

Fig. 4. Expected melting point phase diagram of ST; T = melting point (temperature of the end of fusion), ee = enantiomeric excess.

compounds the reversal of chirality in the deposited crystals never occurs. It should be emphasized that spontaneous isomerization of one enantiomer to the other one never occurred under our recrystallization conditions. Although the mechanism of the enantiomeric resolution phenomenon of ST is yet under investigation, it may be related to the unique polymorphism of the ST crystals described above. If this is true, this enantiomeric resolution phenomenon might be extended and become a powerful general method for the resolution of organic racemates showing similar polymorphism, by which both the racemic crystals and the mixed crystals are simultaneously produced.

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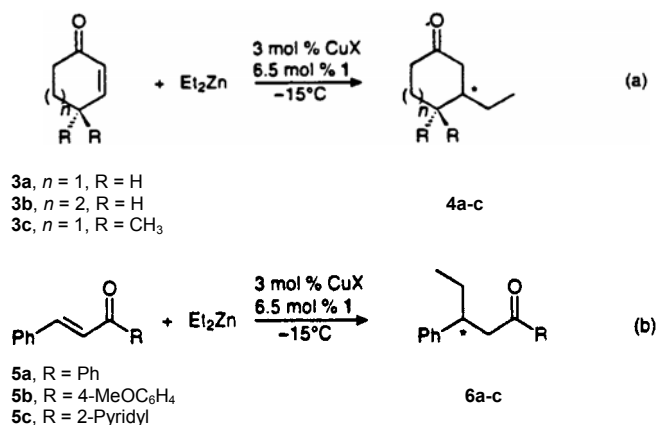
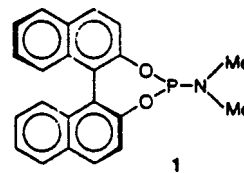
- [1] L. Pasteur, *Ann. Chim. Phys.* **1848**, *24*, 442.
[2] M. Gernez, C. R. *Hebdomadaire des Seances Acad. Sci.* **1866**, *63*, 843.
[3] a) J. Jacques, A. Collet, S. H. Wilen, *Enantiomers, Racemates and Resolutions*, Wiley, New York, **1981**, p. 217; b) A. Collet, M.-J. Brienne, J. Jacques, *Chem. Rev.* **1980**, *80*, 215.
[4] P. Newman, *Optical Resolution Procedures for Chemical Compounds*, Vol. 1–3, Optical Resolution Information Center, New York, **1978**, **1981**, **1984**.
[5] F. Toda, *Top. Curr. Chem.* **1987**, *140*, 43.
[6] *Asymmetric Synthesis*, Vol. 5 (Ed.: J. D. Morrison), Academic Press, Orlando, FL, USA, **1985**.
[7] K. Mori, Y. Funaki, *Tetrahedron* **1988**, *41*, 2369.
[8] *Chromatographic Chiral Separations* (Ed.: M. Zief, L. J. Crane), Marcel Dekker, New York, **1988**.
[9] A. Koda, Y. Yanagihara, N. Matsuura, *Agents Actions* **1991**, *34*, 369.
[10] T. Ushio, K. Yamamoto, *J. Chromatogr. A* **1994**, *684*, 235.
[11] X-ray data for a) the racemate: $P1$, $Z = 2$, $a = 14.638(2)$, $b = 15.681(2)$, $c = 6.2281(6)$ Å, $\alpha = 100.32(1)$, $\beta = 99.781(9)$, $\gamma = 66.258(9)^\circ$, $V = 1280(6)$ Å³, $R = 0.052$, $R_w = 0.049$; b) the (–) isomer: $P1$, $Z = 2$, $a = 10.762(3)$, $b = 15.615(2)$, $c = 8.223(2)$ Å, $\alpha = 100.41(2)$, $\beta = 108.50(2)$, $\gamma = 85.73(2)^\circ$, $V = 1289(1)$ Å³, $R = 0.043$, $R_w = 0.044$; c) a mixed crystal of ca. 1 % ee : $P1$, $Z = 2$, $a = 10.764(5)$, $b = 15.618(3)$, $c = 8.225(2)$ Å, $\alpha = 100.44(2)$, $\beta = 108.47(3)$, $\gamma = 85.62(3)^\circ$, $V = 1289.6(8)$ Å³, $R = 0.044$, $R_w = 0.042$. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-107. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Telefax: Int. code + (1223) 336-033; e-mail: teched@chemcrs.cam.ac.uk).
[12] Polymorphism between the crystals of the racemic compound crystal and racemic mixed crystals is quite rare, see ref. [3], p. 137. For polymorphism between racemic compounds and conglomerates, see M. Leclercq, A. Collet, J. Jacques, *Tetrahedron* **1976**, *32*, 821; E. Eliel, S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, p. 161.

Enantioselective Conjugate Addition of Dialkylzinc Reagents to Cyclic and Acyclic Enones Catalyzed by Chiral Copper Complexes of New Phosphorus Amidites**

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Conjugate addition reactions of organometallic reagents to enones are among the most widely used methods for carbon-carbon bond formation in organic synthesis.^[1] A number of successful methods for stereoselective 1,4-addition based on chiral auxiliaries or stoichiometric organometallic reagents have been developed.^[1, 2] Recently catalytic, enantioselective conjugate additions of organometallic reagent (RMgX, RLi, or R₂Zn) with chiral Cu^I, Ni^{II}, and Zn^{II} complexes have been demonstrated.^[2, 3] All these catalysts, however, show enantioselectivity for only one specific type of enone.^[3] For example, complexes prepared in situ from [Ni(acac)₂] (acac = acetylacetonate) and chiral amino alcohols are enantioselective for the addition of Et₂Zn to acyclic enones, but for cyclic enones no enantioselectivity was found.^[4] On the other hand chiral Cu^I complexes with sulfonylaryloxazoline ligands are only effective in 1,4-addition reactions of Grignard reagents to cyclic enones.^[5] We now report chiral copper catalysts, capable of facilitating conjugate addition of readily available dialkylzinc reagents to cyclic and acyclic enones in high yields and with ee values up to 90%.

Since trivalent phosphorus compounds are known as ligands for stoichiometric conjugate organo-copper additions,^[6, 7] we examined the new chiral phosphorus amidite **1**, recently synthesized in our group from (*S*)-2,2'-binaphthol (**2**) and hexamethyl phosphoramide (HMPT),^[8] as ligand in the Cu^I-catalyzed addition of Et₂Zn to cyclohexenone (**3a**) and chalcone (**5a**) [Eq. (a) and (b)].^[9] Some remarkable results were observed: 1) Amidite **1** represents a new class of chiral ligands, which proved to be essential for this catalytic system. Within 3 h both substrates are converted into the 1,4-product exclusively (GC



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yields greater than 95%), whereas without the ligand the copper-catalyzed reaction is very slow and many side products were found. When a larger amount of **1** (50 mol %) was employed, the reaction proceeds only at room temperature and was far less selective. These observations provide potentially striking advantages for a successful asymmetric catalysis.^[10] 2) For both substrates moderate enantioselectivities were found (**4a**, 35 % (*S*) and **6a**, 47 % (*R*)), which indicates that this chiral catalyst is not limited to one specific type of enone.

With this knowledge we set out to determine the structure of the complex of CuI and **1**. Crystallization from benzene provided white needles (**I**) suitable for X-ray analysis.^[11] The molecular structure is shown in Figure 1.^[12] Three chiral ligands are bound to the copper center creating a C_3 -symmetrical complex. Examination of the structure showed that crucial positions for ligand modifications are the amine moiety and the 3,3'-positions of the binaphthyl part of the ligand.

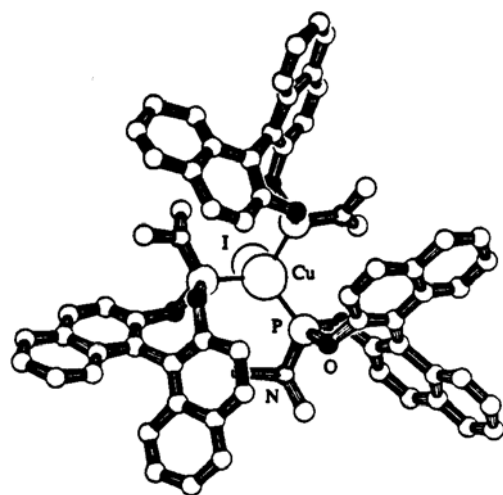
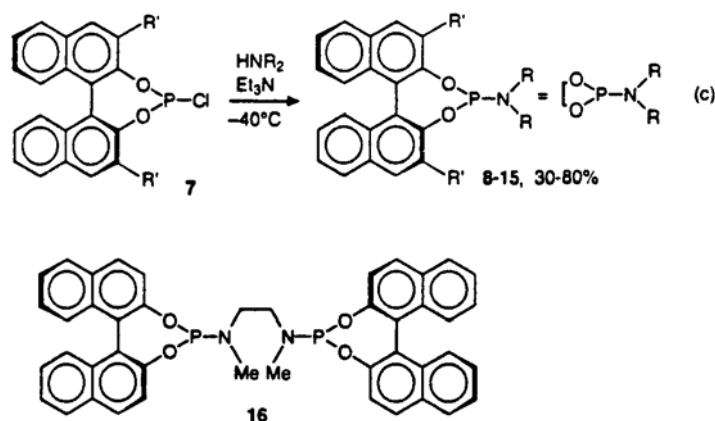


Fig. 1. Crystal structure of [CuI(**1**)] (**I**).

Therefore, starting from phosphoryl chloride (**7**),^[13] several new phosphorus amidites **8** - **16** were prepared [Eq. (c)].^[14] The



complexes generated in situ of these ligands and CuI gave unsatisfactory results, presumably due to low solubility. However, homogeneous catalyst solutions were obtained with CuOTf (Tf = CF₃SO₂), and the influence of the structural modifications in **8** - **15** on the enantiomeric excess of **4a** and **6a** could be determined (Table 1). For both products significant improve-

Table 1. Enantioselective CuOTf-catalyzed addition of Et₂Zn to **3a** and **5a** [a].

No.	Ligand	<i>ee</i> (4a) [%]	<i>ee</i> (6a) [%]
1	8	50	71
2	9	53	53
3	10	55	70
4	11	43	79
5	12	60	83
6	13 , R = Me R' = Me	56	52
7	14 , R = <i>i</i> Pr R' = Me	59	81
8	15 , R = Me R' = Ph	35	<20

[a] Reaction conditions as in Equation (a). Yields of isolated products > 80 %. For *ee* determination see Experimental Procedure.

ment in *ee* was observed when sterically demanding substituents were introduced on the ligand's nitrogen atom. The best results were obtained with the bis(*iso*-propyl)-substituted ligand **12**. Products **4a** and **6a** were isolated in high yields (> 80%) and *ee* values of 60% and 83%, respectively. Ligands **13** and **14** (R' = CH₃) furnished the 1,4-products with comparable *ee* values. With ligand **15** (R' = Ph) lower enantioselectivities were found. Probably different clusters are formed with sterically demanding substituents on the 3- and 3'-position of the ligand creating less selective catalysts. In an effort to enhance the selectivity and realizing that Cu^{II} salts are used as catalyst for conjugate addition,^[15] we investigated Cu(OTf)₂ together with **12** as chiral catalyst. Under the same conditions **4a** and **6a** were isolated with higher *ee* values (Table 2). The actual chiral catalyst is probably a Cu^I species, generated by in situ reduction of the Cu^{II} complex. The chiral copper complex of ligand **12** catalyzes the addition of Et₂Zn to various enones enantioselectively.

Table 2. Enantioselective conjugate addition of Et₂Zn to enones, catalyzed by Cu(OTf)₂ **12** [a].

No.	Enone	1,4-Adduct	Yield [%] [b]	<i>ee</i> [%] [c]
1	3a	4a	78 (68) [d]	63 (71) [d]
2	3b	4b	76	55
3	3c	4c	76	81
4	5a	6a	88	87
5 [e]	5a	6a	84	90
6	5b	6b	85	80

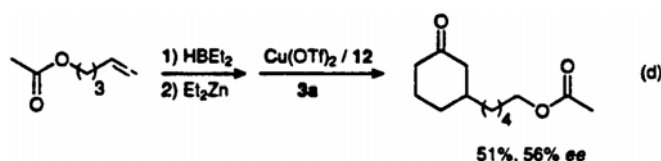
[a] Reaction conditions as in Eq. (a). [b] Yields of isolated products. [c] For *ee* determination see Experimental Procedure. [d] With Cu(SbF₆)₂ [**16**]. Yield of **4a**: 68%. [e] Temperature - 50 °C.

Cyclic and acyclic enones gave the corresponding 1,4-products in 55-90% *ee*. The best results were obtained for 4,4-dimethyl-2-cyclohexen-1-one (**3c**) and **5a**.

Mechanistic studies on the enantioselective catalyst are under way, and at present we emphasize the following observations. 1) With the catalyst derived from bidentate ligand **16** and copper salt (1:1) we achieve the same *ee* values as found for ligand **1**

(2:1), which indicates that during reaction two ligands are bound to the copper ion. The remaining sites in the tetrahedral coordination sphere of the copper ion are likely to be occupied by π -complexation of the enone's double bond,^[17] and an ethyl fragment transferred from zinc.^[18] 2) The pyridyl-substituted chalcone **5c** gave the corresponding 1,4-product in only 29 % *ee*, presumably due to competitive binding of the copper catalyst to the enone's pyridine moiety.

Preliminary experiments showed that dioctylzinc, prepared directly from 1-octene by boron-zinc exchange,^[19] can be used as well; it furnishes the 1,4-products with comparable *ee* values. This protocol can be extended to functionalized diorganozinc reagents. For instance, with the chiral catalyst derived from **12** and Cu(OTf)₂, 4-penten-1-yl acetate was added to **3a** with 56 % *ee*. [Eq. (d)].



In conclusion a new highly efficient catalyst for asymmetric conjugate addition of diorganozinc reagents to enones has been developed. Remarkable features are the excellent chemoselectivity to give nearly pure 1,4-products, the effective ligand acceleration by new phosphorus amidite ligands, the relatively high *ee* values for both cyclic and acyclic enones, the efficiency of a monodentate ligand in this asymmetric catalysis, and the fact that alkenes can be used as starting material.

Experimental Procedure

General procedure for ligands **8**–**16** (argon atmosphere): A warm solution (60 °C) of (S)-2,2'-binaphthol (**2**) (860 mg, 3 mmol) in toluene (25 mL) was added in 5 minutes to a cooled solution (–60 °C) of PCl₃ (270 μ L, 3 mmol), Et₃N (860 μ L, 6 mmol), and toluene (5 mL). The reaction mixture was stirred for 2 h, warmed to room temperature, and filtered. The filtrate was treated with Et₃N (410 μ L, 2.9 mmol) and 2.9 mmol of the appropriate secondary amine at –40 °C. After 16 h at room temperature, the reaction mixture was filtered, concentrated, and purified by chromatography (SiO₂, hexane:CH₂Cl₂ 2:1) to give the pure amidite (yield 30–80%). (S)-**12**: [α]_D = +591 (*c* = 0.68 in CHCl₃); ¹H NMR (200 MHz, CDCl₃): δ = 7.99–7.89 (m, 4 H), 7.55–7.22 (m, 8 H), 3.42 (heptet, *J* = 6.84 Hz, 1 H), 3.37 (heptet, *J* = 6.84 Hz, 1 H), 1.24 (d, *J* = 6.84 Hz, 6 H), 1.19 (d, *J* = 6.84 Hz, 6 H); ¹³C NMR (CDCl₃): δ = 150.2, 150.1, 132.6, 131.2, 130.4, 130.0, 129.2, 128.2, 128.1, 127.0, 125.8, 125.7, 125.6, 124.5, 124.1, 122.4, 122.3, 44.6, 44.4, 24.3, 24.2; ³¹P NMR (CDCl₃): δ = 151.7.

Catalytic conjugate additions (argon atmosphere): A solution of Cu(OTf)₂ (10.9 mg, 0.030 mmol) and **12** (26.0 mg, 0.065 mmol) in toluene (3 mL) was stirred for 1 h. The colorless solution was cooled (–20 °C) and enone (1.2 mmol) and 1.5 equivalent of dialkylzinc solution (1 M in toluene) were added. After 3 h at –15 °C the reaction mixture was poured into 25 mL of 1 M HCl and extracted with diethyl ether (2 \times 25 mL). The combined organic layers were washed with brine (25 mL), dried (MgSO₄), filtered, and evaporated to give the crude 1,4-products. After purification by chromatography (SiO₂, hexane:diethyl ether 5:1) the *ee* values were determined. Cyclic substrates were derivatized with optically pure 1,2-diphenyl ethylene diamine and analyzed by ¹³C NMR [20]. Acyclic substrates were studied by HPLC (Daicel OD or OJ column).

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[1] P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon, Oxford, **1992**.

[2] B. E. Rossiter, N. M. Swingle, *Chem. Rev.* **1992**, *92*, 771.

[3] Recent review: B. L. Feringa, A. H. M. de Vries, in *Advances in Catalytic Processes, Vol 1* (Ed.: M. D. Doyle), JAI Press, Connecticut, **1995**, p. 151.

[4] a) K. Soai, T. Hayasaka, S. Ugajin, *J. Chem. Soc. Chem. Commun.* **1989**, 516; b) C. Bolm, M. Ewald, M. Felder, *Chem. Ber.* **1992**, *125*, 1205; c) A. H. M. de Vries, J. F. G. A. Jansen, B. L. Feringa, *Tetrahedron* **1994**, *50*, 4479.

[5] a) Q.-L. Zhou, A. Pfaltz, *Tetrahedron* **1994**, *50*, 4467. Other examples: b) G. M. Villacorta, C. P. Rao, S. J. Lippard, *J. Am. Chem. Soc.* **1988**, *110*, 3175; c) M. van Klaveren, F. Lambert, D. J. F. M. Eijkelkamp, D. M. Grove, G. van Koten, *Tetrahedron Lett.* **1994**, *35*, 6135; d) M. Spescha, G. Rihs *Helv. Chim. Acta* **1993**, *76*, 1219.

[6] a) G. H. Posner, *An Introduction to Synthesis using Organocopper Reagents*, Wiley, New York, **1980**; b) M. Suzuki, T. Suzuki, T. Kawagishi, Y. Morita, R. Noyori, *Isr. J. Chem.* **1984**, *24*, 118; c) A. Alexakis, S. Mutti, J. F. Normant, *J. Am. Chem. Soc.* **1991**, *113*, 6332.

[7] Recently enantioselective 1,4-addition of Grignard reagents to cyclic enones, catalyzed by a CuI complex containing a chiral, bidentate phosphane ligand, has been reported: M. Kanai, K. Tomioka, *Tetrahedron Lett.* **1995**, *36*, 4275.

[8] R. Hulst, N. K. de Vries, B. L. Feringa, *Tetrahedron: Asymmetry* **1994**, *5*, 699.

[9] Enantioselective CuI-catalyzed addition of Et₂Zn to **3a** has been reported (*ee* 32%); however, with **5a** no *ee* was found: A. Alexakis, J. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, *4*, 2427.

[10] For a discussion about ligand accelerated asymmetric catalysis, see D. J. Berrisford, C. Bolm, K. B. Sharpless, *Angew. Chem.* **1995**, *107*, 1159; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1059.

[11] Crystals of **1** efficiently catalyze the addition of Et₂Zn to **3a** (**4a**: yield 76%, *ee* 32%).

[12] Crystal structure data for **1** C₆₆H₅₄N₃O₆P₃CuI/(C₆H₆)₂: *T* = 130 K; space group *P*2₁2₁2₁, *a* = 15.525(2), *b* = 19.957(2), *c* = 24.535(3) Å, *V* = 7601.7(16) Å³, *Z* = 4. The structure was solved by direct methods and refined to *R*(*F*) = 0.120, *R*_w(*F*) = 0.131. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-179-114. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ UK (fax: int. code +(1223) 336-033; e-mail: teched@chemcrs.cam.ac.uk).

[13] N. Greene, T. P. Kee, *Synth. Commun.* **1993**, *23*, 1651.

[14] All new ligands were remarkably stable to air and fully characterized. The corresponding 3,3'-substituted 2,2'-binaphthols were synthesized according to P. J. Cox, W. Wang, V. Snieckus, *Tetrahedron Lett.* **1992**, *33*, 2253.

[15] H. Sakata, Y. Aoki, I. Kuwajima, *Tetrahedron Lett.* **1990**, *31*, 1161.

[16] D. A. Evans, J. A. Murry, P. von Matt, R. D. Norcross, S. J. Miller, *Angew. Chem.* **1995**, *107*, 864; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 798.

[17] a) C. Ullenius, B. Christenson, *Pure Appl. Chem.* **1988**, *60*, 57; b) N. Krause, R. Wagner, A. Gerold, *J. Am. Chem. Soc.* **1994**, *116*, 381.

[18] Transmetalation of organozinc compounds into the corresponding organocopper reagents is well established: P. Knochel, R. D. Singer, *Chem. Rev.* **1993**, *93*, 2117.

[19] F. Langer, A. Devasagayaram, P.-Y. Chavand, P. Knochel, *Synlett.* **1994**, 410.

[20] A. Alexakis, J. C. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* **1993**, *4*, 2431.

A Catalyst-Specific, Stereocontrolled Ring-Closing Metathesis**

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Ring-closing olefin metatheses have been used increasingly for the synthesis of unsaturated carbo- and heterocycles.^[1] To our knowledge, diastereoselective ring-closing metatheses have not been investigated to date.^[2] We recently explored the synthesis of chiral, α -substituted heterocycles from amino acid derivatives,^[3, 4] and used the chiral center for stereocontrolled secondary reactions of the double bond produced by the metathesis for the synthesis of natural products.^[3]

Natural products or biologically active compounds such as various pheromones and glycosidase inhibitors contain α,α' -disubstituted pyrrolidine or piperidine units.^[5, 6] To selectively ob-

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