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Synthesis of chiral α-amino anilides via a DMEDA-promoted selective C–N coupling reaction of aryl halides and α-aminoamides

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ABSTRACT

A DMEDA-promoted and copper-catalyzed approach has been designed for the coupling of aryl halides and chiral α-aminoamides to afford a range of functionalized chiral α-amino anilides. This method has a higher yield and better reproducibility than those under ligand-free conditions. Of the two amino groups in the same molecule, only the amide NH_2 is observed to react, showing high regioselectivity. In addition, no racemization occurs, and the *ee* can reach 99%. For certain hydroxyl-containing substrates, such as L-tyrosine amide and L-threonine amide, addition of a phase transfer catalyst (15-Crown-5) is necessary for such a transformation.

1. Introduction

Since its discovery, the Goldberg reaction (or the modified Ullmann reaction) has evolved as a powerful tool for the formation of Csp^2–N single bonds.[1] The N-arylation of amides by aryl halides via the C–N coupling reaction offers an alternative approach to the synthesis of N-arylamides.[2] Compared to the Pd-catalyzed Buchwald-Hartwig C–N coupling reaction, Cu-catalyzed Goldberg C–N coupling is more practical since competitive coupling to aliphatic NH_2 rather than the amide NH_2 is often observed in the Pd-catalyzed Buchwald-Hartwig coupling reaction.[2c] However, the copper-catalyzed C–N coupling reaction is sensitive to external conditions, and different parameters will yield different coupling results.[2b,3] In addition, the typical copper-catalyzed Goldberg reaction requires a high temperature, a stoichiometric amount of copper powder, and a long reaction time, and these requirements limit the application of such reactions.[4] Many efforts have been made to overcome these limitations, including the addition of ligands, such as β-diketone,[4] diamine,[5a] salicylamide,[5b] ethylene glycol,[5c] L-proline,[5d] and 1,10-phenanthroline,[5e] to the reaction system, as well as the use of other transition metals, such as manganese,[5d] a manganese/copper bimetallic catalyst,[6a] and Ni(acac)$_2$.[6b] However, more efforts are needed to selectively achieve the carbon-nitrogen coupling of aryl halides and α-aminoamides bearing sensitive groups, including hydroxyl, amino, and amide groups.

Chiral α-amino anilides are useful synthetic intermediates and have a wide range of applications, especially in the field of medicine, such as tocainide, an antiarrhythmic agent;[7a] amoxicillin, a broad-spectrum antibiotic;[7b] histone deacetylases for treating cancer and other disorders;[7c] pH-controlled, light-activated reagents for cancer therapy;[7d] and antimalarial agents.[7e] In addition, the proposed anilides can be used as ligands and catalysts in organic synthesis.[8] Since two amino groups exist on the same chiral α-aminoamide moiety, the key to this reaction is to control the selectivity of C–N coupling at the desired amino group.[8] The previous synthesis of chiral amino anilides involved protection and deprotection of the amino group of the primary amine, and these extra steps made the procedure cumbersome.[9]

In this investigation of the preparation of (S)-2-amino-N-2-diphenyl acetamide (**3a**), a key intermediate in our synthesis of epinastine, from iodobenzene (**1a**) and L-phenylglycinamide (**2a**) in the presence of CuI and K_2CO_3 at 110 °C, we determined that this ligand-free method afforded only a 30% isolated yield

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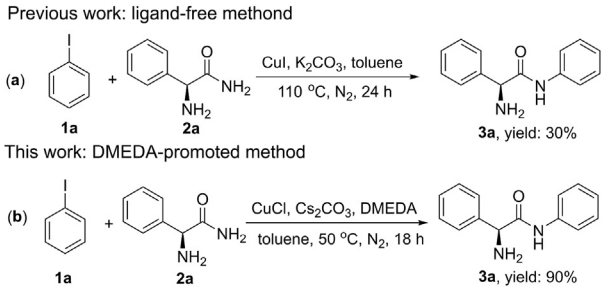


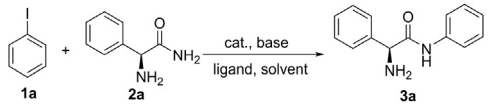
Scheme 1. Results of the DMEDA-promoted and ligand-free methods.

(scheme 1, a).[8] Repeated trials were completed, strictly following the conditions reported; however, the highest yield was still no more than 30%, which was far less than the 90% yield recorded in the literature. Since this yield was far lower than expected and could not meet the requirements of this study, we needed to develop a high-yield method for the preparation of chiral amino anilides. Herein, we report a copper-catalyzed, DMEDA-promoted approach for the synthesis of chiral α-amino anilides.

2. Results and discussion

We initially examined the reaction of iodobenzene (**1a**) with L-phenylglycinamide (**2a**), which were used as the model substrates for the optimization of the selective cross-coupling conditions, and the results are shown in Table 1. Amide **3a** was formed in only 30% yield in the absence of ligands after all attempts to follow the literature procedure (Table 1, entry1).[8] We found that DMEDA (1 eq.) effectively catalyzed the reaction between **1a** and **2a** to give the desired **3a** in a yield of 75% (Table 1, entries 1–2). However, decreasing its loading to 0.5 and 0.2 eq. led to reduced yields of 66% and 34%, respectively, which indicated the positive effects of the nitrogen ligands on the cross-coupling reaction (Table 1, entries 3–4). When the reaction was undertaken using other nitrogen-containing ligands, namely, 1,10-phenanthroline, 2,2′-bipyridine, 4,7-diphenyl-1,10-phenanthroline, and 1,10-phenanthroline-5,6-dione, poor yields that ranged from trace to 43% were obtained (Table 1, entries 5–8). We then turned our attention to an examination of the effects of the base. In most cases, the choice of base has an important effect on the reaction rate, and the reaction can be well conducted if the rate for deprotonating and coupling can be properly matched.[10a] Cs_2CO_3 was the optimal choice of base after screening Cs_2CO_3, K_3PO_4, *t*-BuOK, NaOH and K_2CO_3 (Table 1, entries 9–12 and entry 1). In addition to the ligand and base used, the nature of the solvent was investigated. An increase in the desired product was obtained in toluene and xylene, and a decrease was observed in DMF, DMSO, DMA and DMF/toluene (Table 1, entries 13–17 and entry 9). Various Cu catalysts were screened, and CuCl provided the best results among CuBr, CuCl, $CuCl_2$, $Cu(acac)_2$, and CuO (Table 1, entries 18–23 and entry 9). The temperature also significantly influenced the yield. At room temperature, the reaction yield was 60%. Increasing the reaction temperature to 50 °C substantially improved the yield to 90%. No further improvements

Table 1
Optimization of the reaction conditions.[a]



Entry	Ligand (eq.)	Base	Catalyst	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	–	K_2CO_3	CuI	toluene	110	24	30
2	DMEDA (1.0)	K_2CO_3	CuI	toluene	110	18	75
3	DMEDA (0.5)	K_2CO_3	CuI	toluene	110	18	66
4	DMEDA (0.2)	K_2CO_3	CuI	toluene	110	18	34
5	1,10 -phen (0.5)	K_2CO_3	CuI	toluene	110	18	43
6	bipy (0.5)	K_2CO_3	CuI	toluene	110	18	38
7	4,7-diph-1,10-phen (0.5)	K_2CO_3	CuI	toluene	110	18	13
8	1,10-phen-5,6-dione (0.5)	K_2CO_3	CuI	toluene	110	18	Trace
9	DMEDA (1.0)	Cs_2CO_3	CuI	toluene	110	18	80
10	DMEDA (1.0)	K_3PO_4	CuI	toluene	110	18	74
11	DMEDA (1.0)	*t*-BuOK	CuI	toluene	110	18	23
12	DMEDA (1.0)	NaOH	CuI	toluene	110	18	Trace
13	DMEDA (1.0)	Cs_2CO_3	CuI	DMF	110	18	44
14	DMEDA (1.0)	Cs_2CO_3	CuI	DMSO	110	18	27
15	DMEDA (1.0)	Cs_2CO_3	CuI	DMA	110	18	55
16	DMEDA (1.0)	Cs_2CO_3	CuI	DMF/toluene 1/1	110	18	62
17	DMEDA (1.0)	Cs_2CO_3	CuI	*o*-xyle	110	18	79
18	DMEDA (1.0)	K_2CO_3	–	toluene	110	18	NR
19	DMEDA (1.0)	Cs_2CO_3	$CuCl_2$	toluene	110	18	68
20	DMEDA (1.0)	Cs_2CO_3	CuBr	toluene	110	18	82
21	DMEDA (1.0)	Cs_2CO_3	CuCl	toluene	110	18	87
22	DMEDA (1.0)	Cs_2CO_3	$Cu(acac)_2$	toluene	110	18	72
23	DMEDA (1.0)	Cs_2CO_3	CuO	toluene	110	18	85
24	DMEDA (1.0)	Cs_2CO_3	CuCl	toluene	70	18	86
25	**DMEDA (1.0)**	**Cs_2CO_3**	**CuCl**	**toluene**	**50**	**18**	**90**
26	DMEDA (1.0)	Cs_2CO_3	CuCl	toluene	r.t.	18	60
27	DMEDA (1.0)	Cs_2CO_3	CuCl	toluene	50	12	86
28	DMEDA (1.0)	Cs_2CO_3	CuCl	toluene	50	24	90

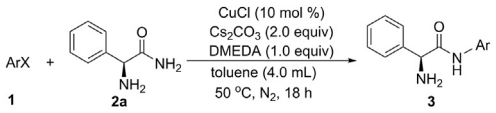
[a] Unless otherwise specified, the reactions were conducted with **1a** (1.0 eq.), **2a** (1.2 mmol), cat. (10 mol %), solvent (4.0 mL), base (2.0 eq.), ligand (X eq.) in a sealed reaction tube under N_2.
[b] Yield of isolated product.

were observed when the temperature was increased to 70 °C (Table 1, entries 24–26). The reaction time was typically 18 h, and altering the reaction time did not increase the product formation (Table 1, entries 27–28). Thus, **1a** (1.2 eq.) and **2a** (1 eq.) as the reactants, CuCl (10 mol%) as the catalyst, DMEDA (1 eq.) as the ligand and toluene (4 mL) as the solvent, a temperature of 50 °C, and a duration of 18 h were defined as the optimized reaction conditions for further studies (Table 1, entry 25).

After establishing the feasibility of the reaction between iodobenzene (**1a**) and L-phenylglycinamide (**2a**), we explore the scope of the process with respect to ArX. In this case, **2a** was taken as the standard chiral α-aminoamide under the optimized conditions mentioned above to react with aryl halides bearing diverse substituents on different positions of the phenyl ring. The first eight substrates employed aryl iodides, which reacted with **1a** to give **3a**-**3h** in good to excellent yields. In addition to iodobenzene, as mentioned previously (Table 2, entry 1), the reaction tolerated a range of substituents on the phenyl ring, including electron-donating Me and OMe (Table 2, entries 2–3) and electron-withdrawing CO_2Me, CF_3 and Cl (Table 2, entries 4–6), except for p-NO_2Ph, which decreased the yield of **3g** to 60% (Table 2, entry 7). In all these cases, good to excellent isolated yields of 83–92% were obtained. Entry 8 demonstrates that fused rings such as naphthyl groups were also good substrates, furnishing **3h** in a yield of 91%. The reaction of pyridine iodide bearing a 2-pyridyl group gave the corresponding coupling product in a yield of 85% (Table 2, entry 9). Bromoarenes and chloroarene such as PhBr (**1j**), 3-bromopyridine (**1k**) and PhCl (**1l**) were also compatible with the reaction, and the corresponding products, **3a**, **3i** and **3a**, were afforded in 50%, 55% and 40% yields, respectively (Table 2, entries 10–12). In some cases, a higher temperature was unfavorable for the conversion, and many by-products were produced from reactions of 4-NO_2–C_6H_4I (**1g**), 4-MeO-C_6H_4I (**1c**), 3-iodopyridine (**1i**) and 3-bromopyridine (**1k**) at 110 °C, resulting in difficult product isolation. Therefore, a lower temperature is essential for the DMEDA-promoted cross-coupling reaction.

The scope of the chiral α-aminoamides was investigated under the same reaction conditions as those summarized in Table 3. Various α-aminoamide derivatives (**2a**-**2g**) were tolerated in the coupling reaction, and most of them gave the corresponding N-aryl

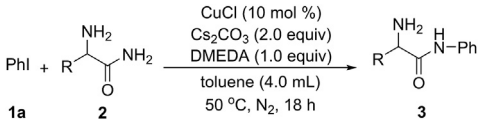
Table 2
Substrate scope for various aryl halides **1** and L-phenylglycinamide **2a**.[a]



Entry	ArX	Product	Yield %[b]
1	PhI (**1a**)	**3a**	90
2	2-Me-C_6H_4I (**1b**)	**3b**	91
3	4-MeO-C_6H_4I (**1c**)	**3c**	92
4	2-I-$C_6H_4COOCH_3$ (**1d**)	**3d**	83
5	2-I-$C_6H_4CF_3$ (**1e**)	**3e**	92
6	3-Cl-C_6H_4I (**1f**)	**3f**	89
7	4-NO_2-C_6H_4I (**1g**)	**3g**	60
8	1-I-naphthalene (**1h**)	**3h**	91
9	3-I-pyridine (**1i**)	**3i**	85
10	PhBr (**1j**)	**3a**	50
11	3-Br-pyridine (**1k**)	**3i**	55
12	PhCl (**1l**)	**3a**	40

[a] Unless otherwise specified, the reaction was conducted with **1** (1.0 mmol), **2a** (1.2 mmol), CuCl (0.1 mmol), DMEDA (1.0 mmol), Cs_2CO_3 (2.0 mmol), and toluene (4.0 mL) at 50 °C 18 h under N_2.
[b] Yield of isolated product.

Table 3
Substrate scope for various chiral α-aminoamides **2** and aryl halides **1a**.[a]



Entry	Chiral α-Aminoamides	Product	Yield %[b]
1[c]	**2a**	**3a**	88
2[d]	(+)-**2a**	(-)-**3a**	90
3	**2b**	**3j**	88
4	**2c**	**3k**	60
5	**2d**	**3l**	82 (92)[e]
6	**2e**	**3m**	84 (96)[e]
7[d]	**2f**	**3n**	75
8	(±)-**2f**	(±)-**3n**	75
9[g]	**2g**	**3o**	20 (74)[f]
10	**2h**	**3p**	Trace (67)[f]
11[g]	**2i**	**3q**	Trace (54)[f]

[a] Unless otherwise specified, the reaction was conducted with **1a** (1.0 mmol), **2** (1.2 mmol), CuCl (0.1 mmol), DMEDA (1.0 mmol), Cs_2CO_3 (2.0 mmol), and toluene (4.0 mL) at 50 °C for 18 h under N_2.
[b] Yield of isolated product.
[c] **2a** with 82.6% optical purity.
[d] 99% enantiomeric excess (*ee*) was obtained (Chiral HPLC trace is given in the Supporting Information).
[e] This reaction was conducted at 110 °C.
[f] Increase in the reaction temperature to 110 °C while adding a phase transfer catalyst, 15-Crown-5 (0.2 mmol).
[g] Cs_2CO_3 (3.0 mmol) was used.

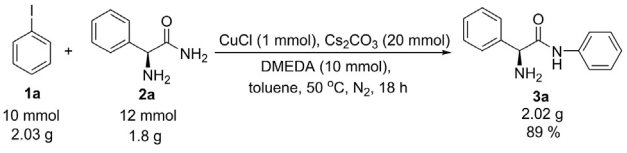
aminoamide (chiral α-amino anilides) in good to excellent yields. For instance, phenylglycinamide **2a** (with 82.6% optical purity)[11] and L-phenylglycinamide ((+)-**2a**) as a pure enantiomer gave good yields (Table 3, entries 1–2). Other aminoamides, D-phenylalaninamide (**2b**), L-alaninamide (**2c**), L-valinamide (**2d**) and L-leucinamide (**2e**), with different chain lengths provided the desired products **3j**-**m** in 60–88% yields (Table 3, entries 3–6). At a higher temperature of 110 °C, the yields of **3l** and **3m** increased to 92% and 96%, compared to 82% and 84% at 50 °C, respectively (Table 3, entries 5–6). Both L-prolinamide (**2f**) and D/L-phenylalaninamide ((±)-**2f**), which contain a saturated five-membered ring, gave a slightly lower yield (75%) (Table 3, entries 7–8). The reactant L-tryptophanamide (**2g**), which bears an indolyl moiety, proved to be less effective (yield of only 20%), but if the temperature was increased to 110 °C and a phase transfer catalyst such as tetrabutylammonium bromide (TBAB) or 15-Crown-5 was used, good yields of up to 70% and 74% respectively were observed (Table 3, entry 9). As recorded in the literature, the reaction of L-tyrosinamide (**2h**) and L-threoninamide (**2i**), which bear an additional hydroxyl group, cannot occur using the method developed by Zeng.[8] In contrast, these two substrates were good candidates for the reaction developed in the present study. At first, trace products were detected under these conditions. Further modification at 110 °C using 15-Crown-5 as a phase transfer catalyst led to much improved yields of 67% for L-tyrosinamide and 54% for L-threoninamide (Table 3, entries 10–11). Notably, the corresponding yields were only 14% and 10%, respectively, without the use of a phase transfer catalyst. The phase transfer catalyst plays a critical role in the reaction of α-aminoamides containing a hydroxy group.

To verify whether racemization occurred during the C–N cross coupling, the *ee* of products **3a** and **3n** was analyzed by chiral HPLC (Table 3, entry 2 and entry 7). The *ee* values of (−)-**3a** and **3n** were 99% with a high level of stereoselectivity (the optical purity of the raw material is 98%), which means that no racemization occurred during coupling. We obtained a satisfactory optical purity without reducing the yield.[8] Finally, to illustrate the synthetic potential of this method, we performed a gram-scale synthesis of the chiral amino acid anilide **3a** and obtained an overall yield of 89% upon isolation (Scheme 2).

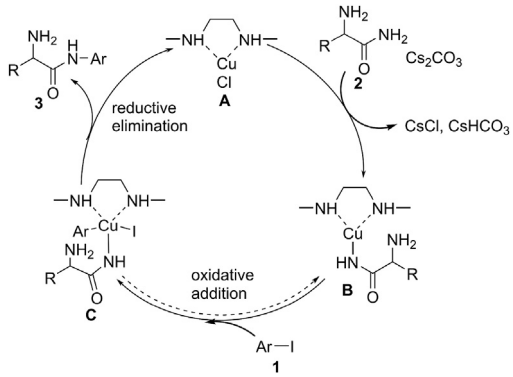
Based on previous related works and the above results,[3b,4,8,10b,10c] a proposed catalytic pathway for the formation of **3** is outlined in Scheme 3. The copper complex **A** is initially formed by the reaction of CuCl and DMEDA. Then the ligand exchange with the amino amide **2** would afford the Cu(III) complex **B**, which could undergo oxidative addition to give the Cu(III) complex **C**. The reductive elimination of **C** would deliver the coupling product and regenerate complex **A**. A lower transition-state energy for the ligand exchange to Cu(I)-amide complexes than for the ligand exchange to Cu(I)-aliphatic amine complexes might make the formation of intermediate **B** easier; therefore, the coupling reaction could proceed smoothly.[12]

3. Conclusion

In summary, a DMEDA-promoted and copper-catalyzed approach has been designed for the synthesis of chiral α-amino anilides from aryl halides and chiral α-aminoamides. This process produced a useful N-aryl-substituted amide in good to excellent yields via a C–N cross-coupling reaction, with a much broader substrate scope compared to previous methods. The result from the addition of DMEDA was significantly better than that without using any ligands, which was confirmed by the reactivity of substrates L-tryptophanamide (**2g**), L-tyrosine amide (**2h**) and L-threonine amide (**2i**). Two chiral α-amino anilides with high *ee* were obtained with retention at the chiral carbon atom. The mild reaction conditions and the high level of regioselectivity make this method an attractive complement to the existing ligand-free C–N coupling reactions.



Scheme 2. Gram-scale synthesis of the chiral amino acid anilide **3a**.



Scheme 3. Proposed catalytic pathway to produce **3.**

4. Experimental section

4.1. General

All reactions were carried out in a Schlenk-type tube (25 mL) under a nitrogen atmosphere, unless otherwise indicated. An oil bath was used as a heating source. All reagents were purchased from commercial sources and used without further treatment, but the solvents used in the reaction were subjected to anhydrous anaerobic treatment before use. NMR spectra were recorded on a Bruker Avance II 400 NMR spectrometer (400 MHz for ^{1}H; 100 MHz for ^{13}C). $CDCl_3$ and DMSO-d_6 were used as the NMR solvent. Chemical shifts are reported in parts per million. Data were reported as follows: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (hertz, Hz), and integration. High-resolution mass spectrometry (HRMS) spectra were recorded on a quadrupole analyzer using an ESI source (Agilent Technologies G6224A). TLC was performed using commercially prepared 100–400-mesh silica gel GF254 (Qingdao Haiyang Chemical Co., Ltd.) plates, and visualization was achieved at 254 nm.

4.1.1. General procedure for the chiral α-amino anilides (*3a*-*3n*)

A 25-mL Schlenk-type tube equipped with a magnetic stir bar was charged with a chiral amino acid amide or its hydrochloride (1.2 mmol), Cs_2CO_3 (2.0 mmol; 3.0 mmol was used when an amino acid amide hydrochloride was used), and CuCl (0.1 mmol) before sealing. A syringe was used under a nitrogen atmosphere to add aryl halide (1.0 mmol), DMEDA (1.0 mmol) and toluene (4.0 mL). If aryl halides were solid at room temperature, they were added with CuCl and Cs_2CO_3 at the same time. The tube was placed into an oil bath pot preheated to 50 °C and stirred at a steady temperature for 18 h. The reaction mixture was then cooled to room temperature, quenched with water, and extracted with ethyl acetate (20 mL) for three times. The organic layers were combined, dried over

anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with a solution of dichloromethane and ethyl alcohol (80/1 to 10/1) to afford the chiral α-amino anilides.

*4.1.2. General procedure for chiral α-amino acid anilides (**3o-3q**)*

A 25-mL of Schlenk-type tube equipped with a magnetic stir bar was charged with a chiral amino acid amide or its hydrochloride (1.2 mmol), Cs_2CO_3 (2.0 mmol; 3.0 mmol used when amino acid amide hydrochloride was used), and CuCl (0.1 mmol) before sealing. A syringe was used under a nitrogen atmosphere to add aryl halide (1.0 mmol), DMEDA (1.0 mmol), toluene (4.0 mL) and 15-Crown-5 (0.2 mmol). The tube was put into an oil bath pot preheated at 110 °C and was stirred at a steady temperature for 18 h. The reaction mixture was then cooled to room temperature, quenched with water, and extracted with ethyl acetate (20 mL) for three times. The organic layers were combined, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography with a solution of dichloromethane and ethyl alcohol (80/1 to 10/1) to afford the chiral α-amino anilides.

*4.1.3. (S)-2-amino-N,2-diphenylacetamide (**3a**)*[8]

White solid, 203 mg, yield: 90%, 99% *ee* (HPLC, Diacel Chiralcel OD-H column, 70:30 hexanes/2-propanol, 0.8 mL/min, 254 nm; (S)-2-amino-N,3-diphenylpropanamide, rt = 10.482 min; (R)-2-amino-N,3-diphenyl-propanamide, rt = 11.570 min). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 7.52 (d, J = 7.8 Hz, 2H), 7.37 (d, J = 7.1 Hz, 2H), 7.33–7.20 (m, 5H), 7.02 (t, J = 7.4 Hz, 1H), 4.57 (s, 1H), 1.75 (s, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.3, 142.3, 138.8, 128.7, 128.1, 127.1, 126.7, 123.3, 119.2, 59.6.

*4.1.4. (S)-2-amino-N-(2-methylphenyl)-2-phenylacetamide (**3b**)*[13a]

White solid, 218 mg, yield: 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.4 Hz, 2H), 7.40–7.28 (m, 3H), 7.24–7.12 (m, 2H), 7.05 (t, J = 7.4 Hz, 1H), 4.61 (s, 1H), 2.26 (s, 3H), 2.05 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 140.6, 135.6, 130.1, 128.7, 127.84, 127.80, 126.7, 126.5, 124.3, 121.1, 60.2, 17.4.

*4.1.5. (S)-2-amino-N-(4-methoxyphenyl)-2-phenylacetamide (**3c**)*[13b]

White solid, 235 mg, yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (s, 1H), 7.50 (d, J = 8.9 Hz, 2H), 7.45 (d, J = 7.3 Hz, 2H), 7.36 (t, J = 7.2 Hz, 2H), 7.32–7.27 (m, 1H), 6.85 (d, J = 8.9 Hz, 2H), 4.71 (s, 1H), 3.78 (s, 3H), 2.01 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 156.3, 140.7, 130.9, 128.9, 128.1, 126.9, 121.1, 114.1, 55.5, 29.7.

*4.1.6. (S)-2-amino-N-(2-methoxycarbonylphenyl)-2-penylacetamide (**3d**)*

White solid, 236 mg, yield: 83%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.10 (s, 1H), 8.74 (d, J = 7.4 Hz, 1H), 8.03 (d, J = 6.5 Hz, 1H), 7.67–7.44 (m, 3H), 7.45–7.29 (m, 3H), 7.07 (s, 1H), 4.71 (s, 1H), 3.95 (s, 3H), 1.97 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.5, 168.2, 141.0, 140.9, 134.5, 130.9, 128.9, 128.1, 127.0, 122.7, 120.5, 115.8, 61.5, 52.4. HRMS (ESI) m/z: Calcd for $C_{16}H_{17}N_2O_3$ ($[M + H]^+$) 285.1239, found 285.1239.

*4.1.7. (S)-2-amino-N-(2-trifluoromethylphenyl)-2-phenylacetamide (**3e**)*

Yellow solid, 270 mg, yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.08 (s, 1H), 8.23 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 7.8 Hz, 1H), 7.36 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 7.1 Hz, 2H), 7.25–7.15 (m, 3H), 7.03 (t, J = 7.6 Hz, 1H), 4.49 (s, 1H), 1.87 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 140.2, 135.3, 132.7, 128.8, 128.1, 126.7, 125.8 (q, J = 5.4 Hz), 125.4, 123.7, 122.7, 119.2 (d, J = 29.8 Hz), 60.2. HRMS (ESI) m/z: Calcd for $C_{15}H_{14}F_3N_2O$ ($[M + H]^+$) 295.1058, found 295.1050.

*4.1.8. (S)-2-amino-N-(3-chlorophenyl)-2-phenylacetamide (**3f**)*[13b]

White solid, 231 mg, yield: 89%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (s, 1H), 7.64 (s, 1H), 7.41–7.32 (m, 3H), 7.30–7.12 (m, 3H), 7.19–7.11 (m, 1H), 6.99 (d, J = 7.9 Hz, 1H), 4.56 (s, 1H), 1.77 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.1, 140.3, 138.8, 134.7, 123.0, 129.0, 128.3, 126.8, 124.2, 119.6, 117.4, 60.3.

*4.1.9. (S)-2-amino-N-(4-nitrophenyl)-2-phenylacetamide (**3g**)*[13b]

Yellow solid, 162 mg, yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H), 8.21 (d, J = 9.1 Hz, 2H), 7.78 (d, J = 9.1 Hz, 2H), 7.46–7.29 (m, 5H), 4.69 (s, 1H), 1.97 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.8, 143.4, 143.3, 139.9, 129.0, 128.3, 126.7, 124.9, 118.9, 60.2.

*4.1.10. (S)-2-amino-N-(naphthalen-1-yl)-2-phenylacetamide (**3h**)*[14a]

White solid, 251 mg, yield: 91%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.72–7.62 (m, 2H), 7.45 (d, J = 8.2 Hz, 1H), 7.34–7.20 (m, 5H), 7.08–7.19 (m, 3H), 4.45 (d, J = 4.2 Hz, 1H), 1.90 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.4, 140.6, 133.8, 132.1, 128.7, 128.5, 127.9, 126.7, 126.1, 126.0, 125.7, 125.6, 124.8, 120.1, 118.4, 60.3.

*4.1.11. (S)-2-amino-2-phenyl-N-(pyridin-3-yl)acetamide (**3i**)*

White solid, 193 mg, yield: 85%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.80 (d, J = 2.4 Hz, 1H), 8.25 (dd, J = 4.7, 1.3 Hz, 1H), 8.08 (ddd, J = 8.3, 2.5, 1.5 Hz, 1H), 7.48 (d, J = 7.3 Hz, 2H), 7.38–7.30 (m, 4H), 7.29–7.22 (m, 1H), 4.57 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.0, 144.3, 141.9, 140.9, 135.5, 128.2, 127.2, 126.8, 126.1, 123.6, 59.7. HRMS (ESI) m/z: Calcd for $C_{13}H_{14}N_3O$ ($[M + H]^+$) 228.1137, found 228.1130.

*4.1.12. (R)-2-amino-N,3-diphenylpropanamide (**3j**)*[8]

White solid, 211 mg, yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (s, 1H), 7.48 (d, J = 7.9 Hz, 2H), 7.23 (s, 4H), 7.19 (s, 3H), 7.01 (t, J = 7.4 Hz, 1H), 3.81 (s, 1H), 3.29 (dd, J = 13.7, 3.8 Hz, 1H), 2.80 (dd, J = 13.7, 8.9 Hz, 1H), 2.28 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.0, 137.6, 137.5, 129.3, 129.0, 128.8, 127.0, 124.2, 119.5, 56.8, 40.6.

*4.1.13. (S)-2-amino-N-phenylpropanamide (**3k**)*[8]

White solid, 98 mg, yield: 60%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.38 (s, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.24 (t, J = 7.6 Hz, 2H), 7.02 (t, J = 7.0 Hz, 1H), 3.55 (d, J = 6.7 Hz, 1H), 1.64 (s, 2H), 1.36 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 137.8, 129.0, 124.0, 119.4, 51.2, 21.6.

*4.1.14. (S)-2-amino-3-methyl-N-phenylbutanamide (**3l**)*[8]

White solid, 157 mg, yield: 82% (92% when temperature is 110 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.43 (s, 1H), 7.52 (d, J = 7.7 Hz, 2H), 7.23 (t, J = 7.9 Hz, 2H), 7.00 (t, J = 7.4 Hz, 1H), 3.27 (d, J = 3.5 Hz, 1H), 2.24–2.41 (m, 1H), 1.54 (s, 2H), 0.94 (d, J = 7.0 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.6, 137.7, 128.8, 123.9, 119.4, 60.3, 30.7, 19.7, 16.0.

*4.1.15. 13 (S)-2-amino-4-methyl-N-phenylpentanamide (**3m**)*[8]

White solid, 173 mg, yield: 84% (96% when temperature is 110 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.45 (s, 1H), 7.50 (d, J = 7.6 Hz, 2H), 7.21 (t, J = 7.9 Hz, 2H), 6.98 (t, J = 7.4 Hz, 1H), 3.38 (m, 1H), 1.74–1.63 (m, 2H), 1.60 (s, 2H), 1.37–1.23 (m, 1H), 0.86 (dd, J = 12.1, 6.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.7, 138.0, 128.7, 123.8, 119.3, 53.8, 43.7, 24.8, 23.2, 21.2.

*4.1.16. 14 (S)-N-phenylpyrrolidine-2-carboxamide (**3n**)*[8]

White solid, 142 mg, yield: 75%, 99% *ee* (HPLC, Diacel Chiralcel OD-H column, 70:30 hexanes/2-propanol, 0.8 mL/min, 254 nm; (R)-N-phenylpyrrolidine-2-carboxamide, rt = 6.489 min; (S)-N-phenylpyrrolidine-2-carboxamide, rt = 7.245 min). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.92 (s, 1H), 7.64 (d, J = 7.9 Hz, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.04 (t, J = 7.3 Hz, 1H), 3.68 (s, 1H), 3.09 (s, 1H), 2.89 (s, 2H), 2.13–1.96 (m, 1H), 1.87–1.72 (m 1H), 1.71–1.56 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.3, 138.5, 128.6, 123.2, 119.0, 60.8, 46.7, 30.4, 25.9.

*4.1.17. (S)-2-amino-3-(1H-indol-2-yl)-N-phenylpropanamide (**3o**)*[8]

White solid, 206 mg, yield: 74%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 8.06 (s, 1H), 7.63 (d, J = 7.7 Hz, 1H), 7.52 (d, J = 7.7 Hz, 2H), 7.35–7.21 (m, 3H), 7.14 (t, J = 7.3 Hz, 1H), 7.09–6.97 (m, 3H), 3.78 (d, J = 6.2 Hz, 1H), 3.41 (d, J = 14.4 Hz, 1H), 3.01–2.92 (m, 1H), 1.57 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.7, 138.8, 136.1, 128.6, 127.4, 123.7, 123.1, 120.8, 119.2, 118.5, 118.2, 111.3, 110.5, 56.2, 30.9.

*4.1.18. (S)-2-amino-3-(4-hydroxyphenyl)-N-phenylpropanamide (**3p**)*[14b]

White solid, 171 mg, yield: 67%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.79 (s, 1H), 9.19 (s, 1H), 7.59 (d, J = 7.9 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.03 (t, J = 7.7 Hz, 3H), 6.66 (d, J = 8.0 Hz, 2H), 3.50 (t, J = 6.4 Hz, 1H), 2.89 (dd, J = 13.3, 5.3 Hz, 1H), 2.62 (dd, J = 13.4, 7.9 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.4, 155.7, 138.8, 130.1, 128.6, 128.3, 123.2, 119.2, 114.9, 57.1.

*4.1.19. 17 (S)-2-amino-3-hydroxy-N-phenylbutanamide (**3q**)*

White solid, 105 mg, yield: 54%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.06 (br, 1H), 7.65 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.9 Hz, 2H), 7.05 (t, J = 7.4 Hz, 1H), 4.81 (br, 1H), 4.01–3.90 (m, 1H), 3.55 (s, 3H), 1.13 (d, J = 6.3 Hz, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 138.6, 128.7, 123.3, 119.1, 69.5, 67.3, 20.8. HRMS (ESI) m/z: Calcd for $C_{10}H_{15}N_2O_2$ ([M + H]$^+$) 195.1134, found 195.1127.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found in the online version, at https://doi.org/10.1016/j.tet.2018.03.003. These data include MOL files and InChiKeys of the most important compounds described in this article.

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