Enantioselective copper-catalyzed conjugate addition of diethylzinc to enones using new chiral P,N ligands composed of (*S*)-2-alkyl-2-aminoethylphosphines and α-substituted pyridines

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Abstract

New P,N ligands prepared from (*S*)-2-alkyl-2-aminoethylphosphines and α-substituted pyridines are efficient chiral ligands for the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexen-1-one and chalcone. The best result (90–91% ee) for the cyclohexenone was obtained with $Cu(OTf)_2$ (0.7–1 mol%) and a P,N ligand **4** derived from (*S*)-1-(diphenylphosphino)-3-methyl-2-butanamine and 6-methylpyridine-2-carboxaldehyde. © 2000 Elsevier Science Ltd. All rights reserved.

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The 1,4-addition of various organometallic reagents to α,β-unsaturated carbonyl or related compounds is an important method for carbon–carbon bond formation. Numerous chiral auxiliaries or stoichiometric reagents have been reported for asymmetric conjugate additions, while only a few chiral catalysts for the highly enantioselective conversions have been developed recently.[1]

Among several metal-catalyzed 1,4-additions, chiral copper and nickel complexes have been most widely investigated in the enantioselective addition of Grignard and dialkylzinc reagents to enones.[2–4] Since the first report on the enantioselective Cu-catalyzed 1,4-addition with diethylzinc in 1993,[5a] a number of chiral phosphoramidites and phosphites have been developed as ligands by several groups, namely, Alexakis,[5] Feringa,[6] Chan[7] and Pfaltz;[8] most of the highly enantioselective ligands are constructed with chiral binaphthol, which is an important framework for efficient enantioselection. Other new types of chiral ligands have been developed recently for efficient Cu-catalyzed conjugate addition of diethylzinc to enones.[9–12] Acyclic

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enones, five-membered enones, and some other α,β-unsaturated compounds are relatively difficult substrates to achieve high ee with diethylzinc and Cu catalysts in comparison with six-membered enones.

Since there are few chiral ligands generally efficient for the asymmetric conjugate addition to most α,β-unsaturated compounds, the development of other new types of chiral ligands is greatly desired.

We have recently developed versatile chiral P,N-bidentate ligands, VALAP (**1**) and its analogs, and C_2-symmetric diphosphine ligands by employing (*S*)-2-alkyl-2-aminoethylphosphines as chiral units, which are readily accessible from chiral aminoalcohols obtained by reduction of α-amino acids, and disclosed that the palladium complexes of these ligands are efficient catalysts in enantioselective allylic substitution of acyclic and cyclic allyl esters.[13] Since the chiral unit, (*S*)-2-alkyl-2-aminoethylphosphine, was found to have an effective chiral environment, we planned to employ it as a useful framework of new ligands for enantioselective copper-catalyzed conjugate additions. In this paper we report the synthesis and application of a series of P,N ligands consisting of the aminoethylphosphines and α-substituted pyridines in the catalytic conjugate addition of diethylzinc to enones.

Chiral units, (*S*)-1-(diphenylphosphino)-3-methyl-2-butanamine and (*S*)-1-(diphenylphosphino)-2-propan-amine, were prepared from (*S*)-valinol and (*S*)-alaninol, respectively, according to the reported procedure.[13a,d,f] Arylidene derivatives (**2–5, 9**)[14] were obtained quantitatively by condensation of the phosphinoalkanamines and the corresponding aromatic aldehydes. Reduction of **4** with lithium aluminum hydride gave **8**. Picolinamide derivatives (**6, 7**) were prepared by acylation with the corresponding acids and a condensing agent (EDCI, HOBT, NEt₃).
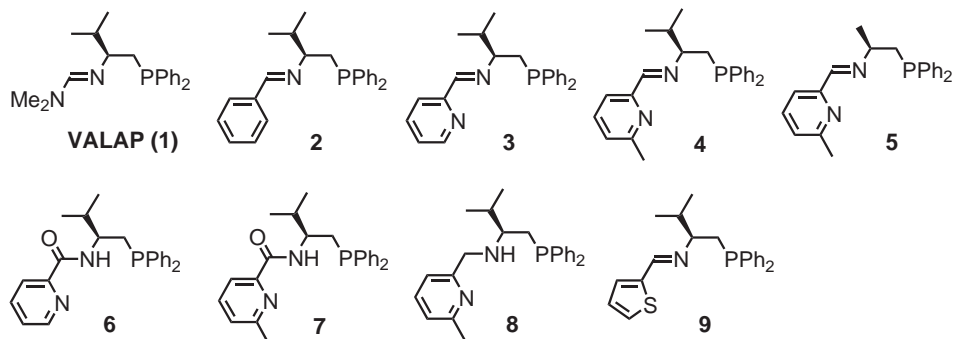
Asymmetric copper-catalyzed conjugate addition of diethylzinc to a cyclic enone, 2-cyclo-hexen-1-one, was chosen as a model reaction for evaluation of the P,N ligands (**1–9**). Typically, the reaction was carried out with Cu(OTf)₂ (1 mol%) and a ligand (2.5 mol%) at 0°C in dichloromethane.[15] The results are summarized in Table 1. Preliminary experiments with P,N-bidentate ligands, VALAP (**1**) and a benzylidene derivative (**2**), gave only products with disappointingly low ee. Then, we envisaged that the introduction of another coordinating group to the ligand **2** might improve the enantioselectivity since the tridentate ligand can stabilize a possible monoalkylcopper(I) intermediate, forming a more rigid chiral environment. As shown in entry 3, a 2-pyridinomethylene derivative (**3**) gave a considerably improved enantioselectivity. Introduction of a methyl group to the 6-position of the pyridine ring of **3** further increased the enantioselectivity up to 91% ee (entry 4, ligand **4**). With an analogous ligand **5** having an (*S*)-2-methyl group in place of the isopropyl group, the enantioselectivity dropped seriously

Table 1

Copper-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one
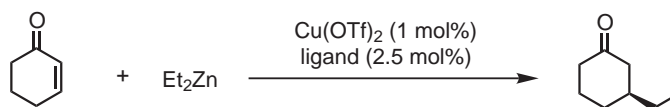
Entry	Ligand	Solvent	Temp. (°C)	Time (h)	Conv. (%)	Ee (%)	Config.
1	**1**	CH_2Cl_2	0	5	81	4	*S*
2	**2**	CH_2Cl_2	0	5	74	~0	–
3	**3**	CH_2Cl_2	0	5	95	55	*S*
4	**4**	CH_2Cl_2	0	5	100	**91**	*S*
5	**4**	Toluene	0	5	100	85	*S*
6	**4**	THF	0	5	100	81	*S*
7	**4**	CH_2Cl_2	20	5	84	80	*S*
8	**4**	CH_2Cl_2	-20	5	70	70	*S*
9	**4**	CH_2Cl_2	-50	5	34	27	*S*
10	**4**[a]	CH_2Cl_2	0	5	100	**90**	*S*
11	**4**[b]	CH_2Cl_2	0	5	26	53	*S*
12	**5**	CH_2Cl_2	0	5	94	36	*S*
13	**6**	Toluene	-20	Overnight	85	52	*S*
14	**7**	Toluene	-20	Overnight	90	40	*S*
15	**8**	CH_2Cl_2	0	5	100	30	*S*
16	**9**	CH_2Cl_2	0	5	41	~0	–

[a] Cu(OTf)$_2$/ligand$=0.7/1$ (mol%).
[b] Cu(OTf)$_2$/ligand$=0.3/0.5$ (mol%).

(entry 12). Use of other solvents such as toluene and THF slightly decreased the enantioselectivity of **4** (entries 5, 6). On the other hand, the reaction temperatures had considerable effect on the enantioselectivity; the temperatures not only higher but lower than 0°C decreased the selectivity (entries 7–9). The amounts of Cu(OTf)$_2$ and ligand **4** could be reduced to 0.7 and 1 mol%, respectively, while keeping the conversion (100%) and the enantioselectivity (90% ee) (entry 10). A further reduction of the Cu(OTf)$_2$ amount to 0.3 mol% resulted in low conversion with an inferior ee (entry 11). α-Pyridinecarboxamide derivatives (**6,7**) showed moderate selectivity in toluene (entries 13, 14). The worse enantioselectivity of **7** and **8** (entries 14, 15) in comparison with the corresponding imino ligand (**4**) indicates that the tridentate phosphino, imino and pyridino groups play important roles in forming a desirable chiral pocket around the Cu atom for alkylation with diethylzinc followed by coordination with cyclohexenone. The importance of the pyridino nitrogen was also demonstrated by the use of a thiophene derivative (**9**), which afforded only a racemic product in a lower yield (entry 16).

A representative acyclic enone, chalcone, was next examined with ligand **4** under typical reaction conditions. The corresponding β-ethylation product was isolated in 90% yield with 71% ee (*R*). It is rare to find highly efficient ligands for the asymmetric conjugate additions to both cyclic and acyclic enones.[9]

Although the mechanism of copper-catalyzed conjugate addition of diethylzinc to enones has not been sufficiently elucidated, a possible reaction path through a monoalkylcopper(I)–ligand complex was postulated.[6b] A possible key intermediate involved in the enantioselection step with

the copper complex of **4** is described later. Recently, we proposed a *Pr/Mr* chirality model to classify most of the chiral bidentate ligands and clarified the correlation between the chirality of the ligands and the absolute configurations of the products in Pd-catalyzed allylic alkylation.[13d,f] According to these results, (*S*)-2-alkyl-2-aminoethylphosphine was elucidated to have *Mr* chirality. On the basis of the present results and some other reported data,[7,8,11] we deduced that *Mr* chirality ligands afford the (*S*)-product in the Cu-catalyzed conjugate addition of diethylzinc to 2-cyclohexen-1-one.

In conclusion, we have developed new tridentate chiral ligands bearing an aminoethylphosphine as a chiral unit and optimized their use in the enantioselective conjugate addition of diethylzinc to enones. Extensive work is in progress to apply the ligands to other asymmetric reactions and to search for related efficient chiral ligands.
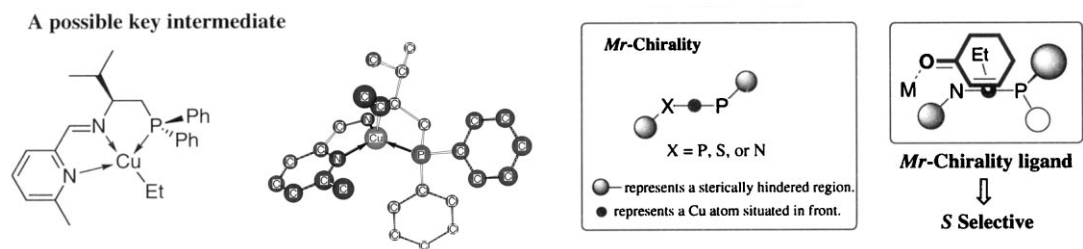
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14. Selected data for **4**: $[\alpha]_D^{23}$ +66.7 (*c* 1.05, CHCl$_3$); ^{1}H NMR (270 MHz, CDCl$_3$) δ: 0.91 (d, 6H, $J = 6.6$ Hz), 2.00–2.05 (m, 1H), 2.47–2.54 (m, 2H), 2.58 (s, 3H), 3.09–3.12 (m, 1H), 7.13–7.65 (m, 13H), 8.17 (s, 1H); IR (CHCl$_3$): 1647 cm^{-1}; FAB-MS: m/z 375 (MH$^+$).

15. Typical procedure for the conjugate addition reaction: a solution of Cu(OTf)$_2$ (3.6 mg, 0.01 mmol) and **4** (9.4 mg, 0.025 mmol) in dichloromethane (1.5 ml) was stirred under Ar atmosphere at room temperature for 0.5 h. To the solution was added 2-cyclohexen-1-one (98 mg, 1 mmol) followed by dropwise addition of Et$_2$Zn (1.5 mmol, 1.5 ml of 1.0 M solution in hexane) at 0°C. After stirring for 5 h at 0°C the reaction mixture was quenched with a 1N HCl solution (1 ml) and was extracted with ether (2×20 ml). The combined organic layer was washed with saturated aq. NaHCO$_3$ and dried over MgSO$_4$. The conversion yield was 100%. After the solvent was evaporated, an oily residue was purified by flash column chromatography (SiO$_2$, hexane/AcOEt = 5/1) to afford 100 mg (79%) of 3-ethylcyclohexanone (91% ee (*S*)). The data on conversion and the ee values of the product were determined by GC with a SE-30 column and a γ-DEX-225 (Supelco) column (30 m×0.25 mm (i.d.)),[9] respectively. The absolute configurations were determined by comparison of their GC retention times with that of an authentic sample.