# Synthesis of a new analogue of BINOL based on a homodimer of substituted 1-hydroxypyrazole

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A new potential ligand for asymmetric synthesis, based on a homodimer of 1-hydroxypyrazole, has been synthesized. The chemistry involved lithiation, iodine–magnesium exchange, magnesium–zinc exchange, and cross-coupling reactions. In a preliminary study, the chemical activity of the ligand as a titanium(IV) complex was investigated in the addition of diethyl zinc to benzaldehyde. Its activity was comparable to the corresponding BINOL–Ti(IV) complex.

## Introduction

Asymmetric catalysis is a major subject in today's organic chemistry. A vast amount of chiral ligands for catalysts have been designed.[1] We have developed methods for regioselective introduction of various substituents in substituted *N*-hydroxy azoles.[2] Combining these two aspects led us to the design of new potential ligands, based on substituted *N*-hydroxyazoles. The resulting ligands hold several heteroatoms in the proximity of the catalyst's $C_2$-symmetric binding site. A general structure of such a ligand is shown in Fig. 1.

One of the key issues to be considered was the rotational barrier around the C5–C5′ single bond. The hydroxy groups are fairly small, thus quite sterically demanding R-groups were desirable.

## Results and discussion

Aromatic groups were first chosen for R, since these can be introduced readily at the 4-position, using Negishi or Suzuki cross-coupling protocols.[3] Various strategies may lead to the target molecule. First, in order to avoid a double cross-coupling reaction or a dianionic species, the 4-substituent was introduced prior to connecting the two pyrazole moieties. However, subsequent coupling of the two *ortho*-substituted rings, was not feasible, probably due to steric hindrance.

Consequently, the bipyrazole framework **2** (Scheme 1) was first established by palladium(0)-catalyzed Negishi cross-coupling of 1-benzyloxy-5-iodopyrazole[4] with 1-benzyloxypyrazol-5-ylzinc(II) chloride, obtained from 1-benzyloxypyrazole (**1**) by lithiation and transmetallation. This cross-coupling sequence proceeded smoothly and in good yield. For further functionalization, two iodines were introduced regioselectively in the 4- and 4′-positions. Treating the substrate with a large excess of iodine monochloride using potassium carbonate as base gave a rapid introduction of the first iodine. At room temperature, satisfactory conversion to the diiodinated compound (**3**) took four days. Heating the reaction resulted in side-reactions.

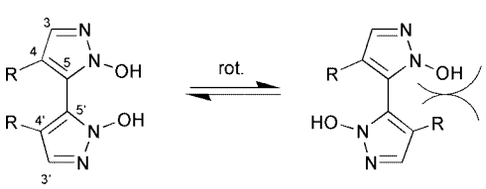
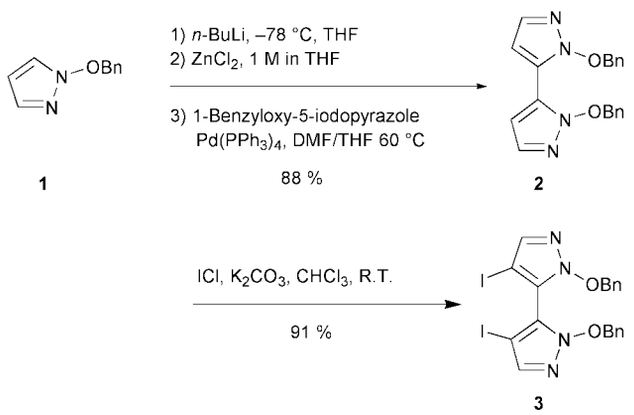
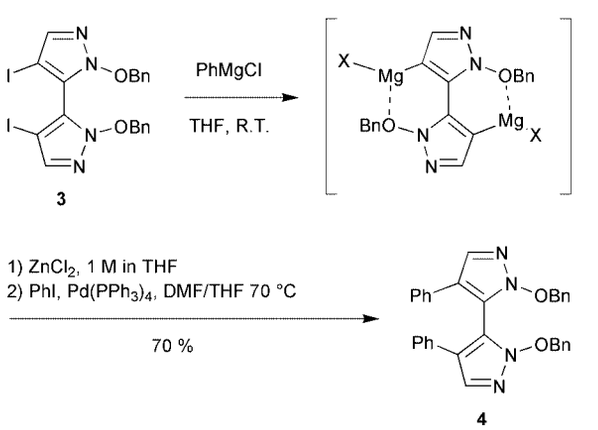



**Fig. 1** A general structure of the new ligands.




**Scheme 1**

The Negishi conditions used in the successful cross-coupling of the bipyrazolyl framework were then tried for the introduction of phenyl groups at C-4 and C-4′. In this case, the iodines of the bipyrazolyl compound (**3**) did not react. However, "umpolung" of the reaction by a double iodine–magnesium exchange to the dimagnesium species, followed by magnesium–zinc exchange, and then cross-coupling with iodobenzene, resulted in the desired diphenyl compound (**4**) as shown in Scheme 2.




**Scheme 2**

A disadvantage of this method was that a huge excess of phenylmagnesium chloride had to be applied to get the dimagnesium species. This necessitated an even bigger excess of

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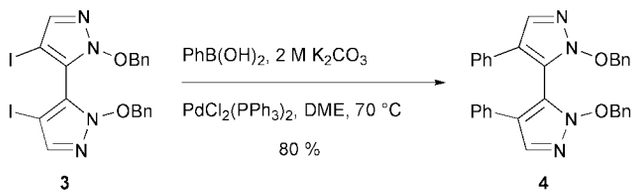
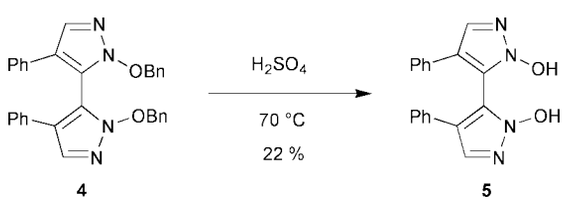
iodobenzene for the next step and caused formation of substantial amounts of biphenyl as a by-product. The more reactive metal reagent isopropylmagnesium chloride was tried, but resulted in reduction of the diiodo species. A plausible explanation could be that the high basicity of the dianionic species led to abstraction of a proton, probably from the isopropyl halide formed, before transmetallation occurs.

To improve the yield and avoid the by-product, Suzuki conditions were applied. In contrast to what was observed using Negishi conditions, the diiodo species (**3**), when reacted with phenylboronic acid, afforded the diphenyl-substituted product (**4**). This indicates that the Suzuki reaction is more tolerant to steric encumbrance than the Negishi reaction. The sequence is shown in Scheme 3.




**Scheme 3**

Finally, the two benzyl groups in **4** were removed. Our first attempt was debenzylation by hydrogenolysis as this has proven successful for related compounds,[4] but for the given compound this was of no avail. The simple dimeric compound **2** has earlier been successfully debenzylated by treatment with HCl and heat, but for **4** this strategy resulted in unchanged starting material. However, heating in concentrated sulfuric acid[5] led to debenzylation, and upon dilution with water, the free dihydroxy compound (**5**) precipitated as a white solid, which was isolated in 22% yield, as shown in Scheme 4.




**Scheme 4**

The racemic compound was subjected to preliminary tests as a catalyst ligand in the addition of diethylzinc to benzaldehyde. The titanium(IV) complex of ligand **5** was prepared *in situ* by reaction with titanium tetraisopropoxide, and the chemical activity of this complex in the above-mentioned reaction was comparable to the corresponding BINOL–Ti(IV) complex. Currently, the rotational barrier of the compound is being determined experimentally in order to establish whether the barrier is sufficiently high to allow optical resolution.

## Conclusion

The synthesis of a new ligand type for asymmetric synthesis has been developed. The ligand is based on a $C_2$-symmetric homodimer of 1-hydroxypyrazole. In the key step, two iodine atoms were introduced and then replaced by two phenyl groups, using cross-coupling conditions. Subsequent deprotection afforded the free ligand, which coordinated to Ti(IV). The Ti(IV) complex served as a catalyst in the addition of diethylzinc to benzaldehyde.

## Experimental

### General

All chemicals and solvents used were of synthesis quality unless otherwise stated. The solution of *n*-BuLi was titrated using *N*-pivaloyl-*o*-toluidine.[6] THF was distilled over sodium. Flash chromatography was performed using silica gel (Merck 60, 70–230 mesh). NMR spectra were recorded on a 300 MHz instrument (Varian Gemini), using TMS as an internal reference. When DMSO-$d_6$ was used as solvent, the ppm values refer to the DMSO-$d_5$ signal (2.50 ppm). Melting points were measured on a Büchi apparatus, and are uncorrected. Elemental analyses were performed by Microanalytical Laboratory, Department of Physical Chemistry, University of Vienna, Austria.

### Synthesis

**1,1′-Bis(benzyloxy)-5,5′-bipyrazolyl (2).** 1-Benzyloxypyrazole (**1**) (4.00 g; 23.0 mmol) was dissolved in dry THF (50 mL), and cooled to −78 °C under a nitrogen atmosphere. A 1.58 M solution of *n*-BuLi in hexane (17.4 mL; 27.6 mmol) was added dropwise over 10 minutes. After an additional 10 minutes, a 1 M solution of $ZnCl_2$ in dry THF (34.4 mL; 34.4 mmol) was added. The reaction mixture was allowed to warm to room temperature, before addition of a solution of 1-benzyloxy-5-iodopyrazole (6.96 g; 23.1 mmol) and tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] (1.33 g; 1.15 mmol; 5 mol%) in dry DMF (25 mL) was added. The reaction mixture was heated to 60 °C for 19 hours, then cooled to room temperature and quenched by adding saturated aqueous ammonium chloride (100 mL). Neutralization and extractive work-up with DCM, followed by chromatography on silica gel, resulted in pale yellow crystals. Recrystallization from EtOAc–heptane gave the product **2** (7.02 g, 88%) as colorless needles, mp 117.0–117.2 °C (Found: C, 69.62; H, 5.03; N, 16.39. $C_{20}H_{18}N_4O_2$ requires C, 69.35; H, 5.24; N, 16.17%); $\delta_H(CDCl_3)$ 5.09 (4H, s, $CH_2$), 6.49 (2H, d, $J$ = 2.4 Hz, H4, Pz), 7.25–7.33 (10H, m, Ph), 7.28 (2H, d, $J$ = 2.4 Hz, H3, Pz); $\delta_C(CDCl_3)$ 80.4 ($CH_2$), 104.0 (C4, Pz), 124.1 (C1, Ph), 128.6 and 130.0 (C2 and C3, Ph), 129.4 (C4, Ph), 133.0 (C5, Pz), 133.1 (C3, Pz).

**1,1′-Bis(benzyloxy)-4,4′-diiodo-5,5′-bipyrazolyl (3).** To a stirred mixture of 1,1′-bis(benzyloxy)-5,5′-bipyrazolyl (**2**) (0.69 g; 2.00 mmol) and potassium carbonate (1.66 g; 12.0 mmol) in chloroform (20 mL) at room temperature under nitrogen, iodine monochloride (1.95 g; 12.0 mmol) in chloroform (2 mL) was added, and the reaction was stirred for four days. The reaction was quenched by addition of a 1 M aqueous solution of sodium sulfite (10 mL), and worked up as described above. The crude product was purified by recrystallization from petroleum ether to give the product **3** (1.09 g, 91%) as a 94% pure solid ($^1$H NMR). An analytical sample was obtained by chromatography; mp 72.2–73.2 °C (Found: C, 40.37; H, 2.54; N, 9.07. $C_{20}H_{16}N_4O_2I_2$ requires C, 40.16; H, 2.70; N, 9.37%); $\delta_H(CDCl_3)$ 5.13 (2H, d, $J$ = 10.1 Hz, $CH_2$), 5.19 (2H, d, $J$ = 10.1 Hz, $CH_2$), 7.15–7.18 and 7.26–7.33 (10H, m, Ph), 7.50 (2H, s, H3, Pz); $\delta_C(CDCl_3)$ 61.2 (C4, Pz), 81.3 ($CH_2$), 125.3 (C1, Ph), 128.8 and 129.6 (C2 and C3, Ph), 129.5 (C4, Ph), 132.8 (C5, Pz), 138.6 (C3, Pz).

**1,1′-Bis(benzyloxy)-4,4′-diphenyl-5,5′-bipyrazolyl (4).** *Method A.* 1,1′-Bis(benzyloxy)-4,4′-diiodo-5,5′-bipyrazolyl (**3**) (0.60 g; 1.00 mmol) was dissolved in dry THF (10 mL) under nitrogen. After cooling to 0 °C, a 1.2 M solution of phenylmagnesium chloride in THF (4.2 mL; 5.0 mmol) was added and the temperature was allowed to rise to room temperature. After 5.5 hours, a 1 M solution of $ZnCl_2$ in dry THF (7.5 mL, 7.5 mmol) was added, followed by addition of a solution of iodobenzene (2.04 g; 10.0 mmol) and $Pd(PPh_3)_4$ (0.12 g; 0.10 mmol; 10 mol%) in dry DMF (7.5 mL). The reaction mixture was heated to 70 °C for 17 hours, then cooled and quenched by addition of saturated ammonium chloride (50 mL), and worked up as above. The crude product was purified by chromatography to give the product **4** (0.35 g, 70%) as a colorless oil;

$\delta_H(CDCl_3)$ 4.86 (2H, d, $J = 9.9$ Hz, $CH_2$), 5.12 (2H, d, $J = 9.9$ Hz, $CH_2$), 7.06–7.09 (4H, m, H3 Bn), 7.16–7.25 (16H, m, H2 + H4 Bn, Ph), 7.70 (2H, s, H3, Pz); $\delta_C(CDCl_3)$ 80.8 ($CH_2$), 120.1 and 122.4 (C1, Ph and Bn), 126.5, 128.7, 129.1, and 129.6 (C2 and C3, Ph and Bn), 127.4 and 129.3 (C4, Ph and Bn), 131.5 (C3, Pz), 131.7 (C4, Pz), 133.3 (C5, Pz).

*Method B.* 1,1′-Bis(benzyloxy)-4,4′-diiodo-5,5′-bipyrazolyl (**3**) (0.50 g; 0.84 mmol) and phenylboronic acid (0.82 g; 6.7 mmol) were dissolved in DME (20 mL). A 2 M aqueous solution of potassium carbonate (6.7 mL) was added, and the mixture was bubbled with nitrogen for 25 minutes. Bis(triphenylphosphine)palladium(II) dichloride was added and the reaction mixture was heated to 70 °C for 24 hours under nitrogen. After cooling to room temperature, the reaction was quenched by addition of saturated sodium hydrogen carbonate (40 mL) and water (40 mL). Work-up as above followed by chromatography gave the product **4** (0.34 g, 80%) as a colorless oil. NMR data obtained were similar to those given above.

**1,1′-Dihydroxy-4,4′-diphenyl-5,5′-bipyrazolyl (5).** 1,1′-Bis-(benzyloxy)-4,4′-diphenyl-5,5′-bipyrazolyl (**4**) (0.28 g; 0.57 mmol) was dissolved in conc. sulfuric acid (5 mL) and heated to 70 °C for 90 minutes. The reaction mixture was cooled and poured into water (30 mL). A white solid precipitated. The solution was centrifuged, and the product **5** was isolated by decantation (39 mg, 22%); mp > 220 °C (Found: C, 67.69; H, 4.41; N, 17.30. $C_{18}H_{14}N_4O_2$ requires C, 67.92; H, 4.43; N, 17.60%); $\delta_H$(DMSO-$d_6$) 7.09–7.21 (10H, m, Ph), 7.77 (2H, s, H3, Pz), 12.64 (2H, br s, OH).

### Addition of diethylzinc to benzaldehyde catalyzed by the titanium(IV)–1,1′-dihydroxy-5,5′-bipyrazolyl complex. Typical procedure

The ligand **5** (15.0 mg, 0.047 mmol) was added to toluene (2.5 ml) at room temperature, followed by titanium tetraisopropoxide (133.9 mg, 0.47 mmol). After 10 minutes, 1 M diethylzinc in toluene (0.95 ml, 0.95 mmol) was added. The reaction was left for another 10 minutes before it was cooled to 0 °C, and benzaldehyde (50 mg, 0.47 mmol) was then added. After 7.5 hours the reaction was quenched by addition of 4 M aqueous hydrochloric acid. Extractive work-up using diethyl ether gave 42.3 mg (66%) of 1-phenylpropan-1-ol; $\delta_H(CDCl_3)$ 0.90 (3H, t, $J = 7.42$ Hz, $CH_3$), 1.78 (2H, m, $CH_2$), 2.92 (1H, br s, OH), 4.59 (1H, t, $J = 6.68$ Hz, CH), 7.33 (5H, s, Ph). The crude product contained 5% unchanged benzaldehyde.

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