Synthesis of new dialkylaminopyridine acylation catalysts and their attachment to insoluble polymer supports

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Dialkylaminopyridines whose *N*-substituents bear a hydroxyl or amino group can be made economically from 4-cyanopyridine. Simple but selective alkylation of these compounds with commercial (chloromethyl) or (3-bromopropyl) polystyrene gives several new solid-phase catalysts which are highly active in promoting the acylation of hindered alcohols. Comparison of syntheses and reactivities, among these and some other heterocyclic polymers, illustrates several useful general principles of reactive polymer chemistry such as local concentration and microenvironment effects.

(Keywords: polymer-bound catalyst; DMAP; dialkylaminopyridine; synthesis; microenvironment effect)

INTRODUCTION

Though simple acylation reactions with acid chloride or anhydride and pyridine have been known since the turn of the century[1], their remarkable catalysis by 4-(*N*,*N*-dimethylamino)pyridine (DMAP) only came to notice approximately fifteen years ago[2]. Since then, a number of other catalytically active dialkylaminopyridines have been developed[3,4], and these reagents have taken their place on the shelves of chemists for a variety of applications from the laboratory bench to the production reactor.

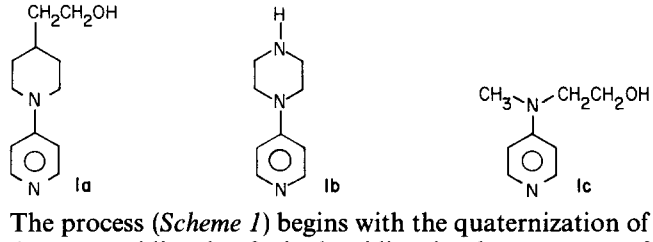
'DMAP' and related compounds have been shown to be effective in catalysing many reactions[3-6], including various acylations, alkylations, silylations, and condensations. In some, such as the acetylation of certain hindered alcohols or amines used in pharmaceutical formulations, it is particularly necessary to ensure that all traces of the catalyst be removed from the product mixture after the reaction. This requirement, and the general advantage of being able to recover and recycle a relatively costly chemical, warrant the development of solid-phase versions of known acylation catalysts; that is, insoluble polymer matrices[7] to which are attached functional groups similar to 4-(*N*,*N*-dimethylamino)pyridine 4-(1-pyrrolidino)pyridine, 4-(1-piperidinopyridine, and others which are reported active in the chemical literature[3,4,8].

Tomoi and coworkers[9] have previously incorporated 4-(*N*-benzyl-*N*-methylamino)pyridine moieties into cross-linked polystyrene beads by reacting the sodium salt of 4-(*N*-methylamino)pyridine with (chloromethyl)styrene using the resulting monomer in suspension copolyperizations. More recently similar structures have been reported in elegant work by Challa *et al.*[9b] Tomoi's method was also used by Menger and McCann[10] who similarly modified linear (chloromethyl)polystyrene to give a soluble but easily precipitable reagent. Reaction of the same anion with the less common (bromopropyl)-[11] and longer (haloalkyl)-[12] polystyrenes gave somewhat more reactive and stable catalysts. Jacquier *et al.* have linked 4(-*N*-piperidino)pyridine moieties to polystyrene through amide bonds[13], but these risk cleavage during reaction or regeneration of the polymer catalyst. Finally, other polymers incorporating interesting dialkylaminopyridine structures have recently been made[14,15], but these lack the attractive physical and/or chemical properties of reticulated polystyrene beads.

The present study examines the syntheses and acylating abilities of several other novel, readily-attainable polymers containing heterocycles, in order to discover and optimize factors which afford effective functional polymers in general, and an efficient solid-phase acylation catalyst in particular.

RESULTS AND DISCUSSION

Several methods have been described for the general preparation of 4-(*N*,*N*-dialkylamino)pyridines, such as the silylation–amination of 4-hydroxyheterocycles developed by chemists at Shering AG[16,17] and improved upon by the same group[18]. Another route which begins with the more available 4-cyanopyridine has been employed by Reilly Tar and Chemical Co. for the industrial preparation of DMAP[4,19]. We began by applying the latter technique towards the synthesis of other structures **1a–c** containing both a catalytic site and a reactive group which could be attached to (chloromethyl)polystyrene or another preformed reactive polymer support.



1a **1b** **1c**

The process (*Scheme 1*) begins with the quaternization of 4-cyanopyridine by 2-vinylpyridine in the presence of HCl to afford **2** by a Michael-type reaction[20].

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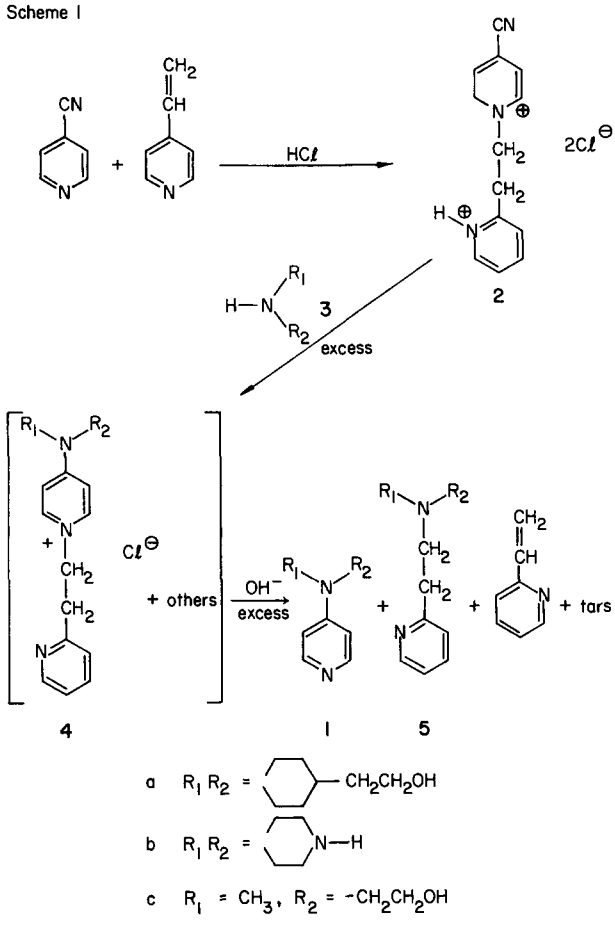
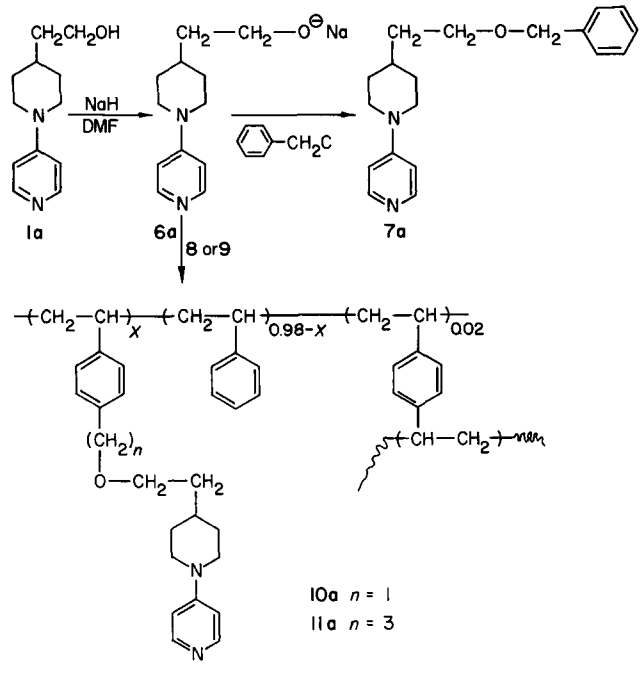
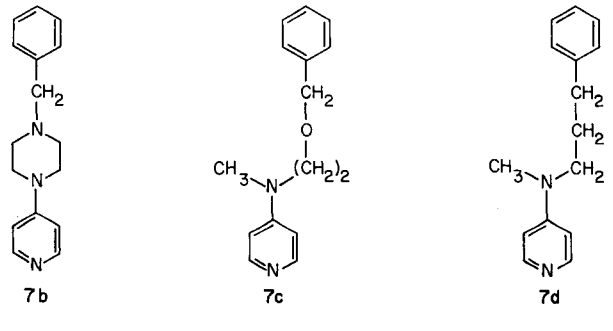
Scheme 1



Scheme 2



The next step is the nucleophilic aromatic substitution of the cyano group on activated **2** with excess secondary amine **3** to produce **4**, which is finally dequaternized by Hofmann elimination in strong aqueous base to give mainly aminopyridine **1** and regenerated 2-vinylpyridine. Though satisfactory, this process was accompanied by others: for example, nucleophilic attacks of amine **3** onto the beta alkyl carbons of either activated starting material **2**, intermediate **4**, and/or byproduct 2-vinylpyridine, all gave a low-boiling (dialkylaminoethyl)pyridine side-product **5**. However, product **1** is only lost in the first of these side-reactions which also regenerates 4-cyanopyridine. This undesirable reversal, which is detectable by n.m.r. of the crude product mixture, could be minimized by addition of **2** to an excess of **3**. In contrast, little could be done to prevent the observed formation of small amounts of coloured tars: these invariably arise through ring-opening and polymerization of quaternary pyridinium salts upon treatment with strong amine or hydroxide bases[21]. The various aminopyridines **1a–c** were isolated by vacuum distillation in yields of 50–60%; all were solids which could be recrystallized from acetone and ethyl acetate.



A single series of model catalysts **7a–d** was synthesized and examined to see how proximal differences in alkyl substituents affect intrinsic catalytic activity of the aminopyridine moiety. **7a–c** were made by the benzylation of the anions of **1a–c** (*Scheme 2*). We had previously made **7d** by a different route[11b] to demonstrate that unlike the *n*-benzyl-*N*-methylaminopyridine moieties used by Tomoi *et al.*, longer *N*-alkyl-*N*-methylaminopyridines are essentially as active as DMAP itself in promoting the acetylation of hindered alcohols (see **7d** in *Table 1*). Others[4] observed a slight deactivation with respect to DMAP when dimethylamino is replaced by piperidino or 4-alkylpiperidino groups, and a much greater deactivation if morpholino is used as ring substituent. They correlated catalyst activity with the ability of substituent nitrogen to donate electrons to the aromatic nucleus, as determined by steric and electronic effects, and as approximately indicated by the chemical shift of the β-pyridine hydrogen in the n.m.r. spectrum of the substituted pyridine nucleus[8,11b,22].

In all cases the test reaction chosen was a standard[4,22] acetylation of 1-methyl-cyclohexanol using 5 mol% of the catalyst in toluene at 60°C and in the presence of excess triethylamine. As all the reactions are done in the presence of triethylamine, itself a stronger base than any

Table 1 Acetylation of 1-methylcyclohexanol: catalytic activity of model compounds[a]

Catalyst	δ[b] (ppm)	Activity relative to DMAP[c] (%) 2h	6h
7a	6.60	83	95
7b	6.60	52	68
7c	6.45	87	98
7d	6.38	93	100

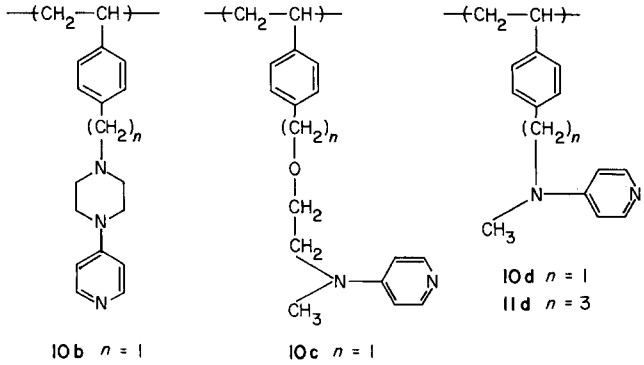
[a] Reaction at 60°C, 0.9 M solution of 1-methylcyclohexanol in toluene with 5 mol% catalyst
[b] Proton n.m.r. of pyridine β-hydrogen
[c] 4-Dimethylaminopyridine (DMAP) taken as reference (100%); with DMAP the yield of ester is 60% after 2 h and 82% after 6 h

of the dialkylaminopyridine catalysts, it is not appropriate to speculate on any simple pKa–activity relationships. General base catalysis may play a role in the operation of the catalysts but it is likely that it is their nucleophilic properties which are of prime importance.

It is interesting to note the relative lack of activity of model **7b** when compared to DMAP or even our other model compounds (*Table 1*). As is the case with its 4-morpholino analogue[4], model **7b** also contains a polar heteroatom gamma to side-chain nitrogen. This additional heteroatom is probably directly responsible for the deactivation of the neighbouring dialkylaminopyridine catalytic site as follows: Protonation of the strongly basic trialkylamine group of **7b**, even in the presence of an exogenous acid acceptor such as triethylamine, may decrease the catalyst's affinity for the acyl group and therefore reduce its performance. Alternately, the presence of such polar moieties within the polymer will likely contribute to an accumulation of both acetic anhydride and acetic acid (or acetate ion) in the immediate vicinity of the catalytic sites. Of particular concern is the concentration of a reaction product near the site of reaction as it would undoubtedly affect the equilibrium leading to the acylpyridinium intermediate and would result in deactivation through product inhibition.

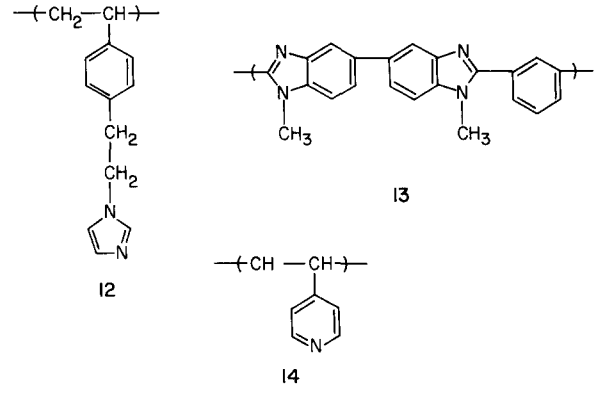
Reduced activity due to product inhibition of the type just described may help explain the reported[4] low activity of 4-morpholino-pyridine. Consideration of the results reported in the literature[4] as well as those given in *Table 1* show that deactivation is lessened if the non-carbon atom is further removed from the catalytic site (**7a**), or even if, still only three atoms distant as in **7c**, it is not held in a (presumably) coordinating position by being part of a six-membered ring (**7c**). Nevertheless, the influence of oxygen is not then entirely undetectable, when compared with an all-carbon analogue in the same reaction (**7d**). It also seems confirmed here that acyclic substituents (**7c** and **7d**) are superior to cyclic ones (**7a**, **7d** and 4-morpholino-pyridine), and that n.m.r. has indeed some value for predicting good catalysis.

Polymer-supported dialkylaminopyridines **10a–c** and **11a–c** were obtained by chemical modification of (chloromethyl)polystyrene **8** or (bromopropyl)-polystyrene **9**, respectively. *Scheme 2* shows a typical reaction sequence used for this modification, in which coupling to polymer was achieved with the pre-formed anion **6a** at room temperature in dimethylformamide (DMF).



10b $n = 1$ **11b** $n = 3$ **10c** $n = 1$ **11c** $n = 3$ **10d** $n = 1$ **11d** $n = 3$

Conversion was quantified by elemental analysis of the product resin, while i.r. spectroscopy was used to verify the absence of impurities arising either from alkylation of pyridine ring nitrogen (giving pyridone absorbing at 1635–1650 cm^{-1})[11] and/or elimination of polymer halogen (from **9** only; giving alkene at 1629 cm^{-1}). These side-reactions were often observed at higher temperatures, under phase-transfer conditions, or in tetrahydrofuran solvent but do not occur in DMF under our experimental conditions. As seen in *Table 2*, excellent functional yields were obtained upon coupling of **1a** and **1c** to polymer **8**, or **1b** to polymer **9**; however, overalkylation by benzylic chloride of ligand nitrogen could not entirely be avoided in the first support (giving some ionic halide in **10b**), nor elimination by alkoxide of primary bromide (the sole reaction in analogous polymers with two-carbon spacers)[23] in the second (giving some C=C in **11a** and **11c**).



12 **13** **14**

These polymers were assayed for catalytic activity under the same conditions as **7a–d** and the results are reported in *Table 3*. (*N*-methyl-*N*-4-pyridinomethyl)-polystyrene **10d**, (*N*-methyl-*N*-4-pyridinopropyl)-polystyrene **11d**, (*N*-imidazoethyl)polystyrene **12**, poly(*N*-methylbenzimidazole) **13** and poly(4-vinyl-pyridine) **14** were included for comparison. Results (*Table 3*) show that reactivities of polymers **10a–d** and **11a–d** follow the same order as for the miniature molecules. Heterocyclic polymers **12–14**, lacking the dialkylamino-pyridine functionality, were relatively inept under these conditions. Amongst polymeric catalysts directly derived from commercial (chloromethyl)polystyrene, **10a** and especially **10c** proved significantly superior to the previously known **10d**, while **10b**, besides presenting problems in its synthesis (see above), was rather worse. Extending the alkyl chain between catalytic site and polymer backbone (**11a–c**) gave detectable improvements in performances of the ether-bound moieties (**11a–11c**), probably by increasing hydrophobicity of the local microenvironment as well as by a general spacer effect[23]; these small improvements are overwhelmed by the adverse electronic effects of trialkyl nitrogen in **11b**.

As noticed in previous studies[9,11,13], polymer-bound versions of otherwise similar acylation catalysts were somewhat less active than the miniature models. This can be partly attributed to steric hindrance, by the polymer, of various steps in the catalytic cycle, but also to the development of high local concentrations of catalyst within the matrix at even moderate degrees of functionalization. In contrast, the corresponding soluble miniature models are evenly dispersed through an entire volume of solvent; since DMAP-like molecules function best in apolar media, but are themselves polar, then the

Table 2 Preparation of polymer-bound catalysts **10a–c** and **11a–c**

Initial structure	Initial *DF*	Reagent	Final structure	Final *DF*	Capacity (mmole/g)	Functional yield (%)
8	0.16	**1a**	**10a**	0.15	1.05	94
8	0.16	**1b**	**10b**	0.12	0.93	75
8	0.16	**1c**	**10c**	0.15	1.12	94
9	0.16	**1a**	**11a**	0.11	0.79	69
9	0.16	**1b**	**11b**	0.14	0.99	88
9	0.16	**1c**	**11c**	0.11	0.80	69

Table 3 Acetylation[a] of 1-methylcyclohexanol: catalytic activity of polymers

Catalyst structure	Capacity (mmole/g)	*DF*	Activity relative to DMAP %		Activity relative to benzylated model[b]	
			2 h	6 h	2 h	6 h
10a	1.05	0.15	64	83	77	87
11a	0.79	0.11	73	90	88	95
10b	0.93	0.12	35	61	68	85
11b	0.99	0.14	38	60	74	83
10c	1.12	0.15	76	90	87	92
11c	0.80	0.11	85	96	98	98
10d	1.34	0.16	60	79	95	95
11d	1.23	0.16	87	98	94	98
11d	3.82	0.96	65	77	70	77
12	1.84	0.29	4	8	–	–
13	5.4	1.00	2	3	–	–
14	>9	0.98	1	2	–	–

[a] Reaction at 60°C, 0.9 M solution of 1-methylcyclohexanol in toluene with 5 mol% catalyst or catalytic moieties on polymer support
[b] Models for **10d** and **11d** were *N*-methyl-N-benzylaminopyridine and *N*-methyl-*N*-phenylpropylaminopyridine, respectively. See ref. 11b for their preparation

catalyst is self-inhibitory and displays negative cooperativity which is greatest in a polymer environment[11]. This principle is most strongly demonstrated in **10b** and **11b**, which contain the most polar moieties (piperazinylpyridine), and hence are least active even with respect to their model **7b**; the ether linkage, on the contrary, seems sufficiently inert to sometimes allow achievement of nearly maximum intrinsic potential (e.g. compare **11c** and **11d**). Additional confirmation of a strong microenvironment effect is provided by experiments involving a polymer with structure **11d** in which essentially all repeating units carry the dialkylaminopyridine functionality. *Table 3* shows that this highly functionalized polymer is much less reactive than a similar catalyst in which approximately 80% styrene had been incorporated. While obviously more polar, the highly loaded catalyst is also very susceptible to product inhibition as the reaction's secondary products (acetic acid and acetate ion) might well concentrate within the polymer rather than in the external toluene reaction medium.

Though none of the solid-phase catalysts described herein exceed, mole for mole, DMAP in acylation potency, several approach it; among these, **10c** in particular is extremely attractive due the ease with which it can be obtained by a simple alkylation with commercially available (chloromethyl)polystyrene.

EXPERIMENTAL

General

All the chemicals were used as purchased (Aldrich) except monomers which were distilled. (Chloromethyl)polystyrene was prepared by chemical modification of Bio-beads SX-1 (Bio-Rad Laboratories) as described previously[7,25]. Polymer **9** was prepared by free radical suspension copolymerization of 4-(3-bromopropyl)styrene[26] with styrene and divinylbenzene in a Buchi BEP 280 autoclave[11]. 4-(2-Hydroxyethyl)piperidine was a gift of Reilly Tar and Chemical Company.

Infra-red spectra were measured on a Nicolet 10-DX FT-IR spectrometer, n.m.r. spectra were recorded in $CDCl_3$ + TMS using Varian EM 360, CFT-80 or XL-300 spectrometers while mass spectra were obtained on a VG-7070E double focusing mass spectrometer usng chemical ionization where appropriate.

Preparation of 4-dialkylaminopyridine (**1**) *(Typical procedure)*

4-(4-(2-Hydroxyethyl)piperidino)pyridine **1a**. 4-cyanopyridine (20.8 g, 0.2 mol) was dissolved in aqueous 25% HCl (50 ml) and 2-vinylpyridine (21 g, 0.2 mol) was added dropwise while stirring. The mixture was then stirred at 60°C for 6 h. After cooling, it was poured into an aqueous solution (400 ml) of 4-(2-hydroxyethyl)piperidine (64.5 g, 0.5 mol), and allowed to stir 2–12 h at room temperature. The mixture turned black during the addition. A 40% NaOH solution (500 g) was then added, causing separation of an organic phase, and the mixture was then refluxed for 2 h. After cooling, the organic phase was decanted and the aqueous phase extracted twice with chloroform. After evaporation of the combined organic fractions, distillation under vacuum afforded first a side-product of spectral characteristics consistent with the structure **5a**. The desired compound followed, and was obtained in a 56% yield (23 g): boiling point (bp) 180°C–182°C (0.2 mm Hg); melting point (mp) 120°C–121°C.

^1H n.m.r. 1.16 (m,2H), 1.48–1.86 (m,6H), 2.82 (t,2H), 3.68–3.88 (m,4H), 6.62 and 8.20 (2d,4H,pyridyl); i.r.

(K Br) 3177 (OH^-); MS: m/e 206 (M^+), 205; analysis calculated for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.79; N, 13.58; found: C, 70.06; H, 9.07; N, 13.67.

4-(Piperazino)pyridine (**1b**)[27]. Yield 55%; bp 195°C–197°C (17 mm Hg); mp 135°C–136°C; ^1H n.m.r. 1.70 (s,1H), 2.70–3.30 (m,8H), 6.55 and 8.15 (2d,4H, pyridyl); i.r. (KBr pellet) 3249 (N–H); MS m/e 163 (M^+), 121.

4-(N-Methyl-N-(2-hydroxyethyl)amino)pyridine (**1c**). Yield 53%; bp 154°C–156°C (0.2 mm Hg); mp 84°C–85°C); ^1H n.m.r. 2.95 (s,3H), 3.45 (t,2H), 3.75 (t,2H), 4.25 (broad,OH), 6.32 and 8.02 (2d,4H,pyridyl); i.r. (KBr) 3166 (OH–); MS m/e 152 (M^+), 121. Analysis calculated for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41; found: C, 63.21; H, 8.04; N, 18.54.

Preparation of miniature analogues (typical procedure[11b,9]

4-(4-(2-Benzyloxyethyl)piperidino)pyridine (**7a**). A solution of (5.2 g, 25 mmol) 4-(4-(2-hydroxyethyl)piperidino)pyridine (**1a**) in dry DMF (50 ml) was treated with sodium hydride (0.66 g, 28 mmol). The mixture then received, by dropwise addition, a solution of benzyl chloride (3 ml, 26 mmol) in DMF (10 ml). After standing overnight, the precipitate was filtered and the filtrate evaporated. The residue as taken up in dichloromethane and the organic solution washed with water, then dried over $MgSO_4$. After evaporation, a first vacuum distillation afforded crude **7a** (contaminated with starting **1a**) in a 77% yield; bp 190°C (0.05 mm Hg). This material was further purified by liquid chromatography on silica gel (methanol: ethyl acetate = 1:1): yield 45%.

^1H n.m.r. 1.23 (m,2H), 1.48–1.88 (m,5H), 2.80 (t,2H), 3.50–3.82 (m,4H), 4.47 (s,2H), 6.60 and 8.19 (2d,4H,pyridyl), 7.12–7.38 (m,5H,phenyl); MS m/e 296 (M^+), 205; analysis calculated for $C_{19}H_{24}N_2O$: C, 76.99; H, 8.16; N, 9.45; found: C, 76.55; H, 8.44; N, 9.43.

4-(4-(Benzyl)piperazino)pyridine **7b**[28]. Yield after recrystallization (ether) 48%; bp 182°C (0.1 mm Hg); mp 87°C–88°C; ^1H n.m.r. 2.54 (t,4H), 3.30 (t,4H), 3.63 (s,2H), 6.60 and 8.22 (2d,4H,pyridyl), 7.20–7.38 (m,5H,phenyl); MS m/e 253 (M^+), 91.

4-(N-Methyl-N-(2-benzyloxyethyl)amino)pyridine **7c**. Yield 36%; bp 183°C–185°C (0.2 mm Hg). ^1H n.m.r. 2.97 (s,3H), 3.54 (t,2H), 3,.60 (t,2H), 4.47 (s,2H), 6.45 and 8.15 (2d,4H,pyridyl), 7.15–7.28 (m,5H,phenyl). MS m/e 242 (M^+), 121. analysis calculated for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56; found: C, 74.57; H, 7.60; N, 11.47.

Polymer-bound dialkylaminopyridines (**10a–c,11a–c**). The general procedure used for the chemical modification of **8** or **9** was similar to that described for the miniature analogues. However, a two-fold excess of the modifying agent was required and the reaction allowed proceed for 4 days. The product polymers were filtered and washed repeatedly with organic and aqueous solvents to remove all soluble contaminants. After drying, nitrogen analysis indicated the capacity of the polymer-bound catalysts (*Table 3*).

(N-Imidazoethyl)polystyrene (**12**). This had been prepared according to a procedure previously described[23]. Analysis calculated ($DF = 0.29$) N, 6.17; found, N, 5.87 (functional yield 95%).

Poly(N-methylbenzimidazole) (**13**). The catalyst was prepared by alkylation of polybenzimidazole (PBI)[24] with iodomethane. PBI (2.5 g, 0.01 mol) was suspended in a mixture of ground KOH (2.8 g, 0.05 mol) in dry acetone (40 ml). Iodomethane (1.25 ml, 0.02 mol) was then added dropwise and the suspension allowed to stir for 4 days. The polymer was then filtered, washed with water until the filtrate was neutral, then dried under vacuum overnight. Analysis calculated ($DF = 1$): N, 16.64; found: N, 15.31.

Evaluation of the catalysts

General procedure. A mixture of 1-methylcyclohexanol (2 ml, 16.2 mmol), dialkylaminopyridine (0.81 mmol, 5 mole%) and triethylamine (3 ml, 21.6 mmol), in toluene to total 20 ml solution, was placed in a thermostatically controlled cell at the desired reaction temperature (60°C). After stirring under nitrogen for 15 min, acetic anhydride (3 ml, 31.6 mmol) was added while stirring continued. Progress of the reaction was monitored by timely withdrawal of 10 μl aliquots for chromatographic analysis (10% SE-30 on Chromosorb G).

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