SYNTHESIS ALERTS

Synthesis Alerts is a new monthly feature to help readers of Synthesis keep abreast of new reagents, catalysts, ligands, chiral auxiliaries, and protecting groups which have appeared in the recent literature. Emphasis is placed on new developments but established reagents, catalysts etc are also covered if they are used in novel and useful reactions. In each abstract, a specific example of a transformation is given in a concise format designed to aid visual retrieval of information.


Georg Thieme Verlag does not accept responsibility for the accuracy, content, or selection of the data.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th><a href="H2O">Cu(S,S)-t-Bu-bis-oxazolinyl</a>2][SbF6]2</th>
</tr>
</thead>
<tbody>
<tr>
<td>The title catalyst is one of three related Cu(II)-based Lewis acids which efficiently catalyse the enantioselective addition of a variety of olefins to glyoxylate esters to provide α-hydroxy esters. These catalysts also catalyse enantioselective Diels-Alder and aldol reactions.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>(R)-2,10-Dibromo-5H-dinaphtho[2,1-g:1′,2′-i][1,5]dioxacycloundecin-3,6,9(7H)-trione</th>
</tr>
</thead>
<tbody>
<tr>
<td>The title compound is one of a set of three related C2-symmetric ketones which form dioxirane intermediates with oxone which can epoxidise alkenes enantioselectively.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Chiral (Salen)Al(III) complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>The chiral (Salen)Al(III) complex A catalyzes the enantioselective addition of HCN to N-allyl imines. Catalyst A is easily prepared on a large scale and has an indefinite shelf life.</td>
<td></td>
</tr>
</tbody>
</table>
### [(p-Cymene)(Cl)Ru(m-Cl)]2Ru(Cl)(PCy3)-(CHCHCPh2)

The Grubbs metathesis catalyst reacts with [(p-cymene)RuCl2]2 to form bimetallic bridged-chloride ruthenium carbenes which are more active than the Grubbs catalyst in ring opening polymerisation reactions and ring closing metathesis reactions.

**Catalyst**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Structure</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (0.5 mol%)</td>
<td><img src="image1.png" alt="Structure" /></td>
<td>PhH, rt</td>
</tr>
</tbody>
</table>


### Aldolase Antibody 38C2

The title antibody catalyses an asymmetric aldol reaction between hydroxyacetone and a functionalised aldehyde. The process represents the first time a catalytic antibody has been used to decrease the total number of synthetic steps and to increase the enantioselectivity of natural product syntheses.

**Catalyst**

Antibody 38C2

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (0.7 mol%)</td>
<td><img src="image2.png" alt="Structure" /></td>
</tr>
</tbody>
</table>

Use of the antibody is illustrated by the short synthesis of various brevicomin derivatives.

**Catalyst**

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Structure</th>
<th>Reaction Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (0.5 mol%)</td>
<td><img src="image3.png" alt="Structure" /></td>
<td>PBS, rt, 1.5 d</td>
</tr>
</tbody>
</table>

55% er = 99:1

PBS = phosphate buffered saline, pH 7.4.


### Cationic allenylidene ruthenium complex

A is utilised as a catalyst for ring closing olefin metathesis.

**Catalyst**

A (5 mol%) | ![Structure](image4.png) |

6 examples (yields 40-90%). The catalyst is easily prepared in three steps from ruthenium(III) chloride.


### Methyl(triphenylphosphane)gold(I)

A is an excellent catalyst for the efficient addition of alcohols to alkynes in the presence of a Lewis or Brønsted acid co-catalyst.

**Catalyst**

A (1x10⁻³ mol%) | ![Structure](image5.png) |

7 examples (no yields given).


### Mercury(II) sulfate

The title compound catalyses the rearrangement of 1-alkynyl-2,3-epoxy alcohols affording a stereocontrolled route to 2,3-dihydro-4H-pyran-4-ones.

**Catalyst**

HgSO4 | ![Structure](image6.png) |

7 examples (yields 50-80%).

**Tetrakis(triphenylphosphine)palladium(0)**

The title compound catalyses the synthesis of enantioenriched homopropargylic alcohols from propargylic mesylates via chiral allenylzinc intermediates.


<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh₃)₄</td>
<td>A</td>
<td>c-C₆H₄ClCHO (0.5 eq)</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A (3 mol%), Et₂Zn (1.2 eq)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>THF, 0°C → rt, 6 h</td>
<td></td>
<td>er anti = 98:2</td>
</tr>
</tbody>
</table>

11 examples (yields 47.85%, 68.32 ≤ anti:syn ≤ 95.5, %ee anti = 86-96%).

**Methyltrioxorhenium (MTO)**

The title compound catalyses the facile oxidation of silyl enol ethers with hydrogen peroxide.


<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeReO₃</td>
<td>A</td>
<td>(0.2 mol%), H₂O₂ (2 eq)</td>
<td>96%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>pyridine (1 eq) MeCN-AcOH (95:5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rt, 15 min</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9 examples (yields 0.78-89%).

**Tetracarbonyldi-µ-chlorodirhodium(I)**

The title compound is a selective catalyst for the [5 + 2] cycloaddition of vinylcyclopropanes and alkynes.


<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Rh(CO)₂Cl]₂</td>
<td>A</td>
<td>(5 mol%)</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDCl₃, 30°C, 14 h</td>
<td></td>
</tr>
</tbody>
</table>

**Chiral (acyloxy)borane (CAB)**

The modified CAB Lewis acid A gives better syn/anti selectivity than the Keck BINOL/Ti catalyst in additions of crotyltributyltin to aldehydes. However, allylations are more enantioselective with the Keck catalyst. A is formed in situ from the corresponding tartrate ester and BH₃•THF.


<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Stereochemistry</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(CF₃CO)₂O (2 eq)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>EtCN, –78°C, 5 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>–78°C, 10 h</td>
<td>70%, syn:anti = 92:8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>er syn = 97:3</td>
<td></td>
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<tr>
<td></td>
<td>(1 eq)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9 examples (yields 42.74%, 78.22 ≤ syn:anti ≤ 98.2, %ee syn = 55-93%).

**1,3-Dichlorotetraethylidistannoxane**

The title reagent catalyses the highly selective acylation of alcohols.


<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>17 examples of the acylation of alcohols (yields 0, 92-99%) and 6 examples of the selective acylation of primary hydroxyls in the presence of secondary hydroxyls (yields 84-99%) are reported.</td>
</tr>
</tbody>
</table>
Chiral Binapthylphosphoramidate

The title Lewis base catalyses the enantioselective ring opening of epoxides with silicon tetrachloride.

\[
\begin{array}{c}
\text{SiCl}_4 (1.1 \text{ eq}), \text{A} (10 \text{ mol\%}) \\
\text{CH}_2\text{Cl}_2, -78^\circ\text{C}, 20 \text{ min}
\end{array}
\]

\[
\begin{array}{c}
\text{Cl} \\
\text{OH}
\end{array}
\]

\[
87\%
\]

\[
er = 54:46
\]


5 examples (yields 87-95\%, \%ee 2-87\%).

Rhodium(II) octanoate

Rhodium catalysed decomposition of 2-diazo-3-siloxybutenoates containing a chiral auxiliary in the presence of vinyl ethers results in the diastereoselective synthesis of cyclopropanes with high asymmetric induction. Desilylation and ring expansion produces 2,3-dihydrofurans with retention of stereochemistry.

\[
\begin{array}{c}
\text{Rh}_2(\text{OOct})_4 \\
\text{A}
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \\
\text{MeO}
\end{array}
\]

\[
\text{N} \text{O}
\]

\[
\begin{array}{c}
\text{OTBS} \\
\text{O}
\end{array}
\]

\[
\begin{array}{c}
\text{Ph} \\
\text{MeO}
\end{array}
\]

\[
\text{O}
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Hafnium(IV) trifluoromethanesulphonate / trifluoromethanesulfonic acid

The title catalyst system mediates the Friedel-Crafts acylation of benzene, chlorobenzene and fluorobenzene.


9 examples (yields 60-83%) are described

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(4S)-4-(2-Naphthyl)oxazolidin-2-one

The title chiral auxiliary and its enantiomer, new Evans auxiliary analogs, are synthesised from 2-vinylanaphthalene in two steps in high yield and excellent enantiomeric excess. The synthesis involves a unique solution-to-solid Sharpless asymmetric aminohydroxylation process.


The (4R) enantiomer was synthesised in a similar manner (yield 54%, %ee 93-99%).

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(2S)-2-(1-Methylhydrazino)butan-1-ol

The enantioselective synthesis of \( \alpha \)-phenylalkanamines via intermediate addition of Grignard reagents to chiral hydrazones derived from the title reagent is described.


7 examples (yields 32-54%, %ee 90-92%).

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2,2′-Bis(diphenylphosphinoamino)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl (H₈-BDPAB)

The title ligand promotes the Rh-catalysed asymmetric hydrogenation of enamides leading to chiral arylamine derivatives with excellent ee.


7 examples; yields typically 100% and ee ≥ 95%. Other aromatic enamides include C₆H₅, p-CF₃C₆H₄, p-CH₃C₆H₄, p-ClC₆H₄, p-FC₆H₄, m-CH₃C₆H₄. The reaction is insensitive to the electronic features of the arene substituents but ortho-substituted arynes do not react for steric reasons.

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N-Methyl-bis[(R)-1-naphthyl]ethyl]amine

Highly diastereo- and enantio-selective 1,3-dipolar cycloadditions of nitrones are catalysed by a complex derived from the title compound, (S)-BINOL, and Yb(OTf)₃.


8 examples; yields typically >88%, ee 79, 85, 89-96%
The title reagent catalyses the stereoselective addition of functionalized dialkylzincs to 1,2-, 1,3- and 1,4-aminoaldehydes.


Ligand

A

BOC

N

H

Ph

O

BOC

N

n-Pr

Ph

OH

90%, er > 99:1

9 examples (yields 42, 74-90%, %ee 24->98%). In addition, 5 examples of 1,2 addition to \(\alpha,\beta\)-unsaturated aminoaldehydes (yields 66-86%, %ee 79-95%) are reported.


Ligand

A

R = i-Pr

B

R = t-Bu

NH

O

O

HN

O

Ph

Ph

Ph

PhO

RuCl_3 (2.5 mol%), NaIO_4

CH_2Cl_2

pH 8 phosphate buffer

4°C, 3 d

One example of enantioselective epoxidation and 3 examples of enantioselective cobalt-catalyzed Michael addition of malonates to chalcone utilising ligand B are reported (yields 12-17%, %ee = 75-89%).


Ligand

A

OH

NH

O

CF_3

O

CF_3

NH

OMe

[RuCl_3(HMB)]_2 (0.25 mol%), i-PrOK (2.5 mol%)

i-PrOH, rt, 5 h

85% overall

A (2.5 equiv.)

TfOH (0.2 mol%)

Et_2O, 10 min

8 examples; yields 86-97%. Selectivity postulated to arise from the high affinity of the electron-rich naphthalene ring for the palladium surface.
### 2-Acetyl-4-nitroindan-1,3-dione

The title compound reacts with primary amines to form 1-(4-nitro-1,3-dioxoindan-2-ylidene)ethyl (Nde) derivatives as stable yellow amorphous solids in good yields. The Nde protecting group is stable towards the reagents commonly employed in solid phase peptide synthesis and its deprotection with 2% hydrazine in DMF can be easily monitored visually.


![Protecting Group](image)

### Di-tert-butylchlorosilane

A novel one-pot selective silylation of the internal hydroxyl group of 1,2-diols is reported.


![Protecting Group](image)

### BOX-Zn-CH₂CH=CH₂

The title compound adds the allyl ligand with high enantioface selectivity to alkynyl ketones.


![Reagent](image)

### Benzyl triphenylmethyl ether

The title reagent reacts with DDQ to give an O-trityl benzaldehyde carbocation which can be used to deliver an O-trityl protecting group.


![Reagent](image)

### [Bis-1,3-diphenylphosphinopropane]nickel(II) chloride/diisobutylaluminium hydride

The title reagent pair effects the clean and efficient deprotection of allyl ethers. The reaction can also be applied to the deprotection of N-allylamines.


![Reagent](image)
**N-tert-Butoxycarbonylmethyl-2-diphenylmethyl-4-phenyloxazolidine**

The lithium enolate of the title glycine equivalent undergoes a highly stereoselective aldol reaction with a variety of aldehydes. Removal of the chiral auxiliary produces chiral β-hydroxy-α-amino acids of erythro stereochemistry.


<table>
<thead>
<tr>
<th>Reagent</th>
<th>Synthesis of 5 examples (aldol yields 73–94%, %de 84–98%).</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(a) LDA, THF, –78°C, 1 h</td>
</tr>
<tr>
<td>B</td>
<td>(b) i-PrCHO, –78°C, 1 h</td>
</tr>
<tr>
<td>A</td>
<td>94%, dr = 99:1</td>
</tr>
<tr>
<td>4 steps</td>
<td>85%</td>
</tr>
<tr>
<td>HO</td>
<td>94%, dr = 99:1</td>
</tr>
<tr>
<td>NH₂</td>
<td>94%, dr = 99:1</td>
</tr>
</tbody>
</table>

**Z-Crotyltrifluorosilane**

The croylation of β-hydroxy α-methyl aldehydes with the title reagent offers an excellent way to install the anti, anti-dipropionate stereotriad.


<table>
<thead>
<tr>
<th>A</th>
<th>TBDPSO OH Sialf3</th>
<th>TBDPSO OH OH Sialf3</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>(3.2 eq) DEOA (5 eq)</td>
<td>CH₂Cl₂, 0°C, 36h</td>
</tr>
<tr>
<td>75%, dr = 93:7</td>
<td>7 examples (yields 44-76%, 50:50 ≤ anti, anti : other diastereomers ≤ 96:4).</td>
<td></td>
</tr>
</tbody>
</table>

**N,N-di-Boc’-tritylguanidine and N,N-di-Cbz’-tritylguanidine**

The title diprotected tritylguanidines are a new class of guanidinylation reagents.


<table>
<thead>
<tr>
<th>A</th>
<th>R = Boc</th>
<th>R = Cbz</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHBoc</td>
<td>NHBoc</td>
<td>NHBoc</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
</tbody>
</table>

11 examples of the guanidinylation of amines, amino acids and peptides (yields 75-100%) are reported.

**Z-1-(Phenylsulfonyl)-4-(trimethylsilyl)-2-butenes**

A and B are synthetic equivalents for the 1-(1,3-butadienyl) anion and the 1,1-(1,3-butadienyl) dianion. Deprotonation and reaction with an electrophile gives the corresponding product with stereochimetrical retention. Elimination of the products from A or B gives selectively the (E)-butadiene.


| A       | BuLi (1.1 eq) | THF, –78°C, 20 min |
| B       | Mel (1.3 eq) | THF, rt, 1 h |
| A       | SI₃Me | SO₂Ph |
| B       | SI₃Me | SO₂Ph |
| 74%     | E/Z > 98.2 |

14 examples of the synthesis of (E)-1-substituted-1,3-butadienes (yields 51-88%, E/Z ≥ 98:2) and 3 examples of A or B acting as a dianion equivalent (yields 71-98%) are reported.

**N-Acryl-N-allyl-o-tert-butanilide (A) and N-(o-tert-Butylphenyl)-2-methylmaleimide (B)**

Iodine- or Lewis acid-mediated asymmetric Diels-Alder reaction of the axially chiral title compounds with various dienes proceeds with high endo and diastereofacial selectivity.


| A       | El₂AlCl (1 eq) | CH₂Cl₂, rt, 20 min |
| B       | (5 eq) | 100%, endo:exo = 97:3 er = 98:2 |
| 100%    | 100% |

Synthesis of A and B and 4 examples of Diels-Alder reactions (yields 84-100%, endo:exo ≥ 20:1, diastereofacial selectivity ≥ 14:1) are reported.