Synthesis and Characterization of Novel Ligands Designed for Secondary Interactions

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Summary: Novel, chiral, aza-15-crown-5-containing phosphite ligands have been designed, synthesized, and characterized. Metal complexes of these ligands are catalytically active and constitute a starting point for the systematic study of the affect of secondary interactions on selectivity.

Although metals ligated by such phosphines as DIPAMP,[1a] BINAP,[1b] and DuPHOS[1c] have been tremendously successful at effecting enantioselective hydrogenations and isomerizations it appears that high selectivity commonly is limited to substrates that are capable of bidentate binding to the metal.[1d] Recently Ito and Sawamura have coined the term "secondary interactions" to describe attractive, catalyst−substrate interactions that occur outside the metal's primary coordination sphere.[2] These interactions involve Coulombic or hydrogen bonding between substrate functional groups and complementary groups attached to the ligands of the metal complex. Although secondary interactions have been invoked for a number of catalytic and noncatalytic processes,[2] direct evidence for such interactions is sparse.[3,4] As a first step in a systematic study of the role of secondary interactions in controlling catalytic selectivity, we report the design, synthesis, and characterization of novel, C_2-symmetric phosphite ligands that contain the aza-15-crown-5 functional group.

The design of phosphites **8a**−**c** employed the following criteria: (1) The secondary interaction must be favorable enough to compete with pathways in which the secondary interaction does not occur. (2) The secondary interaction must be reversible on the time scale of catalytic turnover so that fresh substrate can replace newly transformed product. (3) The secondary interaction must selectively stabilize the desired reaction transition state relative to those of the undesired reaction pathways. Aza-15-crown-5 binds cations strongly and reversibly.[5] For example, alkylammonium salts have binding constants around 10^6 M^{-1} at 25 °C in benzene.[5b,c] These observations indicate that ligands with crown ethers and substrates containing ammonium groups constitute complementary pairs. Examinations with both tactile and computer-generated models suggested that the C_2-symmetric array of crown ethers for square planar complexes of **8a**−**c** favored secondary interaction with one enantioface of π-bound allylammonium salts. Reports by Wink and co-workers demonstrate that tartrate-derived diols are useful precursors to chiral phosphites.[6,7]

An efficient synthesis of **6** from tartaric acid bypasses the intermediary chiral butane diepoxide utilized by Lukyanenko et al.[8] In our hands, the long reaction times (ca. 3 months) and low yield of opening the diepoxide with aza-15-crown-5 render this route impractical. By devising the pathway indicated in Scheme 1, we make multigram quantities of chiral diol in about one week with acceptable yield (50% from tartaric acid, but 81% after the introduction of expensive aza-crown ether).[9−11]

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(11) For the synthesis of (*R,R*)-2,3-diacetoxy-1,4-butanedioyl chloride (**4**), Seebach's procedure[9] was used with the following modification: the anhydride (**2**) was converted to the diacid (**3**) with 2 equiv of water in THF stirred for 3 h, followed by azeotropic distillation with benzene to remove water. This yielded the diacid (**3**) as a white solid rather than the oil reported by Seebach.[9] Our overall yield of **4** was 60−65%, similar to the yield reported by Seebach.[9] Data are as follows. **2**: MS $M + H^+ = m/e$ 217; ^{1}H NMR ($CDCl_3$) δ 5.6 (s, 1H, CH), 2.2 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.7 (*C*(O)CH_3), 163.3 (*C*(O)C*C*(O)), 72.0 (*C*(OAc)H), 20.1 (*C*H_3). **3**: ^{1}H NMR (acetone-d_6) δ 5.9 (s, 1H, CH), 2.3 (s, 3H, CH_3); ^{13}C NMR (acetone-d_6) δ 169.9 (*C*(O)CH_3), 167.3 (COOH), 71.4 (*C*(OAc)H), 20.2 (CH_3). **4**: ^{1}H NMR (acetone-d_6) δ 6.2 (s, 1H, CH), 2.2 (s, 3H, CH_3); ^{13}C NMR (acetone-d_6) δ 168.7 (*C*(O)Cl), 166.9 (*C*(O)-CH_3), 75.4 (*C*(OAc)), 19.7 (CO*C*H_3). The synthesis of (*R,R*)-2,3-diacetoxy-1,4-bis(aza-15-crown-5)butanediamide (**5**) is as follows: 3.71 g (13.7 mmol) of the diacid chloride (**4**) was dissolved in 20 mL of a 1:1 mixture of Et_2O:THF. In a separate flask, 6.00 g of aza-15-crown-5 (27.4 mmol) and 2.79 g of *N*-methylmorpholine (27.4 mmol) were dissolved in 50 mL of a 1:1 mixture of Et_2O:THF. The amine solution was cooled to −78 °C, and the diacid chloride solution was added via cannula over a period of 30 min. A white precipitate formed immediately. After the mixture was stirred overnight, the solution was filtered and washed twice with 20 mL of THF. Chromatography of the filtrate on silica using 1:1 Et_2O:THF yielded pure product by NMR analysis. Yield: 81%. Data: ^{1}H NMR ($CDCl_3$,) δ 5.9 (s, 1H, CH), 3.60−3.62 (m, 20H, ring H's), 2.1 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.7 (*C*(O)N), 166.7 (*C*(O)CH_3), 67.9−71.2 (O*CC*O), 69.8 (*C*OAc), 50.0, 49.3 (*C*, *C*NCO), 20.7 (*C*H_3). Synthesis of (*S,S*)-1,4-bis(aza-15-crown-5)-2,3-butane (**6**): A 2.75 g quantity of diamide (**5**) (4.98 mmol) was taken into 50 mL of distilled THF under an inert atmosphere. This solution was added slowly via cannula into a slurry of 10 g of LAH (263 mmol) with 150 mL of freshly distilled THF at 0 °C. The resulting slurry was allowed to warm to room temperature over 1 h and then was heated to reflux for 48 h. After cooling and quenching with 4:1 THF:H_2O, the solution was filtered and the filter cake was washed thoroughly with THF. Removal of the solvent yielded pure product according to NMR analyses. Yield: 1.56 g (60%). $[\alpha]_D = -11.14$ ($c = 0.7$, absolute EtOH) (Lukyanenko reported $[\alpha]_D = -17.7$ ($c = 2.2$, EtOH)).[8] MS: $M^+ = m/e$ 523. ^{1}H NMR ($CDCl_3$): δ 3.57−3.69 (m, 34H, OCH_2CH_2O and CH), 2.75−2.81 (m, 12H, $3CH_2N$). ^{13}C NMR ($CDCl_3$): δ 68.9−70.4 (4 peaks) (O*CC*O), 68.7 (*C*H), 59.0 (N*C*C(OH)), 55.1 (N*C*CO).

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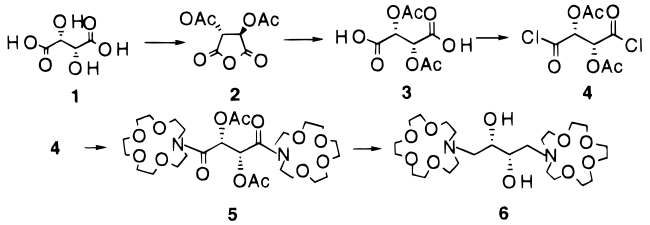
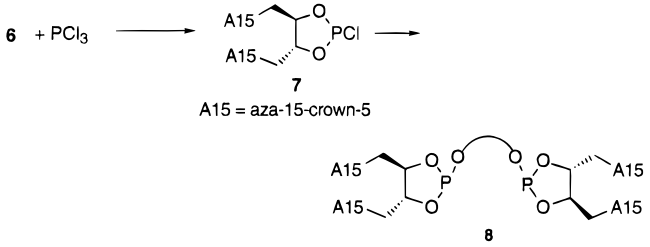
Scheme 1. Synthesis of 1,4-Di-aza-15-crown-5-2,3-butanediol



Scheme 2. General Synthesis of Phosphites



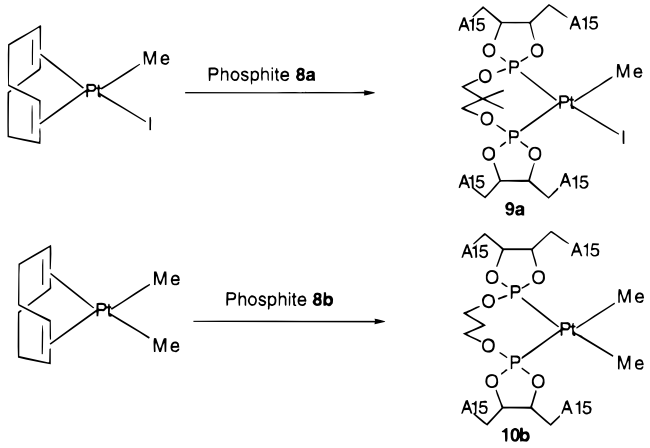
A15 = aza-15-crown-5

Bridging group (**8a,b**)	
8a	neopentyl glycol
8b	1,3-propane diol
8c	MeOH (Non-chelating ligand)

Using standard procedures, reaction of diol **6** with PCl_3 yields the versatile chlorodioxaphospholane (**7**).[12] From this intermediate a family of related ligands can be made by varying the backbone between the phosphites. A dry diol, e.g., neopentyl glycol, added to the chlorodioxaphospholane results in the desired phosphite (Scheme 2).[13] We have successfully synthesized three ligands of this type (**8a**−**c**).

Phosphites **8a**−**c** form stable metal complexes. Phosphite−platinum complexes **9a** and **10a**−**c** were synthesized according to Scheme 3.[14] ^{31}P NMR data for these complexes are distinctive. For example, complex **9a** exhibits P−P coupling (J_{P-P} = 39 Hz), well-separated chemical shifts (δ 102 and 147), and large, inequivalent P−Pt coupling constants[15] (J_{Pt-P} = 6538 and 2774 Hz) as expected for inequivalent P atoms in positions trans to iodo and methyl ligands, respectively. ^1H NMR

Scheme 3. Synthesis of Platinum Complexes (9, 10) of Phosphites (8a,b)



confirms the substitution of phosphite for COD, by the disappearance of the platinum-bound COD vinyl resonances at δ 5.53 and 4.63 and by the presence of free COD vinyl resonances at δ 5.55. The structure of **9a** is further confirmed by the presence of a mass ion at *m/e* 1546 in the LSIMS mass spectrum.

To establish the catalytic competency of these ligands we have successfully performed rhodium-catalyzed hydroformylations with a simple substrate, styrene, and with amide-functionalized substrates.[16,17] Rates and selectivities for hydroformylation reactions are similar to those of other tartrate-derived diphosphites. For example, hydroformylation of styrene with **8b** yields an approximate rate of 27 turnovers/h, similar to rates reported by Wink under similar conditions.[6] Enantioselectivity of the resulting 2-phenylpropanal is low (<10% ee), as is typical for tartrate derived diphosphites.[18] Regioselectivity at an *i/n* ratio of 6.7 is within the range of 1.6 to 43.1 reported by van Leeuwen with

(12) Preparation of **7**: Dry **6** (1.0 g, 1.9 mmol, 1 equiv) was dissolved in 200 mL of distilled, degassed THF. Dry NEt_3 (2.0 mL, 14.4 mmol, 7.6 equiv) was added to the solution, and the solution was cooled to −78 °C. PCl_3 (0.166 mL, 1.9 mmol, 1 equiv) was dissolved in 50 mL of distilled, degassed THF, and the diol/NEt_3 solution was added via cannula with vigorous stirring. A white precipitate immediately formed. The reaction mixture was stirred overnight and used without further purification. ^{31}P NMR: δ 171 (s).

(13) Synthesis of phosphites (**8**): The reaction mixture containing the chlorodioxaphospholane (**7**) was reduced in vacuo to 50−60 mL. Dry 1,3-propane diol (for **8b**) (0.068 mL, 0.95 mmol, 0.5 equiv) was added to 50 mL of distilled, degassed THF, along with additional NEt_3 (0.5 mL, 3.5 mmol, 1.9 equiv). The propane diol/NEt_3 solution was added slowly to the chlorodioxaphospholane solution with vigorous stirring. The reaction mixture was stirred for 1 h before being filtered. THF was removed from the clear, colorless solution to yield a highly viscous pale yellow oil. The oil was extracted with diethyl ether and filtered again. Ether was removed to yield the phosphite as a pale yellow oil. Typical yield: 80% from the bis(aza-crown-ether) diol. All NMR are in $CDCl_3$. **8a:** ^{31}P NMR δ 144 (s); ^1H NMR δ 4.1 (C−H), 3.62 (OCH_2) 2.86 (NCH_2) 1.40 (CH_3), glycol methylene obscured by large peak at δ 3.62. MS (LSIMS, low resolution): M + H^+ = *m/e* 1210. Anal. Calcd for $C_{53}H_{102}N_4O_{22}P_2$: C, 52.64; H, 8.50; N, 4.63. Found: C, 52.04; H, 8.05; N, 4.00. **8a** is a highly viscous oil with variable amounts of THF and ether as persistent contaminants. **8b**: ^{31}P NMR δ 143 (s); ^1H NMR δ 4.1 (C−H), 3.62 (OCH_2), 2.86 (NCH_2), methylenes obscured. MS (LSIMS, low resolution): M + H^+ = *m/e* 1181. **8c**: ^{31}P NMR δ 143 (s); ^1H NMR δ 4.1 (C−H), 3.6 (OCH_2), 3.3 (J_{P-P} = 21 Hz, OMe), 2.86 (NCH_2). MS (LSIMS, low resolution): M + H^+ = *m/e* 585.

(14) (a) Reaction of PtMeI(COD) with **8a**: PtMeI(COD) (10 mg, 0.023 mmol, 1 equiv) (COD = 1,5-cyclooctadiene) was dissolved in 1.0 mL of $CDCl_3$. Phosphite **8a** (27 mg, 0.023 mmol, 1 equiv) was dissolved in $CDCl_3$. The phosphite solution was added to the PtMeI(COD) solution, while the PtMeI(COD) solution solution was gently shaken. Analysis of the ^1H and ^{31}P NMR showed both the desired product in quantitative yield and free COD. Removal of solvent yielded a viscous yellow oil. **9a:** ^{31}P NMR ($CDCl_3$) δ 147 (d) (P trans to Me, J_{P-P} = 39 Hz, J_{Pt-P} = 2774 Hz), 102 (d) (P trans to I, J_{P-P} = 39 Hz, J_{Pt-P} = 6538 Hz); ^1H NMR ($CDCl_3$) δ 5.55 and 2.33 (free COD), 4.25 (C−H), 3.61 (OCH_2), 2.85 (NCH_2), 1.39 (CH_3), 1.15 ($PtCH_3$). MS (LSIMS, low resolution): M^+ = *m/e* 1546. Anal. Calcd for $C_{54}H_{105}N_4O_{22}P_2Pt$: C, 41.94; H, 6.84; N, 3.62. Found: C, 41.64; H, 6.60; N, 3.12. **9a** is a highly viscous oil with variable amounts of THF and ether as persistent contaminants. (b) Reaction of $PtMe_2$(COD) with **8b**: $PtMe_2$(COD) (10 mg, 0.03 mmol, 1 equiv) was dissolved in 1.0 mL of $CDCl_3$. Phosphite **8b** (36 mg, 0.023 mmol, 1 equiv) was dissolved in $CDCl_3$. The phosphite solution was added to the $PtMe_2$(COD) solution, while the $PtMe_2$(COD) solution was gently shaken. Analysis of the ^1H and ^{31}P NMR shows both the desired product and free COD. Removal of solvent yielded a viscous oil. **10a**: ^{31}P NMR (C_6D_6) δ 151 (J_{Pt-P} = 2996 Hz); ^1H NMR (C_6D_6) δ 5.55 and 2.33 (free COD), 3.4−3.8 (OCH_2), 2.92 (NCH_2), 1.37 (PtMe, J_{Pt-P} = 150 Hz), 1.24 (gem dimethyl). **10b**: ^{31}P NMR ($CDCl_3$) δ 151 (J_{Pt-P} = 2989 Hz). **10c**: ^{31}P NMR ($CDCl_3$) δ 152 J_{Pt-P} = 3100 Hz).

(15) ^{195}Pt is 33.8% abundant, I = $^1/_2$, and yields a characteristic satellite "triplet" pattern.

(16) Hydroformylation conditions: A 1:1 mixture of phosphite **8b** and $Rh(acac)(CO)_2$ was dissolved in CH_2Cl_2, and substrate was added. All reactions were run at 35 °C in pressure bottles. For styrene 500 equiv of substrate and 85 psig of 1:1 $CO:H_2$ were used. For the amides, 40 equiv of substrate, and 100 psig of 1:1 $CO:H_2$ were used.

(17) Styrene hydroformylation results: Reactions were followed by GC on a silica column. Average rate = 27 turnovers/h. n/i = 0.15. Estimations of % ee were made by optical rotation. Alkenamide hydroformylation results: All reactions were followed by ^1H NMR. Average rate: 10 ± 2 turnovers/h for all amides. n/i ratios are as follows: 1-butenamide, 0.9; 1-pentenamide, 3.3.

a related diphosphite.[18] Because our paradigm requires tolerance of hydrogen bond donating functionalities on substrates, and because there are few examples of primary amide hydroformylation,[19] we tested 1-butenamide and 1-pentenamide as substrates. Hydroformylation progresses more slowly than the styrene, at 10 ± 2 turnovers/h, but very close to the ca. 11 turnovers/h rates Buchwald reports for the diphosphite−rhodium catalyzed hydroformylation of alkene amides under similar conditions.[19] Importantly, hydroformylation does proceed, establishing the system's tolerance for the hydrogen bond donor presence.

Of possible interest for separation of the catalyst from product is the observation that addition of the tetrafluoroborate salt of allylammonium or $NaBPh_4$ to a CH_2Cl_2 solution of **8b** and $Rh(acac)(CO)_2$ under synthesis gas leads to phase separation with dark orange droplets separating from the originally pale orange homogeneous solution.

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In summary, we have synthesized and characterized a new class of aza-crown-ether functionalized phosphites and their platinum complexes. These phosphites combine with rhodium carbonyl complexes to form active hydroformylation catalysts. Our future work is proceeding on two fronts: the exploration of novel catalytic properties of aza-crown-ether functionalized phosphites and phosphines and the direct characterization of secondary interactions upon binding functionalized alkenes to platinum complexes containing these novel diphosphites.

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Supporting Information Available: NMR spectra for the new compounds **8a** (^1H, ^{31}P, and ^{13}C), **8b** (^1H, ^{13}C, and ^{31}P), **8c** (^1H and ^{31}P NMR), **9a** (^1H, ^{31}P, and ^{13}C), **10a** (^1H and ^{31}P), **10b** (^1H and ^{31}P), and **10c** (^1H and ^{31}P) (17 pages). Ordering information is given on any current masthead page.

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