Combinatorial Chemistry: Carbon-Carbon-Bond Building/Formation

Presented by Dominik Grögel
Contents

1. Resins
2. Types of Reaction
   2.1 Condensation
   2.2 Cycloaddition
   2.3 Carbon - Alkylation
   2.4 Olefin Formation
   2.5 Pd-catalysed Couplings
3. Applications
4. Conclusion
5. References
1. Resins and Linkers

**Merrifield**

**Wang resin**

**Rinkamide**  
\(X=NH\)

**SASRIN**

Furthermore: Safety Catch, trityl, HMPA, traceless, MBHA
2. Types of Reaction

2.1 Condensation

- **Claisen**
  Resins/Linkers: Merrifield, Rinkamide

- **Knoevenagel**
  Resins/Linkers: Wang, SASRIN, Merrifield

- **Mannich**
  Resins/Linkers: 2-chlorotrityl, Merrifield, Wang

Lit.: Reference [1]
2.2 Cycloaddition

Important tool for constructing cyclic systems of different ring-size.

- [2+2] Cycloaddition

\[
\text{Resins: SASRIN, MBHA}
\]

- [4+2] Cycloaddition
  \[\rightarrow\text{Diels-Alder reaction}\]
  \[\text{Resins: Merrifield or PS carboxylic acid resin}\]

Lit.: Reference [1]
2.3 Carbon-Alkylation

- **Aldoladdition**

![Chemical Reaction Diagram](image)

- Alkylation of the \( \alpha \)-carbon of benzophenone imines:
  - → synthesis of unnatural aminoacids on the resin
  - → synthesis of unusual peptides

- Resins: Merrifield, Rink Amide, etc.

Lit.: Reference [1]
2.4 Olefin-Formation

- **Wittig**
  Ylid-based reactions have been successfully transformed to the solid phase

- **Cross Metathesis**

Lit.: Reference [1]
The three "classical" Pd-catalysed C-C-bond building reactions have been successfully transformed to solid-phase chemistry:

- Heck
- Stille
- Suzuki

Also: Sonogashira-Hagihara
2.5 Pd-catalysed Reactions II

- **Stille:**
  In most cases the aryl-halide is bound to the polymer. The aryl/vinyl-stannane must be added.
  Resins/Linkers: Rink, Wang, HMPA, traceless

- **Heck:**
  There is no difference in reactivity if the alkene or the aryl-halide is bound to the resin.
  Resins/Linkers: Wang, Rink, THP, trityl

- **Suzuki:**
  Both polymer-bound aryl-halide and polymer-bound boronic acid give satisfactory results (like Heck).
  Resins/Linkers: Wang, Rink amide, SafetyCatch, THP, traceless

Lit.: Reference [1]
2.5 Pd-catalysed Reactions III

Another possibility: Pd is bound to the polymer

Angew. Int. Ed. 2006, 45

Polyionic gel beads build a highly polar microenvironment, which can be used for:

- Efficient metal scavenging
- Active heterogenous catalyst preparation

Pd-particle size ranged from 3 to 10 nm

Lit.: Reference [4]
Suzuki-Coupling as model for investigating the catalytic activity. Different catalysts have been compared.

$\rightarrow$ Yields have been increased depending to the used catalyst.

Advantage: easy product-isolation and –purification

Disadvantage: Product is not bound to the polymer

---

**Table 1: Comparison of catalytic activity**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield [%] $^{[b]}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_3$/PPh$_3$ $^{[d]}$</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Pd EnCat TPP30</td>
<td>62</td>
</tr>
<tr>
<td>4</td>
<td>Pd$^0$ EnCat 30NP</td>
<td>48</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)$_3$/NBU$_4$Cl$^{[d]}$</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>Pd 2</td>
<td>79</td>
</tr>
</tbody>
</table>

$^{[a]}$ A solution of nBuPhBr (0.149 mmol), PhB(OH)$_2$ (0.179 mmol), and iPr$_2$NH (0.372 mmol) in MeCN/H$_2$O (3:1 v/v; 4 mL) was heated at 85°C for 6.5 h under argon. $^{[b]}$ Determined by GC-MS (internal standard: trans-decahydrophenanthrene). $^{[c]}$ PPh$_3$ (2.1 mol %) was added. $^{[d]}$ NBU$_4$Cl (7.0 mol %) was added.

Lit.: Reference [4]
3. Applications

- **Indole Formation**

\[
\text{O} \quad \text{O} \\
\text{I} \quad \text{NHAc} \\
\text{O} \quad \text{O} \\
\text{R} \quad \text{NHAc} \\
\text{R}
\]

\[
\text{O} \quad \text{O} \\
\text{TMG/dioxane} \\
PdCl_2(PPh_3)_2 \\
\text{Cul, 90°C, 18h} \\
TentaGel
\]

Used in synthesis of trisubstituted indols

Lit.: Reference [3]
Many Carbon-Carbon-bond building reactions, which have their origin in organic solution-phase chemistry, have been successfully transformed and adapted to organic solid-phase chemistry.

Some reactions depend on the use of a certain resin (i.e. Claisen), others not (i.e. C-Alkylation, Aldol)

Reactions can be used in different fields of organic chemistry (Macromolecular Chemistry, Medicinal Chemistry)
5. References


