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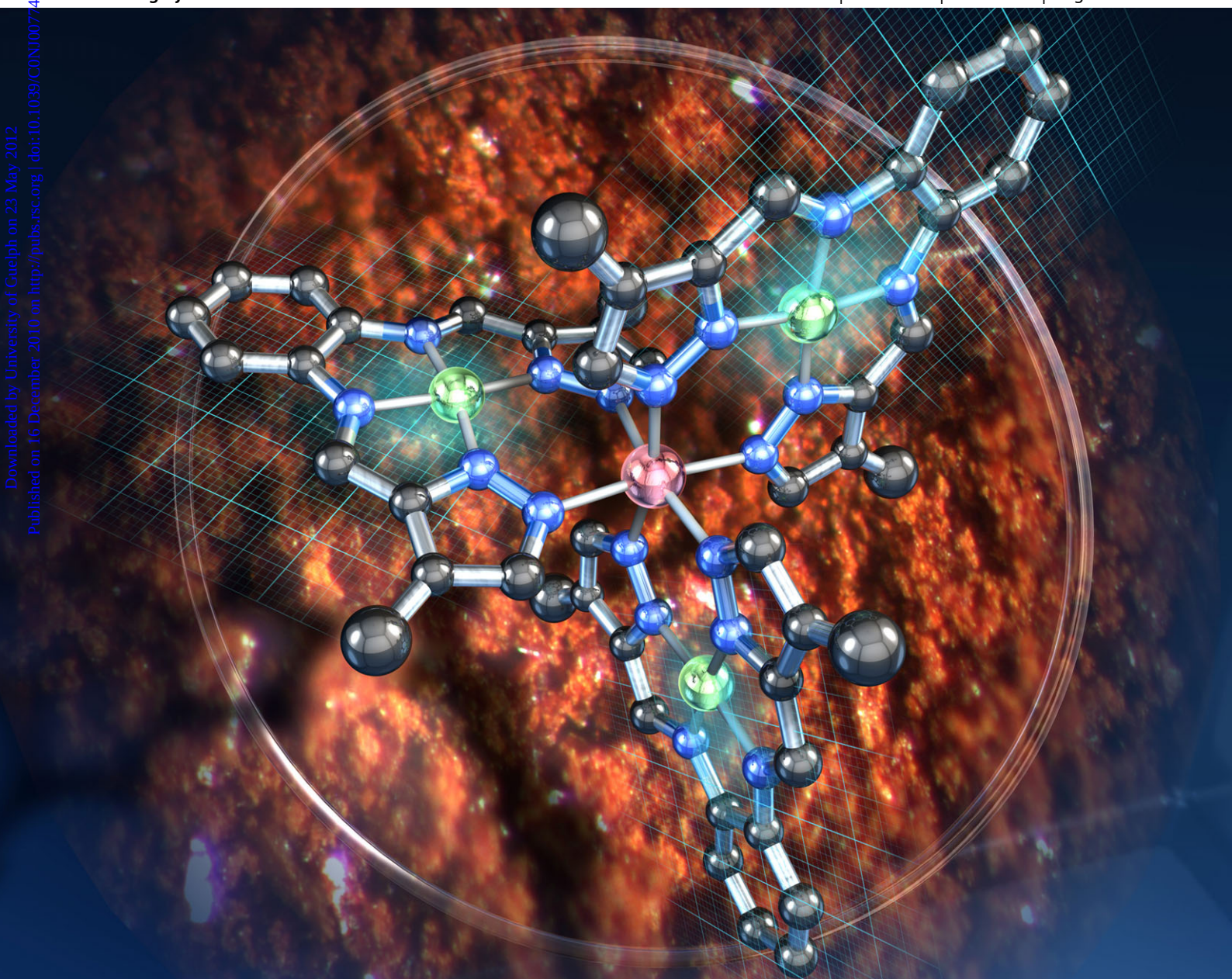

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PAPER

Synthesis of 3- and 5-formyl-4-phenyl-1*H*-pyrazoles: promising head units for the generation of asymmetric imine ligands and mixed metal polynuclear complexes†‡

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Two synthetic methodologies are reported for the generation of 4-phenyl-1*H*-pyrazoles substituted at the 3- and/or 5-positions. Functionalisation of the 4-position of dimethyl-4-iodo-1-(tetrahydropyran-2-yl)-3,5-pyrazolecarboxylate (**10**) to produce dimethyl-4-phenyl-1-(tetrahydropyran-2-yl)-3,5-pyrazolecarboxylate (**14**) was achieved by a C–C Suzuki–Miyaura cross coupling reaction in water. However, low yields for this reaction led us to develop a second methodology wherein functionalisation of *N*-(tetrahydropyran-2-yl)-4-phenylpyrazole (**18**), synthesised from inexpensive phenylacetic acid, with formyl or hydroxymethyl groups was achieved by lithiation methods. The resulting monoaldehydes, 4-phenyl-5-pyrazole carbaldehyde (**20**) and 5-formyl-3-(2′-tetrahydropyranyloxymethyl)-4-phenyl-1-(tetrahydropyran-2-yl)pyrazole (**28**), should facilitate access to new, asymmetric, imine ligands based on a 4-phenyl-1*H*-pyrazole moiety. This was proven by the successful synthesis of the heterometallic tetranuclear complex $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2$·solvents. Likewise, the alcohol isolated en route to **28**, *N*-(tetrahydropyran-2-yl)-5-(hydroxymethyl)-4-phenylpyrazole (**24**), should facilitate access to new, asymmetric, amine ligands.

Introduction

Some iron(II) complexes with an N_6 coordination sphere can be switched between the paramagnetic $(t_{2g})^4(e_g)^2$ high spin (HS) and the diamagnetic $(t_{2g})^6(e_g)^0$ low spin (LS) electronic configurations by means of an external stimulus, such as change in temperature or pressure, light irradiation or applied magnetic field.[1] These spin crossover (SCO) active materials have the potential to be developed for use as molecular switches, data storage, sensors and other nano-devices.[2] Triazole[3] and pyrazole[4,5] are classic examples of ligand systems used for generating SCO-active iron(II) complexes.

Whilst most SCO-active complexes are either polymetallic (polymeric) or monometallic, there is increasing interest in discrete complexes, especially dimetallic,[6] as these can incorporate the best of both worlds. That is to say, bridged metal ions can enhance cooperativity, yet the advantage of being a discrete species that one can hope to fully characterise and understand is retained. Some dinuclear pyrazolate-bridged iron(II) complexes exhibit SCO behaviour.[7] Most of them contain the same *bis-bidentate* 3,5-bis(pyrid-2-yl)-pyrazolate motif.[5] In order to extend the range of pyrazolate ligands employed to generate discrete dimetallic or polymetallic complexes we decided to target new types of imine and amine *bis-terdentate* and *bis-tetradentate* dinucleating ligands. In principle these can be accessed from the 3,5-pyrazoledicarbaldehyde head-unit (Scheme 1).[8,9] This particular head-unit dimerises by intermolecular addition of the NH group to the carbonyl groups,[10] making it highly insoluble in most commonly used organic solvents. This is inconvenient, but the dimer is partially soluble and in solution coexists in equilibrium with the monomer (high temperature and low concentration favour the monomer)[10] so it has been successfully utilised by our group (Scheme 1)[8,9] and others.[11]

With the dual goals of improving the solubility of the dicarbonyl head unit and modifying the properties of the resulting complexes (particularly of iron), we decided to target the introduction of a 4-substitutent into dicarbonyl (e.g. Scheme 1), and related monocarbonyl, head units.

To the best of our knowledge, there is only one example in the literature that deals with functionalization at the 3 and/or 5 positions of a 4-*substituted* pyrazole with either formyl and/or hydroxymethyl groups. Specifically, 3(5)-formylation of 4-methyl-pyrazole was achieved by first protecting the NH,

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† Electronic supplementary information (ESI) available: Details of the crystal structure determination and analysis of the crystal packing of compound **19**. CCDC reference numbers 794574, 794575 and 795288. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0nj00774a

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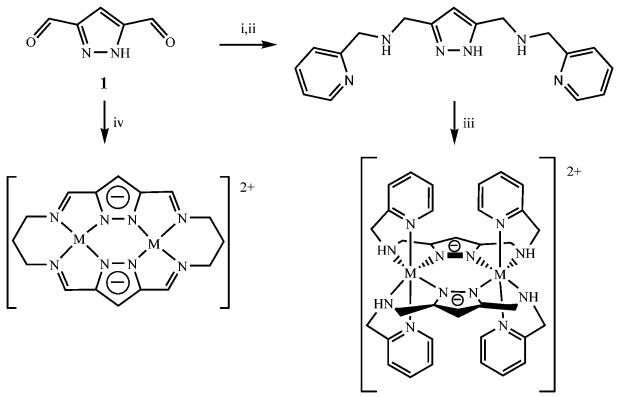
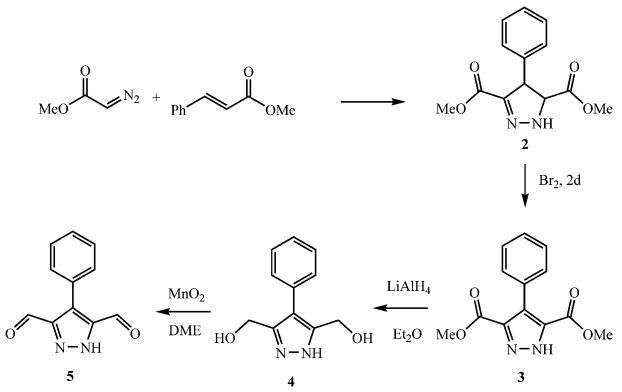


Scheme 1 Synthesis of some dimetallic complexes of amine and imine pyrazolate-based ligands derived from 3,5-pyrazoledicarbaldehyde (**1**). (i) 2 equiv. of 2-(aminomethyl)pyridine in MeOH reflux 1 h; (ii) excess $NaBH_4$, then H_2O and $CHCl_3$ extraction; (iii) $M^{II}X_2$ in MeCN, RT, overnight, where M = Cu, Zn or Ni, and X = BF_4;[9] (iv) 1,3-diaminopropane, $M^{II}X_2$ in isopropanol or MeCN, RT, overnight, where M = Pb and X = ClO_4 or M = Cu and X = BF_4.[8]



Scheme 2 Synthetic route reported by Meyer and co-workers[16] for the synthesis of 4-phenyl substituted diester **3**, dialcohol **4** and dialdehyde **5**.

then treating with *n*BuLi/DMF.[12] The analogous 3-hydroxymethyl compound was obtained by subsequent reduction with $NaBH_4$. Deprotection back to NH was not reported.

An alternative approach is to introduce the 3 and/or 5 formyl and/or hydroxymethyl groups to the 4-*unsubstituted* pyrazole and subsequently introduce the 4-substituent. A number of examples of substitution at the 3- and/or 5-position in the parent *N*-protected-pyrazole ring (4-unsubstituted) have been reported (with a wide variety of 3/5 substituents): all involve lithiation methods.[13,14] McLaughlin and co-workers[15] reported a particularly promising synthetic methodology for such a transformation, in which both the 3- and 5- positions were functionalised with aryl substituents *via* lithiation, and then the 4-position was functionalised with alkyl substituents by means of a Suzuki–Miyaura cross-coupling reaction.

A third option is to prepare two suitably polyfunctionalised molecules that can be brought together to form the pyrazole ring with all of the 3,4,5-substituents already present. During the course of this research, Meyer and co-workers[16] published two synthetic methodologies of this type, one for 4-phenyl- and the other for 4-methyl-substituted 3,5-dicarbonylpyrazoles. To take one of these as an example, 3,5-bis(hydroxymethyl)-4-phenylpyrazole (**4**, Scheme 2) was synthesised in three steps. The first is a dipolar cycloaddition of diazolglycine methyl ester with the methyl ester of cinnamic acid, resulting in pyrazoline **2** (Scheme 2), which was recrystallised from diethyl ether at −30 °C. Oxidation of this pyrazoline diester with bromine affords the pyrazole diester **3** (Scheme 2), before reduction with $LiAlH_4$ gives the pyrazole dialcohol **4** in a good yield (45%) over the three steps. Compound **4** was oxidised to the dialdehyde **5** (Scheme 2) using $MnO_2/CHCl_3$. In the 4-methyl case the diketone, not dialdehyde, was accessed. An advantage of these two protocols is they are relatively short and high yielding. However, they both suffer from the disadvantage that they require the use of toxic and/or potentially explosive reactants, such as Br_2 and diazo compounds.

More recently, Legros and co-workers[17] reported another example of using the pyrazole ring formation approach. They made diester **3** by a catalyst free cycloaddition of methyl phenyl diazoacetate and ethyl propiolate in 60% yield. Again, whilst short, this involves a potentially explosive reactant.

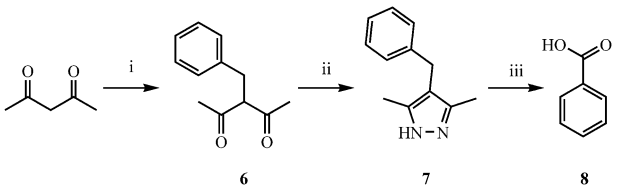
In this paper we present two less hazardous synthetic strategies for the generation of 3,4,5-substituted-1*H*-pyrazoles, in which the 3 and/or 5 substituents are carbonyl or hydroxymethyl groups. One of these methodologies involves a C–C Suzuki–Miyaura cross-coupling reaction between dimethyl-4-iodo-1-(tetrahydropyran-2-yl)-1*H*-pyrazole-3,5-dicarboxylate (**10**) and phenylboronic acid to introduce a 4-phenyl substituent, generating the symmetrical diester **14** (Scheme 4, see later). The second methodology used involves lithiation of *N*-protected 4-phenyl-pyrazoles, **18** and **25** (Scheme 6 and 7, see later), to introduce aldehyde and/or hydroxymethyl functionality, generating the asymmetric monoaldehydes **20** and **28**. Finally, we provide a proof of principle that the asymmetric head unit **20** can be used to generate asymmetric imine ligands that facilitate the assembly of polynuclear complexes, by describing the synthesis and structure of the tetranuclear mixed metal complex $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2 \cdot solvents$ (Scheme 8, see later).

Results and discussion

Synthesis of the monoaldehyde pyrazole-based head units

Ring synthesis with 3,4,5-substituents present. Vogel, Bosnich, Navarro and co-workers[18] reported the multi-step synthesis of 4-*unsubstituted*-3,5-diformylpyrazole **1** (Scheme 1). This involves oxidation of commercially available 3,5-dimethyl-1*H*-pyrazole with $KMnO_4$, to give 3,5-dicarboxylic acid which is converted to the dimethyl ester before being reduced by $LiAlH_4$ to the dihydroxymethyl compound, then oxidised with MnO_2 to the dialdehyde **1**. We wanted to use a similar protocol for the synthesis of 4-*substituted*-3,5-bis(hydroxymethyl)-1*H*-pyrazole.

Hence an appropriately substituted precursor for the pyrazole ring formation reaction, 3-benzylpentane-2,4-dione **6** (Scheme 3), was required. The synthesis of **6** was reported, by McCleverty, Wlodarczyk and co-workers,[19] to occur in 39% yield after fractional distillation under vacuum. In order to improve the yield we used a different protocol, that used for



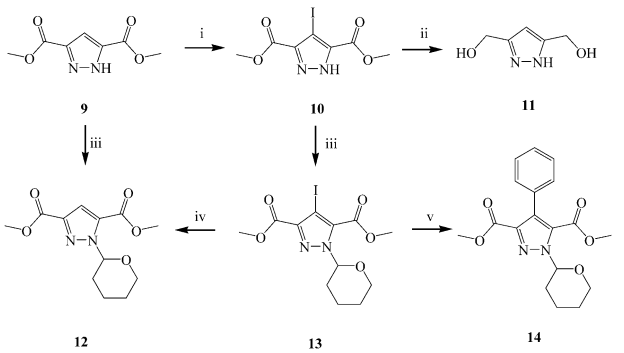
Scheme 3 Synthesis of 4-benzyl-3,5-dimethyl-1*H*-pyrazole (**5**) and the attempted oxidation of the methyl groups to carboxylic acids. (i) Potassium *tert*-butoxide, *tert*-butanol, benzylbromide; (ii) Hydrazine hydrate, ethanol; (iii) $KMnO_4$, water.

the synthesis of the analogous tris-β-diketone 1,3,5-tris-(3′-methyl-2′,4′-pentanedione)-2,4,6-trimethylbenzene.[20] This produced **6** in 51% yield after a simple extraction. Ring cyclisation (condensation) of **6** with hydrazine hydrate in ethanol resulted in 4-benzyl-3,5-dimethyl-1*H*-pyrazole (**7**) in 80% yield, as described in 1994 by McCleverty, Ward, Wlodarczyk and co-workers.[19]

Oxidation of **7** with $KMnO_4$ in boiling water followed by acidification with acetic acid caused a white solid to precipitate. This was identified as benzoic acid (**8**, Scheme 3). Hence use of a milder oxidizing agent, SeO_2, was attempted. A 1 : 1 ratio of SeO_2 to **7** was employed in either dioxane or a pyridine/water mixture (9 : 1), but in both cases starting material was recovered (Scheme 3). This method was therefore abandoned.

4-Substitution of a 3,5-difunctionalised pyrazole. Functionalization of the 4-position of dimethyl-1*H*-3,5-pyrazolecarboxylate (**9**, Scheme 4) was explored next, as this would allow the same subsequent steps as for the preparation of **1** (Scheme 1). Iodination at the 4-position of the *diethyl* ester analogue of **9** was reported by Rodríguez-Franco and co-workers,[21] simply using I_2 and cerium(IV) ammonium nitrate (CAN) in boiling acetonitrile (Scheme 4). While working on this project, Meyer and co-workers[16] described the synthesis of compound **10**, using the same protocol, but no cross coupling reactions were reported by them.

In principle the 4-iodopyrazole derivative **10** (Scheme 4) should allow the synthesis of a wide variety of 4-substituted pyrazoles, an attractive feature of this approach to the target



Scheme 4 Synthesis of dimethyl-4-iodo-3,5-pyrazolecarboxylate (**10**) and conversion to the desired 4-phenyl diester **14**, as well as a summary of the results of other reactions; (i) I_2, CAN, CH_3CN; (ii) $LiAlH_4$, diethyl ether; (iii) (a) HCl/CH_3OH, (b) DHP, CH_2Cl_2; (iv) (a) isopropylmagnesium chloride, THF, 0° C, (b) benzylbromide; (v) phenylboronic acid, Pd(EDTA)Cl_2 (cat), H_2O.

head units. Compound **10** is easily converted to the *N*-protected diester, dimethyl-4-iodo-1-(tetrahydropyran-2-yl)-3,5-pyrazolecarboxylate (**13**, Scheme 4), by reacting **10**·**HCl** with DHP in dichloromethane, as described for the synthesis of the related diester **12**.[11]

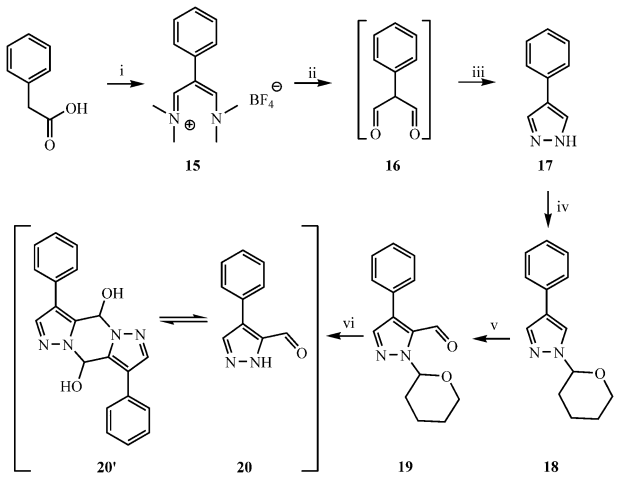
A simple protocol, in water with an air stable Pd(II) catalyst, for Suzuki–Miyaura cross-coupling in pyrazoles has been reported by Korolev and Bumagin.[22] Following this protocol on a modest scale (0.47 g), the Suzuki–Miyaura cross-coupling of the *N*-protected compound **13** and phenylboronic acid gave compound **14** (Scheme 4) in 30% yield after column chromatography work-up. The identity of the product was proven by X-ray crystallography (see below). When this reaction was tried on a bigger scale (1 g) lower yields were obtained (< 10%). This kind of C–C coupling in pyrazole rings has been well documented in the literature[22,23] where the *N*1 position at the pyrazole ring is commonly substituted with a –OBn group and the substituents at the 3(5) position are aliphatic and/or aromatic. The low yield of the present C–C coupling reaction could be due to the presence of the highly deactivating ester groups at the 3 and 5-positions. Hence an attempt was made to reduce the 4-iodo dimethyl ester **10** (with $LiAlH_4$ in diethylether) to the, less deactivated, dihydroxymethyl compound prior to substitution. Unfortunately this resulted in 4-unsubstituted 3,5-bis(hydroxymethyl)-1*H*-pyrazole (**11**, Scheme 4); iodination of **11** was not attempted.

Instead, in an attempt to obtain a 4-substituted pyrazole diester in a better yield **14**, a Grignard reaction was performed. Compound **13** was treated with isopropyl magnesium chloride in THF at 0 °C and quenched with methyl iodide as the electrophile. However, the *N*-protected dimethyl ester **12** (Scheme 4) was obtained: no 4-methyl substituted product was isolated.

The low yields of **14** (20–30% on 0.4 g scale, < 10% on 1 g scale) led us to put aside this method of accessing **5**, however it should be noted that $LiAlH_4$ reduction of **14** followed by oxidation with MnO_2 should generate the desired 4-phenyl-3,5-diformylpyrazole, albeit in very low overall yield.

3(5)-Functionalisation of a 4-substituted pyrazole. Due to the unacceptably low yield of **14** from the above C–C coupling reaction (Scheme 4), our attention turned to a third possible route to the desired compounds: namely functionalisation of a 4-substituted pyrazole at the 3 and/or 5 positions. 4-Phenyl-1*H*-pyrazole (**17**, Scheme 5) was therefore prepared, using a protocol reported for the synthesis of 1,4-bis(pyrazol-4′-yl)-benzene.[24] Under Vilsmeier reaction conditions phenylacetic acid is converted to the intermediate **15** (Scheme 5), which precipitates as a light yellow crystalline material from the 1 : 3 DMF–H_2O solvent mixture when a saturated aqueous solution of $NaBF_4$ is added. Basic hydrolysis of **15** produces the unstable intermediate **16** (Scheme 5) which is, in a one pot reaction, acidified to pH 5 and condensed with hydrazine hydrate, to give the desired compound **17** in moderate yield.

In order to functionalize the 5-position of the pyrazole ring in **17**, the NH group is first protected. As noted in the previous section, the best pyrazole NH protecting group for this system is tetrahydropyran-2-yl. Therefore compound **17** was protected, according to the protocol described by McLaughlin



Scheme 5 Synthesis of 4-phenylpyrazole (**17**) from phenyl acetic acid, followed by synthesis of 3(5)-formyl-4-phenylpyrazole 18 *via* lithiation methods; (i) $POCl_3$, DMF; (ii) NaOH, water; (iii) $N_2H_4{\cdot}H_2O$; (iv) DHP, TFA (cat), toluene; (v) (a) *n*-BuLi, THF, 0 °C, (b) DMF, (c) aqueous HCl; (vi) HCl/methanol, H_2O.

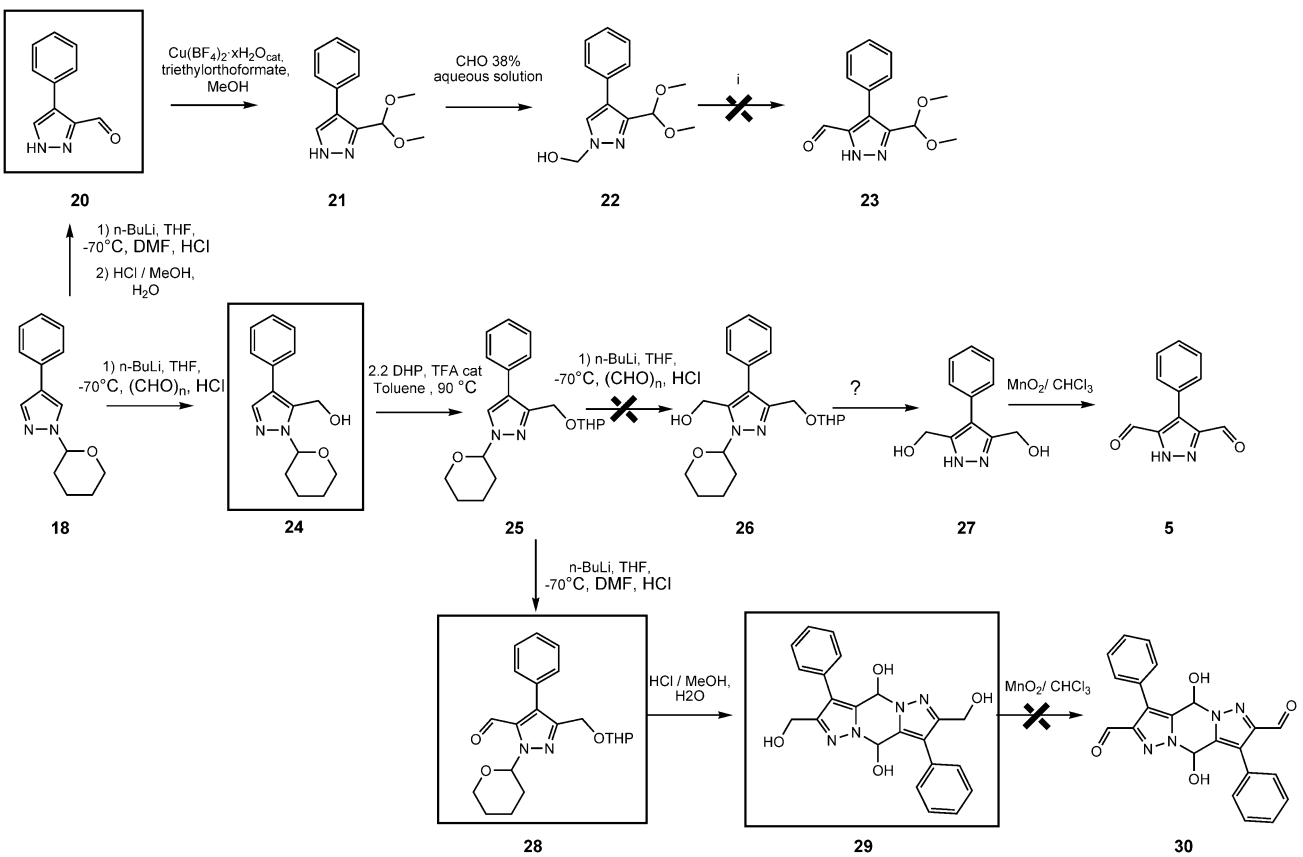
and co-workers,[15] as *N*-(tetrahydropyran-2-yl)-4-phenylpyrazole (**18**, Scheme 5).

The first attempt to introduce formyl groups at the 3 and 5 positions was made by means of lithiation, using 2 equiv. of *n*-BuLi in THF at −70 °C, followed by quenching with 2 equiv. of dry DMF, then hydrolysis with 0.01 M aqueous HCl. Despite the use of 2 equiv. of reagents only the monoaldehyde *N*-(tetrahydropyran-2-yl)-4-phenyl-5-pyrazolecarbaldehyde (**19**, Scheme 5) was obtained in 38% yield after extraction and recrystallisation from ethanol.

Compound **19** can be deprotected by hydrolysis in *ca.* 0.1 M methanolic HCl, followed by the addition of water and then fast removal of the methanol using a rotary evaporator, which causes the precipitation of 4-phenyl-5-pyrazolecarbaldehyde (**20**, Scheme 5), in 67% yield, as a white solid. Formation of the desired 4-substituted monoaldehyde, **20**, in a good yield as a nice white solid *via* a relatively benign method has therefore been achieved.

When the synthesis of **20** was scaled up, a tendency to dimerise, as seen for the unsubstituted dialdehyde **1** (Scheme 1), was observed. Indeed on larger scales (*e.g.* 2 g scale using 250 mL methanol) exclusively the dimer (**20′**, Scheme 5) is obtained. Both the monomer (**20**) and dimer (**20′**) have been characterised.

5-Functionalisation of a 3,4-disubstituted pyrazole. With the successful synthesis of 3(5)-formyl-4-phenylpyrazole **20**, the next challenge was to functionalise the other side of the pyrazole ring of **20** too (Scheme 6). A very well known protecting group for aldehydes is the acetal group. Attempts to protect **20** as 5-(dimethoxymethyl)-4-phenylpyrazole (**21**, Scheme 6), using organic acids such as *p*-toluenesulfonic and trifluoroacetic (TFA) acids in dry methanol, were not successful, with ^{1}H NMR spectra showing that the starting material was recovered. Instead, a rather different protocol described by Kumar and Chakraborti,[25] employing $Cu(BF_4)_2{\cdot}xH_2O$ as a



Scheme 6 Functionalisation at the 3 and/or 5-positions of compound **18**.

catalyst in methanol, was used on **20** to obtain **21** in good yield.

For protection of the pyrazole NH in **21** a hydroxymethyl group was employed rather than a tetrahydropyran-2-yl protecting group, as using TFA in methanol to put the THP group on could lead to hydrolysis of the acetal group. In order to introduce the hydroxylmethyl group, the protocol described by Grotjahn and co-workers[14] was employed. Compound **21** was suspended in THF, an aqueous solution of formaldehyde added and the mixture stirred until a clear solution was obtained. After solvent removal, *N*-(hydroxymethyl)-5-(dimethoxymethyl)-4-phenylpyrazole (**22**, Scheme 6) was obtained as a white solid in good yield (90%).

Doubly protected compound **22** was then treated with two equivalents of *n*-BuLi then DMF, in an attempt to introduce the second formyl group. However, after hydrolysis, a mixture of decomposition products was observed by ^{1}H NMR spectroscopy and there was no sign of the desired aldehyde (**23**, Scheme 6).

Given these difficulties an attempt was made to instead introduce a hydroxymethyl group at the 5-position of the 3,5-*unfunctionalised* pyrazole ring of **18**. Following the procedure described by Grotjahn and co-workers,[14] compound **18** was reacted with one equivalent of *n*-BuLi in THF before adding an excess of paraformaldehyde. After acid hydrolysis, extraction and column work-up *N*-(tetrahydropyran-2-yl)-5-(hydroxymethyl)-4-phenylpyrazole (**24**, Scheme 6) was obtained as a light yellow oil, in moderate yield (53%).

The pyrazole protecting group was then 'switched'[15] to the other nitrogen at the same time as the hydroxyl group was protected, by refluxing compound **24** in toluene in the presence of two equivalents of 3,4-dihydro-2*H*-pyrane. After extraction, the 3,4-substituted compound **25** was isolated in very good yield (95%).

A second lithiation reaction and treatment with paraformaldehyde was attempted on **25**, followed by acid treatment and column chromatography, to try to obtain the 3,4,5-substituted compound **26**. This compound (**26**) could in theory be hydrolysed in acidic methanol to give 3,5-bis-(hydroxymethyl)-4-phenylpyrazole **26**, which is known[16] to be able to be oxidised to **5** using MnO_2 (Scheme 6). However, this attempt to introduce a second hydroxymethyl group to compound **25** did not work.

In contrast, a formyl group could be introduced to the 3,4-substituted compound **25**, forming the desired asymmetric 3,4,5-substituted compound **28**. This was achieved by the same methodology as described above, but using dry DMF as the electrophile instead of paraformaldehyde. After acid treatment and column chromatography, followed by deprotection of the pyrazole ring, the mono-alcohol mono-aldehyde **28** was obtained as a yellow oil in moderate yield. Compound **28** was then deprotected in 0.1 M methanolic HCl to give the dimer **29** in good yield.

Attempts to oxidise dihydroxymethyl compound **29**, by treatment with MnO_2 in dry $CHCl_3$, to give the dialdehyde dimer **30** gave decomposition products (^{1}H NMR spectroscopy).

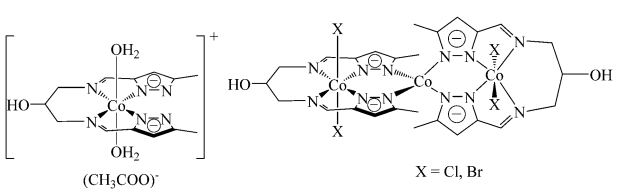
The successful synthesis of the asymmetric *N*-protected aldehyde **28**, and the corresponding *N*-deprotected dimer, **29**, are exciting developments, as this opens the way to new asymmetric polydentate ligands. However our initial focus is firmly on monoaldehyde **20**, which is very readily prepared and also provides access to exciting new asymmetric polydentate ligands.

Synthesis of a heteropolymetallic complex of an asymmetric pyrazole–imine ligand (H_2L^2)

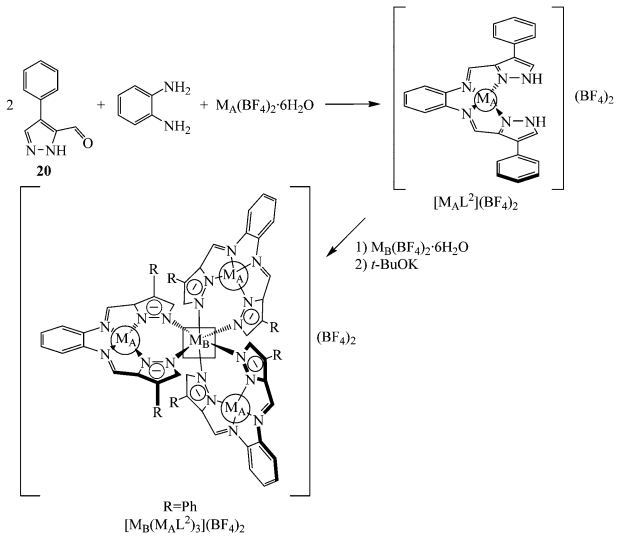
Kar and co-workers[26] showed that the diimine ligand H_2L^1 (Scheme 7), synthesised from the condensation of 2 equiv. of 3-methyl-5-formylpyrazole and one equivalent of 1,3-diamino-2-hydroxypropane, reacts with one equivalent of $Co^{II}(CH_3COO)_2$ to form the mononuclear complex $[Co^{III}(L^1)(H_2O)_2](CH_3COO)$. However when $Co^{II}X_2$ (X = Cl or Br) was reacted with H_2L^1 in the same 1 : 1 metal to ligand ratio the linear mixed valence trinuclear cobalt complex $[Co^{II}(Co^{III}L^1X_2)_2]$ formed, in which two $[Co^{III}(L^1)(X)_2]^-$ complexes have coordinated, *via* the four 'spare' pyrazole groups, to a central tetrahedral cobalt(II) centre (Scheme 7). This suggests that mononuclear complexes such as $[Co^{III}(L^1)(X)_2]^-$ can be used in the synthesis of supramolecular assemblies. However this homometallic trinuclear complex was the only supramolecular system reported with this ligand: no attempts to *intentionally* form other polymetallic, or any mixed metal, complexes were reported.

We decided to intentionally use asymmetric diimine ligands prepared *in situ* from **20** to access mononuclear complexes which could be used as synthons for the self-assembly of star shaped mixed metal tetranuclear complexes in which the central metal centre is coordinated to *three* of the ditopic synthons (Scheme 8). Given our interest in iron(II) SCO-active complexes, the resulting N_6 coordination environment at the 'central' metal ion (M_B) should be ideal for the iron(II) centre. In principle, the choice of metal ion for the 'external' metal ion sites (M_A) can then be used to systematically tune the ligand field experienced by the iron(II) centre, and hence the magnetic properties of the tetranuclear mixed metal complex. Other ways of more substantially tuning the magnetic properties include the use of different diamine linkages (and hence differing ligands) as this should affect the bite angles at the central iron(II) ion. Of course the possibility of examining the properties of iron(II) when it occupies the 'external' sites is also of considerable interest, *i.e.* in our view such systems have considerable potential to generate exciting new complexes. Here we present a 'proof of principle' that a star like mixed metal polymetallic complex can be prepared.

We decided to first try to prepare, in a one pot self-assembly reaction, a complex where the 'external' position is occupied by diamagnetic square planar nickel(II) centres and the 'internal'



Scheme 7 Schematic representation of the mononuclear complex $[Co^{III}(L^1)(H_2O)_2](CH_3COO)$ and mixed valent trinuclear complex $[Co^{II}(Co^{III}L^1X_2)_2]$ synthesised by Kar and co-workers.[26]



Scheme 8 Schematic representation of the synthesised *in situ* mononuclear complex $[Ni^{II}(H_2L)](BF_4)_2$ and the heterometallic tetranuclear complex $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2{\cdot}6H_2O$ synthesised and structurally characterised in this work.

position is occupied by an iron(II) ion. The condensation of 2 equiv. of monoaldehyde **20** with *o*-phenylenediamine should form a tetradentate imine-based ligand (H_2L^2). As aromatic diamines are less reactive than aliphatic diamines, we synthesised this ligand *in situ*, at reflux in a 2 : 1 acetonitrile/methanol mixture, before adding 1 equiv. of $Ni(BF_4)_2{\cdot}6H_2O$. The resulting bright yellow solution was refluxed for 30 min to promote the formation of the mononuclear complex $[Ni(H_2L^2)]^{2+}$. The addition of $\frac{1}{3}$ of an equivalent of $Fe(BF_4)_2{\cdot}6H_2O$ resulted in no change in colour, however on addition of 2 equiv. of solid potassium *tert*-butoxide an orange solution was obtained, which was refluxed for 2 hours. Once the solution had cooled down to room temperature, it was filtered and placed in a diethyl ether vapour diffusion jar. After a few weeks orange crystals suitable for X-ray crystallography were obtained (see below), confirming that the desired star shaped mixed metal tetranuclear complex had formed. A second recrystallisation from 1 : 1 MeCN/MeOH by diethylether vapour diffusion was necessary in order to obtain analytically pure complex. The mixed metal nature of the complex was confirmed by ESI MS. The expected isotopic pattern was observed for the $FeNi_3$ core; this also confirmed that the sample is not a fortuitous 1 : 3 mixture of iron and nickel complexes, but rather that it does have the metal ions localised in the pockets they were intended to occupy.

X-Ray crystallography

The structure of compound **14** was confirmed by X-ray crystallography. Single crystals were obtained by the slow evaporation of an ethanol solution of the compound. It crystallises in the non-centrosymmetric $P2_12_12_1$ space group. The chiral carbon is the one attached to the nitrogen of the pyrazole ring, C(16) (Fig. 1). It was not possible to identify which enantiomer was present in the crystal as it is a light atom structure; however both enantiomers are expected in the bulk

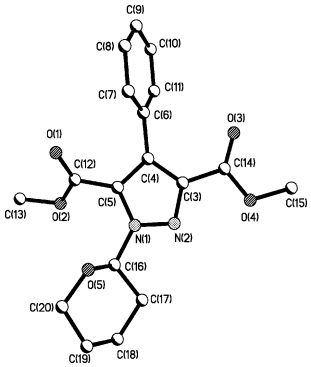


Fig. 1 Ball and stick representation of compound **14**. All hydrogen atoms have been omitted for the sake of clarity.

sample. The asymmetric unit comprises the entire diester **14** (no disorder). As expected, the tetrahydropyranyl (THP) group attached to the $N_{pyrazole}$ adopts a chair conformation. There are no significant interactions within the crystal lattice of this compound.

Single crystals of monoaldehyde **19** were obtained from an ethanol solution and the structure determined. This mono-aldehyde crystallises in the centrosymmetric $P2_1/c$ space group. Once again, the carbon atom in the tetrahydropyranyl group, C(11) (Fig. 2), attached to the nitrogen of the pyrazole ring, is chiral. As it has crystallised in a centrosymmetric space group both enantiomers are present. Once again the THP group adopts a chair conformation.

A detailed analysis of the crystal packing of this compound shows that the molecules stack into supramolecular chains along the *c*-axis due to $\pi\cdots\pi$ and C–H$\cdots$O interactions between neighbouring molecules in the stack (Fig. S2 and S3, ESI†).

The mixed metal tetranuclear complex (Fig. 3) crystallises in the $P\bar{1}$ space group as $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2{\cdot}1.25MeCN{\cdot}1.25MeOH{\cdot}Et_2O$. The asymmetric unit comprises the entire complex (no disorder) as well as a number of disordered solvent molecules of crystallisation (see ESI†). The numbering scheme for this complex is presented in Fig. S1 (ESI†), and a table of selected bond lengths and angles in Table S2 (ESI†).

As anticipated, the nickel(II) centres are located in the 'external' positions of the star shaped complex, and are coordinated to the two imine and two pyrazole N donors of ligand $(L^2)^{2-}$ in a square planar geometry. The average Ni–N bond length is 1.834 Å.

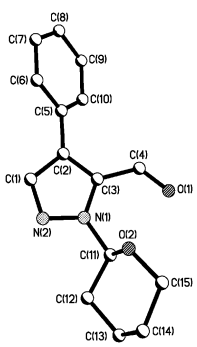


Fig. 2 Ball and stick representation of *N*-protected monoaldehyde **19**. All hydrogen atoms have been omitted for the sake of clarity.

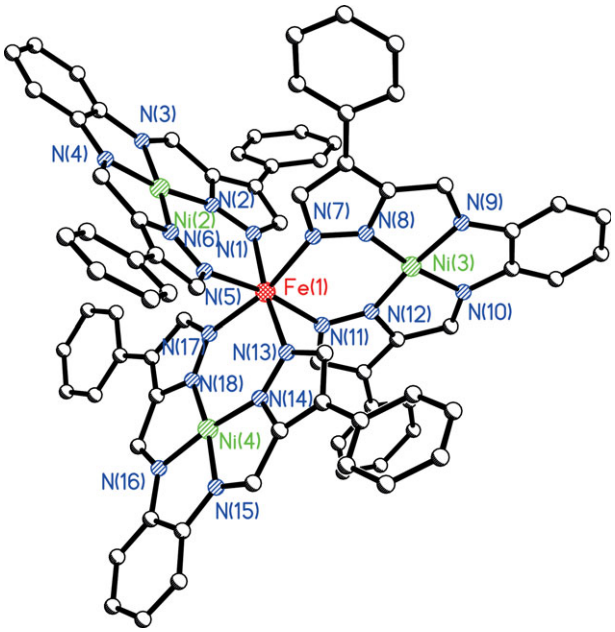


Fig. 3 Ball and stick representation of the cation of complex $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2{\cdot}1.25MeCN{\cdot}1.25MeOH{\cdot}Et_2O$. The solvent molecules and hydrogen atoms have been omitted for the sake of clarity.

The iron(II) centre is in the 'internal' position of the star shaped complex, and is coordinated to three neutral $[NiL^2]$ synthons *via* the 'spare' N donors of the pyrazolate moieties. The Fe(1)–N bond lengths range from 2.119(4) to 2.146(4) Å, with an average of 2.126 Å. This is consistent with the iron(II) centre being in the high spin state at 90 K, the temperature of the data collection. The supramolecular packing of this self-assembled tetranuclear structure creates channels parallel to the *b*-axis, in which the disordered 0.5 occupancy diethyl ether and 0.5 occupancy methanol molecules are accommodated (Fig. 4).

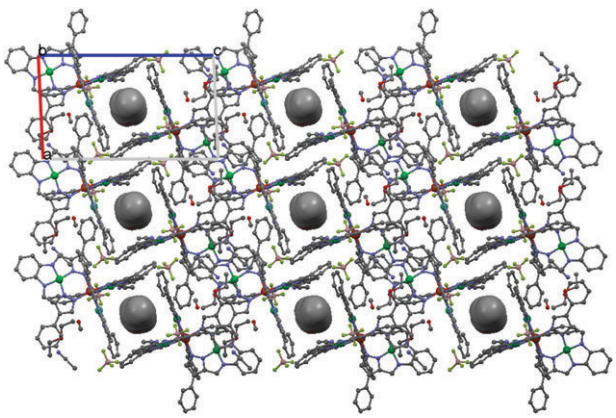


Fig. 4 Crystal packing of $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2{\cdot}1.25MeCN{\cdot}1.25MeOH{\cdot}Et_2O$ viewed down the *b*-axis, highlighting the channels that run parallel to the *b*-axis. The diethylether and methanol molecules that occupy these channels are shown in a space filling representation, whilst the other molecules, including a 0.75 occupancy diethyl ether and methanol molecules, are shown as ball and stick. The hydrogen atoms have been omitted for the sake of clarity.

Conclusion

There are very few experimental protocols available for the generation of symmetrical or asymmetrical 4-substituted-pyrazoles that are also substituted at the 3 and/or 5 positions with hydroxymethyl or carbonyl groups. The reasons for this have become apparent in the course of this work. Nevertheless, the synthesis of the diester **14** has been achieved, by a C–C cross coupling reaction, a safer methodology than that reported by Meyer and co-workers during the course of this work,[16] albeit in a lower yield. As shown by them, compound **14** can be successfully transformed into dialcohol **27** and dialdehyde **5** (Scheme 6) by standard protocols.

More importantly, we show herein that inexpensive 2-phenyl acetic acid can be easily converted to 4-phenylpyrazole **17**, and that after **17** is protected using THP it can be decorated at the 3 and/or 5 positions with hydroxymethyl or formyl groups by lithiation methods. This relatively benign methodology allowed us to generate monoaldehyde **20**, and should also work for other 4-substituted pyrazoles, opening up access to *families* of new asymmetric monoaldehyde head units.

We have gone on to prove that the asymmetric head unit **20** can be used for the synthesis of heterometallic supramolecular assemblies, by generating and structurally characterising the tetranuclear star shaped complex $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2{\cdot}solvents$. The iron(II) in the centre of this complex is in the HS state at 90 K. We are currently focussed on the synthesis and characterisation of a family of such heterometallic complexes, varying the metal ions in the 'internal' and 'external' positions, as these promise to be of both supramolecular and magnetic interest.

Experimental

General

Compounds **7**,[19] **9**,[18] and **10**[21] were synthesized according to the literature. Solvents and reagents (reagent grade) were purchased from commercial suppliers and used without further purification except for THF, which was obtained from a MD6 purification system, and the HPLC grade solvents used in the synthesis of the mixed metal complex. For column chromatography 40– 63 μm grade neutral silica gel was used. Elemental analyses were carried out by the Campbell Microanalytical Laboratory at the University of Otago. Infrared spectra were recorded over the range 4000–400 cm^{-1} with a Perkin–Elmer Spectrum NBX FT-IR spectrophotometer as a potassium bromide pellet or on a Bruker Alpha FT-ATR with an Alpha-P module. ESI mass spectra were recorded on a Bruker MicrOTOF$_Q$ spectrometer by Mr Ian Stewart. ^1H and ^{13}C NMR spectra were recorded on a Varian INOVA-500, INOVA-300, or INOVA-400 NMR spectrometer at 25 °C. ^1H NMR assignments were made from 2D-COSY experiments when necessary. ^{13}C NMR spectra were assigned from gHMBC and gHMQC experiments. X-Ray data (Table S1, ESI†) were collected on a Bruker APEX II area detector diffractometer at the University of Otago using graphite-monochromated MoKα radiation (λ = 0.71073 Å). The data were corrected for Lorentz and polarization effects, and semi-empirical absorption corrections (SCALE) were applied. The structures were solved by

direct methods (SHELXS-97) and refined against all F2 data (SHELXL-97).[27] Hydrogen atoms were inserted at calculated positions and rode on the atoms to which they were attached. All non-hydrogen atoms were made anisotropic except for one 0.5 occupancy methanol and one 0.5 diethyl ether molecule in complex $[Fe(NiL^2)_3](BF_4)_2 \cdot 1.25MeCN \cdot 1.25MeOH \cdot Et_2O$. CCDC 794574, 794575 and 795288 contain the supplementary crystallographic data for this paper.†

3-Benzylpentane-2,4-dione (6)

Acetylacetone (10.0 g, 58.5 mmol) was added to a refluxing solution of potassium *tert*-butoxide (6.56 g, 58.5 mmol) in *tert*-butanol (1 L). Benzyl bromide (5.86 g, 58.5 mmol) was added portionwise over 1 h and the reaction mixture refluxed for a further 1.5 h. The mixture was cooled and filtered, and the filtrate taken to dryness under vacuum. The resulting red-brownish solid was re-dissolved in 100 mL of CH_2Cl_2 and washed with 50 mL of distilled water, the organic phase dried over $MgSO_4$, then the solvent was removed under vacuum. The desired product was isolated in 58% yield (6.50 g, 34.1 mmol) as a light yellow oil. ^{1}H NMR 300 MHz ($CDCl_3$ @ 7.26 ppm): 2.08 (s, CH_3 enol), 2.13 (s, CH_3 keto), 3.15 (d, Ph-CH_2-acac keto), 3.66 (s, Ph-CH_2-acac enol), 4.00 (t, Bn-CH_2-((CO)CH_3)2 keto), 7.13–7.31 (m, *Ph*-CH_2-acac).

Dimethyl-4-iodo-1*H*-pyrazole-3,5-dicarboxylate hydrochloride (10·HCl)

To a solution of dimethyl-4-iodo-1*H*-pyrazole-3,5-dicarboxylate **10** (1.78 g, 5.14 mmol) in 50 mL of methanol, was added 1 mL of concentrated HCl. The solution was stirred for 15 min, then concentrated to approximately 10 mL before 100 mL of diethyl ether was added to precipitate a white solid. This was filtered off and dried under vacuum, resulting in 1.90 g (4.9 mmol, 95% yield) of **10·HCl**. ^{1}H NMR 300 MHz ($CDCl_3$ @ 7.26 ppm); 4.00 (s, 6H, CH_3O(CO)), 5.66 (s (broad), 1H, $N_{pyr}H^+$).

Dimethyl-4-iodo-1-(tetrahydropyran-2-yl)pyrazole-3,5-dicarboxylate (13)

To a suspension of **10·HCl** (2.31 g, 6.05 mmol) in CH_2Cl_2 (100 mL), 3,4-dihydro-2*H*-pyrane (1.02 g, 12.09 mmol) was added dropwise. After stirring overnight the reaction mixture was extracted with a saturated solution of Na_2CO_3 (20 mL). The organic phase was dried over $MgSO_4$ before the solvent was removed *in vacuo*, resulting in **13** as a white solid (2.03 g, 4.33 mmol, 84% yield). Microanalysis (%) calcd. for $C_{12}H_{15}IN_2O_5$ C 27.12, H 2.28, N 9.04; found C 27.14, H 2.38, N 9.06. ^{1}H NMR 400 MHz ($CDCl_3$ @ 7.26 ppm): 1.54–1.72 (m, 3H, 4/5-THP), 2.00–2.15 (m, 2H, 3/4-THP), 2.38–2.50 (m, 1H, 3-THP), 3.68 (m, 1H, 6-THP), 3.93 (overlap with CH_3O(CO), 1H, 4-THP), 3.94 and 3.97 (s each one, 6H, CH_3O(CO)), 6.15 (dd, 1H, 2-THP). ^{13}C NMR 75 MHz ($CDCl_3$ @ 77.36 ppm): 22.12 (3-THP), 24.70 and 29.84 (3/4-THP), 52.44 and 52.62 (CH_3O(CO)), 67.85 (6-THP), 86.90 (2-THP), 137.03 and 143.40 (3/5-Pyr), 159.48 and 159.94 (CH_3O(*C*O)), 161.61 (4-Pyr). IR (ATR) cm^{-1}: 2949 (w), 2861 (w), 1718 (s), 1435 (m), 1417 (m), 1201 (s), 1033 (s), 1020 (s), 916 (m). ESI(+) MS (*m*/*z*) CH_3CN: calcd. for $C_{12}H_{15}IN_2NaO_5^+$ 416.9918, found 416.9922.

Dimethyl-4-phenyl-1-(tetrahydropyran-2-yl)pyrazole-3,5-dicarboxylate (14)

To a suspension of **13** (468 mg, 1 mmol) in water (4 mL) under an Ar atmosphere, potassium carbonate (276 mg, 2 mmol), phenylboronic acid (128 mg, 1.05 mmol) and tetraethyl ammonium bromide (2.00 mg, 1% mol), in that order, were added as solids, and finally 1 mL of a 0.05 M (1% mol) solution of the catalyst, $PdCl_2$–EDTA complex.[22] The reaction mixture was refluxed for 2 h before water (20 mL) was added. The mixture was extracted with $CHCl_3$ (2 × 25 mL), the combined organic phases were filtered through celite, dried over $MgSO_4$ and the solvent removed, resulting in a yellow oily residue. The crude product was purified by a column chromatography (silica gel, column height 10 cm, column width 5 cm, CH_2Cl_2 eluent, Rf = 0.52), giving the product as a yellow solid (103.31 mg, 0.3 mmol, 30% yield). Microanalysis (%) calcd. for $C_{18}H_{20}N_2O_5$ C 62.78, H 5.85, N 8.13; found C 62.30, H 5.94, N 8.17. ^{1}H NMR 300 MHz ($CDCl_3$ @ 7.26 ppm): 1.55–1.78 (m, 3H, 4/5-THP), 2.07–2.14 (m, 2H, 3/4-THP), 2.50–2.60 (m, 1H, 3-THP), 3.62 (s, 3H, CH_3O(CO)), 3.72 (overlap with CH_3O(CO), 1H, 6-THP), 3.77 (s, 3H, CH_3O(CO)), 4.03 (m, 1H, 6-THP), 6.18 (dd, 1H, 2-THP), 7.25 (m, 2H, 2-Ph), 7.37 (m, 3H, 3/4-Ph). ^{13}C NMR 75 MHz ($CDCl_3$ @ 77.36 ppm): 22.51 (5-THP), 24.97 (4-THP), 29.29 (3-THP), 52.14 and 52.26 (CH_3O(CO)), 68.18 (6-THP), 86.46 (2-THP), 127.59 (3-Ph), 127.85 (4-Ph), 129.82 (1-Ph), 129.97 (2-Ph), 131.43 (4-Pyr), 132.27 and 140.57 (3/5-Pyr), 160.37 and 162.20 ($CH_3O(CO)$). IR (ATR) cm^{-1}: 2944 (m), 2920 (m), 2856 (m), 1732 (s), 1469 (m), 1445 (m), 1232 (s), 1173 (m), 1086 (m), 1011 (m), 702 (m). ESI(+) MS (*m*/*z*) CH_3OH: calcd. for $C_{18}H_{20}N_2NaO_5^+$ 367.1264, found 367.1293.

4-Phenyl-1*H*-pyrazole (17)

This method is based on the synthesis of a related compound.[24] To dry DMF (45 mL) cooled in an ice bath, $POCl_3$ (20 mL) was added dropwise over half an hour and then stirred for 1 h at room temperature. Then solid phenyl acetic acid (10 g, 74 mmol) was added in one portion and the solution heated at 85 °C for 3 h. The deep brown reddish solution was cooled down to room temperature before it was poured onto *ca.* 100 mL of ice. The mixture was stirred for 0.5 h, then a saturated solution of $NaBF_4$ (15 g in 10–15 mL of distilled water) was added, precipitating a white yellow solid quantitatively. This was filtered off, washed with ice-cold water (10 mL), and then added to a warm solution of NaOH at 50 °C (6 g in 100 mL of H_2O). The mixture was heated and stirred until all of the solid was dissolved (40 min) before the solution was filtered whilst hot and allowed to cool down to room temperature. The solution was taken to pH = 5 by dropwise addition of a 10% HCl solution until pH = 5 and then 99% hydrazine hydrate (8 mL, 0.26 mol) was added dropwise. The solution was stirred overnight. The next day a white microcrystalline solid was filtered off and dried. It was characterised as microanalytically pure **17** (2.63 g, 45% yield). The mother liquor

was concentrated and left in the fridge overnight, yielding another crop (1.15 g, 12% yield). Total yield 66%. Elemental analysis (%) calcd. for $C_9H_8N_2$ C 74.98, H 5.59, N 19.43; found: C 74.67, H 5.56, N 19.59. ^{1}H NMR 400 MHz (d_6-DMSO @ 2.50 ppm): 7.17 (m, 1H, 4-Ph), 7.34 (m, 2H, 3-Ph), 7.60 (m, 2H, 2-Ph), 7.92 (s broad, 1H, 3/5-Pyr), 8.18 (s broad, 1H, 3/5-pyr), 12.94 (s broad, 1H, $N_{pyr}H$). ^{13}C NMR 75 MHz (d_6-DMSO @ 39.51 ppm): 121.12 (1-Ph), 125.07 (2-Ph), 126.25 (4-Ph), 128.72 (3-Ph), 132.91, 136.13 (3/5/4-Pyr). IR (ATR) cm^{-1}: 3111 (m), 2946 (br), 2746 (br), 1605 (w), 1377 (m), 1033 (m), 948 (m), 878 (m), 826 (s), 755 (s), 688 (s), 505 (s). ESI(+) MS (*m*/*z*) CH_3OH: calcd. for $C_9H_8N_2^+$ 145.0760, found 145.0756.

4-Phenyl-1-(tetrahydropyran-2-yl)pyrazole (18)

4-Phenyl-1*H*-pyrazole (**17**, 2.00 g, 13.8 mmol) was suspended in toluene (50 mL) and a few drops of trifluoroacetic acid added. Then a solution of 3,4-dihydro-2*H*-pyrane (1.16 g, 13.8 mL) in toluene (5 mL) was added dropwise. The mixture was heated to 90 °C for 3 h. After this time the clear yellow solution was allowed to cool to room temperature and then washed with 20 mL of saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting clear yellow oil was dried *in vacuo* resulting in 3.50 g of the desired product as a light yellow waxy material (13.7 mmol, 99% yield). Elemental analysis (%) calcd. for $C_{14}H_{16}N_2O{\cdot}0.5H_2O$ C 70.86, H 7.22, N 11.80; found C 70.51, H 6.96, N 12.08. ^{1}H NMR 400 MHz ($CDCl_3$ @ 7.26 ppm) δ ppm : 1.62–1.75 (m, 3H, H11, 4/5-THP), 2.04–2.18 (m, 3H, H11, 3/4-THP), 3.73 (m, 1H, 6-THP), 4.09 (m, 1H, 6-THP), 5.42 (dd J^{1-2} = 9.2 and J^{1-3} = 3.6 Hz, 1H, 2-THP), 7.23 (t J = 7.2 Hz, 1H, 4-Ph), 7.36 (t J = 7.6 Hz, 2H, 3-Ph), 7.50 (dd J^{1-2} = 8.4 and J^{1-3} = 1.2 Hz, 2H, 2-Ph), 7.84 (s, 1H, 3/5-Pyr), 7.86 (s, 1H, 3/5-Pyr). ^{13}C NMR 75 MHz ($CDCl_3$ @ 77.36 ppm): 22.60 (3-THP), 25.18 and 30.79 (4/5-THP), 68.03 (6-THP), 87.98 (2-THP), 123.71 (1-Ph), 124.69 (3-Pyr), 125.87 (2-Ph), 126.74 (4-Ph), 129.03 (3-Ph), 132.65 and 137.34 (4/5-Pyr). IR (ATR) cm^{-1}: 2933 (m), 2848 (m), 1605 (m), 1562 (m), 1433 (m), 1387 (m), 1288 (w), 1183 (s), 1084 (s), 1046 (s), 953 (m), 909 (m), 754 (s), 689 (s), 507 (s). ESI(+) MS (*m*/*z*) CH_3OH: calcd. for $C_{14}H_{16}N_2ONa^+$ 251.1155, found 251.1143.

5-Formyl-4-phenyl-1-(tetrahydropyran-2-yl)pyrazole (19)

A solution of **18** (3.00 g, 20.0 mmol) in dry THF (250 mL) was cooled down to −70 °C (acetone-dry ice bath). Then *n*-butyllithium (25 mL of a 1.6 M solution in hexanes, 40.0 mmol) was added dropwise over 5 min *via* syringe under nitrogen. The mixture was stirred for 5 min, and then dry DMF (3.11 mL, 40.0 mmol) was added dropwise. The resulting brown solution was stirred at room temperature for 1 h, then 10 mL of a 0.1 N HCl aqueous solution was added and the mixture was stirred for 10 min. The mixture was diluted with water (20 mL) and then extracted with CH_2Cl_2 (100 mL). The aqueous phase was washed with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting brown oily product was redissolved in 50 mL of ethanol, concentrated to half the volume and placed in the fridge. After a few hours **19** was obtained as a colourless crystalline material (1.912 g, 7.50 mmol, 38% yield). Elemental analysis (%) calcd. for $C_9H_8N_2$ C 74.98, H 5.59, N 19.43; found C 74.67, H 5.56, N 19.59. ^{1}H NMR 400 MHz ($CDCl_3$ @ 7.26 ppm) δ ppm: 1.61–1.81 (m, 3H, 4/5-THP), 2.00–2.12 (m, 2H, 3/4-THP), 2.45 (m, 1H, 3-THP), 3.77 (td J^{1-2} = 11.2 and J^{1-3} = 2.4 Hz, 1H, 6-THP), 4.08 (m, 1H, 6-THP), 6.27 (dd J^{1-2} = 10 and J^{1-3} = 2.4 Hz, 1H, 2-THP) 7.42 (m, 5H. Ph), 7.71 (s, 1H, 3-Pyr), 9.86 (s, 1H, Pyr-*CH*O). ^{13}C NMR 75 MHz ($CDCl_3$ @ 77.36 ppm) δ ppm: 22.74 (5-THP), 24.94 (4-THP), 29.50 (3-THP), 68.28 (6-THP), 85.81 (2-THP), 128.31 (4-Ph), 128.86 and 129.41 (2/3-Ph), 130.27 (1-Ph), 132.76 (4-Pyr), 134.29 (5-Pyr), 138.98 (3-Pyr), 180.76 (Pyr-*CH*O). IR (ATR) cm^{-1}: 2940 (m), 2860 (m), 1681 (s), 1464 (m), 1419 (m), 1360 (m), 1210 (m), 1081 (m), 918 (m), 766 (s), 705 (s), 511 (w). ESI(+) MS (*m*/*z*) CH_3CN: calcd. for $C_{14}H_{16}N_2ONa^+$ 251.1155, found 251.1143.

3(5)-Formyl-4-phenyl-1*H*-pyrazole (20)

5-Formyl-4-phenyl-1-(tetrahydropyran-2-yl)pyrazole (**19**, 0.16 g, 0.62 mmol) was suspended in 20 mL of a HCl methanolic solution (10 mL of concentrated HCl in 20 mL of dry MeOH). After 10 min the solid started to dissolve and after the mixture was stirred for 1 h a clear solution was obtained. Water (10 mL) was added before the organic solvent was removed under vacuum, after removal of the organic solvent a white solid precipitated, it was filtered off and washed with water and dried under vacuum, resulting in a white powder (72 mg, 0.42 mmol, 67% yield). Microanalysis (%) calcd. for $C_{10}H_8N_2O{\cdot}0.25H_2O$ C 67.98, H 4.85, N 15.85; found C 67.91, H 4.79, N 16.00. ^{1}H NMR 300 MHz ($CDCl_3$ @ 7.26 ppm): 7.46 (m, 5H, Ph), 7.82 (s, 1H, 3-Pyr), 9.99 (s, 1H, Pyr-*CH*O). IR (ATR) cm^{-1}: 3112 (br), 2836.64 (br), 2964 (br), 1685 (s),1435 (m),1180 (m), 948 (m), 834 (m), 769 (s). The dimer **20′** was synthesised as stated above but using 1.92 g of compound **19**, in 250 mL of methanol and 10 mL of HCl. ^{1}H NMR 400 MHz (d_6-DMSO @ 2.50 ppm): 8.02 (s, 2H, 3-Pyr), 7.98 (d J^{1-2} = 7.2 Hz, 1H, N_{pyr}-*CH* (OH)-C_{Pyr}), 7.73 (m, 2H, H4, 2-Ph), 7.45 (dd J^{1-2} = 10.5 Hz and J^{1-3} = 4.9Hz, 2H, 3-Ph), 7.32 (m, 1H, 4-Ph), 6.75 (d J = 8 Hz, 1H, N_{pyr}-CH(*OH*)-C_{Pyr}). IR (ATR) cm^{-1}: 3112 (br), 1608 (m), 1569 (m), 1492 (m), 1442 (m), 1412 (m), 1368 (m), 1297 (m), 1178 (s), 1127 (m), 1060 (s), 1001 (m), 978, 887 (s), 847, 756 (s), 692 (s), 530 (w), 481 (m), 411 (m).

1-(Hydroxymethyl)-3-(dimethoxymethyl)-4-phenylpyrazole (22)

To **20** (0.500 g, 1.95 mmol) suspended in methanol (50 mL) was added trimethyl orthoformate (0.413 g, 3.9 mmol), followed by solid $Cu(BF_4)_2{\cdot}XH_2O$ (6.5 mg, 0.02 mmol). The suspension was stirred until a clear colourless solution was obtained (approximately 1 h), then the solution was diluted with a saturated solution of $NaHCO_3$ and extracted with $CHCl_3$ (2 × 50 mL). The organic phase was dried over $MgSO_4$ and the solvent removed *in vacuo*. The resulting white powder was then suspended in THF (50 mL) and an aqueous solution of formaldehyde was added (38% w/w, 0.167 g, 1.95 mmol). The suspension was stirred overnight, before the solvent removed *in vacuo*. The resulting white powder was characterised as

compound **22** by ^{1}H NMR spectroscopy and was used without further purification in the next reaction. ^{1}H NMR 300 MHz ($CDCl_3$ @ 7.26 ppm): 3.39 (s, 6H, $(CH_3O)_2$-CH-Pyr), 4.92 (s, 2H, N_{pyr}-CH_2-OH), 5.58 (s, 1H, $(CH_3O)_2$-CH-Pyr), 7.29–7.51 (m, 3H, 3/4-Ph), 7.50 (m, 2H, 2-Ph), 7.70 (s, 1H, 5-Pyr).

5-Hydroxymethyl-4-phenyl-1-(tetrahydropyran-2-yl)pyrazole (24)

Under nitrogen, **18** (5.44 g, 23.84 mmol) was dissolved in dry THF (100 mL), and cooled to −70 °C by means of an acetone-dry ice bath. Then *n*-butyllithium (30.00 mL of a 1.6 M solution in hexanes, 48 mmol) was added dropwise *via* syringe over 5 min and the solution stirred for further 10 min. After this, para-formaldehyde (3.64 g, 121.33 mmol) was added as a solid, at −70 °C, before the mixture was allowed to warm to room temperature, and stirred overnight. Then 20 mL of 1 N HCl was added cautiously and the mixture stirred for 2 h before the addition of 20 mL of water. The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase was dried over $MgSO_4$ and the solvent removed under vacuum, resulting in a black oil. The black oil was re-dissolved in CH_2Cl_2 (100 mL), 4 g of SiO_2 added and the solvent removed *in vacuo*. The adsorbed product was placed at the top of a silica column (10 cm height and 8 cm in diameter) and eluted using a 9 : 1 mixture of petroleum ether/ethylacetate. The desired product (Rf = 0.54 petroleum ether/ethylacetate 1 : 1) is the second fraction collected. After the column and removal of the solvent the product was obtained as a clear yellowish oil in 53% yield (3.28 g, 12.70 mmol). Microanalysis (%) calcd. for $C_{15}H_{18}N_2O_2{\cdot}0.75H_2O$ C 66.28, H 7.23, N 10.31; found C 66.67, H 7.52, N 10.08. ^{1}H NMR 300 MHz ($CDCl_3$ @ 7.26 ppm): 1.67–1.78 (m, 3H, 4/5-THP), 2.17–2.22 (m, 2H, 3/4-THP), 2.42–2.48 (m, 1H, 3-THP), 3.78 (m, 1H, 6-THP), 4.07 (m, 1H, 6-THP), 4.73 (s, 2H, Pyr-CH_2-OH), 5.62 (dd J^{1-2} = 9.3 Hz and J^{1-3} = 2.4 Hz, 1H, 2-THP) 7.43 (m, 5H, Ph), 7.65 (s, 1H, 3-Pyr). ^{13}C NMR 75 MHz (CDCl3 @ 77.36 ppm): 22.46 (5-THP), 25.10 (4-THP), 29.29 (3-THP), 53.65 (Pyr-CH_2-OH), 67.78 (6-THP), 86.13 (2-THP), 123.70 (5-Pyr), 127.09 (4-Ph), 128.49, 128.93 (2/3-Ph), 138.10 (4-Pyr), 138.58 (3-Pyr), 139.4 (1-Ph). ESI(+) MS (*m*/*z*) CH_3CN: calcd. for $C_{15}H_{18}N_2O_2Na^+$ 281.1260, found 281.1234.

3-(2′-Tetrahydropyranyloxymethyl)-4-phenyl-1-(tetrahydropyran-2-yl)-1*H*-pyrazole (25)

5-Hydroxymethyl-4-phenyl-1-(tetrahydropyran-2-yl)pyrazole (**24**, 3.25 g, 12.59 mmol) was dissolved in toluene (150 mL) and few drops of TFA were added before neat 3,4-dihydro-2*H*-pyrane (2.21 g, 26.24 mmol) was added. The mixture was heated at 60 °C for 3 h, but a ^{1}H NMR spectrum showed that the reaction was not complete, so the mixture was refluxed overnight, cooled down to room temperature then washed with a saturated solution of $NaHCO_3$ (100 mL). The organic phase was dried over $MgSO_4$, filtered and the solvent removed *in vacuo* resulting in 4.08 g of **25** as slightly impure brown oil (11.92 mmol, 95% yield) that can be used without purification for the second lithiation step. The product can be purified by column chromatography using SiO_2 as solid support and a mixture of ethylacetate–petroleum ether 9 : 1 as eluent (Rf = 0.50 ethylacetate–petroleum ether 1 : 1). This sample was used for spectroscopic characterisation. Microanalysis for the slightly impure sample (%) calcd. for $C_{20}H_{26}N_2O_3{\cdot}3H_2O{\cdot}2C_7H_8$ C 63.78, H 8.20, N 6.33; found C 63.17, H 7.82, N 5.99. Microanalysis for the pure sample (%) calcd. for $C_{20}H_{26}N_2O_3{\cdot}\frac{1}{2}H_2O$ C 68.35, H 7.74, N 7.97; found C 68.73, H 7.75, N 7.79. ^{1}H NMR 400 MHz ($CDCl_3$ @ 7.26 ppm): 1.57–1.73 (m, 6H, 4-5-*N*-THP and 4-5-*O*-THP), 2.05–2.11 (m, 6H, 3/4-*N*-THP and 3/4-*O*-THP), 3.52 (m, 1H, 3-*N*-THP), 3.72 (m, 1H, 3-*O*-THP), 3.86 (m, 1H, 3-*N*-THP), 4.10 (m, 1H, 3-*O*-THP), 4.55 (dd, J^{1-2} = 11.2 and Hz, J^{1-3} = 4 Hz, 1H, Pyr-CH_2-OTHP), 4.80 (s, 1H, 2-*O*-THP), 4.81 (dd, J^{1-2} = 11.2 and Hz, J^{1-3} = 4 Hz, 1H, Pyr-CH_2-OTHP), 5.40 (m, 1H, 2-*N*-THP), 7.27 (m, 1H, 4-Ph), 7.37 (t, J = 7.6 Hz, 2H, 3-Ph), 7.55 (m, 2H, 2-Ph), 7.73 (s, 1H, 5-Pyr). ^{13}C NMR 75 MHz ($CDCl_3$ @ 77.36 ppm): 19.33 and 19.36 (5-*O*-THP), 22.66 and 22.71 (5-*N*-THP), 25.12 and 25.64 (4-*N*-THP and 4-*O*-THP), 30.60, 30.79 and 30.84 (3-*N*-THP and 3-*O*-THP), 61.86 and 61.98 (5-*N*-THP), 62.02 (Pyr-CH_2-OTHP), 68.14 and 68.16 (6-*O*-THP), 88.00 and 88.03 (2-*N*-THP), 98.10 and 98.13 (2-*O*-THP). 126.46 (5-Pyr), 126.75 (4-Ph), 128.25 (2-Ph), 128.65 (3-Ph), 132.80, 142.12 and 146.51 (4/5-Pyr and 1-Ph). IR (ATR) cm^{-1}: 2940 (m), 2852 (m), 1606 (w), 1543 (w), 1441 (m), 1079 (m), 1038 (s), 1022 (sh), 1008 (s), 763 (s), 699 (s). ESI(+) MS (*m*/*z*) CH_3CN: calcd. for $C_{20}H_{26}N_2O_3Na^+$ 366.1836, found 366.1857.

5-Formyl-3-(2′-tetrahydropyranyloxymethyl)-4-phenyl-1-(tetrahydropyran-2-yl)pyrazole (28)

3-(2′-Tetrahydropyranyloxymethyl)-4-phenyl-1-(tetrahydropyran-2-yl)pyrazole (**25**, 0.77 g, 2.25 mmol) was dissolved in dry THF (125 mL) and the clear solution cooled down to −70 °C by means of an ethanol-dry ice bath, before *n*-butyllithium (2.81 mL of a 1.6 M solution in hexanes, 4.51 mmol) was added dropwise *via* syringe over 2 min, under an argon atmosphere. Still under argon, the yellow solution was stirred at −70 °C for 0.5 h before dry DMF (0.35 mL, 4.51 mmol) was added dropwise *via* syringe. The yellow solution was then stirred under argon for 1.5 h before cautious addition of 0.1 M HCl (10 mL). The mixture was stirred for 1 h, diluted with CH_2Cl_2 (50 mL) and washed with water (20 mL). The organic phase was separated and dried over $MgSO_4$ and the solvent removed under vacuum. The yellow oil was then dissolved in CH_2Cl_2 (20 mL), SiO_2 added (1 g) and the solvent removed under vacuum. Then the adsorbed product was placed at the top of a silica column (5 cm height and 4 cm diameter) and eluted with 10% ethyl acetate in petroleum ether. Compound **28** was isolated as the first fraction (Rf = 0.83 20% ethyl acetate in petroleum ether) as a colourless oil (0.47 g, 1.26 mmol, 56% yield). ^{1}H NMR 400 MHz ($CDCl_3$ @ 7.26 ppm) δ ppm: 1.44–1.81 (m, 6H, 4-5-*N*-THP and 4-5-*O*-THP), 2.00–2.11 (m, 6H, 3/4-*N*-THP and 3/4-*O*-THP), 3.42 (m, 1H, 3-*N*-THP), 3.61 (m, 1H, 3-*O*-THP), 3.69–3.86 (m, 1H, 3-*N*-THP), 4.10 (m, 1H, 3-*O*-THP), 4.46 (dd, J^{1-2} = 27.5 Hz, J^{1-3} = 11.5 Hz, 1H, Pyr-CH_2-OTHP), 4.79–4.63 (m, 2H, 2-*O*-THP and Pyr-CH_2-OTHP), 6.26 (dt, J^{1-2} = 10.3 Hz, J^{1-3} = 2.2 Hz, 1H, 2-*N*-THP), 7.51–7.36 (m, 1H, Ph), 9.69 (s, 1H, Pyr-CHO). ^{13}C NMR 75 MHz ($CDCl_3$ @ 77.36 ppm) δ ppm: 19.16 and

19.08 (5-*O*-THP), 23.02 (5-*N*-THP), 25.16 and 25.62 (4-*N*-THP and 4-*O*-THP), 29.77, 29.81 and 30.51 (3-*N*-THP and 3-*O*-THP), 61.02 and 61.19 (5-*N*-THP), 61.62 and 61.77 (Pyr-CH_2-OTHP), 68.62 (6-*O*-THP), 86.07 (2-*N*-THP), 98.11 and 98.33 (2-*O*-THP). 128.50 and 128.52 (2-Ph), 128.71 (4-Ph), 130.08 and 130.01 (5-pyr) 130.83 and 130.79 (2-Ph), 132.48, 135.81 and 147.79 (3/4-Pyr and 1-Ph), 181.29 (Pyr-*CH*O). ESI(+) MS (*m*/*z*) CH_3CN: calcd. for $C_{21}H_{26}N_2O_4Na^+$ 393.1785, found 393.1814.

3-(Hydroxymethyl)-4-phenyl-5-pyrazolecarbaldehyde dimer (29)

5-Formyl-3-(2′-tetrahydropyranyloxymethyl)-4-phenyl-1-(tetrahydropyran-2-yl)-1*H*-pyrazole (**28**, 0.47 g, 1.25 mmol) was dissolved in a 0.1 M HCl solution in methanol (50 mL). The solution was stirred for 1 h before the solvent was removed *in vacuo*. Water was added (20 mL) to the brown oil residue. The pH of the solution was adjusted to 7 using solid $NaHCO_3$. Then the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL) and $CHCl_3$ (2 × 50 mL). The combined organic phases were dried over $MgSO_4$ before the solvent was removed *in vacuo*. Compound **29** was obtained as a light yellow solid (0.18 g, 0.44 mmol, 70% yield). Microanalysis (%) calcd. for $C_{22}H_{24}N_4O_4{\cdot}0.5H_2O$ C 64.62, H 5.05, N 13.70; found C 64.99, H 5.64, N 13.16. ^{1}H NMR 500 MHz (d_6-DMSO @ 7.26 ppm) δ ppm: 4.44 (m, 4H, Pyr-CH_2-OH), 5.20 (t J = 5.2 Hz, 2H, OH), 5.48 (m, 2H, OH), 6.54 (d, J = 6.9 Hz, 2H, N_{Pyr}-*CH* (OH)-C_{pyr}), 7.47 (m, 4H, 3-Ph), 7.73 (m, 2H, 4-Ph), 7.91 (d J = 7.0 Hz, 4H, 2-Ph). ^{13}C NMR 75 MHz (d_6-DMSO @ 77.36 ppm) δ ppm: 79.61 (Pyr-CH_2-OH), 119.74 (1-Ph), 128.41 (2-Ph), 129.02 (3-Ph), 129.37, 130.21 and 135.19 (3/4/5-Pyr), 150.79 (N_{Pyr}-*CH* (OH)-C_{Pyr}). ESI(+) MS (*m*/*z*) CH_3CN: calcd. for $C_{22}H_{20}N_4O_4Na^+$ 427.1377, found 427.1377.

Complex $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2{\cdot}6H_2O$

To a suspension of 4-phenyl-3(5)formylpyrazole (**20**, 200 mg, 0.780 mmol) in 20 mL of HPLC grade acetonitrile a solution of *o*-phenylenediamine (42.17 mg, 0.39 mmol) in 10 mL of HPLC methanol was added dropwise. The mixture was refluxed for 0.5 h before dropwise addition of 5 mL of a solution of $Ni(BF_4)_2{\cdot}6H_2O$ in HPLC methanol (133.0 mg, 0.39 mmol). The resulting bright yellow solution was refluxed for 0.5 h. Then a solution of $Fe(BF_4)_2{\cdot}6H_2O$ (44.0 mg, 0.13 mmol) in 5 mL of HPLC methanol was added. No colour change was observed. Subsequent addition of solid potassium *tert*-butoxide (87.53 mg, 0.78 mmol) caused an immediate colour change from bright yellow to orange. The solution was refluxed for 2 h before being cooled to room temperature, filtered and placed in a diethyl ether jar. After 2 weeks orange crystals of $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2{\cdot}1.25MeCN{\cdot}1.25MeOH{\cdot}Et_2O$, suitable for X-ray crystallography, were present. The solution was decanted off and the crystals dried under vacuum resulting in an orange solid. According to microanalysis data this product is contaminated with potassium tetrafluoroborate, so it was recrystallised from a 1 : 1 MeOH/MeCN mixture by diethyl ether vapour diffusion to give, after filtration and drying under vacuum, $[Fe^{II}(Ni^{II}L^2)_3](BF_4)_2{\cdot}6H_2O$ as a red solid (44.5 mg, 0.025 mmol, 19% yield). Microanalysis (%) calcd. for $\{Fe[Ni(C_{26}H_{18}N_6)_3\}(BF_4)_2{\cdot}6H_2O$ C 53.32, H 3.79, N 14.35; found C 52.80, H 3.75, N 14.11. IR (ATR) cm^{-1}: 3029 (w), 2919 (w), 1583 (w), 1530 (m), 1310 (s), 1046 (s), 1019 (s), 978 (s), 907 (s), 758 (s) 678 (s), 421 (m). ESI(+) MS (*m*/*z*) MeCN: calcd for $FeNi_3C_{78}H_{56}N_{18}BF_4$ 1563.2360, found 1563.2210.

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