Modular Design of Pyridine-Based Acyl-Transfer Catalysts

Ingmar Held, Shangjie Xu, Hendrik Zipse*

Department Chemie und Biochemie, LMU München, Butenandtstraße 5-13, 81377 München, Germany
Fax +49(89)218077738; E-mail: zipse@cup.uni-muenchen.de

Received 24 January 2007

Abstract: Derivatives of 3,4-diaminopyridine have been synthesized and studied as catalysts for acyl-transfer reactions. The design of these catalysts is guided by the stability of their acetyl intermediates as determined through theoretical calculations at the B3LYP/6-311 + G(d,p)//B3LYP/6-31G(d) level of theory. The most promising catalysts have been synthesized through a three- to five-step synthesis starting from 3,4-diaminopyridine. The catalytic activity has been determined for the acylation of 1-ethynylcyclohexanol with acetic anhydride at 23 °C and with isobutyric anhydride at 40 °C. For both reactions, the catalytic activity depends dramatically on the substitution pattern of the diaminopyridines. Best results are obtained with catalysts containing alkyl substituents at both amine nitrogens.

Key words: catalysis, nucleophilic pyridines, acylation, alcohols

Donor-substituted pyridines play an important role as nucleophilic catalysts for a variety of synthetically important transformations such as the acylation of alcohols, amines, and enolates.[1,2] More recently major advances have been made in kinetic resolution experiments using appropriately substituted derivatives of DMAP [(4-dimethylamino)pyridine, **1**] or PPY [(4-pyrrolidino)pyridine, **2**].[2–8] Despite these efforts, the current status of the field is somewhat uneven, providing multiple effective solutions for some problems (e.g., the kinetic resolution of secondary alcohols), but leaving other synthetic problems unsolved (e.g., the kinetic resolution of primary or tertiary alcohols). In this situation, the development of a modular concept for the design of new catalysts is highly desirable, because it allows for the broad variation of the catalyst structure within one synthetic strategy. Solutions to this problem have recently been provided by Miller et al. in the development of peptide-based catalysts with imidazole as the active nucleophilic center.[2d,9] Peptides are also the variable component in modified versions of PPY (**2**) developed by Kawabata et al. and by Campbell et al.[3,4] In all of these cases the peptide side chain influences the course of the reaction through making additional contacts to the substrates in the rate-limiting step of the catalytic cycle. However, the character of the nucleophilic center remains largely unaffected by these side chain variations. The modular design of 3-substituted derivatives of **1** and **2** (Figure 1) by several groups has the potential to modify both the nucleophilicity of the pyridine nucleus as well as the asymmetry of the two faces of the pyridine ring.[4–8]

SYNTHESIS 2007, No. 8, pp 1185–1196
Advanced online publication: 28.02.2007
DOI: 10.1055/s-2007-965973; Art ID: Z02207SS

However, experimentation has so far concentrated mainly on maximizing the success of stereodifferentiating processes, and it has therefore remained unclear in how far the variation of the substituents attached to the C3 position of pyridines affect the catalytic activity in absolute rate terms. Very recently Han and co-workers have described highly active catalysts based on the 3,4-diaminopyridine skeleton **3**,[10] (Figure 1) prompting us to describe our own results on this class of compounds.

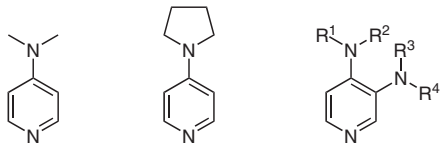
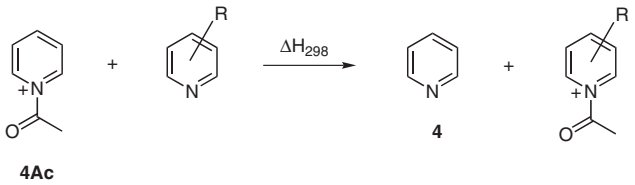


Figure 1 Aminopyridines **1**–**3**

Theoretical Considerations

Earlier studies on the catalytic potential of donor-substituted pyridines in acylation reactions have highlighted the relative stability of acylpyridinium cations as a qualitative criterion for catalyst activity.[11,12] The design of catalysts based on the 3,4-diaminopyridine motif was therefore guided by the theoretical assessment of the stability of the respective acetyl intermediates, as expressed through the reaction enthalpy of the homodesmic acetyl-transfer reaction shown in Equation 1.



Equation 1

The reaction enthalpies for a variety of 3,4-diaminopyridines have been collected in Table 1 together with the values for pyridine derivatives, whose catalytic potential is well known from earlier studies, such as pyridine (**4**), DMAP (**1**), PPY (**2**), and tricyclic DMAP-derivative **5**. A graphical representation of the results is given in Figure 2. The structurally least complex 3,4-diaminopyridine considered here is **6**, which is based on the tetrahydropyrido[3,4-*b*]pyrazine skeleton. The stability of the

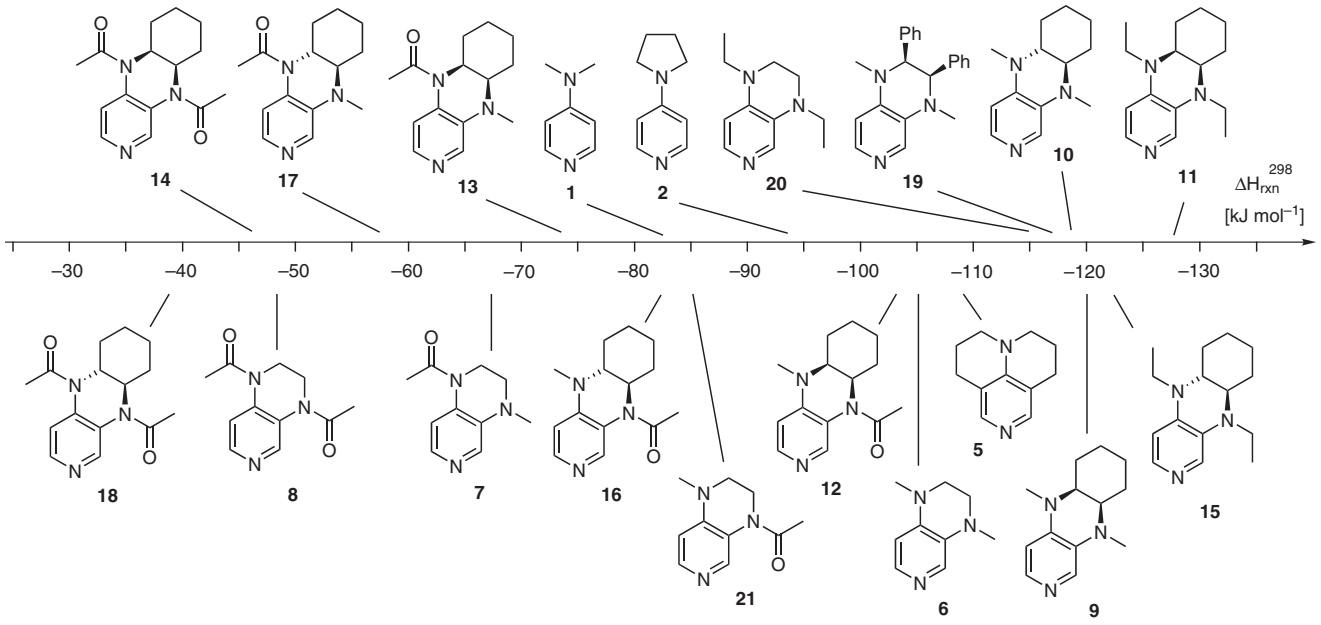


Figure 2 Structures of 3,4-diaminopyridines **6**–**21** together with their respective reaction enthalpies for the acetyl-transfer reaction defined in Equation 1. Data for 4-aminopyridines **1**, **2**, and **5** are also shown.

corresponding acetyl intermediate **6Ac** is close to that of the highly catalytically active **5**.

Replacement of the two methyl groups in **6** by one (as in **7** and **21**) or by two (as in **8**) acetyl groups is found to decrease the electron density in the pyridine ring and thus the stability of the corresponding cations **7Ac** and **8Ac** quite significantly. The stability difference between **6Ac** and **21Ac** (19.5 kJ mol^{-1}) and that between **6Ac** and **7Ac** (37.9 kJ mol^{-1}) indicates that the nitrogen atom at C4 is much more sensitive to changes in the substituent pattern as compared to the nitrogen atom at C3. The combined effect of both substituents as in **8** (56.3 kJ mol^{-1} relative to **6**) is practically identical to the sum of the two individual substitutions (57.4 kJ mol^{-1}). Replacement of the methyl substituents in **6** by ethyl groups enhances the stability of the acetyl intermediate by 10 kJ mol^{-1}. Annulation of a saturated alkyl ring to system **6** in either a *cis*-fashion (yielding **9**) or *trans*-fashion (as in **10**) also enhances their stability of the acetyl intermediates by approximately 15 kJ mol^{-1}. The stability of the acetylpyridinium cations derived from the tricyclic systems **9** and **10** depends on the N-substituents in much the same way as already found for bicyclic system **6**. Introduction of two *N*-ethyl substituents thus leads to the most stable acetyl intermediates **11Ac** and **15Ac**. Finally the introduction of aryl substituents as in **19** also stabilizes the corresponding cationic intermediate (relative **6Ac**), most likely through inductive electron donation to the 3,4-diamino nitrogen atoms. The stability values of the acetyl intermediates of the compounds shown in Figure 2 cover a range of almost 90 kJ mol^{-1}. Perusal of the charge and C–N distance data in Table 1 also shows that larger thermochemical stability correlates with shorter C–N bond distances and smaller acetyl group charges.

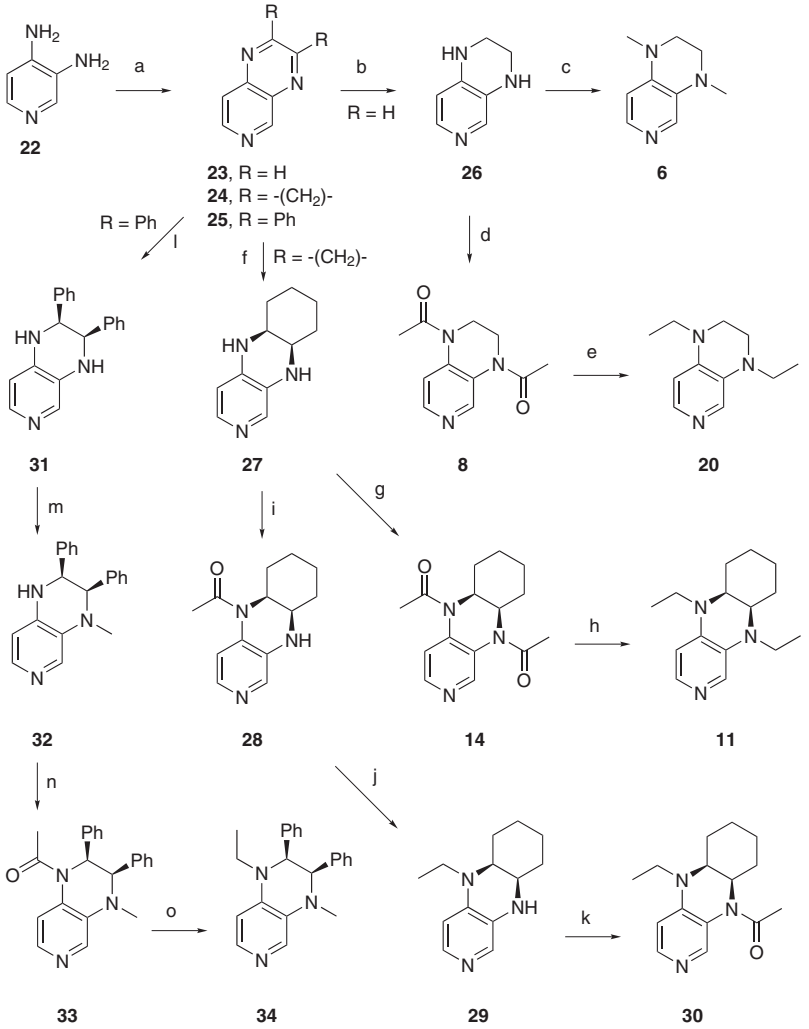
Table 1 Reaction Enthalpies at 298.15 K for the Acetyl-Transfer Reaction Shown in Equation 1 as Calculated at the B3LYP/6-311 + G(d,p)// B3LYP/6-31G(d) Level of Theory (in kJ mol^{-1})

System	ΔH_{rxn} (298) [kJ mol^{-1}]	q (Ac)[a,b]	r (C–N)[b] [pm]
4	0.0	+0.366	153.4
18	–39.0	+0.318	149.7
14	–46.2	+0.321	149.9
8	–48.7	+0.324	150.1
17	–57.3	+0.294	148.7
7	–67.1	+0.310	149.3
13	–73.1	+0.305	149.0
16	–82.0	+0.299	148.7
1	–82.1	+0.298	148.2
21	–85.5	+0.301	148.6
2	–93.1	+0.291	147.9
12	–103.2	+0.291	148.2
6	–105.0	+0.284	147.7
5	–108.9	+0.279	147.1
20	–115.5	+0.278	147.3
19	–116.5	+0.274	147.2
10	–117.9	+0.277	147.5
9	–119.2	+0.277	147.3
15	–122.2	+0.274	147.1
11	–127.1	+0.272	147.1

[a] In units of elemental charge *e*.
[b] Charge and distance parameters of the most favorable conformer.

Synthesis of 3,4-Diaminopyridines

Some of the compounds shown in Figure 2 can efficiently be synthesized from 3,4-diaminopyridine (**22**) in a three- or four-step sequence (Scheme 1). Condensation of **22** with glyoxal, 1,2-cyclohexadione or benzil leads to the diimines **23**–**25** in good yields.[13] Pyridopyrazine **23** (R = H) was subsequently reduced[14] to the tetrahydro derivative **26** and bis-methylated under Eschweiler–Clark conditions to yield compound **6**.[15] The introduction of longer alkyl chains proves more efficient through a two-step sequence involving initial bis-acylation, followed by reduction of the amide groups to the corresponding amines.[16] Starting from **26**, the bis-ethylated compound **20** can be synthesized in this fashion in 48% yield. A similar approach has been taken for the synthesis of the cyclohexyl-annulated system **11**, which is available from the free amine **27** in two steps in 37% yield. The *cis*-annulated diamine **27** is available from **24** through selective reduction with $NaBH_4/BH_3/H_2NCH_2CH_2OH$ in 74% yield[17] or through reduction with $LiAlH_4$ at –40 °C in 90% yield. Application of the simpler reduction conditions used for **26** leads to a mixture of *cis*- and *trans*-annulated diaminopyridines. Use of a milder acylation procedure for the acetylation of **27** shows the C4-amino group to be significantly more reactive than the amino group at C3, yielding amide **28** as the sole product. Reduction of the amide as before to the corresponding amine and acetylation of the remaining amino group at C3 thus provides a strategy for the synthesis of catalysts with two donor substituents of variable strength. The influence of aryl substituents in the bridge connecting the two amino substituents on the catalytic properties was explored with compound **34**. While reduction of the corresponding pyridopyrazine **25** proceeds



Scheme 1 Synthesis of catalysts based on the 3,4-diaminopyridine motif. *Reagents and conditions*: a) glyoxal, 1,2-cyclohexadienone, or benzil, EtOH, 70 °C, 5 h, 90–98%; b) powdered $NaBH_4$, EtOH, 40 °C, 24 h, 50%; c) CH_2O (200 equiv, 37% in H_2O), HCO_2H (100 equiv), 110 °C, 48 h, 57%; d) Ac_2O, pyridine, 100 °C, 24 h, 80%; e) $LiAlH_4$ (4.2 equiv), $AlCl_3$ (2.6 equiv), MTBE, 0 °C, 1 h, then reflux, 8 h, 60%; f) $LiAlH_4$, THF, –40 °C to r.t., 32 h, 90%; g) Ac_2O, 25 mol% PPY, pyridine, 100 °C, 48 h, 68%; h) $LiAlH_4$ (4.2 equiv), $AlCl_3$ (2.6 equiv), MTBE, 0 °C, 1 h, then reflux, 8 h, 55%; i) Ac_2O (1.1 equiv), **2** (0.2 equiv), Et_3N, CH_2Cl_2, r.t., 3 h, 82%; j) $LiAlH_4$ (2.2 equiv), $AlCl_3$ (1.3 equiv), MTBE, 0 °C, 1 h, then reflux, 8 h, 65%; k) 1. *n*-BuLi (1 equiv), THF, –78 °C, 1 h, then 0 °C, 1 h, 2. AcCl (1.1 equiv), THF, –78 °C to r.t., 1 h, 16%; l) powdered $NaBH_4$, EtOH, 40 °C, 48 h, 74%; m) CH_2O (88 equiv, 37% in H_2O), HCO_2H (200 equiv), 110 °C, 48 h, 90%; n) 1. *n*-BuLi (1 equiv), MTBE, –78 °C, 1 h, then 0 °C, 1 h; 2. AcCl (1.1 equiv), MTBE, –78 to 0 °C, 1 h, 36%; o) $LiAlH_4$ (2.2 equiv), $AlCl_3$ (1.3 equiv), THF, 0 °C, 1 h, then reflux, 18 h, 53%.

well under the conditions used before for the synthesis of **26**,[14] the N-methylation under Eschweiler–Clark conditions stops at the stage of singly methylated compound **32**. Acetylation of this latter compound proved surprisingly difficult under all conditions used previously, but could finally be accomplished through initial deprotonation of the amino substituent at C4 with *n*-BuLi, trapping of the amide anion with AcCl, and subsequent reduction with $LiAlH_4/AlCl_3$ yielding **34** as the final product. Compound **5** was synthesized following a slightly modified version of the procedure described by Sakamoto et al.[18]

The composition of all compounds shown in Scheme 1 is supported by high-resolution mass spectra. The integrity of the pyridine ring can in all compounds be inferred directly from the presence of three signals (one singlet, two doublets) in the appropriate range (6.5–8 ppm) of the ^{1}H NMR spectra. This leaves us with the question of the stereochemical assignment of the cyclohexane annulation in compounds **11**, **14**, and **27**–**30**, as well as the question of regiochemical control in the N-alkylation and N-acylation reactions. The ^{1}H NMR signals for the neighboring protons H_a and H_e in structure **11** (see Figure 3) exhibit a coupling constant of $^3J_{H,H}$ = 2.8 Hz and show a positive NOE enhancement signal, in line with either an axial–equatorial or an equatorial–equatorial orientation of the respective protons.[19] An equatorial–equatorial orientation of the two protons can be excluded since the 3,4-diaminopyridine moiety cannot possibly be connected to the cyclohexane ring through diaxial annulation. The regioselectivity of the acetylation of **27** to give **28** could not be determined directly, since the spectroscopic properties of **28** proved inconclusive in this respect. After reduction of **28** to **29** NOE enhancements could be detected between the ethyl substituent and the hydrogen at the C5 position of the pyridine ring, in support of the structure shown in Scheme 1. The regiochemistry of the N-methylation of **31** to yield **32** could be determined through detection of NOE enhancements between the signals for the methyl group protons (2.85 ppm) and those for the proton at C1 of the pyridine ring (7.82 ppm) as well as one of the benzylic protons (4.44 ppm). That this regioselectivity is ultimately conserved in the doubly alkylated product **34** could unequivocally be verified through the X-ray crystal structure analysis of this compound (as crystallized from isohexane–dichloromethane, Figure 4).

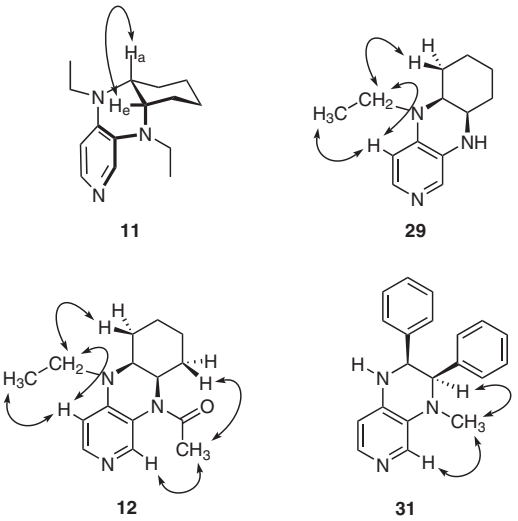


Figure 3 Arrows indicate observed NOE enhancements

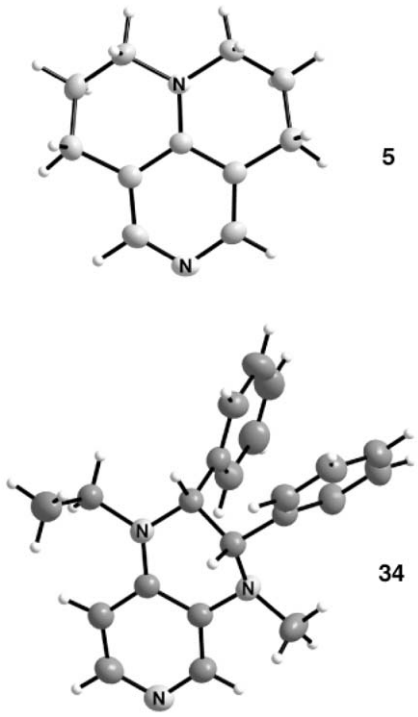
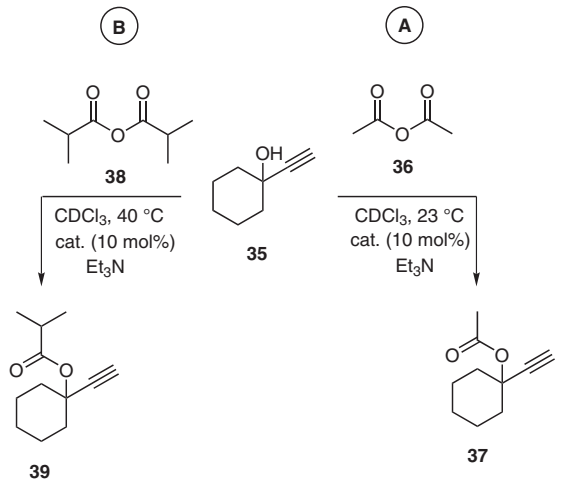


Figure 4 X-ray crystal structures of **34** and **5**

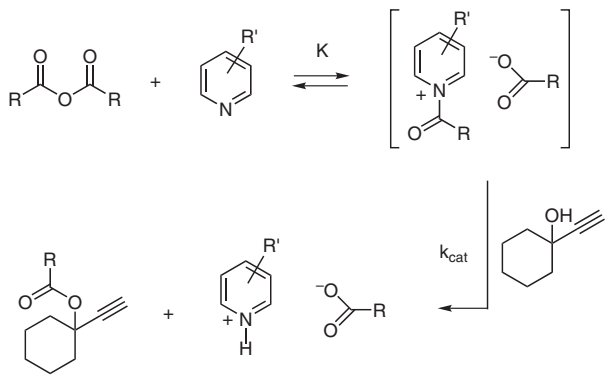
Catalytic Properties

The catalytic potential of pyridines **1**, **2**, **5**, **6**, **8**, **11**, **20** and **34** was tested in the two acylation reactions **A** and **B** shown in Scheme 2. Tertiary alcohol **35** has already been used in the past as a benchmark substrate in acylation reactions due to its very low rate of acylation under uncatalyzed conditions.[11] Acetylation of **35** with acetic anhydride (**36**) in the presence of triethylamine as the auxiliary base (reaction **A**) proceeds quantitatively, provided a catalyst as reactive as DMAP (**1**) is used in a concentration of 10% (relative to **35**). The reaction half-life $\tau_{1/2}$, determined through integration of the reactant and product signals in the ^{1}H NMR spectrum, is taken here as a measure of catalyst activity. Reaction **B** involves the same alcohol, but isobutyric anhydride (**38**) as the acylation reagent. This is an intrinsically slower reaction and the reaction temperature (40 °C) has therefore been chosen such that the absolute reaction half-lives are roughly comparable for both reactions. Based on recent mechanistic studies of DMAP-catalyzed acylation reactions,[20,21] the following minimal reaction mechanism can be assumed to be valid for both anhydrides in apolar solution (Scheme 3). Anhydride and the pyridine catalyst react in

a first (usually rapid) preequilibrium step to form a complex of acylpyridinium cation and carboxylate anion. This complex is not detected by ^{1}H NMR spectroscopy under the conditions used here and we can therefore assume the equilibrium constant K to be small for both reactions studied here. Reaction of the acylpridinium cation then occurs in the rate-limiting step with alcohol **35**, generating the ester products together with the deactivated catalyst. Regeneration of the latter requires the presence of the auxiliary base Et_3N.



Scheme 2



Scheme 3

The reaction half-lives $\tau_{1/2}$ measured here (Table 2) reflect the influence of the catalyst substitution pattern on both of these steps. A clear correlation of $\tau_{1/2}$ with the stability values determined computationally for the acetylpyridinium cations before (Table 1) can thus only be expected, if the substituent effects on K are larger than those on k_{cat}.

The reactivity data shown in Table 2 for compounds **1**, **2**, and **5** are slightly different from those reported earlier for the same reaction under identical conditions.[11] This is due, in part, to small differences in the NMR procedure employed for following the course of the reaction (see experimental details). It was additionally found that results for the more active catalysts such as **5** could only be reproduced if exceedingly pure samples are used for NMR measurements. Still, even for the most active catalysts it is not necessary to perform the reactivity measurements under strictly anaerobic conditions. The reactivity data for catalysts **6**, **11**, and **20** in Table 2 show that alkyl-substituted 3,4-diaminopyridines are more reactive than 4-aminopyridines such as DMAP or PPY.

Table 2 Reaction Half-Lives for Benchmark Reactions **A** and **B**

Catalyst	**A** $\tau_{1/2}$ (min)	**B** $\tau_{1/2}$ (min)
8	>38000[a]	>100000[a]
1 (DMAP)	166	304
34	144	269
30	138[b]	112
2 (PPY)	75	171
6	56	129
20	53	91
11	24 (37)[c]	63 (81)[c]
5	21 (29)[c]	67 (86)[c]

[a] See ref. 22.
[b] See ref. 23.
[c] Results in parentheses were obtained using Hünig's base [EtN(*i*-Pr)$_2$] as the auxiliary base

The best results have been obtained with compound **11**, whose catalytic performance is comparable to that of carbacyclic compound **5**. Comparison of the results for **20** and **11** shows a strong influence of the donor ability of the bridge on the catalytic performance, while the presence of *N*-methyl or *N*-ethyl substituents (**20** vs. **6**) appears to be slightly less relevant. While this trend is in line with the stability values reported in Table 1 and Figure 2, the catalytic performance of **34** is too low, considering the relatively stable acetyl intermediate formed by system **19**. The catalytic performance is reduced through introduction of acceptor substituents as documented by the catalytic activity of **30** (as compared to **11**), as well as the exceedingly slow reactions observed for the N-acetylated compound **8**. While this had to be expected from the low stability of the corresponding acetyl intermediate, we have to acknowledge that the stability scale reported in Figure 2 is not in line with the reactivities reported in Table 2 in all cases. That the latter will also depend on the substrates as well as the temperature chosen for a particular experiment is borne out by comparison of the results for reactions **A** and **B**. The reactivity ratio for the most active diaminopyridine **11** and DMAP amounts to 7.0 for reaction **A** and to 4.8 for reaction **B**. A similar result can be found for carbacyclic catalyst **5** with reactivity ratios of 7.9 and 4.5. The choice of the auxiliary base represents one additional experimental variable, which was again explored for catalysts **5** and **11**. It was surprisingly found that use of a stronger, sterically hindered base such as EtN(*i*-Pr)$_2$ (Hünig's base) leads to uniformly slower reactions as compared to those with Et_3N as the auxiliary base.

In conclusion we have found that alkyl-substituted 3,4-diaminopyridines represent a potent new class of catalysts for the acylation of alcohols. The catalytic efficiency of these catalysts can be varied broadly through variation of the nitrogen substituents within one synthetic approach. The catalytic efficiencies of the best of these catalysts are comparable to the best carbacyclic derivatives of DMAP reported before. In contrast to these latter compounds, the most active 3,4-diaminopyridine catalysts are synthetically accessible through a flexible three- or four-step procedure, which can easily be modified to allow for further structural variation.

Reactions which require anhydrous conditions were carried out under N_2 in absolute solvents in oven- and hot-air-blower-dried glassware using syringe and Schlenk techniques. THF was distilled under N_2 from NaH. MTBE, pyridine, Et_3N and $CDCl_3$ were distilled under N_2 from CaH_2. Ac_2O and isobutyric anhydride were distilled under reduced pressure from P_4O_{10} on anhyd K_2CO_3, filtered and fractionally distilled under reduced pressure. Both anhydrides were kept over 4 Å molecular sieves. EtOH, CH_2Cl_2, EtOAc and MeOH were distilled via rotary evaporation. *n*-BuLi was standardized by titration with diphenylacetic acid. Other reagents, unless otherwise mentioned, were purchased at the highest available commercial quality and used without further purification. TLC was performed on Merck KGaA precoated plates (silica gel 60 F_{254}, layer thickness 0.2 mm) and on Fluka precoated plates (basic alumina F_{254}, Brockmann activity 1, pH 9.5, layer thickness 0.2 mm). Flash chromatography was performed with Merck KGaA silica gel 60 (0.040–0.063 mm) and Fluka basic alumina (Brockman activity 1, pH 9.5, 0.05–0.15 mm) with a N_2 pressure of 1.5 bar for silica gel and 0.5 bar for basic alumina. ^1H and ^{13}C NMR spectra were recorded on Varian Mercury 200, Varian 300, Varian INOVA 400 and Varian 600 instruments. NOE measurements were performed in $CDCl_3$ at 27 °C. Chemical shifts are reported in ppm and referenced to the solvent peak.[24] Peaks in the ^1H and ^{13}C NMR were assigned by DQCOSY, NOESY, HSQC, HMBC and DEPT experiments. ^1H NMR spectra for kinetic experiments were analyzed with the VNMR 4.3 Rev. G0194 program package. Integrals were recorded using a self-written subroutine using MAGICAL™ II Programming. IR spectra were recorded with a PerkinElmer 1420 IR spectrometer using KBr pellets as sample holder and PerkinElmer FT-IR system Spectrum BX for neat measurement of the sample using ATR techniques. Peaks are listed as vs = very strong, s = strong, m = medium and w = weak. Mass spectra were recorded with a Finnigan MAT 95 using either electron impact ionization (EI, 70 eV) or chemical ionization (CI, isobutane). Electro spray injection mass spectra were recorded with Thermo Finnigan LTQ FT instrument. Gas chromatograms were recorded on Varian 3400 using a 25 m CS Supreme-5 capillary column and the Finnigan MAT 95 mass spectrometer as detector. In the case of the electron-rich pyridines **11**, **5**, **6**, **20** and **32**, the solvent was removed after column chromatography via rotary evaporation under reduced pressure, leaking a constant stream of N_2 into the rotavapor.

Geometry optimizations have been performed using the Becke3LYP hybrid functional in combination with the 6-31G(d) basis set. Thermochemical corrections to enthalpies at 298.15 K have been calculated from a harmonic vibrational frequency analysis at this same level. Single point energies have then been calculated at the Becke3LYP/6-311 + G(d,p) level. Combination of these latter energies with thermochemical corrections from the Becke3LYP/6-31G(d) level yield the H_{298} values cited in the text. All calculations have been performed with Gaussian 03.[25]

Reactivity Studies Using Reactions A and B; General Procedure

$CDCl_3$, Et_3N and Hünig's base were freshly distilled under N_2 from CaH_2 before use. All kinetic measurements were recorded at a constant temperature of 23 °C for reaction **A** and 40 °C for reaction **B** on a Varian Mercury 200 spectrometer. The following solutions were prepared in $CDCl_3$ in three dry, calibrated 5 mL flasks:

A: 1.2 M in Ac_2O or isobutyric anhydride, and 0.3 M in anhyd dioxane;

B: 0.6 M in ethynylcyclohexanol and 1.8 M in Et_3N or Hünig's base;

C: 0.06 M in catalyst.

Sample Preparation and Kinetic Measurements for Reaction A

In an NMR tube, 200 μL each of the above mentioned standardized solutions were added using an Eppendorf pipette. The reaction solution was mixed and immediately inserted into the NMR spectrometer. The reaction was monitored by recording NMR spectra within a defined time interval until full conversion.

Sample Preparation and Kinetic Measurements for Reaction B

The reagents were added to the NMR tube in the same way as described above for reaction **A**. In order to prevent evaporation of the solvent at higher reaction temperatures, the NMR tube was then flame-sealed under N_2.

Determination of Half-Life Times for Reaction A

All signals in the ^1H NMR spectrum related to the acetyl group hydrogen atoms were integrated automatically during the course of the reaction (the Ac_2O integral with boundaries of ± 8 Hz, the ester integral with boundaries of ± 2 Hz and the triethylammonium acetate integral with boundaries of ± 6 Hz). The conversion was calculated from these integrals using Equation 2. The time course of the reaction was fitted until self-consistency with Equation 4. The reaction half-life was calculated using function 4 at 50% conversion.

Determination of Half-Life Times for Reaction B

All signals in the ^1H NMR spectrum related to the isobutyrate group as well as the internal standard dioxane were integrated automatically during the course of the reaction (the dioxane integral with boundaries of ± 2 Hz and isobutyric anhydride integral with boundaries of ± 2 Hz). The conversion was calculated from these integrals using Equation 3. The time course of the reaction was fitted until self-consistency with Equation 4. The reaction half-life was calculated using function 4 at 50% conversion.

$$\text{conversion} = \left[\frac{I_{ester}}{0.25\,(I_{Ac_2O} + I_{ester} + I_{Et_3NH^+AcO}} \right] \times 100\%$$

Equation 2

$$\text{conversion} = \left[1 - \frac{I_{anhydride}}{3(I_{ester})} \right] \times 200\%$$

Equation 3

$$y = A \exp\left(- \frac{x - x_0}{t_0} \right) + \text{const.}$$

Equation 4

Pyrido[3,4-*b*]pyrazine (23)

To a solution of glyoxal (40 wt% in H_2O, 2.82 mL, 62.48 mmol) in EtOH (30 mL) was added 3,4-diaminopyridine (**22**; 2.00 g, 18.33 mmol). The mixture was kept at 70 °C oil bath temperature for 5 h. After cooling to r.t., the solvent was distilled off by rotary evaporation. The crude product was purified by flash chromatography (isohexane–EtOAc, 1:9) to afford 2.35 g (98%) of a white solid; R_f = 0.27 (isohexane–EtOAc, 1:9).

IR (KBr): 3435 (vs), 3092 (w), 3023 (m), 1969 (w), 1758 (w), 1631 (w), 1598 (vs), 1562 (m), 1536 (w), 1488 (s), 1436 (vs), 1416 (m), 1381 (m), 1351 (w), 1290 (w), 1279 (m), 1212 (m), 1201 (m), 1148 (w), 1033 (s), 1014 (s), 972 (w), 959 (vs), 931 (m), 881 (vs), 838 (m), 824 (s), 773 (w), 651 (s), 623 (m), 546 (w), 524 (w), 457 cm^{-1} (s).

^1H NMR (200 MHz, $CDCl_3$): δ = 7.94 (dd, ^3J = 5.8, ^4J = 0.6 Hz, 1 H, H-7), 8.83 (d, ^3J = 5.8 Hz, 1 H, H-8), 8.96 (d, ^3J = 1.6 Hz, 1 H, H-3), 9.02 (d, ^3J = 1.6 Hz, 1 H, H-2), 9.56 (d, ^4J = 0.6 Hz, 1 H, H-5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.6 (CH-7), 138.0 (C_q), 145.3 (C_q), 147.3 (CH-8), 146.5 (CH-3), 149.2 (CH-2), 154.8 (CH-5).

GC-MS (EI): t_R = 5.45 min; *m*/*z* (%) = 132 (8), 131 (M^+, 100), 104 (25), 77 (13), 50 (10).

1,2,3,4-Tetrahydropyrido[3,4-*b*]pyrazine (26)

To a solution of quinoxaline **23** (2.90 g, 0.022 mol) in anhyd EtOH (100 mL), was added powdered $NaBH_4$ (2.90 g, 0.076 mol). The mixture was kept at 40 °C for 24 h. After completion of the reaction, the mixture was cooled to r.t.; H_2O (3 mL) was added, and the inorganic precipitate was filtered off and washed with CH_2Cl_2 (2 × 20 mL). The organic solvent was dried (Na_2SO_4) and distilled off via rotary evaporation. The crude material was purified by flash chromatography (basic alumina, EtOAc–MeOH, 10:1) to afford 1.49 g (50%) of a white solid; R_f = 0.15 (basic alumina, CH_2Cl_2–MeOH, 20:1).

IR (KBr): 3349 (m), 2859 (m), 1593 (s), 1534 (s), 1474 (s), 1344 (s), 1311 (s), 1281 (s), 1256 (w), 1228 (m), 1182 (m), 1102 (m), 1051 (w), 1038 (m), 893 (m), 862 (m), 824 (s), 772 cm^{-1} (m).

^1H NMR (200 MHz, $CDCl_3$): δ = 3.37 (d, ^3J = 5.8 Hz, 1 H, H-3), 3.38 (d, ^3J = 5.8 Hz, 1 H, H-2), 6.29 (d, ^3J = 5.4 Hz, 1 H, H-8), 7.67 (d, ^3J = 5.4 Hz, 1 H, H-7), 7.67 (s, 1 H, H-5).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.1 (CH_2), 41.0 (CH_2), 107.8 (C-5), 129.6 (C_q), 135.3 (CH-7), 140.1 (C_q), 141.1 (CH-5).

GC-MS (EI): t_R = 8.09 min; *m*/*z* (%) = 136 (8), 135 (M^+, 79), 134 ($M^+ - H^+$, 100), 133 (10), 132 (7), 131 (2), 120 (4), 107 (7), 105 (4), 94 (2), 93 (7), 80 (2), 79 (3), 78 (4), 67 (4), 66 (2), 53 (2), 52 (2), 52 (3), 51 (2).

HRMS (EI): *m*/*z* calcd for $C_7H_8N_3$ ($M - H^+$): 134.0718; found: 134.0709.

1-(4-Acetyl-3,4-dihydro-2*H*-pyrido[3,4-*b*]pyrazin-1-yl)ethanone (8)

To a solution of dihydroquinoxaline **26** (1.49 g, 0.011 mol) in pyridine (60 mL), was added Ac_2O (23 mL, 24.71 g, 24.20 mol) at 0 °C. The mixture was heated up to 100 °C and kept at that temperature for 48 h. After cooling to r.t., the solvent was distilled off under vacuum and the yellow crude product was purified by flash chromatography (EtOAc–MeOH, 10:3) to afford 1.93 g (80%) of a faint yellow solid; R_f = 0.28 (EtOAc–MeOH, 10:3).

IR (neat): 2960 (w), 1684 (s), 1654 (vs), 1582 (m), 1494 (s), 1407 (vs), 1330 (m), 1320 (vs), 1277 (m), 1259 (s), 1248 (m), 1217 (s), 1248 (s), 1217 (s), 1179 (m), 1150 (w), 1118 (m), 1064 (m), 1033 (s), 969 (s), 886 (w), 857 (m), 846 (s), 799 (s), 764 (w), 749 (w), 704 cm^{-1} (w).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.25 (s, 3 H, CH_3), 2.31 (s, 3 H, CH_3), 3.90 (ddd, ^2J = 12, ^3J = 4, ^3J = 4 Hz, 2 H, CH_2), 3.94 (ddd, ^2J = 12, ^3J = 4, ^3J = 4 Hz, 2 H, CH_2), 7.67 (s, 1 H, H-5), 7.87 (br s, 1 H, H-5), 8.32 (d, ^3J = 4 Hz, 1 H, H-7), 8.46 (m, 1 H, H-8).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 22.8 (CH_3), 42.1, 46.5 (CH_2), 117.4 (C-5), 128.2 (C_q), 139.0 (C_q), 145.7 (C-7), 146.9 (C-8), 168.6 (C=O).

GC-MS (EI): t_R = 9.66 min; *m*/*z* (%) = 220 (14), 219 (M^+, 81), 178 (11), 177 (M^+ – AcO, 100), 176 (10), 162 (3), 159 (2), 136 (7), 135 (78), 134 (M^+ – 2 AcO, 99), 133 (8), 132 (9), 120 (4), 119 (2), 107 (5), 105 (2), 93 (3), 80 (2), 79 (4), 78 (4), 52 (2), 51 (2), 43 (AcO^+, 20).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{13}N_3O_2$ [M^+]: 219.1008; found: 219.0995.

1,4-Diethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine (20)

$AlCl_3$ (1.56 g, 11.69 mmol) was suspended in MTBE (60 mL) at r.t. After stirring for 45 min, the mixture was cooled to 0 °C and $LiAlH_4$ (1.32 g, 34.65 mmol) was added in small portions. The mixture was stirred for 15 min, and then compound **8** was added. The mixture was stirred for 1 h at 0 °C and then refluxed for 8 h. It was then allowed to cool down to r.t. and poured into ice water. The inorganic precipitate was filtered off and washed with CH_2Cl_2 (2 × 30 mL). The aqueous layer was basified with aq NaOH (30%) to pH 12 and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was distilled off via rotary evaporation. The crude material obtained was purified with flash chromatography (EtOAc–MeOH–Et_3N, 10:0.5:1) to afford 0.52 g (60%) of a colorless liquid, which solidified in the freezer; R_f = 0.47 (EtOAc–MeOH–Et_3N, 10:0.5:1).

IR (KBr): 3436 (s), 3112 (w), 3019 (w), 2964 (w), 1661 (s), 1686 (vs), 1583 (m), 1497 (m), 1409 (s), 1363 (w), 1332 (m), 1311 (s), 1260 (m), 1249 (w), 1232 (m), 1220 (m), 1180 (m), 1150 (w), 1119 (m), 1064 (w), 1035 (m), 985 (m), 970 (m), 886 (s), 858 (m), 847 (m), 802 (m), 765 (w), 740 (w), 704 (w), 647 (w), 614 (w), 592 (w), 577(m), 570 (m), 507 cm^{-1} (w).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (q, ^3J = 14 Hz, 6 H, CH_3), 3.22 (m, ^3J = 6 Hz, 2 H, H-3), 3.23 (m, ^2J = 14 Hz, 4 H, CH_2), 3.42 (m, ^3J = 6 Hz, 2 H, H-2), 6.34 (d, ^3J = 5.2 Hz, 1 H, H-8), 7.69 (s, 1 H, H-5), 7.75 (d, ^3J = 5.2 Hz, 1 H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.1, 10.4 (CH_3), 44.6, 46.5 (CH_2-2,3), 44.9, 45.0 (CH_2), 104.0 (C-8), 130.5, 130.1 (C_q), 131.8 (C-5), 140.7 (C-7).

GC-MS (EI): t_R = 8.63 min; *m*/*z* (%) = 192 (10), 191 (M^+, 100), 190 (4), 177 (8), 176 (95), 175 (5), 162 (11), 161 (8), 160 (5), 148 (13), 147 (10), 146 (8), 135 (2), 134 (9), 133 (6), 131 (8), 121 (2), 119 (4), 118 (3), 107 (3), 104 (2), 92 (2), 91 (2), 80 (8), 77 (4).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{17}N_3$ [M^+]: 191.1422; found: 191.1430.

1,4-Dimethyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine (6)

Under ice cooling, formic acid (35 mL) was added slowly to dihydroquinoxaline **26** (1.26 g, 9.32 mmol). Aq formaldehyde (12 mL, <37% in H_2O) was then added and the mixture was kept at 110 °C for 48 h. The mixture was allowed to cool down to r.t., and under ice cooling approximately 20% aq NaOH (150 mL) was added in such a way that the solution had a pH of 12. The mother liquor was extracted with CH_2Cl_2 (250 mL) overnight using a continuous liquid/liquid extractor. The organic phase was dried (Na_2SO_4) and the solvent was removed by rotary evaporation. The crude product was purified twice by flash chromatography (silica gel, EtOAc–MeOH–Et_3N, 10:1:1) and (basic alumina, EtOAc–MeOH, 10:1) to afford **6** (0.849 mg, 57%) as a faint yellow solid; R_f = 0.56 (basic alumina, EtOAc–MeOH, 10:1).

IR (neat): 3378 (w), 3035 (w), 2979 (w), 2873 (m), 2826 (s), 2792 (w), 1581 (s), 1519 (s), 1466 (s), 1454 (s), 1435 (m), 1416 (m), 1380 (w), 1335 (vs), 1290 (s), 1250 (w), 1235 (vs), 1214 (m), 1172 (s), 1114 (s), 1099 (s), 1069 (s), 1030 (m), 936 (w), 911 (w), 883 (s), 815 (s), 800 (s), 783 (s), 746 (m), 709 (m), 622 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.77 (s, 3 H, CH_3), 2.82 (s, 3 H, CH_3), 3.12 (m, 2 H, CH_2-2), 3.37 (m, 2 H, CH_2-3), 6.21 (d, ^3J = 5.6 Hz, 1 H, H-7), 7.56 (s, 1 H, H-5), 7.74 (d, ^3J = 5.6 Hz, 1 H, H-8).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 38.0 (N-1-CH_3), 39.1 (N-4-CH_3), 48.8 (C-3), 49.6 (C-2), 104.0 (C-7), 131.2 (C-5), 132.3 (C-4a), 141.6 (C-7), 142.2 (C-8a).

GC-MS (EI): t_R = 8.05 min; *m*/*z* (%) = 164 (8), 163 (M^+, 100), 162 (21), 161 (5), 149 (4), 148 (40), 147 (9), 146 (8), 134 (8), 133 (11), 132 (6), 121 (4), 120 (2), 119 (6), 107 (3), 105 (2), 93 (2), 92 (4), 81 (6), 80 (4), 79 (2), 78 (4), 66 (3), 51 (2), 42 (4).

HRMS (EI): *m*/*z* calcd for $C_9H_{13}N_3$ [M^+]: 163.1109; found: 163.1089.

6,7,8,9-Tetrahydropyrido[3,4-*b*]quinoxaline (24)

To a suspension of 3,4-diaminopyridine (**22**; 5 g, 45.81 mmol) in EtOH (100 mL) was added 1,2-cyclohexanedione (5.13 g, 45.81 mmol). The flask was immersed in an oil bath and kept at 70 °C oil bath temperature for 5 h. After cooling the mixture to r.t., the solvent was distilled off by rotary evaporation. The solid crude product was purified by flash chromatography with EtOAc as eluent to afford 7.69 g (90%) as a white powder. The product should be used within 48 h and should be kept cool in the refrigerator. Upon standing in an open flask in the sunlight, the compound turned grey-green; R_f = 0.25 (EtOAc–hexane, 20:1).

IR (KBr): 3435 (vs), 2947 (s), 2864 (m), 1594 (s), 1557 (w), 1461 (w), 1421 (m), 1385 (s), 1365 (w), 1330 (w), 1297 (m), 1211 (m), 1140 (w), 979 (m), 949 (w), 901 (m), 849 (m), 679 (w), 629 (w), 570 (w), 412 cm^{-1} (w).

^1H NMR (200 MHz, $CDCl_3$): δ = 2.05 (m, 4 H, H-7,8), 3.18 (m, 4 H, H-6,9), 7.79 (d, ^3J = 5.8 Hz, 1 H), 8.72 (d, ^3J = 5.8 Hz, 1 H), 9.38 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.8 (CH_2, C-7,8), 33.7 (CH_2, C-6,9), 121.2 (CH), 136.9 (C_q), 144.1 (C_q), 146.8 (CH), 153.9 (CH), 156.8 (C_q), 159.9 (C_q).

GC-MS (EI): t_R = 8.44 min; *m*/*z* (%) = 186 (11), 185 (M^+, 100), 184 (39), 183 (3), 182 (3), 171 (2), 170 (21), 169 (4), 158 (2), 157 (5), 156 (5), 131 (2), 104 (2), 103 (4), 78 (3), 76 (4), 67 (2), 64 (2), 51 (2), 50 (6).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{11}N_3$ [M^+]: 185.0953; found: 185.0935.

5,5a,6,7,8,9a,10-Octahydropyrido[3,4-*b*]quinoxaline (27)

Compound **24** (6.13 g, 33.09 mmol) was dissolved in anhyd THF (100 mL) in a 250 mL Schlenk-flask. The solution was cooled to –40 °C and $LiAlH_4$ (3.09 g, 81.42 mmol, 2.5 equiv) was added in small portions. The mixture was allowed to warm to r.t. and stirred at that temperature for 32 h. Afterwards, the mixture was poured into ice water. The aqueous layer was basified with sat. aq K_2CO_3 to pH 12 and the inorganic precipitate was filtered off and was washed with CH_2Cl_2 (2 × 50 mL). The mother liquor was extracted with CH_2Cl_2 (250 mL) for 8 h using a continuous liquid/liquid extractor. The organic layer was separated and dried (Na_2SO_4). Flash chromatography on silica gel (EtOAc–MeOH–Et_3N, 10:1:1) afforded 5.63 g (90%) of a white foam; R_f = 0.36 (EtOAc–MeOH–Et_3N, 10:1:1).

IR (neat): 3220 (s), 2927 (s), 2852 (s), 2354 (m), 1725 (w), 1595 (vs), 1523 (vs), 1456 (w), 1443 (m), 1403 (w), 1362 (s), 1294 (s), 1269 (s), 1240 (m), 1206 (s), 1175 (s), 1087 (m), 1052 (m), 1003 (m), 938 (m), 884 (m), 810 (vs), 725 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.32–1.40 (m, 3 H), 1.56–1.75 (m, 5 H), 3.41 (m, 1 H), 3.46 (s, 1 H, NH), 3.51 (m, 1 H), 4.20 (s, 1 H, NH), 6.29 (d, 1 H, ^3J = 5.4 Hz, H-3), 7.65 (d, 1 H, ^3J = 5.4 Hz, H-4), 7.68 (s, 1 H, H-1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 22.2 (C-7,8), 30.4, 30.8 (CH_2-6,9), 49.2 (CH-5a), 50.1 (CH-9a), 107.7 (C-4), 128.8 (Cq-10a), 134.8 (C-3), 139.2 (Cq-4a), 140.7 (C-4).

GC-MS (EI): t_R = 10.06 min; *m*/*z* (%) = 190 (13), 189 (M^+, 99), 188 (9), 187 (3), 185 (10), 184 (4), 170 (4), 160 (10), 159 (3), 158 (5), 148 (2), 147 (16), 146 (100), 145 (2), 134 (13), 133 (17), 132 (15), 120 (10), 119 (3), 105 (2), 94 (3), 93 (2), 78 (3), 66 (2), 40 (2).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{15}N_3$ [M^+]: 189.1266, found: 189.1259.

The reaction can also be performed in 74% yield following the protocol by Opatz et al. with $NaBH_4/BH_3/H_2NCH_2CH_2OH$ as the reducing agent.[17]

1-(10-Acetyl-6,7,8,9,9a,10-hexahydro-5a*H*-pyrido[3,4-*b*]quinoxalin-5-yl)ethanone (14)

In a 250 mL round-bottomed flask, were added under ice cooling **27** (1.20 g, 6.34 mmol), pyridine (40 mL), Ac_2O (30 mL, 32.36 g, 317 mmol), and PPY (0.234 g, 25 mol%). The mixture was heated to 100 °C and kept at that temperature for 48 h. The reaction can be monitored by TLC on basic alumina (EtOAc–MeOH, 10:1). After cooling to r.t., the solvent was distilled off and the brown crude product obtained was purified with flash chromatography on basic alumina (EtOAc–MeOH, 10:1); R_f = 0.45 (EtOAc–MeOH, 10:1).

IR (neat): 2940 (m), 1660 (vs), 1587 (m), 1559 (w), 1498 (s), 1448 (w), 1427 (w), 1388 (m), 1353 (w), 1337 (m), 1289 (s), 1270 (s), 1248 (s), 1248 (m), 1220 (w), 1183 (w), 1102 (w), 1036 (m), 978 (m), 857 (w), 839 (w), 777 cm^{-1} (w).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (m, 4 H), 1.60 (m, 4 H), 2.23 (s, 3 H, H_3CCON), 2.27 (s, 3 H, H_3CCON), 4.74 (m, 1 H), 4.85 (m, 1 H), 7.25 (d, ^3J = 5.6 Hz, 1 H, H-4), 8.41 (d, ^3J = 5.6 Hz, H-3), 8.49 (s, 1 H, H-1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.7, 21.9 (C-7,8), 23.1, 23.6 (H_3CCON), 28.4, 28.5 (C-6,9), 55.2, 56.0 (CH-5a,9a), 119.6 (C-4), 130.8 (Cq-10a), 141.6 (Cq-4a), 147.1, 147.2 (C-1, C-3), 169.1, 169.2 (C=O).

GC-MS (EI): t_R = 10.45 min; *m*/*z* (%) = 274 (13), 273 (M^+, 58), 232 (15), 231 (100), 230 (42), 216 (5), 214 (5), 213 (5), 203 (3), 202 (4), 190 (13), 189 (84), 188 (45), 173 (5), 172 (6), 160 (7), 159 (5), 158 (5), 147 (8), 146 (40), 134 (6), 133 (13), 132 (15), 120 (7), 43 (9).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{15}N_3$ [M^+]: 273.1477; found: 273.1482.

5,10-Diethyl-5,5a,6,7,8,9,9a,10-octahydropyrido[3,4-*b*]quinoxaline (11)

$AlCl_3$ (3.98 g, 29.9 mmol) was suspended in THF (60 mL) at r.t. After stirring for 45 min, the mixture was cooled to 0 °C and $LiAlH_4$ (1.92 g, 50.62 mmol) was added in small portions. The mixture was stirred for 15 min, and then compound **14** (3.15 g, 11.5 mmol) was added. The mixture was stirred for 1 h at 0 °C and then refluxed for 8 h. It was then allowed to cool down to r.t. and then poured into ice water. The inorganic precipitate was filtered off and washed with CH_2Cl_2 (2 × 30 mL). The aqueous layer was basified with aq NaOH (30%) to pH 12 and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was distilled off by rotary evaporation. The crude product was distilled with a Kugelrohr-distillation setup at 160 °C/0.4 mbar and afterwards further purified by chromatography on basic alumina with

EtOAc–MeOH (10:1) as eluent to afford 1.85 g (66%) of a slight yellow oil which solidified in the freezer; R_f = 0.32 (basic alumina, EtOAc–MeOH, 10:1).

IR (neat): 3436 (s), 2970 (m), 2860 (vs), 2860 (s), 1628 (w), 1576 (vs), 1513 (vs), 1473 (w), 1447 (m), 1348 (s), 1317 (w), 1267 (s), 1211 (s), 1167 (w), 1125 (w), 1107 (w), 1077 (w), 1059 (w), 1040 (w), 920 (w), 798 (s), 777 (m), 746 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.11, 1.13 (t, ^3J = 7.2 Hz, H_3CCH_2N-5, ^3J = 7.2 Hz, H_3CCH_2N-10, 6-H), 1.37 (m, 2 H, H-7,8), 1.56 (m, $^3J_{a,a}$ = 6.8, $^3J_{e,e}$ = 3.2 Hz, 4 H, H-6, H-9, H-7, H-8), 1.76 (m, $^3J_{a,e}$ = 3.2 Hz, 1 H, H-9), 1.89 (m, $^3J_{a,e}$ = 3.2 Hz, 1 H), 3.18 (dq, ^3J = 7.2, ^2J = 14.4 Hz, 2 H, $H_3CCH_{AB}N$-5, $H_3CCH_{AB}N$-10), 3.23 (ddd, $^3J_{a,e}$ = 2.8, $^3J_{a,e}$ = 3.2, $^3J_{a,a}$ = 6.8 Hz, 1 H, H-5a), 3.34 (ddd, $^3J_{a,e}$ = 2.8, $^3J_{a,e}$ = 3.2, $^3J_{a,e}$ = 3.2 Hz, H-1, H-9a), 3.43 (dq, ^3J = 7.2, ^2J = 14.4 Hz, $H_3CCH_{AB}N$-5, $H_3CCH_{AB}N$-10, 2 H, H-1), 6.33 (d, ^3J = 5.6 Hz, 1 H, H-4), 7.67 (s, 1 H, H-1), 7.72 (d, ^3J = 5.6 Hz, 1 H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.8 (H_3CCH_2N-5), 11.8 (H_3CCH_2N-10), 21.7 (C-7), 22.9 (C-8), 27.3 (C-6), 27.8 (C-9), 40.4 (H_3CCH_2N-5), 41.7 (H_3CCH_2N-10), 52.8 (C-9a), 56.4 (C-5a), 104.3 (C-4), 130.6 (C-10a, C-1), 139.4 (C-3), 141.2 (C-4a).

MS (EI): *m*/*z* (%) = 246 (18), 245 (M^+, 100), 231 (9), 230 (57), 217 (7), 216 (44), 207 (6), 186 (7), 174 (15), 162 (6), 160 (16), 158 (6), 148 (12), 146 (6), 132 (8).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{23}N_3$ [M^+]: 245.1892; found: 245.1889.

1-(6,7,8,9,9a,10-Hexahydro-5a*H*-pyrido[3,4-*b*]quinoxalin-5-yl)ethanone (28)

In a 100 mL round-bottomed flask, compound **27** (1.0 g, 5.28 mmol) was dissolved in CH_2Cl_2 (20 mL), and Et_3N (2.20 mL, 15.84 mmol) and PPY (39 mg, 0.264 mmol, 5 mol%) were added. Afterwards, Ac_2O (0.54 mL, 5.81 mmol) was added and the mixture was stirred for 30 min. After 30 min, the reaction was quenched by addition of MeOH (2 mL), and after stirring for 10 min, the solvent was distilled off by rotary evaporation. The crude product obtained was purified by flash chromatography on silica gel (EtOAc–Et_3N–MeOH, 10:1:1) to afford 1 g (82%) of **28**. The product obtained in this way still contained traces of PPY and was used as such without further purification; R_f = 0.44 (EtOAc–Et_3N–MeOH, 10:1:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.44 (m, 5 H), 1.76 (m, 3 H), 2.29 (s, 3 H, H_3CCON), 3.59 (m, 1 H), 4.07 (m, 1 H), 7.08 (br s, 1 H, H-4), 7.85 (d, ^3J = 5.4 Hz, 1 H, H-3), 7.98 (s, 1 H, H-1).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.5 (CH_2), 23.5 (H_3CCON), 24.8, 25.4 (CH_2), 31.08 (CH_2), 48.9 (C-9a), 118.1 (C_q-4a), 127.9 (C_q-10a), 132.2 (C-4), 136.6 (C-1), 138.0 (C-3), 169.0 (C=O).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{17}N_3O$ [M^+]: 231.1372; found: 231.1368.

5-Ethyl-5,5a,6,7,8,9a,10-octahydropyrido[3,4-*b*]quinoxaline (29)

$AlCl_3$ (0.619 g, 4.64 mmol) was suspended in THF (30 mL) at r.t. After stirring for 45 min, the mixture was cooled to 0 °C and $LiAlH_4$ (0.300 g, 7.91 mmol) was added in small portions. The mixture was stirred for 15 min and then compound **28** (0.832 g, 3.59 mmol) was added. The mixture was stirred for 1 h at 0 °C and then refluxed for 8 h. It was then allowed to cool down to r.t. and then poured into ice water (30 mL). The inorganic precipitate was filtered off and washed with CH_2Cl_2 (2 × 30 mL). The aqueous layer was basified with aq NaOH (30%) to pH 12 and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was distilled off by rotary evaporation. The crude material obtained was purified with flash chromatography on silica gel (EtOAc–Et_3N, 10:1) to afford 0.430 mg (55%) of a white foam; R_f = 0.24 (EtOAc–Et_3N, 10:1).

IR (neat): 3212 (m), 3093 (w), 2971 (w), 2928 (s), 2851 (s), 1589 (s), 1560 (m), 1505 (vs), 1470 (w), 1442 (m), 1419 (m), 1363 (s), 1280 (vs), 1244 (s), 1210 (m), 1194 (s), 1177 (m), 1108 (m), 1072 (m), 1039 (m), 1007 (w), 968 (w), 897 (w), 886 (w), 795 (s), 740 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.06 (t, ^3J = 7.2 Hz, 3 H, H_3CCH_2N-5), 1.25 (m, 2 H), 1.54 (m, 5 H), 1.78 (m, 1 H), 3.20 (m, 4 H), 3.79 (s, 1 H, NH), 6.21 (d, ^3J = 5.7 Hz, 1 H, H-4), 7.57 (s, 1 H, H-1), 7.65 (d, ^3J = 5.7 Hz, 1 H, H-3).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (H_3CCH_2N-5), 19.3 (C-7), 24.8 (C-8), 26.8 (C-6), 30.9 (C-9), 42.8 (H_3CCH_2N-5), 47.8 (C-5a), 58.4 (C-9a), 103.9 (C-4), 129.8 (C_q-10a), 133.4 (C-1), 138.4 (C_q-4a), 140.9 (C-3).

GC-MS (EI): t_R = 10.58 min; *m*/*z* (%) = 218 (17), 217 (M^+, 100), 216 (7), 215 (7), 213 (5), 203 (5), 202 (51), 186 (17), 185 (5), 174 (12), 162 (6), 161 (8), 160 (9), 158 (7), 148 (5); 148 (5), 146 (16), 145 (7), 134 (8), 133 (9), 132 (25), 120 (14), 78 (4).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{19}N_3$ [M^+]: 217.1579; found: 215.1573.

1-(5-Ethyl-5a,6,7,8,9,9a-hexahydro-5*H*-pyrido[3,4-*b*]quinoxalin-10-yl)ethanone (30)

Compound **29** (0.250 g, 1.15 mmol) was dissolved in THF (10 mL) THF in a 100 mL Schlenk-flask. The solution was cooled to –78 °C and then *n*-BuLi (0.51 mL, 1.27 mmol, 1.1 equiv, 2.5 M in hexane) was added and the mixture was stirred for 30 min without cooling. After 30 min, the mixture was cooled again to –78 °C and AcCl (0.09 mL, 0.109 g, 1.4 mmol) was added and then allowed to stir for 1 h without cooling. Afterwards, the mixture was quenched with H_2O (4 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was distilled off by rotary evaporation. The crude product was purified by flash chromatography on silica gel (EtOAc–MeOH, 10:2) to yield 16% (48 mg) of pure **30**; R_f = 0.16 (EtOAc–Et_3N, 10:1).

IR (neat): 3398 (s), 2933 (s), 2863 (m), 1731 (m), 1637 (vs), 1595 (vs), 1512 (s), 1546 (w), 1449 (m), 1397 (s), 1365 (s), 1334 (m), 1285 (s), 1239 (m), 1198 (m), 1168 (vs), 1123 (w), 1067 (w), 1068 (w), 1016 (w), 802 (vs), 718 (w), 668 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, ^3J = 7.2 Hz, 3 H, H_3CCH_2N-5), 1.24 (m, 2 H), 1.45 (m, 2 H), 1.58 (m, 2 H), 1.74 (m, 1 H), 2.18 (m, 1 H), 3.34 (m, ^2J = 14.4, ^3J = 7.2 Hz, 1 H, $H_3CCH_{AB}N$-5), 3.53 (m, 1 H, CH), 3.57 (m, ^2J = 15.2, ^3J = 7.2 Hz, 1 H, $H_3CCH_{AB}N$-5), 4.90 (br s, 1 H, CH), 6.62 (d, ^3J = 5.6 Hz, 1 H, H-4), 8.12 (s, 1 H, H-1), 8.08 (d, ^3J = 5.6 Hz, 1 H, H-3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.4 (H_3CCH_2N-5), 18.9 (C-7), 22.8 (H_3CCON-10), 24.7 (C-8), 25.8 (C-6), 28.5 (C-9), 40.0 (H_3CCH_2N-5), 48.7 (C-9a), 53.7 (C-5a), 106.4 (C-4), 120.1 (C_q-10a), 145.1, 145.2 (C-1, C_q-4a), 147.1 (C-3), 167.1 (C=O).

GC-MS (EI): t_R = 10.39 min; *m*/*z* (%) = 260 (11), 259 (M^+, 100), 230 (8), 218 (9), 217 (79), 216 (40), 203 (4), 202 (23), 203 (3), 202 (23), 201 (4), 189 (6), 188 (31), 187 (4), 186 (3), 174 (11), 162 (4), 161 (6), 160 (5), 158 (4), 148 (5), 146 (6), 136 (3), 132 (4), 131 (12), 120 (6), 43 (3).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{21}N_3O$ [M^+]: 259.1685; found: 259.1687.

2,3-Diphenylpyrido[3,4-*b*]quinoxaline (25)

Modified Procedure from Ref. 14: To a suspension of 3,4-diaminopyridine (2.86 g, 0.026 mol) in EtOH (50 mL) was added benzil (5.51 g, 0.026 mol). The flask was immersed in an oil bath and kept

at 70 °C oil bath temperature for 6 h. After cooling to r.t., the yellow precipitate (ice cooling may be useful) was collected by filtration and recrystallized from EtOH to afford 6.91 g (94%) of **25** as a faint yellow solid.

IR (neat): 3061 (w), 1589 (m), 1577 (w), 1538 (w), 1492 (w), 1443 (m), 1419 (w), 1379 (s), 1346 (w), 1326 (m), 1315 (m), 1288 (w), 1211 (m), 1244 (w), 1227 (m), 1212 (w), 1180 (w), 1075 (m), 1058 (m), 1020 (m), 1001 (w), 976 (s), 921 (w), 892 (m), 892 (m), 830 (m), 819 (w), 811 (m), 763 (s), 735 (m), 708 (vs), 629 (s), 615 cm^{-1} (m).

^1H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.42 (m, 6 H, 3,4,5-CH, C_6H_5), 7.54–7.51 (m, 4 H, 2,6-CH, C_6H_5), 7.98 (dd, ^3J = 6, ^4J = 0.8 Hz, 1 H, 7-H), 8.82 (d, ^3J = 6 Hz, 1 H, 8-H), 9.59 (d, ^4J = 0.8 Hz, 1 H, 5-H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.3 (C-7), 128.4, 129.4–129.9 (CH, C_6H_5), 136.3 (C_q-4a), 143.5 (C_q-8a), 147.3 (C-8), 154.5 (C-5), 155.3, 157.9 (C_q, C_6H_5).

GC-MS (EI): t_R = 12.34 min; *m/z* (%) = 285 (3), 284 (M^+ + H, 22), 283 (M^+, 100), 282 (46), 206 (2), 181 (3), 180 (25), 179 (17), 154 (3), 153 (5), 152 (3), 142 (1), 141 (8), 140 (4), 127 (2), 104 (3), 103 (14), 102 (3), 78 (2), 77 (5), 76 (4), 51 (2), 50 (9).

2,3-Diphenyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine (31)

To a solution of **25** (6.25 g, 22.05 mmol) in EtOH (200 mL) in a 500 mL flask, was added powdered $NaBH_4$ (6.25 g, 165.20 mmol). The mixture was kept at 40 °C for 48 h, cooled to r.t. and quenched with cold H_2O (10 mL). After stirring for 10 min, the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed by rotary evaporation. The crude product obtained was purified with flash chromatography on silica gel (EtOAc–Et_3N, 10:1) to afford (4.70 g, 74%) of a faint yellow solid; R_f = 0.23 (EtOAc–Et_3N, 10:1).

IR (neat): 3215 (w), 2830 (w), 1596 (s), 1519 (s), 1493 (w), 1466 (w), 1452 (s), 1360 (m), 1290 (s), 1250 (m), 1231 (m), 1174 (s), 1120 (m), 1072 (m), 1050 (w), 1029 (w), 1005 (w), 989 (w), 950 (w), 905 (w), 844 (w), 810 (m), 770 (m), 723 (m), 675 (vs), 668 (w), 645 (w), 618 cm^{-1} (m).

^1H NMR (300 MHz, $CDCl_3$): δ = 3.99 (s, 1 H, NH), 4.59 (s, 2 H, 2,3-H), 4.62 (s, 1 H, NH), 6.39 (d, ^3J = 5.4 Hz, 1 H, 8-H), 6.80 (dd, ^4J = 1.2, ^3J = 9.3 Hz, 2 H, 2,6-CH, C_6H_5), 6.84 (dd, ^4J = 1.2, ^3J = 9.3 Hz, 2 H, 2,6-CH, C_6H_5), 7.12 (m, 6 H, 3,4,5-CH, C_6H_5).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 58.6, 60.1 (C-2,3), 108.0 (C-8), 127.9–128.4 (CH, C_6H_5), 129.8 (C-4a), 139.8 (C_q, C_6H_5), 140.0 (C_q-8a), 134.9 (C-5), 141.3 (C-7).

MS (EI): *m*/z (%) = 288 (22), 287 (M^+, 100), 286 (24), 285 (7), 284 (6), 283 (8), 282 (5), 211 (13), 210 (78), 209 (5), 208 (13), 197 (4), 196 (26), 181 (13), 179 (3), 127 (4), 104 (7), 92 (3), 91 (32), 77 (5).

HRMS (EI): *m/z* calcd for $C_{19}H_{17}N_3$ [M^+]: 287.1422; found: 287.1402.

4-Methyl-2,3-diphenyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine (32)

In a 100 mL round-bottomed flask was dissolved under ice cooling compound **31** (0.600 g, 2.08 mmol) in formic acid (15.5 mL, 417.6 mmol), and aq formaldehyde solution (5.1 mL; 183.6 mmol, 37% in H_2O) was added. After addition, the ice bath was removed and the mixture was heated at 120 °C oil bath temperature for 48 h. The mixture was then cooled to r.t., and under ice cooling aq NaOH (50%) was added dropwise until the pH of the reaction mixture had reached a value of 12. The mixture was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic phases were dried (Na_2SO_4), and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography ($CHCl_3$–isohexane–Et_3N, 10:2:1) to afford (0.564 g, 90%) of a faint yellow solid; R_f = 0.40 ($CHCl_3$–isohexane–Et_3N, 10:2:1).

IR (neat): 3200 (w), 3158 (w), 3029 (w), 2948 (w), 2881 (w), 2824 (w), 1578 (s), 1516 (vs), 1491 (m), 1452 (m), 1421 (m), 1374 (w), 1353 (w), 1326 (w), 1294 (w), 1256 (m), 1235 (m), 1199 (w), 1157 (m), 1131 (m), 1103 (w), 1073 (m), 1054 (m), 1031 (m), 1013 (m), 969 (w), 922 (w), 842 (w), 810 (s), 766 (s), 755 (m), 733 (m), 641 cm^{-1} (vs).

^1H NMR (400 MHz, $CDCl_3$): δ = 2.85 (s, 3 H, CH_3), 4.42 (s, 1 H, NH), 4.44 (d, ^3J = 3.6 Hz, 1 H, H-3), 4.95 (d, ^3J = 3.6 Hz, 1 H, H-2), 6.50 (d, ^3J = 5.2 Hz, 1 H, H-8), 6.64 (dd, ^4J = 2.8, ^3J = 9.2 Hz, 2 H, 2,6-CH, C_6H_5), 6.90 (m, 2 H, 2,6-CH, C_6H_5), 7.05 (m, 2 H, CH, C_6H_5), 7.16 (m, 4 H, CH, C_6H_5), 7.82 (s, 1 H, H-5), 7.84 (d, ^3J = 5.2 Hz, 1 H, H-7).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 37.2 (CH_3), 57.8 (C-3), 67.9 (C-2), 107.6 (C-8), 127.4–128.5 (CH, C_6H_5), 131.3 (C-5), 131.6 (C_q, C-4a), 137.4, 138.8 (C_q, C_6H_5), 139.9 (C-7, C-8a).

MS (EI): *m/z* (%) = 302 (22), 301 (M^+, 100), 300 (5), 286 (5), 224 (10), 222 (4), 211 (13), 210 (87), 209 (3), 208 (6), 195 (11), 181 (6), 179 (3), 178 (3), 178 (3), 150 (7), 132 (3), 127 (3), 120 (3), 104 (4); 92 (3), 91 (31), 85 (4), 83 (6), 78 (4), 77 (5).

HRMS (EI): *m/z* calcd for $C_{20}H_{19}N_3$ [M^+]: 301.1574; found: 301.1559.

4-(Methyl-2,3-diphenyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazin-1-yl)ethanone (33)

In a 250 mL Schlenk-flask, compound **32** (2.90 g, 9.62 mmol) was dissolved in MTBE (100 mL). The solution was cooled to –78 °C and *n*-BuLi (4.62 mL, 11.50 mmol, 1.1 equiv, 2.5 M in hexane) was added over 10 min. The mixture was stirred without cooling for 30 min, then cooled down again to –78 °C and AcCl (1.0 mL, 0.96 g, 12.55 mmol) was added. The mixture was allowed to warm up to r.t. and stirred for 30 min at that temperature. After quenching the reaction with H_2O (10 mL), the mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was distilled off by rotary evaporation. The crude product can either be purified by recrystallization from EtOAc or purified by flash chromatography on silica gel ($CHCl_3$–isohexane–Et_3N) to afford 1.2 g (36%) of a white solid.

IR (neat): 2428 (m), 2039 (w), 1688 (s), 1613 (w), 1534 (s), 1492 (m), 1454 (w), 1388 (m), 1364 (m), 1345 (m), 1317 (w), 1292 (w), 1292 (w), 1272 (w), 1227 (vs), 1209 (vs), 1122 (w), 1103 (w), 1078 (m), 1028 (m), 998 (m), 822 (s), 799 (m), 768 (m), 704 (m), 691 (m), 638 cm^{-1} (w).

^1H NMR (600 MHz, $CDCl_3$): δ = 2.40 (s, 3 H, H_3CCON), 2.86 (s, 3 H, CH_3), 4.99 (m, 1 H, H-3), 5.35 (d, ^3J = 4.2 Hz, 1 H, H-2), 6.53 (d, ^3J = 7.8 Hz, 2 H, 2,6-CH, C_6H_5), 6.80 (br s, 2 H, 2,6-CH, C_6H_5), 7.08 (t, ^3J = 7.2 Hz, 2 H, CH, C_6H_5), 7.17 (t, ^3J = 6.0 Hz, 2 H, CH, C_6H_5), 7.22 (t, ^3J = 6.0 Hz, 1 H, CH, C_6H_5), 7.25 (t, ^3J = 6.0 Hz, 1 H, CH, C_6H_5), 8.03 (d, ^3J = 6.6 Hz, 1 H, H-8), 8.17 (s, 1 H, H-5), 8.41 (d, ^3J = 6.6 Hz, 1 H, H-7).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 24.60 (H_3CCON), 36.9 (H_3C), 61.8 (C-3), 63.8 (C-2), 116.9 (C-8), 124.6 (C-5), 128.4–128.9 (CH, C_6H_5), 134.7 (C_q-8a), 138.7 (C_q-4a), 171.0 (C=O).

GC-MS (EI): t_R = 1.22 min; *m/z* (%) = 345 (3), 344 (27), 343 (M^+, 100), 315 (6), 302 (7), 301 (41), 300 (84), 224 (6), 223 (4), 222 (5), 211 (4), 210 (27), 208 (9), 195 (6), 181 (9), 179 (4), 178 (4), 146 (4), 118 (15), 104 (5), 92 (9), 91 (94), 78 (4), 77 (4), 43 (6).

HRMS (EI): *m/z* calcd for $C_{22}H_{23}N_3O$ [M^+]: 343.1685; found: 343.1699.

1-Ethyl-4-methyl-2,3-diphenyl-1,2,3,4-tetrahydropyrido[3,4-*b*]pyrazine (34)

$AlCl_3$ (0.575 g, 4.320 mmol) was suspended in THF (20 mL) at r.t. After stirring for 45 min, the mixture was cooled to 0 °C and $LiAlH_4$ (0.277 g, 7.290 mmol) was added in small portions. The mixture was then stirred for 15 min and compound **33** (1.00 g, 3.32 mmol) was added. The mixture was stirred at 0 °C for further 60 min and then refluxed for 12 h. Afterwards, the mixture was cooled to r.t. and poured into ice water. The precipitate was collected by filtration and the mother liquor was extracted with CH_2Cl_2. The combined organic phases were dried (Na_2SO_4) and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (EtOAc–MeOH–Et_3N, 10:1:0.5) to afford 0.580 g (53%) of a faint yellow solid; R_f = 0.57 (EtOAc–MeOH–Et_3N, 10:1:0.5).

IR (neat): 2965 (w), 2818 (w), 1578 (s), 1518 (vs), 1492 (m), 1452 (s), 1430 (w), 1371 (m), 1356 (m), 1308 (m), 1286 (m), 1266 (s), 1241 (s), 1215 (vs), 1165 (m), 1119 (m), 1067 (s), 1023 (s), 884 (w), 867 (w), 828 (w), 810 (s), 764 (s), 749 (m), 705 (vs), 660 (w), 615 cm^{-1} (w).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, ^3J = 7.2 Hz, 3 H, H_3CCH_2N), 2.71 (s, 3 H, H_3C), 3.17 (qd, ^2J = 14.8, ^3J = 7.2 Hz, 1 H, $CH_3CH_{AB}N$), 3.38 (qd, ^2J = 14.8, ^3J = 7.2 Hz, 1 H, $CH_3CH_{AB}N$), 4.40 (d, ^3J = 3.6 Hz, 1 H, H-3), 4.55 (d, ^3J = 3.6 Hz, 1 H, H-2), 6.52 (d, ^3J = 5.6 Hz, 1 H, H-8), 6.73 (m, 4 H, CH, C_6H_5), 7.07 (t, ^3J = 7.2 Hz, 2 H, CH, C_6H_5), 7.11 (t, ^3J = 8 Hz, 2 H, CH, C_6H_5), 7.16 (m, 2 H, CH, C_6H_5), 7.92 (s, 1 H, H-5), 7.96 (d, ^3J = 5.6 Hz, 1 H, H-7).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1 (H_3CCH_2N), 37.1 (H_3CN), 43.3 (H_3CCH_2N), 65.7 (C-2), 66.0 (C-3), 104.3 (C-8), 127.7–129.3 (CH, C_6H_5), 133.0 (C-5), 133.3 (C_q-8a), 137.8, 138.6 (C_q, C_6H_5), 140.8 (C_q-8a), 141.0 (C-7).

LC-HRMS (ESI): t_R = 0.53–1.43 min; *m*/*z* calcd for $C_{44}H_{47}N_6$ [2 M^+ + H]: 659.3862; found: 659.3823; *m*/*z* calcd for $C_{22}H_{24}N_3$ [M^+ + H]: 330.1970; found: 330.1940.

1,6-Naphthyridine (40)

A 1000 mL three-necked round-bottomed flask fitted with a reflux condenser was charged with fresh fuming H_2SO_4 (50 mL, 648 mmol, 20% free SO_3) and nitrobenzene (18.4 mL, 178 mmol). The flask was immersed in an oil bath and kept at 70 °C for 8 h. After cooling to r.t., the mixture was cooled in an ice bath, while slowly glycerin (19.9 mL, 272 mmol) and 4-aminopyridine (7.5 g, 80 mmol) were added. Afterwards demineralized H_2O (40 mL) was added and the mixture was stirred until a homogenous mixture was obtained. The ice bath was removed and the mixture was heated to 130 °C in an oil bath for 5 h. The mixture was allowed to cool to r.t. and then cooled in an ice bath, while slowly adding aqueous NaOH (20%, approx. 400 mL) up to pH 12. The solid precipitate was filtered off by suction and washed with $CHCl_3$ (250 mL). The aqueous phase was extracted with $CHCl_3$ (750 mL) and the combined organic phases were dried ($NaSO_4$). The solvent was distilled off by rotary evaporation and the crude product obtained was used without further purification: 5.10 g (49% yield) of an brown oil which solidified upon standing in the fridge (5.10 g).

8-Bromo-1,6-naphthyridine (41)

A 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer, reflux condenser and addition funnel was charged with anhyd AcOH (100 mL) and 1,6-naphthyridine (**40**; 1.92 g, 14.8 mmol). Br_2 (0.86 mL, 16.3 mmol) was added slowly over a period of 30 min and afterwards the flask was immersed in an oil bath and heated to 80 °C for 12 h. The AcOH was removed by vacuum distillation and the remaining residue was diluted in ice-cold aq sat. K_2CO_3 (50 mL) and $CHCl_3$ (25 mL). The aqueous phase was extracted with $CHCl_3$ (3 × 100 mL). The combined organic phases were dried ($MgSO_4$) and the solvent was removed by rotary evaporation to afford a low melting solid. The crude product was purified on silica gel by chromatography (30:1, $CHCl_3$–MeOH) to give 1.60 g (52%) of a brown solid.

(*E*)-3-(1,6-Naphthyridin-8-yl)acrylate Ethyl Ester (42)

A 100 mL sealed tube equipped with a magnetic stirrer was dried, purged with N_2 and charged with $Pd(OAc)_2$ (30 mg, 0.11 mmol, 2.6 mol%), $(tol)_3P$ (80.9 mg, 0.27 mmol), Et_3N (0.88 mL, 6.29 mmol), ethyl acrylate (1.75 mL, 16.08 mmol), **41** (1.98 g, 9.47 mmol) and MeCN (6 mL). The sealed tube was immersed in a silicon oil bath heated to 120 °C for 16 h. The mixture was diluted with H_2O (10 mL) and extracted with $CHCl_3$ (3 × 35 mL). After extracting the combined organic layers with 2 M aq HCl (3 × 25 mL), the aqueous phases were combined and made basic by the addition of K_2CO_3. The cloudy aqueous phase was then extracted with CH_2Cl_2 (4 × 35 mL) and the combined organic phases were dried (Na_2SO_4). Evaporation of the solvent, followed by flash chromatography of the residue on silica gel using 10% isohexane–EtOAc as the eluent, furnished 1.83 g (85%) of **42** as a faint yellow solid.

4,5,9,10-Tetrahydro-8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridine-6-one (43)

A 250 mL three-necked round-bottomed flask equipped with a magnetic stirrer and a three-way stopcock attached to a N_2 and H_2 inlet was charged with a solution of **42** (4.12 g, 18 mmol) in anhyd EtOH (120 mL) and Pd on activated carbon (10% Pd, 992 mg). The system was purged with N_2 and then purged with H_2. The reaction was monitored by ^1H NMR and was complete after the ^1H-signals for the olefinic and aromatic protons in the 2-, 3- and 4- position were no longer detected. The mixture was filtered through Celite and the solvent was removed by rotary evaporation. The crude product was purified on silica gel by column chromatography (40:1, $CHCl_3$–MeOH, 5.0% Et_3N) to afford a white solid (2.97 g, 87%).

5,6,9,10-Tetrahydro-4*H*,8*H*-pyrido[3,2,1-*ij*][1,6]naphthyridine (5)[18]

A 250 mL Schlenk flask equipped with a magnetic stirrer, reflux condenser, and N_2 inlet was dried, purged with N_2 and charged with THF (120 mL) and $AlCl_3$ (5.33 g, 39 mmol). After the solution was made homogeneous by stirring, $LiAlH_4$ (4.55 g, 120 mmol) and a solution of **43** (2.97 g, 120 mmol) in THF (50 mL) were added. The flask was immersed in an oil bath and the mixture was refluxed for 20 h. After cooling to r.t., the mixture was poured into ice water. The aqueous phase was made basic by adding aq sat. K_2CO_3 solution (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed by rotary evaporation. The crude product was purified on silica gel by column chromatography ($CHCl_3$–MeOH, 10:1, 2.5% Et_3N) to provide 2.05 g (74%) of a white solid.

Crystals of **34** and **5** suitable for single crystal X-ray diffraction studies could be obtained from CH_2Cl_2–hexane mixtures at 5 °C. Data describing the solid state strutcure of **34** and **5** have been deposited in the Cambridge Crystallographic Data Center with deposition number CCDC 622355 for **34** and CCDC 633500 for **5**.

Acknowledgment

This work has been financially supported by the Deutsche Forschungsgemeinschaft (DFG) under the focus program 'organocatalysis'. We thank Herbert Mayr and Wolfgang Steglich for stimulating discussions.

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