Oxidative addition of transition metal centers to unactivated C–N single bonds

Historical context, strategies, and applications

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Select reviews on transition metal-catalyzed C–N bond cleavage

  TM-catalyzed C–N bond cleavage via all mechanisms (including OA); organized by functional group

  TM-catalyzed C–N bond cleavage via all mechanisms (including OA); organized by hybridization of C atom

  Recent advances in OA to C–N bonds; organized by mode of activation

  Activation of C–N and C–O bonds via non-precious metal catalysis (predominantly [Ni]- and [Fe]-cat.)
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Outline

1. Introduction
   - Overview of C–N bonds and oxidative addition

2. Pioneering work, key mechanistic investigations
   - Allylamine electrophiles, activation via protonation, and isolated organometallics

3. Strategies and applications in synthetic method development
   - Recent advances: Lewis acid activation, H-bond activation, directed OA, and undirected addition to neutral bonds
C–N bonds and their role in organic synthesis

- C–N bonds are ubiquitous in biology: comprise the linkages of proteins, DNA
- Of small molecule pharmaceuticals up to 2012, 84% contained ≥ 1 N atom
- Extensive research has been done on the formation of C–N bonds; amide coupling one of the most widely-used reactions in medicinal chemistry
- Buchwald-Hartwig reaction possibly the most well-known transition-metal catalyzed method to form C–N bonds:

![Chemical reaction diagram]

Key bond-forming step:

What about the microscopic reverse: oxidative addition to C–N bonds?

First: an overview on oxidative addition

- Often one of the first steps in transition metal-catalyzed cross-couplings:

\[
\begin{align*}
R^X + M^n & \rightarrow OA \rightarrow R^\cdot M^{n+2} X \quad \text{or} \quad [R^\cdot M^{n+2}]^\oplus X^- \\
\end{align*}
\]

**Factors that favor OA**
- Electron-rich metal center
- Open coord sites/minimal steric
- Properties of electrophile
- Relative bond strengths of SM + pdts

**Mechanisms of OA**
- $S_N2$
- Radical/ET-based
- 3-center concerted

- Electrophiles commonly have *good leaving groups*:

R\(_{\text{Cl}}\) \quad R\(_{\text{Br}}\) \quad R\(_{\text{I}}\) \quad R\(_{\text{OTf}}\) \quad R\(_{\text{OTs}}\) \quad R\(_{\text{OAc}}\)

So, why study OA to C–N bonds?

- Compounds containing C–N bonds are cheap and accessible; could serve as useful synthons
- Unique outcome of oxidative addition to a C–N single bond: 2 reactive species formed

![Chemical structure](image)

**Challenges & considerations**

- Electrophile coupling partner has a poor LG
- Metal amides are: strongly basic, have ionic character, and reactive towards β-hydride elimination
- C–N bonds have moderate to high BDEs (see below)

<table>
<thead>
<tr>
<th>Compound</th>
<th>BDE (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtNMe₂</td>
<td>72.3</td>
</tr>
<tr>
<td>EtNHMe</td>
<td>79.8</td>
</tr>
<tr>
<td>EtNH₂</td>
<td>84.8</td>
</tr>
<tr>
<td>AcNH₂</td>
<td>99.7</td>
</tr>
<tr>
<td>PhNH₂</td>
<td>103.2</td>
</tr>
<tr>
<td>NCNH₂</td>
<td>118.8</td>
</tr>
</tbody>
</table>

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The first hint of OA to an unactivated C–N single bond

- Early evidence came a few years after Tsuji's initial report of Pd-mediated allylation:

Tsuji, 1965:

\[
\begin{align*}
\text{PdCl} & + \text{MeO} \text{O} \text{O} \text{Me} \\
\text{Na} / & \text{MeO} \text{O} \text{O} \text{Me} \\
\text{DMSO/EtOH, rt} & \rightarrow \text{MeO} \text{O} \text{O} \text{Me} + \text{MeO} \text{O} \text{O} \text{Me}
\end{align*}
\]

Atkins, Walker, Manyik, 1970:

\[
\begin{align*}
\text{EtN} & + \text{MeO} \text{O} \text{O} \text{Me} \\
0.5 \text{ mol } \% \text{ Pd(acac)}_2 \text{ and } 1.5 \text{ mol } \% \text{ PPh}_3 & \text{at } 85^\circ \text{C} \\
\rightarrow & \text{70%} \text{ MeO} \text{O} \text{O} \text{Me} + \text{30%} \text{ MeO} \text{O} \text{O} \text{Me}
\end{align*}
\]

Studies late in the decade showed a common theme: acetic acid!

Akiyama, Teranishi, 1977:

\[
\text{NH}_2 + \begin{array}{c}
\text{X} \\
\text{C}_6\text{H}_4
\end{array} \xrightarrow{1 \text{ eq Pd(OAc)}_2, 6:1 \text{ dioxane/AcOH, reflux}} \begin{array}{c}
\text{X} \\
\text{C}_6\text{H}_4=\text{C}_6\text{H}_4
\end{array} + \text{NH}_3
\]

11-40% yield

\(X = \text{H, Me, OMe, Cl, NO}_2\)

Trost, Keinan, 1980:

\[
\text{MeNaNH}_{\text{PMP}} + \begin{array}{c}
\text{NH}_2 \\
\text{C}_6\text{H}_4
\end{array} \xrightarrow{1 \text{ eq Pd(PPh}_3)_4, \text{THF, AcOH}} \begin{array}{c}
\text{Me} \\
\text{C}_6\text{H}_4=\text{C}_6\text{H}_4=\text{N}
\end{array}
\]

The stage was set: Brønsted acid-assisted OA to C–N bonds

A cascade of studies followed, following similar mechanisms of C–N bond activation:

\[
\begin{align*}
\text{R}^+\text{NR}_2 & \xrightarrow{\text{H}^+} \text{R}^-\text{NHR}_2 \\
\text{R}^-\text{NHR}_2 & \xrightarrow{[\text{M}^n]} \text{R}^-\text{MN}^{n+2}\text{NHR}_2 \\
\text{R}^-\text{MN}^{n+2}\text{NHR}_2 & \rightarrow \text{p} \text{d} \text{ts}
\end{align*}
\]

great electrophile!

Murahashi, 1985:

5 mol% Pd(PPh\textsubscript{3})\textsubscript{4} \\
2.5 mol% TFA \\
PhH, 50°C

\[
\begin{align*}
\text{PT} & \rightarrow \text{Me}^+\text{N}^{-} \xrightarrow{\text{OA}} \text{Pd}^{\text{II}}_{\text{II}} \xrightarrow{\text{RE}} \text{Me}^+\text{N}^{-} \\
\text{PT} & \rightarrow \text{Me}^+\text{N}^{-} \xrightarrow{\text{OA}} \text{Pd}^{\text{II}}_{\text{II}} \xrightarrow{\text{RE}} \text{Me}^+\text{N}^{-}
\end{align*}
\]

*Tet. Lett. 1985*, 26, 5563-5566
As TM-catalyzed C–N bond cleavage expanded, the mechanism of activation became clearer

- Various organometallic complexes were isolated over the following decades:

Balch, 1983

Arnold, 1994

Ta(OSi(tBu)₃)₃ \[ \xrightarrow{\text{M}_3(\text{CO})_{12}} \] \[ \xrightarrow{\text{THF, reflux}} \] \[ \xrightarrow{1\% \text{Na/Hg}} \]

Balch, 1983

Arnold, 1994

Hartwig, 2002

Ta(III) OA to anilines: electronic factors govern selectivity

- C–N cleavage: R = CF₃, F, Ph; \( \rho = +2.1 \) (\( R = 0.84 \))
- N–H cleavage: R = H, Me, OMe, NMe₂; \( \rho = -0.69 \) (\( R = 0.93 \))

Proposed mechanism:

JACS 1996, 118, 5132-5133
Ni(0) OA to allylamines: a surprisingly favorable elementary step

- Realized during Hartwig’s mechanistic studies of a hydroamination protocol

\[ \text{N} + \text{HR} \rightarrow \text{C} = \text{N} \text{O} \]

- Allylamine products found to exchange with other amines under reaction conditions

- Poor yields in nucleophilic attack of isolated allyl complex with amine led to investigation of microscopic reverse

- Stoichiometric reactions allowed isolation of C–N OA products:

\[ \text{(DPPF)Ni(COD)} \rightarrow \text{Ni}^{II}(\text{DPPF}) \ + \ \text{free amine} \]

- Racemization of enantioenriched allylic amines occurred under the reaction conditions with chiral ligand

*JACS 2002*, 124, 3669-3679
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Brønsted acid-assisted OA laid the groundwork for other modes of C–N activation.
Lewis acid-assisted C–N oxidative addition

**Trost, 1995:**

\[
\text{N} \quad \text{Me} \\
\text{Me} \quad \text{N} \\
\text{R} \quad \text{B(OH)}_2
\]

\[
\text{R} = \text{aryl, alkenyl}
\]

\[
10 \text{ mol}\% \text{ Ni(COD)}_2 \\
20-40 \text{ mol}\% \text{ BINAPO} \\
10 \text{ mol}\% \text{ KOH} \\
\text{PhH, reflux}
\]

- Evidence for LA activation: reactivity observed in the presence of a Brønsted base, methylation occurred via methylboronic ester, and allyl pyrrolidines were more efficient than diethyl allylamines

**Nakao, 2014:**

\[
\text{PG} \quad \text{N} \quad \text{CN} \\
\text{R}
\]

\[
10 \text{ mol}\% \text{ CpPd(allyl)} \\
10 \text{ mol}\% \text{ Xantphos} \\
40 \text{ mol}\% \text{ BEt}_3 \text{ or BPh}_3 \\
\text{PhMe, 80°C}
\]

\[
\text{Ac} \quad \text{PPh}_3 \\
\text{Ph} \\
\text{PPh}_3
\]

\[
\text{N} \quad \text{Pd}^{II} \quad \text{C≡N} \quad \text{BPh}_3
\]

\[
\text{isolated!}
\]

Hydrogen bond-assisted C–N OA

Zhang, 2011:

\[
\text{allyl} + \text{ketone} \xrightarrow{10 \text{ mol\% } [\text{PdCl(allyl)}]_2, 6 \text{ mol\% DPPF, 1 equiv pyrrolidine}} \text{adduct}
\]

MeOH, rt

Directed C–N OA

Kakiuchi, 2007:

\[
\text{substrate} + \text{alkynylborane} \xrightarrow{4 \text{ mol\% } \text{RuH}_2(\text{CO})(\text{PPh}_3)_3} \text{product}
\]

PhMe, reflux

R = H, alkyl, allyl  \hspace{1cm} R_1 = \text{alkyl, alkenyl, aryl}

JACS 2011, 133, 19354-19357; JACS 2007, 129, 6098-6099
The home run: undirected OA to neutral C–N bonds

First realized in a carbonylative synthesis of amides from allyl amines:

\[
\begin{align*}
\text{Murahashi, 1994:} & \\
R\text{[N]} & \xrightarrow{5 \text{ mol\% Pd(OAc)}_2, 10 \text{ mol\% DPPF}} \xrightarrow{50 \text{ atm CO, PhMe, 110°C}} \text{[N]}\text{O} \\
\text{[N]} &= \text{NET}_2, \text{NMePh, NBu}_2, \text{NMeBn, piperidine}
\end{align*}
\]

Addition of catalytic TFA resulted in lower yields

\[
\begin{align*}
\text{OA} & \xrightarrow{\text{Pd}^{II} \text{N}} \xrightarrow{\text{Pd}^{II} \text{O}} \xrightarrow{\text{M}} \text{RE}
\end{align*}
\]

\textit{Tetrahedron 1994, 50, 453-464}
OA to C–N bonds with partial double bond character even more challenging

- Early success found in decarbonylative phthalimide cleavage:

Matsubara, Kurahashi, 2008:

\[
\begin{align*}
\text{Ar} = \text{electron-deficient} & \quad \text{R} = \text{aryl, alkyl} \\
\end{align*}
\]

- Nickel catalysis also proved effective for amide C–N bond cleavage:

Garg, Houk, 2015:

\[
\begin{align*}
\text{R}_1 = \text{Ph, Ts, Boc} & \quad \text{R}_3 = \text{alkyl} \\
\text{R}_2 = \text{H, Me} & \\
\end{align*}
\]
Extensive computational studies elucidated constraints of the system

Methodology further expanded to: hydrolysis, transamidation, Suzuki XC, Negishi XC, Heck reaction

More electron-rich ligands found to promote OA to alkylamides

An alternative strategy to amide C–N bond cleavage: twisted amides

Nature 2015, 524, 79-83; ACS Catal. 2020, 10, 12109-12126
To date, very few methods exist which involve undirected OA to neutral arylamines

- Shi’s recent report the first to exploit undirected OA to dialkyl arylamines:

\[
\text{R = alkyl} \quad \text{IMes}^\text{Me}^+ \quad \text{NiBr}_2^{2-} \quad \text{IMes}^\text{Me}^\text{Me}\quad \text{THF, 135°C}
\]

- Mg found to be crucial to reactivity; however, MgBr\(_2\) not
- EPR spectroscopy showed evidence of a \textit{Ni(I)/Ni(III) catalytic cycle}:

- Role of Mg in catalytic cycle remains elusive

\textit{JACS 2018, 140, 13575-13579}
Conclusions and outlook

- At its best, C–N bond OA can achieve unique transformations in synthetic chemistry
- However, we are still figuring out how to selectively and efficiently achieve undirected OA to neutral C–N bonds
  - In-depth mechanistic studies are few and far between
- Generally, atom economy is poor, and utility of methods is an issue
  - The majority of methods reported to date lose stoichiometric amine
  - C–N OA has most frequently been applied to known cross-coupling methods; entirely novel reactions are few and far between
  - The few reactions that allow retention of both components of the electrophile are usually intramolecular

A significant question remains: how do we capture the reactive amide before it is lost as a byproduct?