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# Stereoselective Preparation of Homo- and Hetero-1,1-Dihalo-1-alkenes

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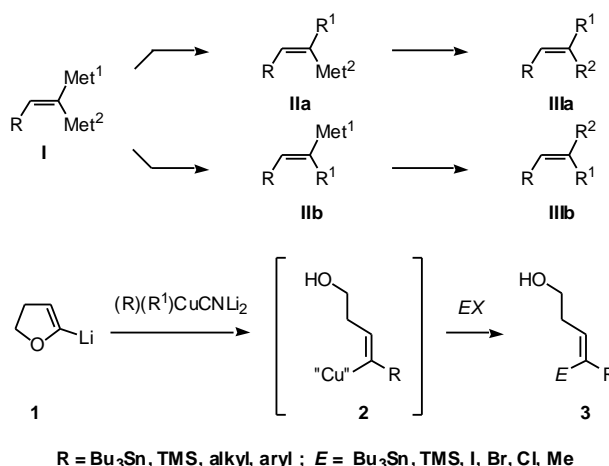
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**Abstract:** Metallate rearrangements performed on 5-lithio-2,3-dihydrofuran **1** gave access to several homo- and hetero-1,1-bimetalated (or pseudo) alkenes **3** upon exposure to a cyanocuprate and quench with an electrophilic reagent *EX*. After metal/halogen exchange, several homo- or hetero-1,1-dihalo-1-alkenes were prepared stereospecifically and in good yields.

Total synthesis in natural compounds involves the stereoselective construction of substituted double bonds.<sup>1</sup> Different methodologies can be applied for this, but stereochemical control remains difficult.



## Scheme 1

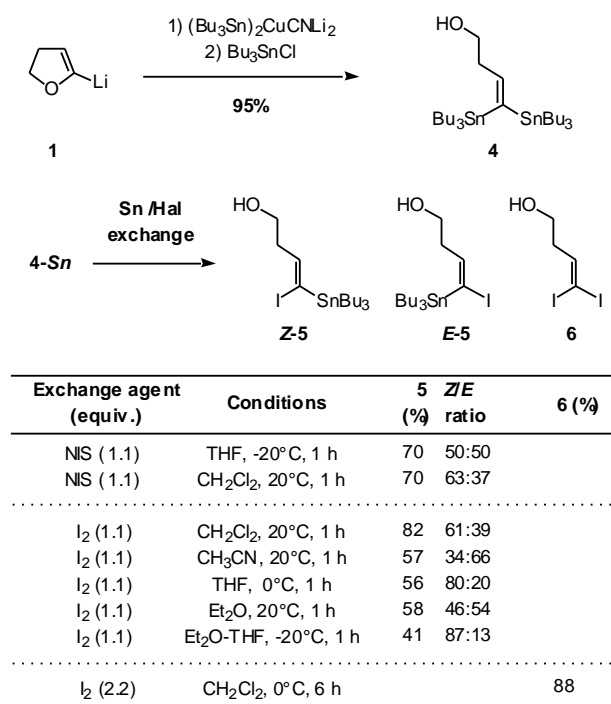
Considering the geminated bimetallic (or pseudobimetallic) olefin **I**,<sup>2</sup> an access to both unsaturated isomeric compound **IIIa** or **IIIb** (Scheme 1) is obtained *via* the monometallated intermediate **IIa** or **IIb** if the two

metallic or pseudometallic atoms Met<sup>1</sup> and Met<sup>2</sup> react selectively with two different electrophilic reagents.

Although 1,1-dibromo-1-alkenes were abundantly used to make substituted double bonds,<sup>3</sup> we wanted to develop a new synthesis of substituted alkenes based on the stereospecific production of hetero-1,1-dihalo-1-alkenes *via* metallate rearrangements. Thus, reaction between a cuprate and lithiodihydrofuran **1** resulted in a rearrangement <sup>4</sup> leading to the vinylcuprate intermediate **2** with complete stereoselectivity (Scheme 1). Subsequent quenching reaction of **2** with several electrophilic agents then delivered the substituted alkenes **3**.<sup>5,6</sup>

We want to present here an extension of our precedent studies <sup>5,6</sup> to the stereoselective preparation of hetero-1,1-dihalo-1-alkenes.

In our initial experiments we tried to functionalize the earlier synthesised **4** ditin compound,<sup>6</sup> using a selective Sn/I exchange (Scheme 2).<sup>7</sup>

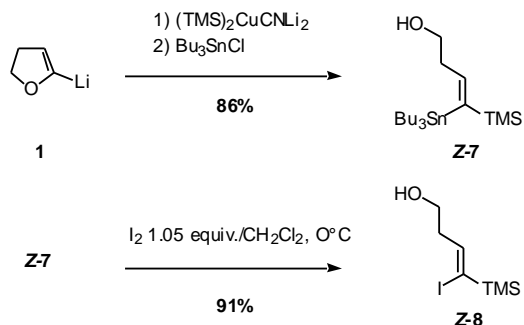


### Scheme 2

Unfortunately, and contrasting with results described by Quayle in another series,<sup>8</sup> no selectivity was obtained for the *Z* or *E* tin function exchange. Both **Z-5** and **E-5** are produced as a 34:66 to 87:13 mixture and in fair yields (41-82%). When 2.2 equivalents of iodine were used, the diiodo derivative **6** was obtained in 88% yield from ditin compound **4**.

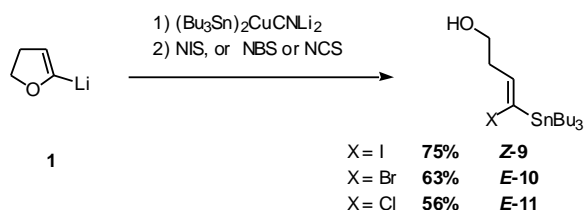
The lack of selectivity of the 1,1-ditin led us to prepare the hetero-1,1-dimetallo or 1,1-dihalo analogues in an indirect way. Starting from the

**Z-7** vinyltin, obtained in a pure form (86%) from the lithiodihydrofuran **1** via a cuprate rearrangement,<sup>9</sup> the Sn/I exchange reaction afforded the **Z-8** vinyliodide in 91% yield (Scheme 3).<sup>10</sup> This method could be considered as an alternative to the procedure described by Lautens *et al.*<sup>11</sup>



### Scheme 3

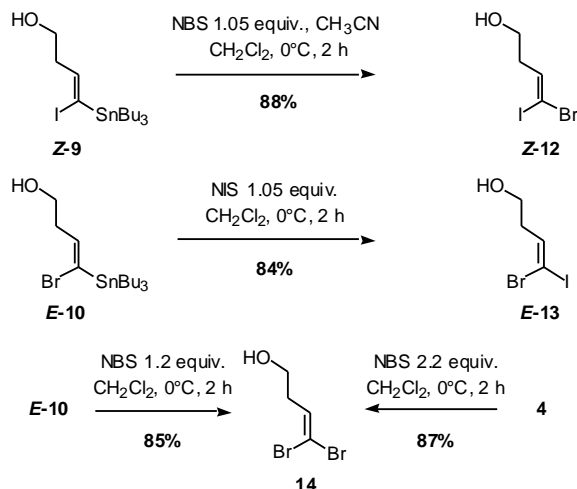
Interestingly, we prepared earlier<sup>12</sup> the halovinyltin derivatives **Z-9**, **E-10** and **E-11** in good yields (75%, 63% and 56%, respectively) via cuprate rearrangements effected on **1** (Scheme 4).



### Scheme 4

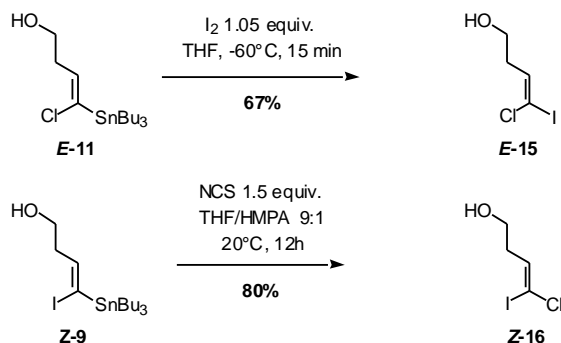
Vinyltin compounds **Z-9** and **E-10** underwent Sn/Br or Sn/I exchange reactions thereby providing the two stereomeric hetero-1,1-dihalo-1-alkene compounds **Z-12** and **E-13** in 88% and 84% yields, respectively, as pure isomers.<sup>13</sup>

A Sn/Br exchange could be also performed with the **E-10** or **4** compound to produce the dibromoalkene **14** in 85% or 87% yield, respectively (Scheme 5).<sup>13</sup>



### Scheme 5

The pure (*E*)-chloroiodo **E-15** was smoothly delivered using a Sn-I exchange from the (*E*)-chlorotin **E-11** in 67% yield (Scheme 6). Initial attempts to generate the (*Z*)-chloroiodo compound **Z-16** were performed on iodotin **Z-9** under NCS, CH<sub>3</sub>CN, Δ conditions; unfortunately, they afforded a 1:1 mixture of iodochloro **Z-15** and **E-15** isomers in low yield.



### Scheme 6

In contrast, exposure of the (*Z*)-iodotin olefin **Z-9** to 1.5 equivalents of NIS in THF/HMPA (9:1) at 20°C for 12 h resulted in its clean conversion to the (*Z*)-chloroiodo derivative **Z-16** in 80% yield along with a minor amount (4%) of **E-15**.<sup>13</sup>

In this study it was shown that cuprate rearrangement is an efficient and stereoselective method to obtain hetero-1,1-dimetallo-1-alkenes and consequently to form hetero-1,1-dihalo-1-alkenes stereoselectively. Further studies, in connection with their abilities to undergo specific palladium-catalysed coupling reactions, are now under scrutiny.

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- 9) Preparation of **Z-7**: A solution of the 5-lithio-2,3-dihydrofuran derivative **1** (2.5 mmol) <sup>9</sup> in THF (4 mL) was added, *via* cannula, to the solution of the *bis*-(trimethylsilyl) dilithiocyanocuprate <sup>14</sup> at -30 °C (2.75 mmol, 1.1 equiv.) in THF-Et<sub>2</sub>O (6 mL/12 mL). The mixture was stirred at -5°- 0 °C for 1 h 30 min. The mixture was then cooled at -40 °C and Bu<sub>3</sub>SnCl (4 equiv.) was added. The temperature was allowed to rise to 0 °C for 1 h, stirring was maintained for 4 h, temperature going up to 20 °C. The reaction mixture was poured into a solution of saturated aqueous NH<sub>4</sub>Cl/concentrated ammonia (4:1) at 0 °C and stirred for 30 min before extraction with diethyl ether. After purification by chromatography on silicagel compound **Z-7** was obtained in 86% yield. IR (Neat)  $\nu^{\text{cm}^{-1}}$ : 3298, 2954, 2923, 2871, 1571, 1463, 1244, 1180, 1046, 960, 871, 830, 743, 685, 620, 591. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.0 (s, 9 H), 0.88 (m, 15 H), 1.32 (m, 6 H + OH), 1.45 (m, 6 H), 2.45 (q, *J* = 6.5 Hz, 2 H), 3.69 (t, *J* = 6.5 Hz, 2 H), 6.72 (t, *J* = 6.5 Hz, 1 H, *J*<sub>H-<sup>119</sup>Sn</sub> = *J*<sub>H-<sup>117</sup>Sn</sub> = 170.0 Hz). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>)  $\delta$  - 0.3 (3 CH<sub>3</sub>), 11.3 (3 CH<sub>2</sub>, *J*<sub>C-<sup>119</sup>Sn</sub> = 318.0 Hz, *J*<sub>C-<sup>117</sup>Sn</sub> = 304.0 Hz), 13.6 (3 CH<sub>3</sub>), 27.4 (3 CH<sub>2</sub>, *J*<sub>C-<sup>119</sup>Sn</sub> = *J*<sub>C-<sup>117</sup>Sn</sub> = 58.0 Hz), 29.2 (3 CH<sub>2</sub>, *J*<sub>C-<sup>119</sup>Sn</sub> = *J*<sub>C-<sup>117</sup>Sn</sub> = 19.0 Hz), 42.4 (CH<sub>2</sub>, *J*<sub>C-<sup>119</sup>Sn</sub> = *J*<sub>C-<sup>117</sup>Sn</sub> = 57.5 Hz), 62.1 (CH<sub>2</sub>), 147.6 (C), 150.7 (CH, *J*<sub>C-<sup>119</sup>Sn</sub> = *J*<sub>C-<sup>117</sup>Sn</sub> = 20.0 Hz). MS (CI, CH<sub>4</sub>): for major <sup>120</sup>Sn isotope, *m/z* 377, 311, 308, 306, 304, 252, 250, 248, 102.
- 10) To a solution of the vinyltin derivative **Z-7** in CH<sub>2</sub>Cl<sub>2</sub> (or CH<sub>3</sub>CN) at 0°C (or below) was slowly added a CH<sub>2</sub>Cl<sub>2</sub> solution of iodine (1.05 equiv.) until persistence of an orange-red colour (1 h at 0°C). The solution was then washed with an aqueous KF and a saturated aqueous Na<sub>2</sub>SO<sub>3</sub> solution before evaporation of the solvent and chromatography on silica gel. Compound **Z-8** was obtained in 91% yield. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>)  $\delta$  0.18 (s, 9H), 2.45 (q, *J* = 6.5 Hz, 2H), 2.5 (s, 1H), 3.72 (t, *J* = 6.5 Hz, 2H),

6.57 (t,  $J = 6.5$  Hz, 1H).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  1.5 ( $3\text{CH}_3$ ), 42.1 ( $\text{CH}_2$ ), 60.6 ( $\text{CH}_2$ ), 116.0 (C), 143.5 (CH). MS (CI,  $\text{CH}_4$ ):  $m/z$  181, 143, 103, 91, 73. Anal. calcd for  $\text{C}_7\text{H}_{15}\text{IOSi}$ : C, 31.12; H, 5.60; I, 46.97; O, 5.92; Si, 10.40; Found: C, 31.32; H, 5.48.

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12) Preparation of **Z-9**, **E-10** and **E-11** derivatives:

A solution of the 5-lithio-2,3-dihydrofuran derivative **1** (2.5 mmol) in THF (4 mL) was added, *via* cannula, to the solution of the *bis*-[(tributyl)stannyl] dilithiocyanocuprate **9** at  $-30$  °C (2.75 mmol, 1.1 equiv.) in THF-Et<sub>2</sub>O (6 mL/12 mL). The mixture was stirred at  $-5$ °-  $0$  °C for 1 h 30 min. The mixture was then cooled at  $-40$  °C and a THF solution (1-2 mL) of the quenching agent, NIS, NBS or NCS (4.0 equiv.), was added. The temperature was allowed to rise to  $0$  °C for 1 h, stirring was maintained for 4 h, temperature going up to  $20$  °C. The reaction mixture was poured into a solution of saturated aqueous  $\text{NH}_4\text{Cl}$ /concentrated ammonia (4:1) at  $0$  °C and stirred for 30 min before extraction with diethyl ether. The **Z-9** compound was obtained in 75% yield. IR (Neat)  $\nu^{\text{cm}^{-1}}$ : 3324, 2950, 2920, 2870, 2850, 1594, 1461, 1376, 1180, 1044, 907, 733, 690, 664, 597.  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  0.85 (t,  $J = 8.0$  Hz, 6 H), 0.96 (t,  $J = 8.0$  Hz, 9 H), 1.30 (m, 6 H), 1.48 (m, 1 H, OH), 2.45 (q,  $J = 6.5$  Hz, 2 H), 3.69 (t,  $J = 6.5$  Hz, 2 H), 6.14 (t,  $J = 6.5$  Hz, 1 H,  $J_{\text{H}-^{119}\text{Sn}} = J_{\text{H}-^{117}\text{Sn}} = 42.0$  Hz).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  11.1 ( $3\text{CH}_2$ ,  $J_{\text{C}-^{119}\text{Sn}} = 348.0$  Hz,  $J_{\text{C}-^{117}\text{Sn}} = 332.0$  Hz), 13.6 ( $3\text{CH}_3$ ), 27.2 ( $3\text{CH}_2$ ,  $J_{\text{C}-^{119}\text{Sn}} = J_{\text{C}-^{117}\text{Sn}} = 60.0$  Hz), 28.6 ( $3\text{CH}_2$ ,  $J_{\text{C}-^{119}\text{Sn}} = J_{\text{C}-^{117}\text{Sn}} = 20.0$  Hz), 42.6 ( $\text{CH}_2$ ,  $J_{\text{C}-^{119}\text{Sn}} = J_{\text{C}-^{117}\text{Sn}} = 32.0$  Hz), 60.9 ( $\text{CH}_2$ ), 110.0 (C), 145.2 (CH,  $J_{\text{C}-^{119}\text{Sn}} = J_{\text{C}-^{117}\text{Sn}} = 20.0$  Hz). MS (CI,  $\text{CH}_4$ ): for major  $^{120}\text{Sn}$  isotope,  $m/z$  377, 322, 307, 252. Anal. calcd for  $\text{C}_{16}\text{H}_{33}\text{IOSn}$ : C, 39.46; H, 6.83; I, 26.06; O, 3.29; Sn 24.37; Found: C, 39.88; H, 7.09.

13) Selected NMR spectroscopic data

**Z-12**:  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.22 (q,  $J = 6.5$  Hz, 2H), 3.63 (t,  $J = 6.5$  Hz, 2H), 6.51 (t,  $J = 6.5$  Hz, 1H).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  40.4 ( $\text{CH}_2$ ), 55.5 (C), 59.9 ( $\text{CH}_2$ ), 143.5 (CH).

**E-13**:  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.37 (q,  $J = 7.0$  Hz, 2H), 3.72 (t,  $J = 7.0$  Hz, 2H), 6.90 (t,  $J = 7.0$  Hz, 1H).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  37.8 ( $\text{CH}_2$ ), 51.0 (C), 60.3 ( $\text{CH}_2$ ), 143.7 (CH).

**14:**  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.8 (s, 1H), 2.44 (q,  $J = 6.5$  Hz, 2H), 3.76 (t,  $J = 6.5$  Hz, 2H), 6.48 (t,  $J = 6.5$  Hz, 1H).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  36.2 ( $\text{CH}_2$ ), 60.3 ( $\text{CH}_2$ ), 90.5 (C), 135.1 (CH).

**E-15:**  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.43 (q,  $J = 7.0$  Hz, 2H), 3.69 (t,  $J = 7.0$  Hz, 2H), 6.51 (t,  $J = 7.0$  Hz, 1H).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  34.9 ( $\text{CH}_2$ ), 60.5 ( $\text{CH}_2$ ), 68.5 (C), 140.3 (CH).

**Z-16:**  $^1\text{H}$  NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  2.34 (q,  $J = 7.0$  Hz, 2H), 3.73 (t,  $J = 7.0$  Hz, 2H), 6.18 (t,  $J = 7.0$  Hz, 1H).  $^{13}\text{C}$  NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  39.2 ( $\text{CH}_2$ ), 60.4 ( $\text{CH}_2$ ), 75.7 (C), 137.3 (CH).

- 14)  $(\text{Me}_3\text{Si})_2\text{CuCNLi}_2$  was prepared by reaction of 2 equivalents of MeLi with 2.2 equivalents of  $(\text{Me}_3\text{Si})_2$  in THF/HMPA (5 mL:1 mL), and 1 equivalent of CuCN at  $-0^\circ\text{C}$ . For preparation of  $\text{Me}_3\text{SiLi}$  see Lipshutz, B. H.; Sharma, S.; Reuter, D. C. *Tetrahedron Lett.* **1990**, *31*, 7253. Still, W. C. *J. Org. Chem.* **1976**, *41*, 3063.