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Synthesis of modular thiophene-oxazoline ligands and their application in the asymmetric phenyl transfer reaction to aldehydes

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Abstract—A series of thiophene mono (oxazoline) N,O-ligands with three sites of diversity were synthesized concisely in two steps from the corresponding thiophene carbonitriles. These ligands were applied to the enantioselective phenyl transfer reaction of aldehydes, resulting in the corresponding chiral diaryl methanol products with excellent yields and moderate to good enantioselectivities.

1. Introduction

Chiral oxazoline-based ligands with various backbones constitute an important class of well-established ligands, which have found widespread use in many metal-catalyzed asymmetric reactions.[1] These ligands have attracted much attention due to their easy accessibility from readily available starting chiral materials, as well as their modular structures, which allow combinatorial variations for a given catalytic task.[2] In particular, chiral oxazoline ligands with a heterocyclic backbone have been used with great success in many asymmetric reactions.[1,3] Heterocyclic scaffolds are advantageous as they may not only offer direct influence on the electronic and steric properties of the ligands but also enable facile and regioselective metalation processes for further modification.[3e,f]

The reaction of asymmetric addition of a phenylzinc reagent to aromatic aldehydes has been well studied in recent years due to the importance of the resulting chiral diarylmethanols as intermediates for the synthesis of biologically and pharmaceutically active compounds.[4] Bolm et al. have reported the successful application of excellent oxazoline ligands with ferrocene and cyrhetrene as skeletons in this reaction, with excellent results being obtained.[5] On the other hand, to the best of our knowledge, despite the recent successful application of a series of five-membered heterocyclic phosphinooxazoline ligands (HetPHOX) in a number of asymmetric reactions,[2] only one report in the literature has dealt with the synthesis of a new class of thiophene diarylhydroxy 2-oxazoline ligands and their applications to the catalytic enantioselective addition of dialkylzinc reagents to aromatic aldehydes.[6]

As a part of our continued interest in the development of efficient ligands for the reactions of organozinc reagents,[7] we herein report the synthesis of a small library of modular thiophene mono (oxazoline) N,O-ligands with three sites of diversity and their application in the enantioselective phenyl transfer reaction to aromatic aldehydes.

2. Results and discussion

The synthesis of ligands **2a**–**g** is shown in Scheme 1. Following William's procedure,[8] oxazoline compounds **1a**–**g** were obtained in moderate to good yields through the reaction of 2-cyanothiophene and various chiral aminoalcohols in the presence of a catalytic amount of $ZnCl_2$. Subsequent selective 3-metalation of the thiophene ring with *n*-BuLi in Et_2O at −78 °C followed by the addition of benzophenone provided the desired ligands **2a**–**g**, which were different in the oxazoline moiety, in moderate yields.

For the convenience of synthesis, examination of the substituent effect of the hydroxy moiety was carried out by using the phenylalaninol derived ligands **2h**–**j**. Formylation

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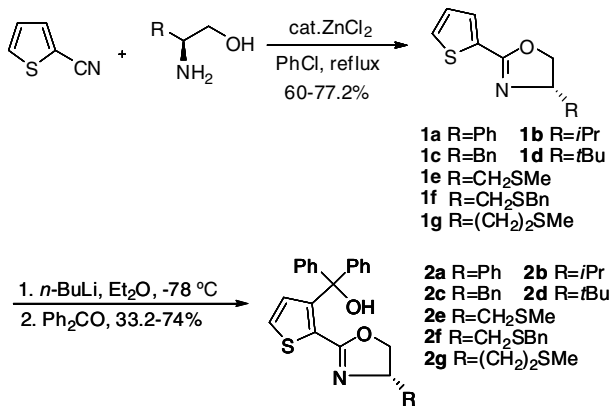


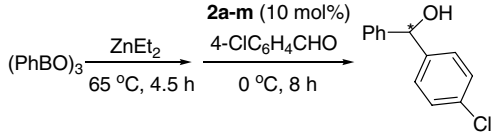
Scheme 1.

of **1c** followed by reduction with $NaBH_4$ furnished ligand **2h** in moderate yield (Scheme 2). Ligands **2i–j** (Fig. 1) were prepared in moderate yields by using acetone and cyclohexanone instead of benzophenone, respectively.

Ligands **2k–l** (Fig. 1) with substituted thiophene skeletons were also prepared successfully in moderate yields from the corresponding 5-substituted thiophene oxazolines **1k–l**, which were prepared from the corresponding 5-substituted 2-cyanothiophenes, following the same procedure for **2a–g**. In the case of ligand **2m** with the oxazoline moiety at the 3-position of the thiophene ring, however, low conversion (30%) of 3-cyanothiophene was obtained in the preparation of the thiophene oxazoline **1m** through the condensation between 3-cyanothiophene and phenylalaninol under the typical reaction conditions[8] even with a prolonged reaction time. Subsequent reaction with benzophenone smoothly afforded ligand **2m** in moderate yield.

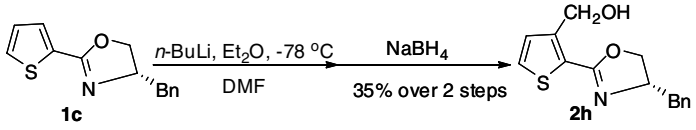
Once ligands **2a–m** were prepared, they were tested in the asymmetric addition of a phenylzinc reagent to aromatic aldehydes using the triphenylboroxin–$ZnEt_2$ protocol we have reported recently.[7] Specifically, the phenylzinc reagent was generated in situ by heating a mixture of diethylzinc and phenylboroxin at 65 °C for 4.5 h. When the resulting phenylzinc reagent was mixed sequentially with 10 mol % of ligand and 4-chlorobenzaldehyde in toluene at 0 °C and stirred for 8 h, the pure product was obtained by column chromatography. The results of ligand screening are presented in Table 1. It was found that the chiral oxazoline moiety greatly influenced the asymmetric inductive ability of the ligands, although the trend was somewhat perplexing (Table 1, entries 1–7). Ligand **2d** bearing the most bulky substituent on the oxazoline ring gave the highest ee value (77%, Table 1, entry 4). The sulfur-containing amino alcohol derived ligand **2e**, which was assumed to serve as a tridentate ligand, also gave a relatively good result (68% ee, Table 1, entry 5). Disappointingly, further modification of the sulfur atom on the oxazoline moiety provided lower ee values (Table 1, entries 6 and 7). Decreasing the steric hindrance of the phenyl group on the hydroxy moiety to a methyl or hydrogen atom greatly lowered the enantioselectivity (Table 1, entries 8 and 9). We were surprised to find that ligand **2j** with a cyclohexyl group afforded the corresponding product of opposite configuration, although the ee value was low (Table 1, entry 10). Changing the substituents on the 5-position of

Table 1. Asymmetric phenylation of 4-chlorobezaldehyde with ligands **2a–m**[a]



Entry	Ligand	Yield[b] (%)	ee[c] (%)	Config.[d]
1	**2a**	91	31	*R*
2	**2b**	98	20	*R*
3	**2c**	93	47	*R*
4	**2d**	93	77	*R*
5	**2e**	86	68	*R*
6	**2f**	90	55	*R*
7	**2g**	91	44	*R*
8	**2h**	84	4	*R*
9	**2i**	94	17	*R*
10	**2j**	92	13	*S*
11	**2k**	92	41	*R*
12	**2l**	91	35	*R*
13	**2m**	95	35	*R*

[a] **2a–m**/$(PhBO)_3$/$ZnEt_2$/aldehyde = 0.1:0.5:4.5:1.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Configuration of the predominant enantiomer of the product.



Scheme 2.

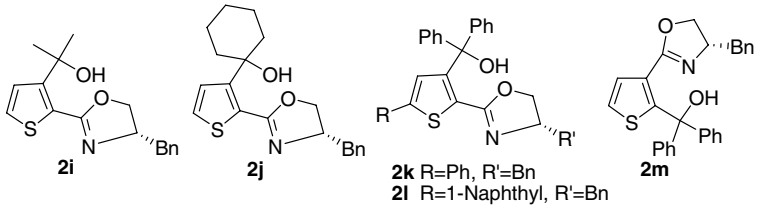
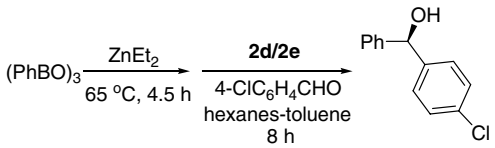


Figure 1.

the thiophene ring or the position of the oxazoline moiety demonstrated much less effect on ee values compared to the former two positions (Table 1, entries 11–13); thus it may be assumed that the sulfur atom of the thiophene ring might interfere little with the catalytic process.

Next, we examined the influence of other reaction conditions on the asymmetric inductive effect of ligands and the results are summarized in Table 2. To our disappointment, when we optimized the conditions with ligand **2d**, neither increasing the loading of **2d** to 20 mol % nor lowering the reaction temperature to −15 °C could make any significant improvement on the enantioselectivity of the reaction. When decreasing the ligand loading to 5 mol %, the enantioselectivity dropped remarkably (Table 2, entries 3 vs 1). As a result, we had to select ligand **2e** for further optimization. Using Et_2O or CH_2Cl_2 as the cosolvent instead of toluene led to worse enantioselectivity (Table 2, entries 6 and 7). Increasing the amount of **2e** made little effect on the enantioselectivity (Table 2, entries 8 and 9). When lowering the temperature to −15 °C, a significant enhancement in the enantioselectivity was observed (Table 2, entry 10). However, further lowering the temperature to −30 °C made no remarkable improvement while a lower chemical yield was observed (Table 2, entry 12). Pretreatment of **2e** with $ZnEt_2$, which was found to be good for the improvement of enantioselectivity by us[7b] and Pu et al.,[9] failed to give a better result in this case (Table 2, entry 11). The effect of additives was also examined. The use of 10 mol % isopropanol gave both lower yield and enantioselectivity (Table 2, entry 14) and 10 mol % of DiMPEG (MW 2000) raised the enantiomeric excess of the products while a sharp decrease in yield was also observed (Table 2, entry 15). Similar observations have also been reported in the recent literature.[10] Thus, the best result in terms of both yield and enantioselectivity was obtained by performing the reaction with 15 mol % of **2e** at −15 °C (Table 2, entry 11).

Table 2. Optimizing reaction conditions using ligands **2d** and **2e**[a]

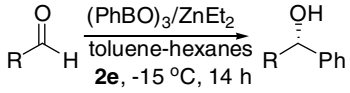


Entry	Ligand (loading/mol %)	Temperature (°C)	Yield[b] (%)	ee[c] (%)
1	**2d** (10)	0	93	77
2	**2d** (20)	0	91	76
3	**2d** (5)	0	90	53
4[d]	**2d** (15)	−15	91	79
5	**2e** (10)	0	86	68
6[e]	**2e** (10)	0	89	29
7[f]	**2e** (10)	0	91	63
8	**2e** (15)	0	86	70
9	**2e** (20)	0	91	71
10[d]	**2e** (10)	−15	92	76
11[d]	**2e** (15)	−15	91	82
12[d]	**2e** (15)	−30	72[g]	83
13	**2e** (10)	0	90	63[h]
14	**2e** (15)	0	61	56[i]
15	**2e** (15)	0	53	73[j]

[a] **2d/2e**/$(PhBO)_3$/$ZnEt_2$/aldehyde = 0.1:0.5:4.5:1.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] The reaction was run for 14 h.
[e] Et_2O was used as the cosolvent instead of toluene.
[f] CH_2Cl_2 was used as the cosolvent instead of toluene.
[g] Based on the recovered aldehyde.
[h] The ligand was pretreated with 0.2 equiv $ZnEt_2$.
[i] Using 10 mol % of isopropanol as an additive.
[j] Using 10 mol % of DiMPEG (MW 2000) as an additive.

The scope and limitation of **2e** in the asymmetric phenyl transfer reaction to aromatic aldehydes was also tested with a selected series of aldehydes under the optimized reaction conditions and the results are summarized in Table 3. In general, all substrates tested gave the corresponding products in excellent yields (around 90%) and ee values ranging from 60% to 82%. *para*-Substituted aldehydes provided better results in terms of ee values than did *meta*- and *ortho*-substituted ones. (Table 3, entry 2 vs entries 3 and 4).

Table 3. Asymmetric phenylation of aromatic aldehydes with ligand **2e**[a]



Entry	R	Yield[b] (%)	ee[c] (%)	Config.[d]
1	4-ClC_6H_4	91	82	*R*
2	4-BrC_6H_4	90	72	*R*
3	3-BrC_6H_4	87	65	*R*
4	2-BrC_6H_4	89	65	*R*
5	4-$MeOC_6H_4$	91	78	*R*
6	4-MeC_6H_4	92	75	*R*
7	2,4-Cl, Cl–C_6H_3	90	60	*R*
8	2-Naphthyl	93	73	*R*
9	*E*-Cinnamyl	89	74	*S*

[a] **2e**/$(PhBO)_3$/$ZnEt_2$/aldehyde = 0.1:0.5:4.5:1.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Configuration of the predominant enantiomer of the product was determined by comparison with the literature data.

3. Conclusion

In conclusion, a small library of modular thiophene mono (oxazoline) N,O-ligands with three sites of diversity were concisely synthesized and applied to the enantioselective phenyl transfer reaction of aromatic aldehydes. The observed changes in ee values resulted from the structural variations of the ligands **2a**–**m** and provided information useful for the design of more efficient ligands. This is the first example of hydroxy thiophene-oxazoline ligands catalyzed asymmetric addition of phenylzinc reagent to aldehydes.

4. Experimental

4.1. General

All reactions were carried out under a dry argon atmosphere. Analytical TLC was performed on precoated silica

gel plates. Column chromatography was conducted with 300–400 mesh silica gels. NMR spectra were recorded at 300 MHz for ^{1}H NMR, and 100 MHz for ^{13}C NMR. Chemical shifts are reported in δ ppm referenced to an internal TMS standard for ^{1}H NMR and chloroform-*d* (δ 77.05) for ^{13}C NMR. Enantiomeric excesses were determined by chiral HPLC analysis. Optical rotations were measured on a JASCO 1030 polarimeter. All solvents were dried before use according to standard procedures.

4.2. Preparation of oxazoline compounds 1a–m

4.2.1. General procedure for the preparation of 1a–m. In a Schlenk flask, $ZnCl_2$ (13.6 mg, 0.1 mmol) was melted under high vacuum and cooled under argon. After cooling to room temperature, chlorobenzene (3 mL) was added followed by thiophenecarbonitriles (1 mmol) and the amino alcohols (1.2 mmol). The mixture was heated at reflux for 24–48 h (monitored by TLC). Then the solvent was removed under reduced pressure to give an oily residue, which was dissolved in CH_2Cl_2 (5 mL), washed with water (3×3 mL), dried with anhydrous Na_2SO_4, concentrated followed by flash column chromatography to afford the title compounds.

4.2.2. (4*R*)-4-Benzylthiomethyl-2-(2-thienyl)-1,3-oxazoline 1f. Yield (69.9%, 202 mg); colorless viscous liquid; $[\alpha]_D^{23} = +2.22$ (*c* 1.11, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.60 (dd, $J = 1.2$, 3.6 Hz, 1H), 7.46 (dd, $J = 1.2$, 5.8 Hz, 1H), 7.30 (m, 5H), 7.08 (dd, $J = 3.6$, 5.8 Hz, 1H), 4.45 (m, 2H), 4.20 (m, 1H), 3.79 (s, 2H), 2.85 (m, 1H), 2.55 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 160.2, 138.1, 130.5, 130.1, 130.0, 128.8, 128.5, 127.5, 127.0, 72.3, 66.7, 36.6, 36.0; IR (film): 3027, 2914, 1646, 1432, 1059, 1018, 954, 716 cm^{-1}; EI-MS: *m*/*z* (%): 289 (M^+, 3), 167 (100), 152 (73), 124 (35), 111 (56), 91 (36); HRMS (EI) calcd for $C_{15}H_{15}NOS_2$: 289.05951, found 289.05853.

4.2.3. (4*S*)-4-Benzyl-2-(5-phenyl-2-thienyl)-1,3-oxazoline 1k. Yield (67.4%, 201 mg); pale yellow solid; mp 91–93 °C; $[\alpha]_D^{24} = +79.9$ (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 7.66 (m, 3H), 7.44–7.27 (m, 9H), 5.39 (m, 1H), 4.80 (m, 1H), 4.29 (m, 1H); 3.26 (dd, $J = 5.0$, 13.8 Hz, 1H), 2.74 (dd, $J = 8.9$, 13.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 159.6, 148.7, 137.8, 133.6, 131.2, 129.2, 129.1, 129.0, 128.5, 128.4, 126.5, 126.0, 123.4, 72.2, 68.0, 41.7; IR (film): 3060, 2924, 2853, 1643, 1602, 1496, 1459, 757, 700 cm^{-1}; EI-MS: *m*/*z* (%): 319 (M^+, 2), 228 (100), 229 (18), 173 (25), 91 (14). Anal. Calcd for $C_{20}H_{17}NOS$ (%): C, 75.20; H, 5.36; N, 4.39; Found: C, 75.43; H, 5.22; N, 4.34.

4.2.4. (4*S*)-4-Benzyl-2-(5-1′-naphthyl-2-thienyl)-1,3-oxazoline 1l. Yield (54.1%, 196 mg); colorless viscous oil; $[\alpha]_D^{28} = +52.4$ (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 8.22 (m, 1H), 7.91 (m, 2H), 7.68 (m, 5H), 7.26 (m, 6H), 4.60 (m, 1H), 4.37 (m, 1H), 4.18 (m, 1H), 3.30 (m, 1H), 2.75 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 159.7, 146.6, 137.9, 133.9, 131.5, 130.6, 130.1, 129.3, 129.1, 128.9, 128.6, 128.4, 128.2, 127.9, 126.7, 126.6, 126.2, 125.4, 125.2, 72.3, 68.1, 41.7; IR (film): 3058, 2956, 2915, 1638, 1491, 1450, 771, 696 cm^{-1}; ESI-MS (*m*/*z*): 370 $[M+1]^+$; HRMS (MALDI) calcd for $C_{24}H_{19}NOS$ MH^+: 370.1271 ± 0.002, found 370.1260.

4.3. Preparation of ligands 2a–m

4.3.1. General procedure for the preparation of 2a–g and 2i–m. To a solution of the corresponding oxazolines (0.50 mmol) in Et_2O (1.5 mL) under argon at −78 °C was added dropwise 0.38 mL (0.60 mmol, 1.6 M in hexanes) *n*-BuLi, and after stirring for 30 min at this temperature and another 30 min at 0 °C, 109 mg (0.6 mmol) of benzophenone in 1 mL Et_2O was added dropwise to the reaction mixture and it was stirred overnight, then quenched with 3 mL satd NH_4Cl, extracted with EtOAc, dried with Na_2SO_4, followed by flash chromatography to provide the title products.

4.3.1.1. (4*S*)-(2-(4-Phenyl-4,5-dihydrooxazol-2-yl)thiophen-3-yl)diphenyl methanol 2a. Yield (33.2%, 288 mg); white solid; mp 179–181 °C; $[\alpha]_D^{20} = +184.3$ (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 9.35 (s, 1H, disappeared when shaken with D_2O), 7.30–7.13 (m, 14H), 6.58 (d, $J = 7.5$ Hz, 2H), 6.35 (d, $J = 5.1$Hz, 1H), 5.33 (m, 1H), 4.70 (m, 1H), 4.05 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.4, 154.7, 147.4 (4), 147.3 (8), 141.3, 132.8, 128.6, 127.8, 127.7, 127.6 (3), 127.5 (8), 127.4, 127.2, 127.0, 125.9, 124.2, 79.3, 75.2, 69.4; IR (film): 3170, 3059, 2923, 1634, 1599, 753, 698 cm^{-1}; EI-MS: *m*/*z* (%): 411 (M^+, 16), 215 (100), 214 (17), 77 (33). Anal. Calcd for $C_{26}H_{21}NO_2S$ (%): C 75.88, H 5.14, N 3.40; Found: C, 75.64; H, 5.01; N, 3.34.

4.3.1.2. (4*S*)-(2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)thiophen-3-yl)diphenyl methanol 2b. Yield (53%, 317 mg); colorless crystal (hexane–ethyl acetate); mp 109–110 °C; $[\alpha]_D^{22} = +90.1$ (*c* 1.0, $CHCl_3$) ^{1}H NMR ($CDCl_3$) δ (ppm): 9.61 (s, 1H), 7.27 (m, 11H), 6.32 (m, 1H), 4.32 (m, 1H), 3.97 (m, 2H), 1.44 (s, 1H), 0.64 (m, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 159.9, 154.2, 147.3, 147.2, 132.5, 127.6, 127.5, 127.4 (6), 126.9, 126.8, 124.5, 79.1, 72.4, 70.9, 32.5, 18.3, 17.8; IR (film): 3086, 3039, 2958, 2925, 2872, 1638, 1447, 1417, 751, 700 cm^{-1}; EI-MS: *m*/*z* (%): 377 (M^+, 100), 300 (84), 215 (92), 214 (53), 105 (17). Anal. Calcd for $C_{23}H_{23}NO_2S$ (%): C, 73.18; H, 6.14; N, 3.71; Found: C, 73.32; H, 5.88; N, 3.62.

4.3.1.3. (4*S*)-(2-(4-Benzyl-4,5-dihydrooxazol-2-yl)thiophen-3-yl)diphenyl methanol 2c. Yield (47.6%, 322 mg); colorless crystal (hexane–ethyl acetate); mp 105–107 °C; $[\alpha]_D^{20} = +119.8$ (*c* 0.75, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ (ppm): 9.27 (s, 1H), 7.27 (m, 14H), 6.99 (d, $J = 6.3$ Hz, 2H), 6.32 (d, $J = 5.4$ Hz, 1H), 4.40 (m, 1H), 4.23 (m, 1H), 3.97 (m, 1H), 2.70 (dd, $J = 5.4$, 14.1 Hz, 1H), 2.19 (dd, $J = 8.1$, 14.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 160.4, 154.4, 147.4, 147.2, 137.3, 132.5, 129.0, 128.5, 127.6, 127.5, 127.0, 126.9, 126.4, 124.4, 79.2, 72.0, 67.3, 40.7; IR (film): 3100, 3085, 1635, 1601, 1447, 1417, 751, 699 cm^{-1}; EI-MS: *m*/*z* (%): 425 (M^+, 60), 348 (26), 215 (82), 105 (30), 91 (100), 77 (40). Anal. Calcd for $C_{27}H_{23}NO_2S$ (%): C, 76.21; H, 5.45; N, 3.29; Found: C, 76.28; H, 5.43; N, 3.23.

4.3.1.4. (4*S*)-(2-(4-*t*-Butyl-4,5-dihydrooxazol-2-yl)thiophen-3-yl)diphenyl methanol 2d.[6] Yield (52%, 222 mg); colorless viscous oil; $[\alpha]_D^{29} = +109.4$ (*c* 1.90, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 9.69 (s, 1H), 7.32 (m, 11H), 6.30 (d, $J = 4.8$ Hz, 1H), 4.26 (m, 1H) 4.09 (m, 1H), 3.93 (m, 1H), 0.57 (s, 9H).

4.3.1.5. (4*R*)-(2-(4-Methylthiomethyl-4,5-dihydrooxazol-3-yl)thiophen-2-yl)diphenyl methanol 2e. Yield (58.9%, 342 mg); colorless crystal (hexane–diethyl ether); mp 118–119 °C; $[\alpha]_D^{25} = +113.6$ (*c* 0.60, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 9.26 (s, 1H), 7.25 (m, 11H), 6.30 (d, $J = 5.1$ Hz, 1H), 4.39–4.24 (m, 2H), 4.16 (m, 1H), 2.40 (dd, $J = 4.4$, 13.2 Hz, 1H), 2.00 (s, 3H), 1.89 (dd, $J = 8.8$, 13.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.0, 154.7, 147.6, 147.0, 132.5, 127.7, 127.6, 127.5, 127.3, 127.0, 126.9, 124.4, 79.1, 72.3, 65.7, 38.0, 15.7; IR (film): 3085, 2959, 1633, 1447, 1418, 750, 701 cm^{-1}; EI-MS: *m*/*z* (%): 395 (M^+, 67), 318 (32), 215 (100), 105 (66), 77 (32), 61 (76). Anal. Calcd for $C_{22}H_{21}NO_2S_2$ (%): C, 66.80; H, 5.35; N, 3.54; Found: C, 67.00, H, 5.48; N, 3.37.

4.3.1.6. (4*R*)-(2-(4-Benzylthiomethyl-4,5-dihydrooxazol-3-yl)thiophen-2-yl)diphenyl methanol 2f. Yield (61%, 278 mg); colorless crystal (hexane–ethyl acetate); mp 117–118 °C; $[\alpha]_D^{24} = +72.4$ (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 9.06 (s, 1H), 7.25 (m, 16H), 6.32 (m, 1H), 4.30 (m, 3H), 3.60 (s, 2H), 2.35 (m, 1H), 1.85 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.0, 154.8, 147.5, 147.0, 138.0, 132.5, 128.8, 128.6, 127.7, 127.5, 127.3, 127.2, 127.0, 126.9, 124.3, 79.1, 72.4, 65.7, 36.5, 35.3; IR (film): 3085, 2955, 2921, 1633, 1447, 1417, 1244, 1071, 752, 700 cm^{-1}; ESI-MS (*m*/*z*): 471 $[M]^+$. Anal. Calcd for $C_{28}H_{25}NO_2S_2$ (%): C, 71.31; H, 5.34; N, 2.97; Found: C, 71.26; H, 5.38; N, 2.79.

4.3.1.7. (4*R*)-(2-(4-Methylthioethyl-4,5-dihydrooxazol-3-yl)thiophen-2-yl)diphenyl methanol 2g. Yield (74%, 378 mg); colorless crystal (hexane–diethyl ether); mp 147–149 °C; $[\alpha]_D^{24} = +60.5$ (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 9.26 (s, 1H), 7.25 (m, 11H), 6.30 (d, $J = 5.1$ Hz, 1H), 4.39 (m, 1H), 4.22 (m, 1H), 3.91 (m, 1H), 2.35–2.15 (m, 2H), 2.03 (s, 3H), 1.55 (m, 1H), 1.28 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 160.2, 154.3, 147.3, 147.1, 132.4, 127.6, 127.5, 127.4 (2), 127.4, 127.1, 126.9, 124.4, 79.0, 72.7, 65.1, 35.1, 30.2, 15.5; IR (film): 3086, 2916, 1636, 1446, 1418, 1240, 1042, 751, 700 cm^{-1}; MALDI-MS (*m*/*z*): 410 $[M+1]^+$. Anal. Calcd for $C_{23}H_{23}NO_2S_2$ (%): C, 67.45; H, 5.66; N, 3.42; Found: C, 67.44; H, 5.65; N, 3.29.

4.3.1.8. (4*S*)-2-(2-(4-Benzyl-4,5-dihydrooxazol-2-yl)thiophen-3-yl)-2-propanol 2i. Yield (74%, 178 mg); colorless liquid; $[\alpha]_D^{28} = -1.15$ (*c* 2.10, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 8.33 (s, 1H), 7.30 (m, 6H), 7.08 (m, 1H), 4.65 (m, 1H), 4.35 (m, 1H), 4.15 (m, 1H), 3.20 (m, 1H), 2.80 (m, 1H), 1.64 (m, 6H); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.0, 155.6, 137.4, 129.1, 128.6, 128.4, 128.3, 126.7, 123.0, 72.3, 70.3, 68.0, 41.5, 30.4; IR (film): 3229, 2978, 2927, 1633, 1417, 960, 701 cm^{-1}; EI-MS: *m*/*z* (%): 301 (M^++1, 1), 286 (100), 152 (70), 151 (94), 91 (71); HRMS (EI) calcd for $C_{15}H_{15}NOS_2$ MH^+: 302.1206 ± 0.002, found 302.1209.

4.3.1.9. (4*S*)-(2-(4-Benzyl-4,5-dihydrooxazol-2-yl)thiophen-3-yl)cyclohexanol 2j. Yield (33%, 118 mg); colorless solid; mp 136–137 °C; $[\alpha]_D^{24} = -25.0$ (*c* 0.35, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ (ppm): 7.92 (s, 1H), 7.37–7.11 (m, 7H), 4.62 (m, 1H), 4.37 (m, 1H), 4.15 (m, 1H), 3.14 (dd, $J = 6.0$, 13.8 Hz, 1H), 2.78 (dd, $J = 7.9$, 13.8 Hz, 1H), 2.22–2.10 (m, 2H), 1.96 (m, 2H), 1.54 (m, 5H), 1.26 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.1, 156.5, 137.5, 129.1, 128.6, 128.4, 127.9, 126.6, 123.1, 72.2, 71.1, 68.0, 41.6, 37.5, 25.8, 21.9; IR (film): 2955, 2926, 1640, 1447, 1366, 1240, 752, 702 cm^{-1}; EI-MS: *m*/*z* (%): 341 (M^+, 6), 284 (14), 91 (16), 77 (10), 40 (100). Anal. Calcd for $C_{20}H_{23}NO_2S$ (%): C, 70.35; H, 6.79; N, 4.10; Found: C, 70.29; H, 6.71; N, 3.81.

4.3.1.10. (4*S*)-(2-(4-Benzyl-4,5-dihydrooxazol-2-yl)-5-phenylthiophen-3-yl)diphenyl methanol 2k. Yield (67.4%, 228 mg); pale yellow solid; mp 149–151 °C; $[\alpha]_D^{24} = +89.4$ (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 9.33 (s, 1H), 7.44–7.15 (m, 18H), 6.97 (m, 2H), 6.54 (m, 1H), 4.38 (m, 1H), 4.20 (m, 1H), 3.96 (m, 1H), 2.70 (m, 1H), 2.20 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 160.3, 155.4, 147.3, 147.1, 145.4, 137.4, 133.1, 129.1, 128.9, 128.5, 128.2, 127.7, 127.6, 127.0, 126.5, 126.0, 123.1, 79.3, 72.0, 67.4, 40.7; IR (film): 3060, 2928, 1633, 1601, 1453, 759, 733, 700 cm^{-1}; EI-MS: *m*/*z* (%): 501 (M^+, 100), 424 (54), 291 (62), 105 (37), 91 (27). Anal. Calcd for $C_{29}H_{27}NO_2S$ (%): C, 79.01; H, 5.43; N, 2.79; Found: C, 78.88; H, 5.69; N, 2.64.

4.3.1.11. (4*S*)-(2-(4-Benzyl-4,5-dihydrooxazol-2-yl)-5-α-naphthyl thiophen-3-yl)diphenyl methanol 2l. Yield (54.1%, 128 mg); pale yellow solid; mp 137–138 °C; $[\alpha]_D^{24} = +105.4$ (*c* 0.65, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 9.35 (s, 1H), 8.07–8.04 (m, 1H), 7.88 (m, 2H), 7.49–7.21 (m, 17H), 7.00 (m, 2H), 6.48 (s, 1H), 4.42 (m, 1H), 4.25 (m, 1H), 4.00 (m, 1H), 2.75 (dd, $J = 5.5$, 13.8 Hz, 1H), 2.20 (dd, $J = 8.1$, 13.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 160.2, 154.6, 147.3, 147.1, 143.3, 137.2, 133.6, 132.6, 131.1, 130.8, 129.0, 128.9, 128.3, 128.2 (5), 128.0, 127.5, 127.4, 126.9, 126.6, 126.3, 126.0, 124.9, 124.8 (7), 79.3, 71.9, 67.2, 40.6; IR (film): 3085, 3059, 3028, 1633, 1447, 751, 732, 700 cm^{-1}; MALDI-MS (*m*/*z*): 552 (M^++1). Anal. Calcd for $C_{34}H_{29}NOS$ (%): C, 80.55; H, 5.30; N, 2.54; Found: C, 80.70; H, 5.56; N, 2.35.

4.3.1.12. (4*S*)-(3-(4-Benzyl-4,5-dihydrooxazol-2-yl)thiophen-2-yl)diphenyl methanol 2m. Yield (67%, 108 mg); colorless crystal (hexane–ethyl acetate); mp 103–105 °C; $[\alpha]_D^{22} = +141.4$ (*c* 0.47, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 9.46 (s, 1H), 6.98–7.39 (m, 17H), 4.35 (m, 1H), 4.21 (m, 1H), 3.93 (m, 1H), 2.65 (dd, $J = 5.4$, 13.7 Hz, 1H), 2.0 (dd, $J = 8.4$, 13.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm): 161.3, 158.2, 147.1, 146.6, 137.4, 129.2, 128.8, 128.3, 127.5, 127.4, 127.3, 127.2, 127.0, 126.2, 125.1, 123.1, 78.3, 71.3, 66.4, 40.5; IR (film): 3085, 3060, 2904, 1644, 1447, 1155, 1024, 980, 754, 699 cm^{-1}; EI-MS: *m*/*z* (%): 426 (M^++1, 64), 214 (61), 141 (55), 105 (60), 77 (60), 44 (100). Anal. Calcd for $C_{27}H_{23}NO_2S$ (%): C, 76.21; H, 5.45; N, 3.29; Found: C, 76.37; H, 5.44; N, 2.99.

4.3.2. Procedure for the preparation of 2h. 0.38 mL (0.98 mmol, 1.6 M in hexanes) *n*-BuLi, was added dropwise to a solution of **1h** (200 mg, 0.82 mmol) in Et_2O (5 mL) at

−78 °C under argon, after stirring for 30 min at this temperature and another 30 min at 0 °C, DMF (74 μL, 0.99 mmol) was added slowly to the resulting yellow solution at −78 °C and the mixture was allowed to stir overnight at room temperature. Then water (6 mL) was added. The aqueous phase was extracted with Et_2O (4 mL × 3), dried over anhydrous $NaSO_4$ and then concentrated in vacuo to give an oily residue, which was used directly in the next step. To a solution of this residue in THF (1.5 mL) under argon, $NaBH_4$ (38 mg, 1.0 mmol) in THF (1.5 mL) was added slowly over 15 min. The reaction was monitored by TLC (petroleum/ethyl acetate = 2:1) to be complete, after usual workup, column chromatography afforded **2h** as a colorless solid (38% yield for two steps). Mp 71–73 °C; $[\alpha]_D^{24} = +35.4$ (*c* 0.67, $CHCl_3$); ^1H NMR ($CDCl_3$) δ (ppm): 7.45 (d, 1H, $J = 3.6$ Hz), 7.33–7.22 (m, 5H), 6.97 (d, 1H, $J = 3.6$ Hz), 4.85 (s, 2H), 4.61–4.51 (m, 1H), 4.35–4.30 (m, 1H), 4.16–4.11 (m, 1H), 3.27–3.21 (m, 1H), 2.76–2.68 (m, 1H), 2.31 (s, 1H); IR (film): 3932, 2923, 1640, 1364, 1062, 1018, 748, 702 cm^{-1}; EI-MS: *m/z* (%): 274 (M^++1, <1), 182 (100), 154 (21), 91 (11), 65 (12). Anal. Calcd for $C_{15}H_{15}NO_2S$ (%): C, 65.91; H, 5.53; N, 5.12; Found: C, 65.64; H, 5.69; N, 4.81.

For the characterization of **1a–d**,[8] **1e**[11] and **1g**,[11] **1m**,[12] see the references indicated, respectively.

4.4. General procedure for the asymmetric phenyl transfer reaction

Under an atmosphere of dry argon, 32 mg (0.1 mmol) of $(PhBO)_3$ was added to a flame-dried Schlenk tube followed by dropwise addition of 0.9 mL $ZnEt_2$ (1.0 M in hexanes). After stirring for 5 min at room temperature, the mixture was heated to 65 °C for 4.5 h, then cooled to room temperature and 12 mg (0.03 mmol) of **2e** was added in 2 mL freshly distilled toluene. Then the mixture was cooled to −15 °C and 28 mg (0.2 mmol) of 4-chlorobenzaldehyde in 0.5 mL toluene was added, after 14 h at this temperature the reaction was quenched with 0.1 mL diluted aqueous HCl, filtered, and concentrated followed by column chromatography to provide 32 mg of the desired product, (*R*)-(4-chlorophenyl)phenylmethanol, as a white solid. Mp 54–55 °C; $[\alpha]_D^{24} = -16.8$ (*c* 0.67, $CHCl_3$) for 82 ee% {lit.[13] $[\alpha]_D^{25} = -18.3$ (*c* 0.86, $CHCl_3$) for 94 ee%}; ^1H NMR ($CDCl_3$) δ (ppm): 7.40–7.25 (m, 9H), 5.82 (d, $J = 3.3$ Hz, 1H), 2.23 (d, $J = 3.3$ Hz, 1H); HPLC: Daicel CHIRALCEL AD column, hexane/IPA = 9:1, 0.75 mL/min, $\lambda = 254$ nm, $t_R(R) = 14.4$ min, $t_R(S) = 15.7$ min.

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