A Convenient Allylic Functionalization of Bis(prop-2-enyl)methanol by Direct Trimetalation

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Abstract: A practical synthesis of functionalized symmetrical dialkenylcarbinols has been developed. Key feature is a direct trilithiation of readily available bis(prop-2-enyl)methanol followed by trapping of the trianion with various electrophiles. This simple protocol allows rapid derivatization and preparation of compounds inaccessible by currently existing methods.

Key words: alkenes, alcohols, lithiation, metalations, organometallic reagent

Mirror symmetrical dialkenylcarbinol moieties of type 1 are important building blocks particularly appealing for desymmetrizing processes.1 A growing number of useful enantioselective transformations have appeared in these past years such as asymmetric epoxidation,2 hydrosilylation,3 carbonyl ene addition,4 cyclopropanation,5 ring-closing metathesis,6 and hydroformylation7 (Scheme 1).

Scheme 1 Enantioselective desymmetrizing processes of dialkenylcarbinol ethers and esters 1

Nevertheless the scope of these methodologies is limited by the scarcity of efficient synthetic procedures to access dialkenylcarbinols 2 bearing diversely functionalized substituents R (Scheme 2). In the course of our investigation towards a desymmetrizing hydroformylation reaction, we have developed an efficient access to this class of compounds through the addition of 2 equivalents of an alkenylmetal species to ethyl formate.7b The alkenylmetal intermediate is generated through Grignard synthesis, halogen/lithium exchange with t-BuLi or, alternatively, through a Shapiro reaction of the trisylhydrazone (trisyl = 2,4,6-triisopropylphenyl).

Scheme 2 Synthetic route to dialkenylcarbinols bearing alkyl substituents

Unfortunately, this approach failed as we tried to prepare dialkenylcarbinols having electron-withdrawing groups at the allylic position. This is mainly due to the propensity of the alkenylmetal to undergo 1,2-elimination, even at low temperatures, to furnish the allene (Scheme 3).8

Scheme 3 Competitive 1,2-elimination of the alkenylmetal species

To circumvent this problem we wondered whether such functionalized dialkenylcarbinol derivatives could be accessed through a direct functionalization of bis(prop-2-enyl)methanol (3) by deprotonation of both allylic positions and subsequent trapping of the trianion with an appropriate electrophile. This would additionally offer the opportunity for rapid derivatization from a common and readily available precursor.9

The deprotonation of methallylic alcohols is known.10 Trost et al. have optimized and extensively used a lithiation protocol using an excess of n-BuLi/TMEDA complex in an Et2O–THF mixture for silylation and stannylation of the formed dianions.11 However, this method suffers from moderate yields mainly due to the formation of side prod-
ucts resulting from undesired vinylic deprotonation. We report herein a general and efficient extension of this method allowing for the direct functionalization of bis(prop-2-eny) methanol (3) through trimetalation.

We started our investigations by adapting the Trost protocol to our system, using MSnCl as the electrophile as we were particularly interested in the rapid generation of carbinols bearing various trialkylstannane moieties (Table 1). Treatment of 3 with 5 equivalents of t-BuLi in a mixture of EtO–hexane–THF in the presence of TMEDA (6 equiv) at 0 °C, further stirring for 4 hours at 25 °C, and subsequent quenching with Me3SnCl led to the detection of only traces of desired product 4 (entry 1). However, the reaction proved to proceed very cleanly with only unreacted starting material present, which left us optimistic for possible improvement. Indeed, switching to slightly more basic t-BuLi under otherwise identical conditions afforded smoothly the desired product in 44% isolated yield together with recovered 3 and only traces of monostannylated product (entry 2). While an increased reaction time led mostly to degradation (entry 3), the modification of the solvent polarity (without THF)12 furnished after standard workup the desired product in 64% yield (entry 4). Finally, treatment of 3 with 2 additional equivalents of t-BuLi and TMEDA allowed the complete conversion to the trianion. Trapping with the tin electrophile gave 4 in 80% isolated yield (entry 5).

Table 1 Optimization of the Trimetalation Protocol of 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base (equiv)</th>
<th>TMEDA (equiv)</th>
<th>Solvent (ratio)a</th>
<th>Time (h)</th>
<th>Yield (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuLi (5)</td>
<td>6</td>
<td>Et2O–hexane–THF</td>
<td>4</td>
<td>n.d.c</td>
</tr>
<tr>
<td>2</td>
<td>s-BuLi (5)</td>
<td>6</td>
<td>Et2O–Cy–THF</td>
<td>4</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>s-BuLi (5)</td>
<td>6</td>
<td>Et2O–Cy–THF</td>
<td>20</td>
<td>n.d.4</td>
</tr>
<tr>
<td>4</td>
<td>s-BuLi (5)</td>
<td>6</td>
<td>Et2O–Cy (3:1)</td>
<td>4</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>s-BuLi (7)</td>
<td>8</td>
<td>Et2O–Cy (3:2)</td>
<td>4</td>
<td>80</td>
</tr>
</tbody>
</table>

Table 2 Scope of the Transformation of 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>Electrophile (equiv)</th>
<th>Product (R)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me3SnCl (3)</td>
<td>4 (Me3Sn)</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Bu3SnCl (3)</td>
<td>5 (Bu3Sn)</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>Davis oxaziridine (5)</td>
<td>6 (OH)</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>PhSSPh (3)</td>
<td>7 (PhS)</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>MeSSMe (5)</td>
<td>8 (MeS)</td>
<td>60</td>
</tr>
<tr>
<td>6</td>
<td>Me3SiCl (5)</td>
<td>9 (Me3Si)</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>Me3PhSiCl (5)</td>
<td>10 (Me3PhSi)</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>Et3SiCl (5)</td>
<td>11 (Et3Si)</td>
<td>79</td>
</tr>
</tbody>
</table>

a Overall yields after desilylation of the hydroxy group (see experimental section).

For further synthetic use, we could selectively protect the primary hydroxy functions of triol 6 to provide carbinol 12 in good yield (Scheme 4), which is a particularly interesting building block for polypropionate synthesis. While our attempts of trapping the trianion with various fluorine electrophiles were unsuccessful, we envisioned to get access to this interesting compound by functionalization of the diallylsilane 9 via an electrophilic fluorodesilylation reaction. Indeed, treatment of diallylsilane 9 with SelectfluorTM in acetonitrile overnight at room temperature furnished smoothly the difluoride 13 in high yield.14

In summary, we have developed a practical and efficient complementary access to functionalized symmetrical dialkenylcarbinols involving a direct trimetalation of readily available bis(prop-2-eny) methanol (3). This method

Scheme 4 Further functionalization of the products
allows rapid derivatization and preparation of compounds otherwise inaccessible by previously developed strategies.

Reactions were performed in flame-dried glassware under argon (purity >99.998%). The solvents were dried by standard procedures, distilled, and stored under argon. Petroleum ether (PE) refers to the fraction with bp 40–60 °C. All temperatures quoted are uncorrected.

1H, 13C NMR spectra: Varian Mercury 300 HFCP, Bruker AM 400 (with CPCI), as internal standard. 19F NMR spectra: Bruker AM 400 with CCl3F as external standard. Melting points: apparatus by Dr. Tottoli (Büchi). Elemental analyses: VarioEL (Elementaranalysen GmbH). Mass spectrometry: Thermo Finnigan MAT 8200 and TSQ 7000. Flash chromatography: Silica gel 40–60 mm (230–400 mesh, Macherey-Nagel). Organolithium reagents were titrated with 2-(phenylhydrazonomethyl)phenol.15 The following compounds were prepared according to literature procedure: 2,4-dimethylpent-2-ylidene (Davis oxaziridine).16

### 2.4-Bis[(trimethylstannyl)methyl]penta-1,4-dien-3-ol (3)

According to the general procedure, deprotonation of 3 (500 mg, 4.4 mmol) with s-BuLi (27.1 mL, 31.2 mmol, 7 equiv, 1.15 M) in the presence of TEMEDA (5.3 mL, 35.6 mmol, 8 equiv) in Et2O (44.5 mL) and subsequent quenching with Me3SnCl (13.3 mL, 13.3 mmol, 3 equiv) furnished after workup and chromatography (EtOAc–PE, 9:1) the title compound 3 (1.55 g, 3.5 mmol, 80%) as a colorless oil.

**1H NMR (400 MHz, CDCl3):** δ = 0.09 (s, 3 H), 1.19 (d, J = 3.4 Hz, 2 H), 1.63 (d, J = 11.7, 0.9 Hz, 2 H), 1.77 (d, J = 11.7, 0.9 Hz, 2 H), 4.15 (d, J = 5.8 Hz, 1 H), 5.24 (m, 2 H), 7.31–7.43 (m, 12 H), 7.53–7.57 (m, 4 H).

**13C NMR (100 MHz, CDCl3):** δ = –8.9 (6 C), 16.4 (2 C), 80.1, 106.6 (2 C), 149.6 (2 C).


**HRMS: m/z calcd for C19H20OSn2 [M + Bu+]: 563.2437; found: 563.2429.**

### 2.4-Bis[(tert-butyldiphenylsilyloxy)methyl]penta-1,4-dien-3-ol (12)

According to the general procedure (except for the workup), deprotonation of 3 (500 mg, 4.4 mmol) with s-BuLi (23.0 mL, 31.2 mmol, 7 equiv, 1.36 M) in the presence of TEMEDA (5.3 mL, 35.6 mmol, 8 equiv) in Et2O (44.5 mL) and subsequent quenching with Davis oxaziridine (5.82 g, 22.2 mmol, 5 equiv) dissolved in THF (18 mL) afforded, after workup (few drops of aq sat. NH4Cl were added at 25 °C; 2 g of silica gel was poured into the mixture, and all volatile materials were removed in vacuo) and chromatography [EtOAc–MeOH, 95:5, Rf = 0.21 (EtOAc–MeOH, 95:5)] the triol 6 (199 mg, 1.3 mmol, 31%) as a light yellow oil, which was directly converted into 12 as follows. Triol 6 (199 mg, 1.3 mmol) was suspended in CHCl3 (13 mL) in the presence of 4 Å MS and the mixture was stirred 1 h at 25 °C and then cooled to −20 °C. TBDPSCl (0.7 mL, 2.7 mmol, 2 equiv) was added to the mixture and a solution of imidazole (282 mg, 4.1 mmol, 3 equiv) in CH2Cl2 (5 mL) was slowly dropped into the mixture and the whole stirred for 2 h at this temperature. After warming to 25 °C, H2O (5 mL) was added, the aqueous phase extracted with CH2Cl2 (3 × 8 mL), the combined organic phases were dried (MgSO4) and the solvents removed in vacuo. Chromatography on silica gel (PE–CH2Cl2–EtOAc, 10:10:1, Rf = 0.24 (PE–EtOAc, 9:1)) furnished the title compound 12 (565 mg, 0.99 mmol, 66%) as a colorless oil.

**1H NMR (400 MHz, CDCl3):** δ = 1.04 (s, 18 H), 3.08 (d, J = 5.8 Hz, 1 H), 4.06 (d, J = 13.3, 1.0 Hz, 2 H), 4.15 (d, J = 13.4 Hz, 2 H), 4.76 (d, J = 5.6 Hz, 1 H), 5.21 (m, 2 H), 5.24 (m, 2 H), 7.31–7.43 (m, 12 H), 7.62–7.67 (m, 8 H).

**13C NMR (100 MHz, CDCl3):** δ = 19.5 (2 C), 26.8 (6 C), 64.9 (2 C), 75.1, 112.5 (2 C), 127.7 (4 C), 129.8 (4 C), 133.2 (2 C), 135.6 (2 C), 147.1 (2 C, 2).

**MS (CI, NH3):** m/z = 621 ([M + H]+, 16), 620 (36), 619 (72), 381 (29), 364 (27), 255 (100).

HRMS: m/z calcd for C38H39O2Sn2 [M + r-Bu+]: 563.2437; found: 563.2429.

### 2.4-Bis[(phenylsulfanyl)methyl]penta-1,4-dien-3-ol (7)

According to the general procedure, deprotonation of 3 (100 mg, 0.8 mmol) with s-BuLi (5.4 mL, 6.2 mmol, 7 equiv, 1.15 M) in the presence of TEMEDA (1.0 mL, 7.1 mmol, 8 equiv) in Et2O (8.9 mL) and subsequent quenching with PhSSPh (584 mg, 2.6 mmol, 3 equiv) dissolved in THF (3 mL) furnished after workup and chromatography [PE–EtOAc, 95:5, Rf = 0.14 (PE–EtOAc, 9:1)] the title compound 7 (99 mg, 0.3 mmol, 38%) as a light yellow oil.

**1H NMR (400 MHz, CDCl3):** δ = 2.21 (br s, 1 H), 3.42 (dd, J = 14.2, 1.2 Hz, 2 H), 3.59 (dd, J = 14.1, 1.1 Hz, 2 H), 5.03 (br s, 1 H), 5.13 (m, 2 H), 5.25 (pt, J = 1.1 Hz, 2 H), 7.17–7.21 (m, 2 H), 7.24–7.29 (m, 4 H), 7.4, 7.31–7.35 (m, 4 H).

**13C NMR (100 MHz, CDCl3):** δ = 36.4 (2 C), 75.6, 115.7 (2 C), 126.6 (2 C), 128.9 (4 C), 130.3 (4 C), 135.9 (2 C), 143.8 (2 C).

**MS (CI, NH3):** m/z = 329 ([M + H]+, 8), 311 (100), 219 (51), 201 (14).

2,4-Bis(methylsulfanyl)methyl]penta-1,4-dien-3-ol (8)

According to the general procedure, deprotonation of 3 (500 mg, 4.4 mmol) with s-BuLi (24.0 mL, 31.2 mmol, 7 equiv, 1.30 M) in the presence of TMEDA (5.3 mL, 35.6 mmol, 8 equiv) in Et2O (44.5 mL) and subsequent quenching with pure MeSSMe (1.9 mL, 22.2 mmol, 5 equiv) afforded after workup and chromatography (PE–EtOAc, 95:5, Rf = 0.14 (PE–EtOAc, 9:1)) the title compound 8 (552 mg, 2.7 mmol, 60%) as a light yellow oil.

1H NMR (400 MHz, CDCl3): δ = 2.03 (s, 6 H), 2.92 (d, J = 5.7 Hz, 1 H), 3.02 (dd, J = 13.9, 1.1 Hz, 2 H), 3.18 (dd, J = 13.9, 1.0 Hz, 2 H), 4.98 (d, J = 5.1 Hz, 1 H), 5.11 (m, 2 H), 5.33 (t, J = 1.3 Hz, 2 H).

13C NMR (100 MHz, CDCl3): δ = 14.9 (2 C), 36.2 (2 C), 75.8, 115.3 (2 C), 143.5 (2 C).

MS (CI, NH3): m/z (%) = 205 ([M + H]+), 4, 186 (100), 157 (20), 139 (32), 109 (11).


2,4-Bis(trimethylsilyl)methyl]penta-1,4-dien-3-ol (9)

According to the general procedure, deprotonation of 3 (1.0 g, 8.9 mmol) with s-BuLi (45.8 mL, 62.4 mmol, 7 equiv, 1.36 M) in the presence of TMEDA (10.6 mL, 71.5 mmol, 8 equiv) in Et2O (90 mL) and subsequent quenching with pure Me3SiCl (5.7 mL, 44.5 mmol, 5 equiv) furnished after workup the crude trisilylated compound, which was hydrolyzed as follows. The crude mixture was dissolved (K2CO3), and the solvents were removed in vacuo. Flash chromatography [PE–Et2O, 9:1, Rf = 0.14 (PE–EtOAc, 9:1)] the title compound 9 (1.71 g, 6.6 mmol, 75%) as a colorless oil.

Analytical data are identical with the literature values.7b

2,4-Bis(dimethylphenylsilyl)methyl]penta-1,4-dien-3-ol (10)

According to the general procedure, deprotonation of 3 (500 mg, 4.4 mmol) with s-BuLi (22.9 mL, 31.2 mmol, 7 equiv, 1.36 M) in the presence of TMEDA (5.3 mL, 35.6 mmol, 8 equiv) in Et2O (45 mL) and subsequent quenching with pure PhMe2SiCl (3.7 mL, 22.2 mmol, 5 equiv) afforded after workup the crude trisilylated compound, which was hydrolyzed as follows. The crude mixture was dissolved in THF (72 mL), H2SO4 (18 mL, 1 M) was slowly added, and the mixture was stirred 30 min at 25 °C. Subsequently, Et2O (70 mL) was added, the phases were separated, and the aqueous phase was extracted with additional Et2O (3 × 40 mL). The combined organic phases were washed with aq sat. Na2CO3 (150 mL), dried (K2CO3), and the solvents were removed in vacuo. Flash chromatography (PE–Et2O, 9:1, Rf = 0.03 (PE–EtOAc, 9:1)) followed by final bulb-to-bulb distillation (120–130 °C/0.1 mmbar) afforded the title compound 10 (500 mg, 4.4 mmol, 79%) as a colorless oil in THF (23 mL), H2SO4 (12 mL, 3 M) was slowly added, and the mixture was stirred overnight at 25 °C. Subsequent workup as described for 9, flash chromatography (PE–Et2O, 95:5, Rf = 0.50 (PE–EtOAc, 9:1)) and final bulb-to-bulb distillation (200–210 °C/0.1 mmbar) afforded the title compound 11 (1.19 g, 3.5 mmol, 79%) as a colorless oil.

1H NMR (400 MHz, CDCl3): δ = 1.96 (d, J = 4.5 Hz, 1 H), 4.82 (dd, J = 19.2, 11.6 Hz, 2 H), 4.90 (br s, 1 H), 4.94 (dd, J = 19.5, 11.6 Hz, 2 H), 5.39 (dq, J = 2.1, 1.1 Hz, 1 H), 5.42 (br s, 2 H).

13C NMR (100 MHz, CDCl3): δ = 73.2, 82.8 (2 C, JCF = 163.0 Hz), 116.1 (2 C, JCF = 10.2 Hz), 143.8 (2 C, JCF = 13.6 Hz).

19F NMR (235 MHz, CDCl3): δ = –217.3 (d, JHF = 47.2, 4.0 Hz, 2 F).

MS (CI, NH3): m/z (%) = 341 ([M + H]+), 21, 323 (47), 311 (55), 209 (100), 131 (97), 115 (36), 103 (33).


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References


(13) A similar protocol as in reference 11a was used. See experimental section.

