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P-Chirogenic Binaphthyl-Substituted Monophosphines: Synthesis and Use in Enolate Vinylation/Arylation Reactions

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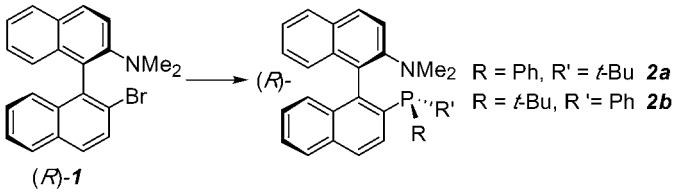
ABSTRACT



New phosphine ligands possessing both axial chirality and a chirogenic phosphorus center were prepared from (*R*)-2-bromo-2′-*N*,*N*-(dimethylamino)-1,1′-binaphthyl (1) via a simple Li−halogen exchange protocol. The asymmetric vinylation of a ketone enolate with (*R*,*R*$_P$)-2-(*tert*-butylphenylphosphino)-2′-*N*,*N*-(dimethylamino)-1,1′-binaphthyl (2a) afforded the coupling product with good enantiomeric excess.

In the past 3 decades, a large number of chiral phosphines have been developed,[1] and their use as ligands in asymmetric catalysis has been studied extensively. These chiral ligands can be divided into three general groups: ligands bearing axial chirality (e.g., BINAP[2] and MOP[3]); ligands possessing carbon stereocenters (e.g., DIOP[4] and DuPHOS[5]); and ligands having chirogenic phosphorus centers (e.g., DIPAMP[6] and Bis-P*[7]). Most chiral phosphines typically possess carbon-based stereogenicity; comparatively few *P*-chiral ligands have been reported. Furthermore, ligands that bear both axial chirality and a chirogenic phosphorus have not been described.[8]

Recently, Hayashi has utilized a binaphthyl-substituted monophosphine ligand (MOP) in asymmetric C−C or C−Si bond formation reactions.[9] Additionally, we reported enantioselective Suzuki couplings[10] and enolate vinylations[11] and arylations[12] that use (*S*)-2-dicyclohexylphosphino-2′-*N*,*N*-(dimethylamino)-1,1′-binaphthyl (**3**) and related phosphines as the chiral supporting ligand (Figure 1). Since monophosphines possessing both axial asymmetry and a stereogenic phosphorus center have not yet been reported, we sought to

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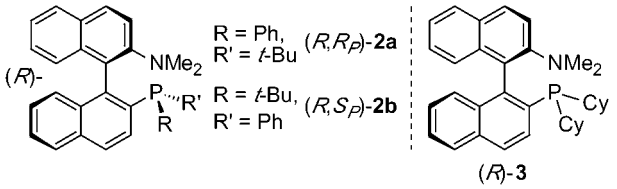
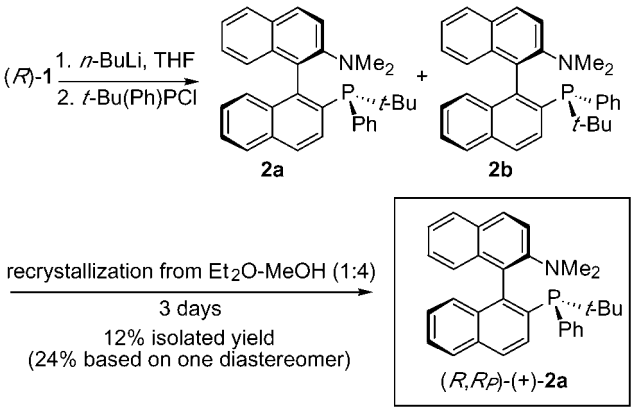


Figure 1. Chiral binaphthyl-substituted monophosphines.

synthesize *P*-chirogenic binaphthyl monophosphines[13] and test their efficacy in enolate vinylation and arylation processes (Figure 1). Furthermore, these ligands may serve as stereochemical probes to assist us in understanding factors important to the design of new ligands.

To synthesize 2-(*tert*-butylphenylphosphino)-2′-(dimethylamino)-1,1′-binaphthyl (**2a** and **2b**), a lithium−halogen exchange protocol with bromide (*R*)-**1**[10] was used. The desired diastereomeric products **2a** and **2b** were formed in good yield. Recrystallization from Et_2O−MeOH (1:2) yielded **2a** and **2b** in a 4:1 ratio, and an additional recrystallization from Et_2O−MeOH (1:4) provided diastereomerically pure (R,R_P)-(+)-**2a** in 12% isolated yield (Scheme 1). The absolute

Scheme 1. Synthesis of (R,R_P)-**2a**



configuration of **2a** was determined by X-ray analysis (Figure 2).

(R,S_P)-**2b** was isolated in diastereomerically pure form as well. The mother liquor resulting from the recrystallization of (R,R_P)-**2a** was stirred with BH_3−THF to furnish phosphine-boranes **4a** and **4b**. The diastereomers were separated by silica gel chromatography. Deprotection of **4b** with triflic

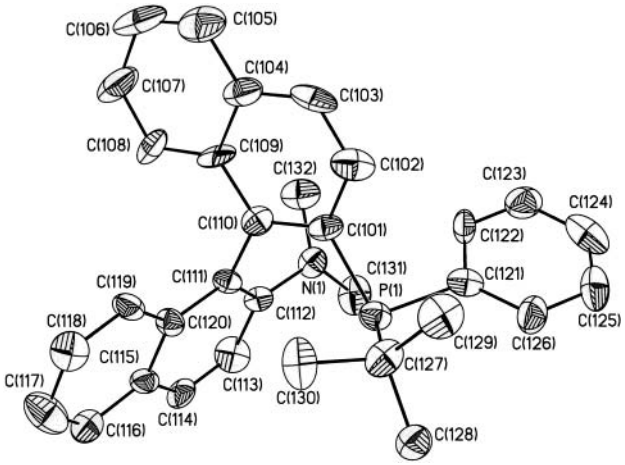
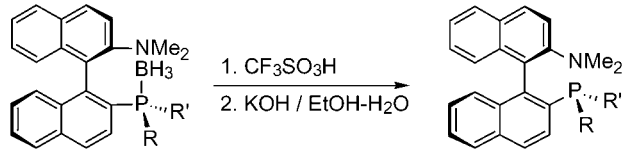


Figure 2. X-ray structure of (R,R_P)-**2a**.

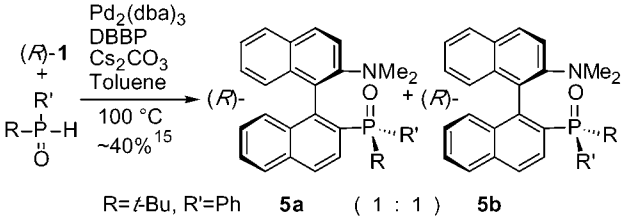
acid[14] proceeded very cleanly (Scheme 2), providing (R,S_P)-(+)-**2b** in 16% overall yield from (*R*)-**1**. Similarly, additional (R,R_P)-(−)-**2a** was obtained in 11% yield from the mother liquor (23% overall yield of **2a**).

Scheme 2. Phosphine-Boranes **4a** and **4b**: Deprotection



An alternative, Pd-based method for the preparation of **2a** and **2b** was also explored.[3,11] The diastereomeric phosphine oxides (**5a** and **5b**) could be prepared by the coupling of (*R*)-**1** and *tert*-butylphenylphosphine oxide using a Pd/bis-(diphenylphosphino)butane (DPPB) catalyst (Scheme 3).[15]

Scheme 3. A Pd-Catalyzed C−P Bond Forming Protocol to Prepare Ligands **2** via Phosphine Oxides **5a** and **5b**



These diastereomeric ligand precursors could be separated using silica gel chromatography. Unfortunately, epimerization at phosphorus occurred upon reduction of **5a** and **5b** using

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(15) Phosphine oxides **5a** and **5b** were not obtained in pure form. Thus, the reported yield is approximate. No attempts optimize this reaction were made since this route proved unsuccessful.

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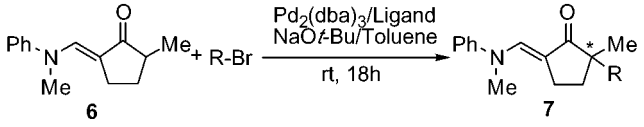
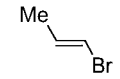
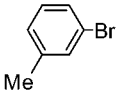
several protocols (e.g., trichlorosilane−R_3N,[6,16] $PhSiH_3$,[17] Ti(O*i*-Pr)$_4$−PMHS,[18] Si_2Cl_6[19]). Thus, this Pd-based route was abandoned.

Ligands **2a** and **2b** were then tested in asymmetric enolate vinylation[11] and arylation[12] reactions. Specifically, the coupling of ketone **6** and *trans*-1-bromopropene or 3-bromotoluene in the presence of 2 mol % Pd/**2a** or Pd/**2b** were studied (Table 1). The catalyst using (R,R_P)-(+)-**2a** as ligand afforded desired vinylation product **7a** in 89% ee and 96% yield, which is similar to the 90% ee observed when dicyclohexylphosphine-substituted ligand **3** was used. Diastereomer (R,S_P)-(−)-**2b** yielded **7a** in low enantiomeric excess (34% ee). In arylations with (R,R_P)-(+)-**2a** or (R,S_P)-(−)-**2b**, enantioselectivities were very low (5−10% ee). It should be noted that **3** provided arylation product **7b** with moderate enantioselectivity (58% ee). These results deviate from a simple double asymmetric scenario where one diastereomeric configuration results in an improved selectivity (matched case) and the other results in a diminished selectivity (mismatched case);[20] at present, we have no simple explanation for these results.

Table 1. Ligands **2a**, **2b**, and **3** in Asymmetric Enolate Vinylation and Arylation Reactions



R-Br	7	(R,R_p)-(+)-**2a**	(R,S_p)-(-)-**2b**	(R)-(-)-**3**
	**7a**	96%[b] 89% ee (S)[c]	91%[b] 34% ee (S)[c]	95%[b] 90% ee (S)[c]
	**7b**	57%[b] 5% ee (S)[c]	83%[b] 10% ee (S)[c]	72%[b] 58% ee (S)[c,d]

[a] Reaction conditions: 1 mol % $Pd_2(dba)_3$, ligand/ Pd = 1.25/1, 1.0 equiv ketone, 2.0 equiv R-Br, 2.0 equiv NaO*t*-Bu, toluene. [b] Isolated yield by silica gel column chromatography. [c] Percent ee determined by HPLC (Daicel CHIRALCEL OD, hexane/*i*PrOH = 9:1, 0.6−1.0 mL/min). [d] 2 mol % $Pd(OAc)_2$ used.

In summary, we have developed a route for the preparation of *P*-chirogenic binaphthyl-substituted monophosphines. The chirogenic phosphine moiety was resolved by use of the axially chiral binaphthyl backbone; the optical resolution of **2a** and **2b** was accomplished by fractional crystallization of the diastereomers. Alternatively, the diastereomeric phosphine-boranes could be separated by silica gel chromatography. The asymmetric vinylation with Pd/**2a** furnished the product with 89% ee. A remarkable difference in the asymmetric vinylation between **2a** and **2b** and ligand **3** indicates that the configuration of the phosphorus center plays an important but complex role in the enantioselectivity-determining step. We are currently examining these ligands in the context of other applications in asymmetric catalysis.

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Supporting Information Available: Experimental procedures and characterization data for ligands **2a** and **2b** and crystal structure data for **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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