Pd-Catalysed Suzuki Couplings in the Pharmaceutical Industry

ReactWise
AI Co-pilot for chemical process optimization

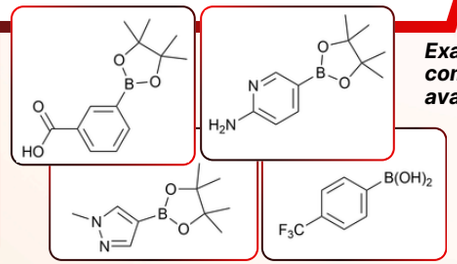
Boronate

- **BPin and B(OH)₂** are typical boronate partners, and are often commercially available
- Boronates in general are **susceptible to protodeboronation** in the presence of H_2O and acidic or basic conditions
- **BPin esters** are more stable than $B(OH)_2$, and are therefore more common for heteroarenes which can be prone to side-reactions
- **BF_3K** is a stable, crystalline, but less popular alternative for Suzuki couplings

Number of commercially available boronates

	Aryl	Heteroaryl	Alkenic
$B(OH)_2$	252 k	124 k	6 k
BPin	84 k	106 k	33 k
BF_3K	3 k	1 k	4 k

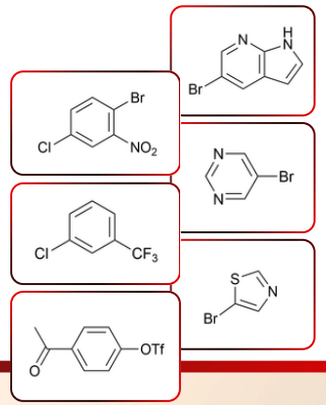
Examples of commercially available boronates



Halide

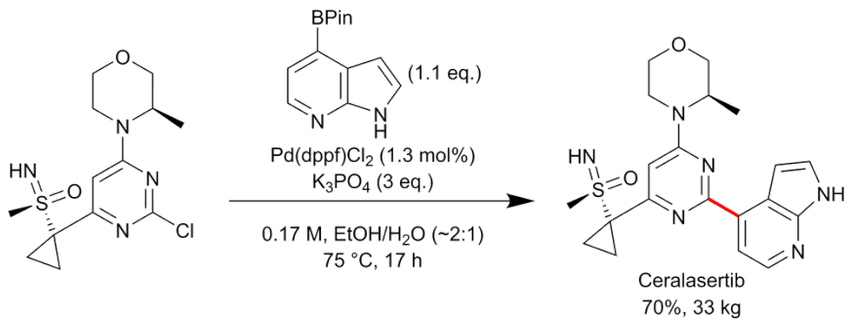
- **F** — **Nonreactive** for Suzuki couplings unless very highly electron deficient
- **Cl** — Common halide partner - often **cheapest** option, but **not the most reactive**
- **Br** — **Ideal halide partner** - exhibits **good reactivity**
- **I** — Less common halide partner - reactions can suffer from **"halide inhibition"**
- **OTf** — **Most common pseudohalide** - moderately reactive but requires generation in situ from parent phenol

Examples of commercially available (pseudo)halides



Example Large-Scale Suzuki Coupling (AstraZeneca, 2020)

Org. Process Res. Dev. 2021, 25, 43−56



Typical Conditions

Temperature
RT to 110 °C

Concentration
0.2 M or greater

Base Equivalents
1.5 to 3

Pd Loading
0.1 to 10%

Boronate Equivalents
1 to 1.3

Ligands and Precatalysts

- On large scale, **Pd is usually introduced as $Pd(PPh_3)_2Cl_2$ or $Pd(OAc)_2$,** whilst **PPh_3 is the most common ligand** added
- Whilst the factors which govern ligand success are complex, a few guidelines can be used to assist ligand selection

Slow oxidative addition (e.g. chlorides or electron rich halide substrates)	Countered by →	**Electron-rich ligands (e.g. XPhos, PEPPSI-^{i}Pr)**
Side reactions (e.g. β-elimination, Pd inactivation)	Countered by →	**Bulky ligands (e.g. CataCXium A, dtbpf)**

Pd Source
$Pd(PPh_3)_2Cl_2$
$Pd(OAc)_2$
$Pd(PPh_3)_4$
$Pd_2(dba)_3$
$Pd(dppf)Cl_2$

Ligand		
PPh_3	BINAP	$P(^tBu)_3$
XantPhos	PCy_3	CataCXium A
RuPhos	dppf	SPhos
XPhos	DavePhos	PEPPSI-^{i}Pr
dtbpf	BrettPhos	APhos

Other Considerations

- The Suzuki reaction typically **tolerates unprotected -OH groups**
- **-COOH can also be tolerated** if an extra equivalent of base is added
- The Suzuki reaction can be sensitive to O_2
- **The Buchwald G3 precatalysts (e.g. XantPhos Pd G3)** are a **bench-stable and convenient Pd source** for Suzuki couplings

Solvents and Bases

- Addition of **water (often 20 v/v%)** to the reaction mixture is very common
- **Milder bases or biphasic conditions can prevent hydrolysis** of pendant functional groups
- Large scale processes **favour EtOH, toluene, K_2CO_3 and K_3PO_4** amongst a range of solvents and bases

Organic Solvent
EtOH
Toluene
Dioxane
THF
DME
DMF

Base
K_2CO_3
K_3PO_4
$KHCO_3$
NaOH
KO^tBu
KF

Common for large-scale Suzuki couplings

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