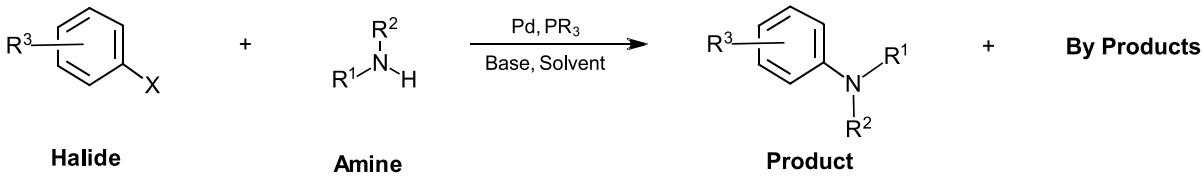
CatSci
BEYOND PROCESS CHEMISTRY

Technical Piece
CATALYSIS

A general approach to the optimisation of Buchwald-Hartwig aminations

INTRODUCTION

The approach advocated below has been routinely employed by CatSci to enable the optimisation of **Buchwald-Hartwig amination** reactions used in the synthesis of complex active pharmaceutical ingredients (APIs). This leads to processes with high reaction conversion and selectivity (**Scheme 1**). It should be noted that the principles outlined will be equally applicable to the development of conditions for other palladium-catalysed reactions.



Scheme 1: *Optimisation of a Buchwald-Hartwig amination (including complex heterocyclic amines)*

ANALYTICS & SAMPLING

Prior to commencing optimisation of any reaction, a reproducible **sampling protocol** (*e.g.* one that overcomes the difficulties of sampling a suspension) and **analytical method** allowing baseline resolution of reactants and products with an **internal standard** must be established (**Figure 1**). Conducting a **familiarisation reaction** will help to establish these protocols with consideration of the following points:

- Determine the concentrations in several solvents for which reactants and products are soluble
- Always take a **T_0 sample** prior to the addition of pre-catalyst or the initiation of catalysis
- Take 3 to 4 evenly spaced samples throughout the course of the reaction to cross-check the robustness of sampling between time points and establish a **conversion *vs.* time profile**
- In early experimentation always include **replicates** to establish the reproducibility of conditions and when establishing the importance of a parameter in fine detail, *e.g.* base pK_a

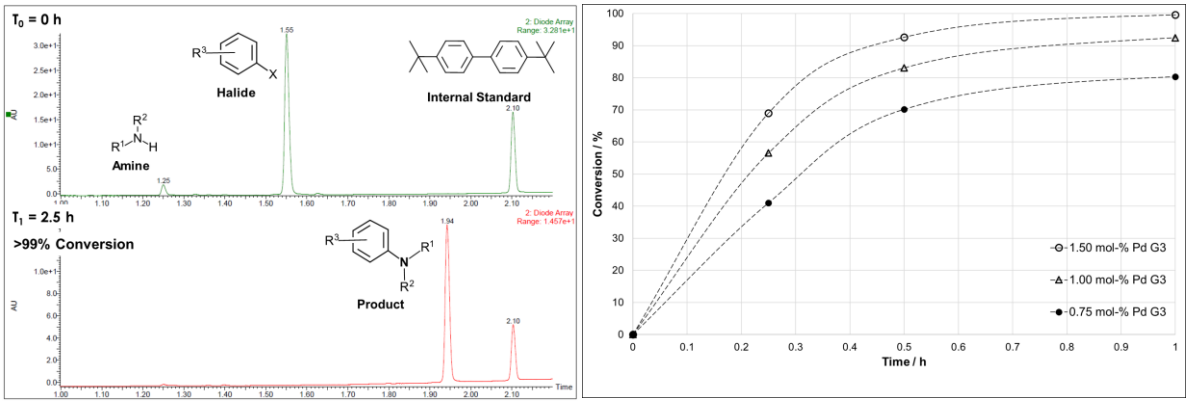


Figure 1: LC Chromatogram for a Buchwald-Hartwig amination (**left**) and a conversion vs. time profile (**right**)

SIGHTING SCREEN

Performing a small **sighting screen** will allow for standard conditions to be established. A **standard reaction** of these conditions should be included as a comparison in every subsequent catalyst screen to enable a meaningful comparison to be made, taking note of the following:

- To increase the accuracy of small-scale reactions, where possible add reactants as solutions; and ideally volumes ≥500 μL should be used to avoid dose related errors between reactions
- Run a small **solvent screen** as early on as possible – it is the bulk component of most reactions and may have a profound effect on reaction conversions and or selectivity (establish the solubility of all components including, where necessary, pre-catalysts and ligands)
- Running a small **base screen** will determine the viability of organic *vs.* inorganic bases and can be helpful in overcoming slurrying of reaction mixtures which is particularly difficult on scale-up
- Compare conversion *vs.* time data for reactions with **relative concentrations** of 0.5 and 1 – this may indicate if the reaction is **inhibited** by solvent (or stabilisers), substrates or product
- Always include one reaction that represents a standard set of conditions in every screen!

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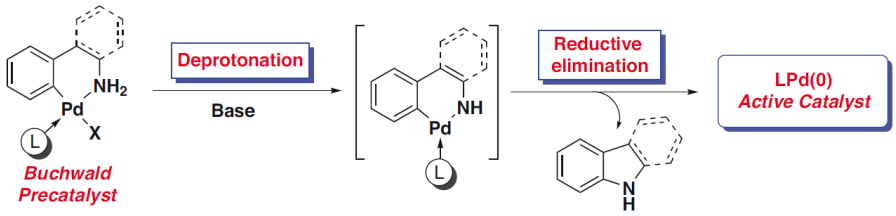
CONTROL REACTIONS

The construction of structurally complex nitrogen-rich APIs *via* Pd-catalysed C-N bond formation has been greatly advanced by the commercial availability of palladacycle pre-catalysts developed by Buchwald (**Scheme 2**).



Scheme 2: *Base mediated activation of a Buchwald palladacycle pre-catalyst (**L** = PR_3)*

Reaction conditions must be carefully developed to avoid decomposition and potential side reactions of heteroatom-rich precursors, thus performing a series of **control reactions** is advisable, including:

- Standard reaction *without* nucleophile: is the aryl halide stable to the reaction conditions, and given that R' is a nucleophilic moiety, are **side-reactions** including homocoupling of spectator or protected functional groups in the aryl halide observed?
- Standard reaction *without* pre-catalyst: is thermal decomposition of the reactants observed? Do impurities originate from base mediated reactions? (perform spiked with product if available)
- When using a palladacycle pre-catalyst (i) validate if the by-product of catalyst activation is present, and (ii) determine if ***in situ* catalyst** generation *via* the free ligand and a cheaper palladium source is possible (note that a ratio of Pd:L >1:1 is often inhibitory)

SUMMARY

The investigations which have been described above can be achieved in no more than 12 experiments which are best performed simultaneously on a reaction block or Radley Carousel Reaction Station. These experiments and a rationale for their execution are summarised in **Table 1**.

Entry	Pre-Catalyst	Base	Solvent / Vols	Conditions / Comments
1	Buchwald Precatalyst	Cs_2CO_3	IPA / 20	Standard Conditions
2	Buchwald Precatalyst	Cs_2CO_3	IPA / 20	No Amine
3	None	Cs_2CO_3	IPA / 20	No Pd/L
4	Buchwald Precatalyst	Cs_2CO_3	IPA / 20	Pre-activation of palladacycle*
5	PR_3 / Pd_2dba_3 (1:1)	Cs_2CO_3	IPA / 20	*In situ* catalyst formation
6	PR_3 / $Pd(OAc)_2$ (1:1)	Cs_2CO_3	IPA / 20	*In situ* catalyst formation
7	Buchwald Precatalyst / PR_3 (1:1)	Cs_2CO_3	IPA / 20	Effect of excess ligand
8	Buchwald Precatalyst	Cs_2CO_3	IPA / 10	Reaction Concentration
9	Buchwald Precatalyst	K_3PO_4	IPA / 20	Base Screen
10	Buchwald Precatalyst	Hünig's Base	IPA / 20	Base Screen
11	Buchwald Precatalyst	Cs_2CO_3	2-MeTHF / 20	Solvent Screen
12	Buchwald Precatalyst	Cs_2CO_3	MePh / 20	Solvent Screen

***** Reverse addition – substrate added to pre-catalyst which had been heated to 60 °C for 15 minutes (look for carbazole formation in entries 1 and 4)

Table 1 – Summary of example optimisation and control reactions