On-line Monitoring of a Heterogenous Reaction Using the Axcend InFocus™ Automated Sampler and Axcend Focus LC®

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Abstract

On-line sampling and analysis of heterogenous reaction mixtures is a critical application of modern process analytical technology (PAT). This application note describes the monitoring of a heterogenous Suzuki coupling reaction using the compact Axcend InFocus™ sampling system coupled to the Axcend Focus LC®, all contained within a standard chemical fume hood. Over the course of the 3-h reaction, samples were taken every ~18 min for the first 1.5 h, and every ~30 min for the second 1.5 h. This process consumed a total of 333 µL of reaction mixture, representing <1% of the 50-mL reaction volume. The solid catalyst was captured using an in-line filter during sampling, which was subsequently flushed back into the reaction vessel. If desired, the system could be operated to collect the catalyst in a separate vessel.

Introduction

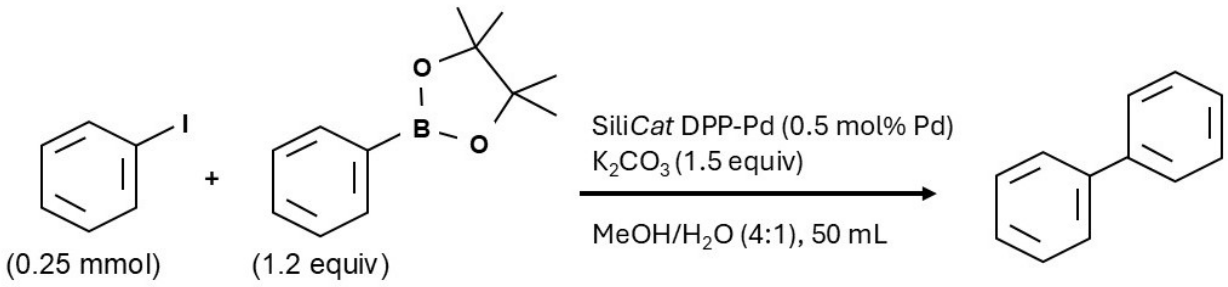
On-line reaction monitoring is a critical PAT that enables automated periodic sampling and analysis of a reaction vessel to provide insights into reaction progression, product/impurity formation, and experimental optimization. For bench-scale reactions in which reaction volumes are small, sampling volumes must be kept to a minimum to avoid impacting the reaction conditions and consuming excess product. Additionally, the analytical instrumentation must be located near the reaction vessel to limit dilution due to Taylor dispersion and changing reaction conditions that occur during transfer

in the sampling lines. Compact capillary-scale reaction monitoring LC systems have previously been used for monitoring homogenous reactions over hours or days requiring only microliters of sample.[1]

Frequently, reactions are conducted in heterogenous mixtures containing solid catalysts, precipitates, or solid salts. For these reactions, on-line monitoring requires filtration before analysis. Using the Axcend InFocus system, samples can be withdrawn in microliter sized aliquots, filtered, and delivered online to the LC for analysis. After sampling, the filter can be rinsed to reclaim trapped catalyst and to prevent clogging. To demonstrate the capabilities of the combined Axcend sampling-LC system, a heterogenous Suzuki coupling reaction was selected as relevant to both pharmaceutical and material science industries. The reaction was sampled every ~18 min for 1.5 h and then every ~30 min for an additional 1.5 h, consuming a total of 333 µL of sample. The use of compact, capillary-scale instrumentation for heterogenous reaction monitoring allows for automated analysis of bench-scale reactions while considerably limiting the sample and solvent consumed during the process.

Materials and Methods

A Suzuki coupling reaction between iodobenzene and phenylboronic acid pinacol ester was performed using a diphenylphosphine palladium (II) catalyst (Sili*Cat* DPP-Pd) bound to ~100 µm particles as shown below:



The reaction was sampled using the InFocus sampling system fitted with a 47 cm long 250 µm inner diameter (i.d.). sample line (~23 µL volume). Samples were taken every ~18 min for the first 1.5 h, and every ~30 min for the subsequent 1.5 h. Samples (60-µL aliquots) were withdrawn from the reaction mixture through a 0.5-µm filter before filling the LC injection loop. After injection, the filter was flushed with 100 µL of methanol (MeOH) back into the reaction mixture, returning the catalyst and allowing heterogenous reaction sampling without rapidly clogging the filter.

Chromatographic Conditions:

Column	Waters 150 mm x 0.3 mm ID, 1.8 µm particles, NanoEase HSS T3
Mobile phase	A) Water with 0.1% trifluoroacetic acid (TFA) B) Acetonitrile with 0.1% TFA
Gradient	70% B to 80% B over 10 min
Flow rate	4 µL/min
Injection volume	20 nL
Temperature	Ambient
UV-absorption detection wavelength	255 nm

Results and Discussion

To follow this reaction, three UV-active chromatographic peaks were monitored: two reactants (iodobenzene and phenylboronic acid pinacol ester) and one product (biphenyl). Overlaid chromatograms taken across the duration of the reaction are shown in Figure 1. Excellent resolution was obtained for all three compounds in under 10 min. By plotting the peak area percentages of both the products and reactants, reaction progression and kinetics can be studied. The reaction progression plot for this study is shown in Figure 2. These results demonstrate the ability to automate the monitoring and optimization of synthesis conditions while limiting sample consumption and waste generation.

The required sampling volume depends heavily on several factors and must be tailored to the specific monitoring setup. The sampling line length should be no longer than needed to reach the reaction vessel, and the inner diameter of the line must be somewhat larger than the expected particulate size to avoid pressure buildup and eventual clogging in the line. Additionally, high particulate concentrations may require larger than typical rinse volumes to minimize the potential for blockage. For this reaction, 60 µL volumes of sample were withdrawn through a 23 µL sample line to provide 37 µL of sample. The remaining volume was returned to the reaction flask. Therefore, while a total of 540 µL of sample was withdrawn from the reaction flask during the reaction, only 333 µL of sample was consumed during the process. Additionally, all solid catalysts could be reclaimed and returned to the reaction vessel or collected for reuse in future reactions.

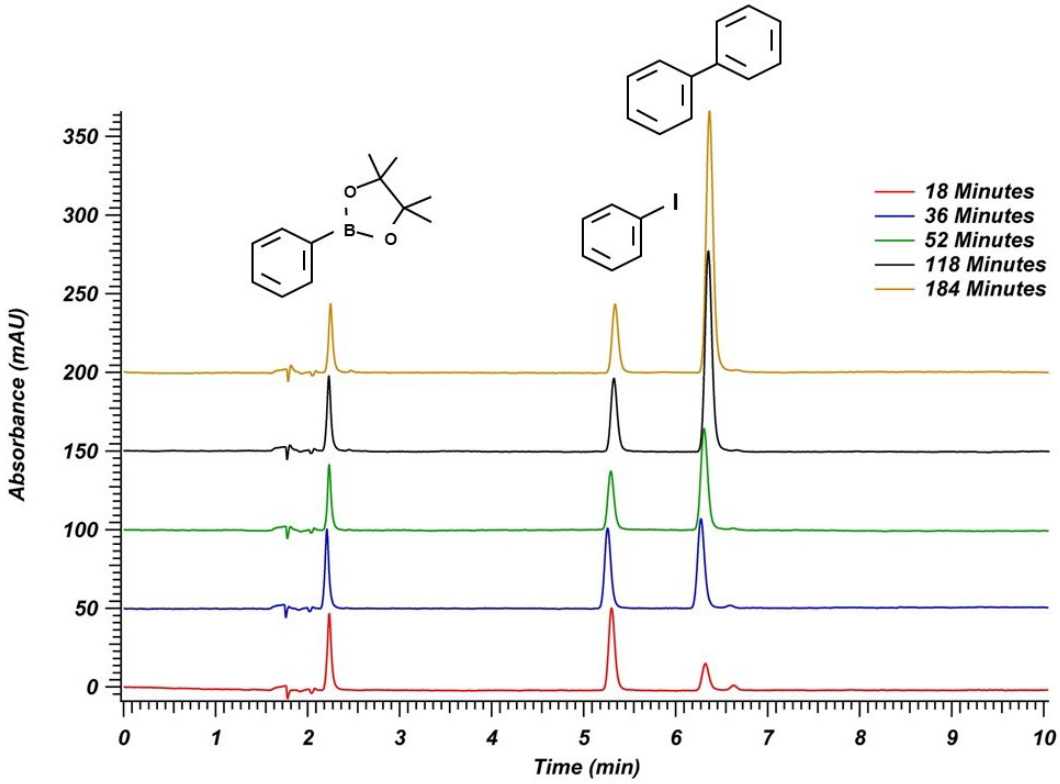


Figure 1. Chromatograms of a Suzuki coupling reaction taken across the duration of the reaction (offset by 50 mAU). The elution order is phenylboronic acid pinacol ester, iodobenzene, and biphenyl.

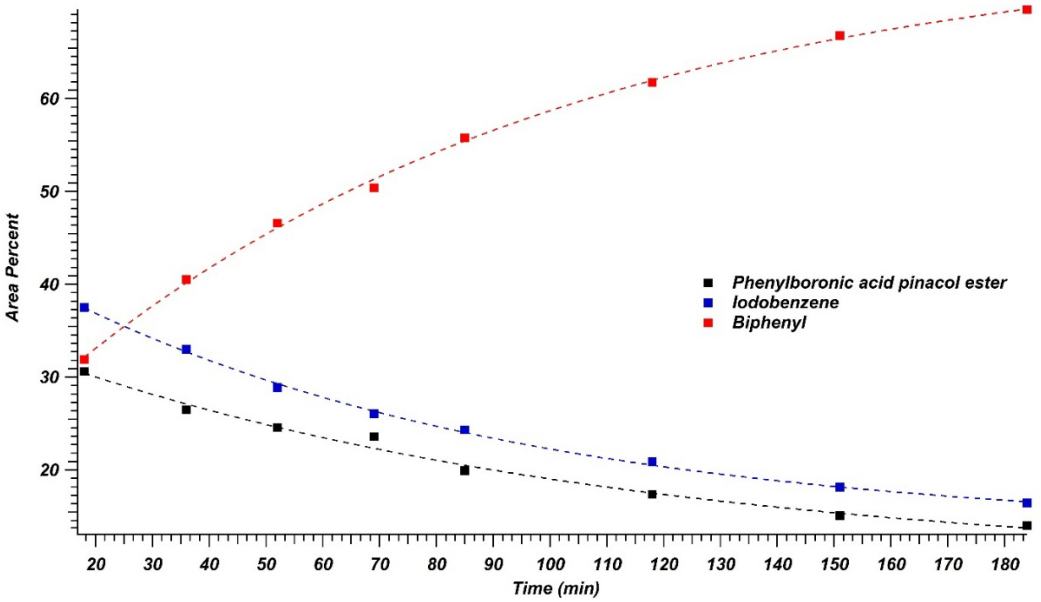


Figure 2. Monitoring reaction progression using area percentage of reactants and product.

Conclusions

On-line reaction monitoring of heterogenous mixtures requires filtering of particulates during sampling and regeneration of the filter to ensure repeatable sampling. In this application, a heterogenous Suzuki coupling reaction using a solid palladium catalyst was performed. Over the course of the 3-h reaction, a total of 333 µL of reaction volume was consumed, representing <1% of the initial reaction volume. The InFocus sampling system coupled to the Axcend Focus LC demonstrated successful automated, repetitive analysis of a heterogenous reaction mixture.

Reference

(1) Foster, S. W.; Xie, X.; Hellmig, J. M.; Moura-Letts, G.; West, W. R.; Lee, M. L.; Grinias, J. P. Online Monitoring of Small Volume Reactions Using Compact Liquid Chromatography Instrumentation. SEPARATION SCIENCE PLUS 2022, 5 (6), 213–219. DOI:10.1002/sscp.202200012.