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Design and synthesis of novel 1,3-diene bridged chiral atropoisomeric diphosphine ligands for asymmetric hydrogenation of α-dehydro amino ketones

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A series of novel atropisomeric diphosphine ligands termed TanPhos were designed and synthesized, which has a smaller bite angle compared with that of other ligands such as BINAP. TanPhos showed high reactivity and enantioselectivity in the rhodium-catalyzed asymmetric hydrogenation of α-dehydro amino ketones, and up 99% yield and 99% ee were obtained for a wide range of chiral α-amino ketones.

diphosphine, asymmetric hydrogenation, chiral ligand

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1 Introduction

In the past few decades, asymmetric catalysis has made rapid development [1–6]. Chiral ligands and catalysts are considered to be the core elements for the control of activity and selectivity, and asymmetric catalysis has become a powerful tool for the rapid construction of single enantiomers both in the laboratory and on an industrial scale. The development of chiral ligands plays a pivotal role in the generation and transfer of chirality. A large number of excellent chiral ligands, especially chiral diphosphine ligands, have emerged (Figure 1). The pioneering work by Kagan *et al*. [7], who designed and synthesized the first chiral diphosphine ligand DIOP for asymmetric hydrogenation and up to 80% ee was achieved in 1971, and resulted in a significant breakthrough in ligand design. The 2001 Nobel Prize was awarded to Knowles and Noyori for their contributions to the synthesis and industrial application of DIPAMP [8] and BINAP [9], respectively. Since then, various *C*2-symmetric diphosphine ligands have been synthesized and applied in asymmetric catalysis. Electron-rich diphosphine ligands BPE and DuPhos developed by Burk and coworkers [10] have been proven to be powerful ligands in asymmetric hydrogenation [11,12]. A novel axially chiral bipyridine ligand P-Phos was developed by Chan and coworkers in 1999. Since then, a wide range of chiral biaryl diphosphine ligands have been developed. In 2001, another trialkyl diphosphine ligand BisP* was developed by Imamoto *et al*. [13]. TangPhos developed by Zhang and coworkers [14] represents another

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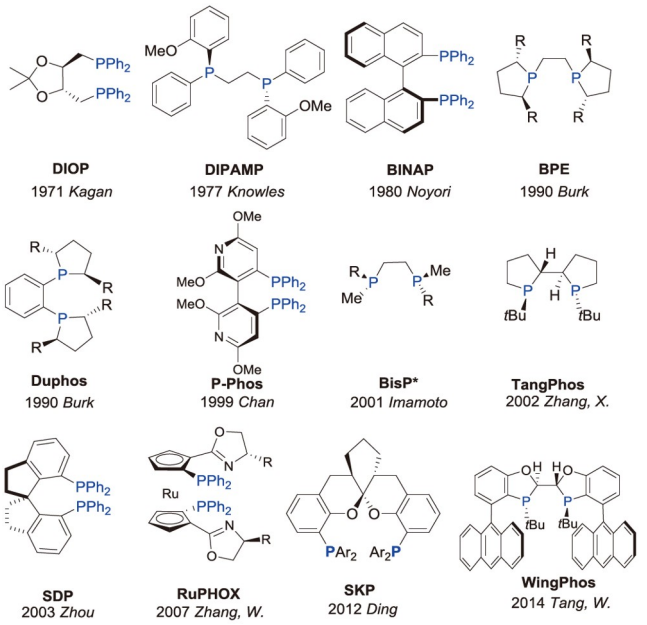
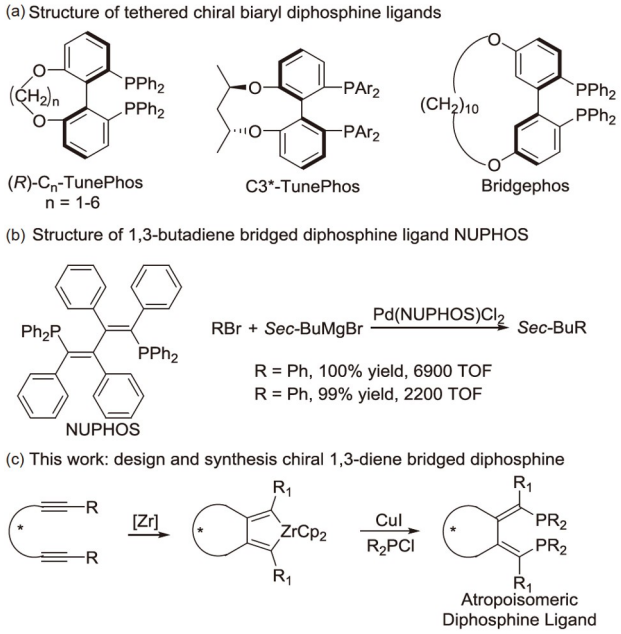


Figure 1 Selected examples of privileged diphosphine ligands (color online).



Scheme 1 Design of chiral atropisomeric diphosphine ligands.

kind of rigidity phospholane ligand. A highly rigid chiral spiro diphosphine ligand was synthesized by Zhou and coworkers [15] in 2003. RuPHOX developed by Zhang and coworkers [16], SKP developed by Ding and coworkers [17] and WingPhos developed by Tang and coworkers [14] also have a great influence on the development of asymmetric catalysis.

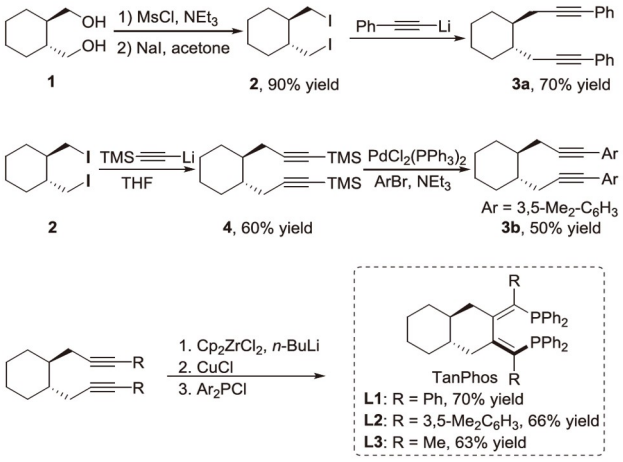
During the development of the chiral diphosphine ligands, rigidity has been proved to be an important factor to consider in the design of chiral ligands and chiral ligands with a rigid backbone often show better chirality control in asymmetric transformations. To increase the rigidity of the biaryl diphosphine ligand, Zhang and coworkers [18–21] designed and synthesized C_n-TunePhos by introducing a linker to the biaryl skeleton, and the dihedral angle of the ligand could be tuned by the length of the linker (Scheme 1a). Subsequently, Zhang and coworkers [22–24] realized the asymmetric synthesis of C_3^*-TunePhos by introducing a chiral linker. In order to further reduce the dihedral angle of the biaryl diphosphine ligand, Zhang and coworkers [25–27] designed and synthesized BridgePhos, in which the linker was introduced on the meta position of the biaryl axis instead of the ortho position. In 2001, a novel 1,3-butadiene racemic bridged diphosphine ligand termed NUPHOS was synthesized by Doherty, Nakajima and coworkers [28,29], which showed high efficiency in palladium-catalyzed cross-coupling reactions of aryl or alkyl bromide and organomagnesium reagent (Scheme 1b). We envision that a chiral 1,3-budiene bridged diphosphine could be synthesized by introducing a chiral linker to the 1,3-butadiene moiety. Herein, we disclose our design and synthesis of novel 1,3-butadiene bridged atropoisomeric diphosphine ligand and its application in asymmetric hydrogenation (Scheme 1c).

2 Results and discussion

2.1 Synthesis of the ligands

We initiated our investigation with the synthesis of the ligand, and the results were depicted in Scheme 2. From commercially available compound **1**, diiodide **2** was easily prepared by the mesylation of chiral diol **1** and subsequent substitution with sodium iodide. The key intermediate **3a** was obtained by S_N2 reaction of **2** and lithium phenylacetylene. Diyne intermediate **3b** was prepared by Sonogashira coupling of compound **4** with aryl bromide. The key oxidative cyclization of diyne **3** proceeded smoothly with Cp_2ZrCl_2 to form a five-membered Zirconium intermediate [30,31], which could undergo transmetallation with copper chloride to form an organocopper species, which is very reactive in C–P bond formation. Subsequent reaction with chlorodiphenylphosphine afforded the desired diphosphine ligands **L1**, **L2** and **L3** (TanPhos) with moderate to high yield.

To give a deep insight into the characteristics of this novel and simple atropisomeric ligand, the crystals of Pd(**L1**)Cl_2 and Pd(**L3**)Cl_2 suitable for X-ray diffraction were grown and unambiguously characterized (CCDC 2277697 and 2277698 respectively). The axial chirality of ligand **L1**–**L3** was unambiguously determined as *S*. **L1** and **L3** have a bite angle of 91.8° and 87.5° respectively, which are smaller than that of BINAP (92.5°), SDP (96.1°) and *O*-SDP (99.1°) [32–34].



Scheme 2 Synthesis of chiral atropoisomeric ligand **L1**–**L3**.

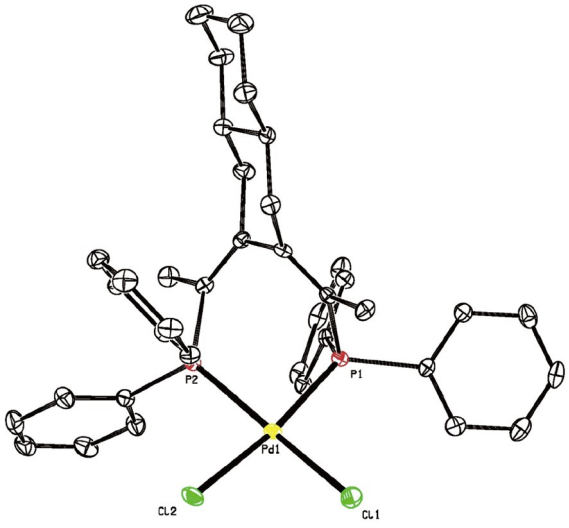
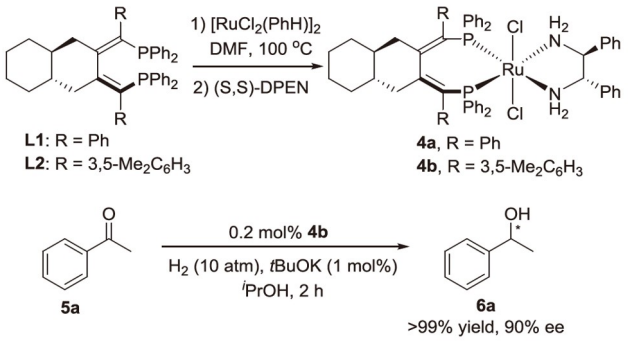


Figure 2 X-ray structure of Pd(**L3**)Cl_2 (color online).

The distance between the two P atoms is 3.247 and 3.123 Å respectively (Figure 2). These inherent properties indicate the uniqueness of this kind of atropisomeric ligand compared with other axial ligands (*e.g.*, BINAP), implying the potential distinctive catalytic activities. An initial test of the Ruthenium diphosphine diamine complex of **L1** and **L2** (**4a** and **4b**) showed good efficiency (>99% yield) and enantiocontrol (90% ee) for the asymmetric hydrogenation of acetophenone **5a** (Scheme 3).

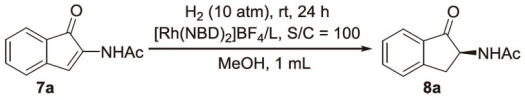
2.2 Condition optimization

To demonstrate the efficacy of the ligand in asymmetric catalysis and considering the synthetic potential of chiral amino ketones [35–38], we evaluate their performance in rhodium-catalyzed asymmetric hydrogenation of α-dehydro amino ketones **7**, which is a challenging substrate in asymmetric hydrogenation. The performance of other diphosphine ligands was first evaluated with **7a** as the model substrate, and the results were depicted in Table 1. With ZhaoPhos as a ligand [39,40], only 39% conversion and 0% ee were achieved (entry 1). DuanPhos was not an effective ligand for this reaction either. Next, chiral biaryl diphosphine ligands BINAP and SegPhos were tested, and the reactivity was excellent for the two ligands, however only 75% and 44% ee were achieved respectively (entries 3 and 4). Spiro diphosphine ligand *O*-SDP [32], which was recently developed in our group could only give 48% ee (entry 5). Cy-BINAP could only give 22% ee either (entry 6). To our delight, with ligand **L1** or **L2** as ligand, 92% ee could be achieved (entries 7 and 8) (Figure 3). The enantioselectivity was improved to



Scheme 3 Synthesis of the Ru(II) complex and their application in asymmetric hydrogenation of ketone.

Table 1 Optimization of the reaction conditions



Entry[a)]	Ligand	Conv. (%)	ee (%)
1	(*S*)-ZhaoPhos	39	*rac*
2	(S_c,R_p)-DuanPhos	nr	–
3	(*S*)-BINAP	> 99	75
4	(*S*)-SegPhos	> 99	44
5	(*S*)-*O*-SDP	> 99	48
6	(*S*)-Cy-BINAP	> 99	23
7	**L1**	> 99	92
8	**L2**	> 99	92
9[b)]	**L1**	66	81
10[c)]	**L1**	> 99	94
11[c)]	**L2**	> 99	96
12[d)]	**L2**	> 99	96

a) The reaction was conducted on 0.1 mol scale. b) $[Rh(COD)Cl]_2$ was utilized as the metal precursor. c) $[Rh(NBD)Cl]_2$ was utilized as the metal precursor. d) The catalyst solution was exposed to 10 atm H_2 for 24 h before use.

96% by changing the metal precursor from $Rh(NBD)_2BF_4$ to $[Rh(NBD)Cl]_2$ (entries 9–11). The absolute configuration of **8a** was determined by comparing its optical rotation with previously reported data [37]. In addition, we found that after exposure to H_2 for 24 h, the rhodium complex of TanPhos maintained its catalytic activity and enantiocontrol ability (entry 12).

2.3 Substrate scope

With the optimal reaction conditions in hand, we next examined the substrate scope of the current reaction, and the results were summarized in Table 2. When the acetyl protective group was replaced with the pivaloyl group, the enantioselectivity was improved to 98% (Table 2, **8b**). The reaction of **8a** on a 1.1-g scale was also conducted, and the desired product **8b** was produced in 98% yield with retention of enantioselectivity. Various substrates containing methyl groups with different substitution patterns were tested to be compatible and highly effective (**8c**–**8g**). The reaction also tolerates various halogen substitutions such as bromide, fluoride, chloride on the phenyl group (**8h**–**8n**). The *oxa*-cyclic six-membered substrates **7o** and **7p** were also evaluated, unfortunately, only moderate yield and low enantioselectivity were achieved.

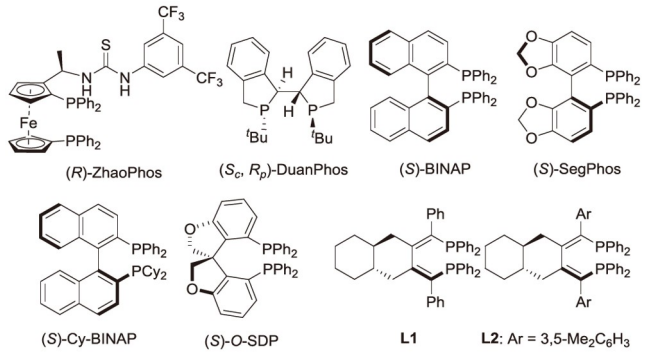
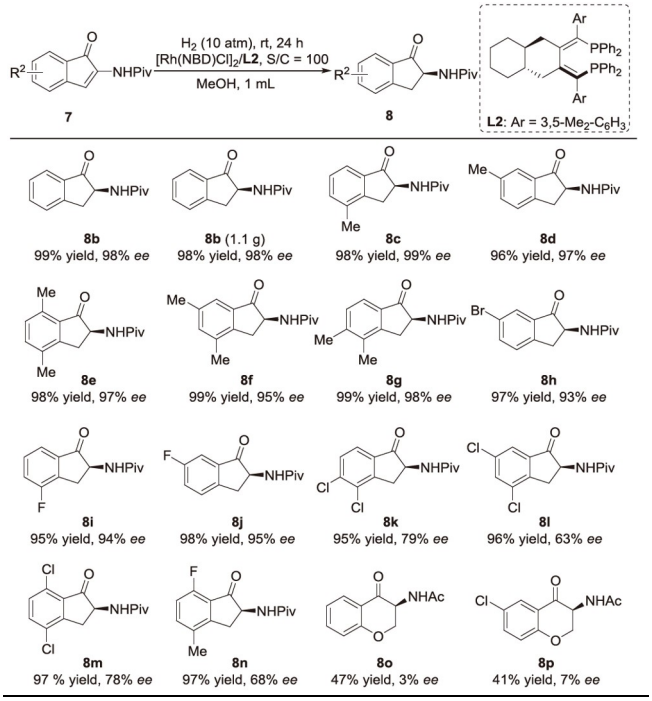


Figure 3 Structure of the ligands that were screened.

Table 2 Substrate scope of the reaction



3 Conclusions

In summary, we have designed and synthesized a novel chiral atropoisomeric chiral diphosphine ligand. The intriguing structural property, *e.g.*, the small bite angle, accounts for its unique catalytic reactivity in specific reactions. In this context, the ligand has been applied in the asymmetric hydrogenation of α-dehydro amino ketones, providing chiral amino ketone derivatives with high yield and enantioselectivity. Further synthetic applications of this novel ligand in asymmetric catalysis were underway in our group and the results will be reported in due course.

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Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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