Accelerating Effect Induced by the Structure of α-Amino Acid in the Copper-Catalyzed Coupling Reaction of Aryl Halides with α-Amino Acids. Synthesis of Benzolactam-V8

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Received May 13, 1998

Abstract: The coupling of optically pure α-amino acids with aryl halides produces enantiopure *N*-aryl-α-amino acids with retention of configuration under the catalysis of CuI. This reaction can complete at much lower temperature than typical Ullmann condensation even for electron-rich aryl halides, which indicates that an accelerating effect induced by the structure of the α-amino acid exists in this reaction. α-Amino acids with larger hydrophobic groups give higher coupling yields, while those with smaller hydrophobic groups only deliver lower yields and no coupling products were detected for those with hydrophilic groups. No racemization was observed in most cases of this coupling reaction. After some controlled experiments, a possible mechanism including the π-complex and the intramolecular substitution reaction is proposed. Based on this catalyzed reaction, a facile and stereoselective synthesis of benzolactam-V8, a new PKC activator, is achieved.

Introduction

Recently, the formation of the carbon−nitrogen bond by the palladium-catalyzed coupling of aryl halides with amines has been achieved.[1] Buchwald[2] and Hartwig[3] independently reported that Pd/P(*o*-tolyl)$_3$ complex under the action of sterically bulky bases such as *t*-BuONa or LHDMS efficiently catalyzed the amination of aromatic bromides. By varying the catalytic systems and reaction conditions, aryl iodides,[4] aryl triflates,[5] and aryl chlorides[6] could be also used as effective amination reagents. Because these palladium-catalyzed reactions could be carried out at much lower temperature than the copper-mediated Ullmann condensation, these results represented a major advance in the development of aromatic amination methodology.[1] Recently, much attention has also been directed to seeking the arylation of more complex amines[7] that may expand the scope of this methodology. However, few reports dealt with optically pure amines.[8] Among numerous functionalized amines, α-amino acid is one of the best building blocks in organic synthesis because of its further transformations.[9] Furthermore, many α-amino acids are commercially available in optically pure form. On the other hand, chiral *N*-aryl-α-amino acids are of the common core structures for a number of synthetically challenging and medicinally important agents. These agents include protein kinase C (PKC) activators, indolactam-V,[10] and its analogue benzolactam-V8;[11] (see Figure 1) Ciba's phenylamide fungicides (*R*)-metalaxyl;[12] fibrinogen receptor antagonist SB 214857;[13] NMDA receptor antagonist L689560[14] and tricyclic quinoxalinediones;[15] ACE inhibitors;[16] and antiulcer agents.[17] In the past two decades, these structures

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(1) For reviews, see: Hartwig, J. F. *Synlett* **1997**, 329.

(2) Guram, S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl*. **1995**, *34*, 1348.

(3) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.

(4) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem*. **1996**, *61*, 1133.

(5) (a) Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem*. **1997**, *62*, 1264. (b) Louie, J.; Driver, M. S.; Hamann, B. C.; Hartwig, J. F. *J. Org. Chem.* **1997**, *62*, 1268. (c) Torisawa, Y.; Hashimoto, A.; Furuta, T.; Minamikawa, J. *Bioorg. Med. Chem. Lett*. **1997**, *14*, 1821.

(6) Reddy, N. P.; Tanaka, M.*Tetrahedron Lett*. **1997**, *38*, 4807.

(7) (a) Beletskaya, I. P.; Bessmertnykh, A. G.; Guilard, R. *Tetrahedron Lett*. **1997**, *38*, 2287. (b) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett*. **1998**, *39*, 1313. (c) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett*. **1998**, *39*, 617. (d) Singer, R. A.; Sadighi, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1998**, *120*, 213. (e) Zhao, S.; Miller, A. K.; Berger, J.; Fippin, L. A. *Tetrahedron Lett.* **1996**, *37*, 7217.

(8) (a) Ma, D.; Yao, J. *Tetrahedron: Asymmetry* **1996**, *7*, 3075. (b) Wagaw, S.; Rennels, R. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **1997**, *119*, 8451.

(9) For reviews, see: (a) Sardina, F. J.; Rapoport, H. *Chem. Rev*. **1996**, *96*, 1825. (b) Coppola, G. M.; Schuster, H. F.; *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*; Wiley: New York, 1987.

(10) (a) Endo, Y.; Shudo, K.; Furuhata, K.; Ogura, H.; Sakai, S.; Aimi, N.; Hitotsuyanagi, Y.; Koyama, Y. *Chem. Pharm. Bull*. **1984**, *32*, 358. (b) Kogan, T. P.; Somers, T. C.; Venuti, M. C. *Tetrahedron* **1990**, *46*, 6623. (c) Semmelhack, M. F.; Rhee, H. *Tetrahedron Lett.* **1993**, *34*, 1395. (d) Quick, J.; Saha, B.; Driedger, P. E. *Tetrahedron Lett.* **1994**, *35*, 8549.

(11) (a) Endo, Y.; Ohno, M.; Hirano, M.; Itai, A.; Shudo, K. *J. Am. Chem. Soc*. **1996**, *118*, 1841 and references therein. (b) Kozikowski, A. P.; Wang, S.; Ma, D.; Yao, J.; Ahmad, S.; Glazer, R. I.; Bogi, K.; Acs, P.; Modarres, S.; Lewin, N. E.; Blumberg, P. M. *J. Med. Chem*. **1997**, *40*, 1316. (c) Endo, Y.; Yamaguchi, M.; Hirano, M.; Shudo, K. *Chem. Pharm. Bull*. **1996**, *44*, 1138.

(12) Voss, G. *CHEMTECH* **1997**, (Apr), 17.

(13) Miller, W. H.; Ku, T. W.; Ali, F. E.; Bondinell, W. E.; Calvo, R. R.; Davis, L. D.; Erhard, K. F.; Hall, L. B.; Huffman, W. F.; Keenan, R. M.; Kwon, C.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Takata, T. D.; Yuan, C. *Tetrahedron Lett.* **1995**, *36*, 9433.

(14) (a) Kemp, J. A.; Leeson, P. D. *Trends Pharmacol. Sci.* **1993**, *14*, 20. (b) Leeson, P. D.; Carling, R. W.; Smith, J. D.; Baker, R.; Foster, A. C.; Kemp, J. A. *Med. Chem. Res.* **1991**, *1*, 64.

(15) Nagata, R.; Ae, N.; Tanno, N. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1527.

(16) De Lombaert, S.; Blanchard, L.; Stamford, L. B.; Sperback, D. M.; Grim, M. D.; Jenson, T. M.; Rodriguez, H. R. *Tetrahedron Lett.* **1994**, *35*, 7513.

10.1021/ja981662f CCC: $15.00
Published on Web 11/19/1998

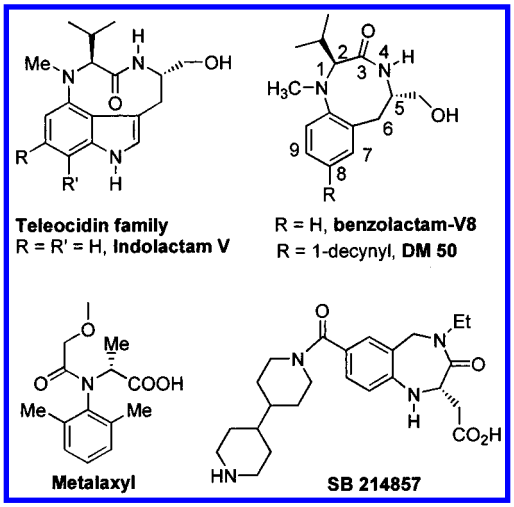
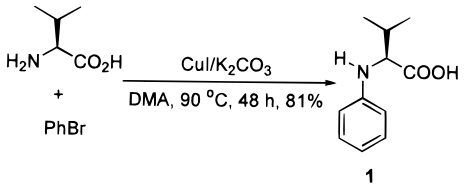


Figure 1.

were assembled via several steps to get the enantiomerically pure form. For example, in the synthesis of indolactam-V8 and its analogues, the chiral *N*-aryl-α-amino acid subunit was built inconveniently by an S_N2 displacement[10,11] of chiral triflate derived from D-valine with arylamine. In the synthesis of L689560,[14b] the corresponding subunit was obtained from the addition of arylamine to dimethyl acetylenedicarboxylate followed by chemical resolution. However, as a more direct and economical way, the coupling of an aryl halide with an α-amino acid derivative was achieved only when the aromatic ring was activated.[10c,13] Therefore, a general coupling reaction of aryl halides with α-amino acids appears attractive and of great value. Stimulated by recent progress on palladium-catalyzed amination, we have developed a Pd/Cu-catalyzed coupling reaction of α-amino acids with aryl halides.[8a] Because this reaction could be carried at 95 °C to give coupling product in high yield even for bromobenzene, which was much different with a typical Ullmann condensation reaction[18] (for unsubstituted aryl halides, the reaction is generally carried out at a temperature in excess of 150 °C), palladium was initially realized to play a key role in this reaction. However, after careful reinvestigation, we found that palladium catalyst was not necessary in this reaction and CuI itself could catalyze the coupling reaction of α-amino acids with aryl halides, which gave enantiomerically pure *N*-aryl-α-amino acids in moderate to excellent yields in most cases. This reaction proceeded under much lower temperature even for electron-rich aryl halides, which provided an unprecedented example of Ullmann-type amination.[18] This result indicated that an accelerating effect induced by the structure of α-amino acid existed in this reaction. In addition, by using this reaction, a facile and stereoselective synthesis of benzolactam-V8, a new protein kinase C activator, was developed. Herein, we disclose our results.

Results and Discussion

Copper-Catalyzed Coupling Reaction of α-Amino Acids with Aryl Halides. We chose the coupling reaction of L-valine with bromobenzene as the model reaction to investigate suitable reaction conditions. Although the original Pd/Cu reaction conditions developed by our laboratory for the coupling reaction of α-amino acids with aryl halides were effective,[8a] after some controlled experiments, it was found that CuI alone could catalyze this coupling reaction (eq 1). Thus, heating a mixture



(1)

of L-valine (1 equiv), bromobenzene (1 equiv), CuI (10 mol %), and K_2CO_3 (1.5 equiv) in DMA at 90 °C for 48 h, we could isolate the coupling product **1** in 81% yield. Other solvents were also checked for this reaction. Over 80% yields were obtained when *tert*-butyl alcohol, DMF, or NMPO was used as solvent, respectively. However, much lower yields were observed if pyridine (33% yield) or water (16% yield) instead of DMA was used as a solvent.

On the basis of these results, the coupling reaction was also tested by a number of different amino acids and aryl halides. The results were summarized in Table 1. It was found that both electron-rich and electron-deficient aryl bromides or aryl iodides worked for this reaction. However, aryl chlorides were poor coupling reagents (entry 13). The yields of the coupling reaction were influenced greatly by the types of α-amino acids. Those with larger hydrophobic groups gave higher coupling yields, while those with smaller hydrophobic groups delivered lower yields, and those with hydrophilic groups even yielded no coupling products at all (entries 10−12). These differences might result from the different solubilities of the α-amino acids or their related intermediates formed during the coupling reaction in the reaction solvent. Cyclic amino acid gave high yield. However, acyclic *N*-alkyl-amino acid gave low yield (entries 3

Table 1. Copper-Catalyzed Couplings of Aryl Halides and α-Amino Acids[a]

entry	aryl halide	amino acid	product	yield[b] (%)
1	PhBr	L-valine	**1**	81
2	PhBr	D-valine	**2**	75
3	PhBr	L-proline	**3**	80
4	PhBr	L-phenylalanine	**5**	92
5	PhBr	L-alanine	**6**	65
6	PhBr	L-methionine	**7**	76
7	PhBr	L-tyrosine	**8**	60
8	PhBr	*N*-methyl-L-valine	**4**	46
9	PhBr	L-tryptophen	**9**	73
10	PhBr	L-glutamic acid		0
11	PhBr	L-serine		0
12	PhBr	glycine		0
13	PhCl	L-valine	**1**	3
14	PhI	L-valine	**1**	83
15	3-$MeOC_6H_4Br$	L-valine	**10**	85
16	4-$BrC_6H_4CO_2H$	L-valine	**11**	75
17	2,5-$Me_2C_6H_3Br$	L-valine	**16**	74
18	2,6-$Me_2C_6H_3Br$	L-valine	**17**	14
19	2,6-$Me_2C_6H_3Br$	L-alanine	**12**	5
20	4-$MeOC_6H_3Br$	L-valine		*c*
21	2-$MeOC_6H_4Br$	L-valine	**18a**	82
22	2-HOC_6H_4Br	L-valine	**18b**	61
23	4-ClC_6H_4Br	L-valine	**13**	83
24	3-$BrC_6H_4CO_2H$	L-valine	**14**	92
25	2-$BrC_6H_4CO_2H$	L-valine	**15**[d]	64
26	2-$IC_6H_4CO_2H$	L-valine	**15**	83

[a] Reaction conditions: 10 mol % CuI, 150 mol % K_2CO_3, ArX (3.2 mmol), amino acid (3.2 mmol), DMA (4 mL), 90 °C, 48 h. [b] Isolated yield. [c] Product decomposed during the isolation. [d] Salicyclic acid was isolated in 30% yield.

(17) Hosokami, T.; Kuretani, M.; Higashi, K.; Asano, M.; Ohya, K.; Takasugi, N.; Mafune, E.; Miki, T. *Chem. Pharm. Bull.* **1992**, *40*, 2712.

(18) (a) Paine, A. J. *J. Am. Chem. Soc.* **1987**, *109*, 1496. (b) Lindley, J. *Tetrahedron*, **1984**, *40*, 1433. (c) For an example of Ullmann-like reductive coupling of aryl, heteroaryl, and alkenyl halides under mild conditions, see: Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312.

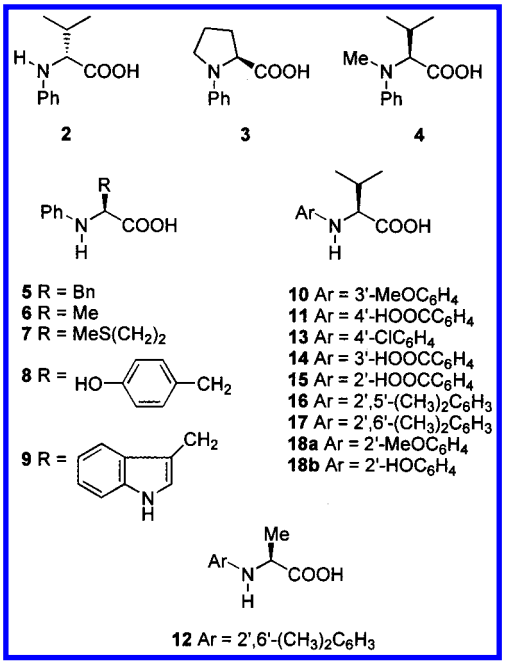


Figure 2. Structures of the coupling products catalyzed by CuI.

and 8). This phenomenon was similar with that found by Driver and Hartwig[19] in Pd-catalyzed coupling of aryl halides and amines. Steric hindrance about the methyl of aryl halides disfavored this reaction. For example, the coupling reaction of 2,6-dimethylbromobenzene with L-valine gave much lower yield than that of 2,5-dimethylbromobenzene with L-valine (entries 17 and 18). In the case of 4-bromoanisole as substrate, although the coupling product was monitored by TLC, it was too unstable to be isolated under ordinary conditions (entry 20). In contrast, the coupling products from 2-bromoanisole or 2-bromophenol could be isolated in 82% and 61% yields, respectively (entries 21 and 22). When 2-bromobenzoic acid was used to couple with L-valine under the same conditions, besides the expected coupling product in 64% yield, a side product, salicylic acid, was also isolated in 30% yield (Table 1, entry 20). However, when 2-iodobenzoic acid was used as substrate, the formation of salicylic acid was not observed.

It is well-known that an optically pure α-amino acid will racemize on heating it under high temperature and strong basic condition.[20] Considering that the present coupling reaction was also carried out under basic conditions and higher temperature, it was possible that the racemization might occur during the course of coupling reaction. To check the optical purity of each coupling product, we transformed the coupling products to their peptide derivatives to see if any diastereoisomers existed. Accordingly, the coupling product **5** (see Figure 2) was coupled with L-alanine methyl ester hydrochloride using EDC to produce **19**. Analysis of **19** by ^{1}H NMR revealed that only one isomer existed, while analysis of **20**, the coupling product of the racemic **5** (prepared from the coupling of DL-phenylalanine with bromobenzene) with L-alanine methyl ester, showed clearly the existence of two isomers by ^{1}H NMR. These results illustrated that the optical purity of **5** was over 97%. In a similar manner, the other products were checked and we found that each of them had over 97% optical purity except for the coupling products **6** and **7**. These two products showed 93% and 71% optical purity, respectively. Thus, we could conclude that the present conditions seemed mild enough to avoid the racemization of either the starting material or the product in most cases. The poorer optical purity of **7** might result from its special structural feature. In **7**, the methylthio group might facilitate the formation of potassium salt **21** and therefore accelerate the racemization (see Figure 3).

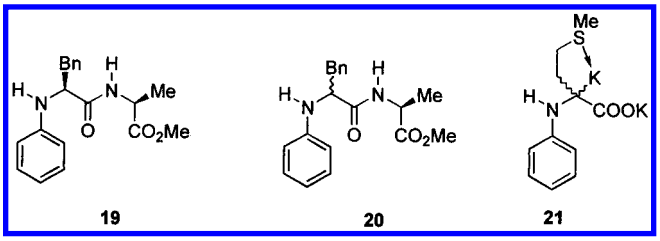


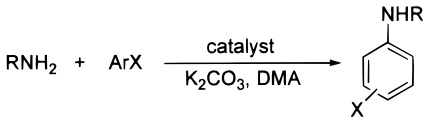
Figure 3. Structures of dipeptides **19** and **20** and potassium salt **21**.

The utility of the present reaction could be illustrated by some reaction products. For example, *N*-phenyl-L-proline (**3**), the direct coupling product of L-valine with iodobenzene, was found as a key precursor for synthesizing antiulcer agents,[17] while the original synthesis for this compound took several steps to give racemic product. *N*-(2,6-Dimethylphenyl)-D-alanine (**12**) could be used in synthesizing Ciba's phenylamide fungicide (*R*)-metalaxyl.[12] Although the yield for this compound by our method is low, the methodology opens a new avenue for synthesizing this class of compounds. Obviously, these *N*-aryl-α-amino acids are also valuable building blocks for peptidomimetic studies. In addition, an example using this reaction for efficient synthesis of a biologically important compound would be discussed here later.

Mechanism Studies. To study the possible mechanism of the present reaction and seek its scope, the coupling reactions of other amines with aryl halides under different copper catalysts were carried out. From the results summarized in Table 2, we could observe that the present reaction had the typical characteristics of an Ullmann condensation in many aspects.[18] First, although the yields were all over 80% after 48 h when $CuSO_4$, $Cu(OAc)_2$, or CuI was used as the catalyst, respectively (entries 1−3), the reaction catalyzed by CuI was faster than those catalyzed by $CuSO_4$ or $Cu(OAc)_2$ (compare entries 4, 5, and 6), while molecular oxygen could inhibit the reaction (entry 13). These results implied that Cu(I) or a related complex might serve as the active catalyst. Second, a strong *o*-carboxylate accelerating effect was also observed while *p*-carboxylate had no similar effect (entries 7−9). Finally, the ease of halogen displacement from the aromatic ring was also found in following order: I > Br > Cl (compare entries 7, 14, and 15). The only exception was that the present reaction could occur at much lower temperature even for unsubstituted or electron-rich aryl halides. For example, the coupling reaction of bromobenzene with L-valine could give 43% conversion at 75 °C after 24 h (entry 7). In contrast, the coupling reaction of bromobenzene with benzylamine only gave 5% conversion at 110 °C after 32 h (entry 10). It was reported that amines with a hydroxyl group at the β- or γ-position were more reactive than butylamine in the Ullmann condensation reaction of haloanthraquinones with amines.[21] We tried the coupling reaction of (*S*)-valinol with bromobenzene and found only 5% conversion at 110 °C after 32 h (entry 12), which was much slower than the reaction of L-valine and bromobenzene (entry 7). These results demonstrated that a strong accelerating effect induced by the structure of α-amino acid existed in the coupling reaction of α-amino acids with aryl halides. As a nucleophilic agent, the reactivity

(19) Driver, M. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **1996**, *118*, 7217.
(20) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Vol. 3.
(21) Arai, S.; Yamagishi, T.; Ototake, S.; Hida, M. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 547.

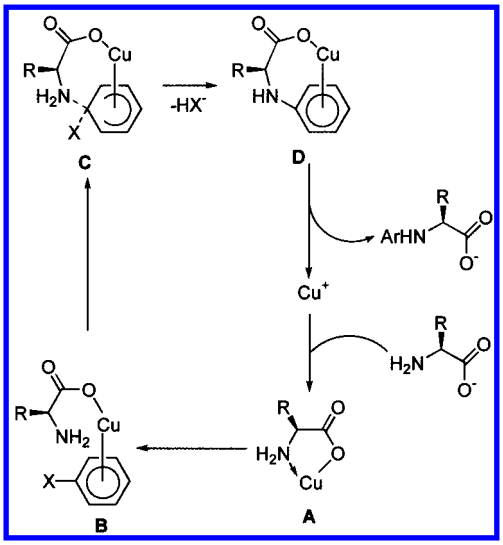
Table 2. Copper Ions-Catalyzed Coupling Reactions of Aryl Halides and Amines[a]



entry	ArX	RNH_2	catalyst	temp (°C)	time (h)	product (yield[b](%))
1	PhBr	L-valine	CuI	90	48	**1** (80)
2	PhBr	L-valine	$CuSO_4$	90	48	**1** (79)
3	PhBr	L-valine	$Cu(OAc)_2$	90	48	**1** (82)
4	PhBr	L-valine	CuI	90	24	**1** (81)
5	PhBr	L-valine	$CuSO_4$	90	24	**1** (44)
6	PhBr	L-valine	$Cu(OAc)_2$	90	24	**1** (51)
7	PhBr	L-valine	CuI	75	24	**1** (45)
8	2-$BrC_6H_4CO_2H$	L-valine	CuI	75	24	**15** (66[c])
9	4-$BrC_6H_4CO_2H$	L-valine	CuI	75	24	**11** (0)
10	PhBr	$PhCH_2NH_2$	CuI	110	32	(5[g])
11	PhBr	$PhCH_2NH_2$	CuI	110	32	(9[d,g])
12	PhBr	(*S*)-valinol	CuI	110	32	(5[h])
13	PhBr	L-phenylalanine	CuI	90	24	**5** (0[e])
14	PhCl	L-valine	CuI	75	24	**1** (0)
15	PhI	L-valine	CuI	75	24	**1** (80)
16	PhBr	*f*	*f*	90	48	**5** (43)

[a] Reaction conditions: 10 mol % CuI, 150 mol % K_2CO_3, ArX (3.2 mmol), amine (3.2 mmol), DMA (4 mL). [b] Isolated yield. [c] Salicylic acid was isolated in 28% yield. [d] L-Valine (10 mol %) was added in this reaction. [e] Reaction was carried out under air. [f] Cu(II)−L-phenylalanine complex ($Cu(H_2NCH(Bn)COO)_2$) was used. [g] Product was *N*-benzylaniline and 80% benzylamine was recovered. [h] Product was (*S*)-*N*-phenylvalinol and 84% (*S*)-valinol was recovered.

Scheme 1. Possible Catalytic Cycle



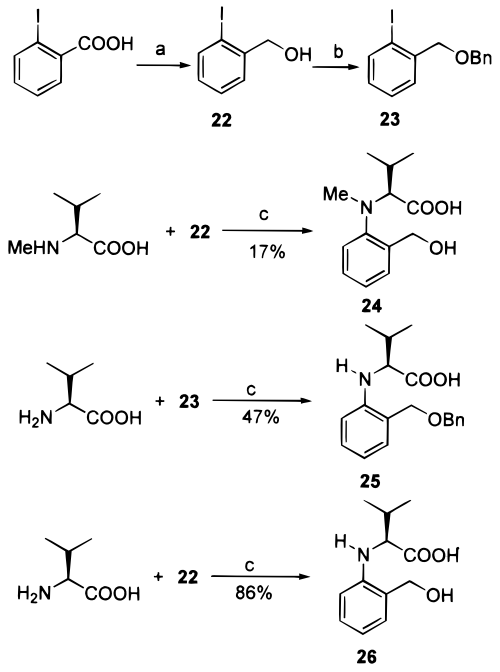
of an α-amino acid is obviously much weaker than a simple aliphatic amine because of the electron-withdrawing effect of the carboxylate in an α-amino acid. Thus, the structural feature of the α-amino acids could contribute to the formation of the present accelerating effect. It is known that copper ions can form chelates with amino acids through the carboxyl and amino groups.[22] These chelates might play a key role in the catalytic cycle. On the basis of this analysis and the known π-complex mechanism[18a] of Ullmann condensation, we proposed the possible catalytic cycle for the present reaction as shown in Scheme 1. First, cuprous ion reacted with an α-amino acid salt to form the chelate **A**, which coordinated with a suitable aryl halides to provide the π-complex **B**. Next, intramolecular nucleophilic substitution occurred at the aromatic ring to give the transition state **C**. This step might be the rate-determining step, and the intramolecular attack would lower the activation energy of this step. This hypothesis could be used to explain the accelerating effect induced by the structure of the α-amino acid. Finally, HX was removed from **C** with the assistance of potassium carbonate to deliver another π-complex **D**, which could decompose to produce the coupling product and regenerate the cuprous ion.

This proposed mechanism was also supported by following experiments: (i) L-Phenylalanine−Cu(II) complex was reacted with bromobenzene in the presence of potassium carbonate in DMA under a nitrogen atmosphere. Although the solubility of this complex was very low in this reaction system, it was found that the coupling product **1** could be isolated in 43% yield after 48 h (Table 2, entry 16). However, the reaction of L-phenylalanine and bromobenzene catalyzed by CuI under air did not give any coupling product and the blue L-phenylalanine−Cu(II) complex was isolated after 24 h (Table 2, entry 13). These results indicated that the active catalyst might be L-phenylalanine−Cu(I) complex but not L-phenylalanine−Cu(II) complex. It was known that Cu(II) could be reduced to Cu(I) by the nucleophile.[18] (ii) Addition of 10 mol % L-valine in the CuI-catalyzed reaction of benzylamine with bromobenzene did not cause a marked accelerating effect (Table 2, entry 11). Because the nucleophilic ability of benzylamine was higher than that of L-valine, this result ruled out the intermolecular substitution mechanism. (iii) It was reported that the glycine−Cu(II) complex was much more stable than the *N*-phenylglycine−Cu(II) complex.[22] Thus, it was reasonable to understand that complex **A** is easier to form than the Cu(I)−coupling product complex in order to make the catalytic cycle continue. Of course, because of the complexity of the Ullmann condensation reaction,[18] the present catalytic cycle was still not completely satisfactory. Other reasonable mechanisms may exist and more detailed studies should be carried out to investigate the true mechanism.

Synthesis of Benzolactam-V8. Benzolactam-V8 (Figure 1) is a core structure of a new class of protein kinase C activators.[11] Although the activity of benzolactam-V8 itself is not so potent, its derivatives with a side chain at the 8 or 9 position showed potency similar to that of teleocidin B4.[11] From benzolactam-

(22) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Wiley: New York, 1961; Vol. 1; p 569.

Scheme 2[a]



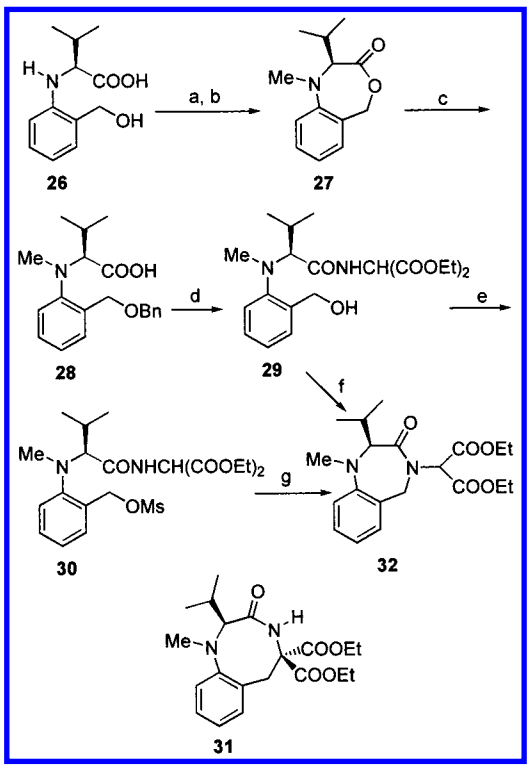
[a] Reagents: (a) ClCOOMe, then $NaBH_4$; (b) NaOH, then BnBr; (c) CuI, K_2CO_3, DMA, 90 °C, 48 h.

V8, 8-decynyl-benzolactam-V8 (DM50) (Figure 1) was synthesized through iodination followed by a Pd-catalyzed coupling reaction with 1-decyne.[11b] Biological studies indicated that DM50 could selectively downregulate PKCβ in MCF-7 and MDA-231 cells and had antiproliferative activity against breast carcinoma cell lines MCF-7 and MDA-MB-231.[11b] However, previous synthesis of benzolactam-V8, using the S_N2 displacement[11] of chiral triflate derived from D-valine with arylamine to introduce the *N*-aryl-valine moiety, was not very efficient. After being successful in directly coupling of L-valine with aryl halides, we believed that the present methodology could provide us a good chance to develop a new synthetic protocol to benzolactam-V8 and its derivatives. Thus, the studies on the CuI-catalyzed coupling reaction of L-valine or *N*-methyl-L-valine with some ortho-substituted iodobenzenes were conducted.

As outlined in Scheme 2, 2-iodobenzoic acid was reduced to 2-iodobenzyl alcohol (**22**) with ClCOOMe/$NaBH_4$. Considering that the hydroxy group could give some trouble in further transformation, it was protected with benzyl group to afford **23**. Initially, the coupling reaction of *N*-methyl-L-valine with **22** under the above typical conditions was tried. Like the coupling of *N*-methyl-L-valine with bromobenzene (Table 1, entry 8), coupling product **24** was obtained in lower yield. Next, the reaction of **23** and L-valine was carried out to produce **25**. However, the yield (47%) was still not satisfactory. Finally, it was found that the coupling reaction of **22** with L-valine could provide the desired product **26** in high yield (86%).

To introduce the amino alcohol moiety necessary for synthesizing benzolactam-V8, some functional groups in **26** should be protected in advance. Thus, **26** was lactonized with DCC and then reduction methylation was carried out with $NaBH_3$-CN and HCHO to produce **27**. After the lactone ring was opened by aqueous NaOH, the resultant sodium salt was dried and then directly reacted with 1 equiv of benzyl bromide under the action of sodium hydride to afford acid **28** in 90% overall yield. Condensation of **28** with diethyl aminomalonate under the ordinary conditions followed by removal of the benzyl protecting group by Pd/C-catalyzed hydrogenation afforded the

Scheme 3[a]



[a] Reagents and conditions: (a) DCC, HOBt, Et_3N, CH_2Cl_2, rt, 82%; (b) $NaBH_3CN$, 37% HCHO, AcOH, CH_3CN, 0 °C, 83%; (c) (i) 1 N NaOH, (ii) NaH, BnBr, (iii) 1 N NaOH; (d) (i) EDC, HOBt, diethyl aminomalonate hydrochloride, Et_3N, CH_2Cl_2, rt, 81%; (ii) Pd/C, H_2, 42%; (e) MsCl, Et_3N; (f) PBu_3, ADDP, 32%; (g) *t*-BuOK, THF, 50%.

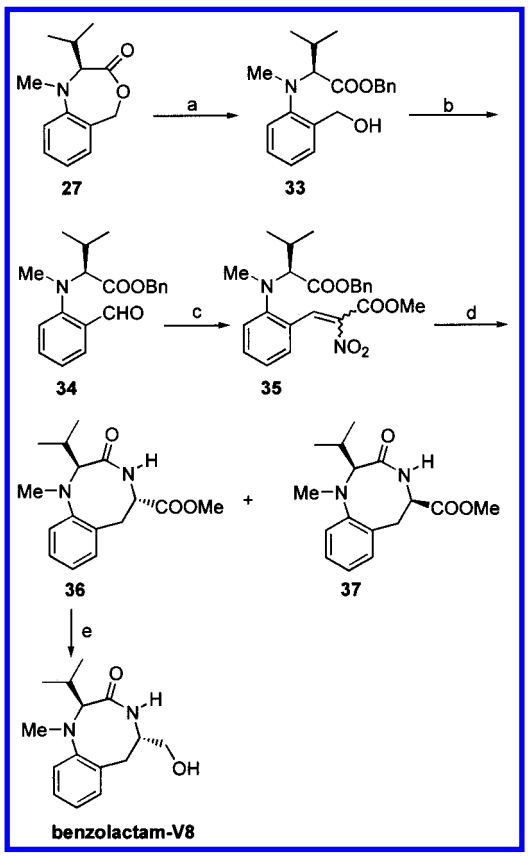
alcohol **29**. At this stage, we planned to build an eight-membered lactam ring by an intramolecular alkylation. It was reported[23] that PBu_3/ADDP could promote the alkylation of malonate esters with suitable alcohols. Under similar conditions, cyclization of **29** was tried. However, no desired product **31** was obtained but a side product **32** was isolated. Base-mediated alkylation of **30** was also tried. Unfortunately, the similar undesired result was observed (Scheme 3).

Because the intramolecular alkylation was not successful in obtaining product **31**, another route was designed to synthesize the target molecule in which the cyclization would be carried out by amide bond formation (Scheme 4). Accordingly, the lactone **27** was treated with 1 equiv of NaOH to open the ring and then the resultant sodium salt was reacted with benzyl bromide to afford ester **33**. Subjecting **33** to Swern oxidation produced aldehyde **34**, which was condensed with methyl 2-nitroacetate under the action of $TiCl_4$ and NMM to furnish olefin **35**.[24] By ^1H NMR it was found that both cis and trans isomers were formed in a ratio of about 1/1.7 and the mixture was directly used for the next step without further separation. Next, reduction of the C=C double bond and nitro group and deprotection of benzyl ester were carried out in one pot by Pd/C-catalyzed hydrogenation to yield crude amino acid, which was cyclized under the action of DPPA to afford a mixture of diastereoisomers **36** (35% overall yield from **35**) and **37** (17% overall yield from **35**). Finally, $LiBH_4$ reduction of **37** afforded benzolactam-V8 in 88% yield. The overall yield was about 17.7% from L-valine, which was better than either of the previous two synthetic routes[11] (overall yields are 7% and

(23) Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett*. **1993**, *34*, 1639.

(24) Lehnert, W. *Tetrahedron* **1972**, *28*, 663.

Scheme 4[a]



[a] Reagents and conditions: (a) 1 N NaOH, then BnBr, 98%; (b) oxalyl chloride, DMSO, −65 °C, then Et_3N 97%; (c) $MeOOCCH_2NO_2$, $TiCl_4$, then NMM, 82%; (d) (i) Pd/C, H_2, MeOH, (ii) DPPA, DMF, 35% for **36**, 17% for **37**; (e) $LiBH_4$, THF, 88%.

10.3%, respectively). It is obvious that we could synthesize 8- or 9-substituted analogues of benzolactam-V8 by this methodology if we started from a suitable substituted 2-iodobenzyl alcohol. Thus, the discovery of the present reaction provides us a very efficient protocol to synthesize this class of compounds with potential therapeutic value.

In summary, we have found CuI is an effective catalyst for direct coupling of aryl halides and α-amino acids under relatively mild conditions. This reaction provides a short and economic way to synthesize chiral *N*-aryl-α-amino acids, which are common core structures for a number of biologically important molecules. The discovery of the accelerating effect induced by the structure of the α-amino acid for the Ullmann condensation reaction would be of benefit for its mechanism studies, as well as catalyst design for aryl amination at lower temperature. Using this methodology to synthesize other complex molecules such as substituted benzolactam-V8 as well as the detailed mechanism studies are being pursued in our laboratory and will be reported in due course.

Experimental Section

General Procedures. IR spectra were measured on a Schimadzu 440 spectrometer. ^{1}H NMR spectra were recorded with TMS as an internal standard at a Brucker AM-300 spectrometer. MS spectra were determined on a Finnigan 4201 spectrometer or a VG Quattro MS/MS spectrometer. Optical rotations were obtained on a Perkin-Elmer 241 Autopol polarimeter. Analytically pure DMF, DMA and NMPO were used directly without further purification. CH_2Cl_2 was distilled from CaH_2, and THF was distilled from a deep blue ketyl prior to use. All other solvents were of reagent grade quality and used as received. Na_2SO_4 was used as the drying agent in all workup procedures. All reactions were run in flame-dried glassware under nitrogen atmosphere unless stated otherwise.

General Procedure for the CuI-Catalyzed Coupling Reaction of Amino Acids with Aryl Halides. A Schlenk tube was charged with amino acid (3.2 mmol), aryl halide (3.2 mmol), K_2CO_3 (4.8 mmol), and CuI (0.32 mmol). Under N_2 atmosphere, DMA (4 mL) was added by syringe. The tube was sealed and heated at 90 °C for 48 h. After being cooled to room temperature, the reaction mixture was diluted with 10 mL of ethyl acetate and 5 mL of water. Under cooling with ice/water, concentrated HCl was added to adjust the pH to 3. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (5 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to dryness by Rotavapor. The residual oil was loaded on a silica gel column and eluted with ethyl acetate/petroleum ether (1/5 to 1/1) to afford the coupling product.

***N*-Phenyl-L-valine (1):** 81% yield; $[\alpha]_D^{25} = -49.1$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 2H), 6.68 (t, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 2H), 3.89 (d, *J* = 5.4 Hz, 1H), 2.18 (m, 1H), 1.05 (d, *J* = 9.4 Hz, 6H); MS *m*/*z* 193 (M^+), 150, 148, 132, 104; HRMS found *m*/*z* 193.167 (M^+), $C_{11}H_{15}NO_2$ requires 193.167. Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.24. Found: C, 68.06; H, 7.76, N, 6.88.

***N*-Phenyl-D-valine (2):** 75% yield; $[\alpha]_D^{25} = +47.2$ (*c* 0.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (t, *J* = 7.8 Hz, 2H), 6.68 (t, *J* = 7.5 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 2H), 3.89 (d, *J* = 5.4 Hz, 1H), 2.18 (m, 1H), 1.05 (d, *J* = 9.4 Hz, 6H); MS *m*/*z* 193 (M^+), 150, 148, 132, 104, 77, 43; HRMS found *m*/*z* 193.168 (M^+), $C_{11}H_{15}NO_2$ requires 193.167.

***N*-Phenyl-L-proline (3):** 80% yield; $[\alpha]_D^{25} = -46.8$ (*c* 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (t, *J* = 8.2 Hz, 2H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 2H), 4.23 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.30 (t, *J* = 7.2 Hz, 2H), 2.35 (m, 2H), 2.12 (m, 2H); MS *m*/*z* 191 (M^+), 146, 117, 104, 77. Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.13; H, 6.81; N, 7.33. Found: C, 68.81; H, 6.97; N, 7.11.

***N*-Phenyl-*N*-methyl-L-valine (4):** 46% yield; $[\alpha]_D^{25} = -88.6$ (*c* 0.93, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.8 Hz, 2H), 6.98 (d, *J* = 7.9 Hz, 2H), 6.82 (t, *J* = 7.8 Hz, 1H), 3.95 (d, *J* = 10.1 Hz, 1H), 3.07 (s, 3H), 2.29 (m, 1H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.9 Hz, 3H); MS *m*/*z* 207 (M^+), 176, 162, 146, 120, 106, 91, 77, 42; HRMS found *m*/*z* 206.1185 ($M^+ - 1$), $C_{12}H_{16}NO_2$ requires 206.1182.

***N*-Phenyl-L-phenylalanine (5):** 92% yield; $[\alpha]_D^{25} = +2.5$ (*c* 0.50, CH_3COCH_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (t, *J* = 8.2 Hz, 2H), 6.79 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 2H), 4.23 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.30 (t, *J* = 7.2 Hz, 2H), 2.35 (m, 2H), 2.12 (m, 2H); MS *m*/*z* 191 (M^+), 146, 117, 104, 77. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.70; H, 6.22; N, 5.81. Found: C, 74.38; H, 6.51, N, 5.58.

***N*-Phenyl-L-alanine (6):** 65% yield; $[\alpha]_D^{25} = -44.8$ (*c* 0.84, CH_3COCH_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.5 Hz, 2H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.62 (d, *J* = 8.2 Hz, 2H), 5.70 (br s, 2H), 4.13 (q, *J* = 7.2 Hz, 1H), 1.53 (d, *J* = 7.2 Hz, 3H); MS *m*/*z* 165 (M^+), 120, 104, 91, 77, 65, 51, 42. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.48; H, 6.67; N, 8.48. Found: C, 65.51; H, 6.73; N, 8.55.

***N*-Phenyl-L-methionine (7):** 76% yield; $[\alpha]_D^{25} = -11.8$ (*c* 1.0, CH_3COCH_3); ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 7.06 (t, *J* = 8.1 Hz, 2H), 6.56 (d, *J* = 7.5 Hz, 2H), 6.54 (m, 1H), 3.99 (dd, *J* = 7.1, 5.2 Hz, 1H), 2.58 (m, 2H), 2.05 (s, 3H), 1.96 (m, 2H); MS *m*/*z* 225 (M^+), 207, 192, 180, 159, 132, 118, 104, 91, 77, 61, 43; HRMS found *m*/*z* 225.0813 (M^+), $C_{11}H_{15}NO_2S$ requires 225.0821.

***N*-Phenyl-L-tyrosine (8):** 60% yield; $[\alpha]_D^{25} = +23.9$ (*c* 0.86, CH_3OH); ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 7.09−7.02 (m, 4H), 6.64(d, *J* = 8.2 Hz, 2H), 6.53 (d, *J* = 8.2 Hz, 2H), 6.50 (m, 1H), 4.00 (t, *J* = 7.6 Hz, 1H), 2.92 (dd, *J* = 13.9, 7.0 Hz, 1H), 2.85 (dd, *J* = 12.8, 7.0 Hz, 1H); MS *m*/*z* 257 (M^+), 212, 150, 132, 118, 104, 91, 77, 51. Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.03; H, 5.88; N, 5.44. Found: C, 70.05; H, 5.85; N, 5.21.

***N*-Phenyl-L-tryptophen (9):** 73% yield; $[\alpha]_D^{25} = +9.2$ (*c* 0.77, CH_3OH); ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 10.86 (s, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.20 (d, *J* = 1.9 Hz, 1H), 7.08−6.93 (m, 4H), 6.57 (d, *J* = 8.4 Hz, 2H), 6.53 (t, *J* = 7.4 Hz, 1H), 4.15

(t, J = 7.1 Hz, 1H), 3.24 (dd, J = 14.4, 6.0 Hz, 1H), 3.12 (dd, J = 14.4, 6.4 Hz, 1H); MS m/z 225 (M^+), 207, 192, 180, 159, 132, 118, 104, 91, 77, 61, 43; HRMS found m/z 225.0813 (M^+), $C_{11}H_{15}NO_2S$ requires 225.0821.

***N*-(3′-Methoxyphenyl)-L-valine (10):** 85% yield; $[\alpha]_D^{25} = -38.5$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (t, J = 8.1 Hz, 1H), 6.33 (dd, J = 8.1, 2.1 Hz, 1H), 6.27 (dd, J = 8.1, 2.0 Hz, 1H), 6.21 (t, J = 2.0 Hz, 1H), 3.87 (d, J = 7.6 Hz, 1H), 3.76 (s, 3H), 2.19 (m, 1H), 1.05 (d, J = 7.2 Hz, 6H); MS m/z 223 (M^+), 178, 162, 152, 134, 123, 107, 92, 83, 77, 43; HRMS found m/z 223.1175 (M^+), $C_{12}H_{17}NO_3$ requires 223.1204.

***N*-(4′-Carboxyphenyl)-L-valine (11):** 75% yield; $[\alpha]_D^{25} = -114.1$ (c 0.93, CH_3COCH_3); ^{1}H NMR (300 MHz, CD_3SOCD_3) δ 12.35 (br s, 1H), 7.65 (d, J = 8.4 Hz, 2H), 6.63 (d, J = 8.4 Hz, 2H), 3.73 (m, 1H), 2.06 (m, 1H), 1.00 (d, J = 7.2 Hz, 3H), 0.96 (d, J = 7.2 Hz, 3H); MS m/z 237 (M^+), 220, 192, 176, 148, 132, 121, 104, 77, 65, 44. Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.94; H, 6.40; N, 6.01.

***N*-(2′,6′-Dimethylphenyl)-L-alanine (12):** 74% yield; $[\alpha]_D^{25} = +39.6$ (c 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 (d, J = 7.5 Hz, 2H), 6.83 (t, J = 7.6 Hz, 1H), 5.25 (br s, 2H), 3.97 (q, J = 7.2 Hz, 1H), 2.29 (s, 6H), 1.42 (d, J = 7.1 Hz, 3H); MS m/z 193 (M^+), 132, 118, 105, 91, 77, 65, 51, 44; HRMS found m/z 193.1076 (M^+), $C_{11}H_{15}NO_2$ requires 193.1100.

***N*-(4′-Chlorophenyl)-L-valine (13):** 83% yield; $[\alpha]_D^{25} = -47.8$ (c 0.94, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, J = 8.2 Hz, 2H), 6.58 (d, J = 8.2 Hz, 2H), 6.28 (br s, 2H), 3.83 (d, J = 5.6 Hz, 1H), 2.17 (m, 1H), 1.06 (d, J = 6.5 Hz, 6H); MS m/z 229 (M^+, ^{37}Cl), 227 (M^+, ^{35}Cl), 184, 182, 166, 147, 140, 138, 127, 111, 99, 75, 55, 43; HRMS found m/z 227.0743 (M^+, ^{35}Cl), $C_{11}H_{14}ClNO_2$ requires 227.0714.

***N*-(3′-Carboxyphenyl)-L-valine (14):** 92% yield; $[\alpha]_D^{25} = -59.7$ (c 1.1, CH_3COCH_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, J = 7.7 Hz, 1H), 7.43 (s, 1H), 7.24 (t, J = 7.7 Hz, 1H), 6.88 (dd, J = 7.9, 2.0 Hz, 1H), 3.95 (d, J = 5.7 Hz, 1H), 2.20 (m, 1H), 1.09 (d, J = 6.9 Hz, 6H); MS m/z 237 (M^+), 192, 176, 148, 132, 121, 103, 93, 77, 43; HRMS found m/z 237.0982 (M^+), $C_{12}H_{15}NO_4$ requires 237.1001.

***N*-(2′-Carboxyphenyl)-L-valine (15):** 83% yield; $[\alpha]_D^{25} = -89.9$ (c 1.1, CH_3COCH_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, J = 7.8 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 6.68 (t, J = 7.6 Hz, 1H), 6.65 (d, J = 7.7 Hz, 1H), 4.03 (d, J = 5.1 Hz, 1H), 2.33 (m, 1H), 1.13 (d, J = 6.9 Hz, 3H), 1.10 (d, J = 6.9 Hz, 3H); MS m/z 237 (M^+), 192, 174, 148, 132, 119, 104, 92, 65, 43; HRMS found m/z 237.1009 (M^+), $C_{12}H_{15}NO_4$ requires 237.1001.

***N*-(2′,5′-Dimethylphenyl)-L-valine (16):** 74% yield; $[\alpha]_D^{25} = -41.5$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 7.6 Hz, 1H), 6.55 (d, J = 7.7 Hz, 1H), 6.40 (s, 1H), 6.10 (br s, 2H), 3.92 (d, J = 5.4 Hz, 1H), 2.27 (s, 3H), 2.24 (m, 1H), 2.18 (s, 3H), 1.11 (d, J = 6.9 Hz, 3H), 1.09 (d, J = 6.9 Hz, 3H); MS m/z 221 (M^+), 178, 132, 104, 65, 45; HRMS found m/z 221.1414 (M^+), $C_{13}H_{19}NO_2$ requires 221.1416.

***N*-(2′,6′-Dimethylphenyl)-L-valine (17):** 14% yield; $[\alpha]_D^{25} = +9.5$ (c 0.86, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 7.8 Hz, 2H), 6.78 (t, J = 7.8 Hz, 1H), 3.80 (d, J = 5.7 Hz, 1H), 2.29 (s, 6H), 2.13 (m, 1H), 1.14 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H); MS m/z 221 (M^+), 178, 132, 120, 105, 77, 65; HRMS found m/z 221.1415 (M^+), $C_{13}H_{19}NO_2$ requires 221.1416.

***N*-(2′-Methoxyphenyl)-L-valine (18a):** 83% yield; $[\alpha]_D^{25} = -12.0$ (c 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.82 (dt, J = 7.8, 1.4 Hz, 1H), 6.76 (dd, J = 7.7, 1.4 Hz, 1H), 6.72 (dt, J = 7.7, 1.4 Hz, 1H), 6.56 (dd, J = 7.6, 1.4 Hz, 1H), 5.89 (br s, 2H), 3.86 (s, 3H), 3.83 (d, J = 5.8 Hz, 1H), 2.24 (m, 1H), 1.08 (d, J = 6.9 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H); MS m/z 223 (M^+), 179, 148, 136, 121, 107, 92, 77, 65; HRMS found m/z 223.1203 (M^+), $C_{12}H_{17}NO_3$ requires 223.1204.

***N*-Methyl-*N*-(2′-hydroxymethylphenyl)-L-valine (24):** 17% yield; $[\alpha]_D^{25} = +17.0$ (c 1.1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27−7.08 (m, 4H), 6.10 (br s, 2H), 4.94 and 4.63 (AB q, d, J = 12.9 Hz, 2H), 3.64 (d, J = 6.9 Hz, 1H), 2.77 (s, 3H), 2.16 (m, 1H), 1.08 (d, J = 7.2 Hz, 3H), 0.95 (d, J = 7.2 Hz, 3H); MS m/z 237 (M^+), 220, 192, 176, 148, 136, 120, 106, 91, 77; HRMS found m/z 237.1355 (M^+), $C_{13}H_{19}NO_3$ requires 237.1365.

***N*-(2′-Benzyloxymethylphenyl)-L-valine (25):** 47% yield; $[\alpha]_D^{25} = -13.8$ (c 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 7.21 (t, J = 7.7 Hz, 1H), 7.08 (d, J = 7.6 Hz, 1H), 6.73 (t, J = 7.7 Hz, 1H), 6.59 (d, J = 7.8 Hz, 1H), 4.67 and 4.60 (AB q, d, J = 12.0 Hz, 2H), 4.52 and 4.45 (AB q, d, J = 11.5 Hz, 1H), 3.86 (d, J = 5.6 Hz, 1H), 2.19 (m, 1H), 1.02 (d, J = 7.1 Hz, 3H), 1.00 (d, J = 7.1 Hz, 3H); MS m/z 313 (M^+), 237, 219, 199, 183, 150, 135, 122, 107, 91, 77, 51; HRMS found m/z 313.1663 (M^+), $C_{19}H_{23}NO_3$ requires 313.1678.

***N*-(2′-Hydroxymethylphenyl)-L-valine (26):** 86% yield; $[\alpha]_D^{25} = -59.7$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, J = 7.8 Hz, 1H), 7.07 (dd, J = 7.7, 1.5 Hz, 1H), 6.71 (t, J = 7.7 Hz, 1H), 6.59 (d, J = 7.8 Hz, 1H), 4.95 (br s, 3H), 4.72 and 4.67 (AB q, d, J = 12.3 Hz, 2H), 3.86 (d, J = 5.6 Hz, 1H), 2.23 (m, 1H), 1.06 (d, J = 7.1 Hz, 6H); MS m/z 223 (M^+), 206, 134, 107, 77, 43; HRMS found m/z 223.1198 (M^+), $C_{12}H_{17}NO_3$ requires 223.1209.

General Procedure for the Catalytic Coupling Reaction of Benzylamine or (*S*)-Valinol with Aryl Halides. A mixture of amine (3.2 mmol), aryl halide (3.2 mmol), K_2CO_3 (4.8 mmol), CuI (0.32 mmol), and DMA (4 mL) in a sealed tube was heated at 110 °C for 32 h. After being cooled to room temperature, the reaction mixture was diluted with 30 mL of 1/2 ethyl acetate/petroleum ether and 10 mL of water. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated to dryness by Rotavapor. The residual was chromatographed to afford the coupling product and starting material.

(*S*)-*N*-Phenylvalinol: 5% yield; $[\alpha]_D^{25} = -29.6$ (c 0.84, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, J = 7.8 Hz, 2H), 6.73 (t, J = 7.7, 1H), 6.66 (d, J = 7.7 Hz, 2H), 3.77 (dd, J = 10.8, 4.2 Hz, 1H), 3.53 (dd, J = 10.8, 6.9 Hz, 1H), 3.32 (m, 1H), 1.88 (m, 1H), 0.98 (d, J = 7.1 Hz, 3H), 0.95 (d, J = 7.2 Hz, 3H); MS m/z 179 (M^+), 148, 136, 118, 92, 77, 55, 43; HRMS found m/z 179.1302 (M^+), $C_{11}H_{17}NO$ requires 179.1311.

Lactone 27. To a solution of **26** (8.31 g, 36.7 mmol) in 100 mL of anhydrous methylene chloride was added triethylamine (5.5 mL, 40.4 mmol) and HOBt (4.90 g, 36.7 mmol). The resultant mixture was cooled with ice/water, and a solution of DCC (7.60 g, 36.7 mmol) in 50 mL of methylene chloride was added dropwise. After the addition, the solution was allowed to be stirred at room temperature overnight. The resultant solid was filtered off, and the filtrate was washed with water and brine, dried over Na_2SO_4, and concentrated to dryness to give an oily product (6.2 g, 82% crude yield).

The above oil was dissolved in 60 mL of acetonitrile and then 37% aqueous HCHO (24 mL) and $NaBH_3CN$ (7.2 g, 114 mmol) were added. The solution was cooled with ice/water, and a solution of AcOH (5 mL) in 10 mL of acetonitrile was added dropwise. After being stirred at this temperature for 30 min, the reaction mixture was warmed to room temperature and stirring was continued overnight. Ether extract workup followed by column chromatography (silica gel, 1/5 ethyl acetate/petroleum ether as eluent) afforded 5.47 g (82%) of **27**: $[\alpha]_D^{25} = -519$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, J = 7.6 Hz, 1H), 7.05 (d, J = 7.6 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 5.55 and 5.00 (AB q, d, J = 14.9 Hz, 2H), 3.79 (d, J = 10.3 Hz, 1H), 2.81 (s, 3H), 2.27 (m, 1H), 1.03 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H); MS m/z 219 (M^+), 192, 175, 148, 132, 117, 105, 91, 77, 43; HRMS found m/z 219.1233 (M^+), $C_{13}H_{17}NO_2$ requires 219.1256.

(*S*)-*N*-Methyl-*N*-(2′-benzyloxymethylphenyl)valine (28). A mixture of **27** (4.21 g, 19.3 mmol), 20 mL of 1 N NaOH, and 40 mL of THF was stirred at room temperature until the starting material disappeared as monitored by TLC. The solution was concentrated, and the residual solid was dried in vacuo for 4 h and then dissolved in 120 mL of anhydrous THF. To this solution, NaH (60%, 1.5 g, 38.6 mmol) was added and the mixture was stirred until no more bubbles appeared. After cooling with ice/water, benzyl bromide (2.5 mL, 21.2 mmol) was added and the reaction mixture was stirred overnight. The solution was acidified to pH 2 by adding 1 N HCl and extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated via Rotavapor. The residual oil was chromatographed (silica gel, 1/3 ethyl acetate/petroleum ether as eluent) to afford 5.40 g (90%) of **28**: $[\alpha]_D^{25} = -4.8$ (c 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (d, J = 7.6 Hz, 1H), 7.39−7.19

(m, 7H), 7.15 (t, $J = 7.5$ Hz, 1H), 4.69 and 4.63 (AB q, d, $J = 13.7$ Hz, 2H), 4.61 (s, 2H), 3.57 (d, $J = 8.5$ Hz, 1H), 2.78 (s, 3H), 2.19 (m, 1H), 1.12 (d, $J = 7.0$ Hz, 3H), 0.92 (d, $J = 7.1$ Hz, 3H); MS *m*/*z* 328 ($M^+ + H^+$), 310, 282, 236, 220, 190, 148, 132, 91, 77, 43; HRMS found *m*/*z*, 327.1825 (M^+), $C_{20}H_{25}NO_3$ requires 327.1835.

Condensation of 28 with Diethyl Aminomalonate. In a 500-mL bottle were placed diethyl aminomalonate hydrochloride (5.11 g, 24.1 mmol) and 150 mL of anhydrous methylene chloride. The suspension solution was stirred, and triethylamine (9 mL, 66.2 mmol) was added. After the stirring was continued for 30 min, the solution was cooled with ice/water and then HOBt (2.60 g, 19.3 mmol), and **28** (5.30 g, 16.2 mmol) were added, respectively. To this stirred solution was added a solution of EDC (3.71 g, 19.3 mmol) in 20 mL of methylene chloride dropwise. After the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. Water (100 mL) was added to quench the reaction and organic layer was separated. The aqueous layer was extracted with methylene chloride (2 × 100 mL), and the combined organic layers were washed with water and dried over Na_2SO_4. After removal of solvent, the residue was loaded onto a silica gel column and eluted with 1/3 ethyl acetate/petroleum ether to afford 6.31 g (81%) of condensed product, which was dissolved in 100 mL of ethanol, and then 0.6 g of 10% Pd/C was introduced. The suspension solution was stirred under hydrogen (55 atm) at 50 °C for 2 days. The catalyst was filtered off, and the filtrate was condensed via Rotavapor. Chromatography of the residual oil afforded 2.67 g (52%) of **29**: $[\alpha]_D^{25} = -8.4$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, $J = 7.5$ Hz, 1H), 7.24−7.04 (m, 4H), 5.05 (d, $J = 7.0$ Hz, 1H), 4.97 and 4.63 (AB q, d, $J = 12.5$ Hz, 2H), 4.20 (m, 4H), 3.51 (d, $J = 8.1$ Hz, 1H), 2.74 (s, 3H), 2.30 (m, 1H), 1.28 (t, $J = 7.2$ Hz, 3H), 1.23 (t, $J = 7.2$ Hz, 3H), 1.10 (d, $J = 7.1$ Hz, 3H), 0.96 (d, $J = 7.2$ Hz, 3H); MS *m*/*z* 395 ($M^+ + H^+$), 377, 349, 192, 174, 148, 95, 77, 43; HRMS found *m*/*z* 394.2122 (M^+), $C_{20}H_{30}N_2O_6$ requires 394.2105.

Mitsunobu Reaction of 29. Under nitrogen atmosphere, alcohol **29** (50 mg, 0.13 mmol) and tributyl phosphine (60 μL, 0.23 mmol) were dissolved in 5 mL of dry THF. The solution was cooled with ice/water and then ADDP (50 mg, 0.21 mmol) was added. After 10 min, the reaction mixture was warmed to room temperature and the stirring was continued for 24 h. Hexane was added to the reaction mixture and the dihydro-ADDP separated out was filtered off. After evaporating the filtrate under reduced procedure, the residual oil was purified by chromatography to afford 15 mg (32%) of **32**: $[\alpha]_D^{25} = -163$ (*c* 0.50, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, $J = 7.8$ Hz, 1H), 6.98 (d, $J = 7.8$ Hz, 1H), 6.91 (d, $J = 7.6$ Hz, 1H), 6.78 (t, $J = 7.7$ Hz, 1H), 6.06 (s, 1H), 5.19 (d, $J = 17.6$ Hz, 1H), 4.35 (d, $J = 17.7$ Hz, 1H), 4.23 (m, 2H), 3.92 (m, 1H), 3.80 (d, $J = 8.9$ Hz, 1H), 3.71 (m, 1H), 2.80 (s, 3H), 2.33 (m, 1H), 1.25 (t, $J = 6.9$ Hz, 3H), 1.00 (d, $J = 6.9$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.85 (t, $J = 6.8$ Hz, 3H); MS *m*/*z* 377 ($M^+ + H^+$), 333, 305, 219, 189, 161, 120, 92, 78, 63, 45; HRMS found *m*/*z* 376.2010 (M^+), $C_{20}H_{28}N_2O_5$ requires 376.1999.

(*S*)-*N*-Methyl-*N*-(2′-hydroxymethylphenyl)valine, Benzyl Ester (33). A mixture of lactone **27** (1.5 g, 6.8 mmol) and 1 N NaOH (6.8 mL, 6.8 mmol) in 20 mL of THF was stirred at room temperature for 3 h. After the solution was concentrated, the obtained residual solid was dried in vacuo for 10 h and then dissolved in 15 mL of anhydrous DMF. The solution was cooled with ice/water, and then benzyl bromide (0.9 mL, 7.4 mmol) was added. The stirring was continued at room temperature for 18 h, and the reaction mixture was partitioned between 70 mL of ethyl acetate and 30 mL of water. The organic layer was washed with water and brine and dried over Na_2SO_4. After the removal of solvent, the residual oil was chromatographed to afford 2.2 g (98%) of **33**: $[\alpha]_D^{25} = +27.9$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 (m, 4H), 7.05 (m, 5H), 4.93 and 4.86 (AB q, d, $J = 12.4$ Hz, 2H), 4.84 and 4.45 (AB q, d, $J = 12.8$ Hz, 2H), 3.78 (br s, 1H), 3.35 (d, $J = 9.2$ Hz, 1H), 2.71 (s, 3H), 2.20 (m, 1H), 1.03 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H); MS *m*/*z* 327 (M^+), 310, 284, 192, 174, 148, 118, 95, 77, 43; HRMS found *m*/*z* 327.1834 (M^+), $C_{20}H_{25}NO_3$ requires 327.1836.

(*S*)-*N*-Methyl-*N*-(2′-formalphenyl)valine, Benzyl Ester (34). To a solution of DMSO (0.16 mL, 2.2 mmol) in 5 mL of anhydrous methylene chloride was added oxalyl chloride (0.12 mL, 1.4 mmol) at −78 °C. After stirring for 15 min from −78 to −65 °C, a solution of **33** (100 mg, 0.3 mmol) in 3 mL of methylene chloride was added. The resultant reaction mixture was stirred for 30 min at −65 °C for 30 min, and then 0.2 mL of triethylamine was added by syringe. The solution was allowed to warm to room temperature, and then water was added to quench the reaction. After being extracted with methylene chloride, the crude product was chromatographed to afford 96 mg (97%) of aldehyde **34**: $[\alpha]_D^{25} = -127$ (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.21 (s, 1H), 7.70 (dd, $J = 7.7$, 1.6 Hz, 1H), 7.29 (t, $J = 7.7$ Hz, 1H), 7.27 (m, 2H), 7.13 (m, 2H), 7.06 (d, $J = 7.6$ Hz, 2H), 6.97 (d, $J = 7.7$ Hz, 1H), 5.04 and 4.96 (AB q, d, $J = 12.6$ Hz, 2H), 3.42 (d, $J = 10.6$ Hz, 1H), 2.92 (s, 3H), 2.25 (m, 1H), 1.07 (d, $J = 6.9$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H); MS *m*/*z* 326 ($M^+ + H^+$), 296, 254, 190, 172, 146, 132, 91, 77, 42; HRMS found *m*/*z* 325.1671 (M^+), $C_{20}H_{23}NO_3$ requires 325.1679.

Condensation of 34 with Methyl 2-Nitroacetate. At room temperature, $TiCl_4$ (0.5 mL, 4.8 mmol) was added to 5 mL of 1,4-dioxane and a yellow solid was formed immediately. To this suspension was added a solution of **34** (200 mg, 0.6 mmol) and methyl 2-nitroacetate (0.06 mL, 0.6 mmol) in 2 mL of 1,4-dioxane dropwise. After stirring for 2 h at room temperature, NMM (1 mL, 9.6 mmol) was added slowly. The reaction mixture was stirred for another 2 h and then partitioned between 20 mL of ethyl acetate and 20 mL of water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Chromatography (silica gel, 1/10 ethyl acetate/petroleum ether as eluent) of the residual oil afforded 210 mg (82%) of the olefin **35** as a mixture of cis and trans isomers: $[\alpha]_D^{25} = -160$ (*c* 0.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (s, 0.37H), 7.86 (s, 0.63H), 7.20 (m, 5H), 7.08−6.86 (m, 4H), 4.95 (s, 1.26H), 4.90 (s, 0.74H), 3.80 (s, 1.89H), 3.62 (s, 1.11H), 3.25 (d, $J = 10.5$ Hz, 0.63H), 3.20 (d, $J = 10.5$ Hz, 0.37H), 2.85 (s, 1.11H), 2.82 (s, 1.89H), 2.27 (m, 1H), 1.08 (d, $J = 6.9$ Hz, 1.89 H), 1.03 (d, $J = 7.0$ Hz, 1.11H), 0.83 (d, $J = 6.9$ Hz, 1.89H), 0.79 (d, $J = 7.0$ Hz, 1.11H); MS *m*/*z* 426 (M^+), 410, 383, 291, 222, 202, 174, 132, 91, 43; HRMS found *m*/*z* 426.1775 (M^+), $C_{23}H_{26}N_2O_6$ requires 426.1791.

Esters 36 and 37. A suspension of **35** (350 mg, 0.8 mmol) and 30 mg of 10% Pd/C in 20 mL of methanol was stirred under hydrogen (40 atm) at room temperature for 3 days. The catalyst was filtered off, and the filtrate was condensed via Rotavapor. The resultant white solid was dried in vacuo for 1 day and then dissolved in 80 mL of dry DMF. The solution was cooled with ice/water and then triethylamine (0.22 mL, 1.6 mmol) and DPPA (0.21 mL, 0.96 mmol) were added, respectively. After the reaction mixture was stirred for 18 h, the solvent was removed at reduced pressure. The residue was partitioned between 80 mL of ethyl acetate and 20 mL of water, and then the organic layer was separated, washed with water and brine, and dried over Na_2SO_4. After removal of solvent, the residual oil was chromatographed (silica gel, 1/4 ethyl acetate/petroleum ether as eluent) to afford 80 mg (35%) of **36** and 39 mg (17%) of **37**.

36: $[\alpha]_D^{25} = -145$ (*c* 0.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, $J = 7.8$ Hz, 1H), 7.14 (d, $J = 7.7$ Hz, 1H), 7.09 (d, $J = 7.7$ Hz, 1H), 6.95 (t, $J = 7.6$ Hz, 1H), 6.26 (m, 1H), 5.20 (m, 1H), 3.82 (s, 3H), 3.58 (dd, $J = 16.3$, 4.2 Hz, 1H), 3.36 (d, $J = 7.3$ Hz, 1H), 2.97 (dd, $J = 16.4$, 8.7 Hz, 1H), 2.77 (s, 3H), 2.38 (m, 1H), 1.09 (d, $J = 6.9$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H); MS *m*/*z* 290 (M^+), 263, 247, 219, 204, 159, 132, 117, 91, 77, 42; HRMS found *m*/*z* 290.1650 (M^+), $C_{16}H_{22}N_2O_3$ requires 290.1632.

37: $[\alpha]_D^{25} = -93.6$ (*c* 0.47, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (t, $J = 7.8$ Hz, 1H), 7.21 (d, $J = 7.5$ Hz, 1H), 7.19 (d, $J = 7.6$ Hz, 1H), 6.98 (t, $J = 7.7$ Hz, 1H), 6.44 (d, $J = 6.4$ Hz, 1H), 4.37 (t, $J = 6.6$ Hz, 1H), 3.82 (s, 3H), 3.23 (d, $J = 15.2$ Hz, 1H), 3.07 (dd, $J = 15.6$, 6.9 Hz, 1H), 3.03 (d, $J = 10.2$ Hz, 1H), 2.91 (s, 3H), 2.44 (m, 1H), 0.96 (d, $J = 6.7$ Hz, 3H), 0.87 (d, $J = 6.7$ Hz, 3H); MS *m*/*z* 290 (M^+), 263, 231, 219, 204, 174, 159, 144, 132, 117, 91, 77, 42; HRMS found *m*/*z* 290.1650 (M^+), $C_{16}H_{22}N_2O_3$ requires 290.1632.

(2*S*,5*S*)-Benzolactam-V8. To a solution of **36** (15 mg, 0.052 mmol) in 1 mL of THF was added $LiBH_4$ (3 mg, 0.14 mmol). The reaction mixture was stirred at room temperature until the reaction was

completed as monitored by TLC. After quenching the reaction by adding 1 mL of water, ethyl acetate extract workup followed by chromatography (silica gel, 1/1 ethyl acetate/petroleum ether as eluent) afforded 12 mg (88%) of benzolactam-V8: $[\alpha]_D^{25} = -346$ (*c* 0.44, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.21 (t, $J = 7.7$ Hz, 1H), 7.04 (d, $J = 7.6$ Hz, 1H), 7.02 (d, $J = 7.7$ Hz, 1H), 6.88 (t, $J = 7.7$ Hz, 1H), 6.86 (br s, 1H), 4.05 (m, 1H), 3.70 (dd, $J = 10.7$, 3.7 Hz, 1H), 3.52 (m, 1H), 3.48 (d, $J = 8.9$ Hz, 1H), 3.40 (br s, 1H), 3.08 (dd, $J = 16.9$, 8.0 Hz, 1H), 2.83 (dd, $J = 15.2$, 2.4 Hz, 1H), 2.80 (s, 3H), 2.43 (m, 1H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.88 (d, $J = 6.6$ Hz, 3H); MS *m*/*z* 262 (M^+), 235, 219, 191, 176, 158, 144, 132, 117, 91, 57, 43.

Acknowledgment. We thank Professor Xiyan Lu for helpful discussion and the Chinese Academy of Sciences and National Natural Science Foundation of China (Grants 29402016 and 29725205) for financial supports.

JA981662F