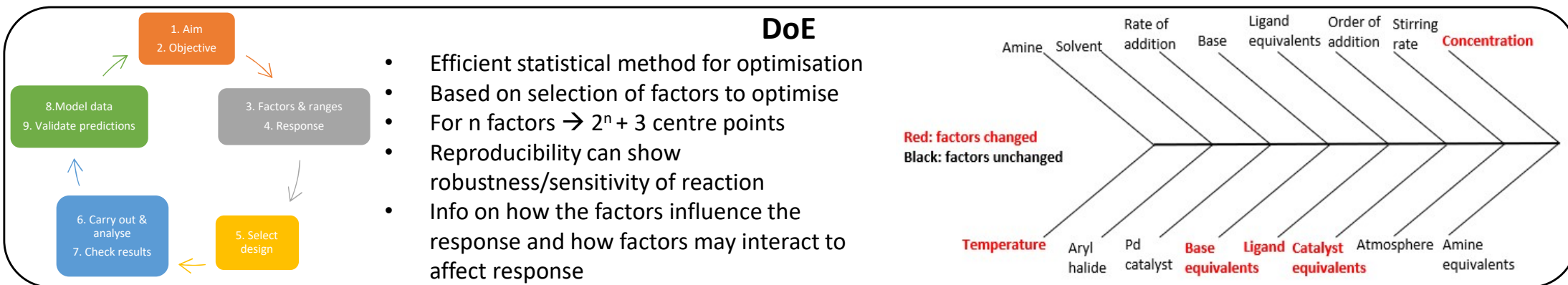# Synergy of Automated Synthesis & Design of Experiment
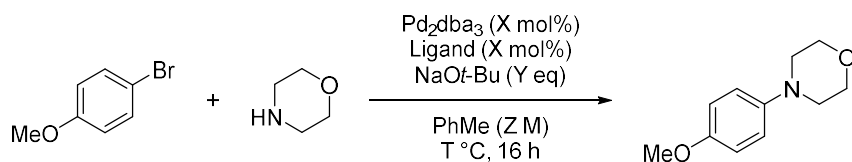
A. Dean, C. Cope, C. Harris, F. de Courcy-Ireland, J. Heeb, J. Heeley, M. Jesani, J. Jiang, V. Juba, B. Banecki

## Introduction

Optimisation of solution yield for a Buchwald–Hartwig amination using Design of Experiment MODDE Software, Chemspeed platform and LCMS for analysis

## DoE

- Efficient statistical method for optimisation
- Based on selection of factors to optimise
- For n factors → $2^n$ + 3 centre points
- Reproducibility can show robustness/sensitivity of reaction
- Info on how the factors influence the response and how factors may interact to affect response



Red: factors changed
Black: factors unchanged

Amine | Solvent | Rate of addition | Base | Ligand equivalents | Order of addition | Stirring rate | Concentration

Temperature | Aryl halide | Pd catalyst | Base equivalents | Ligand equivalents | Catalyst equivalents | Atmosphere | Amine equivalents

## Reaction



$Pd_2dba_3$ (X mol%)
Ligand (X mol%)
NaO$t$-Bu (Y eq)
PhMe (Z M)
T °C, 16 h

- Experiments conducted at high and low values of these factors to assess fringes of chemical space

| Factor | Limits |
|---|---|
| Cat. loading (mol%) | 1–5 |
| Ligand | XPhos, Xantphos |
| NaO$^t$Bu (eq) | 1.2–2.0 |
| PhMe (M) | 0.1–0.4 |
| Temperature (°C) | 80, 100 |

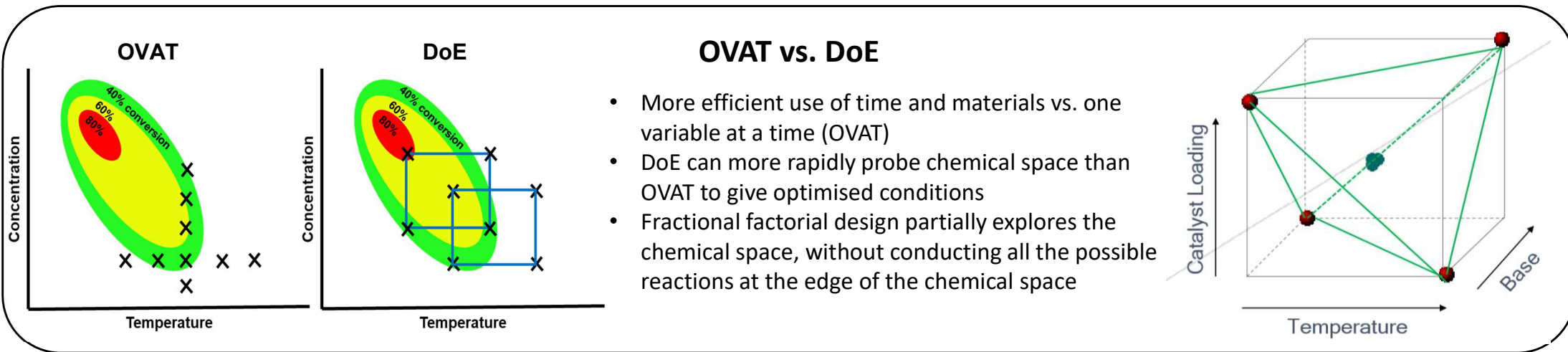**22 reactions for full DoE optimisation**

## Chemspeed

- Manual work required
  - Weighing out base as solid, stock solutions of reactants and catalyst/ligand
  - Programming` heating, stirring and sampling

- Automatic dispensing of stock solutions and sampling

- Inert atmosphere easily applied
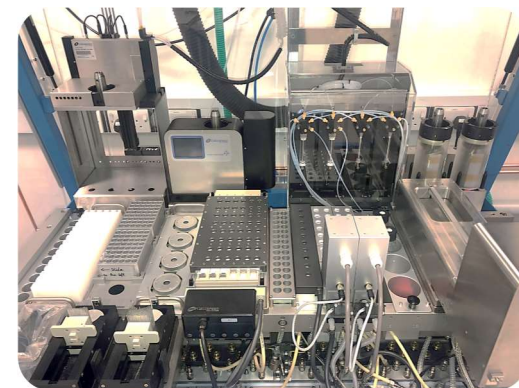


**All 22 reactions completed in 2 days**

# Synergy of Automated Synthesis & Design of Experiment

## OVAT

Concentration / Temperature

40% conversion
60%
80%

## DoE

Concentration / Temperature

40% conversion
60%
80%

## OVAT vs. DoE

- More efficient use of time and materials vs. one variable at a time (OVAT)
- DoE can more rapidly probe chemical space than OVAT to give optimised conditions
- Fractional factorial design partially explores the chemical space, without conducting all the possible reactions at the edge of the chemical space

Catalyst Loading / Base / Temperature

## Analysis

- Carried out using LCMS
- Aliquots taken at 1, 4, 16 h intervals
- Solution yield of product determined against an internal standard

Product / solvent / Aryl Bromide / Internal Standard
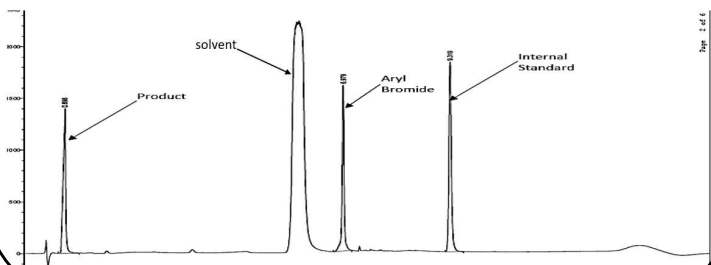
## Results

- Reaction showed a high dependence on catalyst loading and base equivalents

- MODDE produced a model that predicted optimal conditions of:

| Factor | Limits |
|---|---|
| Cat. loading (mol%) | 4.5 |
| Ligand | Xphos |
| NaO$^t$Bu (eq) | 1.7 |
| PhMe (M) | 0.35 |
| Temperature (°C) | 80 |

Base Equiv [equiv] / Catalyst Loading [mol %]
Temp [C] = 90
Temp [C] = 80
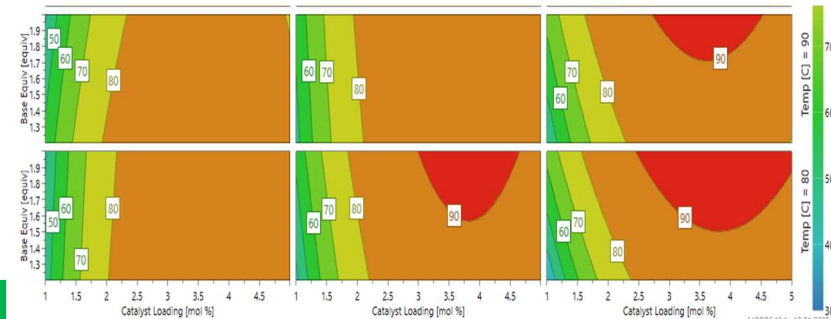
**Yield predicted: 92%**
**Yield observed: 89%, 82%**

## Summary

Full optimisation required 22 reactions over 2 days and predicted 92% yield; optimised conditions gave average of 86% yield