Aza-Bis(oxazolines)-New Chiral Ligands for Asymmetric Catalysis

Martin Glos and Oliver Reiser
Institut für Organische Chemie der Universität Regensburg, Universitätsstr. 31,
D-93040 Regensburg

E-mail: Oliver.Reiser@chemie.uni-regensburg.de

Supplementary Material

General. Melting points were measured with a Büchi melting point apparatus and are uncorrected. Infrared spectra were recorded on a Bio-rad Excalibur Series spectrometer. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter at ambient temperature and are reported as follows: $[\alpha]_\lambda$ (*c* g/100mL, solvent).

^{1}H NMR spectra were recorded on a Bruker AC 250 spectrometer at ambient temperature. Data are as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, and m = multiplet), integration, coupling constant (Hz), and assignment. ^{13}C NMR spectra were recorded on a Bruker AC 250 spectrometer at ambient temperature. Chemical shifts are reported in ppm from internal tetramethylsilane on the δ scale. Combustion analyses were performed by the Central Analytical Department Universität Regensburg on a Heraeus CHN-Rapid.

Analytical thin layer chromatography was performed on Merck TLC aluminum sheets silica gel 60 F_{254}. Visualization was accomplished with UV light and alcoholic ninhydrine solution followed by heating. Liquid chromatography was performed using Merck silica gel 60 (70-230 mesh ASTM). Analytical gas chromatography was performed on Carlo Erba 8160 split mode capillary injection system and flame ionization detector. Analytical HPLC was performed on Kontron Instruments 325 System using a Kontron HPLC 335 detector.

All reactions were carried out in oven dried glassware. When necessary solvents and reagents were purified prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Methanol (MeOH) was distilled from magnesium. Diethylether (Et_2O) was distilled from sodium/potassium alloy. Tetrahydrofuran (THF) was distilled from potassium. Hexanes (hex) and ethyl acetate (EA) were used as commercially available. Methyl diazoacetate was synthesized according to literature procedure.[1] Styrene (Merck), diphenylethene (Acros), L-*tert*-leucine (Degussa-Hüls), *p*-dibromoxylene (Aldrich) and methoxypolyethyleneglycole (MeOPEG 5000) (Fluka) were used as received. L-*tert*-leucinol was prepared from L-*tert*-leucine following literature procedure.[2]

To determine the yield (conversion) of reactions with methoxypolyethyleneglycole

---

1. Searle, N. E. *Org. Synth. Coll. Vol.IV* **1963**, 424-426.
2. Romo, D.; Romine, J. L.; Midura, W.; Meyers, A. I. *Tetrahedron* **1990**, *46*, 4951-4994.

(MeOPEG) the ^{1}H NMR spectrum was analyzed as follows. The integration of the MeOPEG (OCH_3) signal at 3.38 ppm was taken as reference for 3 hydrogen atoms. Since a 250 MHz NMR was used this signal came together with the upfield (3.38-3.32 ppm) ^{13}C-satellite of the PEG signal. Therefore the downfield (3.92-3.88 ppm) ^{13}C-satellite was substracted to get the correct number for 3 hydrogen atoms. The integration of the hydrogen atoms of the attached moieties were divided by this reference to determine the degree of conversion.

5b **6b**

2-Amino-4,5-dihydro-(4*S*)-(1,1-dimethylethyl)-1,3-oxazole (6b). To an ice cooled solution of bromine (5.72 g, 33 mmol) in methanol (40 mL) sodium cyanide (1.62 g, 33 mmol) was added in portions over 1 h. After all was dissolved a solution of (*S*)-*tert*-leucinol (3.52 g, 30 mmol) in methanol (70 mL) was added and stirring continued for 1 h. After treatment with a 25% ammonia solution (15 mL) most of the solvent was evaporated under vacuum. Under vigorous stirring a 20 % NaOH solution (30 mL) was added to the residue and a colorless solid precipitated. The mixture was extracted with ethyl acetate (4 x 40 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated and residual amino alcohol was removed by heating to 60°C under vacuum (0.01 Torr). The remaining product **6b** was obtained as a colorless solid (3.79 g, 89%). Mp 196-198°C; IR (KBr) 3525, 2960, 2913, 1765, 1653, 1492, 1420, 1366, 1327, 1292, 1103, 1026, 939 cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.21 (dd, 1H, $J = 9.3$, 8.3 Hz, CH_2CH), 4.07 (dd, 1H, $J = 8.3$, 7.1 Hz, CH_2CH), 3.74 (dd, 1H, $J = 9.3$, 7.1 Hz, CH_2C*H*), 3.65 (bs, 2H, NH_2), 0.87 (s, 9H, C(C*H*)$_3$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 161.0, 73.7, 69.5, 33.7, 25.6; $[\alpha]_{589} = -41°$ (c = 0.5, MeOH); Anal. Calcd. for $C_7H_{14}N_2O$: C, 59.13; H, 9.92; N, 19.70. Found: C, 59.23; H, 9.90; N, 19.54.

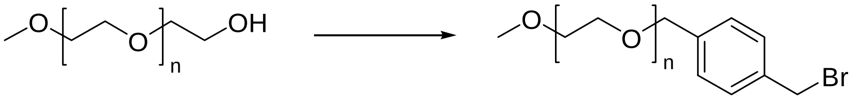
6b **7b**

Bis[4,5-dihydro-(4*S*)-(1,1-dimethylethyl)-1,3-oxazole-2-yl]-amine (7b). A mixture of the aminooxazoline **6b** (1.57 g, 11 mmol), benzaldehyde (1.17 g, 11 mmol, 1.11 mL) and *p*-toluenesulfonic acid hydrate (104 mg, 0.55 mmol) in toluene was heated to reflux for 22 h using a Dean Stark trap. The solvent was evaporated and the residue chromatographed on silica gel (60 g, 1:1 hex/EA to pure EA as eluant). The product **7b** was isolated as colorless solid: 852 mg (58 %). Mp 152-154°C, TLC $R_f = 0.14$ (EA), IR (KBr) 3528, 3193, 2989, 2879, 1762, 1674, 1599, 1481, 1450, 1406, 1370, 1322, 1257, 1087, 1061, 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 8.5 (bs, 1H, N*H*), 4.30 (dd, 2H, *J* = 9.1, 9.1 Hz, CH_2CH), 4.15 (dd, 2H, *J* = 8.9, 6.7 Hz, CH_2CH), 3.81 (dd, 2H, *J* = 9.4, 6.7 Hz, CH_2C*H*), 0.90 (s, 18H, C(C*H*)$_3$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 166.1, 68.8, 67.4, 33.6, 20.0; $[\alpha]_{589}$ = +148.6° (c = 1, MeOH); Anal. Calcd. for $C_{14}H_{25}N_3O_2$: C, 62.89; H, 9.42; N, 15.72. Found: C; 63.08; H, 9.30; N, 15.41

7b

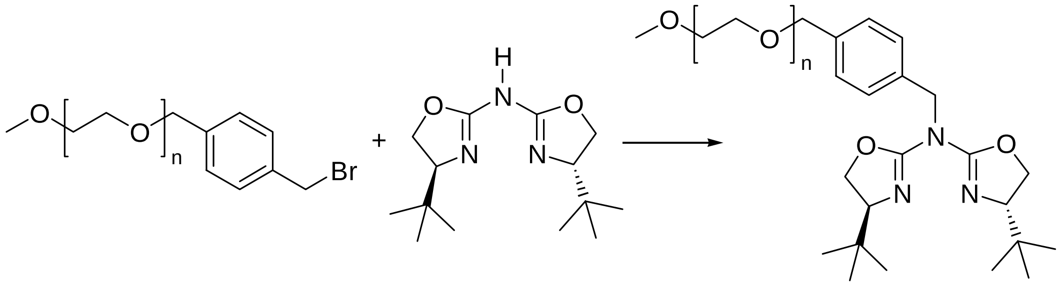
9b

Bis[4,5-dihydro-(4*S*)-(1,1-dimethylethyl)-1,3-oxazole-2-yl]-methylamine (9b). The bis(oxazoline) **7b** (267 mg, 1 mmol) was dissolved in THF (10 mL) and a 15% solution of *n*-butyl lithium in hexane (1.5 N, 688 µL) was added at -78°C. After stirring for 20 min methyl iodide (710 mg, 5 mmol, 312 µL) was added. The cooling bath was removed and stirring at room temperature continued for 10 h. After evaporation of the solvent the residue was partitioned between CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ (10 mL). The aqueous phase was extracted with CH_2Cl_2 (5 mL) and the combined organic phases dried over $MgSO_4$. Evaporation of the solvent yielded the product **9b** as colorless solid (275 mg, 98 %). Mp: 110-111°C, IR (KBr) 3532, 3004, 2913, 1761, 1679, 1479, 1442, 1395, 1366, 1223, 1131, 992, 959 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.35 (dd, 2H, *J* = 9.0. 9.0 Hz, CH_2CH), 4.24 (dd, 2H, *J* = 8.6, 6.7 Hz, CH_2CH), 3.79 (dd, 2H, *J* = 9.5, 6.7 Hz, CH_2C*H*), 3.41 (s, 3H, NCH_3), 0.88 (s, 18H, C(C*H*)$_3$); ^{13}C NMR ($CDCl_3$, 62.5 MHz) δ 157.8, 73.3, 70.2, 37.4, 33.9, 25.5; $[\alpha]_{589}$ = -22.6 (c = 1, MeOH). Anal. Calcd. for $C_{15}H_{27}N_3O_2$: C, 64.03; H, 9.67; N, 14.93. Found: C, 64.00; H, 9.66, N, 14.84



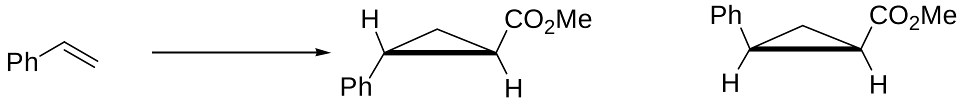
19 **8**

4-(Methoxypolyethyleneglycolyl)bromoxylene (8). Methoxypolyethyleneglycole (MeOPEG 5000) **19** (3 g, 0.6 mmol) was dissolved in warm THF (30 mL) and cooled to room temperature. Sodium hydride (72 mg of a 60 % suspension in paraffin oil, 1.8 mmol) was added and stirring continued until no more gas developed (ca. 10 min). Sodium iodide (163 mg, 0.69 mmol) and α,α'-dibromoxylene (1.584 g, 6 mmol) were added and the mixture was stirred at room temperature for 96 h. After filtration through a plug of Celite the polymer was precipitated by adding diethylether (180 mL). The solid was filtered off and recrystallized from ethanol (35 mL). The product (2.643 g) was obtained as a slightly yellow solid. NMR analysis showed a 70 % conversion. 1H-NMR (CDCl3, 250 MHz) δ 7.35 (d, 2H, *J* = 8.3 Hz, $H_{arom.}$), 7.29 (d, 2H, *J* = 8.7 Hz, $H_{arom.}$), 4.53 (s, 2H, CH_2OPEG), 4.47 (s, 2H, CH_2Br), 3.62 (s, PEG), 3.36 (s, 3H, OCH_3)



8 **7b** **10**

Bis[4,5-dihydro-(4*S*)-(1,1-dimethylethyl)-1,3-oxazole-2-yl]-4-(methoxypolyethyleneglycolyl)xylenyl-amine (10). Under a nitrogen atmosphere a solution of the aza-bis(oxazoline) **7b** (267 mg, 1 mmol) was dissolved in dry THF (5 mL) and cooled to -78°C. Via syringe *n*-BuLi (670 µl of a 1.64 N solution in hexane, 1.1 mmol) was added and the mixture warmed to 0°C. After 10 min. the cooling bath was removed and a solution of **8** (1 g, 0.2 mmol) in THF (80 mL) was added. Stirring at room temperature was continued for 64 h. The reaction mixture was filtered through a plug of Celite and the product was precipitated by adding diethylether (250 mL). The precipitate was recrystallized from ethanol (10 mL) to yield the product **10** as slightly yellow solid (941 mg). NMR analysis showed that 55 % of the polymer was converted to the desired product. ^{1}H-NMR ($CDCl_3$, 250 MHz) δ 7.40 (d, 2H, *J* = 8.3 Hz, $H_{arom.}$), 7.26 (d, 2H, J = 11.5 Hz, $H_{arom.}$), 5.10 (d, 1H, J = 15.1 Hz, CH_2N), 4.95 (d, 1H, J = 14.7 Hz, CH_2N), 4.53 (s, 2H, CH_2OPEG), 4.31 (dd, 2H, J = 9.1, 9.1 Hz, $CHCH_2$), 4.19 (dd, 2H, J = 8.5, 6.5 Hz, $CHCH_2$), 3.92-3.88 (m, ^{13}C-satellite of the PEG-signal), 3.78 (dd, “2H“– integration was not possible because of overlaying with the PEG-signal, J = 9.3, 6.5 Hz, CH_2CH), 3.65 (s, PEG), 3.38 (s, 3H, OCH_3), 3.38-3.32 (m, ^{13}C-satellite of the PEG-signal), 0.78 (s, 18H $C(CH_3)_3$)



13 **15** **16**

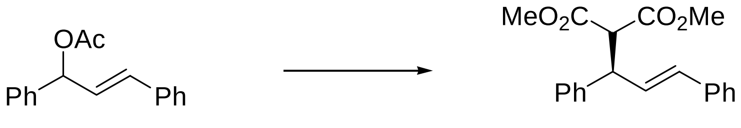
Representative Experimental: Asymmetric Cyclopropanation of Styrene (13): Under nitrogen atmosphere $Cu(OTf)_2$ (3.6 mg. 0.01 mmol) and **9b** (6.2 mg, 0.022 mmol) were dissolved in dry CH_2Cl_2 (2 mL) to give a green solution. Phenylhydrazine (22 µL of a 5 % solution) was added and the color almost disappeared. After addition of styrene (312 mg, 3 mmol, 345 µL) a solution of methyl diazoacetate (1 mmol, 1 mL of a 8 % solution in CH_2Cl_2 diluted with 7 mL CH_2Cl_2) was added over 8 h using a syringe pump. Stirring was continued for 3 h and the solvent evaporated *in vacuo* to give a green oil. This was purified by chomatography on silicagel (3x25 cm silica, 9:1 hex/EA as eluant). The products **15** and **16** were obtained as a clear oil (138 mg, 82 %) showing identical spectroscopical properties as described in the literature.[3] The *trans:cis* ratio was determined by GC (Carlo Erba 8190) using a DB1301 column (60 m x 0.25 mm) and helium as carrier gas. The enantiomeric excess was determined by GC (Fisons 8130) using a CP-Chirasil DEX CB column (25 m x 0.25 mm) and helium as carrier gas. The absolute configuration was assigned by comparison with an authentic sample prepared following the literature procedure.[3]

Representative Experimental: Asymmetric Cyclopropanation of 1,1-Diphenylethene (17): The cyclopropanation of 1,1-diphenylethene was carried out according to the procedure decribed above using 3 mmol 1,1-diphenylethene. The enantiomeric excess was determined by HPLC using a Chiralpak AD Column and hexane:*i*-PrOH (99.92:0.08) as eluent. The absolute configuration was assigned by comparison with an authentic sample prepared following the literature procedure.[3]

---

[3] Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726-728.

Cyclopropanation of Styrene (13) with Polymer-supported Catalyst 10: Under nitrogen atmosphere $Cu(OTf)_2$ (3.6 mg, 0.01 mmol) and **10** (200 mg, 0.02 mmol) were dissolved in dichloromethane (5 mL). Phenylhydrazine (22 µL of a 5 % solution in dichloromethane) and styrene (312 mg, 3 mmol, 345 µL) were added. Methyl diazoacetate (1 mmol, 1 mL of a 8 % solution in dichloromethane diluted with 7 mL dichloromethane) was added over 8 h using a syringe pump. Stirring was continued for 3 h and the reaction mixture was transferred via cannula to a 250 mL septum capped flask. The reaction vessel was rinsed with 3 mL dry dichloromethane. The volume of the solvent was reduced to approximately 5 mL by applying vacuum and 100 mL of dry diethylether were added to precipitate the polymer-supported catalyst. After cooling with ice for 15 min the catalyst was separated from the products by filtration through a sintered glass funnel under nitrogen atmosphere. The filtrate was evaporated *in vacuo* to give a slightly yellow oil, which was purified by chomatography on silicagel (3x25 cm silica, 9:1 hex/EtOAc as eluant). The products **15** and **16** were obtained as a clear oil showing identical spectroscopical properties as described in the literature.[3] For the following reaction cycle the catalyst was dissolved in 10 mL dry dichloromethane and transferred into a new reaction vessel. When necessary the catalyst was activated by addition of phenylhydrazine. Styrene and methyl diazoacetate were added for the next cycle.



11 **12**

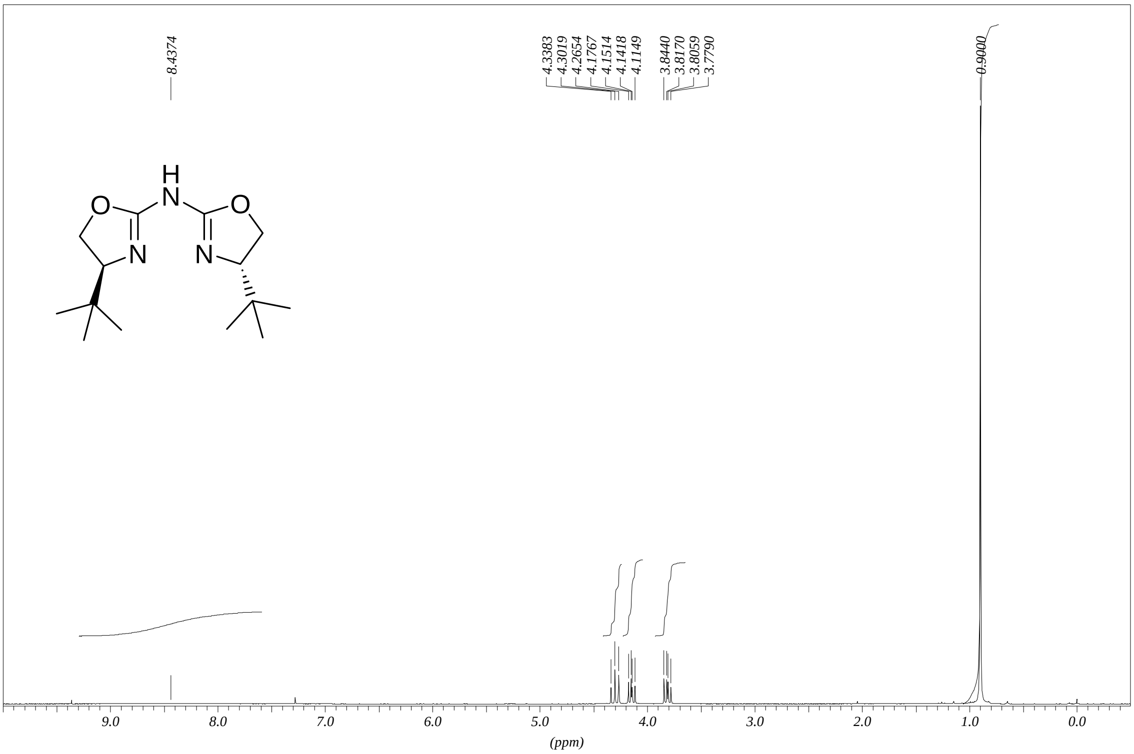
Representative Experimental: Allylic Substitution of 1,3-Diphenylallylacetate (11):

As described by Pfaltz et al.[4] allylpalladium chloride dimer (1.39 mg, 3.8 µmol) and bis[4,5-dihydro-(4*S*)-(1,1-dimethylethyl)-1,3-oxazol-2-yl]-methylamin (**9b**) (2.67 mg, 9.5 µmol) were dissolved in dry dichloromethane (1 ml) and degassed with three freeze/thaw cycles. After stirring at 50 °C for 1 h in a teflon sealed flask and cooling down to room temperature 1,3-diphenylacetate (**11**) (192 mg, 0.76 mmol), dimethylmalonate (301 mg, 2.28 mmol, 261 µl), N,O-bis-(trimethylsilyl)acetamide (BSA) (464 mg, 2.28 mmol, 557 µl) and a few crystals of potassium acatate were added. After three more freeze/thaw cycles the mixture was stirred for 165 h. After addition of diethylether (80 ml) and extraction with saturated ammonium chloride (2 times) the organic phase was dryed over magnesium sulfate. The solvent was evaporated and the residue chromatographed on silica using hexanes/ethylacetate (10/1) as eluent. The product **12** was obtained as colorless oil (94 mg, 38 %) and showed identical spectroscopical properties as described in the literature. The enantiomeric excess was determined by HPLC analysis using a Chiralpak AD column, hexane/ethanol = 90/10, flow = 0.8, 260 nm.

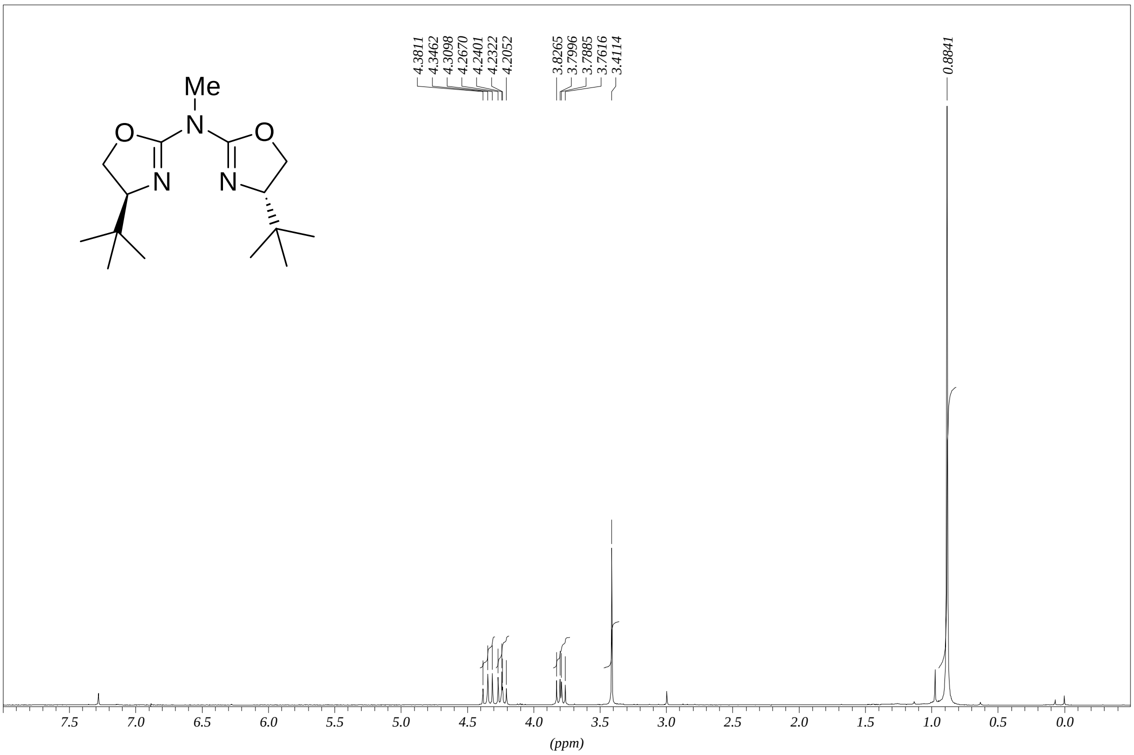
---

[4] Leutenegger, U.; Umbricht, G.; Fahrni, C.; von Matt, P.; Pfaltz, A. *Tetrahedron* **1992**, *48*, 2143-2156.

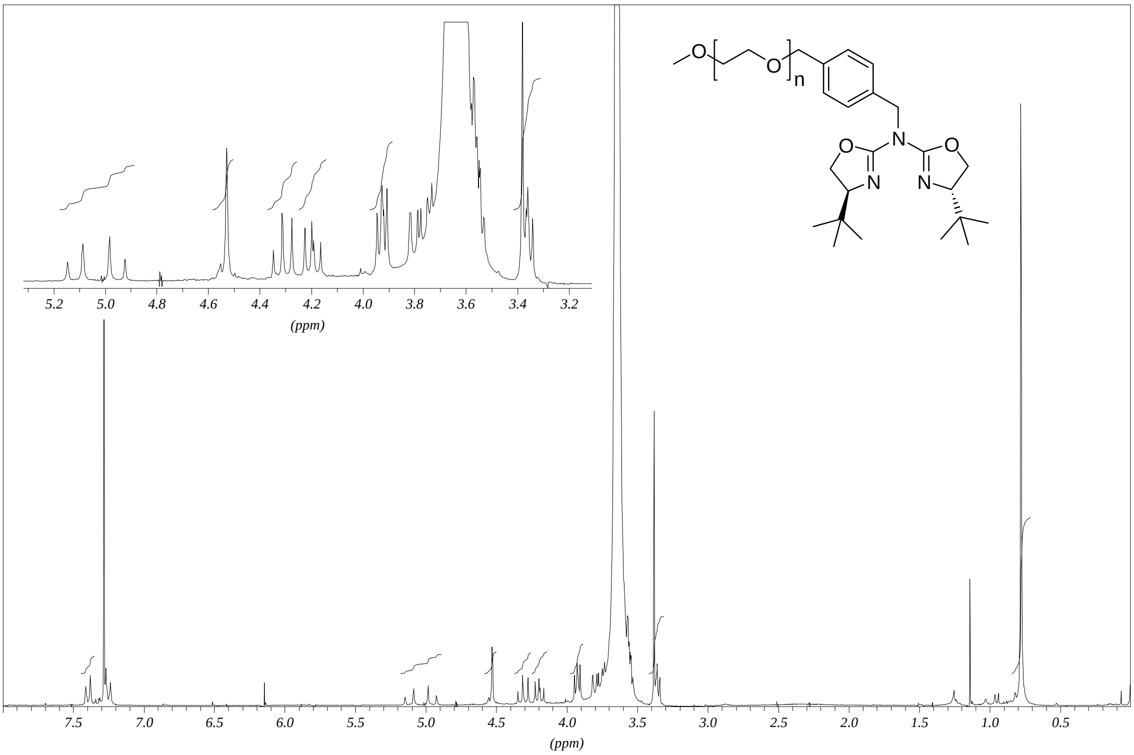
^{1}H NMR of Ligand **7b**



^{1}H NMR of Ligand **9b**



^{1}H NMR of Ligand **10**



Peak Nr.	Data Point	Frequency	PPM	Intensity	%Int.
1	5420	1854.04	7.4122	2622	3.2
2	5441	1845.72	7.3790	4101	5.0
3	5511	1817.98	7.2680	5029	6.2
4	5531	1810.05	7.2364	3065	3.8
5	6850	1287.29	5.1464	1139	1.4
6	6888	1272.23	5.0862	2228	2.7
7	6953	1246.46	4.9832	2658	3.3
8	6990	1231.80	4.9246	1326	1.6
9	7239	1133.11	4.5300	7912	9.7
10	7354	1087.54	4.3478	1838	2.3
11	7376	1078.82	4.3130	4060	5.0
12	7400	1069.30	4.2749	3760	4.6
13	7432	1056.62	4.2242	3197	3.9
14	7448	1050.28	4.1989	3584	4.4
15	7453	1048.30	4.1910	2410	3.0
16	7470	1041.56	4.1640	2324	2.8
17	7688	955.16	3.8186	4074	81.8
18	7708	947.23	3.7869	4252	85.3
19	7715	944.46	3.7758	4354	87.4
20	7732	937.72	3.7489	4983	100.0
21	7964	845.77	3.3813	39913	48.9
22	9606	195.00	0.7796	81581	100.0