PERKIN 1

New chiral pyrazine-based ligands for self-assembly reactions

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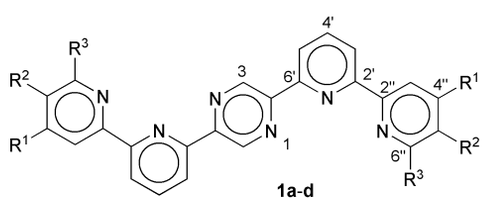
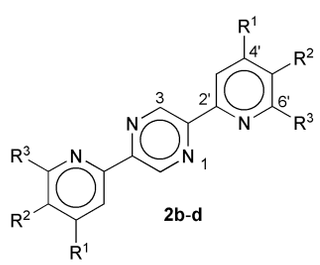
The syntheses of two families of ditopic *N*-heterocyclic ligands are described. All the compounds contain a central pyrazine ring connected to peripheral pyridine or bipyridine moieties, providing bipyridine- and terpyridine-like binding sites, respectively. Annellated terpene fragments render these metal chelators chiral. Thus they face the challenge of introducing stereoselectivity into the formation of chiral, multinuclear co-ordination species.

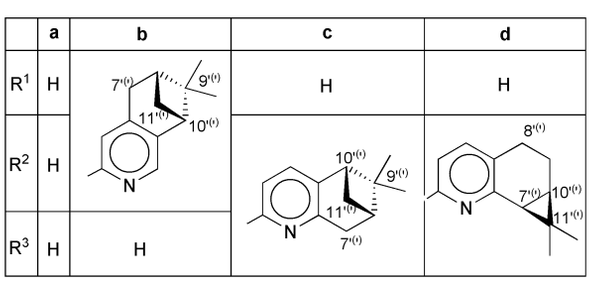
Introduction

Supramolecular chemistry based on co-ordination chemistry is a vast area of current research. A particularly large number of such supramolecular complexes use oligomeric aromatic *N*-heterocycles as ligands. The demand for multitopic (bridging) ligands provides a strong impetus for the development of new synthetic methods for oligopyridines and related compounds.

In this report, we present the development and synthesis of two series of ligands (**1a–d**, **2b–d**) (Scheme 1) which are both based upon 2,5-disubstituted pyrazine. Related ligands, for example, 2,3-[1a,b,c] and 2,5-dipyridylpyrazine,[1a,d] 3,6-dipyridyl-1,2,4,6-tetrazine,[1e,f] 2,3-bis(bipyridinyl)pyrazine[1g] or 4,6-bis(bipyridinyl)pyrimidine[1h,i] have already been used for self-assembly reactions as well as for the stepwise formation of metal complexes. Bis(phenanthrolinyl) derivatives of pyrazine, pyrimidine and pyridazine have all been reported recently.[1j]







Scheme 1 Ligands of type **1** and **2** are derivatives of 2,5-substituted pyrazine. Each of the isomers **b**, **c**, and **d** are chiral and thus potentially useful for stereoselective complex formation. The heterocycles have a cisoid (unnatural) arrangement to point out the bipyridine- and terpyridine-type binding sites.

Ligands **1a–d** are ditopic ligands, that offer two terpyridine-type binding sites. The relative orientation of these binding sites is fixed and anti-parallel. We designed these ligands with the aim of producing a new type of chiral "molecular square" complex. Ligands **1b–d** contain, in addition, annellated chiral terpene fragments. We used the "chiral pool" compounds myrtenal† **7b**, pinocarvone **7c**[2] and car-3(10)-en-2-one **7d** in order to create a series of "tuned" chiral ligands for stereoselective complex formation. Going from **1b** to **1d**, the chiral centres of the terpene fragments move nearer and nearer to the co-ordinated metal centres, which become stereogenic centres when complexed to these ligands. We have recently shown that **1a** forms a chiral, tetrameric, grid-like, D_4-symmetrical complex with Zn^{2+}, which is obtained as a racemic compound. In contrast, a remarkable stereoselectivity in the formation of the corresponding zinc(II) complex using **1b** is observed.[3]

Ligands **2b–d** are chiral derivatives of 2,5-dipyridylpyrazine **2a**, a ditopic ligand with two bipyridine-type binding sites. The parent ligand **2a** has been widely used in self-assembly and stepwise complexation reactions, giving rise to racemic or configurationally undefined products[1a,d] ("isomer problem"). Ligands **2b–d** are currently being investigated with the aim of producing analogous species which show well-defined stereochemical properties.

For the syntheses of these ligands we followed our strategy[4] of creating new pyridine moieties, rather than using the homo-coupling reactions (Stille, Suzuki) that several authors have used for the synthesis of comparable compounds.

The three protocols presented (Scheme 2) are all based on the key compound 2,5-diacetylpyrazine **3**, which is readily available through radical acetylation of pyrazine.[5]

Results and discussion

The achiral ligand **1a** was obtained following two alternative routes (Scheme 2): in both cases the pyridine rings B and B′ are

† The IUPAC name for myrtenal is 6,6-dimethylbicyclo[3.3.1]hept-2-en-2-carboxaldehyde. The IUPAC name for pinocarvone is pin-2(10)-en-3-one.

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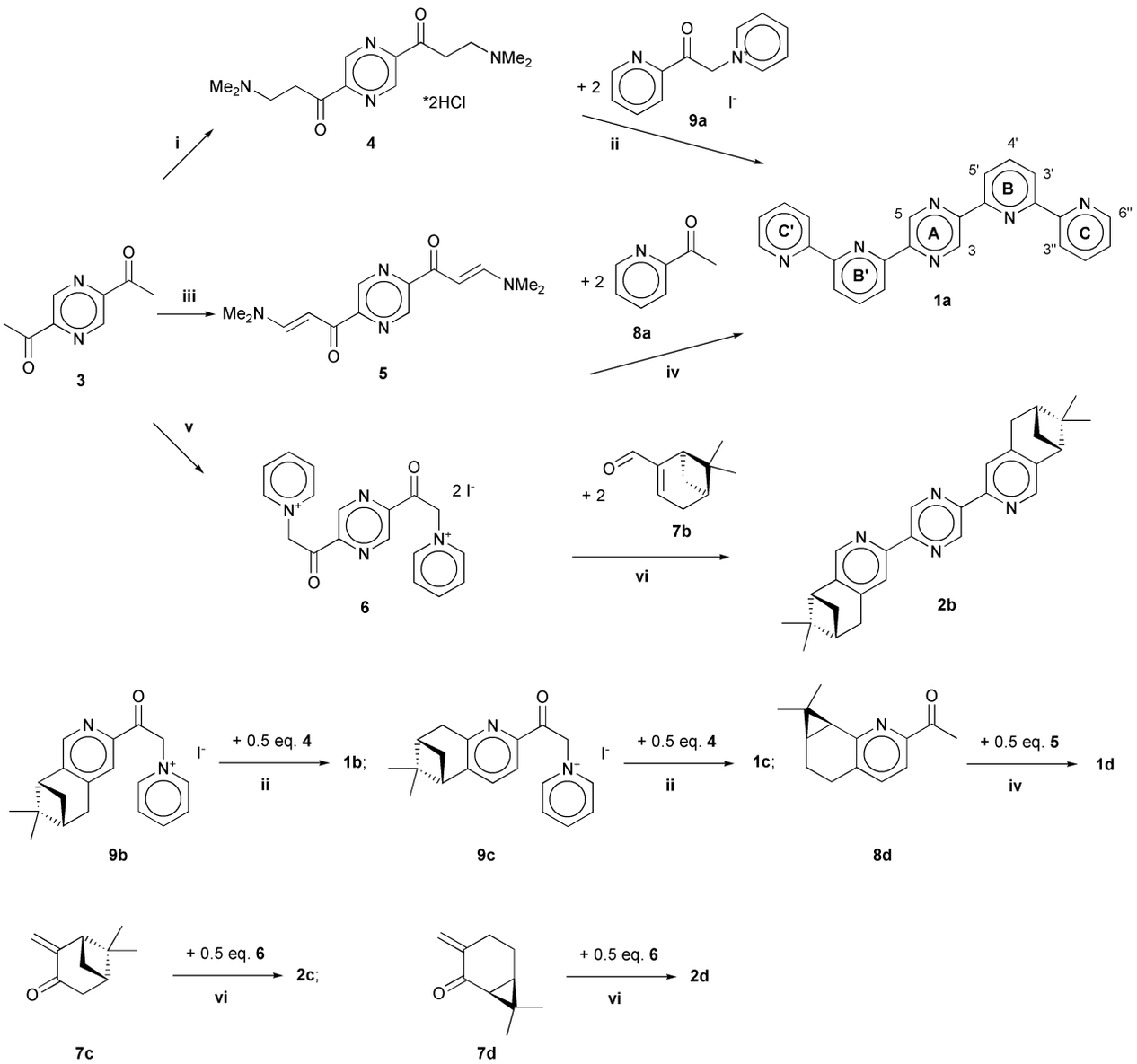
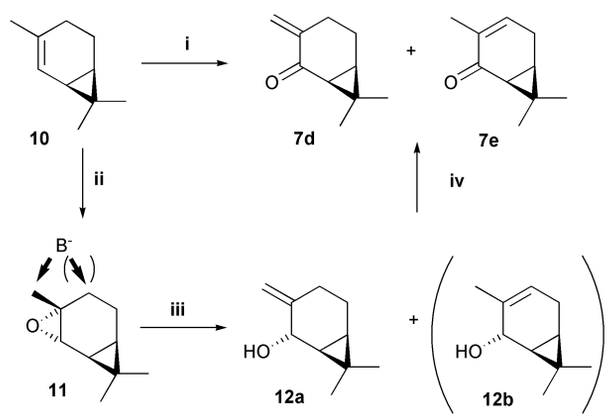


Scheme 2 *Reagents and conditions*: i) $[H_2C{=}N^+Me_2]Cl$, MeCN; ii) NH_4OAc, MeOH; iii) $Me_2N{-}CH(OMe)_2$, μ-waves; iv) 1. **8** + *t*-BuOK, THF; 2. +0.5 eq. **5**; 3. NH_4OAc, HOAc; v) I_2, pyridine; vi) NH_4OAc, solvent.

built up in either a Kröhnke-type reaction,[6] or according to the protocol of Jameson and Guise.[7]

In the case of the Kröhnke reaction, we chose the special version, in which the commonly used α,β-unsaturated ketone was replaced by a Mannich base (**4**). As a result, we obtained the pyridine-containing compound *without* a substituent in the 4′-position. Bis(Mannich base) **4** is easily obtained from **3** and Eschenmoser's salt (chloride). The required Kröhnke salts **9a**,[8] **9b** and **9c**[9] have been described previously. Salts **9b** and **9c** are derived from commercially available myrtenal **7b**, and from pinocarvone **7c**,[2] respectively. Ligands **1a**–**c** can be synthesised on gram scales. Ligand **1d** was more difficult to obtain. The first inconvenience was the lack of an efficient synthesis for the necessary terpenoid enone **7d**.[10,11] In the course of the photo-oxidation[12] of car-2-ene **10**, which we reported some years ago, the largest part of **10** is converted into an undesired regioisomer of **7d**, *i.e.* **7e** (nevertheless, mixtures of **7d** and **7e** can still be used in Kröhnke reactions, as **7e** does not react). We have developed a more demanding protocol, (Scheme 3) which provides pure **7d**; **10** is converted into its epoxide **11**,[13] which is subsequently opened by a strong base to give the corresponding unsaturated alcohol **12a**, as well as smaller amounts of undesired endocyclic enol **12b**.[14,15] Alcohol **12a** can be oxidised to **7d**.



Scheme 3 *Reagents and conditions*: i) O_2, *hv*, Ac_2O, Py, Ph_4porph, CH_2Cl_2; ii) MCPBA, Et_2O; iii) *t*-BuOK, $LiNR_2$, THF; iv) MnO_2, molecular sieves, CH_2Cl_2.

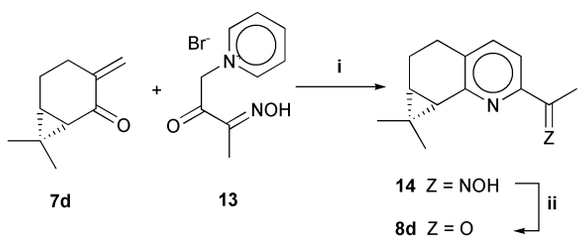
We used the so-called LIDAKOR-reagent[16] for the ring opening. The regioselectivity increases markedly with the bulky alkyl groups of the lithium dialkylamide (Table 1). The best result, *i.e.* the absence of **12b**, was achieved with the LIDAKOR-base, LiTMP–*t*-BuOK (HTMP = 2,2,6,6-tetramethylpiperidine).

Table 1 Regioselectivity of LIDAKOR-mediated oxirane-opening

LIDAKOR base	Yield (%) **12a** + **b**	Ratio[a] **12a** : **12b**
$LiNEt_2$–*t*-BuOK	93	4.6 : 1
$LiN(i\text{-}Pr)_2$–*t*-BuOK	>95	8.7 : 1
$LiN(cy^b)_2$–*t*-BuOK	>95	13.5 : 1
LiTMP[c]–*t*-BuOK	94	>100 : 1

[a] By NMR. [b] Cy = cyclohexyl. [c] HTMP = 2,2,6,6-tetramethylpiperidine.

Allylic alcohol **12a** was oxidised with MnO_2. This last step is not very efficient and leads to an overall yield of **7d** which is only slightly higher than that of the photo-oxidation. Enone **7d** was reacted with the Kröhnke salt **13**[9] to yield the oxime **14** (Scheme 4). The presence of a cyclopropane ring in the carene



Scheme 4 *Reagents and conditions*: i) NH_4OAc, MeOH; ii) $Ce(SO_4)_2 \cdot 4H_2O$, $CaCO_3$, DMF.

moiety renders this material much more delicate than the related, pinene based isomers.[9] For instance, acid promoted deoximination leads to the total degradation of the carene moiety. Several alternative deoximination protocols[17] proved to be unsuitable; only oxidative cleavage by $KMnO_4$ in MeCN[18] (yield: 43%), or better, ceric sulfate[19] in DMF (yield: 68%) provided the desired ketone **8d**. Due to the presence of a C_3-ring in **8d**, the ketone was not converted into a Kröhnke salt of type **9**, as this reaction would demand treatment with bromine or iodine. Therefore we applied the protocol of Jameson and Guise,[7] which does not use any strong electrophile in the course of reaction. The necessary bis(enaminone) **5** was obtained from **3** and *N*,*N*-dimethylformamide dimethyl acetal under microwave heating.[21] We could obtain **5** only by this recently reported method, as under "classical" conditions (reflux), **3** was essentially mono-derivatised. From **5** together with **8a** or **8d**, we obtained ligands **1a** and **1d** in 22% and 14% yields, respectively. These are rather low yields, but yet they become acceptable, if we consider that this is the first bis-reaction of its type, and that for the corresponding mono-reactions the yields are generally moderate also.[7,22] The smaller ligands **2b**–**d**, which offer two bpy-type co-ordination sites, are obtained in an analogous way to the group of chiral terpy-type ligands, which our group has previously synthesised.[23] Precautions in the synthesis of bis(Kröhnke salt) **6** have to be taken, as **6**, as well as the intermediate mono-Kröhnke salt, are only weakly soluble. Condensation of **6** with two equivalents of enal **7b** or enones **7c**,**d** gave ligands **2b**–**d**, respectively, in acceptable yields.

We were able to determine the crystal structure of **1b**. The crystal structure exhibited the expected transoid arrangement of the *N*-heterocycles. The inherent C_2-symmetry of the ligand is broken, as one of the two bipyridine moieties is considerably twisted out of the plane defined by the central pyrazine ring. This gives a banana-like shape to the whole molecule (Fig. 1).

Conclusion

We have presented two new families of pyrazine-derived ligands, which have been designed for use in self-assembly reactions as well as for classical, stepwise complex formation. The use of the chiral members of these families (**1b**–**d**, **2b**–**d**) should help to solve the isomer problem, which is still a challenge in the field of supramolecular co-ordination chemistry.

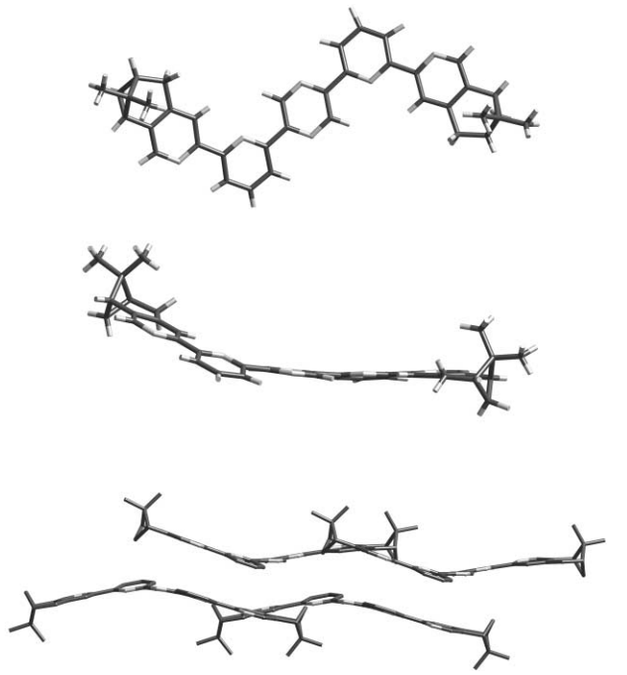


Fig. 1 Crystal structure of **1b**. Top: transoid arrangement of *N*-heterocycles. Middle: one bpy-unit is tilted. Bottom: crystal packing.

Experimental

General

NMR-spectra were recorded on a Bruker Avance 400 or 500, or a Varian Gemini 300 and all coupling constants are measured in Hz. Elemental analyses were performed at the Fribourg Engineering School, 1700 Fribourg, Switzerland. Solvents were distilled, and if noted, they were dried (THF, Et_2O: Na + Ph_2CO; MeOH: $Mg(OMe)_2$; pyridine: BaO; dialkylamines: CaH_2; CH_2Cl_2: P_4O_{10}). Formamide is dried by percolation through 4 Å molecular sieves. Myrtenal, pyrazine, MCPBA and *N*,*N*-dimethylformamide dimethyl acetal have been obtained from ACROS, α-pinene (97% ee, for **7c**) and car-2-ene from Aldrich, and Eschenmoser's salt from Fluka.

2,5-Bis[3-(*N*,*N*-dimethylamino)propionyl]pyrazine dihydrochloride, 4

Compound **3** (4.464 g, 27.19 mmol), Eschenmoser's salt (chloride) (5.85 g, 62.54 mmol) and conc. H_2SO_4 (140 µl) were combined in dry acetonitrile (200 ml). A precipitate formed slowly, which was removed by filtration after 3 days. It was washed with a small amount of MeCN and Et_2O. For purification, it was treated with dry MeOH (150 ml) for 2 h at RT. The solid was filtered off and was dried *in vacuo*. A white, hygroscopic powder (6.080 g, 64%) was obtained. ^{1}H-NMR (300 MHz, CD_3OD) δ 10.78 (s, 2 arom. H), 5.27, 5.07 (AA′BB′ system, J = 6.2, CH_2–CH_2), 4.45 (s, 12H, Me); analysis for $C_{14}H_{24}Cl_2N_4O_2$: found (req.) C, 47.80 (47.87); H, 7.00 (6.89); N, 15.68 (15.95%).

(*E*,*E*)-2,5-Bis[3-(*N*,*N*-dimethylamino)acryloyl]pyrazine 5

Compound **3** (7.14 g, 43.5 mmol) and *N*,*N*-dimethylformamide dimethyl acetal (22.0 ml, 165 mmol) were heated to reflux under argon at normal pressure in a modified microwave oven; **3** dissolved within 5 min (power = 800 W). When the reaction had started (dark coloration, appearance of a precipitate) the power was reduced to 130 W. Heating was continued for 20 min. The cooled reaction mixture was taken up with Et_2O (200 ml) and the brown product was collected by filtration. Fractional recrystallisation from hot chloroform yielded **5** as dark red crystals, which lost solvent to become yellow and amorphous

upon drying (6.89 g, 58%). Mp_{CHCl_3} >300 °C; FAB-MS (*m*-NBA): 275 (100%, M^+), 136 (48%); ^{1}H-NMR ($CDCl_3$, 400.13 MHz) δ 9.26 (s, 2 arom. H), 7.91 (d, 2H, J = 12.6, C(O)–C*H*=CH), 6.39 (br d, 2H, J = 12, C(O)–CH=C*H*), 3.18 (s, 6H, NMe_aMe$_b$), 2.99 (s, 6H, NMe$_a$*Me$_b$*); ^{13}C-NMR ($CDCl_3$, 75.46 MHz) δ 185.11 (q, C=O), 155.04 ($C_{arom.}$–H), 151.02 (q, $C_{arom.}$), 142.27 (C(O)–*C*H=C), 91.47 (br, C(O)–CH=*C*H), 45.31, 37.57 (NMe_aMe$_b$); combustion analysis for $C_{14}H_{18}N_4O_2$: found (req.) C, 60.95 (61.30); H, 6.58 (6.61); N, 20.30 (20.42%).

2,5-Bis[(1-pyridinio)ethanoyl]pyrazine diiodide 6

Compound **3** (4.500 g, 27.41 mmol), dissolved in dry pyridine (120 ml), was added dropwise over 4 h to a solution of iodine (19.45 g, 76.8 mmol) in dry pyridine (70 ml) at 100 °C under dry nitrogen. Heating was continued for 2 h. A brown solid was collected by filtration from the cooled mixture. It was washed with a little pyridine, followed by Et_2O. In order to remove the co-product, pyridinium iodide, the solid was treated with refluxing, dry MeOH (150 ml) for 1 h. The cooled mixture was filtered and the brown solid washed with MeOH and Et_2O and dried *in vacuo*. A dark brown, non-hygroscopic powder (14.03 g, 24.43 mmol, 89%, *ca.* 95% pure) was obtained. ^{1}H-NMR (300.08 MHz, [D$_6$]DMSO) δ 9.48 (s, 2H, C_{pz}(3,6)-H), 9.02 (d, 4H, J = 5.5, C_{py}(2,6)-H), 8.78 (t, 2H, J = 7.8, C_{py}(4)-H), 8.32 (dd, 4H, J = 7.8, 6.5, C_{py}(3,5)-H); ^{13}C-NMR (75.46 MHz, [D$_6$]dmso) δ 190.27 (q, C=O), 147.89 (q, C_{pz} (2, 5)), 146.67 (C_{py}(4)), 146.34 (C_{py}(2)), 142.33 (C_{pz}(3, 6)), 127.82 (C_{py}(3)), 66.48 (CH_2); combustion analysis for $C_{18}H_{16}I_2N_4O_2$: found (req.) C, 38.48 (37.65); H, 2.79 (2.81); N, 9.68 (9.76%).

(1*S*,2*S*)-Car-3(10)-en-2-ol 12a

The hexane was removed from a BuLi solution (1.6 M in hexanes, 30 ml, 48 mmol) *in vacuo* at 0 °C. Dry THF (70 ml) and dry 2,2,6,6-tetramethylpiperidine (8.4 ml, 50 mmol) were added at −70 °C. After 15 min at 0 °C, the solution was cooled to −45 °C and *t*-BuOK (5.4 g, 48 mmol) was added. After 20 min, the dark yellow solution was cooled in an acetone slush bath (*ca.* −90 °C). Car-2-ene oxide[12] (4.59 g, 30.2 mmol) was added *via* syringe at once. The stirred reaction mixture was allowed to warm up slowly in the acetone bath. After 18 h, −30 °C was reached, and the reaction was quenched (50 ml H_2O). The THF was removed *in vacuo* (<30 °C) and the residue was partitioned between H_2O and pentane. The organic phase was washed (2 × 5% aq. citric acid, 1 × aq. $NaHCO_3$), dried ($CaSO_4$·½H_2O) and concentrated. Compound **12a** was obtained as a relatively pure, light yellow oil (4.33 g, 94%). An analytical probe was recrystallised from pentane at −20 °C. When dialkylamines other than HTMP were used, (1*S*,2*S*)-car-3(4)-en-2-ol **12b** was formed as a by-product (Table 1). EI-MS (70 eV): 152 (5%, M^+), 135 (100%, $[M - OH]^+$), 109 (73%, $[M - Pr]^+$); ^{1}H-NMR ($CDCl_3$, 500.13 MHz) δ 4.91 (dd, 1H, J = 1.7, 1.6, H_Z–C(10)), 4.78 (dd, 1H, J = 2.0, 1.9, H_E–C(10)), 4.24 (br s, 1H, H–C(2)), 2.26 (ddddd, 1H, J = 13.1, 13.0, 6.6, 1.8, 1.5, H_R–C(4)), 2.06 (dddd, 1H, J = 14.2, 9.2, 6.6, 2.5, H_S–C(5)), 1.90 (ddd, 1H, J = 13.0, 5.2, 2.5, H_S–C(4)), 1.6 (br s, 1H, OH), 1.32 (m, 1H, H_R–C(5)), 0.99 (s, 3H, Me$_S$(9)), 0.89 (s, 3H, Me$_R$(8)), 0.82 (ddd, 1H, J = 9.2, 8.9, 3.8, H–C(6)), 0.77 (dd, 1H, J = 8.8, 1.0, H–C(1)); ^{13}C-NMR ($CDCl_3$, 100.62 MHz) δ 151.14 (q, C(3)), 111.48 (C(10)), 69.58 (C(2)), 29.15 (C(1)), 28.99 (Me$_S$(9)), 27.55 (C(4)), 20.63 (C(5)), 19.42 (C(6)), 17.02 (q, C(7)), 14.78 (Me$_R$(8)); combustion analysis for $C_{10}H_{16}O$: found (req.) C, 79.10 (78.90); H, 10.90 (10.59%).

(1*S*)-Car-3(10)-en-2-one, 7d

MnO_2 (Fluka 63548, dried, 24 g) was added portionwise to a solution of **12a** (1.224 g, 8.04 mmol) in dry CH_2Cl_2 (75 ml). Molecular sieves (10 g, 3 Å) were added, and the mixture was stirred for two days. The solids were collected by filtration and washed with CH_2Cl_2. Concentration *in vacuo* yields relatively pure **7d** (0.461 g, 3.07 mmol, 38%), which can be directly used in Kröhnke-type reactions. Purification using chromatography (silica gel, hexanes–EtOAc 9 : 1). For analytical data, see ref. 11.

3,3-Dimethyl-11-azatricyclo[5.4.0.0^{2,4}]undeca-1,8,10-trien-10-yl)ethanone oxime14

N-(3-Oximino-2-oxobutan-1-yl)pyridinium bromide (14.63 g, 56.46 mmol) and dry NH_4OAc (20 g) were dissolved in dry MeOH (80 ml). Compound **7d** (8.41 g, 56.0 mmol) was added. The reaction mixture was slowly heated to 60 °C and kept under nitrogen at this temperature overnight. The clear, red solution was diluted with water (500 ml) (precipitation) and extracted with hexanes–Et_2O (1 : 1 3 × 200 ml). The combined organic phases were dried ($MgSO_4$), concentrated *in vacuo* and recrystallised from hexanes. The mother liquor yielded a further batch of **14** after acid–base extraction and recrystallisation from hexanes. In total 8.62 g (67%) of **14** was obtained as brown crystals. An analytical probe was recrystallised from warm Et_2O. Mp_{Et_2O}: 155–156 °C; R_f (silica gel, hexanes–EtOAc 7 : 3) 0.60; EI-MS (70 eV): 230 (100%, M^+), 213 (21%), 198 (12%), 156 (13%); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.41 (br s, 1H, NOH), 7.45 (d, 1H, J = 7.9, C(3)–H), 7.27 (d, 1H, J = 7.9, C(4)–H), 2.80–2.70 (m, 1H, C(6)–H_R), 2.54–2.45 (m, 1H, C(6)–H_S), 2.38 (s, 3H, CNOH–*Me*), 2.09–1.97 (m, 1H, C(7)–H_S), 1.97 (d, 1H, J = 8.6, C(9)–H), 1.84–1.76 (m, 1H, C(7)–H_R), 1.36–1.30 (m, 1H, C(8)–H), 1.23 (s, 3H, Me$_R$(13)), 0.78 (s, 3H, Me$_S$(12)); ^{13}C-NMR ($CDCl_3$, 75.46 MHz) δ 157.07, 156.31, 151.97 (q), 135.96 (C(4)), 132.08 (q), 117.55 (C(3)), 28.99 (Me$_R$(13)), 28.26 (2C, C(6) and C(9)), 25.21 (q), 24.89 (C(8)), 18.85 (C(7)), 16.26 (Me$_R$(12)), 11.21 (CNOH–*Me*); combustion analysis for $C_{14}H_{18}N_2O$: found (req.) C, 72.95 (73.01); H, 8.05 (7.88); N, 12.15 (12.16%).

3,3-Dimethyl-11-azatricyclo[5.4.0.0^{2,4}]undeca-1,8,10-trien-10-yl)ethanone 8d

Compound **14** (3.481 g, 15.11 mmol) was dissolved in DMF (140 ml). $Ce(SO_4)_2$·4H_2O (25 g, 62 mmol) and $CaCO_3$ (25 g, 0.25 mol) were added portionwise over two days. The mixture was diluted with Et_2O (600 ml) and was filtered through Celite. The filtrate was washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by chromatography (silica gel, hexanes–EtOAc 9 : 28) to yield 2.226 g (68%) of a solidifying oil. $Mp_{hexanes}$: 52.5–53 °C; R_f (silica gel, hexanes–EtOAc 85 : 15) 0.34; EI-MS (70 eV): 215 (100%, M^+), 200 (63%, $[M - CH_3]^+$), 174 (47%), 130 (43%), 78 (30%); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, 1H, J = 7.9, C(3)–H), 7.39 (d, 1H, J = 7.8, C(4)–H), 2.77 (m, 1H, C(8)–H_R), 2.70 (s, 3H, CO–Me), 2.56 (m, 1H, C(8)–H_S), 2.05 (m, 1H, C(9)–H_S), 1.97 (d, 1H, J = 8.5, C(7)–H), 1.86–1.75 (m, 1H, C(9)–H_R), 1.37 (m, 1H, C(10)–H), 1.25 (s, 3H, Me$_R$(13)), 0.77 (s, 3H, Me$_S$(12)); ^{13}C-NMR ($CDCl_3$, 75.46 MHz) δ 200.86 (q, C=O), 156.53 (q), 151.74 (q), 136.17 (q), 136.06 (C(4)), 118.65 (C(3)), 29.03 (C(12)), 28.74 (C(8)), 28.38 (C(7)), 25.81 (CO–*Me*), 18.73 (C(9)), 16.31 (C(13)); combustion analysis for $C_{14}H_{17}NO$: found (req.) C, 77.95 (78.10); H, 8.05 (7.96); N, 6.73 (6.51%).

When this oxidation was conducted with 2.25 eq. $(NH_4)_2Ce(NO_3)_6$ in MeCN, 26% of **8d** and 23% of the 2-(1,1-dinitroethyl) derivative were isolated by chromatography (silica gel, hexanes–Et_2O 8 : 2); ^{1}H-NMR very similar but with an extra signal at 2.64 ppm (s, 3H, $C(NO_2)_2$–C*H*$_3$); IR 1570 cm^{-1} (N=O); ESI-MS (MeCN–MeOH; capillary voltage 50 V) 292 (100%, $[M + H]^+$), 246 (95%, $[M - NO_2 + H]^+$); combustion analysis for $C_{14}H_{17}N_3O_4$: found (req.) C, 58.11 (57.72); H, 6.02 (5.88); N, 14.43 (14.42%).

Protocol A (Kröhnke synthesis) for ligands of type 1

Dry ammonium acetate, **4**, and a Kröhnke salt of type **9** were combined in a given solvent, and were heated under dry nitrogen. The reaction mixture was poured into ten times its

volume of water. The crude ligand was collected by filtration, dried and taken up with CH_2Cl_2. It was purified by column chromatography on weakly basic alumina (Merck Alox 90).

Protocol B for the syntheses of 1a and 1d

t-BuOK was dissolved in dry THF. A 2-acetylpyridine of type **8** was added. The reaction mixture was kept at RT for 2 h under argon. Then, solid **5** was added, and the mixture, which became violet, was stirred at RT for 20 h. Dry NH_4OAc and glacial acetic acid were added and the THF was distilled off (80–150 °C over 4 h). Workup and purification were carried out as in *protocol A*.

Protocol C for ligands of type 2

Dry NH_4OAc and **6** were dissolved or suspended in a given dry solvent. An unsaturated carbonyl compound of type **7** was added. The reaction mixture was heated with stirring under dry nitrogen. Workup and purification were carried out as in *protocol A*.

2,5-Bis(2,2′-bipyridin-6-yl)pyrazine 1a

Compound **4** (9.000 g, 25.63 mmol), **9a** (24.00 g, 76.88 mol) and NH_4OAc (100 g) in refluxing MeOH (250 ml) were treated according to *protocol A* for two days to yield 2.586 g (26%) of **1a** after workup, chromatography (CH_2Cl_2) and recrystallisation from CH_2Cl_2. $Mp_{CH_2Cl_2}$: 266–267 °C; ^{1}H-NMR(400 MHz, $CDCl_3$) δ 9.88 (s, 2H, C(3)–H), 8.71 (ddd, 2H, J = 4.8, 1.8, 0.8, C(6″)-H), 8.65 (ddd, 2H, J = 7.8, 1.2, 0.8, C(3″)–H), 8.52 (dd, 2H, J = 7.9, 1.0, C(3′/5′)–H), 8.48 (dd, 2H, J = 7.8, 1.0, C(3′/5′)–H), 8.00 (t, 2H, J = 7.8, C(4′)–H), 7.89 (ddd, 2H, J = 7.8, 7.6, 1.8, C(4″)–H), 7.35 (ddd, 2H, J = 7.6, 4.8, 1.2, C(5″)–H); ^{13}C-NMR (100.61 MHz, $CDCl_3$) δ 155.86 (q), 155.71 (q), 153.57 (q), 150.56 (q), 142.09, 138.13, 137.02, 124.00, 121.64, 121.49, 121.24; EI-MS (70 eV): 388 (100%, M^+), 233 (31, $[M - bpy]^+$), 182 (49), 156 (66, bpy^+), 78 (40, py^+); combustion analysis for $C_{24}H_{16}N_6$, found (req.) C, 73.78 (74.21); H, 4.14 (4.15); N, 21.44 (21.64%).

Applying *protocol B*, **8a** (0.44 ml, 3.9 mmol), *t*-BuOK (880 mg, 7.86 mmol), and **5** (400 mg, 1.46 mmol), which were reacted in THF (20 ml) for 4 days, followed by treatment with NH_4OAc (5 g) in HOAc (10 ml), yielded 22% of **1a**.

Pinene pyrazine derivative[24] ‡ 1b

Compound **9b** (containing HPyI, 12.6 mmol net), **4** (2.00 g, 5.69 mmol) and dry NH_4OAc (20 g) were treated according to *protocol A* in dry formamide (40 ml) (15 h at 60 °C, then 5 h at 80 °C). After work-up, chromatography (silica gel, hexanes–NEt_3–$HNEt_2$ 90 : 10 : 1.5) and recrystallisation (CH_2Cl_2–acetone) 1.474 g, (45%) of **1b** was obtained. $Mp_{CH_2Cl_2–acetone}$: 270–272 °C; R_f (alumina, CH_2Cl_2) 0.63; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.91 (s, 2H, C(3)–H), 8.51 (d, 2H, J = 7.8, C(3′ or 5′)–H), 8.45 (s, 2H, C(6″)–H), 8.44 (d, 2H, J = 7.8, C(3′ or 5′)–H), 8.25 (s, 2H, C(3″)–H), 7.98 (dd, 2H, J = 7.9, 7.8, C(4′)–H), 3.12–3.13 (2s, 4H, C(7″)–H_RH_S), 2.90 (dd, 2H, J = 5.3, 5.5, C(10″)–H), 2.74 (ddd, 2H, J = 9.6, 5.9, 5.6, C(11″)–H_S), 2.36 (m, 2H, C(8″)–H), 1.43 (s, 6H, Me(13″)), 1.27 (d, 2H, J = 9.6, C(11″)–H_R), 0.68 (s, 6H, Me(12″)); ^{13}C-NMR ($CDCl_3$, 75.46 MHz) δ 155.74 (q), 153.75 (q), 153.38 (q), 150.60 (q), 146.08 (q), 145.09 (C(3″ or 6″)), 143.55 (q), 142.11 (C(3)), 138.08 (C(4′)), 121.49, 121.09 (C(3′ and 5′)), 120.75 (C(3″ or 6″)), 44.58 (C(10″)), 40.10 (q, C(9″)), 39.30 (C(8″)), 33.14 (C(7″)), 31.80 (C(11″), 26.02 (C(13″)), 21.44 (C(12″)); FAB-MS (*m*-NBA) 577 (100%, M^+), 533 (12%), 149 (21%); combustion analysis for $C_{38}H_{36}N_6$: found (req.) C, 79.35 (79.14); H, 6.42 (6.29); N, 14.10 (14.57%).

‡ The numbering for the NMR data is given in Scheme 1.

Pinene pyrazine derivative[24] ‡ 1c

Compound **9c** (containing HPyI, 11.3 mmol net), **4** (1.983 g, 5.645 mmol) and dry NH_4OAc (20 g) were treated in MeOH (50 ml) for 20 h at 80 °C according to *protocol A*. After workup, chromatography (hexanes–CH_2Cl_2 (1 : 1) ⟶ CH_2Cl_2) and recrystallisation (CH_2Cl_2–acetone), 1.050 g (32%) of **1c** was obtained. $Mp_{CH_2Cl_2–acetone}$: 294 °C (decomp.); R_f (alumina, hexanes–CH_2Cl_2: 1 : 1) 0.22; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.86 (s, 2H, C(3)–H), 8.49 (dd, 2H, J = 7.9, 1.1, C(3′ or 5′)–H)), 8.42 (dd, 2H, J = 7.8, 1.1, C(3′ or 5′)–H)), 8.32 (d, 2H, J = 7.7, C(3″)–H), 7.95 (dd, 2H, J = 7.9, 7.8, C(4′)–H), 7.38 (d, 2H, J = 7.8, C(4″)–H), 3.20 (2s, 4H, C(7″)–H_RH_S), 2.84 (dd, 2H, J = 5.8, 5.6, C(10″)–H), 2.72 (ddd, 2H, J = 9.5, 5.8, 5.6, C(11″)–H_S), 2.41 (m, 2H, C(8″)–H), 1.43 (s, 6H, Me(12″)), 1.33 (d, 2H, J = 9.5, C(11″)–H_R), 0.70 (s, 4H, Me(13″); ^{13}C-NMR ($CDCl_3$, 75.46 MHz) δ 156.46 (q), 156.28 (q), 153.42 (q), 153.21 (q), 150.59 (q), 142.58 (q), 142.04 (C(3)), 137.90 (C(4′)), 133.82 (C(4″)), 121.28 (C(3′) or C(5′)), 120.77 (C(3′) or C(5′)), 118.01 (C(3″)), 46.53 (C(10″)), 40.25 (C(8″)), 39.56 (q, C(9″)), 36.72 (C(7″)), 31.95 (C(11″)), 26.07 (C(12)), 21.35 (C(13)); FAB-MS (*m*-NBA) 577 (100%, M^+), 307 (39%), 136 (80%); combustion analysis for $C_{38}H_{36}N_6$: found (req.) C, 78.54 (79.14); H, 6.40 (6.29); N, 14.50 (14.57%).

Carene pyrazine derivative[24] ‡ 1d

According to *protocol B*, **8d** (776 mg, 3.60 mmol), *t*-BuOK (870 mg, 7.21 mmol) and **5** were reacted in THF (20 ml). After treating with NH_4OAc (5 g) and HOAc (10 ml), workup and chromatography (CH_2Cl_2–hexanes 1 : 1) a white powder was obtained (116.2 mg, 14%). Mp > 310 °C; R_f (alumina, hexanes–CH_2Cl_2 1 : 1) 0.18; ESI-MS ($CHCl_3$, MeOH) 577 (95%, $[HM]^+$), 289 (100%, $[H_2M]^{2+}$); ^{1}H-NMR ($CDCl_3$, 400.13 MHz) δ 9.86 (s, 2H, H–C(3)), 8.54 (dd, 2H, J = 7.8, 1.0, H–C(3′ or 5′)), 8.41 (dd, 2H, J = 7.6, 1.0, H–C(3′ or 5′)), 8.30 (d, 2H, J = 7.8, H–C(3″)), 7.96 (t, 2H, J = 7.8, H–C(4′)), 7.48 (d, 2H, J = 8.1, H–C(4″)), 2.83 (m, 2H, H_R–C(8)), 2.63–2.55 (m, 2H, H_S–C(8)), 2.15–2.04 (m, 2H, H_S–C(9)), 2.05 (d, 2H, J = 8.6, H–C(7)), 1.90–1.82 (m, 2H, H_R–C(9)), 1.39 (td, 2H, J = *ca.* 8, 3.8, H–C(10)), 1.28 (s, 6H, Me_R(13)), 0.84 (s, 6H, Me_S(12)); ^{13}C-NMR ($CDCl_3$, 100.62 MHz) δ 156.44 (q), 156.40 (q), 153.56 (q), 153.38 (q), 142.05 (C(3)), 137.87 (C(4′)), 136.47 (C(4″)), 132.35 (q), 121.68 (C(3′ or 5′)), 120.83 (C(3′ or 5′)), 118.20 (C(3″)), 29.16 (C(13)), 28.62 (C(7)), 28.38 (C(8)), 25.11 (q), 25.03 (C(10)), 18.88 (C(9)), 16.39 (C(12)); combustion analysis for $C_{38}H_{36}N_6$: found (req.) C, 79.35 (79.14); H, 6.47 (6.29); N, 14.70 (14.57%).

Pinene pyrazine derivative[24] ‡ 2b

Compound **6** (6.000 g, 10.45 mmol), NH_4OAc (12 g) and (*R*)-myrthenal **7b** (3.140 g, 20.90 mmol) were reacted in dry formamide (40 ml) according to *protocol C* at 60 °C overnight. After workup, chromatography (hexanes–Et_2O 2 : 1) and recrystallisation (CH_2Cl_2–acetone), a light lemon, microcrystalline powder (1.666 g, 38%) was obtained. $Mp_{CH_2Cl_2–acetone}$: 267–268 °C; R_f (silica gel, hexanes–EtOAc–NEt_3 80 : 20 : 5) 0.49; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 9.56 (s, 2H, C(3,6)–H), 8.24 (s, 2H, C(6′)–H), 8.19 (s, 2H, C(3′)–H), 3.06–3.05 (2s, 4H, C(7′)–H_RH_S), 2.87 (dd, 2H, J = 5.3, 5.4, C(10′)–H), 2.71 (ddd, 2H, J = 9.5, 5.9, 5.6, C(11′)–H_S), 2.31 (m, 1H, C(8′)–H), 1.41 (s, 6H, Me(13′)), 1.23 (d, 2H, J = 9.6, C(11′)–H_R), 0.65 (s, 6H, Me(12′)); ^{13}C-NMR ($CDCl_3$, 75.46 MHz) δ 125.60 (q), 150.56 (q), 145.87 (C(6′)), 145.63 (q), 143.70 (q), 141.63 (C(3,6)), 120.96 (C(3′)), 44.59 (C(10′)), 40.04 (C(8′)), 39.26 (q, C(11′)), 32.94 (C(7′)), 31.77 (C(11′)), 26.00 (Me(13)), 21.40 (Me(12)); FAB-MS (*m*-NBA) 423 (100%, $[HM]^+$), 379 (20%); combustion analysis for $C_{28}H_{30}N_4$: found (req.) C, 79.80 (79.59); H, 7.40 (7.16); N, 13.38 (13.26%).

Pinene pyrazine derivative[24] ‡ 2c

Compound **6** (4.000 g, 6.967 mmol), NH_4OAc (10 g) and pinocarvone **7c** (3.15 g, 20.1 mmol) were reacted according to *protocol C* in HOAc (30 ml) and Ac_2O (3 ml) for 5 h at reflux. After workup, chromatography (hexanes–CH_2Cl_2 5 : 4 ⟶ 3 : 5) and recrystallisation ($CHCl_3$–hexanes), 1.844 g (63%) of pale lemon crystals were obtained. $Mp_{CHCl_3\text{–hexanes}}$: 267–268 °C; R_f (alumina, CH_2Cl_2–hexanes 4 : 5) 0.28; FAB-MS (*m*-NBA) 423 (100%, M^+); ^{1}H-NMR ($CDCl_3$, 400.13 MHz) δ 9.55 (s, 2H, H–C(3)), 8.06 (d, 2H, J = 7.8, H–C(3′)), 7.33 (d, 2H, J = 7.8, H–C(4′)), 3.20 (d, 4H, J = 3.04, HH–C(7′)), 2.81 (dd, 2H, J = 5.8, 5.6, H–C(10′)), 2.71 (dt, 2H, J = 9.6, 5.8, H_S–C(11′)), 2.40 (ddd, 2H, J = 9.1, 6.1, 3.0, H–C(8′)), 1.41 (s, 6H, Me(12′)), 1.31 (d, 2H, J = 9.6, H_R–C(11′)), 0.68 (s, 6H, Me(13′)); ^{13}C-NMR ($CDCl_3$, 100.62 MHz) δ 156.94 (q), 151.75 (q), 150.51 (q), 142.91 (q), 141.67 (C(3/5)), 133.77 (C(4′)), 118.77 (C(3′)), 46.64 (C(10′)), 40.23 (C(8′)), 39.57 (q, C(9′)), 36.70 (C(7′)), 31.90 (C(11′)), 26.06 (C(12′)), 21.37 (C(13′)); combustion analysis for $C_{28}H_{30}N_4$: found (req.) C, 79.33 (79.59); H, 7.28 (7.16); N, 13.01 (13.26%).

Carene pyrazine derivative[24] ‡ 2d

Compound **6** (1.000 g, 1.742 mmol) and **7d** (0.52 g, 3.5 mmol) were reacted according to *protocol C* in DMF–MeOH (1 : 1, 8 ml) for 12 h at 65 °C. After workup, chromatography (hexanes–CH_2Cl_2 1 : 1) and recrystallisation from hot MeCN, fine needles (131 mg, 18%) were obtained. Mp_{MeCN}: 208.5–209.5 °C; R_f (silica gel, hexanes–EtOAc–NEt_3 80 : 20 : 5) 0.66; FAB-MS (*m*-NBA) 423 (100%, M^+); ^{1}H-NMR ($CDCl_3$, 400.13 MHz) δ 9.61 (s, 2H, H–C(3,6)), 8.06 (d, 2H, J = 7.8, H–C(3′)), 7.45 (d, 2H, J = 7.8, H–C(4′)), 2.82 (dt, 2H, J = 16.2, 7.3, H_R–C(8)), 2.58 (dt, 2H, J = 16,4, 6.8, H_S–C(8)), 2.10–2.03 (m, 4H, H_S–C(9), H–C(7′)), 1.90–1.82 (m, 2H, H_R–C(9′)), 1.39 (ddd, 2H, J = 8.3, 7.4, 3.7, H–C(10′)), 1.28 (s, 6H, Me_R), 0.84 (s, 6H, Me_S); ^{13}C-NMR ($CDCl_3$, 100.62 MHz) δ 156.85 (q), 152.07 (q), 141.98 (q), 136.52 (C(3,6)), 132.66 (C(4′)), 121.94 (q), 118.60 (C(3′)), 29.15 (Me_R), 28.58 (C(7′)), 28.37 (C(8)), 25.27 (C(10′)), 25.11 (q, C(12′)), 18.80 (C(9)), 16.41 (Me_S); combustion analysis for $C_{28}H_{30}N_4$: found (req.) C, 79.35 (79.59); H, 7.29 (7.16); N, 13.10 (13.26%).

Crystal structure analysis

Compound **1b**, $C_{38}H_{36}N_6$, M_r = 576.73, colourless rod 0.50 × 0.20 × 0.15 mm^3. Orthorhombic, $P2_12_12_1$, Z = 4, a = 12.9950(8), b = 12.0640(10), c = 19.5348(13) Å, $\alpha = \beta = \gamma = 90°$, V = 3062.5(4) Å^3, ρ_{calcd} = 1251 kg m^{-3}, μ = 0.075 mm^{-1}. Data were collected on a Stoe Image Plate diffraction system using graphite monochromated Mo-Kα radiation (0.71073 Å). Image plate distance 70 mm, ϕ oscillation scans 0–147°, step $\Delta\phi$ = 1°, 2θ range 3.96–51.7°, d_{max}–d_{min} = 12.45–0.81 Å. The structure was solved by direct methods using SHELXS-97[25a] and refined using SHELXL-97.[25b] The majority of the H-atoms were located from Fourier difference maps and refined isotropically. The remainder were included in calculated positions and treated as riding atoms using SHELXL-97 default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least-squares on F^2. From 17585 reflections, 5846 were independent and used to refine 512 parameters. 2403 reflections were observed ($I > 2\sigma(I)$). R_1 = 0.0348 (observed), 0.1207 (all data); wR_2 = 0.0518 (observed), 0.0610 (all data). Residual electron density −0.122/+0.117 e Å^{-3}. It was not possible to determine the absolute structure.

CCDC reference number 174482. See http://www.rsc.org/suppdata/p1/b2/b205563p/ for crystallographic files in .cif or other electronic format.

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