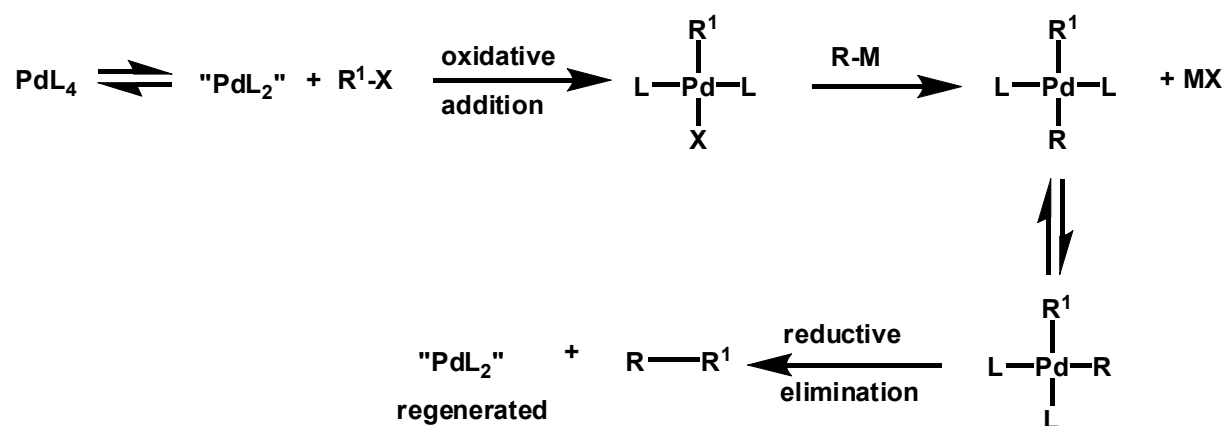


## Cross-Coupling Chemistry

One of the most ideal ways to make new carbon-carbon bonds would be able to do  $R-M + R'-X$  to give every  $R-R'$  in the world. The reasons this isn't always done are:

- 1) Alkyl  $R'-X$  's are not as reactive as you'd like to  $R-M$ , or at least there are significant side reaction possibilities;
- 2)  $sp^2$  hybridized  $R'-X$  and  $sp$  hybridized  $R-X$  don't do  $S_N2$  reactions  
-keep in mind that  $S_{RN}1$  and addition-elimination processes can occur, but aren't that widely applicable

The overall transformation *is* possible often, however, simply through the addition of a catalytic amount of a transition metal species, most often a  $Pd^0$  or  $Ni^0$  source. This is due to the availability of *oxidative addition* and *reductive elimination* mechanistic steps. A very generalized and oversimplified mechanistic cycle is as follows:



The oversimplification is fairly severe. The 'active'  $Pd^0$  species is probably only  $PdL_2$  when the  $R'-X$  is an iodide ( $PdL$  with chlorides, and a mixture of the two for bromides)(Barrios-Landeros, F.; Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 8141). For  $Ni^0$  mediated versions, there are probably pentacoordinated intermediates.

Nevertheless, this works pretty well, and especially for aryl and alkenyl containing systems. The parameters for these cross-coupling reactions occurring well are as follows:

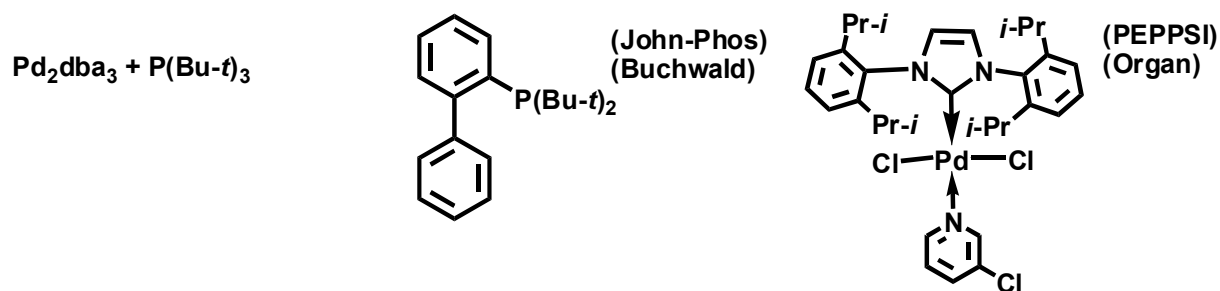
### The Metal Catalyst

The frequently used catalysts involved  $Pd > Ni \gg Pt \gg$  all others

Rather than handling the often air-sensitive  $Pd^0$  and  $Ni^0$  reagents *per se*, it is often done by employing air-stable  $Pd^{2+}$  and  $Ni^{2+}$  reagents as *precatalysts*, as the  $R-M$  will reduce them to  $Pd^0$  and  $Ni^0$  *in situ*. Some of the older, original catalysts include:

$\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Pd}_2(\text{dba})_3\text{-CHCl}_3$ ,  $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ ,  $\text{Cl}_2\text{Pd}((\text{o-tol})_3\text{P})_2$ ,  $\text{Cl}_2\text{Pd}(\text{dppe})$ ,  $\text{Cl}_2\text{Pd}(\text{dppf})$ ,  $\text{Cl}_2\text{Ni}(\text{PPh}_3)_2$ ,  $\text{Cl}_2\text{Ni}(\text{dppe})$ .

There are many newer catalysts, most aimed at being sterically hindered, so that larger concentrations of  $\text{PdL}_1$  are generated in solution, and making oxidative additions go more rapidly (especially for the aryl chlorides):



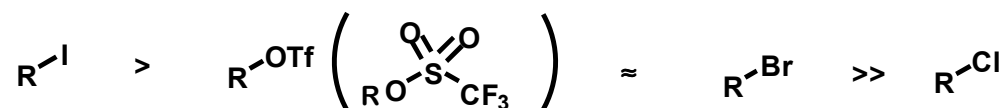
Unfortunately, it is still something of a black box as to which one to choose.

### The X's

The normal leaving groups in cross-coupling reactions are organic iodides, bromides, triflates (trifluoromethanesulphonates), and chlorides.

With Ni catalysts,  $\text{R}'\text{-SR}$  ( $\text{R} = \text{Me}, i\text{-Pr}$ ) are also known

The order of reactivity (fastest to slowest) is:



The relative position of triflates (especially wrt bromides) can vary case by case, and is dependent upon whether there is any added  $\text{LiCl}$ .

### The R-M Metal

The too close to ionic organometallics ( $\text{Li}, \text{Na}, \text{K}$ ) are almost never used. The most common ones are below, in order of decreasing reactivity.

Metal	Reaction Name	Water stable?	Functional Group Stability?	Commercially Available
$\text{R-MgBr}$	Kharasch reaction Or Kumada-Corriu Tamao reaction	no	poor	A few
$\text{R-ZnX}$	Negishi reaction	no	some	Very few
$\text{R-B(OH)}_2$	<b>Suzuki-Miyaura reaction</b>	<b>yes</b>	<b>good</b>	<b>Many</b>
$\text{R-SnBu}_3$	Stille coupling	yes	good	A few

R-SiR <sub>3</sub>	Hiyama(-Denmark) reaction	Yes mostly	good	A few
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In addition, organocoppers of all sorts, including R-Cu, R<sub>2</sub>CuLi, R<sub>2</sub>Cu(CN)Li<sub>2</sub> have been used in cross-coupling reactions.

Other metals R-Al<sup>III</sup>, R-Zr<sup>IV</sup> are known but much rarer.

### Comments

**R-MgX** - In the case of Grignard reagents, Ni based catalysts are as common, perhaps even more common, than Pd based catalysts.

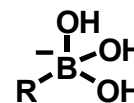
Aldehydes, ketones, esters, amines, and nitro groups don't survive, so the functional group tolerance isn't that good.

**R-SnBu<sub>3</sub>** ( or R-SnMe<sub>3</sub>) – The alkyl groups could in principle also couple with the R'-X, but they are the least easily transferred groups from Sn. The order of ease of transfer is:

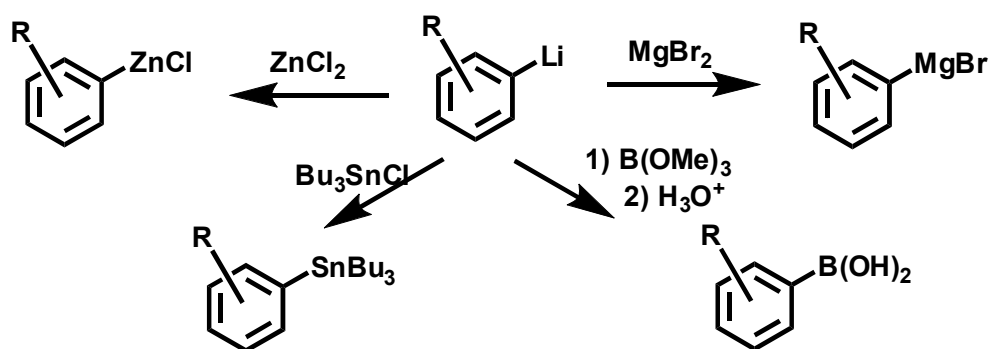
R-C≡C-Sn > RCH=CH-Sn ≈ Ar-Sn > R-CH=CH-CH<sub>2</sub>-Sn ≈ Ar-CH<sub>2</sub>-Sn > RO-CH<sub>2</sub>-Sn > alkyl-Sn

Organotins are potentially toxic, but with four sizeable groups around tin, this is less of an issue. This is why R-SnBu<sub>3</sub> are much more heavily encountered than R-SnMe<sub>3</sub>

**R-B(OH)<sub>2</sub>** - Most popular due to the combination of water stability, commercial availability, low toxicity, and functional group tolerance. They are often used in biphasic organic-aqueous solvent systems, and a base is normally added because the reactive species is the tetravalent borate anion (Na<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, Ba(OH)<sub>2</sub>, KF, CsF). Molander has made extensive use of R-BF<sub>3</sub><sup>-</sup> K<sup>+</sup> reagents; they likely hydrolyze to the boronic acids in the reaction.

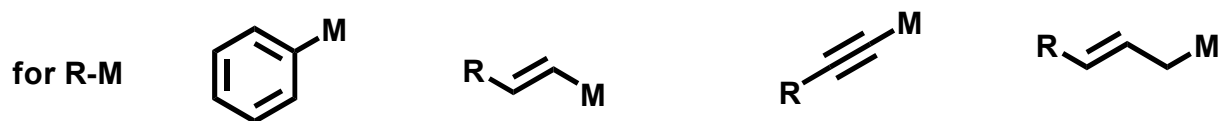


Each of the major classes of compounds can be made from the organolithiums, so this is often used in combination with directed lithiation chemistry.

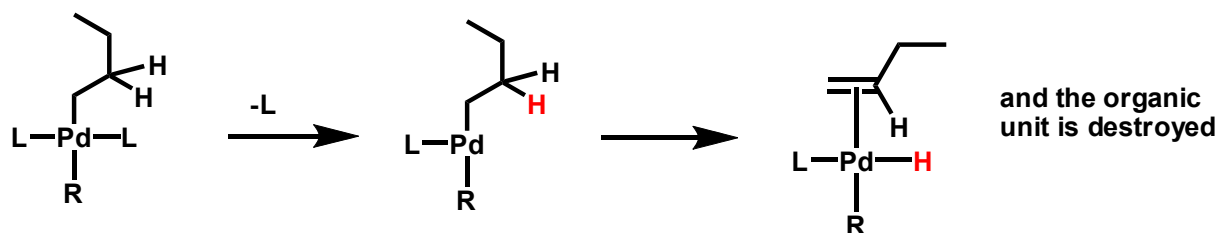


### The Organic Substrate

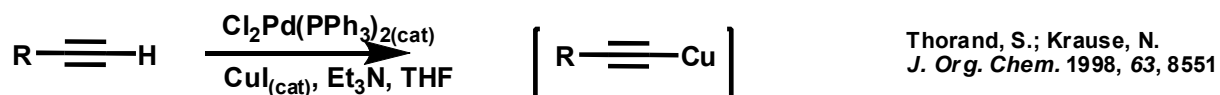
The basic rule here is that everything except alkyls works pretty well:



Note: The *problem* with alkyls is that they are subject to  **$\beta$ -hydride elimination**

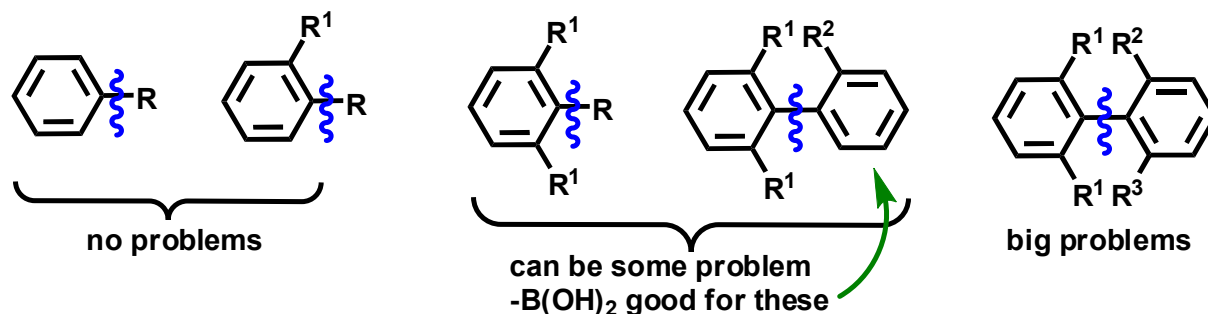


For **terminal alkynes**, it is far more common for  $R-C\equiv C-M$  to be generated *in situ* from the terminal alkyne +  $Cu^I$  salt + amine + Pd catalyst. Cross couplings of this type are known as Sonogashira reactions.



Note: There is a trend towards copper free conditions; i.e., *Chem. Eur. J.* 2007, 13, 666.

For **arenes**, there is a susceptibility to steric hindrance due to *ortho* substitution



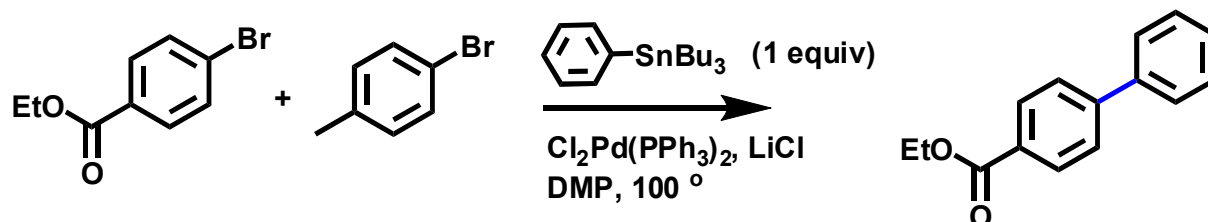
For **vinyl-M**, the coupling generally goes with retention of configuration at the vinyl carbon

For **R-X** (the organic halide/pseudohalide)

-once again, the alkyls are more problematic than the others



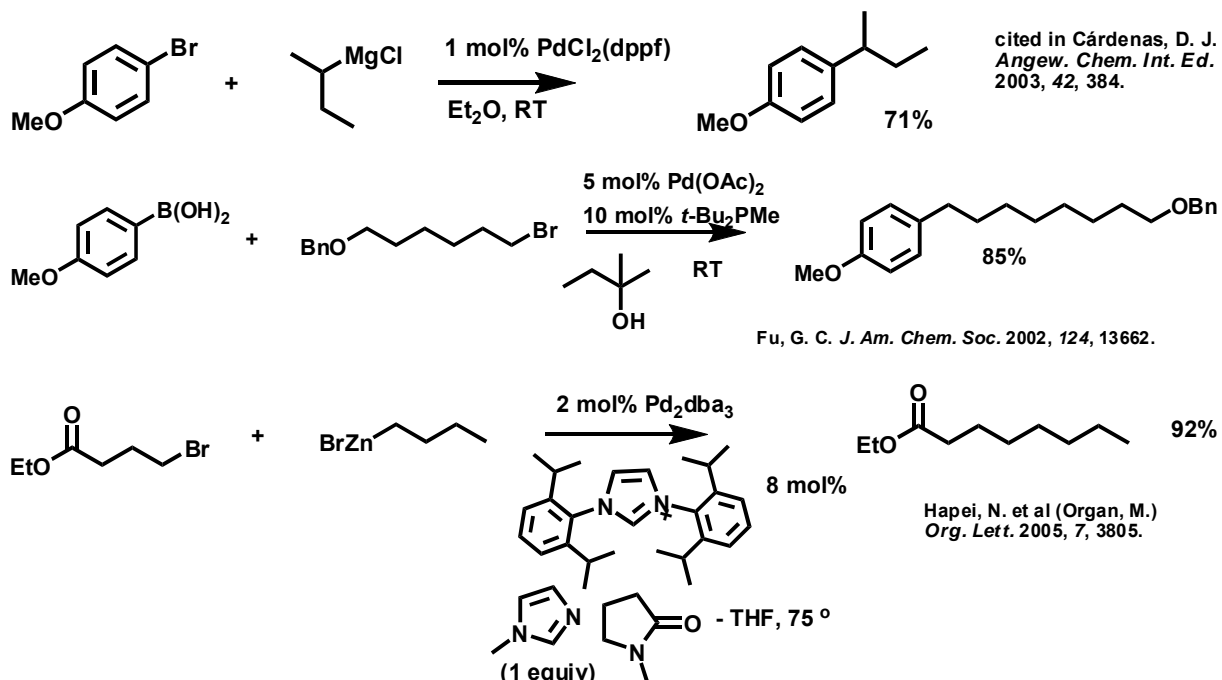
In the aryl-X cases, the reactions are sped up by electron withdrawing groups, especially *ortho*- and *para*-. This is due to a faster oxidative addition step.

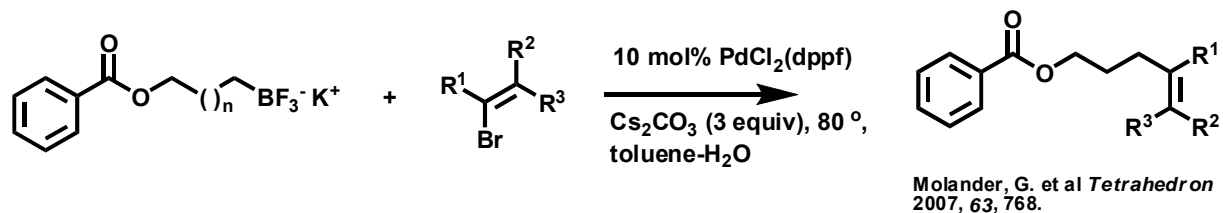


### The Dreaded Alkyls

Cross coupling reactions of alkyl organometallics and/or alkyl halides/pseudohalides is not as impossible as feared, and might in the near future become routine. First of all, alkyls *without*  $\beta$ -hydride sources couple without significant problems.

There are increasing reports of success in these transformations, even in  $\beta$ -elimination prone chemistry. While it is not quite general yet, many results suggest that systems using very sterically hindered phosphines or N-heterocyclic carbenes as ligands for Pd or Ni give a reasonable chance of success. Certainly the level of problem increases from  $1^\circ < 2^\circ < 3^\circ$  cases. Some individual examples are shown below.





Recent reviews

Kambe, Nobuaki; Iwasaki, Takanori; Terao, *Chemical Society Reviews* (2011), 40(10), 4937-4947

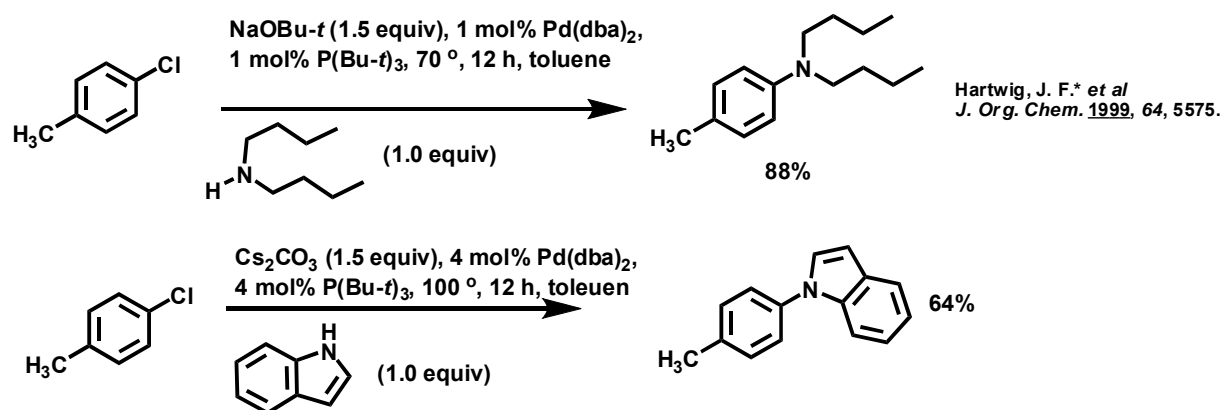
Taylor, Buck L. H.; Jarvo, Elizabeth R. *Synlett* (2011), (19), 2761-2765.

Joshi-Pangu, Amruta; Biscoe, Mark R. *Synlett* (2012), 23(8), 1103-1107.

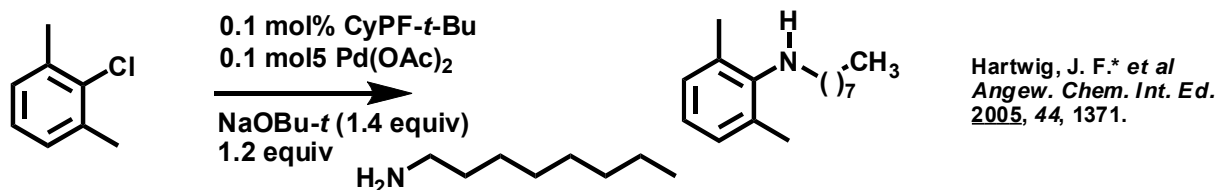
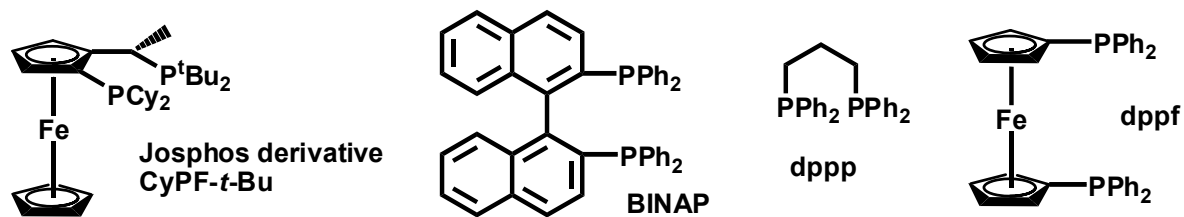
### Aminations of Arenes by Coupling

Over the past 10-15 years, it has become practical to do aryl C-N coupling reactions by a similar approach, by using an amine and a base rather than a discretely formed  $M-NR_2$ . The mechanism is similar to the carbon based cross coupling reactions, while the actual catalyst protocol is slightly different depending on whether a  $1^\circ$  or  $2^\circ$  amine is being coupled.

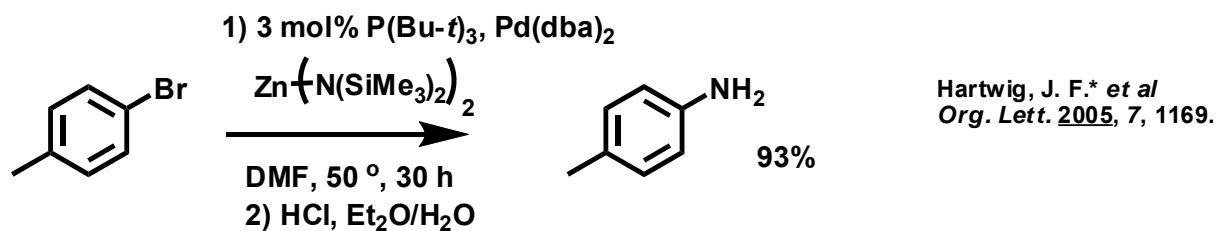
**For  $2^\circ$  Amines:** The ligand is normally a sterically hindered monodentate phosphine, such as  $P(t-Bu)_3$  or one of the Buchwald biaryldialkylphosphines (John-Phos type ligands). The base added is usually  $NaOtBu$ , LiHMDS, or even  $Cs_2CO_3$ .



**For  $1^\circ$  Amines:** The ligand is normally a *bidentate* ligand that is sterically hindered. Hartwig in particular touts the Josiphos class of ligands, while BINAP, dppp, and dppf have also seen use. The base added tends to fall within the same group as for  $2^\circ$  amine coupling.



**Ammonia itself:** NH<sub>2</sub> is a more difficult group directly, and so indirect ways have been developed to put in this group. Here is one example:



For a review on these aminations, see: Hartwig, J. F. *Synlett* 2006, 1283.