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Novel multitopic diphos-type ligands.

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ABSTRACT

Seven novel imidazole and thiazole derivatives of diphos-type ligands are presented. They are of the general structure $R_2P(CH_2)_2PR_2$, where R is imidazol-2-yl (**1**), 1-methylimidazol-2-yl (**2**), 1-methylbenzimidazol-2-yl (**3**), 1-methylimidazol-5-yl (**4**), 2-isopropylimidazol-4(5)-yl (**5**), thiazol-2-yl (**6**), benzothiazol-2-yl (**7**), thiazol-4-yl (**8**) or thiazol-5-yl (**9**). Syntheses involved direct metallation or halogen–metal exchange reactions. Their solubility, especially in aqueous solution, is strongly dependent on the nature of the substituents as is their partition coefficient log *D*. The crystal structures of compounds **2**, **3**, **7a** and **9** as well as the structure of the rhodium complex $[(\mathbf{2})_2Rh_2Cl_2]Cl_2$ (**10**) have been determined.

1. Introduction

Undoubtedly, diphosphane ligands play a key role in homogenous catalysis. The rare amino acid L-DOPA is synthesised using the rhodium(I) complex [Rh{(*R,R*)-DiPAMP}(cod)]BF_4 of the chiral diphosphane (*R,R*)-DiPAMP for which Knowles received the Nobel price in 2001. Especially the development of chiral diphosphanes such as DIOP, Norphos and Chiraphos or *P*-stereogenic ligands as DiPAMP or BisP* has been pursued due to their abilities to induce high enantioselectivities [1,2]. For the use in biphasic catalysis, water-soluble diphosphanes were developed. Usually these have charged functional groups as carboxylato, sulfonato or phosphonato groups or quaternary ammonium groups. But still, compared to the wide variety of diphosphanes used in catalysis, water-soluble diphosphanes are scarce. Beside the importance of phosphanes in catalysis, phosphane complexes in medicinal chemistry gain more and more attention; For example the Ru(II) complex [(η^6-*p*-cymene)$RuCl_2$(pta)] of the water-soluble pta ligand (pta = 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane) has been reported to exhibit antibacterial activity [3] and the gold(I) complex $[(dppe)_2Au]Cl$ exhibits antitumor activity in different cell lines [4]. For the use in biomedical applications the (di)phosphane ligands and their complexes have to fulfil certain demands. Not only do they need to be water-soluble, but have to exhibit a finely adjusted hydrophilicity/hydrophobicity profile, as this determines both their pharmacokinetic and pharmacodynamics. For example, clinical trials on $[(dppe)_2Au]Cl$ were hampered by high hepato- and cardiotoxicity related to the highly hydrophobic nature of this complex [5,6]. To circumvent the lipophilicity related side effects, more hydrophilic diphos complexes have to be developed and one approach is to replace the phenyl rings of dppe by pyridine [7–11]. We have developed imidazole-based water-soluble phosphane ligands for application as enzyme models and for biomedical applications in the past [12,13]. Based upon our previous findings, we herein report on synthetic routes towards diverse imidazolyl as well as thiazolyl substituted diphosphane ligands, which should exhibit similar properties concerning their use in biological media. To evaluate the new ligands exact hydrophilicity/hydrophobicity profile, their *n*-octanol/water partition coefficients at pH = 7.4 were determined.

2. Results and discussion

Symmetrical diphosphanes of the diphos-type $R_2P(CH_2)_2PR_2$ were prepared by reaction of bis(dichlorophosphino)ethane with nucleophiles. The starting material bis(dichlorophosphino)ethane was prepared from ethylene, phosphorus trichloride and white phosphorus in an steel autoclave according to the high-pressure procedure of Chatt [14]. While it has been reported, that after several runs the autoclave begins to deteriorate [15], we observed corrosion especially of the needle-valves.

Ligands **2** and **6** were synthesised according procedures for tris(*N*-methylimidazol-2-yl)phosphane and tris(thiazol-2-yl)

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phosphane by Moore and Whitesides [16]. For the preparation of **2** bis(dichlorophosphino)ethane was treated with 1-methyl-2-trimethylsilylimidazole. After lithiation of either *N*-methylbenzimidazole or thiazole and the following reaction with bis(dichlorophosphino)ethane ligands **3** and **6**, respectively, were obtained in good yields, whereas the reaction of 2-bromothiazole with *n*-butyl lithium did not yield the desired product.

Ligands **1** and **5** were prepared starting from the corresponding diethoxymethyl-protected imidazoles [17,18], which were lithiated using *n*-butyl lithium and *tert*-butyl lithium respectively. The lithiated species were reacted with bis(dichlorophosphino)ethane to obtain the DEM-protected ligands. Direct deprotection was achieved by refluxing the products in a 10:1 mixture of acetone/water, from which the analytically pure ligands precipitated upon cooling.

For the synthesis of **4**, which is a regioisomer of **2**, a different approach had to be taken. Prior to forming the P–C bonds a halogen–metal exchange was carried out [19]. Therefore, 5-bromo-1-methylimidazole was reacted in dichloromethane with ethyl magnesium bromide and the resulting Grignard component reacted with bis(dichlorophosphino)ethane to give ligand **4**. The three isomeric thiazole ligands **6**, **8** and **9** were prepared in a similar manner. Ligand **6** was prepared by direct lithiation of thiazole, where as ligands **8** and **9** were prepared via metal–halogen exchange of the corresponding 4- and 5-bromothiazole. The benzimidazole ligand **3** and the benzothiazole ligand **7** have been reported previously by Richards and Al-Dulaymmi in the preparation of different metal complexes. However, the syntheses of the ligands were not mentioned and the ligands themselves not characterised [20–22].

Compounds **1**–**9** are potent chelating ligands as can be already seen in the MALDI mass spectra of these ligands. Besides the molecular ion and characteristic fragments, copper complexes are observed. The source of the copper is unknown, but seems to be the probe slit of the mass spectrometer. All ligands were characterised by ^{1}H, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectroscopy (data summarised in Tables 1 and 2). Structural assignments were achieved with the help of a combination of 2D NMR experiments and by comparison of ^{1}H NMR data with those reported previously for analogous phosphanes. The signal of the protons of the ethylene bridge appears as a deceptively simple triplet [21] in the region of 2.1 to 3.1 ppm (Table 1).

The signals of the methylene bridge in the $^{13}C\{^{1}H\}$ NMR spectra are split due to the coupling with the two phosphorous atoms. For each carbon atom a second order system AA'X results. Furthermore, for the CH carbon atoms in the thiazole ring of **6** and the CH carbon atoms in the benzothiazole substituents in **7** assignments of specific signals could not be accomplished on the basis of H,C-COSY, HMBC and HMQC NMR and thus remain ambiguous.

Table 1
$^{31}P\{^{1}H\}$ and ^{1}H chemical shifts (δ/ppm) of diphos-type ligands.

Ligand	R	$\delta(^{31}P\{^{1}H\})$/ppm	$\delta(^{1}H)$/ppm	
			$-C_2H_4-$	Other signals
1	Imidazol-2-yl	−50	2.30	7.22
2	1-Methylimidazol-2-yl	−54	2.62	3.63, 7.12, 7.26
3	1-Methyl-benzimidazol-2-yl	−45	3.09	3.72, 7.16–7.31, 7.63–7.75
4	1-Methylimidazol-5-yl	−73	2.20	7.09, 7.56
5	2-Isopropylimidazol-4(5)-yl	−63	2.03	1.28, 3.04, 7.00
6	Thiazol-2-yl	−20	2.73	7.58, 8.06
7	Benzothiazol-2-yl	−15	3.01	7.30–7.59, 7.78–7.85, 8.02–8.10
8	Thiazol-4-yl	−19	2.64	7.44
9	Thiazol-5-yl	−52	2.15	8.04, 9.01

Table 2
$^{13}C\{^{1}H\}$ chemical shifts (δ/ppm) of diphos-type ligands.

Ligand	R	δ ($^{13}C\{^{1}H\}$)/ppm	
		$-C_2H_4-$	Other signals
1	Imidazol-2-yl	22.6	124.9, 143.1
2	1-Methylimidazol-2-yl	21.7	35.0 (NCH_3), 127.1 (C_5), 129.5 (C_4), 144.1
3	1-Methyl-benzimidazol-2-yl	21.0	29.5, 109.9, 120.5, 122.8, 123.8, 161.3
4	1-Methylimidazol-5-yl	22.4	32.8 (NCH_3), 124.4 (C_2), 137.3 (C_4), 142.3 (C_5)
5	2-Isopropylimidazol-4(5)-yl	28.2	20.5 (CH_3), 48 (CH), 130.1 ($C_{4(5)}$), 153.7 ($C_{5(4)}$), 157.7 (C_2).
6	Thiazol-2-yl	25.7	123.8 ($C_{4/5}$), 145.6 ($C_{4/5}$), 167.9 (C_2)
7	Benzothiazol-2-yl	25.0	121.8, 124.0, 126.0, 126.5, 137.3, 155.0
8	Thiazol-4-yl	25.4	122.3 (C_2), 128.0 (C_5), 168.2 (C_4)
9	Thiazol-5-yl	28.5	132.5 (C_5), 151.0 (C_4), 159.0 (C_2)

In the case of the reactions to the three isomeric thiazole ligands different reaction products were obtained, as can be easily seen from the different resonances in the $^{31}P\{^{1}H\}$ NMR spectra. The unambiguous assignment to the thiazol-2-yl, 4-yl and 5-yl ligands **6**, **8** and **9** was not possible based upon the spectroscopic data, as during the course of the reaction isomerisation of the metallated thiazole moieties might have occurred [23,24]. The final assignment of the 2-, 4- and 5-yl isomers to **6**, **8** and **9** was achieved by determination of the solid-state structure of **6** and **9**. However, the data of the structure of **6** was not sufficient for publication but clearly shows the 2-yl connectivity.

2.1. Hydrophilic/hydrophobic balance

The partition coefficients of the compounds were determined using the shake-flask method (Table 3). The coefficients of the highly hydrophobic benzylated compounds **3** and **7** could not be determined by this method. As expected, compound **5** with the isopropyl groups shows the lowest hydrophilicity of the imidazolyl based compounds. Interestingly, both N-methylated imidazolyl compounds (**2** and **4**) seem to be more hydrophilic than **1** which bears no alkyl groups at the nitrogen atoms. Presumably, **1** can form hydrogen bonds towards solvent molecules e.g. *n*-octanol and these solvates are than more lipophilic than the structure of **1** might suggest. The log $D_{7.4}$ values for the three isomeric 2-, 4- and 5-yl thiazoles **6**, **8** and **9** are within the range of 0.6–1.0 and therefore are less hydrophilic than the isomeric imidazols **2** and **4**.

In order to validate the log *D* values determined by UV/Vis spectroscopy we measured the partition coefficient of a sample of 2 by ^{31}P NMR spectroscopy. Compound 2 was dissolved in *n*-octanol/PBS buffer and both phases were measured using a glass inlet tube with PPh_3 as internal standard. To ensure that no nuclear

Table 3
Log $D_{7.4}$ values and standard deviation determined via the shake-flask method.

Ligand	R	log $D_{7.4\ (exp.)}$
1	Imidazol-2-yl	0.19 ± 0.07
2	1-Methylimidazol-2-yl	−0.73 ± 0.03
3	1-Methyl-benzimidazol-2-yl	n.d.
4	1-Methylimidazol-5-yl	−0.02 ± 0.05
5	2-Isopropylimidazol-4(5)-yl	0.85 ± 0.04
6	Thiazol-2-yl	0.73 ± 0.01
7	Benzothiazol-2-yl	n.d.
8	Thiazol-4-yl	0.61 ± 0.05
9	Thiazol-5-yl	0.97 ± 0.07

n.d. not determined due to low solubility in water and/or *n*-octanol.

Overhauser effect was observed we used standard inverse gated decoupling and additional delay time of 10 s for complete relaxation of the nuclei. Here, the log D value was determined to -0.76 ± 0.06 which is in good agreement with the value determined by UV/Vis spectroscopy.

2.2. Solid state structures

Crystals for X-ray analysis were grown by vapour diffusion. During the crystallisation process **7** was oxidised to the corresponding diphosphane dioxide **7a**. The crystallographic data for **2**, **3**, **9** and **7a** are summarised in Table 4. Tables with all angles and bond lengths can be found in the supporting information. The metric parameters are within the range found in diphos ligands [24,25]. In all structures, the asymmetric unit contains only half of the corresponding ligand. The other half is either generated by a 4_2 symmetry element (for **2**) or an inversion centre (for all other structures), respectively (Fig. 1–5).

The reaction of **2** with $[\{(CO)_2RhCl\}_2]$ in chloroform did not yield a ligand-stabilized rhodium carbonyl complex, as was seen by the missing carbonyl bands in the IR spectrum. Oxidation occurred to a binuclear rhodium(II) complex of the composition $[(\mathbf{2})_2Rh_2Cl_2]Cl_2$ (**10**). We were able to obtain red crystals of **10** as solvate (Fig. 6). In the cation, each rhodium carries a ligand **2** chelating through the phosphorus atoms, and a imidazolyl group from each phosphorus ligates the second rhodium through nitrogen, to give a 'Double-A-Frame' geometry and the Rh–Rh distance of 2.6626(3) Å is within the range associated with a Rh–Rh single-bond. Such a 'Double-A-Frame' geometry is also observed in analogues compounds of **7** [20,22].

3. Conclusion

We presented a variety of isomeric new imidazole and thiazole based bisphosphanes are accessible. The hydrophilic/hydrophobic balance of such diphos-type ligands can be addressed by the nature and the connectivity of the azole substituents. Due to the topology of the donor atoms in the azole substituents these ligands should display a plethora of coordination modes. The availability of these ligands should be useful for investigation of new organometallic reagents for use in aqueous and biphasic catalysis as well as in bioorganometallic chemistry(Scheme 1).

4. Experimental section

Compounds 1-diethoxymethylimidazol [18], 1-diethoxymethyl-2-isopropylimidazole [17], 1-methyl-2-trimethylsilyimidazole and bis(dichlorphosphino)ethane [14] were prepared according to the literature procedures. All preparations were carried out in Schlenk tubes under an atmosphere of dry nitrogen using anhydrous solvents purified according to standard procedures. All chemicals were used as purchased. NMR spectra were recorded on a Bruker DRX 200 or Bruker DRX 500 spectrometer. The ^1H and ^{13}C NMR spectra were calibrated against the residual proton signals and the carbon signals of the solvents as internal references ($[D_1]$ chloroform: $\delta_H = 7.24$ ppm and $\delta_C = 77.0$ ppm; $[D_4]$methanol: $\delta_H = 3.31$ ppm and $\delta_C = 49.1$ ppm) while the $^{31}P\{^1H\}$ NMR spectra were referenced to external 85% H_3PO_4. Infrared spectra were recorded with a Bruker IFS 66 FT-IR spectrometer. Time-of-flight mass spectra were recorded on a Bruker Ultraflex TOF, ESI mass spectra on an ion-trap mass spectrometer Finnigan LCQ Deca and EI mass spectra on a GC/MS-system Thermo Finnigan Trace DSQ.

4.1. Synthesis of bis(diimidazol-2-ylphosphino)ethane, 2-dimpe (*1*)

A solution of *n*-butyl lithium in hexane (1.6 M, 15 mL, 24 mmol) was added drop-wise to a solution of 3.7 g (22 mmol) of 1-diethoxymethylimidazole in diethyl ether (300 mL) at −78 °C. The reaction mixture was stirred at −40 °C for 1 h and at ambient temperature for 2 h. The reaction mixture was cooled to −78 °C and bis(dichlorophosphino)ethane (1.00 g, 4.31 mmol) was added. The reaction mixture was stirred at ambient temperature over night. The precipitate was removed by filtration and the filtrate was concentrated in vacuo. The resulting orange oil was dissolved in

Table 4
Crystallographic data for compounds **2**, **3**, **7a**·$(C_5H_{10})_2$, **9** and **10**·C_4H_8O·½C_2H_5OH.

	2	**3**	**7a**·$(C_5H_{10})_2$	**9**	**10**·C_4H_8O·½C_2H_5OH
Formula	$C_{18}H_{24}N_8P_2$	$C_{34}H_{32}N_8P_2$	$C_{40}H_{40}N_4O_2P_2S_4$	$C_{14}H_{12}N_4P_2S_4$	$C_{46}H_{70}Cl_4N_{16}O_3P_4Rh_2$
M (g mol^{-1})	414.39	614.62	798.94	426.46	1366.68
Crystal system	Tetragonal	Monoclinic	Triclinic	Triclinic	Monoclinic
Space group	$P4_2$	$P2_1/c$	P−1	P−1	C2/c
a (Å)	12.5078(3)	9.0807(2)	9.7003(3)	5.6563(6)	25.3183(3)
b (Å)	12.5078(3)	10.4579(2)	10.3399(2)	8.4971(9)	16.88021(16)
c (Å)	6.7689(2)	15.9180(3)	10.6682(3)	10.1074(9)	13.51874(12)
α (°)			98.5494(19)	104.719(8)	
β (°)		91.494(2)	108.157(2)	102.660(8)	102.903(1)
γ (°)			97.012(2)	93.637(8)	
V (Å^3)	1058.96(5)	1511.14(5)	989.17(4)	454.75(8)	5631.7(1)
Z	2	2	1	1	4
δ_{calc} (g cm^{-3})	1.300	1.351	1.341	1.557	1.612
Linear absorption coefficient (mm^{-1})	0.226	0.184	0.362	0.703	0.946
Crystal size (mm^3)	0.19 × 0.14 × 0.06	0.62 × 0.25 × 0.19	0.41 × 0.30 × 0.25	0.36 × 0.14 × 0.05	0.37 × 0.32 × 0.25
Crystal description	colourless plate	colourless prism	colourless prism	colourless plate	light pink block
Measured reflections	6350	19990	27475	10020	63619
Unique reflections/R_{int}	2164/0.0489	5749/0.0311	7535/0.0229	2758/0.0298	10732/0.0307
Observed reflections	1369	3779	6021	2098	8491
Completeness to theta	99.7%/26.37°	99.9%/33.14°	100.0%/33.14°	100.0%/30.50°	100.0%/33.14°
Max. and min. transmission	0.9865/0.9451	0.9659/0.8955	0.9150/0.8727	0.9657 /0.8587	0.7981/0.7803
Refined parameters /restraints	129/1	203/0	235 /0	109/0	338/12
GooF	0.962	0.966	1.064	1.027	1.069
$R_1(F)$ /wR_2 (F^2) [$I>2\sigma(I)$]	0.0598/0.1220	0.0579/0.1397	0.0447/0.1353	0.0372/0.0932	0.0373/0.1122
$R_1(F)$ /wR_2 (F^2) (all data)	0.1074/0.1334	0.0945/0.1534	0.0555/0.1400	0.0572/0.0983	0.0509/0.1172
Flack parameter	−0.1(2)				
Largest diff. peak and hole (e Å^{-3})	0.680/−0.202	0.611/−0.221	0.785/−0.452	0.720/−0.289	1.142/−0.724

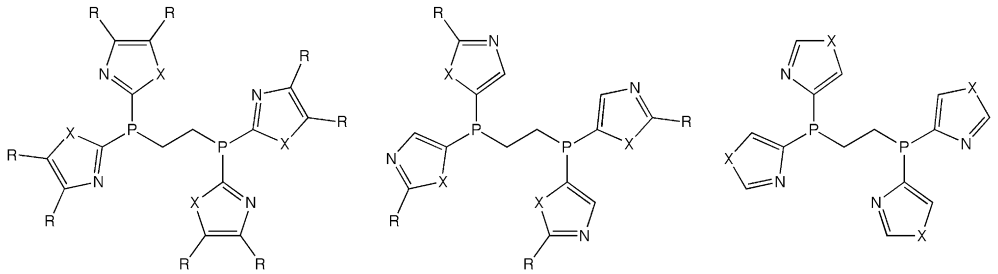


Fig. 1. Azole-based diphosphane ligands **1**–**9**.

$CHCl_3$ (200 mL) and 2 mL of ammonia solution added. The organic phase was collected and all volatiles were removed in vacuo. The oily residue was dissolved in 100 mL acetone/water (10:1) and stirred at ambient temperature for 72 h. After cooling in an ice bath, the resulting precipitate was collected by filtration and dried in vacuo. Yield 0.97 g (63%). ^{1}H-NMR (200 MHz, 296 K, MeOD-d_4): δ/ppm = 2.30 (t, 4 H, (CH_2)$_2$), 7.22 (s, 8 H, H_{im}). ^{1}H-NMR (500 MHz, 296 K, dmso-d_6): δ/ppm = 2.20 (t, 4 H, (CH_2)$_2$), 7.20–7.25 (m, 8 H, H_{im}), 12.57 (s, 4 H, N*H*). ^{13}C{^{1}H}-NMR (125 MHz, 296 K, dmso-d_6): δ/ppm = 22.6 ((CH_2)$_2$), 124.9 (broad, C_2), 143.1 (C_4, C_5). ^{31}P{^{1}H}-NMR (81 MHz, 296 K, MeOD-d_4): δ/ppm = −50 (s). ^{31}P{^{1}H}-NMR (81 MHz, 296 K, dmso-d_6): δ/ppm = −49 (s). EI MS (Pt, 210 °C): *m/z* (%) = 68 (100) ([$C_3H_4N_2$]$^+$), 222 (4.7) ([M-2im]$^+$), 290 (1.3) ([M-im]$^+$), 358 (0.4) ([M]$^+$). $C_{14}H_{16}N_8P_2$ CH_3OH H_2O (408.13): calcd. C 45.1, H 5.3, N 28.1; found C 45.4, H 5.4, N 28.5.

4.2. Synthesis of bis(di-1-methylimidazol-2-ylphosphino)ethane, 2-dimpe^{NMe} (*2*)

Bis(dichlorophosphino)ethane (635 mg, 2.74 mmol) was added drop-wise to 2.1 g (14 mmol) of neat 1-methyl-2-trimethylsilylimidazole at 0 °C. The reaction mixture was stirred for 14 h at ambient temperature. All volatiles were removed in vacuo. The residue was washed several times with *n*-hexane and dried in vacuo to yield 0.73 g (76%) of a white solid. ^{1}H-NMR (200 MHz, 296 K, MeOD-d_4): δ/ppm = 2.62 (t, 4 H, (CH_2)$_2$), 3.63 (s, 12 H, NMe), 7.12 (s, 4 H, H_4), 7.26 (s, 4 H, H_5). ^{13}C{^{1}H}-NMR (125 MHz, 296 K, MeOD-d_4): δ/ppm = 21.7 ((CH_2)$_2$), 35.0 (NCH_3), 127.1 (C_5), 129.5 (C_4), 144.1 (C_2). ^{31}P{^{1}H}-NMR (81 MHz, 296 K, MeOD-d_4): δ/ppm = −54 (s). ESI$^+$ (MeOH): *m/z* = 333.3 [M-im^{NMe}]$^+$, 415.3 [M+H]$^+$, 437.4 [M+Na]$^+$. $C_{18}H_{24}N_8P_2$ $2H_2O$ (450.41): calcd. C 48.0, N 6.3, H 24.9; found C 48.1, H 6.0, N 24.3.

4.3. Synthesis of bis(di-1-methylbenzimidazol-2-ylphosphino) ethane, 2-dbimpe^{NMe} (*3*)

A solution of *n*-butyl lithium in hexane (1.6 M, 6.3 mL) was added drop-wise to a solution of 1-methylbenzimidazol (1.44 g) in toluene at −78 °C. The reaction mixture was stirred for 2 h and then bis(dichlorophosphino)ethane (500 mg, 0.32 mL) was added, the solution stirred for another hour at −78 °C and over night at ambient temperature. Concentrated ammonia solution (5 mL) was added, the phases separated and the organic layer dried over Na_2SO_4. The volatiles were removed in vacuo to yield a slightly yellow solid, which was crystallised from methanol/toluene. Yield (80%). ^{1}H-NMR (200 MHz, 296 K, $CDCl_3$): δ/ppm = 3.09 (t, 4H, (CH_2)$_2$), 3.72 (s, 12H, NCH_3), 7.16–7.31 (m, 12H, bzim), 7.63–7.75 (m, 4H, bzim). ^{13}C{^{1}H}-NMR (125 MHz, 296 K, $CDCl_3$): δ/ppm = 21.0, 29.5, 109.9, 120.5, 122.8, 123.8, 161.3. ^{31}P{^{1}H}-NMR (81 MHz, 296 K, $CDCl_3$): δ/ppm = −45 (s). MALDI TOF (DIT, $CHCl_3$): *m/z* = 483.1

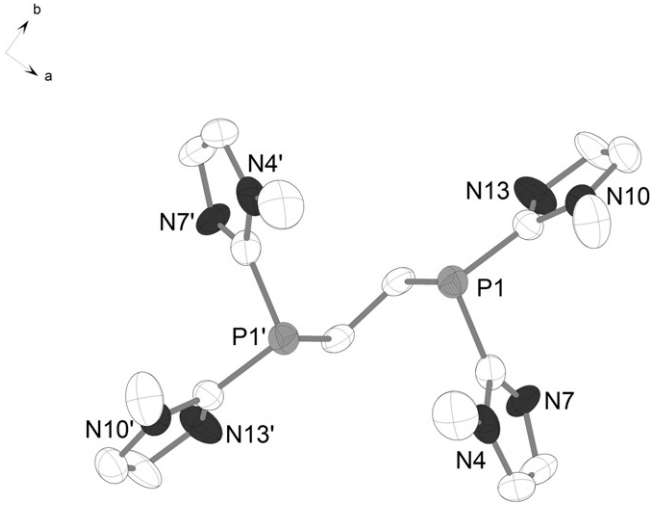


Fig. 2. Molecular structure of **2**. The displacement ellipsoids are shown on a 50% level and hydrogen atoms are omitted for clarity.

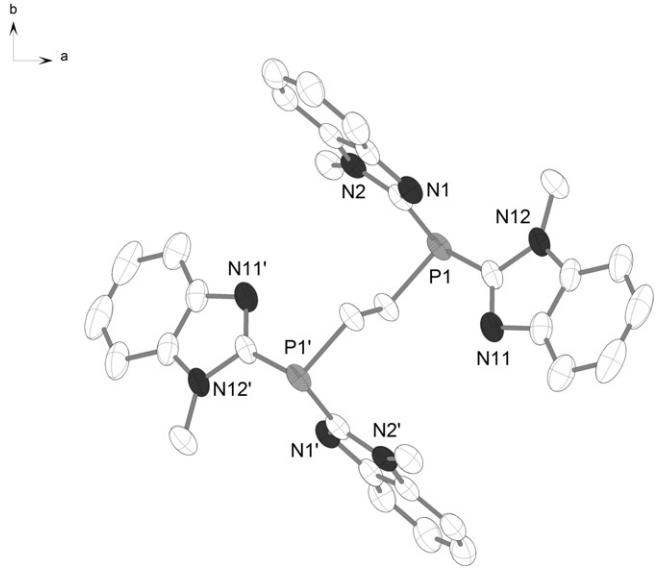


Fig. 3. Molecular structure of **3**. The displacement ellipsoids are shown on a 50% level and hydrogen atoms are omitted for clarity.

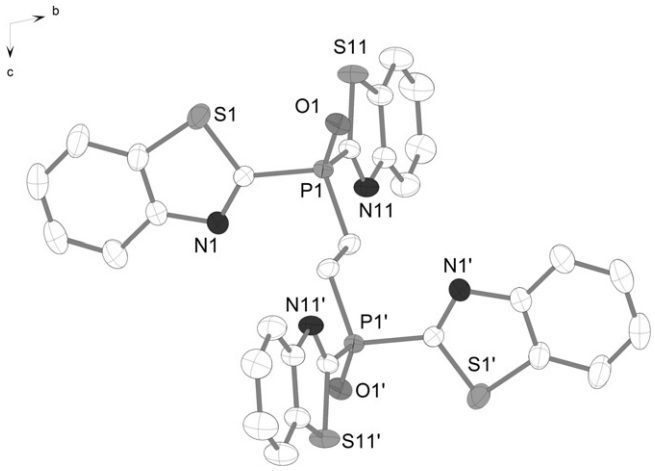


Fig. 4. Molecular structure of the dioxide of **7** (**7a**). The displacement ellipsoids are shown on a 50% level. Hydrogen atoms and solvent molecules are omitted for clarity.

$[M\text{-}C_8H_7N_2]^+$, 615.2 $[M]^+$, 647.2 $[M+O]^+$, 677.9 $[M+Cu]^+$. $C_{34}H_{32}N_8P_2$ 6MeOH (806.88): calcd. C 59.5, H 6.9, N 13.9; found C 59.9, H 6.3, N 13.5.

4.4. Synthesis of bis(di-1-methylimidazol-5-ylphosphino)ethane, 5-dimpe^{NMe} (**4**)

To a solution of 5-bromo-1-methylimidazole (2.13 g, 13.2 mmol) in 20 mL of dichloromethane 4.4 mL of ethylmagnesium bromide in diethyl ether (3.0 M, 4.4 mL, 13.2 mmol) were added at ambient temperature. The solution was stirred for 1 h at ambient temperature, then bis(dichlorophosphino)ethane (0.4 mL, 2.6 mmol) in dichloromethane (10 mL) was added drop-wise. The suspension was stirred over night, then a brine solution (5 mL) added and the organic layer extracted with bidistilled water (3 × 10 mL) and dried over Na_2SO_4. After filtration and evaporation the residue was stirred in *n*-hexane, the white precipitate isolated by filtration and dissolved in methanol. After filtration, *n*-hexane was added to the clear filtrate and the precipitate dried in vacuo to yield 0.57 g (62%) of a white solid. ^{1}H-NMR (500 MHz, 296 K, $CDCl_3$): δ/ppm = 2.20 (t, 4H, (CH_2)$_2$), 3.51 (s, 12H, NMe), 7.09 (s, 4 H, H_4), 7.56 (s, 4H, H_2). ^{13}C

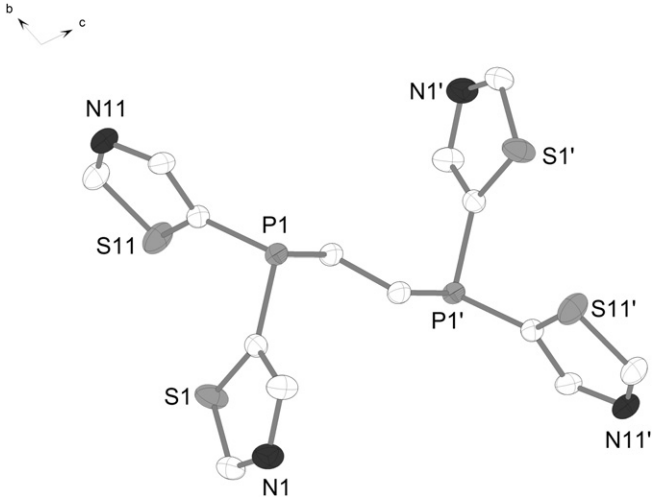


Fig. 5. Molecular structure of **9**. The displacement ellipsoids are shown on a 50% level and hydrogen atoms are omitted for clarity.

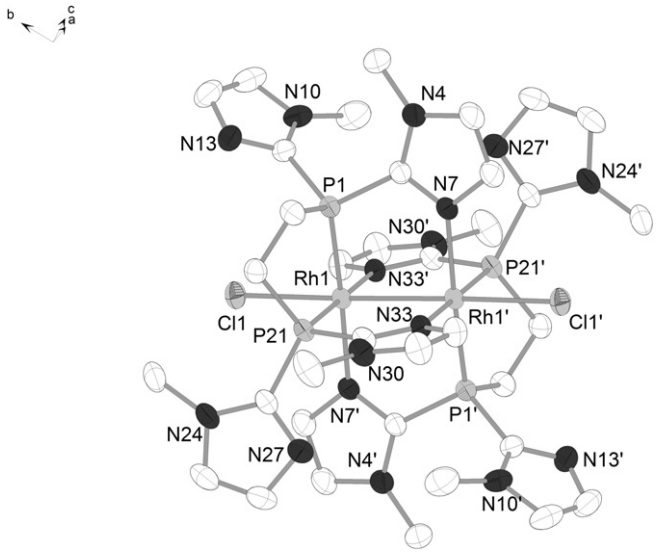


Fig. 6. Molecular structure of **10**·C_4H_8O·½C_2H_5OH. Displacement ellipsoids are shown on a 50% level. The counter-ions, solvent molecules and hydrogen atoms are omitted for clarity.

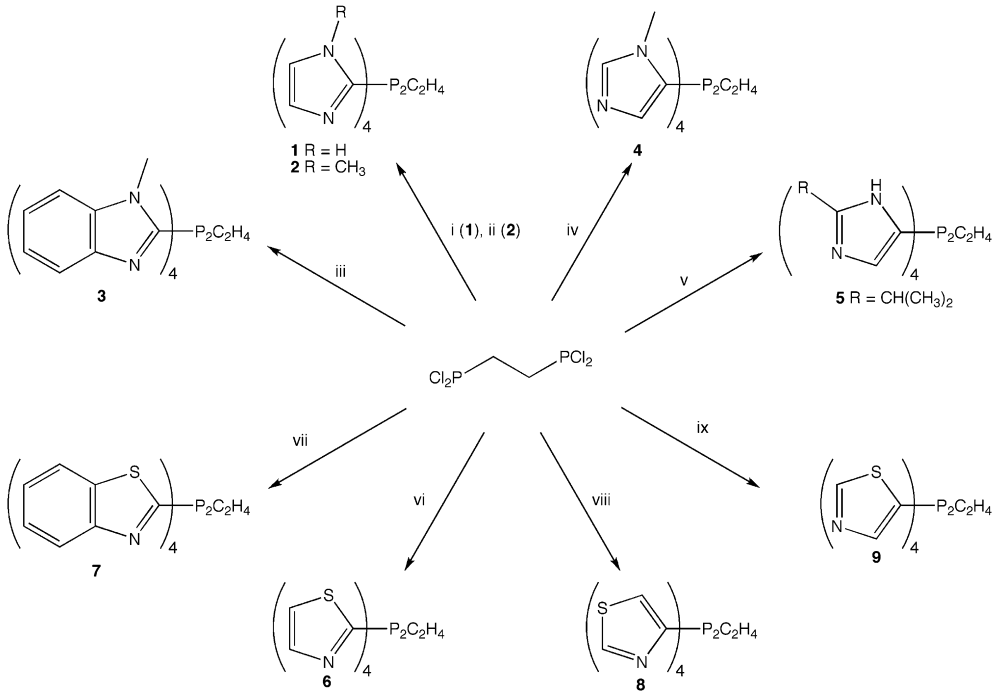
{^{1}H}-NMR (125 MHz, 296 K, $CDCl_3$): δ/ppm = 22.4 ((CH_2)$_2$), 32.8 (NCH_3), 124.4 (C_5), 137.3 (C_4), 142.3 (C_2). ^{31}P{^{1}H}-NMR (81 MHz, 296 K, $CDCl_3$): δ/ppm = −73 (*s*). MALDI TOF (DIT, $CHCl_3$): *m/z* = 415.0 $[M+H]^+$, 431.0 $[M+O+H]^+$. $C_{18}H_{24}N_8P_2$ 2MeOH H_2O (450.41): calcd. C 48.4, H 6.9, N 22.6; found C 48.1, H 6.3, N 22.3.

4.5. Synthesis of bis(di-2-isopropylimidazol-4(5)-ylphosphino) ethane, 4-dimpe^{iPr} (**5**)

To 1-diethoxymethyl-2-isopropylimidazol (2.3 g, 11 mmol) in thf (100 mL) was added *tert*-butyl lithium in hexane (1.6 M, 6.9 mL, 11 mmol) at −78 °C. The solution was stirred at −78 °C for 1 h and then bis(dichlorophosphino)ethane (500 mg, 0.32 mL, 2.2 mmol) added. The reaction mixture was stirred over night at ambient temperature, ammonia solution (3 mL) added and concentrated in vacuo to 20 mL. Dichloromethane (100 mL) was added and the organic phase extracted with brine. The organic layer was separated, all volatiles removed in vacuo, 100 mL acetone/water (10:1) added and the solution stirred at ambient temperature over night. The resulting white precipitate was filtered, washed with acetone and dried in vacuo to yield 0.48 g (42%) of the product. ^{1}H-NMR (200 MHz, 296 K, MeOD-d_4): δ/ppm = 1.28 (d, *J* = 7.0 Hz, 24H, CH(CH_3)$_2$), 2.03 (t, 4 H, (CH_2)$_2$), 3.04 (sept., *J* = 7.0 Hz, 4H, CH(CH_3)$_2$), 7.00 (s, 4H, $H_{4(5)}$). ^{13}C{^{1}H}-NMR (125 MHz, 296 K, MeOD-d_4): δ/ppm = 20.5 (CH_3), 28.2 (CH_2), 48 (CH), 130.1 ($C_{4(5)}$), 153.7 ($C_{5(4)}$), 157.7 (C_2). ^{31}P{^{1}H}-NMR (81 MHz, 296 K, MeOD-d_4): δ/ppm = −63 (*s*). ESI^+ (MeOH): *m/z* = 417.5 $[M\text{-}im^{iPr}]^+$, 527.5 $[M+H]^+$. $C_{26}H_{40}N_8P_2$ 1/2C_3H_6O 3/2H_2O (582.32): calcd. C 56.7, H 8.0, N 19.2; found C 56.4, H 7.6, N 19.6.

4.6. Synthesis of bis(dithiazol-2-ylphosphino)ethane, 2-dthiape (**6**)

A solution of thiazole (930 mg, 0.78 mL) in 100 mL of toluene was cooled to −78 °C and 6.3 mL *n*-butyl lithium in hexanes (1.6 M) were added. The solution was stirred at −78 °C for 2 h and then bis (dichlorophosphino)ethane (500 mg, 0.32 mL, 2.2 mmol) was added, the solution stirred for another hour at −78 °C and over night at ambient temperature. Concentrated ammonia solution (5 mL) was added, the phases separated and the organic layer dried over Na_2SO_4. The volatiles were removed in vacuo to yield a slightly



Scheme 1. Reaction conditions for the preparation of the different 1,2-bis(diazoylphosphino)ethanes **1**–**9**: i) neat 1-methyl-2-TMS-imidazole; ii) 1. DEM-imidazole, *n*-BuLi, thf, −78 °C, 2. H_2O/acetone; iii) 1-methylbenzimidazole, *n*-BuLi, thf, −78 °C; iv) 5-bromoimidazole, EtMgBr, CH_2Cl_2; v) 1-DEM-2-isopropylimidazole, *n*-BuLi, thf, −78 °C, 2. H_2O/acetone; vi) thiazole, *n*-BuLi, thf, −78 °C; vii) benzothiazole, *n*-BuLi, thf, −78 °C; viii) benzothiazole, *n*-BuLi, thf, −78 °C; viii) 4-bromothiazole, EtMgBr, CH_2Cl_2; ix) 5-bromothiazole, EtMgBr, CH_2Cl_2.

yellow solid. After solution in methanol, the product was precipitated upon addition of diethyl ether and dried in vacuo to yield 0.58 g (62%) of a white solid. ^{1}H-NMR (200 MHz, 296 K, $CDCl_3$): δ/ppm = 2.73 (t, 4H, $(CH_2)_2$), 7.58 (d, 4H, J = 3.0 Hz, $H_{4/5}$), 8.06 (d, 4H, J = 3.0 Hz, $H_{4/5}$). ^{13}C{^{1}H}-NMR (125 MHz, 296 K, $CDCl_3$): δ/ppm = 25.7 ($(CH_2)_2$), 123.8 ($C_{4/5}$), 145.6 ($C_{4/5}$), 167.9 (C_2). ^{31}P{^{1}H}-NMR (81 MHz, 296 K, $CDCl_3$): δ/ppm = −23 (s). ESI$^+$ (MeOH): m/z = 342.3 [M-C_3H_2NS]$^+$, 427.1 [M+H]$^+$, 449.3 [M+Na]$^+$. $C_{14}H_{12}N_4P_2S_4$ CH_3OH (457.97): calcd. C 39.3, H 3.5, N 12.2; found C 39.2, H 3.3, N 11.9.

4.7. Synthesis of bis(dibenzothiazol-2-yl)ethane,2-dbthiape (**7**)

Benzothiazole (1.13 mL, 10.0 mmol) in thf (100 mL were treated with *n*-butyl lithium (1.6 M in hexane, 6.3 mL, 10.0 mmol) at −78 °C. The deep red solution was stirred at −78 °C for 90 min and then bis(dichlorophosphino)ethane (500 mg, 0.32 mL, 2.2 mmol) was added, the solution stirred for another hour at −78 °C and over night at ambient temperature. Ammonia solution was added (20 mL), stirred and the suspension concentrated to about 80 mL in vacuo. The precipitate was filtered, washed with water (100 mL) and ethyl ether (100 mL) and dried in vacuo. Yield 1.09 g (78%). ^{1}H-NMR (200 MHz, 296 K, $CDCl_3$): δ/ppm = 3.01 (t, 4H, $(CH_2)_2$), 7.30–7.59 (m, 8H), 7.78–7.85 (m, 4H), 8.02–8.10 (m, 4H). ^{13}C{^{1}H}-NMR (125 MHz, 296 K, $CDCl_3$): δ/ppm = 25.0, 121.8, 124.0, 126.0, 126.5, 137.3, 155.0. ^{31}P{^{1}H}-NMR (81 MHz, 296 K, $CDCl_3$): δ/ppm = −15 (s). MALDI TOF (DIT, $CHCl_3$): m/z = 626.9 [M]$^+$, 642.0 [M+O]$^+$, 658.9 [M+2O+H]$^+$, 688.9 [M+Cu]$^+$. $C_{30}H_{20}N_4P_2S_4$ H_2O (644.01): calcd. C 55.9, H 3.4, N 8.7; found C 56.1, H 3.4, N 8.6.

4.8. Synthesis of bis(dithiazol-4-ylphosphino)ethane, 4-dthiape (**8**)

To a solution of 4-bromothiazole (1 g, 6 mmol) in dichloromethane (200 mL) a solution of ethylmagnesium bromide in diethyl ether (3.0 M, 2.03 mL, 6.1 mmol) was added. The solution was stirred for 1.5 h at ambient temperature, then bis(dichlorophosphino)ethane (0.2 mL, 1.3 mmol) in dichloromethane (10 mL) was added drop wise and the suspension stirred over night. The mixture was quenched by addition of conc. ammonia (25%, 5 mL) and brine (10 mL). The organic solvents were removed in vacuo, the precipitate was removed by filtration, washed with bidistilled water and diethyl ether and the off-white solid dried in vacuo. The solid was dissolved in dichloromethane (50 mL), died over Na_2SO_4, and after filtration and concentration in vacuo the product was precipitated upon addition of diethyl ether. Yield 0.36 g (65%). ^{1}H-NMR (200 MHz, 296 K, $CDCl_3$): δ/ppm = 2.64 (t, 4 H, $(CH_2)_2$), 7.44 (m, 4H). ^{13}C{^{1}H}-NMR (125 MHz, 296 K, $CDCl_3$): δ/ppm = 25.4 ($(CH_2)_2$), 122.3 (C_2), 128.0 (C_5), 168.2 (C_4). ^{31}P{^{1}H}-NMR (81 MHz, 296 K, $CDCl_3$): δ/ppm = −19 (s). EI MS (Pt, 200 °C): m/z (%) = 426 (10.6) [M]$^+$. $C_{14}H_{12}N_4P_2S_4$ 3.5$CHCl_3$ (838.65): calcd. C 24.9, H 1.9, N 6.6; found C 25.2, H 1.7, N 6.9.

4.9. Synthesis of bis(dithiazol-5-ylphosphino)ethane, 5-dthiape (**9**)

To a solution of 5-bromothiazole (0.96 g, 5.7 mmol) in dichloromethane (100 mL) a solution of ethylmagnesium bromide in diethyl ether (3.0 M, 2.01 mL, 5.7 mmol) was added. The solution was stirred for 1.5 h at ambient temperature, then bis(dichlorophosphino)ethane (0.27 g, 1.2 mmol) in dichloromethane (10 mL) was added drop-wise and the suspension stirred over night. The mixture was quenched by addition of conc. ammonia (25%, 5 mL). The mixture was filtered through a plug of Celite, the organic layer extracted with bidistilled water and the aqueous layer with dichloromethane. The combined organic layers were dried over Na_2SO_4, and after filtration and all volatiles were removed in vacuo. The product was washed with bidistilled water and diethyl ether and dried in vacuo. Yield 0.35 g (58%). ^{1}H-NMR (200 MHz, 296 K, $CDCl_3$): δ/ppm = 2.15 (t, 4 H, $(CH_2)_2$), 8.04 (m, 4H), 9.01 (s, 4H). ^{13}C

{^{1}H}-NMR (125 MHz, 296 K, $CDCl_3$): δ/ppm = 28.5 ((CH_2)$_2$), 132.5 (C_5), 151.0 (C_4), 159.0 (C_2). ^{31}P{^{1}H}-NMR (81 MHz, 296 K, $CDCl_3$): δ/ppm = −52 (s). EI MS (Pt, 210 °C): *m/z* (%) = 426 (2.4) $[M]^+$. $C_{14}H_{12}N_4P_2S_4$ H_2O (443.95): calcd. C 37.8, H 3.2, N 12.6; found C 38.2, H 3.3, N 12.1.

4.10. Synthesis of [(**2**)$_2$Rh$_2$Cl$_2$]Cl$_2$ (**10**)

[{(CO)$_2$RhCl}$_2$] (30 mg, 77 μmol) was added to a solution of **2** (63.9 mg, 154 μmol) in $CHCl_3$. The solution was stirred at ambient temperature for 1.5 h. The volume was concentrated to one third, then *n*-hexane added. The resulting red precipitate was removed by centrifugation, washed with *n*-hexane and dried in vacuo. Yield 19 mg, 21%. Crystals were grown form EtOH/thf. ^{1}H NMR (200 MHz, 296 K, MeOD-d$_4$): δ/ppm = 2.47 (m, 4H, CH_2, broad), 3.79 (s, 12H, NCH_3 broad), 7.17 (s, 4H, H_{im}), 7.40 (s, 4H, H_{im}), 7.45 (s, 4H, H_{im}), 7.76 (s, 4H, H_{im}). ^{13}C{^{1}H} NMR (125 MHz, 296 K, MeOD-d$_4$): δ/ppm = 25.0 ((CH_2)$_2$), 33.5 (NCH_3), 27.0 (*C*im, 2 signals), 129.3 (*C*im), 130.2 (*C*im). ^{31}P{^{1}H} NMR (81 MHz, 296 K, MeOD-d$_4$): δ/ppm = 34.0 ppm (d, J = 126 Hz). MALDI TOF (DIT, $CHCl_3$): *m/z* = 1034.1 $[L_2Rh_2]^+$, 1069.1 $[L_2Rh_2Cl]^+$, 1104.1 $[L_2Rh_2Cl_2]^+$. $C_{36}H_{48}N_{16}Cl_4P_4Rh_2 \cdot CH_2Cl_2 \cdot 4H_2O$ (1333.40): calcd. C 33.3, H 4.4, N 16.8; found C 33.4, H 4.5, N 16.45. IR (KBr): ν/cm^{-1} = 3395 (s, broad), 3102 (m), 2956 (m), 1281 (m), 773 (m), 565 (s), 513 (m).

5. Measurement of lipophilicity (log *D*)

The *n*-octanol–water partition coefficients of the compounds **1** – **9** were determined using a shake-flask method. PBS buffered bidistilled water (100 mL, phosphate buffer, $c(PO_4^{3-})$ = 10 mM, c (NaCl) = 0.15 M, pH adjusted to 7.4 with HCl) and *n*-octanol (100 mL) were shaken together using a laboratory shaker (Perkin–Elmer), for 72 h to allow saturation of both phases. 1 mg of each compound was mixed in 1 mL of aqueous and organic phase, respectively for 10 min using a laboratory vortexer. The resultant emulsion was centrifuged (3000 × g, 5 min) to separate the phases. The concentrations of the compounds in the organic and aqueous phases were then determined using UV absorbance spectroscopy (230 nm). Log D_{pH} was defined as the logarithm of the ratio of the concentrations of the complex in the organic and aqueous phases ($\log D = \log\{[\text{diphos}_{(org)}]/[\text{diphos}_{(aq)}]\}$; the value reported is the mean of three separate determinations.

6. Crystallographic studies

Crystallographic data were collected at 183(2) K on an Oxford Diffraction Xcalibur system with a Ruby detector using Mo K_α radiation (λ = 0.7107 Å) that was graphite-monochromated. Suitable crystals were covered with oil (Infineum V8512, formerly known as Paratone N), mounted on top of a glass fibre and immediately transferred to the diffractometer. The program suite CrysAlis^{Pro} was used for data collection, semi-empirical absorption correction and data reduction [26]. Structures were solved with direct methods using SIR97 [27] and were refined by full-matrix least-squares methods on F^2 with SHELXL-97 [28]. The structures were checked for higher symmetry with help of the program Platon [29]. A disordered THF molecule was found in **10**·C_4H_8O·½C_2H_5OH, the two orientations were refined with a ratio of 6:4. In addition a half occupied ethanol molecule near a centre of inversion was found. In both cases, appropriate restraints were applied.

Appendix. Supporting material

Supplementary information associated with this article could be found online, at doi:10.1016/j.jorganchem.2010.04.028

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