

## A NEW METHOD FOR THE *In Situ* GENERATION OF $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ (SCHWARTZ' REAGENT)<sup>#</sup>

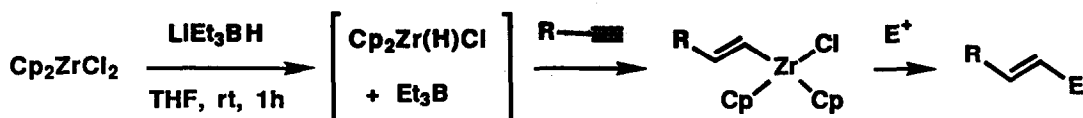
Bruce H. Lipshutz,\* Robert Kell, and Edmund L. Ellsworth<sup>1</sup>

Department of Chemistry

University of California, Santa Barbara, CA 93106

**Summary:** Treatment of  $\text{Cp}_2\text{ZrCl}_2$  with  $\text{LiEt}_3\text{BH}$  in THF leads to formation of  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ . Subsequently introduced terminal acetylenes undergo hydrozirconation without compromising acid-sensitive functionality present in the alkyne.

The process of hydrozirconation developed years ago by Schwartz is a proven, highly valued route to functionalized carbon chains.<sup>2</sup> The reagent,  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ , nowadays referred to as "Schwartz' reagent" (S.R.), is commercially obtainable, albeit quite expensive. The financial burden, however, is offset by the rewards of a mild, stereoselective and usually efficient addition, in particular, to 1-alkynes.<sup>2</sup> Unfortunately, there is one major drawback in that  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  does not have good shelf-life. In our hands, chemistry realized from a newly opened bottle is oftentimes not reproducible with routine use over time.<sup>3</sup> Notwithstanding improvements in large scale availability of  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  *via* the Buchwald procedure,<sup>4</sup> which dramatically reduces the cost factor by utilizing inexpensive  $\text{Cp}_2\text{ZrCl}_2$  (purchased from Boulder Scientific Co.),<sup>5</sup> the issue of stability remains. Alternative *in situ* protocols have been developed,<sup>6</sup> as summarized by Negishi,<sup>7</sup> which give rise to freshly formed  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$  as needed. As part of our newly instituted program on transmetalations of zirconium intermediates,<sup>8</sup> we decided to examine these existing methods for generating S.R. from  $\text{Cp}_2\text{ZrCl}_2$  prior to introduction of an alkyne. It was quickly observed that no one procedure (e.g., using LAH or Red-Al) is satisfactory<sup>9</sup> for acetylenes containing, e.g., a protected hydroxyl group sensitive to acid. The culprit in these schemes was reasoned to be the powerful Lewis acid by-product(s) which is released once a reducing agent has been spent. We now report a new process for *in situ* formation of S.R. and subsequent hydrozirconation which relies on a readily available source of hydride:  $\text{LiEt}_3\text{BH}$ . The by-product of mixing  $\text{Cp}_2\text{ZrCl}_2$  in THF at

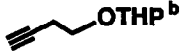


<sup>#</sup>Warmly dedicated to Professor Harry H. Wasserman in celebration of his 70th birthday.

room temperature with a THF solution of  $\text{LiEt}_3\text{BH}$ , which forms  $\text{Cp}_2\text{Zr}(\text{H})\text{Cl}$ , is presumably  $\text{Et}_3\text{B}$ . Due to the very mildly Lewis acidic character of this trialkylborane, it was anticipated that Lewis acid sensitive groups would not be affected.

To demonstrate that this proposal is correct, 1-octyne and the THP derivative of 3-butyn-1-ol were individually subjected to hydrozirconation using fresh S.R., as well as to S.R. prepared from reduction of  $\text{Cp}_2\text{ZrCl}_2$  with  $\text{LiEt}_3\text{BH}$ , Red-Al, and *t*-BuMgCl<sup>10</sup> (Table I). Yields in all cases were excellent for the former substrate. With the protected alcohol, however, the latter two methods are not compatible due to the presence of aluminum and magnesium salt by-products, respectively. No such problem arises using  $\text{LiEt}_3\text{BH}$ .

Table I. Comparison hydrozirconations between S.R. & various *in situ* procedures.

% Yield <sup>a</sup> from:	$\text{Cp}_2\text{ZrCl}_2$ +			
	S.R.	$\text{LiEt}_3\text{BH}$	Red-Al	<i>t</i> -BuMgCl
Octyne	80-100	95	95	100
 OTHP <sup>b</sup>	77	75	50	<10
Decene	80-100	88	80	95

<sup>a</sup>Isolated yields of protio quenched materials. <sup>b</sup>Isolated yields.

Results from the *in situ* hydrozirconation/electrophilic quenching of several representative acetylenes are illustrated in Table II, along with yields realized employing commercially obtained S.R. of high quality.<sup>5</sup> These examples point out that, in addition to a tolerance to sulfide, imide, and ester functionality, a sensitive trimethylsilyl ether linkage remains intact. Yields of derived vinylic halides or monosubstituted (or deuterated) olefins in all cases using  $\text{Cp}_2\text{ZrCl}_2/\text{LiEt}_3\text{BH}$  are comparable to those obtained from bottled S.R. With "aged" S.R., however, the comparison was far in favor of this new *in situ* sequence.<sup>11</sup>

A typical procedure (Table II, entry 6) is as follows: A flame-dried 10 mL flask with stir bar, cooled under argon, was charged with 163 mg (0.56 mmol) of  $\text{Cp}_2\text{ZrCl}_2$  followed by 4 mL of THF. To this solution was added, dropwise over 2 minutes, 0.56 mL of a 1M solution of  $\text{LiEt}_3\text{BH}$  in THF ("SuperHydride", Aldrich). The solution was stirred, shielded from light, for one hour at ambient temperature. After this time, 59 mg (0.28 mmol) of 4-methyl-4-trimethylsilyloxy-1-octyne (dried azeotropically with toluene at room temperature) was added and the mixture stirred for 10 minutes to provide a clear, yellow solution. Introduction of N-bromosuccinimide (recrystallized and dried azeotropically with toluene) led to a cloudy mixture which was stirred for 5

Table II. Comparison study of hydrozirconations using S.R. vs.  $\text{Cp}_2\text{ZrCl}_2/\text{LiEt}_3\text{BH}$ .

Acetylene	Electrophile	Product	$\text{Cp}_2\text{Zr(H)Cl}^{\text{a}}$ (%) <sup>c</sup>	$\text{Cp}_2\text{ZrCl}_2/\text{LiEt}_3\text{BH}^{\text{b}}$ (%) <sup>c</sup>
	$\text{I}_2$		86	80
	$\text{H}_2\text{O}$		84	87
	$\text{D}_2\text{O}$		86	93
	$\text{H}_2\text{O}$		85	88
	$\text{I}_2$		72	83
	NBS		93	83

<sup>a</sup>1.5 eq used. <sup>b</sup>1.5-2.0 eq used. <sup>c</sup>Isolated, chromatographically pure materials, fully characterized by IR, NMR, MS, & HRMS data. <sup>d</sup>Pre-treated in both cases with 1 eq  $\text{LiEt}_3\text{BH}$ .

minutes at room temperature. The reaction was then poured into 20 mL of saturated aqueous  $\text{NaHCO}_3$  and extracted with 10%  $\text{EtOAc}$ /hexanes (15mL, 2x). The combined organic layers were washed with saturated aqueous  $\text{NaCl}$ , dried over  $\text{Na}_2\text{SO}_4$ , and filtered through a pad of Celite atop silica gel. Rotary evaporation *in vacuo* afforded a clear oil (68mg, 83%), pure by VPC analysis, the chromatographic and spectral properties of which were identical with those of an authentic sample (prepared by bromination of the corresponding vinyl stannane).

In summary, a new route to *in situ* generated  $\text{Cp}_2\text{Zr(H)Cl}$  has been described which allows for a 1-pot hydrozirconation of terminal acetylenes (as well as alkenes; see Table I). The key features of this development include (1) confidence as to the quality of the S.R. to be used; (2) considerable savings in terms of cost starting with relatively inexpensive  $\text{Cp}_2\text{ZrCl}_2$ ; and most significantly, (3) compatibility of the reagent mix with functional groups present in the unsaturated educt, not found with other, pre-existing *in situ* routes to  $\text{Cp}_2\text{Zr(H)Cl}$ .<sup>12</sup>

**Acknowledgement.** Financial support provided by the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Glaxo (fellowship to R.K.) is gratefully acknowledged.

### References and Notes

1. Recipient of an American Chemical Society Graduate Fellowship, sponsored by the Proctor and Gamble Company.
2. Schwartz, J., Labinger, J.A., *Angew. Chem. Int. Ed. Engl.*, **1976**, 15, 333.
3. We consistently find that by careful handling of S.R. it can last *ca.* 3 months. After this period, although its appearance is unchanged, it rapidly loses its efficacy.
4. Buchwald, S.L., LaMaire, S.J., Nielsen, R.B., Watson, B.T., King, S.M., *Tetrahedron Letters*, **1987**, 28, 3895.
5. We warmly thank Mr. Lee Kelly and Mr. Jeff Sullivan (Boulder Scientific Co.) for providing samples of  $\text{Cp}_2\text{ZrCl}_2$  and  $\text{Cp}_2\text{Zr(H)Cl}$  used in this study, which were found to be of excellent quality.
6. (a) Carr, D.B., Schwartz, J., *J. Am. Chem. Soc.*, **1979**, 101, 3521; (b) Wailes, P.C., *Inorg. Syn.*, **1979**, XIX, 223; (c) Negishi, E., Miller, J.A., Yoshida, T., *Tetrahedron Letters*, **1984**, 25, 3407.
7. Negishi, E., Takahashi, T., *Aldrichimica Acta*, **1985**, 18, 31; see also, *Synthesis*, **1988**, 1.
8. Lipshutz, B.H., Ellsworth, E.L., *J. Am. Chem. Soc.*, in press.
9. Indeed, as stated by Negishi: "...It should be mentioned, however, that these modified procedures may not always give the same results as those observed with pure  $\text{Cp}_2\text{Zr(H)Cl}$ ."<sup>7</sup>
10. Use of  $\text{Cp}_2\text{ZrCl}_2/t\text{-BuMgCl}$ , to our knowledge, had not previously been applied to acetylenes.<sup>6c</sup> We found that using benzene/ $\text{Et}_2\text{O}$  as solvent and adding the alkyne *after* mixing the dichloride with the Grignard (for 10 min) led to excellent results for the single case shown.
11. The lower yields (e.g., anywhere from 80-0%) reflect a lack of consumption of starting material rather than competing reaction pathways.
12. One limitation found with this *in situ* protocol involves primary acetylenic tosylates, which undergo hydrozirconation with S.R. but are incompatible with the  $\text{Cp}_2\text{ZrCl}_2/\text{LiEt}_3\text{BH}$  conditions described herein.