Chiral Phosphinooxazolidine Ligand Derived from Prolinol: Application to the Pd-Catalyzed Asymmetric Allylic Alkylation

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Pd-catalyzed asymmetric allylic alkylation is recognized as an useful asymmetric carbon-carbon forming process, in which racemic or achiral allylic substrates can be converted to optically active products in the presence of palladium complex of chiral ligand.[1,2] Numerous chiral ligands have been developed in order to achieve high enantioselectivity in the reaction. Phosphinooxazolines such as **1** have received considerable attention as very effective chiral P,N-bidentate ligands.[3] Recently, we developed new phosphinooxazolidine ligands **2** bearing sp^3 nitrogen donor for the asymmetric catalysis.[4] The oxazolidines obtainable by simple synthetic route seem to be potential ligands for the asymmetric catalysis. In the context of our research directed towards the development of new oxazolidine ligands, we here present phosphinooxazolidine ligands derived from optically active prolinols, together with their application to the Pd-catalyzed asymmetric allylation.

1   **2**

3   **4**
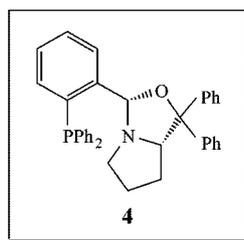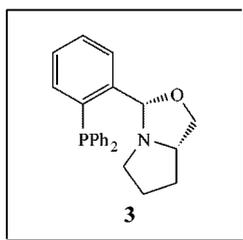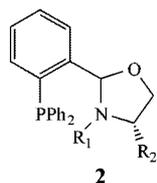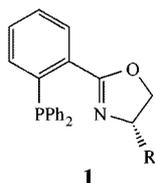
The phosphinooxazolidines **3** and **4** were easily prepared through condensation of commercially available 2-(diphenyl-phosphino)benzaldehyde and L-prolinol or α,α-diphenyl-L-prolinol in refluxing benzene over 12 h. The reaction leads to the formation of new stereocenter C2 on the oxazolidine ring. Interestingly, **3** and **4** were diastereomerically pure within NMR detection limits. The *cis*-relative configuration at C2 was assigned on the basis of the ^{1}H NMR spectral data and the previous studies.[4]

The catalytic properties of the palladium complexes formed *in situ* from the ligands and [Pd(π-C$_3$H$_5$)Cl]$_2$ were investigated in the asymmetric allylic alkylation of 1,3-

**Table 1**. Pd-catalyzed asymmetric allylic alkylation of **5** with dimethyl malonate[a]

(±)- **5**   (R)- **6**
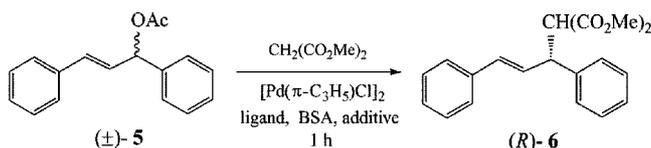
Entry	Ligand	Solvent	additive	Temp. (^{o}C)	Yield (%)[b]	ee (%)[c]
1	**3**	THF	KOAc	0	91	81
2	**3**	THF	KOAc	10	97	84
3	**3**	THF	KOAc	22	98	82
4	**3**	CH$_2$Cl$_2$	KOAc	10	98	82
5	**3**	THF	LiOAc	10	96	86
6	**3**	THF	NaOAc	10	95	81
7[d]	**3**	THF	KOAc	10	92	84
8	**4**	THF	LiOAc	10	70	86
9	**4**	CH$_2$Cl$_2$	KOAc	10	81	81

[a]Reactions were carried out with [Pd(π-C$_3$H$_5$)Cl]$_2$ (2 mol%), ligand (5 mol%), BSA (3 equiv.), additive (4 mol%) and dimethyl malonate (3 equiv.) unless noted otherwise. [b]Measured as %-conversion into the product by GC. [c]Determined by HPLC with a chiralcel OD-H column. Absolute configuration was assigned by the sign of the optical rotation and the elution order from a chiral column. [d][Pd(π-C$_3$H$_5$)Cl]$_2$ (1 mol%) and ligand (2.5 mol%) were used.

diphenyl-2-propenyl acetate **5** with dimethyl malonate. *N,O*-Bis-(trimethylsilyl)acetamide (BSA) combined with a small amount of KOAc, NaOAc or LiOAc was used as a base. The data obtained are summarized in Table 1. Optimum results were obtained when the reaction was performed at 10 ^{o}C in THF. Use of THF is more desirable than CH$_2$Cl$_2$ in terms of enantioselectivity. Additive source seems to have a little influence on the ee. BSA-LiOAc gave somewhat better enantioselctivity. Ligand **3** afforded the product (*R*)-**6** with 86% ee under this condition and the alkylation proceeded remarkably fast (entry 5). Reducing the amount of catalyst to 2 mol% based on the amount of substrate was still efficient for the reaction (entry 7). Ligand **4** having diphenyl group on oxazolidine ring gave same enantioselectivity as ligand **3** (entry 8 and 9). It is interesting that the presence of substituent at C5 on oxazolidine ring seems to have little influenece on the ee.

The asymmetric induction by ligand **3** can be briefly explained as follows.
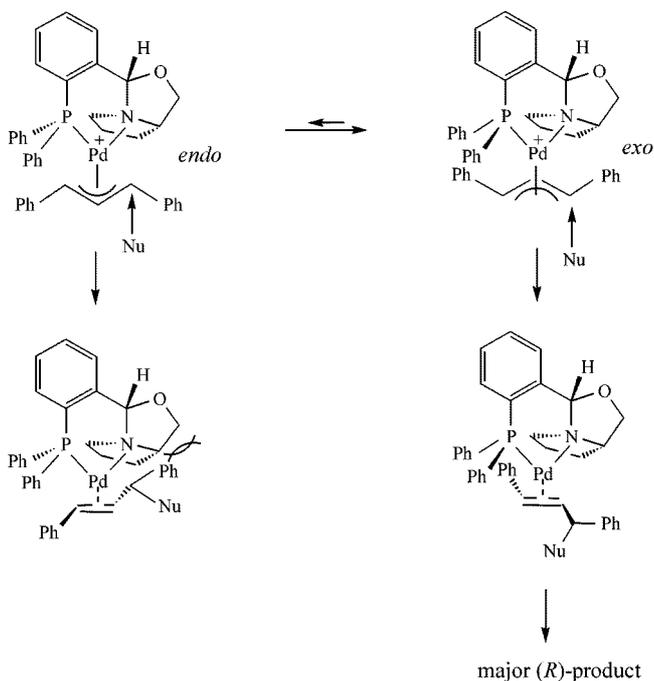
Scheme 1

It has been well known that the nucleophilic attack to π-allyl complex occurs at the allyl terminal carbon trans to the phosphorus which is better π-acceptor in the P,N-ligand. Presumably, the nucleophilic substitution would proceed preferentially through *exo-π*-allylpalladium complex as a major path in which the nucleophilic attack leads to the less sterically-hindered Pd-olefin complex.[3g,6] In the case of *endo-π*-allyl complex, severe steric repulsion is generated during the formation of the Pd-olefin complex. Therefore, (*R*)-isomer is formed as the major product, in accordance with the experimental result (Scheme 1). Considering this mechanism, the alkyl substituent at C4 is related to the ee of the reaction. Excellent enantioselectivity has been observed with ligand **2** bearing a bulky group at C4.[4] In comparison to the ligand **2**, ligand **3** having conformationally rigid pyrrolidine ring gave comparable catalytic activity but lower ee.

In conclusion, we have easily prepared a new kinds of prolinol-based phosphinooxazolidines, which could serve as efficient ligands in the asymmeric Pd-catalyzed allylic alkylation. Further synthesis of chiral oxazolidines and their application are underway in our laboratory.

Experimental Section

Reactions were carried out under an inert nitrogen atmosphere using dried glassware. All the commercially available reagents were used without further purification. NMR spectra were recorded on a Bruker AC 250 NMR spectrometer. Elemental analyses were carried out with CE instrument EA 1110 elemental analyzer. Optical rotation were measured with a Perkin-Elmer 241 polarimeter. The enantiomeric excesses were determined by HPLC analysis (chiralcel OD column; flow rate, 0.5 mL/min; detection, 254 nm).

Preparation of pyrrolidinylphosphinooxazolidines. To a solution of 2-(diphenylphosphino)benzaldehyde (0.25 g, 0.86 mmol) in degassed benzene (3 mL) was added L-prolinol or α,α-diphenyl-L-prolinol (0.95 mmol). The mixture was gradually heated to 80 ^{o}C and allowed to react for 18 h, observing the progress of the reaction by GC. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was purified by short column chromatography on silica gel pretreated with tri-ethylamine (10% EtOAc-5% Et$_3$N/hexane).

(2S,5S)-1-Aza-2-(2-diphenylphosphino)phenyl-3-oxa-bicyclo[3.3.0]octane (3). yield 85%; $[\alpha]_D^{20} = +45.7$ (c=1.2, CHCl$_3$); MS (EI) *m*/z 373 (M$^+$); ^{1}H-NMR: (CDCl$_3$, 250 MHz) δ 7.65 (m, 1H), 7.65-7.15 (m, 12H), 6.95 (m, 1H), 6.03 (d, *J* 3.0 Hz, 1H), 3.85 (t, *J* 6.4 Hz, 1H), 3.32 (m, 2H), 3.05 (m, 1H), 2.72 (m, 1H), 1.85-1.35 (m, 4H); Anal. Calcd for C$_{24}$H$_{24}$NOP: C, 77.19; H, 6.48; N, 3.75. Found: C, 77.05; H, 6.39; N, 3.67.

(2S,5S)-1-Aza-2-(2-diphenylphosphino)phenyl-3-oxa-4,4-diphenylbicyclo[3.3.0]octane (4). yield 75%; $[\alpha]_D^{20} = -94.8$ (c=1.2, CHCl$_3$); MS: *m*/z 525 (M$^+$); ^{1}H-NMR: (CDCl$_3$, 250 MHz) δ 7.62 (m, 1H), 7.11-7.38 (m, 22H), 6.88 (m, 1H), 6.36 (d, *J* 6.3 Hz, 1H), 4.31 (t, *J* 7.0 Hz, 1H), 2.93 (m, 1H) 2.75 (m, 1H), 1.43-1.70 (m, 4H); Anal. Calcd for C$_{36}$H$_{32}$NOP: C, 82.26; H, 6.14; N, 2.66. Found: C, 81.97; H, 6.09; N, 2.51.

Typical procedure for the Pd-catalyzed asymmetric allylic alylation. In a Schlenk tube a solution of the oxazo-lidine ligand (0.025 mmol) and allylpalladium chloride dimer (3.7 mg, 0.01 mmol) in THF (1.2 mL) was stirred at room temperature for 20 min. To this solution were successively added 1,3-diphenyl-2-propenyl acetate (126 mg, 0.5 mmol) in THF (1.6 mL), dimethyl malonate (198 mg, 1.5 mmol), *N,O*-bis(trimethylsilyl)acetamide (305 mg, 1.5 mmol) and metal acetate (0.05 mmol). The mixture was stirred at a given temperature. After the reaction was complete, the reaction mixture was diluted with ether, washed with cold saturated aqueous ammonium chloride solution. The organic layer was dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (15% EtOAc/hexane). The enantiomeric excess was determined by HPLC analysis (chiralcel OD-H column; flow rate, 0.5 mL/min; hexane : isopropanol = 99 : 1, *tr* = 23.4 min, *ts* = 25.0 min).

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