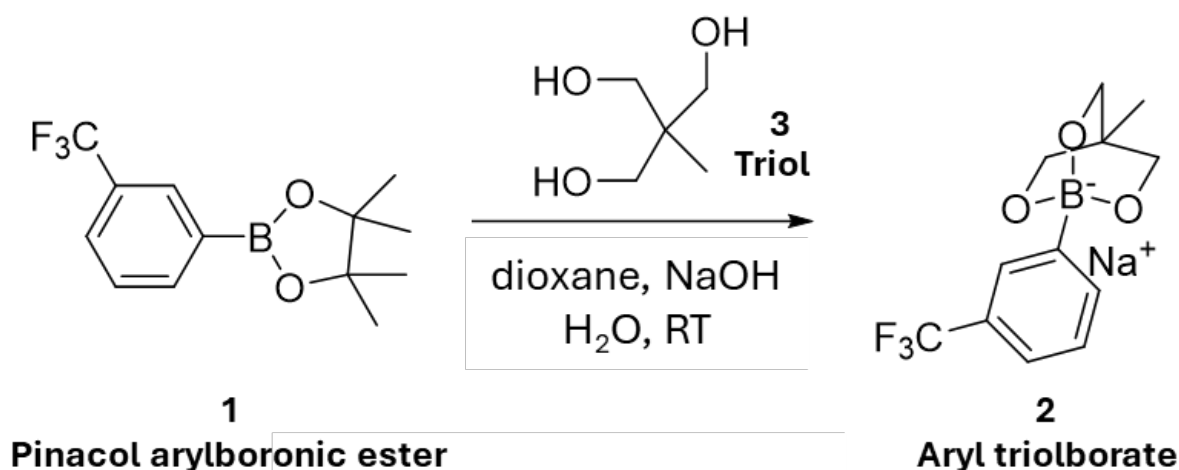


Transesterification of Pinacol Arylboronic Ester

How to monitor heterogeneous reactions online by benchtop NMR

A growing application for Spinsolve benchtop NMR spectrometers is reaction monitoring, where chemists can follow their reactions on-line and get real-time feedback about the reaction progress, observe short-lived intermediates, or detect other physical and chemical changes in the reaction mixture. The implementation of closed-loop sample transfer systems to follow chemical reactions with homogenous liquid mixtures has been described in previous Magritek applications notes ([Quantifying the Formation of Stereoisomers](#), [Optimising a Two-Step Hydrogenation Reaction](#)) and numerous journal papers. However, depending on the chemistry, the reaction mixture can change from homogeneous (all the species are in solution) to heterogeneous (presence of precipitation, or immiscible liquids). Monitoring heterogeneous mixtures with NMR is challenging due to the presence of solids or multiple phases in the samples, resulting in loss of spectral resolution (due to line broadening) as well as possible clogging of the transfer lines, which can hinder the sampling process and even cause safety issues.

In this application note we show how benchtop NMR can be used to determine precipitation events quantitatively while following the chemical reaction in real time. The key to keeping solids out of the transfer lines and preventing them from entering the NMR sensor, is to use adequate inlet or inline filters. The reaction selected for this study is the transesterification reaction of a pinacol arylboronic ester (Scheme 1), which can be simultaneously monitored by ^1H and ^{19}F NMR. We incorporated a HPLC solvent inlet filter (Idex Inlet Solvent filter 10 μM , for 1/8" OD, part number: A-302A) at the intake of a 1/8" PTFE tubing to prevent solids from entering the sample transfer system and the flow cell.



Scheme 1. Transesterification of a pinacol arylboronic ester to an aryl triolborate.

Experimental Setup

The reaction was carried out following the procedure outlined in Li *et al.* [1]. The flow-system was set up with the Spinsolve™ Reaction Monitoring Kit, which includes a glass flow cell and a peristaltic pump connected to the reaction vessel in a closed loop. The inlet tubing inside the reaction vessel was equipped with an Idex Inlet Solvent Filter 10 μm , for 1/8" OD. In the reaction vessel, a solution of a pinacol arylboronic ester (**1**, 200 mM), 1,1,1-tris(hydroxymethyl)ethane (**3**, 200 mM), NaOH (200 mM) in a mixture of regular (protonated) 1,4-dioxane (80 mL) and water (0.85 mL) was stirred at ambient temperature. The reaction mixture was circulated continuously through the instrument with a flow rate of 0.6 mL/min and monitored for 24 hours. The use of regular solvents dioxane and water requires effective suppression of the solvent peaks for accurate quantitation of the analytes. One-dimensional ^1H with WET solvent suppression and 1D ^{19}F data were simultaneously collected and analyzed easily with the RMX interface in the Spinsolve software. Each 1D ^1H spectrum was acquired in 14 seconds, whereas each 1D ^{19}F spectrum was acquired in 10 seconds.

As seen in Fig. 1, at the beginning of the reaction (left), all the starting materials dissolved completely resulting in a clear, homogeneous mixture. Towards the end of the reaction, white solid precipitation was present in the reaction flask. There was no clogging observed in the transfer line and no resolution loss (line shape degradation), which was an indication that the Idex Inlet Solvent Filter was sufficient for preventing any particles from getting into the transfer line, and subsequently the glass flow cell.

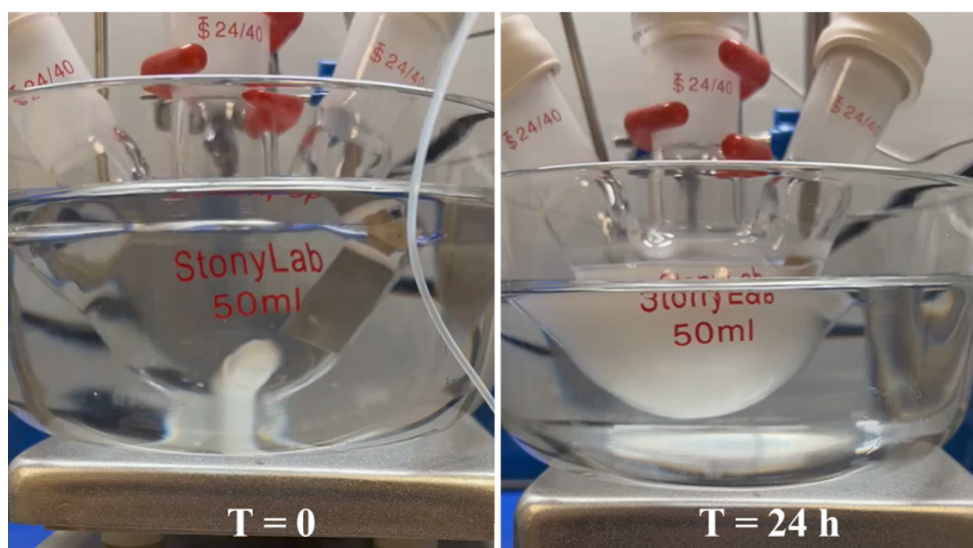


Figure 1. Appearance of the reaction mixture at the beginning and end of the reaction.

NMR Results & Discussion

The 1D ^1H spectra of the pinacol arylboronic ester **1** in 1,4-dioxane/water with and without solvent suppression are shown in Figure 2. The WET solvent suppression was implemented along with ^{13}C decoupling to attenuate the 1,4-dioxane signal and collapse its ^{13}C satellites to afford a clean baseline in this region. The singlet at 1.28 ppm corresponds to the 4 methyl groups of compound **1**.

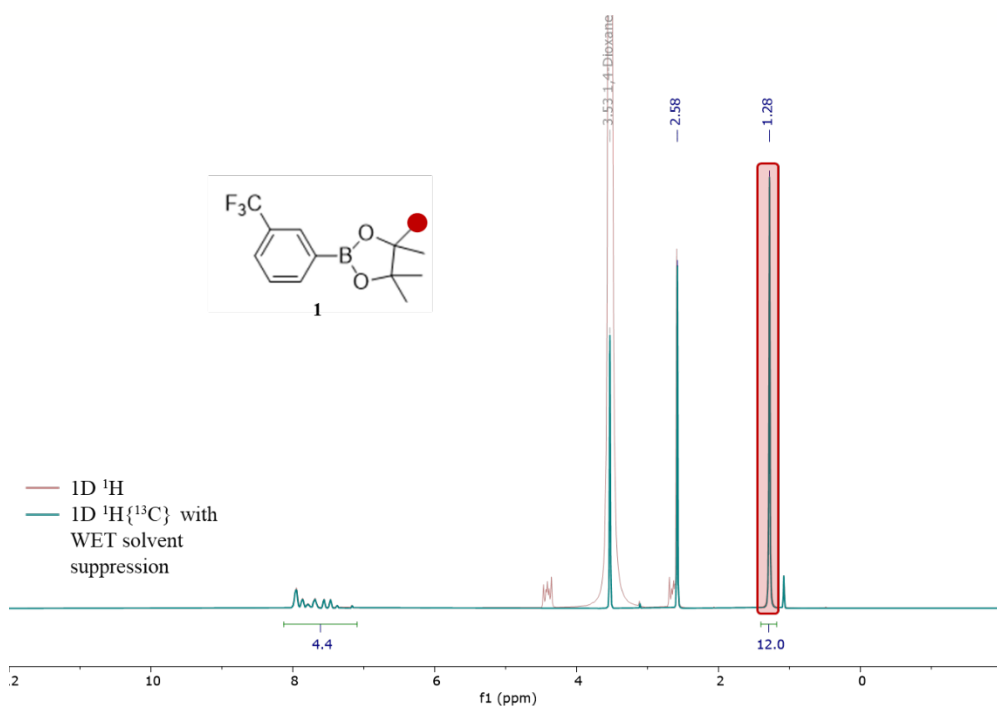


Figure 2. Superimposed 1D ^1H NMR spectra of the pinacol arylboronic ester **1** without (red) and with WET solvent suppression and ^{13}C decoupling (teal).

Figure 3A shows the superposition of 500 1D ^1H spectra with WET solvent suppression in the region between 1.7 and -0.2 ppm. This narrow region consists of signals from methyl groups in different species, from starting reagents, to intermediates and then final products that are cleanly resolved to allow for the simultaneous monitoring of these compounds. The integral values of different signals were converted to concentration (mM) in the concentration vs. time plot (

Figure 3B) through a calibration factor determined before the start of the reaction. The concentration of the pinacol arylboronic ester **1** (red) quickly decreased, whereas the concentration of the other starting reagent, triol **3** (green), showed a slower rate of decrease. At least one intermediate can be observed (purple) where its concentration increased during the first 3 hours of the reaction before decreasing throughout the rest of the reaction progress.

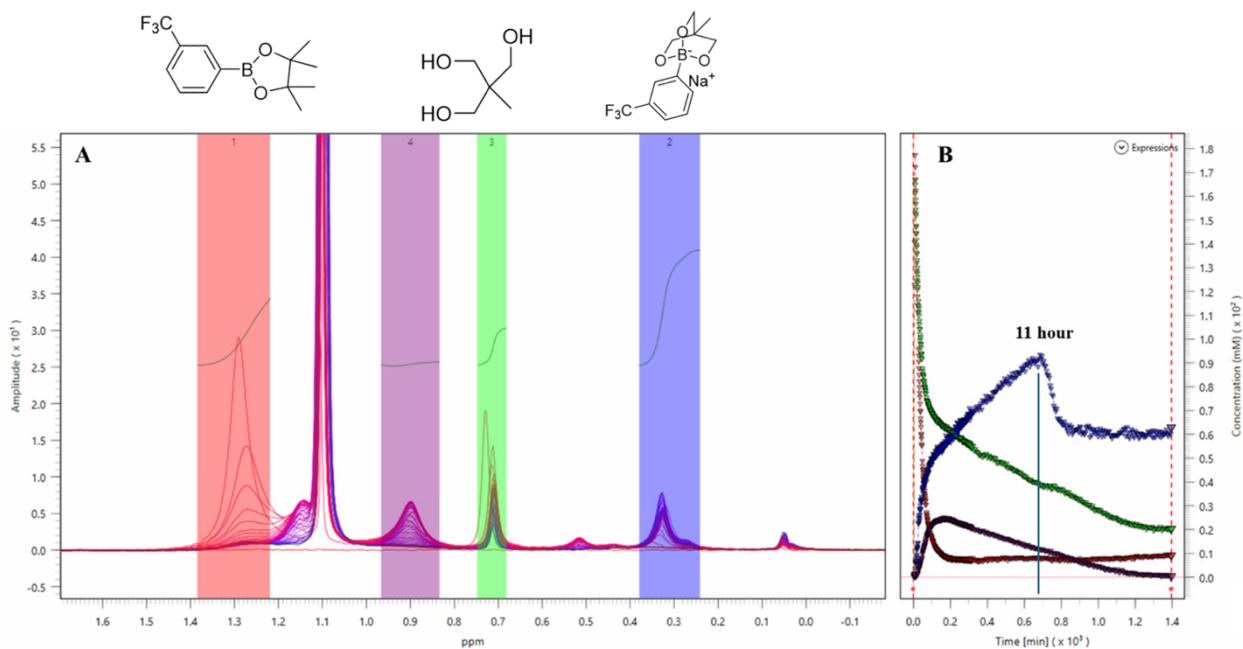


Figure 3. A) Superimposed 1D ¹H NMR spectra recorded during the reaction progress. B) Concentration vs. time plot.

The final product, the aryl triolborate **2** (blue), shows an interesting kinetic profile. Its concentration increases steadily until the reaction reaches the 11-hour mark. A sharp drop in concentration was observed from 95 mM to 60 mM, and it plateaus at this concentration for the remainder of the reaction process. At the 11th hour mark of the reaction, white solid starts to appear in the reaction flask as aryl triolborate **2** starts to crash out from the reaction mixture. While the concentration of **2** remains constant for the rest of the reaction, the concentrations of triol **3** (green) and intermediate (purple) continue to decrease. This suggests that the concentration of **2** reaches an equilibrium where the rate of precipitation is the same as the rate of production.

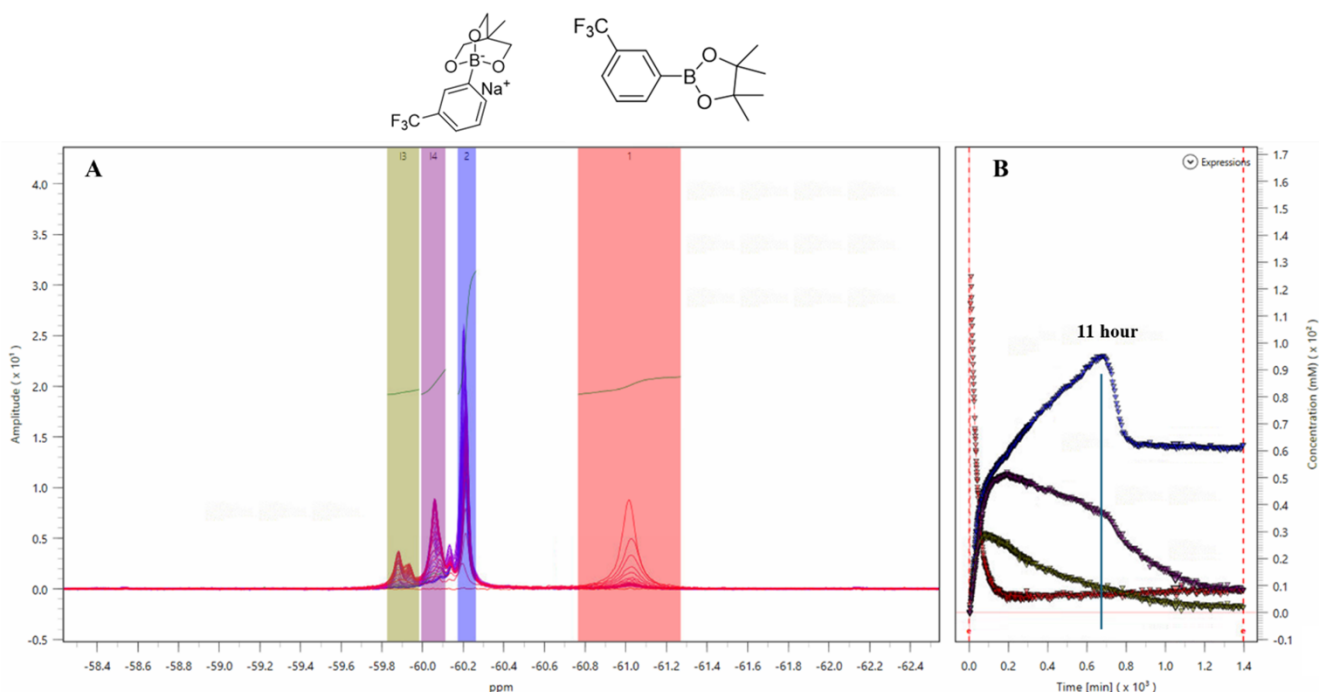


Figure 4. A) Superimposed 1D ¹⁹F NMR spectra recorded during the reaction progress. B) Concentration vs. time plot

The 1D ^{19}F data shows a similar trend observed with 1D ^1H data in Fig. 4. The starting reagent **1** can be followed by the signal at -61 ppm. The final product aryl triolborate **2** (blue) signal appears at -60.2 ppm, with the same kinetic profile as 1D ^1H data where a sharp drop in concentration is observed at 11th hour of the reaction. The other signals in the spectra correspond to different intermediates which are produced at the beginning of the reaction, but then used up towards the end of the process.

Conclusion

Overall, the monitoring of the synthesis of an aryl triolborate with a Spinsolve benchtop NMR gives rich insight into the mechanism of the reaction. Multiple intermediates were observed in both ^1H and ^{19}F spectra with great resolution and reliable quantitation. This suggests that the reaction proceeds through a complex mechanism which involves intermediate steps with different kinetic properties. Beside mechanistic insights, monitoring a process with NMR also enables the detection of different events regarding the physical appearance of the reaction mixture. In this reaction, the precipitation of the final product is reflected in its change in concentration. Finally, this example also highlights the successful sampling of a heterogeneous reaction by the incorporation of an inlet filter. The reaction was monitored for 24 hours without any clogging to deliver reliable and high-quality NMR data.

References

1. Gao-Qiang Li, Shunsuke Kiyomura, Yasunori Yamamoto, Norio Miyaura, Direct Conversion of Pinacol Arylboronic Esters to Aryl Triolborates, *Chemistry Letters*, Volume 40, Issue 7, July 2011, Pages 702–704, <https://doi.org/10.1246/cl.2011.702>