

## Triethylborane-Induced Radical Reaction with Schwartz Reagent

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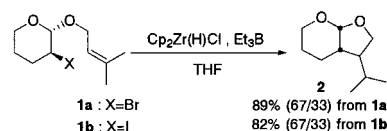
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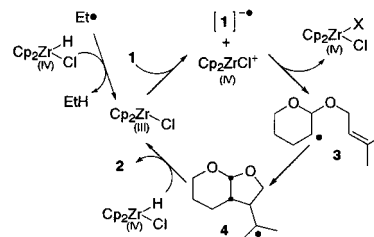
Since the 1970s, hydrozirconation of alkynes and alkenes with bis(cyclopentadienyl)zirconium chloride hydride ( $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ , Schwartz reagent) has been extensively studied and is widely used in organic synthesis.<sup>1,2</sup> Scope and limitations have been well investigated owing to the outstanding usefulness of  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  as a hydrozirconation reagent. Carbonyl compounds such as aldehydes, ketones, carboxylic acids, and esters are reduced to alcohols with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  because of its strong hydridic character. Imines and nitriles are also converted into the corresponding amines and aldehydes, respectively.<sup>2</sup> However, the issue of the reaction with organic halides remains obscure. Little attention has been paid to the reaction of  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  with organic halides.<sup>1,3</sup> Here we describe a novel type of reaction with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ . Reduction of halides with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  proceeded smoothly via a radical process, which is similar to reduction with  $n\text{-Bu}_3\text{SnH}$ , in the presence of triethylborane as an initiator.<sup>4</sup>

We chose halo acetals<sup>5</sup> **1a** and **1b** as model substrates. Treatment of **1a** (0.5 mmol) with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  (1.5 mmol) in the presence of  $\text{Et}_3\text{B}$  (0.5 mmol)<sup>6</sup> in THF (5 mL) at 25 °C for 3 h provided the cyclized product **2** in 89% yield. Iodo acetal **1b** also afforded **2** in 82% yield. Interestingly, the stereochemical outcome of **2** was quite similar to that in the previous report of radical reaction mediated by  $\text{EtMgBr}$  in THF at 25 °C.<sup>7</sup> In addition, the reduction of **1a** and **1b** with  $n\text{-Bu}_3\text{SnH}$ , instead of  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ , afforded **2** with the same selectivity. Therefore, the structure of the transition state of radical cyclization would be the same in all of these reactions including the  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ -mediated reaction. The plausible reaction mechanism is shown in Scheme 2 in analogy with the case of  $n\text{-Bu}_3\text{SnH}$ . An ethyl radical, generated from  $\text{Et}_3\text{B}$  by the action of a trace amount of oxygen, would abstract hydrogen homolytically from  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  to give a zirconium(III) radical species ( $\text{Cp}_2\text{Zr}(\cdot)\text{Cl}$ ). A single electron transfer<sup>8</sup> from  $\text{Cp}_2\text{ZrCl}$  to **1** gives the radical anion of **1**. A halide ion is immediately liberated as  $\text{Cp}_2\text{ZrClX}$  ( $X = \text{Br}$  or  $\text{I}$ ) and the resulting carbon-centered radical **3** cyclizes to afford **4**. The radical

### Scheme 1



### Scheme 2



**4** would abstract hydrogen from  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  to provide the product **2** and regenerate the zirconium(III) species.

The reaction in Scheme 1 did not complete without  $\text{Et}_3\text{B}$ . After being stirred for 1.5 h, **2** was obtained in 24% yield and **1a** was recovered (68%). Moreover, no product was obtained in the presence of a radical scavenger, 2,2,6,6-tetramethylpiperidine-*N*-oxyl. These observations support the radical mechanism in Scheme 2. It is also notable that  $\beta$ -alkoxy elimination did not take place in the  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ -mediated reaction. 3-Methyl-2-buten-1-ol or 9-methyl-6-oxa-4,8-decadien-1-ol was not detected in the reaction mixture. Therefore, a mechanism involving bromine–zirconium exchange followed by intramolecular carbonyl-zirconation would be improbable.<sup>9</sup> Last, the reaction conditions were also applicable to the reduction of 1-bromoadamantane, which is difficult to debrominate via an ionic process such as  $\text{S}_{\text{N}}2$  reaction, to provide adamantane quantitatively.

The use of  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ , prepared in situ from  $\text{Cp}_2\text{ZrCl}_2$  and Red-Al [ $\text{NaAlH}_2(\text{OCH}_2\text{CH}_2\text{OCH}_3)_2$ ],<sup>1</sup> was also effective for the radical reaction. Various halides were examined, and the results are summarized in Table 1.<sup>10</sup> The stereochemistry of the products is again highly suggestive of the 3-oxa-5-hexenyl radical intermediates.<sup>7,11</sup> It is worth noting that  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  is a comparable hydrogen donor with  $n\text{-Bu}_3\text{SnH}$ . The less reactive benzylic radical resulting from cyclization of **7a** can abstract hydrogen from  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  to afford **8**. However, the reactivity toward organic halides of  $\text{Cp}_2\text{ZrCl}$  proved to be inferior to that of the tin-centered radical. Chloro acetal **7d** was not a good substrate. The cyclized product **9** was obtained in 46% yield even at elevated temperature. Although the allylic ether of *o*-iodophenol **11a** was a suitable substrate to construct the dihydrobenzofuran skeleton, a bromo

(1) (a) Hart, D. W.; Schwartz, J. *J. Am. Chem. Soc.* **1974**, *96*, 8115–8116. (b) Wailes P. C.; Weigold, H. *J. Organomet. Chem.* **1970**, *24*, 405–411.

(2) For review: (a) Labinger, J. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 8, Chapter 3.9. (b) Negishi, E.; Takahashi, T. *Aldrichim. Acta* **1985**, *18*, 31–47. (c) Schwartz, J.; Labinger, J. A. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 333–340.

(3) (a) Tam, W.; Rettig, M. F. *J. Organomet. Chem.* **1976**, *108*, C1–C4. (b) Gibson, T. *Organometallics* **1987**, *6*, 918–922. (c) Buchwald, S. L.; LaMaire, S. J.; Nielsen, R. B.; Watson, B. T.; King, S. M. *Tetrahedron Lett.* **1987**, *28*, 3895–3898. In these reports, little discussion on the reduction of organic halides was found.

(4) Nozaki, K.; Oshima, K.; Utimoto, K. *J. Am. Chem. Soc.* **1987**, *109*, 2547–2548.

(5) (a) Ueno, Y.; Chino, K.; Watanabe, M.; Moriya, O.; Okawara, M. *J. Am. Chem. Soc.* **1982**, *104*, 5564–5566. (b) Stork, G.; Mook, R., Jr.; Biller, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1983**, *105*, 3741–3742.

(6) When a catalytic amount of  $\text{Et}_3\text{B}$  (10 mol %) was used, **2** was obtained in 56% yield and **1a** (39%) was recovered after the reaction mixture was stirred for 1.5 h.

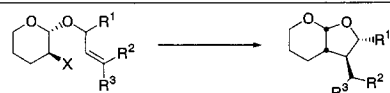
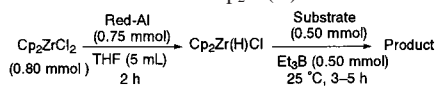
(7) Inoue, A.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2000**, *2*, 651–653. In this report, the reaction proceeded via an atom transfer process. The products were **2** (48%, diastereomer ratio = 67/33) and its isopropenyl analogue (36%, 65/35).

(8) A single electron transfer from Zr(III) species to alkyl halide is proposed: (a) William, G. M.; Gell, K. I.; Schwartz, J. *J. Am. Chem. Soc.* **1980**, *102*, 3660–3662. (b) William, G. M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 1122–1124. (c) Barden, M. C.; Schwartz, J. *J. Org. Chem.* **1997**, *62*, 7520–7521. A single electron transfer from a trivalent titanium complex to organic halides is suggested: (d) Liu, Y.; Schwartz, J. *Tetrahedron* **1995**, *51*, 4471–4482.

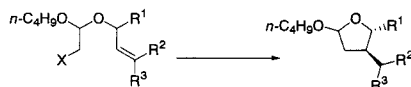
(9) A recent study on the PhLi-initiated cyclization of olefinic alkyl iodides suggests that  $\beta$ -alkoxy elimination may be the result of rapid expulsion of the allyloxy anion from an electron-rich iodine ate complex prior to completion of the lithium–iodine exchange reaction. See: Bailey, W. F.; Carson, M. W. *J. Org. Chem.* **1998**, *63*, 9960–9967.

(10) Simple alkyl halides were also reduced to the corresponding hydrocarbons: 1-bromoadamantane (89%, 5 h), 2-bromododecane (94%, 5 h), 1-bromododecane (93%, 3 h), 1-chloroadamantane (88%, 17 h), and 1-chlorododecane (73%, 40 h).

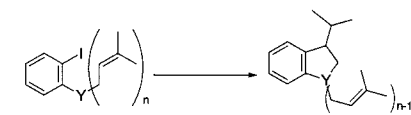
(11) (a) Manganese-ate complex-mediated reaction in THF at 0 °C: Inoue, R.; Nakao, J.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2039–2049. (b) Tri-2-furanylgermane-mediated reaction in THF at 25 °C: Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* **1999**, 1415–1416. (c) Hypophosphorus acid-mediated reaction in ethanol at 25 or 78 °C: Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Chem. Lett.* **2000**, 104–105.

**Table 1.** Radical Reaction with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  Generated in Situ

Substrate	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Product	Yield <sup>a</sup>
<b>1a</b>	Br	H	Me	Me	<b>2</b>	92% (69/31)
<b>1b</b>	I	H	Me	Me	<b>2</b>	89% (66/34)
<b>1c</b>	Br	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	H	H	<b>5</b>	75% (52/48) <sup>b</sup>
<b>1c</b>	Br	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	H	H	<b>5</b>	72% (54/46) <sup>c</sup>
<b>1d</b>	I	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	H	H	<b>5</b>	82% (56/44)
<b>1d</b>	I	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	H	H	<b>5</b>	88% (59/41) <sup>c</sup>
<b>1e</b>	I	H	H	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<b>6</b>	87% (82/18)
<b>1e</b>	I	H	H	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<b>6</b>	92% (79/21) <sup>c</sup>



Substrate	X	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Product	Yield <sup>a</sup>
<b>7a</b>	I	H	H	Ph	<b>8</b>	70% (55/45)
<b>7b</b>	Br	H	Me	Me	<b>9</b>	90% (66/34)
<b>7c</b>	I	H	Me	Me	<b>9</b>	86% (67/33)
<b>7d</b>	Cl	H	Me	Me	<b>9</b>	46% (59/41) <sup>d</sup>
<b>7e</b>	Br	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	H	H	<b>10</b>	94% (53/47)
<b>7e</b>	Br	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	H	H	<b>10</b>	74% (53/47) <sup>c</sup>
<b>7f</b>	I	<i>n</i> -C <sub>8</sub> H <sub>17</sub>	H	H	<b>10</b>	90% (51/49)



Substrate	Y	n	Product	Yield
<b>11a</b>	O	1	<b>12</b>	67%
<b>11b</b>	N	2	<b>13</b>	68%

<sup>a</sup> Diastereomer ratios are in parentheses. <sup>b</sup> See Scheme 3. <sup>c</sup> The reaction was carried out in refluxing THF in the absence of Et<sub>3</sub>B. <sup>d</sup> In refluxing THF for 15 h. **7d** (12%) was recovered.

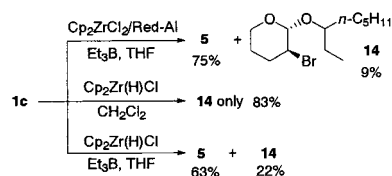
analogue of **11a** did not give the cyclized product under the same conditions (<5% yield). *o*-Bromophenol and the starting material were obtained in 60% and 35% yields, respectively.<sup>12</sup>

Surprisingly, the reaction proceeded in the absence of Et<sub>3</sub>B at higher temperature (Table 1). For example, in refluxing THF, **1e** was treated with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  generated in situ to yield **6** in 92% yield.<sup>13</sup> Although the Zr(II) species is known to undergo single electron transfer to alkyl halide,<sup>14</sup> the Et<sub>3</sub>B-free system ruled out the possibility of the existence of Zr(II) species that might be generated from some sort of transmetalation to Zr(IV) species

(12) Yielding *o*-bromophenol might support the single electron transfer mechanism. A single electron transfer possibly resulted in releasing 2-bromophenoxide anion and the stable allylic radical, whereas iodide and the aryl radical were formed in the case of **11a**.

(13) In some cases, the cyclic products were obtained even at 25 °C in the absence of Et<sub>3</sub>B. However, reproducibility is problematic. Et<sub>3</sub>B is essential to render the reactions at 25 °C steady. What initiated the reaction is not clear. A trace amount of oxygen and some kinds of electron transfer from Zr and/or Al compounds could be initiators. Once the reaction started to a small extent, higher temperature might sustain the radical chain. Organometallics, inorganic salts, or other additives can initiate radical reactions: (a) *i*-Bu<sub>3</sub>AlH, Red-Al, Me<sub>3</sub>Al, Et<sub>2</sub>AlCl, and methylaluminoxane: Chakraborty, A.; Marek, I. *Chem. Commun.* **1999**, 2375–2376. (b) LiAlH<sub>4</sub>: Ashby, E. C.; Pham, T. N.; Amrollah-Madjdabadi, A. *J. Org. Chem.* **1991**, *56*, 1596–1603. (c) 9-BBN: Schiesser, C. H.; Perchyonok, V. T. *Tetrahedron Lett.* **1998**, *39*, 5437–5438. (d) Et<sub>2</sub>Zn: Ryu, I.; Araki, F.; Minakata, S.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 6335–6336. (e) MgX<sub>2</sub>: Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 9701–9702. (f) ZnCl<sub>2</sub>: Yamamoto, Y.; Onuki, S.; Yumoto, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 421–422. (g) CuCl: Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *Tetrahedron Lett.* **1999**, *40*, 2133–2136. (h) Sonication: Nakamura, E.; Imanishi, Y.; Machii, D. *J. Org. Chem.* **1994**, *59*, 8178–8186.

(14) For the reaction with alkyl halide, see refs 8a and 8b. Reduction of vinylic and aromatic halides with  $\text{Cp}_2\text{Zr}(\text{1-butene})$  is also reported, although a radical mechanism is not proposed: (a) Takahashi, T.; Kitora, M.; Fischer, R.; Nishihara, Y.; Nakajima, K. *J. Am. Chem. Soc.* **1995**, *117*, 11039–11040. (b) Hara, R.; Sun, W.-H.; Nishihara, Y.; Takahashi, T. *Chem. Lett.* **1997**, 1251–1252.

**Scheme 3****Table 2.** Radical Reaction with a Catalytic Amount of  $\text{Cp}_2\text{ZrCl}_2$ <sup>a</sup>

substrate	product	yield, % (diastereomer ratio)
<b>1a</b>	<b>2</b>	80 (61/39) <sup>b</sup>
<b>1b</b>	<b>2</b>	82 (66/34)
<b>1d</b>	<b>5</b>	96 (53/47)
<b>7b</b>	<b>9</b>	82 (64/36) <sup>b</sup>
<b>7c</b>	<b>9</b>	80 (65/35)
<b>7e</b>	<b>10</b>	77 (56/44) <sup>b</sup>
<b>7f</b>	<b>10</b>	96 (53/47)
<b>11b</b>	<b>13</b>	83
1-bromoadamantane	adamantane	98

<sup>a</sup> The reaction was performed at room temperature in THF for 3–5 h.  $\text{Cp}_2\text{ZrCl}_2$  (0.2 equiv), Red-Al (1.5 equiv), and Et<sub>3</sub>B (1.0 equiv) were employed. <sup>b</sup> In refluxing THF for 5 h.  $\text{Cp}_2\text{ZrCl}_2$  (0.3 equiv) was used.

giving zirconocene ethyl hydride, which then undergoes reductive elimination.<sup>15</sup>

In each case in Table 1, the overall process, that is, a set of single electron transfer, elimination of halogen, radical cyclization, and hydride donation, was preferred to the hydrozirconation reaction under the above reaction conditions. The reaction of the substrate bearing an internal double bond proceeded without contamination by products derived from the hydrozirconation. On the other hand, treatment of **1c** that has a terminal alkene moiety with  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  generated in situ in the presence of Et<sub>3</sub>B in THF afforded the anticipated bicyclic acetal **5** in 75% yield along with the hydrozirconation product **14** (9%). More interesting, we have found that the reaction path heavily depends on the reaction conditions (Scheme 3). Treatment of **1c** with three equimolar amounts of purchased  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  gave **14** in the absence of Et<sub>3</sub>B in CH<sub>2</sub>Cl<sub>2</sub> in 83% yield with no trace of **5**. In the presence of Et<sub>3</sub>B, **5** (63%) and **14** (22%) were obtained employing the purchased  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  in THF.

Finally, a catalytic reaction was examined. An addition of triethylborane (1.0 mmol) to a solution of iodo acetal (**1b**, 1.0 mmol),  $\text{Cp}_2\text{ZrCl}_2$  (0.2 mmol), and Red-Al (1.5 mmol) in THF afforded **2** in 82% yield (Table 2). Bromo acetals were generally less reactive than iodo acetals, and higher temperature was necessary to complete the reduction of bromo acetals.

In conclusion, we have found a new way to use Schwartz reagent, an efficient alternative to tributyltin hydride as a radical chain carrier.<sup>16</sup> The key steps would be homolytic cleavage of the zirconium–hydrogen bond and halogen reduction by  $\text{Cp}_2\text{ZrCl}$ . Although these fundamental reactions are well established in the case of hydrosilanes, hydrogermanes, and hydrostannanes, the present results will develop a new and attractive aspect of transition metal–hydrido complexes.

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**Supporting Information Available:** Experimental details and characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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