Buchwald-Hartwig Aminations in the Pharmaceutical Industry

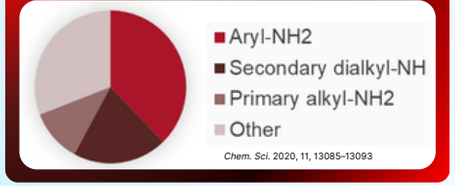
ReactWise

AI Co-pilot for chemical process optimization

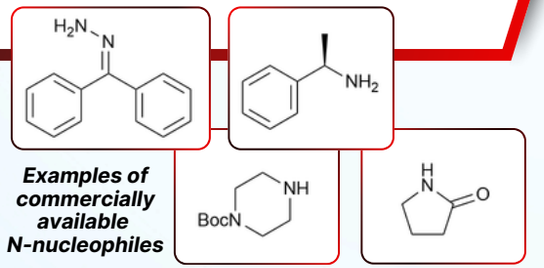
Amine

- *The **range of N-nucleophiles** which can be engaged in Buchwald-Hartwig aminations is **exceptionally diverse** – (Hetero)aromatic, aliphatic primary and secondary amines, as well as amides are popular substrates*
- *In general, **substrate reactivity** is a function of the likelihood of **side reactions, sterics, the possibility of Pd inhibition**, as well as nucleophilicity*

Top 3 nucleophiles used in a literature screen of Buchwald-Hartwig couplings



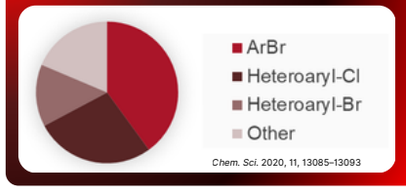
Examples of commercially available N-nucleophiles



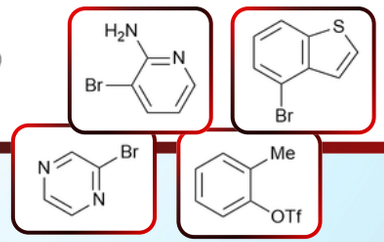
Halide

- **F** — ***Inert** in Buchwald-Hartwig reactions, except where **S_NAr** is an alternative mechanism*
- **Cl** — *Common halide partner - often **cheapest** option, but **not the most reactive***
- **Br** — ***Ideal halide partner** - exhibits **good reactivity***
- **I** — *Less common halide partner - reactions can suffer from **"halide inhibition"***
- **OTf** — ***Most common pseudohalide** - moderately reactive but requires generation in situ from parent phenol*

Top 3 halides used in a literature screen of Buchwald-Hartwig couplings

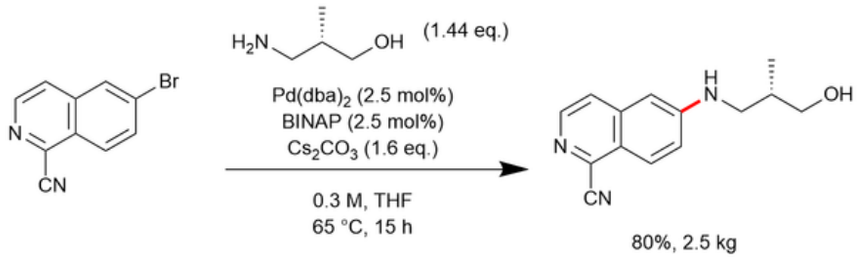


Examples of commercially available (pseudo)halides



Example Large-Scale Buchwald-Hartwig Amination (Pfizer, 2014)

Org. Process Res. Dev. 2014, 18, 1752–1758



Typical Conditions

Temperature
40 to 110 °C

Concentration
0.2 M or greater

Base Equivalents
1.1 to 3

Pd Loading
0.1 to 10%

N-Nucleophile equivalents
1 to 2

Ligands and Precatalysts

- *On large scale, Pd is usually introduced as **$Pd_2(dba)_3$ or $Pd(OAc)_2$, whilst PPh_3 is the most common ligand** added*
- ***The top six ligands**, highlighted below, cumulatively **cover more than 75%** of literature Buchwald-Hartwig couplings*
- *As Pd(0) is the active species, **Pd(II) sources such as $Pd(OAc)_2$ have to be reduced in situ**, usually by spontaneous sacrificial oxidation of excess amine or ligand*
- *The **Buchwald G3 precatalysts** (e.g. XantPhos Pd G3) are a **bench-stable and convenient** Pd source*

Other Considerations

- *The reaction is **sensitive to O_2**, which can deactivate the active Pd(0) species*
- ***Amine substrates** are often contaminated with **impurities which can inhibit the Buchwald-Hartwig reaction***
- ***Highly-coordinating N-nucleophiles** can **inhibit reactivity**; this can sometimes be bypassed with additional ligand*

Solvents and Bases

- *Only a **small number of bases** have been used in large-scale Buchwald-Hartwig couplings, where **NaO^tBu and Cs_2CO_3 are most common***
- ***Substrate deprotonation occurs on the surface of insoluble bases**, necessitating strong stirring and consideration of base particle size*

Organic Solvent
Toluene
2-MeTHF
Dioxane
THF
^{t}BuOH
DMF

Base
Na/KO^{t}Bu
Cs/K_2CO_3
K_3PO_4
LiHMDS
Na/KOH
DBU

Pd Source
$Pd_2(dba)_3$
$Pd(OAc)_2$
$Pd(dba)_2$
$[Pd(allyl)Cl]_2$

Ligand		
XantPhos	BrettPhos	tBu_3P
BINAP	dppf	XPhos
RuPhos	PEPPSI-iPr	JohnPhos
DavePhos	^{t}BuXPhos	CyJohnPhos
DPEphos	MorDalPhos	SPhos

Common for large-scale Buchwald-Hartwig aminations

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