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COPPER(I) IODIDE-CATALYZED COUPLING REACTION OF HALOINDOLES WITH α-AMINO ACIDS

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Abstract – Copper(I) iodide-catalyzed amination of haloindoles with amino acids using a combination of Cs_2CO_3 in DMSO was explored. Amino acid derivatives with indole skeleton were smoothly afforded in moderate yields.

INTRODUCTION

(–)-Indolactam-V (**1**), isolated from *Streptoverticillium blastmyceticum* NA 34-17,[1] is a 9-membered cyclic dipeptide of valine bridged to the 4 position of tryptophan and constitutes the core unit of tereocidins (lyngbyatoxins)[2] as well-known tumor promoters (Figure 1). **1** itself is also an activator of protein kinase C[3] and is biosynthesized from three amino acid units of L-tryptophan, L-valine, and L-methionine.[4]

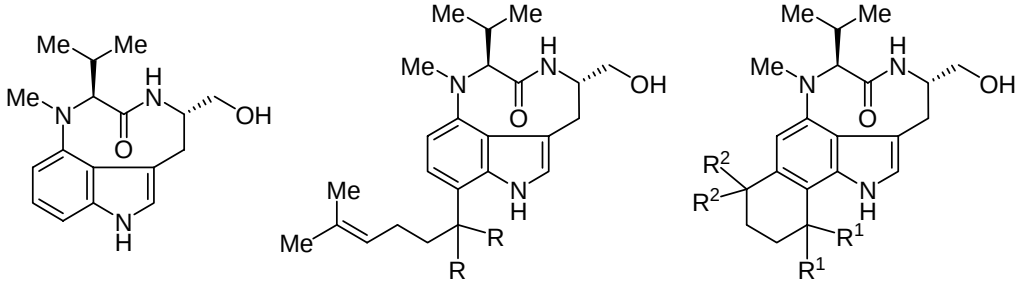
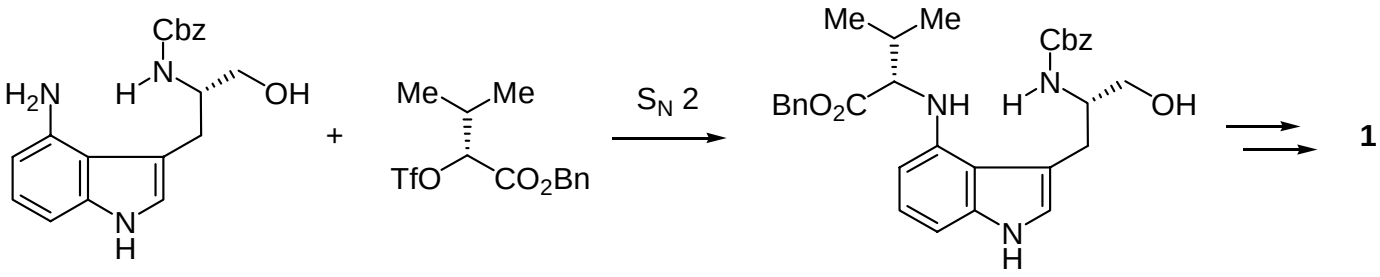


Figure 1. Structures of (–)-indolactam-V (**1**) and tereocidins

Until now the total synthesis of indolactam-V (**1**) has been reported by eight groups,[5] among which five ones[5a-5e] succeed in the synthesis of the optically active form. Interestingly, all of the groups used the substitution reaction of 2-hydroxy-3-methylbutanoic acid derivatives with 4-aminotryptophanol derivatives for the introduction of valine unit to indole skeleton as a common synthetic strategy, as shown in Scheme 1. To our knowledge, access by *N*-alkylation of valine with 4-haloindole has never been reported.

Scheme 1. A typical strategy for the introduction of valine unit to indole skeleton toward (–)-indolactam-V (**1**) synthesis in literatures



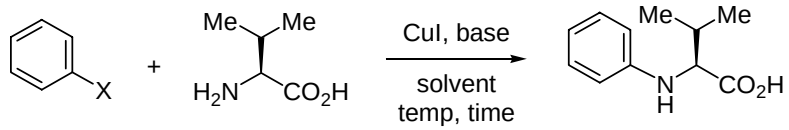
Ma *et al.*[6] had synthesized benzolactam-V8 by coupling reaction of 2-iodobenzyl alcohol with valine in the presence of copper(I) iodide (CuI), to give *N*-[2-(hydroxymethyl)phenyl]valine in high yield. Twieg and Lu[7] had also reported similar CuI-catalyzed reaction using dimethylaminoethanol as a ligand under aqueous conditions; however, no application to haloindoles has been reported. On the other hand, Buchwald and co-workers had developed coupling reactions of a variety of amines with 5-bromoindole in the presence of palladium (Pd) catalyst,[8] and with iodobenzene derivatives in the presence of CuI,[9] respectively. A similar CuI-mediated amination of aryl iodides had also been examined by Fukuyama and co-workers.[10] However, amino acid derivatives had never been included as amine sources in these two groups. In this paper we present the CuI-catalyzed *N*-alkylation of amino acids with haloindoles using a combination of cesium carbonate (Cs_2CO_3) in dimethyl sulfoxide (DMSO).

RESULTS AND DISCUSSION

At first, we followed the CuI-catalyzed coupling reaction of iodo- (**2**) or bromobenzenes (**3**) with L-valine under the reported conditions[6] with some modifications (Table 1). The reaction in the presence of CuI (20 mol%) and potassium carbonate (K_2CO_3) (2 eq) in dimethylacetaminde (DMA) at 90 °C for 48 h afforded a coupling product **4** in 81% yield, as in the literature[6] (entry 1). Reaction at higher temperature lowered the yield (entry 2). The reaction in dimethyl sulfoxide (DMSO) in place of DMA gave **4** in slightly higher 86% yield (entry 3), whereas the use of dimethylimidazolidinone (DMI) resulted in lowering the yield (entry 4).

Next, effect of base on the CuI-catalyzed reaction in DMSO was examined (entries 5 and 6). The better yield was given in the use of Cs_2CO_3, in which a coupling product **4** was formed in 93% yield (entry 6). The same result was obtained even in the use of smaller amounts of the catalyst and the base (entries 7-9), indicating that the combination of CuI (3-6 mol%) and Cs_2CO_3 (1.5-2.0 eq) in DMSO could be accepted as optimized conditions in the coupling reaction of iodobenzene (**2**) and L-valine. Effectiveness of the combination of Cs_2CO_3 in DMSO was also shown in the displacement of iodobenzene (**2**) to bromobenzene (**3**) as a halobenzene substrate (entries 10-12).

Table 1. CuI-catalyzed amination of halobenzenes with L-valine



2 : X = I
3 : X = Br

(1.2 eq)

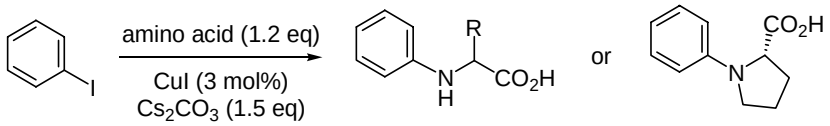
4

Entry	**2** or **3**	CuI (mol%)	Base (eq)	Solvent	Temp (°C)	Time (h)	**4** (%)
1	**2**	20	K_2CO_3 (2)	DMA	90	48	81
2	**2**	20	K_2CO_3 (2)	DMA	150	36	63
3	**2**	20	K_2CO_3 (2)	DMSO	90	48	86
4	**2**	20	K_2CO_3 (2)	DMI	90	48	40
5	**2**	20	K_3PO_4 (2)	DMSO	90	48	80
6	**2**	20	Cs_2CO_3 (2)	DMSO	90	48	93
7	**2**	6	Cs_2CO_3 (2)	DMSO	90	48	94
8	**2**	6	Cs_2CO_3 (1.5)	DMSO	90	48	94
9	**2**	3	Cs_2CO_3 (1.5)	DMSO	90	48	94
10	**3**	20	Cs_2CO_3 (2)	DMA	90	48	84
11	**3**	20	Cs_2CO_3 (2)	DMSO	90	48	93
12	**3**	10	Cs_2CO_3 (1.5)	DMSO	90	48	93

[a] Ma *et al.*[6] reported the formation of **4** in the similar yield (83%) even in the use of smaller amounts of CuI (10 mol%).

The CuI-catalyzed amination of iodobenzene (**2**) with amino acids other than L-valine under the conditions optimized above were further examined (Table 2). Excellent to good yields, comparable to Ma's results, were obtained.

Table 2. CuI-catalyzed amination of iodobenzene (**2**) with various amino acids.



2

5 : R = β-CH_2Ph
6 : R = α-$(CH_2)_2$SMe

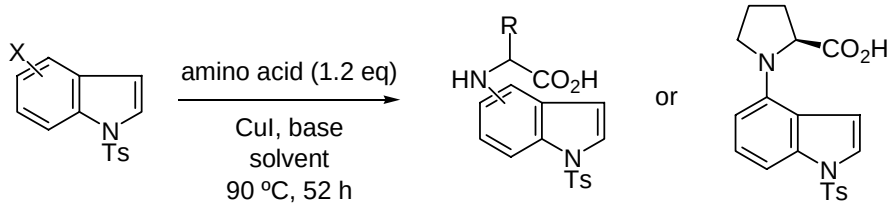
7

Entry	Amino Acid	Product (%)	Ma's result (%)[6]
1	L-Phenylalanine	**5** (94)	92
2	D-Methionine	**6** (86)	76
3	L-Proline	**7** (67)	80

As parallel experiments, we examined the CuI-catalyzed amination of *N*-tosyl protected haloindoles in place of halobenzene (Table 3). The reaction of 4-iodo- **8**[11] or 4-bromoindoles **9**[12] with L-valine based on the Ma's protocol[6] afforded 4-aminated indole **11** in moderate yields in spite of the character of

halogen substituted (entries 1-2). The use of stoichiometric amount of CuI resulted in lowering the yield (entry 3). Effects of base and solvent on the reactions were also examined using 4-bromoindole **9** (entries 4-10) and the combination of Cs_2CO_3 (1.5 eq) in DMSO was found to be the most suitable, where 3 mol% of CuI could act effectively for the coupling reaction (entry 10). This optimized condition was applied to the reactions of 4-bromo- **9** or 5-bromoindoles **10**[13] using other amino acids (entries 11-15). Although no formation occurred in the case of L-proline (entry 13), smooth coupling reactions were generally observed.

Table 3. CuI-catalyzed amination of haloindoles with amino acids.



8 : 4-I
9 : 4-Br
10 : 5-Br

11 : 4-(β-$CHMe_2$)
12 : 4-(β-CH_2Ph)
13 : 4-(α-$(CH_2)_2SMe$)
14 : 5-(β-$CHMe_2$)
15 : 5-(β-CH_2Ph)

16

Entry	Haloindole	Amino acid	CuI (mol%)	Base (eq)	Solvent	Product (%)
1	**8**	L-valine	20	K_2CO_3 (2)	DMA	**11** (43)
2	**9**	L-valine	20	K_2CO_3 (2)	DMA	**11** (45)
3	**9**	L-valine	100	K_2CO_3 (2)	DMA	**11** (9)
4	**9**	L-valine	20	K_2CO_3 (2)	DMF	**11** (9)
5	**9**	L-valine	20	K_2CO_3 (2)	DMSO	**11** (51)
6	**9**	L-valine	20	K_3PO_4 (2)	DMA	**11** (23)
7	**9**	L-valine	20	Cs_2CO_3 (2)	DMA	**11** (53)
8	**9**	L-valine	20	Cs_2CO_3 (2)	DMSO	**11** (59)
9	**9**	L-valine	10	Cs_2CO_3 (1.5)	DMSO	**11** (62)
10	**9**	L-valine	3	Cs_2CO_3 (1.5)	DMSO	**11** (63)
11	**9**	L-phenylalanine	10	Cs_2CO_3 (1.5)	DMSO	**12** (62)
12	**9**	D-methionine	10	Cs_2CO_3 (1.5)	DMSO	**13** (40)
13	**9**	L-proline	10	Cs_2CO_3 (1.5)	DMSO	**16** (trace)
14	**10**	L-valine	10	Cs_2CO_3 (1.5)	DMSO	**14** (61)
15	**10**	L-phenylalanine	10	Cs_2CO_3 (1.5)	DMSO	**15** (61)

The uses of *N*-free- and *N*-Boc-4-bromoindoles, in place of the *N*-tosylindole, led to poor results (data not shown). The Pd-catalyzed protocol[8] reported by Buchwald's group seems to be an alternative possible method for the introduction of amino acid unit to indole skeleton if amino acid could be used as an amine source. However, treatment of 5-bromo-*N*-tosylindole (**10**) with L-valine under their reported

conditions resulted in no reaction.

CONCLUSION

In summary, modified CuI-catalyzed *N*-alkylation of amino acids with haloaromatics, including haloindoles, using a combination of Cs_2CO_3 in DMSO was explored. It could be reasonably supported by the Ma's results[6] that no racemization occurs in this coupling reaction. At present we are in progress on the elaboration of this method for application to the enantioselective synthesis of (–)-indolactam-V (**1**) and its analogs.

EXPERIMENTAL

General Experimental Procedures. Melting points were determined on a micro melting point hot-stage instrument (Yanagimoto) and are uncorrected. IR spectra were recorded on a JASCO FT/IR-300E spectrophotometer. Specific rotation, $[\alpha]_D$, was recorded on a JASCO DIP-140 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with JEOL JNM ECP 400 and JEOL GSX-500α spectrometers in $CDCl_3$ unless otherwise stated. HRFABMS were perfomed on JEOL JMX-HX 110A spectrometer with *m*-nitrobenzylalcohol as a matrix. For column chromatography silica gel 60 or 60N (spherical, 70-230 mesh, Kanto) was used.

General Procedure for Aminations of Haloaromatics with Amino Acid

A mixture of amino acid (1.2 eq), haloaromatics (1 mmol), Cs_2CO_3 (1.5 eq), CuI (3 or 10 mol%) and DMSO (1 mL) in a sealed tube was stirred at 90 °C for 48 h under argon atmosphere and diluted AcOEt (10 mL) and H_2O (10 mL). After removal of organic layer, the aqueous layer was acidified with 6N HCl to pH 3 under ice-cooling and extracted with AcOEt (20 mL x 4). The combined organic layers were washed with brine (15 mL), dried over Na_2SO_4, and evaporated. Purification of the residue by column chromatography (SiO_2, *n*-hexane/AcOEt) afforded an aminated benzene or indole.

(*S*)-3-Methyl-2-(phenylamino)butanoic Acid [(*S*)-4] (Entry 9 in Table 1)

The title compound was obtained as colorless needles [mp 118.5-119.0 °C (lit.,[7] 116.9-118.5 °C)]; IR (ATR) ν_{max} 3257, 3250-2800, 1700 cm^{-1}; ^{1}H-NMR (400 MHz) δ: 1.06 (3H, d, J = 7.0 Hz, C_4-H), 1.10 (3H, d, J = 7.0 Hz, C_3-CH_3), 2.20-2.28 (1H, m, C_3-H), 3.86 (1H, d, J = 5.3 Hz, C_2-H), 6.66 (2H, dd, J = 7.7, 0.9 Hz, Ar-H), 6.80 (1H, td, J = 7.7, 7.7, 0.9 Hz, Ar-H), 7.20 (2H, td, J = 7.7, 7.7, 0.9 Hz, Ar-H); $[\alpha]_D^{24}$ –48.8° (*c* 0.415, $CHCl_3$) [lit.,[6] $[\alpha]_D^{25}$ –49.1° (*c* 1.00, $CHCl_3$) for (*S*)-**4**].

(*S*)-2-Phenylamino-3-phenylpropanoic Acid [(*S*)-5] (Entry 1 in Table 2)

The title compound was obtained as pale yellow prisms [mp 176-177 °C (lit.,[7] 168.6-169.6 °C)]; IR (ATR) ν_{max} 3257, 3080-2960, 1714 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.91 (1H, dd, *J* = 13.6, 8.1 Hz, C_3-H), 3.01 (1H, dd, *J* = 13.6, 5.6 Hz, C_3-H), 4.06 (1H, dd, *J* = 8.1, 5.6 Hz, 1H, C_2-H), 6.46-6.53 (3H, m, Ar-H), 6.97-7.01 (2H, dd, *J* = 8.6, 7.3 Hz, Ar-H), 7.12-7.17 (1H, m, Ar-H), 7.19-7.26 (4H, m, Ar-H); $[\alpha]_D^{24}$ +2.80° (*c* 0.346, acetone) [lit.,[6] $[\alpha]_D^{25}$ +2.5° (*c* 0.50, acetone) for (*S*)-**5**].

(*R*)-4-Methylthio-2-(phenylamino)butanoic Acid [(*R*)-6] (Entry 2 in Table 2)

The title compound was obtained as pale yellow prisms (mp 141.5-142.5 °C); IR (ATR) ν_{max} 3200-2600, 1566 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.90-2.00 (2H, m, C_3-H), 2.04 (3H, s, S-CH_3), 2.52-2.62 (2H, m, C_4-H), 3.99 (1H, dd, *J* = 8.3, 5.0 Hz, C_2-H), 6.52-6.56 (3H, m, Ar-H), 7.06 (2H, dd, *J* = 7.9, 7.9 Hz, Ar-H); $[\alpha]_D^{22}$ +39.2° (*c* 0.314, acetone) [lit.,[6] $[\alpha]_D^{25}$ –11.8° (*c* 1.0, acetone) for (*S*)-**6**].

(*S*)-1-Phenylpyrrolidine-2-carboxylic Acid [(*S*)-7] (Entry 3 in Table 2)

The title compound was obtained as pale red oil; IR (ATR) ν_{max} 3250-2800, 1711 cm^{-1}; ^{1}H-NMR (400 MHz) δ: 2.05-2.13 (2H, m, C_4-H), 2.26-2.36 (2H, m, C_3-H), 3.31 (1H, dd, *J* = 16.7, 8.4 Hz, C_5-H), 3.62-3.69 (1H, m, C_5-H), 4.19 (1H, dd, *J* = 8.9, 2.8 Hz, C_2-H), 6.64 (2H, dd, *J* = 8.8, 0.9 Hz, Ar-H), 6.80-6.86 (1H, m, Ar-H), 7.24-7.30 (2H, m, Ar-H); $[\alpha]_D^{23}$ –47.2° (*c* 0.370, $CHCl_3$) [lit.,[6] $[\alpha]_D^{25}$ –46.8° (*c* 1.1, $CHCl_3$) for (*S*)-**7**].

(*S*)-3-Methyl-2-[(1-*p*-toluenesulfonylindol-4-yl)amino]butanoic Acid [(*S*)-11] (Entry 9 in Table 3)

The title compound was obtained as pale yellow oil; IR (ATR) ν_{max} 3600-2800, 1709, 1363, 1192, 1165, 1128 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 1.05 (3H, d, *J* = 6.8 Hz, C_4-H), 1.10 (3H, d, *J* = 6.8 Hz, C_3-CH_3), 2.14-2.24 (1H, m, C_3-H), 2.34 (3H, s, Ar-CH_3), 3.89 (1H, d, *J* = 7.0 Hz, C_2-H), 5.21 (1H, br d, *J* = 7.1 Hz, N-H), 6.42 (1H, d, *J* = 8.0 Hz, Ar-H), 7.06 (1H, d, *J* = 3.8 Hz, Ar-H), 7.11 (1H, dd, *J* = 8.0, 8.0 Hz, Ar-H), 7.31-7.37 (3H, m, Ar-H), 7.54 (1H, d, *J* = 3.8 Hz, Ar-H), 7.83 (2H, d, *J* = 8.2 Hz, Ar-H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 19.4, 19.5, 21.4, 31.7, 63.1, 103.9, 104.6, 107.0, 120.1, 124.8, 126.8, 127.7 (C x 2), 130.8 (C x 2), 136.2, 136.6, 142.5, 146.2, 174.8; HRFABMS *m/z*: 386.1301, calcd for $C_{20}H_{22}N_2O_4S$: 386.1300; $[\alpha]_D^{23}$ –13.8° (*c* 0.370, acetone).

(*S*)-3-Phenyl-2-[(1-*p*-toluenesulfonylindol-4-yl)amino]propanoic Acid [(*S*)-12] (Entry 11 in Table 3)

The title compound was obtained as yellow oil; IR (ATR) ν_{max} 3600-2900, 1701, 1362, 1190, 1165, 1128 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 2.32 (3H, s, Ar-CH_3), 3.14 (1H, dd, *J* = 13.7, 7.7 Hz, C_3-H), 3.25 (1H, dd, *J* = 13.7, 5.7 Hz, C_3-H), 4.41 (1H, dd, *J* = 7.5, 5.7 Hz, C_2-H), 5.39 (1H, br s, N-H), 6.40 (1H,

d, *J* = 8.0 Hz, Ar-H), 6.94 (1H, dd, *J* = 3.7, 0.8 Hz, Ar-H), 7.15 (1H, dd, *J* = 8.0, 8.0 Hz, Ar-H), 7.16-7.22 (1H, m, Ar-H), 7.23-7.27 (2H, m, Ar-H), 7.29-7.36 (5H, m, Ar-H), 7.53 (1H, d, *J* = 3.7 Hz, Ar-H); 7.81 (2H, dt, *J* = 8.4, 1.9, 1.9 Hz, Ar-H); ^{13}C-NMR (125 MHz, acetone-d_6) δ: 21.4, 38.9, 58.4, 104.0, 104.5, 106.9, 120.0, 124.8, 126.8, 127.4, 127.7 (C x 2), 129.1 (C x 2), 130.2 (C x 2), 130.8 (C x 2), 136.1, 136.6, 138.5, 141.8, 146.2, 174.5; HRFABMS *m/z*: 434.1291, calcd for $C_{24}H_{22}N_2O_4S$: 434.1300; $[\alpha]_D^{24}$ –212° (*c* 0.201, acetone).

(*R*)-4-Methylthio-2-[(1-*p*-toluenesulfonylindol-4-yl)amino]butanoic Acid [(*R*)-13] (Entry 12 in Table 3)

The title compound was obtained as yellow oil; IR (ATR) ν_{max} 3400-2900 (NH, OH), 1705 (CO), 1363, 1195-1100 ($ArSO_2N$) cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 2.07 (3H, s, S-CH_3), 2.08-2.19 (2H, m, C_3-H), 2.31 (3H, s, Ar-CH_3), 2.64-2.73 (2H, m, C_4-H), 4.32 (1H, dd, *J* = 8.5, 5.0 Hz, C_2-H), 6.39 (1H, d, *J* = 8.0 Hz, Ar-H), 7.01 (1H, dd, *J* = 3.8, 0.8 Hz, Ar-H), 7.12 (1H, dd, *J* = 8.0, 8.0 Hz, Ar-H), 7.30-7.36 (3H, m, Ar-H), 7.53 (1H, d, *J* = 3.8 Hz, Ar-H), 7.82 (2H, d, *J* = 8.6 Hz, Ar-H); ^{13}C-NMR (125 MHz, acetone-d_6) δ: 15.2, 21.4, 31.1, 32.7, 55.8, 104.0, 104.4, 107.1, 120.1, 124.8, 126.8, 127.7 (C x 2), 130.8 (C x 2), 136.2, 136.6, 142.2, 146.2, 175.1; HRFABMS *m/z*: 418.1000, calcd for $C_{20}H_{22}N_2O_4S_2$: 418.1021; $[\alpha]_D^{22}$ +11.7° (*c* 0.410, acetone).

(*S*)-3-Methyl-2-[(1-*p*-toluenesulfonylindol-5-yl)amino]butanoic Acid [(*S*)-14] (Entry 14 in Table 3)

The title compound was obtained as colorless prisms (mp 166.0-167.0 °C); IR (ATR) ν_{max} 3300-3160, 1684, 1371, 1180-1120 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 1.04 (3H, d, *J* = 6.8 Hz, C_4-H), 1.06 (3H, d, *J* = 6.8 Hz, C_3-CH_3), 2.09-2.17 (1H, m, C_3-H), 2.33 (3H, s, Ar-CH_3), 3.80 (1H, d, *J* = 6.2 Hz, C_2-H), 6.59 (1H, dd, *J* = 3.7, 0.7 Hz, Ar-H), 6.76 (1H, d, *J* = 2.3 Hz, Ar-H), 6.84 (1H, dd, *J* = 8.9, 2.3 Hz, Ar-H), 7.33 (2H, d, *J* = 8.3 Hz, Ar-H), 7.52 (1H, d, *J* = 3.7 Hz, Ar-H), 7.74 (1H, dd, *J* = 8.9, 0.7 Hz, Ar-H), 7.79 (2H, d, *J* = 8.3 Hz, Ar-H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 19.1, 19.6, 21.4, 31.9, 63.7, 103.8, 110.3, 114.4, 114.9, 127.7 (C x 3), 128.9, 130.8 (C x 2), 133.2, 136.2, 146.0, 146.1, 174.9; Anal. calcd for $C_{20}H_{22}N_2O_4S$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.17; H, 5.68; N, 7.14; $[\alpha]_D^{24}$ –67.1° (*c* 0.400, acetone).

(*S*)-3-Phenyl-2-[(1-*p*-toluenesulfonylindol-5-yl)amino]propanoic Acid [(*S*)-15] (Entry 15 in Table 3)

The title compound was obtained as colorless prisms (mp 147.0-147.7 °C); IR (ATR) ν_{max} 3600-3200, 1726, 1370, 1180-1120 cm^{-1}; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 2.33 (3H, s, Ar-CH_3), 3.07 (dd, *J* = 13.7, 7.6 Hz, 1H, C_3-H); 3.20 (1H, dd, *J* = 13.7, 5.8 Hz, C_3-H), 4.32 (1H, dd, *J* = 7.6, 5.8 Hz, C_2-H), 6.58 (1H,

dd, *J* = 3.7, 0.7 Hz, Ar-H), 6.75 (1H, d, *J* = 2.3 Hz, Ar-H), 6.78 (1H, dd, *J* = 8.8, 2.3 Hz, Ar-H), 7.16-7.21 (1H, m, Ar-H), 7.23-7.28 (2H, m, Ar-H), 7.29-7.34 (4H, m, Ar-H), 7.51 (1H, d, *J* = 3.7 Hz, Ar-H), 7.74 (1H, dd, *J* = 8.8, 0.7 Hz, Ar-H), 7.78 (2H, d, *J* = 8.4 Hz, Ar-H); ^{13}C-NMR (125 MHz, acetone-d_6) δ: 21.4, 39.1, 59.0, 103.8, 110.3, 114.2, 115.0, 127.4, 127.7 (C x 3), 128.9, 129.1 (C x 2), 130.2 (C x 2), 130.8 (C x 2), 133.2, 136.2, 138.6, 145.3, 146.0, 174.6; Anal. Calcd for $C_{24}H_{22}N_2O_4S$: C, 66.34; H, 5.10; N, 6.45. Found: C, 66.10; H, 5.21; N, 6.44; $[\alpha]_D^{23}$ –3.6° (*c* 0.200, acetone).

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