A Combined Experimental and Theoretical Study of the Ammonium Bifluoride Catalyzed Regioselective Synthesis of Quinoxalines and Pyrido[2,3-b]pyrazines

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A Combined Experimental and Theoretical Study of the Ammonium-Bifluoride-Catalyzed Regioselective Synthesis of Quinoxalines and Pyrido[2,3-*b*]pyrazines

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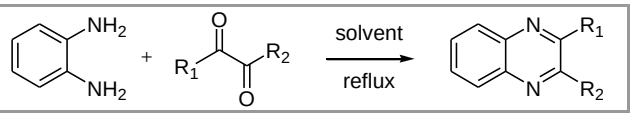
Abstract: Ammonium bifluoride was efficiently used (at a 0.5 mol % loading) to catalyze the cyclocondensation between 1,2-arylenediamines and 1,2-dicarbonyl compounds at room temperature in methanol-water, affording quinoxalines and pyrido[2,3-*b*]pyrazines in excellent yields. Importantly, 2,8-disubstituted quinoxalines and 3-substituted pyrido[2,3-*b*]pyrazines were regioselectively formed by reacting aryl glyoxals with 3-methyl-1,2-phenylenediamine and 2,3-diaminopyridine, respectively. Analysis of the DFT reactivity indices allowed to explain the catalytic role of ammonium bifluoride.

Key words: quinoxalines, pyrido[2,3-*b*]pyrazines, regioselectivity, ammonium bifluoride, catalysis, DFT reactivity indices

Quinoxalines and pyrido[2,3-*b*]pyrazines belong to an important class of nitrogen heterocyclic compounds. Derivatives are endowed with interesting biological activities[1] and used in therapeutics. Others serve as intermediates to targets such as organic dyes,[2] electroluminescent materials,[3] and semiconductors.[4] The most common synthetic route used to reach these structures is the condensation of 1,2-dicarbonyl reagents with 1,2-arylenediamines in refluxing ethanol or acetic acid (Scheme 1).[5]



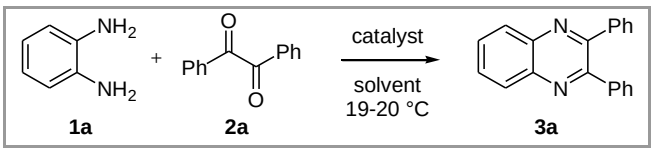
Scheme 1 Most common synthetic route to 2,3-disubstituted quinoxalines

In these last years, a large range of catalysts,[6] as well as green processes,[7] have been developed to carry out this reaction. A few studies have also been devoted to reactions in which regioselectivity can be an issue. In particular, 2,8-disubstituted quinoxalines were regioselectively synthesized from 2,3-diaminobenzoic acid and aryl glyoxals, at methanol reflux, by Wang and co-workers.[8] Besides, 3-substituted pyrido[2,3-*b*]pyrazines were similarly formed from 2,3-diaminopyridine.[9]

A few examples in the literature state the use of bifluoride anion. Among them, Bu_4NHF_2 was recognized as a fluorinating reagent.[10] More recently, quaternary ammonium bifluorides were identified as catalysts for asymmetric nitroaldol reaction of silyl nitronates to aldehydes.[11] To our knowledge, NH_4HF_2 (ammonium bifluoride or ammonium hydrogen fluoride, ABF) was only used recently as Brönsted acid catalyst in organic synthesis.[12] In the course of testing numerous ammonium salts as Brönsted acid sources for condensation to quinoxaline, we identified ABF as a good candidate, and here report the results of the study. In addition, the high regioselectivities noted for the reaction using either 3-methyl-1,2-phenylenediamine or 2,3-diaminopyridine with unsymmetrical 1,2-dicarbonyl compounds were rationalized.

An experimental study of the ABF-catalyzed condensation reactions.

The condensation of 1,2-phenylenediamine (**1a**) to benzil (**2a**) in the presence of ABF (1 mol %) at room temperature was first selected to optimize the reaction solvent (Scheme 2, Table 1). Three polar media, which are water, 4:1 methanol-water, and 4:1 ethanol-water, were compared: in the two organic solvents, quantitative yields of **3a** were obtained in 5 and 15 min, respectively (Table 1, entries 1,2) while in pure water a lower 80% yield was recorded, even after 1 hour reaction (Table 1, entry 3). In 4:1 methanol-water and 4:1 ethanol-water, the amount of catalyst could even be reduced to 0.5 mol % provided that extended reaction times of 15 and 30 min are used (Table 1, entries 4,5). Dichloromethane and ethyl acetate were also evaluated: in these solvents, the reaction proved less efficient, and increasing the catalyst loading to 10 mol % and the reaction time to 1 h only led to 90% yields (Table 1, entries 6,7).



Scheme 2 Optimization of the synthesis of 2,3-diphenylquinoxaline using ABF

Table 1 ABF-catalyzed synthesis of **3a** at 20 °C using different solvents

Entry	Solvent	ABF (mol %)	Time (min)	Yield (%)
1	4:1 MeOH-H_2O	1	5	>99
2	4:1 EtOH-H_2O	1	15	>99
3	H_2O	1	60 or more	80
4	4:1 MeOH-H_2O	0.5	15	>99
5	4:1 EtOH-H_2O	0.5	30	>99
6	CH_2Cl_2	10	60	90
7	$MeCO_2Et$	10	60	90

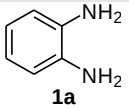
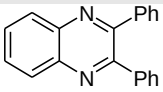
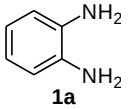
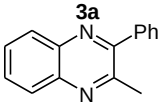
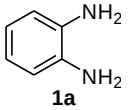
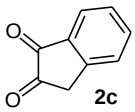
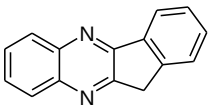
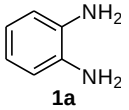
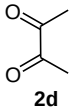
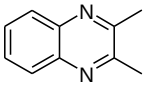
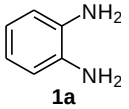
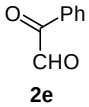
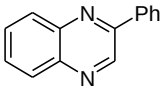
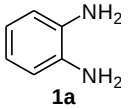
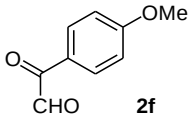
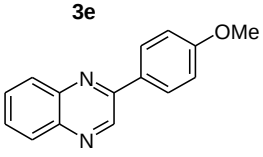
Using the same mixture of solvents, NH_4Cl,[13] NH_4F, *para*-toluenesulfonic acid (PTSA), trichloroacetic acid, HCl and HF were compared to ABF (Scheme 2, Table 2). The quantitative yield of **3a** obtained after 5 min at room temperature using 1 mol % of ABF (Table 2, entry 1) was reproduced using NH_4Cl, but provided that 50 mol % were employed (Table 2, entry 2). After the same reaction time, NH_4F (50 mol %) afforded **3a** in 92% yield (Table 2, entry 3). Among the catalysts capable of acting as Brönsted acids, HF proved the best to promote the formation of the quinoxaline derivative.

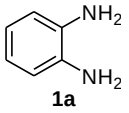
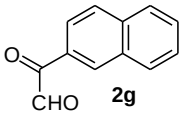
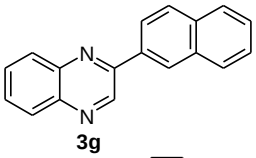
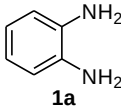
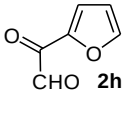
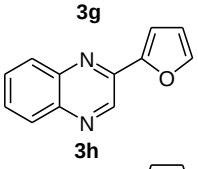
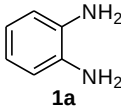
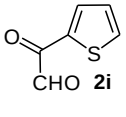
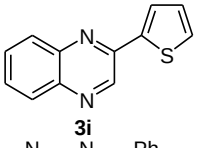
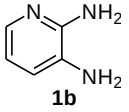
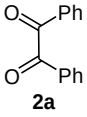
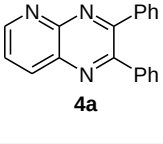
Table 2 Synthesis of **3a** in 4:1 MeOH-H_2O at 20 °C using different catalysts (reaction time: 5 min)

Entry	Catalyst (mol %)	Yield (%)
1	NH_4HF_2 (1)	>99
2	NH_4Cl (50)	>99
3	NH_4F (50)	92
4	PTSA (1)	90
5	Cl_3CCO_2H (1)	83
6	HCl (1)	88
7	HF (1)	>99

The optimized conditions in hands, we evaluated the scope of the reaction by testing different 1,2-dicarbonyl compounds (Table 3). Benzil (**2a**), pyruvophenone (**2b**), 1,2-indanedione (**2c**), and even 1,2-butanedione (**2d**) reacted very easily with 1,2-phenylenediamine (**1a**), affording after simple filtration the corresponding 2,3-disubstituted quinoxalines **3a-d** in high yields (Table 3, entries 1-4). ABF proved for example a catalyst superior to gallium(III) triflate, which does not allow the formation of **3d** when used in methanol at room temperature.[14] Besides 1,2-diketones, ketoaldehydes were also involved in the reaction. Phenyl glyoxal (**2e**), 4-anisyl glyoxal (**2f**), 2-naphthyl glyoxal (**2g**), 2-furyl glyoxal (**2h**) and 2-thienyl glyoxal (**2i**) led to the expected monosubstituted derivatives **3e-i**, respectively, in high yields (Table 3, entries 5-9). Reacting benzyl (**2a**) with 2,3-pyridinediamine (**1b**) also furnished the expected 2,3-diphenyl derivative **4a** satisfactorily (Table 3, entry 10).

Table 3 ABF-catalyzed synthesis of the quinoxalines **3** and pyrido[2,3-*b*]pyrazine **4** from the 1,2-arylenediamines **1** and 1,2-dicarbonyl compounds **2** in 4:1 MeOH-H_2O at 20 °C[a]

Entry	**1**	**2**	**3** or **4**	Yield (%)
1	 **1a**	 **2a**	 **3a**	>99
2	 **1a**	 **2b**	 **3b**	97
3	 **1a**	 **2c**	 **3c**	92
4	 **1a**	 **2d**	 **3d**	98
5	 **1a**	 **2e**	 **3e**	>99
6	 **1a**	 **2f**	 **3f**	97

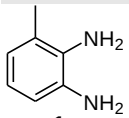
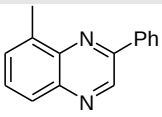
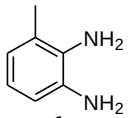
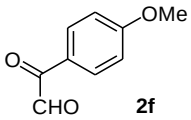
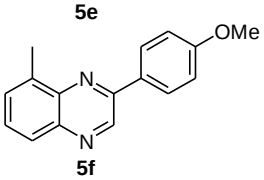
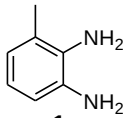
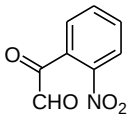
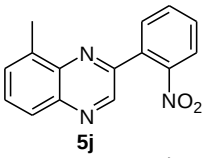
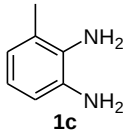
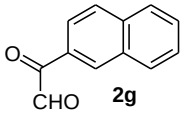
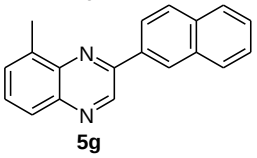
7	 **1a**	 **2g**	 **3g**	98
8	 **1a**	 **2h**	 **3h**	98
9	 **1a**	 **2i**	 **3i**	94
10	 **1b**	 **2a**	 **4a**	90[b]

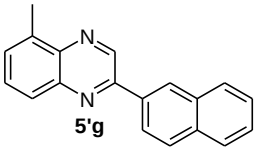
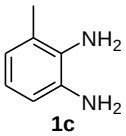
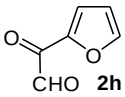
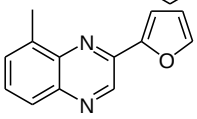
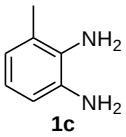
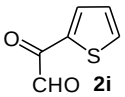
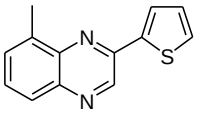
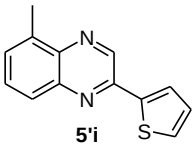
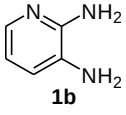
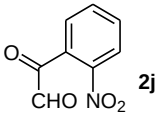
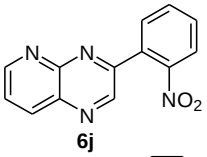
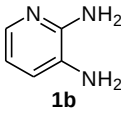
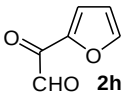
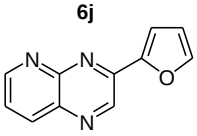
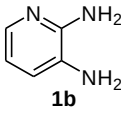
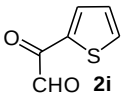
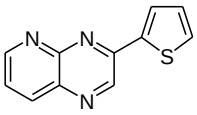
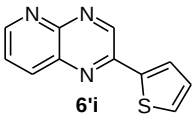
[a] Reaction conditions: diamine (1.0 mmol), dicarbonyl compound used as hydrate (1.0 mmol), ABF (0.5 mol %), MeOH (2 mL), H_2O (0.5 mL), 15 min, room temperature. [b] Reaction performed overnight using 5 mol % ABF.

Interestingly, a regioselectivity resulted from reactions between both unsymmetrical 1,2-dicarbonyl compounds and 1,2-arylenediamines (Table 4). So, when 3-methyl-1,2-phenylenediamine (**1c**) was reacted with phenyl glyoxal (**2e**), the regioisomer identified as **5e** was isolated by column chromatography in 94% yield (Table 4, entry 1). A similar result was noted by using 4-anisyl glyoxal (**2f**), 2-nitrophenyl glyoxal (**2j**), 2-naphthyl glyoxal (**2g**), 2-furyl glyoxal (**2h**) and 2-thienyl glyoxal (**2i**), to give as predominant isomer the compounds **5f**, **5j**, **5g**, **5h** and **5i**, respectively (Table 4, entries 2-6). The major disubstituted quinoxalines **5e-j**, as well as the minor disubstituted quinoxalines **5'g** and **5'i**, were unequivocally identified as by X-ray structure analysis (Figure 1). In a first approach, the regioselectivity observed could be rationalized by a favored reaction between the less congested amino group and the more reactive carbonyl function.

2,3-Pyridinediamine (**1b**), which possesses a more reactive amino group at C3, also furnished the expected monosubstituted pyrido[2,3-*b*]pyrazines **6j**, **6h** and **6i** by using 2-nitrophenyl glyoxal (**2j**), 2-furyl glyoxal (**2h**) and 2-thienyl glyoxal (**2i**), respectively (Table 4, entries 7-9, Figure 2). This demonstrates the potential extension of the reaction to other 1,2-arylenediamines benefitting from different amine reactivities and/or steric hindrances.

Table 4 ABF-catalyzed synthesis of the quinoxalines **5** and pyrido[2,3-*b*]pyrazines **6** from both unsymmetrical 1,2-arylenediamines **1** and 1,2-dicarbonyl compounds **2** in 4:1 MeOH-H_2O at 20 °C[a]

Entry	**1**	**2**	**5** or **6**	Yield (%)
1	 **1c**	 **2e**	 **5e**	94[b]
2	 **1c**	 **2f**	 **5f**	95[b]
3	 **1c**	 **2j**	 **5j**	91[c]
4	 **1c**	 **2g**	 **5g**	94[b]
				5[d]

			 **5'g**	
5	 **1c**	 **2h**	 **5h**	95[c]
6	 **1c**	 **2i**	 **5i**	95[b]
			 **5'i**	5[d]
7	 **1b**	 **2j**	 **6j**	90
8	 **1b**	 **2h**	 **6h**	93[c]
9	 **1b**	 **2i**	 **6i**	95[b]
			 **6'i**	5[d]

[a] Reaction conditions: diamine (1.0 mmol), dicarbonyl compound used as hydrate (1.0 mmol), ABF (0.5 mol %), MeOH (2mL), H_2O (0.5mL), 15 min, room temperature. [b] Major isomer isolated by silica gel chromatography. [c] Only one regioisomer formed in this case. [d] Minor isomer isolated by silica gel chromatography.

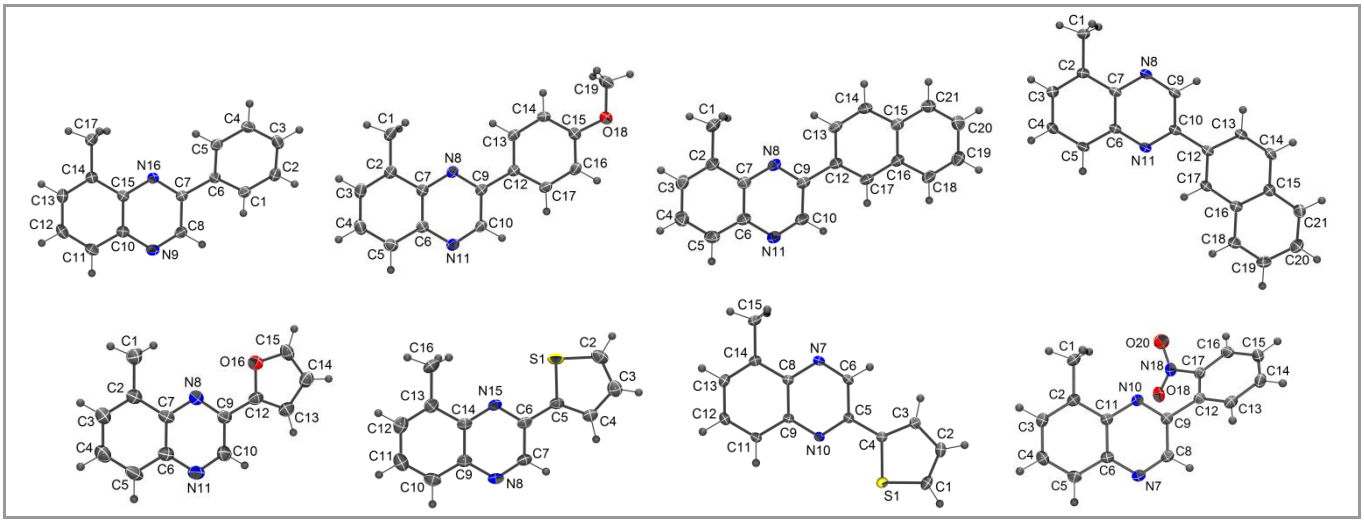


Figure 1 ORTEP diagram (50% probability) of **5e**, **5f**, **5g**, **5'g**, **5h**, **5i**, **5'i** and **5j**

Thus, ABF gave **3a** in a quantitative yield after a short reaction time. Even at a loading lower than 1 mol %, a rapid reaction was observed at room temperature. The derivatives were isolated in high purity after simple

filtration. The reusability of the filtrate ABF was evaluated using the optimized procedure. The filtrates could be recycled five times without noticeable change of the catalytic activity of ABF.

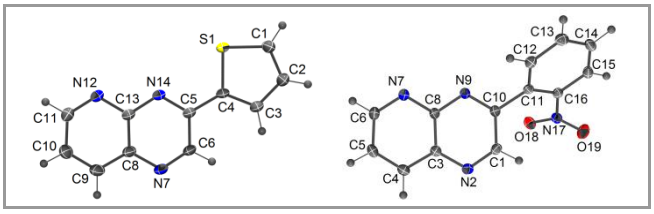


Figure 2 ORTEP diagram (50% probability) of **6i** and **6j**

A DFT reactivity analysis of the ABF catalyzed condensation reactions.

The ABF catalyzed condensation reaction of 1,2-arylenediamines with 1,2-dicarbonyl compounds was analyzed using the reactivity indices defined within the conceptual DFT.[15] In a polar protic solvent, ABF can be dissociated yielding different charged species. Consequently, three molecular complexes catalyzing the nucleophilic attack of 1,2-arylenediamines to dicarbonyl compounds were considered: i) in model I, namely **2i**:ABF, an ammonium hydrogen atom of ABF molecular complex was hydrogen-bonded to the ketone oxygen atom; ii) in model II, namely **2i**:NH4, the ammonium cation NH_4^+ was hydrogen-bonded to the ketone oxygen atom, and finally iii) in model III, namely **2i**:H, a proton was bonded to the ketone oxygen atom (see Figure 3). Note that the molecular complex **2i**:H would be considered as a Brönsted catalysis model.[16] The values of global descriptors, namely, electronic chemical potential μ, chemical hardness η, global electrophilicity ω, and global nucleophilicity *N* indices for some representative reagents involved in these condensation reactions are given in Table 5.

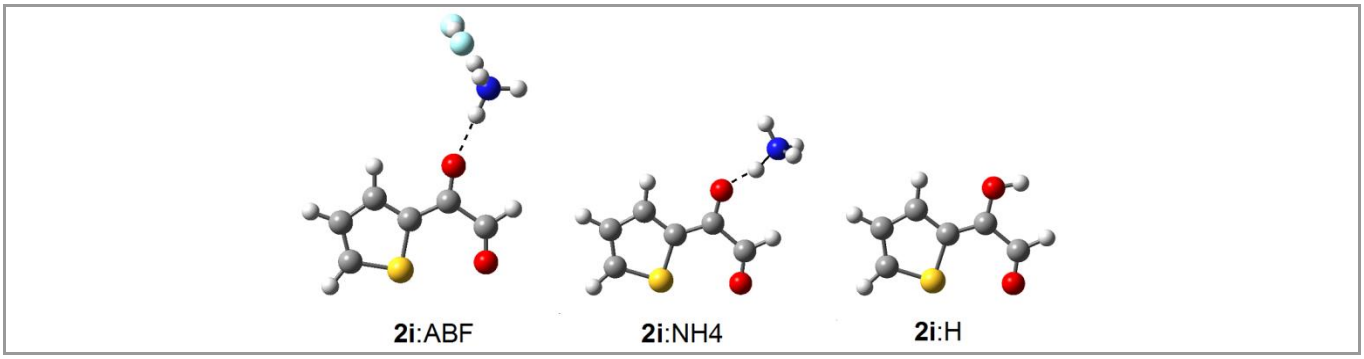


Figure 3 B3LYP/6-31G(d,p) structure of the molecular complexes **2i**:ABF, **2i**:NH4 and **2i**:H

Table 5 B3LYP/6-31G(d,p) electronic chemical potential μ, chemical hardness η, global electrophilicity ω, and global nucleophilicity *N* indices, in eV, of some representative reagents involved in the condensation reactions

	μ	η	ω	*N*
2i:H	-10.35	3.61	14.87	-3.04
2i:NH4	-8.54	3.67	9.92	-1.26
2i:ABF	-5.52	3.93	3.87	1.63
2i	-4.94	4.06	3.01	2.15
1b	-2.66	5.27	0.67	3.82
1c	-2.19	5.58	0.43	4.14

The electrophilicity ω index[17] of the 1,2-dicarbonyl compound **2i** is very high, 3.01 eV, being classified as a strong electrophile.[18] Formation of a hydrogen bond between ABF and the ketone oxygen atom of **2i** increases the electrophilicity ω index of complex **2i**:ABF to 3.87 eV.[19] A more drastic electrophilic activation is found when the NH_4^+ cation is hydrogen-bonded to the carbonyl oxygen atom in **2i**:NH4, ω = 9.92 eV. Finally, protonation of the oxygen atom considerably increases the electrophilicity ω index of complex **2i**:H to 14.87 eV. Clearly, both the ammonium cation and the proton are able to catalyze the addition reactions.

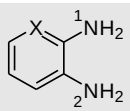
The 1,2-arylenediamines present a high nucleophilicity *N* index,[20] 3.82 (**1b**) and 4.14 (**1c**) eV, respectively, being classified as strong nucleophiles.[21] Note that the tolyl derivative **1c** is more nucleophilic than the pyridine one **1b**.

The high electrophilic character of complexes **2i**:H and **2i**:NH4, together with the high nucleophilic character of **1c** and **1b**, account for the feasibility of these condensation reactions which are initialized by the nucleophilic attack of one amine nitrogen atom of these 1,2-arylenediamine derivatives on the activated carbonyl carbon of complexes **2i**:H or **2i**:NH4.

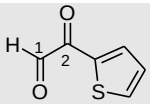
The local electrophilicity ω_k indices[22] in **2i**, **2i**:ABF, **2i**:NH4 and **2i**:H, and the local nucleophilicity N_k indices[23] in **1c** and **1b** were analyzed in order to explain the regioselectivity (see Table 6). The ketone C2 carbon of **2i**, ω_{C2} = 0.53 eV, is slightly more electrophilically activated that the aldehyde C1 carbon, ω_{C1} = 0.45 eV. Interestingly, formation of the

hydrogen bond between ABF and the ketone oxygen atom of **2i** does not only increase the global electrophilicity of **2i**:ABF, but it also makes the reaction chemoselective since the ketone carbonyl carbon, ω_{C2} = 0.90 eV, is twice more electrophilic that the aldehyde one, ω_{C1} = 0.52 eV. A more noticeable local activation is found in complexes **2i**:NH4 and **2i**:H in which the carbonyl C2 carbon is strongly activated, the addition being completely chemoselective (see Table 6).

Table 6 Local electrophilicity ω_{Ck} indices at the carbonyl carbon atoms of **2i**, **2i**:ABF, **2i**:NH4 and **2i**:H, and local nucleophilicity N_{Nk} indices at the nitrogen atoms of the 1,2-arylenediamines **1b** and **1c**, in eV



X = N, CMe



	ω_{C1}	ω_{C2}	N_{N1}	N_{N2}
2i:H	0.54	6.02		
2i:NH4	0.96	3.27		
2i:ABF	0.52	0.90		
2i	0.45	0.53		
1b			0.85	0.86
1c			0.96	0.75

Analysis of the local nucleophilicity N_k index at the pyridine derivative **1b** indicates that there is not a clear differentiation between the two nitrogen atoms. However, when they are analyzed in the tolyl derivative **1c**, the nitrogen N1 atom located in the *ortho* position to the methyl group is more nucleophilically activated than the nitrogen N2 atom.

This poor local nucleophilic discrimination between the two nitrogen atoms can be in relation with the total electron-density considered when computing the Parr functions. However, along the nucleophilic attack, only the non-bonding lone pairs of these nitrogen atoms participate in the addition. A natural bond orbital (NBO) analysis of the two 1,2-arylenediamines indicates that the lone pair of the N2 nitrogen atom is 3.07 (**1b**) and 4.57 (**1c**) kcal/mol below in energy than the lone pair of the N1 nitrogen atom. Consequently, it is expected that along the nucleophilic attack of these 1,2-arylenediamines on the most electrophilic C2 carbon of **2i**:NH4 or **2i**:H, the more energetic N1 lone pair will participate more efficiently.

In summary, we have developed a safe and economical process for the room temperature and catalytic synthesis of quinoxaline and pyrido[2,3-*b*]pyrazine derivatives from 1,2-arylenediamines and 1,2-dicarbonyl compounds. The reusability of the catalyst, easy handling (no glassware etching at this concentration and temperature), and commercial availability, together with the mild reaction conditions, the simple work-up procedure and the short reaction time in spite of low catalyst concentrations, are the strong practical points of the presented method.

The reactivity and regioselectivity observed in the course of reactions using both unsymmetrical 1,2-dicarbonyl compound and 1,2-arylenediamine was rationalized in the light of theoretical studies based on the DFT global and local reactivity indices. While the global electrophilicity ω index explains correctly the electrophilic activation of the 1,2-dicarbonyl compound by formation of a hydrogen bond to the ABF catalyst, the local counterpart explains the local activation of the C2 carbonyl carbon atom.

Liquid chromatography separations were achieved on silica gel Merck-Geduran Si 60 (63-200 µm). Nuclear Magnetic Resonance spectra were acquired using Bruker AC-300 spectrometer (300 MHz and 75 MHz for ^{1}H and ^{13}C respectively). ^{1}H chemical shifts (δ) are given in ppm relative to the residual solvent peak, and ^{13}C chemical shifts relative to the central peak of the solvent signal.[24]

Phenyl glyoxal (**2e**) is commercially available. 1,2-Indanedione (**2c**),[25] 4-anisyl glyoxal (**2f**),[26] 2-naphthyl glyoxal (**2g**),[27] 2-furyl glyoxal (**2h**),[28] 2-thienyl glyoxal (**2i**)[29] and 2-nitrophenyl glyoxal (**2j**)[30] were prepared according to literature references.[27]

X-ray Crystallography. The samples were studied with graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å). The X-ray diffraction data were collected using APEXII, Bruker-AXS diffractometer at T = 150(2) K. All structures were solved by direct methods using the SIR97 program,[32] and then refined with full-matrix least-square methods based on F^2 (SHELX-97)[33] with the aid of the WINGX program.[34] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. H atoms were finally included in their calculated positions. Molecular diagrams were generated by ORTEP-3 (version 2.02).[34]

General procedure 1 for the synthesis of the quinoxalines 3. The 1,2-arylenediamine (1.0 mmol) was added to a stirred mixture of the 1,2-dicarbonyl compound (1.0 mmol) in H_2O (0.5 mL) and 2.0 mL of $2.5.10^{-3}$ mol L^{-1} NH_4HF_2 (5.0 μmol) in MeOH at room temperature. After 15 min reaction time, the mixture was cooled using an ice bath. The solid was filtered, washed with water, and dried to afford the pure expected product.

2,3-Diphenylquinoxaline (3a) was prepared from 1,2-phenylenediamine (**1a**) and benzil (**2a**) according to the general procedure 1 in a quantitative yield (0.28 g) as a white powder: mp 128-130 °C (lit.[35] 130-131 °C).

2-Methyl-3-phenylquinoxaline (3b) was prepared from 1,2-phenylenediamine (**1a**) and pyruvophenone (**2b**) according to the general procedure 1 in 97% yield (0.21 g) as a red powder: mp 58 °C (lit.[36] 57-58 °C).

11*H*-Indeno[1,2-*b*]quinoxaline (3c) was prepared from 1,2-phenylenediamine (**1a**) and 1,2-indanedione (**2c**) according to the general procedure 1 in 92% yield (0.20 g) as a yellow powder. The analyses were found similar to those previously reported.[9d]

2,3-Dimethylquinoxaline (3d) was prepared from 1,2-phenylenediamine (**1a**) and 1,2-butanedione (**2d**) according to the general procedure 1 in 98% yield (0.16 g) as a pale yellow powder: mp 106 °C (lit.[37] 104-106 °C).

2-Phenylquinoxaline (3e) was prepared from 1,2-phenylenediamine (**1a**) and phenyl glyoxal (**2e**) according to the general procedure 1 in a quantitative yield (0.21 g) as a white powder: mp 78 °C (lit.[38] 78-79 °C).

2-(4-Methoxyphenyl)quinoxaline (3f) was prepared from 1,2-phenylenediamine (**1a**) and 4-anisyl glyoxal (**2f**) according to the general procedure 1 in 97% yield (0.23 g) as a white powder: mp 100-102 °C (lit.[39] 100-101 °C).

2-(2-Naphthyl)quinoxaline (3g) was prepared from 1,2-phenylenediamine (**1a**) and 2-naphthyl glyoxal (**2g**) according to the general procedure 1 in 98% yield (0.25 g) as a white powder: mp 140 °C (lit.[40] 141-142 °C).

2-(2-Furyl)quinoxaline (3h) was prepared from 1,2-phenylenediamine (**1a**) and 2-furyl glyoxal (**2h**) according to the general procedure 1 in 98% yield (0.20 g) as a beige powder: mp 102-104 °C (lit.[41] 99-100 °C).

2-(2-Thienyl)quinoxaline (3i) was prepared from 1,2-phenylenediamine (**1a**) and 2-thienyl glyoxal (**2i**) according to the general procedure 1 in 94% yield (0.20 g) as a pale yellow powder: mp 120-122 °C (lit.[42] 120-121 °C).

2,3-Diphenylpyrido[2,3-*b*]pyrazine (4a). 2,3-Diaminopyridine (**1b**, 1.0 mmol) was added to 2.0 mL of $2.5.10^{-2}$ mol L^{-1} NH_4HF_2 (50 μmol) in MeOH and benzil (**2a**, 1.0 mmol) in H_2O (0.5 mL) at room temperature. The mixture was stirred overnight and cooled using an ice bath. The solid was filtered, washed with water, and dried to afford the pure expected product in 90% yield (0.25 g) as a pale yellow powder: mp 148 °C (lit.[35] 144-145 °C).

General procedure 2 for the synthesis of the quinoxalines 5. The 1,2-arylenediamine (1.0 mmol) was added to a stirred mixture of the 1,2-dicarbonyl compound (1.0 mmol) in H_2O (0.5 mL) and 2.0 mL of $2.5.10^{-3}$ mol L^{-1} NH_4HF_2 (5.0 μmol) in MeOH at room temperature. After 15 min, the mixture was cooled using an ice bath. The solid was filtered, washed with water, dried and (except for the nitro compounds) chromatographed over silica gel (the eluent is given in the product description).

8-Methyl-2-phenylquinoxaline (5e) was prepared from 3-methyl-1,2-phenylenediamine (**1c**) and phenyl glyoxal (**2e**) according to the general procedure 2 in 94% yield (0.21 g) as a pale yellow powder: R_f 0.21 (pentane:EtOAc 4:1); mp 104 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.88 (s, 3H), 7.50-7.65 (m, 5H), 7.93-7.97 (m, 1H), 8.23-8.28 (m, 2H); 9.33 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.2, 127.0, 127.5 (2C), 129.2 (2C), 129.4, 130.1, 130.3, 137.1, 138.1, 141.4, 141.7, 142.6, 150.3. The spectral data are analogous to those described previously.[43] Crystal data for **5e**: $C_{15}H_{12}N_2$, M_r = 220.26, monoclinic, *C*2/*c*, *a* = 25.6227(11), *b* = 3.8431(2), *c* = 22.7091(13) Å, *β* = 92.300(2) °, *V* = 2234.4(2) Å^3, *Z* = 8, ρ_c = 1.31 g cm^{-3}, μ = 0.078 mm^{-1} (a final refinement on F^2 with 2519 unique intensities and 155 parameters converged at w$R(F^2)$ = 0.1044 ($R(F)$ = 0.0431) for 1989 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 887677).[40]

2-(4-Methoxyphenyl)-8-methylquinoxaline (5f) was prepared from 3-methyl-1,2-phenylenediamine (**1c**) and 4-anisyl glyoxal (**2f**) according to the general procedure 2 in 95% yield (0.24 g) as a pale yellow powder: R_f 0.50 (CH_2Cl_2:pentane: 4:1); mp 96 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.84 (s, 3H), 3.87 (s, 3H), 7.04 (d, 2H, *J* = 9.0), 7.56 (d, 2H, *J* = 5.9), 7.91 (dd, 1H, *J* = 5.9 and 4.0), 8.19 (d, 2H, *J* = 9.0), 9.26 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.2, 55.5, 114.5 (2C), 126.9, 128.8, 128.9 (2C), 129.7, 130.1, 137.7, 141.3, 141.3, 142.3, 149.8, 161.4. Crystal data for **5f**: $C_{16}H_{14}N_2O$, M_r = 250.29, monoclinic, *C*2/*c*, *a* = 24.4240(16), *b* = 3.9155(2), *c* = 27.2910(15) Å, *β* = 107.981(3) °, *V* = 2482.4(2) Å^3, *Z* = 8, ρ_c = 1.339 g cm^{-3}, μ = 0.085 mm^{-1} (a final refinement on F^2 with 2808 unique intensities and 174 parameters converged at w$R(F^2)$ = 0.1155 ($R(F)$ = 0.0459) for 2176 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 1034992).[40]

8-Methyl-2-(2-nitrophenyl)quinoxaline (5j) was prepared from 3-methyl-1,2-phenylenediamine (**1c**) and 2-nitrophenyl glyoxal (**2j**) according to the

general procedure 2 in 91% yield (0.25 g) as a white powder: mp 128 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.75 (s, 3H), 7.62-7.84 (m, 5H), 7.97-8.02 (m, 2H), 9.04 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.1, 124.9, 127.0, 130.2, 130.4, 130.6, 131.5, 132.7, 132.8, 138.3, 141.0, 141.8, 143.4, 148.9, 149.6. Crystal data for **5j**: $C_{15}H_{11}N_3O_2$, M_r = 265.27, monoclinic, $P2_1/n$, a = 7.7038(3), b = 13.4722(6), c = 12.1711(6) Å, β = 96.793(2) °, V = 1254.34(10) Å^3, Z = 4, ρ_c = 1.405 g cm^{-3}, μ = 0.097 mm^{-1} (a final refinement on F^2 with 2861 unique intensities and 182 parameters converged at w$R(F^2)$ = 0.1018 ($R(F)$ = 0.0385) for 2416 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 1034993).[40]

8-Methyl-2-(2-naphthyl)quinoxaline (5g) was prepared from 3-methyl-1,2-phenylenediamine (**1c**) and 2-naphthyl glyoxal (**2g**) according to the general procedure 2 in 94% yield (0.25 g) as a pale yellow powder: R_f 0.37 (CH_2Cl_2:pentane 95:5); mp 148-150 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.93 (s, 3H), 7.55-7.59 (m, 2H), 7.63-7.66 (m, 2H), 7.90-8.05 (m, 4H), 8.46 (dd, 1H, J = 8.4 and 1.8), 8.69 (d, 1H, J = 1.2), 9.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.3, 124.6, 126.6, 126.9, 127.2, 127.2, 127.8, 128.9, 129.0, 129.4, 130.3, 133.4, 134.1, 134.4, 138.0, 141.4, 141.6, 142.7, 150.0. Crystal data for **5g**: $C_{19}H_{14}N_2$, M_r = 270.32, monoclinic, $P2_1/n$, a = 14.4579(13), b = 4.6502(4), c = 20.8516(17) Å, β = 103.783(3) °, V = 1361.5(2) Å^3, Z = 4, ρ_c = 1.319 g cm^{-3}, μ = 0.078 mm^{-1} (a final refinement on F^2 with 3105 unique intensities and 191 parameters converged at w$R(F^2)$ = 0.1334 ($R(F)$ = 0.0542) for 1796 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 1034994).[40] **5-Methyl-2-(2-naphthyl)quinoxaline (5'g)** was similarly isolated in 5% yield (13 mg) as a pale yellow powder and identified unambiguously by X-ray diffraction; R_f 0.51 (CH_2Cl_2:pentane 95:5); mp 154 °C. Crystal data for **5'g**: $C_{19}H_{14}N_2$, M_r = 270.32, monoclinic, $P2_1/c$, a = 12.7711(10), b = 4.4124(3), c = 23.9462(16) Å, β = 95.816(3) °, V = 1342.45(17) Å^3, Z = 4, ρ_c = 1.337 g cm^{-3}, μ = 0.079 mm^{-1} (a final refinement on F^2 with 3068 unique intensities and 191 parameters converged at w$R(F^2)$ = 0.112 ($R(F)$ = 0.0418) for 2388 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 1034995).[40]

2-(2-Furyl)-8-methylquinoxaline (5h) was prepared from 3-methyl-1,2-phenylenediamine (**1c**) and 2-furyl glyoxal (**2h**) according to the general procedure 2 in 95% yield (0.20 g) as a beige powder: R_f 0.21 (CH_2Cl_2:pentane 9:1); mp 70-72 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.81 (s, 3H), 6.62 (dd, 1H, J = 3.5 and 1.8), 7.33 (dd, 1H, J = 3.5 and 0.8), 7.56-7.59 (m, 2H), 7.66 (dd, 1H, J = 1.8 and 0.8), 7.89 (dd, 1H, J = 5.4 and 4.5), 9.25 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.0, 111.2, 112.4, 127.0, 128.9, 130.2, 137.4, 141.1, 141.3, 141.3, 142.6, 144.6, 152.2. Crystal data for **5h**: 2($C_{13}H_{10}N_2O$), M_r = 420.46, monoclinic, $P2_1/c$, a = 17.698(3), b = 4.7568(7), c = 24.587(4) Å, β = 92.295(6) °, V = 2068.2(6) Å^3, Z = 4, ρ_c = 1.35 g cm^{-3}, μ = 0.088 mm^{-1} (a final refinement on F^2 with 4713 unique intensities and 292 parameters converged at w$R(F^2)$ = 0.1677 ($R(F)$ = 0.0778) for 1926 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 901747).[40]

8-Methyl-2-(2-thienyl)quinoxaline (5i) was prepared from 3-methyl-1,2-phenylenediamine (**1b**) and 2-thienyl glyoxal (**2i**) according to the general procedure 2 in 95% yield (0.22 g) as a pale yellow powder: R_f 0.26 (CH_2Cl_2:pentane 9:1); mp 120 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.81 (s, 3H), 7.18 (dd, 1H, J = 5.0 and 3.7), 7.51 (dd, 1H, J = 5.0 and 1.1), 7.52-7.58 (m, 2H), 7.83 (dd, 1H, J = 3.7 and 1.1), 7.86-7.90 (m, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.0, 126.6, 127.0, 128.5, 129.0, 129.7, 130.5, 137.6, 141.2, 141.4, 141.5, 143.0, 146.2. Crystal data for **5i**: $C_{13}H_{10}N_2S$, M_r = 226.29, monoclinic, $P2_1/c$, a = 12.868(2), b = 4.5228(8), c = 18.899(3) Å, β = 92.293(6) °, V = 1099.0(3) Å^3, Z = 4, ρ_c = 1.368 g cm^{-3}, μ = 0.265 mm^{-1} (a final refinement on F^2 with 2496 unique intensities and 146 parameters converged at w$R(F^2)$ = 0.1249 ($R(F)$ = 0.0535) for 1579 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 887678).[40] **5-Methyl-2-(2-thienyl)quinoxaline (5'i)** was similarly isolated in 5% yield (11 mg) as a pale yellow powder and identified unambiguously by X-ray diffraction: R_f 0.40 (CH_2Cl_2:pentane 9:1); mp 178-180 °C. Crystal data for **5'i**: $C_{13}H_{10}N_2S$, M_r = 226.29, monoclinic, $P2_1/c$, a = 12.4419(6), b = 4.7272(2), c = 18.1617(9) Å, β = 98.448(2) °, V = 1056.60(9) Å^3, Z = 4, ρ_c = 1.423 g cm^{-3}, μ = 0.275 mm^{-1} (a final refinement on F^2 with 2418 unique intensities and 146 parameters converged at w$R(F^2)$ = 0.0936 ($R(F)$ = 0.0352) for 2126 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 887679).[40]

3-(2-(2-Nitrophenyl))pyrido[2,3-*b*]pyrazine (6j) was prepared from 2,3-diaminopyridine (**1c**) and 2-nitrophenyl glyoxal (**2j**) according to the general procedure 2 in 90% yield (0.23 g) as a pale yellow powder: mp 188 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.69-7.85 (m, 4H), 8.21 (d, 1H, J = 7.8), 8.55 (dd, 1H, J = 8.1 and 1.8), 9.00 (s, 1H), 9.23 (dd, 1H, J = 4.2 and 1.8); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 125.1, 125.7, 130.9, 132.5, 132.6, 133.8, 136.9, 138.5, 145.9, 148.3, 150.5, 154.7, 154.8. Crystal data for **6j**: $C_{13}H_8N_4O_2$, M_r = 252.23, triclinic, P -1, a = 7.4757(4), b = 8.1279(5), c = 9.8407(6) Å, α = 107.383(2), β = 101.006(2), γ = 94.012(2) °, V = 554.96(6) Å^3, Z = 2, ρ_c = 1.509 g cm^{-3}, μ = 0.107 mm^{-1} (a final refinement on F^2 with 2515 unique intensities and 172 parameters converged at w$R(F^2)$ = 0.0987 ($R(F)$ = 0.0390) for 2105 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 1034996).[40]

3-(2-Furyl)pyrido[2,3-*b*]pyrazine (6h) was prepared from 2,3-diaminopyridine (**1c**) and 2-furyl glyoxal (**2h**) according to the general procedure 2 in 93% yield (0.18 g) as a beige solid: R_f 0.30 (CH_2Cl_2:EtOAc 4:1); mp 132 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.67 (dd, 1H, *J* = 3.6 and 1.8), 7.59 (dd, 1H, *J* = 3.6 and 0.9), 7.66 (dd, 1H, *J* = 8.4 and 4.5), 7.72 (dd, 1H, *J* = 1.8 and 0.9), 8.43 (dd, 1H, *J* = 8.4 and 2.1), 9.15 (dd, 1H, *J* = 4.2 and 2.1), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 113.1, 114.0, 124.5, 136.6, 138.2, 143.1, 145.7, 146.6, 150.8, 151.3, 154.6.

3-(2-Thienyl)pyrido[2,3-*b*]pyrazine (6i) was prepared from 2,3-diaminopyridine (**1c**) and 2-thienyl glyoxal (**2i**) according to the general procedure 2 in 95% yield (0.20 g) as a pale yellow powder. The analyses were found similar to those previously reported.[9d] Crystal data for **6i**: $C_{11}H_7N_3S$, M_r = 213.26, monoclinic, $P2_1/c$, *a* = 7.0026(3), *b* = 13.0291(6), *c* = 11.0955(4) Å, β = 101.885(2) °, *V* = 990.62(7) Å^3, *Z* = 4, ρ_c = 1.43 g cm^{-3}, μ = 0.291 mm^{-1} (a final refinement on F^2 with 2258 unique intensities and 136 parameters converged at w$R(F^2)$ = 0.0929 ($R(F)$ = 0.0356) for 1945 observed reflections with $I > 2\sigma(I)$). The data were deposited to the Cambridge Crystallographic Data Centre (CCDC 887680).[40] **2-(2-Thienyl)pyrido[2,3-*b*]pyrazine (6'i)** was similarly isolated in 5% yield (11 mg) as a pale yellow powder. The analyses were found similar to those previously reported.[9d]

DFT computations were carried out using the B3LYP[45] functional, together with the standard 6-31G(d,p) basis set.[46] The electronic structures of the TSs were analysed by the natural bond orbital (NBO) method.[47] The global electrophilicity index,[17] ω, is given by the following expression, $\omega = (\mu^2 / 2\eta)$, based on the electronic chemical potential μ and the chemical hardness η. Both quantities may be approached in terms of the one-electron energies of the frontier molecular orbital HOMO and LUMO, ε_H and ε_L, as $\mu \approx (\varepsilon_H + \varepsilon_L)/2$ and $\eta \approx (\varepsilon_L - \varepsilon_H)$, respectively.[48] The global nucleophilicity index,[20] *N*, based on the HOMO energies obtained within the Kohn-Sham scheme,[49] is defined as $N = E_{HOMO}(Nu) - E_{HOMO}(TCE)$. This relative nucleophilicity index refers to tetracyanoethylene (TCE). The local electrophilicity ω_k indices[22] and local nucleophilicity N_k indices[23] were computed by using the electrophilic P_k^+ and nucleophilic P_k^- Parr functions.[50] All computations were carried out with the Gaussian 09 suite of programs.[51]

Supporting Information for this article (NMR spectra of the compounds **3c**, **5e**, **5f**, **5j**, **5g**, **5h**, **5i**, **6j**, **6h** and **6i**) is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000084.

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