In catalyzed cross-coupling...
3-arylpyridine ligands are useful for alkylzinc reagents, allowing for the formation of aryl-zinc bonds with high selectivity and yield. The use of these ligands suppresses the elimination of alkenes, providing a more efficient route to alkylzinc reagents.

Mechanistic discussion:

- In the presence of nickel(0) catalyst, alkylzinc reagents undergo cross-coupling with aryl halides to form aryl-zinc bonds. The use of 2,6-dipyridylpyrazolyl ligands helps to suppress the elimination of alkenes, leading to high yields of the desired products.

- The reaction is believed to proceed through a nickel(0) intermediate, which then undergoes oxidative addition to form the aryl-zinc bond. The use of nickel(0) catalysts is crucial for the success of the reaction, and the choice of ligand can greatly affect the reaction outcome.

- Studies have shown that the reaction can be performed under a wide range of conditions, with both air and water as the solvents. The use of nickel(0) catalysts can be achieved through a variety of methods, including pre-catalyst activation and catalyst recycling.

- The reaction is particularly useful for the synthesis of aryl-zinc reagents, which can then be used in a variety of organic transformations, including cross-coupling reactions with other nucleophiles.
Revisiting Nickel

Jacob T. Edwards

Baran Group Meeting

3/26/15

**Proposed mechanism:**

1. BrZNAr
2. ZnBr
3. Ar\[Br

**Mechanistic insights:**

1. Reaction is essentially ELP stirring (involves Ni(II) and Fe(II))
2. High selectivity for formation of the C-C bond
3. N(I)X(R) complexes with pyridine/amine ligands (intricate oxidative)

**Some other enantioselective transformations:**

1. **General N(I)(III) mechanism:**
   - Evidence of radical intermediates:
   - N(I)F \[ Ni(III)

2. **First catalytic enantioselective cross-coupling of α,β-unsaturated electrophiles:**
   - Fischer and Fu, J. Am. Chem. Soc. 2000, 122, 4694

3. **Second catalytic enantioselective cross-coupling of α,β-unsaturated electrophiles:**
   - Jimenez and Fu, J. Am. Chem. Soc. 2000, 122, 4694

4. **Third catalytic enantioselective cross-coupling of α,β-unsaturated electrophiles:**
   - Feringa and Fu, J. Am. Chem. Soc. 2000, 122, 4694

5. **Fourth catalytic enantioselective cross-coupling of α,β-unsaturated electrophiles:**
   - Feringa and Fu, J. Am. Chem. Soc. 2000, 122, 4694

**Key findings:**

1. **Potential for nickel-mediated radical chemistry:**
   - (S)-+$\text{Ph}_2N\text{-BOX}$
   - (R)-+$\text{Ph}_2N\text{-BOX}$

2. **Elevated yield of the desired product:**
   - Curing = 50.2% ee

3. **High selectivity for the C=C bond formation:**
   - Ni(III)X(R) complexes with pyridine/amine ligands (intricate oxidative)

**Proposed mechanism:**

1. BRZNAr
2. ZnBr
3. Ar\[Br

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Cross-coupling with allyl electrophiles

For coupling with allyl Grignard reagents:

- THF, rt, 2.0 equiv.

- CuI, 12 mol% (12 mol% of Ni).

- Aryl halides, coupling with allylic radical.

- NiCl₂, DME, 2 mol%.

- Allylic radical addition is kinetically favored.

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C-N electrophilic:


Oxidative addition: S$_2$-like nucleophilic ring-opening

Reductive elimination proceeds through inversion through either homolysis or heterolysis of the N-N bond. Incorrected or scrambled stereochemistry, respectively.

Extension to cross-coupling:


Proposed mechanism (Jamison):
Revisiting Nickel: Cross-coupling and More

Jacob T. Edwards

Baran Group Meeting 3/26/15

C-H Activation with Nickel:


What type of catalysis is this? Ni(0)/Ni(II)? Ni(I)/Ni(III)? Ni(II)/Ni(IV)?

1. TEMPO did not inhibit the reaction.
2. Catalysis works with both Ni(0) and Ni(II) precatalysts.
3. No biaryl product is formed when Ni(0) is used.
4. Catalysis works with both Ni(0) and Ni(II) precatalysts.

For related transformations (not all-inclusive):

C-H activation of heterocyclic C-H bonds:


C-H alkylation of aromatic C-H bonds:


First example of a transformation of an ortho C-H bond using chelation assistance:

Some key players in Ni chemistry:

- muscoride A
  - Itami and coworkers, J. Am. Chem. Soc. 2012, 134, 13573
  - Ananikov, ACS Catal. 2015, 5, 1964

- isodomoic acid G and H
  - Montgomery and coworkers, J. Am. Chem. Soc. 2009, 131, 17714

Some topics not covered (extensively or at all) for the sake of time:

1. Nickel and photochemistry
2. Ni-catalyzed cycloadditions
3. Ni-catalyzed conjugate additions
4. Reductive coupling
5. Olefin, alkene, and diene functionalization
6. Homo-reductive coupling of organic halides

Useful reviews/book chapters:
- Jamison and coworkers, Nature 2014, 509, 299
- Ananikov, ACS Cat. 2015, 5, 1964

Applications in synthesis:
<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Nucleophile</th>
<th>Ligand</th>
<th>Conditions</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>R(_1)O</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alkyl</td>
<td>Br</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>R(_2)=</td>
<td>arylic, alkényl</td>
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</tr>
<tr>
<td>NiCl(_2)•glyme</td>
<td>(10 mol%)</td>
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<tr>
<td></td>
<td>(12 mol%)</td>
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<tr>
<td>TBAT (2.0 equiv)</td>
<td>(2.0 equiv)</td>
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<tr>
<td>dioxane, rt</td>
<td></td>
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<tr>
<td>First catalytic asymmetric arylation of (\alpha)-halo carbonyl compounds</td>
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<tr>
<td>Notes</td>
<td>Conditions</td>
<td>Reagents/ Additives</td>
<td>Ligands (s)</td>
<td>R'</td>
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</table>

**Asymmetric sp²–sp³**

**Jacob T. Edwards**

Baran Group Meeting

3/26/15

Macmillan, Fu, and coworkers.


Liang and Fu, J. Am. Chem. Soc. 2015, 137, 1832.

<table>
<thead>
<tr>
<th>Reactants</th>
<th>Nucleophile</th>
<th>Electrophile</th>
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</tr>
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<tbody>
<tr>
<td>NiCl₂ • glyme (10 mol%)</td>
<td>PhN=O</td>
<td>1° alkyl</td>
<td>Ref.</td>
</tr>
<tr>
<td>i-PrN=O</td>
<td>1° alkyl</td>
<td>Ref.</td>
<td></td>
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<tr>
<td>NiCl₂ • diglyme (10 mol%)</td>
<td>PhN=O</td>
<td>1° alkyl</td>
<td>Ref.</td>
</tr>
<tr>
<td>NiCl₂ • diglyme (5 mol%)</td>
<td>PhN=O</td>
<td>1° alkyl</td>
<td>Ref.</td>
</tr>
<tr>
<td>NiBr₂ • diglyme (10 mol%)</td>
<td>PhN=O</td>
<td>1° alkyl</td>
<td>Ref.</td>
</tr>
<tr>
<td>NiBr₂ • diglyme (5 mol%)</td>
<td>PhN=O</td>
<td>1° alkyl</td>
<td>Ref.</td>
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</tbody>
</table>
Asymmetric sp<sub>3</sub>−sp<sub>3</sub>−sp<sub>3</sub>

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1 \textit{Am. Chem. Soc.} 2013, 135, 10946. (Asymmetric sp<sub>3</sub>−sp<sub>3</sub>−sp<sub>3</sub>)

1 \textit{Am. Chem. Soc.} 2012, 134, 7794. (Electrophile Nucleophile)

1 \textit{Am. Chem. Soc.} 2012, 135, 5794. (Mechanistic study suggests transmetallation is rate-limiting)

1 \textit{Am. Chem. Soc.} 2013, 135, 10946. (Irreversible oxidative addition)

1 \textit{Am. Chem. Soc.} 2011, 133, 8154. (Acyclic nuc. results in significant branched product)

1 \textit{Am. Chem. Soc.} 2010, 132, 7654. (First example of racemic nuc. in enantioconvergent reaction)

1 \textit{J. Am. Chem. Soc.} 2009, 131, 7386. (Cong and Fu)


Notes

Conditions

Reagents/Additives

Ligand(s)

Ref.