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Synthesis of novel BINOL-derived chiral bisphosphorus ligands and their application in catalytic asymmetric hydrogenation

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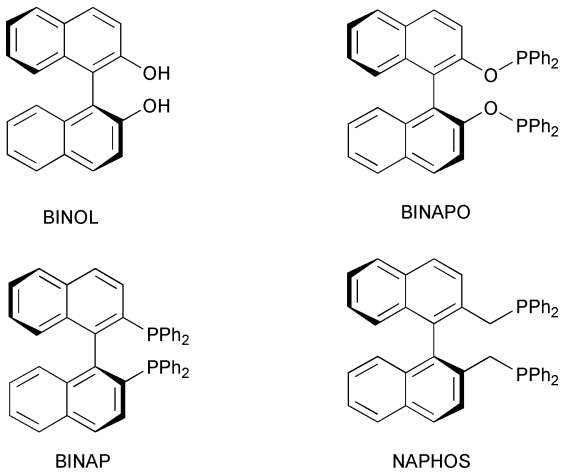
Some novel *ortho*-substituted BINOL-derived bisphosphorus ligands (*o*-BINAPO and *o*-NAPHOS) were synthesis from readily available (*S*)-BINOL; these ligands showed excellent enantioselectivities (up to 99% ee) in Rh(I)-catalyzed asymmetric hydrogenation of functionalized olefins.

The design and synthesis of chiral ligands has played an important role in the development of transition metal-catalysed asymmetric reactions.[1] In general, metal-complexes of the effective chiral phosphine ligands are 5, 6 or 7-membered rings. While a big bite angle (P–M–P) has a special effect in asymmetric catalysis.[2] It is difficult to develop effective catalysts with a 9-membered chelating ring. Biaryl atropisomeric ligands have been explored as effective scaffolds for many asymmetric transformations.[3] Among them, two most frequently used chiral chelating ligands (Scheme 1) are BINAP[4] and BINOL,[5] which form 7-membered with metals. However, their simple analogues (Scheme 1), NAPHOS[6] and BINAPO,[7] which form 9-membered ring with metals, are not effective ligands for asymmetric hydrogenation due to their conformational flexibility. We believe that there are two possible reasons: (1) the additional methylene groups in NAPHOS and oxygen atoms in BINAPO increase the distance between the chiral binaphthyl moiety and PPh_2 groups and therefore decrease the influence of the binaphthyl functionality on the orientation of the phenyl ring of PPh_2 groups. (2) The presence of the C–O–P moiety in BINAPO and the C–CH_2–P moiety in NAPHOS substantially increases the flexibility of the metal-ligand complexes and consequently decreases the enantioselectivity. By the conformational analysis of BINAPO and NAPHOS metal complexes, we propose that if a group (especially an aryl) can be introduced to 3,3′-positions of the binaphthyl scaffold, these groups might improve the conformational rigidity by controlling the orientation of the phenyl ring adjacent to phosphine atoms of their metal complexes.[8] Herein we report the synthesis of these novel chiral bisphosphorus ligands and their application in Rh(I)-catalyzed asymmetric hydrogenation of functionalized olefins.

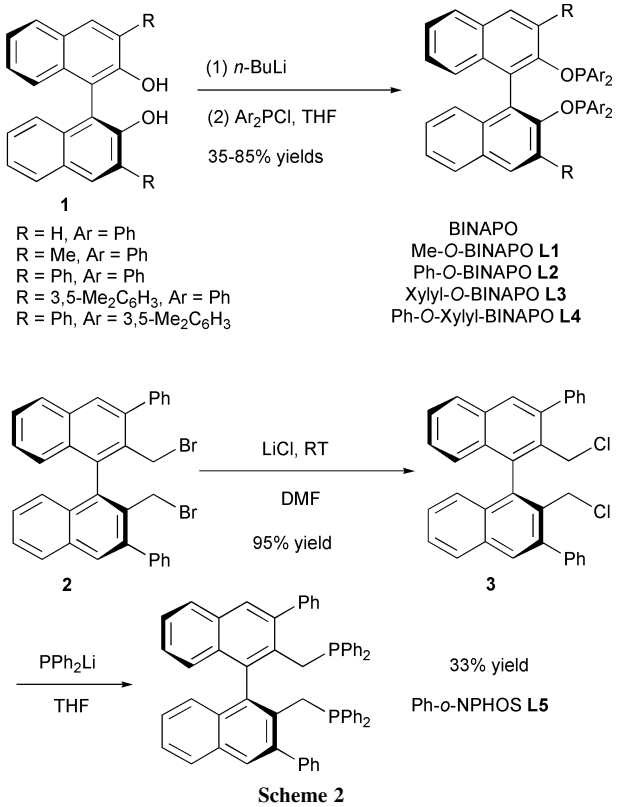


Scheme 1

Our synthetic routes are shown in Scheme 2, three 3,3′(*ortho*)-disubstituted BINOL derivatives **1** were synthesized from commercially available (*S*)-BINOL according to the known literature methods.[9] Chiral bisphosphinite ligands **L1**, **L2**, **L3** and **L4** (abbreviated as *o*-BINAPO) were prepared through reaction of chlorodiarylphosphine with the corresponding chiral diols in high yields. C_2-symmetry chiral bisphosphine ligand **L5** (abbreviated as *o*-NAPHOS) was synthesized from the known compound (*S*)-3,3′-diphenyl-2,2-dibromomethyl-1,1′-binaphthyl **2**[10] in two steps (Scheme 2).

In our previous work on synthesis of a ligand called binaphane,[11] we found that less reactive 2,2′-dichloromethyl-1,1′-binaphthyl is more desirable for making chiral phosphines than 2,2′-dibromomethyl-1,1′-binaphthyl. We tried the known compound **2**[10] for the synthesis of **L5**, no desired product was obtained. A simple anion exchange of compound **2** with lithium chloride in DMF afforded (*S*)-3,3′-diphenyl-2,2-dichoromethyl-1,1′-binaphthyl **3** in 95% yield. Nucleophilic attack of compound **3** with lithium diphenylphosphinide in THF produced the desired bisphosphine ligands **L5**. The product was further purified by a short silica gel column eluted with hexane–DCM–EtOAc (80 : 20 : 1) in a glove box to give a white solid in 33% yield.

With these new ligands in hand, catalytic asymmetric hydrogenation of α-dehydroamino acid derivatives **4** and enamides **5** have been examined. Methyl (*Z*)-2-acetamidoacrylate **4a** and *N*-acetyl-1-phenylethenamide **5a** were used as standard substrates. The optimized results were shown in Table



Scheme 2

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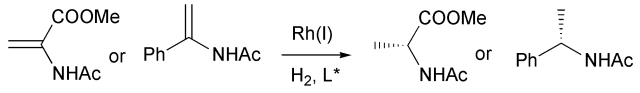
Table 1 The Rh(I)-catalyzed asymmetric hydrogenation of α-dehydroamino acids **4a** and enamides **5a**[a]

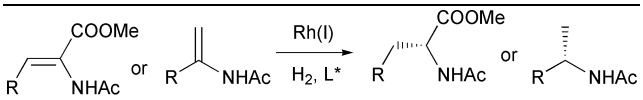


4a **5a** **6a** **7a**

Entry	Substrates (R)		Ligands	Ee[b]
1	**4a**	H	BINAPO[c]	73.2
2	**4a**	H	**L1**	94.8
3	**4a**	H	**L2**	99.9
4	**4a**	H	**L3**	95.4
5	**4a**	H	**L4**	93.0
6	**4a**	H	**L5**	98.7
7	**4a**	H	NAPHOS	54.0
8	**5a**	Ph	BINAPO	28.3
9	**5a**	Ph	**L1**	67.2
10	**5a**	Ph	**L2**	94.3
11	**5a**	Ph	**L3**	89.4
12	**5a**	Ph	**L4**	90.3
13	**5a**	Ph	**L5**	81.8

[a] The reactions were carried out at rt under 45 psi of H_2 for 12 h in 3 mL solvent with 100% conversion [substrate (0.5 mmol scale):Rh: Ligand = 1: 0.01: 0.011]. For *o*-BINAPO ligands, optimized reaction conditions of substrate **4**: $Rh(COD)_2PF_6$, toluene; substrate **5**: $Rh(COD)_2SbF_6$, THF. For *o*-NAPHOS ligand **L5**, optimized reaction conditions of substrate **4**: $Rh(COD)_2PF_6$, methanol; substrate **5**: $Rh(COD)_2PF_6$, methanol. The *S* absolute configurations were assigned by comparison of optical rotations with the known reported data. [b] The ees were measured by GC chiral columns (Chiralsil VAL III and Chiralselect 1000). [c] The result was reported in *Tetrahedron Lett*., 1977, 1879.

Table 2 The Rh(I)-catalyzed asymmetric hydrogenation of α-dehydroamino acids **4** and enamides **5**[a]



4 **5** **6** **7**

Entry	Substrates (R)		Ligand	Ee[b]
1	**4b**	Ph	**L5**	97.8
2	**4c**	*p*-FC_6H_4	**L5**	96.6
3	**4d**	*p*-$MeOC_6H_4$	**L5**	95.8
4	**4e**	*m*-BrC_6H_4	**L5**	97.8
5	**4f**	*o*-ClC_6H_4	**L5**	97.4
6	**4g**	2-Naphthyl	**L5**	97.4
7	**4c**	*p*-FC_6H_4	**L2**	93.4
8	**4d**	*p*-$MeOC_6H_4$	**L2**	87.2
9	**4e**	*m*-BrC_6H_4	**L2**	92.6
10	**4f**	*o*-ClC_6H_4	**L2**	81.5
11	**4g**	2-Naphthyl	**L2**	97.3
12	**5b**	*p*-$CF_3C_6H_4$	**L2**	95.7
13	**5c**	*m*-MeC_6H_4	**L2**	96.3
14	**5d**	*p*-PhC_6H_4	**L2**	94.2
15	**5e**	2-Naphthyl	**L2**	94.1

[a] The reactions were carried out at rt under 45 psi of H_2 for 12 h in 3 mL solvent with 100% conversion [substrate (0.5 mmol scale):Rh: ligand = 1: 0.01: 0.011]. For *o*-BINAPO ligands, optimized reaction conditions of substrate **4**: $Rh(COD)_2PF_6$, toluene; substrate **5**: $Rh(COD)_2SbF_6$, THF. For *o*-NAPHOS ligand **L5**, optimized reaction conditions of substrate **4**: $Rh(COD)_2PF_6$, methanol; substrate **5**: $Rh(COD)_2PF_6$, methanol. The *S* absolute configurations were assigned by comparison of optical rotations with the known reported data. [b] The ees were measured by GC (Chiral VAL III and Chiral select 1000) or HPLC using chiral columns (Chiralcel OJ).

1. We found that 3,3'-disubstituted bisphosphinite ligands *o*-BINAPO are better than nonsubstituted BINAPO. For substrate **4a**, ee increased from 73.2 to 99.9%. For substrate **5a**, ee changed from 28.3 to 94.3%. A 3,3'-disubtituted bisphosphine ligand **L5** (*o*-NAPHOS) is also more effective for asymmetric hydrogenation than the corresponding NAPHOS ligand, enantioselectivity increased from 54.0 to 98.7% for hydrogenation of **4a** by changing ligand NAPHOS to **L5**. These results supported our hypothesis of the importance of conformational rigidity in asymmetric catalysis. With *o*-BINAPO ligands, our hydrogenation results are comparable with those obtained with other chiral phosphorus-rhodium catalysts. For example, the ee values (%) of **6a** reported in the literature[12] are as follows: DIPAMP, 94; DIOP, 73; ChiraPhos, 91; BPPM, 98.5; BINAP, 67; BICP, 97.5; Et-DuPhos, 99.4; SpirOP, 99.9.

A variety of α-dehydroamino acid derivatives **4** were employed as substrates for the Rh-catalyzed hydrogenation reaction using **L5** as ligand, the result was shown in Table 2 (entries 1–6). High enantiomeric excesses have been achieved. There is no major electronic effect on the substitution pattern of **4**. However, for an *o*-BINAPO ligand **L2**, the ees were substrate-dependent (entries 7–11).

To expand the utility of *o*-BINAPO ligands system, we have examined Rh(I)-catalyzed enantioselective hydrogenation of simple enamides **5** using **L2** as ligand (entries 12–15). High enantioselectivities (94.1–96.3% ee) have also been achieved.

In conclusion, we have developed some novel, highly effective chiral bisphosphorus ligands based on a chiral binaphthyl backbone for catalytic asymmetric hydrogenation of enamides and α-dehydroamino acids. The 9-membered ring chelation with transition metals is still effective for asymmetric catalysis, and these ligands are likely to be effective for other catalytic reactions due to the big P–M–P bite angle. Further studies of other transition metal complexes of these ligands and their applications are in progress.

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