Syntheses of Zinc Complexes with Multidentate Nitrogen Ligands: New Catalysts for Aldol Reactions

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The ligands 2,6-bis{[(pyrid-2-ylmethyl)amino]methyl}-pyridine with an N_5 pattern and (6-{[(pyrid-2-ylmethyl)amino]methyl}pyrid-2-yl)methanol with an N_3O pattern were synthesized. Zn^{II} complexes of the two ligands could be obtained, and the single-crystal X-ray structure of (2,6-bis{[(pyrid-2-ylmethyl)amino]methyl}pyridine)zinc chloride showed Zn coordination to all five nitrogen atoms. The strong complexation of 2,6-bis{[(pyrid-2-ylmethyl)-amino]methyl}pyridine and (6-{[(pyrid-2-ylmethyl)amino]-methyl}pyrid-2-yl)methanol with Zn^{II} were demonstrated by ^1H NMR spectroscopic studies and electrospray mass spectrometry. The coupling of 2-hydroxyacetophenone and benzaldehyde was studied in the presence of the prepared Zn complexes, and it was shown that the coupling product was obtained at room temperature in up to 60% yield with 7.5 mol % of the zinc catalyst. The present complexes mimic the active site of the zinc-dependent class II aldolases, where Zn^{II} is coordinated to three nitrogen atoms.

Introduction

The aldol reaction is of central importance for construction of C−C bonds in organic chemistry.[1] It is therefore not surprising that several catalysts and reagents have been developed in order to achieve efficient condensation with high diastereomeric and enantiomeric selectivity.[2] Furthermore, due to its importance for organic synthesis, the asymmetric aldol reaction has become, without doubt, one of the most important topics in modern catalytic synthesis.

From the several methods available for the aldol reaction, the direct condensation of an aldehyde with a ketone[3] is a most attractive approach since it does not require the isolation of preformed enolates.[4] Therefore, the development of new catalysts for the direct condensation is a field of considerable importance.

In nature, aldol reactions also constitute an important reaction class that is mediated by aldolases, ubiquitous enzymes that catalyze among other reactions, the reversible aldol cleavage of fructose-1,6-bis(phosphate) (FBP) in glycolysis. Aldolases are divided into two distinct classes according to their enzymatic mechanism. Whereas the class I aldolases form a Schiff base intermediate between the e-amino group of a lysine residue and the carbonyl carbon atom of the substrate, class II aldolases are zinc-dependent.[5] Three histidine side chains and a carboxylate group of a glutamic acid are coordinated to the Zn^{II} ion in class II fuculose 1-phosphate aldolase produced by *E. coli*.[6] Upon substrate binding, the carboxylate group dissociates from the Zn^{II} reaction center and moves away, providing space for the hydroxy ketone to bind to the Zn^{II} ion and at the same time deprotonating the carbon atom in the α-position to the carbonyl group. The resulting enediolate is proposed to be stabilized through binding to the zinc ion and to act as a nucleophile (Figure 1).[6]

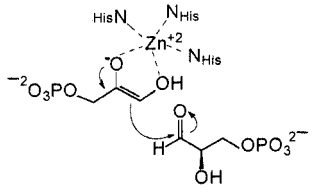

Figure 1. Proposed mechanism for the aldol reaction catalyzed by type II aldolase[6]

Although it has been demonstrated that Zn^{II} salts catalyze the aldol condensation,[7] Zn complexes with nitrogen ligands have not been explored much as catalysts for aldol reactions. In a structural model for aldolases, a modified tris(pyrazolyl)borate ligand[8] was used to mimic the three nitrogen atoms in the enzyme's active site. A model with four nitrogen atoms and a carbonyl group bound to the zinc ion has also been developed.[9] Proline has been used as an asymmetric catalyst,[10,11] and some early work has shown that the Zn^{II} ion coordinated to pyridine and bi- and ter(pyridine)s can catalyze the reaction of aldehydes and ketones to give unsaturated ketones.[12]

Chiral dinuclear Zn complexes with chiral binol as ligand as well as other oxygen-containing ligands have been re-

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cently reported to catalyze asymmetric aldol reactions.[13−18]

Inspired by the Zn^{II} coordination site in the active site of the class II aldolases, we have prepared ligands containing nitrogen-binding sites in order to develop novel catalysts for the aldol reaction.

Here we report on the efficient synthesis of ligands containing nitrogen as binding sites (N_5 and N_3O), the synthesis of new Zn^{II} complexes where the zinc center is coordinated to nitrogen atoms, and our first results on the activity of the new zinc complexes as catalysts for the condensation of benzaldehyde and 2-hydroxyacetophenone.

Results and Discussion

The syntheses of the ligands with N_5 and N_3O coordination sites (**6** and **9**) are shown in Scheme 1. Synthesis of tosylamine **3** was achieved by treatment of 2-(aminomethyl)-pyridine with NaOH and tosyl choride in a two-phase system (H_2O/diethyl ether) in 89% yield.[19] Coupling of **3** with 2,6-bis(bromomethyl)pyridine (**4**), also in a two-phase system and nBu_4NBr as a phase-transfer catalyst, gave product **5**, which could be isolated after chromatography in 86% yield. The tosyl group was removed by heating the tosylate **5** with concentrated sulfuric acid to yield the ligand **6** in 94% yield. The three-step synthesis gives **6** in an overall yield of 72%. There are two reports in the literature of compounds related to **6**; in the first the tetraammonium salt of **6** is prepared by a different procedure,[20] and in the second G. Newkome et al.[19] report the synthesis of **6** in 28% yield. The latter authors describe the product obtained as an unstable oil whereas we isolated **6** as a brownish, stable solid.

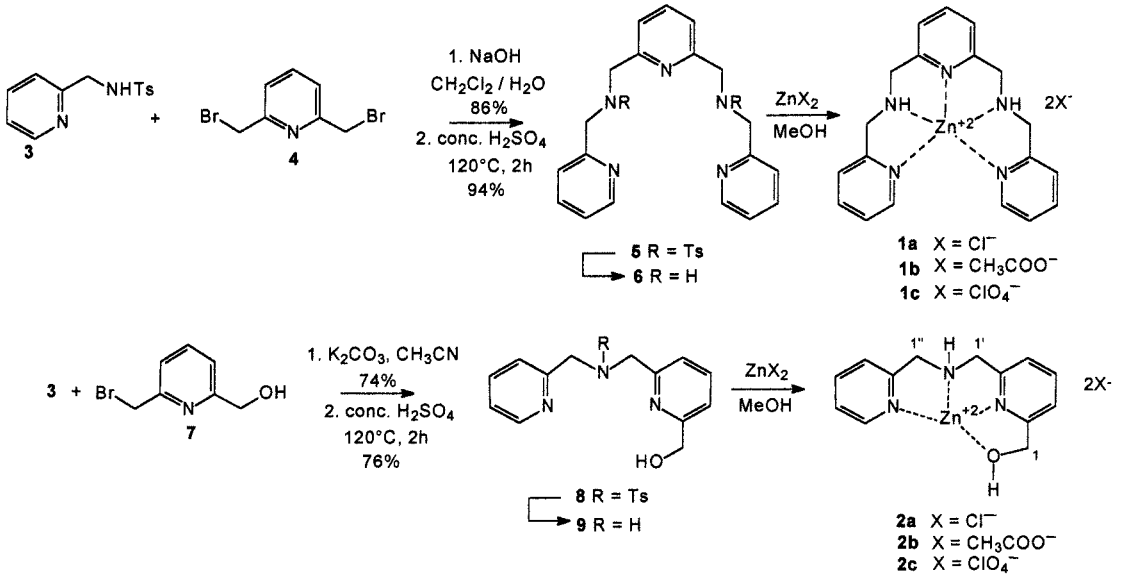
For the synthesis of the new ligand **9**, the tosylamine **3** was alkylated with [6-(bromomethyl)pyrid-2-yl]methanol (**7**) in the presence of K_2CO_3 in acetonitrile to give **8** in 74% yield. The latter was deprotected in the same way as **5** to give **9** in 76% yield (Scheme 1).

The ligands **6** and **9** became readily available in a few steps and high yields by the syntheses developed here.

Complexation of 6 and 9 with Zn Salts

Having the two ligands **6** and **9** at hand, we have prepared a series of Zn^{II} complexes to test their ability to act as catalysts for aldol reactions. Thus, ligand **6** was refluxed with $ZnCl_2$, $Zn(CH_3COO)_2{\cdot}2H_2O$ or $Zn(ClO_4)_2{\cdot}6H_2O$ in a 1:1 ration in MeOH to give the corresponding complexes **1a**, **1b** and **1c** in 64%, 82% and 81% yield, respectively. All three complexes could be identified by their ^1H and ^{13}C NMR spectra, and ESI-MS. The ^1H NMR spectrum in CD_3OD of **1a**, **1b**, **1c** showed shifts of the signals for the pyridine hydrogen atoms as well as for the two methylene groups [the signals of the $pyCH_2N$ methylene groups appear at δ = 3.97 ppm (8 H) for the ligand **6** and at δ = 4.28 ppm (4 H) and δ = 4.39 ppm (4 H) for the acetate complex **1b**]. The ESI-MS data showed for the three complexes, **1a**, **1b** and **1c**, peaks at *m*/*z* = 382, 384, 386, that can be assigned to [**6** − H^+ + Zn^{II}], with relative intensities of 100:59:41 for **1a**, 100:61:38 for **1b** and 100:59:41 for **1c**, in good agreement with the calculated intensities of 100:60:42 for the three zinc isotopes. Furthermore, the peaks for [**6** + Zn^{II} + Cl^-] at *m*/*z* = 418, 420 and 422 are also observed for **1a**, as well as the peaks for the [**6** + Zn^{II} + CH_3COO^-] at *m*/*z* = 442,444 and 446 and for the [**6** + Zn^{II} + ClO_4^-] at *m*/*z* = 482, 484 and 486 for **1b** and **1c**, respectively. The free ligand **6**, however, could not be detected in the ESI-MS.

Insight into the geometry of the complexes and the binding mode of the zinc atom with the ligand **6** was obtained by single-crystal X-ray analysis. The reaction of **6** with $ZnCl_2$ gave two pseudo-polymorphs, **1a**·CH_3OH solvate and **1a**·$2H_2O$. Here the Zn^{II} ion is coordinated to the five



Scheme 1

nitrogen atoms of the ligand and to a chloride anion, producing complexes with pseudo-C_2 symmetry (for example, see Figure 2). The zinc atoms and the pyridine rings of the side chain are almost co-planar. The amine N atoms, N2 and N4, are displaced above this plane towards the central pyridine ring. The reaction of **6** with $Zn(ClO_4)_2$ gave **1c**, in which the metal ion is pentacoordinate, with all five nitrogen atoms coordinated to the metal (Figure 3). Due to the lack of a sixth ligand, the two pyridine rings are bent downwards, but the complex retains the pseudo-C_2 symmetry. The bond angles N1−Zn−N3 and N3−Zn−N5 have an average value of 128.3° relative to 89.3° for the two hexacoordinate **1a** complexes. The zinc−N bond lengths in **1c** are notably shorter than those observed in complexes **1a**·CH_3OH and **1a**·$2H_2O$. These differences are particularly important for the central Zn−N(pyridine) distance (ca. 0.1 Å) and the outer Zn−N(pyridine) distances (ca. 0.15 Å). Selected bond lengths and angles for the three structures are given in Table 1.

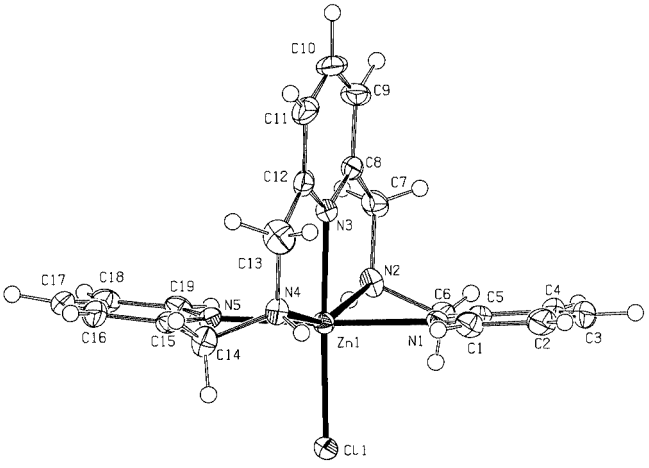


Figure 2. Perspective view of cation **1a**·CH_3OH solvate, showing the crystallographic numbering scheme, and thermal ellipsoids at 50% probability; the Cl^- anion and the CH_3OH solvent molecule have been omitted for clarity

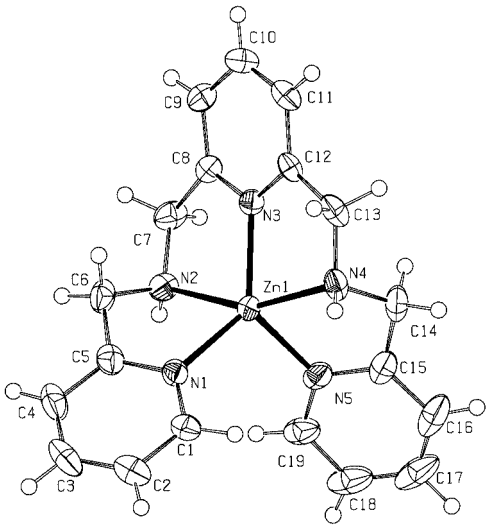


Figure 3. Perspective view of cation **1c**, showing the crystallographic numbering scheme, and thermal ellipsoids at 50% probability; the ClO_4^- anions have been omitted for clarity

Table 1. Selected bond lengths [Å] and angles [°] for complexes **1a**·CH_3OH solvate, **1a**·$2H_2O$ and **1c**

	1a·CH_3OH	**1a**·$2H_2O$	**1c**
Zn−N1	2.199(3)	2.214(2)	2.051(2)
Zn−N2	2.221(3)	2.200(2)	2.174(2)
Zn−N3	2.12183)	2.121(2)	2.029(2)
Zn−N4	2.200(3)	2.212(2)	2.179(2)
Zn−N5	2.190(3)	2.154(2)	2.027(2)
Zn−Cl1	2.376(1)	2.383(1)	
N1−Zn−N2	77.71(10)	77.81(7)	81.07(10)
N1−Zn−N3	86.73(11)	88.26(6)	128.98(9)
N1−Zn−N4	101.02(11)	101.38(7)	114.16(9)
N1−Zn−N5	176.87(11)	179.36(7)	103.44(10)
N2−Zn−N3	77.18(12)	77.74(7)	78.64(9)
N2−Zn−N4	154.44(12)	155.26(7)	157.32(01)
N2−Zn−N5	101.44(10)	102.82(7)	111.89(10)
N3−Zn−N4	77.26(11)	77.52(7)	78.69(10)
N3−Zn−N5	90.14(11)	91.87(6)	127.55(9)
N4−Zn−N5	78.41(11)	78.03(7)	81.95(10)
Cl1−Zn−N1	91.18(8)	89.08(5)	
Cl1−Zn−N2	101.32(9)	101.73(5)	
Cl1−Zn−N3	177.64(8)	177.34(5)	
Cl1−Zn−N4	104.24(9)	102.99(5)	
Cl1−Zn−N5	91.95(8)	90.79(5)	

Complexes **2a**, **2b** and **2c** were obtained by refluxing the zinc salts and **9** in a 1:1 ratio in methanol. Partial evaporation of the solvent and addition of diethyl ether gave [(6-{[(pyrid-2-ylmethyl)amino]methyl}pyrid-2-yl)methanol]zinc dichloride (**2a**), [(6-{[(pyrid-2-ylmethyl)amino]methyl}-pyrid-2-yl)methanol]zinc diacetate (**2b**) and [(6-{[(pyrid-2-ylmethyl)amino]methyl}pyrid-2-yl)methanol]zinc diperchlorate (**2c**) as white solids (Scheme 1), in 41, 62 and 66% yields, respectively.

The complexes **2a**, **2b**, **2c** were characterized by ^1H and ^{13}C NMR spectroscopy, and ESI-MS. The ^1H NMR spectrum in [D_4]methanol of **9**, **2b** and **2c** are shown in Figure 4. In general, we can see that for the three methylene groups a strong downfield shift is observed upon complexation, whereas the aromatic protons are less influenced by the Zn coordination. For ligand **9**, three signals for the 6 H atoms in the positions 1, 1′ and 1′′ (see numbering in Scheme 1) can be seen; a singlet at δ = 4.72 ppm (2 H1), and two close singlets (δ = 3.95 and 3.96 ppm) corresponding to four protons (2 H1′ and 2 H1′′). After complexation, five signals appeared for the same six hydrogen atoms and the two H1, two H1′ and two H1′′ atoms, became nonequivalent. We observe two broad signal at δ = 5.05 and 4.97 ppm for the two H1 atoms, a broad signal at δ = 4.54 ppm for two hydrogen atoms (1 H1′ and 1 H1′′) and two broad doublets at δ = 4.16 and 3.82 ppm for the remaining two hydrogen atoms (1 H1′ and 1 H1′′). For **2c** the signals are well defined.

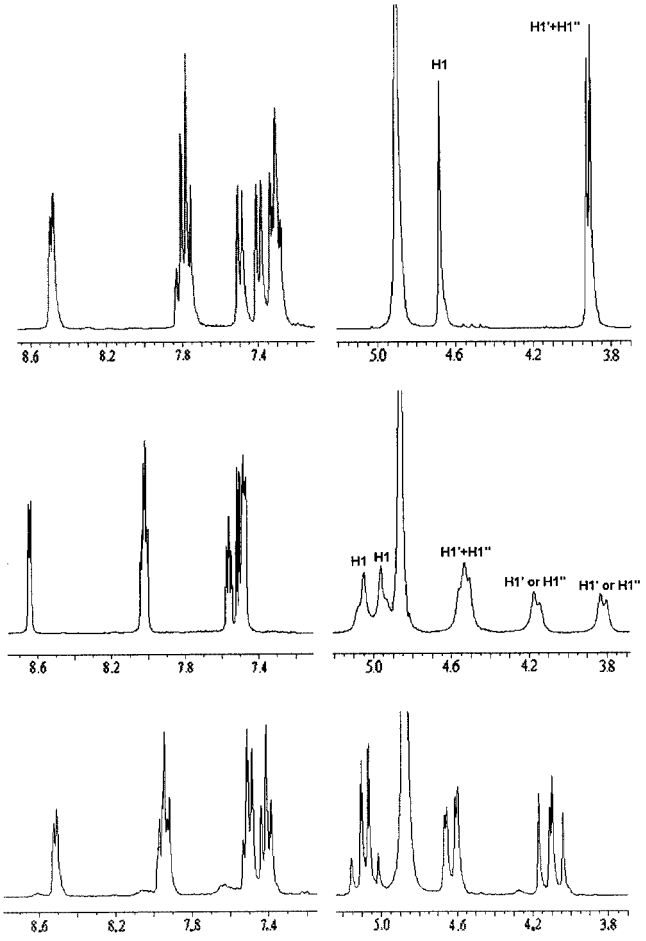


Figure 4. Top: ^{1}H NMR in CD_3OD of ligand **9**; center: ^{1}H NMR spectrum, in CD_3OD, of complex **2b**; bottom: ^{1}H NMR spectrum in CD_3OD of complex **2c**; the aromatic region and the methylene groups are shown (in ppm)

The assignment of the hydrogen signals in the ^{1}H NMR spectrum of complex **2b** was determined by a ^{1}H-^{1}H COSY measurement.

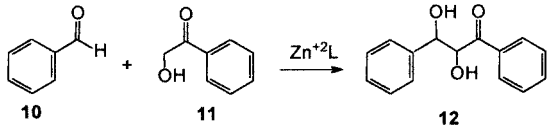
The electrospray mass spectra of **2a**, **2b** and **2c** show the peaks corresponding to [**9** − H^+ + Zn^{II}] at m/z = 292, 294 and 296 in the expected relative intensities, consistent with the structure shown in Scheme 1. The peaks corresponding to [**9** − H^+ + Zn^{II} + Cl^-] for **2a** and [**9** − H^+ + Zn^{II} + CH_3COO^-] for **2b** are also present. Similar to the complexes of **6**, the peak corresponding to the free ligand **9** is not observed in the ESI-MS.

The structures for the complexes **2a**, **2b**, **2c** in Scheme 1 indicate a protonated hydroxy group, although deprotonation cannot be excluded. The presence of a hydroxy group was inferred by the fact that the ^{1}H NMR spectrum of the acetate complex **2b** showed six protons for two acetate anions, indicating the presence of two counter-anions in **2b**.

The acetates **1b** and **2b** proved to be soluble in a variety of organic solvents, an important property for efficient catalysis of organic reactions. The acetate anion can also act as a base to deprotonate a ketone in the aldol reaction. Therefore, the preliminary reactivity studies described below were conducted with the acetates.

Reactivity Studies

In order to explore the ability of the new zinc complexes to act as catalysts for aldol reactions, the zinc-catalyzed reaction of benzaldehyde (**10**) with 2-hydroxyacetophenone (**11**) to give 1,3-diphenylpropan-1-one (**12**) was investigated (Scheme 2).



Scheme 2

The results are summarized in Tables 2−4. The aldol product **12** was formed when a mixture of 1.0 equiv. of benzaldehyde (**10**) and 1.5 equiv. of 2-hydroxyacetophenone (**11**) reacted in the presence of 7.5 mol % of either **6** or **9** and 7.5 mol % of zinc acetate.[21] The reaction took place in THF but also in a protic solvent, methanol, and the yields improved with addition of 0.5 equiv. of triethylamine. The ligand **9** was the more efficient of the two ligands studied, giving the addition product in 53% in methanol and 56% in THF. The conversion was higher when diethylzinc was added to **9** (62%, Entry 7, Table 3). The preformed complexes **1b** and **2b** could also catalyze the aldol reaction; **2b** gave the higher yield (59%) of **12**. We have also observed that an excess of benzaldehyde or 2-hydroxyacetophenone can lead to better yields (51−52%) when **1b** is the catalyst (Entries 4 and 7 in Table 4). The *syn*/*anti* ratio of **12**, determined by ^{1}H NMR spectroscopy for the reactions shown in the tables, was 1:1 for all the experiments with exception of Entry 4 inTable 3 (1.5:1 *syn*/*anti* ratio) and Entry 5 in Table 3 (3:1 *syn*/*anti* ratio).

Table 2. Aldol reaction using the ligands **6** and **9** and zinc salts as catalysts in MeOH (in all experiments, 0.5 mmol of benzaldehyde, 0.75 mmol of 2-hydroxyacetophenone and 0.05 mmol of catalyst were used; **12** was obtained as a 1:1 *syn*/*anti* mixture and the yields and diastereomeric ratios were determined by ^{1}H NMR spectroscopy; Py: pyridine; Im: imidazole; Et_3N: triethylamine)

Entry	Catalyst (7.5 mol %)	Additives	Yield of **12** (%)
1	**6**		0
2	**6**, $Zn(Ac)_2$		37
3	**6**, $Zn(CH_3COO)_2$	0.25 mmol Et_3N	45
4	**6**, $Zn(CH_3COO)_2$	0.25 mmol py	24
5	**6**, $Zn(CH_3COO)_2$	0.25 mmol Im	17
6	**9**		0
7	**9**, $Zn(CH_3COO)_2$		38
8	**9**, $Zn(CH_3COO)_2$	0.25 mmol Et_3N	53
9	**9**, $Zn(CH_3COO)_2$	Na_2SO_4	35

Table 3. Aldol reaction using the ligands **6** and **9** and zinc salts as catalysts in THF (in all experiments, 0.5 mmol of benzaldehyde, 0.75 mmol of 2-hydroxyacetophenone and 0.05 mmol of catalyst were used; **12** was obtained as a 1:1 syn/*anti* ratio and the yields and diastereomeric ratios were determined by ^{1}H NMR spectroscopy; Py: pyridine; Et_3N: triethylamine; MS: molecular sieves

Entry	Catalyst (7.5 mol %)	Additives	Yield of **12** (%)
1	**6**, $Zn(CH_3COO)_2$		40
2	**6**, $Zn(CH_3COO)_2$	MS	40
3	**6**, $Zn(CH_3COO)_2$	0.25 mmol Et_3N, MS	50
4	**6**, $Zn(CH_3COO)_2$	0.25 mmol py, MS	48
5	**9**,$Zn(CH_3COO)_2$	MS	38
6	**9**,$Zn(CH_3COO)_2$	0.25 mmol Et_3N, MS	56
7	**9**, $Zn(Et)_2$		62

Table 4. Aldol reaction using the complexes **1b** and **2b** as catalysts (Entries 1−9 in THF; Entries 10, 11 in MeOH)

Entry	Catalyst (7.5 mol %)	Additives	Yield of **12** (%)
1[a]	1b	MS	40
2[a]	1b	0.25 mmol Et_3N, MS	48
3[a]]	1b	0.25 mmol py, MS	38
4[b]	**1b**	MS	51[c]
5[b]	**1b**	0.25 mmol Et_3N, MS	39[d]
6[e]	**1b**	MS	45
7[e]	**1b**	0.25 mmol Et_3N, MS	52
8[a]	2b	MS	41
9[a]	**2b**	0.25 mmol Et_3N, MS	59
10[a]	2b		29
11[a]	**2b**	Na_2SO_4	23

[a] 0.5 mmol benzaldehyde, 0.75 mmol 2-hydroxyacetophenone. [b] 1 mmol benzaldehyde, 0.25 mmol 2-hydroxyacetophenone. [c] 1.5:1 *syn*/*anti*. [d] 3:1 *syn*/*anti*. The yields and diastereomeric ratios were determined by ^{1}H NMR spectroscopy. MS: molecular sieves. Py: pyridine; Et_3N: triethylamine. [e] 0.25 mmol benzaldehyde, 0.75 mmol 2-hydroxyacetophenone. In all experiments 0.05 mmol of catalyst was used. **12** was obtained as a 1:1 *syn*/*anti* ratio with the exception of footnotes [c] and [d].

Further studies of the catalytic system developed with other substrates and screening for reaction conditions that will lead to improved yields are now under way.

Conclusions

In a search for new Zn^{II} complexes that can act as catalysts for aldol reactions, we have prepared novel zinc complexes with N_5 and N_3O coordination. For that, the ligands **6** and **9** were synthesized in a few steps with high yields. The complexes prepared catalyze the reaction of hydroxyacetophenone and benzaldehyde to give 2,3-diphenylpropan-1-one in yields of 60% when **9** plus diethylzinc or the preformed zinc complex **2b** were the catalysts.

Experimental Section

General Remarks: All reactions were carried out, unless mentioned, in open flasks, without exclusion of O_2 or H_2O. Technical solvents were distilled prior to use. Chemicals were purchased from commercial suppliers (FLUKA and Aldrich) and, unless otherwise stated, used without further purification. Acetonitrile was refluxed under nitrogen for 2 h in the presence of CaH_2, distilled and kept over molecular sieves. Column chromatography (CC): silica gel 60 from FLUKA; thin layer chromatography (TLC): silica gel plates Alugram® Sil G/UV254; visualization was made with a UV lamp (λ = 254 nm) or with 10% ninhydrin solution in 90% ethanol. NMR spectra: Bruker AC-300 spectrometer, 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts δ are given in ppm and were calibrated against the deuterated solvent. The multiplicity of the ^{13}C NMR peaks were determined by ^{13}C NMR DEPT spectra and the expected chemical shifts; the *J* values are in Hz. Mass spectra were provided by the Service of Mass Spectrometry of the Department of Chemistry and Biochemistry in Bern. Infrared spectroscopy was performed with a Perkin-Elmer 1600 series FTIR spectrometer. Frequencies $\tilde{\nu}$ are given in cm^{-1} (s strong, m medium, w weak).

Caution: Perchlorates are potentially explosive and should be handled with the necessary precautions.[22]

2-[(Tosylamino)methyl]pyridine (3): Prepared as described.[19] Tosyl chloride (14.12 g, 74 mmol) in diethyl ether (14 mL) was added to a mixture of 2-(aminomethyl)pyridine (8 g, 74 mmol) and NaOH (4.4 g, 110 mmol) in water (20 mL). The two-phase reaction mixture was stirred in a closed flask for 18 h. The ether was then evaporated and the pH of the aqueous phase adjusted to 7 with 1 M HCl solution. The precipitated white solid was filtered, dried and dissolved in ethanol. The ethanol was evaporated to yield **3** as a white solid (17.36 g, 89% yield). ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3 H, CH_3Ts), 4.24 (d, *J* = 5.49, 2 H, NCH_2Py), 5.90 (br. t, 1 H, NH), 7.14−7.19 (m, 2 H, 3-pyH and 5-pyH), 7.23−7.26 (m, 2 H, 3-phH), 7.61 (ddd, 1 H, 4-pyH), 7.74 (d, *J* = 7.7, 12 H, 2-phH), 8.45 (d, *J* = 4.77, 1 H, 6-pyH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.17 (q), 48.05 (t), 122.65 (d), 123.29 (d), 127.91 (d), 130.8 (d), 137.52 (d), 144.04 (q), 149.57 (d), 155.47 (q) ppm.

2,6-Bis(bromomethyl)pyridine (4) and [6-(Bromomethyl)pyrid-2-yl]-methanol (7): 2,6-bis(hydroxymethyl)pyridine (2 g,14.4 mmol) was heated for 15 h in 48% HBr solution (20 mL). The solution was cooled with an ice bath and 10 M NaOH was added until pH = 12 was reached. After extraction with ether (3 × 60 mL), the ether phase was dried with $MgSO_4$, filtered and the ether evaporated to give a white solid. The products were separated by column chromatography (diethyl ether/hexane, 3:7) to give two fractions. Fraction A: **4** (1.94 g, yield 51%) as white needle-like crystals. R_f = 0.4 (diethyl ether/hexane, 3:7). ^{1}H NMR ($CDCl_3$): δ = 4.55 (s, 4 H, CH_2Py), 7.39 (d, *J* = 7.74 Hz, 2 H, 3-pyH), 7.72 (ap. t, *J* = 7.73 Hz, 1 H, 4-pyH) ppm. ^{13}C NMR ($CDCl_3$): δ = 33.45 (t), 122.79 (d), 138.11 (d), 156.73 (s) ppm. Fraction B: **7** (720 mg, yield 24%) as white needle-like crystals. R_f = 0.05 (diethyl ether/hexane, 3:7). ^{1}H NMR ($CDCl_3$): δ =3.66 (br. s, 1 H, OH), 4.56 (s, 2 H, OCH_2py), 4.77 (s, 2 H, $BrCH_2$py), 7.18 (d, *J* = 7.7 Hz, 1 H,), 7.36 (d, *J* = 7.5 Hz, 2 H), 7.61 (app t, *J* = 7.7 Hz, 1 H, 4-pyH) ppm. By adding more HBr after 15 h and refluxing for a longer time, the yield of **4** could be increased to 69%. By stopping the reaction immediately after all the 2,6-bis(hydroxymethyl)pyridine had disappeared on the TLC the yield of **7** could be increased to 37%.

2,6-Bis{[(pyrid-2-ylmethyl)(tosyl)amino]methyl}pyridine (5): $n$$Bu_4NBr$ (6.48 g) and KOH (80 g) in water (240 mL) was added to 2-[(tosylamino)methyl]pyridine (**3**) (8 g, 30.4 mmol) in dichloromethane (800 mL). The reaction mixture was heated to reflux and 2,6-bis(bromomethyl)pyridine (**4**) (4 g, 15.2 mmol) in dichloromethane was added at once. The reaction mixture was refluxed for 14 h. The

two phases were separated and the dichloromethane was evaporated to leave a brown oil. Column chromatography (hexane/ethyl acetate, 1:1 with 1% triethylamine) yielded **5** as a brown viscous oil (8.25 g, yield 86%). R_f = 0.1 (hexane/ethyl acetate, 1:1). ^{1}H NMR ($CDCl_3$): δ = 2.39 (s, 3 H, $TsCH_3$), 4.36 (s, 4 H, $pyCH_2$), 4.49 (s, 4 H, $pyCH_2$), 7.05−7.09 (m, 4 H,3,5-pyH), 7.23 (d, J = 8.1 Hz, 4 H, phH), 7.31 (d, J = 7.92 Hz, 2 H, 3,5-pyH), 7.36 (ap. t, J = 7.71 Hz, 1 H, 4-pyH), 7.53 (ddd, J = 7.63, J = 1.6 Hz, 2 H, 4-pyH), 7.65 (d, J = 8.2 Hz, 4 H, phH), 8.34 (d, J = 4.2 Hz, 2 H, 6-pyH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.16 (q), 54.31 (t), 54.56 (t), 121.83 (d), 123.02 (d), 123.36 (d), 128.06 (d), 130.24 (d), 137.26 (d), 137.61 (d), 144.03 (s), 149.44 (d), 156.42 (s), 157.14 (s) ppm.

2,6-Bis{[(pyrid-2-ylmethyl)amino]methyl}pyridine (6): **5** (7.6 g, 12.1 mmol) was dissolved in 98% H_2SO_4 (10 mL) and heated to 120 °C for 3 h. The liquid turned black. The solution was poured into a brine/NaOH solution (20 mL) and the pH of the solution was adjusted to 12 with an NaOH solution The aqueous solution was extracted with dichloromethane (4 × 100 mL). The organic phase was dried with $MgSO_4$, filtered and the dichloromethane evaporated to give **6** as a brown solid (3.65 g, yield 94%). ^{1}H NMR ($CDCl_3$): δ = 2.32 (s, 2 H, NH), 3.96 and 3.98 (2s, 8 H, CH_2py), 7.13−7.15 (m, 2 H, pyH), 7.21 (d, J = 7.71, 2 H, pyH), 7.35 (d, J = 7.71 Hz, 2 H, 3,5-pyH), 7.57−7.66 (m, 3 H, 4-pyH), 8.54 (d, J = 4.8 Hz, 2 H, 6-pyH) ppm. ^{13}C NMR ($CDCl_3$): δ = 55.31 (t) 55.44 (t), 121.15 (d), 122.63 (d), 123.01 (d), 137.15 (d), 137.59 (d), 149.96 (d), 159.70 (s), 160.31 (s) ppm. IR ($CHCl_3$): ṽ = 3425 s, 1604 m, 1215 s, 742 s, 668 s cm^{-1}. MS: m/z (%) = 319 (1.6) [M$^+$], 241 (2.6), 227 (3.0), 213 (71), 107 (88), 93 (100). FAB (DTT/DTE): m/z = 320 [M + 1]. HRMS: calculated for $C_{19}H_{21}N_5$ 319.179696, found 319.179690.

[6-{[(Pyrid-2-ylmethyl)(tosyl)amino]methyl}pyrid-2-yl]methanol (8): A mixture of **3** (1.9 g, 7.2 mmol), **7** (1.5 g, 7.2 mmol) and K_2CO_3 (2.7 g) in acetonitrile (140 mL) was refluxed for 6 h. The precipitate was collected by vacuum filtration and washed with acetonitrile. The acetonitrile was evaporated to give an orange oil. Chromatography using a gradient (ethyl acetate/hexane/triethylamine, 1000:100:1 to ethyl acetate/methanol/triethylamine, 1000:100:1) gave **8** as a colorless viscous oil (2.05 g, yield 74%). R_f = 0.62 (ethyl acetate/methanol, 25:2). ^{1}H NMR ($CDCl_3$): δ =2.42 (s, 3 H, CH_3Ts), 4.54−4.56 (3 s, 6 H, CH_2py), 6.98 (d, J = 7.8 Hz, 1 H, 3-pyH), 7.06−7.10 (m, 1 H, 5-pyH), 7.16 (d, J = 7.35 Hz, 1 H, 5-pyH), 7.27 (d, J = 7.71 Hz, 2 H, phH), 7.35 (d, J = 8.1 Hz, 1 H, 3,5-pyH), 7.48- 7.58 (m, 2 H, 4-pyH), 7.70 (d, J = 8.34 Hz, 2 H, phH), 8.33 (d, J = 4.77 Hz, 1 H, 6-pyH) ppm. ^{13}C NMR ($CDCl_3$): δ = 22.17 (q), 54.01 (t), 54.61 (t), 64.40 (t), 119.65 (d), 122.03 (d), 123.04 (d), 123.44 (d), 127.98 (d), 130.30 (d), 137.20 (d), 137.31 (s), 137.79 (d), 144.15 (s), 149.57 (d), 155.70 (s), 157.12 (s), 159.99 (s) ppm. IR ($CHCl_3$): ṽ = 3018 m, 1597 s, 1576 s, 1339 s, 1159 s, 1091 m, 756 s, 668 m cm^{-1}. MS: m/z (%) = 207 (11), 162 (27), 155 (30), 134 (33), 105 (30), 91 (52), 69 (69), 57 (100). FAB-NBA: m/z = 384 [M + 1]. High resolution LSIMS: calculated for $C_{20}H_{22}N_3O_3S$ 384.138189; found 384.13812.

[6-{[(Pyrid-2-ylmethyl)amino]methyl}pyrid-2-yl]methanol (9): The tosylate **8** (2.0 g, 5.2 mmol) was dissolved in 98% H_2SO_4 (10 mL) and heated to 120 °C for 3 h. The liquid turned black. The solution was poured into a brine/NaOH solution (20 mL), and the pH was adjusted to 12 with NaOH solution. The water phase was extracted with dichloromethane (4 × 100 mL). The organic phase was dried with $MgSO_4$, filtered and the dichloromethane evaporated to give **9** as an oil with a slight orange color (0.91 g, yield 76%). ^{1}H NMR ($CDCl_3$): δ = 3.15 (br. s, 2 H, OH + NH), 3.95 and 3.96 (2 s, 4 H, CH_2py), 4.72 (s, 2 H, $pyCH_2O$), 7.10 (d, J = 7.71 Hz, 1 H, 3-pyH), 7.14−7.18 (m, 1 H, 5-pyH), 7.23 (d, J = 7.71 Hz, 1 H, 3-pyH), 7.33 (d, J = 7.7 Hz, 1 H, 5-pyH), 7.59−7.66 (m, 2 H, 4-pyH), 8.55 (d, J = 4.05 Hz, 1 H, 6-pyH) ppm. ^{1}H NMR(CD_3OD): δ = 3.91 and 3.93 (2 s, 4 H), 4.69 (s, 2 H), 7.25−7.34 (m, 2 H), 7.40 (d, J = 7.74 Hz, 1 H), 7.50 (d, J = 7.71 Hz, 1 H), 7.72−7.85 (m, 2 H), 8.49 (d, J = 4.02 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 54.97 (t), 55.24 (t), 64.68 (t), 119.34 (d), 121.44 (d), 122.74 (d), 123.08 (d), 137.23 (d), 137.81 (d), 149.98 (d), 159.02 (s), 159.37 (s), 159.99 (s) ppm. IR ($CHCl_3$): ṽ = 3016 w, 1595 m, 1576 m, 1216 s, 754 s, 668 m cm^{-1}. FAB-NBA: m/z = 230 [M + 1]. High resolution ESI-TOF-MS: calculated for $C_{13}H_{16}N_3O$: 230.1293; found 230.1288.

(2,6-Bis{[(pyrid-2-ylmethyl)amino]methyl}pyridine)zinc Dichloride (1a): 2,6-bis{[(pyrid-2-ylmethyl)amino]methyl}pyridine (**6**) (200 mg, 0.63 mmol) and $ZnCl_2$ (85 mg, 0.63 mmol) were dissolved in methanol (15 mL) and chloroform (3 mL). The solution was refluxed for 3 h. The methanol was reduced to 3 mL, and complex **1a** could be obtained as crystals (183 mg; yield 64%) by gradually adding (day by day 0.3−0.5 mL) diethyl ether. ^{13}C NMR ($CDCl_3$): δ = 52.29 (t), 54.28 (t), 123.32 (d), 125.49 (d), 125.97 (d), 142.01 (d), 142.64 (d) 148.83 (d), 155.32 (s), 157.87 (s) ppm. IR: ṽ = 3462 s, 3196 s, 1653 w, 1627 w, 1603 s, 1586 m, 1434 s, 1097 m, 915 m, 781 m, 771 s, 760 s cm^{-1}. ESI-MS: m/z (%) = 382 (86) [**6**-H$^+$ + ^{64}Zn], 384 (51) [**6**-H$^+$ + ^{66}Zn], 386 (35) [**6**-H$^+$ + ^{68}Zn], 418 (100) [**6** + ^{64}Zn + ^{35}C] , 420 (92) [**6** + ^{64}Zn+ ^{37}Cl, **6** + ^{66}Zn+ ^{35}Cl], 422 (65) [**6** + ^{66}Zn + ^{37}Cl, **6** + ^{68}Zn + ^{35}Cl]. High resolution ESI-TOF-MS: $C_{19}H_{20}N_5Zn$ calcd. 382.1010, found 382.1005; $C_{19}H_{20}ClN_5Zn$ calcd. 418.0776; found 418.0742. For X-ray structure see X-ray section.

(2,6-Bis{[(pyrid-2-ylmethyl)amino]methyl}pyridine)zinc Diacetate (1b): **6** (150 mg, 0.5 mmol) and $Zn(CH_3COO)_2$ (108 mg, 0.5 mmol) were dissolved in methanol (5 mL). After refluxing for 3 h, the methanol was evaporated to leave the **1b** complex as a brown viscous oil (200 mg, yield 82%). The complex was soluble in various organic solvents (THF, acetonitrile, dichloromethane and methanol). ^{1}H NMR (MeOD): δ = 1.83 (s, $COOCH_3$, 6 H), 4.28 and 4.39 (2 br. s, 8 H, CH_2py), 7.34−7.43 (m, 4 H, pyH), 7.54 (d, J = 7.71 Hz, 2 H, pyH), 7.87−7.99 (m, 3 H, pyH), 8.49 (d, J = 3.66 Hz, 2 H, 6-pyH) ppm. ^{13}C NMR (CD_3OD): δ = 23.46 (q), 52.54 (t), 54.14 (t), 122.91 (d), 124.95 (d), 125.30 (d), 140.95 (d), 141.81 (d), 148.87 (d), 155.68 (s), 157.62 (s) ppm. IR: ṽ = 3447 s, 1653 m, 1560 s, 1419 m, 1215 w, 770 s cm^{-1}. FAB MS (matrix: 3-NBA): m/z (%) = 382 (100) [**6**-H$^+$ + ^{64}Zn], 384 (61) [**6**-H$^+$ + ^{66}Zn], 386 (38) [**6**-H$^+$ + ^{68}Zn], 442 (34) [**6** + ^{64}Zn + CH_3COO^-], 444 (19) [**6** + ^{66}Zn + CH_3COO^-], 446 (12) [**6** + ^{68}Zn + CH_3COO^-]. HR ESI-TOF-MS: $C_{19}H_{20}N_5Zn$ calcd. 382.1010, found 382.1027; $C_{21}H_{24}N_5O_2Zn$ calcd. 442.1221, found 442.1226.

(2,6-Bis{[(pyrid-2-ylmethyl)amino]methyl}pyridine)zinc Diperchlorate (1c): **6** (150 mg, 0.5 mmol) and $Zn(ClO_4)_2$ (175 mg, 0.5 mmol) were dissolved in methanol (4 mL) The solution was refluxed for 3 h. By addition of the $Zn(ClO_4)_2$ a white solid immediately precipitated. The methanol was evaporated to leave **1c** as a white solid (235 mg, yield 81%). The solid was dissolved in acetonitrile and upon slow evaporation crystals were obtained. ^{1}H NMR (DMSO): δ = 4.10 (br. s, 4 H, CH_2py), 4.57 (br. d, 4 H, CH_2py), 5.77 (br. t, N−H, 2 H), 7.43 (d, J = 7.71 Hz, 2 H, 5-pyH), 7.58 (t, J = 6.26 Hz, 2 H, 3-pyH), 7.66 (d, J = 7.71 Hz, 2 H, 3,5-pyH), 7.97 (t, J = 7.73 Hz, 1 H, 4-pyH), 8.10 (dd, J = 7.71, J = 1.47 Hz, 2 H, 6-pyH) ppm. ^{13}C NMR (CD_3OD): δ =60.84 (t), 62.47 (t), 131.26 (d), 133.70 (d), 133.94 (d), 150.27 (d), 150.55 (d), 157.00 (d), 163.09 (s), 165.96 (s) ppm. IR ($CHCl_3$): ṽ = 3500 s, 1610 s, 1450 s, 1100 s, 770 s, 620 s cm^{-1}. ESI-MS: m/z (%) = 382 (22) [**6**-H$^+$ + ^{64}Zn], 384 (13) [**6**-H$^+$ + ^{66}Zn], 386 (9) [**6**-H$^+$ + ^{68}Zn], 482 (100) [**6** +

$^{64}Zn+ {}^{35}ClO_4$], 484 (95) [**6** + ^{64}Zn + $^{37}ClO_4$, **6** + ^{66}Zn + $^{35}ClO_4$, 486 (63) [**6** + ^{66}Zn + $^{37}ClO_4$, **6** + ^{68}Zn + $^{35}ClO_4$]. HR ESI-TOF-MS: $C_{19}H_{21}N_5O_4ClZn$ calcd. 482.0573, found 482.0586; $C_{19}H_{20}N_5Zn$ calcd. 382.1010, found 382.1035.

(6-{[(Pyrid-2-ylmethyl)amino]methyl}pyrid-2-yl]methanol)zinc Chloride (2a): 9 (150 mg, 0.66 mmol) and $Zn(Cl)_2$ (89 mg, 0.66 mmol) were dissolved in methanol (15 mL) and refluxed for 1 h. The methanol was reduced to 3−4 mL and by addition of diethyl ether **2a** precipitated as a white amorphous solid (98 mg, 41%). Recrystallization from ethanol/dichloromethane gave crystals that were too small to perform X-ray analysis. ^1H NMR (CD_3OD): δ = 3.77 (br. d, 1 H, CH_2py), 4.23 (br. d, 1 H, CH_2py), 4.45−4.66 (br. m, 2 H, CH_2py), 5.05 (br. d, 2 H, $pyCH_2O$), 7.51−7.66 (m, 4 H, 3,5-pyH), 8.09 (dd, *J* = 7.80, *J* = 5.31 Hz, 2 H, 4-pyH), 8.61 (d, *J* = 5.3 Hz, 1 H, 6-pyH) ppm. ^{13}C NMR (CD_3OD): δ = 51.69 (t), 52.85 (t), 61.86 (t), 122.28 (d), 123.86 (d), 124.94 (d), 126.04 (d), 142.34 (d), 142.60 (d), 148.79 (d), 155.81 (s), 157.69 (s), 158.10 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3414 s, 3223 s, 2908 m, 1604 s, 1575 m, 1465 m, 1452 m, 1444 m, 1285 w, 1063 s, 1012 s, 802 m, 767 s, 644 w cm^{-1}. ESI-MS: *m*/*z* (%) = 292 (100) [**9**-H^+ + ^{64}Zn], 294 (57) [**9**-H^+ + ^{66}Zn], 296 (38) [**9**-H^+ + ^{68}Zn], 328 (24) [**9** + ^{64}Zn + $^{35}Cl^-$], 330 (21) [**9** + ^{64}Zn+ $^{37}Cl^-$, **9** + ^{66}Zn+ $^{35}Cl^-$], 332 (14) [**9** + ^{66}Zn+ $^{37}Cl^-$, **9** + ^{68}Zn+ $^{35}Cl^-$]. HR ESI-TOF-MS: $C_{13}H_{14}N_3OZn$ calcd. 292.0428, found 292.0429; $C_{13}H_{15}ClN_3OZn$ calcd. 328.0195, found 328.0214.

[(6-{[(Pyrid-2-ylmethyl)amino]methyl}pyrid-2-yl)methanol)]zinc Acetate (2b): 9 (150 mg, 0.66 mmol) and $Zn(CH_3COO)_2$ (143 mg, 0.66 mmol) in methanol (15 mL) were refluxed for 1 h. The methanol was reduced to 3−4 mL and the complex precipitated by addition of diethyl ether to give **2b** as a white amorphous solid (168 mg, 62% yield). ^1H NMR (MeOD): δ = 1.93 (s, $COOCH_3$, 6 H), 3.82 (br. d, 1 H, CH_2py), 4.16 (br. d, 1 H, CH_2py), 4.47−4.60 (br. m, 2 H, CH_2py), 5.01 (br. d, 2 H, $pyCH_2O$), 7.43−7.58 (m, 4 H, 3,5-pyH), 7.97−8.06 (m, 2 H, 4-pyH), 8.64 (d, *J* = 4.77, 1 H, 6-pyH) ppm. ^{13}C NMR (MeOD): δ = 22.98 (q), 52.09 (t), 52.78 (t), 62.64 (t), 121.87 (d), 123.20 (d), 124.56 (d), 125.63 (d), 141.78 (d), 142.00 (d), 148.97 (d), 155.68 (s), 157.97 (s), 159.03 (s), 180.89 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3406 m, 2924 w, 1606 s, 1385 s, 1080 m, 1014 m, 668 w cm^{-1}. ESI-MS: *m*/*z* (%) = 292 (100) [**9**-H^+ + ^{64}Zn], 294 (55) [**9**-H^+ + ^{66}Zn], 296 (33) [**9**-H^+ + ^{68}Zn]. HR ESI-MS-TOF: $C_{13}H_{14}N_3OZn$ calcd. 292.0428, found 292.0438.

[(6-{[(Pyrid-2-ylmethyl)amino]methyl}pyrid-2-yl)methanol]zinc Perchlorate (2c): 9 (400 mg, 1.74 mmol) and $Zn(ClO_4)_2·6H_2O$ (650 mg, 1.74 mmol) in methanol (25 mL) were refluxed for 1 h. The methanol was reduced to 3−4 mL and the complex precipitated by addition of diethyl ether to give **2b** as a white amorphous solid (565 mg, 66% yield). ^1H NMR (CD_3OD): δ = 4.04−4.17 (2 d, 2 H, CH_2py), 4.50−4.70 (2 d, 2 H, CH_2py), 5.00−5.16 (2 d, 2 H, $pyCH_2O$), 7.40−7.53 (m, 4 H, 3,5-pyH), 7.92−8.00 (m, 2 H, 4-pyH), 8.51 (d, 1 H, 6-pyH) ppm. ^{13}C NMR (CD_3OD): δ = 53.99 (t), 54.70 (t), 61.40 (t), 121.78 (d), 123.28 (d), 125.23 (d), 125.85 (d), 141.60 (d), 142.04 (d), 148.04 (d), 154.49 (s), 155.18 (s), 156.70 (s) ppm. IR: $\tilde{\nu}$ = 3331 s, 2739 s, 2330 w, 2023 w, 1615 s, 1486 s, 1109 s, 658 s cm^{-1}. ESI-MS: *m*/*z* (%) = 292 (100) [**9**-H^+ + ^{64}Zn], 294 (58) [**9**-H^+ + ^{66}Zn], 296 (37) [**9**-H^+ + ^{68}Zn]. HR ESI-TOF-MS: $C_{13}H_{14}N_3OZn$ calcd. 292.0428, found 292.0418.

X-ray Crystallography: Intensity data for crystals of **1a**·CH_3OH solvate (0.25 × 0.15 × 0.15mm), **1a**·$2H_2O$ (0.25 × 0.18 × 0.15 mm), and **1c** (0.40 × 0.35 × 0.35 mm), were collected at 153 K with a Stoe Image Plate Diffraction System[23] using Mo-K_α graphite-monochromated radiation. Image plate distance 70 mm, φ oscillation scans 0−180° or 0−200°, step Δφ = 1.2°, 1.5° and 2°, respectively. 2θ range 3.27−52.1°, $d_{max.}-d_{min.}$ = 12.45−0.81 Å. The structures were solved by direct methods using the program SHELXS-97.[24] Refinement and all further calculations were carried out using SHELXL-97.[25] The H atoms were located from difference maps and refined isotropically. In **1a**·CH_3OH, the solvent H atoms were included in calculated positions and treated as riding atoms using SHELXL default parameters. The non-H atoms were refined anisotropically, using weighted full-matrix least squares on F^2. The molecular structure and crystallographic numbering schemes are illustrated in the PLATON[26] figures. Further crystallographic data are summarized in Table 5. CCDC-183956 (**1a**·CH_3OH), -183957 (**1a**·$2H_2O$) and -183958 (**1c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cam-

Table 5. Crystallographic data for complexes **1a**·CH_3OH, **1a**·$2H_2O$, and **1c**

	1a·CH_3OH	**1a**·$2H_2O$	**1c**
Empirical formula	$C_{19}H_{20}Cl_2N_5Zn·CH_3OH$	$C_{19}H_{20}Cl_2N_5Zn·2H_2O$	$C_{19}H_{21}N_5Zn·(ClO_4)_2$
Formula mass [g mol^{-1}]	487.72	491.71	583.68
a [Å]	8.9211(6)	9.0366(7)	13.4064(13)
b [Å]	9.2475(6)	16.1489(14)	14.3351(14)
c [Å]	26.2005(14)	15.2881(11)	12.2712(11)
α [°]	90	90	90
β [°]	95.58(1)	97.34(10)	102.01(1)
γ [°]	90	90	90
V [$Å^3$]	2154.6(2)	2212.7(3)	2306.7(4)
Z	4	4	4
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
T [K]	153(2)	153(2)	153(2)
$\rho_{calcd.}$ [g cm^{-1}]	1.504	1.476	1.681
λ [Å]	0.71073	0.71073	0.71073
μ [mm^{-1}]	1.409	1.376	1.354
*R*1[a] (obsd. data)	0.0381	0.0261	0.0329
*wR*2[b] (obsd. data)	0.0764	0.0537	0.0761

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. [b] $wR2 = [\Sigma w(|F_o^2| - |F_c^2|)^2/\Sigma wF_o^4]^{1/2}$.

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Reactivity Tests: All reactivity tests were performed using the 12 place Carousel Reaction Station with Reflux Heads from Radleys Discovery Technologies (RR98030) or the Cooled Carousel Reaction Station from Radleys Discovery Technologies (RR99900). All the reactions were performed under nitrogen at room temperature in 5 mL of solvent. For more details refer to the result section. The benzaldehyde was distilled prior to use and 2-hydroxyacetophenone was purified on a silica gel column (hexane/ethyl acetate, 1:1). Procedure A (Entry 7, Table 2): diethylzinc (46 μL, 1.1 M) in toluene was added to ligand **9** (11.5 mg, 0.0.05 mmol) in dry THF (5 mL). After 10 min, benzaldehyde (53 mg, 0.5 mmol), and hydroxyacetophenone (90 mg, 0.66 mmol) were added, and the reaction mixture was stirred under N_2 for 48 h. The solvent was evaporated and the products analyzed by ^{1}H NMR spectroscopy. The coupling product **12** was formed in 62% yield. The ^{1}H NMR spectroscopic yields were determined by the ratio of the areas of the following peaks: benzaldehyde (δ = 10.03 ppm, 1 H), 2-hydroxyacetophenone (δ = 4.90 ppm, 2 H) and the four doublets corresponding to the two diastereomers of **12** (*anti*: δ = 5.41 ppm, 1 H and δ = 5.08 ppm, 1 H; *syn*: δ = 5.24 ppm, 1 H and δ = 4.95 ppm, 1 H).[27] Procedure B: Benzaldehyde (53 mg, 0.5 mmol), 2-hydroxyacetophenone (90 mg, 0.66 mmol), **2b** (20.1 mg, 0.049 mmol) and 35 μL of triethylamine in dry methanol (5 mL) were stirred at room temperature under N_2 for 48 h. The reaction mixture was analyzed as described above to give 59% of product **12**.

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