

Enantioselective Hydrogenation over Chiral Cobalt Complexes with (+)-(1*S*,2*S*,5*R*)-Neomenthyl-diphenylphosphine and (–)-(1*R*,2*R*)-2,2-Dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane

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Abstract—The optical yield in enantioselective hydrogenation of methyl α -acetamidocinnamate over mono- and diphosphine cobalt(II) complexes CoX_2L_2 [where X = Cl or CF_3SO_3 , L = (+)-(1*S*,2*S*,5*R*)-neomenthyl-diphenylphosphine or L₂ = (–)-(1*R*,2*R*)-2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane], which are generated *in situ*, in the presence of sodium tetrahydridoborate increases with rise in the phosphine-to-metal ratio and hydrogen pressure. The maximal optical yields of (+)-(*S*)-*N*-acetylphenylalanine methyl ester attain 40% (CoX_2L_2) and 42% (CoX_2L_2).

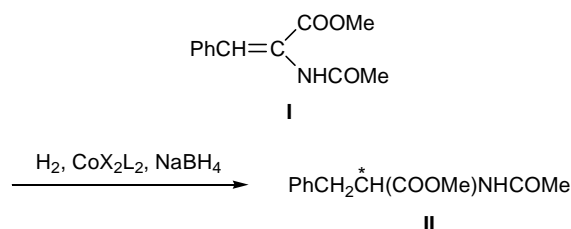
Metal-complex catalysts derived from base metals (Co, Ni, Fe) have been studied poorly in enantioselective hydrogenation of prochiral substrates containing C=C and C=O bonds, as well as in other asymmetric reactions, although such catalysts are much less expensive than rhodium, ruthenium, or iridium complexes [1–6]. The latter occupy dominant position in both fundamental studies and large-scale syntheses of drugs and insecticides [7].

In the presence of cobalt(II) complexes with nitrogen-containing ligands (in particular, chiral Schiff bases) as precursors of efficient catalysts for reduction of olefins and ketones with sodium tetrahydridoborate and molecular hydrogen, enantiomeric excess in the reduction of α,β -unsaturated carboxylic acid esters [8] and cyclic ketones [9] attained 96 and 94%, respectively. The cobalt complex with dimethylglyoxime and quinine was found to be effective in asymmetric hydrogenation of benzil to benzoin with molecular hydrogen (optical yield 61–74%) [10, 11]. Poorer results were obtained in hydrogenation of compounds with a prochiral C=C bond over chiral phosphine ligands: carbonyl–phosphine cobalt complexes afforded an optical yield of 16% in the hydrogenation of α,β -unsaturated ketones [4], and the optical yield in the hydrogenation of α -acetaminocinnamic acid over

cobalt complexes with chiral polymeric phosphonite ligands was as poor as 25% [6].

We previously [1, 2] studied the hydrogenation of methyl α -acetaminocinnamate (**I**) using the catalytic system $\text{CoCl}_2\text{--L--NaBH}_4$ (molar ratio **I**:Co = 25) and obtained *N*-acetylphenylalanine methyl ester (**II**) with a chemical yield of up to 78% and an optical yield of 40 to 60%.

In the present work we examined enantioselective hydrogenation of ester **I** with molecular hydrogen over mono- and diphosphine cobalt(II) complexes CoX_2L_2 , where X = Cl or CF_3SO_3 , L = (+)-neomenthyl-diphenylphosphine or L₂ = (–)-(1*R*,2*R*)-2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane (DIOP), which were generated *in situ*. Sodium tetrahydridoborate was used to reduce the transition metal to the catalytically active form. The results obtained by hydrogenation of compound **I** in a 1:2 toluene–ethanol



Hydrogenation of methyl α -acetylaminocinnamate [toluene– C_2H_5OH , 1:2, $p(H_2) = 30$ atm, $80^\circ C$, 24 h, $NaBH_4-Co$ 2:1, $c_1 = 0.5$ M]

Run no.	$c_{Co} \times 10^2, M$	X	Ligand, ^a (L:Co)	Conversion, %	Optical yield, % (isomer)
1 ^b	2	Cl	L (1:1)	27.7	11.3 (S)
2 ^b	1	Cl	L (1:1)	26.0	9.7 (S)
3	1	Cl	L (1:1)	48.0	8.4 (S)
4	1	Cl	L (2:1)	39.0	28.7 (S)
5 ^c	1	Cl	L (2:1)	61.0	40.0 (S)
6	1	CF ₃ SO ₃	L (1.7:1)	56.0	35.7 (S)
7	1	Cl	L ₂ (1:1)	31.6	40.5 (S)
8 ^b	1	Cl	L ₂ (1:1)	18.0	42.0 (S)
9 ^d	1	Cl	L ₂ (1:1)	10.5	0.0
10	1.7	CF ₃ SO ₃	L ₂ (1:1)	65.0	26.0 (S)

^a L is (1*S*,2*S*,5*R*)-(+)-neomenthylidiphenylphosphine; L₂ is (R,R)-(-)-2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane.

^b At $25^\circ C$.

^c $p(H_2) = 60$ atm.

^d 5 equiv of Et₃N was added.

mixture are given in table. No reaction occurred under mild conditions (hydrogen pressure 1–2 atm). Under more severe conditions (hydrogen pressure 30 atm, $80^\circ C$), the catalysts showed a moderate activity, and the substrate conversion was 15–65% in 24 h at a substrate-to-catalyst molar ratio of 50:1.

The optical yield of the hydrogenation product over CoX_2L_2 complexes increased with rise in the phosphine-to-cobalt ratio and hydrogen pressure. When the reaction was performed with cationic trifluoromethanesulfonate cobalt complex (which was prepared from $CoCl_2L_2$ by exchange reaction with silver trifluoromethanesulfonate and was used without isolation, after separation of AgCl) under similar conditions [$p(H_2) = 30$ atm, $80^\circ C$], the optical yield was somewhat greater, as compared to the covalent chloride complex $CoCl_2L_2$. The same result was obtained by raising the hydrogen pressure; in this case, the substrate conversion also increased (see table).

Hydrogenation over $CoX_2L'_2$ ($L'_2 = DIOP$) ensured higher optical yield of (+)-(*S*)-*N*-acetylphenylalanine, the substrate conversion remaining moderate. No asymmetric induction was observed on addition of triethylamine to the reaction system ($Et_3N:Co = 5:1$), for in this case generation of carboxylate ion from

the substrate is impossible. In the hydrogenation of α -acetamidocinnamic acid over rhodium complexes, addition of an amine increases the optical yield [12]. Presumably, optically active phosphine is expelled from the metal coordination sphere by excess triethylamine to give achiral cobalt complexes with the amine, which are also active in the hydrogenation of double bond.

The maximal conversion of the substrate into *N*-acetylphenylalanine methyl ester (65%) was achieved with the bis(trifluoromethanesulfonate)-cobalt(II) complex with chiral diphosphine L₂, which was prepared *in situ* via exchange reaction of the chloride complex with silver trifluoromethanesulfonate. We can conclude that removal of covalent-bonded chlorine from the inner coordination sphere of the metal increases the activity of the catalytic system but reduces its stereoselectivity (see table, run no. 10). Our results show that the chloride cobalt(II) complex with (-)-(*R,R*)-2,2-dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane is more promising as catalytic precursor in the hydrogenation of prochiral dehydro amino acids, as compared to both trifluoromethanesulfonate complex and with the same ligand and chloride and trifluoromethanesulfonate complexes with ligand L.

EXPERIMENTAL

The ¹H and ³¹P NMR spectra were recorded on a Bruker DPX-400 spectrometer at 400 and 162 MHz, respectively, using HMDS as internal reference (for ¹H); the chemical shifts are given relative to TMS (¹H) and H₃PO₄ (³¹P). The specific optical rotations were measured on a Polamat A instrument at λ 546 nm and were recalculated to λ 589 nm using a factor of 1.17543. The solvents used in the hydrogenation were thoroughly dried and deoxygenated.

The synthesis of (+)-neomenthylidiphenylphosphine (L) was described in [13]; mp $98-99^\circ C$. ³¹P NMR spectrum (C_6D_6): $\delta_P -15.4$ ppm. $[\alpha]_D^{20} = -91.8^\circ$ ($c = 0.89$, CH_2Cl_2), optical purity 97%.

(-)-(*R,R*)-2,2-Dimethyl-4,5-bis(diphenylphosphinomethyl)-1,3-dioxolane (L₂) was synthesized by the procedure reported in [14]; mp $89-90^\circ C$, $[\alpha]_D^{20} = -12.4^\circ$ ($c = 0.71$, benzene). ³¹P NMR spectrum ($CDCl_3$): $\delta_P -24.3$ ppm.

Hydrogenation of methyl α -acetaminocinnamate (I). Anhydrous $CoCl_2$, 0.1–0.2 mmol, toluene, 3 ml, ethanol, 7 ml, and ligand (+)-L or (-)-L₂, 0.2–

0.4 mmol, were mixed under dry argon. The mixture was stirred for 15 min, and 0.2–0.4 mmol of NaBH₄ was added. Compound **I**, 1.025 g, was added to the resulting red–brown solution, and (after complete dissolution) the solution was transferred into a preliminarily evacuated high-pressure reactor. Hydrogen was supplied to the reactor to a pressure of 30–60 atm, and the reactor was shaken for 24 h. The product was removed from the catalyst by passing the mixture through a column charged with aluminum oxide using ethyl acetate–hexane (1:3) as eluent. The chemical yield was determined by ¹H NMR spectroscopy from the intensity ratio of signals belonging to acetyl groups of the substrate [$\delta(\text{CH}_3\text{CO})$ 2.14 ppm] and hydrogenation product [$\delta(\text{CH}_3\text{CO})$ 1.96 ppm]. The optical yield was determined by polarimetry from the ratio of specific optical rotations of the product and pure (–)-(R)-N-acetylphenylalanine methyl ester, $[\alpha]_{\text{D}} = 21.4^\circ$ ($c = 1.9$, MeOH) [15] or $[\alpha]_{\text{D}} = 101.3^\circ$ ($c = 1$, CHCl₃) [16].

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