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New phosphoramidite and phosphito-N chiral ligands based on 8-substituted quinolines and (*S*)-binaphthol; applications in the Cu-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one

Carmela G. Arena, GianPiero Calabrò, Giancarlo Franciò and Felice Faraone*

Dipartimento di Chimica Inorganica, Chimica Analitica e Chimica Fisica dell'Università di Messina, Salita Sperone 31, Villaggio S. Agata, 98166 Messina, Italy

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Abstract

The copper(II)-catalyzed enantioselective conjugate addition of diethylzinc to 2-cyclohexen-1-one, in the presence of phosphoramidite, and of phosphito-N chiral ligands, derived from 8-chloroquinoline or 8-hydroxyquinoline and (*S*)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]binaphthalene, resulted in *ee*'s of 70 and 51%, respectively.

1. Introduction

The conjugate addition of dialkylzinc to α,β-unsaturated enones is a reliable method for the synthesis of β-substituted carbonyl compounds.[1] Although primary diorganozinc compounds do not generally react with α,β-unsaturated cyclic and acyclic enones,[2] these reactions occur in the presence of catalytic amounts of Cu^{I}, Ni^{II} and Zn^{II} salts.[3] The catalytic effect has been explained either by alkyl transfer or by changes in the linear geometry and bond energy of the dialkylzinc reagent upon coordination of the ligands.[2–5] Recently, catalytic enantioselective conjugate addition of organometallic reagents, particularly dialkylzinc, to enones has been achieved by chiral Cu^{I}, Ni^{II} and Zn^{II} complexes.[4] A variety of chiral ligands have been used in the metal-catalyzed 1,4-addition of dialkylzinc to enones.[4,6–8] Feringa et al.[7] have successfully used phosphoramidite chiral ligands based on a chiral amine-moiety and on 3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]-binaphthalene. With this ligand complete enantiocontrol in the Cu-catalyzed 1,4-additions of dialkylzinc to cyclohexenone has been achieved. Several chiral-P,N ligands have also been developed.[8] Pfaltz et al.[8b] used chiral oxazoline-phosphite ligands in the Cu-catalyzed conjugate addition of

* Corresponding author. E-mail: faraone@chem.unime.it

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organometallic compounds to enones, while Stangeland and Sammakia[8c] employed chiral oxazoline-phosphine ligands in the same type of reactions. Zhang et al.[8d] successfully used a chiral P,N ligand that combines a diarylphosphine group and a substituted pyridine with a chiral binaphthyl system.

We are interested in developing bulk mono- and bidentate-chiral ligands based on the rigid quinoline backbone and in their applications in enantioselective homogeneous catalysis.[9,10] Herein, we wish to report the synthesis of new chiral phosphito-N ligands derived from the 8-hydroxy-quinoline or on the 8-hydroxy-2-methyl-quinoline and (*S*)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]binaphthalene, **1** and **2**, and their applications in the enantioselective copper-catalyzed conjugate addition of Et_2Zn to 2-cyclohexen-1-one, **4**. The chiral phosphoramidite ligand **3** was also tested in the same type of reaction.

2. Results and discussion

The new chiral phosphito-P,N ligands **1** and **2** (Fig. 1) were obtained by adding equimolar solutions of (*S*)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]binaphthalene to 8-hydroxy-quinoline or 8-hydroxy-2-methyl-quinoline in the presence of NEt_3 at 0°C in toluene. Compounds **1** and **2** are white moisture-sensitive solids that are soluble in most common solvents except alkanes. The new compounds were fully characterized by elemental analysis and NMR spectroscopy. In the $^{31}P\{^1H\}$ NMR spectrum, in $CDCl_3$, they exhibit resonances at δ 142.7 (**1**) and δ 141.3 (**2**) respectively; in the ^1H NMR spectrum of **2**, in $CDCl_3$, the protons of the methyl group in 2-position of the quinoline ring give rise to a signal at δ 2.67.

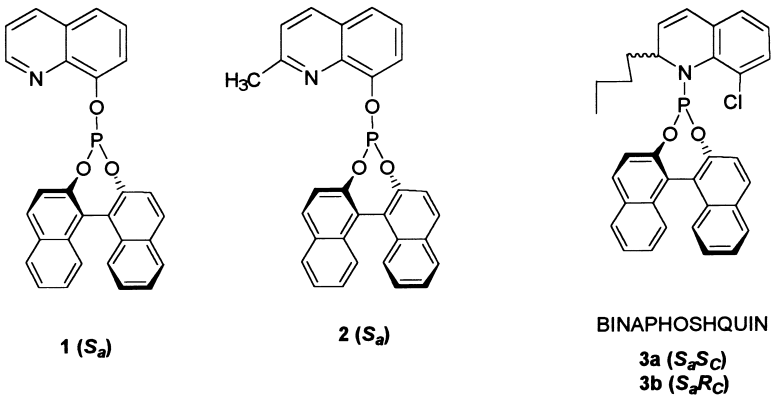
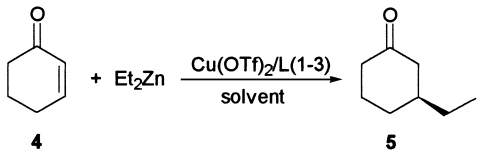


Figure 1.

The phosphoramidite ligand **3** (BINAPHOSHQUIN) (Fig. 1) has been previously reported by us[9] together with its rhodium(III), palladium(II) and platinum(II) complexes. Compound **3** was obtained by allowing 8-chloroquinoline to react with *n*-BuLi in a 1:1 molar ratio in tetrahydrofuran at –78°C and subsequent addition of (*S*)-4-chloro-3,5-dioxa-4-phosphacyclohepta-[2,1-*a*;3,4-*a*′]binaphthalene. The (S_aS_C)-**3** (**3a**) and (S_aR_C)-**3** (**3b**) diastereomers of BINAPHOSHQUIN were separated by means of their different solubilities in hexane. Their absolute configurations were derived from the crystal structure of a platinum(II) compound synthesized using only one diastereomer.[9]

We selected 2-cyclohexen-1-one, **4**, as a typical substrate to test the efficiency of the catalytic system formed by $Cu(OTf)_2$ and the ligands **1**, **2** and **3** in the enantioselective conjugate addition of Et_2Zn to enones (Scheme 1).



Scheme 1.

The results are summarized in Table 1. Comparison of the experimental data obtained with the ligands **1** and **2** (entries 1–7) clearly indicates that in the latter the methyl group in the *ortho* position to the nitrogen atom exerts a beneficial effect on the enantioselectivity of the process. The $Cu(OTf)_2$:**4** molar ratio and the solvent have a significant effect on the reaction time and on the enantioselectivity. The most promising result was obtained using ligand **2** with a $Cu(OTf)_2$:**4** molar ratio of 0.03 at –15°C, in CH_2Cl_2 as a solvent. Under these conditions the conversion is almost complete within 2 h and (*S*)-3-ethylcyclohexanone **5** was obtained in 51% *ee* (entry 7). In toluene the corresponding *ee* value was lowered to 35% (entry 5). The reaction proceeded more slowly and less selectively when the catalyst loading was reduced (entry 6).

Table 1
Cu-catalyzed enantioselective 1,4-addition of diethylzinc to cyclohex-2-enone **4**

Entry	L	$Cu(OTf)_2$/**5**	Solvent	T (°C)	t (h)	L/Cu	Conv (%)[a]	*ee* (%)[b]
1	**1**	0.03	Toluene	-15	2	1	100	16 (S)
2	**1**	0.03	CH_2Cl_2	-15	4	1	94	23 (S)
3	**2**	0.01	Toluene	0	2	1	100	26 (S)
4	**2**	0.01	Toluene	-15	1	1	80	20 (S)
5	**2**	0.03	Toluene	-15	1	1	100	35 (S)
6	**2**	0.01	CH_2Cl_2	-15	3	1	97	37 (S)
7	**2**	0.03	CH_2Cl_2	-15	2	1	95	51 (S)
8	**2**	0.01	Toluene	0	3	2	100	33 (S)
9	**3a**	0.03	Toluene	-15	0.5	2	100	0
10	**3b**	0.03	Toluene	-15	5	2	96	70 (S)
11	**3b**	0.03	Toluene	-30	24	2	90	54 (S)
12	**3b**	0.03	Toluene	-15	21	4	60	23(S)

a) The conversions were measured by GC analysis. b) Determined by ^{13}C NMR spectroscopy after derivatization with 1,2-diphenylethylendiammine[12]

Using the phosphoramidite **3a** as a ligand in the reaction under investigation, the addition is very fast at –15°C and **5** was obtained as a racemic mixture (entry 9). In contrast to **3a**, employing the diastereomer **3b** as a ligand, **5** was obtained in more than 96% yield with an enantiomeric excess of 70%. The reaction was run in toluene at –15°C, in the presence of an excess of Et_2Zn, and using a molar ratio **3b**:$Cu(OTf)_2 = 2$ (entry 10). When the reaction temperature was lowered from –15°C to –30°C the enantioselectivity decreased to 54% and a longer reaction time was

needed to obtain quantitative conversion (entry 11). Similar effects of the reaction temperature on related reactions have been reported.[11] Toluene was found to be the solvent of choice if the reactions were performed with ligand **3b**, whereas higher *ee*'s could be achieved with ligands **1** or **2** if CH_2Cl_2 was used instead.[4e,f] The coordinating solvent acetonitrile diminishes both the conversion rate and the *ee*. Increasing the molar ratio of **3b**: $Cu(OTf)_2$ from 2:1 to 4:1 decreased the catalytic activity as well as the enantioselectivity (compare entries 10 and 12). The excess ligand probably prevents the formation of open coordination sites required for the transfer of the ethyl-group from Et_2Zn to the Cu-complex. A similar effect was observed by Chan et al. using chiral aryl-diphosphites.[12]

The striking difference in the catalytic behaviour of the diastereomeric forms S_aS_C and S_aR_C of **3** may be related to the different orientation of the quinoline's chlorine atom in the intermediate copper complex. It was demonstrated that the different nature of the products obtained by allowing the diastereomers (R_aR_C)-**3** and (R_aS_C)-**3** to react with $[Rh(CO)_2Cl]_2$ is due to the position assumed by the Cl atom relative to the metal. Only in the case of the diastereomer (R_aR_C)-**3** was intramolecular redox addition of the C–Cl bond to the rhodium centre observed.[9] Furthermore, the relative configuration of the stereogenic centre in respect of the atropoisomeric moiety was found to be a crucial factor in determining *matching* and *mis-matching* combinations in enantioselective reactions for related bidentate ligands.[10]

Although the phosphoramidite ligand **3b** allows acceptable enantioselectivity in copper-catalyzed conjugate addition of Et_2Zn to 2-cyclohexen-1-one, the results are less satisfactory than those obtained by Feringa et al. using similar ligands. The two ligand systems have an identical dioxaphosphepine unit but different substituents on the nitrogen. The nitrogen atom is part of a C_1-symmetrical heterocycle in the new ligand **3b**, whereas two chiral substituents at nitrogen lead to an overall C_2 symmetry for Feringa's ligand system. C_2-Symmetrical ligands are also usually more effective chiral auxiliaries for other catalytic processes such as hydrogenation, although significant exceptions are known.[13]

In summary, we reported on the synthesis of two new chiral-P,N ligands and on their application in the Cu-catalyzed asymmetric conjugate addition of diethylzinc. Enantioselectivities up to 70% were reached with phosphoramidite ligand BINAPHOSHQUIN. Further studies on other reactions with these ligands are in progress.

3. Experimental

A published method was used to prepare the compound (*S*)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]binaphthalene.[9] All other reagents were purchased from Sigma–Aldrich and were used as supplied. Solvents were dried by standard procedures. All experiments were performed under purified nitrogen. For column chromatography, silica gel 60 (220–440 mesh) purchased from Fluka was used. NMR experiments were carried out using a Bruker AMX R300 spectrometer. ^1H NMR spectra were referenced to internal tetramethylsilane and $^{31}P\{^1H\}$ spectra to external 85% H_3PO_4. Elemental analyses were performed by Redox s.n.c., Cologno Monzese, Milano.

*3.1. General procedure for the synthesis of phosphite-quinoline ligands **1–2***

A solution of the appropriate quinoline (8-hydroxyquinoline for **1** and 8-hydroxy-2-methylquinoline for **2**) (3.28 mmol) and Et_3N (0.653 g, 6.57 mmol) in toluene (10 mL) was added

dropwise to a solution of (*S*)-4-chloro-3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]binaphthalene (1.390 g, 3.28 mmol) in the same solvent (15 mL) at 0°C. The reaction mixture was stirred overnight at room temperature and then the precipitate of $Et_3N{\cdot}HCl$ formed was removed by filtration. The toluene was evaporated from the filtrate. The residue was washed with hexane (5 mL) and dried. A white solid was obtained in 90% yield. Compound **1**: anal. calcd for $C_{29}H_{18}NO_3P$: C, 75.81; H, 3.95; N, 3.05. Found: C, 75.77; H, 3.91; N, 2.98. ^1H NMR (C_6D_6) δ 7.15–8.15 (m, 17H, C*H*), 9.01 (d, 1H, C*H*). $^{31}P\{^1H\}$ NMR (C_6D_6) 142.7 (s). Compound **2**: anal. calcd for $C_{30}H_{20}NO_3P$: C, 76.10; H, 4.26; N, 2.96. Found: C, 76.22; H, 4.30; N, 2.93. ^1H NMR (C_6D_6) δ 2.67 (s, 3H, CH_3); 6.76–7.73 (m, 17H, C*H*). $^{31}P\{^1H\}$ NMR (C_6D_6) 141.3 (s).

3.2. General procedure for asymmetric 1,4-conjugate addition

A solution of $Cu(OTf)_2$ (18.1 mg, 0.050 mmol) and **3b** (53.8 mg, 0.100 mmol) in toluene (5 mL) was stirred for 1 h. The dark-pink solution was cooled (–15°C) and 2-cyclohexen-1-one (159.6 mg, 1.666 mmol) and 1.6 mL of Et_2Zn (1.1 M solution in toluene) were added slowly. The resulting mixture was stirred at –15°C until the conversion was almost complete. Then HCl 1N (25 mL) was added and the mixture extracted with Et_2O (2×20 mL). The organic phase was washed with brine (20 mL), dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (hexane:diethyl ether, 5:1) to afford the 1,4-product. The *ee* values were determined by ^{13}C NMR.[14]

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References

1. (a) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Tetrahedron Organic Chemistry Series, No 9, Pergamon: Oxford, 1992. (b) Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771.
2. Knochel, P.; Singer, R. *Chem. Rev.* **1993**, *93*, 2117.
3. (a) Lipshutz, B. H.; Wood, M. R.; Tirado, R. *J. Am. Chem. Soc.* **1995**, *117*, 6126. (b) Alexakis, A.; Vastra, J.; Mangeney, P. *Tetrahedron Lett.* **1997**, *38*, 7745. (c) Tamaru, Y.; Tanigawa, H.; Yamamoto, T.; Yoshida, Z. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 351. (d) Sibille, S.; Ratovelomanana, V.; Périchon, J. *J. Chem. Soc., Chem. Commun.* **1992**, 283.
4. (a) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283. (b) Villacorta, G. M.; Rao, Ch. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175. (c) Bolm, C.; Ewald, M.; Felder, M. *Chem. Ber.* **1992**, *125*, 1205. (d) Soai, K.; Yokoyama, S.; Hayasaka, T.; Ebihara, K. *J. Org. Chem.* **1988**, *53*, 4149. (e) Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3193. (f) Alexakis, A.; Burton, J.; Vastra, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1997**, *8*, 3987. (g) Zhou, Q. L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467. (h) Alexakis, A. In *Transition Metal Catalysed Reactions*; Murahashi, S.-I.; Davies, S. G., Eds.; IUPAC Blackwell Science: Oxford 1999, p. 303. (i) Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427.
5. (a) Boersma, J. *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon: Oxford, 1982; Vol. 2, Chapter 16.
6. (a) De Vries, A. H. M.; Imbos, R.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1467. (b) Corma, A.; Iglesias, M.; Martin, V.; Asami, M.; Usui, K.; Higuchi, S.; Inoue, S. *Chem. Lett.* **1994**, 297. (c) Uemura, M.; Miyaki, R.; Nakayama, K.; Hayashi, I. *Tetrahedron: Asymmetry* **1992**, *3*, 713. (d) Zhang, F. Y.; Chan, A. S. C. *Tetrahedron: Asymmetry* **1998**, *9*, 1179.

7. (a) De Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (c) Keller, E.; Maurer, J.; Naasz, R.; Schder, T.; Meetsma, A.; Feringa, B. L. *Tetrahedron: Asymmetry* **1998**, *9*, 2409.
8. (a) Alexakis, A.; Vastra, J.; Benhaim, C.; Mangeney, P. *Tetrahedron Lett.* **1998**, *39*, 7869. (b) Knobel, A. K. H.; Escher, I. H.; Pfaltz, A. *Synlett* **1997**, 1429. (c) Stangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503. (d) Hu, X.; Chen, H.; Zhang, X. *Angew. Chem., Int. Ed.* **1999**, *38*, 3518. (e) Yan, M.; Chan, A. S. C. *Tetrahedron Lett.* **1999**, *40*, 6645.
9. Franciò, G.; Arena, C. G.; Faraone, F.; Graiff, C.; Lanfranchi, M.; Tiripicchio, A. *Eur. J. Inorg. Chem.* **1999**, 1219.
10. Franciò, G.; Faraone, F.; Leitner, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 1428.
11. (a) Noyori, R., Ed.; *Asymmetric Catalysis in Organic Synthesis*; Wiley-Interscience: New York, 1994. (b) Ojima, I., Ed.; *Catalytic Asymmetric Synthesis*; VCH: New York, 1993.
12. Yan, M.; Yang, L. W.; Wong, K. Y.; Chan, A. S. C. *Chem. Commun.* **1999**, 11.
13. Mori, T.; Kosaka, K.; Nakagawa, Y.; Nagaoka, Y.; Tomioka, K. *Tetrahedron: Asymmetry* **1998**, *9*, 3175.
14. Alexakis, A.; Frutos, J. C.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2431.