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Divergent synthesis of chiral spiro (isoxazole–isoxazoline) hybrid ligands

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ABSTRACT

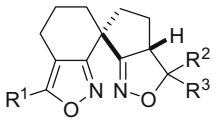
An efficient synthetic method for chiral (isoxazole–isoxazoline) ligands based on a spiro[4.5]decane framework has been developed. A variety of enantiomerically pure ligands were readily prepared via the Suzuki–Miyaura coupling. The palladium complexes of these ligands have proven to be effective catalysts for the asymmetric Wacker-type cyclization of an alkenyl alcohol.

1. Introduction

The development of novel chiral ligands is one of the most important tasks in the area of asymmetric catalysis. The spirocyclic framework has received considerable attention as a promising chiral skeleton over the past decade because ligands containing such a unique backbone are expected to exhibit unusual reactivity and selectivity.[1,2] For instance, great effort has been made toward the preparation of chiral spiro phosphorus ligands by Zhou et al.[1,3] They demonstrated the usefulness of these ligands for catalytic asymmetric reactions in which known chiral ligands did not provide any successful results. We have also been investigating the utility of chiral spiro ligands, for example, spiro bis(isoxazoline)s (SPRIXs),[4] which promote Pd-catalyzed asymmetric cyclization reactions.[4b–d]

In this class of chiral ligands, C_2-symmetric spiro scaffolds occupying a prominent position have been developed. By contrast, we have recently succeeded in the development of novel chiral (isoxazole–isoxazoline) hybrid ligands **1** bearing an *unsymmetrical* spiro[4.5]decane skeleton.[5] These hybrid ligands were found to be useful in the Pd-catalyzed enantioselective tandem cyclization of a dialkenyl alcohol producing a peculiar bicyclic product. A combination of the isoxazole and the isoxazoline coordination sites may contribute to the particular reactivity in the catalysis. It is possible that the weak donor abilities of both the heterocycles built on the fairly rigid scaffold keep the strong Lewis acidity of the 'naked' Pd metal almost intact, allowing high activity of the catalysts. Although these hybrid ligands display specific properties, synthetic limitation has emerged as a serious problem. Since a multistep process is indispensable for the preparation of all the ligands,[5] much time can be spent on arrangements for a wide variety of chiral spiro ligands. This problem therefore imposes a restriction on the development of new catalytic enantioselective reactions using the chiral spiro hybrid ligands **1**. Herein, we report an efficient strategy for the preparation of chiral spiro hybrid ligands **1**, in which Pd-catalyzed cross-coupling reaction of a key precursor for **1** is involved as the final step.

spiro[4.5]decane skeleton

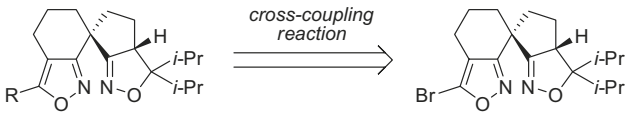


chiral spiro hybrid ligands **1**

2. Results and discussion

2.1. Design and preparation of a key precursor

The previous results imply two structural pieces of information for the design of useful chiral ligands.[5] One is the importance of two *i*-Pr groups on the isoxazoline ring (substituents R^2 and R^3) to create an effective asymmetric environment. The other is the R^1 on the isoxazole ring that significantly affects not only the enantioselectivity but also the catalytic activity. As a result, we designed 3-bromo-3′,3′-diisopropyl-3′,3a′,4′,5,5′,6-hexahydro-4*H*-spiro[2,1-benzisoxazole-7,6′-cyclopenta[*c*]isoxazole] **1a** as a key synthetic precursor (Scheme 1). The bromo group at the 3-position of the isoxazole ring can be replaced with various functional



a library of ligands **1** **1a**

Scheme 1. Divergent synthetic strategy towards chiral spiro hybrid ligands **1**.

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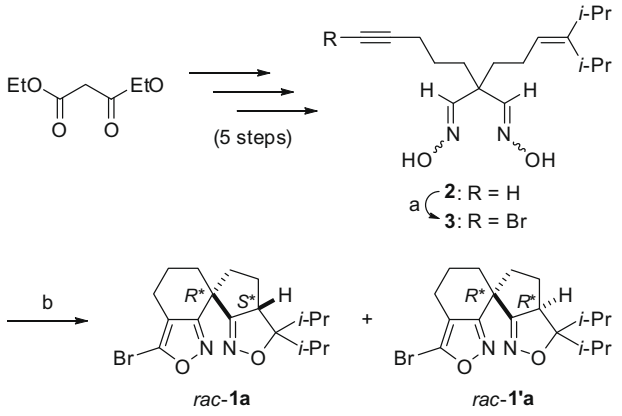
groups via cross-coupling reactions, which leads to the facile construction of a library of chiral spiro hybrid ligands **1**.

The racemic compound **1a** was readily prepared from diethyl malonate in 7 steps via the known dioxime **2**[5] (Scheme 2). Thus treatment of **2** with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of $AgNO_3$ in DMF gave the dioxime with a brominated acetylene **3** in 77% yield.[6] The following double nitrile oxide cycloaddition proceeded smoothly to afford ca. 2:1 diastereomeric mixture of **1a** and **1′a** in 63% combined yield.[7] The desired isomer **1a** was isolated by column chromatography on silica gel and identified by NMR, ESI-MS, and elemental analysis.



Scheme 2. Synthesis of the key precursor **1a**. Reagents and conditions: (a) $AgNO_3$ (10 mol %), NBS (1.3 equiv), DMF, rt, 22.5 h, 77%; (b) aq NaOCl (1.2 equiv), CH_2Cl_2, 0 °C then rt, 17 h, 42% for **1a**, 20% for **1′a**.

Once the key precursor was obtained in an enantiomerically pure form, the tedious resolution for each ligand normally required was not needed: this is the marked advantage in the present method. Gratifyingly, enantiomerically pure **1a** was obtained by optical resolution using HPLC equipped with a preparative-scale chiral stationary phase column (Daicel Chiralpak AD). In addition, single crystals of one of the enantiomers (2nd peak in the HPLC chart) were obtained from a solution of the enantiopure **1a** in Et_2O/hexane by slow evaporation. The structure of **1a** was unambiguously established by X-ray analysis (Fig. 1).[8] The distance between the two nitrogen atoms is 3.62 Å, which is nearly identical to that of the previously reported spiro hybrid ligand (3.71 Å).[5] The X-ray diffraction study also revealed the absolute configuration of the enantiomer to be (*R*,*S*).[9]

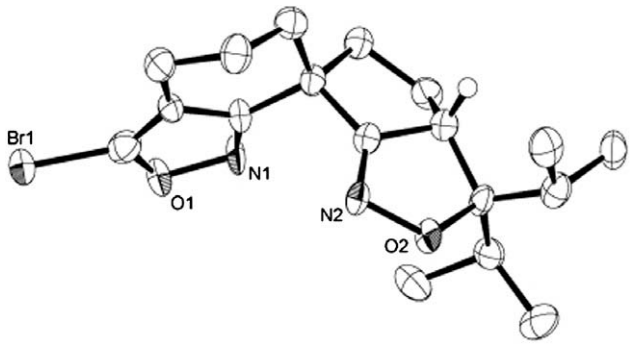
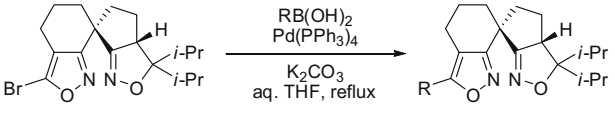


Figure 1. ORTEP drawing of (*R*,*S*)-**1a**. One molecule of two independent molecules in a unit cell is presented. The hydrogen atoms are omitted for clarity. Selected distance: N···N = 3.62 Å.

2.2. Divergent synthesis of various chiral spiro ligands

With the enantiomerically pure **1a** in hand, we applied the Suzuki–Miyaura cross-coupling to the divergent synthesis of chiral spiro hybrid ligands (Table 1). As expected, the key precursor **1a** reacted with 1.5 equiv of phenylboronic acid in the presence of K_2CO_3 and $Pd(PPh_3)_4$ catalysts in aqueous THF at reflux temperature to give the enantiomerically pure spiro ligand **1b** with a phenyl group in 94% yield (entry 1). Similarly, the spiro hybrid ligands **1c**–**g** with a *para*-substituted phenyl group were obtained in good to excellent yields (entries 2–6). It was also feasible to introduce a naphthyl group onto the isoxazole ring: compounds **1h** and **1i** were obtained in 43% and 27% yields, respectively (entries 7 and 8). The sterically more demanding 9-anthrylboronic acid, however, was inapplicable to this synthetic method under the same reaction conditions. It was found that the reaction progressed when 1,2-dimethoxyethane (DME) as the solvent and $Ba(OH)_2{\cdot}8H_2O$ as the base were used.[10] Thus, a mixture of the key precursor **1a**, 9-anthrylboronic acid (1.5 equiv), and $Ba(OH)_2{\cdot}8H_2O$ (2 equiv) in aqueous DME was refluxed for 24.5 h to furnish the spiro hybrid ligand **1j** possessing a 9-anthryl group in 57% yield (entry 9). Under these conditions, the reactions of **1a** with less reactive boronic acids (2,6-xylyl-, 2-biphenyl-, 2-trifluoromethylphenyl-, and 3,5-bis(trifluoromethyl)phenyl-boronic acids) were carried out to give the corresponding spiro hybrid ligands **1k**–**n** in excellent yields (entries 10–13).

Table 1
Preparation of enantiomerically pure aryl-substituted spiro hybrid ligands[a]



1a 1

Entry	R		Time (h)	Yield[b] (%)	Absolute configuration
1	Ph	**1b**	24	94	(*S*,*R*)
2	4-$MeOC_6H_4$	**1c**	24	92	(*R*,*S*)
3	4-$MeSC_6H_4$	**1d**	22	99	(*S*,*R*)
4	4-$Me_2NC_6H_4$	**1e**	22	78	(*S*,*R*)
5	4-$MeOCOC_6H_4$	**1f**	21	97	(*S*,*R*)
6	4-FC_6H_4	**1g**	14	99	(*S*,*R*)
7	1-Naphthyl	**1h**	24	43	(*S*,*R*)
8	2-Naphthyl	**1i**	24	27	(*S*,*R*)
9[c]	9-Anthryl	**1j**	24.5	57	(*R*,*S*)
10[c]	2,6-Xylyl	**1k**	30	95	(*S*,*R*)
11[c]	2-Biphenyl	**1l**	32.5	97	(*R*,*S*)
12[c]	2-$CF_3C_6H_4$	**1m**	21	97	(*R*,*S*)
13[c]	3,5-$(CF_3)_2C_6H_3$	**1n**	25.5	89	(*S*,*R*)

[a] All reactions were performed with **1a**, arylboronic acid (1.5 equiv), K_2CO_3 (2 equiv), and $Pd(PPh_3)_4$ (5–10 mol %) at reflux in aqueous THF.
[b] Isolated yield.
[c] DME and $Ba(OH)_2{\cdot}8H_2O$ were used instead of THF and K_2CO_3, respectively.

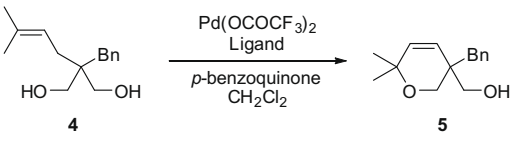
Since the Suzuki–Miyaura reaction realized a divergent synthetic protocol for chiral spiro hybrid ligands (vide supra), other Pd-catalyzed cross-coupling reactions of **1a** were examined. To our disappointment, the Mizoroki–Heck, the Sonogashira–Hagihara, and the Buchwald–Hartwig reactions did not work, instead resulting in the formation of a complex mixture or the quantitative recovery of **1a**.

2.3. Utility of spiro hybrid ligands for the Pd-catalyzed asymmetric Wacker-type cyclization

The chiral spiro hybrid ligands have proven to be effective for the asymmetric Wacker-type cyclization.[5] To explore the utility of the novel ligands **1**, we elected to study the Pd-catalyzed asymmetric oxidative cyclization of an alkenyl alcohol affording pyran derivatives,[4b] which are ubiquitous substructures among biologically active molecules. The reaction of 2-benzyl-2-(3-methyl-2-

butenyl)-1,3-propanediol **4** was carried out in the presence of 10 mol % of $Pd(OCOCF_3)_2$ and 12 mol % of chiral ligand in CH_2Cl_2 to give 6-*endo* cyclized product **5**. Representative results are summarized in Table 2. The key precursor over the course of ligand synthesis, **1a**, itself acted as a chiral ligand. Thus, a catalyst prepared in situ from the Pd salt and **1a** promoted the reaction at 25 °C, leading to the formation of **5** in 62% yield with 48% ee (entry 1). While the loss of catalytic activity was observed in the reaction employing the phenyl-substituted ligand **1b**, the enantioselectivity of **5** was slightly increased to 56% ee (entry 2). No appreciable effects were detected upon changing the electronic factor of the substituted phenyl ring (entries 3–6). The use of the bulkier 1-naphthyl ligand **1h** improved neither the chemical yield nor the enantioselectivity (entry 7). The ligands showing a high acceleration in the reaction at 25 °C, **1j**–**n**, were subjected to further investigation at lower temperatures (entries 8–12). Among them, ligand **1l** carrying a 2-biphenyl group displayed the highest selectivity at 15 °C while maintaining catalytic activity (69% yield with 82% ee, entry 10). This result was comparable to that obtained with **1o** having a *t*-Bu group on the isoxazole ring, the best ligand in the previous report,[5] suggesting the high efficiency of the present method for the preparation of useful chiral ligands (entry 13).

Table 2
Pd-catalyzed asymmetric oxidative cyclization of **4**[a]



4 **5**

Entry	Ligand	Temp. (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	25	39	62	48
2	**1b**	25	31	48[d]	56
3	**1c**	25	31	42	71
4	**1e**	25	38.5	56	67
5	**1f**	25	31	41[d]	63
6	**1g**	25	31	44	68
7	**1h**	25	34	55[d]	55
8	**1j**	15	48	54	63
9	**1k**	15	48	72	66
10	**1l**	15	48	69	82
11	**1m**	15	48	73	70
12	**1n**	15	48	65	74
13	**1o**[e]	15	48	61	78

[a] All reactions were performed in CH_2Cl_2 under an argon atmosphere. The ratio of **4** (mol)/Pd (mol)/ligand (mol)/*p*-benzoquinone (mol)/CH_2Cl_2 (L) = 1.0/0.1/0.12/4.0/4.0.
[b] GC yield using hexamethylbenzene as an internal standard unless otherwise noted.
[c] Determined by Daicel Chiralpak AD column, hexane/2-propanol (9/1).
[d] NMR yield using 1,4-dimethoxybenzene as an internal standard.
[e] For the structure of ligand **1o**, see Scheme 1 (R = *t*-Bu).[5]

3. Conclusion

In conclusion, we have developed a new efficient synthetic method toward chiral (isoxazole–isoxazoline) hybrid ligands based on an unsymmetrical spiro[4.5]decane backbone. A variety of enatiomerically pure spiro hybrid ligands were successfully synthesized via the Suzuki–Miyaura cross-coupling reaction of the key precursor, which contained a bromo group at the 3-position of the isoxazole ring. Single crystal X-ray analysis of the key precursor elucidated the absolute configuration as well as the molecular structure. The chiral spiro hybrid ligands were effective ligands for the Pd-catalyzed asymmetric oxidative cyclization of an alkenyl alcohol. Further investigation of the present methodology for the preparation of novel chiral ligands and applications of the resulting ligands to asymmetric catalysis are currently underway and will be reported in due course.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. All NMR spectra were recorded in $CDCl_3$ at 25 °C on JEOL JNM-EX270 (270 MHz for ^1H, 67.7 MHz for ^{13}C). Chemical shifts are reported δ in ppm referenced to an internal Me_4Si standard for ^1H NMR. Chemical shifts of ^{13}C NMR are given relative to $CDCl_3$ (δ 77.0). IR spectra were obtained with Perkin–Elmer System 200 FT-IR instrument. Optical rotations were measured with JASCO P-1030 polarimeter. GC analysis was carried out on a GL Sciences GC-4000 with a capillary column, InertCap 5. Enantiomeric excesses were determined by HPLC analysis equipped with a chiral stationary phase column (Daicel Chiralpak AD). Mass spectra were recorded on JEOL JMS-T100LC (ESI-MS). Melting points were measured with Yanaco micro melting point apparatus MP-S9, and were uncorrected.

4.2. Materials

CH_2Cl_2 and DMF were distilled from CaH_2 prior to use. Anhydrous THF was purchased from Kanto Chemicals and used without any purification. *p*-Benzoquinone was purified by sublimation under vacuum. Column chromatography was performed on Merck Silica Gel 60 (63–200 μm). $Pd(PPh_3)_4$,[11] 2-(pent-4-yn-1-yl)-2-(4-isopropyl-5-methylhex-3-en-1-yl)-malonaldehyde dioxime **2**,[5] and 2-benzyl-2-(3-methyl-2-butenyl)-1,3-propanediol **4**[4b] were prepared according to the reported procedures. All other chemicals were purchased from commercial suppliers and used as received.

4.3. Preparation of 2-(5-bromopent-4-yn-1-yl)-2-(4-isopropyl-5-methylhex-3-en-1-yl)-malonaldehyde dioxime 3

To a solution of **2** (2.62 g, 8.55 mmol) in dry DMF (26 mL) were added *N*-bromosuccinimide (1.98 g, 11.1 mmol) and $AgNO_3$ (0.146 g, 0.855 mmol), which was stirred at room temperature for 22.5 h. After the reaction was quenched by the addition of ethyl acetate and H_2O, the mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 7/1–6/1) to give **3** (2.55 g, 77%) as a white solid. Mp: 52–55 °C. ^1H NMR: δ 0.98 (d, J = 6.9 Hz, 6H), 0.99 (d, J = 6.9 Hz, 6H), 1.50–1.58 (m, 2H), 1.64–1.71 (m, 2H), 1.74–1.80 (m, 2H), 1.99–2.08 (m, 2H), 2.19–2.31 (m, 3H), 2.72 (sept, J = 6.9 Hz, 1H), 5.02 (t, J = 7.2 Hz, 1H), 7.42 (s, 2H). ^{13}C NMR: δ 20.1, 21.3, 21.9, 23.0, 24.7, 28.7, 29.4, 34.9, 36.9, 38.5, 45.7, 79.5, 119.7, 152.2, 153.7. IR (KBr): 3272, 2962, 2869, 1887, 1731, 1461, 1363, 1301, 1103, 942, 717 cm^{-1}. MS (ESI): m/z 407, 409 ($[M+Na]^+$).

4.4. Preparation of 3-bromo-3′,3′-diisopropyl-3′,3a′,4′,5,5′,6-hexahydro-4*H*-spiro[2,1-benzisoxazole-7,6′-cyclopenta-[*c*]isoxazole] (1a and 1′a)

To a solution of **3** (2.55 g, 6.62 mmol) in CH_2Cl_2 (13 mL) was added aq NaOCl (>5.0% chlorine, 10.4 mL, 8.22 mmol) at 0 °C, which was stirred at room temperature for 17 h. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. After removal of the desiccant and volatiles, the crude product was

purified by column chromatography on silica gel (hexane/acetone = 80/1–60/1) to give **1a** (1.06 g, 42%) and **1′a** (0.500 g, 20%) as white solids.

Compound **1a:** Mp: 135–138 °C. ^{1}H NMR: δ 0.87–1.01 (m, 12H), 1.73–1.97 (m, 6H), 2.15–2.37 (m, 4H), 2.49–2.56 (m, 1H), 2.77–2.84 (m, 1H), 3.75 (dd, J = 11.2 Hz, J = 8.1 Hz, 1H). ^{13}C NMR: δ 17.7, 18.3, 18.6, 18.6, 18.7, 19.6, 23.9, 31.3, 31.7, 34.9, 39.3, 44.2, 55.4, 95.9, 114.2, 136.9, 166.3, 172.1. IR (KBr): 3850, 2976, 1404, 939, 850 cm^{-1}. MS (ESI): m/z 403, 405 ([M+Na]$^+$). Anal. Calcd for $C_{18}H_{25}BrN_2O_2$: C, 56.70; H, 6.61; N, 7.35. Found: C, 56.70; H, 6.65; N, 7.30.

The enantiomers were separated by using Daicel Chiralpak AD [2 cm $\Phi \times$ 25 cm, hexane/i-PrOH = 20/1, 4.0 mL/min], 17 min for (*S*,*R*)-**1a**, 34.5 min for (*R*,*S*)-**1a**). (*S*,*R*)-**1a**: $[\alpha]_D^{19} = -175.0$ (c 0.500, $CHCl_3$). (*R*,*S*)-**1a**: $[\alpha]_D^{19} = +177.3$ (c 0.500, $CHCl_3$).

Compound **1′a**: ^{1}H NMR: δ 0.85–1.00 (m, 12H), 1.72–1.99 (m, 5H), 2.10–2.68 (m, 7H), 4.07 (t, J = 9.7 Hz, 1H). ^{13}C NMR: δ 17.2, 17.8, 18.1, 18.6, 18.8, 20.0, 21.1, 31.5, 31.5, 33.3, 39.3, 43.5, 54.6, 95.9, 114.0, 136.8, 166.1, 171.0. IR (KBr): 3851, 2956, 1607, 1403, 851 cm^{-1}. MS (ESI): m/z 403, 405 ([M+Na]$^+$).

4.5. General procedure for the Suzuki–Miyaura cross-coupling reaction

To a solution of **1a** (38.1 mg, 0.100 mmol), arylboronic acid (0.150 mmol), and $Pd(PPh_3)_4$ (11.6 mg, 0.0100 mmol) in dry THF (1.4 mL) was added aqueous K_2CO_3 solution (1 M, 0.2 mL), which was refluxed for the time indicated in Table 1. After being cooled to room temperature, the reaction mixture was poured into aqueous HCl (1 M), and then extracted with ethyl acetate. The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate) to produce the arylated ligand.

4.5.1. (*S*,*R*)-1b

94% yield. White solid. Mp: 209–213 °C. $[\alpha]_D^{22} = -185.5$ (c 0.605, $CHCl_3$). ^{1}H NMR: δ 0.93–1.10 (m, 12H), 1.75–2.53 (m, 9H), 2.63–2.75 (m, 1H), 2.89–2.99 (m, 2H), 3.81 (dd, J = 11.5 Hz, J = 8.1 Hz, 1H), 7.36–7.48 (m, 3H), 7.73 (dd, J = 8.2 Hz, J = 1.7 Hz, 2H). ^{13}C NMR: δ 17.8, 18.4, 18.7, 18.8, 20.3, 20.9, 24.0, 31.3, 31.8, 34.8, 39.4, 44.9, 55.6, 95.8, 110.1, 125.8, 128.5, 128.7, 129.1, 147.8, 162.7, 165.4. IR (KBr): 2969, 2941, 1446, 1428, 1387, 769, 691 cm^{-1}. MS (ESI): m/z 401 ([M+Na]$^+$).

4.5.2. (*R*,*S*)-1c

92% yield. White solid. Mp: 161–164 °C. $[\alpha]_D^{21} = +182.0$ (c 0.500, $CHCl_3$). ^{1}H NMR: δ 0.92–1.10 (m, 12H), 1.66–2.70 (m, 10H), 2.87–2.94 (m, 2H), 3.80 (dd, J = 11.4 Hz, J = 8.3 Hz, 1H), 3.84 (s, 3H), 6.96 (d, J = 8.9 Hz, 2H), 7.66 (d, J = 8.9 Hz, 2H). ^{13}C NMR: δ 17.8, 18.4, 18.7, 18.8, 20.3, 20.8, 24.0, 31.3, 31.8, 34.8, 39.4, 44.9, 55.3, 55.7, 95.7, 108.6, 114.2, 121.4, 127.3, 160.1, 162.7, 165.3, 172.8. IR (KBr): 3851, 2971, 2562, 1892, 1608, 1515, 1428, 1256, 1175, 1030, 834 cm^{-1}. MS (ESI): m/z 431 ([M+Na]$^+$). Anal. Calcd for $C_{25}H_{32}N_2O_3$: C, 73.50; H, 7.90; N, 6.86. Found: C, 73.29; H, 7.95; N, 6.81.

4.5.3. (*S*,*R*)-1d

99% yield. White solid. Mp: 137–140 °C. $[\alpha]_D^{22} = -174.0$ (c 0.500, $CHCl_3$). ^{1}H NMR: δ 0.92–1.10 (m, 12H), 1.73–2.71 (m, 13H), 2.87–2.94 (m, 2H), 3.80 (dd, J = 11.4 Hz, J = 8.2 Hz, 1H), 7.29 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H). ^{13}C NMR: δ 15.3, 17.8, 18.3, 18.7, 18.8, 20.2, 20.9, 23.9, 31.3, 31.8, 34.7, 39.4, 44.9, 55.6, 95.7, 109.7, 125.1, 126.0, 126.0, 140.3, 162.3, 165.4, 172.7. IR (KBr): 3748, 1731, 1442 cm^{-1}. MS (ESI): m/z 447 ([M+Na]$^+$).

4.5.4. (*S*,*R*)-1e

78% yield. Yellow solid. Mp: 215 °C. $[\alpha]_D^{23} = -157.9$ (c 0.615, $CHCl_3$). ^{1}H NMR: δ 0.92–1.11 (m, 12H), 1.73–2.70 (m, 10H), 2.87–3.05 (m, 8H), 3.80 (dd, J = 11.4 Hz, J = 8.2 Hz, 1H), 6.74 (d, J = 8.7 Hz, 2H), 7.61 (d, J = 8.7 Hz, 2H). ^{13}C NMR: δ 17.8, 18.4, 18.7, 18.8, 18.8, 20.4, 20.9, 24.0, 31.3, 31.8, 34.9, 39.4, 40.2, 45.0, 55.8, 95.6, 107.3, 111.9, 127.0, 150.5, 163.5, 165.1, 172.9. IR (KBr): 3757, 2967, 1607, 1487, 1367, 820 cm^{-1}. MS (ESI): m/z 444 ([M+Na]$^+$).

4.5.5. (*S*,*R*)-1f

97% yield. White solid. Mp: 159–161 °C. $[\alpha]_D^{23} = -157.7$ (c 0.615, $CHCl_3$). ^{1}H NMR: δ 0.92–1.09 (m, 12H), 1.75–2.50 (m, 9H), 2.65–2.77 (m, 1H), 2.88–2.98 (m, 2H), 3.81 (dd, J = 11.1 Hz, J = 8.3 Hz, 1H), 3.94 (s, 3H), 7.79 (d, J = 8.4 Hz, 2H), 8.11 (d, J = 8.4 Hz, 2H). ^{13}C NMR: δ 17.8, 18.4, 18.7, 18.8, 20.2, 21.0, 24.0, 31.3, 31.8, 34.6, 39.4, 44.8, 52.3, 55.6, 95.9, 111.8, 125.5, 130.0, 130.3, 132.3, 161.5, 165.6, 166.3, 172.6. IR (KBr): 3752, 2971, 1725, 1440, 1284, 1112, 756 cm^{-1}. MS (ESI): m/z 459 ([M+Na]$^+$).

4.5.6. (*S*,*R*)-1g

99% yield. White solid. Mp: 159–161 °C. $[\alpha]_D^{23} = -153.9$ (c 0.730, $CHCl_3$). ^{1}H NMR: δ 0.92–1.09 (m, 12H), 1.74–2.50 (m, 9H), 2.59–2.71 (m, 1H), 2.85–2.94 (m, 2H), 3.81 (dd, J = 11.4 Hz, J = 8.0 Hz, 1H), 7.14 (virtual t, J = 8.7 Hz, 2H), 7.70 (dd, J = 8.9 Hz, J = 5.3 Hz, 2H). ^{13}C NMR: δ 16.0, 17.8, 18.3, 18.7, 18.7, 20.2, 20.8, 24.0, 31.3, 31.8, 34.7, 39.4, 44.8, 55.6, 95.8, 109.8 (d, J = 1.1 Hz), 115.9 (d, J = 21.9 Hz), 124.9 (d, J = 3.5 Hz), 127.8 (d, J = 8.4 Hz), 161.8, 162.9 (d, J = 249 Hz), 165.4, 172.7. IR (KBr): 3852, 2971, 1515, 1445, 1240, 840 cm^{-1}. MS (ESI): m/z 419 ([M+Na]$^+$).

4.5.7. (*S*,*R*)-1h

43% yield. White solid. Mp: 57–63 °C. $[\alpha]_D^{24} = -138.2$ (c 0.455, $CHCl_3$). ^{1}H NMR: δ 0.94–1.15 (m, 12H), 1.81–2.09 (m, 6H), 2.26–2.55 (m, 4H), 2.63–2.71 (m, 1H), 2.99 (ddd, J = 12.0 Hz, J = 7.3 Hz, J = 2.0 Hz, 1H), 3.84 (dd, J = 11.3 Hz, J = 8.2 Hz, 1H), 7.51–7.64 (m, 4H), 7.87–7.96 (m, 2H), 8.03–8.07 (m, 1H). ^{13}C NMR: δ 17.8, 18.4, 18.7, 18.8, 20.2, 20.3, 23.9, 31.4, 31.8, 35.2, 39.5, 45.0, 55.6, 95.8, 112.5, 124.9, 125.7, 125.8, 126.2, 126.9, 127.6, 128.3, 130.2, 130.7, 133.6, 163.9, 164.9, 172.8. IR (KBr): 3851, 2961, 1456, 1393, 777 cm^{-1}. MS (ESI): m/z 451 ([M+Na]$^+$).

4.5.8. (*S*,*R*)-1i

27% yield. White solid. Mp: 232–233 °C (decomposed). $[\alpha]_D^{23} = -87.1$ (c 0.465, $CHCl_3$). ^{1}H NMR: δ 0.86–1.12 (m, 12H), 1.83–2.54 (m, 9H), 2.74–3.11 (m, 3H), 3.83 (dd, J = 11.5 Hz, J = 8.2 Hz, 1H), 7.51–7.54 (m, 2H), 7.84–7.93 (m, 4H), 8.19 (s, 1H). ^{13}C NMR: δ 17.8, 18.4, 18.7, 18.8, 20.3, 21.0, 24.0, 31.3, 31.8, 34.8, 39.5, 45.0, 55.7, 95.8, 110.4, 123.0, 125.5, 126.0, 126.6, 126.9, 127.7, 128.5, 128.5, 133.0, 133.2, 162.7, 165.5, 172.8. IR (KBr): 3749, 2940, 1427, 1387, 1267, 857, 817, 751 cm^{-1}. MS (ESI): m/z 451 ([M+Na]$^+$).

4.5.9. (*R*,*S*)-1j

57% yield. Yellow solid. Mp: 100–104 °C. $[\alpha]_D^{23} = +124.5$ (c 0.805, $CHCl_3$). ^{1}H NMR: δ 0.96–1.19 (m, 12H), 1.81–2.58 (m, 11H), 3.05–3.13 (m, 1H), 3.88 (dd, J = 11.1 Hz, J = 8.2 Hz, 1H), 7.47–7.66 (m, 4H), 7.52–7.78 (m, 2H), 8.03–8.08 (m, 2H), 8.59 (s, 1H). ^{13}C NMR: δ 17.8, 18.4, 18.7, 18.8, 19.2, 20.1, 23.8, 31.5, 31.8, 35.3, 39.7, 44.7, 55.5, 95.9, 115.0, 121.6, 125.2, 125.4, 125.5, 125.7, 126.5, 127.1, 128.3, 128.6, 129.6, 130.6, 130.7, 130.9, 131.1, 162.5, 164.7, 172.6. IR (KBr): 3748, 2959, 2360, 1446, 739 cm^{-1}. MS (ESI): m/z 501 ([M+Na]$^+$).

4.5.10. (*S*,*R*)-1k

95% yield. White solid. Mp: 45–47 °C. $[\alpha]_D^{24} = -140.8$ (c 0.500, $CHCl_3$). ^{1}H NMR: δ 0.92–1.10 (m, 12H), 1.67–2.40 (m, 17H), 2.91–

2.98 (m, 1H), 3.81 (dd, J = 11.2 Hz, J = 8.2 Hz, 1H), 7.09 (d, J = 7.6 Hz, 2H), 7.24 (t, J = 7.6 Hz, 1H). ^{13}C NMR: δ 17.8, 18.4, 18.7, 19.1, 19.9, 20.2, 23.8, 31.5, 31.8, 35.2, 39.6, 44.6, 55.5, 95.7, 112.2, 127.1+127.3 (br, 3,5-Ar*C*, due to the hindered rotation), 127.5, 129.6, 138.0+138.5 (br, 2,6-Ar*C*, due to the hindered rotation), 164.1, 164.3, 172.4, signals for CH_3 groups on the Ar ring could not be observed. IR (KBr): 3749, 2962, 1635, 1447, 1386, 1268, 1118, 776 cm^{-1}. MS (ESI): m/z 429 ([M+Na]$^+$).

4.5.11. (*R*,*S*)-1l

97% yield. White solid. Mp: 57–58 °C. $[\alpha]_D^{24} = +158.1$ (c 0.500, $CHCl_3$). ^{1}H NMR: δ 0.90–1.10 (m, 12H), 1.25–1.58 (m, 4H), 1.72–2.01 (m, 4H), 2.14–2.41 (m, 3H), 2.77–2.85 (m, 1H), 3.74 (dd, J = 11.5 Hz, J = 8.1 Hz, 1H), 7.18–7.63 (m, 9H). ^{13}C NMR: δ 17.8, 18.4, 18.7, 18.8, 19.0, 20.0, 23.8, 31.3, 31.7, 35.0, 39.3, 45.0, 55.6, 95.6, 111.8, 126.9, 127.1, 127.2, 128.2, 128.8, 129.8, 130.2, 130.3, 140.2, 141.2, 164.0, 164.6, 172.7. IR (KBr): 3851. 2944, 1715, 1634, 1458, 1009, 701, 667 cm^{-1}. MS (ESI): m/z 477 ([M+Na]$^+$).

4.5.12. (*R*,*S*)-1m

97% yield. White solid. Mp: 108–112 °C. $[\alpha]_D^{24} = +157.2$ (c 0.500, $CHCl_3$). ^{1}H NMR: δ 0.92–1.09 (m, 12H), 1.74–2.33 (m, 6H), 2.22–2.47 (m, 4H), 2.60–2.66 (m, 1H), 2.93 (dd, J = 12.9 Hz, J = 7.3 Hz, 1H), 3.81 (dd, J = 11.4 Hz, J = 8.1 Hz, 1H), 7.51–7.66 (m, 3H), 7.78 (d, J = 7.7 Hz, 1H). ^{13}C NMR: δ 17.8, 18.3, 18.7, 18.7, 19.2, 20.1, 23.9, 31.3, 31.7, 35.0, 39.4, 45.0, 55.7, 95.7, 112.9, 123.3 (q, J = 273 Hz), 126.7 (q, J = 5.0 Hz), 126.7 (q, J = 4.0 Hz), 129.6 (q, J = 31.4 Hz), 129.8, 131.3, 131.6, 161.4, 164.5, 172.6. IR (KBr): 3851, 2965, 1442, 1427, 1317, 1174, 1137, 1037, 771 cm^{-1}. MS (ESI): m/z 469 ([M+Na]$^+$).

4.5.13. (*S*,*R*)-1n

89% yield. Colorless oil. $[\alpha]_D^{24} = -134.7$ (c 0.500, $CHCl_3$). ^{1}H NMR: δ 0.92–1.09 (m, 12H), 1.75–2.51 (m, 9H), 2.68–2.80 (m, 1H), 2.88–3.00 (m, 2H), 3.82 (dd, J = 11.3 Hz, J = 8.1 Hz, 1H), 7.89 (br s, 1H), 8.15 (br s, 2H). ^{13}C NMR: δ 17.7, 18.3, 18.7, 18.7, 20.0, 20.7, 24.0, 31.4, 31.8, 34.5, 39.4, 44.5, 55.6, 96.0, 112.6, 122.4 (sept, J = 3.8 Hz), 122.9 (q, J = 272 Hz), 125.6 (m), 130.3, 132.4 (q, J = 33.7 Hz), 159.5, 166.0, 172.5. IR (KBr): 3748, 2965, 2359, 1809, 1716, 1622, 1471, 1446, 1373, 1280, 1145, 899, 847, 807, 712, 700 cm^{-1}. MS (ESI): m/z 537 ([M+Na]$^+$).

4.6. Typical procedure for Pd-catalyzed oxidative cyclization of 2-benzyl-2-(3-methyl-2-butenyl)-1,3-propanediol 4

A solution of enantiopure ligand (0.012 mmol) and $Pd(OCOCF_3)_2$ (3.3 mg, 0.010 mmol) in CH_2Cl_2 (0.4 mL) was stirred at 25 °C for 2 h under an argon atmosphere. To this solution were added *p*-benzoquinone (43.2 mg, 0.40 mmol) and **4** (23.4 mg, 0.100 mmol). The reaction mixture was stirred at the indicated temperature, and the reaction course was monitored by TLC. After completion, the reaction mixture was filtered through a short pad of silica gel, which was rinsed with ethyl acetate. The filtrate was concentrated under reduced pressure. Product yield was determined by GC analysis (hexamethylbenzene was used as an internal standard, T_{COL} = 180 °C, T_{INJ} = 250 °C, T_{DET} = 250 °C: hexamethylbenzene, 4.96 min; **5**, 10.97 min) or NMR analysis (1,4-dimethoxybenzene was used as an internal standard). The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 7/1) to afford product **5**. The enantiomeric excess of the product was determined by HPLC analysis using a chiral stationary phase column (Daicel Chiralpak AD, hexane/*i*-PrOH = 9/1, flow rate = 1.0 mL/min, λ = 215 nm: 5.6 min and 6.9 min).

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