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Unexpected catalysis: aprotic pyridinium ions as active and recyclable Brønsted acid catalysts in protic media

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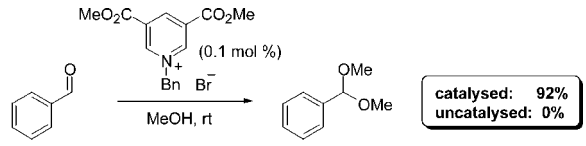
ABSTRACT

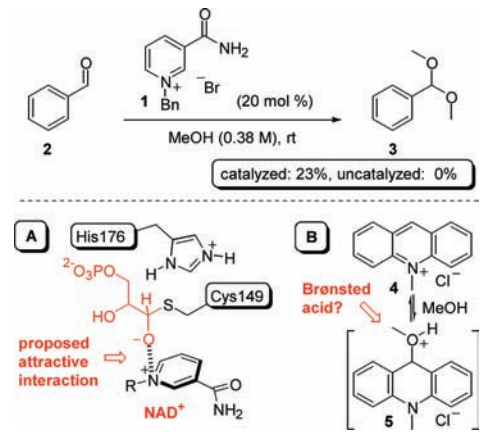


Simple pyridinium salt derivatives have been (rather unexpectedly) shown to promote highly efficient acetalization reactions of both aldehydes and ketones at ambient temperature. The optimum catalyst is aprotic, yet it can promote the formation of benzaldehyde dimethyl acetal at 0.1 mol % loading more efficiently than a protic Brønsted acid catalyst with a pK_a of 2.2. The process is of wide scope with respect to both the nucleophilic and electrophilic components, and the ionic catalyst can be readily recovered by precipitation and reused without loss of activity.

The controlled, enzyme-catalyzed interconversion of pyridinium ions to the corresponding dihydropyridine compounds (i.e., NAD^+ to NADH and vice versa) is a key transformation in all cellular life which underpins a multitude of biochemical processes.[1] In biological systems, the role of these species is primarily one of a stoichiometric cofactor that participates in a redox process as reduced by the substrate as required. We were therefore quite surprised to observe in the course of a research program focused on the design of artificial ketoreductase catalysts[2] that the simple nicotinamide-derived pyridinium ion **1** appeared to catalyze the conversion of benzaldehyde (**2**) to its dimethyl acetal **3** in methanolic solution in the absence of any discernible uncatalyzed process (Scheme 1).

While synthetic dihydropyridines have been used as catalysts in redox processes in conjunction with stoichiometric coreductants,[2,3] we are not aware of examples of the explicit use of soluble *N*-alkyl pyridinium ions in a truly catalytic capacity[4] save in electrochemical and photoinduced polymerization processes[5,6] which in all likelihood involve redox in situ. We were naturally intrigued at the highly unusual catalysis pathway (albeit inefficient) and were accordingly encouraged to investigate the phenomenon further. A literature survey identified two possible candidates

Scheme 1. Catalysis by a Pyridinium Ion: Initial Observation and Possible Modes of Action



* E-mail:

(1) Berg, J. M.; Tymoczko, J. L.; Stryer, L. *Biochemistry*, 5th ed.; Freeman: New York, 2002.
(2) Procuranti, B.; Connon, S. J. *Chem. Commun.* **2007**, 1421.
(3) Xu, H.-J.; Liu, Y.-C.; Fu, Y.; Wu, Y.-D. *Org. Lett.* **2006**, *8*, 3449.

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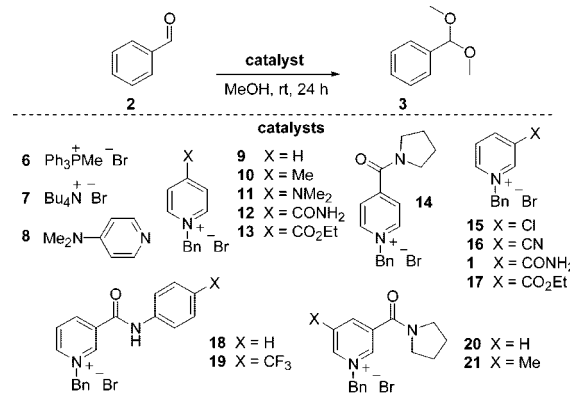
for the catalyst's mode of action, first based on X-ray diffraction data Park et al.[7] postulated that in the oxidation of glyceraldehyde catalyzed by glyceraldehyde-3-phosphate dehydrogenase (*E. coli*) an ionic attraction between the NAD^+ pyridinium nitrogen and the oxyanion derived from attack on the substrate by Cys149 was responsible for the stabilization of the tetrahedral intermediate (**A**, Scheme 1).[8] Thus, it is possible, if not entirely plausible outside the rigidly controlled environment of an enzyme active site, that such an interaction[9] could play a role in the acetalization process.[10]

The second candidate is an unprecedented variant of Brønsted acid catalysis. Kano[11] reported that the *N*-methylacridinium ion **4** underwent reversible conversion to the acridane adduct **5** in dilute methanol (**B**, Scheme 1). While neither this material nor its corresponding ammonium ion form[12] were isolated, the formation of (presumably acidic) **5** has subsequently been indirectly implied in recent unrelated studies concerned with rotaxane/calixarene design[13] and aldehyde oxidation.[14] While we could find no examples of this type of base-free alcoholysis of simple pyridinium ions in the literature,[15,16] were such an equilibrium present in methanolic solutions of **1** it could be catalytically relevant and worthy of investigation.

In order to better understand the origins of the observed catalysis we evaluated the influence of ionic compounds **6**−**21** (20 mol %) on the acetalization of benzaldehyde with methanol at ambient temperature (Table 1). In the absence of an additive no reaction was observed, while sodium chloride and simple alkyl ammonium/phosphonium salts failed to promote the condensation to a significant extent (entries 1−4). As expected, we observed no reaction in the presence of a tertiary amine base (entry 5) while *N*-benzylpyridinium bromide (**9**) and variants with electron-

Table 1. Initial Catalyst Screening



entry	catalyst	loading (mol %)	solvent	concn[a] (M)	yield[b] (%)
1	none		MeOH	0.38	0
2	NaCl	20	MeOH	0.38	4
3	**6**	20	MeOH	0.38	<2
4	**7**	20	MeOH	0.38	0
5	**8**	20	MeOH	0.38	0
6	**9**	20	MeOH	0.38	0
7	**10**	20	MeOH	0.38	0
8	**11**	20	MeOH	0.38	0
9	**12**	20	MeOH	0.38	>99
10	**13**	20	MeOH	0.38	>99
11	**14**	20	MeOH	0.38	30
12	**15**	20	MeOH	0.38	20
13	**16**	20	MeOH	0.38	47
14	**1**	20	MeOH	0.38	23
15	**17**	20	MeOH	0.38	>99
16	**18**	20	MeOH	0.38	22
17	**19**	20	MeOH	0.38	31
18	**20**	20	MeOH	0.38	>99
19	**21**	20	MeOH	0.38	>99
20	**12**	1	MeOH	0.38	10
21	**13**	1	MeOH	0.38	42
22	**17**	1	MeOH	0.38	91
23	**21**	1	MeOH	0.38	3
24	**17**	1	MeOH	1.0	91
25	**17**	1	MeOH	2.0	85
26	**17**	1	MeOH	6.0 equiv	77
27	**17**	1	MeOH	2.0 equiv	48
28	3-NO_2-BA[c]	1	MeOH	0.38	37
29	2-NO_2-BA[d]	1	MeOH	0.38	>99
30	2-NO_2-BA[d]	0.1	MeOH	0.38	80
31	**17** + DABCO[e]	20	MeOH	0.38	0

[a] Refers to the concentration of the aldehyde in the solvent. [b] Determined by ^1H NMR spectroscopy using styrene as an internal standard [c] 3-Nitrobenzoic acid. [d] 2-Nitrobenzoic acid. [e] DABCO = [2.2.2]bicyclooctane; both catalysts were employed at 20 mol % levels.

(4) Catalysts/ionic liquids which incorporate *N*-alkylpyridinium ions for which no specific catalytic role has been identified for the pyridinium ring other than as a polar/or electron-deficient group have been reported; for representative recent examples, see: (a) Maki, T.; Ishihara, K.; Yamamoto, H. *Org. Lett.* **2005**, *7*, 5043. (b) Rix, D.; Clavier, H.; Coutard, Y.; Gulajski, L.; Grela, K.; Mauduit, M. *J. Organomet. Chem.* **2006**, *691*, 5397. (c) Ni, B.; Zhang, Q.; Headley, A. D. *J. Org. Chem.* **2006**, *71*, 9857. (d) Zhang, L.; Luo, S.; Mi, X.; Liu, S.; Qiao, Y.; Xu, H.; Cheng, J. -P. *Org. Biomol. Chem.* **2008**, *6*, 567. (e) Ni, B.; Zhang, Q.; Headley, A. D. *Tetrahedron: Asymmetry* **2008**, *49*, 1249. (f) Kull, T.; Peters, R. *Angew. Chem., Int. Ed.* **2008**, *47*, 5461.

(5) For examples, see: (a) Elstner, E. F.; Fischer, H. P.; Osswald, W.; Kwiatkowski, G. *Z. Naturforsch.* **1980**, *35C*, 770. (b) Seshadri, G. *Electrochem. Soc. Interface* **1994**, *3*, 51. (c) Yagci, Y.; Endo, T. *Adv. Polym. Sci.* **1997**, *127*, 59.

(6) Pyridinium ionic liquid solvents have also recently been shown to facilitate photoinduced electron-transfer processes: Vieira, R. C.; Falvey, D. E *J. Am. Chem. Soc.* **2008**, *130*, 1552.

(7) Yun, M.; Park, C.-G.; Kim, J.-Y.; Park, H.-W. *Biochemistry* **2000**, *39*, 10702.

(8) It should be noted that this is not compatible with the more usual stablization of the oxyanion by hydrogen bonding in the "oxyanion hole" postulated as being key in several serine/cysteine proteases.

(9) The Kamlet−Taft parameters for several ionic liquids containing a pyridinium cation have recently been determined; see: Lee, J.-M.; Ruckes, S.; Prausnitz, J. M. *J. Phys. Chem. B* **2008**, *112*, 1473–1476.

(10) A catalysis mode involving hydrogen bonding mediated by the primary amide moiety was considered unlikely in methanolic solvent.

(11) (a) Kano, K.; Zhou, B.; Hashimoto, S. *Chem. Lett.* **1985**, 791. (b) Kano, K.; Zhou, B.; Hashimoto, S. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1633.

(12) After proton transfer from oxygen to nitrogen.

(13) (a) Grubert, L.; Abraham, W. *Tetrahedron* **2007**, *63*, 10778. (b) Abraham, W.; Buck, K.; Orda-Zgadzaj, M.; Schmidt-Schäffer, S.; Grummt, U.-W. *Chem. Commun.* **2007**, 3094.

(14) Lu, Y.; Endicott, D.; Kuester, W. *Tetrahedron Lett.* **2007**, *48*, 6356.

(15) Under alkaline conditions, it is known that *N*-alkylpyridinium ions derived from nicotinamide underwent addition of hydroxide at C-4: Dittmer, D. C.; Koyler, J. M. *J. Org. Chem.* **1963**, *28*, 2228.

(16) Similarly, under basic conditions, thiolates and enolates have been shown to reversibly add to pyridinium ions. For a review and a recent (noncatalytic) application of this reaction class, respectively, see: (a) Kellogg, R. M. *Angew. Chem., Int. Ed.* **1984**, *23*, 782. (b) Leleu, S.; Penhoat, M.; Bouet, A.; Dupas, G.; Papamicaël, C.; Marsais, F.; Levacher, V. *J. Am. Chem. Soc.* **2005**, *127*, 15668.

donating substituents at C-4 also proved ineffectual (i.e., **10** and **11**, entries 6−8).

Interestingly, analogues with electron withdrawing functionality in the same position (i.e., **12**−**13**) all proved highly active—furnishing acetal **3** in near-quantitative yields with the exception of the pyrrolidinamide **14** which was less efficacious yet still active (entries 9−11). Pyridinium ions **15**−**17** with electron-withdrawing substituents at C-3 also promoted the reaction, although only the ethyl ester-substituted material **17** efficiently so (entries 12−15).[17] It appears that hydrogen-bonding to the C-3 substituent does not play a significant role in catalysis − as can be surmized from the similar performance of amides **18** and **19** to that of the parent nicotinamide compound **1** (entries 14, 16, and 17). The C-3 substituted pyrrolidinamide **20** and its C-5 methylated analogue **21** were both catalytically competent (entries 18 and 19).

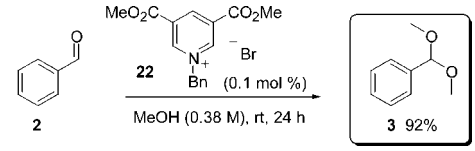
The materials which promoted the acetalization to completion were then re-evaluated at 1 mol% loading (entries 20−23). Under these more challenging conditions ester **17** could be clearly identified as the superior promoter of the reaction. It is also noteworthy that **13** is considerably more active than **12** (entries 20 and 21)—indicating that the ability of the C-3/C-4 substituent to activate the pyridinium ring by electron-withdrawal is the dominant factor influencing catalyst efficacy.

It was found that the effect of concentration on product yield was marginal and that moderate-good yields of **3** could be obtained with as little as 2−6 equiv of methanol (entries 24−27). In an attempt to put the performance of **17** in some context, we found that it proved a better catalyst for this process than 3-nitrobenzoic acid (pK_a H_2O, 25 °C = 3.46[18]) but was inferior the 2-nitro analogue (pK_a = 2.19,[18] entries 28−30). The complete inactivity of **17** (even at 20 mol % levels) in the presence of an equimolar amount of the amine base DABCO (entry 31) strongly suggests that these catalysts operate via proton donation.

Given the relationship between the electronic characteristics of the pyridinium ion and catalytic activity which emerges from an examination of Table 1, we postulated that an analogue of **17** possessing a second ester moiety would be of some promise. Synthesis and evaluation of the 3,5-diester **22** resulted in a highly active catalyst capable of promoting the formation of **3** in excellent yield at just 0.1 mol % levels (Scheme 2). We found it remarkable that **22**, *which does not possess any obvious Brønsted-acidic characteristics is capable of outperforming the quite acidic catalyst 2-nitrobenzoic acid in this reaction* (compare with entry 31, Table 1).[19]

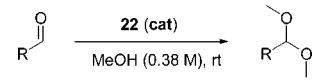
With an active and readily prepared catalyst in hand, our attention now turned to the question of substrate scope (Table 2). Catalyst **22** readily promoted the acetalization of a range of aromatic aldehydes efficiently under mild conditions using low catalyst loadings (entries 1−4). As expected, hindered

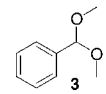
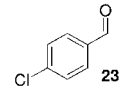
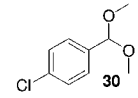
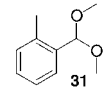
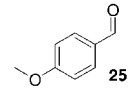
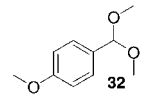
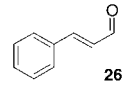
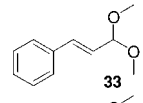
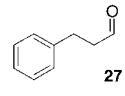
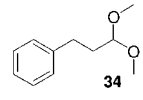
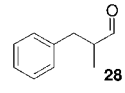
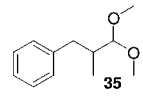
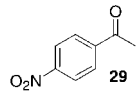
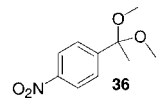
Scheme 2. An Improved Bis-ester-Substituted Catalyst



(i.e., **24**) and electron-rich (**25**) substrates provided more of a challenge than either **2** or **23**; however, high yields of isolated product were obtained in all cases without requiring recourse to high reaction temperatures. The catalyst was also compatible with an α,β-unsaturated aldehyde substrate, furnishing the protected cinnamaldehyde derivative **33** in excellent yield. Saturated aldehydes underwent particularly rapid catalyzed acetalization: the reaction between methanol and **27** was complete inside 1 min using 1 mol % catalyst, while the more hindered α-methyl analogue **28** required just 25 min for complete reaction.[20] Ketone **29** also underwent conversion to ketal **36** in the presence of **22** although at a considerably slower rate.

Table 2. Evaluation of Reaction Scope



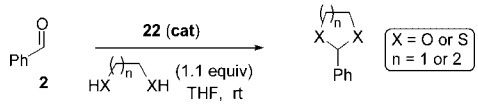
entry	substrate	product	*t* (h)	loading (mol %)	yield (%)[a]
1	 **2**	 **3**	24	1	92
2	 **23**	 **30**	24	1	99
3	 **24**	 **31**	24	5	92
4[b]	 **25**	 **32**	24	5	82
5	 **26**	 **33**	24	5	81
6	 **27**	 **34**	1 min	1	98[c]
7	 **28**	 **35**	25 min	1	97[c]
8[b]	 **29**	 **36**	48	10	52

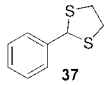
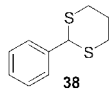
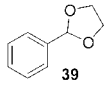
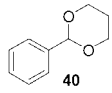
[a] Isolated yield. [b] At 35 °C. [c] Determined by ^{1}H NMR spectroscopy using an internal standard due to product decomposition on isolation.

(17) Significant decomposition of the nitrile **16** was observed.
(18) Jover, J.; Bosque, R.; Sales, J. *QSAR Comb. Sci.* **2008**, *27*, 563.
(19) A *N*-methylated analogue of **22** was found to be less active. Acetic acid proved a more useful (yet inferior to **22**) catalyst under these conditions than its pK_a would suggest (0.1 mol %, 89% yield).

The scope of catalyst **22** is not confined to methanolysis (Table 3). The protection of benzaldehyde as a dithiolane (a

Table 3. Dioxolane, Dioxane, Dithiolate, And Dithane Protection



entry	substrate	product	*t* (h)	loading (mol %)	yield (%)[a]
1			24	5	96
2			24	5	70
3			24	10	41
4[b]			40	5	88(91)

[a] Isolated yield. [b] Value in parentheses using 10 mol % of **22** for 24 h.

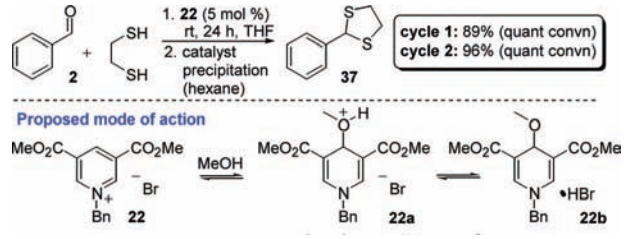
reaction which usually requires elevated temperatures) proceeded in the presence of **22**(5 mol%) under conditions which resulted in no reaction in its absence (entry 1). 1,3-Dithane and -dioxane protection is also possible (entries 2 and 4); however, acetalization with ethylene glycol furnished unsatisfactory product yields (entry 3).

Catalyst **22** can also be conveniently recovered and recycled. To demonstrate the principle, we carried out the protection of **23** as its 1,3-dithiolane **37** catalyzed by **22** (5 mol %). After ^{1}H NMR spectroscopy indicated quantitative formation of **37**, hexane was added and the solution containing the product was decanted and dried in vacuo to give spectroscopically pure product (89% after chromatography). The solution containing the catalyst was then concentrated in vacuo and reused in a second identical cycle without any loss of catalytic activity being observed (Scheme 3).

We would propose that these preliminary results indicate that the hitherto undocumented ability of pyridinium ions to promote these reactions may be due to the addition of the alcohol nucleophile to (for example) **22** to generate the equilibrating species **22a** and **22b** which then serve as the

(20) In the corresponding control reactions in the absence of **22** conversion had not reached 5% after this reaction time in the reactions involving **27** and **28**.

Scheme 3. Catalyst Recycling and the Proposed Mode of Action



Brønsted-acidic catalytically active species in solution (Scheme 3).[21] This is supported by the superiority of **22** over less electrophilic (and C-4 substituted) pyridinium ions, the inactivity of **22** in the presence of base and the surprising failure of ethylene glycol (the nucleophilicity of which is reduced due to mutual inductive withdrawal with the proximal oxygen atoms) to serve as a useful nucleophile in these reactions. Interestingly, such a mode of action could have profound implications for a near-forgotten but unresolved debate concerning the potential existence (and catalytic relevance) of an adduct derived from the addition of an active site cysteine-derived thiol residue to bound NAD^+ in biochemical processes involving enzymes such as glyceraldehyde-3-phosphate dehydrogenases.[22]

Studies are underway to further explore the scope, potential and mode of action of this new class of organocatalyst which is acidic only under controllable, protic conditions (and not otherwise), and recyclable without requiring column chromatography.

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Supporting Information Available: General experimental procedures, ^{1}H and ^{13}C NMR spectra, characterization data, and HPLC assays. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) While no new species were observed in the ^{1}H NMR spectrum of **22** when recorded in CD_3OD (as opposed to $CDCl_3$), its UV spectrum (9.8×10^{-5} M) is significantly different in MeOH than that recorded in H_2O and in a 9/1 H_2O/MeOH mixture. Strong absorption bands not observed in the aqueous spectra are present with maxima at 250, 269, and 352 nm. See the Supporting Information for details and spectra.

(22) Kellogg (and others) have suggested (on the basis of both model studies, X-ray structural studies, and UV-spectral data from biochemical experiments) that in these aldehyde−oxidation reactions the thiol adds to the NAD^+ at C-4 *before* attacking the aldehyde substrate to form the hemithioacetal. While this idea has not gained widespread currency, it has begun to be re-examined recently. For representative references see: (a) Kellogg, R. M. *Angew. Chem., Int. Ed.* **1984**, *23*, 782. (b) Wymore, T.; Deerfield, D. W.; Hempel, J. *Biochemistry* **2007**, *46*, 9495.