

Copper-catalyzed enantioselective conjugate addition of diethylzinc using axially chiral aminoethoxy-phosphine ligands

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Received 18 January 2007; revised 9 February 2007; accepted 16 February 2007

Available online 1 March 2007

Abstract—New axially chiral P,O,N-type ligands bearing both a diphenylphosphino group and 2-(dialkylamino)ethoxy (or 2-pyridylmethoxy) groups were designed and prepared along with P,O,O-type ligands by employing an easily available chiral component, (*R*)-2-hydroxy-2'-diphenylphosphinyl-1,1'-binaphthyl. Among the ligands the simplest P,O,N-type one bearing a 2-(dimethylamino)ethoxy group was found to be the most efficient in copper-catalyzed enantioselective conjugate addition of diethylzinc to a cyclic enone, 2-cyclohexen-1-one, providing high enantioselectivity up to 99% ee.

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The enantioselective conjugate addition of organometallic reagents to α,β -unsaturated carbonyl and related compounds constitutes an important synthetic method for chiral carbon–carbon bond formation in high enantioselectivity. The development of chiral catalyst systems has been extensively investigated, and various efficient catalysts using copper complexes of chiral ligands have been developed in the reaction of dialkylzinc with enones.¹ Several types of chiral phosphorus ligands, such as phosphoramidites, phosphites, P, N ligands, and some others, have been found to be highly efficient (>90% ee) in copper-catalyzed conjugate addition of diethylzinc to cyclic enones, linear enones, or/and some electron-deficient olefins. The chiral source of the efficient ligands is mainly composed of a binaphthyl skeleton. The phosphoramidites and phosphites (including a special example, P,N-type ligand **1**²) were derived from 1,1'-bi-(2-naphthol), and P,N ligands **2** and **3**^{3,4} were from 2-amino-2'-hydroxy-1,1'-binaphthyl or its analogs. Recently, we developed an atropisomeric sulfonamide-type P,N ligand **4**, which was found to be very efficient in copper-catalyzed enantioselective conjugate addition of diethylzinc to linear enones, benzylideneacetones.⁵ Although the atropisomeric P,N ligands **2–4** were very efficient in terms of the enantioselectivity especially for linear enones, there was a major drawback that many reaction steps were needed for their preparation from naphthol or binaphthol (Fig. 1).

We therefore planned to develop a new efficient type of ligand **5** by using (*R*)-2-diphenylphosphinyl-2'-hydroxy-1,1'-binaphthyl **6** as a chiral component which is conveniently available via three steps from binaphthol (*O,O'*-ditriflation followed by diphenylphosphination and hydrolysis).⁶ Since a hard bidentate moiety such as a linear O–C–C–N (or O–C–C–O) framework will make a stable chelation with a hard metal such as zinc or magnesium, forming a favorable rigid environment, we envisioned that a ligand bearing both an O–C–C–N (or O–C–C–O) framework and a phosphino group would be efficient in copper-catalyzed enantioselective conjugate addition of dialkylzinc.

Starting from (*R*)-2-diphenylphosphinyl-2'-hydroxy-1,1'-binaphthyl **6**, ligands **5a** (P,OH-type) and **5b** (MOP) and a ligand **5c** (P,O,O-type) were prepared according to a reported procedure.⁶ A new P,O,O-type ligand **5d** bearing a 2-(methoxy)ethoxy group was also prepared similarly. New hetero-hybrid P,O,N-type ligands **5e–i**⁷ were conveniently prepared in good overall yields by O-alkylation with 2-chloroethylamines or 2-(chloromethyl)pyridines in the presence of potassium carbonate (or O-carbamoylmethylation with 2-bromoacetamides in the presence of potassium carbonate and reduction with borane (in case of **5f,g**)) followed by reduction with trichlorosilane (Scheme 1).

First asymmetric copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexen-1-one was chosen as a model reaction for evaluation of P,O,O-type ligands **5c,d** along with P,O-type ligands, **5a** and MOP **5b**. The reaction

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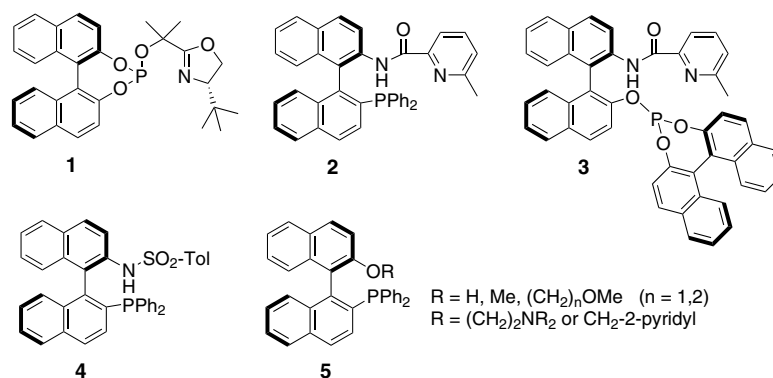
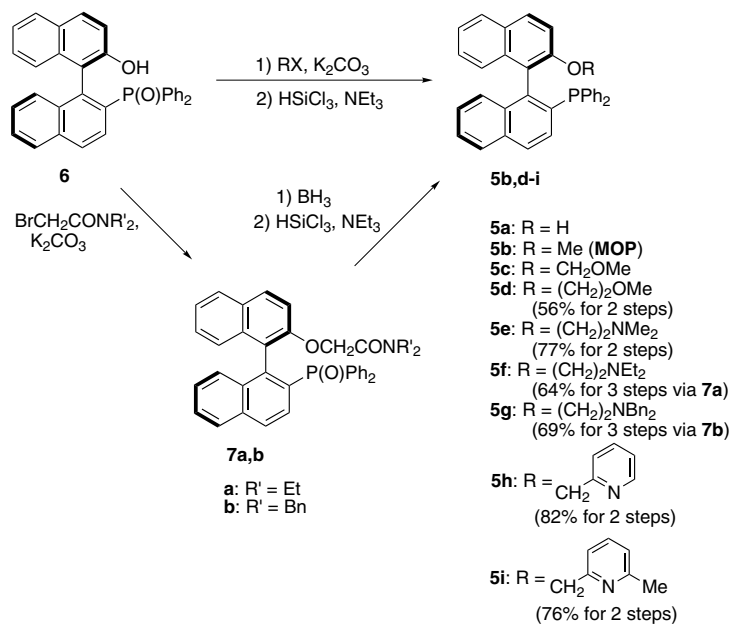


Figure 1. Binaphthyl P,N-type ligands 1–5.



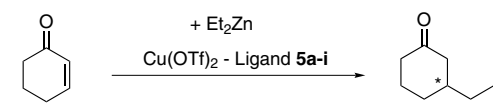
Scheme 1. Synthesis of (*R*)-binaphthyl P,O,O- and P,O,N-type ligands 5.

was carried out with 1 mol % of copper(II) triflate and 2 mol % of the ligand at 0 °C in dichloromethane. The results are described in Table 1 (entries 1–4). All the reactions except with **5d** proceeded completely after 5 h, but high enantioselectivity was not attained with these P,O,(O)-type ligands. It is interesting that ligands **5b,c** bearing a MeO group and a MOMO group showed a reverse selectivity (*S*) in comparison with the *R*-selectivity with **5a**. Although this phenomenon cannot be explained clearly, rigid bonding of the ligand to a zinc atom may induce the enantioselectivity to be *R*. Next P,O,N-type ligands **5e–g** were also evaluated under the same reaction conditions (entries 5–7). The simplest ligand **5e** showed the best enantioselectivity (94% ee, *R*). When the bulkiness of the N-alkyl groups increased, the enantioselectivity decreased dramatically along with the reactivity. Ligand **5h** bearing a 2-pyridylmethoxy group also showed high enantioselectivity, but the selectivity with **5g** bearing a 6-methyl-2-pyridylmethoxy group dropped dramatically (entries 8 and 9). All the results showed that the bulkiness of the hard hetero-functional groups in the ligands has significant steric effects

(usually unfavorable effects) on the enantioselectivity and the catalytic activity.

By employing the best ligand **5e** the effects of different reaction parameters were investigated for solvents, temperatures, amounts of ligand, and different copper salts. The results are summarized in Table 2. Among the solvents used (entries 1–3), dichloromethane was found to be better than others (toluene and ether). When the amount of the ligand was reduced to 1.5 mol %, the enantioselectivity was decreased (entry 3, in parentheses). The highest enantioselectivity was attained at –5 °C. Among relatively broad temperatures from rt to –5 °C, high enantioselectivity (94–99% ee) was maintained, though the selectivity was considerably dropped to 73% ee at –20 °C (entry 6). In place of copper(II) triflate, copper(I) triflate was also employed efficiently (entry 7), but copper(I) thiophene-2-carboxylate was found to be less efficient in all the solvents used (entries 8–10).

We also examined the reaction of benzylideneacetone as a typical linear enone under the present conditions with

Table 1. Copper-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one^a


Entry	Ligand	Conv. ^b (%)	ee ^c (%)	Config. ^d
1	5a	100	41	<i>R</i>
2	5b	100	44	<i>S</i>
3	5c	100	33	<i>S</i>
4	5d	72	8	<i>R</i>
5	5e	100	94	<i>R</i>
6	5f	41	28	<i>R</i>
7	5g	48	7	<i>R</i>
8	5h	100	84	<i>R</i>
9	5i	98	6	<i>R</i>

^a Reaction conditions: Cu(OTf)₂ (0.005 mmol), **5** (0.01 mmol), 2-cyclohexen-1-one (0.5 mmol), Et₂Zn (0.75 mmol, 0.75 mL of 1 M hexane solution); CH₂Cl₂ (1.5 mL); 0 °C; 5 h.

^b Conversion determined by GC.

^c Ee determined by GC using a γ-DEX 225 column.

^d The absolute configuration was assigned by GC analysis in comparison with an authentic sample.

Table 2. Screening of reaction conditions for copper-catalyzed conjugate addition using ligand **5e**^a

Entry	Cu salt	Solvent	Temp (°C)	Conv. (%)	ee ^b (%)
1	Cu(OTf) ₂	Toluene	0	100	89
2	Cu(OTf) ₂	Et ₂ O	0	100	88
3	Cu(OTf) ₂	CH ₂ Cl ₂	0	100	94 (87) ^c
4	Cu(OTf) ₂	CH ₂ Cl ₂	rt	100	94
5	Cu(OTf) ₂	CH ₂ Cl ₂	-5	100	99
6	Cu(OTf) ₂	CH ₂ Cl ₂	-20	94	73
7	(CuOTf) ₂ ·tol	CH ₂ Cl ₂	0	100	96
8	CuTC ^d	CH ₂ Cl ₂	0	100	86
9	CuTC	Toluene	0	100	77
10	CuTC	Et ₂ O	0	100	75

^a Under the similar reaction conditions described in a footnote of Table 1 (except solvent, temp, or copper salt).

^b The absolute configuration of all the products was *R*.

^c Compound **5e**: 1.5 mol %.

^d CuTC: copper(I) thiophene-2-carboxylate.

ligand **5e**. However, the enantioselectivity was modest (49% ee).

In conclusion, we have developed several new P,O,N-type ligands and found that the simplest one bearing an *O*-(dimethylamino)ethyl group is efficient for a copper-catalyzed enantioselective conjugate addition to 2-cyclohexen-1-one.⁸

References and notes

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- Preparation of a typical ligand **5e**: To a mixture of (*R*)-2'-(diphenylphosphoryl)-1,1'-binaphthyl-2-ol (**6**) (120 mg, 0.26 mmol) and K₂CO₃ (219 mg, 1.6 mmol) in acetone (3 mL) was added 2-dimethylaminoethyl chloride (114 mg, 0.78 mmol). The mixture was stirred and heated under reflux for 13 h and cooled to room temperature. The solvent was removed and the residue was dissolved in a saturated solution of Na₂CO₃. The aqueous solution was extracted with AcOEt. The organic phase was washed with H₂O and brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with MeOH to yield (*R*)-2-(2'-diphenylphosphoryl)-1,1'-binaphthyl-2-yloxy-*N,N*-dimethylethanamine as a white solid (121 mg, 88%). To a mixture of (*R*)-2-(2'-diphenylphosphoryl)-1,1'-binaphthyl-2-yloxy-*N,N*-dimethylethanamine (80 mg, 0.148 mmol) and triethylamine (0.42 mL, 3.0 mmol) in xylene (3.3 mL) was added trichlorosilane (0.08 mL, 0.74 mmol) at 0 °C, the mixture was refluxed under Ar for 18 h. After being cooled to room temperature, the mixture was treated with 30% NaOH. The mixture was stirred and heated at 80 °C for 1 h under Ar, cooled, and extracted with AcOEt. The organic phase was washed with a saturated solution of Na₂CO₃ and brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel with MeOH to yield (*R*)-2'-(diphenylphosphino)-1,1'-binaphthyl-2-ol (**5e**) as a white solid (68 mg, 88%). ¹H NMR (CDCl₃, 500 MHz) δ: 1.87 (3H × 2, s), 2.09–2.14 (1H, m), 2.21–2.26 (1H, m), 3.75–3.79 (1H, m), 3.93–3.97 (1H, m), 6.09 (1H, d, *J* = 7.9 Hz), 7.06–7.09 (3H, m), 7.14–7.26 (11H, m), 7.32 (1H, d, *J* = 8.5 Hz), 7.42–7.46 (2H, m), 7.83, 7.86 (3H, m), 7.97 (1H, d, *J* = 9.1 Hz). Selected ¹³C NMR (CDCl₃, 125 MHz) δ: 45.57, 57.62, 67.14. IR (cm⁻¹) (film): 2343.8, 2361.2, 2770.1, 2851.1, 2920.5, 2955.2, 3055.5, 3069.0. FAB-MS: 562 (MH⁺). [α]_D +40.9 (*c* 0.85, CHCl₃).
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