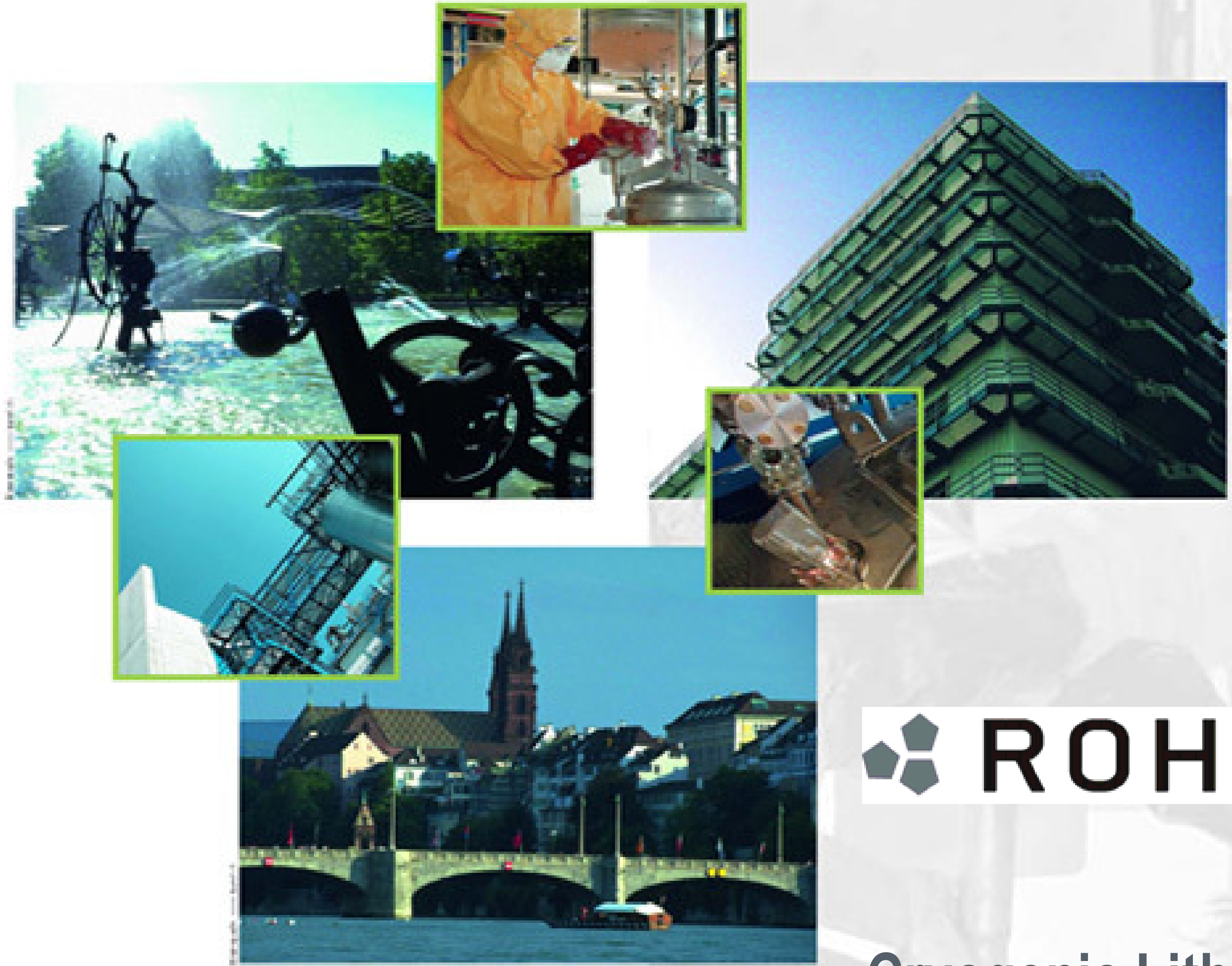

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Cryogenic Lithiation Reactions for the Production of Starting Materials for Transition Metal Catalyzed Reactions

TMC Transition Metal Catalysis

Agenda

- Introduction
- Synthesis of Boronic acid
- Synthesis of Carboxylic Derivatives by Transition Metal Catalysis
- Synthesis of Carboxylic Acid by Cryogenic Lithiation
- Conclusion

Selectivity

- convert a specific functional group in highly complex molecules
- avoid protecting group chemistry

Selectivity

- avoid the formation of by products and tedious work-up and purification

Selectivity

- get high yields and low costs

From Classical Aromatic Chemistry to TMC

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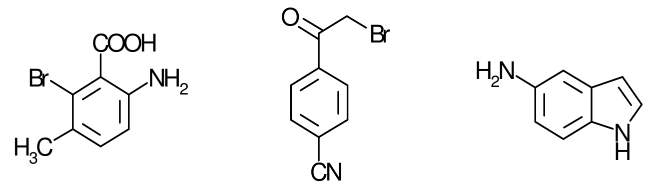
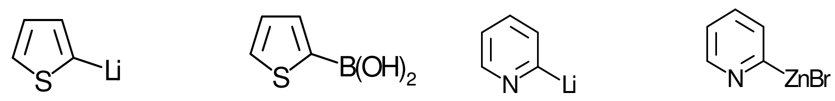
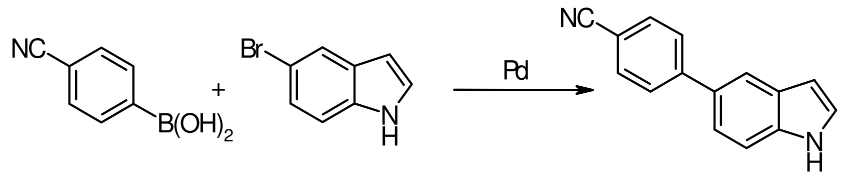
- **Classical aromatic Chemistry**
- **Substituted Arenes**



- **Organometallic Chemistry**
- **Organometallics**



- **Complex Intermediates and APIs**



RohnerChem's Focus

Cryogenic Reactions, Asym. Hydrogenation, Cyanation,
C-C Coupling, Carbonylation

Focus on TMC and cryogenic reactions ***on commercial scale***

- Equipment / hardware from lab to production scale
- R&D activities focused on up-scaling aspects

Rohner provides **state of the art chemistry**

- In-house TMC expertise
- Cooperation with Technology Providers for catalyst screening and supply

Rohner combines **traditional / classical chemical know-how and expertise with TMC and cryogenic technology**

- Seamless integration of TMC in multi-step reactions
- Robust, reliable and cost efficient processes

Special Feature Equipment

High pressure equipment

Lab	1L	60 Bar / 900 psi
Kg-Lab	20L	20 Bar / 300 psi
Pilot	400L	60 Bar / 900 psi
Production	4000L	60 Bar / 900 psi

Low temperature equipment

Lab	1L	-80°C
Kg-Lab	20L	-80°C
Pilot	60L / 400L	-85°C
Production	2500L	-80°C

CO chemistry

Lab	0.2L	10 Bar / 150 psi
Kg-Lab	20L	20 Bar / 300 psi
Pilot	400L	60 Bar / 900 psi

Boronic acids: Starting Materials for Suzukui coupling

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Synthesis of Boronic Acid

Transition Metal Catalysis

Boronic Acid for Use in Suzuki Coupling

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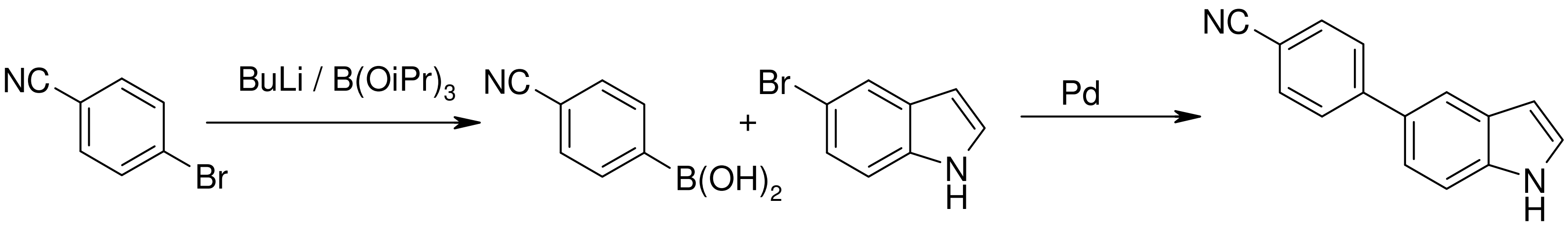
Catalyzed C-C Coupling: Model reaction

- Synthesis of Boronic acid
- Suzuki Reaction



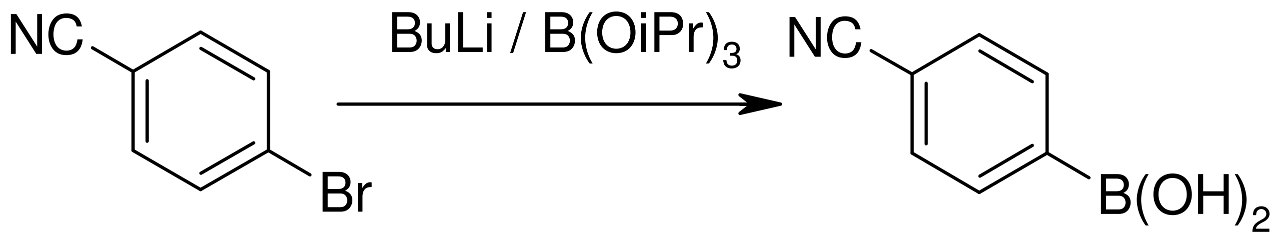
Transition Metal Catalysis

Understand the Scale-up

Quick realisation:

- Development and production in *4 months* only
  - Development of boronic acid synthesis
  - Catalyst screening
  - Optimisation of reaction parameters
  - Optimisation of work-up
  - Analytical method development
  - Safety analysis
  - Removal of Pd
- Yield: 75%; Purity: 98 %
- Palladium content < 10 ppm

Low Temperature Synthesis of Boronic acid



Challenges

- find an efficient synthesis of the boronic acid
- avoid highly sophisticated and expensive reagents
- avoid protecting group chemistry
- direct conversion of the 4-Bromo-benzonitrile to the boronic acid
- Nitrile group reacts with metal organic reagents

Low Temperature Synthesis of Boronic acid

Critical parameters

- low temperature reaction conditions (< 65°C)
- dosage of BuLi to a cold mixture of Triisopropyl borate and 4-Bromo-benzonitrile*
- hydrolyzation of reaction mixture at low temperature

*W. Li, D. P. Nelson, M. S. Jensen, R. S. Hoerrner, D. Cai, R. D. Larsen, P. J. Reider, J. Org. Chem. 2002, 67, 5394-5397.

Synthesis of Carboxylic Derivatives by Transition Metal Catalysis

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- Synergies between cryogenic metalation and TMC

Synthesis of Different Functional Groups by TMC

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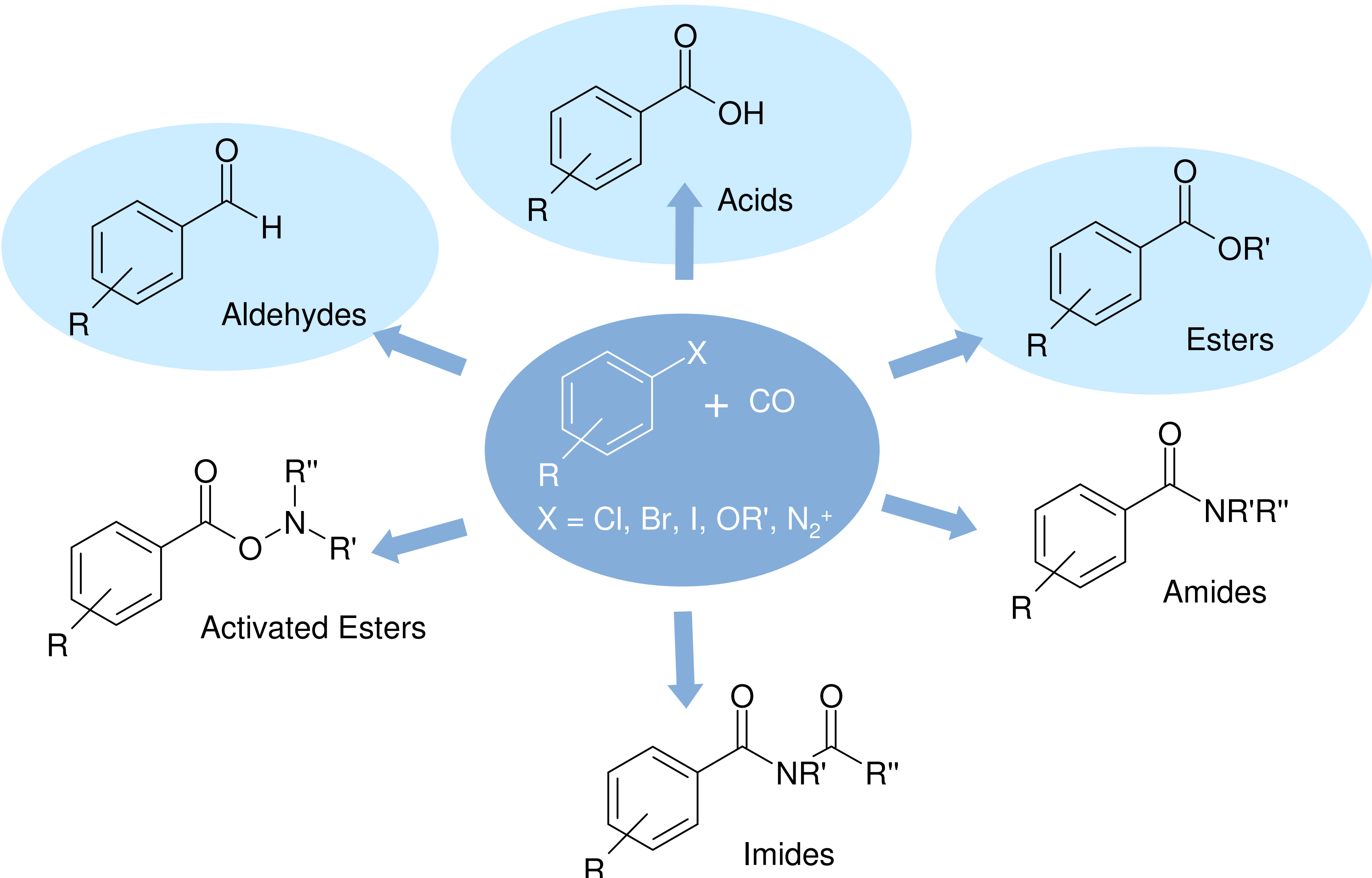
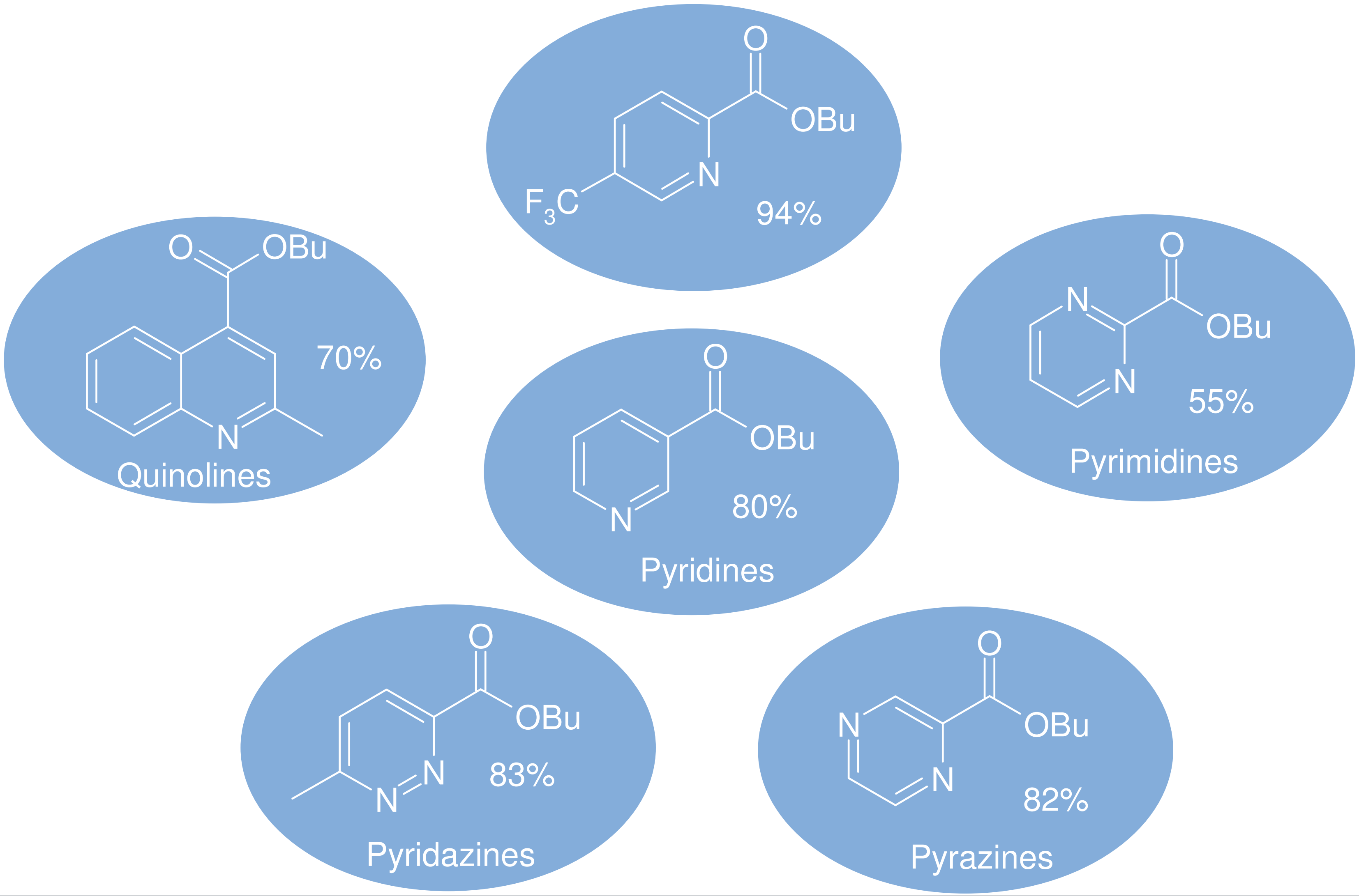
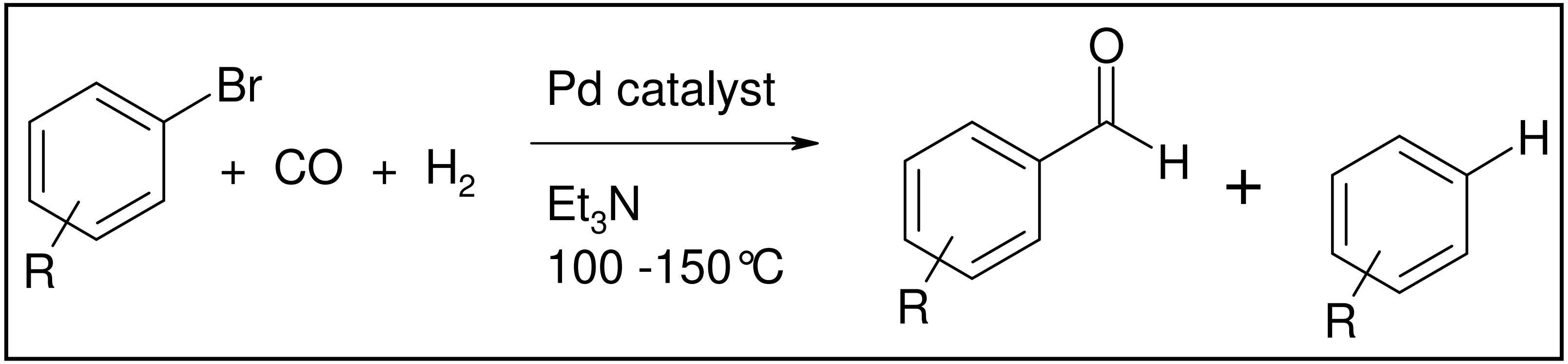


Different Substrate Classes by TMC

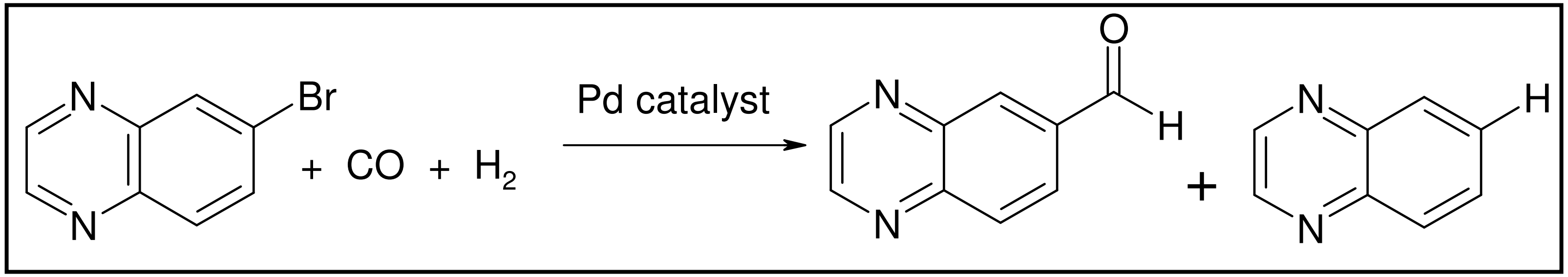


Reductive Carbonylation - Test Reactions

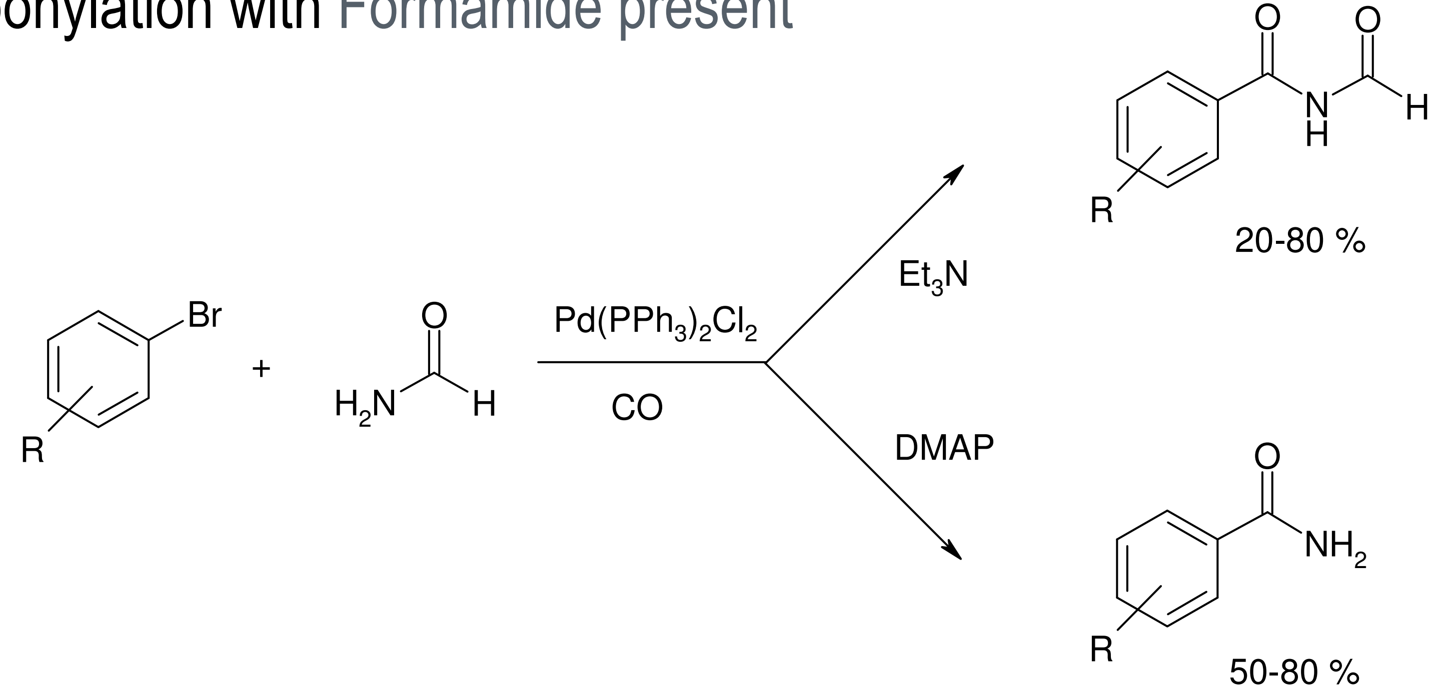


R = 4-MeO, 3-CF_3, 4-CF_3

G. Mehltretter, Diploma Thesis 1999.



Carbonylation with Formamide present

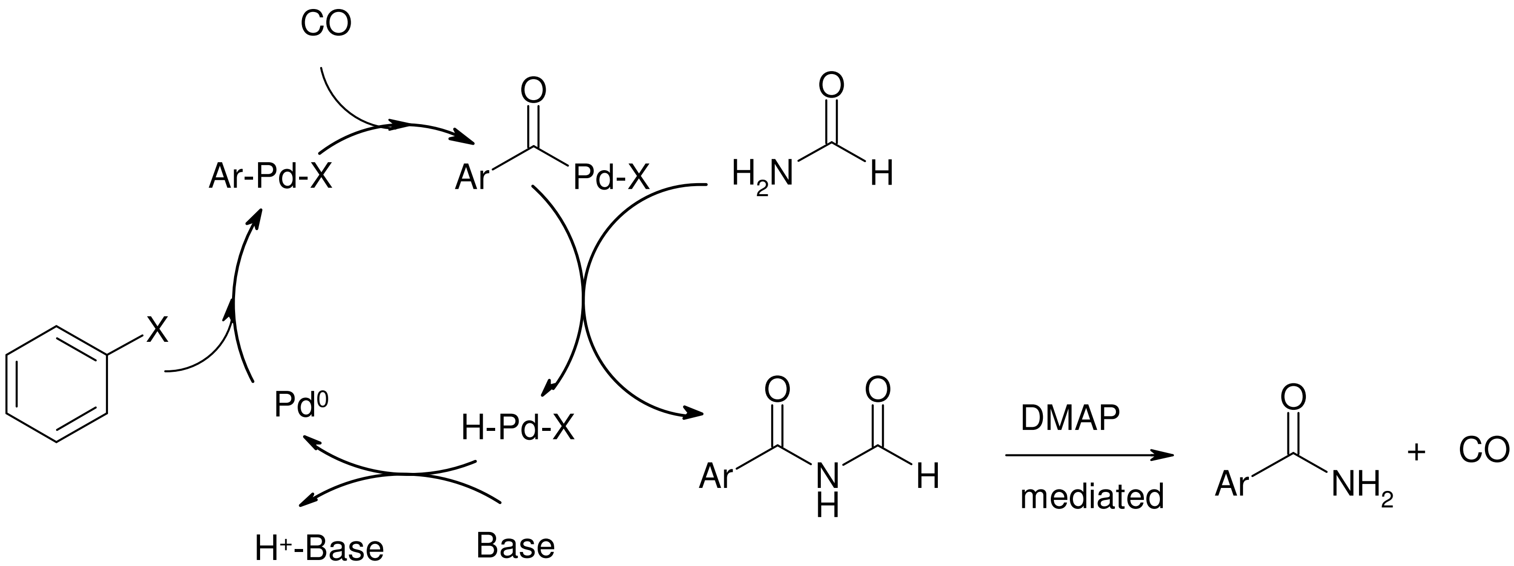


- Mild reaction conditions: 5 to 10 bar at 100 - 120°C

A. Schnyder, A. Indolese, **J. Org, Chem. 2002**, 67, 594-597.

Proposed reaction mechanism

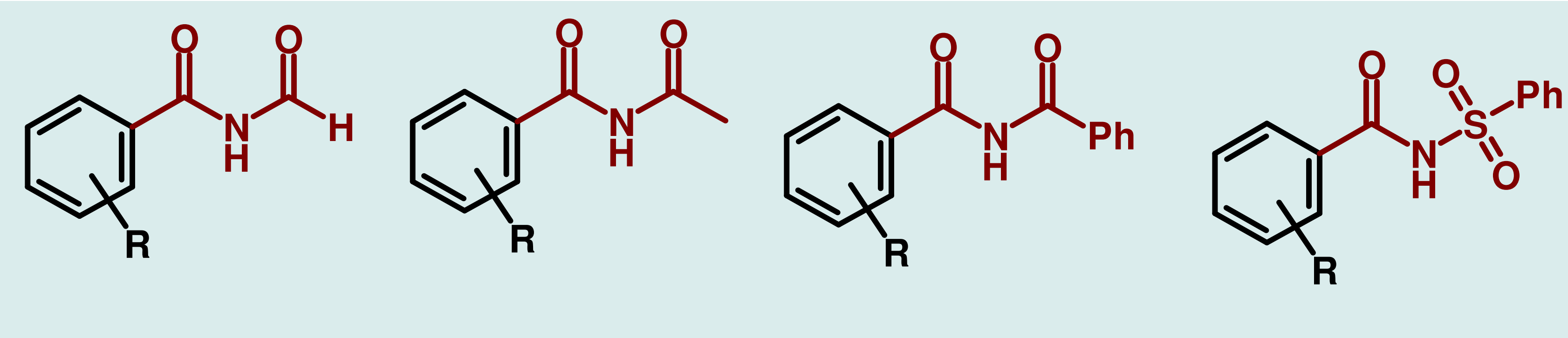
Carbonylation with Formamide present

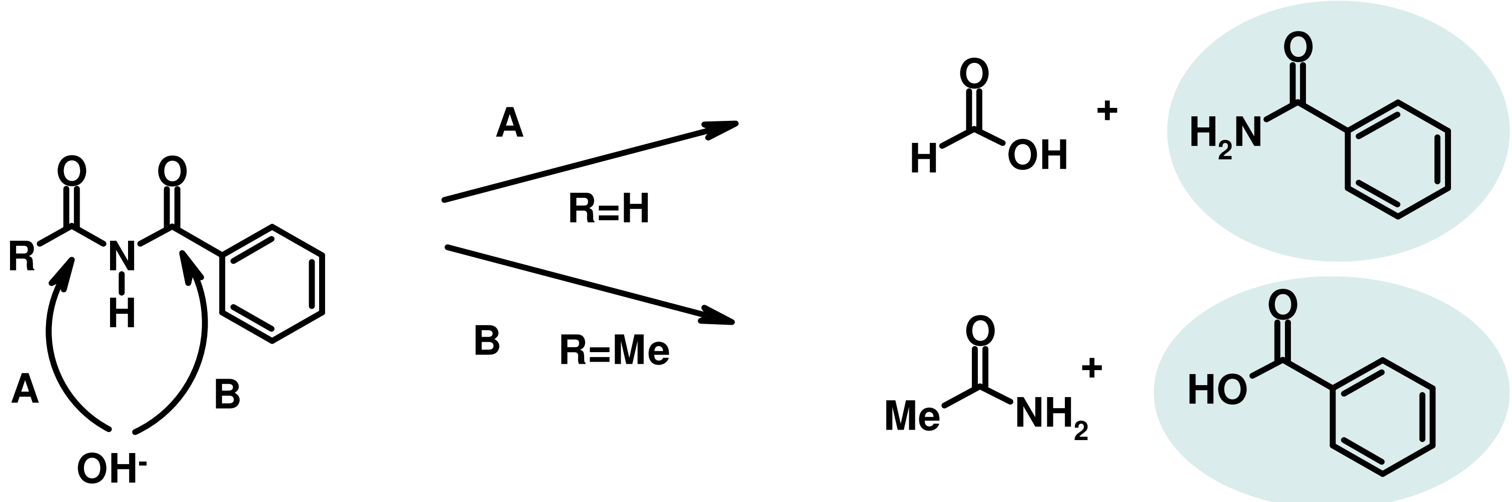


- DMAP mediated CO release in the last step

See also “Evolution of Carbonylation Catalysis: No Need for Carbon for Carbon Monoxide“, T. Morimoto, **Angew. Chem. Int. Ed. 2004**, *43*, 42, 5580-5588.

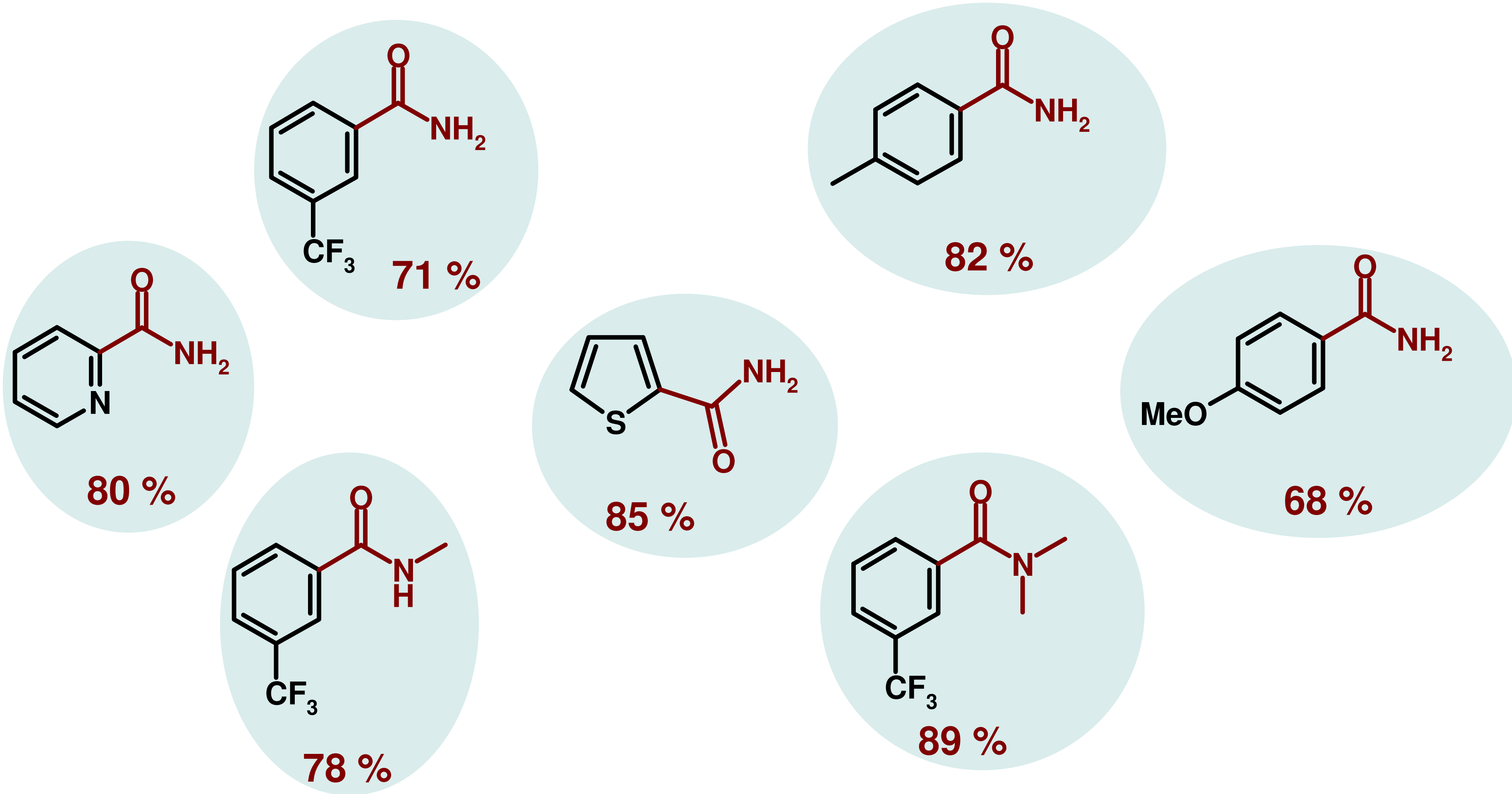
Scope and Reactivity of Imide Synthesis





A. Schnyder, A. F. Indolese, J. Org, Chem. 2002, 67, 594-597

Scope of Amide Synthesis



A. Schnyder, M. Beller, G. Mehltretter, T. Nsenda, M. Studer, A. Indolese, J. Org, Chem. 2001, 66, 4311.

Synthesis of Activated Esters

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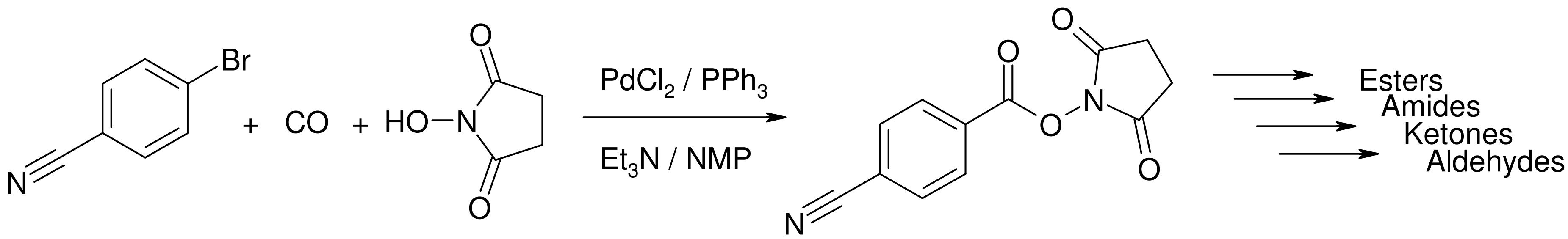
Carbonylation: Model reaction

- Formation of an activated ester



Fast and Reliable Scale-up

Quick realisation:

- Target identification, development and production in *2 months* only
  - Catalyst screening
  - Optimisation of reaction parameters
  - Optimisation of work-up
  - Analytical method development
  - Safety analysis
  - Removal of Palladium
- Yield: 70%; Purity: 95 %
- Palladium content < 10 ppm

Transition Metal Catalysis

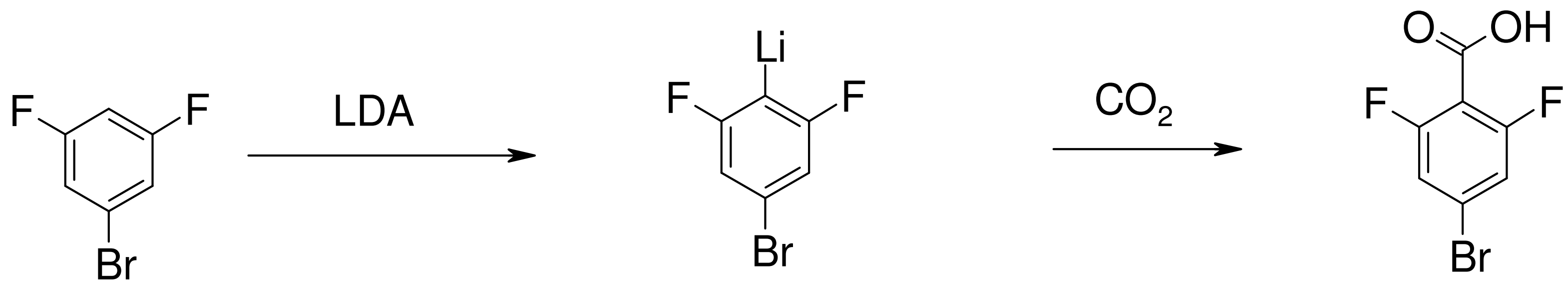
Synthesis of a Benzoic Acid by Cryogenic Lithiation

- Synergies between cryogenic metalation and TMC

Production of Benzoic acid by Cryogenic Lithiation

Ortho directed hydrogen / lithium exchange

Quench with carbon dioxide



Low Temperature Synthesis of Carbonic acid

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Challenges

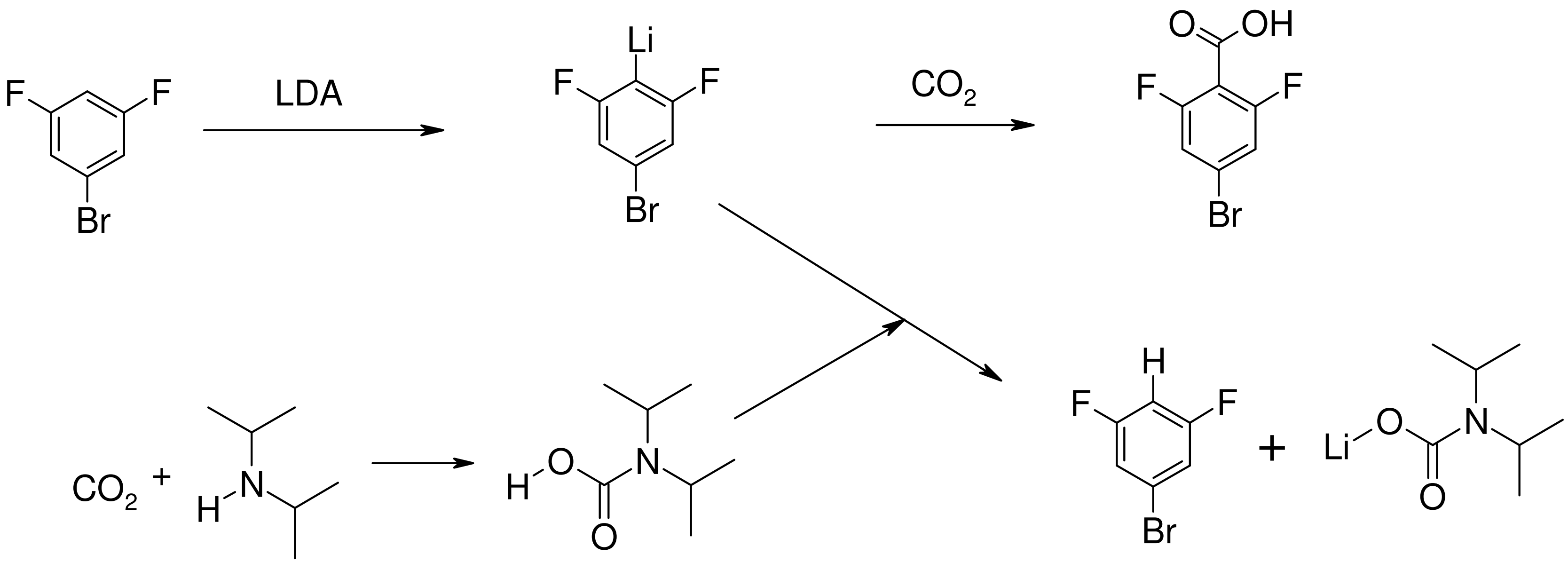
- Quality of starting materials
- Stability of the lithiated intermediate: Aryne formation
- Side reactions: bromine / lithium exchange
- Back reaction → protonation of lithiated species

Transition Metal Catalysis

Critical parameters

- LDA (Lithium diisopropylamide) must be produced freshly at low temperature
- Lithiation must be carried out at – 65 °C
- Violent decomposition takes place above – 20 °C
  → preventive safety measure are required
- Stoichiometry of 1:1 must be observed
- Lithiation goes to completion (checked by online IR), but during CO_2 addition, the starting material is formed back

Lithiation and Back Reaction



Conclusion

- Synergies between cryogenic metalation and TMC

Conclusion

The quest for better selectivity continues

Cryogenic lithiation and transition metal catalysis are formidable tools to synthesize efficiently very complex molecules

The specific requirements of these reactions for scale-up must be understood

Acknowledgment

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T. Aemmer
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A. Christen

Thank You

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