Two Fundamental Challenges in C-H Activation
Reactivity and Selectivity

- Use of Transition metals
  Transition metals can react with C-H bonds to produce C-M bonds

- Use of Directing Groups
  DG bind to the metal center
  And selectively deliver the catalyst to a proximal C-H bond

T. W. Lyons, M. S. Sanford, Chem. Rev. 2010, 110, 1147
C. S. Yeung, V. M. Dong, Chem. Rev. 2011, 111, 1215
Limitations of Directing Groups

DG-assisted C-H ACTIVATION

- Increased reactivity because of metal pre-coordination
- High regio-selectivity
- DG must be pre-installed and remains in the product
- Generally limited to ortho selectivity

C-H ACTIVATION of simple arenes

- No extra steps required to install and/or remove DG
- Possibility of meta or para selectivity

CHALLENGES

- Increase of REACTIVITY Toward transition metals
- Devise new strategies to control REGIOSELECTIVITY

C-C Bond Formation

Biaryl Formation

- Two classes of C-H arylation reactions

1) direct arylation

Ar-X + H-Ar

or

Ar-H + M-Ar

2) dehydrogenative cross-coupling

- Non-Oxidative Direct Arylation
- Oxidative Direct Arylation Using Iodonium Salts
- Oxidative Direct Arylation (Ar-H + Ar-M)
- Cross-Dehydrogenative Couplings (CDC)
- Chelate-Assisted Cross-Dehydrogenative Couplings
Biaryl Formation
Non-Oxidative Direct Arylation (Ar-X + Ar-H)

Rhodium(I) complex that bears two bulky, p-accepting phosphite ligands and that was proposed to promote C-H activation through an electrophilic metalation pathway.

Concerted metalation–deprotonation (CMD) mechanism

In CMD mechanism in the carbonate base, coordinated to the palladium-aryl intermediate, promotes the C-H activation step on the polyfluorinated arene via a six-membered transition state.

Thus, reactivity and regioselectivity were found to correlate well with the acidity of the functionalized fluoroarene.

Oxidative Direct Arylation Using Iodonium Salts

The choice of ligand for the palladium catalyst was shown to be crucial for the selective arylation process. The iodonium salt played a dual role as both substrate and oxidant.

Oxidative Direct Arylation (Ar-H+Ar-M)

As oxidative addition of a latetransition metal into an aryl C-H bond does not generally occur, stoichiometric amounts of an additional oxidant are required for these reactions. To avoid undesired homocoupling of the boronic acid, acidic conditions, which retard transmetalation of the boronic acid onto the catalyst, were applied.

Cross-Dehydrogenative Couplings (CDC)

- The most elegant and environmentally attractive method for the construction of the biaryl motif.
- Employing readily available arene starting materials and does not generate stoichiometric amounts of halogenated or organometallic by-products.

- How reactivity of an unreactive arene
- How the catalyst differentiates between the two C-H bond-containing components to achieve a chemoselective reaction.
- The regioselectivity issues of the reactants themselves.

There are two distinct chemoselectivity-determining factors: 1) the amount of trifluoroacetic acid 2) the ratio of the coupling partners.

However, under the optimized conditions, the formation of significant amounts of homo-coupled biaryl compounds could not be avoided.


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<thead>
<tr>
<th>Reaction Conditions</th>
<th>Yield (TON)</th>
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<tbody>
<tr>
<td>2.5 mol% Pd(OAc)_2</td>
<td>56:44[a] TON = 5.8</td>
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<tr>
<td>1.5 equiv K_2S_2O_8</td>
<td>11 equiv 1 equiv 6.3 equiv TFA</td>
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<td>TFA, RT, 24 h</td>
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<tr>
<td>25 equiv 1 equiv</td>
<td>not observed 15% (93%[b]) TON = 3.1</td>
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<tr>
<td>100 equiv 1 equiv</td>
<td>not observed 32% (&gt;99%[b]) TON = 3.2</td>
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Fagnou and others demonstrated that a CMD-type mechanism is surprisingly operative for the C-H activation of both reaction partners, but not the initial hypothesis that chemoselectivity might be controlled by a difference in C-H activation mechanism.
Chelate-Assisted Cross-Dehydrogenative Couplings

The cross-coupling of two different simple arenes can be achieved when a chelating group is installed onto one coupling partner.

The reaction can be influenced by three parameters:
1) the amount of BQ,
2) the acid additive,
3) the nature of a ligand X on the metal center.

When one equivalent of BQ was used, C-H activation was reversible and complexation of BQ to the intermediary palladium diaryl species was proposed to be rate and selectivity determining.

Under these conditions, arylation occurred predominantly at the sterically less-hindered position of 1,3-dimethoxybenzene. This effect could become further pronounced by the addition of acetic acid.

Para-selective arylation of mono-substituted arenes

The crucial reagents that afforded this reactivity and selectivity were F⁺ oxidants, which recently have been proven to promote otherwise difficult reductive eliminations from Pd⁴⁺ intermediates. A mechanism involving electrophilic palladation was proposed, as a KIE of 1.0 was observed.

Alkylation of Simple Arenes

Mono-substituted arenes were alkylated with exclusive para selectivity

Alkenylation of Simple Arenes

The ligand was found to be crucial for sufficient reactivity (it is bound to the palladium catalyst by a single bond, thus leaving free coordination sites for substrate) and selectivity.

Appropriate catalyst design virtually permits site-selective C-H activation reactions

Alkynylation of Simple Arenes

\[
\begin{align*}
\text{ArH} & \quad + \quad \text{H-yn} \quad \text{R}^2 \\
\text{R}_n & \quad \text{2.0 equiv} \quad \text{1.0 equiv} \\
& \quad \text{5 mol\% [AuCl(PPh_3)]} \\
& \quad 1.5 \text{ equiv Phl(OAc)_2} \\
& \quad 1.0 \text{ equiv NaHCO}_3 \\
& \quad (\text{CH}_2\text{Cl}_2) \\
& \quad 90 \text{ °C, 12 h} \\
\end{align*}
\]

This regioselectivity is consistent with an electrophilic-type C-H activation mechanism that involves nucleophilic attack of the arene onto either a gold-activated alkyne species or onto gold(III) itself.

\[ T. \text{ de Haro, C. Nevado, J. Am. Chem. Soc. 2010, 132, 1512 –1513.} \]
Carboxylation of Simple Arenes

Palladium-catalyzed carboxylation of arenes with formic acid

\[
\begin{align*}
R^1 & \quad + \quad HCOOH \\
1.0 \text{ equiv} & \quad 6.6 \text{ equiv} \\
\text{CF}_3\text{CO}_2\text{H}/(\text{CF}_3\text{CO})_2\text{O} (10:1) & \quad \text{30 °C, 48 h} \\
& \quad 53\text{-}93\% \\
\end{align*}
\]

Selected examples:

- \( \text{Ar} - \text{COOH} \) with \( \alpha/m/p = 18:31:51 \) (89% yield)
- \( \text{Ar} - \text{COOH} \) with \( a/b/c = 14:9:77 \) (71% yield)
- \( \text{Ar} - \text{COOH} \) with 80% single regioisomer


Gold- or copper-catalyzed carboxylation of polyfluorobenzenes with \( \text{CO}_2 \)

\[
\begin{align*}
\text{Ar} - \text{COOH} & \quad \text{Method A: 1.5 mol\% [(IPr)AuOH]} \\
1.05 \text{ equiv KOH, CO}_2 & \quad \text{THF, 20 °C, 12 h} \\
& \quad \text{Method A: 88\%} \\
\text{Ar} - \text{COOH} & \quad \text{Method B: 3 mol\% [(IPr)CuOH]} \\
1.1 \text{ equiv CsOH, CO}_2 & \quad \text{THF, 65 °C, 8 h} \\
& \quad \text{Method B: 85\%} \\
\end{align*}
\]

C-Heteroatom Bond Formation

To be continued next time … …