



Johnson Matthey
Catalysis and Chiral Technologies



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Small-Scale Optimization Studies of Homogeneous Hydrogenation

Antonio Zanotti-Gerosa





Johnson Matthey

1817

Percival Norton Johnson establishes business as gold assayer in London

1964

Commercializes catalysts for fine chemical applications

1974

World's first catalysts to control vehicle pollution are produced at Royston, UK

1983

Pharmaceutical portfolio initiated with platinum based anticancer therapies





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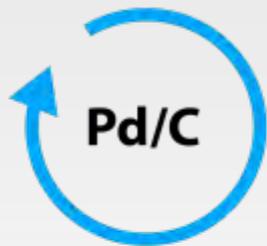
PHARMACEUTICAL • FINE CHEMICAL • AGROCHEMICAL





STATE OF THE ARTS FACILITIES THAT MAINTAIN EXACTING STANDARDS





HETEROGENEOUS
CATALYSTS



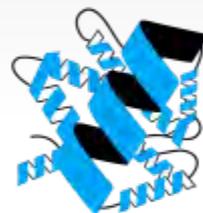
HOMOGENEOUS
CATALYSTS



LIGANDS



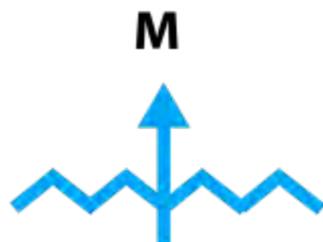
CHIRAL CATALYSTS



BIOCATALYSTS



CHIRAL ALCOHOLS



SCAVENGING
TECHNOLOGIES



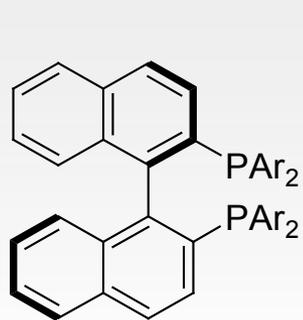
REFINING



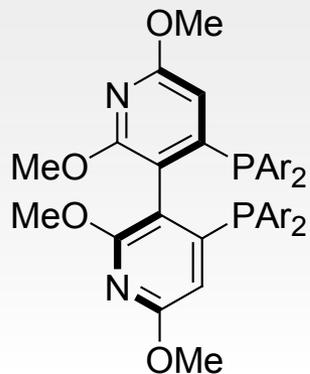
CATALYTIC SERVICES



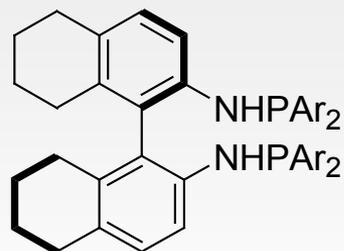
Core Ligand Classes of Chiral Technologies



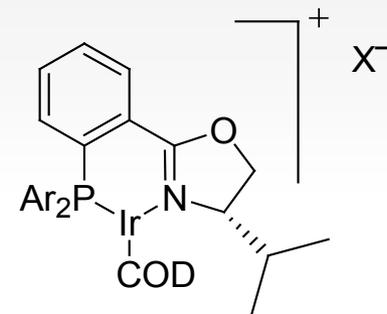
(R)-Binap and
(R)-TolBinap



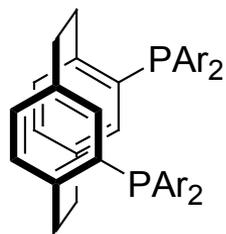
(R)-P-Phos



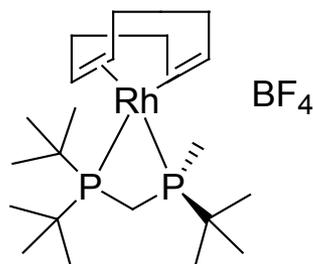
(R)-H₈-BINAM-P



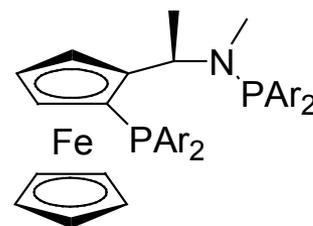
[PHOX Ir cod]X



(S)-Phanephos

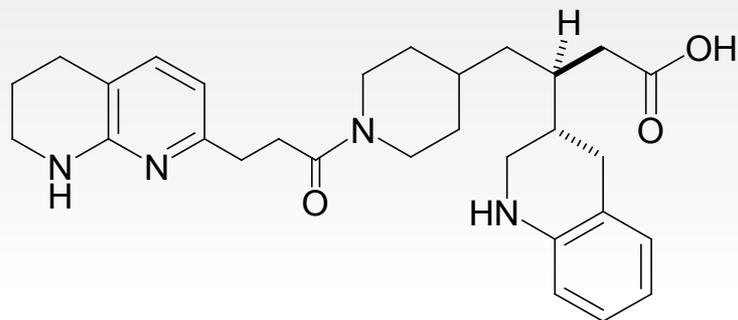


(R)-[Rh cod TCFP]BF₄

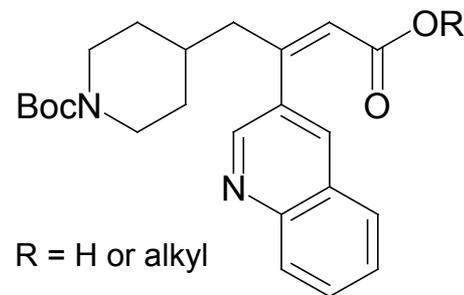
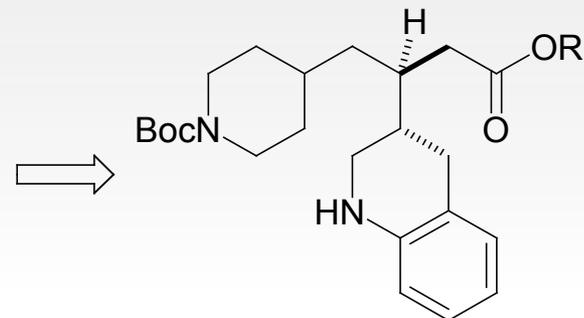


(R)-MeBoPhoz

Asymmetric Route to JNJ-26076713



Potent, selective $\alpha_v\beta_3/\alpha_v\beta_5$ Integrin antagonist – cell adhesion inhibitor - age related macular degeneration



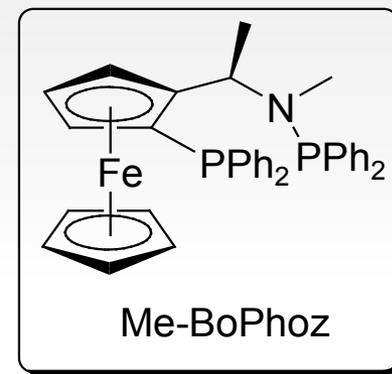
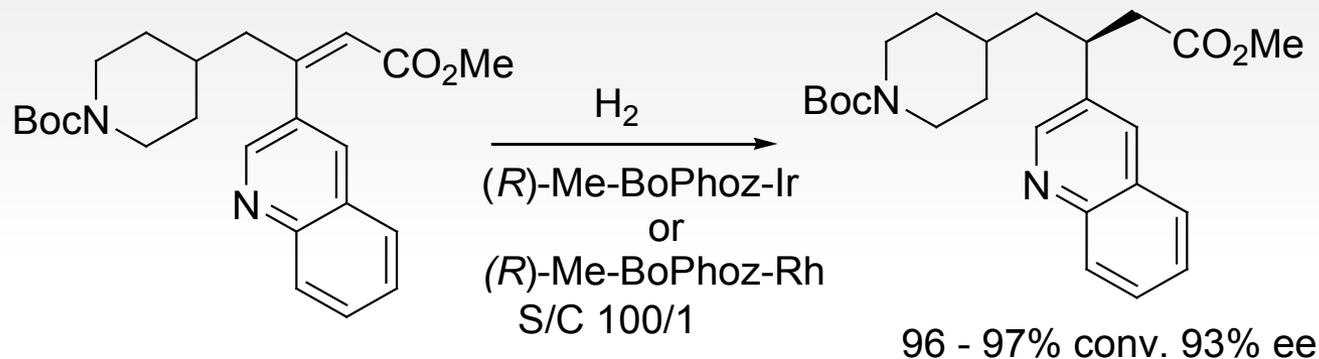
MedChem route required chromatographic separations of four diastereoisomers

Two parallel routes from the acid and the ester were evaluated at JM CCT

Johnson & Johnson



Ester Hydrogenation Route



A broad screen identified a novel catalyst

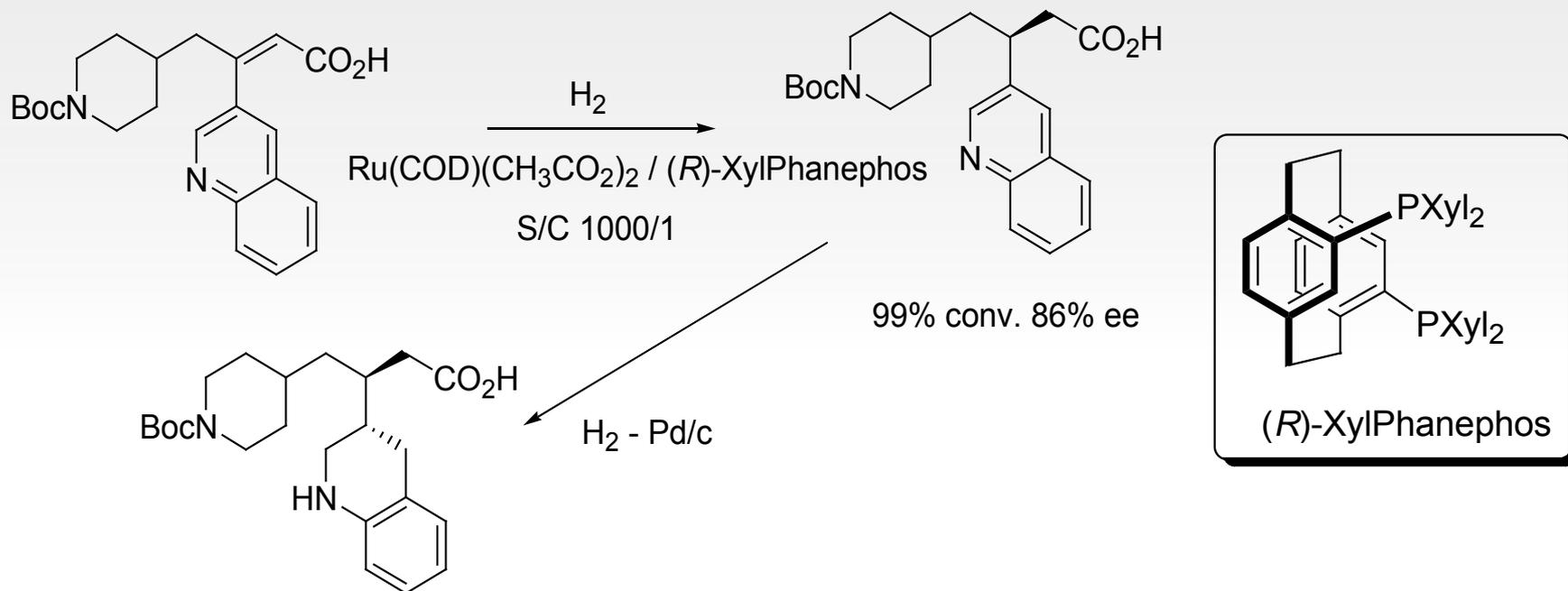
Addition of Iodine can modify the iridium catalyst to reduce the quinoline ring

Kinney, Telhea, Zanotti-Gerosa, Grasa *et al. Tetr. Asymmetry* **2008**, 19, 938

Johnson & Johnson



Acid Hydrogenation Route



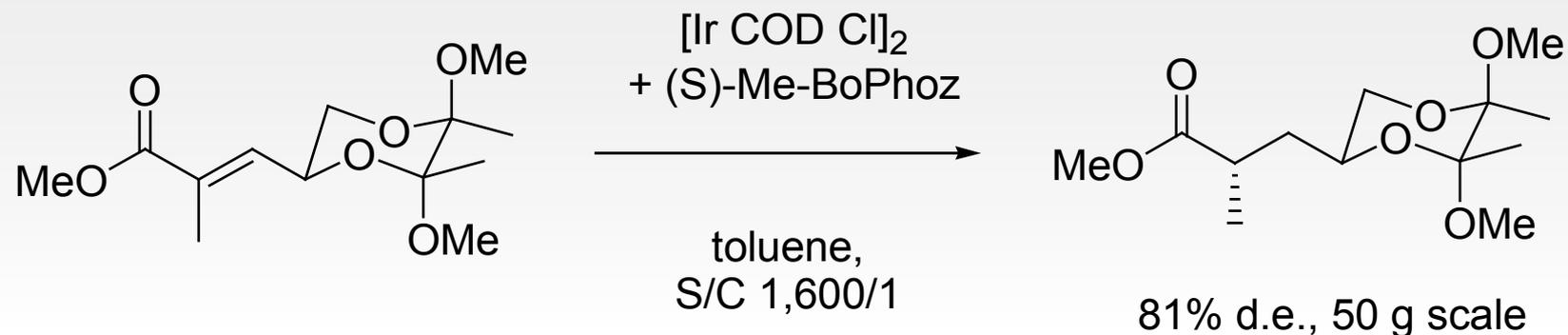
Acid was more reactive with lower ee, which was upgraded to 99% on work-up

Kinney, Telhea, Zanotti-Gerosa, Grasa *et al.* *J.Org.Chem.* **2008**, 73, 2302; *Tetr. Lett.* **2008**, 49, 5328.

Johnson & Johnson

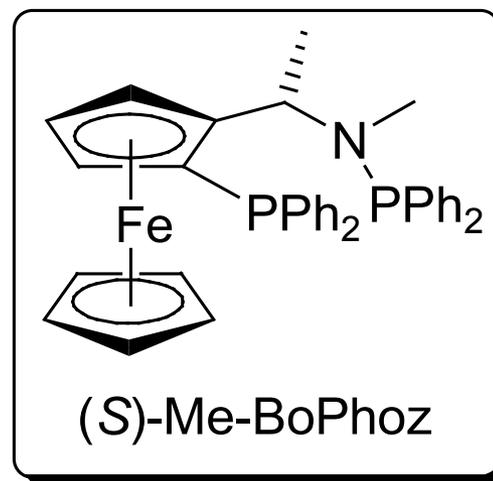


Diastereoselective Ester Hydrogenation

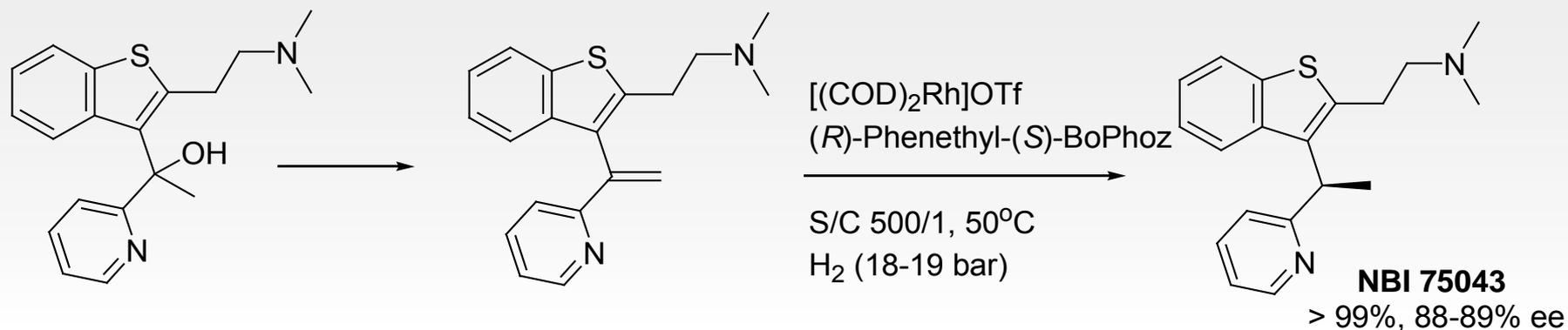


Starting material for natural product
synthesis in S.V. Ley's group

Newton, Ley, Grainger, Casas-Arcé
et al. Adv. Synth. Catal. **2012**, 1805



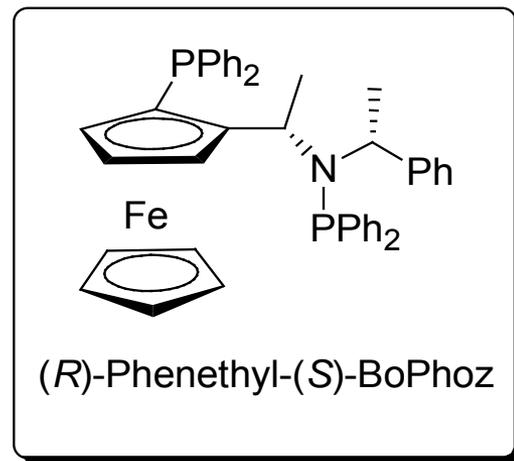
Unconventional Alkene Hydrogenation



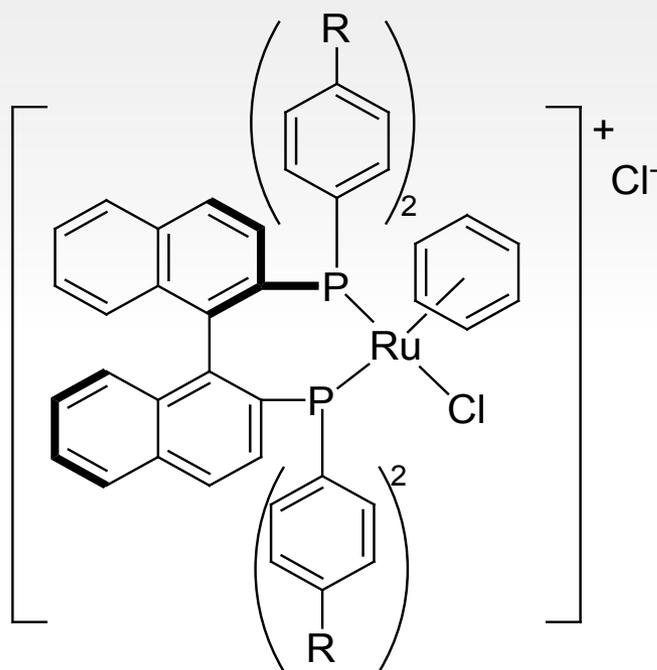
The ee increased from 12% (Me-BoPhoz) to 90% (PhEt-BoPhoz) by modification of N-substituent

Gross, Zook, Reddy *et al.* *OPRD* **2008**, 12, 929

Gross, Zook, Zanotti-Gerosa *et al.* *Tetr. Lett.* **2012**, 53, 1025



Binap Asymmetric Hydrogenation Catalysts



$[(R)\text{-Binap Ru (benzene)Cl}] \text{Cl}$

R = H: Binap

R = CH₃ Tol-Binap

Binap, Tol-Binap and Xyl-Binap ligands are off-patent

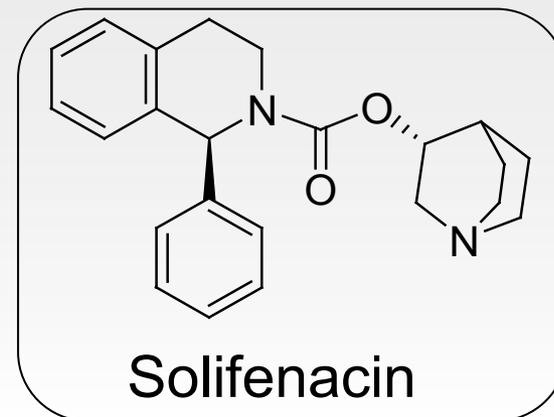
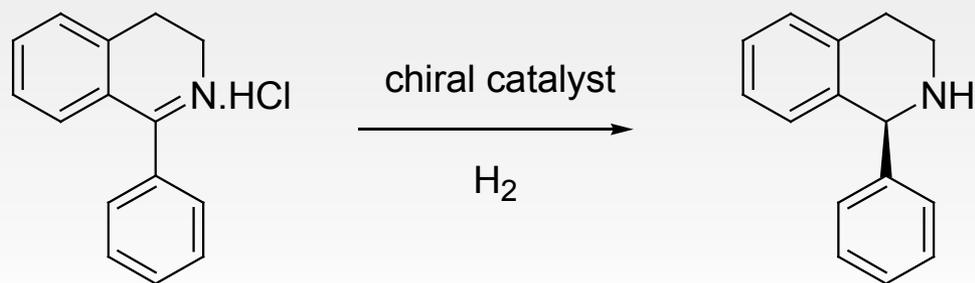
Binap-Ruthenium catalysts:
C=O, C=N hydrogenation (ketoesters, reductive amination, JST technology)

Binap-Iridium catalysts:
C=N hydrogenation

Binap-Rhodium catalysts:
hydrogenation, allylic isomerisation, 1,4-additions, hydroacylation.....



New Route to Solifenacin



In 2008, literature precedents suggested two main areas:

Transfer hydrogenation

Iridium-catalysed hydrogenation

Not yet published in 2008: *Angew.Chem.Int.Ed.* **2011**, *50*, 10679

$[\{\text{Ir}(\text{H})\text{-}[(\text{S},\text{S})\text{-}(\text{f})\text{-}\text{Binaphane}]\}_2(\mu\text{-I})_3]^+\text{I}^-$, S/C 2,000/1, DCM, I₂, HI, RT, 24 h, 95% ee



Ružič, Pečavar, Prudič, Kralj, Scriban, Zanotti-Gerosa, *OPRD*
2012, *16*, 1293



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Iridium Catalysts, Additives, Solvents Screen

25 ligands tested in situ with $[\text{Ir COD Cl}]_2$ in MeOH and DCE:

Best results in DCE: P-Phos (84% ee), Tol-P-Phos (78% ee),

Binap (60% ee), Binaphane (95% ee but only 24% conv)

Binap + $[\text{Ir COD Cl}]_2$ tested in 9 solvents and two additives (I_2 and iodide)

Binap + $[\text{Ir COD Cl}]_2$ tested in THF solvent with 25 additives:

ee increased to 78% ee with AcOH

ee increased to 87% ee with H_3PO_4

Ružič, Pečavar, Prudič, Kralj, Scriban, Zanotti-Gerosa ,
OPRD **2012**, 16, 1293



Solvent and Acid Optimisation

DCM	81% ee Binap,	85% ee P-Phos
AcOH in DCM:	81% ee Binap,	87% ee P-Phos

toluene:	60% ee Binap,	
AcOH in toluene:	82% ee Binap,	88% ee P-Phos

IPA:	72% ee Binap,	
AcOH in IPA:	70% ee Binap,	
H ₃ PO ₄ in IPA:	90% ee Binap,	91% ee P-Phos

THF	66% ee Binap,	
H ₃ PO ₄ in THF	87% ee Binap,	95% ee P-Phos
H ₃ PO ₄ in THF + KI	82% ee Binap,	92% ee P-Phos

30 bar H₂, 50°C, 16 h, S/C 43/1 to 425/1

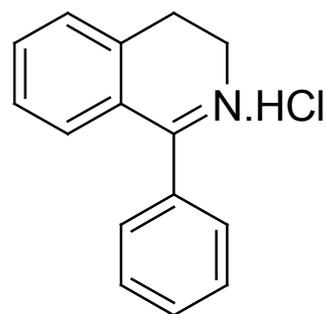


Final Reaction Conditions

Catalyst: (S)-P-Phos + [Ir COD Cl]₂ (*in situ*, >95% ee); Binap viable alternative (87% ee)

Solvent: THF / H₃PO₄ or IPA/ H₃PO₄

Loading: 2500/1 (1.5 g), S/C 1500/1 (15 g), 1000/1 (200 g)

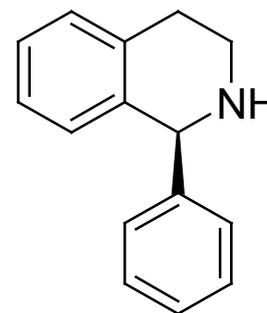


200 g

S/C 1000/1, (S)-P-Phos + [Ir COD Cl]₂

THF, 1.5 eq. of H₃PO₄ aq. 85%

60°C, 20 bar H₂, 48 h

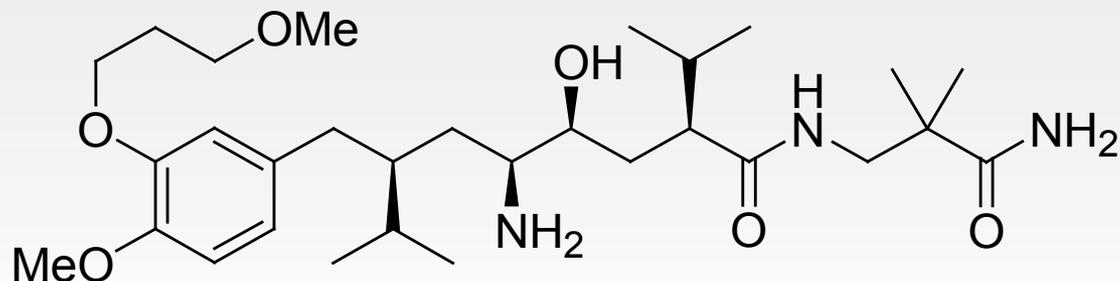


>97% conversion, 95-98% ee (S),
>99% purity, >98% ee after recrystallization
(95% yield)

Ružič, Pečavar, Prudič, Kralj, Scriban, Zanotti-Gerosa ,
OPRD **2012**, 16, 1293



New Synthesis of Aliskiren



Aliskiren is a direct renin inhibitor, marketed by Novartis for the treatment of hypertension

Chemessentia aimed at original and cost-effective synthesis of this API

Chemessentia devised route in collaboration with University of Siena (Italy)

Catalytic expertise was brought by Johnson Matthey, Catalysis and Chiral Technologies



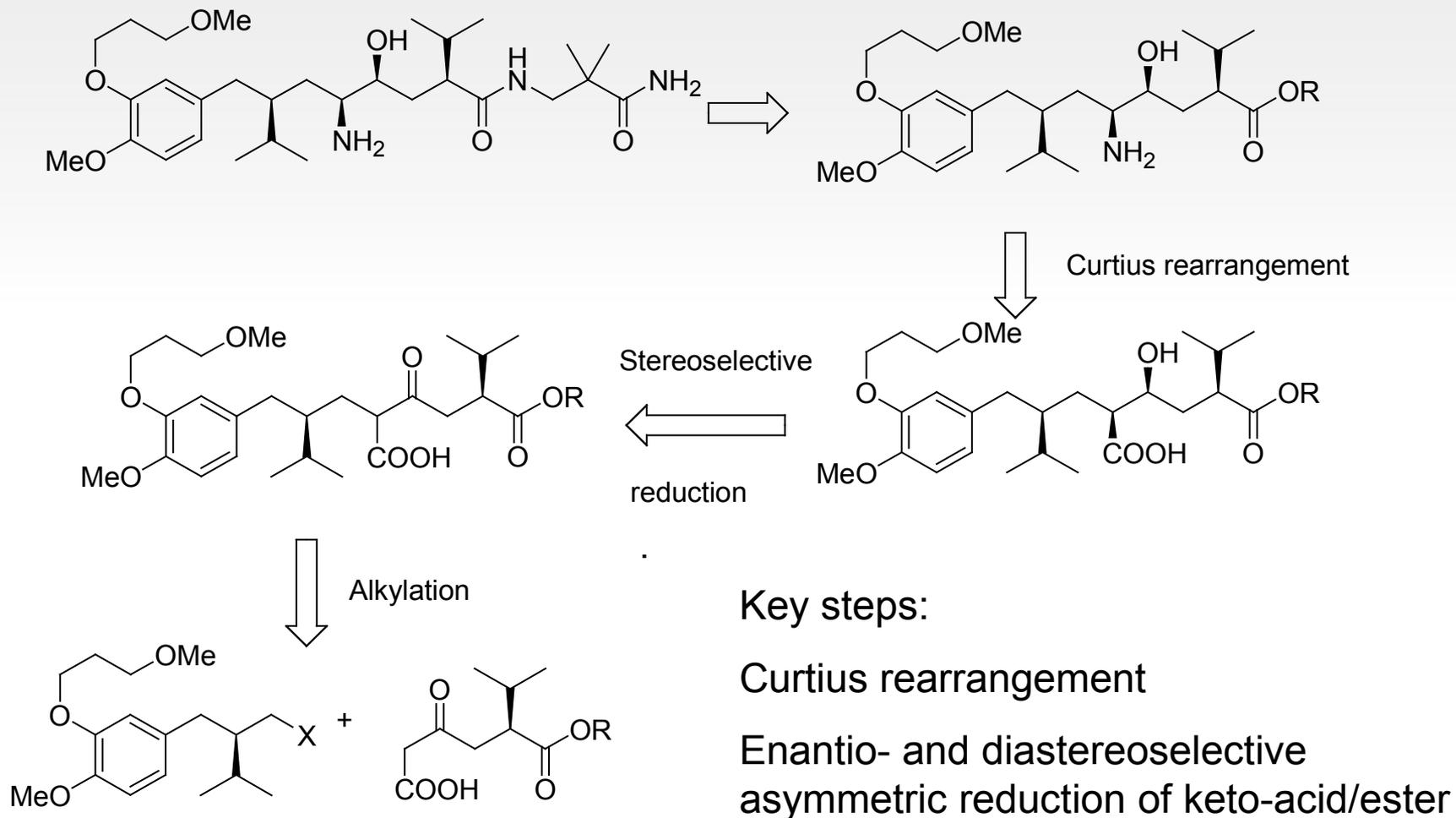
Arena, Barreca, Carcone, Cini, Marras, Nedden, Rasparini,
Roseblade, Russo, Taddei, Zanotti-Gerosa
Adv. Synth. Catal. **2013**, in press, DOI: 10.1002/adsc.201200934

Barreca, Carcone, Cini, Marras, Rasparini, Russo, Taddei
La Chimica e l'Industria, March **2013**, 129

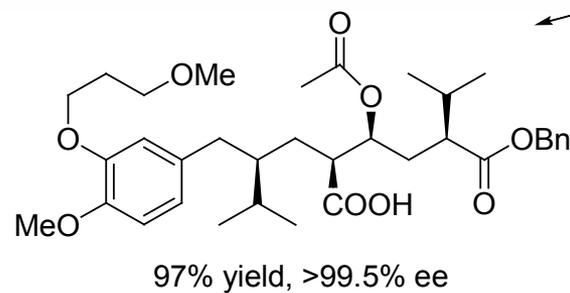
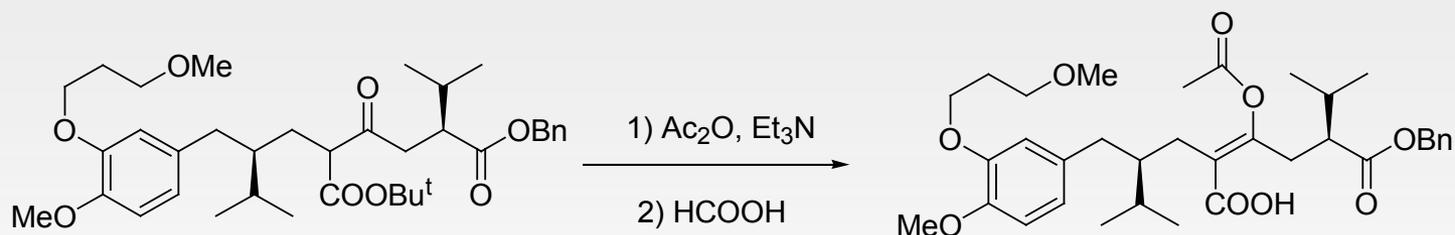


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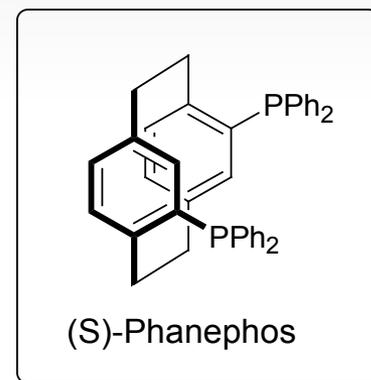
Aliskiren: Retrosynthesis



Enol Ester Asymmetric Hydrogenation



[(S)-Phanephos Rh COD]BF₄
S/C 2,000/1, 30 bar H₂, 30°C,
0.7 eq. Et₃N, MeOH



(S)-Phanephos

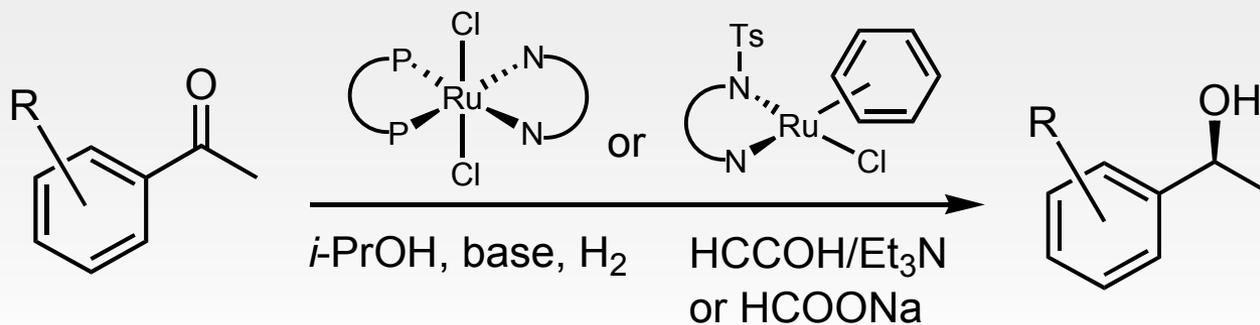
Heterogeneous and homogeneous, chiral and achiral catalysts were tested

Choice of protective group was key to success (acid preferable to ester)

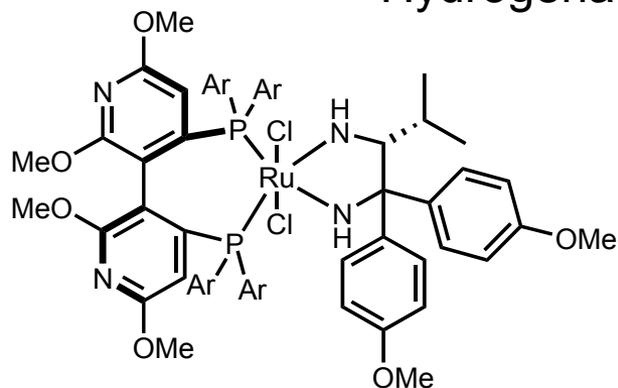
Enol-acetate hydrogenation preferred to ketoester hydrogenation with Ru-Binap

[(S)-Phanephos Rh COD]BF₄ provided high enantio- and diastereoselectivity

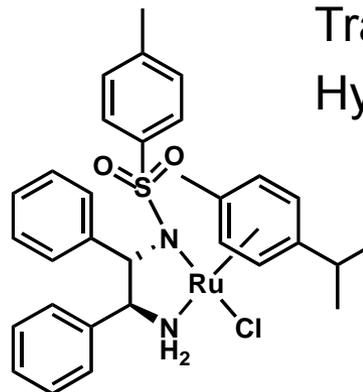
Noyori Ketone Reduction



Hydrogenation



Transfer Hydrogenation



Licensed to JM CCT from the Japanese Science and Technology Corp. (JST) in 2003



Hydrogenation vs Transfer Hydrogenation

Hydrogenation

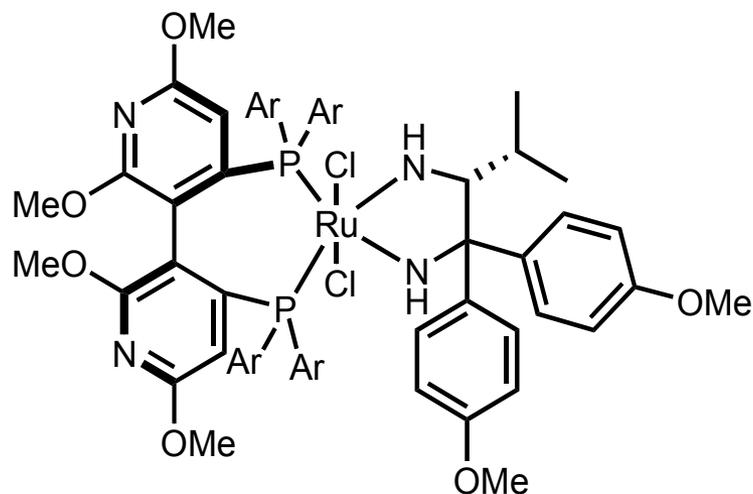
C=O reduction

Basic conditions (alcohol + t-BuOK)

Pressure equipment (1 to 100 bar)

TON 1,000 - > 10,000/1 upon optimisation

Catalyst BisphosphineRuCl₂Diamine



Transfer Hydrogenation

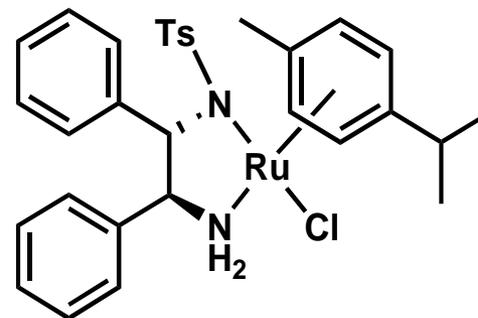
C=O and C=N reduction

Acidic to basic conditions (HCOOH/Et₃N or Na-formate)

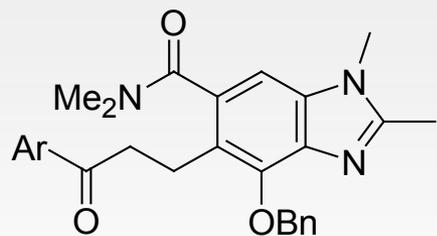
Larger variety of conditions can be tested

TON 100 - > 3,000/1 upon optimisation

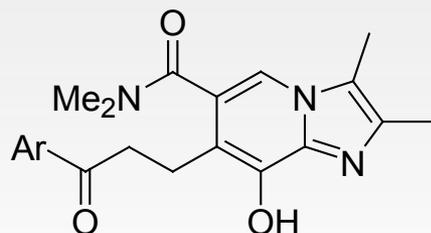
Catalyst RuCl Arene Sulfonated-Diamine



Hydrogenation of Heterocyclic Ketones

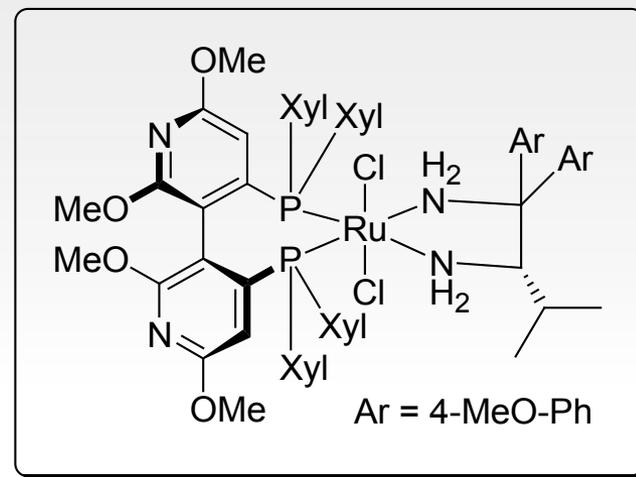


S/C 2,500/1, w/w 1,000/1,
> 95% ee



S/C 3000/1, >95% ee

[(S)-Xyl-P-Phos RuCl₂ (S)-DAIPEN]



Imidazo-pyridine-ketone: [Xyl-P-Phos RuCl₂ DAIPEN] superior to the Binap analogue: TON up to 3,000, >95% ee

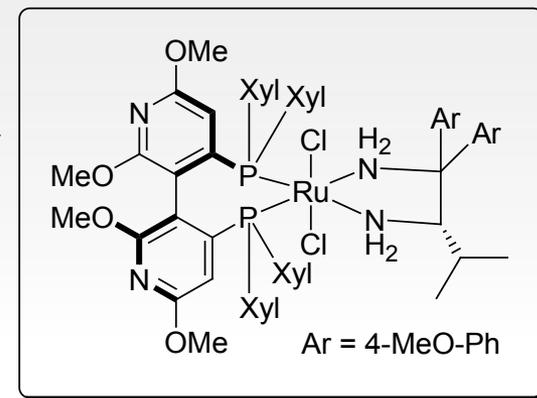
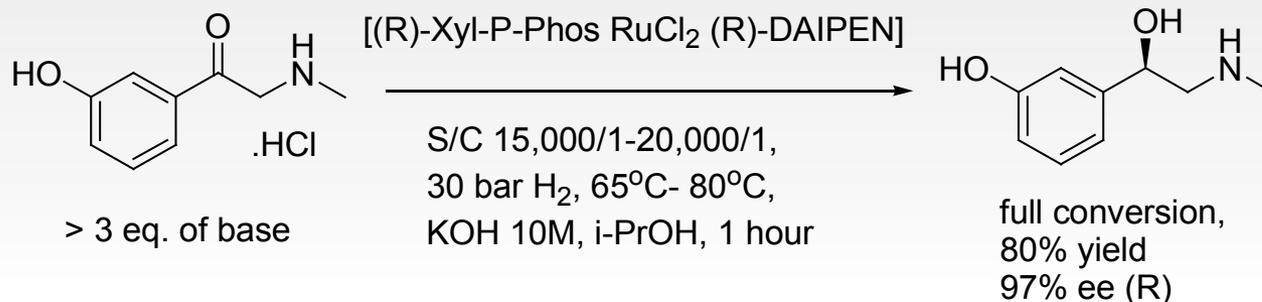
Benzoimidazole-ketone: [Xyl-P-Phos RuCl₂ DAIPEN] applied on Kg scale on the O-Bn substrate: TON 2,500, >90% ee



Palmer, Zanotti *et al.* *Tetr.: Asymm.* **2008**, 19, 1310; *Tetr. Asymm.* **2008**, 19, 2102
Palmer *et al.* *OPRD* **2008**, 12, 1170



New Route to (S)-Phenylephrine



Requirements: high enantioselectivity and productivity, avoiding protection/deprotection.

Competing catalytic processes: biocatalysis and rhodium-catalysed asymmetric hydrogenation

HCl salt of the unprotected substrate was successfully reduced using an excess base:
fast reaction to minimize side-products

Lonza

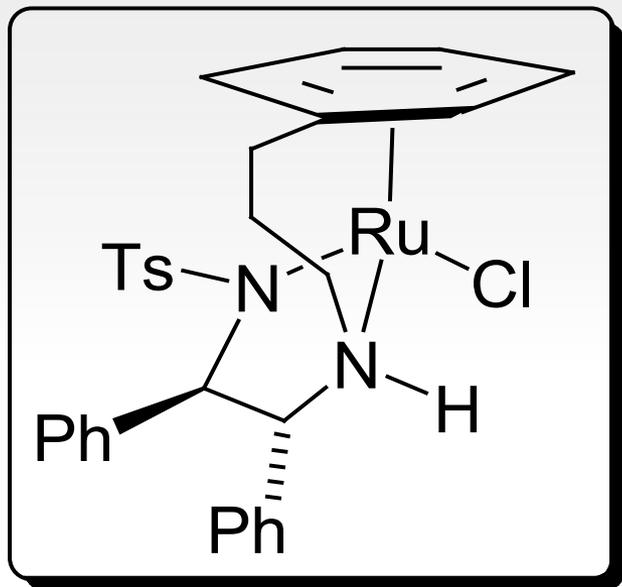
Acc.Chem.Res. **2007**, *40*, 1367

McGarrity, Zanotti-Gerosa *Tetrahedron: Asymmetry* **2010**, *21*, 2479



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Wills Tethered Catalyst



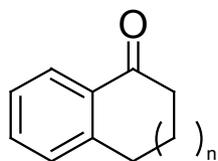
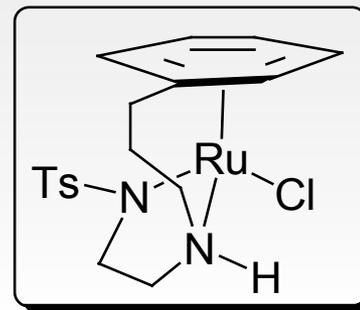
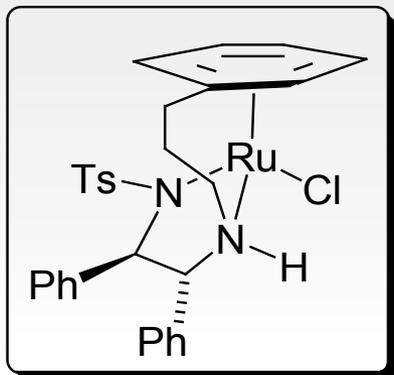
Tethered catalyst increases activity and robustness against polyfunctionalised substrates

It can be used in both transfer hydrogenation and hydrogenation

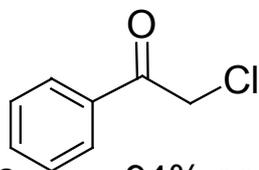
2006: mg sample sent by Prof Wills tested in customer project
2010-11: commercial production on Kg scale



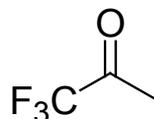
Phosphine-Free Asymmetric Hydrogenation



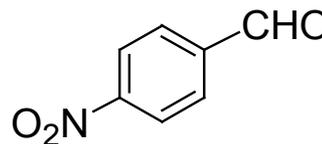
n=1 97% ee
n=0 99% ee



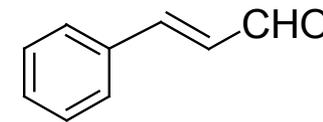
94% ee



94% ee
MeOH/H₂O



94%
MeOH/H₂O 90/10



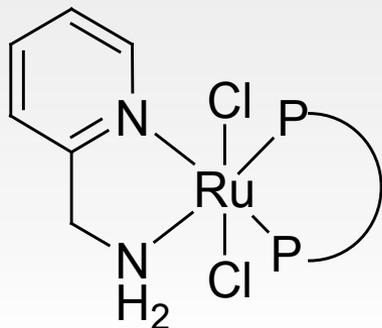
96% (3.5% sat alcohol)
MeOH

S/C 500/1, MeOH or MeH/H₂O, 0.5 M, 30 bar H₂, 60°C

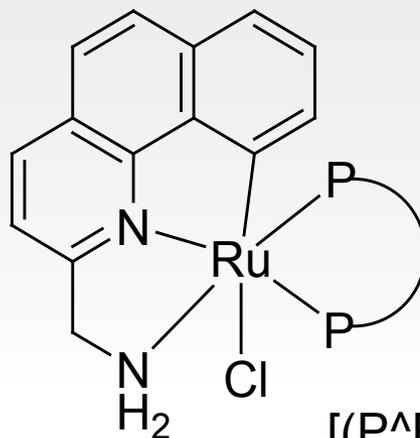
Wills, Jolley, Zanotti-Gerosa, Nedden, Seger *et al. Adv. Synth. Catal.* **2012**, 354, 2545



Baratta's Catalysts



$[(P^P) RuCl_2 (Ampy)]$



$[(P^P) RuCl (AMBQ)]$

$[(P^P) Ru Cl_2 Ampy]$ and $[(P^P) RuCl (AMBQ)]$ catalyse both transfer hydrogenation (Baratta) and hydrogenation (Noyori, alkyl ketones) with very high activity (TON > 10,000)

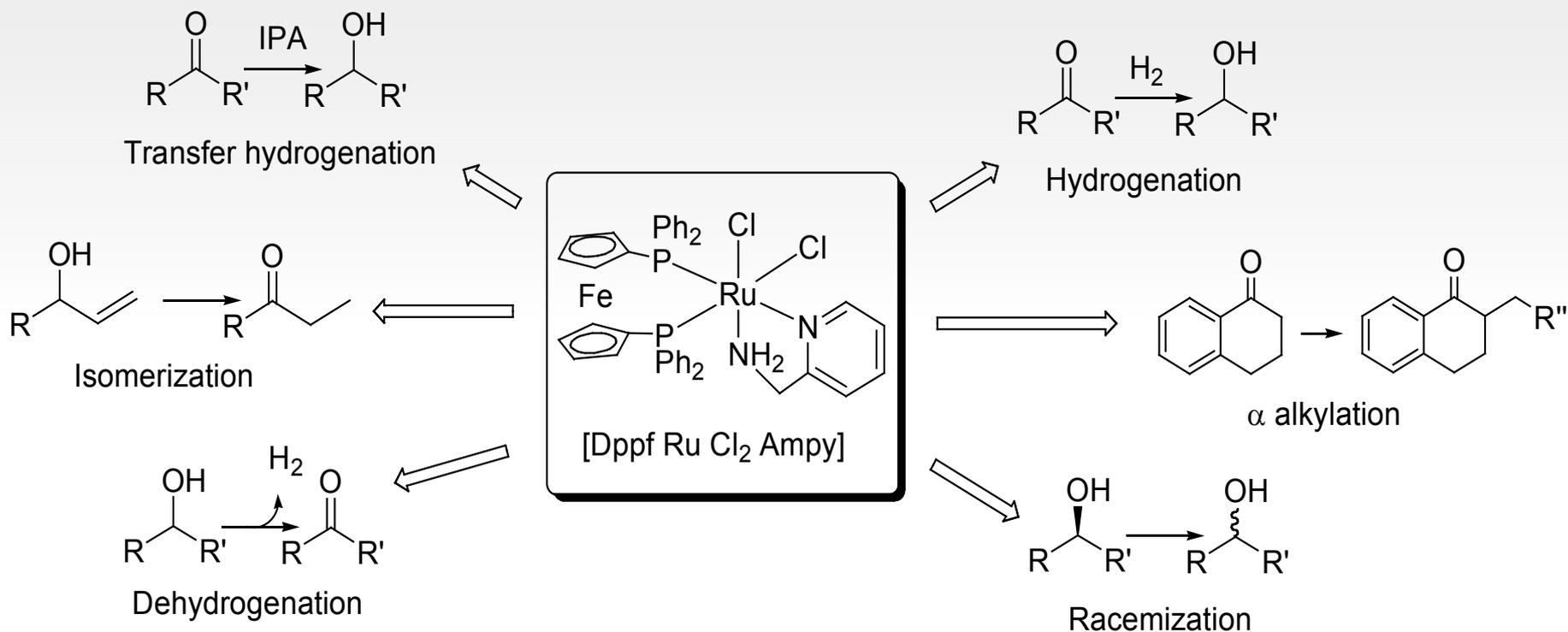
Under licence from the University of Udine (Italy)

Baratta *et al.* *Chem. Eur. J.* **2008**, *14*, 9148

Baratta *et al.* *Angew.Chem.Int.Ed.* **2007**, *46*, 7651



'Multitasking' Catalysts

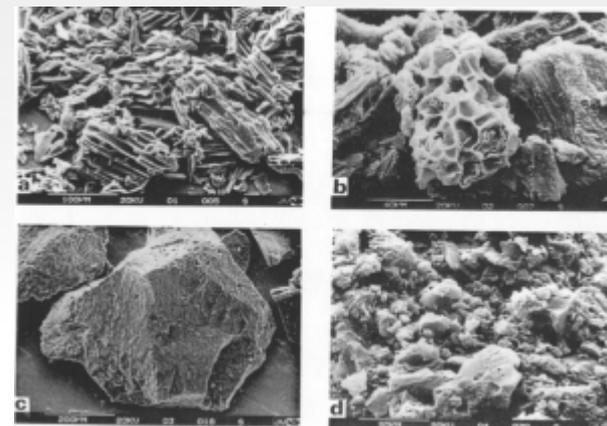
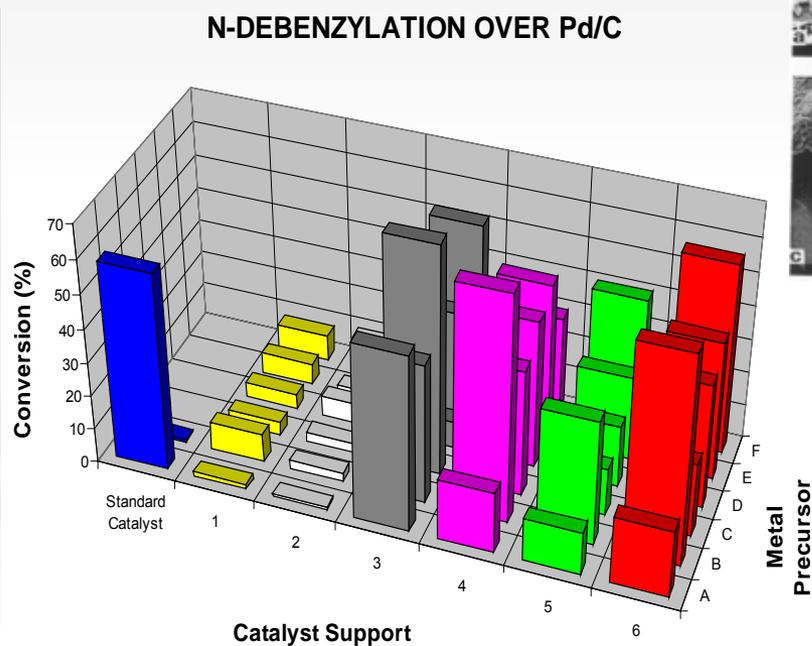
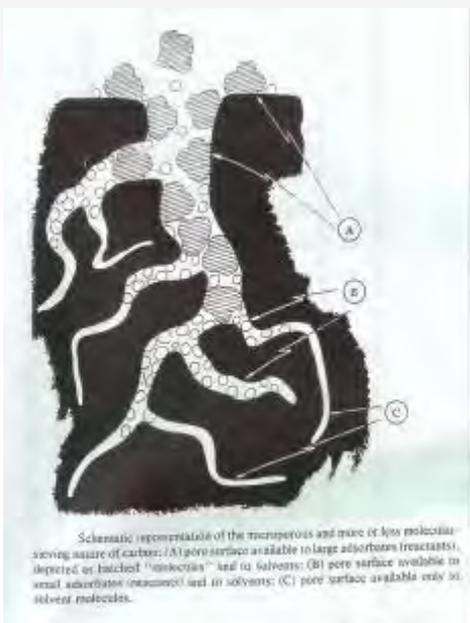


[Dppf RuCl₂ Ampy]: multitasking catalyst for carbonyl / alcohol interconversion reactions

Baratta *et al.* *Organometallics* **2012**, 31, 1133

Heterogeneous Catalysts

metal dispersion
metal location
particle size

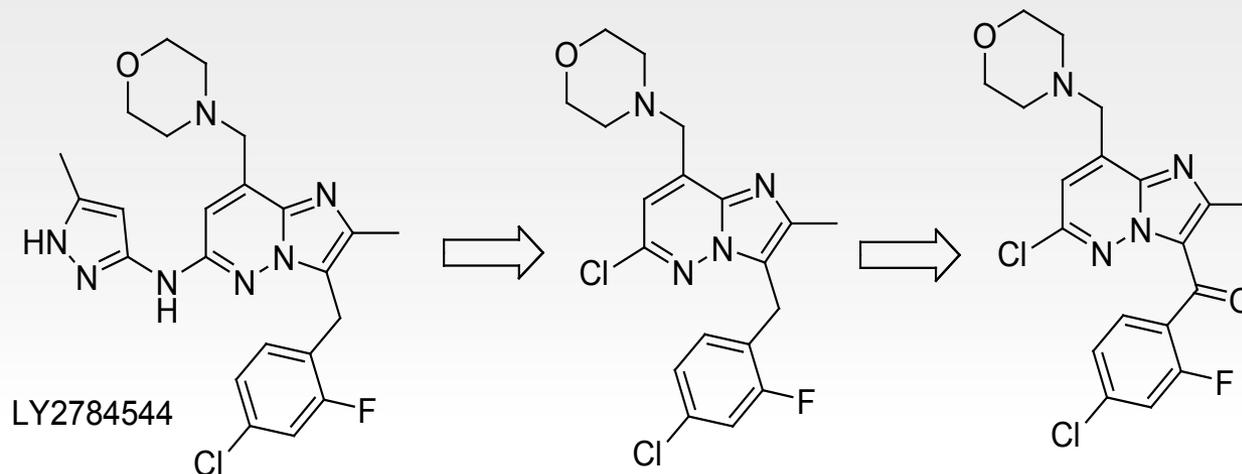


a = wood
b = peat
c = coconut
d = coal

egg shell / uniform



JM-Lilly Research Collaboration



The aryl(imidazo[1,2-b]pyridazinyl)methane intermediate to LY2784544, a JAK2 inhibitor, is obtained in a single step by treatment of ketone with 6 eq. of Et_3SiH and 12 eq. of CF_3COOH . Alternative processes have drawbacks (e.g. $\text{Cl}_3\text{SiH} / \text{Et}_3\text{N}$, H_3PO_2) or did not work (e.g. Wolff-Kishner).

Mitchell, Cole, Pollock, Coppert, Burkholder, Clayton *Org. Process. Res. Dev.* **2012**, *16*, 70;
Campbell, Cole, Martinelli, May, Mitchell, Pollok, Sullivan *Org. Process. Res. Dev.* **2013**, *17*, 273

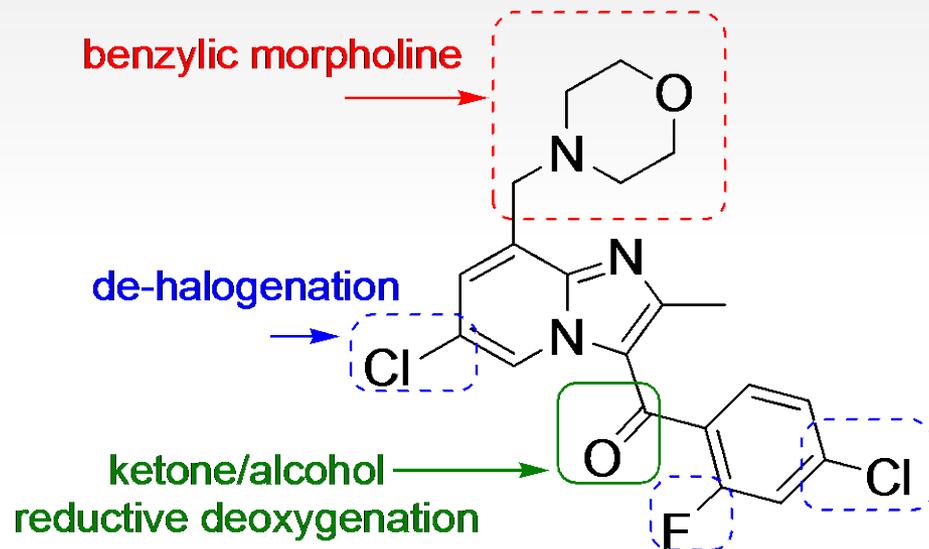


A Challenging Hydrogenation

One-pot ketone hydrogenation and alcohol hydrogenolysis would provide the most straightforward approach

but

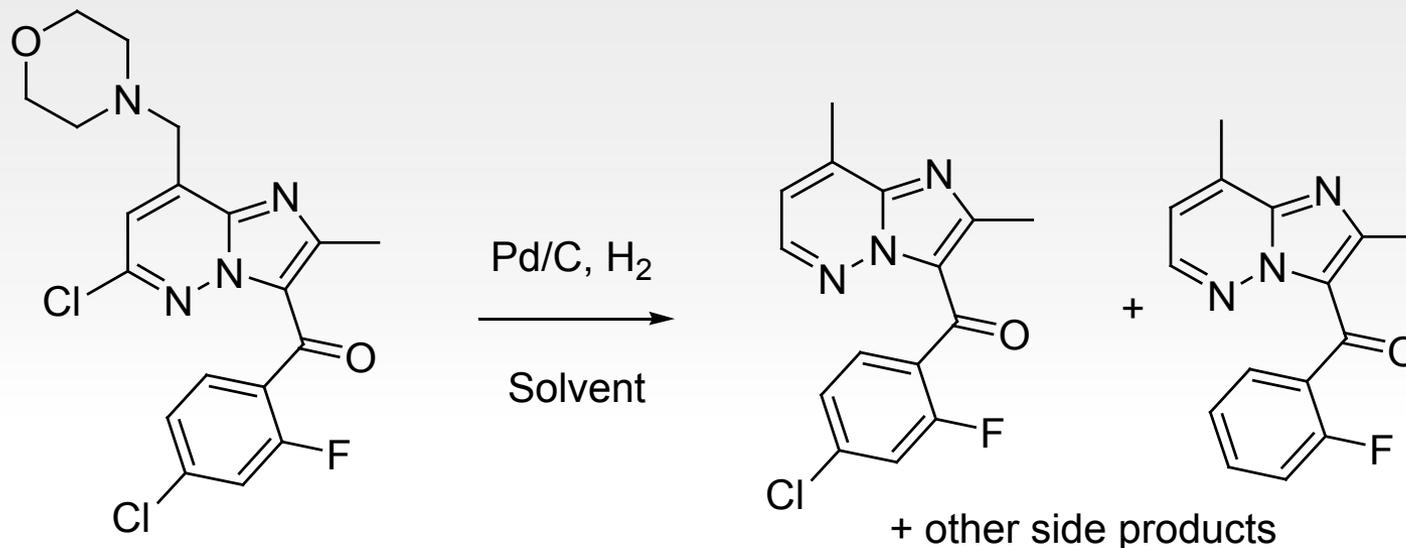
several side-reactions are possible due to the complexity of the molecule



Grainger, Zanotti-Gerosa, Cole, Mitchell, May, Pollock, Calvin *ChemCatChem* **2013**, *in press*
DOI: 10.1002/cctc.201200526



One-Step Hydrogenolysis



Pd/C and other heterogeneous catalysts were tested:

Solvents (THF, toluene, AcOH, water);

Pressure (6 to 30 bar H₂);

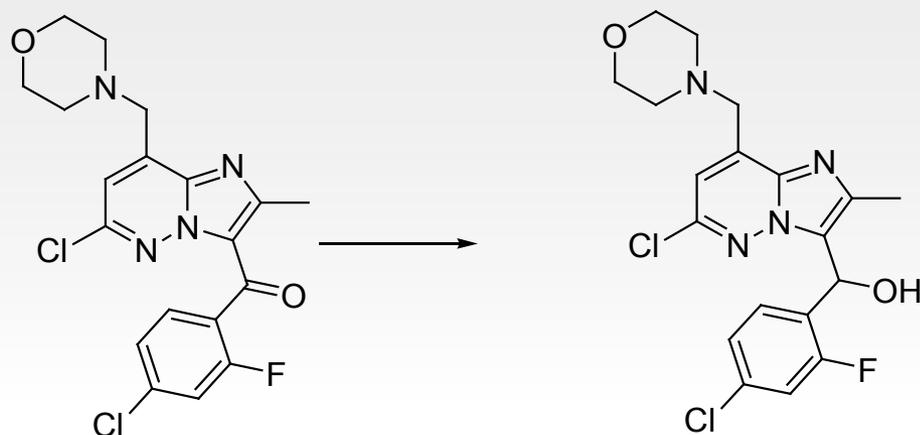
Temperatures (30 to 70°C);

Additives (HCl, NaCl, ZnCl₂, CuCl₂, CuSO₄).

Only side-products were formed, mainly from morpholine cleavage and dechlorination
Tentative structural assignment based on LC/MS analysis



Ketone Reduction to Alcohol Intermediate



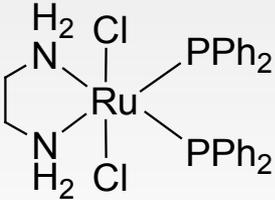
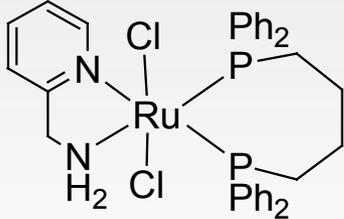
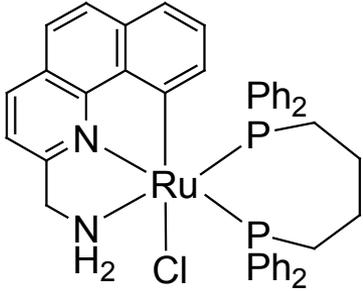
Heterogeneous catalysts: Ir/CaCO₃ (JM type30) gave clean alcohol in MeOH but only with incomplete conversion

Homogeneous catalysts for hydrogenation and transfer hydrogenation were tested in search for improved chemoselectivity:

Noyori-type hydrogenation and transfer hydrogenation (first-generation);
Baratta and Wills catalysts (second-generation)



Baratta Hydrogenation Catalysts

Catalyst	S/C	Conv.		
$[(\text{Ph}_3\text{P})_2 \text{RuCl}_2 \text{EN}]$	1,000/1	4%	$[(\text{Ph}_3\text{P})_2 \text{RuCl}_2 \text{EN}]$	$[\text{Dppb RuCl}_2 \text{AMPY}]$
$[\text{Dppb RuCl}_2 \text{AMPY}]$	1,000/1	71%		
$[\text{Dppb RuCl}_2 \text{AMBQ}]$	1,000/1	100%		
$[\text{Dppb RuCl}_2 \text{AMBQ}]$	2,000/1	99%		

Reaction conditions:

Baratta's AMPY and AMBQ catalysts: MeOH, 5% t-BuOK, 50-60°C, 27 bar H₂

first-generation Noyori catalysts: i-PrOH, 5% t-BuOK, 50°C, 27 bar H₂



Wills Transfer Hydrogenation Catalysts

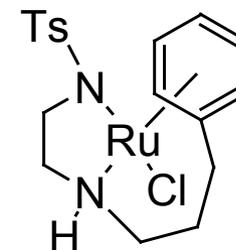
Catalyst	S/C	Formate	Conv.
[Ts-EN RuCl (p-cym)]	1,000/1	NH ₄ OOCH	60%
[Ts-EN-teth RuCl]	5,000/1	NH ₄ OOCH	100%
[Ts-EN-teth RuCl]	10,000/1	NH ₄ OOCH	99.5%
[Ts-EN-teth RuCl]	5,000/1	NaOOCH	41%

Reaction conditions : AcOEt/water 4/1, 80°C, 16 h

Achiral Wills catalyst provided much higher activity than first generation achiral Noyori catalyst



[Ts-EN RuCl (p-cym)]



[Ts-EN-teth RuCl]

Alcohol Hydrogenolysis with Copper Salts

Solvent (4/1)	Additive	Conv.	Product
THF/ HCl aq.	-	96%	-
THF/HCl aq.	10% CuSO ₄	43%	41%
AcOH/HCl aq.	10% CuSO ₄	>99%	75%
AcOH/HCl aq.	1% CuSO ₄	>99%	95%

Catalyst: 5% Pd/C 5R39

Other salts (FeCl₂, NiCl₂, CeCl₃, Zn(OAc)₂, MgBr₂) only gave side-products

Replacement of AcOH with of H₃PO₄ and use of Hastelloy autoclaves provided higher reproducibility



Why Copper ?

Hydrogenation with Cu modifiers with Pd supported catalysts or preformed bimetallic Pd-Cu catalysts has some precedents:

selective dechlorination in the presence of C=C bonds,

denitration of water

diastereoselective imine reduction

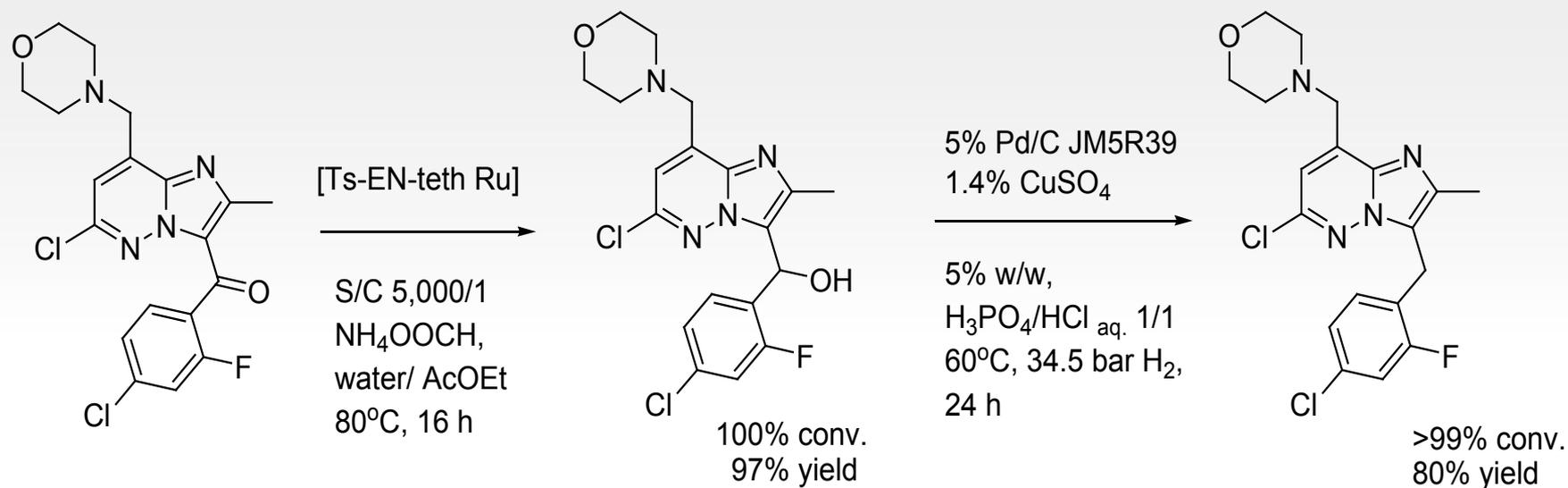
.....but not for alcohol hydrogenolysis....

Depending on the different applications different mechanistic suggestions have been proposed

Under the reaction conditions copper precipitation may occur to form a metal layer and act as modifier of the palladium catalyst



JM-Lilly Collaboration: Conclusions



Stepwise approach using *both* heterogeneous and homogeneous catalysts

Homogeneous catalysts have provided high activity and perfect chemoselectivity

A combination of Pd/C and Cu salts has provided high chemoselectivity



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