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Synthesis of Aryl Sulfones via L-Proline-Promoted CuI-Catalyzed Coupling Reaction of Aryl Halides with Sulfinic Acid Salts

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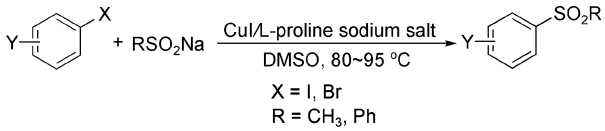

The CuI/L-proline sodium salt catalyzed coupling reaction of aryl halides with sulfinic acid salts readily occurs at 80−95 °C in DMSO to give the corresponding aryl sulfones in good to excellent yields. This process is well-tolerated by a wide range of functional groups including hydroxyl, amino, acetanilide, ketone, ester, and nitrile. Using this method, 4-phenylsulfonyl- and 4-methanesulfonyl-substituted L-phenylalanine derivatives are prepared.

Introduction

The aryl sulfone moiety has been found in numerous biologically interesting compounds. These compounds include antifungal, antibacterial, or antitumor agents[1] and inhibitors for several enzymes such as cyclooxygenase-2 (COX-2),[2] HIV-1 reverse transcriptase,[3] intrgrin VLA-4,[4] and the ATPase.[5] The traditional procedures[6,7] for assembling these compounds are mainly based on the oxidation of the corresponding sulfides and the sulfonylation of suitable arenes. The drawbacks of limited substrate sources or toleration problems for many functional groups have stimulated considerable efforts to explore alternative methods.[8−11] Among emerging strategies, direct coupling of aryl halides and sulfinic acid salts (eq 1) showed some advantages because it worked at

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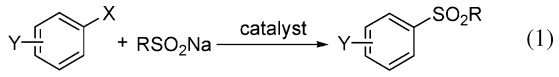
weakly basic conditions and was therefore suitable for the preparation of aryl sulfones containing olefin, amine and other acid- or oxidation-sensitive moieties.[8−10] In



(1)

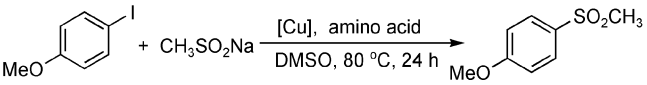
1995, Suzuki and Abe first reported that this process could be catalyzed by CuI in DMF at 110 °C.[8] The requirement of 1.5 equiv of CuI in this case had prompted Baskin and Wang to develop a more efficient catalytic procedure, which relied on the use of *N*,*N*′-dimethylethylenediamine as an additive.[9] However, this procedure was still limited to aryl iodides because low yields were observed when aryl bromides were used. In addition, it required less conveniently available catalyst ($(CuOTf)_2$·PhH) and relatively higher reaction temperature (110 °C). Very recently, Cacchi and co-workers disclosed that the combination of $Pd_2(dba)_3$/Xantphos was a powerful catalytic system for this conversion which allowed synthesis of diaryl sulfones from either aryl iodides or aryl bromides.[10] However, its practical application for largescale preparation is problematic mainly because of the high cost of the Pd catalyst and the phosphine ligand.

Based on our previous investigations[12] and inspired by relative studies reported by other groups,[13,14] we have discovered that some amino acids could promote CuI-catalyzed C−N, C−O, and C−C bond formation reactions.[15] As an extension of this research, we have explored the coupling reaction of aryl halides with sulfinic acid salts using Cu(I)/amino acid as a catalytic system. It was found that this combination was superior to that reported by Baskin and Wang[9] in many aspects. Herein we disclose our results

Results and discussions

As indicated in Table 1, we chose the coupling of 4-iodoanisole with sodium methanesulfinate as a model for exploring the optimized reaction condition. It was found that if CuI was used alone, the reaction in DMSO at 80 °C for 24 h gave the coupling product in only 25% yield (entry 1). When 20 mol % *N*-methylglycine sodium salt generated in situ was added, the reaction yield jumped to 73% (entry 2). Using *N*,*N*-dimethylglycine sodium salt resulted in lower yield of the product (entry 3). The best result was observed when L-proline sodium salt gererated in situ was used as a promoter (entry 4). No difference in yield was found when L-proline sodium salt was directly used (entry 5). Next, several Cu(I) and Cu(II) salts such as CuBr, CuCl, $Cu(OAc)_2$, and CuO were screened for this coupling reaction. It was found that CuI gave the best result and Cu(I) salts generally showed better reactivity than Cu(II) salts (compare entries 5−9). In addition, several solvents such as DMSO, DMF, dioxane, toluene, acetonitirle and ethanol were tested and DMSO was found to be the best for this reaction.

TABLE 1. Coupling Reaction of 4-iodoanisole with CH_3SO_2Na under the Catalysis of Copper Salts and Amino Acids[a]



entry	catalytic system	yield[b] (%)
1	CuI	25
2	CuI/*N*-methylglycine/20 mol % NaOH	73
3	CuI/*N*,*N*-dimethylglycine hydrochloride salt/40 mol % NaOH	62
4	CuI/L-proline/20 mol % NaOH	84
5	CuI/L-proline sodium salt	84
6	CuBr/L-proline sodium salt	74
7	CuCl/L-proline sodium salt	60
8	$Cu(OAc)_2$/L-proline sodium salt	32
9	CuO/L-proline sodium salt	trace

[a] Reaction conditions: CuI (0.1 mmol), amino acid (0.2 mmol), 4-iodoanisole (1 mmol), CH_3SO_2Na (1.2 mmol), DMSO (2 mL), 80 °C, under Ar atmosphere, 24 h. [b] Isolated yield.

Based on above results, we concluded that using CuI/L-proline sodium salt as the catalytic system and DMSO as the solvent are optimized combination for this coupling reaction. Its scope was next explored with different aryl halides, and the results are summarized in Table 2. We were pleased to find that both electron-rich and electron-deficient aryl iodides worked to provide the aryl methyl sulfones in good to excellent yields (entries 1−7). It is important to note that is that unprotected hydoxyl group or amino group in aryl iodides did not hinder the reaction and no *O*- or *N*-arylating product was detected in these cases (entries 2 and 4). When reaction of 4-iodoacetanilide and CH_3SO_2Na was carried out under Wang's conditions, poor yield of the product was obtained.[9] However, in our case this reaction gave 82% yield (entry 3), which might be caused by the relatively low reaction temperature used here.

Two heterocyclic aryl iodides were also compatible with the present procedure (entries 8 and 9). For sterically hindered aryl iodides, higher reaction temperature and longer reaction time were necessary to ensure complete conversion (compare entries 10 and 11, 12 and 13).

Since the coupling reaction of unactivated aryl bromides with sulfinic acid salts was reportedly unsuccessful under the previous conditions,[8,9] we next checked these substrates using our catalytic system. To our delight, many aryl bromides worked well in our hands although higher reaction temperature and longer reaction time were required in comparison with aryl iodides. Interestingly, electron-rich aryl bromides displayed higher reactivity than those electron-deficient aryl bromides (compare entries 15−17 and 18−19). A similar phenomenon has been observed in CuI/L-proline sodium salt catalyzed

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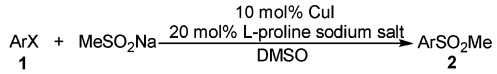
TABLE 2. Coupling Reaction of Aryl Halides with CH_3SO_2Na under the Catalysis of CuI/L-Proline Sodium Salt[a]



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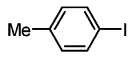
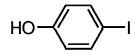
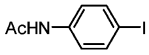
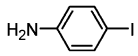
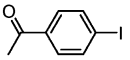
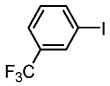
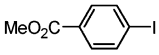
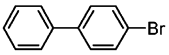
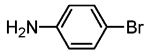
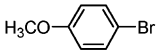
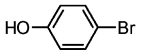
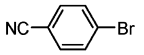
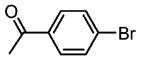
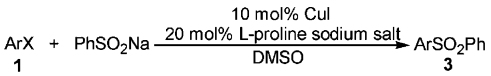
1		80	24	93
2		80	24	93
3		80	24	82
4		80	24	81
5		80	24	80
6		80	24	92
7		80	36	77
8		80	24	86
9		80	24	89
10		80	24	70[c]
11		90	36	92
12		80	24	55[c]
13		90	36	85
14		95	36	76
15		95	36	78
16		95	36	83
17		95	36	89
18		95	36	70[c]
19		95	48	62[c]
20		95	36	88

[a] Reaction conditions: CuI (0.1 mmol), L-proline sodium salt (0.2 mmol), aryl halide (1 mmol), CH_3SO_2Na (1.2 mmol), DMSO (2 mL), under Ar atmosphere. [b] Isolated yield. [c] Unreacted iodides or bromides were recovered in 20−30% yields.

TABLE 3. Coupling Reaction of Aryl Halides with $PhSO_2Na$ under the Catalysis of CuI/L-Proline Sodium Salt



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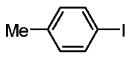
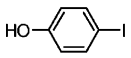
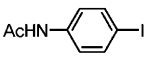
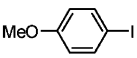
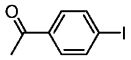
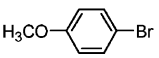
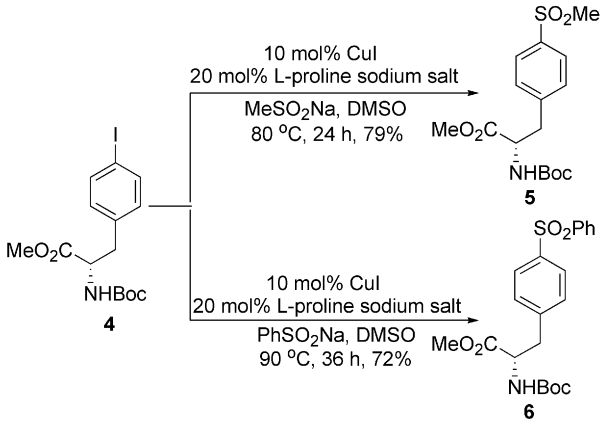
1		90	36	77
2		90	36	90
3		90	36	81
4		90	36	85
5		90	36	60
6		90	48	57[c]
7		95	48	46[d]

[a] Reaction conditions: CuI (0.1 mmol), L-proline sodium salt (0.2 mmol), aryl halide (1 mmol), $PhSO_2Na$ (1.2 mmol), DMSO (2 mL), under Ar atmosphere. [b] Isolated yield. [c] Unreacted iodide was recovered in 37% yields. [d] Unreacted bromide was recovered in 46% yields.

SCHEME 1



coupling of aryl halides with sodium azide.[15e] These results implied that the mechanism of these two coupling reactions might slightly differ from that of CuI/amino acid-catalyzed aryl amination and diaryl ether formation reactions. More investigations are needed to address this issue.

As shown in Table 3, the coupling reaction between aryl halides and sodium benzenesulfinate was explored in order to extend the present method to the synthesis of diaryl sulfones. For most of the aryl iodides tested, good yields were obtained when the reaction was carried out at 90 °C (entries 1−5). However, poor conversion was seen when 4′-iodoacetophenone was used (entry 6), which was consistent with the observation for reaction of 4′-bromoacetophenone with sodium methanesulfinate. In addition, aryl bromides also gave poor conversion as

evidenced by that the reaction of 4-bromoanisole provided the coupling product in only 46% yield (entry 7).

To further demonstrate the applicability of the present procedure, iodide **4** derived from L-phenylalanine was checked. It was found that reaction of **4** with sodium methanesulfinate or sodium benzenesulfinate gave the cross-coupling product **5** or **6** in good yields (Scheme 1). These two products might serve as useful building blocks for the synthesis of peptide mimics.

In conclusion, we have reported here a more effective Cu(I) catalytic system, which allowed for coupling reaction of aryl halides with sulfinic acid salts at relatively low temperatures and was suitable for more substrates especially to aryl bromides. A wide range of functional groups such as hydroxyl, amino, acetanilide, ketone, ester, and nitrile groups were compatible with the present reaction conditions, which would permit to assemble aryl sulfones with great diversity. Further applications to the synthesis of biologically important molecules and mechanism studies are in progress.

Experimental

General Procedure for Coupling Reaction of 4-Iodoanisole with CH_3SO_2Na (Table 1). A mixture of 4-iodoanisole (1 mmol), sodium methanesulfunate (1.2 mmol), copper salt (0.1 mmol), amino acid (0.2 mmol), and base (0.2 mmol) (or 0.2 mmol of proline sodium salt) in 2 mL of DMSO in a sealed tube was heated at 80 °C under argon for 24 h. The cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was loaded on a silica gel column and eluted with petroleum ether to afford the product.

General Procedure for CuI-Catalyzed Coupling of Aryl Halides and Sodium Methanesulfunate. A mixture of aryl halide (1 mmol), sodium methanesulfunate (1.2 mmol), copper iodide (0.1 mmol), L-proline sodium salt (0.2 mmol), and 2 mL of DMSO in a sealed tube was heated to 80 or 95 °C (for aryl bromides) under argon. The cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was loaded on a silica gel column and eluted with 4:1 petroleum ether/ethyl acetate to afford the product.

1-Methoxy-4-(methanesulfonyl)benzene 2a: white solid; mp 118−120 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.05 (s, 3H), 3.90 (s, 3H), 7.04 (dd, J = 7.5, 2.1 Hz, 2H), 7.88 (dd, J = 7.5, 2.1 Hz, 2H); EI-MS (*m/z*) 186 (M^+), 171, 155, 139, 123, 107, 92, 77, 63.

1-Methyl-4-(methanesulfonyl)benzene 2b: white solid; mp 85−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 3.04 (s, 3H), 7.36 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H); EI-MS (*m/z*) 170 (M^+), 155, 139, 121, 107, 91, 77, 65, 51, 39.

4-(Methanesulfonyl)phenol 2c: white solid; mp 94−96 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 3.09 (s, 3H), 6.93 (m, 2H), 7.71 (m, 2H), 10.6 (br s, 1H); EI-MS (*m/z*) 172 (M^+), 157, 141, 109, 94, 79, 65, 43.

***N*-(4-Methanesulfonylphenyl)acetamide 2d:** yellow solid; mp 185−187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 3.04 (s, 3H), 7.60 (s, 1H), 7.72 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H); EI-MS (*m/z*) 213 (M^+), 198, 171, 156, 140, 108, 92, 81, 65.

4-Methanesulfonylaniline 2e: yellow solid; mp 136−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (s, 3H), 4.22 (br, 2H), 6.71 (m 2H), 7.69 (m, 2H); EI-MS (*m/z*) 171 (M^+), 156, 140, 108, 92, 80, 65.

1-(4-(Methanesulfonyl)phenyl)ethanone 2f: pale yellow solid; mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (s, 3 H), 3.09 (s, 3 H), 8.05 (d, J = 8.2 Hz, 2 H), 8.13 (d, J = 8.2 Hz, 2H); EI-MS (*m/z*) 198 (M^+), 183, 167, 152, 139, 121, 104, 91, 76, 63, 43.

1-(Trifluoromethyl)-3-(methanesulfonyl)benzene 2g: white solid; mp 58−60 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.11 (s, 3H), 7.76 (t, J = 8.0 Hz, 1H), 7.93 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 8.0 Hz, 1H); 8.23 (s, 1H); EI-MS (*m/z*) 224 (M^+), 209, 205, 193, 177, 162, 145, 125, 114, 95, 75, 63, 50, 39.

Methyl 4-(methanesulfonyl)benzoate 2h: white solid; mp 118−120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.09 (s, 3 H), 3.98 (s, 3H), 8.03 (d, J = 7.4 Hz, 2H), 8.22 (d, J = 7.4 Hz, 2H); EI-MS (*m/z*) 214 (M^+), 199, 183, 166, 152, 135, 121, 104, 91, 77, 57, 43.

2-(Methanesulfonyl)thiophene 2i: white solid; mp 45−47 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (s, 3H), 7.61 (m, 1H), 7.73 (m, 2H); EI-MS (*m/z*) 162 (M^+), 147, 131, 115, 99, 83, 71, 57, 45, 39.

3-Methanesulfonylpyridine 2j: white solid; mp 52−54 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.13 (s, 3H), 7.54 (m, 1H), 8.24 (m, 1H), 8.90 (m, 1H), 9.18 (d, J = 2.3 Hz, 1H); EI-MS (*m/z*) 157 (M^+), 142, 126, 110, 95, 82, 78, 66, 51.

1-Methyl-2-(methanesulfonyl)benzene 2k: white solid; mp 54−56 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.72 (s, 3H), 3.09 (s, 3H), 7.35 (m, 1H), 7.38 (m, 1H), 7.52 (m, 1H), 8.03 (m, 1H); EI-MS (*m/z*) 170 (M^+), 155, 107, 91, 77, 65, 51, 39.

1-(Methanesulfonyl)naphthalene 2m: yellow solid; mp 99−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (s, 3H), 7.61 (m, 1H), 7.63 (m, 1H), 7.73 (m, 1H), 7.99 (d, J = 8.2 Hz, 1H), 8.13 (d, J = 8.2 Hz, 1H), 8.35 (m, 1H), 8.73 (m, 1H); EI-MS (*m/z*) 206 (M^+), 191, 183, 175, 143, 127, 115, 101, 91, 77, 63, 51, 39.

4-Methanesulfonyl-1-phenylbenzene 2n: yellow solid; mp 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 3H), 7.45 (m, 3H), 7.61 (d, J = 7.8 Hz, 2H), 7.77 (d, J = 8.2 Hz, 2H), 8.01 (d, J = 8.2 Hz, 2H); EI-MS (*m/z*) 232 (M^+), 217, 201, 185, 169, 152, 141, 127, 115, 76.

4-Methanesulfonylbenzonitrile 2o: white solid; mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.10 (s, 3H), 7.90 (m 2H), 8.09 (m, 2H); EI-MS (*m/z*) 181 (M^+), 166, 150, 119, 102, 75.

***tert*-Butyl (*S*)-1-(Methoxycarbonyl)-2-(4-(methanesulfonyl)phenyl)ethylcarbamate 5:** yellow solid; mp 78−80 °C; $[\alpha]^{23}_D$ = +44.9 (*c* = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 3.05 (s, 3H), 3.05−3.20 (m, 2H), 3.74 (s, 3H), 4.62 (m, 1H), 5.09 (d, J = 7.3 Hz, 1H), 7.35 (d, J = 7.8 Hz, 2H), 7.87 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 154.6, 142.6, 138.7, 129.9, 127.0, 79.6, 53.7, 52.0, 43.0, 37.7, 27.8; ESI-MS (*m/z*) 380.2 $(M + Na)^+$; ESI HRMS found *m/z* 380.1146 $(M + Na)^+$, $C_{16}H_{23}NO_6SNa$ requires 380.1144;

General Procedure for CuI-Catalyzed Coupling of Aryl Halides and Sodium Benzenesulfonate. A mixture of aryl halide (1 mmol), sodium benzenesulfonate (1.2 mmol), copper iodide (0.1 mmol), L-proline sodium salt (0.2 mmol), and 2 mL of DMSO in a sealed tube was heated at the temperature indicated in Table 3 under argon. After 24 or 36 h (for aryl bromides), the cooled mixture was partitioned between ethyl acetate and water. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residual oil was loaded on a silica gel column and eluted with 4:1 petroleum ether/ethyl acetate to afford the product.

1-(*p*-Tolylsulfonyl)benzene 3a: white solid; mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 7.29 (d, J = 8.3 Hz, 2H), 7.50 (m, 3H), 7.82 (d, J = 8.2 Hz, 2H), 7.93 (m, 2H); EI-MS (*m/z*) 232 (M^+), 184, 165, 152, 139, 125, 107, 91, 77, 65, 51, 39.

4-(Benzenesulfonyl)phenol 3b: brown solid; mp 135−137 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.28 (br s, 1H), 6.88 (d, J =

8.0 Hz, 2H), 7.47 (m, 3H), 7.72 (d, J = 8.0 Hz, 2H), 7.85 (d, J = 8.0 Hz, 2H); EI-MS (*m/z*) 234 (M^+), 191, 175, 161, 78, 63, 45.

***N*-(4-Benzenesulfonylphenyl)acetamide 3c:** yellow solid; mp 191−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 7.35−7.60 (m, 3H), 7.65 (d, J = 8.7 Hz, 2H), 7.83−7.91 (m, 5H); EI-MS (*m/z*) 275 (M^+), 233, 169, 156, 140, 125, 108, 77, 43.

1-(4-Methoxyphenylsulfonyl)benzene 3d: yellow solid; mp 88−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (s, 3H), 6.96 (m, 2H), 7.51 (m, 3H), 7.90 (m, 4H); EI-MS (*m/z*) 248 (M^+), 184, 169, 155, 141, 123, 107, 92, 77, 51.

2-(Benzenesulfonyl)thiophene 3e: yellow solid; mp 119−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 1H), 7.52−7.70 (m, 5H), 7.99 (m, 2H); EI-MS (*m/z*) 224 (M^+), 160, 131, 125, 115, 99, 83, 71, 51, 45, 39.

1-(4-(Benzenesulfonyl)phenyl)ethanone 3f: yellow solid; mp 132−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.62 (s, 3H), 7.51−7.60 (m, 3H), 7.95−8.05 (m, 6H); EI-MS (*m/z*) 260 (M^+), 245, 217, 191, 167, 152, 141, 125, 104, 97, 77, 51, 43.

***tert*-Butyl (*S*)-1-(methoxycarbonyl)-2-(4-(benzenesulfonyl)phenyl)ethylcarbamate 6:** yellow solid; mp 82−84 °C; $[\alpha]^{23}_D$ = +33.6 (c = 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H), 3.05−3.20 (m, 2H), 3.74 (s, 3H), 4.60 (m, 1H), 5.00 (d, J = 7.3 Hz, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.55 (m, 3H), 7.86 (d, J = 7.8 Hz, 2H), 7.93 (d, J = 7.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 154.5, 142.0, 141.1, 139.7, 132.7, 129.8, 128.8, 127.3, 127.1, 79.7, 53.6, 52.0, 37.8, 27.7; ESI-MS (*m/z*) 442.2 $(M + Na)^+$; ESI HRMS found *m/z* 442.1293 $(M + Na)^+$, $C_{21}H_{25}NO_6SNa$ requires 442.1300.

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