Designing the adequate base solid catalyst with Lewis or Bronsted basic sites or with acid–base pairs

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Abstract

A series of heterogeneous catalysts with Lewis and Bronsted basic sites, and acid–base bifunctional pairs has been used in order to perform organic reactions. By changing the chemical composition and activation conditions it is possible to have predominantly Lewis or Bronsted base catalysts within a large range of well defined basicities. This allows to select the most appropriate catalyst for a specific reaction. Thus, MgO, calcined hydrotalcites, rehydrated hydrotalcites and grafted quaternary organic ammonium hydroxides on MCM-41, have been used as catalysts in Knoevenagel condensation, aldolization and Michael additions. Catalysts containing mild acid–base pairs such as those existing in amorphous aluminophosphates (ALPOs) allow to achieve high selectivities with still very reasonable activities. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Knoevenagel condensation; Aldol condensation; Michael addition; MgO; Calcined hydrotalcites; Rehydrated hydrotalcite; ALPO; MCM-41 functionalized; Bronsted base catalyst; Lewis base catalysts; Acid–base bifunctional catalyst

1. Introduction

Nowadays there is an urgent need to develop green chemistry processes, where the use and generation of noxious substances can be avoided. The generation of wastes is dramatically important in the case of the synthesis of fine chemicals and pharmaceuticals, and they consist primarily of inorganic salts formed in the reaction or in subsequent neutralization steps. In this sense, heterogeneous catalysts play an important role. The replacement of liquid by solid base catalysts for the production of fine chemicals not only allow easy separation and recycle of the catalyst from the reaction mixture, but also in many cases, the possibility to prepare solid base catalysts with a different nature of active sites (Bronsted, Lewis or chiral sites), with a wide range of basic strengths, or even acid–base bifunctional catalysts. In the present work we have selected a series of heterogeneous catalysts with Lewis and Bronsted basic sites, and acid–base bifunctional pairs in order to perform different organic reactions.

2. Experimental

2.1. Materials

Beta zeolite (Si/Al = 13) was supplied by PQ corporation in the acidic form. Acid HY zeolite (Si/Al = 5.2) was prepared from a NaY (SK-40) zeolite by NH_4^+ exchange followed by deep calcination at 550 °C. This procedure was repeated three times in order to reduce the Na^+ content of the sample. CsNaX

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zeolite was prepared by repeated exchange of a NaX zeolite (13X) with aqueous solution of CsCl (0.5 M) at room temperature. Al-MCM-41 (Si/Al = 15) with a pore diameter (o.d.) 3.5 nm, was prepared following the procedure given in [1]. Pure silica MCM-41, and the grafted quaternary organic ammonium hydroxide on MCM-41 (MCM-41-OH) were prepared following the procedure reported in [2]. MgO sample with a surface area of 246 m^2/g was prepared starting from magnesium oxalate following the method described by Putanov et al. [3].

Al–Mg hydrotalcite with a Mg/Al ratio of 3, was prepared from gels produced by mixing two solutions: solution A containing $(3-x)$ mol of $Mg(NO_3)_2 \cdot 6H_2O$ and x mol of $Al(NO_3)_3 \cdot 9H_2O$ in the Al + Mg concentration of 1.5 mol/l for a ratio $x/3$ of 0.25, and another solution B of $(6+x)$ mol of NaOH and 2 mol of Na_2CO_3 dissolved in the same volume of the solution A. Further the both solutions are co-added at a rate of 1 ml/min under a vigorous mechanical stirring at room temperature. The suspension was left overnight at 60 °C. The hydrotalcite was filtered and washed until filtrate pH = 7 and the solid was dried at 60 °C for a night. The hydrotalcite was activated by calcining at 723 K in a dry nitrogen flow. The temperature was raised at the rate of 2 °C/min to reach 723 K and maintained for 6 h. The surface area of the solid was 227 m^2/g. Rehydration of calcined hydrotalcite was carried out under a flow of nitrogen gas (40 ml/min) saturated with water vapor.

The KF/Al_2O_3 sample with a 40 wt.% of KF was purchased from Aldrich.

Amorphous aluminophosphate (ALPO) with a P/Al of 1 and surface area 211 m^2/g, was prepared following the method proposed by Lindblad et al. [4]. Amorphous silica alumina (SAM) with a Si/Al ratio of 50 and surface area of 719 m^2/g was prepared according to [5].

Silicon aluminophosphates (SAPOs) with a SiO_2 content of 10% was prepared starting from an aqueous solution of H_3PO_4, $AlCl_3$ and tetraethyl orthosilicate (TEOS) acidified with nitric acid at pH < 0. A hydrogel with typical composition $1.0P_2O_5$: $1.0Al_2O_3$:$0.6SiO_2$, was then formed by adding concentrated ammonia solution until a pH of 6. After 1 h the solvent was filtered off and the hydrogel washed with distilled water. The solid was dried at 393 K for 16 h and calcined at 773 K.

2.2. Reaction procedure

Typically the catalyst was added to a mixture of reactants in a three-necked bottom flask equipped with a condenser system. The resultant suspension was heated while stirring at the desired temperature under inert atmosphere in an oil bath equipped with automatic temperature control system. Zeolites and Al-MCM-41 catalysts, were activated before reaction, at 323 K under vacuum (1 Torr) for 3 h. Samples of the reaction mixture were periodically withdrawn by a filtering syringe and analyzed by gas chromatography (GC) (Hewlett-Packard 5990A spectrometer provided with a 25 m capillary column of cross-linked 5% phenylmethylsilicone).

Quantitative determinations were based on the measured response factors of the reactants and reaction products. Each reaction product was identified by ^{1}H NMR spectroscopy (Varian VXR-400 S, 400 MHz) and GC–MS (Hewlett-Packard 5988A mass spectrometer connected with a 25 m capillary column of phenylmethylsilicone).

3. Results and discussion

Solid base catalysts such as alkali exchanged zeolites [6], sepiolites [7], organic resins [8], mixed magnesium aluminum oxides derived from hydrotalcites [9,10] and more recently, aluminophosphates oxinitrides (ALPONs) [11] which can cover a wide range of the basic strength have been used on laboratory scale for different organic reactions. Among those, processes which involve the creation of new C–C are of paramount importance in organic synthesis. Thus, Knoevenagel condensation, aldolization and Michael additions, which can be carried out under base catalysis, have been extensively studied in homogeneous and heterogeneous systems. Here we present some examples of these type of reactions catalyzed by different heterogeneous basic catalysts.

3.1. Heterogeneous catalysts with Lewis basic sites

Knoevenagel condensation [12] is one important C–C bond-forming reaction widely used in synthesis of important intermediates and end products for perfumes [13], pharmaceuticals [14] and polymers [15].
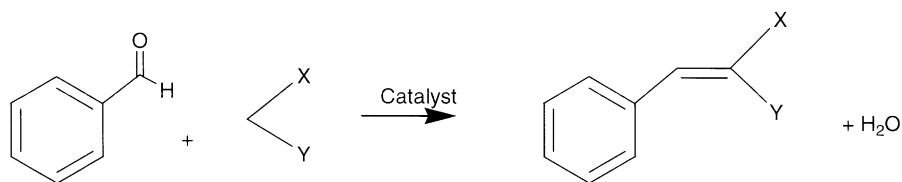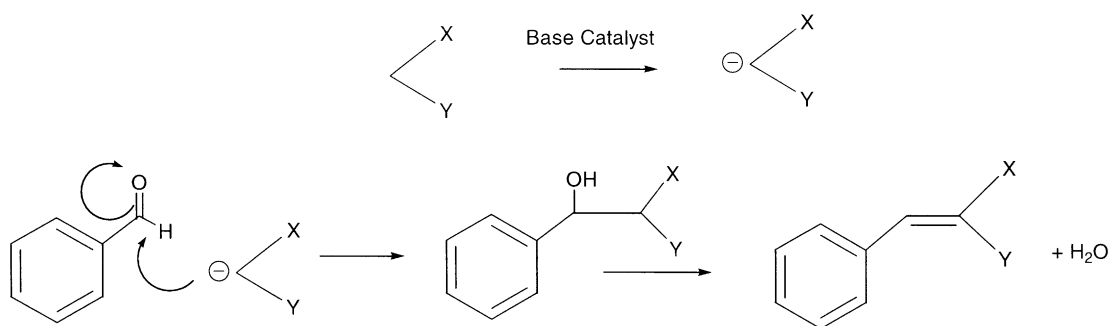
MN: X= CN, Y=CN
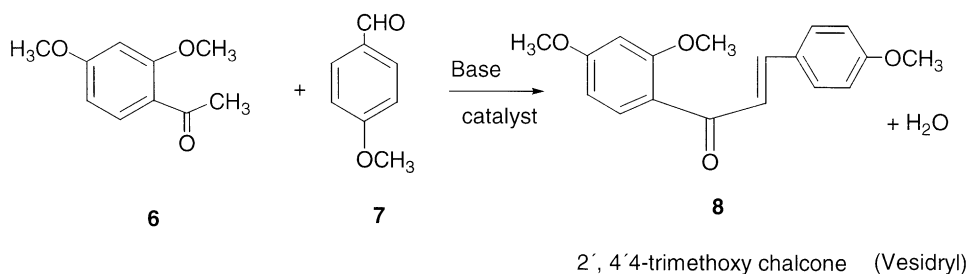ECA: X=CN, Y= COOEt
DEM: X= COOEt, Y= COOEt

Scheme 1.

Moreover, it has been used as a test reaction in order to establish the basic properties of the solids [6]. Thus, by comparing the catalytic activity of different basic catalysts for carrying out the Knoevenagel condensation reaction of benzaldehyde with molecules containing active methylenic groups with different pK_a values, it is possible to obtain information about the total number of basic sites and on the relative basic strength of different base catalysts. In this work, we have selected three heterogeneous base catalysts where the basic sites are of Lewis type: a caesium exchanged X zeolite, MgO and a Mg–Al mixed oxide derived from hydrotalcite (HT). The Knoevenagel condensations between benzaldehyde and malononitrile (MN) ($pK_a = 11$), ethyl cyanoacetate (ECA) ($pK_a = 9$) and diethyl malonate (DEM) ($pK_a = 13.3$) have been performed in the presence of these solid basic catalysts (Scheme 1). It has been established [6,7] that the reaction mechanism is the same in the homogeneously

catalyzed reaction in solution as it is when solid catalysts are used. It was found that the rate-controlling step of the condensation reaction on basic solids is the attack by the carbanion intermediate on the carbonyl group (Scheme 2). In Table 1 the results obtained for the three reactions on the different catalysts are presented.

It is interesting to point out, that according to the pK_a's reported in literature and which were determined in aqueous solutions, the decreasing order of acidity of the reactants is ECA > MN > DEM. However, calculations of the positive charge density of the hydrogen at the methylenic groups give us values of 0.337, 0.318 and 0.302 for MN, ECA and DEM, respectively, indicating that the order in acidity is MN > ECA > DEM. Then, according to this, when the most acidic reagent (MN) was used, the results of Table 1 indicate that the order of activity is CsX > MgO > HT, in all cases the selectivity to Knoevenagel adduct

Scheme 2.

Table 1
Knoevenagel condensation between benzaldehyde and methylene active compounds on different basic catalysts[a]

Catalysts	MN		ECA		DEM	
	r_0 (min^{-1})	Conversion[b]	r_0 (min^{-1})	Conversion[c]	r_0 (min^{-1})	Conversion[d]
CsX	6.3	91 (100)	0.1	7 (100)	0.05	5 (100)
MgO	3.4	62 (100)	2.3	80 (99)	0.20	43 (39)
HT	2.1	54 (100)	1.3	46 (98)	0.13	54 (27)

[a] Selectivity to Knoevenagel adduct is in parenthesis. All reactions were carried out in the absence of solvent.
[b] Conversion of the methylene active compound at 1 h reaction time, 5 wt.% of catalyst at 333 K.
[c] Conversion of the methylene active compound at 2 h reaction time, 5 wt.% of catalyst at 333 K.
[d] Conversion of the methylene active compound at 10 h reaction time, 10 wt.% of catalysts at 383 K.

$$Ph\text{-}CHO + CH_2\text{-}(CH_2)_4\text{-}CH_3 \longrightarrow Ph\text{-}CH{=}\overset{CHO}{C}\text{-}(CH_2)_4\text{-}CH_3 + CH_3\text{-}(CH_2)_5\text{-}CH{=}\overset{CHO}{C}\text{-}(CH_2)_4\text{-}CH_3$$

1   **2**   **3**   **4**
(Jasminaldehyde)

Scheme 3.

being of 100%. This indicates that the total number of basic sites is higher in CsX zeolite than in MgO and HT. When using a more demanding reagent (ECA), MgO exhibits higher activity than CsX and HT, and when a less acidic compound is used (DEM) only MgO and HT are able to perform the Knoevenagel condensation, being the selectivity to the Knoevenagel product sensibly lower. In fact, other products coming from Michael addition to the Knoevenagel compound were detected [11]. Taking into account that Michael addition is a reaction requiring stronger basic sites, these results allow us to conclude that while the total number of basic sites on the oxides is lower, they are stronger than on CsX. Then, considering the results of activity obtained for the three catalysts it is possible to establish the following order of basicity: HT > MgO > CsX.

These solids have been used as base catalysts for the synthesis of a fine chemical, i.e. jasminaldehyde (α-n-amylcinnamaldehyde) [16]. This is a traditional perfumery product with violet scent that can be obtained by the aldol condensation of benzaldehyde (**1**) with heptanal (**2**) (Scheme 3). It is interesting to point out that during the synthesis of jasminaldehyde (**3**), different by-products can be formed that reduce the yield of amylcinnamic aldehyde. The most important undesired product comes from the self-condensation

of heptanal to form 2-n-pentyl-2-n-nonenal (**4**). We can see (Table 2) that the catalytic activity obtained for this condensation with the different catalysts are in good agreement with those obtained using the Knoevenagel condensation with methylenic groups of different acidity as test reaction. Indeed, the less basic catalyst (CsX), exhibit the higher selectivity to jasminaldehyde, whereas strong basic catalysts such as MgO, calcined hydrotalcined and KF/Al$_2$O$_3$ give higher conversions of heptanal but poor selectivity to jasminaldehyde.

Table 2
Condensation of benzaldehyde (**1**) with heptanal (**2**) in the presence of different solid base catalysts[a]

Catalysts	$r_0 \times 10^3$ (mol/min g)	Conversion of **2**	Selectivity (%)		
			3	**4**	**5**[b]
CsX	0.1	32	84	15	–
MgO	3.3	97	43	51	5
HT	1.5	94	47	45	6
KF/Al$_2$O$_3$	3.9	78[c]	64	32	4

[a] Molar ratio of benzaldehyde/heptanal was 5 using 10 wt.% of catalyst without solvent at 398 K after 8 h reaction time.
[b] Structure of **5** was assigned by mass spectroscopy to a compound coming from Michael addition of heptanal to **4**.
[c] 5% of heptanoic acid was detected.

Scheme 4.

3.2. Heterogeneous catalysts with Bronsted basic sites

Up to now we have established the order of basicity for three heterogeneous catalysts with Lewis sites. However, there is also the possibility to prepare heterogeneous catalysts with basic Bronsted sites that can be more adequate for catalyzing some reactions. In this way, it has recently been reported [17] that the catalytic activity of calcined hydrotalcites can be enhanced by rehydration at room temperature if the presence of CO_2 is avoided. This treatment results in the restoration of the original layered structure where the compensating anions in the interlayer are now OH^-. Although up to now little is know about the nature and number of active Bronsted basic sites and the mechanism involved for their formation, this material, is able to catalyze aldol [18–23] and Claisen–Schmidt condensation at 273 K [24]. Because of the new possibilities exhibited by rehydrated hydrotalcites as base catalyst for the aldol and Claisen–Schmidt condensations, we have tested this catalyst in the synthesis of Vesidryl ($2',4,4'$-trimethoxychalcone) (Scheme 4). This product is of pharmacological interests owing to its diuretic and chloleretic properties [25] and can be obtained by the Claisen–Schmidt condensation between 2,4-dimethoxy acetophenone (6) and 4-methoxy benzaldehyde (7) under base catalysis.

In Table 3 the results obtained with calcined-rehydrated hydrotalcite is compared with those obtained with other heterogeneous catalysts such as KF/Al_2O_3, a calcined hydrotalcite, and an acid catalyst such as faujasite (HY) zeolite. The results show that whereas acid catalyzed condensation gives low yield to Vesidryl, base catalysis is a more convenient route for carrying out this synthesis. However, between the different basic catalyst tested, we can see that rehydrated hydrotalcite, with Bronsted basic sites, gives higher activity than the calcined sample which is supposed to have only Lewis basicity. The relatively high activity of KF/Al_2O_3 is not surprising considering the high activity as basic catalyst shown by this supported material in many highly basic strength demanding reactions, such as Michael additions or aldol condensations [26]. Nevertheless, its high basicity can be responsible of its low selectivity to chalcone. Finally, when the reaction is carried out in homogeneous phase using a strong conventional

Table 3
Synthesis of Vesidryl (8) on different catalysts

Catalysts	Catalyst weight (%)	Time (h)	T (°C)	Yield of 8	Selectivity to 8
HT (rehydrated)[a]	12	4	80	78	99
HT	12	4	120	20	99
KF/Al$_2$O$_3$	12	4	80	57	62
HY-100	10	22	150	15	98
KOH/EtOH[b]	57	4	30	90	98

[a] 26 wt.% of water content.
[b] Volume of reactant: 1 ml organic; 5 ml EtOH + H_2O.

Table 4
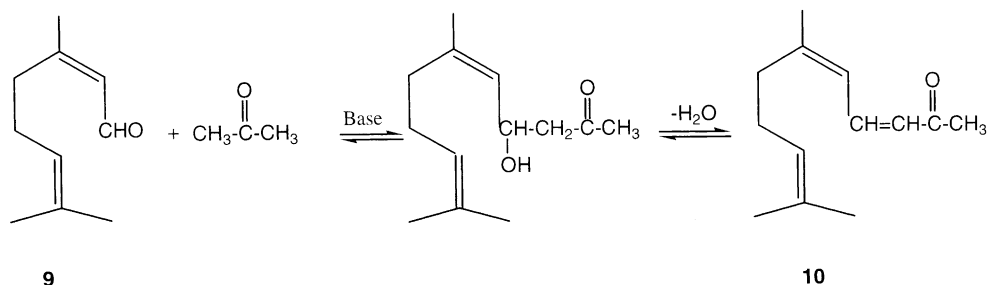Condensation of benzaldehyde (**1**) with heptanal (**2**)[a]

Catalysts	$r_0 \times 10^3$ (mol/min g)	Conversion of **2**	Selectivity (%)		
			3	**4**	**5**
HT	1.5	94[b]	47	45	6
HT (rehydrated)[c]	5.3	90[d]	67	27	4

[a] Molar ratio of benzaldehyde/heptanal was 5 using 10 wt.% of catalyst at 398 K.

[b] 8 h reaction time.

[c] 26 wt.% of water content.

[d] 4 h reaction time.

Scheme 5.

base (KOH in ethanol), we can see that in order to obtain a good selectivity to Vesidryl it is necessary to decrease the reaction temperature and therefore a high concentration of base should be used.

On the other hand, when rehydrated hydrotalcite was tested as basic catalyst in the condensation of heptanal and benzaldehyde in order to obtain jasminaldehyde, results of Table 4 show that the rehydrated sample is more active and selective to jasminaldehyde than the calcined sample, achieving a conversion of heptanal of 90% with a selectivity of 67% to jasminaldehyde at 4 h reaction time.

Another example of cross-aldol condensation that show the influence of the nature of basic sites of the catalyst on its activity and selectivity, is the synthesis of pseudoinones by condensation between citral (**9**) and acetone (Scheme 5). This condensation was carried out with different basic catalysts (Table 5). In all cases the main product obtained was a mixture of *cis*- and *trans*-pseudoinone (6,7-dimethyl-3,5,9-undecatrien-2-one (**10**)), although by-products coming from the self-condensation of citral, and oligomers derived from citral were also detected in the reaction mixture. In fact, the selectivity to

pseudoionone strongly depends on the nature of the basic sites involved in the reaction. As we can observe, catalysts bearing Lewis basic sites (MgO and calcined hydrotalcite) give lower selectivity to pseudoionone than rehydrated hydrotalcite. These results are in good agreement with reported results concerning to the aldol condensation of benzaldehyde with acetone [17]. The reaction requires basic sites with medium basic strength such as the exhibited by OH groups on the rehydrated hydrotalcites.

On the other hand, when the influence of the acetone/citral molar ratio on the activity of the catalyst was studied, we observed that the rehydrated

Table 5
Condensation of citral (**9**) with acetone[a]

Catalysts	Citral (**9**) conversion	Yield of **10**	Others	Selectivity to **10**
MgO	99	68	31	68
HT	86	68	18	79
HT (rehydrated)[b]	96	95	1	99

[a] Molar ratio of acetone/citral was 2.7 using 16.6 wt.% of catalyst at 333 K after 1 h reaction time.
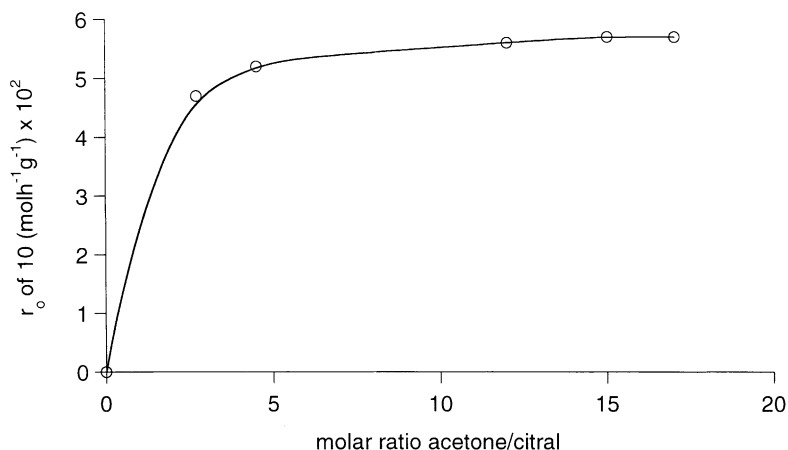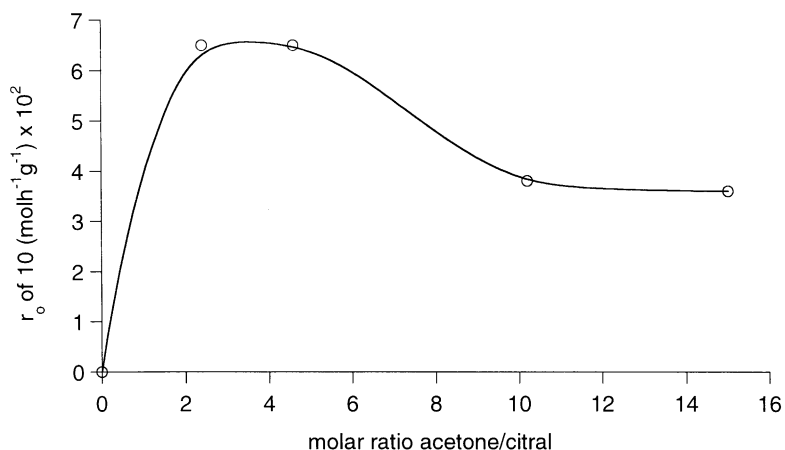
[b] 36 wt.% of water content.

Fig. 1. Influence of the molar ratio acetone/citral on the initial rate of formation of pseudoionone **10** (○) using calcined HT (40 wt.% of catalyst with respect to citral) at 333 K.

hydrotalcite does not follow the same behavior than the calcined sample (see Figs. 1 and 2). Indeed, for the calcined sample the initial rate of formation of **10** increases when increasing the molar ratio until a value of 4.5. Higher ratios have little influence on the initial activity (Fig. 1). In the case of the rehydrated sample activity increases when increasing the acetone/citral ratio up to a value close to 3. After this, a decrease of the catalyst activity is observed when further increasing the acetone/citral ratio (Fig. 2). These results indicate that the nature and distribution of basic sites

in the rehydrated catalyst has strong influence on the kinetic behavior of the reaction and hence on the final yield and selectivity towards pseudoionone.

These examples show the importance to select for a given process, the most appropriate catalysts from the point of view of the nature and strength of the active basic sites.

Recently we have reported [2] the preparation of a strong Bronsted base catalyst obtained by preparing an inorganic–organic composite formed by an organic ammonium quaternary salt anchored on the

Fig. 2. Influence of the molar ratio acetone/citral on the initial rate of formation of pseudoionone **10** (○) using rehydrated HT with 36 wt.% of water content (40 wt.% catalyst with respect to citral) at 333 K.
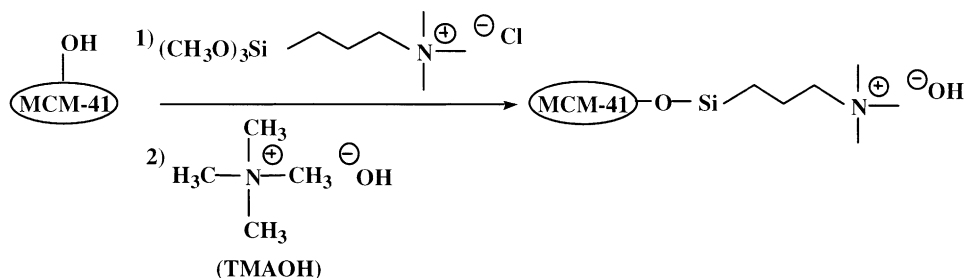
Scheme 6.

surface of a pure silica MCM-41 (MCM-41-OH). The functional tetraalkylammonium groups were anchored to the Si-MCM-41 surface by reacting trimethoxysilyl-propyl-*N*,*N*,*N*-trimethylammonium chloride (SiNR$_4$Cl) with hydroxyl groups located at the surface. The exchange of chloride by hydroxide anions was carried out by contacting the functionalized MCM-41 samples with a 0.21 M methanolic solution of tetramethylammonium hydroxide (TMAOH) at room temperature for 10 min using a liquid to solid ratio of 50 g/g (Scheme 6).

MCM-41-OH1 was tested as basic catalyst for the Knoevenagel condensation of benzaldehyde with ECA under different reaction conditions (Table 6). We can see that the initial rate was proportional to the amount of mmol of hydroxide tetraalkylammonium salt anchored, indicating that a highly homogeneous strength distribution of basic sites is obtained on these catalysts and there is a total accessibility of reactants to the active sites. In spite of the good accessibility of reactants to the active sites, the initial rate per mmol of OH$^-$ is practically one half than that obtained when NMe$_4$OH was used as a homogeneous catalyst. This lower intrinsic activity shown by MCM-41-OH could be attributed to a possible interaction between the hydroxide group with the remaining silanol groups located at the inner part of the MCM-41 channels, decreasing in this way the base strength of the anchored NMe$_4$OH.

MCM-41-OH1 catalyst was tested as basic catalyst for carrying out Michael additions using different donor and acceptor substrates (Scheme 7; Table 7). When ECA was used as donor substrate, the double Michael addition product was detected. The selectivity for the single or double addition can be controlled by changing the concentration of reactants, time,

Table 6
Knoevenagel condensation between benzaldehyde (**1**) and ECA in the presence of MCM-41-OH[a]

Catalysts	Anchored NMe$_4$OH (mmol/g)	$r_0 \times 10^4$ (mol/min g)	TON $\times 10^3$ (mol/min mmol) (r_0/mmol NMe$_4$OH)	Conversion of ECA	Selectivity to Knoevenagel product
MCM-41-OH1[b]	1.22	17.8	1.45	88[c]	100
MCM-41-OH2[b]	0.88	11.0	1.25	77[c]	100
MCM-41-OH1[d]	1.22	217	17.8	95[e]	100
MCM-41-OH2[d]	0.88	163	18.6	90[e]	100
NMe$_4$OH[d]	0.064[f]	208[g]	32.5	100[e]	100

[a] Reaction conditions: benzaldehyde (10 mmol) and ECA (8 mmol) in the presence of MCM-41-OH (80 mg) at 60 °C under N$_2$.
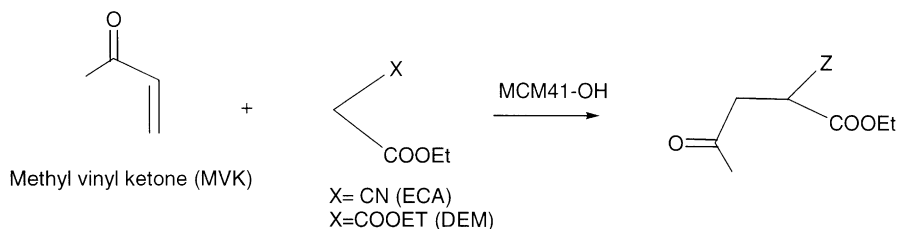[b] Chloroform as solvent (5 ml).
[c] Without solvent.
[d] 2 h reaction time.
[e] 0.5 h reaction time.
[f] mmol of NMe$_4$OH added.
[g] This value is in mol/min.

Scheme 7.

Table 7
MCM-41-OH1 as a catalyst for Michael reactions[a]

Entry	Donor	Acceptor	T (°C)	Time (h)	Conversion of acceptor	Selectivity to Michael adduct
1	ECA	MVK	20	2	100	70
2	ECA	MVK	60	1	95	61
3	ECA	Cyclopentanone	80	2	60	83
4	ECA	Cyclohexanone	80	2	35	100
5	DEM	MVK	60	2	10	100

[a] Reaction conditions: 8 mmol of donor; 8 mmol of acceptor; 60 mg of catalyst; 2 ml CH_3CN under N_2.

and reaction temperature (Table 7, entries 1 and 2). However, when the less acidic DEM was used as donor, longer reaction times are needed to obtain higher conversions (entry 5). In general, high selectivities to the 1,4-adduct can be achieved which must be attributed to the well-defined strong basicity of the MCM-41-OH.

These results show that MCM-41-OH is an efficient catalyst to perform several Michael additions with acceptable yields and selectivities when working under mild conditions with large substrates. This is in contrast with other modified MCM-41 materials reported previously, such as Cs-MCM-41 materials, which can only catalyze Michael reactions under much more drastic conditions [27]. Also for the MCM-TBD catalyst [28] the bulky immobilized

1,5,7-triazabicyclo[4.4.0]dec-5-ene reduces the pore size of the catalyst inducing a transition state shape selectivity or even limiting the accessibility of bulky reactants to the active sites.

Owing to the success of MCM-41-OH1 for carrying out Knoevenagel and Michael reactions, we have applied this catalyst to the preparation of chromenes and coumarins. Chromenes (2H-1-benzopyran derivatives) and coumarins (2H-1-benzopyran-2-one derivatives) are widely distributed in plants, and several of them are being produced synthetically because of their commercial interest for the preparation of pharmaceuticals. They can be prepared by reacting salicylaldehyde derivatives with the commercially available diethyl 2-pentenedicarboxylate, and their synthesis involves one Michael and one Knoevenagel type
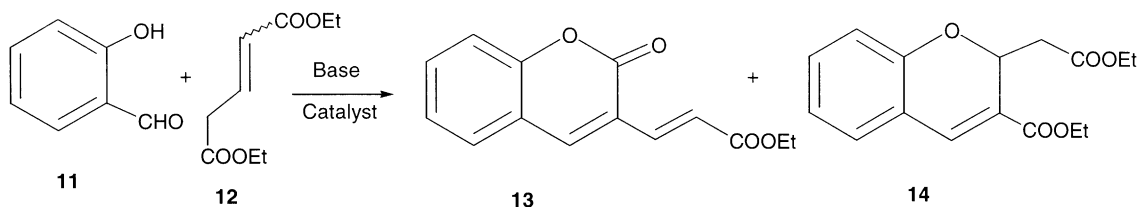
Scheme 8.
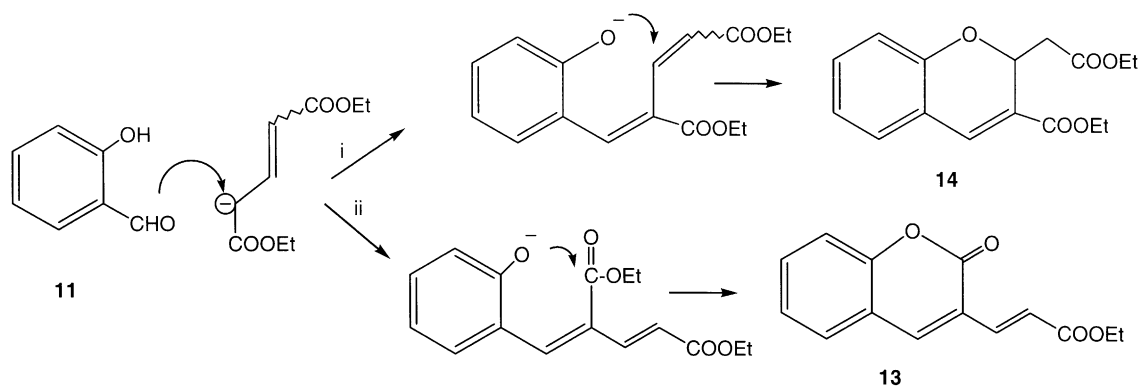
Scheme 9.

condensation steps (Scheme 8). The use of MCM-41-OH as basic catalyst is certainly of interest, since we found that other solid bases such as MgO and hydrotalcites present low activity for catalyzing the formation of chromene and coumarins under mild conditions.

The condensation of salicylaldehyde derivative (**11**) with diethyl 2-pentenedicarboxylate (diethyl glutaconate) (**12**) under Knoevenagel conditions leads to coumarin-3-acrylates (**13**) and chromene derivatives (**14**) [29] (Scheme 8). Formation of coumarin and chromene can arise from a first step which involves the Knoevenagel condensation between salicylaldehyde and diethyl glutaconate followed by the attack of the phenolic group of the Knoevenagel condensation intermediate to the olefinic bond (intramolecular Michael addition) (via (i) in Scheme 9) yielding chromenes, or by the attack of the phenolic group to the carbethoxy function leading to coumarins (via (ii) in Scheme 9). It is known that the nature of the substituents in the salicylaldehyde aromatic ring can have a strong influence on selectivity [29] but it would also be possible that the difference in the order in which the Knoevenagel condensation and Michael addition reactions occur, could be an important factor affecting the selectivity to chromene or coumarin. If it is so, the basic strength of the catalyst could also play an important role on the preferential formation of chromene or coumarin. In this case, it would be then possible by controlling the base strength to direct the synthesis to the desired product regardless of the type of substituent present in the molecule.

When the reaction between **11** and **12** was carried out in the presence of MCM-41-OH1 in refluxing

ethanol, we found that, surprisingly, the expected coumarin derivative was not the main product of the reaction, but chromene was produced in higher yield (Fig. 3), in clear contrast with what is reported in the literature when piperidine is used as catalyst [29].

When the reaction was carried out at 110 °C without solvent, with MCM-41-OH1 as catalyst, also high conversion (90%) and high selectivity (90%) to chromene was achieved within 6 h of reaction time (Fig. 4).

In clear contrast, when the condensation between **11** and **12** was carried out using NMe₄OH as homogeneous catalyst in refluxing ethanol (Fig. 5) we found that the rate of coumarin formation was higher on homogeneous than on the MCM-41-OH catalyst. These results clearly indicate that the ratio chromene/coumarin produced is highly influenced by the base strength of the catalyst.

3.3. Acid–base bifunctional catalysts

Up to now we have showed different examples of base catalyzed organic reactions, in where yields and selectivities towards the different reaction products are highly influenced by the concentration, basic strength and nature (Lewis or Bronsted) of the basic sites on the solid catalyst. However, in some cases a bifunctional acid–base catalyst where both functions are well balanced can show selectivities never achieved by monofunctional acid or base catalysts. Indeed, in a previous work [30] we found that amorphous ALPO was more active and selective than other acidic solids such as zeolites and mesoporous aluminosilicates for producing jasminaldehyde from condensation of benzaldehyde
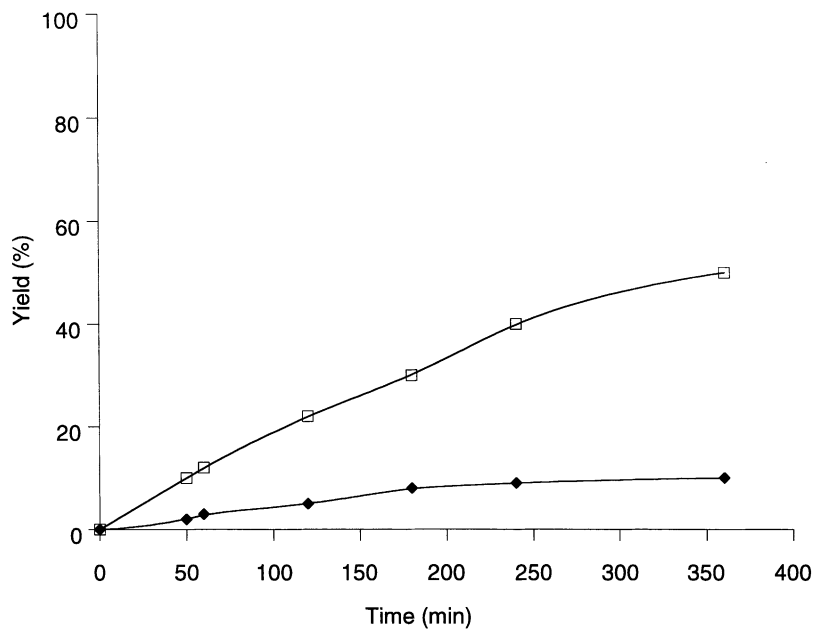
Fig. 3. Yield of coumarin (**13**) (◆) and chromene (**14**) (□) vs. time obtained in the reaction between **11** (4 mmol) and **12** (4 mmol) in refluxing ethanol (2.5 ml) in the presence of MCM-41-OH1 (160 mg) as catalyst (**13** and **14** were the only products observed).
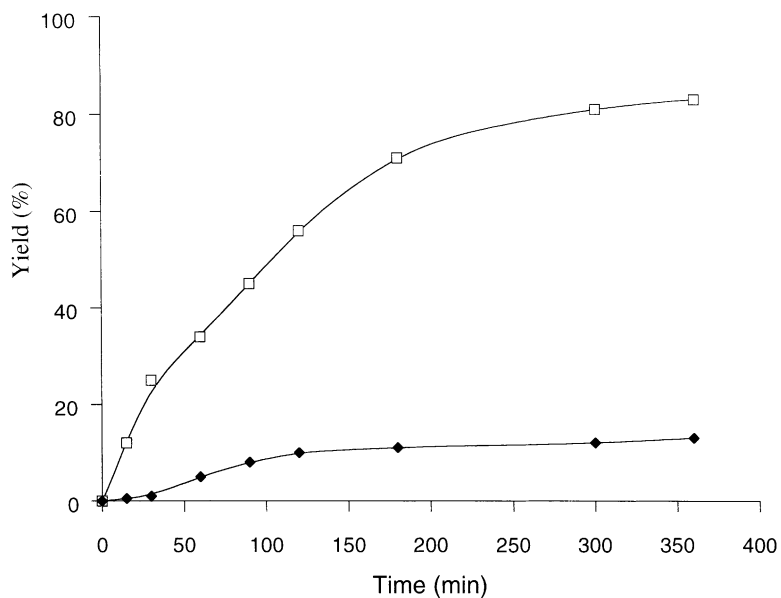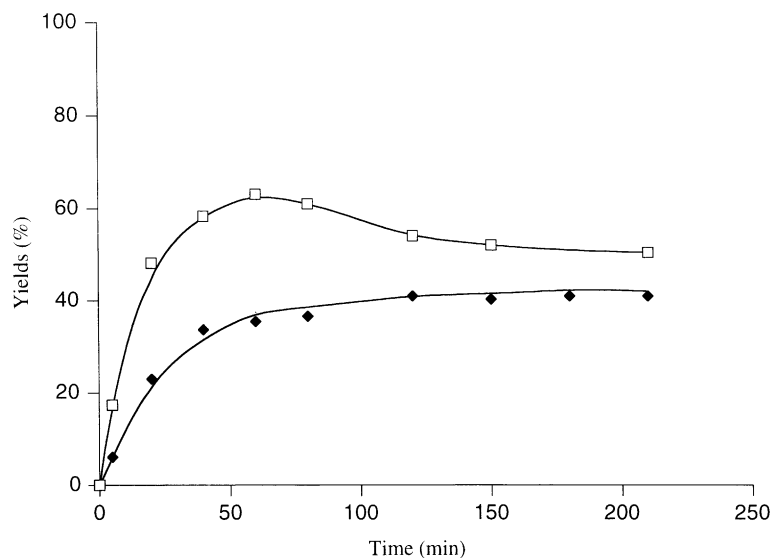

Fig. 4. Yield of coumarin (**13**) (◆) and chromene (**14**) (□) vs. time obtained in the reaction between **11** (4 mmol) and **12** (4 mmol) without solvent in the presence of MCM-41-OH1 (160 mg) as catalyst at 383 K (**13** and **14** were the only products observed).

Fig. 5. Yield of coumarin (**13**) (◆) and chromene (**14**) (□) vs. time obtained in the reaction between **11** (4 mmol) and **12** (4 mmol) in refluxing ethanol (2.5 ml) in the presence of NMe$_4$OH (0.2 mmol) as catalyst (**13** and **14** were the only products observed).

and heptanal (Table 8). Moreover, we have found that ALPO, also exhibit better activity and selectivity to jasminaldehyde than purely basic catalysts (see Table 2). Since these results are difficult to explain by considering either a single acid or basic mechanism, the following hypothesis can be introduced: the superior behavior of ALPO over more acid or basic catalysts could be due to a combined acid–base catalyzed condensation where the acid sites of ALPO associated to phosphorol groups (POH) are interacting with the carbonyl group of benzaldehyde producing a polarization of this group, and as consequence increasing

the positive charge on the corresponding carbon atom. This should favor the attack of the enolate heptanal intermediate from the relative weak Lewis basic sites which corresponds to bridged oxygen (Scheme 10).

Supporting the hypothesis that an acid–base bifunctional catalyst bearing weak acid–base pairs, exhibit larger catalytic activity than other acid or basic solid catalyst, we present another reaction, i.e. the Knoevenagel condensation between DEM and benzaldehyde, which requires strong basic sites, and which can be easily performed with high conversion and selectivity in the presence of an ALPO catalyst [31].

Table 8
Results obtained in the condensation of benzaldehyde and heptanal with different catalysts[a]

Catalysts	Time (h)	Conversion (%)	Poison in the catalyst (%)[b]	Selectivity (%)		
				3	**4**	Others[c]
Beta	6	93[d]	5.1	21	43	25
HY-100	16	53	7.4	52	28	5
Al-MCM-41	10	99	–	56	35	8
ALPO	3	96	1.5	86	13	–

[a] Molar ratio of benzaldehyde/heptanal was 5 using 10 wt.% of catalysts at 398 K in the absence of solvent.
[b] Determined by TG analysis and based on moles of heptanal retained.
[c] Phenyl heptene was produced.
[d] 5% of heptanoic acid was detected.
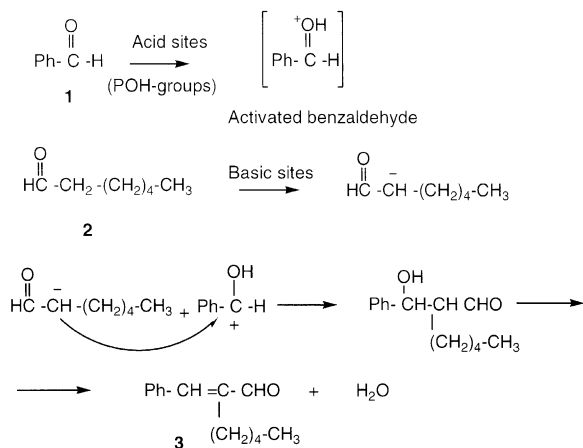
Scheme 10.

We have showed above (see Table 1) that only strong base catalysts (MgO and HT) are able to perform this condensation with high conversion but with a very low selectivity to the Knoevenagel adduct. On the other hand, since Knoevenagel condensations can be carried out in the presence of acid catalysts [32] we have tested the Knoevenagel condensation of different methylenic active compounds in the presence of solid acid catalysts (Table 9).

From the results of Table 9 we can see that acid catalyst, included *p*-toluene sulfonic acid (*p*-TSA), are not active catalysts when the more acidic active methylenic compounds (MN and ECA) are involved in the reaction. Only, DEM reacts under acid catalysis, being the ALPO activity higher than those obtained on the different acid catalysts, included *p*-TSA. From

Table 9
Knoevenagel condensation between benzaldehyde and methylene active compounds on different acid catalysts[a]

Catalysts	MN[b]		ECA[c]		DEM[c]	
	r_0 (min^{-1})	Conversion	r_0 (min^{-1})	Conversion	r_0 (min^{-1})	Conversion
Beta	–	–	–	–	0.23	31 (100)
MCM-41	–	–	–	–	0.55	60 (99)
SAM	–	–	–	–	0.13	40 (99)
p-TSA	–	–	<0.1	6	0.9	85 (99)
ALPO	1.2	78 (100)	0.20	55 (80)	1.57	85 (96)

[a] Selectivity to Knoevenagel adduct is in parenthesis.
[b] 5 h reaction time; 5 wt.% of catalysts at 333 K.
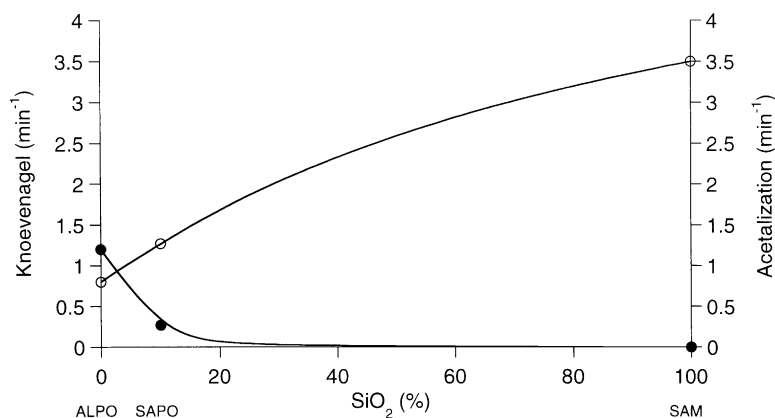[c] 10 h reaction time; 10 wt.% of catalyst at 383 K.

Fig. 6. Results of the Knoevenagel condensation between benzaldehyde and MN (10 mmol of reactants, 5 wt.% of catalyst at 333 K, without solvent) (●), and acetalization of benzaldehyde with TMOF (benzaldehyde: 10 mmol, TMOF: 50 mmol; 5 wt.% of catalyst at reflux temperature of Cl₄C (15 ml)) (○), in the presence of ALPO, SAPO and SAM as catalysts.

Table 10
Knoevenagel condensation between benzaldehyde and DEM on different catalysts[a]

Catalysts	ECA	
	r_0 (min^{-1})	Conversion[b]
ALPO	1.57	85 (96)
SAPO	1.07	67 (95)
SAM	0.13	40 (99)

[a] Selectivity to Knoevenagel adduct is in parenthesis.
[b] 10 h reaction time; 10 wt.% of catalyst at 383 K.

these results, we could think that an acid mechanism could be operating when the condensation of DEM with benzaldehyde is performed using ALPO catalyst. Then, in order to do a deep study of the mechanism

involved in this condensation it would be interesting to proceed now from the amorphous ALPO to SAPO. In this case by increasing the Si content we should be increasing the acidity of the material while decreasing its basicity, being the most acidic material that with no phosphorous (amorphous silica alumina, SAM). In order to show this, and to measure the acid–base character of these materials we have performed two test reactions: the acetalization of benzaldehyde with trimethyl orthoformate (TMOF), which is a reaction catalyzed by purely acid sites and a reaction which is only catalyzed by bases: the Knoevenagel condensation of MN with benzaldehyde. In Fig. 6 we can see that for the acetalization reaction the activity increases with respect to the ALPO when the Si content
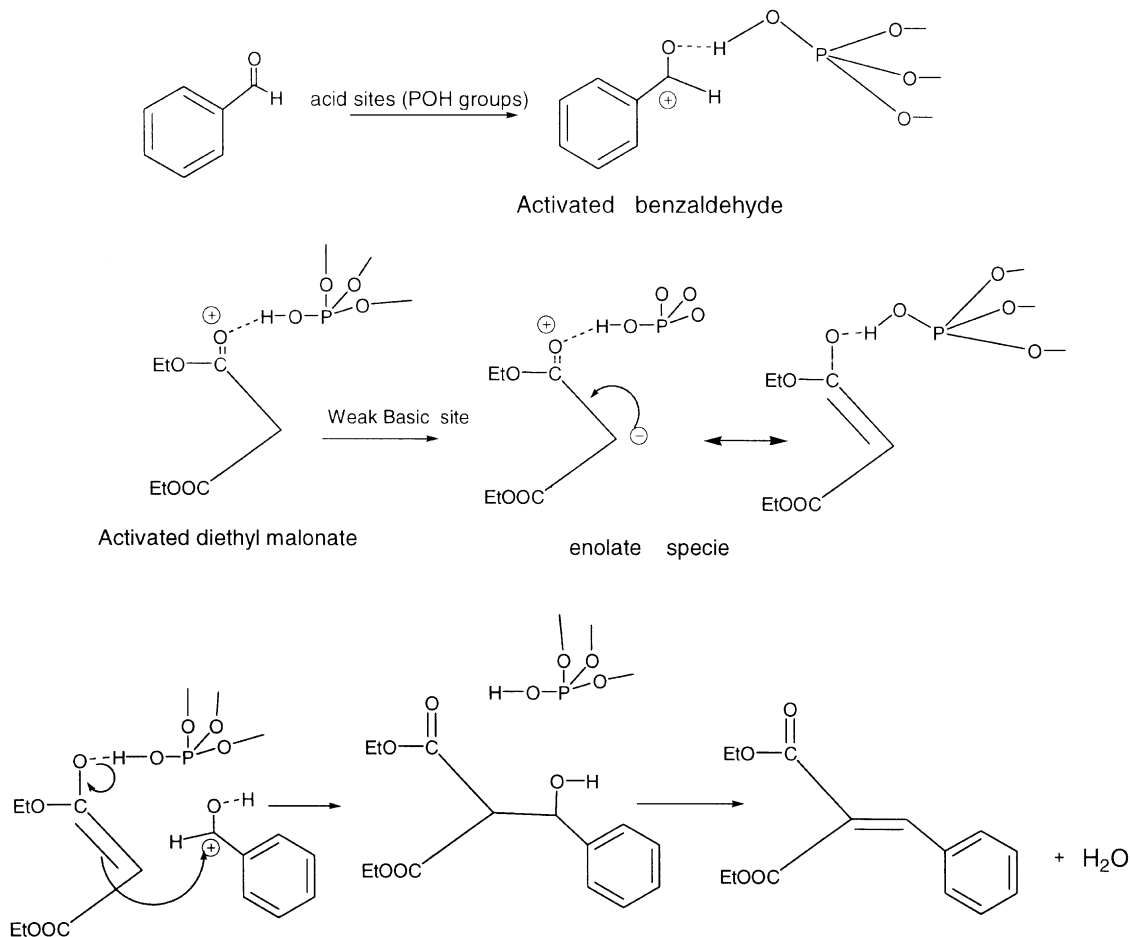
Scheme 11.

of the sample was increased. On the other hand, for the Knoevenagel condensation, the activity is lower when higher is the silicon content of the sample indicating a decrease in basicity.

Then, when the above samples were used as catalysts for the Knoevenagel condensation of DEM and benzaldehyde (Table 10) we can see that the three samples give appreciable activity and selectivity to the Knoevenagel compound, however, the activity increases when increasing the basicity, and decreases when increasing the acidity being ALPO the most active material. These results indicate that on ALPO surface weak acid and basic sites coexist in adequate proportion in such way that it should be possible that an acid–base bifunctional catalysis was operating. Then, we propose a mechanism where a weak Bronsted acid site (POH group) will interact with the carbonyl group (of the benzaldehyde, or of the DEM) polarizing the C–O bond and increasing the density of positive charge on the carbon supporting the carbonyl group. Then, in the case of benzaldehyde, this makes this carbon more prompt to be attacked by a carbanion. At the same time, in the case of the DEM the increase of positive charge on the carbon of the carbonyl group will produce an enhancement of the acidity of the hydrogen at the methylenic group. In fact, calculations of the density of positive charge on the hydrogen atoms attached to the methylenic group of a protonated DEM species give a value of 0.356, clearly superior to that of the neutral species (0.302). This increase of acidity in the protonated DEM could explain that the weak basic sites existing on ALPO were able to generate a carbanion species which reacts with the activated benzaldehyde (Scheme 11).

4. Conclusions

We have showed here, that a large variety of base solid catalysts exists. By changing the chemical composition and activation conditions it is possible to have predominantly Lewis or Bronsted base catalysts within a large range of well defined basicities. This allows to select the most appropriate catalyst for a specific reaction. While we have concentrated here on condensation reactions, the above is valid for a large number of base catalyzed reactions which involve:

double bond isomerization, alkyl chain alkylation, alkene dimerization, transesterification reactions and dehydrogenation of alkylamines to nitriles.

It has to be remarked that excellent catalytic results have been obtained with catalysts containing acid–base pairs. In this case, a cooperative role of both sites has been found that allow to substitute strong bases by very simple catalysts with mild acid–base pairs. This results in enhanced selectivities with still very reasonable activities. This concept of acid–base pairs and its cooperative action in some base catalyzed reaction merits further considerations.

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