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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 161–166

Asymmetric π-allylic etherification of cycloalkenyl esters with phenols in water using a resin-supported chiral palladium complex

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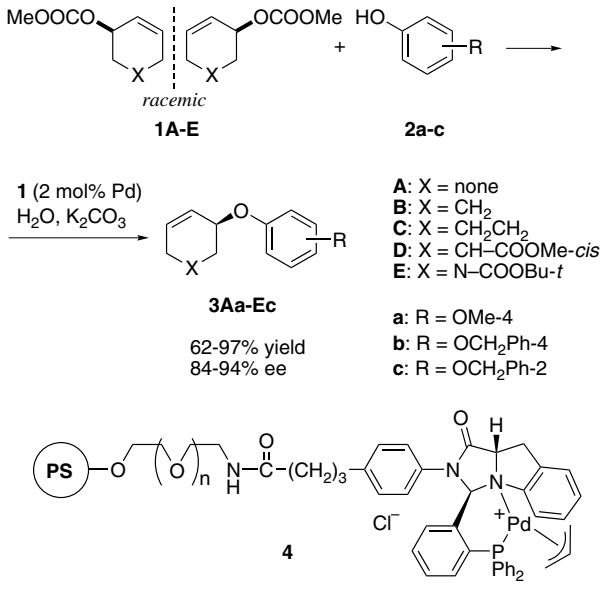
Received 15 November 2005; accepted 25 November 2005
Available online 9 January 2006

Abstract—Catalytic asymmetric etherification of cycloalkenyl esters with phenolic nucleophiles was achieved in water as the sole reaction medium under heterogeneous conditions by using 2 mol % palladium of a PS-PEG resin-supported palladium–imidazoindolephosphine complex to give optically active aryl(cycloalkenyl) ethers with up to 94% ee.

1. Introduction

Catalytic asymmetric functionalization of carbon frameworks, such as palladium-catalyzed asymmetric π-allylic substitution, constitutes one of the most exciting challenges in modern synthetic chemistry today.[1] Aqueous- and heterogeneous-switching of a given organic transformation is rapidly gaining importance for its ability to provide safe, green, and high-throughput chemical processes.[2,3] We have previously reported the heterogeneous aquacatalytic chiral process with catalytic asymmetric π-allylic alkylation and amination of cycloalkenyl esters using a palladium catalyst coordinated with a novel optically active ligand, (3*R*,9a*S*)-(2-aryl-3-(2-diphenylphosphino)phenyl)tetrahydro-1*H*-imidazo[1,5-*a*]indole-1-one,[4] anchored onto an amphiphilic polystyrene–poly(ethylene glycol) copolymer (PS–PEG) resin.[5] As part of our ongoing efforts to develop a wide utility of this system,[6] we decided to examine π-allylic etherification of cycloalkenyl esters. A vast amount of research has been devoted to the asymmetric π-allylic substitution of acyclic esters (e.g., 1,3-diphenylpropenyl esters) with carbon and nitrogen nucleophiles. However, the well-developed research on catalytic asymmetric substitution of cyclic substrates[7] with oxygen nucleophiles has been limited to isolated reports.[8–10] We herein report, the heterogeneous aquacatalytic asymmetric etherification of cycloalkenyl esters with phenolic nucleophiles, which is catalyzed by the PS–PEG resin-supported palladium–imidazoindolephosphine complex to give optically active aryl(cycloalkenyl) ethers in up to 94% ee (Scheme 1). The resulting aryl(cycloalkenyl) ethers underwent a Claisen rearrangement to give



Scheme 1.

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doi:10.1016/j.tetasy.2005.11.026

cycloalkenylarenes, where the chiral C–O bond catalytically generated was readily converted to the corresponding C–C bond with high stereochemical integrity.

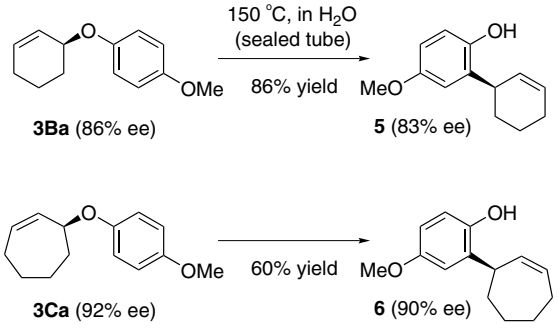
2. Results and discussion

The reaction of methyl cyclohexenylcarbonate *rac*-**1B** (X = CH_2) and 1.0 equiv of 4-methoxyphenol **2a** was carried out in the presence of an amphiphilic polystyrene–poly(ethylene glycol) copolymer (PS–PEG)[11,12] resin-supported palladium complex **4** (2 mol % Pd) and K_2CO_3 (1 mol equiv) in water at 25 °C with shaking for 12 h to give 3-(4-methoxyphenoxy)cyclohexene **3Ba**. Analytically pure **3Ba** was isolated by silica gel chromatography in 89% yield with an (*S*)-configuration as determined by the specific rotation {$[\alpha]_D^{25} = -102.5$ (*c* 1.3, dichloromethane). Lit. for (*S*)-**3Ba** of 97% ee: $[\alpha]_D^{25} = -129.1$ (*c* 2.0, dichloromethane)[9]}. The enantiomeric purity of **3Ba** was determined by HPLC analysis with a chiral stationary phase column (Chiralcel AD, 2-propanol/hexane = 1/300) to be 86% ee. The results obtained for the asymmetric etherification of various cycloalkenylcarbonates **1A**–**E** with phenols **2a**–**2c** are summarized in Table 1. Cyclopentenyl carbonate **1A** also reacted with **2a** under similar reaction conditions to give cyclopentenyl 4-methoxyphenyl ether **3Aa** in 84% ee (entry 1). Cyclohexenyl carbonate **1B** (X = CH_2) underwent etherification with 4-benzyloxy- and 2-benzyloxyphenol **2b** and **2c** under similar reaction conditions to give the corresponding cyclohexenyl aryl ethers **3Bb** (92% yield, 84% ee; entry 5) and **3Bc** (80% yield, 86% ee; entry 6). The reaction using cycloheptenyl carbonate **1C** (X = CH_2CH_2) gave the cycloheptenyl aryl ethers, **3Ca**, **3Cb**, and **3Cc**, in 92% ee, 89% ee, and 93% ee, respectively (entries 7–9). The enantioselectivity increased as the steric bulk of the substituent X increased. Thus, by using the racemic *cis*-5-carbomethoxy-2-cyclohexenyl methyl carbonate **1D** (X = CHCOOMe), 4-methoxyphenyl ether **3Da**, 4-benzyloxyphenyl ether **3Db**, and 2-benzyloxyphenyl ether **3Dc** were obtained in 93% ee (entry 10), 93% ee (entry 11), and 94% ee (entry 12), respectively, while the reaction of **1B**, which lacks the carbomethoxy substituent at the 5-position, with phenols **2a**–**2c** resulted in lower enantioselectivity ranging from 84% to 86% ee (entries 2–6). The exclusive formation of cycloalkenyl ethers **3D** with a *cis*-configuration from the *cis*-allylic ester **1D** revealed that the π-allylic etherification proceeds via a double-inversion pathway (stereoinversive π-allylpalladium formation and stereoinversive nucleophilic attack with a phenol)[13] in water under the present conditions. The catalytic asymmetric introduction of oxygen functionalities onto a piperidine framework also took place with high stereoselectivity. Tetrahydropyridyl carbonate **1E** reacted with phenols **2a**–**2c** under similar conditions to afford phenoxypiperidines **3Ea**–**3Ec** with 92–94% enantiomeric excesses (entries 13–15). Recycling experiments were examined for etherification of cyclohexenyl carbonate **1B** (entries 2–4). After the first use of the polymeric chiral palladium catalyst (Table 1, run 2) to give 86% ee of the aryl cyclohexenyl ether **3Ba**, the recovered catalyst beads were subsequently reused twice and exhibited stable catalytic activity (entries 3 and 4).

Table 1. Asymmetric etherification of cycloalkenyl esters in water catalyzed by polymeric catalyst **4**[a]

Entry	Allylic ester	Phenol	Product	Yield[b] (%)	%ee[c]
1	**1A**	**2a**	**3Aa**	80	84
2	**1B**	**2a**	**3Ba**	89	86
3		(1st reuse)		95	86
4		(2nd reuse)		97	86
5		**2b**	**3Bb**	92	84
6		**2c**	**3Bc**	80	86
7	**1C**	**2a**	**3Ca**	90	92
8		**2b**	**3Cb**	94	89
9		**2c**	**3Cc**	90	93
10	**1D**	**2a**	**3Da**	93	93
11		**2b**	**3Db**	93	93
12		**2c**	**3Dc**	88	94
13	**1E**	**2a**	**3Ea**	80	94
14		**2b**	**3Eb**	72	94
15		**2c**	**3Ec**	62	92

[a] All reactions were carried out at 25 °C for 12 h in water under a nitrogen atmosphere. The ratio of cycloalkenyl ester (mol)/ArOH (mol)/catalyst (Pd equiv)/base (mol)/H_2O (L) = 1.0/1.0/0.02/1.0/1.0.
[b] Isolated yield by silica gel column chromatography.
[c] Determined by HPLC analysis with use of a chiral stationary phase column.



Scheme 2.

The synthetic utility of the optically active aryl cycloalkenyl ethers is demonstrated by the Claisen rearrangement to form 2-arylcycloalkenes. Preliminary results are shown in Scheme 2. Thus, the Claisen rearrangement of methoxyphenyl ethers (*S*)-**3Ba** (86% ee) and (*S*)-**3Ca** (92% ee) took place in emulsive aqueous conditions at 150 °C for 72 h to give 83% ee of the 2-arylcyclohexene **5** and 90% ee of 2-arylcycloheptene **6**, respectively, with high transfer of chirality.

3. Conclusion

In conclusion, the asymmetric allylic etherification of cycloalkenyl esters with phenolic nucleophiles was achieved in up to 94% ee in water under heterogeneous conditions by use of the recyclable amphiphilic PS–PEG resin-supported palladium–imidazoindolephosphine complex to give the aryl cycloalkenyl ethers, which were readily convertible to the 3-arylcycloalkenes via the

Claisen rearrangement. The π-allylic etherification and the Claisen rearrangement were carried out in water without any organic solvents to meet green chemical requirements.

4. Experimental

4.1. General

All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. NMR spectra were recorded on a JEOL JNM-AL400 spectrometer (400 MHz for ^1H and 100 MHz for ^{13}C), JEOL JNM-LA500 spectrometer (500 MHz for ^1H and 126 MHz for ^{13}C), or JEOL JNM-A500 spectrometer (500 MHz for ^1H and 126 MHz for ^{13}C). All NMR spectra were recorded in chloroform-D at 25 °C unless otherwise noted. HPLC analysis was performed on a JASCO PU-1580 liquid chromatograph system. GC–MS analysis was performed on an HP 6890 Series Gas Chromatograph and a 5973 Network Mass Selective Detector (YOKOGAWA ANALYTICAL SYSTEM). FAB mass spectra were recorded on a JEOL JMS-777V spectrometer; 3-nitrobenzyl alcohol was used as the matrix. Optical rotations were measured on a JASCO P-1020 polarimeter. The agitation of the reaction mixture containing resin-supported catalysts was performed on a Wrist-action shaker (Burrel Scientific, Inc.) or a Peti-Syzer (HiPep Laboratories).

4.2. General procedure for the asymmetric allylic etherification in water

4.2.1. (*S*)-cyclohex-2-enyl 4′-methoxyphenyl ether 3Ba. A typical procedure was given for the reaction of cyclohexenyl carbonate **1B** with 4-methoxyphenol **2a** in the presence of **4** to give (*S*)-cyclohex-2-enyl 4′-methoxyphenyl ether **3Ba**. A mixture of cyclohexenyl carbonate **1B** (31 mg, 0.2 mmol), 4-methoxyphenol **2a** (25 mg, 0.2 mmol), **4** (14 mg, 0.004 mmol Pd), potassium carbonate (28 mg, 0.2 mmol) and H_2O (0.2 mL) was shaken at 25 °C for 12 h. The reaction mixture was filtered and the resin beads rinsed three times with ethyl acetate. The combined filtrate and washings were dried over Na_2SO_4. After removal of solvent, the residual oil was chromatographed on silica gel to give **3Ba** (37 mg) in 87% yield; $[\alpha]_D^{25} = -102.5$ (*c* 1.3, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 6.87 (d, *J* = 9.3 Hz, 2H), 6.81 (d, *J* = 9.3 Hz, 2H), 5.94 (m, 1H), 5.85 (dm, *J* = 10.0 Hz, 1H), 4.67 (br, 1H), 3.77 (s, 3H), 1.98 (m, 2H), 1.86 (m, 3H), 1.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.8, 151.7, 131.8, 126.6, 117.3, 114.6, 72.0, 55.7, 28.4, 25.2, 19.1. MS (EI): *m*/*z* (rel%) 204 (8, M^+), 124 (bp), 109 (68), 79 (46). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel AD, eluent; *n*-hexane/2-propanol = 300/1, flow rate; 0.5 mL/min, retention times; major isomer 18.5 min and minor 20.8 min) to be 86% ee. The absolute configuration was determined by comparison of the specific rotation to the literature value;[9b] $[\alpha]_D^{25} = -129.1$ (*c* 2.0, dichloromethane) for enantiomerically enriched **3Ba** (97% ee). CAS registry number: (*S*)-175735-28-1.

4.2.2. Cyclopent-2-enyl 4′-methoxyphenyl ether 3Aa. Yield 80%; $[\alpha]_D^{25} = -68.0$ (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.82–6.87 (m, 4H), 6.12 (m, 1H), 5.95 (m, 1H), 5.25 (m, 1H), 3.77 (s, 3H), 2.58 (m, 1H), 2.33 (m, 2H), 1.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.7, 152.4, 137.0, 129.0, 116.6, 114.7, 83.7, 55.7, 31.3, 30.1. MS (EI): *m*/*z* (rel%) 190 (4, M^+), 124 (bp), 109 (67). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OJ, eluent; *n*-hexane/2-propanol = 300/1, flow rate; 1.0 mL/min, retention times; major isomer 23.7 min and minor 27.8 min) to be 84% ee. CAS registry number: 200552-03-0.

4.2.3. 4′-Benzyloxyphenyl cyclohex-2-enyl ether 3Bb. Yield 92%; $[\alpha]_D^{25} = -78.2$ (*c* 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41 (d, *J* = 7.3 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 2H), 7.30 (d, *J* = 7.3 Hz, 1H), 6.85–6.90 (m, 4H), 5.93 (dt, *J* = 3.7, 10.4 Hz, 1H), 5.84 (dd, *J* = 2.4, 10.4 Hz, 1H), 5.00 (s, 2H), 4.66 (br, 1H), 2.11 (m, 1H), 2.00 (m, 1H), 1.85 (m, 3H), 1.61 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.1, 152.1, 137.3, 131.9, 128.5, 127.9, 127.5, 126.6, 117.3, 115.8, 71.9, 70.7, 28.3, 25.1, 19.0. MS (EI): *m*/*z* (rel%) 280 (4, M^+), 200 (29), 91 (bp). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel AD, eluent; *n*-hexane/2-propanol = 300/1, flow rate; 1.0 mL/min, retention times; major isomer 15.4 min and minor 19.2 min) to be 84% ee. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.59; H, 7.13.

4.2.4. 2′-Benzyloxyphenyl cyclohex-2-enyl ether 3Bc. Yield 80%; $[\alpha]_D^{25} = -81.0$ (*c* 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.43 (d, *J* = 7.3 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.29 (d, *J* = 7.3 Hz, 1H), 6.88–7.01 (m, 4H), 5.92 (m, 2H), 5.12 (s, 2H), 4.76 (m, 1H), 2.13 (m, 1H), 2.00 (m, 1H), 1.90 (m, 3H), 1.62 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 150.1, 148.3, 137.5, 131.7, 128.4, 127.7, 127.3, 126.9, 122.0, 121.7, 118.3, 115.7, 73.2, 71.3, 28.6, 25.2, 19.1. MS (EI): *m*/*z* (rel%) 280 (1, M^+), 200 (16), 91 (bp). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, eluent; *n*-hexane/2-propanol = 300/1, flow rate; 1.0 mL/min, retention times; major isomer 32.0 min and minor 35.1 min) to be 86% ee. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.23; H, 7.19.

4.2.5. Cyclohept-2-enyl 4′-methoxyphenyl ether 3Ca. Yield 90%; $[\alpha]_D^{24} = +3.4$ (*c* 1.2, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.82 (s, 4H), 5.79–5.88 (m, 2H), 4.78 (br d, *J* = 10.3 Hz, 1H), 3.76 (s, 3H), 2.23 (m, 1H), 2.01–2.13 (m, 3H), 1.61–1.76 (m, 3H), 1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.8, 151.8, 135.9, 130.8, 116.9, 114.7, 78.1, 55.7, 33.1, 28.6, 27.5, 26.6. MS (EI): *m*/*z* (rel%) 218 (4, M^+), 124 (bp), 109 (38). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, eluent; *n*-hexane/2-propanol = 300/1, flow

rate; 0.5 mL/min, retention times; major isomer 17.4 min and minor 15.3 min) to be 92% ee. The absolute configuration was determined by comparison of the specific rotation to the literature;[9b] $[\alpha]_D^{25} = +3.4$ (*c* 2.0, CH_2Cl_2) for enantiomerically enriched **3Ca** (92% ee). CAS registry number: (*S*)-200552-09-6.

4.2.6. 4′-Benzyloxyphenyl cyclohept-2-enyl ether 3Cb. Yield 94%; $[\alpha]_D^{25} = +7.4$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29–7.42 (m, 5H), 6.88 (d, $J = 9.3$ Hz, 2H), 6.80 (d, $J = 9.3$ Hz, 2H), 5.78–5.88 (m, 2H), 5.00 (s, 2H), 4.78 (br d, $J = 10.5$ Hz, 1H), 2.22 (m, 1H), 2.00–2.12 (m, 3H), 1.60–1.76 (m, 3H), 1.39 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 152.9, 152.0, 137.3, 135.8, 130.8, 128.5, 127.9, 127.5, 116.8, 115.8, 78.0, 70.7, 33.1, 28.5, 27.5, 26.5. MS (EI): *m*/*z* (rel%) 294 (2, M^+), 200 (21), 91 (bp). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OJ, eluent; *n*-hexane/2-propanol = 98/2, flow rate; 1.0 mL/min, retention times; major isomer 29.2 min and minor 22.9 min) to be 89% ee. Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.70; H, 7.50.

4.2.7. 2′-Benzyloxyphenyl cyclohept-2-enyl ether 3Cc. Yield 90%; $[\alpha]_D^{25} = -8.1$ (*c* 1.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.44 (d, $J = 7.3$ Hz, 2H), 7.34 (t, $J = 7.3$ Hz, 2H), 7.29 (dm, $J = 7.3$ Hz, 1H), 6.84–6.94 (m, 4H), 5.81–5.92 (m, 2H), 5.12 (s, 2H), 4.90 (br d, $J = 10.3$ Hz, 1H), 2.23 (m, 1H), 2.01–2.11 (m, 3H), 1.83 (m, 1H), 1.59–1.71 (m, 2H), 1.40 (m, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 149.5, 148.2, 137.6, 135.9, 130.6, 128.4, 127.7, 127.3, 121.7, 121.4, 116.6, 115.8, 79.0, 71.4, 33.2, 28.6, 27.4, 26.6. MS (EI): *m*/*z* (rel%) 292 (1, $[M-H_2]^+$), 200 (17), 91 (bp). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel AD, eluent; *n*-hexane/2-propanol = 300/1, flow rate; 1.0 mL/min, retention times; major isomer 12.0 min and minor 13.6 min) to be 93% ee. Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.39; H, 7.45.

4.2.8. *cis*-(5′-Methoxycarbonyl)cyclohex-2′-enyl 4-methoxyphenyl ether 3Da. Yield 93%; $[\alpha]_D^{25} = +5.9$ (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.86 (d, $J = 9.0$ Hz, 2H), 6.81 (d, $J = 9.0$ Hz, 2H), 5.86 (m, 2H), 4.80 (m, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 2.69 (dddd, $J = 2.7$, 6.8, 9.5, 12.5 Hz, 1H), 2.43 (ddd, $J = 2.7$, 5.6, 12.5 Hz, 1H), 2.33 (m, 2H), 1.83 (ddd, $J = 12.5$, 12.5, 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.8, 154.3, 151.5, 128.5, 127.7, 117.6, 114.7, 73.5, 55.7, 51.9, 38.1, 31.3, 27.6. MS (FAB+): *m*/*z* (rel%) 262 (29, M^+), 139 (bp), 124 (91), 79 (32). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, eluent; *n*-hexane/2-propanol = 300/1, flow rate; 1.0 mL/min, retention times; major isomer 30.7 min and minor 37.5 min) to be 93% ee. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.62; H, 6.75.

4.2.9. *cis*-(5′-Methoxycarbonyl)cyclohex-2′-enyl 4-benzyloxyphenyl ether 3Db. Yield 93%; $[\alpha]_D^{25} = +7.1$ (*c* 1.3, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30–7.43 (m, 5H), 6.89 (d, $J = 9.3$ Hz, 2H), 6.85 (d, $J = 9.3$ Hz, 2H), 5.85 (m, 2H), 5.01 (s, 2H), 4.80 (m, 1H), 3.69 (s, 3H), 2.68 (dddd, $J = 2.9$, 6.6, 9.5, 12.7 Hz, 1H), 2.42 (ddd, $J = 12.7$, 5.6, 2.9 Hz, 1H), 2.33 (m, 2H), 1.80 (ddd, $J = 12.7$, 12.7, 9.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.7, 153.4, 151.7, 137.3, 128.54, 128.50, 127.9, 127.6, 127.5, 117.5, 115.9, 73.4, 70.6, 51.8, 38.1, 31.3, 27.5. MS (EI): *m*/*z* (rel%) 338 (16, M^+), 306 (19), 215 (22), 187 (36), 91 (bp). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, eluent; *n*-hexane/2-propanol = 20/1, flow rate; 1.0 mL/min, retention times; major isomer 14.2 min and minor 17.9 min) to be 93% ee. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.75; H, 6.50.

4.2.10. *cis*-(5′-Methoxycarbonyl)cyclohex-2′-enyl 2-benzyloxyphenyl ether 3Dc. Yield 88%; $[\alpha]_D^{25} = +1.0$ (*c* 1.2, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28–7.44 (m, 5H), 6.88–7.00 (m, 4H), 5.89 (dm, $J = 10.3$ Hz, 1H), 5.83 (m, 1H), 5.12 (s, 2H), 4.89 (m, 1H), 3.69 (s, 3H), 2.65 (dddd, $J = 2.7$, 6.6, 9.8, 12.7 Hz, 1H), 2.45 (dm, $J = 12.7$ Hz, 1H), 2.32 (m, 2H), 1.87 (ddd, $J = 12.7$, 12.7, 9.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 174.8, 150.1, 147.8, 137.3, 128.4, 128.10, 128.09, 127.7, 127.3, 122.5, 121.6, 118.7, 115.5, 74.9, 71.2, 51.8, 38.3, 31.5, 27.6. MS (FAB+): *m*/*z* (rel%) 338 (5, M^+), 200 (29), 139 (bp), 91 (80), 79 (29). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OJ-H, eluent; *n*-hexane/2-propanol = 20/1, flow rate; 1.0 mL/min, retention times; major isomer 21.9 min and minor 24.4 min) to be 94% ee. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.51; H, 6.52.

4.2.11. *tert*-Butyl 3-(4′-methoxyphenoxy)-1,2,3,6-tetrahydropyridine-1-carboxylate 3Ea. Yield 80%; $[\alpha]_D^{25} = -45.7$ (*c* 0.8, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz, −10 °C, mixture of rotamers in a ratio of 1:1.5): δ 6.83–6.94 (m, 4H), 5.89–6.02 (m, 2H), 4.69 (m, 1H), 3.84–4.09 and 3.30–3.34 (m, 3H), 3.78 and 3.79 (s, 3H), 3.64–3.72 (m, 1H), 1.40 and 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz, −10 °C, mixture of rotamer at a ratio of 1:1.5): δ 154.7, 154.6, 154.2, 153.9, 151.1, 151.0, 129.3, 127.8, 125.9, 124.9, 117.7, 116.9, 114.5, 80.1, 80.0, 70.3, 69.2, 55.65, 55.58, 44.2, 43.5, 43.4, 42.8, 28.3, 28.2 (there is one missing resonance of an aromatic carbon of the minor rotamer, which should overlap with the other aromatic resonance). MS (EI): *m*/*z* (rel%) 305 (10, M^+), 232 (10), 176 (20), 124 (bp), 80 (59), 57 (63). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, eluent; *n*-hexane/2-propanol = 98/2, flow rate; 1.0 mL/min, retention times; major isomer 8.6 min and minor 10.8 min) to be 94% ee. Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.59; H, 7.52; N, 4.49.

4.2.12. *tert*-Butyl 3-(4′-benzyloxyphenoxy)-1,2,3,6-tetrahydropyridine-1-carboxylate 3Eb. Yield 72%; $[\alpha]_D^{25} = -34.7$ (*c* 0.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz, −10 °C, mixture of rotamers in a ratio of 1:1.2): δ 7.33–7.46 (m, 5H), 6.88–6.94 (m, 3H), 5.89–6.02 (m,

2H), 5.02 and 5.04 (s, 2H), 4.68 (m, 1H), 3.80–4.09 and 3.26–3.33 (m, 4H), 3.63–3.72 (m, 1H), 1.39 and 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz, −10 °C, mixture of rotamers in a ratio of 1:1.2): δ 154.7, 154.6, 153.4, 153.1, 151.3, 151.2, 136.92, 136.87, 129.3, 128.6, 127.9, 127.7, 127.53, 127.49, 125.9, 124.9, 117.6, 116.8, 115.56, 115.53, 80.1, 79.9, 70.32, 70.29, 70.2, 69.1, 44.2, 43.5, 43.4, 42.8, 28.3, 28.2 (there are two missing resonances of aromatic carbons of the minor rotamer which should overlap with the other aromatic resonances). MS (FAB+): *m*/*z* (rel%) 381 (39, M^+), 326 (20), 200 (16), 149 (44), 126 (96), 91 (bp), 82 (68), 57 (78). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, eluent; *n*-hexane/2-propanol = 98/2, flow rate; 1.0 mL/min, retention times; major isomer 20.2 min and minor 17.8 min) to be 94% ee. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.34; H, 7.12; N, 3.67.

4.2.13. *tert*-Butyl 3-(2′-benzyloxyphenoxy)-1,2,3,6-tetrahydropyridine-1-carboxylate 3Ec. Yield 62%; $[\alpha]_D^{25} = -45.1$ (*c* 0.7, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz, −10 °C, mixture of rotamers in a ratio of 1:1) δ 7.32–7.46 (m, 5H), 6.91–7.10 (m, 4H), 5.87–6.06 (m, 2H), 5.09–5.16 (m, 2H), 4.76 (m, 1H), 3.44–4.03 (m, 4H), 1.45 and 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz, −10 °C, mixture of rotamers in a ratio of 1:1): δ 154.72, 154.70, 149.8, 149.6, 147.1, 146.9, 137.1, 137.0, 128.7, 128.48, 128.45, 127.8, 127.7, 127.6, 127.1, 126.1, 125.2, 123.0, 122.6, 121.5, 121.2, 119.1, 118.1, 114.6, 80.0 (overlapped), 71.3, 70.6 (overlapped), 70.5, 44.5, 43.5, 43.4, 42.8, 28.33, 28.30 (there are two missing resonances of aromatic carbons of the minor rotamer which should overlap with the other aromatic resonances). MS (FAB+): *m*/*z* (rel%) 382 (6, $[M+H]^+$), 326 (15), 126 (61), 91 (72), 57 (bp), 43 (68). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD-H, eluent; *n*-hexane/2-propanol = 98/2, flow rate; 1.0 mL/min, retention times; major isomer 18.1 min and minor 28.8 min) to be 92% ee. Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.13; H, 7.20; N, 3.74.

4.3. General procedure for the Claisen rearrangement in water

4.3.1. (*R*)-2′-(Cyclohex-2-enyl)-4′-methoxyphenol 5. A typical procedure was given for the reaction of (*S*)-cyclohex-2-enyl 4′-methoxyphenyl ether **3Ba** to give (*R*)-2′-(cyclohex-2-enyl)-4′-methoxyphenol**5**. A mixture of **3Ba** (30 mg, 0.15 mmol) and H_2O (2.0 mL) was stirred at 150 °C in a sealed tube for 72 h. The reactant was extracted with ethyl acetate and dried over Na_2SO_4. After removal of solvent, the residual oil was chromatographed on silica gel to give **5** (25 mg) in 83% yield; $[\alpha]_D^{25} = +95.0$ (*c* 1.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.72 (d, $J = 8.5$ Hz, 1H), 6.69 (d, $J = 2.9$ Hz, 1H), 6.65 (dd, $J = 8.5$, 2.9 Hz, 1H), 6.03 (m, 1H), 5.79 (dd, $J = 2.0$, 10.0 Hz, 1H), 5.01 (s, 1H), 3.75 (s, 3H), 3.54 (m, 1H), 2.12 (m, 2H), 2.01 (m, 1H), 1.80 (m, 1H), 1.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.5, 147.9, 132.2, 130.8, 129.4, 116.6, 115.3, 112.1, 55.7, 38.0, 29.8, 25.0, 21.3. MS (EI): *m*/*z* (rel%) 204 (bp, M^+), 161 (38). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel AD, eluent; *n*-hexane/2-propanol = 98/2, flow rate; 1.0 mL/min, retention times; major isomer 30.3 min and minor 36.3 min) to be 83% ee. The absolute configuration was determined by comparison of the special rotation to the literature;[9b] $[\alpha]_D^{25} = +109.7$ (*c* 2.0, CH_2Cl_2) for enantiomerically enriched **5** (97% ee). CAS registry number: (*R*)-200552-23-4.

4.3.2. (*R*)-2′-(Cyclohept-2-enyl)-4′-methoxyphenol 6. Yield 60%; $[\alpha]_D^{25} = +35.5$ (*c* 1.1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.74 (d, $J = 3.1$ Hz, 1H), 6.72 (d, $J = 8.5$ Hz, 1H), 6.63 (dd, $J = 3.1$ Hz, $J = 8.5$ Hz, 1H), 5.94 (m, 1H), 5.71 (br d, $J = 12.2$ Hz, 1H), 4.70 (s, 1H), 3.76 (s, 3H), 3.73 (m, 1H), 2.30 (m 1H), 2.23 (m, 1H), 1.97 (m, 1H), 1.81 (m, 3H), 1.65 (m, 1H), 1.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.8, 146.9, 135.4, 134.1, 133.4, 116.5, 114.2, 111.8, 55.7, 41.9, 34.1, 30.0, 28.8, 27.1. MS (EI): *m*/*z* (rel%) 218 (bp, M^+), 137 (68). The enantiomeric excess was determined by HPLC analysis using a chiral stationary phase column (Chiralcel AD, eluent; *n*-hexane/2-propanol = 98/2, flow rate; 1.0 mL/min, retention times; major isomer 32.7 min and minor 35.0 min) to be 90% ee. The absolute configuration was determined by comparison of the specific rotation to the literature;[9b] $[\alpha]_D^{25} = +31.0$ (*c* 1.6, CH_2Cl_2) for enantiomerically enriched **6** (96% ee). CAS registry number: (*R*)-200552-24-5.

Acknowledgements

This work was supported by the CREST program, sponsored by the JST. We also thank the JSPS (GRANT-in-AID for Scientific Research, No. 15205015) and the MEXT (Scientific Research on Priority Areas, No. 420), for partial financial support of this work.

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