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# Annelated Pyridines as Highly Nucleophilic and Lewis Basic Catalysts for Acylation Reactions

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**Abstract:** New heterocyclic derivatives of 9-azajulolidine have been synthesized and characterized with respect to their nucleophilicity and Lewis basicity. The Lewis basicity of these bases as quantified through their theoretically calculated methyl-cation affinities correlate well with the experimentally measured reaction rates for addition to benzhydryl cations. All newly synthesized pyridines show exceptional catalytic activities in benchmark acylation reactions, which correlate only poorly with Lewis basicity or nucleophilicity parameters. A combination of Lewis basicity with charge and geometric parameters in the framework of a three-component quantitative structure–activity relationship (QSAR) model is, however, highly predictive.

**Keywords:** acylation · nucleophilic catalysis · organocatalysis · structure–activity relationships

## Introduction

The catalytic potential of donor-substituted pyridines in acylation reactions is well established, since the reports on 4-*N*,*N*-dimethylaminopyridine (DMAP; **1**) by Litvinenko et al. in 1967 and by Steglich et al. in 1969.[1–3] A small improvement in catalytic activity was soon after documented for 4-(pyrrolidinyl)pyridine (PPY; **2**),[4] but it took until 2003 that a larger increase in activity could be realized with annelated pyridines such as 9-azajulolidine (**3**).[5] Pyridine derivative **3** is a powerful organocatalyst not only suitable for acylation reactions, but also for other transformations such as the aza-Morita–Baylis–Hillman reaction.[6] Further development of this class of catalysts through modification of the attached ring systems thus seems desirable, but faces significant synthetic hurdles. We, therefore, explore here the potential of the respective di- and trinitrogen-substituted systems **4** and **5** (Figure 1).

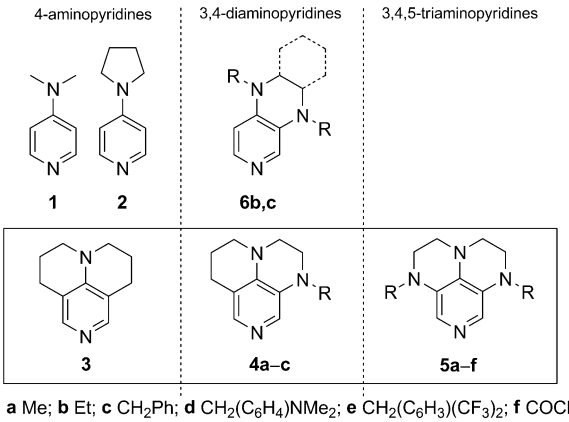


Figure 1. Structures of pyridine derivatives based on the DMAP motif used as nucleophilic organocatalysts.

Selected members of this family were recently characterized with respect to their affinity towards carbocation electrophiles.[7] These data show that the additional amino-substituents attached to the 3- and 5-position of pyridines **4** and **5** further increase the Lewis basicity relative to the all-carbon analogue **3**. Furthermore, for some derivatives of **5** it was recently shown in kinetic studies that the reaction rates for addition to benzhydryl cations correlate with theoretically calculated Lewis basicity.[8] We now show how the Lewis base properties of the tricyclic catalysts **3**–**5** depend on their particular substituent pattern, and also test the catalytic activity of these compounds using the acylation of 1-ethinylcyclohexanol as a benchmark reaction.

## Results and Discussion

**Synthesis and structure**: The synthesis of catalysts of general structure **4** follows the same strategy used to access pyridine derivatives **6**.[9,10] This involves initial condensation of 3,4-di-

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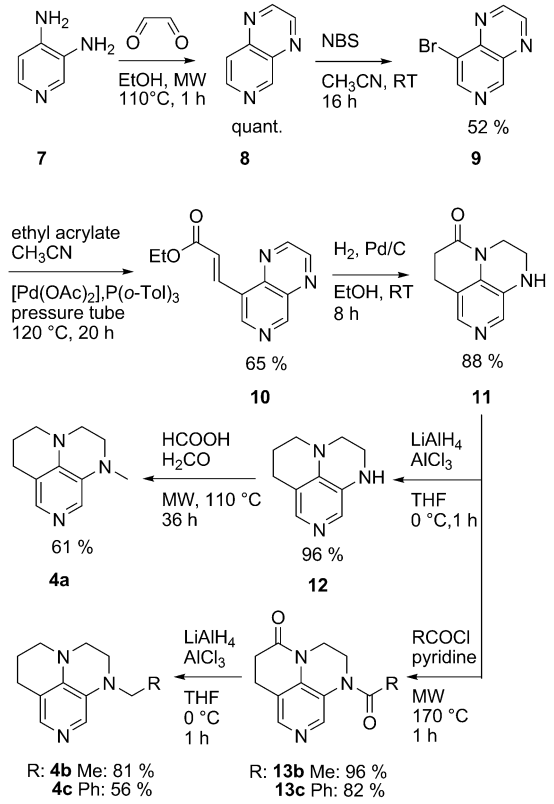
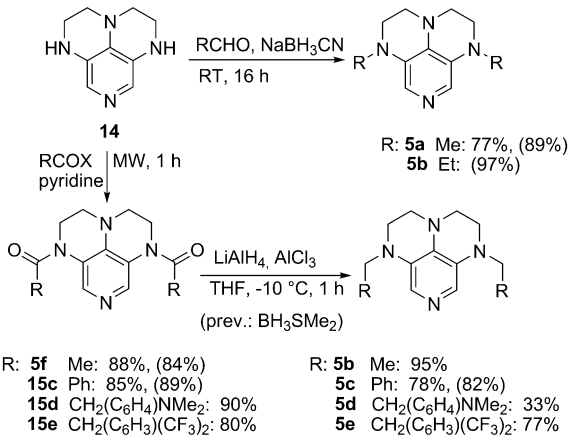
aminopyridine (**7**) with glyoxal and subsequent bromination at C5-position of the pyridine ring with *N*-bromosuccinimide (NBS) in acetonitrile at room temperature. Subsequent Heck reaction of **9** with ethyl acrylate worked best on large scale with minimal solvent in a pressure tube. The reduction and immediate cyclization of **10** to core structure **11** was accomplished using palladium on charcoal in 88% yield. Catalysts **4a–c** can all be synthesized starting from **11**. Synthesis of **4a** was accomplished through reduction with $LiAlH_4$/$AlCl_3$ to furnish 96% of **12** and subsequent Eschweiler–Clark reaction providing *N*-methylated product **4a** in 61% yield (Scheme 1). It should be noted that the acidic reaction




Scheme 1. Synthesis of compounds **4a–c** from 3,4-diaminopyridine (**7**) and glyoxal.

conditions used under Eschweiler–Clark conditions are significantly more effective than alkylation under basic conditions due to the intermediate protonation (and thus deactivation) of the pyridine nitrogen atom. Catalysts **4b** and **c** were synthesized by microwave-induced acylation of the amino group of **11** with the appropriate acid chloride in pyridine. The acylated species **13b** (96%) and **13c** (82%) were obtained in good to excellent yields. Subsequent reduction of both amide groups in **13** with $LiAlH_4$/$AlCl_3$ furnished **4b** (81%) and **4c** (56%) in just one hour reaction time.

Catalysts **5a–e** were synthesized from the 3,4,5-triaminopridine derivative **14**, whose efficient synthesis was recently described by David et al.[8] Although catalyst **5a** was synthesized in 77% yield by reductive amination according to the



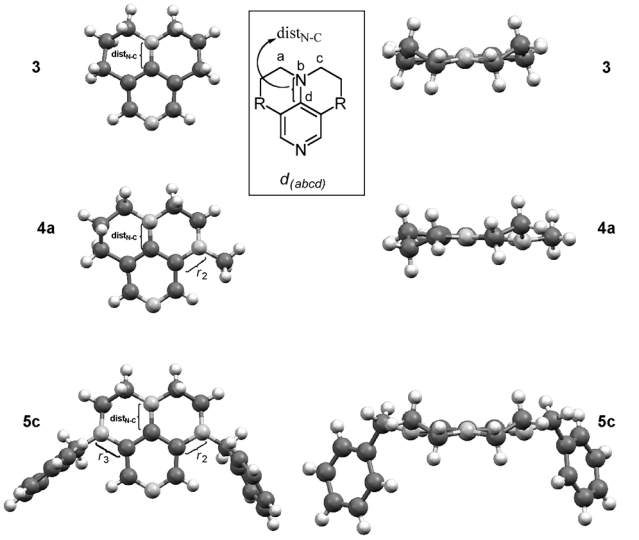

Scheme 2. Synthesis of catalysts **5a–e**. Previously obtained yields by David et al.[8] are given in brackets.

originally proposed route (Scheme 2),[8] minor modifications in workup procedures and the choice of reducing agent were introduced in the synthesis of **5b** and **c**. Changes include the use of microwave irradiation (instead of conventional heating) in the respective acylation reactions, which reduces reaction times for the acylation of **14** from six hours (**5f**) or three days (**15c**) to just one hour (for both systems) without any detriment of yield. Final reduction of the bisamides **15** was accomplished with $LiAlH_4$/$AlCl_3$ (instead of $BH_3{\cdot}SMe_2$ used by David et al.) in just one hour at −10 °C yielding **5b** and **c** in comparable yields (Scheme 2). Following the same strategy additional derivatives of **5** bearing strongly electron-donating groups in the aryl ring (as in **5d**) as well as electron-withdrawing groups (as in **5e**) were synthesized in order to investigate different electronic effects on the catalyst reactivity. The acylation of **14** with four different acyl donors and subsequent reduction of the amide intermediates proceeded smoothly and in good to excellent yields in all cases, except for catalyst **5d**. Due to the high basicity of this latter compound the final product isolation and purification steps after reduction of amide **15d** could only be executed with substantial loss of material.

It should be noted at this point that purification of compounds of type **4** and **5** requires repeated chromatography on basic aluminum oxide[11] (Brockmann 3) until analytically pure material was obtained (as determined by $^1$H NMR spectroscopy). Such material solidified on standing and was further purified through recrystallization from ethyl acetate under nitrogen and dried in high vacuum for at least eight hours and stored in an exsiccator in the dark at −4 °C. The evaporation of solvent in all synthetic and purification steps of **4** and **5** was performed in a rotatory evaporator operated under nitrogen and at a water bath temperature not exceeding 30 °C. The catalytic activity of **4** and **5** depends significantly on their purity, and deviations from the purification protocol outlined above may thus lead to significant reduction of reaction rates. The Lewis basicity of amino-substituted pyridines depends on the alignment of the substituent nitrogen lone pair orbital with the pyridine π system. Structur-

al parameters connected to this orbital interaction are the 4-N–C bond length $dist_{N-C}$ (the distance between the pyridine carbon atom at the 4-position and the nitrogen atom attached to the same position) as well as the degree of pyramidalization of the nitrogen substituent ($d_{(abcd)}$). Shorter N–C bond lengths and smaller pyramidalization angles are commonly considered to reflect better orbital alignment. These parameters are shown in Figure 2 in the crystal structures of pyridines **3**, **4a**, and **5c** as depicted in front (left) and top (right) view.



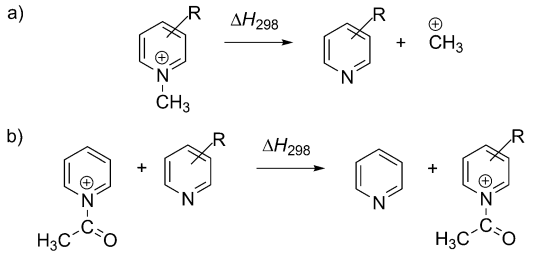

| | 3 | | 4a | | 5c | |
|---|---|---|---|---|---|---|
| | $dist_{N-C}$/pm | $d_{(abcd)}$ | $dist_{N-C}$/pm | $d_{(abcd)}$ | $dist_{N-C}$/pm | $d_{(abcd)}$ |
| crystal structure | 137.5 | 12.7 ° | 137.3 | 1.0 ° | 137.7 | 11.4 ° |
| best conformer[a] | 138.8 | 12.9 ° | 139.4 | 2.1 ° | 140.4 | 21.1 ° |

[a] MP2/6-31+G(2d,p)//B98/6-31G(d) with PCM/UAHF/RHF/6-31G(d) solvation energies for chloroform.

Figure 2. Crystal structures of **3**, **4a**, and **5c**. 4-N–C bond lengths ($dist_{N-C}$/pm) and pyramidalization angles $d_{(abcd)}$ of crystal structure and best computed conformer.

The 4-N–C bond lengths in the crystal structures of mono-, di-, and triaminopyridines are actually identical within experimental uncertainty (137.5 ± 0.2 pm), whereas the structures optimized at B98/6-31G(d) level (best conformer each) show slightly larger bond lengths in all cases. For the pyramidalization angles ($d_{(abcd)}$) the best conformers of **3** and **4a** reflect the experimental results rather well. For **5c** the best conformer shows a 10° higher pyramidalization angle as compared to the crystal structure. For this latter system a second conformer exists only 1 kJ mol$^{-1}$ higher in energy with a deformation angle of 10.7°, which is closely similar to the crystal structure. This implies that conformational reorientation of the annelated six-membered rings and accompanying variations in the pyramidalization of the central nitrogen atom occurs with rather little increase in energy. From all structures analyzed it appears that catalysts **4a** and **5d** (see Supporting Information) provide the best orbital alignment between the nitrogen lone-pair electrons and pyridine π-system.

**Cation affinity data**: In order to match these structural properties to actual Lewis basicities, methyl-cation affinities (MCA) and acylation enthalpies $\Delta H_{ac}$ as defined in Scheme 3a




Scheme 3. Definitions of a) methyl-cation affinities and b) isodesmic acetyl-transfer reaction.

and b have been collected in Table 1 for most of the synthesized pyridines. The definition chosen here for methyl-cation affinities follows the mass-spectrometric definition of the gas-phase proton affinity as recently applied to a larger number of Lewis bases.[12,7] The acylation enthalpies as defined in Scheme 3b reflect relative acetyl-cation affinities between the selected Lewis base and pyridine as the reference system. This latter definition was also used in previous studies matching the Lewis basicities of pyridines with the respective catalytic activity in acylation reactions. Both measures of Lewis basicity have been quantified here at the MP2/6-31+G(2d,p)//B98/6-31G(d) level of theory in the gas phase. How solvent effects impact the Lewis basicity has been tested for the acylation enthalpies using the polarizable-continuum model (PCM) in chloroform at the RHF/6-31G(d) level with UAHF radii.

All three types of affinity data indicate quite clearly, that all tricyclic catalysts displayed in Figure 1 are stronger Lewis bases than the parent DMAP. The triaminopyridine **5d** is the strongest Lewis base, irrespective of the choice of Lewis basicity indicator.

**Nucleophilicity**: In how far the theoretically calculated Lewis basicity correlates well with reaction rates for reaction with reference electrophiles was next tested for additions to benzhydrylium cations. This type of addition reaction provides the basis for Mayr's comprehensive nucleophilicity scale according to the linear free energy relationship [Eq. (1)].

$$\log k_2\ (20\,^{\circ}\mathrm{C}) = s_N(N + E) \qquad (1)$$

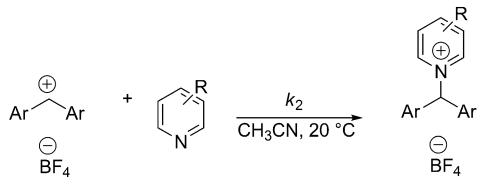
Table 1. Half-life times and affinity numbers for the catalysts synthesized.

| Cat. | MCA [kJ mol$^{-1}$] | $\Delta H_{ac}$ MP2-5[a] [kJ mol$^{-1}$] | $\Delta H_{ac/solv}$ MP2-5/solv[a] [kJ mol$^{-1}$] | $N$ ($s_N$)[b] | $t_{1/2}$[c] [min] |
|---|---|---|---|---|---|
| 10 mol % catalyst loading | | | | | |
| **5d** | 661.3 | −163.7 | −106.7 | – | 38.4 ± 1.0 |
| **5c** | 636.8 | −141.3 | −98.3 | 17.69 (0.57)[e] | 65.4 ± 3.1 |
| **5b** | 621.6 | −120.6 | −87.8 | 16.81 (0.60)[e] | 44.2 ± 1.5 |
| **4c** | 620.8 | −123.4 | −90.2 | – | 34.3 ± 0.2 |
| **5a** | 618.7 | −118.0 | −89.2 | 16.65 (0.58)[e] | 38.0 ± 1.5 |
| **4b** | 613.3 | −113.5 | −87.5 | – | 13.8 ± 0.4 |
| **4a** | 611.0 | −111.0 | −86.8 | – | 17.9 ± 0.9 |
| **3** | 602.7 | −102.3 | −82.2 | 15.60 (0.68) | 14.7 ± 0.5[g] |
| **5e** | 596.8 | −101.5 | −69.5 | – | 227.3 ± 0.5 |
| **2** | 590.1 | −87.5 | −67.6 | 14.99 (0.68) | 67.0 ± 0.1[h] |
| **1** | 581.2 | −77.1 | −61.2 | 14.95 (0.67)[e,f] | 151.0 ± 1.7[h] |
| **18** | – | −90.1[d] | −55.0[d] | – | 878.1 ± 59.9 |
| **5f** | – | −71.6 | −48.2 | 15.39 (0.60)[e] | ≥2880[i] |
| 3 mol % catalyst loading | | | | | |
| **4b** | 613.3 | −113.5 | −87.5 | – | 45.9 |
| **4a** | 611.0 | −111.0 | −86.8 | – | 57.4 |
| **3** | 602.7 | −102.3 | −82.2 | 15.60 (0.68) | 46.7 |

[a] Levels of theory: "MP2-5": MP2/6-31+G(2d,p)//B98/6-31G(d), "MP2-5/solv": MP2/6-31+G(2d,p)//B98/6-31G(d) with PCM/UAHF/RHF/6-31G(d) solvation energies for chloroform. [b] Nucleophilicity parameters in acetonitrile according to equation (1). [c] Half-life times (min) for acylation reaction (Scheme 5). [d] Extrapolated (for details see the Supporting Information). [e] Data from [8]. [f] New measurements: 15.51 (0.62)[14]. [g] Remeasured and in line with published data (15 ± 0.1)[10]. [h] Data from [10]. [i] Extrapolated (13 % conversion after 12 h).

The rate constants for nucleophile/electrophile combination reactions $k_2$ were determined as described in the Supporting Information. The $k_2$ values were combined with the solvent independent electrophilicity parameter $E$ for different cations (see Supporting Information) to yield the solvent dependent nucleophilicity parameter $N$ (nucleophilicity) and $s_N$ (nucleophile-dependent sensitivity) as shown in Scheme 4 and Figure 3. These parameters are available for a variety of pyridines in several solvents such as $CH_2Cl_2$ and $CH_3CN$.[13]

In order to compare the nucleophilic reactivities of **1**–**5** with the corresponding acylation enthalpies according to




Scheme 4. Reactions of pyridines with benzhydrylium cations in $CH_3CN$ at 20 °C.

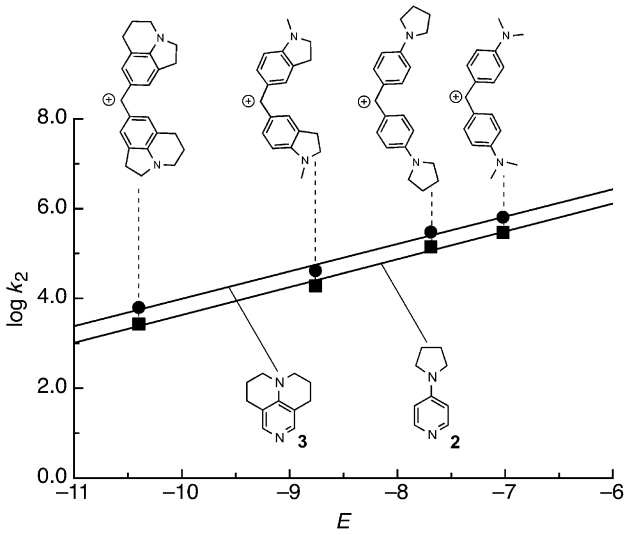



Figure 3. Correlation of acylation enthalpies ($\Delta H_{ac/solv}$) with $N$-parameters.

Scheme 3b the nucleophilicity parameters of **2** and **3** were determined in acetonitrile (Figure 3).

Figure 4 shows that nucleophilic reactivities of pyridines **1**–**3**,**5** correlate quite well (with $R^2 = 0.9022$) with acylation enthalpies in chloroform and even better with the gas phase acylation enthalpies ($R^2 = 0.9702$) (see Supporting Information).

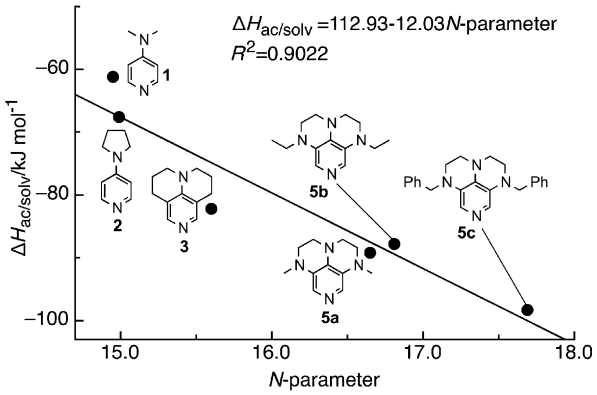
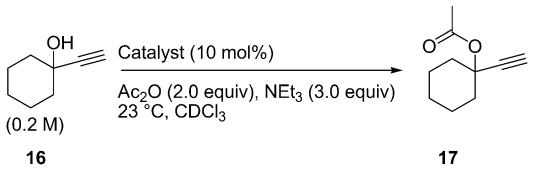



Figure 4. Determination of nucleophilicity parameters $N$ and $s_N$ (nucleophile-dependent sensitivity) through combination of rate constants $k_2$ with electrophilicity parameter $E$ for different cations.

We can thus conclude that the kinetic data for single-step addition to cationic electrophiles are related to the thermodynamic data for this structurally quite homogenous set of nucleophiles.

**Catalytic activity**: The catalytic potential of the synthesized catalysts has subsequently been explored in the acetylation of tertiary alcohol **16** (Scheme 5). The reactions were followed by $^1$H NMR spectroscopy in $CDCl_3$ as the solvent. All reactions eventually proceed to full conversion and the




Scheme 5. Acylation reaction in $CDCl_3$.

rates of the reactions can thus be characterized by the reaction half-life $t_{1/2}$ using an approach described previously.[10] As expected from the calculated Lewis basicity and the experimentally measured *N*-parameters, all annelated pyridine derivatives except **5e** and **5f** are more reactive than DMAP (**1**) (Table 1, last column).

The substantial influence of conformational fixation on the reactivity is illustrated by the 60-fold decrease in activity going from catalyst **3** to **18** (compare Table 1, the structure of catalyst **18** is depicted in Figure 5). In catalyst **18**, formally even more inductive effects than in the annelated **3** are present, but without any conformational fixation.

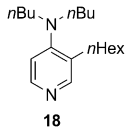



Figure 5. Conformationally unrestricted catalyst **18**.

A comparison of the catalytic activities of the annelated catalyst systems shows that the conformationally constrained 4-aminopyridine **3** and the 3,4-diaminopyridines **4** are significantly more active than the 3,4,5-triaminopyridines **5** (Table 1). This is in remarkable contrast to the rather high Lewis basicity and *N*-parameters determined for this latter class of nucleophiles. The optimum balance between catalytic activity and nucleophilicity is thus achieved in pyridines **3** and **4**, in which one or two nitrogen atoms are incorporated into conformationally-restricted ring systems. The most active catalyst is the newly synthesized catalyst **4b**, which displays an even shorter half-life time than the most active catalyst **6b** in previous studies[10] and is also slightly more active than 9-azajulolidine (**3**). These catalysts are more than ten times more active than DMAP (**1**) (151 min) and thus very potent acyl-transfer reagents. It is of note that in series **4**, ethyl-substituted compounds are slightly more efficient than methyl derivatives, whereas in the 3,4,5-triaminopyridine series the ethyl-substituted compound **5b** is less effective than the methyl-substituted **5a**. The benzylic compound **4c** is, in comparison, much less active than the alkyl-substituted compounds **4a** and **b**. This ordering is also found for the 3,4,5-triaminopyridines **5a**–**c**. Comparison of the benzylic compounds **5c**–**e** shows that electron-donating groups shorten the reaction half-life whereas electron-withdrawing groups decrease the catalytic activity tremendously (e.g., **5e** has a half-life time of 227 min whereas that of **5c** amounts to 65 min). Reaction times are very short at 10% catalyst loading for some of the annelated pyridine derivatives, making precise measurements and an accurate comparison of the most active systems difficult. Reaction rates

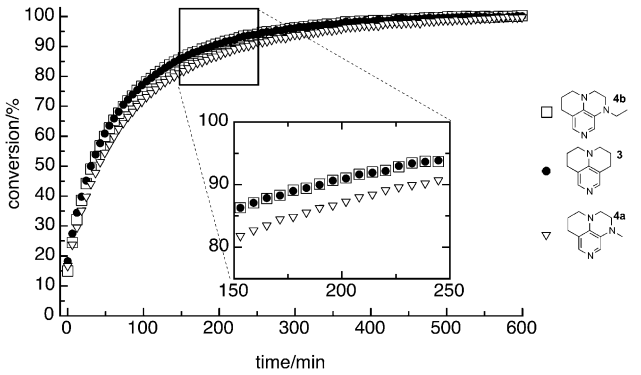



Figure 6. Conversion–time plots for catalysts **4b**, **3**, and **4a** at 3 mol% catalyst loading.

for these systems were therefore redetermined at 3% catalyst loading. From the conversion data shown in Figure 6 and reaction half-lives in Table 1 one can see that catalysts **4b** and **3** are equally active under these conditions. With reaction half-lives of 46–47 min they are more than three times faster at 3% catalyst loading than DMAP (**1**) at 10% loading and thus the most active catalysts among the highly nucleophilic pyridines. With a half-life of 57.4 min, catalyst **4a** is still somewhat less active than the **3** and **4b**, but still more active at 3 mol% than PPY (**2**) at 10 mol%.

The unexpectedly moderate catalytic activity of the strongly Lewis basic 3,4,5-triaminopyridines **5** raises the question whether the reaction mechanism is the same for all aminopyridines studied here. One of the key questions concerns the dependence of the reaction rate on the catalyst concentration. Earlier studies had established a clear first-order dependence for aminopyridines such as DMAP (**1**) for benchmark reaction (Scheme 5).[15] Using catalyst concentrations between 2.5–10 mol% a first-order dependence can also be established for the triaminopyridine **5c** (Figure 7), which is one of the most Lewis basic candidates of series **5**. This excludes the possibility that a second catalyst molecule acts as general base in the rate-limiting step.

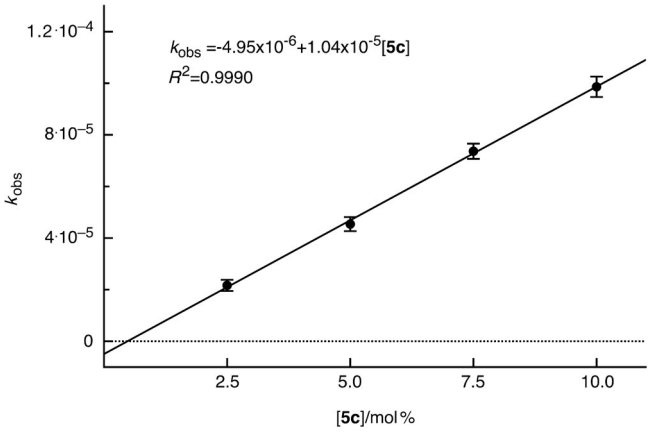
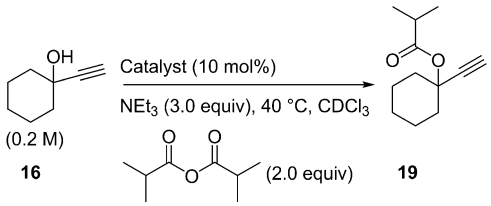



Figure 7. Variation of the reaction rate as a function of the concentration of catalyst **5c** in acylation reaction shown in Scheme 5.

The rather small intercept of the correlation line with the ordinate axis also indicates a negligible background reaction and the reaction mechanism thus seems to be identical to that for DMAP (**1**).

How annelated catalysts **5** respond to changes in the steric demand of the acylating reagent was subsequently tested by reacting alcohol **16** with isobutyric anhydride (Scheme 6). These studies were performed at slightly elevated temperatures (40 °C) in deuterochloroform (Scheme 4). As reported earlier for simple aminopyridines such as PPY (**2**), the rates of this latter transformation are much slower than that of the benchmark reaction shown in Scheme 5 (Table 2). The ratio of half-life times for these two transformations displays a distinct dependence on the absolute catalyst activity in that the most active catalyst **3** reacts most sensitively to the steric demand of the acylating agent.




Scheme 6. Isobutyrylation of alcohol **16** in chloroform at 40 °C.

Table 2. Comparison of half-life times[a] for benchmark reactions shown in Scheme 5 ($t_{1/2}$(S 5)) and Scheme 6 ($t_{1/2}$(S 6)) and the ratio of these two reactivity parameters.

| Cat. | $t_{1/2}$(S5) | $t_{1/2}$(S6) | Ratio |
|---|---|---|---|
| **3** | 67[b] | 14.7 ± 0.5 | 4.56 |
| **5b** | 114 | 44.2 ± 1.5 | 2.56 |
| **2** | 171[b] | 67 ± 0.1[c] | 2.55 |
| **1** | 302[b] | 151 ± 1.7[c] | 2.00 |

[a] Half-life time (min). [b] Data from [9a]. [c] Data from [10]

Previous studies have clearly established that Lewis base catalyzed acylations work best in apolar organic solvents such as toluene, but can be quite slow in polar organic solvents.[4,16] We therefore examined acylation reaction (Scheme 5) in different solvents using commercially available **2** as the catalyst. Among all tested solvents the reaction was found to be fastest in $CDCl_3$ (for details see Supporting Information). Also, earlier studies by Han et al. indicate that catalysts **3** and **5b** react with comparable rates with **16** according to Scheme 5 in $CD_2Cl_2$.[17] As these results differ from our findings in $CDCl_3$ (Table 1) we have now reinvestigated benchmark reaction (Scheme 5) in $CD_2Cl_2$.

The results obtained at 10% catalyst loading (Figure 8, Table 3) indicate that reactions can indeed be slightly slower in $CD_2Cl_2$ than in $CDCl_3$, but that the magnitude of the solvent effect depends on the nature of the catalyst. In both solvents, however, we find that catalyst **3** is clearly more effective than the 3,4,5-triaminopyridine **5b**. The lack of correlation between Lewis basicity and nucleophilicity parameters on one hand and catalytic performance in acylation reactions at different catalyst loadings in the other hand is thus clearly not an issue of solvent polarity.

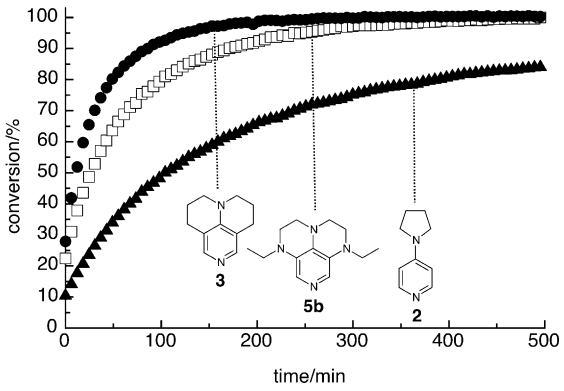



Figure 8. Conversion–time plots for catalysts **2**, **3**, and **5b** for acylation reactions (Scheme 5) in dichloromethane.

Table 3. Half-life times for catalysts **2**, **3** and **5b** for reactions (Scheme 5) in dichloromethane ($t_{1/2}(CD_2Cl_2)$) and chloroform ($t_{1/2}(CDCl_3)$), and the ratio of these kinetic parameters.

| Cat. | $t_{1/2}(CD_2Cl_2)$ | $t_{1/2}(CDCl_3)$ | Ratio |
|---|---|---|---|
| **3** | 20.8 ± 0.6 | 14.7 ± 0.5 | 1.42 |
| **5b** | 42.6 ± 0.6 | 44.2 ± 1.5 | 0.96 |
| **2** | 108.3 ± 0.9 | 67 ± 0.1[b] | 1.61 |

[a] Half-life time (min). [b] Data from [10].

The catalytic activities for the benchmark reaction shown in Scheme 5 correlate poorly with the calculated acylation enthalpies ($R^2 = 0.2733$, Figure 9). This is in contrast to earlier studies for less Lewis basic catalysts,[18] in which significantly better correlations were found. Could the nature of the one-step reaction underlying the quantification of Lewis basicity and nucleophilicities (as described above) in comparison to the multistep nature of catalytic processes be the

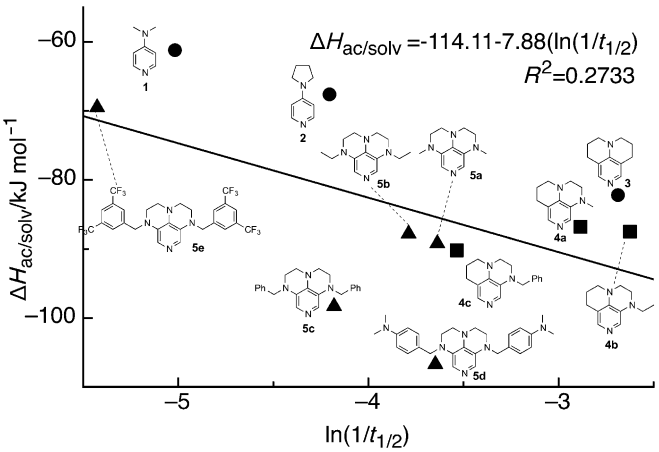



Figure 9. Correlation of acylation enthalpies ($\Delta H_{ac/solv}$) with kinetic data for acylation reactions (Scheme 5) for **1**–**3** (circles), **4a**–**c** (squares), **5a**–**e** (triangles).

reason for this discrepancy? As noted in previous studies, none of the ground state descriptors for the pyridine nitrogen atom (that is: the reaction center) has significant predictive value.[18]

The possibility to predict catalytic rates using a multiparameter QSAR model was therefore tested, starting from an initial set of eight different parameters (see Supporting Information for details). The most important descriptors could be identified as the acylation enthalpies including solvation terms in chloroform ($\Delta H_{ac/solv}$, in kJ mol$^{-1}$), the charge of the *ortho*-hydrogen atom of the free catalyst ($q_{ortho-H}$, in units of elemental charge, e) and the bond length ($dist_{N-C}$, in Å) between the carbon atom at the 4-position and the pyridine nitrogen atom attached to the same position. A QSAR model based on these three parameters for catalysts **1–5** (11 structures) constructed with Sybyl X 2.0 yields good correlations between actual and predicted catalytic activity ($R^2 = 0.9320$, $Q^2 = 0.7880$, see Figure 10). The QSAR Equation (2) contains the acylation enthalpies $\Delta H_{ac/solv}$ as a dominant term (term 2), more negative acylation enthalpies implying faster reaction rates. The *ortho*-hydrogen charge and the N–C distance parameters, in contrast, enter the QSAR equation as term 3 and 4 with negative sign, implying slower reaction rates for catalysts with more positively charged *ortho*-hydrogen atoms and larger N–C bond lengths.

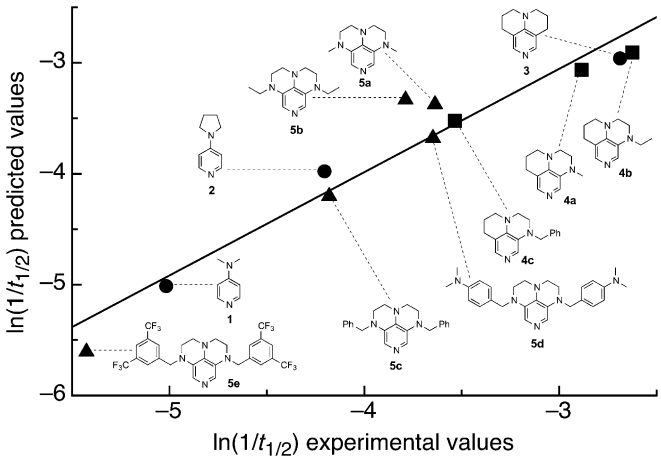



Figure 10. Experimental versus predicted values for $\ln(1/t_{1/2})$ for the three-parameter QSAR model involving $\Delta H_{ac/solv}$, $q_{ortho-H}$ and $dist_{N-C}$.

$$\ln 1/t_{1/2} = \underbrace{85.867}_{\text{term 1}} \underbrace{- 0.080 \bullet \Delta H_{ac/solv}}_{\text{term 2}} \underbrace{- 162.8 \bullet q_{ortho-H}}_{\text{term 3}} \underbrace{- 44.0 \bullet dist_{N-C}}_{\text{term 4}} \quad (2)$$

As is readily seen from the data collected in Table 4 for catalysts **3**, **4a**, and **5a**, the last two terms are those relevant for predicting slower reactions for catalysts of higher Lewis basicity such as **5a**.

The value of this QSAR model, which is exclusively based on parameters available from theoretical data for the catalysts and their acylated intermediates, lies in the potential to further optimize the catalytic activity of pyridine catalysts.

Table 4. Comparison of QSAR parameters of annelated catalysts **3**, **4a**, and **5a**.

| Cat. | $\Delta H_{ac/solv}$ [kJ mol$^{-1}$] | $q_{ortho-H}$ | $dist_{N-C}$ [Å] | $\ln(1/t_{1/2})$ exptl | $\ln(1/t_{1/2})$ calcd | residual |
|---|---|---|---|---|---|---|
| **3** | −82.20 | 0.2108 | 1.3884 | −2.6879 | −2.9648 | 0.2769 |
| **4a** | −86.80 | 0.2122 | 1.3939 | −2.8848 | −3.0668 | 0.1820 |
| **5a** | −89.20 | 0.2137 | 1.3997 | −3.6376 | −3.3741 | −0.2635 |

## Conclusion

In conclusion we synthesized several new derivatives of 9-azajulolidine (**3**) and proved their structures by X-ray analysis. All new derivatives are strong Lewis bases relative to the parent DMAP (**1**) system. The Lewis basicity correlates rather well with reaction rates for addition to cationic electrophiles, but not with rate data for the catalytic acylation of tertiary alcohol **16**. In qualitative terms this implies that catalysts with greater Lewis basicity will eventually slow down catalytic processes due to the increasing difficulty of detaching the product electrophiles. This general observation has recently also been made by Christmann et al. in the Lewis base catalyzed isomerization of (*Z*)-allylic alcohols.[19]

## Experimental Section

All air and water sensitive manipulations were carried out under a nitrogen atmosphere using standard Schlenk techniques. Calibrated flasks for kinetic measurements were dried in the oven at 120 °C for at least 12 h prior to use and then assembled quickly when still hot, cooled under a nitrogen stream and sealed with a rubber septum. All commercial chemicals were of reagent grade and were used as received unless otherwise noted. Acetonitrile (Acros > 99.9 %, extra dry), was purchased and used without further purification. $CDCl_3$ was refluxed for at least one hour over $CaH_2$ and subsequently distilled. $^1$H and $^{13}$C NMR spectra were recorded on Varian 300 or Varian INOVA 400 and 600 machines at room temperature. All $^1$H chemical shifts are reported in ppm ($\delta$) relative to TMS (0.00); $^{13}$C chemical shifts are reported in ppm ($\delta$) relative to $CDCl_3$ (77.16). $^1$H NMR kinetic data were measured on a Varian Mercury 200 MHz spectrometer at 23 °C. HRMS spectra (ESI-MS) were carried out using a Thermo Finnigan LTQ FT instrument. IR spectra were measured on a Perkin–Elmer FT-IR BX spectrometer mounting ATR technology. Reactions utilizing microwave technology were conducted in a CEM Discover Benchmate microwave reactor (model nr. 908010). Analytical TLC was carried out using aluminum sheets with silica gel Si 60 F254. 9-Azajulolidine (**3**) was obtained from TCI China (CAS.nr.: 6052–72–8), purity: > 97.0 % (GC).

Reaction kinetics were followed using $^1$H NMR spectroscopy and evaluated according to a previously published method[10] as described in detail in the Supporting Information.

The measurements of *N*-parameters were carried out according to the method described by Mayr et al.[20,13b]

Detailed procedures for the synthesis of all new compounds and catalysts have been compiled in the Supporting Information together with the required analytic data. CCDC-633500 (**3a**), CCDC-914973 (**4a**), CCDC-

914974 (**5c**), CCDC-914975 (**5d**) and CCDC-914976 (**5e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[1] a) L. M. Litvinenko, A. I. Kirichenko, *Dokl. Akad. Nauk SSSR Ser. Khim.* **1967**, *176*, 97–100; b) W. Steglich, G. Höfle, *Angew. Chem.* **1969**, *81*, 1001; *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 981.
[2] a) G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem.* **1978**, *90*, 602–615; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 569–583.
[3] Review: N. De Rycke, F. Couty, O. R. P. David, *Chem. Eur. J.* **2011**, *17*, 12852–12871.
[4] A. Hassner, L. R. Krepski, V. Alexanian, *Tetrahedron* **1978**, *34*, 2069–2076.
[5] M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich, H. Zipse, *Angew. Chem.* **2003**, *115*, 4975; *Angew. Chem. Int. Ed.* **2003**, *42*, 4826–4828.
[6] C. Lindner, R. Tandon, Y. Liu, B. Maryasin, H. Zipse, *Org. Biomol. Chem.* **2012**, *10*, 3210–3218.
[7] C. Lindner, R. Tandon, B. Maryasin, E. Larionov, H. Zipse, *Beilstein J. Org. Chem.* **2012**, *8*, 1406–1442.
[8] N. De Rycke, G. Berionni, F. Couty, H. Mayr, R. Goumont, O. R. P. David, *Org. Lett.* **2011**, *13*, 530–533.
[9] a) I. Held, S. Xu, H. Zipse, *Synthesis* **2007**, 1185–1196; b) H. Zipse, I. Held, Bayer Material Science LLC, US 2008/0176747 A1, **2008**.
[10] I. Held, E. Larionov, C. Bozler, F. Wagner, H. Zipse, *Synthesis* **2009**, 2267–2277.
[11] The catalyst was found to bind strongly to silica gel and was difficult to recover.
[12] a) C. Lindner, B. Maryasin, F. Richter, H. Zipse, *J. Phys. Org. Chem.* **2010**, *23*, 1036–1042; b) Y. Wei, G. N. Sastry, H. Zipse, *J. Am. Chem. Soc.* **2008**, *130*, 3473–3477; c) Y. Wei, T. Singer, H. Mayr, G. N. Sastry, H. Zipse, *J. Comp. Chem.* **2008**, *29*, 291–297.
[13] a) H. Mayr, B. Kempf, A. R. Ofial, *Acc. Chem. Res.* **2003**, *36*, 66–77; b) H. Mayr, M. Patz, *Angew. Chem.* **1994**, *106*, 990–1010; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 938–957; c) H. Mayr, M. Patz, M. F. Gotta, A. R. Ofial, *Pure Appl. Chem.* **1998**, *70*, 1993–2000; d) H. Mayr, A. R. Ofial in *Carbocation Chemistry* (Eds.: G. A. Olah, G. K. S. Prakash), Wiley, New York, **2004**, pp. 331–358; e) H. Mayr, A. R. Ofial, *Pure Appl. Chem.* **2005**, *77*, 1807–1821; f) R. Lucius, R. Loos, H. Mayr, *Angew. Chem.* **2002**, *114*, 97–102; *Angew. Chem. Int. Ed.* **2002**, *41*, 91–95; g) M. Baidya, S. Kobayashi, F. Brotzel, U. Schmidhammer, E. Riedle, H. Mayr, *Angew. Chem.* **2007**, *119*, 6288–6292; *Angew. Chem. Int. Ed.* **2007**, *46*, 6176–6179; h) H. Mayr, J. Bartl, G. Hagen, *Angew. Chem.* **1992**, *104*, 1689–1691; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1613–1615.
[14] T. A. Nigst, J. Ammer, H. Mayr, *J. Phys. Chem. A* **2012**, *116*, 8494–8499.
[15] S. Xu, I. Held, B. Kempf, H. Mayr, W. Steglich, H. Zipse, *Chem. Eur. J.* **2005**, *11*, 4751–4757.
[16] A. Sakakura, K. Kawajiri, T. Ohkubo, Y. Kosugi, K. Ishihara, *J. Am. Chem. Soc.* **2007**, *129*, 14775–14779.
[17] a) S. Singh, G. Das, O. V. Singh, H. Han, *Org. Lett.* **2007**, *9*, 401–404; b) S. Singh, G. Das, O. V. Singh, H. Han, *Tetrahedron Lett.* **2007**, *48*, 1983–1986.
[18] E. Larionov, F. Achrainer, J. Humin, H. Zipse, *ChemCatChem.* **2012**, *4*, 559–566.
[19] D. Könning, W. Hiller, M. Christmann, *Org. Lett.* **2012**, *14*, 5258–5261..
[20] H. Mayr, T. Bug, M. F. Gotta, N. Hering, B. Irrgang, B. Janker, B. Kempf, R. Loos, A. R. Ofial, G. Remennikov, H. Schimmel, *J. Am. Chem. Soc.* **2001**, *123*, 9500–9512. For a comprehensive listing of nucleophilicity parameters $N$, $s_N$ and electrophilicity parameters $E$ see http://www.cup.uni-muenchen.de/oc/mayr/DBintro.html.

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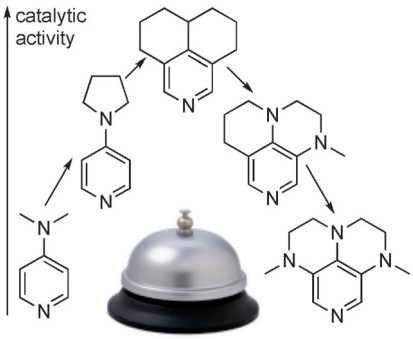
**A special relationship**: Highly nucleophilic and Lewis basic derivatives of 9-azajulolidine have been synthesized and a good correlation between Lewis basicity and nucleophilicity has been obtained. The catalytic performance of these compounds in acylation reactions of sterically hindered alcohols is found to be more complex and quantitative prediction of reaction rates requires a three-component quantitative structure–activity relationship (QSAR) model including Lewis basicity, structural, and charge distribution parameters (see figure).




**Lewis Base Catalysis**

*R. Tandon, T. Unzner, T. A. Nigst, N. De Rycke, P. Mayer, B. Wendt, O. R. P. David, H. Zipse* ...* ▮▮▮▮–▮▮▮▮

**Annelated Pyridines as Highly Nucleophilic and Lewis Basic Catalysts for Acylation Reactions**