COPPER(II) IN ORGANIC SYNTHESIS. VIII[1] ENANTIOSELECTIVE MICHAEL REACTIONS WITH CHIRAL COPPER(II) COMPLEXES AS CATALYSTS

G. DESIMONI,* P. QUADRELLI and P. P. RIGHETTI

Dipartimento di Chimica Organica dell'Università
Viale Taramelli, 10, 27100 Pavia, Italy

Abstract - Using copper(II) chiral complexes as catalysts, enantioselective Michael reactions were performed. The degree of enantioselectivity depended on the design of the catalyst and the best results (70% e.e.) were obtained with tetradentate ligands.

The catalytic enantioselective Michael reaction is still a process of fundamental importance even though it has already been achieved using alkaloids,[2] polymer-bound alkaloids,[3] chiral crown ethers and bases,[4] optically active Co(II) complexes,[5] and natural proteins[6] as catalysts.

Since 1,3-dicarbonyl compounds are preparatively alkylated with α,β-unsaturated carbonyl derivatives using Cu(II) acetate as catalyst,[7] the development of optically active Cu(II) complexes was the obvious extension to prove the feasibility of performing enantioselective Michael reactions under these catalytic conditions. To compare our hoped results with those known from the literature, we selected as a test the conversion of methyl indan-1-one-2-carboxylate (1) into 3-butene-2-one (2) (Scheme 1), whose (R)-product (3) is known to have a maximum rotation of $[\alpha]_{578}= +77.0°$ (c, 2, benzene, 25 °C).[2]

The first step was to test two enantiomeric copper(II) complexes, 4 and 5, [with Schiff's bases, derived from salicylaldehyde and (R)- and (S)-α-methyl benzylamine[8] respectively, behaving as bidentate ligands] whose tetrahedral structures can be proposed in analogy with the X-ray structures taken from the literature.[9]

In dioxan (20 °C - 48h) with a molar ratio [1]:[catalyst] = 10, the Michael reaction occurred in about quantitative yield, but 3 was optically inactive.

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Scheme 1

|			
1	**2**	**(R)-3**	**(S)-3**
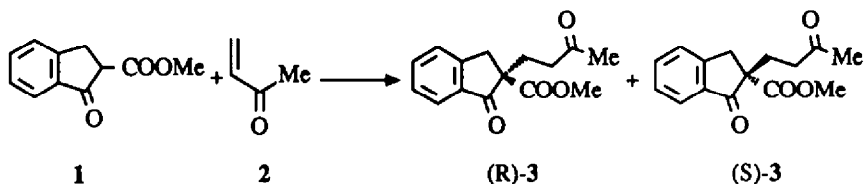
As a general comment to transition-metal-catalyzed Michael reactions, the mechanism[5,7] involves displacement of one bidentate ligand from the complex to bind the deprotonated 1,3-dicarbonyl compound whose two faces become diastereotopic if the complex offers a chiral environment. To induce a good enantioselection, the complex should fulfil the following requirements: a) rigidity; b) high degree of regioselectivity in complexation of the 1,3-dicarbonyl reagent; c) anchimeric assistance to the attack of the acceptor reagent offered by some group in the complex (which should greatly favour enantioselection).

The failure of **4** and **5** to induce enantioselectivity could be due either to a low regioselective complexation of deprotonated **1** or to an inefficient chiral environment in a non-rigid structure.

(R)-4	**(S)-5**
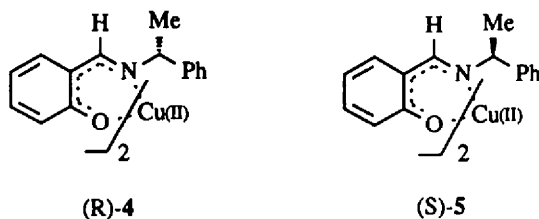
To increase the rigidity of the complex, tridentate Schiff's bases derived from salicylaldehyde and (R)- and (S)-2-aminobutanol and -2-amino-2-phenyl ethanol were prepared. These gave dimeric copper(II) complexes (**6-9**) whose structures can be proposed in analogy with those derived by X-ray analysis[10,11] of similar complexes. In addition to the square-planar coordination of dimers,[10,11] pyridoxal Schiff's base ligands have given tetrameric structures with a square-pyramidal coordination around each copper atom,[12] but in the present case the mass spectra of **6-9** rule out this possibility.

Whereas **6** and **7** easily crystallized with variable amounts of solvent which can be removed by heating under vacuum, **8** and **9** crystallized with four water molecules (see Experimental) and this could be the result of a preferred six-coordination around each copper atom.

(R)-**6**: R=Et	(S)-**7**: R=Et
(R)-**8**: R=Ph	(S)-**9**: R=Ph
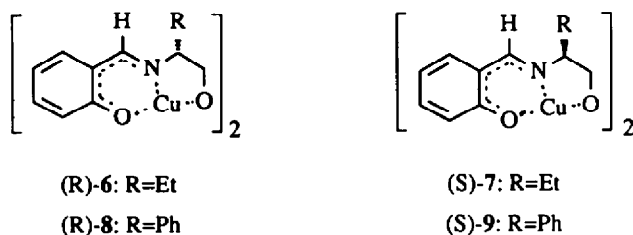
When the copper(II) complexes derived from tridentate ligands were tested as Michael catalysts under the conditions reported in Table 1, these not only gave almost quantitative yields of **3**, but optical induction was observed.

Table 1 - Cu(II)-catalyzed Michael addition of **1** and **2** with tridentate complexes

| Entry	Catalyst[a]	Conditions			e.e.% [b]
		Solvent	t°C	time	
1	6	dioxan	20	2d	13 ± 2 (R)
2	6	CCl$_4$	20	2d	54 ± 2 (R)
3	6	toluene	-70	3d	19 ± 2 (R)
4	7	dioxan	20	2d	16 ± 1 (S)
5	7	CCl$_4$	20	2d	50 ± 3 (S)
6	7	toluene	-70	3d	17 ± 2 (S)
7	8	dioxan	20	2d	5 ± 1 (S)
8	8	CCl$_4$	20	2d	7 ± 1 (S)
9	8	toluene	-70	3d	9 ± 2 (S)
10	9	dioxan	20	2d	3 ± 1 (R)
11	9	CCl$_4$	20	2d	5 ± 1 (R)
12	9	toluene	-70	3d	11 ± 2 (R)

(a) Molar ratio [**1**]:[catalyst]=10. (b) The chemical yield of **3** is always nearly quantitative and the main configuration of **3** is reported. The enantiomeric excess is the average of at least three indipendent experiments.

The ethyl-substituted complexes (**6** and **7**) gave an optical induction in the range 11 - 50%. This was not a function of the dielectric constant of the solvent, as in alkaloid-catalyzed Michael additions[12] (ϵ_r values of dioxan, carbon tetrachloride and toluene are 2.21, 2.23, 2.38 respectively), but a negative factor seems to be the ability of the solvent to enter in competition as a ligand.

A dramatic reduction of the optical induction was observed for the phenyl-substituted complexes (**8** and **9**). Furthermore, the configuration of the ligand did not have the same effect on the configuration of **3** [**6** and **8** preferentially gave (R)- and (S)-**3** respectively].

The above data clearly suggested a further step in the design of the catalyst: an increase in its rigidity to be realized if one axial position is occupied by the ligand itself, if a tetradentate ligand is used.

The Schiff's bases of salicylaldehyde with either (S)-2-amino-1,5-pentandiol or (S,S)-2-amino-3-phenyl-1,3-propandiol were prepared and their dimeric copper(II) complexes **10** and **11** were isolated. These crystallized with two and four water molecules respectively, this again being the result of a preferred six-coordination around the metal.
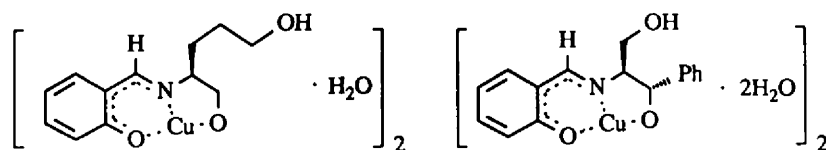
(S)-**10**   (S,S)-**11**

Only **10** has the "side arm" suitably designed to allow the hydroxy group to behave as axial ligand, but, if that of **11** is involved in hydrogen bonding with an axially placed molecule of water the required rigidity could be secured to the complex. Under these assumptions, both **10** and **11** have chiral copper atoms.

When these catalysts were tested on the Michael reaction of **1** and **2**, the results reported in Table 2 were obtained.

Table 2 - Cu(II) catalyzed Michael addition of **1** and **2** with tetradentate complexes

Entry	Catalyst	Ratio [1] : [cat.]	Conditions			e.e.%[a]
			Solvent	t°C	time	
1	**10**	10	dioxan	20	2d	8 ± 1 (S)
2	**10**	10	CCl_4	20	2d	60 ± 3 (S)
3	**10**	10	CCl_4	-20	3d	69 ± 4 (S)
4	**10**	100	CCl_4	-20	3d	70 ± 2 (S)
5	**10**	10	toluene	-70	3d	60 ± 3 (S)
6	**10**	10	Et_2O	-70	3d	10 ± 2 (S)
7	**11**[b]	10	dioxan	20	2d	8 ± 1 (S)
8	**11**[b]	10	CCl_4	20	2d	54 ± 3 (S)
9	**11**[b]	10	CCl_4	-20	3d	68 ± 2 (S)
10	**11**[b]	100	CCl_4	-20	3d	70 ± 2 (S)
11	**11**[b]	10	toluene	-70	3d	60 ± 2 (S)
12	**11**[b]	10	Et_2O	-70	3d	8 ± 2 (S)

(a) The chemical yield of **3** is always nearly quantitative and tha main configuration of **3** is reported.   The enantiomeric excess is the average of at least three indipendent experiments. (b) Hydrated complex (see Experimental).

Both catalysts gave nearly identical results. The enantiomeric excess was poor in dioxan at room temperature (entries 1, 7) but in carbon tetrachloride, both at r.t. and at -20 °C, and in toluene at -70 °C (entries 2, 3, 5, 8, 9, 11), the results became comparable with those obtained when alkaloids[2] or chiral cobalt complexes[5] are used as catalysts.

The reaction was tested with a ratio [1] : [catalyst] = 100 and the results were even better (entries 4, 10).

A mechanism can be proposed which allows the rationalization of the behaviour of the copper(II) catalysts (Scheme 2). When **10** reacts with **1**, the octahedral complex **12** is formed, which has a Δ-configuration if the ketone-carbonyl group of deprotonated **1** occupies the axial position and the ester carbonyl the equatorial one. This should be the most stable configuration as suggested by Brünner.[5] At this stage the attack of **2** will be directed on the *Re* face of the complexed substrate by the hydrogen bonding assistance of the -CH_2OH equatorial ligand.

This model not only accounts for the preferred formation of (S)-**3** when **10** and **11** (axial water molecule with hydrogen bonding bridging) are used as catalysts, but rationalizes the poor enantiomeric excess obtained when dioxan is used as solvent. This can be involved in hydrogen-bonding with hydroxy groups either acting as axial ligands (lowering the rigidity of the complex) or as equatorial ligands (loosing the anchimeric assistance to the attack of **2**).

As a further support to the above mechanism, when diethyl ether was used as solvent at -70 °C, only 10% enantiomeric excess was obtained (entries 6, 12).

Scheme 2
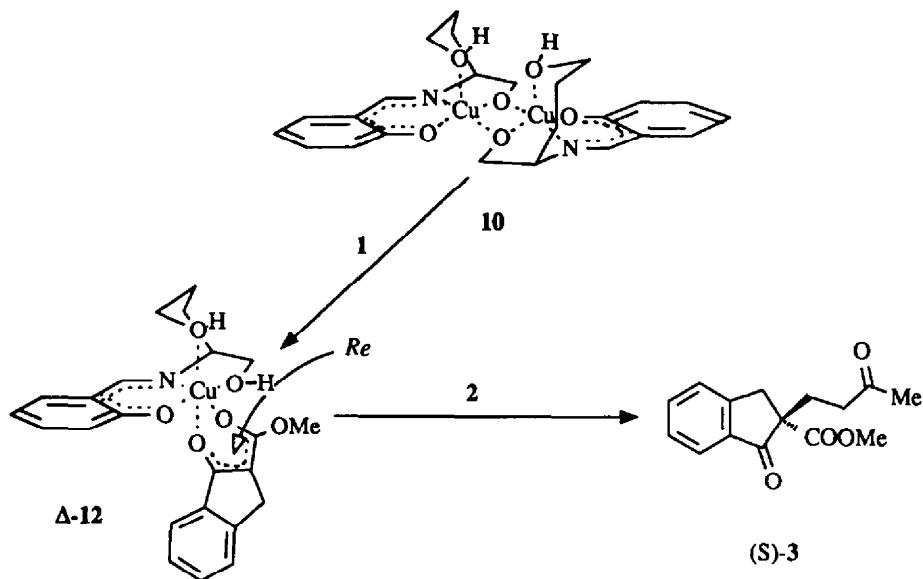
Conclusion

Chiral copper(II) complexes, if suitably designed, can act as good catalysts in enantioselective Michael reaction. If a comparison is made with the catalysts known in the literature, only the Cram's crown ether[4] has a superior activity.

The main property that induces enantioselection is rigidity and this is obtained if tetradentate ligands are used. The further step will concern the synthesis of similar structures but with a better choice of the ligand points.

Experimental

Melting points were determined by the capillary method on a Tottoli apparatus (Büchi). Elemental analyses were made on Erba CHN analyzer mod. 1106. ^{1}H-NMR spectra on Brüker WP80SY spectrometer (CDCl$_3$ was the solvent, chemical shifts were reported in ppm on the δ scale). Optical rotations were measured at room temperature on a Perkin Elmer 241 polarimeter with 1 dm cells. The mass spectra of the copper(II) complexes (desorption chemical ionization with ammonia - 63 Pa pressure and 150 °C source temperature) on a Finnigan MAT 8222 mass spectrometer.

Schiff's bases (4'-11'). General procedure. Salicylaldehyde (3.66 g, 30 mmol) and the suitable chiral amine (30 mmol), dissolved in benzene (200 cm³), were refluxed with a Dean-Stark apparatus until the water was completely separated. The solvent was evaporated and the residue was crystalized from ethanol. Yields were in the range 90 - 95%. The physical characters of each product are described below.

(R)-1-phenyl-N-(2-hydroxybenzylidene) ethylamine (4'). This was obtained from (R)-phenethylamine. M.p. 78-79 °C, $[\alpha]_D$= -186.2° (c = 1.05, MeOH). Lit. m.p. 75-76 °C[14], $[\alpha]_D$= -181° (c = 1.04, MeOH).[8]

(S)-1-phenyl-N-(2-hydroxybenzylidene) ethylamine (5'). This was obtained from (S)-phenethylamine. M.p. 77-78 °C, $[\alpha]_D$= +184.6° (c = 1.04, MeOH). Lit. m.p. 75-76 °C[14], $[\alpha]_D$= +188° (c = 1.04, MeOH).[8]

(R)-2-(2-hydroxybenzylideneamino)-1-butanol (6'). This was obtained from (R)-2-aminobutan-1-ol. M.p. 50-51 °C, $[\alpha]_D$= +15.4° (c = 1.57, acetone). Lit.[15] m.p. 47-50 °C, $[\alpha]_D$= +40.1 (c = 1.26, acetone).

(S)-2-(2-hydroxybenzylideneamino)-1-butanol (7'). This was obtained from (S)-2-aminobutan-1-ol. M.p. 51-52 °C, $[\alpha]_D$= -16.5° (c = 1.50, acetone). (Found: C, 68.4; H, 7.8; N, 7.3. Calc. for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.3%). ¹H-MNR: 0.90 (t, 3H, CH₃), 1.61 (m, 2H, H-3), 3.18 (m, 1H, H-2), 3,72 (m, 2H, H-1), 6.7 - 7.5 (m, 4H, aromatics), 8.35 (s, 1H, benzylidenic H).

(R)-2-(2-hydroxybenzylideneamino)-2-phenylethanol (8'). This was obtained from (R)-2-hydroxy-1-phenylethylamine. M.p. 85-86 °C, $[\alpha]_D$= +173.7° (c = 1.00, chloroform). (Found: C, 74.3; H, 6.1; N, 5.5. Calc. for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.3; N, 5.8%). ¹H-MNR: 3.89 (d, 2H, H-1), 4.45 (t, 1H, H-1), 6.7 - 7.5 (m, 9H, aromatics), 8.43 (s, 1H, benzylidenic H).

(S)-2-(2-hydroxybenzylideneamino)-2-phenylethanol (9'). This was obtained from (S)-2-hydroxy-1-phenylethylamine. M.p. 89-90 °C, $[\alpha]_D$= -169.6° (c = 1.00, chloroform). (Found: C, 74.8; H, 6.2; N, 5.8. Calc. for $C_{15}H_{15}NO_2$: C, 74.7; H, 6.3; N, 5.8%). ¹H-MNR identical to that of 8'.

(S)-2-(2-hydroxybenzylideneamino)-1,5-pentanediol (10'). This was obtained from (S)-2-amino-1,5-pentadiol (prepared by LiAlH₄ reduction of diethyl-L-glutamate[16]). Viscous yellow oil $[\alpha]_D$= -36.2° (c = 0.84, acetone). (Found: C, 65.2; H, 7.7; N, 5.8. Calc. for $C_{12}H_{17}NO_3$: C, 64.6; H, 7.7; N, 6.3%). ¹H-MNR: 1.60 (m, 4H, H-3 and H-4), 3.30 (m, 1H, H-2), 3.65 (m, 4H, H-1), 6.7 - 7.5 (m, 4H, aromatics), 8.38 (s, 1H, benzylidenic H). Mass spectrum: 223 (M)⁺ m/z.

(S,S)-2-(2-hydroxybenzylideneamino)-1-phenyl-1,3-propanediol (11'). This was obtained from (S,S)-2-amino-1-phenylpropan-1,3-diol. M.p. 181-182 °C, $[\alpha]_D$= +297.3° (c = 0.30, MeOH). Lit.[15] m.p.183-185 °C, $[\alpha]_D$= +290° (c = 0.30, MeOH).

Copper(II) complexes (4 - 11). General procedure. The suitable ligand (4' - 11') (30 mmol) was dissolved in methanol (150 cm³) and ground $Cu_2(CH_3CO_2)_4 \cdot 2\ H_2O$ (6.0 g, 15 mmol) was added. The mixture was refluxed 1.5-2 hrs under magnetical stirring, the solvent was evaporated and the residue was crystallized from the minimum amount of solvent (8 and 9 separated upon cooling form the methanolic reaction mixture). Yields are in the range 80-90% and the physical characteristics of each product are reported in Table 3.

Michael reaction of (1 and 2). General procedure. To a solution of 1[17] (0.38 g - 2 mmol) and 2 (0.42 g - 6 mmol) in the suitable solvent (30 cm³), the ground copper(II) complex (for the ratio 1 : complex see Tables 1 and 2) was added. The mixture was stirred at the required temperature until tlc showed the disappearance of 1. The solvent was evaporated under vacuum and the residue was chromatographed over 25 g of Merck 230-400 mesh silica gel. Elution of 3 was accomplished with 200 cm³ of cyclohexane/ethyl acetate 65:35. The solvent was distilled off, the residual 3 was crystallized from diethyl ether end the rotatory power was determined. The copper(II) catalyst can be recovered in more than 75% yield from the absorbed silica gel by extraction with acetone-diethyl ether 1:1, its rotatory power being unchanged.

Table 3 - Physical properties and elemental analyses of copper(II) complexes

Complex	M.p. °C colour[a]	Elemental analyses[b]			$[\alpha]_D$ (c, solvent)	Mass spectrum m/z
		C	H	N		
4	142-143[c,d] black				+22.1° (0.07,CHCl₃)	
5	142-143[d,e] black				-18.1° (0.07,CHCl₃)	
6	144-145[f,g] green	$C_{22}H_{26}Cu_2N_2O_4$	(51.8)(5.1)(5.3) 51.7 5.4 5.4		-132.1° (0.03,acetone)	509 (M+H)⁺
7	159-160[f,g] green	$C_{22}H_{26}Cu_2N_2O_4$	(51.8)(5.1)(5.3) 51.8 5.1 5.4		+151.4° (0.03,acetone)	509 (M+H)⁺
8	195-196[d] green	$C_{30}H_{26}Cu_2N_2O_4$ .4H₂O	(53.2)(5.0)(4.1) 53.0 4.8 4.1		+54.0° (0.05,CHCl₃)	605 (M+H)⁺
9	196-197[d] green	$C_{30}H_{26}Cu_2N_2O_4$ .4H₂O	(53.2)(5.0)(4.1) 53.4 4.8 4.0		-56.0° (0.05,CHCl₃)	605 (M+H)⁺
10	153-154[h] green	$C_{24}H_{30}Cu_2N_2O_6$ .2H₂O	(47,6)(5.6)(4.6) 48,1 5,2 4,3		+50,0° (0,02,acetone)	569 (M+H)⁺
11	130-131[f] green	$C_{32}H_{30}Cu_2N_2O_6$ .4H₂O	(52.1)(5.2)(3.8) 52.9 5.3 3.4		+71.1° (0.04,CHCl₃)	665 (M+H)⁺
	213-214[i]	$C_{32}H_{30}Cu_2N_2O_6$	(57.7)(4.5)(4.2) 57,0 4.4 4.0		-16.8° (0.07,CHCl₃)	

(a) **4** and **5, 6 -11** as soft crystals. (b) Calculated values in parentheses. (c) Lit.: m.p. 143-144 °C[8]. (d) From ethanol. (e) Lit.: m.p. 142-143 °C[8]. (f) From diisopropyl ether. (g) After drying 4 days at 78 °C under 25 mm Hg vacuum. (h) From ethyl acetate. (i) After drying 4 days at 117 °C under 25 mm Hg vacuum.

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