Tools for Organic Synthesis
• Chemetall – The Lithium Company
• New Reagents for Lithium Assisted Addition and Deprotonation Reactions:
  - Improving Grignard-addition reactions - $\text{LaCl}_3 \times \text{LiCl}$
  - Li-powered metalation reactions - New Mg- and Zn-amide bases
Group Structure 2008

Rockwood – Global specialty chemicals and advanced materials company
Chemetall Group – At a glance 2008

1923 Lithium operations started by Metallgesellschaft
1992 Dynamit Nobel-Group
1998 Acquisition Foote Corp.
2004 Rockwood Holdings

Chemetall-Group

Sales: 847 million €
Employees: 3008
Subsidiaries: More than 40
Production sites: 33

Fine Chemicals
- Lithium
- Special Metals
- Metal Sulphides

Surface Treatment
- Automotive Technologies
- Advanced Technologies
- Performance Products
- System Technologies

...the Lithium company
Chemetall Lithium - Manufacturing Sites

- New Johnsonville, TN, USA
- Silver Peak, NV, USA
- Antofagasta, Chile
- Kings Mountain, NC, USA
- La Porte, TX, USA
- Langelsheim, Germany
- Taichung, Taiwan
# Lithium – Selected Applications

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The “Lithium Tree”

Comments

- Providing lithium compounds throughout all stages of the value chain
- Constant expansion due to new applications
- Optimization according to customer needs
Application Areas

Specialties for Deprotonation Metal - Solutions

Halogen/Metal-Exchange Reactions

Reductions with Metal Hydrides in Organic Synthesis

C-C Coupling Reactions in Organic Synthesis

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1,2-Addition Reactions with R-MgX

Most Grignard products are used for 1,2-addition reactions to carbonyl compounds:

\[
\begin{align*}
R_2\text{CH}_2\text{R}_3 + R_4\text{MgX} &\rightarrow R_2\text{CH}_2\text{R}_3\text{OMgX} \\
&\quad + R_4\text{MgX} \\
\end{align*}
\]

Especially when bulky groups are present in the molecule side reactions take place which

- lead to lower yields
- require extensive purification of the product
- sometimes inhibit the desired reaction
Reducing formation of by-products by Lewis-acid activation of the ketone:

State of the art solution is the use of water free Ce (III) salts (Imamoto method)

- Low solubility of CeCl$_3$ in process solvent THF (0.6 weight%) results in inhomogeneous reaction mixtures
- Handling of highly hygroscopic CeCl$_3$
- Only special grades (pretreatment) CeCl$_3$ result in good results

Improved Chemetall solution is the use of LaCl$_3$ x 2 LiCl solution in THF

+ High solubility of LaCl$_3$ due to addition of LiCl
+ Ready to use product
+ Easy handling and dosing
+ Low water content
+ Lots of examples described in the literature
LaCl₃ x LiCl - Examples

\[ \text{without additive} \quad 3\% - 5\% \]
\[ \text{CeCl}_3 \text{ (Imamoto, Dimitriov)} \quad 80\% \]
\[ \text{LnCl}_3*2 \text{ LiCl} \quad > 90\% \]

\[ \text{without additive} \quad 4\% \]
\[ \text{CeCl}_3 \text{ (Imamoto, Dimitriov)} \quad - \]
\[ \text{LnCl}_3*2 \text{ LiCl} \quad > 90\% \]

\[ \text{without additive} \quad 21\% \]
\[ \text{CeCl}_3 \text{ (Imamoto, Dimitriov)} \quad - \]
\[ \text{LnCl}_3*2 \text{ LiCl} \quad > 90\% \]

LaCl₃ x LiCl - Influence of Stoichiometry

**MgBr·LiCl** + **PhMeCO** → **PhHO**

- **without additive**: 33 %
- **LaCl₃·2 LiCl (30 mol%)**: 87 %
- **LaCl₃·2 LiCl (100 mol%)**: 93 %

**i-PrMgCl** + **PhPhCO** → **PhOHMePh**

- **without additive**: 3 %
- **LaCl₃·2 LiCl (30 mol%)**: 65 %
- **LaCl₃·2 LiCl (100 mol%)**: 86 %

A. Metzger, G. Gavryushin, P. Knochel, *Synlett*, **2009**, 9, 1433
LaCl₃ x LiCl – Synthesis of Tryptamines

1. iPrMgCl · LiCl;
2. LaCl₃ · 2 LiCl;
3. 78% without isolation of intermediates

“An expedient strategy for the synthesis of tryptamines and other heterocycles...”

Key intermediate for aspidophytine

LaCl₃ x LiCl – Industrial Interest

**Challenge:**
Suppression of side products generated by enolization of ketone intermediate

![Chemical structure](image)

**Method A:** 1 equiv. anhydrous CeCl₃
- Special two step drying method is essential
- Special crystal habit of CeCl₃ is critical
- Tedious activation method is required
- Low solubility results in heterogeneous reaction mixture


**Method B:** LaCl₃*2 LiCl – THF solution
- Highly soluble, homogenous reaction conditions
- Water-free product
- Lower LaCl₃/ester ratios possible:
  - 1.0 equiv. LaCl₃: 94.9% yield
  - 0.5 equiv. LaCl₃: 88.3% yield

EP 2 014 633 (Lonza AG)

key intermediate in the synthesis of Montelukast
Application Areas

- Specialties for Deprotonation Metal - Solutions
- Halogen/Metal-Exchange Reactions
- Reductions with Metal Hydrides in Organic Synthesis
- C-C Coupling Reactions in Organic Synthesis

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Directed ortho-Metalation (DOM) Reactions

DG = directing group
FG = functional group
Base = e.g. BuLi, LDA, MDA or other

M = Li (BuLi, TMPLi, LDA ..)
- High reactivity
- Low functional group tolerance

M = Mg, Zn
- Lower reactivity
- Higher selectivity and functional group tolerance
Hauser Base with LiCl

- the combination of Mg and Li increases the deprotonation power
- nevertheless selectivity and functional group tolerance remain at a high level
- reagent exhibits excellent solubility and stability in THF
Source of powerful magnesiating ability:

- active basic ligand binds to Mg (not to Li)
- four-coordinate Mg center is coordinatively saturated, but has a labile THF ligand geminal to TMPH
- bimetallic, ate („Li+MgR₃⁻) constitution could be a key factor for the enhanced magnesiating ability

TMP-MgCl x LiCl - Examples

high functional group tolerance...

DG = O\text{Boc}, CO_2R, COR.....
FG = CO_2R, CN, COR,.... not FG = CHO, NO_2

...different selectivity
TMP-MgCl x LiCl – Synthesis of Talnetant


under research for treatment of schizophrenia and as potential antipsychotic
Multiple functionalization of 3-chlorobenzoate by successive magnesations:

1) TMPMgCl, LiCl, 1.2 equiv, 0 °C, 6 h
2) TsCN

1) TMPMgCl, LiCl, 1.5 equiv, -20 °C, 5 h
2) EtOCOCN

1) TMPMgCl, LiCl, 1.2 equiv, -50 °C to -30 °C, 30 min
2) ZnCl₂
3) Pd(PPh₃)₄ (2 mol%), EIOCOCl (1.5 equiv)

Lithiation of pyrimidines is difficult due to high reactivity of the ring towards addition reactions therefore requiring low temperatures.

\[
\begin{align*}
\text{S-Cl-N} & \quad \text{TMP-MgCl LiCl (1,1 equiv.)} \\
& \quad \text{THF, 25°C, 5 min} \\
\end{align*}
\]

\[
\begin{align*}
\text{E}^+ \\
\text{S-Cl-N} & \quad \text{TMP-MgCl LiCl} \\
\end{align*}
\]

\[
\begin{align*}
\text{Cl-Cl-N-Cl} & \quad \text{TMP-MgCl LiCl (1,1 equiv.)} \\
& \quad \text{THF, 25°C, 30 min} \\
\end{align*}
\]

\[
\begin{align*}
\text{ClLi ClMg} & \quad \text{Cl-Cl-N-Cl} \\
\end{align*}
\]

\[
\begin{align*}
\text{E}^+ \\
\end{align*}
\]

Even higher functional group tolerance – Zn-Amides

In contrast to TMPMgCl/LiCl, TMP$_2$Zn/2MgCl$_2$/LiCl

- tolerates NO$_2$ and CHO functionalities
- as well as labile hetero-arenes
- both TMP-groups are active!!
Zn-amides - Examples

High functional group tolerance:

\[
\text{O}_2\text{N} \quad \text{Cl} \quad \text{Zn} \quad \text{CuCN} \cdot 2\text{LiCl} \quad (5 \text{ mol\%})
\]

\[
\text{TMP}_2\text{Zn} \quad (0.55 \text{ Eq.}) \quad \text{THF}, \ -25 \ ^\circ\text{C}, \ 1.5 \text{ h}
\]

\[
\text{TMP}_2\text{Zn} \quad \text{CuCN} \cdot 2\text{LiCl} \quad (5 \text{ mol\%})
\]

\[
\text{TMP}_2\text{Zn} = \text{TMP}_2\text{Zn}/2\text{MgCl}_2/2\text{LiCl}
\]

Zn-amides – increasing selectivity...

- highly chemoselective deprotonation (zincation)
- of various sensitive aromatics and heteroaromatics
- even at room temperature (25°C)


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TMP-ZnCl/LiCl - Examples

- Zincation of electron poor aromatics
- With highly sensitive functional group
- At 25°C!

Regio- and chemoselective deprotonation of diazines at 25°C

Chemetall Products – Mg- and Zn-amides

**reactivity**

**selectivity**

Chemetall offers:

- a tool box of bases for effective and selective deprotonation reactions
- with varying basicity and selectivity
- for the synthesis of (highly) substituted aromatics and heteroaromatics
- under reasonable reaction conditions
Thank you very much for your kind attention