Journal of the Iranian Chemical Society
https://doi.org/10.1007/s13738-019-01830-z

ORIGINAL PAPER

One-pot synthesis and biological and catalytic applications of organometallic complexes involving oxazolines and (R)/(S)-a-phenylethylamine

Mei Luo[1] · **Hong Mei Li**[2]

Received: 11 September 2018 / Accepted: 7 December 2019

Abstract
The crystal structures of zinc complexes **1** and **3** were determined following synthesis via a one-pot method involving the reaction of 2-hydro-6-methyl-nicotinonitrile and 2-cyanopyridine with different L-amino alcohols mediated by 120–130 mol% $ZnCl_2$. Copper complex **4** and cobalt complex **5** were prepared by reacting (R)/(S)-a-phenylethylamine with dimethyl dichloride silane in the presence of 52 mol% $CuCl_2$ or 50 mol% $CoCl_2$ as the third components. Crystalline compounds **1**–**5** were all characterized by elemental analysis, IR and NMR spectroscopies, and X-ray diffraction. Then, complexes **1** and **3**–**5** were evaluated for cytotoxicity against the human tumor cell line SMMC-7721 and were also used as catalysts in the nucleophilic addition reaction of trimethylsilonitrile with diphenylketimine. Both complexes exhibited anticancer activity against the human tumor cell line SMMC-7721 and showed enhanced catalytic effects.

Keywords Organometallic complexes · One-pot method · Nitriles · L-amino alcohols · (R)/(S)-a-phenylethylamine · Dimethyl dichloride silane · Cytotoxicity · Nucleophilic addition reaction of trimethylsilonitrile with diphenylketimine

Introduction

Chiral organometallic complexes containing oxazolines exhibit a broad range of catalytic activities [1–4]. Many syntheses of these organometallic complexes and supermolecular complexes have been reported in the literature [5–9]. For example, NCN-pincer metal complexes (Ti, Cr, V, Zr, Hf and Nb) of the Phebox ligand (S,S)-2,6-bis(4′-isopropyl-2′-oxazolinyl)phenyl were tested as precatalysts in ethene polymerization [5]; chiral CNN pincer palladium(II) complexes with 2-aryl-6-(oxazolinyl)pyridine ligands are used for enantioselective allylation of isatins and the Suzuki–Miyaura coupling reaction [6]. The Phebox-Rh and Phebox-Ru complexes serve as efficient and selective catalysts in asymmetric reactions for carbon–carbon bond formation [7]; chiral bifunctional rhodium complexes bearing chiral bis(oxazolinyl) Ph ligand (Phebox) can serve as a mild Lewis acid catalyst for asymmetric allylation, hetero-Diels-Alder and Michael reactions [8]. These complexes exhibit moderate to significant catalytic effects in the above organic reactions. In addition, supramolecular compounds such as foldamers and their complexes with anions have the potential to imitate biomolecular analogues by strongly binding to specific guests or selectively catalyzing reactions [9]. Additionally, the supermolecular complex of anionic cyclodextrin can also be used for high-sensitivity fluorescence spectrophotometry to detect residual methylene blue in plasma [10]. Inspired by the pioneering works, our research group has reported the crystal structures of zinc-oxazolinyl complexes and copper and cobalt complexes involving (R)/(S)-a-phenylethylamine and applied them to the research on anticancer activity and nucleophilic addition reaction of trimethylsilonitrile with diphenylketimine [11].

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s13738-019-01830-z) contains supplementary material, which is available to authorized users.

✉ Mei Luo
luomei@pku.edu.cn

[1] College of Chemistry and Chemical Engineering, Hefei University of Technology, Hefei 230009, People's Republic of China

[2] State Key Laboratory of Phytochemistry and Plant Resource in West China, Kunming Institute of Botany, Chinese Academy of Science, Kunming 650201, China

Published online: 17 December 2019

Experimental section

Materials and measurements

Unless otherwise stated, 2-hydro-6-methyl-nicotinonitrile and 2-cyanopyridine, S-leucinol, S-phenylalaninol, (R)/(S) -1-phenylethylamine and dimethyl dichloride silane were purchased from Acros, Aldrich or Fluka, USA. Flash column chromatography was performed using Merck silica gel (60, particle size 0.02–0.03 mm). ^{1}H and ^{13}C NMR spectra were recorded using Bruker AM-500 and Bruker AM-600 spectrometers. Chemical shifts are reported in ppm (δ) with the solvent relative to tetramethylsilane (TMS) employed as the internal standard (residual $CHCl_3$, δH 7.26 ppm; $CDCl_3$, *c* 77 ppm). The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. Infrared spectra were recorded on a Mattson Galaxy Series FTIR 3000 spectrometer; peaks are reported in cm^{-1}. Elemental analyses were performed on an Elemental Analyzer AE-3000. High-resolution mass spectra (HRMS) were obtained on a Micro GCT-MS equipped with an EI ion source. Optical rotations were measured on a WZZ-1 automatic polarimeter with a 2-cm cell recorded at the sodium D-line.

X-ray analyses

X-ray crystal data were collected on a Bruker SMART diffractometer equipped with graphite monochromatic MoKα radiation ($\lambda = 0.7103$ Å). The structure was solved by full-matrix least squares on F2 using the SHELXTL program. All non-H atoms were refined with anisotropic thermal parameters. All hydrogen atoms were located theoretically and refined with riding model position parameters and fixed isotropic thermal parameters. Crystallographic parameters are listed in Table 1.

Cytotoxicity assay

The human tumor cell lines SMMC-7721 (Liver cancer) was used in the cytotoxic assay. These cell lines were obtained from ATCC (Manassas, VA, USA). Cells were cultured in RMPI-1640 or DMEM (Biological Industries, Kibbutz Beit Haemek, Israel) supplemented with 10% fetal bovine serum (Biological Industries) at 37 °C in a humidified atmosphere with 5% CO_2. The cytotoxicity assay was evaluated by the MTS (Promega, Madison, WI, USA) assay.

The cytotoxicity assay was evaluated by the 3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, inner salt (MTS) (Promega, Madison, WI, USA) assay [12]. Briefly, cells were seeded into each well of a 96-well cell culture plate. After 12 h of incubation at 37 °C, the test compound (100 μM) was added. After incubated for 48 h, cells were subjected to the MTS assay. Compounds with a growth inhibition rate of 50% were further evaluated at concentrations of 0.064, 0.32, 1.6, 8, 40 and 100 (μM) in triplicate, with cisplatin and paclitaxel (Sigma, St. Louis, MO, USA) as positive controls. The IC50 value of each compound was calculated with Reed and Muench's method [13]. The results are given in Table 4.

Synthesis of compounds 1–5

2-(4S-Isobutyl-4,5-dihydro-oxazol-2-yl)-pyridine zinc, complex (1)

Dry $ZnCl_2$ 1.5603 g (11.45 mmol), 2-cyanopyridine 1.0018 g (7.47 mmol) and L-leucinol 2.0789 g (17.7 mmol) were added under anhydrous and oxygen-free conditions to a dry 100-mL Schlenk flask. They were dissolved in 40 mL of dry chlorobenzene, and the reaction mixture was refluxed for 60 h. The solvent was removed under reduced pressure, and the residue was dissolved in 15 mL of H_2O and extracted with 10 × 3 mL of dichloromethane. The solvent was removed under vacuum, giving a crude red oil. Further purification was performed on silica gel (petroleum ether/dichloromethane 1/4). Colorless crystals were obtained in 58% yield. $[a]_D^5 = +20.83°$ ($c = 0.288$, CH_3OH): δ_H (600 MHz, DMSO-d_6, 27 °C) 8.80–8.81 (m, 1H), 8.20–8.24 (m, 1H), 8.04–8.06 (m, 1H), 7.87–7.90 (m, 1H), 5.05–5.09 (m, 1H), 4.58–4.70 (m, 1H), 4.54 (t, $J = 8.6$ Hz, 1H), 1.96–2.00 (m, 2H), 1.52–1.56 (m, 1H), 1.00–1.04 (dd, J = 6.3 Hz, 6.4 Hz, 6H); δ_C (125 MHz, $CDCl_3$) 166.1, 149.9, 141.3, 140.5, 129.8, 124.1, 78.4, 62.2, 44.1, 25.5, 22.7, 22.2. IR: 3445, 3071, 2957, 2870, 1652, 1592, 1493, 1474, 1442, 1404, 1389, 1298, 1280, 1160, 10,921, 1050, 1019, 941, 833, 753, 664, 636, 459; Elemental analysis for $C_{24}H_{32}Cl_4N_4O_2Zn_2$: Found: C: 42.51, H: 5.10, N: 8.02%; Calculated: 42.32, H: 4.74, N: 8.23%.

Leucinol hydrochloride, compound 2

This was prepared using the same procedure described above for compound **1**. Further purification was performed on silica gel (petroleum ether/dichloromethane 1/9) to obtain the colorless crystals of second component, yield: 15%; m.p.: 68–70 °C, $[a]_D^5 = -10.2°$ (*c* 0.098, CH_3OH); ^{1}H NMR (500 MHz, $CDCl_3$) 7.90 (s, 1H), 5.27 (s, 1H), 3.54 (s, 1H), 3.04 (s, 1H), 1.66 (s, 1H), 1.35 (s, 2H), 0.84 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) 62.7, 52.9, 39.7,25.5, 24.4, 23.9; calculated: C, 46.90; H, 10.50; N, 9.12%; found: C, 46.68; H, 10.66; N, 8.98%; IR (KBr): 3415, 3291, 3196, 3062, 2929, 2855, 1586, 1535, 1497, 1454, 1378, 1266, 1195, 1156, 1056, 1011, 901, 846, 760.

Table 1 Crystal data and structure refinement for compounds **1**–**5**

Complexes	**1**	**2**	**3**	**4**	**5**
Formula	$C_{24}H_{32}Cl_4Zn_2N_4O_2$	$C_6H_{16}ClNO$	$C_{70}H_{74}Cl_7Zn_4N_9O_{14}$	$C_{16}H_{24}Cl_4CuN_2$	$C_{24}H_{36}Cl_5CoN_3$
Formula weight	681.07	153.65	1711.01	449.71	602.74
μ (mm^{-1})	1.957	0.340	1.284	0.713	1.021
D_c (g cm^{-3})	1.488	1.073	1.235	1.549	1.317
Formula weight	681.07	153.65	1711.01	449.71	602.74
Color	Colorless	Colorless	Colorless	Green	Blue
Shape	Prismatic	Prismatic	Prismatic	Prismatic	Prismatic
Size (mm^3)	0.20×0.16×0.10	0.180×0.140×0.050	0.12×0.06×0.04	0.211×0.175×0.078	0.211×0.121×0.076
T (K)	293(2)	293(2)	140(2)	293(2)	293(2)
Crystal system	Triclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic
Space group	P 1	P2(1)	P 2(1) 2(1) 2(1)	C 2	P 2(1)
a (Å)	8.4425(15)	12.399(7)	15.717(2)	10.5223(14)	14.061(2)
b (Å)	9.8894(17)	5.378(3)	23.088(3)	7.2285(14)	7.5110(13)
c (Å)	9.9721(17)	14.309(8)	25.358(4)	13.872(2)	14.554(3)
α	90	90	90	90	90
β (°)	98.582(3)	94.540(11)	90	95.929(4)	98.685(4)
γ (°)	94.654(3)	90	90	90	90
V ($Å^3$)	111.089(3)	951.2(9)	9202(2)	1049.5(4)	1519.4(5)
Z	1	4	4	2	2
Wavelength	λ = 0.71073	λ = 0.71073	λ = 0.71073	λ = 0.71073	λ = 0.71073
Radiation type	MoKα	MoKα	MoKα	MoKα	MoKα
Θ_{min} (°)	2.088	1.428	3.048	2.99	1.88
Θ_{max} (°)	25.494	25.994	52	25.99	25.05
Measured refl.	4370	5399	66,283	3152	8034
Independent refl.	3503	3620	18,077	1974	5091
Reflection with $I > 2/(I)$	3503	3620	18,077	1974	5091
R_{int}	0.0163	0.0801	0.1284	0.0294	0.0521
Parameters	329	230	821	119	304
Restraints	4	69	105	4	1
Largest diff. peak and hole	0.388, −0.182	0.520, −0.477	0.832, −0.715	0.314, −0.283	1.030, −0.604
GoodF	1.017	0.971	1.061	1.001	1.273
wR_2 (all data)	0.0841	0.2638	0.1218	0.0698	0.0947
wR_2	0.0807	0.2142	0.1301	0.0690	0.2028
R_1 (all data)	0.0369	0.2529	0.1077	0.0289	0.0859
R_1	0.0314	0.0926	0.0698	0.0277	0.1989

Tris-*N*-[3(R)-(2-hydroxy-1-phenyl-ethylamino)-2-phenyl-propyl]-2,5-dimethyl-benzamide zinc (II), complex 3

This was prepared using the same procedure described above for compound 1 by refluxing a mixture of anhydrous $ZnCl_2$ (3.7653 g, 27.63 mmol), 2-hydro-6-methyl-nicotinonitrile (2.2152 g, 16.51 mmol) and L-phenylglycinol (4.0020 g, 58.33 mmol) in 40 mL of dry chlorobenzene. The product was obtained in 46% yield as colorless crystals after column chromatography (petroleum ether/dichloromethane 4/1). m.p. 162–164 °C, $[\alpha]_D^{25} = +29.76°$ (c = 1.428, CH_3OH); δ_H (600 MHz, DMSO-d_6, 27 °C), 12.47–12.49 (m, 1H), 10.50–10.61 (m 1H), 10.32 (s, 2H), 8.28 (s, 1H), 8.14 (s, 2H), 7.95–8.02 (m, 1H), 7.20–7.26 (m, 32H), 6.28 (s, 2H), 5.06 (s, 3H), 4.77 (s, 3H), 4.32 (s, 1H), 3.67 (d, J = 3.5 Hz, 4H), 3.39–3.41 (m, 4H), 3.26 (s 2H), 2.68 (s, 3H), 2.59–2.60 (m, 3H), 2.27 (s 9H); δ_C (150 MHz, DMSO-d_6) 163.6, 163.4, 151.3, 144.4, 142.5, 141.9, 128.8, 128.6, 127.9, 127.4 127.3, 126.8, 117.5, 106.4, 79.6, 66.9, 64.7, 56.5, 53.3, 19.0; ν_{max} 3423, 3031, 2928, 1660, 1613, 1585, 1562, 1495, 1384, 1324, 1265, 1199, 1148, 1057, 791, 761, 701, 704, 570, 535. Elemental analysis: Found C: 48.93, H: 4.68, N: 7.21%; $C_{70}H_{74}Cl_7N_9O_{10}Zn_4$ calculated C: 49.14, H: 4.36, N: 7.37%.

Chiral (R)-1-phenylethylamine hydrochloride copper chloride, complex 4

A mixture of anhydrous $CuCl_2{\cdot}2H_2O$ (4.3747 g, 25.67 mmol), (R)-1-phenylethylamine (5.9138 g, 48.80 mmol) and diphenyldichlorosilane (5.0 mL) was refluxed in chlorobenzene for 72 h. The chlorobenzene was then removed, and the residue was crystallized from chloroform and anhydrous methanol to afford the final product. Yield: 90%, m.p.: 154–156 °C, $[\alpha]_D^{25} = +3.82°$ (0.130, CH_3OH), Elemental analysis: Found C: 42.25%, H: 5.13%, N: 6.31%; $C_{16}H_{24}Cl_4N_2Cu$ calculated C: 42.73%, H: 5.38%, N: 6.23%; IR (KBr): 3424, 3106, 2982, 2952, 2656, 2553, 2456, 1884,1594, 1564, 1494, 1456, 1386, 1370, 1351, 1335, 1315, 1288, 1223, 1160, 1083, 1059, 1030, 971, 919, 766, 749, 698, 578, 536, 476.

Chiral (S)-1-phenylethylamine hydrochloride cobalt chloride, complex 5

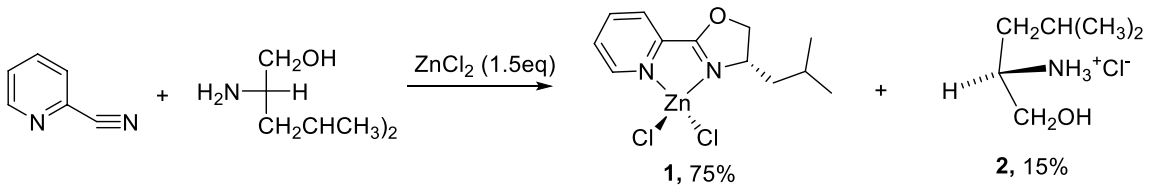
This was prepared using the same procedure described above for compound **4** by refluxing a mixture of anhydrous $CoCl_2{\cdot}6H_2O$ (4.3747 g, 25.58 mmol), (S)-1-phenylethylamine (5.9138 g, 948.8 mmol) and diphenyldichlorosilane (5.0 mL) in chlorobenzene for 72 h. The chlorobenzene was removed, and the residue was crystallized from chloroform and anhydrous methanol to afford green crystals. Yield: 88%, m.p.: 123–125 °C, $[a]_D^5 = -27.2°$ (0.0736, CH_3OH). δ_H (500 MHz, $CDCl_3$, 27 °C) 8.36(d, $J = 0.7$ Hz, 2H), 7.42–7.50 (m, 3H), 4.39–4.41 (m, 1H), 2.50–2.52 (m, 3H), 1.51(d, $J = 6.8$ Hz, 2H); δ_C (125 MHz, $CDCl_3$) 139.9, 130.1, 129.8, 128.1, 51.5, 22.8. Elemental analysis: Found C: 37.93, H: 4.88, N: 5.26%, $C_{24}H_{36}Cl_5N_3O_{10}Co$ calculated C: 37.79, H: 4.76, N: 5.51%. IR (KBr): 3550, 3425, 3111, 2934, 2568, 2452, 1593, 1486, 1457, 1386, 1316, 1290, 1224, 1168, 1086, 1063, 1030, 970, 920, 767, 698.

Results and discussion

Syntheses

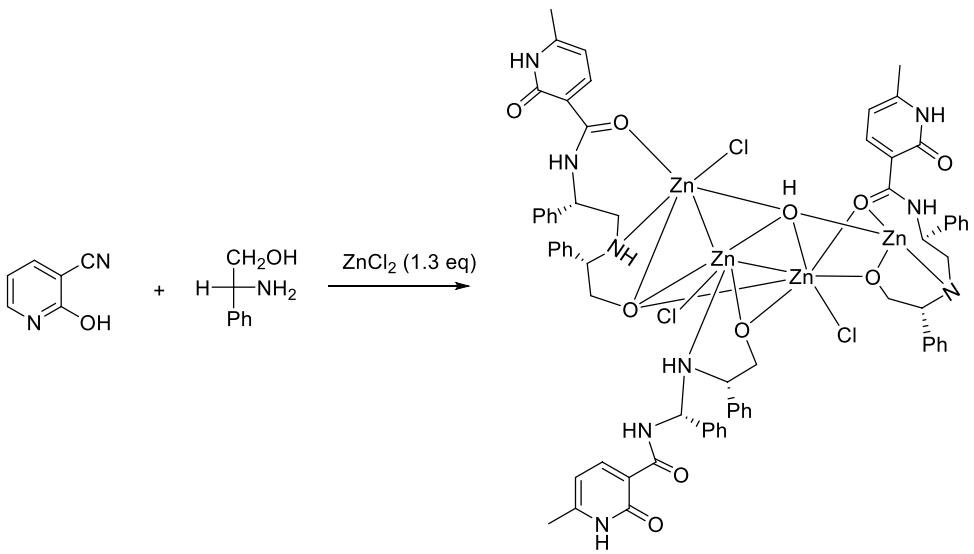
The synthetic routes for compounds **1**–**5** are shown in Schemes 1, 2 and 3.

The direct reactions of 2-hydro-6-methyl-nicotinonitrile with L-phenylglycinol and 2-cyanopyridine with L-leucinol mediated by 131 mol% or 153 mol% ZnCl2 afforded complexes **1** and **3**, respectively. Additionally, by-product

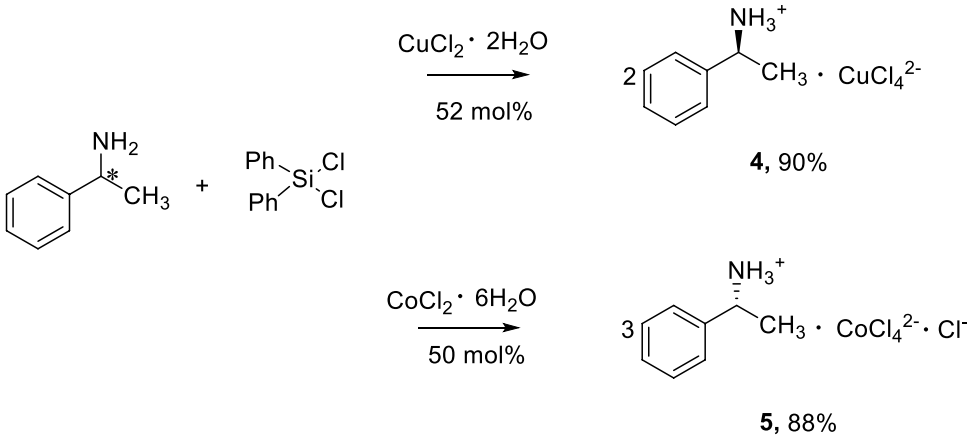


Scheme 1 Synthetic route for complex **1** and compound **2**

Scheme 2 Synthetic route for complex **3**



Scheme 3 Synthetic routes for complexes **4**–**5**



compound **2** was also obtained in preparing complex **1**. After column chromatography, slow evaporation was used to obtain the crystal structures.

Complexes **4** and **5** were both obtained by a general one-pot method from the reaction of cobalt chloride hexahydrate or copper chloride dihydrate, (R)/(S)-1-phenylethylamine and diphenyldichlorosilane in refluxing chlorobenzene for 72 h. Unfortunately, the target complexes with three components containing the silicon atom were not generated, and only the chiral a-phenylethylamine hydrochloride metal chloride salts, which contain two of the reactants, were generated.

Description of the crystal structures

In complex **1**, the zinc center adopts the expected square planar coordination geometry (Fig. 1: left) [10], and the pyox ligand is approximately planar except for the isobutyl group substituent at the 4th position of the oxazoline ring. The absolute configuration at the center is S. It is interesting to note that the Zn–N (oxazoline) bond [2.062(8) Å] is shorter than the zinc-*N*(pyridine) bond [2.200(2) Å]. Additionally, the Zn–Cl bond [2.191(2) Å] trans to the oxazoline is shorter than the Zn–Cl bond that is trans to the pyridine donor. The crystal structures of compound **2** consisted of (S) a-phenylethylamine molecule and a hydrochloride molecule with a free root. The C–N bond lengths and C=C bond lengths and angles in compound **2** were also in agreement with the literature and presented no unusual features (Fig. 1: right).

Interestingly, complex **3** was not the oxazolinyl zinc complex that would be similar to the reported structures [14]. Complex **3** shows octahedral hexa-coordination, which includes three *N*-[3(R)-(2-hydroxy-1-phenyl-ethylamino)-2-phenyl-propyl]-2,5-dimethyl-benzamide ligands in the lattice (Fig. 2). The three ligands are tridentate and encapsulate the central zinc atom. Both amino alcohol residues are coordinated to the zinc atom via their amino group (N2, N4 and N6) and hydroxyl group (O1–O6), forming a square planar coordination geometry and completing the octahedral coordination. Notably, only two acyloxy groups are attached to the zinc atom. The Zn–Cl bond lengths in complex **3** are 2.277(3) and 2.246(2) Å, and the Zn–N bond lengths in

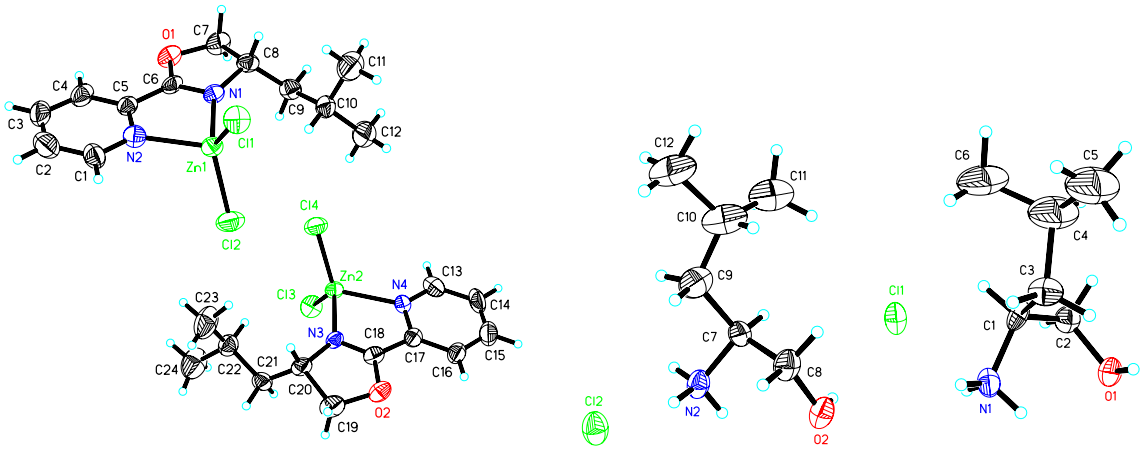


Fig. 1 ORTEP diagram of complex **1** and by-product **2** (30% probability thermal ellipsoids) (left: complex **1**, right: compound **2**)

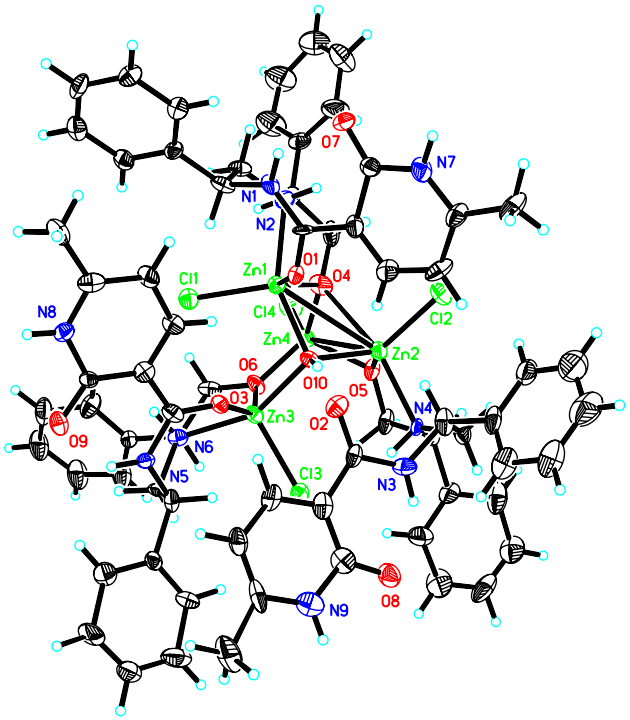


Fig. 2 ORTEP diagram of complex **3** (50% probability thermal ellipsoids)

complex **3** are 2.155(7), 2.149(6) and 2.128(7) Å. However, the three zinc atoms are connected to the oxygen of a rooted hydroxyl group (O(10)), which is 2.035(5), 2.001(5) and 2.061(5) Å from zinc atoms Zn1, Zn2 and Zn3, respectively, while the O(4) donor hydroxyl group is 2.025, 2.416 and 2.006(7) Å from zinc atoms Zn1, Zn2 and Zn4, respectively.

The crystal structures of copper complex **4** and cobalt complex **5** are very similar; for example, the Fig. 3 (left: complex **4**, right: complex **5**) (R)/(S)-1-phenylethylamine ligands are protonated with MCl_4^- as the anion, the structures consist of a distorted tetrahedral MCl_4^{2-} ion and two a-phenylethylamine ions, and complex salts of this type are well known in the literature for both of these compounds [11]. However, surprisingly, cobalt complex **5** had a chloride ion in its lattice and an extra a-phenylethylamine ion. The two equal Cu–Cl bond distances are 2.2285 and 2.2586 Å, but the four unequal Co–Cl bond distances are 2.250, 2.257, 2.276 and 2.287 Å. In complex **4**, three of the Cl–Cu–Cl angles are approximately $93 \pm 3°$, and the other is 152.2°; complex **5** was found to have six nearly equal Cl–Co–Cl angles of $110 \pm 5°$. The ligands on complexes **4** and **5** are all involved in N–H–Cl-type hydrogen bonding, and one bifurcated hydrogen bond was found. The chloride ion in the lattice and one a-phenylethylamine ion are disordered as a result of hydrogen bonding. Although first row transition metals, such as zinc, copper and cobalt, have a greater affinity for nitrogen than oxygen, for complexes **4** and **5**, they are supermolecular structures, and the N-donor auxiliary a-phenylethylamine ligand was not coordinated with metals. The supramolecular structures were connected with molecular interactions between N–H···Cl hydrogen bonds.

Tables 1, 2 and 3 list the bond lengths and angles for complexes **1** and **3**–**5** and the hydrogen bond lengths and angles for complexes **1** and **3**–**5**.

Symmetry transformations used to generate equivalent atoms for complex 1:

Cl4 $[x+1/2, -y+3/2, -z+2]$

Symmetry transformations used to generate equivalent atoms:

#1 $x-1/2, -y+3/2, -z+1$ #2 $-x+1/2, -y+1, z+1/2$

Symmetry transformations used to generate equivalent atoms for complex **3**:

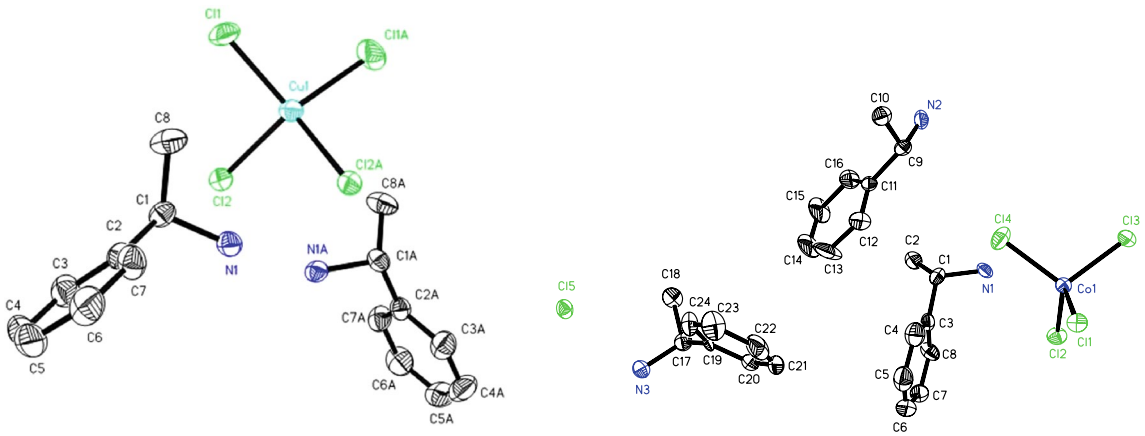


Fig. 3 ORTEP diagram of complexes **4** and **5** (50% probability thermal ellipsoids) (left: complex **4**, right: complex **5**)

Table 2 Selected bond lengths (Å) and bond angels (°) for complexes **1** and **3**

Bond (1)	Dist.	Bond (I)	Dist.	Bond (I)	Dist.
Zn(1)–N(1)	2.062(8)	Zn(1)–N(2)	2.118(7)	Zn(1)-Cl(1)	2.191(2)
Zn(1)–Cl(2)	2.200(2)				
Angle (1)	(°)	Angle (I)	(°)	Angle (I)	(°)
N(1)–Zn(1)–N(2)	80.3(3)	N(1)–Zn(1)–Cl(1)	114.41 (19)	N(2)–Zn(1)–Cl(1)	111.6(2)
N(4)–Zn(1)–Cl(2)	115.43(19)	N(2)–Zn(1)–Cl(2)	107.2(2)	Cl(1)–Zn(2)–Cl(2)	120.29(10)
Bond (3)	Dist	Bond (2)	Dist	Bond (3)	Dist
Zn(1)–O(4)	2.025(6)	Zn(2)–O(10)	2.001(5)	Zn(3)–N(6)	2.128(7)
Zn(1)–O(10)	2.035(5)	Zn(2)–N(4)	2.149(6)	Zn(3)–O(3)	2.164(6)
Zn(1)–O(1)	2.103(6)	Zn(2)–Cl(2)	2.246(2)	Zn(3)–Cl(3)	2.280()
Zn(1)–N(2)	2.155(7)	Zn(2)–O(4)	2.416(7)	Zn(4)–O(6)	1.913(6)
Zn(1)–Cl(1)	2.277(3)	Zn(2)–Zn(4)	2.9950(15)	Zn(4)–O(5)	1.970(6)
Zn(1)–Zn(2)	3.1595(15)	Zn(3)–O(6)	2.049(6)	Zn(4)–O(4)	2.006(7)
Zn(2)–O(5)	1.965(6)	Zn(3)–O(10)	2.061(5)	Zn(4)–Cl(4)	2.207(3)
Angle (3)	(°)	Angle (2)	(°)	Angle (3)	(°)
O(4)–Zn(1)–O(10)	82.1(2)	O(5)–Zn(2)–O(4)	6.9(2)	N(6)–Zn(3)–O(3)	86.1(2)
O(4)–Zn(1)–O(1)	132.8(2)	O(10)–Zn(2)–O(4)	73.6(2)	O(6)–Zn(3)–Cl(3)	109.99(18)
O(10)–Zn(1)–O(1)	85.1(2)	N(4)–Zn(2)–O(4)	158.0(2)	O(10)–Zn(3)–Cl(3)	103.18(16)
O(4)–Zn(1)–N(2)	81.1(3)	Cl(2)–Zn(2)–O(4)	96.13(17)	N(6)–Zn(3)–Cl(3)	103.27(19)
O(10)–Zn(1)–N(2)	150.8(3)	O(5)–Zn(2)–Zn(4)	40.51(16)	O(3)–Zn(3)–Cl(3)	105.62(16)
O(1)–Zn(1)–N(2)	89.1(3)	O(10)–Zn(2)–Zn(4)	80.43(16)	O(6)–Zn(4)–O(5)	104.9(3)
O(4)–Zn(1)–Cl(1)	115.0(2)	N(4)–Zn(2)–Zn(4)	116.22(17)	O(6)–Zn(4)–O(4)	106.8(2)
O(10)–Zn(1)–Cl(1)	105.62(16)	Cl(2)–Zn(2)–Zn(4)	129.51(9)	O(5)–Zn(4)–O(4)	87.4(3)
O(1)–Zn(1)–Cl(1)	112.17(17)	O(4)–Zn(2)–Zn(4)	41.84(16)	O(6)–Zn(4)–Cl(4)	118.12(18)
N(2)–Zn(1)–Cl(1)	103.0(2)	O(5)–Zn(2)–Zn(1)	108.73(17)	O(5)–Zn(4)–Cl(4)	121.40(19)
O(4)–Zn(1)–Zn(2)	49.88(19)	O(10)–Zn(2)–Zn(1)	38.88(15)	O(4)–Zn(4)–Cl(4)	113.47(19)
O(10)–Zn(1)–Zn(2)	38.10(15)	N(4)–Zn(2)–Zn(1)	144.05(19)	O(6)–Zn(4)–Zn(2)	93.04(17)
O(1)–Zn(1)–Zn(2)	95.69(15)	Cl(2)–Zn(2)–Zn(1)	97.84(8)	O(5)–Zn(4)–Zn(2)	40.39(17)
N(2)–Zn(1)–Zn(2)	114.7(2)	O(4)–Zn(2)–Zn(1)	39.85(13)	O(4)–Zn(4)–Zn(2)	53.45(19)
Cl(1)–Zn(1)–Zn(2)	133.17(7)	Zn(4)–Zn(2)–Zn(1)	68.22(3)	Cl(4)–Zn(4)–Zn(2)	148.78(8)
O(5)–Zn(2)–O(10)	112.4(2)	O(6)–Zn(3)–O(10)	92.7(2)	Zn(2)–O(10)–Zn(1)	103.0(2)
O(5)–Zn(2)–N(4)	83.6(2)	O(6)–Zn(3)–N(6)	81.9(2)	Zn(2)–O(10)–Zn(3)	121.3(3)
O(10)–Zn(2)–N(4)	105.2(2)	O(10)–Zn(3)–N(6)	153.3(2)	Zn(1)–O(10)–Zn(3)	108.4(2)
O(5)–Zn(2)–Cl(2)	123.14(19)	O(6)–Zn(3)–O(3)	144.1(2)	N(4)–Zn(2)–Cl(2)	103.10(18)
O(10)–Zn(2)–Cl(2)	119.46(17)	O(10)–Zn(3)–O(3)	83.1(2)		
Bond (4)	Dist	Bond (4)	Dist	Bond (3)	Dist
Cu(1)–Cl(1)	2.2285(8)	Cu(1)–Cl(2)#1	2.2586(7)	Cu(1)–Cl(2)	2.2586(7)
Cu(1)–Cl(1)#1	2.2285(8)				
Angle (4)	(°)	Angle (3)	(°)	Angle (4)	(°)
Cl(1)–Cu(1)–Cl(1)#1	96.04(5)	Cl(1)#1–Cu(1)–Cl(2)#1	92.82(3)	Cl(1)#1–Cu(1)–Cl(2)	152.22(3)
Cl(1)–Cu(1)–Cl(2)#1	152.22(3)	Cl(1)–Cu(1)–Cl(2)	92.82(3)	Cl(2)#1–Cu(1)–Cl(2)	91.45(4)
Bond (5)	Dist	Bond (4)	Dist	Bond (II)	Dist
Co(1)–Cl(4)	2.250(3)	Co(1)–Cl(1)	2.276(3)	Co(1)–Cl(3)	2.287(2)
Co(1)–Cl(2)	2.257(2)				
Angle (5)	(°)	Angle (4)	(°)	Angle (I)	(°)
Cl(4)–Co(1)–Cl(2)	110.72(11)	Cl(2)–Co(1)–Cl(1)	110.91(10)	Cl(2)–Co(1)–Cl(3)	110.35(10)

Table 2 (continued)

Angle (5)	(°)	Angle (4)	(°)	Angle (I)	(°)
Cl(4)–Co(1)–Cl(1)	112.36(13)	Cl(4)–Co(1)–Cl(3)	105.65(12)	Cl(1)–Co(1)–Cl(3)	106.63(10)

Table 3 Hydrogen bond lengths (Å) and bond angles (°) for complexes **1** and **3**–**5**

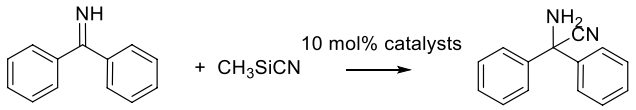
D–H···A (complex **1**)	*d* (D–H)	*d* (H···A)	*d* (D···A)	∠DHA
C(13)–H(13)···Cl(1)#2	0.93	2.83	148.5	3.656(13)
D–H···A (complex 3)	d(D–H)	d(H···A)	d(D···A)	∠DHA
N(1)–H(1B)…Cl(2)#2	0.827(18)	2.64(3)	3.229(3)	129(3)
N(1)–H(1B)…Cl(1)#2	0.827(18)	2.71(2)	3.480(3)	155(3)
N(1)–H(1A)…Cl(2)#1	0.825(18)	2.44(2)	3.217(2)	156(3)
N(1)–H(1A)…Cl(2)	0.825(18)	2.87(3)	3.425(3)	126(3)
N(1)–H(1C)…Cl(1)#3	0.828(18)	2.37(2)	3.170(3)	163(3)
D–H···A (complex 3)	d(D–H)	d(H···A)	d(D···A)	∠DHA
C(73)–H(73)…Cl(1)	1.00	2.70	3.55(3)	143.0
C(57)–H(57)…Cl(2)	1.00	2.87	3.581(15)	128.7
C(42)–H(42B)…Cl(6)	0.99	2.96	3.776(14)	140.5
C(42)–H(42B)…Cl(1)	0.99	2.88	3.532(13)	124.2
C(33)–H(33)…Cl(3)	1.00	2.59	3.444(13)	143.3
C(32)–H(32C)…O(8)#1	0.98	2.57	3.431(17)	146.8
C(32)–H(32A)…Cl(4)#2	0.98	2.90	3.548(13)	124.1
N(8)–H(8D)…Cl(4)#2	0.88	2.44	3.303(10)	165.4
C(18)–H(18A)…Cl(4)	0.99	2.90	3.625(14)	130.9
C(17)–H(17)…Cl(6)	1.00	2.94	3.923(16)	167.4
C(9)–H(9)…Cl(1)	1.00	2.73	3.558(12)	140.5
N(7)–H(7A)…O(9)#1	0.88	1.96	2.829(13)	171.7
N(6)–H(6A)…Cl(1)	1.00	2.97	3.580(9)	120.4
N(5)–H(5A)…O(9)	0.88	2.04	2.721(13)	133.5
N(4)–H(4A)…Cl(3)	1.00	2.46	3.395(9)	154.8
N(3)–H(3A)…O(8)	0.88	1.91	2.631(14)	137.4
N(1)–H(1A)…O(7)	0.88	1.97	2.685(12)	137.2
O(10)–H(10C)…O(2)	1.00	1.94	2.899(11)	160.3
D–H···A (complex 4)	d(D–H)	d(H···A)	d(D···A)	∠DHA
N(3)–H(3C)…Cl(1)#1	0.89	2.51	3.293(8)	146.8
N(3)–H(3B)…Cl(3)#2	0.89	2.36	3.236(9)	167.4
N(3)–H(3A)…Cl(5)	0.89	2.30	3.184(9)	173.3
N(2)–H(2C)…Cl(5)#3	0.89	2.28	3.109(8)	155.7
N(2)–H(2B)…Cl(1)#4	0.89	2.33	3.192(8)	162.6
N(1)–H(1C)…Cl(3)#5	0.89	2.30	3.182(9)	168.9
N(1)–H(1B)…Cl(1)#4	0.89	2.43	3.274(8)	158.1
N(1)–H(1A)…Cl(4)	0.89	2.83	3.350(8)	119.0
N(1)–H(1A)…Cl(2)	0.89	2.51	3.332(9)	153.3

Table 4 Cytotoxicity of complexes **1**–**4** against human tumor cell lines SMMC-7721

Complex	IC_{50} (μM)[a]				
	1	3	4	5	Cisplatin
SMMC-7721	86.19	14.01 ± 0.42	> 100	> 100	12.41

[a]Cytotoxicity as IC_{50} values for each cell line, the concentration of complex that caused a 50% reduction relative to untreated cells determined by the SRB assay

Table 5 Catalytic activity of complexes **1** and **3**–**5** to the addition reaction



Entry	Catalyst	Time (h)	Conv. (%)[a]
1	Complex 1	5	78.1
2	Complex 3	5	75.7
3	Complex 4	5	49.5
4	Complex 5	5	70.9
5	No	5	37.0

Reactions were carried out on 0.1 mL $(Ph)_2NH$ with 0.3 mL $(CH_3)_3SiCN$ in 2 mL CH_3OH at room temperature (10–20 °C)

[a]Conv. % was determined by ^{1}HNMR

#1 $-x+2, y, -z+2$ #2 $x-1/2, y-1/2, z$ #3 $x, y-1, z$

Symmetry transformations used to generate equivalent atoms for complex **4**:

#1 $x, y-1, z+1$ #2 $x, y, z+1$ #3 $x, y, z-1$ #4 $x, y-1, z$

All complexes **1** and **3**–**5** were evaluated for cytotoxicity against human tumor cell lines SMMC-7721. The results are presented in Table 4.

By comparing the activity of complexes **1** and **3**–**5**, complex **3** showed the relative best cytotoxic effects against SMMC-7721 cell line, with IC50 value 14.01 μM. Cisplatin was also shown for the sake of comparison, as given in Table 4 (supporting information).

Additionally, all complexes **1** and **3**–**5** were also used as the catalysts in nucleophilic addition of trimethylsilonitrile with diphenylketimine. Complexes **1** and **3**–**5** showed moderate to high conversions (50–78%). Among them, complex **1** afforded the relatively good catalytic effect. Table 5 lists the results of catalytic effects of all complexes **1** and **3**–**5**.

Conclusions

The crystal structures of complexes **1** and **3**–**5** were all obtained following their synthesis via a one-pot method. The structures directly demonstrate that one-pot three-component reactions can generate these novel organometallic complexes. Among the complexes, complex **3** exhibits relatively good anticancer activity and catalytic effects in the nucleophilic addition of trimethylsilonitrile with diphenylketimine. The reason for this finding is closely related to the complexity and macromolecular structure of this complex. The modified structures of complexes **1** and **3**–**5** are further applied in other organic reactions such as the coupling of amides with olefins and aldehydes, and their bioactivities, such as anticancer and HIV activities, are currently ongoing.

Acknowledgements This work was supported by the Hefei University of Technology and State Key Laboratory of Phytochemistry and Plant Resource in West China.

References

1. G. Desimoni, G. Faita, K.A. Jorgensen, Chem. Rev. **111**, 284 (2016)
2. D.-R. Hou, K. Burgess, Org. Lett. **1**, 1745–1747 (1999)
3. G. Martin, R. Oliver, Org. Lett. **2**, 2045 (2000)
4. J.M. Benito, C.A. Christensen, M. Meldal, Org. Lett. **7**, 581–584 (2005)
5. G. Bauer, M.D. Wodrich, R. Scopelliti, X. Hu, Organometallics **34**, 289–298 (2015)
6. T. Wang, X.-Q. Hao, J.-J. Huang, K. Wang, J.-F. Gong, M.-P. Song, Organometallics **33**, 194 (2014)
7. J.-I. Ito, H. Nishiyama, Synlett **23**, 509–523 (2012)
8. J.-I. Ito, H. Nishiyama, Top. Organometal. Chem. **37**, 185 (2011)
9. S. Debnath, A. Sengupta, K.V. Jose, K. Raghavachari, J. Chem. Theory Comput. **14**, 6226–6239 (2018)
10. R.W. Gunasekara, Y. Zhao, Langmuir **31**, 3919 (2015)
11. N. Sato, M. Jitsuoka, S. Ishikawa, K. Nagai, H. Tsuge, M. Ando, O. Okamoto, H. Iwaasa, A. Gomori, A. Ishihara, A. Kanatani, T. Fukami, Bio. Med. Chem. Lett. **19**, 1670 (2009)
12. A.H. Cory et al., Use of an aqueous soluble tetrazolium/formazan assay for cell growth assays in culture. Cancer Commun. **3**, 207 (1991)
13. L.J. Reed, H. Muench, A simple method of estimating fifty percent endpoints. Am. J. Hyg. **27**, 493 (1938)
14. M. Luo, J.C. Zhang, W.M. Pang, K.K. Hii, Chem. Cent. J. **11**, 81–89 (2017)