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# A new chiral 2-sulfonylamino-2′-phosphino-1,1′-binaphthyl ligand for highly enantioselective copper-catalyzed conjugate addition of diethylzinc to benzylideneacetones

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**Abstract**—A new axially chiral phosphine–sulfonamide ligand was prepared via a chiral component (*R*)-2-amino-2′-diphenylphosphinyl-1,1′-binaphthyl, which was conveniently synthesized through a new route involving hydrolysis of (*R*)-2-cyano-2′-phosphinyl-1,1′-binaphthyl followed by Hofmann rearrangement of the amide group. The new ligand was found to be very efficient in copper-catalyzed enantioselective conjugate addition of diethylzinc to acyclic enones such as benzylideneacetones, providing very high enantioselectivity up to 99% ee.


The enantioselective conjugate addition of organometallics to α,β-unsaturated carbonyl and related compounds is an important strategy for the construction of chiral carbon–carbon bonds in the synthesis of optically pure compounds including physiologically active ones.[1] For practical and theoretical purposes the development of chiral catalyst systems has been widely investigated, and several efficient catalysts using copper complexes of chiral ligands have been developed in the reaction of dialkylzinc with enones.[1,2] Several types of chiral phosphorous ligands, such as phosphoramidites,[3] phosphites,[4] P,N ligands,[5] and some others,[6] have been found to be highly efficient (>90% ee) in copper-catalyzed conjugate addition of diethylzinc to cyclic enones. However, only a few types of ligands are efficient for the reaction of acyclic enones such as chalcones and benzylideneacetones.[3c,d,5b,e,f,i–m,6c]

Several years ago, we prepared amidine **1a** and imine **1b** derivatives of a chiral component (*S*)-2-(amino)alkylphosphine and found that they are useful ligands in palladium-catalyzed enantioselective allylic alkylation[7] but not efficient in copper-catalyzed conjugate addition of diethylzinc.[5c] As an extension of the utility of the chiral component we developed novel chiral P,N ligands **3**, **4** by condensation of the component with 2-pyridinecarboxaldehyde and 2-picolinic acid or their analogs,[5c,g] and found that the 2-pyridylmethyleneamino derivatives **3** are the most efficient ligands in copper-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one, providing high enantioselectivity up to 91–95% ee. However, these ligands could not give high enantioselectivity in the reaction of acyclic enones such as chalcone (71% ee) and benzylideneacetone (48% ee) (Fig. 1).

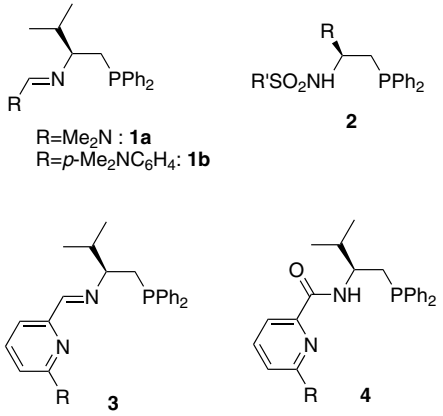


**Figure 1.** P,N ligands derived from β-aminoalkylphosphine.

*Keywords*: Chiral binaphthyl ligand; Copper catalyst; Conjugate addition; Enantioselectivity; Enones.
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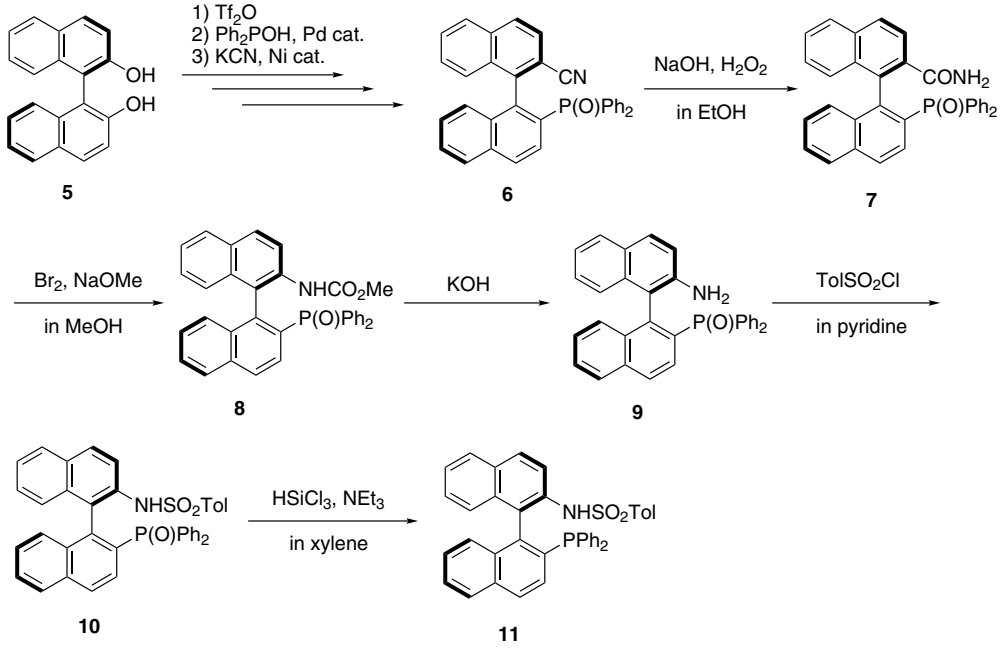
On the other hand, *N*-monosubstituted sulfonamide was first found in 1996 to accelerate the copper-catalyzed conjugate addition of dialkylzinc to enones,[8] and chiral mono- or bis-sulfonamides were employed as the ligands for the copper-catalyzed enantioselective conjugate addition, though the enantioselectivity was low (~32% or ~28% ee).[9a,b] A series of efficient chiral ligands, *N*-alkyl-β-(*N*′-salicylideneamino)alkanesulfonamides, was later developed by high-throughput screening of a parallel library.[6a] In 1990 we developed a novel type of chiral ligands, 2-(sulfonylamino)alkylphosphines **2**, which were found to be efficient in enantioselective palladium-catalyzed hydrosilylation and Heck-type hydroarylation of olefins.[10] In a previous symposium,[5g] we reported that *N*-alkylsulfonyl derivatives **2** of the chiral aminophosphine component are effective for the copper-catalyzed conjugate addition to a cyclic enone, giving good enantioselectivity. Very recently, an analogous trifluoromethylsulfonyl derivative of a 2-(amino)alkylphosphine was reported to be a highly efficient ligand for copper-catalyzed conjugate addition to cyclic enones.[5h] However, the *N*-sulfonyl ligands **2** derived from (*S*)-2-(amino)alkylphosphines could not give high enantioselectivity in the reaction of acyclic enones such as chalcone and benzylideneacetone.

We then envisioned that the introduction of sulfonyl groups to other chiral aminophosphine components might be useful for developing more efficient ligands in the metal-catalyzed conjugate addition to acyclic enones. Since an axially chiral binaphthyl skeleton has been well documented to construct an effective chiral template, chiral 1,1′-binaphthyl derivatives bearing both a 2-sulfonylamino group and a 2′-diphenylphosphino group were designed as efficient ligands.

The preparation of an axially chiral aminophosphine component, (*R*)-2-amino-2′-diphenylphosphino-1,1′-binaphthyl (MAP), was first reported by Vyskocil et al.[11] starting from (*R*)-2-amino-2′-hydroxy-1,1′-binaphthyl (NOBIN). (*R*)- and (*S*)-NOBIN were prepared by coupling of 2-naphthylamine and 2-naphthol with $CuCl_2$ in the presence of (*R*)-1-phenylethylamine followed by repeated diastereoselective crystallization,[12] or obtained from racemic NOBIN by resolution with (1*S*)- or (1*R*)-camphor-10-sulfonic acid.[13] Later, Singer and Buchwald reported the preparation of (*R*)-NOBIN via palladium-catalyzed amination of *O*-protected (*R*)-BINOL monotriflate with benzophenone imine.[14] (*S*)-NOBIN was recently prepared via (*S*)-*O*-methyl NOBIN obtained by Curtius rearrangement of (*S*)-2′-methoxy-1,1′-binaphthyl-2-carboxylic acid, which was synthesized by diastereoselective nucleophilic aromatic substitution of a (−)-menthyl naphthalenecarboxylate with a Grignard reagent.[15] However, there are several drawbacks to the above procedures for the preparation of enantiopure MAP via NOBIN such as low overall yield and the necessity for tedious optical resolution, and, therefore, the development of new efficient methodology is still desired. We report herein a convenient preparation of an *N*-sulfonyl derivative **11** of the chiral binaphthyl component (*R*)-MAP from (*R*)-BINOL **5** and its use as an efficient ligand in copper-catalyzed enantioselective conjugate addition of diethylzinc to acyclic enones such as benzylideneacetone and its analogs.

The synthetic route of the new P,N-type ligand **11** is described in Scheme 1. The chiral component, (*R*)-2-amino-2′-dipenylphosphinyl-1,1′-binaphthyl **9** was conveniently prepared via a known compound, (*R*)-2-cyano-2′-diphenylphosphinyl-1,1′-binaphthyl **6**. According to the procedure of Hayashi and co-workers,[16] the triflate of (*R*)-1,1′-bi-2-naphthol (BINOL) **5** was catalyti-




**Scheme 1.** Synthesis of a phosphine–sulfonamide ligand **11**.

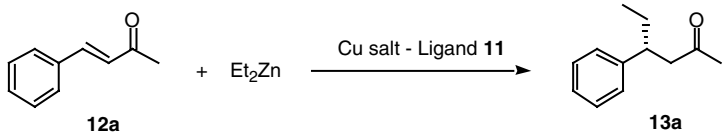
cally converted to a monophosphinylation product, which was allowed to react with potassium cyanide in the presence of a nickel catalyst, affording (*R*)-2-cyano-2′-diphenylphosphinyl-1,1′-binaphthyl **6** in high overall yield. Several attempts to achieve acid or alkaline hydrolysis of the cyano compound **6** with sulfuric acid or sodium hydroxide failed. However, we were able to accomplish the hydrolysis of **6** to the corresponding amide **7** in 96% yield by prolonged heating with alkaline hydrogen peroxide in ethanol. Modified Hofmann rearrangement[17] of the amide **7** with bromine and sodium methoxide in methanol yielded the methoxycarbamoyl derivative **8** (92%),[18] which was converted to the corresponding amine derivative **9** (97%) by alkaline hydrolysis. *N*-Sulfonylation with *p*-toluenesulfonyl chloride in pyridine gave the 2-tosylamino-2′-phosphinyl derivative **10** (90%).[19] The phosphinyl group of **10** was reduced with trichlorosilane to afford the aimed P,N-type ligand, (*R*)-2-*p*-tosylamino-2′-diphenylphosphino-1,1′-binaphthyl **11** (97%).[20]

The copper-catalyzed enantioselective conjugate addition of diethylzinc to benzylideneacetone **12a** was chosen as a model reaction for evaluation of the capability of the newly prepared chiral ligand **11**.[21] The effects of different reaction parameters were investigated for solvents, temperatures, amounts of copper salt and **11**, and different copper salts. The results are summarized in Table 1. High ee values (96–99% ee) were obtained by using the ligand **11** (5 mol%) and copper triflate (2 mol%) at 0 °C in all the solvents (toluene, dichloromethane, and ether) used.[22] Even when the amount of copper triflate was reduced to 0.5 mol% (ligand 1 mol%), the high enantioselectivity was maintained along with good yield of the product. The ee values at 0 °C were generally better than those at −20 and 20 °C. Some different copper salts also showed high enantioselectivity at 0 °C. To the best of our knowledge, the enantioselectivity of up to 96–99% ee thus obtained with ligand **11** is the highest among the reported data for the enantioselective conjugate addition of diethylzinc to benzylideneacetone.

As an extension of the substrate, several *para*-, *meta*-, and *ortho*-substituted benzylideneacetones **12b–f** were selected and allowed to react with diethylzinc at 0 °C in toluene in the presence of copper triflate (0.5 mol%) and ligand **11** (1 mol%). The results are summarized in Table 2. The reactions with substituted benzylideneacetones **12b–e** afforded the corresponding products in high enantioselectivity (95–97% ee), though the ee with a methylenedioxy derivative **12f** was somewhat lower.[23]

In conclusion, we have synthesized a new chiral binaphthyl ligand bearing both a phosphino group and a sulfonylamino group through a convenient route involving hydrolysis and Hofmann rearrangement. We also presented an application of the new ligand to the copper-catalyzed enantioselective conjugate addition of diethylzinc to an acyclic enone, benzylideneacetone, where very high enantioselectivity (94–99% ee) was obtained even under various reaction conditions (solvent: toluene, dichloromethane, ether; temperature: −20 to 20 °C; Cu: 0.5–2 mol%). Several substituted benzylideneacetones were also converted to the corresponding conjugate addition products with high enantioselectivity (84–98% ee). Further investigation is in progress to reveal the scope and utility of the ligand and some other ligands derived from the synthetic intermediates, and to apply the present reaction to the synthesis of physiologically active compounds.

**Table 1.** Copper-catalyzed enantioselective conjugate addition of diethylzinc to benzylideneacetone **12a**[a]

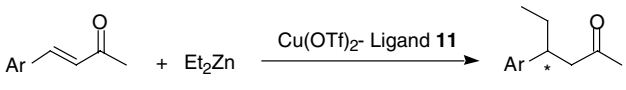



**12a** **13a**

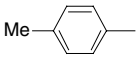
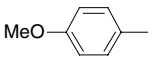
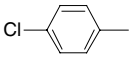
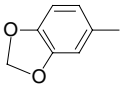
| Entry | Cu salt (mol%) | Ligand **11**/Cu | Solvent | Temp. (°C) | Yield (%)[b] | ee (%)[b] | Config.[c] |
|---|---|---|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ (2) | 2.5:1 | Toluene | 0 | 33 | 99 | *R* |
| 2 | $Cu(OTf)_2$ (2) | 2.5:1 | $CH_2Cl_2$ | 0 | 72 | 98 | *R* |
| 3 | $Cu(OTf)_2$ (2) | 2.5:1 | $Et_2O$ | 0 | 71 | 96 | *R* |
| 4 | $Cu(OTf)_2$ (2) | 2.5:1 | Toluene | 20 | 62 | 94 | *R* |
| 5 | $Cu(OTf)_2$ (2) | 2.5:1 | Toluene | −20 | 32 | 94 | *R* |
| 6 | $Cu(OTf)_2$ (1) | 1.5:1 | Toluene | 0 | 71 | 96 | *R* |
| 7 | $Cu(OTf)_2$ (0.5) | 2:1 | Toluene | 0 | 80 | 97 | *R* |
| 8 | $(CuOTf)_2$·Tol (1) | 2.5:1 | Toluene | 0 | 80 | 96 | *R* |
| 9 | $(CuOTf)_2$·Tol (1) | 1.5:1 | Toluene | 0 | 55 | 97 | *R* |
| 10 | $(CuOTf)_2$·Tol (1) | 2.5:1 | Toluene | −20 | 43 | 96 | *R* |
| 11 | $Cu(OAc)_2·H_2O$ (2) | 2.5:1 | Toluene | 0 | 74 | 96 | *R* |
| 12 | $Cu(OAc)_2·H_2O$ (2) | 1.5:1 | Toluene | 0 | 61 | 97 | *R* |
| 13 | $Cu(OAc)_2·H_2O$ (2) | 2.5:1 | Toluene | −20 | 36 | 94 | *R* |

[a] *Reaction conditions*: benzylideneacetone **12a** (0.5 mmol), diethylzinc (0.75 mmol, 0.75 mL of 1 M hexane solution); solvent (3 mL); 5 h.
[b] Yield and ee determined by GC (capillary column: Supelco γ-DEX 225) using *n*-dodecane as an internal standard.
[c] The absolute configuration was assigned by comparison of specific rotation data.

**Table 2.** Copper-catalyzed enantioselective conjugate addition of diethylzinc to benzylideneacetones **12a–f**[a]




**12a-f** **13a-f**

| Entry | Ar | Product | Yield (%)[b] | ee (%)[c] | Config.[e] |
|---|---|---|---|---|---|
| 1 |  | **13a** | 63 | 96 | *R* |
| 2 |  | **13b** | 50 | 95 | –[f] |
| 3 |  | **13c** | 44 | 96 | –[f] |
| 4 |  | **13d** | 50 | 97 | –[f] |
| 5 |  | **13e** | 51 | 98 | +[f] |
| 6 |  | **13f** | 49 | 84[d] | –[f] |

[a] *Reaction conditions*: $Cu(OTf)_2$ (0.005 mmol), **11** (0.01 mmol), **12** (1.0 mmol), $Et_2Zn$ (1.5 mmol, 1.5 mL of 1 M hexane solution); toluene (6 mL); 0 °C; 5 h.
[b] Yield based on the isolated product.
[c] ee determined by GC using a γ-DEX 225 column.
[d] ee determined by HPLC using a Chiralcel OJ column.
[e] The absolute configuration was assigned by comparison of specific rotation data.
[f] Sign of the optical rotation of addition product.

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18. (*R*)-2-*N*-Carbomethoxyamino-2′-diphenylphosphinyl-1,1′-binaphthyl **8**: To a methanol (1 mL) solution of (*R*)-2-carbamoyl-2′-diphenylphosphinyl-1,1′-binaphthyl **7** (137 mg, 0.28 mmol), which was prepared by hydrolysis of (*R*)-2-cyano-2′-diphenylphosphinyl-1,1′-binaphthyl **6** with alkaline hydrogen peroxide in ethanol at 50–60 °C for 1 d, was added a solution of sodium methoxide in methanol (1 M solution, 0.82 mL, 0.82 mmol). The methanol solution was ice-cooled with stirring and a methanol solution of bromine (0.5 M, 0.55 mL, 0.28 mmol) was added dropwise. The mixture was gradually heated up to 65 °C during 1 h and kept at the same temperature for 15 min. The solvent was removed by evaporation and saturated $NaHCO_3$ was added. The mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (AcOEt) to give **8** (134 mg, 92%) as a solid. $[\alpha]_D^{24}$ −135.8 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 3.58 (s, 3H), 6.49–7.97 (m, 22H), 8.69 (br s, 1H); IR ($CHCl_3$) 2996, 1725, 1508 $cm^{-1}$; FAB-MS *m*/*z* 528 ($[MH]^+$). Anal. Calcd for $C_{34}H_{26}NO_3P{\cdot}H_2O$: C, 74.85; H, 5.17; N, 2.57. Found: C, 74.72; H, 4.95; N, 2.22.
19. (*R*)-2-*p*-Tolylsulfonylamino-2′-diphenylphosphinyl-1,1′-binaphthyl **10**: To a dichloromethane (3.0 mL) solution of (*R*)-2-amino-2′-diphenylphosphinyl-1,1′-binaphthyl **9** (85 mg, 0.18 mmol), which was prepared by alkaline hydrolysis of **8**, was added pyridine (0.1 mL), and cooled in an ice-bath. To the cooled solution was added a pyridine (0.1 mL) solution of *p*-toluenesulfonyl chloride (69 mg, 0.36 mmol) and the mixture was stirred for 3 h. The reaction mixture was acidified with hydrochloric acid (1 M) and extracted with AcOEt (30 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (toluene/AcOEt = 20/1) to yield **10** (102 mg, 90%) as a solid. $[\alpha]_D^{26}$ −28.6 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 2.16 (s, 3H), 8.01–6.38 (m, 26H), 10.07 (s, 1H); IR ($CHCl_3$) 1159 $cm^{-1}$; FAB-MS *m*/*z* 624 ($[MH]^+$). Anal. Calcd for $C_{39}H_{30}NO_3PS{\cdot}H_2O$: C, 72.99; H, 5.03; N, 2.18. Found: C, 72.89; H, 4.87; N, 1.81.
20. (*R*)-2-*p*-Tolylsulfonylamino-2′-diphenylphosphino-1,1′-binaphthyl **11**: To a cooled xylene (5.0 mL) solution of **10** (102 mg, 0.16 mmol) in a pressure tube was added triethylamine (0.46 mL, 3.27 mmol) and trichlorosilane (0.08 mL, 0.82 mmol). After ventilation with Ar, the mixture was stirred and heated at 130 °C for 5 h. The reaction mixture was cooled and 30% NaOH was added. The mixture was heated at 60 °C for 0.5 h under Ar. After cooling to room temperature, the mixture was extracted with AcOEt. The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (toluene) to afford **11** (96 mg, 97%) as a white solid. $[\alpha]_D^{25}$ −21.4 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) $\delta$ 2.30 (s, 3H), 6.06 (s, 1H), 6.49–7.99 (m, 26H); IR ($CHCl_3$) 1163 $cm^{-1}$; FAB-MS *m*/*z* 608 ($[MH]^+$). Anal. Calcd for $C_{39}H_{30}NO_2PS$: C, 77.08; H, 4.98; N, 2.30. Found: C, 76.41 ; H, 5.24; N, 2.10.
21. Typical procedure for the copper-catalyzed conjugate addition: The reaction was carried out under an argon atmosphere. The catalyst solution was prepared in situ by stirring 0.5 mol% of $Cu(OTf)_2$ (0.005 mmol) and 1 mol% of ligand **11** (0.01 mmol) in dry, degassed toluene (3 mL) for 30 min. The catalyst solution was cooled to 0 °C and a solution of benzylideneacetone **12** (1 mmol) in toluene (3 mL) was added followed by addition of a solution of diethylzinc in hexane (1.0 M, 1.5 mL, 1.5 mmol) and *n*-dodecane (0.5 mmol) as an internal standard. After stirring for 5 h at 0 °C, the reaction mixture was quenched with 1 N aqueous HCl and extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by silica gel column chromatography (hexane/AcOEt = 3/1) to give the corresponding 1,4-addition product, 4-phenylhexan-2-one **13**. The yields and the ee values of the addition products were determined by GC analysis (before or after purification) with a chiral capillary column, Superco γ-DEX 225 or HPLC analysis with a chiral column, Daicel Chiralcel OJ.
22. The highest ee value was obtained in toluene, though it was not clearly explained that the yield of the product in toluene was lower than those obtained in other solvents or by using smaller molar ratios of the ligand to copper triflate. The lower yield may be rationalized by the

explanation that a considerable part of copper complexes (higher ratios of ligand to copper: 2/1 or/and more) formed are less active (aggregated, less soluble in toluene; less active as a catalyst for the conjugate addition but active for by-reactions).

23. For further evaluation of the ligand, the reaction of a representative cyclic enone, 2-cyclohexen-1-one with diethylzinc was also carried out under similar conditions, affording (*R*)-3-ethylcyclohexan-1-one in lower selectivity (52% ee).