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ASYMMETRIC SYNTHESIS OF CHRYSANTHEMIC ACID. AN APPLICATION OF COPPER CARBENOID REACTION

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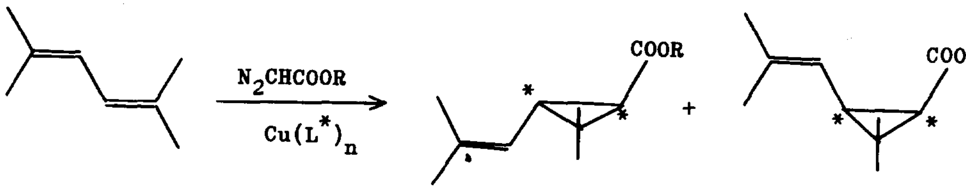
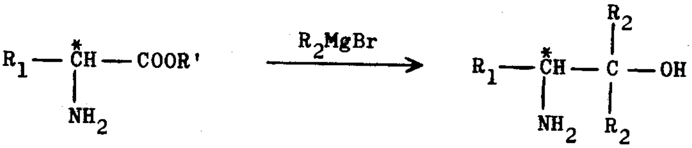
Asymmetric induction was observed in the decomposition of diazoalkanes in the presence of certain chiral copper complexes.[1] We have applied this chiral carbenoid reaction to the synthesis of chrysanthemic acid[2] (eq. 1). Systematic studies have been carried out to achieve an optical yield of 60-70%.[3]



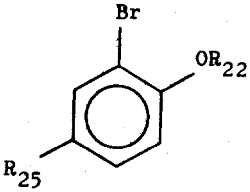
I-*trans* I-*cis* (1)

A catalyst is prepared as follows. (*L*)-Alanine ethyl ester (II, R_1 = Me, R' = Et) was allowed to react (70°, 5 hr) with a Grignard reagent (5 molar excess) derived from 2-bromo-4-*t*-butylphenyl octyl ether (IV, R_{22} = octyl, R_{25} = *t*-Bu) in tetrahydrofuran to give (*S*)-2-amino-1,1-di(5-*t*-butyl-2-octyloxyphenyl)-1-propanol (III, R_1 = Me, R_2 = 5-*t*-butyl-2-octyloxyphenyl), a viscous oil, $[\alpha]_D$ -25.5° (*c* 1.80, chloroform) in 73% yield after column chromatography (silica gel, benzene-ether).[4] Treatment of an ethanolic solution of salicylaldimine of the amino alcohol III with an equimolar amount of cupric acetate followed by alkaline workup afforded a binuclear copper (II) complex (S)-V (R_1 = Me, R_2 = 5-t-butyl-2-octyloxyphenyl), a green mass, $[\alpha]_{546}$ -550° (c 0.06, benzene) in 86% yield.[5] Upon addition of pyridine the complex V was converted to a mononuclear complex VI (the same O,N,O ligand as in V; L = pyridine).

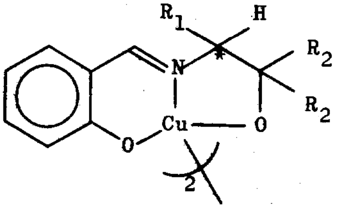


(2)

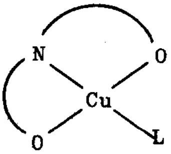
II III



IV



V



VI

Ethyl diazoacetate was decomposed (40°, 5 hr) in 2,5-dimethyl-2,4-hexadiene (4 molar excess) in the presence of the catalyst (S)-V (1 mol %) to give a mixture of cis- and trans-ethyl chrysanthemate (I, R = Et), b.p. 60°/0.5 mm, α_D -13.52° (neat, 1 dm) in 54% yield. Hydrolysis of the ester gave the acid I (R = H), b.p. 80°/0.5 mm, $[\alpha]_D$ -38.76° (c 5.10, chloroform), whose optical isomers were analyzed by gas chromatography as the corresponding (-)-2-octyl ester[6]: (-)-trans,43.3%; (+)-trans, 8.1%; (-)-cis, 39.4% and (+)-cis, 9.2%. The enantiomeric excess is calculated to be 68% for trans isomer and 62% for cis one. It should be noted that the pyridine adduct VI is as effective as the binuclear complex V in the asymmetric synthesis.

Other catalysts V were prepared in the combination of optically active α-amino ester II (R_1 = Me, i-Pr, i-Bu, CH_2Ph, and Ph; R' = Et) and 2,5-disubstituted phenyl bromide IV (R_{22}, R_{25} = Me, i-Pr, n-Bu, t-Bu and so on). Results of the asymmetric synthesis are summarized in Table I, which reveals the following facts. First, the catalyst V of (*S*)-configuration leads to the predominant formation of levorotatory chrysanthemic acid (both of (1*S*,3*S*)-*trans* and (1*S*,3*R*)-*cis* isomer) over dextrotatory one. On the other hand, dextrotatory chrysanthemic acid is the preferred product in the case of the catalyst (*R*)-V. Second, the optical activity of the product increases with the bulkiness of the substituent R_2 (R_{22} and R_{25}) of V.[7]

A copper-carbene complex such as VI (L = CHCOOR or $N_2CHCOOR$) might be responsible for the asymmetric induction.[8] Experiments directed on this line are now in progress.

Table I. Asymmetric Synthesis of Chrysanthemic Acid[a]

Catalyst V				Ester I (R = Et)			Acid I (R = H)
Confign	R_1	R_{22}	R_{25}	Yield,%[b]	*cis*/*trans*[c]	α_D (neat)[d]	$[\alpha]_D$[e]
(*S*)	Me	Me	H	64	38/62	-3.74	-11.02
(*S*)	Me	*n*-Bu	Me	60	41/59	-7.22	-20.46
(*S*)	Me	*n*-Bu	*t*-Bu	54	42/58	-11.58	-35.84
(*R*)	CH_2Ph	Me	H	58	38/62	+8.01	+23.10
(*R*)	CH_2Ph	*i*-Pr	H	53	42/58	+8.80	+25.48
(*R*)	CH_2Ph	*n*-Bu	*t*-Bu	52	43/57	+10.26	+29.84
(*S*)	*i*-Pr	*n*-Bu	*t*-Bu	59	40/60	-9.67	-24.60
(*S*)	*i*-Bu	*n*-Bu	*t*-Bu	46	42/58	-5.65	-16.90
(*R*)	Ph	Me	H	51	33/67	+1.18	+3.54

[a] For the reaction conditions, see the text.

[b] Based on ethyl diazoacetate.

[c] Determined on gas chromatography (Golay column).

[d] Measured with a cell of 1 dm length at room temperature.

[e] The concentration *c* (g/100 ml chloroform) was *ca*. 5. Optically pure acid shows the rotation of $[\alpha]_D$ +26.8° for (+)-*trans* isomer and that of $[\alpha]_D$ +87.9° for (+)-*cis* one.

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Addendum. Very recently the effectiveness of bis(camphorquinonedioximato)-cobalt(II) was demonstrated in the asymmetric synthesis of ethyl 2-phenylcyclopropanecarboxylate: Y. Tatsuno, A. Konishi, A. Nakamura, and S. Otsuka, J. Chem. Soc., Chem. Commun., 588 (1974).