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Journal of Organometallic Chemistry 637–639 (2001) 762–766

Journal of Organometallic Chemistry

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Note

Novel ferrocene modified *P*,*N*-ligands for enantioselective palladium-catalyzed allylic substitution reactions

Shu-Li You, Xue-Long Hou *, Li-Xin Dai

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, People's Republic of China

Received 2 January 2001; received in revised form 29 January 2001; accepted 29 January 2001

Abstract

Novel ferrocene modified *P*,*N*-ligands (*R*,*R*,*Sp*)-**8** and (*S*,*S*,*Sp*)-**9** were synthesized conveniently from enantiopure cyclohexanediamine and (*Sp*)-2-phosphinoferrocenyl carboxylic acid. They were used as chiral ligands for palladium-catalyzed allylic substitutions of *rac*-1, 3-diphenylprop-2-enyl acetate with dimethylmalonate and benzylamine. (*R*,*R*,*Sp*)-**8** was found to be a better ligand containing matched chiralities (central chirality and planar chirality) and showed a higher enantioselectivity.

Keywords: Alkylation; Amination; Ferrocenyl-derived ligands; Planar chirality

1. Introduction

Chirotechnology is one of the most interesting and challenging technologies of recent years [1]. The recognition of the importance of chirality in biological systems has made the production of enantiomerically pure chiral drugs to be an important requisite in drug design and development for the pharmaceutical industry. As a consequence, great efforts have been made towards the asymmetric catalytic processes by chemists. Therein design and synthesis of chiral ligands are always the key point. Among them, ferrocene containing ligands are one kind of the most interesting ligands because of the easily introduction of planar chirality and the inherent special electronic properties of ferrocene itself [2]. In comparison with the phenyl analogues, the ferrocenyl derived ligands with planar chirality usually showed higher selectivity and reactivity [3]. Sammakia [4] found that ferrocene derived ligand **1** was efficient in copper catalyzed conjugate addition of Grignard reagents to enones. The product was formed with high regioselectivity and 82% ee. However, poor regioselectivities and zero enantioselectivity were obtained with the corresponding phenyl derived ligands. Bolm [5] studied the role of planar chirality on addition reaction of diethylzinc to aldehydes with the hydroxyl-ferrocenyl-oxazoline ligand **2**. At the same time, we investigated the role of planar chirality in palladium-catalyzed allylic alkylation reaction with thioether ferrocenyl oxazoline **3** [6]. Both Bolm and us compared the results with that from the corresponding phenyl derived ligands and concluded that introduction of a matched chirality on the ferrocene system often increases the enantioselectivity. In addition to the increase of enantioselectivity the ferrocenyl-derived ligands frequently showed higher reactivity in some metal-catalyzed reactions than that of phenyl derived ligands [6a].

Ligand **4** has been proved very effective in asymmetric palladium-catalyzed allylic substitutions [7,8]. Recently, ligands **6** and **7**, the ferrocene analogues of ligand **4**, containing two kinds of chiralities were synthesized by Zhang [9c] and us [9a,b]. Among them, the chiralities in ligand **6** were found to be matched and better results were provided by comparison with ligand **4** in some cases [9a,b]. We have demonstrated that the presence of an additional proper planar chirality would improve the

* Corresponding author. Tel.: +86-21-6416-3300; fax: +86-21-6416-6128.

E-mail address: xlhou@pub.sioc.ac.cn (X.-L. Hou).

0022-328X/01/$ - see front matter
PII: S0022-328X(01)00911-1

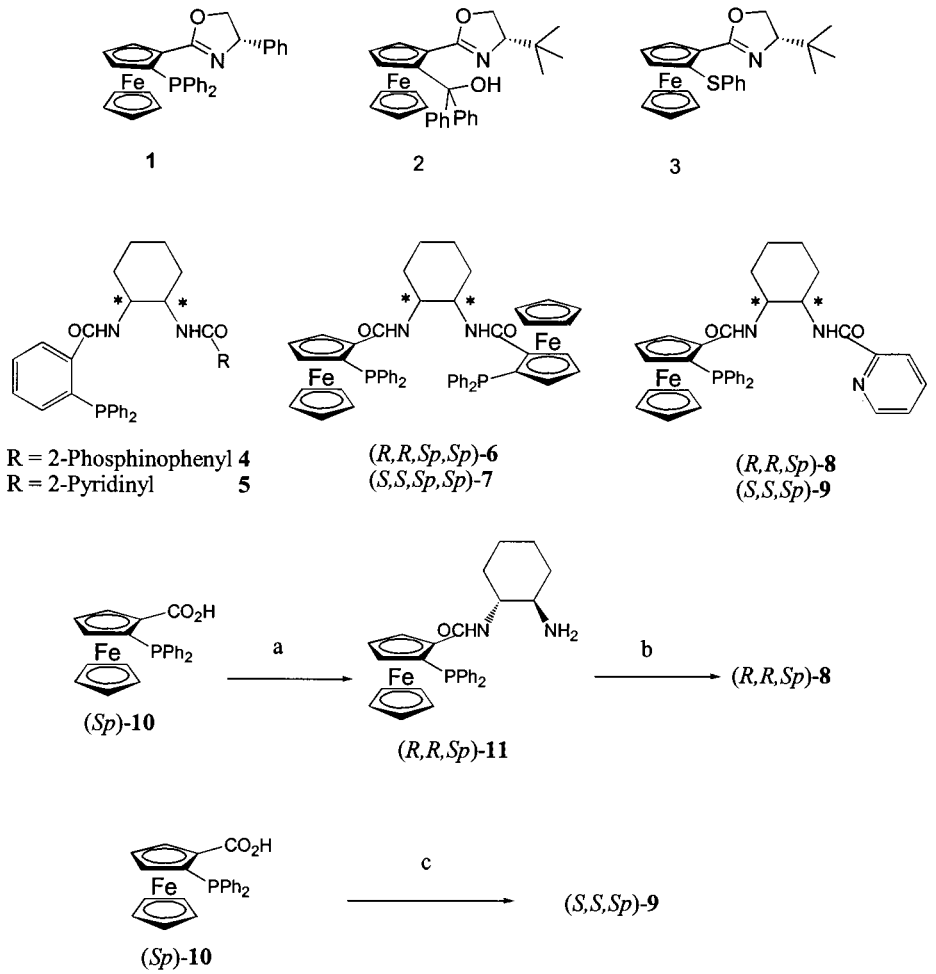
efficiency of asymmetric induction [10,11]. Ligand **5** was also found to be effective in palladium-catalyzed alkylation recently [12]. It was applied into enantioselective cyclization to form 9-azabicyclo[4,2,1] nonane skeleton. The later was the key intermediate for synthesis of (−)-anatoxin-a [12]. The former success encouraged our further efforts to introduce the planar chiral ferrocene moiety into this ligand. In this paper, we report the synthesis of ferrocene modified *P*,*N*-ligands (*R*,*R*,*Sp*)-**8** and (*S*,*S*,*Sp*)-**9** and their applications as chiral ligands in palladium-catalyzed asymmetric allylic substitutions.

2. Results and discussion

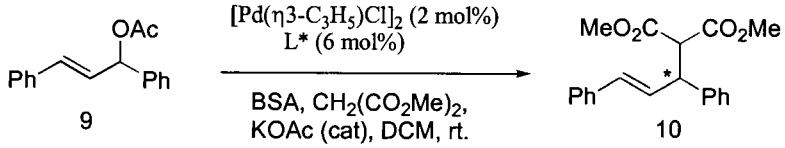
The synthesis of ligands **8** and **9** was straightforward and is shown in Scheme 1. (*Sp*)-2-Phosphinoferrocenyl carboxylic acid **10** is a key intermediate, which was synthesized from phosphinoferrocenyl oxazoline easily as reported previously [9a]. Condensation of (*Sp*)-**10** and (*R*,*R*)-cyclohexanediamine in the presence of DCC afforded (*R*,*R*,*Sp*)-**11** in moderate yield. Treatment of (*R*,*R*,*Sp*)-**11** with DCC and 2-Pyridine carboxylic acid gave rise to the desired chiral ligand (*R*,*R*,*Sp*)-**8** in high yield. Following the same methods, (*S*,*S*,*Sp*)-**9** was synthesized from (*S*,*S*)-cyclohexanediamine in moderate yield.

To examine the catalytic efficiency of **8** and **9** as chiral ligands in palladium-catalyzed allylic substitution, the usual model reaction, reaction of 1,3-diphenylprop-2-enyl acetate with the nucleophile derived from dimethylmalonate was chosen (Scheme 2) and the results are summarized in Table 1.

From the results listed in Table 1, we found that the reaction ran smoothly with ligand (*R*,*R*,*Sp*)-**8** in THF or CH_2Cl_2 to give the product **13** in high yield and moderate enantioselectivity (entries 1 and 2 in Table 1). The enantioselectivity was raised to 85% ee when Cs_2CO_3 was used as the base in CH_2Cl_2 (entry 3 in Table 1). Change of solvent from CH_2Cl_2 to CH_3CN or toluene resulted in the decrease of both yield and enantioselectivity (entries 4 and 5 in Table 1). It is interesting that change of configuration of central chirality from (*R*,*R*) in ligand **8** to (*S*,*S*) in **9** does not invert the configuration



Scheme 1. Reagent and conditions: (a) (*R*,*R*)-cyclohexanediamine, DCC, DMAP, DCM, 45%; (b) 2-pyridinyl carboxylic acid, DCC, DMAP, DCM, 84%; (c) (*R*,*R*)-cyclohexanediamine, DCC, DMAP, DCM and procedure b, 35% (two steps).



Scheme 2.

of product but decreases the enantioselectivity (entries 3 and 6). These results demonstrate that the planar chirality is responsible mainly for dominating both the configuration and enantioselectivity of the product. It is also indicated that (*R*,*R*,*Sp*)-**8** possessed matched chiralities.

In order to reveal the efficiency of the ligands and also the role of the planar chirality further, asymmetric allylic amination reaction was carried out by using $BnNH_2$ as nucleophile (Scheme 3). The results were listed in Table 2. Both ligand **8** and **9** gave moderate yield and enantioselectivity even the reaction was performed at 40 °C. Ligand **8** gave better yield and enantioselectivity still because the presence of matched chiralities.

Although fair enantioselectivities can be achieved with (*R*,*R*,*Sp*)-**8** in palladium-catalyzed alkylation, there is no significant increase on enantioselectivity compared with phenyl-derived ligand **5** (82% yield and 86% ee). We believe that better results may well be achieved in other type of asymmetric syntheses.

3. Conclusions

Novel ferrocene modified *P*,*N*-ligands (*R*,*R*,*Sp*)-**8** and (*S*,*S*,*Sp*)-**9** were synthesized, and their catalytic efficiency for palladium-catalyzed allylic alkylation and amination of *rac*-1,3-diphenyl-2-propenyl acetate were examined. In both reactions, (*R*,*R*,*Sp*)-**8** was found to be the better one of the two, perhaps because it contains matched chiralities. Moderate to good enantioselectivity was achieved with this ligand in palladium catalyzed allylic amination and alkylation, respectively. Unfortunately, no significant increase of the enantioselectivity or activity was observed with two ferrocenyl-derived ligands than that of the phenyl-derived ligand. Further study with these ligands in other metal-catalyzed asymmetric reactions is in progress.

4. Experimental

4.1. General methods

All reactions were performed under an atmosphere of either argon or nitrogen using oven-dried glassware. Solvents were treated prior to use according to the standard method. The commercially available reagents were used as received without further purification. Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AMX-400 (400 MHz) spectrometer in $CDCl_3$ at room temperature (r.t.). ^{31}P-NMR spectra were recorded on a Bruker AMX-400 (162 MHz) spectrometer and the chemical shifts were referenced to external 85% H_3PO_4. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard. Optical rotations were measured using a Perkin–Elmer 241 MC polarimeter with a thermally jacketed 10 cm cell at 25 °C (concentration *c* given as g 100 ml^{-1}). IR spectra were measured in cm^{-1}, using a Shimadzu IR-440 infrared spectrophotometer. Mass spectra and high-resolution mass spectra were taken using HP5989A and Finnigan MAT mass spectrometers, respectively. Elemental analyses were performed on a Foss-Heraeus Vario EL instrument. Ee values were determined by chiral HPLC on Chiralcel OD or OJ column.

4.2. (*R*,*R*,*Sp*)-*N*-[2-(Diphenylphosphino)ferrocenylcarbonyl]-diaminocyclohexane (**11**)

To a solution of (*Sp*)-2-phosphinoferrocenyl carboxylic acid (**10**) (414 mg, 1 mmol), (*R*,*R*)-cyclohexanediamine (23 mg, 2 mmol) and DMAP (5.5 mg, 0.05 mmol) in dry dichloromethane (5 ml) were added DCC (226 mg, 1 mmol) at r.t. After the completion of the material, the reaction mixture was diluted with 15 ml

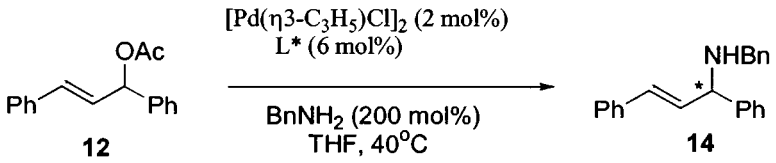
Table 1
Asymmetric palladium-catalyzed allylic alkylation with *rac*-1,3-diphenyl-2-propenyl acetate and dimethylmalonate [a]

Entry	Ligand	Solvent	Base	Yield (%) [b]	ee (%) [c]
1	**8**	THF	NaH	95	72 (*R*)
2	**8**	CH_2Cl_2	BSA	98	74 (*R*)
3	**8**	CH_2Cl_2	Cs_2CO_3	84	85 (*R*)
4	**8**	CH_3CN	Cs_2CO_3	53	79 (*R*)
5	**8**	Toluene	Cs_2CO_3	23	80 (*R*)
6	**9**	CH_2Cl_2	Cs_2CO_3	86	69 (*R*)

[a] Molecular ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/**13**/$CH_2(CO_2Me)_2$/Base = 2/6/100/300/300.

[b] Isolated yield based on 1,3-diphenyl-2-propenyl acetate.

[c] Determined by HPLC (chiracel OD column) and the absolute configuration of product was assigned through comparison of the sign of specific rotations with the literature data [13].



Scheme 3.

dichloromethane and quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was extracted twice with dichloromethane. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to give the crude product, which was subsequently purified by column chromatography (EtOAc:Et_3N = 1:1) to give the main compound **11** (230 mg, 45%) as an orange solid: ^{1}H-NMR δ 7.42–7.55 (m, 5H), 7.18–7.19 (m, 6H), 5.18 (t, 1H, $J = 1.2$ Hz), 4.45 (t, 1H, $J = 2.5$ Hz), 4.15(s, 5H), 3.71 (m, 1H), 3.55–3.62 (m, 1H), 2.28 (td, 1H, $J_1 = 10.8$ Hz; $J_2 = 4.0$ Hz), 2.13–2.16 (m, 1H), 1.88–1.92 (m, 1H), 1.74–1.77 (m, 2H), 1.01–1.45 (m, 6H); ^{31}P-NMR δ –19.92; MS (EI) m/z (rel intensity) 510 ([M^+], 9), 445 (100), 411 (32), 346 (8), 309 (13), 201 (9), 121 (5); IR (KBr, cm^{-1}) 3297 (m), 2926 (m), 1737 (w), 1634 (s), 1434 (m), 1262 (m), 818 (s); $[\alpha]_D^{20} = -223°$ (c 0.55, $CHCl_3$); m.p. 70–73 °C; HRMS Calc. for $C_{29}H_{31}FeN_2OP$: 510.15530. Found: 510.15693.

4.3. (R,R,Sp)-N-[2-(Diphenylphosphino)-ferrocenylcarbonyl]-N-[2-pyridinyl carbonyl]-diamino cyclohexane (**8**)

To a solution of (*R*,*R*,*Sp*)-**11** (204 mg, 0.4 mmol), 2-pyridine carboxylic acid (98 mg, 0.8 mmol) and DMAP (2.2 mg, 0.02 mmol) in dry dichloromethane (5 ml) were added DCC (181 mg, 0.8 mmol) at r.t. After the completion of the material, the reaction mixture was diluted with 10 ml dichloromethane and quenched with saturated aqueous $NaHCO_3$ solution. The organic layer was extracted twice with dichloromethane. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to give the crude product, which was subsequently purified by column chromatography (EtOAc:Et_3N = 1:1) to give the main compound **8** (207 mg, 84%) as an orange solid: ^{1}H-NMR δ 8.49–8.51 (m, 1H), 8.18 (d, 1H, $J = 7.2$ Hz), 8.10 (d, 1H, $J = 8.7$ Hz), 7.77 (td, 1H, $J_1 = 8.7$ Hz; $J_2 = 1.6$ Hz), 7.46 (td, 2H, $J_1 = 7.6$ Hz; $J_2 = 1.6$ Hz), 7.31–7.37 (m, 4H), 7.01–7.07 (m, 6H), 4.89 (m, 1H), 4.33 (m, 1H), 3.92 (s, 5H), 3.68 (m, 1H), 2.15–2.24 (m, 2H), 1.24–1.79 (m, 8H); ^{31}P-NMR δ –18.88; MS (EI) m/z (rel intensity) 615 ([M^+], 3), 550 (100), 412 (8); IR (KBr, cm^{-1}) 3336 (m), 3261 (w), 3067 (w), 2929 (m), 1659 (s), 1639 (s), 1531 (s), 1434 (m); $[\alpha]_D^{20} = -112°$ (c 0.38, $CHCl_3$); m.p. 180–185 °C (dec); Anal Calc. for $C_{35}H_{34}FeN_3O_2P$: C, 68.30; H, 5.57; N, 6.82. Found: C, 68.11; H, 5.68; N, 6.56%.

4.4. (S,S,Sp)-N-[2-(Diphenylphosphino) ferrocenylcarbonyl]-N-[2-pyridinylcarbonyl]-diaminocyclohexane (**9**)

A similar procedure as for (*R*,*R*,*Sp*)-**8** but from (*S*,*S*)-cyclohexanediamine gave (*S*,*S*,*Sp*)-**9** in 35% yield (two steps) as an orange solid: ^{1}H-NMR δ 8.59–8.61 (m, 1H), 8.40 (d, 1H, $J = 8.3$ Hz), 8.23 (d, 1H, $J = 7.8$ Hz), 7.81 (td, 1H, $J_1 = 7.7$ Hz; $J_2 = 1.7$ Hz), 7.51 (td, 2H, $J_1 = 7.8$ Hz; $J_2 = 1.6$ Hz), 7.37–7.47 (m, 5H), 7.12–7.22 (m, 5H), 5.02 (m, 1H), 4.35 (m, 1H), 3.99–4.08 (m, 1H), 3.92(s, 5H), 3.70 (m, 1H), 2.20–2.22 (m, 1H), 1.90–1.93 (m, 1H), 1.67–1.79 (m, 2H), 1.17–1.44 (m, 5H); ^{31}P-NMR δ –20.02; MS (EI) m/z (rel intensity) 615 ([M^+], 3), 550 (100), 412 (8); IR (KBr, cm^{-1}) 3302 (m), 3053 (w), 2930 (m), 1645 (s), 1589 (s), 1523 (s), 1434 (m); $[\alpha]_D^{20} = -108°$ (c 0.45, $CHCl_3$); m.p. 94–96 °C; Anal Calc. for $C_{35}H_{34}FeN_3O_2P$: C, 68.30; H, 5.57; N, 6.82. Found: C, 68.10; H, 5.62; N, 6.62%.

4.5. General procedure for the palladium-catalyzed allylic alkylation of rac-1,3-diphenyl-2-propenyl acetate

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3.7 mg, 0.01 mmol) and the ligand (18.5 mg, 0.03 mmol) were dissolved in dry CH_2Cl_2 (2 ml), and then stirred for 30 min at r.t. under an atmosphere of argon. To this solution *rac*-1,3-diphenyl-2-propenyl acetate (126 mg, 0.5 mmol), dimethylmalonate (0.17 ml, 1.5 mmol), and proper base (1.5 mmol) were added successively. The reaction mixture was stirred at r.t. and monitored by TLC. After completion, the reaction mixture was diluted with CH_2Cl_2 (20 ml) and washed twice with ice-cold saturated aqueous ammonium chloride. The organic phase was

Table 2
Asymmetric palladium-catalyzed allylic amination with *rac*-1,3-diphenyl-2-propenyl acetate and benzylamine [a]

Entry	Ligand	Yield (%) [b]	ee (%) [c]
1	**8**	52	79 (*S*)
2	**9**	37	39 (*S*)

[a] Reaction was performed in THF at 40 °C. Molecular ratio: $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$/ligand/**13**/$BnNH_2$ = 2/6/100/200.

[b] Isolated yield based on 1,3-diphenyl-2-propenyl acetate.

[c] Determined by HPLC (chiracel OJ column) and the absolute configuration of product was assigned through comparison of the sign of specific rotations with the literature data [14].

dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc:petroleum ether = 1:15) to give the pure product. The enantiomeric purities were determined by HPLC analysis (Chiralcel OD column, hexane:isopropanol (80:20); flow rate = 0.7 ml min^{-1}; $t_R = 18.7$ min, $t_S = 20.4$ min).

4.6. General procedure for the palladium-catalyzed allylic amination of rac-1,3-diphenyl-2-propenyl acetate

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3.7 mg, 0.01 mmol) and the ligand (18.5 mg, 0.03 mmol) were dissolved in dry THF (2 ml), and then stirred for 30 min at r.t. under an atmosphere of argon. To this solution *rac*-1,3-diphenyl-2-propenyl acetate (126 mg, 0.5 mmol), $BnNH_2$ (0.11 ml, 1.0 mmol) were successively added. The reaction mixture was stirred at 40 °C and monitored by TLC. After completion, the reaction mixture was diluted with Et_2O (20 ml) and washed twice with ice-cold saturated aqueous ammonium chloride. The organic phase was dried over anhydrous $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by preparative TLC (EtOAc:petroleum ether = 1:10) to give the pure product. The enantiomeric purities were determined by HPLC analysis (Chiralcel OJ column, hexane:isopropanol (87:13); flow rate = 0.6 ml min^{-1}; $t_S = 20.3$ min, $t_R = 24.3$ min).

Acknowledgements

This research was financially supported by the Major Basic Research Development Program (grant no. G2000077506), National Natural Science Foundation of China, National Outstanding Youth Fund, Chinese Academy of Sciences, and Shanghai Committee of Science and Technology.

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