

# A Synthesis of RGD Model Cyclic Peptide by Palladium-Catalyzed Carbonylative Macrolactamization

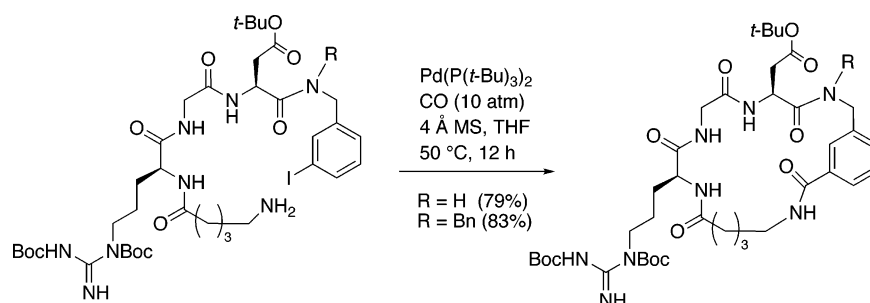
Takayuki Doi,\* Seiji Kamioka, Sayaka Shimazu, and Takashi Takahashi\*

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

doi@apc.titech.ac.jp; ttak@apc.titech.ac.jp

Received December 8, 2007

## ABSTRACT



Cyclic peptidic RGD models were efficiently synthesized by Pd(P(t-Bu)<sub>3</sub>)<sub>2</sub>-catalyzed carbonylative macrolactamization in the presence of 4 Å molecular sieves under 10 atm of carbon monoxide.

Peptidomimetics are important for drug discovery, especially macrocyclic ones that are useful to find potent drug candidates by precise tuning of their conformation.<sup>1</sup> Several approaches to construction of the macrocyclic peptide mimetics have been reported, such as S<sub>N</sub>2 alkylation with S-nucleophiles,<sup>2,3</sup> S<sub>N</sub>Ar macrocyclization,<sup>3</sup> alkene metathesis,<sup>4</sup> Mizoroki–Heck reaction,<sup>5</sup> Suzuki coupling,<sup>6</sup> Sonogashira coupling,<sup>7</sup> (3 + 2)-cycloaddition,<sup>8</sup> radical cyclization,<sup>9</sup> and ene–yne cycloisomerization.<sup>10</sup>

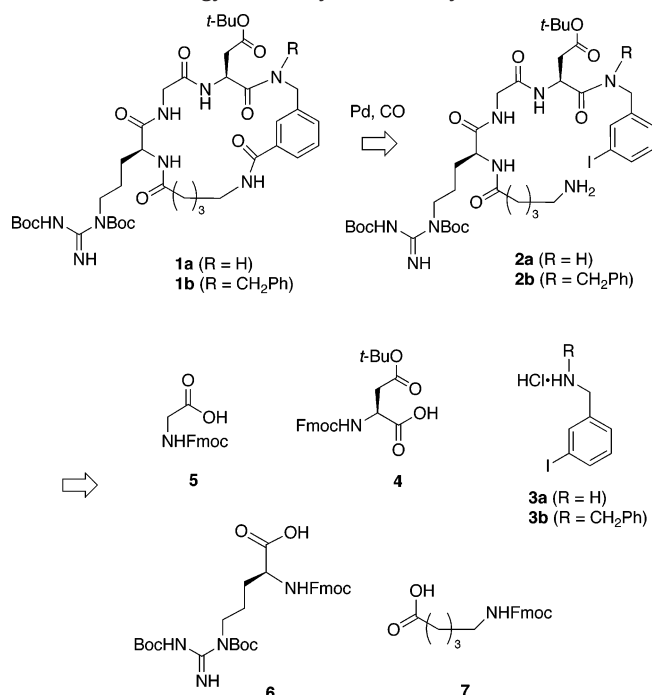
Recently, we reported palladium-catalyzed carbonylation is a powerful reaction in a combinatorial library synthesis. Both carbonylative amidation and esterification were per-

formed on solid phase, utilizing various alkenyl iodides, alkenyl bromides, aryl iodides, and aryl triflates that are good

- (1) Kahn, M. *Synlett* **1993**, 821–826.  
(2) Barker, P. L.; Bullens, S.; Bunting, S.; Burdick, D. J.; Chan, K. S.; Deisher, T.; Eigenbrot, C.; Gadek, T. R.; Gantz, R.; Lipari, M. T.; Muir, C. D.; Napier, M. A.; Pitti, R. M.; Padua, A.; Quan, C.; Stanley, M.; Struble, M.; Tom, J. Y. K.; Burnier, J. P. *J. Med. Chem.* **1992**, 35, 2040–2048.  
(3) (a) Burgess, K. *Acc. Chem. Res.* **2001**, 34, 826–835. (b) Lee, H. B.; Pattarawarapan, M.; Roy, S.; Burgess, K. *Chem. Commun.* **2003**, 1674–1675. (c) Reyes, S. J.; Burgess, K. *Tetrahedron: Asymmetry* **2005**, 16, 1061–1069.

- (4) (a) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, 118, 9606–9614. (b) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, 117, 12364–12365. (c) Pernerstorfer, J.; Schuster, M.; Blechert, S. *Chem. Commun.* **1997**, 1949–1950. (d) Ripka, A. S.; Bohacek, R. S.; Rich, D. H. *Bioorg. Med. Chem. Lett.* **1998**, 8, 357–360. (e) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, 120, 4334–4344. (f) Reichwein, J. F.; Wels, B.; Kruijtz, J. A. W.; Versluis, C.; Liskamp, R. M. J. *Angew. Chem., Int. Ed.* **1999**, 38, 3684–3687. (g) Schafmeister, C. E.; Po, J.; Verdine, G. L. *J. Am. Chem. Soc.* **2000**, 122, 5891–5892. (h) Rajesh, S.; Banerji, B.; Iqbal, J. *J. Org. Chem.* **2002**, 67, 7852–7857. (i) Martin, W. H. C.; Blechert, S. *Curr. Top. Med. Chem.* **2005**, 5, 1521–1540.  
(5) (a) Akaji, K.; Teruya, K.; Akaji, M.; Aimoto, S. *Tetrahedron* **2001**, 57, 2293–2303. (b) Reddy, P. R.; Balraju, V.; Madhavan, G. R.; Banerji, B.; Iqbal, J. *Tetrahedron Lett.* **2003**, 44, 353–356.  
(6) Li, W.; Burgess, K. *Tetrahedron Lett.* **1999**, 40, 6527–6530.  
(7) (a) Spivey, A. C.; McKendrick, J.; Srikan, R.; Helm, B. A. *J. Org. Chem.* **2003**, 68, 1843–1851. (b) Balraju, V.; Reddy, S.; Periasamy, M.; Iqbal, J. *J. Org. Chem.* **2005**, 70, 9626–9628. (c) ten Brink, H. T.; Rijkers, D. T. S.; Liskamp, R. M. J. *J. Org. Chem.* **2006**, 71, 1817–1824.  
(8) (a) Angell, Y.; Burgess, K. *J. Org. Chem.* **2005**, 70, 9595–9598. (b) Bock, V. D.; Perciaccante, R.; Jansen, P.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2006**, 8, 919–922.

### Scheme 1. Strategy for the Synthesis of Cyclic RGD Model 1



precursors as masked activated esters.<sup>11</sup> It was also applied to the construction of macrocyclic lactones.<sup>12,13</sup> For example, we reported a combinatorial synthesis of a 128-member macrophelide library, utilizing palladium-catalyzed carbonylative macrolactonization on solid-phase.<sup>11d</sup> We report an efficient synthesis of cyclic peptidic RGD models utilizing palladium-catalyzed carbonylative macrolactamization.

Cyclic RGD models have been studied as a selective integrin receptor antagonist.<sup>2,3,14</sup> We designed RGD peptidomimetics **1** that contain a RGD sequence, an (amino-

(9) Balraju, V.; Reddy, S.; Periasamy, M.; Iqbal, J. *Tetrahedron Lett.* **2005**, *46*, 5207–5210.

(10) Balraju, V.; Dev, R. V.; Reddy, D. S.; Iqbal, J. *Tetrahedron Lett.* **2006**, *47*, 3569–3571.

(11) (a) Takahashi, T.; Inoue, H.; Tomida, S.; Doi, T.; Bray, A. *Tetrahedron Lett.* **1999**, *40*, 7843–7846. (b) Takahashi, T.; Inoue, H.; Yamamura, Y.; Doi, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 3230–3233. (c) Hashimoto, M.; Mori, A.; Inoue, H.; Nagamiya, H.; Doi, T.; Takahashi, T. *Tetrahedron Lett.* **2003**, *44*, 1251–1254. (d) Takahashi, T.; Kusaka, S.; Doi, T.; Sunazuka, T.; Omura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 5230–5234. (e) Doi, T.; Inoue, H.; Tokita, M.; Watanabe, J.; Takahashi, T. *J. Comb. Chem.* **2008**, *10*, 135–141.

(12) (a) Takahashi, T.; Nagashima, T.; Tsuji, J. *Chem. Lett.* **1980**, 369–372. (b) Takahashi, T.; Ikeda, H.; Tsuji, J. *Tetrahedron Lett.* **1980**, *21*, 3885–3888.

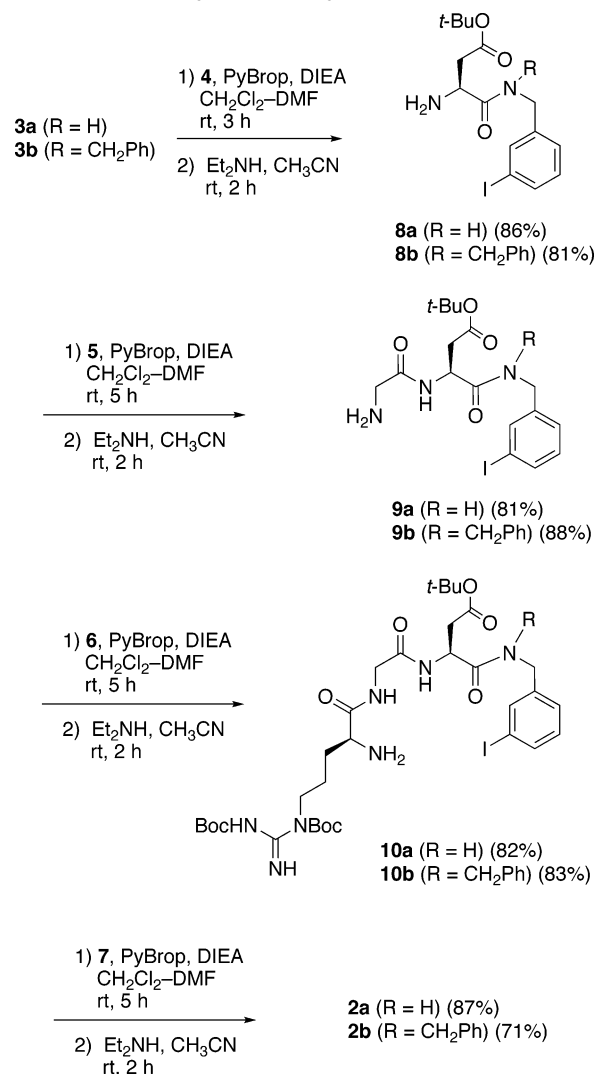
(13) Lu, S.-M.; Apler, H. *Chem. Eur. J.* **2007**, *13*, 5908–5916.

(14) (a) Aumailley, M.; Gurrath, M.; Müller, G.; Calvete, J.; Timpl, R.; Kessler, H. *FEBS Lett.* **1991**, *291*, 50–54. (b) Lender, A.; Yao, W. Q.; Sprengler, P. A.; Spanevello, R. A.; Furst, G. T.; Hirschmann, R.; Smith, A. B., III. *Int. J. Peptide Protein Res.* **1993**, *42*, 509–517. (c) Cheng, S.; Craig, W. S.; Mullen, D.; Tschopp, J. F.; Dixon, D.; Pierschbacher, M. D. *J. Med. Chem.* **1994**, *37*, 1–8. (d) Jackson, S.; DeGrado, W.; Dwivedi, A.; Parthasarathy, A.; Higley, A.; Krywko, J.; Rockwell, A.; Markwalder, J.; Wells, G.; Wexler, R.; Mousa, S.; Harlow, R. *J. Am. Chem. Soc.* **1994**, *116*, 3220–3230. (e) Haubner, R.; Gratias, R.; Diefenbach, B.; Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7461–7472. (f) Dechantsreiter, M. A.; Planker, E.; Mathä, B.; Lohof, E.; Hölzemann, G.; Jonczyk, A.; Goodman, S. L.; Kessler, H. *J. Med. Chem.* **1999**, *42*, 3033–3049. (g) Oishi, S.; Kamano, T.; Niida, A.; Odagaki, Y.; Hamanaka, N.; Yamamoto, M.; Ajito, K.; Tamamura, H.; Otake, A.; Fujii, N. *J. Org. Chem.* **2002**, *67*, 6162–6173.

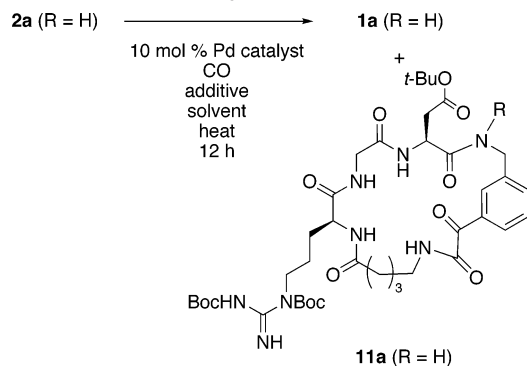
methyl)benzoic acid, and an  $\omega$ -amino acid. Assembly of (aminomethyl)benzoic acids substituted at the ortho, meta, and para positions and  $\omega$ -amino acids with different numbers of the methylene unit would lead to a variety of cyclic RGD models. As a part of the synthesis of a combinatorial library of cyclic RGD models, we initially planned the syntheses of **1a** (R = H) and **1b** (R = CH<sub>2</sub>Ph), containing *m*-(aminomethyl)benzoic acids<sup>14d,15</sup> and  $\omega$ -aminovaleric acid. Synthetic strategy for **1** is illustrated in Scheme 1. The cyclic peptide **1** can be synthesized by palladium-catalyzed carbonylative macrolactamization of **2**. It would be of interest to know the effect of the R-substituent in **2** in this cyclization. The cyclization precursor **2** would be prepared by sequential amidation of *m*-iodobenzylamines **3**, Fmoc-Asp(Ot-Bu)-OH (**4**), Fmoc-Gly-OH (**5**), Fmoc-Arg(Boc)<sub>2</sub>-OH (**6**), and *N*-Fmoc- $\omega$ -aminovaleric acid (**7**).

The cyclization precursors **2** were prepared as shown in Scheme 2. Coupling of amine **3a** and Fmoc-Asp(Ot-Bu)-OH (**4**) was performed using PyBrop-diisopropylethylamine (DIEA) in CH<sub>2</sub>Cl<sub>2</sub>–DMF (9:1) at ambient temperature.<sup>16</sup> Removal of the Fmoc group using diethylamine in acetonitrile

### Scheme 2. Synthesis of Cyclization Precursors 2



**Scheme 3.** Palladium-Catalyzed Carbonylative Macrocyclization of **2a**



trile afforded **8a** (R = H) in 86% yield.<sup>17</sup> Sequential peptide elongation with Fmoc-Gly-OH (**5**), Fmoc-Arg(Boc)<sub>2</sub>-OH (**6**), and *N*-Fmoc- $\omega$ -aminovaleric acid (**7**) under the same reaction conditions described above provided **2a** in good yield. *N*-Benzyl derivative **2b** was also prepared from *N*-benzyl-*m*-iodobenzylamine (**3b**) in a similar manner.

Palladium-catalyzed carbonylative macrolactamization of **2a** was investigated (Table 1). We initially compared the

**Table 1.** Optimization of Palladium-Catalyzed Carbonylative Macrocyclization of **2a**

| entry | Pd catalyst                                     | additives                       | CO (atm) | solvent     | temp (°C) | yield (%)<br><b>1a</b> ( <b>11a</b> ) |
|-------|-------------------------------------------------|---------------------------------|----------|-------------|-----------|---------------------------------------|
| 1     | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | NEt <sub>3</sub> -DMAP          | 10       | DMF         | 50        | 41                                    |
| 2     | POPd                                            | NEt <sub>3</sub> -DMAP          | 10       | DMF         | 50        | 12                                    |
| 3     | Pd(PPh <sub>3</sub> ) <sub>4</sub>              | NEt <sub>3</sub> -DMAP          | 10       | DMF         | 50        | 9                                     |
| 4     | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 3 Å MS                          | 10       | DMF         | 50        | 49                                    |
| 5     | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 10       | DMF         | 50        | 64(7)                                 |
| 6     | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | Ag <sub>2</sub> CO <sub>3</sub> | 10       | DMF         | 50        | 51                                    |
| 7     | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | TMEDA                           | 10       | DMF         | 50        | 21                                    |
| 8     | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 5        | DMF         | 50        | 43(trace)                             |
| 9     | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 20       | DMF         | 50        | 61(9)                                 |
| 10    | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 30       | DMF         | 50        | 63(7)                                 |
| 11    | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 10       | THF         | 50        | 79(9)                                 |
| 12    | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 10       | NMP         | 50        | 32                                    |
| 13    | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 10       | DMPU        | 50        | 41                                    |
| 14    | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 10       | 1,4-dioxane | 50        | trace                                 |
| 15    | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 10       | THF         | 40        | 49                                    |
| 16    | Pd(P( <i>t</i> -Bu) <sub>3</sub> ) <sub>2</sub> | 4 Å MS                          | 10       | THF         | 65        | 21                                    |

effect of palladium-catalysts [Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub>],<sup>18</sup> POPd,<sup>19</sup> Pd(PPh<sub>3</sub>)<sub>4</sub>. The reaction was carried out in the presence of 10 mol % of the Pd-catalyst with NEt<sub>3</sub>-DMAP in DMF at 50 °C for 12 h under CO (10 atm). The starting material was

(15) Smythe, M. L.; von Itzstein, M. *J. Am. Chem. Soc.* **1994**, *116*, 2725–2733.

(16) PyBroP = bromo-tris-pyrrolidino-phosphonium hexafluorophosphate. (a) Coste, J.; Dufour, M.-N.; Pantaloni, A.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 669–672. (b) Coste, J.; Frérot, E.; Jouin, P.; Castro, B. *Tetrahedron Lett.* **1991**, *32*, 1967–1970.

(17) (a) Carpino, L. A.; Han, G. Y. *J. Org. Chem.* **1972**, *37*, 3404–3409. (b) Carpino, L. A. *Acc. Chem. Res.* **1987**, *20*, 401–407.

(18) Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343–6348.

(19) POPd = PdCl<sub>2</sub>[P(OH)(*t*-Bu)<sub>2</sub>]<sub>2</sub> Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513–1516.

completely consumed when Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub> was used as a catalyst. The desired product **1a** was obtained in 41% yield (entry 1). POPd and Pd(PPh<sub>3</sub>)<sub>4</sub> are less effective (12%, 9% yield, entries 2 and 3). Probably, P(*t*-Bu)<sub>3</sub> ligand electronically and sterically accelerates both the oxidative addition of **2a** to palladium(0) and final reductive elimination in the formation of amide **1a**.

Because the Boc group was partially removed under the above reaction conditions, we examined the effect of various additives in place of NEt<sub>3</sub>-DMAP (3 Å MS, 4 Å MS, Ag<sub>2</sub>CO<sub>3</sub>, TMEDA). Actually, the yield was dramatically affected by the base, and the use of 4 Å MS increased the yield up to 64% (entry 5), and the Boc group was sustained.<sup>20</sup> A small amount of double carbonylated product **11a** was detected by LC-MS (7%).<sup>21</sup> Then, the effect of CO pressure was investigated. When the reaction was carried out under 5 atm of CO, the reaction was not complete, but only a trace amount of **11a** was observed (entry 8). On the other hand, no effect of the higher pressure of CO under 20 and 30 atm was observed (entries 9 and 10 vs entry 5).

The solvent effect was found to be crucial. It was found that THF is an effective solvent in this reaction. The yield of **1a** increased to 79%, and double carbonylative product **11a** was also observed in 9% yield (entry 11 vs entries 5, 12, 13, and 14). Interestingly, the desired reaction did not proceed in 1,4-dioxane (entry 14). The reaction temperature is also important to control the reaction. The reaction was not complete at 40 °C (entry 15), whereas removal of the Boc group was observed at 65 °C (entry 16).

Using the optimized reaction conditions, we performed cyclization of *N*-benzyl derivative **2b**. The palladium-catalyzed carbonylative macrolactamization efficiently proceeded [Pd(P(*t*-Bu)<sub>3</sub>)<sub>2</sub> (10 mol %)/CO (10 atm)/4 Å MS/THF/50 °C/12 h] to furnish the desired **1b** in 83% yield. Since the double carbonylation product was not detected, it was found that the *N*-benzyl substituent in **2b** suppresses the double carbonylation.

In conclusion, we have demonstrated the palladium-catalyzed carbonylative macrolactamization of **2a** and **2b** in the synthesis of RGD cyclic peptide mimetics **1a** and **1b**. The reaction of *N*-benzyl group **2b** provided **1b** in better yield than in **2a**. It was suggested that the *N*-benzyl group can be effectively utilized as a linker on solid-phase toward a combinatorial library synthesis of various RGD cyclic models.

**Acknowledgment.** This work was supported by Grant-in-Aid for Scientific Research on Priority Areas (No. 16350051) from MEXT.

**Supporting Information Available:** Experimental details, NMR spectra of **8a–10a**, **8b–10b**, **2a**, **2b**, **1a**, and **1b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL702965R

(20) Urata, H.; Hu, N.-X.; Maekawa, H.; Fuchikami, T. *Tetrahedron Lett.* **1991**, *32*, 4733–4736.

(21) Ozawa, F.; Soyama, H.; Yanagihara, H.; Aoyama, I.; Takino, H.; Izawa, K.; Yamamoto, T.; Yamamoto, A. *J. Am. Chem. Soc.* **1985**, *107*, 3235–3245.