Beyond this presentation

Transfer Hydrogenation

1903, first report by Knoevenagel
1925 MVP reduction
1960 TM-catalysts of group 8, 9, 10 11 were introduced
1980 first reports on ATH (NP 2001 Noyori & Knowles)
1989 first organocatalyzed ATH

Alkene Metathesis

1950's Ziegler among others find polymerization catalysts
1960's mechanistic studies on novel polymerization catalysts
1967 Calderon coins metathesis reactions
1970 Chauvin mechanism was introduced
1990's Schrock and Grubbs introduce their metathesis catalysts
2005 NP to Chauvin, Schrock and Grubbs

Rearrangements, Isomerizations and Alkyne Metathesis as well as heterogeneous and Enzyme mediated reactions are not covered in this topic

Background

ISODESMIC Reactions:
"...are bond separation reactions in which there is retention of the number of bonds of a given formal type, but with a change in their relation to one another. Such processes in general may be termed isodesmic" (JACS, 1970, 92, 4796.)

ISOFUNCTIONAL (subclass of isodesmic reactions)
"...the number and type of functional groups is conserved throughout the reaction. This can be considered a subclass of isodesmic reactions..."

ERGONEUTRALITY
The energy of starting materials and products should have negligible $\Delta G^\circ$ values. This vindicates that isofunctional reactions are inherently reversible.

Isofunctional reactions

Unimolecular Isomerization and Rearrangement Reaction

Shuttle Catalysis Reaction

Metathesis Reaction

(AEIE, DOI: 10.1002/anie.201803797)
**Shuttle Catalysis**

**Forward Reaction: Functionalization**

![Diagram of forward reaction]

**Reverse Reaction: Defunctionalization**

![Diagram of reverse reaction]

A Shuttle Catalysis process provides a platform for performing functionalization defunctionalization under similar conditions.

Particular attractive if the use of the bare shuttled group should be avoided due to toxicity or instability.

**The Equilibrium**

Key challenge is to shift the equilibrium to afford synthetically useful yields of the desired product. Thermodynamic strategies can be employed to drive the reaction forward.

1) Ring strain release:

Experimentally determined heats of formation ($\Delta H_f$) and calculated strain energies ($SE$), and entropies ($S^*$) olefinic strain release ($OS$)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\Delta H_f$ (kJ/mol)</th>
<th>$SE$</th>
<th>$S^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5H8</td>
<td>12.73</td>
<td>27.5</td>
<td>56.8</td>
</tr>
<tr>
<td>C6H10</td>
<td>6.78</td>
<td>26.5</td>
<td>63.4</td>
</tr>
<tr>
<td>C7H12</td>
<td>-18.44</td>
<td>6.2</td>
<td>70.0</td>
</tr>
<tr>
<td>C8H14</td>
<td>-29.5</td>
<td>0</td>
<td>71.3</td>
</tr>
<tr>
<td>C9H16</td>
<td>21.1</td>
<td>19.2</td>
<td>4.8</td>
</tr>
<tr>
<td>C10H18</td>
<td>-1.08</td>
<td>0.3</td>
<td>74.3</td>
</tr>
</tbody>
</table>

**ACIE, 1986, 25, 312.**

2) Le Chateliers principle

![Diagram showing le chateliers principle]

**HCN transfer**

- **Ni(COD)$_2$ (5 mol%), DPEphos (5 mol%), AlMe$_2$Cl (20 mol%),**
- PhMe
- 100-130 °C, 16 h

- **Ni(COD)$_2$ (2.5 mol%), DPEphos (2.5 mol%), AlMe$_2$Cl (10 mol%),**
- PhMe
- rt, 16 h

The role of the Lewis acid co-catalyst was corroborated by computational studies.

Every step is intrinsically reversible.

For every essential mechanistic step a microscopic reverse exists.

(ACIE, DOI: 10.1002/anie.201803797)
**H₂/CO transfer**

Otto Roelen, 1938

\[
\text{H₂ + CO} \rightarrow \text{H} + \text{CO}
\]

120–170 °C, 200–300 bar

[Rh] (2 mol%), TMS

60 °C, 24 h

50 equiv

Lenges et al., ACIE, 1999, 38, 3533.

isolated example of the forward reaction

**H₂/CO shuttleted group**

Murphy et al., Science, 2016, 347, 56.

no isomerization of products observed, reaction runs under kinetic control

**HCl/CO transfer**

Walter Reppe, 1940's

\[
\text{HCl + CO} \rightarrow \text{Nu} + \text{CO}
\]

T, p

Pd₂dba₃ (5 mol%), Xantphos (10 mol%), NBE (2 equiv), ThMe₂, 100 °C, 16 h

Reaction is more feasible with alkynes as compared to alkene

**Dehydroxymethylation**

[Chiodi et al., JACS, 2018, 140, 10126.]

**Product yield:**

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBF</td>
<td>0%</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>0%</td>
</tr>
<tr>
<td>I⁻</td>
<td>6%</td>
</tr>
<tr>
<td>O⁻</td>
<td>27%</td>
</tr>
<tr>
<td>Me⁻</td>
<td>27%</td>
</tr>
<tr>
<td>O⁻Me⁻</td>
<td>99%</td>
</tr>
</tbody>
</table>
RCHO transfer

Polymerization of styrene products as additional driving force

Transfer hydrogen strategy
**H₂O transfer**

Traditional approach required harsh conditions, which are poorly compatible with polar functional groups and causes epimerization.


**X - transfer**

3-membered cyclic compounds are well-documented intermediates in organic synthesis.


The reaction proceeds via σ-bond metathesis of the Ag-cat. into the strained Si–C bond, followed by a β-silyl elimination.


First report by Cooper and Finkbeiner in 1962. It is shown that NiCl₂ and Cp₂TiCl₂ catalyze the homomagnesiation reaction as well.


Further report on Hydromagnesiation-type reactions by the group of Xi (2016, Ti-cat., without ligands) utilizing alkynes is a non-isofunctional process.

Greenhalgh et al., JACS, 2012, 134, 272.
Greenhalgh et al., Organometallics, 2014, 33, 5811.
Differentiation between $\pi$ bond and $\sigma$ bond metathesis/ bond multiplicity

**Classification**

Type 1) Metathesis between two functionally **identical** bonds

$$
\text{R}^1\text{H} + \text{R}^2\text{H} \rightleftharpoons \text{R}^1\text{H} + \text{H} + \text{R}^2\text{H}
$$

Type 2) Metathesis between two functionally **different** bonds

$$
\text{R}^1\text{H} + \text{R}^2\text{X} \rightleftharpoons \text{R}^2\text{H} + \text{R}^1\text{X}
$$

**Bond Distribution**

Depending on the directionality of a bond less products will be formed

1) 2 non-directional bonds

$$
\text{R}^1\text{H} + \text{R}^2\text{H} + \text{R}^3\text{H} + \text{R}^4\text{H} \rightleftharpoons \text{R}^1\text{H} + \text{R}^2\text{H} + \text{R}^3\text{H} + \text{R}^4\text{H} + 5 \text{ other new products}
$$

2) 1 non-directional and 1 directional bond

$$
\text{R}^1\text{H} + \text{R}^2\text{X} + \text{R}^3\text{X} + \text{R}^4\text{H} \rightleftharpoons \text{R}^1\text{H} + \text{R}^2\text{X} + \text{R}^3\text{X} + \text{R}^4\text{H} + 3 \text{ other new products}
$$

3) 2 directional bonds

$$
\text{R}^1\text{X} + \text{R}^2\text{X} + \text{R}^3\text{X} + \text{R}^4\text{X} \rightleftharpoons \text{R}^1\text{X} + \text{R}^2\text{X} + \text{R}^3\text{X} + \text{R}^4\text{X} + 52 \text{ other new products}
$$

Metathesis of more than one bond in the same starting material (mainly $\sigma$ bond metathesis)

$$
\text{R}^1\text{X} + \text{R}^2\text{X} \rightleftharpoons \text{R}^1\text{X} + \text{R}^2\text{X} + \text{R}^3\text{X} + \text{R}^4\text{X} + 52 \text{ other new products}
$$

**Chauvin Mechanism**

1971 proposed by Chauvin

$$
\text{(Scheme of Chauvin mechanism)}
$$

**π Bond Metathesis**

Additional to alkene and alkyne metathesis, four more are known

1) Imine/Imine Metathesis

$$
\text{C=N/C=N} \quad \text{Type 1}
$$

$$
\text{Ph}_2\text{N} + \text{p-Tol}_{\text{N}^\text{p-Tol}} \rightarrow \text{Ph}_{\text{p-Tol}} + \text{N}^\text{p-Tol}\text{N}_{\text{p-Tol}} \quad \text{Mo (4 mol%), C}_6\text{D}_6, 80-90 ^\circ \text{C}, 22\text{ h, 1:1:1:1 ratio of imines}}
$$

Other systems catalyzed by Zr, Ta, Ti, Re and Nb: reactivity via carbonyl intermediates were studied.

2) Nitrile/Nitrile Metathesis

$$
\text{C=N/C=N} \quad \text{Type 1}
$$

$$
\text{Ph}_2\text{N} + \text{Me}^{15\text{N}} \rightarrow \text{Ph}_2\text{N} + \text{Me}^{15\text{N}} \quad \text{[M] (cat), d}_6\text{-THF, rt, 1:1:1 ratio of nitriles}}
$$

Crisholm, 2003, t-BuO, t-BuO

3) Nitrile/Alkyne Metathesis

$$
\text{C=C/C=O} \quad \text{Type 2}
$$

$$
\text{N}^\text{R} + \text{C=C=O} \rightarrow \text{N}^\text{R} + \text{C=C=O} \quad \text{W} [5\text{ mol%}, d}_{6}\text{-Me, 95 \text{ C, 6-31 h}}
$$

Johnson, 2007, R = C(CF)\text{3}CH$_3$

Recent example of Fürstner is non-isofunctional

4) Carbonyl/Alkene Metathesis

$$
\text{C=C/C=O} \quad \text{Type 2}
$$

$$
\text{Ar}_\text{O} + \text{C=C=O} \rightarrow \text{Ar}_\text{O} + \text{C=C=O} \quad \text{FeCl}_3 [5\text{ mol%}, \text{DCE, rt, 1-24 h}}\text{, n = 1, 2, n = 1, 2}}
$$

Other report by Schindler, ROM with GaCl$_3$

Organocatalytic examples by Lambert (ROM, tropylium) and Franzén (Ph$_3$CBF$_4$)
**σ Bond Metathesis**

**C–C Metathesis Reaction**

direct bond cleavage depends on:
- ring strain release
- activation of the cleavable bond

\[
\text{RhH(CO)(PPh}_3)_3 \quad (5 \text{ mol\%})
\]
\[
dppe (10 \text{ mol\%})
\]

\[
\text{DMA} \quad 150 \degree C, 12 \text{ h}
\]

+ corresponding Di-Chloride

group of Goldman and Brookhart: tandem dehydrogenation/alkene metathesis, [Ir]/[Mo]-catalyzed system

group of Zhou alkynyl group exchange, [Lu]-catalyzed

**C–N and C–O Metathesis Reaction**

\[
R^1= \text{aliphatic}
\]
\[
R^2= \text{aliphatic, carbonyl}
\]

\[
X=O, \text{ (Esterification)} \quad \text{Transesterification is well known and broadly applied.}
\]
\[
X=\text{N, (Amidation)} \quad \text{Transamination pose challenges because of lower reactivity and an acidic NH bond:}
\]

**Brønsted base catalyzed imine initiated approach** for sec. amides: Gellman and Stahl
**Lewis acidic activation** \(\text{AlCl}_3, \text{Sc(OTf)}_3, \text{Ti(NMe}_2)_4, \text{Zr(NMe}_2)_4\) for tert. amides heavily investigated by Gellman and Stahl

**Activation of the Amides** enabled Ni- or Pd- catalyzed reactions (Szoszak, Garg)

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**σ Bond Metathesis**

**C–Y Metathesis Reaction**

\[\text{C} – \text{Si}/\text{C} – \text{H}
\]

Type 2

\[\text{RuCl(CO)(PPh}_3)_3
\]

\[\text{PhMe or THF}
\]

\[140 \degree C, 14 \text{ h}
\]

\[\text{R}^2=\text{SiMe}_2\text{R}^1
\]

\[\text{[Ru]}-\text{H}
\]

\[\text{[Ru]}-\text{SiMe}_2\text{R}^1
\]

\]

**X–Y Metathesis Reaction**

Traditionally functional group transformations are irreversible

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**C–Hal/C–Hal Metathesis**

\[\text{R}^2=\text{X}^1
\]

\[\text{R}^2=\text{X}^2
\]

**C–Hal/C–Hal [Cu]-cat. metathesis on alkynes discovered by Hein (2017)**

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**Driving forces**:

**Synthesis of Aryl iodides**: Sterically congested, or electron deficient aryl chlorides were employed

**Synthesis of Aroyl Chlorides**: Iodobenzene was used in excess or an electron rich aryl iodide
σ Bond Metathesis

**C–Y Metathesis Reaction**


\[
\begin{array}{c}
\text{SMe} \\
\text{R}^1 \\
+ \\
\text{SR}
\end{array}
\xrightarrow{\text{[Pd] (0.4 mol%), LiHMDS (2.6 equiv.), PhMe, 100 °C, 12 h}}
\begin{array}{c}
\text{SMe} \\
\text{R}^1 \\
+ \\
\text{SR}
\end{array}
\]

Similar as in C–O Metathesis the thioether exchange is scarce
LiHMDS withdraws the thiomethiothioxyde with is considered to drive the reaction


**C–P/C–P Type 1**

\[
\begin{array}{c}
\text{X} \\
\text{PPh}_2 \\
\text{PPh}_2
\end{array}
\xrightarrow{\text{[(allyl)PdCl]_2 (5 mol%), PhMe, 140 °C, 24 h}}
\begin{array}{c}
\text{X} \\
\text{PPh}_2 \\
\text{PPh}_2
\end{array}
\]

Chelation assisted C(sp²)-P cleavage and Phosphonium ion formation is considered mechanistically
Purification of products after oxidation