



# Synthesis of novel chiral biquinolyl diphosphine ligand and its applications in palladium-catalyzed asymmetric allylic substitution reactions



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## ABSTRACT

A novel chiral diphosphine ligand, 6,6'-bis(diphenylphosphino)-5,5'-biquinoline (BIQAP) was synthesized via two step reactions using optical pure BIQOL as starting material and the molecular structure of (*R*)-BIQAP was determined by single-crystal X-ray diffraction. The ligand was used for Pd-catalyzed asymmetric allylic substitution reactions. High enantioselectivities were obtained in the corresponding C–C and C–N bond formation of 1,3-diphenyl-2-propenyl acetate, with dimethyl malonate (up to 94% ee) and with potassium phthalimide (up to 96% ee).

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## Introduction

Chiral phosphine ligands are a very successful type of ligands used in asymmetric catalysis.<sup>1</sup> Among them, BINAP is no doubt one of the most effective chiral diphosphine ligands.<sup>2</sup> So far diphosphine–metal complexes have been found to be versatile in many catalytic reactions such as asymmetric hydrogenation,<sup>3</sup> arylation,<sup>4</sup> allylic alkylation,<sup>5</sup> etc. Moreover, a large number of examples of industrialization have been reported.<sup>6</sup>

Pd-catalyzed asymmetric allylic alkylation<sup>7</sup> is a powerful approach to stereoselective C–C, C–N, and C–O bonds formation in synthetic organic chemistry. As such its asymmetric version using a chiral ligand has also been extensively studied in the past decades.<sup>8</sup> In order to achieve high enantioselectivity from racemic or achiral allylic substrates, the development of a novel chiral ligand is an essential and challenging task.<sup>9</sup> In 2000, Chan and co-workers once reported a C<sub>2</sub>-symmetric, heterocyclic chiral ligand, 6,6'-dihydroxy-5,5'-biquinoline (BIQOL)<sup>10</sup> which has a skeleton similar to that of BINOL. Since then the BIQOL ligand has been applied to many kinds of reactions and showed good enantioselectivity.<sup>10,11</sup> Herein we report its further development for the preparation of novel BIQAP ligand 6,6'-bis(diphenylphosphino)-5,5'-biquinoline and the corresponding application in

Pd-catalyzed asymmetric allylic substitution reactions (see Scheme 1 and Scheme 2).

## Results and discussion

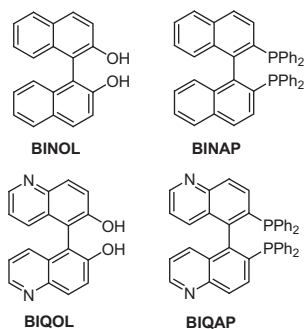
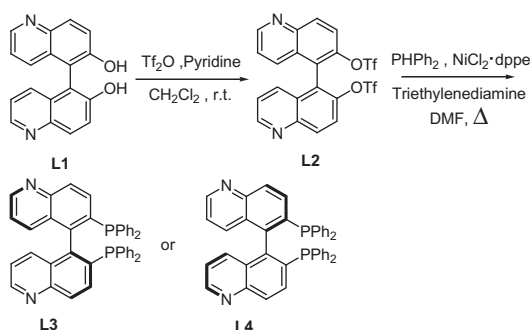
The chiral BIQAP ligand was obtained through a straightforward two-step synthetic route using optical pure BIQOL as the starting material. At first, ditriflate of (*R*)-BIQOL was prepared using (*R*)-BIQOL and triflate in an ice bath. Then, a coupling reaction between ditriflate **L2** and diphenylphosphine was carried out with a Ni-based catalyst and 1,4-diaza[2.2.2]bicyclooctane (DABCO) in DMF at 120 °C for 72 h. Numerous nickel catalysts such as NiCl<sub>2</sub>, NiCl<sub>2</sub>/dppp, NiCl<sub>2</sub>-dppe, NiCl<sub>2</sub>-(Ph<sub>3</sub>P)<sub>2</sub> were screened and it is found that only NiCl<sub>2</sub>-dppe catalyzed (*R*)-BIQAP formation.

X-ray single crystal diffraction analysis of (*R*)-BIQAP revealed the presence of diphenylphosphino moiety in the ligand via C–P binding in an orthorhombic crystal system and the space-group is P2<sub>1</sub> 2<sub>1</sub> 2<sub>1</sub> (19). The interplanar angle of the least-squares of the biquinoline is 90° (Fig. 1).

With chiral ligand BIQAP in hand, we first examined its catalytic activity under the Pd-catalyzed asymmetric allylic alkylation reaction. *rac*-1,3-Diphenylpropen-1-yl acetate reacted with dimethyl malonate (3.0 equiv) in the presence of (*S*)-BIQAP (5.0 mol %), [Pd(η<sup>3</sup>-C<sub>3</sub>H<sub>5</sub>)Cl]<sub>2</sub> (2.5 mol %), *N,O*-bis(trimethylsilyl)acetamide (BSA, 3 equiv) and Zn(OAc)<sub>2</sub> (0.1 equiv). The latter was acted as BSA activator.

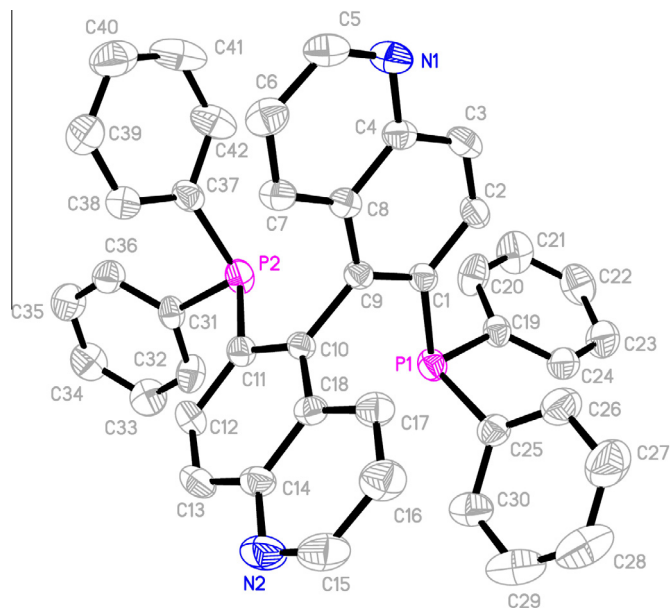
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Scheme 1.  $C_2$ -symmetric chiral ligands.

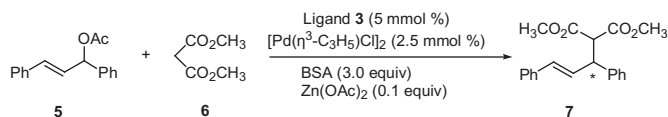
Scheme 2. Synthesis of chiral BIQAP ligand.

Solvent screening experiments showed that toluene, THF or EtOAc as solvent provided good enantioselection. Yet,  $\text{CH}_2\text{Cl}_2$  was the best one with ee value up to 90% (Table 1, entries 1–5). After selecting  $\text{CH}_2\text{Cl}_2$  as the solvent, we then investigated the effect of palladium sources (Table 1, entries 2, 6–9) and found that  $[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$  was the most favorable choice among the studied

Figure 1. The crystal structure of (*R*)-BIQAP.

precursors. Decreasing the catalyst loading of ligand **3** from 5.0 mol % to 2.5 mol % afforded almost the same result (99% yield, 91% ee, Table 1, entry 10). 1 mol % catalyst loading still gave the product in 99% yield with 92% ee (Table 1, entry 11). Similar results were obtained using (*R*)- or (*S*)-BIQAP as the ligand under the same conditions (Table 1, entries 11 and 12). An interesting phenomenon was also observed that there was no influence in enantioselectivity without  $\text{Zn}(\text{OAc})_2$  as the activator (Table 1, entries 13 and 14). In addition, temperature decrease from 25 °C to –10 °C brought about an enantioselectivity increase from 92% to 94% ee (Table 1, entries 14–16). The catalytic activity was further

**Table 1**  
The Pd-catalyzed asymmetric allylic alkylation reaction<sup>a,12</sup>



Entry	Solvent	[Pd]	Ligand (%)	Activator	Temp (°C)	Time (h)	Yield <sup>b</sup> (%)	ee <sup>c</sup> (%)
1	Toluene	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	5.0	$\text{Zn}(\text{OAc})_2$	25	24	99	84 (S)
2	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	5.0	$\text{Zn}(\text{OAc})_2$	25	24	99	90 (S)
3	THF	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	5.0	$\text{Zn}(\text{OAc})_2$	25	24	75	83 (S)
4	EtOAc	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	5.0	$\text{Zn}(\text{OAc})_2$	25	24	99	84 (S)
5	$\text{CH}_3\text{CN}$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	5.0	$\text{Zn}(\text{OAc})_2$	25	24	97	7 (S)
6	$\text{CH}_2\text{Cl}_2$	$\text{Pd}(\text{bda})_2$	5.0	$\text{Zn}(\text{OAc})_2$	25	24	29	81 (S)
7	$\text{CH}_2\text{Cl}_2$	$\text{Pd}_2(\text{bda})_3$	5.0	$\text{Zn}(\text{OAc})_2$	25	24	87	78 (S)
8	$\text{CH}_2\text{Cl}_2$	$\text{Pd}(\text{OAc})_2$	5.0	$\text{Zn}(\text{OAc})_2$	25	24	8	79 (S)
9	$\text{CH}_2\text{Cl}_2$	$\text{PdCl}_2$	5.0	$\text{Zn}(\text{OAc})_2$	25	24	0	n.d.
10	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	2.5	$\text{Zn}(\text{OAc})_2$	25	24	99	91 (S)
11	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	1.0	$\text{Zn}(\text{OAc})_2$	25	24	99	92 (S)
12 <sup>d</sup>	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	1.0	$\text{Zn}(\text{OAc})_2$	25	24	99	92 (R)
13	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	5.0	–	25	24	99	91 (S)
14	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	1.0	–	25	24	99	92 (S)
15	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	1.0	–	0	24	99	93 (S)
16	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	1.0	–	–10	24	99	94 (S)
17	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	1.0	–	–10	12	99	94 (S)
18	$\text{CH}_2\text{Cl}_2$	$[\text{Pd}(\eta^3\text{-C}_3\text{H}_5)\text{Cl}]_2$	1.0	–	–10	6	99	94 (S)

<sup>a</sup> Reaction conditions: 0.5 mmol 1,3-diphenylprop-1-en-1-yl acetate, 1.5 mmol BSA, 1.5 mmol dimethyl malonate, 2.0 mL of solvent.

<sup>b</sup> Yield of isolated product.

<sup>c</sup> Determined by HPLC on a Chiralcel OD-H column.

<sup>d</sup> (*R*)-BIQAP as ligand.

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