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DEVELOPMENT OF NEW LIGANDS FOR THE RECYCLABLE CATALYTIC ASYMMETRIC TRANSFER HYDROGENATION IN IONIC LIQUID

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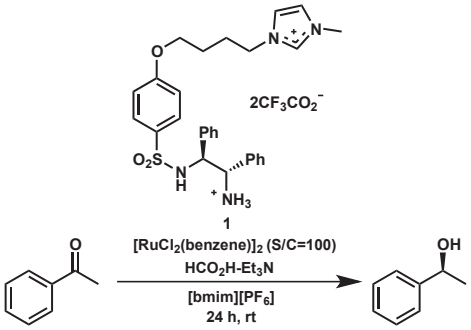
Abstract – The new ligands with improved enantioselectivity, recyclable catalytic asymmetric transfer hydrogenation (RCATH) reaction efficiency, and physical properties were synthesized. The new ligands were synthesized and used in RCATH. Among them, ligands **2e** and **2f** provided high enantioselectivity and reaction efficiency compared to a previously reported ligand **1** used in RCATH.

INTRODUCTION

Optically active secondary alcohols are important intermediates for many bioactive compounds. In addition, the asymmetric reduction of prochiral ketones is one of most useful strategies in the production of chiral alcohols.[1]

Although many types of homogeneous catalytic hydrogenations have been developed,[2] the catalytic asymmetric hydrogenation of various ketones with high reactivity and enantioselectivity remains important and challenging. Catalytic asymmetric transfer hydrogenation (CATH) using Ru and chiral ligands was reported by Noyori *et al*.,[3,4] who also conducted many applied studies.[4] We have synthesized ligand **1** and used it for CATH in order to demonstrate a practical asymmetric synthesis.[5]



Cycle	Conversion (ee)[a]
1st	98 (92)
2nd	> 99 (93)
3rd	99 (93)
4th	92 (93)
5th	75 (90)

[a] Determined by capillary GLC analysis using a chiral Cyclodex-B column.

Scheme 1. Previous work

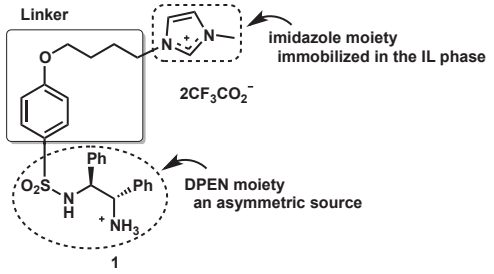


Figure 1. Components of ligand **1**

CATH is a very useful method as an alternative to catalytic asymmetric hydrogenation with molecular hydrogen for obtaining optically active secondary alcohols from prochiral ketones.[6] CATH has many advantages in terms of safety and convenience compared with conventional hydrogenation because it employs 2-propanol or formic acid as a hydrogen source. In our previous study, we demonstrated the reactivity of a Ru-ligand **1** complex in ionic liquid and catalyst recyclability in a recyclable catalytic asymmetric transfer hydrogenation (RCATH) system (Scheme 1). However, ligand **1** was not sufficiently reactive to be reuse more than 5 times and was unwieldy because it was in the form of oil at room temperature.[5] Ligand **1** comprises three scaffolds: a diphenylethylenediamine (DPEN) moiety as an asymmetric coordination site, an imidazolium moiety that immobilizes with the ionic liquid and a linker group (Figure 1). Based on our previous results, we hypothesize that altering the electron density of the aromatic linker should be improved ligand reactivity and stability and possibly also enhance its physical properties. Therefore, in this study, we focused our efforts on the linker group connecting the DPEN moiety and the imidazolium moiety of ligand **1**. We present novel chiral ligands **2**, prepared by modifying the linker group of ligand **1**, and utilize these new ligands in RCATH, critically examining their reactivity and physical properties.

RESULTS AND DISCUSSION

The synthetic goal was to screen the linker group that connects the DPEN and imidazolium moieties (Figure 2). The rationale for this approach was to optimize the linker in order to strengthen Ru coordination because the coordination of chiral DPEN depends on linker structure as well as the electron density of the aromatic ring. In particular, ligands with a new linker site, including 4-[(alkylenoyl)oxy]phenyl, 4-(alkylenoxycarbonyl)phenyl, or

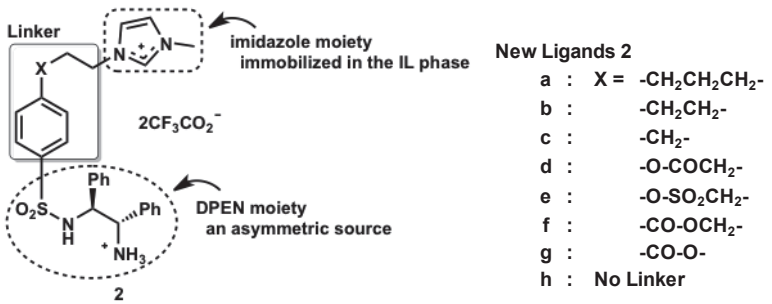


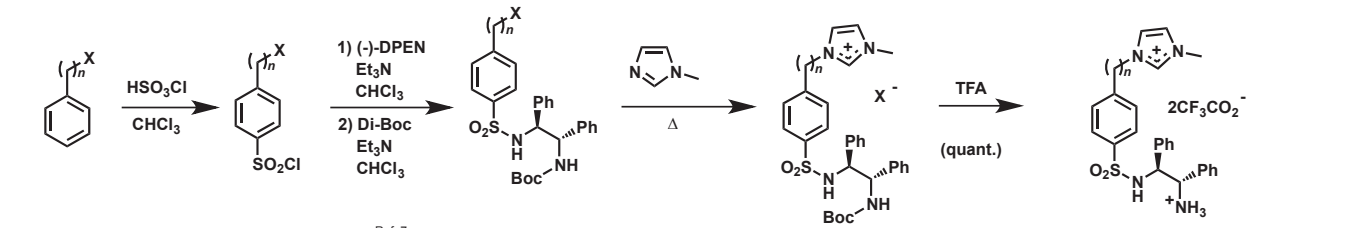
Figure 2. New ligand **2**

4-[(alkylenesulfonyl)oxy]phenyl groups were synthesized. In addition, ligands that directly connect the DPEN and imidazolium moieties were studied.

The novel ligands **2** were utilized in the RCATH of acetophenone to examine the reactivity and reuse efficiency.

Ligands **2a–c** with various alkyl chain lengths were synthesized as shown in Scheme 2.

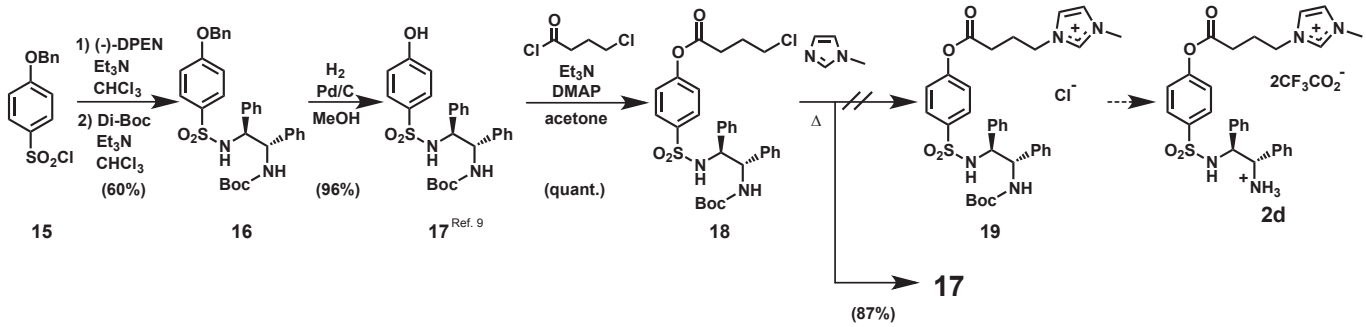
The sulfonation of commercially available compound **3** generated sulfonyl chloride **6**[7] in 93% yield. Subsequently, **6** underwent amidation using chiral diamine and Boc protection to obtain amide **9** in 72% yield. The desired imidazolium salt **2a** was obtained by *N*-alkylation and Boc deprotection in excellent yield (98%). Overall, ligand **2a** was achieved in four steps with a total yield of 61%, representing a reasonably good yield over a relatively short synthetic process. Ligands **2b** and **2c** were also prepared from their corresponding alkyl chlorides through sulfonyl chlorides **7**[8] (for **2b**) or **8**[8] (for **2c**) via a similar approach. Ligand **2b**, which has a tetramethylene group in the linker moiety, was produced in an overall yield of 50% in four steps, and ligand **2c**, which has a trimethylene group in the linker moiety, was achieved in 46% overall yield in four steps. Furthermore, ligands **2a** and **2b** were pale yellow solids, whereas ligand **2c** was an oil.



Scheme 2. Synthesis of **2a-c**

Preparation of ligand **2d**, which contains an ester group, was attempted as shown in Scheme 3.

Compound **17** was synthesized as described in the literature,[9] and a linker moiety was introduced to **17** in order to give phenyl ester **18** in high yield. We attempted to introduce the imidazolium moiety to the

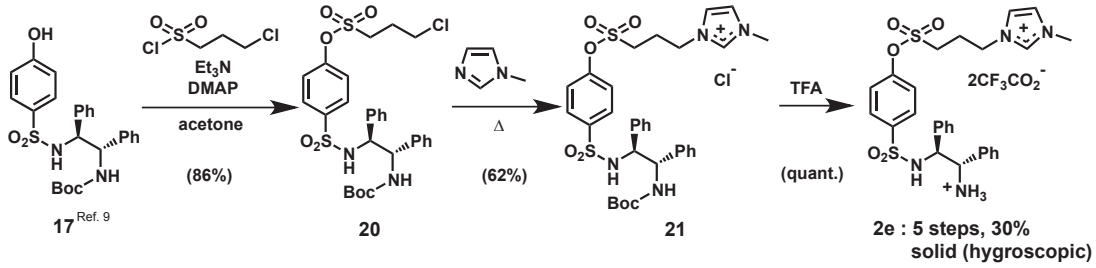


Scheme 3. Attempt of synthesis of **2d**

phenyl ester **18**, and instead of achieving the target compound **19**, we obtained **17** with a cleaved ester. Based on this, the synthesis of ligand **2d** was abandoned.

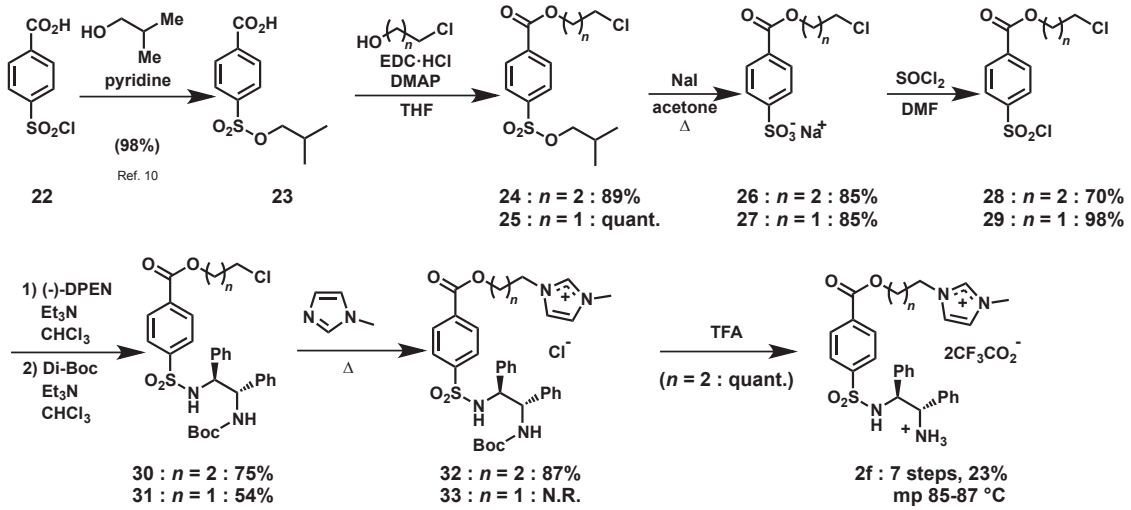
Next, we synthesized ligand **2e** containing a sulfonate ester scaffold instead of the ester group (Scheme 4).

As described previously, the linker moiety was introduced into compound **17** and we obtained the sulfonate ester **20** in good yield. A substitution reaction of the sulfonate ester **20** followed by Boc deprotection gave the imidazolium salt **2e**, and the target ligand **2e** was isolated in 30% overall yield in five steps. Ligand **2e** is a solid but hygroscopic at room temperature.



Scheme 4. Synthesis of **2e**

Ligand **2f**, containing an ester, was synthesized according to Scheme 5.

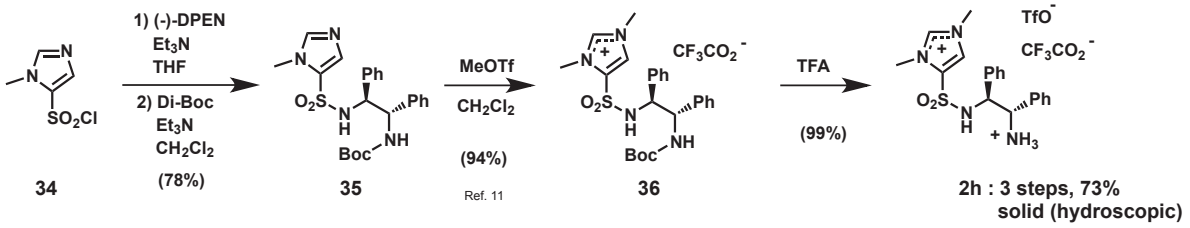


Scheme 5. Synthesis of **2f**

After the sulfonyl site of the commercial reagent 4-(chlorosulfonyl)benzoic acid **22** was protected,[10] sulfonate **24** was obtained by introduction of the linker moiety. Benzoate ester **24** was deprotected and chlorinated to give sulfonyl chloride **28** in good yield. The successive introduction of Boc protected chiral diamine and an imidazolium moiety to compound **28** was performed, followed by Boc deprotection. As a

result, the target ligand **2f** was prepared in 23% overall yield in seven steps. Ligand **2f** is a solid at ambient temperature and pressure. Furthermore, to compare the effects of carbon chain length on reactivity and physical properties, we attempted to synthesize ligand **2g**. However, this synthesis attempt, in same manner as that for ligand **2f**, led to ester cleavage.

Ligand **2h** was synthesized as depicted in Scheme 6.



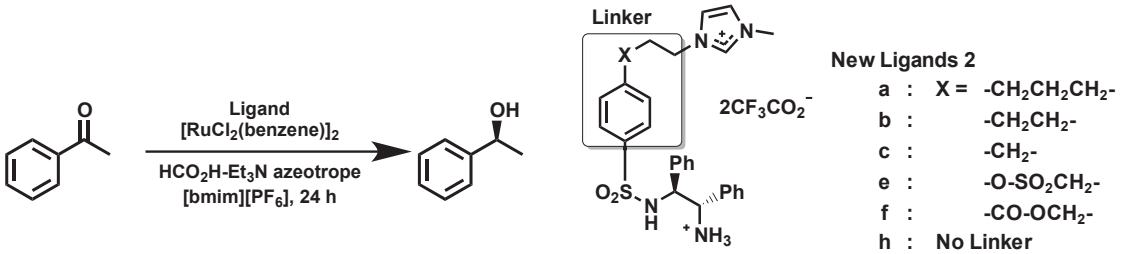
Scheme 6. Synthesis of **2h**

Commercially available 1-methyl-1*H*-imidazole-4-sulfonyl chloride (**34**) was used as a starting material. Amidation of the chiral diamine and Boc protection directly produced amide **35** in 78% yield. The target ligand **2h** was obtained in 93% overall yield from **35** in two steps by *N*-methylation using methyl triflate[11] and Boc deprotection. Ligand **2h** is an amorphous solid at ambient temperature and pressure.

Among the synthesized compounds, **2a**, **2b**, **2e**, **2f**, and **2h** are solids and are thus easier to handle than ligand **1**, which is an oil.

We initiated RCATH with the synthetic ligands and compared their performance based on the reactivity and enantioselectivity with acetophenone which was chosen as a representative prochiral ketone (Table 1).

Table 1. RCATH with ligand **1** or **2**



Cycle	Conv. (%ee)*						
	1 [Ref. 5]	2a	2b	2c	2e	2f	2h
1st	98% (92)	99% (93)	98% (94)	99% (93)	99% (94)	99% (92)	>99% (87)
2nd	>99% (93)	99% (93)	98% (94)	99% (94)	83% (94)	99% (94)	>99% (87)
3rd	99% (93)	96% (94)	81% (95)	97% (95)	73% (95)	>99% (94)	97% (84)
4th	92% (93)	71% (94)	58% (96)	60% (95)	63% (94)	98% (94)	94% (87)
5th	75% (90)	43% (94)	22% (96)	25% (94)	29% (94)	93% (94)	91% (87)

* Determined by GLC.

Table 2. Percentages of remaining Ru in ionic liquid after RCATH

	Catalyst 1	Ru/ligand complex					
		2a	2b	2c	2e	2f	2h
% of remaining Ru in ionic liquid	>99%	61.3%	38.6%	70.2%	32.7%	>99%	95.9%

Our method yielded the chiral secondary alcohol in up to 96% ee using ligands **2a–c**, **e**, and **f** with the linker moiety, which are good results in comparison with ligand **1** with the ether linker. Although the enantioselectivity of ligand **2h** without the linker moiety decreased slightly, the overall catalytic activity was maintained. Of these ligands, ligand **2f** maintained 93% conversion rates in the 5th recycling. In addition, the reactivity and reuse efficiency was improved in some of the synthesized ligands compared with ligand **1**.

From the above results, it is evident that the introduction of electron withdrawing groups to the linker in the ligand strengthens the complex formation between Ru and the ligand; this is in good agreement with the report on the advantages of this type of approach in CATH.[12] Furthermore, we found that the enantioselectivity by the ligand containing a linker group such as **2f** showed better result than the ligand without a linker (**2h**), and reactivity was maintained whether the ligand contained an ester group at a linker moiety (**2f**) or not, i.e., a less lipophilic ligand (**2h**). However, comparison of ligands **2a–c** suggests that the reactivity of the Ru-ligand complex improves with increasing alkyl chain length of the linker. From this, it is considered that other factors affect recyclability, in addition to lipophilicity which influences ligand retention in the ionic liquid.

To confirm the effects of ligand structure on recyclability in more detail, we quantified the residual Ru in the ionic liquid phase after the RCATH reaction (Table 2). After the 5th cycle of the reaction using ligands **2**, inductively coupled plasma mass spectrometry (ICP-MS) was employed to determine the quantity of Ru remaining in the ionic liquid phase.

In the case of **2f** and **2h**, more than 90% of the Ru was detected in the ionic liquid, indicating a significant correlation between remaining Ru and the conversion rates in RCATH. Conversely, a lower percentage of Ru ions remained in the ionic liquid after RCATH with ligands **2a–c** and **2e**, leading to a decrease in the conversion rates in the 5th cycle of RCATH. However, the results obtained from ligands **2a–c** suggest that loss of Ru from the ionic liquid is not the only cause for the decline of the active complex. Surprisingly, most of the Ru remained in the ionic liquid phases when ligands **1** and **2f** (>99%) were employed; however, the use of **2f** gave better results (93%, 5th cycle) compared with **1** (75%, 5th cycle). From these facts, we hypothesize that recyclability in RCATH is not only determined by ligand stability

but also by the solubility of the ligand in an organic solvent, with lower solubility providing better recyclability.

In conclusion, the aim of this study was to develop new chiral ligands that could perform RCATH efficiently. Among the series of chiral ligands **2** synthesized in this study, we found that ligand **2f** was most suitable for RCATH. Good enantioselectivity was achieved by reducing the electron density of the benzene ring in comparison with ligand **1**. The good conversion rate by **2f** was explained by the percentage of residual Ru in the ionic liquid after 5th cycle of RCATH as determined by ICP-MS. In addition, ligand **2f** has better physical properties, i.e., it is solid at ambient temperature and pressure, making it easier to handle than ligand **1**, which is an oil.

EXPERIMENTAL

^{1}H, ^{13}C, and ^{19}F NMR spectra were obtained using a JEOL ECA-500 (^{1}H: 500 MHz, ^{13}C: 125 MHz, ^{19}F: 470 MHz) or JEOL JNM-ECP400 (^{1}H: 400 MHz, ^{13}C: 100 MHz). Proton and carbon chemical shifts are expressed in ppm and referenced to the tetramethylsilane singlet. ^{19}F NMR spectra are referenced to trifluoroacetic acid. Mass spectra were obtained using a JEOL MStation JMS-700 spectrometer. IR spectra were obtained using an IRAffinity-1 spectrometer (Shimadzu). Elemental analyses were performed on a PERKIN ELMER series II CHNS/O Analyzer 2400. Silica gel column chromatography was performed with a Merck Art. 7734. Preparative thin-layer chromatography was performed on Nacalai Silica gel 60 PF_{254} pre-coated plates. Optical rotations were measured with a Jasco P-1020 Polarimeter in a 1 cm path length cell. GLC was performed on an Agilent Technologies 6890N instrument equipped with a J&W Scientific chiral Cyclodex-B column (ϕ 0.25 mm × 30 m). Helium was used as the carrier gas and FID as the detector. ICP-MS was measured with an Agilent 7700x/Mass Hunter. All reagents and starting materials were purchased from commercial sources and used without further purification unless otherwise indicated.

1-[5-[4-[[[(1*S*,2*S*)-2-Amino-1,2-diphenylethyl]amino]sulfonyl]phenyl]pentyl]-3-methyl-1*H*-imidazolium Mono(trifluoroacetate) Salt with Trifluoroacetic Acid (2a)

TFA (0.115 mL, 1.50 mmol) was added to **12** (103 mg, 0.150 mmol) at 0 °C under N_2, and the mixture was stirred for 3.5 h. The volatile material was removed under reduced pressure. Toluene was added to the residue, and the volatile material was removed (×3) to obtain compound **2a**.

Yield: 110 mg (quant.). Light yellow solid. Mp 84.8-87.4 °C. $[\alpha]_D^{24}$ −57.4 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.27-1.35 (2H, m, C$\underline{H}_2$), 1.58 (2H, quint, *J* = 7.7 Hz, C$\underline{H}_2$), 1.89 (2H, quint, *J* = 7.5 Hz, C$\underline{H}_2$), 2.55 (2H, t, *J* = 7.5 Hz, ArC$\underline{H}_2$), 3.91 (3H, s, N-C$\underline{H}_3$), 4.19 (2H, t, *J* = 7.3 Hz, C$\underline{H}_2$N), 4.52 (1H, d, *J* = 11.0 Hz, C$\underline{H}$(Ph)NH), 4.56 (1H, d, *J* = 11.0 Hz, C$\underline{H}$(Ph)NH), 6.71-6.93 (5H, m, Ph-$\underline{H}$), 7.04 (2H, d, *J* = 8.5 Hz, SO_2Ar-$\underline{H}$), 7.18-7.23 (5H, m, Ph-$\underline{H}$), 7.47 (2H, d, *J* = 8.4 Hz, SO_2Ar-$\underline{H}$), 7.54 (1H, t, *J* = 1.6 Hz,

imidazole-H), 7.60 (1H, t, *J* = 1.6 Hz, imidazole-H), 8.92 (1H, s, 2-imidazole-H). ^{13}C-NMR (CD_3OD) δ: 26.6, 30.7, 31.4, 32.1, 36.4, 50.7, 60.7, 63.0, 123.6, 124.9, 128.2, 128.7, 128.9, 129.1, 129.2, 129.7, 130.0, 130.4, 134.7, 136.5, 137.8, 139.0, 148.8. ^{19}F-NMR (CD_3OD) δ: 1.62 (s). IR (KBr) cm^{-1}: 3424, 3065, 2940, 2864, 1684, 1458, 1331, 1204, 1163, 1132, 700, 586. FABMS (NBA) *m/z*: 503 ([M-2CF_3CO_2-H]$^+$). FABMS (NBA) *m/z*: 113 ([CF_3CO_2]$^-$). *Anal.* Calcd for $C_{33}H_{36}F_6N_4O_6S \cdot H_2O$: C, 52.94; H, 5.12; N, 7.48. Found: C, 52.90; H, 5.21; N, 7.69.

1-[5-[4-[[[(1*S*,2*S*)-2-Amino-1,2-diphenylethyl]amino]sulfonyl]phenyl]butyl]-3-methyl-1*H*-imidazolium Mono(trifluoroacetate) Salt with Trifluoroacetic Acid (2b)

Compound **2b** was synthesized from **13** (115 mg, 0.18 mmol) in the same manner as the synthesis of **2a**. Yield: 128 mg (quant.). Light yellow solid. Mp 99.7-101.8 °C. $[\alpha]_D^{24}$ −63.1 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.52-1.60 (2H, m, CH$_2$), 1.81-1.88 (2H, m, CH$_2$), 2.60 (2H, t, *J* = 7.7 Hz, Ar-CH$_2$), 3.91 (3H, s, N-CH$_3$), 4.21 (2H, t, *J* = 7.3 Hz, CH$_2$N), 4.50 (1H, d, *J* = 10.2 Hz, CH(Ph)NH_3^+), 4.66 (1H, d, *J* = 10.6 Hz, CH(Ph)NH), 6.72 (2H, d, *J* = 7.4 Hz, SO_2Ar-H), 6.82-6.91 (3H, m, Ph-H), 7.06 (2H, m, Ph-H), 7.17-7.23 (5H, m, Ph-H), 7.47 (2H, d, *J* = 8.4 Hz, SO_2Ar-H), 7.55 (1H, s, imidazole-H), 7.60 (1H, s, imidazole-H), 8.92 (1H, s, 2-imidazole-H). ^{13}C-NMR (CD_3OD) δ: 28.6, 30.5, 35.7, 36.5, 50.5, 60.8, 63.1, 123.7, 125.1, 128.4, 128.8, 128.9, 129.17, 129.23, 129.8, 130.0, 130.4, 134.8, 136.6, 137.9, 139.4, 148.2. ^{19}F-NMR (CD_3OD) δ: 1.97 (s). IR (KBr) cm^{-1}: 3065, 2941, 2868, 1674, 1458, 1330, 1204, 1161, 1132. FABMS (Gly) *m/z*: 489 ([M-2CF_3CO_2-H]$^+$). FABMS (NBA) *m/z*: 113 ([CF_3CO_2]$^-$). *Anal.* Calcd for $C_{32}H_{34}F_6N_4O_6S$: C, 53.63; H, 4.78; N, 7.82. Found: C, 53.42; H, 5.00; N, 8.03.

1-[5-[4-[[[(1*S*, 2*S*)-2-Amino-1,2-diphenylethyl]amino]sulfonyl]phenyl]propyl]-3-methyl-1*H*-imidazolium Mono(trifluoroacetate) Salt with Trifluoroacetic Acid (2c)

Compound **2c** was synthesized from **14** (57 mg, 0.12 mmol) in the same manner as the synthesis of **2a**. Yield: 83 mg (quant.). Light yellow oil. $[\alpha]_D^{22}$ −58.7 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 2.08-2.15 (2H, m, CH$_2$), 2.62 (2H, t, *J* = 7.7 Hz, Ar-CH$_2$), 3.90 (3H, s, N-CH$_3$), 4.19 (2H, t, *J* = 7.1 Hz, CH$_2$N), 4.48-4.51 (1H, m, CH(Ph)NH), 4.65-4.68 (1H, m, CH(Ph)NH), 6.73 (2H, d, *J* = 7.2 Hz, SO_2Ar-H), 6.83-6.92 (3H, m, Ph-H), 7.09 (2H, d, *J* = 7.7 Hz, Ph-H), 7.17-7.23 (5H, m, Ph-H), 7.49 (2H, d, *J* = 8.0 Hz, SO_2Ar-H), 7.54 (1H, s, imidazole-H), 7.60 (1H, s, imidazole-H), 8.89 (1H, s, 2-imidazole-H). ^{13}C-NMR (CD_3OD) δ: 32.2, 33.1, 36.5, 50.4, 60.8, 63.1, 123.6, 125.1, 128.5, 128.8, 129.0, 129.2, 129.3, 129.8, 130.0, 130.5, 134.8, 136.6, 138.0, 139.7, 146.9. ^{19}F-NMR (CD_3OD) δ: 1.61 (s). IR (KBr) cm^{-1}: 3433, 3092, 3065, 2957, 2872, 1678, 1601, 1331, 1204, 1163. FABMS (NBA) *m/z*: 475 ([M-2CF_3CO_2-H]$^+$). FABMS (NBA) *m/z*: 113 ([CF_3CO_2]$^-$). *Anal.* Calcd for $C_{31}H_{32}F_6N_4O_6S$: C, 52.99; H, 4.59; N, 7.97. Found: C, 52.97; H, 4.79; N, 8.19.

1-[3-[4-[[[(1*S*,2*S*)-2-Amino-1,2-diphenylethyl]amino]sulfonyl]phenoxyl]sulfonylpropyl]-3-methyl-1*H*-imidazolium Mono(trifluoroacetate) Salt with Trifluoroacetic Acid (2e)

Compound **2e** was synthesized from **21** (30 mg, 0.043 mmol) in the same manner as the synthesis of **2a**. Yield: 34 mg (quant.). White hygroscopic solid. $[\alpha]_D^{24}$ −21.7 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 2.51 (2H, quint, *J* = 7.3 Hz, $CH_2C\underline{H}_2CH_2$), 3.51 (2H, t, *J* = 7.4 Hz, $C\underline{H}_2$), 3.92 (3H, s, N-$C\underline{H}_3$), 4.42 (2H, t, *J* = 7.3 Hz, $C\underline{H}_2$), 4.54 (1H, d, *J* = 11.0 Hz, C<u>H</u>(Ph)NH), 4.71 (1H, d, *J* = 11.0 Hz, C<u>H</u>(Ph)NH), 6.74-6.96 (5H, m, Ph-<u>H</u>), 7.15 (2H, dt, *J* = 8.8 and 2.6 Hz, SO_2Ar-<u>H</u>), 7.19-7.24 (5H, m, Ph-<u>H</u>), 7.58 (1H, t, *J* = 1.7 Hz, imidazole-<u>H</u>), 7.63 (2H, dt, *J* = 9.2 and 2.4 Hz, SO_2Ar-<u>H</u>), 7.67 (1H, t, *J* = 1.9 Hz, imidazole-<u>H</u>), 8.97 (1H, s, 2-imidazole-<u>H</u>). ^{13}C-NMR (CD_3OD) δ: 24.9, 35.9, 47.8, 48.1, 59.9, 62.5, 122.8, 123.0, 124.6, 128.1, 128.5, 128.5, 128.7, 129.4, 129.7, 129.8, 134.1, 135.6, 137.7, 140.1, 152.2. ^{19}F-NMR (CD_3OD) δ: 1.49 (s). IR (KBr) cm^{-1}: 3435, 3066, 2875, 1678, 1203, 1174, 1149, 869. FABMS (NBA) *m/z*: 555 ($[M-2CF_3CO_2-H]^+$). FABMS (NBA) *m/z*: 113 ($[CF_3CO_2]^-$). *Anal.* Calcd for $C_{31}H_{32}F_6N_4O_9S_2 \cdot 1/2H_2O$: C, 47.03; H, 4.20; N, 7.08. Found: C, 47.27; H, 4.50; N, 7.34.

1-[3-[4-[[[(1*S*,2*S*)-2-Amino-1,2-diphenylethyl]amino]sulfonyl]benzoyloxy]propyl]-3-methyl-1*H*-imidazolium Mono(trifluoroacetate) Salt with Trifluoroacetic Acid (2f)

Compound **2f** was synthesized from **32** (81 mg, 0.125 mmol) in the same manner as the synthesis of **2a**. Yield: 93 mg (quant.). Colorless solid. Mp 85.1-86.9 °C. $[\alpha]_D^{24}$ −64.1 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 2.35 (2H, quint, *J* = 6.6 Hz, $OCH_2C\underline{H}_2CH_2$), 3.86 (3H, s, N-$C\underline{H}_3$), 4.37 (2H, t, *J* = 7.1 Hz, $C\underline{H}_2$N), 4.37 (1H, t, *J* = 6.0 Hz, $OC\underline{H}_2$), 4.52 (1H, d, *J* = 10.9 Hz, C<u>H</u>(Ph)NH), 4.74 (1H, d, *J* = 10.9 Hz, C<u>H</u>(Ph)NH), 6.75 (2H, dt, *J* = 6.9 and 1.9 Hz, Ph-<u>H</u>), 6.82-7.22 (10H, m, Ar-<u>H</u>), 7.53 (1H, t, *J* = 1.8 Hz, imidazole-<u>H</u>), 7.67 (1H, t, *J* = 1.8 Hz, imidazole-<u>H</u>), 7.80 (2H, dt, *J* = 8.8 and 1.8 Hz, Ph-<u>H</u>), 8.96 (1H, s, 2-imidazole-<u>H</u>). ^{13}C-NMR (CD_3OD) δ: 30.2, 36.4, 48.1, 60.6, 62.2, 63.2, 123.7, 125.1, 128.3, 128.8, 129.0, 129.1, 129.3, 130.0, 130.4, 130.8, 134.2, 134.7, 136.4, 138.1, 146.0, 166.2. ^{19}F-NMR (CD_3OD) δ: 1.58 (s). IR (KBr) cm^{-1}: 3414, 3067, 2878, 1678, 1203, 1128, 700, 611. FABMS (NBA) *m/z*: 519 ($[M-2CF_3CO_2-H]^+$). FABMS (NBA) *m/z*: 113 ($[CF_3CO_2]^-$). *Anal.* Calcd for $C_{32}H_{32}F_6N_4O_8S$: C, 51.47; H, 4.32; N, 7.50. Found: C, 51.33; H, 4.43; N, 7.60.

1,3-Dimethyl-[[[(1*S*,2*S*)-2-amino-1,2-diphenylethyl]amino]sulfonyl]-1*H*-imidazolium Mono(trifluoromethanesulfonate) Salt with Trifluoroacetic Acid (2h)

Compound **2h** was synthesized from **36** (66 mg, 0.104 mmol) in the same manner as the synthesis of **2a**. Yield: 63 mg (quant.). White hygroscopic solid. $[\alpha]_D^{25}$ −46.61 (c 1.24, MeOH). ^{1}H-NMR (DMSO-d_6) δ: 3.57 (3H, s, N-$C\underline{H}_3$), 3.72 (3H, s, N-$C\underline{H}_3$), 4.66 (1H, d, *J* = 4.5 Hz, C<u>H</u>(Ph)NH), 4.71 (1H, d, *J* = 10.1 Hz, C<u>H</u>(Ph)NH), 6.96-7.26 (10H, m, 2 × Ph-<u>H</u>), 7.88 (1H, d, *J* = 1.6 Hz, 5-imidazole-<u>H</u>), 8.93 (4H, s, N<u>H</u> and $N\underline{H}_3$), 10.2 (1H, s, 2-imidazole-<u>H</u>). ^{13}C-NMR (DMSO-d_6) δ: 34.9, 36.0, 57.7, 61.7, 127.7, 128.1, 128.2,

128.4, 128.7, 129.1, 129.3, 130.7, 134.0, 135.4, 140.4. ^{19}F-NMR (CD_3OD) δ: −1.60 (s), 1.33 (s). IR (KBr) cm^{-1}: 3396, 3190, 3044, 2900, 2850, 1685, 1670, 1580, 1276, 1250, 1200, 1172, 1027, 638. HRMS (FAB^+) *m/z*: Found, 371.1547 ([M-CF_3CO_2-TfO-H]$^+$) (Calcd for $C_{19}H_{23}N_4O_2S^+$: 371.1542). MS (CI) *m/z* (rel. int. %): 113 ($CF_3CO_2^-$, 100). MS (CI) *m/z* (rel. int. %): 149 ($CF_3O_3S^-$, 100). *Anal.* Calcd for $C_{22}H_{24}F_6N_4O_7S_2 \cdot 2H_2O$: C, 39.40; H, 4.21; N, 8.35. Found: C, 39.22; H, 3.95; N, 8.10.

4-(5-Bromopentyl)benzenesulfonyl chloride (6)[7]

To a solution of 5-phenylpentyl bromide **3** (0.54 mL, 2.95 mmol) in $CHCl_3$ (12.5 mL), a solution of chloroslfonic acid 2.0 mL (30 mmol) was slowly added at 0 °C. The mixture was stirred for 18 h at room temperature. The solvent was added sat. aq. $NaHCO_3$ and extracted with AcOEt. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (AcOEt : *n*-hexane = 10 : 1) to give compound **6**.

Yield: 882 mg (93%). Light yellow oil.

4-(4-Chlorobutyl)benzenesulfonyl chloride (7)[8]

Compound **7** was synthesized from **4** (0.49 mL, 3.00 mmol) in the same manner as the synthesis of **6**.

Yield: 542 mg (68%). Colorless oil.

4-(3-Chloropropyl)-benzenesulfonyl chloride (8)[8]

Compound **7** was synthesized from **5** (0.44 mL, 3.00 mmol) in the same manner as the synthesis of **6**.

Yield: 509 mg (67%). Colorless oil.

***N*-[(1*S*,2*S*)-2-*t*-Butoxycarbonylamino-1,2-diphenylethyl]-4-(5-bromopentyl)benzenesulfonamide (9)**

To a solution of (1*S*,2*S*)-(−)-1,2-diphenylethylenediamine (DPEN) (552 mg, 2.60 mmol) and Et_3N (0.145 mL, 1.04 mmol) in $CHCl_3$ (5.00 mL), a solution of **6** (846 mg, 2.60 mmol) in $CHCl_3$ (10.0 mL) and a solution of Et_3N (0.580 mL, 4.16 mmol) in $CHCl_3$ (10.0 mL) were slowly added at the same time at 0 °C. After stirring for 19 h at room temperature (rt), a solution of $(Boc)_2O$ (852 mg, 3.90 mmol) and Et_3N (0.544 mL, 3.90 mmol) in $CHCl_3$ (5.00 mL) was added to the above solution. The mixture was stirred for 16 h at rt. The solvent was removed under reduced pressure and sat. aq. $NaHCO_3$ was added to the residue. The product was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (AcOEt : *n*-hexane : $CHCl_3$ = 1 : 5 : 2) to give compound **9**.

Yield: 1.12 g (72%). White solid (recryst. from *n*-hexane/$CHCl_3$). Mp 198.5-199.3 °C. $[\alpha]_D^{24}$ −25.8 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.38-1.46 (2H, m, C$\underline{H}_2$), 1.46 (9H, s, C(C$\underline{H}_3$)$_3$), 1.52-1.60 (2H, m, C$\underline{H}_2$), 1.82-1.90 (2H, m, C$\underline{H}_2$), 2.56 (2H, t, *J* = 7.7 Hz, ArC$\underline{H}_2$), 3.38 (2H, t, *J* = 6.8 Hz, C$\underline{H}_2$Br), 4.59 (1H, dd, *J* = 7.4 and 9.6 Hz, C$\underline{H}$(Ph)NH), 4.79 (1H, t, *J* = 8.8 Hz, C$\underline{H}$(Ph)NH), 5.26 (1H, br-d, *J* = 7.7 Hz, N$\underline{H}$), 6.11 (1H, br-s, N$\underline{H}$), 6.76 (2H, d, *J* = 6.9 Hz, Ar-$\underline{H}$), 6.92-7.16 (10H, m, Ar-$\underline{H}$), 7.44 (2H, d, *J* = 8.4 Hz, Ar-$\underline{H}$).

^{13}C-NMR ($CDCl_3$) δ: 27.6, 28.3, 30.1, 32.4, 33.4, 35.4, 60.0, 63.9, 80.6, 127.0, 127.3, 127.3, 127.4, 127.8, 127.9, 128.4, 128.5, 137.7, 138.1, 138.2, 146.9, 156.8. IR ($CHCl_3$) cm^{-1}: 3026, 2937, 1693, 1492, 1159, 700. FABMS (NBA) *m/z*: 601 ($[M+H]^+$). *Anal.* Calcd for $C_{30}H_{37}BrN_2O_4S$: C, 59.89; H, 6.20; N, 4.66. Found: C, 59.90; H, 6.28; N, 4.65.

***N*-[(1*S*,2*S*)-2-*t*-Butoxycarbonylamino-1,2-diphenylethyl]-4-(4-chlorobutyl)benzenesulfonamide (10)**

Compound **10** was synthesized from **7** (538 mg, 2.00 mmol) in the same manner as the synthesis of **9**. Yield: 837 mg (77%). White solid (recryst. from AcOEt). Mp 203.4-205.4 °C. $[\alpha]_D^{24}$ −34.7 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.66-1.75 (4H, m, C<u>H</u>$_2$), 2.58 (2H, t, *J* = 7.0 Hz, Ar-C<u>H</u>$_2$), 3.52 (2H, t, *J* = 6.2 Hz, C<u>H</u>$_2$Cl), 4.60 (1H, dd, *J* = 9.5 and 7.3 Hz, C<u>H</u>(Ph)NH), 4.80 (1H, t, *J* = 8.8 Hz, C<u>H</u>(Ph)NH), 5.28 (1H, N<u>H</u>), 6.17 (1H, N<u>H</u>), 6.76 (2H, d, *J* = 7.3 Hz, SO_2Ar-<u>H</u>), 6.92-7.02 (7H, m, Ph-<u>H</u>), 7.16 (3H, t, *J* = 3.7 Hz, Ph-<u>H</u>), 7.44 (2H, d, *J* = 8.1 Hz, SO_2Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 28.1, 28.3, 31.8, 34.8, 44.6, 60.1, 64.0, 80.7, 127.1, 127.3, 127.4, 127.5, 127.91, 127.95, 128.4, 128.5, 137.7, 138.1, 138.4, 146.4, 156.9. IR ($CHCl_3$) cm^{-1}: 3686, 3017, 2943, 1694, 1601, 1495, 1159. FABMS (NBA) *m/z*: 543 ($[M+H]^+$). *Anal.* Calcd for $C_{29}H_{35}ClN_2O_4S$: C, 64.13; H, 6.50; N, 5.16. Found: C, 63.98; H, 6.60; N, 5.14.

***N*-[(1*S*,2*S*)-2-*t*-Butoxycarbonylamino-1,2-diphenylethyl]-4-(3-chloropropyl)benzenesulfonamide (11)**

Compound **11** was synthesized from **8** (301 mg, 1.18 mmol) in the same manner as the synthesis of **9**. Yield: 471 mg (75%). White solid (recryst. from AcOEt). Mp 207.8-209.6 °C. $[\alpha]_D^{24}$ −37.1 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.46 (9H, s, C(C<u>H</u>$_3$)$_3$), 1.95-2.04 (2H, m, C<u>H</u>$_2$), 2.71 (2H, t, *J* = 7.3 Hz, Ar-C<u>H</u>$_2$), 3.42 (2H, t, *J* = 6.4 Hz, C<u>H</u>$_2$Cl), 4.61 (1H, dd, *J* = 9.5 and 7.4 Hz, C<u>H</u>(Ph)NH), 4.80 (1H, t, *J* = 8.8 Hz, C<u>H</u>(Ph)NH), 5.28 (1H, d, *J* = 3.2 Hz, N<u>H</u>), 6.20 (1H, N<u>H</u>), 6.76 (2H, d, *J* = 7.0 Hz, SO_2Ar-<u>H</u>), 6.91-7.03 (7H, m, Ph-<u>H</u>), 7.16 (3H, t, *J* = 3.3 Hz, Ph-<u>H</u>), 7.45 (2H, d, *J* = 6.6 Hz, SO_2Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 28.3, 32.5, 33.5, 43.7, 60.1, 64.1, 80.7, 127.2, 127.35, 127.37, 127.5, 127.93, 127.95, 128.55, 128.58, 137.7, 138.1, 138.8, 145.3, 156.9. IR ($CHCl_3$) cm^{-1}: 3686, 3028, 2955, 1697, 1601, 1489, 1161. EIMS *m/z*: Found, 528 (M^+, 0.03), 455 (2.24), 412 (0.65), 322 (27.16), 206 (29.72), 150 (48.09), 106 (100), 57 (13.28). *Anal.* Calcd for $C_{28}H_{33}ClN_2O_4S$: C, 63.56; H, 6.29; N, 5.29. Found: C, 63.42; H, 6.35; N, 5.33.

1-[5-[4-[[[(1*S*,2*S*)-2-[(*t*-Butoxycarbonyl)amino]-1,2-diphenylethyl]amino]sulfonyl]phenyl]pentyl]-3-methyl-1*H*-imidazolium Bromide (12)

A mixture of **9** (150 mg, 0.249 mmol) and 1-methylimidazole (0.198 mL, 2.50 mmol) was heated at 75 ºC for 12 h under N_2. The volatile material was removed under reduced pressure in a glass tube oven, and the residue was washed with AcOEt to obtain compound **12**.

Yield: 168 mg (98%). White solid (recryst. from MeOH/AcOEt). Mp 165.9-167.5 °C. $[\alpha]_D^{24}$ −31.7 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.27-1.35 (2H, m, C$\underline{H}_2$), 1.38 (9H, s, C(C$\underline{H}_3$)$_3$), 1.60 (2H, quint, *J* = 7.6 Hz, C$\underline{H}_2$), 1.89 (2H, quint, *J* = 7.6 Hz, C$\underline{H}_2$), 2.56 (2H, t, *J* = 7.7 Hz, ArC$\underline{H}_2$), 3.90 (3H, s, N-C$\underline{H}_3$), 4.18 (2H, t, *J* = 7.4 Hz, C$\underline{H}_2$N), 4.55 (1H, d, *J* = 8.5 Hz, C$\underline{H}$(Ph)NH), 4.79 (1H, t, *J* = 7.3 Hz, C$\underline{H}$(Ph)NH), 6.85-7.12 (12H, m, Ar-$\underline{H}$), 7.36 (2H, d, *J* = 8.0 Hz, Ar-$\underline{H}$), 7.52 (1H, d, *J* = 1.8 Hz, imidazole-$\underline{H}$), 7.59 (1H, d, *J* = 1.8 Hz, imidazole-$\underline{H}$), 8.91 (1H, s, 2-imidazole-$\underline{H}$). ^{13}C-NMR (CD_3OD) δ: 26.5, 28.7, 30.7, 31.3, 36.1, 36.5, 50.6, 61.1, 64.1, 80.6, 123.6, 124.9, 127.9, 128.1, 128.2, 128.4, 128.6, 128.6, 128.9, 129.1, 129.6, 139.6, 139.9, 140.9, 148.2, 157.8. IR (KBr) cm^{-1}: 3387, 3062, 1685, 1517, 1325, 1157, 700, 590. FABMS (NBA) *m/z*: 603 ([M-Br]$^+$). *Anal.* Calcd for $C_{34}H_{43}BrN_4O_4S \cdot 1/2H_2O$: C, 58.95; H, 6.40; N, 8.09. Found: C, 58.70; H, 6.41; N, 8.00.

1-[5-[4-[[[(1*S*,2*S*)-2-[(*t*-Butoxycarbonyl)amino]-1,2-diphenylethyl]amino]sulfonyl]phenyl]butyl]-3-methyl-1*H*-imidazolium Chloride (13)

Compound **13** was synthesized from **10** (100 mg, 0.18 mmol) in the same manner as the synthesis of **12**. Yield: 107 mg (93%). White solid (recryst. from MeOH/AcOEt). Mp 125.0-127.8 °C. $[\alpha]_D^{25}$ −36.1 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.39 (9H, s, C(C$\underline{H}_3$)$_3$), 1.55-1.62 (2H, m, C$\underline{H}_2$), 1.82-1.89 (2H, m, C$\underline{H}_2$), 2.62 (2H, t, *J* = 7.5 Hz, Ar-C$\underline{H}_2$), 3.91 (3H, s, N-C$\underline{H}_3$), 4.21 (2H, t, *J* = 7.3 Hz, C$\underline{H}_2$N), 4.56 (1H, d, *J* = 8.8 Hz, C$\underline{H}$(Ph)NH), 4.79 (1H, d, *J* = 8.8 Hz, C$\underline{H}$(Ph)NH), 6.85-6.95 (5H, m, SO_2Ar-$\underline{H}$ + Ph-$\underline{H}$), 7.03-7.11 (7H, m, Ph-$\underline{H}$), 7.38 (2H, d, *J* = 7.6 Hz, SO_2Ar-$\underline{H}$), 7.55 (1H, d, *J* = 1.8 Hz, imidazole-$\underline{H}$), 7.60 (1H, d, *J* = 1.8 Hz, imidazole-$\underline{H}$), 8.91 (1H, s, 2-imidazole-$\underline{H}$). ^{13}C-NMR (CD_3OD) δ: 28.6, 28.7, 30.5, 35.7, 36.5, 50.5, 61.1, 64.1, 80.7, 123.6, 125.0, 128.0, 128.1, 128.2, 128.4, 128.7×2, 128.9, 129.1, 129.6, 139.7, 140.3, 141.0, 147.5, 157.9. IR (KBr) cm^{-1}: 3401, 3231, 3148, 3063, 2978, 1705, 1454, 1366, 1319, 1157. FABMS (Gly) *m/z*: 589 ([M-Cl]$^+$). *Anal.* Calcd for $C_{33}H_{41}ClN_4O_4S \cdot 7/3H_2O$: C, 59.40; H, 6.90; N, 8.40. Found: C, 59.49; H, 6.70; N, 8.20.

1-[5-[4-[[[(1*S*,2*S*)-2-[(*t*-Butoxycarbonyl)amino]-1,2-diphenylethyl]amino]sulfonyl]phenyl]propyl]-3-methyl-1*H*-imidazolium Chloride (14)

Compound **14** was synthesized from **11** (100 mg, 0.19 mmol) in the same manner as the synthesis of **12**. Yield: 106 mg (91%). White solid (recryst. from MeOH/AcOEt). Mp 207.0-209.9 °C. $[\alpha]_D^{24}$ −40.1 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.38 (9H, s, C(C$\underline{H}_3$)$_3$), 2.10-2.18 (2H, m, C$\underline{H}_2$), 2.63 (2H, t, *J* = 7.9 Hz, Ar-C$\underline{H}_2$), 3.89 (3H, s, N-C$\underline{H}_3$), 4.19 (2H, t, *J* = 7.3 Hz, C$\underline{H}_2$N), 4.57 (1H, d, *J* = 8.4 Hz, C$\underline{H}$(Ph)NH), 4.79 (1H, d, *J* = 8.4 Hz, C$\underline{H}$(Ph)NH), 6.86-6.88 (2H, m, SO_2Ar-$\underline{H}$), 6.94-6.96 (3H, m, Ph-$\underline{H}$), 7.04-7.12 (7H, m, Ph-$\underline{H}$), 7.39 (2H, d, *J* = 8.4 Hz, SO_2Ar-$\underline{H}$), 7.52 (1H, d, *J* = 1.8 Hz, imidazole-$\underline{H}$), 7.59 (1H, d, *J* = 2.2 Hz, imidazole-$\underline{H}$), 8.89 (1H, s, 2-imidazole-$\underline{H}$). ^{13}C-NMR (CD_3OD) δ: 28.7, 32.1, 33.1, 36.5, 50.3, 61.1, 64.1, 80.7, 123.6, 125.0, 128.11, 128.16, 128.25, 128.4, 128.7×2, 128.9, 129.1, 129.7, 139.7, 140.6, 140.9,

146.2, 157.8. IR (KBr) cm^{-1}: 3401, 3231, 3148, 3063, 2978, 1705, 1454, 1366, 1319, 1157. FABMS (NBA) *m/z*: 575 ($[M-Cl]^+$). *Anal.* Calcd for $C_{32}H_{39}ClN_4O_4S \cdot 1/3H_2O$: C, 62.27; H, 6.48; N, 9.08. Found: C, 62.42; H, 6.53; N, 9.07.

4-[*N*-[(1*S*,2*S*)-2-*t*-Butoxycarbonylamino-1,2-diphenylethyl]sulfamoyl]phenyl 4-Chlorobutanoate (18)

To a solution of **17** (203 mg, 0.433 mmol), Et_3N (0.130 mL, 0.936 mmol), and trace DMAP in acetone (3.00 mL), 4-chlorobutyryl chloride (0.060 mg, 0.534 mmol) was added at 0 °C. The mixture was stirred over night at rt. The solvent was removed under reduced pressure and H_2O was added to the residue. The product was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography (AcOEt : *n*-hexane = 1 : 2) to give compound **18**.

Yield: 120 mg (quant.). White solid (recryst. from *n*-hexane/AcOEt). Mp 213.6-215.5 °C. $[\alpha]_D^{23}$ −6.1 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.19 (2H, quint, *J* = 6.7 Hz, C<u>H</u>$_2$), 2.75 (2H, t, *J* = 7.2 Hz, ArC<u>H</u>$_2$), 3.65 (2H, t, *J* = 6.2 Hz, C<u>H</u>$_2$Cl), 4.61-4.65 (1H, m, C<u>H</u>(Ph)NH), 4.78-4.82 (1H, m, C<u>H</u>(Ph)NH), 5.23 (1H, br-d, *J* = 7.3 Hz, N<u>H</u>), 6.32 (1H, br-s, N<u>H</u>), 6.77-7.19 (12H, m, Ar-<u>H</u> and Ph-<u>H</u>), 7.52 (2H, dt, *J* = 8.8 and 2.4 Hz, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 27.3, 28.3, 31.2, 43.7, 60.1, 77.2, 80.9, 121.5, 127.3, 127.4, 128.0, 128.1, 128.4, 128.4, 128.6, 137.5, 137.8, 138.4, 153.1, 170.2. IR ($CHCl_3$) cm^{-1}: 3026, 2937, 1693, 1492, 1159, 700. FABMS (NBA) *m/z*: 601 ($[M+H]^+$). *Anal.* Calcd for $C_{30}H_{37}BrN_2O_4S$: C, 59.89; H, 6.20; N, 4.66. Found: C, 59.90; H, 6.28; N, 4.65.

4-[*N*-[(1*S*,2*S*)-2-*t*-Butoxycarbonylamino-1,2-diphenylethyl]sulfamoyl]phenyl 3-Chloropropane-1-sulfonate (20)

To a solution of **17** (203 mg, 0.433 mmol), Et_3N (0.269 mL, 1.93 mmol), and trace DMAP in acetone (5.00 mL), (3-chloropropane)sulfonyl chloride (0.125 mg, 1.03 mmol) was added at 0 °C. The mixture was stirred for 1.5 h at rt. The solvent was removed under reduced pressure, and H_2O was added to the residue. The product was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (AcOEt : *n*-hexane = 1 : 3) to give compound **20**.

Yield: 226 mg (87%). White solid (recryst. from *n*-hexane/$CHCl_3$). Mp 190.1-192.6 °C. $[\alpha]_D^{23}$ −34.9 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.47 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.37-2.44 (2H, m, C<u>H</u>$_2$), 3.41 (2H, t, *J* = 7.4 Hz, C<u>H</u>$_2$), 3.70 (2H, t, *J* = 6.0 Hz, C<u>H</u>$_2$), 4.67 (1H, dd, *J* = 6.6 and 9.2 Hz, C<u>H</u>(Ph)NH), 4.81 (1H, dd, *J* = 8.1 and 9.5 Hz, C<u>H</u>(Ph)NH), 5.27 (1H, br-s, N<u>H</u>), 6.57 (1H, br-s, N<u>H</u>), 6.76 (2H, br-d, *J* = 7.8 Hz, Ar-<u>H</u>), 6.92-7.01 (5H, m, Ar-<u>H</u>), 7.06 (2H, dt, *J* = 8.8 and 2.4 Hz, Ar-<u>H</u>), 7.16 (3H, t, *J* = 3.3 Hz, Ar-<u>H</u>), 7.51 (2H, d, *J* = 8.8 Hz, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 26.6, 28.3, 42.1, 48.2, 60.1, 64.5, 81.0, 121.8, 127.3, 127.4,

127.6, 128.1, 128.1, 128.6, 128.9, 137.2, 137.6, 140.1, 151.0, 157.2. IR ($CHCl_3$) cm^{-1}: 3439, 3030, 1689, 1489, 1165, 1149, 871, 700. FABMS (NBA) *m/z*: 609 ($[M+H]^+$). *Anal.* Calcd for $C_{28}H_{33}ClN_2O_7S_2$: C, 55.21; H, 5.46; N, 4.60. Found: C, 55.07; H, 5.60; N, 4.55.

1-[3-[4-[[[(1*S*,2*S*)-2-[(*t*-Butoxycarbonyl)amino]-1,2-diphenylethyl]amino]sulfonyl]phenoxyl]-sulfonylpropyl]-3-methyl-1*H*-imidazolium Chloride (21)

Compound **21** was synthesized from **20** (85 mg, 0.14 mmol) in the same manner as the synthesis of **12**.

Yield: 60 mg (62%). White solid (recryst. from MeOH/AcOEt). Mp 199.6-201.5 °C. $[\alpha]_D^{24}$ −36.2 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.38 (9H, s, C($C\underline{H}_3$)$_3$), 2.51 (2H, quint, *J* = 7.3 Hz, $CH_2C\underline{H}_2CH_2$), 3.52 (2H, t, *J* = 7.5 Hz, $C\underline{H}_2$), 3.92 (3H, s, N-$C\underline{H}_3$), 4.42 (2H, t, *J* = 7.4 Hz, $C\underline{H}_2$), 4.62 (1H, d, *J* = 8.4 Hz, C<u>H</u>(Ph)NH), 4.82 (1H, d, *J* = 8.4 Hz, C<u>H</u>(Ph)NH), 6.87-6.90 (2H, m, SO_2Ar-<u>H</u>), 6.95-7.15 (10H, m, 2 × Ph-<u>H</u>), 7.51 (2H, d, *J* = 8.4 Hz, SO_2Ar-<u>H</u>), 7.57 (1H, d, *J* = 2.2 Hz, imidazole-<u>H</u>), 7.66 (1H, d, *J* = 2.2 Hz, imidazole-<u>H</u>), 8.97 (1H, s, 2-imidazole-<u>H</u>). ^{13}C-NMR (CD_3OD) δ: 24.9, 28.0, 25.9, 47.9, 60.2, 60.8, 63.6, 80.0, 122.7, 122.9, 124.6, 127.7, 127.7, 128.0, 128.4, 128.5, 129.3, 138.8, 140.2, 141.0, 151.8, 157.1. IR (KBr) cm^{-1}: 3392, 3097, 1699, 1375, 1166, 1149, 869. FABMS (NBA) m/z: 655 ($[M-Cl]^+$). *Anal.* Calcd for $C_{32}H_{39}ClN_4O_7S_2 \cdot 3/2H2O$: C, 53.51; H, 5.89; N, 7.80. Found: C, 53.75; H, 5.73; N, 7.83.

3-Chloropropyl 4-[(2-Methyl)propoxysulfonyl]benzoate (24)

To a solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) (374 mg, 1.95 mmol) and DMAP trace in THF (10.0 mL), 3-chloro-1-propanol (0.163 mg, 1.95 mmol) was added at rt. After stirring for 1 h, a solution of **23** (336 mg, 1.30 mmol) in THF (10.0 mL) was added to the reaction mixture. The mixture was stirred over night at rt. The solvent was removed under reduced pressure, and 10% HCl was added to the residue. The product was extracted with AcOEt. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by column chromatography (AcOEt : *n*-hexane = 1 : 4) to give compound **24**.

Yield: 385 mg (89%). Light brown oil. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, *J* = 6.9 Hz, -CH($C\underline{H}_3$)$_2$), 1.96 (1H, sept, *J* = 6.6 Hz, -C<u>H</u>(CH_3)$_2$), 2.27 (2H, quintet, *J* = 6.2 Hz, -$OCH_2C\underline{H}_2CH_2Cl$), 3.70 (2H, t, *J* = 6.2 Hz, $C\underline{H}_2Cl$), 3.85 (2H, d, *J* = 6.6 Hz, -$C\underline{H}_2CH(CH_3)_2$), 4.53 (2H, t, *J* = 6.2 Hz, $OC\underline{H}_2$), 7.98 (2H, dt, *J* = 8.8 and 1.8 Hz, Ar-<u>H</u>), 8.20 (2H, dt, *J* = 8.8 and 1.8 Hz, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 18.5, 28.0, 30.3, 31.5, 41.0, 62.5, 127.9, 130.3, 134.6, 140.3, 164.7. IR ($CHCl_3$) cm^{-1}: 2968, 1726, 1273, 1186, 615. EIMS *m/z* (rel. int. %): 334 (M^+, 14), 279 (34), 261 (100), 185 (73), 121 (13), 76 (26). *Anal.* Calcd for $C_{14}H_{19}ClO_5S$: C, 50.22; H, 5.72. Found: C, 50.10; H, 5.83.

2-Chloroethyl 4-[(2-Methyl)propoxysulfonyl]benzoate (25)

Compound **25** was synthesized from **23** (1.41 g, 5.47 mmol) in the same manner as the synthesis of **24**.

Yield: 1753 mg (quant.). Colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (6H, d, *J* = 7.0 Hz, -CH($C\underline{H}_3$)$_2$),

1.91-2.01 (1H, m, -C<u>H</u>(CH_3)$_2$), 3.84 (2H, t, *J* = 5.5 Hz, C<u>H_2</u>Cl), 3.86 (2H, d, *J* = 7.0 Hz, -C<u>H_2</u>CH(CH_3)$_2$), 4.63 (2H, t, *J* = 5.5 Hz, OC<u>H_2</u>), 8.00 (2H, dt, *J* = 8.8 and 1.8 Hz, Ar-<u>H</u>), 8.24 (2H, dt, *J* = 8.4 and 1.8 Hz, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 18.5, 28.1, 41.4, 65.1, 77.0, 127.9, 130.5, 134.3, 140.1, 164.6. IR ($CHCl_3$) cm^{-1}: 2966, 1728, 1366, 1186, 1121, 972, 615. EIMS *m/z* (rel. int. %): 320 (M^+, 7), 265 (47), 247 (100), 241 (28), 185 (63), 183 (46), 104 (25), 56 (83). *Anal.* Calcd for $C_{13}H_{17}ClO_5S$: C, 48.67; H, 5.34. Found: C, 48.47; H, 5.54.

4-[(3-Chloropropyloxy)carbonyl]benzenesulfonate Sodium Salt (26)

A solution of **24** (554 mg, 1.65 mmol) and NaI (372 mg, 2.48 mmol) in acetone (25.0 mL) was heated under reflux for 4 h. The resulting precipitate was collected and washed repeatedly with acetone to give compound **26**.

Yield: 424 mg (85%). White solid. Mp >300 °C. ^{1}H-NMR (DMSO-d_6) δ: 2.18 (2H, quintet, *J* = 6.3 Hz, -OCH$_2$C<u>H_2</u>CH$_2$Cl), 3.79 (2H, t, *J* = 6.6 Hz, C<u>H_2</u>Cl), 4.39 (2H, t, *J* = 6.1 Hz, OC<u>H_2</u>), 7.75 (2H, d, *J* = 8.4 Hz, Ar-<u>H</u>), 7.96 (2H, d, *J* = 8.5 Hz, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 31.0, 41.8, 61.7, 125.7, 128.8, 129.4, 152.5, 165.2. IR (KBr) cm^{-1}: 3437, 1712, 1280, 1232, 1174, 1112, 765, 744, 653. FABMS (NBA) *m/z*: 277 ([M-Na]$^-$). HRMS (FAB$^-$) *m/z*: Found, 276.9939 (M-Na)$^-$ (Calcd for $C_{10}H_{10}ClO_5S^-$: 276.9937).

4-[(2-Chloroethoxy)carbonyl]benzenesulfonate Sodium Salt (27)

Compound **27** was synthesized from **25** (873 mg, 2.72 mmol) in the same manner as the synthesis of **26**.

Yield: 665 mg (85%). White solid. Mp >300 °C. ^{1}H-NMR (DMSO-d_6) δ: 3.97 (2H, t, *J* = 5.1 Hz, C<u>H_2</u>Cl), 4.54 (2H, t, *J* = 5.1 Hz, OC<u>H_2</u>), 7.76 (2H, dt, *J* = 8.4 and 1.8 Hz, Ar-<u>H</u>), 7.96 (2H, dt, *J* = 8.4 and 1.8 Hz, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 42.5, 64.6, 125.9, 128.9, 129.1, 152.8, 165.1. IR (KBr) cm^{-1}: 3422, 1712, 1285, 1256, 1223, 1121, 765, 743, 650. FABMS (GLY) *m/z*: 263 ([M-Na]$^-$). *Anal.* Calcd for $C_9H_8NaO_5S$: C, 37.71; H, 2.81. Found: C, 37.85; H, 3.01.

3-Chloropropyl 4-(Chlorosulfonyl)benzoate (28)

A mixture of compound of **26** (500 mg, 1.66 mmol) and a drop of DMF in thionyl chloride (1.21 mL, 16.6 mmol) was heated under reflux for 15 h. The solvent was evaporated. The residue product was purified by column chromatography (AcOEt : *n*-hexane = 1 : 5) to give compound **28**.

Yield: 344 mg (70%). White solid (recryst. from *n*-hexane/AcOEt). Mp 60.4-61.8 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.27 (2H, quintet, *J* = 6.2 Hz, -OCH$_2$C<u>H_2</u>CH$_2$Cl), 3.70 (2H, t, *J* = 6.2 Hz, C<u>H_2</u>Cl), 4.56 (2H, t, *J* = 6.0 Hz, OC<u>H_2</u>), 8.12 (2H, dt, *J* = 8.8 and 1.8 Hz, Ar-<u>H</u>), 8.26 (2H, dt, *J* = 8.8 and 2.2 Hz, Ar-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 31.4, 40.9, 62.8, 127.0, 130.8, 135.9, 147.6, 164.2. IR ($CHCl_3$) cm^{-1}: 3018, 1728, 1382, 1273, 1172, 1118, 594. EIMS *m/z* (rel. int. %): 296 (M^+, 10), 261 (23), 221 (77), 203 (100), 185 (22), 121 (14), 76 (78). *Anal.* Calcd for $C_{10}H_{10}Cl_2O_4S$: C, 40.42; H, 3.39. Found: C, 40.50; H, 3.38.

2-Chloroethyl 4-(Chlorosulfonyl)benzoate (29)

Compound **29** was synthesized from **27** (573 mg, 2.00 mmol) in the same manner as the synthesis of **28**. Yield: 553 mg (98%). Yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 3.84 (2H, t, *J* = 5.5 Hz, C$\underline{H_2}$Cl), 4.64 (2H, t, *J* = 5.5 Hz, OC$\underline{H_2}$), 8.14 (2H, dt, *J* = 8.8 and 1.8 Hz, Ar-$\underline{H}$), 8.30 (2H, dt, *J* = 8.8 and 1.8 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 41.4, 65.4, 127.1, 131.0, 135.6, 147.8, 164.1. IR ($CHCl_3$) cm^{-1}: 1732, 1383, 1275, 1194, 1173, 1107, 594. EIMS *m/z* (rel. int. %): 282 (M^+, 17), 247 (24), 220 (27), 203 (100), 185 (86), 104 (31), 76 (31). IR ($CHCl_3$) cm^{-1}: 1732, 1383, 1275, 1194, 1173, 1107, 594. *Anal.* Calcd for $C_9H_8Cl_2O_4S$: C, 38.18; H, 2.85. Found: C, 38.38; H, 2.83.

3-Chloropropyl 4-[*N*-[(1*S*,2*S*)-2-*t*-Butoxycarbonylamino-1,2-diphenylethyl]sulfamoyl]benzoate (30)

Compound **30** was synthesized from **28** (300 mg, 1.01 mmol) in the same manner as the synthesis of **9**. Yield: 435 mg (75%). White solid (recryst. from n-hexane/AcOEt). Mp 146.0-148.5 °C. $[\alpha]_D^{23}$ −28.0 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s, C(C$\underline{H_3}$)$_3$), 2.23 (2H, quintet, *J* = 6.2 Hz, -OCH$_2$C$\underline{H_2}$CH$_2$Cl), 3.67 (2H, t, *J* = 6.2 Hz, C$\underline{H_2}$Cl), 4.48 (2H, t, *J* = 6.2 Hz, OC$\underline{H_2}$), 4.68 (1H, dd, *J* = 9.9 and 7.0 Hz, C$\underline{H}$(Ph)NH), 4.81 (1H, dd, *J* = 9.7 and 7.9 Hz, C$\underline{H}$(Ph)NH), 5.24 (1H, br-s, N$\underline{H}$), 6.59 (1H, br-s, N$\underline{H}$), 6.78-6.79 (2H, m, Ph-$\underline{H}$), 6.92-7.01 (5H, m, Ph-$\underline{H}$), 7.15-7.18 (3H, m, Ph-$\underline{H}$), 7.57 (2H, d, *J* = 8.8 Hz, Ar-$\underline{H}$), 7.84 (2H, dt, *J* = 8.4 and 1.8 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 28.3, 31.6, 41.0, 60.2, 62.3, 64.6, 81.1, 126.8, 127.3, 127.5, 127.6, 128.07, 128.13, 128.7, 129.6, 132.9, 137.5, 137.7, 145.2, 157.3, 165.0. IR ($CHCl_3$) cm^{-1}: 3439, 3030, 1722, 1694, 1493, 1368, 1273, 1163, 700. FABMS (NBA) *m/z*: 573 ($[M+H]^+$). *Anal.* Calcd for $C_{29}H_{33}ClN_2O_6S$: C, 60.78; H, 5.80; N, 4.89. Found: C, 60.67; H, 5.86; N, 4.87.

2-Chloroethyl 4-[*N*-[(1*S*,2*S*)-2-*t*-Butoxycarbonylamino-1,2-diphenylethyl]sulfamoyl]benzoate (31)

Compound **31** was synthesized from **29** (484 mg, 1.71 mmol) in the same manner as the synthesis of **9**. Yield: 514 mg (54%). White solid (recryst. from n-hexane/AcOEt). Mp 146.0-148.5 °C. $[\alpha]_D^{21}$ −32.19 (c 1.0, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (9H, s, C(C$\underline{H_3}$)$_3$), 3.80 (2H, t, *J* = 5.7 Hz, C$\underline{H_2}$Cl), 4.56 (2H, dd, *J* = 6.3 and 4.8 Hz, OC$\underline{H_2}$), 4.68 (1H, dd, *J* = 9.9 and 6.6 Hz, C$\underline{H}$(Ph)NH), 4.80 (1H, dd, *J* = 9.7 and 7.9 Hz, C$\underline{H}$(Ph)NH), 5.20 (1H, br-d, *J* = 5.9 Hz, N$\underline{H}$), 6.56 (1H, br-s, N$\underline{H}$), 6.77-6.79 (2H, m, Ph-$\underline{H}$), 6.92-7.05 (5H, m, Ph-$\underline{H}$), 7.15-7.18 (3H, m, Ph-$\underline{H}$), 7.58 (2H, d, *J* = 8.5 Hz, Ar-$\underline{H}$), 7.88 (2H, dt, *J* = 8.4 and 1.7 Hz, Ar-$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 28.4, 41.5, 60.3, 64.7, 64.9, 81.1, 126.8, 127.4, 127.5, 127.6, 128.1, 128.2, 128.7, 129.8, 132.5, 137.5, 137.7, 145.4, 157.3, 164.8. IR ($CHCl_3$) cm^{-1}: 3439, 3030, 1724, 1693, 1493, 1274, 1165, 1107, 700. FABMS (NBA) *m/z*: 559 ($[M+H]^+$). *Anal.* Calcd for $C_{28}H_{31}ClN_2O_6S$: C, 60.15; H, 5.59; N, 5.01. Found: C, 60.28; H, 5.70; N, 5.00.

1-[3-[4-[[[(1*S*,2*S*)-2-[(*t*-Butoxycarbonyl)amino]-1,2-diphenylethyl]amino]sulfonyl]benzoyloxy]-propyl]-3-methyl-1*H*-imidazolium Chloride (32)

Compound **32** was synthesized from **30** (85 mg, 0.15 mmol) in the same manner as the synthesis of **12**.

Yield: 85 mg (87%). White solid (recryst. from MeOH/AcOEt). Mp 194.0-195.9 °C. $[\alpha]_D^{24}$ −39.1 (c 1.0, MeOH). ^{1}H-NMR (CD_3OD) δ: 1.37 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.37 (2H, quint, *J* = 6.6 Hz, OCH$_2$C<u>H</u>$_2$CH$_2$), 3.86 (3H, s, imidazole-C<u>H</u>$_3$), 4.39 (2H, t, *J* = 7.4 Hz, C<u>H</u>$_2$N), 4.39 (2H, t, *J* = 5.9 Hz, OC<u>H</u>$_2$), 4,66 (1H, d, *J* = 8.1 Hz, C<u>H</u>(Ph)NH), 4.83 (1H, d, *J* = 7.3 Hz, C<u>H</u>(Ph)NH), 6.90-7.12 (10H, m, Ar-<u>H</u>), 7.53 (1H, t, *J* = 1.7 Hz, imidazole-<u>H</u>), 7.57 (2H, dt, *J* = 8.8 and 1.9 Hz, Ph-<u>H</u>), 7.67 (1H, t, *J* = 1.7 Hz, imidazole-<u>H</u>), 7.80 (2H, dt, *J* = 8.8 and 1.8 Hz, Ph-<u>H</u>), 8.99 (1H, s, 2-imidazole-<u>H</u>). ^{13}C-NMR (CD_3OD) δ: 29.1, 30.6, 36.9, 48.5, 61.4, 63.6, 64.7, 81.1, 124.1, 125.5, 128.3, 128.3, 128.7, 128.8, 129.0, 129.0, 129.4, 129.5, 131.1, 134.2, 140.0, 141.2, 147.5, 158.2, 166.8. IR (KBr) cm^{-1}: 3390, 3089, 1705, 1271, 1163, 702, 609. FABMS (NBA) m/z: 619 ([M-Cl]$^+$). *Anal.* Calcd for $C_{33}H_{39}ClN_4O_6S \cdot 1/3H_2O$: C, 59.94; H, 6.05; N, 8.47. Found: C, 59.98; H, 6.04; N, 8.47.

***N*-[(1*S*,2*S*)-2-*t*-Butoxycarbonylamino-1,2-diphenylethyl]-1-methyl-1*H*-imidazolylsulfonamide (35)**

Compound **35** was synthesized from **34** (100 mg, 0.554 mmol) in the same manner as the synthesis of **9**.

Yield: 197 mg (78%). White needles (recryst. from AcOEt). Mp 224.1-225.0 °C. $[\alpha]_D^{27}$ −10.80 (c 1.0, MeOH). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.51 (3H, s, N-C<u>H</u>$_3$), 4.76 (1H, t, *J* = 7.9 Hz, C<u>H</u>(Ph)NH), 4.84 (1H, t, *J* = 7.5 Hz, C<u>H</u>(Ph)NH), 5.68 (1H, br-s, N<u>H</u>), 6.41 (1H, br-s, N<u>H</u>), 6.91 (2H, d, *J* = 1.3 Hz, 5-imidazole-<u>H</u>), 6.95-7.16 (10H, m, 2 × Ph-<u>H</u>), 7.27 (1H, br-s, 2-imidazole-<u>H</u>). ^{13}C-NMR ($CDCl_3$) δ: 28.5, 33.8, 59.7, 63.6, 80.2, 123.7, 127.4, 127.7, 127.8, 127.9, 128.0, 128.5, 138.5, 138.6, 138.7, 141.3, 156.4. IR ($CHCl_3$) cm^{-1}: 3410, 3350, 2980, 1697, 1489, 1156, 1116. FABMS (NBA) *m/z*: 457 ([M+H]$^+$). *Anal.* Calcd for $C_{23}H_{29}N_4O_4S$: C, 60.51; H, 6.18; N, 12.27. Found: C, 60.42; H, 6.18; N, 12.18.

1,3-Dimethyl-[[[(1*S*,2*S*)-2-[(*t*-butoxycarbonyl)amino]1,2-diphenylethyl]amino]sulfonyl]-1*H*-imidazolium Trifluoromethanesulfonate (36)

A mixture of **35** (91.0 mg, 0.199 mmol) and methyl triflate (0.062 mL, 0.550 mmol) was stirred for 3.5 h under N_2. The volatile material was removed, and the residue was washed with AcOEt to obtain compound **36**.

Yield: 117 mg (94%). Light yellow hygroscopic solid. $[\alpha]_D^{25}$ −16.51 (c 0.86, MeOH). ^{1}H-NMR (DMSO-d_6) δ: 1.27 (9H, s, C(C<u>H</u>$_3$)$_3$), 3.55 (3H, s, N-C<u>H</u>$_3$), 3.57 (3H, s, N-C<u>H</u>$_3$), 4.20 (1H, br-d, *J* = 3.3 Hz, C<u>H</u>(Ph)NH), 4.45 (1H, br-d, *J* = 3.5 Hz, C<u>H</u>(Ph)NH), 6.27 (1H, br-d, *J* = 6.6 Hz, N<u>H</u>), 7.05-7.29 (12H, m, N<u>H</u>, 2 × Ph-<u>H</u> and 5-imidazole-<u>H</u>), 8.49 (1H, s, 2-imidazole-<u>H</u>). ^{13}C-NMR (DMSO-d_6) δ: 28.3, 34.2, 35.2, 60.9, 64.8, 78.0, 121.8, 125.8, 126.1, 126.5, 127.37, 127.42, 127.5, 137.2, 138.6, 143.0, 145.8, 155.0. ^{19}F-NMR (CD_3OD) δ: -1.50 (s). IR (KBr) cm^{-1}: 3340, 3127, 3060, 2960, 1688, 1579, 1273, 1247, 1168, 1025, 637. FABMS (NBA) *m/z*: 277 ([M-Na]$^-$). HRMS (FAB$^+$) *m/z*: Found, 471.2063 ([M-CF_3CO_2]$^+$) (Calcd for $C_{24}H_{31}N_4O_4S^+$: 471.2066).

Typical Procedure of RCATH

The corresponding acetophenone (1.0 mmol) was added to a solution of ionic ligands **2** (0.011 mmol) and $[RuCl_2(benzene)]_2$ (2.5 mg, 0.005 mmol) in [bmim][PF_6] (1.0 mL) with stirring under N_2, followed by addition of a formic acid–triethylamine azeotropic mixture (108 °C boiling point/29 mmHg; 0.5 mL). The reaction mixture was stirred at rt for 24 h. Next, *n*-hexane 5 mL was added to the reaction mixture and the mixture was stirred for 5 min. Subsequently the solution was quiescent and the supernatant (organic solution) was decanted. And the residual IL phase was dried *in vacuo* for 30 min. Acetophenone (1.0 mmol) and formic acid–triethylamine azeotropic mixture (0.5 mL) were added to the remaining IL solution, and the next cycle of the reaction was started. The organic solution was extracted with H_2O. The organic layer was dried over $MgSO_4$, filtered. This organic layer was determained by GLC.

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