**SYNTHESIS ALERTS**

*Synthesis Alerts* is a 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.

---

**Zinc**

Synthesis of thiol esters from acyl chlorides and thiols in the presence of activated zinc is described. A can be recovered and reused after reactivation.


18 examples (yields 89-91%).

**Homochiral Phosphoramidate Lewis Base**

The title phosphoramide catalyses an asymmetric aldol reaction between a range of trichlorosilyl enolates and aromatic aldehydes, with high anti-diastereoselectivity and moderate to high enantioselectivity.


5 examples (yields 91-97%, 15:1 ≤ anti: syn ≤ 35:1).

**Vanadyl Acetylacetonate**

Tertiary cyclopropanol systems react with a catalytic amount of A under an oxygen atmosphere to afford β-hydroxyketones and β-diketones.


9 examples (combined yields 46-85%).
### Tetrakis(triphenylphosphine)palladium(0)

A variety of N-heterocycles are synthesized from lactams via Pd(0)-catalysed couplings of their corresponding enol phosphates.

K. C. Nicolaou, G.-Q. Shi, K. Namato, F. Bernal

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Me_2SiCl.CH (3 eq)</th>
<th>A (10 mol%), CuI (10 mol%)</th>
<th>Et_3NH-THF (2:1), rt, 4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(PPh_3)_4</td>
<td><strong>A</strong></td>
<td><strong>Boc</strong></td>
<td><strong>TMS</strong></td>
</tr>
</tbody>
</table>

8 examples (yields 72-93%).

### Methylaluminium bis(4-bromo-2,6-di-tert-butylphenoxide)

As little as 5 mol% of the title reagent enhances the catalytic activity of trialkylsilyl sulphonates in the Mukaiyama directed aldol condensation.

M. Oishi, S. Aratake, and H. Yamamoto

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Me_2SiOTf</th>
<th>A (5 mol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al(OBu')_2</td>
<td><strong>A</strong></td>
<td><strong>PhOH</strong></td>
</tr>
</tbody>
</table>

The title reagent acts as a cocatalyst stabilising a silyl counteranion. 8 examples involving aldehydes and ketones. Yields 60-91%.

### Tributyltin Hydride

The catalytic reduction of nitroalkanes to alkanes with **A** is reported.

J. Tormo, D. S. Hays, G. C. Fu

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Bu_3SnH</th>
<th><strong>A</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>TBSO NO_2</td>
<td><strong>A</strong> (10 mol%), PhSiH_3 (50 mol%)</td>
<td></td>
</tr>
</tbody>
</table>

ACHN = 1,1'-Azobis(cyclohexanecarbonitrile)

7 examples (yields 61-76%).

### Potassium Ephedrinate

The title compound allows the synthesis of axially dissymmetric 1,3-dioxanes via highly enantioselective dehydrohalogenation reactions.

M. Amadji, J. Vadecard, D. Cahard, L. Duhamel, P. Duhamel, J.-C. Plaquevent

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>KH (2.5 eq)</th>
<th><strong>A</strong> (10 mol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH (4 mol%)</td>
<td>THF, –80°C, 3 d</td>
<td></td>
</tr>
</tbody>
</table>

82%

er = 97:3

8 examples (yields 70-86%, %ee ≤ 65%).

### N-(Di-p-anisylphosphoryl)-(S)-α,α'-diphenyl-2-pyrrolidinemethanol

The title compound catalyses the asymmetric reduction of ketones by borane.

M. P. Gamble, A. R. C. Smith, M. Wills

<table>
<thead>
<tr>
<th>Catalyst</th>
<th><strong>A</strong> (10 mol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BH_3•SMe_2 (1.05 eq)</td>
<td>PhMe, Δ</td>
</tr>
</tbody>
</table>

91%

er = 98:2

16 examples (yields 65-91%, %ee 56-95%).
**Cobalt(II) Acetylacetonate**

The title catalyst mediates the coupling of vinylic halides with organomagnesium reagents.

\[ \text{Co(acac)}_2 \rightarrow \text{A} \]

G. Cahiez, H. Avedissian


13 examples (yields 36-90%). Importantly no isomerisation of secondary alkyl groups is observed. The reaction is less efficient for the introduction of tertiary alkyl groups.

\[ \text{Cl} \rightarrow \text{Bu} \]

**Cobalt (II) Acetylacetonate**

The title catalyst mediates the coupling of vinylic halides with organozinc reagents, with retention of alkene stereochemistry.

\[ \text{Cl} \rightarrow \text{AcO(CH}_2\text{)}_4\text{ZnI} \]

H. Avedissian, L. Bérillon, G. Cahiez, P. Knochel


7 examples (yields 50-77%) are described.

**Palladium(II) Acetate**

The title reagent mediates the catalytic oxidation of primary and secondary alcohols, using oxygen, to their corresponding aldehydes and ketones.

\[ \text{Pd(OAc)}_2 \rightarrow \text{A} \]

T. Nishimura, T. Onoue, K. Che, S. Uemura


9 examples (yields 58-96%) are described.

**N\text{-N}′-Bis(p-methoxybenzyl)-3-isopropylpiperazine-2,5-dione**

The title auxiliary is used in the asymmetric synthesis of \( \alpha \)-amino acids in high yield and with excellent diastereoselectivity.

\[ \text{NHOH} \rightarrow \text{NH}_2 \]

S. D. Bull, S. G. Davies, S. W. Epstein, M. A. Leech, J. V. A. Ouzman


6 examples (yields 64-88%, %de 89-98%).

**4-(N-Carboxhydroxamic acid)-10,10-dimethyl-5-thia-4-azatricyclo[5.2.1.0]decane-5,5-Dioxide**

The acyl nitroso compound derived from \( \text{A} \) undergoes [4+2] cycloaddition with a range of dienes in high yield and with excellent diastereoselectivity.

\[ \text{O} \rightarrow \text{NH}_{2} \]

V. Gouverneur, S. J. McCarthy, C. Mineur, D. Belotti, G. Dive, L. Ghosez


3 examples (yields 75-94%, %de > 98%).
The acetoxy-oxazine derived from A is utilized in a Lewis acid-promoted coupling with allyltrimethylsilane in good yield and with good-excellent selectivity. The methodology is used to prepare hydroxymethylene and hydroxyethylene peptide isosteres.


Homochiral phosphine

The title ligand is utilized in the palladium catalysed allylic alkylation of 2-cyclopentyl chloride with acetoxymalonate. The methodology is used in the construction of lactone B, a building block for several natural products.


2,2-Bis[2-{(4S)-4,5-dihydro-4-(tert-butyl)oxazolyl}]propane

A copper(I) complex derived from the title ligand catalyses the asymmetric cyclopropanation of silyl enol ethers with diazoacetates. Cyclopropane ring cleavage affords γ-keto carboxylates in excellent yield and high stereoselectivity.


2,2-Bis[2-{(4S)-4,5-dihydro-4-(tert-butyl)oxazolyl}]propane

Copper(I) bisoxazolines prepared from the title ligand are potent catalysts for the asymmetric hetero-Diels-Alder reactions pyruvate esters and 1,2-diketones.


(1R,2S)-(−)-Ephedrine

The first example of a thermodynamically controlled enantioselective aldol reaction is reported. The chelating chiral ligand A mediates the addition of arylacetonitriles to aldehydes in the asymmetric, anti-selective synthesis of β-hydroxynitriles.

2-Methyl-6-[[1S,2S]-1,3,3-trimethyl-2-(benzylsulfanyl)bicyclo[2.2.1]hept-2-yl][methyl]pyridine

The title ligand is utilised in a highly enantioselective palladium-catalysed allylic substitution.


Ligand

8,10-Methano-11-butyl-9,9-dimethyl-8,9,10,11-tetrahydrobenzo[β] [1,10] phenanthroline

Five new chiral 1,10-phenanthrolines including the title compound have been synthesised and evaluated in an enantioselective palladium catalysed allylic substitution reaction.


Ligand

8-Diphenylyphosphino-8'-methoxy-1,1'-binaphthyl

The title ligand mediates the enantioselective palladium-catalysed reduction of allylic esters to the corresponding olefins.


Ligand

Tetrabutylammonium Hydrogen Peroxide (TBAH)

A mild and efficient removal of camphorsultam using A is reported.

T. Hasegawa, H. Yamamoto Synlett 1998, 882

Reagent

n-Butyllithium / Dibutylimagnesium

The title reagent pair metallates 2-substituted-1,3-dithianes. Results are superior to those obtained with n-BuLi alone.


Reagent
Tetrathiafulvalene

The radical cation of the title reagent is generated in situ and used in the stereoselective synthesis of the tetracyclic core of Aspidosperma alkaloids. Cyclisation proceeds via a one-pot ‘radical-polar crossover’.


Reagent

![Tetrathiafulvalene structure](image)

\[
\text{NH}_2 \quad \text{Ms} \quad \text{OH}
\]

(a) NOBF₂₄ (1.2 eq) CH₂Cl₂, 0°C, 1.5 h
(b) A (1.2 eq) Me₂CO, 0°C, 2 h

75%, single isomer

4 examples (yields 27-75%).

Samarium(II) Iodide

The title reagent is used in the synthesis of 6- and 7-membered rings via sequential ketyl-olefin coupling / intramolecular nucleophilic acyl substitution.


Reagent

![Samarium(II) Iodide structure](image)

\[
\text{Cl}
\]

(a) A (6 eq), t-BuOH (1 eq) H₂C=CMeto(CO₂Me) (1 eq) THF, –78°C → r.t., 30 min
(b) HMPA 0°C → r.t., 30 min

74%

\(dr = 1:4:1\)

18 examples (yields 0, 54-74%).

Tri[(S)-2-hydroxy-1-propyl]amine

A pre-catalyst made from the title reagent and zirconium tetra-tert-butoxide effects enantioselective cleavage of meso epoxides using azidotrimethylsilane and allyl bromide to give O-silyl bromohydrins.


Reagent

![Tri[(S)-2-hydroxy-1-propyl]amine structure](image)

\[
\text{OH}
\]

(a) Zr(OBu₄)₂ (b) TMSOTf

7 examples including 5-, 6-, 7- and 8-membered ring meso epoxides.

Yields 81-92%; ee 84-96%.

Toluene- p -sulfonylhyrazine

N-tert-Butyl(dimethylsil)yl aldehyde tosylhydrazones prepared from the title reagent react with alkylolithium reagents to give adducts that extrude nitrogen in a free radical process


Reagent

![Toluene- p -sulfonylhyrazine structure](image)

\[
\text{ArSO₂NO–NH₂}
\]

(a) THF, –78°C, 15 min
(b) HOAc, CF₃CH₂O⁺

16 examples. yields 78-96%. The reaction involves addition of the lithium reagent and protonation of the adduct followed by elimination of p-toluenesulfonic acid, protodesilylation, and loss of nitrogen. Lithium acetylides or Grignard reagents add slowly or not at all. The reaction works well with complex substrates.

Tris(dimethylamino)sulphonium difluorotrimethylsilicate (TAS-F)

The title reagent is a useful replacement for TBAF in the deprotection of TBS, TES, and TBDPS ethers, 2-(trimethylsilyl)ethyl esters and 2-(trimethylsilyl)ethyl carbamates. Base-catalysed dehydroxylation reactions attending deprotections with TBAF are not observed.


Reagent

![Tris(dimethylamino)sulphonium difluorotrimethylsilicate (TAS-F) structure](image)

\[
\text{Me}_3\text{SiOBrTMS N}_3\] (1.2 eq) "pre-catalyst" (0.12 mg atom Zr)
Br-CH₂=CH₂ (large excess) PhCl, 25°C, 48 h

89%, ee 98:2

89%, er = 98:2

10 examples; yields 75-95%. TAS-F in DMF offers the mildest conditions reported to date for the deprotection of primary TBDPS ethers.
**Zinc/acetyl chloride**

Reduction of sulfonyl chlorides with zinc in the presence of acetyl chloride provides an efficient and cheap source of symmetrical thiosulfonic S-esters which are more reactive than disulfides as sulfenylating agents and more stable than the alternative sulfonyl chlorides.

F. Chemla, Synlett, 1998, 894

**Reagent**

\[ \text{Zn (1.6 eq), AcCl (1.0 eq)} \]

\[ \text{Br-CH}_2\text{-CH}_2\text{-Br (2 drops)} \]

\[ \text{TMSCl (3 drops)} \]

\[ \text{EtOAc, r.t., 90%} \]

8 examples (yields 34-90%) including both alkyl and aryl sulfonyl chlorides. The yields are lower with alkylsulfonyl chlorides. Disulfones (RSO\(_2\)SO\(_2\)R) are minor byproducts in all cases and the major product in the case of p-iodobenzenesulfonyl chloride.

**Allyldimethyltritylsilane (ADTS)**

The title compound gives a variety of cyclopentanols via Lewis acid mediated annulation to electron deficient olefins.


**Reagent**

\[ \text{SiMe}_2\text{CPh}_3 \]

\[ \text{A (1.2 eq)} \]

\[ \text{TiCl}_4 \]

\[ \text{CH}_2\text{Cl}_2, –78°C \]

\[ \text{∅, 0°C, 4 h} \]

\[ \text{85%, dr > 97:3} \]

\[ \text{OH} \]

\[ \text{67%, dr > 97:3} \]

8 examples of annulation (yields 40-85%, %ide 80->94%).

**S-(1-Oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate**

The title compound is utilised in the preparation of hindered Barton esters.


**Reagent**

\[ \text{A (1.5 eq), Et}_3\text{N (3 eq)} \]

\[ \text{DMAP (10 mol%) \text{THF, rt, 40 min}} \]

\[ \text{t-dodecanethiol (2 eq)} \text{, 40 min} \]

\[ 76 \% \]

5 examples (yields 50-78%).

**Sodium Bromate / Sodium Hydrogensulfite**

The title reagent pair mediate the selective bromination of alkylbenzenes.


**Reagent**

\[ \text{NaBrO}_3 \]

\[ \text{A (3 eq), B (3 eq)} \]

\[ \text{NaHSO}_3 \]

\[ \text{EtOAc-H}_2\text{O (4:3), rt, 4 h} \]

\[ 72% \]

14 examples (conversion ≥ 80%).

**Tributylstannyldiiodomethane**

The title reagent is used to convert aliphatic aldehydes to their corresponding E-alkenyl tributylstannanes.


**Reagent**

\[ \text{Bu}_3\text{SnCH}_2 \]

\[ \text{A (2 eq), CrCl}_2 \]

\[ \text{DMF, rt, 2.5 h} \]

\[ 80\% \]

3 examples (yields 80-89%) are described.
Borane-N-trimethylsilyl-morpholine complex

The title reagent is an air-stable crystalline material which mediates the hydroboration of alkenes.


1 example is described. This reagent provides a convenient alternative to other borane complexes due to its stability. Furthermore, upon aqueous work-up, it yields volatile or water-soluble by-products.

\[
\text{Me}_3\text{Si} - \text{BH}_3
\]

1-Fluoro-2,4-dinitrophenyl-5-(R,S)-phenylethylamine (FDPEA)

The title reagent can be used for the determination of absolute configuration of \(\alpha\)-chiral primary amines. Candidates are derivatised by the displacement of fluorine in \(A\).


The above amine was derivatised with FDPEA and with Mosher acid for comparison. Greater anisotropy was observed with the derivative of \(A\).

\[
\begin{align*}
\text{NO}_2 & \quad \text{F} \\
\text{O}_2 & \quad \text{N} \\
\text{H} & \quad \text{N} \\
\text{A} & \quad \text{Ph}
\end{align*}
\]

(t-Butyldimethylsilyloxy)allene

Alpha-deprotonation of the title reagent (followed by O to C silicon migration) generates a nucleophile which adds to aldehydes to give \(\alpha,\beta\)-unsaturated acylsilanes.


9 examples (yields 53-85%) are described. This reagent represents the synthetic equivalent of acrolein enolate.

\[
\begin{align*}
\text{CHO} \\
\text{TBSO}
\end{align*}
\]

Homochiral Oxazaborolidine / Catecholborane

The title reagent pair mediates the enantioselective reduction of a variety of arytrifluoromethyl ketones.


5 examples (yields 73-95%, %ee 72-90%) are described. Slightly lower enantioselectivity is observed using 10 mol% of \(A\).

\[
\begin{align*}
\text{Ar} & \quad \text{OH} \\
\text{Ar} = \text{p-MeO(C}_6\text{H}_4\text{)}
\end{align*}
\]

Lithium (\(\alpha\)-methylbenzyl)(3,4-dimethoxybenzyl)amide

The title reagent behaves as a chiral differentially protected ammonia equivalent which undergoes stereoselective conjugate addition.


1 example is described.