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ENANTIOSELECTIVE SYNTHESIS OF SPIRO (ISOXAZOLE-ISOXAZOLINE) HYBRID LIGANDS

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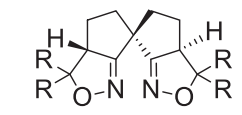
Dedicated to Professor Dr. Kiyoshi Tomioka on the occasion of his 70th birthday

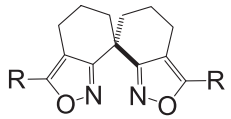
Abstract – Enantioselective synthesis of chiral spiro hybrid ligand (*R,S*)-**1** possessing isoxazole and isoxazoline rings as coordination sites was accomplished through a process involving desymmetrized intermediate **5**. The key intermediate **5** was readily obtained *via* chiral Cu-catalyzed mono-acylation of 1,3-diol **3** or enzymatic mono-deacylation of diester **6**.

INTRODUCTION

Chiral spiro ligands bearing a rigid spirocyclic framework are expected to minimize the formation of a number of undesirable conformations while achieving high stereoselectivity during asymmetric reactions.[1] On account of these distinct advantages associated with spirocyclic skeletons, the asymmetric construction of spirocyclic ligands aimed at the discovery of new chiral catalytic processes has recently attracted a great deal of attention.[2] Our group has previously investigated the efficacy of a spiro skeleton in the design of ligands and has developed several spiro ligands such as spiro bis(isoxazolines) (SPRIXs)[1b,3] and spiro bis(isoxazoles).[1b,4] These chiral spiro ligands exert a peculiar accelerative effect on various Pd-catalyzed oxidative cyclizations that stems from the lower σ-donor ability of the isoxazoline and/or isoxazole coordination sites than those of oxazolines and/or oxazoles.[2b,5]



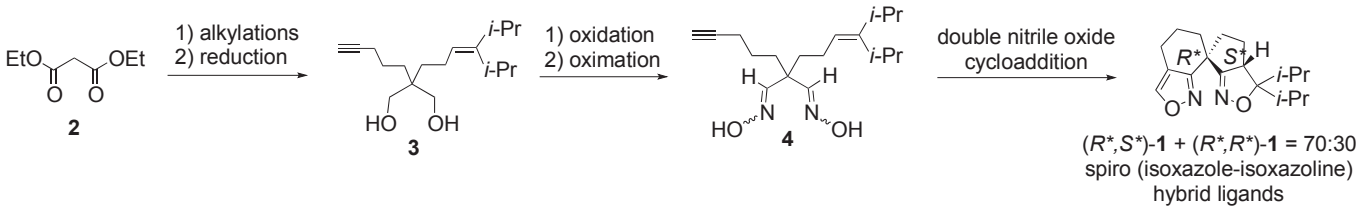
spiro bis(isoxazoline)
SPRIX



spiro bis(isoxazole)

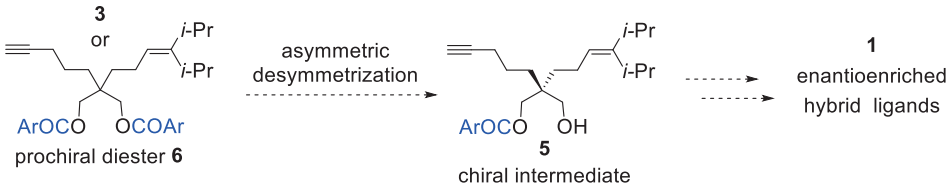
In 2007, we also developed novel chiral (isoxazole–isoxazoline) hybrid ligands **1**, which bear an unsymmetrical spiro[4.5]decane skeleton.[6] As shown in Scheme 1, two differential alkylations of diethyl

malonate (**2**) followed by reduction yielded 2,2-disubstituted 1,3-propanediol **3**. The diol **3** converted to dioxime **4** in the two steps (oxidation and oximation). Finally, the intramolecular double nitrile oxide cycloaddition of **4** afforded the desired ligand (*R*,S**)-**1** together with its diastereomer (*R*,R**)-**1**. The ligand and its diastereomer could be separated by silica gel column chromatography. However, to obtain enantiomerically pure ligand **1**, a resolution of the racemate **1** by chiral column chromatography was essential.



Scheme 1. Synthetic route of spiro (isoxazole–isoxazoline) hybrid ligand **1** (previous work)

The enantioselective desymmetrization of prochiral 2,2-disubstituted 1,3-diol derivatives is extensively studied using various enzymatic[7] and non-enzymatic[8] catalysts, and it has been established as a powerful tool for the preparation of chiral mono-ols. In contrast to the classical kinetic resolution,[9] enantiotopos-differentiating transformation of these diols affords a theoretical yield of 100%. We envisioned that chiral ligand **1** could be prepared from optically pure key intermediate **5** *via* asymmetric desymmetrization of diol **3** or diester **6** (Scheme 2). This synthetic route would produce enantiomerically pure ligand **1**, thereby circumventing the use of chiral column chromatography. Herein, we report the first enantioselective synthesis of spiro hybrid ligand **1** through the chiral Cu-catalyzed mono-acylation of 1,3-diol **3** and the enzymatic mono-deacylation of diester **6**.



Scheme 2. Synthesis of spiro hybrid ligand **1** *via* formation of optically pure intermediate **5** by asymmetric desymmetrization (this work)

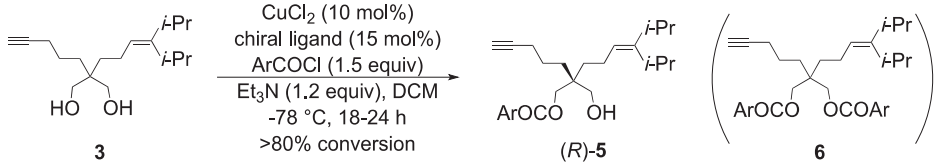
RESULTS AND DISCUSSION

Cu-Catalyzed Asymmetric Desymmetrization

In 2011, Kang *et al.* demonstrated an efficient catalytic method for the desymmetrization of a wide range of 2,2-disubstituted 1,3-propanediols *via* benzoylation using a chiral Cu catalyst.[8c] As a starting point of this work, we performed the benzoylation of **3** using the standard reaction conditions [$CuCl_2$ (10 mol%),

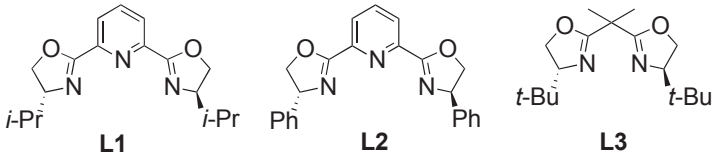
chiral ligand (15 mol%), ArCOCl (1.5 equiv), and Et_3N (1.2 equiv) in dichloromethane (DCM) at −78 °C] reported by Kang. Among the chiral catalysts screened by us (entries 1–3, Table 1), Cu(II)-PhPyBox (**L2**) exhibited better outcome, affording **5a** (Ar = Ph) in 65% yield and 48% ee (entry 2), together with the over-protected dibenzoate **6a**. Next, we investigated the effect of other ArCOCl with Cu(II)-**L2** catalyst (entries 4–6). When 2-furoyl chloride[10] (Ar = 2-furyl) was used instead of benzoyl chloride, product **5d** was obtained in higher yield with moderate ee (75% yield and 59% ee, entry 6). In terms of enantioselectivity, the use of toluene as a solvent proved effective (93% ee, entry 7). Eventually, both high chemical yield and asymmetric induction of **5d** (80% yield and 93% ee, entry 9) were achieved when a mixed solvent system of toluene and DCM in a ratio of 1:1 was used. Since the time course investigation indicated that the ee value of **5d** was kept at 93% until substrate **3** was totally consumed, it can be concluded that neither a kinetic resolution nor racemization of **5d** *via* intramolecular acyl migration[10] occurs in this process.

Table 1. Desymmetrization of 1,3-diol **3** catalyzed by chiral Cu complexes[a]



entry	chiral ligand	Ar	% yield of **5**[b] (% yield of **6**)[b]	% ee of **5**[c]
1	**L1**	Ph	**5a** 65 (**6a** 20)	**5a** 21
2	**L2**	Ph	**5a** 70 (**6a**15)	**5a** 48
3	**L3**	Ph	**5a** 55 (**6a** 21)	**5a** rac
4	**L2**	4-F-C_6H_4	**5b** 81 (**6b** 6)	**5b** 20
5	**L2**	1-naphthyl	**5c** 75 (**6c** 13)	**5c** 5
6	**L2**	2-furyl	**5d** 75 (**6d** 10)	**5d** 59
7[d]	**L2**	2-furyl	**5d** 67 (**6d** 7)	**5d** 93
8[e]	**L2**	2-furyl	**5d** 65 (**6d** 8)	**5d** 53
9[f]	**L2**	2-furyl	**5d** 80 (**6d** 5)	**5d** 93

[a]The reaction was performed with 10 mol% $CuCl_2$, 15 mol% **L**, ArCOCl (1.5 equiv), and Et_3N (1.2 equiv) in DCM at −78 °C. [b]Isolated yield. [c]Determined by using HPLC with DAICEL Chiralpak OD-H or IC. [d]Toluene was used. [e]THF was used. [f]Mixed solvent (toluene/DCM = 1/1) was used.



Enzymatic Enantioselective Desymmetrization

Enzymatic catalysts are also among the most valuable tools for the enantiotopos-differentiating transformation of prochiral 1,3-diol derivatives.[9b] These biocatalysts exhibit high compatibility with a wide range of functional groups and are environmentally benign in terms of the easy and safe work-up procedures involved.

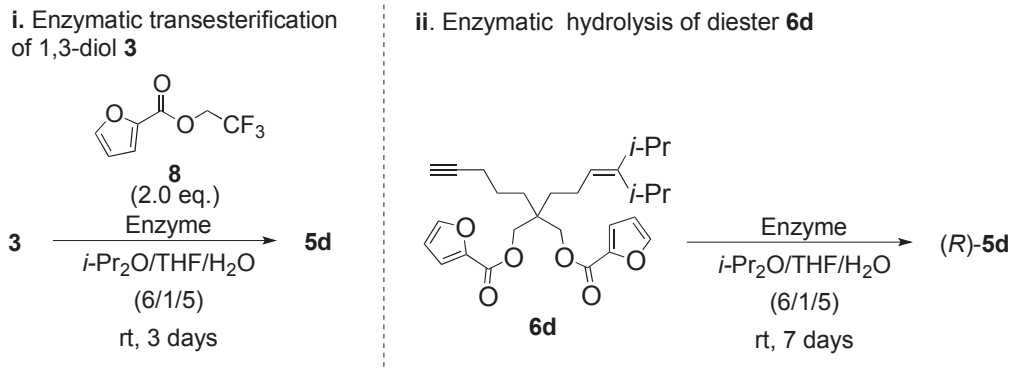
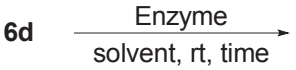


Figure 1. Enzymatic enantioselective desymmetrization

Table 2. Enzymatic hydrolytic desymmetrization of difuroate **6d**



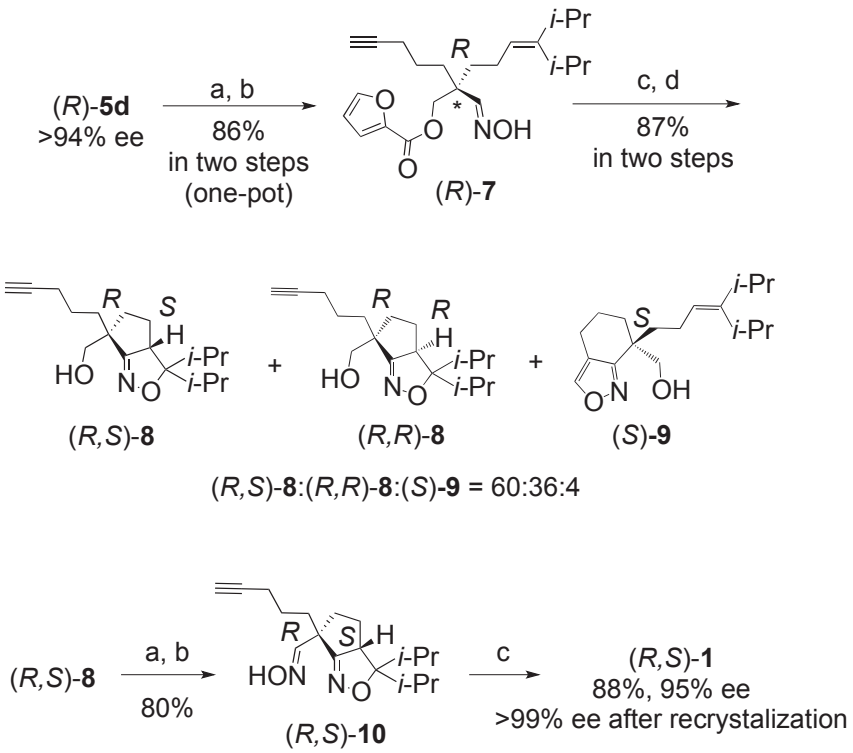
Entry	Enzyme	solvent	time (h)	% conv.[e]	% ee[f]
1[a]	Lipase OF	*i*-Pr_2O/H_2O(1/1)	48	10	67
2[a]	TOYOBO-LIP	*i*-Pr_2O/H_2O(1/1)	48	10	89
3[a]	Lipase TL	*i*-Pr_2O/H_2O(1/1)	48	10	98
4[a]	Lipase TL	*i*-Pr_2O/H_2O(1/2)	24	10	89
5[a]	Lipase TL	*i*-Pr_2O/H_2O(2/1)	24	22	94
6[a]	Lipase TL	DCM/H_2O(2/1)	96	-	-
7[a]	Lipase TL	toluene/H_2O(2/1)	96	Trace	-
8[a]	Lipase TL	EtOH/H_2O(2/1)	96	80	48
9[a]	Lipase TL	acetone/H_2O(2/1)	48	90	96
10[b]	Lipase TL	acetone/H_2O(2/1)	96	82	89
11[c]	Lipase TL	acetone/H_2O(2/1)	20	80	96
12	Lipase TL	acetone/H_2O(2/1)	72	90(72)[d]	94

[a]10 w/w of Lipase was used. [b]5 w/w of Lipase TL was used. [c]20 w/w of Lipase TL was used. [d]100 mg scale (isolated yield). [e]Conversion based on ^{1}H NMR. [f]Determined using HPLC with DAICEL Chiralpak OD-H or IC.

Initially, we attempted the enzymatic transesterification of 1,3-diol **3** (5 mg scale) with an active ester furoate such as 2,2,2-trifluoroethyl furan-2-carboxylate in a mixture of *i*-Pr_2O/THF/H_2O (6/1/5) as the reaction solvent at rt (Figure 1i).[10] However, the desired product **5d** was not obtained. Only lipase AYS Amano (from *Candida rugosa*) (10 w/w) exhibited some catalytic activity in the transformation of **3**, although with less than 5% yield with 17% ee. Other lipases [PS Amano (from *Burkholderia cepacia*), F-AP15 (from *Rhizopus oryzae*), AK Amano (from *Pseudomonas fluorescens*), and AS Amano (from *Aspergillus niger*)] led to quantitative recovery of starting material **3**. Therefore, we decided to study the hydrolytic desymmetrization of prochiral diester **6d** (Figure 1ii). The prochiral difuroate **6d** was quantitatively prepared from diol **3** by its condensation with 2-furoyl chloride in the presence of DMAP in DCM as a solvent. We started by testing the same lipases mentioned above in the hydrolysis of diester **6d** to **5d**. Interestingly, lipase AYS Amano catalyzed the hydrolysis of **6d** to give **5d** in a 10% yield with 56% ee. Encouraged by this result, we then screened other lipases for the hydrolytic desymmetrization of **6d** (Table 2). To our delight, lipase TL (from *Pseudomonas stutzeri*) showed higher enantioselectivity (98% ee, entry 3) than Lipase OF (from *Candida cylindracea*) (67% ee, entry 1) or TOYOBO-LP31 (from *Pseudomonas sp.*) (89% ee, entry 2) in *i*-Pr_2O/H_2O (1/1) at rt. To find the optimal reaction conditions, various reaction solvents and reaction times were investigated. Finally, the highest conversion (90%) and enantioselectivity (96% ee) were obtained in acetone/water (1/1) (entry 9). Furthermore, high reproducibility of yields and ees was observed even after changing the amount of lipase (5 w/w to 20 w/w, entries 10 and 11) and on a large scale (over 100 mg); the optically active monofuroate **5d** was thereby obtained in 71% isolated yield with 94% ee (entry 12).

Synthesis of Spiro-type Chiral Ligand

With the enantioenriched monoester **5d** in hand, we next focused our attention on the preparation of optically pure spiro hybrid ligand (*R,S*)-**1** (Scheme 3). The desymmetrized intermediate (*R*)-**5d** was converted into monoxime (*R*)-**7** *via* Swern oxidation followed by oximation in one pot. Since the first intramolecular nitrile oxide cycloaddition of (*R*)-**7** afforded inseparable isoxazoline and isoxazole derivatives, the mixture was then treated with lithium hydroxide to deprotect the 2-furoyl group. As a result, (*R,S*)-**8**, (*R,R*)-**8**, and (*S*)-**9** were obtained in a ratio of 60:36:4 as easily separable products by silica gel column chromatography in 87% total yields in two steps. Finally, (*R,S*)-**1** was synthesized from the obtained (*R,S*)-**8** following above-mentioned three step sequence. Optically pure (*R,S*)-**1** (>99% ee) was obtained by single recrystallization from *n*-hexane and ether. The absolute configurations of **1**, **5**, and **7**–**10** were assigned by comparison with the reported data.[6]



Scheme 3. Enantioselective synthesis of spiro (isoxazole–isoxazoline) hybrid ligand **1**. Reagents and conditions: (a) Swern oxidation. $(COCl)_2$, CH_2Cl_2, DMSO, −78 °C, Et_3N; (b) $NH_2OH{\cdot}HCl$, pyridine, 0 °C then rt; (c) aq. NaOCl, CH_2Cl_2, 0 °C then rt; (d) $LiOH{\cdot}H_2O$, THF/MeOH/H_2O (1/1/1), rt.

CONCLUSION

In summary, we successfully performed enantioselective synthesis of enantiomerically pure spiro (isoxazole–isoxazoline) hybrid ligand (*R,S*)-**1** *via* asymmetric desymmetrization of 1,3-diol derivatives using enzymatic and non-enzymatic catalysts. Further efforts are currently focused on the investigation of asymmetric induction and its application to the synthesis of other spiro ligands.

EXPERIMENTAL

All reactions were performed with standard Schlenk technique under N_2 atmosphere. Anhydrous CH_2Cl_2, Et_2O, THF, toluene and DMF were purchased from Kanto Chemicals and further purified by passage through activated alumina using a Glass Contour solvent purification system. Other solvents were purified prior to use by standard techniques. All other chemicals were purchased from commercial suppliers and used as received. Reactions were monitored by thin layer chromatography, on glass plates coated with silica gel with fluorescent indicator (Merck). Column chromatography was conducted on Kishida Silica Gel (spherical, 63–200 μm). Melting points (Mps) were measured using Yanaco melting point apparatus MP-S9 and were uncorrected. All NMR spectra were recorded at 25 °C on JEOL ECS400

spectrometer (400 MHz for ^{1}H and 100 MHz for ^{13}C). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^{1}H-NMR. Chemical shifts of ^{13}C-NMR are given relative to $CDCl_3$ (δ 77.16). Data for ^{1}H-NMR are reported as follows: chemical shifts (δ ppm), multiplicity, (s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublet of doublets, dq = doublet of quartets, brs = broad singlet, m = multiplets), integration and coupling constants (Hz). ESI mass spectra were recorded on a Thermo Fisher LTQ ORBITRAP XL. HPLC analyses were performed on JASCO HPLC system (JASCO PU 2080 pump and MD-2010 UV/Vis detector) using a mixture of *n*-hexane and *i*-PrOH eluents. Two types of HPLC columns have been used: Daicel columns: CHIRALCEL (OD-H, IC). Optical rotations were measured with JASCO P-1030 polarimeter. FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR4100).

Preparation of 2-(4-isopropyl-5-methylhex-3-en-1-yl)-2-(pent-4-yn-1-yl)propane-1,3-diol (3)[6]

Diethyl malonate (**2**) (5.35 mL) was readily converted into 1,3-diol **3** (7.5 g, 26.7 mmol, 76% overall yield in three steps) according to the procedure reported in reference 6; White solid (Mp 58-60 °C); ^{1}H-NMR ($CDCl_3$) δ 5.07 (t, *J* = 7.1 Hz, 1H), 3.60 (s, 4H), 2.72-2.82 (m, 1H), 2.17-2.32 (m, 5H), 1.96-2.05 (m, 3H), 1.42-1.55 (m, 4H), 1.26-1.30 (m, 2H), 1.00 (d, *J* = 7.0 Hz, 6H), 0.99 (d, *J* = 7.0 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 151.7, 120.8, 84.4, 69.1, 68.6, 41.2, 31.5, 29.9, 29.4, 28.7, 24.6, 22.3, 21.3, 20.8, 19.2; HRMS (ESI): calcd for $C_{18}H_{32}O_2Na$: *m/z* 303.2295 ($[M+Na]^+$), found: *m/z* 303.2297.

Representative Procedure for the $CuCl_2$ Catalytic Asymmetric Desymmetrization of 3

A mixture of $CuCl_2$ (10 mol%, 1.34 mg, 0.01 mmol) and PhPyBox **L2** (15 mol%, 5.54 mg, 0.015 mmol) was taken in dry CH_2Cl_2 (0.8 mL) in a reaction tube and then the mixture was stirred at room temperature for 3 h under nitrogen atmosphere. To this greenish colored catalyst solution was added the substrate **3** (28.1 mg, 0.1 mmol) dissolved in CH_2Cl_2 (0.5 mL) at −78 ºC. To this cooled solution were added furoyl chloride (14.8 μL, 0.15 mmol) and Et_3N (15.3 μL, 0.12 mmol) in sequence. The reaction was monitored upon TLC analysis until the consumption of starting material **3**. The reaction was quenched with saturated aqueous NH_4Cl (0.5 mL) at −78 ºC followed by addition of H_2O (0.2 mL) at room temperature. The normal work-up followed by chromatographic purification (EtOAc/*n*-hexane = 2/7) produced the monoester **5**.

(*R*)-2-(Hydroxymethyl)-6-isopropyl-7-methyl-2-(pent-4-yn-1-yl)oct-5-en-1-yl benzoate (5a)

Colorless oil (26.9 mg, 70% yield, 48% ee); ^{1}H-NMR ($CDCl_3$) δ 8.02-8.09 (m, 2H), 7.56-7.60 (m, 1H), 7.43-7.47 (m, 2H), 5.10 (t, *J* = 7.1 Hz, 1H), 4.23-4.33 (m, 2H), 3.41-3.47 (m, 2H), 2.72-2.88 (m, 1H), 2.15-2.32 (m, 3H), 2.01-2.14 (m, 2H), 1.92-1.96 (m, 1H), 1.24-1.66 (m, 7H), 1.00 (d, *J* = 2.3 Hz, 6H)

0.98 (d, J = 2.3 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 167.2, 151.9, 133.3, 130.0, 129.8, 128.5, 120.6, 84.3, 68.7, 66.7, 64.8, 41.8, 31.4, 29.9, 29.4, 28.7, 24.6, 22.1, 21.4, 21.3, 20.7, 19.2; HRMS (ESI): calcd for $C_{25}H_{36}O_3$: *m/z* 407.2557 ([M+Na]$^+$), found: *m/z* 407.2558 Enantiomeric excess: 48%, determined by HPLC (Daicel CHIRALCEL OD-H), eluent: *n*-hexane/*i*-PrOH = 8/1, flow rate: 1.0 mL/min, 25 °C, 248 nm) t_R = 17.81 min (minor), t_R = 20.45 min (major); $[\alpha]_D^{25}$ +2.1 (*c* 0.16, $CHCl_3$).

(*R*)-2-(Hydroxymethyl)-6-isopropyl-7-methyl-2-(pent-4-yn-1-yl)oct-5-en-1-yl 4-fluorobenzoate (5b)

Colorless oil (32.6 mg, 81% yield, 20% ee); ^{1}H-NMR ($CDCl_3$) δ 8.03-8.08 (m, 2H), 7.09-7.15 (m, 2H), 5.09 (t, J = 7.3 Hz, 1H), 4.10-4.28 (m, 2H), 3.43 (s, 2H), 2.73-2.83 (m, 1H), 2.18-2.32 (m, 3H), 2.01-2.13 (m, 2H), 1.95-2.01 (m, 1H), 1.41-1.62 (m, 7H), 1.00 (d, J = 1.8 Hz, 6H), 0.98 (d, J = 1.8 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 166.2, 152.0, 132.4, 132.3, 126.3, 120.6, 115.8, 115.6, 84.3, 68.7, 66.8, 64.8, 41.8, 31.4, 29.9, 29.8, 29.4, 28.7, 24.6, 22.1, 21.4, 20.7, 19.2; HRMS (ESI): calcd for $C_{25}H_{35}NaFO_3$: *m/z* 425.2462 ([M+Na]$^+$), found: *m/z* 425.2463; Enantiomeric excess: 20%, determined by HPLC (Daicel CHIRALCEL OD-H), eluent: *n*-hexane/*i*-PrOH = 7/1, flow rate: 1.0 mL/min, 25 °C, 254 nm) t_R = 13 min (minor), t_R = 11.5 min (major); $[\alpha]_D^{25}$ +1.3 (*c* 0.21, $CHCl_3$).

(*R*)-2-(Hydroxymethyl)-6-isopropyl-7-methyl-2-(pent-4-yn-1-yl)oct-5-en-1-yl 1-naphthoate (5c)

Colorless oil (32.6 mg, 75% yield, 5% ee); ^{1}H-NMR ($CDCl_3$) δ 8.60 (s, 1H), 7.88-8.08 (m, 4H), 7.54-7.63 (m, 2H), 5.12 (t, J = 7.0 Hz, 1H), 4.25-4.36 (m, 2H), 3.45-3.51 (m, 2H), 2.76-2.86 (m, 1H), 2.21-2.33 (m, 3H), 2.04-2.15 (m, 2H), 1.96 (q, J = 3.1 Hz, 1H), 1.23-1.66 (m, 7H), 1.01 (d, J = 3.2 Hz, 6H), 0.99 (d, J = 3.2 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 167.5, 151.9, 135.7, 132.5, 131.4, 129.5, 128.5, 128.4, 127.9, 127.2, 126.9, 125.3, 120.6, 84.3, 68.8, 66.8, 64.8, 41.9, 31.4, 31.0, 29.9, 29.4, 28.7, 24.6, 22.1, 21.41, 21.36, 20.8, 19.2; HRMS (ESI): calcd for $C_{29}H_{38}NaO_3$: *m/z* 457.2713 ([M+Na]$^+$), found: *m/z* 457.2709; Enantiomeric excess: 5%, determined by HPLC (Daicel CHIRALCEL OD-H), eluent: *n*-hexane/*i*-PrOH = 7/1, flow rate: 1.0 mL/min, 25 °C, 249 nm) t_R = 27.1 min (minor), t_R = 20.8 min (major); $[\alpha]_D^{25}$ +0.83 (*c* 0.16, $CHCl_3$).

(*R*)-2-(Hydroxymethyl)-6-isopropyl-7-methyl-2-(pent-4-yn-1-yl)oct-5-en-1-yl furan-2-carboxylate (5d)

Colorless oil (30.0 mg, 80% yield, 93% ee); ^{1}H-NMR ($CDCl_3$) δ 7.59-7.60 (m,1H), 7.19-7.20 (m, 1H), 6.52-6.53 (m, 1H), 5.08 (t, J = 6.8 Hz, 1H), 4.23 (dd, J = 10.8, 16 Hz, 4H), 3.40-3.48 (m, 2H), 2.78 (sept, J = 6.8 Hz, 1H), 2.19-2.32 (m, 4H), 2.00-2.11 (m, 3H), 1.95 (t, J = 2.8 Hz, 1H), 1.24-1.61 (m, 8H), 1.00 (d, J = 2.7 Hz, 6H), 0.98 (d, J = 2.7 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 151.8, 146.6, 120.5, 118.3, 111.9, 84.2, 68.6, 67.0, 64.9, 60.4, 41.6, 31.2, 29.7, 29.3, 28.6, 24.5, 22.0, 21.3, 20.6, 19.1; HRMS (ESI): calcd for

$C_{23}H_{34}NaO_4$: *m/z* 397.2349 ([M+Na]$^+$), found: *m/z* 397.2354; Enantiomeric excess: 93%, determined by HPLC (Daicel Chiralpak OD-H, eluent: *n*-hexane/*i*-PrOH = 4/1, flow rate: 1.0 mL/min, 25 °C, 254 nm) t_R = 14.3 min (minor), t_R = 20.5 min (major); $[\alpha]_D^{24}$ +8.27 (*c* 0.75, $CHCl_3$).

Preparation of 2-(4-isopropyl-5-methylhex-3-en-1-yl)-2-(pent-4-yn-1-yl)propane-1,3-diyl bis(furan-2-carboxylate) (6d)

To a solution of 2-(4-isopropyl-5-methylhex-3-en-1-yl)-2-(pent-4-yn-1-yl) propane-1,3-diol (**3**) (300 mg, 1.07 mmol) in CH_2Cl_2 (15 mL) was added 4-DMAP (287 mg, 2.35 mmol) at 0 °C. To the mixture was added 2-furoyl chloride (0.233 mL, 2.35 mmol) dropwise, and the reaction mixture was stirred at rt for 22 h. The reaction was quenched by the addition of sat. aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with sat. aq. $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography (*n*-hexane/EtOAc = 98/2 to 3/1) to afford 2-(4-isopropyl-5-methylhex-3-en-1-yl)-2-(pent-4-yn-1-yl)propane-1,3-diyl bis(furan-2-carboxylate) (**6d**) (500 mg, quant); white solid (Mp 84.9-86.5 °C); ^{1}H-NMR ($CDCl_3$) δ 7.57 (m, 2H), 7.16 (m, 2H), 6.49-6.50 (m, 2H), 5.06 (t, 1H, *J* = 6.8 Hz), 4.26 (s, 4H), 2.73 (sept, 1H, *J* = 6.8 Hz), 2.29-2.30 (m, 3H), 2.04-2.11 (m, 2H), 1.91 (t, 1H, *J* = 2.4 Hz), 1.58-1.60 (m, 4H), 1.43-1.48 (m, 2H), 0.94-0.98 (m, 12H); ^{13}C-NMR ($CDCl_3$) δ 158.5, 152.2, 146.5, 144.4, 120.0, 118.0, 111.8, 83.8, 68.7, 66.5, 39.9, 30.6, 29.3, 28.6, 24.5, 22.0, 21.2, 20.7, 19.0; HRMS (ESI): calcd for $C_{28}H_{36}NaO_6$: *m/z* 491.2410 ([M+Na]$^+$), found: *m/z* 491.2390.

General procedure for enzymatic preparation of (*R*)-(+)-2-(hydroxymethyl)-6-isopropyl-7-methyl-2-(pent-4-yn-1-yl)oct-5-en-1-yl furan-2-carboxylate ((*R*)-5d)

To a round bottom vessel (100 mL) with a stir bar were added **6d** (100 mg, 0.214 mmol) and Lipase TL (1.00 g, 10 w/w for **6d**), followed by the addition of acetone (20 mL) and water (10 mL). After being stirred at rt for 70 h, the reaction mixture was filtered through a Celite pad. The filtrate was concentrated, and the residue was diluted with ether. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The resulting residue was purified by silica gel chromatography (*n*-hexane/EtOAc = 20/1 to 4/1 to 3/1) to afford (*R*)-**5d** (57.7 mg, 72% yield, 94% ee) as a colorless oil; enantiomeric excess: 94% ee, determined by HPLC (Daicel Chiralpak IC, eluent: *n*-hexane/*i*-PrOH = 7/1, flow rate: 0.8 mL/min, 25 °C, 254 nm) t_R = 18.4 min (minor), t_R = 24.1 min (major); $[\alpha]_D^{25}$ +8.42 (*c* 0.202, $CHCl_3$).

Preparation of (*R*)-2-((hydroxyimino)methyl)-6-isopropyl-7-methyl-2-(pent-4-yn-1-yl)oct-5-en-1-yl furan-2-carboxylate ((*R*)-7)

To a solution of $(COCl)_2$ (25.3 μL, 0.29 mmol) in CH_2Cl_2 (0.5 mL) was added a solution of DMSO (27.8 μL, 0.39 mmol) in CH_2Cl_2 (0.2 mL) slowly at −78 °C, and the mixture was stirred for 30 min. To the mixture was added a solution of (*R*)-**5d** (56.6 mg, 0.151 mmol) in CH_2Cl_2 (0.7 mL) dropwise at −78 °C, and the reaction mixture was stirred for 30 min. Et_3N (94.6 μL, 0.68 mmol) was then added to the reaction mixture at −78 °C. After being stirred for 1 h at rt, to the reaction mixture were added pyridine (0.38 mL) and NH_2OH-HCl (27.3 mg, 0.39 mmol) at 0 °C. The reaction mixture was stirred overnight at rt. The mixture was diluted with EtOAc, washed with 1N aq. HCl, brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/EtOAc = 20/1 to 3/1 to 1/1) to give (*R*)-**7** (50.6 mg, 86% yield) as a colourless oil; ^{1}H-NMR ($CDCl_3$) δ 7.58-7.59 (m, 1H), 7.34 (s, 1H), 7.16-7.17 (m, 1H), 7.13 (s, 1H), 6.50-6.51 (m, 1H), 5.05 (t, *J* = 6.8 Hz, 1H), 4.35 (s, 2H), 2.72 (sept, *J* = 6.8 Hz, 1H), 2.18-2.30 (m, 3H), 1.97-2.11 (m, 2H), 1.93 (t, *J* = 2.8 Hz, 1H), 1.49-1.78 (m, 6H), 0.95-0.98 (m, 12H); ^{13}C-NMR ($CDCl_3$) δ 158.4, 155.0, 152.2, 146.5, 144.4, 119.9, 118.0, 111.8, 83.8, 68.8, 66.1, 43.1, 34.6, 33.0, 29.3, 28.6, 24.5, 22.5, 21.3, 21.2, 21.2, 18.9; HRMS (ESI): calcd for $C_{23}H_{33}NNaO_4$: *m/z* 410.2307 ([M+Na]$^+$), found: *m/z* 410.2291; $[\alpha]_D^{25}$ +27.3 (*c* 0.015, $CHCl_3$).

Preparation of (*R,S*)-8, (*R,R*)-8 and (*S*)-9

To a solution of (*R*)-**7** (33.1 mg, 0.085 mmol) in CH_2Cl_2 (3.6 mL) was added aq. NaOCl (>8.5% chlorine, 0.360 mL) at 0 °C, and the mixture was stirred for 5 min at 0 °C, then 24 h at rt. The reaction was quenched by the addition of 2N aq. HCl and water, and extracted with EtOAc. The organic layer was washed with brine and concentrated. The resulting residue was purified by silica gel chromatography (hexane/EtOAc = 20/1 to 2/1) to afford mixture of inseparable isoxazoline and isoxazole derivatives as a colourless oil. Therefore, to a solution of the obtained mixture in THF/MeOH/water (1/1/1, 0.9 mL) was added lithium hydroxide monohydrate (10.6 mg, 0.253 mmol) at 0 °C, and the mixture was stirred overnight at rt. The reaction was quenched by the addition of water, and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/EtOAc = 20/1 to 2/1) to afford (*R,S*)-**8**, (*R,R*)-**8** and (*S*)-**9** (21.7 mg, 87% total yield). (*R,S*)-**8**: colourless oil; ^{1}H-NMR ($CDCl_3$) δ 3.56-3.69 (m, 3H), 2.22-2.32 (m, 3H), 2.02-2.13 (m, 2H), 1.96 (t, *J* = 2.8 Hz, 1H), 1.59-1.92 (m, 5H), 1.45-1.54 (m, 1H), 0.88-1.02 (m, 12H); ^{13}C-NMR ($CDCl_3$) δ 173.2, 94.9, 83.9, 68.7, 66.5, 56.4, 45.1, 38.1, 34.3, 31.8, 31.5, 18.8, 18.6, 18.3, 18.1, 17.4; HRMS (ESI): calcd for $C_{18}H_{29}NNaO_2$: *m/z* 314.2096 ([M+Na]$^+$), found: *m/z* 314.2083; $[\alpha]_D^{26}$ +33.3 (*c* 0.060, $CHCl_3$). (*R,R*)-**8**: colourless oil; ^{1}H-NMR ($CDCl_3$) δ 3.52-3.67 (m, 3H), 2.19-2.31 (m, 3H), 2.03-2.14 (m, 2H), 1.52-1.95 (m, 8H), 0.87-1.02 (m, 12H); ^{13}C-NMR ($CDCl_3$) δ 172.4, 94.9, 84.1, 68.6, 66.8, 56.4, 44.9, 37.9, 33.7, 31.7, 31.5, 23.6, 22.7, 18.9, 18.8, 18.2, 17.6; HRMS (ESI): calcd for $C_{18}H_{29}NNaO_2$: *m/z* 314.2096 ([M+Na]$^+$), found: *m/z* 314.2086; $[\alpha]_D^{23}$ −193.3 (*c* 0.015, $CHCl_3$). (*S*)-**9**:

colourless oil; ^{1}H-NMR ($CDCl_3$) δ 8.08 (d, *J* = 1.6 Hz, 1H), δ 5.02 (t, *J* = 6.5 Hz, 1H), 3.68 (m, 2H), 2.70-2.78 (t, *J* = 7.1 Hz, 2H), 2.21-2.33 (m, 2H), 1.89-2.01 (m, 4H), 1.50-1.30 (m, 5H), 1.00 (d, *J* = 6.9 Hz, 6H) 0.97 (d, *J* = 6.9, Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ 165.0, 153.2, 150.3, 114.7, 86.9, 69.1, 40.2, 35.8, 30.3, 29.8, 25.5, 24.6, 21.2, 19.5.

Preparation of (+)-3,3-diisopropyl-6-(pent-4-yn-1-yl)-3a,4,5,6-tetrahydro-3H-cyclopenta[c]isoxazole-6-carbaldehyde oxime ((*R,S*)-10)

To a solution of $(COCl)_2$ (9.6 μL, 0.11 mmol) in CH_2Cl_2 (0.3 mL) was added a solution of DMSO (10.8 μL, 0.15 mmol) in CH_2Cl_2 (0.3 mL) slowly at −78 °C, and the mixture was stirred for 30 min. To the mixture was added a solution of (*R,S*)-**8** (16.8 mg, 0.058 mmol) in CH_2Cl_2 (0.5 mL) dropwise at −78 °C, and the reaction mixture was stirred for 30 min. Et_3N (36.3 μL, 0.26 mmol) was then added to the reaction mixture at −78 °C. After being stirred for 2 h at rt, to the reaction mixture were added pyridine (0.2 mL, 2.48 mmol) and NH_2OH-HCl (17.0 mg, 0.25 mmol) at 0 °C. The reaction mixture was stirred for 2 h at rt before quenching by the addition of 1N aq. HCl at 0 °C. The resulting mixture was extracted with EtOAc, washed with water, brine, dried over Na_2SO_4, and concentrated. The crude product was purified by silica gel chromatography (*n*-hexane/EtOAc = 3/1) to give (*R,S*)-**10** (80% yield) as a pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 7.54 (s, 1H), 7.50 (brs, 1H), 3.67 (dd, *J* = 9.2, 10 Hz, 1H), 2.69-2.76 (m, 1H), 2.16-2.44 (m, 3H), 2.01-2.09 (m, 1H), 1.50-1.97 (m, 8H), 0.87-1.01 (m, 12H); ^{13}C-NMR ($CDCl_3$) δ 170.8, 153.0, 95.7, 83.7, 68.9, 55.1, 44.7, 39.4, 36.5, 31.6, 31.3, 23.9, 22.4, 18.7, 18.5, 18.4, 17.9, 17.5; HRMS (ESI): calcd for $C_{18}H_{28}N_2NaO_2$: *m/z* 327.2048 ($[M+Na]^+$), found: *m/z* 327.2032; $[\alpha]_D^{23}$ +156.9 (*c* 0.065, $CHCl_3$).

Preparation of chiral spiro (isoxazole–isoxazoline) hybrid ligand (*R,S*)-1[6]

To a solution of (*R,S*)-**10** (13.0 mg, 0.043 mmol) in CH_2Cl_2 (1.2 mL) was added aq. NaOCl (>8.5% chlorine, 0.120 mL) at 0 °C, and the mixture was stirred for 30 min at 0 °C, then overnight at rt. The reaction was quenched by the addition of 2N aq. HCl and water, and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The resulting residue was purified by silica gel chromatography (*n*-hexane/EtOAc = 20/1 to 1/1) to afford (*R,S*)-**1** (11.4 mg, 88% yield) as a white solid (Mp 115-116 °C, lit.[6a] Mp 116 °C). After the recrystallization (*n*-hexane/Et_2O), the optical purity was raised to 99.5% ee; ^{1}H-NMR ($CDCl_3$) δ 8.10 (d, *J* = 1.4 Hz, 1H), 3.79 (dd, *J* = 11.7, 8.0 Hz, 1H), 2.87 (ddd, *J* = 12.9, 7.4, 1.9 Hz, 1H), 2.74 (dq, *J* = 16.0, 2.9 Hz, 1H), 2.21-2.51 (m, 4H), 1.72-2.09 (m, 6H), 0.91-1.06 (m, 12H); ^{13}C-NMR ($CDCl_3$) δ 173.0, 164.1, 153.5, 114.3, 95.9, 55.6, 44.9, 39.2, 35.3, 31.8, 31.3, 23.9, 20.1, 18.8, 18.7, 18.33, 18.30, 17.8; HRMS (ESI): calcd for $C_{18}H_{26}N_2NaO_2$: *m/z* 325.19 ($[M+Na]^+$), found: *m/z* 325.19; Enantiomeric excess: 99.5% ee, determined by HPLC (Daicel Chiralpak

IC, eluent: *n*-hexane/*i*-PrOH = 9/1, flow rate: 0.9 mL/min, 25 °C, 225 nm) t_R = 20.5 min (minor), t_R = 23.2 min (major); $[\alpha]_D^{23}$ −171 (*c* 0.054, $CHCl_3$), lit.[6a] $[\alpha]_D^{29}$ −178 (*c* 0.11, $CHCl_3$).

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