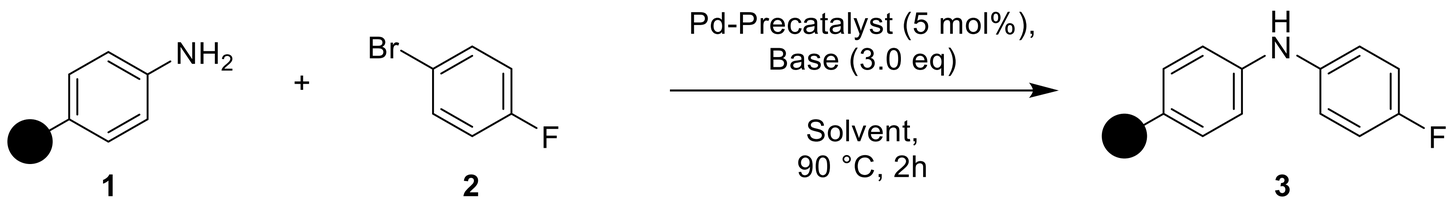
Rapid Optimization of a Buchwald–Hartwig Amination using Design of Experiments (DoE)

Ravi Pathak and Andrew Jordan

Charnwood Discovery, Charnwood Campus, Summerpool Road, Loughborough LE11 5RD

Introduction

The rapid identification of Buchwald–Hartwig amination conditions was required for the synthesis of building block **3**. We initially conducted a literature review of potential reaction conditions and prepared a shortlist of different options. This shortlist of conditions was subsequently screened on a Radleys Mya 4 Reaction Station using minimum quantities of material, leading to the identification of a set of "hit" conditions. We also screened several greener reaction solvents as alternatives to 1,4-dioxane, leading to the identification of *t*BuOH as an effective replacement.



1 + **2** → **3**

Finally, this new process was optimizing using "Design of Experiments" (DoE) software, allowing us to fully explore multiple reaction parameters and variables in as few experiments as possible. In this way, we avoided the fallacy of a "false optimum", which is often encountered when changing one factor at a time. The desired product was isolated in high yield from our highly optimized process.

Catalyst/Base Screening

The high throughput screening capabilities of the Radleys Mya 4 Reaction Station allowed for the rapid screening of all sixteen of our shortlisted catalyst-base combinations for this reaction. In this way, a full suite of reaction data was generated, including the UPLC-MS analysis of all 16 reactions, within 2 hours. The results of this screening process revealed that the use of K_3PO_4 with Xphos Pd G3 gave the highest conversion to product (Table 1). Notably, the use of KO*t*Bu led to bis-addition impurities.

	BrettPhos Pd G4	RuPhos Pd G3	Xphos Pd G3	tBuXPhos Pd G3
KO*t*Bu				
K_2CO_3				
K_3PO_4				
KOAc				

*Table 1: Catalyst/Base screening results for the formation of **3**. Green = conversion to product as determined by UPLC-MS. Red = By-products and unreacted starting materials.*

Dioxane Solvent Swap - Safety and Sustainability

As a known carcinogen,[1] the use of 1,4-dioxane as a reaction solvent raises significant environmental, health and safety (EHS) concerns, highlighting the need for more benign alternatives. With this in mind, a set of greener, sustainable solvents was screened against the best conditions identified from the catalyst-base screening exercise. The solvents used in this experiment were chosen based on well-documented solvent selection guides for greener, more sustainable solvents.[1,2] Pleasingly, *t*BuOH gave comparable results to 1,4-dioxane and was selected for further optimization work (Table 2).

Solvent	% Product Conversion
1,4-Dioxane - Control	88
Toluene	84
2-MeTHF	87
TBME	80
***t*BuOH**	**90**
CPME	80
TPGS-750-M	62
DMC	73

Table 2: Alternative solvents screened as potential replacements for 1,4-dioxane
**CPME: Cyclopentyl methyl ether, TPGS: DL-α-Tocopherol methoxypolyethylene glycol succinate, DMC: Dimethyl carbonate. Reactions conducted in a sealed tube.*

Optimum conditions identified when changing one factor at a time: Xphos Pd G3 (5 mol%), K_3PO_4 (3 eq.), *t* BuOH (0.4 M conc.), reflux, 2 h – 90% Product

Design of Experiments - DoE

Finally, the reaction was subjected to further optimization using DoE software from Design Expert. This work focused on several key rection parameters, including catalyst loading, equivalents of base, temperature and concentration. The results of these experiments were used to build a surface response plot (Figure 1), as well as a statistical model of the Buchwald–Hartwig reaction, leading to further improvements in the yield of the reaction (98% yield), as well as avoiding the potential for a "false optimum",[3] which can be encountered when changing just one factor at a time.

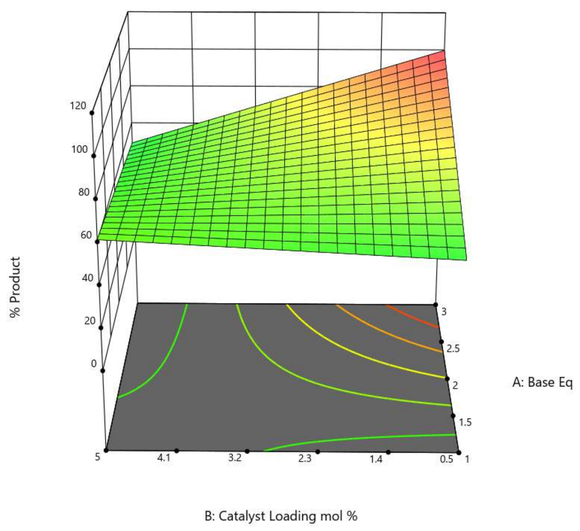


Figure 1: Left: 3D surface response with respect to catalyst loading and equivalency of base. Right: Radleys Mya 4 Reaction Station

Conclusion

In summary, the rapid optimization of a Buchwald–Hartwig amination reaction was achieved using the Radleys Mya 4 Reaction Station together with DoE software from Design Expert. Further improvements to the reaction were made by replacing 1,4-dioxane with *t* BuOH, which represents a much safer and sustainable reaction solvent.

The use DoE allowed for the generation of a statistical model of the reaction based on multiple factors, as well as the identification of important two-factor interactions. In this way, the model allowed the prediction of optimum conditions for maximizing yield, resulting in 98% conversion to product **3**.

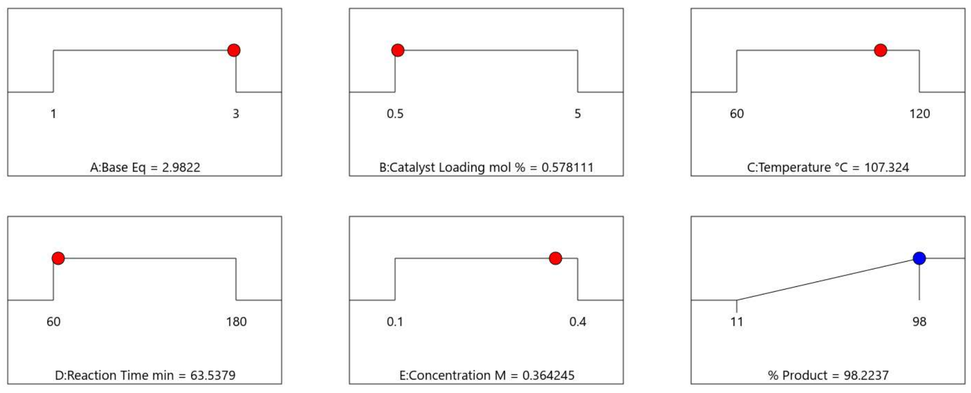


Figure 2: Optimized reaction conditions for maximizing the amount product, according to the statistical model

DoE-optimized Conditions : Xphos Pd G3 (0.5 mol%), K_3PO_4 (3 eq.), tBuOH (0.36 M conc.), reflux, 1 h – 98% Product.

1) *Chem Rev* **2022**, *122*, *6*, 6749–6794 2) *Green Chem* **2016**, *18*, 3879–3890 3) *Sci Rep* **2019**, *9*, 11370