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
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. 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 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 reused more than 5 times and was unwieldy because it was in the form of oil at room temperature. Ligand 1 comprises three scaffolds: a diphenylethlenediamine (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 improve 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...
4-[(alkylenesulfonyl)oxy]phenyl groups were synthesized. In addition, ligands that directly connect the DPEN and imidazolium moieties were studied. The novel ligands were utilized in the RCATH of acetophenone to examine the reactivity and reuse efficiency.

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

Scheme 2. Synthesis of 2a-c

Preparation of ligand , which contains an ester group, was attempted as shown in Scheme 3. Compound was synthesized as described in the literature, and a linker moiety was introduced to in order to give phenyl ester 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-1H-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 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]

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<th>Cycle</th>
<th>Conv. (%ee)*</th>
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<tr>
<td></td>
<td>1st</td>
</tr>
<tr>
<td>1st</td>
<td>98% (92)</td>
</tr>
<tr>
<td>2nd</td>
<td>&gt;99% (93)</td>
</tr>
<tr>
<td>3rd</td>
<td>99% (93)</td>
</tr>
<tr>
<td>4th</td>
<td>92% (93)</td>
</tr>
<tr>
<td>5th</td>
<td>75% (90)</td>
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* Determined by GLC.
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. 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.

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

<table>
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<tr>
<th>Catalyst 1</th>
<th>Ru/ligand complex</th>
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<tr>
<td></td>
<td>2a</td>
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<tr>
<td>% of remaining Ru in ionic liquid</td>
<td>&gt;99%</td>
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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**

1H, 13C, and 19F NMR spectra were obtained using a JEOL ECA-500 (1H: 500 MHz, 13C: 125 MHz, 19F: 470 MHz) or JEOL JNM-ECP400 (1H: 400 MHz, 13C: 100 MHz). Proton and carbon chemical shifts are expressed in ppm and referenced to the tetramethylsilane singlet. 19F 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 PF254 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-][(1S,2S)-2-Amino-1,2-diphenylethyl]amino]sulfonyl]phenyl]pentyl]-3-methyl-1H-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 N2, 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. [α]D24 −57.4 (c 1.0, MeOH). 1H-NMR (CD3OD) δ: 1.27-1.35 (2H, m, CH2), 1.58 (2H, quint, J = 7.7 Hz, CH2), 1.89 (2H, quint, J = 7.5 Hz, CH2), 2.55 (2H, t, J = 7.5 Hz, ArCH2), 3.91 (3H, s, N-CH3), 4.19 (2H, t, J = 7.3 Hz, CH2N), 4.52 (1H, d, J = 11.0 Hz, CH(Ph)NH), 4.56 (1H, d, J = 11.0 Hz, CH(Ph)NH), 6.71-6.93 (5H, m, Ph-H), 7.04 (2H, d, J = 8.5 Hz, SO2Ar-H), 7.18-7.23 (5H, m, Ph-H), 7.47 (2H, d, J = 8.4 Hz, SO2Ar-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$_3$OD) 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, 137.8, 139.0, 148.8. $^{19}$F-NMR (CD$_3$OD) 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$_3$CO$_2$-H]$^+$). FABMS (NBA) m/z: 113 ([CF$_3$CO$_2^-\)$. Anal. Calcd for C$_{33}$H$_{36}$F$_6$N$_4$O$_6$S·H$_2$O: C, 52.94; H, 5.12; N, 7.48. Found: C, 52.90; H, 5.21; N, 7.69.

1-[5-[4-[[[1S,2S)-2-Amino-1,2-diphenylethyl]amino]sulfonyl]phenyl]butyl]-3-methyl-1H-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 qC. [$\alpha$]$_D^{24}$−63.1 (c 1.0, MeOH). $^1$H-NMR (CD$_3$OD) 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$_2$Ar-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$_2$Ar-H), 7.55 (1H, s, imidazole-H), 7.60 (1H, s, imidazole-H), 8.92 (1H, s, 2-imidazole-H). $^{13}$C-NMR (CD$_3$OD) δ: 28.6, 30.5, 35.7, 36.5, 50.5, 60.8, 63.1, 123.7, 125.1, 128.4, 128.8, 129.7, 129.2, 129.8, 130.0, 130.4, 134.8, 136.6, 137.9, 139.4, 148.2. $^{19}$F-NMR (CD$_3$OD) δ: 1.97 (s). IR (KBr) cm$^{-1}$: 3065, 2941, 2868, 1674, 1330, 1204, 1161, 1132. FABMS (Gly) m/z: 489 ([M-2CF$_3$CO$_2$-H]$^+$). FABMS (NBA) m/z: 113 ([CF$_3$CO$_2^-$]$^-\). Anal. Calcd for C$_{32}$H$_{34}$F$_6$N$_4$O$_6$S: C, 53.63; H, 4.78; N, 7.82. Found: C, 54.42; H, 4.70; N, 8.03.

1-[5-[4-[[[1S,2S)-2-Amino-1,2-diphenylethyl]amino]sulfonyl]phenyl]propyl]-3-methyl-1H-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$_3$OD) 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$_2$Ar-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$_2$Ar-H), 7.54 (1H, s, imidazole-H), 7.60 (1H, s, imidazole-H), 8.89 (1H, s, 2-imidazole-H). $^{13}$C-NMR (CD$_3$OD) δ: 22.2, 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, 133.8, 136.6, 138.0, 139.7, 146.9. $^{19}$F-NMR (CD$_3$OD) 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$_3$CO$_2$-H]$^+$). FABMS (NBA) m/z: 113 ([CF$_3$CO$_2^-$]$^-\). Anal. Calcd for C$_{32}$H$_{33}$F$_6$N$_4$O$_6$S·H$_2$O: C, 52.99; H, 4.59; N, 7.97. Found: C, 52.97; H, 4.79; N, 8.19.
1-[3-[4-[[1(S,2S)]-2-Amino-1,2-diphenylethyl]amino]sulfonyl]benzoyloxy]propyl]-3-methyl-1H-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. \([\alpha]_D^{24} = -21.7 (c 1.0, \text{MeOH})\). \(^1\)H-NMR (CD\(_3\)OD) \(\delta\): 2.51 (2H, quint, \(J = 7.3\) Hz, CH\(_2\)CH\(_2\)CH\(_2\)), 3.51 (2H, t, \(J = 7.4\) Hz, CH\(_3\)), 3.92 (3H, s, N-CH\(_3\)), 4.42 (2H, t, \(J = 7.3\) Hz, CH\(_3\)), 4.54 (1H, d, \(J = 11.0\) Hz, CH(Ph)NH), 4.71 (1H, d, \(J = 11.0\) Hz, CH(Ph)NH), 6.74-6.96 (5H, m, Ph-H), 7.15 (2H, dt, \(J = 8.8\) and 2.6 Hz, SO\(_2\)Ar-H), 7.19-7.24 (5H, m, Ph-H), 7.58 (1H, t, \(J = 1.7\) Hz, imidazole-H), 7.63 (2H, dt, \(J = 9.2\) and 2.4 Hz, SO\(_2\)Ar-H), 7.67 (1H, t, \(J = 1.9\) Hz, imidazole-H), 8.97 (1H, s, 2-imidazole-H). \(^{13}\)C-NMR (CD\(_3\)OD) \(\delta\): 24.9, 35.9, 47.8, 48.1, 59.9, 62.5, 122.8, 123.0, 124.6, 128.1, 128.5, 128.7, 129.4, 129.7, 130.0, 130.4, 130.8, 134.1, 135.6, 137.7, 140.1, 152.2. \(^{19}\)F-NMR (CD\(_3\)OD): 1.49 (s). IR (KBr) cm\(^{-1}\): 3435, 3066, 2875, 1678, 1203, 1174, 1149, 869. FABMS (NBA) \(m/z\): 555 ([M-2CF\(_3\)CO\(_2\)-H\(^+\)]. FABMS (NBA) \(m/z\): 113 ([CF\(_3\)CO\(_2\)]\(^-\)). Anal. Calcd for C\(_{31}\)H\(_{32}\)F\(_6\)N\(_4\)O\(_9\)S\(_2\)\(\cdot\)1/2H\(_2\)O: C, 47.03; H, 4.20; N, 7.08. Found: C, 47.27; H, 4.50; N, 7.34.

1-[3-[4-[[1(S,2S)]-2-Amino-1,2-diphenylethyl]amino]sulfonyl]benzoyloxy]propyl]-3-methyl-1H-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. \([\alpha]_D^{24} = -64.1 (c 1.0, \text{MeOH})\). \(^1\)H-NMR (CD\(_3\)OD) \(\delta\): 2.35 (2H, quint, \(J = 6.6\) Hz, OCH\(_2\)CH\(_2\)CH\(_2\)), 3.86 (3H, s, N-CH\(_3\)), 4.37 (2H, t, \(J = 7.1\) Hz, CH\(_3\)), 4.37 (1H, t, \(J = 6.0\) Hz, OCH\(_2\)), 4.52 (1H, d, \(J = 10.9\) Hz, CH(Ph)NH), 4.74 (1H, d, \(J = 10.9\) Hz, CH(Ph)NH), 6.75 (2H, dt, \(J = 6.9\) and 1.9 Hz, Ph-H), 6.82-7.22 (10H, m, Ar-H), 7.53 (1H, t, \(J = 1.8\) Hz, imidazole-H), 7.67 (1H, t, \(J = 1.8\) Hz, imidazole-H), 7.80 (2H, dt, \(J = 8.8\) and 1.8 Hz, Ph-H), 8.96 (1H, s, 2-imidazole-H). \(^{13}\)C-NMR (CD\(_3\)OD) \(\delta\): 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\(_3\)OD) \(\delta\): 1.49 (s). IR (KBr) cm\(^{-1}\): 3414, 3067, 2878, 1678, 1203, 1174, 1149, 869. FABMS (NBA) \(m/z\): 519 ([M-2CF\(_3\)CO\(_2\)-H\(^+\)]. FABMS (NBA) \(m/z\): 113 ([CF\(_3\)CO\(_2\)]\(^-\)). Anal. Calcd for C\(_{31}\)H\(_{32}\)F\(_6\)N\(_4\)O\(_8\)S: C, 51.47; H, 4.32; N, 7.50. Found: C, 51.33; H, 4.43; N, 7.60.

1,3-Dimethyl-[[1(S,2S)]-2-amino-1,2-diphenylethyl]amino]sulfonyl]-1H-imidazolium Mono(trifluorooromethanesulfonate) 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. \([\alpha]_D^{25} = -46.61 (c 1.24, \text{MeOH})\). \(^1\)H-NMR (DMSO-\(d_6\)) \(\delta\): 3.57 (3H, s, N-CH\(_3\)), 3.72 (3H, s, N-CH\(_3\)), 4.66 (1H, d, \(J = 4.5\) Hz, CH(Ph)NH), 4.71 (1H, d, \(J = 10.1\) Hz, CH(Ph)NH), 6.96-7.26 (10H, m, 2 × Ph-H), 7.88 (1H, d, \(J = 1.6\) Hz, 5-imidazole-H), 8.93 (4H, s, NH and NH\(_3\)), 10.2 (1H, s, 2-imidazole-H). \(^{13}\)C-NMR (DMSO-\(d_6\)) \(\delta\): 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$_3$OD) $\delta$: −1.60 (s), 1.33 (s). IR (KBr) cm$^{-1}$: 3396, 3190, 3044, 2900, 1685, 1670, 1580, 1276, 1250, 1200, 1172, 1027, 638. HRMS (FAB$^+$) m/z: Found, 371.1547 ([M-CH$_3$CO$_2$-TfO-H]$^+$) (Calcd for C$_{19}$H$_{23}$N$_4$O$_2$S$: 371.1542). MS (CI) m/z (rel. int. %): 113 (CF$_3$CO$_2^-$, 100). MS (CI) m/z (rel. int. %): 149 (CF$_3$O$_3$S$^-$, 100).

**4-(5-Bromopentyl)benzenesulfonyl chloride (6)**

To a solution of 5-phenylpentyl bromide 3 (0.54 mL, 2.95 mmol) in CHCl$_3$ (12.5 mL), a solution of chlorosulfonic 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)**

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)**

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

To a solution of (1S,2S)-(−)-1,2-diphenylethlenediamine (DPEN) (552 mg, 2.60 mmol) and Et$_3$N (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$_3$N (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)$_2$O (852 mg, 3.90 mmol) and Et$_3$N (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$_3$) $\delta$: 1.38-1.46 (2H, m, CH$_2$), 1.46 (9H, s, C(CH$_3$)$_2$), 1.52-1.60 (2H, m, CH$_2$), 1.82-1.90 (2H, m, CH$_2$), 2.56 (2H, t, $J = 7.7$ Hz, ArCH$_2$), 3.38 (2H, t, $J = 6.8$ Hz, CH$_2$Br), 4.59 (1H, dd, $J = 7.4$ and 9.6 Hz, CH(Ph)NH), 4.79 (1H, t, $J = 8.8$ Hz, CH(Ph)NH), 5.26 (1H, br-d, $J = 7.7$ Hz, NH), 6.11 (1H, br-s, NH), 6.76 (2H, d, $J = 6.9$ Hz, Ar-H), 6.92-7.16 (10H, m, Ar-H), 7.44 (2H, d, $J = 8.4$ Hz, Ar-H).
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. [α]D24^24 −34.7 (c 1.0, CHCl3). \(^1\)H-NMR (CDCl3) δ: 1.46 (9H, s, C(CH3)3), 1.66-1.75 (4H, m, CH2), 2.58 (2H, t, J = 7.0 Hz, Ar-CH2), 3.52 (2H, t, J = 6.2 Hz, CH2Cl), 4.60 (1H, dd, J = 9.5 and 7.3 Hz, CH(Ph)NH), 4.80 (1H, t, J = 8.8 Hz, CH(Ph)NH), 5.28 (1H, NH), 6.17 (1H, NH), 6.76 (2H, d, J = 7.3 Hz, SO2Ar-H), 6.92-7.02 (7H, m, Ph-H), 7.16 (3H, t, J = 3.7 Hz, Ph-H), 7.44 (2H, d, J = 8.1 Hz, SO2Ar-H). \(^13\)C-NMR (CDCl3) 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 (CHCl3) cm⁻¹: 3026, 2937, 1693, 1492, 1159, 700. FABMS (NBA) m/z: 601 ([M+H]+).


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. [α]D24^24 −37.1 (c 1.0, CHCl3). \(^1\)H-NMR (CDCl3) δ: 1.46 (9H, s, C(CH3)3), 1.95-2.04 (2H, m, CH2), 2.71 (2H, t, J = 7.3 Hz, Ar-CH2), 3.42 (2H, t, J = 6.4 Hz, CH2Cl), 4.61 (1H, dd, J = 9.5 and 7.4 Hz, CH(Ph)NH), 4.80 (1H, t, J = 8.8 Hz, CH(Ph)NH), 5.28 (1H, d, J = 3.2 Hz, NH), 6.20 (1H, NH), 6.76 (2H, d, J = 7.0 Hz, SO2Ar-H), 6.91-7.03 (7H, m, Ph-H), 7.16 (3H, t, J = 3.3 Hz, Ph-H), 7.45 (2H, d, J = 6.6 Hz, SO2Ar-H). \(^13\)C-NMR (CDCl3) 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, 128.4, 128.5, 128.55, 128.58, 137.7, 138.1, 138.8, 145.3, 156.9. IR (CHCl3) 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 C29H35ClN2O4S: C, 64.13; H, 6.50; N, 5.16. Found: C, 63.98; H, 6.60; N, 5.14.

1-[5-[[4-[[[(1S,2S)-2-[(t-Butoxycarbonylamino)-1,2-diphenylethyl]amino)sulfonyl]phenyl]pentyl]-3-methyl-1H-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 °C for 12 h under N2. 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. [α]D 24 = -31.7 (c 1.0, MeOH). 1H-NMR (CD3OD) δ: 1.27-1.35 (2H, m, CH2), 1.38 (9H, s, C(CH3)3), 1.60 (2H, quint, J = 7.6 Hz, CH2), 1.89 (2H, quint, J = 7.6 Hz, CH2), 2.56 (2H, t, J = 7.7 Hz, ArCH2), 3.90 (3H, s, N-CH3), 4.18 (2H, t, J = 7.6 Hz, CH2N), 4.55 (1H, d, J = 8.5 Hz, CH(Ph)NH), 4.79 (1H, t, J = 7.3 Hz, CH(Ph)NH), 6.85-7.12 (12H, m, Ar-H), 7.36 (2H, d, J = 8.0 Hz, Ar-H), 7.52 (1H, d, J = 1.8 Hz, imidazole-H), 7.59 (1H, d, J = 1.8 Hz, imidazole-H), 8.91 (1H, s, 2-imidazole-H). 13C-NMR (CD3OD): 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, 128.9, 129.1, 129.6, 139.9, 140.9, 147.8, 157.8. IR (KBr) cm⁻¹: 3387, 3062, 1685, 1517, 1325, 1157, 700, 590. FABMS (NBA) m/z: 603 ([M-Br]+).

Anal. Calcd for C34H43BrN4O4S·½H2O: C, 58.95; H, 6.40; N, 8.09. Found: C, 58.70; H, 6.41; N, 8.00.

1-[5-[4-[[[(1S,2S)-2-[((t-Butoxycarbonyl)amino]-1,2-diphenylethyl]amino]sulfonyl]phenyl]butyl]-3-methyl-1H-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. [α]D 25 = -36.1 (c 1.0, MeOH). 1H-NMR (CD3OD) δ: 1.39 (9H, s, C(CH3)3), 1.55-1.62 (2H, m, CH2), 1.82-1.89 (2H, m, CH2), 2.62 (2H, t, J = 7.5 Hz, Ar-CH2), 3.91 (3H, s, N-CH3), 4.21 (2H, t, J = 7.3 Hz, CH2N), 4.56 (1H, d, J = 8.8 Hz, CH(Ph)NH), 4.79 (1H, d, J = 8.8 Hz, CH(Ph)NH), 6.85-6.95 (5H, m, SO2Ar-H + Ph-H), 7.03-7.11 (7H, m, Ph-H), 7.38 (2H, d, J = 7.6 Hz, SO2Ar-H), 7.55 (1H, d, J = 1.8 Hz, imidazole-H), 7.60 (1H, d, J = 1.8 Hz, imidazole-H), 8.91 (1H, s, 2-imidazole-H). 13C-NMR (CD3OD): 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]+).


1-[5-[4-[[[(1S,2S)-2-[((t-Butoxycarbonyl)amino]-1,2-diphenylethyl]amino]sulfonyl]phenyl]propyl]-3-methyl-1H-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. [α]D 24 = -40.1 (c 1.0, MeOH). 1H-NMR (CD3OD) δ: 1.38 (9H, s, C(CH3)3), 2.10-2.18 (2H, m, CH2), 2.63 (2H, t, J = 7.9 Hz, Ar-CH2), 3.89 (3H, s, N-CH3), 4.19 (2H, t, J = 7.3 Hz, CH2N), 4.57 (1H, d, J = 8.4 Hz, CH(Ph)NH), 4.79 (1H, d, J = 8.4 Hz, CH(Ph)NH), 6.86-6.88 (2H, m, SO2Ar-H), 6.94-6.96 (3H, m, Ph-H), 7.04-7.12 (7H, m, Ph-H), 7.39 (2H, d, J = 8.4 Hz, SO2Ar-H), 7.52 (1H, d, J = 1.8 Hz, imidazole-H), 7.59 (1H, d, J = 2.2 Hz, imidazole-H), 8.89 (1H, s, 2-imidazole-H). 13C-NMR (CD3OD): 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\(_4\)O\(_4\)S\(\cdot\)1/3H\(_2\)O: C, 62.27; H, 6.48; N, 9.08. Found: C, 62.42; H, 6.53; N, 9.07.

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

To a solution of 17 (203 mg, 0.433 mmol), Et\(_3\)N (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 overnight at rt. The solvent was removed under reduced pressure and H\(_2\)O 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\(_3\)) \(\delta\): 1.47 (9H, s, C(CH\(_3\))\(_3\)), 2.19 (2H, quint, \(J = 6.7\) Hz, CH\(_2\)), 2.75 (2H, t, \(J = 7.2\) Hz, ArCH\(_2\)), 3.65 (2H, t, \(J = 6.2\) Hz, CH\(_2\)Cl), 4.61-4.65 (1H, m, CH(Ph)NH), 4.78-4.82 (1H, m, CH(Ph)NH), 5.23 (1H, br-d, \(J = 7.3\) Hz, NH), 6.32 (1H, br-s, NH), 6.77-7.19 (12H, m, Ar-H and Ph-H), 7.52 (2H, dt, \(J = 8.8\) and 2.4 Hz, Ar-H). \(^13\)C-NMR (CDCl\(_3\)) \(\delta\): 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, 128.6, 137.5, 137.8, 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\(_2\)O\(_4\)S: C, 59.89; H, 6.20; N, 4.66. Found: C, 59.90; H, 6.28; N, 4.65.

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

To a solution of 17 (203 mg, 0.433 mmol), Et\(_3\)N (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\(_2\)O 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\(_3\)) \(\delta\): 1.47 (9H, s, C(CH\(_3\))\(_3\)), 2.37-2.44 (2H, m, CH\(_2\)), 3.41 (2H, t, \(J = 6.7\) Hz, CH\(_2\)), 3.70 (2H, t, \(J = 6.0\) Hz, CH\(_2\)), 4.67 (1H, dd, \(J = 6.6\) and 9.2 Hz, CH(Ph)NH), 4.81 (1H, dd, \(J = 8.1\) and 9.5 Hz, CH(Ph)NH), 5.27 (1H, br-s, NH), 6.57 (1H, br-s, NH), 6.76 (2H, br-d, \(J = 7.8\) Hz, Ar-H), 6.92-7.01 (5H, m, Ar-H), 7.06 (2H, dt, \(J = 8.8\) and 2.4 Hz, Ar-H), 7.16 (3H, t, \(J = 3.3\) Hz, Ar-H), 7.51 (2H, d, \(J = 8.8\) Hz, Ar-H). \(^13\)C-NMR (CDCl\(_3\)) \(\delta\): 26.6, 28.3, 42.1, 48.2, 60.1, 64.5, 81.0, 121.8, 127.3, 127.4,
127.6, 128.1, 128.6, 128.9, 137.2, 137.6, 140.1, 151.0, 157.2. IR (CHCl₃) cm⁻¹: 3439, 3030, 1689, 1489, 1165, 1149, 871, 700. FABMS (NBA) m/z: 609 ([M+H]⁺). Anal. Calcd for C₂₈H₃₃ClN₂O₇S₂: C, 55.21; H, 5.46; N, 4.60. Found: C, 55.07; H, 5.60; N, 4.55.

1-[3-[(1S,2S)-2-[(t-Butoxycarbonyl)amino]-1,2-diphenylethyl]amino]sulfonyl]propyl]-3-methyl-1H-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. [α]D²⁴ − 36.2 (c 1.0, MeOH). ¹H-NMR (CD₃OD): 1.38 (9H, s, C(CH₃)₃), 2.51 (2H, quint, J = 7.3 Hz, CH₂CH₂CH₂), 3.52 (2H, t, J = 7.5 Hz, CH₂), 3.92 (3H, s, N-CH₃), 4.42 (2H, t, J = 7.4 Hz, CH₂), 4.62 (1H, d, J = 8.4 Hz, CH(Ph)NH), 4.82 (1H, d, J = 8.4 Hz, CH(Ph)NH), 6.87-6.90 (2H, m, SO₂Ar-H), 6.95-7.15 (10H, m, 2 × Ph-H), 7.51 (2H, d, J = 8.4 Hz, SO₂Ar-H), 7.57 (1H, d, J = 2.2 Hz, imidazole-H), 7.66 (1H, d, J = 2.2 Hz, imidazole-H), 8.97 (1H, s, 2-imidazole-H). ¹³C-NMR (CD₃OD): 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 C₃₂H₃₉ClN₄O₇S₂·½H₂O: 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 MgSO₄, 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. ¹H-NMR (CDCl₃): 0.90 (6H, d, J = 6.9 Hz, -CH(CH₃)₂), 1.96 (1H, sept, J = 6.6 Hz, -CH(CH₃)₂)), 2.27 (2H, quint, J = 6.2 Hz, -OCH₂CH₂CH₂Cl), 3.70 (2H, t, J = 6.2 Hz, CH₂Cl), 3.85 (2H, d, J = 6.6 Hz, -CH₂CH(CH₃)₂), 4.53 (2H, t, J = 6.2 Hz, OCH₂), 7.98 (2H, dt, J = 8.8 and 1.8 Hz, Ar-H), 8.20 (2H, dt, J = 8.8 and 1.8 Hz, Ar-H). ¹³C-NMR (CDCl₃): 18.5, 28.0, 30.3, 31.5, 41.0, 62.5, 127.9, 130.3, 134.6, 140.3, 164.7. IR (CHCl₃) 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 C₁₄H₁₉ClO₅S·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. ¹H-NMR (CDCl₃): 0.90 (6H, d, J = 7.0 Hz, -CH(CH₃)₂),
1.91-2.01 (1H, m, -CH(CH₃)₂), 3.84 (2H, t, J = 5.5 Hz, CH₂Cl), 3.86 (2H, d, J = 7.0 Hz, -CH₂CH(CH₃)₂), 4.63 (2H, t, J = 5.5 Hz, OCH₂), 8.00 (2H, dt, J = 8.8 and 1.8 Hz, Ar-H), 8.24 (2H, dt, J = 8.4 and 1.8 Hz, Ar-H). ¹³C-NMR (CDCl₃) δ: 18.5, 28.1, 41.4, 65.1, 77.0, 127.9, 130.5, 134.3, 140.1, 164.6. IR (CHCl₃) 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 C₁₃H₁₇ClO₅S: 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. ¹H-NMR (DMSO-d₆) δ: 2.18 (2H, quintet, J = 6.3 Hz, -OCH₂CH₂CH₂Cl), 3.79 (2H, t, J = 6.6 Hz, CH₂Cl), 4.39 (2H, t, J = 6.1 Hz, OCH₂), 7.75 (2H, d, J = 8.4 Hz, Ar-H), 7.96 (2H, d, J = 8.5 Hz, Ar-H). ¹³C-NMR (CDCl₃) 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 C₁₀H₁₀ClO₅S⁺: 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. ¹H-NMR (DMSO-d₆) δ: 3.97 (2H, t, J = 5.1 Hz, CH₂Cl), 4.54 (2H, t, J = 5.1 Hz, OCH₂), 7.76 (2H, dt, J = 8.4 and 1.8 Hz, Ar-H), 7.96 (2H, dt, J = 8.4 and 1.8 Hz, Ar-H). ¹³C-NMR (CDCl₃) 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 C₉H₈NaO₅S: 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. ¹H-NMR (CDCl₃) δ: 2.27 (2H, quintet, J = 6.2 Hz, -OCH₂CH₂CH₂Cl), 3.70 (2H, t, J = 6.2 Hz, CH₂Cl), 4.56 (2H, t, J = 6.0 Hz, OCH₂), 8.12 (2H, dt, J = 8.8 and 1.8 Hz, Ar-H), 8.26 (2H, dt, J = 8.8 and 2.2 Hz, Ar-H). ¹³C-NMR (CDCl₃) δ: 31.4, 40.9, 62.8, 127.0, 130.8, 135.9, 147.6, 164.2. IR (CHCl₃) 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 C₁₀H₁₀Cl₂O₄S: 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$_3$): 3.84 (2H, t, $J = 5.5$ Hz, CH$_2$Cl), 4.64 (2H, t, $J = 5.5$ Hz, OCH$_2$), 8.14 (2H, dt, $J = 8.8$ and 1.8 Hz, Ar-H), 8.30 (2H, dt, $J = 8.8$ and 1.8 Hz, Ar-H).

$^{13}$C-NMR (CDCl$_3$): 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$_9$H$_8$Cl$_2$O$_4$S: C, 38.18; H, 2.85. Found: C, 38.38; H, 2.83.

3-Chloropropyl 4-N-[1(S,2S)-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 $^\circ$C. $[^\alpha]_D^{23}$ −28.0 (c 1.0, CHCl$_3$). $^1$H-NMR (CDCl$_3$): 1.48 (9H, s, C(CH$_3$)$_3$), 2.23 (2H, quintet, $J = 6.2$ Hz, -OCH$_2$CH$_2$Cl), 3.67 (2H, t, $J = 6.2$ Hz, CH$_2$Cl), 4.48 (2H, t, $J = 6.2$ Hz, OCH$_2$), 4.68 (1H, dd, $J = 9.9$ and 7.0 Hz, CH(Ph)NH), 4.81 (1H, dd, $J = 9.7$ and 7.9 Hz, CH(Ph)NH), 5.24 (1H, br-s, NH), 6.59 (1H, br-s, NH), 6.78-6.79 (2H, m, Ph-H), 6.92-7.05 (5H, m, Ph-H), 7.15-7.18 (3H, m, Ph-H), 7.57 (2H, d, $J = 8.8$ Hz, Ar-H), 7.84 (2H, dt, $J = 8.4$ and 1.8 Hz, Ar-H). $^{13}$C-NMR (CDCl$_3$): 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$_2$O$_6$S: 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,2S)-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 $^\circ$C. $[^\alpha]_D^{21}$ −32.19 (c 1.0, CHCl$_3$). $^1$H-NMR (CDCl$_3$): 1.48 (9H, s, C(CH$_3$)$_3$), 3.80 (2H, t, $J = 5.7$ Hz, CH$_2$Cl), 4.56 (2H, dd, $J = 6.3$ and 4.8 Hz, OCH$_2$), 4.68 (1H, dd, $J = 9.9$ and 6.6 Hz, CH(Ph)NH), 5.24 (1H, br-s, NH), 6.59 (1H, br-s, NH), 6.78-6.79 (2H, m, Ph-H), 7.15-7.18 (3H, m, Ph-H), 7.57 (2H, d, $J = 8.8$ Hz, Ar-H), 7.84 (2H, dt, $J = 8.4$ and 1.8 Hz, Ar-H). $^{13}$C-NMR (CDCl$_3$): 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: 559 ([M+H$^+$]). Anal. Calcd for C$_{28}$H$_{31}$ClN$_2$O$_6$S: C, 60.15; H, 5.59; N, 5.01. Found: C, 60.28; H, 5.70; N, 5.00.

1-[3-[4-[[1(S,2S)-2-t-Butoxycarbonylamino]-1,2-diphenylethyl]amino][sulfonyl]benzoyloxy]-propyl]-3-methyl-1H-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. [α]D 24° –39.1 (c 1.0, MeOH). 1H-NMR (CD3OD) δ: 1.37 (9H, s, C(CH3)3), 2.37 (2H, quint, J = 6.6 Hz, OCH2CH2CH2), 3.86 (3H, s, imidazole-CH3), 4.39 (2H, t, J = 7.4 Hz, CH2N), 4.39 (2H, t, J = 5.9 Hz, OCH2), 4.66 (1H, d, J = 8.1 Hz, CH(Ph)NH), 4.83 (1H, d, J = 7.3 Hz, CH(Ph)NH), 6.90-7.12 (10H, m, Ar-H), 7.53 (1H, t, J = 1.7 Hz, imidazole-H), 7.57 (2H, dt, J = 8.8 and 1.9 Hz, Ph-H), 7.67 (1H, t, J = 1.7 Hz, imidazole-H), 7.80 (2H, dt, J = 8.8 and 1.8 Hz, Ph-H), 8.99 (1H, s, 2-imidazole-H). 13C-NMR (CD3OD): 29.1, 30.6, 36.9, 48.5, 53.2, 61.4, 63.6, 64.7, 81.1, 124.1, 125.5, 128.3, 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]+).

**N-[(1S,2S)-2-t-Butoxycarbonylamino-1,2-diphenylethyl]-1-methyl-1H-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. [α]D 27° –10.80 (c 1.0, MeOH). 1H-NMR (CDCl3) δ: 1.40 (9H, s, C(CH3)3), 3.51 (3H, s, N-CH3), 4.76 (1H, t, J = 7.9 Hz, CH(Ph)NH), 4.84 (1H, t, J = 7.5 Hz, CH(Ph)NH), 5.68 (1H, br-s, NH), 6.41 (1H, br-s, NH), 6.91 (2H, d, J = 1.3 Hz, 5-imidazole-H), 6.95-7.16 (10H, m, 2 × Ph-H), 7.27 (1H, br-s, 2-imidazole-H). 13C-NMR (CDCl3): 28.5, 33.8, 59.7, 60.9, 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 (KBr) cm–1: 3410, 3350, 2980, 1697, 1489, 1156, 1116. FABMS (NBA) m/z: 457 ([M-H]+). Anal. Calcd for C23H29N4O4S: C, 60.51; H, 6.18; N, 12.27. Found: C, 60.42; H, 6.18; N, 12.18.

**1,3-Dimethyl-[[[(1S,2S)-2-[(t-butoxycarbonyl)amino]1,2-diphenylethyl]amino]sulfonyl]-1H-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 N2. The volatile material was removed, and the residue was washed with AcOEt to obtain compound 36.

Yield: 117 mg (94%). Light yellow hygroscopic solid. [α]D 25° –16.51 (c 0.86, MeOH). 1H-NMR (DMSO-d6) δ: 1.27 (9H, s, C(CH3)3), 3.55 (3H, s, N-CH3), 4.20 (1H, br-d, J = 3.3 Hz, CH(Ph)NH), 4.45 (1H, br-d, J = 3.5 Hz, CH(Ph)NH), 6.27 (1H, br-d, J = 6.6 Hz, NH), 7.05-7.29 (12H, m, NH, 2 × Ph-H and 5-imidazole-H), 8.49 (1H, s, 2-imidazole-H). 13C-NMR (DMSO-d6): 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. 19F-NMR (CD3OD) 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-CF3CO2]+) (Calcd for C24H34N4O5S+: 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 [RuCl₂(benzene)]₂ (2.5 mg, 0.005 mmol) in [bmim][PF₆] (1.0 mL) with stirring under N₂, 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 H₂O. The organic layer was dried over MgSO₄, filtered. This organic layer was determined by GLC.

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