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1,3-Dipolar cycloaddition of cyanopyridines to heterocyclic *N*-imines: experimental and theoretical study

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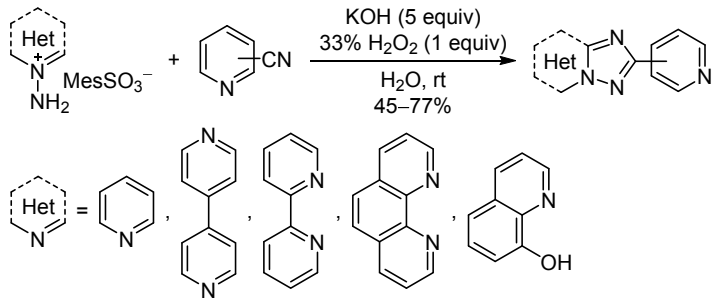
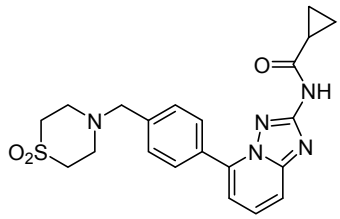


Series of 2-pyridyl[1,2,4]triazolo[1,5-*a*]azines have been synthesized by cycloaddition of cyanopyridines with *N*-aminoazinium mesitylenesulfonates under basic conditions (KOH/H_2O). An improved protocol for pyridyl-substituted [1,2,4]triazolo[1,5-*a*]pyridines synthesis based on addition of H_2O_2 as internal oxidant has been suggested. In the case of quinolinium and isoquinolinium salts, only dimerization of the corresponding *N*-imines has been observed, while pyrazinium-*N*-imine has not shown any reactivity toward cycloaddition. DFT studies have shown that the cycloaddition proceeds through concerted mechanism.

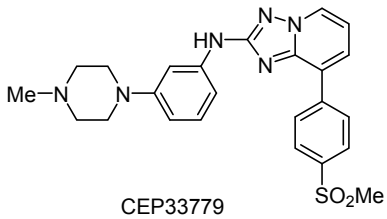
Keywords: *N*-imines, [1,2,4]triazolo[1,5-*a*]azines, DFT, 1,3-dipolar cycloaddition.

[1,2,4]Triazolo[1,5-*a*]azines have attracted much attention from both medicinal chemistry and materials science communities. Thus, [1,2,4]triazolo[1,5-*a*]pyridine scaffold was used in design of TDP2,[1] HIF PHD-1,[2] VEGFR-2,[3] and various types of Janus kinase inhibitors.[4,5] Furthermore, triazolo[1,5-*a*]pyridine derivatives GLPG0634 (filgotinib)[5] and CEP33779[4] (Fig. 1) are highly selective inhibitors of Janus kinases type 1 and 2, respectively, and they are regarded as promising drug candidates. Also this heterocyclic unit was shown to be useful in design of host materials for high-performance red,[6] white and RGB,[7] or green[8] PhOLEDs (phosphorescent organic light-emitting diodes). Similarly, [1,2,4]triazolo[1,5-*a*]pyrimidines, the chemistry of which has been recently reviewed,[9] have a broad spectrum of biological activity. [1,2,4]Triazolo[1,5-*a*]-pyrazines[10,11] and -quinoxalines[12,13] were used in design of A_{2A} and A_3 adenosine receptors antagonists.

The practical significance of such heterocyclic scaffolds has stimulated the development of viable synthetic methods for their preparation.[9,14] One of the common approaches to



GLPG0634 (filgotinib)
Selective JAK1 inhibitor



CEP33779
Selective JAK2 inhibitor

Figure 1. Medicinally important [1,2,4]triazolo[1,5-*a*]pyridines.

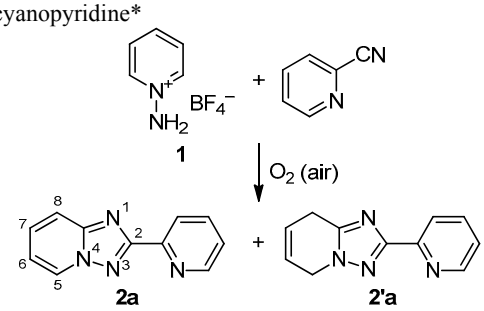
[1,2,4]triazolo[1,5-*a*]azine synthesis is the oxidative cyclization of 2-pyridyl-, 2-pyrazinyl-, 2-pyrimidyl-, and other amidines or guanidines to form the N–N bond. Various oxidants such as $Pb(OAc)_4$,[15] $PhI(OCOCF_3)_2$,[16] I_2,[17] or N–Cl reagents[18,19] have been suggested. During the past decade several catalytic procedures utilizing oxygen as oxidant and (2-pyridyl)guanidine[20] or 2-aminopyridine and a nitrile[21] as starting materials were developed. Despite of their great potential these methods have a significant limitation, requiring α-aminoazines as starting compounds.

Another group of methods is based on the use of *N*-aminoazinium salts which are readily available by *N*-amination of parent azines with *O*-(mesitylenesulfonyl)-hydroxylamine and related reagents.[22] 1,2-Diaminoazinium salts undergo cyclization with acid anhydrides or aldehydes[11,23,24] leading to the corresponding triazoloazines. However, these salts also have to be prepared starting from α-aminoazines. *N*-Aminopyridium salts readily give the corresponding pyridinium-*N*-imines upon deprotonation. Such imines are known to react with nitriles to yield [1,2,4]-triazolo[1,5-*a*]pyridines.[25,26] This reaction was applied to the synthesis of deuterated[27] or 2-aryl-substituted derivative library for antifungal[28] and anticancer[29] activity screening. Cycloaddition of ethyl cyanoformate to tetrahydroiso-quinoline azomethine imines was used for the synthesis of [1,2,4]triazoloisoquinoline derivatives.[30]

Recently, our group employed *N*-amination combined with nitrile cycloaddition for the modification of commonly used ligands such as 8-oxiquinoline and 1,10-phenanthro-line. The otained triazoles were used for the synthesis of fluorescent rhenium coordination compounds.[31] The aim of this work is to study the scope of nitrile cycloaddition to various azine-*N*-imines. Cyanopyridines were chosen as model nitriles, since pyridyl-substituted azoloazines thus obtained could be of interest for coordination chemists.

Initially, we applied previously described conditions[29] to pyridinium salt **1** and 2-cyanopyridine (Table 1, entry 1). However, poor yield of desired pyrazolopyridine **2a** was obtained. Noticeable amount of dihydropyrazolopyridine **2'a** was also found in the reaction mixture. Then, we screened effect of the base and solvent on the reaction yield. It turned out that increase of amount of KOH from 1 to 5 equiv (entries 2–5) led to rise in yield of both products **2a** and **2'a**. Further increase of base quantity up to 10 equiv (entry 6) did not significantly affect the triazolopyridine **2a** output, however the amount of product **2'a** has slightly decreased. The best results were achieved in H_2O as a solvent, although similar results were obtained in EtOH. However, it should be noted, that cyanopyridine is better to be added as solution in a minimum amount of EtOH in the case of a multigram-scale reaction in view of lesser solubility of cyanopyridines in H_2O. Other solvent/base pairs tested (entries 10–12) did not give satisfactory results. Interestingly, that the reaction could proceed in 1-butyl-3-methylimidazolium tetrafluoroborate (BMIM-BF_4) as ionic liquid solvent (entries 13, 14), nevertheless the yields were low. Attempts of using a copper catalyst (entry 15) were unsuccessful. Next, we tried to oxidize product **2'a** with different agents to improve the yield of triazolo-

Table 1. Condition optimization for reaction of salt **1** with 2-cyanopyridine*



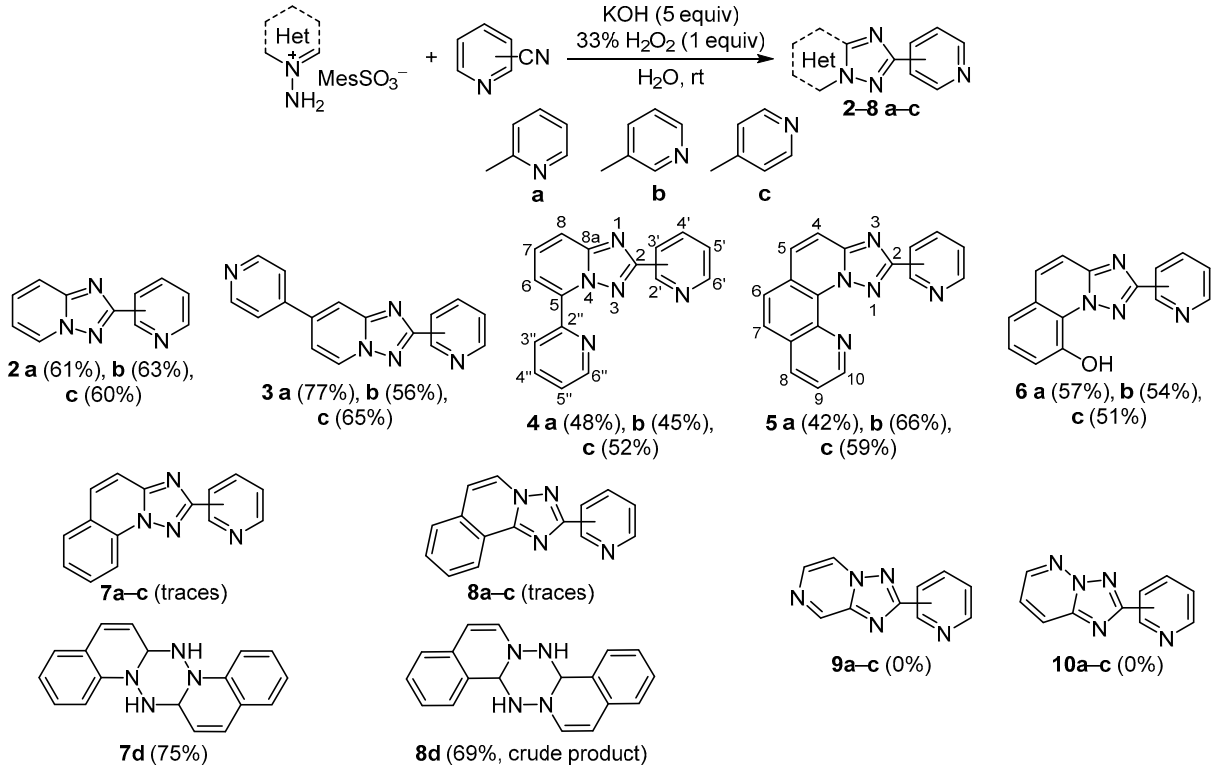
Entry	Conditions**	Yield of compound **2a**, %	Ratio **2'a**:**2a**
1	1 equiv KOH in H_2O/EtOH	8	1:4.3
2	2 equiv KOH in H_2O/EtOH	35	1:2.6
3	3 equiv KOH in H_2O/EtOH	42	1:2.5
4	4 equiv KOH in H_2O/EtOH	43	1:2.9
5	5 equiv KOH in H_2O/EtOH	46	1:3.6
6	10 equiv KOH in H_2O/EtOH	46	1:6.6
7	5 equiv KOH in H_2O	48	1:6.8
8	5 equiv K_2CO_3 in H_2O	–	–
9	5 equiv KOH in EtOH	45	1:17
10	5 equiv K_2CO_3 in MeCN	25	–***
11	5 equiv MeONa in MeOH	–	–
12	5 equiv *t*-AmylONa in *t*-AmylOH	11	–***
13	5 equiv KOH in BMIM-BF_4	20	–***
14	5 equiv DBU in BMIM-BF_4	25	–***
15	5 equiv KOH, $CuCl_2$ or CuCl (1 mol %) in H_2O	–	–
16	5 equiv KOH, 1 equiv H_2O_2 in H_2O	64	–***

* The yield and product ratio were determined by ^{1}H NMR spectroscopy with CH_2Br_2 as internal standard.
** Reaction was carried out at 0.1 mmol scale, 2 N solution of a base in the respective solvent.
*** No product **2'a** was detected.

pyridine **2a**. Unfortunately, oxidants, such as chloranil, DDQ, bromine, MnO_2, led to complicated reaction mixtures which were hard to separate. Addition of H_2O_2 at the beginning of the reaction yielded 64% of product **2a** without contamination with compound **2'a** (entry 16). Increasing the quantity of H_2O_2 had no further impact on the reaction yield.

Both 3- and 4-cyanopyridines also reacted readily with *N*-aminopyridinium salt **1** leading to the corresponding tri-azolopyridines **2b**,**c** with nearly the same yields (Scheme 1). With the optimized conditions in hand, the scope of heterocyclic *N*-imines in this transformation was investi-gated. 1-Amino-4,4'-bipyridinium and 1-amino-2,2'-bipyri-dinium mesitylenesulfonates readily gave triazolopyridines **3**, **4 a–c** and were found to form dihydro derivatives similar to compound **2'a** as byproducts in the absence of H_2O_2. Both 1-amino-1,10-phenanthrolinium and 1-amino-8-hydroxy-quinolinium mesitylenesulfonates gave triazoloazines **5**, **6 a–c** with satisfactory yields. In the case of 1-aminoquinolinium

Scheme 1. Synthesis of [1,2,4]triazolo[1,5-*a*]azines



and 2-aminoisoquinolinium mesitylenesulfonate, only trace amount of triazoloazines **7** , **8 a**–**c** were formed along with water-insoluble solids. The solids were identified by NMR as dimers of the corresponding *N*-imines (structures **7d** and **8d**). Previously, such compounds were prepared from corresponding *N*-amino derivatives in basic media.[32,33] These dimers have been shown to react with range of dipolarophiles yielding different heterocyclic products.[33]

Our attempts to obtain products **7a**–**c** from quinolinium-*N*-imine dimer **7d** were unsuccessful, and only traces of the desired product were observed by GC-MS and NMR studies. *N*-Amino derivatives of pyrazine and pyridazine did not give the corresponding pyrazinotriazoles **9a**–**c** or pyridazinotriazoles **10a**–**c**, and only *N*-imines, starting nitriles, and nicotinamides were identified in the reaction mixtures by ^{1}H NMR. Such behavior may be explained by lower contribution of 1,3-dipolar structure **11A** to the resonance hybrid along with higher role of structure **11B** and, thus, low 1,3-dipole character of *N*-imine (Fig. 2).

The structures of compounds **2**–**6 a**–**c** were confirmed by NMR spectra. For pyrazolopyridine **2a**, signal assignment was made by COSY, ^{1}H–^{13}C HMBC, and ^{1}H–^{13}C HSQC NMR experiments. All substances have appropriate signals of pyridyl substituents in ^{1}H and ^{13}C NMR spectra. For 2-pyridyl and 3-pyridyl fragments, AMPX and for 4-pyridyl substituent, AA'BB' spin systems were observed in ^{1}H NMR spectra. Compounds **2a**–**c** have typical AMPX spin system of triazolo[1,5-*a*]pyridine ring in ^{1}H NMR spectra. Compounds **3a**–**c** and **4a**–**c** feature a AMX spin system. In the case of triazolo[1,5-*a*][1,10]phenanthrolines **5a**–**c**, AMX system for H-8,9,10 protons and two AB systems for H-6,7 and H-4,5 protons were observed, except of a singlet signal of H-6,7 protons for compound **5a**. [1,2,4]Triazolo[1,5-*a*]quinolin-9-oles **6a**–**c** also have a AB system for H-4,5 protons, and AMX for H-6,7,8 protons and a broad signal of the OH group. For all compounds, the corresponding molecular ions were observed in high-resolution mass spectra.

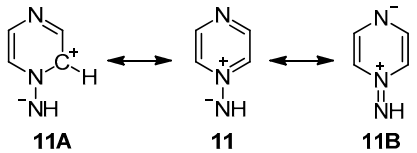


Figure 2. Dipolar resonance structures of pyrazinium-*N*-imine.

To get more insights into the reactions of *N*-imines with nitriles, a DFT study (on the B3LYP/L1 level of theory with RI approximation and SMD solvation, see the Supplementary information file for details) of the cycloaddition process was performed. For cycloaddition of pyridinium-*N*-imine to 4-cyanopyridine, the transition state **TS1** corresponding to concerted mechanism was localized (Fig. 3*a*). The geometry of transition state **TS1** is similar to that of the previously reported transition state structures[34,35] involved in the cycloaddition of dimethyl acetylenedicarboxylate to pyridinium-*N*-imines. However, in the case of nitrile, a latter transition state is realized due to a shorter distance between pyridinium-*N*-imine and cyanopyridine. As shown on energetic diagram (Fig. 4), the reaction is slightly exothermic and cycloadduct **12** formed is much less stable than rearrangement product **13**. Although sigmatropic hydrogen shifts in cycloadduct **12** are unlikely, formation of structure **13** may proceed through base-mediated double bond migration. Product **2c**, in turn, is formed from adduct **12** by oxidation with air.

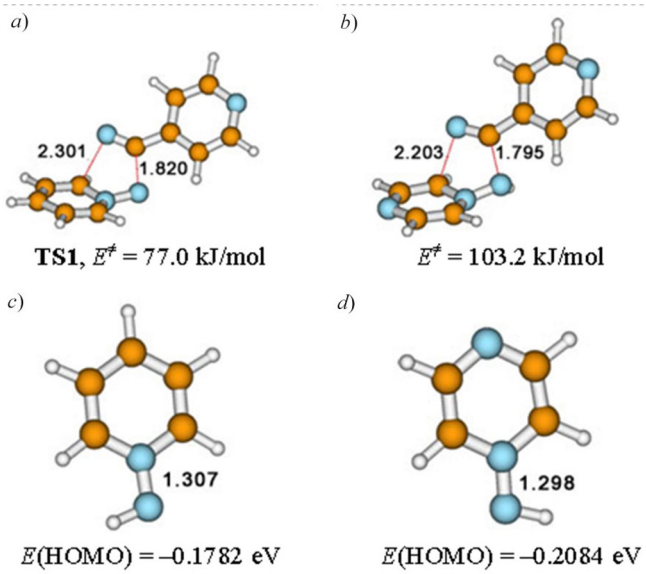


Figure 3. Structures of transition states of nitrile cycloaddition to *a*) pyridinium- and *b*) pyrazinium-*N*-imines, and structures of *c*) pyridinium- and *d*) pyrazinium-*N*-imines with their HOMO energy level.

The other pathway to cycloadduct **12** is the stepwise addition *via* dipolar intermediate **14** (Fig. 4). We weren't able to localize this structure as minimum on potential energy surface. Previous computational[36–38] and kinetic[39] studies of nitrile cycloadditions to nitrones indicate that reactions are likely to proceed through concerted mechanism.

Pyrazinium-*N*-imine has slightly shorter N–N bond (Fig. 3*d*) that reflects higher contribution of structure **11A** to the resonance hybrid (Fig. 2). At the same time, this imine has significantly lower HOMO energy level compared to pyridinium-*N*-imine, probably due to electron-withdrawal properties of nitrogen atom. Thus, significantly increased activation energy was found for reaction of pyrazinium-*N*-imine with 4-cyanopyridine (Fig. 3*b*).

In the case of quinolinium-*N*-imine, a substantially higher barrier ($E^{\neq}$ = 123.0 kJ/mol) was also observed.

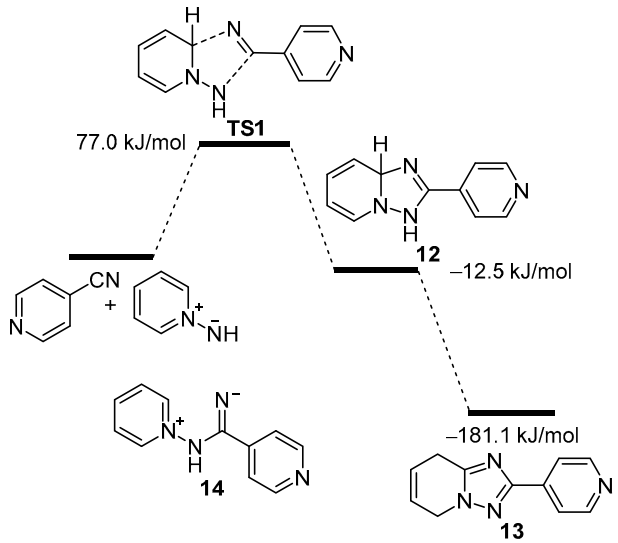


Figure 4. Energy diagram of cycloaddition of *N*-imine to 4-cyanopyridine and structure of **TS1**.

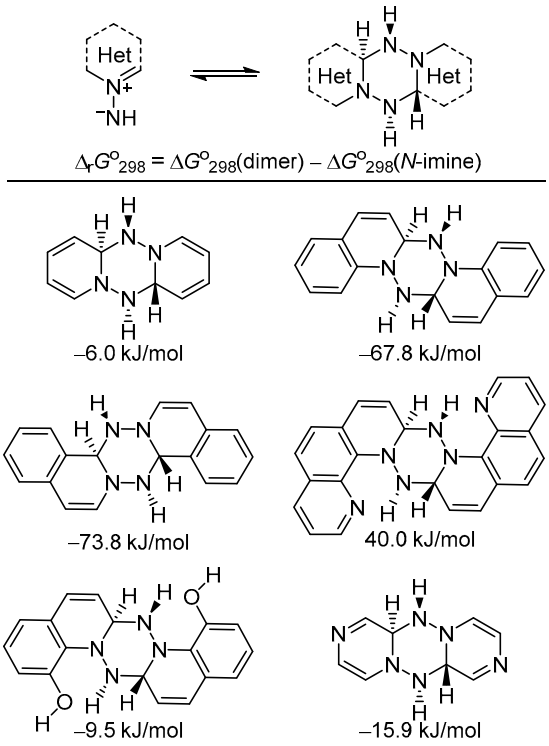


Figure 5. Calculated dimerization energies ($\Delta_r G^\circ_{298}$) of *N*-imines.

At the same time, dimerization of this imine is strongly favorable (Fig. 5). Even higher negative energy of dimerization was obtained for isoquinolinium-*N*-imine, and, notably, the most stable dimer formed by the reaction at position 1 of the both rings. This fact is in accordance with the direction of nucleophilic attack in *N*-substituted isoquinolines. Pyridinium-*N*-imines, pyrazinium-*N*-imines, and, especially, 1,10-phenanthrolinium-*N*-imine possess significantly more positive energy of dimerization, therefore, cycloaddition reaction of these imines does not have dimerization as complicating factor.

In summary, cycloaddition of cyanopyridines to various azinium-*N*-imines generated from the corresponding *N*-aminoazinium salts in KOH/H_2O system was studied. In the case of pyridinium-*N*-imines and 2,2'- and 4,4'-bipyridinium derivatives, the presence of hydrogen peroxide was essential to increase yields of 2-pyridyl[1,2,4]triazolo[1,5-*a*]-pyridines and to avoid formation of hydrogenated products. For 1,10-phenanthrolinium and 8-hydroxyquinolinium mesitylenesulfonates, the corresponding [1,2,4]triazolo[1,5-*a*]-azines were obtained under basic conditions and with air oxygen as oxidant. In the case of qiunolinium- and isoquinolinium-*N*-imines, their dimers were isolated as the only products. Pyrazinium and pyridazinium imines were unreactive and did not undergo cycloaddition or dimerization. Quantum-chemical DFT studies showed that reaction proceeds *via* concerted 1,3-cycloaddition. Substantially higher activation barriers for addition of 4-cyanopyridine to quinolinium- and pyrazinium-*N*-imines, than to pyridinium-*N*-imine were observed. Besides, quinolinium and isoqinolinium imines possess strong tendency to dimerization according to the calculated values of dimerization energies.

Experimental

^{1}H NMR spectra were recorded on Bruker AC-200 (200 MHz), Bruker Avance 300 (300 MHz), or Bruker Avance 400 (400 MHz) instruments. ^{13}C NMR spectra were recorded on a Bruker Avance 400 (100 MHz) instrument. All NMR spectra were recorded in $CDCl_3$ solution, using the residual proton and carbon signals of the solvent (δ_H 7.24 ppm, δ_C 77.16 ppm) as internal standards. The 2D NMR studies were performed on a Bruker Avance 300 instrument. High-resolution mass spectra were recorded on a DFS Thermo scientific instrument (EI, 70 eV). Melting points were determined using a Kofler hot stage microscope and are uncorrected. The TLC was carried out on Sorbfil silica plates (UV 254) with further UV light visualization. Flash column chromatography was performed on silica gel (Macherey Nagel, pore size 60 Å, 230–400 mesh).

Starting materials unless otherwise noted were obtained from commercial suppliers and used without purification. *O*-(Mesitylenesulfonyl)hydroxylamine[22] (MSH), 1-aminopyridinium tetrafluoroborate,[27] 1-aminoquinolinium,[22] 1-aminoisoquinolinium,[22] 1-aminopyrazinium,[22] 1-amino-8-hydroxyquinolinium,[31] 1-amino-1,10-phenanthrolinium,[31] 1-amino-2,2'-bipyridinium,[35] and 1-amino-4,4'-bipyridium[40] mesitylenesulfonates were obtained as described in literature. Concentration of commercial H_2O_2 was determined by iodometric titration.

Synthesis of 2-pyridinyl[1,2,4]triazolo[1,5-*a*]azines 2–6 a–c (General method). The appropriate *N*-aminoazinium salt (0.5 mmol) was dissolved with stirring in 1 M aqueous KOH solution (2.5 ml, 2.5 mmol). Color of the reaction mixture changed to deep violet immediately. After 1–2 min, 2-, 3-, or 4-cyanopyridine (52.0 mg, 0.5 mmol) and 33% aqueous H_2O_2 (46 μl, 0.5 mmol) were added. The reaction mixture was stirred until color of the initially formed *N*-imine disappeared (usually overnight). Then the mixture was neutralized with 5% HCl and extracted with CH_2Cl_2 (3×10 ml). The organic phases were combined, dried over Na_2SO_4, and evaporated under reduced pressure. The crude product was washed with Me_2CO or purified by chromatography on silica gel as indicated below.

2-(Pyridin-2-yl)[1,2,4]triazolo[1,5-*a*]pyridine (2a). Purified by chromatography ($CHCl_3$–MeOH, 50:1). Yield 59.7 mg (61%), white solid, mp 196–198°C. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.04 (1H, td, *J* = 6.9, *J* = 1.3, H-7); 7.36 (1H, ddd, *J* = 7.6, *J* = 4.8, *J* = 1.2, H-5'); 7.53 (1H, ddd, *J* = 9.0, *J* = 6.9, *J* = 1.3, H-6); 7.78 (1H, dt, *J* = 9.0, *J* = 1.2, H-8); 7.83 (1H, td, *J* = 7.9, *J* = 1.7, H-4'); 8.31 (1H, dt, *J* = 7.9, *J* = 1.2, H-3'); 8.65 (1H, dt, *J* = 6.9, *J* = 1.2, H-5); 8.78 (1H, ddd, *J* = 4.8, *J* = 1.7, *J* = 0.8, H-6'). ^{13}C NMR spectrum, δ, ppm: 114.1 (C-7); 116.7 (C-8); 122.4 (C-3'); 124.4 (C-5'); 128.5 (C-5); 129.7 (C-6); 136.7 (C-4'); 149.5 (C-8a); 150.0 (C-6'); 151.5 (C-2'); 163.3 (C-2). Found, *m*/*z*: 196.0753 $[M]^+$. $C_{11}H_8N_4$. Calculated, *m*/*z*: 196.0744. The reaction mixture was analyzed by COSY, ^{1}H–^{13}C HMBC, and ^{1}H–^{13}C HSQC to determine the structure of compound **2'a**.

2-(Pyridin-2-yl)-5,8-dihydro[1,2,4]triazolo[1,5-*a*]pyridine (2'a). Was identified in mixture with product **2a** by 2D NMR studies. Attempts to isolate pure product **2'a** were unsuccessful. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 3.59–3.63 (2H, m) and 4.80–4.84 (2H, m, 5,8-CH_2); 5.91–6.02 (2H, m, 6,7-CH); 7.26 (1H, ddd, *J* = 7.5, *J* = 4.8, *J* = 1.0, H-5'); 7.73 (1H, td, *J* = 7.6, *J* = 1.7, H-4'); 8.06 (1H, dm, *J* = 7.8, H-3'); 8.68 (1H, dm, *J* = 4.5, H-6'). ^{13}C NMR spectrum, δ, ppm: 24.8 (C-8); 46.3 (C-5); 120.1 (C-6(7)); 121.0 (C-3'); 121.6 (C-7(6)); 123.6 (C-5'); 136.5 (C-4'); 149.4 (C-6'); 150.7 (C-8a); 160.1 (C-2). Signal for C-2' atom was not identified.

2-(Pyridin-3-yl)[1,2,4]triazolo[1,5-*a*]pyridine (2b). Purified by chromatography ($CHCl_3$–MeOH, 50:1). Yield 59.6 mg (63%), white solid, mp 158.5–160°C. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.05 (1H, td, *J* = 6.9, *J* = 1.2, H-7); 7.43 (1H, dddd, *J* = 7.9, *J* = 4.9, *J* = 1.7, *J* = 0.9, H-5'); 7.54 (1H, ddd, *J* = 9.0, *J* = 6.9, *J* = 1.2, H-6); 7.77 (1H, dm, *J* = 9.0, H-8); 8.54 (1H, dt, *J* = 7.9, *J* = 1.7, H-4'); 8.61 (1H, dm, *J* = 6.9, H-5); 8.69 (1H, dd, *J* = 4.9, *J* = 1.6, H-6'); 9.49 (1H, dm, *J* = 2.0, H-2'). ^{13}C NMR spectrum, δ, ppm: 114.1; 116.6; 123.6; 127.0; 128.5; 130.0; 134.7; 148.7; 150.9; 151.8; 161.9. The spectral data is in accordance with those reported previously.[41] Found, *m*/*z*: 196.0751 $[M]^+$. $C_{11}H_8N_4$. Calculated, *m*/*z*: 196.0744.

2-(Pyridin-4-yl)[1,2,4]triazolo[1,5-*a*]pyridine (2c). Purified by chromatography ($CHCl_3$–MeOH, 50:1). Yield 53.7 mg (60%), white solid, mp 190–192°C (mp 190–192°C[23,42]). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.05 (1H, t, *J* = 6.9, H-7); 7.54 (1H, dd, *J* = 8.9, *J* = 6.9, H-6); 7.77 (1H, d, *J* = 8.9, H-8); 8.11–8.14 (2H, m, H-3',5'); 8.60 (1H, d, *J* = 6.9, H-5); 8.72–8.76 (2H, m, H-2',6'). The spectral data is in accordance with those reported previously.[41,42]

2-(Pyridin-2-yl)-7-(pyridin-4-yl)[1,2,4]triazolo[1,5-*a*]-pyridine (3a). The crude product was washed with Me_2CO to yield pure compound **3a**. Yield 105.5 mg (77%), white solid, mp 239–241°C. If the reaction was carried out in EtOH, the product was obtained in 35% yield. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 7.25 (1H, dd, *J* = 7.1, *J* = 1.9, H-6); 7.36 (1H, ddd, *J* = 7.6, *J* = 4.8, *J* = 1.1, H-5'); 7.51–7.54 (2H, m, H-3",5"); 7.81 (1H, td, *J* = 7.7, *J* = 1.8, H-4'); 7.96–7.97 (1H, m, H-8); 8.28 (1H, dt, *J* = 7.8, *J* = 1.1, H-3'); 8.68–8.73 (3H, m, H-5,2",6"); 8.76 (1H, dm, *J* = 4.8, H-6'). ^{13}C NMR spectrum, δ, ppm: 113.3; 114.5; 121.5; 122.8; 124.9; 129.1; 137.1; 140.2; 145.1; 149.4; 150.4; 150.9; 151.9; 164.5. Found, *m*/*z*: 273.1006 $[M]^+$. $C_{16}H_{11}N_5$. Calculated, *m*/*z*: 273.1009.

2-(Pyridin-3-yl)-7-(pyridin-4-yl)[1,2,4]triazolo[1,5-*a*]-pyridine (3b). The crude product was washed with Me_2CO to yield pure compound **3b**. Yield 76.4 mg (56%), white solid, mp 235–237°C. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.30 (1H, dd, *J* = 7.1, *J* = 1.9, H-6); 7.44 (1H, ddd, *J* = 8.8, *J* = 4.8, *J* = 0.9, H-5'); 7.57–7.58 (2H, m, H-3",5"); 8.00 (1H, dd, *J* = 1.9, *J* = 0.9, H-4); 8.54 (1H, ddd, *J* = 7.9, *J* = 2.2, *J* = 1.7, H-4'); 8.69 (1H, dd, *J* = 7.1, *J* = 0.9, H-7); 8.70 (1H, dd, *J* = 4.8, *J* = 1.7, H-6'); 8.71–8.82 (2H, m, H-2",6"); 9.51 (1H, d, *J* = 1.9, H-2'). ^{13}C NMR spectrum, δ, ppm: 113.2; 114.2; 121.6; 123.8; 126.8; 128.9; 134.7; 140.3; 145.1; 148.9; 151.0; 151.3; 152.0; 163.1. Found, *m*/*z*: 273.1007 $[M]^+$. $C_{16}H_{11}N_5$. Calculated, *m*/*z*: 273.1009.

2,7-Di(pyridin-4-yl)[1,2,4]triazolo[1,5-*a*]pyridine (3c). The crude product was washed with Me_2CO to yield pure compound **3c**. Yield 88.7 mg (65%), white solid, mp 206–207°C. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.30 (1H, dd, *J* = 7.1, *J* = 1.9, H-6); 7.54–7.57 (2H, m, H-3",5"); 8.00 (1H, dd, *J* = 1.9, *J* = 0.9, H-4); 8.08–8.14 (2H, m, H-3',5'); 8.68 (1H, dd, *J* = 7.1, *J* = 0.9, H-7); 8.73–8.77 (4H, m, H-2',6',2",6"). ^{13}C NMR spectrum, δ, ppm: 113.5; 114.5; 121.5 (2C); 129.0; 138.1; 140.5; 145.0; 150.7; 151.1; 152.1; 163.2. Found, *m*/*z*: 273.1001 $[M]^+$. $C_{16}H_{11}N_5$. Calculated, *m*/*z*: 273.1009.

2,5-Di(pyridin-2-yl)[1,2,4]triazolo[1,5-*a*]pyridine (4a). Purified by chromatography ($CHCl_3$–MeOH, 50:1). Yield 65.5 mg (48%), yellow oil. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 7.27–7.34 (2H, m, H Ar); 7.61 (1H, dd, *J* = 8.8, *J* = 7.4, H-5); 7.76 (1H, td, *J* = 7.5, *J* = 1.6, H-4(6)); 7.80 (1H, d, *J* = 8.8, H Ar); 7.83–7.88 (2H, m, H Ar); 8.30 (1H, d, *J* = 7.8, H Ar); 8.70 (1H, d, *J* = 4.7, H Ar); 8.74 (1H, d, *J* = 4.7, H Ar); 8.93 (1H, d, *J* = 8.1, H-6(4)). ^{13}C NMR spectrum, δ, ppm: 115.5; 116.8; 122.9; 124.4; 124.5; 125.1; 129.9; 136.8 (2C); 139.2; 149.3; 149.8 (2C); 150.1; 152.9; 162.9. Found, *m*/*z*: 273.1008 $[M]^+$. $C_{16}H_{11}N_5$. Calculated, *m*/*z*: 273.1009.

5-(Pyridin-2-yl)-2-(pyridin-3-yl)[1,2,4]triazolo[1,5-*a*]-pyridine (4b). Purified by chromatography ($CHCl_3$–MeOH, 50:1). Yield 61.4 mg (45%), white solid, mp 171–173°C. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.34–7.38 (2H, m, H-5',5"); 7.62 (1H, dd, *J* = 8.8, *J* = 7.7, H-5); 7.77 (1H, dd, *J* = 8.8, *J* = 1.4, H-4(6)); 7.86–7.92 (2H, m, H Ar); 8.51 (1H, dt, *J* = 7.8, *J* = 2.0, H-4'); 8.65 (1H, dd, *J* = 4.8, *J* = 1.6, H-6'); 8.73 (1H, d, *J* = 4.8, H-6"); 8.93 (1H, d, *J* = 7.7, H-6(4)); 9.50 (1H, dd, *J* = 2.2, *J* = 0.9, H-2'). ^{13}C NMR spectrum, δ, ppm: 115.4; 116.3; 123.5; 124.5; 125.1; 127.1; 130.0; 134.7; 136.7; 139.1; 149.0; 149.3; 149.9; 151.0; 152.9; 161.4. Found, *m*/*z*: 273.1007 $[M]^+$. $C_{16}H_{11}N_5$. Calculated, *m*/*z*: 273.1009.

5-(Pyridin-2-yl)-2-(pyridin-4-yl)[1,2,4]triazolo[1,5-*a*]-pyridine (4c). Purified by chromatography ($CHCl_3$–MeOH, 50:1). Yield 70.9 mg (52%), white solid, mp 172–174°C. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.40 (1H, ddd, *J* = 7.6, *J* = 4.8, *J* = 1.1, H-5"); 7.67 (1H, dd, *J* = 8.8, *J* = 7.4, H-5); 7.84 (1H, dd, *J* = 8.8, *J* = 1.4, H-4(6)); 7.91–7.99 (2H, m, H-3',5'); 8.16–8.19 (2H, m, H-3",4"); 8.73–8.76 (2H, m, H-2',6'); 8.79 (1H, d, *J* = 4.8, H-6"); 8.93 (1H, d, *J* = 7.4, H-6(4)). ^{13}C NMR spectrum, δ, ppm: 115.7; 116.6; 121.5; 124.5; 125.0; 130.1; 136.6; 138.4; 139.1; 149.1; 149.9; 150.5; 152.9; 161.4 Found, *m*/*z*: 273.1006 $[M]^+$. $C_{16}H_{11}N_5$. Calculated, *m*/*z*: 273.1009.

2-(Pyridin-2-yl)[1,2,4]triazolo[1,5-*a*][1,10]phenanthroline (5a). Purified by chromatography ($CHCl_3$–MeOH, 20:1). Yield 62.6 mg (42%), yellowish solid, mp 226–228.5°C (mp 226–228.5°C[31]). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 7.39 (1H, ddd, *J* = 7.6, *J* = 4.9, *J* = 1.1, H-5'); 7.70 (1H, dd, *J* = 8.0, *J* = 4.3, H-9); 7.88 (1H, td, *J* = 7.6, *J* = 1.7, H-4'); 7.92 (1H, d, *J* = 8.5, H-4(5)); 7.95 (1H, d, *J* = 8.5, H-5(4)); 8.04 (2H, s, H-6,7); 8.36 (1H, dd, *J* = 8.1, *J* = 1.7, H-8); 8.55 (1H, d, *J* = 8.0, H-3'); 8.84 (1H, ddd, *J* = 4.9, *J* = 1.7, *J* = 1.1, H-6'); 9.45 (1H, dd, *J* = 4.3, *J* = 1.8, H-10). ^{13}C NMR spectrum, δ, ppm: 117.3; 122.7; 123.3; 124.5; 124.9; 126.4; 126.9; 129.5; 131.0; 131.2; 136.4; 136.9; 139.8; 150.2 (2C); 151.1; 152.5; 164.1. The spectral data is in accordance with those reported previously.[31] Found, *m*/*z*: 297.1018 $[M]^+$. $C_{18}H_{11}N_5$. Calculated, *m*/*z*: 297.1009.

2-(Pyridin-3-yl)[1,2,4]triazolo[1,5-*a*][1,10]phenanthroline (5b). Purified by chromatography ($CHCl_3$–MeOH, 20:1). Yield 98.3 mg (66%), yellowish solid, mp 217.5–219°C. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.32 (1H, ddd, *J* = 7.9, *J* = 4.9, *J* = 0.9, H-5'); 7.54 (1H, dd, *J* = 8.3, *J* = 4.3, H-9); 7.71 (1H, d, *J* = 8.6, H-4(5)); 7.75 (1H, d, *J* = 8.6, H-5(4)); 7.83 (1H, d, *J* = 9.2, H-6(7)); 7.86 (1H, d, *J* = 9.2, H-7(6)); 8.18 (1H, dd, *J* = 8.3, *J* = 1.8, H-8); 8.60 (1H, dd, *J* = 4.9, *J* = 1.8, H-6'); 8.65 (1H, ddd, *J* = 7.9, *J* = 2.1, *J* = 1.8, H-4'); 9.26 (1H, dd, *J* = 4.3, *J* = 1.8, H-10); 9.60 (1H, dd, *J* = 2.2, *J* = 0.9, H-2'). ^{13}C NMR spectrum, δ, ppm: 116.6; 122.6; 123.4; 124.5; 126.2; 126.7; 127.3; 129.3; 130.5; 131.1; 134.9; 136.2; 139.6; 149.1; 150.7; 150.8; 152.3; 162.4. Found, *m*/*z*: 297.1017 $[M]^+$. $C_{18}H_{11}N_5$. Calculated, *m*/*z*: 297.1009.

2-(Pyridin-4-yl)[1,2,4]triazolo[1,5-*a*][1,10]phenanthroline (5c). Purified by chromatography ($CHCl_3$–MeOH, 20:1). Yield 74.5 mg (59%), yellowish solid, mp 265.5–267.5°C. ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.72 (1H, dd, *J* = 8.2, *J* = 4.3, H-9); 7.93 (1H, d, *J* = 8.7, H-4(5)); 7.98 (1H, d, *J* = 8.7, H-5(4)); 8.04 (1H, d, *J* = 9.2, H-6(7)); 8.07 (1H, d, *J* = 9.2, H-7(6)); 8.35–8.39 (2H, m, H-3',5'); 8.38 (1H, dd, *J* = 8.2, *J* = 1.9, H-8); 8.78–8.82 (2H, m, H-2',6'); 9.43 (1H, dd, *J* = 4.3, *J* = 1.8, H-10). ^{13}C NMR spectrum, δ, ppm: 117.0; 121.8; 122.8; 124.8; 126.6; 126.9; 129.5; 130.7; 131.6; 136.5; 138.6; 139.7; 150.6; 151.1; 152.6; 162.8. Found, *m*/*z*: 297.1018 $[M]^+$. $C_{18}H_{11}N_5$. Calculated, *m*/*z*: 297.1009.

2-(Pyridin-2-yl)[1,2,4]triazolo[1,5-*a*]quinolin-9-ol (6a). Purified by chromatography ($CHCl_3$–MeOH, 50:1). Yield 74.7 mg (57%), white solid, mp 237–239°C (EtOH) (mp 237–239°C[31]). ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 7.25–7.43 (4H, m, H-5',6,7,8); 7.63 (1H, d, *J* = 9.4, H-4(5)); 7.79–7.86 (2H, m, H-4',5(4)); 8.25 (1H, dt, *J* = 7.9, *J* = 1.0, H-3'); 8.78 (1H, dd *J* = 4.8, *J* = 1.8, H-6'); 10.86 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 114.9; 116.6; 119.1; 121.9; 122.7; 124.8; 125.1; 127.3; 132.4; 137.0; 147.7; 148.8; 149.8; 150.3; 161.0. The spectral data is in accordance with those reported previously.[31] Found, *m*/*z*: 262.0841 $[M]^+$. $C_{15}H_{10}N_4O$. Calculated, *m*/*z*: 262.0849.

2-(Pyridin-3-yl)[1,2,4]triazolo[1,5-*a*]quinolin-9-ol (6b). Purified by chromatography ($CHCl_3$–MeOH, 50:1). Yield 70.8 mg (54%), white solid, mp 215–216.5°C (EtOH). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.22–7.42 (4H, m, H-5',6,7,8); 7.56 (1H, d, *J* = 9.4, H-4(5)); 7.78 (1H, dd, *J* = 9.4, H-5(4)); 8.44 (1H, ddd, *J* = 7.9, *J* = 2.3, *J* = 1.7, H-4'); 8.67 (1H, dd, *J* = 4.8, *J* = 1.7, H-6'); 9.42 (1H, dd, *J* = 2.3, *J* = 0.9, H-2'); 10.71 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 114.5; 116.6; 119.2; 121.8; 123.7; 125.0; 125.9; 127.3; 132.5; 134.4; 147.6; 148.6; 149.7; 151.3; 159.3. Found, *m*/*z*: 262.0847 $[M]^+$. $C_{15}H_{10}N_4O$. Calculated, *m*/*z*: 262.0849.

2-(Pyridin-4-yl)[1,2,4]triazolo[1,5-*a*]quinolin-9-ol (6c). Purified by chromatography ($CHCl_3$–MeOH, 50:1). Yield 66.8 mg (51%), white solid, mp 202–204°C (EtOH). ^{1}H NMR spectrum (300 MHz), δ, ppm (*J*, Hz): 7.27 (1H, dd, *J* = 7.9, *J* = 1.2, H-8(6)); 7.34 (1H, dd, *J* = 7.9, *J* = 1.2, H-6(8));

7.43 (1H, t, *J* = 7.9, H-7); 7.58 (1H, d, *J* = 7.6, H-4(5)); 7.82 (1H, d, *J* = 7.6, H-5(4)); 8.02–8.07 (2H, m, H-3',5'); 8.71–8.76 (2H, m, H-2',6'); 10.67 (1H, s, OH). ^{13}C NMR spectrum, δ, ppm: 114.6; 116.8; 119.3; 121.1; 121.7; 125.1; 127.6; 132.7; 137.2; 147.6; 149.8; 150.7; 159.5. Found, *m*/*z*: 262.0843 $[M]^+$. $C_{15}H_{10}N_4O$. Calculated, *m*/*z*: 262.0849.

Gram-scale synthesis of compound 2a. *N*-Aminopyridinium tetrafluoroborate (3.00 g, 16.5 mmol) was dissolved in 1 M aqueous KOH solution (100 ml). Color of the reaction mixture changed to deep violet immediately. After stirring for 5 min, a solution of 2-cyanopyridine (1.71g, 16.5 mmol) in EtOH (5 ml) was added dropwise. After 5 min, 33% aqueous H_2O_2 (1.52 ml) was added dropwise and the mixture was kept stirring until violet color of *N*-imine disappeared (~24 h). Then reaction mixture was neutralized with 5% HCl and extracted with $CHCl_3$ (3×50 ml). The organic extracts were combined, dried over Na_2SO_4, and evaporated. The solid residue was purified by column chromatography (eluent $CHCl_3$–MeOH, 50:1). Yield 1.77 g (55%).

6a,7,14a,15-Tetrahydro[1,2,4,5]tetrazino[1,6-*a*:4,3-*a*']-diquinoline (quinolinium-*N*-imine dimer) (7d).[32,33] *N*-Aminoquinolinium mesitylenesulfonate (172 mg, 0.5 mmol) was dissolved with stirring in 2 M aqueous KOH solution (10 ml). Then 2-cyanopyridine (52.0 mg, 0.5 mmol) was added and the reaction mixture was stirred overnight. White solid was collected by filtration. Yield 54.0 mg (75%), yellowish powder. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 3.72 (2H, d, *J* = 11.9, 2NH); 5.45 (2H, ddd, *J* = 11.9, *J* = 4.0, *J* = 1.3, 6a,14a-CH); 5.59 (2H, dd, *J* = 9.8, *J* = 4.0, 6,14-CH); 6.54 (2H, dm, *J* = 9.8, 5,13-CH); 6.69 (2H, td, *J* = 7.4, *J* = 1.2, H-1(4),9(12)); 6.94 (2H, dd, *J* = 7.4, *J* = 1.5, H-2(3),10(11)); 7.15 (2H, ddd, *J* = 8.2, *J* = 7.3, *J* = 1.5, H-3(2),11(10)); 7.26 (2H, dm, *J* = 8.2, H-4(1),12(9)). The ^{1}H NMR data is in accordance with those reported previously.[33] ^{13}C NMR spectrum, δ, ppm: 70.9; 112.1; 118.7; 118.9; 119.7; 127.6; 130.0; 130.1; 143.0.

8,8a,16,16a-Tetrahydro[1,2,4,5]tetrazino[3,2-*a*:6,5-*a*']-diisoquinoline (isoquinolinium-*N*-imine dimer) (8d).[33] *N*-Aminoisoquinolinium mesitylenesulfonate (172 mg, 0.5 mmol) was dissolved with stirring in 2 M aqueous KOH solution (10 ml). Then 2-cyanopyridine (52.0 mg, 0.5 mmol) was added and reaction mixture was stirred overnight. White solid was collected by filtration. Yield of crude product 49.7 mg (69%), yellowish powder, which turns dark after a few hours. ^{1}H NMR spectrum (400 MHz), δ, ppm (*J*, Hz): 4.36 (2H, d, *J* = 12.1, 2NH); 5.36 (2H, d, *J* = 7.6, 6,14-CH); 5.80 (2H, d, *J* = 12.1, 8a,16a-CH); 6.42 (2H, dd, *J* = 7.6, *J* = 1.0, 5,13-CH); 6.93 (2H, dd, *J* = 7.5, *J* = 1.4, H-1(4),9(12)); 7.09 (2H, td, *J* = 7.5, *J* = 1.3, H-2(3),10(11)); 7.20 (2H, td, *J* = 7.5, *J* = 1.4, H-3(2),11(10)); 7.26 (2H, ddd, *J* = 7.5, *J* = 1.4, *J* = 0.7, H-4(1),12(9)). The ^{1}H NMR data is in accordance with those reported previously.[33]

DFT RI-B3LYP calculations were carried out with the PRIRODA program[43,44] with L1 basis set[45] (similar to the cc-pVDZ basis) for gas phase. SMD[46] solvation calculations were performed with the GAMESS[47] package for DFT B3LYP/cc-pVDZ. Simple thermodynamic cycle (Fig. 6) was applied to calculate standard Gibbs free energies $\Delta_rG°_{298}$ of

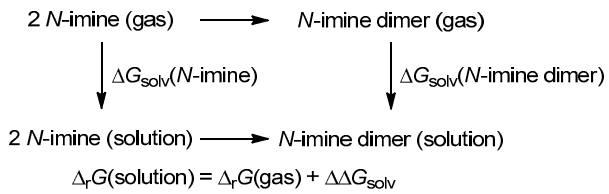


Figure 6. Thermodynamic cycle for calculation of Gibbs free energy of *N*-imine dimerization in solution.

N-imines dimerization reactions. At the first step, gas phase $\Delta_rG°_{298}$ free energies were calculated. Then the solvation energies (ΔG_{solv}) of *N*-imine and its dimer were obtained with SMD model.

The nature of optimized stationary points was confirmed with hessians calculation. For transition states, one imaginary mode was observed, and IRC procedure leads to the starting molecules or the corresponding products. ZPVEs were used without correction. Thermodynamic properties and activation free energies for the reactions were calculated at 298.15K and 1 atm.

Supplementary information file containing copies of ^{1}H, ^{13}C, and 2D NMR spectra along with atomic coordinates for DFT-optimized structures is available at the journal website at http://link.springer.com/journal/10593.

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