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SYNTHESIS, ESI AND FAB MASS SPECTROMETRY, AND X-RAY ANALYSIS OF DI- AND TRICATIONIC PYRIDINIUM SUBSTITUTED PYRIMIDINES

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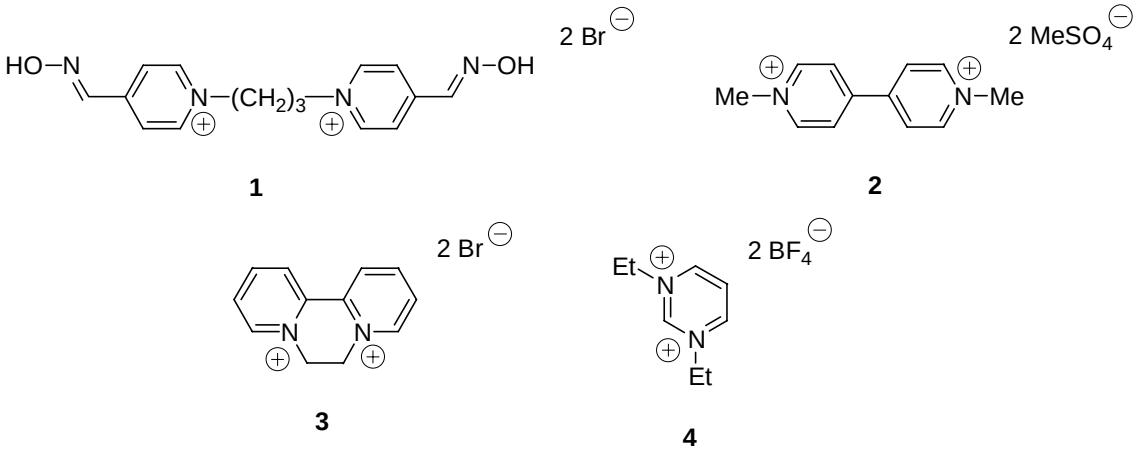
Abstract - Reaction of trichloropyrimidine (**5**) with 4-(dimethylamino)pyridine or 4-(pyrrolidin-1-yl)pyridine in ethyl acetate in the presence of sodium tetraphenylborate yielded the tricationic pyrimidines (**7**) and (**8**). Applying the same reaction conditions to tetrachloropyrimidine (**6**) resulted in the formation of highly reactive 5-chloro substituted trications (**9**) and (**10**), which could be intercepted by anhydrous alcohols to give the dicationic species (**11**) and (**12**). Characterizations by means of ESIMS and FABMS, a semiempirical calculation and an X-Ray analysis were performed.

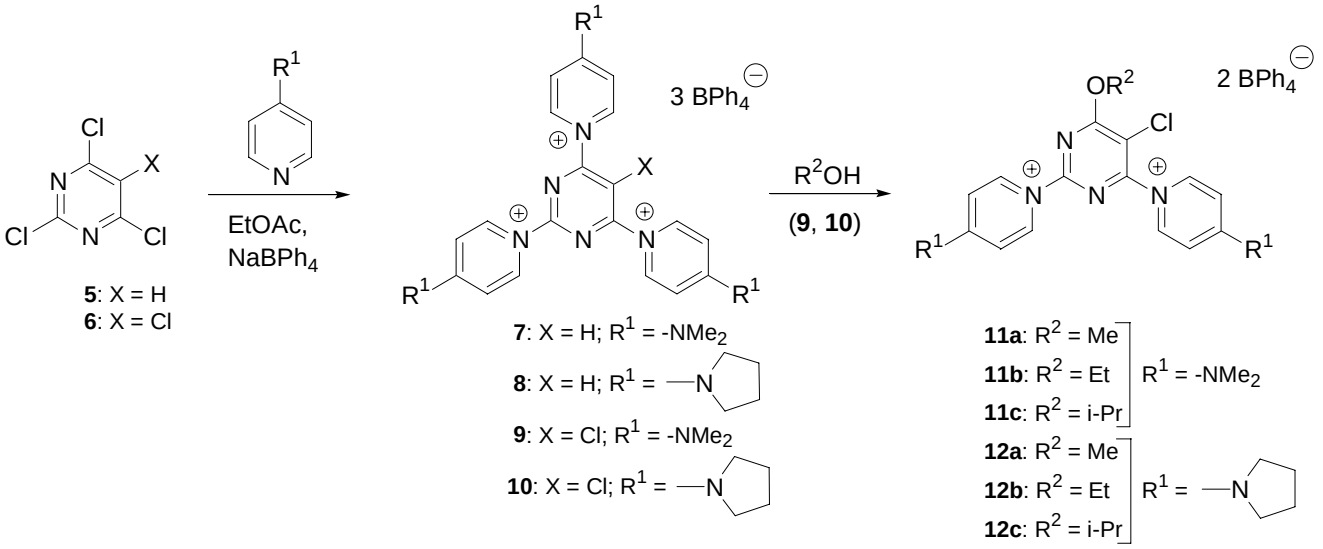
The reaction of chloropyrimidines with various nucleophiles is well-known and numerous publications are dealing with S_N*(AE)* substitutions,[1] ring transformations,[2] or *ipso*-substitutions *via* the S_N*(ANRORC)* mechanism.[3] We describe here the characterizations of reaction products with heteroaromatic nucleophiles leading to oligocationic systems. Some morefold positively charged pyridines and pyrimidines are known to be stable and biologically active, among these *isolated* as well as *conjugated* dications. Examples are the acetylcholinesterase reactivator (**1**),[4] the herbicides paraquat (**2**) and diquat (**3**),[5] and the diethylpyrimidindiium (**4**).[6]



1 **2** **3** **4**

Scheme 1

Trifold displacement reactions on trichloropyrimidine (**5**) with *aliphatic* nucleophiles usually afford vigorous reaction conditions or are impossible.[7] Monosubstitution with *heteroaromatic* nucleophiles, however, improves the leaving group tendency of the remaining chlorine atoms due to the well-known additivity of substituent effects.[8] Thus, reaction of 4-(dimethylamino)pyridine or 4-(pyrrolidin-1-yl)pyridine with trichloropyrimidine in anhydrous ethyl acetate in the presence of sodium tetraphenylborate yields sodium chloride and the tricationic species (**7**) and (**8**) in one single step and in 100 and 76% yields, respectively. In contrast to the corresponding trichlorides, the 1,1′, 1′′-(pyrimidin-2,4,6-triyl)-tris-(4-pyridinium)-tris-(tetraphenylborates) are stable, non-hygroscopic compounds. Starting from tetrachloropyrimidine (**6**), reaction with 4-(dimethylamino)pyridine and 4-(pyrrolidin-1-yl)pyridine under the same reaction conditions resulted in the spontaneous formation of instable solids. Freshly prepared samples of **9** and **10** display the α-protons of the pyridinium rings at 9.25 ppm / 8.89 ppm and 9.35 ppm / 9.22 ppm in 1:2 ratio, respectively, in DMSO-d_6 under an inert atmosphere, together with decomposition products. Interception, however, of this highly reactive intermediates (**9**) and (**10**) with a mixture of dry methanol, ethanol, or isopropanol in acetone, respectively, gives the 1,1′-(5-chloro-6-alkoxypyrimidin-2,4-diyl)-bis-(4-pyridinium)-bis-(tetraphenylborates) (**11a-c**) and (**12a-c**).



Scheme 2

According to an AM1 calculation the trication (**7**) adopts a propeller-like conformation in the ground state which is shown in Figure 1. The calculated torsion angles of the pyridinium rings are the result of maximum *p*-overlapping of the two π-electron systems and steric repulsion. They result in interatomic distances of the α-hydrogens and 5-*H* of the central pyrimidine that are smaller than the twofold *van-der Waals*-radii of hydrogen (2 r H_{vdW} = 240 pm).[9] On the other hand, the interaction between the lone-pairs of nitrogen such as N(1) and N(3) of pyrimidine and heteroaromatic C-H-bonds such as α-hydrogens of the pyridinium rings is known to be an attractive one.[10] Correspondingly, the torsion angle of the C(2)-bound pyridinium ring is smaller. Some interatomic distances are given in Figure 2, and dihedral angles as well as bond lengths are presented in Table 1.[11]

Table 1. Selected results of an AM1 calculation of trication (**7**).

Dihedral angles		Bond lengths [pm]			
N(1)-C(2)-N^+-C(α)	34.4°	C(2)-N^+	144.0	N^+-C(α)	139.1
N(2)-C(4)-N^+-C(α′)	39.9°	C(4)-N^+	143.1	C(α)-C(β)	136.9
N(1)-C(6)-N^+-C(α′′)	39.9°	C(6)-N^+	143.1	C(β)-C(γ)	145.0
				C(γ)-NMe_2	134.3

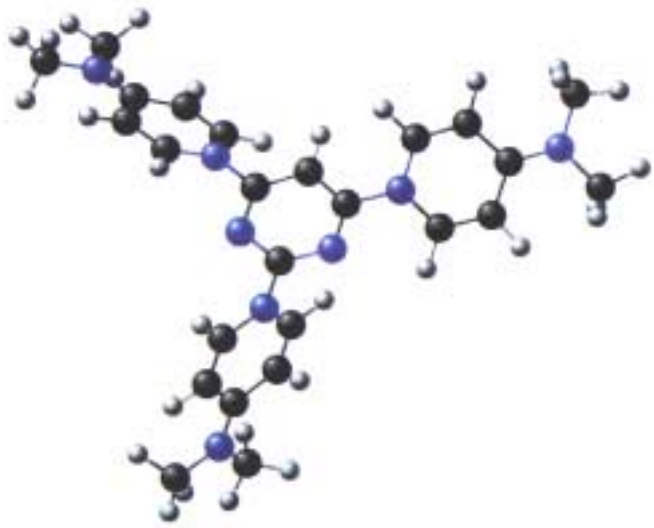


Figure 1

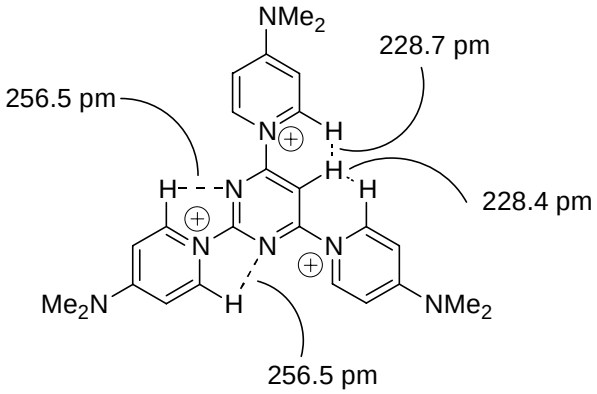


Figure 2

The electrospray ionization MS spectra (ESIMS) of **7** (M = 443.57 amu) sprayed from dry acetonitrile clearly show the peaks of the threefold positively charged species at *m/z* = $M^{3+}/3$ = 147.85 amu (Figure 3). The base peak at *m/z* = 1081.59 amu corresponds to the adduct of the trication (**7**) with two tetraphenylborate anions. The peak at *m/z* = 337.18 amu is due to substitution of one pyridinium ring by water, yielding a monocationic molecule (**13**). Likewise, substitution by chloride to **14** results in a peak of a monocationic tetraphenylborate adduct at *m/z* = 675.31 amu. Compound (**7**) is not suited for fast atom bombardement mass spectrometry (FABMS).

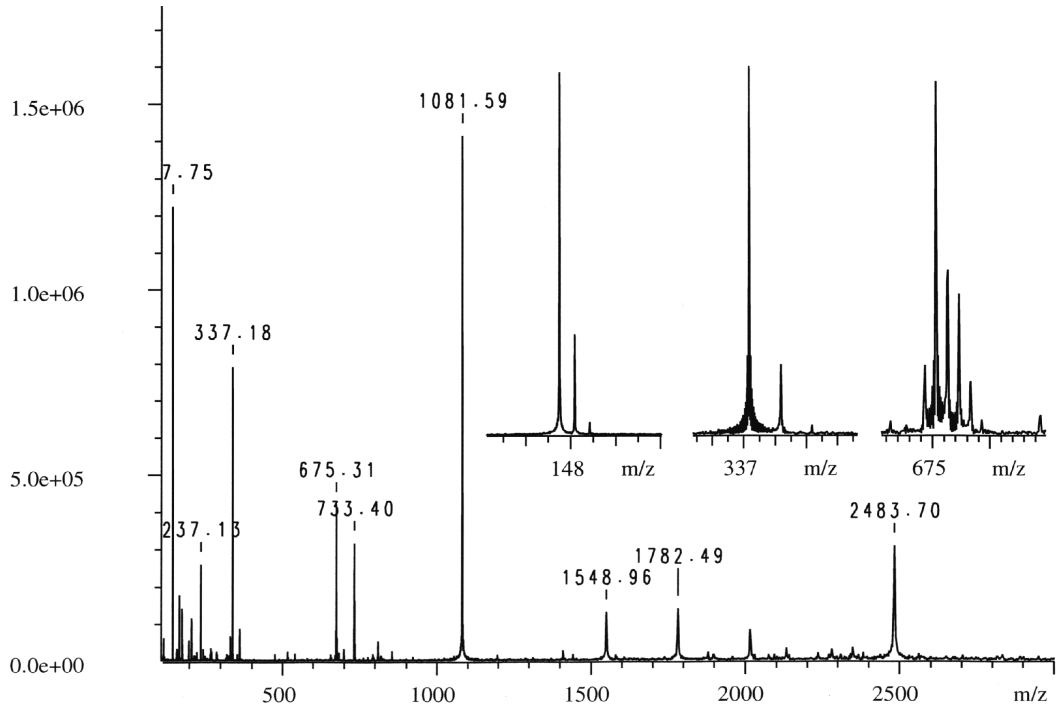
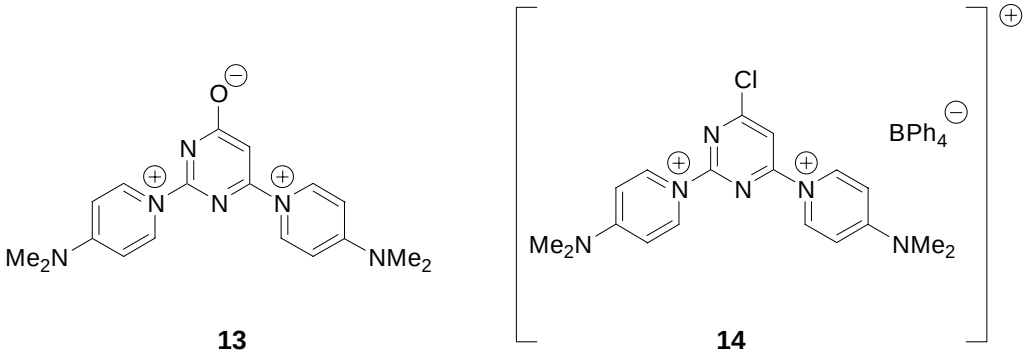


Figure 3



13

M^+ = 337.18 u

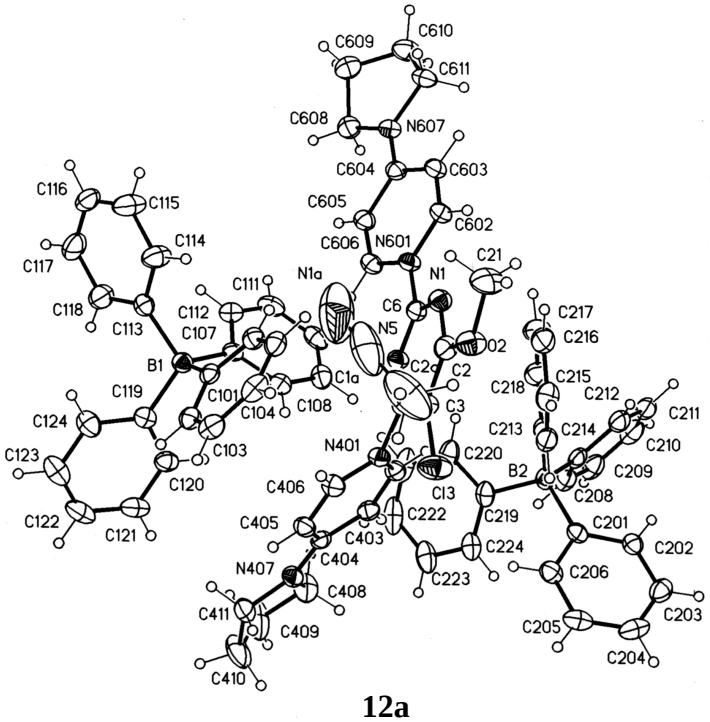
m/z = 337.18

14

$[M^{2+} + BPh_4^-]^+$ = 675.31 u

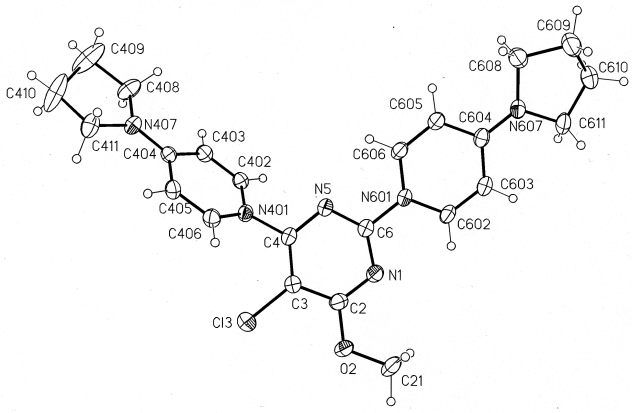
Scheme 3

Monoclinic single crystals of the 1,1´-(5-chloro-6-methoxypyrimidin-2,4-diyl)-bis-[4-(pyrrolidin-1-yl)pyridinium]-bis(tetraphenylborate) (**12a**) were obtained by slow evaporation of a concentrated solution in acetonitrile, so that we were able to perform an X-Ray single crystal structure analysis.[14] The ORTEP-plot and the elemental cell are presented in Figures 4, 5 (**12a** without anions), and 6, respectively. In the elemental cell, the molecule adopts a nonplanar conformation with the pyridinium substituents and the methoxy group twisted from the central pyrimidine plane. Similar to the predicted results of the semiempirical calculation on **7** the torsion angle of the C(2)-bound pyridinium is much smaller than the corresponding angle of the C(4)-bound ring. The two C-N^+ bonds that join the pyridinium rings to the central pyrimidine core of the molecule are shortened. They are σ-bonds with considerable π-contributions. Correspondingly, the pyridinium rings have short C(α)-C(β) and long C(β)-C(γ) bond lengths which hint at considerable quinoidal characters. The molecule crystallized with one molecule of acetonitrile which is shown in Figure 4 without numbering. Some representative angles and bond lengths are given in Table 2.



12a

Figure 4



12a

Figure 5

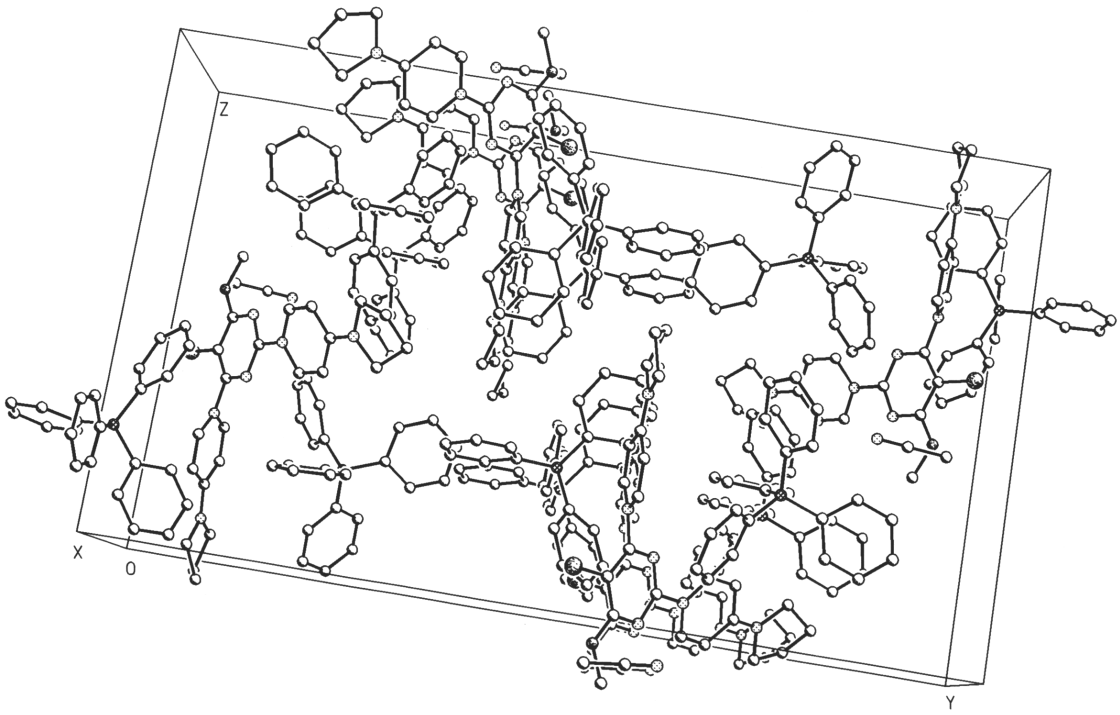


Figure 6

Table 2. Selected results of the X-Ray analysis of **12a**. Crystallographic numbering.

Dihedral angles		Bond lengths [pm]			
N(5)-C(6)-N(601)-C(606)	19.82(16)°	C(4)-N(401)	143.00(14)	N(401)-C(402)	136.81(15)
N(5)-C(4)-N(401)-C(402)	49.50(15)°	C(6)-N(601)	141.88(15)	C(402)-C(403)	134.35(16)
N(1)-C(2)-O(2)-C(21)	4.96(18)°	C(2)-O(2)	132.43(15)	C(403)-C(404)	142.75(16)
C(6)-N(1)-C(2)-C(3)	-1.09(18)°	C(3)-Cl(3)	171.26(13)	C(404)-N(407)	132.33(14)
N(1)-C(2)-C(3)-C(4)	0.19(19)°	N(1)-C(2)	131.99(16)	N(601)-C(606)	137.36(15)
Cl(3)-C(3)-C(4)-N(5)	-177.53(10)°	C(2)-C(3)	141.31(17)	C(605)-C(606)	134.11(17)
N(5)-C(4)-N(401)-C(406)	-118.30(12)°	C(3)-C(4)	136.88(17)	C(604)-C(605)	142.66(16)
N(1)-C(6)-N(601)-C(606)	-158.56(11)°	C(4)-N(5)	133.47(15)	C(604)-N(607)	131.88(16)
C(403)-C(404)-N(407)-C(408)	-2.07(18)°	N(5)-C(6)	131.96(14)	C(21)-O(2)	145.57(15)

Fast atom bombardement MS spectrometry (FABMS) is a suited method for the detection of dicationic species.[17] Thus, **12b** (M = 400.2 amu) gives a peak at *m/z* = $M^{2+}/2$ = 200.1 amu. Other peaks are characteristic for FABMS measurements in 3-nitrobenzyl alcohol (*m*-NBA) which prevents reductions by electrons present in the matrix.[17] *m*-NBA serves as electron scavenger and converts radicals back into the original materials.[18] Thus, the molecular mass of the radical cation $M^{2+} + e^- = M^{+\bullet}$ is detectable at *m/z* = 400.2 amu. In addition, a characteristic hydride adduct $M^{2+} + H^-$ at *m/z* = 401.2 amu is detectable. Adducts which result from fragmentation of the matrix such as nitrite are characteristic for FABMS spectrometry. Correspondingly, **12b** gives a characteristic peak of the monocationic species $[M^{2+} + NO_2^-]^+$ at *m/z* = 446.1 amu. In addition, loss of ethene and DMAP from **12b** gives peaks at *m/z* = 371.1 amu and 278.1 amu, respectively.

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11. Semiempirical calculations were carried out using MOPAC 6.0[12,13] on a IBM workstation RS/6000, AIX 3.4 to perform the AM1 calculations. The structures were first optimized with the default gradient requirements and subsequently refined with the options EF DMAX = 0.05, GNORM = 0.1, SCFCRT = 1×10^{-15}. The absolute minima were proved by a force calculation. The option CHARGE = +3 was used.
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14. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-176968. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk). Some crystal data of **12a**: $C_{22}H_{25}N_6OCl$ - 2 $B(C_6H_5)_4$ - MeCN; M = 1118.43; space group $P2_1/n$ (no. 14); dimensions 0.60 x 0.35 x 0.35 mm^3, a = 10.0059(3), b = 32.4566(10), c = 18.8193(4) Å; β = 94.561(2) ° ; V = 6092.4(3) $Å^3$, D_c = 1.219 MG m^{-3}, Z = 4, μ(MoKα) = 0.115 mm^{-1}; T = 123(2) K; F(000) = 2368, 64249 reflections were collected in a Nonius KappaCD diffractometer ($2\Theta_{max.}$ = 56.4 ° , -13 < h < 13, -42 < k < 42, -22 < l < 23), 13859 symmetry independent reflections (R_{int} = 0.0462) were used for the structure solution (direct methods)[15] and refinement (full-matrix least-squares on F^2,[16] 758 parameters), non-hydrogen atoms were refined anisotropically, H atoms localized by difference electron density, and were

defined using a riding model; wR2 (all data) = 0.0910 [R1 = 0.0384 for 8534 I>2σ(I)].
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