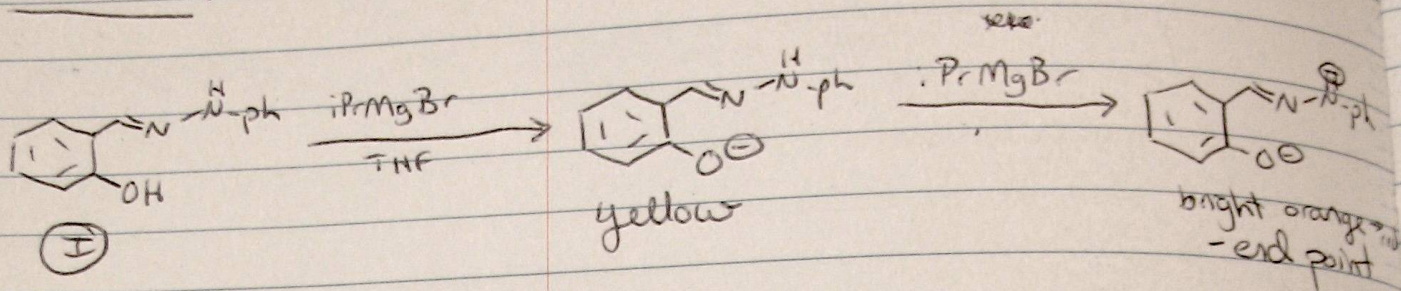


Titration:

Reference: JOC, 1999, 64, 3755

Procedure: flame-dried RB (eep II-102) dissolved 60.2 mg in 10 mL THF (sh11), while stirring well under  $N_2$  added Grignard slowly

- turns yellow
- orange endpoint

eep II-91

- used 0.37 mL Grignard  
= 0.77 M

	amt	source	mw	mmol
Ⓡ	60.2 mg	Eep II-902	212.25	0.2836
THF	10 mL	sh11		
$iPrMgBr$	- needed 0.37 mL	Eep II-91		

→ so 0.77 M

## The Use of Salicylaldehyde Phenylhydrazone as an Indicator for the Titration of Organometallic Reagents

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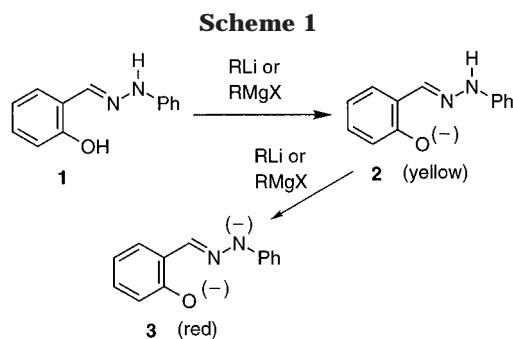
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Though there are a number of reagents available which can serve as indicators for the titration of organolithium compounds,<sup>1</sup> only a few are suitable for use with Grignard reagents. Those that can be used with Grignard reagents such as 1-pyreneacetic acid<sup>3</sup> and diphenyl ditelluride<sup>4</sup> tend to be expensive and/or have other limitations.<sup>5</sup> Other reagents such as *N*-phenyl-1-naphthylamine<sup>7</sup> and 1,10-phenanthroline<sup>8</sup> are more reasonably priced but must be used in conjunction with a standardized anhydrous solution of 2-butanol in xylene, which is tedious to prepare. Potentiometric titration is perhaps the most accurate means of determining the concentration of a Grignard reagent, but it too requires a standardized 2-butanol solution, as well as expensive electrochemical equipment.<sup>9</sup>

### Results and Discussion

Here we report the use of salicylaldehyde phenylhydrazone **1** (Scheme 1) as an indicator for the titration of organometallic species, including Grignard reagents. It is easily prepared in good yield from inexpensive starting materials and is simple to isolate in pure form. Addition of an organometallic reagent to a solution of **1** produces the yellow monoanion **2**, and further addition of the reagent produces a red color, attributed to the dianion **3**. The first drop of organometallic reagent in excess of 1 equiv is manifested by a change in the color of the solution from yellow to bright orange, which thus serves as the end point of the titration. Prior to reaching the end point, each drop of organometallic reagent produces a localized formation of the dianion (which quickly dissipates with efficient stirring) but provides a preview of the color change to be observed at the end point. Though there is not a large chromatic shift (yellow



**Table 1. Titration of Grignard Reagents**

reagent	calculated molarity using <b>1</b> <sup>a</sup>	calculated molarity using PhTeTePh
MeMgBr	2.18 ± 0.06	2.10
<i>n</i> -PrMgCl	1.60 ± 0.13	1.58
<i>i</i> -PrMgCl	1.50 ± 0.04	1.53
<i>n</i> -BuMgCl	1.31 ± 0.17	1.27
<i>t</i> -BuMgCl	1.75 ± 0.08	<i>b</i>
<i>n</i> -C <sub>6</sub> H <sub>13</sub> MgBr	1.45 ± 0.03	1.42
PhMgCl	1.19 ± 0.08	1.22

<sup>a</sup> Average of three trials. <sup>b</sup> Titration of *tert*-butyl magnesium chloride with diphenyl ditelluride as an indicator was impractical due to the slow reaction rates—more than a minute was required between addition of a drop of *tert*-butyl magnesium chloride and the observation of its effect on the color of the diphenyl ditelluride solution.

**Table 2. Titration of Organolithium Reagents**

reagent	calculated molarity using <b>1</b> <sup>a</sup>	calculated molarity using NPOT <sup>b</sup>
MeLi	1.15 ± 0.04	1.20
<i>n</i> -BuLi	1.28 ± 0.05	1.28
<i>s</i> -BuLi	0.96 ± 0.01	0.98
<i>t</i> -BuLi	0.99 ± 0.12	1.08

<sup>a</sup> Average of three trials. <sup>b</sup> NPOT = *N*-pivaloyl-*o*-toluidine.

to orange), the end point is nevertheless distinct and easy to observe.

The titration can be carried out simply by dissolving an accurately weighed sample of **1** in freshly distilled THF and maintaining this solution under an atmosphere of dry nitrogen while the organometallic reagent is added by means of a gastight syringe. The results are quite reproducible, given the accuracy of the syringe,<sup>10</sup> and agree well with values obtained using previously reported indicators (Tables 1 and 2).

Not only Grignard reagents and organolithiums but also solutions of hydridic species such as lithium aluminum hydride (LAH) and sodium bis(2-methoxyethoxy)aluminum hydride (Vitride or Red-Al) can be titrated using **1** as an indicator (Table 3). The concentration of these solutions is commonly determined by iodometric titration<sup>11</sup> or by treatment with benzyl alcohol and either measurement of evolved hydrogen gas<sup>12</sup> or observation of the development of color in the presence of 1,10-

(1) Some commonly used examples include the following: diphenylacetic acid,<sup>2a</sup> 1,3-diphenyl-2-propanone *p*-tosylhydrazone,<sup>2b</sup> 4-biphenylmethanol,<sup>2c</sup> and *N*-pivaloyl-*o*-toluidine,<sup>2d</sup> though a number of others have been reported.

(2) (a) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879. (b) Lipton, M. F.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155. (c) Juaristi, E.; Martinez-Richa, A.; Garcia-Riviera, A.; Cruz-Sanchez, J. S. *J. Org. Chem.* **1983**, *48*, 2603. (d) Suffert, J. *J. Org. Chem.* **1989**, *54*, 509.

(3) Kiljunen, H.; Hase, T. A. *J. Org. Chem.* **1991**, *56*, 6950.

(4) Aso, Y.; Yamashita, H.; Otsubo, T.; Ogura, F. *J. Org. Chem.* **1989**, *54*, 5627.

(5) 1-Pyreneacetic acid now costs approximately \$28 per gram,<sup>6</sup> and the commercial material often contains colored impurities which obscure the end point. Diphenyl ditelluride now costs approximately \$20 per gram<sup>6</sup> and produces malodorous alkylphenyl tellurides which are potentially toxic.

(6) Aldrich Chemical Co.

(7) Bergbreiter, D. E.; Pendergrass, E. *J. Org. Chem.* **1981**, *46*, 219.

(8) Watson, S. C.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165.

(9) Silverman, G. S., Ed. *Handbook of Grignard Reagents*; Marcel Dekker: New York 1996; pp 89–92.

(10) A 1.00 mL syringe with calibration marks every 0.02 mL was used. With the amounts of **1** employed (60.0–80.0 mg), an error of 0.01 mL in the amount of titrant used changes the calculated molarity by approximately 0.05–0.1 M. Use of larger amounts of **1** generally gave more precise results.

(11) Felkin, H. *Bull. Soc. Chim. Fr.* **1951**, 347.

(12) Rickborn, B.; Quartucci, J. *J. Org. Chem.* **1964**, *29*, 3185.

**Table 3. Titration of Hydride Reagents**

reagent	calculated molarity using <b>1</b> <sup>a</sup>	calculated molarity using 9-fluorenone
LiAlH <sub>4</sub>	3.71 ± 0.03	3.57
Red-Al	2.69 ± 0.09	2.78 <sup>b</sup>

<sup>a</sup> Average of three trials. <sup>b</sup> In this case the end point was indicated by the development of a dark color, rather than the disappearance of the yellow color, as was reported (and observed) for LAH.

phenanthroline.<sup>13</sup> More recently, a procedure which utilizes 9-fluorenone has also been reported.<sup>14</sup> As with the previous organometallic species, sharp end points were observed, that for LAH being more distinct than that observed with the other organometallic species, and the Red-Al being less so.

All four of the hydrogens on LAH take part in the reaction, and thus the calculated molarity is four times the actual molarity of the reagent.<sup>15</sup> With sodium bis(2-methoxyethoxy)aluminum hydride, both of the hydrogens react, and thus the calculated molarity is double the actual molarity of the reagent.

The phenylhydrazones of the isomeric compounds *m*-hydroxybenzaldehyde and *p*-hydroxybenzaldehyde were also tested for their ability to serve as indicators for the titration of organometallic species. Both exhibited very similar characteristics to those of **1**, but since they offered no significant advantage over the indicator derived from the less expensive salicylaldehyde, their use was not investigated further.

(13) Villieras, J.; Rambaud, M.; Kirschleger, B. *J. Organomet. Chem.* **1983**, 249, 315.

(14) Brown, E.; Lézé, A.; Touet, J. *Tetrahedron Lett.* **1991**, 32, 4309.

(15) Titration of LAH required the use of larger amounts of **1** than were necessary for organolithium and Grignard reagent titrations. Use of approximately 200 mg of **1** gave accurate and reproducible results, while lesser amounts (50 mg) led to greater variations in calculated molarity.

In summary, salicylaldehyde phenylhydrazone **1** has been found to be a useful indicator for the titration of a wide range of commonly used reagents.<sup>16</sup> It can be prepared easily from inexpensive starting materials and provides clear and accurate end point determinations.

## Experimental Section

**General Methods.** THF was freshly distilled under nitrogen from sodium benzophenone ketyl.

**Salicylaldehyde Phenylhydrazone (1)** A 2.92 g (27.0 mmol) sample of phenylhydrazine was dissolved in 10 mL of 95% ethanol and stirred while 3.30 g (27.0 mmol) of salicylaldehyde, dissolved in 15 mL of ethanol, was added. The solution was stirred for 30 min at room temperature (a precipitate formed within a minute) and then cooled to -15 °C. The white solid was collected by vacuum filtration and washed with ice cold ethanol to give (after drying in vacuo) 4.73 g (82.5%) of product melting at 140–145 °C (lit.<sup>17</sup>mp 142 °C). The product can be recrystallized from CHCl<sub>3</sub> (recovery: 85%), but the melting point is not changed significantly, and the product obtained prior to recrystallization is typically suitable for use as a titration indicator. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 10.96 (s, 1H), 7.78 (s, 1H), 7.50 (s, 1H), 7.4–7.2 (m, 3H), 7.2–6.8 (m, 6H); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 157.48, 143.89, 141.69, 130.53, 130.08, 129.91, 121.39, 120.04, 119.05, 117.09, 113.17.

**Titration Procedure.** An accurately weighed sample of **1** (typically between 60.0 and 80.0 mg) is dissolved in 10 mL of freshly distilled THF and stirred at room temperature under nitrogen while the organometallic reagent is added slowly by means of a gastight syringe. A yellow color (the monoanion) forms initially, the end point being indicated by a change in this color to bright golden orange.

JO982433E

(16) This reagent did not, however, exhibit a satisfactory end point when titrated with a solution of LDA.

(17) Rappoport, Z., Ed. *Handbook of Tables for Organic Compound Identification*, 3rd ed.; The Chemical Rubber Co.: Cleveland, 1967.