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Nonaromatic Amidine Derivatives as Acylation Catalysts

Vladimir B. Birman,* Ximin Li, and Zhenfu Han

Department of Chemistry, Washington University, Campus Box 1134, One Brookings Drive, St. Louis, Missouri 63130

birman@wustl.edu

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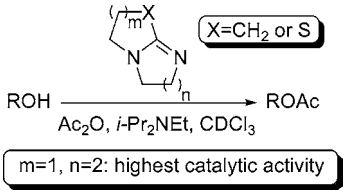
ABSTRACT



Catalytic activity of nonaromatic bicyclic amidines and bicyclic isothioureas in acylation reactions was found to be remarkably dependent on the sizes of both rings. DBN and especially its thia-analogue (THTP) have been identified as highly active acylation catalysts.

4-(Dimethylamino)pyridine (DMAP) **1**[1] and *N*-methylimidazole (NMI) **2**[2] are among the best known achiral acylation catalysts (Figure 1). As such, their structures have been used extensively as cataliaphores[3] for designing nonenzymatic asymmetric acylation catalysts.[4] Finding effective chiraphores for these planar aromatic heterocycles, however, is not a trivial matter.[5,6] Three years ago, we identified dihydroimidazo[1,2-*a*]pyridine (DHIP) **3** as a moderately active acylation catalyst.[7a] Although DHIP was less active than DMAP **1** and even NMI **2** in a preliminary catalytic activity test, it had one important advantage from the viewpoint of asymmetric catalyst design: a tetrahedral carbon α to the nucleophilic nitrogen, which permitted effective and straightforward discrimination of the two faces of the molecule.

Two easily obtainable chiral DHIP derivatives, CF_3-PIP **4**[5a] and Cl-PIQ **5**[5b], proved to be effective catalysts for kinetic resolution of benzylic and allylic alcohols. Subsequently, we demonstrated that tetramisole **6**, lacking the pyridine ring, is also competent in this capacity, albeit not very active. Its benzannellated analogue BTM **7** displayed improved catalytic activity and far superior enantioselectivity.[5c−e]

Despite the modest catalytic activity of tetramisole itself, we wished to explore nonaromatic heterocycles of this type further. The presence of tetrahedral carbon atoms in both of the rings would make them potentially attractive catalaphores, by providing an opportunity for introducing additional stereocenters, compared to the partly aromatic structures (cf. **4**, **5**, and **7**) and thus leading to greater diversity of possible structural variations. The key questions were as follows: (a) What makes tetramisole catalytically active? (b) How can it be made more active without introducing the benzene ring?

Initially, we set out to determine which part of our catalyst design constitutes "the minimal catalaphore". Would the amidine moiety itself be sufficient for a compound to function as an acylation catalyst? In order to test this possibility, we decided to investigate the catalytic activity

(1) For reviews, see: (a) Höfle, G.; Steglich, W.; Vorbrüggen, A. *Angew. Chem., Int. Ed.* **1978**, *17*, 569; (b) Spivey, A. C.; Arseniyadis, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5436.

(2) See, e.g.: Connors, K. A.; Pandit, N. K. *Anal. Chem.* **1978**, *50*, 1542.

(3) For discussion of terms "chiraphore" and "cataliaphore", 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.

(4) For review of nonenzymatic kinetic resolution of alcohols and leading references to various catalyst designs, see: Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

(5) For the most successful DMAP-based design, see: Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542 and references cited therein.

(6) For the most successful imidazole-based designs, see: (a) Miller, S. J. *Acc. Chem. Res.* **2004**, *37*, 601 and references cited therein. (b) Ishihara, K.; Kosugi, Y.; Akakura, M. *J. Am. Chem. Soc.* **2004**, *126*, 12212.

(7) (a) Birman, V. B.; Uffman, E. W.; Jiang, H.; Li, X.; Kilbane, C. J. *J. Am. Chem. Soc.* **2004**, *126*, 12226. (b) Birman, V. B.; Jiang, H. *Org. Lett.* **2005**, *7*, 3445. (c) Birman, V. B.; Li, X. *Org. Lett.* **2006**, *8*, 1351. (d) Birman, V. B.; Jiang, H.; Li, X.; Guo, L.; Uffman, E. W. *J. Am. Chem. Soc.* **2006**, *128*, 6536. (e) Birman, V. B.; Guo, L. *Org. Lett.* **2006**, *8*, 4859.

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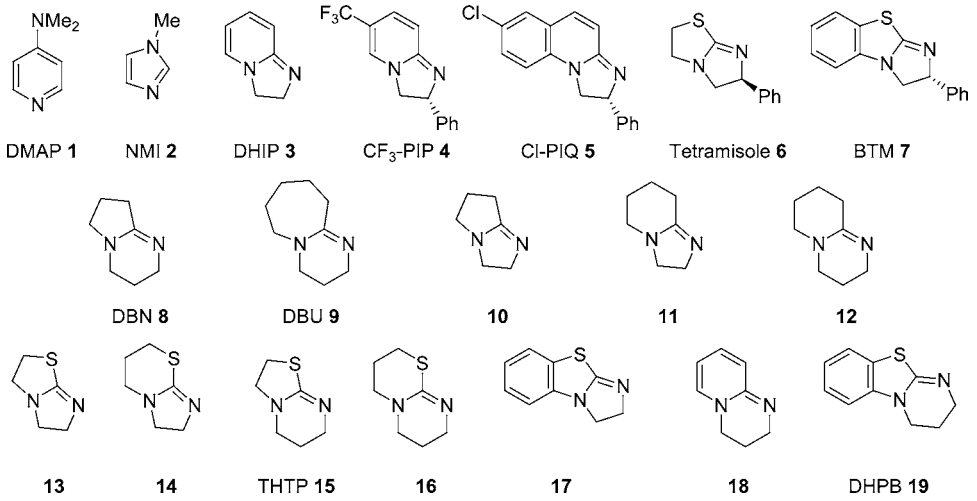


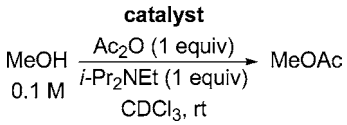
Figure 1. Known and potential acylation catalysts.

of simple bicyclic amidines, such as **8**−**12**. Naturally, we first turned our attention to the commercially available DBN **8** and DBU **9**.[8] Although these reagents have long been regarded as non-nucleophilic bases, there is now sufficient evidence in the literature that this is not the case.[9] However, we have not been able to find any reports of their use as catalysts in acylations with carboxylic anhydrides. We began by comparing DBN and DBU with the known achiral acylation catalysts **1**−**3** using a simple test: acylation of methanol with acetic anhydride in the presence of stoichiometric amounts of Hünig's base. A 5 mol % catalyst loading was adopted for most compounds in this study in order to permit direct comparison of their catalytic activities; however, the most active catalysts, such as DMAP, had to be employed in a 50-fold lower concentration to obtain conveniently measurable reaction times. The reactions were monitored by ^{1}H NMR to determine the time required for 50% conversion ($t_{1/2}$). The results are summarized in Table 1.

To our surprise, DBN (Table 1, entries 5 and 6) turned out to be a highly active catalyst, whereas DBU (entry 7) displayed virtually no activity. Intrigued by these results, we synthesized the rest of the amidines shown in Figure 1 (Scheme 1).[10] None of these compounds showed any appreciable activity (entries 8−10). On one hand, these findings confirmed that simple bicyclic amidines can be highly catalytically active. On the other hand, the striking difference between DBN and all the other bicyclic amidines indicated the critical importance of the sizes of both rings for the catalytic activity. We reasoned that systematic variation of the ring sizes could also hold the key to improving the catalytic activity of the bicyclic isothiourea catalaphore **13** present in our original nonaromatic "lead compound", tetramisole (**6**).

While this work was in progress, we became aware of a related recent study by Okamoto and Kobayashi.[11] They compared the catalytic activities of **3** (DHIP) and **17** (the

Table 1. Methanol Test



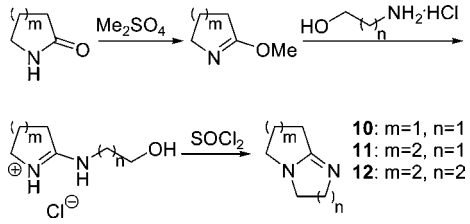
entry	catalyst	catalyst loading (mol %)	$t_{1/2}$[a]
1	none		18 h
2	DMAP **1**	0.1	16 min
3	NMI **2**	5	1.3 h
4	DHIP **3**	5	1.8 h
5	DBN **8**	5	4.0 min
6	DBN **8**	1	40 min
7	DBU **9**	5	12 h
8	**10**	5	18 h
9	**11**	5	16 h
10	**12**	5	18 h
11	**13**	5	14 h
12	**14**	5	7.5 h
13	THTP **15**	0.1	25 min
14	**16**	5	3.5 h
15	DHPB **19**	0.1	10 min
16	CF_3-PIP **4**	5	38 min
17	Cl-PIQ **5**	5	12 min
18	Tetramisole **6**	5	16 h
19	BTM **7**	5	9.0 h

[a] Time required to achieve 50% conversion was determined by monitoring the reactions by ^{1}H NMR.

(8) For review of traditional synthetic applications of DBU and DBN, see: Oediger, H.; Möller, F.; Eiter, K. *Synthesis* **1972**, 591.

(9) For examples of nucleophilic catalysis with bicyclic amidines, see: (a) DBU in Morita−Baylis−Hillman reaction: Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311. (b) DBU in esterification of carboxylic acids with dimethyl carbonate: Shieh, W.-C.; Dell, S.; Repič, O. *J. Org. Chem.* **2002**, *67*, 2188. (c) DBU and DBN in cyanoacylation of ketones: Zhang, W.; Shi, M. *Org. Biomol. Chem.* **2006**, *4*, 1671. (d) A chiral derivative of **8** has been used in the synthesis of β-lactams: Taggi, A. E.; Hafez, A. M.; Dudding, T.; Lectka, T. *Tetrahedron* **2002**, *58*, 8351. (e) For leading references to other examples of nucleophilic behavior of DBU, see: Ghosh, N. *Synlett* **2004**, 574.

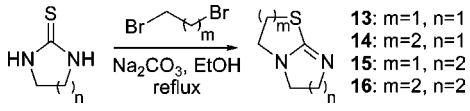
Scheme 1. Synthesis of Bicyclic Amidines



core structure of BTM) with those of their ring-expanded analogues **18** and **19** and found the latter (abbreviated herein DHPB, for 3,4-dihydro-2*H*-pyrimido[2,1-*b*]benzothiazole) to be remarkably active in acetylation of 1-phenylethanol, surpassing even the "benchmark" catalyst DMAP.

Okamoto's findings provided further stimulus for our effort to identify active catalysts among nonaromatic bicyclic isothioureas. Compounds **13**−**16** were easily prepared by cycloalkylation of cyclic thioureas as shown in Scheme 2.[12] DHPB **19** was also synthesized for comparison purposes.

Scheme 2. Synthesis of Bicyclic Isothioureas

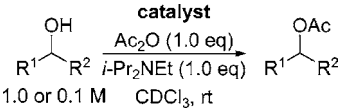


To our delight, **15** (dubbed THTP, for 2,3,6,7-tetrahydro-5*H*-thiazolo[3,2-*a*]pyrimidine) displayed outstanding catalytic activity (Table 1, entry 13), comparable to DMAP (entry 2) and DHPB (entry 15). All other bicyclic isothioureas were several orders of magnitude less active than THTP (entries 11, 12, and 14).

Keeping in mind that the catalytic activity in acylation of methanol might not necessarily correlate with that displayed in the acylation of other types of substrates, we subjected chiral catalysts **4**−**7** to the methanol test for comparison. Indeed, only catalysts **4** and **5**, but not **6** and **7**, proved reasonably active (Table 1, entries 16−19), despite the fact that all four of them had proved competent in acylation of secondary benzylic alcohols.

Clearly, we could not rely on the methanol test alone to identify new catalysts. Thus, we decided to screen all the achiral catalyst candidates again using acetylation of (±)-1-phenylethanol as the test reaction, to make sure that we did not miss any potential catalysts for acylation of benzylic substrates (Table 2).

Table 2. Acylation of Secondary Alcohols



entry	catalyst (mol %)	substrate (concn, M)	$t_{1/2}$[a]
1	none	PhCH(OH)Me (1.0)	27 h
2	DMAP **1** (0.1)	PhCH(OH)Me (1.0)	3.5 min
3	NMI **2** (5)	PhCH(OH)Me (1.0)	9.0 min
4	DHIP **3** (5)	PhCH(OH)Me (1.0)	5.2 h
5	DBN **8** (5)	PhCH(OH)Me (1.0)	15 min
6	DBU **9** (5)	PhCH(OH)Me (1.0)	17 h
7	**10** (5)	PhCH(OH)Me (1.0)	11 h
8	**11** (5)	PhCH(OH)Me (1.0)	12 h
9	**12** (5)	PhCH(OH)Me (1.0)	18 h
10	**13** (5)	PhCH(OH)Me (1.0)	8.7 h
11	**14** (5)	PhCH(OH)Me (1.0)	1.6 h
12	THTP **15** (1)	PhCH(OH)Me (1.0)	7.5 min
13	THTP **15** (0.1)	PhCH(OH)Me (1.0)	2.4 h
14	**16** (5)	PhCH(OH)Me (1.0)	2.7 h
15	DHPB **19** (0.1)	PhCH(OH)Me (1.0)	24 min
16	DMAP **1** (1)	PhCH(OH)Me (0.1)	34 min
17	THTP **15** (1)	PhCH(OH)Me (0.1)	30 min
18	DHPB **19** (1)	PhCH(OH)Me (0.1)	10 min
19	DMAP **1** (5)	PhCH(OH)Me (0.1)	5 min
20	THTP **15** (5)	PhCH(OH)Me (0.1)	2 min
21	DHPB **19** (5)	PhCH(OH)Me (0.1)	<2 min
22	DMAP **1** (5)	Cyclohexanol (0.1)	18 min
23	THTP **15** (5)	Cyclohexanol (0.1)	46 min
24	DHPB **19** (5)	Cyclohexanol (0.1)	10 min
25	DMAP **1** (5)	*i*-PrCH(OH)Me (0.1)	24 min
26	THTP **15** (5)	*i*-PrCH(OH)Me (0.1)	4 h
27	DHPB **19** (5)	*i*-PrCH(OH)Me (0.1)	20 min

[a] Time required to achieve 50% conversion was determined by monitoring the reactions by ^{1}H NMR.

In contrast to the methanol test, bicyclic isothioureas **14** and **16** exhibited modest activity in the acetylation of phenylethanol (Table 2, entries 11 and 14). However, amidines **9**−**12** and isothiourea **13** again proved virtually inactive (entries 6−10). The failure of **13** in this test was unexpected, given the fact that its phenyl-substituted analogue **6** was a moderately active catalyst for the propionylation of the same substrate.[7c,13] Initially, we were surprised to find that under the standard conditions of our phenylethanol test DHPB **19** (entry 15) and especially THTP **15** (entries 12 and 13) fell far behind DMAP (entry 2). These results were in stark contrast to both Okamoto's observations[11] with the same substrate and our methanol test (vide supra). However, when we lowered the concentration of the reactants to 0.1 M, while keeping the catalyst concentrations constant at 0.001 M, both DHPB and THTP proved superior to DMAP (entries 16−18). At 5 mol % catalyst loadings, this effect was even more pronounced (entries 19−21). Finally, we compared the relative activities of **1**, **15**, and **19** in acetylation of two other secondary alcohols—cyclohexanol

(10) Preparation of amidines **10**−**12** has been described: Rokach, J.; Hamel, P.; Hunter, N. R.; Reader, G.; Rooney, C. S.; Anderson, P. S.; Cragoe, E. J., Jr.; Mandel, L. R. *J. Med. Chem.* **1979**, *22*, 237.

(11) Kobayashi, M.; Okamoto, S. *Tetrahedron Lett.* **2006**, *47*, 4347. We thank Prof. Okamoto for communicating their results to us prior to publication.

(12) Preparation of bicyclic isothioureas **13**−**16** (isolated as hydrobromides or hydrochlorides) has been described, e.g.: (a) Cort, L. A. *J. Chem. Soc. C* **1966**, 1226. (b) Dehuri, S. N.; Nayak, A. *J. Indian Chem. Soc.* **1982**, *59*, 1170.

(13) Preliminary studies suggest that this behavior may be due to rapid catalyst deactivation, rather than inherent lack of activity.

(entries 22−24) and 3-methyl-2-butanol (entries 25−27). With these substrates, DHPB was still more active than DMAP, albeit by a smaller margin than in the case of 1-phenylethanol, whereas THTP proved much less active. Plots of percent conversion vs time provided in the Supporting Information indicate that the initial reaction rate with THTP is considerably faster than that with DMAP in acetylation of phenylethanol and comparable in the acetylation of the rest of the substrates examined. However, THTP undergoes gradual deactivation under the reaction conditions, which accounts, at least partly, for its lower overall efficacy.

It is noteworthy that the structures of the three most successful catalysts identified in our and Okamoto's studies—**8**, **15**, and **19**—all contain five-membered rings fused to a tetrahydropyrimidine ring. The structure−activity trends observed within this series may be interpreted as follows: (1) the amidine moiety in itself constitutes a viable catalaphore (**8**), but is subject to stringent geometric requirements; (2) introduction of the sulfur atom results in a sharp increase in catalytic activity (**8** → **15**), which may be ascribed to the nonbonded S−O interactions with the carbonyl oxygen leading to the stabilization of the N-acylated form;[14] (3) benzannellation leads to further enhancement of the catalytic activity (**15** → **19**), which may be due to the aromatic stabilization of the N-acylated form.

While the validity of the above interpretation remains to be verified by future investigations, our findings clearly demonstrate that nonaromatic amidine derivatives can indeed be highly catalytically active in acylation reactions. THTP, an easily obtainable and extremely active achiral acylation catalyst, holds significant promise as a catalaphore for asymmetric catalyst design. Investigation of its utility in other reactions requiring nucleophilic catalysis and preparation and study of its chiral derivatives are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) (a) For examples of intramolecular nonbonded S−O interactions in structurally similar cases, see, e.g.: Nagao, Y.; Hirata, T.; Goto, S.; Sano, S.; Kakehi, A.; Iizuka, K.; Shiro, M. *J. Am. Chem. Soc.* **1998**, *120*, 3104. (b) We thank Prof. Glaser (University of Missouri—Columbia) for bringing this phenomenon to our attention.