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Chiral aminophosphine phosphinite–palladium catalysts in asymmetric allylic alkylations

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Abstract

Palladium complexes of chiral aminophosphine phosphinites were investigated for the asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate with dimethyl malonate. The chirality of the carbon bonded to O-PPh_2 in the ligands was found to be very important to the enantioselectivity of the catalysts. Introduction of this stereogenic center has led to significantly improved enantioselectivities.

1. Introduction

The enantioselective palladium catalyzed nucleophilic substitution of allylic acetates with carbon-based soft nucleophiles is among the most important methods for carbon–carbon bond formation in asymmetric catalysis. A large number of chiral ligands containing P,P-, P,N- and N,N-chelating atoms have shown high enantioselectivity in this process.[1] Chiral amino alcohols can be easily prepared from natural or unnatural amino acids, and are very inexpensive chirality sources for the design of chiral ligands. The chiral ligands with O-PPh_2 or N-PPh_2 groups, such as diaminophosphines, diphosphinites and aminophosphine-phosphinites, have been synthesized and studied.[2] However, few chiral aminophosphine-phosphinites exhibit excellent enantioselectivity for asymmetric allylic alkylations. In 1991, Cesarotti studied the nucleophilic addition to the allyl complex of palladium containing *N*-diphenylphosphino-2-(diphenylphosphinoxymethyl)pyrroline ligand **1** and found very low enantioselectivities (20–30% e.e.). A detailed mechanistic study on the basis of X-ray and NMR data suggested that the soft nucleophile should attack the allyl terminus *trans* to N-PPh_2.[3] This indicates that site C-3 in complex **1** is

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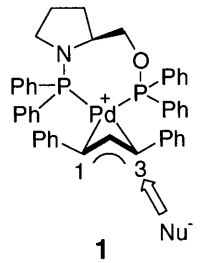
more electrophilic than C-1. According to this transition state, we propose that the low enantioselectivity might derive from the long distance between the stereogenic center and the reaction site in **1**. The distal relationship between the incoming nucleophile and the chiral environment of the Pd complexes might make the chirality transfer rather inefficient.[4] If the carbon bonded to the O-PPh_2 group is also stereogenic as shown in **2**, it may provide more stereocontrol for the reaction and lead to better enantioselectivity. In our previous work, we have found that ligand **2a** shows excellent enantioselective induction in asymmetric hydrogenation of dehydroamino acid derivatives.[5a,b] Herein, our investigation on using this new type of chiral aminophosphine-phosphinite ligand in the palladium catalyzed allylic alkylation will be described.



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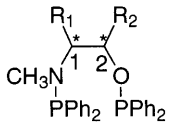

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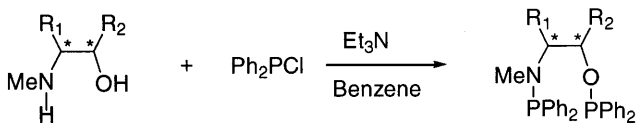
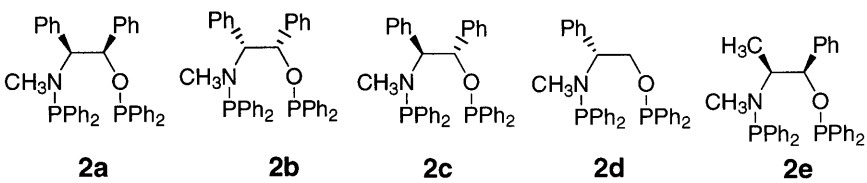
2. Results and discussion

2.1. Synthesis of the chiral ligands

Ligands **2a**–**e** were synthesized from the reaction of chlorodiphenylphosphine (Ph_2PCl) with the corresponding optically active aminoethanols[5] (Scheme 1).



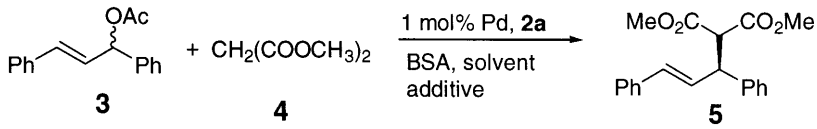


2a **2b** **2c** **2d** **2e**

Scheme 1. Synthesis of chiral ligands

2.2. Asymmetric allylic alkylation of rac-1,3-diphenyl-2-propenyl acetate with dimethyl malonate catalyzed by complexes of palladium and *2a*

The reaction of *rac*-1,3-diphenyl-2-propenyl acetate with dimethyl malonate was carried out with bis-trimethylsilyl acetamide (BSA) as base at room temperature for 24 h in the presence of 1 mol% palladium complex of **2a** (Scheme 2). A variety of reaction conditions have been investigated and the results are summarized in Table 1.



Scheme 2. The enantioselective allylic alkylation of **3** with dimethyl malonate

Table 1
The enantioselective allylic alkylation of **3** with dimethyl malonate

Entry	Palladium	Pd:**2a**	Solvent	Additive	Yield (%)[a]	E.e.%[b] (config.)[c]
1	$[Pd(allyl)Cl]_2$	1:1.25	Toluene	LiOAc	93	56 (*S*)
2	$Pd(OAc)_2$	1:1.25	Toluene	LiOAc	67	56 (*S*)
3	$Pd_2(dba)_3{\cdot}CHCl_3$	1:1.25	Toluene	LiOAc	86	46 (*S*)
4	$Pd(dba)_2$	1:1.25	Toluene	LiOAc	95	58 (*S*)
5	$Pd(dba)_2$	1:1.25	THF	LiOAc	96	52 (*S*)
6	$Pd(dba)_2$	1:1.25	CH_2Cl_2	LiOAc	98	52 (*S*)
7	$Pd(dba)_2$	1:1.25	DCE	LiOAc	96	51 (*S*)
8	$Pd(dba)_2$	1:1.25	Hexane	LiOAc	97	24 (*S*)
9	$Pd(dba)_2$	1:1	Toluene	LiOAc	84	45 (*S*)
10	$Pd(dba)_2$	1:2	Toluene	LiOAc	96	60 (*S*)
11	$Pd(dba)_2$	1:1.25	Toluene	KOAc	96	43 (*S*)
12	$Pd(dba)_2$	1:1.25	Toluene	Bu_4NBr	79	42 (*S*)

[a] Isolated yield.
[b] Measured by HPLC (Chiralcel OD, *n*-hexane:2-propanol = 99:1).
[c] The absolute configuration was determined by comparing the specific rotation with the literature value.[6]

In this reaction, the palladium sources significantly affected the reactivity. The use of $[Pd(allyl)Cl]_2$, $Pd_2(dba)_3{\cdot}CHCl_3$ and $Pd(dba)_2$ gave the product in high yield. The catalyst made from $Pd(dba)_2$ showed the best reactivity and enantioselectivity (entry 4). Toluene is the best solvent for this reaction. Increasing the ratio of **2a** to Pd from 1:1 to 1:2 (entries 9 and 10) improved the e.e. from 45 to 60%. Changing the additive from LiOAc to other salts caused a reduction in enantioselectivity (entries 4, 11 and 12).

*2.3. The relationship between structures of ligands **2a–e** and enantioselectivities*

In the presence of 1 mol% of $[Pd(allyl)Cl]_2$, ligands **2b–e** were also examined for the reaction of **3** with **4**, and the results are shown in Table 2. All **2**–palladium complexes exhibited high catalytic activity and gave 100% conversion for the reactions. As we expected, the stereogenic carbon bonded to the O-PPh_2 in these ligands is very important for the improved enantioselectivity from **2d** to **2a**. Without the second stereogenic center, ligand **2d** gave very low enantioselectivity (11% e.e.) (entry 4). The configuration of the product is also controlled by the carbon bonded to O-PPh_2. When the configuration of this carbon is inverted, but that of the carbon bonded to N-PPh_2 maintained, as shown from **2a** to **2c**, the configuration of the product **5** is inverted from *S* to *R* (entries 1 and 3). When a methyl group replaced the phenyl group bonded to C-1 (ligand **2e**), the enantiomeric excess was reduced to 42% (entry 5).

Table 2
Enantioselective allylic alkylation catalyzed by the complexes of $[Pd(allyl)Cl]_2$ and **2a–e**

Entry	Ligand	Additive	Conversion (%)[a]	E.e.%[b] (config.)[c]
1	**2a**	LiOAc	100	56 (*S*)
2	**2b**	LiOAc	100	56 (*R*)
3	**2c**	LiOAc	100	52 (*R*)
4	**2d**	LiOAc	100	11 (*S*)
5	**2e**	LiOAc	100	42 (*S*)

[a] Measured by HPLC.
[b] Measured by HPLC (Chiralcel OD, *n*-hexane:isopropanol = 99:1).
[c] The absolute configuration was determined by comparing the optical rotation with the literature value.[6]

3. Conclusion

In summary, we have demonstrated that the configuration of the carbon bonded to O-PPh_2 in the aminophosphine-phosphinite ligands plays a very important role for the palladium catalyzed enantioselective allylic alkylation. Introduction of this stereogenic center has led to significantly improved enantioselectivities. This work indicates that further enhancement in enantioselectivity could be achieved by further modification of the chiral environment at both of the stereogenic centers in these ligands and particularly at the phosphinite site.

4. Experimental

4.1. General data

THF and toluene were distilled from sodium/benzophenone under nitrogen. Dichloromethane, hexane and 1,2-dichloroethane were distilled from CaH_2. The palladium complexes were gifts from Professor Yoshinori Yamamoto at Tohuko University in Japan.

Melting points were measured on a digital melting point apparatus and were uncorrected. IR spectra were obtained on a Nicolet 200SXV spectrometer. ^{1}H NMR spectra were recorded on a Bruker AC-E 300 and Bruker AC-E 200 instruments. The e.e. and conversion were determined by HPLC on a Beckman-110A chromatograph with a Beckman 165 variable wavelength detector. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The Chiralcel OD column was purchased from Daicel Chemical Industries, Ltd.

4.1.1. Preparation of (1R,2S)-*2a*

To a Schlenk flask charged with (1*R*,2*S*)-1,2-diphenyl-2-(*N*-methyl)aminoethanol (100 mg, 0.44 mmol) and benzene (5 mL) at 0°C was added Et_3N (0.26 mL, 1.80 mmol) and Ph_2PCl (0.24 mL, 1.45 mmol). The reaction mixture was warmed up to room temperature and stirred for 24 h. After flash chromatography (eluent: benzene), the solvent was removed in vacuo to yield product as a white needle crystal (140 mg, yield: 53%). Mp 91–93°C; $[\alpha]_D^{20} = -38.1$ ($c = 0.278$, C_6H_6); IR (KBr): 3400, 3040, 2910, 1430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.21 (d, 3H, $J_{P-H} = 2.5$ Hz, CH_3), 4.94 (dd, 1H, $J_{H-H} = 10.4$ Hz, $J_{P-H} = 14.2$ Hz, NCH), 5.57 (dd, 1H, $J_{H-H} = 10.1$ Hz, $J_{P-H} = 8.3$ Hz, OCH), 6.53–7.52 (m, 30H, Ar–H). ^{13}C NMR (50 MHz, CD_2Cl_2)

δ 33.6, 75.13, 83.5, 128.0, 128.4, 128.6, 128.7, 128.8, 129.1, 129.2, 129.4, 129.5, 129.6, 130.8, 131.0, 131.2, 132.4, 132.6, 132.8, 139.3, 139.4, 140.5, 141.3, 142.3, 142.4, 142.9, 143.1; ^{31}P NMR (MeOH) δ 64.8 (s, $P_{(N)}$), 111.8 (s, $P_{(O)}$).

*4.1.2. Preparation of (1*S*,2*R*)-**2b***

Yield: 54%; mp 94–96°C; $[\alpha]_D^{20}=+37.8$ ($c=0.218$, C_6H_6); IR (KBr): 3410, 3050, 2920, 1430 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.21 (d, 3H, $J_{P-H}=2.4$ Hz, CH_3), 4.94 (dd, 1H, $J_{H-H}=10.0$ Hz, $J_{P-H}=14.4$ Hz, NCH), 5.57 (dd, 1H, $J_{H-H}=10.4$ Hz, $J_{P-H}=8.4$ Hz, OCH), 6.53–7.74 (m, 30H, Ar–H); ^{31}P NMR ($CDCl_3$) δ 65.9 (s, $P_{(N)}$), 113.3 (s, $P_{(O)}$).

*4.1.3. Preparation of (1*S*,2*S*)-**2c***

Yield: 66%; mp 148–150°C; $[\alpha]_D^{20}=-46.5$ ($c=0.172$, C_6H_6); IR (KBr): 3450, 3060, 2960, 1435 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.42 (d, 3H, $J_{P-H}=2.4$ Hz, CH_3), 4.86 (dd, 1H, $J_{H-H}=10.0$ Hz, $J_{P-H}=10.4$ Hz, NCH), 5.39 (dd, 1H, $J_{H-H}=9.2$ Hz, $J_{P-H}=6.8$ Hz, OCH), 6.90–7.78 (m, 30H, Ar–H); ^{31}P NMR ($CDCl_3$) δ 63.7 (s, $P_{(N)}$), 106.3 (s, $P_{(O)}$).

4.1.4. General procedure for asymmetric allylic alkylation of rac-*1,3-diphenyl-2-propenyl acetate with dimethyl malonate*

To a Schlenk flask charged with $Pd(dba)_2$ (5.7 mg, 0.01 mmol) and **2a** (7.2 mg, 0.012 mmol) was added toluene (1 mL) under nitrogen. The resulting solution was stirred at room temperature for 1 h, and then was added a solution of **3** (252 mg, 1 mmol) in toluene (2 mL), BSA (0.74 mL, 3 mmol), **4** (0.34 mL, 3 mmol) and LiOAc (2.8 mg, 0.04 mmol) sequentially. The reaction mixture was degassed with three freeze–thaw cycles, and finally warmed up to room temperature for 20 h. The reaction was quenched by the addition of water (5 mL) and EtOAc (10 mL). The aqueous layer was extracted with EtOAc. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel (eluent: EtOAc:hexane=1:9) to give **5** (308 mg, 95%) as a colorless oil. Enantiomeric excess (*S*-major): 56% e.e., was determined on HPLC (Chiralcel OD column, eluent: hexane:2-propanol=99:1, flow rate: 0.5 mL min^{-1}, retention time: $t_R=26.24$ min, $t_S=28.67$ min).

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