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Copper (II) in Organic Synthesis. XI.[1] Evaluation of the Ligand Architecture on the Efficiency of a Copper (II) Catalyst for Enantioselective Michael Reactions.

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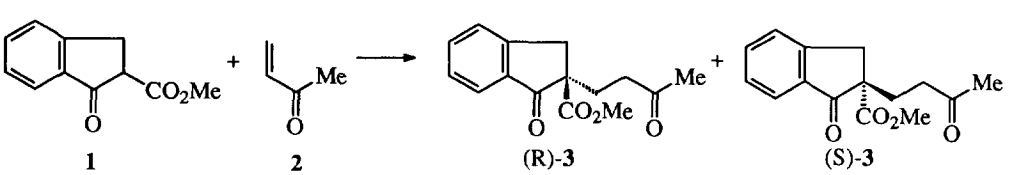
Abstract: Several bis-copper (II) complexes with chiral ligands derived from 2-substituted 2-(salicylideneamino) ethanols have been tested as catalysts of enantioselective Michael reactions. The degree of enantioselection is strongly affected by the architecture of the ligand. The best result (75% e.e.) was obtained for a ligand having a substituent potentially suitable to induce the formation of a bis-tetradentate copper (II) complex with a square pyramidal coordination.

Recently, chiral metal complexes have been shown to catalyze enantioselective Michael reactions.[1-6]

Taking as a test of the catalyst efficiency the reaction of methyl indan-1-one-2-carboxylate (**1**) with 3-buten-2-one (**2**) to give (R)- and (S)-**3** (Scheme 1), the best results (70% e.e.) were obtained[2] with the copper (II) complex **4**, derived from (S)-2-(2-hydroxybenzylideneamino)-1,5-pentandiol (Figure 1).

In the previous paper of this series,[1] the 3-hydroxy propyl branch was substituted by a series of alkyl groups and the increase of the steric hindrance of the substituent increased the degree of enantioselection (benzyl group 65% e.e.).

Scheme 1



1 **2** (R)-**3** (S)-**3**

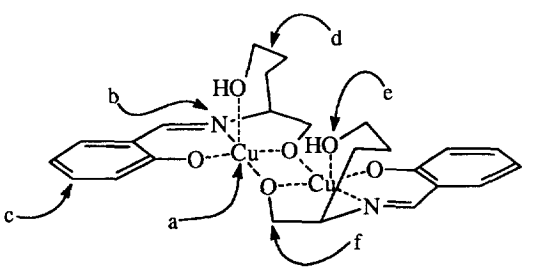


Figure 1. Tunable sites on copper (II) catalyst **4**.

The superior efficiency of **4** *vs* the alkyl substituted complexes was considered to be the result of the hydroxy group behaving as an axial ligand, thus giving rigid dimeric tetradentate complexes with square pyramidal coordination (Fig. 1). These structure are well-known in substituted salicylideneamino copper (II) complexes, the axial ligand being either an anion,[7] or a ligand of the adjacent molecular unit,[8,9] or a water molecule[10], or a ligand group bound to the equatorial belt,[11,12] a behaviour conceivable to **4**.

The architecture of the ligand is characterized by several tunable sites and, among the differing options, the following ones were kept constant:

a) type and oxidation state of the metal;

b) the sequence of the equatorial ligand centres: O,N,O;

c) salicylaldehyde (SA) fragment.

The modifications to be tested concerned:

d) the length of the branch, changing the trimethylene group of **4**;

e) the nature of the supposed axial ligand, alternative to the hydroxy group;

f) an increase of the steric hindrance of the equatorial belt with a modification of the CH_2 unit.

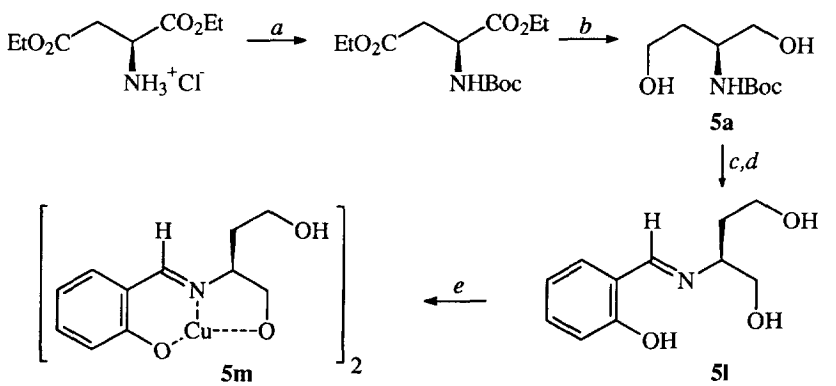
RESULTS

Syntheses of the modified copper (II) complexes.

Starting materials for the modified chiral ligands were the esters of some naturally occuring amino acids.

a) Derivatives of (S)-aspartic acid. The amino group of diethyl aspartate hydrochloride, prepared as reported in the literature,[13] was protected as Boc-derivative and the product, reduced with $LiAlH_4$, gave (S)-2-(Boc-amino)-1,4-butandiol (**5a**). Deprotection of the amino group with trifluoroacetic acid and condensation with an equimolecular amount of SA gave (S)-2-(2-hydroxybenzylideneamino)-1,4-butandiol (**5l**). Its copper (II) complex (**5m**) (as well as those below described) was prepared by refluxing a methanolic solution of the ligand and an equimolecular amount of copper (II) acetate (Scheme 2).

Scheme 2



a) $(Boc)_2O/Et_3N$/Dioxane/H_2O/rt; *b)* $LiAlH_4/Et_2O/\Delta$; *c)* CF_3COOH/0 °C →rt; *d)* SA/MeOH/K_2CO_3/Δ; *e)* $Cu(OAc)_2$/MeOH/Δ.

All ligands were characterized by elemental analyses and spectral data (ir, nmr, and specific rotation), the copper (II) complexes were identified from the elemental analyses and the mass spectra (desorption chemical ionization with ammonia as reagent gas) that evidenced their dimeric structure.

b) Derivatives of (R)-cysteine. From the commercially available (R)-2-amino-3-methylthiopropanoic acid (commonly known as S-methyl-L-cysteine), by standard procedure, the methyl ester was obtained (as hydrochloride), later protected as Boc-derivative. $LiAlH_4$ reduction of this gave (R)-2-(Boc-amino)-3-methylthio-1-propanol (**6a**). This was the starting product of two ligands.

Deprotection of **6a** and condensation with SA gave (R)-2-(2-hydroxybenzylideneamino)-3-methylthio-1-propanol (**6l**), converted into its copper (II) complex **6m**.

A *m*.chloroperbenzoic acid (MCPBA) oxidation of **6a** gave (R)-2-(Boc-amino)-3-methylsulfonyl-1-propanol (**7a**), deprotected and condensed with SA to give (R)-2-(hydroxybenzylideneamino)-3-methylsulfonyl-1-propanol (**7l**), converted into its copper (II) complex **7m**.

From S-methyl-L-cysteine methyl ester hydrochloride, the free base was easily separated and its reaction with PhMgBr excess gave (R)-2-amino-1,1-diphenyl-3-methylthio-1-propanol (**8a**). This, condensed with SA, gave ligand **8l** significantly hindered in the equatorial belt by two phenyl groups. The reaction with copper (II) acetate, under standard conditions, gave the required metal complex **8m**.

All the above series of reactions are summarized in Scheme 3.

c) Derivatives of (S)-Methionine. Methionin derivatives were the starting products of four different copper (II) complexes.

From the commercially available L-methionine methyl ester hydrochloride, the free base was easily prepared. This was reduced to (S)-2-amino-4-methylthio-1-butanol (**9a**) (alternatively available as the commercially known methioninol) that was condensed with SA to give (S)-2-(2-hydroxybenzylideneamino)-4-methylthio-1-butanol (**9l**) and then its copper (II) complex **9m**.

Methioninol **9a** was Boc-protected and oxidized with MCPBA to give (S)-2-(Boc-amino)-4-methylsulfonyl-1-butanol (**10a**). Deprotection with CF_3COOH and condensation with SA allowed to isolate (S)-2-(2-hydroxybenzylideneamino)-4-methylsulfonyl-1-butanol (**10l**), converted into its copper (II) complex **10m**.

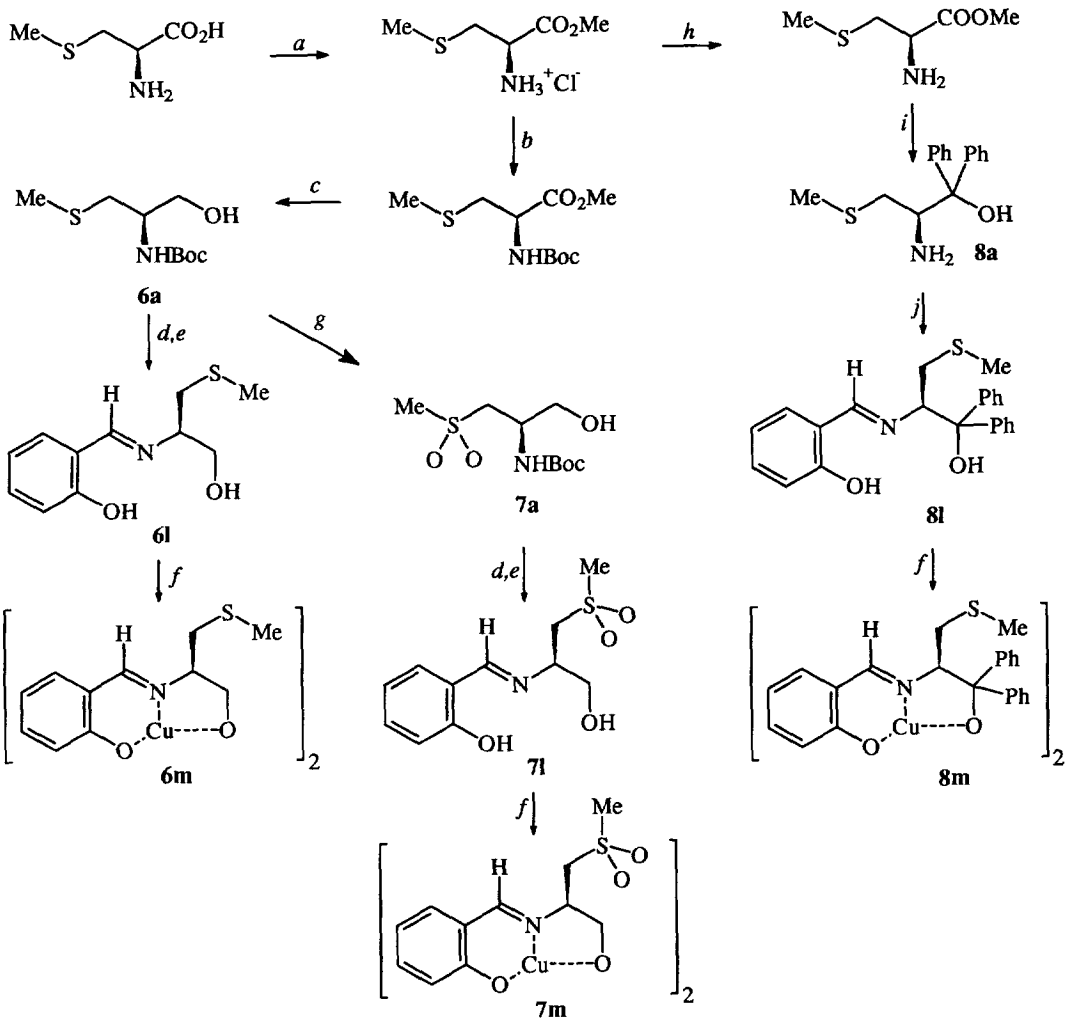
Finally, L-methionine methyl ester was made to react with excess of both MeMgJ and PhMgBr. (S)-2-amino-1,1-dimethyl-4-methylthio-1-butanol (**11a**: R = Me) was condensed with SA and (S)-1,1-dimethyl-2-(2-hydroxybenzylideneamino)-4-methylthio-1-butanol (**11l**: R = Me) was converted into the copper (II) complex **11m** (R = Me). From (S)-2-amino-1,1-diphenyl-4-methylthio-1-butanol (**12a**: R = Ph), condensation with SA gave (S)-1,1-diphenyl-2-(2-hydroxybenzylideneamino)-4-methylthio-1-butanol (**12l**: R = Ph), converted into the copper (II) complex **12m** (R = Ph).

The above series of reactions are summarized in Scheme 4.

Copper (II) complex-catalyzed Michael reactions.

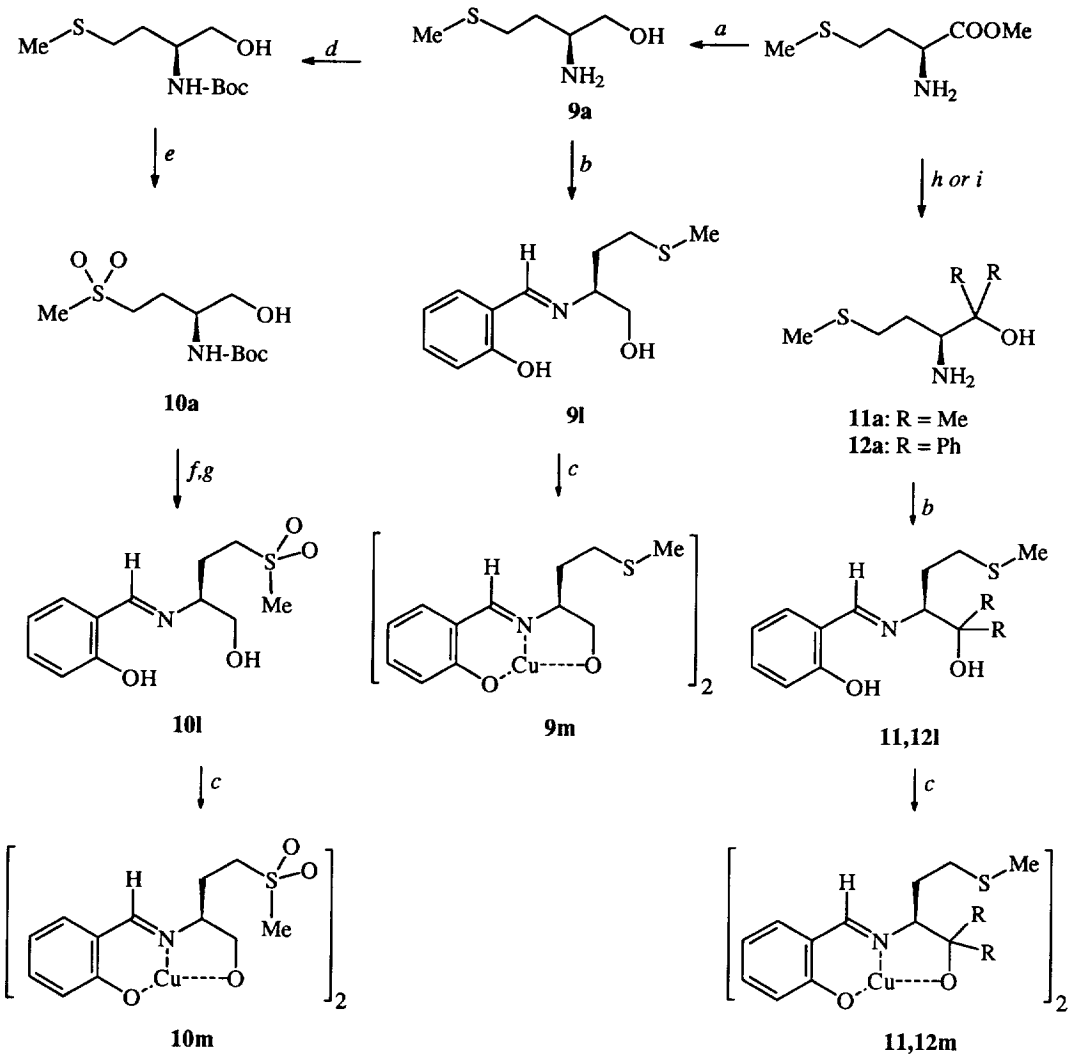
The eight new copper (II) complexes (**5-12m**) that satisfy the different options to modify the ligand architecture were tested *vs* the Michael reaction reported in Scheme 1. To compare their behaviour with those of the previously available catalysts (and specially with that of **4**), all experiments were run in carbon tetrachloride as solvent, at -20 °C, with a ratio [**1**] : [catalyst] = 100.[1,3]

Scheme 3



a) $SOCl_2$/MeOH/-8 °C → rt; *b)* $(Boc)_2O/Et_3N$/Dioxane/H_2O/rt; *c)* $LiAlH_4/Et_2O/\Delta$; *d)* CF_3COOH/0 °C → rt; *e)* SA/MeOH/K_2CO_3/Δ; *f)* $Cu(OAc)_2$/MeOH/Δ; *g)* MCPBA/CH_2Cl_2/0 °C → rt; *h)* $NaHCO_3/H_2O$; *i)* $PhMgBr/Et_2O/\Delta$; *j)* SA/MeOH/Δ.

Scheme 4



a) $LiAlH_4/Et_2O/\Delta$; *b)* SA/MeOH/Δ; *c)* $Cu(OAc)_2$/MeOH/Δ; *d)* $(Boc)_2O/Et_3N$/Dioxane/H_2O/rt; *e)* MCPBA/CH_2Cl_2/0 °C → rt; *f)* CF_3COOH/0 °C → rt; *g)* SA/MeOH/K_2CO_3/Δ; *h)* MeMgJ/Et_2O Δ (**11a**); *i)* PhMgBr/Et_2O/Δ (**12a**).

All catalysts, under the above conditions, gave nearly quantitative yields of **3** within 3 days. A rather unexpected low chemical yield was observed in the reaction with the methyl sulfonyl substituted catalyst **10m** even if the reaction is run with a molar ratio [**1**] : [**10m**] = 10 (entries 6 and 7). No satisfactory explanation for this behaviour can be offered. Solvent was then evaporated, the residue chromatographed through a short siliga-gel column, **3** was separated, recrystallized from diethyl ether and its rotatory power was measured in benzene. The enantiomeric excess values reported in Table 1 are the average of three independent experiments, (S)-**3** was always the main product.

Table 1. Cu (II)-catalyzed Michael reactions of **1** and **2**.

Entry	Catalyst[a]	e.e. %[b]
1	**4**	70 ± 2[c]
2	**5m**	75 ± 2
3	**6m**	61 ± 1
4	**9m**	56 ± 3
5	**7m**	56 ± 1
6	**10m**	66 ± 3[d]
7	**10m**[e]	64[d]
8	**8m**	45 ± 1
9	**11m**	20 ± 1
10	**12m**	42 ± 1

[a]Molar ratio [**1**] : [catalyst] = 100; reaction conditions: solvent CCl_4, -20 °C, 3 days; [b]The enantiomeric excess is the average of three independent experiments and (S)-**3** was always the main product; the purity of the starting chiral amino acid (97-99%) was not taken into account; [c]data taken from the literature (ref. 3); [d]after 3 days **3** was isolated in about 50% yield, not significantly ameliorated after a longer reaction time; [e]single experiment run with a molar ratio [1] : [catalyst] = 10.

DISCUSSION

With the above data in hands, the effect of the architecture of the ligand on the degree of enantioselection induced in the Michael reaction between **1** and **2** can be discussed.

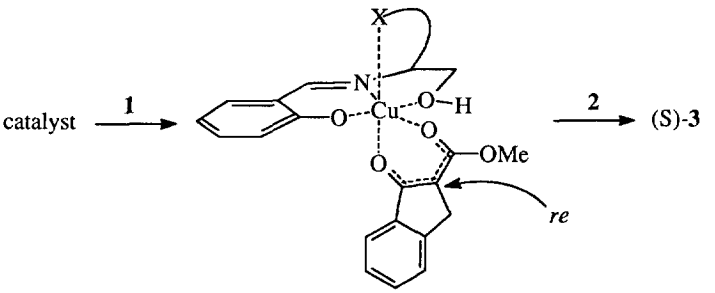
First of all the negative effect of an increase of the steric hindrance of the equatorial belt of the complex can be pointed out from the e.e.s obtained from **8,11,12m**, lower than those (**7m** and **9m** respectively) obtained if a methylene group is mantained at the tunable site *f* (Fig. 1). This negative effect is stronger for methyl than for phenyl groups (**11m** *vs* **12m**).

These results are sharply in contrast with those of Brunner and Miehling[14] and Aratani,[15] whose excellent results in the efficiency of a chiral copper (II) catalyst for enantioselective cyclopropanation were obtained when the chiral 2-(2-hydroxybenzylideneamino)-3-substituted-1-propanol ligand had two phenyl

groups (Brunner) or two 2-butoxy-5-*tert*-butylphenyl groups (Aratani) in the 1-position. Obviously the differing intermediates involved make a ligand tailored for cyclopropanation unappropriate for a Michael reaction.

The supposed axial ligand is also important for the efficiency of the catalyst. Each other part of the ligand being constant, the effect of three groups can be compared (OH, SMe, SO_2Me in **5m**, **9m**, and **10m**) comparing their respective e.e.s: 75, 56, and 66% respectively. The best result is obtained if the ethylene fragment has OH as the terminal group. Taking into account the effect of 3-ethyl and 3-*i*.butil groups[1] (50 and 53% e.e.), these are not too far from those of 2-(methylthio)ethyl and 2-(methylsulfonyl)ethyl groups. This could mean that, whereas OH behaves as an axial ligand, SMe and SO_2Me are ordinary steric hindering groups. This seems to be further supported by the results of methionine derivatives (**9,10m**), very close to those of methylcysteine derivatives (**6,7m**), the sulfur atom of these being unable to behave as ligand for the insufficient length of the chain. The result obtained with all these catalysts can be due to the steric effect of substituents X that hinder a face of the catalyst, force a selective complexation of deprotonated **1** and, given the configuration of the chiral centre, favour the attack of **2** to the *re* face thus giving (S)-**3** (Scheme 5).

Scheme 5



The last point to be discussed is the comparison of the results obtained with **4** *vs* **5m**. The ligand derived from aspartic acid gives a catalyst more efficient than that derived from glutamic acid. Assuming that both complexes are tetradentate with a square pyramidal coordination, the seven-membered ring Cu-O-C-C-C-C-N detectable in **4**, becomes a conformationally more favoured six-membered ring in **5m**, and this could be the reason of a better rigidity and efficiency of the latter catalyst.

In conclusion, the metal catalysts of the Michael reaction between **1** and **2** that give the best results in terms of enantioselectivity are those supposed to be tetradentate.

Unfortunately a direct proof of this cannot be given since any attempt to obtain crystals of **4** or **5m**, suitable for X-ray analysis, failed. Certainly the less efficient copper (II) catalyst **12m** is tridentate since its crystal structure[16] shows the sulfur atom faraway from the axial position over the copper.

The detailled research and its results reported in this paper suggest that efficient copper (II) catalysts for enantioselective Michael reactions can be prepared with Schiff base ligands from SA and amino alcohols derived from aspartic and glutamic acids.

Small changes of the architecture of these catalysts will not be enough to ensure significant improvements of the enantioselectivity of the catalytic process and different routes should be experienced.

EXPERIMENTAL

Melting points were determined by the capillary method and are uncorrected. Elemental analyses were made on C. Erba CHN analyzer mod. 1106. ^{1}H-Nmr ($CDCl_3$, TMS as standard) were recorded on a Bruker AC 300 spectrometer, i.r. spectra (nujol mulls) on a Perkin Elmer 983 spectrophotometer, optical rotations at room temperature on a Perkin Elmer 241 polarimeter with 1 dm cell, mass spectra of the copper (II) complexes [desorption chemical ionization (CDI) with ammonia, 63 Pa pressure and 150 °C source temperature, rhenium wire programmed with 20 mA/s up to 1 A] on a Finnigan MAT 8222 mass spectrometer.

Materials. L-Aspartic acid, L-methionine methyl ester hydrochloride, (S)-methioninol, and S-methyl-L-cysteine were commercial product (Aldrich).

(S)-tert-Butoxycarbonylamino aspartic acid diethyl ester. The procedure adopted follows the general method of preparation of *tert*.butyloxycarbonylated amino acids.[17] (S)-Aspartic acid diethyl ester hydrochloride[13] (20 g - 89 mmol) was dissolved in 20 ml H_2O and 50 ml dioxane and cooled at 0 °C. Under stirring, triethylamine (24.8 ml - 0.18 mol) and then di-*tert*.butyl-dicarbonate (25.2 g - 0.115 mol) were added. Stirring was continued for two hours, the solvent was evaporated and the residue stirred with an aqueous 10% solution of citric acid, adjusting the pH at 2-3. The aqueous solution was extracted with diethyl ether, the organic phase dried and evaporated to give the Boc-derivative as a light yellow oil (24.2 g - 94%). Ir: $\nu_{C=O}$ = 1730 cm^{-1}. ^{1}H-Nmr: δ = 1.38 (3H, t, J = 7 Hz, -CH_2CH_3), 1.40 (3H, t, J = 7 Hz, -CH_2CH_3), 1.50 (9H, s, *ter.Bu*), 2.93 (2H, m, *H*-3), 4.25 (4H, m, -OCH_2-), 4.63 (1H, m, *H*-2), and 5.6 (1H, bs, -N*H*). This product can be used without any further purification.

(S)-2-(tert-Butoxycarbonylamino)-1,4-butandiol (5a). An ethereal solution of (S)-N-Boc-aspartic acid diethyl ester (6.36 g - 22 mmol) was added dropwise to a stirred ethereal suspension of $LiAlH_4$ (3.34 g - 88 mmol). The reaction mixture was refluxed for one hour, then quenched with ethyl acetate, brine and water. The organic layer was separated and the aqueous phase was extracted with four portions of diethyl ether. All the ethereal phases were collected, dried, and the solvent evaporated. **5a** was obtained as a viscous oil that crystallized on standing (2.9 g - 64%). Soft white needles, m.p. 64-5 °C (after 4 hrs drying at 50 °C/0.1 torr), were obtained from diethyl ether. Ir: $\nu_{OH,NH}$ = 3340 cm^{-1} (broad band), $\nu_{C=O}$ = 1686 cm^{-1}. ^{1}H-Nmr: δ = 1.45 (9H, s, *ter.Bu*), 1.62 (2H, m, *H*-3), 3.5 (1H, bs, -O*H*, exch. D_2O), 3.65 (4H, m, -CH_2O-), 3.8 (2H, m, *H*-2 and -O*H*, one exch. D_2O), 5.19 (1H, d, -N*H*, exch. D_2O). Elem. anal.; calc. for $C_9H_{19}NO_4$: C, 52.7; H, 9.3; N, 6.8. Found: C, 53.0; H, 9.6; N, 6.8. $[\alpha]_D$ = -9° (c = 1.00, chloroform).

Methyl (R)-2-amino-3-methylthiopropanoate hydrochloride. Thionyl chloride (26 ml) was added dropwise to methanol (100 ml) stirred ad cooled at -10 °C, then (S)-methyl-L-cysteine (13.5 g - 0.1 mol) was added portionwise. Stirring was continued at room temperature for further two hours, then the clear solution was set aside for one night. The solvent was evaporated and to the white residue, dissolved in methanol (50 ml), anhydrous diethyl ether (250 ml) was added. The methyl ester separated as hydrochloride (16.1 g - 87%). M.p. 143-4 °C (Lit.,[18] 142-3 °C).

Methyl (R)-2-(tert.butoxycarbonylamino)-3-methylthiopropanoate. To the above described S-methyl-L-cysteine methyl ester hydrochloride (10 g - 54 mmol) in water (10 ml) and dioxane (30 ml), triethylamine (15 ml) and then di-*tert*-butyl-dicarbonate (15.3 g - 70 mmol) were added. Following the method[17] above reported, the Boc-derivative was obtained as colourless oil (12.6 g - 94%), whose ^{1}H-nmr spectrum was identical to that reported in the literature.[19]

(R)-2-(tert.butoxycarbonylamino)-3-methylthio-1-propanol (6a). An ethereal solution of N-Boc-(S)-methyl-L-cysteine methyl ester (12.2 g - 48.8 mmol) was added dropwise to a stirred ethereal suspension of $LiAlH_4$ (4.63 g - 122 mmol). The reaction mixture was refluxed 30 minutes, then quenched. **6a** was isolated following the protocol described for **5a** and a viscous oil was obtained that crystallized on standing (8.24 g - 76%). White crystals, m.p. 56-7 °C (after drying 8 hrs at 40 °C/0.1 torr), were obtained from benzene. Ir: $\nu_{OH,NH}$ = 3350 cm^{-1} (broad band), $\nu_{C=O}$ = 1680 cm^{-1}. ^{1}H-Nmr: δ = 1.48 (9H, s, *ter.Bu*), 2.12 (3H, s, S*Me*), 2.60 (1H, bs, -O*H*, exch. D_2O), 2.69 (2H, m, *H*-3), 3.75 (3H, m, *H*-1 and *H*-2), 5.05 (1H, bs, -N*H*, exch. D_2O). Elem. anal.; calc. for $C_9H_{19}NO_3S$: C, 48.9; H, 8.7; N, 6.3. Found: C, 49.0; H, 8.8; N, 6.3. $[\alpha]_D$ = -25° (c = 1.00, chloroform).

(R)-2-(tert.butoxycarbonylamino)-3-methylsulfonyl-1-propanol (7a). Commercial 50% 3-chloroperbenzoic acid (12.5 g - 36 mmol) was added portionwise under stirring to an ice-cooled solution of **6a** (4.0 g - 18 mmol) in dichloromethane (100 ml). Stirring was continued at room temperature for one hour, then *m*.chlorobenzoic acid was filtered and the solvent was eliminated. The white residue was dissolved in 100 ml of water and solid $NaHCO_3$ (about 5 g) was added. The solution, whose pH was about 8, was extracted several times with chloroform. This, dried and evaporated, gave **7a** (4.25 g - 95%) crystallized from benzene, m.p. 124-5 °C (after 2 hrs drying at 80 °C/0.1 torr). Ir: $\nu_{OH,NH}$ = 3360 cm^{-1} (broad band), $\nu_{C=O}$ = 1690 cm^{-1}. ^{1}H-Nmr: δ = 1.45 (9H, s, *ter.Bu*), 2.75 (1H, s, O*H*, exch. D_2O), 3.00 (3H, s, SO_2*Me*), 3.38 (2H, m, $J_{2,3}$ = 6 Hz, SO_2CH_2), 3.88 (2H, m, $J_{1,2}$ = 4.2 Hz, CH_2OH), 4.43 (1H, m, C*H*NH), 5.35 (1H, bd, N*H*, exch D_2O). Elem. anal.; calc. for $C_9H_{19}NO_5S$: C, 42.7; H, 7.6; N, 5.5. Found: C, 43.0; H, 7.6; N, 5.5. $[\alpha]_D$ = -5° (c = 0.31, chloroform).

(R)-2-amino-1,1-diphenyl-3-methylthio-1-propanol (8a). An ethereal solution of methyl (R)-2-amino-3-methylthiopropanoate (5.0 g - 33 mmol - from the above described hydrochloride dissolved in water, neutralized to pH 8 with solid $NaHCO_3$ and extracted several times with ethyl acetate - yield 84%) was added dropwise under stirring to a solution of phenyl magnesium bromide (0.15 mol) in 60 ml of diethyl ether. The reaction mixture was refluxed one hour, then quenched with aqueous ammonium chloride. The organic layer was separated and the aqueous phase was extracted three times with diethyl ether. After drying, the organic fractions were evaporated and the oilly residue was column chromatographed over silica gel 230-400 mesh, cyclohexane/ethyl acetate 8:2 being the eluant. **8a** was obtained as white crystals, m.p. 59-60 °C (after 8 hrs drying at 40 °C/0.1 torr) from cyclohexane/light petrol ether (5.5 g - 60%). ^{1}H-Nmr: δ = 1.60 (3H, bs, -O*H* and -NH_2, exch. D_2O), 2.05 (3H, s, S*Me*), 2.40 (2H, *H*-3, AB part of ABX system, $J_{3,3'}$ = -13.5 Hz, J_{23} = 3 Hz, $J_{23'}$ = 10.5 Hz), 4.05 (1H, dd, *H*-2), 7.1-7.6 (10H, m, *aromatics*). Elem. anal.; calc. for $C_{16}H_{19}NOS$: C, 70.3; H, 7.0; N, 5.1. Found: C, 70.3; H, 7.1; N, 5.1. $[\alpha]_D$ = -75° (c = 0.66, chloroform).

(S)-2-(tert.butoxycarbonylamino)-4-methylthio-1-butanol. To a dioxane solution (15 ml) of (S)-2-amino-4-methylthio-1-butanol (**9a**) (1.0 g - 7.4 mmol), under stirring and cooling, triethylamine (1.0 ml - 7.4 mmol) and then di-*tert*.butyl-dicarbonate (2.1 g - 9.6 mmol) were added. Following the method[17] above

reported, the Boc-derivative of methioninol was obtained as a viscous oil that crystallized on standing (1.6 g - 92%), m.p. 47-8 °C (Lit.[20] m.p. 44-6 °C). The ^{1}H-nmr spectrum is identical to that reported in the literature,[20] whose synthesis was performed following a different strategy.

*(S)-2-(tert.butoxycarbonylamino)-4-methylsulfonyl-1-butanol (**10a**).* Commercial 50% *m*.chloroperbenzoic acid (4.7 g - 13.6 mmol) was added portionwise, under stirring, to an ice-cooled solution in dichloromethane (40 ml) of Boc-methioninol (1.6 g - 6.8 mmol). Following the methodology previously decribed for **7a**, **10a** was obtained (1.7 g - 94%) as white crystals, m.p. 99-100 °C from benzene. Ir: $\nu_{OH,}$ = 3530 cm^{-1}, ν_{NH} = 3360 cm^{-1}, $\nu_{C=O}$ = 1684 cm^{-1}. ^{1}H-Nmr: δ = 1.45 (9H, s, *ter.Bu*), 2.10 (2H, m, *H*-3), 2.40 (1H, bs, -O*H*, exch. D_2O), 2.90 (3H, s, SO_2*Me*), 3.10 (2H, t, *J* = 8 Hz, *H*-4), 3.70 (3H, m, *H*-1 and *H*-2), 4.91 (1H, d, -N*H*, exch. D_2O). Elem. anal.; calc. for $C_{10}H_{21}NO_5S$: C, 44.9; H, 7.9; N, 5.2. Found: C, 45.2; H, 8.1; N, 5.3. $[\alpha]_D$ = +0.1°; $[\alpha]_{578}$ = +0.6° (c = 0.80, chloroform).

*(S)-2-amino-1,1-dimethyl-4-methylthio-1-butanolo (**11a**).* An ethereal solution of methyl (S)-methioninate (5.5 g - 33.8 mmol - from the commercially available hydrochloride dissolved in water, neutralized to pH 8 with solid $NaHCO_3$, and extracted several times with ethyl acetate - yield 69% - Lit.[21] b.p. 121-3 °C/12 torr) was added dropwise and under stirring to a solution of methyl magnesium iodide (0.15 mol) in 60 ml diethyl ether. Following the procedure described for **8a** an oilly residue was obtained that was distilled under vacuum. **11a** was obtained as a light yellow oil (1.6 g - 29%), b.p. 90 °C/0.5 torr. Ir: $\nu_{OH,,NH}$ = 3370 cm^{-1}. ^{1}H-Nmr: δ = 1.10 and 1.20 (3H + 3H, s + s, -C*Me*$_2$), 1.50 (3H, -N*H*$_2$, -O*H*, exch. D_2O), 1.4 and 1.9 (1H + 1H, m + m, *H*-3), 2.10 (3H, s, -S*Me*), 2.65 (3H, m, *H*-2 and *H*-4). Elem. anal.; calc. for $C_7H_{17}NOS$: C, 51.5; H, 10.5; N, 8.6. Found: C, 51.9; H, 10.8; N, 8.4. $[\alpha]_D$ = -44°; (c = 1.06, chloroform)

*(S)-2-amino-1,1-diphenyl-4-methylthio-1-butanolo (**12a**).* An ethereal solution of methyl (S)-methioninate (5.1 g - 31.3 mmol) was added dropwise and under stirring to a solution of phenyl magnesium bromide (0.143 mol) in 60 ml diethyl ether. Following the procedure described for **8a** a pasty solid was obtained that crystallized from cyclohexane/light petrol ether (5.3 g - 59%) m.p. 97-8 °C (Lit.,[22] m.p. 96-8 °C). The ^{1}H-nmr spectrum is identical to that reported in the literature.[22]

*Preparation of 2-(2-hydroxybenzylideneamino) derivatives **5-12l**. General procedure.*

a) To the cooled and stirred 3- (or 4-) substituted 2-(Boc-amino)-1-propanol (or -1-butanol) **5-7,10a** (5 mmol), trifluoroacetic acid (5 ml) was added dropwise. After half an hour stirring at room temperature, the acid was eliminated under vacuum. Methanol (50 ml), K_2CO_3 (0.83 g - 6 mmol) and salicylaldehyde (0.61 g - 5 mmol) were added to the brownish residue and the mixture was refluxed under stirring for 4 hours. The yellow solution was evaporated, ethyl acetate (30 ml) was added that let inorganic salts undissolved. The ethyl acetate solution was evaporated and the residue was column chromatographed over silica gel 230-400 mesh and eluted with a mixture of cyclohexane/ethyl acetate to give the ligands as pure products.

b) A solution of 3- or 4-substituted 2-amino-1-propanol (or 1-butanol) **8,9,11,12a** (5 mmol) and salicylaldehyde (0.61 g - 5 mmol) in methanol (50 ml) was refluxed for 4 hours. The yellow solution was evaporated and the residue was column chromatographed as above.

Further details of the separation, yields and the physical and spectroscopic data are reported in Table 2.

Table 2. Physical and spectroscopic properties and elemental analyses of 2-(2-hydroxybenzylideneamino) derivatives **5-12l**.

Ligand	Method prep.	Yield %	M.p. °C solvent	$[\alpha]_D$ $[\alpha]_{578}$ (c, solvent)	Elemental analyses[a] Formula	C	H	N	^{1}H-Nmr spectrum
5l	(a)[b]	55	c	-61 -64 (0.61, $CHCl_3$)	$C_{11}H_{15}NO_3$	(63.1) 63.5	(7.2) 6.9	(6.7) 6.8	8.40 (1H, s, benzylidene H)
6l	(a)[f]	67	59-60 diisop. ether	-166 -172 (1.02, $CHCl_3$)	$C_{11}H_{15}NO_2S$	(58.6) 58.8	(6.7) 6.7	(6.2) 6.0	2.12 (3H, s, SCH_3), 8.41 (1H, s, benzylidene H)
7l	(a)[e]	52	120-1 n.butanol	-156 -163 (1.02, $CHCl_3$)	$C_{11}H_{15}NO_4S$	(51.3) 51.2	(5.9) 5.9	(5.4) 5.3	2.85 (3H, s, SO_2CH_3), 8.50 (1H, s, benzylidene H)
8l	(b)[d]	95	125-6 cyclohexane	-56 -58 (2.09, $CHCl_3$)	$C_{23}H_{23}NO_2S$	(73.2) 73.3	(6.1) 6.0	(3.7) 3.6	1.95 (3H, s, SCH_3), 4.33 (1H, dd, J = 3.5 and 8.5 Hz, *H*-2), 8.43 (1H, s, benzylidene H)
9l	(b)[d]	85	43-5 cyclohexane	-133 -139 (1.0, $CHCl_3$)	$C_{12}H_{17}NO_2S$	(60.2) 60.4	(7.2) 7.3	(5.9) 5.9	2.08 (3H, s, SCH_3), 8.40 (1H, s, benzylidene H)
10l	(a)[e]	40	94-5 benzene	-86 -91 (0.8, $CHCl_3$)	$C_{12}H_{17}NO_4S$	(53.1) 53.6	(6.3) 6.3	(5.2) 5.0	2.88 (3H, s, SO_2CH_3), 8.35 (1H, s, benzylidene H)
11l	(b)[b]	46	g	-110 -116 (1.42, $CHCl_3$)	$C_{14}H_{21}NO_2S$	(62.9) 62.7	(7.9) 8.0	(5.2) 4.9	1.28 and 1.29 (3H+3H, s+s, CMe_2), 2.06 (3H, s, SCH_3), 3.20 (1H, dd, J = 10 and 3 Hz, *H*-2), 8.38 (1H, s, benzylidene H)
12l	(b)[b]	59	157-9 cyclohexane	-31 -31 (1.31, $CHCl_3$)	$C_{24}H_{25}NO_2S$	(73.6) 73.5	(6.4) 6.5	(3.6) 3.5	1.92 (3H, s, SCH_3), 4.51 (1H,dd, J=2.5 and 10 Hz, *H*-2) 8.32 (1H, s, benzylidene H)

[a]Calculated values in parentheses; [b]eluant: cyclohexane-ethyl acetate 7:3; [c]yellowish viscous oil distilled bulb to bulb at about 180 °C/0.1 torr; [d]purified by crystallization; [e]eluant: cyclohexane-ethyl acetate 8:2; [f]eluant: cyclohexane-ethyl acetate 6:4; [g]yellow oil.

Table 3. Physical and spectroscopic properties and elemental analyses of bis [copper (II)] complexes **5-12m**.

Ligand	Yield %	M.p. °C solvent	$[\alpha]_D$ $[\alpha]_{578}$ (c, solvent)	Formula	Elemental analyses[a] C	H	N	Mass spectrum[b] (m/z)
5m	95	150-2[c] ethyl acetate	+380 +369 (0.045, acetone)	$C_{22}H_{26}N_2O_6Cu_2$[d]	(45.7) 45.9	(5.2) 4.8	(4.7) 4.7	541 $(M + H)^+$
6m	58	138-40 EtOH/dii.pr ether	-166 -175 (1.02, $CHCl_3$)	$C_{22}H_{26}N_2O_4S_2Cu_2$	(46.0) 45.9	(4.6) 4.2	(4.9) 4.7	574 $(M + H)^+$
7m	89	225-8[c] [e]	-22 -133 (0.03, acetone)	$C_{22}H_{26}N_2O_8S_2Cu_2$	(41.4) 41.0	(4.1) 3.9	(4.4) 4.3	638 $(M + H)^+$
8m	92	215-6[c] MeOH	-308 -512 (0.025, acetone)	$C_{46}H_{42}N_2O_4S_2Cu_2$	(62.9) 62.7	(4.8) 4.8	(3.2) 3.2	879 $(M + H)^+$
9m	93	125-6[f] EtOH/dii.pr ether	-40 -88 (0.05, acetone)	$C_{24}H_{30}N_2O_4S_2Cu_2$	(47.9) 48.1	(5.0) 5.0	(4.7) 4.5	601 $(M + H)^+$
10m	88	258-60 [e]	[g]	$C_{24}H_{30}N_2O_8S_2Cu_2$	(43.3) 43.9	(4.5) 4.5	(4.2) 4.2	667 $(M + H)^+$
11m	96	267-8[c] dii.pr ether	+750 +359 (0.022, acetone)	$C_{28}H_{38}N_2O_4S_2Cu_2$	(51.1) 51.1	(5.8) 5.8	(4.3) 4.2	658 $(M + H)^+$
12m	95	142-3[c] EtOH	-333 -433 (0.02, acetone)	$C_{48}H_{46}N_2O_4S_2Cu_2$	(63.6) 63.3	(5.1) 4.8	(3.1) 3.4	907 $(M + H)^+$

[a]Calculated values in parentheses; [b]DCI; [c]after drying for 3 days (130 °C, 1 torr); [d]analyzed with 2 H_2O; [e]the crude filtered product is wash with hot methanol (15 ml) and ethanol (15 ml) and used without any further purification; [f]after drying for 3 days (78 °C, 1 torr); [g]the solubility in ordinary organic solvents was too low to determine the optical rotations.

Preparation of the bis[copper (II)] complexes ***5-12m****. General method.*

The suitable ligand **5-12l** (4 mmol) was dissolved in methanol (50-70 ml) and finely divided $Cu(OAc)_2$ (0.8 g - 4 mmol) was added. The mixture was refluxed for 4 hrs under magnetic stirring. **10m** separated out from the hot reaction mixture and was filtered out. If the green copper (II) complex separated on cooling from the reaction mixture (**7,8m**), it was filtered off; otherwise methanol was evaporated and the green residue was recrystallized from the suitable solvent. Further crops of **7m** and **8m** were obtained from the evaporated mother liquors. Yields, physical and spectroscopic properties and the elemental analyses of all bis [copper (II)] complexes are reported in Table 3.

Catalyzed Michael reaction of ***1*** *and* ***2****. General procedure.*

To a solution of **1**[23] (0.38 g - 2 mmol) and freshly distilled **2** (0.42 g - 6 mmol) in carbon tetrachloride (30 ml), the copper (II) complex **5-12m** (0.02 mmol) was added. The mixture was stirred at -20 °C untill tlc showed the disappearance of **1** (about 3 days - for **10m** see data in Table 1). Solvent was evaporated under vacuum and the residue was chromatographed (dichloromethane as eluant) over 25 g of 230-400 mesh silicagel. After an eventual crop of starting product **1** (for **10m**), **3** was separated, the solvent evaporated, and the residue dissolved in diethyl ether. After cooling at -15 °C, **3** was filtered off and its rotatory power was measured at 578 nm in benzene (c = 2) at room temperature. The e.e. was determined taking into account the rotatory power of pure (R)-3 was $[\alpha]_{578}$ = +77.0 (c = 2, benzene, 25 °C).[24]

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REFERENCES AND NOTES

1) Part X. Desimoni, G.; Faita, G.; Mellerio, G.; Righetti, P.P.; Zanelli, C. *Gazz. Chim. Ital.* **1992**, *122*, 269.
2) Brunner, H.; Hammer, B. *Angew. Chem. Int., Ed. Eng.* **1984**, *23*, 312.
3) Desimoni, G.; Quadrelli, P.; Righetti, P.P. *Tetrahedron* **1990**, *46*, 2927.
4) Botteghi, C.; Paganelli, S.; Schionato, A.; Boga, C.; Fava, A. *J. Mol. Catal.* **1991**, *6*, 7.
5) Aoki, S.; Sasaki, S.; Koga, K. *Heterocycles* **1992**, *33*, 493.
6) Bonadies, F.; Lattanzi, A.; Orelli, L.R.; Pesci, S.; Scettri, A. *Tetrahedron Lett.* **1993**, *34*, 7649.
7) Chiari, B.; Piovesana, O.; Tarantelli, T.; Zanazzi, P.F. *Inorg. Chem.* **1989**, *28*, 2141.
8) Astheimer, H.; Nepven, F.; Walz, L.; Haase, W. *J. Chem. Soc. Dalton Trans.* **1985**, 315.
9) Damiano, P.; Musatti, A.; Nardelli, M.; Pelizzi, C.; Predieri, G. *J. Chem. Soc. Dalton Trans.* **1979**, 1266.
10) Belokon', Y.N.; Zel'tzer, I.E.; Bakhmutor, V.I.; Saporovskaya, M.B.; Ryzhov, M.G.; Yanovsky, A.I.; Struchkov, Y.T.; Belikov, V.M. *J. Am. Chem. Soc.* **1983**, *105*, 2010.
11) du Preez, J.G.H.; van Brecht, B.J.A.M. *J. Chem. Soc. Dalton Trans.* **1989**, 253.
12) Sugimori, T.; Shibakawa, K.; Masuda, H.; Odami, A.; Yamanchi, O. *Inorg. Chem.* **1993**, *32*, 4951.
13) Neuman, R.E.; Smith, E.L. *Biol. Chem.* **1951**, *193*, 97.

14) Brunner, H.; Miehling, W. *Monatsch. Chem.* **1984**, *115*, 1237.
15) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839 and references therein.
16) Tadini, C. to be published.
17) Moroder, L.; Hallett, A.; Wünsch, E.; Keller, O.; Wersin, G.; Hoppe-Seyler's Z. *Physiol. Chem.* **1976**, *357*, 1651.
18) Damoglou, A.P.; Lindley, H.; Stapleton, I.W. *Biochem. J.* **1971**, *123*, 379.
19) Climie, I.J.G.; Evans, D.A. *Tetrahedron* **1982**, *38*, 697.
20) Tani, K.; Otsuka, S.; Kido, M.; Miura, I.J. *J. Am. Chem. Soc.* **1980**, *102*, 7394.
21) Brenner, M.; Huber, W. *Helv. Chim. Acta* **1953**, *36*, 1109.
22) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc. Perkin Trans. I* **1985**, 2039.
23) House, H.O.; Hudson, C.B. *J. Org. Chem.* **1970**, *35*, 647.
24) Wynberg, H.; Helder, R. *Tetrahedron Lett.* **1975**, 405.

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