



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

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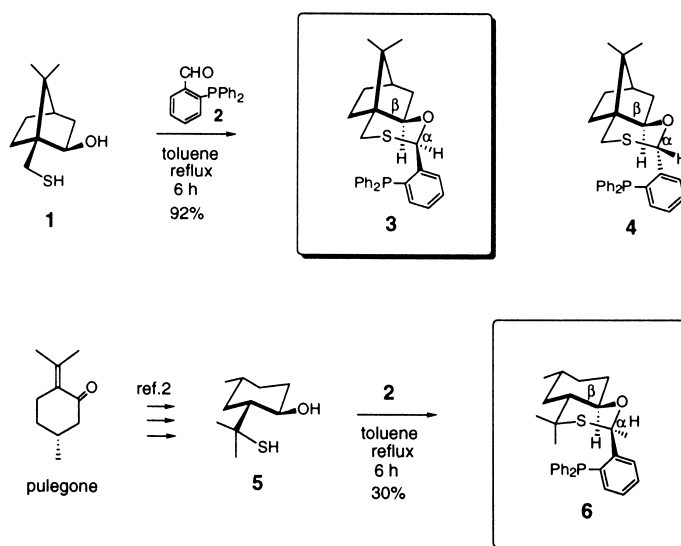
Abstract

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 $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ and 2 mol% of **3**. © 2000 Elsevier Science Ltd. All rights reserved.

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 ¹³C 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 -allyl-palladium 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% $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ 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% $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ 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% $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ 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. Furthermore, 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% $[\text{PdCl}(\eta^3\text{-C}_3\text{H}_5)]_2$ 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).

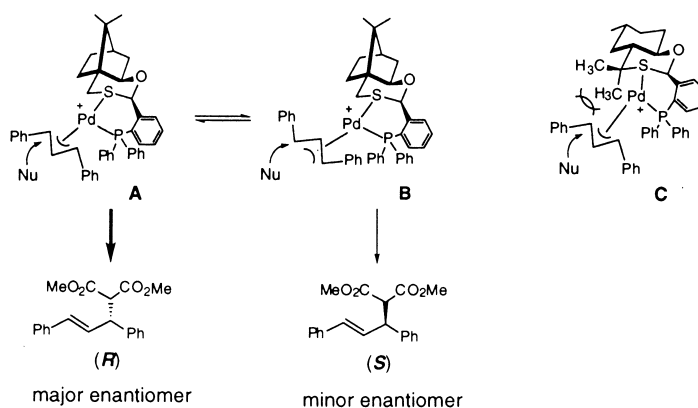
Table 1
Asymmetric Pd-catalyzed allylation of acetates **7** and **9**

7 : R=Ph
9 : R=H

8 10 11

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 ₂ Cl ₂	CH ₃ CO ₂ K	3	8	96	89
2	7	3	2	0	CH ₂ Cl ₂	CH ₃ CO ₂ K	7	8	75	91
3	7	3	2	-30	CH ₂ Cl ₂	CH ₃ CO ₂ K	24	8	80	94
4	7	3	2	-50	CH ₂ Cl ₂	CH ₃ CO ₂ K	24	8	62	94
5	7	3	2	-78	CH ₂ Cl ₂	CH ₃ CO ₂ K	24	8	13	90
6	7	3	2	-30	toluene	CH ₃ CO ₂ K	24	8	44	93
7 ^b	7	3	2	-30	CH ₃ CN	TBAF	24	8	39	88
8 ^c	7	3	1	-30	CH ₂ Cl ₂	CH ₃ CO ₂ K	24	8	41	92
9	7	4	2	-30	CH ₂ Cl ₂	CH ₃ CO ₂ K	24	8	21	26
10	7	6	2	-30	CH ₂ Cl ₂	CH ₃ CO ₂ K	48	8	42	16
11	9	3	2	r.t.	CH ₂ Cl ₂	CH ₃ CO ₂ K	1	10+11	100 (10/11=25/75)	13
12	9	3	2	-30	CH ₂ Cl ₂	CH ₃ CO ₂ K	6	10+11	95 (10/11=20/80)	61

a) Molar ratio for entries 1-6 and 9-12 : [PdCl(η³-C₃H₅)₂] (0.01 equiv.), dimethyl malonate (3 equiv.), *N,O*-bis-(trimethylsilyl)acetamide (BSA) (3 equiv.), potassium acetate (0.02 equiv.). b) Molar ratio for entry 7: [PdCl(η³-C₃H₅)₂] (0.01 equiv.), dimethyl malonate (3 equiv.), BSA (3 equiv.), TBAF (3 equiv.). c) Molar ratio for entry 8: [PdCl(η³-C₃H₅)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.

References

- (a) von Matt, P.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 566–568. (b) Sprinz, J.; Helmchen, G. *Tetrahedron Lett.* **1993**, *34*, 1769–1772. (c) Togni, A.; Venzani, L. M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 497–526. (d) Trost, B. M.; van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422. (e) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025. (f) Ogasawara, M.; Yoshida, K.; Kamei, H.; Kato, K.; Uozumi, Y.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1779–1787. (f) Gilbertson, S. R.; Chang, C.-W. T. *J. Org. Chem.* **1998**, *63*, 8424–8431. (g) Hayashi, T.; Kawatsura, M.; Uozumi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1681–1687. (h) Yonehara, K.; Hashizume, T.; Mori, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 9374–9380. (i) Hilgraf, R.; Pfaltz, A. *Synlett* **1999**, *11*, 1814–1816. (j) Saitoh, A.; Misawa, M.; Morimoto, T. *Synlett* **1999**, *11*, 483–485. (k) Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Yu, Y.-H.; Xia, W. *Chem. Commun.* **2000**, 285–286. (l) Fuji, K.; Ohnishi, H.; Moriyama, S.; Tanaka, K.; Kawabata, T.; Tsubaki, K. *Synlett* **2000**, *12*, 351–352.
- Aggarwal, V. K.; Ford, J. G.; Jones, R. V. H.; Fieldhouse, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1801–1807.
- Ligand **3**: mp 52–54°C, $[\alpha]_D^{23} = -96.05$ (c 1.51, CHCl₃). ¹H NMR (CDCl₃) 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 C₂₉H₃₁OPS: C, 72.95; H, 6.81. Found: C, 72.65; H, 6.53. MS *m/z*: 458 (M⁺).
- ¹H NMR data of ligands **4** and **6**: Compound **4**: δ (CDCl₃): 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 (CDCl₃): 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).
- Eliel, E. L.; Lynch, J. E. *Tetrahedron Lett.* **1981**, *22*, 2855–2858.
- Typical procedure for asymmetric reaction (entry 3): a mixture of ligand **3** (3.7 mg, 0.008 mmol) and [PdCl(η^3 -C₃H₅)]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 NH₄Cl. The organic layer was washed with brine and dried over MgSO₄. 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).
- (a) Akermarck, B.; Hansson, S.; Krakenberger, B.; Vitagliano, A.; Zetterberg, K. *Organometallics* **1984**, *3*, 679–682. (b) Sprinz, J.; Kiefer, M.; Helmchen, G.; Resselin, M. *Tetrahedron Lett.* **1994**, *35*, 1523–1526. (c) Allen, J. V.; Williams, J. M. J. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2065–2072. (d) Anderson, J. C.; James, D. S.; Mathias, J. P. *Tetrahedron: Asymmetry* **1998**, *9*, 753–756.