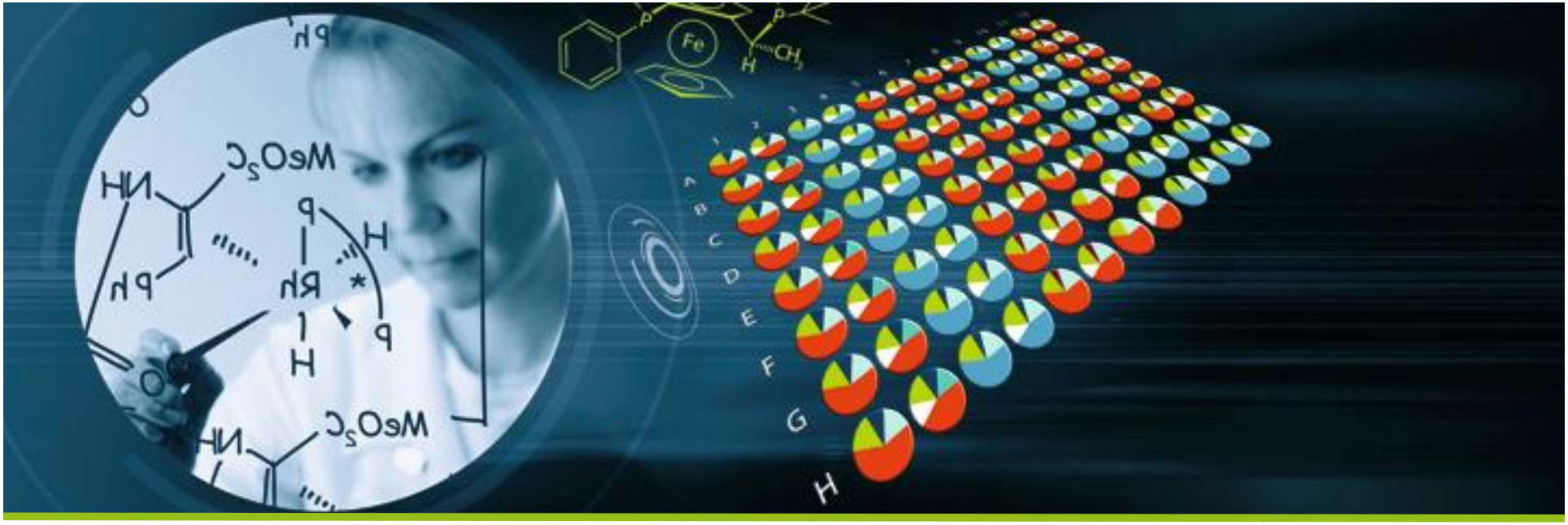
solvias

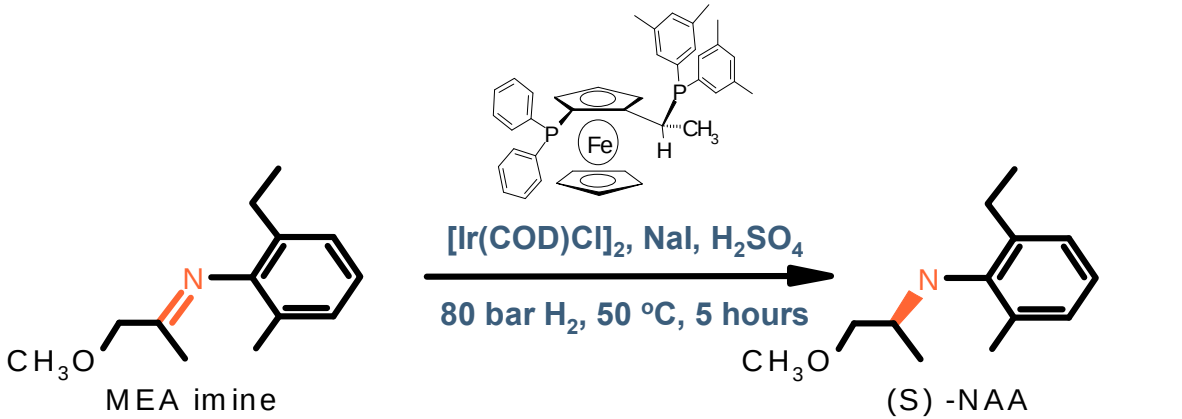


Enabling Catalysis in the Pharmaceutical Industry with High Throughput Screening (HTS)

Amazing where you can go

Asymmetric Hydrogenation: What It's All About

Metolachlor Josiphos Application (Syngenta's (S)-Dual)



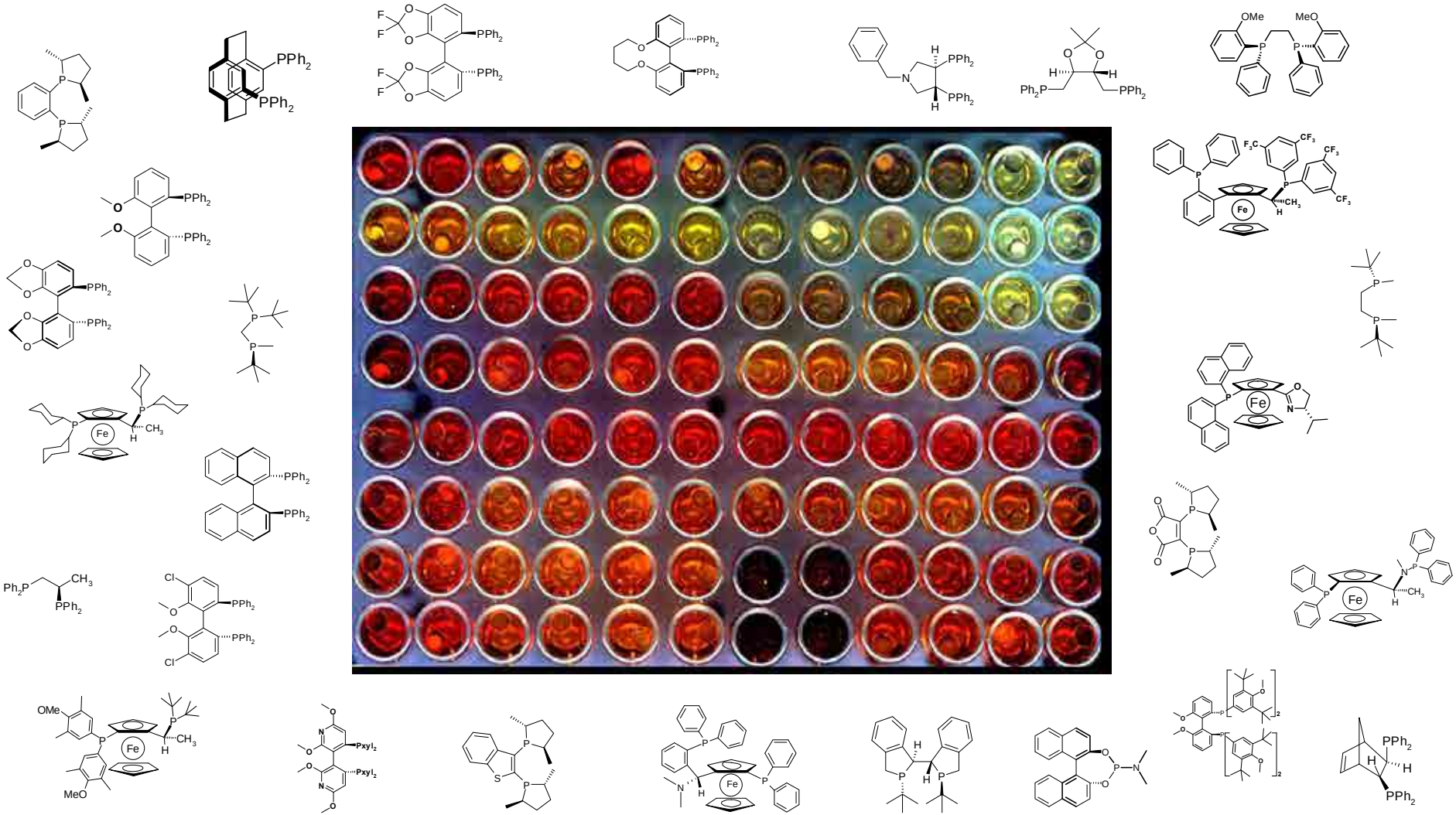
S/C ratio = 1,000,000 : 1
e.e. = 79%

Syngenta's Racemic Switch: Lifecycle Management of an Herbicide

- Originally marketed as a racemate (One enantiomer of the herbicide is active)
- 79% e.e. is OK for a herbicide
- 1,000,000:1 S/C ensures a cheap product with more potency than racemate
- 10,000 ton/year (10 ton batches, 16g Ir precursor & 32g ligand!)

Asymmetric Hydrogenation: Cheap, efficient, *surmountable* manufacturing technology

It All Starts with Screening...

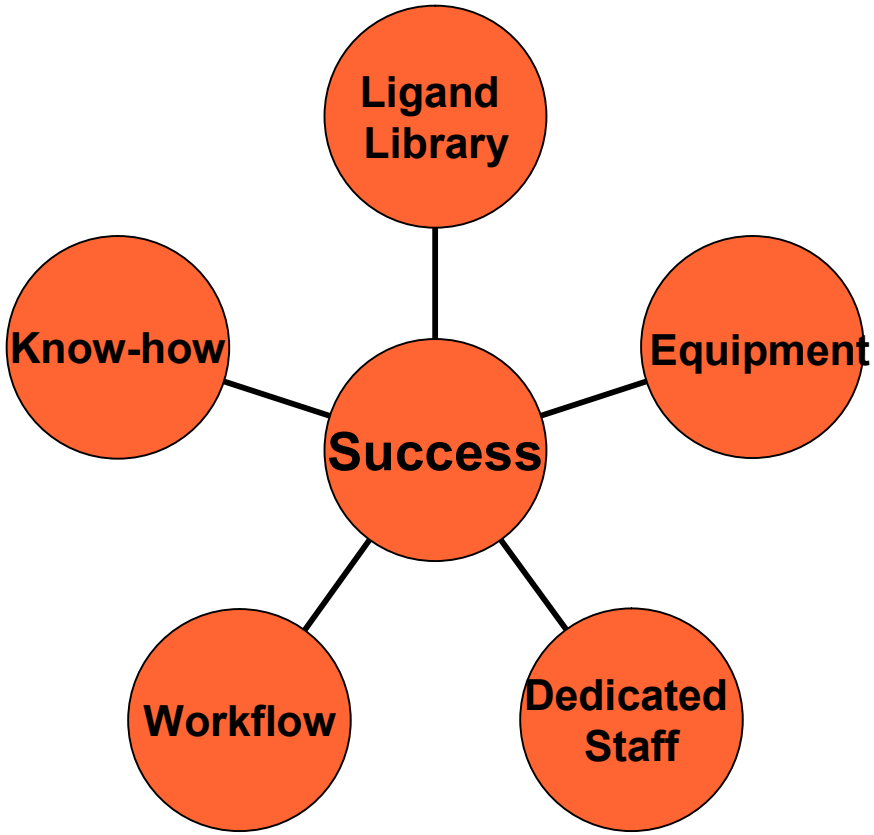


It's All About Options....

Choose the right lead for development!

- Productivity and activity (s/c and reaction time)
- Substrate quality tolerance
- Ligand/catalyst availability in bulk
- Price of catalyst (metal and ligand)
- Infrastructure requirements (alloy, pressure...)

Success Factors in Screening



HTS Equipment

Symyx core module in N_2 filled glovebox

96-well plate (0.4 mL, 100 bar H_2 or CO)

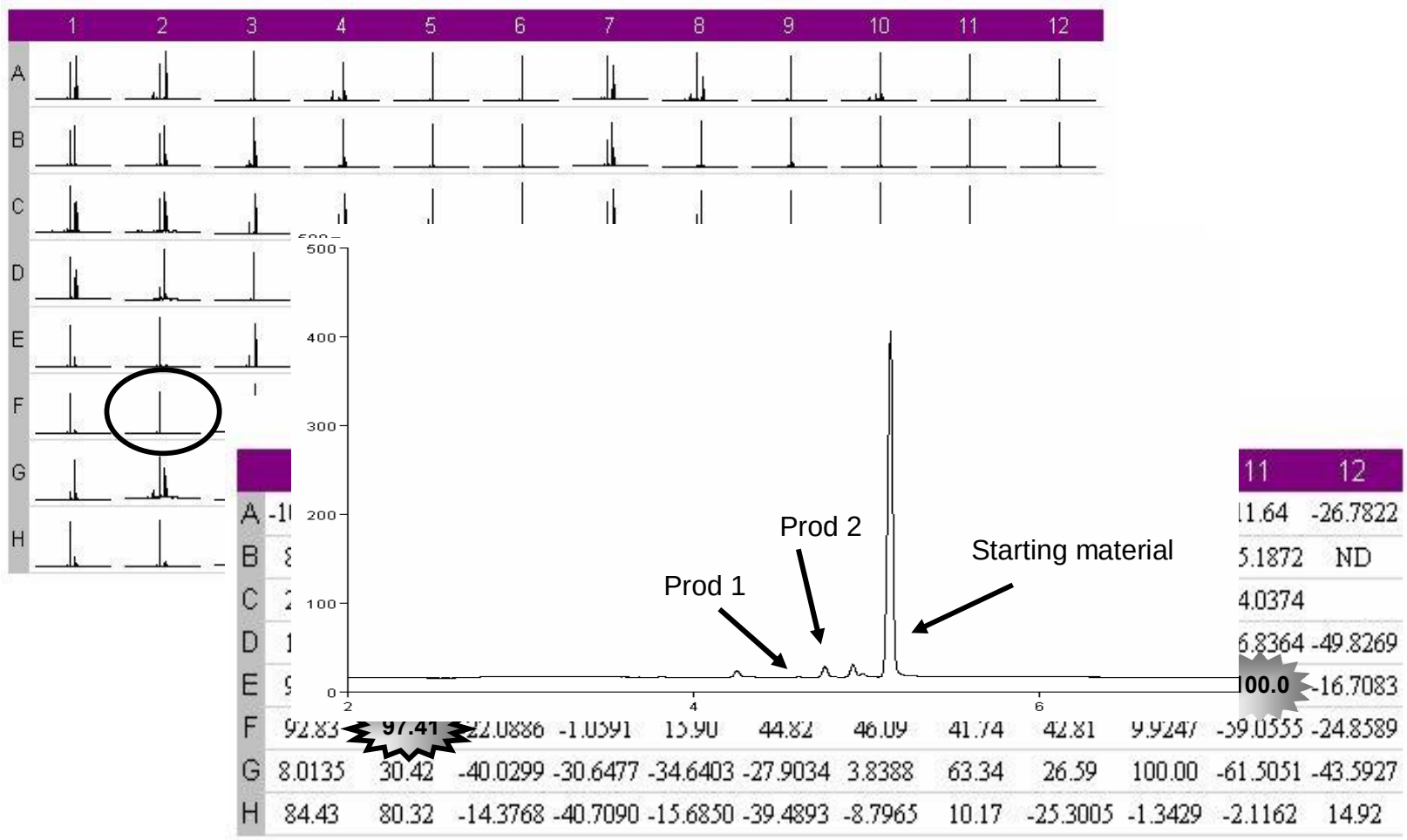
Highlights

- Inert handling
- Robotic dispensing
- SFC Analysis
- Symyx software

Benefits

- No O_2 (Piece of mind)
- Accuracy with robotics (Piece of mind)
- Fast time to hits
- Serendipity

Data Organization Made Easy: Asymmetric H_2 96-Well Plate Analysis Example



LEA Software

The Staff

- All staff has an 'ausbildung' in automation
- All HTS - All day - Every day
- Consistency of operation (wheel not reinvented)
- No need to train every chemist on equipment
- Excellent suggestions to solve uncommon problems

The Ligand Library

- >600 Chiral Ligands
- (>100 CX Coupling ligands/catalysts)
- Storage (air sensitive/non-air sensitive)
- Updated on a regular basis

The Workflow

HTS plate design is done by a catalysis expert

→ Combination of know-how and (!) serendipity results
in powerful shortcuts to solutions

Ligands, additives, metals: Test wide experimental space
→ Robot takes over dispensing and setting up of reactions
< 10% of manpower and time required vs non-robotized setup

In situ Catalyst generation from ligand and precursor
→ Highest possible flexibility (metal, precursor type, ligand, counterion)

HTS Analytics
Need for speed (rt << 15 min / sample required)
→ SFC, GC, fast HPLC

The Know-How (Nuts and Bolts)

Applied research

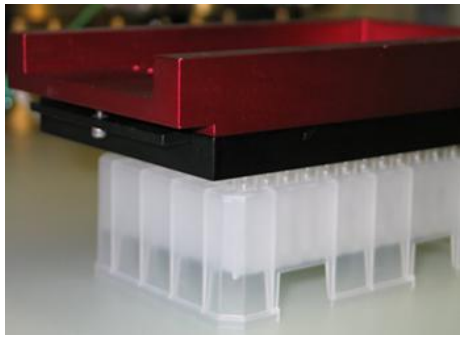
•Comparison: hand exp's vs plate exp's.
- -How to stir (magnetic, shaking, stir shape)
- -Addition order
- -Residency times

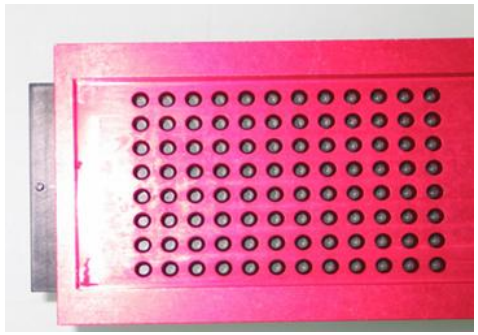
•Cleaning robot needle after drawing a slurry.

•Dosing a solid.

•What's easy / what's hard?

Nuts and Bolts: The Solutions



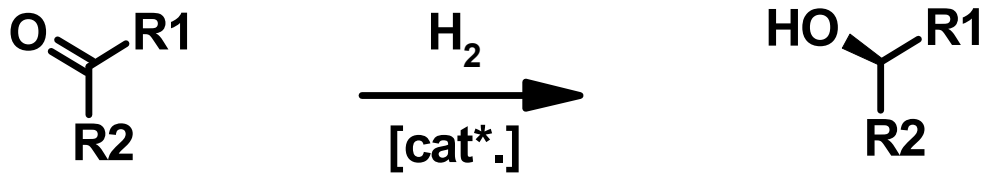


Solids handling
(trap door unit)

Needle cleaning
(after drawing a slurry of hetero catalyst)

Filtration x 96

Case 1: Hydrogenation of Ketone



Targets:

- >90% ee
- s/c >1000

State of the Art:

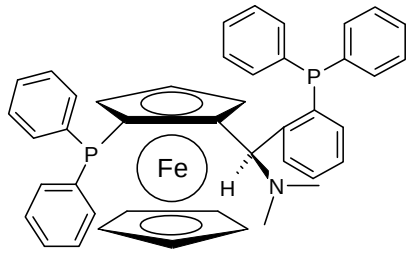
-Only ca. 40% ee (PP)*(NN)*Ru Noyori-type catalysts

-Low e.e. likely due to 'catalyst poison' in R2 group

Design and Results of 1st HTS Plate (Rational and Serendipity Design)

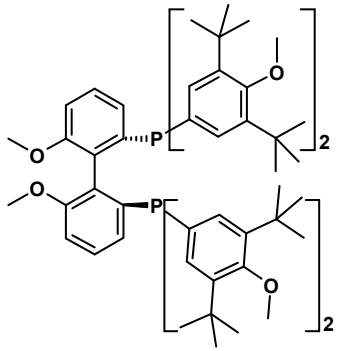
- Precursors: $[Rh(nbd)_2]BF_4$, $[(Rh(nbd)Cl]_2$, $[Ir(cod)Cl]_2$, $[Ru(p\text{-}cymene)I_2]_2$
- Ligands: 16 ligands from 6 ligand classes
- 3 solvents and Et_3N additive

Best results



T001-1 (Taniaphos)

MeOH
$[RuI_2(p\text{-}cymene)]_2$
81% e.e.



A109-2 (MeO-Biphep)

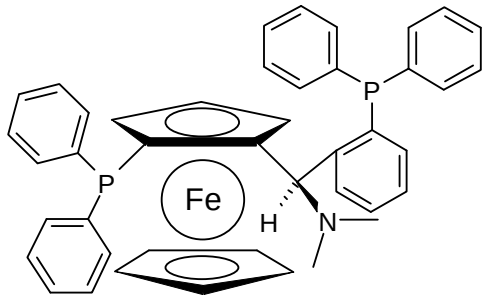
$MeOH/Et_3N$
$[Rh(nbd)]Cl]_2$
87% e.e.

- A good start, but not quite good enough.
- 2nd plate will be designed based on results of the first emphasizing:
  - Taniaphos derivatives/Ru systems
  - MeO-Biphep derivatives/Rh systems

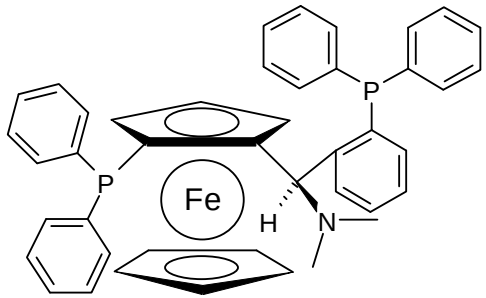
Design and Results of 2nd HTS Plate (Built Upon Results of the 1st HTS Plate)

- Precursors (all Ru and Rh): $[Ru(p\text{-cymene})Cl_2]_2$, $[Ru(p\text{-cymene})I_2]_2$, $[Rh(nbd)Cl]_2$, $[Rh(nbd)TFA_2]$, $[Ru(cod)TFA_2]$
- Ligands: 11 ligands (incl. 8 from MeO-Biphep and Taniaphos classes)
- MeOH (single solvent) and Et_3N additive

Best results



T001-1 (Taniaphos)
MeOH/Et_3N
$[RuI_2(p\text{-cymene})]_2$
90% e.e.

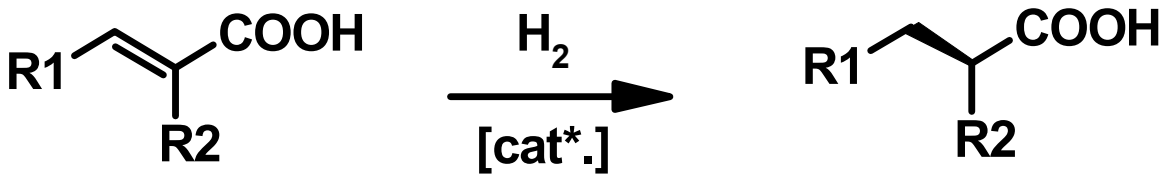


T001-1 (Taniaphos)
MeOH/Et_3N
$[Ru(cod)(TFA)_2]$
85% e.e.

- Higher e.e.'s with the 'best' ligand from 1st plate (just different parameters!)
- Big advantage to screen ligands with multiple precursors of same metal (Ru)

Optimized to 3000:1 S/C with e.e.'s of 93%

Case 2: Hydrogenation of Acrylic Acid



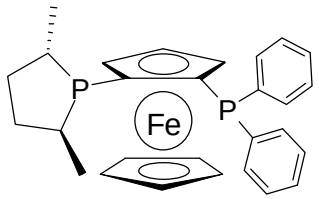
Targets:

- >95% ee
- 3 kg product delivery ASAP

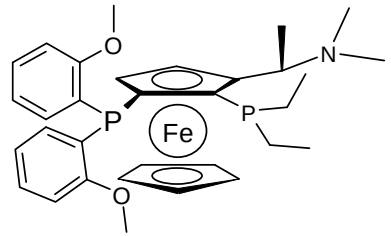
1st HTS plate:

-Highly diverse design of 32 ligands x 3 parameters (Rh, Ru precursors)

-Hits of 90% ee with Rh/P053-2 and Rh/F056-1:



kephos

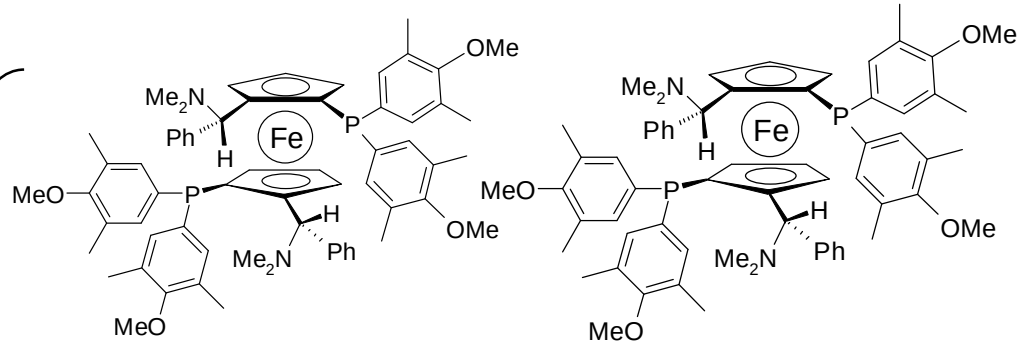


fengphos

Design and Results of 2nd HTS Plate (Built Upon Results of the 1st HTS Plate)

- Precursors: [Rh(nbd)2]BF4, [(Rh(cod)Cl]2, [Ir(cod)Cl]2, [Ru(p-cymene)I2]2
- Ligands: 27 ligands (incl. 16 from Kephos and Fengphos classes)
- 3 solvents: MeOH, DCE, Toluene

Best results



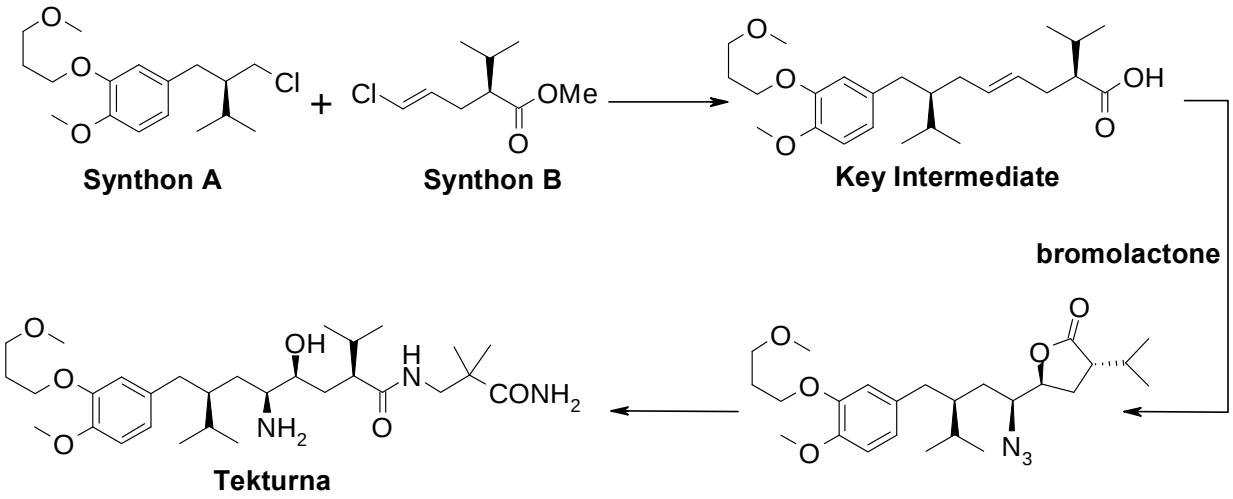
M004-1 (Mandyphos)	M004-1 (Mandyphos)
MeOH	MeOH/DCE
$[RuI_2(p\text{-cymene})]_2$	$[Ir(COD)Cl]_2$
>98% e.e. (R)	87% e.e. (S)

- Screening deeper into Fengphos and Kephos was unsuccessful
- BUT...Serendipity provided 2 hits (same ligand, different metals, different enantiomers)

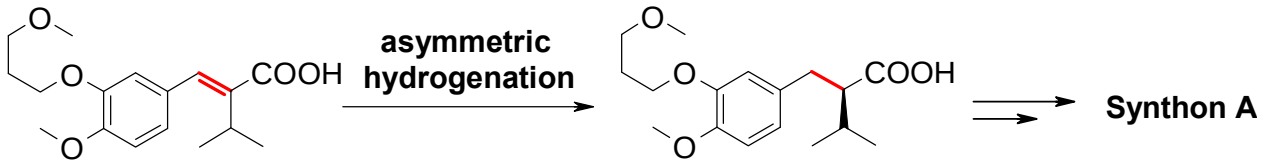
Ru system optimized to 1000:1 S/C and scaled to 3 kg (5 wks!)

Tekturna: It all started with screening

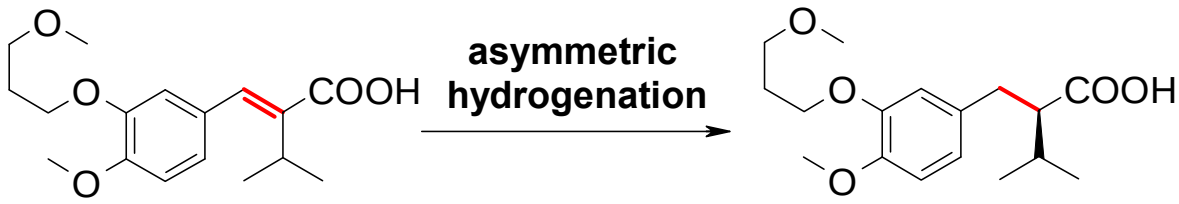
Route design based on chiral synthons and known chemistry



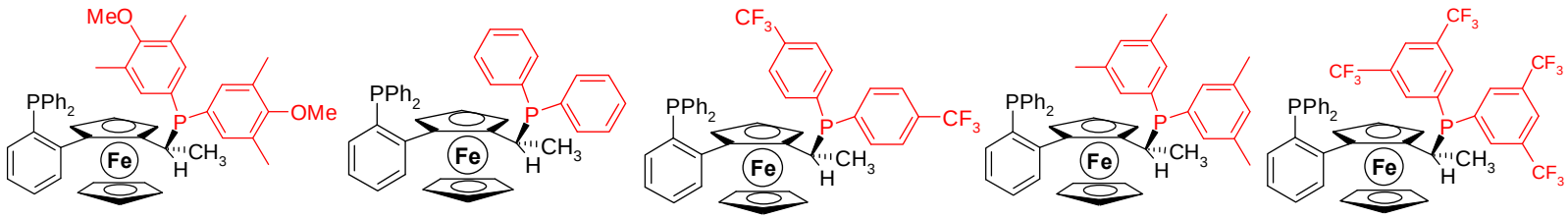
'The Crux' is the development of an asymmetric hydrogenation



Solvias Catalysis Solutions: From Screening to Implementation



- Wide variety of commercial ligands screened
- Interesting push-pull ee trend shown in Walphos series w/ $[Rh(NBD)_2]BF_4$ precursor:



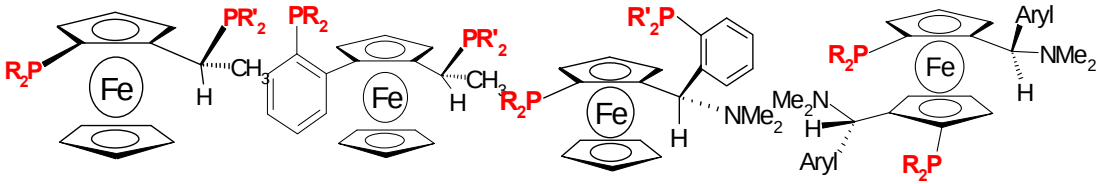
79% ee **84% ee** **89% ee** **90% ee** **95% ee**

- Screening + ability to systematically probe electronic/steric differences is powerful combination

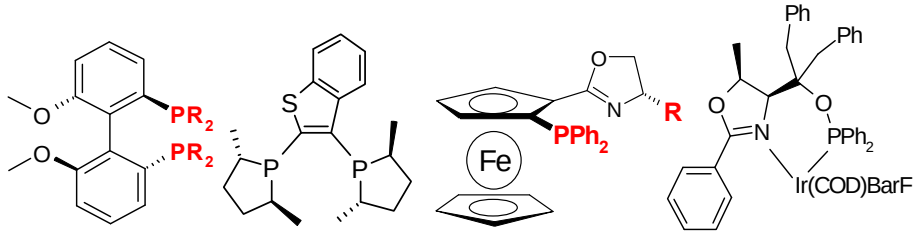
- The advantage of a large, easily modifiable ligand library.

Industrial Chiral Ligands:
Kg Scale Quantities for Your Process

Solvias Chiral Ligands

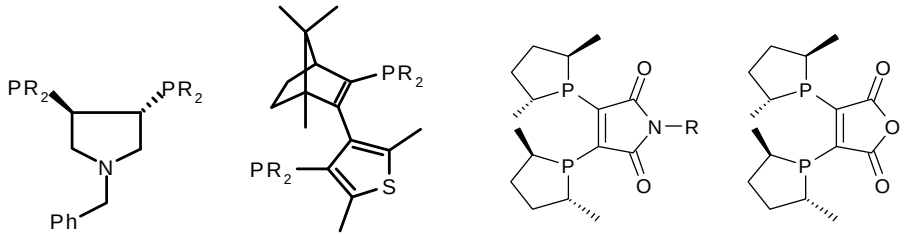


Josiphos | Walphos | Taniaphos (Umicore) | Mandyphos (Umicore)



MeO-Biphep | Butiphane | Naud-Cat. | Ubaphox

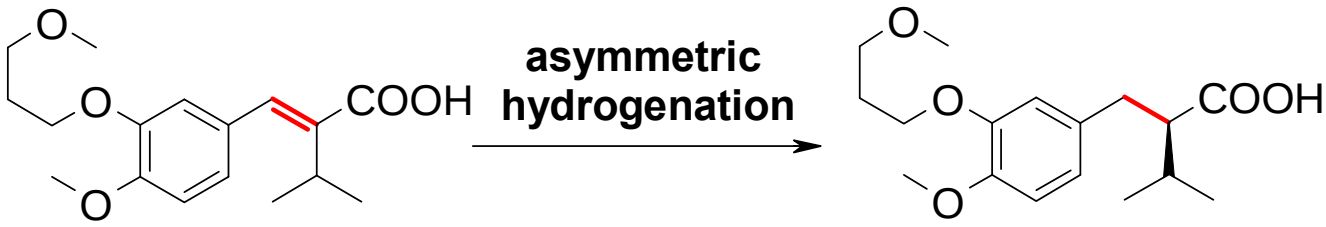
NEW from Evonik...



catASium D | catASium T | catASium MN | catASium M

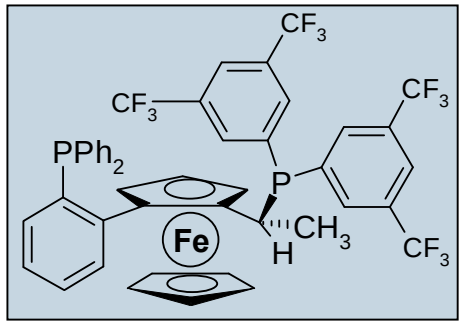
Solvias has acquired an exclusive license from Evonik Degussa Gmbh to manufacture, market, and use the **catASium and cataCXium** *ligand product lines.*

Synthon A key step for Tekturna process



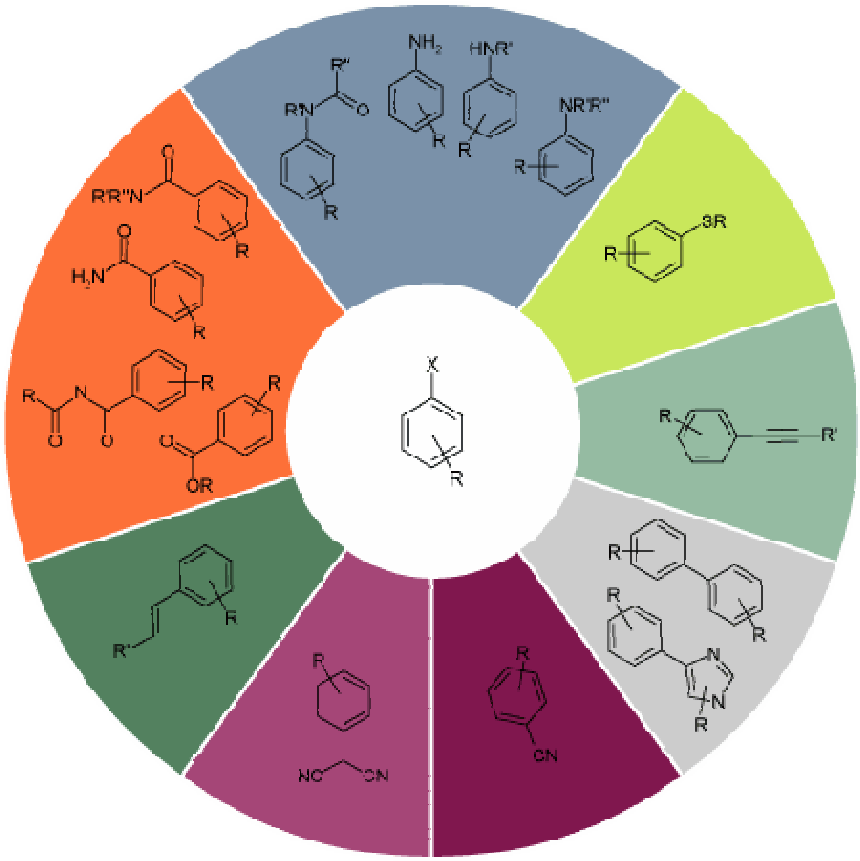
Conditions:

- Walphos ligand
- $[Rh(NBD)_2]BF_4$
- 100 bar H_2
- 80 °C
- 15 h
- **5000:1 S/C**
- **95% e.e.**



- Screening lead optimized for catalyst loading and manufacturing robustness
- Technical transfer of the best process to a 3rd party for manufacturing
- Process is performed at ton scale (with Solvias Walphos ligand)

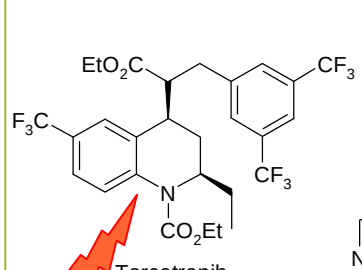
CX Coupling:
Widespread Industrial Prevalence



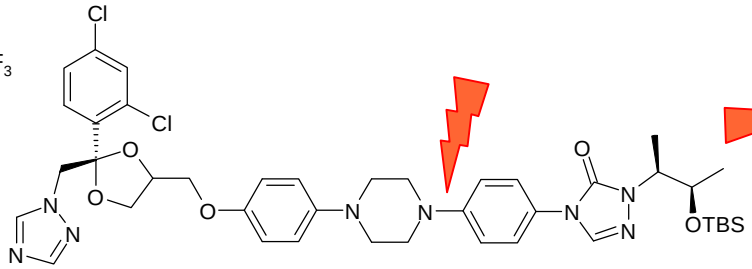
- Widespread industrial prevalance
- Tend to be developed with in-house expertise with standard reaction equipment
- Applying HTS screening alleviates 'lead bottleneck'

Focus on Industrial CN Coupling

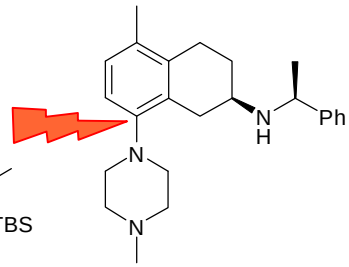
Misc. Published Examples



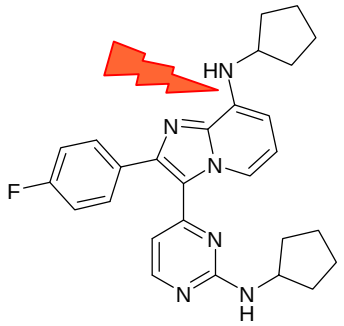
Torcetrapib
OPRD **2006**, *10*, 472



Tet. Lett. **1998**, *39*, 6845



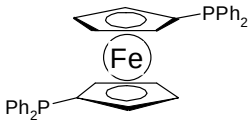
Acc. Chem. Res. **2007**, *40*, 1377



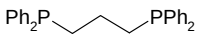
Organic Letters, **2003**, *5*, 1369

24 Ligand x 4 Parameter Design (CN Coupling)

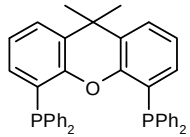
Diphosphines



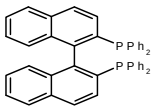
Dppf
Generic



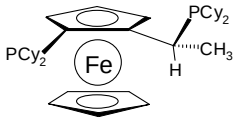
Dppp
Generic



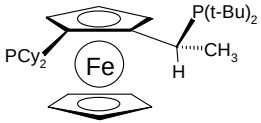
Xantphos
Generic



Binap
Generic

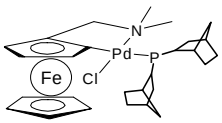


Josiphos
Solvias

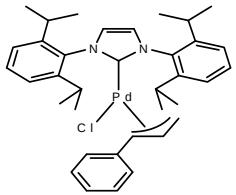


Josiphos
Solvias

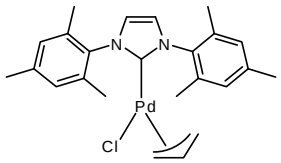
Complexes



CC02
Solvias

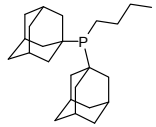


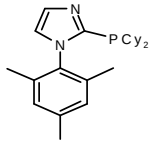
CX31
Umicore

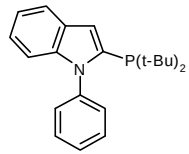


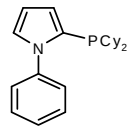
CX22
Umicore

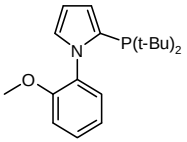
Monodentate





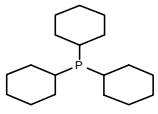




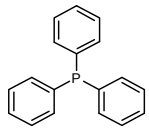


cataCXium® A
Solvias

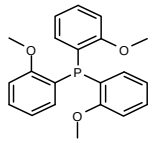
cataCXium® P series (Solvias)



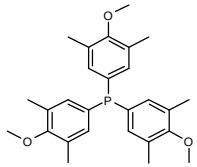
PCy3
Generic



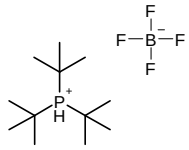
PPh3
Generic



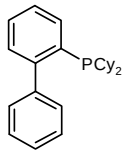
$P(o\text{-anisyl})_3$
Generic



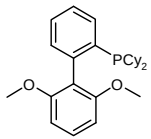
$P(MOD)_3$
Generic



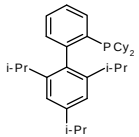
$P(t\text{-Bu})_3$
Generic



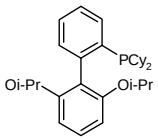
Johnphos
Shasun



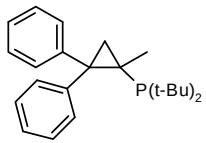
Sphos
Shasun



Xphos
Shasun

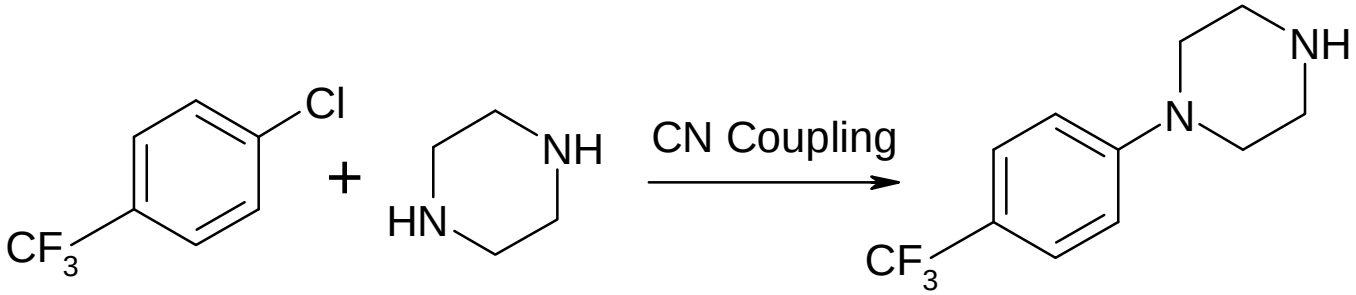


Ruphos
Shasun



c-bridp
Takasago

What is the Best Ligand System for CN Coupling?

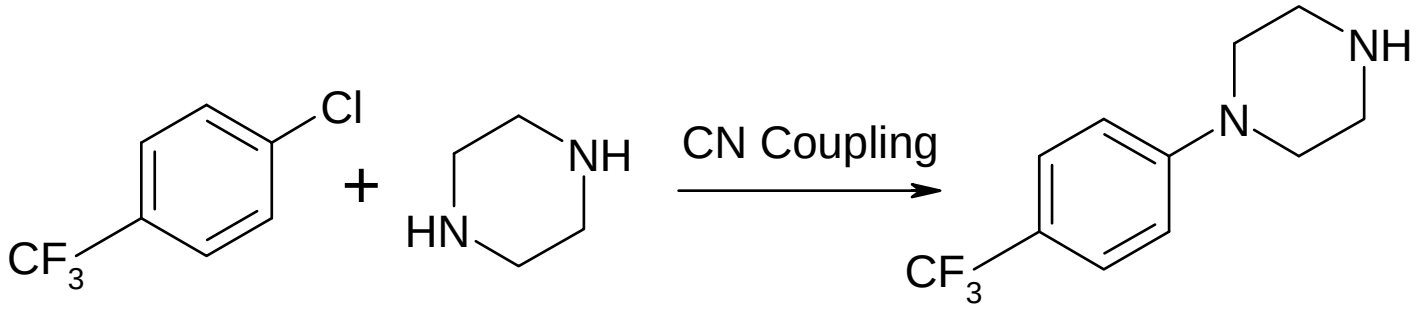


- Buchwald system with X-Phos scaled to 100g at Saltigo (X-Phos, $Pd_2(dba)_3$, NaOtBu, Toluene, MeoH, 78 ^oC).*

Can HTS provide alternative answers to this system?

*Presented by Dr. Buchwald at Dr. Pfaltz' 60th birthday symposium in 2008.

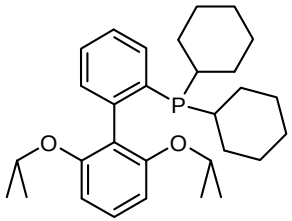
HTS Screening of Buchwald System



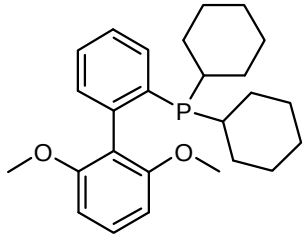
- Solvias performed standard 24 ligand x 4 design on transformation
- Judged conversion vs internal standard (because of sm volatility)
- Examined % conversion and by-product formation (incl. double addition)
- Parameters:
  - Pd(OAc)2, Toluene, NaOtBu
  - Pd2(dba)3, DME, K3PO4
  - Pd(OAc)2, Toluene, K3PO4
  - Pd2(dba)3, DME, NaOtBu
- Conditions: 1 eq. ArCl, 1.5 eq. Piperazine, 2 eq. Base, 0.25 eq. Trimethoxybenzene (internal standard), 80 C, 100:1 S/C, 16 hours

Screening results

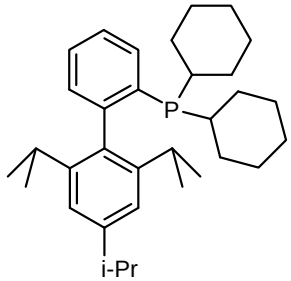
Buchwald hits*



Pd2(dba)3, DME, K3PO4 (74%)
Pd(OAc)2, Tol, NaOtBu (66%)
Pd2(dba)3, DME, NaOtBu (57%)



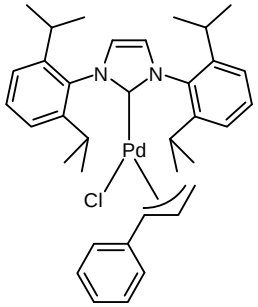
Pd2(dba)3, DME, K3PO4 (67%)
Pd(OAc)2, Tol, K3PO4 (56%)



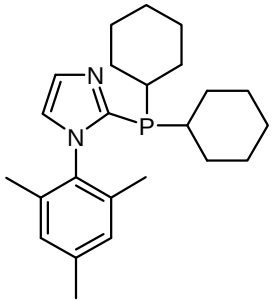
Pd2(dba)3, DME, K3PO4 (69%)

- **<0.5% double addition observed for these hits!**
- **Highest conversion for generic ligand was 47% (system: t(Bu)3P)**

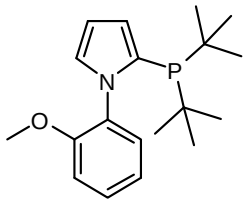
Other hits*



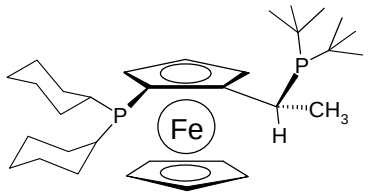
DME, K3PO4 (63%)



Pd(OAc)2, Tol, NaOtBu (72%)
Pd2(dba)3, DME, K3PO4 (61%)

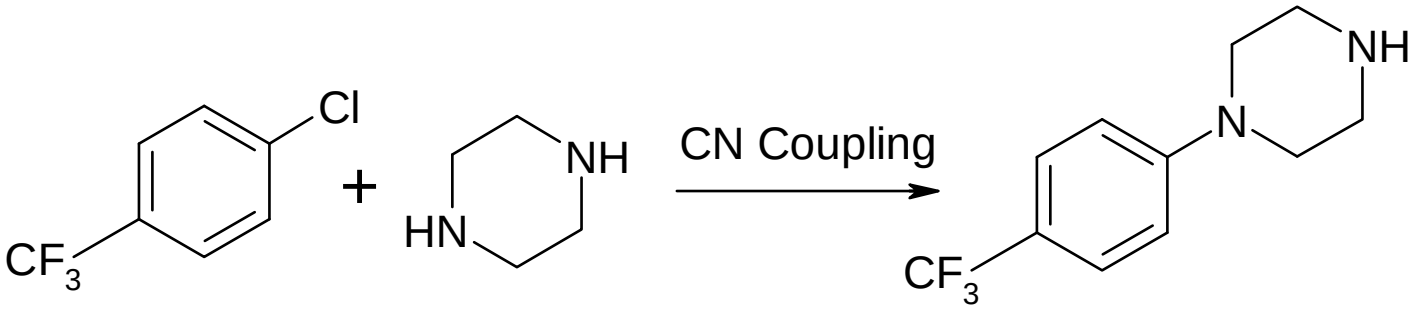


Pd2(dba)3, DME, K3PO4 (70%)



Pd(OAc)2, Tol, NaOtBu (57%)

HTS Buchwald substrate conclusion



Four alternative viable ligand systems were found!

-Allows for the choice of the *best* system for development (chemistry and cost)

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