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REGULAR ARTICLE

A study of enantioselective syntheses by Sharpless asymmetric oxidation for aryl sulfoxides containing oxygen groups at the ortho position

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Abstract. While ortho-alkoxy aryl sulfoxides including various substituents were synthesized by Sharpless asymmetric oxidation reaction, we optimized the reaction conditions and screened better combination of starting materials to obtain high enantioselectivity. The result suggested new information that electron-withdrawing substituents on the aromatic ring have a strong influence upon enantioselectivity of the products. Also, several chiral ligands for Sharpless asymmetric oxidation reaction were evaluated to improve the enantioselectivity.

Keywords. Sharpless asymmetric oxidation; sulfide; chiral sulfoxide.

1. Introduction

In recent years, chiral sulfoxides are getting more attention as ligands and chiral auxiliaries for asymmetric syntheses. Chiral aryl sulfoxides are utilized in various reactions such as coupling reactions and asymmetric syntheses, taking advantage of their bulky structures.[1–5] Moreover, they can also function as pharmacophores so that these structures have been incorporated into several pharmaceuticals, for instance, esomeprazole which is a proton pump inhibitor (PPI), and sparsomycin which has antitumor activity.[6–8] Many studies have shown that the chirality of sulfoxides has a great influence on pharmacokinetics and pharmacological activity.[9–18] Therefore, chiral sulfoxides are considered one of the most useful functional groups in organic and medicinal chemistry fields.

Asymmetric syntheses of chiral sulfoxides are classified into three groups, which are nucleophilic substitution reaction with chiral sulfinates, diastereoselective asymmetric syntheses reaction, and enantioselective asymmetric oxidation.[19] Among these methods, the enantioselective asymmetric oxidation is the most applicable since the reaction can be carried out under mild conditions when metal catalysts are used. For example, sulfoxidation by Sharpless asymmetric oxidation reactions, using $Ti(O\text{-}i\text{-}Pr)_4$ as Lewis acids, diethyl tartrate (DET) as ligands, and *t*-butyl hydroperoxide (TBHP) or similar oxidants, showed high enantioselectivities although they are fairly simple reactions.[20–24] However, few enantioselective syntheses using Sharpless asymmetric oxidation have been reported for aryl sulfoxides containing functional group at the ortho position, and reproducible high enantioselectivity has not been yet achieved.

Figure 1 shows examples of aryl sulfoxide compounds having polar functional groups used as chiral ligands and intermediates of asymmetric syntheses.[5,25–28] No simple enantioselective synthesis method has been reported for the Chiral ligands A in Figure 1. Some reported the syntheses of aryl sulfoxide compounds having polar functional groups at the ortho position to enhance the coordination force,[29–31] yet most of them are nucleophilic substitution reactions on the chiral sulfoxide with protected polar

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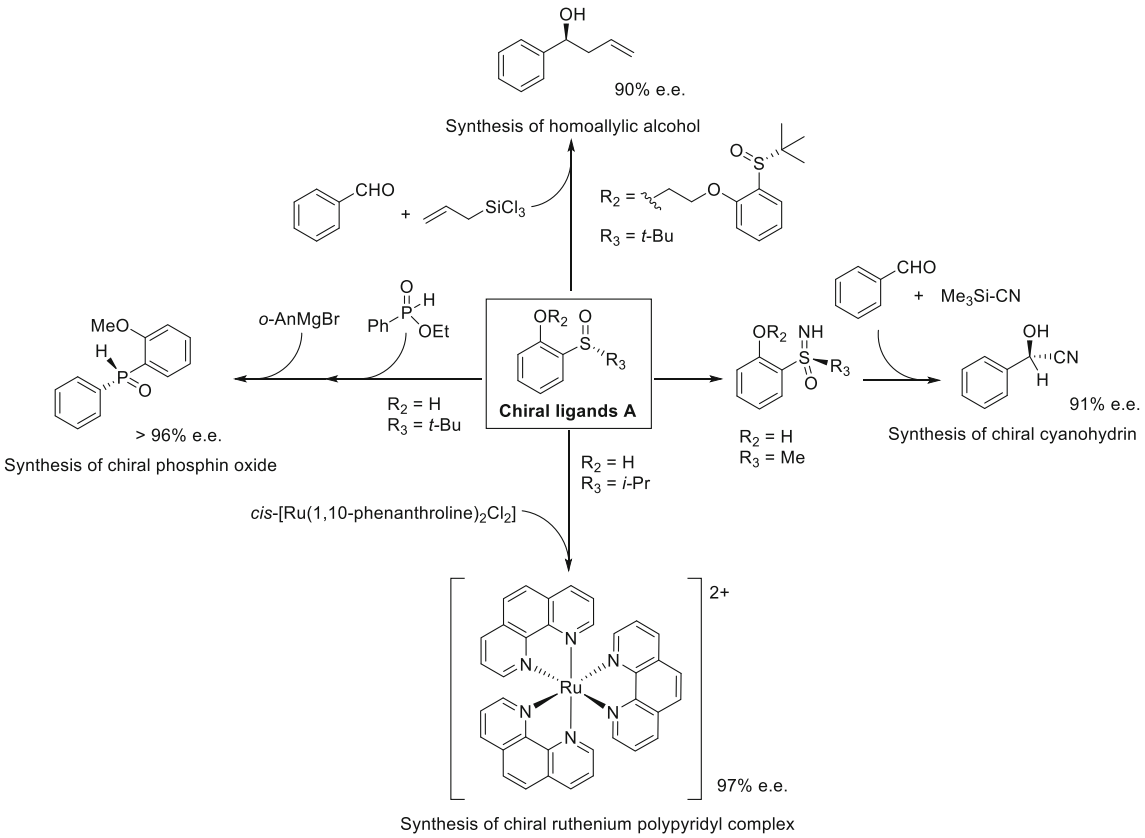


Figure 1. Application of the chiral aryl sulfoxide incorporating oxygen functional groups at the ortho position.

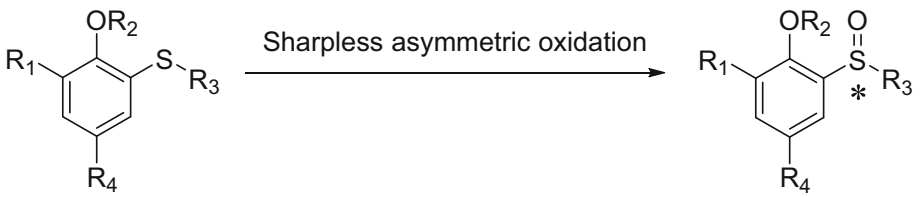
functional groups, in addition, the reactant containing carbonyl groups could not be used in the synthesis.[19,29]

Others reported a synthesis method using a polypyridyl complex,[32–34] but the method is not suitable for large-scale production. Therefore, we have focused on building simple enantioselective synthesis methods to obtain various chiral aryl sulfoxides containing oxygen functional group at the ortho position (Scheme 1). We accomplished this by Sharpless asymmetric oxidation after optimizing the reaction condition and screened the combinations of starting materials to achieve high enantioselectivity.

2. Experimental

2.1 *Materials and physical measurements*

All the reagents and solvents were purchased from commercial sources and used without further purification. Reagents for Sharpless oxidation such as Ti(O-*i*-Pr)$_4$, diethyl tartrate (DET) and cumene hydroperoxide (CHP) were supplied from Sigma-Aldrich Co. (USA). Reagents for other reactions were supplied from Tokyo Chemical Industry Co., Ltd. (Japan), Wako Pure Chemical Industries Ltd. (Japan) and



R$_1$, R$_4$ = various substituents
R$_2$ = H, Me, MOM
R$_3$ = alkyl groups

Scheme 1. Sharpless asymmetric oxidation for aryl sulfoxide containing ortho oxygen groups.

Kanto Chemical Co., Inc. (Japan). Flash chromatography was performed on 40–50 μm silica gel or 75 μm activated alumina. Enantiomeric excess (e.e.) was determined by HPLC using DAICEL CHIRALPAK IF or AY-3. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Varian-400MR using $CDCl_3$ containing 0.03% TMS. IR spectra were recorded as neat or as solids in KBr pellets on IRAffinity-1. Mass spectra were recorded on JMS-700(2). Elemental analyses were measured on CHN CORDER MT-6. Specific optical rotations were measured in $CHCl_3$ on JASCOO P-1020 polarimeter. All measurements of X-ray crystal structure analysis were made on a R-AXIS RAPID diffractometer using filtered Mo-Kα radiation (λ = 0.71075 Å).

2.2 *General procedure for methylation of phenol*

NaOH in water, tetrabutylammonium bromide (TBAB) and dimethyl sulfate were added to the solution of phenol in CH_2Cl_2 (10 mL), and then the biphasic system was allowed to stir at room temperature for 2 h. The reaction mixture was extracted with EtOAc (25 mL × 2), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The reaction mixture was purified by column chromatography on silica gel.

1-Bromo-2-methoxy-3-methylbenzene (2b)[35] Compound **2b** was followed by general procedure for methylation of phenol using 6-bromo-*o*-cresol **1b** (5.00 g, 26.7 mmol), NaOH (3.21 g, 80.2 mmol) in water (25 mL), TBAB (0.862 g, 2.67 mmol), dimethyl sulfate (6.17 mL, 61.5 mmol) in CH_2Cl_2 (25 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **2b** (5.91 g, > 99%) as a colorless oil.

5-Iodo-2-methoxy-1-methyl-3-[(R)-methylsulfinyl]benzene (R-11) Compound ***R-11*** was followed by general procedure for methylation of phenol using phenol ***R-10*** (0.960 g, 3.24 mmol, > 99% e.e.), NaOH (0.389 g, 9.73 mmol) in water (10 mL), TBAB (0.105 g, 0.324 mmol), dimethyl sulfate (0.71 mL, 7.46 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product ***R-11*** (1.02 g, > 99%, > 99% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 96: 4, 0.75 mL/min, 250 nm, t_{major} = 34.82 min, t_{minor} = 39.75 min). M.p.: 80–82 °C; $[\alpha]_D$ = +94 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 2.0 Hz, 1H), 7.62 (d, J = 2.0 Hz, 1H), 3.77 (s, 3H), 2.75 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 152.7, 140.6, 134.0, 130.9, 88.6, 61.1, 42.3, 15.2; IR (KBr) 3054, 2954, 2915, 1462, 1416, 1254, 1215, 1162, 1061 cm^{-1}; HRMS (EI) for $C_9H_{11}O_2SI$ calcd 309.9524 (M^+), found 309.9545; Anal. Calcd for $C_9H_{11}O_2SI$: C, 34.85; H, 3.57; N, 0.00. found: C, 35.10; H, 3.47; N, 0.00.

2.3 *General procedure for protection by MOM group*

K_2CO_3 and chloromethyl methyl ether (MOM-Cl) were added to the solution of phenol in dry acetone, and the mixture was allowed to stir at 40 °C for 1 h. The reaction mixture was concentrated by evaporation and extracted with EtOAc (25 mL × 2), washed with brine, dried over Na_2SO_4, and concentrated by evaporation. The residue was purified by column chromatography on silica gel.

1-Bromo-2-(methoxymethoxy)benzene (4a)[36] Compound **4a** was followed by the general procedure for protection by MOM group using 2-bromophenol **1a** (5.00 g, 28.9 mmol), K_2CO_3 (7.99 g, 57.8 mmol), MOM-Cl (> 80%, 4.0 mL, 42.2 mmol) in dry acetone (25 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **4a** (6.37 g, > 99%) as a colorless oil.

1-Bromo-2-(methoxymethoxy)-3-methylbenzene (4b) Compound **4b** was followed by general procedure of protection by MOM group using 6-bromo-*o*-cresol **1b** (5.22 g, 27.9 mmol), K_2CO_3 (7.71 g, 55.8 mmol), MOM-Cl (> 80%, 3.9 mL, 40.7 mmol) in dry acetone (30 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **4b** (6.40 g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dd, J = 7.6, 1.6 Hz, 1H), 7.12 (dd, J = 7.6, 1.6 Hz, 1H), 6.90 (t, J = 7.6 Hz, 1H), 5.08 (s, 2H), 3.65 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 133.8, 131.0, 130.3, 125.3, 117.3, 99.5, 57.7, 17.3; IR (neat) 2954, 2934, 1458, 1159, 1072, 960 cm^{-1}; HRMS (EI) for $C_9H_{11}{}^{79}BrO_2$ calcd 229.9942 (M^+), found 229.9928, $C_9H_{11}{}^{81}BrO_2$ calcd 231.9922 (M^+), found 231.9902.

2-Bromo-1-(methoxymethoxy)-4-methylbenzene (4c)[37] Compound **4c** was followed by the general procedure of protection by MOM group using 2-bromo-*p*-cresol **1c** (5.00 g, 26.7 mmol), K_2CO_3 (7.40 g, 53.5 mmol), MOM-Cl (> 80%, 3.7 mL, 39.0 mmol) in dry acetone (30 mL). The reaction mixture was purified by column chromatography on

silica gel using hexane/EtOAc (10: 1) to give the product **4c** (5.55 g, 90%) as a colorless oil.

1-Bromo-4-fluoro-2-(methoxymethoxy)benzene (4d)[38] Compound **4d** was followed by the general procedure of protection by MOM group using 2-bromo-5-fluorophenol **1d** (5.00 g, 26.2 mmol), K_2CO_3 (7.24 g, 52.4 mmol), MOM-Cl (> 80%, 3.6 mL, 38.2 mmol) in dry acetone (25 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **4d** (6.07 g, 99%) as a colorless oil.

2-Bromo-4-fluoro-1-(methoxymethoxy)benzene (4e)[39] Compound **4e** was followed by general procedure of protection by MOM group using 2-bromo-4-fluorophenol **1e** (5.00 g, 26.2 mmol), K_2CO_3 (7.24 g, 52.4 mmol), MOM-Cl (> 80%, 3.6 mL, 38.2 mmol) in dry acetone (25 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **4e** (6.02 g, 98%) as a colorless oil.

1-Bromo-3-methoxy-2-(methoxymethoxy)benzene (4f)[36] Compound **4f** was followed by general procedure of protection by MOM group using 2-bromo-6-methoxyphenol **1f** (3.00 g, 14.8 mmol), K_2CO_3 (4.09 g, 29.6 mmol), MOM-Cl (> 80%, 2.1 mL, 21.6 mmol) in dry acetone (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **4f** (3.81 g, > 99%) as a colorless oil.

2-Bromo-4-methoxy-1-(methoxymethoxy)benzene (4g)[40] Compound **4g** was followed by general procedure of protection by MOM group using 2-bromo-4-methoxyphenol **1g** (1.00 g, 4.93 mmol), K_2CO_3 (1.35 g, 9.80 mmol), MOM-Cl (> 80%, 0.68 mL, 7.15 mmol) in dry acetone (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (30: 1) to give the product **4g** (1.13 g, 92%) as a colorless oil.

2-Bromo-1-(methoxymethoxy)-4-nitrobenzene (4h)[41] Compound **4h** was followed by the general procedure of protection by MOM group using 2-bromo-4-nitrophenol **1h** (3.73 g, 17.1 mmol), K_2CO_3 (4.73 g, 34.2 mmol), MOM-Cl (> 80%, 2.4 mL, 25.0 mmol) in dry acetone (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **4h** (4.35 g, 97%) as a white solid.

Methyl 3-bromo-4-(methoxymethoxy)benzoate (4i)[42] Compound **4i** was followed by the general procedure of protection by MOM group using methyl 3-bromo-4-hydroxybenzoate **1i** (5.00 g, 21.6 mmol), K_2CO_3 (5.98 g, 43.3 mmol), MOM-Cl (> 80%, 3.0 mL, 31.6 mmol) in dry acetone (35 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **4i** (5.81 g, 98%) as a white solid.

3-Bromo-4-(methoxymethoxy)benzaldehyde (4j)[43] Compound **4j** was followed by the general procedure of protection by MOM group using 3-bromo-4-hydroxybenzaldehyde **1j** (5.00 g, 24.9 mmol), K_2CO_3 (6.88 g, 49.7 mmol), MOM-Cl (> 80%, 3.5 mL, 36.3 mmol) in dry acetone (35 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **4j** (5.94 g, 97%) as a white solid.

1-(Methoxymethoxy)-2-(methylsulfanyl)-4-nitrobenzene (5h) Compound **5h** was followed by general procedure of protection by MOM group using phenol **16** (0.290 g, 1.57 mmol), K_2CO_3 (0.433 g, 3.13 mmol), MOM-Cl (> 80%, 0.22 mL, 2.29 mmol) in dry acetone (5.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (8: 1) to give the product **5h** (0.344 g, 96%) as a pale yellow solid. M.p.: 79–81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (dd, J = 8.8, 2.8 Hz, 1H), 7.98 (d, J = 2.8 Hz, 1H), 7.14 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 3.52 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 142.7, 130.8, 121.5, 120.0, 112.5, 94.7, 56.6, 14.2; IR (KBr) 3113, 3092, 2990, 2947, 2920, 2859, 2830, 1574, 1510, 1495, 1476, 1443, 1342, 1329, 1302, 1267, 1244, 1204, 1165, 1142, 1128, 1086, 1063, 961 cm^{-1}; HRMS (EI) for $C_9H_{11}NO_4S$ calcd 229.0409 (M^+), found 229.0410; Anal. Calcd for $C_9H_{11}NO_4S$: C, 47.15; H, 4.84; N, 6.11. found C, 47.44; H, 4.91; N, 5.95.

2.4 *General procedure for introduction of sulfide into an aromatic ring (method A)*

A flask was charged with aryl bromide and evacuated and backfilled Ar gas. Aryl bromide was diluted with dry Et_2O and cooled to − 78 °C. The solution was added dropwise *t*-BuLi and allowed to stir at − 78 °C for 1 h. Then, disulfide was added dropwise and the reaction mixture was allowed to stir at room temperature for 1 h. The reaction mixture was extracted with Et_2O (25 mL × 2) and washed brine, dried over Na_2SO_4 and concentrated by evaporation. The residue was purified by column chromatography on silica gel or recrystallization.

2-Methoxy-1-methyl-3-(methylsulfanyl)benzene (3b)[44] Compound **3b** was followed by general procedure of method A using aryl bromide **2b** (3.56 g, 17.7 mmol), 1.56 M *t*-BuLi in *n*-pentane (25.0 mL,

39.0 mmol), dimethyl disulfide (2.7 mL, 30.1 mmol) in dry Et_2O (30 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **3b** (2.62 g, 88%) as a colorless oil.

1-(Methoxymethoxy)-2-(methylsulfanyl)benzene (5a)[45] Compound **5a** was followed by the general procedure of method A using aryl bromide **4a** (1.00 g, 4.60 mmol), 1.56 M *t*-BuLi in *n*-pentane (6.5 mL, 10.1 mmol), dimethyl disulfide (0.7 mL, 7.84 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/CH_2Cl_2 (10: 1) to give the product **5a** (0.837 g, 99%) as a colorless oil.

2-(Methoxymethoxy)-1-methyl-3-(methylsulfanyl)benzene (5b) Compound **5b** was followed by general procedure of method A using aryl bromide **4b** (5.00 g, 21.6 mmol), 1.56 M *t*-BuLi in *n*-pentane (30.5 mL, 47.6 mmol), dimethyl disulfide (3.3 mL, 36.8 mmol) in dry Et_2O (40 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **5b** (4.06 g, 95%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05–6.96 (m, 3H), 5.05 (s, 2H), 3.65 (s, 3H), 2.42 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.7, 132.4, 131.6, 127.8, 124.8, 123.7, 98.9, 57.6, 16.8, 14.8; IR (neat) 2954, 2923, 2826, 1495, 1458, 1437, 1427, 1396, 1254, 1236, 1228, 1202, 1158, 1072, 964 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_2S$ calcd 198.0715 (M^+), found 198.0717.

1-(Methoxymethoxy)-4-methyl-2-(methylsulfanyl)benzene (5c) Compound **5c** was followed by general procedure of method A using aryl bromide **4c** (1.00 g, 4.33 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.2 mL, 9.52 mmol), dimethyl disulfide (1.2 mL, 7.36 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **5c** (0.853 g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 8.0 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 8.0, 2.0 Hz, 1H), 5.19 (s, 2H), 3.50 (s, 3H), 2.41 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.7, 131.9, 127.7, 126.5, 126.1, 114.4, 95.0, 56.1, 20.7, 14.6; IR (neat) 2953, 2920, 2824, 1487, 1439, 1233, 1198, 1155, 1142, 1086, 1065, 995 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_2S$ calcd 198.0715 (M^+), found 198.0709.

4-Fluoro-2-(methoxymethoxy)-1-(methylsulfanyl)benzene (5d) Compound **5d** was followed by general procedure of method A using aryl bromide **4d** (1.00 g, 4.25 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.1 mL, 9.36 mmol), dimethyl disulfide (0.64 mL, 7.23 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **5d** (0.834 g, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, J = 8.4, 6.4 Hz, 1H), 6.88 (dd, J = 10.4, 2.8 Hz, 1H), 6.71 (dt, J = 8.4, 2.8 Hz, 1H), 5.23 (s, 2H), 3.50 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (d, J = 243.6 Hz), 155.1 (d, J = 9.9 Hz), 127.9 (d, J = 9.1 Hz), 122.4 (d, J = 3.0 Hz), 108.7 (d, J = 22.0 Hz), 102.6 (d, J = 25.8 Hz), 94.7, 56.1, 15.3; IR (neat) 2957, 2920, 2830, 1593, 1481, 1441, 1425, 1389, 1273, 1244, 1153, 1121, 1088, 1061, 999 cm^{-1}; HRMS (EI) for $C_9H_{11}FO_2S$ calcd 202.0464 (M^+), found 202.0461.

4-Fluoro-1-(methoxymethoxy)-2-(methylsulfanyl)benzene (5e) Compound **5e** was followed by general procedure of method A using aryl bromide **4e** (1.00 g, 4.25 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.1 mL, 9.36 mmol), dimethyl disulfide (0.64 mL, 7.23 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **5e** (0.860 g, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (dd, J = 8.8, 4.8 Hz, 1H), 6.82 (dd, J = 8.8, 2.8 Hz, 1H), 6.75 (dt, J = 8.4, 2.8 Hz, 1H), 5.17 (s, 2H), 3.50 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4 (d, J = 239.8 Hz), 149.5 (d, J = 2.3 Hz), 130.8 (d, J = 7.6 Hz), 115.4 (d, J = 8.3 Hz), 111.9 (d, J = 25.8 Hz), 111.0 (d, J = 22.8 Hz), 95.4, 56.1, 14.1; IR (neat) 2955, 2922, 2905, 2826, 1601, 1587, 1483, 1439, 1396, 1263, 1238, 1186, 1153, 1128, 1082, 1059, 995 cm^{-1}; HRMS (EI) for $C_9H_{11}FO_2S$ calcd 202.0464 (M^+), found 202.0467.

1-Methoxy-2-(methoxymethoxy)-3-(methylsulfanyl)benzene (5f) Compound **5f** was followed by general procedure of method A using aryl bromide **4f** (1.00 g, 4.05 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.4 mL, 8.90 mmol), dimethyl disulfide (0.61 mL, 6.89 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (25: 1) to give the product **5f** (0.574 g, 66%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, J = 8.0 Hz, 1H), 6.77 (dd, J = 8.0, 1.2 Hz, 1H), 6.74 (dd, J = 8.0, 1.2 Hz, 1H), 5.17 (s, 2H), 3.04 (s, 3H), 3.66 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 142.3, 133.6, 124.6, 117.6, 109.3, 98.3, 57.8, 55.9, 14.8; IR (neat) 2994, 2959, 2920, 2835, 1584, 1468, 1437, 1398, 1292, 1265, 1157, 1074, 959 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_3S$ calcd 214.0664 (M^+), found 214.0663.

4-Methoxy-1-(methoxymethoxy)-2-(methylsulfanyl)benzene (5g) Compound **5g** was followed by general procedure of method A using aryl bromide **4g** (1.00 g, 4.05 mmol), 1.64 M *t*-BuLi in *n*-pentane

(5.43 mL, 8.90 mmol), dimethyl disulfide (0.61 mL, 6.89 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (50: 1) to give the product **5g** (0.856 g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, J = 8.8 Hz, 1H), 6.71 (d, J = 3.2 Hz, 1H), 6.60 (dd, J = 8.8, 3.2 Hz, 1H), 5.15 (s, 2H), 3.77 (s, 3H), 3.52 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 147.9, 129.9, 115.9, 112.2, 109.3, 95.7, 56.1, 55.6, 14.4; IR (neat) 2994, 2953, 2938, 2920, 2905, 2832, 1585, 1487, 1437, 1273, 1221, 1196, 1155, 1140, 1082, 1059, 1043, 995 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_3S$ calcd 214.0664 (M^+), found 214.0661.

1-(Ethylsulfanyl)-2-(methoxymethoxy)benzene (12a) Compound **12a** was followed by general procedure of method A using aryl bromide **4a** (1.00 g, 4.60 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.6 mL, 10.1 mmol), diethyl disulfide (0.96 mL, 7.84 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **12a** (0.900 g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, J = 7.6, 1.6 Hz, 1H), 7.13 (dt, J = 7.6, 1.6Hz, 1H), 7.08 (dd, J = 7.6, 1.6 Hz, 1H), 6.97 (ddd, J = 7.6, 1.6, 0.8 Hz, 1H), 5.24 (s, 2H), 3.50 (s, 3H), 2.92 (q, J = 7.6 Hz, 2H), 1.32 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 128.4, 126.4, 126.1, 122.2, 114.5, 94.7, 56.1, 25.7, 13.9; IR (neat) 2963, 2928, 2826, 1580, 1474,1439, 1261, 1231, 1198, 1155, 1132, 1086, 1067, 1043, 993 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_2S$ calcd 198.0715 (M^+), found 198.0718.

1-(Ethylsulfanyl)-2-(methoxymethoxy)-3-methylbenzene (12b) Compound **12b** was followed by general procedure of method A using aryl bromide **4b** (6.00 g, 26.0 mmol), 1.53 M *t*-BuLi in *n*-pentane (35.7 mL, 57.1 mmol), diethyl disulfide (5.4 mL, 44.1 mmol) in dry Et_2O (30 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **12b** (5.36 g, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12–7.08 (m, 1H), 7.01–6.97 (m, 2H), 5.07 (s, 2H), 3.65 (s, 3H), 2.91 (q, J = 7.2 Hz, 2H), 2.32 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 131.8, 130.5, 128.3, 126.1, 124.5, 98.9, 57.4, 26.0, 16.8, 13.9; IR (neat) 2969, 2929, 2872, 2834, 1457, 1429, 1255, 1226, 1202, 1158, 1072, 967 cm^{-1}; HRMS (EI) for $C_{11}H_{16}O_2S$ calcd 212.0871 (M^+), found 212.0858.

2-(Ethylsulfanyl)-1-(methoxymethoxy)-4-methylbenzene (12c) Compound **12c** was followed by general procedure of method A using aryl bromide **4c** (1.00 g, 4.33 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.8 mL, 9.52 mmol), diethyl disulfide (0.90 mL, 7.36 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **12c** (0.911 g, 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (d, J = 2.0 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.92 (dd, J = 8.4, 2.0 Hz, 1H), 5.20 (s, 2H), 3.50 (s, 3H), 2.91 (q, J = 7.2 Hz, 2H), 2.28 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.6, 131.7, 129.2, 127.0, 125.7, 114.7, 94.9, 56.0, 25.9, 20.6, 13.9; IR (neat) 2963, 2926, 2824, 1738, 1487, 1233, 1198, 1157, 1142, 1086, 1065, 999 cm^{-1}; HRMS (EI) for $C_{11}H_{16}O_2S$ calcd 212.0871 (M^+), found 212.0867.

1-(Ethylsulfanyl)-4-fluoro-2-(methoxymethoxy)benzene (12d) Compound **12d** was followed by general procedure of method A using aryl bromide **4d** (1.00 g, 4.25 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.1 mL, 9.36 mmol), diethyl disulfide (0.88 mL, 7.23 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **12d** (0.902 g, 98%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, J = 8.4, 6.4 Hz, 1H), 6.90 (dd, J = 10.8, 2.4 Hz, 1H), 6.69 (dt, J = 8.4, 2.4 Hz, 1H), 5.23 (s, 2H), 3.50 (s, 3H), 2.87 (q, J = 7.6 Hz, 2H), 1.27 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (d, J = 244.3 Hz), 156.4 (d, J = 9.8 Hz), 131.6 (d, J = 9.1 Hz), 120.1 (d, J = 3.8 Hz), 108.6 (d, J = 22.0 Hz), 102.9 (d, J = 25.8 Hz), 94.7, 56.1, 26.8, 14.0; IR (neat) 2963, 2928, 2870, 2830, 1593, 1481, 1425, 1389, 1271, 1153, 1121, 1088, 1061, 999 cm^{-1}; HRMS (EI) for $C_{10}H_{13}FO_2S$ calcd 216.0620 (M^+), found 216.0624.

2-(Ethylsulfanyl)-4-fluoro-1-(methoxymethoxy)benzene (12e) Compound **12e** was followed by general procedure of method A using aryl bromide **4e** (1.00 g, 4.25 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.1 mL, 9.36 mmol), diethyl disulfide (0.88 mL, 7.23 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **12e** (0.949 g, $>$ 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (dd, J = 9.2, 4.8 Hz, 1H), 6.91 (dd, J = 9.2, 3.2 Hz, 1H), 6.77 (ddd, J = 9.2, 8.4, 3.2 Hz), 5.17 (s, 2H), 3.50 (s, 3H), 2.90 (q, J = 7.6 Hz, 2H), 1.35 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (d, J = 239.8 Hz), 150.2 (d, J = 3.0 Hz), 129.1 (d, J = 7.6 Hz), 115.7 (d, J = 8.4 Hz), 113.7 (d, J = 25.8 Hz), 111.7 (d, J = 22.7 Hz), 95.3, 56.1, 25.3, 13.5; IR (neat) 2967, 2930, 2903, 2874, 2826, 1601, 1587, 1481, 1396, 1260, 1240, 1188, 1153, 1082, 1059, 995 cm^{-1}; HRMS (EI) for $C_{10}H_{13}FO_2S$ calcd 216.0620 (M^+), found 216.0622.

1-(Ethylsulfanyl)-3-methoxy-2-(methoxymethoxy)benzene (12f) Compound **12f** was followed by general procedure of method A using aryl bromide **4f** (1.00 g, 4.05 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.4 mL, 8.90 mmol), diethyl disulfide (0.84 mL, 6.89 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (50: 1) to give the product **12f** (0.721 g, 78%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (t, J = 8.0 Hz, 1H), 6.84 (dd, J = 8.0, 1.6 Hz, 1H), 6.74 (dd, J = 6.4, 1.6 Hz, 1H), 5.16 (s, 2H), 3.82 (s, 3H), 3.66 (s, 3H), 2.91 (q, J = 7.2 Hz, 2H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 143.0, 131.8, 124.3, 119.8, 109.7, 98.2, 57.7, 55.7, 25.9, 13.9; IR (neat) 2999, 2965, 2930, 2837, 1582, 1466, 1437, 1398, 1294, 1265, 1157, 1074, 1047, 961 cm^{-1}; HRMS (EI) for $C_{11}H_{16}O_3S$ calcd 228.0820 (M^+), found 228.0825.

2-(Ethylsulfanyl)-4-methoxy-1-(methoxymethoxy)benzene (12g) Compound **12g** was followed by general procedure of method A using aryl bromide **4g** (1.00 g, 4.05 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.4 mL, 8.90 mmol), diethyl disulfide (0.84 mL, 6.89 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (50: 1) to give the product **12g** (0.852 g, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 8.8 Hz, 1H), 6.80 (d, J = 3.2 Hz, 1H), 6.63 (dd, J = 8.8, 3.2 Hz, 1H), 5.15 (s, 2H), 3.75 (s, 3H), 3.51 (s, 3H), 2.91 (q, J = 7.2 Hz, 2H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 148.6, 128.0, 116.2, 114.1, 110.2, 95.6, 56.0, 55.4, 25.6, 13.7; IR (neat) 2959, 2930, 2903, 2872, 2832, 1595, 1485, 1464, 1398, 1263, 1219, 1196, 1155, 1140, 1082, 1058, 1042, 997 cm^{-1}; HRMS (EI) for $C_{11}H_{16}O_3S$ calcd 228.0820 (M^+), found 228.0814.

1-(Methoxymethoxy)-2-(propan-2-ylsulfanyl)benzene (13a) Compound **13a** was followed by general procedure of method A using aryl bromide **4a** (1.00 g, 4.60 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.6 mL, 10.1 mmol), diisopropyl disulfide (1.3 mL, 7.84 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **13a** (0.859 g, 86%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, J = 8.0, 1.6 Hz, 1H), 7.17 (dt, J = 8.0, 1.6 Hz, 1H), 7.11 (dd, J = 8.0, 1.6 Hz, 1H), 6.96 (dt, J = 8.0, 1.6 Hz, 1H), 5.24 (s, 2H), 3.50 (s, 3H), 3.49 (sep, J = 6.4 Hz, 1H), 1.30 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 131.9, 127.6, 124.9, 122.1, 114.7, 94.7, 56.1, 36.0, 22.9; IR (neat) 2961, 2926, 2864, 1582, 1474, 1439, 1242, 1229, 1198, 1153, 1130, 1084, 1065, 1042, 995 cm^{-1}; HRMS (EI) for $C_{11}H_{16}O_2S$ calcd 212.0871 (M^+), found 212.0867.

2-(Methoxymethoxy)-1-methyl-3-(propan-2-ylsulfanyl)benzene (13b) Compound **13b** was followed by general procedure of method A using aryl bromide **4b** (3.50 g, 15.1 mmol), 1.53 M *t*-BuLi in *n*-pentane (19.0 mL, 30.3 mmol), diisopropyl disulfide (4.1 mL, 25.7 mmol) in dry Et_2O (25 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **13b** (3.64 g, $>$ 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (dd, J = 7.6, 1.2 Hz, 1H), 7.04 (dd, J = 7.6, 1.2 Hz, 1H), 6.98 (t, J = 7.6 Hz, 1H), 5.09 (s, 2H), 3.64 (s, 3H), 3.46 (sep, J = 6.4 Hz, 1H), 2.33 (s, 3H), 1.29 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 132.2, 129.5, 129.4, 124.4, 99.2, 57.5, 57.5, 36.5, 23.0, 17.0; IR (neat) 2963, 2926, 1454, 1157, 1072, 966 cm^{-1}; HRMS (EI) for $C_{12}H_{18}O_2S$ calcd 226.1028 (M^+), found 226.1031.

1-(Methoxymethoxy)-4-methyl-2-(propan-2-ylsulfanyl)benzene (13c) Compound **13c** was followed by general procedure of method A using aryl bromide **4c** (1.00 g, 4.33 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.8 mL, 9.52 mmol), diisopropyl disulfide (1.2 mL, 7.36 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **13c** (0.901 g, 92%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (d, J = 2.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.96 (dd, J = 8.4, 2.0 Hz, 1H), 5.20 (s, 2H), 3.49 (s, 3H), 3.48 (sep, J = 6.8 Hz, 1H), 2.27 (s, 3H), 1.29 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 132.7, 131.5, 128.2, 124.5, 114.9, 94.9, 56.0, 36.1, 23.0, 20.4; IR (neat) 2961, 2924, 2864, 2824, 1487, 1233, 1198, 1157, 1144, 1084, 1065, 1001 cm^{-1}; HRMS (EI) for $C_{12}H_{18}O_2S$ calcd 226.1028 (M^+), found 226.1026.

4-Fluoro-2-(methoxymethoxy)-1-(propan-2-ylsulfanyl)benzene (13d) Compound **13d** was followed by general procedure of method A using aryl bromide **4d** (1.00 g, 4.25 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.1 mL, 9.36 mmol), diisopropyl disulfide (1.2 mL, 7.23 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **13d** (0.562 g, 57%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.4, 6.4 Hz, 1H), 6.91 (dd, J = 10.8, 2.8 Hz, 1H), 6.68 (ddd, J = 8.4, 8.0, 2.8 Hz, 1H), 5.24 (s, 2H), 3.50 (3H), 3.40 (sep, 6.4 Hz, 1H), 1.25 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.9 (d, J = 245.1), 157.8 (d, J = 10.7), 135.1 (d, J = 9.8 Hz), 119.1 (d, J = 3.8 Hz), 108.6 (d, J = 21.3 Hz), 103.0 (d, J = 25.8 Hz), 94.8, 56.2, 37.0, 22.9; IR (neat)

2961, 2926, 2866, 2830, 1585, 1479, 1425, 1387, 1273, 1246, 1153, 1117, 1088, 1061, 1001 cm^{-1}; HRMS (EI) for $C_{11}H_{15}FO_2S$ calcd 230.0777 (M^+), found 230.0775.

4-Fluoro-1-(methoxymethoxy)-2-(propan-2-ylsulfanyl)benzene (13e) Compound **13e** was followed by general procedure of method A using aryl bromide **4e** (1.00 g, 4.25 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.1 mL, 9.36 mmol), diisopropyl disulfide (1.2 mL, 7.23 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **13e** (0.933 g, 95%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.05 (dd, J = 9.2, 5.2 Hz, 1H), 7.01 (dd, J = 9.2, 3.2 Hz, 1H), 6.82 (ddd, J = 9.2, 8.0, 3.2 Hz, 1H), 5.18 (d, 2H), 3.50 (s, 3H), 3.47 (sep, J = 6.8 Hz, 1H), 1.33 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8 (d, J = 240.5 Hz), 151.4 (d, J = 3.1 Hz), 127.8 (d, J = 8.4 Hz), 116.6 (d, J = 24.3 Hz), 116.0 (d, J = 8.3 Hz), 112.9 (d, J = 22.8 Hz), 95.4, 56.1, 35.7, 22.8; IR (neat) 2963, 2928, 2907, 2866, 2826, 1601, 1589, 1481, 1395, 1261, 1244, 1186, 1153, 1082, 1059, 997 cm^{-1}; HRMS (EI) for $C_{11}H_{15}FO_2S$ calcd 230.0777 (M^+), found 230.0776.

1-Methoxy-2-(methoxymethoxy)-3-(propan-2-ylsulfanyl)benzene (13f) Compound **13f** was followed by general procedure of method A using aryl bromide **4f** (1.00 g, 4.05 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.4 mL, 8.90 mmol), diisopropyl disulfide (1.1 mL, 6.89 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (25: 1) to give the product **13f** (0.742 g, 76%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.01 (t, J = 8.0 Hz, 1H), 6.95 (dd, J = 8.0, 1.6 Hz, 1H), 6.79 (dd, J = 8.0, 1.6 Hz, 1H), 5.16 (s, 2H), 3.83 (s, 3H), 3.66 (s, 3H), 3.50 (sep, J = 6.4 Hz, 1H), 1.30 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 144.5, 130.8, 124.3, 123.2, 110.6, 98.4, 57.8, 55.8, 36.4, 23.0; IR (neat) 2961, 2926, 2864, 2835, 1574, 1466, 1452, 1435, 1396, 1292, 1261, 1227, 1204, 1157, 1072, 1047, 961 cm^{-1}; HRMS (EI) for $C_{12}H_{18}O_3S$ calcd 242.0977 (M^+), found 242.0977.

4-Methoxy-1-(methoxymethoxy)-2-(propan-2-ylsulfanyl)benzene (13g) Compound **13g** was followed by general procedure of method A using aryl bromide **4g** (1.00 g, 4.05 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.4 mL, 8.90 mmol), diisopropyl disulfide (1.1 mL, 6.89 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (25: 1) to give the product **13g** (0.917 g, 94%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 3.2 Hz, 1H), 6.69 (dd, J = 8.8, 3.2 Hz, 1H), 5.16 (s, 2H), 3.76 (s, 3H), 3.51 (s, 3H), 3.49 (sep, J = 6.8 Hz, 1H), 1.31 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 149.8, 126.7, 117.1, 116.5, 111.8, 95.6, 56.1, 55.6, 36.0, 22.9; IR (neat) 2959, 2928, 2905, 2864, 2832, 1595, 1582, 1485, 1466, 1439, 1398, 1273, 1244, 1221, 1196, 1155, 1142, 1082, 1059, 1040, 999 cm^{-1}; HRMS (EI) for $C_{12}H_{18}O_3S$ calcd 242.0977 (M^+), found 242.0972.

1-(Methoxymethoxy)-2-[(4-methylphenyl)sulfanyl]benzene (15a) Compound **15a** was followed by general procedure of method A using aryl bromide **4a** (1.00 g, 4.60 mmol), 1.53 M *t*-BuLi in *n*-pentane (6.6 mL, 10.1 mmol), di-*p*-tolyl disulfide (1.93 g, 7.84 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **15a** (1.16 g, 97%) as a white solid. M.p.: 42–43 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, J = 8.0 Hz, 2H), 7.15–7.10 (m, 4H), 6.96 (dd, J = 7.6, 1.2 Hz, 1H), 6.87 (dt, J = 7.6, 1.2 Hz, 1H), 5.22 (s, 2H), 3.46 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 137.7, 132.9, 130.0, 130.0, 129.8, 127.4, 126.8, 122.4, 114.7, 94.8, 56.2, 21.1; IR (KBr) 2990, 2957, 2907, 2843, 2822, 1578, 1476, 1439, 1234, 1202, 1155, 1130, 1084, 1059, 993 cm^{-1}; HRMS (EI) for $C_{15}H_{16}O_2S$ calcd 260.0871 (M^+), found 260.0871; Anal. Calcd for $C_{15}H_{16}O_2S$: C, 69.20; H, 6.19; N, 0.00. found C, 69.38; H, 6.22; N, 0.00.

2-(Methoxymethoxy)-1-methyl-3-[(4-methylphenyl)-sulfanyl]benzene (15b) Compound **15b** was followed by general procedure of method A using aryl bromide **4b** (1.00 g, 4.33 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.8 mL, 9.52 mmol), di-*p*-tolyl disulfide (1.81 g, 7.36 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **15b** (1.03 g, 87%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 6.99 (dd, J = 7.6, 1.6 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H), 6.79 (dd, J = 7.6, 1.6 Hz, 1H), 5.10 (s, 2H), 3.64 (s, 3H), 2.33 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 137.7, 132.8, 132.0, 131.2, 130.1, 130.1, 129.2, 128.0, 124.7, 99.2, 57.6, 21.1, 16.9; IR (neat) 2922, 2868, 2826, 1491, 1456, 1427, 1395, 1254, 1198, 1157, 1070, 962 cm^{-1}; HRMS (EI) for $C_{16}H_{18}O_2S$ calcd 274.1028 (M^+), found 274.1024.

1-(Methoxymethoxy)-4-methyl-2-[(4-methylphenyl)-sulfanyl]benzene (15c) Compound **15c** was followed by general procedure of method A using aryl bromide **4c** (1.00 g, 4.33 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.8 mL, 9.52 mmol), di-*p*-tolyl disulfide (1.81 g,

7.36 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **15c** (0.866 g, 73%) as a white solid. M.p.: 42 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.0 Hz, 2H), 7.01 (d, J = 8.4 Hz, 1H), 6.95 (dd, J = 8.4, 2.0 Hz, 1H), 6.84 (d, J = 2.0 Hz, 1H), 5.17 (s, 2H), 3.44 (s, 3H), 2.34 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 137.3, 132.2, 132.0, 131.2, 130.5, 129.9, 128.3, 126.0, 115.0, 95.0, 56.1, 21.1, 20.5; IR (KBr) 2995, 2961, 2938, 2907, 2853, 2828, 1597, 1485, 1395, 1319, 1233, 1202, 1180, 1160, 1142, 1082, 1060, 1007, 995 cm^{-1}; HRMS (EI) for $C_{16}H_{18}O_2S$ calcd 274.1028 (M^+), found 274.1029; Anal. Calcd for $C_{16}H_{18}O_2S$: C, 70.04; H, 6.61; N, 0.00. found C, 70.32; H, 6.64; N, 0.00.

4-Fluoro-2-(methoxymethoxy)-1-[(4-methylphenyl)-sulfanyl]benzene (15d) Compound **15d** was followed by general procedure of method A using aryl bromide **4d** (1.00 g, 4.25 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.7 mL, 9.36 mmol), di-*p*-tolyl disulfide (1.78 g, 7.23 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **15d** (1.00 g, 85%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.09 (dd, J = 8.8, 6.4 Hz, 1H), 6.91 (dd, J = 10.8, 2.8 Hz, 1H), 6.63 (dt, J = 8.4, 2.8 Hz, 1H), 5.17 (s, 2H), 3.39 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8 (d, J = 245.9 Hz), 156.2 (d, J = 10.7 Hz), 137.0, 133.0 (d, J = 9.9 Hz), 131.1, 131.1, 129.9, 120.4 (d, J = 3.8 Hz), 109.0 (d, J = 21.2 Hz), 103.1 (d, J = 25.9 Hz), 94.7, 56.2, 21.0; IR (neat) 2957, 2920, 2868, 2830, 1593, 1585, 1479, 1425, 1389, 1273, 1244, 1153, 1117, 1086, 1057, 999 cm^{-1}; HRMS (EI) for $C_{15}H_{15}FO_2S$ calcd 278.0777 (M^+), found 278.0772.

4-Fluoro-1-(methoxymethoxy)-2-[(4-methylphenyl)-sulfanyl]benzene (15e) Compound **15e** was followed by general procedure of method A using aryl bromide **4e** (1.00 g, 4.25 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.7 mL, 9.36 mmol), di-*p*-tolyl disulfide (1.78 g, 7.23 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by recrystallization using hexane-EtOAc to give the product **15e** (0.845 g, 71%) as a white solid. M.p.: 37–39 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.03 (dd, J = 8.8, 4.8 Hz, 1H), 6.75 (ddd, J = 8.8, 8.0, 3.2 Hz, 1H), 6.48 (dd, J = 9.2, 3.2 Hz, 1H), 5.19 (s, 2H), 3.51 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2 (d, J = 240.6 Hz), 149.5 (d, J = 2.2 Hz), 139.0, 134.5, 130.7 (d, J = 8.4 Hz), 130.5, 127.7, 115.9 (d, J = 8.4), 114.6 (d, J = 26.6), 112.5 (d, J = 22.7), 95.6, 56.3, 21.2; IR (KBr) 3071, 3026, 3003, 2980, 2957, 2938, 2911, 2855, 2828, 1599, 1481, 1450, 1396, 1261, 1238, 1186, 1150, 1130, 1082, 1053, 995 cm^{-1}; HRMS (EI) for $C_{15}H_{15}FO_2S$ calcd 278.0777 (M^+), found 278.0775; Anal. Calcd for $C_{15}H_{15}FO_2S$: C, 64.73; H, 5.43; N, 0.00. found C, 64.96; H, 5.45; N, 0.00.

1-Methoxy-2-(methoxymethoxy)-3-[(4-methylphenyl)sulfanyl]benzene (15f) Compound **15f** was followed by general procedure of method A using aryl bromide **4f** (1.00 g, 4.05 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.4 mL, 8.90 mmol), di-*p*-tolyl disulfide (1.70 g, 6.89 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (25: 1) to give the product **15f** (0.812 g, 69%) as a white solid. M.p.: 56–58 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 6.89 (t, J = 8.0 Hz, 1H), 6.73 (dd, J = 8.0, 1.2 Hz, 1H), 6.48 (dd, J = 8.0, 1.2 Hz, 1H), 5.20 (s, 2H), 3.83 (s, 3H), 3.68 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 142.7, 138.0, 133.5, 132.9, 130.1, 129.7, 124.5, 121.3, 110.1, 98.4, 57.9, 55.9, 21.1; IR (KBr) 3007, 2994, 2963, 2930, 2901, 2837, 2820, 1578, 1491, 1468, 1449, 1435, 1395, 1296, 1265, 1229, 1207, 1175, 1155, 1069, 1045, 1016, 962, 952 cm^{-1}; HRMS (EI) for $C_{16}H_{18}O_3S$ calcd 290.0977 (M^+), found 290.0972; Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; N, 0.00. found C, 66.26; H, 6.28; N, 0.00.

4-Methoxy-1-(methoxymethoxy)-2-[(4-methylphenyl)sulfanyl]benzene (15g) Compound **15g** was followed by general procedure of method A using aryl bromide **4g** (1.00 g, 4.05 mmol), 1.64 M *t*-BuLi in *n*-pentane (5.4 mL, 8.90 mmol), di-*p*-tolyl disulfide (1.70 g, 6.89 mmol) in dry Et_2O (10 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (25: 1) to give the product **15g** (1.04 g, 89%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 8.8 Hz, 1H), 6.64 (dd, J = 8.8, 3.2 Hz, 1H), 6.47 (d, J = 3.2 Hz, 1H), 5.14 (s, 2H), 3.63 (s, 3H), 3.49 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 148.2, 138.0, 133.3, 130.1, 129.1, 128.9, 116.5, 115.2, 111.5, 95.7, 56.1, 55.5, 21.1; IR (neat) 2995, 2951, 2938, 2903, 2832, 1595, 1487, 1464, 1439, 1398, 1290, 1271, 1221, 1196, 1155, 1140, 1082, 1053, 1040, 995 cm^{-1}; HRMS (EI) for $C_{16}H_{18}O_3S$ caldc 290.0977 (M^+), found 290.0977.

2.5 *General procedure for introduction of sulfide into an aromatic ring using t-BuONa as a base (Method B-1)*

A flask was charged with *t*-BuONa and evacuated and backfilled Ar gas, then degassed xylene was added to a flask and allowed to stir. The suspension was cooled to 0 °C and *t*-butyl mercaptan was added dropwise. The resulting mixture was then warmed to room temperature and stirred for 1 h. The mixture of Aryl bromide, xantphos and $Pd_2(dba)_3$ in degassed xylene was allowed to stir at room temperature for 20 min and was added transferred via a syringe to the previously formed sodium thiolate. The dark solution was heated to reflux for 1.5–2 h. After the resulting orange suspension was cooled to room temperature, the mixture was filtrated by silica gel pad using hexane/EtOAc (10: 1). The residue was concentrated by evaporation and purified by column chromatography on silica gel.

1-(tert-Butylsulfanyl)-2-(methoxymethoxy)benzene (14a) Compound **14a** was followed by general procedure of method B-1 using aryl bromide **4a** (0.500 g, 2.30 mmol), *t*-BuONa (0.277 g, 2.88 mmol), *t*-BuSH (0.33 mL, 2.88 mmol), xantphos (0.016 g, 0.0276 mmol), $Pd_2(dba)_3$ (0.021 g, 0.0230 mmol) in degassed xylene (8.0 mL). The mixture was allowed to stir at reflux for 1.5 h. The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **14a** (0.519 g, > 99%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.0, 1.6 Hz, 1H), 7.30 (dt, J = 8.0, 1.6 Hz, 1H), 7.19 (dd, J = 8.0, 1.6 Hz, 1H), 6.95 (dt, J = 8.0, 1.6 Hz, 1H), 5.21 (s, 2H), 3.48 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 140.3, 130.7, 121.6, 121.5, 115.1, 95.1, 56.3, 46.9, 31.0; IR (neat) 2959, 2940, 2920, 2897, 2860, 2826,1582, 1474, 1437, 1364, 1269, 1233, 1198, 1153, 1128, 1084, 1063, 999 cm^{-1}; HRMS (EI) for $C_{12}H_{18}O_2S$ calcd 226.1028 (M^+), found 226.1038.

1-(Tert-Butylsulfanyl)-2-(methoxymethoxy)-3-methylbenzene (14b) Compound **14b** was followed by general procedure of method B-1 using aryl bromide **4b** (0.500 g, 2.16 mmol), *t*-BuONa (0.259 g, 2.70 mmol), *t*-BuSH (0.30 mL, 2.70 mmol), xantphos (0.015 g, 0.0259 mmol), $Pd_2(dba)_3$ (0.020 g, 0.0216 mmol) in degassed xylene (8.0 mL). The mixture was allowed to stir at reflux for 2 h. The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **14b** (0.523 g, > 99%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (dd, J = 8.0, 1.6 Hz, 1H), 7.18 (dd, J = 8.0, 1.6 Hz, 1H), 6.96 (t, J = 8.0 Hz, 1H), 5.10 (s, 2H), 3.60 (s, 3H), 2.34 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 137.7, 132.5, 132.2, 125.9, 123.8, 100.3, 57.6, 47.4, 31.1, 17.2; IR (neat) 2959, 2938, 2922, 2895, 2860, 2830, 1470, 1454, 1424, 1391, 1364, 1256, 1196, 1157, 1142, 1070, 970 cm^{-1}; HRMS (EI) for $C_{13}H_{20}O_2S$ calcd 240.1184 (M^+), found 240.1181.

2-(tert-Butylsulfanyl)-1-(methoxymethoxy)-4-methylbenzene (14c) Compound **14c** was followed by general procedure of method B-1 using aryl bromide **4c** (0.500 g, 2.16 mmol), *t*-BuONa (0.259 g, 2.70 mmol), *t*-BuSH (0.30 mL, 2.70 mmol), xantphos (0.015 g, 0.0259 mmol), $Pd_2(dba)_3$ (0.020 g, 0.0216 mmol) in degassed xylene (8.0 mL). The mixture was allowed to stir at reflux for 1.5 h. The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **14c** (0.502 g, 97%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 2.0 Hz, 1H), 7.11–7.10 (m, 2H), 5.20 (s, 2H), 3.49 (s, 3H), 2.84 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 140.5, 131.1, 130.9, 121.1, 115.1, 95.2, 56.1, 46.7, 31.0, 20.2; IR (neat) 2959, 2940, 2920, 2895, 2860, 2826, 1487, 1472, 1456, 1362, 1275, 1236, 1198, 1161, 1144, 1084, 1061, 1005 cm^{-1}; HRMS (EI) for $C_{13}H_{20}O_2S$ calcd 240.1184 (M^+), found 240.1185.

1-(tert-Butylsulfanyl)-4-fluoro-2-(methoxymethoxy)benzene (14d) Compound **14d** was followed by general procedure of method B-1 using aryl bromide **4d** (0.500 g, 2.13 mmol), *t*-BuONa (0.256 g, 2.66 mmol), *t*-BuSH (0.30 mL, 2.66 mmol), xantphos (0.015 g, 0.0255 mmol), $Pd_2(dba)_3$ (0.019 g, 0.0213 mmol) in degassed xylene (8.0 mL). The mixture was allowed to stir at reflux for 2.5 h. The reaction mixture was purified by column chromatography on silica gel using hexane/toluene/EtOAc (1: 1: 0.02) to give the product **14d** (0.497 g, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (dd, J = 8.4, 6.8 Hz, 1H), 6.94 (dd, J = 10.8, 2.8 Hz, 1H), 6.65 (dt, J = 8.4, 2.8 Hz, 1H), 5.18 (s, 2H), 3.46 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1 (d, J = 247.5 Hz), 160.6 (d, J = 10.6 Hz), 141.1 (d, J = 9.8 Hz), 116.6 (d, J = 3.7 Hz), 108.4 (d, J = 21.2 Hz), 103.1 (d, J = 25.8 Hz), 95.1, 56.3, 46.8, 30.8; IR (neat) 2961, 2940, 2920, 2897, 2864, 2832, 1584, 1474, 1456, 1423, 1387, 1364, 1271, 1153, 1113, 1086, 1059, 1003 cm^{-1}; HRMS (EI) for $C_{12}H_{17}FO_2S$ calcd 244.0933 (M^+), found 244.0931.

2-(tert-Butylsulfanyl)-4-fluoro-1-(methoxymethoxy)benzene (14e) Compound **14e** was followed by general procedure of method B-1 using aryl bromide **4e** (0.500 g, 2.13 mmol), *t*-BuONa (0.256 g, 2.66 mmol), *t*-BuSH (0.30 mL, 2.66 mmol), xantphos (0.015 g, 0.0255 mmol), $Pd_2(dba)_3$ (0.019 g,

0.0213 mmol) in degassed xylene (8.0 mL). The mixture was allowed to stir at reflux for 2 h. The reaction mixture was purified by column chromatography on silica gel using hexane/acetone (100: 1) to give the product **14e** (0.460 g, 89%) as a pale yellow solid. M.p.: 35–36 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (dd, J = 8.4, 3.2 Hz, 1H), 7.17 (dd, J = 9.2, 4.8 Hz, 1H), 7.02 (ddd, J = 9.2, 7.6, 3.2 Hz, 1H), 5.18 (s, 2H), 3.51 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8 (d, J = 213.2 Hz), 155.6 (d, J = 25.8 Hz), 125.7 (d, J = 21.3 Hz), 123.4 (d, J = 7.6 Hz), 116.8 (d, J = 22.0 Hz), 116.4 (d, J = 7.6 Hz), 95.7, 56.2, 47.4, 31.0; IR (KBr) 2970, 2957, 2924, 2909, 2860, 2826, 1485, 1456, 1387, 1364, 1306, 1261, 1248, 1204, 1186, 1157, 1132, 1078, 1049, 1005 cm^{-1}; HRMS (EI) for $C_{12}H_{17}FO_2S$ calcd 244.0933 (M^+), found 244.0930; Anal. Calcd for $C_{12}H_{17}FO_2S$: C, 58.99; H, 7.01; N, 0.00. found C, 58.85; H, 6.94; N, 0.00.

1-(tert-Butylsulfanyl)-3-methoxy-2-(methoxymethoxy)benzene (14f) Compound **14f** was followed by general procedure of method B-1 using aryl bromide **4f** (0.550 g, 2.23 mmol), *t*-BuONa (0.267 g, 2.78 mmol), *t*-BuSH (0.31 mL, 2.78 mmol), xantphos (0.015 g, 0.0267 mmol), $Pd_2(dba)_3$ (0.020 g, 0.0223 mmol) in degassed xylene (8.0 mL). The mixture was allowed to stir at reflux for 2 h. The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (100: 1) to give the product **14f** (0.474 g, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (dd, J = 7.6, 1.6 Hz, 1H), 7.02 (t, J = 7.6 Hz, 1H), 6.94 (dd, J = 7.6, 1.6 Hz, 1H), 5.14 (s, 2H), 3.85 (s, 3H), 3.68 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 148.5, 131.3, 127.5, 123.7, 113.2, 99.2, 57.7, 55.8, 47.4, 31.1; IR (neat) 2961, 2938, 2920, 2895, 2862, 2835, 1738, 1574, 1462, 1435, 1395, 1364, 1292, 1258, 1157, 1072, 1047, 964 cm^{-1}; HRMS (EI) for $C_{13}H_{20}O_3S$ calcd 256.1133 (M^+), found 256.1143.

2-(tert-Butylsulfanyl)-4-methoxy-1-(methoxymethoxy)benzene (14g) Compound **14g** was followed by general procedure of method B-1 using aryl bromide **4g** (0.500 g, 2.02 mmol), *t*-BuONa (0.240 g, 2.53 mmol), *t*-BuSH (0.29 mL, 2.53 mmol), xantphos (0.014 g, 0.0243 mmol), $Pd_2(dba)_3$ (0.019 g, 0.0202 mmol) in degassed xylene (8.0 mL). The mixture was allowed to stir at reflux for 2 h. The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (50: 1) to give the product **14g** (0.485 g, 94%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 9.2 Hz, 1H), 7.05 (d, J = 3.2 Hz, 1H), 6.82 (dd, J = 9.2, 3.2 Hz, 1H), 5.11 (s, 2H), 3.73 (s, 3H), 3.46 (s, 3H), 1.28 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 153.6, 124.7, 122.7, 116.7, 115.8, 95.9, 56.1, 55.6, 47.1, 31.0; IR (neat) 2959, 2940, 2920, 2897, 2860, 2832, 1597, 1489, 1456, 1439, 1389, 1364, 1287, 1269, 1155, 1142, 1080, 1057, 1040, 1003 cm^{-1}; HRMS (EI) for $C_{13}H_{20}O_3S$ calcd 256.1133 (M^+), found 256.1127.

2.6 *General procedure for introduction of sulfide into aromatic ring using i-Pr$_2$NEt as base (Method B-2)*

To the solution of Aryl bromide in degassed 1,4-dioxane was added *i*-Pr_2NEt, thiol, xantphos and $Pd_2(dba)_3$. The mixture was allowed to stir at 70–110 °C for 3–5.5 h. After the resulting orange suspension was cooled to room temperature, the mixture was filtrated by silica gel pad using hexane/EtOAc (10: 1). The residue was concentrated by evaporation and purified by column chromatography or recrystallization.

2-(Ethylsulfanyl)-1-(methoxymethoxy)-4-nitrobenzene (12h) Compound **12h** was followed by general procedure of method B-2 using aryl bromide **4h** (0.500 g, 1.91 mmol), *i*-Pr_2NEt (0.66 mL, 3.82 mmol), EtSH (0.16 mL, 2.10 mmol), xantphos (0.055 g, 0.0954 mmol), $Pd_2(dba)_3$ (0.044 g, 0.0477 mmol) in degassed 1,4-dioxane (5.0 mL). The mixture was allowed to stir at 70 °C for 3 h. The reaction mixture was purified by column chromatography on silica gel using hexane/acetone (100: 1) to give the product **12h** (0.433 g, 93%) as a pale yellow solid. M.p.: 50–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 2.8 Hz, 1H), 8.01 (dd, J = 8.8, 2.8 Hz, 1H), 7.15 (d, J = 8.8 Hz, 1H), 5.34 (s, 2H), 3.52 (s, 3H), 3.01 (q, J = 7.2 Hz, 2H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 142.6, 129.2, 121.9, 121.8, 112.9, 94.8, 56.7, 25.3, 13.4; IR (KBr) 3111, 3090, 2970, 2947, 2932, 2909, 2872, 2837, 1576, 1506, 1481, 1472, 1447, 1352, 1263, 1236, 1204, 1161, 1140, 1084, 1065, 974 cm^{-1}; HRMS (EI) for $C_{10}H_{13}NO_4S$ calcd 243.0565 (M^+), found 243.0564; Anal. Calcd for $C_{10}H_{13}NO_4S$: C, 49.37; H, 5.39; N, 5.76. found C, 49.66; H, 5.43; N, 5.53.

1-(Methoxymethoxy)-4-nitro-2-(propan-2-ylsulfanyl)benzene (13h) Compound **13h** was followed by general procedure of method B-2 using aryl bromide **4h** (0.800 g, 3.05 mmol), *i*-Pr_2NEt (1.1 mL, 6.11 mmol), *i*-PrSH (0.31 mL, 3.36 mmol), xantphos (0.088 g, 0.153 mmol), $Pd_2(dba)_3$ (0.070 g, 0.0763 mmol) in degassed 1,4-dioxane (8.0 mL). The mixture was allowed to stir at 70 °C for 5.5 h. The reaction mixture was purified by column chromatography on silica gel

using hexane/CH_2Cl_2/EtOAc (10: 1: 0.1) to give the product **13h** (0.765 g, 97%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 2.4, 1H), 8.04 (dd, J = 9.2, 2.8 Hz, 1H), 7.18 (d, J = 9.2 Hz, 1H), 5.34 (s, 2H), 3.58 (sep, J = 6.4 Hz, 1H), 3.52 (s, 3H), 1.38 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 142.3, 127.8, 124.7, 122.7, 113.2, 94.7, 56.6, 35.6, 22.7; IR (neat) 3103, 3086, 2965, 2926, 2909, 2866, 2830, 1576, 1516, 1474, 1342, 1263, 1250, 1161, 1138, 1088, 1061, 974 cm^{-1}; HRMS (EI) for $C_{11}H_{15}NO_4S$ calcd 257.0721 (M^+), found 257.0722.

2-(tert-Butylsulfanyl)-1-(methoxymethoxy)-4-nitrobenzene (14h) Compound **14h** was followed by general procedure of method B-2 using aryl bromide **4h** (1.00 g, 3.82 mmol), *i*-Pr_2NEt (1.3 mL, 7.63 mmol), *t*-BuSH (0.47 mL, 4.20 mmol), xantphos (0.110 g, 0.191 mmol), $Pd_2(dba)_3$ (0.0874 g, 0.0954 mmol) in degassed 1,4-dioxane (10 mL). The mixture was allowed to stir at 80 °C for 4 h. The reaction mixture was purified by column chromatography on silica gel using hexane/acetone (100: 1) to give the product **14h** (1.02 g, 99%) as a pale yellow solid. M.p.: 85–87 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, J = 2.8 Hz, 1H), 8.21 (dd, J = 9.2, 2.8 Hz, 1H), 7.29 (d, J = 9.2 Hz, 1H), 5.33 (s, 2H), 3.52 (s, 3H), 1.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2, 141.5, 134.8, 126.3, 123.2, 114.1, 95.0, 56.8, 47.9, 31.0; IR (KBr) 3105, 3084, 2963, 2922, 2899, 2859, 2828, 1593, 1578, 1506, 1472, 1456, 1342, 1261, 1163, 1138, 1125, 1082, 1051, 974 cm^{-1}; HRMS (EI) for $C_{12}H_{17}NO_4S$ calcd 271.0878 (M^+), found 271.0871; Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.12; H, 6.31; N, 5.16. found C, 53.38; H, 6.26; N, 4.91.

Methyl 3-(tert-butylsulfanyl)-4-(methoxymethoxy)-benzoate (14i) Compound **14i** was followed by general procedure of method B-2 using aryl bromide **4i** (1.00 g, 3.64 mmol), *i*-Pr_2NEt (1.3 mL, 7.27 mmol), *t*-BuSH (0.45 mL, 4.00 mmol), xantphos (0.105 g, 0.182 mmol), $Pd_2(dba)_3$ (0.0832 g, 0.0909 mmol) in degassed 1,4-dioxane (10 mL). The mixture was allowed to stir at 80 °C for 22 h. The reaction mixture was purified by recrystallization using hexane-EtOAc to give the product **14i** (0.674 g, 65%) as a white solid. M.p.: 69–70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 2.4 Hz, 1H), 8.01 (dd, J = 8.8, 2.4 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 5.29 (s, 2H), 3.90 (s, 3H), 3.51 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 163.0, 141.6, 132.4, 123.4, 121.7, 114.1, 94.8, 56.6, 52.0, 47.3, 31.0; IR (KBr) 2990, 2957, 2922, 2899, 2860, 2832, 1709, 1591, 1485, 1456, 1427, 1385, 1364, 1300, 1287, 1256, 1206, 1146, 1113, 1084, 1057, 984 cm^{-1}; HRMS (EI) for $C_{14}H_{20}O_4S$ calcd 284.1082 (M^+), found 284.1084; Anal. Calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09; N, 0.00. found C, 59.13; H, 7.04; N, 0.00.

3-(tert-Butylsulfanyl)-4-(methoxymethoxy)benzaldehyde (14j) Compound **14j** was followed by general procedure of method B-2 using aryl bromide **4j** (1.00 g, 4.08 mmol), *i*-Pr_2NEt (1.4 mL, 8.16 mmol), *t*-BuSH (0.51 mL, 4.49 mmol), xantphos (0.118 g, 0.204 mmol), $Pd_2(dba)_3$ (0.0934 g, 0.102 mmol) in degassed 1,4-dioxane (10 mL). The mixture was allowed to stir at 80 °C for 22 h. The reaction mixture was purified by recrystallization using hexane-EtOAc to give the product **14j** (0.814 g, 78%) as a white solid. M.p.: 63–66 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 8.4, 2.0 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 5.33 (s, 2H), 3.52 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.5, 164.2, 141.9, 132.3, 130.4, 122.7, 114.7, 94.8, 56.7, 47.5, 31.0; IR (KBr) 2957, 2938, 2920, 2897, 2860, 2826, 2720, 1695, 1678, 1589, 1564, 1481, 1470, 1456, 1379, 1364, 1263, 1246, 1198, 1165, 1140, 1080, 1051, 980 cm^{-1}; HRMS (EI) for $C_{13}H_{18}O_3S$ calcd 254.0977 (M^+), found 254.0974; Anal. Calcd for $C_{13}H_{18}O_3S$: C, 61.39; H, 7.13; N, 0.00. found C, 61.37; H, 7.08; N, 0.00.

2.7 *General procedure for introduction of sulfide into aromatic ring using MeSNa (Method B-3)*

To the solution of Aryl bromide in degassed 1,4-dioxane was added xantphos, $Pd_2(dba)_3$ and MeSNa. The mixture was allowed to stir at reflux for 4 h. After the resulting orange suspension was cooled to room temperature, the mixture was filtrated by silica gel pad using hexane/EtOAc (10: 1). The residue was concentrated by evaporation and the product was purified by column chromatography or recrystallization using hexane-EtOAc.

Methyl 4-(methoxymethoxy)-3-(methylsulfanyl)benzoate (5i) Compound **5i** was followed by general procedure of method B-3 using aryl bromide **4i** (0.500 g, 1.82 mmol), MeSNa (0.140 g, 2.00 mmol), xantphos (0.053 g, 0.0909 mmol), $Pd_2(dba)_3$ (0.042 g, 0.0454 mmol) in degassed 1,4-dioxane (5.0 mL). The reaction mixture was purified by recrystallization using hexane-EtOAc to give the product **5i** (0.268 g, 61%) as a pale yellow solid. M.p.: 54–55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.79 (m, 2H), 7.10 (d, J = 8.0 Hz, 1H), 5.31 (s, 2H), 3.90 (s, 3H), 3.51 (s, 3H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 157.1, 128.7, 127.7, 126.7, 124.2, 112.8, 94.5, 56.4, 52.0, 14.4; IR (KBr) 3105, 3009, 3001, 2984, 2967, 2947, 2918, 2833, 1713, 1587, 1487, 1429, 1321, 1290,

1258, 1240, 1207, 1165, 1146, 1113, 1088, 1065, 980, 966 cm^{-1}; HRMS (EI) for $C_{11}H_{14}O_4S$ calcd 242.0613 (M^+), found 242.0627; Anal. Calcd for $C_{11}H_{14}O_4S$: C, 54.53; H, 5.82; N, 0.00. found C, 54.74; H, 5.83; N, 0.00.

4-(Methoxymethoxy)-3-(methylsulfanyl)benzaldehyde (5j) Compound **5j** was followed by general procedure of method B-3 using aryl bromide **4j** (0.500 g, 2.04 mmol), MeSNa (0.157 g, 2.24 mmol), xantphos (0.059 g, 0.102 mmol), $Pd_2(dba)_3$ (0.047 g, 0.0510 mmol) in degassed 1,4-dioxane (5.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **5j** (0.364 g, 84%) as a pale yellow solid. M.p.: 45–49 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 7.67 (d, J = 2.0 Hz, 1H), 7.61 (dd, J = 8.0, 2.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 5.34 (s, 2H), 3.52 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 158.2, 131.0, 130.3, 129.4, 124.9, 112.9, 94.5, 56.5, 14.1; IR (KBr) 3103, 3001, 2982, 2957, 2938, 2924, 2903, 2847, 2830, 2806, 2756, 1697, 1587, 1572, 1487, 1369, 1319, 1240, 1204, 1167, 1140, 1092, 1065, 986 cm^{-1}; HRMS (EI) for $C_{10}H_{12}O_3S$ calcd 212.0507 (M^+), found 212.0516; Anal. Calcd for $C_{10}H_{12}O_3S$: C, 56.58; H, 5.70; N, 0.00. found C, 56.83; H, 5.71; N, 0.00.

2.8 *Transalkylation of alkyl aryl sulfide*

2-(methylsulfanyl)-4-nitrophenol (16)[46] Iodomethane (1.2 mL, 18.4 mmol) was added to the solution of *tert*-butyl aryl sulfide **14h** (0.500 g, 1.84 mmol) in dry DMF (5 mL) and the mixture was allowed to stir at 80 °C for 24 h. The reaction mixture was extracted with EtOAc (25 mL × 3) and the organic layer washed with brine, dried over Na_2SO_4 and concentrated. The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (5: 1) to give the product **16** (0.322 g, 94%) as yellow solid.

2.9 *General procedure for Sharpless asymmetric oxidation of aryl sulfide*

A flask was charged with aryl sulfide and backfilled Ar gas. Aryl sulfide was diluted with dry CH_2Cl_2, and to the solution was added L or D-DET and Ti(O-*i*-Pr)$_4$, and allowed to stir for 1 h at room temperature. The reaction mixture was cooled to − 25 °C and 80% CHP added slowly, and the mixture was stirred for 24 h at − 25 °C, and then the reaction mixture was diluted with EtOAc and quenched with 10% $Na_2S_2O_4$ aq.. After filtration by celite pad, and the filtrate was extracted with EtOAc (2 × 25 mL) and the combined organic layer washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on alumina or silica gel.

2-[(R)-methylsulfinyl]phenol (R-7a)[47]: Compound ***R-7a*** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **6a** (0.200 g, 1.43 mmol), L-DET (0.49 mL, 2.85 mmol), Ti(O-*i*-Pr)$_4$ (0.42 mL, 1.43 mmol), 80% CHP (0.29 mL, 1.57 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (3: 7) to give the product ***R-7a*** (0.136 g, 61%, 4.3% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH: trifluoroacetic acid = 96: 4: 0.1, 0.75 mL/min, 250 nm, t_{major} = 33.39 min, t_{minor} = 35.92 min).

1-Methoxy-2-[(R)-methylsulfinyl]benzene (R-8a)[48]: Compound ***R-8a*** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **3a** (0.200 g, 1.30 mmol), L-DET (0.44 mL, 2.59 mmol), Ti(O-*i*-Pr)$_4$ (0.38 mL, 1.30 mmol), 80% CHP (0.26 mL, 1.43 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (6: 4) to give the product ***R-8a*** (0.226 g, > 99%, 91% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 96: 4, 0.75 mL/min, 250 nm, t_{major} = 57.12 min, t_{minor} = 60.62 min).

2-Methoxy-1-methyl-3-[(R)-methylsulfinyl]benzene (R-8b) Compound ***R-8b*** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **3b** (0.200 g, 1.19 mmol), L-DET (0.41 mL, 2.38 mmol), Ti(O-*i*-Pr)$_4$ (0.35 mL, 1.19 mmol), 80% CHP (0.24 mL, 1.31 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product ***R-8b*** (0.192 g, 88%, 89% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 96: 4, 0.75 mL/min, 250 nm, t_{major} = 33.32 min, t_{minor} = 36.21 min). $[\alpha]_D$ = +267.3 (c = 1.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (dd, J = 7.6, 1.6 Hz, 1H), 7.32 (dd, J = 7.6, 1.6 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 3.81 (s, 3H), 2.78 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 138.5, 134.0, 131.3, 125.1, 122.0, 60.9, 42.3, 15.4; IR (neat) 3474, 2995, 2940, 2860, 2835, 1468, 1412, 1290, 1258, 1223, 1171, 1148, 1057, 999 cm^{-1}; HRMS (EI) for $C_9H_{12}O_2S$ calcd 184.0558 (M^+), found 184.0564.

1-(Methoxymethoxy)-2-[(R)-methylsulfinyl]benzene (R-9a) Compound ***R-9a*** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5a** (0.200 g, 1.09 mmol), L-DET (0.37 mL, 2.17 mmol), Ti(O-*i*-Pr)$_4$ (0.32 mL, 1.09 mmol), 80% CHP (0.18 mL, 1.19 mmol) in dry CH_2Cl_2 (5.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product ***R-9a*** (0.222 g, > 99%, 91% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, MeCN only, 0.50 mL/min, 250 nm, t_{major} = 10.80 min, t_{minor} = 11.62 min). $[\alpha]_D$ = +269.3 (c = 2.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.0, 1.6 Hz, 1H), 7.43 (dt, J = 8.0, 1.6 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 5.27 (d, J = 6.8 Hz, 1H), 5.23 (d, J = 6.8 Hz, 1H), 3.49 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 152.3, 133.7, 131.8, 124.5, 122.7, 113.8, 94.4, 56.4, 41.4; IR (KBr) 3069, 3001, 2951, 2922, 2911, 2828, 1585, 1472, 1441, 1410, 1315, 1269, 1229, 1200, 1150, 1132, 1082, 1062, 1034, 980 cm^{-1}; HRMS (EI) for $C_9H_{12}O_3S$ calcd 200.0507 (M^+), found 200.0500; Anal. Calcd for $C_9H_{12}O_3S$: C, 53.98; H, 6.04; N, 0.00. found: C, 54.16; H, 5.96; N, 0.00.

2-(Methoxymethoxy)-1-methyl-3-[(S)-methylsulfinyl]benzene (S-9b) Compound ***S-9b*** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5b** (1.00 g, 5.04 mmol), D-DET (1.7 mL, 10.1 mmol), Ti(O-*i*-Pr)$_4$ (1.5 mL, 5.04 mmol), 80% CHP (1.0 mL, 5.55 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product ***S-9b*** (1.12 g, > 99%, 92% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 96: 4, 0.75 mL/min, 250 nm, t_{major} = 65.90 min, t_{minor} = 74.66 min). $[\alpha]_D$ = -246.0 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, J = 1.6, 7.6 Hz, 1H), 7.33 (dd, J = 1.6, 7.4 Hz, 1H), 7.29 (t, J = 7.6 Hz, 1H), 5.04 (d, J = 6.0 Hz, 1H), 5.02 (d, J = 6.0 Hz, 1H), 3.61 (s, 3H), 2.79 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.0, 139.1, 134.0, 131.5, 125.3, 122.0, 99.5, 57.7, 41.9, 16.3; IR (neat) 3503, 2992, 2955, 2932, 1462, 1398, 1159, 1057, 959, 945 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_3S$ calcd 214.0664 (M^+), found 214.0660.

2-(Methoxymethoxy)-1-methyl-3-[(R)-methylsulfinyl]benzene (R-9b) Compound ***R-9b*** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5b** (1.00 g, 5.04 mmol), L-DET (1.7 mL, 10.1 mmol), Ti(O-*i*-Pr)$_4$ (1.5 mL, 5.04 mmol), 80% CHP (1.0 mL, 5.55 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product ***R-9b*** (1.06 g, 99%, 94% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 96: 4, 0.75 mL/min, 250 nm, t_{major} = 73.89 min, t_{minor} = 66.96 min). $[\alpha]_D$ = +242.0 (c = 1.0 in $CHCl_3$); HRMS (EI) for $C_{10}H_{14}O_3S$ calcd 214.0664 (M^+), found 214.0661.

1-(Methoxymethoxy)-4-methyl-2-(methylsulfinyl)benzene (9c) Compound **9c** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5c** (0.200 g, 1.01 mmol), L-DET (0.35 mL, 2.02 mmol), Ti(O-*i*-Pr)$_4$ (0.30 mL, 1.01 mmol), 80% CHP (0.21 mL, 1.11 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **9c** (0.179 g, 83%, 95% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 37.17 min, t_{minor} = 39.65 min). $[\alpha]_D$ = +213.2 (c = 1.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 2.0 Hz, 1H), 7.21 (dd, J = 8.4, 2.0 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 5.24 (d, J = 6.8 Hz, 1H), 5.19 (d, J = 6.8 Hz, 1H), 3.47 (s, 3H), 2.79 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 133.2, 132.5, 132.2, 124.5, 113.8, 94.4, 56.2, 41.3, 20.4; IR (neat) 3495, 2994, 2953, 2920, 2828, 1489, 1416, 1271, 1159, 1142, 1084, 1070, 1038, 982 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_3S$ calcd 214.0664 (M^+), found 214.0661.

4-Fluoro-2-(methoxymethoxy)-1-(methylsulfinyl)benzene (9d) Compound **9d** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5d** (0.200 g, 0.989 mmol), L-DET (0.32 mL, 1.88 mmol), Ti(O-*i*-Pr)$_4$ (0.28 mL, 0.989 mmol), 80% CHP (0.19 mL, 1.04 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **9d** (0.187 g, 87%, 93% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 96: 4, 0.50 mL/min, 250 nm, t_{major} = 63.75 min, t_{minor} = 61.10 min). $[\alpha]_D$ = +235.8 (c = 1.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, J = 8.4, 6.4 Hz, 1H), 6.97–6.91 (m, 2 H), 5.25 (d, J = 6.8 Hz, 1H), 5.22 (d, J = 6.8 Hz, 1H), 3.49 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (d, J = 248.9 Hz), 153.5 (d, J = 11.0 Hz), 129.2 (d, J = 3.0 Hz), 126.2 (d, J = 10.2 Hz), 109.6 (d, J = 22.0 Hz), 102.5

(d, J = 27.0 Hz), 94.7, 56.6, 41.6 (d, J = 1.5 Hz); IR (KBr) 3102, 3073, 3038, 2994, 2967, 2907, 2880, 2833, 1607, 1587, 1477, 1450, 1429, 1408, 1393, 1312, 1275, 1236, 1225, 1169, 1152, 1094, 1067, 1034, 988 cm^{-1}; HRMS (EI) for $C_9H_{11}FO_3S$ calcd 218.0413 (M^+), found 218.0410; Anal. Calcd for $C_9H_{11}FO_3S$: C, 49.53; H, 5.08; N, 0.00. found: C, 49.81; H, 5.03; N, 0.00.

4-Fluoro-1-(methoxymethoxy)-2-(methylsulfinyl)benzene (9e) Compound **9e** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5e** (0.200 g, 0.989 mmol), L-DET (0.32 mL, 1.88 mmol), Ti(O-*i*-Pr)$_4$ (0.28 mL, 0.989 mmol), 80% CHP (0.19 mL, 1.04 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **9e** (0.196 g, 91%, 92% e.e.) as a white solid. The yield was 69% and the enantiomeric excess was 99% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 90: 10, 0.50 mL/min, 250 nm, t_{major} = 27.14 min, t_{minor} = 35.00 min). M.p.: 57–60 °C; $[\alpha]_D$ = +249.0 (c = 3.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, J = 7.6, 2.4 Hz, 1H), 7.15–7.08 (m, 2H), 5.23 (d, J = 6.8 Hz, 1H), 5.19 (d, J = 6.8 Hz, 1H), 3.49 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.5 (d, J = 243.6 Hz), 148.3 (d, J = 2.3 Hz), 136.1 (d, J = 6.1 Hz), 118.3 (d, J = 23.5 Hz), 115.5 (d, J = 7.6 Hz), 111.8 (d, J = 25.8 Hz), 95.0, 56.5, 41.4; IR (KBr) 3105, 3034, 3003, 2961, 2947, 2911, 2835, 1485, 1479, 1406, 1315, 1288, 1263, 1244, 1209, 1184, 1153, 1132, 1088, 1065, 1030, 982 cm^{-1}; HRMS (EI) for $C_9H_{11}FO_3S$ calcd 218.0413 (M^+), found 218.0413; Anal. Calcd for $C_9H_{11}FO_3S$: C, 49.53; H, 5.08; N, 0.00. found: C, 49.58; H, 5.03; N, 0.00.

1-Methoxy-2-(methoxymethoxy)-3-(methylsulfinyl)benzene (9f) Compound **9f** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5f** (0.200 g, 0.933 mmol), L-DET (0.32 mL, 1.87 mmol), Ti(O-*i*-Pr)$_4$ (0.27 mL, 0.933 mmol), 80% CHP (0.19 mL, 1.03 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **9f** (0.154 g, 72%, 93% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 46.63 min, t_{minor} = 42.42 min). $[\alpha]_D$ = +159.0 (c = 1.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, J = 8.0, 1.6 Hz, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.05 (dd, J = 8.0, 1.6 Hz, 1H), 5.29 (d, J = 6.0 Hz, 1H), 5.14 (d, J = 6.0 Hz, 1H), 3.89 (s, 3H), 3.57 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 140.6, 139.6, 125.2, 115.6, 114.7, 98.6, 57.9, 56.0, 42.0; IR (neat) 3026, 3001, 2957, 2943, 2911, 2847, 2828, 1582, 1489, 1472, 1450, 1441, 1306, 1265, 1192, 1163, 1067, 1043, 1028, 941 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_4S$ calcd 230.0613 (M^+), found 230.0617.

4-Methoxy-1-(methoxymethoxy)-2-(methylsulfinyl)benzene (9g) Compound **9g** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5g** (0.200 g, 0.933 mmol), L-DET (0.32 mL, 1.87 mmol), Ti(O-*i*-Pr)$_4$ (0.27 mL, 0.933 mmol), 80% CHP (0.19 mL, 1.03 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 3) to give the product **9g** (0.210 g, 99%, 92% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 30.89 min, t_{minor} = 35.37 min). $[\alpha]_D$ = +195.4 (c = 1.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 3.2 Hz, 1H), 7.09 (d, J = 9.2 Hz, 1H), 6.94 (dd, J = 9.2, 3.2 Hz, 1H), 5.20 (d, J = 6.4 Hz, 1H), 5.15 (d, J = 6.4 Hz, 1H), 3.85 (s, 3H), 3.48 (s, 3H), 2.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 146.0, 134.9, 118.2, 115.8, 108.2, 95.1, 56.3, 55.9, 41.4; IR (neat) 2995, 2968, 2953, 2941, 2828, 1609, 1491, 1470, 1433, 1317, 1269, 1215, 1198, 1157, 1140, 1084, 1061, 1024, 986 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_4S$ calcd 230.0613 (M^+), found 230.0609.

1-(Methoxymethoxy)-2-(methylsulfinyl)-4-nitrobenzene (9h) Compound **9h** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5h** (0.100 g, 0.436 mmol), L-DET (0.15 mL, 0.872 mmol), Ti(O-*i*-Pr)$_4$ (0.13 mL, 0.436 mmol), 80% CHP (0.090 mL, 0.480 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **9h** (0.0976 g, 91%, 99% e.e.) as a white solid. The yield was 44% and the enantiomeric excess was > 99% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 70: 30, 0.75 mL/min, 250 nm, t_{major} = 95.22 min, t_{minor} = 31.35 min). M.p.: 110–111 °C; $[\alpha]_D$ = +200.0 (c = 1.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, J = 2.8 Hz, 1H), 8.33 (dd, J = 8.8, 2.8 Hz, 1H), 7.29 (d, J = 8.8 Hz, 1H), 5.39 (d, J = 6.8 Hz, 1H), 5.35 (d, J = 6.8 Hz, 1H), 3.52 (s, 3H), 2.85 (s,

3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 143.2, 136.1, 127.8, 121.4, 114.0, 95.0, 57.0, 41.2; IR (KBr) 3102, 2970, 2922, 2839, 1587, 1512, 1487, 1472, 1341, 1261, 1231, 1206, 1167, 1134, 1088, 1059, 1028, 949 cm^{-1}; HRMS (EI) for $C_9H_{11}NO_5S$ calcd 245.0358 (M^+), found 245.0354; Anal. Calcd for $C_9H_{11}NO_5S$: C, 44.08; H, 4.52; N, 5.71. found: C, 44.33; H, 4.60; N, 5.87.

Methyl 4-(methoxymethoxy)-3-(methylsulfinyl)benzoate (9i) Compound **9i** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5i** (0.100 g, 0.413 mmol), L-DET (0.14 mL, 0.825 mmol), Ti(O-*i*-Pr)$_4$ (0.12 mL, 0.413 mmol), 80% CHP (0.084 mL, 0.454 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 3) to give the product **9i** (0.109 g, > 99%, 96% e.e.) as a white solid. The yield was 47% and the enantiomeric excess was > 99% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 70: 30, 0.75 mL/min, 250 nm, t_{major} = 17.63 min, t_{minor} = 20.00 min). M.p.: 70–74 °C; $[\alpha]_D$ = +172.1 (c = 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 2.4 Hz, 1H), 8.15 (dd, J = 8.8, 2.4 Hz, 1H), 7.20 (d, J = 8.8 Hz, 1H), 5.33 (d, J = 6.8 Hz, 1H), 5.29 (d, J = 6.8 Hz, 1H), 3.92 (s, 3H), 3.50 (s, 3H), 2.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 155.8, 134.3, 133.9, 126.6, 125.1, 113.5, 94.6, 56.8, 52.2, 41.4; IR (KBr) 3078, 3007, 2980, 2955, 2922, 2841, 1709, 1599, 1489, 1445, 1321, 1312, 1287, 1254, 1207, 1165, 1148, 1115, 1086, 1069, 1034, 955 cm^{-1}; HRMS (EI) for $C_{11}H_{14}O_5S$ calcd 258.0562 (M^+), found 258.0575; Anal. Calcd for $C_{11}H_{14}O_5S$: C, 51.15; H, 5.46; N, 0.00. found: C, 51.37; H, 5.46; N, 0.00.

4-(Methoxymethoxy)-3-(methylsulfinyl)benzaldehyde (9j) Compound **9j** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **5j** (0.100 g, 0.471 mmol), L-DET (0.16 mL, 0.942 mmol), Ti(O-*i*-Pr)$_4$ (0.14 mL, 0.471 mmol), 80% CHP (0.096 mL, 0.518 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 3) to give the product **9j** (0.0980 g, 91%, 94% e.e.) as a white solid. The yield was 53% and the enantiomeric excess was > 99% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 75: 25, 0.75 mL/min, 250 nm, t_{major} = 23.64 min, t_{minor} = 29.88 min). M.p.: 99–101 °C; $[\alpha]_D$ = +203.5 (c = 1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.01 (s, 1H), 8.39 (d, J = 2.0 Hz, 1H), 8.02 (dd, J = 8.4, 2.0 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 5.37 (d, J = 6.8 Hz, 1H), 5.33 (d, J = 6.8 Hz, 1H), 3.51 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.0, 156.9, 135.1, 132.6, 131.4, 127.9, 114.1, 94.7, 56.9, 41.2; IR (KBr) 3078, 3038, 2974, 2832, 2803, 2737, 1694, 1682, 1595, 1576, 1495, 1474, 1416, 1398, 1277, 1250, 1206, 1186, 1171, 1101, 1061, 1032, 943 cm^{-1}; HRMS (EI) for $C_{10}H_{12}O_4S$ calcd 228.0456 (M^+), found 228.0458; Anal. Calcd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30; N, 0.00. found: C, 52.72; H, 5.34; N, 0.00.

1-(Ethylsulfinyl)-2-(methoxymethoxy)benzene (17a) Compound **17a** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **12a** (0.200 g, 1.01 mmol), L-DET (0.35 mL, 2.02 mmol), Ti(O-*i*-Pr)$_4$ (0.30 mL, 1.01 mmol), 80% CHP (0.16 mL, 1.11 mmol) in dry CH_2Cl_2 (5.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **17a** (0.190 g, 88%, 68% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, MeCN only, 0.50 mL/min, 250 nm, t_{major} = 10.80 min, t_{minor} = 11.62 min). $[\alpha]_D$ = +215.3 (c = 3.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 8.0, 2.0 Hz, 1H), 7.42 (dt, J = 8.0, 2.0 Hz, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 8.0 Hz, 1H), 5.26 (d, J = 6.8 Hz, 1H), 5.22 (d, J = 6.8 Hz, 1H), 3.48 (s, 3H), 3.08 (dq, J = 14.0, 7.2 Hz, 1H), 2.83 (dq, J = 14.0, 7.2 Hz, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.4, 131.6, 130.9, 125.5, 122.2, 113.7, 94.3, 56.2, 46.5, 5.4; IR (neat) 3466, 2967, 2934, 2845, 1585, 1474, 1441, 1269, 1155, 1130, 1084, 1070, 1036, 978 cm^{-1}; HRMS (EI) for $C_{10}H_{14}O_3S$ calcd 214.0664 (M^+), found 214.0665.

1-(Ethylsulfinyl)-2-(methoxymethoxy)-3-methylbenzene (17b) Compound **17b** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **12b** (0.200 g, 0.942 mmol), L-DET (0.32 mL, 1.88 mmol), Ti(O-*i*-Pr)$_4$ (0.28 mL, 0.942 mmol), 80% CHP (0.19 mL, 1.04 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **17b** (0.183 g, 85%, 67% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: *i*-PrOH = 96: 4, 0.75 mL/min, 250 nm, t_{major} = 74.45 min, t_{minor} = 71.06 min). $[\alpha]_D$ = +215.5 (c = 3.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (dd, J = 7.6, 2.0 Hz, 1H), 7.32 (dd, J = 7.6, 2.0 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H),

5.04 (d, J = 6.0 Hz, 1H), 5.02 (d, J = 6.0 Hz, 1H), 3.60 (s, 3H), 3.09 (dq, J = 13.6, 7.2 Hz, 1H), 2.82 (dq, J = 13.6, 7.2 Hz, 1H), 2.33 (s, 3H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2, 136.3, 133.9, 131.4, 124.9, 123.2, 99.5, 57.7, 47.5, 16.3, 5.7; IR (neat) 3466, 2967, 2934, 2876, 2828, 1460, 1429, 1398, 1159, 1072, 1057, 1045, 1022, 949 cm^{-1}; HRMS (EI) for $C_{11}H_{16}O_3S$ calcd 228.0820 (M^+), found 228.0821.

2-(Ethylsulfinyl)-1-(methoxymethoxy)-4-methylbenzene (17c) Compound **17c** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **12c** (0.200 g, 0.942 mmol), L-DET (0.32 mL, 1.88 mmol), Ti(O-*i*-Pr)$_4$ (0.28 mL, 0.942 mmol), 80% CHP (0.19 mL, 1.04 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 3) to give the product **17c** (0.216 g, > 99%, 74% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: *i*-PrOH = 90: 10, 0.50 mL/min, 250 nm, t_{major} = 54.99 min, t_{minor} = 40.27 min). $[\alpha]_D$ = +191.4 (c = 1.5 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 2.0 Hz, 1H), 7.20 (dd, J = 8.4, 2.0 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 5.23 (d, J = 6.8 Hz, 1H), 5.17 (d, J = 6.8 Hz, 1H), 3.47 (s, 3H), 3.07 (dq, J = 13.6, 7.6 Hz, 1H), 2.82 (dq, J = 13.6, 7.6 Hz, 1H), 2.37 (s, 3H), 1.23 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 132.2, 132.1, 130.6, 125.6, 113.8, 94.5, 56.2, 46.7, 20.4, 5.6; IR (neat) 3487, 2967, 2932, 2874, 2826, 1491, 1456, 1271, 1159, 1142, 1084, 1069, 1038, 982 cm^{-1}; HRMS (EI) for $C_{11}H_{16}O_3S$ calcd 228.0820 (M^+), found 228.0823.

1-(Ethylsulfinyl)-4-fluoro-2-(methoxymethoxy)benzene (17d) Compound **17d** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **12d** (0.200 g, 0.925 mmol), L-DET (0.32 mL, 1.85 mmol), Ti(O-*i*-Pr)$_4$ (0.27 mL, 0.925 mmol), 80% CHP (0.19 mL, 1.02 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **17d** (0.202 g, 94%, 62% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: *i*-PrOH = 95: 5, 0.50 mL/min, 250 nm, t_{major} = 60.63 min, t_{minor} = 58.38 min). $[\alpha]_D$ = +179.3 (c = 2.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (dd, J = 9.2, 6.4 Hz, 1H), 6.84–6.79 (m, 2H), 5.14 (d, J = 6.8 Hz, 1H), 5.13 (d, J = 6.8 Hz, 1H), 3.38 (s, 3H), 2.95 (dq, J = 13.6, 7.2 Hz, 1H), 2.69 (dq, J = 13.6, 7.2 Hz, 1H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9 (d, J = 248.9 Hz), 153.5 (d, J = 10.6 Hz), 127.1 (d, J = 9.9 Hz), 126.4 (d, J = 3.1 Hz), 109.1 (d, J = 22.0 Hz), 102.3 (d, J = 26.6 Hz), 94.5, 56.4, 46.6, 5.3; IR (neat) 3495, 2967, 2934, 2876, 2832, 1605, 1587, 1479, 1427, 1391, 1275, 1117, 1086, 1069, 1024, 988 cm^{-1}; HRMS (EI) for $C_{10}H_{13}FO_3S$ calcd 232.0569 (M^+), found 232.0568.

2-(Ethylsulfinyl)-4-fluoro-1-(methoxymethoxy)benzene (17e) Compound **17e** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **12e** (0.200 g, 0.925 mmol), L-DET (0.32 mL, 1.85 mmol), Ti(O-*i*-Pr)$_4$ (0.27 mL, 0.925 mmol), 80% CHP (0.19 mL, 1.02 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **17e** (0.228 g, > 99%, 68% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 90: 10, 0.50 mL/min, 250 nm, t_{major} = 22.40 min, t_{minor} = 30.75 min). $[\alpha]_D$ = +177.4 (c = 4.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, J = 7.6, 2.8 Hz, 1H), 7.06–6.97 (m, 2H), 5.14 (d, J = 6.8 Hz, 1H), 5.09 (d, J = 6.8 Hz, 1H), 3.39 (s, 3H), 3.00 (dq, J = 13.6, 7.6 Hz, 1H), 2.74 (dq, J = 13.6, 7.6 Hz, 1H), 1.13 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (d, J = 242.5 Hz), 148.5 (d, J = 3.0 Hz), 133.3 (d, J = 5.3 Hz), 118.0 (d, J = 22.7 Hz), 115.4 (d, J = 7.6 Hz), 112.7 (d, J = 26.6 Hz), 94.9, 56.3, 46.5, 5.4; IR (neat) 3503, 2967, 2936, 2911, 2878, 2828, 1485, 1400, 1258, 1184, 1157, 1128, 1084, 1067, 1026, 979 cm^{-1}; HRMS (EI) for $C_{10}H_{13}FO_3S$ calcd 232.0569 (M^+), found 232.0567.

1-(Ethylsulfinyl)-3-methoxy-2-(methoxymethoxy)benzene (17f) Compound **17f** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **12f** (0.200 g, 0.877 mmol), L-DET (0.30 mL, 1.75 mmol), Ti(O-*i*-Pr)$_4$ (0.26 mL, 0.877 mmol), 80% CHP (0.18 mL, 0.965 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 3) to give the product **17f** (0.138 g, 64%, 66% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 40.87 min, t_{minor} = 36.86 min). $[\alpha]_D$ = +131.5 (c = 2.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 8.0, 1.6 Hz, 1H), 7.28 (t, J = 8.0 Hz, 1H), 7.04 (dd, J = 8.0, 1.6 Hz, 1H), 5.28 (d, J = 6.0 Hz, 1H), 5.13 (d, J = 6.0 Hz, 1H), 3.88 (s, 3H), 3.58 (s, 3H), 3.10 (dq, J = 13.6, 7.6 Hz, 1H), 2.85 (dq, J = 13.6, 7.6 Hz, 1H), 1.21 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 140.8, 137.0, 124.8, 116.9,

114.6, 98.6, 57.9, 56.0, 47.5, 5.8; IR (neat) 3464, 2967, 2936, 2839, 1589, 1477, 1450, 1439, 1300, 1267, 1190, 1177, 1159, 1072, 1059, 1036, 945 cm^{-1}; HRMS (EI) for $C_{11}H_{16}O_4S$ calcd 244.0769 (M^+), found 244.0768.

2-(Ethylsulfinyl)-4-methoxy-1-(methoxymethoxy)benzene (17g) Compound **17g** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **12g** (0.200 g, 0.877 mmol), L-DET (0.30 mL, 1.75 mmol), Ti(O-*i*-Pr)$_4$ (0.26 mL, 0.877 mmol), 80% CHP (0.18 mL, 0.965 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 3) to give the product **17g** (0.200 g, 92%, 78% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 25.99 min, t_{minor} = 32.94 min). $[\alpha]_D$ = +159.8 (c = 2.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, J = 3.2 Hz, 1H), 7.09 (d, J = 8.8 Hz, 1H), 6.93 (dd, J = 8.8, 3.2 Hz, 1H), 5.19 (d, J = 6.8 Hz, 1H), 5.14 (d, J = 6.8 Hz, 1H), 3.84 (s, 3H), 3.48 (s, 3H), 3.08 (dq, J = 13.6, 7.6 Hz, 1H), 2.83 (dq, J = 13.6, 7.6 Hz, 1H), 1.24 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 146.2, 132.2, 117.8, 115.7, 109.4, 95.0, 56.2, 55.7, 46.7, 5.6; IR (neat) 3482, 2959, 2936, 2909, 2832, 1491, 1441, 1267, 1194, 1157, 1138, 1082, 1067, 1043, 1026, 984 cm^{-1}; HRMS (EI) for $C_{11}H_{16}O_4S$ calcd 244.0769 (M^+), found 244.0762.

2-(Ethylsulfinyl)-1-(methoxymethoxy)-4-nitrobenzene (17h) Compound **17h** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **12h** (0.130 g, 0.534 mmol), L-DET (0.18 mL, 1.07 mmol), Ti(O-*i*-Pr)$_4$ (0.16 mL, 0.534 mmol), 80% CHP (0.11 mL, 0.588 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 3) to give the product **17h** (0.135 g, 97%, 78% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 70: 30, 0.75 mL/min, 250 nm, t_{major} = 46.48 min, t_{minor} = 28.95 min). $[\alpha]_D$ = +177.7 (c = 1.8 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, J = 2.4 Hz, 1H), 8.33 (dd, J = 8.8, 2.4 Hz, 1H), 7.28 (d, J = 8.8 Hz, 1H), 5.38 (d, J = 6.8 Hz, 1H), 5.33 (d, J = 6.8 Hz, 1H), 3.51 (s, 3H), 3.13 (dq, J = 14.8, 7.2 Hz, 1H), 2.85 (dq, J = 14.8, 7.2 Hz, 1H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 143.1, 133.5, 127.7, 122.4, 113.9, 94.9, 57.0, 46.6, 5.6; IR (KBr) 3102, 2978, 2940, 2916, 2876, 2835, 1585, 1510, 1487, 1458, 1342, 1261, 1200, 1159, 1132, 1088, 1061, 1026, 945 cm^{-1}; HRMS (EI) for $C_{10}H_{13}NO_5S$ calcd 259.0514 (M^+), found 259.0517; Anal. Calcd for $C_{10}H_{13}NO_5S$: C, 46.32; H, 5.05; N, 5.40. found: C, 46.62; H, 5.09; N, 5.53.

1-(Methoxymethoxy)-2-(propan-2-ylsulfinyl)benzene (18a)[30]: Compound **18a** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **13a** (0.200 g, 0.943 mmol), L-DET (0.32 mL, 1.89 mmol), Ti(O-*i*-Pr)$_4$ (0.28 mL, 0.943 mmol), 80% CHP (0.19 mL, 1.04 mmol) in dry CH_2Cl_2 (5.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **18a** (0.170 g, 79%, 26% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, MeCN only, 0.50 mL/min, 250 nm, t_{major} = 10.70 min, t_{minor} = 11.70 min).

2-(Methoxymethoxy)-1-methyl-3-(propan-2-ylsulfinyl)benzene (18b) Compound **18b** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **13b** (0.300 g, 1.33 mmol), L-DET (0.45 mL, 2.65 mmol), Ti(O-*i*-Pr)$_4$ (0.39 mL, 1.33 mmol), 80% CHP (0.27 mL, 1.45 mmol) in dry CH_2Cl_2 (5.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 1) to give the product **18b** (0.258 g, 80%, 33% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, MeCN only, 0.50 mL/min, 250 nm, t_{major} = 12.65 min, t_{minor} = 13.60 min). $[\alpha]_D$ = +103.8 (c = 3.7 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, J = 7.6, 1.2 Hz, 1H), 7.31 (dd, J = 7.6, 1.2 Hz, 1H), 7.25 (t, J = 7.6 Hz, 1H), 5.04 (s, 2H), 3.61 (s, 3H), 3.12 (sep, J = 6.8 Hz, 1H), 2.33 (s, 3H), 1.39 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 135.6, 133.9, 131.5, 124.8, 123.9, 99.5, 57.7, 51.8, 17.3, 16.4, 12.3; KBr (neat) 3466, 2967, 2930, 2868, 1462, 1429, 1396, 1159, 1072, 1057, 1024, 949 cm^{-1}; HRMS (EI) for $C_{12}H_{18}O_3S$ calcd 242.0977 (M^+), found 242.0977.

1-(Methoxymethoxy)-4-methyl-2-(propan-2-ylsulfinyl)benzene (18c) Compound **18c** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **13c** (0.200 g, 0.884 mmol), L-DET (0.30 mL, 1.77 mmol), Ti(O-*i*-Pr)$_4$ (0.26 mL, 0.884 mmol), 80% CHP (0.18 mL, 0.972 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 3) to give the product **18c** (0.161 g, 75%, 41% e.e.) as a pale yellow oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: *i*-PrOH = 90: 10, 0.50 mL/min, 250 nm, t_{major} = 60.53 min,

t_{minor} = 30.64 min). $[\alpha]_D$ = +85.6 (*c* = 1.9 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.4 Hz, 1H), 7.19 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.03 (d, *J* = 8.4 Hz, 1H), 5.22 (d, *J* = 6.8 Hz, 1H), 5.16 (d, *J* = 6.8 Hz, 1H), 3.47 (s, 3H), 3.10 (sep, *J* = 6.8 Hz, 1H), 2.36 (s, 3H), 1.41 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 132.1, 132.0, 130.2, 126.2, 113.9, 94.6, 56.2, 51.1, 20.5, 17.2, 12.5; IR (neat) 3474, 2968, 2930, 2868, 2826, 1489, 1464, 1271, 1159, 1142, 1084, 1070, 1040, 1022, 984 cm^{-1}; HRMS (EI) for $C_{12}H_{18}O_3S$ calcd 242.0977 (M^+), found 242.0979.

4-Fluoro-2-(methoxymethoxy)-1-(propan-2-yl-sulfinyl)benzene (18d) Compound **18d** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **13d** (0.200 g, 0.868 mmol), L-DET (0.30 mL, 1.74 mmol), Ti(O-*i*-Pr)$_4$ (0.26 mL, 0.868 mmol), 80% CHP (0.18 mL, 0.955 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 1) to give the product **18d** (0.209 g, 98%, 15% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 18.39 min, t_{minor} = 14.97 min). $[\alpha]_D$ = +35.7 (*c* = 2.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 9.2, 6.4 Hz, 1H), 6.94–6.89 (m, 2H), 5.25 (d, *J* = 6.8 Hz, 1H), 5.21 (d, *J* = 6.8 Hz, 1H), 3.49 (s, 3H), 3.06 (sep, *J* = 6.8 Hz, 1H), 1.40 (d, *J* = 6.8 Hz, 3H), 1.03 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0 (d, *J* = 249.0 Hz), 154.1 (d, *J* = 11.3 Hz), 127.7 (d, *J* = 10.6 Hz), 126.0 (d, *J* = 3.0 Hz), 109.1 (d, *J* = 22.0 Hz), 102.3 (d, *J* = 26.6 Hz), 94.6, 56.4, 51.2, 16.9, 12.3; IR (neat) 3503, 2968, 2932, 2870, 2832, 1605, 1587, 1479, 1427, 1391, 1275, 1152, 1086, 1067, 1043, 1024, 988 cm^{-1}; HRMS (EI) for $C_{11}H_{15}FO_3S$ calcd 246.0726 (M^+), found 246.0728.

4-Fluoro-1-(methoxymethoxy)-2-(propan-2-yl-sulfinyl)benzene (18e) Compound **18e** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **13e** (0.200 g, 0.868 mmol), L-DET (0.30 mL, 1.74 mmol), Ti(O-*i*-Pr)$_4$ (0.26 mL, 0.868 mmol), 80% CHP (0.18 mL, 0.955 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (5: 1) to give the product **18e** (0.130 g, 68%, 38% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 21.92 min, t_{minor} = 19.18 min). $[\alpha]_D$ = +108.9 (*c* = 1.6 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 (dd, *J* = 8.0, 2.8 Hz, 1H), 7.15–7.06 (m, 2H), 5.23 (d, *J* = 6.8 Hz, 1H), 5.17 (d, *J* = 6.8 Hz, 1H), 3.48 (s, 3H), 3.13 (sep, *J* = 6.8 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 3H), 1.02 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (d, *J* = 243.6 Hz), 148.9 (d, *J* = 2.3 Hz), 133.0 (d, *J* = 5.3 Hz), 118.1 (d, *J* = 23.5 Hz), 115.5 (d, *J* = 7.6 Hz), 113.1 (d, *J* = 25.8 Hz), 95.0, 56.3, 51.1, 17.2, 12.2; IR (neat) 3482, 2970, 2934, 2909, 2870, 2828, 1485, 1400, 1258, 1184, 1157, 1128, 1084, 1069, 1022, 982 cm^{-1}; HRMS (EI) for $C_{11}H_{15}FO_3S$ calcd 246.0726 (M^+), found 246.0724.

1-Methoxy-2-(methoxymethoxy)-3-(propan-2-yl-sulfinyl)benzene (18f) Compound **18f** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **13f** (0.200 g, 0.826 mmol), L-DET (0.28 mL, 1.65 mmol), Ti(O-*i*-Pr)$_4$ (0.25 mL, 0.826 mmol), 80% CHP (0.17 mL, 0.909 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **18f** (0.145 g, 68%, 16% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 34.34 min, t_{minor} = 30.80 min). $[\alpha]_D$ = +25.5 (*c* = 1.5 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 1H), 7.03 (dd, *J* = 8.4, 1.6 Hz, 1H), 5.26 (d, *J* = 5.6 Hz, 1H), 5.14 (d, *J* = 5.6 Hz, 1H), 3.88 (s, 3H), 3.59 (s, 3H), 3.15 (sep, *J* = 6.8 Hz, 1H), 1.41 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 141.2, 136.3, 124.6, 117.5, 114.5, 98.6, 58.0, 56.0, 51.8, 17.5, 12.4; IR (neat) 3462, 2967, 2934, 2839, 1587, 1476, 1450, 1439, 1300, 1267, 1190, 1175, 1159, 1072, 1059, 1038, 1024, 945 cm^{-1}; HRMS (EI) for $C_{12}H_{18}O_4S$ calcd 258.0926 (M^+), found 258.0926.

4-Methoxy-1-(methoxymethoxy)-2-(propan-2-yl-sulfinyl)benzene (18g)[30]: Compound **18g** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **13g** (0.200 g, 0.826 mmol), L-DET (0.28 mL, 1.65 mmol), Ti(O-*i*-Pr)$_4$ (0.25 mL, 0.826 mmol), 80% CHP (0.17 mL, 0.909 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 3) to give the product **18g** (0.130 g, 61%, 55% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 22.64 min, t_{minor} = 33.58 min).

1-(Methoxymethoxy)-4-nitro-2-(propan-2-yl-sulfinyl)benzene (18h) Compound **18h** was followed by general procedure for Sharpless asymmetric

oxidation of aryl sulfide using aryl sulfide **13h** (0.200 g, 0.777 mmol), L-DET (0.27 mL, 1.55 mmol), Ti(O-*i*-Pr)$_4$ (0.23 mL, 0.777 mmol), 80% CHP (0.16 mL, 0.855 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (13: 7) to give the product **18h** (0.165 g, 78%, 61% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 70: 30, 0.75 mL/min, 250 nm, t_{major} = 83.46 min, t_{minor} = 21.66 min). $[\alpha]_D$ = +136.8 (c = 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 2.8 Hz, 1H), 8.29 (dd, J = 9.2, 2.8 Hz, 1H), 7.26 (d, J = 9.2 Hz, 1H), 5.36 (d, J = 6.8 Hz, 1H), 5.30 (d, J = 6.8 Hz, 1H), 3.49 (s, 3H), 3.12 (sep, J = 6.8 Hz, 1H), 1.45 (d, J = 6.8 Hz, 3H), 1.02 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 143.0, 133.1, 127.6, 122.8, 113.9, 95.0, 57.0, 51.3, 17.3, 12.5; IR (KBr) 3102, 2968, 2928, 2870, 2832, 1585, 1514, 1489, 1470, 1344, 1261, 1227, 1198, 1165, 1132, 1088, 1065, 1026, 955 cm^{-1}; HRMS (EI) for $C_{11}H_{15}NO_5S$ calcd 273.0671 (M^+), found 273.0669; Anal. Calcd for $C_{11}H_{15}NO_5S$: C, 48.34; H, 5.53; N, 5.12. found: C, 48.31; H, 5.47; N, 4.90.

1-(tert-butylsulfinyl)-2-(methoxymethoxy)benzene (19a)[26]: Compound **19a** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14a** (0.200 g, 0.884 mmol), L-DET (0.30 mL, 1.77 mmol), Ti(O-*i*-Pr)$_4$ (0.26 mL, 0.884 mmol), 80% CHP (0.18 mL, 0.972 mmol) in dry CH_2Cl_2 (3.0 mL). L-DET was eliminated by short column chromatography on activated alumina using hexane/EtOAc (1: 1), then the mixture was purified by column chromatography on silica gel using hexane/EtOAc (4: 1) to give the product **19a** (0.168 g, 78%, 64% e.e.) as a white solid. The yield was 46% and the enantiomeric excess was 98% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 23.60 min, t_{minor} = 14.11 min).

1-(tert-Butylsulfinyl)-2-(methoxymethoxy)-3-methylbenzene (19b) Compound **19b** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14b** (0.200 g, 0.832 mmol), L-DET (0.28 mL, 1.66 mmol), Ti(O-*i*-Pr)$_4$ (0.25 mL, 0.832 mmol), 80% CHP (0.17 mL, 0.915 mmol) in dry CH_2Cl_2 (3.0 mL). L-DET was eliminated by short column chromatography on activated alumina using hexane/EtOAc (4: 1), then the mixture was purified by column chromatography on silica gel using hexane/EtOAc (4: 1) to give the product **19b** (0.108 g, 50%, 55% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 23.28 min, t_{minor} = 21.07 min). $[\alpha]_D$ = +146.0 (c = 1.6 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (dd, J = 7.6, 1.2 Hz, 1H), 7.32 (dd, J = 7.6, 1.2 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 5.06 (d, J = 5.6 Hz, 1H), 5.03 (d, J = 5.6 Hz, 1H), 3.62 (s, 3H), 2.34 (s, 3H), 1.19 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 134.2, 134.0, 131.7, 125.0, 124.5, 99.5, 57.9, 57.8, 22.9, 16.5; IR (neat) 3447, 2961, 2928, 2903, 2868, 2828, 1458, 1429, 1396, 1364, 1256, 1159, 1072, 1043, 951 cm^{-1}; HRMS (EI) for $C_{13}H_{20}O_3S$ calcd 256.1133 (M^+), found 256.1128; Anal. Calcd for $C_{13}H_{20}O_3S$: C, 60.91; H, 7.86; N, 0.00. found: C, 60.96; H, 7.72; N, 0.00.

2-(tert-Butylsulfinyl)-1-(methoxymethoxy)-4-methylbenzene (19c) Compound **19c** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14c** (0.200 g, 0.832 mmol), L-DET (0.28 mL, 1.66 mmol), Ti(O-*i*-Pr)$_4$ (0.25 mL, 0.832 mmol), 80% CHP (0.17 mL, 0.915 mmol) in dry CH_2Cl_2 (3.0 mL). L-DET was eliminated by short column chromatography on activated alumina using EtOAc, then the mixture was purified by column chromatography on silica gel using hexane/EtOAc (7: 3) to give the product **19c** (0.146 g, 68%, 65% e.e.) as a white solid. The yield was 27% and the enantiomeric excess was > 99% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 32.43 min, t_{minor} = 10.03 min). M.p.: 84–85 °C; $[\alpha]_D$ = +189.8 (c = 1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 2.4 Hz, 1H), 7.20 (dd, J = 8.4, 2.4 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 5.20 (d, J = 6.8 Hz, 1H), 5.13 (d, J = 6.8 Hz, 1H), 3.47 (s, 3H), 2.36 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 132.8, 131.8, 128.9, 127.3, 114.2, 94.9, 57.3, 56.4, 22.9, 20.6; IR (KBr) 2980, 2963, 2924, 2864, 2832, 1487, 1447, 1412, 1393, 1366, 1358, 1314, 1275, 1238, 1207, 1169, 1146, 1084, 1057, 1028, 980 cm^{-1}; HRMS (FAB) for $C_{13}H_{21}O_3S$ calcd 257.1211 (MH^+), found 257.1214; Anal. Calcd for $C_{13}H_{20}O_3S$: C, 60.91; H, 7.86; N, 0.00. found: C, 61.13; H, 7.79; N, 0.00.

1-(tert-Butylsulfinyl)-4-fluoro-2-(methoxymethoxy)benzene (19d) Compound **19d** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14d** (0.200 g, 0.819 mmol), L-DET (0.28 mL, 1.64 mmol), Ti(O-*i*-Pr)$_4$ (0.24 mL, 0.819 mmol), 80% CHP (0.17 mL, 0.900 mmol) in dry CH_2Cl_2 (3.0 mL). The

reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (7: 3) to give the product **19d** (0.164 g, 77%, 62% e.e.) as a white solid. The yield was 42% and the enantiomeric excess was 87% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 19.60 min, t_{minor} = 11.07 min). $[\alpha]_D$ = +94.1 (c = 1.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.8, 6.8 Hz, 1H), 6.95–6.88 (m, 2H), 5.21 (d, J = 6.8 Hz, 1H), 5.17 (d, J = 6.8 Hz, 1H), 3.48 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (d, J = 249.7 Hz), 156.2 (d, J = 10.6 Hz), 129.0 (d, J = 10.7 Hz), 124.9 (d, J = 3.0 Hz), 109.3 (d, J = 22.8 Hz), 102.4 (d, J = 25.8 Hz), 95.0, 57.4, 56.6, 22.8; IR (KBr) 3096, 3073, 3034, 2988, 2970, 2928, 2828, 1605, 1589, 1476, 1454, 1427, 1396, 1368, 1315, 1273, 1240, 1219, 1161, 1121, 1084, 1053, 1032, 989 cm^{-1}; HRMS (FAB) for $C_{12}H_{18}FO_3S$ calcd 261.0961 (MH^+), found 261.0959; Anal. Calcd for $C_{12}H_{17}FO_3S$: C, 55.36; H, 6.58; N, 0.00. found: C, 55.42; H, 6.58; N, 0.00.

2-(tert-Butylsulfinyl)-4-fluoro-1-(methoxymethoxy)benzene (19e) Compound **19e** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14e** (0.200 g, 0.819 mmol), L-DET (0.28 mL, 1.64 mmol), Ti(O-i-Pr)$_4$ (0.24 mL, 0.819 mmol), 80% CHP (0.17 mL, 0.900 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (3: 1) to give the product **19e** (0.106 g, 50%, 67% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: i-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 21.92 min, t_{minor} = 19.18 min). $[\alpha]_D$ = +149.6 (c = 1.4 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.0, 2.8 Hz, 1H), 7.17–7.07 (m, 2H), 5.19 (d, J = 6.8 Hz, 1H), 5.13 (d, J = 6.8 Hz, 1H), 3.48 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0 (d, J = 242.9 Hz), 151.1 (d, J = 2.2 Hz), 131.7 (d, J = 5.3 Hz), 118.9 (d, J = 23.6 Hz), 115.8 (d, J = 6.9 Hz), 114.1 (d, J = 25.1 Hz), 95.4, 58.0, 56.5, 22.9; IR (KBr) 2965, 2928, 2909, 2868, 2830, 1489, 1472, 1458, 1394, 1366, 1263, 1190, 1161, 1132, 1084, 1053, 1030, 986 cm^{-1}; HRMS (FAB) for $C_{12}H_{18}FO_3S$ calcd 261.1138 (MH^+), found 261.0964; Anal. Calcd for $C_{12}H_{17}FO_3S$: C, 55.36; H, 6.58; N, 0.00. found: C, 55.54; H, 6.54; N, 0.00.

1-(tert-Butylsulfinyl)-3-methoxy-2-(methoxymethoxy)benzene (19f) Compound **19f** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14f** (0.200 g, 0.780 mmol), L-DET (0.26 mL, 1.56 mmol), Ti(O-i-Pr)$_4$ (0.23 mL, 0.780 mmol), 80% CHP (0.16 mL, 0.858 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (3: 1) to give the product **19f** (0.0939 g, 44%, 47% e.e.) as a white solid. The yield was 27% and the enantiomeric excess was 68% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 23.11 min, t_{minor} = 34.58 min). $[\alpha]_D$ = +77.8 (c = 1.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (dd, J = 8.0, 1.6 Hz, 1H), 7.25 (t, J = 8.0 Hz, 1H), 7.03 (dd, J = 8.0, 1.6 Hz, 1H), 5.21 (d, J = 5.6 Hz, 1H), 5.13 (d, J = 5.6 Hz, 1H), 3.88 (s, 3H), 3.62 (s, 3H), 1.22 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 143.1, 134.9, 124.3, 118.5, 114.7, 98.6, 58.1, 57.9, 55.9, 23.0; IR (KBr) 3071, 3028, 2999, 2976, 2957, 2899, 2862, 2837, 2781, 1581, 1481, 1440, 1391, 1366, 1360, 1304, 1265, 1234, 1200, 1163, 1076, 1049, 1011 cm^{-1}; HRMS (FAB) for $C_{13}H_{21}O_4S$ calcd 273.1161 (MH^+), found 273.1163; Anal. Calcd for $C_{13}H_{20}O_4S$: C, 57.33; H, 7.40; N, 0.00. found: C, 57.17; H, 7.31; N, 0.00.

2-(tert-Butylsulfinyl)-4-methoxy-1-(methoxymethoxy)benzene (19g) Compound **19g** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14g** (0.200 g, 0.780 mmol), L-DET (0.26 mL, 1.56 mmol), Ti(O-i-Pr)$_4$ (0.23 mL, 0.780 mmol), 80% CHP (0.16 mL, 0.858 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (7: 3) to give the product **19g** (0.165 g, 78%, 51% e.e.) as a white solid. The yield was 32% and the enantiomeric excess was 97% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: i-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 25.06 min, t_{minor} = 57.10 min). M.p.: 96–98 °C; $[\alpha]_D$ = +171.4 (c = 1.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (d, J = 3.2 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 6.95 (dd, J = 8.8, 3.2 Hz, 1H), 5.17 (d, J = 6.8 Hz, 1H), 5.09 (d, J = 6.8 Hz, 1H), 3.82 (s, 3H), 3.48 (s, 3H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 149.0, 130.4, 118.8, 116.1, 110.9, 95.5, 57.7, 56.4, 55.9, 23.0; IR (KBr) 3073, 3057, 2982, 2967, 2938, 2914, 2862, 2828, 1491, 1466, 1437, 1396, 1364, 1317, 1298, 1265, 1217, 1157, 1138, 1080, 1053, 1026, 980 cm^{-1}; HRMS (EI) for $C_{13}H_{20}O_4S$ calcd 272.1082 (M^+), found 272.1076.

2-(tert-Butylsulfinyl)-1-(methoxymethoxy)-4-nitrobenzene (19h) Compound **19h** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14h** (0.200 g, 0.737 mmol), L-DET (0.25 mL, 1.47 mmol), Ti(O-*i*-Pr)$_4$ (0.22 mL, 0.737 mmol), 80% CHP (0.15 mL, 0.811 mmol) in dry CH_2Cl_2 (3.0 mL). L-DET was eliminated by short column chromatography on activated alumina using hexane/EtOAc (3: 2), then the mixture was purified by column chromatography on silica gel using hexane/EtOAc (3: 2) to give the product **15h** (0.174 g, 82%, 88% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 70: 30, 0.75 mL/min, 250 nm, t_{major} = 34.55 min, t_{minor} = 16.29 min). $[\alpha]_D$ = +157.0 (c = 1.7 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, J = 2.8 Hz, 1H), 8.31 (d, J = 9.2, 2.8 Hz, 1H), 7.30 (d, J = 9.2 H, 1H), 5.34 (d, J = 6.8 Hz, 1H), 5.28 (d, J = 6.8 Hz, 1H), 3.51 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 142.7, 131.8, 127.9, 123.9, 114.2, 95.2, 58.3, 57.1, 22.9; IR (KBr) 3107, 3082, 3067, 2978, 2963, 2930, 2860, 2830, 1587, 1520, 1506, 1479, 1458, 1342, 1306, 1269, 1171, 1146, 1090, 1053, 1030, 947 cm^{-1}; HRMS (FAB) for $C_{12}H_{18}NO_5S$ calcd 288.0906 (MH^+), found 288.0907; Anal. Calcd for $C_{12}H_{17}NO_5S$: C, 50.16; H, 5.96; N, 4.87. found: C, 50.23; H, 5.99; N, 4.78.

Methyl 3-(tert-butylsulfinyl)-4-(methoxymethoxy)-benzoate (19i) Compound **19i** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14i** (0.200 g, 0.703 mmol), L-DET (0.24 mL, 1.41 mmol), Ti(O-*i*-Pr)$_4$ (0.21 mL, 0.703 mmol), 80% CHP (0.14 mL, 0.774 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (2: 3) to give the product **19i** (0.114 g, 54%, 87% e.e.) as a white solid. The yield was 30% and the enantiomeric excess was > 99% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 80: 20, 0.75 mL/min, 250 nm, t_{major} = 15.40 min, t_{minor} = 44.96 min). M.p.: 118–120 °C; $[\alpha]_D$ = +173.2 (c = 1.2 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 2.0 Hz, 1H), 8.12 (dd, J = 8.8, 2.0 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 5.29 (d, J = 6.8 Hz, 1H), 5.24 (d, J = 6.8 Hz, 1H), 3.91 (s, 3H), 3.49 (s, 3H), 1.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 158.4, 134.1, 129.9, 129.3, 124.4, 113.7, 94.8, 57.7, 56.8, 52.2, 22.9; IR (KBr) 3009, 2967, 2943, 2928, 1709, 1597, 1487, 1437, 1300, 1259, 1231, 1200, 1171, 1148, 1125, 1090, 1055, 1032, 978, 953 cm^{-1}; HRMS (FAB) for $C_{14}H_{21}O_5S$ calcd 301.1110 (MH^+), found 301.1115; Anal. Calcd for $C_{14}H_{20}O_5S$: C, 55.98; H, 6.71; N, 0.00. found: C, 56.23; H, 6.63; N, 0.00.

3-(tert-Butylsulfinyl)-4-(methoxymethoxy)benzaldehyde (19j) Compound **19j** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **14j** (0.200 g, 0.786 mmol), L-DET (0.27 mL, 1.57 mmol), Ti(O-*i*-Pr)$_4$ (0.23 mL, 0.786 mmol), 80% CHP (0.16 mL, 0.865 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product **19j** (0.218 g, > 99%, 76% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 80: 20, 0.75 mL/min, 250 nm, t_{major} = 20.77 min, t_{minor} = 52.21 min). $[\alpha]_D$ = +143.0 (c = 4.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.99 (s, 1H), 8.31 (d, J = 2.0 Hz 1H), 8.00 (dd, J = 8.8, 2.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 5.33 (d, J = 6.8 Hz, 1H), 5.27 (d, J = 6.8 Hz, 1H), 3.51 (s, 3H), 1.26 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.1, 159.4, 132.7, 130.9, 130.8, 130.7, 114.4, 94.9, 57.9, 56.9, 22.9; IR (KBr) 3105, 2999, 2965, 2930, 2866, 2830, 1686, 1595, 1493, 1375, 1366, 1319, 1248, 1198, 1163, 1140, 1090, 1026, 968 cm^{-1}; HRMS (FAB) for $C_{13}H_{19}O_4S$ calcd 271.1004 (MH^+), found 271.1010; Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; N, 0.00. found: C, 57.61; H, 6.64; N, 0.00.

1-(Methoxymethoxy)-2-[(4-methylphenyl)-sulfinyl]benzene (20a) Compound **20a** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **15a** (0.200 g, 0.768 mmol), L-DET (0.26 mL, 1.54 mmol), Ti(O-*i*-Pr)$_4$ (0.23 mL, 0.768 mmol), 80% CHP (0.12 mL, 0.845 mmol) in dry CH_2Cl_2 (5.0 mL). The reaction mixture was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (5: 1) to give the product **20a** (0.0634 g, 30%, 7.2% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: *i*-PrOH = 90: 10, 0.50 mL/min, 250 nm, t_{major} = 45.27 min, t_{minor} = 51.71 min). $[\alpha]_D$ = +12.1 (c = 1.3 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (dd, J = 7.6, 1.6 Hz, 1H), 7.59 (d, J = 8.0 Hz, 2H), 7.37 (ddd, J = 7.6, 1.6, 0.8 Hz, 1H), 7.23–7.19 (m, 3H), 7.06 (dd, J = 7.6, 0.8 Hz, 1H), 5.17 (d, J = 6.8 Hz, 1H), 5.09 (d, J = 6.8 Hz, 1H), 3.28 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.0, 142.3, 141.4, 133.7, 131.9, 129.6, 125.6, 124.6, 122.5, 114.0, 94.2, 56.2, 21.3; IR (KBr) 3004, 2983, 2961, 2945, 2916, 2903, 2868, 2824, 1582, 1495, 1474, 1449,

1435, 1398, 1310, 1271, 1229, 1198, 1165, 1152, 1128, 1086, 1061, 1030, 1015, 980 cm^{-1}; HRMS (EI) for $C_{15}H_{16}O_3S$ calcd 276.0820 (M^+), found 276.0824; Anal. Calcd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84; N, 0.00. found: C, 65.49; H, 5.77; N, 0.00.

2-(Methoxymethoxy)-1-methyl-3-[(4-methylphenyl)-sulfinyl]benzene (20b) Compound **20b** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **15b** (0.200 g, 0.729 mmol), L-DET (0.25 mL, 1.46 mmol), Ti(O-*i*-Pr)$_4$ (0.22 mL, 0.729 mmol), 80% CHP (0.15 mL, 0.802 mmol) in dry CH_2Cl_2 (3.0 mL). L-DET was eliminated by short column chromatography on activated alumina using hexane/EtOAc (3: 1), then the mixture was purified by column chromatography on silica gel using hexane/EtOAc (3: 1) to give the product **20b** (0.0889 g, 42%, 4.9% e.e.) as a colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 33.72 min, t_{minor} = 28.66 min). $[\alpha]_D$ = -12.4 (c = 1.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J = 7.6, 1.6 Hz, 1H), 7.58 (d, J = 8.4 Hz, 2H), 7.27–7.18 (m, 4H), 5.10 (d, J = 5.6 Hz, 1H), 5.07 (d, J = 5.6 Hz, 1H), 3.65 (s, 3H), 2.34 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 142.3, 141.2, 139.2, 134.2, 131.9, 129.7, 125.3, 125.0, 122.7, 99.8, 57.9, 21.3, 16.5; IR (neat) 3503,2953, 2926, 2828, 1401, 1460, 1429, 1396, 1159, 1082, 1072, 1047, 949 cm^{-1}; HRMS (EI) for $C_{16}H_{18}O_3S$ calcd 290.0977 (M^+), found 290.0982.

1-(Methoxymethoxy)-4-methyl-2-[(4-methylphenyl)-sulfinyl]benzene (20c) Compound **20c** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **15c** (0.200 g, 0.729 mmol), L-DET (0.25 mL, 1.46 mmol), Ti(O-*i*-Pr)$_4$ (0.22 mL, 0.729 mmol), 80% CHP (0.15 mL, 0.802 mmol) in dry CH_2Cl_2 (3.0 mL). L-DET was eliminated by short column chromatography on activated alumina using hexane/EtOAc (3: 1), then the mixture was purified by column chromatography on silica gel using hexane/EtOAc (3: 1) to give the product **20c** (0.0664 g, 31%, 1.3% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 27.33 min, t_{minor} = 24.32 min). $[\alpha]_D$ = +2.9 (c = 1.1 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 2.4 Hz, 1H), 7.57 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.13 (dd, J = 8.4, 2.4 Hz, 1H), 6.92 (d, J = 8.4 Hz, 1H), 5.10 (d, J = 6.8 Hz, 1H), 5.03 (d, J = 6.8 Hz, 1H), 3.26 (s, 3H), 2.33 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.9, 142.4, 141.3, 133.3, 132.4, 132.4, 129.6, 125.5, 124.6, 114.1, 94.4, 56.1, 21.3, 20.6; IR (KBr) 3038, 3009, 2978, 2961, 2918, 2822, 1595, 1487, 1310, 1267, 1234, 1196, 1159, 1134, 1088, 1078, 1055, 1030, 1015, 986 cm^{-1}; HRMS (EI) for $C_{16}H_{18}O_3S$ calcd 290.0977 (M^+), found 290.0978; Anal. Calcd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25; N, 0.00. found: C, 66.04; H, 6.10; N, 0.00.

4-Fluoro-2-(methoxymethoxy)-1-[(4-methylphenyl)-sulfinyl]benzene (20d) Compound **20d** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **15d** (0.200 g, 0.719 mmol), L-DET (0.25 mL, 1.44 mmol), Ti(O-*i*-Pr)$_4$ (0.21 mL, 0.719 mmol), 80% CHP (0.15 mL, 0.790 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (4: 1) to give the product **20d** (0.107 g, 51%, 5.2% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 22.78 min, t_{minor} = 24.80 min). $[\alpha]_D$ = +9.7 (c = 1.9 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.4, 6.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 2H), 7.23 (d, J = 8.4 Hz, 2H), 6.90 (dt, J = 8.4, 2.4 Hz, 1H), 6.82 (dd, J = 10.4, 2.4 Hz, 1H), 5.15 (d, J = 6.8 Hz, 1H), 5.08 (d, J = 6.8 Hz, 1H), 3.27 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (d, J = 249.0 Hz), 154.2 (d, J = 10.6 Hz), 142.2, 141.6, 129.7, 129.4 (d, J = 3.1 Hz), 126.3 (d, J = 10.6 Hz), 125.5, 109.4 (d, J = 22.0 Hz), 102.6 (d, J = 26.6 Hz), 94.5, 56.3, 21.4; IR (KBr) 3100, 3073, 3059, 3038, 3003, 2988, 2955, 2916, 2901, 2874, 2828, 1605, 1585, 1493, 1479, 1458, 1429, 1385, 1306, 1269, 1233, 1209, 1177, 1148, 1126, 1088, 1038, 988 cm^{-1}; HRMS (EI) for $C_{15}H_{15}FO_3S$ calcd 294.0726 (M^+), found 294.0732; Anal. Calcd for $C_{15}H_{15}FO_3S$: C, 61.21; H, 5.14; N, 0.00. found: C, 61.36; H, 5.10; N, 0.00.

4-Fluoro-1-(methoxymethoxy)-2-[(4-methylphenyl)-sulfinyl]benzene (20e) Compound **20e** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **15e** (0.200 g, 0.719 mmol), L-DET (0.25 mL, 1.44 mmol), Ti(O-*i*-Pr)$_4$ (0.21 mL, 0.719 mmol), 80% CHP (0.15 mL, 0.790 mmol) in dry CH_2Cl_2 (3.0 mL). The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (10: 1) to give the product **20e** (0.0387 g, 18%, 15% e.e.) as a white solid. The yield was 11% and the enantiomeric excess was 20% e.e. after one recrystallization using hexane-EtOAc. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: EtOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 19.60

min, t_{minor} = 27.45 min). $[\alpha]_D$ = +35.4 (*c* = 1.0 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 7.6, 2.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.05–7.03 (m, 2H), 5.12 (d, *J* = 6.8 Hz, 1H), 5.04 (d, *J* = 6.8 Hz, 1H), 3.30 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3 (d, *J* = 243.6 Hz), 149.0 (d, *J* = 2.3 Hz), 141.8, 141.7, 136.0 (d, *J* = 5.4 Hz), 129.7, 125.5, 118.3 (d, *J* = 23.5 Hz), 115.7 (d, *J* = 6.8 Hz), 111.5 (d, *J* = 25.8 Hz), 94.8, 56.2, 21.4; IR (KBr) 3103, 3084, 2984, 2949, 2936, 2924, 2826, 1595, 1483, 1460, 1402, 1312, 1258, 1188, 1157, 1128, 1086, 1053, 1024, 1015, 980 cm^{-1}; HRMS (EI) for $C_{15}H_{15}FO_3S$ calcd 294.0726 (M^+), found 294.0731; Anal. Calcd for $C_{15}H_{15}FO_3S$: C, 61.21; H, 5.14; N, 0.00. found: C, 61.28; H, 5.18; N, 0.00.

1-Methoxy-2-(methoxymethoxy)-3-[(4-methylphenyl)sulfinyl]benzene (20f) Compound **20f** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **15f** (0.200 g, 0.689 mmol), L-DET (0.24 mL, 1.38 mmol), Ti(O-*i*-Pr)$_4$ (0.20 mL, 0.689 mmol), 80% CHP (0.14 mL, 0.758 mmol) in dry CH_2Cl_2 (3.0 mL). L-DET was eliminated by short column chromatography on activated alumina using CH_2Cl_2/EtOAc (5: 1), then the mixture was purified by column chromatography on silica gel using CH_2Cl_2/EtOAc (5: 1) to give the product **20f** (0.0295 g, 14%, 28% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK AY-3, hexane: *i*-PrOH = 85: 15, 0.75 mL/min, 250 nm, t_{major} = 54.37 min, t_{minor} = 59.30 min). $[\alpha]_D$ = -40.1 (*c* = 2.1 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.0 Hz, 2H), 7.47 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.97 (dd, *J* = 8.0, 1.6 Hz, 1H), 5.31 (d, *J* = 5.6 Hz, 1H), 5.13 (d, *J* = 5.6 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 142.5, 141.6, 141.1, 139.8, 129.8, 125.1, 125.0, 115.9, 114.6, 98.7, 58.1, 55.9, 21.3; IR (KBr) 3007, 2994, 2963, 2932, 2901, 2837, 2819, 1578, 1491, 1477, 1468, 1435, 1395, 1296, 1265, 1229, 1207, 1175, 1155, 1069, 1045, 962 cm^{-1}; HRMS (EI) for $C_{16}H_{18}O_4S$ calcd 306.0926 (M^+), found 306.0923; Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92; N, 0.00. found: C, 63.01; H, 5.99; N, 0.00.

4-Methoxy-1-(methoxymethoxy)-2-[(4-methylphenyl)sulfinyl]benzene (20g) Compound **20g** was followed by general procedure for Sharpless asymmetric oxidation of aryl sulfide using aryl sulfide **15g** (0.200 g, 0.689 mmol), L-DET (0.24 mL, 1.38 mmol), Ti(O-*i*-Pr)$_4$ (0.20 mL, 0.689 mmol), 80% CHP (0.14 mL, 0.758 mmol) in dry CH_2Cl_2 (3.0 mL). L-DET was eliminated by short column chromatography on activated alumina using hexane/EtOAc (7: 3), then the mixture was purified by column chromatography on silica gel using hexane/EtOAc (7: 3) to give the product **20g** (0.0905 g, 43%, 8.6% e.e.) as a white solid. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: *i*-PrOH = 90: 10, 0.75 mL/min, 250 nm, t_{major} = 48.09 min, t_{minor} = 55.83 min). $[\alpha]_D$ = +2.4 (*c* = 1.2 in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.50 (d, *J* = 3.2 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.89 (dd, *J* = 8.8, 3.2 Hz, 1H), 5.07 (d, *J* = 6.8 Hz, 1H), 5.00 (d, *J* = 6.8 Hz, 1H), 3.84 (s, 3H), 3.31 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.4, 146.9, 142.3, 141.5, 134.8, 129.7, 125.6, 118.2, 116.1, 108.4, 95.0, 56.1, 56.0, 21.4; IR (KBr) 2951, 2926, 2895, 2832, 1589, 1489, 1474, 1441, 1319, 1267, 1209, 1196, 1161, 1140, 1088, 1057, 1040, 1024, 982 cm^{-1}; HRMS (EI) for $C_{16}H_{18}O_4S$ calcd 306.0926 (M^+), found 306.0933; Anal. Calcd for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92; N, 0.00. found: C, 63.01; H, 5.94; N, 0.00.

2.9a *MOM deprotection*: *2-Methyl-6-[(R)-methylsulfinyl]phenol (R-7b)*[49]: 10% HCl aq. (6.9 mL, 18.9 mmol) was added dropwise to the solution of sulfoxide ***R-9b*** (0.387 g, 1.80 mmol, 94% e.e.) in EtOH (5 mL) at 0 °C. The solution was allowed to stir at room temperature for 16 h. The reaction mixture was extracted with EtOAc (25 mL × 2) and the organic layer washed with brine, dried over Na_2SO_4 and concentrated. The reaction mixture was purified by column chromatography on silica gel using hexane/EtOAc (1: 1) to give the product ***R-7b*** (0.280 g, 91%, 94% e.e.) as colorless oil. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 96: 4, 0.75 mL/min, 250 nm, t_{major} = 22.19 min, t_{minor} = 30.05 min). $[\alpha]_D$ = +114 (*c* = 1.0 in $CHCl_3$); HRMS (EI) for $C_8H_{10}O_2S$ calcd 170.0402 (M^+), found 170.0407.

2.9b *Iodination of aromatic ring*: *4-Iodo-2-methyl-6-[(R)-methylsulfinyl]phenol (R-10)* NaOH (0.605 g, 15.1 mmol) and NaI (2.21 g, 14.8 mmol) were added to the solution of *o*-hydroxy Aryl sulfoxide ***R-7b*** (2.04 g, 12.0 mmol, 92% e.e.) in THF (50 mL). 5% NaClO (11 mL, 7.39 mmol) was added dropwise at 0 °C, and then the mixture was allowed to stir at 0 °C for 30 min. The reaction mixture was quenched with 10% $Na_2S_2O_3$ and prepared to pH 6–7 using 10% HCl at 0 °C. The mixture was extracted with EtOAc (25 mL × 2), the organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The reaction

mixture was purified by recrystallization using hexane-EtOAc to give the product ***R-10*** (2.27 g, 64%, > 99% e.e.) as a colorless crystal. The enantiomeric excess was determined by chiral HPLC (DAICEL CHIRALPAK IF, hexane: EtOH = 96: 4, 1.00 mL/min, 250 nm, t_{major} = 18.14 min, t_{minor} = 24.96 min). M.p.: 155–158 °C; $[\alpha]_D$ = +178 (c = 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.5 (s, 1H), 7.53 (d, J = 2.0 Hz, 1H), 7.18 (d, J = 2.0 Hz, 1H), 2.95 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.6, 142.1, 131.7, 130.4, 124.0, 80.2, 41.7, 15.0; IR (KBr) 2920, 1465, 1414, 1340, 1260, 1215, 1016 cm^{-1}; HRMS (EI) for $C_8H_9O_2SI$ calcd 295.9368 (M^+), found 295.9389; Anal. Calcd for $C_8H_9O_2SI$: C, 32.45; H, 3.06; N, 0.00. found: C, 32.74; H, 3.11; N, 0.00.

3. Results and Discussion

3.1 *Sharpless asymmetric oxidation of ortho-alkoxy aryl sulfides*

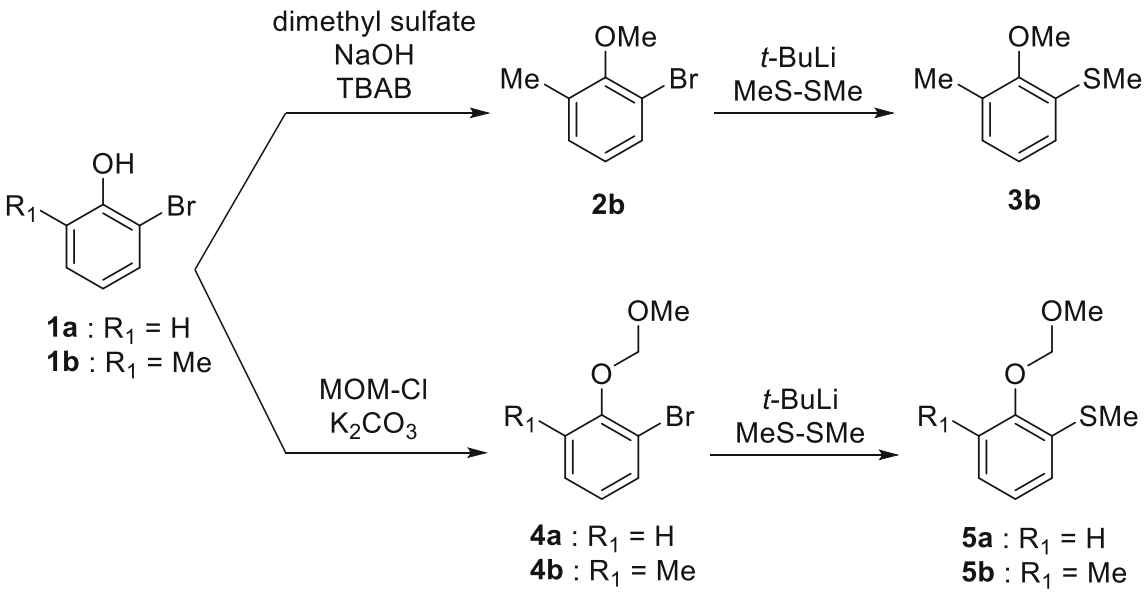
The aryl sulfides, **3** and **5**, which are starting materials used for Sharpless asymmetric oxidation reactions, were synthesized with methylsulfide after protecting the hydroxy group at ortho position by methyl or methoxymethyl (MOM) groups (Scheme 2).[50]

Sharpless asymmetric oxidation reactions were performed to evaluate enantioselectivity by reacting sulfide/Ti(O-*i*-Pr)$_4$/DET at 1/1/2 ratio. For these reactions, CHP was used as the oxidant in CH_2Cl_2 (Table 1). It was reported by Kagan *et al.*, that aryl sulfoxide compounds having hydroxyl group at the para position showed 50% e.e.,[20] but few enantioselective syntheses using Sharpless asymmetric oxidation have been reported for aryl sulfoxides containing functional group at the ortho position, and reproducible high enantioselectivity has not been yet achieved. We initially evaluated the oxidation reaction with a commercially available compound **6a** with phenolic hydroxyl group at ortho position. However, the yield was poor with a low enantioselectivity (Entry 1–2).

Subsequently, we evaluated Sharpless asymmetric oxidation on the compounds **3a** and **3b** with protected phenolic hydroxyl function at ortho position with a methyl group. Sharpless oxidations method typically requires a small amount of water[20–22] but we discovered that the enantioselectivity was higher when no water was added during the reaction (Entry 3–6). Although the enantioselectivity was quite high, deprotection of the methyl groups is generally very difficult. Therefore, we examined aryl sulfoxide compound **5a** and **5b** which are protected with MOM. The compound **5a** and **5b** resulted in higher enantioselectivity than those of **3a** and **3b**, and the presence/absence of water also affected the result the same way (Entry 7–10).

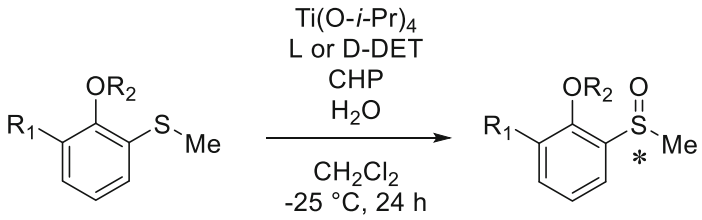
Compound **5b**, which showed the highest enantioselectivity, was used to synthesize the enantiomer using a chiral ligand D-DET (Entry 11).

In conclusion, protecting the phenolic hydroxyl group and having anhydrous condition for the oxidation are found to be important to achieve high enantioselectivity by Sharpless asymmetric oxidation for the ortho-substituted aryl sulfides.



Scheme 2. Syntheses of aryl sulfides **3b** and **5a-b**.

Table 1. Sharpless asymmetric oxidation of **3a–b**, **5a–b** and **6a**.[a]

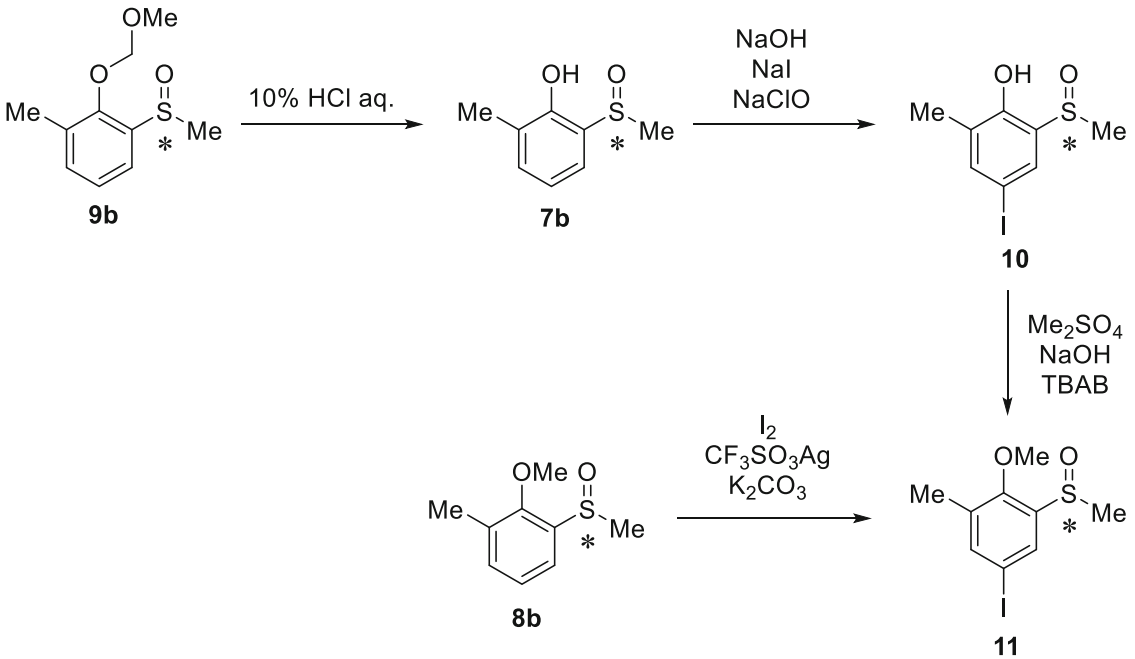


6a : R_1 = H, R_2 = H
3a : R_1 = H, R_2 = Me
3b : R_1 = Me, R_2 = Me
5a : R_1 = H, R_2 = MOM
5b : R_1 = Me, R_2 = MOM

7a : R_1 = H, R_2 = H
8a : R_1 = H, R_2 = Me
8b : R_1 = Me, R_2 = Me
9a : R_1 = H, R_2 = MOM
9b : R_1 = Me, R_2 = MOM

Entry	Sulfoxide	Ligand	H_2O (eq.)	Yield (%)[b]	e.e. (%)[c]	Config.
1	**7a**	L-DET	1.0	51	3.1	*R*[47]
2	**7a**	L-DET	0	61	4.3	*R*[47]
3	**8a**	L-DET	1.0	> 99	83	*R*[48]
4	**8a**	L-DET	0	> 99	91	*R*[48]
5	**8b**	L-DET	1.0	88	79	*R*
6	**8b**	L-DET	0	88	89	*R*
7	**9a**	L-DET	1.0	87	86	*R*
8	**9a**	L-DET	0	> 99	91	*R*
9	**9b**	L-DET	1.0	97	87	*R*
10	**9b**	L-DET	0	99	94	*R*
11	**9b**	D-DET	0	94	93	*S*

[a]Reaction condition: aryl sulfide/Ti(O-*i*-Pr)$_4$/DET/CHP = 1: 1: 2: 1.1.
[b]Isolated yield with column flash chromatography.
[c]Determined by HPLC analyses on CHIRALPAK IF or CHIRALPAK AY-3.



Scheme 3. Syntheses of compounds **10** and **11** for determination of absolute configuration.

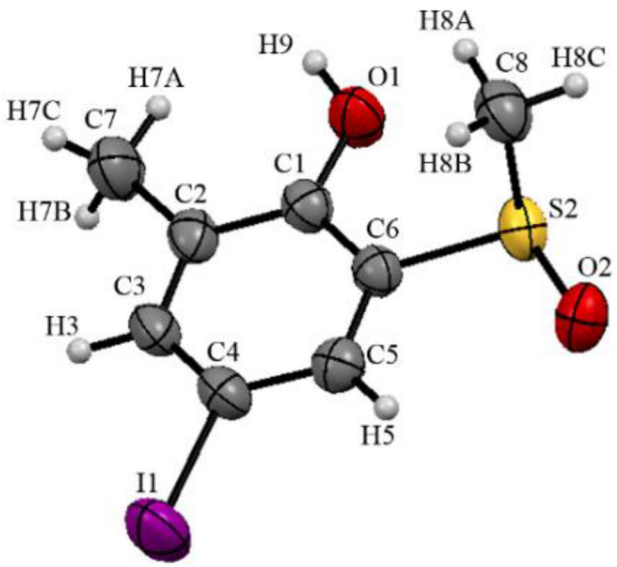


Figure 2. X-ray crystal structure analysis of compound ***R-10***.

The compound **9b** which was synthesized by Sharpless asymmetric oxidation was transformed to compound **10** (Scheme 3) via deprotection of MOM group and the iodization. The resulting material was analyzed by X-ray single-crystal diffraction analysis to confirm the absolute configuration. The crystal structure confirmed that the absolute configuration of compound **10**, which was synthesized from compound **9b** using L-DET as a chiral ligand, is *R* (Figure 2). This showed that enantioselective synthesis from compound **5b** is possible by selecting L-DET (to form *R* enantiomer) or D-DET (to form *S* enantiomer) in the Sharpless asymmetric oxidation. The absolute configuration of **8b** was confirmed after it was converted to **11** and analyzing it by chiral HPLC and optical rotation, and by comparing the data to the compound **11** obtained from compound **10** whose absolute stereochemistry is known. The absolute configuration of **9a** was confirmed by converting it to **7a**, whose stereochemistry has been reported, by performing chiral HPLC and optical rotation analyses.[48]

3.2 *Effects of substituents combinations on the sulfide and the aromatic ring for Sharpless asymmetric oxidations*

In the previous chapter, it was shown that protecting the phenolic hydroxyl group with MOM groups helped to achieve high enantioselectivity during Sharpless asymmetric oxidation reactions. To evaluate the effectiveness of substituents, various substituent combinations in the aromatic ring and the sulfide group were evaluated.

For the sulfide, methyl (Me), ethyl (Et), isopropyl (*i*-Pr), *tert*-butyl (*t*-Bu), and para-tolyl (*p*-Tol) substituents were evaluated. For the aromatic ring, methyl

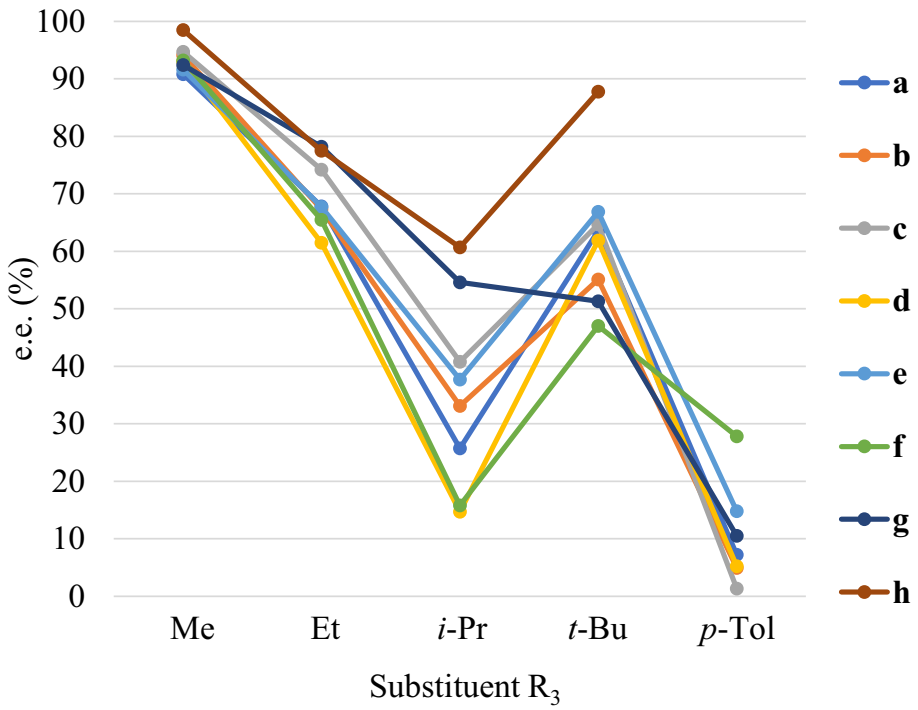
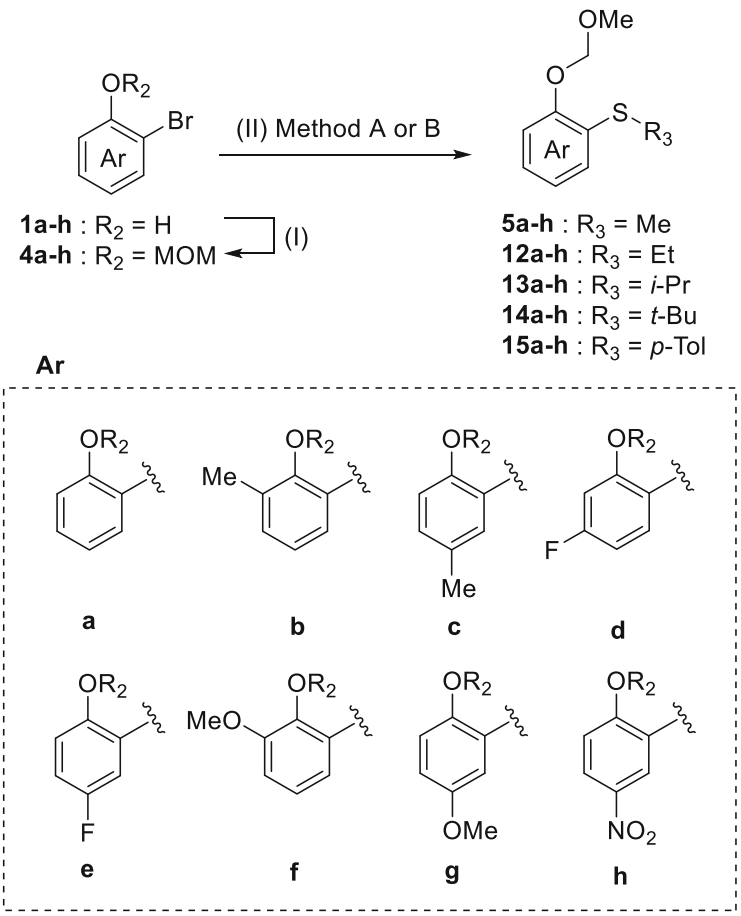
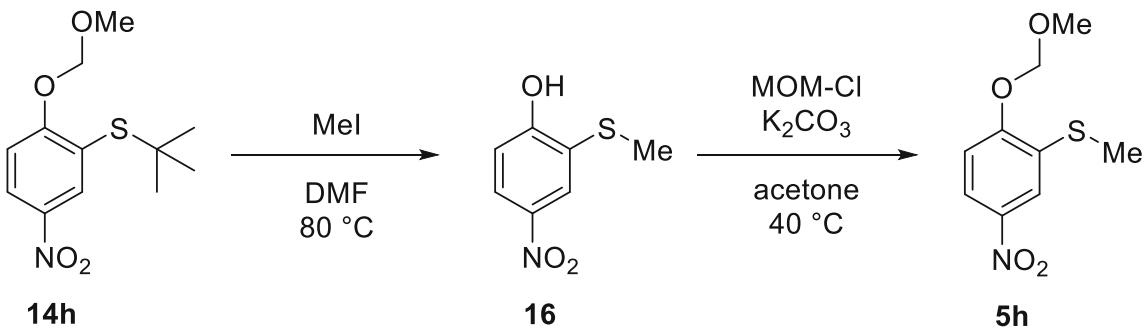


Figure 3. The effect of the sulfoxide substituents on enantioselectivity in Sharpless asymmetric oxidation.



Reagents and conditions: (I) K_2CO_3, MOM-Cl, acetone, 40 °C; (II) Method A : *t*-BuLi, R_3S-SR_3, Et_2O, -78 °C to r.t.; Method B-1 : *t*-BuONa, *t*-BuSH, cat. $Pd_2(dba)_3$, cat. xantphos, xylene, reflux; Method B-2 : *i*-Pr_2NEt, R_3SH, cat. $Pd_2(dba)_3$, cat. xantphos, 1,4-dioxane, 70-80 °C; Method B-3 : MeSNa, cat. $Pd_2(dba)_3$, cat. xantphos, 1,4-dioxane, reflux.

Scheme 4. Syntheses of aryl sulfides **5** and **12–15** with various substituents on aromatic ring.



14h **16** **5h**

Scheme 5. Synthesis of aryl sulfide **5h**.

and methoxy substituents were evaluated as electron-donating groups, fluoro, nitro, methyl-ester, and aldehyde substituents were evaluated as electron-withdrawing groups.

The starting materials for Sharpless asymmetric oxidations, **5** and **12–15** (Scheme 4), were obtained by a two-step synthesis as follows: The phenolic hydroxyl group on bromophenol was protected with a methoxymethyl, followed by a nucleophilic substitution reaction with *t*-BuLi and disulfide (Method A),[50] or a coupling reaction with Pd and xantphos (Method B)[51,52] to add the sulfide substituent to the aromatic

Table 2. The effect of substituents on enantioselectivity in Sharpless asymmetric oxidation.

Sulfoxide	R_3	Yield (%)[a]	e.e. (%)[b]	$[\alpha]^{25}_D$ (in $CHCl_3$)
9a	Me	> 99	91	+269.3 (*c* = 2.3)
17a	Et	88	68	+215.3 (*c* = 3.2)
18a	*i*-Pr	79	26	+81.3 (*c* = 3.1)
19a	*t*-Bu	78	64 (98)[c]	+160.1[d] (*c* = 3.1)
20a	*p*-Tol	30	7.2	+12.1 (*c* = 1.1)
9b	Me	99	94	+242.0 (*c* = 1.0)
17b	Et	85	67	+215.5 (*c* = 3.6)
18b	*i*-Pr	80	33	+103.8 (*c* = 3.6)
19b	*t*-Bu	50	55	+146.0 (*c* = 1.6)
20b	*p*-Tol	42	4.9	−12.4 (*c* = 1.9)
9c	Me	83	95	+213.2 (*c* = 1.5)
17c	Et	> 99	74	+191.4 (*c* = 1.5)
18c	*i*-Pr	75	41	+85.6 (*c* = 1.9)
19c	*t*-Bu	68	65 (> 99)[c]	+189.8[d] (*c* = 1.2)
20c	*p*-Tol	31	1.3	+2.9 (*c* = 1.1)
9d	Me	87	93	+235.8 (*c* = 1.4)
17d	Et	94	62	+179.3 (*c* = 2.6)
18d	*i*-Pr	98	15	+35.7 (*c* = 2.0)
19d	*t*-Bu	77	62 (87)[c]	+94.1[d] (*c* = 1.4)
20d	*p*-Tol	51	5.2	+9.7 (*c* = 1.9)
9e	Me	91	92 (> 99)[c]	+249.0[d] (*c* = 3.1)
17e	Et	> 99	68	+177.4 (*c* = 4.1)
18e	*i*-Pr	82	38	+108.9 (*c* = 1.6)
19e	*t*-Bu	61	67	+149.6 (*c* = 1.4)
20e	*p*-Tol	18	15 (20)[c]	+35.4[d] (*c* = 1.0)
9f	Me	72	93	+159.0 (*c* = 1.4)
17f	Et	64	66	+131.5 (*c* = 2.1)
18f	*i*-Pr	68	16	+25.5 (*c* = 1.5)
19f	*t*-Bu	44	47 (68)[c]	+77.8[d] (*c* = 1.1)
20f	*p*-Tol	14	28	-40.1 (*c* = 2.1)
9g	Me	99	92	+195.4 (*c* = 1.5)
17g	Et	92	78	+159.8 (*c* = 2.1)
18g	*i*-Pr	60	55	+130.6 (*c* = 1.5)
19g	*t*-Bu	78	51 (97)[c]	+171.4[d] (*c* = 1.1)
20g	*p*-Tol	43	11	+2.4 (*c* = 1.2)
9h	Me	91	99 (> 99)[c]	+200.0[d] (*c* = 1.1)
17h	Et	97	78	+177.7 (*c* = 1.8)
18h	*i*-Pr	85	61	+136.8 (*c* = 1.3)
19h	*t*-Bu	82	88	+157.0 (*c* = 1.7)

[a]Isolated yield via column flash chromatography

[b]Determined by HPLC analyses on CHIRALPAK IF or CHIRALPAK AY-3

[c]Enantiomeric excess (e.e.) after one recrystallization

[d]Specific rotation after one recrystallization.

ring, with one exception (compound **5h**).[53] The substitution reaction cleaved the MOM group from **14h**, and therefore the MOM protection step was added after the sulfide group was added (Scheme 5).

The same reaction method was used for the Sharpless asymmetric oxidation with aryl sulfides **5** and **12–15**, and the results are summarized in Table 2. The yield and measured enantioselectivity (e.e.) are listed within. No Sharpless oxidation was observed for **15h**, *p*-Tol nitro-substituted compounds.

The results showed that the yield from the Sharpless oxidation is related to the size of the substituent (R_3) on the sulfide where the larger substituents lead to lower yields (Table 2). The e.e. data also showed the same tendency when R_3 was Me, Et, or *i*-Pr, except for *t*-Bu substituent on sulfide showed much better e.e. than materials with *i*-Pr. It was an interesting result since *t*-Bu group is larger than *i*-Pr (Figure 3). However, there was one exception that **19g** (*t*-Bu), which has a methoxy group on the aromatic ring, had a

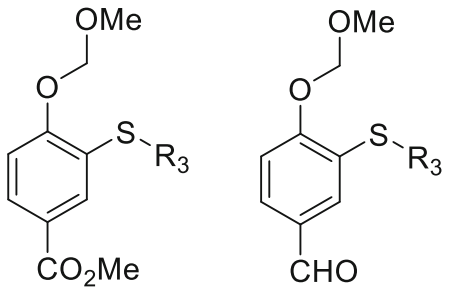


Figure 4. Structure of aryl sulfides **5i**, **j** and **14i**, **j**.

slightly lower e.e. than **18g** (*i*-Pr). On the contrary, **19h** (*t*-Bu), which had a nitro substituent on the aromatic ring showed quite a high e.e., even exceeding that of **17h** (Et). The starting materials with *p*-Tol substituents showed poor enantioselectivity. However, high enantioselectivity was reported for Sharpless asymmetric oxidation of nitrophenyl pyrrolyl sulfides,[54] therefore, it may be possible to achieve higher enantioselectivity for compounds **20a-h** with a nitro group in the *p*-Tol substituent. Since Sharpless oxidation didn't work for **15h**, this requires further investigation.

Comparing the substituents on the sulfide, it appeared that higher e.e. was achieved with electron-withdrawing groups on aryl ring compared to electron-donating groups. Therefore, two additional electron-withdrawing substituents, methyl-ester (**i**) and aldehyde (**j**), were added to evaluate their impact on enantioselectivity.

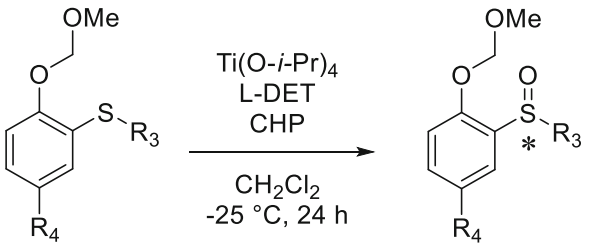
The synthesis of **5i**, **j** and **14i**, **j** was achieved using the same methods employed for **5** and **12–15** (Figure 4). Even though a nucleophilic addition reaction can easily occur to the ester substituent, **9i** and **19i** were obtained without a problem. Also, the aldehyde substituent can easily undergo nucleophilic addition reactions and oxidation reactions, but there were no issues with obtaining **9j** and **19j**. As expected, both **i** and **j** showed high enantioselectivity (Table 3).

3.3 *Evaluation of Other Chiral Ligands*

Throughout our study thus far, L-DET was used as the chiral ligand, but when R_3 on the sulfide was *i*-Pr group, high enantioselectivity was not observed. Therefore, we evaluated other ligands which are similar to L-DET and having high steric hindrance.

Di-*tert*-butyl tartrate (DTBT), dibenzyl tartrate (DBT), and *N*,*N*'-dibenzyl tartrate diamide (DBTDA)

Table 3. The effect of ester (**i**) and aldehyde (**j**) on enantioselectivity in Sharpless asymmetric oxidation.



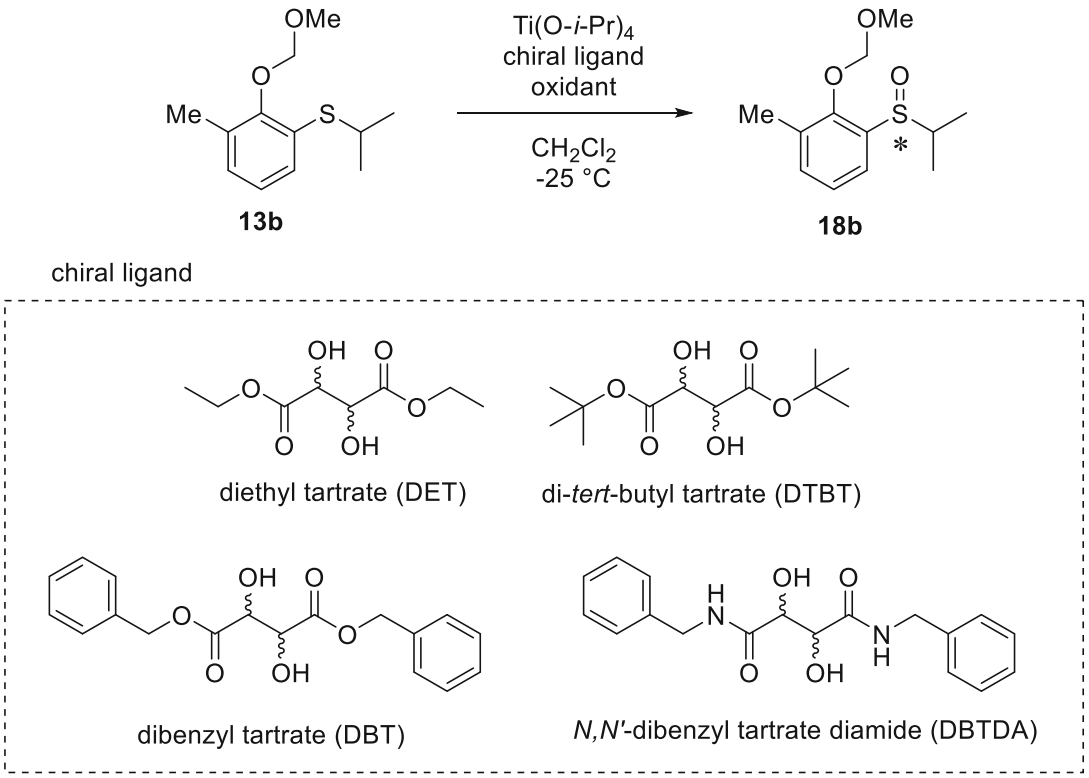
5i : R_3 = Me, R_4 = CO_2Me
14i : R_3 = *t*-Bu, R_4 = CO_2Me
5j : R_3 = Me, R_4 = CHO
14j : R_3 = *t*-Bu, R_4 = CHO

9i : R_3 = Me, R_4 = CO_2Me
19i : R_3 = *t*-Bu, R_4 = CO_2Me
9j : R_3 = Me, R_4 = CHO
19j : R_3 = *t*-Bu, R_4 = CHO

Compd.	R_3	Yield (%)[a]	e.e. (%)[b]	$[\alpha]^{25}_D$ (in $CHCl_3$)
9i	Me	> 99	96 (> 99)[c]	+178.0[d] (*c* = 1.3)
19i	*t*-Bu	54	87 (> 99)[c]	+173.2[d] (*c* = 1.2)
9j	Me	84	94 (> 99)[c]	+203.5[d] (*c* = 1.2)
19j	*t*-Bu	> 99	76	+143.0 (*c* = 4.0)

[a]Isolated yield with column flash chromatography.
[b]Determined by HPLC analyses on CHIRALPAK IF or CHIRALPAK AY-3.
[c]Enantiomeric excess (e.e.) after one recrystallization.
[d]Specific rotation after one recrystallization.

Table 4. The effect of bulky chiral ligands on enantioselectivity in Sharpless asymmetric oxidation.



Entry	Ligand	Oxidant	Yield (%)[a]	e.e. (%)[b]
1	L-DET	CHP	80	33
2	L-DET	TBHP	92	31
3	L-DTBT	CHP	56	56
4	L-DTBT	TBHP	50	53
5	D-DBT	CHP	98	4.3
6	D-DBT	TBHP	> 99	9.0
7	L-DBTDA	CHP	13	1.5
8	L-DBTDA	TBHP	10	0

[a]Isolated yield with column flash chromatography

[b]Determined by HPLC analyses on CHIRALPAK IF

were evaluated to see whether these ligands would afford high enantioselectivity (Table 4). For the Sharpless asymmetric oxidation reactions, *tert*-butyl hydroperoxide (TBHP) was used as oxidants in addition to CHP to determine the impact of TBHP in the reactions.

Initially, aryl sulfide **13b** were evaluated and the results are summarized in Table 4. When DTBT was used as the ligand, e.e. was improved by more than 20%, but e.e. of 56% is not high compared to other sulfide alkyl substitution compounds (R_3 = Me, Et, *t*-Bu). DBT showed nearly no enantioselectivity although the yield was quite high. On the other hand, extremely poor yield was obtained with DBTDA with no enantioselectively. Between the two oxidants CHP and TBHP, little difference was observed in terms of yield.

4. Conclusions

Simple asymmetric syntheses of various aryl sulfoxides containing ortho-oxygen substituents are accomplished by optimizing Sharpless oxidation conditions for the first time. Reproducible higher enantioselectivity of the Sharpless oxidation was observed under anhydrous reaction conditions which were unexpected since Sharpless asymmetric oxidation typically

requires a small amount of water. Moreover, the enantioselectivity (e.e.) of the oxidation of the aryl sulfoxide was further improved when an electron-withdrawing group was present on the aromatic ring of the aryl sulfoxide. The success of asymmetric synthesis was confirmed by determining the absolute configuration of one of the products (compound **10)** by X-ray single-crystal diffraction. The yield of the Sharpless oxidation was in general higher when the size of the alkyl substituent R_3 on the sulfide was smaller. For the e.e., high enantioselectivity was observed when R_3 was methyl group regardless of the substituent on the aromatic ring, and the result is in agreement with Kagan's data reported previously.[55] Moreover, the e.e. results followed the same trend with the yields, except when R_3 was *t*-Bu, the e.e. was much higher than *i*-Pr. One of the cases, however, showed slightly better e.e. with *i*-Pr, was when the aromatic ring contained a methoxy group (**18g** with *i*-Pr exhibited slightly higher e.e. than **19g** with *t*-Bu). The effect of the substituents on the aromatic ring was further investigated and it was discovered that a higher e.e. can be achieved when substituent R_4 on the aromatic ring is an electron-withdrawing substituent compared to electron-donating substituents. In addition to DET, three other ligands (DTBT, DBT, DBTDA) were investigated for the Sharpless oxidation of compound **13b**. Of four ligands evaluated, DTBT showed 20% improvement in e.e. Based on this result, a possibility that bulkier non-aromatic ligands may offer better enantioselectivity was suggested.

Supplementary Information (SI)

Crystallographic data for the structural analysis of compound ***R-10*** has been deposited with the Cambridge Crystallographic Data Centre bearing the CCDC No. 2034188. Copies of this information are available on request at free of charge from CCDC, Union Road, Cambridge, CB21EZ, UK (fax: +44-1223-336-03; e-mail: deposit@ccdc.ac.uk or http://www.ccdc.cam.ac.uk). ^{1}H NMR and ^{n}C NMR spectra (Figure S1 to S172), HPLC chromatogram (Figure S173 to S222) are available at www.ias.ac.in/chemsci.

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