Catalytic phosphorylation using a bifunctional imidazole derived nucleophilic catalyst†

Simon Jones,*[a] Julian Northen[b] and Alan Rolfe[a]

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A bifunctional catalyst containing a polyether backbone and a nucleophilic imidazole moiety has been prepared that demonstrates cooperative catalysis in the presence of added group 1 and 2 salts for the phosphorylation of alcohols.

The use of nucleophilic catalysts has grown enormously since the origins of this work over seven decades ago.[1] In the last five years significant progress has been made directed towards the design, synthesis and applicability of many chiral nucleophilic catalysts that can achieve high levels of stereoselectivity in a host of synthetic transformations.[2] By far the most intensely studied has been the use of such catalysts in the kinetic resolution of racemic alcohols through acylation and considerable success has been enjoyed by groups using a diverse range of catalyst systems.[3] In the early development of some of these catalyst systems, the main problem lay in the functionalization of the nucleophilic catalyst moiety while at the same time *maintaining the same or increased rates of catalysis*. Reports on the enantioselective acylation of racemic alcohols by Vedejs illustrate this issue whereby the catalytic activity of chiral 2-substituted pyridines was suppressed by the additional steric congestion.[4] More recent work by Miller has elegantly demonstrated the use of small peptides containing histidine residues as nucleophilic catalysts for acylation and phosphoryl transfer.[5] Here the conformation and binding properties of the peptide allow dramatic rate acceleration, in addition to affording excellent levels of stereoselectivity. However, one drawback is the synthetic complexity and high molecular weight of the catalyst. Thus, an attractive nucleophilic catalyst would be a simpler system that allows conformational control of the active catalyst, facilitating the incorporation of sites suitable for further functionalization, but at the same time maintaining a good rate of catalysis.

Our specific interest in catalytic systems that can affect phosphoryl transfer led to the development of bifunctional polyether catalyst **1**. Bifunctional catalysts have enjoyed considerable success in recent years since reactivity may be modulated using the properties of both active sites.[6] It was postulated that this catalyst would maintain catalytic activity by coordination of the polyether side-chain to an added cation, providing extra stabilization of the intermediate **2** that would offset the extra steric requirements imposed by addition of the polyether in the 2-position. Additionally it was hoped that this target would adopt a defined conformation such that the later introduction of stereodirecting groups in the appropriate position would result in asymmetric induction in an analogous fashion to Miller's peptides (Fig. 1).

The synthesis of catalyst **1** was easily accomplished by reaction of the bromo polyether with the sodium alkoxide of (1-methylimidazol-2-yl)methanol **3**[7] giving the target polyether **1** in reasonable overall yield (Scheme 1). For comparison purposes, the hydrocarbon analogue **4** was also prepared by reaction of the same alcohol **3** with the tosylate of n-heptanol.

Catalysts **1** and **4** were then evaluated in the phosphorylation of cyclohexanol using 1 eq. of $(PhO)_2P(O)Cl$ and 1 eq. Et_3N in the presence of added inorganic salts (Table 1). $NaPF_6$ and KPF_6 were chosen for their chemical inertness, since a wide range of Lewis acids can catalyze this reaction.[8] Initial studies were performed at room temperature, and the rate of background reaction without

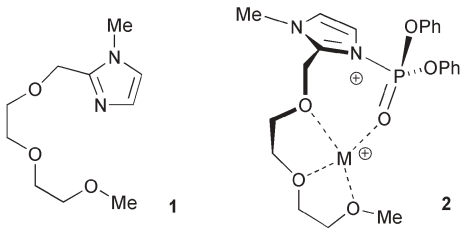
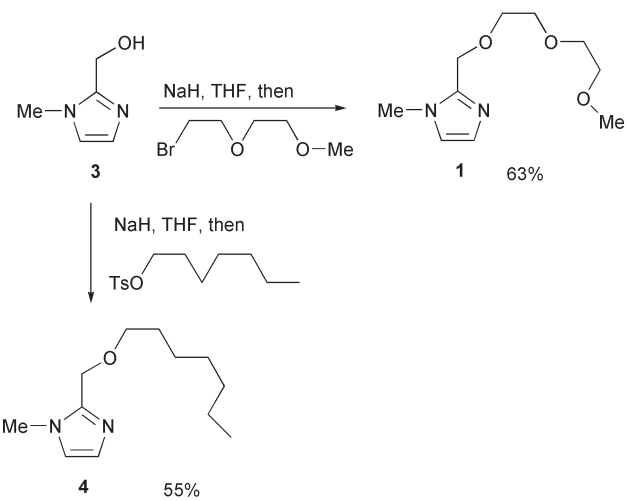


Fig. 1 Polyether catalyst **1** and postulated intermediate **2**.



Scheme 1 Preparation of catalysts **1** and **4**.

[a]*Department of Chemistry, Dainton Building, University of Sheffield, Brook Hill, Sheffield, UK. E-mail: simon.jones@sheffield.ac.uk; Fax: +44 (0)114 222 93463; Tel: +44 (0)114 222 9483*
[b]*Onyx Scientific, Units 97/98, Silverbriar, Sunderland Enterprise Park East, Sunderland, UK*

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Table 1 Effect of added inorganic salts on the phosphorylation of cyclohexanol with and without catalyst **1** and **4**

Entry	Conditions[a]	Catalyst (0.1 eq.)	Additive (0.1 eq.)	Product (%)[b]
1	A	None	None	9
2	A	NMI	None	99
3	A	**1**	None	69
4	A	None	$NaPF_6$	12
5	A	**1**	$NaPF_6$	68
6	A	None	KPF_6	9
7	A	**1**	KPF_6	85
8	B	NMI	None	79
9	B	NMI	KPF_6	76
10	B	**1**	None	35
11	B	**1**	KPF_6	57
12	B	**4**	None	14
13	B	**4**	KPF_6	14

[a] Conditions: **A** Reactions performed for 30 min at 30 °C; **B** Reactions performed for 15 min at −10 °C. [b] Calculated from the ratios of the integrals of starting material and product in the ^{1}H NMR spectrum of the crude reaction mixture.

catalyst, with or without added inorganic salts, was essentially the same (entries 1, 4 and 6). This confirmed the original hypothesis that $NaPF_6$ and KPF_6 were not acting as Lewis acids. Reaction with catalyst **1** without other additives gave a small drop in reactivity compared to *N*-methylimidazole (NMI, entries 2 and 3), which is in-line with the hypothesis that additional steric bulk of the polyether adjacent to the nucleophilic centre slows the rate of reaction. While use of catalyst **1** with $NaPF_6$ (entry 5) showed no increase in rate, addition of KPF_6 (entry 7) led to a significant increase in the amount of product formed inferring a cooperative effect from both nucleophilic catalyst and the added KPF_6. Simple kinetic studies more clearly illustrated this data (Fig. 2) and tentative first order rate constants were calculated for these catalysts. The steric requirements imposed by the polyether chain when the catalyst **1** is used by itself leads to a 3.8 fold decrease in rate compared to that of the parent *N*-methylimidazole. However, the cooperative effect of both catalyst **1** and KPF_6 leads to a 2.6 fold increase in reaction rate. Notably, the un-catalyzed reaction with and without KPF_6 gave essentially identical results over the period of the study.

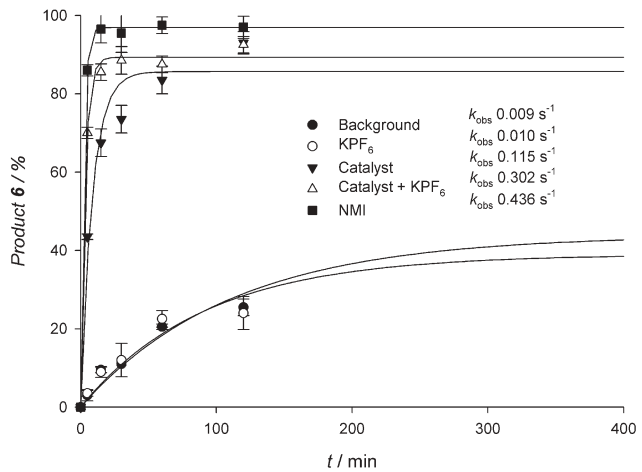
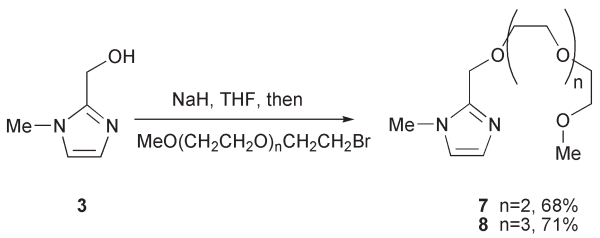


Fig. 2 Kinetic studies of phosphorylation of cyclohexanol in the presence of catalyst **1** with and without added KPF_6 according to Table 1, conditions **A**.

Further control reactions were conducted at −10 °C in order to slow the reaction rate with *N*-methyl imidazole thus allowing genuine increases and decreases in conversion to be observed. No increase in reaction rate was observed when KPF_6 was added to a solution containing *N*-methylimidazole indicating that KPF_6 does not enhance the reactivity of this nucleophilic catalyst (Table 1, entries 8 and 9). However, in reactions performed with catalyst **1**, complete solubilisation of the KPF_6 was observed which was not the case when using *N*-methylimidazole. Concerned by the fact that the polyether side-chain was simply solubilising the KPF_6, the reaction was performed in the presence of *N*-methylimidazole, KPF_6 and either 18-crown-6 or 1-methoxy-2-[2-(2-methoxy-ethoxy)-ethoxy]-ethane. In each case the solubility of the KPF_6 in CH_2Cl_2 was enhanced as observed in reactions with the catalyst **1**. However, no rate acceleration was observed in any of these experiments ruling out the possibility of catalyst **1** simply acting as a solubilizing agent for the KPF_6. Finally, the hydrocarbon catalyst **4** was evaluated giving a surprisingly poor conversion to product on its own which was not enhanced by addition of KPF_6 (entries 12 and 13). These combined facts provided good evidence to support the hypothesis of catalyst **1** acting in a bifunctional manner.

If the catalyst was indeed operating in a co-operative manner, there would presumably be an optimum cation/polyether combination. Thus, catalysts **7** and **8** where prepared employing similar methodology to that in the synthesis of the original catalyst **1** (Scheme 2).

The three polyether homologues were evaluated against a small number of additives in the phosphorylation of 1-phenylethanol (Table 2).‡ The results showed that as before no rate enhancement was observed when the additive was present without catalyst and all catalysts **1**, **7** and **8** showed a substantial drop in reactivity compared to the parent NMI. However, in the presence of the additives significant increases in the reaction rate were observed in



Scheme 2 Preparation of catalysts **7** and **8**.

Table 2 Effect of polyether chain length *vs.* metal salt on the phosphorylation of 1-phenyl ethanol **9**[a,b]

	Additive				
Catalyst	None	KPF_6	$Mg(OTf)_2$	$Cu(OTf)_2$	$La(OTf)_3$
None	0	0	0	0	0
1	33	42	50	23	56
7	43	47	64	22	62
8	40	49	70	16	60
NMI	95	NA	NA	NA	NA

[a] All reactions were performed on a 1.18 mmol scale in CH_2Cl_2 (4 cm^3) at −10 °C for 15 min, followed by aqueous workup. [b] Conversion calculated from the ratios of the integrals of starting material and product in the ^{1}H NMR spectrum of the crude reaction mixture.

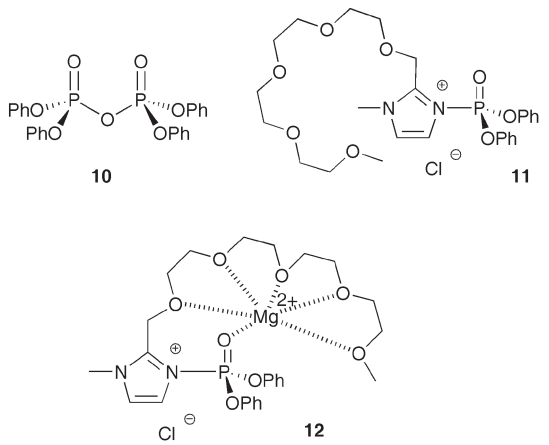


Fig. 3 Intermediates observed in the ^{31}P NMR spectrum.

all cases except $Cu(OTf)_2$, the best combination being with the longest chain polyether **8** in combination with $Mg(OTf)_2$.

Further evidence for the intermediacy of a coordinated intermediate was provided from ^{31}P NMR data. An equimolar ratio of catalyst **8** and $(PhO)_2P(O)Cl$ gave three signals at δ −25.27 ppm, −11.78 ppm and −4.89 ppm corresponding to the pyrophosphate **10**, the imidazolium phosphate **11**[9] and diphenylchlorophosphate, respectively (Fig. 3). The presence of the pyrophosphate comes from the partial hydrolysis of the chlorophosphate by advantageous water followed by reaction of the diphenylphosphate with more chlorophosphate and is a common phenomenon in these systems.[10] Upon addition of $Mg(OTf)_2$, the signal at −11.78 ppm completely disappeared and a new signal at −16.32 ppm appeared which was assigned as the co-ordinated catalyst **12**. Addition of $MgBr_2$, $MgCl_2$ or $Mg(ClO_4)_2$ all led to a reduction in the signal at −11.78 ppm and appearance of the same signal, ruling out the possibility of counter-ion exchange effects. Furthermore there is a good correlation between the level of cooperative rate enhancement and the stability of the species corresponding to this signal. For example, in the case of catalyst **1** and KPF_6, only a small rate enhancement was observed (see Table 2), and consequently no additional signal was seen in the ^{31}P NMR spectrum.

In conclusion, we have developed a nucleophilic catalyst based upon a polyether imidazole where the reduction in rate imposed by the additional steric bulk of a polyether side-chain may be overcome to some degree by addition of $Mg(OTf)_2$. Although direct identification of the postulated intermediate **2** was not possible, compelling evidence infers such a species. Further work is in progress to conclusively identify any supramolecular reactive intermediates that are formed in this reaction and use this as a basis for the preparation of chiral bifunctional catalysts.

Notes and references

‡ 1-Phenylethanol was used in these studies instead of cyclohexanol to help develop analytical methods to determine enantiomeric excess at a later date. Similar trends were observed with cyclohexanol.

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