ESPHOS and SEMI-ESPHOS: A New Family of Mono- and Bidentate Diazaphospholidine Ligands for Asymmetric Catalysis

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Introduction

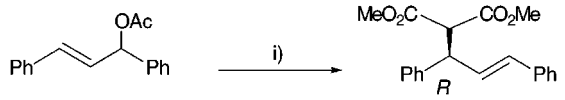
A large number of phosphorus-donor ligands have been developed for use in catalytic asymmetric reactions.[1] The most widely studied class reported to date are phosphines, notably BINAP[2] and DuPHOS,[3] both of which have been widely adopted in commercially important applications such as asymmetric hydrogenation.

In contrast, phosphorus ligands containing alternative donor units, such as phosphites[4] or diazaphospholidines,[5] have been less widely examined. In this paper we report the synthesis and preliminary studies on catalytic applications of a family of readily available ligands based on the diazaphospholidine structure, which consist of both monodentate and bidentate derivatives.

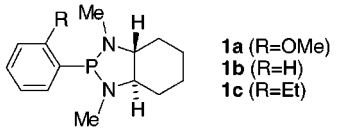
Results and Discussion

In a series of ongoing studies directed at the evaluation of P donor ligands containing P−N bonds,[6] we recently examined the use of diazaphospholidine ligands **1** derived from enantiomerically pure 1,2-diaminocyclohexane in the control of the allylic substitution reaction of diphenyl-3-acetoxy-1-propene with benzylamine and dimethyl malonate (Scheme 1).[7] Of the ligands which we studied, the derivative containing an *o*-methoxy group on the aromatic ring bound to the phosphorus atom gave the products with the highest enantioselectivity. Deletion of the methoxy group in the ligand results in almost complete loss of enantioselectivity and reversal of configuration in the product while, unexpectedly, the replacement of methoxy with ethyl results in a product of identical absolute configuration but somewhat reduced ee (Table 1). These results suggest that the methoxy group in **1a** is performing a somewhat unquantified role as a "hemilabile" ligand.[8−11]

Scheme 1[a]



[a] Reagents and conditions: (i) 10 mol% **1a**−**c**, 5 mol% $[PdCl(CH_2CHCH_2)]_2$, NaOAc, BSA, $CH_2(CO_2Me)_2$.



1a (R=OMe)
1b (R=H)
1c (R=Et)

Such a "hemilabile" effect of a methoxy group has been previously described by other researchers. An excellent recent example has been reported by Rajanbabu, who employed the methoxy-substituted phosphine ligand MOP in a nickel-catalyzed hydrovinylation reaction to give a product of 63% ee.[8] In a study analogous to ours, replacement of the methoxy group of MOP with ethyl resulted in a dramatic decrease in selectivity (to 13% ee), while its replacement with benzyloxy resulted in a modest improvement to the overall selectivity (to 80% ee). In prior studies Hayashi had already demonstrated that the methoxy group in the MOP ligand, while essential for high selectivities, does not form a full bond to the metal in palladium-catalyzed allylic substitution reactions.[9] Other well-known ligands containing hemilabile methoxy groups include the well-established DiPAMP, for which again replacement of methoxy by ethyl results in a reduction, but not complete loss, of selectivity in asymmetric hydrogenations.[10] A number of other diphos-

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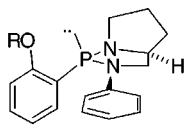
Table 1

ligand	yield, %	ee, %/configuration
1a	97	89 (*R*)
1b	97	28 (*S*)
1c	84	59 (*R*)

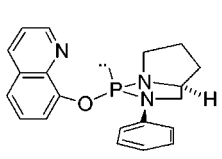
phine ligands containing alkoxy groups which exhibit important hemilabile properties have also been reported.[11]

Having demonstrated that monodentate diazaphospholidine ligands would act as efficient ligands for asymmetric catalysis, we wished to devise methods to increase the asymmetric inductions achieved. The ligands **1a-c** described above rely on a "relay" of chiral information from the rigid, *C*2 symmetric backbone to the methyl groups on the nitrogen atoms, which in turn exert a stereochemical influence over the reaction. The rigidity of this type of "conformational relay" is not strong and may be overcome by other interactions in a catalytic complex. To achieve an improvement in enantioinduction we reasoned that the replacement of the cyclohexyldiamine backbone with a 2-(aminomethyl)pyrrolidine group would furnish a ligand with a more rigidly defined structure.[5] Provided that the derived ligand **2** could be prepared as a single diastereoisomer, the three-carbon pyrrolidine ring would be rigidly "projected" into the area in which reactions were taking place.

Materials related to **2** have already been reported in asymmetric catalysis. In a series of studies concurrent with our own, Buono has reported the use of ligand **3** (and closely related derivatives) in the control of asymmetric palladium-catalyzed allylic substitution reactions. In the Buono work, however, the ligands contain an additional coordinating group such as a pyridine or quinoline structure and are thus bidentate.[12a–c] In addition Buono has reported the synthesis of **2** as an intermediate in the preparation of a ketone reduction catalyst.[12d] In our initial work we wished to examine the synthetic value of specifically *monodonor* ligands.[7] We found that the reaction between *o*-(bis(dimethylamino)-phosphinoanisole and (*S*)-2-(phenylaminomethyl)pyrrolidine in toluene at elevated temperature proceeded smoothly to furnish ligand **2** (SEMI-ESPHOS)[13] as a single diastereoisomer in 69% yield after recrystallization. X-ray crystallographic analysis revealed that the relative stereochemistry at the phosphorus-centered chiral center was that expected on the basis of reported work, i.e., the aromatic group on phosphorus is *cis* to the hydrogen atom on the ring junction carbon atom.[12]



2 (R=Me) (SEMI-ESPHOS)
4 (R=CH_2Ph)



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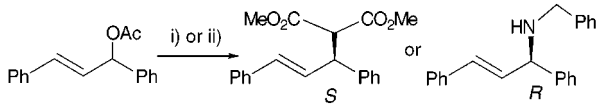
(13) The trivial names for the ligands (ESPHOS and SEMI-ESPHOS) are derived from suggestions from the nearest and dearest of one of us (S.B.).

Scheme 2[a]



[a] Reagents and conditions; (i) 10 mol% **2**, **4**, **5**, 2.5 mol% $[Pd_2(dba)_3]$, NaOAc, BSA, $CH_2(CO_2Me)_2$. (ii) 2.5 mol%, $[Pd_2(dba)_3]$, $PhCH_2NH_2$, CH_2Cl_2.

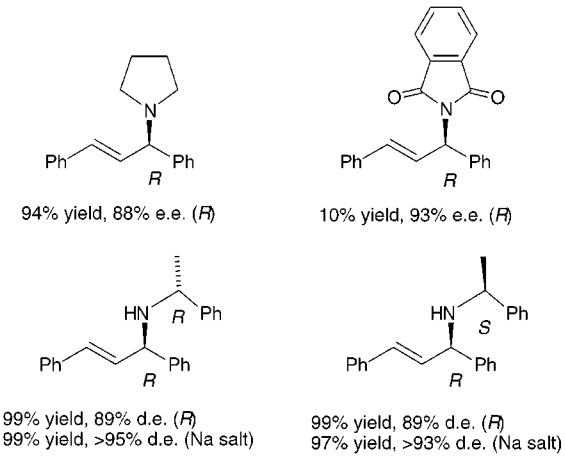


Figure 1. Addition compounds formed using ligand **2**.

Table 2

nucleophile	ligand	yield, %	ee, %/configuration
$MeO_2CCH_2CO_2Me$	**2**	85	83 (*S*)
$PhCH_2NH_2$	**2**	88	90 (*R*)
$PhCH_2NHNa$	**2**	80	95 (*R*)
$PhCH_2NH_2$	**4**	96	93 (*R*)
$PhCH_2NHNa$	**4**	87	95 (*R*)
$MeO_2CCH_2CO_2Me$	**5**	38	96 (*R*)
$PhCH_2NH_2$	**5**	15	60 (*S*)

Diazaphospholidine **2** proved to be an excellent ligand for the control of asymmetric allylic alkylation reactions. Using the well-established prototype reaction of diphenyl-3-acetoxy-1-propene with both dimethyl malonate and benzylamine (Scheme 2, Table 2). The amination reaction gave the better result (90% ee) which could be improved further (to 95% ee) using the sodium salt. The use of pyrrolidine or potassium phthalimide as nucleophiles both gave products in excellent ee, although the yield in the latter case, while unoptimized, was quite low, perhaps reflecting low reactivity in the intermediate allylic complex (Figure 1). The use of both enantiomers of α-methylbenzylamine gave diastereoisomeric products in equally high selectivity (Figure 1), confirming that the ligand was fully controlling the substitution reaction and overriding any inherent selectivity due to the chiral amine nucleophile. Intrigued by the result of Rajanbabu in his hydrovinylation work,[8] we wished to investigate the effect of replacing the methoxy group with a benzyloxy group on the ligand. Ligand **4** was prepared by a similar process to that for **2** and was employed in the allylic amination reaction. The results for this reaction were excellent (Scheme 2), and the product was formed in an improved enantioselectivity (up to 95% ee). This very interesting result closely mimics that achieved in the hydrovinylation process and again underlines the issue surrounding hemilabile effects of alkoxy ligands.[8–11] At present we have no direct evidence to account for the sense and magnitude of asymmetric induction; however, we believe, on the basis of previous studies and related

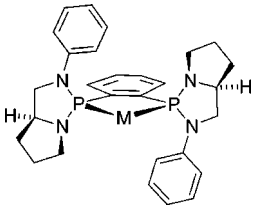
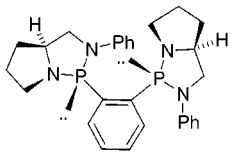


Figure 2.

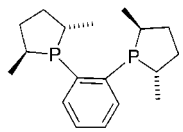
work, that the ligand acts primarily as a monodentate species and that the alkoxy ligand does not engage in a chelating interaction with the palladium atom.

Having achieved an excellent result for the asymmetric allylic substitution using SEMI-ESPHOS **2**, we were attracted by the possibility of the synthesis of a bidentate analogue of the material. Such a ligand would be attractive since it would possess *C*2-symmetric characteristics and would be sterically similar (although electronically quite different) to the well-established diphosphine DuPHOS **6**. Through a similar condensation reaction between 2 equiv of (*S*)-2-(phenylaminomethyl)pyrrolidine and 1 equiv of 1,2-bis(dimethylamino)benzene[14] at elevated temperature we were able to prepare the target bis(diazaphospholidine) ligand **5** (ESPHOS[13]) in 76% yield. The product was a single diastereoisomer which was demonstrated by X-ray crystallography to contain the relative stereochemistry illustrated.

ESPHOS **5** proved to be an good ligand for the catalysis of asymmetric allylic substitution reactions, but was not as effective as SEMI-ESPHOS **2**. In the case of addition of both dimethyl malonate and benzylamine (Scheme 2, Table 2) the yields were low, and the ee of amination was only 60%. However, in contrast, the ee for the methyl malonate addition was very high (96%). When both phosphorus atoms in ESPHOS coordinate to a metal, the ligand constitutes a well-defined and rigid asymmetric environment which is *C*2 symmetric in structure (Figure 2). Such a well-defined environment makes the ligand highly attractive for asymmetric catalytic applications and we are presently examining its application to a number of reactions.



5 (ESPHOS)



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To gain further information about the nature of the complexes of our novel ligands with palladium, we carried out a number of ^{31}P NMR investigations. Addition of an 2 equiv of SEMI-ESPHOS to a benzene-d_6 solution of $Pd_2(dba)_3$ resulted in a significant downfield shift (from δ 95.0 to 108.8) in the observed peak for the phosphorus atom in the ligand, consistent with complexation to a metal. These results do not, however, serve to confirm the accuracy or otherwise of our speculated structure in Figure 2, and we are currently working toward the preparation and X-ray crystallographic analysis of palladium complexes of both **2** and **5**. The results of these studies will be reported in due course.

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Conclusions

We have reported the synthesis of a family of closely related mono- and bidentate ligands containing a rigid and well-defined diazaphospholidine heterocycle structure. The monodonor ligand demonstrates an excellent ability to control the allylic substitution of symmetrical allylic acetates in high ee, particularly in the case of amination reactions.

Experimental Section

SEMI-ESPHOS 2. To a stirred solution of (*S*)-2-(phenylaminomethyl)pyrrolidine[15] (1.96 g, 11.12 mmol) in toluene (10 mL) was added a solution of 2-anisyl(bis-dimethylamino)phosphine[16] (2.52 g, 11.12 mmol) in toluene (15 mL). The resulting solution was refluxed for 42 h after which time the solvent was then removed in vacuo to yield a pale yellow solid. This was recrystallized from toluene (10 mL) to yield the product **2** as colorless crystals (2.39 g, 69%). Mp 154−156 °C; $[\alpha]_D$ −493.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR, (C_6D_6 400 MHz) δ 1.20−1.29 (1H, m), 1.42−1.49 (2H, m), 1.54−1.63 (1H, m), 2.75−2.81 (1H, m), 3.09−3.21 (2H, m), 3.28 (3H, s), 3.29−3.38 (1H, m), 3.72−3.84 (1H, m), 6.48 (1H, dd, J = 3.9 and 8.1 Hz), 6.76−6.84 (2H, m), 6.98−7.04 (2H, m), 7.08−7.13 (1H, m), 7.16−7.23 (2H, m), 7.43 (1H, ddd, J 1.8, 3.9, and 7.4 Hz); ^{31}P NMR (C_6D_6) δ 95.0; ^{13}C NMR, (C_6D_6 100 MHz) δ 26.1 (d, J_{C-P} 6.2 Hz), 31.3, 52.6 (d, J_{C-P} 30.0 Hz), 53.3 (d, J_{C-P} 5.2 Hz), 54.9, 64.5 (d, J_{C-P} 8.6 Hz), 110.8, 115.9 (d, J_{C-P} 12.9 Hz), 117.9 (d, J_{C-P} 1.4 Hz), 120.5, 129.2 (d, J_{C-P} 1.0 Hz), 130.6, 131.0 (d, J_{C-P} 3.3 Hz),147.6, 147.9, 161.9 (d, J_{C-P} 15.3 Hz); *m*/*z* (EI) 312 (M^+, 43%). Anal. Calcd for $C_{18}H_{21}N_2OP$; C, 69.2; H, 6.77; N, 8.97. Found; C, 69.28; H, 6.75; N, 8.95.

ESPHOS 5. To a stirred solution of (*S*)-2-(phenylaminomethyl)pyrrolidine[15] (3.99 g, 22.7 mmol) in toluene (10 mL) was added a solution of 1,2-bis[bis(dimethylamino)phosphine]benzene[14] (3.57 g, 11.3 mmol) in toluene (20 mL). The resulting mixture was refluxed for 72 h under a positive stream of nitrogen. The solvent was then removed in vacuo to yield a pale yellow solid which was recrystallized from toluene (20 mL) to yield the product **5** as colorless crystals (4.15 g, 76%). Mp 172−174 °C; $[\alpha]_D$ −674.2 (*c* 0.5, $CHCl_3$); ^{1}H NMR, (C_6D_6 400 MHz) δ 1.27−1.38 (2H, m), 1.41−1.62 (4H, m), 1.63−1.78 (2H, m), 2.74 (2H, br.t, J = 8.6 Hz), 3.05−3.19 (4H, m), 3.42−3.55 (2H, m), 3.71 (2H, ddd, J = 2.0, 7.9 and 14.8 Hz), 6.81 (2H, t, J = 7.2 Hz), 6.90 (2H, dt, J = 7.2 and 2.0 Hz), 7.08 (4H, m), 7.23 (4H, m), 7.39 (2H, m); ^{31}P NMR (C_6D_6) δ 101.9; ^{13}C NMR, (C_6D_6 100 MHz) δ 25.9 (d, J_{C-P} 2.3 Hz), 31.2, 52.5 (d, J_{C-P} 14.1 Hz), 54.6 (d, J_{C-P} 2.0 Hz), 64.3 (d, J_{C-P} 4.6 Hz), 115.3 (d, J_{C-P} 6.9 Hz), 118.0, 129.3, 126.9, 129.8 (t, J_{C-P} 6.0 Hz), 147.6 (d, J_{C-P} 9.2 Hz), 148.3 (d, J_{C-P} 7.8 Hz); *m*/*z* (EI) 487 (M + H^+, 38%), 486 (M^+, 100). Anal. Calcd for $C_{28}H_{32}N_4P_2$ (+0.5C_7H_8, 1/2 toluene of crystallization); C, 71.04; H, 6.81; N, 10.52. Found; C, 71.00; H,6.79; N, 10.54.

Allylic Substitution Reaction with Dimethyl Malonate. To a solution of ligand **2** (24.6 mg, 0.079 mmol) in CH_2Cl_2 (1.0 mL) was added tris(dibenzylideneacetone)palladium(0) (18.1 mg, 0.02 mmol). The resulting solution was stirred for 15 min, during which time the color changed from purple to orange. 1,3-Diphenyl-3-acetoxy-1-propene (200 mg, 0.79 mmol) was then added as a solution in CH_2Cl_2 (1.0 mL), followed by dimethyl malonate (115 mg, 0.1 mL, 0.87 mmol), *N*,*O*-bis(trimethylsilyl)-acetamide (176 mg, 0.22 mL, 0.87 mmol), and sodium acetate (1 mg). After 3 h the solution was diluted with diethyl ether (10 mL) and quenched by the addition of saturated ammonium chloride solution (10 mL). The aqueous phase was extracted with Et_2O (3 × 10 mL), the combined organics were dried over magnesium sulfate and filtered, and the solvent was removed in vacuo to yield an orange oil. Purification by chromatography on silica eluting with 20% EtOAc/hexane gave the product as a clear oil that solidified on standing (190.2 mg, 74%). ^{1}H NMR, ($CDCl_3$ 400 MHz) δ 3.52 (3H, s), 3.70 (3H, s), 3.95 (1H, d, J = 10.9 Hz), 4.26 (1H, dd, J = 10.9 and 8.4 Hz), 6.32 (1H, dd, J = 15.8 and 8.4 Hz), 6.47 (1H, d, J = 15.8 Hz), 7.17−7.34 (10H, m);

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^{13}C NMR, ($CDCl_3$ 100 MHz) δ 49.1, 52.4, 52.5, 57.6, 126.3, 127.1, 127.5, 128.1, 128.4, 128.7, 129.1, 131.8, 136.8, 140.1, 167.7, 168.1; *m/z* (CI) 324 (M^+, 19%). The enantiomeric excess was determined to be 83% (S) by chiral shift NMR using (+)-Eu(hfc)$_3$. Substrate (20.0 mg) was dissolved in 1.0 mL of $CDCl_3$, and (+)-Eu(hfc)$_3$ (36.8 mg, 0.5 equiv) was added. The solution was shaken for a few seconds during which time a bright yellow solution formed. NMR analysis of this sample (400 MHz) gave four singlets in the region of 4.0 ppm. The ratio of the signal at 4.24 ppm to the signal at 4.13 ppm is a measure of the enantiomeric excess, with the signal at 4.13 ppm being the major peak corresponding to the *S*-enantiomer in this system. All the above data agrees with literature values.[6b]

Allylic Substitution Reaction with Benzylamine. To a solution of benzylamine (85.7 mg, 0.8 mmol) in dry THF (4 mL) was added sodium hydride (32 mg of a 60% dispersion in mineral oil, 0.8 mmol). After 2 h the solvent was removed in vacuo and the sodium salt resuspended in CH_2Cl_2 (2.0 mL). Meanwhile, to a solution of ligand **2** (12.5 mg, 0.04 mmol) in CH_2Cl_2 (1.0 mL) was added tris(dibenzylidineacetone)palladium(0) (9.2 mg, 0.01 mmol) and the resulting solution stirred for 15 min, during which time the color changed from purple to orange. 1,3-Diphenyl-3-acetoxy-1-propene (100.8 mg, 0.4 mmol) was then added as a solution in CH_2Cl_2 (1.0 mL), followed by the suspension of the sodium salt of benzylamine as prepared above. After 48 h, the solution was diluted with Et_2O (10 mL) and quenched by the addition of saturated ammonium chloride solution (10 mL). The aqueous phase was extracted with Et_2O, the combined organics were dried over magnesium sulfate and filtered, and the solvent was removed in vacuo to yield a yellow oil. Purification by chromatography on silica eluting with 20% EtOAc/hexane gave the product as a clear oil (96.4 mg, 81%); ^{1}H NMR, ($CDCl_3$ 400 MHz) δ 1.75 (1H, brs), 3.57 (1H, d, J = 13.4 Hz), 3.89 (1H, d, J = 13.4 Hz), 4.38 (1H, d, J = 7.3 Hz), 6.29 (1H, dd, J = 15.8 and 7.4 Hz), 6.57 (1H, d, J = 15.8 Hz), 7.14−7.45 (10H, m); ^{13}C NMR, ($CDCl_3$ 100 MHz) δ 51.4, 64.6, 126.4, 126.9, 127.3, 127.4, 127.4, 128.1, 128.4, 128.5, 128.6, 130.3, 132.6, 136.9, 140.4, 142.9; *m/z* (CI) 299 (M^+, 28%). The enantiomeric excess was determined to be 95% (R) by chiral HPLC using a Chiralcel OD column, 200:1:0.2 hexane:2-propanol: diethylamine, 0.5 mL/min, 254 nm, t_r for (*R*) isomer = 41.43, t_r for (*S*) isomer = 47.11. All the above data agrees with literature values.[17]

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Supporting Information Available: X-ray crystal structure data of **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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