Kinetics of a C-H Activation Reaction
Sampling Air-Sensitive Reactions

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Based on studies by **Brian Vanderplas** and **David Place, Pfizer**

Understanding the kinetics profile and mechanism of impurity formation to assign an end-point to maximize yield and reduce undesired impurities.

Sampling this C-H Activation reaction is particularly difficult as it is air-sensitive. Introduction of 5000 ppm of oxygen into the reactor headspace stalls the reaction and results in a 50 % increase in reaction time. Samples exposed to air during the sampling process, before reactive species are quenched, are altered and their associated data reflects this change. The aim of this experiment was to study the kinetics profile, mechanism of impurity formation, and assign a reasonable end-point for the C-H activation reaction. Automated *in situ* sampling with EasySampler was applied to gain representative samples from the reaction, without introducing air into the reactor headspace or the sample before quenching reactive species. In addition, the unattended sampling by EasySampler offered the advantage of sampling the long reaction over a 24 hour period in order to determine the time and mechanism of impurity formation.
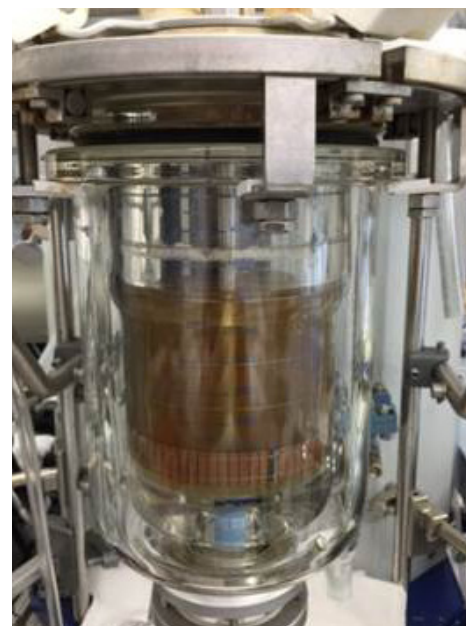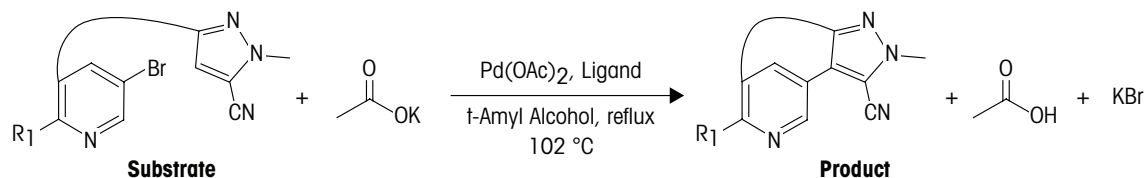

Figure 1. Air-sensitive palladium catalyzed C-H Activation sampled with EasySampler

The C-H activation reaction with a palladium catalyst was run in the presence of potassium acetate in an RC1 reaction vessel (Figure 1). Using EasySampler, twelve samples were acquired over a 24 hour period and analyzed by UPLC.
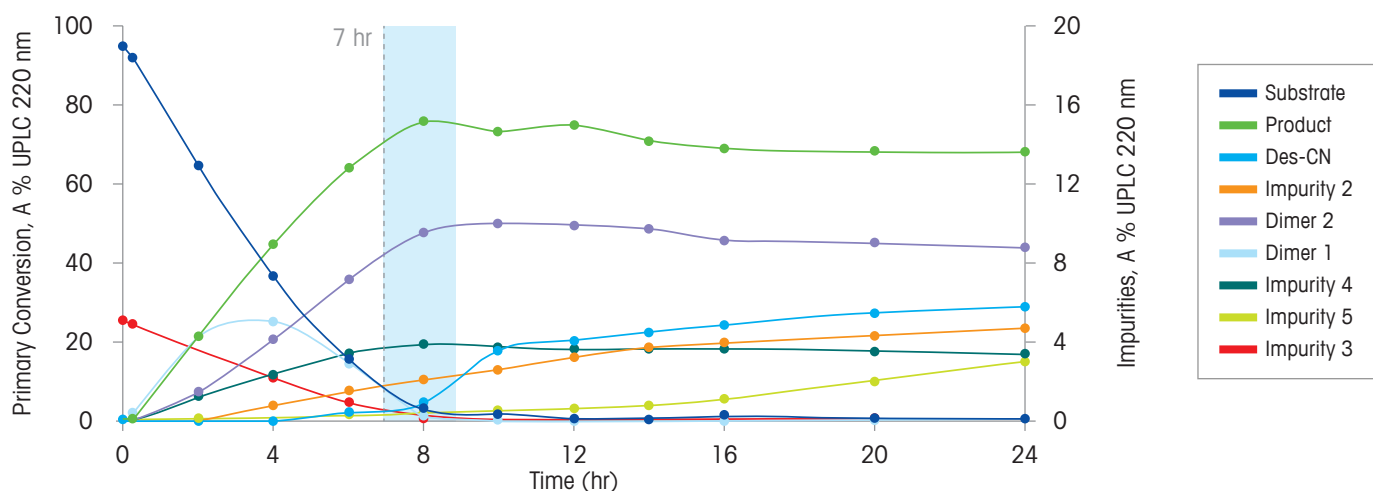

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Figure 2. Reaction profile of C-H activation reaction gained by UPLC analysis of representative samples acquired by EasySampler over 24 hours

Results

From a single experiment, the complete reaction profile was achieved by sampling over 24 hours (Figure 2). The primary conversion and low-level impurity profiles provide insight into the interconnectivities of the impurities observed in the mixture, and especially highlight the need for a tight reaction cycle time. The reaction profile shows that when the product reaches a maximum conversion at approximately 7 to 8 hours, the undesired Des-CN impurity suddenly forms. This impurity cannot be removed easily in subsequent work-up and reaction steps, and should be avoided.

Conclusions

Based on the information in the reaction profiles achieved using the automated representative sampling capabilities of EasySampler, researchers were able to quickly implement in-process controls to relate reaction time with primary conversion and impurity levels to quickly cool the reaction to 20 °C to avoid the Des-CN impurity formation, and maximize product quality.

EasySampler: Unattended, Representative Sampling

Difficult to Sample Reactions
Eliminate the risk of exposing samples and the reaction to air to ensure representative reaction samples for accurate analytical data.

Representative and Reproducible
Sample reactions in the same way, and into a pocket of fixed volume for highly reproducible samples.

Automated and Unattended
Continued unattended sampling operations to gain a complete data set for the duration of the reaction, without affecting reaction progression.

EasySampler™

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