An Efficient Method for the Preparation of Enantiomerically Pure *N*-Acylarylsulfonamides Having an Asymmetric Center at the α-Position: Condensation of Acid Chlorides and Arylsulfonamides Under Solid-Liquid Two-Phase Conditions

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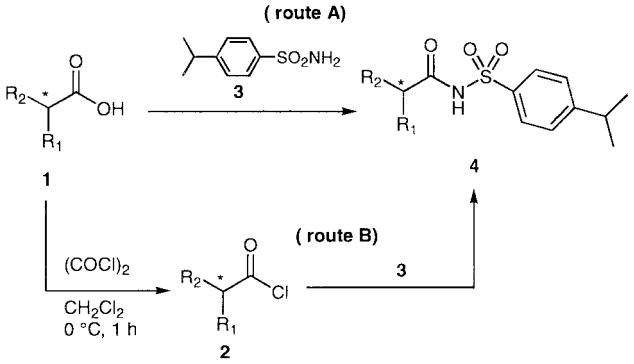
Abstract: A convenient synthetic method for the preparation of enantiomerically pure *N*-acylarylsulfonamides having an asymmetric center at the α-position of the carbonyl group is described. Chiral phenylacetic acids are first converted to the corresponding acid chlorides, which in turn are condensed with arylsulfonamides in the presence of powdered alkaline hydroxide in CH_2Cl_2, giving the corresponding *N*-acylarylsulfonamides with good optical and chemical yields. A more convenient one-pot procedure is also possible.

Key words: chiral *N*-acylarylsulfonamides, chiral phenylacetic acid, racemization, solid-liquid two-phase conditions, powdered alkaline hydroxide



Scheme

N-Acylsulfonamides, forming a class of acidic functional groups, have been widely employed as carboxylic acid bioisosteres in medicinal chemistry.[1] They have similar pKa values to those of the corresponding carboxylic acids[2] and offer the possibility for a wide range of structural modifications. Acylation of sulfonamides with acid chlorides,[3] acid anhydrides[4] or reactive esters[5] have traditionally been used for the preparation of *N*-acylsulfonamides.[6] More recently, direct condensation of carboxylic acids and sulfonamides in the presence of condensing agents, such as carbonyldiimidazole (CDI),[7] 2-chloro-*N*-methylpyridinium iodide (CMPI)[8] or carbodiimides,[9] have also been employed for this purpose.

During the course of development of our endothelin receptor antagonists, we found that *N*-acylarylsulfonamide (*R*)-**4a** is a potent endothelin-A receptor antagonist.[10] This compound has one asymmetric center at the α-position of the carbonyl group. In order to prepare (*R*)-**4a**, enantiomerically pure (*R*)-**1a** was allowed to react with arylsulfonamide **3** in the presence of various condensing agents (Scheme). Although these methods gave **4a** in good to excellent yields, the product was completely or partially racemized in all cases. Acylation of **3** with the corresponding acid chloride (*R*)-**2a** in the presence of triethylamine also resulted in the racemized product (*vide infra*).

The increasing importance of preparing the enantiomerically pure form of biologically active compounds in drug development studies[11] prompted us to survey a hitherto undocumented efficient method for the synthesis of chiral *N*-acylarylsulfonamide having an asymmetric center at the α-position of the carbonyl group.[12] In this paper, we describe a simple and economically feasible method for the preparation of **4** as a model of such chiral *N*-acylarylsulfonamides, which include the condensation of acid chloride **2**, readily available from the corresponding optically active phenylacetic acid derivative **1**, and arylsulfonamide **3** in the presence of powdered alkaline hydroxide in CH_2Cl_2. The product **4** thus obtained is enantiomerically pure enough for further elaboration.

The results of the direct condensation of (*R*)-**1a** and **3** in the presence of condensing agents (route A) are summarized as Entries 1−6 in Table 1. Each reaction was carried out by reported methods. The optical purity of each of the starting materials and the products were determined by chiral HPLC analysis. The CDI method of Drummond and Johnson[7] resulted in good yield of **4a**, but the product was completely racemized (Entry 1). CMPI method[8] also gave the racemate (Entry 2). On the other hand, carbodiimide-DMAP (4-dimethylaminopyridine) methods[9a,b] at room temperature afforded 89−91% ee of (*R*)-**4a** in 70−88% yields after silica gel chromatography (Entries 3 and 4). Lowering the temperature to 0 °C improved the optical purity of the product, giving 99% ee of (*R*)-**4a**; however the yield was only 34% after 10 h and a considerable amount of the starting material was recovered (Entry 5). Replacing DMAP with less basic 1-hydroxybenzotriazole (HOBt)[9c] resulted in significant loss of reaction rate even at room temperature, giving 40% ee of the product in 19% yield after 24 hours (Entry 6).

We next turned our attention to the stepwise methods which include conversion of **1** to acid chloride **2** (route B).

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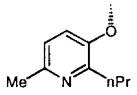
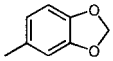
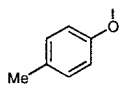
Table 1 Results of Condensation of Chiral Phenylacetic Acids **1** or Chlorides **2** with **3**

Entry	R_1	R_2	Starting Material[a]	Reagent[b]	Solvent	Conditions	Product	ee (%)[c]	Yield (%)[c]
1			(*R*)-**1a**	CDI, DBU	THF	r.t., 1 h; r.t., 1h	(*R*)-**4a**	2	74
2				CMPI, Et_3N	CH_2Cl_2	r.t., 1 h		0	55
3				DCC, DMAP	CH_2Cl_2	r.t., 2 h		89	88
4				EDC, DMAP	CH_2Cl_2	r.t., 2 h		91	70
5				EDC, DMAP	CH_2Cl_2	0 °C, 24 h		99	34
6				EDC, HOBt	CH_2Cl_2	r.t., 24 h		40	19
7			(*R*)-**2a**	Et_3N	CH_2Cl_2	0 °C, 2.5 h		13	37
8				powdered KOH	CH_2Cl_2	0 °C, 1.5 h		99	90
9				powdered KOH	CH_2Cl_2	0 °C, 1.5 h		100[d]	85[d]
10				powdered KOH	CH_2Cl_2 (wet)[e]	0 °C, 1.5 h		99	92
11				powdered KOH (one-pot)	CH_2Cl_2	0 °C, 2 h		98	83
12				powdered NaOH	CH_2Cl_2	0 °C, 1.5 h		99	88
13				powdered NaOH	CH_2Cl_2 (wet)[e]	0 °C, 1.5 h		99	85
14				powdered LiOH	CH_2Cl_2	0 °C, 2.5 h		95	84
15				powdered LiOH•H_2O	CH_2Cl_2	0 °C, 2.5 h		97	61
16	OMe		(*R*)-**1b**	CDI, DBU	THF	r.t., 1h; r.t., 1h	(*R*)-**4b**	42	81
17				EDC, DMAP	CH_2Cl_2	r.t., 2 h		98	19
18				EDC, DMAP	CH_2Cl_2	r.t., 24 h		11	87
19			(*R*)-**2b**	powdered KOH	CH_2Cl_2	0 °C, 1 h		100	77
20				powdered KOH (one-pot)	CH_2Cl_2	0 °C, 1 h		100	93
21			(+)-**2c**	powdered KOH	CH_2Cl_2	0 °C, 1 h	(+)-**4c**	100	80
22			(*S*)-**2d**	powdered KOH	CH_2Cl_2	0 °C, 3 h	(*S*)-**4d**	95	54
23				powdered KOH (one-pot)	CH_2Cl_2	0 °C, 3 h		96	52

[a] For optical purity of **1a**–**d**, see experimental section.
[b] Abbreviations used: CDI = 1,1'-carbonyldiimidazole; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene; CMPI = 2-chloro-*N*-methylpyridinium iodide; DCC = dicyclohexylcarbodiimide; EDC = 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride; DMAP = 4-dimethylaminopyridine; HOBt = 1-Hydroxybenzotriazole.
[c] Unless otherwise stated, optical purity and yield were determined after chromatographic separation of the product.
[d] Optical purity and isolated yield were determined after recrystallization as HCl salt.
[e] Saturated with H_2O (0.2% w/v).

The acid chloride (*R*)-**2a** was readily obtained on treatment of (*R*)-**1a** with oxalyl chloride in CH_2Cl_2 at 0 °C followed by evaporation of the volatile portion at room temperature.[13] It was then allowed to react with **3** in CH_2Cl_2 at 0 °C in the presence of various bases. The results are summarized as Entries 7–15 in Table 1.

Table 2 Time Course of Optical Purity of (*R*)-**2a** and (*R*)-**4a** in Dichloromethane at 0 °C

Substrate	Time (h)	ee (%)
(*R*)-**2a**	0.5	98
	1.0	98
	2.0	98
(*R*)-**2a** + Et_3N	0.5	18
	1.0	8
	1.5	0
(*R*)-**4a** + Et_3N	1.0	99
	2.0	98
	2.5	98

When Et_3N was used as a base,[3a] only 13% ee of (*R*)-**4a** was obtained in 37% yield (Entry 7). The time course study of racemization of (*R*)-**2a** and (*R*)-**4a** in CH_2Cl_2 at 0 °C revealed that (*R*)-**2a** was stable in the absence of Et_3N, but rapidly racemized in its presence. On the other hand, (*R*)-**4a** was recovered unchanged even after 2.5 hours (Table 2). Clearly, the presence of Et_3N enhanced the racemization of (*R*)-**2a**.[14]

These results prompted us to survey inorganic bases as an alternative to Et_3N, and satisfactory results were obtained by using powdered alkaline hydroxides as the base. In a typical procedure, (*R*)-**2a** was allowed to react with **3** (1.1 equiv) in the presence of powdered potassium hydroxide (3.3 equiv)[15] in CH_2Cl_2 at 0 °C, to give 99% ee of (*R*)-**4a** in 90% yield after column chromatography (Entry 8). The analytically pure (*R*)-**4a** (100% ee) was also obtained in 85% yield simply by extraction followed by recrystallization as the HCl salt (Entry 9). Similar results were also obtained using powdered sodium or lithium hydroxide as base (Entries 12 and 14). Essentially identical results were

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obtained even in the presence of small amount of water as demonstrated by the reactions carried out in wet CH_2Cl_2 (Entries 10 and 13) or the reaction with hydrated lithium hydroxide (Entry 15). These results indicate that the condensation reaction can be carried out under conventional reaction conditions without exclusion of contaminated water.

In a similar manner, enantiomerically pure **1b**−**d**[16,17] were converted to the corresponding acid chlorides **2b**−**d**.[18] They were then allowed to react with **3** under conditions similar to those of entry 8.[19] The results are summarized as Entries 19−23 together with those of some direct methods (Entries 16−18). The CDI method resulted in substantial loss of optical purity of the product (Entry 16). Although the carbodiimide-DMAP method gave 98% ee of the product at room temperature for 2 hours, the yield was far from satisfactory (Entry 17). In this case, longer reaction time led to considerable loss of optical purity (Entry 18). In contrast, the present method provided the products in good to excellent optical and chemical yields (Entries 19, 21 and 22).

A more convenient one-pot procedure was also possible. In a typical procedure, chiral **1** was treated with oxalyl chloride (1.1 equiv) in CH_2Cl_2 at room temperature for 1 hour. Without isolation of **2**, the sulfonamide **3** (1.1 equiv) and powdered potassium hydroxide (3.3 equiv)[19] were successively added to the reaction mixture at 0 °C. Satisfactory optical and chemical yields comparable to those of the stepwise procedures were obtained in all cases (Entry 8 vs 11, 19 vs 20 and 22 vs 23).

In summary, we have described a convenient synthetic method for the preparation of enantiomerically pure *N*-acylarylsulfonamide **4** starting from chiral phenylacetic acid **1**. The asymmetry can be retained during the course of the reaction. The key feature is the condensation of acid chloride **2** and arylsulfonamide **3** under the solid-liquid two-phase conditions in the presence of powdered alkaline hydroxide as base. The operation and isolation of the products are simple, and the reagents are all inexpensive. Thus, this method should be widely applicable to the synthesis of various *N*-acylarylsulfonamide derivatives with an asymmetric center at the α-position of the carbonyl group.

All reactions were carried out under N_2. The solvents were dried over molecular sieve 4 A. Wet CH_2Cl_2 was prepared by shaking CH_2Cl_2 with H_2O in separatory funnel and separating the layers. Reagent grade KOH (85%) and NaOH (96%) pellets were pulverized using laboratory blender (Phoenix, Blender KB-1) and stocked in a sealed vessel. Anhyd and hydrated LiOH were pulverized using a mortar. Contamination of H_2O for dried and wet CH_2Cl_2 and powdered KOH were determined by Karl-Fischer analysis, to be <0.1% (w/v), 0.20% (w/v) and 12.1% (w/w), respectively. Melting points were determined on a Yanagimoto hot plate apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian VXR-300 spectrometer and are reported in ppm (δ) relative to TMS as an internal standard. Column chromatography was performed with Merck silica gel 60 (70−230 mesh). Preparative TLC was performed with Merck precoated TLC plates silica gel 60 F_{254}.

The optical purity of each starting material and product was independently determined under one of the following conditions.

Condition A: column, Sumichiral OA4900 (4.6 × 250 mm, Sumitomo Chemical); solvent, 20 mM NH_4OAc in MeOH; flow rate, 1.0 mL/min; detection wavelength, 286 or 240 nm; Condition B: column, CHIRALPAK OJ-R (4.6 × 150 mm, Daicel Chemical); solvent, MeCN/H_2O/TFA (70:30:0.1, v/v), flow rate, 0.5 mL/min; detection wavelength 230 nm; Condition C: column, CHIRALPAK AD (4.6 × 250 mm, Daicel Chemical); solvent, hexane/EtOH/TFA (90:10:0.1, v/v); flow rate, 0.5 mL/min; detection wavelength, 254 nm.

(*R*)-(−)-α-(6-Methyl-2-propyl-3-pyridyloxy)-1,3-benzodioxol-5-acetic Acid [(*R*)-1a][20]

Racemic **1a** was prepared from ethyl α-bromo-1,3-benzodioxole-5-acetate[21] and 6-methyl-2-propylpyridin-3-ol[22] similar to a reported procedure.[12c] Compound **1a** (66.04 g, 201 mmol) and (1*S*,2*S*)-(+)-2-amino-1-phenylpropane-1,3-diol (33.61 g, 201 mmol) were dissolved in hot *i*-PrOH (149 mL), and then EtOAc (223 mL) was added. The resulting precipitate was collected and recrystallized twice from *i*-PrOH, giving the corresponding amine salt (35.5g, 99% ee, 71% yield) as colorless crystals. To a suspension of the amine salt in H_2O (355 mL) was added 1 N HCl (71.5 mL) at 0 °C. The mixture was extracted with $CHCl_3$/MeOH (9:1) and the organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was recrystallized from EtOH to give (*R*)-**1a** (17.5 g, 53% from **1a**) as colorless crystals; mp 156−158 °C; $[\alpha]_D^{20}$ −109.8 (*c* = 1.00, MeOH); HPLC (condition A at 286 nm): t_R = 12.2 min; 100% ee.

^{1}H NMR (CD_3OD): δ = 0.97 (t, 3 H, *J* = 7.4 Hz), 1.62−1.85 (m, 2 H), 2.52 (s, 3 H), 2.80−3.07 (t, 2 H, *J* = 8.2 Hz), 5.59 (s, 1 H), 5.96 (s, 2 H), 6.81−7.53 (m, 5 H).

(+)-(4-Methyphenoxy)-α-phenylacetic Acid [(+)-1c]

Racemic α-(4-methyphenoxy)phenylacetic acid (1.50 g, 6.19 mmol) and (1*S*,2*S*)-(+)-2-amino-1-phenylpropane-1,3-diol (1.04 g, 6.19 mmol) were dissolved in hot EtOH (9 mL). The mixture was allowed to cool to r.t., and the resulting precipitate was collected and recrystallized from EtOH twice to give the corresponding amine salt (717 mg, 57%) as colorless crystals. To a suspension of the amine salt (547 mg, 1.34 mmol) in H_2O (5.5 mL) was added 1 N HCl (1.34 mL) at 0°C. After similar workup as in the case of (*R*)-**1a**, the product was recrystallized from hexane to give (+)-**1c** (296 mg, 42%) as colorless crystals; mp 109.5−110.5 °C; $[\alpha]_D^{25}$ +126.2 (*c* = 1.00, MeOH); HPLC (condition A at 240 nm): t_R = 17.9 min; 100% ee.

^{1}H NMR ($CDCl_3$): δ = 2.27 (s, 3 H), 5.60 (s, 1 H), 6.84 (d, 2 H, *J* = 8.6 Hz), 7.06 (d, 2 H, *J* = 8.6 Hz), 7.36−7.44 (m, 3 H), 7.54−7.59 (m, 2 H).

(*R*)-**1b** and (*S*)-**1c** were prepared according to literature methods.[16,17]

(*R*)-(−)-α-Methoxyphenylacetic Acid [(*R*)-1b]

Colorless crystals; mp 66−68 °C; $[\alpha]_D^{22}$ −151.7 (*c* = 1.38, EtOH); HPLC (condition A at 240 nm): t_R = 17.9 min; 100% ee (Lit.[16] mp 65−66 °C; $[\alpha]_D^{20}$ −150.7 (*c* = 0.57, EtOH))

(*S*)-(+)-α-Cyclohexylphenylacetic Acid [(*S*)-1c]

Colorless crystals; mp 100−101.5 °C; $[\alpha]_D^{25}$ +40.8 (*c* = 1.00, MeOH); HPLC (condition B): t_R = 3.6 min; 99% ee (Lit.[17] mp 100−102 °C; $[\alpha]_D^{25}$ +38.7 (*c* = 20, $CHCl_3$)).

(*R*)-(−)-*N*-(4-Isopropylphenylsulfonyl)-α-(6-methyl-2-propyl-3-pyridyloxy)-1,3-benzodioxol-5-acetamide [(*R*)-4a][20]; Typical Procedures

(a) CDI Method[7] (Table 1, Entry 1)

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After a mixture of 1,1'-carbonyldiimidazole (108 mg, 0.668 mmol) and (*R*)-**1a** (200 mg, 0.607 mmol) in THF (3 mL) was stirred at r.t. for 1 h, **3** (133 mg, 0.668 mmol) and DBU (100 μL, 0.668 mmol) were successively added and stirring was continued for an additional 1 h at r.t. The mixture was poured into H_2O and extracted with EtOAc. The organic layer was washed with H_2O, brine, dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH, 95:5) to give (*R*)-**4a** as a colorless oil (228 mg, 74%, 2% ee).

(b) CMPI Method[8] (Entry 2)

A solution of **3** (12 mg, 0.061 mmol) and Et_3N (15 mg, 0.146 mmol) in CH_2Cl_2 (1 mL) was added to a suspension of (*R*)-**1a** (20 mg, 0.061 mmol) and 2-chloro-*N*-methylpyridinium iodide (19 mg, 0.073 mmol) in CH_2Cl_2 (2 mL), and the mixture was stirred at r.t. for 1 h. After similar workup as given in (a), the crude product was purified by preparative TLC ($CHCl_3$/MeOH, 95:5) to give **4a** (17 mg, 55%, 0% ee).

(c) Carbodiimide-DMAP Method[9a,b] (Entry 4)

EDC (*N*-ethyl-*N*'-(3,3-dimethylamino)propylcarbodiimide hydrochloride, 96 mg, 0.501 mmol) was added to a mixture of (*R*)-**1a** (150 mg, 0.455 mmol), **3** (100 mg, 0.501 mmol) and DMAP (61 mg, 0.501 mmol) in CH_2Cl_2 (3 mL) and the mixture was stirred at r.t. for 2 h. The sulfonamide (*R*)-**4a** was obtained by a similar workup and purification as (a) (162 mg, 70%, 91% ee).

(d) Carbodiimide-HOBt Method[9c] (Entry 6)

EDC (128 mg, 0.668 mmol) was added to a mixture of (*R*)-**1a** (200 mg, 0.607 mmol), **3** (133 mg, 0.668 mmol) and 1-hydroxybenzotriazole (90 mg, 0.668 mmol) in CH_2Cl_2 (4 mL) and the mixture was stirred at r.t. for 24 h. The sulfonamide (*R*)-**4a** was obtained by a similar workup and purification as (a) (59 mg, 19%, 40% ee).

(e) Et_3N Method[3a] (Entry 7)

Oxalyl chloride (57 μL, 0.637 mmol) was added dropwise to a suspension of (*R*)-**1a** (200 mg, 0.607 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After stirring at 0 °C for 1 h, the mixture was concentrated in vacuo at r.t. to give (*R*)-**2a** as a colorless oil. This material was used without further purification. To a solution of **3** (133 mg, 0.668 mmol) and Et_3N (186 μL, 1.34 mmol) in CH_2Cl_2 (2 mL) was added (*R*)-**2a** in CH_2Cl_2 (2 mL) at 0 °C dropwise, and the mixture was stirred at 0 °C for 2.5 h. (*R*)-**4a** was obtained after a similar workup and purification as (a) (114 mg, 37%, 13% ee).

(f) Powdered Alkaline Hydroxide Method; Stepwise Procedure (Entries 8 and 9)

Oxalyl chloride (57 μL, 0.637 mmol) was dropwise added to a suspension of (*R*)-**1a** (200 mg, 0.607 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After stirring at 0 °C for 1 h, the mixture was concentrated in vacuo at r.t. to give (*R*)-**2a** as a colorless oil. Powdered KOH (85%; 132 mg, 2.00 mmol) and **3** (133 mg, 0.668 mmol) were stirred in CH_2Cl_2 (2 mL) at r.t. for 1 h in advance. A solution of (*R*)-**2a** in CH_2Cl_2 (2.5 mL) was added dropwise at 0 °C and the mixture was stirred for 1.5 h. After H_2O (2 mL) and 1 N HCl (0.79 mL) were added to the mixture, the usual workup and purification as (a) afforded (*R*)-**4a** (280 mg, 90%) as a colorless oil; $[\alpha]_D^{23}$ −76.2 (*c* = 1.00, MeOH); HPLC (condition A at 286 nm): t_R = 21.4 min; 99% ee.

^{1}H NMR (DMSO-d_6): δ = 0.85 (t, 3 H, *J* = 7.3 Hz), 1.20 (d, 6 H, *J* = 6.8 Hz), 1.50−1.70 (m, 2 H), 2.33 (s, 3 H), 2.60−2.75 (m, 2 H), 2.90−3.10 (m, 1 H), 5.60 (s, 1 H), 6.04 (m, 2 H), 6.80−7.00 (m, 5 H), 7.41 (d, 2 H, *J* = 8.4 Hz), 7.69 (d, 2 H, *J* = 8.4 Hz).

(*R*)-**4a**•HCl (Table 1, Entry 9)

Crude (*R*)-**4a** obtained after extraction was dissolved in EtOAc (3 mL) and treated with 4 N HCl in EtOAc (0.167 mL, 0.668 mmol) at 0 °C. The resulting precipitate was filtered off and washed with EtOAc. The product was recrystallized from EtOH to give HCl salt of (*R*)-**4a** (283 mg, 85%) as colorless crystals; mp 171−175 °C; $[\alpha]_D^{22}$ −75.8 (*c* = 1.00, MeOH); HPLC (condition A at 286 nm): t_R = 21.4 min; 100% ee.

^{1}H NMR($CDCl_3$): δ = 0.96 (t, 3 H, *J* = 7.4 Hz), 1.27 (d, 6 H, *J* = 6.4 Hz), 1.61−1.80 (m, 2 H), 2.64 (s, 3 H), 2.93−3.07 (m, 3 H), 5.82 (s, 1 H), 5.99 (s, 2 H), 6.76−6.93 (m, 3 H), 7.42 (d, 2 H, *J* = 8.2 Hz), 7.51−7.56 (m, 1 H), 7.74−7.82 (m, 3 H).

(g) Powdered Alkaline Hydroxide Method; One-Pot Procedure (Entry 11)

Oxalyl chloride (59 μL, 0.668 mmol) was dropwise added to a suspension of (*R*)-**1a** (200 mg, 0.607 mmol) in CH_2Cl_2 (4 mL) at 0 °C, and stirred at the same temperature for 1 h. To the solution were added successively **3** (133 mg, 0.668 mmol) and powdered KOH (85%; 132 mg, 2.00 mmol). The resulting suspension was stirred at 0 °C for 2 h, and then H_2O and 1 N HCl (0.79 mL) were added. The usual workup and purification as given in (a) afforded (*R*)-**4a** (258 mg, 83%) as a colorless oil; $[\alpha]_D^{25}$ −16.4 (*c* = 1.00, MeOH); HPLC (condition A at 240 nm); t_R = 31.9 min; 100% ee, mp 89–91 °C.

Chiral **4b**−**4d**

These were prepared in a similar manner to Methods (f) or (g).[18,19]

(*R*)-*N*-(4-Isopropylbenzenesulfonyl)-α-methoxyphenylacetamide [(*R*)-4b]

Crude (*R*)-**4b** (100% ee). An analytical sample was obtained by recrystallization from acetone/isopropyl ether: colorless crystals.

^{1}H NMR ($CDCl_3$): δ = 1.25 (m, 6 H), 2.90−3.04 (m, 1 H), 3.34 (s, 3 H), 4.59 (s, 1 H), 7.22−7.35 (m, 7 H), 7.94 (d, 2 H, *J* = 7.8 Hz), 9.12 (br, 1 H).

(+)-*N*-(4-Isopropylbenzenesulfonyl)-α-(4-methylphenoxy)phenylacetamide [(+)-4c]

Crude **(+)-4c** (100% ee). An analytical sample was obtained by recrystallization from EtOAc/hexane; colorless crystals; mp 137−138.5 °C; $[\alpha]_D^{25}$ +14.5 (*c* = 1.00, MeOH); HPLC (condition A at 240 nm): t_R = 36.1 min; 100% ee.

^{1}H NMR ($CDCl_3$): δ = 1.25−1.28 (m, 6 H), 2.26 (s, 3 H), 2.90−3.04 (m, 1 H), 5.42 (s, 1 H), 6.73 (d, 2 H, *J* = 8.6 Hz), 7.01 (d, 2 H, *J* = 8.6 Hz), 7.30−7.36 (m, 7 H), 7.88 (d, 2 H, *J* = 8.6 Hz), 9.04 (br, 1 H),

(*S*)-*N*-(4-Isopropylbenzenesulfonyl)-α-cyclohexylphenylacetamide [(*S*)-4d]

Crude (*S*)-**4d** (95% ee). An analytical sample was obtained after column chromatography on silica gel (CH_3Cl/MeOH, 95/5); colorless foam; $[\alpha]_D^{26}$ +92.8 (*c* = 1.00, MeOH); HPLC (condition C): t_R = 13.9 min; 95% ee.

^{1}H NMR ($CDCl_3$): δ = 0.61−0.72 (m, 1 H), 0.80−0.93 (m, 1 H), 1.05−1.10 (m, 2 H), 1.19 (br, 2 H), 1.27 (d, 6 H, *J* = 7.2 Hz), 1.58 (br, 4 H), 1.90−2.05 (m, 1 H), 2.93−3.02 (m, 1 H), 3.00 (d, 1 H, *J* = 9.9 Hz), 7.05−7.09 (m, 2 H), 7.21−7.23 (m, 3 H), 7.31 (d, 2 H, *J* = 8.3 Hz), 7.80 (d, 2 H, *J* = 8.3 Hz), 8.23 (br, 1 H).

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(18) A catalytic amount of DMF was added for the preparation of **2b**–**d**.
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