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2-Aminopyridinium Ions Activate Nitroalkenes through Hydrogen Bonding

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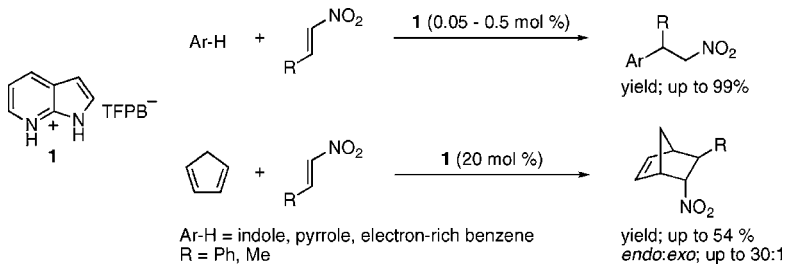
ABSTRACT



2-Aminopyridinium ions were found to activate nitroalkenes toward conjugate addition of heteroaromatic compounds with low catalyst loadings and the Diels–Alder reaction with the periselectivity opposite to that observed with metal Lewis acids, raising the possibility that a 2-aminopyridinium core might be a promising catalaphore for the asymmetric catalyst design.

Nitroalkanes are important compounds in organic synthesis due to their propensity to undergo facile α-alkylation reactions and interconversions to other organic functional groups.[1] The Michael reaction of carbon-centered nucleophiles with nitroalkenes represents one of the most direct approaches to chiral nitroalkanes.[1c,d,2] Among such methods, the Friedel−Crafts alkylation of heteroaromatic compounds with nitroalkenes[3,4] has received relatively little attention, although it is a powerful carbon−carbon bond forming reaction that provides the stereochemical motif with a privileged status in medicinal chemistry.[5] Despite recent advances in this process, identification of new efficient catalysts, even achiral ones, that lower the LUMO of nitroalkenes remains an important challenge. It is described herein that new 7-azaindolium tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (TFPB) activated nitroalkenes toward conjugate addition of heteroaromatic compounds with low catalyst loadings and also catalyzed the Diels−Alder reaction of nitroalkenes with the periselectivity opposite to that observed with metal Lewis acids.

Electrophile activation by small-molecule chiral hydrogen bond (abbreviated as H-bond) donors has recently emerged as an important paradigm for enantioselective catalysis.[6] Among them, (thio)ureas are becoming a class of privileged catalaphores[7] for designing asymmetric double H-bonding catalysts. On the other hand, Göbel et al. studied acceleration

(1) Selected references: (a) Czekelius, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 612−615. (b) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592−1604. For reviews, see: (c) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A.; Petrini, M. *Chem. Rev.* **2005**, *105*, 933−971. (d) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.

(2) For a review, see: Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877−1894.

(3) For the Friedel−Crafts alkylation of heteroaromatic compounds with nitroalkenes catalyzed by substoichiometric amount of *achiral* catalysts, see: (a) Gu, Y.; Ogawa, C.; Kobayashi, S. *Org. Lett.* **2007**, *9*, 175−178. (b) Bartoli, G.; Bosco, M.; Giuli, S.; Giuliani, A.; Lucarelli, L.; Marcantoni, E.; Sambri, L.; Torregiani, E. *J. Org. Chem.* **2005**, *70*, 1941−1944. (c) Murugan, R.; Karthikeyan, M.; Perumal, P. T.; Reddy, B. S. R. *Tetrahedron* **2005**, *61*, 12275−12281. (d) Lin, C.; Hsu, J.; Sastry, M. N. V.; Fang, H.; Tu, Z.; Liu, J.-T.; Ching-Fa, Y. *Tetrahedron* **2005**, *61*, 11751−11757. (e) Gabriella, D.; Herrera, R. P.; Ricci, A. *Synlett* **2004**, 2374−2378. (f) Alam, M. M.; Varala, R.; Adapa, S. R. *Tetrahedron Lett.* **2003**, *44*, 5115−5119. (g) Komoto, I.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 1115−1118. (h) Harrington, P. E.; Kerr, M. A. *Synlett* **1996**, 1047−1048.

(4) For the Friedel−Crafts alkylation of heteroaromatic compounds with nitroalkenes catalyzed by substoichiometric amount of *chiral* catalysts, see: (a) Fleming, E. M.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, *47*, 7037−7042. (b) Lu, S.-F.; Du, D.-M.; Xu, J. *Org. Lett.* **2006**, *8*, 2115−2118. (c) Jia, Y.-X.; Zhu, S.-F.; Yang, Y.; Zhou, Q.-L. *J. Org. Chem.* **2006**, *71*, 75−80. (d) Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6576−6579. (e) Bandini, M.; Garelli, A.; Rovinetti, M.; Tommasi, S.; Umani-Ronchi, A. *Chirality* **2005**, *17*, 522−529. (f) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 2566−2571.

(5) Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 7894−7895 and references cited therein.

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of the Diels−Alder reaction by amidinium ions (including 2-benzylaminopyridinium TFPB[8c] **2**, Table 1) and subsequently developed enantiopure amidinium catalysts.[8,9]

In this context, we are intrigued in particular by the unique structural feature of 2-aminopyridinium ions (Figure 1). This

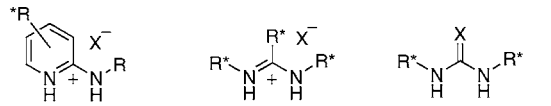
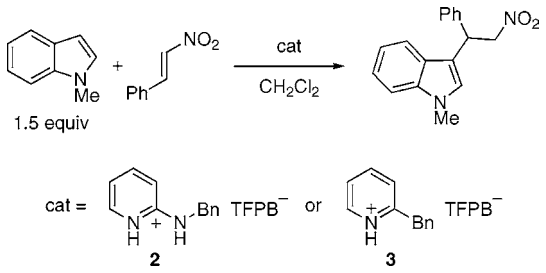


Figure 1. General structures of 2-aminopyridinium, amidinium ions, and (thio)urea; R* denotes that the skeleton is chiral.

is that its double H-bonding part is embedded in its skeleton where chirality can be introduced, and thus the relative conformational ambiguity between the center of reactivity and the chiral element could be minimized in principle. As such, the 2-aminopyridinium core appears to be a potentially attractive catalaphore compared to amidinium and (thio)-urea catalysts in which catalaphores and chiraphores[7] are connected via a rotary single bond.

Table 1. Model Reaction with Different H-Bond Donors

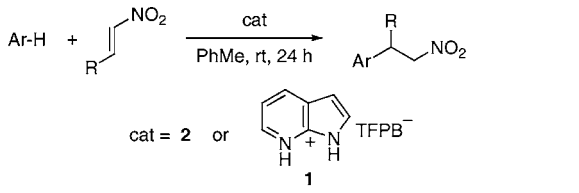


entry	cat (mol %)	temp (°C)	time (h)	yield w/**2** (%)	yield w/**3** (%)
1	1	0	24	99	75
2	1	−20	24	56	22
3	10	−50	72	51	trace

We set out to study 2-benzylaminopyridinium TFPB **2** since there is not much information in the literature regarding its ability as a H-bonding catalyst.[8c] To our delight, it turned out to efficiently catalyze the conjugate addition of *N*-methylindole to *β*-nitrostyrene[3e] (Table 1, entry 1). With respect to the mode of catalysis, we hypothesized that if **2** activates *β*-nitrostyrene via specific acid catalysis[6a] more acidic 2-benzylpyridinium TFPB[10] **3** should be a better catalyst than **2**.[11,12] However, under all three conditions investigated, the catalyst **2** clearly showed reactivity higher than that of **3** (entries 1−3). It is difficult to explain the superior reactivity of the 2-benzylaminopyridinium ion to the 2-benzylpyridinium ion by the difference in their acidities. Therefore, these results imply the cooperative double H-bonding ability of 2-benzylaminopyridinium TFPB on the analogy of (thio)ureas and bisphenols.[13]

The level of catalyst loadings was next investigated (Table 2). The reaction became sluggish when less than 0.1 mol % of **2** was employed (entries 1 and 2). However, 7-azaindolium TFPB **1**, which was originally synthesized in connection with the Diels−Alder reaction (vide infra), promoted the reaction well with catalyst loadings as low as 0.05 mol % (entry 4).

Table 2. 7-Azaindolium Ion Catalyzed Friedel−Crafts Reactions



entry[a]	Ar-H	R	cat	mol %	product	yield (%)
1		Ph	**2**	0.1		75 (4)[b]
2		Ph	**2**	0.05		52
3		Ph	**1**	0.1		99
4		Ph	**1**	0.05		93
5[c]		Ph	**1**	0.5		99 (4)[b]
6[d]		Ph	**1**	0.1		75 (8)[b]
7		Me	**1**	0.5		97 (33)[b]
8[e]		Ph	**1**	0.5		97 (16)[b]
9[e]		Ph	**1**	0.1		60
10[f]		Ph	**1**	0.5		82 (0)[b]
11[f]		Ph	**1**	0.1		22
12[g]		Ph	**1**	0.5		98 (11)[b]
13[g]		Ph	**1**	0.1		68
14		Ph	**1**	0.5		95 (<1)[b]
15		Ph	**1**	0.1		70

[a] Unless otherwise noted, Ar−H (1.5 mmol) and nitroalkenes (1.0 mmol) were used for all entries. [b] Yields without catalysts. [c] Equimolar amounts (1.0 mmol) of *N*-methylindole and *β*-nitrostyrene were reacted for 48 h. [d] Nondistilled PhMe was used. [e] The reaction was run for 2 h. [f] *N*-Methylpyrrole (4 equiv) was used. [g] The reaction was run at 0 °C for 1 h.

(6) For reviews, see: (a) Taylor, M. S.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 1520−1543. (b) Connon, S. J. *Chem.—Eur. J.* **2006**, *12*, 5418−5427. (c) Akiyama, T.; Itoh, J.; Fuchibe, K. *Adv. Synth. Catal.* **2006**, *348*, 999−1010. (d) Takemoto, Y. *Org. Biomol. Chem.* **2005**, *3*, 4299−4306. (e) Bolm, C.; Rantanen, T.; Schiffers, I.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758−1763. (f) Pihko, P. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2062−2064. (g) Schreiner, P. R. *Chem. Soc. Rev.* **2003**, *32*, 289−296.

(7) For discussion of terms "catalaphore" and "chiraphore", see: Mulzer, J. Basic Principles of Asymmetric Synthesis. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, Heidelberg, 2004; Vol. 1, Chapter 3.

(8) (a) Tsogoeva, S. B.; Dürner, G.; Bolte, M.; Göbel, M. W. *Eur. J. Org. Chem.* **2003**, 1661−1664. (b) Schuster, T.; Bauch, M.; Dürner, G.; Göbel, M. W. *Org. Lett.* **2000**, *2*, 179−181. (c) Schuster, T.; Kurz, M.; Göbel, M. W. *J. Org. Chem.* **2000**, *65*, 1697−1701.

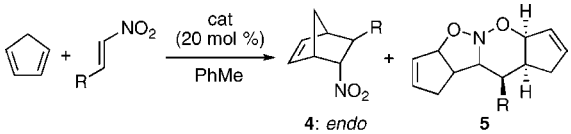
This result is reproducible at 10 mmol scale. The high catalyst activity of **1** might be attributable to its favorable geometry for double H-bonding and increased acidity.[14] The following is also worthy of mention: Only 0.5 mol % of **1** was enough to complete the reaction with equimolar amounts of substrates (entry 5). **1** tolerated nondistilled toluene presumably because it is a nonhygroscopic, bench-stable salt (entry 6). Furthermore, the 2-position of the indole nucleus may also be accessed with the present method since the dihydroindole[15] reacted well (entry 12). Overall, the reaction was effectively catalyzed with 0.5 mol % of 7-azaindolium TFPB, which represents the lowest catalyst/substrate ratio for the Friedel−Crafts alkylation reaction with nitroalkenes.

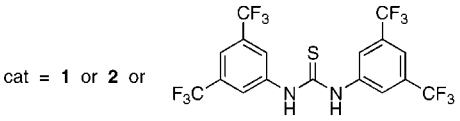
The Diels−Alder (DA) reaction of nitroalkenes has proven highly useful in organic synthesis; however, the catalysis of this process remains quite elusive.[1d] The reaction of cyclopentadiene and nitroalkenes provides the DA products under thermal conditions. In contrast, Denmark et al. reported that the same reaction undergoes the inverse-electron-demand hetero-Diels−Alder (HDA) reaction in the presence of Lewis acid catalysts, such as $SnCl_4$.[16] They rationally pointed out that unsymmetrical coordination of the Lewis acid with *one* of the oxygen atoms of the nitro group serves to localize double-bond character (O═N), resulting in a reversal of periselectivity. The study of this reaction in the presence of H-bonding catalysts has not been reported to our knowledge, thus it was conducted (Table 3).[17]

2-Benzylaminopyridinium ion **2** provided the desired DA product **4** in 44% yield with a high *endo*/*exo* ratio and the product **5** in 11%, which resulted presumably from sequential HDA and [3 + 2] reactions (entry 2).[18] On the basis of Denmark's study, we hypothesized that the charge on oxygen is evenly dispersed within the O−N−O bonding array in the nitroalkene complexed with a symmetrical double H-bond donor, and thus it may not electronically participate as a diene. Therefore, symmetric thiourea[6] **6** was tested and found to provide neither HDA products nor **5** (entries 3, 7, and 11). Hence, we synthesized the 7-azaindolium catalyst **1** with the expectation that both of its N−H bonds are somewhat similar in nature due to enhanced electronic communication between two nitrogen atoms.[19] It gave higher periselectivity than the 2-benzylaminopyridinium ion did (entries 4, 8, and 12). This is an interesting observation, although a definitive answer regarding the periselectivity is still to be firmly established. Since metal Lewis acids do not promote the formation of DA products, even these achiral H-bonding catalysts are very useful tools to obtain them with high *endo*-selectivity. It should be mentioned that the yield of an *endo*-isomer (R = Ph) of the H-bonding catalyzed reaction is comparable to that of the corresponding thermal reaction.[20]

The experimental observation about competing DA and HDA reactions[21] and shifts in product ratios by different catalysts could be understood from the expected electronic structure of the nitro group complexed with a catalyst and the single malleable bis-pericyclic transition state (TS) model

Table 3. Nitroalkene Diels−Alder Reactions Catalyzed by Double H-Bond Donors





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entry[a]	cat	R	temp (°C)	time (h)	yield (**4**) (%)	*endo*:*exo* (**4**)	yield (**5**) (%)
1		Ph	rt	8	9	7:1	0
2	**2**	Ph	rt	8	44	25:1	11
3	**6**	Ph	rt	8	42	25:1	0
4	**1**	Ph	rt	8	49	22:1	trace
5		Ph	6	72	13	9:1	0
6	**2**	Ph	6	72	46	30:1	10
7	**6**	Ph	6	72	49	30:1	0
8	**1**	Ph	6	72	54	25:1	trace
9		Me	−10	36	7	25:1	0
10	**2**	Me	−10	36	30	>30:1	2
11	**6**	Me	−10	36	24	>30:1	0
12	**1**	Me	−10	36	37	>30:1	trace

[a] CP (1.0 mmol) and nitroalkenes (0.5 mmol) were used for all entries.

(9) For recent examples of highly enantioselective reactions catalyzed by amidinium and guanidinium ions, see: (a) Singh, A.; Yoder, R. A.; Shen, B.; Johnston, J. N. *J. Am. Chem. Soc.* **2007**, *129*, 3466−3467. (b) Terada, M.; Nakano, M.; Ube, H. *J. Am. Chem. Soc.* **2006**, *128*, 16044−16045. (c) Shen, J.; Nguyen, T. T.; Goh, Y.-P.; Ye, W.; Fu, X.; Xu, J.; Tan, C.-H. *J. Am. Chem. Soc.* **2006**, *128*, 13692−13693. (d) Terada, M.; Ube, H.; Yaguchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 1454−1455. (e) Nugent, B. M.; Yoder, R. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 3418−3419. (f) Corey, E. J.; Grogan, M. J. *Org. Lett.* **1999**, *1*, 157−160.

(10) 2-Benzylpyridine was chosen instead of pyridine to guarantee sufficient solubility of the corresponding salt.

(11) The pK_a of 2-benzylpyridinium ion is 5.1 (H_2O). See: (a) Linnell, R. H. *J. Org. Chem.* **1960**, *25*, 290−291. The pK_a of 2-aminopyridinium ion is 6.9 (H_2O). See: (b) Angyal, S. J.; Angyal, C. L. *J. Chem. Soc.* **1952**, 1461−1466.

(12) A 1:1 mixture of **3** and 2-benzylaminopyridine in DMSO-d_6 completely and cleanly shifted to a mixture of 2-benzylpyridine and **2** by ^{1}H NMR in the transprotonation experiment, indicating the distinct acidity difference between **2** and **3**.

(13) Kelly, T. R.; Meghani, P.; Ekkundi, V. S. *Tetrahedron Lett.* **1990**, *31*, 3381−3384.

(14) The pK_a of 7-azaindolium ion is 4.6 (H_2O). See: Adler, T. K.; Albert, A. *J. Chem. Soc.* **1960**, 1794−1797.

(15) (a) Evans, D. A.; Fandrick, K. R. *Org. Lett.* **2006**, *8*, 2249−2252. (b) Çavdar, H.; Saraçoglu, N. *Tetrahedron*, **2005**, *61*, 2401−2405.

(16) Denmark, S. E.; Kesler, B. S.; Moon, Y.-C. *J. Org. Chem.* **1992**, *57*, 4912−4924.

(17) The intramolecular Diels−Alder reaction of nitroalkene was catalyzed by silica gel. See: Jubert, C.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 5431−5438.

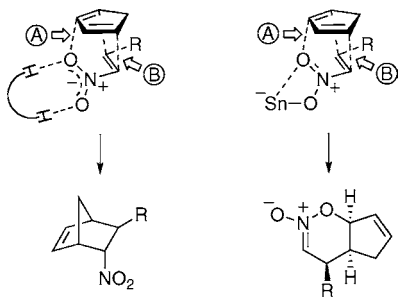
(18) CP and the corresponding *syn*-nitronate prepared according to ref 16 provided **5** (R = Ph) in the presence of **2**. See Supporting Information.

(19) Mérour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *5*, 471−506 and references cited therein.

(20) (a) Node, M.; Nishide, K.; Imazato, H.; Kurosaki, R.; Inoue, T.; Ikariya, T. *Chem. Commun.* **1996**, 2559−2560. (b) Bourguignon, J.; Nard, G. L.; Queguiner, G. *Can. J. Chem.* **1985**, *63*, 2354−2361. (c) Parham, W. E.; Hunter, W. T.; Hanson, R. *J. Am. Chem. Soc.* **1951**, *73*, 5068−5070.

(21) DA and HDA products are potentially related to each other by a [3,3] sigmatropic rearrangement; however, control experiments (R = Ph) indicated that, under the conditions of the reaction, no product interconversion was occurring. See Supporting Information.

Scheme 1. TS Models for Competing DA and HDA Reactions



recently reported by Houk et al.[22] (Scheme 1). The nitroalkene complexed with a symmetrical double H-bond donor would undergo the TS in which orbital interaction is less at A than at B due to the evenly dispersed charge within the nitro group, leading mainly to the DA product. On the other hand, unsymmetrical coordination of $SnCl_4$ would localize double-bond character and thus increase orbital interaction at A in the TS,[23] resulting in the HDA product. The electronic structure of the nitro group coordinated with unsymmetrical H-bond donor **2** is expected to be between the two cases shown in Scheme 1, leading to the TS in which orbital interactions at both A and B are important.

In summary, 2-aminopyridinium ions were identified as efficient LUMO-lowering catalysts for nitroalkenes. These catalysts promoted conjugate addition of heteroaromatic compounds to nitroalkenes with low catalyst loadings. Furthermore, they were also found to promote the Diels−Alder reaction of nitroalkenes with high diastereoselectivity. They can therefore be expected to complement ongoing (thio)urea systems and thus to be attractive catalaphores for the designs of new asymmetric catalysts, which are currently underway and will be reported in due course.

Acknowledgment. We thank the University of Miami for financial support.

Supporting Information Available: Preparation of catalysts, experimental details, and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(22) Çelebi-Ölçüm, N.; Ess, D. H.; Aviyente, V.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 4528−4529.

(23) Coordination of $SnCl_4$ to β-nitrostyrene causes a significant decrease in the LUMO coefficient of the carbon adjacent to the nitro group by calculations. See ref 22.