Synthesis and Evaluation of C2-Symmetric SPIROL-Based *bis*-Oxazoline Ligands

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Abstract: This communication describes the synthesis of new *bis*-oxazoline chiral ligands (SPIROX) derived from the C2-symmetric spirocyclic scaffold (SPIROL). The readily available **(*R,R,R*)-SPIROL (2)** previously developed by our group was subjected to a three-step sequence that provided key diacid intermediate **(*R,R,R*)-7** in 75% yield. This intermediate was subsequently coupled with (*R*)- and (*S*)-phenylglycinols to provide diastereomeric products, the cyclization of which led to two diastereomeric SPIROX ligands **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** in 85% and 79% yield, respectively. The complexation of **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** with CuCl and $Cu(OTf)_2$ resulted in active catalysts that promoted the asymmetric reaction of α-diazopropionate and phenol. The resultant O-H insertion product was formed in 88% yield, and with excellent selectivity (97% ee) when ligand **(*R,R,R,R,R*)-3a** was used.

Keywords: chiral ligands; spirocyclic; asymmetric catalysis; carbenoid; O-H insertion

1. Introduction

For many decades total synthesis has played a vital role in the development of various fields and disciplines related to molecular medicine and drug discovery. The tremendous advances in total synthesis over past several decades would not have been possible without breakthroughs in synthetic methodology and catalysis, and asymmetric catalysis in particular [1,2]. The role chiral catalysts play for chemical synthesis extends far beyond their original use for controlling the enantioselective formation of product, and many modern applications of chiral catalysts are focused on imposing diastereoselectivity [3] and site-selectivity in complex settings [4]. These numerous and diverse applications of chiral catalysts have, in turn, been fueled by the rapidly increasing availability of structurally diverse chiral ligands and new chiral backbones used for the ligand design. In particular, the developments in the design of C2-symmetric spirocyclic ligands has greatly impacted the field of asymmetric catalysis, and thousands of recent studies are focused on exploring such ligands in asymmetric synthesis and catalysis [5–8]. Powered by our long-term interests in chiral phosphoric acid catalysis [9–14], our group has been engaged in the development and exploration of new spiroketal-based C2-symmetric spirocyclic ligands (SPIROLs) [15,16]. Thus, in 2018 we described the one-step asymmetric synthesis of diastereomeric ***(S,S,S)***- and **(*R,S,S*)-SPIROL (2)** cores from the readily available chiral alcohols **(*S*)-1** (Scheme 1A). This operation was ultimately performed on 23 g scale without erosion in yield or selectivity, and the resultant **(*R,S,S*)-2** was elaborated to two diastereomeric sets of ligands exemplified by **(*S,S,S*)-SPIRAP** and **(*R,S,S*)-SPIRAPO**. The ability to access both **(*R,S,S*)-/(*S,R,R*)-** and **(*S,S,S*)-/(*R,R,R*)-**

diastereomeric scaffolds is of significance, and uniquely distinguishes **SPIROL**s from other C2-symmetric spirocyclic scaffolds as these diastereomeric ligands were found to have different profiles in various asymmetric transition metal-catalyzed transformations. Thus, for example, **(*S,S,S*)-SPIRAP** was found to be an excellent ligand for the asymmetric Ir-catalyzed hydroarylation reaction (*cf*. Scheme 1B), while the same reaction with its diastereomer **(*R,S,S*)-SPIRAP** as the ligand did not produce any product [15]. Similarly, **(*R,S,S*)-SPIRAPO** was found to be a superior ligand for the Ir-catalyzed dearomatizative hydrogenation of heterocyclic compounds that was used to accomplish gram-scale synthesis of (–)-(*R*)-angustureine (cf. Scheme 1C). Not only did **(*R,S,S*)-SPIRAPO** consistently outperform other, more established types of ligands (i.e., **BINOL**s, **H8-BINOL**s, **SPINOL**, etc.) in these hydrogenation reactions, but it was also found to be superior to its diastereomeric equivalent, **(*S,S,S*)-SPIRAPO** [16].

With these observations in mind, this article described the synthesis and exploration of chiral SPIROL-based ligands **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** (*cf*. Scheme 1D). We discovered that these diastereomeric ligands could be efficiently generated in five steps from the common precursor **(*R,R,R*)-SPIROL (2).** The subsequent side-by-side evaluation of **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** as ligands in Cu(I)-catalyzed phenol OH insertion with diazoesters revealed that the use of **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** leads to opposite enantioselectivities for the formation of **4**. In addition, we discovered that ligand **(*R,R,R,R,R*)-3a** used in combination with Cu(I) chloride results in highly efficient and enantioselective formation of **4** (88% yield, 97% ee).

2. Materials and Methods

The general information about reagents and equipment and the copies of ^{1}H and ^{13}C NMR spectra for compounds 2–8 and HPLC traces for chiral product 4 are provided in Supplementary Information.

(1*R*,3*R*,3'*R*)-3,3'-diethyl-3*H*,3'*H*-1,1'-spirobi[isobenzofuran]-7,7'-diyl bis(trifluoromethanesulfonate) ((*R,R,R*)-5)

Enantiopure **(*R,R,R*)-SPIROL (2) [15,16]** (500.0 mg, 1.60 mmol, 1.0 equiv.) and pyridine (2.85 mL, 37.8 mmol, 23.6 equiv.) were dissolved with DCM (25.0 mL) in a dry, round-bottom flask under nitrogen and cooled to 0 °C. Trifluoromethanesulfonic anhydride (2.68 mL, 16.0 mmol, 10.0 equiv.) was added to the solution with a syringe over 30 min at 0 °C. The reaction mixture was then warmed to room temperature with stirring. After 2 h, a saturated aqueous solution of $NaHCO_3$ (25.0 mL) was added. After separating layers, the aqueous phase was extracted with DCM (2 × 15.0 mL). Combined organic was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by the column chromatography (SiO_2, 10% EtOAc in hexanes) to afford the product as a slight yellow oil (895 mg, 97%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 (t, *J* = 7.9 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.23 (d, *J* = 8.2 Hz, 2H), 5.38 (dd, *J* = 7.3, 4.6 Hz, 2H), 2.05 – 1.84 (m, 4H), 1.05 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 147.4, 144.8, 132.1, 130.3, 121.2, 119.6, 118.9 (q, *J* = 320.1 Hz, CF_3), 114.5, 84.8, 30.1, 9.5. **^{19}F NMR** (471 MHz, $CDCl_3$) δ −74.6. **ESI-HRMS** Calcd. for $C_{21}H_{19}F_6O_8S_2^+$ 577.0426 $[M + H]^+$, found 577.0418. **IR** (film): ν_{max} = 2973, 2880, 1470, 1422, 1207, 1137, 935, 852, 749 cm^{-1}. **$[\alpha]_D$**: +3.2 (c = 1.0 in $CHCl_3$).

Dimethyl (1*R*,3*R*,3'*R*)-3,3'-diethyl-3*H*,3'*H*-1,1'-spirobi[isobenzofuran]-7,7'-dicarboxylate ((*R,R,R*)-6)

(*R,R,R*)-5 (894.8 mg, 1.55 mmol, 1.0 equiv.), $Pd(OAc)_2$ (35.9 mg, 0.16 mmol, 0.1 equiv.), and 1,3-bis(diphenylphosphino)propane (66.0 mg, 0.16 mmol, 0.1 equiv.) were added to a dry, round-bottom flask in the glovebox and then carried outside. Distilled triethylamine (3.80 mL), methanol (9.40 mL), and DMSO (15.00 mL) were added to the flask at room temperature, and the reaction atmosphere was then carefully purged with CO balloon. The reaction mixture was heated to and maintained at reflux for overnight. After TLC indicated a full consumption of the starting material, the reaction mixture was cooled to room temperature and concentrated to approximately half of its volume. The crude product was purified by column chromatography (SiO_2, 20% EtOAc in hexanes) to afford the product as white solids (479 mg, 78%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.94 (dd, *J* = 7.1, 1.8 Hz, 2H), 7.51 – 7.43 (m, 4H), 5.22 (dd, *J* = 7.7, 4.1 Hz, 2H), 3.29 (s, 6H), 2.06 – 1.85 (m, 4H), 1.09 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.8, 145.2, 140.2, 130.5, 128.7, 125.6, 125.0, 118.3, 84.2, 51.4, 30.4, 9.9. **ESI-HRMS** Calcd. for $C_{23}H_{25}O_6^+$ 397.1645 $[M + H]^+$, found 397.1640. **IR** (powder): ν_{max} = 2965, 2936, 2876, 1717, 1456, 1433, 1297, 1263, 1196, 1144, 1007, 923, 747 cm^{-1}. **$[\alpha]_D$**: –89 (c = 2.0 in $CHCl_3$).

(1*R*,3*R*,3'*R*)-3,3'-diethyl-3*H*,3'*H*-1,1'-spirobi[isobenzofuran]-7,7'-dicarboxylic acid ((*R,R,R*)-7)
Ester **(*R,R,R*)-6** (479.1 mg, 1.21 mmol, 1.0 equiv.), 30% KOH aqueous solution (3.00 mL), and MeOH (3.00 mL) were added to a round-bottom flask, and the reaction mixture was heated to 80 °C. After TLC indicated a full conversion, the reaction mixture was cooled to room temperature and concentrated to half of its volume. 1M HCl was slowly added to the reaction mixture until the solution pH was around 5–6, and then DCM (15.0 mL) was added to the mixture. After separating layers, the aqueous phase was extracted with DCM (4 × 15.0 mL). Combined organic was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 5% MeOH in DCM) to afford the product as a white solid (445 mg, 99%). **^{1}H NMR** (400 MHz, CD_3OD) δ 7.85 (dd, *J* = 6.2, 2.6 Hz, 2H), 7.57 – 7.36 (m, 4H), 5.18 (dd, *J* = 7.6, 3.9 Hz, 2H), 1.96 (ddq, *J* = 11.0, 7.6, 3.8 Hz, 2H), 1.83 (dt, *J* = 14.3, 7.3 Hz, 2H), 1.02 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (100 MHz, CD_3OD) δ 167.2, 145.4, 140.2, 129.8, 128.5, 126.2, 124.7, 118.6, 84.3, 29.7, 8.9. **ESI-HRMS** Calcd. for $C_{21}H_{20}O_6Na^+$ 391.1152 $[M + Na]^+$, found 391.1158. **IR** (powder): ν_{max} = 3021(br), 2964, 2926, 2876, 2654, 1703, 1601, 1459, 1264, 1194, 1011, 928, 758 cm^{-1}**. $[\alpha]_D$**: –42 (c = 0.20 in $CHCl_3$).

(1*R*,3*R*,3'*R*)-3,3'-diethyl-*N*^{7},*N*$^{7'}$-bis((*R*)-2-hydroxy-1-phenylethyl)-3*H*,3'*H*-1,1'-spirobi[isobenzofuran]-7,7'-dicarboxamide ((*R,R,R,R,R*)-8a)
(*R,R,R*)-7 (130.0 mg, 0.35 mmol, 1.0 equiv.), (*R*)-(-)-2-phenylglycinol (288.1 mg, 2.10 mmol, 6.0 equiv.), 1-hydroxybenzotriazole hydrate (222.2 mg, 1.65 mmol, 4.7 equiv.), and EDCI (332.4 mg, 2.14 mmol, 6.1 equiv.) were added to a round-bottom flask under nitrogen. Dry THF (15.0 mL) was added to the flask and cooled to 0 °C. After 1 h, the reaction mixture was spontaneously warmed to room temperature and stirred overnight. After TLC indicated a full conversion, the reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, 5% MeOH in DCM) to afford the product as a white solid (208 mg, 98%). **^{1}H NMR** (700 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.29 (dd, *J* = 8.1, 6.3 Hz, 4H), 7.06 (dd, *J* = 7.0, 1.9 Hz, 4H), 7.00 (d, *J* = 6.5 Hz, 2H), 4.97 (dd, *J* = 8.1, 4.9 Hz, 2H), 4.65 (td, *J* = 6.8, 3.7 Hz, 2H), 3.49 (dd, *J* = 11.4, 3.8 Hz, 2H), 3.35 (dd, *J* = 11.4, 6.9 Hz, 2H), 1.98 – 1.86 (m, 4H), 1.06 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 168.2, 145.4, 137.9,

135.3, 131.5, 129.7, 128.7, 128.1, 127.9, 126.9, 123.4, 84.2, 66.3, 56.6, 30.6, 10.4. **ESI-HRMS** Calcd. for $C_{37}H_{39}N_2O_6^+$ 607.2803 $[M + H]^+$, found 607.2790. **IR** (powder): ν_{max} = 3327(br), 3062, 2966, 2934, 2875, 2244, 1643, 1521, 1453, 1340, 1268, 1007, 906, 726 cm^{-1}. **$[\alpha]_D$**: +40 (c = 0.30 in $CHCl_3$).

(1*R*,3*R*,3'*R*)-3,3'-diethyl-*N*^{7},*N*$^{7'}$-bis((*S*)-2-hydroxy-1-phenylethyl)-3*H*,3'*H*-1,1'-spirobi[isobenzofuran]-7,7'-dicarboxamide ((*R,R,R,S,S*)-8b)

(*R,R,R,S,S*)-8b was obtained as a white solid (213 mg, 99%) using the above-described coupling of **(*R,R,R*)-7** (130.0 mg, 0.35 mmol, 1.0 equiv.) and (*S*)-(-)-2-phenylglycinol (288.5 mg, 2.10 mmol, 6.0 equiv). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.49 (m, 4H), 7.38 (d, *J* = 7.6 Hz, 4H), 7.27 – 7.19 (m, 6H), 6.88 (d, *J* = 6.9 Hz, 2H), 4.53 (td, *J* = 5.8, 3.4 Hz, 2H), 4.42 (dd, *J* = 8.4, 4.6 Hz, 2H), 3.93 – 3.86 (m, 2H), 3.71 (dt, *J* = 11.5, 5.7 Hz, 2H), 3.44 – 3.36 (m, 2H), 1.96 – 1.77 (m, 4H), 1.01 (t, *J* = 7.4 Hz, 6H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 168.3, 146.0, 138.8, 135.3, 131.3, 129.6, 128.8, 128.1, 127.4, 127.1, 124.1, 84.1, 65.9, 56.7, 30.3, 10.4. **ESI-HRMS** Calcd. for $C_{37}H_{39}N_2O_6^+$ 607.2803 $[M + H]^+$, found 607.2797. **IR** (powder): ν_{max} = 3259(br), 3062, 2964, 2925, 2875, 1644, 1598, 1534, 1454, 1359, 1270, 1214, 1053, 1008, 933, 747 cm^{-1}. **$[\alpha]_D$**: +87 (c = 0.10 in $CHCl_3$).

(4*R*,4'*R*)-2,2'-((1*R*,3*R*,3'*R*)-3,3'-diethyl-3*H*,3'*H*-1,1'-spirobi[isobenzofuran]-7,7'-diyl)bis(4-phenyl-4,5-dihydrooxazole) ((*R,R,R,R,R*)-3a)

A solution of **(*R,R,R,R,R*)-8a** (208.3 mg, 0.34 mmol, 1.0 equiv.) and DMAP (4.4 mg, 0.034 mmol, 10 mol%) in dry DCM (20.0 mL) was cooled to 0 °C under nitrogen. Distilled triethylamine (0.20 mL) and MsCl (120.0 µL) were added and the solution was stirred at 0 °C for 30 min. Additional triethylamine (1.00 mL) was added, and the reaction mixture was spontaneously warmed to room temperature and stirred overnight. After TLC indicated a full conversion, the reaction mixture was concentrated in vacuo. The crude product was purified by the column chromatography (SiO_2, 6% EtOAc in DCM) to afford the product as white solids (168 mg, 87%). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.27 – 7.17 (m, 8H), 6.97 – 6.92 (m, 4H), 5.17 (dd, *J* = 7.7, 4.2 Hz, 2H), 5.00 (dd, *J* = 10.2, 7.8 Hz, 2H), 3.92 (dd, *J* = 10.2, 8.3 Hz, 2H), 3.81 (t, *J* = 8.3 Hz, 2H), 1.94 (ddq, *J* = 28.8, 14.1, 7.7, 7.2 Hz, 4H), 1.10 (t, *J* = 7.3 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 163.4, 145.8, 142.1, 138.8, 129.6, 128.7, 128.5, 127.2, 126.6, 123.5, 123.0, 118.2, 84.3, 74.2, 69.8, 30.3, 10.1. **ESI-HRMS** Calcd. for $C_{37}H_{35}N_2O_4^+$ 571.2592 $[M + H]^+$, found 571.2588. **IR** (powder): ν_{max} = 3061, 3028, 2964, 2933, 2875, 2242, 1953, 1647, 1590, 1493, 1477, 1453, 1364, 1315, 1266, 1172, 1130, 1008, 942, 754 cm^{-1}. **$[\alpha]_D$**: +78.13 (c = 0.10 in $CHCl_3$).

(4*S*,4'*S*)-2,2'-((1*R*,3*R*,3'*R*)-3,3'-diethyl-3*H*,3'*H*-1,1'-spirobi[isobenzofuran]-7,7'-diyl)bis(4-phenyl-4,5-dihydrooxazole) ((*R,R,R,S,S*)-3b)

(*R,R,R,S,S*)-3b was obtained from **(*R,R,R,S,S*)-8b** as a white solid (155 mg, 80%) using the procedure abovementioned. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.7 Hz, 2H), 7.36 – 7.28 (m, 4H), 7.23 – 7.17 (m, 6H), 7.01 – 6.96 (m, 4H), 5.14 (dd, *J* = 7.8, 4.3 Hz, 2H), 4.90 – 4.82 (m, 2H), 4.38 – 4.30 (m, 2H), 3.29 – 3.21 (m, 2H), 2.01 – 1.92 (m, 4H), 1.12 (dd, *J* = 8.6, 6.5 Hz, 6H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 163.4, 146.0, 141.7, 138.6, 129.6, 128.7, 128.4, 127.3, 126.9, 123.4, 123.1, 117.8, 84.3, 74.6, 69.9, 30.4, 10.2. **ESI-HRMS** Calcd. for $C_{37}H_{35}N_2O_4^+$ 571.2592 $[M + H]^+$, found 571.2604. **IR** (powder): ν_{max} = 3062, 3028, 2962, 2919, 2850, 1980,1643, 1592, 1493, 1453, 1364, 1266, 1175, 1131, 1010, 946, 757 cm^{-1}. **$[\alpha]_D$**: −27.05 (c = 1.00 in $CHCl_3$).

Ethyl (*S*)-2-phenoxypropanoate (4). The CuCl (1.0 mg, 0.01 mmol), **(*R,R,R,R,R*)-3a** (6.8 mg, 0.012 mmol), NaBArF (11.3 mg, 0.012 mmol), and 300 mg 4 Å molecular sieves were introduced into an oven-dried 1-dram vial. DCM (2.0 mL) was added, and the solution was stirred at room temperature under nitrogen for 2 h. Phenol (94.1 mg, 1.0 mmol) and ethyl α-diazopropionate (26.0 mg, 0.2 mmol) were added to the reaction mixture, and the resulting mixture was stirred at room temperature for 3 h. After filtrating and removing solvent in vacuum, the product was purified by column chromatography (SiO_2, 6% Et_2OAc in hexanes) to afford the product as a clear oil (34 mg, 88%, 97% ee). **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 6.97 (td, *J* = 7.4, 1.1 Hz, 1H), 6.90 – 6.86 (m, 2H), 4.75 (q, *J* = 6.8 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 1.62 (d, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (176 MHz, $CDCl_3$) δ 172.3, 157.6, 129.5, 121.5, 115.1, 72.6, 61.2, 18.6, 14.1. **ESI-HRMS** Calcd. for $C_{11}H_{15}O_3^+$ 195.1016 $[M + H]^+$, found 195.1011. **IR** (film): ν_{max} = 2986, 2938, 2125, 1751, 1732, 1600, 1588, 1494, 1445, 1375, 1273, 1238, 1191, 1174, 1132, 1096, 1078, 1049, 1017, 945, 884, 750, 624 cm^{-1}. **$[\alpha]_D$**: −23.20 (c = 2.00 in $CHCl_3$) [Literature [16] **$[\alpha]_D$**: −41.3 (c = 0.8 in $CHCl_3$) for 90% ee]. **ee:** 97% ee [HPLC condition: Chiralcel OD-H column, n-Hexane/i-PrOH = 90:10, flow rate = 1.0 mL/min, t_R = 5.02 min for (*S*)-enantiomer, t_R = 8.41 min for (*R*)-enantiomer].

3. Results and Discussion

3.1. Introduction

Metal-catalyzed asymmetric insertion of α-diazocarbonyl compounds into X−H (X = C, N, O, S, Si) bonds is among the most useful methods for constructing chiral C-X bonds [17,18]. Since chiral α-alkyloxy, α-aryloxy or α-hydroxy esters and ketones, and oxygen containing heterocyclic compounds are important intermediates in the total syntheses of various biologically active compounds [19,20], there is an urgent need for establishing efficient asymmetric methods for their construction. In 2006, Fu and coworkers reported the first effective method for catalytic enantioselective insertions into O−H bonds [21]. They successfully utilized copper(II) salts with bisazaferrocene ligands to accomplish OH insertion of α-diazocarbonyl compounds into alcohols. Subsequently, Zhou et al. investigated a related carbenoid insertion into O−H bonds of phenols [22]. They discovered that chiral **SPINOL**-based oxazoline ligands (**Spirobox**) could catalyze the reaction up to 88% yield and 99.6% ee, and both carbenoid insertion into water [23] and the intramolecular variant of this reaction [24] was described in their following studies. In addition, Zhou et al. explored iron(II) chloride complexes with **Spirobox**, and discovered that such complexes could also catalyze the reaction with exceptional enantioselectivities under mild reaction conditions [25]. In a related study, Uozumi and coworkers attempted the asymmetric carbenoid insertion into phenolic O–H bonds with a copper(I) imidazoindolephosphine catalyst, and up to 91% ee was achieved in their α-aryloxy products [26]. Finally, recent explorations by Simonneaux et al. demonstrated the utility of chiral bicyclo bisoxazoline ligands in O–H insertion reaction of carbenoids [16].

These aforementioned results suggested that chiral bisoxazoline-based ligand complexes with transition metals could efficiently promote various carbenoid O–H insertion reactions. Viewing these prior results as a benchmark, our studies focused on generating **SPIROL** ligands functionalized with oxazoline substituents (termed "**SPIROX**" in this manuscript). The subsequent subsections of this article describe the synthesis of these **SPIROX** ligands (Section 3.2) and

evaluation of their Cu(I) complexes as the catalysts for the phenol O–H insertion reactions (Section 3.3).

3.2. Synthesis of C2-Symmetric SPIROL-Based Bisoxazoline Ligands (SPIROX)

Our studies commenced with the **(*R,R,R*)-SPIROL (2)** (Scheme 2), which was obtained in an enantiopure form after recrystallization using the protocol previously described by our group [15,16]. Using **2** as the starting material, the bistriflate **(*R,R,R*)-5** was synthesized in 97% yield by reacting it with triflic anhydride and pyridine. The successful preparation of **(*R,R,R*)-5** prompted the subsequent carbonylation studies with the objective to obtain the diester **(*R,R,R*)-6.** After the optimization of the reaction conditions, the carbonylation of **(*R,R,R*)-5** leading to compound **(*R,R,R*)-6** was indeed successfully accomplished in 78% yield. The optimal conditions included using $Pd(OAc)_2$ complexed to dppp as the catalyst, triethylamine and carbon monoxide (1 atm) as the reagents/additives, and methanol/DMSO mixture as the reagent and solvents. The use of 1,3-bis(diphenylphosphino)propane (dppp) was crucial for this step, as the yield was dramatically decreased when either 1,1'-bis(diphenylphosphino)ferrocene (dppf) or 1,4-bis(diphenylphosphino)butane (dppb) were employed for this reaction instead. Considering the successful product formation observed with dppp, no other ligands such as 1,2-bis(diphenylphosphino)ethane (dppe) were evaluated; however, further reaction and ligand optimization may lead to improvements in yields. With these results in hand, biscarboxylic acid **(*R,R,R*)-7** was accessed via hydrolysis with KOH in methanol followed by an acidic work up. Since acid **7** is chiral, its condensation with optically active amino alcohol would produce two diastereomeric products. Therefore, when (*R*)- or (*S*)-2-phenylglycinol was used in the presence of hydroxybenzotriazole (HOBt) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC), two pseudoenantiomeric bisamides **(*R,R,R,R,R*)-8a** and **(*R,R,R,S,S*)-8b** were made respectively. The oxazoline ring formation was achieved by treatment with methanesulfonyl chloride (MsCl), 4-dimethylaminopyridine (DMAP), and triethylamine to afford **SPIROX** ligands **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** in 80% and 87% yield, respectively [27].

3.3. Application of SPIROL-Based Bisoxazoline Ligands in Insertion of Carbenoids into O-H Bonds

To demonstrate that SPIROX ligand complexes may promote highly enantioselective O-H insertion reactions, we examined the performances of **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** complexes with Cu(I) salts under the conditions previously developed by Zhou et al. for SPINOL-based ligands [22]. Thus, we investigated the insertion of ethyl 2-diazopropionate into the O–H bond of phenol using 5 mol% of CuCl or $Cu(OTf)_2$, 6 mol% of ligands **(*R,R,R,R,R*)-3a** or **(*R,R,R,S,S*)-3b,** 6 mol% of NaBArF, 4 Å MS, and dichloromethane as the solvent (Table 1). When copper(I) chloride was used as the copper source, both **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** ligand complexes provided full conversion to product **4** (entries 1 and 3). The use of the **(*R,R,R,R,R*)-3a**-based complex resulted in highly enantioselective formation of **4** (97% ee, entry 1) that was comparable with the selectivities observed by Zhou et al. with SPINOL-based ligands (97% ee) [22], and the resultant product **4** was isolated in 88% yield. The diastereomeric **(*R,R,R,S,S*)-3b** provided opposite selectivity, and resulted in opposite enantiomer of **4** as the major product, but with significantly lower selectivity (–22% ee, entry 3). Copper triflate was also tested under the same reaction conditions, and its complexes with **(*R,R,R,R,R*)-3a** also resulted in highly enantioselective formation of **4** (95% ee, entry 2). As before, $Cu(OTf)_2$ complexes with **(*R,R,R,S,S*)-3b** favored the

opposite enantiomer of **4**, but, to our surprise, this reaction was significantly more selective than for the copper(I) chloride case (–62% ee, entry 4). This may suggest that TfO^- to $BArF^-$ anion exchange was not complete, and that counterions may have a significant impact on the selectivity of this reaction. It should be also noted that the results observed with **(*R,R,R,S,S*)-3b** complexes with CuCl and $Cu(OTf)_2$ and leading to the selectivity switch contrast with what was previously observed for the equivalent diastereomeric **(*Sa,S,S*)**- and **(*Ra,S,S*)-Spirobox** ligands by Zhou and coworkers [22–25]. In these studies, the authors observed similar yields and selectivities for **(*Sa,S,S*)-Spirobox**, but nearly racemic reactions for **(*Ra,S,S*)-Spirobox** ligands, while, in our case, moderately selective formation of the enantiomer of **4** was observed for the **(*R,R,R,S,S*)-3b** (–62% ee, Table 1, entry 4). These observations may suggest that the spiroketal moiety and additional stereogenic centers present in **SPIROX** ligands may significantly impact the stereoselectivity, and our ongoing work is focused on exploring these effects.

4. Conclusions

In summary, this article described the development of two new spirocyclic C2-symmetric **SPIROX** ligands **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** based on the spiroketal-based chiral scaffold (e.g., **SPIROL**) previously developed by our group. Unlike many other spirocyclic ligands, **SPIROX** ligands contain an additional substitution that could be explored for fine-tuning the reaction selectivity and are readily available through direct asymmetric synthesis that does not require chiral resolution. These diastereomeric ligands were explored in Cu(I)-catalyzed asymmetric O–H insertion between ethyl 2-diazopropionate and phenol that resulted in chiral α-aryloxypropionate **4**. Despite the same configuration of the spirocyclic core, the oxazoline substituents were found to play an important role in determining the selectivity of this reaction. Thus, using **(*R,R,R,R,R*)-3a** complexes with Cu(I) resulted in efficient and highly enantioselective formation of the product **4** (97% ee for CuCl and 95% ee for $Cu(OTf)_2$). On the contrary, **(*R,R,R,S,S*)-3b** complexes produced the opposite enantiomer of **4** in low (CuCl, –22% ee) to moderate ($Cu(OTf)_2$, –62% ee) selectivities. The observed copper(I) counterion effects suggest that this reaction could be further improved by selecting a different counterion. In addition, the enantioselectivity switch observed with **(*R,R,R,S,S*)-3b** complexes implies that the additional benzylic stereocenters and spiroketal moiety present in **(*R,R,R,S,S*)-3b** are not simple bystanders, and further exploration of their effects is the subject of the ongoing studies in our laboratories.

Supplementary Materials: 1H and 13C NMR spectral data for compounds **2**–**8** and HPLC traces for chiral product **4** are available online at www.mdpi.com/xxx/s1.

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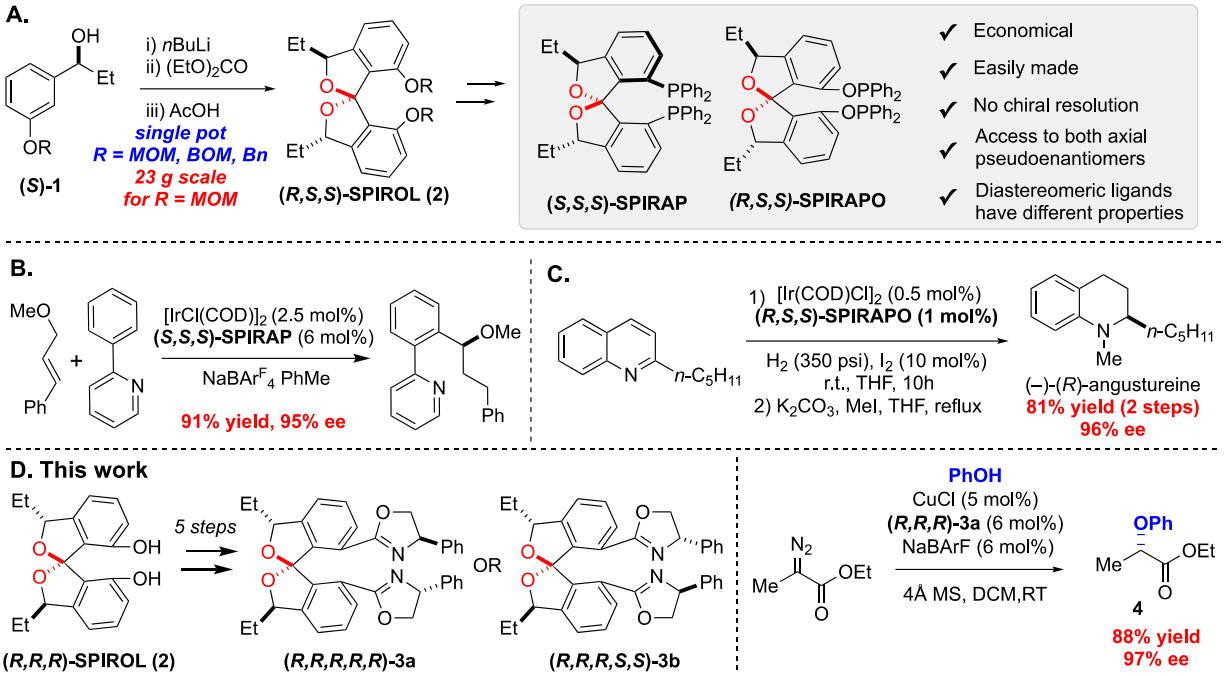
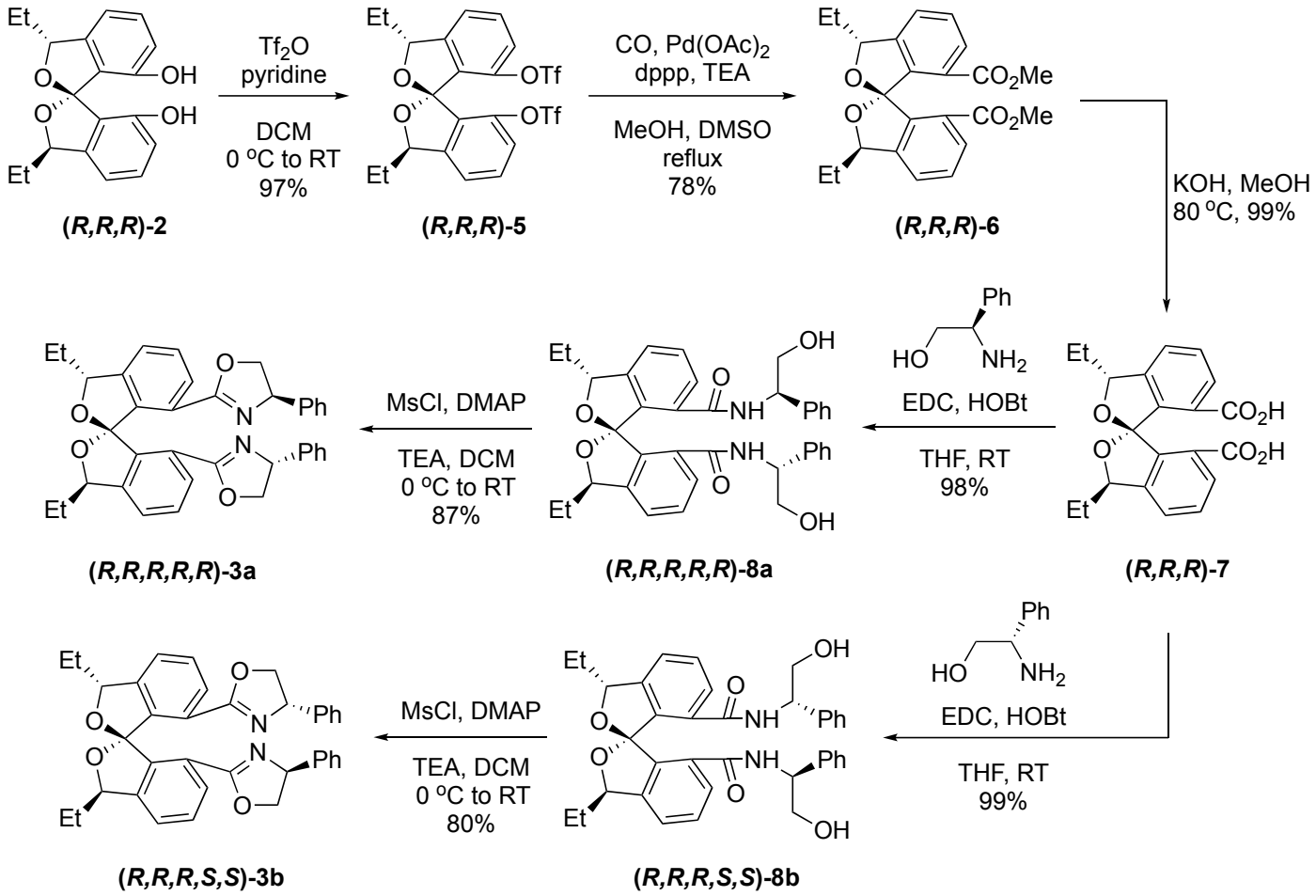
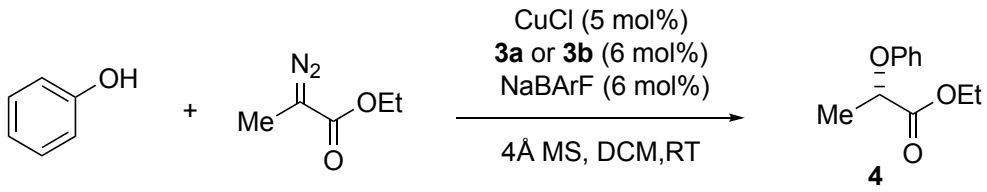


Scheme 1. (**A**). One-step synthesis of (*R,S,S*)-SPIROL core, and examples of diastereomeric SPIROL-based ligands. (**B**). Example of the use of (*S,S,S*)-SPIRAP ligands for the Ir-catalyzed asymmetric hydroarylation reaction. (**C**). Application of (*R,S,S*)-SPIRAPO ligands for the asymmetric dearomatizative hydrogenation reaction for the synthesis of alkaloid (–)-(*R*)-angustureine. (**D**). Current work describing the development of diastereomeric ligands **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b** and their application of the enantioselective Cu(I)-catalyzed OH insertion leading to **4**.



Scheme 2. Synthesis of two diastereomeric SPIROX ligands **(*R,R,R,R,R*)-3a** and **(*R,R,R,S,S*)-3b.**

Table 1. Evaluation of SPIROX ligands for Cu-catalyzed asymmetric O-H insertion [a].



Entry	Ligand	[Cu]	Conversion (%) [b]	ee (%) [c]
1	**(*R,R,R,R,R*)-3a**	CuCl	99(88% yield)	97
2	**(*R,R,R,R,R*)-3a**	$Cu(OTf)_2$	99	95
3	**(*R,R,R,S,S*)-3b**	CuCl	99	–22
4	**(*R,R,R,S,S*)-3b**	$Cu(OTf)_2$	99	–62

[a] Reactions were carried out at r.t. with [Cu] (0.01 mmol), ligand (0.012 mmol), NaBARF (0.012 mmol), 4 Å molecular sieves (300 mg), and DCM (2 mL) while stirring under nitrogen for 2 h. Then, phenol (1.0 mmol) and ethyl a-diazopropionate (0.2 mmol) were added, and the reaction mixture was stirred for an additional 3 h. [b] Determined by 1H NMR. [c] Determined by chiral HPLC using Chiralcel OD-H column.