ORGANIC
LETTERS

2011
Vol. 13, No. 3
530−533

Synthesis and Reactivity of Highly Nucleophilic Pyridines

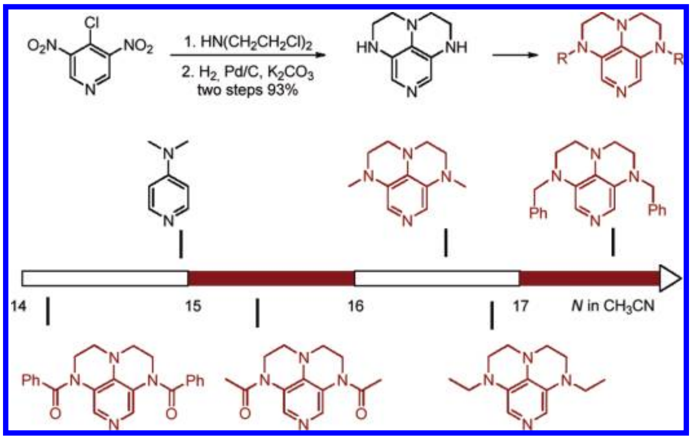
**Nicolas De Rycke,[†] Guillaume Berionni,[‡] François Couty,[†] Herbert Mayr,[‡]
Regis Goumont,[†] and Olivier R. P. David*,[†]**

*UniverSud Paris, Institut Lavoisier, Université de Versailles St. Quentin-en-Yvelines,
UMR 8180, 45 avenue des Etats-Unis, 78035, Versailles, France, and
Ludwig-Maximilians-Universität München, Department Chemie, Butenandtstr.
5-13, 81377 München, Germany*

odavid@chimie.uvsq.fr

Received December 7, 2010

ABSTRACT



3,4,5-Triamino-substituted pyridines are avid for electrophiles but are still willing to give them back. In these compounds three amino groups conjoin their forces into the heterocyclic nitrogen, making it a powerful Lewis base. A short and efficient synthesis is described, and the origin of its unique activity in nucleophilic organocatalysis is rationalized by kinetics and thermodynamic quantifications.

4-Dimethylaminopyridine (DMAP) **1** is a classical nucleophilic organocatalyst which was initially employed as an acylation catalyst.[1,2] Chiral derivatives have later been developed to promote diverse enantioselective transformations.[3] By embedding the dimethylamino group of DMAP in a tricyclic framework, it is possible to improve the catalytic activity of DMAP.[4]

[†] Université de Versailles St. Quentin-en-Yvelines.

[‡] Ludwig-Maximilians-Universität München.

(1) (a) Steglich, W.; Höfle, G. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 981. (b) Höfle, G.; Steglich, W. *Synthesis* **1972**, 619–621. (c) Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk SSSR Ser. Khim.* **1967**, *176*, 97–100.

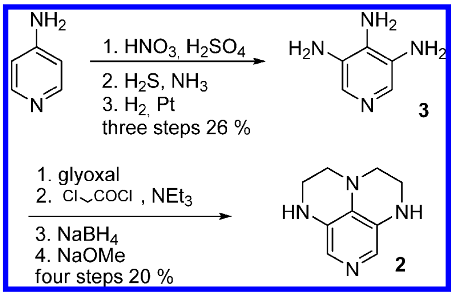
(2) (a) Höfle, G.; Steglich, W.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569–583. (b) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129–161. (c) Hassner, A. In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 3; Paquette, L. A., Ed.; Wiley: Chichester, 1995; pp *2022*−2024. (d) Murugan, R.; Scriven, E. F. V. *Aldrichimica Acta* **2003**, *36*, 21–27. (e) Ragnarsson, U.; Grehn, L. *Acc. Chem. Res.* **1998**, *31*, 494–501. (f) Steglich, W.; Höfle, G. *Tetrahedron Lett.* **1970**, *54*, 4727–4730. (g) Hassner, A.; Krepski, L. R.; Alexanian, V. *Tetrahedron* **1978**, *34*, 2069–2076.

(3) For reviews on chiral DMAPs: (a) Spivey, A. C.; Maddaford, A.; Redgrave, A. *Org. Prep. Proc. Int.* **2000**, *32*, 331–365. (b) France, S.; Guerin, D. J.; Miller, S. J.; Lectka, T. *Chem. Rev.* **2003**, *103*, 2985–3012. (c) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412–420. (d) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542–547. (e) Fu, G. C. *Acc. Chem. Res.* **2006**, *39*, 853–860. (f) Wurz, R. P. *Chem. Rev.* **2007**, *107*, 5570–5595. (g) Marion, N. M.; Fu, G. C. Applications of Aza- and Phosphaferrocenes and Related Compounds in Asymmetric Catalysis. *Chiral Ferrocenes in Asymmetric Catalysis*; Dai, L.-X., Hou, X.-L., Eds.; Wiley-VCH: New York, 2010; Chapter 11. For recent primary literature: (h) Spivey, A. C.; Leese, D. P.; Zhu, F.; Daveya, S. G.; Jarvest, R. L. *Tetrahedron* **2004**, *60*, 4513–4525. (i) Spivey, A. C.; Arseniyadis, S.; Fekner, T.; Maddaford, A.; Leese, D. P. *Tetrahedron* **2006**, *62*, 295–301. (j) Shaw, S. A.; Aleman, P.; Christy, J.; Kampf, J. W.; Va, P.; Vedejs, E. *J. Am. Chem. Soc.* **2006**, *128*, 925–934. (k) Dochnahl, M.; Fu, G. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2391–2393. (l) Duffey, T. A.; Shaw, S. A.; Vedejs, E. *J. Am. Chem. Soc.* **2009**, *131*, 14–15.

10.1021/ol1029589

More recently, this strategy was combined with the introduction of additional amino moieties at the 3- and 5-positions, which further increases electron density in the pyridine ring.[5] In the context of our research, we became interested in the work of Han's group on triaminopyridine catalysts derived from **2** (see Scheme 1).[5b]

Scheme 1. Han's Synthesis of Key Intermediate **2**

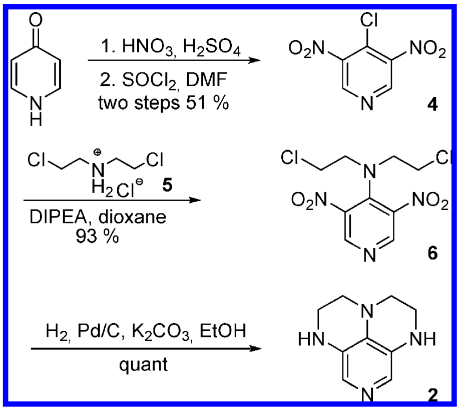


These compounds display very good catalytic activity and are able to promote the acetylation of very hindered and deactivated alcohols for which DMAP is inefficient. These improved catalytic activities were found to correlate with calculated acyl-transfer enthalpies. We now report on an efficient access and modification of these compounds and characterize their nucleophilic reactivities by the benzhydrylium method employing three-parameter eq 1[6] where *E* and *N* parameters measure the strength of the electrophile and the nucleophile, respectively, while the *s* parameter characterizes the sensitivity of the nucleophile on variation of the electrophile.

$$\log k(20\ °\mathrm{C}) = s(N + E) \qquad (1)$$

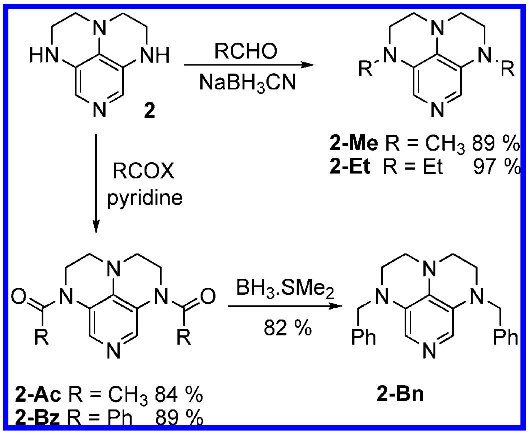
Key intermediate **2** was initially prepared by Han[5b] in four steps from 3,4,5-triaminopyridine **3**, the latter being prepared in three steps from 4-aminopyridine[7] as depicted in Scheme 1.

Scheme 2. Four-Step Synthesis of Unsubstituted superDMAP **2**



Our new preparation of key compound **2**, depicted in Scheme 2, takes advantage of the facile S_NAr reaction of secondary amines with pyridine **4** prepared by double nitration of 4-pyridone[8] and subsequent chlorination.[9,10] Nucleophilic aromatic substitution of **4** with bis-(2-chloroethyl)-amine **5** yielded 93% of **6**. Catalytic hydrogenation using palladium on charcoal under an atmospheric pressure of hydrogen, in the presence of potassium carbonate, gave **2** as the sole product after simple filtration in essentially quantitative yield.

Scheme 3. superDMAP Derivatives **2** and **2-R**



With multigram quantities of compound **2** in hand, we prepared a small library of diversely substituted superDMAPs; see Scheme 3. Dimethyl- and diethyl- derivatives **2-Me** and **2-Et** were prepared by reductive amination as previously described by Han, although a modified procedure for the purification step increased the yield to 89% for **2-Me** and 97% for **2-Et**. As reductive amination was unsuccessful with benzaldehyde, we switched to a two-step procedure involving acylation and amide reduction to prepare the dibenzyl derivative **2-Bn**. Double benzoylation with benzoyl chloride in

---

(4) For a review on DMAP derivatives potency: (a) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436–5441. For primary literature: (b) Heinrich, M. R.; Klisa, H. S.; Mayr, H.; Steglich, W.; Zipse, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4826–4828. (c) Singh, S.; Das, G.; Singh, O. V.; Han, H. *Tetrahedron Lett.* **2007**, *48*, 1983–1986. (d) Wong, K. T.; Ku, S. Y.; Yen, F. W. *Tetrahedron Lett.* **2007**, *48*, 5051–5054.

(5) (a) Held, I.; Xu, S. J.; Zipse, H. *Synthesis* **2007**, *8*, 1185–1196. (b) Singh, S.; Das, G.; Singh, O. V.; Han, H. *Org. Lett.* **2007**, *9*, 401–404. (c) Held, I.; Larionov, E.; Bozler, C.; Wagner, F.; Zipse, H. *Synthesis* **2009**, 2267–2277.

(6) General reviews: (a) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77. (b) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938–957. (c) Mayr, H.; Patz, M.; Gotta, M. F.; Ofial, A. R. *Pure Appl. Chem.* **1998**, *70*, 1993–2000. (d) Mayr, H.; Ofial, A. R. In *Carbocation Chemistry*; Olah, G. A., Prakash, G. K. S., Eds.; Wiley: Hoboken, NJ, 2004; Chapter *13*, pp 331−358. (e) Mayr, H.; Ofial, A. R. *Pure Appl. Chem.* **2005**, *77*, 1807–1821. (f) Lucius, R.; Loos, R.; Mayr, H. *Angew. Chem., Int. Ed.* **2002**, *41*, 91–95. (g) Baidya, M.; Kobayashi, S.; Brotzel, F.; Schmidhammer, U.; Riedle, E.; Mayr, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 6176–6179. (g) Nucleophilicities of arenes: (h) Mayr, H.; Bartl, J.; Hagen, G. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1613–1615.

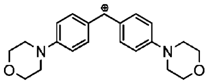
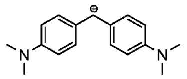
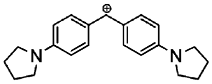
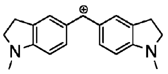
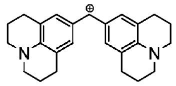
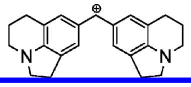
(7) Graboyes, H.; Day, A. R. *J. Am. Chem. Soc.* **1957**, *79*, 6421–6426.

(8) Diehl, R.; Walworth, B. Patent US3826643 1974/07/30, American Cyanamid Co.

(9) Okafor, C. O. *J. Org. Chem.* **1967**, *32*, 2006–2007.

(10) Petrow, V. A.; Rewald, E. L. *J. Chem. Soc.* **1945**, 313–315.

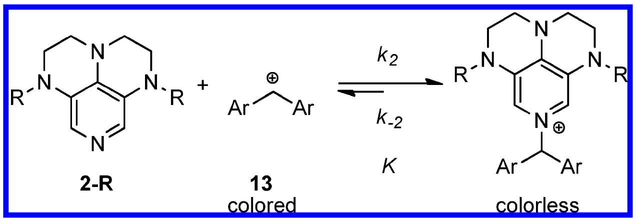
Table 1. Benzhydrylium Ions **13a−f** Used As Reference Electrophiles in This Work

electrophiles	(Ar$_2$CH$^+$.BF$_4^-$)	λ_{max} (nm)	*E*
13a		610	-5.53
13b		605	-7.02
13c		611	-7.69
13d		616	-8.76
13e		635	-9.45
13f		632	-10.04

pyridine gave **2-Bz** in 89% yield, which was reduced with the borane−DMS complex to yield 82% of **2-Bn**. The diacetylated compound **2-Ac** was prepared using acetic anhydride in pyridine and was isolated in 84% yield.

In order to compare the nucleophilic reactivities of these substituted pyridines **2-R** with those of other pyridines, we have measured the rates of their reactions with benzhydrylium ions **13a−f** (see Scheme 4 and Table 1) in acetonitrile.

Scheme 4. Reaction of superDMAP **2-R** with Benzhydrylium Ions **13**



The decay of the benzhydrylium ion absorbances was followed photometrically after combining benzhydrylium tetrafluoroborates **13a−f** with variable excesses of DMAPs in a stopped-flow apparatus. Plots of pseudo-first-order rate constants k_{obs} versus the concentration were linear in all reactions studied (see Supporting Information), with the second-order rate constants k_2 (Table 2) being the slopes of the correlation lines. Plots of log k_2 versus the electrophilicity parameter *E* of benzhydrylium ions (Figure 1) are linear as required by eq 1.

From the slopes and the intercepts on the abscissa, we have derived the nucleophilicity *N* and the nucleophile-specific parameter *s*, respectively, which are listed in the fourth column of Table 2. As the catalytic activities of tertiary amines depend not only on their nucleophilicities but also on their Lewis basicities,[12] we have also measured some equilibrium constants (*K*) which are listed in Table 3. As benzhydrylium ions are colored and the resulting adducts are colorless, the equilibrium constants for the reaction depicted in Scheme 4 could be determined by UV−vis

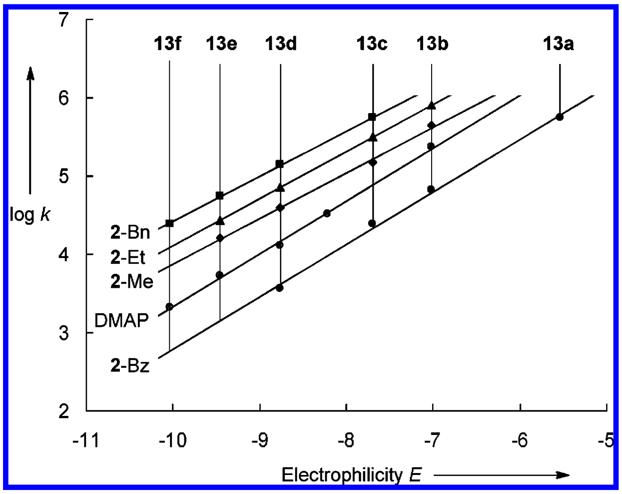


Figure 1. Plots of log *k* versus *E* for the reactions of DMAP derivatives **2-R** with benzhydrylium ions **13a−f**.

Table 2. Second-Order Rate Constants for Reactions of DMAP Derivatives **2-R** and DMAP **1**, with Benzhydrylium Tetrafluoroborates **13a−f** in Acetonitrile at 20 °C

derivative	Ar$_2$CH$^+$	*k* [M^{-1} s^{-1}]	*N*/*s*
2-Me	**13b**	4.46×10^5	16.65/0.58
	13c	1.51×10^5	
	13d	3.99×10^4	
	13e	1.63×10^4	
2-Et	**13b**	7.93×10^5	16.81/0.60
	13c	3.21×10^5	
	13d	7.05×10^4	
	13e	2.75×10^4	
2-Bn	**13c**	5.52×10^5	17.69/0.57
	13d	1.42×10^5	
	13e	5.43×10^4	
	13f	2.48×10^4	
2-Ac	**13a**	9.82×10^5	15.39/0.60
	13b	1.25×10^5	
	13c	5.81×10^4	
	13d	1.00×10^4	
2-Bz	**13a**	5.45×10^5	14.19/0.67
	13b	6.75×10^4	
	13c	2.47×10^4	
	13d	3.69×10^3	
DMAP**1**		4.46×10^5	14.95/0.68[11]

---

[11] Brotzel, F.; Kempf, B.; Singer, T.; Zipse, H.; Mayr, H. *Chem.−Eur. J.* **2007**, *13*, 336–345.

[12] Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560–1638.

Table 3. Equilibrium Constants K [M^{-1}] in Acetonitrile at 20°C for DMAP **1** and **2-R** Ordered According to N values, with k_2 and k_{-2}

$$K = \frac{[\mathrm{Ar_2CH.DMAP^+}]}{[\mathrm{Ar_2CH^+}][\mathrm{DMAP}]} = \frac{(A - A_0)}{A[\mathrm{DMAP}]} = \frac{(A - A_0)}{A\left\{[\mathrm{DMAP}]_0 - \dfrac{(A - A_0)}{\varepsilon\, d}\right\}}$$

	reaction with **13d**			reaction with **13e**		
	k_2	K	k_{-2}	k_2	K	k_{-2}
2-Bz	3.69×10^3	1.07×10^4	0.34	1.34×10^3	7.89×10^2	1.7
2-Ac	1.00×10^4	6.40×10^3	1.56	3.66×10^3	4.30×10^2	8.5
1	1.29×10^4	5.60×10^5	0.023	5.30×10^3	2.60×10^4	0.20
2-Et	7.05×10^4	9.10×10^5	0.077	2.75×10^4	8.08×10^4	0.34
2-Bn	1.42×10^5	1.47×10^6	0.096	5.43×10^4	1.89×10^5	0.28

spectroscopy. They can be expressed by the initial absorbance of benzhydrylium ions (A_0) and its final absorbance (A) after the addition of DMAP derivatives, as shown in the following equation.[6g]

Table 3, which compares rate and equilibrium constants of two reaction series, shows that the substituents in pyridine have significantly different effects on rate and equilibrium constants. The trend that **13d** is approximately 2.5 times more electrophilic (k), but 8−21 times more Lewis acidic (K), than **13e** has previously been observed in reactions of these benzhydrylium ions with other nucleophiles[13] and shall not be discussed here. Table 3 values also show that the acetyl substituted compound **2-Ac** has a similar nucleophilicity (N) as DMAP while its Lewis basicity (K) is 102 times smaller. This difference is due to the much higher (102 times) leaving group ability of **2-Ac** compared with that of DMAP. A similar effect is observed in the comparison of **2-Bz** with DMAP: **2-Bz** is 3−4 times less nucleophilic and 30−50 times less Lewis basic than DMAP. Thus, **2-Ac** and **2-Bz** may be suitable catalysts in processes requiring nucleophiles comparable to DMAP but having a much better leaving group ability.

At present, the N-alkyl substituted compounds **2-Me**, **2-Et**, and **2-Bn** have greater practical relevance, as already demonstrated by Han et al.[5b] for the first two of these compounds. In Figure 1 and Table 3 one can see that the nucleophilic reactivities increase from DMAP over **2-Me** and **2-Et** to **2-Bn**, which reacts 10 times faster than DMAP and is thus the most nucleophilic pyridine reported to date. As the increase of nucleophilicity is combined with a weaker increase in Lewis basicity, one can calculate that the pyridines **2-Et** and **2-Bn** are not only much better nucleophiles than DMAP but also, at the same time, somewhat better nucleofuges. The unprecedented catalytic activity of these derivatives is presently elucidated.

The straightforward access to this new class of pyridines and the surprising observation that the nucleophilicity of pyridines **2-Me** and **2-Et** developed by Han et al. can further be augmented by variation of the alkyl side chain (Figure 2) stimulates further activities to generate tailor-made DMAP derivatives suitable for variable catalytic processes.

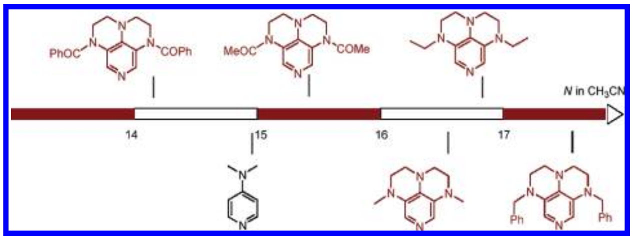


Figure 2. Nucleophilicity scale for compounds **1** and **2-R**.

Acknowledgment. We would like to acknowledge the technical expertise of Dr. Elyane Kizilian (Université de Versailles St Quentin-en-Yvelines) in kinetics measurements. We thank Dr. Armin Ofial (Ludwig-Maximilians-Universität München) for data accuracy checking and Dr. Sami Lakhdar (Ludwig-Maximilians-Universität München) for fruitful discussions.

Supporting Information Available: Full experimental description, copies of proton and carbon NMR spectra, rate constants and equilibrium constants measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1029589

---

(13) Schaller, H. F.; Tishkov, A. A.; Feng, X.; Mayr, H. *J. Am. Chem. Soc.* **2008**, *130*, 3012–3022.