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Heterogeneous Catalysis

A Magnetic-Nanoparticle-Supported 4-*N*,*N*-Dialkylaminopyridine Catalyst: Excellent Reactivity Combined with Facile Catalyst Recovery and Recyclability**

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Dedicated to Professor A. Frank Hegarty on the occasion of his 65th birthday

By definition, catalysts should remain unchanged after reaction, and their simple recovery and reuse is highly desirable from both economic and environmental standpoints. Since its development in the late 1960s as an acylation catalyst,[1] 4-*N*,*N*-dimethylaminopyridine (DMAP) has risen to prominence as an active, commercially available "hypernucleophilic" promoter of a diverse range of synthetically useful transformations.[2] Several strategies have emerged for the immobilization of DMAP on both organic[3,4] and inorganic[5,6] heterogeneous polymer supports. However, the activity of these materials is often inconveniently lower than that of DMAP itself, and more crucially in our view, while catalyst recycle and reuse has often been demonstrated, most often this is limited to five iterative cycles or less. Recently, Lin and co-workers developed a DMAP derivative immobilized on mesoporous-silica nanospheres (400-nm average diameter) by an innovative alkoxysilane cocondensation methodology.[7] This catalyst proved useful for the acylation of secondary alcohols at elevated temperature (7.5 mol% catalyst, 2.0 equiv Ac_2O, 1.5 equiv NEt_3, 60 °C)[8,9] and could be recycled 10 times without measurable loss of activity. McQuade et al. very recently reported heterogeneous microencapsulated polystyrene-bound variants of 4-(*N*-benzyl-*N*-methyl)aminopyridine, which are more active (in the acetylation of 1-phenylethanol) than the non-immobilized analogue (but not DMAP) at very low loadings (ca. 0.5 mol%) and which can be recycled three times with a small loss (5%) in efficiency.[10] Thus, while remarkable progress has been made in recent years from both activity and recyclability standpoints, latitude for further development remains. To our knowledge, an immobilized heterogeneous[11] DMAP analogue that operates efficiently at room temperature across a range of reactions at low loadings (ca. 5 mol%) and that has also been demonstrably recycled more than 10 times without significant loss of activity has yet to be reported.

A successful design for any useful heterogeneous catalyst system (i.e., highly active and recoverable) for which the corresponding unsupported (soluble) catalyst is known to be active and stable must meet three criteria: 1) substrate access to the catalytically active sites must be maximized; 2) the heterogeneous support must be as robust as possible to prevent degradation upon use/recycle and should not interact with the catalyst moieties or otherwise interfere (destructively) with activity; and 3) the support must be compatible with a facile (relatively free of mechanical loss) recovery methodology. Recently, magnetic nanoparticles have emerged as viable alternatives to porous materials for use as robust, readily available, high-surface-area heterogeneous supports in catalytic transformations. They possess the added advantage of being magnetically recoverable, thereby eliminating the requirement for either solvent swelling before or catalyst filtration after the reaction.[12] At the outset of this study, no example of a nanoparticle-supported organocatalyst system had been reported,[13] despite the potential inherent stability and activity of such a (metal-free) species. We were, thus, intrigued by the possibility of applying nanotechnology to the design of a novel, active, recyclable, and magnetically recoverable DMAP derivative for the first time.

The supported DMAP analogue was prepared by the concise route outlined in Scheme 1. Magnetite (Fe_3O_4) nanoparticles of 9.6-nm average diameter[14] were prepared by the coprecipitation technique.[15–17] In a departure from conventional catalyst loading strategies, the particles were then coated with a silica layer[18] by preliminary dispersion in aqueous tetramethylammonium hydroxide followed by exposure to sodium silicate.[19] This step was carried out to address concerns regarding potential particle oxidation and aggregation[20] and to obviate potential interactions between the iron oxide particle core and the organocatalyst moiety or reaction intermediates.[21] Treatment of the silica-coated nanoparticles with excess triethoxysilane derivative **1**[22] in THF at reflux and subsequent reaction with *n*-propyltrimethoxysilane to cap remaining (acidic) surface silanol groups afforded catalyst **2**. It is noteworthy that only a single catalyst-loading step is necessary. The loading process proceeded cleanly and could be quantitatively and conveniently monitored (0.20 mmol g^{-1}

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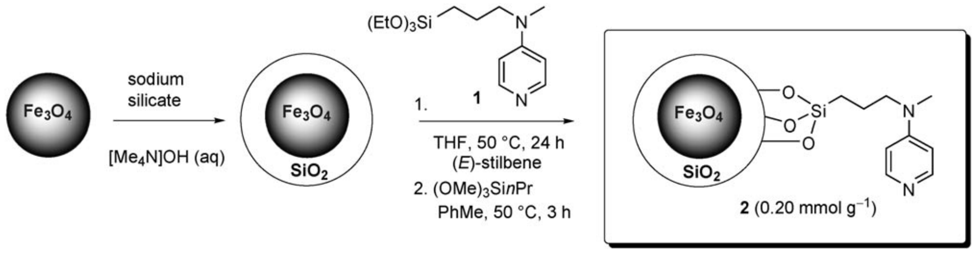


Scheme 1. Synthesis of the magnetic-nanoparticle-supported 4-*N*,*N*-dialkylaminopyridine catalyst **2**.

loading, consistent between batches) by ^{1}H NMR spectroscopy in the presence of (*E*)-stilbene as an internal standard. Transmission electron microscopy (TEM) demonstrates the core–shell structure of the particles and confirms the presence of the silica coating (Figure 1).[23]

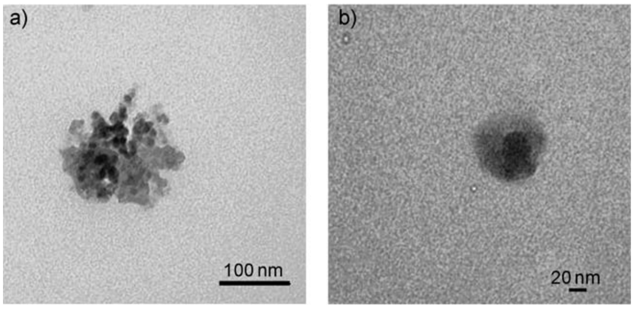
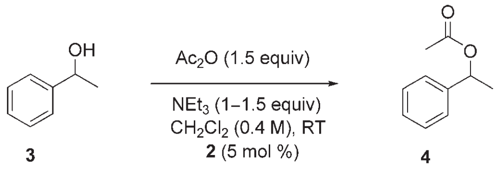


Figure 1. TEM images of a) an aggregate of particles and b) a single particle of catalyst **2**.

Nanoparticle-supported catalyst **2** was first evaluated as a promoter of the acetylation of 1-phenylethanol (**3**) by acetic anhydride. Gratifyingly, **2** (at 5 mol % loading) exhibited high catalytic activity, allowing the smooth and quantitative conversion of **3** to acetyl derivative **4** at ambient temperature with mechanical agitation (Table 1, entry 1). The catalyst was easily separated from the products by exposure of the reaction vessel to an external magnet and decantation of the reaction solution. The remaining catalyst was washed with THF to remove residual product and dried under high vacuum. This material could then be subsequently reused in 13 further iterative cycles, furnishing the acylated product with 94–>98 % conversion in each case (entries 2–14, Table 1). The excellent activity and recyclability of **2** in this reaction is illustrated by the finding that the 14th consecutive acylation cycle was 97 % complete after a reaction time of only 1 h (entry 14, Table 1). The corresponding reaction in the absence of **2** (under otherwise identical conditions) gave only 3 % conversion to **4**. This same catalyst material was subsequently found to be also active when employed at loadings as low as 0.2 mol % (Scheme 2).

Encouraged by the results of the preliminary acylation study, our attention now turned to the issue of reaction scope. We tested the same batch of **2** used to promote the 15 acylation experiments (Table 1 and Scheme 2) as a nucleophilic catalyst for a number of distinct transformations of high synthetic utility (Table 2). Employing the same catalyst-recovery methodology as before, we found that **2** (at a loading as low as 1 mol %) could promote the recently developed[24] bishydroalkoxylation of alkyne **5** to give the monoprotected 1,3-dicarbonyl product **6** (a formal alkyne oxidation) in excellent isolated yield in each of three consecutive cycles (Table 2, entries 1–3).

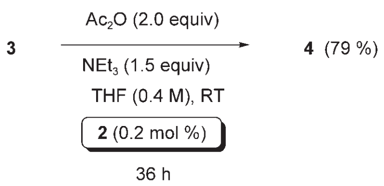
Table 1: Evaluation of **2** as a recyclable catalyst for the acetylation of 1-phenylethanol (**3**).



Entry	Cycle	*t* [h]	Conversion [%][a]
1	1	16	> 98
2	2	16	94
3	3	16	97
4	4	16	> 98
5	5	16	> 98
6	6	16	> 98
7	7	16	> 98
8	8	16	97
9	9	16	98
10	10	16	97
11[b]	11	16	> 98
12[b]	12	16	> 98
13	13	3	94
14	14	1	97

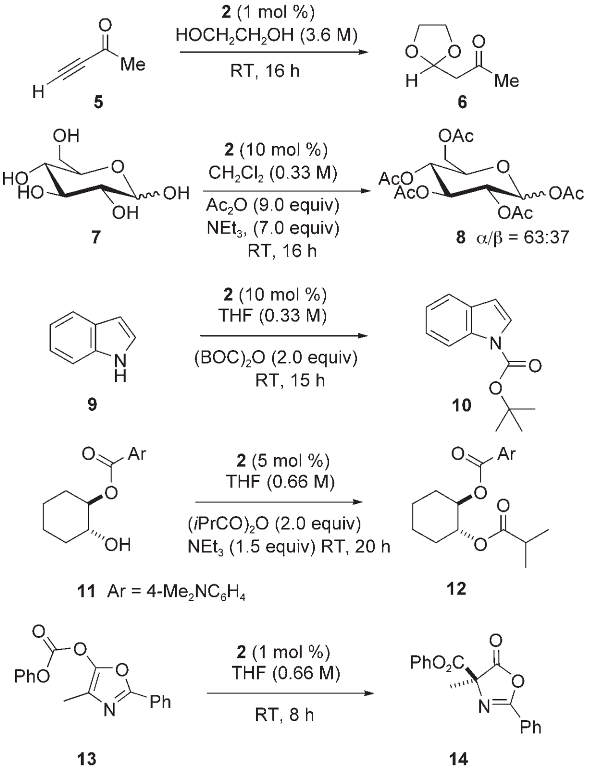
[a] Determined by ^{1}H NMR spectroscopy. [b] 2.0 equiv Ac_2O.

The robust nature and excellent activity of this catalyst is further underlined by its subsequent ability to efficiently promote challenging, yet synthetically useful reactions which (to our knowledge) have not been previously catalyzed by a heterogeneous nucleophilic promoter. For example, **2** catalyzes the room-temperature peracetylation of D-glucose (Table 2, entries 4–6), which requires the catalyst to mediate five separate acylation events per glucose molecule (which is also initially insoluble under the reaction conditions), and the *tert*-butoxycarbonyl (BOC) protection of indole (entries 7–9,



Scheme 2. Acetylation of 1-phenylethanol (**3**) at a low catalyst loading (cycle 15).

Table 2: Application of **2** as a recyclable catalyst in reactions of synthetic interest.



Entry	Cycle	Substrate	Product	Loading [mol %]	*t* [h]	Yield[a] [%]
1	16	**5**	**6**	1	16	91
2	17	**5**	**6**	1	16	90
3	18	**5**	**6**	1	16	88
4	19	**7**	**8**	10	16	96
5	20	**7**	**8**	10	16	95
6	21	**7**	**8**	10	16	96
7	22	**9**	**10**	10	15	97
8	23	**9**	**10**	10	15	98
9	24	**9**	**10**	10	15	98
10	25	**11**	**12**	5	20	91
11	26	**11**	**12**	5	20	91
12	27	**11**	**12**	5	20	94
13	28	**13**	**14**	1	8	94
14	29	**13**	**14**	1	8	97
15	30	**13**	**14**	1	8	93

[a] Yield of isolated product.

Table 2). The catalyst is compatible with the hindered acylating agent isobutyric anhydride (allowing the esterification of monoprotected diol **11**; entries 10–12, Table 2) and promotes the rearrangement of *O*-acyl enolate **13** to afford the azalactone **14** (entries 13–15, Table 2), which incorporates a quaternary stereogenic centre.[25,26]

No catalyst degradation (physical or chemical) was discernable after 30 consecutive catalyst cycles (Tables 1 and 2). To demonstrate that **2** had retained high catalytic activity at this juncture, the acylation of **3** with 0.2 mol% catalyst loading (Scheme 2) was repeated. Pleasingly, an almost identical level of conversion to **4** (80%) was observed in the 31st cycle.

In summary, we have developed the first magnetic-nanoparticle-supported DMAP analogue for use as a robust heterogeneous nucleophilic catalyst of unprecedented activity and recyclability. The catalyst is readily prepared by a concise route from inexpensive commercially available starting materials using standard laboratory techniques. It is readily (quantifiably) loaded onto the support in a single step and is capable of promoting a range of synthetically useful reactions at room temperature with loadings (as low as 0.2 mol%) not generally associated with heterogeneous organocatalysis.[27] Recovery of the catalyst by decantation of the reaction mixture in the presence of an external magnet is both convenient and efficient. The ease of recovery, combined with the intrinsic stability of both the organic and nanoparticle catalyst components, allows the catalyst to be recycled over 30 times in a number of transformations without any discernible loss in activity. Studies to further explore the potential of this powerful immobilization strategy for the preparation of other heterogeneous organocatalysts of high synthetic utility are underway.

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[1] a) L. M. Litvinenko, A. I. Kirichenko, *Dokl. Chem.* **1967**, 763; b) W. Steglich, G. Höfle, *Angew. Chem.* **1969**, *81*, 1001; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 981.

[2] For reviews, see: a) A. C. Spivey, S. Arseniyadis, *Angew. Chem.* **2004**, *116*, 5552; *Angew. Chem. Int. Ed.* **2004**, *43*, 5436; b) R. Murugan, E. F. V. Scriven, *Aldrichimica Acta* **2003**, *36*, 3401; c) U. Ragnarsson, L. Grehn, *Acc. Chem. Res.* **1998**, *31*, 494; d) E. F. V. Scriven, *Chem. Soc. Rev.* **1983**, *12*, 129; e) G. Höfle, W. Steglich, H. Vorbruggen, *Angew. Chem.* **1978**, *90*, 602; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569.

[3] a) M. A. Hierl, E. P. Gamson, I. M. Klotz, *J. Am. Chem. Soc.* **1979**, *101*, 6020; b) E. J. Delaney, L. Wood, I. M. Klotz, *J. Am. Chem. Soc.* **1982**, *104*, 799; c) S. Shinkai, H. Tsuji, Y. Hara, O. Manabe, *Bull. Chem. Soc. Jpn.* **1981**, *54*, 631; d) M. Tomoi, Y. Akada, H. Kakiuchi, *Makromol. Chem. Rapid Commun.* **1982**, *3*, 537; e) F. M. Menger, D. J. McCann, *J. Org. Chem.* **1985**, *50*, 3928; f) W. Storck, G. Manecke, *J. Mol. Catal.* **1985**, *30*, 145; g) F. Guendouz, R. Jacquier, J. Verducci, *Tetrahedron* **1988**, *44*, 7095; h) A. Corma, H. Garcia, A. Leyva, *Chem. Commun.* **2003**, 2806; i) J.-W. Huang, M. Shi, *Adv. Synth. Catal.* **2003**, *345*, 953; j) G. Preim, B. Pelotier, S. J. F. Macdonald, M. S. Anson, I. B. Campbell, *Synlett* **2003**, 679.

[4] For reviews, see: a) M. Benaglia, A. Puglisi, F. Cozzi, *Chem. Rev.* **2003**, *103*, 3401; b) F. Cozzi, *Adv. Synth. Catal.* **2006**, *348*, 1367; c) M. Benaglia, *New J. Chem.* **2006**, *30*, 1525.

[5] a) S. Rubinsztajn, M. Zeldin, W. K. Fife, *Macromolecules* **1990**, *23*, 4026; b) S. Rubinsztajn, M. Zeldin, W. K. Fife, *Macromolecules* **1991**, *24*, 2682.

[6] General review: C. E. Song, S.-G. Lee, *Chem. Rev.* **2002**, *102*, 3495.

[7] H.-T. Chen, S. Huh, J. W. Wiench, M. Pruski, V. S.-Y. Lin, *J. Am. Chem. Soc.* **2005**, *127*, 13305.

[8] The authors reported a slow but appreciable rate of background acylation (33% yield compared to 93% for the catalyzed process) in the absence of catalyst under these conditions.

[9] The catalyst is also an active promoter of the challenging Baylis–Hillman reaction at higher catalyst loadings (30 mol%).

[10] K. E. Price, B. P. Mason, A. R. Bogdan, S. J. Broadwater, J. L. Steinbacher, D. T. McQuade, *J. Am. Chem. Soc.* **2006**, *128*, 10376.

[11] For pioneering work on the development of highly active and recyclable homogeneous polymer-bound DMAP derivatives that can be precipitated/extracted after reaction, see: a) D. E. Bergbreiter, P. L. Osburn, C. Li, *Org. Lett.* **2002**, *4*, 737; b) D. E. Bergbreiter, C. Li, *Org. Lett.* **2003**, *5*, 2445.

[12] a) T.-J. Yoon, W. Lee, Y.-S. Oh, J.-K. Lee, *New J. Chem.* **2003**, *27*, 227; b) A.-H. Lu, W. Schmidt, N. Matoussevitch, H. Bönnemann, B. Spliethoff, B. Tesche, E. Bill, W. Kiefer, F. Schüth, *Angew. Chem.* **2004**, *116*, 4403; *Angew. Chem. Int. Ed.* **2004**, *43*, 4303; c) H. M. R. Gardimalla, D. Mandal, P. D. Stevens, M. Yen, Y. Gao, *Chem. Commun.* **2005**, 4432; d) A. Hu, G. T. Yee, W. Lin, *J. Am. Chem. Soc.* **2005**, *127*, 12486; e) P. D. Stevens, J. Fan, H. M. R. Gardimalla, M. Yen, T. Gao, *Org. Lett.* **2005**, *7*, 2085; f) Y. Zheng, P. D. Stevens, Y. Gao, *J. Org. Chem.* **2006**, *71*, 537; g) D. Lee, J. Lee, H. Lee, S. Jin, T. Hyeon, B. M. Kim, *Adv. Synth. Catal.* **2006**, *348*, 41; h) R. Abu-Reziq, H. Alper, D. Wang, M. L. Post, *J. Am. Chem. Soc.* **2006**, *128*, 5279.

[13] During the preparation of this manuscript, an achiral magnetic-nanoparticle-supported phase-transfer catalyst based on a quaternary ammonium salt was reported for the butylation of sodium phenoxide at 100 °C. The catalyst is active at a loading of 4 mol% and could be recycled four times with only a 5% reduction in yield: M. Kawamura, K. Sato, *Chem. Commun.* **2006**, 4718.

[14] Calculated from X-ray diffraction (XRD) data, using the Debye–Scherrer equation: R. M. Cornell, U. Schwertmann, *The Iron Oxides*, Wiley-VCH, Weinheim, **1996**.

[15] R. Massart, *IEEE Trans. Magn.* **1981**, *17*, 1247.

[16] X. P. Qiu, *Chin. J. Chem.* **2000**, *18*, 834.

[17] See the Supporting Information for details.

[18] A. P. Philipse, M. P. B. Vanbruggen, C. Pathmamanoharan, *Langmuir* **1994**, *10*, 92.

[19] The nanoparticles were characterized by FTIR and Raman spectroscopy, XRD, and TEM. See the Supporting Information.

[20] L. M. Liz-Marzan, M. Giersig, P. Mulvaney, *Langmuir* **1996**, *12*, 4329.

[21] A particular cause for potential concern in the current study would be the ammonium-cation-binding properties of uncoated Fe_3O_4 nanoparticles; all reactions catalyzed by DMAP pass through key pyridinium-ion intermediates, while nucleophile-catalyzed acylations of alcohols in the presence of a stoichiometric amine base generate ammonium salts. For a recent report detailing the binding of magnetite to ammonium cations, see: W. Li, C. Gao, H. Qian, J. Ren, D. Yan, *J. Mater. Chem.* **2006**, *16*, 1852.

[22] **1** can be prepared in one step from commercially available 4-*N*-methylpyridine (Aldrich) and (3-chloropropyl)triethoxysilane. See reference [7] or the Supporting Information for details.

[23] Supplementary TEM images showing particle aggregates can be found in the Supporting Information.

[24] J. E. Murtagh, S. H. McCooey, S. J. Connon, *Chem. Commun.* **2005**, 227.

[25] W. Steglich, G. Höfle, *Angew. Chem.* **1968**, *80*, 78; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 61.

[26] Control reactions for the formation of **6**, **10**, **12**, and **14** in the absence of **2** under otherwise identical conditions to those in Table 2 proceeded to 0, 0, 1, and 0% conversion respectively.

[27] We have also found that an analogue of **2** prepared from the direct coupling of **1** with magnetite nanoparticles (without a silica layer) can serve as an active and recyclable acylation catalyst in the BOC protection of indole (under conditions identical to those in Table 2, entries 7–9). In these experiments, **10** could be prepared from **9** in quantitative conversion in each of five consecutive cycles.