Metal-Free Intramolecular Carbonyl-Olefin Metathesis of ortho-Prenyl-arylketones

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Supporting Information

Table of Contents

General Methods ................................................................. 2
Representative Procedures ....................................................... 2
Procedures and Characterization of Products........................... 3
$^1$H and $^{13}$C spectra ............................................................ 7
References ............................................................................ 13
Experimental Section

General Methods

All reagents were commercially purchased from Aldrich Chemical Co. or Acros Organics and used as received without further purification. Moisture or oxygen sensitive reactions were carried out in oven-dried glassware containing argon. Thin-layer chromatography was conducted with Macherey-Nagel ALUGRAM® SIL G/UV254 silica gel plates (0.2 mm thickness) and visualized under UV (λ = 254 nm) or by staining with a solution of potassium permanganate or p-methoxybenzaldehyde followed by heating. Flash chromatography was performed using Macherey-Nagel silica gel 60 (0.040-0.063 mm / 230-240 mesh ASTM). ¹H NMR spectra were recorded on a Bruker AV 300 or a Bruker DPX 300 NMR spectrometer and are reported in ppm at room temperature relative to signal of chloroform-d (δ = 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, dt = doublet of triplets. ¹³C NMR spectra were detected proton-decoupled on a Bruker AV 300 or a Bruker DPX 300 NMR spectrometer (75 MHz). All IR spectra were recorded as thin films on a Perkin-Elmer Paragon 100 FT-IR-ATR spectrometer and are listed in frequency of absorption (cm⁻¹). Intensity reported as: s = strong, m = medium, w = weak. High resolution mass spectrometric analysis (HRMS) was performed on Finnigan MAT 900 S spectrometer.

Representative Procedure A:

Suzuki cross-coupling of 2-acetylphenylboronic acid with allylic bromides (preparation of compounds 13a-c).¹¹ An argon-flooded Schlenk tube containing 2-acetylphenylboronic acid (ca. 3 mmol, 1 equiv.) in dry toluene (30 mL) was charged with potassium carbonate (9 equiv.), the required allylic bromide (12a-c) (2 equiv.) and tris(dibenzylideneacetone)dipalladium(0) (0.07 equiv.). After refluxing for 18 h, the crude mixture was cooled to room temperature and filtered through a short pad of Celite. After addition of brine (50 mL) and extraction with toluene (3 x 50 mL) the organic phase was dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (EtOAc/CycHex = 1:10) to provide compounds 13a-c.

Representative Procedure B:

BF₃-induced ring closing metathesis (preparation of compounds 17 and 18). In an argon-flooded Schlenk tube the required arylphenone (13a-c or 16) (1 equiv.) was dissolved in dry CH₂Cl₂ (0.05 M) and the solution was cooled to -40 °C. Dropwise addition of boron trifluoride etherate (1.5 equiv.) then afforded a yellow solution which was stirred for 1 h at -40 °C. After addition of NaHCO₃ (saturated aqueous solution, 20 mL) at 0 °C, the mixture was extracted with CH₂Cl₂ (3 x 40 mL). The organic phase was dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by filtration on silica gel using cyclohexane to provide compounds 17 or 18, respectively.
Procedures and characterization of products

1-(2-(3-Methylbut-2-en-1-yl)phenyl)ethanone (13a)\textsuperscript{[2]} Following general procedure A, 2-acetylphenylboronic acid (0.50 g, 3.05 mmol) in dry toluene (30 mL), potassium carbonate (3.80 g, 27.5 mmol), prenyl bromide (12a) (0.71 mL, 0.92 g, 6.10 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.20 g, 0.21 mmol) were used. The crude product was purified by flash chromatography on silica gel (EtOAc/CycHex = 1:10) to provide pure 13a (448 mg, 2.37 mmol, 78%).

Yellow oil, R\textsubscript{f} = 0.50 (EtOAc/CycHex = 1:10); \textsuperscript{1}H NMR: \(\delta\) (300 MHz, CDCl\textsubscript{3}) = 1.70 (s, 3H), 1.72 (s, 3H), 2.56 (s, 3H), 3.58 (d, 2H), 5.24 (t, 1H), 7.27 (m, 2H), 7.39 (m, 1H), 7.60 (d, 1H); \textsuperscript{13}C NMR: \(\delta\) (75 MHz, CDCl\textsubscript{3}) = 17.9, 25.7, 29.9, 32.3, 123.0, 125.7, 128.6, 130.6, 131.3, 132.7, 138.3, 141.3, 202.6; IR-ATR: \(v\textsubscript{max}\) (film) = 2966 (w), 2911 (w), 2853 (w), 1681 (s), 1600 (w), 1570 (w), 1480 (w), 1443 (w), 1373 (w), 1352 (m), 1249 (m), 1096 (w), 1066 (w), 1040 (w), 954 (w), 920 (w), 853 (w), 756 (w); MS (EI, 70 eV): \(m/z\) (%) = 188 (15) [M+], 173 (17), 155 (10), 145 (100), 132 (58), 115 (41), 104 (17), 91 (15), 77 (14), 63 (5), 53 (2), 43 (7); HRMS (EI, 70 eV): calcd. 188.1201; found 188.120.

\((E/Z)-1-(2-(But-2-en-1-yl)phenyl)ethanone (13b)\). Following general procedure A, 2-acetylphenylboronic acid (0.50g, 3.05 mmol) in dry toluene (30 mL), potassium carbonate (3.80 g, 27.45 mmol), crotyl bromide (12b) (85/15 \(E/Z\)-mixture) (0.63 mL, 0.82 g, 6.10 mmol) and tris(dibenzylideneacetone)dipalladium(0) (0.20 g, 0.21 mmol) were used. The crude product was purified by flash chromatography on silica gel (EtOAc/CycHex = 1:10) to provide 13b (314 mg, 1.80 mmol, 59%) as a mixture of diastereomers.

\(E/Z = 86/14\) (\textsuperscript{1}H NMR, GCMS)

Yellow oil, \(R_f = 0.52\) (EtOAc/CycHex = 1:10); \textsuperscript{1}H NMR: \(\delta\) (300 MHz, CDCl\textsubscript{3}) = 1.64/1.66 (d, \(E/Z = 86/14\), 3H), 2.56/2.58 (s, \(E/Z = 86/14\), 3H), 3.55/3.57 (d, \(E/Z = 86/14\), 2H), 5.42-5.62 (m, 2H, -HC=CH-), 7.27 (m, 2H), 7.39 (m, 1H), 7.61 (m, 1H); \textsuperscript{13}C NMR: \(\delta\) (75 MHz, CDCl\textsubscript{3}) = 17.9, 29.9, 36.8, 125.9, 126.5, 128.7, 129.9, 131.0, 131.3, 138.2, 140.6, 202.4; IR-ATR: \(v\textsubscript{max}\) (film) = 3020 (w), 2913 (w), 2853 (w), 1683 (s), 1597 (w), 1569 (w), 1482 (w), 1434 (w), 1353 (m), 1249 (s), 1070 (w),
\[(E)-1-(2-(3,7-Dimethylocta-2,6-dien-1-yl)phenyl)ethanone\] (13c). Following general procedure A, 2-acetylphenylboronic acid (0.50 g, 3.05 mmol) in dry toluene (30 mL), potassium carbonate (3.80 g, 27.45 mmol), geranyl bromide (12c) (1.16 mL, 1.33 g, 6.10 mmol) and tris(benzylideneacetone)dipalladium(0) (0.20 g, 0.21 mmol) were used. The crude product was purified by flash chromatography on silica gel (EtOAc/CycHex = 1:10) to provide pure 13c (435 mg, 1.70 mmol, 56%).

Yellow oil, \(R_f = 0.47\) (EtOAc/CycHex = 1:10); \(^1H\) NMR: \(\delta_H\) (300 MHz, CDCl\textsubscript{3}) = 1.60 (m, 3H), 1.69 (m, 6H), 1.97-2.17 (m, 4H, -CH\textsubscript{2}-CH\textsubscript{2}-), 2.54 (s, 3H), 3.60 (d, 2H) 5.09-5.13 (dd, 1H), 5.26 (t, \(J = 7.2\) Hz, 1H), 7.25 (m, 2H), 7.37 (m, 1H), 7.58 (d, 1H); \(^13C\) NMR: \(\delta_C\) (75 MHz, CDCl\textsubscript{3}) = 16.0, 17.5, 25.6, 26.5, 29.8, 32.0, 39.6, 122.8, 123.5, 124.1, 125.5, 128.5, 130.4, 131.2, 136.3, 138.2, 141.2, 202.3; IR-ATR: \(v_{\text{max}}\) (film) = 3060 (w), 3021 (w), 2961 (w), 2913 (m), 2852 (w), 1681 (s), 1597 (m), 1569 (m), 1482 (m), 1433 (s), 1352 (s), 1247 (s), 1163 (w), 1070 (w), 1040 (w), 1012 (w), 966 (s), 756 (s), 717 (m); MS (EI, 70 eV): m/z (%) = 256 (8) [M+], 238 (6), 223 (9), 195 (12), 169 (34), 145 (100), 129 (92), 115 (96), 91 (23), 69 (57), 55 (24); HRMS (EI, 70 eV): calcd. 256.1827; found 256.240.

1-(2-(4-Methylpent-3-en-1-yl)phenyl)ethanone (16).

An argon-flooded Schlenk tube containing isopropyltriphenylphosphonium iodide (prepared by solvent free reaction of triphenylphosphine and isopropyl iodide\[^3\]) (1.072 g, 2.48 mmol, 1.05 equiv.) in dry THF (7.1 mL, 0.3 M) was cooled to -78°C followed by dropwise addition of n-butyl lithium (1.48 mL, 1.6 M in hexane, 2.36 mmol, 1.00 equiv.). The resulting red solution was stirred for 2 h at
-78 °C. Then the ketoaldehyde (0.500 g, 2.84 mmol, 1.20 equiv.; synthesized from 1-tetralone (14) by addition of MeMgI, subsequent dehydration and ozonolysis) was slowly added. The mixture was warmed to room temperature over 30 min and stirred for 16 h. After filtration through a short pad of Celite, brine (50 mL) was added and the mixture was extracted with MTBE (3 x 50 mL). The organic phases were dried (MgSO$_4$) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (EtOAc/CycHex = 1:10) to provide 16 (142 mg, 0.70 mmol, 30%).

Yellow oil, R$_f$ = 0.50 (EtOAc/CycHex = 1:10); $^1$H NMR: δ$_H$ (300 MHz, CDCl$_3$) = 1.53 (s, 3H), 1.67 (s, 3H), 2.25 (dd, 2H) 2.56 (s, 3H), 2.87 (m, 2H) 5.17 (t, 1H), 7.25 (m, 2H), 7.37 (m, 1H), 7.61 (m, 1H); $^{13}$C NMR: δ$_C$ (75 MHz, CDCl$_3$) = 17.9, 26.1, 30.3, 30.7, 34.4, 124.1, 126.0, 129.2, 129.3, 131.7, 132.6, 138.5, 142.6, 202.5; IR-ATR: v$_{max}$ (film) = 3058 (w), 2962 (m), 2921 (s), 2855 (ms), 1684 (s), 1597 (m), 1569 (m), 1483 (m), 1443 (s), 1374 (m), 1352 (s), 1247 (s), 953 (m), 757 (s); MS (EI, 70 eV): m/z (%) = 202 (2) [M+], 190 (26), 173 (68), 159 (8), 152 (6), 145 (49), 129 (45), 119 (100), 105 (41), 91 (92), 77 (35), 69 (20), 51 (12); HRMS (EI, 70 eV): Calcd. 188.1358; found 202.137.

**BF$_3$OEt$_2$-mediated carbonyl-olefin metathesis:**

**Preparation of 3-methyl-1H-indene (17).** Applying general procedure B, the reaction of substrates 13a-c with BF$_3$OEt$_2$ afforded compound 17 in the given yields (isolated, after purification):

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Amount</th>
<th>BF$_3$OEt$_2$</th>
<th>CH$_2$Cl$_2$</th>
<th>yield of 17 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>ortho</em>-prenyl acetophenone (13a)</td>
<td>250 mg</td>
<td>0.25 mL</td>
<td>26 mL</td>
<td>150 mg (78 %)</td>
</tr>
<tr>
<td>2</td>
<td><em>ortho</em>-crotyl acetophenone (13b)</td>
<td>190 mg</td>
<td>0.21 mL</td>
<td>***(a)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><em>ortho</em>-geranyl acetophenone (13c)</td>
<td>150 mg</td>
<td>0.12 mL</td>
<td>12 mL</td>
<td>29 mg (38 %)</td>
</tr>
</tbody>
</table>

(a) Only traces of 17 could be detected by GC-MS in the reaction mixture.

Colourless oil, R$_f$ = 0.65 (pentane); $^1$H NMR: δ$_H$ (300 MHz, CDCl$_3$) = 2.18 (dd, 3H), 3.33 (m, 2H), 6.21 (d, 1H) 7.20 (dt, 1H), 7.33 (q, 2H), 7.46 (d, 1H); $^{13}$C NMR: δ$_C$ (75 MHz, CDCl$_3$) = 13.0, 37.6,
118.8, 123.6, 124.4, 126.0, 128.7, 139.9, 144.3, 146.1; IR-ATR: $v_{\text{max}}$ (film) = 3013 (w), 2931 (w), 1746 (w), 1712 (w), 1681 (m), 1613 (w), 1570 (w), 1460 (m), 1396 (w), 1379 (m), 1346 (w), 1255 (w), 1167 (w), 1103 (w), 1080 (w), 1015 (m), 943 (m), 914 (w), 760 (s), 717 (s); MS (EI, 70 eV): m/z (%) = 130 (100) [M+], 115 (81), 102 (6), 89 (5), 77 (7), 64 (11), 51 (10), 39 (4); HRMS (EI, 70 eV): Calcd. 130.0782; found 130.079.

4-Methyl-1,2-dihydronaphthalene (18). Following general procedure B, 2-homoprenyl acetophenone (16) (47 mg, 0.23 mmol), CH$_2$Cl$_2$ (2.3 mL) and BF$_3$·OEt$_2$ (0.044 mL, 0.35 mmol) were used. Flash-filtration through silica with cyclohexane afforded 18 (25 mg, 17.3 mmol, 75%).

![18](image)

Colourless oil, $R_f = 0.57$ (pentane); $^1$H NMR: $\delta_H$ (300 MHz, CDCl$_3$) = 2.03 (s, 3H), 2.22 (d, 2H), 2.73 (t, 2H) 5.82 (s, 1H), 7.10-7.19 (m, 4H); $^{13}$C NMR: $\delta_C$ (75 MHz, CDCl$_3$) = 19.3, 23.2, 28.3, 122.7, 125.3, 126.3, 126.6, 127.3, 132.1, 135.8, 136.2; IR-ATR: $v_{\text{max}}$ (film) = 3094 (w), 3057 (w), 3023 (m), 2965 (m), 2929 (s), 2880 (s), 2827 (s), 1623 (w), 1485 (s), 1448 (s), 1436 (s), 1376 (s), 1334 (m), 1276 (m), 1238 (s), 1187 (m), 1159 (w), 1067 (s), 1038 (s), 1019 (s), 992 (w), 935 (m), 903 (w), 867 (m), 810 (s), 790 (s), 751 (s), 729 (s), 703 (s); MS (EI, 70 eV): m/z (%) = 144 (49) [M+], 129 (100), 115 (28), 102 (6), 91 (9), 73 (69), 57 (13); HRMS (EI, 70 eV): determined mass: 144.094 u, exact mass: 144.0939 u.
$^1$H and $^{13}$C NMR spectra in CDCl$_3$.

$^1$H NMR spectra of compound 13a

$^{13}$C NMR spectra of compound 13a
$^1$H NMR spectra of compound 13b

$^{13}$C NMR spectra of compound 13b
$^1$H NMR spectra compound 13c

$^{13}$C NMR spectra of compound 13c
$^1$H NMR spectra of compound 16

$^{13}$C NMR spectra of compound 16
$^1$H NMR spectra of compound 17

$^{13}$C NMR spectra of compound 17
$^1$H NMR spectra of compound 18

$^{13}$C NMR spectra compound 18
References:


