Cooperative Catalysis

1. Definition

The term cooperative catalysis is used when "two catalysts and two catalytic cycles work in concert to create a single new bond". In other words, a single chemical transformation is achieved by activating both the nucleophile and the electrophile by two different catalysts.

In classical catalysis, a catalyst activates one reagent (in this example, the electrophile) while the other reactant (the nucleophile) is not activated. By activation of the second reagent (the nucleophile), the HOMO-LUMO gap between the electrophile and the nucleophile is diminished even further. This is called cooperative catalysis. In other words, the activation barrier for the reaction of activated electrophile and activated nucleophile is lowered. By cooperative catalysis reaction rates are increased and previously unsuccessful reactions due to high activation energy barriers can be realized.


2. Synonyms

Besides the term “cooperative catalysis” other authors prefer to use different terms to describe the same principle:

- Synergistic Catalysis (MacMillan)
- Cooperative Dual Catalysis (Jacobsen)
- Contemporaneous dual catalysis (Trost)

Jacobsen, JACS 2004, 126, 9928
Trost, JACS 2011, 133, 1706

3. Distinction

Cooperative catalysis has to be distinguished from other multi-catalyst reactions shown below:
3.1. Bifunctional catalysis

The catalyst activates two reactants using different functional groups within the same catalyst. The Corey-Bakshi-Shibata-catalyst is a classic example of a bifunctional catalyst, binding and activating both borane (via the Lewis basic nitrogen) and the carbonyl (via the Lewis acidic boron), to achieve reduction of carbonyls.

[Chemical reaction diagram]

Corey, JACS 1987, 109, 7925

3.2. Cascade catalysis

As the name suggests, cascade catalysis describes one transformation catalyzed by one catalyst that is followed by another independent transformation catalyzed by a different catalyst.

[Chemical reaction diagram]

Rovis, JACS 2009, 131, 13628
3.3. Double activation catalysis

Two different catalysts activate the same substrate. An example of this is the simultaneous activation of triple bond by palladium and gold reported by Blum. The following catalytic cycle shows that sometimes it is hard to distinguish between the above-mentioned catalysis modes. Whereas the highlighted key intermediate is a good example of double activation catalysis, the pre-activation of the terminal alkyne by gold (facilitating the oxidative activation) could also count as cooperative catalysis.

Blum, JACS 2008, 130, 2168

4. Cooperative catalysis in nature

Like many other key concepts of organic synthesis, cooperative catalysis can be found in nature. For example, dihydrofolate reductase activates dihydrofolate by protonation of the imine. The second reactant, NADP\(^+\), is catalytically activated to form NADPH, which binds to the enzyme and transfers a hydride to the activated dihydrofolate. Overall, dihydrofolate is reduced to tetrahydrofolate and NADP\(^+\) is regenerated.

Kraut, Faraday Discuss. 1992, 93, 217
5. Challenges

5.1. Kinetics

Despite the obvious advantages in chemical transformations mentioned above, cooperative catalysis has to overcome an intrinsic kinetic problem. As shown below, reactant A gets activated by Cat1 to form reactive intermediate A' and similarly for reactant B.

\[
\begin{align*}
A + \text{Cat}^1 & \underset{k_A'}{\overset{k_A}{\rightleftharpoons}} A' \\
B + \text{Cat}^2 & \underset{k_B'}{\overset{k_B}{\rightleftharpoons}} B'
\end{align*}
\]

\[K_A = \frac{k_{A'}}{k_A} \quad \text{with} \quad K_A \ll 1\]

The equilibrium constant \(K_A\) is much smaller than 1 as the activated species A' inherently has a greater Free Energy. In other words, the concentration of A' in the reaction mixture is very low.

The same applies to \(K_B\):

\[K_B = \frac{k_{B'}}{k_B} \quad \text{with} \quad K_B \ll 1\]

Combining this information with the rate law for the product formation gives:

\[
\frac{d[C]}{dt} = k \cdot [A'] \cdot [B']
\]

This indicates that when the reactants A' and B' are present in very low concentrations, there is a decrease in reaction rate compared to a reaction where only one of the reactants is activated by a catalyst. The increase in reactivity by activating both reactants has to overcome the low concentrations by increasing the reaction constant \(k\) significantly.

The growing number of chemical transformations enabled by cooperative catalysis demonstrates the feasibility of overcoming this kinetic problem. Nevertheless, it is always useful to keep the kinetics in mind when studying this class of catalytic transformations.

5.2. Background reactions

Related to this issue is the un-(cooperatively)-catalyzed background reactions. In enantioselective catalysis the background reaction has a major effect on the enantiomeric excess of the reaction. Ideally, the background reactions does not, or only very slowly, occur. Otherwise the (racemic) background reaction results in a decrease of enantiomeric excess.

This is an important criterion especially in the case of cooperative catalysis, since both reactants are independently activated by catalysts and are potentially also reactive towards the corresponding unactivated reaction substrate leading to a racemic background reaction. It is possible that the chiral information is transferred by the other catalyst or by the combination of both catalysts.

The challenge of enantioselective cooperative catalysis is to avoid these background reactions. Having established conditions to avoid background reactions, cooperative catalysis provides access to transformations that have so far not been possible.
5.3. Orthogonality

As two catalysts are used for the reaction, the catalysts are free to interact with each other. This can potentially result in self-quenching, which results in deactivating both catalysts. This can occur through a variety of processes, such as strong complexation of a Lewis acid and a Lewis base or a redox interaction. This challenge can be overcome by careful selection of appropriate catalyst combinations.


Reviews:

6. Metal/metal cooperative catalysis

6.1. An early example: Sonogashira coupling

Arguably one of the most important cross-coupling reactions is the Sonogashira reaction first disclosed in 1975 by Sonogashira, Tohda and Hagihara. Despite the term “cooperative catalysis” had not been introduced at that time, the Sonogashira coupling is an instructive example for cooperative catalysis.

Two catalytic cycles work together: palladium activates the aryl halide by insertion into the Ar-X bond. Copper facilitates the deprotonation (reductive elimination) of the sp-bound proton by coordination to the triple bond and forms an organocopper species that undergoes transmetallation to palladium.

Sonogashira, Tetrahedron Lett. 1975, 50, 4467
6.2. Allyl additions to CH-acidic compounds by Pd/Rh catalysis

Ito described an enantioselective allyl addition to α-cyano carbonyls. Rhodium forms an activated enolate attacking the π-allylpalladium(II) complex to form α-allyl-α-cyano-carbonyls (esters, amides and phosphonates) in excellent ee’s and yields. Whereas without palladium no conversion is observed, the expected classic Tsuji-Trost reaction takes place when only the palladium catalyst is used. Interestingly, the reaction rate is significantly lower and no enantioselectivity can be achieved even if chiral Pd-catalysts are used:

The proposed mechanism below explains this behavior. While palladium forms the reactive π-allyl complex, rhodium is coordinated by the nitrile-N to form an activated enolate. This activation results in a higher reaction rate when both catalysts are used. The chiral ligand (AnisTRAP) at rhodium creates a chiral environment around the enolate leading to an enantiospecific addition of the π-allyl fragment.

\[ \text{NC} \quad \text{O} \quad \text{Pr} \quad \text{Me} \]
\[ \text{O} \]
\[ \text{CF}_3 \]

\[ \text{Rh(acec)(CO)}_2(1 \text{ mol%)} \]
\[ \text{[Pd(Cp)[κ^2-C3H5]](1 \text{ mol%)}} \]
\[ \text{AnisTRAP}(2 \text{ mol%)} \]
\[ \text{THF, -40} \, ^\circ \text{C} \]

93 % yield, 99 % ee

(Rh only: 0 % yield, 0 % ee)
(Pd only: 91 % yield, 0 % ee)

\[ \text{Ito, JACS 1996, 118, 3309} \]
6.3. Allyl-trapping of Meyer-Schuster-rearranged propargyl alcohols

Trost developed a dual catalytic tandem reaction involving a propargyl alcohol that undergoes a vanadium-catalyzed Meyer-Schuster-rearrangement followed by subsequent addition of an allyl carbonate. The above reaction does not proceed without both catalysts being present, and in each case when only one catalyst is present, different products are obtained. As shown in the scheme below, if vanadium is used alone, the classical Meyer-Schuster rearranged propargyl alcohol is the only product and the allyl carbonate can be recovered quantitatively. When only palladium is used, the expected Tsuji-Trost product (trapping of the π-allyl palladium complex with propargyl alcohol) is obtained in 85% yield.

When both vanadium and palladium catalysts are used, the propargyl alcohol undergoes Meyer-Schuster rearrangement but instead of a simple protometallation (reductive elimination), the allyl fragment is added.

In order to exclude a simple cascade reaction, the products obtained from the single catalysis reactions were subjected to reaction conditions with the other catalyst. But the dual catalysis product was not obtained, demonstrating that both catalysts are needed simultaneously for the desired transformation.

As shown in the mechanism below, the propargyl alcohol undergoes transesterification with the vanadium catalysts. Subsequent Meyer-Schuster rearrangement gives the vanadium allenolate, which in turn gets intercepted by the π-allyl palladium intermediate. In his prior work, Trost demonstrated that this vanadium allenolate could also be intercepted by aldehydes and imines.
6.4. Direct coupling of aryl halides with pyridine derivatives

Chang developed a Pd/Ru-catalyzed coupling reaction using ruthenium to decarbonylate the pyridine derivative followed by transmetallation to palladium with an insertion of CO into the Pd-OCH$_2$-bond. These reaction conditions allowed the carbonylative coupling without the need for a CO atmosphere typically used in classical carbonylative cross-couplings.

Following a similar mechanism without decarbonylation, the scope could be expanded to pyridyl formamides and quinolone-carboxyaldehydes as substrates for the carbonylative coupling.

Chang, JOC 2003, 68, 1607
6.5. Direct arylborylation of alkenes

Semba and Nakao developed a method for the direct arylborylation of styrenes using palladium and copper catalysis.

Both electron-rich and poor aryl bromides and styrenes are tolerated. Importantly, sensitive or reactive groups like tertiary amines, nitriles and esters can be used under the reaction conditions.

Semba and Nakao proposed that a borylcopper species is generated by reaction of a copper alkoxide with \( \text{B}_2(\text{pin})_2 \). By reaction with styrene a \( \beta \)-borylalkylcopper intermediate is formed which is transmetalated to \( \text{LPdArX} \). Reductive elimination affords the product and regenerates the Pd catalyst.

Semba, Nakao, JACS 2014, 136, 7567
6.6. Direct difluoromethylation of aryl bromides and iodides

Shen reported a Pd/Ag bimetallic catalyst system that cooperatively catalysed the direct difluoromethylation of a broad range of aryl bromides and iodides with readily available reagent TMSCF₂H as the difluoromethyl source under mild conditions. The difluoromethylation method was compatible with a wild range of functional groups.

![Chemical reaction and mechanism diagram]

6.7. Synthesis of substituted butenolides and isocoumarins using Lewis acid and Lewis base

Blum showcased this reaction in the synthesis of substituted butenolides and isocoumarins, which are structural motifs present in numerous biologically active compounds.

Blum employed a carbophilic Lewis acidic Au catalyst to catalyze the cross-coupling reactivity of a second Lewis basic Pd catalyst in order to functionalize vinylgold intermediates arising from intramolecular substrate rearrangements. The Au catalyzes both the initial rearrangement step and the subsequent Pd oxidative addition step, first by lowering the energy of the allene anti-bonding orbital and then by redistributing this electron deficiency through the substrate’s rearrangement via lowering of the energy of the allyl-oxygen anti-bonding orbital in oxonium.
7. Metal/photoredox cooperative catalysis

7.1. Single electron transmetallation in organoboron cross coupling

Cross-coupling reactions are highly effective for $\text{C}_{\text{sp}2}-\text{C}_{\text{sp}2}$ coupling. Extension to $\text{C}_{\text{sp}3}$ has proven to be difficult regarding slower oxidative addition and transmetallation, and possible $\beta$–hydride elimination.

Alkylboron species suffer from slow transmetallation in two-electron processes. To solve this problem, Molander et al. developed a model, which is based on a SET mechanism. They proposed a cooperative catalysis mechanism involving a monomeric Ni(0) catalyst for the cross-coupling cycle and Ir catalyst for the photoredox cycle with visible light. The aryl halide undergoes fast oxidative addition at Ni(0) to form a Ni(II) intermediate. This intermediate captures an alkyl radical (generated in the photoredox cycle) to give the highvalent Ni(III) intermediate, which undergoes reductive elimination to give the product.

The alkyl radical is produced by the excited state of the photoredox-catalyst resulting in the reduced form of the photocatalyst. In a redox reaction between reduced form of the photocatalyst and Ni(I) both catalytic cycles are closed by regenerating both initial catalysts.

Electronic modification of the organo-trifluoroborates had moderate effect on reaction yield: electron-rich trifluoroborate components performed better than those substituted with electron-withdrawing groups. Substrates possessing an ortho-substituent were also well tolerated. Aryl halides bearing electrophilic or protic functional groups (which would be incompatible with more reactive organometallic nucleophiles like Grignard or organozinc reagents) were tolerated.

R-BF$_3$K Scope:

<table>
<thead>
<tr>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN</td>
<td>82%</td>
</tr>
</tbody>
</table>

Ar-Br Scope:

<table>
<thead>
<tr>
<th>Ph</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF$_3$</td>
<td>79%</td>
</tr>
<tr>
<td>OH</td>
<td>63%</td>
</tr>
</tbody>
</table>

Molander, Science 2014, 345, 433
7.2. Alpha alkylation of aldehydes via organo-/photoredox catalysis

MacMillan showed that it is possible to combine organo- and photoredox-catalysts as a method of $\alpha$-alkylation of aldehydes. With this dual catalysis mode it was possible for the first time to expand the scope of enamine catalysis towards the use of alkyl halides as electrophiles. Previously, this generally resulted in catalyst deactivation by alkylation when classical enamine catalysis conditions were used.

The key aspect of this reaction is the formation of an electron-deficient radical, which is intercepted by the electron-rich transient enamine.

MacMillan, Science 2008, 322, 77
7.3. Coupling of $\alpha$-carboxyl $sp^3$–carbons with aryl halides

MacMillian and Doyle demonstrated that simple $\alpha$-amino acids could be used as alkyl radical sources instead of organo-trifluoroborates (as in Molander’s example above) in a similar cooperative catalysis system. The mechanism is analogous to the example above except for the radical decarboxylation. Iodo-, chloro- and bromoarenes can be used as substrates and both electron rich and electron poor arenes are tolerated. Aryl chlorides showed to be also efficient coupling partners if the arenes are electron-deficient.

Aryl halide Scope:

<table>
<thead>
<tr>
<th>Aryl halide</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br-Ar</td>
<td>86%</td>
</tr>
<tr>
<td>N-Ac</td>
<td>88%</td>
</tr>
<tr>
<td>CF$_3$-Ar</td>
<td>75%</td>
</tr>
<tr>
<td>F-C≡N</td>
<td>60%</td>
</tr>
</tbody>
</table>

MacMillan, Doyle, Science 2014, 345, 437
8. Metal/organo- catalysis

8.1. Lewis acid/Lewis base catalyzed enantioselective cyanation of carbonyls

Corey developed a dual catalyzed cyanohydrin formation involving the chiral Lewis acid Mg-BOX activating the aldehyde, and the Lewis base BOX forming a chiral cyanide nucleophile. While BOX alone results in racemic cyanohydrin adducts, Mg-BOX alone only achieves moderate selectivity (65% ee).

It is proposed that TMSCN is hydrolyzed by traces of water to form HCN, which is then activated by BOX to form the chiral cyanide nucleophile.

Even though BOX alone leads to racemic cyanohydrin adducts, the selectivity drops significantly (38 %ee) if the mismatched opposite enantiomer of BOX is used in combination with Mg-BOX.

Corey, Tetrahedron Lett. 1993, 34, 4001

8.2. Asymmetric α-allylation of α-branched aldehydes by Pd/enamine-catalysis

List and coworkers achieved asymmetric direct allylation of carbonyl compounds through three catalytic species: [Pd(PPH₃)₂], benzhydryl allyl amine and (R)-TRIP, a chiral Brønsted acid.

The mechanism of the allylation involves a chiral Brønsted acid-catalyzed condensation to give an enammonium salt, which in turn reacted with the Pd(0) species producing π-allyl-Pd complex known as an ‘asymmetric counteranion-directed catalysis (ACDC) complex’. This complex involves all three catalysts to form a configurationally defined E-enamine, Pd(II) and the chiral counteranion, which resulted in high enantioselectivity.
### 8.3. α-Trifluoromethylation of aldehydes by organo-/Cu catalysis

MacMillan combined an organocatalyst and a Lewis acid in a synergistic way. While the copper cleaves the I-O bond to produce an electrophilic iodonium intermediate, the aldehyde coordinates to the imidazolidinone catalyst to give an enamine, which is sufficiently nucleophilic to attack the iodonium species. This results in the transient iminium species, which hydrolyzes to regenerate the imidazolidinone catalyst. The product is a trifluoro-methylated aldehyde achieved in high yield and ee.

**Table 1:**

<table>
<thead>
<tr>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>yield</th>
<th>ee %</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>yield</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>97</td>
<td>97</td>
<td>4-Ph-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>98</td>
<td>96</td>
</tr>
<tr>
<td>4-MeO-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>95</td>
<td>97</td>
<td>4-Cl-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>98</td>
<td>95</td>
</tr>
<tr>
<td>4-Me-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>94</td>
<td>99</td>
<td>2-F-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>94</td>
<td>96</td>
</tr>
<tr>
<td>3-Me-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>94</td>
<td>96</td>
<td>3-F-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;</td>
<td>97</td>
<td>96</td>
</tr>
</tbody>
</table>

Jiang, List, *ACIE* 2011, 50, 9471

MacMillan, *JACS* 2010, 132, 4986
8.4. Enantio- and diastereo-divergent dual catalysis

Recently, Carreira developed iridium- and organo-catalyzed methods of $\alpha$-allylation in branched aldehydes. The outstanding feature of this reaction is the complete absolute and relative stereocontrol. By using the enantiomers of the ligand and/or the organocatalyst, both enantiomers of both diastereomers are accessible selectively.

When the reaction was carried out with an achiral amine and an achiral ligand, the reaction yields 71% of a racemic mixture of diastereomers (dr 3:1). If a chiral amine is combined with an achiral ligand or vice versa, excellent enantioselectivities (92 to 99% ee) can be achieved for one diastereomer, but the diastereomeric ratio is low (1:1:3 to 1:3). This shows that both amine and ligand are able to control only one stereocenter each without the ability to control the relative configuration. If a chiral amine and a chiral ligand are combined, excellent relative and absolute stereocontrol is obtained.

Note that the enatio- and diastereoselectivity is not reduced with a mismatched catalyst combination, as expected in many other examples. It has been suggested that both activated substrates have a planar geometry and therefore in the transition state of the reaction both catalysts are localized at opposite sides thus minimizing unwanted interactions.

Carreira, Science 2013, 340, 1065
9. **Organo-/organo- cooperative catalysis**

9.1. **Brønsted acid/amine catalyzed γ-benzylation of enals**

If the Brønsted acid and amine base pair is chosen judiciously an inactivation of the catalysts by salt formation can be avoided and catalysis is possible. Melchiorre demonstrated this concept for the γ-benzylation of enals.

The acid protonates the dibenzylic alcohol to form a stabilized carbocation with a chiral phosphate counterion. Through a network of non-covalent interactions a highly ordered transition state is formed in which the transiently formed dienamine attacks the carbocation.

If the catalysts are mismatched both yields and ee's drop significantly (<30%, <21% ee) supporting the simultaneous participation of acid and amine in the transition state.

Melchiorre, *ACIE* 2010, 49, 9685
9.2. tert-Leucine and pyrrolidine catalyzed enantioselective synthesis of tetrahydroxanthenones

Xu et al. reported the synthesis of various tetrahydroxanthenones using substituted pyrrolidine and tert-leucine as shown below.

The simultaneous activation of cyclohexenone and salicylic aldehyde by pyrrolidine and achiral Leucine respectively generates an ion pair through the iminium moiety in the pyrrolidine catalyst. The reaction proceeds to enantioselective domino oxa-Michael addition and intramolecular Mannich reaction, which give the cyclized product upon hydrolysis.

<table>
<thead>
<tr>
<th>$R_1$</th>
<th>$R_2$</th>
<th>yield</th>
<th>ee %</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>89</td>
<td>92</td>
</tr>
<tr>
<td>OMe</td>
<td>H</td>
<td>90</td>
<td>95</td>
</tr>
<tr>
<td>H</td>
<td>OMe</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td>F</td>
<td>H</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>H</td>
<td>Br</td>
<td>86</td>
<td>93</td>
</tr>
<tr>
<td>H</td>
<td>F</td>
<td>95</td>
<td>93</td>
</tr>
</tbody>
</table>