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Synthesis of α-Hydroxycarboxylic Acid Anilides via Copper-Catalyzed C–N Coupling of α-Hydroxyamides with Aryl Halides

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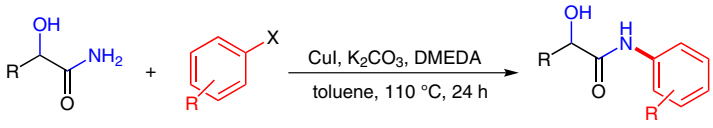

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Abstract The synthesis of highly important α-hydroxycarboxylic acid anilides via copper-catalyzed chemoselective C–N coupling reactions of α-hydroxyamides and aryl halides is described. This highly selective N-arylation process demonstrates wide substrate scope, cost savings and easy operation. In addition, the chirality of L-3-phenyllactamide is preserved during the reaction.

Key words α-hydroxycarboxylic acid anilides, copper, cross-coupling, α-hydroxyamides, catalysis, chemoselectivity

α-Hydroxycarboxylic acid anilides are used widely in medicine and agriculture (Figure 1). So far as lactic acid anilides are concerned, both naproanilide[1] and clomeprop[2] exhibit highly selective herbicidal activities in rice fields. Iopamidol[3] and ioglucomide[4] are non-ionic iodinated contrast agents, commonly used in radiology, whilst *p*-lactophenetide has analgesic and antipyretic activity.[5] Bicalutamide is an oral non-steroidal anti-androgen used in the treatment of prostate cancer,[6] and hirsutism[7] and hydroxyflutamide are other examples of commonly used anti-androgen agents.[8]

In addition, many further examples of bioactive 3-aryllactic acid anilides have been discovered. Diltiazem, which is marketed as a single 2*S*,3*S*-diastereomer, has emerged as one of the most important calcium channel blockers in clinical use.[9] Other bioactive compounds belonging to this class of anilides are used as anticancer agents,[10] coagulation factor IXa inhibitors,[11] and as inhibitors of factor Xa for preventing or treating coagulation disorders.[12] Finally, BMS961, a mandelic acid anilide derivative, is a selective agonist of RARγ, a transcriptional regulator.[13]

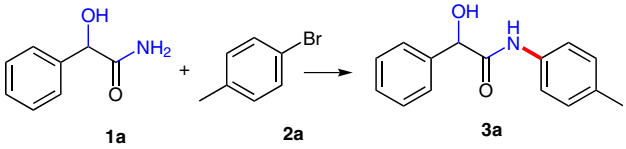
There are three mainly synthetic methods for the preparation of highly valuable α-hydroxycarboxylic acid anilides currently available: (1) the transformation of α-hydroxycarboxylic acids into acyl chlorides using halogenating reagents, followed by condensation of the resulting acyl halides with anilines;[14] (2) the condensation of α-hydroxycarboxylic acids and anilines with the assistance of condensation reagents;[15] (3) titanium tetrachloride ($TiCl_4$) mediated additions of isocyanides to aldehydes.[16]

It should be noted that lactic acid anilides and mandelic acid anilides can be synthesized using other methods. For example, the condensation of mandelic acid and *N*-tosylanilines,[17] the copper-catalyzed transamidation of mandelamide and anilines,[18] the nickel–*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (Ni–TMEDA) catalyzed reduction of 2-oxo-*N*-2-diphenylacetamide,[19] and the coupling of (±)-lactamide and iodobenzene to afford the corresponding racemic lactic acid anilide.[20]

Chemoselective carbon–heteroatom cross-coupling reactions of hydrazides,[21] amino alcohols,[22] *o*-aminobenzamides,[23] aminophenols,[24] phenols and aliphatic alcohols,[25] 2-aminobenzimidazoles,[26] and α-aminoamides[27] have been successfully developed. Hence it is worthwhile to further study chemoselective C–N cross-coupling reactions of α-hydroxyamides, which have two types of nucleophilic group: acylamino and hydroxy.

In continuation of our studies on coupling reactions,[27,28] and in view of the importance of α-hydroxycarboxylic acid anilides and the practicality of Ullmann-type C–N coupling reactions,[29] we have investigated chemoselective C–N cross-coupling reactions of α-hydroxyamides for the synthesis of α-hydroxycarboxylic acid anilides, and our results are reported herein.

Table 1 Optimization of the Reaction Conditions for the Coupling of Mandelamide and *p*-Bromotoluene[a]



1a **2a** **3a**

Entry	Solvent	Catalyst	Ligand	Base	Yield (%)[b]
1[c]	toluene	$Pd_2(dba)_3$	JohnPhos	K_2CO_3	–
2	DMF	CuI	DMEDA	K_2CO_3	73
3	DMSO	CuI	DMEDA	K_2CO_3	58
4	1,4-dioxane	CuI	DMEDA	K_2CO_3	87
5	toluene	CuI	DMEDA	K_2CO_3	88
6	toluene	CuBr	DMEDA	K_2CO_3	53
7	toluene	CuCl	DMEDA	K_2CO_3	58
8	toluene	CuI	TMEDA	K_2CO_3	80
9	toluene	CuI	phenanthroline	K_2CO_3	70
10	toluene	CuI	L-proline	K_2CO_3	26
11	toluene	CuI	BINOL	K_2CO_3	40
12	toluene	CuI	–	K_2CO_3	53
13	toluene	CuI	DMEDA	Cs_2CO_3	81
14	toluene	CuI	DMEDA	K_3PO_4	67
15	toluene	CuI	DMEDA	KOH	trace
16	toluene	CuI	DMEDA	*t*-BuOK	trace
17[d]	toluene	CuI	DMEDA	K_2CO_3	60
18[e]	toluene	CuI	DMEDA	K_2CO_3	89
19[f]	toluene	CuI	DMEDA	K_2CO_3	58
20[g]	toluene	CuI	DMEDA	K_2CO_3	64
21[h]	toluene	CuI	DMEDA	K_2CO_3	86
22[i]	toluene	CuI	DMEDA	K_2CO_3	78

[a] Reaction conditions: mandelamide (1.2 mmol), *p*-bromotoluene (1.0 mmol), CuI (0.05 mmol), K_2CO_3 (2.0 mmol), DMEDA (0.1 mmol), toluene (5 mL), 110 °C, 24 h (unless otherwise noted).
[b] Yield of isolated product.
[c] An intractable reaction mixture was obtained.
[d] Reaction time was 15 h.
[e] Reaction time was 48 h.
[f] Reaction run at 90 °C.
[g] Reaction run at 120 °C.
[h] Mandelamide (1.0 mmol) and *p*-bromotoluene (1.0 mmol) were used.
[i] Mandelamide (1.0 mmol) and *p*-bromotoluene (1.2 mmol) were used.

DL-mandelamide and *p*-bromotoluene were chosen as model substrates in order to investigate the coupling reaction (Table 1). Initially, the cross-coupling of these substrates was performed using tris(dibenzylideneacetone)dipalladium(0) [$Pd_2(dba)_3$] as the catalyst and 2-(di-*tert*-butylphosphino)biphenyl (JohnPhos) as the ligand, however, the reaction mixture proved intractable and no product was isolated (Table 1, entry 1). Other palladium catalytic systems were examined, which were equally unsuccessful, the reasons probably being due to the similar acidities of the acylamino and hydroxy groups in mandelamide,[30,31] and enolization.[32]

Next, an Ullmann-type coupling reaction was adopted for the desired transformation. Under common Ullmann-type reaction conditions, the target product, 2-hydroxy-2-phenyl-*N*-(*p*-tolyl)acetamide, was obtained in 73% yield (Table 1, entry 2). Furthermore, unwanted *o*-phenylation products were not detected.

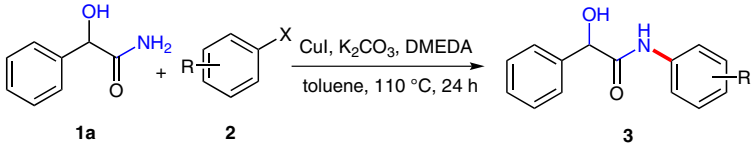
Examination of different solvents demonstrated that weakly polar non-protic solvents were more suitable for the coupling reaction (Table 1, entries 2–5), with toluene giving the highest yield among those tested (Table 1, entry 5). Copper sources such as copper(I) bromide (CuBr) and copper(I) chloride (CuCl) (Table 1, entries 6 and 7), and other ligands including *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), phenanthroline, L-proline and 1,1′-bi-2-naphthol (BINOL) (Table 1, entries 8–11) all gave poorer results. In contrast to C–N coupling reactions of α-aminoamides,[29] the use of a copper catalyst (CuI) without a ligand gave a moderate yield of the desired product (Table 1, entry 12).

Weak bases such as cesium carbonate (Cs_2CO_3) and potassium phosphate (K_3PO_4) gave lower yields compared to potassium carbonate (K_2CO_3) (Table 1, entries 13 and 14 vs 5), whilst strong bases including potassium hydroxide (KOH) and potassium *tert*-butoxide (*t*-BuOK) resulted in only trace amounts of the desired product (Table 1, entries 15 and 16). Shortening the reaction time to 15 hours resulted in a lower yield (Table 1, entry 17), and doubling the reaction time gave only a marginal increase in the amount of product (Table 1, entry 18). Tuning the temperature (Table 1, entries 19 and 20) and manipulating the ratio of mandelamide and *p*-bromotoluene (Table 1, entries 5 vs 21 and 22) were not beneficial to the reaction outcome.

With optimized reaction conditions in hand, we next performed reactions between various aryl halides and mandelamide (Table 2). The position of the substituents on the aromatic ring of the aryl bromide had an obvious influence on the results (Table 2, entries 2 and 3). The use of *m*-bromotoluene resulted in a lower yield than that obtained with *p*-bromotoluene (Table 2, entries 2 vs 1); *o*-bromotoluene was the poorest substrate among the methyl-substituted aryl bromides examined (Table 2, entry 3). The coupling reaction with bromobenzene also gave a poorer result (72% yield) (Table 2, entries 4 vs 1), whilst chlorobenzene afforded a substantially lower 18% yield (Table 2, entries 5 vs 4). In contrast, iodobenzene proved to be a better substrate (Table 2, entry 6).

From the above-described results, it appears that substrates with weak electron-donating groups promote this coupling reaction. Both the *m*- and *p*-isomers of bromo- and iodotoluenes offered better yields than those obtained from bromo- and iodobenzene, respectively (Table 2, entries 1 and 2 vs 4, and entries 7 and 8 vs 6). However, it

Table 2 Reactions of Mandelamide and Different Aryl Halides[a]



1a 2 3

Entry	ArX	Product	Yield (%)[b]
1	4-MeC_6H_4Br (**2a**)	**3a**	88
2	3-MeC_6H_4Br (**2b**)	**3b**	82
3	2-MeC_6H_4Br (**2c**)	**3c**	60
4	PhBr (**2d**)	**3d**	72
5	PhCl (**2e**)	**3d**	18
6	PhI (**2f**)	**3d**	79
7	3-MeC_6H_4I (**2g**)	**3b**	84
8	4-MeC_6H_4I (**2h**)	**3a**	90
9	4-$MeOC_6H_4I$ (**2i**)	**3e**	81
10	4-$O_2NC_6H_4Br$ (**2j**)	**3f**	trace
11	2-ClC_6H_4I (**2k**)	**3g**	42

[a] Reaction conditions: mandelamide (1.2 mmol), aryl halide (1.0 mmol), CuI (0.05 mmol), K_2CO_3 (2.0 mmol), DMEDA (0.1 mmol), toluene (5 mL), 110 °C, 24 h.
[b] Yield of isolated product.

should be noted that an aryl halide with a strong electron-donating group such as methoxy gave a slightly lower yield than those with a weak example (Table 2, entry 9).

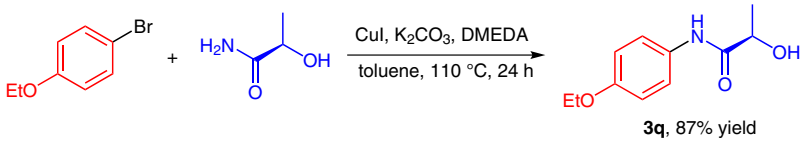
In general, electron-withdrawing groups on aryl halides favor copper-catalyzed C–N cross-coupling reactions.[22] However, 1-bromo-4-nitrobenzene gave only a trace of product in this coupling reaction (Table 2, entry 10). *o*-Chloroiodobenzene also gave the corresponding N-arylated product, but in a lower yield (Table 2, entry 11) due to steric hindrance and the poorer reactivity of the *ortho*-chloro substituent.

In the next step, the reactions of various α-hydroxyamides with iodobenzene were examined (Table 3). Except for *p*-bromomandelamide, which gave a moderate yield, all the mandelamides afforded the target products in good to high yields (Table 3, entries 1–8). Interestingly, a mandelamide with an *ortho*-substituent also gave a good yield of the expected product (Table 3, entries 4 vs 3). This is probably due to the fact that the substituent is placed far enough away from the reaction site and thus the effect of its steric hindrance is marginal.

It should also be mentioned that *p*-bromomandelamide gave a lower yield, probably because the highly active bromo group of this substrate resulted in a self-coupling reaction (Table 3, entry 6). The product of the coupling of lactamide and iodobenzene (Table 3, entry 7) is the core structure of three drugs, namely naproanilide, clomeprop and *p*-lactophenetide. The coupling of DL-3-phenyllactamide with iodobenzene afforded the target product in a very high yield of 97% (Table 3, entry 8).

In view of the satisfying reaction result of DL-3-phenyllactamide (see Table 3, entry 8), both the L- and DL-isomers were examined in reactions with three different aryl iodides (Table 4). The L-isomer gave yields similar to those obtained with the DL-isomer (Table 4, entries 1–6). Delightfully, all the L-3-phenyllactic acid anilides were formed with extremely high enantioselectivities (Table 4, entries 2, 4 and 6), and no obvious racemization occurred under the reaction conditions.

The analgesic and antipyretic agent (*R*)-*p*-lactophenetide (**3q**)[5] was easily prepared in 87% yield using our reported method (Scheme 1).



3q, 87% yield

Scheme 1 Synthesis of (*R*)-*p*-lactophenetide (**3q**)

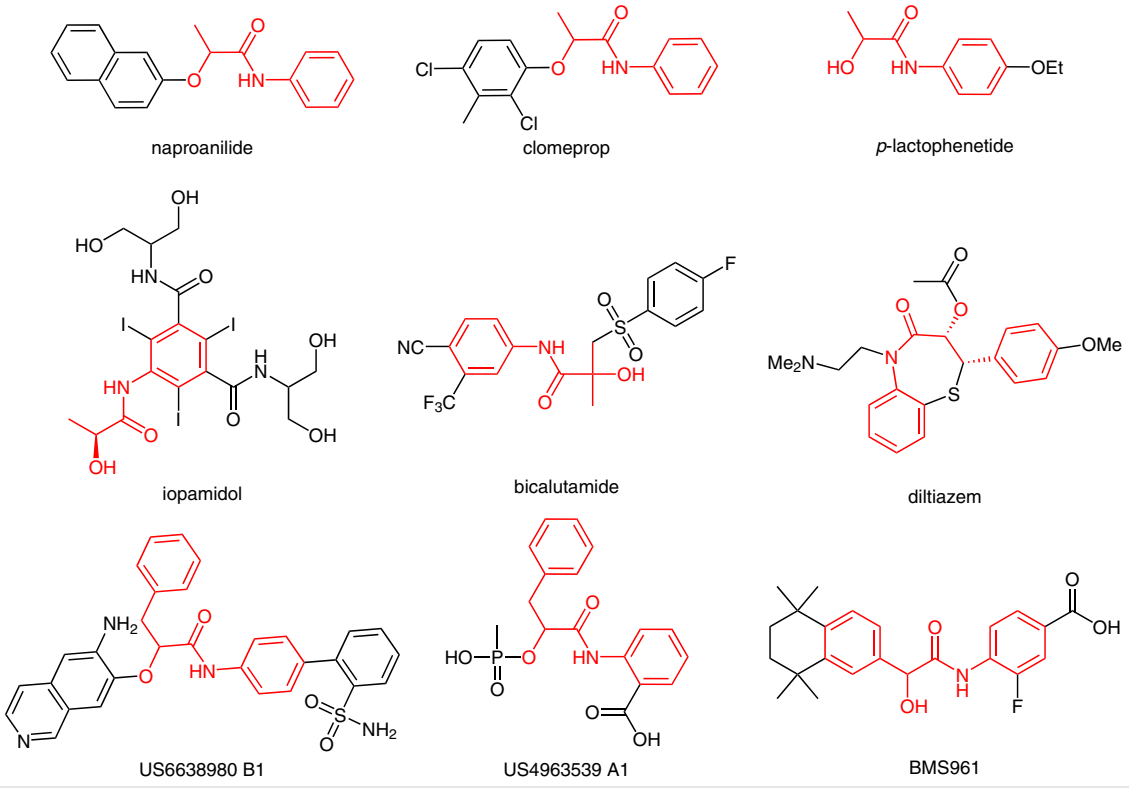
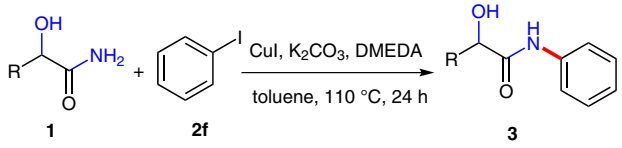


Figure 1 Some representative α-hydroxycarboxylic acid anilides

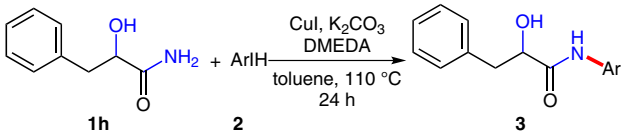
Table 3 Reactions of Different α-Hydroxyamides with Iodobenzene[a]



Entry	R	Product	Yield (%)[b]
1	Ph (**1a**)	**3d**	76
2	4-BnOC$_6$H$_4$ (**1b**)	**3h**	84
3	4-ClC$_6$H$_4$ (**1c**)	**3i**	93
4	2-ClC$_6$H$_4$ (**1d**)	**3j**	87
5	3-ClC$_6$H$_4$ (**1e**)	**3k**	78
6	4-BrC$_6$H$_4$ (**1f**)	**3l**	58
7	Me (**1g**)	**3m**	74
8	PhCH$_2$ (**1h**)	**3n**	97

[a] Reaction conditions: α-hydroxyamide (1.2 mmol), iodobenzene (1.0 mmol), CuI (0.05 mmol), K_2CO_3 (2.0 mmol), DMEDA (0.1 mmol), toluene (5 mL), 110 °C, 24 h.
[b] Yield of isolated product.

Table 4 Reactions of DL- and L-3-Phenyllactamide with Different Aryl Iodides[a]



Entry	Isomer (**1h**)	Ar	Product	Yield (%)[b]	ee (%)[c]
1	DL	Ph (**2f**)	DL-**3n**	97	–
2	L	Ph (**2f**)	L-**3n**	96	99
3	DL	4-MeC$_6$H$_4$ (**2h**)	DL-**3o**	92	–
4	L	4-MeC$_6$H$_4$ (**2h**)	L-**3o**	95	93
5	DL	4-MeOC$_6$H$_4$ (**2i**)	DL-**3p**	97	–
6	L	4-MeOC$_6$H$_4$ (**2i**)	L-**3p**	94	95

[a] Reaction conditions: DL- or L-3-phenyllactamide (1.2 mmol), aryl halide (1.0 mmol), CuI (0.05 mmol), K_2CO_3 (2.0 mmol), DMEDA (0.1 mmol), toluene (5 mL), 110 °C, 24 h.
[b] Yield of isolated product.
[c] Enantiomeric excess determined by chiral HPLC.

In conclusion, the synthesis of valuable α-hydroxycarboxylic acid anilides via the chemoselective copper(I) iodide catalyzed C–N cross-coupling of α-hydroxyamides with aryl halides has been studied. All the α-hydroxyamides gave only α-hydroxycarboxylic acid anilides without any of the corresponding O-arylated products being detect-

ed, thereby verifying that the selectivity of the N-arylation of α-hydroxyamides is excellent. Moreover, the configuration of the chiral 3-phenyllactamide substrate is maintained during the coupling reaction.

All reactions were carried out under an argon atmosphere. All glassware was dried in an electric oven at 120 °C. All chemicals were purchased from Alfa Aesar, Shanghai Aladdin Reagent Co., Ltd, and Chengdu Changzheng Chemical Co., and were used as received. Petroleum ether (PE) refers to the fraction boiling in the 60–90 °C range. Products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy and by HRMS, unless otherwise mentioned. Compounds **3a**,[19] **3c**,[33] **3d**,[18] **3e**,[34] **3g**,[33] **3i**,[35] **3k**,[36] **3l**,[37] DL-**3n**,[16a] L-**3n**,[38] DL-**3p**[39] and **3q**[40] have been described in the literature. Melting points were determined using a Shanghai Jingke SGW X-4 microscope melting point apparatus. Optical rotations were recorded on a Rudolph Research Analytical Autopol IV auto rotation instrument (Na D line, cell length = 10 cm, λ = 589 nm). IR spectra were recorded on a Bruker Tensor-27 infrared spectrometer. NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer or a Bruker Avance III 400 MHz spectrometer. ^{1}H NMR chemical shifts (δ) are reported in parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm), DMSO (2.50 ppm) or acetone (2.05 ppm) in the deuterated solvent, unless otherwise stated. ^{13}C NMR spectra are reported in ppm relative to deuterated chloroform (77.2 ppm), DMSO (39.5 ppm) or acetone (206.7 ppm for C=O), unless otherwise stated, and were obtained with ^{1}H decoupling. High-resolution mass spectra were recorded on a Shimadzu LCMS-IT-TOF instrument. Chiral HPLC analyses were performed by liquid chromatography on a Shimadzu LC-10ATVP with a Daicel Chiralcel OD-H chiral column (4.6 mm × 250 mm × 5 μm).

N-*p*-Tolylmandelamide (3a); Typical Procedure

To an oven-dried test tube possessing a ground joint neck and containing a magnetic stir bar was added mandelamide (1.2 mmol), *p*-bromotoluene (1 mmol), CuI (0.05 mmol), K_2CO_3 (2 mmol), DMEDA (0.1 mmol) and toluene (5 mL). The test tube was sealed with a rubber sleeve stopper and then evacuated and refilled with argon (three cycles). The test tube was placed in an oil bath preheated to 110 °C for 24 h. After cooling, the reaction mixture was quenched with H_2O (5 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was dried over anhydrous $MgSO_4$, filtered and the filtrate concentrated under vacuum. The residue was purified by silica gel column chromatography (mixed solvent of PE–EtOAc, 5:1 to 2:1) to give *N*-*p*-tolylmandelamide (**3a**) (0.2122 mg, 88%) as a white solid.

N-*m*-Tolylmandelamide (3b)

Yield: 0.1976 g (82%); white solid; mp 166–169 °C.

IR (KBr): 3307, 3210, 1652, 1613, 1564, 1494, 1304, 1071, 777, 771, 693 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.82 (s, 1 H), 7.53–7.46 (m, 4 H), 7.37 (t, *J* = 16.0 Hz, 2 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 16.0 Hz, 1 H), 6.87 (d, *J* = 8.0 Hz, 1 H), 6.42 (d, *J* = 4.0 Hz, 1 H), 5.09 (d, *J* = 4.0 Hz, 1 H), 2.25 (s, 3 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 171.53 (s), 141.34 (s), 138.89 (s), 138.26 (s), 128.93 (s), 128.55 (s), 128.06 (s), 127.01 (s), 124.67 (s), 120.61 (s), 117.28 (s), 74.41 (s), 21.64 (s).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NO_2Na$: 264.0995; found: 264.0983.

N-Phenyl-*p*-benzyloxymandelamide (3h)

Yield: 0.2798 g (84%); pale yellow solid; mp 110–113 °C.

IR (KBr): 3275, 1637, 1595, 1533, 1446, 1246, 1174, 1067, 1008, 754, 696 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (s, 1 H), 7.58 (t, *J* = 8.0 Hz, 2 H), 7.45–7.36 (m, 6 H), 7.35–7.31 (m, 3 H), 7.15 (d, *J* = 4.0 Hz, 1 H), 7.01 (q, *J* = 8.0 Hz, 2 H), 5.14 (d, *J* = 4.0 Hz, 1 H), 5.08 (s, 2 H), 3.37 (d, *J* = 4.0 Hz, 1 H).

^{13}C NMR (101 MHz, acetone-d_6): δ = 170.81 (s), 158.63 (s), 138.70 (s), 137.49 (s), 133.08 (s), 128.64 (s), 128.39 (s), 127.94 (s), 127.71 (s), 127.50 (s), 123.59 (s), 119.39 (d, *J* = 9.0 Hz), 114.54 (d, *J* = 15.0 Hz), 73.97 (s), 69.48 (s).

HRMS (ESI-TOF): *m*/*z* [M – H]$^+$ calcd for $C_{21}H_{18}NO_3$: 332.1292; found: 332.1279.

N-Phenyl-*o*-chloromandelamide (3j)

Yield: 0.2271 g (87%); pale yellow solid; mp 147–149 °C.

IR (KBr): 3308, 1659, 1600, 1546, 1445, 1070, 755, 696 cm^{-1}.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.02 (s, 1 H), 7.73 (d, *J* = 10.4 Hz, 2 H), 7.58 (t, *J* = 12.0 Hz, 1 H), 7.46–7.43 (m, 1 H), 7.36–7.28 (m, 4 H), 7.09 (d, *J* = 9.6 Hz, 1 H), 6.65 (d, *J* = 6.8 Hz, 1 H), 5.48 (d, *J* = 6.8 Hz, 1 H).

^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.47 (s), 139.16 (s), 138.95 (s), 133.04 (s), 130.05–129.41 (m), 129.08 (s), 127.65 (s), 124.10 (s), 120.24 (s), 71.60 (s).

HRMS (ESI-TOF): *m*/*z* [M – H]$^+$ calcd for $C_{14}H_{11}ClNO_2$: 260.0484; found: 260.0487.

(*R*)-*N*-Phenyllactamide (3m)

Yield: 0.1221 g (74%); white solid; mp 45–48 °C; $[\alpha]_D^{12}$ +9.6 (*c* 0.68, acetone).

IR (KBr): 3294, 1656, 1601, 1538, 1496, 1445, 1321, 1123, 1076, 1042, 756, 694 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.70 (s, 1 H), 7.54 (t, *J* = 8.0 Hz, 2 H), 7.34–7.29 (m, 2 H), 7.15 (t, *J* = 12.0 Hz, 1 H), 4.33 (q, *J* = 12.0 Hz, 1 H), 4.19 (s, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.36 (s), 137.02 (s), 129.06 (s), 124.75 (s), 120.03 (s), 68.70 (s), 21.08 (d, *J* = 9.7 Hz).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_9H_{11}NO_2Na$: 188.0682; found: 188.0657.

N-*p*-Tolyl-DL-3-phenyllactamide (DL-3o)

Yield: 0.2346 g (92%); white solid; mp 128–130 °C.

IR (KBr): 3323, 1652, 1596, 1549, 1104, 1075, 821, 726, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.28–7.25 (m, 3 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 4.40 (t, *J* = 8.0 Hz, 1 H), 3.34 (dd, *J* = 4.0, 4.0 Hz, 1 H), 2.99–2.93 (m, 1 H), 2.64 (d, *J* = 4.0 Hz, 1 H), 2.30 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.38 (s), 136.65 (s), 134.53 (s), 134.23 (s), 129.55 (d, *J* = 3.4 Hz), 128.92 (s), 127.20 (s), 119.88 (s), 40.88 (s), 20.91 (s).

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{17}NO_2Na$: 278.1151; found: 278.1107.

HPLC (Chiracel OD-H): t_R = 45.70 min (*S* form), 54.04 min (*R* form) (*n*-hexane–propan-2-ol, 8:2).

***N*-*p*-Tolyl-L-3-phenyllactamide (L-3o)**

Yield: 0.2423 g (95%); white solid; mp 143–145 °C; $[\alpha]_D^{12}$ –60.5 (*c* 0.43, acetone).

IR (KBr): 3323, 1652, 1596, 1549, 1104, 1075, 821, 726, 698 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.22 (s, 1 H), 7.39 (d, *J* = 8.0 Hz, 2 H), 7.35 (d, *J* = 8.0 Hz, 2 H), 7.28–7.25 (m, 3 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 4.40 (t, *J* = 8.0 Hz, 1 H), 3.34 (dd, *J* = 4.0, 4.0 Hz, 1 H), 2.99–2.93 (m, 1 H), 2.64 (d, *J* = 4.0 Hz, 1 H), 2.30 (s, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.38 (s), 136.65 (s), 134.53 (s), 134.23 (s), 129.55 (d, *J* = 3.4 Hz), 128.92 (s), 127.20 (s), 119.88 (s), 40.88 (s), 20.91 (s).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{17}NO_2Na$: 278.1151; found: 278.1107.

HPLC (Chiracel OD-H): 93% ee (*S* form) (*n*-hexane–propan-2-ol, 8:2).

***N*-*p*-Methoxyphenyl-L-3-phenyllactamide (L-3p)**

Yield: 0.2547 g (94%); white solid; mp 126–128 °C; $[\alpha]_D^{12}$ –52.0 (*c* 0.40, acetone).

IR (KBr): 3300, 1652, 1550, 1510, 1247, 1110, 1033, 836, 736, 696 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.39 (t, *J* = 8.0 Hz, 2 H), 7.31–7.29 (m, 2 H), 7.26–7.23 (m, 3 H), 6.84–6.82 (m, 2 H), 4.38 (t, *J* = 8.0 Hz, 1 H), 3.76 (s, 3 H), 3.31 (dd, *J* = 4.0, 4.0 Hz, 1 H), 2.97–2.94 (m, 1 H), 2.67 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 170.32 (s), 156.56 (s), 136.68 (s), 130.22 (s), 129.57 (s), 128.90 (s), 127.19 (s), 121.60 (s), 114.17 (s), 73.16 (s), 55.49 (s), 40.89 (s).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{17}NO_3Na$: 294.1101; found: 294.1057.

HPLC (Chiracel OD-H): 95% ee (*S* form), (*n*-hexane–propan-2-ol, 7:3).

***N*-*p*-Ethoxyphenyl-L-lactamide [(*R*)-*p*-lactophenetide] (3q)**

Yield: 0.1818 g (87%); white solid; mp 101–105 °C; $[\alpha]_D^{12}$ +15.5 (*c* 0.68, acetone).

IR (KBr): 3274, 2979, 1648, 1553, 1510, 1246, 1114, 1043, 837, 786, 680, 521 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.42 (s, 1 H), 7.43–7.41 (m, 2 H), 6.85–6.82 (m, 2 H), 4.33–4.30 (m, 1 H), 4.02–3.96 (m, 2 H), 3.42 (d, *J* = 4.0 Hz, 1 H), 1.50 (d, *J* = 8.0 Hz, 3 H), 1.41 (q, *J* = 12.0 Hz, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.50 (s), 155.94 (s), 130.18 (s), 121.57 (s), 114.81 (s), 68.79 (s), 63.71 (s), 29.86–29.35 (m), 21.19 (s), 14.83 (s).

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{15}NO_3Na$: 232.0944; found: 232.0925.

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Supporting Information

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