Reviews:

Overview:
• The reductive amination of aldehydes and ketones is an important method for the synthesis of primary, secondary, and tertiary amines.

• Reductive amination is a powerful and reliable strategy for the formation of C–N bonds, and can avoid the problem of overalkylation that often accompanies direct alkylation of amines with alkyl halides.

Mechanism:
• Reductive amination involves a one- or two-step procedure in which an amine and a carbonyl compound condense to afford an imine or iminium ion that is reduced in situ or subsequently to form an amine product.

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Reducing Agents
• Common reducing agents: NaCNBH3, Na(OAc)3BH, H2/catalyst

• Iminium ions are reduced selectively in the presence of their carbonyl precursors. Reagents such as sodium cyanoborohydride and sodium triacetoxyborohydride react selectively with iminium ions and are frequently used for reductive aminations.

Reduction with Sodium Cyanoborohydride:
• Borch and co-workers showed that sodium cyanoborohydride and lithium cyanoborohydride are acid-stable reagents capable of rapidly reducing carbonyl compounds to alcohols at pH 3–4, presumably via a protonated carbonyl cation.

\[
\begin{align*}
\text{Ph} & \text{CH}_3 \quad \text{NaBH}_3\text{CN} \\
\text{Ph} & \text{CH}_3 \quad \text{CH}_3\text{OH} \\
\text{pH} 3, 23^\circ \text{C}, 1 \text{ h} & \quad 93\%
\end{align*}
\]


• At pH 7, reduction of carbonyl compounds with lithium cyanoborohydride is very slow, even at reflux in methanol.

\[
\begin{align*}
\text{Ph} & \text{CH}_3 \quad \text{LiBH}_3\text{CN} \\
\text{Ph} & \text{CH}_3 \quad \text{CH}_3\text{OH} \\
\text{pH} 7, \text{ reflux}, 72 \text{ h} & \quad 36\%
\end{align*}
\]


Jonathan William Medley, Fan Liu
• With care to maintain a pH of 6–7, a mixture of a ketone or aldehyde reactant, an amine, and sodium cyanohydride provides products of reductive amination selectively, without competitive reduction of the carbonyl substrate.
• Though the conditions of the Borch reduction are mild, sodium cyanoborohydride is highly toxic, as are its byproducts.

\[
\text{R}_1\text{R}_2\text{O} + \text{R}_3\text{N}\text{H} \xrightarrow{\text{NaBH}_3\text{CN, CH}_3\text{OH, pH 6–8, °C}} \text{R}_1\text{R}_2\text{NH}_3\text{R}_4
\]

<table>
<thead>
<tr>
<th>carbonyl compound</th>
<th>amine</th>
<th>product</th>
<th>isolated yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cycloheptanone</td>
<td></td>
<td></td>
<td>79</td>
</tr>
<tr>
<td>PhCH(CH_3)CCH_3</td>
<td>CH_3NH_2</td>
<td>H_3CCH_3PhNH_2</td>
<td>90</td>
</tr>
<tr>
<td>PhCH(CH_3)CCH_3</td>
<td>H_2NOH</td>
<td></td>
<td>66</td>
</tr>
<tr>
<td>PhCH(CH_3)CCH_3</td>
<td></td>
<td>H_3CCH_3NHPh</td>
<td>78</td>
</tr>
<tr>
<td>PhCH(CH_3)CCH_3</td>
<td></td>
<td>HO-CH-CH-COOH</td>
<td>51</td>
</tr>
</tbody>
</table>

*The pH was maintained by addition of HCl and/or KOH as needed using bromocresol green as an indicator.


**Reduction with Sodium Triacetoxyborohydride:**
• Sodium triacetoxyborohydride has been found to be a highly selective reducing agent for reductive amination; acetic acid is frequently employed as a proton donor.
• This protocol is generally high yielding, highly functional group tolerant, and proceeds without release of cyanide salts. The substrate scope includes aromatic and aliphatic aldehydes, ketones, and primary and secondary amines. Ammonia can be employed successfully if used in large excess as its acetate salt.

\[
\text{R}_1\text{R}_2\text{C} + \text{R}_3\text{NH}_3\text{R}_4 \xrightarrow{\text{NaBH(OAc)_3, Method a}} \text{R}_1\text{R}_2\text{NH}_3\text{R}_4
\]

<table>
<thead>
<tr>
<th>carbonyl compound</th>
<th>amine</th>
<th>method</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhCH(CH_3)CCH_3</td>
<td></td>
<td>II</td>
<td>PhCH(CH_3)CCH_3NHPh</td>
<td>96</td>
</tr>
<tr>
<td>PhCH(CH_3)CCH_3</td>
<td></td>
<td>IIb</td>
<td>cycloheptylamine</td>
<td>80c</td>
</tr>
<tr>
<td>PhCH(CH_3)CCH_3</td>
<td></td>
<td>I</td>
<td>PhCH(CH_3)CCH_3NHPh</td>
<td>96</td>
</tr>
<tr>
<td>PhCH(CH_3)CCH_3</td>
<td></td>
<td>II</td>
<td>PhCH(CH_3)CCH_3NHPh</td>
<td>95</td>
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<tr>
<td>PhCH(CH_3)CCH_3</td>
<td></td>
<td>II</td>
<td>PhCH(CH_3)CCH_3NHPh</td>
<td>88</td>
</tr>
</tbody>
</table>

*Method I: CIC_6H_4CH_2Cl, AcOH (1–2 equiv), NaBH(OAc)_3 (1.3–1.6 equiv). Method II: CIC_6H_4CH_2Cl, NaBH(OAc)_3 (1.3–1.6 equiv). *Et_3N (1.5–2.0 equiv) added. **yield of HCl salt.
Reductive amination of carbonyl compounds with primary amines can be complicated by overalkylation. In these cases, formation and isolation of the imine followed by reduction can prove to be a superior alternative.

- It was found that the use of methanol as solvent allows for rapid (< 3h) and nearly quantitative imine formation from aldehydes without the need for dehydrating reagents.

<table>
<thead>
<tr>
<th>carbonyl compound</th>
<th>amine</th>
<th>method(^a)</th>
<th>product</th>
<th>yield (%)</th>
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\(^a\)Method III: \(\text{ClCH}_2\text{CH}_2\text{Cl}, \text{AcOH} (1 \text{ equiv}), \text{NaBH}(\text{OAc})_3 (1.4 \text{ equiv})\). Method IV: \(\text{ClCH}_2\text{CH}_2\text{Cl}, \text{AcOH} (2–5 \text{ equiv}), \text{carbonyl compound} (1.5–2 \text{ equiv}), \text{NaBH}(\text{OAc})_3 (2.0–2.8 \text{ equiv})\). \(^b\)yield of HCl salt. \(^c\)Et\(_3\)N (2.0 equiv) added.

Reduction with Sodium Borohydride:

- Reductive amination of carbonyl compounds with primary amines can be complicated by overalkylation. In these cases, formation and isolation of the imine followed by reduction can prove to be a superior alternative.

- It was found that the use of methanol as solvent allows for rapid (< 3h) and nearly quantitative imine formation from aldehydes without the need for dehydrating reagents.

<table>
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<tr>
<th>aldehyde</th>
<th>amine</th>
<th>product</th>
<th>yield (%)(^a)</th>
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<tr>
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</tbody>
</table>

\(^a\)products isolated as HCl salts.

Examples in Synthesis


Mark G. Charest, Fan Liu
In a complex transformation, a tryptamine derivative and an enantoenriched dialdehyde were combined to give a cyclic bis-hemiaminal intermediate; electrophilic activation with trifluoroacetic anhydride initiated a Mannich/Sakurai cascade. Subsequent iminium reduction with sodium cyanoborohydride afforded a pentacyclic diamine en route to \((-\text{aspidophytine}).\)

\[
\begin{align*}
\text{R} &= \text{CH}_2\text{COO}^-\text{-Pr} \\
\text{NaBH}_3\text{CN} &\quad (5 \text{ equiv}) \\
\text{66\%}
\end{align*}
\]

Regio- and stereoselective indolenine reduction and reductive methylation of two secondary amines was achieved using Borch conditions en route to \((+\text{-haplophytine}).\)

\[
\begin{align*}
\text{5 steps} \\
\text{CO}_2\text{CH}_3 \\
\text{NaB(OAc)}_3 \\
\text{HCHO, NaBH}_3\text{CN} \\
\text{AcOH}
\end{align*}
\]

\[
\begin{align*}
\text{1. 1N NaOH, CH}_3\text{OH, 60 °C} \\
\text{2. K}_3\text{Fe(CN)}_6, \text{NaHCO}_3, \text{t-BuOH, H}_2\text{O, 70\% (2 steps).}
\end{align*}
\]


C–N Bond-Forming Reaction: The Buchwald-Hartwig Reaction

**Reviews:**


**Industrial Review of C-N and C-O Coupling:**


---

**The Buchwald-Hartwig reaction is the coupling of an amine with an aryl halide mediated by a palladium catalyst.**

\[
\begin{align*}
R^1\text{NH} & \text{ + } X\text{-Ar} & \text{PdL}_n & \rightarrow R^1\text{N-Ar} \\
\text{Base, Solvent} & & & \\
\end{align*}
\]

**Mechanism:**

**The Base (bolded bases are the most commonly used):**

- For fast reactions: strong bases such as NaOtBu, KOH (uncrushed pellets)
- For substrates bearing sensitive functional groups: weaker bases such as K\textsubscript{3}PO\textsubscript{4}, Cs\textsubscript{2}CO\textsubscript{3}, K\textsubscript{2}CO\textsubscript{3} with t-BuOH or t-amyl alcohol
- For substrates bearing acidic functional groups, use of LiHMDS as base affords lithiates that can prevent catalyst inhibition.


**Solvant Choices:**

- Most general: toluene, THF, DME, dioxane, and tertiary alcohols
- Water is compatible but rates of reaction are often slower.
- DMF, NMP, MeCN, acetone, etc., should be avoided as single solvents, but they can be great co-solvents, especially for substrates containing potentially chelating functional groups that otherwise might inhibit catalysis.

**Activation**

- In order for the catalytic cycle to begin, palladium must be in the Pd(0) oxidation state. One of the most common Pd(0) sources is Pd\textsubscript{2}dba\textsubscript{3}.

- Pd(II) sources can be used and are more stable, but they require reduction to Pd(0). One of most common activation methods is via reduction of Pd(OAc)\textsubscript{2} with PR\textsubscript{3}, water, and heat.

\[
\begin{align*}
Pd(II)(OAc)\textsubscript{2} & \text{ + } 2PR\textsubscript{3} & \rightarrow (R\textsubscript{3}P)Pd(0)(OAc) & \text{ + } AcOPR\textsubscript{3} & \text{H}_2O & \rightarrow Pd(0)PR\textsubscript{3} & \text{O=PR}\textsubscript{3} & \text{ + } 2\text{HOAc} \\
\end{align*}
\]


- Precatalyst systems allow for lower reaction temperatures.


Oxidative Addition

- Electron-rich and sterically hindered aryl halides undergo slower oxidative addition. Reactivity order: I > Br > OTf > Cl > OTs.

\[
\text{I} \quad \xrightarrow{\text{H}_2\text{N}-\text{R}} \quad \text{R}_2\text{NH} \quad \xrightarrow{\text{Pd}_2(\text{dba})_2, \text{Xantphos}} \quad \text{R}_3\text{NH} \quad 90\%
\]

\[
\text{Br} \quad \xrightarrow{\text{NaOtf-Bu, toluene}} \quad \text{Br}_2 \quad \xrightarrow{80^\circ \text{C}} \quad \text{Br}_2 \quad 96\%
\]


- OTf and OTs may undergo competing hydrolysis.
- Iodides are less frequently used because they tend to be more expensive, dehalogenate more readily, and tend to form bridged palladium dimers.
- Halides in the 2- and 4-positions of 6-membered hetercycles are predisposed towards oxidative addition.

Coordination

- Electron-rich amines are superior substrates due to their enhanced nucleophilicities.

Deprotonation

- Binding to Pd increases the acidity of the amine, which facilitates deprotonation.

Reductive Elimination

- Electron deficient amines undergo slower reductive elimination.
- Bulky ligands help to accelerate reductive elimination through steric repulsion.

### Examples of Ligands

**Buchwald**

- RuPhos (for 2º amines)
- BrettPhos (for 1º amines)

**Hartwig**

- Josiphos
- CyPfI-Bu

**Stradiotto**

- Mor-DalPhos
- BippyPhos

Rob Singer, David Bernhardson


C–N Bond-Forming Reaction: The Buchwald-Hartwig Reaction

Nitrogen nucleophiles

- Listed, in decreasing order, by approximate ease of coupling: anilines, secondary amines, primary amines, amides, sulfamides, five-membered heterocycles (i.e. pyrazole, imidazole, etc.), and ammonia.

Anilines

\[
\begin{align*}
\text{Br} & \quad \text{N} \quad \text{N} \quad \text{O} \quad \text{R} \\
& \quad \text{ArNH}_2, \text{K}_3\text{PO}_4, \text{DME}, 80^\circ\text{C} \\
\text{Pd}_2(\text{dba})_3, \text{BINAP} & \quad 61-81\%
\end{align*}
\]


- A selective C–N coupling reaction was used in the synthesis of the core of variolins, a group of marine natural products with potent cytotoxic activities against murine leukemia cells:

\[
\begin{align*}
\text{Cl} & \quad \text{Br} \\
& \quad \text{H}_2\text{N}-\text{N} \\
& \quad (1.2 \text{ eq}) \\
\text{Pd(OAc)}_2 (5 \text{ mol%}) & \quad \text{JohnPhos} (10 \text{ mol%}) \\
\text{NaO}\text{t-Bu} (1.4\text{eq}) & \quad \text{THF}, 70 \text{ °C}, 83\%
\end{align*}
\]


- The selectivity in this case is attributed to the directing effects of the neighboring nitrogen atoms.

Secondary Amines vs. Primary Amines

- Ligand choice is important. A catalyst that is too hindered inhibits reactions with secondary amines, while primary amines require a hindered ligand, to avoid double arylation.

\[
\begin{align*}
\text{PdL} & \quad \text{Pre-Ru} - 99\% (\text{GC}) \\
& \quad \text{Pre-Brett} - 17\% (\text{GC}) \\
\text{PdL} & \quad \text{Pre-Ru} - 30\% (\text{GC}), n = 7 \\
& \quad \text{Pre-Brett} - 99\% (\text{GC}), n = 7
\end{align*}
\]


- The combination of Pd(OAc)\textsubscript{2} and CyPF\textsubscript{T-Bu} is highly effective for monoarylation of primary amines. While it can be used to effect arylation of secondary amines, the rate is slower and higher catalyst loading is required:

\[
\begin{align*}
\text{Pd(OAc)}_2 (1 \text{ mol%}) & \quad \text{CyPF}-\text{Bu} (1 \text{ mol%}) \\
& \quad \text{NaO}\text{t-Bu}, \text{DME}, 90^\circ\text{C} \\
& \quad 100\% (\text{GC}) \\
& \quad 92\% (\text{isolated})
\end{align*}
\]

C–N Bond-Forming Reaction: The Buchwald-Hartwig Reaction

Challenging Substrate for Coupling

- Aminopyridines frequently function as chelating ligands with palladium. This effect can be mitigated by the use of LiHMDS and hindered, reactive ligands.

\[
\text{Pre-Ru} - 79\% \text{ (isolated)} \\
\text{Pre-Brett} - <10\% \text{ (GC)}
\]


Selective Coupling of Primary over Secondary Amines

\[
\text{Pre-Brett (1 mol\%)} \\
\text{BrettPhos (1 mol\%)} \\
\text{NaO-But, dioxane} \\
80 \text{ °C, 89%}
\]


Large-Scale Amination

• Application to the synthesis of a CNS-Active aminotetralin:

\[
\text{Pre-Brett} \ (1 \text{ mol\%}) \\
\text{BrettPhos \ (1 \text{ mol\%})} \\
\text{NaO-But, \ dioxane} \\
80 \text{ °C, 89%}
\]


Amides as Substrates

\[
\text{[Pd(allyl)Cl]_2 \ (1 \text{ mol\%})} \\
\text{JackiePhos \ (5 \text{ mol\%})} \\
\text{Cs_2CO_3, \ 3Å MS} \\
toluene, \ 130 \text{ °C}, \ 81\%
\]


• Application to the synthesis of an HIV-1 integrase inhibitor:

\[
1. \text{Pd(OAc)_2, Xantphos} \\
\text{Cs_2CO_3, dioxane, \ 65 \text{ °C}} \\
2. \text{TMSCl, NaI} \\
\text{MeCN, 92%}
\]


Ureas as Substrates

• Application to the synthesis of a TRPV1 receptor antagonist:

\[
\text{F_3C} \\
\text{F_3C}
\]

Rob Singer, David Bernhardson
**Sulfamides as Substrates**

- Application to the synthesis of a c-Met Kinase Inhibitor:

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{Br} & \quad \text{Pd} \text{Cl}_2 \text{(dba)}_3 (6.6 \text{ mol\%}) \quad \text{Xantphos (15 mol\%)} \\
\text{Cs}_2\text{CO}_3, \text{THF} & \quad 60 \degree \text{C, 69\%} \\
\end{align*}
\]


**Carbamates as Substrates**

- Application to the synthesis of an intermediate en route to a tetracycline antibiotic:

\[
\begin{align*}
\text{Br} & \quad \text{O} \\
\text{Pd} \text{Cl}_2 \text{(dba)}_3 (5 \text{ mol\%}) \quad \text{Xantphos (15 mol\%)} \\
\text{Cs}_2\text{CO}_3, \text{dioxane} & \quad 80 \degree \text{C, 62\%} \\
\end{align*}
\]


**N-Heterocycles as Substrates**

- Application to the synthesis of an intermediate en route to a tetracycline antibiotic:

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{O} \\
\text{NH} & \quad \text{Pd} \text{Cl}_2 \text{(dba)}_3 (0.5 \text{ mol\%}) \quad \text{Xantphos (1.5 mol\%)} \\
\text{Na}_2\text{CO}_3, \text{dioxane} & \quad 70 \degree \text{C, 73\%} \\
\end{align*}
\]

Ammonia as a substrate

\[ \text{[Pd(cinnamyl)Cl}_2 \text{(1.5 mol\%)}] \]
\[ \text{Mor-DalPhos (2.25 mol\%)} \]
\[ \text{NaO}_t\text{-Bu, NH}_3, 1,4\text{-dioxane} \]
\[ 110 \degree \text{C, 79\%} \]

\[ \text{[Pd(cinnamyl)Cl}_2 \text{(3.0 mol\%)}] \]
\[ \text{Mor-DalPhos (4.5 mol\%)} \]
\[ \text{NaO}_t\text{-Bu, NH}_3, 1,4\text{-dioxane} \]
\[ 110 \degree \text{C, 69\%} \]

Ammonia Surrogates

- Application to the synthesis of a JAK2 Inhibitor:

\[ \text{Pd}_2\text{(dba)}_3, \text{Xantphos} \]
\[ \text{Cs}_2\text{CO}_3, \text{dioxane, 90\degree C} \]
\[ 2. \text{HCl, water, THF, 2 min} \]
\[ 23 \degree \text{C, 89\%} \]

- Application to the synthesis of Vitamin E Amines:

1. \[ \text{Pd(OAc)}_2, \text{BINAP} \]
\[ \text{NaO}_t\text{-Bu, toluene, 80 \degree C} \]

2. \[ \text{Pd/C, HCO}_2\text{NH}_4 \]
\[ \text{MeOH, 65 \degree C} \]
\[ 67\% (2 \text{ steps}) \]

14-kg scale, 86%


PCT Int. Appl., 2011028864, 10 Mar 2011.
The Ullman-type reaction involves coupling amines and other nitrogen nucleophiles with an aryl halide, catalyzed by copper salts. Copper is highly effective for coupling aryl halides with amides, carbamates, azoles and ureas. These substrates tend to be problematic in Pd-catalyzed couplings. The mechanism may follow the same cycle as with Pd, but is more likely to involve coordination of the amine prior to oxidative addition (Strieter, E. R.; Blackmond, D. G.; Buchwald, S. L. J. Am. Chem. Soc. 2005, 127, 4120–4121).

Mechanism:

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Typical Ligands:
- 1,2-diamines (most common), amino acids, 1,3-dicarbonyls, 1,2-amino alcohols, 1,2-diols
- Examples

Typical Cu salts:
- CuI (most common), CuBr, CuOAc, Cu₂O.

Typical Solvents:
- NMP, DMAC, DMSO, DMF, toluene, THF, DME, dioxane.

Typical Bases:
- Most general: Cs₂CO₃. Commonly used: K₂CO₃, K₃PO₄.
- May be used: KOH, CsF, CsOAc.

• 1,2-Diamines are among the most general supporting ligands in Cu-Catalyzed C-N Couplings: The amine nucleophiles often coordinate to copper to form a stable bis-amine complex which impedes catalysis. Diamine chelation suppresses this undesired pathway.

Critical Features of Ligand Design:
- Ethylene or cyclohexane backbone is most effective.
- Further substitution to give tertiary amine, such as TMEDA, leads to ineffective ligands.
- R = CH₃ gives highest reaction rate; larger groups impede rate.
- R = H leads to ligand arylation.

Rob Singer, David Bernhardson
Preparation of benzimidazoles:

\[
\text{NH}_2 + R' \xrightarrow{\text{CuI (5 mol%), Cs}_2\text{CO}_3, \text{dioxane, 90 }^\circ\text{C}} R\text{N} \quad 68-93\%
\]


Selective coupling of pyridazinone in the presence of a sulfonamide and a secondary amide:

\[
\text{HN} \quad \text{NH} \quad \text{CH}_3 \quad \text{H}_3\text{C} \quad \text{N} \quad \text{O}
\]


Preparation of quinolones:

\[
\text{Br} + \text{NH}_2 \xrightarrow{\text{CuI (10 mol%), K}_2\text{CO}_3, \text{toluene, 110 }^\circ\text{C}} \text{N} \quad 67-89\%
\]


Lactams couple selectively over secondary amines:

\[
\text{HN} \quad \text{NH} \quad \text{CH}_3 \quad \text{H}_3\text{C} \quad \text{N} \quad \text{O}
\]


Application to the Synthesis of the Natural Product Geldanamycin

\[
\text{HN} \quad \text{NH} \quad \text{CH}_3 \quad \text{H}_3\text{C} \quad \text{N} \quad \text{O}
\]


Rob Singer, David Bernhardson
Couplings of Azoles

\[
\begin{align*}
\text{N} & \text{N} + \text{I} \text{Br} & \xrightarrow{\text{Cu}_2O (5 \text{ mol\%}) \text{, Cs}_2\text{CO}_3, \text{MeCN}} & \text{N} \text{Br} \\
\text{N} & \text{N} + \text{I} \text{Br} & \xrightarrow{\text{CuBr (10 \text{ mol\%}) \text{, Cs}_2\text{CO}_3, \text{DMSO}}} & \text{N} \text{Br}
\end{align*}
\]


- Inexpensive amino acids can be used as ligands and demonstrate a broad substrate scope:

\[
\begin{align*}
\text{I} & \text{NH} \xrightarrow{\text{Cul (10 \text{ mol\%}) \text{, L-proline (20 \text{ mol\%}) \text{, K}_2\text{CO}_3, \text{DMSO}}} & \text{III}
\end{align*}
\]


- Ligand III is effective for heterocycles and even activated aryl chlorides:

\[
\begin{align*}
\text{I} & \text{NH} \xrightarrow{\text{Cul (10 \text{ mol\%}) \text{, L-proline (20 \text{ mol\%}) \text{, K}_2\text{CO}_3, \text{DMSO}}} & \text{III}
\end{align*}
\]


- Couplings catalyzed by Ligand IV proceed under mild conditions and with a low loading of the copper catalyst:

\[
\begin{align*}
\text{N} & \text{N} + \text{I} \text{O}_2\text{N} & \xrightarrow{\text{CuBr (1 \text{ mol\%}) \text{, IV (2 \text{ mol\%}) \text{, Cs}_2\text{CO}_3, \text{DMSO}}} & \text{N} \text{O}_2\text{N}
\end{align*}
\]


Couplings of Primary Amines:

- Proline is one of few ligands that can facilitate Cu-catalyzed C–N coupling with anilines:

\[
\begin{align*}
\text{I} & \text{N} & \xrightarrow{\text{Cul (20 \text{ mol\%}) \text{, L-proline (40 \text{ mol\%}) \text{, K}_2\text{CO}_3, \text{DMSO}}} & \text{OCH}_3
\end{align*}
\]


Room-temperature C–N coupling can be achieved using ligand V:

\[
\begin{align*}
\text{II} & \xrightarrow{\text{Cul (5 \text{ mol\%}) \text{, V (20 \text{ mol\%}) \text{, Cs}_2\text{CO}_3, \text{DMF}}} & \text{III}
\end{align*}
\]


- Couplings of acyclic secondary amines was virtually unprecedented until the discovery of DMPAO as a supporting ligand:

\[
\begin{align*}
\text{IV} & \xrightarrow{\text{Cul (10 \text{ mol\%}) \text{, DMPAO (20 \text{ mol\%}) \text{, K}_3\text{PO}_4, \text{DMSO}}} & \text{V}
\end{align*}
\]


This methodology can also be applied to primary amines and cyclic secondary amines, but not to anilines:

\[
\begin{align*}
\text{VI} & \xrightarrow{\text{Cul (10 \text{ mol\%}) \text{, DMPAO (20 \text{ mol\%}) \text{, K}_3\text{PO}_4, \text{DMSO}}} & \text{VII}
\end{align*}
\]


DMPAO can also be applied to the synthesis of aryl carbamates:

\[
\begin{align*}
\text{VII} & \xrightarrow{\text{Cul (20 \text{ mol\%}) \text{, DMPAO (40 \text{ mol\%}) \text{, n-BuOH}}} & \text{VIII}
\end{align*}
\]

Ligand-controlled N-Arylation versus O-arylation of amino alcohols


* Chemoselective N-Arylation of 1,2-amino alcohols: the substrate functions as the ligand. The choice of solvent dictates C–N versus C–O bond formation.


C–N Bond-Forming Reaction: Cu-Catalyzed, Ullmann-Type Couplings


* C–N coupling can be facilitated by ortho-chelating groups:

Heterocycle formation via tandem coupling and hydroamidation


Cu-catalyzed C–N couplings with boronic acids

