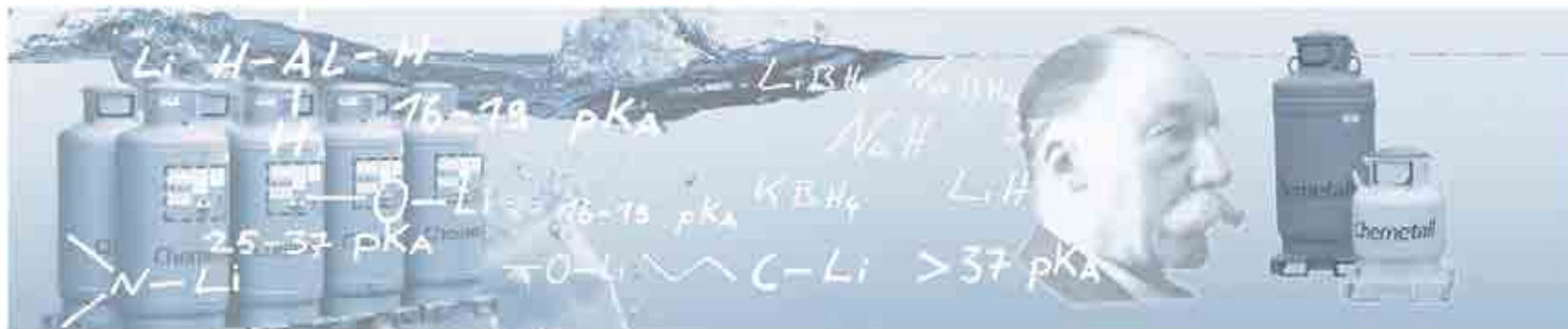


# Chemetall

## Tools for Organic Synthesis



Jens Röder – Business Development Lithium

- **Chemetall – The Lithium Company**
- **New Reagents for Lithium Assisted Addition and Deprotonation Reactions:**
  - **Improving Grignard-addition reactions -  
LaCl<sub>3</sub> x LiCl**
  - **Li-powered metalation reactions - New  
Mg- and Zn-amide bases**



**Net Sales: \$ 3.380**  
**Employees: 10.000**

**Specialty  
Chemicals  
(Chemetall)**

**Net Sales: \$ 1.233**



**Pigments &  
Additivs**

**Net Sales: \$ 1.370**



**Advanced  
Materials**

**Net Sales: \$ 767**



**Rockwood – Global specialty chemicals and advanced materials company**

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

## Chemetall-Group

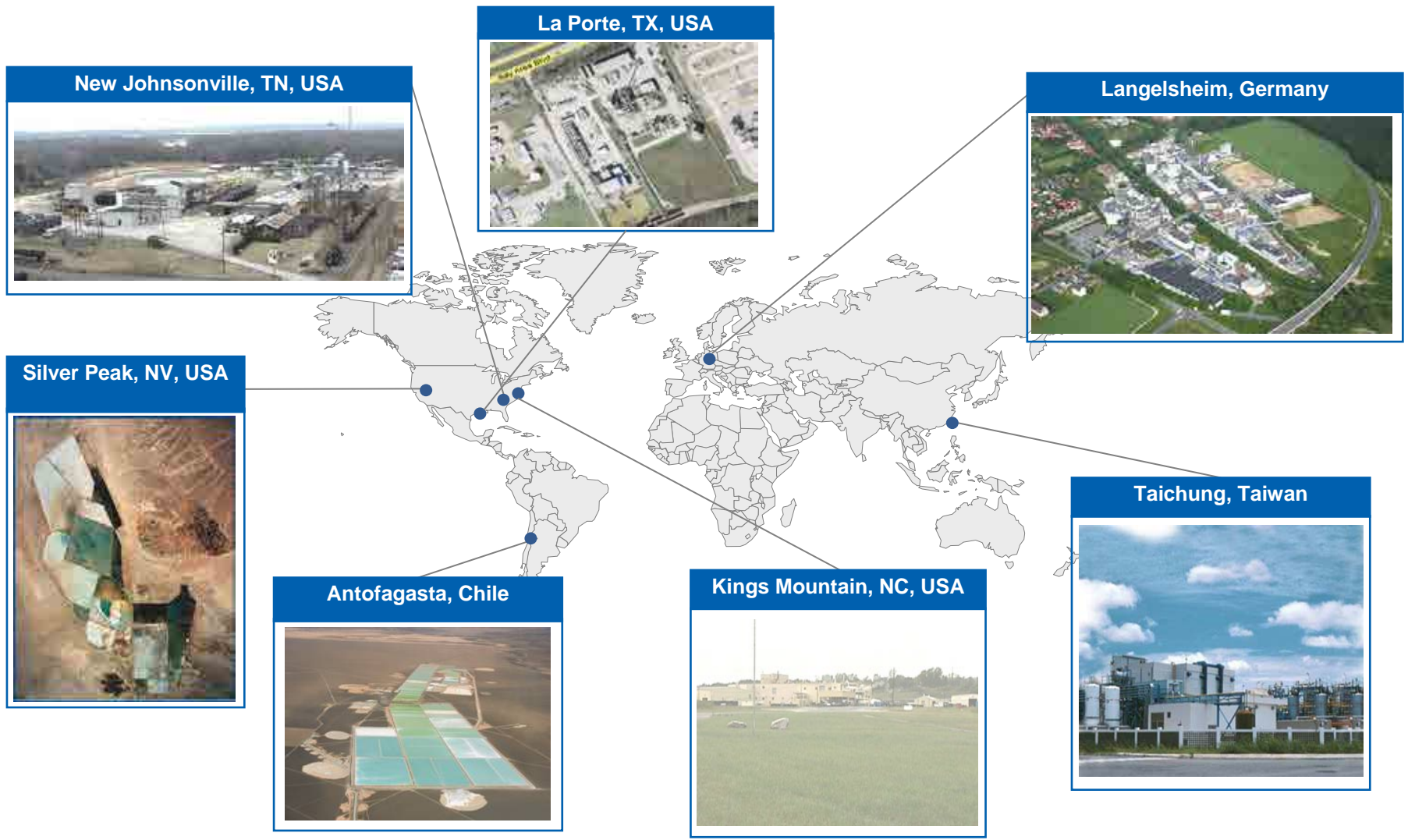
**Sales:** 847 million €  
**Employees:** 3008  
**Subsidiaries:** More than 40  
**Production sites:** 33

### Fine Chemicals

- **Lithium**
- Special Metals
- Metal Sulphides

### Surface Treatment

- Automotive Technologies
- Advanced Technologies
- Performance Products
- System Technologies



## Key Products

## Key Applications

**Lithium carbonate**



Li-Ionen-Batteries



Glass ceramics



Cement



Aluminum

**Lithium hydroxide**



Li-Ionen-Batterien



Grease



CO<sub>2</sub> Absorption



Mining

**Lithium metal**



Lithium Batteries



Pharmaceuticals



Al - alloys

**Butyl-lithium**



Elastomers



Pharmaceuticals



Agrochemicals

**Lithium specialties**



Electronic Materials

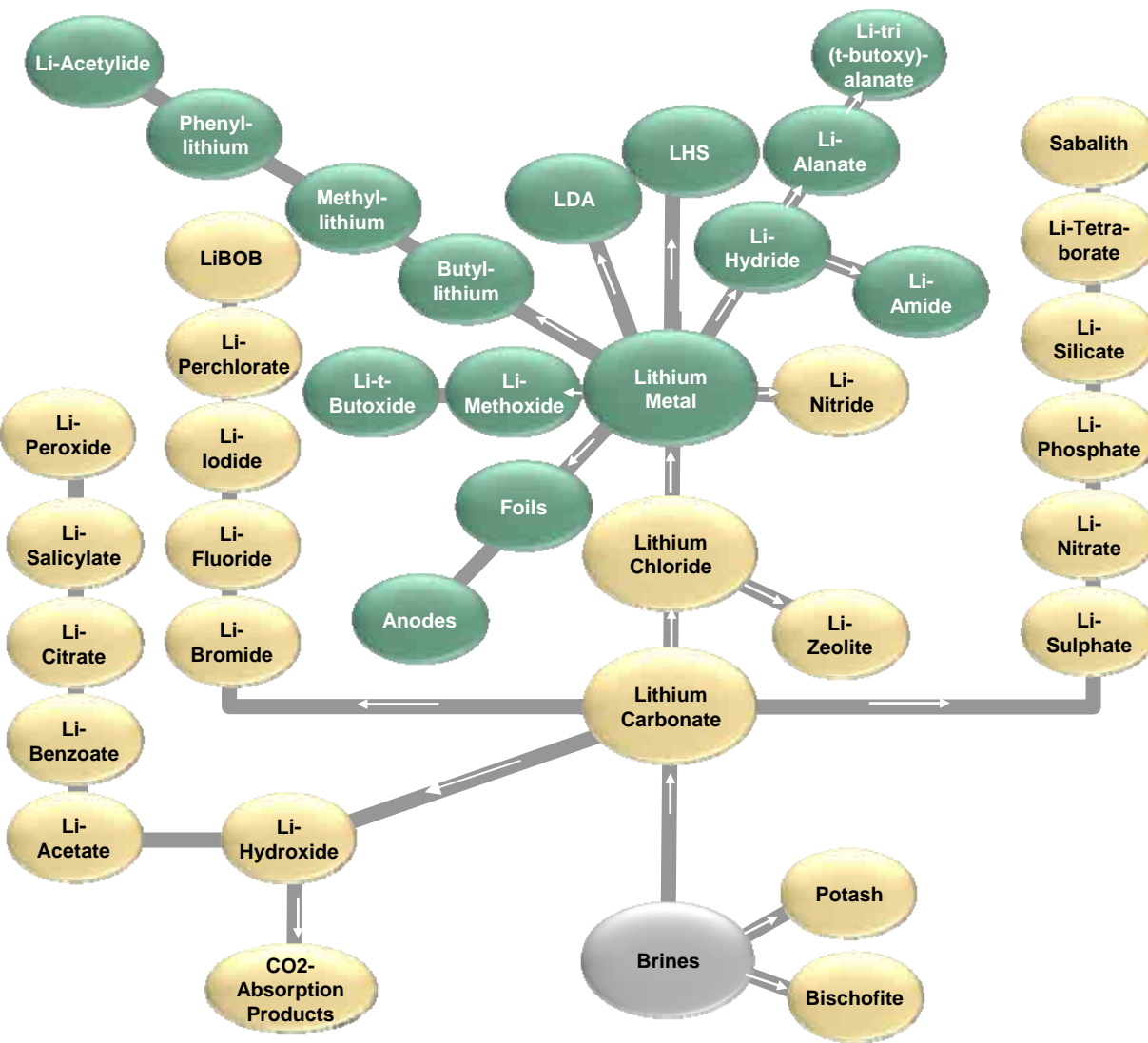


Pharmaceuticals



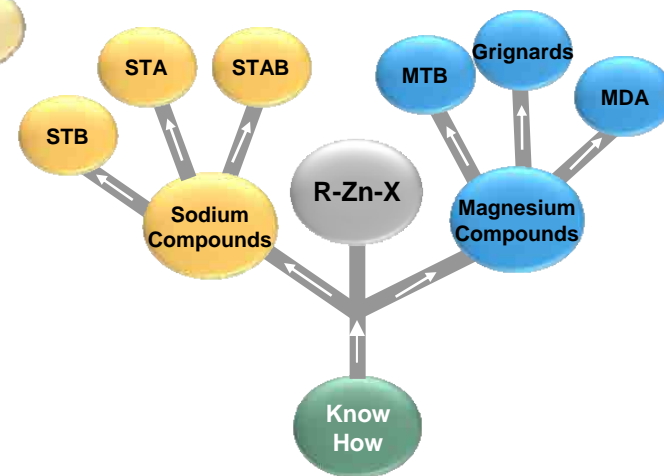
Agrochemicals

# 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**

**Lithium**   
company

**Chemetall**

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**Halogen/Metal-Exchange Reactions**

**Lithium**   
company

**Chemetall**

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**Reductions with Metal Hydrides  
in Organic Synthesis**

**Lithium**   
company

**Chemetall**

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**C-C Coupling Reactions in  
Organic Synthesis**

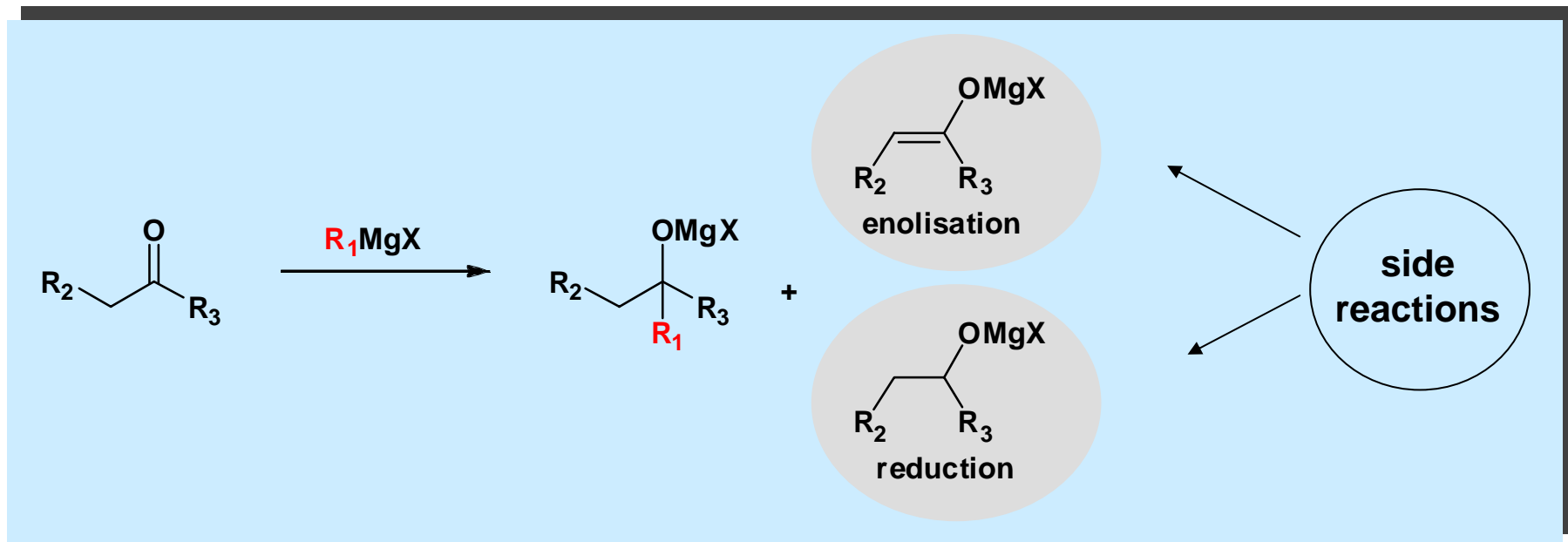
**Lithium**   
company

**Chemetall**

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



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:

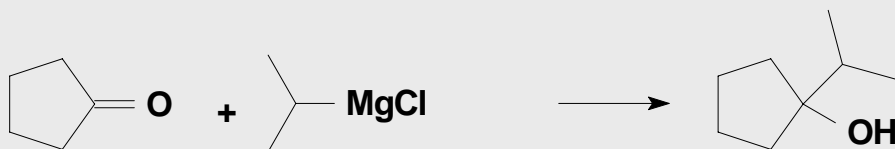
State of the art solution is the use of water free Ce (III) salts (Imamoto method)

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



Improved Chemetall solution is the use of  $\text{LaCl}_3 \times 2 \text{LiCl}$  solution in THF

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



without additive  
CeCl<sub>3</sub> (Imamoto, Dimitriov)  
**LnCl<sub>3</sub>\*2 LiCl**

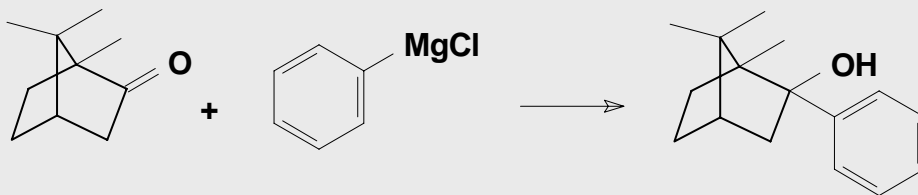
3 - 5%  
80%  
**> 90%**

**Ln = La, Ce, Nd**



without additive  
CeCl<sub>3</sub> (Imamoto, Dimitriov)  
**LnCl<sub>3</sub>\*2 LiCl**

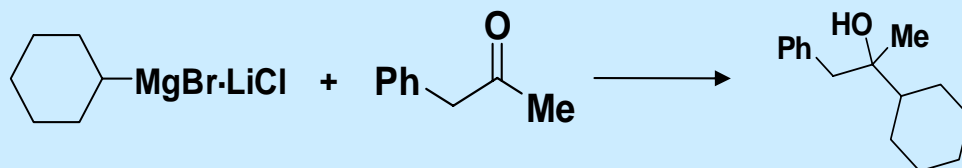
4%  
-  
**> 90%**



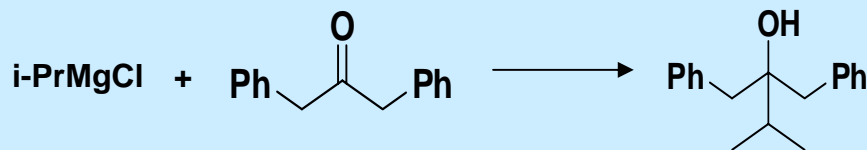
without additive  
CeCl<sub>3</sub> (Imamoto, Dimitriov)  
**LnCl<sub>3</sub>\*2 LiCl**

21%  
-  
**> 90%**

A. Krasovskiy, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, 45,497-500.

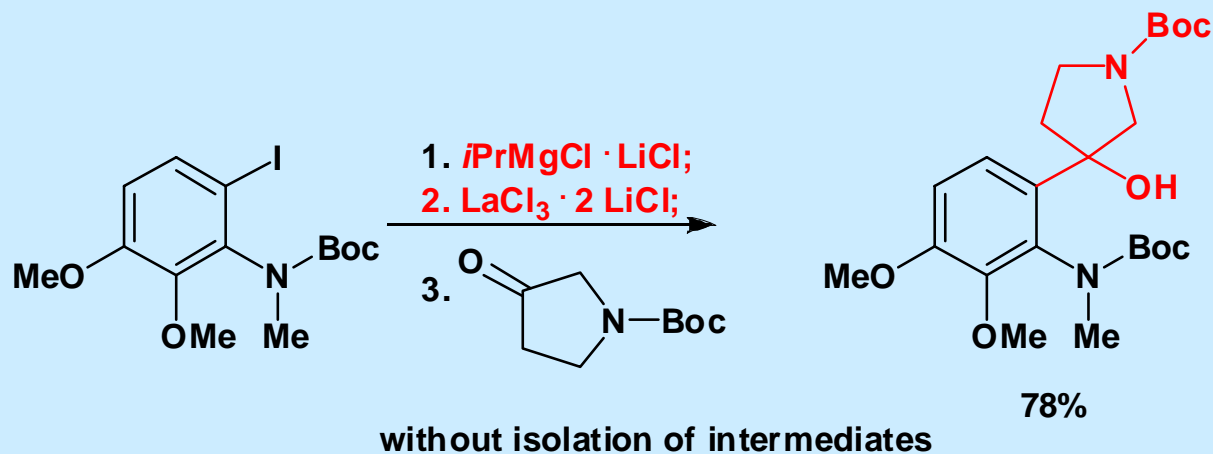


without additive:	33 %
<b>LaCl<sub>3</sub> · 2 LiCl (30 mol%)</b>	<b>87 %</b>
<b>LaCl<sub>3</sub> · 2 LiCl (100 mol%)</b>	<b>93 %</b>

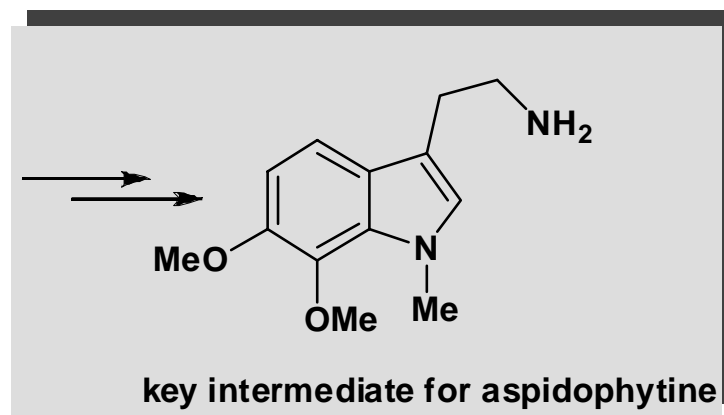


without additive:	3 %
<b>LaCl<sub>3</sub> · 2 LiCl (30 mol%)</b>	<b>65 %</b>
<b>LaCl<sub>3</sub> · 2 LiCl (100 mol%)</b>	<b>86 %</b>

A. Metzger, G. Gavryushin, P. Knochel, *Synlett*, **2009**, 9, 1433



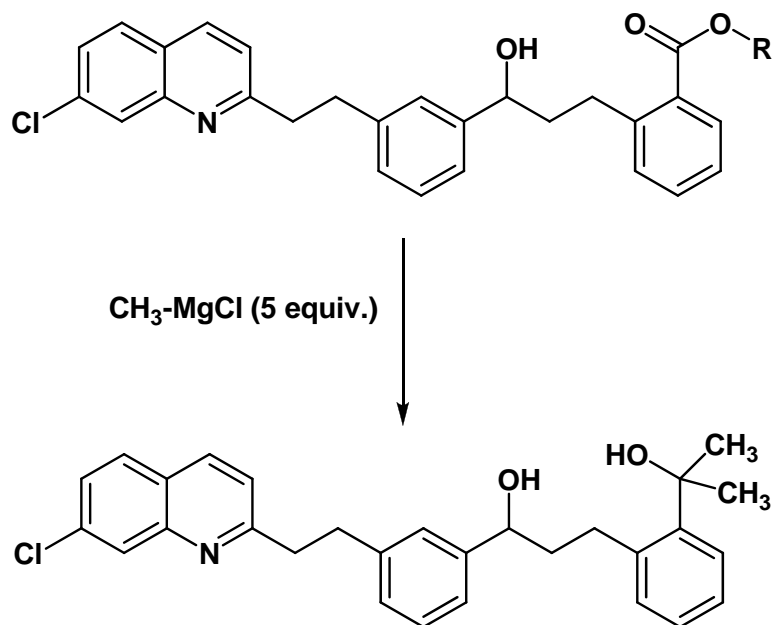
“An expedient strategy for the synthesis of tryptamines and other heterocycles...”



K. C. Nicolaou *et al*, *Angew. Chem. Int. Ed* **2008**, 47, 4217.

**Challenge:**

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



**key intermediate in the synthesis of Montelukast**

**Method A: 1 equiv. anhydrous CeCl<sub>3</sub>**

- Special two step drying method is essential
- Special crystal habit of CeCl<sub>3</sub> is critical
- Tedious activation method is required
- Low solubility results in heterogenous reaction mixture

*Adv. Synth. Catal.* 2004, 346, 1307


**Method B: LaCl<sub>3</sub>\*2 LiCl – THF solution**

- Highly soluble, homogenous reaction conditions
- Water-free product
- Lower LaCl<sub>3</sub>/ester ratios possible:
  - 1.0 equiv. LaCl<sub>3</sub>: 94,9% yield
  - 0.5 equiv. LaCl<sub>3</sub>: 88,3% yield

*EP 2 014 633 (Lonza AG)*

## Application Areas

**Specialties for Deprotonation  
Metal - Solutions**



**Chemetall**

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**Halogen/Metal-Exchange Reactions**



**Chemetall**

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**Reductions with Metal Hydrides  
in Organic Synthesis**



**Chemetall**

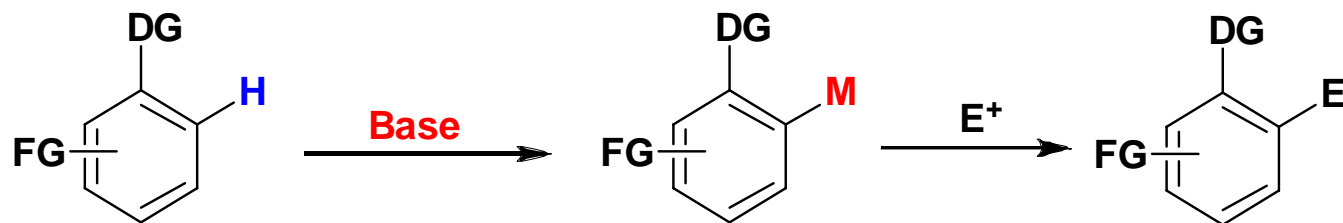
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**C-C Coupling Reactions in  
Organic Synthesis**



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

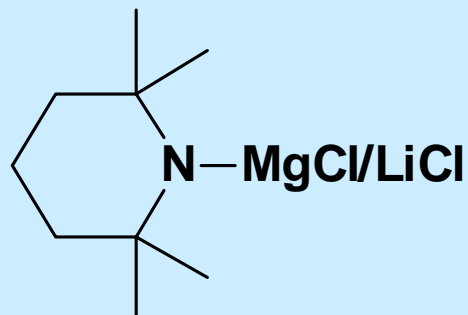
**M = Li (BuLi, TMPLi, LDA ..)**

- High reactivity
- Low functional group tolerance

**M = Mg, Zn**

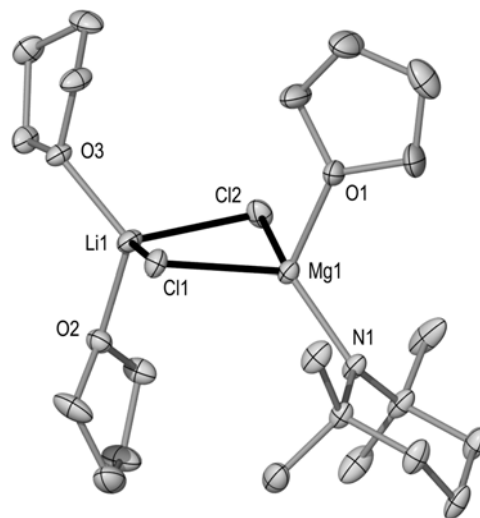
- Lower reactivity
- Higher selectivity and functional group tolerance





**(TMP- MgCl/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

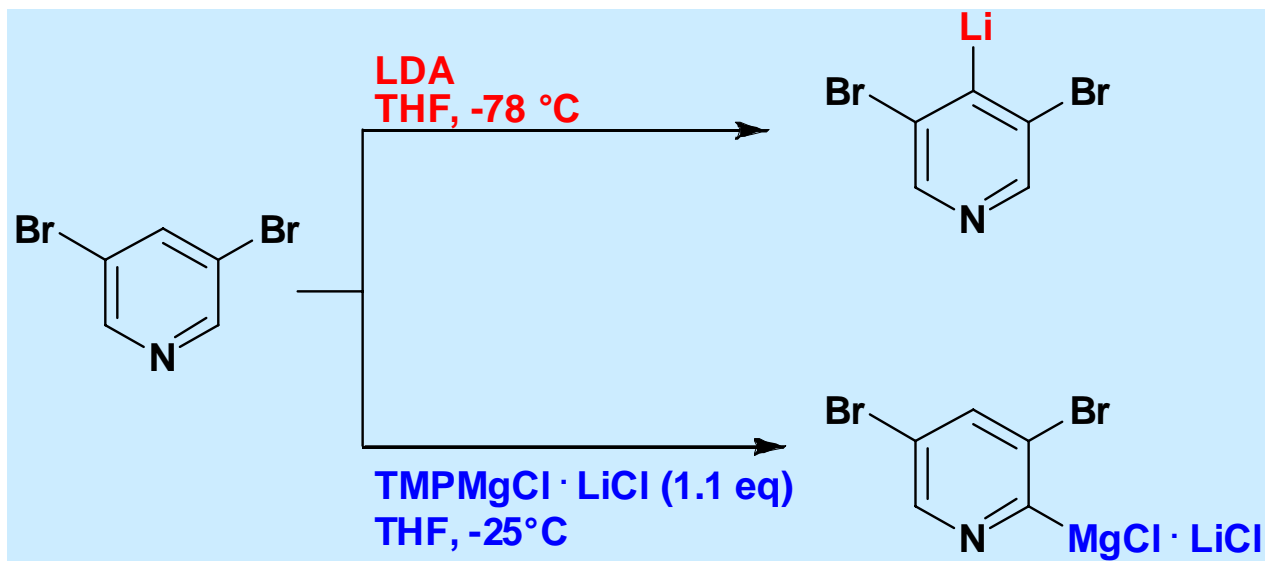
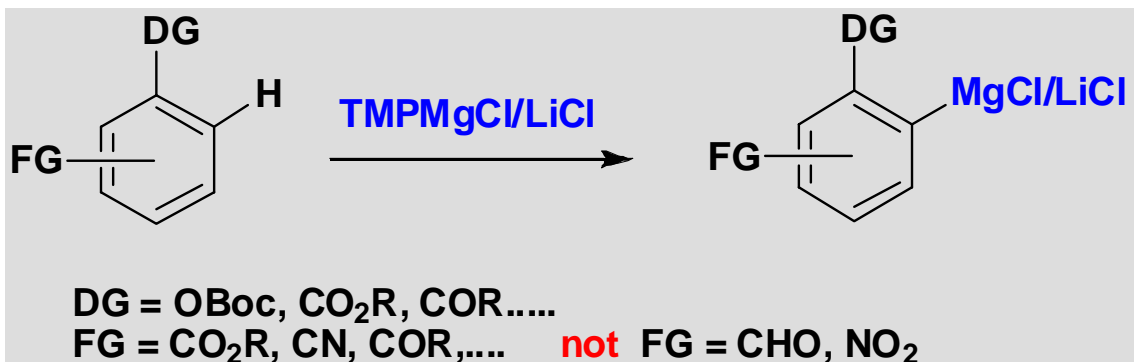


### Source of powerful magnesiating ability:

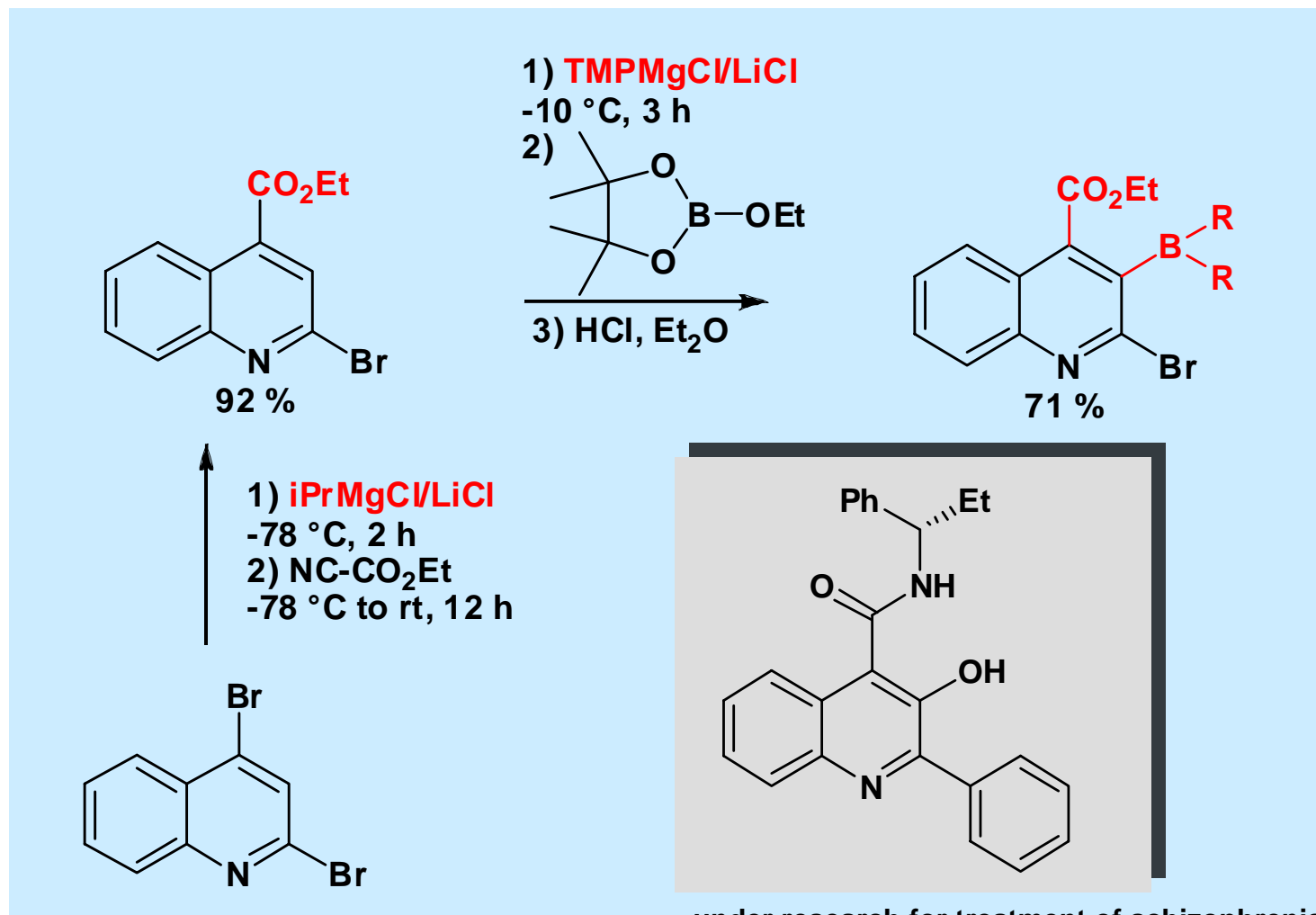
- active basic ligand binds to Mg (not to Li)
- four-coordinate Mg center is coordinatively saturated, but has a labile THF ligand geminal to TMPH
- bimetallic, ate ( $\text{Li}^+\text{MgR}_3^-$ ) constitution could be a key factor for the enhanced magnesiating ability

P. Garcia-Alvarez, R. E. Mulvey, *Angew. Chem.Int. Ed.* **2008**, *47*, 8079-8081.

high functional group tolerance...



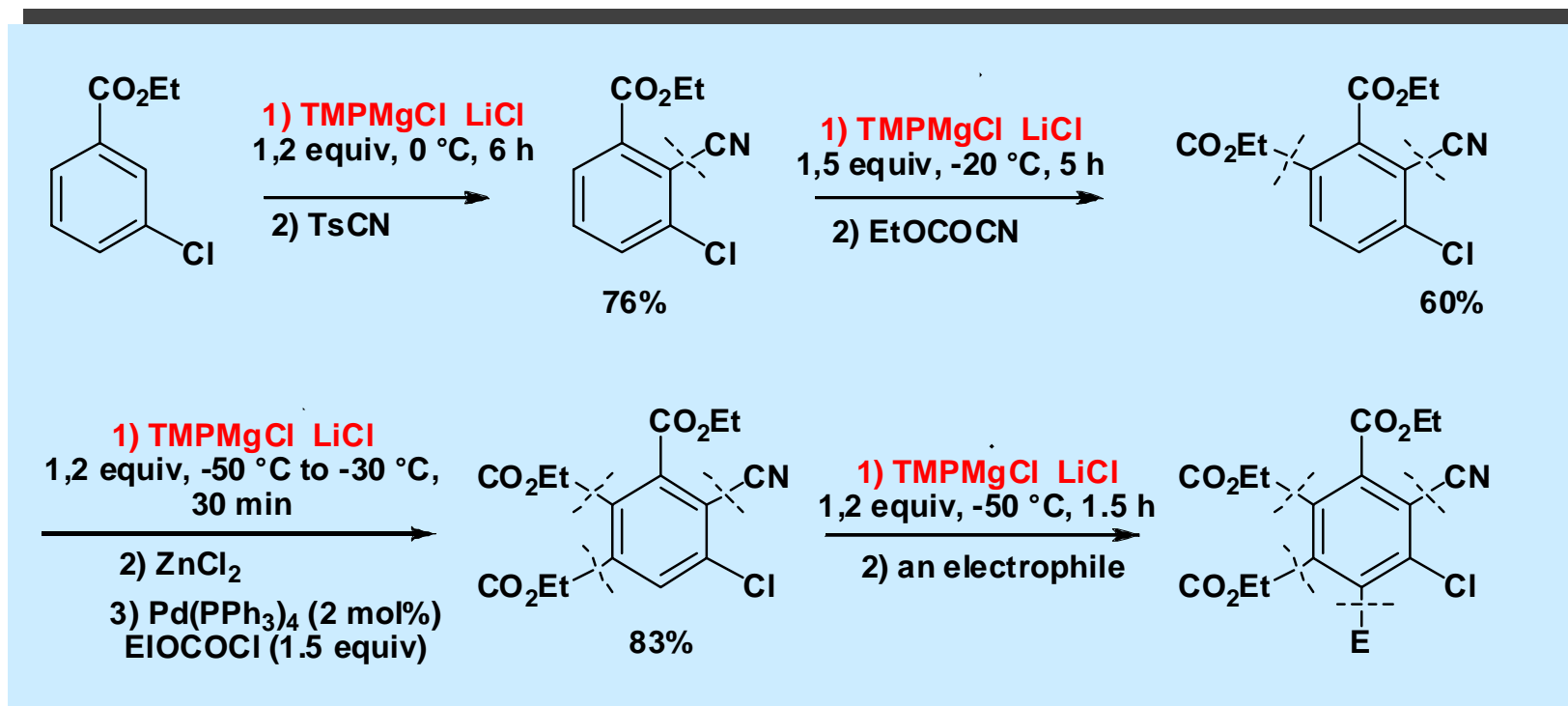
...different selectivity



under research for treatment of schizophrenia  
and as potential antipsychotic

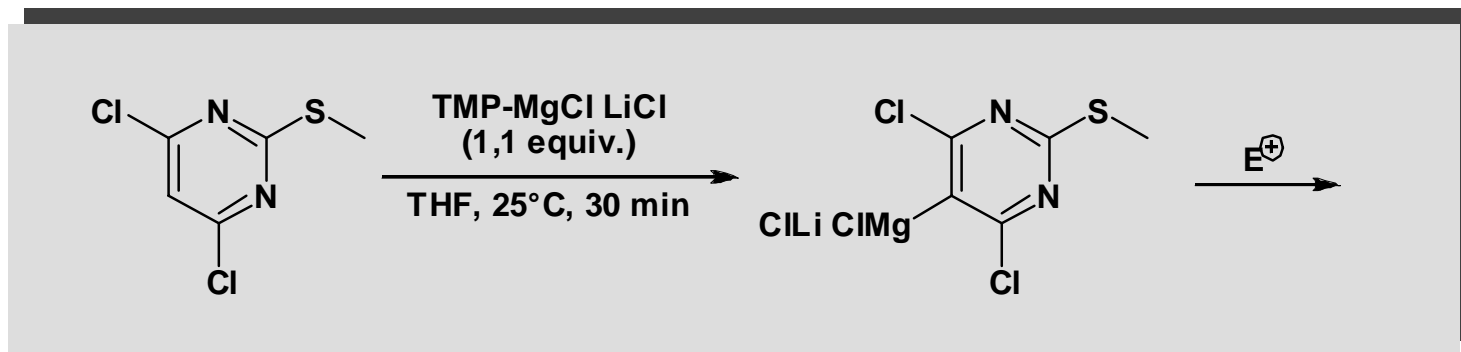
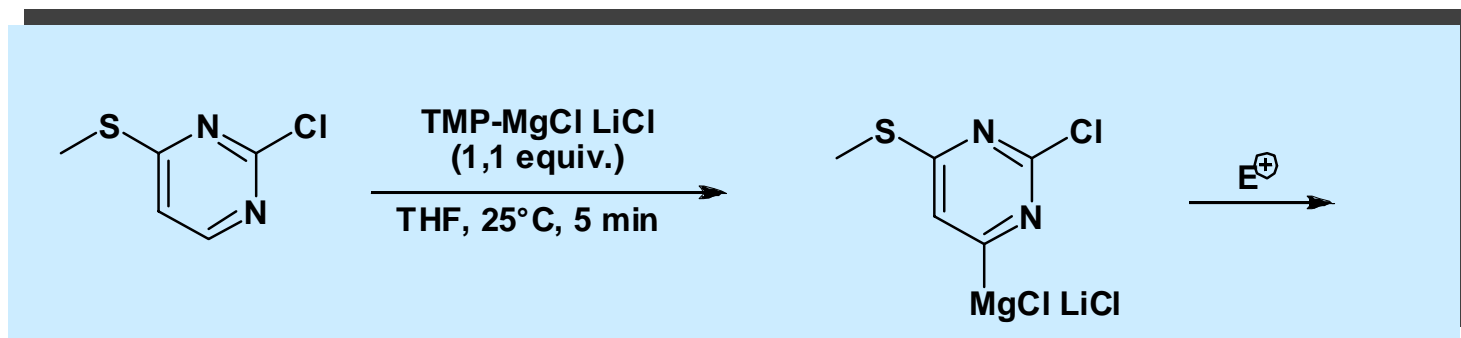
Nadege Boudet, P. Knochel, *Org. Lett.*, **2007**,9, 5525-5528.

Multiple functionalization of 3-chlorobenzoate by successive magnesations:

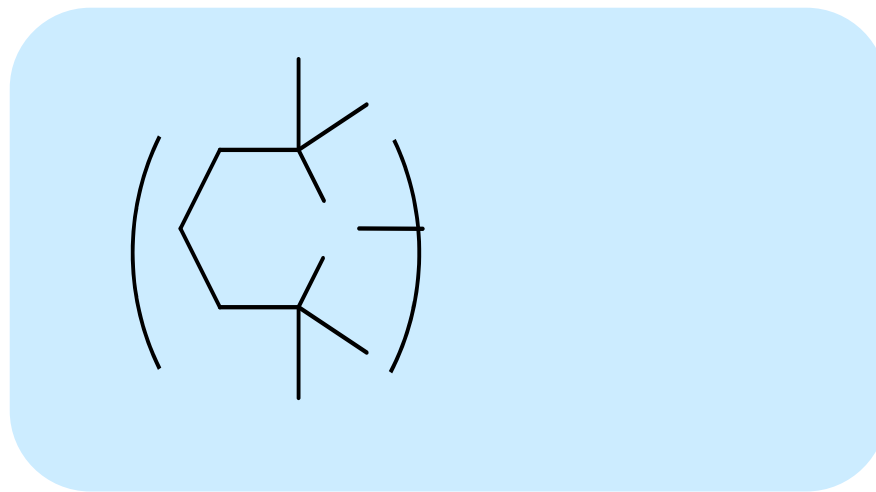


W. Lin, O. Baron, P. Knochel, *Org. Lett.* **2006**, 8, 5673 - 5676

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



M. Mosrin, P. Knochel, *Chem. Eur. J.* **2009**, 15, 1468



In contrast to  $\text{TMPMgCl/LiCl}$ ,  $\text{TMP}_2\text{Zn}/2\text{MgCl}_2/\text{LiCl}$

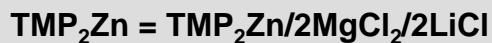
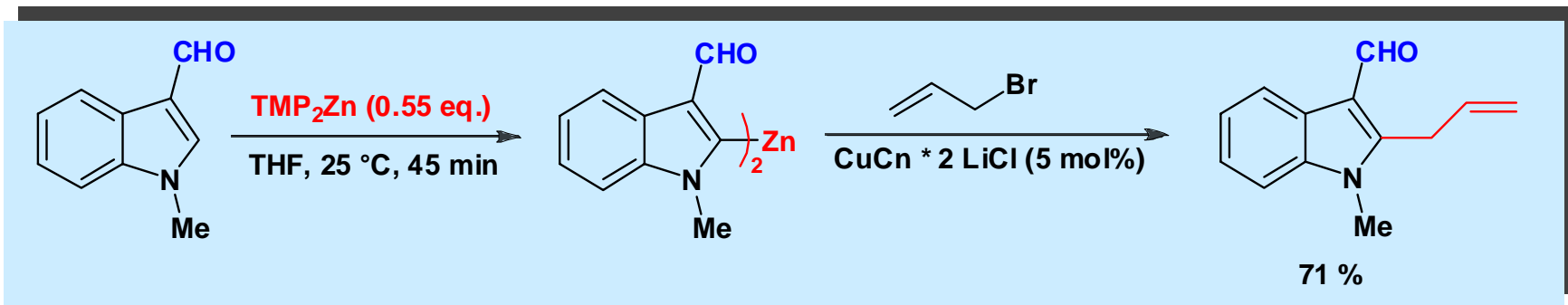
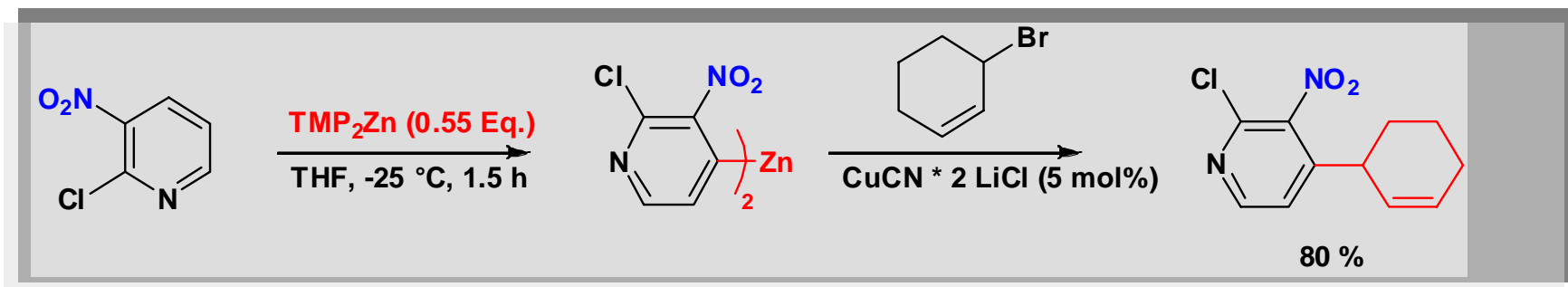
- tolerates  $\text{NO}_2$  and CHO functionalities
- as well as labile hetero-arenes
- both TMP-groups are active !!

N

Z

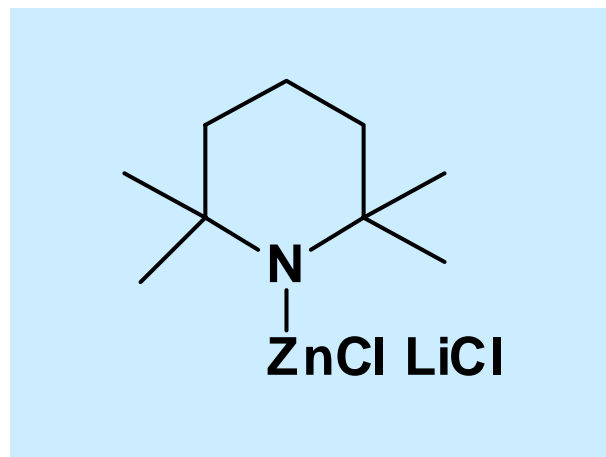
2

## High functional group tolerance:



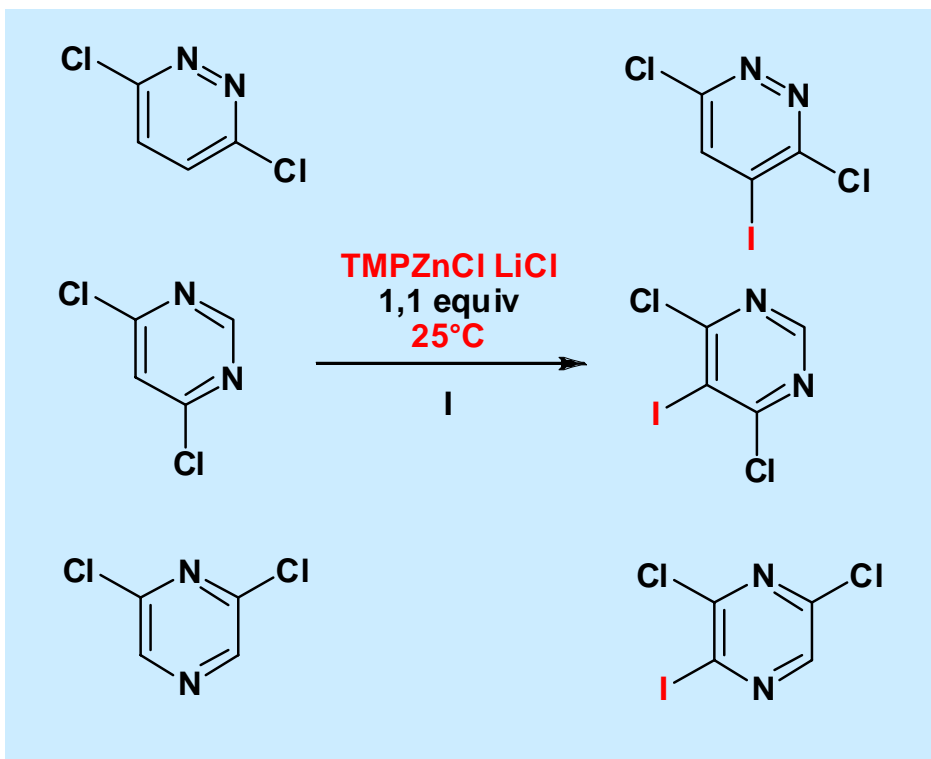
S. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, 46, 7685.





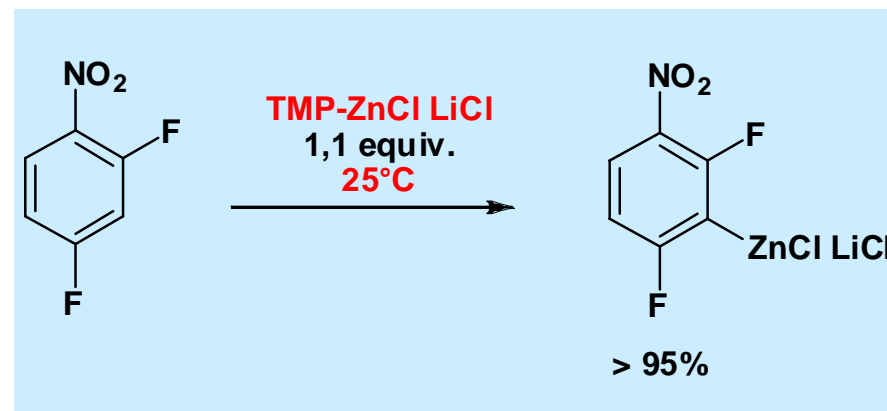
- highly chemoselective deprotonation (zincation)
- of various sensitive aromatics and heteroaromatics
- even at room temperature (25° C)

M.Mosrin, P. Knochel, *Org. Lett.* **2009**, 11, 1837

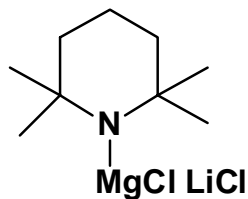


regio- and chemoselective  
deprotonation of diazines at 25°C

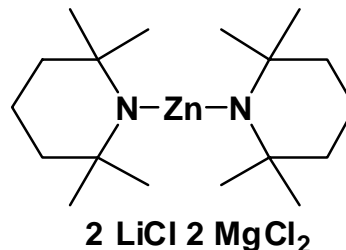
- zincation of electron poor aromatics
- with highly sensitive functional group
- at 25°C !



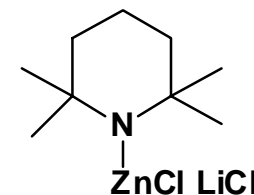
M.Mosrin, P. Knochel, *Org. Lett.* **2009**, 11, 1837



20% solution in THF/toluene



15% solution in THF/toluene



20% solution in THF

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

**Chemetall**

**Tools for Organic Synthesis**

