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ASYMMETRIC SYNTHESIS OF DIPEPTIDES BY MEANS OF HOMOGENEOUS HYDROGENATION CATALYZED BY CHIRAL RHODIUM COMPLEXES

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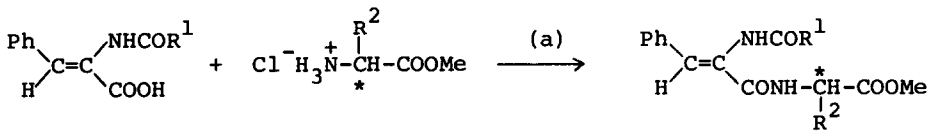
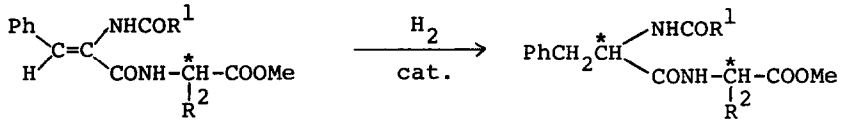
Summary: Asymmetric hydrogenation of dehydrodipeptides, α-acylaminocinnamoyl-(S)-amino esters, catalyzed by rhodium complexes with chiral diphosphines gave either (R)-N-acylphenylalanyl-(S)-amino esters or (S)-N-acylphenylalanyl-(S)-amino esters with high diastereomeric purity up to 98-99% on using proper chiral ligands.

Homogeneous asymmetric hydrogenation of olefins and carbonyl compounds catalyzed by rhodium complexes with chiral diphosphine ligands has been extensively studied,[1] and especially that of (Z)-α-acylaminocinnamic acid and its derivatives has achieved excellent stereoselectivities. However, little attention has been drawn to the asymmetric hydrogenation of dehydrodipeptides[2] such as (Z)-α-acylaminocinnamoyl-(S)-phenylalanine methyl ester, which may serve as new efficient route to dipeptides. One of the most interesting points involved in this reaction is whether the chiral center of the dehydrodipeptide has a strong influence upon the way of asymmetric induction by chiral catalyst or not. Namely, if the optical purity of the newly forming chiral center is not affected by the already existing chiral center, we can synthesize the dipeptides having desired configurations. Bearing this in mind, we prepared dehydrodipeptides by the condensation of (Z)-α-acylaminocinnamic acid with (S)-α-amino ester hydrochloride as shown in eqn. (1), and performed the asymmetric hydrogenation.



(1)

(a): *dicyclohexylcarbodiimide, 1-hydroxy benztriazole, N-methylmorpholine*



(2)

The asymmetric hydrogenation of dehydrodipeptides thus obtained was carried out by using rhodium complexes with (2S,4S)-N-(N'-p-bromophenylcarbamoyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine[3] (p-Br-C_6H_4-CAPP), (2S,4S)-N-t-butoxycarbonyl-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine[4] (BPPM), (+)- and (-)-2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane[5] ((+)DIOP and (-)DIOP), and (1R,2R)-1,2-ethanediylbis[(o-methoxyphenyl)phenylphosphine][6] (diPAMP). The chiral catalysts were prepared in situ by simply mixing chiral diphosphine ligand with $[Rh(NBD)_2]^+ClO_4^-$ (NBD = norbornadiene) or $[Rh(COD)Cl]_2$ (COD = 1,5-cyclooctadiene). Results are summarized in Table 1. As Table 1 shows, the stereoselectivities exhibited in the reactions using p-Br-C_6H_4-CAPP, BPPM and diPAMP as chiral ligand, are extremely high, and the direction of asymmetric induction is turned to be the same as that observed in the simple asymmetric hydrogenation of (Z)-α-acylaminocinnamic acid.[1] It is also disclosed that the influence of the chiral center in a dehydrodipeptide on the asymmetric induction caused by chiral rhodium catalysts is virtually negligible although (R,S)-isomer is found to be preferred on using achiral catalyst, 10% Pd-C. As for the reaction rate, the asymmetric hydrogenation of these dehydrodipeptides is found to be slower than that of α-acylaminocinnamic acid. Thus, in some cases gentle warming (40-50°C) or pressurization (5-10 atm.) is very efficient to promote the reaction smoothly. The relative rate of the reaction is, of course, dependent upon the catalyst used, which decreases in the order Br-C_6H_4-CAPP ∿ BPPM > DIOP >> diPAMP.

Table 1. Asymmetric Hydrogenation of Dehydrodipeptides[a]

Substrate R^1	Substrate R^2	Catalyst[b]	Conditions (H_2 press., Temp., Time)	(R,S)/(S,S)[c]
Ph	Ph	p-Br-C_6H_4-CAPP-Rh^+	1 atm., 40°C, 24 h	98.1/1.9
		BPPM-Rh^N	5 atm., 30°C, 24 h	96.0/4.0
		(+)DIOP-Rh^+	5 atm., 25°C, 15 h	16.4/83.6
		(-)DIOP-Rh^+	5 atm., 25°C, 15 h	84.1/15.9
		diPAMP-Rh^+	10 atm., 50°C, 15 h	2.2/97.8
		10% Pd-C	1 atm., 25°C, 5 h	60.0/40.0
Me	Ph	BPPM-Rh^+	1 atm., 40°C, 24 h	98.0/2.0
		BPPM-Rh^N	1 atm., 40°C, 48 h	94.9/5.1
		(+)DIOP-Rh^+	5 atm., 30°C, 24 h	7.3/92.7
		10% Pd-C	1 atm., 25°C, 15 h	60.2/39.8
Me	Me	p-Br-C_6H_4-CAPP-Rh^+	5 atm., 25°C, 18 h	99.0/1.0
		p-Br-C_6H_4-CAPP-Rh^N	5 atm., 40°C, 18 h	95.4/4.6
		(+)DIOP-Rh^+	5 atm., 25°C, 18 h	8.6/91.4
		10% Pd-C	1 atm., 25°C, 18 h	61.2/38.8

[a] All reactions were run with 1 mmol of the substrate, 1×10^{-2} mmol of the catalyst (except 10% Pd-C: 200 mg/ 1 mmol of the substrate) in 30 ml of ethanol. Chemical yield was almost quantitative in every case. [b] L-Rh^+ = L + $[Rh(NBD)_2]^+ClO_4^-$; L-Rh^N = L + 1/2$[Rh(COD)Cl]_2$. [c] Diastereomer ratio was estimated on the basis of HLPC analysis using a column packed with TOYO SODA LS 410K (ODS SIL) and MeOH-H_2O as eluent.

Further investigation using a variety of dehydrodipeptides and chiral diphosphine ligands is actively in progress.

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