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New chiral phosphinooxathiane ligands for palladium-catalyzed asymmetric allylic substitution reactions

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Abstract

New chiral ligands, phosphinooxathianes **3** and **6**, were synthesized easily and their ability as ligands were examined in Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate to give an allylation product. Enantiomeric excess of up to 94% has been obtained using 1 mol% of $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 2 mol% of **3**.

During the last decade, several efficient enantioselective catalysts have been explored for the Pd-catalyzed asymmetric allylic substitutions.[1] However, oxathianes are not popular as a chiral ligand and have not been involved so far in this area. To the best of our knowledge, oxathianes have been used only in the asymmetric carbonyl epoxidation.[2] In this communication, we wish to report the synthesis of a new type of two chiral ligands, norbornane-based phosphinooxathiane **3** and pulegone-based phosphinooxathiane **6**, followed by the application to Pd-catalyzed allylic alkylation. This is the first example that uses oxathianes as a chiral ligand to Pd-catalyzed asymmetric allylic substitutions.

Preparations of the chiral ligands **3** and **6** are described in Scheme 1. The chiral norbornane-based phosphinooxathiane **3**[3] was readily synthesized in 92% yield by the condensation of commercially available (1*S*)-(–)-10-mercaptoisoborneol **1** with 2-(diphenylphosphino)benzaldehyde **2** in refluxing toluene using a Dean–Stark apparatus. In addition, this reaction gave the ligand **3** in 82% yield with 7% yield of the diastereomer **4**[4] when benzene was used as a solvent. (+)-Pulegone-based phosphinooxathiane **6**[4] was obtained from the hydroxy thiol (a diastereomeric mixture of which the major component **5** constitutes 82% as indicated by ^{13}C NMR)[5] with **2** in refluxing toluene. The stereochemistries of the newly created stereogenic center at the α-position of the 1,3-oxathiane ring for **3** and **6** were determined by the NOE measurement of ^1H NMR spectra, respectively. Thus, the NOE experience for **3** and **6** confirmed an interaction between the hydrogen at the α-position and at the β-position, respectively.

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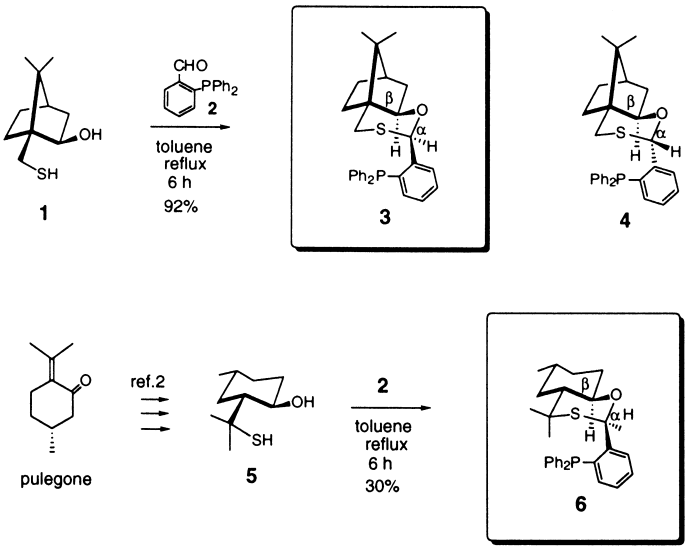
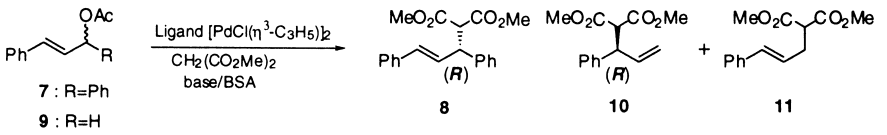


Scheme 1.

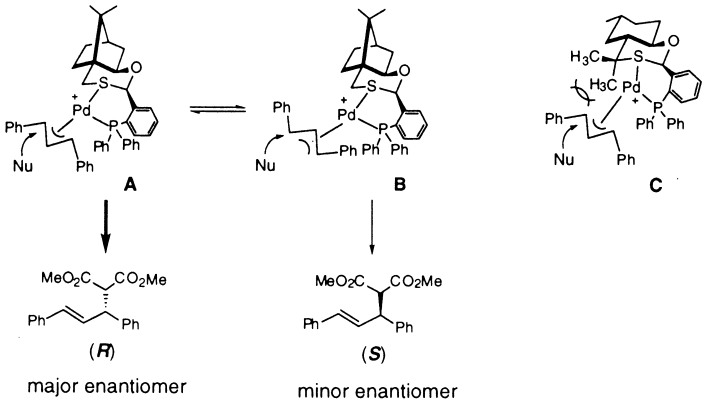
In order to examine the effectiveness of the ligands, the enantioselective allylic alkylation of 1,3-diphenyl-2-propenyl acetate **7** with dimethyl malonate was tried in the presence of π-allylpalladium chloride dimer to give allylation product **8**. The results are summarized in Table 1. The reactions were tried under the BSA standard conditions (entries 1–10). When the reactions were carried out at room temperature and 0°C by using 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 2 mol% ligand **3**, respectively, outstanding results were not obtained for the enantiomeric excesses (ee) (rt: 89% ee, 0°C: 91% ee), although the reactions proceeded fast and in good chemical yields (rt: 96%, 0°C: 75%) (entries 1 and 2). A satisfactory result (80% and 94% ee) was achieved by using 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 2 mol% ligand **3** at –30°C for 24 h (entry 3).[6] The same enantiomeric excess (94% ee) was obtained at –50°C, although the chemical yield was moderate (62%) (entry 4). The same reaction at –78°C gave the product **8** in quite low chemical yield (13%) (entry 5). High enantiomeric excess (93% ee) was confirmed when toluene was used as a solvent, but the chemical yield was not good (entry 6). The condition using tetrabutylammonium fluoride (TBAF) gave 39% and 88% ee (entry 7). The reaction was tried by using 0.5 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 1 mol% ligand **3** under the same reaction conditions of entry 3 (entry 8). However, these reaction conditions did not give any better result in comparison with entry 3. Next, we tested the effectiveness of the chiral ligands **4** and **6**, and found, both **4** and pulegone-based phosphinooxathiane **6** were less effective under these reaction conditions (entries 9 and 10). From the above results, it is seen that phosphinooxathiane **3** is an excellent ligand in this allylation under the reaction conditions of entry 3. Futhermore, we examined the regio- and stereoselective allylation of cinnamyl acetate **9** with dimethyl malonate in the presence of the chiral ligand **3** and the palladium catalyst.[1e,g–i] The reactions when performed at rt and –30°C for 24 h in CH_2Cl_2 using 1 mol% $[PdCl(\eta^3\text{-}C_3H_5)]_2$ and 2 mol% ligand **3** (entries 11 and 12) proceeded to give almost quantitative yields. However, the regioselectivity for branched product **10** was not high (rt: **10**/**11** = 25/75, –30°C: **10**/**11** = 20/80) and the enantioselectivity of **10** was at a moderate level (61% ee) at –30°C (Table 1).

Table 1
Asymmetric Pd-catalyzed allylation of acetates **7** and **9**



Entry	Substrate	Ligand	Ligand (mol%)	Temp. (°C)	Solvent	Base	Time (h)	Product	Yield[d] (%)	E.e.[e,f] (%)
1[a]	**7**	**3**	2	r.t.	CH_2Cl_2	CH_3CO_2K	3	**8**	96	89
2	**7**	**3**	2	0	CH_2Cl_2	CH_3CO_2K	7	**8**	75	91
3	**7**	**3**	2	-30	CH_2Cl_2	CH_3CO_2K	24	**8**	80	94
4	**7**	**3**	2	-50	CH_2Cl_2	CH_3CO_2K	24	**8**	62	94
5	**7**	**3**	2	-78	CH_2Cl_2	CH_3CO_2K	24	**8**	13	90
6	**7**	**3**	2	-30	toluene	CH_3CO_2K	24	**8**	44	93
7[b]	**7**	**3**	2	-30	CH_3CN	TBAF	24	**8**	39	88
8[c]	**7**	**3**	1	-30	CH_2Cl_2	CH_3CO_2K	24	**8**	41	92
9	**7**	**4**	2	-30	CH_2Cl_2	CH_3CO_2K	24	**8**	21	26
10	**7**	**6**	2	-30	CH_2Cl_2	CH_3CO_2K	48	**8**	42	16
11	**9**	**3**	2	r.t.	CH_2Cl_2	CH_3CO_2K	1	**10+11**	100 (**10**/**11**=25/75)	13
12	**9**	**3**	2	-30	CH_2Cl_2	CH_3CO_2K	6	**10+11**	95 (**10**/**11**=20/80)	61

a) Molar ratio for entries 1-6 and 9-12 : $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.01 equiv.), dimethyl malonate (3 equiv.), *N,O*-bis-(trimethylsilyl)acetoamide (BSA) (3 equiv.), potassium acetate (0.02 equiv.) . b) Molar ratio for entry 7: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.01 equiv.), dimethyl malonate (3 equiv.), BSA (3 equiv.), TBAF (3 equiv.). c) Molar ratio for entry 8: $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (0.005 equiv.), dimethyl malonate (3 equiv.), BSA (3 equiv.), potassium acetate (0.02 equiv.). d) Isolated yields. e) Determined by HPLC analysis using a DAICEL Chiralcel OD-H (entries 1-10) and Chiralcel OJ (entries 11 and 12) columns. f) *R*-Configuration based on the specific rotation with literature data,[1a,b,h]



Scheme 2.

It is considered that the enantiodifferentiation step in Pd-catalyzed allylation is the substitution of π-allyl complexes with nucleophiles, and nucleophilic attack occurs predominantly at the allyl terminus from *trans* to the better π-acceptor (P > > S).[7] Since the (*R*) product was obtained as the major enantiomer, the reaction probably proceeds through an M-type **A** rather than a W-type **B** intermediate.[7] In addition, the differentiation of chemical yields and enantiomeric excesses for ligands **3** and **6** may be explained by steric inferences. Thus, ligand **6** has a bulky *gem*-dimethyl group in the oxathiane ring that obstructs the construction of the π-allyl palladium complex **C** (Scheme 2).

In conclusion, we have prepared two kinds of new chiral ligands **3** and **6**. Particularly, **3** was a good and effective ligand for allylic substitution reactions to give excellent chemical yield and enantiomeric excess. Further applications and modifications of the ligand **3** are in progress.

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2. Aggarwal, V. K.; Ford, J. G.; Jones, R. V. H.; Fieldhouse, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1801–1807.
3. Ligand **3**: mp 52–54°C, $[\alpha]_D^{23} = -96.05$ (*c* 1.51, $CHCl_3$). ^1H NMR ($CDCl_3$) δ 7.71 (m, 1H), 7.35–7.46 (m, 12H), 6.92 (m, 1H), 6.39 (d, $J = 7.6$ Hz, 1H), 3.59 (dd, $J = 7.0$, 3.0 Hz, 1H), 3.19 (d, $J = 14.2$ Hz, 1H), 2.70 (d, $J = 14.2$ Hz, 1H), 1.88 (m, 1H), 1.59–1.72 (m, 3H) 1.47 (m, 1H), 1.46 (s, 3H), 0.88–1.10 (m, 2H), 0.92 (s, 3H). Anal. calcd for $C_{29}H_{31}OPS$: C, 72.95; H, 6.81. Found: C, 72.65; H, 6.53. MS *m*/*z*: 458 (M^+).
4. ^1H NMR data of ligands **4** and **6**: Compound **4**: δ ($CDCl_3$): 7.82 (m, 1H), 7.15–7.43 (m, 11H), 6.91 (m, 1H), 5.81 (d, $J = 9.2$ Hz, 1H), 3.77 (m, 1H), 2.80 (d, $J = 11.2$ Hz, 1H), 2.33 (d, $J = 11.2$ Hz, 1H), 1.57–1.78 (m, 2H), 1.18–1.44 (m, 3H), 0.91–1.08 (m, 2H), 0.97 (s, 3H), 0.76 (s, 3H). Compound **6**: δ ($CDCl_3$): 7.76 (m, 1H), 7.25–7.39 (m, 11H), 7.17 (t, $J = 7.4$ Hz, 1H), 6.89 (m, 1H), 6.61 (d, $J = 8.2$ Hz, 1H), 3.39 (t, $J = 10.1$ Hz, 1H), 1.82 (m, 1H), 1.66–1.79 (m, 2H), 1.50 (m, 1H), 1.36 (s, 3H), 1.19 (s, 3H), 1.10 (q, $J = 12.2$ Hz, 1H), 0.87 (d, $J = 6.6$ Hz, 1H), 0.86 (m, 1H).
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6. Typical procedure for asymmetric reaction (entry 3): a mixture of ligand **3** (3.7 mg, 0.008 mmol) and $[PdCl(\eta^3\text{-}C_3H_5)]_2$ (1.46 mg, 0.004 mmol) in dry dichloromethane (1 ml) was stirred at room temperature for 1 h and the resulting yellow solution was added to a mixture of acetate **7** (100 mg, 0.4 mmol) and potassium acetate (0.8 mg, 0.008 mmol) in dry dichloromethane (1 ml) using a syringe followed by the addition of dimethyl malonate (160 mg, 1.2 mmol) and BSA (244 mg, 1.2 mmol). The reaction was carried out at –30°C for 24 h and the reaction mixture was diluted with ether and was quenched with satd NH_4Cl. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was purified by preparative TLC (hexane:ether = 5:1) to give a pure product **8**.[1a,b] The enantiomeric excess was determined by HPLC (Chiralcel OD-H, 0.5 ml/min, hexane:2-propanol = 98:2).
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