Tetrahedron 65 (2009) 4652–4658

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Polykis(pyrazol-1-yl)benzenes: preparation, structure, and complexation with copper and palladium

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ARTICLE INFO

Article history:
Received 3 February 2009
Received in revised form 22 March 2009
Accepted 9 April 2009
Available online 17 April 2009

Keywords:
Polykis(pyrazol-1-yl)benzenes
Polyfluorobenzenes
Nucleophilic substitution
Regioselectivity
Complexes with transition metals

ABSTRACT

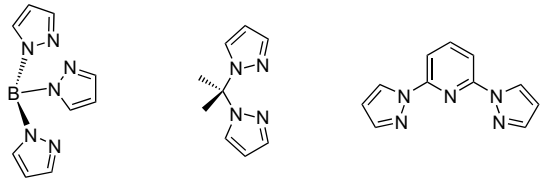
A series of polykis(pyrazol-1-yl)benzenes, potential chelating ligands for transition metals, have been prepared by nucleophilic substitution of fluorine in 1,2-difluoro-, 1,2,3,4-tetrafluoro-, 1,2,4,5-tetrafluoro-, and hexafluorobenzenes. The observed substitution pattern indicated formation of early TS, making activation by fluorines *ortho*- to the site of nucleophilic attack dominant. Complexation of the synthesized ligands with copper(II) and palladium(II) was analyzed by ESI mass spectrometry. X-ray structures were determined for palladium(II) complex with 1,2-bis(pyrazol-1-yl)benzene and copper(II) complex with 1,4-difluoro-2,3-bis(pyrazol-1-yl)benzene, revealing an unusual seven-membered chelate cycle formation.

1. Introduction

Pyrazole-based chelating ligands have attracted significant attention since their first introduction in 1966.[1] Currently, the representatives of this family that hold the most interest are polypyrazolylborates (scorpionates) **1** (Fig. 1),[2] polypyrazolylmethanes **2**,[3,4] and 2,6-bis(pyrazolyl)pyridines **3**.[5]

On the other hand, few groups have researched polykis(pyrazol-1-yl)benzenes, possibly due to difficulties concerning their preparation. To date only two such compounds have been studied (Fig. 2). The Elguero group focused on hexakis(pyrazol-1-yl)benzene (**4**), prepared in high yield by nucleophilic substitution of fluorine in hexafluorobenzene.[6,7] The Hosseini group reported synthesis of 1,2,4,5-tetrakis(pyrazol-1-yl)benzene (**5**) in moderate yield by nucleophilic substitution of bromine in 1,2,4,5-tetrabromobenzene, although no data for this compound were given except the X-ray structure and the formation of an unusual metallocyclophane upon complexation with Cu(II).[8]

In addition, our group has successfully used nucleophilic substitution of fluorine in the preparation of polykis(dialkylamino)benzenes[9] and phosphine ligands,[10] and more recently we have demonstrated the advantage of fluorine nucleophilic substitution over Buchwald–Hartwig C–N cross-coupling in the preparation of 1,2-bis(pyrazol-1-yl)benzene (**6**) (Scheme 1).[11] Taking into account both our own results and those of the aforementioned groups, we decided to develop a general approach to chelating polykis(pyrazol-1-yl)benzenes starting from polyfluoroarenes with a particular fluorine orientation.



1 2 3

Figure 1.

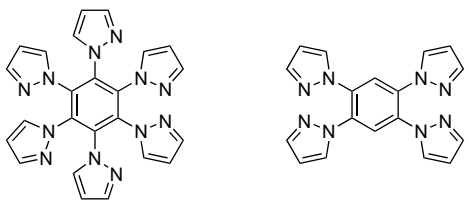


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Figure 2.

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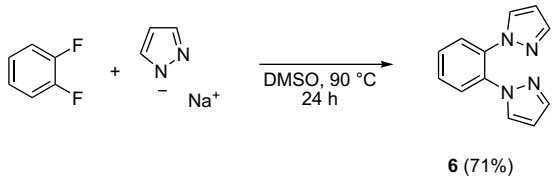
doi:10.1016/j.tet.2009.04.035



6 (71%)

Scheme 1.

2. Results and discussion

2.1. Synthesis and structure

To provide the necessary pyrazol-1-yl groups' arrangement capable of forming chelates with transition metals as starting points for the investigation of nucleophilic substitution of fluorine, we selected commercially available 1,2-difluoro-, 1,2,3,4-tetrafluoro-, 1,2,4,5-tetrafluoro-, and hexafluorobenzenes, the latter case chosen to focus on finding optimal conditions for the isolation of the tetrasubstituted product, since **4** has been well studied previously. Initially, we planned to gradually increase nucleophile strength to avoid any uncontrolled reaction, especially in the case of highly electron-deficient fluoroarenes. Pyrazole should be the least active, followed by 1-(trimethylsilyl)-1*H*-pyrazole. In the latter case, the formation of strong Si–F bonds during the reaction should cause it to demonstrate greater activity in comparison with the pyrazole and excellent selectivity in comparison with the corresponding anion.[12] Finally, sodium pyrazol-1-ide was chosen as the most active compound. 1-(Trimethylsilyl)-1*H*-pyrazole was generated without isolation by reaction of sodium pyrazol-1-ide with chlorotrimethylsilane. However, neither of the aforementioned fluoroaromatics react with pyrazole itself, and only hexafluorobenzene reacts with 1-(trimethylsilyl)-1*H*-pyrazole, leading to a mixture of products after 7 days. Thus, only the results for sodium pyrazolide are further presented.

1,2-Bis(pyrazol-1-yl)benzene (**6**) was prepared for subsequent investigations according to our previous method.[11] We did not succeed in growing crystals of neutral **6** to confirm and study its structure. However, taking into account its basic nature, it looks more promising to prepare a salt of **6** with a strong acid. This was also of interest to determine whether this salt would form a seven-membered intramolecular hydrogen bond between pyridine-type nitrogens of the neighboring pyrazole rings. The X-ray data of 1-(2-(pyrazol-1-yl)phenyl)pyrazol-2-ium perchlorate confirmed the structure of the parent compound. However, greater interest lies in the formation of crystals of the assembly between two protonated molecules (Fig. 3), in which the pyrazolyl groups deviate from the benzene ring by 67° for the group containing protonated nitrogen atom and by nearly 52° for the non-protonated nitrogen. In addition, the intermolecular hydrogen bond formed between the pyridine atoms of different molecules had an N–H length of 0.860 Å and an N···H length of 1.916 Å. Benzene rings in this assembly were located at different sites of the plane, which encompasses atoms involved in hydrogen bonds. It is obvious that the formation of such a pair is more favorable than the more sterically strained and less energetically effective seven-membered intramolecular bond.

To study the influence of solvent polarity on the reaction course, we planned to test the reaction of sodium pyrazolide with 1,2,3,4-tetrafluorobenzene (**7**), 1,2,4,5-tetrafluorobenzene (**8**), and hexafluorobenzene in THF and DMF. DMSO was avoided, despite the success with preparation of **6**, because the mineral oil from NaH dissolves slowly in this solvent, resulting in inconvenience.

The main question that arises before the start of any practical work is the substitution pattern, namely the order in which the fluorine atoms substitute. Previous investigations in related fields, starting with the work of Chambers[13] and including more recent studies,[14,15] have shown the applicability of the empirical rule: the most favorable substitution site should have the greatest number of neighboring *ortho*- and *meta*-fluorines. For example, in the case of 1,2,3,4-tetrafluorobenzene (**7**), the first substitution site is predicted to be F-2, followed by F-3. However, this rule was established and tested using nucleophiles such as SR^-, OR^-, etc., which introduce electron-donating groups to the molecule. In our case, we aim to work with sodium pyrazolide, which introduces the slightly electron-attracting pyrazolyl group to the polyfluoroaromatic molecule. It may have a different influence on the substitution pattern of subsequent pyrazolyls.

The substitution patterns observed experimentally in the reaction of tetrafluorobenzene **7** with sodium pyrazolide, noteworthy, are in agreement with predictions based on empirical rule (Scheme 2). The reaction begins with the substitution of the fluorine atom at position 2, leading to product **9**. Next, the fluorine at position 3 is replaced, despite the fact that it seems sterically unfavorable. The formation of **9**, but not of the isomer with substitution of F-1, is supported by NMR data. For example, the ^{19}F NMR spectra contain only one $^3J_{FF}$ coupling constant near 20 Hz. It is interesting to note that the amounts of **9** and **11** in the reaction mass did not exceed several percent, even if 1 or 3 equiv of nucleophile was used, and the main products are either **10** or **12**. The best conditions for preparation of **10** was the dropwise addition of 2 equiv of a solution of sodium pyrazolide in DMF to a solution of **7** in the same solvent at room temperature. In this case, 76% yield of product can be achieved. If THF is used, good yields within a reasonable time require heating of the reaction mass to 50 °C. This

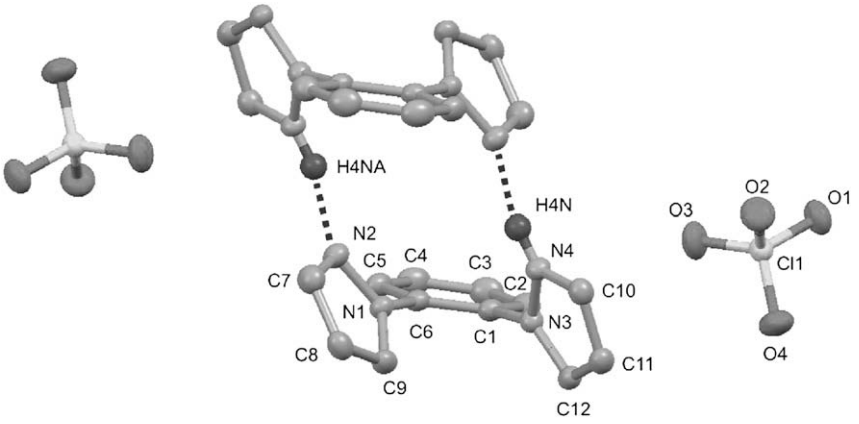
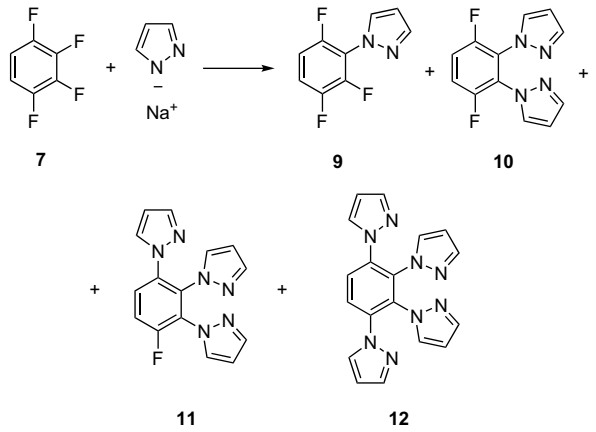
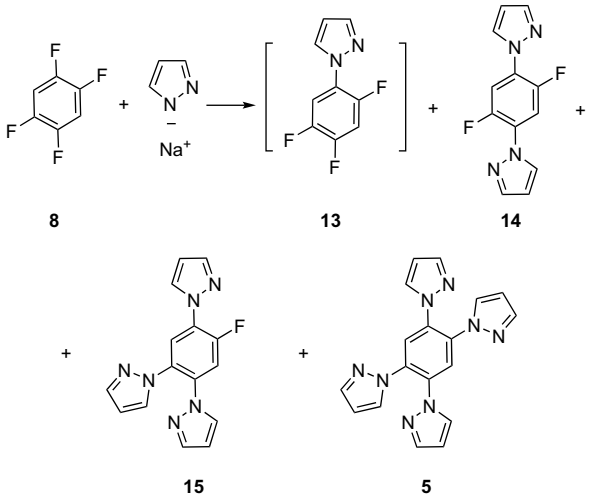


Figure 3. 1-(2-(Pyrazol-1-yl)phenyl)pyrazol-2-ium perchlorate (**6**·$HClO_4$) molecule assembly crystal form, according to X-ray. Hydrogen atoms, with the exception of those involved in intermolecular hydrogen bonding, were omitted for clarity.



Scheme 2.



Scheme 3.

leads to some loss of selectivity and the isolated yield drops to 52%, since **12** is formed as a by-product. On the other hand, the tetrasubstituted derivative **12** can be prepared by the addition of 4 equiv of sodium pyrazolide to **7**, either in DMF or in THF, both at 50 °C, with 94 and 71% isolated yields, respectively.

Unfortunately, we cannot grow suitable crystals of **10** or its salts to verify the substitution pattern with the one established by heteronuclear NMR to check whether this was a case of formation of same assembly, as it was for **6**·$HClO_4$. However, the structure of the fully substituted derivative **12** was determined (Fig. 4).

In crystals of compound **12**, pyrazolyl groups deviate from the plane of the benzene ring, but if less sterically strained pyrazolyl groups at 1 and 4 positions bend at an angle of 35°, more strained rings at positions 2 and 3 deviate by a much greater angle of 73°. In addition, pyridine nitrogens are in turn above–under–above–under the benzene plane, possibly to reduce repulsion of their lone pairs.

The reaction of a nucleophile with 1,2,4,5-tetrafluorobenzene (**8**) proceeds according to Scheme 3. In this case, however, we were not able to detect monosubstituted derivative **13** in the reaction mass. Additionally, the amount of **15** did not exceed 2%, regardless of the conditions used.

Compound **14** is desired as a possible precursor of 'mixed' ligands, containing pyrazolyl groups and other substituents with lone electron pairs capable of forming complexes with metals. However, we found that THF is not a good solvent for the preparation of **14**. The main product obtained in this solvent, irrespective of the amount of nucleophile used, is tetrasubstituted derivative **5**, and the isolated yield of **14** did not exceed 20%. The ^{19}F NMR spectrum of **14** has no F–F coupling, and the ^{13}C spectrum contains signals from 6 carbon atoms. In DMF, we succeeded in reaching greater selectivity toward a disubstituted derivative by dropwise addition of the nucleophile to **8** at rt, obtaining a mixture containing 67% of **14** and 23% of **5**, but the isolated yield of **14** was only 25%. Increasing the temperature increases the conversion but lowers the selectivity toward **14**. For example, at 50 °C, the mixture consists of 45% of **14** and 54% of **5**, but the isolated yield of **14** increased to 36%.

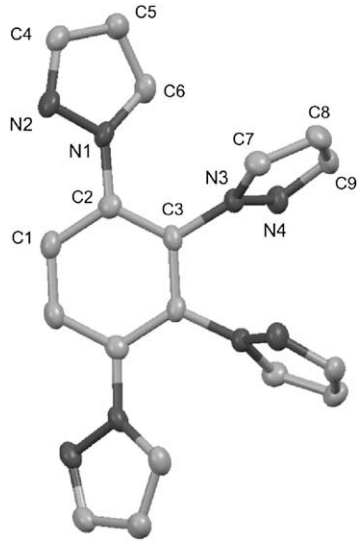
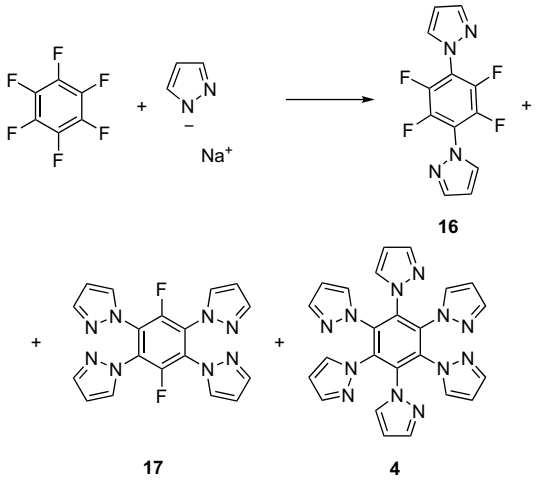


Figure 4. Crystal structure of 1,2,3,4-tetrakis(pyrazol-1-yl)benzene (**12**); hydrogen atoms are omitted for clarity.

Tetrasubstituted derivative **5**, on the other hand, can be prepared with good yields either in THF or in DMF, but in all cases, heating is required to achieve full transformation. For a reaction conducted in THF, the yield was 72%, and in DMF, it increased to 83%. It should be noted that substitution of fluorine is a much more effective method for preparation of **5** compared to substitution of bromine (68% yield) or chlorine (8%) atoms in corresponding 1,2,4,5-tetrahalobenzenes, as done by the Hosseini group.[8]

Hexafluorobenzene was the most electron-deficient fluorocarbon among those used in this work, and its reaction with sodium pyrazolide was expected to be less controllable. Since we were not interested in hexasubstituted derivative **4**, all our attempts were focused on the preparation of tetra- and disubstituted derivatives. Reactions in THF were mostly disappointing since, due to the very low solubility of **4** in this solvent, even if 2 or 4 equiv of nucleophile was used, the reaction resulted in substantial amounts of **4**. For example, the reaction of hexafluorobenzene with 2 equiv of sodium pyrazolide at rt produces a mixture containing 46% of di- (**16**), 4% of tetra- (**17**), and 50% of hexasubstituted (**4**) derivative (Scheme 4); no other products were detected in the reaction mass. The presence of only one singlet in the ^{19}F NMR spectrum of the disubstituted product confirms the formation of **16** and indicates no deviation from the previously observed substitution pattern for other nucleophiles.[9,14,15] Reaction in DMF proceeds more selectively, but in this case we also did not detect any other products besides **16**, **17**, and **4**.

More suitable conditions for preparation of **16** were found to be dropwise addition of 2 equiv of nucleophile to hexafluorobenzene at rt, giving a mixture of **16** (65%), **17** (32%), and **4** (3%), from which the disubstituted derivative can be isolated in 35% yield, along with 18% of **17**. However, to prepare **17**, it was more effective to add 4 equiv of sodium pyrazolide to hexafluorobenzene under the same conditions, which gave a mixture of **17** (79%) and **4** (21%); the isolated yield of tetrasubstituted derivative was then 55%.



Scheme 4.

We were interested in the crystal structure of **17** to compare it with published data for **5** and to observe the influence made by the fluorine atoms. Unfortunately, we only succeeded in growing crystals of the diprotonated salt with perchloric acid. As one can see from Figure 5, intermolecular hydrogen bonds were formed between **17**·2$HClO_4$ and two water molecules, with an N–H bond length of 0.900 Å and an O···H length of 1.733 Å. Formation of such shorter and less hindered bonds with small water molecules may prevent formation of any assemblies between **17**·$2H^+$ fragments. Bend angles of pyrazolyl groups from the benzene ring plane were very close to those observed for **6**·$HClO_4$, near 63° for protonated groups and near 55° for neutrals. It is also interesting that, due to the formation of short contacts between the N4 atom of one molecule and the hydrogen atom bonded to C4 of the other molecule, and possibly also due to the repulsion by the fluorine atom electron shell, we did not observe the nitrogen atom arrangement pattern of above–under–above–under relative to the benzene ring plane, as seen for **12** or reported for **5** by Hosseini.[8]

In conclusion to this section, the agreement between the site of the nucleophile attack, predicted on the base of empirical rule and the experimentally observed pattern should be noted, indicating that the regioselectivity of these processes depends upon the reactivity of the nucleophile and the electrophile, which affects the position of the transition state. For the highly reactive pyrazolide nucleophile and highly reactive perfluoroaromatic electrophiles, an early TS is formed and the regiochemistry is, therefore, dominated by polar effects in the initial states, making activation by fluorine *ortho*- to the site of nucleophilic attack dominant, similar to established by Chambers for other nucleophilic substitution reactions involving polyfluoroaromatics.[14]

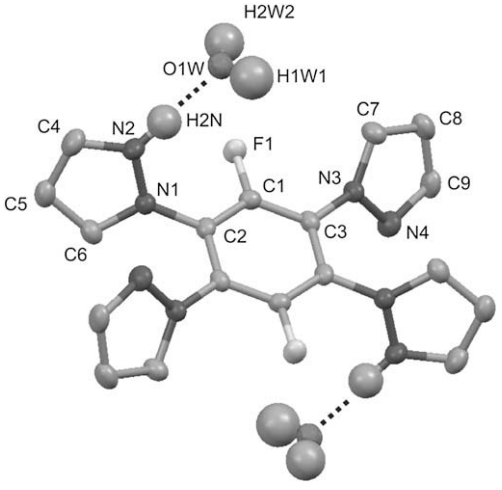


Figure 5. Crystal structure of 1,1′-(2,5-di(1*H*-pyrazol-1-yl)-1,4-phenylene) bis(1*H*-pyrazol-2-ium) diperchlorate (**17**·2$HClO_4$); hydrogen atoms, except those involved in hydrogen bonding and perchlorate anions, are omitted for clarity.

2.2. Complexation with Cu(II) and Pd(II)

Cu(II) and Pd(II) were selected as central ions for studying the complexation ability of synthesized compounds **5**, **6**, **10**, **12**, and **17**. Complexes were prepared from appropriate amounts of $CuCl_2 \cdot 2H_2O$ or $PdCl_2(CH_3CN)_2$ and ligand in methanol for copper or dichloromethane for palladium. The resulting complexes were isolated in the solid state for subsequent investigation. For **6** and **10**, only the 1:1 (metal/ligand) composition was studied; for ligands **5**, **12**, and **17**, the 2:1 ratio was also analyzed to investigate the possibility of forming bidentate complexes. Electrospray ionization mass spectrometry (ESI-MS) was used to elucidate the formation of complexes and their composition. We also intended to utilize NMR spectroscopy to study Pd complexes, but their very low solubility did not permit this.

There are some similarities as well as differences in mass spectra of **6** and **10** copper complexes. First, both spectra showed clear signals corresponding to $[Cu_2L_2Cl_3]^+$ dimeric species (for example, with mass 652 in the case of **6**) as well signals that can be attributed to $[CuL]^+$ ions (for example, with mass 309 for **10**). The latter resulted from the reduction of Cu^{2+} to Cu^+, often observed for copper in ESI-MS.[16] On the other hand, in the mass spectra of **10** complex with copper, in contrast to **6**, signals assigned to $[CuL_2Cl]^+$ and $[CuL_2]^+$ were observed, indicating the tendency of this ligand to form 1:2 species in solution. Formation of dimeric species $[Cu_2L_2Cl_3]^+$ in solution correlates with X-ray data for the crystal of **10** copper complex (Fig. 6), in which two structurally independent dimeric species with bridge chlorine atoms are present.

Another peculiarity of the presented structure is the formation of a seven-membered metallo-ring with Cu1–N2 length of 2.033 Å; Cu1–N4—2.019 Å; Cu1′–N1′—2.008 Å; Cu1′–N4′—1.997 Å; Cu1–Cl1—2.252 Å; Cu1′–Cl1′—2.225 Å; Cu1–Cl2—2.286 and 2.563 Å; Cu1′–Cl2′—2.290 and 2.697 Å. The coordination sphere around the pentacoordinated Cu(II) cation is composed of two nitrogen atoms and three chloride anions, producing a distorted square pyramidal geometry.

Potential bidentate ligands **5** and **17** demonstrate similarities with their monodentate analogs **6** and **10** in complexation with copper when a 1:1 metal/ligand composition was used. In both cases, signals corresponding to $[Cu_2L_2Cl_3]^+$ and $[CuL]^+$ were present in the mass spectra. For **17**, there was an additional signal that can be assigned to the $[CuL_2]^+$ species. Unfortunately, we were not able to

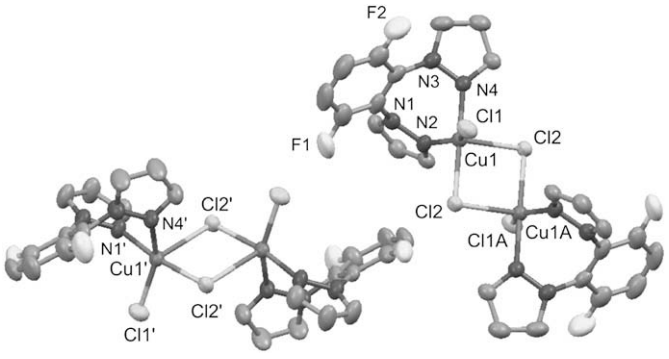


Figure 6. Crystal structure of Cu(II) complex with **10** as ligand. For clarity, most atom labels, except for the coordination sphere, are omitted.

grow suitable crystals to elucidate the type of coordination realized in this case in solid state. However, the presence of $[Cu_2L_2Cl_3]^+$ in solution can indicate the formation of either metallocyclophane type species, as reported by Hosseini,[8] or dimeric species with bridged chlorines, similar to that shown in Figure 6. It is interesting that the copper complex with ligand **12** demonstrated different behaviors in solution. Only one signal, corresponding to the $[CuL]^+$ species, was present in the mass spectrum. This may indicate that steric complications, due in this case to the presence of neighboring pyrazolyl groups, prevent dimeric species from forming. If a 2:1 (copper/ligand) composition was used, the results were not as clear. In all cases in the mass spectra, signals corresponding to the $[CuL]^+$ species were present. Furthermore, in the cases of **10** and **17**, signals that can be attributed to $[Cu_2LCl]^{2+}$ with masses 505 and 541, respectively, were also observed. When **5** was used as the ligand, all signals in the mass spectrum were at noise level, indicating low solubility of the formed complexes, although in this case, a signal corresponding to $[CuL]^+$ was present. As a result, ESI-MS data does not allow definite claims about the formation of 2:1 complexes, and additional investigation using other methods is required.

The mass spectra of all 1:1 palladium complexes contained masses corresponding to $[PdLCl]^+$ and $[Pd_2L_2Cl_3]^+$ species. But also a lot of signals, which we cannot interpret unambiguously, presented, possibly indicating complex interactions of metal and ligand in solution and fragmentations undergone by complexes. On the other hand, X-ray data for crystals grown from the 1:1 complex of Pd(II) and ligand **6** show the formation of a seven-membered metallo-chelate (Fig. 7).

In these crystals, two independent units were present, similar to those observed with copper. Selected parameters are: Pd1–N1—2.010; Pd1–N3—2.013; Pd1–Cl1—2.282; Pd1–Cl2—2.288; Pd2–N5—2.006; Pd2–N7—2.020; Pd2–Cl3—2.269; Pd2–Cl4—2.292 Å; N3–Pd1–Cl1 angle—90.01°; and N1–Pd1–N3—87.48°. The coordination sphere around the tetracoordinated Pd(II) cation is composed of two nitrogen atoms and two chloride anions, giving a distorted square geometry; the angle between plane drawn through Cl1, Pd1, Cl2 and plane N3, Pd1, N3 is 5.79°; in the other unit, it is 5.21°.

If the 2:1 (palladium/ligand) composition was used, potential bidentate ligands **5**, **10**, **12**, and **17** showed similarities in ESI-MS. In all spectra, signals corresponding to $[PdL]^+$ and $[Pd_2L_2Cl_3]^+$ were observed. Furthermore, signals attributed to $[Pd_2LCl_3]^+$ and $[Pd_2LCl_2]^{2+}$ were present, indicating formation of the desired complexes.

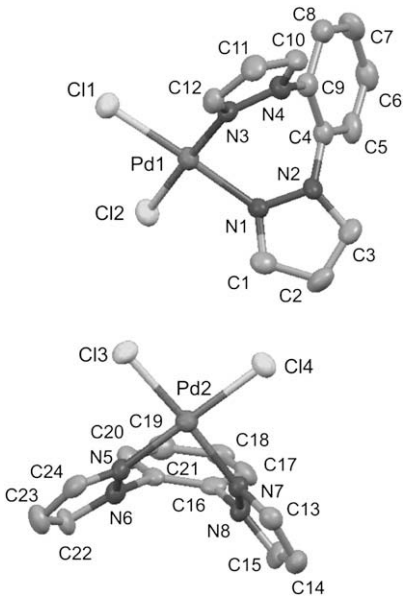


Figure 7. Structure of Pd(II) and ligand **6** 1:1 complex, according to X-ray data. Hydrogen atoms are not shown.

In conclusion, a simple method for the preparation of previously little-known polykis(pyrazol-1-yl)benzenes is presented based on nucleophilic substitution of fluorine in polyfluoroaromatic compounds by sodium pyrazolide. Using this method, a series of potential chelating ligands for transition metals were made, and their complexation abilities toward copper(II) and palladium(II) were demonstrated.

3. Experimental section

3.1. General remarks

Polyfluoroaromatics and 60% suspension of NaH in mineral oil were purchased from Alfa Aesar. THF, DMF, and DMSO were purified and made anhydrous according to literature procedures.[17] NMR spectra were recorded on a Varian Unity-300. ^{1}H NMR and ^{13}C NMR spectra were recorded using Me_4Si as an internal standard. ^{19}F NMR was recorded using $CFCl_3$ as an internal standard. EI mass spectra were recorded on Finnigan Mat. INCOS 50 at 70 eV. ESI-MS spectra were recorded on Finnigan Mat. LSQ-ms; acetone or acetonitrile was used as solvent.

3.2. Nucleophilic substitution of fluorine

3.2.1. General procedure

To a stirred solution of pyrazole (1 mmol) in the selected solvent (5 mL), 1 mmol of 60% suspension of NaH in mineral oil was added (CAUTION! Rapid hydrogen evolution). The reaction mass was stirred for 30 min, and the resulting sodium pyrazolide was added dropwise to a solution of the corresponding amount of a polyfluoroaromatic compound in the same solvent. The resulting solution was stirred for 10 h at the selected temperature and then poured into water. Products were extracted with CH_2Cl_2; the organic phase was dried with Na_2SO_4 and evaporated to dryness. The residue was either crystallized from the appropriate solvent or separated by column chromatography.

*3.2.2. 1,4-Difluoro-2,3-bis(pyrazol-1-yl)benzene (**10**)*

Compound **10** was prepared according to the general procedure using DMF as the solvent and 2 equiv of nucleophile at rt. Yield was 76%, with colorless plates from diethyl ether, mp 133–134 °C; [Found: C, 58.52; H, 3.28; N, 22.78. $C_{12}H_8F_2N_4$ requires: C, 58.54; H, 3.27; N, 22.76%]; ν_{max} (KBr) 3101, 1594, 1529, 1392, 1245, 1043, 837 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.28 (2H, dd, *J* 2.5, 1.9 Hz, *H*-4′ (pyrazolyl)), 7.30 (2H, m, *J* 8.3, 6.1, 4.9 Hz, *H*-5,6), 7.32 (2H, dd, *J* 0.5 Hz, *H*-5′ (pyrazolyl)), 7.60 (2H, dd, *H*-3′ (pyrazolyl)); δ_C (63 MHz, $CDCl_3$) 153.76 (dd, *J* 252.1, 4.2 Hz, *C*-1,4), 141.83 (s, *C*-3′ (pyrazolyl)), 132.15 (s, *C*-5′ (pyrazolyl)), 126.92 (dd, *J* 10.1, 6.7 Hz, *C*-2,3), 117.21 (dd, *J* 17.5, 13.9 Hz, *C*-5,6), 107.37 (s, *C*-4′ (pyrazolyl)); δ_F (272 MHz, $CDCl_3$) −147.65 (dd, *F*-1,3); *m*/*z* (EI) 246 (100, M^+), 245 (84), 218 (41), 206 (21), 165 (26), 139 (19), 112 (26), 52 (29), 39 (22%).

*3.2.3. 1,2,3,4-Tetrakis(pyrazol-1-yl)benzene (**12**)*

Compound **12** was prepared according to the general procedure using DMF as the solvent and 4 equiv of nucleophile at 50 °C. Yield was 94%, with colorless needles from methanol, mp 213–214 °C; [Found: C, 63.10; H, 4.13; N, 32.75. $C_{18}H_{14}N_8$ requires: C, 63.15; H, 4.12; N, 32.73%]; ν_{max} (KBr) 3118, 1606, 1517, 1396, 1195, 1041, 763 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.22 (2H, dd, *J* 2.4, 1.9 Hz, *H*-4″ (2,3-pyrazolyl)), 6.22 (2H, dd, *J* 2.6, 1.8 Hz, *H*-4′ (1,4-pyrazolyl)), 6.76 (2H, dd, *J* 0.5 Hz, *H*-5′ (1,4-pyrazolyl)), 7.29 (2H, dd, *J* 0.6 Hz, *H*-5″ (2,3-pyrazolyl)), 7.55 (2H, dd, *H*-3″ (2,3-pyrazolyl)), 7.63 (2H, dd, *H*-3′ (1,4-pyrazolyl)), 8.17 (2H, s, *H*-5,6); δ_C (63 MHz, $CDCl_3$) 141.58 (s, *C*-3′ (1,4-pyrazolyl)), 141.38 (s, *C*-3″ (2,3-pyrazolyl)), 136.85 (s, *C*-1,4), 132.47 (s, *C*-5′ (1,4-pyrazolyl)), 131.22 (s, *C*-2,3), 129.79 (s, *C*-5,6),

126.61 (s, *C*-5″ (2,3-pyrazolyl)), 108.05 (s, *C*-4″ (2,3-pyrazolyl)), 107.38 (s, *C*-4′ (1,4-pyrazolyl)); *m*/*z* (EI) 342 (100, M^+), 341 (88), 314 (13), 246 (13), 207 (13), 180 (18), 168 (23), 103 (23), 79 (34), 64 (41), 57 (44), 52 (73), 44 (76), 39 (61%).

3.2.4. 1,4-Difluoro-2,5-bis(pyrazol-1-yl)benzene (**14**)

Compound **14** was prepared according to the general procedure using DMF as the solvent and 2 equiv of nucleophile at 50 °C. To isolate **14**, the crude reaction mass was separated by column chromatography on alumina using $CHCl_3$/hexanes (2:1) as eluent. Isolated yield was 36%, with colorless crystals from $CHCl_3$, mp 140–141 °C; [Found: C, 58.54; H, 3.26; N, 22.77. $C_{12}H_8F_2N_4$ requires: C, 58.54; H, 3.27; N, 22.76%]; ν_{max} (KBr) 3124, 1633, 1539, 1473, 1402, 1191, 1035, 937, 771 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.49 (2H, dd, *J* 2.5, 1.9 Hz, *H*-4′ (pyrazolyl)), 7.73 (2H, d, *H*-5′ (pyrazolyl)), 7.90 (2H, dd, *J* 9.2, 9.2 Hz, *H*-3,6), 8.07 (2H, br m, *H*-3′ (pyrazolyl)); δ_C (63 MHz, $CDCl_3$) 149.07 (dd, *J* 246.5, 3.7 Hz, *C*-1,4), 141.52 (s, *C*-3′ (pyrazolyl)), 130.83 (dd, *J* 14.9, 8.3 Hz, *C*-3,6), 112.06 (dt, *J* 18.0, 5.4 Hz, *C*-2,5), 108.48 (s, *C*-4′ (pyrazolyl)); δ_F (272 MHz, $CDCl_3$) −128.43 (2F, dd, *F*-1,4); *m*/*z* (EI) 246 (100, M^+), 218 (4), 191 (6), 167 (11), 152 (7), 125 (7%).

3.2.5. 1,2,4,5-Tetrakis(pyrazol-1-yl)benzene (**5**)

Compound **5** was prepared according to the general procedure using DMF as the solvent and 4 equiv of nucleophile at 50 °C. Yield was 83%, with colorless crystals from methanol, mp 204–205 °C; [Found: C, 63.12; H, 4.10; N, 32.74. $C_{18}H_{14}N_8$ requires: C, 63.15; H, 4.12; N, 32.73%]; ν_{max} (KBr) 3101, 1539, 1481, 1407, 1319, 1197, 1047, 777 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.32 (4H, dd, *J* 2.5, 1.8 Hz, *H*-4′ (pyrazolyl)), 7.05 (4H, dd, *J* 0.4 Hz, *H*-5′ (pyrazolyl)), 7.70 (4H, dd, *H*-3′ (pyrazolyl)), 8.09 (2H, s, *H*-3,6); δ_C (63 MHz, $CDCl_3$) 142.01 (s, *C*-3′ (pyrazolyl)), 133.97 (s, *C*-1,2,4,5), 130.68 (s, *C*-5′ (pyrazolyl)), 125.47 (s, *C*-3,6), 108.36 (s, *C*-4′ (pyrazolyl)); *m*/*z* (EI) 342 (100, M^+), 341 (47), 314 (6), 287 (6), 171 (11), 157 (12), 130 (9), 117 (9), 103 (9), 76 (20), 52 (53), 39 (35%).

3.2.6. 1,2,4,5-Tetrafluoro-3,6-bis(pyrazol-1-yl)benzene (**16**)

Compound **16** was prepared according to the general procedure using DMF as the solvent and 2 equiv of nucleophile at rt. To isolate **16**, the crude reaction mass was separated by column chromatography on alumina using $CHCl_3$ as eluent. Isolated yield was 35%, with colorless crystals from methanol, mp 161–162 °C; [Found: C, 51.04; H, 2.16; N, 19.86. $C_{12}H_6F_4N_2$ requires: C, 51.07; H, 2.14; N, 19.85%]; ν_{max} (KBr) 3126, 1540, 1392, 1176, 1087, 987, 775 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.59 (2H, dd, *J* 2.5, 1.9 Hz, *H*-4′ (pyrazolyl)), 7.77 (2H, dd, *J* 0.1 Hz, H-5′ (pyrazolyl)), 7.87 (2H, dd, *H*-3′ (pyrazolyl)); δ_C (63 MHz, $CDCl_3$) 142.82 (s, *C*-3′ (pyrazolyl)), 132.24 (s, *C*-5′ (pyrazolyl)), 108.22 (s, *C*-4′ (pyrazolyl)); δ_F (272 MHz, $CDCl_3$) −170.22 (4F, s); *m*/*z* (EI) 282 (100, M^+), 228 (8), 215 (10), 209 (16), 203 (26), 188 (21), 161 (26), 148 (19), 117 (16), 98 (16), 69 (17), 52 (31), 40 (34%).

3.2.7. 1,4-Difluoro-2,3,5,6-tetrakis(pyrazol-1-yl)benzene (**17**)

Compound **17** was prepared according to the general procedure using DMF as the solvent and 4 equiv of nucleophile at rt. To isolate **17**, the crude reaction mass was separated by column chromatography on alumina, using $CHCl_3$ as eluent. Isolated yield of product was 55%, with colorless crystals from methanol, mp 257–258 °C; [Found: C, 57.13; H, 3.22; N, 29.60. $C_{18}H_{12}F_2N_8$ requires: C, 57.14; H, 3.20; N, 29.62%]; ν_{max} (KBr) 3120, 1633, 1535, 1486, 1396, 1049, 952, 858, 748 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.38 (4H, dd, *J* 2.5, 1.8 Hz, *H*-4′ (pyrazolyl)), 7.47 (4H, dd, *H*-5′ (pyrazolyl)), 7.67 (4H, dd, *H*-3′ (pyrazolyl)); δ_C (63 MHz, $CDCl_3$) 148.00 (dd, *J* 255.3 Hz, *C*-1,4), 142.42 (s, *C*-3′ (pyrazolyl)), 132.24 (s, *C*-5′ (pyrazolyl)), 127.01 (m, *C*-2,3,5,6), 107.95 (s, *C*-4′ (pyrazolyl)); δ_F (272 MHz, $CDCl_3$) −153.74 (2F, s); *m*/*z* (EI) 282, 378 (53, M^+), 243 (6), 216 (8), 189 (12), 175 (13), 162 (12), 150 (12), 124 (12), 112 (13), 100 (14), 94 (26), 79 (31), 69 (19), 52 (100), 39 (74%).

3.3. Preparation of complexes

To prepare the Cu(II) complexes, 1 or 2 equiv of $CuCl_2 \cdot 2H_2O$ solution in methanol (3 mL) was added to a stirred solution of ligand (0.1 mmol) in CH_2Cl_2 (3 mL). The reaction mass was stirred overnight, and the precipitated complex was isolated by filtration, washed with methanol, and dried for subsequent analysis by ESI-MS or crystal growth.

To prepare the Pd(II) complexes, 1 or 2 equiv of $PdCl_2(CH_3CN)_2$ solution in CH_2Cl_2 (3 mL) was added to a stirred solution of ligand (0.1 mmol) in CH_2Cl_2 (3 mL). The reaction mass was stirred overnight, and the precipitated complex was isolated by filtration, washed with CH_2Cl_2, and dried for subsequent analysis by ESI-MS or crystal growth.

3.4. X-ray crystallographic analysis

Crystals of the compounds were grown by slow evaporation of their solutions in methanol (**6**·$HClO_4$, **12**, **17**·$2HClO_4$, and Pd(II) complex of **6**) or CH_2Cl_2 (Cu(II) complex of **10**). The data were collected on a Bruker SMART 1000 CCD diffractometer using Mo Kα radiation. SHELX-97 provided the method of absorption correction, method of solution, and refinement.[18]

3.4.1. Compound **6**·$HClO_4$

$C_{12}H_{11}N_4ClO_4$ *M*=310.70, monoclinic, space group *P*21/*c*, *a*=8.6564(5), *b*=14.3458(9), *c*=10.6481(7) Å, *β*=96.3130(10)°, *V*=1314.29(14) $Å^3$, *Z*=4, *ρ*=1.570 g cm^{-3}, crystal size=0.35×0.30×0.20 mm, *T*=120 K; 13,032 reflections measured, 3125 unique (R_{int}=0.0229), which were used in all calculations, cut-off criterion $I>2\backslash s(I)$, *μ*=0.314 mm^{-1}, the final *R* and *wR*(F^2) were 0.0423, 0.0759 (all data), residual electron density max, min 0.332, −0.441 e $Å^{-3}$.

3.4.2. Compound **12**

$C_{18}H_{14}N_8$ *M*=342.37, monoclinic, space group *C*2/*c*, *a*=20.966(2), *b*=9.0322(13), *c*=9.2325(11) Å, *β*=111.202(4)°, *V*=1630.0(4) $Å^3$, *Z*=4, *ρ*=1.395 g cm^{-3}, crystal size=0.60×0.20×0.15 mm, *T*=100 K; 8179 reflections measured, 1756 unique (R_{int}=0.0607), which were used in all calculations, cut-off criterion $I>2\backslash s(I)$, *μ*=0.091 mm^{-1}, the final *R* and *wR*(F^2) were 0.0664, 0.0971 (all data), residual electron density max, min 0.219, −0.240 e $Å^{-3}$.

3.4.3. Compound **17**·$2HClO_4$

$C_{18}H_{20}N_8Cl_2F_2O_8$ *M*=585.32, triclinic, space group *P*-1, *a*=7.1932(8), *b*=9.4900(11), *c*=9.8025(11) Å, *α*=76.255(2) *β*=70.499(2), *γ*=74.909(2)°, *V*=600.61(12) $Å^3$, *Z*=1, *ρ*=1.618 g cm^{-3}, crystal size=0.35×0.30×0.20 mm, *T*=100 K; 6943 reflections measured, 3412 unique (R_{int}=0.0289), which were used in all calculations, cut-off criterion $I>2\backslash s(I)$, *μ*=0.349 mm^{-1}, the final *R* and *wR*(F^2) were 0.0775, 0.1102 (all data), residual electron density max, min 0.392, −0.353 e $Å^{-3}$.

3.4.4. Cu(II) complex of **10**

$C_{12}H_8N_4Cl_2F_2Cu$ *M*=380.66, monoclinic, space group *P*21/*c*, *a*=15.915(4), *b*=14.063(3), *c*=13.560(3) Å, *β*=106.267(4)°, *V*=2913.4(11) $Å^3$, *Z*=8, *ρ*=1.736 g cm^{-3}, crystal size=0.45×0.30×0.20 mm, *T*=120 K; 28,591 reflections measured, 6939 unique (R_{int}=0.0943), which were used in all calculations, cut-off criterion $I>2\backslash s(I)$, *μ*=1.884 mm^{-1}, the final *R* and *wR*(F^2) were 0.1074, 0.1153 (all data), residual electron density max, min 0.989, −0.494 e $Å^{-3}$.

3.4.5. Pd(II) complex of **6**

$C_{12}H_{10}N_4Cl_2Pd$ *M*=387.54, monoclinic, space group *P*21/*c*, *a*=7.2352(4), *b*=27.9533(16), *c*=13.3461(8) Å, *β*=100.0030(10)°, *V*=2658.2(3) $Å^3$, *Z*=8, *ρ*=1.937 g cm^{-3}, crystal size=0.40×0.25×0.20 mm, *T*=120 K; 24,879 reflections measured, 5741 unique

(R_{int}=0.0711), which were used in all calculations, cut-off criterion $I>2\backslash s(I)$, μ=1.787 mm^{-1}, the final R and $wR(F^2)$ were 0.0819, 0.0756 (all data), residual electron density max, min 1.549, −0.641 e Å^{-3}.

Crystallographic data for the structures in this paper have been deposited in the Cambridge Crystallographic Data Center as a supplementary publication (**6**·$HClO_4$, CCDC 718737; **12**, CCDC 718736; **17**·$2HClO_4$, CCDC 718738; Cu(II) complex of **10**, CCDC 718740 and Pd(II) complex of **6**, CCDC 718739). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB12 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

The authors wish to express their appreciation to Dr. Anatoly Chernyshev and Prof. Valery Ozeryanskii for useful discussion and assistance, and especially to Drs. Muir and Baker from Parallel Quantum Solutions for quantum-mechanical predictions of substitution pattern, not included in this paper.

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