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Palladium-catalyzed coupling reaction of amino acids (esters) with aryl bromides and chlorides

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ABSTRACT

The bulky and electron-rich MOP type ligands and $Pd(dba)_2$ combinations showed high efficiency for the coupling reactions of amino acids and inactive aryl halides to give *N*-aryl amino acids. Under the catalytic conditions, not only α-amino acids, but also β-, γ-, and δ-amino acids have been coupled with aryl chlorides in moderate to high yields; in the case of optically pure β-amino acids as substrates, the optical purities of the coupling products retained.

1. Introduction

Palladium-catalyzed cross-coupling reactions of aryl halides and amines provide an invaluable entry toward the synthesis of a wide range of compounds, such as, pharmaceutical and agrochemical products, electronic materials, polymers, and liquid crystals.[1–8] These compounds, especially pharmaceuticals and natural products, are always multi-functionalized complex molecules. Therefore, much attention has also been directed to the seeking of arylation of more complex amines as a more direct and economical way.[9–11] Among numerous functionalized amines, amino acids are commercially available and are one of the best building blocks for the synthesis of peptides, lactams, heterocycles, and physiologically active substances.[12,13] Furthermore, *N*-aryl amino acids are important synthetic intermediates and structural components of medicinally molecules.[14–20] As a result, amino acids or esters are very attractive coupling partners for the transition metal-catalyzed processes. The coupling with amino acids or esters with aryl halides can be conducted with catalytic amounts of copper, however, the substrates are generally limited to aryl iodides or bromides and α- or β-amino acids (esters).[21–29] Of the aryl halides, aryl chlorides are generally the most attractive substrates for cross-coupling reactions because they are less expensive and more readily available. Similarly, only a few reports on palladium-catalyzed the coupling reaction of inactive aryl halides with amino acids or esters have been published.[30–32] Therefore, there is still a need to develop a general and versatile catalyst for coupling inactivated aryl halides with amino acids (esters).

The major problem encountered with the multi-functionalized compounds as the substrates of the metal-catalyzed coupling reaction is: the competitive coordination of the substrates with the counter anion of the catalyst, which might cause deactivation of the catalyst, such as in the palladium-catalyzed coupling reaction of amides or malonates.[33–36] Recent studies demonstrate that the bulky and electron-rich ligands may contribute to carry out the coupling reaction of the multi-functionalized compounds with inactive aryl halides.[33–36]

We recently reported the synthesis of the bulky and electron-rich MOP type ligands and their applications in the palladium-catalyzed arylation of amines and β-dicarbonyl compounds.[36,37] Herein, we report the application of these ligands in the palladium-catalyzed arylation of amino acids as functionalized amines.

2. Results and discussion

The coupling of PhBr with DL-alanine was chosen as the model reaction to test the feasibility of palladium-catalyzed coupling reaction of aryl halides and amino acids. The bidentate aryl phosphine ligands, BINAP and DPPF, which are fairly general and efficient ligands for palladium-catalyzed reaction of PhBr and amines,[38,39] were ineffective in the arylation of the amino acids

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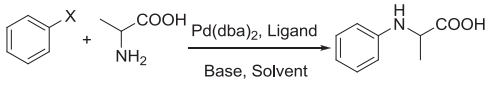
(Table 1, entries 1 and 2). This might be ascribed to the coordination of the central metal with the carboxyl group of amino acids, which retained after the formation of Pd–N bond, making the aryl-Pd–N complexes too stable to reductive elimination.[40,41] Similar results were also detected in other Pd-catalyzed coupling reactions of multi-functionalized compounds. For example, in the arylation reaction of β-dicarbonylate, the coinstantaneous coordination of two carbonyl groups with Pd prevented the formed aryl palladium complex from reductive elimination.[33] When our sterically hindered electron-rich MOP type ligand (**L1**) was used, to our pleasure, the reaction occurred with 69% yield of the desired product (Table 1, entry 3). However, dramatic decrease of the activity of the catalyst was observed by lowering the steric hindrance of the alkyl phosphine ligands (Table 1, entries 4–6). When **L2** with dicyclohexyl phosphino group was used as ligand, the coupling yield was decreased to 14% (Table 1, entry 4); in the cases when the dialkylbiarylphosphines (**L3** and **L4**) were used as ligand, hardly any or only trace product was obtained. These were in accordance with the reports that increasing the steric hindrance of the ligands would promote the reductive elimination during the C–N bond-forming step.[41–46] More significantly, the catalytic combination, Pd(dba)$_2$/**L1**, was also effective for the coupling reactions of inactive aryl chlorides with amino acids; a 61% yield was obtained when PhCl and DL-analine were used as substrates (Table 1, entry 7). We also found that ^{t}BuOH was the optimal solvent for the transformation presumably because amino acids are much more soluble in a protic solvent rather than in an ethereal or a hydrocarbon solvent (Table 1, entries 8–10). Finally, stronger bases, such as ^{t}BuONa and KOH (Table 1, entries 10 and 11), were found to be more effective than phosphates, carbonates and NaOH (Table 1, entries 12–15). With respect to its low price and easy handling, KOH was employed as the base in further studies, and the reaction condition in entry 11, Table 1, was chosen as the optimal reaction condition.

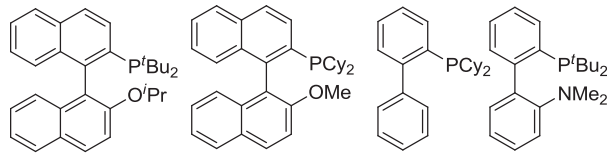
On the basis of these results, the scope of Pd(dba)$_2$/**L1** catalyzed amination of aryl halides with DL-alanine was explored, and the results were summarized in Table 2. Reactions of aryl chlorides possessing an electron-withdrawing group, such as trifluoromethyl or carboxyl group, with amino acids occurred in high yields (entries 1–3). Even with the electron-rich aryl halides (chloride or bromide) (entries 4–14), coupling reactions occurred in moderate to excellent yields. The coupling reaction of 4-methyl-chlorobenzene was conducted with 82% yield. In the case of 4-bromoanisole as substrate, the desired product was obtained in 93% yield after recrystallization (entry 10). *Noticeably, the coupling product was too unstable to be isolated in the previously reports*.[9] Moreover, the steric effect of *o*-methyl or *o*-methoxyl group of aryl halide was inconspicuous for the coupling reaction (entries 6, 7, and 14). For aryl halides bearing a base-sensitive functional group, the coupling reaction was also accomplished in high yields by transforming the amino acid to amino ester and using Cs_2CO_3 as base and dioxane as solvent (Scheme 1). The functional groups, such as esters, were well tolerated under the reaction conditions.

Table 1
Effect of ligands, solvents and bases on the Pd-catalyzed coupling reaction of aryl halide with DL-alanine[a]



1a 2a 3aa

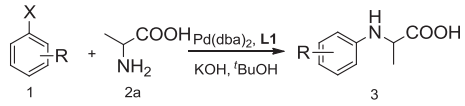
Entry	Ligand	Base	Solvent	Yield[d] (%)
1[b]	DPPF	^{t}BuONa	Toluene	0
2[b]	BINAP	^{t}BuONa	Toluene	0
3[b]	**L1**	^{t}BuONa	Toluene	69
4[b]	**L2**	^{t}BuONa	Toluene	14
5[b]	**L3**	^{t}BuONa	Toluene	0
6[b]	**L4**	^{t}BuONa	Toluene	Trace
7[c]	**L1**	^{t}BuONa	Toluene	61
8[c]	**L1**	^{t}BuONa	THF	80
9[c]	**L1**	^{t}BuONa	Dioxane	83
10[c]	**L1**	^{t}BuONa	^{t}BuOH	90
11[c]	**L1**	KOH	^{t}BuOH	85
12[c]	**L1**	NaOH	^{t}BuOH	43
13[c]	**L1**	Cs_2CO_3	^{t}BuOH	Trace
14[c]	**L1**	K_3PO_4	^{t}BuOH	0
15[c]	**L1**	K_2CO_3	^{t}BuOH	0



L1 L2 L3 L4

[a] Reaction conditions: aryl halide (1.0 mmol), DL-alanine (1.2 mmol), KOH (3.0 mmol), Pd(dba)$_2$ (2.0 mmol %), **L1** (3.0 mmol %), ^{t}BuOH (2.5 mL), 90 °C, 20 h.
[b] X=Br.
[c] X=Cl.
[d] Isolated yield.

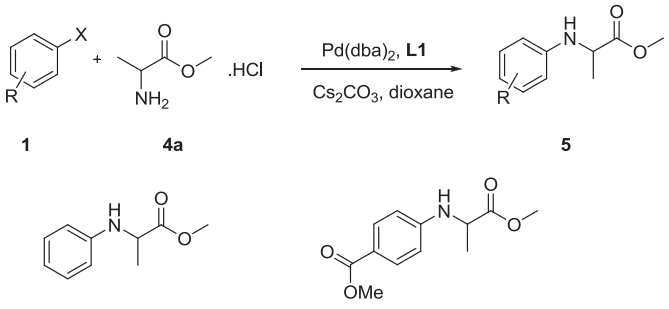
Table 2
Palladium/**L1**-catalyzed coupling reaction of aryl halides with DL-alanine[a]



1 2a 3

Entry	ArX		Product	Yield[b] (%)
	R	X		
1	4-CF_3	Cl (**1b**)	**3ba**	94
2	4-COOH	Cl (**1c**)	**3ca**	88
3	3-COOH	Cl (**1d**)	**3da**	84
4	4-Me	Br (**1e**)	**3ea**	90
5		Cl (**1e′**)		82
6	2-Me	Br (**1f**)	**3fa**	86
7		Cl (**1f′**)		88
8	3,5-DiMe	Br (**1g**)	**3ga**	84
9	4-^{t}Bu	Br (**1h**)	**3ha**	94
10	4-MeO	Br (**1i**)	**3ia**	93
11		Cl (**1i′**)		67
12	3-MeO	Br (**1j**)	**3ja**	84
13		Cl (**1j′**)		80
14	2-MeO	Cl (**1k**)	**3ka**	79

[a] Reaction conditions: aryl halide (1.0 mmol), DL-alanine (1.2 mmol), KOH (3.0 mmol), Pd(dba)$_2$ (2.0 mmol %), **L1** (3.0 mmol %), ^{t}BuOH (2.5 mL), 90 °C, 20 h.
[b] Isolated yield.



1 4a 5

5aa 5la

X=Br, 91%
X=Cl, 84%

X=Br, 92%
X=Cl, 86%

Scheme 1. Palladium/**L1**-catalyzed coupling reaction of aryl halides with methyl alaninate. Reaction conditions: aryl halide (1.0 mmol), methyl DL-alaninate hydrochloride (1.2 mmol), Cs_2CO_3 (3.0 mmol), Pd(dba)$_2$ (2.0 mmol %), **L1** (4.0 mmol %), 1,4-dioxane (2.5 mL), 90 °C, 20 h.

We then expanded the applicability of the catalytic system to diversified amino acids, and the results were summarized in Table 3. Not only α-amino acids and β-amino acids could be arylated in good yields (Table 3, entries 4 and 14), but also the coupling reactions of γ-, δ-amino acids or 4-aminobenzoic acid, which cannot be catalyzed by CuI,[22] occurred in moderate yields (entries 18, 19, and 21). However, the coupling yields were greatly influenced by the structure of amino acids. Amino acids without extra coordinating groups gave high coupling yields. For example, the coupling reaction of the simple α-amino acids (Table 3, entries 1–8) occurred in excellent yields (80%–96%); the β-amino acids (Table 3, entries 14–17) could be also coupled in moderate to excellent yields; 4-aminobutanoic acid was arylated in 71% yield. For amino acids with other adjacent coordinating group, such as a heteroatom, the coupling yields decreased remarkably. In the cases of the coupling reaction of L-methionine, the yields of *N*-arylation dropped to 64% (Table 3, entries 9). Moreover, our catalytic system was ineffective for proline, serine and glutamic acid (Table 3, entries 11–13). It may also be due to the fact that such substrates have more heteroatoms or functional groups binding to Pd, which enhance the stability of the aryl-Pd–N complex and consequently inhibit it from reductive elimination. In order to solve the problem, we increased the amount of catalyst to 3.0% of $Pd(dba)_2$ and 4.5% of **L1**, which led to increase the coupling yield to 84% in the case of methionine (Table 3, entry 9). We also tried to protect the coordinating group to facilitate the coupling reaction. The transformation of glutamic acid to the di-*tert*-butyl ester (**4b**) made that the arylation occurred in 31% yield (Table 3, entry 22). In case of the coupling of L-tryptophan, 2-amino-3-(1-phenyl-1*H*-indol-3-yl) propanoic acid (**3as**) was isolated as coupling product in 36% yield (Table 3, entry 10), resulting from the coupling with nitrogen atom on indyl-cycle under the catalytic condition.

Table 3
Palladium/**L1**-catalyzed coupling reaction of amino acid with chlorobenzene[a]

Entry	Amino acid (ester)	Product	Yield (%)	ee[b] (%)
1	L-Alanine **2b**	**3ab**	83	75
2	L-Valine **2c**	**3ac**	90	96
3	D-Valine **2d**	**3ad**	88	97
4	L-Isoleucine **2e**	**3ae**	80	93
5	L-Leucine **2f**	**3af**	96	78
6	L-Phenylalanine **2g**	**3ag**	84	41
7	D-Phenylalanine **2h**	**3ah**	87	33
8	L-Phenylglycine **2i**	**3ai**	89	1
9	L-Methionine **2j**	**3aj**	66 (84)[c]	29
10	*L*-Tryptophan **2s**	**3as**	36	—
11	L-Proline **2t**	—	0	—
12	L-Serine **2u**	—	0	—
13	L-Glutamic acid **2v**	—	0	—
14	(*S*)-3-Aminobutanoic acid **2k**	**3ak**	73	97
15	(*R*)-3-Aminopentanoic acid **2l**	**3al**	78	99
16	(*S*)-3-Amino-3-cyclohexylpropanoic acid **2m**	**3am**	81	96
17	(*S*)-3-Amino-3-phenylpropanoic acid **2n**	**3an**	95	>99
18	4-Aminobutanoic acid **2o**	**3ao**	71	—
19	5-Aminopentanoic acid **2p**	**3ap**	66	—
20	2-Aminobenzoic acid **2q**	**3aq**	81	—
21	4-Aminobenzoic acid **2r**	**3ar**	75	—
22[d]	Di-*tert*-butyl 2-aminopentanedioate hydrochloride **4b**	**5ab**	31	—

[a] Reaction conditions: chlorobenzene (1.0 mmol), amino acid (1.2 mmol), KOH (3.0 mmol), $Pd(dba)_2$ (2.0 mmol %), **L1** (3.0 mmol %), ^{t}BuOH (2.5 mL), 90 °C, 20 h.
[b] ee of the corresponding methyl ester of the coupling product.
[c] $Pd(dba)_2$ (3.0 mmol %), **L1** (4.5 mmol %).
[d] $Pd(dba)_2$ (2.0 mmol %), **L1** (4.0 mmol %), Cs_2CO_3 (3.0 mmol), 1,4-dioxane (2.5 mL).

Due to the importance of the chiral amino acids in the pharmaceutical industry, we expected to extend this methodology to the synthesis of optically pure *N*-aryl amino acids. The optical purities of the coupling products of chiral amino acids were investigated by transforming them to the corresponding methyl esters[45–47] and analyzing their esters by HPLC. The results were also summarized in Table 3. The coupling of α-amino acids with bulky alkyl group at α-carbon, such as valine or isoleucine, gave corresponding *N*-arylation products with high optical purities (Table 3, entries 2–4.) However, when it comes to *N*-arylation products of α-amino acids with a phenyl group at α- or β-carbon, optical purities of the coupling products decreased greatly (entries 6–8). The coupling reaction of chiral β-amino acids, whatever the substituent at β-carbon is, afforded the coupling products with their original optical purities (entries 14–17).

3. Conclusion

In conclusion, we have developed a general and useful catalytic system for palladium-catalyzed coupling reaction of amino acids or esters with inactive aryl halides under mild conditions. In the catalytic system, the bulky and electron-rich MOP type phosphine was used as ligand; amino acids including α- and β-amino acids, long alkyl aliphatic amino acids and aromatic amino acids worked well in this reaction to give coupling products in moderate to good yields. Coupling of 4-bromoanisole with amino acids was realized and decent yields were obtained. Furthermore, this method has been proven useful for preparing enantiopure *N*-aryl β-amino acids and *N*-aryl α-amino acids with a bulk alkyl group at α-carbon.

4. Experimental sections

4.1. General procedure for the palladium-catalyzed coupling reaction of amino acids with aryl halides

An oven-dried resealable Schlenk flask was charged with $Pd(dba)_2$ (11.4 mg, 0.02 mmol), **L1** (13.6 mg, 0.03 mmol), base (3.0 mmol), and amino acid (1.20 mmol) under N_2. ^{t}BuOH (2.5 mL) and aryl halides (1.00 mmol) were added in sequence via a syringe. The flask was sealed, and the mixture was allowed to heat to 90 °C for 20 h. After being cooled to room temperature, the reaction mixture was diluted with 2 mL of water and 3 mL of $CHCl_3$, and then adjusted to pH=3 with concentrated HCl. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (5 mL×3). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residual oil was purified by column chromatography on silica gel ($CHCl_3$/CH_3OH) to afford the coupling product.

*4.1.1. N-Phenyl alanine (**3aa**)*[9]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.54 (d, *J*=7.2 Hz, 3H), 4.12 (q, *J*=6.8 Hz, 1H), 6.40 (d, *J*=7.6 Hz, 2H), 6.80 (t, *J*=7.6 Hz, 1H), 7.21 (td, *J*=8.0, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 18.5, 51.3, 112.7, 116.7, 129.2, 148.1, 176.5.

*4.1.2. (S)-N-Phenyl alanine (**3ab**)*[9]. $[\alpha]_D^{25}$ −45.3 (*c* 1.25, $CHCl_3$); ee% (the methyl ester): 75 (HPLC: Chiralcel OJ-H Column, hexane/^{i}PrOH 90/10, 0.5 mL/min, 254 nm, t_1=28.3 min, t_2=45.4 min).

*4.1.3. (S)-N-Phenyl valine (**3ac**)*[9]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07 (d, *J*=6.8 Hz, 6H), 2.18–2.26 (m, 1H), 3.86 (d, *J*=5.6 Hz, 1H), 6.66 (d, *J*=8.8 Hz, 2H), 6.78 (t, *J*=8.4 Hz, 1H), 7.20 (t, *J*=7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 19.0, 19.3, 30.4, 61.9, 112.5, 116.2, 128.9, 148.4, 174.9. $[\alpha]_D^{25}$ −75.6 (*c* 1.02, $CHCl_3$); ee% (the methyl ester): 96 (HPLC

Chiralcel OJ-H column, hexane/^{i}PrOH 90/10, 0.5 mL/min, 254 nm, t_1=11.0 min, t_2=15.7 min).

*4.1.4. (R)-N-Phenyl valine (**3ad**)*[9]. $[\alpha]_D^{25}$ +72.9 (*c* 1.04, $CHCl_3$); ee% (the methyl ester): 97 (HPLC: Chiralcel OJ-H column, hexane/^{i}PrOH 90/10, 0.5 mL/min, 254 nm, t_1=10.7 min, t_2=16.0 min).

*4.1.5. (S)-N-Phenyl isoleucine (**3ae**)*[11]. White solid. Mp: 166–169 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 (t, *J*=7.6 Hz, 3H), 1.03 (d, *J*=6.8 Hz, 3H), 1.29–1.37 (m, 1H), 1.61–1.67 (m, 1H), 1.91–1.96 (m, 1H), 3,93–3.94 (d, *J*=5.6 Hz, 1H), 6.64 (dt, *J*=7.6, 1.2 Hz, 2H), 6.77 (tt, *J*=7.6, 1.2 Hz, 1H), 7.16–7.19 (m, 1H), 7.20 (t, *J*=6.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 11.8, 16.2, 25.8, 37.3, 61.2, 116.8, 129.5, 148.9, 175.5. IR (cm^{-1}): 3251, 2958, 2871, 2362, 2339, 1748, 1697, 1507, 1230, 942, 896, 763. HRMS: calcd for $C_{12}H_{17}NO_2$: 207.1259; found: 207.1263. $[\alpha]_D^{25}$ −50.3 (*c* 1.07, CH_3OH); ee% (the methyl ester): 93 (HPLC: Chiralcel OJ-H column, hexane/^{i}PrOH 90/10, 0.8 mL/min, 254 nm, t_1=9.8 min, t_2=14.6 min).

*4.1.6. (S)-N-Phenyl leucine (**3af**)*[11]. White solid. Mp: 115–116 °C. ^{1}H NMR (400 MHz, DMSO): δ 0.85 (d, *J*=6.4 Hz, 3H), 0.92 (d, *J*=7.2 Hz, 3H), 1.49–1.64 (m, 2H), 1.71–1.81 (m, 1H), 3.81 (dd, *J*=8.4, 6.0 Hz, 1H), 6.50–6.54 (m, 3H), 7.03 (t, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 22.7, 23.6, 25.4, 42.1, 55.1, 113.2, 117.1, 122.9, 149.1, 177.0. IR (cm^{-1}): 3246, 2965, 2934, 2876, 2360, 2337, 1684, 1497, 1214, 922, 776, 751. HRMS: calcd for $C_{12}H_{17}NO_2$: 207.1259, found: 207.1262: $[\alpha]_D^{25}$ −55.7 (*c* 0.98, CH_3OH); ee% (the methyl ester): 78 (HPLC: Chiralcel OJ-H column, hexane/^{i}PrOH 90/10, 0.8 mL/min, 254 nm, t_1=9.1 min, t_2=12.7 min).

*4.1.7. (S)-N-Phenyl phenylalanine (**3ag**)*[9]. ^{1}H NMR (400 MHz, DMSO): δ 2.91 (q, *J*=8.4 Hz, 1H), 2.95 (q, *J*=7.6 Hz, 1H), 4.07 (q, *J*=8.4 Hz, 1H), 5.91 (s, 1H), 6.49–6.55 (m, 3H), 7.01–7.05 (m, 2H), 7.16–7.19 (m, 1H), 7.23–7.29 (m, 4H); ^{13}C NMR (100 MHz, DMSO): δ 37.9, 57.6, 112.7, 116.6, 126.5, 128.3, 129.1, 129.4, 138.1, 147.9, 174.9; $[\alpha]_D^{25}$ −15.4 (*c* 1.12, $CHCl_3$); ee% (the methyl ester): 41 (HPLC: Chiralcel OJ-H column, hexane/^{i}PrOH 90/10, 0.8 mL/min, 254 nm, t_1=13.3 min, t_2=59.1 min).

*4.1.8. (R)-N-Phenyl phenylalanine (**3ah**)*[9]. $[\alpha]_D^{25}$ +12.2 (*c* 1.02, CH_3OH); ee% (the methyl ester): 33 (HPLC: Chiralcel OJ-H column, hexane/^{i}PrOH 90/10, 0.8 mL/min, 254 nm, t_1=43.1 min, t_2=60.3 min).

*4.1.9. (S)-N-Phenyl phenylglycine (**3ai**)*[48]. ^{1}H NMR (400 MHz, DMSO): δ 5.06 (s, 1H), 6.52 (t, *J*=6.8 Hz, 1H), 6.63 (d, *J*=6.8 Hz, 2H), 7.00 (d, *J*=7.6 Hz, 2H), 7.02 (d, *J*=7.6 Hz, 1H), 7.27–7.36 (m, 2H), 7.48 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 60.2, 113.7, 117.3, 128.1, 129.0, 129.6, 139.2, 147.6, 173.7; ee% (the methyl ester): 1 (HPLC: Chiralcel OJ-H column, hexane/^{i}PrOH 90/10, 0.8 mL/min, 254 nm, t_1=46.5 min, t_2=50.0 min).

*4.1.10. (S)-N-Phenyl methionine (**3aj**)*[9]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99–2.10 (m, 1H), 2.11 (s, 3H), 2.17–2.25 (m, 1H), 2.65–2.69 (m, 2H), 4.25–4.28 (m, 1H), 6.67 (d, *J*=7.6 Hz, 2H), 6.79 (t, *J*=8.4 Hz, 1H), 7.19 (t, *J*=7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 14.7, 30.0, 31.7, 54.7, 112.5, 116.5, 129.0, 148.1, 175.3. $[\alpha]_D^{25}$ −3.4 (*c* 0.41, CH_3OH); ee% (the methyl ester): 29 (HPLC: Chiralcel OJ-H column, hexane/^{i}PrOH 90/10, 0.8 mL/min, 254 nm, t_1=29.7 min, t_2=39.3 min).

*4.1.11. (S)-3-(Phenylamino)butanoic acid (**3ak**)*[22]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (d, *J*=6.8 Hz, 3H), 2.46–2.69 (m, 2H), 3.91–3.96 (m, 1H), 5.70 (br, 2H), 6.90 (d, *J*=8.0 Hz, 2H), 6.78 (t, *J*=7.6 Hz, 1H), 720 (d, *J*=6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5, 40.5, 46.5, 114.4, 1118.7, 129.5, 146.0, 177.0. $[\alpha]_D^{25}$ +19.6 (*c* 1.18, $CHCl_3$); ee% (the methyl ester): 97 (Original ee of substrate: 97%. HPLC: Chiralcel OD-H column, hexane/^{i}PrOH 99/1, 0.8 mL/min, 254 nm, t_1=19.1 min, t_2=23.0 min).

*4.1.12. (R)-3-(Phenylamino)pentanoic acid (**3al**)*[49]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.99 (t, *J*=7.6 Hz, 3H), 1.64–1.67 (m, 2H), 2.57–2.59 (m, 2H), 3.70–3.77 (m, 1H), 6.70 (d, *J*=8.4 Hz, 2H), 6.76 (t, *J*=7.2 Hz, 1H), 7.19 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 10.2, 26.9, 38.1, 52.7, 114.8, 118.9, 129.3, 145.6, 177.5. $[\alpha]_D^{25}$ +7.6 (*c* 0.99, $CHCl_3$); ee% (the methyl ester): >99 (HPLC: Chiralcel OD-H column, hexane/^{i}PrOH 99/1, 0.8 mL/min, 254 nm, t_1=25.1 min, t_2=29.0 min).

*4.1.13. (S)-3-(Phenylamino)-3-cyclohexyl propanoic acid (**3am**)*[22]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.07–1.27 (m, 5H), 1.56–1.88 (m, 6H), 2.50 (dd, *J*=16.0 Hz, 6.8 Hz, 1H), 2.60 (dd, *J*=16.0 Hz, 6.0 Hz, 1H), 3.68 (q, *J*=6.8 Hz, 1H), 6.66 (d, *J*=8.0 Hz, 2H), 6.72 (d, *J*=7.6 Hz, 1H), 7.17 (dt, *J*=7.2 Hz, 1.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.3, 29.1, 29.3, 36.5, 41.6, 55.3, 113.8, 117.7, 128.4, 129.3, 130.1, 147.1, 178.4. $[\alpha]_D^{25}$ −5.9 (*c* 0.74, $CHCl_3$); ee% (the methyl ester): 96 (Original ee of substrate: 96%. HPLC: Chiralcel OD-H column, hexane/^{i}PrOH 99/1, 0.8 mL/min, 254 nm, t_1=10.9 min, t_2=14.1 min).

*4.1.14. (S)-3-(Phenylamino)-3-phenyl propanoic acid (**3an**)*[50]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85 (d, *J*=6.4 Hz, 2H), 4.85 (t, *J*=6.8 Hz, 1H), 6.59 (d, *J*=8.0 Hz, 2H), 6.71 (t, *J*=7.2 Hz, 1H), 7.12 (t, *J*=7.6 Hz, 2H),7.25–7.38 (m, 5H); ^{13}C NMR (100 MHz, DMSO): δ 44.2, 54.9, 114.2, 117.2, 127.8, 128.1, 129.5, 130.0, 114.8, 148.9, 173.3. $[\alpha]_D^{25}$ −11.2 (*c* 1.00, $CHCl_3$); ee% (the methyl ester): >99 (HPLC: Chiralcel OD-H column, hexane/^{i}PrOH 99/1, 0.8 mL/min, 254 nm, t_1=52.3 min, t_2=60.2 min).

*4.1.15. 4-(Phenylamino)butanoic acid (**3ao**)*[51]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.93–2.00 (m, 2H), 2.50 (t, *J*=7.6 Hz, 2H), 3.21 (t, *J*=6.8 Hz, 2H), 6.62 (d, *J*=8.0 Hz, 2H) 6.71 (t, *J*=7.6 Hz, 1H), 7.18 (t, *J*=7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 31.6, 43.2, 112.9, 124.2, 129.2, 147.8, 179.2.

*4.1.16. 6-(Phenylamino)hexanoic acid (**3ap**)*[24]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.44–1.50 (m, 2H), 1.61–1,73 (m, 4H), 2.39 (t, *J*=14.0 Hz, 2H), 3.12 (t, *J*=6.8 Hz, 2H), 5.49 (br, 1H), 6.60 (d, *J*=8.0 Hz, 2H), 6.70 (t, *J*=7.6 Hz, 1H), 7.17 (t, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.3, 26.4, 28.9, 34.0, 43.9, 113.1, 117.6, 129.1, 147.8, 179.8.

*4.1.17. 2-(Phenylamino)benzoic acid (**3aq**)*[52]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.76 (t, *J*=8.4 Hz, 1H), 7.13 (t, *J*=8.4 Hz, 1H), 7.11–7.28 (m, 3H), 7.34–7.39 (m, 3H), 8.04 (dd, *J*=8.0 Hz, *J*=1.6 Hz, 1H), 9.32 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 112.5, 112.8, 116.4, 116.7, 128.2, 129.1, 129.2, 129.5, 138.1, 147.9, 174.9.

*4.1.18. 4-(Phenylamino)benzoic acid (**3ar**)*[53]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.09 (br, 1H), 7.00 (d, *J*=8.0 Hz, 2H), 7.09 (t, *J*=7.6 Hz, 1H), 7.19 (d, *J*=8.4 Hz, 2H), 7.36 (t, *J*=7.6 Hz, 3H), 7.99 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 114.0, 119.2, 120.3, 121.7, 129.4, 131.3, 141.5, 148.2, 167.2.

*4.1.19. 2-Amino-3-(1-phenyl-1H-indol-3-yl)propanoic acid (**3as**)*[54]. ^{1}H NMR (400 MHz, DMSO): δ 3.11–3.17 (m, 2H), 3.52–3.61 (m, 1H), 7.13 (t, *J*=7.6 Hz, 1H), 7.18 (t, *J*=7.6 Hz, 1H), 7.36–7.40 (m, 1H), 7.54–7.58 (m, 5H), 7.71 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO) δ 26.9, 54.3, 110.2, 112.1, 119.0, 119.9, 122.4, 123.6, 126.1, 127.4, 129.2, 129.7, 135.3, 139.2.

*4.1.20. N-(4-Trifluoromethylphenyl)-alanine (**3ba**)*[55]. White solid. Mp: 197–198 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.56 (d, *J*=7.2 Hz, 3H), 4.21 (q, *J*=7.2 Hz, 1H), 6.62 (d, *J*=7.6 Hz, 2H), 7.43 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6, 51.3, 112.8, 126.7–126.8 (m),

148.7, 179.5. IR (cm^{-1}): 3352, 3254, 2362, 2338, 1715, 1618, 1533, 1319, 1225, 1108, 1069, 829, 754. HRMS: calcd for $C_{10}H_{10}NO_2F_3$: 233.0664; found: 233.0663.

*4.1.21. N-(4-Carboxylphenyl)alanine (**3ca**)*[56]. White solid. Mp: 128–131 °C. ^1H NMR (400 MHz, DMSO) δ 1.39 (d, J=7.2 Hz, 3H), 4.02–4.05 (m, 1H), 6.56 (d, J=8.8 Hz, 2H), 6.70 (br, 1H), 7.67 (d, J=8.4 Hz 2H), 12.3 (br, 2H); ^{13}C NMR (100 MHz, DMSO) δ 19.7, 52.4, 113.1, 119.4, 132.9, 153.5, 169.3, 177.0. IR (cm^{-1}): 3404, 2973, 2360, 2337, 1671, 1602, 1522, 1420, 1289, 1177, 1118, 929, 835, 766. HRMS: calcd for $C_{10}H_{11}NO_4$: 209.0688; found: 209.0685.

*4.1.22. N-(3-Carboxylphenyl)alanine (**3da**).* White solid. Mp: 202–204 °C. ^1H NMR (400 MHz, DMSO) δ 1.36 (d, J=7.2 Hz, 3H), 3.93 (q, J=6.8 Hz, 1H), 6.22 (br, 1H), 6.75 (d, J=6.8 Hz, 1H), 7.11–7.20 (m, 3H), 12.65 (br, 2H); ^{13}C NMR (100 MHz, DMSO) δ 19.1, 52.0, 113.8, 117.7, 118.3, 130.0, 132.4, 149.0, 168.9, 176.8. IR (cm^{-1}): 3243, 2360, 2337, 1697, 1437, 1291, 1229, 946, 812, 751. HRMS: calcd for $C_{10}H_{11}NO_4$: 209.0688; found: 209.0687.

*4.1.23. N-(4-Methylphenyl)alanine (**3ea**)*[57]. ^1H NMR (400 MHz, $CDCl_3$): δ 1.53 (d, J=7.2 Hz, 3H), 2.25 (s, 3H), 4.05 (q, J=6.8 Hz, 1H), 6.57 (d, J=7.6 Hz, 2H), 7.02 (d, J=7.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 19.3, 21.1, 52.2, 113.5, 125.6, 130.3, 146.6, 177.1.

*4.1.24. N-(2-Methylphenyl)alanine (**3fa**)*[58]. ^1H NMR (400 MHz, $CDCl_3$): δ 1.57 (d, J=6.8 Hz, 3H), 2.20 (s, 3H), 4.18 (q, J=7.2 Hz, 1H), 6.55 (d, J=8.4 Hz, 1H), 6.72 (t, J=6.8 Hz, 1H), 7.08–7.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.3, 18.8, 51.9, 110.6, 118.4, 122.8, 127.1, 130.4, 144.0, 180.5.

*4.1.25. N-(3,5-Dimethylphenyl)alanine (**3ga**).* White solid. Mp: 122–124 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.52 (d, J=7.2 Hz, 3H), 2.24 (s, 6H), 4.05–4.10 (m, 1H), 6.28 (s, 2H), 6.48 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 21.4, 52.6, 111.9, 121.2, 139.1, 145.8, 179.7. IR (cm^{-1}): 3186, 2973, 2361, 2338, 1584, 1520, 1456, 1396, 1359, 856. HRMS: calcd for $C_{11}H_{15}NO_2$: 193.1107; found: 193.1103.

*4.1.26. N-(4-tert-Butylphenyl)alanine (**3ha**).* White solid. Mp: 118–120 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H), 1.52 (d, J=7.2 Hz, 3H), 4.08 (q, J=7.6 Hz, 1H), 6.59 (d, J=8.4 Hz, 2H), 7.23 (d, J=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.5, 31.4, 33.9, 53.1, 114.1, 126.2, 142.4, 142.9, 179.2. IR (cm^{-1}): 3384, 3062, 2960, 2899, 2780, 2682, 2501, 2360, 2337, 1699, 1616, 1521, 1362, 1233, 1041, 817. HRMS: calcd for $C_{13}H_{19}NO_2$: 221.1416; found: 221.1415.

*4.1.27. N-(4-Methoxylphenyl)alanine (**3ia**)*[59]. White solid. Mp: 148–150 °C. ^1H NMR (400 MHz, DMSO): δ 1.31 (d, J=6.8 Hz, 3H), 3.60 (s, 3H), 3.84 (q, J=7.2 Hz, 1H), 6.49 (d, J=9.2 Hz, 2H), 6.68 (dd, J=9.2, J=2.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO): δ 18.4, 51.9, 55.4, 113.7, 114.6, 142.1, 151.2, 176.4. IR (cm^{-1}): 3081, 2999, 2362, 2339, 1567, 1513, 1486, 1408, 1360, 1266, 1030, 853, 820, 750. HRMS: calcd for $C_{10}H_{13}NO_3$: 195.0895; found: 195.0900.

*4.1.28. N-(3-Methoxylphenyl)alanine (**3ja**)*[60]. White solid. Mp: 93–94 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.53 (d, J=7.2 Hz, 3H), 3.76 (s, 3H), 4.12 (q, J=6.4 Hz, 1H), 6.17 (s, 1H), 6.24 (dd, J=8.0, 1.6 Hz, 1H), 6.35 (dd, J=8.0, 1.6 Hz, 1H), 7.10 (t, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 52.1, 55.0, 99.7, 104.0, 106.5, 130.1, 147.4, 160.9, 179.7. IR (cm^{-1}): 3250, 3010, 2361, 2338, 1715, 1602, 1461, 1208, 1154, 1040, 868, 778, 725. HRMS: calcd for $C_{10}H_{13}NO_3$: 195.0895; found: 195.0894.

*4.1.29. N-(2-Methoxylphenyl)alanine (**3ka**)*[60]. White solid. Mp: 116–119 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, J=7.2 Hz, 3H), 3.85 (s, 3H), 4.08 (q, J=6.0 Hz, 1H), 6.58 (dd, J=8.0, 2.0 Hz, 1H), 6.77–6.85 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 51.8, 55.4, 109.8, 110.6, 118.1, 121.1, 136.0, 147.0, 180.0. IR (cm^{-1}): 3408, 3249, 2361, 2333, 1715, 1516, 1456, 1223, 1183, 1023, 907, 743. HRMS: calcd for $C_{10}H_{13}NO_3$: 195.0895; found: 195.0896.

4.2. General procedure for the Palladium-catalyzed coupling reaction of amino esters with aryl halides

An oven-dried Schlenk flask was charged with $Pd(dba)_2$ (11.4 mg, 0.02 mmol), **L1** (13.6 mg, 0.03 mmol), Cs_2CO_3 (3.0 mmol), 2-aminopropanoate hydrochloride (1.2 mmol). Dioxane (2.5 mL) and aryl halides (1.00 mmol) were added in sequence via a syringe. The flask was sealed and the mixture was heated at 100 °C for 20 h. After cooling to room temperature, the mixture was neutralized with saturated NH_4Cl. The aqueous layer was extracted with diethyl ether; the combined organic phase was dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane) to afford the coupling product.

*4.2.1. Methyl 2-(phenylamino)propanoate (**5aa**)*[61]. ^1H NMR (400 MHz, $CDCl_3$): δ 1.47 (d, J=6.4 Hz, 3H), 3.73 (s, 3H), 4.14–4.15 (m, 2H), 6.59–6.61 (m, 1H), 6.72–6.76 (m, 1H), 7.16–7.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 52.1, 52.5, 113.5, 118.6, 129.56, 129.59, 146.7, 175.4.

*4.2.2. Methyl 4-(1-methoxy-1-oxopropan-2-ylamino)benzoate (**5la**)* . Red solid. Mp: 59–60 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 1.50 (d, J=6.8 Hz, 3H), 3.76 (s, 3H), 3.85 (s, 3H), 4.21 (d, J=7.2, 1H), 4.61 (s, 1H), 6.54–6.57 (m, 2H), 7.86–7.88 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.8, 51.4, 51.7, 52.6, 112.1, 115.3, 119.4, 131.7, 131.9, 150.3, 167.3, 174.4. IR (cm^{-1}): 3379, 2952, 2356, 1732, 1687, 1603, 1530, 1437, 1338, 1279, 1171, 1117, 1055, 840, 735. HRMS: calcd for $C_{12}H_{15}NO_4$: 237.1001; found: 237.1003.

*4.2.3. Di-tert-butyl 2-(phenylamino)pentanedioate (**5ab**).* ^1H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 1.44 (s, 9H), 2.00–2.11 (m, 2H), 2.35–2.41 (m, 2H), 3.98–3.99 (m, 1H), 4.18 (br, 1H), 6.62 (d, J=6.8 Hz, 1H), 6.72 (t, J=6.8 Hz, 1H), 7.16 (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.2, 28.3, 31.9, 56.9, 80.8, 82.0, 113.8, 118.4, 129.5, 147.3, 172.6, 173.1.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.09.109.

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