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NEW CHIRAL PHOSPHINOOXATHIOLANE LIGANDS FOR PALLADIUM-CATALYZED ASYMMETRIC ALLYLATIONS

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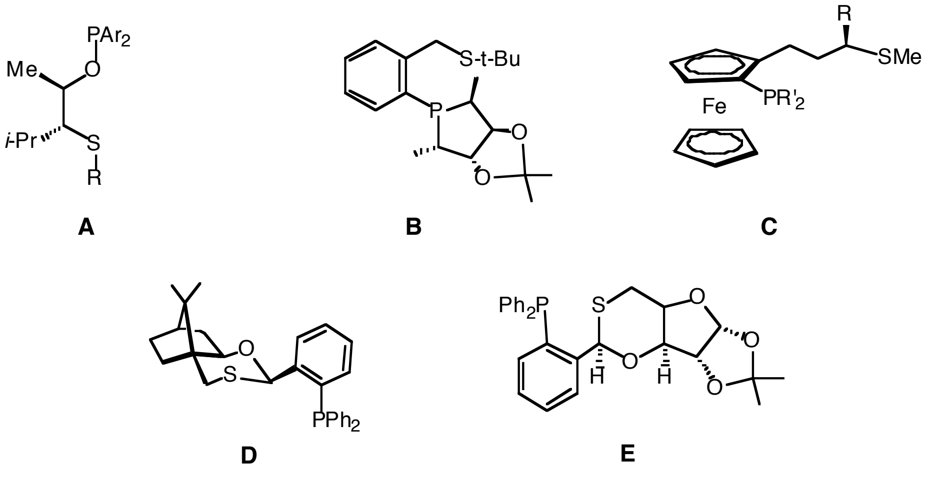
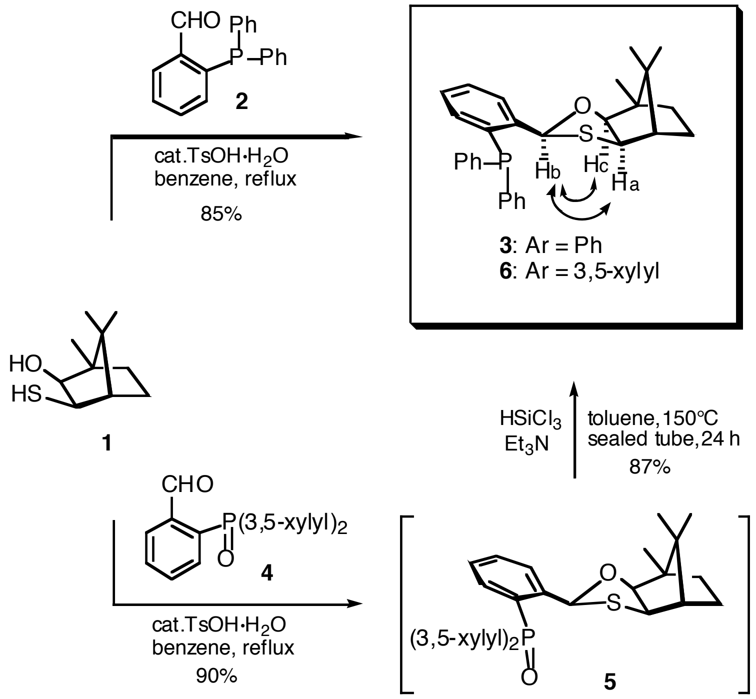
Abstract - A new chiral phosphinooxathiolane ligands were synthesized and their abilities as chiral catalysts were examined in palladium-catalyzed allylic alkylation and amination.

Palladium-catalyzed allylation[1] is one of the most important methods for carbon-carbon bond formation in synthetic organic chemistry. As such, its asymmetric version using a chiral ligand has also been extensively studied during the last decade.[2] Several efficient chiral nitrogen-nitrogen (N-N), phosphorus-phosphorus (P-P) and nitrogen-phosphorus (N-P) ligands[2] have been explored for this reaction. Recently, sulfur-phosphorous (S-P) type ligands such as **A-E** were shown to be effective in this reaction similarly to the above type ligands by our (**B** and **C**)[3] and other (**A-C**)[4] groups. To the best of our knowledge, phosphinooxathiolanes as S-P type ligand have never been involved in this area. With the aim of exploiting the less popular oxathiolane, we prepared chiral phosphinooxathiolanes (**3** and **6**) as S-P type ligands. In this paper, we wish to report the first application of the oxathiolane as a chiral ligand to the palladium-catalyzed asymmetric allylic alkylation and amination.



Scheme 1

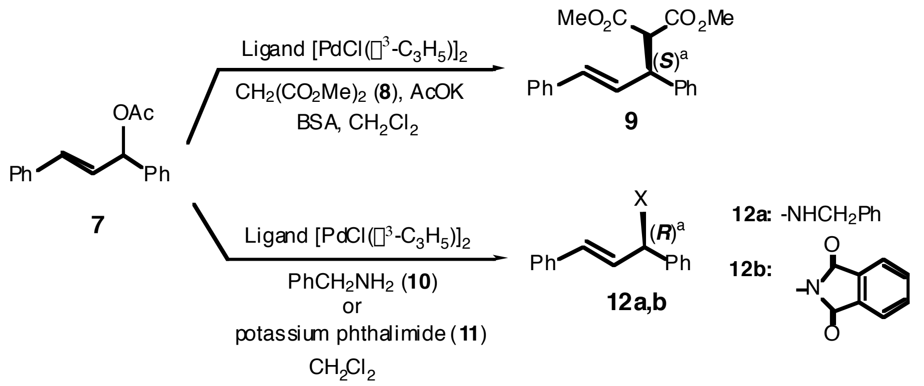
Synthesis of phosphinooxathiolane ligands (**3** and **6**) are shown in Scheme 2. Chiral ligand (**3**) was easily prepared by the condensation of known (1*R*,2*S*,3*R*)-3-mercaptocamphan-2-ol (**1**)[5] with commercially available aldehyde (**2**) in refluxing benzene in good yield (91%). Furthermore, the condensation of **1** with aldehyde (**4**)[6] followed by the reduction of precursor (**5**) with $HSiCl_3$ and Et_3N[6] afforded the desired chiral ligand (**6**) in 87% yield. The assigned stereochemistry at the □-position of the 1,3-oxathiolane rings for **3** and **6** was determined by the NOE difference spectrum (NOEDS). Enhancement was observed between the H_a and H_b and between H_b and H_c, respectively (Scheme 2).[3,6]



Scheme 2

The obtained chiral phosphinooxathiolane ligands (**3** and **6**) were applied to the Pd-catalyzed allylic alkylations of 1,3-diphenyl-2-propenyl acetate (**7**) with dimethyl malonate (**8**) as a carbon nucleophile. The reaction was carried out in the standard conditions using π-allylpalladium chloride dimer $[PdCl(\eta^3\text{-}C_3H_5)]_2$, *N,O*-bis(trimethylsilyl)acetamide (BSA),[7] and potassium acetate (Entries 1-7) in dichloromethane. The results are summarized in Table 1. The reaction at room temperature was almost proceeded in a few hours to give the product (**9**) in excellent chemical yield (98%), but with moderate enantiomeric excess (ee)(74% ee)(Entry 1). Decreasing the temperature to 0°C brought about a decrease of the reaction rate without a fluctuation in enantioselectivity (73% ee)(Entry 2). Further decreasing the temperature to –30°C gave good ee (84% ee), although chemical yield was 68%, even in 90 h (Entry 3). Varying the catalyst loading to 5 mol% of chiral ligand (**3**) gave the best enantioselectivity (85% ee) with 74% in 40 h, even at -30°C (Entry 4). Reactions with bulky ligand (**6**) under the same conditions were also examined (Entries 5-7). However, outstanding results were not observed for enantioselectivity, and the chemical yields decreased under the conditions corresponding to that of ligand (**3**). Based on the above results, chiral phosphinooxathiolane ligand (**3**) was more effective than **6** for this allylic alkylation.

Table 1. Asymmetric Pd-catalyzed allylic alkylation and amination of acetate (**7**)



Entry	Ligand	Ligand (mol%)	Nu	Temp. (°C)	Time (h)	Yield[b] (%)	e.e.[c] (%)
1	**3**	2	**8**	rt	□3	98	74
2	**3**	2	**8**	0	48	60	73
3	**3**	2	**8**	-30	90	68	84
4	**3**	5	**8**	-30	40	74	85
5	**6**	2	**8**	rt	24	66	71
6	**6**	2	**8**	0	90	41	72
7	**6**	2	**8**	-30	110	42	82
8	**3**	5	**10**	rt	24	39	48
9	**3**	5	**10**	0	96	14	51
10	**3**	5	**11**	rt	48	98	63
11	**3**	5	**11**	0	48	96	66
12	**3**	5	**11**	-30	---	---	---
13	**6**	5	**11**	0	40	76	30

[a] Absolute configurations based on the specific rotation with literature data.[3] [b] Isolated yields. [c] Determined by HPLC analysis using a DAICEL Chiralcel OD-H ◫ column.

We next examined the palladium-catalyzed allylic amination[8] of acetate (**7**) with benzylamine (**10**) as a nitrogen nucleophile using the chiral phosphinooxathiolane ligand (**3**), which showed efficient ability in allylic alkylation. The reaction was carried out in CH_2Cl_2 using a catalyst generated by mixing 2.5 mol % of [PdCl(□^{3}-C_3H_5)]$_2$ with 5 mol % of chiral ligand (**3**), respectively, to give the aminated product

(**12a**). The results are summarized in Table 1. When the reaction was carried out at room temperature, the product (**12a**) was obtained in low chemical yield (39%) and ee (48% ee)(Entry 8). Decreasing the temperature to 0°C led to a substantial decrease in chemical yield (14%), although the ee was slightly increased (Entry 9). Furthermore, the same reaction was examined using potassium phthalimide (**10**) as a bulky and a reactive nitrogen nucleophile (Entries 10-13). The reaction at room temperature gave the product (**12b**) in excellent chemical yield (98%) and moderate enantioselectivity (63% ee)(Entry 10). Although the excellent chemical yield (96%) was obtained even at 0°C, a good enantioseletivity was not observed (Entry 11). In addition, the reaction did not proceed at –30°C (Entry 12). Bulky ligand (**6**) was applied to the reaction using **13**. However, the catalytic activity of **6** is weaker than that of **3** and the reaction gave the product (**12b**) in poor enantioselectivity (30% ee)(Entry 13).

In summary, chiral phosphinooxathiolanes (**3** and **6**) were exploited, and applied to Pd-catalyzed asymmetric alkylation and amination for the first time. As the results, chiral oxathiolane ligand (**3**) was more effective than **6** in the allylic alkylation. However, ligands (**3** and **6**) were not effective in the allylic amination for achieving high enantioselectivity. It is expected that **3** and **6** would act as good ligands in other catalytic asymmetric reactions.

EXPERIMENTAL

General. IR spectra were measured with a PERKIN ELMER 1725X spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-GSX 270 and a JEOL JNM-LA 600 spectrometers with TMS as an internal standard. MS was taken on a JEOL-JNM-DX 303 spectrometers and elemental analysis was performed by a PERKIN-ELMER 2400 CHN Elemental Analyzer. Optical rotations were measured with a JASCO-DPI-370 digital polarimeter.

[1*R*,2*S*,4*S*,6*S*,7*S*]-4-(2-Diphenylphosphino)phenyl-1,10,10-trimethyl-3-oxa-5-thiatricyclo[5.2.1.0]-decane (3): Mercapto alchohol (**1**) (93 mg, 0.5 mmol), 2-(diphenylphosphino)benzaldehyde (**2**) (150 mg 0.5 mmol), *p*-toluenesulfonic acid monohydrate (9.5 mg, 0.05 mmol), and benzene (10 mL) were placed in a flask equipped with a Dean-stark trap and the mixture was refluxed for 1 h. The solvent was evaporated under a reduced pressure, and the residue was purified by column chromatography on silica gel (elution with AcOEt : hexane = 1 : 20) to afford **3**.Yield 87% (0.2 g)**,** white solid. mp 120-122°C. [□]$_D^{22}$ = –72.8° (c 2.0, $CHCl_3$). IR (KBr): 850, 740, 695 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 7.88-7.91 (m, 1H), 7.40 (t, J = 7.6 Hz, 1H), 7.20-7.34 (m, 11H), 6.93-6.97 (m, 1H), 6.74 (d, J = 6.9, 1H), 3.95 (d, J = 7.3, 1H), 3.69 (d, J = 7.3, 1H), 1.82-1.87 (m, 2H), 1.42-1.57 (m, 1H), 1.42 (s, 3H), 1.10 (s, 3H), 0.80-1.10 (m, 2H), 0.83 (s, 3H). ^{13}C-NMR ($CDCl_3$) □: 142.21, 141.85, 136.76, 134.34, 134.12, 134.09, 133.83, 133.54, 133.50, 133.22, 129.67, 128.62, 128.45, 128.41, 128.40, 128.32, 126.10, 126.02, 93.64, 85.65, 58.03, 47.90, 32.42, 28.50, 23.11, 21.97, 12.24. HRMS m/z: Calcd for $C_{29}H_{31}OPS$ (M^+): 458.1835. Found: 458.1833.

[1*R*,2*S*,4*S*,6*S*,7*S*]-4-[2-Di(3,5-xylyl)phosphino]phenyl-1,10,10-trimethyl-3-oxa-5-thiatricyclo-[5.2.1.0]decane (6): Compound (**1**) (0.1 g, 0.54 mmol), 2-[bis(3,5-dimethylphenyl)phosphinoyl]-benzaldehyde (**4**)(0.19 g, 0.54 mmol), *p*-toluenesulfonic acid monohydrate (0.01 g, 0.054 mmol), and benzene (10 mL) were placed in a flask equipped with a Dean-Stark trap. The mixture was refluxed for 12 h. The solvent was evaporated under a reduced pressure to give a crude product (**5**). The residue (**5**) was used the next reaction without the purification. To a mixture of **5** (0.435 g, 0.82 mmol) and Et_3N (1.66 g, 16.4 mmol) in toluene (20 mL) was added trichlorosilane (1.11 g, 8.2 mmol) at 0°C. The reaction mixture was stirred at 150°C for 24 h. After cooling to rt, the reaction mixture was diluted with Et_2O and quenched with small amount of saturated $NaHCO_3$. The resulting suspension was filtered through Celite, and solid was washed with Et_2O. The combined organic layer was dried over anhydrous $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (elution with AcOEt : hexane = 1 : 20) to afford **6**. Yield 87% (0.367 g), white solid. mp 70-71°C. [□]$_D^{23}$ = –59.4° (c 1.1, $CHCl_3$). IR (KBr): 846, 745, 696 cm^{-1}. ^{1}H-NMR ($CDCl_3$) □: 7.86-7.90 (m, 1H), 7.39 (t, J = 7.4, 1H), 7.19-7.25 (m, 2H), 6.95-7.01 (m, 2H), 6.84-6.89 (m, 4H), 6.71 (d, J = 6.9, 1H), 3.95 (d, J = 7.3, 1H), 3.69 (d, J = 7.3, 1H), 2.25 (br s, 12H), 1.87-1.88 (m, 2H), 1.44-1.52 (m, 1H), 1.44 (s, 3H), 1.06 (s, 3H), 0.96-1.06 (m, 2H), 0.84 (s, 3H). ^{13}C-NMR ($CDCl_3$) □: 141.98, 141.62, 137.58, 137.48, 134.12, 131.33, 131.12, 131.04, 130.84, 130.31, 130.23, 129.40, 128.20, 125.94, 125.85, 93.49, 85.80, 57.87, 48.84, 47.79, 32.33, 28.40, 23.00, 21.88, 21.31, 21.28, 12.11. HRMS m/z: Calcd for $C_{33}H_{39}OPS$ (M^+): 514.2484. Found: 514.2464.

General Procedure for Pd-Catalyzed Asymmetric Allylation of (±)-1,3-Diphenyl-2-propenyl Acetate (7) with Dimethyl Malonate.

A mixture of the ligand (**3**) [9.0 mg, 0.02 mmol (5 mol%) or 3.6 mg, 0.008 mmol (2 mol%)] and [PdCl(□^{3}-C_3H_5)]$_2$ (3.6 mg, 0.01 mmol or 1.45 mg, 0.004 mmol), respectively, in dry dichloromethane (1 mL) was stirred at rt for 1 h and the resulting yellow solution was added to a mixture of acetate (**20**) (100 mg, 0.40 mmol) and potassium acetate (0.8 mg, 0.008 mmol) in dry dichloromethane (1 mL), followed by the addition of dimethyl malonate (160 mg, 1.2 mmol) and BSA (240 mg, 1.2 mmol). The reaction was carried out at ambient temperature. The reaction mixtures were diluted with ether and quenched with sat. NH_4Cl. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated under a reduced pressure and the residue was purified by preparative TLC (hexane : ether = 5 : 1) to give a pure product (**9**). The enantiomeric excess was determined by HPLC (Chiralcel OD-H, 0.5 mL/min, hexane : 2-propanol = 98 : 2). The absolute configuration was determined by the specific rotation.[3]

General Procedure for Palladium-Catalyzed Allylic Amination of *rac*-1,3-Diphenyl-2-propenyl Acetate (7) with Benzylamine (10).

A mixture of the ligand (**3**) [9 mg, 0.02 mmol (5 mol%)] and [PdCl(□^{3}-C_3H_5)]$_2$ (3.6 mg, 0.01 mmol) in dry CH_2Cl_2 (1 mL) was stirred at rt for 1 h under Ar. To the solution, a solution of 1,3-diphenyl-2-propenyl acetate (**7**) (100 mg, 0.4 mmol) in CH_2Cl_2 (1 mL) and benzylamine (**10**) (0.11 ml, 1 mmol) was added. The reaction mixture was stirred at a temperature and a reaction time as shown in Table 1. The mixture was subjected directly to column chromatography on silica gel (hexane/EtOAc = 5/1 as eluent) to give the product (**12a**). The enantiomeric excess was determined by HPLC (Chiralcel OD-H, 0.5 mL/min, hexane/2-propanol = 199/1). The absolute configuration was determined by the specific rotation.[3]

General Procedure for Palladium-Catalyzed Allylic Amination of *rac*-1,3-Diphenyl-2-propenyl Acetate (7) with Potassium Phthalimide (11).

A mixture of the ligand (**3**) [9 mg, 0.02 mmol (5 mol%)] and [PdCl(□^{3}-C_3H_5)]$_2$ (3.6 mg, 0.01 mmol) in dry CH_2Cl_2 (1 mL) was stirred at rt for 1 h under Ar. The solution and the CH_2Cl_2 solution (1 mL) of 1,3-

diphenyl-2-propenyl acetate (**7**) (100 mg, 0.4 mmol) was added to the suspension of potassium phthalimide (**11**) (220 mg, 1.2 mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at a temperature and a reaction time as shown in Table 2. The mixture was quenched with water and extracted with ether. The organic layer was dried over anhydrous $MgSO_4$ and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was chromatographed on silica gel (hexane/EtOAc = 5/1 as eluent) to give the pure product (**12b**). The enantiomeric excess was determined by HPLC (Chiralcel OD-H, 0.5 mL/min, hexane/2-propanol = 98/2). The absolute configuration was determined by the specific rotation.[3]

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