Metal-Catalyzed Di-tert-butylsilylene Transfer: Synthesis and Reactivity of Silacyclop propane

Cirakovic, J.; Driver, T. G.; Woerpel, K. A.

JOC, ASAP (Release date: Feb. 10, 2004)

\[ n-Bu \rightarrow \text{AgOC(O)CF}_3 \text{ (5-10 mol \%)} \]
\[ \textbf{Cul or ZnI}_2 \text{ (20 mol \%)} \]
\[ \text{PhCH=CHCHO} \]

\[ t-Bu \quad t-Bu \]
\[ t-Bu \quad Si-O \]
\[ Si-\quad \rightarrow \quad n-Bu \]
\[ (1,2\text{-isomer}) \]

\[ t-Bu \quad t-Bu \quad t-Bu \quad Si-O \quad t-Bu \]
\[ n-Bu \quad \rightarrow \quad n-Bu \quad \text{CHO} \]
\[ \begin{align*}
17a \\
(1,2\text{-isomer}) \\
\end{align*} \]

\[ t-Bu \quad t-Bu \quad \text{CHO} \]
\[ \begin{align*}
17b \\
(1,3\text{-isomer})
\end{align*} \]
Silylenes: The Beginning

- "It should be recognized that the scope of the application of hexamethylsilirane will be limited by the extremely high reactivity of the silacyclop propane ring system toward many classes of compounds."

Seyferth, D. and Annarelli, D. C. JACS, 1975, 97, 7162-7163.
Silacyclopropane Insertions: Thermally mediated

- Regioselectivity is rationalized based on the equatorially-positioned isopropyl being less sterically crowded than an apically-positioned isopropyl.
- Thermally mediated process is limited to amide insertion.
- Vigorous reaction conditions represent a limitation.

Franz, A. K.; Woerpel, K. A. 
Silacyclopropane Insertions: Copper mediated

- The use of CuBr$_2$ results in the 1,2-regioisomer via insertion into the more substituted Si-C bond.
- Unsaturated aldehydes, esters (especially formate esters) and amides give the insertion product.
- Saturated aldehydes are unreactive.

Franz, A. K.; Woerpel, K. A. 
Silacyclop propane Insertions: Zinc mediated

- The use of ZnBr₂ results in the 1,3-regioisomer via insertion into the less substituted Si-C bond.
- Saturated and unsaturated aldehydes, esters (especially formate esters) and amides give the insertion product.

Franz, A. K.; Woerpel, K. A.
Catalysts Screened for Silylene Transfer

\[ \text{Si}^t\text{Bu} + \text{n-Bu} = \text{MX}_n \rightarrow \text{Si}^t\text{Bu} \]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst (10 mol %)</th>
<th>temp, °C</th>
<th>time</th>
<th>% transfer$^{a,b}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>130</td>
<td>36 h</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Zn(OTf)$_2$</td>
<td>55</td>
<td>12 h</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>CeCl$_3$</td>
<td>25</td>
<td>15 h</td>
<td>69</td>
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<tr>
<td>4</td>
<td>CuF$_2$</td>
<td>25</td>
<td>18 h</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>AgI</td>
<td>25</td>
<td>30 min</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OTf)$_2$</td>
<td>25</td>
<td>17 min</td>
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<tr>
<td>7</td>
<td>Cu(OTf)$_2$</td>
<td>0</td>
<td>2 h</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)$_2$-$\text{PhH}$</td>
<td>0</td>
<td>2 h</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>AgOTf</td>
<td>-27</td>
<td>2 h</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>AgOC(0)CF$_3$</td>
<td>-27</td>
<td>2 h</td>
<td>100</td>
</tr>
</tbody>
</table>

$^a$ As determined by $^1$H MMR spectroscopic analysis of the reaction mixture. $^b$ Reaction took place in a sealed NMR tube with C$_6$D$_6$ as a solvent.

- Silver salts gave the best rate enhancement (lowest temperature and shortest time with 100% transfer).
- Control experiments indicate that the silylene transfer is irreversible between monosubstituted olefins (i.e. n-butylsilacyclop propane to allylbenzene does not occur)

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Scope: Monosubstituted Olefins

\[
\text{R} \xrightarrow{\text{AgOTf (5-10 mol%)}} \text{R} \quad \text{Si} \quad 2a-j
\]

toluene-d8, 2 h, -27 °C then TMEDA

<table>
<thead>
<tr>
<th>entry</th>
<th>( \text{R}^a )</th>
<th>product ( 2 )</th>
<th>% yield ( b )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( n-\text{Bu} )</td>
<td>( 2a )</td>
<td>90</td>
</tr>
<tr>
<td>2c</td>
<td>( t-\text{Pr} )</td>
<td>( 2b )</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>( t-\text{Bu} )</td>
<td>( 2c )</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>( \text{Bn} )</td>
<td>( 2d )</td>
<td>90</td>
</tr>
<tr>
<td>5</td>
<td>( \text{TIPS}-(\text{CH}_2)_2 )</td>
<td>( 2e )</td>
<td>82</td>
</tr>
<tr>
<td>6</td>
<td>( \text{BnO}-(\text{CH}_2)_2 )</td>
<td>( 2f )</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>( t-\text{Bu(O)CO}-(\text{CH}_2)_2 )</td>
<td>( 2g )</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>( \text{MeO} \quad \text{O} \quad \text{Bn} \quad \text{CH}_2 )</td>
<td>( 2h )</td>
<td>61</td>
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<tr>
<td>9</td>
<td>( \text{MeO} \quad \text{OTIPS} \quad \text{CH}_2 )</td>
<td>( 2i )</td>
<td>72</td>
</tr>
<tr>
<td>10</td>
<td>( \text{MeO} \quad \text{OC(O)}t-\text{Bu} \quad \text{CH}_2 )</td>
<td>( 2j )</td>
<td>83</td>
</tr>
</tbody>
</table>

\( ^a \) 1.3 equiv of alkene was used. \( ^b \) As determined by \(^1\text{H} \) NMR spectroscopic analysis of the product mixture relative to an internal \( \text{PhSi(CH}_3)_3 \) standard. \( ^c \) An excess of alkene was used (ca. 10 equiv).

- not affected by steric
- aryl, benzyl and silyl ethers are tolerated
- pivaloyl esters are tolerated

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Scope: Disubstituted Alkenes

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene&lt;sup&gt;a&lt;/sup&gt;</th>
<th>product</th>
<th>% yield&lt;sup&gt;b&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>1</td>
<td>cis-2-butene&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image" alt="" /></td>
<td>89&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>2</td>
<td>trans-2-butene&lt;sup&gt;c&lt;/sup&gt;</td>
<td><img src="image" alt="" /></td>
<td>92&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>OTIPS&lt;sup&gt;e&lt;/sup&gt;</td>
<td><img src="image" alt="" /></td>
<td>85&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>Me&lt;sup&gt;e&lt;/sup&gt;</td>
<td><img src="image" alt="" /></td>
<td>72&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Me&lt;sup&gt;e&lt;/sup&gt;</td>
<td><img src="image" alt="" /></td>
<td>90&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>OTIPS&lt;sup&gt;e&lt;/sup&gt;</td>
<td><img src="image" alt="" /></td>
<td>79&lt;sup*e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> 1.3 equiv of alkene were used. <sup>b</sup> As determined by <sup>1</sup>H NMR spectroscopic analysis of the product mixture relative to an internal <sup>1</sup>H<sub>3</sub>Si(CH<sub>3</sub>)<sub>3</sub> or 1,3-dimethoxybenzene standard. <sup>c</sup> An excess of alkene was used (ca. 10 equiv). <sup>d</sup> One diastereomer was visible by <sup>1</sup>H NMR and <sup>29</sup>Si NMR spectroscopy (dr ≥ 95:5). <sup>*dr</sup> = 89:11, as determined by <sup>29</sup>Si NMR spectroscopy.

- Stereospecific (entries 1 and 2)
- Diastereoselective (entries 3-5)
- Improvement in diastereoselectivity when compared to thermal or t-Bu<sub>2</sub>SiCl<sub>2</sub> / Li methods (JACS, 2002, 124, 6524-6525).

Cirakovic, J. et. al. JOC, ASAP (Release date: Feb. 10, 2004)
Isolation of Silacyclop propane s

<table>
<thead>
<tr>
<th>entry</th>
<th>alkene</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cis-2-butene</td>
<td><img src="image1" alt="" /></td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>trans-2-butene</td>
<td><img src="image2" alt="" /></td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>1-hexene</td>
<td><img src="image3" alt="" /></td>
<td>90</td>
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</tbody>
</table>

* Isolated yield after bulb-to-bulb distillation.

- Silver salts (10 mol %) are implicated in the initial isolation problems.
- The catalyst loading was decreased to 5 mol %.
- Crude reaction mixture was schlenk filtered then distilled to afford pure silacyclop propane s.

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In situ Preparation of Silacyclopropanes and Methyl Formate Insertion

\[
\begin{align*}
\text{R} & \rightarrow \text{Si-O} \\
\text{AgOTf (5-10 mol %)} & \quad \text{ZnBr}_2 (20 \text{ mol %}) \\
& \quad \text{HCO}_2\text{CH}_3
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>regioselectivity</th>
<th>d.r.</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu</td>
<td>&gt;99:1</td>
<td>76:24</td>
<td>14a</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>i-Pr</td>
<td>&gt;99:1</td>
<td>70:30</td>
<td>14b</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>t-Bu</td>
<td>74:26</td>
<td>major, 70:30</td>
<td>14c</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>minor, 91.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Bn</td>
<td>97:3</td>
<td>major, 70:30</td>
<td>14d</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>Br\text{O(\text{CH}_2)_2}</td>
<td>&gt;99:1</td>
<td>64:36</td>
<td>14e</td>
<td>81</td>
</tr>
<tr>
<td>6</td>
<td>TIPS\text{O(\text{CH}_2)_2}</td>
<td>96:4</td>
<td>70:30</td>
<td>14f</td>
<td>61</td>
</tr>
<tr>
<td>7</td>
<td>MeO &amp; \text{OTIPS}</td>
<td>&gt;99:1</td>
<td>70:30</td>
<td>14g</td>
<td>82</td>
</tr>
</tbody>
</table>

\text{\textsuperscript{a}} As determined by \textsuperscript{1}H NMR spectroscopic analysis of the unpurified product mixture. \text{\textsuperscript{b}} Isolated yield over two steps after purification by flash chromatography.

One-Flask Silylene Transfer, Carbonyl Insertion

\[
\begin{align*}
&\text{R} \\
&\text{AgOC(O)CF}_3 \text{ (5-10 mol %)} \\
&\text{ZnBr}_2 \text{ or ZnI}_2 \\
&\text{R}_1\text{R}_2\text{CO} \\
&\xrightarrow{t-\text{Bu}} \\
&\text{15a - e} \\
&15\text{a}, R^1 = \text{Ph}, R^2 = \text{H} \\
&15\text{b}, R^1 = \text{CH}=\text{CHMe}, R^2 = \text{H} \\
&15\text{c}, R^1 = 3\text{-furanyl}, R^2 = \text{H} \\
&15\text{d}, R^1, R^2 = \text{Et} \\
&15\text{e}, R^1 = \text{Me}, R^2 = \text{Ph}
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>MX_n</th>
<th>R^1R^2CO</th>
<th>d.r.</th>
<th>% yield\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-Bu</td>
<td>ZnBr_2</td>
<td></td>
<td>65:35</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>PhCH_2</td>
<td>ZnI_2</td>
<td></td>
<td>64:36</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>PhCH_2</td>
<td>ZnI_2</td>
<td></td>
<td>65:35</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>PhCH_2</td>
<td>ZnI_2</td>
<td></td>
<td>--</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>PhCH_2</td>
<td>ZnI_2</td>
<td></td>
<td>55:45</td>
<td>71</td>
</tr>
</tbody>
</table>

\textsuperscript{a}20 \text{ mol % of MX}\_n \text{ used.} \textsuperscript{b}Isolated yield over two steps after purification by flash chromatography.

- completely regioselective
- diastereoselectivity was low
- ZnBr\_2 and ZnI\_2 equally effective
- Aliphatic aldehydes required less than 1 mol % AgOTf for the insertion.

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Thomas Graham @ Wipf Group
Regioselectivity Depends on the Metal Halide Additive

\[
\text{entry} & \quad \text{MX}_n & \quad 17a:17b & \quad 1,2 \text{ dr} & \quad 1,3 \text{ dr} & \quad \% \text{ yield}\quad b \\
1 & \text{CuI} & 96:4 & 82:18 & & 85 \\
2 & \text{ZnI}_2 & 1:99 & & 76:24 & 82 \\
\]

\(^a\) 20 mol\% of MXn used. \(^b\) Isolated yield over two steps after purification by flash chromatography.

- CuI gives insertion into the more substituted Si - C bond (1,2-isomer)
- ZnI\(_2\) gives insertion into the less substitutes Si - C bond (1,3 isomer)
- dr and yields are similar

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Disubstituted Silacyclop propane

- At 5 mol % AgOTf, no 2,3-disubstituted products were formed with any carbonyl compounds.
- Higher yields were obtained when the silacyclop propane was isolated in the first step.
- Speculated that excess AgOTf accelerates the decomposition.

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Synthetic Utility: Example # 1

1) Me$\text{Et}^+$, SnBr$_4$; 95%, d.r. = 90:9:1

2) Ph$_3$P$^+$CH$_3$Br$^-$, n-BuLi; 73%

2) t-BuOOH, KH, CsF, n-Bu$_4$NF; 90%

- 4 contiguous stereocenters set in 6 steps, 38% overall yield.

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Synthetic Utility: Example # 2

\[
\begin{align*}
\text{5} & \quad \text{t-Bu} \quad \text{t-Bu} \\
\text{H} & \quad \text{Et} \quad \text{OTIPS} \\
\text{H} & \quad \text{Et} \quad \text{OTIPS} \\
\text{22} & \quad \text{t-Bu} \quad \text{t-Bu} \\
& \quad \text{H} \quad \text{Si} \quad \text{O} \\
& \quad \text{H} \quad \text{OH} \\
& \quad \text{H} \quad \text{OTIPS} \\
& \quad \text{t-Bu} \quad \text{t-Bu} \\
& \quad \text{OH} \quad \text{OH} \\
& \quad \text{Et} \quad \text{H} \quad \text{HO}
\end{align*}
\]

1) Ac₂O
2) allyl-TMS, SnBr₄
3) t-BuOOH, KH

42% 80% (3 steps)

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The Proposed Catalytic Cycle for Silylene Transfer

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Conclusions:

- A mild and efficient method for silacyclop propane synthesis was presented.

- The lower temperature results in better diastereoselectivity and improved substrate compatibility.

- Low catalyst loading (0.5 mol %)

- Method has broad-scope (mono- and disubstituted olefins) and offers access to a diverse set of oxasilacyclopentanes.
Future Directions:

- If a silver-stabilized silylene is an intermediate, then can stereoselectivity be induced via ligands on the silver (or other metals)?

\[
\text{[Diagram showing chemical reaction]}\]

- Can the diastereoselectivity be improved?

\[
\text{[Diagram showing chemical reaction]}\]

- Are there other sources of silylenes that are more “user-friendly”? 