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Chiral diaminophosphine ligands with stable C(aryl)–N(amine) axial chirality derived from prolinol

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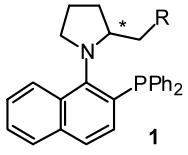
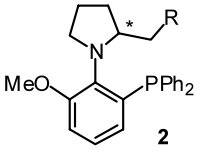
Abstract—New type chiral ligands **3**, which have a chiral carbon center and stable C(aryl)-N(amine) axial chirality, were prepared from chiral prolinol-derived aminophosphine oxide **4**. Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**6**) with a dimethyl malonate–BSA–LiOAc system was successfully carried out in the presence of **3d** resulting in a good yield with good enantioselectivity (up to 95% ee).

Pd-catalyzed allylic alkylation is a process that is widely used in organic synthesis,[1] and the development of efficient enantioselective catalysis for this reaction is awaited.[2] It has been reported that chiral 2-(phosphinoaryl)oxazoline can induce high enantiomeric excesses in this reaction.[3] Following this pioneering study, aminophosphines have been used as ligands, in particular, pyrrolidinyl-containing aminophosphines such as **1**[4] and **2**[5] have been found to be efficient chiral sources.[6] Here, we report the preparation of new type chiral diaminophosphines **3**, which have a chiral carbon center and C(aryl)–N(amine) axial chirality, and discuss their application to Pd-catalyzed asymmetric allylic alkylation. We found that the C(aryl)–N(amine) axial chirality of ligands **3** is an important factor in the reactivity and enantioselectivity of Pd-catalyzed allylic alkylation.



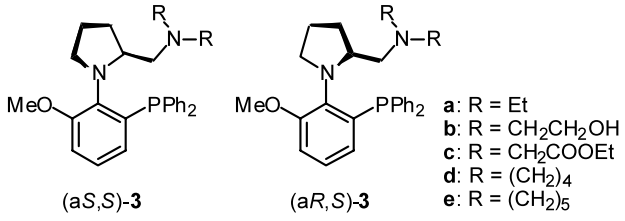
1

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

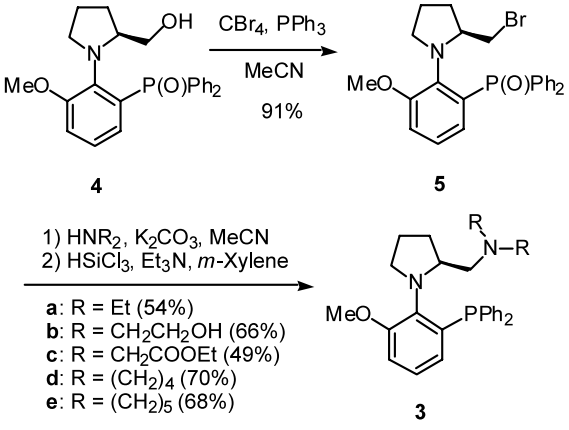
a: R = OMe
b: R = OH



(a*S*,*S*)-**3** (a*R*,*S*)-**3**

a: R = Et
b: R = CH_2CH_2OH
c: R = CH_2COOEt
d: R = $(CH_2)_4$
e: R = $(CH_2)_5$

The chiral diaminophosphine ligands **3** were easily prepared from prolinol-derived aminophosphine oxide **4**[5b] in three steps (Scheme 1). Aminophosphine oxide **4** was converted into the corresponding bromide compound **5** using carbon tetrabromide–triphenylphosphine with a 91% yield. Using various amines such as diethylamine, the amination of bromide compound **5** gave the corresponding diaminophosphine oxide. This diaminophos-



4 **5** **3**

Scheme 1.

Keywords: P,N-ligand; C–N axial chirality; palladium; asymmetric allylic alkylation.

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phine oxide was directly converted into the desired chiral diaminophosphine ligand **3a** using trichlorosilane–triethylamine with a good yield. The other ligands **3b–e** were prepared in the same manner.

The diastereoisomer at chiral carbon center and C(aryl)–N(amine) axial chirality were not observed with diaminophosphine **1f**, its related ligands[4d] and aminophosphine **2**[5]. However, in the NMR spectra of crude reaction mixtures of **3** diastereomeric atropisomers were observed at room temperature. Diaminophosphines **3a**[7] and **3b**[8] could not be separated into atropisomers by chromatography. In the case of **3c**,[9] only the less polar atropisomer (a*S*,*S*)-**3c** was separated. The more polar atropisomer (a*R*,*S*)-**3c** was difficult to separate from the less polar atropisomer (a*S*,*S*)-**3c**. Diaminophosphines **3d**[10] and **3e**[11] were successfully obtained as stable single atropisomers after purification by chromatography. Epimerization did not occur in either atropisomer at room temperature for over nine months. The stereochemistries of **3c–e** were determined on the basis of NOE experiments performed on (a*S*,*S*)-**3d** and (a*R*,*S*)-**3d** (Fig. 1).

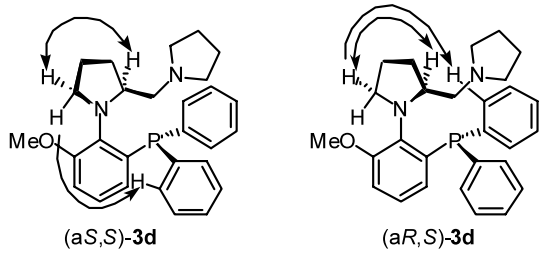
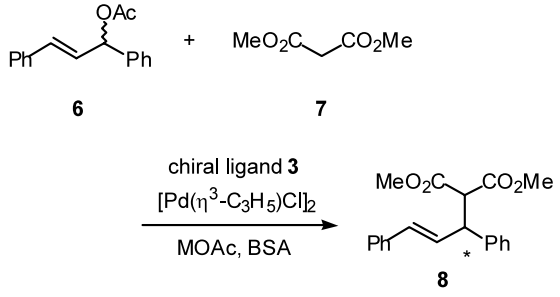


Figure 1. Selected NOE correlations of **3d**.



Scheme 2.

These chiral diaminophosphines **3** were applied to the chiral ligands for the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**6**) with dimethyl malonate (**7**) as a model reaction. This reaction was carried out in the presence of 2 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 4 mol% of **3**, and a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 2 mol% of LiOAc in toluene (Scheme 2, Table 1).[12]

Using ligand (a*S*,*S*)-**3d**, (*S*)-**8** was obtained with a good chemical yield, but the enantiomeric excess was moderate at room temperature in toluene (entry 1). When the reaction was carried out using the diastereomeric atropisomer (a*R*,*S*)-**3d**, the reactivity and enantioselectivity of **8** were decreased and the configuration of **8** was inverted (entry 2). This observation indicates that C(aryl)–N(amine) axial chirality is the more influential factor determining the stereochemical outcome of allylic alkylation than central chirality in pyrrolidine. Next a reaction was carried out using (a*S*,*S*)-**3d** at −10°C (Entry 3). Although the enantioselectivity was improved to 91% ee, the reaction rate became slow.

We tried to change the similar solvent as toluene. When the reaction was carried out in α,α,α-trifluorotoluene at −10°C, reactivity was dramatically increased without

Table 1. Palladium-catalyzed asymmetric allylic alkylation using **3**[a]

Entry	Ligand	M	Solv.	Temp. (°C)	Yield (%)[b]	Ee (%)[c]	Config.[c]
1	(a*S*,*S*)-**3d**	Li	PhMe	Rt	93	82	*S*
2	(a*R*,*S*)-**3d**	Li	PhMe	Rt	65	15	*R*
3	(a*S*,*S*)-**3d**	Li	PhMe	−10	15	91	*S*
4	(a*S*,*S*)-**3d**	Li	$PhCF_3$	−10	95	91	*S*
5	(a*S*,*S*)-**3d**	K	$PhCF_3$	−10	89	86	*S*
6	(*S*)-**3d**	Li	$PhCF_3$	−10	91	91	*S*
7	(a*R*,*S*)-**3d**	Li	$PhCF_3$	−10	NR	–	–
8	(a*S*,*S*)-**3e**	Li	$PhCF_3$	−10	89	90	*S*
9	(a*R*,*S*)-**3e**	Li	$PhCF_3$	−10	NR	–	–
10	(*S*)-**3a**	Li	$PhCF_3$	−10	92	92	*S*
11[d]	(*S*)-**3b**	Li	$PhCF_3$	−10	84	91	*S*
12	(a*S*,*S*)-**3c**	Li	$PhCF_3$	−10	94	85	*S*
13	(a*S*,*S*)-**3d**	Li	DCM	−10	97	90	*S*
14	(a*S*,*S*)-**3d**	Li	THF	−10	97	93	*S*
15	(a*S*,*S*)-**3d**	Li	CPME[e]	−10	96	93	*S*
16	(a*S*,*S*)-**3d**	Li	Ether	−10	99	95	*S*

[a] All reactions were carried out for 24 h.
[b] Isolated yields.
[c] Determined by HPLC analysis using a chiral column (Chiralcel OD-H).
[d] This reaction was carried out for 48 h.
[e] Cyclopentyl methyl ether.

decrease in enantioselectivity (entry 3 versus 4). When the mixture of atropisomer (*S*)-**3d**[13] was used as a ligand instead of (a*S*,*S*)-**3d**, (*S*)-**8** was obtained in good yield without decrease of the enantioselectivity (entry 6). In this condition, we again carried out a reaction using the atropisomeric ligand (a*R*,*S*)-**3d** (entry 7). But the reaction did not occur after 24 h. This was also the case for ligand **3e** (entry 8 versus entry 9). (*S*)-**8** with good enantioselectivity was obtained only when the reaction was carried out using (a*S*,*S*)-**3e** (entry 8). These results mean that enantioselectivity in Pd-catalyzed asymmetric allylic alkylation is not decreased by using diastereomeric mixtures of ligands **3**. When the reactions were carried out using the diastereomeric mixture of (*S*)-**3a** (entry 10) and (*S*)-**3b** (entry 11) at −10°C, (*S*)-**8** with good enantioselectivity was obtained, but the reaction rate became slightly slow. In the case of (a*S*,*S*)-**3c**, product **8** with moderate enantioselectivity was obtained (entry 12). In order to improve the enantioselectivity, we further examined the effect of reaction solvents using the ligand (a*S*,*S*)-**3d**. A reaction carried out in ether improved the enantioselectivity to 95% ee (entry 16).

We successfully obtained chiral diaminophosphine with stable C(aryl)–N(amine) axial chirality such as that seen for **3** and demonstrated the Pd-catalyzed asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate (**6**) with dimethyl malonate (**7**) using it with high enantiomeric excess. Further studies on optimization of the ligand and application to other asymmetric reactions are underway in our group.

Acknowledgements

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7. Rate of (a*S*,*S*)-**3a**/(a*R*,*S*)-**3a** was ca. 2.3 determined by NMR.
8. Rate of (a*S*,*S*)-**3b**/(a*R*,*S*)-**3b** was ca. 2.5 determined by NMR.
9. Rate of (a*S*,*S*)-**3c**/(a*R*,*S*)-**3c** was ca. 2.0 determined by NMR.
10. (a*S*,*S*)-**3d** (less polar): 41%; mp 112–113°C; $[\alpha]_D^{25}=41.7°$ (*c* 0.10, $CHCl_3$): ^{1}H NMR ($CDCl_3$) δ: 1.56–1.71 (m, 7H), 2.03–2.13 (m, 1H), 2.16–2.36 (m, 6H), 2.53–2.62 (m, 1H), 2.78 (dd, $J=7.6$ and 15.4 Hz, 1H), 3.66-3.75 (m, 1H), 3.79 (s, 3H), 6.40–6.43 (m, 1H), 6.40 (ddd, $J=1.3$, 2.8, and 7.6 Hz, 1H), 6.86 (dd, $J=0.6$ and 8.0 Hz, 1H), 7.05 (ddd, $J=0.8$, 7.9, and 8.7 Hz, 1H), 7.25–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) δ: 23.4, 24.2, 29.7, 31.5, 48.52, 51.9, 54.7, 55.0, 61.1, 61.7 (d, $J_{cp}=3.3$ Hz), 112.4, 124.9, 126.3, 128.1–128.2 (m), 134.0, 134.1, 134.3, 134.4, 138.7 (d, $J_{cp}=13.2$ Hz), 139.2 (d, $J_{cp}=14.6$ Hz), 140.5, 142.7 (d, $J_{cp}=4.1$ Hz), 158.3 (d, $J_{cp}=3.6$ Hz); ^{31}P NMR ($CDCl_3$) δ: −15.05; FAB-MS *m*/*z* (rel intensity): 445 (M^++1, 100); HRMS (FAB-MS) *m*/*z* calcd for $C_{28}H_{34}N_2OP$+H 445.2409, found 445.2382. (a*R*,*S*)-**3d** (more polar): 29%; mp 150–151°C; $[\alpha]_D^{25}=11.1°$ (*c* 0.10, $CHCl_3$): ^{1}H NMR ($CDCl_3$) δ: 1.08–1.18 (m, 1H), 1.34–1.44 (m, 2H), 1.51–1.55 (m, 1H), 1.56–1.65 (m, 4H), 1.89 (d, $J=11.5$ Hz, 1H), 2.19–2.31 (m, 4H), 2.68–2.76 (m 2H), 2.98–30.7 (m, 2H), 3.77 (s, 3H), 6.22 (ddd, $J=1.2$, 2.7, and 7.6 Hz, 1H), 6.85 (d, $J=8.1$ Hz, 1H), 7.03 (ddd, $J=1.2$, 7.6, and 8.1 Hz, 1H), 7.21–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$) δ: 23.0, 24.9, 30.5, 50.2, 51.3, 55.0, 55.1, 61.4, 122.4, 124.3, 124.3, 126.8, 128.1–128.3 (m), 133.8, 134.0, 134.1, 134.3, 138.9 (d, $J_{cp}=9.7$ Hz), 139.1 (d, $J_{cp}=10.5$ Hz), 140.9 (d, $J_{cp}=2.8$ Hz), 142.4 (d, $J_{cp}=18.6$ Hz), 159.0 (d, $J_{cp}=2.6$ Hz); ^{31}P NMR ($CDCl_3$) δ: −13.45; FAB-MS *m*/*z* (rel intensity): 445 (M^++1, 100); HRMS (FAB-MS) *m*/*z* calcd for $C_{28}H_{34}N_2OP$+H 445.2409, found 445.2369.
11. Rate of (a*S*,*S*)-**3e**/(a*R*,*S*)-**3e** was ca. 1.8 determined by NMR.
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13. Rate of (a*S*,*S*)-**3d**/(a*R*,*S*)-**3d** was ca. 1.4 determined by NMR.