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Readily Available Chiral Phosphine−Aminophosphine Ligands for Highly Efficient Rh-Catalyzed Asymmetric Hydrogenation of α-Enol Ester Phosphonates and α-Enamido Phosphonates

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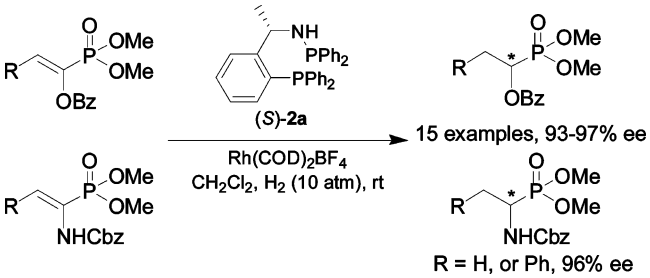

A new class of unsymmetrical hybrid phosphine−aminophosphine ligands has been prepared from commercially available, inexpensive (*S*)-1-phenylethylamine through a concise synthetic procedure. These ligands are not very sensitive to air and moisture, and displayed good enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of various dimethyl α-benzoyloxyethenephosphonates bearing *β*-aryl, *β*-alkyl, and *β*-alkoxy substituents and *N*-benzyloxycarbonyl α-enamido phosphonates, in which up to 97% ee was obtained. A side-by-side comparison study disclosed that these new phosphine−aminophosphine ligands showed better enantioselectivity than BoPhoz ligands.

Metal-catalyzed asymmetric synthesis is an important and challenging area of contemporary synthetic organic chemistry, in which choosing a suitable chiral ligand is a crucial task.[1] In the past decades, a large number of chiral bidentate phosphorus-containing ligands have been developed successfully for various Rh-catalyzed asymmetric hydrogenations, and most of these ligands have a C_2-symmetrical structure or hold two closely related binding sites.[2] C_2-symmetry reduces the number of possible catalyst−substrate arrangements and, consequently, the number of competing reaction pathways by a factor of 2, which can have a beneficial effect on the enantioselectivity.[1a] However, this does not mean that C_2-symmetry is a necessary motif in ligand design, and a highly dissymmetric C_1-symmetry structure will equally fulfill the above conditions. Indeed, many recent examples have clearly demonstrated the value of unsymmetrical hybrid ligand design for obtaining more selective and efficient catalysts, although the number is still significantly less than that of C_2-symmetrical ligands.[2,3]

A combination of phosphine and aminophosphine fragments has proved to be an effective arrangement for the construction of unsymmetrical hybrid bidentate phosphorus ligands. In the past few years, a few examples of phosphine−aminophosphine species based on a chiral ferrocenylethyl backbone have emerged as ligands for highly efficient catalytic asymmetric hydrogenations.[4] These phosphine−aminophosphine ligands have advantages of being highly modular, stable toward air and moisture, and easily optimized by tuning the electronic and steric properties of phosphino and aminophosphino moieties for certain hydrogenation reactions. The first successful phosphine−aminophosphine ligand was known as BoPhoz, reported by Boaz et al. in 2002, which showed excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives, itacontate derivatives, and α-ketoesters.[4a] However, the results in the Rh-catalyzed asymmetric hydrogenation of enamides with these BoPhoz ligands were less satisfactory. Yip and Chan et al. found that using the fluorinated BoPhoz-type ligands could dramatically increase the enantioselectivity in the Rh-catalyzed asymmetric hydrogenation of enamides.[4d] Very recently, Chen et al. have introduced a stereogenic phosphorus atom into Bophoz-type ligands, and the comparative results demonstrate that *P*-chirality improves the enantioselectivity when acting cooperatively with the planar chirality and the chirality at the carbon center.[4g] However, in

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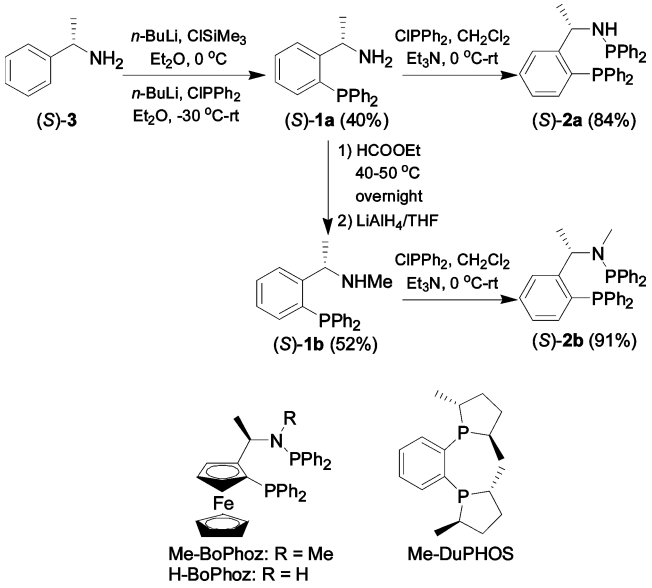
SCHEME 1. Synthesis of New Phosphine-Aminophosphine Ligands (2)

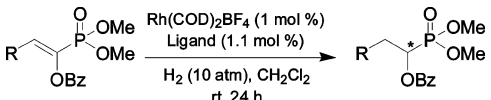


addition to these ferrocene-based ligands, there was no other phosphine−aminophosphine skeleton reported for the use in the asymmetric catalysis, which prompted us to develop new and modular phosphine−aminophosphine ligands for the hydrogenation of some challenging substrates. Our interest was augmented by having access to a chiral amino-phosphine precursor, (*S*)-1-[2-(diphenylphosphino)phenyl]ethylamine [(*S*)-DPPNH$_2$, **1a**], an intermediate in the synthesis of a variety of our recently introduced phosphine−phosphoramidite ligands (PEAPhos) for highly efficient Rh-catalyzed asymmetric hydrogenation.[5a] It can be prepared by a one-step transformation from commercially available, inexpensive chiral (*S*)-1-phenylethylamine. As a result, herein we report a new and readily available chiral phosphine−aminophosphine ligand derived from (*S*)-1-phenylethylamine, which promoted excellent enantioselectivities in the Rh-catalyzed asymmetric hydrogenation of various dimethyl α-benzoyloxyethenephosphonates bearing *β*-aryl, *β*-alkyl, and *β*-alkoxy substituents and dimethyl α-benzyloxycarbonylamino-ethenephosphonates.

New phosphine−aminophosphine ligands were synthesized as outlined in Scheme 1. As we have reported, the intermediates (*S*)-DPPNH$_2$ (**1a**) and (*S*)-DPPNHMe (**1b**) can be easily prepared from commerically available, inexpensive (*S*)-1-phenylethylamine (**3**) through a concise procedure.[5] By the treatment of (*S*)-DPPNH$_2$ (**1a**) and (*S*)-DPPNHMe (**1b**) with 1.1 equiv of ClPPh$_2$ in CH_2Cl_2 at 0 °C in the presence of Et_3N as a scavenger for HCl eliminated, the target phosphine−aminophosphine ligands (*S*)-**2a** and (*S*)-**2b** were obtained in good yields. To our delight, these ligands are not sensitive to air and moisture. Even after being held at ambient temperature in open air for 1 month, these ligands did not show any changes in its ^{1}H and ^{31}P NMR spectra. This salient feature makes these new phosphine−aminophosphine ligands highly practical for general laboratory preparations as well as scale-up operations.

In the first set of experiments, we used the Rh-catalyzed asymmetric hydrogenation of the challenging substrates, *β*-aryl-α-enol ester phosphonates **4a**−**j**, to benchmark the potential of these newly developed phosphine−aminophosphine ligands. The reaction was conducted in CH_2Cl_2 at room temperature under a H_2 pressure of 10 atm in the presence of 1 mol % of catalysts prepared in situ from Rh(COD)$_2$BF$_4$ and 1.1 equiv of chiral ligands, and the results are summarized in Table 1. The reduction of *β*-aryl-α-enol ester phosphonates for the synthesis of biologically and synthetically important chiral α-hydroxy phosphonates is of great interest, since the latter can provide convenient access to important phosphorus analogues of phenylalanine, tyrosine, or DOPA.[6] The catalytic asymmetric hydrogenation of *β*-aryl-α-enol ester phosphonates **4** has proved to be highly difficult, and many famous biphosphine ligands such as DuPHOS, BPE, and MiniPHOS, which are highly efficient for the asymmetric hydrogenation of various functionalized olefins, gave unsatisfactory results.[7] It is only very recently that some unsymmetrical hybrid phosphane−phosphite and phosphine−phosphoramidite ligands were found to show excellent enantioselectivities in this transformation.[8] Therefore, the search for new chiral ligands with properties superior to those of their predecessors for this transformation is still highly desirable. It is found that these

TABLE 1. Rh-Catalyzed Asymmetric Hydrogenation of α-Enol Ester Phosphonates 4 (*β*-Aryl), 5 (*β*-Alkyl), and 6 (*β*-Alkoxy)[a]



entry[a]	ligand	substrate (R)	yield (%)[b]	ee (%) (confign)[c]
1	Me-BoPhoz	**4a**: R = Ph	98	5
2	**2b**	**4a**: R = Ph	97	85 (*S*)
3	H-BoPhoz	**4a**: R = Ph	99	89
4	**2a**	**4a**: R = Ph	98	96 (*S*)
5	Me-DuPHOS	**4a**: R = Ph	96	92
6	**2a**	**4b**: R = *p*-FC$_6$H$_4$	99	96 (+)
7	**2a**	**4c**: R = *p*-ClC$_6$H$_4$	98	94 (+)
8	**2a**	**4d**: R = *p*-BrC$_6$H$_4$	95	97 (+)
9	**2a**	**4e**: R = *p*-NO$_2$C$_6$H$_4$	99	95 (+)
10	**2a**	**4f**: R = *p*-MeOC$_6$H$_4$	99	95 (*S*)
11	**2a**	**4g**: R = *m*-MeOC$_6$H$_4$	98	96 (+)
12	**2a**	**4h**: R = *o*-ClC$_6$H$_4$	98	94 (+)
13	**2a**	**4i**: R = 1-nathphyl	98	95 (+)
14	**2a**	**4j**: R = 2-thienyl	98	95 (+)
15	**2a**	**5a**: R = H	94	93 (*S*)
16	**2a**	**5b**: R = Me	99	96 (*S*)
17	**2a**	**5c**: R = Et	99	96 (*S*)
18	**2a**	**5d**: R = (CH$_2$)$_9$CH$_3$	97	96 (*S*)
19	**2a**	**6a**: R = OMe	99	94 (*S*)
20	**2a**	**6b**: R = OEt	99	93 (+)

[a] All reactions were performed with 1.0 mmol of substrate at room temperature under a H_2 pressure of 10 atm in 4 mL of CH_2Cl_2 for 24 h unless otherwise specified. Substrate/Rh(COD)$_2$BF$_4$/ligand = 1/0.01/0.011. Full conversions were achieved in all reactions. [b] Isolated yields. [c] The ee values were determined by HPLC on a chiral column. The absolute configuration was determined by comparing the sign of optical rotation with reported data or by comparison of chiral HPLC elution order with configurationally defined examples.

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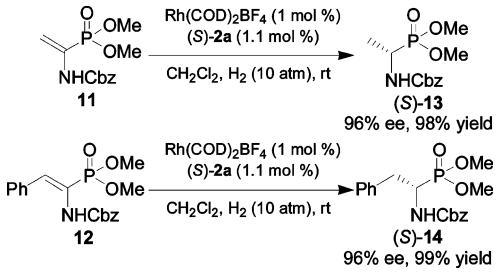
newly developed phosphine−aminophosphine ligands, despite their simple appearances, displayed extraordinarily high enantioselectivities in this rhodium-catalyzed asymmetric hydrogenation in comparison with some other bidenate phosphorus ligands. As shown in Table 1, Me-BoPhoz was ineffective for this hydrogenation in terms of enantioselectivity, although full conversion and 98% isolated yield were achieved (entry 1). In sharp contrast, ligand **2b**, bearing a similar structure to that of Me-BoPhoz, surprisingly gave the promising result of an ee value of up to 85% (entry 2). The presence of an N−H proton in these ligands proved to be advantageous to achieving higher enantioselectivity. Thus, when ligand **2a** with an N−H proton on the amino moiety was applied in the reaction, the enantioselectivity was further increased to 96% ee (entry 4). Under the same hydrogenation conditions, Me-DuPHOS exhibited 92% ee (entry 5). The solvent screening experiment revealed that CH_2Cl_2 was the best reaction media in terms of activity and selectivity.

A wide range of β-aryl-α-enol ester phosphonate substrates were then examined with this methodology. The results indicated that the reaction system had a high tolerance to the substitution pattern and electronic properties of the substrates, and all of substrates were hydrogenated in over 94% ee (entries 6−14). The highest enantioselectivity was obtained in the hydrogenation of β-(*p*-bromophenyl)-α-enol ester phosphonate **4d**, affording the corresponding hydrogenation product in 97% ee (entry 8). The hydrogenation of a variety of β-alkyl- and β-alkoxy-substituted α-enol ester phosphonates **5** and **6** was also investigated under the reaction condition as employed in the hydrogenation of β-aryl-α-enol ester phosphonates. As expected, good enantioselectivities were retained in the hydrogenation of these substrates, indicating high efficiency of this catalytic system (entries 15−20). As reported by Burk et al., the deprotection of the benzoyl group of the hydrogenation product, α-benzoyloxy phosphonate, can be easily performed by treatment with K_2CO_3 in methanol at room temperature to generate the corresponding α-hydroxy phosphonate without loss of optical purity in high yields.[7a]

To further demonstrate the scope and flexibility of the present catalytic system, we decided to apply the phosphine−aminophosphine ligand **2a** to the hydrogenation of α-enamido phosphonates **11** and **12**. The reaction was performed under the optimized conditions (CH_2Cl_2 as the reaction media, H_2 pressure of 10 atm, and room temperature for 24 h) as employed in the hydrogenation of α-enol ester phosphonates. Although catalytic asymmetric hydrogenation of dehydroamino acid derivatives is one of the most studied and widely applied methods for the enantioselective preparation of α-amino acids, there are only a few catalytic hydrogenation methods available to access optically active α-amino phosphonic acid derivatives.[7a,c,9] To our delight, Rh/(*S*)-**2a** complex is also highly efficient for the hydrogenation of this substrate class. As shown in Scheme 2, both dimethyl α-benzyloxycarbonylaminoethenephosphonate (**11**) and dimethyl (*E*)-α-benzyloxycarbonylamino-β-phenylethenephosphonate (**12**) were hydrogenated completely to give the corresponding α-aminophosphonates with 96% ee. This result

SCHEME 2. Rh-Catalyzed Asymmetric Hydrogenation of α-Benzyloxycarbonylaminoethenephosphonates 11 and 12



demonstrates the potential usefulness of the present catalytic system for the preparation of optically active α-aminophosphonates.

In summary, we have developed a new class of readily available, air-stable chiral phosphine−aminophosphine ligands and successfully applied them to the enantioselective hydrogenation of various α-enol ester phosphonates and α-enamido phosphonates. The results indicated that these new phosphine−aminophosphine ligands exhibited superior enantioselectivity to that obtained with BoPhoz analogues. Excellent enantioselectivities (93−97% ee) have been achieved in the hydrogenation of all substrates tested, demonstrating the high potential of these phosphine−aminophosphine ligands in the preparation of optically active α-hydroxyphosphonates and α-aminophosphonates. Studies further investigating the scope of these ligands are currently in progress.

Experimental Section

(*S*)-DPPNH$_2$ **1a** and (*S*)-DPPNHMe **1b** were prepared according to our recently reported method.[5] α-Enol ester phosphonates **4**−**6** and α-enamido phosphonates **11** and **12** were prepared as reported by Burk et al.[7a]

General Procedure for the Synthesis of α-Phenylethylamine-Derived Phosphine−Aminophosphine Ligands 2. Amine-phosphine intermediate (*S*)-DPPNH$_2$ **1a** (305 mg, 1.0 mmol) was dissolved in 4 mL of dried and degassed toluene, to which 0.42 mL of triethylamine (3.0 mmol) was added. The mixture was cooled in an ice−water bath, and then chlorodiphenylphosphine (0.2 mL, 1.1 mmol, 1.1 equiv) was added dropwise. The reaction mixture was allowed to warm to ambient temperature overnight at which point TLC indicated no **1a**. After the precipitate was filtered off, the reaction mixture was concentrated in vacuum. The residue was purified by column chromatography, resulting in 411 mg (84% yield) of (*S*)-**2a** as a colorless viscous oil. $[\alpha]^{25}_D$ −3.6 (0.156, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, J = 6.4 Hz, 3H), 2.37−2.40 (m, 1H), 5.12−5.18 (m, 1H), 6.87−6.88 (m, 1H), 7.13−7.20 (m, 1H), 7.22−7.34 (m, 22H), 7.56−7.58 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.5, 53.2, 127.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 129.4, 131.1, 131.2, 131.3, 133.7, 133.8, 133.9, 134.0, 134.2, 137.0, 142.5, 151.4, 151.6. ^{31}P NMR (162 MHz, $CDCl_3$) δ −16.9, 34.0. HRMS (EI) calcd for $C_{32}H_{29}NP_2$ [M^+] 489.1775, found 489.1783.

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General Hydrogenation Procedure. To a solution of [Rh(COD)$_2$]BF_4 (4.0 mg, 0.01 mmol) in anhydrous and degassed CH_2Cl_2 (2 mL), which was placed in a nitrogen-filled glovebox, was added phosphine−aminophosphine ligand **2a** (5.4 mg, 0.011 mmol). The reaction mixture was stirred at room temperature for 30 min, and then a solution of α-enol ester phosphonate (1.0 mmol) in 2 mL of CH_2Cl_2 was added. The mixture was transferred to a Parr stainless autoclave. The autoclave was purged three times with hydrogen, and maintained a hydrogen pressure of 10 atm. The hydrogenation was performed at room temperature for 24 h. After carefully releasing the hydrogen, the solvent was removed. The residue was filtered through a short SiO_2 column to remove the catalyst. The filtrate was concentrated under reduced pressure, and the enantiomeric excess was determined by HPLC on a chiral column.

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Supporting Information Available: ^1H, ^{31}P, and ^{13}C NMR spectra of ligands **2a**,**b** and the hydrogenation products **7**−**9**, **13**, and **14**, and analysis of ee values of these hydrogenation products. This material is available free of charge via the Internet at http://pubs.acs.org.

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