



# Development of a Late-Stage Buchwald Amination



## The challenge

CatSci was tasked with the development of a regioselective Buchwald-Hartwig amination for the final bond forming step of an API. The inherited conditions were not robust with respect to reaction conversion leading to scalability concerns.



## How?

A mechanism informed approach used medium throughput experimentation to probe product inhibition and the influence of potential poisons on catalytic cycle robustness.



## The achievement

A room temperature Buchwald-Hartwig amination was developed with >99% conversion and regioselectivity for the API. A system with tBuXPhos Pd G3 was rendered homogeneous by replacing inorganic bases with MTBD. Optimisation studies identified DBU (\$60/kg) as a cheaper drop-in alternative to MTBD (\$8,000/kg). DBU could be used without the need for a slow addition, unlike contemporaneous state of the art reports from the Buchwald group. A recirculating flow scavenging protocol removed >90% of the residual palladium. The transfer to the kilo lab facility proceeded 'right first time'.



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### Old Process

Poor reaction conversion <30%

Slurry reaction – Poor mixing

25 relative volumes

Residual Pd: 1800 ppm



### New Process

Robust & regioselective >99%

Homogeneous reaction

5 relative volumes

Residual Pd: <100 ppm

## Facts and Figures

**PMI**  
**50% lower**



**Stage CoG**  
**40% lower**



**Failed batches to date**  
**0**

