Phenylalanine-Derived Imidazolines Bearing Heteroaromatic Pendants: Synthesis, Characterization, and Application in the Asymmetric *Henry* Reaction

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Starting from L-phenylalanine, (2*S*)-3-phenylpropane-1,2-diamine has been prepared and used as building block for the construction of the imidazoline ring. Four new optically pure NH-imidazolines bearing different six-membered heteroaromatic substituents on the C(2) position have been prepared and subsequently N-modified. N-Substitution afforded two regioisomers that were separated. Some of them proved to be instable and hydrolyzed to diamides. The molecular structures of NH-imidazolines, both N-substituted regioisomers, as well as diamides, were unambiguously confirmed by X-ray-analysis and NMR spectra. The successfully prepared imidazolines, as well as diamides, were applied as catalysts in a Cu(II)-catalyzed *Henry* reaction achieving 26–98% chemical yields and enantiomeric excesses of 3–42%.

Introduction. – Within last two decades, imidazolines evolved into widely investigated compounds, mainly due to their prospective applications in pharmaceutics and organic synthesis. Shortly after the discovery of the imidazoline receptor (imidazoline binding site) in 1984 [1][2], imidazoline became a medicinally interesting organic scaffold. In organic synthesis, imidazoline derivatives are mostly investigated as organocatalysts or ligands, generally introducing a chiral environment and providing chelating properties. Various imidazoline complexes with different transition metals and ions were successfully applied as optically active catalysts in asymmetric reactions such as *Henry* [3][4], *Heck* [5–9], *Suzuki* [10][11], *Diels–Alder* [12][13], and *Friedel–Crafts* reactions [14–19], as well as in allylic substitutions [20–22] and asymmetric reductions [23][24]. Imidazolines were also tested as organocatalysts in diastereoselective synthesis of *trans*-β-lactams [25] and in nitro *Michael* reaction [26][27] achieving chemical yields up to 51% and 98% with diastereomeric ratios 50:1 and 20:1, respectively.

In general, the imidazoline derivatives can be synthesized from different starting compounds such as 1,2-amino alcohols [28–30], aziridines [31–33], and oxazolinones [34][35]. However, the most frequently used synthetic pathway utilizes 1,2-diamines as starting compounds. *Botteghi* and *Schionato* have shown the first optically pure imidazoline synthesized this way and its use in asymmetric catalysis already in 1989 [36]. Moreover, there are several well-explored synthetic approaches leading to

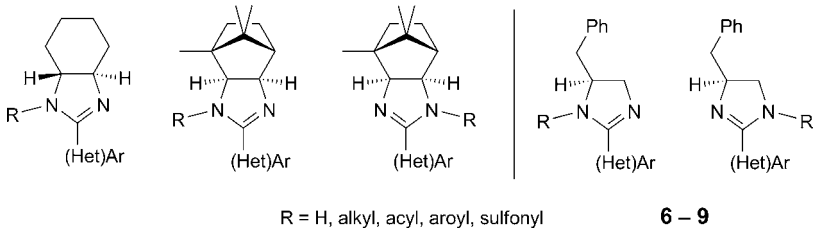


Fig. 1. *Previous and new imidazoline derivatives*

optically pure 1,2-diamines [37–42], which makes this synthetic strategy even more attractive and general.

Apart from very popular 4,5-diphenylimidazolines [4][12][14–18][20][23][24][26][27], we have recently reported on two new series of imidazolines including hexahydro-1*H*-benzo[*d*]imidazoles (cyclohexane-imidazolines) [43] and camphor-imidazolines [44][45] with different substituents at C(2) (*Fig. 1*).

In order to extend these series and based on our ample experience with α-amino acid transformations into five membered imidazoles [46–52], we report herein on the synthesis, characterization, and further application of imidazolines **6**–**9** featuring the L-phenylalanine motive, various C(2) pendants, and an anisoyl N-substituent. Several general procedures allowing stereoselective conversion of α-amino acids to optically pure 1,2-diamines exist to date [39–42]. Hence, starting from L-phenylalanine, we have prepared the corresponding (2*S*)-3-phenylpropane-1,2-diamine **1** in a three step synthesis [53][54]. With diamine **1** in hand, we have attempted the synthesis of a series of imidazolines bearing heteroaromatic moieties attached at C(2). Due to unsymmetrical C(4)/C(5) substitution of such imidazolines, subsequent N-modification led to two regioisomers **a** and **b**, the structures of which were unambiguously assigned. Some of these target molecules underwent facile ring opening providing diamides that were also structurally characterized. Such observed instability is in contrasts to the current literature reports in which only few hints were mentioned [29][55]. Similarly to imidazole [49], imidazoline [43–45], or imidazolidinone [56][57] derived ligands, the catalytic activity of the target imidazolines as well as diamides was preliminarily tested in the Cu(II)-catalyzed *Henry* reaction.

Results and Discussion. – The synthesis of the desired imidazoline derivatives **6**–**9** is outlined in the *Scheme*. Optically pure 1,2-diamine **1** was prepared from L-phenylalanine by its activation by treatment with $SOCl_2$ and subsequent reaction with gaseous NH_3 providing an amino-amide, which was finally reduced by $LiAlH_4$. (2*S*)-3-Phenylpropane-1,2-diamine (**1**) was obtained in 32% overall yield with the optical purity $>99\%$, which was checked by ^{1}H-NMR spectra measured with *Mosher*'s acid.

Various heteroaromatic nitriles were utilized as a source of the imidazoline C(2) and the appended heterocyclic substituents (pyridin-2-yl, pyrazin-2-yl, pyrimidin-2-yl, and isoquinolin-1-yl; *Table 1*). These were *in-situ* converted into the corresponding imidates by the reaction with MeOH catalyzed by MeONa. The imidates were subsequently reacted with diamine **1** to afford the desired (4*S*)-4-benzyl-4,5-dihydro-1*H*-imidazoles (benzyl-imidazolines) **2**–**5**. The attained yields vary within the range of

Scheme. *Synthesis Pathway to Benzyl-Imidazolines* **2**–**5** *and* **6**–**9** *and Their Observed Ring Opening during Column Chromatography*

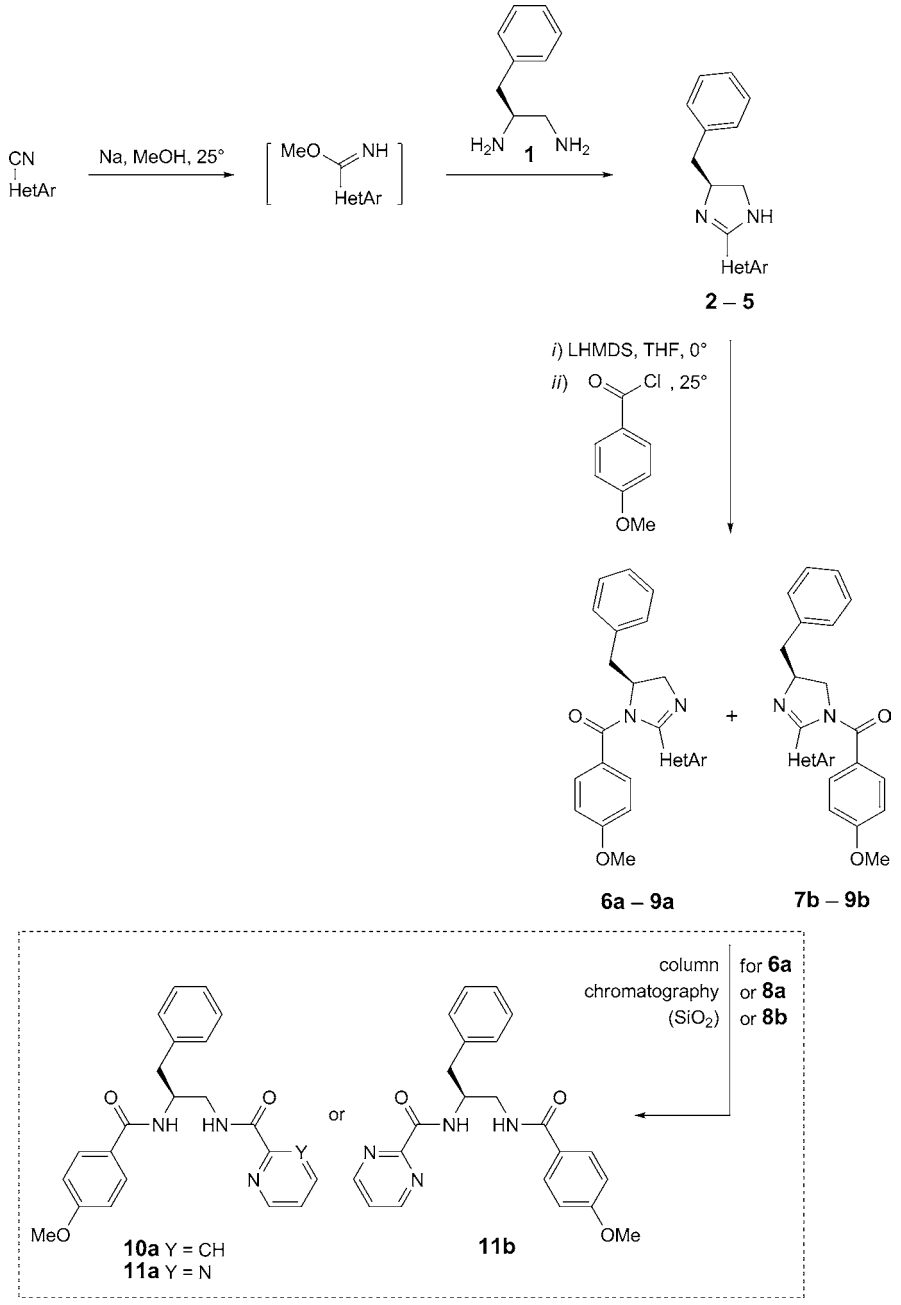


Table 1. *Yields and Properties of NH-Imidazolines* **2**–**5**, *N-Anisoylated Imidazolines* **6**–**9**, *and Diamides* **10** *and* **11**

Product	HetAr	Yield [%]	M.p. [°]	$[\alpha]_D^{20}$ ($c = 0.5$, MeOH)
2	Pyridin-2-yl	59	oil	− 26.6
3	Pyrazin-2-yl	93	92 – 95	− 31.0
4	Pyrimidin-2-yl	68	oil	− 21.8
5	Isoquinolin-1-yl	25	oil	− 78.4
6a	Pyridin-2-yl	42	oil	+ 78.6
7a	Pyrazin-2-yl	30	oil	+ 156.0
7b	Pyrazin-2-yl	31	oil	− 2.4
8b	Pyrimidin-2-yl	38	147 – 169	− 3.6
9a	Isoquinolin-1-yl	26	oil	+ 36.0
9b	Isoquinolin-1-yl	63	oil	− 5.8
10a	Y = CH	6	oil	+ 2.2
11a	Y = N	6	oil	+ 7.2
11b	–	13	oil	− 1.6

59 – 93% (*Table 1*), while the yield of imidazoline **5** was only 25%. This was caused by a competitive substitution of the nitrile group by MeO during the *in situ* preparation of isoquinoline imidate as indicated by EI-MS. In order to prevent imidazoline tautomerism and tune the electronic and chelating properties [43 – 45], NH-imidazolines **2**–**5** were further N-substituted. Their treatment with lithium bis(trimethylsilyl)amide and subsequent reaction with 4-methoxybenzoyl chloride (anisoyl chloride) afforded compounds **6**–**9**. As previously observed on camphor-imidazolines, this N-substitution yielded in most cases two regioisomers **a** and **b** that were separable by column chromatography (*Table 1*). The rate of formation of both regioisomers depends on the C(2) substituent and stability of the imidazoline formed. In the case of pyridin-2-yl substituent, only regioisomer **6a** was isolated. Both regioisomers **a** and **b** were isolated or detected for all remaining imidazolines **7**–**9**. Similarly to our previous observations made on cyclohexyl- and camphor-imidazolines [43 – 45], separation of both regioisomers *via* column chromatography was accompanied by a slow hydrolytic imidazoline ring opening (*Scheme*). This decomposition can be suppressed by column pretreatment and storing the target compounds with Et_3N. Despite such precautions, imidazolines **6a**, **8a**, and **8b** afforded noticeable amounts of diamides **10a**, **11a**, and **11b** that were isolated and fully characterized. Imidazoline **8b** was only detected in the crude reaction mixture, however, it could not be isolated and diamide **11a** was isolated instead. It should be noted, that imidazoline ring opening in terms of its hydrolysis has been utilized as one of the methods used for the preparation of 1,2-diamines [58][59].

The molecular structures of all isolated imidazolines **2**–**5** and **6**–**9**, as well as diamides **10** and **11**, have been confirmed by ^{1}H- and ^{13}C-NMR. The correct signal assignment has been accomplished through NMR correlation spectra such as ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HMQC, and HMBC. Moreover, the molecular structures of NH-imidazoline **3** and regioisomer **8b** were also confirmed by X-ray analyses as shown in *Fig. 2*.

Crystals suitable for X-ray measurements were prepared by slow evaporation of AcOEt and CD_3OD solutions of **3** and **8b**, respectively. Both imidazolines crystallize in

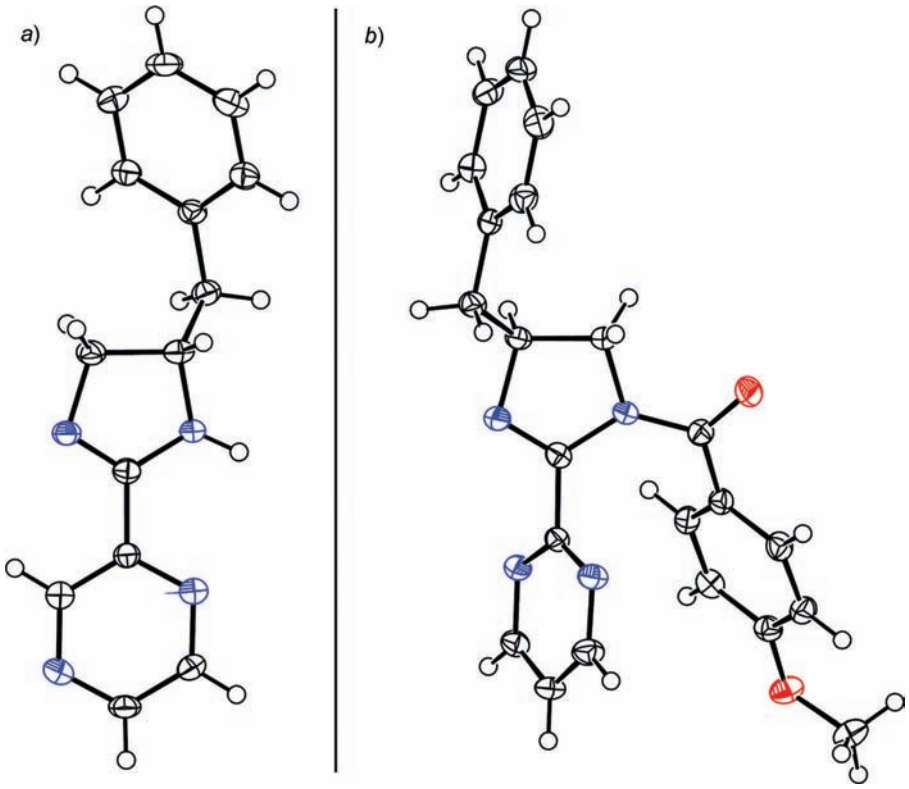


Fig. 2. *ORTEP Representations of NH-imidazoline* **3** (*a*) *and regioisomer* **8b** (*b*). The ellipsoids are shown at 50% probability level (150 K, $R = 0.04$ and 0.03).

the monoclinic space group *P*2 with two molecules within the unit cell. The measured interatomic distances and angles in both structures proved the positions of the C=N bond with respect to the benzyl substituent. Whereas in NH-imidazoline **3** the benzyl group at position C(5), in regioisomer **8b** it is at C(4), and adopts *anti* arrangement with respect to the anisoyl substituent at N(1). In NH-imidazoline **3**, a close intermolecular N–H ··· N (3.327 Å) contact was found, which forms chain structures as shown in *Fig. 3*. This solid-state structure further confirms the anticipated aggregation and tautomerism in NH-imidazolines **2** – **5**. On the contrary, H-bonding is not present in the solid state of the N-substituted imidazoline **8b**, but a chain structure was also observed mostly due to short contacts (π–π stacking-like) between aromatic rings (*Fig. 3*). All the observed bond lengths and angles in both compounds are in good agreement with previously published X-ray structures of imidazolines.

Considering the N=C–C=N binding pocket in the successfully isolated ligands **6a**, **7a**, **9a**, and **7b** – **9b**, their catalytic activities and enantioselectivities were preliminarily tested in a Cu(II)-catalyzed asymmetric nitroaldol reaction (*Henry* reaction). The reactions were carried out on a 0.5 mmol scale with 4-nitrobenzaldehyde/$MeNO_2$ in EtOH and were catalyzed by $Cu(OAc)_2$/ligand system (*Table 2*). No additional base

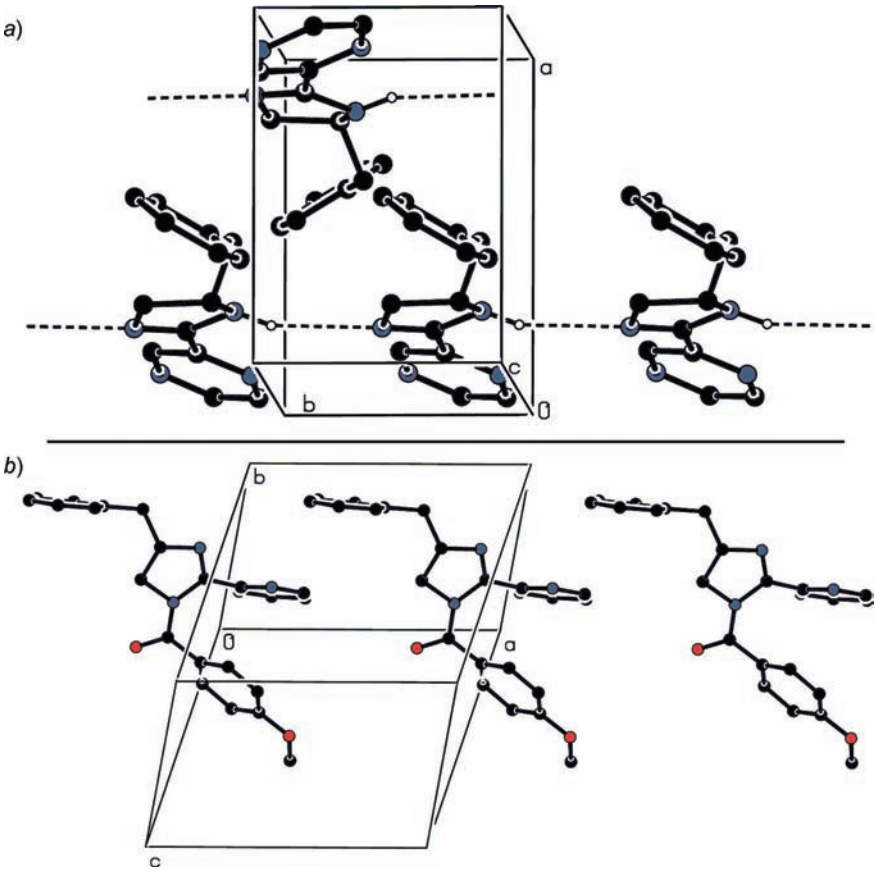
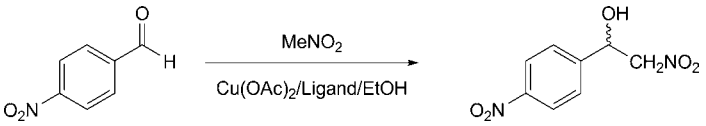


Fig. 3. *Hydrogen bonding and supramolecular architecture in the solid state of* **3** (*a*) *and* **8b** (*b*)

was used, and all reactions were run for 24 h in order to compare particular ligands [44][45][49]. All N-anisoylated imidazolines afforded in the *Henry* reaction nitroaldol products in 41 – 94% chemical yields (*Table 2*, *Entries 1 – 6*). The attained enantiomeric excesses are within the range of 3 to 26%. This is in contrast to NH-imidazolines **2** – **5** that were also able to catalyze nitroaldol reaction, but always delivered the nitroaldol as a racemate. Hence, imidazoline tautomerism in **2** – **5** most likely leads to a formation of two active catalytic sites leading to opposite enantioselectivities. This can further be demonstrated by comparing efficiencies of two particular regioisomers **a** and **b**. Whereas regioisomers **a** always afforded the nitroaldol with (*R*)-configuration, regioisomers **b** provided the (*S*)-nitroaldol (*Table 2*). Hence, by simply choosing the imidazoline *syn* or *anti* regioisomer (with respect to the benzyl and anisoyl substituent orientation along the imidazoline ring), we could modulate the stereochemical outcome of the *Henry* reaction. On the other hand, the effect of the C(2)-heteroaromatic moiety did not show any trends and is less predictable. With diamides **10** and **11** in hand, we curiously tested their performance in similar nitroaldol reactions

Table 2. *Asymmetric* Henry *Reaction*[a])



Entry	Ligand	Yield [%][b])	ee [%]/configuration[c])
1	**6a**	94	5/(*R*)
2	**7a**	51	20/(*R*)
3	**7b**	41	3/(*S*)
4	**8b**	98	26/(*S*)
5	**9a**	52	10/(*R*)
6	**9b**	90	11/(*S*)
7	**10a**	26	42/(*R*)
8	**11a**	32	racemate
9	**11b**	51	racemate

[a]) All reactions were carried out on a 0.5 mmol scale with $Cu(OAc)_2$ (10%) and ligands (10.5%) with $MeNO_2$ (10 equiv.) in EtOH (5 ml) at room temperature for 24 h. [b]) Yields of isolated products after column chromatography. [c]) Determined by HPLC analysis with a *Chiracel OD-H* column.

(*Table 2*, *Entries 7–9*). These diamides generally provided the desired nitroaldol in lower chemical yields than the corresponding imidazolines and mostly as a racemate. This is in accordance to our previous observations made with camphor-imidazolines [44][45]. However, diamide **10a** afforded the nitroaldol in good enantiomeric excess of 42%. In contrast to pyrimidine, the lower electron-withdrawing character of the pyridine ring would lead to higher electron saturation of the active Cu(II)-complex, which results in its higher stability. Hence, the *Henry* reaction may take place exclusively on the active chiral catalyst with asymmetric induction of 42%.

Conclusions. – Starting from an easily accessible L-phenylalanine-derived 1,2-diamine and commercial heteroaromatic nitriles, novel and optically pure benzyl-imidazolines were synthesized in a three step modular reaction. Final *N*-anisoylation yielded two regioisomers that were separable by column chromatography. Some of the target ligands proved unstable and underwent ring opening during purification. The resulting products were isolated and fully characterized. The molecular structures of each particular derivative were assigned based on 2D-NMR spectra as well as X-ray analysis. Both *N*-anisoyl imidazolines and incidental diamides were applied as ligands in the asymmetric version of the Cu(II)-catalyzed *Henry* reaction achieving good chemical yields, but only moderate enantioselectivities. Ligand structure–catalytic activity relationships were also elucidated.

Experimental Part

General. The starting (2*S*)-3-phenylpropan-1,2-diamine was synthesized from (*S*)-phenylalanine according to literature procedures [53][54]. Preliminary enantioselectivity screening of ligands in the Cu(II)-catalyzed *Henry* reaction was carried out according to the literature [49].

Reagents and solvents were reagent-grade and were purchased from *Aldrich*, *Acros*, and *Penta*, and used as received. THF was freshly distilled from Na-K/benzophenone under Ar. Evaporation and concentration *in vacuo* was performed on *Heidolph Laborota 4001*. Column chromatography (CC) was carried out with SiO_2 *60* (particle size 0.040–0.063 mm, 230–400 mesh; *Merck*) and commercially available solvents. Thin-layer chromatography (TLC) was conducted on aluminum sheets coated with SiO_2 *60* F_{254} obtained from *Merck*, with visualization by a UV lamp (254 or 360 nm). The enantiomeric excesses were determined by HPLC with a *Chiralcel OD-H* column (85:15 hexane/^{i}PrOH, 0.8 ml/min, 230 nm): (*R*)-enantiomer $t_R = 23.19$ min, (*S*)-enantiomer 28.59 min. M.p.: *Büchi B-540* melting-point apparatus in open capillaries; uncorrected. Optical rotation values were measured on a *PerkinElmer 341* instrument, concentration *c* is given in g/100 ml MeOH. ^{1}H- and ^{13}C-NMR spectra: in CD_3OD at 400 MHz or 100 MHz, resp., with *Bruker AVANCE 400* instruments at 25°; chemical shifts are reported in ppm relative to the signal of Me_4Si; residual solvent signals in the ^{1}H and ^{13}C spectra were used as the internal reference (CD_3OD: 3.31 and 49.15 ppm for ^{1}H- and ^{13}C-NMR, resp.); coupling constants (*J*) are given in Hz; the following abbreviations were used for easy signal assignment in ^{1}H-NMR spectra: Py (pyridine), Pz (pyrazine), Pm (pyrimidine), Iq (isoquinoline), and Ani (anisoyl); additional NMR techniques such as ^{1}H,^{1}H-COSY, ^{1}H,^{13}C-HMQC, and ^{1}H,^{13}C-HMBC were used for regular signal assignment. MALDI-HR-MS: *LTQ Orbitrap XL* instrument (*Thermo Fisher Scientific*, Bremen, Germany) equipped by N_2 UV laser (337 nm, 60 Hz). *LTQ Orbitrap* was measuring in positive mode in the mass range *m*/*z* 50–2000 with parameters: distinction 100000 with *m*/*z* 400, laser energy 17 mJ, number of laser shots 5, DCTB as a matrix.

General Method for the Synthesis of NH-Imidazolines **2**–**5**. Na (15 mg) was dissolved in dry MeOH (10 ml) under Ar, whereupon the appropriate heteroaromatic nitrile (1.33 mmol) was added. The resulting soln. was stirred at 25° until TLC (SiO_2; AcOEt) or GC/MS showed complete conversion of the nitrile to imidate (usually 1–4 h). (2*S*)-3-Phenylpropane-1,2-diamine (**1**; 200 mg, 1.33 mmol), Et_3N (0.3 ml, 2.15 mmol), and AcOH (0.1 ml, 1.75 mmol) were then added, and the mixture was stirred at 40° for 12 h. The solvent was evaporated *in vacuo* and the crude product was purified by CC (SiO_2; AcOEt/MeOH 2:1).

*2-[(4*S*)-4-Benzyl-4,5-dihydro-1*H*-imidazol-2-yl]pyridine* (**2**). The title compound was synthesized from pyridine-2-carbonitrile (138 mg) following the general method. Viscous oil. Yield 186 mg (59%). R_f 0.25 (AcOEt/MeOH 2:1). $[\alpha]_D^{20} = -26.6$ ($c = 0.5$ g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 2.74–2.79 (*m*, 1 H of CH_2Ph); 2.95–3.00 (*m*, 1 H of CH_2Ph); 3.56–3.61 (*m*, 1 H of CH_2N); 3.76–3.81 (*m*, 1 H of CH_2N); 4.31–4.39 (*m*, CHN); 7.15–7.27 (*m*, 5 H of Ph); 7.44 (*t*, $J = 6.0$, 1 H of Py); 7.84 (*t*, $J = 7.6$, 1 H of Py); 8.00 (*d*, $J = 7.6$, 1 H of Py); 8.59 (*d*, $J = 4.4$, 1 H of Py). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 42.64; 55.27; 62.98; 123.86; 127.37; 127.69; 129.69; 130.50; 138.42; 139.03; 148.06; 150.48; 165.05. HR-MALDI-MS: 238.1343 ($C_{15}H_{16}N_3^+$, $[M + H]^+$; calc. 238.1339).

*2-[(4*S*)-4-Benzyl-4,5-dihydro-1*H*-imidazol-2-yl]pyrazine* (**3**). The title compound was synthesized from pyrazine-2-carbonitrile (140 mg) following the general method. Off-white solid. Yield 295 mg (93%). M.p. 92–94°. R_f 0.43 (AcOEt/MeOH 2:1). $[\alpha]_D^{20} = -31.0$ ($c = 0.5$ g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 2.77–2.83 (*m*, 1 H of CH_2Ph); 3.98–3.30 (*m*, 1 H of CH_2Ph); 3.58–3.32 (*m*, 1 H of CH_2N); 3.78–3.84 (*m*, 1 H of CH_2N); 4.34–4.42 (*m*, CHN); 7.17–7.21 (*m*, 1 H of Ph); 7.24–7.28 (*m*, 4 H of Ph); 8.65–8.68 (*m*, 2 H of Pz); 9.15 (*d*, $J = 1.6$, 1 H of Pz). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 42.84; 56.05; 63.80; 127.65; 129.66; 130.56; 139.36; 144.69; 145.21; 145.46; 147.33; 163.35. HR-MALDI-MS: 239.1291 ($C_{14}H_{15}N_4^+$, $[M + H]^+$; calc. 239.1291).

*2-[(4*S*)-4-Benzyl-4,5-dihydro-1*H*-imidazol-2-yl]pyrimidine* (**4**). The title compound was synthesized from pyrimidine-2-carbonitrile (140 mg) following the general method. Viscous oil. Yield 215 mg (68%). R_f 0.15 (AcOEt/MeOH 2:1). $[\alpha]_D^{20} = -21.8$ ($c = 0.5$ g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 2.95–3.00 (*m*, 1 H of CH_2Ph); 3.10–3.15 (*m*, 1 H of CH_2Ph); 3.81–3.32 (*m*, 1 H of CH_2N); 4.02–4.08 (*m*, 1 H of CH_2N); 4.68–4.75 (*m*, CHN); 7.20–7.24 (*m*, 1 H of Ph); 7.28 (*d*, $J = 4.4$, 4 H of Ph); 7.70 (*t*, $J = 5.2$, 2 H of Pm); 8.99 (*d*, $J = 5.2$, 2 H of Pm). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 42.72; 46.72; 53.67; 124.52; 127.66; 129.78; 130.48; 139.96; 158.76; 159.05; 165.31. HR-MALDI-MS: 239.1298 ($C_{14}H_{15}N_4^+$, $[M + H]^+$; calc. 239.1291).

*1-[(4*S*)-4-Benzyl-4,5-dihydro-1*H*-imidazol-2-yl]isoquinoline* (**5**). The title compound was synthesized from isoquinoline-1-carbonitrile (205 mg) following the general method. Viscous oil. Yield 96 mg

(25%). R_f 0.46 (AcOEt/MeOH 2:1). $[\alpha]_D^{20} = -78.4$ ($c = 0.5$ g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 2.86–2.91 (*m*, 1 H of CH_2Ph); 3.04–3.09 (*m*, 1 H of CH_2Ph); 3.66–3.71 (*m*, 1 H of CH_2N); 3.85–3.90 (*m*, 1 H of CH_2N); 4.39–4.44 (*m*, CHN); 7.21–7.24 (*m*, 1 H of Ph); 7.30 (*d*, $J = 4.4$, 4 H of Ph); 7.65 (*t*, $J = 8.4$, 1 H of Iq); 7.76 (*t*, $J = 8.4$, 1 H of Iq); 7.84 (*d*, $J = 5.6$, 1 H of Iq); 7.92 (*d*, $J = 8.4$, 1 H of Iq); 8.47 (*d*, $J = 5.6$, 1 H of Iq); 8.65 (*d*, $J = 8.4$, 1 H of Iq). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 42.92; 56.46; 64.07; 124.24; 127.62; 127.91; 128.16; 128.34; 129.45; 129.70; 130.66; 132.21; 138.28; 139.63; 142.27; 150.93; 165.07. HR-MALDI-MS: 288.1495 ($C_{19}H_{18}N_3^+$, $[M + H]^+$; calc. 288.1495).

General Method for the Synthesis of Imidazolines **6**–**9**. Lithium bis(trimethylsilyl)amide (0.92 ml, 0.92 mmol, 1M soln. in THF, LHMDS) was added to a soln. of imidazoline **2**–**5** (0.61 mmol) in dry THF (10 ml) under Ar at 0°. The resulting yellow soln. was stirred for 30 min, whereupon a soln. of 4-anisoylchloride (0.1 ml, 0.74 mmol) in THF (1 ml) was added dropwise, and the mixture was then stirred at 25° for an additional 3 h (monitored by TLC). The reaction was quenched with aq. NH_4Cl (5 drops), the solvents were evaporated *in vacuo*, and the crude mixture of regioisomers was purified by column chromatography (CC; SiO_2; indicated solvent system). Et_3N (5 drops) was added to the combined fractions from the CC before the solvent was evaporated.

*[(5S)-5-Benzyl-4,5-dihydro-2-(pyridin-2-yl)-1*H*-imidazol-1-yl](4-methoxyphenyl)methanone* (**6a**). The title compound was synthesized from NH-imidazoline **2** (145 mg) following the general method. Viscous oil. Yield 96 mg (42%). R_f 0.31 (AcOEt/CH_2Cl_2/NH_3 aq. 1:1:0.01). $[\alpha]_D^{20} = -78.6$ ($c = 0.5$ g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 2.98–3.03 (*m*, 1 H of CH_2Ph); 3.36–3.40 (*m*, 1 H of CH_2Ph); 3.69 (*s*, MeO); 3.86–3.91 (*m*, 1 H of CH_2N); 3.98–4.04 (*m*, 1 H of CH_2N); 4.93–4.95 (*m*, CHN); 6.65 (*d*, $J = 8.8$, 2 H of Ani); 7.15–7.22 (*m*, 2 H of Ani); 7.26–7.34 (*m*, 6 H of Ph + Py); 7.48 (*d*, $J = 8.0$, 1 H of Py); 7.65 (*t*, $J = 8.0$, 1 H of Py); 8.19 (*d*, $J = 4.8$, 1 H of Py). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 39.56; 55.99; 58.40; 64.43; 114.41; 125.78; 125.94; 127.98; 129.45; 129.80; 130.99; 131.67; 138.02; 138.15; 149.82; 150.90; 161.15; 163.54; 171.09. HR-MALDI-MS: 372.1722 ($C_{23}H_{22}N_3O_2^+$, $[M + H]^+$; calc. 372.1707).

*[(5S)-5-Benzyl-4,5-dihydro-2-(pyrazin-2-yl)-1*H*-imidazol-1-yl](4-methoxyphenyl)methanone* (**7a**). The title compound was synthesized from NH-imidazoline **3** (145 mg) following the general method. Viscous oil. Yield 68 mg (30%). R_f 0.22 (AcOEt/CH_2Cl_2/NH_3 aq. 1:1:0.01). $[\alpha]_D^{20} = +156.0$ ($c = 0.5$ g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 3.05–3.11 (*m*, 1 H of CH_2Ph); 3.25–3.29 (*m*, 1 H of CH_2Ph); 3.72 (*s*, MeO); 3.95–3.99 (*m*, 1 H of CH_2N); 4.07–4.13 (*m*, 1 H of CH_2N); 4.94–4.98 (*m*, CHN); 6.70 (*d*, $J = 8.8$, 2 H of Ani); 7.16–7.02 (*m*, 1 H of Ph); 7.24–7.32 (*m*, 4 H of Ph); 7.36 (*d*, $J = 8.8$, 2 H of Ani); 8.23 (*dd*, $^3J = 2.4$, $^4J = 1.6$, 1 H of Pz); 8.36 (*d*, $^3J = 2.4$, 1 H of Pz); 8.65 (*d*, $^4J = 1.6$, 1 H of Pz). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 39.70; 56.10; 58.95; 64.21; 114.66; 128.03; 129.16; 129.76; 131.06; 131.75; 137.73; 144.86; 145.85; 146.05; 147.39; 159.10; 163.80; 170.95. HR-MALDI-MS: 373.1668 ($C_{22}H_{21}N_4O_2^+$, $[M + H]^+$; calc. 373.1659).

*[(4S)-4-Benzyl-4,5-dihydro-2-(pyrazin-2-yl)-1*H*-imidazol-1-yl](4-methoxyphenyl)methanone* (**7b**). The title compound was synthesized from NH-imidazoline **3** (145 mg) following the general method. Viscous oil. Yield 70 mg (31%). R_f 0.15 (AcOEt/CH_2Cl_2/NH_3 aq. 1:1:0.01). $[\alpha]_D^{20} = -2.4$ ($c = 0.5$ g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 2.98–3.03 (*m*, 1 H of CH_2Ph); 3.06–3.10 (*m*, 1 H of CH_2Ph); 3.76 (*s*, MeO); 3.99–4.03 (*m*, 1 H of CH_2N); 4.21–4.26 (*m*, 1 H of CH_2N); 4.66–4.69 (*m*, CHN); 6.75 (*d*, $J = 8.8$, 2 H of Ani); 7.17 (*d*, $J = 8.8$, 2 H of Ani); 7.21–7.24 (*m*, 1 H of Ph); 7.29–7.30 (*m*, 4 H of Ph); 8.34 (*dd*, $^3J = 2.8$, $^4J = 1.2$, 1 H of Pz); 8.50 (*d*, $^3J = 2.8$, 1 H of Pz); 8.85 (*d*, $^4J = 1.2$, 1 H of Pz). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 41.23; 55.11; 56.14; 67.27; 114.64; 127.67; 128.11; 129.70; 131.01; 131.93; 138.04; 145.00; 145.55; 146.45; 147.53; 159.56; 164.21; 170.45. HR-MALDI-MS: 373.1658 ($C_{22}H_{21}N_4O_2^+$, $[M + H]^+$; calc. 373.1659).

*[(5S)-5-Benzyl-4,5-dihydro-2-(pyrimidin-2-yl)-1*H*-imidazol-1-yl](4-methoxyphenyl)methanone* (**8a**). The title compound was synthesized from NH-imidazoline **4** (145 mg) following the general method but decomposed directly during column chromatography (see below).

*[(4S)-4-Benzyl-4,5-dihydro-2-(pyrimidin-2-yl)-1*H*-imidazol-1-yl](4-methoxyphenyl)methanone* (**8b**). The title compound was synthesized from NH-imidazoline **4** (145 mg) following the general method. Off-white solid. Yield 86 mg (38%). M.p. 147–149°. R_f 0.37 (AcOEt/CH_2Cl_2/MeOH/NH_3 aq. 1:1:0.1:0.01). $[\alpha]_D^{20} = -3.6$ ($c = 0.5$ g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 2.96–3.01 (*m*, 1 H of CH_2Ph); 3.10–3.15 (*m*, 1 H of CH_2Ph); 3.76 (*s*, MeO); 3.96–4.00 (*m*, 1 H of CH_2N); 4.19–4.24

(*m*, 1 H of CH_2N); 4.64–4.68 (*m*, CHN); 6.75 (*d*, *J* = 8.8, 2 H of Ani); 7.21–7.23 (*m*, 3 H of Ani + Pm); 7.26–7.36 (*m*, 5 H of Ph); 8.68 (*d*, *J* = 5.2, 2 H of Pm). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 41.31; 54.96; 56.10; 67.60; 114.64; 122.80; 127.81; 127.98; 129.70; 131.00; 131.71; 138.16; 158.58; 159.84; 160.01; 164.08; 170.27. HR-MALDI-MS: 373.1657 ($C_{22}H_{21}N_4O_2^+$, $[M + H]^+$; calc. 373.1659).

*[(5*S*)-5-Benzyl-4,5-dihydro-2-(isoquinolin-1-yl)-1*H*-imidazol-1-yl](4-methoxyphenyl)methanone* (**9a**). The title compound was synthesized from NH-imidazoline **5** (175 mg) following the general method. Viscous oil. Yield 67 mg (26%). R_f 0.52 (AcOEt/CH_2Cl_2/NH_3 aq. 1:1:0.01). $[\alpha]_D^{20} = +36.0$ (*c* = 0.5 g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 3.06–3.12 (*m*, 1 H of CH_2Ph); 3.43–3.47 (*m*, 1 H of CH_2Ph); 3.56 (*s*, MeO); 4.07–4.12 (*m*, 1 H of CH_2N); 4.20–4.26 (*m*, 1 H of CH_2N); 5.09–5.11 (*m*, CHN); 6.32 (*d*, *J* = 8.8, 2 H of Ani); 7.13 (*d*, *J* = 8.8, 2 H of Ani); 7.30–7.37 (*m*, 5 H of Ph); 7.61 (*d*, *J* = 5.6, 1 H of Iq); 7.67 (*t*, *J* = 8.4, 1 H of Iq); 7.76 (*t*, *J* = 8.4, 1 H of Iq); 7.84 (*d*, *J* = 8.4, 1 H of Iq); 7.94 (*d*, *J* = 8.4, 1 H of Iq); 8.20 (*d*, *J* = 5.6, 1 H of Iq). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 39.18; 55.89; 59.21; 62.83; 113.99; 123.57; 127.03; 128.18; 128.23; 128.46; 128.82; 129.81; 130.01; 130.82; 131.15; 132.41; 137.87; 138.06; 142.15; 152.04; 159.12; 163.19; 170.84. HR-MALDI-MS: 422.1860 ($C_{27}H_{23}N_3NaO_2^+$, $[M + Na]^+$; calc. 422.1863).

*[(4*S*)-4-Benzyl-4,5-dihydro-2-(isoquinolin-1-yl)-1*H*-imidazol-1-yl](4-methoxyphenyl)methanone* (**9b**). The title compound was synthesized from NH-imidazoline **5** (175 mg) following the general method. Viscous oil. Yield 162 mg (63%). R_f 0.44 (AcOEt/CH_2Cl_2/NH_3 aq. 1:1:0.01). $[\alpha]_D^{20} = -5.8$ (*c* = 0.5 g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 3.06–3.11 (*m*, 1 H of CH_2Ph); 3.26–3.29 (*m*, 1 H of CH_2Ph); 3.61 (*s*, MeO); 4.08–4.12 (*m*, 1 H of CH_2N); 4.26–4.31 (*m*, 1 H of CH_2N); 4.78–4.82 (*m*, CHN); 6.44 (*d*, *J* = 8.8, 2 H of Ani); 7.12 (*d*, *J* = 8.8, 2 H of Ani); 7.24–7.28 (*m*, 1 H of Ph); 7.33–7.40 (*m*, 4 H of Ph); 7.66–7.71 (*m*, 2 H of Iq); 7.77 (*t*, *J* = 8.4, 1 H of Iq); 7.86 (*d*, *J* = 8.4, 1 H of Iq); 8.11 (*d*, *J* = 8.4, 1 H of Iq); 8.26 (*d*, *J* = 5.6, 1 H of Iq). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 41.81; 54.36; 55.93; 67.98; 114.14; 123.66; 127.18; 127.90; 128.02; 128.25; 129.67; 129.86; 130.93; 131.02; 132.39; 137.91; 138.84; 142.10; 152.07; 159.14; 163.49; 170.40 (one signal of quaternary carbon is missing). HR-MALDI-MS: 422.1868 ($C_{27}H_{23}N_3NaO_2^+$, $[M + Na]^+$; calc. 422.1863).

Ring Opening. Above prepared regioisomers **6a**, **8a**, and **8b** underwent spontaneous hydrolysis to diamides **10a**, **11a**, and **11b** during purification, which were isolated as side products during column chromatography (SiO_2). The yields were calculated from the stoichiometry of final N-substitution reaction.

N-*{(2*S*)-1-[(4-Methoxybenzoyl)amino]-3-phenylpropan-2-yl}pyridine-2-carboxamide* (**10a**). The title compound was obtained from regioisomer **6a**. Viscous oil. Yield 14 mg (6%). R_f 0.49 (AcOEt/CH_2Cl_2/NH_3 aq. 1:1:0.01). $[\alpha]_D^{20} = +2.2$ (*c* = 0.5 g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 2.97–2.99 (*m*, C*H*$_2$Ph); 3.59–3.70 (*m*, CH_2N); 3.82 (*s*, MeO); 4.52–4.59 (*m*, CHN); 6.92 (*d*, *J* = 8.8, 2 H of Ani); 7.16–7.20 (*m*, 1 H of Ph); 7.24–7.31 (*m*, 4 H of Ph); 7.49–7.53 (*m*, 1 H of Py); 7.66 (*d*, *J* = 8.8, 2 H of Ani); 7.90–7.94 (*m*, 1 H of Py); 8.05 (*d*, *J* = 8.0, 1 H of Py); 8.59 (*d*, *J* = 4.8, 1 H of Py). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 39.52; 44.20; 53.26; 56.04; 114.76; 123.25; 127.64; 127.91; 129.60; 130.29; 130.50; 138.89; 139.67; 149.94; 150.99; 163.99; 165.33; 167.48; 170.23. HR-MALDI-MS: 390.1824 ($C_{23}H_{24}N_3O_3^+$, $[M + H]^+$; calc. 390.1812).

N-*{(2*S*)-2-[(4-Methoxybenzoyl)amino]-3-phenylpropyl}pyrimidine-2-carboxamide* (**11a**). The title compound was obtained from regioisomer **8a**. Viscous oil. Yield 14 mg (6%). R_f 0.32 (AcOEt/CH_2Cl_2/MeOH/NH_3 aq. 1:1:0.1:0.01). $[\alpha]_D^{20} = +7.2$ (*c* = 0.5 g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 2.99 (*d*, *J* = 6.8, 2 H, CH_2Ph), 3.67 (*d*, *J* = 6.8, 2 H, CH_2N), 3.81 (*s*, MeO); 4.57 (*q*, *J* = 6.8, CHN); 6.91 (*d*, *J* = 8.8, 2 H of Ani); 7.15–7.19 (*m*, 1 H of Ph); 7.24–7.31 (*m*, 4 H of Ph); 7.58 (*t*, *J* = 4.8, 1 H of Pm); 7.66 (*d*, *J* = 8.8, 2 H of Ani); 8.89 (*d*, *J* = 4.8, 2 H of Pm). ^{13}C-NMR (100 MHz, CD_3OD, 25°): 39.56; 44.60; 53.26; 56.02; 114.77; 124.49; 127.64; 127.94; 129.60; 130.30; 130.49; 139.66; 158.69; 159.04; 164.00; 165.45; 170.24. HR-MALDI-MS: 413.1586 ($C_{22}H_{22}N_4NaO_3^+$, $[M + Na]^+$; calc. 413.1584).

N-*{(2*S*)-1-[(4-Methoxybenzoyl)amino]-3-phenylpropan-2-yl}pyrimidine-2-carboxamide* (**11b**). The title compound was obtained from regioisomer **8b**. Viscous oil. Yield 31 mg (13%). R_f 0.26 (AcOEt/CH_2Cl_2/MeOH/NH_3 aq. 1:1:0.1:0.01). $[\alpha]_D^{20} = -1.6$ (*c* = 0.5 g/100 ml MeOH). ^{1}H-NMR (400 MHz, CD_3OD, 25°): 3.02 (*d*, *J* = 7.2, C*H*$_2$Ph); 3.63–3.65 (*m*, CH_2N); 3.81 (*s*, MeO); 4.56–4.63 (*m*, CHN); 6.92 (*d*, *J* = 8.8, 2 H of Ani); 7.16 (*t*, *J* = 7.2, 1 H of Ph); 7.24 (*t*, *J* = 7.2, 2 H of Ph); 7.31 (*d*, *J* = 7.2, 2 H of Ph); 7.58 (*t*, *J* = 4.8, 1 H of Pm); 7.71 (*d*, *J* = 8.8, 2 H of Ani); 8.89 (*d*, *J* = 4.8, 2 H of Pm). ^{13}C-NMR (100 MHz,

CD_3OD, 25°): 39.44; 44.47; 53.64; 56.03; 114.81; 124.48; 127.70; 127.76; 129.61; 130.33; 130.50; 139.46; 158.63; 159.03; 164.05; 164.89; 170.59. HR-MALDI-MS: 413.1585 ($C_{22}H_{22}N_4NaO_3^+$, $[M+Na]^+$; calc. 413.1584).

The X-ray data for colorless crystals of **3** and **8b** were obtained at 150K using *Oxford Cryostream* low-temperature device on a *Nonius KappaCCD* diffractometer with MoK_α radiation ($\lambda = 0.71073$ Å), a graphite monochromator, and the ϕ and χ scan mode. Data reductions were performed with DENZO-SMN [60]. The absorption was corrected by integration methods [61]. Structures were solved by direct methods (SIR92) [62] and refined by full matrix least-square based on F^2 (SHELXL97) [63]. H-atoms were mostly localized on a difference *Fourier* map, however to ensure uniformity of treatment of crystal, all hydrogens were recalculated into idealized positions (riding model) and assigned temperature factors $H_{iso}(H) = 1.2\ U_{eq}$ (pivot atom) or of $1.5\ U_{eq}$ (Me). H-atoms in Me, CH_2, CH moieties and H-atoms in aromatic rings were placed with C–H distances of 0.96, 0.97, 0.98, and 0.93 Å. The H-atom of NH group in **3** has been assigned from the *Fourier* difference map.

$R_{int} = \Sigma|F_o^2 - F_{o,mean}^2|/\Sigma F_o^2$, $GOF = [\Sigma(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{1/2}$ for all data, $R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ for observed data, $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{1/2}$ for all data.

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Centre, with CCDC no. 1030229 and 1030230 for **3** and **8b**, resp. Copies of this information may be obtained free of charge from the Director, *CCDC*, 12 Union Road, Cambridge CB21EY, UK (fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

Crystallographic Data for **3**: $C_{14}H_{14}N_4$, $M = 238.29$, monoclinic, $P\ 21$, $a = 7.9790(3)$, $b = 5.5430(2)$, $c = 13.4051(4)$ Å, $\beta = 90.989(2)°$, $Z = 2$, $V = 592.79(4)$ Å^3, $D_c = 1.335$ g cm^{-3}, $\mu = 0.084$ mm^{-1}, $T_{min}/T_{max} = 0.984/0.992$; $-10 \le h \le 9$, $-7 \le k \le 6$, $-17 \le l \le 17$; 6135 reflections measured ($\theta_{max} = 27.5°$), 6115 independent ($R_{int} = 0.0293$), 2560 with $I > 2\sigma(I)$, 167 parameters, $S = 1.157$, *R1* (obs. data) = 0.0405, *wR2* (all data) = 0.0843; max., min. residual electron density = 0.160, −0.204 eÅ^{-3}.

Crystallographic Data for **8b**: $C_{22}H_{20}N_4O_2$, $M = 372.42$, monoclinic, $P\ 21$, $a = 10.2221(6)$, $b = 8.1960(4)$, $c = 11.9840(6)$ Å, $\beta = 110.522(5)°$, $Z = 2$, $V = 940.31(9)$ Å^3, $D_c = 1.315$ g cm^{-3}, $\mu = 0.087$ mm^{-1}, $T_{min}/T_{max} = 0.969/0.977$; $-13 \le h \le 12$, $-10 \le k \le 9$, $-15 \le l \le 15$; 6729 reflections measured ($\theta_{max} = 27.35°$), 3554 independent ($R_{int} = 0.0197$), 3554 with $I > 2\sigma(I)$, 253 parameters, $S = 1.105$, *R1* (obs. data) = 0.0293, *wR2* (all data) = 0.0708; max., min. residual electron density = 0.183, −0.160 eÅ^{-3}.

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