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SYNTHESIS OF CHIRAL DEPSIPEPTIDE BUILDING BLOCK BY THE ASYMMETRIC REDUCTION OF N-(α-KETOACYL)-α-AMINO ESTERS

Iwao OJIMA*, Toshiyuki TANAKA, and Tetsuo KOGURE
Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229

Asymmetric reduction of N-(α-ketoacyl)-α-amino esters was performed by using homogeneous hydrosilylation and hydrogenation catalyzed by rhodium(I) complexes. The asymmetric hydrosilylation achieved good to high stereoselectivities giving the corresponding N-(α-hydroxyacyl)-α-amino esters, whereas only simple asymmetric induction arising from the chiral center of the substrate was observed in the case of hydrogenation.

Recently, asymmetric synthesis of dipeptides by means of catalytic asymmetric hydrogenation of dehydrodipeptides has been developed.[1-3] There have been no report, however, on the asymmetric synthesis of depsipeptide building block by stereoselective reduction of N-(α-ketoacyl)-α-amino esters (1) although asymmetric hydrogenation of simple α-keto amide was reported.[4,5] We wish to describe here the first examples of the asymmetric reduction of N-(α-ketoacyl)-α-amino esters (1) by means of hydrosilylation and hydrogenation.

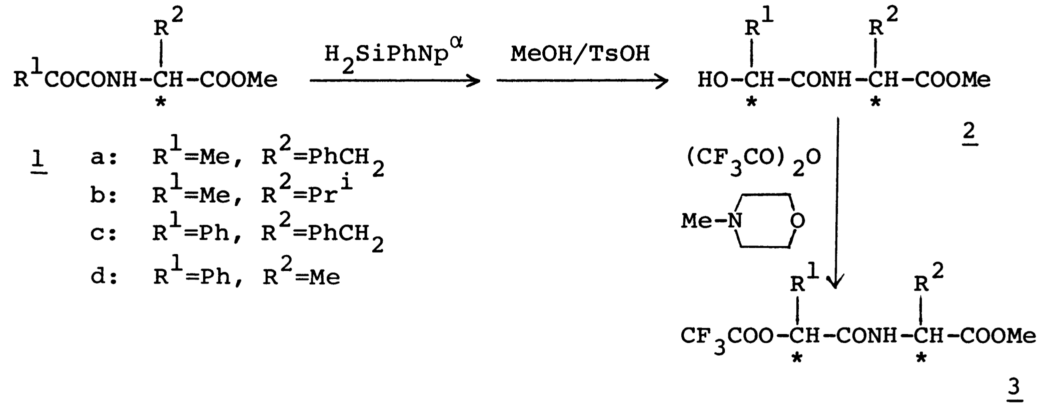
The N-(α-ketoacyl)-α-amino esters (1) were readily prepared in high yields by the reaction of α-ketoacyl chlorides[6] with hydrogen chloride salts of α-amino acid methyl esters in the presence of N-methylmorphorine (eq. 1).

$$R^1COCOCl + Cl^-H_3N^+\text{-}\overset{R^2}{\underset{*}{C}}H\text{-}COOMe \xrightarrow{\text{N-methylmorpholine}} R^1CONH\text{-}\overset{R^2}{\underset{*}{C}}H\text{-}COOMe \quad (1)$$

$$\underline{1}$$

The asymmetric hydrosilylation of α-ketoacylamino esters (1) followed by methanolysis was carried out by using α-naphthylphenylsilane as reducing agent and rhodium(I) complexes with (+)DIOP,[7] (-)DIOP,[7] and PPh_3. Attempted determination of the optical purity of the product (2) by nmr using shift reagent resulted in unsatisfactory separation of key signal(s). Thus, all α-hydroxyacylamino esters (2) were transformed to the corresponding trifluoroacetates (3) by reacting with trifluoroacetic anhydride in the presence of N-methylmorpholine. The trifluoroacetates (3) were submitted to ^{19}F nmr analysis using $Eu(fod)_3$ as shift reagent, and the optical purities were successfully determined. The absolute configurations of the trifluoroacetates (3) thus obtained were also determined by the comparison with authentic samples based on nmr analysis. Results are summarized in Table 1.

As Table 1 shows, asymmetric induction by the chiral catalyst predominates over that by the chiral center involved in the substrate (1). Namely, no significant double asymmetric induction[8] was observed except the case of 1c. Nevertheless, relatively large simple asymmetric induction was observed on using an achiral catalyst, $Rh(PPh_3)_3Cl$.



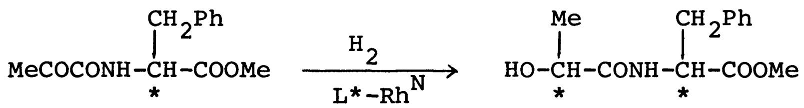
(2)

Table 1. Asymmetric Reduction of 1 via Hydrosilylation[a]

2	Catalyst[b]	Isolated Yield(%)	(R,S)/(S,S)[c]	%excess diastereomer
HO-CH(Me)-CO-Phe-OMe	(+)DIOP-Rh^N	75	17/83	66
	(-)DIOP-Rh^N	78	84/16	68
	$Rh(PPh_3)_3Cl$[d]	64	33/67	34
HO-CH(Me)-CO-Val-OMe	(+)DIOP-Rh^N	70	16/84	68
	(-)DIOP-Rh^N	78	86/14	72
	$Rh(PPh_3)_3Cl$[d]	71	29/71	42
HO-CH(Ph)-CO-Phe-OMe	(+)DIOP-Rh^N	79	9/91	82
	(-)DIOP-Rh^N	83	71/29	42
	$Rh(PPh_3)_3Cl$[d]	62	22/78	56
HO-CH(Ph)-CO-Ala-OMe	(+)DIOP-Rh^N	72	15/85	70
	(-)DIOP-Rh^N	71	81/19	62
	$Rh(PPh_3)_3Cl$[d]	50	49/51	2

[a]Reactions were run with 5 mmol of 1, 7.5 mmol of $H_2SiPhNp^{\alpha}$ and 0.025 mmol of catalyst in 5 ml of benzene at 20°C for 24 hr and at 40°C for 12 hr unless otherwise noted. Methanolysis was carried out by using 50 ml of methanol containing 100 mg of p-toluenesulphonic acid (TsOH) at 40°C for 1 hr. After the solvent was removed, the residue was submitted to short column chromatography on silica gel to give 2, which was carefully done to avoid resolution. [b]DIOP-Rh^N= DIOP + $1/2[Rh(COD)Cl]_2$ (COD = 1,5-cyclooctadiene). [c]Determined by ^{19}F nmr analysis. [d]Reaction was run with 0.1 mmol of catalyst at 20°C for 24 hr and at 40°C for 4 days.

On the other hand, the asymmetric hydrogenation of 1a catalyzed by rhodium(I) complexes with (+)DIOP, (-)DIOP, BPPM,[9] p-Br-C_6H_4-CAPP,[10] and PPh_3, gave rise to almost the same extent of asymmetric induction in the same direction as shown in Table 2. This means that only a simple asymmetric induction arising from the chiral center of 1a takes place, and the rhodium catalyst bearing chiral ligand does not act as chiral catalyst at all. These results form a sharp contrast to those for the asymmetric hydrogenation of α-keto esters catalyzed by the same chiral rhodium complexes.[11] The results may indicate that chiral phosphines only act as mono-dentate ligand because of the strong coordination of the substrate (1) with the rhodium center of the catalyst.



1a 2a (3)

Table 2. Asymmetric Hydrogenation of 1a[a]

Product	Catalyst	Conditions (H_2, temp., time)	Conversion[b] (%)	(R,S)/(S,S)	%excess diastereomer
	(+)DIOP-Rh^N	50 atm, 40°C, 20 hr	100	37/63	26
	(-)DIOP-Rh^N	50 atm, 40°C, 20 hr	100	37/63	26
HO-CH(Me)-CO-Phe-OMe (* at CH)	BPPM-Rh^N	50 atm, 25°C, 64 hr	100	36/64	28
	p-Br-C_6H_4-CAPP-Rh^N	50 atm, 25°C, 64 hr	100	37/63	26
	$Rh(PPh_3)_3Cl$	50 atm, 25°C, 64 hr	100	40/60	20
	10% Pd-C[c]	1 atm, 20°C, 2h hr	100	58/42	16

[a]Reactions were run with 1.0 mmol of 1a and 0.01 mmol of catalyst in 5 ml of benzene in a stainless autoclave unless otherwise noted. [b]The yield of 2a was quantitative in every case. [c]Reaction was run in a usual galss apparatus for hydrogenation using 500 mg of 10% Pd-C.

References and Notes

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