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SYNTHESIS OF CHIRAL (SULFINYL)FURYL OXAZOLINE LIGANDS AND ITS APPLICATION TO ENANTIOSELECTIVE PALLADIUM-CATALYZED ALLYLIC ALKYLATION†

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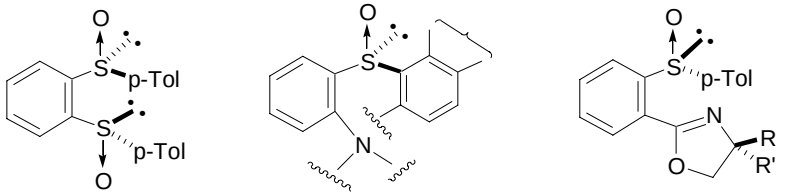
Abstract – Chiral ligands containing an oxazoline substituent and a sulfur functionality at the furan ring have been synthesized and examined for enantioselective palladium catalyzed allylic substitution reaction. The enantioselectivity observed was found to be dependent upon the nature of the sulfur center and oxazoline group, up to 91% ee was given with chiral (3-sulfinyl)furan-2-yl ligand.

INTRODUCTION

During the last decade, chiral oxazolines as a ligand in Pd-catalyzed reactions have contributed to much development of asymmetric synthesis.[1] Chiral sulfoxides have proven to be efficient chiral auxiliaries;[2] however, little is known about the use for asymmetric reactions as a catalyst. To date, although some efficient chiral sulfinyl ligands as catalysts for asymmetric synthesis have been reported, most methodology is centered to the use of a benzene ring as a tether. Taking into account that the S,S- and S,N-bidentate metal-coordinating ligands (**A**[3], **B**[4] and **C**[5]) have been found to be effective, we focused upon the use of a 5-membered aromatic heterocyle as the backbone, which would narrow the bite angle of the ligand.[6] Furan ligands (**1**) would exert steric and electronic control by introducing a sulfinyl and oxazoline groups through the furan backbone as a tether enough to reach the metal canter. As an extension of our studies on the chiral sulfoxides, [7] we describe herein the preparation of chiral sulfoxides having an oxazoline moiety and the



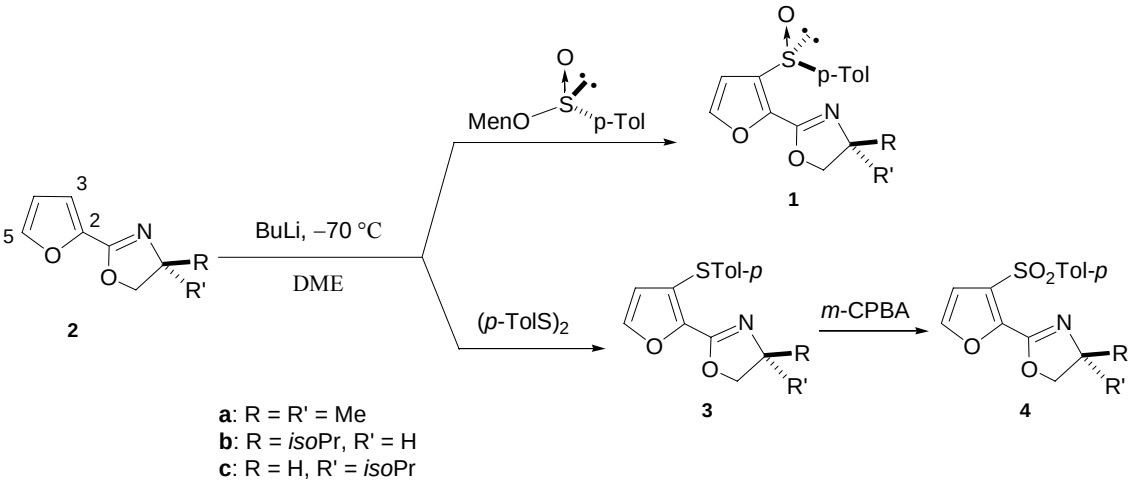
A **B** **C**

† Dedicated to Professor Ryoji Noyori in celebration of his 70th birthday.

Pd-catalyzed allylic alkylation with the ligands.[8]

RESULTS AND DISCUSSION

We undertook to introduce a sulfur substituent into the C(3) position of the furan (**2**), which has the oxazoline group in C(2) position *via* direct metallation (Scheme 1). To obtain **1a**, the first reaction

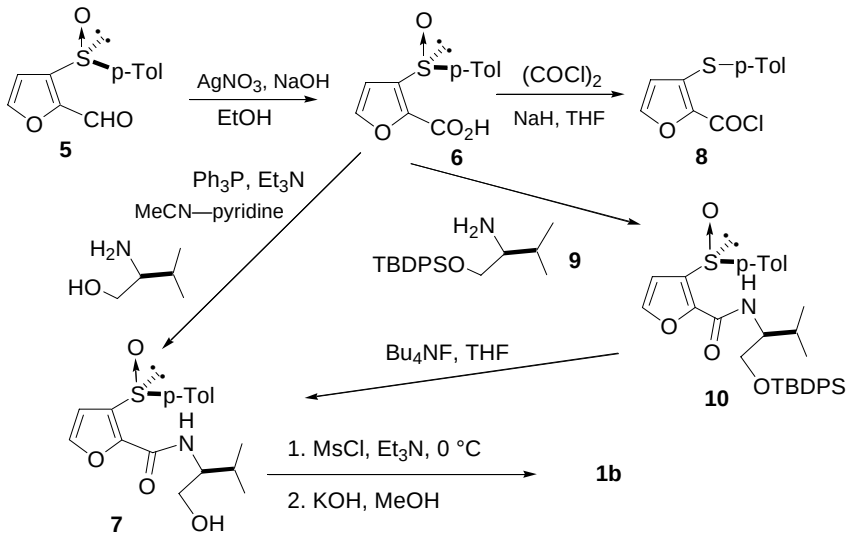


Scheme 1

examined was that of a bond formation between the 2-(2-furyl)oxazoline **2a** with *l*-menthyl *p*-toluenesulfinate. Previously, Chadwick *et al*.[9] reported that the metallation of **2a** with *n*-BuLi using dimethoxyethane (DME) as a solvent produced the 3-lithio intermediate predominantly. In fact, readily available oxazoline **2a** was treated with *n*-BuLi followed by addition of menthyl *p*-toluenesulfinate to lead to the sulfinyl oxazoline **1a** in 78% yield (80% ee). As described in the literature,[9] proper choice of DME as a solvent is as crucial as performing the regioselectivity in THF leads to the introduction of the sulfinyl group at the C(5) position in low yield. In a similar manner, oxazoline **2b** afforded the sulfinylated product **1b** in low yield (27%).

As an alternative method for the preparation of **1b**, we next turned our attention to the formation of the oxazoline ring starting from (3-sulfinyl)furanaldehyde (**5**) [10] (Scheme 2). Oxidation of **5** with silver nitrate[11] afforded carboxylic acid (**6**) in high yield. One pot condensation of acid **6** with L-valinol developed by Vorbrüggen[12] produced amide alcohol (**7)** in 10% yield. Although several methods for the formation of the amide **7** *via* acid chloride have been reported,[13] the use of oxalyl chloride or thionyl chloride resulted in deoxygenation of the sulfoxide leading to the sulfide (**8**) (*see Experimental*). Another method was a three-step sequence formation of the amide and ring closure, starting from **6**. A typical coupling reagent[14] for peptide syntheses was applicable to the acid **6**. Treatment of **6** with protected valinol (**9**) with (*N*-[(1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yloxy)(dimethylamino)methylene]-*N*-methyl-methanaminium hexafluorophosphate (*O*-HATU) and 7-aza-1-hyroxybenzotriazole (HOAt) was

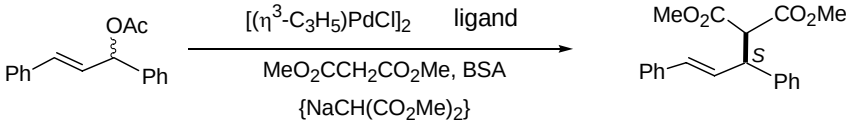
performed to produce the requisite product (**10**). Upon treatment of the TBDPS ether **10** with tetrabutylammonium fluoride under standard conditions, smooth cleavage occurred to generate the alcohol **7** quantitatively. Ring formation of the oxazoline **1b** was accomplished by a two-step sequence[15]: mesylation of **7** and subsequent exposure to base in 57% overall yield (99% de). To compare the potential of the sulfinyl ligand **1b** in catalytic effectiveness in the palladium catalyzed alkylation, the corresponding sulfide **3b** and sulfone (**4b**) were also prepared.



Scheme 2

With the ligands in hand, the effect of the ligands in the allylic alkylations of (±)-1,3-diphenyl-2-propenylacetate (**11**) with dimethyl malonate was investigated (Table).

Table Palladium-Catalyzed Alkylations of **11** with a Ligand (**1**, **3** and **4**)



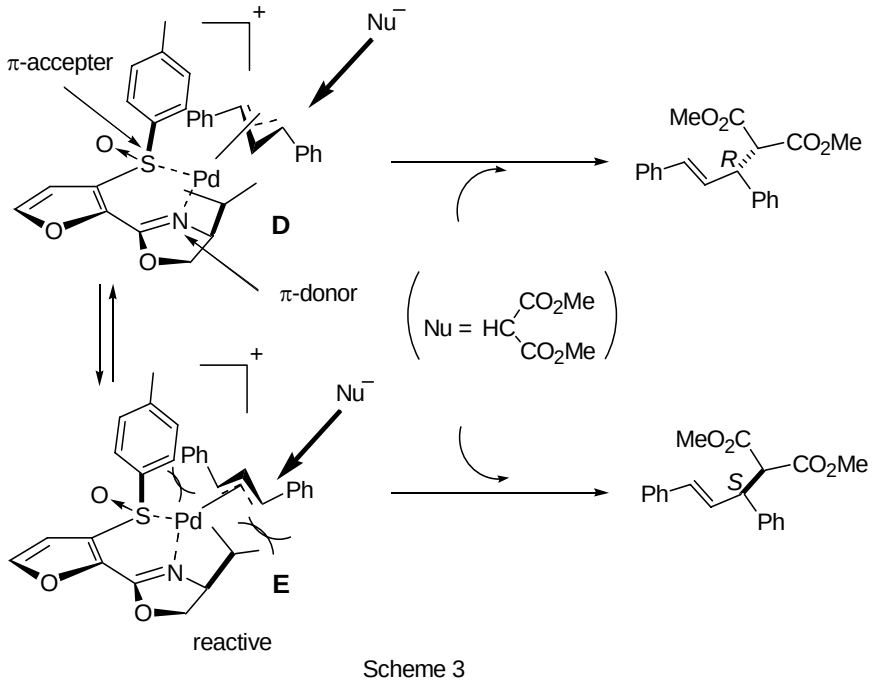
Entry	Ligand	Time/h	Solvent	Yield/%	Ee/% (*S* configuration)
1[a]	**1a**	82	CH_2Cl_2	97	19
2[a]	**1b**	66	CH_2Cl_2	<1[c]	91
3[a]	**1b**	89	MeCN	23[c]	80
4[a]	**1b**	89	*n*-C_6H_{14}	20[c]	82
5[b]	**1b**	67	THF	98	83
6[a]	**3b**	96	MeCN	91	69
7[b]	**3b**	27	THF	56	8
8[a]	**4b**	144	MeCN	8[c]	2
9[b]	**4b**	48	THF	2[c]	2

[a] Reactions conducted with dimethyl malonate, BSA and AcOK. [b] Reactions performed by the carbanion of dimethyl malonate generated treating with sodium hydride in THF as solvent. [c] Reactions were sluggish, resulted in mass recovery of starting material **11**.

A mixture of the acetate **11** with dimethyl sodiomalonate (generated with sodium hydride) or a combination of dimethyl malonate and *N*,*O*-bis(trimethylsilyl)acetamide (BSA)[16] under standard conditions[17] was treated with 5 mol% of the allylic palladium dimer and 10 mol% of one of the ligands. Good to excellent levels of enantiocontrol of the product **12** were achieved by the use of the sulfinyl ligand **1b**. Thus, the isopropyl group in the oxazoline ring gave high enantioselectivities (ee's)(entries 3–5). On the other hand, sulfide ligand **3b** in which the sulfur group is achiral gave slightly lower enantioselectivities (entries 6 and 7) than the sulfoxide ligand **1b**. The use of the sulfone ligand **4b** provided only a racemic product in poor yields.

Judging from the results (poor yields) of the sulfone ligand, it is likely that the sulfone is not capable of binding to palladium with the oxygen atom in the sulfonyl group. Sulfide ligand **3b** afforded good levels of enantioselectivities (entries 6 and 7). We believe that the enantiocontrol provided by S,N-ligands are controlled by coordination of palladium with the sulfur atom of the sulfide or sulfoxide and with the nitrogen atom of the oxazoline. The absolute stereochemistry of the product that has *S* configuration was established by chiral HPLC analysis.

Although the reason for the observed selectivity is not clear, it is speculated that the π-allyl intermediate is controlled by steric and electronic properties. Focusing on the sulfinyl ligand **1b**, the sterically favored conformation **D** due to the bulky substituents (*i.e.*, two phenyl, isopropyl and *p*-tolyl groups) may produce the *R*-isomer (Scheme 3). In the S,N-ligands, it is likely that the sulfur atom will behave as a π-acceptor[18] and the nitrogen atom would act as a π-donor.[19a] Therefore, the nucleophile should attack the more nucleophilic *trans* allylic terminus to the sulfur, leading to the *R*-isomer. On the other hand, the sterically disfavored intermediate **E** will provide the *S*-isomer. As reported by Reiser, the allylic substitution would often proceed *via* the less stable and/or reactive species[19] to result in the *S*-isomer. The observed enantioselectivity might be compatible with these results.



Scheme 3

EXPERIMENTAL

The symbol S_s expresses that the absolute configuration of the sulfinyl stereogenic center is *S*. Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. Boiling point for bulb-to-bulb distillation indicates bath temperature. IR spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer. NMR spectra were measured in $CDCl_3$ solution with tetramethylsilane as internal standard, on an EX-400 spectrometer. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), multiplet (m), and broad (br). *J*-Values are given in Hz. Mass spectra were taken with a JEOL JMS-D300 or JMS-SX102A spectrometer. Optical rotations were recorded on a JASCO DIP-360 digital polarimeter. Extracts were dried over anhydrous $MgSO_4$ before evaporation of solvents on a rotary evaporator under reduced pressure. Dry THF and diethyl ether were freshly distilled from sodium benzophenone ketyl prior to use. *m*-Chloroperoxybenzoic acid (*m*-CPBA) was used after purification by washing with phosphate buffer, pH 7.5, according to the literature method.[20] TLC analyses were performed using Merck precoated silica $60F_{254}$ plates (0.2 mm). Column chromatography was carried out on Merck silica (70–230 mesh) or Merck silica (230–400 mesh). Chiral HPLC analyses were performed using a chiral column (4.6×250 mm). Peak ratios by HPLC were determined with an integrator (Shimadzu Chromatopac C-R6A).

(4*S*)-Isopropyl-2-(furan-2-yl)-4,5-dihydrooxazole (2b) The furanyloxazoline **2b** was prepared according to the procedure for preparation of the 2-(2-thienyl)oxazolines developed by Williams *et al.*[18b] A mixture of anhydrous $ZnCl_2$ (117 mg, 0.85 mmol), L-valinol (3.54 g, 34.3 mmol) and 2-furancarbonitrile (1 mL, 11.4 mmol) in dry chlorobenzene (20 mL) was heated at reflux for 12 h. The reaction mixture was quenched by H_2O and the aqueous layer was extracted with Et_2O (20 mL×3). The combined organic layer was washed with brine, dried, and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using hexane–AcOEt (1:0→1:2) as eluent to give **2b** (1.61 g, 79 %). An analytical sample was prepared by distillation under reduced pressure. Oxazoline **2b**: A colorless oil; bp 110–120 °C / 0.8 kPa; $[\alpha]_D^{20}$ –84.7 (*c* 1.0, $CHCl_3$) for >99% ee (*S*>*R*). IR cm^{-1} (neat) 1673, 1092. ^{1}H-NMR (400 MHz) δ 0.93 (3H, d, *J* = 6.7, Me), 1.04 (3H, d, *J* = 6.7, Me), 1.86 (1H, m, CH), 4.12 (2H, m, CH_2), 4.39 (1H, m, CH), 6.48 (1H, dd, *J* = 3.5 and 1.8, furan), 6.93 (1H, dd, *J* = 3.5 and 0.7, furan), 7.54 (1H, dd, *J* = 1.8 and 0.7, furan), ^{13}C-NMR (100 MHz) δ 18.1, 18.9, 32.6, 70.2, 72.7, 111.4, 114.0, 143.0, 145.0, 155.7. EI-MS *m/z* 179 (M^+), 149, 136, 108, 83. EI-HR-MS Calcd for $C_{10}H_{13}NO_2$: 179.09463. Found: 179.09411. The ee of **2b** was confirmed by chiral HPLC of the sulfide derivative **3b** (*vide infra*).

In a similar manner, the products **2c** (bp 115–125 °C / 0.9 kPa; $[\alpha]_D^{21}$ +76.9 (*c* 1.2, $CHCl_3$) and was obtained in 78% yield.

4,4-Dimethyl-2-[(S_s)-3-(*p*-tolylsulfinyl)furan-2-yl]-4,5-dihydrooxazole (1a) To a cooled solution of the oxazoline **2a**[8] (200 mg, 1.34 mmol) in dry DME (5 mL) at –70 °C was added *n*-BuLi (0.84 mL of a 1.58 mol dm^{-3} solution in hexane, 1.34 mmol) and the mixture was stirred for 15 min at the same temperature. To the solution was added a solution of (S_S)-(–)-*l*-menthyl *p*-toluenesulfinate (395 mg, 1.34 mmol) in dry DME (5 mL). The mixture was stirred for 22 h at the same temperature and then quenched with a saturated NH_4Cl solution, and the aqueous layer was extracted with Et_2O (20 mL×3). The combined organic phase was washed with brine, dried, and concentrated. The crude product was purified by flash chromatography on silica gel using hexane–AcOEt (2:1) as eluent to give **1a** (318 mg, 78 %). Sulfoxide **1a**: A colorless oil; $[\alpha]_D^{19}$ –23.5 (*c* 1.0, $CHCl_3$) for 80% ee (S_s>R_s). IR cm^{-1} (neat) 1651 (C=N), 1050 (S→O). ^{1}H-NMR (400 MHz) δ 1.40 (6H, s, Me), 2.39 (3H, s, Me), 4.14 (2H, m, CH_2), 6.75 (1H, d, *J* = 2.0, furan), 7.29 (2H, d, *J* = 7.8, *p*-Tol), 7.49 (1H, d, *J* = 2.0, furan), 7.64 (2H, d, *J* = 7.8, *p*-Tol). ^{13}C-NMR (100 MHz) δ 21.4, 28.2, 28.3, 68.2, 79.6, 109.0, 124.6 (3C), 129.9 (2C), 135.1, 141.6, 141.7, 145.2, 153.2. EI-MS *m/z* 303 (M^+), 287, 272, 254, 232, 217. EI-HR-MS Calcd for $C_{16}H_{17}NO_3S$: 303.09292. Found: 323.09388. Chiral HPLC: Chiracel OJ-H 254 nm, hexane–2-propanol: 40:1, 0.5 mL/min; **1a**: 98.0 min, *ent*-**1a**: 85.4 min.

In a similar manner, the products **1b** and was obtained from **2b** in 27% yield. The optimized procedure for the preparation of **1b** by the other route is shown in other experimental section (*vide infra*).

(4*S*)-Isopropyl-2-[3-(*p*-tolylsulfanyl)furan-2-yl]-4,5-dihydrooxazole (3b) The reported procedure for introduction of an electrophile to the C(5) position of 2-oxazolinylfurans was followed.[8] To a cooled solution of the oxazoline **2b** (52 mg, 0.29 mmol) in dry DME (2 mL) at –70 °C was added *n*-BuLi (1.8 mL of a 1.58 mol dm^{-3} solution in hexane, 0.29 mmol) and the mixture was stirred for 10 min at the same temperature. A solution of *p*-tolyl disulfide (71.5 mg, 0.29 mmol) in dry DME (3 mL) was added. The mixture was stirred for 18 h at the same temperature and then quenched with a saturated aqueous NH_4Cl solution, and the aqueous layer was extracted with Et_2O (15 mL×3). The combined organic phase was washed with brine, dried, and concentrated. The crude product was purified by flash chromatography on silica gel using hexane–AcOEt (2:1) as eluent to give **1b** (26 mg, 30 %) accompanied by recovered unchanged **2b** (23 mg, 44%) and a small amount of the regioisomer of **3b**. Sulfide **3b**: mp 49–51 °C (from hexane); $[\alpha]_D^{20}$ –47.7 (*c* 1.0, $CHCl_3$) for >99% ee. IR cm^{-1} ($CHCl_3$) 1655. ^{1}H-NMR (400 MHz) δ 0.94 (3H, d, J = 6.8, Me), 1.05 (3H, d, *J* = 6.8, Me), 1.85 (1H, m, CH), 2.36 (3H, s, Me), 4.15 (2H, m, CH_2), 4.44 (1H, m, CH), 6.00 (1H, d, *J* = 1.9, furan), 7.17 (2H, d, *J* = 8.1, *p*-Tol), 7.37 (1H, d, *J* = 1.9, furan), 7.42 (2H, d, *J* = 8.1, *p*-Tol). ^{13}C-NMR (100 MHz) δ 18.3, 19.1, 21.2, 32.9, 70.5, 72.7, 113.0, 126.4, 129.1, 130.1 (2C), 133.5 (2C), 137.2, 138.6, 144.2, 155.7. *Anal*. Calcd for $C_{17}H_{19}NO_2S$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.81; H, 6.31; N, 4.61.

For determination of the enantiomeric excess of **3b**, an analytical sample of the enantiomer, **3c** was prepared from **2c** in a similar manner, and the ee of **3b** was estimated as >99%. Chiral HPLC: Chiralpak AD-H, 254 nm, hexane–2-propanol: 50:1; 1.0 mL/min; **3b**: 18.2 min, **3c** (= *ent*-**3b**): 21.6 min.

The regioisomer of **3b** (*i.e.*, the 2-[5-(p-tolysulfinyl)furyl]-4,4-dimethyl-4,5-dihydrooxazoline, $J_{3',4'}$ = 3.4 Hz) was also characterized by the coupling constant of the ^{1}H NMR spectrum since the value of $J_{3',4'}$ of the 2',5'-disubstituted furans is larger than that of $J_{4',5'}$ in 2',3'-disubstituted furans.

(4*S*)-Isopropyl-2-[3-(*p*-tolylsulfonyl)furan-2-yl]-4,5-dihydrooxazole (4b) To a cooled solution of the oxazoline **3b** (33 mg, 0.11 mmol) in dry dichloromethane (5 mL) at 0 °C was added *m*-CPBA (43 mg, 0.25 mmol) and the mixture was stirred for 2 h at the same temperature. The mixture was diluted with Et_2O (40 mL) and the organic phase was then washed with an aqueous 1% NaOH (10 mL×2). The organic extracts were washed with brine, dried, and concentrated. The crude product was purified by flash chromatography on silica gel using hexane–AcOEt (1:1) as eluent to give **4b** (29 mg, 79 %). Sulfone **4b**: A colorless oil; $[\alpha]_D^{18}$ –63.8 (*c* 1.5, $CHCl_3$) for >99% ee. IR cm^{-1} ($CHCl_3$) 1659, 1329, 1152. ^{1}H-NMR (400 MHz) δ 0.89 (3H, d, *J* = 6.8, Me), 1.00 (3H, d, *J* = 6.8, Me), 1.8 (1H, m, CH), 2.42 (3H, s, Me), 4.1 (2H, m, CH_2), 4.4 (1H, m, CH), 6.97 (1H, d, *J* = 2.0, furan), 7.30 (2H, d, *J* = 8.4, *p*-Tol), 7.50 (1H, d, *J* = 2.0, furan), 7.95 (2H, d, *J* = 8.4, *p*-Tol). ^{13}C-NMR (100 MHz) δ 18.3, 18.9, 21.6, 32.6, 70.8, 73.0, 113.1, 128.4 (2C), 129.3, 131.3, 138.3, 142.1, 143.5, 144.5, 153.8. EI-MS *m/z* 290 (M^+–C_3H_7), 290, 268, 198, 91. FAB-HR-MS Calcd for $C_{17}H_{20}NO_4S$(M^++H): 334.11130. Found: 334.11230.

(S_s)-3-(*p*-Tolylsulfinyl)furan-2-carboxylic acid (6) A mixture of the sufinylaldehyde (**5**)[11] (>98% ee, 275 mg, 1.17 mmol) and silver nitrate (250 mg, 1.47 mmol) in EtOH (10 mL) was treated with a solution of 12% of aqueous NaOH (6 mL; w/v) at rt. After being stirred for 0.5 h, the mixture was filtered through a short pad of Celite and the filtrate was extracted with $CHCl_3$ (10 mL). The aqueous layer was acidified to pH 3 and the acidic solution was extracted with $CHCl_3$ (20 mL×3). The combined extracts from the acidic aqueous layer were washed with saturated brine (30 mL), dried, and concentrated to give the acid **6** (275 mg, 94%) as a solid. mp 172–174 °C (from EtOAc/hexane); $[\alpha]_D^{26}$ –198 (*c* 1.8, $CHCl_3$) for 99% ee (S_s>R_s). IR cm^{-1} (KBr) 3200~2800, 1705 (C=O), 1025 (S→O). ^{1}H-NMR (400 MHz) δ 2.41 (3H, s, Me), 6.67 (1H, d, *J* = 1.8, furan), 7.33 (2H, d, *J* = 8.2, *p*-Tol), 7.61 (1H, d, *J* = 1.8, furan), 7.66 (2H, d, *J* = 8.2, *p*-Tol). ^{13}C-NMR (100 MHz, CD_3OD) δ 21.4, 110.1, 126.1 (2C), 131.2 (2C), 139.0, 142.3, 143.3, 143.9, 148.2, 159.9. EI-MS *m/z* 250 (M^+), 234, 202, 108, 91. *Anal*. Calcd for $C_{12}H_{10}O_4S$: C, 57.60; H, 4.03. Found: C, 57.53; H, 4.05.

***N*-[(1*S*)-1-(*tert*-Butyldiphenylsilyloxy)methyl-2-methylpropyl]-(S_s)-2-(3-*p*-tolylsulfinyl)furamide (10)** A mixture of the acid **6** (60 mg, 0.24 mmol), *O*-(*tert*-butyldiphenylsilyl)-L-valinol **9**[21] (90 mg, 0.26 mmol), HATU (182 mg, 0.48 mmol), HOAt (66 mg, 0.48 mmol) and *i*Pr_2NEt (0.3 mL) in dry CH_2Cl_2

(20 mL) was stirred at rt overnight. The mixture was washed sequentially with sat. $NaHCO_3$ and sat. brine. The organic phase was dried and concentrated in vacuo. The crude product was purified by flash chromatography on silica gel using hexane–AcOEt (1:3) as eluent to give **10** (136 mg, 99 %) as a solid. mp 148–150 °C (from EtOAc); $[\alpha]_D^{22}$ –196 (*c* 1.0, $CHCl_3$) for 99% ee (S_s,1*S*>R_s,1*R*); 99% de (S_s,1*S*>R_s,1*S*). IR cm^{-1} (KBr) 3426, 1662 (C=O), 1053 (S→O). ^{1}H-NMR (400 MHz) δ 0.91 (3H, d, *J* = 6.8, Me), 0.95 (3H, d, *J* = 6.8, Me), 1.07 (9H, s, Me×3), 2.05 (1H, m, CH), 2.36 (3H, s, Me), 3.74 (1H, dd, *J* = 11.0, 4.2, CHH), 3.8–3.9 (2H, m, N-CH and CHH), 6.74 (1H, br, NH), 6.92 (1H, d, *J* = 1.9, furan), 7.24 (2H, d, *J* = 8.3, *p*-Tol), 7.2–7.75 (10H, m, ArH), 7.40 (1H, d, *J* = 1.9, furan), 7.75 (2H, d, *J* = 8.3, *p*-Tol). ^{13}C-NMR (100 MHz) δ 19.0, 19.3, 19.5, 21.4, 26.9 (2C), 29.2, 55.8, 63.5, 109.3, 124.7, 127.7 (2C), 127.8 (2C), 129.8 (2C), 129.9 (2C), 133.0 (2C), 135.5 (2C), 136.2, 141.4, 142.4, 143.5, 143.8, 156.7. EI-MS *m/z* 516 (M^+–C_4H_9), 500, 430, 199. *Anal*. Calcd for $C_{33}H_{39}NO_4SiS$: C, 69.08; H, 6.85; N, 2.44. Found: C, 69.01; H, 6.82; N, 2.39.

***N*-[(1*S*)-1-Hydroxymethyl-2-methylpropyl]-(S_s)-2-(3-*p*-tolylsulfinyl)furamide (7)** To a solution of tetrabutylammonium fluoride (9 mL of a 0.2 mol dm^{-3} solution in THF, 1.8 mmol) was added the TBDPS ether **10** (370 mg, 0.6 mmol) in dry THF (20 mL) at rt. After being stirred for 1 h, the mixture was diluted with Et_2O (30 mL). The organic phase was washed sequentially with sat. $NaHCO_3$ and sat. brine. The organic phase was dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica gel using MeOH–AcOEt (1:9) as eluent to give **7** (201 mg, 93%). mp 172–173 °C (from EtOAc/hexane); $[\alpha]_D^{20}$ –280 (*c* 0.8, $CHCl_3$) for 99% ee (S_s,1*S*>R_s,1*R*); 99% de (S_s,1*S*>R_s,1*S*). IR cm^{-1} ($CHCl_3$) 3429, 1651, 1011 (S→O). ^{1}H-NMR (400 MHz) δ 0.94 (3H, d, *J* = 6.8, Me), 1.00 (3H, d, *J* = 6.8, Me), 1.98 (1H, m, CH), 2.37 (3H, s, Me), 3.0 (1H, br, OH), 3.79 (2H, d, *J* = 3.8, CH_2), 3.88 (1H, m, CH), 6.77 (1H, d, *J* = 1.8, furan), 7.07 (1H, br d, J = 8.6, NH), 7.27 (2H, d, *J* = 8.0, *p*-Tol), 7.38 (1H, d, *J* = 1.8, furan), 7.71 (2H, d, *J* = 8.0, *p*-Tol). ^{13}C-NMR (67.5 MHz) δ 19.0, 19.5, 21.4, 29.1, 57.0, 62.8, 109.3, 124.7 (2C), 129.9 (2C), 135.3, 141.5, 141.8, 144.0 (2C), 157.5. EI-MS *m/z* 335 (M^+), 304, 233, 217, 161. *Anal*. Calcd for $C_{17}H_{21}NO_4S$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.64; H, 6.21; N, 4.22.

Attempts to obtain the alcohol **7** from the acid **6** *via* the acid chloride were unsuccessful, resulted in the formation of the deoxygenated product of **7** *via* the acid chloride **8**. Although the intermediate **8** was not isolated, the structure of the deoxygenated product of **7** was confirmed by transformation into the sulfoxide **7** by oxidation with *m*-CPBA.

(4*S*)-Isopropyl-2-[(S_s)-3-(*p*-tolylsulfinyl)furan-2-yl]-4,5-dihydrooxazole (1b) To a solution of the alcohol **7** (115 mg, 0.34 mmol) and triethylamine (0.24 mL) in CH_2Cl_2 (15 mL) at 0 °C was added methanesulfonyl chloride (0.06 mL, 0.82 mmol) in one portion. After being stirred at the same temperature for 1 h, the mixture was diluted with $CHCl_3$ (40 mL). The solution was washed sequentially

with sat. aqueous $NaHCO_3$ solution and sat. brine. The organic phase was dried and concentrated in vacuo. To the residue (140 mg, 0.34 mmol) in MeOH–THF (21 mL, 2:5) was added KOH (95 mg, 1.7 mmol) and the mixture was stirred vigorously at rt for 1 h. After removal of the solvent, the residue was partitioned between $CHCl_3$ (40 mL) and sat. brine (15 mL). The organic phase was dried and evaporated in vacuo. The crude product was purified by flash chromatography on silica using MeOH–AcOEt (1:2) as eluent to give **1b** (62 m g, 57%) as an oil. $[\alpha]_D^{17}$ –29.2 (*c* 1.0, $CHCl_3$) for ee >99% (S_s,4*S*>R_s,4*R*); de >99% (S_s,4*S*>R_s,4*S*). IR cm^{-1} ($CHCl_3$) 1651 (C=N), 1052 (S→O). ^{1}H-NMR (400 MHz) δ 0.94 (3H, d, *J* = 6.8, Me), 1.03 (3H, d, *J* = 6.8, Me), 1.89 (1H, m, CH), 2.38 (3H, s, Me), 4.17 (2H, m, CH_2), 4.47 (1H, m, CH), 6.80 (1H, d, *J* = 1.8, furan), 7.27 (2H, d, *J* = 8.1, *p*-Tol), 7.50 (1H, d, *J* = 1.8, furan), 7.67 (2H, d, *J* = 8.1, *p*-Tol). ^{13}C-NMR (100 MHz) δ 18.3, 18.9, 21.4, 32.7, 70.8, 73.0, 77.3, 109.0, 124.7 (2C), 129.9 (2C), 135.3, 140.1, 141.6, 141.8, 145.1, 154.5. EI-MS *m/z* 317 (M^+), 301, 274, 258, 217, 201, 182. HR-MS Calcd for $C_{17}H_{19}NO_3S(M^+)$: 317.10857. Found: 317.10880.

For determination of the diastereoisomeric excess of **1b**, an analytical sample of **1b** (S_s,4*S*) and the diastereoisomer of **1b** (*dia*-**1b**, R_s,4*S*) was prepared by oxidation of **3b** with *m*-CPBA. Chiral HPLC: Chiralcel OJ-H, 254 nm, hexane–2-propanol: 30:1; 1.0 mL/min; **3b**: 46.6 min, *dia*-**1b**: 30.4 min.

For the determination of the enantiomeric excess of **1b**, an analytical sample of **1b**, and the enantiomer of **1b** (= **1c**) was obtained by the reaction sequence as below.

In a similar manner to the procedure of **2a**, the oxazoline **2c** ($[\alpha]_D^{21}$ +76.9 (*c* 1.2, $CHCl_3$) for 99% ee) was obtained as a colorless oil; bp 115–125 °C/0.9 kPa. Regioselective lithiation of **2c** by the use of *n*-BuLi in DME as solvent followed by trapping with *p*-tolyl disulfide produced the sulfide **3c**.

Typical Procedure for Pd-catalyzed Asymmetric Nucleophilic Substitution reaction of 1,3-diphenyl-2-propenyl acetate 11 with chiral, sulfur-containing oxazolines.

(*Entry 3 in Table*). Under an argon atmosphere, to a suspension of $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (3.7 mg, 0.01 mmol, 5 mol%) in acetonitrile (0.5 mL) was added a solution of the ligand **1b** (6.3 mg, 0.02 mmol, 10 mol%) in acetonitrile (1 mL) at rt. After being stirred for 1 h at the same temperature, to the mixture was added a suspension of (±)-1,3-diphenyl-2-propenyl acetate **11** (50 mg, 0.198 mmol), *N*,*O*-bis(trimethylsilyl)acetamide (0.15 mL, 0.594 mmol) and potassium acetate (2 mg, 0.0198 mmol). After being stirred for 89 h, the reaction was quenched with a sat. aqueous NH_4Cl solution. The aqueous layer was extracted with Et_2O (10 mL×3). The combined extracts were washed with brine, dried, and concentrated. The crude product was purified by preparative TLC on silica gel using hexane–AcOEt (4:1) as eluent to give *S*-**12** (14.6 mg, 23%, 91% ee). Chiral HPLC: Chiralcel AD-H, 254 nm, hexane–2-propanol: 50:1; 1.0 mL/min; *R*-**12**: 30.8 min; *S*-**12**: 44.3 min.

(*Entry 5 in Table***)** To an ice-cooled suspension of NaH (68 mg, 2.85 mmol, mineral oil free) in dry THF (10 ml) was added dimethyl malonate (0.323 ml, 2.85 mmol) *via* syringe and the suspension was stirred at rt to become a clear solution for 0.5 h. In another flamed-dried flask, $[(\eta^3\text{-}C_3H_5)PdCl]_2$ (17.4 mg, 0.0475 mmol, 5 mol%) and the ligand **3a** (30.2 mg, 0.095 mmol, 10 mol%) in dry THF (3 ml) was added. After being stirred for 1 h at rt, the acetate **11** (240 mg, 0.95 mmol) in dry THF (3 ml) was added to the mixture. To the resulting mixture was added the solution of sodio dimethyl malonate. The mixture was stirred at rt for 21 h. After a usual work-up, the product *S*-**12** (303 mg, 98%) was obtained and the ee showed 82% by chiral HPLC.

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