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Synthesis of Chiral N-Aryl-α-Amino Acids by Pd-Cu Catalyzed Couplings of Chiral α-Amino Acids with Aryl Halides

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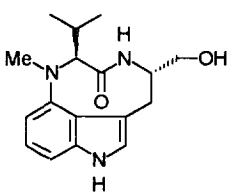
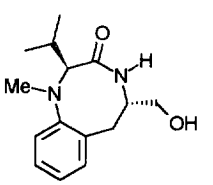
Abstract: A concise synthesis of chiral N-aryl-α-amino acids, the common core structures for several biologically important molecules, by Pd-Cu catalyzed coupling of L- or D-α-amino acids and aryl halides, is described.

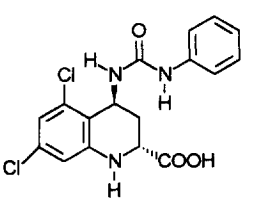
The chiral N-aryl-α-amino acids are the common core structures for a number of synthetically challenging and medicinally important agents such as protein kinase C (PKC) activators, indolactam-V[1] and its analogue benzolactam-V8[2]; fibrinogen receptor antagonist SB 214857[3]; NMDA receptor antagonist L689560[4] and tricyclic quinoxalinediones[5]; ACE inhibitors[6]; antiulcer agents[7]. The construction for this subunit often needs several steps to get the enantiomerically pure form. For example, in the synthesis of indolactams-Vs and its analogues, the chiral N-aryl-α-amino acid subunit was built by the S_N2 displacement of arylamine with chiral triflate deriving from D-valine.[1,2] In the synthesis of L689560[4b], the corresponding subunit was obtained from the addition of aryl amine with dimethyl acetylenedicarboxylate followed by chemical resolution. While 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.[1c,3]



indolactam-V



benzolactam-V8



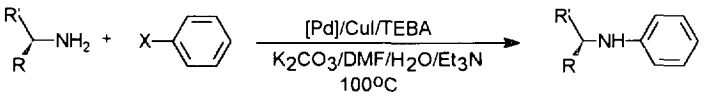
L689560

Recently, several successful transition-metal catalyzed C-N couplings were reported.[8-10] Buchwald et al.[8] and Hartwig et al.[9] independently found that aliphatic and aromatic amines reacted with substituted aryl halides under the presentation of a catalytic amount of palladium and stoichiometric amounts of a sterically

hindered base such as NaO-*t*-Bu or LiHMDS to afford coupling product in good yield. Davydov and coworker discovered the Pd- and Cu-catalyzed coupling of aryliodides and diarylamines in water-organic emulsion[10]. These results open a new avenue for synthesizing many biologically important molecules that are otherwise difficult to prepare.[11] Herein, we wish to report a new reaction condition suitable for preparing chiral N-aryl-α-amino acids by Pd-Cu catalyzed coupling of L- or D-α-amino acids with aryl halides.

Initially, we tried the coupling of L-valine with bromobenzene by employing Buchwald's condition directly. It was our thinking that L-valine could react with 1 equiv of sodium tert-butoxide to form a salt first thereby serving as a protected amine to process the further coupling reaction. However, we found that this reaction did not work under Buchwald's condition even employing more polar solvent such as dioxane. Then we turned our attention to Davydov's phase-transfer conditions.[10] Thus, heated a mixture of L-valine (5 mmol), bromobenzene (5 mmol), $Pd[P(o\text{-}toyl)_3]_2Cl_2$ (0.25 mmol), CuI (0.25 mmol), K_2CO_3 (5 mmol), TEBA (0.75 mmol) in DMF (10 mL) and water (1 mL) at 100°C for 24 h, we can get desired product **3a**[12] in 20% yield (Table I, entry 1). Encouraged by the initial success, a brief optimization study was undertaken. After some experimentation, we found that adding 2 equiv of triethyl amine could improve the yield to 69% dramatically. It looked as if that triethyl amine might react with α-amino acid to form a salt thereby increasing the solubility of amino acid unit in DMF. As shown in Table I, the method was then tested by a number of different aryl halides and amino acids. In general, both aryl bromide and aryl iodide were shown to provide good yields (entries 3 and 4). Tetrakis(triphenylphosphine)palladium was also an effective catalyst for this reaction (entry 9). By using D-valine as starting material, we could also get D-isomer of **3a** (entry 5).

Table I: Pd-Cu catalyzed coupling of L or D-α-amino acids and aryl halides[a]

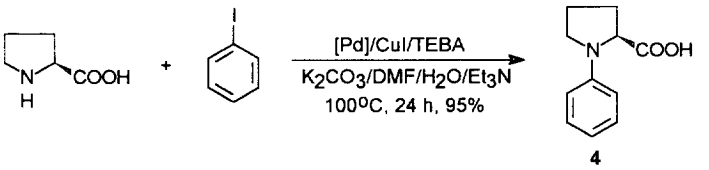


1 2 3

Entry	Compound **3**	R	R'	X	[Pd][b]	Time (h)	Yield (%)[c]
1[d]	a	i-Pr	COOH	Br	A	20	22
2	a	i-Pr	COOH	Br	A	19	69
3	b	$PhCH_2$	COOH	I	A	18	80
4	b	$PhCH_2$	COOH	Br	A	22	72
5	c	COOH	i-Pr	Br	A	24	67
6	d	$HOCH_2$	COOH	Br	A	23	0
7	e	$HOOCCH_2CH_2$	COOH	Br	A	23	0
8[e]	a	i-Pr	COOH	I	A	24	0
9	b	$PhCH_2$	COOH	Br	B	22	82

[a]All reactions were carried out at 100 °C under N_2 atmosphere in the same manner as described in the text, unless otherwise noted. [b]Catalysts: A: $Pd[P(o\text{-}tolyl)_3]_2Cl_2$; B: $Pd(Ph_3P)_4$. [c]Isolated yield. [d]No triethylamine was added. [e]No CuI was added.

Under the similar condition, the coupling of L-proline and iodobenzene produced **4**[13] in 95% yield. It is note worth that the product **4**, which was obtained originally in racemic form through several steps, is an important precursor for synthesizing antiulcer agents[7]; while the coupling product **3a** could be used to synthesize benzolactam-V8[2]. Unfortunately, when L-glutamic acid or L-serine was used, no coupling products were obtained (entries 6 and 7).



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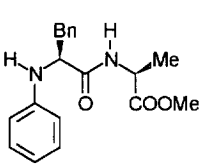
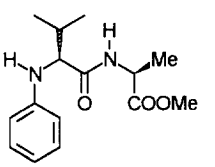
A representative experimental procedure is given by the catalyzed coupling of L-phenylalanine and bromobenzene: A mixture of L-phenylalanine (2.6 mmol), bromobenzene (2.6 mmol), $Pd[P(o\text{-}toyl)_3]_2Cl_2$ (0.13 mmol), CuI (0.13 mmol), K_2CO_3 (2.6 mmol), TEBA (0.44 mmol), Et_3N (1 mL) in DMF (5 mL) and water (0.5 mL) was heated at 100°C under argon atmosphere for 22 h. To the resulting mixture was added 20 mL of water and 20 mL of ethyl acetate, and then 6 N HCl was added to adjust the PH = 2~3. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 x 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residual oil was chromatographed (silica gel, 2/3 ethyl acetate/petroleum ether as eluent) to afford 460 mg of **3b**.

To examine if any racemization occurred in these coupling reactions, the product **3b** was coupled with L-alanine methyl ester hydrochloride according to the standard method (DCC/triethylamine/methylene chloride) to produce **5**. Analysis of **5** by HPLC revealed that only one isomer existed, while analysis of the coupling product of the racemic **3b** (prepared from the coupling of DL-phenylalanine with bromobenzene) with L-alanine methyl ester by HPLC clearly showed that two isomers existed. In a similar manner, **3a** and **3c** were converted to **6** ($[\alpha]_D^{25}$ = -14.7 (CH_3Cl, c = 0.02)) and **7** ($[\alpha]_D^{25}$ = +38.4 (CH_3Cl, c = 0.13)) respectively. Both **6** and **7** were found to be a single isomer by their different ^{1}H-NMR spectra[14]. These results implied that the present coupling reactions proceeded without racemization.



5



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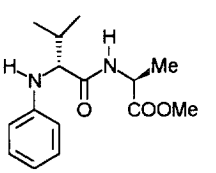

7

The catalytic amount of CuI is necessary for this reaction. As shown in Table I, no coupling occured when CuI was absent (entry 8). However, the mechanism for present coupling reaction is unclear. Thus, search for better reaction conditions suitable for more substrates, as well as the studies for possible mechanism are actively being pursued in our laboratory and will be reported in due course.

Acknowledgments: The authors are grateful to the Chinese Academy of Sciences and National Natural Science Foundation of China for their financial supports.

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12. Selected data for **3a**: $[\alpha]_D^{25}$ = -28 (CH_3Cl, c = 0.20); ^1H 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.
13. Selected data for **4**: $[\alpha]_D^{25}$ = +1.3 (CH_3Cl, c = 0.45); ^1H 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.
14. ^1H NMR (300 MHz, $CDCl_3$) for **6**: δ 7.22 (m, 3H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 2H), 6.36 (s, 1H), 4.60 (m, 1H), 3.66 (s, 3H), 3.59 (d, *J* = 4.2 Hz, 1H), 2.38 (m, 1H), 1.39 (d, *J* = 7.3 Hz, 3H), 1.10 (d, *J* = 7.4 Hz, 3H), 1.04 (d, *J* = 7.4 Hz, 3H); for **7**: δ 7.20 (m, 3H), 6.80 (t, *J* = 7.5 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 2H), 6.37 (s, 1H), 4.63 (m, 1H), 3.72 (s, 3H), 3.60 (d, *J* = 4.1 Hz, 1H), 2.40 (m, 1H), 1.26 (d, *J* = 7.4 Hz, 3H), 1.07 (d, *J* = 7.5 Hz, 3H), 1.03 (d, *J* = 7.5 Hz, 3H).

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