Metal-Catalyzed Rearrangement of Enantiomerically Pure Alkylidenecyclopropane Derivatives as a New Access to Cyclobutenes Possessing Quaternary Stereocenters

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1. General Procedures

General procedure for the preparation of cyclobutene derivatives with Pt-catalyst (procedure A):

PtCl₂ (53.2 mg, 0.2 mmol) was added to a solution of alkylidenecyclopropane 1 (1 mmol) in 1,2-dichloroethane (10 mL) under Argon atmosphere. The resulting mixture was then stirred at 80 °C for 12 hours (monitored by TLC). The mixture was then filtered through a short pad of silica and the filtrate was evaporated. The crude product was purified by column chromatography on silica gel (hexane as eluent) to give products 2 and/or 3.

General procedure for the preparation of cyclobutene derivatives 2a-b with Pt-catalyst under CO atmosphere (procedure C):

PtCl₂ (53.2 mg, 0.2 mmol) was added to a solution of alkylidenecyclopropane 1 (1 mmol) in toluene (10 mL). The resulting mixture was then stirred at 80 °C under CO atmosphere (1 atm). The mixture was then filtered through a short pad of silica and the filtrate was evaporated. The crude product was purified by column chromatography on silica gel (hexane as eluent) to give products 2 and/or 3.

General procedure for the preparation of cyclobutene derivatives with Pd-catalyst (procedure B):

To a solution of alkylidenecyclopropane 1 (1 mmol) in 1, 2-dichloroethane (10 mL) was added palladium acetate (22.45 mg, 0.1 mmol) and copper(II) bromide (44.67 mg, 0.2 mmol). The mixture was stirred under Ar atmosphere for 6-10 hours at 80 °C (monitored by TLC). Then the mixture was filtered through a short pad of silica, the solvent was removed under reduced pressure and the crude was subjected to a flash column chromatography on silica gel (hexane as eluent) to give the products 2 and/or 3.
General procedure for the preparation of dicarbonyl derivatives 11-12 from cyclobutenes (procedure D):
RuO$_2$ (13.31 mg, 0.1 mmol) was added to a solution of cyclobutene 2 (0.5 mmol) and NaIO$_4$ (3 mmol) in CDCl$_3$ (4 mL) and H$_2$O (2 mL). The resulting mixture was then stirred at room temperature for 10 h (monitored by TLC). The aqueous layer was then extracted with ether (3×3 mL), the organic phases were combined and washed with brine (1×3 mL), separated, dried and evaporated. The crude product was purified by column chromatography on silica gel (eluent: hexane / ethyl acetate 10:1) to give products 11 or 12.

2. Characterisation Data

(3-ethyl-3-methylcyclobut-1-enyl)benzene (2a). Was prepared from the general procedure C. Pale yellow oil isolated in 70% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.83 (t, $J = 8.6$ Hz, 3H), 1.13 (s, 3H), 1.47 (dq, $J_1 = 1.7$ Hz, $J_2 = 8.0$ Hz, 2H), 2.37 (dd, $J_1 = 12.5$ Hz, $J_2 = 36.5$ Hz, 2H), 6.42 (s, 1H), 7.24-7.36 (m, 5H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 10.4, 23.9, 32.9, 40.7, 43.6, 124.7, 127.7, 128.6, 135.6, 136.0, 142.9.

1-(3-ethyl-3-methylcyclobut-1-enyl)-4-methylbenzene (2b). Was prepared from the general procedure C. Pale yellow oil isolated in 74% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.87 (t, $J = 7.4$ Hz, 3H), 1.16 (s, 3H), 1.50 (dq, $J_1 = 1.6$ Hz, $J_2 = 7.9$ Hz, 2H), 2.29 (s, 3H), 2.39 (dd, $J_1 = 12.5$ Hz, $J_2 = 36.2$ Hz, 2H), 6.31 (s, 1H), 7.20 (d, $J = 8.1$ Hz, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 10.3, 21.6, 23.9, 32.9, 40.7, 43.6, 124.7, 127.7, 128.6, 135.6, 136.0, 142.7.

1,3-dibromo-5-(3-ethyl-3-methylcyclobut-1-enyl)benzene (2c). Was prepared from the general procedure A. Pale yellow oil isolated in 56% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.85 (t, $J = 7.5$ Hz, 3H), 1.14 (s, 3H), 1.48 (dq, $J_1 = 1.9$ Hz, $J_2 = 8.1$ Hz, 2H), 2.34 (dd, $J_1 = 12.6$ Hz, $J_2 = 37.5$ Hz, 2H), 6.44 (s, 1H), 7.31 (d, $J = 1.8$ Hz, 2H), 7.44 (t, $J = 1.8$ Hz, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 10.2, 23.6, 32.6, 40.6, 44.1, 123.2, 126.5, 132.8, 138.9, 139.6, 140.4.

1,3-dibromo-5-(3-ethyl-3-methylcyclobut-1-enyl)benzene (2d). Was prepared from the general procedure A. Pale yellow solid isolated in 82% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.92 (t, $J = 7.5$ Hz, 3H), 1.2 (s, 3H), 1.54 (dq, $J_1 = 1.8$ Hz, $J_2 = 8.0$ Hz, 2H), 2.42 (dd, $J_1 = 12.3$ Hz, $J_2 = 35.7$ Hz, 2H), 3.76 (s, 3H), 6.70 (s, 1H), 6.84 (d, $J = 9.3$ Hz, 2H).
Hz, 2H), 7.27 (d, J = 6.6 Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 9.6, 23.2, 32.3, 40.1, 42.6, 54.8, 113.2, 125.3, 128.0, 132.6, 141.6, 158.7.

1-(benzyloxy)-2-(3-ethyl-3-methylcyclobut-1-enyl)benzene (2e). Was prepared from the general procedure B. Pale yellow oil isolated in 85% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 0.90 (t, J = 7.5 Hz, 3H), 1.18 (s, 3H), 1.53 (dq, J$_1$ = 1.2 Hz, J$_2$ = 7.6 Hz, 2H), 2.49 (dd, J$_1$ = 12.3 Hz, J$_2$ = 35.4 Hz, 2H), 5.11 (s, 2H), 6.45 (s, 1H), 6.88-6.94 (m, 2H), 7.13-7.19 (m, 2H), 7.28-7.46 (m, 5H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 9.6, 23.1, 32.2, 41.1, 43.5, 69.6, 111.2, 120.1, 123.8, 126.6, 127.1, 127.4, 127.9, 128.1, 136.7, 138.4, 140.5, 156.9.

(2-(3-ethyl-3-methylcyclobut-1-enyl)ethyl)benzene (2f). Was prepared from the general procedure A. Pale yellow oil isolated in 60% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 0.79 (t, J = 7.4 Hz, 3H), 1.03 (s, 3H), 1.37 (dq, J$_1$ = 1.6 Hz, J$_2$ = 7.6 Hz, 2H), 2.01 (dd, J$_1$ = 12.8 Hz, J$_2$ = 35.3 Hz, 2H), 2.24 (dt, J$_1$ = 1.1 Hz, J$_2$ = 8.0 Hz, 2H), 2.68 (t, J = 6.0 Hz, 2H), 5.76 (t, J = 1.4 Hz, 1H), 7.09-7.24 (m, 5H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 10.3, 23.9, 32.7, 32.9, 33.5, 39.1, 43.3, 123.1, 128.5, 128.6, 136.2, 142.6, 146.2.

(3-buty1-3-methylcyclobut-1-enyl)benzene (2g). Was prepared from the general procedure B. Pale yellow oil isolated in 55% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 0.84 (t, J = 5.6 Hz, 3H), 1.19 (s, 3H), 1.23-1.33 (m, 4H), 1.43-1.50 (m, 2H), 2.40 (dd, J$_1$ = 12.5 Hz, J$_2$ = 34.7 Hz, 2H), 6.37 (s, 1H), 7.14-7.19 (m, 2H), 7.23-7.31 (m, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 14.5, 23.7, 24.4, 28.4, 40.1, 41.2, 43.1, 124.6, 127.7, 128.5, 135.5, 136.3, 142.6.

(3-allyl-3-methylcyclobut-1-enyl)benzene (2h). Was prepared from the general procedure B. Pale yellow oil isolated in 60% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 1.13 (s, 3H), 2.23 (t, J = 6.2 Hz, 2H), 2.46 (dd, J$_1$ = 12.6 Hz, J$_2$ = 45.8 Hz, 2H), 4.95-5.03 (m, 2H), 5.74-5.88 (m, 1H) 6.36 (s, 1H), 7.17-7.30 (m, 5H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 23.6, 39.8, 41.8, 44.0, 115.9, 123.7, 124.6, 126.8, 128.2, 134.7, 135.7, 141.9.

1-bromo-4-(3-ethyl-3-methylcyclobut-1-enyl)benzene (2i). Was prepared from the general procedure B. Pale yellow oil isolated in 50% yield. $^1$H NMR (300 MHz, CDCl$_3$) δ 0.86 (t, J = 8.9 Hz, 3H), 1.16 (s, 3H), 1.50 (dq, J$_1$ = 1.5 Hz, J$_2$ = 7.9 Hz, 2H), 2.40 (dd, J$_1$ = 12.6 Hz, J$_2$ = 36.3 Hz, 2H), 6.38 (s, 1H), 7.14-7.35 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 9.6, 23.0, 32.1, 39.9, 42.8, 123.8, 126.9, 127.8, 134.7, 135.2, 142.1.
1-(3-butyl-3-methylcyclobut-1-enyl)-4-methylbenzene (2j). Was prepared from the general procedure B. Pale yellow oil isolated in 68% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.84 (t, $J = 7.1$ Hz, 3H), 1.15 (s, 3H), 1.23-1.31 (m, 4H), 1.43-1.50 (m, 2H), 2.28 (s, 3H), 2.39 (dd, $J_1 = 12.5$ Hz, $J_2 = 34.7$ Hz, 2H), 6.30 (s, 1H), 7.06 (d, $J = 7.8$ Hz, 2H), 7.19 (d, $J = 7.8$ Hz, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 13.7, 20.9, 23.0, 23.7, 27.7, 39.4, 40.5, 42.2, 123.8, 128.5, 132.1, 134.3, 136.7, 141.8.

2-ethyl-2-methyl-4-oxo-6-phenylhexanal (11). Was prepared from the general procedure D. Pale yellow oil isolated in 80% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.72 (t, $J = 7.4$ Hz, 3H), 1.05 (s, 3H), 1.44-1.52 (m, 2H), 2.47-2.71 (m, 4H), 2.81 (t, $J = 10.1$ Hz, 2H), 7.10-7.24 (m, 5H), 9.48 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 7.6, 18.2, 28.1, 29.2, 44.4, 48.1, 49.7, 125.7, 127.8, 128.0, 140.3, 204.9, 207.4.

2-ethyl-2-methyl-4-oxo-4-phenylbutanal (12). Was prepared from the general procedure D. Pale yellow oil isolated in 82% yield. $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 0.82 (t, $J = 9.0$ Hz, 3H), 1.15 (s, 3H), 1.56-1.71 (m, 2H), 3.22 (dd, $J_1 = 17.7$ Hz, $J_2 = 28.5$ Hz, 2H), 7.38-7.43 (m, 2H), 7.43-7.54 (m, 1H), 7.87-7.90 (m, 2H), 9.62 (s, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 1.3, 19.2, 29.1, 32.6, 45.1, 128.3, 128.9, 133.4, 133.7, 198.2, 205.8.

Determination of enantiomeric excesses.

(S)-(3-ethyl-3-methylcyclobut-1-enyl)benzene (2a). [α]$_D^{25}$ -22.76 (c 0.018, diethyl ether). Determination of the ee of 2a by GC (column: TFA-β-Cyclodextrin; 50 °C ;
600 min).

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**Enantioenriched mixture**

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*(S)-2-ethyl-2-methyl-4-oxo-6-phenylhexanal* (11). The enantiomeric ratio was determined by HPLC using a 0.46 x 25 cm Chiralcell-AD-H column; flow rate: 0.3 mL.min⁻¹; eluent: (hexane: 2-propanol, 98:2).
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NMR and NOE analyses

$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 2a
$^1$C NMR spectrum (75 MHz, CDCl$_3$) of 2a
$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 2b
\(^{13}\)C NMR spectrum (75 MHz, CDCl\(_3\)) of 2b
$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 2c
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 2c
$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 2d
\( ^{13} \text{C NMR spectrum (75 MHz, CDCl}_3 \text{)} \) of 2d
$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 2e
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 2e
$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 2f
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 2f
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$^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 2h
$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 2i
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 21
$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 2j
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 2j
$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 11
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 11
$^1$H NMR spectrum (300 MHz, CDCl$_3$) of 12
$^{13}$C NMR spectrum (75 MHz, CDCl$_3$) of 12
NOE data of 2d

Spectrum 1

Spectrum 2

Spectrum 3

Spectrum 4

Spectrum 5

Spectrum 6