Design of Experiments: Optimisation of a Chan-Lam Coupling

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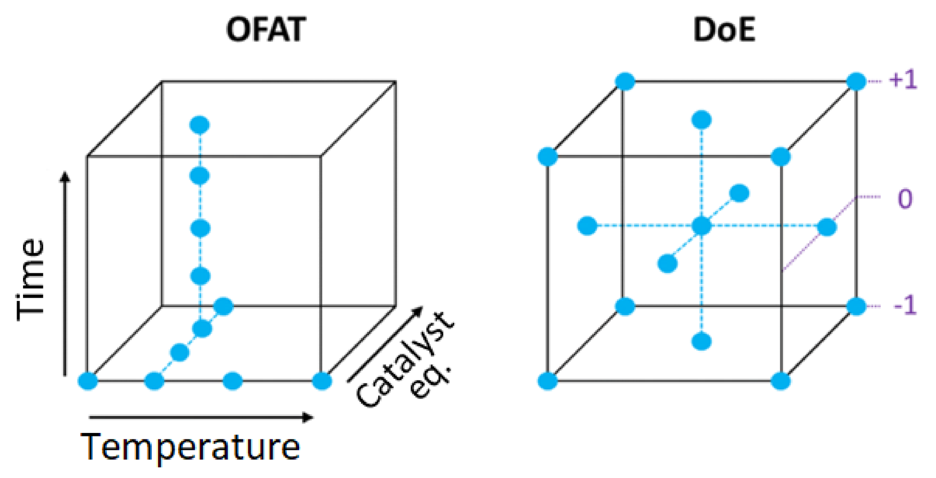
1 DoE and Background

Project Aims
Use of an automated reactor (Chemspeed) coupled with a design of experiments approach to optimise yield of Chan Lam coupling

Fractional Factorial Design
Economically investigates cause-and-effect relationships of significance in a given experimental setting

Design of Experiment > OVAT
- Effect estimates more precise
- Factor interactions identified
- More efficient
- Design orthogonality

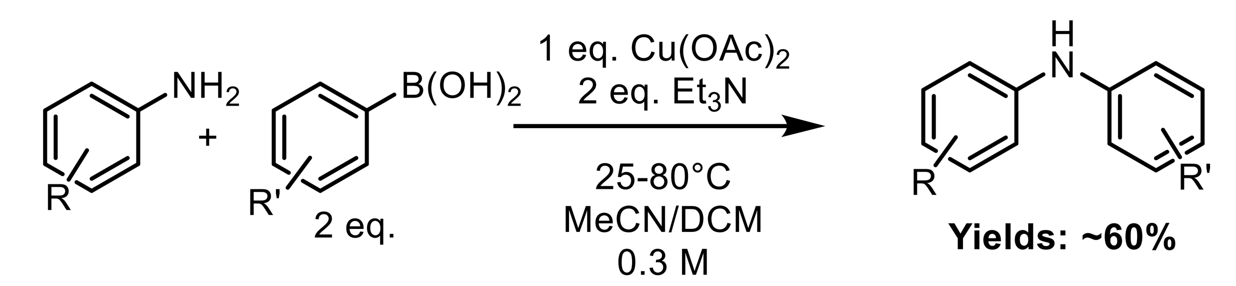


Chan-Lam Coupling Investigation
- Frac Fac Res IV: ¼ factorial design.
- 2 levels: high/low.
- 6 experimental factors to investigate
- 6 centre points to test validity and reproducibility.

Total number of experiments:
Fractional factorial design x (Levels ^{Factors})
+ centre points
$= ¼ * (2^6) + 6$
= 22 experiments

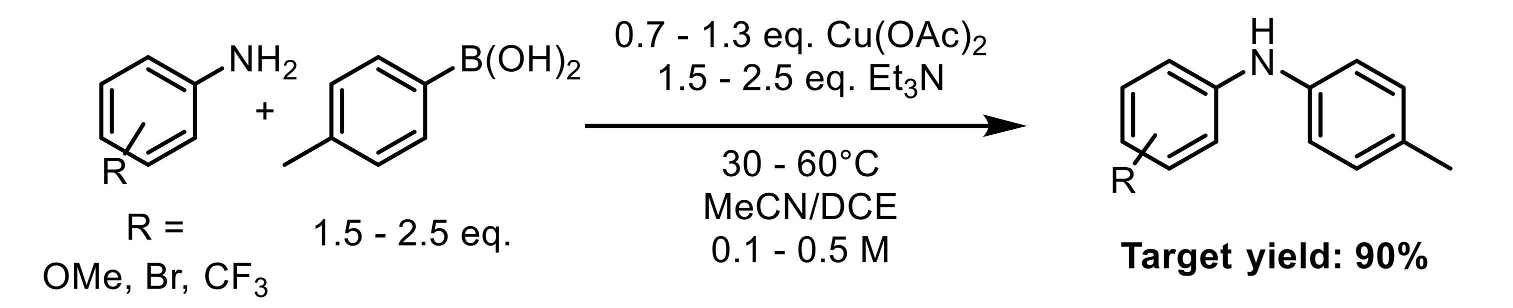
2 Chan-Lam Coupling Investigation

Chan-Lam C-N Cross Coupling in the Literature



- Inexpensive $Cu(OAc)_2$ copper catalyst
- Conducted at room temperature
- Oxygen from air used as stoichiometric oxidant

Factors Investigated

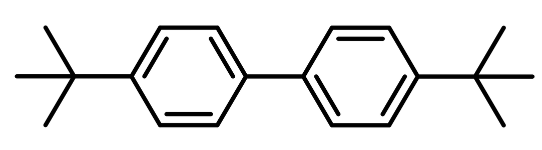


Investigated with 22 experiments in 2 batches performed using ChemSpeed automation

- Amine
- Boronic acid equivalents
- Catalyst equivalents
- Base equivalents
- Temperature
- Solvent
- Concentration

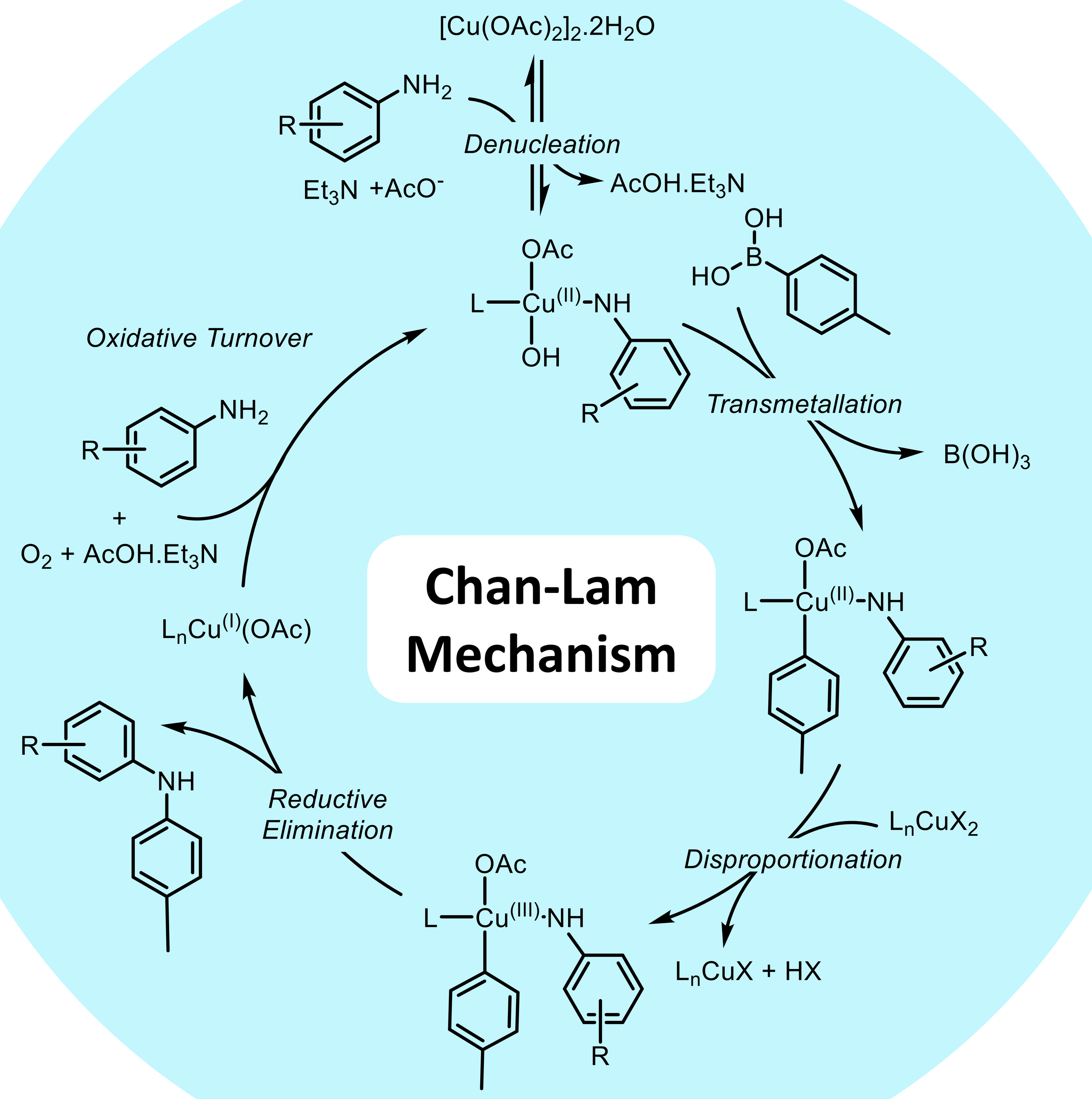
Responses measured

LCMS yields at 9 h and 18 h

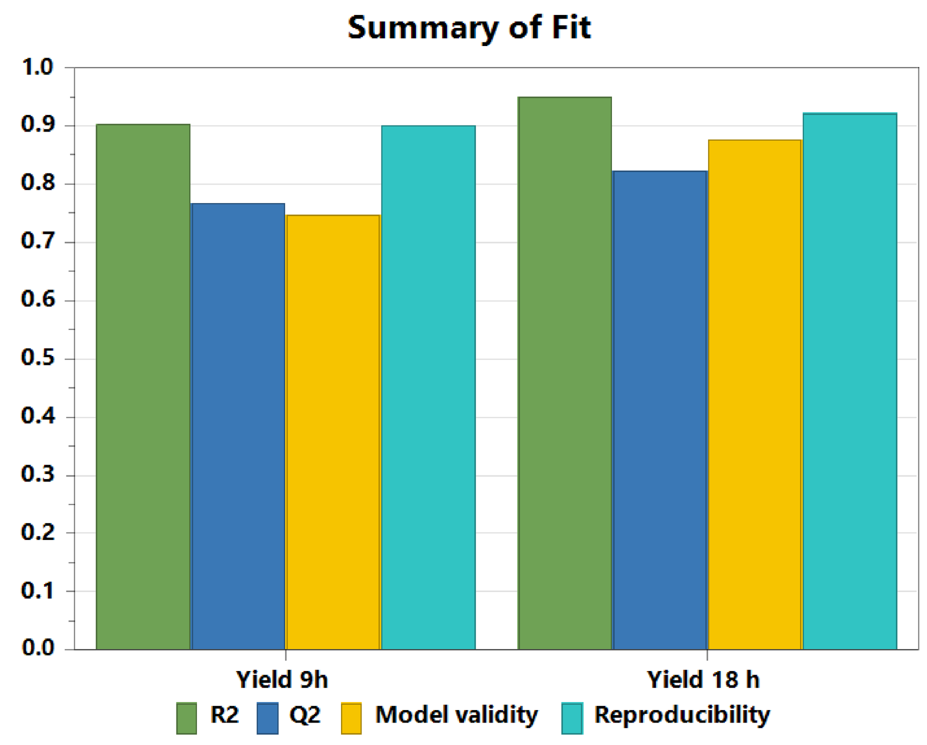


4,4′-Di-*tert*-butylbiphenyl internal standard

Chan-Lam Mechanism

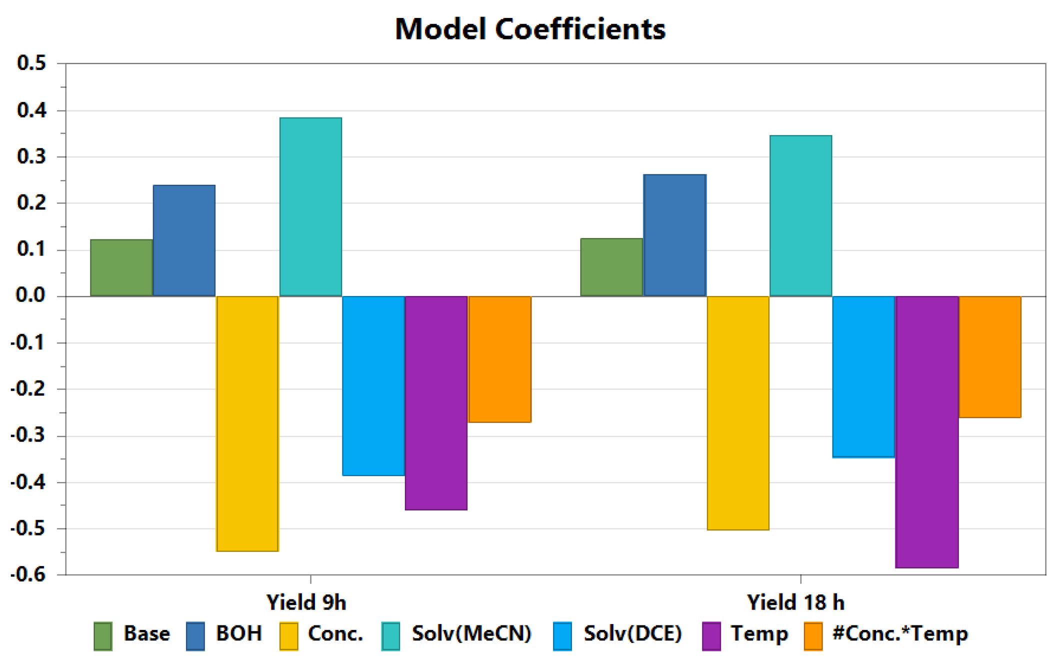


3 Model Fit and Coefficients



Summary of Fit
- Describes model fit, predictive power, validity and variations in data
- **Q2** is the best indicator for model predictivity
- **Q2** > 0.5 and **R2–Q2** < 0.3 indicates a good model

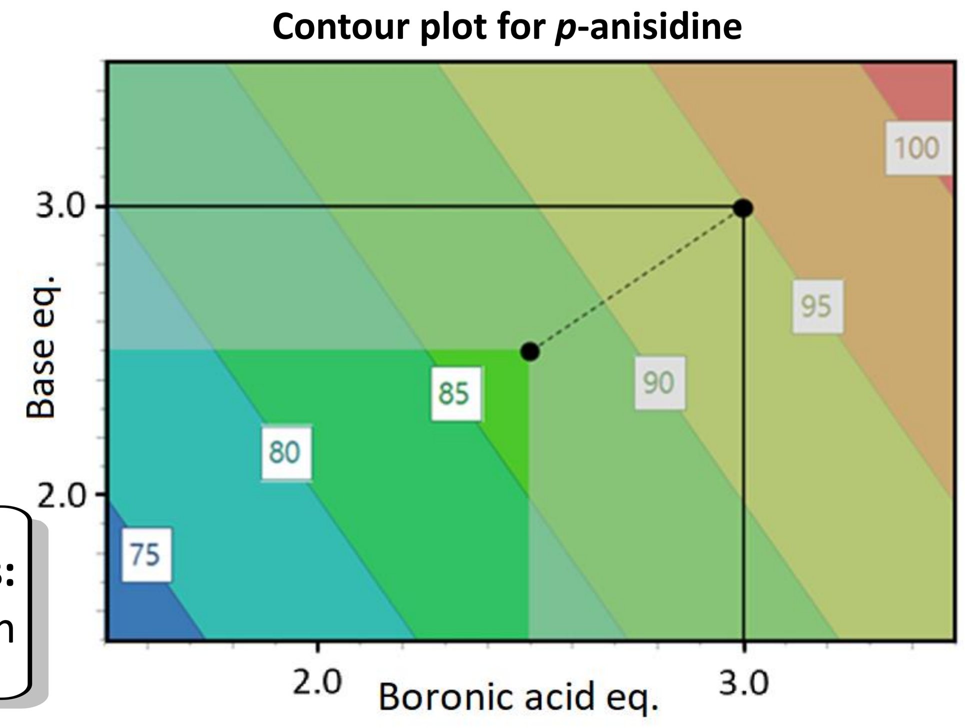
Model Coefficients
- Describes the impact on the response (yield) by each factor
- Positive coefficients indicate a positive impact on yield
- Only significant terms were included ($p \leq 0.05$)
- The most significant factors were concentration and temperature
- Catalyst equivalents was the only non-significant term



4 Results

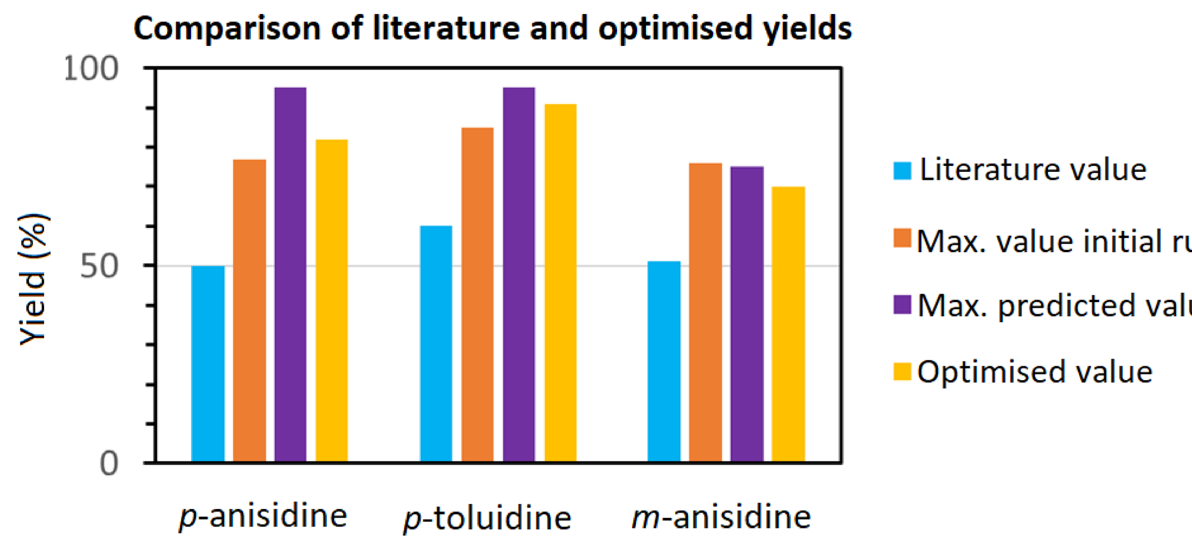
- Using our model and extrapolation, optimised conditions were found

Contour plot for *p*-anisidine



***p*-anisidine optimised conditions:**
MeCN, 0.15 mmol/mL, 23 °C, 18 h

- The contour plot shows predicted yields for the coupling of *p*-anisidine and *p*-tolyl boronic acid. Numbers in squares indicate percentage yield for each shaded region, where dark blue = 75 % and red = 100 %



Conclusion
- Yields were significantly increased from the literature values to at least 70 % for all three amines
- Combining DoE and Chemspeed automation allows for optimum conditions to be quickly determined

TECS Centre for Doctoral Training

References: (a) Tetrahedron Lett., 1998, **39** (19), 2933-2936. (b) Chem. Rev., 2019, **119** (24), 12491–12523. (c) J. Flow Chem., 2021, **11**, 75-86. (d) Am. Stat., 1999, **53**, 126-131.