Chemocatalysis –
a Tool of Green Chemistry

Florian Baechle, PhD

Leading Scientist &
Product Manager Ligands

June 26, 2019

What we do

Custom Synthesis

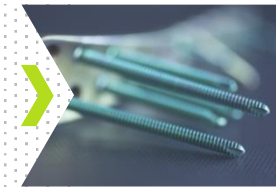
Extractables & Leachables

Elemental & Trace Analysis

Ligands & Catalysis

Troubleshooting

Medical Device Analytics



Small Molecule Analysis

DNA Analysis

Environmental Monitoring

Polymorph, Salts & Crystallization

Bio Analysis & Cell Based Bioassays

Inhaled Drug Products

Biopharmaceutical Analysis

Process Analytical Technology Probes

Quality Control

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Custom synthesis, API manufacturing, Ligands & Catalysis

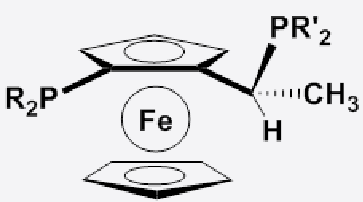
Solvias – Integrated Services

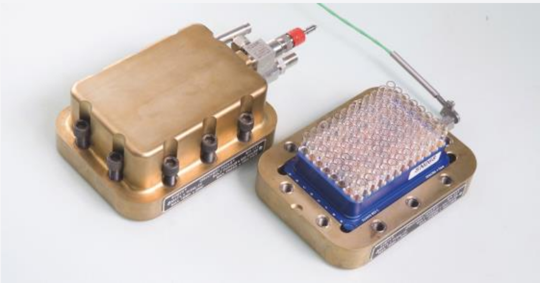
Creating unique value by utilizing intra-company synergies

1 **Catalysis** meets **Synthesis**

V + W ⟶ **A + B** —[Cat*]⟶ **C*** ⟶ **P***

Ligands & Catalysts ↔ **Catalysis Services**





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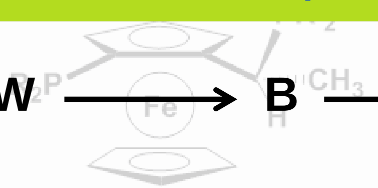

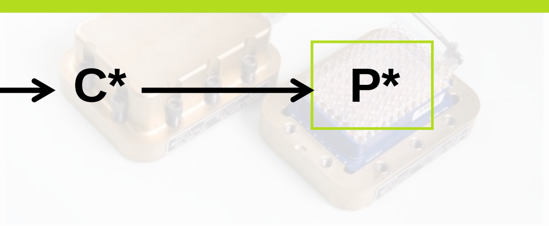

V + W ⟶ **B** ⟶ **D*** ⟶ **C*** ⟶ **P***

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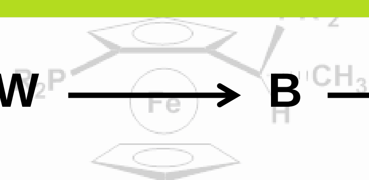

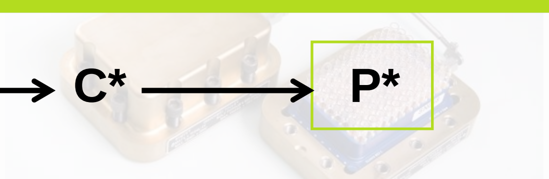

V + W ⟶ B ⟶ D* ⟶ C* ⟶ P*

3 Supported by our **analytical department** incl. **microbiology**

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Prerequisites towards an Industrial Application

FIND CATALYST LEADS

- screen large variety of ligands / catalysts

large variety of ligands (~100 mg)
(Solvias platform: ~500 chiral ligands)

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- optimize ligand structure
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few ligands (10 g – 100 g)

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- pilot
- prepare / buy ligand / cat. in kg quantities

one ligand (1 – 100 kg/y)

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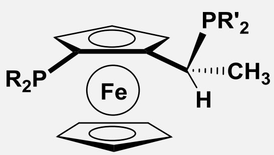
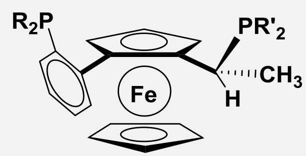
Commercial Solvias Ligand Families

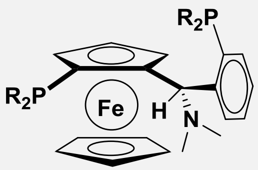
Modular Chiral Ligands



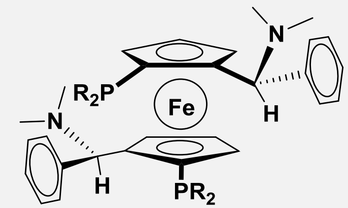
Josiphos



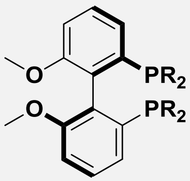
Walphos



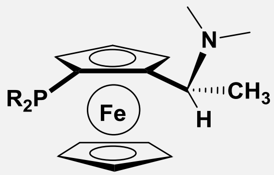
Taniaphos (Umicore)



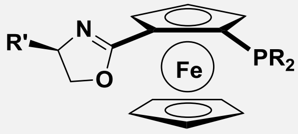
Mandyphos (Umicore)



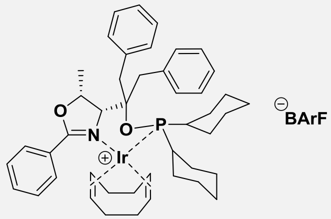
MeO-Biphep (Roche)



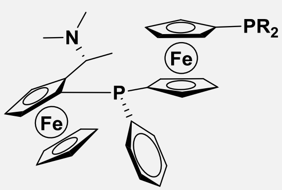
PFA



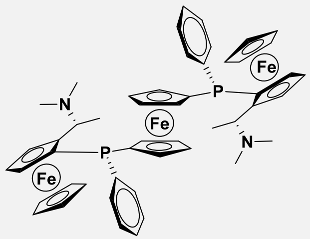
POX



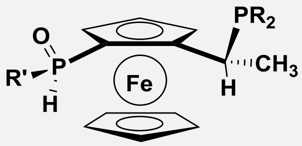
Ubaphox



Chenphos



Trifer



JoSPOphos

>100 chiral Solvias ligands are commercially available | **additional derivatives on demand (most ligands are modular)**

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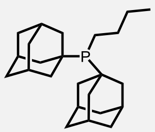
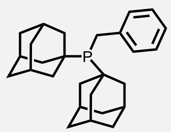
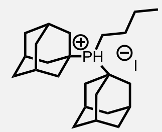
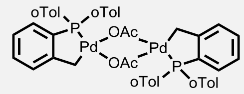
Commercial Solvias Ligand Families

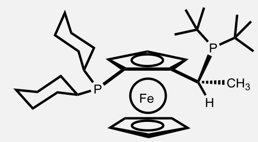
Ligands for C-X coupling

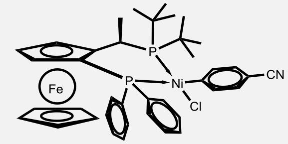

CataCXium A

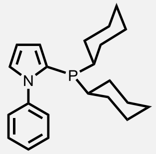

CataCXium Abn

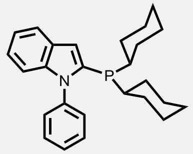

CataCXium AHI

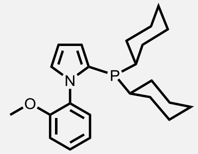

CataCXium C

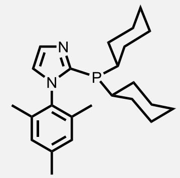

$[PdCl_2(PP)]$
SK-K319-1a

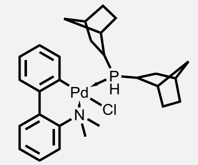

SK-J002-1n


CataCXium PCy


CataCXium PInCy


CataCXium POMeCy


CataCXium PICy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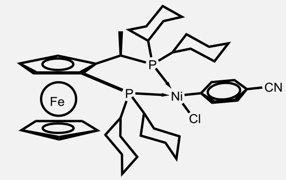
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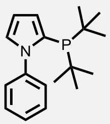
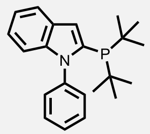
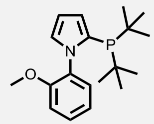
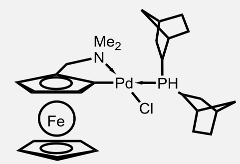

CataCXium PtB


CataCXium PIntB


CataCXium POMetB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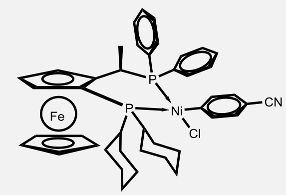
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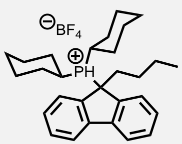
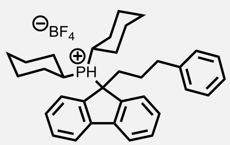
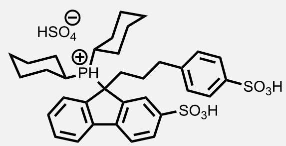
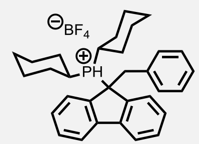
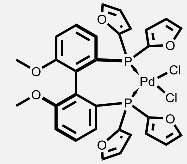

CataCXium FBu


CataCXium FPrPh


CataCXium FSulf


CataCXium FBn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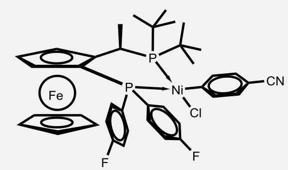
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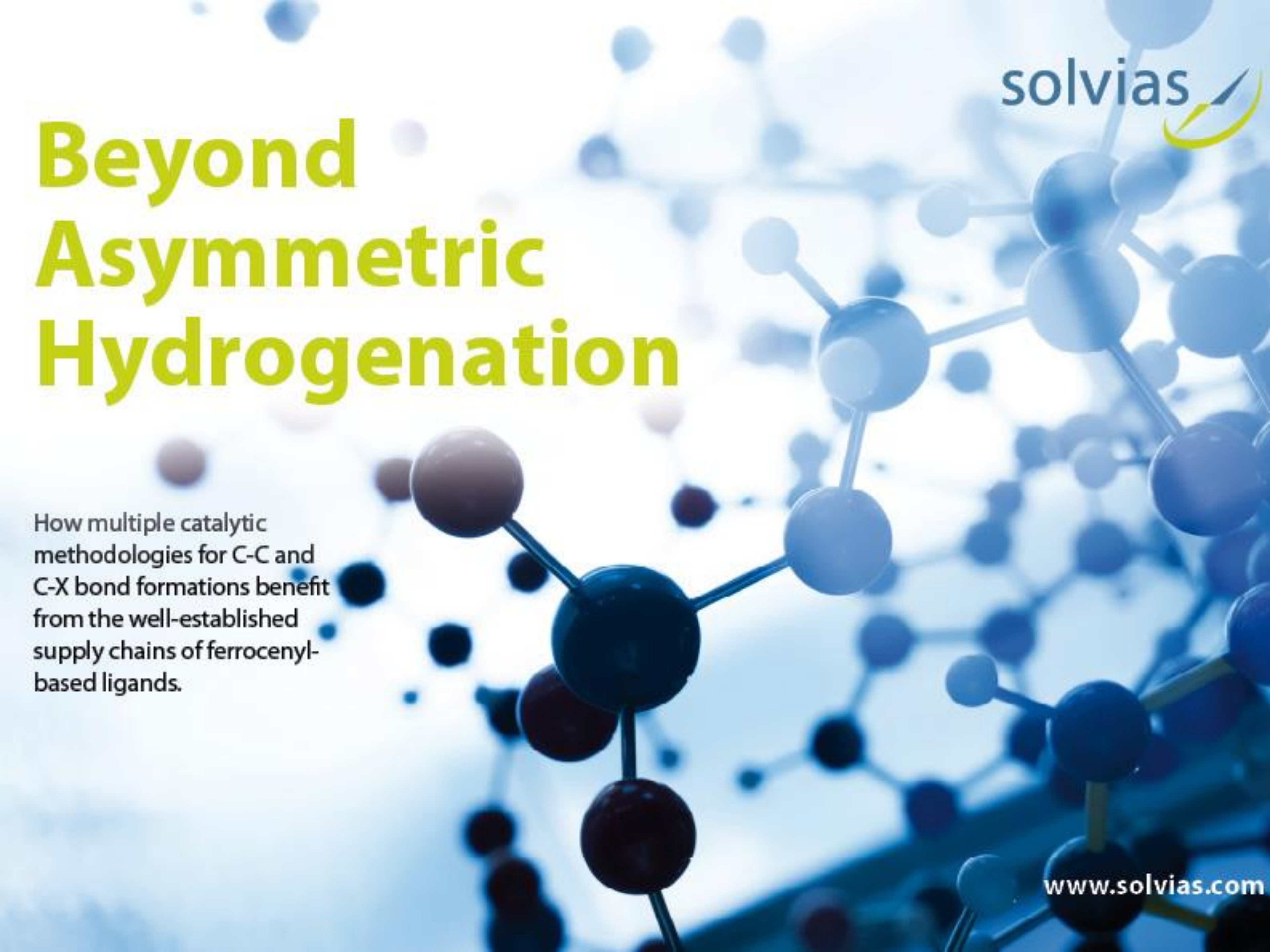
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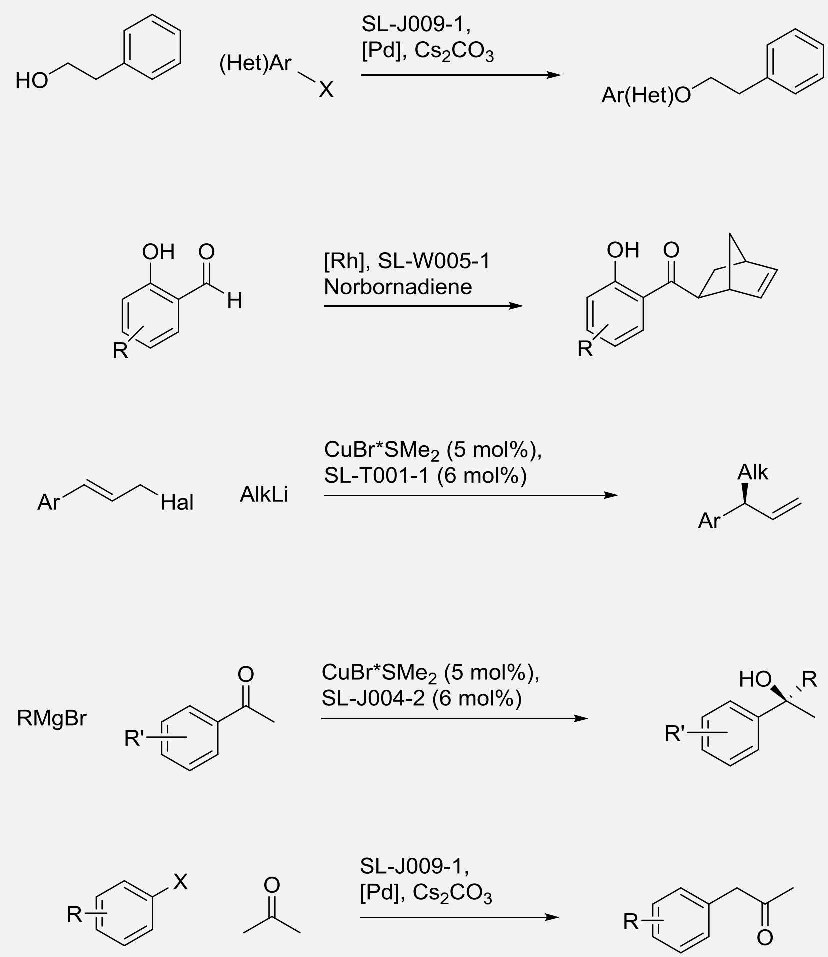
Beyond Asymmetric Hydrogenation
How multiple catalytic methodologies for C-C and C-X bond formations benefit from the well-established supply chains of ferrocenyl-based ligands.
www.solvias.com

Beyond Asymmetric Hydrogenation

- Asymmetric hydrogenation
- **(asym.) C-X, C-O cross coupling**
- (asym.) Hydroamination
- **(asym.) Hydroacylation**
- Asymmetric Mannich-type reactions
- Asymmetric 1,4-addition
- **(asym.) Allylic substitution**
- Asymmetric cycloadditions
- Asymmetric ring-opening
- Asymmetric reductive coupling
- **Asymmetric 1,2-addition**
- Hydroformylation
- Alkoxycarbonylation
- Carbonylative C-X coupling
- C-H activation
- Monoarylation of ammonia
- **α-Arylation of ketones**
- etc.



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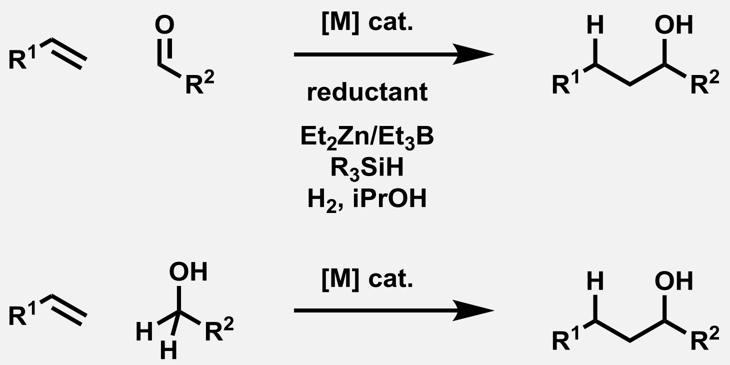
Asymmetric Reductive Addition of Olefins to Ketones

Why would a metal-cat. reductive coupling of olefin derived nuc. be important?

- α-olefins and carbonyls are orthogonal feedstocks
- alternatives to classical carbonyl additions
- catalyzed asymmetric variants of Grignard
- Autotransfer of hydrogen allows alcohol to be reductant and proelectrophile
  - **by-product free carbonyl addition**
  - **lower alcohols can be converted to higher alcohols**



Krische et al; *Science*. **2016**, *354*, 300.

Buchwald et al; *JACS* **2018**, *140*, 2007.

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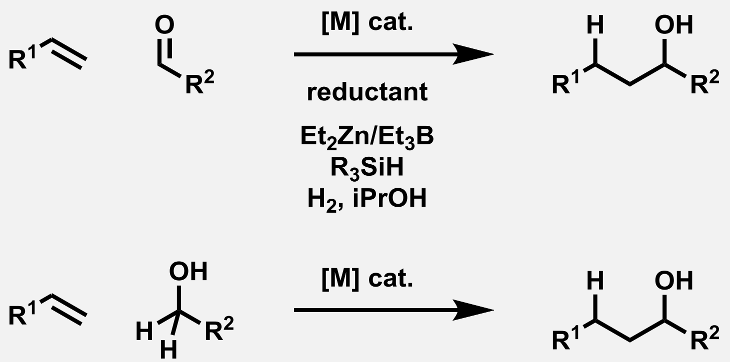
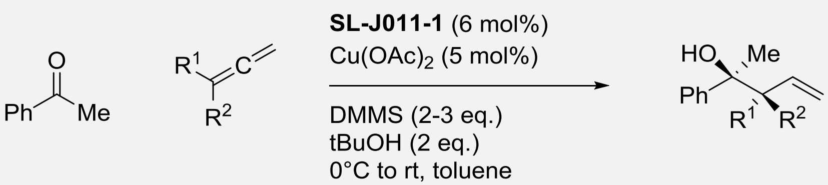
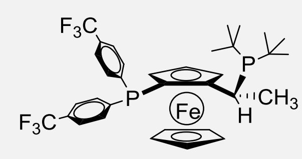


- **Recent precedence in literature - Ketone allylation with terminal allenes**





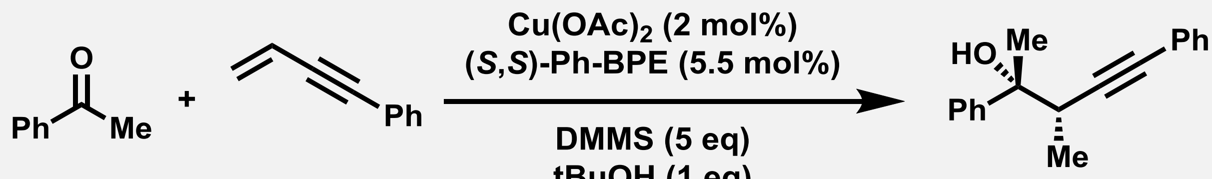
SL-J011-1

Krische et al; *Science*. **2016**, *354*, 300.

Buchwald et al; *JACS* **2018**, *140*, 2007.

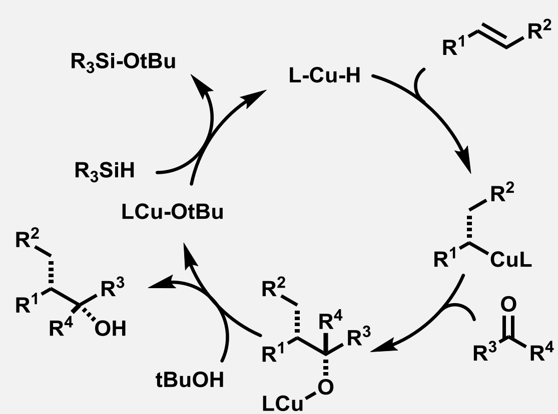
Asymmetric Reductive Addition of Olefins to Ketones

S. L. Buchwald 2016



86% yield, 10:1 dr
96%ee

- Ligand plays a crucial role in suppressing the undesired CuH-catalyzed ketone reduction
- No exogenous acidic or basic additives are required
  - **increased functional group tolerance**



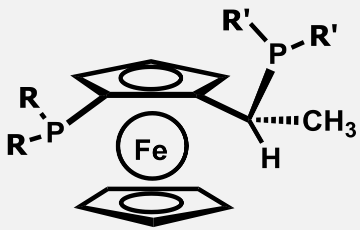
irreversible, enantio-determining step

diastereoselectivity-determining step

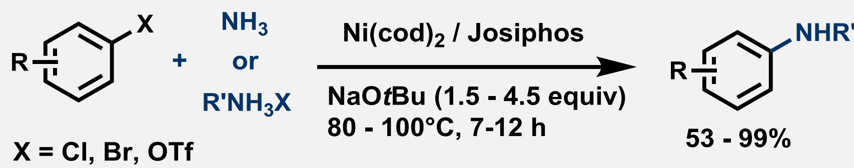
Y. Yang, I. B. Perry, G. Lu, P. Liu, S. L. Buchwald, *Science* **2016**, *353*, 144–150.

Buchwald-Hartwig Amination with Ammonia

What is the benefit of an Amination with Ammonia?



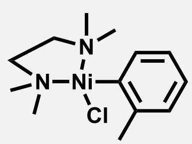
SL-J001-1: R = Ph, R' = tBu
SL-J004-1: R = Cy, R' = Ph



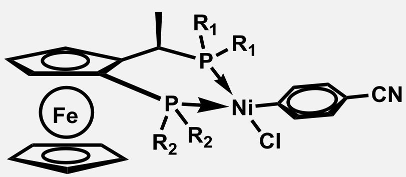
Ligand	amine source
SL-J001-1	NH_3 (5 equiv), $(NH_4)_2SO_4$ (1.5 equiv), $MeNH_3Cl$ (3 equiv)
SL-J004-1	$EtNH_3Cl$ (3 equiv)

[Ni(cod)$_2$]

air sensitive



fairly air stable



air-stable over months

A. Borzenko, N. L. Rotta-Loria, P. M. MacQueen, C. M. Lavoie, R. McDonald, M. Stradiotto, *Angew. Chem. Int. Ed.* **2015**, 54, 3773.

R. A. Green, J. F. Hartwig, Angew. *Chem. Int. Ed.* **2015**, *54*, 3768.

J. S. K. Clark, C. M. Lavoie, P. M. MacQueen, M. J. Ferguson, M. Stradiotto, *Organometallics* **2016**, *35*, 3248.

J. Schranck, J. Rotzler, *Org. Proc. Res. Dev.* **2015**, *19*, 1936.

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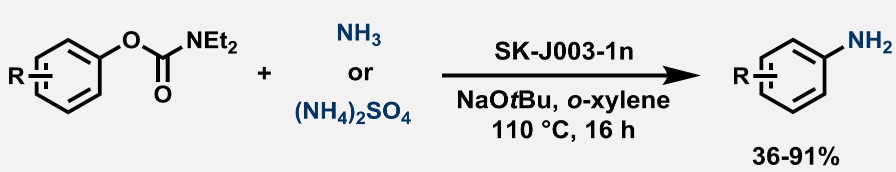
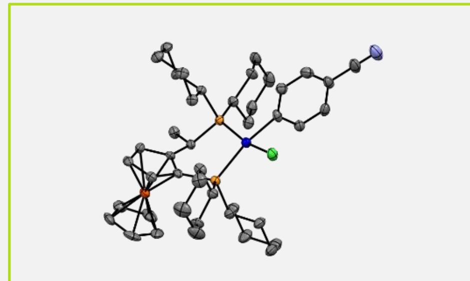
Buchwald-Hartwig Amination with Ammonia

Amination of Carbamates – a Halogen and Sulfonate free C-N coupling





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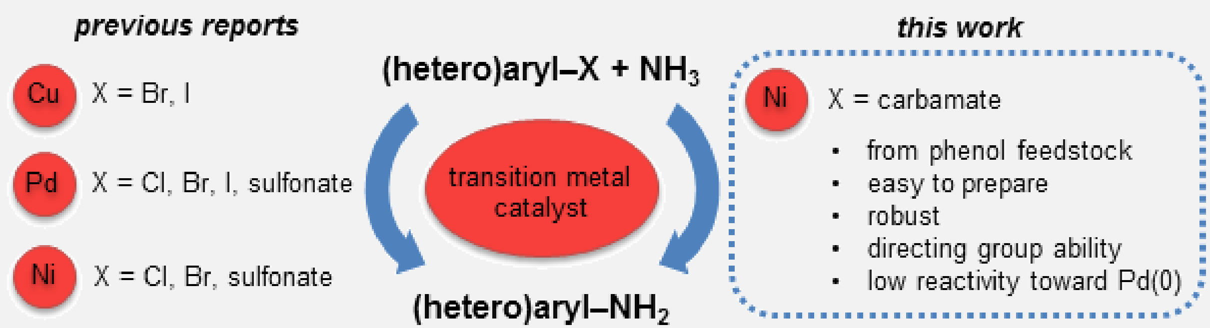

J. Schranck, P. Furer, V. Hartmann, A. Tlili, *Eur. J. Org. Chem.* **2017**, 3496-3500.

P. M. MacQueen, M. Stradiotto, *Synlett* **2017,** *28*, 1652-1656.


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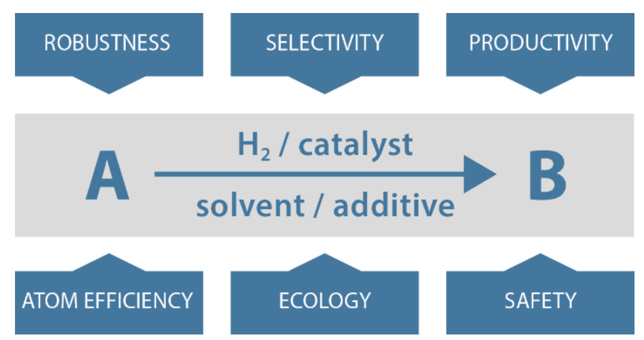

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C≡C, C=C, C=O, C≡N, C=N hydrogenolysis of activated bonds

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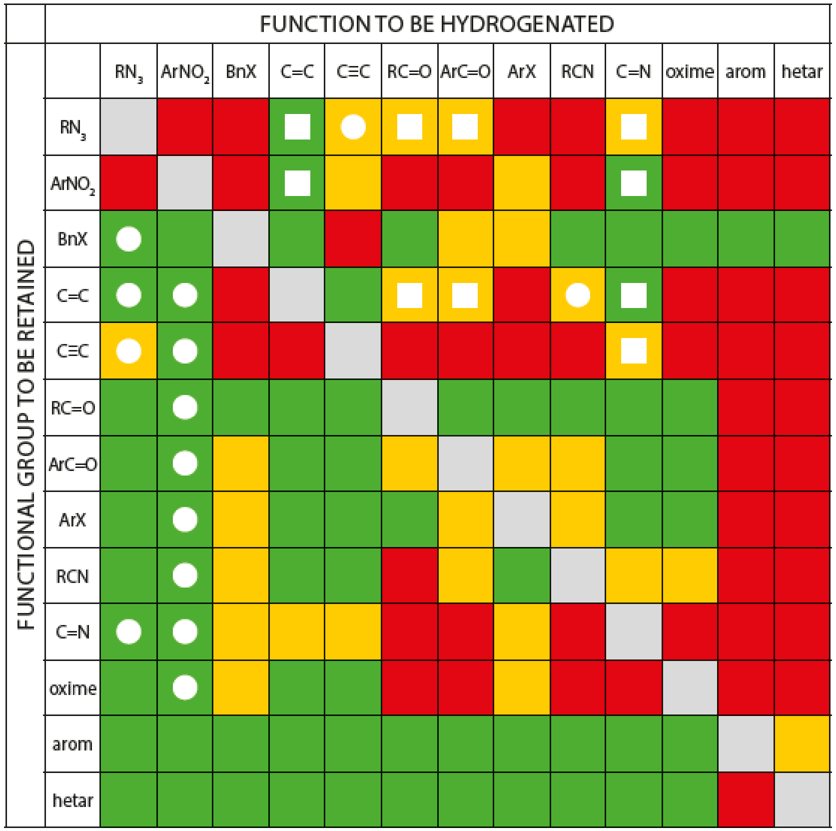
Heterogeneous Catalysis at Solvias



Routine transformation using standard heterogenous catalysts with selectivities >90%

Moderately difficult and/or with tailored/modified heterogenous catalysts and/or S <90%

Difficult and/or only in special cases with tailored/modified catalyst and/or S <50%

○ heterogenous catalyst (modified)

□ homogenous catalyst

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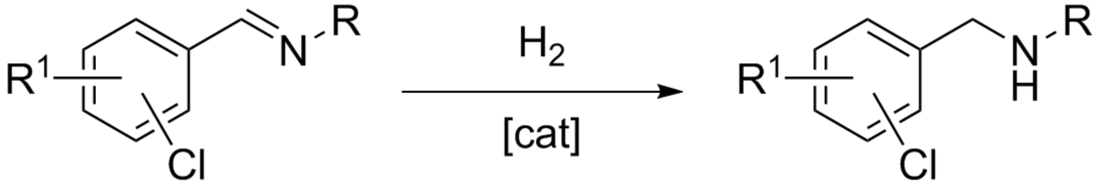
Heterogeneous Catalysis at Solvias

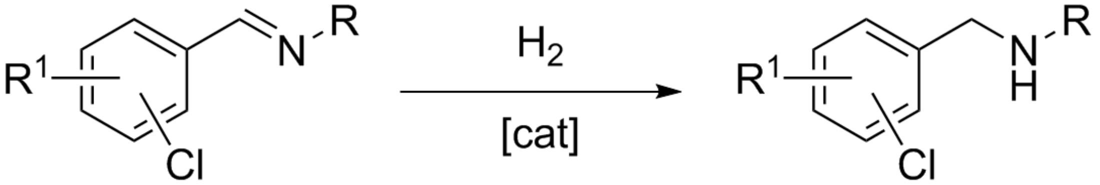
Case study for the application of HTE in Heterogeneous Hydrogenation



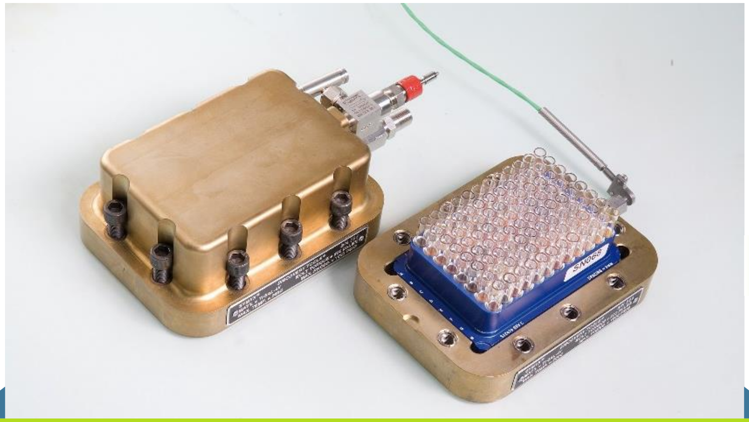
R^1 = labile C-C bond

Heterogeneous Catalysis at Solvias

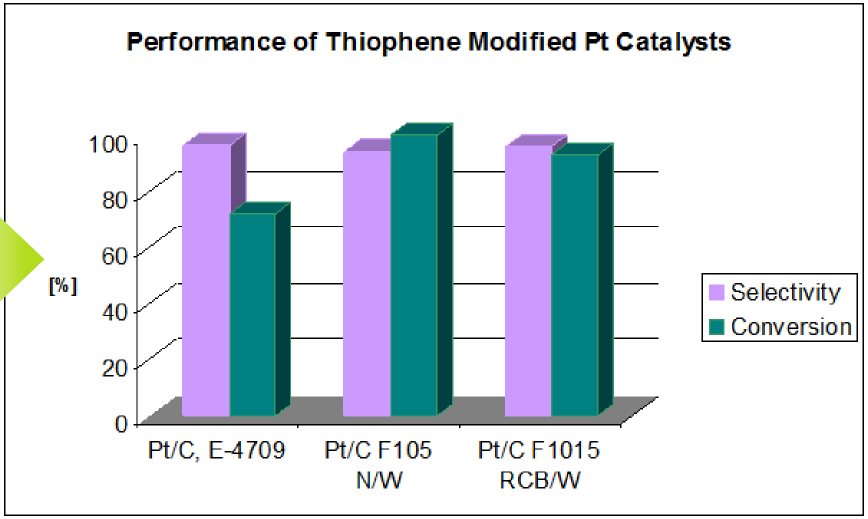
Case study for the application of HTE in Heterogeneous Hydrogenation



R1 = labile C-C bond



HTE screening of heterogeneous catalysts



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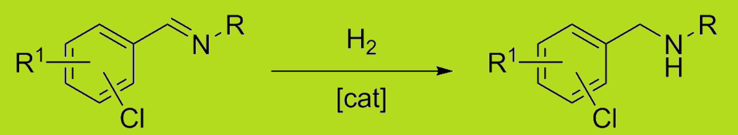
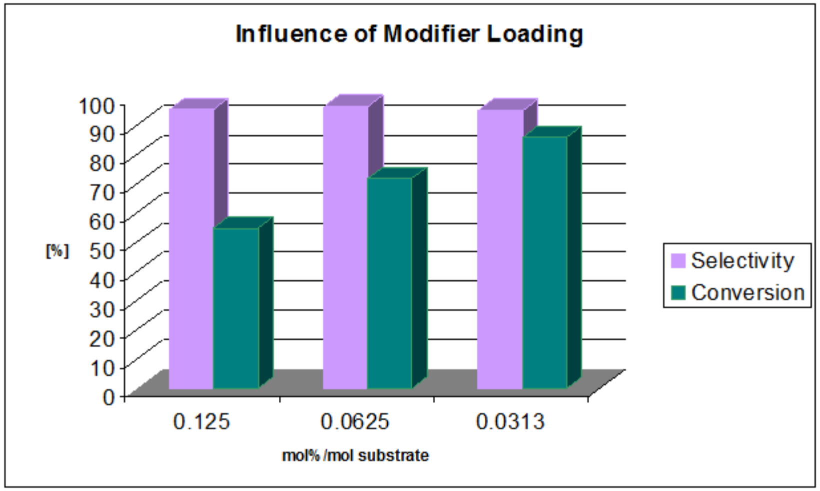
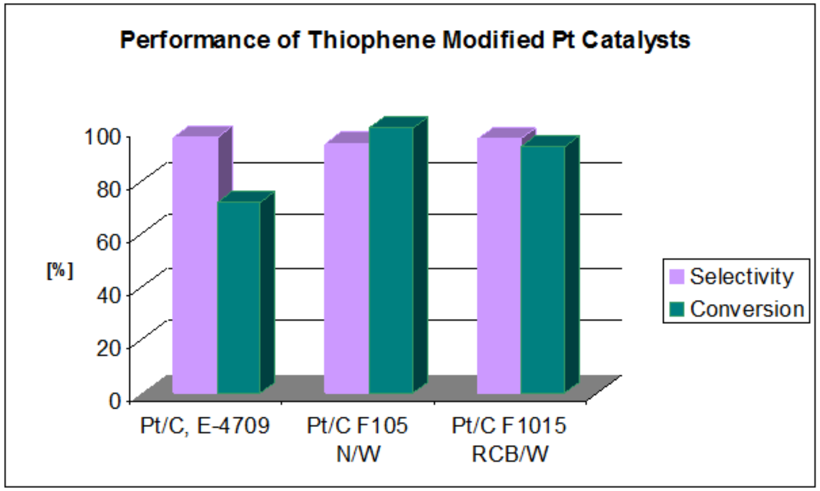
Case study for the application of HTE in Heterogeneous Hydrogenation



>95% selectivity of crude product prior to work-up

R^1 = labile C-C bond





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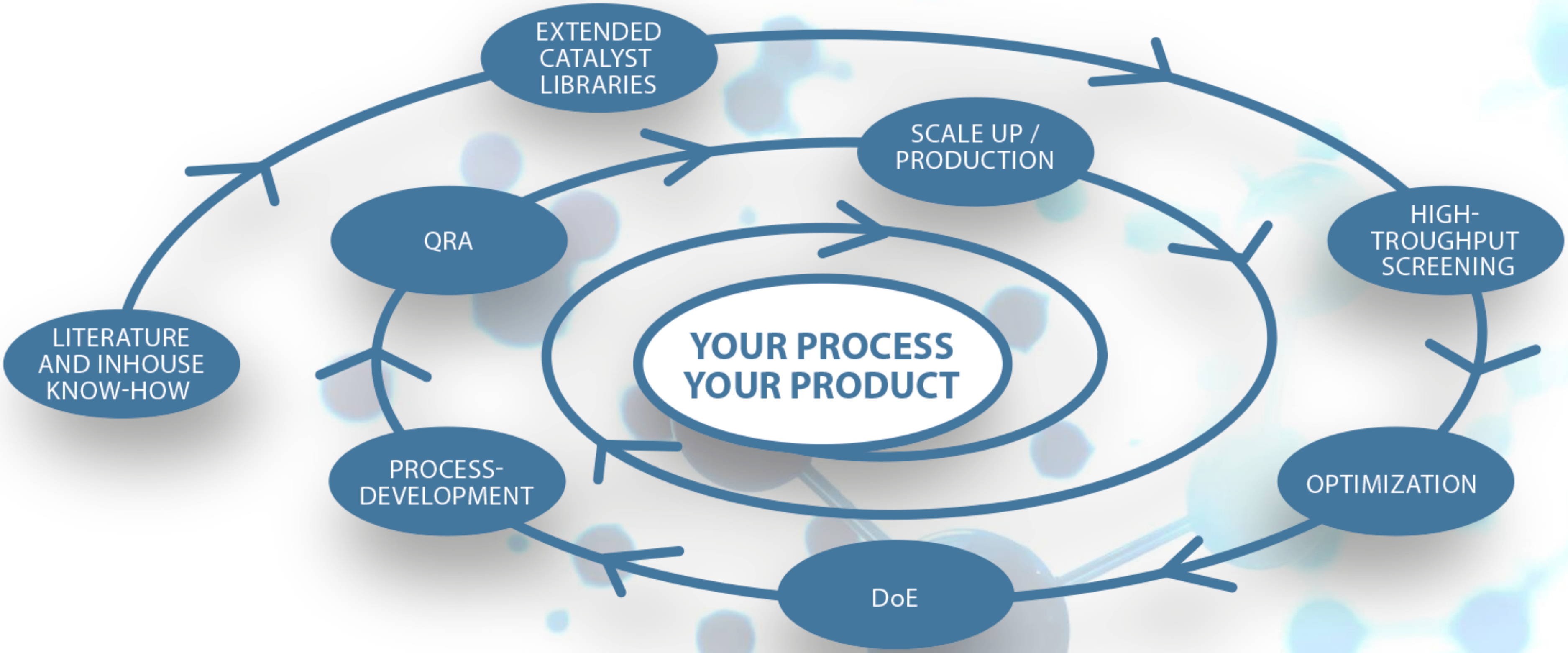

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