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Novel phosphine-phosphite and phosphine-phosphinite ligands for highly enantioselective asymmetric hydrogenation

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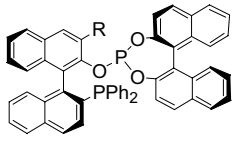
Abstract—Two novel phosphine-phosphite (*S*,*R*)-*o*-BINAPHOS and phosphine-phosphinite (*S*)-*o*-BIPNITE ligands based on *ortho* phenyl substituted (*S*)-BINOL have been synthesized. Extremely high enantioselectivity (over 99% ee in most cases) has been achieved for the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives.

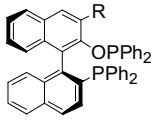
Transition metal complex catalyzed asymmetric hydrogenation has attracted a great deal of interest because of its high efficiency for the preparation of enantiomerically pure compounds.[1] Since the enantioselectivity is dependent on the chiral environment provided by ligands when chelated to the metal centre and subtle changes of electronic and/or steric properties of chiral ligands often have a dramatic influence on the enantioselectivity, the search for novel well designed chiral ligands plays an important role in the field of catalytic asymmetric hydrogenation.[1a]

Chiral bidentate electron-donating phosphines and phosphalanes are the most widely used classes of ligands for catalytic asymmetric hydrogenation.[1a] Recently, phosphine-phosphite and phosphine-phosphinite ligands, which combine phosphorus groups with different electronic properties, have shown their potential utilities in asymmetric hydrogenation.[2] In some cases better enantioselectivities were observed when compared with analogous bisphosphines.[2g] However, the substrate scope is limited and only a few examples have been reported.

Herein we report the design and synthesis of two new (*S*)-BINOL based phosphine-phosphite (*S*,*R*)-*o*-BINAPHOS **1** and phosphine-phosphinite (*S*)-*o*-BIPNITE **2** ligands and their applications in the highly enantioselective hydrogenation of α-dehydroamino acid derivatives.



R=Ph, **1** (*S*,*R*)-*o*-BINAPHOS
R=H, **3** (*S*,*R*)-BINAPHOS



R=Ph, **2** (*S*)-*o*-BIPNITE
R=H, **4** (*S*)-BIPNITE

Ligands bearing a chiral binaphthyl backbone have been widely utilized in a variety of asymmetric reactions. Among them, BINAPHOS **3**[3] and BIPNITE **4**[3g] have been successfully applied to asymmetric hydroformylation. To the best of our knowledge, asymmetric hydrogenation using these two ligands has not been reported yet. Recently, a perfluoroalkyl-substituted BINAPHOS derivative was utilized in the asymmetric hydrogenation of 2-acetamido methyl acrylate and dimethyl itaconate in supercritical carbon dioxide.[2f] Structural analysis of BINAPHOS and BIPNITE revealed that further modifications are required to achieve higher enantioselectivity. Compared with the chelating phosphorus atoms of the phosphine moieties, which are directly attached to the chiral binaphthyl backbone, the phosphorus atoms of the phosphite and phosphinite moieties are one atom further away from the chiral backbone, thus making the asymmetric induction less effective. Moreover, the presence of flexible C–O–P bonds in the phosphinite and phosphite moieties decreases the conformational rigidity. We envisioned that these disadvantages related to C–O–P bonds might be overcome by the introduction of a phenyl substituent onto the *ortho* position of the binaphthyl backbone. Recently we successfully applied

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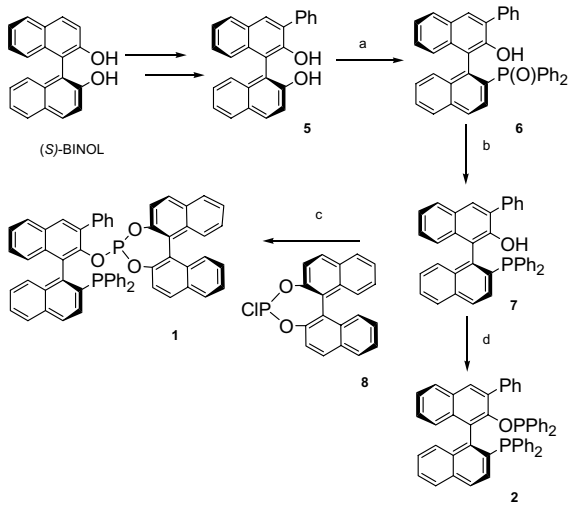
this strategy in the development of several *ortho* substituted biphenyl and binaphthyl ligands for high enantioselective hydrogenations.[4]

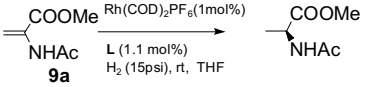
The synthesis of ligands **1** and **2** is outlined in Scheme 1, which follows a similar reaction sequence for the synthesis of BINAPHOS with slight modifications of the reaction conditions.[2e] The starting material, (*S*)-3-phenyl-1,1′-bi-2-naphthol **5** was readily prepared from the commercially available (*S*)-BINOL according to literature procedures.[5] Ditosylation and subsequent Pd-catalyzed monophosphinylation gave the corresponding phosphine oxide, which without further purification, underwent hydrolysis in aqueous NaOH to give the hydroxy phosphine oxide **6** in 68% overall yield. No phosphinylation products were observed when using Ni as catalyst under a variety of reaction conditions. The reduction of the hydroxy phosphine oxide **6** with trichlorosilane $HSiCl_3$ afforded the hydroxy phosphine **7** in 69% yield. The deprotonation of hydroxy phosphine **7** with *n*-BuLi followed by treatment with (*R*)-(1,1′-binaphthalene-2,2′-dioxy)chlorophosphine **8** and diphenylchlorophosphine provided the desired phosphine-phosphite ligand **1**[6] and phosphine-phosphinite ligand **2**[7] in 75% and 70% yields, respectively.

With ligands **1** and **2** in hand, we then examined the Rh-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives. The commercially available α-(*N*-acetamido)acrylate **9a** was used as a standard substrate to screen the reaction conditions. The cationic Rh(I) complexes were prepared in situ by mixing the corresponding Rh precursor with 1.1 molar equiv of the ligand under nitrogen in a suitable solvent. Hydrogenation was performed at room temperature and under 1 atm of hydrogen in the presence of the catalyst. Table 1 shows the results of the hydrogenation of α-(*N*-acetamido)acrylate under optimized reaction conditions. As shown in Table 1, *ortho* phenyl substituted ligands were



Scheme 1. Reagents and conditions: (a) i. Tf_2O, pyridine, rt, ii. $Ph_2P(O)H$, $Pd(OAc)_2$, dppb, DMSO, 100 °C, iii. NaOH, 68% from **5**; (b) $HSiCl_3$, Et_3N, 69%; (c) i. *n*-BuLi, ii. **8**, 75%; (d) i. *n*-BuLi, ii. PPh_2Cl, 70%.

Table 1. The Rh(I)-catalyzed asymmetric hydrogenation of α-(*N*-acetamido)acrylate **9a**[a]



Entry	Substrate	Ligand	Ee %[b]
1	**9a**	**1**	>99
2	**9a**	**2**	>99
3	**9a**	**3**	96
4	**9a**	**4**	77

[a] The reactions were carried out at rt under 15 psi of H_2 for 12 h with 100% conversion. The catalyst was prepared in situ by stirring a solution of $Rh(COD)_2PF_6$ and chiral ligand in 3 mL of THF [substrate 0.5 mmol/[Rh]/**L** 1:0.01:0.011].

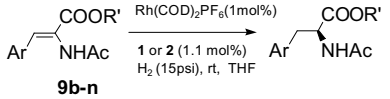
[b] The *S* absolute configuration was assigned by comparison of the specific rotation with reported data. Enantiomeric excesses were determined by chiral GC (Chiralsil-VAL III FSOT).

all better than their corresponding nonsubstituted ligands. A dramatic increase in enantioselectivity was observed when using *ortho* substituted phosphine-phosphinite ligand (*S*)-*o*-BIPNITE **2** (over 99% ee) instead of (*S*)-BIPNITE (77% ee) **4** (entry 2 vs 4). The *ortho* substituted phosphine phosphite ligand **1** (*S*,*R*)-*o*-BINAPHOS is also more effective than the corresponding (*S*,*R*)-BINAPHOS **3**, enantioselectivity increased from 96% ee to over 99% (entry 1 vs 3). These results clearly demonstrate that the introduction of an *ortho* phenyl substituent helps to improve the enantioselectivity.

Table 2 summarizes the results of Rh-catalyzed asymmetric hydrogenation for a variety of trisubstituted α-dehydroamino acid derivatives **9b**–**n**. All the reactions went to completion under the optimized conditions. In most cases, extremely high enantioselectivity (>99% ee) was obtained for both ligands **1** and **2**. Halogen substituted substrates **9c**–**e** (entries 3–8), **9i**–**k** (entries 15–20) were hydrogenated with >99% ee, regardless of the substituent or substitution position. The 2-naphthyl **9f** (entries 9 and 10), **9l** (entries 21 and 22) as well as the *N*-benzoyl **9g** (entries 11 and 12), **9m** (entries 23 and 24) derivatives, were also hydrogenated with high enantioselectivities (>99% ee). The enantioselectivities for 2-thienyl substrate **9n** were slightly lower (95% ee for both ligand **1** and **2**, entries 25 and 26). For the hydrogenation of substrates **9b**,**c** (entries 1–4) and **9i** (entries 15 and 16), ligand **2** afforded slight better enantioselectivity (>99% ee) than ligand **1** (99% ee). It is noteworthy that in nonprotic THF, both ligands could tolerate the acidic substrates (entries 1–12). The enantioselectivity obtained for Rh(I)-catalyzed hydrogenation of α-dehydroamino acid derivatives with these ligands are the best among phosphine-phosphite and phosphine-phosphinite ligands and comparable to the best enantioselectivity previously attained with other bisphosphine or bisphosphalane ligands.[1a]

In conclusion, we have developed two novel phosphine phosphinite and phosphine-phosphite ligands derived from *ortho* phenyl substituted BINOL. These ligands

Table 2. The Rh(I)-catalyzed asymmetric hydrogenation of α-dehydroamino acid derivatives **9b–n**[a]



9b-n

Entry	Substrate	Ar	R′	Ligand	Ee %[b]
1	**9b**	Ph	H	**1**	99
2	**9b**	Ph	H	**2**	>99
3	**9c**	*p*-FPh	H	**1**	99
4	**9c**	*p*-FPh	H	**2**	>99
5	**9d**	*m*-BrPh	H	**1**	>99
6	**9d**	*m*-BrPh	H	**2**	>99
7	**9e**	*o*-ClPh	H	**1**	>99
8	**9e**	*o*-ClPh	H	**2**	>99
9	**9f**	2-Naphthyl	H	**1**	>99
10	**9f**	2-Naphthyl	H	**2**	>99
11	**9g**	Ph	H, *N*-Bz	**1**	>99
12	**9g**	Ph	H, *N*-Bz	**2**	>99
13	**9h**	Ph	CH_3	**1**	>99
14	**9h**	Ph	CH_3	**2**	>99
15	**9i**	*p*-FPh	CH_3	**1**	99
16	**9i**	*p*-FPh	CH_3	**2**	>99
17	**9j**	*m*-BrPh	CH_3	**1**	>99
18	**9j**	*m*-BrPh	CH_3	**2**	>99
19	**9k**	*o*-ClPh	CH_3	**1**	>99
20	**9k**	*o*-ClPh	CH_3	**2**	>99
21	**9l**	2-Naphthyl	CH_3	**1**	>99
22	**9l**	2-Naphthyl	CH_3	**2**	>99
23	**9m**	Ph	CH_3, *N*-Bz	**1**	>99
24	**9m**	Ph	CH_3, *N*-Bz	**2**	>99
25	**9n**	2-Thienyl	CH_3	**1**	95
26	**9n**	2-Thienyl	CH_3	**2**	95

[a] The reactions were carried out at rt under 15 psi of H_2 for 12 h with 100% conversion. The catalyst was prepared in situ by stirring a solution of $Rh(COD)_2PF_6$ and chiral ligand in 3 mL of THF [substrate 0.5 mmol/[Rh]/**L** 1:0.01:0.011].

[b] The *S* absolute configuration was assigned by comparison of the specific rotation with reported data. Enantiomeric excesses were determined by chiral GC (Chiralsil-VAL III FSOT). The enantiomeric excesses of the acids were determined with the corresponding methyl ester.

show excellent enantioselectivity in asymmetric hydrogenation of α-dehydroamino acid derivatives. Further investigations of other asymmetric applications using these two ligands are now underway and will be reported in due course.

Acknowledgements

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6. Spectra data for **1**: $[\alpha]_D^{20} = -193.6$ (*c* 0.5, $CHCl_3$); ^1H NMR (CD_2Cl_2, 300 MHz) δ 8.18–8.02 (m, 3H), 7.90–7.82 (m, 3H), 7.78–7.60 (m, 7H), 7.55–7.02 (m, 18H), 6.99–6.93 (m, 1H), 6.90–6.85 (m, 1H), 6.76 (d, $J = 8.8$ Hz, 1H), 6.64–6.58 (m, 2H), 6.24 (d, $J = 8.8$ Hz, 1H), 5.84 (d, $J = 8.8$ Hz, 1H) ppm; ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 148.07, 148.01, 147.02, 146.25, 146.17, 141.64, 141.19, 138.92, 137.88, 137.71, 137.06, 136.89, 135.79, 135.75, 134.53, 134.26, 133.41, 133.17, 132.75, 131.31, 131.27, 131.07, 130.26, 129.48, 128.93, 128.78, 128.71, 128.61, 128.51, 128.41, 128.21, 128.13, 128.05, 128.92, 127.47, 127.05, 126.99, 126.57, 126.53, 126.41, 126.24, 125.69, 125.31, 125.13, 122.25 ppm; ^{31}P NMR (CD_2Cl_2, 146 MHz) δ 145.2 (d, $J_{pp} = 21.1$ Hz), −12.9 (d, $J_{pp} = 21.1$ Hz) ppm; HRMS calculated for $C_{58}H_{39}O_3P_2$ (MH^+): 845.2369, found 845.2369.
7. Spectra data for **2**: $[\alpha]_D^{20} = +73.0$ (*c* 0.5, CH_3Cl); ^1H NMR (CD_2Cl_2, 300 MHz) δ 7.94 (s, 1H), 7.88 (d, $J = 8.1$ Hz, 1H), 7.69 (d, $J = 8.5$ Hz, 1H), 7.62–7.56 (m, 3H), 7.49–7.44 (m, 6H), 7.36–6.85 (m, 17H), 6.79–6.67 (m, 5H), 6.55–6.48 (m, 2H) ppm; ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 152.66, 152.55, 142.60, 142.43, 142.39, 142.15, 141.97, 141.89, 138.71, 138.67, 138.54, 138.13, 135.91, 134.80, 134.53, 133.98, 133.71, 133.44, 131.18, 130.65, 129.63, 129.37, 129.30, 129.04, 128.96, 128.86, 128.77, 128.68, 128.45, 128.36, 128.27, 127.95, 127.84, 127.73, 127.60, 127.50, 127.49, 126.77, 126.33, 125.16 ppm; ^{31}P NMR (CD_2Cl_2, 146 MHz) δ 114.2 (d, $J_{pp} = 5.2$ Hz), −12.4 (d, $J_{pp} = 4.7$ Hz) ppm; HRMS calculated for $C_{50}H_{37}OP_2$ (MH^+): 715.2289, found 715.2314.