Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 33–35

TETRAHEDRON:
ASYMMETRY

Preparation of a new FerroPHOS derivative for palladium-catalyzed asymmetric allylic alkylations

Jahyo Kang,* Jun Hee Lee and Jung Sun Choi

Department of Chemistry, Sogang University, Seoul 121-742, South Korea

Received 28 November 2000; accepted 4 January 2001

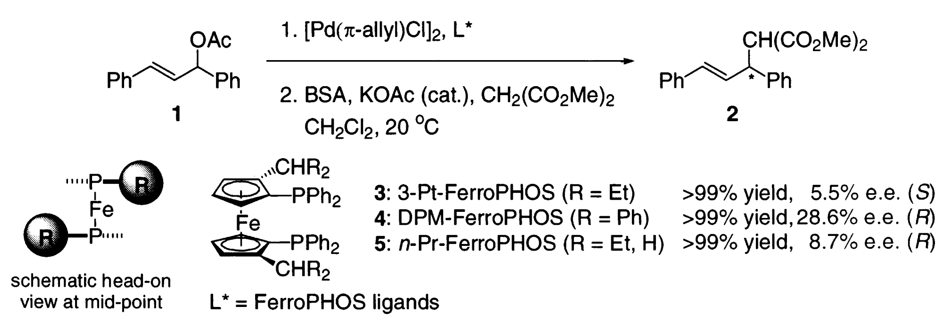
Abstract—A new C_2-symmetric only cylindrically chiral FerroPHOS derivative possessing (1-methoxy-1-methyl)ethyl substituents was prepared and applied to the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl acetate. Both high catalytic activity (up to 500 turnovers) and enantioselectivity (e.e.'s of up to 96.3%) were attained in reactions using the new diphosphine ligand. © 2001 Elsevier Science Ltd. All rights reserved.

Chiral ferrocene based ligands, and most especially ferrocenyl-diphosphines, have been the subject of intensive recent research.[1] However, most of these ferrocenyl ligands possess not only planar chirality but also central chirality and, due to the limitations of synthetic methodology,[2,3] less attention has been paid to ferrocenyl ligands with solely planar chirality.

In connection with our ongoing study on dual planar chirality (cylindrical chirality) as the sole element of chirality, we reported the preparation of several cylindrically chiral C_2-symmetric and air stable ferrocenyl diphosphines (FerroPHOS derivatives) and their successful application in some asymmetric reactions.[4] The aim of this study was to investigate the effect of changing the volume of substituents on the ligand to the levels of asymmetric induction.

The metal-catalyzed asymmetric allylic alkylation is a highly versatile tool for asymmetric C–C bond formation and numerous efficient chiral ligands are now available.[5] The palladium-catalyzed asymmetric allylic substitution reaction of 1,3-diphenylprop-2-en-1-yl acetate **1** with stabilized nucleophiles is an excellent model reaction for testing the efficiency of the artificial chiral ligands. Consequently, we decided to test our FerroPHOS ligands in the palladium-catalyzed asymmetric allylic alkylation of **1** with a nucleophile derived from dimethyl malonate as a nucleophile.

In the preliminary experiments, the known FerroPHOS ligands[4] were briefly screened (Scheme 1). The reaction of **1** with a nucleophile derived from dimethyl malonate using the Pd complexes derived from mixing 1.0 mol% $[Pd(\pi\text{-ally})Cl]_2$ with 2.2 mol% of each FerroPHOS



Scheme 1. The palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenylprop-2-en-1-yl acetate **1**.

---

* Corresponding author. Tel.: (82)-2-705-8439; fax: (82)-2-701-0967; e-mail: kangj@ccs.sogang.ac.kr

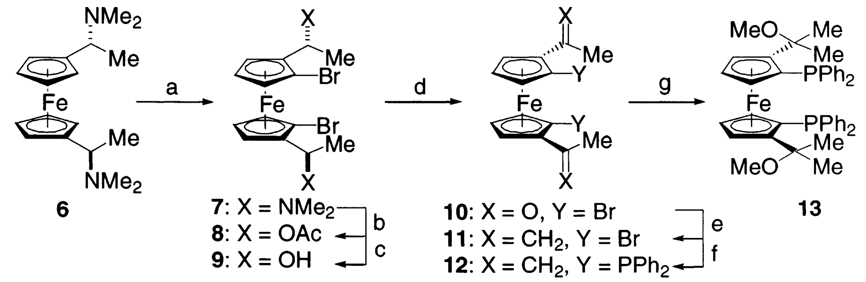
PII: S0957-4166(01)00019-2

ligand **3**–**5**, was carried out. To isolate the effect of the ligand, all other reaction conditions were fixed: BSA[6] along with 5.0 mol% KOAc was employed as a base and the reaction was carried out in a 0.5 M dichloromethane solution at 20°C under an inert nitrogen atmosphere. The new palladium complexes showed an extremely high catalytic activity, such that the reactions were complete in a few minutes and all the reactions gave quantitative yields. However, regardless of the ligands, low enantioselectivities were obtained and the configurations of the major enantiomer in products **2** did not show any recognizable trend.

We previously observed that the enantioselectivity of FerroPHOS ligands in Rh-catalyzed asymmetric hydroboration reactions was largely dependent on the size of side chain volumes.[4b] Accordingly, we anticipated that a new FerroPHOS ligand possessing more bulky tertiary side chains would be beneficial to the enantioselectivity in the asymmetric allylic alkylation of **1**.

The preparation of FerroPHOS derivative **13**, possessing more sterically demanding *tert*-alkoxyalkyl substituents, is summarized in Scheme 2. The twofold diastereoselective lithiation of the known diamine **6**[7] with *n*-BuLi and subsequent treatment with an excess of $(BrCCl_2)_2$ in THF afforded the dibromide **7** in good yield as a single diastereomer.[8] The diacetate **8** prepared by the reaction of diamine **7** with excess Ac_2O was then treated with 3 M aqueous KOH at rt to afford the diol **9** in 99% yield. Oxidation of the diol **9** using TPAP/NMO[9] yielded the chiral diacetylferrocene **10** in excellent yield. After purification by recrystallization (CH_2Cl_2/*n*-hexane), the diacetylferrocene **10** was reacted with $Ph_2P{=}CH_2$ in refluxing THF to afford the di-*iso*-propenylferrocene **11**. Pure diphosphine **12** was then obtained by the usual two-step sequence from **11** (the dual lithium–bromine exchange followed by quenching the dilithio derivative with $ClPPh_2$) in 80% yield after recrystallization (CH_2Cl_2/MeOH). The new FerroPHOS derivative **13** (hereafter, abbreviated to MME-FerroPHOS),[10] carrying two bulky (1-methoxy-1-methyl)ethyl groups as substituents, was obtained by the dual Markovnikov addition of MeOH into the *iso*-propenyl moieties of **12** in the presence of HBF_4-OMe_2.

Switching to the new FerroPHOS derivative **13** led to impressive results, as shown in Table 1. Both high catalytic activity and remarkably high enantioselectivity were attained using MME-FerroPHOS **13**. Thus, the reaction catalyzed by a chiral Pd-**13** complex was completed in a few minutes to give (*S*)-**2** with an e.e. of 94.2% in quantitative yield (entry 2). A slightly lower e.e. of 92.3% (entry 1) was obtained in the reaction with the nucleophile, sodium dimethyl malonate. Lowering the reaction temperature had a positive effect on the e.e. of the reactions and little effect on catalytic activity. Thus, the reaction at 0°C was also complete in 5



Scheme 2. *Reagents and conditions*: (a) (i) *n*-BuLi, ether, rt, 12 h, (ii) $(BrCCl_2)_2$, THF, −78°C to rt, 78%; (b) Ac_2O, 70°C, 10 h, 85%; (c) 3.0 M KOH, MeOH/THF, 1 h, 99%; (d) TPAP (5 mol%), NMO, CH_2Cl_2/CH_3CN, rt, 1 h, 95%; (e) $Ph_2P{=}CH_2$, THF, reflux, 5 h, 78%; (f) (i) *n*-BuLi, THF, −78°C, 0.5 h, (ii) $ClPPh_2$, −78°C to rt, 80%; (g) HBF_4-OMe_2, MeOH, rt, 12 h, 48%.

Table 1. Asymmetric allylic alkylation of **1** catalyzed by a Pd–MME-FerroPHOS complex[a]

Entry	Base	Temp. (°C)	Time (min)	Yield (%)[b]	E.e. (%)[c]	Config.[d]
1	NaH	20	10	>99	92.3	*S*-(−)
2	BSA	20	5	>99	94.2	*S*-(−)
3	BSA	0	5	>99	95.5	*S*-(−)
4	BSA	−30	360	>98	96.3[e]	*S*-(−)
5[f]	BSA	0	150	>98	95.1	*S*-(−)

[a] Unless otherwise stated, all reactions were carried out in CH_2Cl_2 (0.5 M) in the presence of 2.0 mol% Pd catalyst, 3 equiv. of dimethyl malonate and 3 equiv. of base under N_2.

[b] Isolated yield.

[c] Determined by chiral HPLC analysis (Daicel Chiralpak AD column; 10% 2-propanol/*n*-hexane; 0.8 mL/min). As a reference sample, racemic **2** was prepared using a Pd-dppf catalyst.

[d] Confirmed by comparing the specific rotation with a literature value.[11]

[e] $[\alpha]_D^{27}$ −19.6 (*c* 1.4, EtOH).

[f] The reaction was carried out in the presence of 0.20 mol% Pd catalyst.

minutes and resulted in an improved e.e. of 95.5% (entry 3), the yield was also quantitative. The best result, with an e.e. of 96.3% (entry 4) was obtained when the reaction was carried out at −30°C, though a longer reaction time of 6 hours was required for complete conversion, and a slight decrease in the yield of the reaction to 98% was seen. The most noteworthy feature of this chemistry is that the reactions are catalyzed by only 0.20 mol% of the Pd-catalyst (500 turnovers, entry 5) and were complete after 150 minutes at 0°C without a significant erosion of either the e.e. or yield (the e.e was 95.1%, with >98% yield). These results demonstrate the profound side chain volume effects in this type of FerroPHOS ligand on the enantioselectivity in Pd-catalyzed asymmetric allylic alkylations.

As described above, the cylindrically chiral MME-FerroPHOS is a highly efficient chiral ligand for the Pd-catalyzed asymmetric allylic alkylation of **1**. Further investigations into cylindrical chirality are now in progress in our laboratory.

Acknowledgements

This work was supported by grant No. (1999-1-12300-001-5) from the Basic Research Program of the Korea Science & Engineering Foundation.

References

1. (a) Togni, A.; Halterman, R. L. *Metallocenes*; Wiley-VCH: Weinheim, 1998; Vol. 2, pp. 685–721; (b) Richards, C. J.; Locke, A. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2377–2407; (c) *Ferrocenes*; Togni, A.; Hayashi, T., Eds.; VCH: Weinheim, 1995.
2. To the best of our knowledge only two other types of C_2-symmetric ferrocenyl diphosphine possessing only planar chirality have been reported so far: (a) Radoslaw, S. L.; Veith, U.; Taylor, N. J.; Snieckus, V. *Org. Lett.* **2000**, *2*, 629–631 and Jendralla, H.; Paulus, E. *Synlett* **1997**, 471–472; (b) Zhang, W.; Shimanuki, T.; Kida, T.; Nakatsuji, T.; Ikeda, I. *J. Org. Chem.* **1999**, *64*, 6247–6251 and references cited therein.
3. Selected papers for other ferrocene-based ligands with only planar chirality: (a) Argouarch, G.; Samuel, O.; Riant, O.; Daran, J.-C.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, 2893–2899; (b) Argouarch, G.; Samuel, O.; Kagan, H. B. *Eur. J. Org. Chem.* **2000**, 2885–2891; (c) Reetz, M. T.; Beuttenmüller, E. W.; Goddard, R.; Pastó, M. *Tetrahedron Lett.* **1999**, *40*, 4977–4980; (d) Kuwano, R.; Uemura, T.; Saitoh, M.; Ito, Y. *Tetrahedron Lett.* **1999**, *40*, 1327–1330.
4. (a) Kang, J.; Lee, J. H.; Ahn, S. H.; Choi, J. S. *Tetrahedron Lett.* **1998**, *39*, 5523–5526; (b) Kang, J.; Lee, J. H.; Kim, J. B.; Kim, G. J. *Chirality* **2000**, *12*, 378–382.
5. For reviews, see: (a) Pfaltz, A.; Lautens, M. *Allylic Substitution Reactions*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds. *Comprehensive asymmetric catalysis II*. Springer: New York, 1999; pp. 833–884. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395–422.
6. BSA = *N*,*O*-bis(trimethylsilyl)acetamide: Trost, B. M.; Murphy, D. J. *Organometallics* **1985**, *4*, 1143–1145.
7. (a) Schwink, L.; Knochel, P. *Chem. Eur. J.* **1998**, *4*, 950–968; (b) Schwink, L.; Knochel, P. *Tetrahedron Lett.* **1996**, *37*, 25–28.
8. All new compounds have been fully characterized spectroscopically and elemental composition established by low resolution mass spectroscopy and combustion analysis.
9. For review, see: Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639–666.
10. Selected spectroscopic data for MME-FerroPHOS {($_pS$,$_pS$)-1,1′-bis(diphenylphosphino)-2,2′-bis[(1-methoxy-1-methyl)]ethylferrocene **13**}: $[\alpha]_D^{29}$ −9.33 (*c* 0.54, $CHCl_3$); mp 163–165°C (dec.); anal. calcd for $C_{42}H_{44}FeO_2P_2$: C, 72.21; H, 6.35. Found: C, 72.28; H, 6.41; MS (EI, low resolution) *m*/*z* (relative intensity) 698 (M^+, 14.8); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.21–7.13 (m, 16H), 7.11–7.08 (m, 4H), 4.58 (t, $J = 2.0$ Hz, 2H), 4.45–4.44 (m, 2H), 3.08 (m, 2H), 2.80 (s, 6H), 1.73 (s, 6H), 1.51 (s, 6H); ^{31}P NMR ($CDCl_3$, 202.4 MHz, 85% H_3PO_4 as an external reference) δ −23.84 (s).
11. Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191–194.