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RuO_4-Mediated oxidation of N-benzylated tertiary amines. Four- and three-membered azacycloalkanes as substrates

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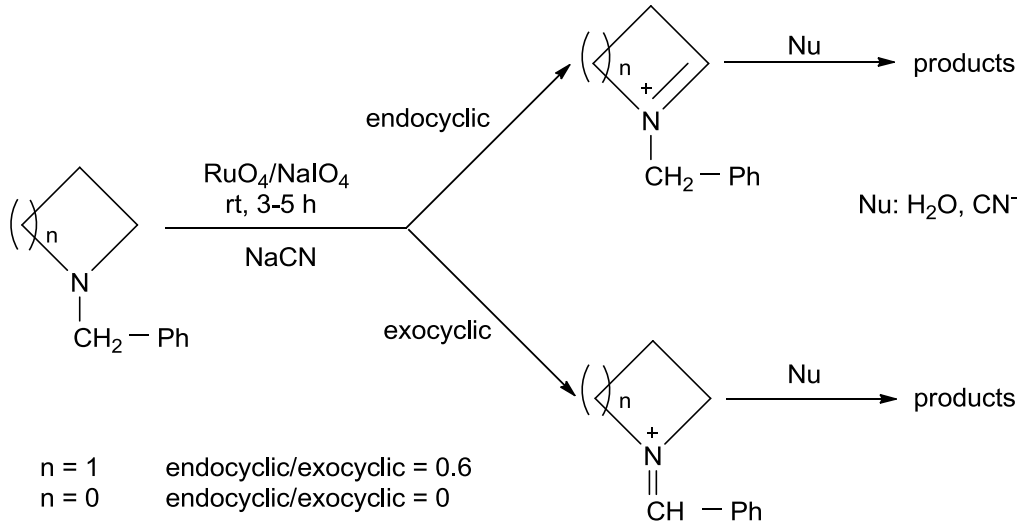
Abstract

Similarly to *N*-benzylpiperidine and -pyrrolidine, *N*-benzylazetidine underwent RuO_4-catalyzed oxidation by attack at both types of *N*-methylene C-H bonds: endocyclic and exocyclic (benzylic). If the reaction is performed in the presence of cyanide, α-aminonitriles were obtained instead of amides. The regioselectivity (endocyclic/exocyclic) decreased constantly with the decrease of the azacycle size, from about 2 (for *N*-benzylpiperidine) to about 0.6 (for *N*-benzylazetidine). The highest regioselectivity was found for *N*-benzylaziridine, for which only products of benzylic functionalization resulted. Iminium ions, complexed to ruthenium species, were proposed as reactive intermediates during the oxidation of *N*-benzylated azacycloalkanes.



Keywords: Oxidation, azacycloalkanes, ruthenium tetroxide, iminium ions, α-aminonitriles

Introduction

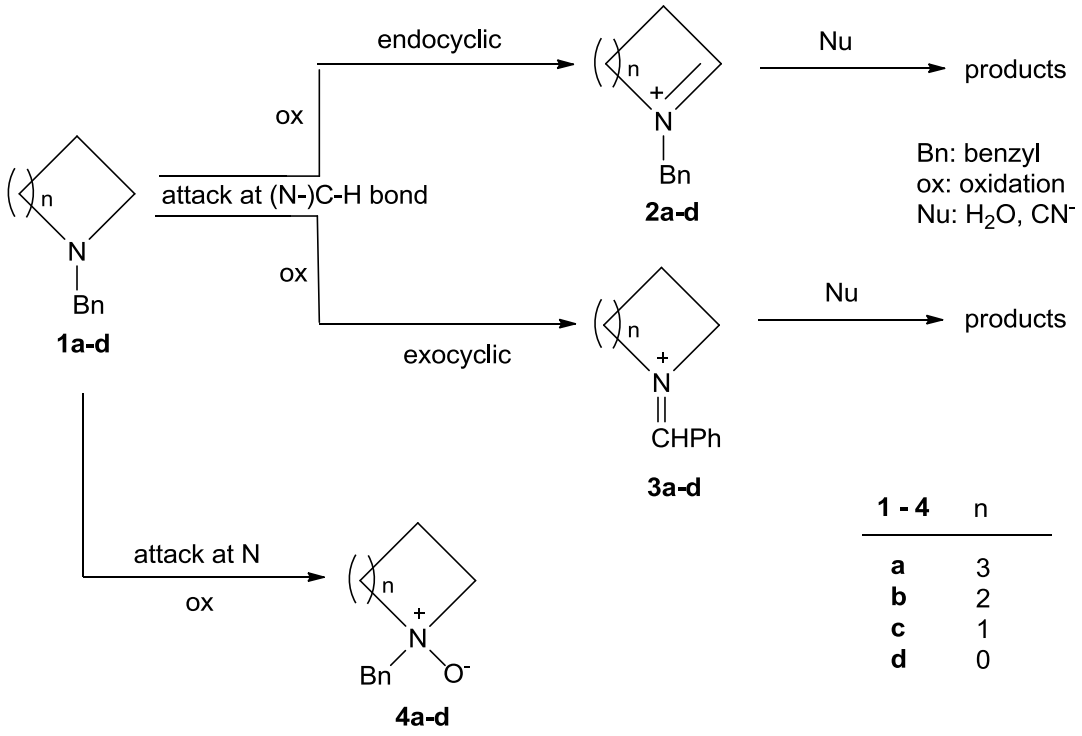
The powerful oxidant ruthenium tetroxide (RuO_4)[1] is widely used to functionalize C-H bonds in various organic compounds, such as hydrocarbons,[2,3] halides,[4] ethers,[5] alcohols,[6] amines,[7-12] or amides.[13] Rarely, the oxidative attack takes place at a heteroatom, like in the transformation of sulfide into sulfone.[14] Since RuO_4 has electrophilic character, the more electron-rich C-H bonds are attacked first. This explains why the C-H bonds in α-position to a heteroatom are oxidized preferentially in alcohols, ethers or amines.[1] In most cases these reactions result in products that are biologically active intermediates useful in the synthesis of amino acids, fragrances and drugs.[4,7,11,12,14]

Regarding the oxidation of amines, primary or secondary ones (R_2CH-NH-R) are transformed by RuO_4 into imines (R_2C=N-R), by a formal 1,2-dehydrogenation process.[15,16] In addition, a less common 1,1-dehydrogenation reaction transforms tertiary amines (R-CH_2-NR_2) to amides (R-CO-NR_2), with iminium ions as intermediates.[7-11]

Our previous research on oxidation of tertiary amines focused on the oxidative behaviour of medium-size azacycloalkanes, namely 1-benzylpiperidine (**1a**) and 1-benzylpyrrolidine (**1b**).[8] In this paper the studies are completed with the oxidation of small-ring analogues, 1-benzylazetidine (**1c**) and -aziridine (**1d**) (Scheme 1).

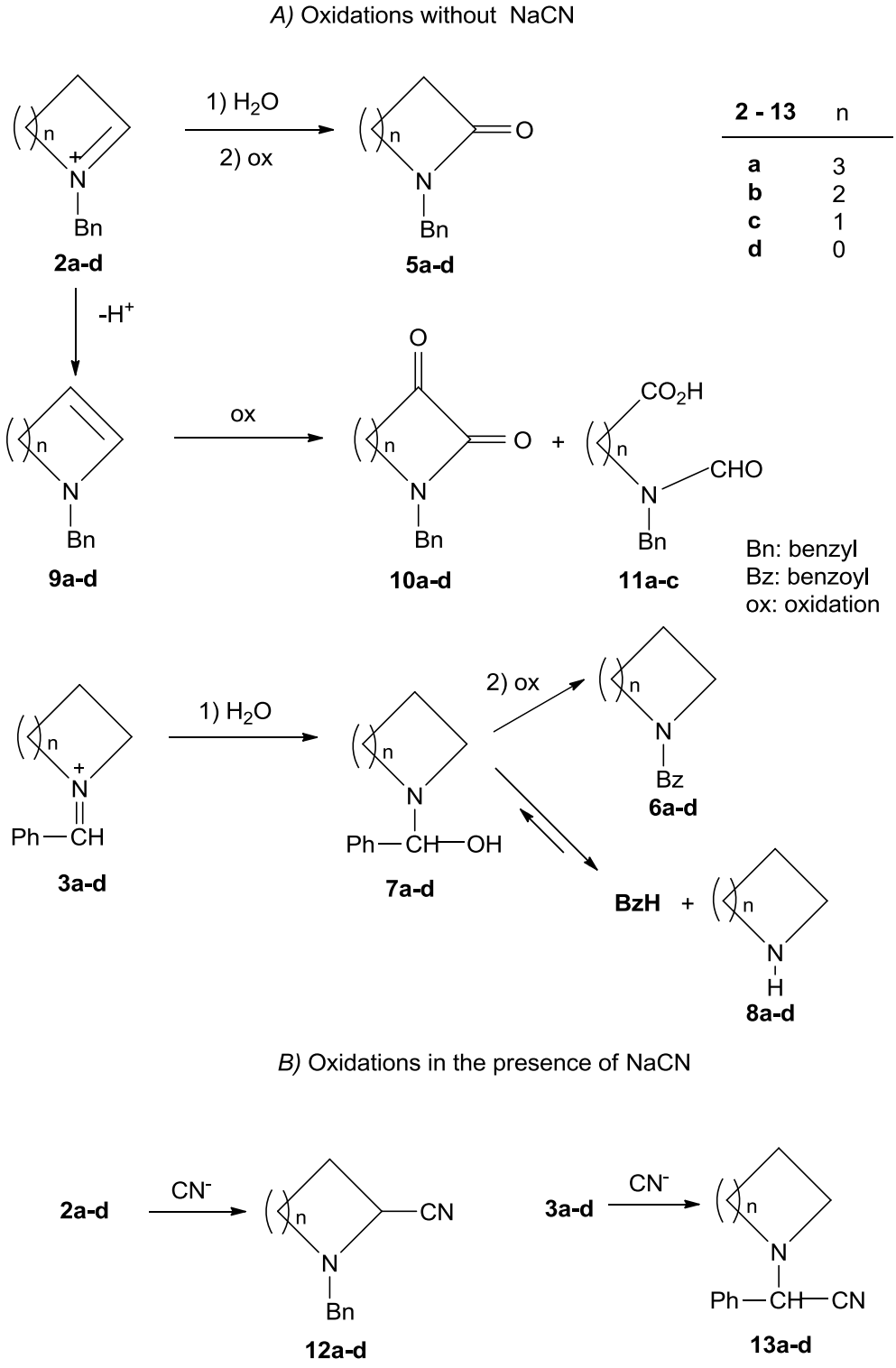
Results and Discussion

A general overview of the oxidation reactions of 1-benzylazacycloalkanes is presented in Scheme 1. Influence of the ring size on the reactivity and regioselectivity, in the RuO_4-mediated oxidation, revealed interesting aspects of the reaction mechanism.



Scheme 1. Oxidative routes for **1a**-**d**.

Previously studied[8] substrates **1a**-**b** are tertiary amines with two types of N-CH_2 groups: endocyclic and exocyclic (benzylic). Both types of methylene C-H bonds are attacked to yield the corresponding iminium ions as intermediates (Scheme 1): endocyclic (**2a**-**b**) and exocyclic (**3a**-**b**). At the same time, small amounts of *N*-oxides (**4a**-**b**) were present in the reaction mixtures, indicating that an *N*-oxidative attack (Scheme 1) was possible only to a minor extent.



Scheme 2. Oxidation products of **1a**-**d**.

The cations gave the final oxidation products after capture by nucleophiles, namely water under normal conditions (Scheme 2; part *A*). Along this pathway, the expected lactams **5a**-**b** resulted from **2a**-**b**, respectively, in essentially two steps. These steps are similar to those shown explicitly for the transformation of **3a**-**b** into **6a**-**b**: (i) formation of hemiaminals **7a**-**b** and (ii) oxidation of these alcohols to yield benzamides **6a**-**b**, respectively. Alternatively, the hemiaminals can split into benzaldehyde (**BzH**) and the corresponding unsubstituted azacycloalkanes **8a**-**b**. Since iminium ions **2a**-**b** carry β-*N* protons, stabilization to enamines **9a**-**b** through deprotonation can occur. Further oxidation of the C=C double bond in **9a**-**b** was the source of dioxygenated derivatives **10a**-**b** and **11a**-**b**.

When the oxidation was performed in the presence of NaCN, the initial iminium ions were trapped as the corresponding cyano derivatives **12a**-**b** and **13a**-**b** (Scheme 2, part *B*).

In this work, identically to the case of **1a**-**b**,[8] the oxidation of **1c**-**d** was performed in two ways: in the absence of cyanide (conditions *A*) or in its presence (conditions *B*). The respective results are presented in Table 1, together with those previously obtained for **1a**-**b**.[8] For simplicity, the desired entry (x) of Table 1 will be cited as T-x. Since free benzoic acid is always derived from benzaldehyde (**BzH**),[8-10,15,16] the amount quoted in Table 1 for **BzH** actually refers to the sum **BzH**+benzoic acid.

Values of endocyclic/exocyclic ratio (*Selectivity*) are shown in the last column of Table 1. Values smaller than 1 indicate that the exocyclic attack is favored. Analogously, the endocyclic attack will be favored when the *Selectivity* is greater than 1. A value of 1 for *Selectivity* means no regioselectivity. *Selectivity* was calculated with equations (1)-(3), where the amount of a particular compound is symbolized by its number in brackets:

endocyclic = (**5**) + (**10**) + (**11**) + (**12**) [plus (**unk**) for T-2] (**1**)

exocyclic = (**BzH**) + (**6**) + (**13**) (**2**)

Selectivity = endocyclic/(2 * exocyclic) (**3**)

Since there are two identical endocyclic CH_2 groups, but only one exocyclic (benzylic), a statistical correction (the factor 2) is needed in equation (3).

Table 1. Oxidation of azacycloalkanes **1a**-**d**

Entry no.	Substrate (recovd., %)[a]	Reaction products (molar, %)[a,b]	*Selectivity*[c]
0	1	2	3
		A) Oxidations without NaCN [d]	
1	**1a** (0)[e]	**4a** (4), **5a** (33.5),[f] **10a** (1), **11a** (42), **BzH** (16), **6a** (2)	2.1
2	**1b** (0)[e]	**4b** (6.5), **5b** (40.5),[g] **10b** (1.5), **11b** (13.5), **unk** (5.5),[h] **BzH** (27), **6b** (4)	1.0
3	**1c** (7)	**5c** (0.4), **BzH** (43.1), **6c** (40)	0.002
4	**1d** (10)	**BzH** (51.3), **6d** (3.2),[i] **15** (2.7), **16** (0.5), **17** (1.3)	0
		B) Oxidations in the presence of NaCN [d]	
5	**1a** (52)[e]	**4a** (1.9), **5a** (0.2), **11a** (0.2), **12a** (38.2), **BzH** (0.2), **13a** (7.9)	2.4
6	**1b** (6)[e]	**4b** (4.7), **5b** (<0.5), **11b** (<0.5), **12b** (60.6), **BzH** (1.9), **6b** (0.5), **13b** (24)	1.2
7	**1c** (82)	**4c** (0.1), **12c** (6.5), **BzH** (0.3), **13c** (5.4)	0.6
8	**1d** (92)	**BzH** (0.2), **15** (1.7), **23** (0.4)	-

[a] Molar amounts calculated against the initially added substrate, taken as 100; see also Experimental. [b] Formulae in Schemes 1-3. [c] Regioselectivity (endocyclic/ exocyclic) was calculated with eqs. (1)-(3). [d] Reaction conditions (for 1 mmol of substrate): *A* - $RuO_2.xH_2O$ (10-15 mg), co-oxidant $NaIO_4$ (4 mmol), CCl_4 (for **1a**-**b**) or $CHCl_3$ (for **1c**-**d**) (10 mL), water (10 mL), room temperature, 3-5 h; *B* - as in *A*, but NaCN (4 mmol) in water (10 mL) was also added. [e] Data from ref. 8. [f] Including 1% of 1-benzyl-2,6-piperidinedione. [g] Including 1% of 1-benzyl-2,5-pyrrolidinedione. [h] Unknown benzylic compound. [i] Including variable amounts of oxazoline **14** (see text).

Oxidation of azetidine 1c

In the absence of cyanide (conditions *A*), azetidine **1c** gave mainly benzaldehyde and benzamide **6c** (T-3). Azetidinone **5c** was formed too, albeit in a very small amount (T-3). No doubly oxygenated compounds such as **10c**[17] or **11c**[18] were present, in contrast to the results obtained for piperidine **1a** (T-1) or pyrrolidine **1b** (T-2).

In the presence of cyanide (conditions *B*), comparable amounts of cyano derivatives **12c** and **13c** resulted from **1c** (T-7), indicating that both iminium ions **2c** and **3c** (Scheme 1) were generated. The presence of the *N*-oxide **4c**, although in a relatively small amount, indicated that the third oxidative route (by *N*-attack, Scheme 1) was also active. Therefore, the oxidation of azetidine **1c** follows the same scheme as that previously discussed for **1a**-**b**.

Judging from the substrate recovery (7% in T-3, 82% in T-7), it appears that the oxidation occurred with more difficulty under conditions *B*. This appears to be true also for **1a** and **1d** (see below), but not for **1b**. Some of this effect could be due to the involvement of cyanide in another reaction, namely the oxidation towards cyanogen.[19] This reaction subtracts both cyanide and periodate (co-oxidant) from the desired amine oxidation.

Interesting aspects come from the values of *Selectivity*. On one hand, the decrease of the size of the azacycle (**1a** → **1b** → **1c**) led to decreasing *Selectivity* values. Thus, the endocyclic route is relatively prefered by piperidine **1a** (*Selectivity* ~ 2 in T-1 and T-5), no selectivity is shown by pyrrolidine **1b** (*Selectivity* ~ 1 in T-2 and T-6), and the exocyclic route becomes favored in the case of azetidine **1c** (*Selectivity* ~ 0 in T-3, but 0.6 in T-7). Practically, the absence of one CH_2 unit in the heterocycle resulted in a two-fold reduction of *Selectivity*, at least under conditions *B*.

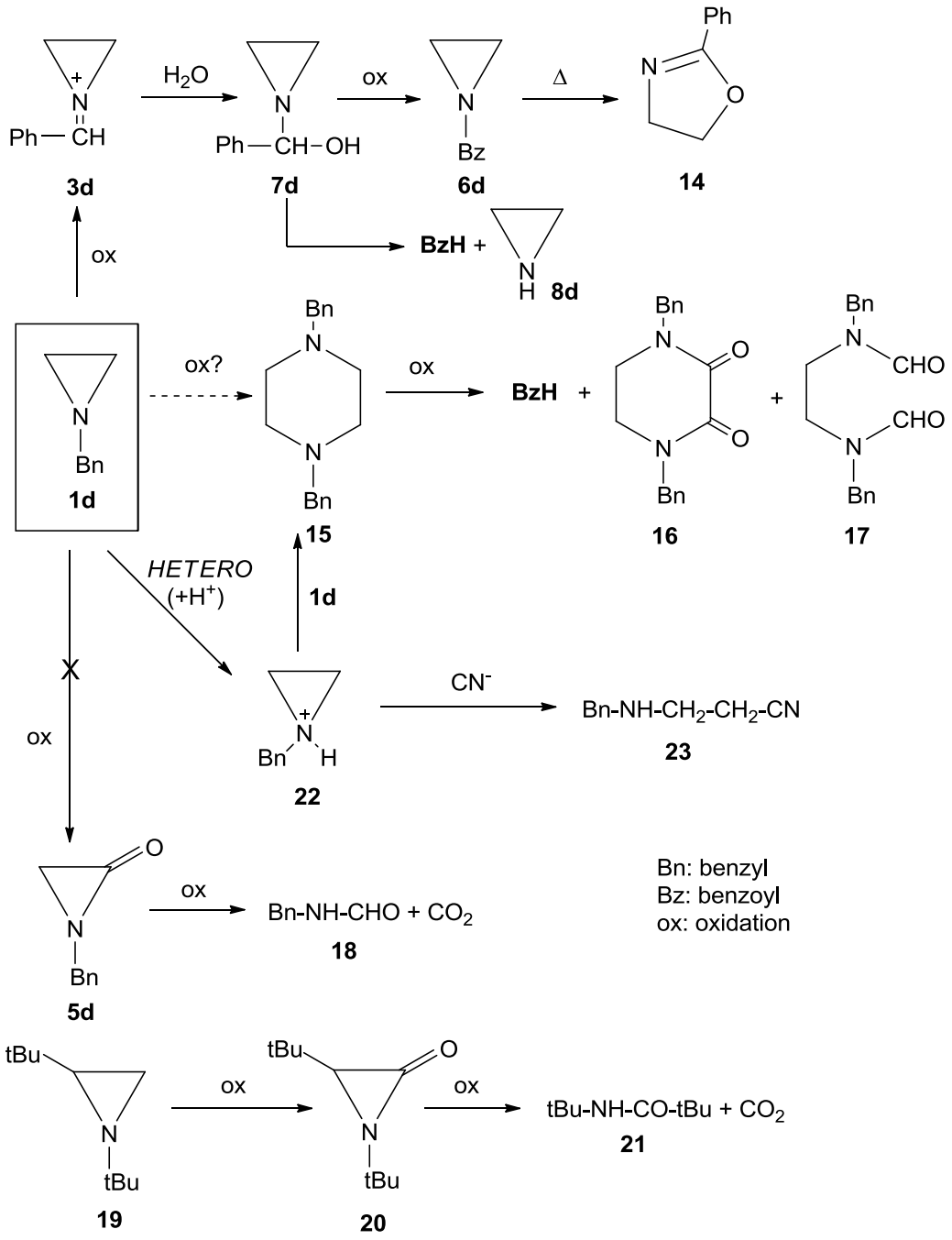
On the other hand, for the same substrate, *Selectivity* has higher values under conditions *B* than under conditions *A*. In the case of **1a**-**b**, there is only a tendency, but in the case of azetidine **1c** the difference is quite clear: still being less favored than the exocyclic route, the endocyclic route seems to recover some order of magnitude on passing from conditions *A* (*Selectivity* = 0.002) to conditions *B* (*Selectivity* = 0.6). No explanation can be given for this yet. For instance, at first sight, one could invoke a possible change in the active oxidant, in connection with the known relationship[1,20] between pH and the most stable oxidant structure: $Ru^{VIII}O_4$ under conditions *A* (pH ~ 5), but possibly the less aggressive agent $[Ru^{VII}O_4]^-$ under conditions *B* (pH ~ 9). This could explain the aforementioned variation of substrate recovery, but not that of *Selectivity*. In fact, a softer oxidant (like perruthenate) should be more selective than a stronger one (like ruthenium tetroxide), which is just opposite to the experimental evidence.

2-Cyanoazetidines like **12c** are versatile intermediates for a wide variety of catalysts,[21] biological amines,[22] or nitrogen heterocycles.[23] Even if it is out of the scope of this paper, the RuO_4-oxidation of **1c** under cyanide-trapping conditions (T-7) might be viewed, after further optimization, as a new way to synthesize 2-cyanoazetidines and may be added to the already known methods.[24,25]

Oxidation of aziridine 1d

Aziridine **1d** behaved differently (Scheme 3) than **1a**-**c**. Under conditions *A* (T-4), **BzH** was by far the main reaction product, but some benzamide **6d** was detected too. Sometimes, **6d** was accompanied by variable amounts of its isomer, the oxazoline **14**, thermally formed during work-up.[26] The reaction mixture contained also the piperazine **15** (a "dimer" of **1d**), piperazinedione **16** and the acyclic diformamide **17** (Scheme 3). It is worth mentioning that **BzH**, **16** and **17** are, all three, main products of the RuO_4-oxidation of **15**.[10] At the same time, it is known that **15** undergoes oxidation more easily than **1d**.[27] Taking into account also that the value of 2.6 for the ratio (**17)**/(**16)** is almost the same as that found in the RuO_4-oxidation of **15**,[10] it appears logical that **6d**+**14** came from **3d** and **16**+**17** from **15**. At the same time, since both routes produce benzaldehyde, the value of 51.3% in T-4 is the sum of two contributions: from **3d** ($\mathbf{BzH_{from\ 3d}}$) and from **15** ($\mathbf{BzH_{from\ 15}}$). No aziridinone **5d**[28] was detected, but, at first sight, this does not exclude its transient formation and subsequent fast oxidation towards formamide **18** and CO_2 (Scheme 3). This is suggested by the known[29] behaviour of aziridine **19** (lower part of Scheme 3), for which the intermediacy of the non isolable aziridinone **20** was proven: both **19** and **20** (synthesized independently) gave the same products, **21** and CO_2. In our case, formamide **18** was not detected in the oxidation mixture of **1d** (T-4). Therefore, the existence of **5d**, even transiently, can be ruled out, as indicated in Scheme 3.

Several previous works,[27,30,31] performed with **1d** and oxidants acting according to known mechanisms (*bona fide* oxidants) certified that dimer **15** can result from **1d** either by oxidation or heterolytically (*HETERO*). In the latter case, the aziridinium ion **22**, generated transiently from **1d**, undergoes an S_N2-type ring opening by reaction with **1d** itself,[32,33] followed by ring closure to **15**.



Scheme 3 Reaction products of **1d**.

Control experiments were performed with **1d** under conditions similar to those of T-4, but without oxidants. Working in the two-layer system of $CHCl_3$/buffered water (pH 5), 1 mmole of **1d** gave 50 µmoles of **15**, corresponding to a relative amount of 5%. This value is quite close to that found in T-4 [(**15**)+(**16**)+(**17**)+(**BzH**$_{\text{from 15}}$) = 4.5+(**BzH**$_{\text{from 15}}$)]. Therefore, the dotted arrow marked by "ox ?" connecting **1d** and **15** in Scheme 3 can be safely cancelled out.

Thus, the exclusive oxidation products of **1d** in T-4 are **BzH**$_{\text{from 3d}}$ and **6d**. Since only the benzylic position of **1d** has been attacked, the corresponding value of *Selectivity* is zero.

Under cyanide-trapping conditions (T-8), aziridine **1d** did not give the nitriles **12c** and **13c** (Scheme 2). Instead, piperazine **15** and the open chain nitrile **23** (Scheme 3) have been detected in the reaction mixture.

Control experiments with **1d** at pH 9 and without oxidants showed the formation of **15** and **23** in 1.5% and 0.3% molar amounts, respectively, values close to those found in T-8. Therefore, piperazine **15** and nitrile **23** resulted both by a *HETERO* mechanism, as discussed before for T-4. Summing up, it appears that RuO_4 was practically not active towards **1d** in the presence of cyanide, in contrast to the aforementioned cases of **1 a-c**.

Therefore, the behaviour of aziridine **1d** is a consequence of the competition between the RuO_4-mediated oxidation and the heterolytic steps, just as in other oxidative media.[27,30,31] In the case of RuO_4-oxidation, only the exocyclic (benzylic) route was active under conditions *A*, as in the case of azetidine **1c**. However, unlike **1c**, the oxidation of **1d** is largely or totally suppressed under conditions *B* and the reaction follows only the *HETERO* route.

Mechanistic considerations

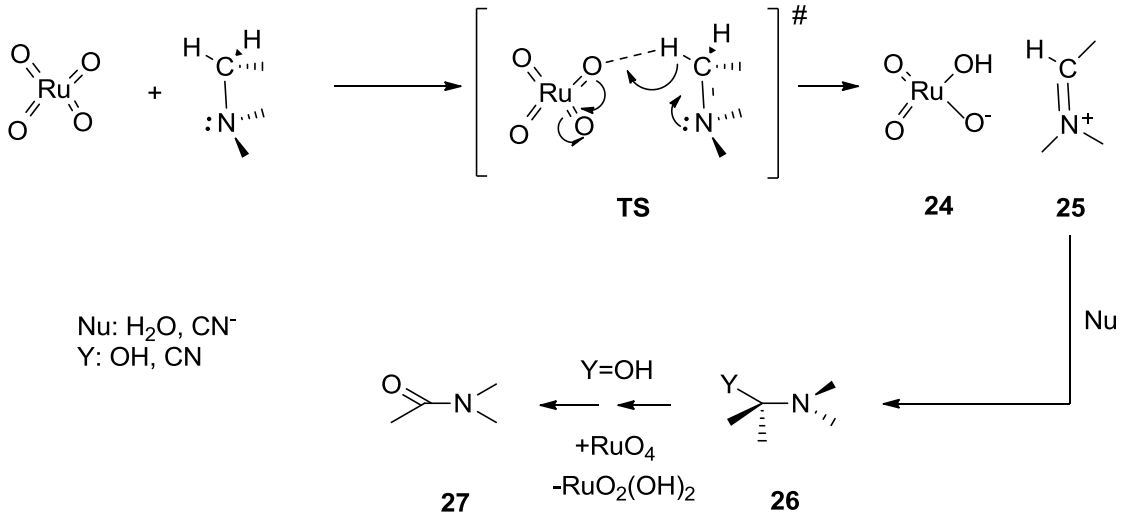
Two very similar mechanisms have been proposed so far[1,7,11,12] for the oxidation by RuO_4 of tertiary amines like **1a**-**d**. Based on these we propose the multi-step mechanism of Scheme 4.[8-10] The first step consists in the formation of the ion pair consisting of ruthenate (Ru^{VI}) anion **24** and iminium ion **25**. In the corresponding transition state (**TS**), the electronic lone pair on nitrogen is used to create a new C=N double bond (*E*lectron *T*ransfer process), concomitantly to hydrogen abstraction (*HAB*) and generation of a Ru^{VI} species. The existence of both *ET* and *HAB* processes in the rate-determining step was already proven.[4,7] Prior to *ET*+*HAB*, the substrate could give also a complex with a low-valent ruthenium species[7] (not displayed in Scheme 4).

Cation **25** is then trapped by nucleophiles, in our case water or cyanide, to form the corresponding derivative **26**. The reaction stops at this stage if Y=CN, but in the case of a hemiaminal (**26**, Y=OH), the reaction continues with two new oxidation steps, giving the final product, amide **27**. The hemiaminal is a transient, non-isolable intermediate: it undergoes oxidation presumably faster than the initial amine, because the involved C-H bond is now in α-position to two electron-rich heteroatoms (O and N). The catalytic cycle is completed by oxidizing back all Ru^{VI} species to Ru^{VIII}, at the expense of the co-oxidant (for instance $NaIO_4$).

The substrate reactivity and the corresponding endocyclic/exocyclic *Selectivity* should be governed by the activation energies required on passing from the reactants to the respective transition states **TS**. The governing factors could be of (i) electronic (*ET*+*HAB*) and (ii) steric nature, as presented below.

A high electron-donating ability of the nitrogen atom is known to reduce the energy of the adjacent C-H bond. Since the donating ability decreases with the increase of the *s*-character of the nitrogen lone pair,[32] it emerges that, within the homologous series **1a**-**d**, the highest C-H bond energy will belong to aziridine **1d**. However, the energies of both endocyclic and exocyclic α-C-H bonds are influenced in the same way and, consequently, the regioselectivity of a particular substrate might remain unchanged.

At the same time, on going from **1a** to **1d**, that is towards azacycles with increasing geometrical constraints,[34] the accommodation of the new C=N bond in **TS** should be easier in the exocyclic position relative to that in the more energetically demanding endocyclic position. An approximation of this effect might be revealed by the differences in heats of formation ($\Delta\Delta H_f$) calculated for endocyclic-**25** and exocyclic-**25.** We remember that the system **24**+**25** could be a good approximation for **TS**, if **TS** is structurally more similar to the products than to the reactants. By a proper choice of ruthenium catalyst and reaction conditions, this hypothesis was already experimentally proven.[7] Working with the PM6 method (free MNDO-version), the computed $\Delta\Delta H_f$'s were: -1.4 (**2a**-**3a**), +1.5 (**2b**-**3b**), +13.4 (**2c**-**3c**), and +24.5 kcal/mol (**2d**-**3d**). These differences parallel closely the experimental endocyclic/exocyclic selectivities (Table 1, column 3).



Scheme 4. Mechanism of the RuO_4-oxidation of tertiary amines

For the steric factor (ii), RuO_4 is supposed to approach less easily the endocyclic position of the amine than the exocyclic one. This derives from the more rigid azacycle structure compared to the freely rotating benzylic group around the $PhCH_2$-N bond. The energetic difference between the endocyclic and exocyclic attack seems to increase in the order **1a**<**1b**<**1c**<**1d**. Since the endocyclic and the exocyclic transition states are both more polar than the reactants, solvation could influence the relative stability. More sophisticated theoretical calculations are needed for better accuracy.

Summing up, all these considerations suggest that *Selectivity* (endocyclic/exocyclic) should decrease going from **1a** to **1d**, in accord with the experimental findings.

Conclusions

1-Benzylazetidine (**1c**) showed the same RuO_4-oxidation pattern as that followed by the analogous 1-benzylpiperidine (**1a**) and 1-benzylpyrrolidine (**1b**) derivatives: both endocyclic and exocyclic (benzylic) C-H bonds in α to the nitrogen atom are attacked. If the reaction is conducted in the presence of cyanide, α-aminonitriles were obtained instead of amides. The statistically corrected endocyclic/exocyclic regioselectivity diminishes constantly with the decrease of the azacycle size, from 2.4 for **1a** to 0.6 for **1c**. The oxidation of 1-benzylaziridine (**1d**) occurred only in the absence of cyanide and took place exclusively at the benzylic position. The proposed reaction mechanism was discussed and used to explain the variation of selectivity. The key step is the formation of an ion pair: an iminium ion and a ruthenate anion.

Experimental Section

General. NMR spectra were acquired mainly on a Varian ICON 300 apparatus, operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). In particular cases, a Bruker Avance DRX 400 spectrometer, operating at 400 MHz (^{1}H) and 100 MHz (^{13}C), was employed. Mass spectra were obtained with a GC 6890 Agilent Technologies gas-

chromatograph coupled with a MS 5975 B quadrupole mass spectrometer, using the standard 70 eV ionization energy.

Hydrated RuO_2, oxazoline **14**, aminonitrile **18**, $NaIO_4$, and the organic solvents were used as purchased from commercial sources, except for $CHCl_3$, which was stored over anhydrous Na_2CO_3 and filtered prior to use.

All information on the synthesis and characterization of piperidine **1a**, pyrrolidine **1b,** and their reaction products of type **4**, **5, 6, 10, 11**, **12**, and **13** was already reported.[8] Azetidine **1c**[35,36] and some of its identified oxidation products (**4c**,[36] **5c**,[37] **6c**,[38] **12c**[24]) are all known compounds and were synthesized according to the indicated procedures. The same is true for aziridine **1d**[27] and the corresponding reaction products (**6d**,[39] **14**,[26] **15**,[10,27,30,40] **16**,[10] **17**[41]).

Oxidations by RuO_4/$NaIO_4$ (with or without NaCN)

To a heterogeneous mixture of $CHCl_3$ (5 mL) and aqueous solution of $NaIO_4$ (0.4 M; 10 mL, 4 mmol) was added solid $RuO_2 \cdot xH_2O$ (10-15 mg), followed by the substrate (1 mmol of **1c** or **1d**), previously dissolved in $CHCl_3$ (5 mL) (reaction conditions *A*). In the case of the cyanide-trapping experiments (reaction conditions *B*), to the NaCN solution [196 mg (4 mmol) in water (10 mL)] was added RuO_2, the substrate (1 mmol in 10 mL of $CHCl_3$), and the co-oxidant $NaIO_4$ solution (10 mL, as before), in this order. The heterogeneous reaction mixture was magnetically stirred at room temperature for 3-5 h and then worked-up as described in a previous paper.[19]

Identification of the various reaction products was made by comparison of the NMR and GC-MS spectra before and after the addition of small samples of the pure compounds into the analyzed samples.

The amounts quoted in Table 1 were calculated from the NMR and GC-MS data obtained in the presence of 1.4-dimethoxybenzene, added as internal standard.[19]

2-(1-Azetidinyl)-2-phenylacetonitrile (13c). Aqueous $NaHSO_3$ solution (39%, 0.4 mL, 2 mmol) was added under stirring to benzaldehyde (0.2 mL, 2 mmol). To the formed white solid a suspension of azetidine hydrochloride (187 mg, 2 mmol) in cold, aqueous NaOH solution (80 mg, 2 mmol; 1.5 mL of water) was added and the reaction mixture was stirred at room temperature for one hour. A solution of NaCN (98 mg, 2 mmol; 1 mL of water) was added and the stirring was maintained for another hour. The mixture was extracted with $CHCl_3$, the organic extract was dried over Na_2SO_4, and the solvent was evaporated. The residue was cromatographed on a silica gel column eluted first with benzene (30 mL). The fraction eluted with PhH/EtOAc (9/1, v/v) afforded 110 mg of oily **13c**.

Yield: 32%. Anal. calcd. for $C_{11}H_{12}N_2$: C, 76.72; H, 7.01; N, 16.27%. Found: C, 76.42; H, 6.87; N, 16.45%. ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.13 (2H, *quintet*, ^3J 7.1 Hz, N-CH_2-C**H**$_2$), 3.31+3.39 (2+2H, symmetrical *q+q* , ^3J 7.0 Hz, CH_2-N-CH_2), 4.69 (1H, *s*, CH), 7.30-7.55 (5H, *m*, arom.). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 17.3 (N-CH_2-**C**H_2), 51.9 (**C**H_2-N-**C**H_2), 61.3 (CH), 116.2 (CN), 127.6 (*o*), 128.9 (*m*), 129.0 (*p*), 133.1 (*i*). EI-MS [70 eV, *m/z* (relative abundance, %)]: 172 (M^+, 43.5), 171 (78), 117 (15), 116 (100), 95 (7), 91 (7), 90 (6), 89 (20).

Spectral data of selected compounds

The ^{1}H and ^{13}C NMR chemical shifts of the following compounds are referenced to internal (C**H**$_3$)$_4$Si (δ_H = 0) and **C**DCl_3 (δ_C = 77.16 ppm).[42] Aromatic *ortho*, *meta*, and *para* hydrogens or carbons are labeled *o*, *m*, and *p*, respectively; *ipso* carbons are abbreviated as *i*. All NMR data were in accordance with those cited in literature, but with complete assignments. In addition, the corresponding MS data are presented, except for **4c** (unstable), **16** and **17** (experimental limitations).

1-Benzylazetidine (1c).[35,36] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.07 (2H, *quintet*, ^3J 7.1 Hz, N-CH_2-C**H**$_2$), 3.20 (4H, *t*, ^3J 7.1 Hz, CH_2-N-CH_2), 3.55 (2H, *s*, Ph-C**H**$_2$), 7.20-7.32 (5H, *m*, arom.). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 17.6 (N-CH_2-**C**H_2), 55.1 (CH_2-N-CH_2), 63.9 (Ph-**C**H_2), 126.8 (*p*), 128.2 (*o*), 128.4 (*m*), 138.4 (*i*). EI-MS [70 eV, *m/z* (relative abundance, %)]: 147 (M^+; 22), 146 (47), 92 (9.5), 91 (100), 70 (5.5), 65 (11).

1-Benzylaziridine (1d).[27] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 1.23-1.29 + 1.78-1.83 (2+2H, *m*+*m*, C**H**$_2$-C**H**$_2$), 3.37 (2H, *s*, Ph-C**H**$_2$), 7.20-7.40 (5H, *m*, arom.). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 27.6 (**C**H$_2$-**C**H$_2$), 65.3 (Ph-**C**H$_2$), 127.1 (*p*), 128.0 (*o*), 128.4 (*m*), 139.3 (*i*). EI-MS [70 eV, *m/z* (relative abundance, %)]: 133 (M^+; 13), 132 (45), 105 (6.0), 104 (8), 92 (8), 91 (100), 89 (7), 77 (10), 65 (22), 63 (7), 51 (10), 42 (57).

1-Benzylazetidine-1-oxide (4c).[36] ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.90-1.94 + 2.33-2.40 (1+1H, *m*+*m*, N^+-CH_2-C**H**$_2$), 4.25-4.29 (4H, *m*, C**H**$_2$-N^+-C**H**$_2$), 4.41 (2H, *s*, Ph-C**H**$_2$), 7.33-7.44 (3H, *m*, *m*+*p*), 7.54 (2H, *d*, *J* 6.4 Hz, *o*). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 12.1 (N^+-CH_2-**C**H$_2$), 68.9 (**C**H$_2$-N^+-**C**H$_2$), 70.2 (Ph-**C**H$_2$), 128.4 (*p*), 129.3 (*m*), 130.1 (*i*), 131.9 (*o*).

1-Benzyl-2-azetidinone (**5c**).[37] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.94 (2H, *t*, *J* 4.0 Hz, N-CH_2-C**H**$_2$), 3.12 (2H, *t*, *J* 4.0 Hz, N-C**H**$_2$-CH_2), 4.36 (2H, s, Ph-C**H**$_2$), 7.25-7.35 (5H, *m*, arom.). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 36.6 (N-CH_2-**C**H$_2$), 38.3 (N-**C**H$_2$-CH_2), 46.0 (Ph-**C**H$_2$), 127.5 (*p*), 128.0 (*o*), 128.5 (*m*), 135.5 (*i*), 167.5 (CO). EI-MS [70 eV, *m/z* (relative abundance, %)]: 161 (M^+; 41.5), 133 (28.5), 132 (11), 105 (55), 104 (15), 92 (8.5), 91 (100), 77 (24).

1-Benzoylazetidine (**6c**).[38] (*the underlined signals show the C-H correspondence*). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.32 (2H, *quintet*, *J* 7.4 Hz, N-CH_2-C**H**$_2$), 4.22 + <u>4.28</u> (2+2H, *t*+*t*, *J* 7.4 Hz, CH_2-N-CH_2), 7.32-7.48 (3H, m, *m*+*p*), 7.62 (2H, *dd*, ^3J 7.8 Hz, ^4J 1.5, *o*). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 15.9 (N-CH_2-**C**H$_2$), <u>48.7</u> + 53.2 (CH_2-N-CH_2), 127.6 (*o*), 128.1 (*m*), 130.7 (*p*), 133.1 (*i*), 170.1 (CO). EI-MS [70 eV, *m/z* (relative abundance, %)]: 161 (M^+, 25), 160 (7), 106 (8.5), 105 (100), 77 (43.5).

1-Benzoylaziridine (**6d**).[39] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.39 (4H, *s*, C**H**$_2$-C**H**$_2$), 7.55-7.65 (3H, *m*, *m*+*p*), 8.07 (2H, *d*, *J* 7.6 Hz, 2H, *o*). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 26.1 (**C**H$_2$-**C**H$_2$), 128.0 (*o*), 129.3 (*m*), 132.9 (*p*), 134.2 (*i*), 179.3 (CO). EI-MS [70 eV, *m/z* (relative abundance, %)]: 147 (M^+, 7), 105 (100), 77 (72), 51 (19).

1-Benzylazetidine-2-carbonitrile (**12c**).[24] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.35-2.45 (2H, *m*, N-CH_2-C**H**$_2$), 3.12+3.35 (1+1H, *q*+*q*, *J* 7.2 Hz, N-C**H**$_2$-CH_2), 3.64+3.72 [1+1H, *d*+*d* (*ABq*), J_{AB} 13.2 Hz, Ph-C**H**$_2$], 3.90 (1H, *t*, *J* 7.2 Hz, CH-CN), 7.15-7.18 (5H, *m*, arom.). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 22.9 (N-CH_2-**C**H$_2$), 51.7 (**C**H-CN), 52.4 (N-**C**H$_2$-CH_2), 60.8 (Ph-**C**H$_2$), 118.8 (CN), 127.5 (*o*), 128.6 (*p*), 128.8 (*m*), 136.1 (*i*). EI-MS [70 eV, *m/z* (relative abundance, %)]: 172 (M^+, 22), 171 (20), 120 (9), 95 (8), 92 (15), 91 (100), 81 (6), 65 (13).

2-Phenyloxazoline (**14**).[43] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 4.05 (2H, *t*, *J* 9.2 Hz, N-CH_2), 4.41 (2H, *t*, *J* 9.2 Hz, O-CH_2), 7.35-7.50 (3H, *m*, *m*+*p*), 7.94 (2H, *d*, *J* 7.8 Hz, *o*) ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 54.9 (N-CH_2), 67.5 (O-CH_2), 127.7 (*i*), 128.1+128.2 (*o*+*m*), 131.2 (*p*), 164.4 (C=N). EI-MS [70 eV, *m/z* (relative abundance, %)]: 148 (10), 147 (M^+, 85), 118 (15), 117 (100), 105 (12), 91 (13), 77 (25), 51 (13).

1,4-Dibenzylpiperazine (**15**).[10] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.48 (8H, *s*, C**H**$_2$-C**H**$_2$), 3.51 (4H, *s*, 4H, Ph-C**H**$_2$), 7.21-7.30 (10H, *m*, arom.). ^{13}C-NMR (75 MHz $CDCl_3$) δ (ppm) 53.1 (**C**H$_2$-**C**H$_2$), 63.1 (Ph-**C**H$_2$), 127.0 (*p*), 128.2 (*o*), 129.2 (*m*), 138.2 (*i*). EI-MS [70 eV, *m/z* (relative abundance, %)]: 266 (M^+, 25), 175 (42), 146 (11), 132 (12), 120 (28), 119 (7.5), 92 (8), 91 (100), 65 (9).

1,4-Dibenzyl-2,3-piperazinedione (**16**).[16] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 3.34 (4H, *s*, C**H**$_2$-C**H**$_2$), 4.67 (4H, *s*, Ph-C**H**$_2$), 7.20-7.33 (10H, *m*, arom.). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 43.6 (**C**H$_2$-**C**H$_2$), 50.7 (Ph-**C**H$_2$), 128.2 (*p*), 128.6 (*o*), 129.0 (*m*), 135.6 (*i*), 157.6 (CO).

Bis-(N-Benzylformamido)ethylene (**17**).[41] Mixture of 3 isomers: *A* (48%; asymmetric *E*,*Z*), *B* (45%; symmetric *E*,*E*), and *C* (7%; symmetric *Z*,*Z*). No specific assignements could be made for the aromatic *m*+*p* protons and carbons (see below under isomers *A*+*B*+*C*). The following integrals are intended for the considered isomer.

Isomer *A*: [the N atoms are labelled as (*E*)-N^1 and (*Z*)-N^2]. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 3.19 (2H, *t*, *J* 6.4 Hz, N^2-CH_2), 3.29 (2H, *t*, *J* 6.4 Hz, N^1-CH_2), 4.31 (2H, *s*, Ph-C**H**$_2$-N^1), 4.48 (2H, *s*, Ph-C**H**$_2$-N^2), 7.15 (2H, *d*, *J* 6.4 Hz, (*o* of **Ph**-CH_2-N^1), 7.20 (2H, *d*, *J* 6.4 Hz, *o* of **Ph**-CH_2-N^2), 8.01 (1H, *s*, N^2-CHO), 8.30 (1H, *s*, N^1-CHO). ^{13}C-NMR

(100 MHz, $CDCl_3$) δ (ppm) 40.9 (N^1-CH_2), 43.6 (N^2-CH_2), 45.3 (Ph-**C**H_2-N^2), 52.2 (Ph-**C**H_2-N^1), 127.6 (*o* of **Ph**-CH_2-N^1), 128.3 (*o* of **Ph**-CH_2-N^2), 135.4 (*i* of **Ph**-CH_2-N^2), 136.1 (*i* of **Ph**-CH_2-N^1), 162.7 (N^2-CHO), 163.0 (N^1-CHO).
Isomer *B*: ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 3.38 (4H, s, C**H**$_2$-C**H**$_2$), 4.46 (4H, s, Ph-C**H**$_2$), 7.21 (4H, *d*, *J* 6.8 Hz, *o*), 8.26 (2H, *s*, CHO). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 37.7 (**C**H_2-**C**H_2), 50.8 (Ph-**C**H_2), 127.6 (*o*), 128.8 (*m*), 135.7 (*i*), 163.3 (CHO).
Isomer *C*: ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 3.17 (4H, *s*, C**H**$_2$-C**H**$_2$), 4.49 (4H, *s*, Ph-**C**H_2), 7.21 (4H, *d*, *J* 6.8 Hz, *o*), 7.91 (2H, *s*, CHO). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 45.3 (**C**H_2-**C**H_2), 46.0 (Ph-**C**H_2), 128.4 (*o*), 135.9 (*i*), 162.6 (sh, CHO).
Isomers *A*+*B*+*C*: ^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25-7.40 (10H, *m*, *m*+*p*). ^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) 127.7+128.0+128.2+128.7+128.9+129.0 (*m*+*p*).
3-(Benzylamino)propanenitrile (**18**).[44] ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm) 2.45 (2H, *t*, *J* 6.5 Hz, CH_2-CN), 2.87 (2H, *t*, *J* 6.5 Hz, N-C**H**$_2$-CH_2), 3.80 (2H, *s*, Ph-C**H**$_2$), 7.20-7.40 (5H, *m*, arom.). ^{13}C-NMR (75 MHz, $CDCl_3$) δ (ppm) 18.7 (**C**H_2-CN), 44.3 (N-**C**H_2-CH_2), 53.1 (Ph-**C**H_2), 118.7 (CN), 127.1 (*p*), 128.0 (*m*), 128.4 (*o*), 139.5 (*i*). EI-MS [70 eV, *m/z* (relative abundance, %)]: 160 (M^+, 5), 120 (40), 92 (10), 91 (100); 65(15).

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