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Palladium(0)-catalyzed Mizoroki–Heck reaction and Rh(I)-catalyzed asymmetric hydrogenation of polymer-supported dehydroalanine system

Takayuki Doi, Nobuaki Fujimoto, Jun Watanabe and Takashi Takahashi*

Department of Applied Chemistry, Tokyo Institute of Technology, 2-12-1 Ookayama, Meguro, Tokyo 152-8552, Japan

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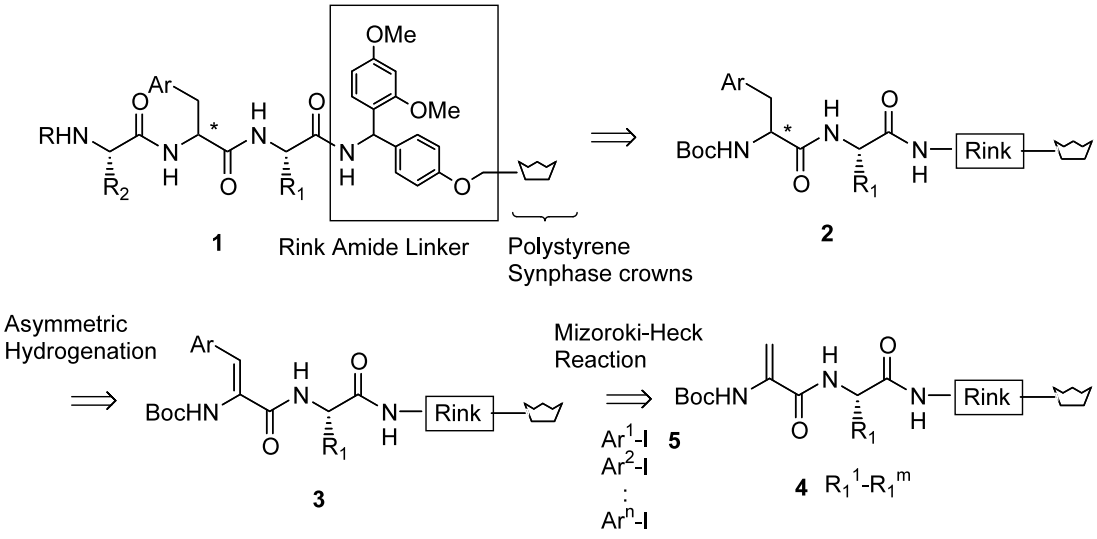
Dedicated to the late Professor Hideshi Nakamura

Abstract—We have developed a practical route for the synthesis of peptides containing unnatural amino acids. Mizoroki–Heck reaction of polymer-supported dehydroalanine, followed by asymmetric hydrogenation was accomplished using Pd(0) and Rh(I)–DuPHOS catalysts, respectively, leading to 36 dipeptides containing phenylalanine derivatives with high stereocontrol.

Peptide inhibitors are widely found among naturally isolated compounds, whose side chains are often modified in a variety of alkyl and functional groups in order to elucidate structure–activity relationships and to find more potent analogs. The use of unnatural amino acids are often important for precise tuning for binding to a protein.[1] Block type solid-phase synthesis is an efficient approach to the synthesis of various peptide analogs.[2] However, one has to prepare building blocks one by one when they are not commercially available. In this letter, we wish to report a synthetic method for the introduction of a variety of unnatural amino acid residues into peptide chains from a single common precursor on polymer-support.



Scheme 1. Strategy for solid-phase synthesis of peptides containing unnatural amino acids.

* Corresponding author.

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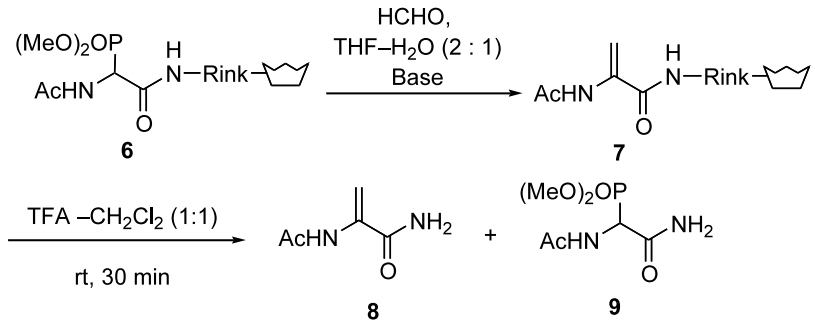


Scheme 2.

Our strategy is outlined in Scheme 1. Palladium(0)-catalyzed Mizoroki–Heck reaction[3,4] of dehydroalanine residue **4** having various substituents (R_1^1-R_1^m) with various aryl iodides **5** (Ar^1-Ar^n) can provide dehydrophenylalanine derivatives in the peptide **3**.[5] If catalyst-controlled asymmetric hydrogenation of **3** can take place, unnatural amino acid residues can be introduced into the peptide **2** with *R*- and *S*-configurations, respectively.[6] In order to synthesize this combinatorial library, we decided to perform these reactions on polymer-support. Rink amide was selected as a linker, which is standard for solid-phase peptide synthesis and is stable under these reaction conditions. A *t*-butoxycarbonyl (Boc) group is a good candidate for the protective group at the N-terminus. This group will be stable during the Pd-catalyzed reaction and should be important for Rh(I)-catalyzed asymmetric hydrogenation as a group assisting bidentate chelation which is essential for chiral induction.[5,6] Since a Boc group can be selectively cleaved in the presence of Rink amide,[7] further elongation of the peptide chains could provide a peptide library **1** containing unnatural amino acids.

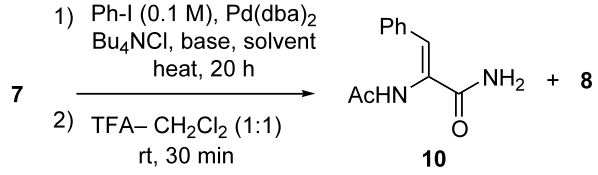
The Pd(0)-catalyzed Mizoroki–Heck reaction of polymer-supported dehydroalanine **7** was initially investigated using *N*-acetyl protection (Scheme 3). There are many examples of Mizoroki–Heck reaction of polymer-supported aryl halides.[8] However, there are less examples of a polymer-supported alkene with aryl halides in solution. Condensation of *N*-acetyl dehydroalanine using various coupling reagents resulted in modest yields,[9,10] therefore, phosphonoglycine was immobilized on polymer-support (DIC/HOBt, Synphase Rink-amino PS-Crowns™)[11] and Horner–Emmons reaction of **6** was performed (Scheme 2).[12] Potassium carbonate was found to be a good base to accomplish this reaction leading to **7** at 40°C (Table 1, entry 3).[13,14]

The Pd(0)-catalyzed Mizoroki–Heck reaction of **7** with iodobenzene was carried out (Scheme 3).[15,16] Products were cleaved with TFA–CH_2Cl_2 (1:1) and were analyzed by LC–MS to determine the ratio of **10** and **8** to monitor the progress of this reaction.[14] The results are shown in Table 2. It was found that 4 mM $Pd(dba)_2$ in acetonitrile at 80°C for 3 h in the presence of Bu_4NCl and triethylamine was optimal (entry 5). These conditions were utilized for the construction of a library.

Table 1. Preparation of polymer-supported dehydroalanine **7**

Entry	Base	Time (h)	Temp. (°C)	Conversion[a] (**8**:**9**)
1	K_2CO_3	12	25	52:48
2	K_2CO_3	24	25	86:14
3	K_2CO_3	24	40	99:1
4	NEt_3	12	25	Trace

[a] Conversion was determined by ^1H NMR measurement after cleavage with TFA–CH_2Cl_2 (1:1).



Scheme 3.

Hydrogenation of polymer-supported Ac-ΔPhe-Leu-Rink **11** was investigated utilizing Rh(I)-catalyst in a mixed solvent system, ethanol–toluene (1:1) (Scheme 4).[17,18] We found that [Rh(COD)(*R*,*R*)-Me-DuPHOS]$^+$ ClO_4^- provided (*R*)-configuration with 99% dr and [Rh(COD)(*S*,*S*)-Me-DuPHOS]$^+ClO_4^-$ afforded (*S*)-configuration with 97% dr.[14,16,19,20] It should be noted that catalyst-controlled asymmetric hydrogenation was accomplished when the Rh(I)–DuPHOS was used as the catalyst.[21]

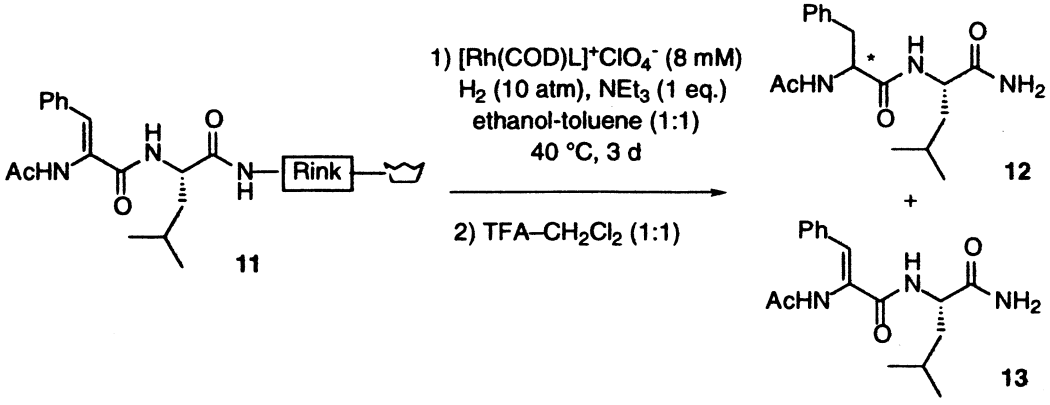
The synthesis of a peptide library incorporating unnatural amino acids was performed using a split and mix method, tagging with colored Cogs and Spindles[11] (Scheme 5): (i) immobilization of glycine, alanine, and leucine on Rink amino Crowns (R_1 = H, Me, *i*-Bu), (ii) preparation of dehydroalanine on the peptide, (iii) Pd(0)-catalyzed Mizoroki–Heck reaction with 8 aryl iodides **5**, (iv) asymmetric hydrogenation with [Rh(COD)(*R*,*R*)-Me-DuPHOS]$^+ClO_4^-$ and [Rh(COD)-(*S*,*S*)-Me-DuPHOS]$^+ClO_4^-$.

Rink amino Crowns were coupled with Fmoc protected glycine, alanine, and leucine (DIC/HOBt) with different colored Spindles to afford **14**, which were mixed and washed with DMF several times. After deprotection of

Table 2. Mizoroki–Heck reaction of polymer-supported dehydroalanine **7**[a]

Entry	Pd Concentration (mM)	Base	Solvent	Temp. (°C)	Conversion[b] (**10**:**8**)
1	2	K_2CO_3	DMF	100	95:5
2	2	$NaHCO_3$	DMF	100	98:2
3	2	NEt_3	DMF	100	94:6
4	2	NEt_3	CH_3CN	80	98:2
5[c]	4	NEt_3	CH_3CN	80	100:0

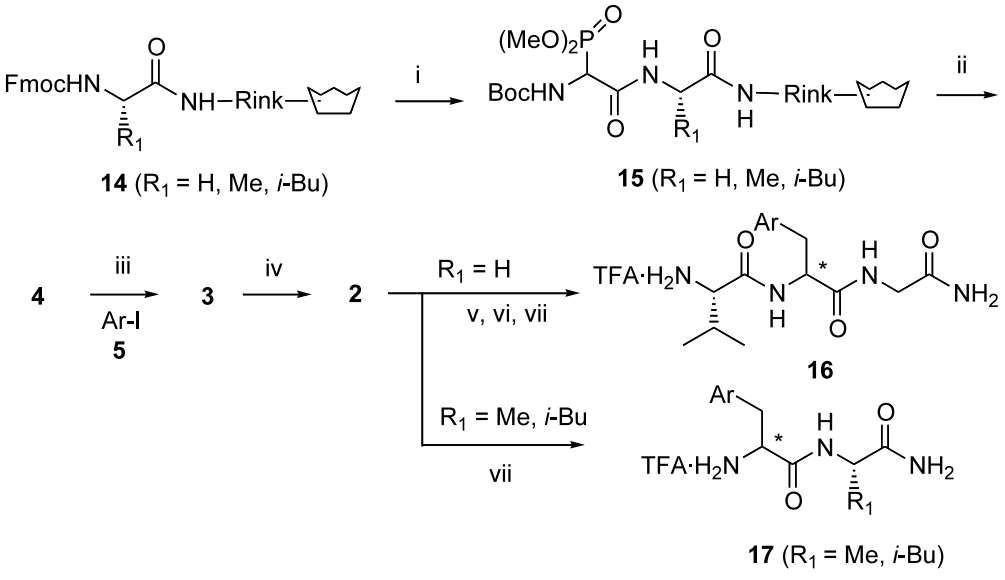
[a] The reactions were carried out in 1 mL solvent/1 Crown.
[b] Conversions were calculated by HPLC analysis of the ratio of peak intensities at 214 nm.
[c] The reaction time was 3 h.



Ligand (L*)	Conversion[a] / (12 : 13)	dr[a] of 12 (*R* : *S*)
(*R* ,*R*)-Me-DuPHOS	99 : 1	99 : 1
(*S* ,*S*)-Me-DuPHOS	99 : 1	2 : 98

[a]Conversion and diastereomeric ratio (dr) were determined by ^{1}H NMR measurement after acid cleavage.

Scheme 4.



Scheme 5. *Reagents and conditions*: (i) *N*-Boc-2-(dimethylphosphono)glycine, DIC, HOBt, DMF; (ii) HCHO, K_2CO_3, THF–H_2O (2:1), 40°C; (iii) Ar-I **5**, $Pd(dba)_2$, CH_3CN, NEt_3, Bu_4NCl, 80°C; (iv) H_2 (10 atm), [Rh(COD)Me-DuPHOS]$^+ClO_4^-$, NEt_3, 40°C, ethanol–toluene (1:1); (v) TMS(OTf), 2,6-lutidine, then methanol; (vi) Boc-Val-OH, DIC, HOBt, DMF; (vii) TFA–CH_2Cl_2 (1:1), rt, 30 min.

Table 3. Mizoroki–Heck reaction of aryl iodides **5** to **4**

Entry	Ar	Purity[a] (%)		
		$R_1 = H$	$R_1 = Me$	$R_1 = i$-Bu
1	Ph	96	87	98
2	4-(MeO)-C_6H_4	95	94	98
3	1-Naphthyl	86	98	99
4	4-Me-C_6H_4	90	93	87
5	3-Me-C_6H_4	90	93	96
6	2-Me-C_6H_4	87	90	99
7	4-Ac-C_6H_4	45	52	60
8	4-NO_2-C_6H_4	No reaction	No reaction	No reaction

[a] Purities were determined by HPLC analysis of the ratio of peak intensities at 214 nm after acid cleavage.

the Fmoc group, *N*-Boc-2-(dimethoxyphosphono)-glycine was coupled using the same coupling protocol with *N*-methylmorpholine as base. Treatment of **15** with formaldehyde, K_2CO_3, 40°C, THF–H_2O (2:1), afforded **4** (97–99%).[22] The Crowns **4** were divided into eight sets according to the colored Cogs. Pd(0)-catalyzed Mizoroki–Heck reaction of **4** with eight aryl iodides **5** was carried out.[16] The results are shown in Table 3. The reactions generally proceeded under the conditions described above, with the exception of entries 7 (45–60%) and 8 (0%) in which an electron withdrawing group is attached to the benzene ring. The Crowns **3** obtained in entries 1–6 (Table 3) were divided into two sets and used for the next reaction. Asymmetric hydrogenation of **3** catalyzed by [Rh(COD)(*R*,*R*)-Me-DuPHOS]$^+ClO_4^-$ and [Rh(COD)-(*S*,*S*)-Me-DuPHOS]$^+ClO_4^-$ was performed.[16] Since the products **2** ($R_1 = H$) have a single chiral center, these were treated with TMSOTf in the presence of 2,6-lutidine and then with methanol,[7] followed by coupling of Boc-Val-OH to the *N*-free terminus (DIC/HOBt). Finally, all Crowns were treated with TFA–CH_2Cl_2 (1:1) in parallel to provide the desired tripeptide **16** ($R_1 = H$) and dipeptides **17** ($R_1 =$ Me, *i*-Bu), which were analyzed by LC–MS (Table 4).[14,23] It should be noted that Rh(I)–(*R*,*R*)-Me-DuPHOS afforded *R*-configuration in the hydrogenation and Rh(I)–(*S*,*S*)-Me-DuPHOS provided the *S*-configuration, respectively, with high diastereomeric ratios. The stereochemistries of **16** and **17** (Ar = Ph and naphthyl) were determined by the ^1H NMR spectra and retention times compared with those of authentic samples prepared by condensation from commercially available amino acids.

Table 4. Asymmetric hydrogenation of polymer-supported **3**

Entry	R_1	Ar	Catalyst[a]	Product	Diastereomeric ratio[b] (*R*:*S*)
1	H	Ph	A	**16**	99:1
2	H	Ph	B	**16**	1:99
3	H	4-(MeO)-C_6H_4	A	**16**	96:4
4	H	4-(MeO)-C_6H_4	B	**16**	7:93
5	H	1-Naphthyl	A	**16**	95:5
6	H	1-Naphthyl	B	**16**	8:92
7	H	4-Me-C_6H_4	A	**16**	99:1
8	H	4-Me-C_6H_4	B	**16**	10:90
9	H	3-Me-C_6H_4	A	**16**	99:1
10	H	3-Me-C_6H_4	B	**16**	1:99
11	H	2-Me-C_6H_4	A	**16**	99:1
12	H	2-Me-C_6H_4	B	**16**	7:93
13	Me	Ph	A	**17**	99:1
14	Me	Ph	B	**17**	6:94
15	Me	4-(MeO)-C_6H_4	A	**17**	96:4
16	Me	4-(MeO)-C_6H_4	B	**17**	6:94
17	Me	1-Naphthyl	A	**17**	98:2
18	Me	1-Naphthyl	B	**17**	7:93
19	Me	4-Me-C_6H_4	A	**17**	99:1
20	Me	4-Me-C_6H_4	B	**17**	7:93
21	Me	3-Me-C_6H_4	A	**17**	99:1
22	Me	3-Me-C_6H_4	B	**17**	5:95
23	Me	2-Me-C_6H_4	A	**17**	99:1
24	Me	2-Me-C_6H_4	B	**17**	4:96
25	*i*-Bu	Ph	A	**17**	93:7
26	*i*-Bu	Ph	B	**17**	6:94
27	*i*-Bu	4-(MeO)-C_6H_8	A	**17**	93:7
28	*i*-Bu	4-(MeO)-C_6H_9	B	**17**	6:94
29	*i*-Bu	1-Naphthyl	A	**17**	93:7
30	*i*-Bu	1-Naphthyl	B	**17**	4:96
31	*i*-Bu	4-Me-C_6H_4	A	**17**	99:1
32	*i*-Bu	4-Me-C_6H_4	B	**17**	9:91
33	*i*-Bu	3-Me-C_6H_4	A	**17**	93:7
34	*i*-Bu	3-Me-C_6H_4	B	**17**	6:94
35	*i*-Bu	2-Me-C_6H_4	A	**17**	99:1
36	*i*-Bu	2-Me-C_6H_4	B	**17**	4:96

[a] Catalyst A [Rh(COD)(*R*,*R*)-Me-DuPHOS]$^+ClO_4^-$. Catalyst B [Rh(COD)(*S*,*S*)-Me-DuPHOS]$^+ClO_4^-$.
[b] The ratio was determined by HPLC.

In summary, we have demonstrated the stereoselective synthesis of 36 dipeptides containing unnatural amino acids utilizing the Pd(0)-catalyzed Mizoroki–Heck reaction of dehydroalanine derivatives and Rh(I)–DuPHOS catalyzed asymmetric hydrogenation on polymer-support. Syntheses of a variety of peptides containing unnatural amino acid residues utilizing this methodology are underway in our laboratory.

Acknowledgements

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Rh(COD)(Me-DuPHOS)]$^+ClO_4^-$ (49.4 mg, 0.080 mmol) was placed in a glass vessel under an argon atmosphere, then freeze-dried Crowns (18 Crowns, 0.14 mmol), degassed ethanol–toluene (1:1, 10 mL), and triethylamine[20] (20 μL, 0.14 mmol) were added to this vessel. The mixture was placed in a 50 mL autoclave and treated with hydrogen (10 atm) at 40°C. After 3 days, the Crowns were successively washed with THF, DMF, methanol, and dichloromethane and dried in vacuo. The Crowns were subsequently soaked in a solution of TFA–dichloromethane (1:1). After 30 min, the solutions were concentrated in vacuo to afford the cleaved products which were analyzed by LC–MS.
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22. No racemization was observed.
23. The corresponding $[M+H]^+$ (ESI-TOF) was observed in all products with 30–60% purities analyzed by HPLC with the peak intensities at 220 nm.