

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

Historical context, strategies, and applications



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Group Meeting

September 24th, 2021

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

- *Chem. Rev.* **2015**, 115, 21, 12045-12090

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

- *Chem. Soc. Rev.* **2016**, 45, 1257-1272

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

- *ACS Catal.* **2020**, 10, 12738-12759

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

- *ACS Catal.* **2020**, 10, 12109-12126

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

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2. Pioneering work, key mechanistic investigations

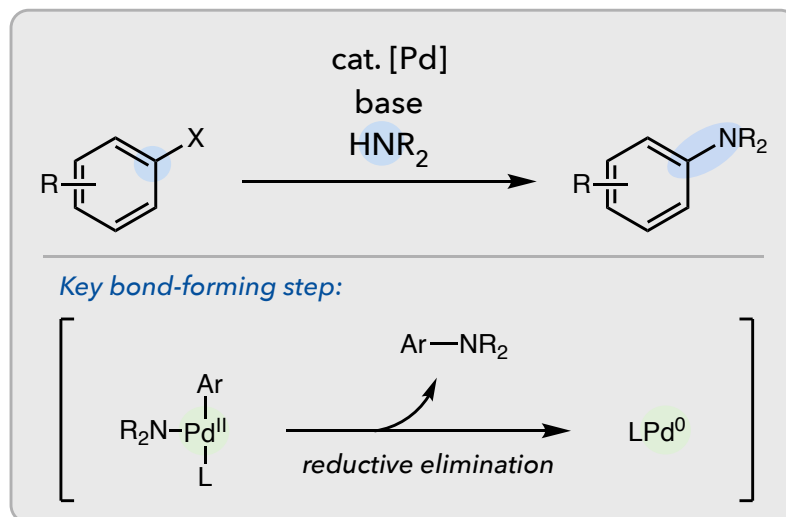
- Allylamine electrophiles, activation via protonation, and isolated organometallics

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

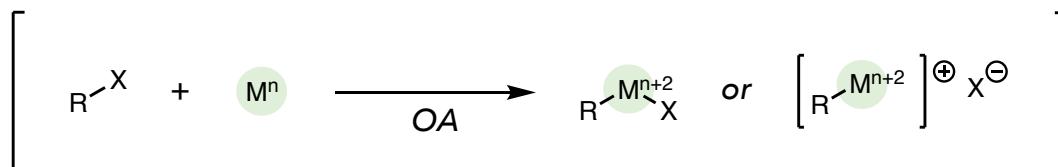
- C–N bonds are ubiquitous in biology: comprise the linkages of proteins, DNA
- Of small molecule pharmaceuticals up to 2012, 84% contained ≥ 1 N atom
- Extensive research has been done on the formation of C–N bonds; amide coupling one of the most widely-used reactions in medicinal chemistry
- Buchwald-Hartwig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



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:



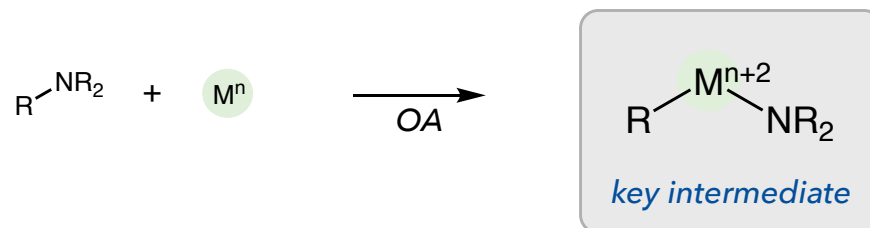
| Factors that favor OA | Mechanisms of OA |
|---|--|
| <ul style="list-style-type: none">· Electron-rich metal center· Open coord sites/minimal sterics· Properties of electrophile· Relative bond strengths of SM + pdts | <ul style="list-style-type: none">· S_N2· Radical/ET-based· 3-center concerted |

- Electrophiles commonly have *good leaving groups*:



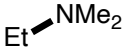
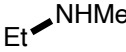
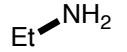
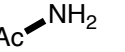
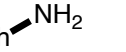
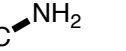
So, why study OA to C–N bonds?

- 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*



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)

| | | | | | | |
|-----------------|---|---|---|---|---|---|
| |  |  |  |  |  |  |
| BDE (kcal/mol): | 72.3 | 79.8 | 84.8 | 99.7 | 103.2 | 118.8 |

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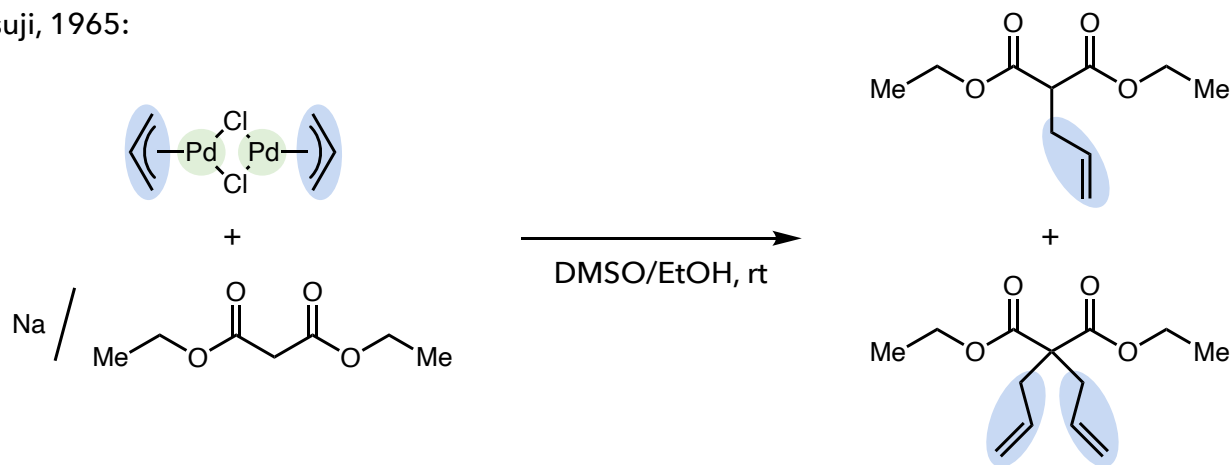
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- Recent advances: Lewis acid activation, H-bond activation, directed OA, and undirected addition to neutral bonds

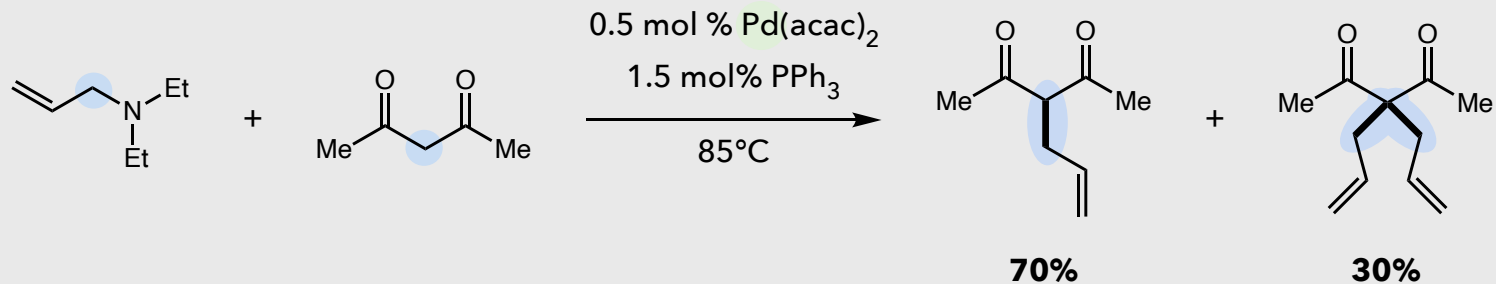
The first hint of OA to an unactivated C–N single bond

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

Tsuji, 1965:

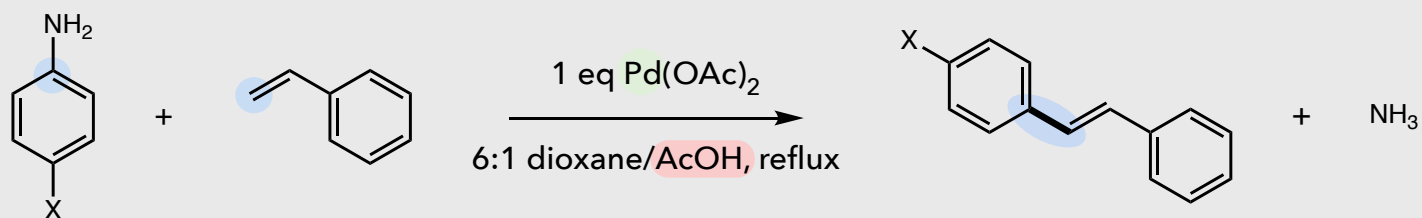


Atkins, Walker, Manyik, 1970:



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

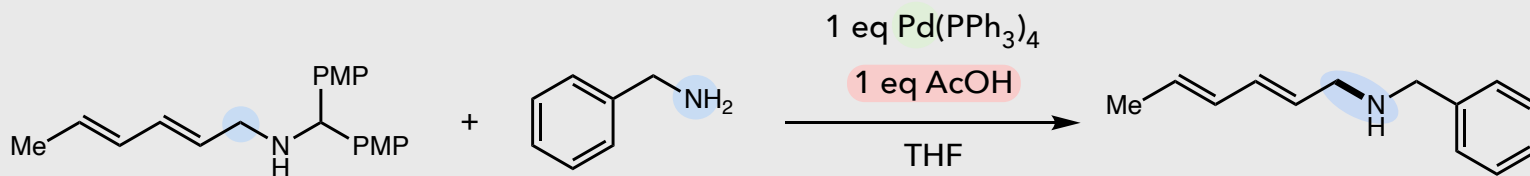
Akiyama, Teranishi, 1977:



11-40% yield

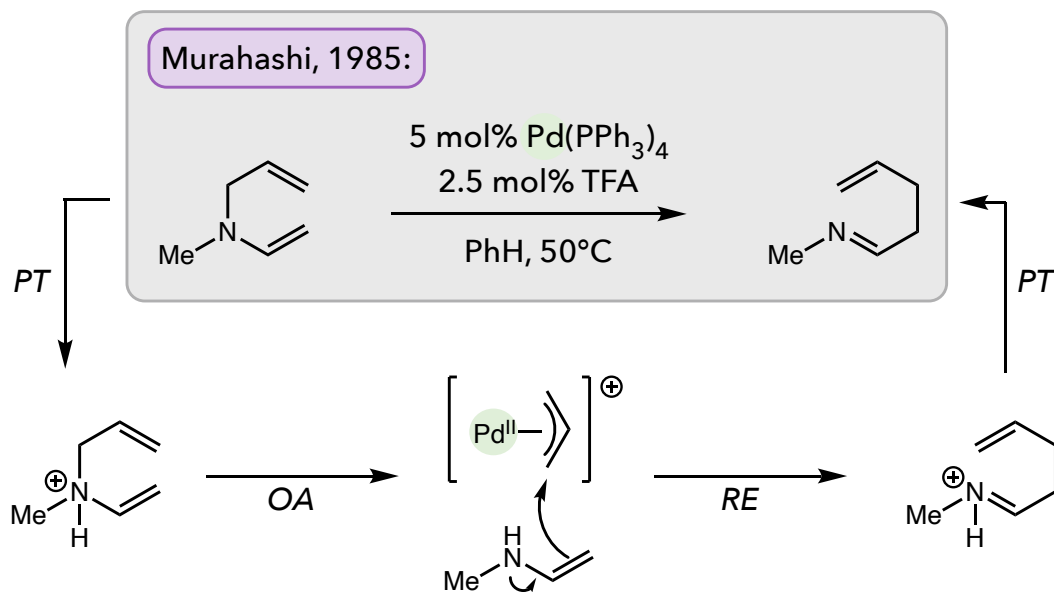
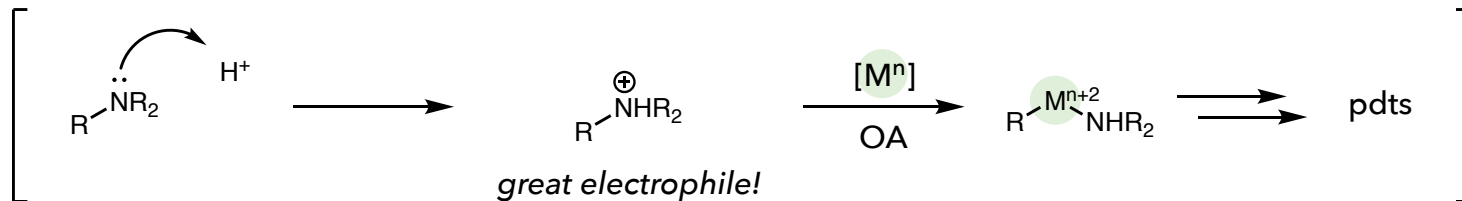
X = H, Me, OMe, Cl, NO₂

Trost, Keinan, 1980:



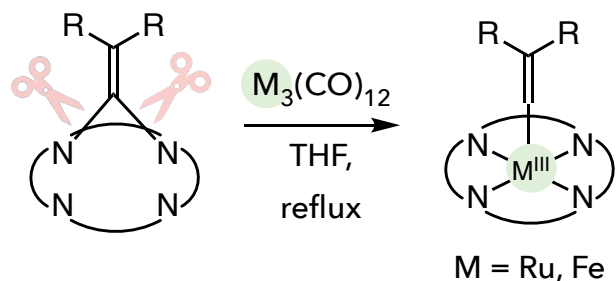
The stage was set: Brønsted acid-assisted OA to C–N bonds

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



As TM-catalyzed C–N bond cleavage expanded, the mechanism of activation became clearer

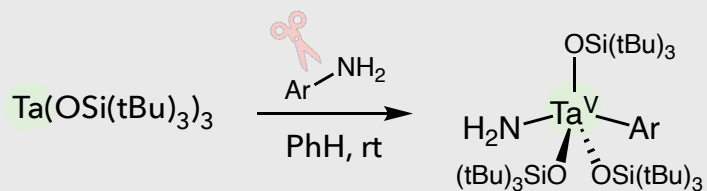
- Various organometallic complexes were isolated over the following decades:



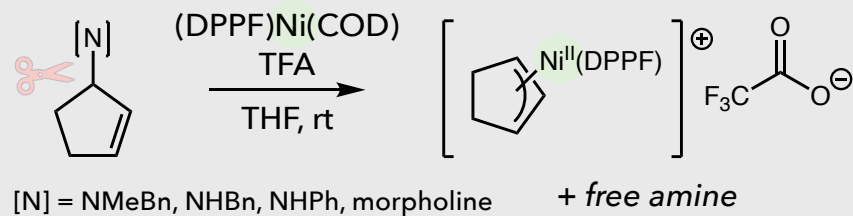
Balch, 1983



Arnold, 1994

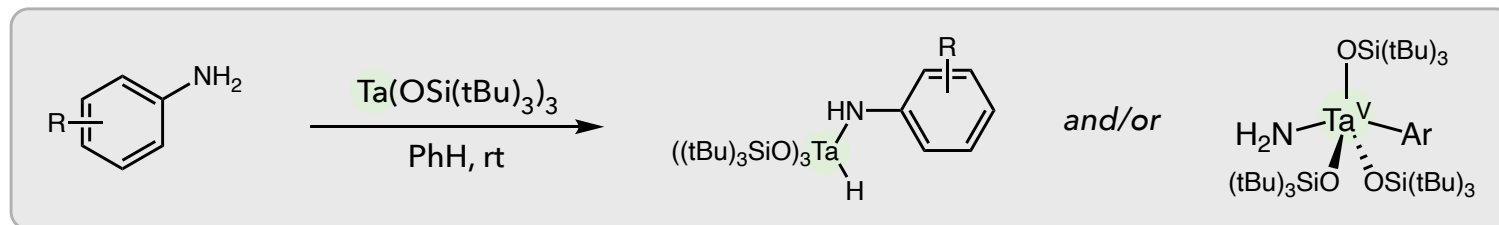


Wolczanski, 1996



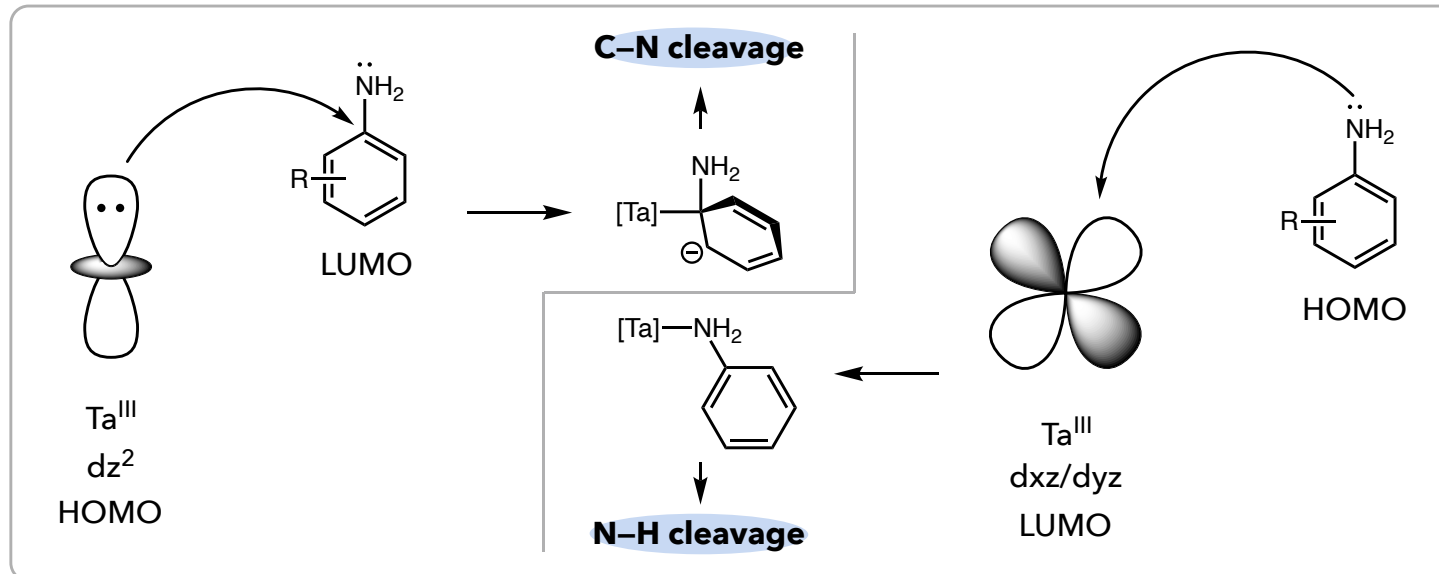
Hartwig, 2002

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



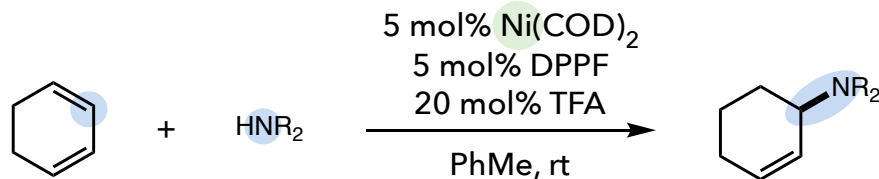
- C-N cleavage: R = CF₃, F, Ph; $\rho = +2.1$ (R = 0.84)
- N-H cleavage: R = H, Me, OMe, NMe₂; $\rho = -0.69$ (R = 0.93)

proposed mechanism:

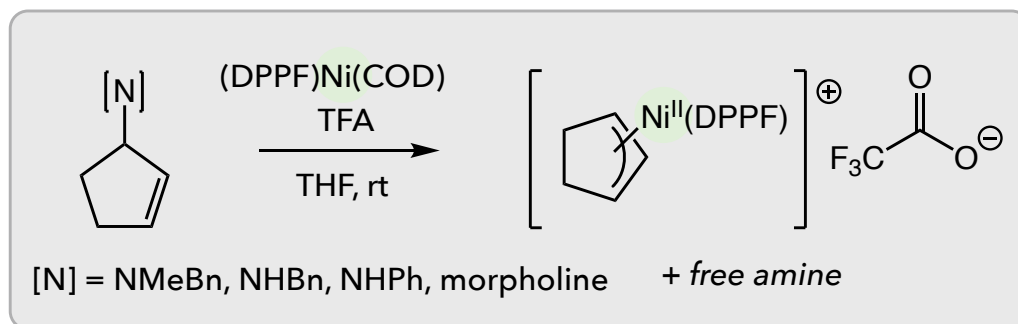


Ni(0) OA to allyl amines: a surprisingly favorable elementary step

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



- 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:



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

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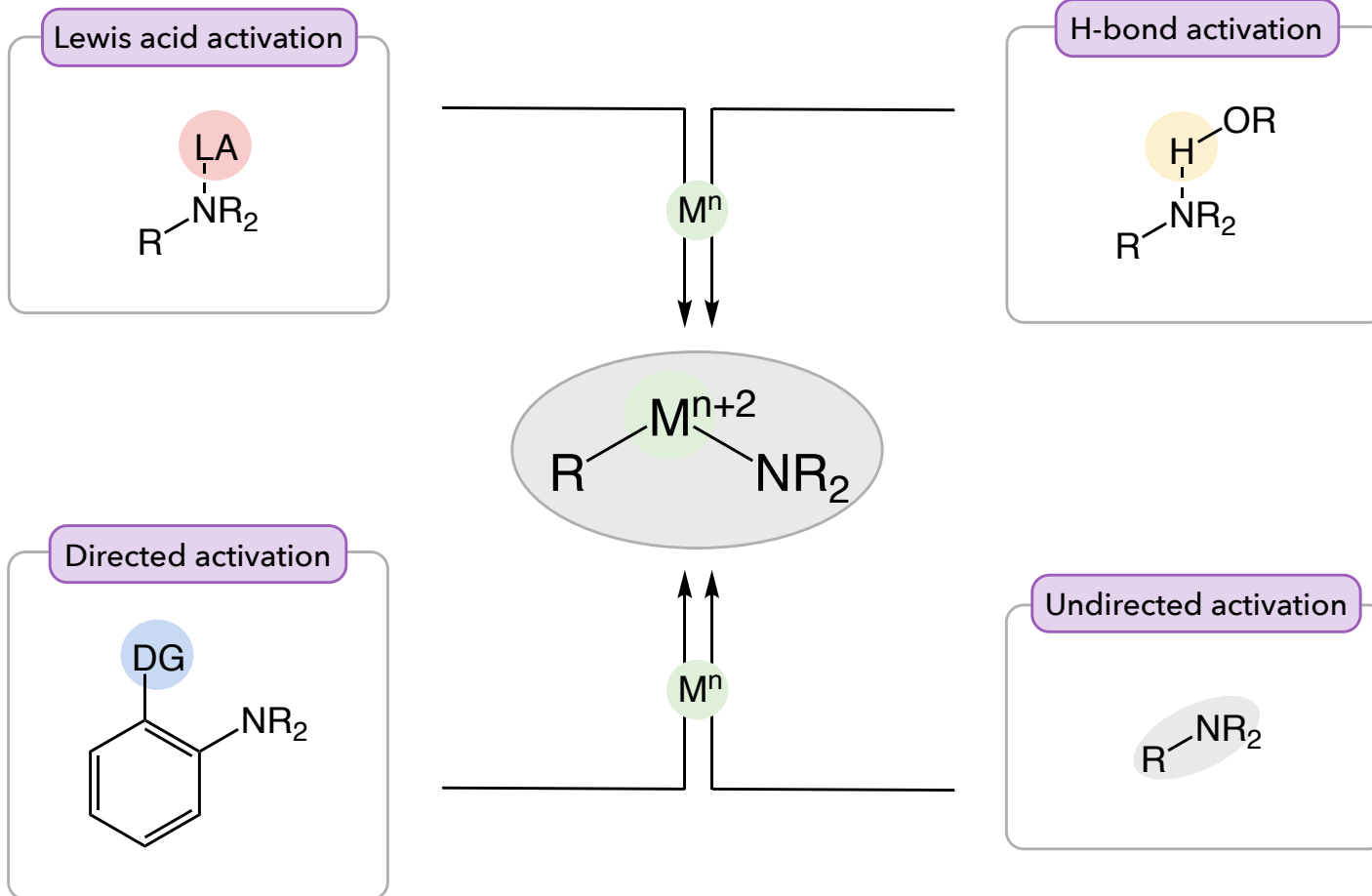
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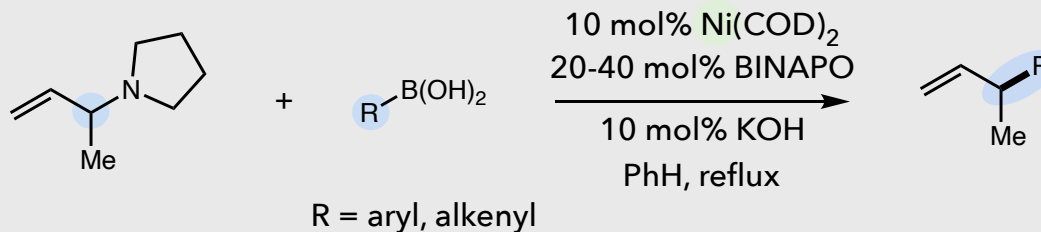
- **Recent advances: Lewis acid activation, H-bond activation, directed OA, and undirected addition to neutral bonds**

Brønsted acid-assisted OA laid the groundwork for other modes of C–N activation



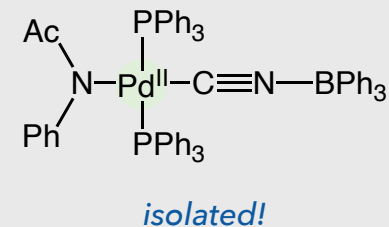
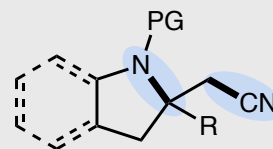
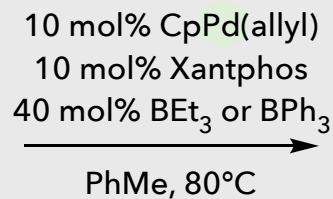
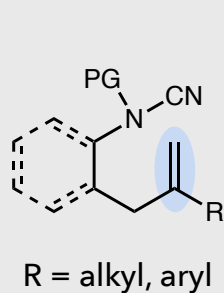
Lewis acid-assisted C–N oxidative addition

Trost, 1995:



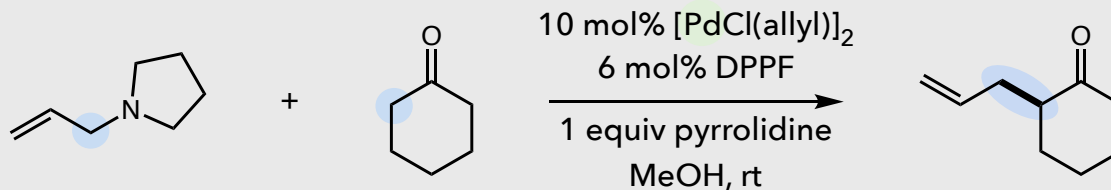
- Evidence for LA activation: reactivity observed in the presence of a *Brønsted base*, methylation occurred via *methylboronic ester*, and allyl pyrrolidines were more efficient than *diethyl allylamines*

Nakao, 2014:



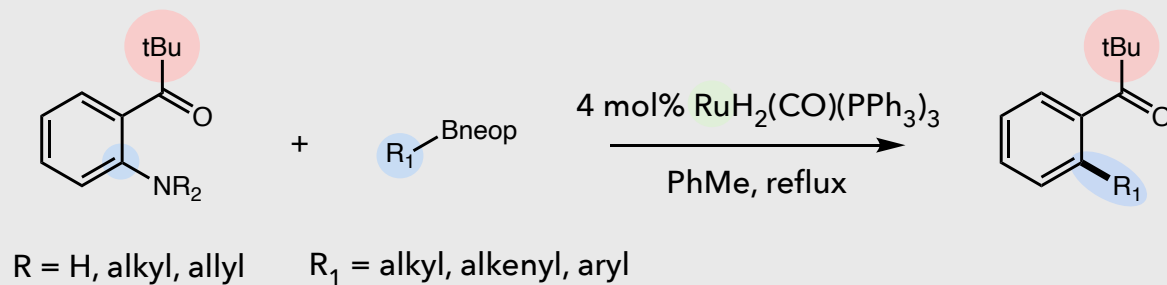
Hydrogen bond-assisted C–N OA

Zhang, 2011:



Directed C–N OA

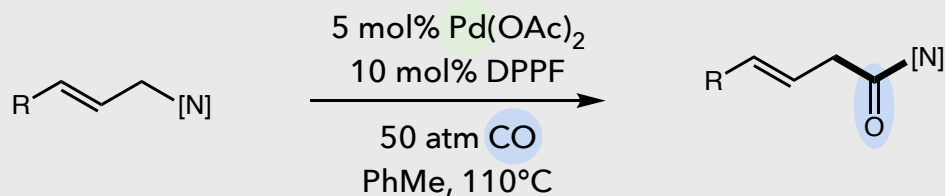
Kakiuchi, 2007:



The home run: undirected OA to neutral C–N bonds

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

Murahashi, 1994:

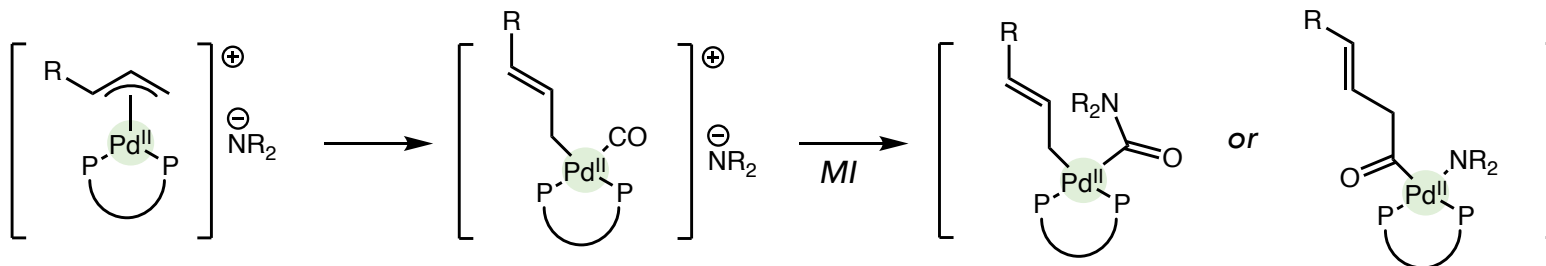


[N] = NEt_2 , NMePh, NBu_2 , NMeBn, piperidine

OA

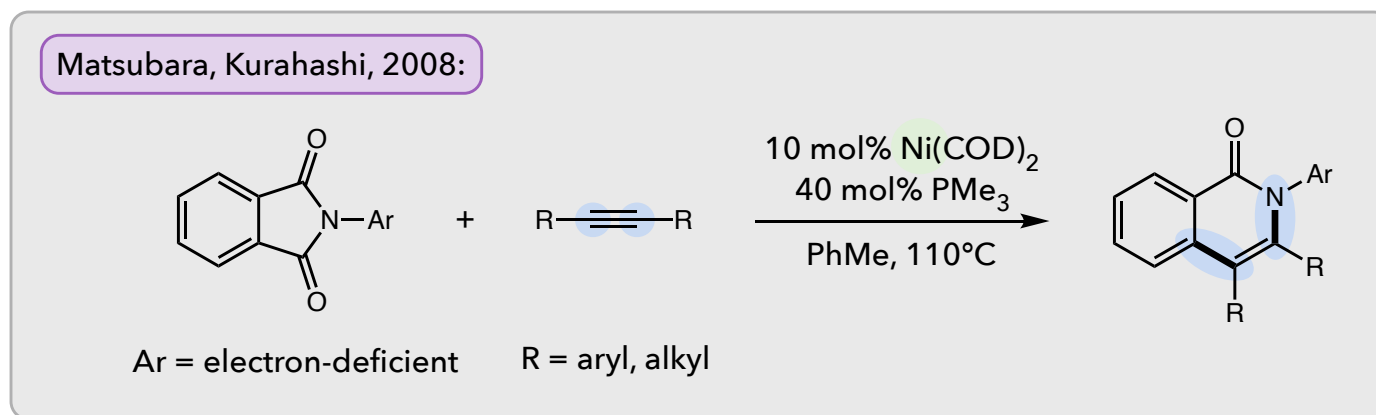
RE

- Addition of catalytic TFA resulted in lower yields

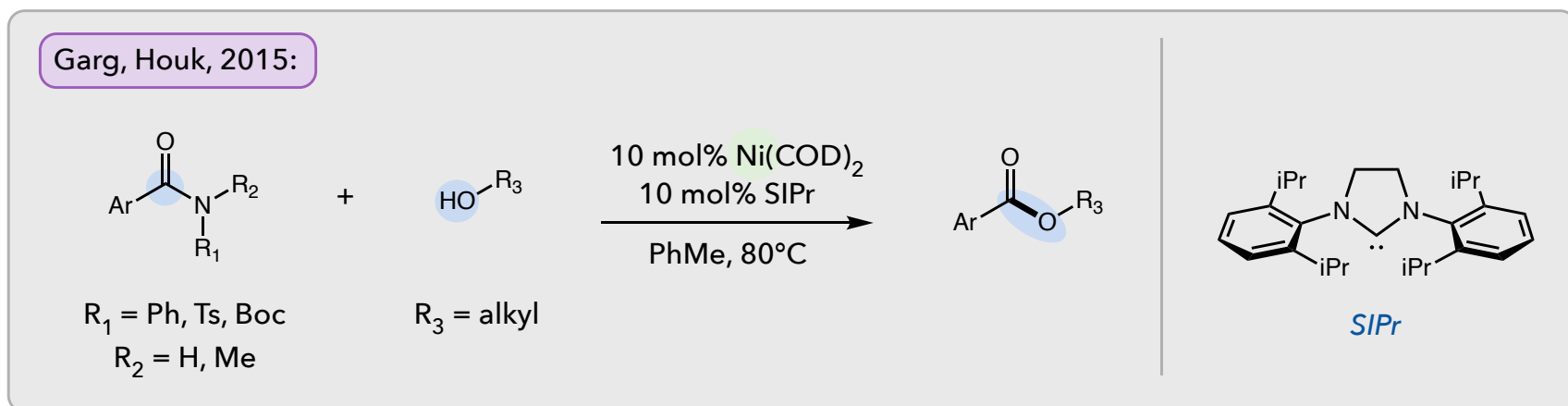


OA to C–N bonds with partial double bond character even more challenging

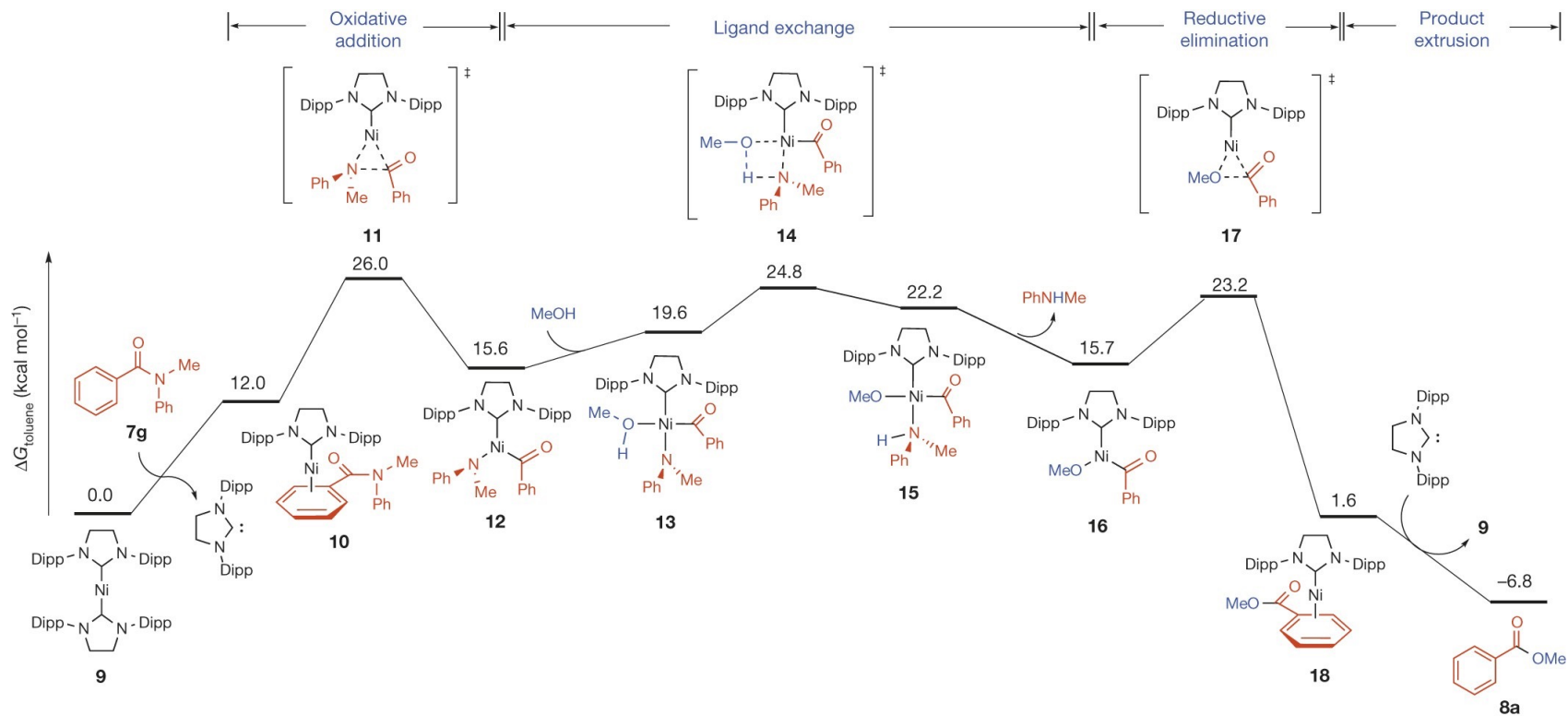
- Early success found in decarbonylative phthalimide cleavage:



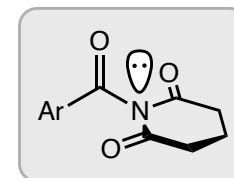
- Nickel catalysis also proved effective for amide C–N bond cleavage:



Extensive computational studies elucidated constraints of the system

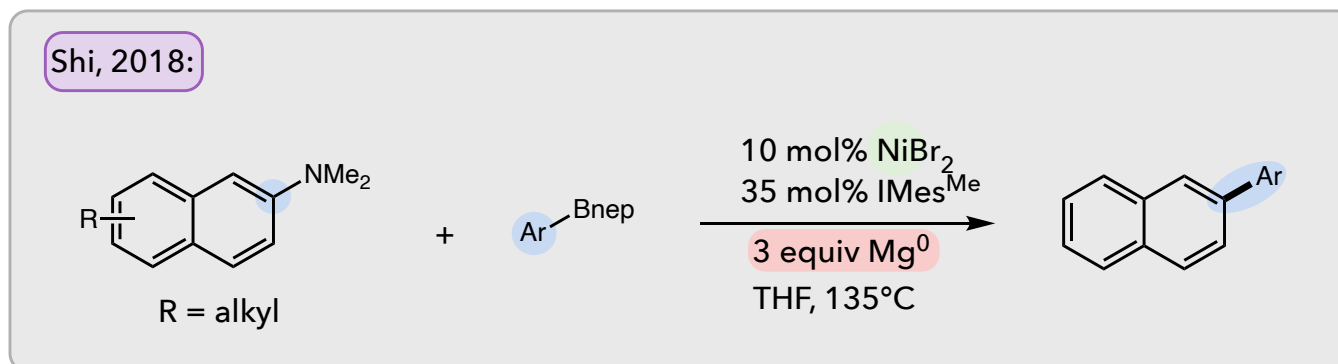


- Methodology further expanded to: hydrolysis, transamidation, Suzuki XC, Negishi XC, Heck reaction
- More electron-rich ligands found to promote OA to alkylamides
- An alternative strategy to amide C–N bond cleavage: twisted amides

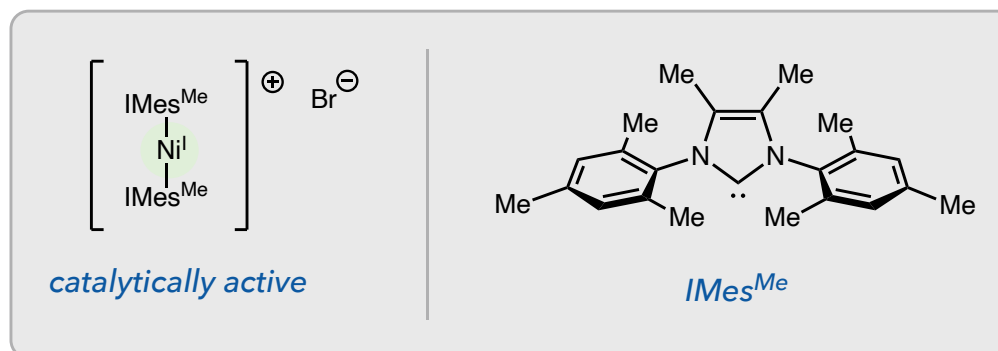


To date, very few methods exist which involve undirected OA to neutral arylamines

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



- Mg found to be crucial to reactivity; however, MgBr_2 not
- EPR spectroscopy showed evidence of a *Ni(I)/Ni(III)* catalytic cycle:



- Role of Mg in catalytic cycle remains elusive

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?*