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Enantioselective Construction of Bridgehead Quaternary Carbon Containing Bicyclo[3.3.1]nonanes by Palladium-Catalyzed Desymmetric Arylation

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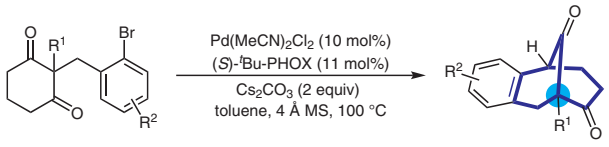

√ *bicyclo[3.3.1] nonane core*
√ *bridgehead quaternary carbon*
√ *readily available starting materials*
√ *up to 84% yield and 86% ee*

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Abstract An enantioselective and catalytic method for the synthesis of bridgehead quaternary carbon containing bicyclo[3.3.1]nonanes is described. The intramolecular desymmetric arylation of α-disubstituted 1,3-diketones was achieved using a chiral Pd/PHOX complex. A variety of bridged cyclic molecules, common skeleton for polyprenylated acylphloroglucinols, were obtained in up to 84% yield with 86% ee.

Key words asymmetric catalysis, desymmetrization, all-carbon quaternary center, palladium, arylation, bicyclic compound

Quaternary carbon stereocenters, which are carbon atoms attached to four different carbon substituents, are widely found in a variety of complex natural products and biologically active molecules.[1] In particular, polycyclic polyprenylated acylphloroglucinols, with broad-spectrum bioactivities and as potential therapeutic agents for the treatment of neurodegenerative disease, possess a bridgehead quaternary carbon and a highly oxygenated bicyclo[3.3.1]nonane core structure (Figure 1).[2] Common pathway toward these complex targets involved the formation of core and the manipulation of such motif afterwards.[3] Consequently, significant synthetic efforts have been devoted to construct the bridged core, but largely limited to racemic synthesis, or chiral auxiliary directed synthesis.[4] To date, only a handful of examples utilizing asymmetric catalysts have been realized to access the highly oxygenated skeletons.[5] Therefore, it is still an appealing goal to develop a straightforward system to access these motifs in a highly enantioselective manner.

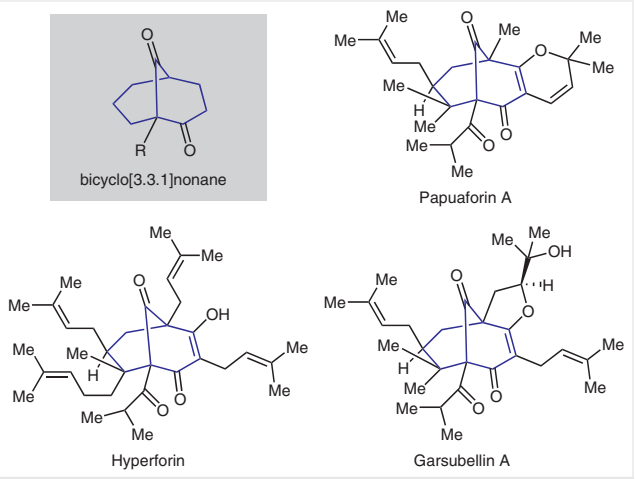


Figure 1 Representative natural products with bicyclo[3.3.1]nonane core

In 2016, an elegant report by Jia et al. disclosed that the combination of palladium complex and L-proline enabled α-arylative desymmetrization of cyclohexanones, and provided 2-azabicyclo[3.3.1]nonanes in synthetically useful yield and enantioselectivity.[6] Inspired by this work, we envisioned that the enantioenriched chiral bridgehead quaternary carbon containing bicyclo[3.3.1]nonanes could be accessed by introducing a prochiral quaternary carbon at the α-position of 1,3-diketones, followed by an intramolecular asymmetric palladium-catalyzed desymmetric arylation of the two ketones.[7,8] Given the facts that the vast availability, high reactivity, feasible functionalization of 1,3-diketones, and the importance of the corresponding bicyclo[3.3.1]nonane products, this method should have potential applications in total synthesis of related natural products. Herein, we describe our studies toward this approach.[9]

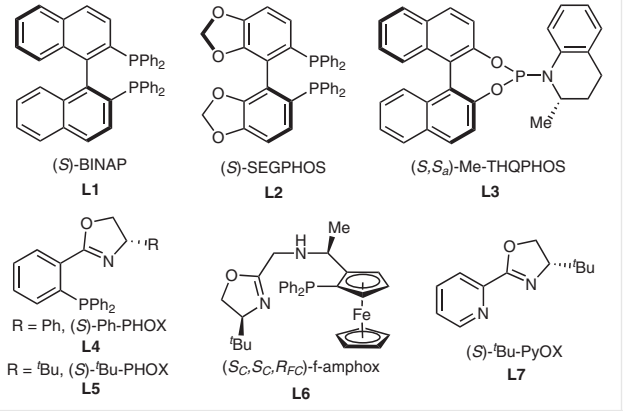
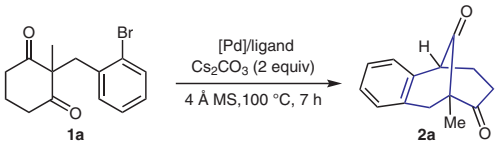


Figure 2 Structures of chiral ligands **L1–L6**

We began our investigations by performing a model reaction in toluene using 2-(2-bromobenzyl)-2-methylcyclohexane-1,3-dione (**1a**) as substrate, palladium complex derived from $Pd(MeCN)_2Cl_2$, and (*S*)-BINAP (**L1**) as catalyst, and cesium carbonate as base. To our delight, the desired bicyclic product **2a** was obtained, although only in 27% yield (Table 1, entry 1). Addition of molecular sieves to the reaction mixture was essential to improve the yield to 45% with 11% ee (entry 2). A series of chiral ligands (Figure 2) were tested in the palladium-catalyzed arylation and the results are summarized in Table 1. Bidentate phosphine **L2** showed moderate reactivity with 33% ee (entry 3). While with monodentate phosphoramidite **L3**,[10] no desired product was observed (entry 4). Gratifyingly, P,N-chelating chiral phosphinooxazoline **L4**[11] was found to effect the enantiocontrol resulting a dramatic increase in ee (77% ee, entry 5). Further optimizations revealed that bulkier *tert*-butyl

Table 1 Optimization of Reaction Conditions[a]



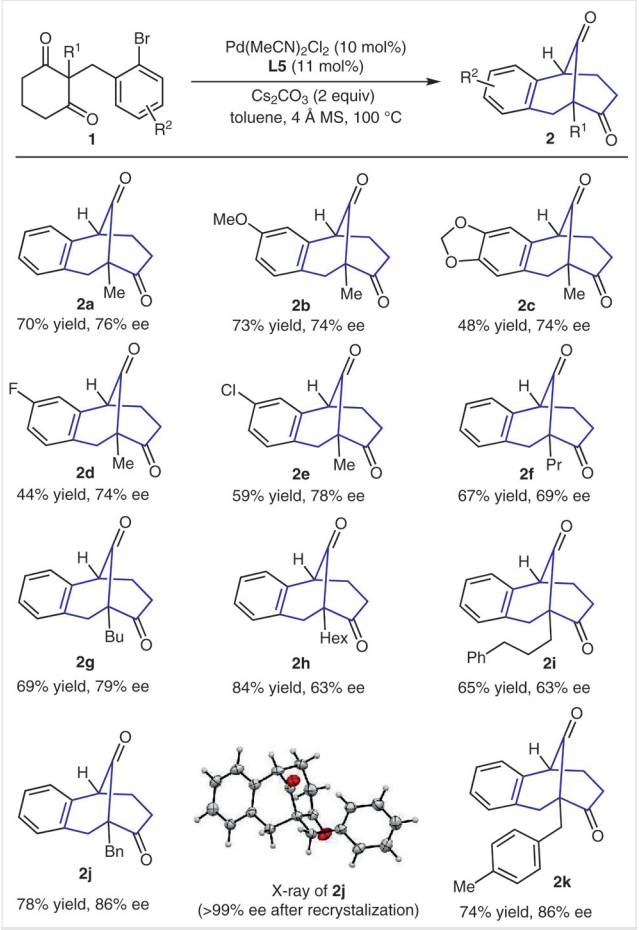
Entry	[Pd] (mol%)	Ligand (mol%)	Base	Solvent	Yield (%)[b]	ee (%)[c]
1[d]	$Pd(MeCN)_2Cl_2$ (10)	**L1** (11)	Cs_2CO_3	toluene	27	–
2	$Pd(MeCN)_2Cl_2$ (10)	**L1** (11)	Cs_2CO_3	toluene	45	11
3	$Pd(MeCN)_2Cl_2$ (10)	**L2** (11)	Cs_2CO_3	toluene	54	33
4	$Pd(MeCN)_2Cl_2$ (10)	**L3** (22)	Cs_2CO_3	toluene	NR	–
5	$Pd(MeCN)_2Cl_2$ (10)	**L4** (11)	Cs_2CO_3	toluene	57	77
6	**$Pd(MeCN)_2Cl_2$ (10)**	**L5 (11)**	**Cs_2CO_3**	**toluene**	**87 (70)[e]**	**76**
7	$Pd(MeCN)_2Cl_2$ (10)	**L6** (11)	Cs_2CO_3	toluene	NR	–
8	$Pd(MeCN)_2Cl_2$ (10)	**L7** (11)	Cs_2CO_3	toluene	NR	–
9	$Pd(MeCN)_2Cl_2$ (5)	**L5** (5.5)	Cs_2CO_3	toluene	76	62
10	$Pd_2(dba)_3$ (5)	**L5** (11)	Cs_2CO_3	toluene	57	60
11	$Pd(OAc)_2$ (10)	**L5** (11)	Cs_2CO_3	toluene	68	68
12	$Pd(MeCN)_2Cl_2$ (10)	**L5** (11)	Cs_2CO_3	DCE[f]	21	72
13	$Pd(MeCN)_2Cl_2$ (10)	**L5** (11)	Cs_2CO_3	THF[f]	36	76
14	$Pd(MeCN)_2Cl_2$ (10)	**L5** (11)	Cs_2CO_3	1,4-dioxane	69	64
15	$Pd(MeCN)_2Cl_2$ (10)	**L5** (11)	Cs_2CO_3	DMF	NR	–
16	$Pd(MeCN)_2Cl_2$ (10)	**L5** (11)	K_2CO_3	toluene	NR	–
17	$Pd(MeCN)_2Cl_2$ (10)	**L5** (11)	K_3PO_4	toluene	40	78
18	$Pd(MeCN)_2Cl_2$ (10)	**L5** (11)	Et_3N	toluene	<5	–

[a] Reactions performed with 0.2 mmol of **1a**, 0.4 mmol of base, and 50 mg of 4 Å MS in 1 mL of solvent at 100 °C for 7 h.
[b] Determined by ^1H NMR analysis of the crude mixture using an internal standard.
[c] Determined by HPLC using a chiral column (Chiralcel OJ-H).
[d] Without 4 Å MS.
[e] Yield of isolated product **2a**.
[f] Reflux
NR = no reaction

phosphinooxazoline **L5** enabled the transformation in an improved yield while maintaining the enantioselctivity (entry 6). Ligands **L6**[12] and **L7**[13] were also examined and resulted in a total lack of reactivity (entries 7 and 8). Next, we found that either reducing the catalyst loading or using other palladium precursors, such as $Pd_2(dba)_3$ and $Pd(OAc)_2$, gave a lower yield and ee (entries 9–11). Further screening of solvents (entries 12–15) and bases (entries 16–18) identified the optimal reaction conditions: 10 mol% of $Pd(MeCN)_2Cl_2$, 11 mol% of **L5**, and 2 equivalents of Cs_2CO_3 in toluene at 100 °C (entry 6).

With optimized conditions for the intramolecular arylation established, we next turned our efforts to explore the substrate scope (Scheme 1). Various α-disubstituted 1,3-diketones were synthesized and subjected to the standard reaction conditions. Electron-rich substituents on the aryl bromide moiety were well tolerated and resulted in 48–73% yield with 74% ee (**2b** and **2c**). Electron-withdrawing group (i.e., F, Cl) containing substrates provided products **2d** and **2e** in lower yield but with similar ee (44–59% yield, 74–78% ee). By varying the substituents at prochiral quaternary carbon of the starting materials, bicyclic skeletons with versatile chiral bridgehead quaternary carbon were achieved. We investigated the influence of alkyl chain attached to the prochiral center to the desymmetric reaction. Diketones with *n*-propyl (Pr), *n*-butyl (Bu), *n*-hexyl (Hex), and 3-phenylpropyl substituents were compatible and delivered the corresponding bicyclo[3.3.1]nonanes **2f–i** in 65–84% yield with 63–79% ee. In comparison with methyl substituent, longer alkyl group in general led to a decrease in enantioselectivity (i.e., for **2a**, 76% ee; for **2h**, 63% ee). Notably, benzyl-type group bearing diketones **2j** and **2k** gave both good yield and increased enantioselectivity. Additionally, reaction with α-phenyldiketone was found to be very sluggish under the standard conditions.[14] The absolute configuration of the enantiopure product **2j** (>99% ee)[15] was determined as *R* at the bridgehead quaternary carbon by X-ray crystallographic analysis.[16] The absolute configuration for all other bicyclo[3.3.1]nonane products were assigned by analogy.

In conclusion, we have developed a palladium-catalyzed asymmetric desymmetrization reaction to synthesize bicyclo[3.3.1]nonane skeletons in a single step. Starting with a prochiral quaternary carbon containing compounds, chiral bridgehead quaternary carbon was accessed in good yield and enantioselectivity. Further elaborations of this method in natural product synthesis are currently ongoing in our laboratory.



Scheme 1 Substrate scope. Reactions were conducted under the conditions of Table 1, entry 6. The reported yields are those of the products isolated by column chromatography. Enantiomeric excess (ee) was determined by HPLC with chiral stationary phases.

All experiments were carried out in flamed-dried glassware using anhydrous solvents under argon. ^{1}H NMR spectra were recorded at r.t. on Bruker Avance III 400 MHz spectrometers and were reported relative to residual $CDCl_3$ (δ = 7.26). ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer (100 MHz) and were reported relative to $CDCl_3$ (δ = 77.00). Data for ^{1}H NMR were reported as follows: chemical shift (δ ppm) [multiplicity, coupling constant (Hz), integration]. Standard abbreviations were used to report multiplicities. Data for ^{13}C NMR and ^{19}F NMR were reported in terms of chemical shifts (δ ppm). Optical rotations were measured with a PerkinElmer 343 Polarimeter and were reported as: $[\alpha]_D^T$ (concentration in g/100 mL, solvent). Enantiomeric excess (ee) was performed with an Agilent 1260 Series HPLC utilizing DAICEL Chiralpak (AD-H or IC) or Chiralcel (OD-H, OJ-H, or OB-H) columns (4.6 mm × 25 cm). IR spectra were recorded on a Nicolet IS10 spectrophotometer. High-resolution mass spectra (HRMS) were obtained from a Bruker Compact TOF mass spectrometer in electrospray ionization mode (ESI). Single-crystal X-ray data were collected using a Bruker Kappa Apex-DUO CCD diffractometer. Melting points were measured in open capillary tubes on a RY-1 melting point and are uncorrected. Unless otherwise noted, all reagents were purchased commercially and used without further purification, or synthesized according to the reported procedures.

For details of the determination of ee of the products **2a–k** and the crystal structure analysis of the product **2j**, see the Supporting Information.

(9*R*)-9-Methyl-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2a); Typical Procedure

In a N_2-filled glove box, $Pd(MeCN)_2Cl_2$ (5.2 mg, 0.02 mmol, 10 mol%), ligand **L5** (8.5 mg, 0.022 mmol, 11 mol%), and a stirring bar were added to a 2 Dram scintillation vial in toluene (1 mL). After the vial was capped and the contents were stirred at 100 °C for 30 min, 2-(2-bromobenzyl)-2-methylcyclohexane-1,3-dione (**1a**; 58.8 mg, 0.2 mmol) and Cs_2CO_3 (130.4 mg, 0.4 mmol, 2.0 equiv) were added. The vial was sealed and the contents were stirred at 100 °C until substrate **1a** was fully converted, as indicated by TLC. Toluene was evaporated and the crude mixture was then dissolved in CH_2Cl_2, filtered through a Celite pad, rinsed with CH_2Cl_2, and concentrated under reduced pressure. The crude reaction mixture was purified by silica gel flash chromatography (2% EtOAc in PE) to afford **2a**; yield: 30.1 mg (70%); colorless oil; R_f = 0.3 (10% EtOAc in PE); $[\alpha]_D^{20}$ –149.5 (*c* 1.0, CH_2Cl_2).

HPLC: Chiralcel OJ-H column (4.6 mm × 25 cm), 10% *i*-PrOH in *n*-hexane, 0.6 mL/min, λ = 210 nm, t_R (min): major = 51.15, minor = 26.31; 76% ee.

IR (neat film, KBr): 2984, 2936, 2866, 1736, 1700, 1489, 1454, 1376, 1272, 1088, 1076, 1022, 847, 749 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.23 (m, 2 H), 7.14–7.08 (m, 2 H), 3.85 (t, *J* = 3.3 Hz, 1 H), 3.33 (d, *J* = 17.5 Hz, 1 H), 3.21 (d, *J* = 17.5 Hz, 1 H), 2.52–2.45 (m, 1 H), 2.42–2.30 (m, 1 H), 2.11–1.97 (m, 2 H), 1.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.1, 207.6, 137.4, 133.1, 128.1, 127.7, 127.6, 127.1, 64.6, 50.4, 46.1, 34.9, 28.5, 15.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{14}O_2Na$: 237.0886; found: 237.0887.

(9*R*)-3-Methoxy-9-methyl-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2b)

Yield: 35.6 mg (73%); yellow solid; mp 62–64 °C; R_f = 0.3 (20% EtOAc in PE); $[\alpha]_D^{20}$ –153.6 (*c* 0.3, CH_2Cl_2).

HPLC: Chiralpak IC column (4.6 mm × 25 cm), 5% *i*-PrOH in *n*-hexane, 0.8 mL/min, λ = 210 nm, t_R (min): major = 31.78, minor = 28.36; 74% ee.

IR (neat film, KBr): 2920, 2849, 1735, 1700, 1608, 1501, 1278, 1235, 1037, 1022, 817 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.03 (d, *J* = 8.5 Hz, 1 H), 6.83 (dd, *J* = 8.5, 2.6 Hz, 1 H), 6.60 (d, *J* = 2.5 Hz, 1 H), 3.80 (t, *J* = 3.3 Hz, 1 H), 3.78 (s, 3 H), 3.28 (d, *J* = 17.6 Hz, 1 H), 3.18 (d, *J* = 17.5 Hz, 1 H), 2.51–2.43 (m, 1 H), 2.42–2.32 (m, 1 H), 2.03–1.97 (m, 2 H), 1.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 207.9, 159.0, 134.3, 129.4, 129.1, 114.1, 111.7, 64.2, 55.3, 49.7, 46.2, 34.9, 28.5, 15.8.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{16}O_3Na$: 267.0992; found: 267.0996.

(9*R*)-9-Methyl-6,7,9,10-tetrahydro-5,9-methanocycloocta[4,5]benzo[1,2-*d*][1,3]dioxole-8,12(5*H*)-dione (2c)

Yield: 24.8 mg (48%); yellow solid; mp 186–188 °C; R_f = 0.3 (30% EtOAc in PE); $[\alpha]_D^{20}$ –84.0 (*c* 0.3, CH_2Cl_2).

HPLC: Chiralcel OD-H column (4.6 mm × 25 cm), 2% *i*-PrOH in *n*-hexane, 0.8 mL/min, λ = 210 nm, t_R (min): major = 45.48, minor = 40.66; 74% ee.

IR (neat film, KBr): 3191, 2982, 2919, 2850, 1727, 1695, 1482, 1254, 1224, 1038, 1024, 935, 863 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.54 (s, 1 H), 6.53 (s, 1 H), 5.95 (s, 2 H), 3.71 (t, *J* = 4.0 Hz, 1 H), 3.19 (d, *J* = 17.3 Hz, 1 H), 3.10 (d, *J* = 17.3 Hz, 1 H), 2.52–2.45 (m, 1 H), 2.44–2.36 (m, 1 H), 2.08–1.92 (m, 2 H), 1.29 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.2, 207.5, 147.5, 147.3, 130.0, 126.3, 107.5, 106.9, 101.3, 64.1, 50.2, 45.9, 34.8, 28.2, 15.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{14}O_4Na$: 281.0784; found: 281.0778.

(9*R*)-3-Fluoro-9-methyl-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2d)

Yield: 20.4 mg (44%); white solid; mp 69–71 °C; R_f = 0.4 (10% EtOAc in PE); $[\alpha]_D^{20}$ –110.8 (*c* 0.3, CH_2Cl_2).

HPLC: Chiralpak IC column (4.6 mm × 25 cm), 3% *i*-PrOH in *n*-hexane, 0.5 mL/min, λ = 210 nm, t_R (min): major = 43.97, minor = 35.80; 74% ee.

IR (neat film, KBr): 2985, 2921, 2850, 1739, 1703, 1497, 1426, 1290, 1271, 1223, 1113, 1023, 826, 811 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.10 (dd, *J* = 8.5, 5.6 Hz, 1 H), 6.99 (td, *J* = 8.4, 2.6 Hz, 1 H), 6.81 (dd, *J* = 9.2, 2.4 Hz, 1 H), 3.84 (t, *J* = 3.2 Hz, 1 H), 3.30 (d, *J* = 17.7 Hz, 1 H), 3.18 (d, *J* = 17.8 Hz, 1 H), 2.54–2.46 (m, 1 H), 2.40–2.30 (m, 1 H), 2.06–2.00 (m, 2 H), 1.32 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.6, 207.1, 162.0 (d, $J_{C,F}$ = 245.5 Hz), 135.2 (d, $J_{C,F}$ = 7.6 Hz), 133.1 (d, $J_{C,F}$ = 3.0 Hz), 129.7 (d, $J_{C,F}$ = 8.3 Hz), 115.2 (d, $J_{C,F}$ = 21.6 Hz), 113.8 (d, $J_{C,F}$ = 21. 6 Hz), 64.0, 49.7, 45.6, 34.7, 28.4, 15.7.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.3.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}FO_2$: 233.0972; found: 233.0944.

(9*R*)-3-Chloro-9-methyl-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2e)

Yield: 29.3 mg (59%); white solid; mp 80–82 °C; R_f = 0.4 (10% EtOAc in PE); $[\alpha]_D^{20}$ –129.9 (*c* 1.0, CH_2Cl_2).

HPLC: Chiralpak IC column (4.6 mm × 25 cm), 3% *i*-PrOH in *n*-hexane, 0.8 mL/min, λ = 210 nm, t_R (min): major = 27.62, minor = 24.59; 78% ee.

IR (neat film, KBr): 2922, 2851, 1738, 1702, 1484, 1089, 1022, 887, 822 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.25 (dd, *J* = 8.4, 2.0 Hz, 1 H), 7.10 (s, 1 H), 7.06 (d, *J* = 8.4 Hz, 1 H), 3.82 (t, *J* = 3.2 Hz, 1 H), 3.28 (d, *J* = 17.6 Hz, 1 H), 3.16 (d, *J* = 18.0 Hz, 1 H), 2.53–2.46 (m, 1 H), 2.40–2.28 (m, 1 H), 2.06–2.00 (m, 2 H), 1.31 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.4, 206.8, 135.9, 134.9, 133.4, 129.4, 128.0, 127.1, 64.1, 49.8, 45.4, 34.7, 28.3, 15.7.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{13}ClO_2Na$: 271.0496; found: 271.0499.

(9*R*)-9-Propyl-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2f)

Yield: 32.4 mg (67%); white solid; mp 61–63 °C; R_f = 0.3 (10% EtOAc in PE); $[\alpha]_D^{20}$ –341.2 (*c* 0.3, CH_2Cl_2).

HPLC: Chiralcel OD-H column (4.6 mm × 25 cm), 2% *i*-PrOH in *n*-hexane, 0.6 mL/min, λ = 210 nm, t_R (min): major = 14.71, minor = 13.35; 69% ee.

IR (neat film, KBr): 2960, 2920, 2870, 1735, 1699, 1454, 1344, 1035, 777, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 2 H), 7.12–7.05 (m, 2 H), 3.83 (t, *J* = 3.2 Hz, 1 H), 3.27 (d, *J* = 17.2 Hz, 1 H), 3.19 (d, *J* = 17.2 Hz, 1 H), 2.49–2.41 (m, 1 H), 2.32–2.22 (m, 1 H), 2.09–2.03 (m, 2 H), 1.83–1.73 (m, 2 H), 1.48–1.36 (m, 1 H), 1.30–1.18 (m, 1 H), 0.96 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.3, 208.0, 137.7, 133.2, 128.0, 127.7, 127.6, 127.4, 67.6, 50.5, 45.6, 35.5, 33.1, 27.6, 18.0, 14.9.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{18}O_2Na$: 265.1199; found: 265.1199.

(9*R*)-9-Butyl-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2g)

Yield: 35.3 mg (69%); colorless oil; R_f = 0.3 (10% EtOAc in PE); $[\alpha]_D^{20}$ –80.8 (*c* 0.3, CH_2Cl_2).

HPLC: Chiralcel OD-H column (4.6 mm × 25 cm), 1% *i*-PrOH in *n*-hexane, 0.5 mL/min, λ = 210 nm, t_R (min): major = 16.37, minor = 15.30; 79% ee.

IR (neat film, KBr): 2955, 2929, 2870, 1736, 1700, 1489, 1455, 1347, 1272, 1224, 1124, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.20 (m, 2 H), 7.12–7.06 (m, 2 H), 3.83 (t, *J* = 3.6 Hz, 1 H), 3.27 (d, *J* = 17.2 Hz, 1 H), 3.19 (d, *J* = 17.2 Hz, 1 H), 2.49–2.40 (m, 1 H), 2.32–2.21 (m, 1 H), 2.10–2.03 (m, 2 H), 1.84–1.77 (m, 2 H), 1.43–1.31 (m, 3 H), 1.24–1.13 (m, 1 H), 0.91 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.4, 208.0, 137.8, 133.3, 128.0, 127.7, 127.6, 127.4, 67.6, 50.5, 45.6, 35.5, 30.7, 27.6, 27.0, 23.5, 14.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{17}H_{20}O_2Na$: 279.1356; found: 279.1350.

(9*R*)-9-Hexyl-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2h)

Yield: 50.1 mg (84%); colorless oil; R_f = 0.3 (10% EtOAc in PE); $[\alpha]_D^{20}$ –77.2 (*c* = 0.3, CH_2Cl_2).

HPLC: Chiralcel OD-H column (4.6 mm × 25 cm), 2% *i*-PrOH in *n*-hexane, 0.6 mL/min, λ = 210 nm, t_R (min): major = 12.06, minor = 11.21; 63% ee.

IR (neat film, KBr): 2921, 2851, 1735, 1700, 1469, 1455, 1410, 1345, 1271, 1123, 748 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.19 (m, 2 H), 7.12–7.05 (m, 2 H), 3.82 (t, *J* = 3.2 Hz, 1 H), 3.26 (d, *J* = 17.2 Hz, 1 H), 3.18 (d, *J* = 17.2 Hz, 1 H), 2.48–2.40 (m, 1 H), 2.33–2.21 (m, 1 H), 2.10–2.03 (m, 2 H), 1.86–1.75 (m, 2 H), 1.45–1.13 (m, 8 H), 0.88 (t, *J* = 6.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.4, 208.0, 137.7, 133.2, 128.0, 127.6, 127.5, 127.4, 67.6, 50.5, 45.6, 35.5, 31.6, 30.9, 30.1, 27.5, 24.7, 22.6, 14.1.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{19}H_{24}O_2Na$: 307.1669; found: 307.1639.

(9*R*)-9-(3-Phenylpropyl)-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2i)

Yield: 41.3 mg (65%); colorless oil; R_f = 0.3 (10% EtOAC in PE); $[\alpha]_D^{20}$ –116.4 (*c* 0.3, CH_2Cl_2).

HPLC: Chiralcel OD-H column (4.6 mm × 25 cm), 2% *i*-PrOH in *n*-hexane, 0.6 mL/min, λ = 210 nm, t_R (min): major = 27.38, minor = 23.39; 63% ee.

IR (neat film, KBr): 3060, 3024, 2921, 2852, 1735, 1698, 1489, 1453, 1346, 1224, 1029, 749, 700 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.15 (m, 7 H), 7.12–7.04 (m, 2 H), 3.82 (t, *J* = 3.2 Hz, 1 H), 3.26 (d, *J* = 17.2 Hz, 1 H), 3.19 (d, *J* = 17.1 Hz, 1 H), 2.75–2.61 (m, 2 H), 2.48–2.39 (m, 1 H), 2.32–2.20 (m, 1 H), 2.12–1.97 (m, 2 H), 1.93–1.84 (m, 2 H), 1.82–1.69 (m, 1 H), 1.64–1.48 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.1, 207.8, 142.3, 137.6, 133.1, 128.4, 128.2, 128.0, 127.7, 127.6, 127.3, 125.7, 67.6, 50.5, 45.6, 36.6, 35.4, 30.7, 27.5, 26.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{22}H_{22}O_2Na$: 341.1512; found: 341.1514.

(9*R*)-9-Benzyl-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2j)

Yield: 45.2 mg (78%); white solid; mp 65–67 °C; R_f = 0.4 (10% EtOAc in PE); $[\alpha]_D^{20}$ –95.6 (>99% ee, *c* = 0.3, CH_2Cl_2).

HPLC: Chiralpak IC column (4.6 mm × 25 cm), 3% *i*-PrOH in *n*-hexane, 0.8 mL/min, λ = 210 nm, t_R (min): major = 17.43, minor = 15.37; 86% ee.

IR (neat film, KBr): 3061, 3027, 2920, 2850, 1735, 1701, 1494, 1454, 1266, 1194, 1122, 1081, 1030, 737, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.33 (m, 2 H), 7.29–7.23 (m, 3 H), 7.22–7.16 (m, 2 H), 7.13–7.04 (m, 2 H), 3.89 (t, *J* = 3.6 Hz, 1 H), 3.42 (d, *J* = 14.0 Hz, 1 H), 3.26 (s, 2 H), 3.21 (d, *J* = 14.0 Hz, 1 H), 2.32–2.26 (m, 2 H), 2.14–2.00 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.6, 207.5, 137.6, 137.4, 133.1, 131.1, 128.03, 128.02, 127.7, 127.6, 126.2, 68.4, 50.6, 44.3, 35.7, 35.0, 27.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{18}O_2Na$: 313.1199; found: 313.1199.

(9*R*)-9-(4-Methylbenzyl)-6,7,9,10-tetrahydro-5,9-methanobenzo[8]annulene-8,11(5*H*)-dione (2k)

Yield: 45.0 mg (74%); colorless oil; R_f = 0.4 (10% EtOAc in PE); $[\alpha]_D^{20}$ –79.6 (*c* 0.3, CH_2Cl_2).

HPLC: Chiralpak IC column (4.6 mm × 25 cm), 3% *i*-PrOH in *n*-hexane, 0.8 mL/min, λ = 210 nm, t_R (min): major = 18.98, minor = 17.32; 86% ee.

IR (neat film, KBr): 3022, 2924, 2864, 1735, 1700, 1514, 1454, 812, 752 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25–7.17 (m, 4 H), 7.12–7.02 (m, 4 H), 3.87 (t, *J* = 3.6 Hz, 1 H), 3.36 (d, *J* = 14.0 Hz, 1 H), 3.25 (s, 2 H), 3.16 (d, *J* = 14.4 Hz, 1 H), 2.30 (s, 3 H), 2.29–2.26 (m, 2 H), 2.14–1.98 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.7, 207.6, 137.7, 135.7, 134.2, 133.1, 131.0, 128.7, 128.0, 127.6, 127.54, 127.51, 68.4, 50.6, 44.2, 35.8, 34.6, 27.7, 21.0.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{20}O_2Na$: 327.1356; found: 327.1359.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591751.

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(14) No desired arylation product was observed on treatment of 2-(2-bromobenzyl)-2-phenylcyclohexane-1,3-dione under the standard conditions.

(15) Enantiopure **2j** was obtained by single recrystallization from *i*-PrOH/hexane.

(16) CCDC 1589080 contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.