Exploration of Aryllithium-derived Copper Reagents for Quaternary-Stereogenic-Center-Forming Allylic Substitution of γ,γ-Disubstituted Secondary Allylic Picolinates

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Experimental S2
Reference S16
Chiral HPLC S17
Spectra S22
General Remarks. The $^1$H (300 MHz) and $^{13}$C NMR (75 MHz) spectroscopic data were recorded in CDCl$_3$ using Me$_4$Si ($\delta = 0$ ppm) and the centerline of the triplet ($\delta = 77.1$ ppm), respectively, as internal standards. Signal patterns are indicated as br s (broad singlet), s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). Coupling constants ($J$) are given in Hertz (Hz). Chemical shifts of carbons are accompanied by minus (for C and CH$_2$) and plus (for CH and CH$_3$) signs of the attached proton test (APT) experiments. High-resolution mass spectroscopy (HRMS) was performed with a double-focusing mass spectrometer with an ionization mode of positive FAB or EI as indicated for each compound. The solvents that were distilled prior to use are THF (from Na/benzophenone), Et$_2$O (from Na/benzophenone), and CH$_2$Cl$_2$ (from CaH$_2$). CuTC was prepared according to the literature. MgBr$_2$·OEt$_2$ purchased from Aldrich was diluted in THF to prepare a 0.20 M solution.

2-Methyl-7-phenylhept-2-en-4-yl Picolinate (1)

\[
\begin{align*}
\text{CHO} & \quad \text{OH (CH$_2$)$_3$Ph} & \quad \text{OCOPy (CH$_2$)$_3$Ph} \\
& \quad \quad 1
\end{align*}
\]

To an ice-cold solution of prenal (653.5 mg, 7.77 mmol) in THF (13 mL) was added Ph(CH$_2$)$_3$MgCl (0.43 M in THF, 19.0 mL, 8.17 mmol). The mixture was stirred at rt for 2 h, and saturated NH$_4$Cl and EtOAc were added with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO$_4$, and concentrated to afford alcohol, which was used for the next reaction without further purification.

To an ice-cold solution of the above alcohol in CH$_2$Cl$_2$ (38 mL) was added picolinic acid (1.94 g, 15.7 mmol), Et$_3$N (5.65 mL, 40.5 mmol), DMAP (1.43 g, 11.7 mmol), and 2-chloro-1-methylpyridinium iodide (3.98 g, 15.6 mmol). The mixture was stirred at rt overnight and diluted with saturated NaHCO$_3$ with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO$_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford picolinate 1.
(1.87 g, 78% from 3-methyl-2-butenal) as a colorless oil. The $^1$H NMR spectrum was consistent with the reported data.$^2$

**$(E)$-4,8-Dimethylnona-3,7-dien-2-ol (rac-11)**

![Diagram](image)

To a suspension of MS4A (8.13 g), TPAP (56.2 mg, 0.160 mmol), NMO (2.86 g, 24.4 mmol) in CH$_2$Cl$_2$ (38 mL) was added geraniol (10) (2.87 mL, 16.4 mmol). The mixture was stirred at rt for 22 h and filtered through a pad of silica gel. The filtrate was concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford geranaldehyde (2.20 g, 88%) as a colorless oil. The $^1$H NMR spectrum was consistent with the reported data.$^2$

To an ice-cold solution of the above aldehyde (1.63 g, 10.7 mmol) in THF (30 mL) was added MeMgCl (3.0 M in THF, 7.25 mL, 21.8 mmol) dropwise. The resulting mixture was stirred at 0 ºC for 1 h, and saturated NH$_4$Cl was added with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO$_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol rac-11 (1.70 g, 95%) as a colorless oil. The $^1$H NMR spectrum was consistent with the reported data.$^2$

**$(E)$-6,10-Dimethyl-1-phenylundeca-5,9-dien-4-yl Picolinate (rac-8)**

![Diagram](image)

To an ice-cold solution of alcohol rac-11 (997 mg, 5.93 mmol) in CH$_2$Cl$_2$ (20 mL) was added picolinic acid (1.47 g, 11.9 mmol), Et$_3$N (4.20 mL, 30.1 mmol), DMAP (1.08 g, 8.84 mmol), and 2-chloro-1-methylpyridinium iodide (2.99 g, 11.7 mmol). The mixture was
stirred at rt overnight, and brine was added with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford picolinate *rac-8* (1.30 g, 80%) as a colorless oil. The ¹H NMR spectrum was consistent with the reported data.²

\[(R,E)-4,8\text{-Dimethylnona-3,7-dien-2-ol (}(R)-11)\]

To an ice-cold suspension of MS₄A (275 mg) and Ti(O-\(i\)-Pr)₄ (0.260 mL, 0.878 mmol) in CH₂Cl₂ (8 mL) was added L-(+)‐DIPT (0.280 mL, 1.36 mmol). The resulting mixture was stirred at 0 °C for 30 min and cooled to –20 °C. A solution of alcohol *rac-11* (1.52 g, 9.06 mmol) in CH₂Cl₂ (4 mL) was added to it. The mixture was stirred at –20 °C for 30 min and cooled to –40 °C. A solution of \(t\)-BuOOH (4.91 M in CH₂Cl₂, 1.85 mL, 9.08 mmol) was added to it. The reaction was carried out at –18 °C for 20 h, and quenched by addition of Me₂S (1.35 mL, 18.4 mmol). The mixture was stirred at –18 °C for 30 min and filtered through a pad of Celite. To the filtrate were added 10% aqueous tartaric acid (5.45 mL), NaF (1.94 g, 46.2 mmol), and Celite (3.81 g). The resulting mixture was stirred at rt for 2 h and filtered through a pad of Celite. The filtrate was mixed with 1 N NaOH and the mixture was stirred at rt for 30 min. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford alcohol (\(R\)-11) (416 mg, 27%) as a colorless oil: 97% ee by HPLC analysis (Chiralcel OD-H, hexane/\(i\)-PrOH = 99.5/0.5, 0.5 mL/min, 27 °C; \(t_R\) (min) = 34.6 (\(R\)), 36.2 (\(S\)).

The kinetic resolution was repeated several times and the combined alcohol with 98% ee was used for the next reaction.
**Allylic Substitution via Method A:**

**(E)-(6-Methylhept-4-ene-1,6-diyl)dibenzene (2a)**

To an ice-cold suspension of CuTC (91.6 mg, 0.480 mmol) in THF (1.5 mL) were added PhLi (1.07 M in cyclohexane/Et₂O, 0.840 mL, 0.899 mmol) and MgBr₂·OEt₂ (0.20 M in THF, 4.80 mL, 0.960 mmol) slowly. The resulting mixture was stirred at 0 °C for 30 min, cooled to −40 °C. A solution of picolinate 1 (93.4 mg, 0.302 mmol) in THF (1.5 mL) was added to it dropwise. The resulting mixture was allowed to warm to −5 °C over 2 h, and saturated NH₄Cl was added with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford 2a (70.6 mg, 88%) as a colorless oil. Gamma/alpha = 98 : 2 by ¹H NMR spectroscopy: ¹H NMR (300 MHz, CDCl₃) δ 1.38 (s, 6 H), 1.72 (quint, J = 7.6 Hz, 2 H), 2.09 (dd, J = 7.4, 6.9 Hz, 2 H), 2.62 (t, J = 8.0 Hz, 2 H), 5.44 (dt, J = 15.6, 6.9 Hz, 1 H), 5.64 (dt, J = 15.6, 1.2 Hz, 1 H), 7.14–7.21 (m, 4 H), 7.24–
7.38 (m, 6 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 29.0 (+), 31.5 (–), 32.2 (–), 35.5 (–), 40.4 (–), 125.70 (+), 125.72 (+), 126.1 (+), 126.2 (+), 128.1 (+), 128.3 (+), 128.5 (+), 140.6 (+), 142.6 (–), 149.4 (–).

**Allylic Substitution via Method B:**

*(E)-1-Methyl-4-(2-methyl-7-phenylhept-3-en-2-yl)benzene (7b)*

![Chemical Structure](image)

To an ice-cold solution of 4-iodotoluene (140 mg, 0.640 mmol) in Et$_2$O (1 mL) was added t-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol) slowly. The resulting mixture was stirred at 0 ºC for 30 min, and added CuTC (61.0 mg, 0.320 mmol) and MgBr$_2$·OEt$_2$ (0.20 M in THF, 6.40 mL, 1.28 mmol). The resulting mixture was stirred at 0 ºC for 30 min and cooled to –40 ºC. A solution of picolinate 1 (61.9 mg, 0.200 mmol) in THF (1 mL) was added to the mixture dropwise. The resulting mixture was allowed to warm to –20 ºC over 2 h, and diluted with saturated NH$_4$Cl and aqueous NH$_4$OH with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO$_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane) to afford 7b (39.4 mg, 71%) as a colorless oil. Gamma/alpha = 99 : 1 by $^1$H NMR spectroscopy. The $^1$H NMR spectrum of the product was consistent with that obtained above: $^1$H NMR (300 MHz, CDCl$_3$) δ 1.36 (s, 6 H), 1.66–1.77 (m, 2 H), 2.08 (q, $J = 7.0$ Hz, 2 H), 2.32 (s, 3 H), 2.62 (t, $J = 7.8$ Hz, 2 H), 5.43 (dt, $J = 15.6$, 6.9 Hz, 1 H), 5.62 (d, $J = 15.6$ Hz, 1 H), 7.07–7.32 (m, 9 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 21.0 (+), 29.0 (+), 31.5 (–), 32.2 (–), 35.5 (–), 40.0 (–), 125.7 (+), 125.9 (+), 126.1 (+), 128.3 (+), 128.5 (+), 128.8 (+), 135.1 (–), 140.7 (+), 142.7 (–), 146.5 (–).

**Allylic Substitution via Method C:**

*(E)-2-(2-(4,8-Dimethylnona-2,7-dien-4-yl)phenyl)-4,4-dimethyl-4,5-dihydrooxazole (rac-9h)*
To an ice-cold solution of 4,4-dimethyl-2-phenyl-2-oxazoline (112 mg, 0.641 mmol) in THF (1 mL) was added n-BuLi (1.60 M in hexane, 0.375 mL, 0.600 mmol) slowly. The resulting mixture was stirred at 0 ºC for 1.5 h and CuTC (61.0 mg, 0.320 mmol) and MgBr₂·OEt₂ (0.20 M in THF, 3.20 mL, 0.640 mmol) were added to the mixture. The resulting mixture was stirred at 0 ºC for 30 min and cooled to –40 ºC. A solution of picolinate rac-8 (54.6 mg, 0.200 mmol) in THF (1 mL) was added to it dropwise. The resulting mixture was allowed to warm to –20 ºC over 2 h, and saturated NH₄Cl and aqueous NH₄OH were added with vigorous stirring. The layers were separated and the aqueous layer was extracted with EtOAc three times. The combined extracts were washed with brine, dried over MgSO₄, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford rac-9h (46.0 mg, 71% yield) as a colorless oil. Gamma/alpha = 99 : 1 by ¹H NMR spectroscopy: ¹H NMR (300 MHz, CDCl₃)  δ 1.36 (s, 3 H), 1.37 (s, 3 H), 1.48 (s, 3 H), 1.53 (s, 3 H), 1.65 (s, 3 H), 1.70–1.98 (m, 4 H), 1.73 (dd, ³J = 6.3, 1.7 Hz, 3 H), 4.01 (s, 2 H), 5.05–5.13 (m, 1 H), 5.40 (dq, ³J = 15.6, 6.3 Hz, 1 H), 5.76 (dq, ³J = 15.6, 1.7 Hz, 1 H), 7.19 (dt, ³J = 1.5, 7.4 Hz, 1 H), 7.30–7.42 (m, 3 H); ¹³C NMR (75 MHz, CDCl₃)  δ 17.7 (+), 18.7 (+), 23.6 (–), 25.8 (+), 27.5 (+), 28.05 (+), 28.11 (+), 41.9 (–), 44.8 (–), 67.4 (–), 79.0 (–), 122.4 (+), 125.0 (+), 125.6 (+), 128.1 (+), 129.2 (–), 129.6 (+), 131.2 (–), 131.6 (+), 139.9 (+), 147.0 (–), 165.3 (–). HRMS (FAB) calcd for C₂₂H₃₂NO [(M + H)⁺] 326.2484, found 326.2483.

(E)-1-Methoxy-4-(2-methyl-7-phenylhept-3-en-2-yl)benzene (7e)

According to the general procedure via Method B, a solution of picolinate 1 (62.2 mg, 0.201 mmol) in THF (1 mL) was added to a mixture of 4-iodoanisole (150 mg, 0.642
mmol), t-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (61.4 mg, 0.322 mmol), and MgBr₂·Et₂ (0.20 M in THF, 6.40 mL, 1.28 mmol) in Et₂O (1 mL) at −40 °C, and the mixture was allowed to warm to −20 °C over 2 h to afford 7b (45.2 mg, 76%) as a colorless oil. Gamma/alpha = 96 : 4 by ¹H NMR spectroscopy: ¹H NMR (300 MHz, CDCl₃) δ 1.36 (s, 6 H), 1.66–1.77 (m, 2 H), 2.08 (q, J = 6.9 Hz, 2 H), 2.62 (t, J = 7.7 Hz, 2 H), 3.79 (s, 3 H), 5.42 (dt, J = 15.6, 6.9 Hz, 1 H), 5.62 (d, J = 15.6 Hz, 1 H), 6.83 (d, J = 9.0 Hz, 2 H), 7.14–7.21 (m, 3 H), 7.23–7.31 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ 29.2 (+), 31.5 (–), 32.2 (+), 35.5 (–), 39.7 (–), 55.3 (+), 113.4 (+), 125.7 (+), 125.8 (+), 127.2 (+), 128.3 (+), 128.5 (+), 140.8 (+), 141.5 (–), 142.7 (–), 157.5 (–).

(E)-(4,8-Dimethylnona-2,7-dien-4-yl)benzene (rac-9a)

According to the general procedure via Method A, a solution of picolinate rac-8 (54.7 mg, 0.200 mmol) in THF (1 mL) was added to a mixture of PhLi (1.08 M in cyclohexane/Et₂O, 0.555 mL, 0.599 mmol), CuTC (61.2 mg, 0.321 mmol), and MgBr₂·Et₂ (0.20 M in THF, 3.20 mL, 0.640 mmol) in THF (1 mL) at −40 °C, and the mixture was allowed to warm to −10 °C over 2 h to afford a mixture of rac-9a and Ph₂ in a 95 : 5 ratio by ¹H NMR analysis (43.9 mg in total, 92% yield of rac-9a) as a colorless oil. Gamma/alpha = 98 : 2 by ¹H NMR spectroscopy: ¹H NMR (300 MHz, CDCl₃) δ 1.36 (s, 3 H), 1.51 (s, 3 H), 1.65 (s, 3 H), 1.65–1.88 (m, 4 H), 1.72 (dd, J = 6.2, 1.6 Hz, 3 H), 5.04–5.12 (m, 1 H), 5.44 (dq, J = 15.6, 6.2 Hz, 1 H), 5.65 (dq, J = 15.6, 1.6 Hz, 1 H), 7.13–7.20 (m, 1 H), 7.24–7.34 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃) δ 17.6 (+), 18.3 (+), 23.4 (–), 25.6 (+), 25.8 (+), 41.8 (–), 43.6 (–), 122.1 (+), 124.9 (+), 125.6 (+), 126.7 (+), 128.1 (+), 131.3 (–), 140.0 (+), 148.4 (–).

(E)-(4,8-Dimethylnona-2,7-dien-4-yl)benzene (rac-9a)
According to the general procedure via Method B, a solution of picolinate \( \text{rac-8} \) (54.9 mg, 0.201 mmol) in THF (1 mL) was added to a mixture of bromobenzene (101 mg, 0.643 mmol), \( t\text{-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (60.8 mg, 0.319 mmol), and MgBr}_2 \cdot \text{OEt}_2 \) (0.20 M in THF, 6.40 mL, 1.28 mmol) in \( \text{Et}_2\text{O (1 mL) at } -40 \, ^\circ\text{C}, \) and the mixture was allowed to warm to \(-20 \, ^\circ\text{C over 2 h to afford a mixture of rac-9a and Ph}_2 \) in a 87 : 13 ratio by \(^1\text{H NMR analysis (45.1 mg in total, 89% yield of rac-9a)} \) as a colorless oil. Gamma/alpha = 99 : 1 by \(^1\text{H NMR spectroscopy. The } ^1\text{H NMR spectrum of the product was consistent with that obtained above.} \)

\((E\text{-})1\text{-}(4,8\text{-Dimethylnona-2,7-dien-4-yl)-4-methylbenzene (rac-9b)}\)

According to the general procedure via Method B, a solution of picolinate \( \text{rac-8} \) (54.9 mg, 0.201 mmol) in THF (1 mL) was added to a mixture of 4-iodotoluene (139 mg, 0.639 mmol), \( t\text{-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (61.2 mg, 0.321 mmol), and MgBr}_2 \cdot \text{OEt}_2 \) (0.20 M in THF, 6.40 mL, 1.28 mmol) in \( \text{Et}_2\text{O (1 mL) at } -40 \, ^\circ\text{C}, \) and the mixture was allowed to warm to \(-20 \, ^\circ\text{C over 2 h to afford a mixture of rac-9b and (4-MeC}_6\text{H}_4)_2 \) in a 93 : 7 ratio by \(^1\text{H NMR analysis (45.5 mg in total, 89% yield of rac-9b)} \) as a colorless oil. Gamma/alpha = 96 : 4 by \(^1\text{H NMR spectroscopy: } ^1\text{H NMR (300 MHz, CDCl}_3 \) \( \delta \) 1.33 (s, 3 H), 1.52 (s, 3 H), 1.58–1.89 (m, 4 H), 1.65 (s, 3 H), 1.71 (dd, \( J = 6.3, 1.6 \text{ Hz, 3 H}), 2.31 (s, 3 H), 5.03–5.12 (m, 1 H), 5.42 (dq, \( J = 15.6, 6.3 \text{ Hz, 1 H}), 5.62 (dq, J = 15.6, 1.6 \text{ Hz, 1 H}), 7.10 (d, \( J = 8.1 \text{ Hz, 2 H}), 7.20 (d, J = 8.1 \text{ Hz, 2 H}); ^{13}\text{C NMR (75 MHz, CDCl}_3\) \( \delta \) 17.7 (+), 18.3 (+), 21.0 (+), 23.4 (–), 25.6 (+), 25.8 (+), 41.8 (–), 43.2 (–), 121.8 (+), 125.0 (+), 126.6 (+), 128.8 (+), 131.2 (–), 135.0 (–), 140.2 (+), 145.4 (–). HRMS (EI) calcd for C\(_{18}\)H\(_{26}\) (M\(^+\)) 242.2035, found 242.2035.
According to the general procedure via Method B, a solution of picolinate rac-8 (54.9 mg, 0.201 mmol) in THF (1 mL) was added to a mixture of 3-bromotoluene (110 mg, 0.641 mmol), t-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (61.1 mg, 0.320 mmol), and MgBr₂·OEt₂ (0.20 M in THF, 6.40 mL, 1.28 mmol) in Et₂O (1 mL) at −40 °C, and the mixture was allowed to warm to −20 °C over 2 h to afford a mixture of rac-9c and (3-MeC₆H₄)₂ in a 93 : 7 ratio by ¹H NMR analysis (47.6 mg in total, 92% yield of rac-9c) as a colorless oil. Gamma/alpha = 99 : 1 by ¹H NMR spectroscopy: ¹H NMR (300 MHz, CDCl₃) δ 1.34 (s, 3 H), 1.52 (s, 3 H), 1.60–1.88 (m, 4 H), 1.66 (s, 3 H), 1.72 (dd, J = 6.3, 1.5 Hz, 3 H), 2.34 (s, 3 H), 5.04–5.13 (m, 1 H), 5.43 (dq, J = 15.8, 6.3 Hz, 1 H), 5.64 (dq, J = 15.8, 1.5 Hz, 1 H), 6.98 (d, J = 7.2 Hz, 1 H), 7.08–7.21 (m, 3 H); ¹³C NMR (75 MHz, CDCl₃) δ 17.6 (+), 18.3 (+), 21.8 (+), 23.5 (−), 25.6 (+), 25.8 (+), 41.8 (−), 43.4 (−), 121.9 (+), 123.7 (+), 125.0 (+), 126.4 (+), 127.4 (+), 127.9 (+), 131.2 (−), 137.4 (−), 140.1 (+), 148.4 (−). HRMS (EI) calcd for C₁₈H₂₆ (M⁺) 242.2035, found 242.2033.

According to the general procedure via Method B, a solution of picolinate rac-8 (54.5 mg, 0.199 mmol) in THF (1 mL) was added to a mixture of 2-bromotoluene (110 mg, 0.643 mmol), t-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (61.1 mg, 0.320 mmol), and MgBr₂·OEt₂ (0.20 M in THF, 6.40 mL, 1.28 mmol) in Et₂O (1 mL) at −40 °C, and the mixture was allowed to warm to −20 °C over 2 h to afford a mixture of rac-9d and
(2-MeC₆H₄)₂ in a 88 : 12 ratio by ¹H NMR analysis (48.9 mg in total, 92% yield of product rac-9d) as a colorless oil. Gamma/alpha = 99 : 1 by ¹H NMR spectroscopy: ¹H NMR (300 MHz, CDCl₃) δ 1.41 (s, 3 H), 1.50 (s, 3 H), 1.58–2.03 (m, 4 H), 1.65 (s, 3 H), 1.67 (dd, J = 6.6, 1.7 Hz, 3 H), 2.36 (s, 3 H), 5.04–5.11 (m, 1 H), 5.29 (dq, J = 15.6, 6.6 Hz, 1 H), 5.66 (dq, J = 15.6, 1.7 Hz, 1 H), 7.08–7.17 (m, 3 H), 7.28–7.33 (m, 1 H); ¹³C NMR (75 MHz, CDCl₃) δ 17.6 (+), 18.2 (+), 22.7 (+), 23.5 (−), 25.8 (+), 27.4 (+), 40.1 (−), 44.3 (−), 121.6 (+), 125.0 (+), 125.5 (+), 126.1 (+), 127.3 (+), 131.3 (−), 132.4 (+), 137.2 (−), 140.6 (+), 145.0 (−). HRMS (EI) calcd for C₁₈H₂₆ (M⁺) 242.2035, found 242.2035.

(E)-1-(4,8-Dimethylnona-2,7-dien-4-yl)-4-methoxybenzene (rac-9e)

According to the general procedure via Method B, a solution of picolinate rac-8 (54.7 mg, 0.200 mmol) in THF (1 mL) was added to a mixture of 4-iodoanisole (150 mg, 0.640 mmol), t-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (61.2 mg, 0.321 mmol), and MgBr₂·OEt₂ (0.20 M in THF, 6.40 mL, 1.28 mmol) in Et₂O (1 mL) at −40 °C, and the mixture was allowed to warm to −20 °C over 2 h to afford a mixture of rac-9e, (4-MeOC₆H₄)₂, and 4-iodoanisole in a 82 : 8 : 10 ratio by ¹H NMR analysis (57.3 mg in total, 93% yield of rac-9e) as a colorless oil. Gamma/alpha = 99 : 1 by ¹H NMR spectroscopy: ¹H NMR (300 MHz, CDCl₃) δ 1.33 (s, 3 H), 1.52 (s, 3 H) 1.61–1.90 (m, 4 H), 1.66 (s, 3 H), 1.71 (dd, J = 6.3, 1.5 Hz, 3 H), 3.79 (s, 3 H), 5.04–5.12 (m, 1 H), 5.41 (dq, J = 15.8, 6.3 Hz, 1 H), 5.62 (dq, J = 15.8, 1.5 Hz, 1 H), 6.83 (d, J = 9.0 Hz, 2 H), 7.22 (d, J = 9.0 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ 17.7 (+), 18.3 (+), 23.4 (−), 25.7 (+), 25.8 (+), 41.9 (−), 42.9 (−), 55.3 (+), 113.3 (+), 121.8 (+), 125.0 (+), 127.7 (+), 131.2 (−), 140.3 (+), 140.5 (−), 157.4 (−). HRMS (FAB) calcd for C₅₇H₅₆O (M⁺) 258.1984, found 258.1982.

(E)-1-(4,8-Dimethylnona-2,7-dien-4-yl)-4-methoxybenzene (rac-9f)
According to the general procedure via Method B, a solution of picolinate \textit{rac-8} (54.9 mg, 0.201 mmol) in THF (1 mL) was added to a mixture of 4-fluorobromobenzene (112 mg, 0.642 mmol), \textit{t}-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (60.9 mg, 0.319 mmol), and MgBr$_2$OEt$_2$ (0.20 M in THF, 6.40 mL, 1.28 mmol) in Et$_2$O (1 mL) at $-40 \, ^\circ\text{C}$, and the mixture was allowed to warm to $-20 \, ^\circ\text{C}$ over 2 h to afford a mixture of \textit{rac-9f} and (4-FC$_6$H$_4$)$_2$ in a 91 : 9 ratio by $^1$H NMR analysis (44.7 mg in total, 84\% yield of \textit{rac-9f}) as a colorless oil. Gamma/alpha = 99 : 1 by $^1$H NMR spectroscopy: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.34 (s, 3 H), 1.51 (s, 3 H), 1.59–1.89 (m, 4 H), 1.65 (s, 3 H), 1.72 (dd, $J = 6.3, 1.6$ Hz, 3 H), 5.02–5.11 (m, 1 H), 5.42 (dq, $J = 15.6, 6.3$ Hz, 1 H), 5.61 (dq, $J = 15.6, 1.6$ Hz, 1 H), 6.96 (t, $J = 8.9$ Hz, 2 H), 7.22–7.30 (m, 2 H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 17.6 (+), 18.3 (+), 23.4 (–), 25.76 (+), 25.79 (+), 42.0 (–), 43.2 (–), 114.6 (d, $J = 21$ Hz) (+), 122.3 (+), 124.7 (+), 128.2 (d, $J = 8$ Hz) (+), 131.4 (–), 139.8 (+), 144.1 (–), 161.0 (d, $J = 242$ Hz) (–). HRMS (EI) calcd for C$_{17}$H$_{23}$F (M$^+$) 246.1784, found 246.1785.

\((E)-1-(4,8-\text{Dimethylnona}-2,7-\text{dien}-4-\text{yl})-1,2,3-\text{trimethoxybenzene (rac-9g)}\)

According to the general procedure via Method B, a solution of picolinate \textit{rac-8} (54.9 mg, 0.201 mmol) in THF (1 mL) was added to a mixture of 3,4,5-trimethoxybromobenzene (159 mg, 0.642 mmol), \textit{t}-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (61.2 mg, 0.321 mmol), and MgBr$_2$OEt$_2$ (0.20 M in THF, 6.40 mL, 1.28 mmol) in Et$_2$O (1 mL) at $-40 \, ^\circ\text{C}$, and the mixture was allowed to warm to $-20 \, ^\circ\text{C}$ over 2 h to afford \textit{rac-9g} (60.2 mg, 94\% yield) as a colorless oil. Gamma/alpha = 99 : 1 by $^1$H NMR spectroscopy: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.34 (s, 3 H), 1.53 (s, 3 H), 1.62–1.90 (m, 4 H), 1.66 (s, 3 H), 1.73 (dd, $J = 6.2, 1.5$ Hz, 3 H), 3.83 (s, 3 H), 3.85 (s, 6 H), 5.05–5.13 (m, 1 H), 5.46 (dq, $J = 15.6, 6.2$ Hz, 1 H).
Hz, 1 H), 5.62 (dq, J = 15.6, 1.5 Hz, 1 H), 6.53 (s, 2 H); 13C NMR (75 MHz, CDCl3) δ 17.6 (+), 18.2 (+), 23.4 (−), 25.6 (+), 25.7 (+), 41.8 (−), 43.8 (−), 56.1 (+), 60.9 (+), 104.1 (+), 122.1 (+), 124.8 (+), 131.3 (−), 136.0 (−), 139.7 (+), 144.3 (−), 152.7 (−). HRMS (FAB) calcd for C20H30O3 (M+) 318.2195, found 318.2194.

(R,E)-(4,8-Dimethylnona-2,7-dien-4-yl)benzene ((R)-9a)

\[
\begin{align*}
(R)-8 & \quad \rightarrow \quad (R)-9a
\end{align*}
\]

According to the general procedure via Method B, a solution of picolinate (R)-8 (55.0 mg, 0.201 mmol, 98% ee) in THF (1 mL) was added to a mixture of bromobenzene (101 mg, 0.642 mmol), t-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (61.1 mg, 0.320 mmol), and MgBr2·OEt2 (0.20 M in THF, 6.40 mL, 1.28 mmol) in Et2O (1 mL) at −40 °C, and the mixture was allowed to warm to −20 °C over 2 h to afford a mixture of (R)-9a and Ph2 in a 95 : 5 ratio by 1H NMR analysis (40.4 mg in total, 85% yield of (R)-9a) as a colorless oil. Gamma/alpha = 99 : 1 by 1H NMR spectroscopy. The enantiomeric purity of 95% ee was determined by chiral HPLC analysis: Chiralcel OJ-H, hexane/i-PrOH = 99.8/0.2, 0.3 mL/min, 30 °C, tR/min = 18.6 (S-isomer), 20.2 (R-isomer). The 1H NMR spectrum of the product was consistent with that obtained above.

(R,E)-1-(4,8-Dimethylnona-2,7-dien-4-yl)-4-methoxybenzene ((R)-9e)

\[
\begin{align*}
(R)-8 & \quad \rightarrow \quad (R)-9e
\end{align*}
\]

According to the general procedure via Method B, a solution of picolinate (R)-8 (54.6 mg, 0.200 mmol, 98% ee) in THF (1 mL) was added to a mixture of 4-bromoanisole (120 mg, 0.642 mmol), t-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (61.2 mg, 0.321 mmol), and MgBr2·OEt2 (0.20 M in THF, 6.40 mL, 1.28 mmol) in Et2O (1 mL) at −40 °C, and the mixture was allowed to warm to −20 °C over 2 h to afford a mixture of (R)-9e and
(4-MeOC₆H₄)₂ in a 84 : 16 ratio by ¹H NMR analysis (52.1 mg in total, 87% yield of (R)-9e) as a colorless oil. Gamma/alpha = 97 : 3 by ¹H NMR spectroscopy. The enantiomeric purity of 96% ee was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/i-PrOH = 99.9/0.1, 1.0 mL/min, 30 °C, tᵣ/min = 6.6 (R-isomer), 7.2 (S-isomer). The ¹H NMR spectrum of the product was consistent with that obtained above.

(R,E)-1-(4,8-Dimethylnona-2,7-dien-4-yl)-4-methoxybenzene ((R)-9e)

According to the general procedure via Method B, a solution of picolinate (R)-8 (54.7 mg, 0.200 mmol, 98% ee) in THF (1 mL) was added to a mixture of 4-idoanisole (150 mg, 0.641 mmol), t-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (61.1 mg, 0.320 mmol), and MgBr₂·OEt₂ (0.20 M in THF, 6.40 mL, 1.28 mmol) in Et₂O (1 mL) at −40 °C, and the mixture was allowed to warm to −20 °C over 2 h to afford a mixture of (R)-9e, (4-MeOC₆H₄)₂, and 4-idoanisole in a 86 : 10 : 4 ratio by ¹H NMR analysis (53.6 mg in total, 91% yield of (R)-9e) as a colorless oil. Gamma/alpha = 98 : 2 by ¹H NMR spectroscopy. The enantiomeric purity of 87% ee was determined by chiral HPLC analysis: Chiralcel OD-H, hexane/i-PrOH = 99.9/0.1, 1.0 mL/min, 30 °C, tᵣ/min = 6.5 (R-isomer), 7.1 (S-isomer). The ¹H NMR spectrum of the product was consistent with that obtained above.

(R,E)-1-(4,8-Dimethylnona-2,7-dien-4-yl)-4-fluorobenzene ((R)-9f)

According to the general procedure via Method B, a solution of picolinate (R)-8 (54.6 mg, 0.200 mmol) in THF (1 mL) was added to a mixture of 4-fluorobromobenzene (112 mg, 0.642 mmol), t-BuLi (1.77 M in pentane, 0.670 mL, 1.19 mmol), CuTC (60.9 mg, 0.319
mmol), and MgBr$_2$·OEt$_2$(0.20 M in THF, 6.40 mL, 1.28 mmol) in Et$_2$O (1 mL) at −40 °C, and the mixture was allowed to warm to −20 °C over 2 h to afford a mixture of (R)-9f and (4-FC$_6$H$_4$)$_2$ in a 89 : 11 ratio by $^1$H NMR analysis (41.7 mg in total, 78% yield of (R)-9f) as a colorless oil. Gamma/alpha = 99 : 1 by $^1$H NMR spectroscopy. The enantiomeric purity of >95% ee was determined by chiral HPLC analysis: Chiralcel OD-H, hexane, 0.5 mL/min, 30 °C, $t_R$/min = 8.3 (R-isomer), 8.6 (S-isomer). The $^1$H NMR spectrum of the product was consistent with that obtained above.

**(S)-2-(4-Methoxyphenyl)-2-methylpentanедial**

![Structural formula of (S)-2-(4-Methoxyphenyl)-2-methylpentanедial]

According to the literature procedure,$^3$ a stream of O$_3$/O$_2$ was gently bubbled to a solution of (R)-9e (19.3 mg, 0.0747 mmol, 87% ee) and pyridine (0.030 mL, 0.373 mmol) in CH$_2$Cl$_2$ (7 mL) at −78 °C for 20 min. Argon was bubbled into the solution for 30 min to purge excess O$_3$ and saturated NaHCO$_3$ was added with vigorous stirring. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ three times. The combined extracts were washed with brine, dried over MgSO$_4$, and concentrated to give a residue, which was purified by chromatography on silica gel (hexane/EtOAc) to afford the title aldehyde (10.3 mg, 63%) as a yellow oil: $^1$H NMR (300 MHz, CDCl$_3$) δ 1.45 (s, 3 H), 2.01–2.41 (m, 4 H), 3.81 (s, 3 H), 6.92 (d, $J = 6.6$ Hz, 2 H), 7.15 (d, $J = 6.6$ Hz, 2 H), 9.45 (s, 1 H), 9.67 (s, 1 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 18.8 (+), 28.1 (−), 39.1 (−), 52.6 (−), 55.4 (+), 114.6 (+), 128.4 (+), 130.4 (−), 159.1 (−), 201.5 (+). [$\alpha$]$^2_D$ +23.0 (c 1.03, CHCl$_3$); lit.$^4$ [$\alpha$]$^2_D$ +65.2 (c 1.45, CHCl$_3$) for the (R)-isomer.
References

<クロマトグラム>

rac-11

D:\data\vozaki\8684 rac 27c 0.5mlm 0.5p OD-H.lcd

mAU

1500
1000
500
0

36 37 38 39 40 41 42 43 min

PDA Multi 1

1 PDA Multi 1/206nm 4nm

(R)-11

D:\data\vozaki\741 opt 27c 0.5mlm 0.5p OD-H.lcd

mAU

1500
1000
500
0

32 33 34 35 36 37 38 min

PDA Multi 1

1 PDA Multi 1/206nm 4nm
<クロマトグラム>

rac-9a

D:\data\ozaki\710 rac 30c 0.3mlm 0.2p OJ-H.lcd

mAU

16.5 17.0 17.5 18.0 18.5 19.0 19.5 20.0
18.635 / 2.552
17.403 / 44.778
18.631 / 30.222

1 PDA Multi 1/254nm 4nm

<クロマトグラム>

(R)-9a

D:\data\ozaki\848 opt 30c 0.3mlm 0.2p OJ-H.lcd

mAU

18.0 18.5 19.0 19.5 20.0 20.5 21.0 21.5 22.0
18.635 / 2.552
20.152 / 97.438

1 PDA Multi 1/254nm 4nm
From 4-MeOC₆H₄Br

S19
rac-9e

From 4-MeOC₆H₄I

(F)-9e
2a

$^1$H NMR, CDCl$_3$, 300 MHz

$^{13}$C–APT, CDCl$_3$, 75 MHz
$^{1}H$ NMR, CDCl$_3$, 300 MHz

$^{13}$C–APT, CDCl$_3$, 75 MHz
$^{1}H$ NMR, CDCl$_3$, 300 MHz

$^{13}$C–APT, CDCl$_3$, 75 MHz

7e
rac-9a

$^1$H NMR, CDCl$_3$, 300 MHz

rac-9a

$^{13}$C–APT, CDCl$_3$, 75 MHz
rac-9b

$^1$H NMR, CDCl$_3$, 300 MHz

rac-9b

$^{13}$C–APT, CDCl$_3$, 75 MHz
rac-9c

$^1$H NMR, CDCl$_3$, 300 MHz

$^{13}$C–APT, CDCl$_3$, 75 MHz
rac-9d

$^1$H NMR, CDCl$_3$, 300 MHz

rac-9d
$^{13}$C–APT, CDCl$_3$, 75 MHz
$^{1} \text{H NMR, CDCl}_3, 300 \text{ MHz}$

$^{13} \text{C–APT, CDCl}_3, 75 \text{ MHz}$
rac-9f

$^1$H NMR, CDCl$_3$, 300 MHz

rac-9f

$^{13}$C–APT, CDCl$_3$, 75 MHz
\(^1\)H NMR, CDCl\(_3\), 300 MHz

\(^{13}\)C–APT, CDCl\(_3\), 75 MHz
rac-9h

$^{1}H$ NMR, CDCl$_3$, 300 MHz

rac-9h

$^{13}C$–APT, CDCl$_3$, 75 MHz
$^{13}$C–APT, CDCl$_3$, 75 MHz

$^{1}$H NMR, CDCl$_3$, 300 MHz