Tetrahedron Letters,Vol.23,No.38,pp 3913-3916,1982 0040-4039/82/383913-04$03.00/0
Printed in Great Britain

SYNTHESIS OF CHIRAL TRIPEPTIDES BY ASYMMETRIC HYDROGENATION OF DEHYDROTRIPEPTIDES REMARKABLE EFFECTS OF N-PROTECTING GROUPS ON STEREOSELECTIVITY AND REACTIVITY

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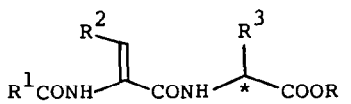
Summary Dehydrotripeptides, X-$\overset{*}{C}$H(R^i)-ΔPhe-$\overset{*}{C}$H(R^k)COOMe (3 X = ^{t}BOC-NH, CBZ-NH, CF_3CONH and N_3), were employed for the asymmetric hydrogenation catalyzed by chiral rhodium complexes and it was found that ^{t}BOC-3 brought about by far the best results Stereoselective dideuteration of a ^{t}BOC-3 was successfully performed

Recently, new synthetic route to the chiral dipeptides has been developed by using the asymmetric hydrogenation of dehydrodipeptides catalyzed by chiral rhodium complexes,[1,2] and it has been disclosed that the dehydrodipeptides of the type 1 are very good substrates for the reaction to achieve quite high stereoselectivities[1] whereas the dehydrodipeptides of the type 2 realize



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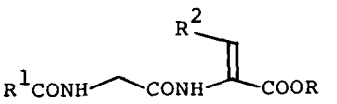

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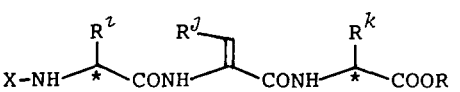
only moderate to fairly good stereoselectivities [2] Although these reported results provide interesting and significant informations about the applicability of homogeneous asymmetric hydrogenation to peptide synthesis, the chiral dipeptides so far obtained in the asymmetric hydrogenation of the type 1 and 2 dehydrodipeptides where R^1 is methyl or phenyl, are not necessarily good building blocks for polypeptide syntheses since it is hard to remove the acetyl or benzoyl protecting group Accordingly, we prepared dehydrotripeptides of the type 3 where X is t-butoxycarbonyl (^{t}BOC), benzyloxycarbonyl (CBZ), or trifluoroacetyl, which could provide versatile tri-

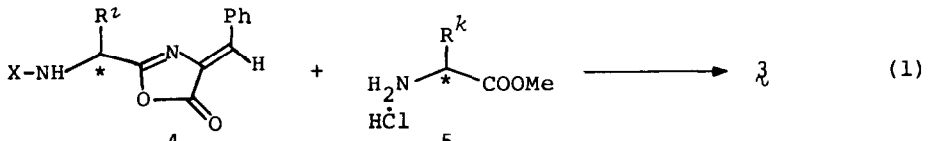


3 X = ^{t}BOC, CBZ, CF_3CO

peptide building blocks after the asymmetric hydrogenation Now, we describe here effective asymmetric hydrogenation of the type 3 dehydrotripeptides and remarkable effects of N-protecting groups on stereoselectivity and reactivity

The dehydrotripeptides (3) where R^j is phenyl and R is methyl in the present study, were easily prepared by the reaction of azlactones (4) with α-amino acid ester hydrochlorides (5) in

the presence of N-methylmorpholine (NMM) in chloroform at room temperature in good yields (eq 1)[3]



(1)

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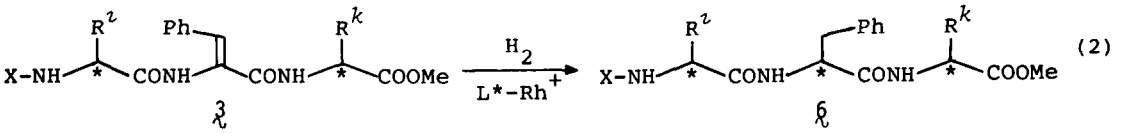
a: X = ^{t}BOC; b: X = CBZ; c: X = CF_3CO

For the comparison purpose, N_3CH_2CO-ΔPhe-(*S*)-Leu-OMe (3d) which is equivalent to Gly-ΔPhe-(*S*)-Leu-OMe, was also prepared in a similar manner [3]

The asymmetric hydrogenation of 3 thus prepared revealed that both the catalyst efficiency and the stereoselectivity of the reaction was strongly governed by the sort of N-protecting group



(2)

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For instance, the asymmetric hydrogenation of 3a-l, 3b ∿ 3d where R^2 is hydrogen and R^K is isobutyl (*S*) by using Ph-CAPP-Rh^+ as catalyst[4] (40°C in ethanol) gave the following results 3a-l (cat 1 0 mol%, 10 atm of H_2, 45 h) 100% conversion, (*R,S*)/(*S,S*) = 96 9/3 1, 3b (cat 2 0 mol%, 10 atm of H_2, 40 h) 82% conversion, (*R,S*)/(*S,S*) = 85 4/14 6, 3c (cat 5 0 mol%, 50 atm of H_2, 50 h) 93% conversion, (*R,S*)/(*S,S*) = 61 5/38 5, 3d (cat 5 0 mol%, 50 atm of H_2, 45 h) 0% conversion [5,10] As typically exemplified in these results, 3 bearing ^{t}BOC group (3a) brings about by far the best stereoselectivity as well as catalyst efficiency As for the asymmetric hydrogenation of 3b, we further carried out the reaction with higher concentration of chiral catalysts and found that high stereoselectivities could be realized by using 5 0 mol% of the chiral catalyst, and in the case of diPAMP-Rh^+ catalyst, 2 0 mol% concentration was enough to attain high stereoselectivity Results are listed in Table 1 [10]

The asymmetric hydrogenation of 3a series, 3a-l ∿ 3a-3, proceeded smoothly by using 1 0 mol% of chiral catalysts to give the corresponding tripeptides (6a-l ∿ 6a-3) in quantitative yields Results are summarized in Table 2 [10]

In connection with the regiospecific and stereoselective labeling of polypeptides, we carried out the dideuteration of 3a-l as a model system by using Ph-CAPP-Rh^+ and diPAMP-Rh^+ as catalysts [4,6] The reactions were run with 1 0 mol% of the chiral catalyst[10] in ethanol at 40°C and 10 atm of hydrogen for 18 h, and the corresponding dideuteriotripeptides were obtained in quantitative yields without any scrambling of deuterium (eq 3), Ph-CAPP-Rh^+ (*R,R,S*)/(*S,S,S*) = 93 0/7 0, diPAMP-Rh^+ (*R,R,S*)/(*S,S,S*) = 2 6/97 4

In conclusion, it is demonstrated that the asymmetric hydrogenation catalyzed by chiral rhodium complexes is readily applicable to the asymmetric synthesis of tripeptide building blocks by the entry of ^{t}BOC for protecting N-terminus, and also to the stereoselective labeling of these building blocks An application of this method to the asymmetric synthesis of Enkephalin analog will be described in the follwing paper

Table 1 Asymmetric Hydrogenation of CBZ-Gly-ΔPhe-(*S*)-Leu-OMe (3b)[a]

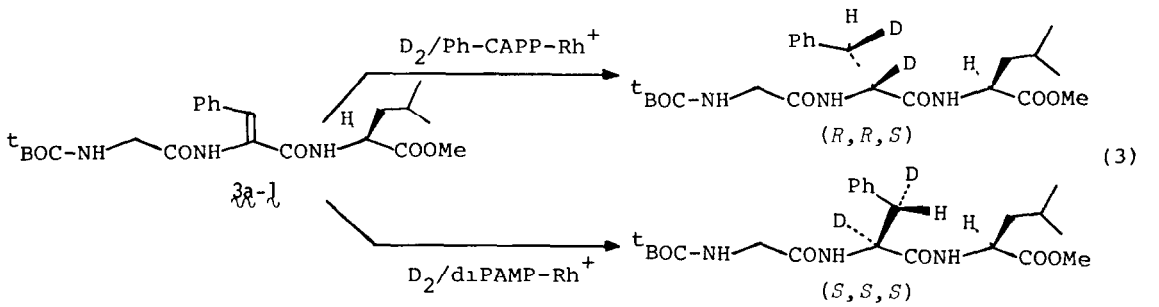
Entry	Chiral Ligand	Cat (mol%)	Conditions H_2 Press , Temp , Time	Conversion(%)[b]	(*R*,*S*)/(*S*,*S*)[b] (±0 1%)
1	(+)BPPM[c]	2 0	10 atm, 40°C, 65 h	88	20 8/79 2
2		5 0	10 atm, 40°C, 65 h	100	8 0/92 0
3	(-)BPPM[d]	2 0	10 atm, 40°C, 47 h	79	85 8/14 2
4		5 0	10 atm, 40°C, 42 h	100	93 0/7 0
5	Ph-CAPP[e]	2 0	10 atm, 40°C, 40 h	82	86 4/13 6
6		5 0	10 atm, 40°C, 40 h	100	94 1/5 9
7	(+)DIOP[f]	5 0	10 atm, 40°C, 40 h	100	27 6/72 4
8	(-)DIOP[f]	5 0	10 atm, 40°C, 40 h	100	75 9/24 1
9	diPAMP[g]	2 0	10 atm, 40°C, 65 h	100	3 3/96 7
10		5 0	50 atm, 40°C, 42 h	100	3 6/96 4

a All reactions were run with 0 3 mmol of 3b and 0 6 ∿ 1 5 × 10^{-2} mmol of chiral catalyst in ethanol (9 ml) *b* Determined by HPLC analysis (see note 5) *c* See ref 7 *d* See ref 8 *e* See ref 4 *f* See ref 9 *g* See ref 6

Table 2 Asymmetric Hydrogenation of ^{t}BOC-Dehydrotripeptides (3a)[a]

Entry	Substrate	Chiral Ligand	Tripeptide (*R*,*S*)/(*S*,*S*)[b]	Tripeptide (*S*,*R*,*S*)/(*S*,*S*,*S*)[b]
1	^{t}BOC-Gly-ΔPhe-(*S*)-Leu-OMe	Ph-CAPP	96 9/3 1	
2	3a-1	(-)BPPM	94 0/6 0	
3		(+)BPPM	8 0/92 0	
4		(-)DIOP	84 4/15 6	
5		(+)DIOP	33 5/66 5	
6		diPAMP	1 1/98 9	
7	^{t}BOC-(*S*)-Ala-ΔPhe-(*S*)-Leu-OMe	Ph-CAPP		92 5/7 5
8	3a-2	(-)BPPM		90 8/9 2
9		(+)BPPM		17 9/82 1
10		diPAMP		5 0/95 0
11	^{t}BOC-(*S*)-Phe-ΔPhe-(*S*)-Leu-OMe	Ph-CAPP		94 4/5 6
12	3a-3	(-)BPPM		89 0/11 0
13		(+)BPPM		24 9/75 1
14		diPAMP		4 1/95 9

a All reactions were run with 0 30 mmol of 3a and 3 0 × 10^{-3} mmol of catalyst in ethanol (9 0 ml) at 40°C and 10 atm of hydrogen for 18 h *b* Determined by HPLC analysis (±0 1%)(see note 5)



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Acknowledgment The authors are grateful to Dr W S Knowles of Monsanto Company for his generous gift of a chiral ligand, diPAMP

References and Notes

1 (a) I Ojima, T Suzuki, Tetrahedron Lett , 21, 1239 (1980) (b) I Ojima, T Kogure, N Yoda, T Suzuki, M Yatabe, T Tanaka, J Org Chem , 47, 1329 (1982) (c) D Meyer, J -P Poulin, H B Kagan, H Levine-Pinto, J -L Morgat, J Org Chem , 45, 4680 (1980) (d) K Onuma, T Ito, A Nakamura, Chem Lett , 481 (1980)

2 A Kleemann, J Martens, M Samson, W Bergstein, Synthesis, 740 (1981)

3 3a-1 mp 192-193°C, $[\alpha]_D^{20}$ -25 3° (c 1 002, MeOH) 3a-2 mp 163-164°C, $[\alpha]_D^{20}$ -50 0° (c 1 001, MeOH) 3a-3 mp 162 5-163°C, $[\alpha]_D^{20}$ -77 2°(c 1 002, MeOH) 3b mp 133 5-135 5°C, $[\alpha]_D^{20}$ -16 3° (c 1 003, MeOH) 3c mp 188-189 5°C, $[\alpha]_D^{20}$ -18 9° (c 1 005, MeOH) 3d mp 152-153 5°C, $[\alpha]_D^{20}$ -5 7°(c 1 001, MeOH) All compounds gave satisfactory elemental analyses and spectral data

4 Ph-CAPP stands for (2*S*,4*S*)-N-(N-phenylcarbamoyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine I Ojima and N Yoda, Tetrahedron Lett , 21, 1051 (1980)

5 HPLC analyses were carried out by using a reversed phase column packed with TOYO SODA LS 410K (ODS SIL) and aqueous methanol as eluant

6 diPAMP stands for (1*R*,2*R*)-1,2-ethanediylbis[(o-anisylphenyl)phosphine] B D Vineyard, W S Knowles, M J Sabacky, G L Bachmann, and D J Weinkauff, J Am Chem Soc , 99, 5946 (1977)

7 (+)BPPM stands for (2*R*,4*R*)-N-(t-butoxycarbonyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine G L Baker, S J Fritschel, J R Stille, and J K Stille, J Org Chem , 46, 2954 (1981) See also ref 1(b)

8 (-)BPPM stands for (2*S*,4*S*)-N-(t-butoxycarbonyl)-4-diphenylphosphino-2-diphenylphosphinomethylpyrrolidine K Achiwa, J Am Chem Soc , 98, 8265 (1976)

9. DIOP stands for 2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane H B Kagan and T -P Dang, J Am Chem Soc , 94, 6429 (1972)

10 Chiral catalysts were prepared in situ by reacting chiral ligands with $[Rh(NBD)_2]ClO_4$ (NBD = norbornadiene) in degassed ethanol

(Received in Japan 24 April 1982)