,<sup>15,16</sup> are partially cleaved from the surface. During preparation, the solution of sodium hydrogen carbonate in aqueous methanol facilitates the cleavage of the imine bond. Some of the phenolate groups are thus removed

**Table 1** Elemental analysis of the phenolate catalysts prepared *via* methods a and b

Catalyst	Loading of N/mmol g <sup>-1</sup>	Loading of C/mmol g <sup>-1</sup>	C : N ratio	Loading of Na/mmol g <sup>-1</sup>
<b>1</b>	0.85	3.16	3.17	—
<b>2a</b> (OH form)	0.81	6.86	8.50	—
<b>2a</b>	0.77	2.94	3.80	0.02
<b>3a</b>	0.80	5.86	7.30	0.07
<b>4a</b>	0.79	4.13	5.20	0.06
<b>2b</b>	0.54	5.60	10.37	0.15
<b>3b</b>	0.46	4.60	10.00	0.33
<b>4b</b>	0.68	6.93	10.19	0.30

from the surface of the catalyst and then washed away in the filtrate.

### New catalysts prepared by method b

In light of these results, method b was developed for the preparation of the catalysts under much more anhydrous conditions, Scheme 2. An alternative source of sodium ions was used, which would dissolve in a solvent other than water. Also, the sodium ions were exchanged before the imine was made, to minimise cleavage of the imine bond.

The elemental analysis results showed that higher surface loadings were achieved by using the new method of preparation. The above substituted phenolate catalysts were made following the new method with increased surface loadings. The results can be seen in Table 1.

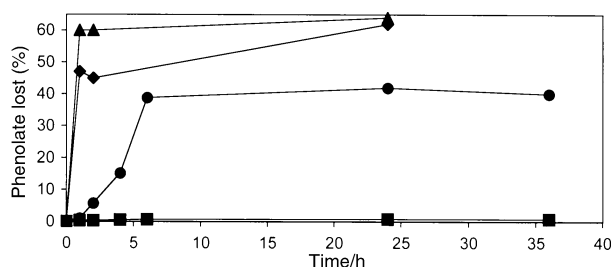
The catalysts made *via* the new method, catalysts **2b**, **3b** and **4b**, (Scheme 1), showed a high surface loading of phenol groups with a higher conversion to phenolate groups than the previous catalysts made *via* method a. The C : N ratio indicates essentially 100% conversion to imine and the sodium loadings are increased, which shows a conversion of ArOH to ArONa of 28%, 36% and 44% for **2b**, **3b** and **4b**, respectively.

IR analysis confirmed the presence of an imine band in all three catalysts, as with the previous catalysts. Thermal analysis showed a small loss in weight at about 100 °C, which corresponds with the loss of either residual solvent and/or water. There was also a small loss (*ca.* 1%) at approximately 250 °C, which could be the loss of physisorbed groups from the surface. No other losses were seen up to a maximum temperature of 625 °C.

### Solution stability study

To prove that the imine bond within the catalysts is susceptible to cleavage in aqueous solutions, and to define reaction conditions under which the catalyst would be stable, a study into catalyst stability was undertaken. Catalyst **4b** was used in all cases. Graph 1 shows the results of this study.

The results show a large loss in phenolate groups in aqueous basic and acidic solutions, but negligible losses in alcohol. The main loss in surface groups occurs very rapidly, with negligible losses afterwards. This shows that rapid cleavage of the imine bond occurs. This is therefore likely to be the reason for the low surface loading associated with method a preparation. When only 2 molar equiv. of water are employed, under the conditions used to produce the imine bond initially, only 5% of surface groups are lost. Effective deprotonation of the phenol without cleavage of the imine is thus likely to be very sensitive to the exact reaction conditions, thus use of an alcoholic base may be more successful. This also indicates that while some of the imine bonds are cleaved easily there are others that are held differently or bound more strongly to the surface and are not cleaved so readily. These groups could also be located in varying chemical environments, making cleavage easier or harder. Lack of accessibility is unlikely to be a possible reason for the stability of the remaining imine



**Graph 1** Catalyst stability when stirred in different solutions; (●) water, (■) methanol, (▲) dilute NaHCO<sub>3</sub>, (◆) dilute HCl.

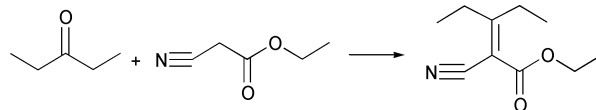
bonds, since this is not consistent with the activity of the catalysts before and after the removal of the 'loose' imines (see later). Rather, changes in the nature of the environment of the remaining groups, such as altered hydrophobicity, hydrophilicity, organophilicity and reduced extent of lateral interactions between the remaining groups are more likely to be involved.

### Knoevenagel reaction (Scheme 3)

The catalysts were compared in the Knoevenagel reaction of ethyl cyanoacetate and pentan-3-one, a reaction in which they have not previously been evaluated. As can be seen in Table 2, the activity of the phenolate imine catalysts is excellent, being significantly more active than AMPS (one of the most active base catalysts for this reaction). This demonstrates that the catalysis observed is not due to the residual amino groups. It can also be seen that the catalysts produced by method b are less active than those made using method a.

In order to investigate whether it is the few remaining sites that are the most active, catalyst **4b** was washed with water for 36 h, to take off the labile surface groups. In doing this the activity of catalyst **4b** was increased. The results can be seen in Graph 2. This was repeated for all of the catalysts produced *via* method b and the same increase in activity was seen.

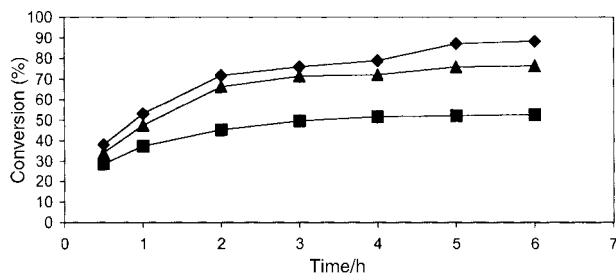
**Effect of changing or removing the phenolate cation.** The cation was changed (by reaction of phenols with KOH, LiOH and NMe<sub>4</sub>OH) to test the effect it would have on the activity of the catalyst in the Knoevenagel reaction. These catalysts (catalysts **5**, **6** and **7**, Scheme 4), showed activities similar to those of the sodium containing catalysts, showing that the cation has little effect on activity. Equivalent catalysts were also made that either contained the OH group, rather than the phenolate, or had no phenol groups and these were also used in the Knoevenagel reaction (catalysts **8** and **9**, Scheme



**Scheme 3** Knoevenagel reaction of ethyl cyanoacetate and pentan-3-one.

**Table 2** Comparison of various catalysts in the Knoevenagel reaction of ethyl cyanoacetate and pentan-3-one

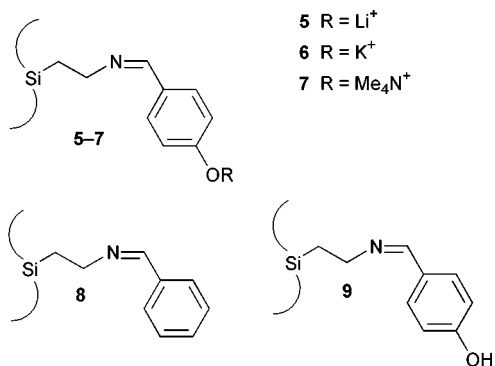
	%Yield after time/h						
	0.5	1	2	3	4	5	6
Phenolate catalysts prepared <i>via</i> methods a and b							
<b>1</b>	10.6	16.5	23.9	30.1	36.8	43.7	49.1
<b>2a</b>	38.0	53.0	71.8	75.8	78.8	87.1	88.3
<b>3a</b>	15.3	22.6	31.0	36.7	38.5	39.7	44.6
<b>4a</b>	43.1	57.5	72.6	76.5	82.8	82.0	86.8
<b>2b</b>	31.8	43.8	55.2	60.8	64.2	66.7	67.1
<b>3b</b>	5.6	7.7	10.4	11.7	13.0	14.0	14.6
<b>4b</b>	28.6	37.4	45.3	49.6	51.5	52.1	52.5
Phenolate catalysts with no or different active cations							
<b>5</b>	28.9	39.2	49.3	54.7	58.4	60.0	60.7
<b>6</b>	31.2	41.5	52.4	58.6	62.6	63.7	64.8
<b>7</b>	24.4	32.5	40.0	45.2	47.7	48.9	49.7
<b>8</b>	39.2	54.4	62.0	69.3	69.6	71.9	81.1
<b>9</b>	33.0	41.0	49.1	54.5	60.0	60.0	60.0
Imine catalysts							
<b>10</b>	6.0	9.2	13.6	16.3	17.9	19.4	23.3
<b>11</b>	27.5	50.6	69.1	69.2	76.0	75.7	—
<b>12</b>	44.0	58.1	69.8	72.7	76.7	82.8	—
<b>13</b>	16.5	23.4	29.8	31.6	32.5	33.7	34.8
<b>14</b>	38.0	53.7	67.1	72.7	74.4	79.0	80.1
<b>15</b>	67.2	69.3	81.5	88.2	92.9	98.6	99.5
<b>16</b>	37.6	49.4	70.5	74.9	80.3	86.8	86.2



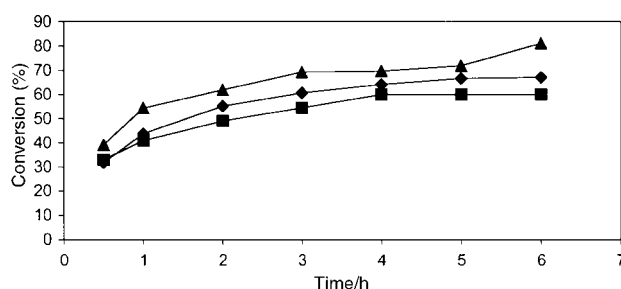
**Graph 2** Comparison of phenolate catalysts prepared *via* methods a and b and washed catalysts prepared *via* method b: (◆) **2a**, (■) **2b**, (●) **2b** washed.

4). These catalysts displayed similar behaviour to the phenolate catalysts. The results can be seen in Table 2 and Graph 3.

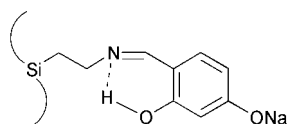
Thus it can be seen that changing the cation or removing it completely has little effect on the activity of the catalyst. It is the imine group, therefore, which is providing the basicity that catalyses the reaction. This has also been found in other supported systems.<sup>17</sup> This explains why the 2,4-substituted phenolate catalysts are lower in activity in this case. The nitrogen lone pair is delocalised within the H-bonding system and therefore, the catalyst is far less basic.<sup>4,5,11</sup> This can be seen in Scheme 5. Similar results have been obtained for the 2-substituted phenolate catalyst. Also, it is the lower loading catalysts that are more active so the few imine bonded sites that are not cleaved by hydrolysis are actually responsible for the catalytic action of the catalyst. Intermolecular H-bonding



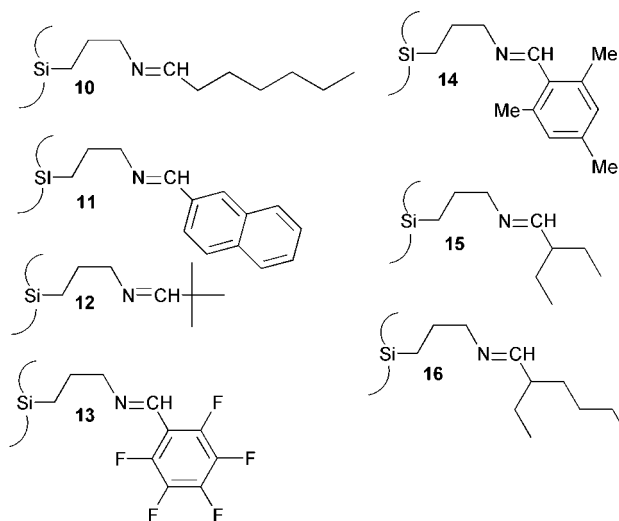
**Scheme 4** Phenolate catalysts with different active cations and with the active cations removed, compared in the Knoevenagel reaction of ethyl cyanoacetate and pentan-3-one.



**Graph 3** Comparison of phenolate catalyst, phenol catalyst and catalyst with no active cation: (◆) **2b**, (■) **8**, (●) **9**.



**Scheme 5** Intramolecular hydrogen bonding found in the 2,4-substituted phenolate catalyst.



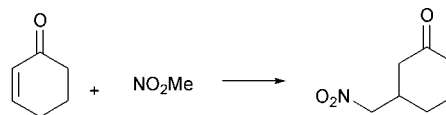
**Scheme 6** Imine catalysts with different substituent groups, compared in the Knoevenagel reaction of ethyl cyanoacetate and pentan-3-one.

through lateral interactions could explain the reduced activity of the catalysts with a higher surface loading.

**Non-phenolic catalysts.** To investigate this theory, a series of imine-containing catalysts, shown in Scheme 6, were prepared from different aldehydes. The results in Table 2 show that the different groups have an influence on the activity of the catalysts. They also show the effectiveness of the imine group as a base catalyst. While the reasons for the different activities seen in this group are not fully understood, it appears that more bulky substituents such as the *tert*-butyl group favour higher activity, a factor that may reduce SiOH–imine H-bonding interactions, making the imine more available for base catalysis.

### Michael reaction

A selection of catalysts were tried in the Michael reaction of nitromethane and 2-cyclohexen-1-one, Scheme 7, and the results can be seen in Table 3. Initially, the imine catalysts were more active than the phenolate catalysts, though after 6 h there was little difference in conversion. Heavier products were seen in all the reactions though it was only the phenolate catalysts that showed a decrease in yield. This indicates that some subtle differences do exist between the phenolate and imine catalysts in some cases. Again, the imine group appears to be the catalytic centre of the catalysts.



**Scheme 7** Michael reaction of nitromethane and 2-cyclohexen-1-one.

**Table 3** Comparison of phenolate catalysts prepared *via* methods a and b and other imine catalysts in the Michael reaction of nitromethane and 2-cyclohexen-1-one

Catalyst	%Yield after time/h						
	0.5	1	2	3	4	5	6
<b>2a</b>	27.5	36.6	48.0	52.4	57.6	52.8	50.8
<b>2b</b>	24.5	34.1	44.1	47.8	48.0	47.2	45.8
<b>12</b>	23.6	32.7	42.2	47.7	53.0	54.0	57.6
<b>14</b>	13.6	21.3	31.8	39.1	45.8	48.2	53.0
<b>16</b>	22.0	31.5	37.8	42.5	43.2	44.0	45.1

## Conclusions

A series of supported phenolate catalysts were prepared by attaching formyl phenols to aminopropyl silica. These imine-bonded catalysts outperform AMPS in catalytic activity in the Knoevenagel reaction. The stability of the imine bond was investigated. A large initial loss of surface groups is seen through hydrolysis, whereas only small losses are seen after. This abrupt change indicates that a small amount of imine groups are held in a different environment or bound more strongly to the surface. It is these strongly held groups that appear to be the most catalytically active centres of the catalyst. Changing the active cation, and even removing it, has little or no effect on the activity of the catalyst. Changing the groups attached to the imine bond has a significant effect on the reactivity of the catalyst, increasing or decreasing the basicity due to the mesomeric and inductive effects of the 'end groups'. The 2,4-substituted phenolate demonstrates that H-bonding effectively 'ties up' the nitrogen lone pair, which in turn decreases activity. Imines that are bound in a certain way and that are not susceptible to hydrolysis are the source of the catalytic activity of the catalyst.

## Acknowledgements

D.J.M. thanks the Royal Society for a University Research Fellowship, K.A.U. thanks EPSRC for a project studentship.

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