# A Bis(oxazolinyl)pyrrole as a New Monoanionic Tridentate Supporting Ligand:  Synthesis of a Highly Active Palladium Catalyst for Suzuki-Type C−C Coupling

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*Summary: Reaction of pyrrole-2,5-biscarbonitrile with 2-amino-2-methyl-1-propanol gave the bis{2-(4,4′-dimethyl-4,5-dihydrooxazolyl)}pyrrole (dmoxpH) (1), which was deprotonated and reacted with [PdCl₂(COD] to give [Pd₂(dmoxp)₂Cl₂] (2) and [Pd₃(dmoxp)₂Cl₄] (3). The former is an active catalyst in the Suzuki cross coupling of phenylboronic acid with activated and nonactivated aryl bromides at 70 °C and catalyst/substrate ratios of $10^{-4}$ to $10^{-5}$.*

From the point of view of ligand design, nitrogen donor ligands, for which in principle a great variety of synthetic strategies are available, may generate catalytically active complexes which are complementary to the known phosphine-based systems.[1] Oxazolines and their derivatives have been particularly intensely studied in a wide range of applications in asymmetric catalysis.[2,3] In this paper we report the synthesis of a novel monoanionic tridentate ligand containing two oxazoline units, the synthesis of two di- and trinuclear Pd complexes, and a first study into the catalytic activity of these species.

Reaction of the known pyrrole-2,5-biscarbonitrile[4] with an excess of 2-amino-2-methyl-1-propanol in chlorobenzene in the presence of anhydrous $ZnCl_2$ selectively yielded the 2,5-bis{2-(4,4′-dimethyl-4,5-dihydrooxazolyl)}pyrrole (dmoxpH) (1), which was isolated after chromatographic workup (Scheme 1).[5] Compound 1 may be viewed as a precursor to a monoanionic analogue of the well-established family of pybox ligands, which have found manifold application in asymmetric catalysis in recent years.[6] The monoanionic charge of the deprotonated molecule and the more open structure of this derivative of the five-membered pyrrol ring in comparison with the ligands containing a central pyridine unit are expected to result in somewhat different complex structures in comparison to pybox complexes.

## Scheme 1.  Synthesis of Bis{2-(4,4′-dimethyl-4,5-dihydrooxazolyl)}pyrrole (dmoxpH) (1) and the Reaction of Its Lithium Salt with [PdCl₂(COD)] to Give [Pd₂(dmoxp)₂Cl₂] (2) and [Pd₃(dmoxp)₂Cl₄] (3)
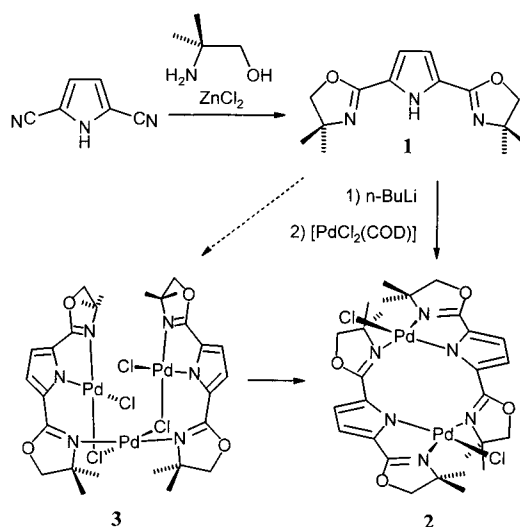


The pyrrole derivative 1 was lithiated at −78 °C with ⁿBuLi in ether and the lithium pyrollate stirred with 1

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(5) Preparation of 1:  $ZnCl_2$ (1.164 g; 8.54 mmol; 0.5 equiv) was melted in vacuo and then cooled under an atmosphere of nitrogen for 15 min. A slurry of pyrrole-2,5-biscarbonitrile (2 g; 17.6 mmoL) and 2-amino-2-methyl-1-propanol (4.263 g; 47.82 mmol; 2.8 equiv) in chlorobenzene (25 mL) was added and refluxed for 24 h. The solvent was removed in vacuo and the orange-brown residue chromatographed on silica gel (hexanes−EtOAc (1:1); $R_f$ = 0.43), yielding 4.263 g of an off-white solid (yield = 72%). ¹H NMR (300 MHz; CDCl₃): δ 11.4 (br s; 1H; NH$_{pyrr}$), 6.71 (s; 2H; H$_{3/4\ pyrr}$), 4.05 (s; 4H; CH$_2$ $_{oxa}$), 1.34 (s; 12H; CH$_3$ $_{oxa}$). ¹³C NMR (75 MHz; CDCl₃):  δ 155.6 (C=N$_{oxa}$), 123.0 (C$_{2/5\ pyrr}$), 112.9 (C$_{3/4\ pyrr}$), 79.0 (CH$_2$ $_{oxa}$), 67.4 (C$_{quat\ oxa}$), 28.2 (CH$_3$ $_{oxa}$). IR (KBr disk):  2969, 1660, 1612, 1499, 1404, 702 cm⁻¹. MS (EI 70 eV):  261 [M]⁺, 246 [M − CH₃]⁺, 174 [M − CH₃ − (CH₃)₂CCH₂O]⁺. Preparation of 2:  To a diethyl ether solution (50 mL) of 1 (1.5 g; 5.74 mmoL) was added ⁿBuLi (1.6 M in hexanes; 3.59 mL) at −78 °C. The reaction mixture was stirred for 15 min and then allowed to warm to room temperature. After an additional hour, a suspension of dichlorobis-(1,5-cyclooctadiene)palladium (1.639 g; 5.74 mmoL) in diethyl ether was added, and the resulting mixture was stirred for 12 h at room temperature. The reaction was then filtered, and the resulting orange oil was purified by flash chromatograpy (silica gel, hexanes−EtOAc (1:1); $R_f$ = 0.56), yielding 2 (0.859 mg; 19%) as an orange air stable solid. ¹H NMR (300 MHz; CDCl₃):  δ 6.64 (br d; 2H; H$_{3/4\ oxa}$), 4.38 (d; 1H; CH₂ $_{oxa}$), 4.24 (t; 2H; CH₂ $_{oxa}$), 4.17 (d; 1H; CH₂ $_{oxa}$), 1.92 (s; 3H; CH$_3$ $_{oxa}$), 1.57 (s; 3H; CH₃ $_{oxa}$), 1.43 (s; 3H; CH₃ $_{oxa}$), 1.15 (s; 3H; CH₃ $_{oxa}$). ¹³C NMR (75 MHz; CDCl₃):  δ 167.8 (C=N$_{oxa}$), 164.9 (C=N$_{oxa}$), 133.1 (C$_{2/5\ pyrr}$), 131.9 (C$_{5/2\ pyrr}$), 117.1 (C$_{3/4\ pyrr}$), 112.2 (C$_{4/3\ oxa}$), 83.2 (CH₂ $_{oxa}$), 80.0 (CH₂ $_{oxa}$), 67.9 (C $_{quat\ oxa}$), 65.9 (C $_{quat\ oxa}$), 30.4 (CH₃ $_{oxa}$), 27.8 (CH₃ $_{oxa}$), 27.5 (CH$_3$ $_{oxa}$), 26.7 (CH₃ $_{oxa}$). IR (KBr disk):  2964, 1632, 1521, 1376, 721, 362 cm⁻¹. Anal. Calcd for $C_{28}H_{38}Cl_2N_6O_5Pd_2$ (822.36):  C 41.81, H 4.51. Found:  C 41.95, H 4.73.
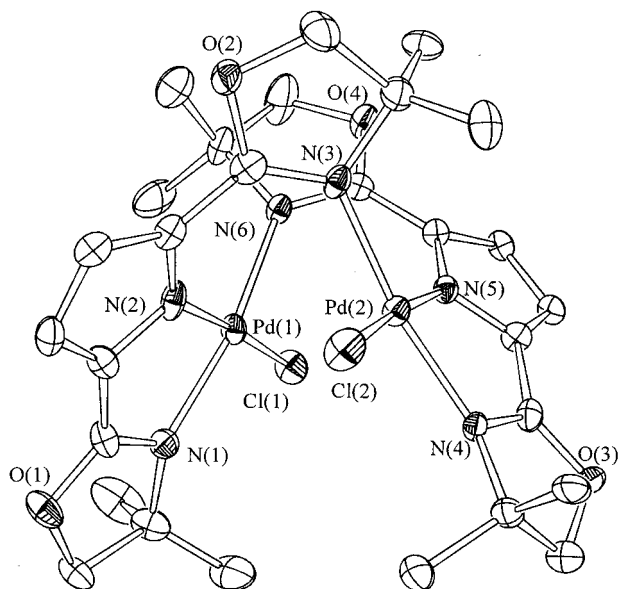
**Figure 1.** Molecular structure of [Pd$_2$(dmoxp)$_2$Cl$_2$] (**2**). Selected bond lengths (Å) and interbond angles (deg): Pd(1)−Cl(1) 2.296(3), Pd(1)−N(1) 2.052(8), Pd(1)−N(2) 2.039(8), Pd(1)−N(6) 2.036(8), Pd(2)−Cl(2) 2.287(3), Pd(2)−N(3) 2.043(8), Pd(2)−N(4) 2.025(7), Pd(2)−N(5) 2.039(8), N(2)−Pd(1)−N(6) 97.7(3), N(1)−Pd(1)−N(2) 79.8(3), Cl(1)−Pd(1)−N(1) 96.5(2), N(3)−Pd(2)−N(5) 97.7(3), N(4)−Pd(2)−N(5) 79.9(3), N(2)−C(28)−C(8)−N(3) 29.3, N(2)−C(4)−C(3)−N(1) 1.7, N(5)−C(19)−C(22)−N(6) 26.4, N(4)−C(17)−C(18)−N(5) 6.9.

molar equiv of [PdCl$_2$(COD)] for 12 h at room temperature. After workup by flash chromatography the complex [Pd$_2$(dmoxp)$_2$Cl$_2$] (**2**) was isolated as an orange solid, for which the signal patterns in the NMR spectra indicated an aggregation to an oligomeric species.[5] Apart from the major component obtained from this reaction, yellow crystals of a second very minor reaction product, the trinuclear complex [Pd$_3$(dmoxp)$_2$Cl$_4$] (**3**), were isolated. To establish unambiguously the molecular structures of both compounds, single-crystal X-ray diffraction studies of **2** and **3** were carried out.[7] The molecular structures are depicted in Figures 1 and 2 along with the principal bond lengths and interbond angles.

Compound **2** is a dimeric palladium complex both in solution as well as in the solid state (Figure 1) in which the tridentate bis(oxazolinyl)pyrollide bridges the two
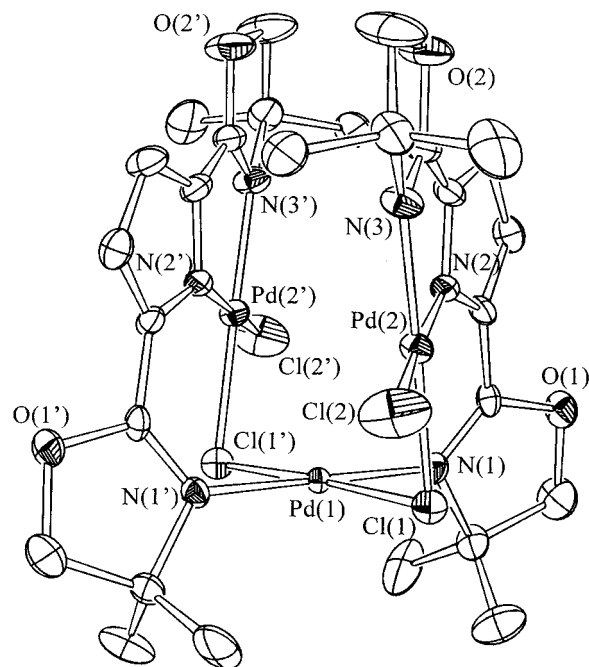
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(7) Crystal data for [Pd$_2$(dmoxp)$_2$Cl$_2$] (**2**): C$_{28}$H$_{38}$Cl$_2$N$_6$O$_5$Pd$_2$, orange blocks, crystal dimensions 0.16 × 0.08 × 0.02 mm, $M$ = 822.36, monoclinic, space group $C$2, $a$ = 19.733(1) Å, $b$ = 9.9775(5) Å, $c$ = 16.8832(9) Å, $\beta$ = 95.021(5)°, $U$ = 331.3(3) Å$^3$, $Z$ = 4, $D_c$ = 1.65 g cm$^{-3}$, $\mu$ = 1.293 mm$^{-1}$, $F(000)$ = 1656, 5478 reflections collected (2.50° < $\theta$ < 27.09°) at 173(2) K, 4263 used in the structure refinement; $R_1$ = 0.048 [$I > 3\sigma(I)$], $wR_2$ = 0.066, GOF = 1.179 for 387 parameters and 0 restraints. Crystal data *for* [Pd$_3$(dmoxp)$_2$Cl$_4$] (**3**): C$_{28}$H$_{36}$Cl$_4$N$_6$O$_4$Pd$_3$, orange blocks, crystal dimensions 0.20 × 0.20 × 0.16 mm, $M$ = 981.65, tetragonal, space group $P$4$_3$2$_1$2, $a$ = 12.2834(1) Å, $b$ = 12.8234(1) Å, $c$ = 23.3398(4) Å, $\beta$ = 90°, $U$ = 3596.99(7) Å$^3$, $Z$ = 4, $D_c$ = 1.810 g cm$^{-3}$, $\mu$ = 1.822 mm$^{-1}$, $F(000)$ = 1936, 6454 reflections collected (2.50° < $\theta$ < 27.47°) at 173(2) K, 2163 used in the structure refinement; $R_1$ = 0.027 [$I > 3\sigma(I)$], $wR_2$ = 0.042, GOF = 1.022 for 204 parameters and 0 restraints.

**Figure 2.** Molecular structure of [Pd$_3$(dmoxp)$_2$Cl$_4$] (**3**). Selected bond lengths (Å) and interbond angles (deg): Pd(1)−Cl(1) 2.283(1), Pd(1)−N(1) 2.011(3), Pd(2)−Cl(2) 2.275(2), Pd(2)−N(2) 2.057(4), Pd(2)−N(3) 2.010(4), Pd(2)−Cl(1) 2.281(1), Cl(1)−Pd(1)−N(1) 85.3(1), N(1)−Pd(1)−Cl(1) 94.7(1), N(3)−Pd(2)−N(2) 81.6(2), Cl(2)−Pd(2)−N(3) 95.8(1), Cl(1)−Pd(2)−Cl(2) 85.6(6), Cl(2)−Pd(2)−N(2) 174.9(1), N(2)−C(6)−C(3)−N(1) 32.6, N(2)−C(9)−C(10)−N(3) 4.3.

metal centers. Whereas one of the oxazolyl rings and the charged pyrollide are coordinated to the one Pd center and adopt an almost coplanar arrangement, the second oxazolyl ring is twisted relative to the pyrrolide plane and coordinates to the second palladium atom. Each metal center is distorted square planar with the chloro ligand trans disposed to the anionic pyrrolide. Overall a helical dimeric structure is thus formed which is reminiscent of double helices formed by oligopyridine complexes.[8] There is precedent in the literature of Ag complexes containing the pybox ligand which aggregate to form binuclear and trinuclear species.[9]

The trinuclear complex **3** crystallizes in the tetragonal space group $P$4$_3$2$_1$2. Its molecular structure comprises two {*cis*-PdCl$_2$($\kappa^2N$-dmoxp)} units related to each other by a 2-fold crystallographic axis (Figure 2). The third metal atom Pd(1), resides on this axis and is coordinated by, respectively, the uncoordinated oxazoline N atom N(1) and a bridging chloro ligand Cl(1). Overall, this creates a mutually orthogonal arrangement of three square planar complex fragments as represented in Figure 2. Dissolution or attempted recrystallization of **3** quantatively affords complex **2** and PdCl$_2$, which precipitates. This indicates that, while it is generated during the complexation of the deprotonated ligand, it is not due to a secondary transformation of **2** or in equilibrium with this compound. Even extended heating of **2** with [PdCl$_2$(COD)] did not lead to a detectible conversion to the trinuclear species.

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**Table 1.  Selected Suzuki-Type C−C Coupling Reactions Catalyzed by Complex 2**
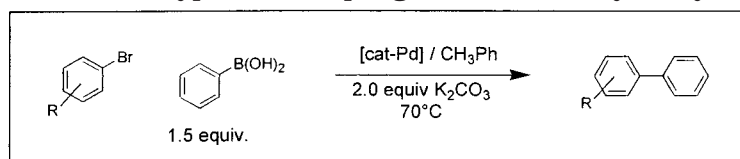


| Entry | Aryl halide | Product | Reaction Time | [cat-Pd] / substrat | Isolated yield |
|-------|-------------|---------|---------------|---------------------|----------------|
| 1 | | | 2h | $10^{-4}$ | 97% |
| 2 | | | 2h | $10^{-4}$ | 89% |
| 3 | | | 1h | $10^{-4}$ | 92% |
| 4 | | | 4h[a] | $10^{-5}$ | 82%[b] |
| 5 | | | 4h | $10^{-4}$ | 95% |
| 6 | | | 6h[a] | $10^{-4}$ | 88% |
| 7 | | | 4h[a] | $10^{-5}$ | 54%[b] |

[a] Reaction times have not been optimized. [b] Reaction carried out at 110 °C.

Until very recently, ligand design in Pd-catalyzed coupling reactions focused upon phospine- or phosphine-derived systems.[10,11] The observation that N-nucleophilic heterocarbenes,[12] S-containing palladacycles,[13] or cyclometalated imines[14] may serve as mono- or polydentate ancillary ligands in palladium catalysis indicates that efficient catalysts may be based on structural motifs which lie outside the well-established pattern.

Compound **2** was found to be a highly active catalyst in the Suzuki type coupling of phenylboronic acid with aryl bromides at relatively moderate temperature (Table 1). In the general procedure a catalyst/substrate ratio of $10^{-4}$ was used and the aryl bromide and phenylboronic acid were stirred at 70 °C in toluene in the presence of $K_2CO_3$ as auxiliary base. The new catalyst was found to be highly stable under the conditions of the Suzuki coupling, and no palladium black was formed during the reaction. The catalytic reaction was followed by GC−MS, and 100% conversion was obtained both with activated and deactivated bromides after 1−6 h. Decrease of the catalyst/substrate ratio to $10^{-5}$ still gave 82% isolated yield of 4-bromoacetophenone and 54% 4-methoxyacetophenone after 4 h, amounting to turnover numbers of 82 000 and 54 000, respectively. In contrast to the reactivity toward aryl bromides, the catalyst proved to possess only very low activity toward the corresponding chlorides, with the reaction effectively stopping after a few cycles at 110 °C.

In conclusion, the phosphine-free, totally nitrogen-donor-based ligand system developed by us may be used in an effective way in palladium complex catalysis. Compound **2** is an active catalyst in the Suzuki cross coupling for both activated and nonactivated aryl bromides and is highly thermally and air stable. The type of system employed in this study is to our knowledge without precedent in Pd-catalyzed C−C coupling. We note, however, that Grasa and co-workers very recently have reported Suzuki coupling using (neutral) diazabutadiene ligands.[15] The nature of the ligand allows for the facile extension of this approach to chiral catalysts. This and a closer investigation of the mechanism of the C−C coupling reacting with the present system are under way in our laboratory.

**Supporting Information Available:** Text detailing the structure determination and tables of crystallographic data, the positional and thermal parameters and interatomic distances and angles for **2** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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