HETEROCYCLES, Vol. 61, No. 1, 2003, pp. 9 - 13
Received, 26th September, 2002, Accepted, 11th November, 2002, Published online, 15th November, 2002

PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION USING CHIRAL PROLINOL-DERIVED AMINOPHOSPHINE LIGANDS

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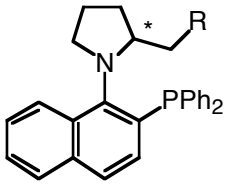
Abstract – Palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (4) with a dimethyl malonate-BSA-LiOAc system has been successfully carried out in the presence of a new chiral prolinol-derived aminophosphine ligand (3e) in good yield with good enantioselectivity (up to 96% ee).

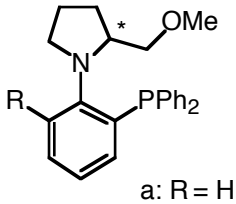
INTRODUCTION

Palladium-catalyzed allylic alkylation is a widely used process in organic synthesis,[1] and the development of efficient enantioselective catalysis for this reaction is awaited.[2] Chiral 2-(phosphinoaryl)oxazoline can induce high enantiomeric excesses in this reaction.[3] Following this pioneering study, aminophosphines have been used as ligands for this reaction. Especially pyrrolidinyl-containing aminophosphines such as **1**[4] and **2**[4c, 5] were found to be efficient chiral sources.[6, 7]



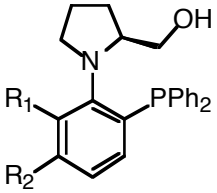
1

a: R = H
b: R = OMe
c: R = OCH_2CH_2OMe
d: R = $O(CH_2CH_2O)_2Me$
e: R = OBn
f: R = Pyrrolidinyl



2

a: R = H
b: R = OMe



3

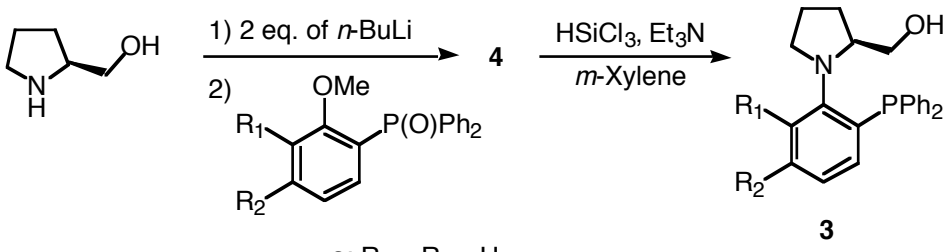
a: $R_1 = R_2 = H$
b: R_1 - R_2 = -CH=CH-CH=CH-
c: R_1 = Me, R_2 = H
d: R_1 = Et, R_2 = H
e: R_1 = OMe, R_2 = H
f: R_1 = Ph, R_2 = H

Here, we report palladium-catalyzed asymmetric allylic alkylation using chiral aminophosphine ligands (**3**) which have a hydroxymethyl group on the pyrrolidine backbone.

RESULTS AND DISCUSSION

The chiral aminophosphine ligands (**3**) were easily prepared from (*S*)-prolinol and corresponding phosphine oxides in 2 steps (Scheme 1). A nucleophilic aromatic substitution (SNAr) reaction[8] of a phosphine oxide compound such as diphenyl(2-methoxyphenyl)phosphine oxide with bislithiated (*S*)-

prolinol gave the corresponding aminophosphine oxide (**4a**). This aminophosphine oxide (**4a**) was converted into the desired chiral aminophosphine ligand (**3a**) using trichlorosilane-triethylamine in good yield. The other ligands (**3b-f**) were prepared in the same manner (Table 1).



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b: R_1 - R_2 = -CH=CH-CH=CH-
c: R_1 = Me, R_2 = H
d: R_1 = Et, R_2 = H
e: R_1 = OMe, R_2 = H
f: R_1 = Ph, R_2 = H

Scheme 1

Table1. Preparation of Aminophosphine Ligands (**3**).

Entry	**4**, Yield / %[a]	**3**, Yield / %[a]
1	**4a**, 61	**3a**, 90
2	**4b**, 75	**3b**, 65[b]
3	**4c**, 39	**3c**, 91
4	**4d**, 36	**3d**, 78
5	**4e**, 76	**3e**, 83
6	**4f**, 63	**3f**, 75

[a] Isolated yields.
[b] Ref 4c.

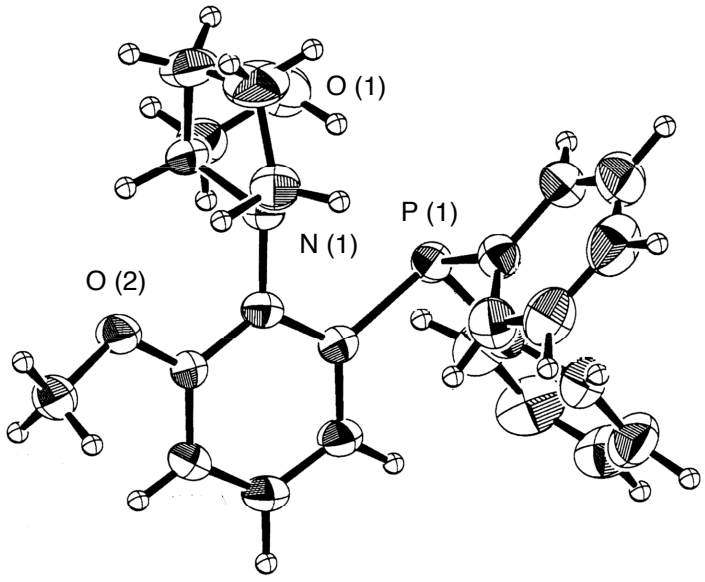
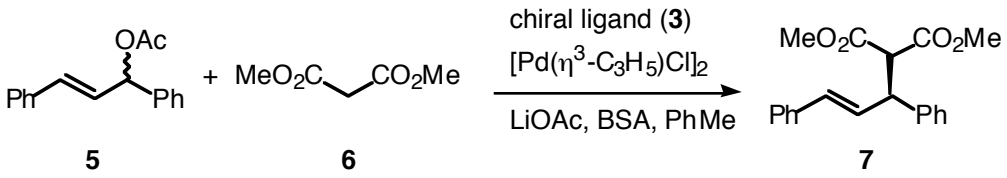


Figure 1. X-Ray crystal structure of **3e**.

The X-Ray crystal structure of (*S*)-**3e**[9] in Figure 1 shows that more stable structure is *a*S-type conformation about the C(Ar)–N bond. This trend appeared in the case of 2-(methoxymethyl)pyrrolidine derived ligand (**2b**).

These chiral aminophosphine ligands (**3**) were applied to the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**5**) with dimethyl malonate (**6**). This reaction was carried out in the presence of 2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4 mol% of a chiral ligand, and a mixture of *N,O*-bis(trimethylsilyl) acetamide (BSA) and 2 mol% of LiOAc in toluene (Scheme 2, Table 2).[10, 11]



5 **6** **7**

Scheme 2

Table 2. Asymmetric Allylic Alkylation Catalyzed by Palladium Complexes with Ligands (**3**).[a]

Entry	Ligand	Temp. / °C	Yield / %[b]	Ee / %[c]
1	**3a**	rt	98	58
2	**3b**	rt	86	89
3	**3c**	rt	94	92
4	**3d**	rt	89	87
5	**3e**	rt	91	93
6	**3f**	rt	93	83
7[d]	**3e**	0	94	94
8[e]	**3e**	-20	41	96
9[f]	(*R*)-**2a**	rt	97	40 (*R*)
10[f]	(*R*)-**1b**	rt	94	76 (*R*)

[a] The reaction was carried out at rt for 24 h.
[b] Isolated yields.
[c] Determing by HPLC analysis using a chiral column (Chiralcel OD-H).
[d] This reaction was carried out for 3 d.
[e] This reaction was carried out for 7 d.
[f] Ref 4c

Using ligand (**3a**), the product (**7**) was obtained in good chemical yield, but the enantiomeric excess was moderate (Entry 1). The ligand (**3a**) gave higher enantioselectivity than the ligand (**2a**) (Entry 1 vs. Entry 9). This manner appeared in the case of a naphthyl backbone type ligand such as **3b** versus **1b** (Entry 2 vs. Entry 10). When the reaction was carried out using the ligand (**3e**), the product (**7**) was obtained in the best enantioselectivity (93% ee) in these ligands (**3**) (Entry 5). In order to improve the

enantioselectivity, we further examined the effect of reaction temperature using the ligand (**3e**). The reaction at 0 °C further improved the enantioselectivity to 94% ee (Entry 7). Although enantioselectivity was improved to 96% ee by further depressing the temperature (-20 °C), the reaction rate became slow (Entry 8). The absolute configuration of the product (**7**) in these reactions was proved to be *S* as determined from the sign of the optical rotation.[12]

We showed the palladium-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**5**) with dimethyl malonate (**6**) using chiral aminophosphine ligands (**3**) with high enantiomeric excess.

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9. Ligand (**3e**): mp 119-120°C; $[\alpha]_D^{25}$ = +68.1° (*c* 1.04, $CHCl_3$): ^{1}H NMR ($CDCl_3$) δ: 1.52-1.69 (m, 2H), 1.89-1.96 (m, 3H), 2.81 (q, *J* = 8.1 Hz, 1H), 3.39 (t, *J* = 10.5 Hz, 1H), 3.59-3.68 (m, 2H), 3.81 (s, 3H), 4.20-4.30 (m, 1H), 6.40-6.43 (m, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 7.10 (t, *J* = 7.9 Hz, 1H), 7.21-7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ: 25.3, 27.8, 52.8, 55.0, 62.9, 63.7, 112.8, 124.6, 127.1 (d, J_{cp} = 2.1 Hz), 128.3-128.5 (m), 129.0, 133.7, 133.9, 134.4, 134.6, 136.3 (d, J_{cp} = 3.8 Hz), 137.5, 137.6, 140.1, 140.4, 141.9 (d, J_{cp} = 4.1 Hz), 158.2 (d, J_{cp} = 3.8 Hz); ^{31}P NMR ($CDCl_3$) δ: -17.15; FAB-MS m/z (rel intensity): 392 (M^++1, 77); HRMS (FAB-MS) m/z calcd for $C_{24}H_{26}NO_2P$+H 392.1779, found 392.1777; The X-Ray crystal structure analysis indicated the monoclinic space group, $P2_1$, *a* = 9.266(1) Å, *b* = 14.797(2) Å, *c* = 17.491(2) Å, β = 97.6600, *V* = 2376.8(5) Å^3, *Z* = 4, ρ = 1.133 g/cm^3, μ (MoKα)= 1.35 cm^{-1}; *R* = 0.096, *Rw* = 0.081 for 1958 reflections. The structure was solved by the direct method and refined by the method of full-matrix least-squares.

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11. General Procedure for the Palladium-Catalyzed Allylic Alkylation: To mixture of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.01 mmol, 0.004 g), chiral aminophosphine ligand (**3**) (0.02 mmol), and metal acetate (1.0 μmol) in toluene (1 mL) was added BSA (1.5 mmol, 0.37 mL), racemic 1,3-diphenyl-2-propenyl acetate (**5**) (0.5 mmol, 0.126 g), and dimethyl malonate (**6**) (1.5 mmol, 0.17 mL) at room temperature under an argon atmosphere. After being stirred for 24 h, the reaction mixture was diluted with ether and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator and the residue was purified by column chromatography.

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