Pd-catalyzed asymmetric allylic substitutions have received considerable attention as useful asymmetric carbon–carbon bond or carbon–heteroatom bond-forming reactions, where racemic or achiral allylic substrates can be converted into optically active products in the presence of a palladium–chiral ligand complex. Extensive efforts have been directed towards the development of effective chiral ligands for this transformation. Over the past two decades, we have focused on the development of chiral phosphorus ligands for transition metal-catalyzed asymmetric allylic substitutions. In 2004, we developed a new class of chiral phosphorus ligands: aspartic acid-derived P-chiral diaminophosphine oxide and its derivatives (DIAPHOXs). These pentavalent phosphorus compounds, preligands, are activated in situ by N,O-bis(trimethylsilyl)acetamide (BSA) induced P(V)→P(III) tautomerization to afford trivalent phosphorus species such as, which function as actual ligands (Chart 1). These preligands have been successfully applied to Pd- and Ir-catalyzed asymmetric allylic substitution reactions. Detailed investigations into the reaction mechanism using a Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylallyl acetate with dimethyl malonate revealed that complex [Pd-L-(1 : 2) complex] was the active catalyst. With this result in hand, we became interested in the development of bidentate P-chiral diaminophosphine oxide preligands with an achiral diphenylphosphine moiety as the second coordinating group. Herein, we report the design and synthesis of novel phenylalanine derived-bidentate P-chiral diaminophosphine oxide preligands that can be applied to Pd-catalyzed asymmetric allylic alkylation and amination.

Results and Discussion

Our ligand design is outlined in Fig. 1. The original DIAPHOX preligands involve an arylmethylene unit on a nitrogen atom adjacent to the phosphorus atom, which is introduced by reduction of the corresponding benzamide. The commercial availability of 2-diphenylphosphinobenzoic acid led us to introduce a diphenylphosphine moiety into the DIAPHOX framework by reducing the corresponding benzamide prepared from this reagent. Thus, we set up the methylene-tethered P-chiral diaminophosphine oxide–triphenylphosphine hybrids as our target ligands. (S)-Phenylalanine was selected as the starting material to prepare both diastereomers of chiral ligands originating from the chirality of the phosphorus atom.

Our ligand synthesis started with commercially available N-Z-(S)-phenylalanine 4 (Chart 2). First, 4 was reacted with aniline using 1-ethyl-3-(3-diethylaminopropyl)-carbodiimide·hydrochloride (EDC) as a coupling reagent to give the corresponding anilide, which was converted into the known primary amine derivative 5 through reductive removal of the Z group (94% yield, 2 steps). Subsequent condensation of 5 with 2-diphenylphosphinobenzoic acid using 1 eq of dicyclo...
hexylcarbodiimide (DCC) and 10 mol% of N,N-dimethylaminopyridine (DMAP) provided 6 in 98% yield. Reduction of the amide groups of 6 using in situ-generated BH₃ afforded a mixture of the desired diamine 8 (63% yield) and the monoamine 7 (25% yield). Recovered the monoamine 7 in 99% yield, respectively. When the reaction was performed using 1 mol% of [Pd(2-tolene)Cl]₂ and 2 mol% of (S,S)-PDIAPHOX (entry 1). Using (S,S)-PDIAPHOX derived from a single chiral source, (R,S)-D-amino acid-derived DIAPHOX preligands, such as (S,R)-9a and (S,S)-9b as chiral phosphorus ligands for a Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenylallyl acetate 11 with dimethyl malonate (Table 1). We first examined the reaction using the corresponding monodentate-type DIAPHOX (S,R)-10a as the control experiments. Using 1 mol% of [PdCl₂(C₆H₃)₂] and 4 mol% of (S,R)-10a (Pd/ligand=1/2), the reaction proceeded smoothly at 4 °C to provide (S)-12 in 99% yield with 95% ee (entry 1). Using (S,S)-PDIAPHOX 10b, however, the same reaction proceeded very sluggishly, affording the product with an opposite stereochemistry to that obtained with DIAPHOXs bearing (S,R) configurations (entry 5). It is noteworthy that both enantiomers were accessible with high enantiomeric purity using the structurally related DIAPHOX preligands derived from a single chiral source, (S)-L-phenylalanine. The Pd-(S,S)-9b catalyst system was also applicable to asymmetric allylic amination. When benzylamine and morpholine were utilized as nucleophiles, the corresponding products (S)-13 and (S)-14 were obtained in 96% yield with 85% ee and in 98% yield with 80% ee, respectively (Chart 3).

In conclusion, we developed a novel phenylalanine derived-bidentate chiral diaminophosphine oxide preligand (S,S)-9b, which was successfully applied to Pd-catalyzed asymmetric allylic alkylation and amination. Both enantiomers were accessible in a highly enantioselective manner using (S,S)-9b and (S,R)-10a, both of which can be prepared from a single chiral source. Detailed mechanistic investigations into the present catalyst system, as well as studies on the application of bidentate-type DIAPHOX preligands to other catalytic asymmetric reactions, are in progress.

**Experimental**

**General** Infrared (IR) spectra were recorded on a JASCO Fourier transform (FT) FTIR 230 Fourier transform infrared spectrophotometer, equipped with ATR (Smiths Detection, DuraSample IR II, Canada). NMR spectra were recorded on a JEOL ecp 400 spectrometer, operating at 400 MHz for 1H-NMR, 100 MHz for 13C-NMR, and 160 MHz for 31P-NMR. Optical rotations were measured on a JASCO P-1020 polarimeter. Electrospray ionization (ESI) mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100LP. The enantiomeric excess was determined by HPLC analysis. HPLC experiments were measured on a JASCO P-1020 polarimeter. Electrospay ionization (ESI) mass spectra were measured on JEOL AccuTOF LC-plus JMS-T100LP. The enantiomeric excess was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UV-970, measured at 254 nm. Reactions were carried out in dry solvent. Other reagents were purified by the usual methods.

**Preparation of Bidentate P-Chiral Diaminophosphine Oxide (S,R)-9a and (S,S)-9b, Compound 6** To a stirred solution of 5 (200 mg, 0.832 mmol), which was prepared using the reported method (94% yield, 2 steps from 4, 2-diphenylphosphinobenzoic acid (280.4 mg, 0.915 mmol)}
and DMAP (11.18 mg, 0.015 ml) in CHCl₃ (4.1 ml) at room temperature was added DCC (206.3 mg, 1.00 mmol). The resulting mixture was kept stirring at the same temperature. After 24 h, the mixture was filtered through a short pad of celite, and the filtrate was evaporated under reduced pressure. The crude residue was purified by flash column chromatography (SiO₂, hexane/AcOEt=10/1) to give 6 (430.9 mg, 98% yield) as white solids. IR (ATR) v 3264, 3058, 1678, 1584, 1504, 1496, 1444, 1343, 1329, 1251, 738, 692 cm⁻¹; ¹H-NMR (CDCl₃) δ: 2.91 (dd, J = 7.6, 14.4 Hz, 1H), 3.20 (dd, J = 6.8, 14.4 Hz, 1H), 4.84 (dd, J = 6.8, 7.2, 7.6 Hz, 1H), 6.33 (d, J = 7.2 Hz, 1H), 6.97—7.01 (m, 1H), 7.06—7.11 (m, 2H), 7.21—7.38 (m, 18H), 7.40—7.44 (m, 1H), 7.48—7.50 (m, 2H), 8.44 (s, 1H); ¹³C-NMR (CDCl₃) δ: 37.5, 55.9, 120.2 (2C), 124.3, 127.0, 127.8 (d, J = 5.8 Hz), 128.7 (d, J = 7.2 Hz) (2C), 128.7 (2C), 128.8 (2C), 128.9 (d, J = 7.3 Hz) (2C), 129.2 (1H), 129.8—129.2 (m, 3C), 130.6, 133.6 (d, J = 13.0 Hz) (2C), 133.8 (d, J = 13.4 Hz) (2C), 134.3, 135.5—138.4 (m, 3C), 136.7, 140.5, 166.8, 169.4; ¹³P-NMR (CDCl₃) δ: −10.7; ESI-high resolution (HR)-MS. Calculated for C₅₆H₄₆N₄O₆P (M + Na⁺) 551.1864. Found: 551.1859; [α]D [γ] = +48.0 (c = 2.41, CHCl₃).

**Compound 8**

To a stirred suspension of 6 (427.3 mg, 0.81 mmol) and NaBH₄ (184.7 mg, 4.86 mmol) in tetrahydrofuran (THF) (4.1 ml) was added a THF solution of I₂ (308.4 mg, 2.43 mmol in 4 ml of THF) at 0 °C over 414 Vol. 59, No. 3

References and Notes


Aspartic acid-derived P-chiral DIAPHOX preligands with (S,S,S) configurations are not accessible because of the characteristic reaction pathway in the stage of introduction of the phosphine oxide moiety. See ref. 9 for details.

The absolute configuration of the phosphorus atom of 9a and 9b was predicted by comparing the measured optical rotation with that of (S,R,R)-(−)-10a and (S,R,R),(+)-10b.

The Pd-ligand ratio (Pd/10a or Pd/10b=1/2) was set based on the previous examinations using DIAPHOX 1. See ref. 9 for details.