Organic Process Research & Development **2006**, *10,* 1258–1262

# Process Safety Evaluation of a Magnesium−Iodine Exchange Reaction

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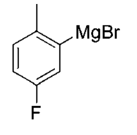
## Abstract:

**An unexpected highly exothermic decomposition was observed during routine safety analysis of the magnesium−iodine exchange reaction of 2-iodo-4-fluorotoluene (3) with commercially available *i*-PrMgCl (2.0 M solution in THF). When the reaction mixture was scanned in an adiabatic calorimeter with the use of a 2 °C/min temperature ramp, a rapid exothermic decomposition with an onset temperature of approximately 80 °C was observed. The system temperature rapidly rose to 210 °C at a peak rate of 200 °C/min. Subsequent testing of three simplified substrates showed the same type of exothermic decomposition for all cases. Control experiments indicated that the decomposition requires both aryl iodide and *i*-PrMgCl (or arylMgCl and *i*-PrI). While the onset temperatures for all cases studied were generally well above the typical operating temperature for these reactions (0−10 °C), it is nonetheless important to cautiously evaluate these types of processes and install proper engineering controls for analogous decomposition events.**

## Introduction

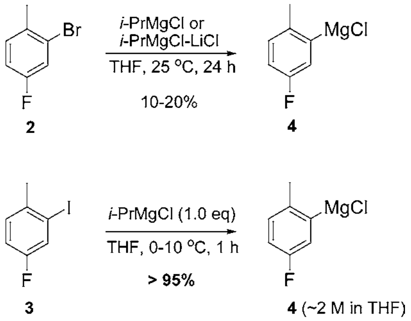
The generation of aryl Grignard reagents has traditionally been accomplished by treatment of aryl halides (Cl, Br, or I) with magnesium metal in etheral solvents. In recent years, however, an attractive alternative has emerged. Developed by Knochel and co-workers,[1] this procedure involves treatment of an aryl bromide or iodide with commercially available *i*-PrMgCl or the more powerful reagents *i*-PrMgCl·LiCl[2] and *i*-$Pr_2$Mg·LiCl[3] in THF at temperatures of −20 °C to room temperature. Aryl and heteroaryl Grignard reagents may smoothly and rapidly be generated and may contain functional groups that are not tolerated by the traditional magnesium metal-mediated process. The mild temperatures and typically homogeneous solution composition of these reactions are attractive features, particularly considering that the magnesium metal-mediated processes often require heating for Grignard formation, and the initiation may be unpredictable. Due to the demonstrated generality, simplicity of reaction conditions, and the excellent functional group compatibility, the magnesium−halogen exchange reaction is increasingly being employed in both academic laboratories and industrial settings.



**1** (0.5 M in THF)

***Figure 1.***

***Scheme 1.*** **Magnesium−halogen exchange for generation of Grignard 4**



In one of our recent process development programs, we required 2-methyl-5-fluorophenylmagnesium bromide (**1**, Figure 1). This reagent is commercially available as a 0.5 M solution in THF. However, the low concentration and high cost of this reagent are not desirable for large-scale production of the API. In the search for economical alternatives to the commercial Grignard solution, we considered generating this Grignard reagent through a magnesium−halogen exchange reaction.

We investigated the magnesium−halogen exchange reaction using 2-bromo-4-fluorotoluene (**2**, Scheme 1) and 2-iodo-4-fluorotoluene (**3**) with commercially available *i*-PrMgCl (2.0 M solution in THF). The reaction of bromide **2** with 1.0 equiv of *i*-PrMgCl or *i*-PrMgCl·LiCl gave only 10−20% exchange after 24 h at 20−25 °C as monitored by HPLC analysis of reaction aliquots quenched into MeOH. The reaction of iodide **3** with *i*-PrMgCl (1.0 equiv), however, was complete (≥95% exchange) after 45 min at 0 °C (Scheme 1). The resultant Grignard reagent **4** proved to be suitable for use in our subsequent synthetic sequence. The optimized procedure for Grignard formation consisted of charging 1.0 equiv of *i*-PrMgCl (2.0 M in THF) to the reactor, cooling the solution to 0 °C, and charging **3** at a rate to maintain the temperature between 0 and 10 °C. The reaction mixture was agitated for 45 min to 1 h at 0−10 °C after completion of the addition of **3** to achieve complete

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(1) (a) Boymond, L.; Rottländer, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701. (b) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, *4*, 565. (c) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302.

(2) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333.

(3) Krasovskiy, A.; Straub, B. F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 159.

10.1021/op060145b CCC: $33.50

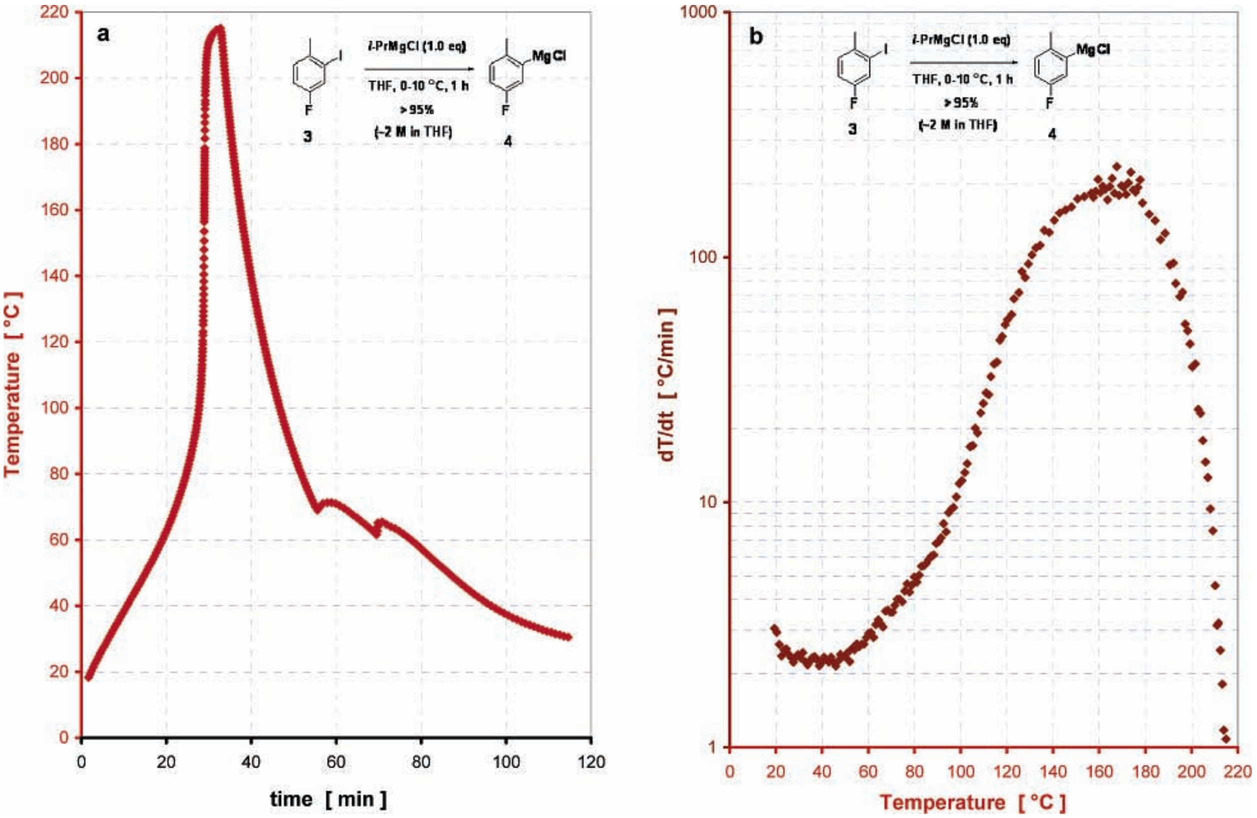


*Figure 2.* **Thermal safety evaluation of Grignard 4 formation. Plots derived from ARSST calorimetry data. (a) Temperature vs time plot. Heat-up and cool-down portions are shown here. (b) Temperature rise rate vs temperature plot. Only the heat-up portion is shown here.**

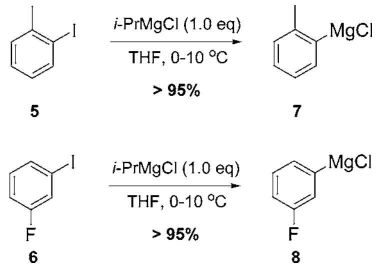
(≥95%) formation of **4**. Since the commercial 2.0 M solution of *i*-PrMgCl was used as the solvent for the reaction, a ~2 M solution of **4** was produced, and the overall volume efficiency of this process was excellent. In addition, iodide **3** was readily available in bulk at a low price, rendering this process economically attractive.

In preparation for scale-up of this procedure in the pilot plant, a routine safety analysis was performed. To our surprise, the safety study showed that there was a highly exothermic decomposition process with an onset temperature of ~80 °C. This presented an unexpected process safety concern. The details of this study including our analysis of related substrates are discussed in this paper.

## Results and Discussion

According to our internal standard operating procedures, the process safety of every reaction must be evaluated prior to scale-up in the kilo-lab and pilot plant. Routine safety testing of the process described above for the *i*-PrMgCl exchange reaction with **3** was performed as follows. A 10-mL sample of the reaction mixture was taken after the exchange reaction was complete (confirmed by HPLC after aging at 0−10 °C for 45 min to 1 h) and was scanned in an Advanced Reactive Systems Screening Tool[4] (see Experimental Section for details) at a rate of 2 °C/min. A rapid exothermic decomposition with an onset temperature of approximately 80 °C was observed (Figure 2). The system temperature rapidly rose to 210 °C at a peak rate of 200 °C/min. The system pressure also showed a sharp increase.

*Scheme 2.* **Generation of Grignard reagents 7 and 8 for testing substituent contributions to decomposition reaction**



As a control experiment, the commercial 0.5 M solution of Grignard reagent **1** was also subjected to the same thermal safety testing. In this case, no decomposition event was observed, suggesting a dependence of the decomposition event on both the aryl iodide **3** and *i*-PrMgCl (and/or the products derived from their reaction). Dilution of the magnesium−iodine exchange reaction 4-fold (to generate a ~0.5 M solution of **4**) still gave the decomposition event, albeit with a reduced magnitude. In this case the onset temperature was also 80 °C, but the peak rate of temperature rise was lesser at 20 °C/min.

Given the above data obtained for Grignard reagents **1** and **4**, we became interested in the generality of this decomposition for magnesium−iodine exchange of other substrates. In order to ascertain the effect of the methyl and fluorine groups, 2-iodotoluene (**5**) and 3-fluoroiodobenzene

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[4] Burelbach, J. P.; Theis, A. E. Thermal Hazards Evaluation Using the ARSST. Third International Symposium on Runaway Reaction, Pressure Relief Design and Effluent Handling, Cincinnati, OH, November 1−3, 2005.

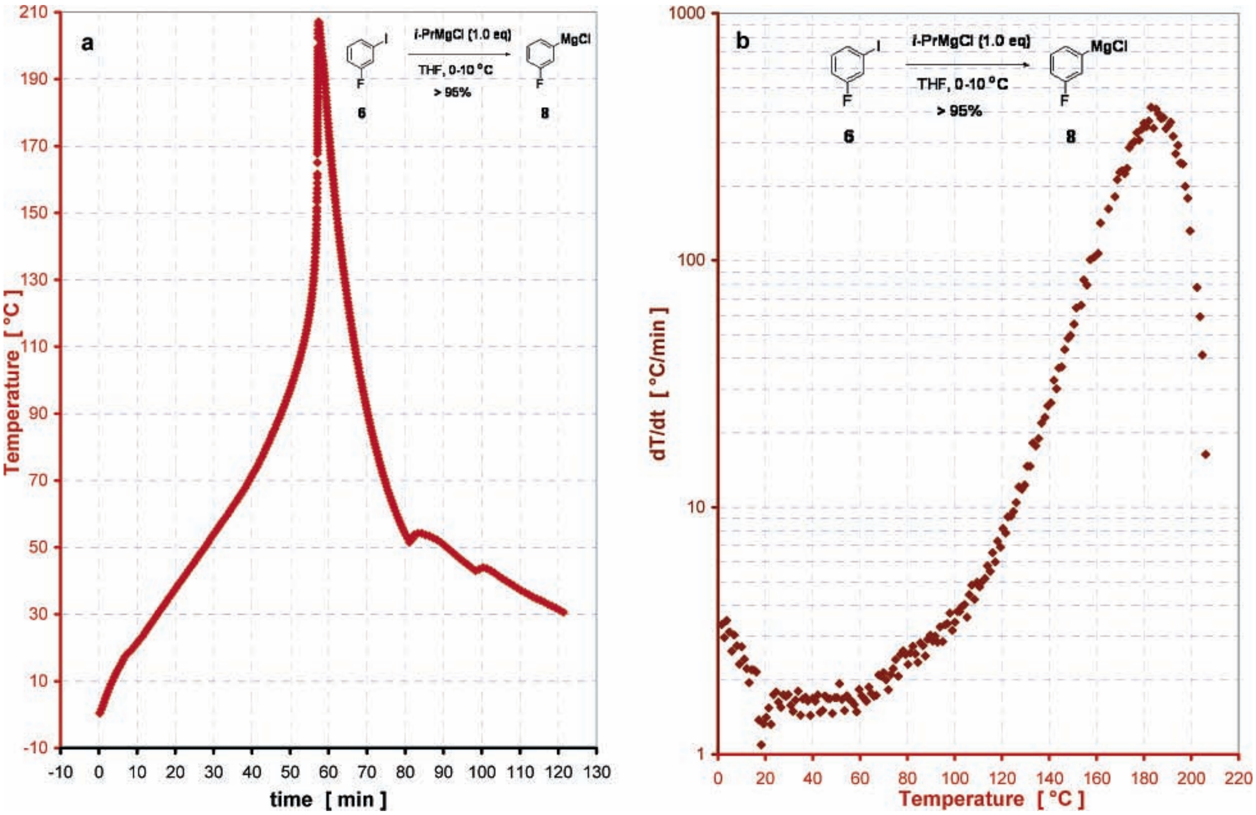


*Figure 3.* **Thermal safety evaluation of Grignard 8 formation. Plots derived from ARSST calorimetry data. (a) Temperature vs time plot. Heat-up and cool-down portions are shown here. (b) Temperature rise rate vs temperature plot. Only the heat-up portion is shown here.**

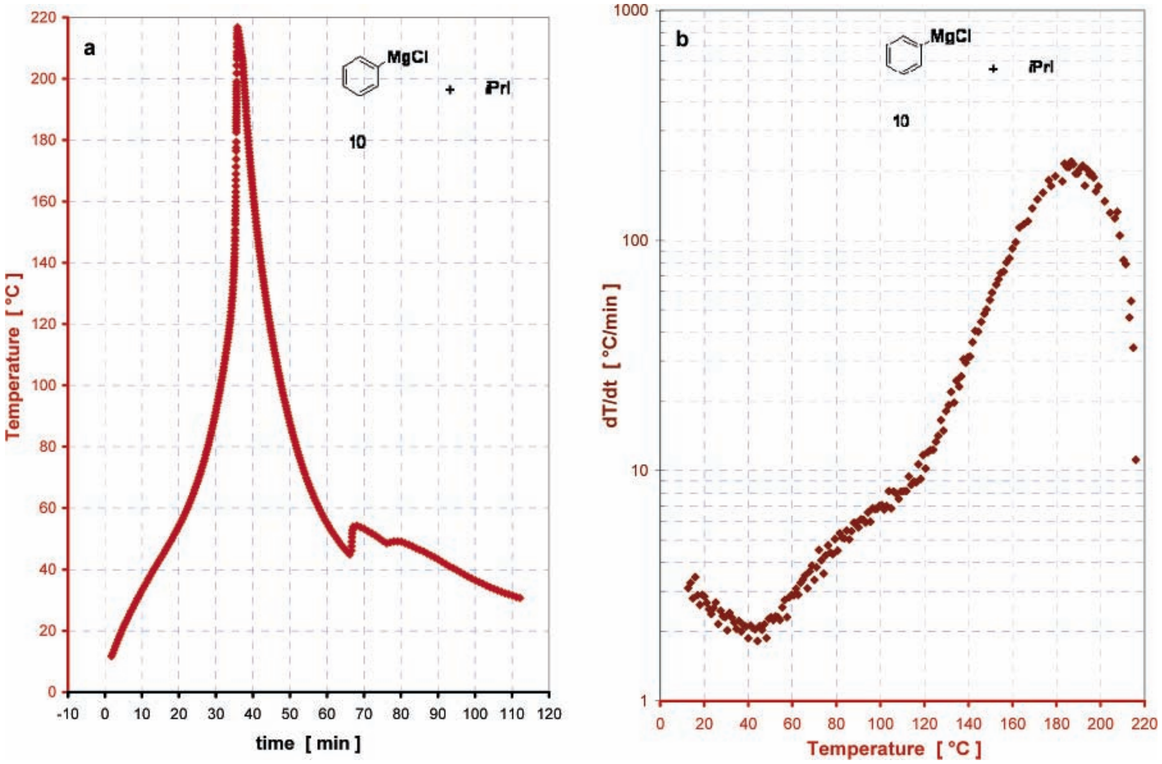
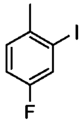
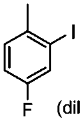
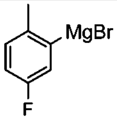
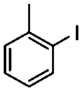
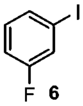
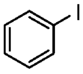
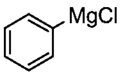
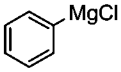


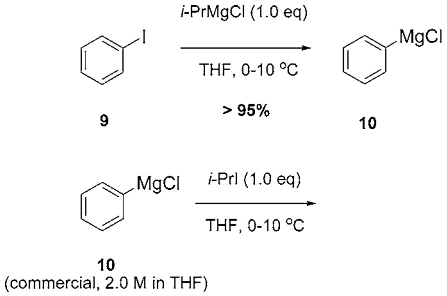
*Figure 4.* **Thermal safety evaluation of Grignard 10 and mixture derived from mixing commercial PhMgCl and *i*-PrI. Plots derived from ARSST calorimetry data. (a) Temperature vs time plot. Heat-up and cool-down portions are shown here. (b) Temperature rise rate vs temperature plot. Only the heat-up portion is shown here.**

(**6**) were subjected to the same magnesium−iodine exchange reaction conditions as **3**, producing the Grignard reagents **7** and **8**, respectively, in >95% conversion by HPLC analysis (Scheme 2). Thermal safety evaluation of aliquots of

***Table 1.*** **Summary of Thermal Safety Evaluation Data**

| Experiment | Analyte(s) | Thermal Event | Onset Temperature (°C) | Peak Temperature Rise Rate (°C/min) |
|---|---|---|---|---|
| 1 |  + *i*-PrMgCl<br>**3** | Yes | 80 | 200 |
| 2 |  + *i*-PrMgCl<br>(diluted ~4-fold)<br>**3** | Yes | 80 | 20 |
| 3 | <br>**1** | No | - | - |
| 4 |  + *i*-PrMgCl<br>**5** | Yes | 80 | 25 |
| 5 |  + *i*-PrMgCl<br>**6** | Yes | 80 | 410 |
| 6 |  + *i*-PrMgCl<br>**9** | Yes | 110 | 105 |
| 7 |  + *i*-PrI | Yes | 80 | 220 |
| 8 |  | No | - | - |
| 9 | *i*-PrMgCl | No | - | - |
| 10 | *i*-PrI | No | - | - |

***Scheme 3.*** **Generation of Grignard reagent 10 by magnesium−iodine exchange and mixing of a commercial solution of 10 with *i*-PrI**



Grignard reagents **7** and **8** were performed. In both cases, similar thermal events were observed, although at different magnitudes. For **7**, the onset temperature of the decomposition was 80 °C, and the peak rate of the temperature rise was 25 °C/min. For **8**, the onset temperature was again 80 °C, while the peak rate of the temperature rise was much larger at 410 °C/min (Figure 3).

These results prompted us to investigate the reaction mixture derived from magnesium−iodine exchange of the simplest substrate, iodobenzene (**9**), to give phenylmagnesium chloride (**10**) (Scheme 3). Again, a similar exothermic event occurred. The onset temperature was slightly higher at 110 °C, and the peak rate of the temperature rise was 105 °C/min. A series of control experiments were subsequently conducted. It was found that a commercial phenylmagnesium chloride solution (2.0 M in THF), commercial *i*-PrMgCl solution (2.0 M in THF), and pure isopropyl iodide (dissolved in THF) were thermally stable. However, when a 1:1 molar mixture of phenylmagnesium chloride (2.0 M in THF) and isopropyl iodide was tested, the mixture ran away with an onset temperature of 80 °C at a peak rate of 220 °C/min (Figure 4).

These data seemed to suggest that the interaction of the byproduct of the magnesium−iodine exchange reaction (i.e., *i*-PrI) with the aryl Grignard reagent was necessary for the decomposition reaction to occur. This is consistent with the observation that dilution slows down the decomposition and reduces the severity of the event, as was observed for the 4-fold dilution in the preparation of Grignard reagent **4**.

In summary, we have observed an unexpected thermal event for simple magnesium−iodine exchange reactions of a few substituted phenyl iodides with *i*-PrMgCl (Table 1). It was interesting to note that even for the simplest substrate, phenyl iodide, there was a thermal event starting at 110 °C. Control experiments showed that *i*-PrI, generated in the magnesium−iodine exchange reaction, is not simply an inert byproduct. It might participate in certain decomposition reactions at elevated temperatures, causing a process safety concern. In view of our observation from this safety study, it is strongly recommended that extra attention should be paid to this class of reactions which are increasingly finding industrial applications. Although the onset temperature is above the operating temperature of this particular reaction, the onset temperature is still well within the heating capability of the equipment and the severity of the observed thermal decomposition is considerable. Therefore, proper engineering controls and vent sizing for credible upset scenarios (e.g., accidental dumping and overheating) must be put in place before any scale-up.

## Experimental Section

**General.** All reagents were purchased from commercial sources and used without further purification. HPLC analysis was performed on an Agilent 1100 series HPLC using a Tosohass Super-ODS column; flow rate of 1.0 mL/min; UV detection at 220 and 254 nm; mobile phase 10% MeCN in water (0.05% TFA) to 90% MeCN in water in 15 min, hold for 5 min, then back to 10% MeCN in water.

**General Procedure for Magnesium−Iodine Exchange.** A nitrogen-purged flask with magnetic stir bar was charged with *i*-PrMgCl solution (20.0 mL, 40.0 mmol, 2.0 M in THF). The reaction mixture was cooled to an internal temperature of 0 °C, and **3** (9.4 g, 40.0 mmol) was added over 10 min, keeping internal temperature between 0 and 10 °C. The reaction mixture was stirred at 10 °C for 45 min, at which time HPLC analysis (aliquot into MeOH) showed $\geq$95% consumption of **3**. A ~10 mL sample was withdrawn for thermal safety analysis. The magnesium−iodine exchange of iodides **5**, **6**, and **9** was performed in the same manner and on the same scale (40.0 mmol). HPLC was used to monitor the completion of the exchange, which generally required 0.5−2.0 h. For the preparation of a mixture of PhMgCl and *i*-PrI, 10.0 mL (20.0 mmol, 2.0 M in THF) of commercial PhMgCl was cooled to 0 °C and treated with *i*-PrI (2.0 mL, 20.0 mmol). The mixture was used directly for thermal safety analysis. Samples of PhMgCl and *i*-PrMgCl (10.0 mL, 20.0 mmol, both as commercial 2.0 M THF solutions) were used directly for safety analysis, while *i*-PrI (2.0 mL, 20.0 mmol) was dissolved in 10 mL of anhydrous THF, and the resultant solution was used for testing.

**Collection of Thermal Safety Data.** Experimental data were collected on an Advanced Reactive Systems Screening Tool (ARSST) manufactured by Fauske and Associates.[4] ARSST is a quasi-adiabatic instrument that works on the basis of the heat loss compensation principle. The basic component of the ARSST includes a spherical 10-mL glass test cell, its surrounding "bottom heater" jacket and insulation, thermocouple, pressure transducer, and a 350-mL containment vessel that serves as both pressure simulator and safety vessel. Tests are performed in the open test cell in closed containment. Nitrogen pressure in the containment vessel is used to suppress the boiling point of the sample. The sample temperature is measured by a thermocouple inside the test cell. A magnetic stir bar is placed inside the test cell and driven by an external magnetic stirrer. A key feature of the apparatus is its low effective heat capacity relative to that of the sample (low $\varphi$ factor). Thus, the heat released by chemical reaction goes to heat up the sample with negligible energy absorbed by the test cell itself. A fill tube is used to add the mixtures to the purged test cell. ARSST containment including the reaction cell was purged many times with nitrogen before introducing the reaction mixtures to the system by syringe through the fill tube. All ARSST data were collected with the use of a 2 °C/min temperature ramp. In all experiments 10 mL of reaction mixture was used.

## Supporting Information Available

Corresponding time−pressure plots for all of the above experiments and time−temperature plots for formation of Grignard reagents **7** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

Received for review July 20, 2006.

OP060145B