

# EasySampler™

Unattended, Representative Sampling of Chemical Reactions



La Calorimetria di Reazione  
per lo Sviluppo e la Sicurezza  
dei Processi Chimici  
Milano, 21 Ottobre 2015

**METTLER TOLEDO**

# All Chemical Reactions are Sampled



## Chemical reactions must be sampled to determine:

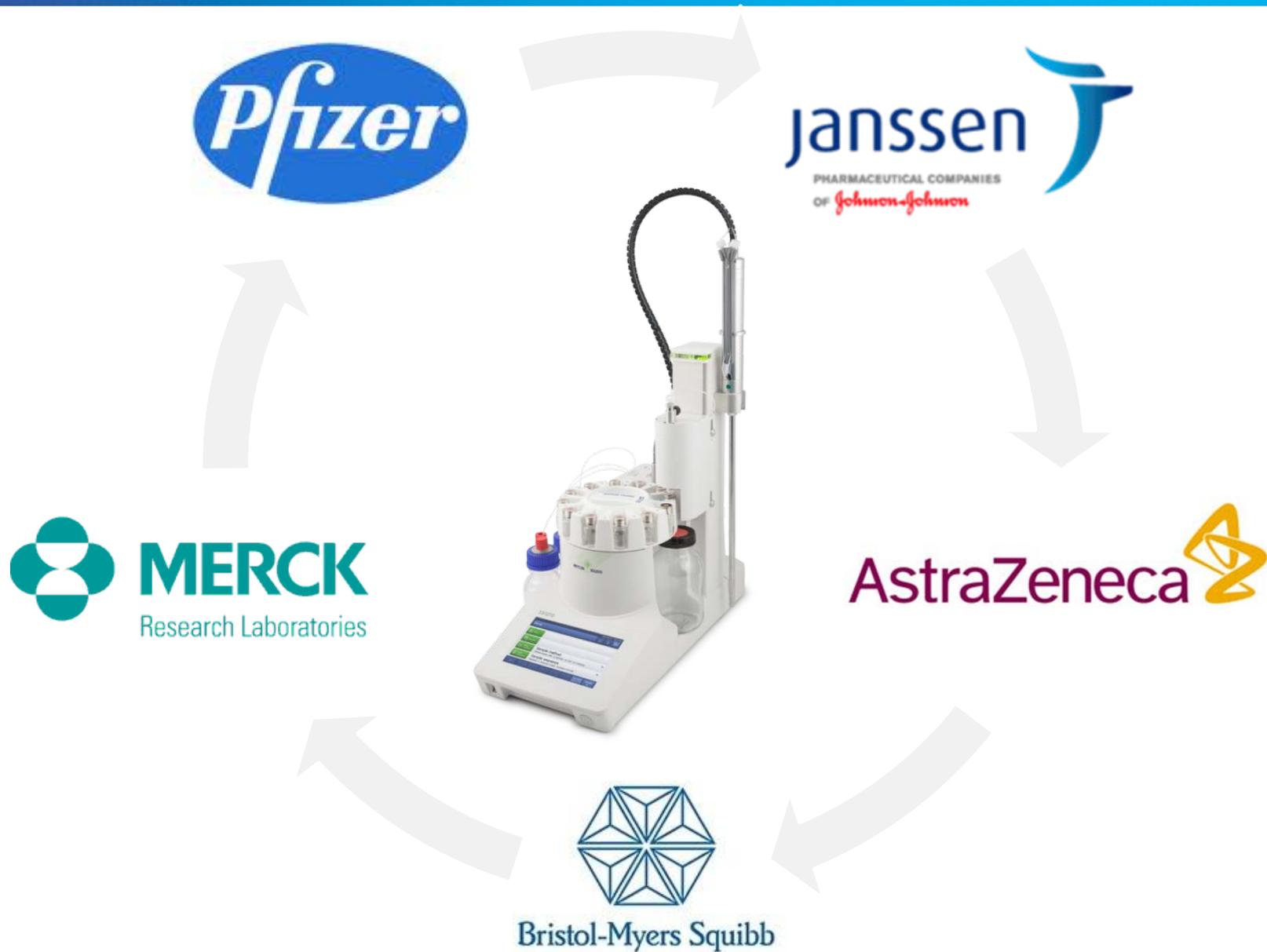
- conversion
  - yield
  - by-products
  - Impurities
- 
- Inline measurements (e.g. ReactIR™) for real-time process understanding
    - Enable real-time decisions
  - Offline measurements, HPLC and NMR are still the most commonly used analytical technologies for the Organic Chemist - sampling is needed

# Current Sampling Methods

- Sampling devices are based on Aspirating and Dispensing
  - "sucking in and blowing out"
- Manual Sampling
  - Pipettes and needles
- Automated Sampling
  - tubes/capillaries and needles
- Pull by market for advanced sampling technology



# Open Innovation Project



# EasySampler Eliminates Sampling Challenges

## Sampling Challenges

## EasySampler Solution

Human Error

- Automated sampling process
  - Same volume and sampling point in reactor

Sample only while chemist is available

- Unattended Sampling 24/7
  - Gain representative reaction information
  - Increase productivity
  - Sampling information is logged

Difficult to sample reproducibly and representatively

- Quench in place at reaction conditions for representation of reaction at the time of sampling

Aspiration causes clogging of tubing/capillary

- Reaction sample fills the pocket
  - Sample dissolves before moving through lines

Difficult and unsafe to sample (elevated temps, hazardous)

- Automated sampling process
  - Elevated temperatures and pressures
  - Samples hazardous reactions eliminating user safety risk

Dilution take place post-process

- Automated dilution of sample to desired concentration for HPLC / GC (or other offline) analysis

# Comparing Sampling Reproducibility

- **Challenge:**
  - Try to sample a solution manually 10 times
  - Can you get the same result each time?
  
- **Double the challenge:**
  - Try to do the same from a slurry
  - What do you need to do to ensure precise sampling?
  
- **"Now, which method do you feel most confident in using if you only get to sample once?"**

## Manual sampling compared with EasySampler

	<b>Homogeneous</b> Variability in Sampling Naphthalene	<b>Heterogeneous</b> Variability in Sampling Acetaminophen Slurry
<b>Micropipette</b> 	4 %	22 %
<b>Micropipette with Cut Tip</b> 	--	19 %
<b>Transfer Pipette</b> 	6 %	52 %
<b>Volumetric Pipette</b> 	10 %	61 %
<b>Syringe</b> 	46 %	37 %
<b>EasySampler</b> 	5 %	4 %

# Unattended, Representative Sampling



## Representative Samples

- Capture and immediate quench of reaction samples provides samples representative of the reaction
- Advantageous for low temperature and air-sensitive chemistry

Trust your data and make sound decisions



## Unattended 24/7

- Samples are taken at the touch of a button
- Sample sequences can be programmed for unattended continued sampling operations, day or night
- Gain representative reaction information
- Same volume and point of sampling in the reactor

Never miss a sample again



## Heterogeneous Reactions

- Sample slurry reactions with precision
- Capture reaction samples, including the solids, into a pocket of fixed volume
- Solids dissolution begins immediately, with quench and dilution
- Deliver a dissolved sample to the vial
- To gain precise and accurate analytical data.

Gain precise and accurate data



## User Safety

- Fully automated sampling includes quench, dilution and transfer of samples to vials
- Eliminates manual handling of liquids
  - ▶ highly toxic chemistry, or dangerous reactions at elevated temps and other hazardous reaction conditions

Eliminate safety risk

# Representative Samples

- Quench immediately at point of sampling
  - Sample is a representation of the reaction at the time of sampling
  - Air and moisture sensitive chemistry
  - Low temperature chemistry
- Sample at the same point every time
- Sample the same volume every time
  
- Reliable and reproducible results
  - Confidence in data
  - Reduce the number of experiments
  - Reduce costs



Trust in data for good decisions on reactions and processes

# Unattended 24/7

Sample reactions overnight or while chemist is unavailable

- ▶ Increase number of data points

Reproducible samples

- ▶ Reduce number of experiments
- ▶ Confidence in data

Immediate quench at reaction conditions for representative samples

Accurate sample information

- ▶ date, time, solvents, dilution factor

Eliminate Human error

Save time by reducing steps necessary to prepare sample for offline analysis



**Increase productivity and confidence in data**

# Heterogeneous Chemical Reactions

- Sample slurry reactions with precision
  - Capture reaction samples, including the solids, into a pocket of fixed volume
- Deliver a dissolved sample to the vial to gain precise and accurate analytical data
- Eliminate the frustration of clogged needles and capillaries



Reliably and robustly sample slurry reactions

# User Safety

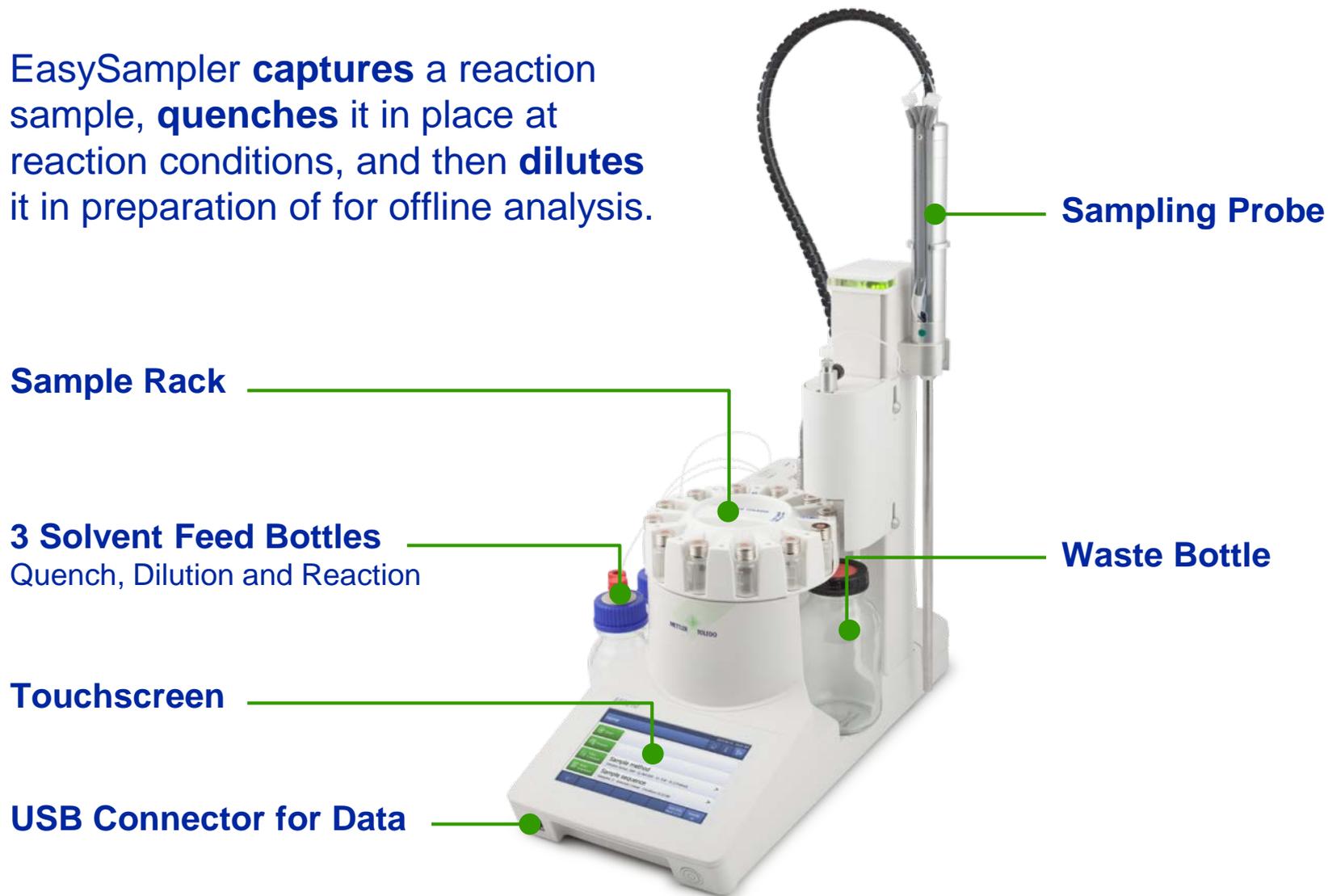
- Fully automated sampling includes quench, dilution & transfer of samples to vials
- Eliminate manual handling of
  - liquids
  - highly toxic chemistry
  - dangerous reactions at elevated temperatures
  - other hazardous reaction conditions



**Eliminate health and safety risks associated with sampling chemical reactions**

# EasySampler 1210

- EasySampler **captures** a reaction sample, **quenches** it in place at reaction conditions, and then **dilutes** it in preparation of for offline analysis.



# EasySampler 1210

## Automatic Sample Preparation

Liquid handling system allows quench, dilute and clean.

## EasySampler 1210

12 x 10 mL vials. Samples are diluted to the specified concentration.

## 3 Solvent Feed Bottles

Reaction, Quench and Dilution solvents.

## Touchscreen

Controlling pre-programmed sampling operation.

## USB Connector for Data

Data sampling transfer to USB stick.

## Sampling Probe

Capable of taking 95% of all desired samples.

## Connectivity Kit

Optional kit to integrate process data with EasyMax, OptiMax or RX-10 data

## Waste Bottle

500 mL waste bottle.



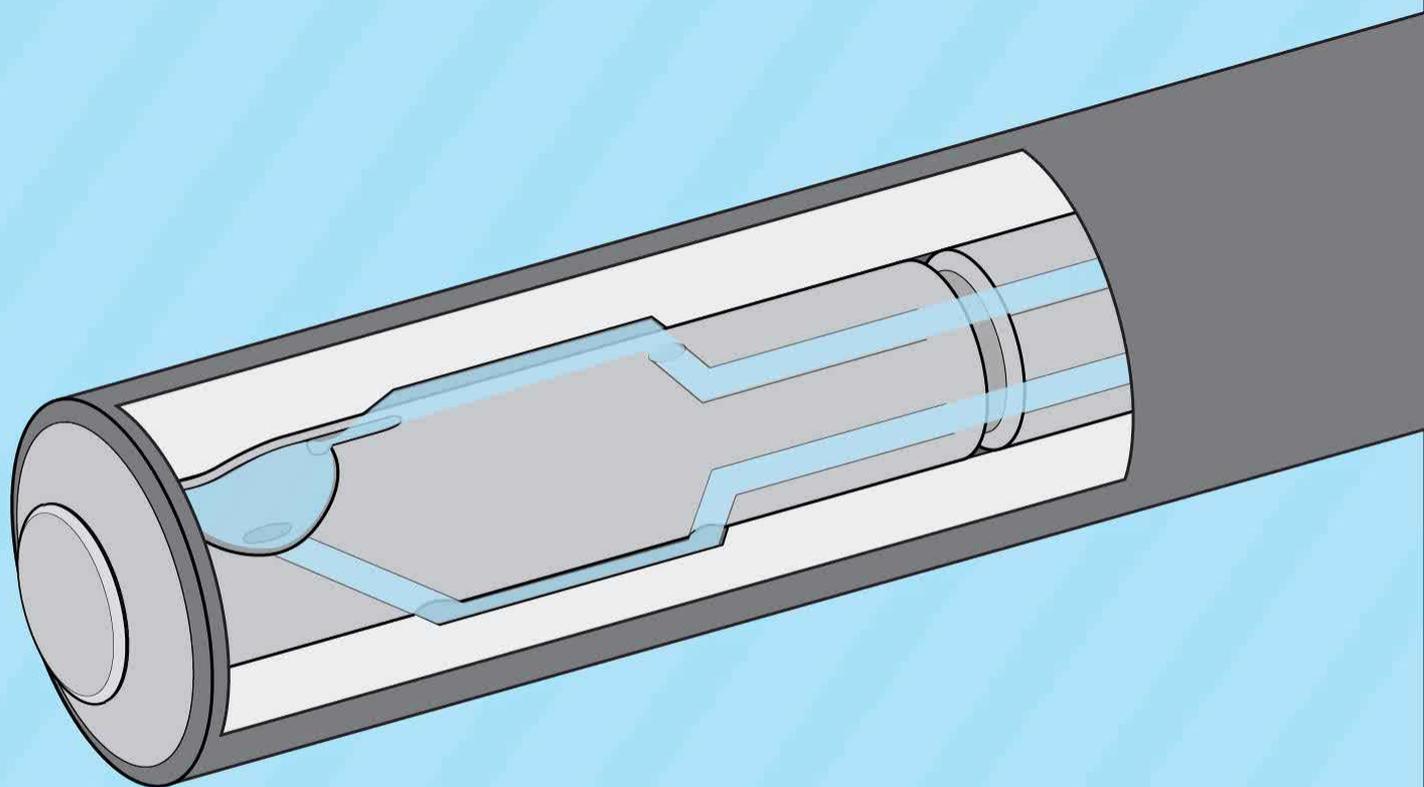
# Probe – Basis for EasySampler Technology

- Patented technology
  - US 20120141338 A1 (POCKET SHAPE)
  - US 8789431 B2 (method of capturing)
  - US 8312780 B2
  - US 20110314900 A1
  - US 20130074581 A1
- Captures a samples of fixed volume of  $20\mu\text{l} \pm 10\%$
- Enables quenching of the sample, immediately and in place
- Enables dilution of sample in preparation for offline analysis



It is the probe technology that makes EasySampler so unique

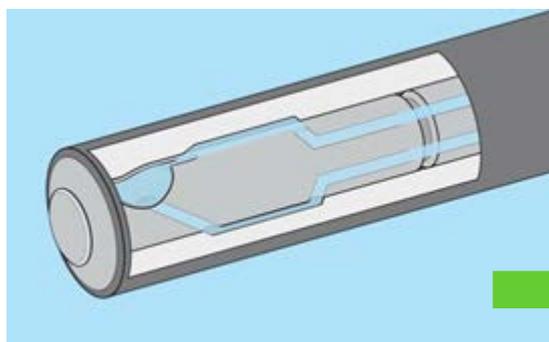
# Sampling Technology



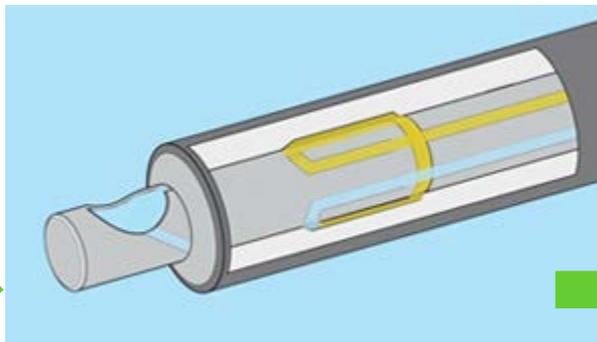
**Reaction solvent fills the lines and  
EasySampler is ready to take a sample.**

[www.mt.com/EasySampler](http://www.mt.com/EasySampler)

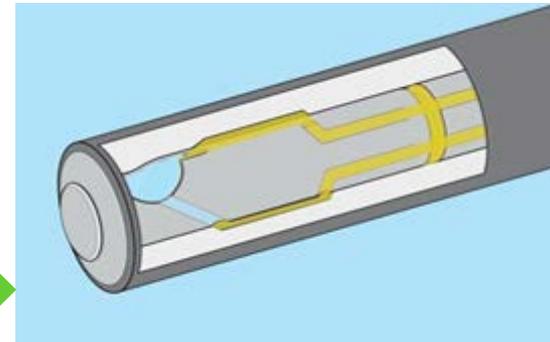
# Sampling Technology



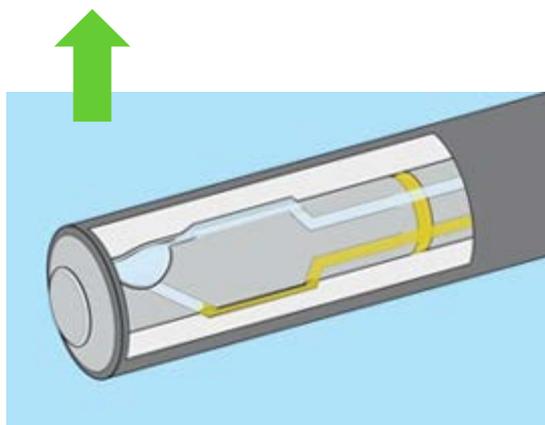
Reaction solvent fills the lines and EasySampler is ready to take a sample



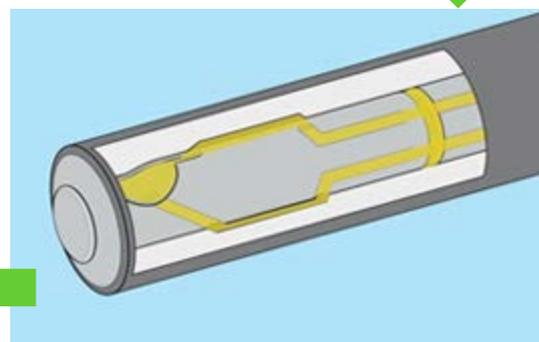
To take a sample, the pocket moves out and reaction mix fills the pocket while quench fills the lines



As the reaction sample is drawn in, quench is in place at reaction conditions



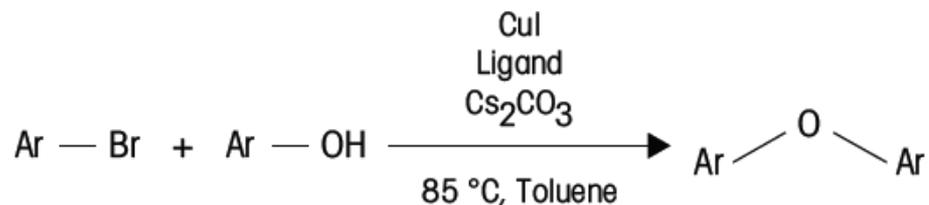
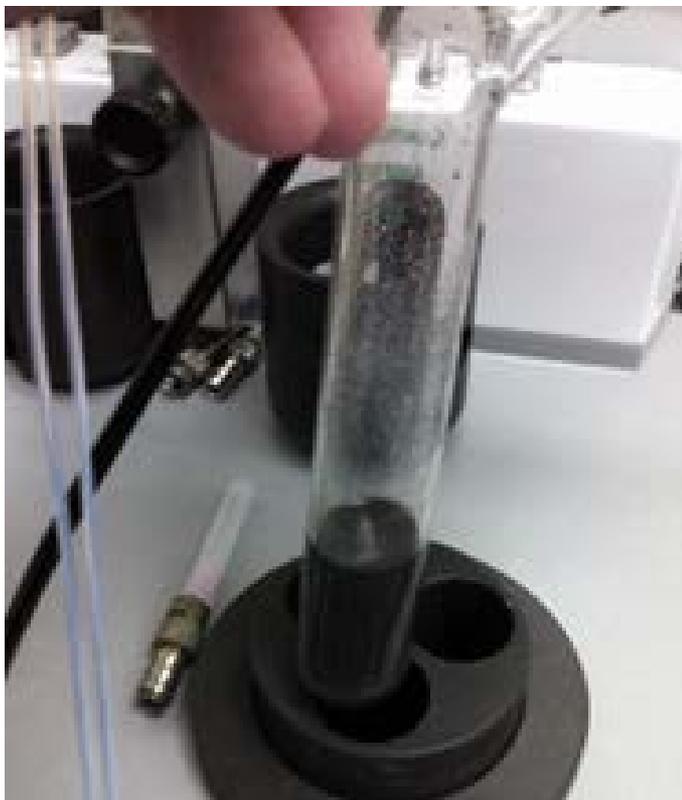
Quenched sample is diluted to a specified concentration by a solvent of choice, and dispensed into a vial, ready for offline analysis



Sample is quenched by back and forth pumping / oscillation

# Removing Barriers for Impurity & Kinetics Profiling

## ■ Ullman Reaction



Easy

Difficult



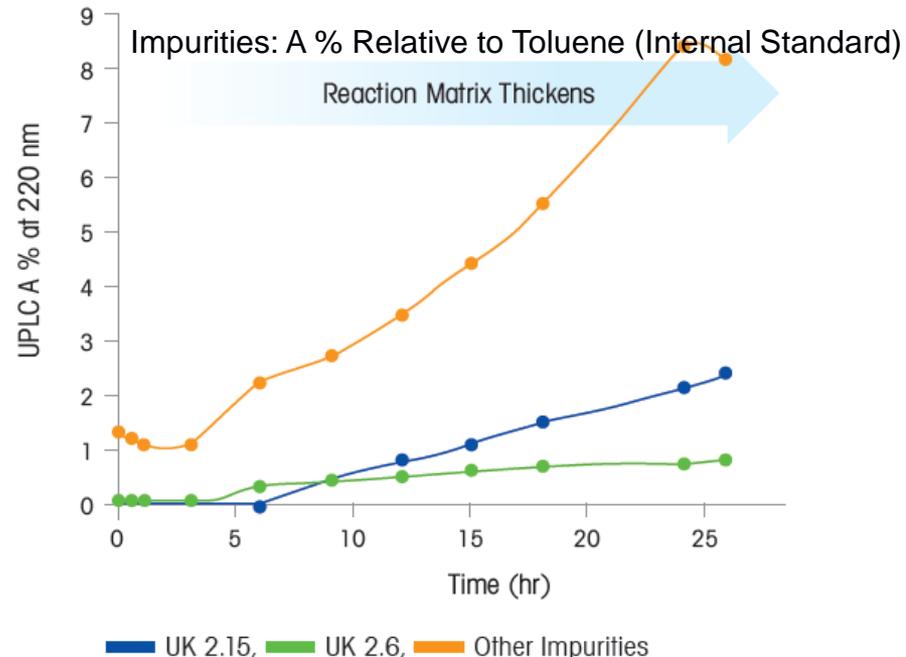
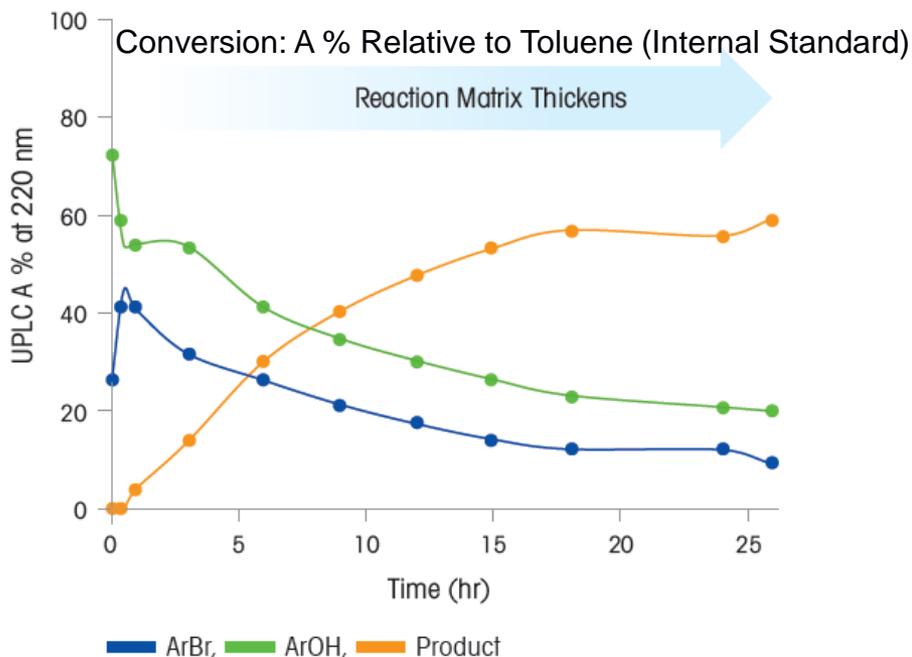
- Reaction Conc.: ~125 mg/mL
- Temperature: 85 °C
- EasySampler Settings:
  - Q,D = 1 v/v% water in DMSO
  - R = Toluene

- Consistency changes over the course of the reaction
- Dark reaction makes it difficult to see what is being sampled
- Known insolubilities of certain reagents in the reaction mix
- Sampling needed to occur over 30 hrs, overnight

# Removing Barriers for Impurity & Kinetics Profiling

## Results

- UPLC results of the Ullman Reaction.
- Samples were obtained by EasySampler, including during overnight hours.
- Product formation stalls after 18 hours
- Impurity formation continues through the course of the reaction



Accurate kinetic and impurity profiles as well as end-point information can be collected using EasySampler, even when away from the lab

# For More Information



[www.mt.com/EasySampler](http://www.mt.com/EasySampler)