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A C(aryl)–N(amine) bond atropisomeric aminophosphine: preparation and use as a ligand in a catalytic asymmetric allylic alkylation

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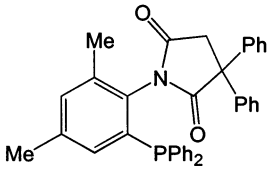
Abstract—The existence of **3** as a pair of stable atropisomers has been demonstrated analytically through chiral phase LC–CD investigations. Resolution of **3d** was achieved by preparative chiral HPLC. Finally, the ability of the first C(aryl)–N(amine) axially chiral phosphine ligand **3d** is demonstrated in a catalytic asymmetric reaction.

Asymmetric catalysis has been advanced in many areas by the discovery and application of atropisomeric ligand BINAP.[1] The chiral environment imposed by the orthogonal naphthalene ring in addition to the chelating nature of this ligand has proven effective for inducing high stereoselectivity in a variety of asymmetric reactions.[2] The binaphthylmono-phosphines (MOP's) and related ligands have also found use in catalytic asymmetric reactions.[3] More recently, C(aryl)–C(aryl) bond atropisomeric aminophosphine ligands such as QUINAP[4] and MAP[5] were applied to transition-metal catalyzed asymmetric reactions. The synthesis of new axially chiral biaryls, however, remains a challenge due to the difficulties in forming the central sterically hindered C(aryl)–C(aryl) bond.[6] In the case of nonbiaryl C–C bond atropisomeric ligands, C(aryl)–C(amide carbonyl) bond atropisomeric phosphine ligands[7] and C(aryl)–N bond atropisomeric phosphine ligands such as *N*-arylimide type ligand **1**[8] and quinazolinone-containing *N*-anilide type ligand **2**[9] have been reported. However, C(aryl)–N(amine) bond atropisomeric compounds have been described only rarely, with examples including, for *N*-aryl pyrroles,[10] *N*,*N*-di(1-naphthyl)-indolo[3,2-*b*]-carbazole,[11] and murrastifoline-F.[12] To the best of our knowledge, C(aryl)–N(amine) bond atropisomeric amines have never been employed as chiral ligands in catalytic asymmetric reactions, including their use as substrates in asymmetric reactions. We have applied them to the synthesis of pyrrolidinyl-containing aminophosphines with the aim of exploiting the less popular amines.[13]



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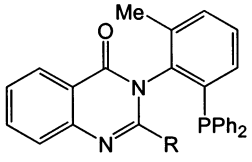
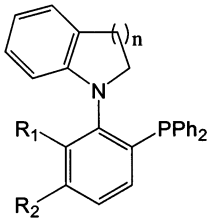


2

a: R = -Me
b: R = -CH=CH-2-Pyridyl



3

a: R_1, R_2 = -CH=CH-CH=CH-, n = 1
b: R_1 = MeO, R_2 = H, n = 1
c: R_1 = MeO, R_2 = H, n = 2
d: R_1 = Me, R_2 = H, n = 1

Herein, we report the first synthesis and resolution of C(aryl)–N(amine) bond atropisomeric amines such as aminophosphines **3** with a bulky substituent at R_1 and apply them to transition-metal catalyzed asymmetric reactions, such as palladium-catalyzed asymmetric allylic alkylation.

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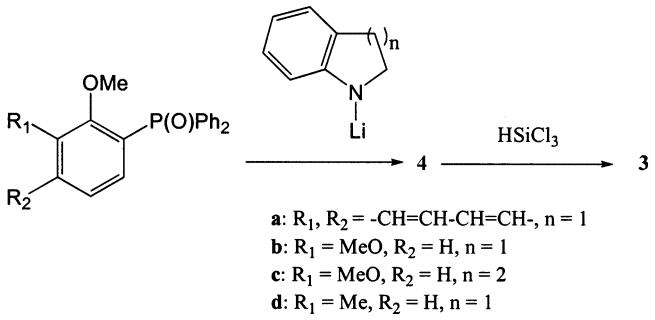


Scheme 1.

Aminophosphine ligands **3** were easily prepared in two steps. A nucleophilic aromatic substitution (S_NAr) reaction of the corresponding phosphine oxides such as 1-methoxy-2-(diphenylphosphino)naphthalene oxide with the lithium salt of indoline gave the corresponding aminophosphine oxide **4a**. This aminophosphine oxide was converted into the desired aminophosphine ligand **3a** using trichlorosilane-triethylamine in good yield (Scheme 1). The other ligands were easily prepared in the same manner.

We successfully conducted X-ray crystallographic analyses of racemic aminophosphines **3b**–**d**: however, attempts on **3a** have been unsuccessful to date. The ORTEP drawings of **3b**–**d** are shown in Figure 1. In all cases, C(aryl)–N(amine) bonds were twisted between an aryl ring with diphenylphosphine and an indoline or tetrahydroquinoline ring.

We attempted to separate these isomers by using HPLC on a chiral phase. We were able to obtain an almost-resolved UV plot for aminophosphines **3**, except **3c**, in addition to a pair of clear positive and negative CD signals of an HPLC run at 254 nm on Chiralcel® OJ (Fig. 2). In the case of **3c**, although a pair of clear positive and negative CD signals appeared, no UV plot was obtained for the resolution peaks. This phenomenon means that the C(aryl)–N(amine) bond of **3c** was rotated slowly on the chiral column at room temperature.

We conducted a study on the thermal racemization of chiral **3**, except **3c**, separated by HPLC on a chiral phase by heating its toluene solution. A small portion of the solution was taken out at regular intervals up to 4 h, and subsequently analyzed for enantiomeric excess by chiral HPLC analysis. We conducted this experiment at more than three different temperatures in each case. For **3d**, the half-life was found to be about 4.7×10^2 days in toluene at 25°C, which corresponds to a rotational barrier ($\Delta G^{\ddagger}$) of 28.5 kcal/mol (Table 1).

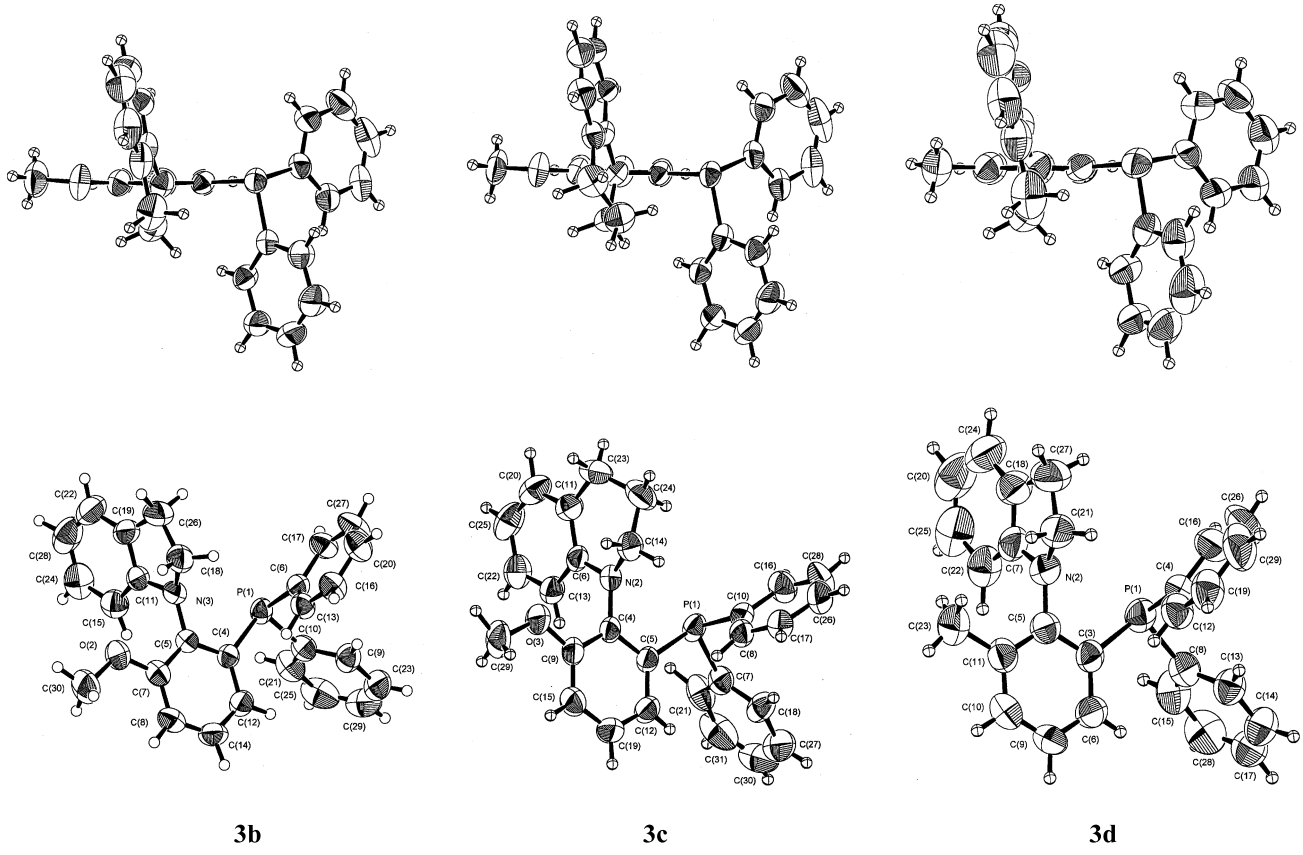


Figure 1. The ORTEP drawing of **3b**–**d**.

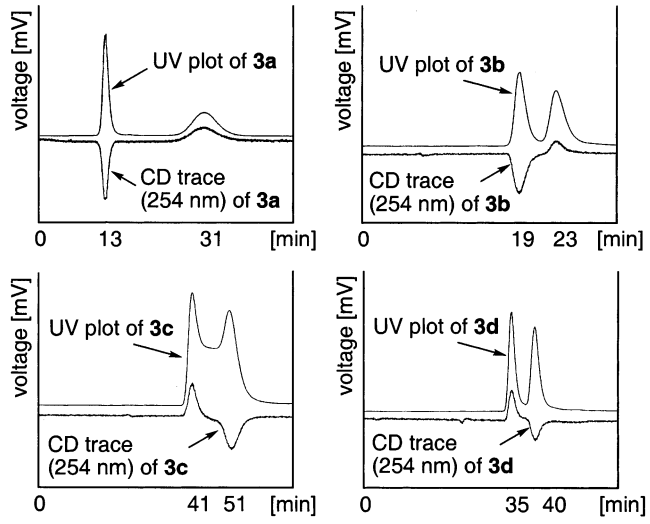


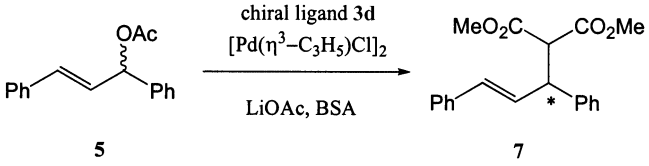
Figure 2. HPLC-UV and -CD analysis of **3** using a chiral phase.

Table 1. Racemization energies of **3a**, **3b** and **3d** at 25°C in toluene

	3a	**3b**	**3d**
$\Delta G^{\ddagger}$ (kcal/mol)	27.6	24.5	28.5
$\Delta H^{\ddagger}$ (kcal/mol)	29.9	27.3	25.4
$\Delta S^{\ddagger}$ (cal/mol·K)	7.92	9.25	−10.3
E_{rac}(kcal/mol)	30.5	27.9	26.0
k_{rac} (s^{-1})	3.95×10^{-8}	6.81×10^{-6}	8.59×10^{-9}
$t_{1/2}$ (day)	102	0.59	467

In fact, the enantiopure **3d** (>99% ee) racemized to 82% ee after 130 days in toluene at room temperature. In the case of an ethanol solution, the racemization of **3d** was slower, such as the 98% ee of **3d** was decreased to 92% ee after 130 days at room temperature. The half-lives of **3a** and **3b** were shorter than **3d**. Optically active atropisomeric aminophosphine **3d** on a preparative scale, such as a 100 mg scale, was obtained using a semi-preparative chiral phase column (Chiralcel® OJ: 25 cm×1 cm i.d.).

The chiral aminophosphine **3d** was then applied as the chiral ligand for the transition-metal catalyzed asymmetric reaction such as a palladium-catalyzed asymmetric allylic alkylation (AAA)[14] of 1,3-diphenyl-2-propenyl acetate **5** with dimethyl malonate **6**. This reaction was carried out in the presence of 5 mol% of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 10 mol% of **3d**, and a mixture of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and 5 mol% of LiOAc (Scheme 2 and Table 2).



Scheme 2.

(+)- and (−)-**3d** were able to induce moderate enantioselectivities in toluene at room temperature (entries 1 and 2). Next a reaction was carried out using (−)-**3d** at 0°C (entry 3). Although the reaction rate decreased, the enantioselectivity of (*S*)-**7** was improved to 91% ee. We further examined the effect of reaction solvents using the chiral ligand **3d**. A reaction carried out in CH_2Cl_2 improved the reaction yield to 88% with 87% ee (entry 4). Low reactivity was observed in THF as opposed to other solvents (entry 5).

In summary, we have shown that the synthesis of aminophosphines **3** could be achieved in good yields by nucleophilic aromatic substitution (S_NAr) followed by silane reduction. The existence of **3** as a pair of stable atropisomers was demonstrated analytically through chiral phase LC–CD investigations. Resolution of **3d** was achieved by preparative chiral HPLC. Finally, the ability of the first C(aryl)–N(amine) axially chiral phosphine ligand **3d** is demonstrated in catalytic asymmetric reactions such as a palladium-catalyzed asymmetric allylic alkylation.

Table 2. Pd-Catalyzed AAA reaction using chiral atropisomeric aminophosphine **3d**

Entry	Ligand	Solv.	Temp. (°C)	Time (h)	Yield[a] (%)	Ee[b] (%)	Config.[c]
1	(+)-**3d**	PhMe	rt	24	60	74	*R*
2	(−)-**3d**	PhMe	rt	24	60	76	*S*
3	(−)-**3d**	PhMe	0	72	63	91	*S*
4	(+)-**3d**	DCM	0	72	88	87	*R*
5	(−)-**3d**	THF	0	72	38	80	*S*
6	(−)-**3d**	$PhCF_3$	0	72	61	75	*S*

[a] Isolated yields.
[b] Enantiomeric excesses were determined by HPLC on Chiral phase (Chiralcel® OD-H).
[c] The absolute stereochemistry was determined by HPLC retention times.

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